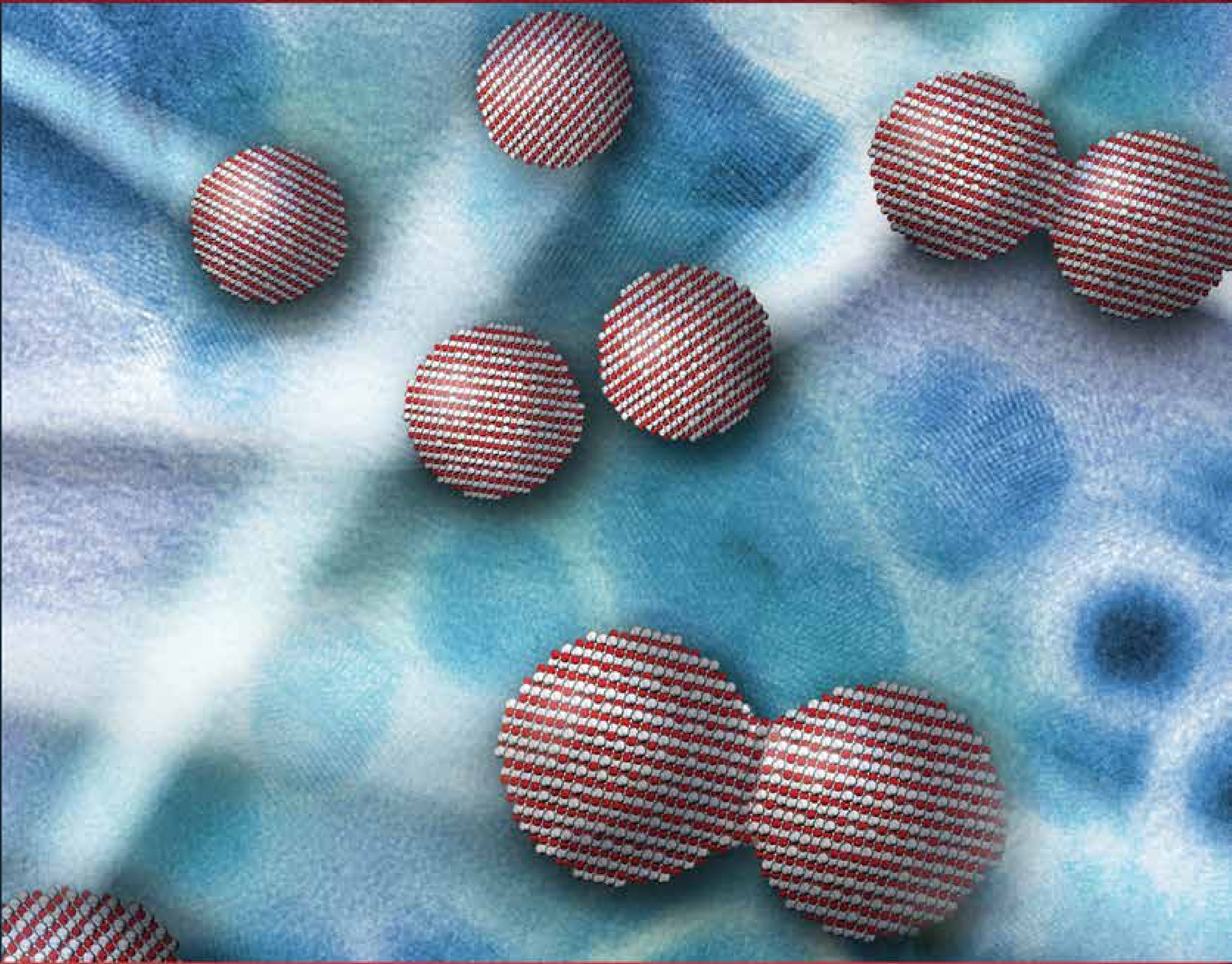
Basic Research Needs for

Synthesis Science



Report of the Basic Energy Sciences Workshop on

Basic Research Needs for Synthesis Science for Energy Relevant Technology

May 2–4, 2016

*The artwork depicts nanoparticles of iron oxyhydroxide undergoing oriented attachment. In this process, which is captured in the background in situ transmission electron microscope image, nanocrystals approach one another, align their crystal lattices and fuse to form a single crystal. This growth mechanism is being investigated as a means of synthesizing hierarchical nanostructures with unique properties. Transmission electron microscope image courtesy of Dr. Dongsheng Li (Pacific Northwest National Laboratory). Artwork by Zina Deretsky (*http://www.zina-studio.com*).*

BASIC RESEARCH NEEDS WORKSHOP ON

Synthesis Science for Energy Relevant Technology

REPORT OF THE BASIC ENERGY SCIENCES WORKSHOP ON SYNTHESIS SCIENCE FOR ENERGY RELEVANT TECHNOLOGY

Chair:
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Co-chairs:
David Mandrus (University of Tennessee/Oak Ridge National Laboratory)

Lynda Soderholm (Argonne National Laboratory)

Panel Leads:

Mechanisms of Synthesis under Kinetic and Thermodynamic Controls
Tori Forbes (University of Iowa)
Mercouri Kanatzidis (Northwestern University)

Establishing the Design Rules for Supramolecular and Hybrid Assemblies
Uli Wiesner (Cornell University)
Ting Xu (University of California–Berkeley)

Interface-Defined Matter
Sarah Tolbert (University of California–Los Angeles)
Michael Zaworotko (University of Limerick)

Crystalline Matter: Challenges in Discovery and Directed Synthesis
Julia Chan (University of Texas–Dallas)
John Mitchell (Argonne National Laboratory)

Emerging Approaches to Synthesis at All Length Scales
Jonah Erlebacher (Johns Hopkins University)
Julia Laskin (Pacific Northwest National Laboratory)

Transformative Research Capabilities I: In Situ Characterization
Simon Billinge (Columbia University)

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https://science.energy.gov/bes/community-resources/reports/

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Abbreviations, Acronyms, and Initialisms

0D	zero-dimensional
1D	1-dimensional
2D	2-dimensional
3D	3-dimensional
AFM	atomic force microscopy/microscope
ALD	atomic layer deposition
BES	Office of Basic Energy Sciences
BESAC	Basic Energy Sciences Advisory Committee
BRN	Basic Research Needs
CNT	carbon nanotube
COF	covalent organic framework
CVD	chemical vapor deposition
DFT	density functional theory
DNA	deoxyribonucleic acid
DOE	Department of Energy
DPD	dissipative particle dynamics
DTEM	dynamic transmission electron microscopy/microscope
EDLC	electric double layer capacitor
EELS	electron energy loss spectroscopy
EXAFS	extended x-ray absorption fine structure
EDXRD	energy dispersive x-ray diffraction
GISAX	grazing-incidence small-angle x-ray scattering
GSGO	global space-group optimization
LCLS	Linac Coherent Light Source
LDH	layered double hydroxide
LED	light-emitting diode
LP-TEM	liquid phase transmission electron microscopy
MBE	molecular beam epitaxy
MOF	metal-organic framework
NERSC	National Energy Research Scientific Computing Center
NMR	nuclear magnetic resonance
PDF	pair distribution function
PLD	pulsed laser deposition

PRD	Priority Research Direction
PSM	postsynthetic modification
PV	photovoltaic
SANS	small-angle neutron scattering
SAXS	small-angle x-ray scattering
SDA	structure-directing agent
SEM	scanning electron microscopy/microscope
SPD	severe plastic deformation
SPM	scanning probe microscopy/microscope
SRM	stimuli-responsive material
SRM-IP	stimuli-responsive molecularly imprinted polymers
STEM	scanning transmission electron microscopy/microscope
STM	scanning tunneling microscopy/microscope
STXM	scanning transmission x-ray microscopy
TEM	transmission electron microscopy/microscope
UED	ultrafast electron diffraction
UV	ultraviolet
WAXS	wide-angle x-ray scattering
XAS	x-ray absorption
XFEL	x-ray free electron laser
XRD	x-ray diffraction

Executive Summary

The technology that lies at our fingertips becomes more powerful each day. Smartphones connect us instantly to family, friends, and co-workers around the globe; give us access to a limitless stream of information; control the heating in our homes; and serve as our cameras, calculators, flashlights, music players, boarding passes and, on occasion, our phones. Cars are ever more fuel-efficient, safer, semi-autonomous, and have more computing power than the systems that guided humankind to the moon. LED lighting and solar panels are becoming commonplace, replacing less efficient technologies and expanding the energy options available worldwide. Novel polymers and nanoparticles are playing a crucial role in enhanced oil recovery. None of these advances would have been possible without the discovery and development of, and ability to create, new materials and chemical processes.

Now imagine what our world would be like if we could accelerate those discoveries a thousandfold. What if the only limit to synthesizing new forms of matter were the imagination? We could build complex assemblies of atoms and molecules with architectures and capabilities far exceeding those of materials found in nature—for example, develop catalysts that turn garbage into fuels, design solar cells to power our homes directly from sunlight, make batteries with the energy density of gasoline, and create one- and two-dimensional solids that transport charge hundreds of times faster than silicon or allow us to build quantum bits based on the spins of electrons or photons to realize the promise of "beyond Moore's law" computing.

Advances in synthesis science are required to bring about this future—we not only must know how to design new molecules and materials with desired functions and properties through theory and computational techniques; we also must be able to make the materials we envision. New approaches to discovering as yet unimagined matter require a sea change in the way we think about the science of synthesis. Chemical and materials sciences have traditionally focused on understanding structure–function relationships with the goal of predicting *where the atoms should be placed* to achieve a targeted property or process. Much less effort has been directed toward a predictive science of synthesis—understanding *how to get the atoms where they need to go* to achieve the desired structure.

This report, which is the result of the Basic Energy Sciences Workshop on Basic Research Needs for Synthesis Science for Energy Technologies, lays out the scientific challenges and opportunities in synthesis science. The workshop was attended by more than 100 leading national and international scientific experts. Its five topical and two crosscutting panels identified four priority research directions (PRDs) for realizing the vision of predictive, science-directed synthesis:

Achieve mechanistic control of synthesis to access new states of matter

The opportunities for synthesizing new materials are almost limitless. The challenge is to combine prior experience and examples with new theoretical, computational, and experimental tools in a measured way that will allow us to tease out specific molecular structures with targeted properties. Harnessing the rulebook that atoms and molecules use to self-assemble will accelerate the discovery of new matter and the means to most effectively make it.

Accelerate materials discovery by exploiting extreme conditions, complex chemistries and molecules, and interfacial systems

Even as our theoretical understanding of synthetic processes increases, many future discoveries will come from regions of parameter space that are relatively unexplored and beyond current predictive capabilities. These include extreme conditions of high fluxes, fields, and forces; complex chemistries and heterogeneous structures; and the high-information content made possible by sequence-defined macromolecules such as DNA. This PRD emphasizes that materials synthesis will remain a voyage of discovery, and that synthetic, characterization, and theoretical tools will need to continuously adapt to new developments.

Harness the complex functionality of hierarchical matter

Hierarchical matter exploits the coupling among the different types of atomic assemblies, or heterogeneities, distributed across multiple length scales. These interactions lead to emergent properties not possible in homogeneous materials. Dramatic advances in the complex functions required for energy production, storage, and use will result from control over the transport of charge, mass, and spin; dissipative response to external stimuli; and localization of sequential and parallel chemical reactions made possible by hierarchical matter.

Integrate emerging theoretical, computational, and in situ characterization tools to achieve directed synthesis with real time adaptive control

Theory, computation, and characterization are critical components to the effective discovery and design of new molecules and materials. Important but insufficient is the prediction of the final composition and structure. Critical to the process is knowing and predicting how materials assemble and the consequences of the assembly for final material properties. Combining in situ probes with theory and modeling to guide the synthetic process in real time, while allowing adaptive control to accommodate system variations, will dramatically shorten the time and energy requirements for the development of new molecules and materials.

The historical impact of chemistry and materials on society makes a compelling case for developing a foundational science of synthesis. Doing so will enable the quick prediction and discovery of new molecules and materials and mastery of their synthesis for rapid deployment in new technologies, especially those for energy generation and end use. The PRDs identified in this workshop hold the promise of enabling the dream of synthesizing these new molecules and materials on demand by finally realizing the ability to link *predictive design* to *predictive synthesis*.

1. Introduction

The importance of synthesis science to the future of energy technology reflects the historical link between new materials and new technologies.[1,2] Synthesis has long been the engine of technological advancement: the march of civilization has been marked by signature materials—the Stone Age, the Bronze Age, the Iron Age, and so on (Figure 1). Even the Information Age is referred to as the “silicon age,” because it depended upon the development of a new material: the silicon-semiconductor p-n junction. This ascent of civilization from one material to the next has never been the result of crisis but rather of opportunity. As an oil minister once said, “The Stone Age didn’t end for lack of stone.”[3] In the same way, the transition to a new energy economy in the 21st century will come about when new energy technologies are enabled by the synthesis of new materials.

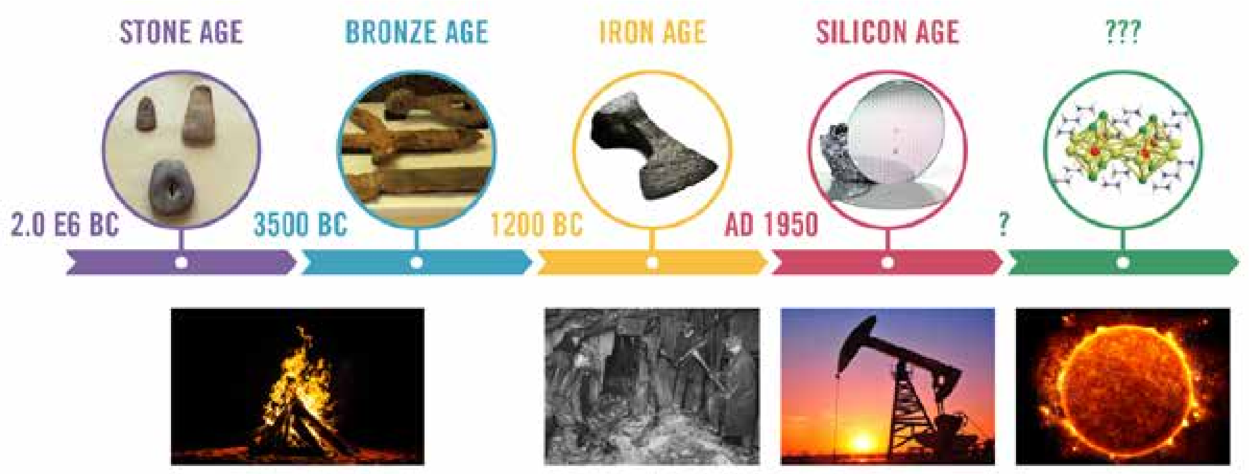
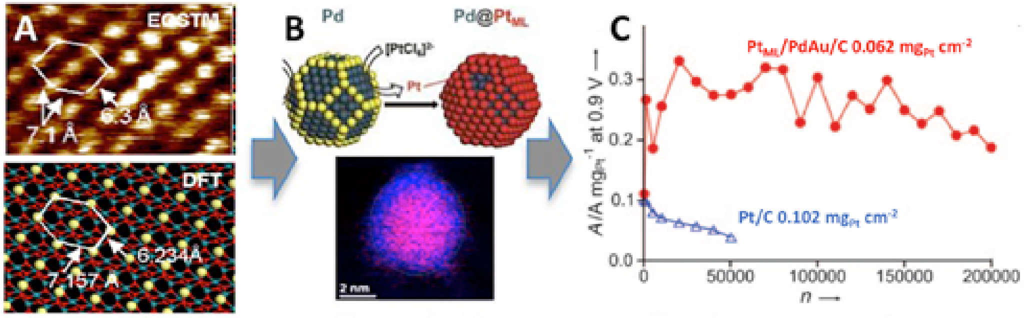


Figure 1. The advancement of human civilization has been chronicled by the development of new materials. **|** *Image courtesy of Pacific Northwest National Laboratory.* **|** *[Top right] Reprinted with permission from M. A. Loi and J. C. Hummelen. 2013. “Hybrid Solar Cells: Perovskites under the Sun.” Nature Materials 12 [12]: 1087–89. DOI: 10.1038/nmat3815. © 2013 Macmillan Publishers.*

In the past few decades, the extent to which discoveries of new molecules and materials have impacted technology in general, and energy technologies in particular, has been dramatic (see the sidebar *From materials discovery to energy technology*).[4,5] Discoveries of conducting polymers, high-temperature superconductors, Buckyballs, graphene, and many other novel materials have opened entirely new fields of research, making their debut with much fanfare and promise for revolutionary impacts on energy technologies in the coming years. Many others—such as carbon fiber composites, platinum-group catalysts, and lithium ion conductors—have already quietly transformed the way we live, finding their way into chemical production, energy production and use, transportation, and information technology.

The journey to application of new molecules and materials often follows a pathway captured pictorially by the so-called Materials Pyramid [6,7] (Figure 2). At the top of the pyramid lies application and societal impact, for instance solid-state lighting or high-performance batteries. The path downward leads through progressively larger subsets of candidate materials, explored for their underlying chemical and materials properties and evaluated for functionality. Finally, at the pyramid base lie many compounds and materials proposed theoretically, or discovered experimentally. This diversity itself offers fundamental insights into structure and function, with few candidates possessing the sought-after properties. The crucible of discovery lies at this lowest level, where new opportunities launch toward the top of the pyramid. It is the essential work at the pyramid base that creates the critical path to ultimate application, and where investment in design, exploration, discovery, and synthesis sets the stage for future dividends realized on the pyramid’s higher levels. Despite wide recognition of the importance of such efforts at the pyramid base, and considerable work devoted to systematizing discovery synthesis, there remain significant challenges to both predicting and realizing new molecules and materials. Fundamental to this workshop are these questions: How can we push the boundaries of synthesis science to discover new states of matter? What are the controlled, energy-efficient synthesis pathways that will translate these discoveries into innovative technologies at the top of the pyramid? Ultimately these questions are tied to an overarching workshop theme: "How do we link predictive design to predictive synthesis?"

From materials discovery to energy technology



Principles and methods of electrocatalysis by single atomic layers

Core-shell electrocatalysts developed for high activity with ultralow Pt mass

Performance and durability in subsystem membrane electrode assemblies, licensing, and manufacturing

Materials discoveries in recent decades have had a profound impact on society, enabling many promising revolutionary changes in energy technologies. While numerous discoveries have been recognized through major scientific awards, others stand as unsung accomplishments that have transformed our lives with little fanfare. Most of these discoveries have relied upon intuitive and deductive reasoning combined with extensive empirical efforts based on post-synthetic analysis. The emergence of powerful computational approaches and in situ characterization tools promises to dramatically accelerate both discovery and maturation of new materials with high efficiencies and novel functions that will usher in a new energy economy.[4,5,8] ❙ *[A] Reprinted with permission from M. B. Vukmirovic et al. "Controllable Deposition of Platinum Layers on Oxide Surfaces for the Synthesis of Fuel Cell Catalysts." Chemelectrochem 3 [10]: 1635–40. DOI: 10.1002/celc.201600255. © 2016 John Wiley and Sons.* ❙ *[B] Reprinted with permission from Y. Zhang et al. "High Performance Pt Mono Layer Catalysts Produced via Core-Catalyzed Coating in Ethanol." ACS Catalysis 4 [3]: 738–42. DOI: 10.1021/cs401091u. © 2014 American Chemical Society.* ❙ *[C] Reprinted with permission from K. Sasaki et al. "Core-Protected Platinum Monolayer Shell High-Stability Electrocatalysts for Fuel-Cell Cathodes." Angewandte Chemie International Edition 49 [46]: 8602–07. DOI: 10.1002/anie.201004287. © 2010 John Wiley and Sons.*

Major recent discoveries	Unsung heroes
Conducting polymers (1982)*	Carbon fiber composites (1960s)
High T_c superconductors (1986)*	High-Si alumino-Si zeolites (1980s)
Buckyballs, C_{60} (1985)*	Platinum-group catalysts (1980s)
Dye-sensitized solar cell (1990)*	Transparent conducting oxide (1980s)
Carbon nanotubes (1991)$	Rare earth phosphors (1970s)
Quantum dots (1992)$	Lithium ion conductors (1984)
GaN semiconductors (1993)*,#	Metal organic frameworks (1995)
Magnetoresistive materials (1995)#	Bismuth chalcogenides (1997)
Graphene (2004)*	Hybrid perovskites (2009)

* Nobel Prize $ Kavli Prize # Millennium Prize

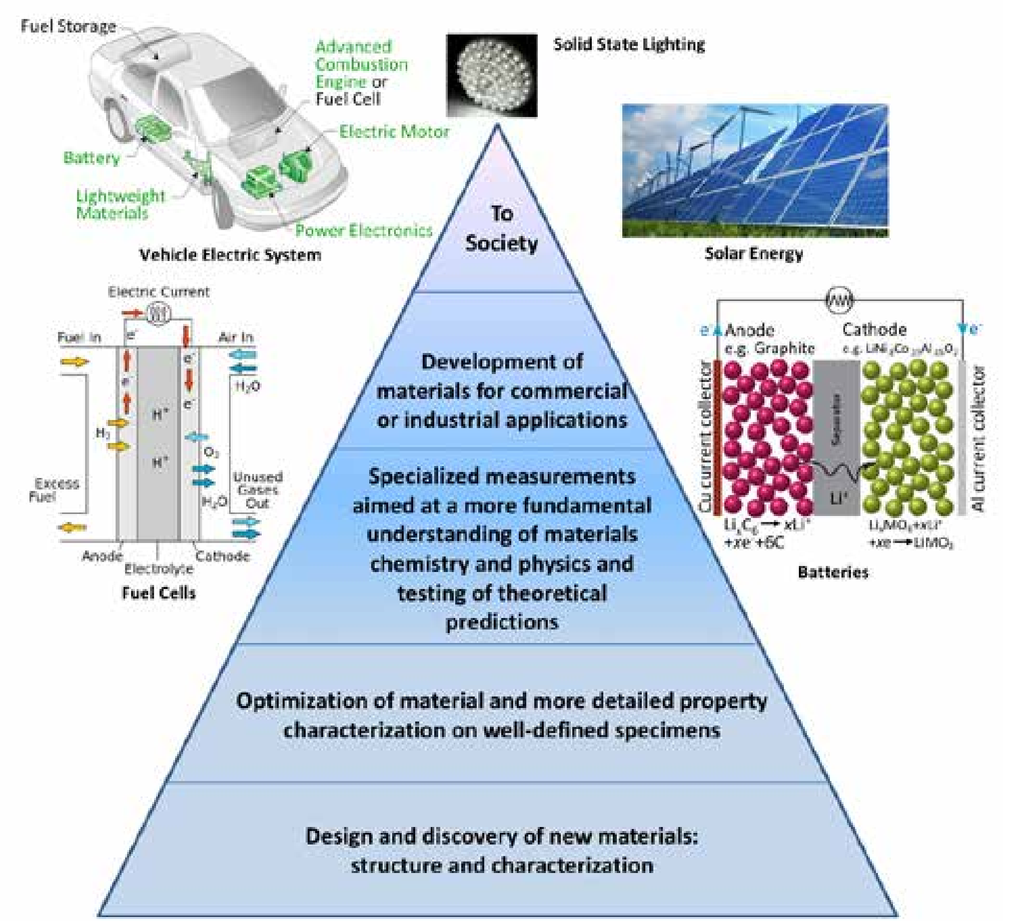


Figure 2. The Materials Pyramid. | *Adapted from an image from B. C. Sales, Oak Ridge National Laboratory*

Computational methods for predictive design have come a long way toward joining with empirical knowledge to tell us ***where*** to put atoms for specific function. Yet there is much further to go in developing computational methods that tell us ***how*** to put them there. That is, although many molecules and materials can be created in silico, there are still substantial challenges to creating them in the laboratory. Nonetheless, some successes have been achieved and pathways laid for the future. These knowledge-based approaches represent a potential new avenue for accelerating the synthetic component of any predict-synthesize-measure feedback loop.

The importance of advancing synthesis science for energy technology and the intimate link between the two is reflected in many earlier Basic Energy Sciences (BES) Basic Research Needs (BRN) Workshop reports that highlight synthesis as an enabling capability for solar energy,[9] electrical energy storage,[10] catalysis,[11] solid state lighting,[12] carbon capture,[13] and quantum materials.[14] The advances required to realize the synthesis goals cited in these BRN reports are well summarized in the BES Advisory Committee report *Challenges at the Frontiers of Matter and Energy: Transformative Opportunities for Discovery Science*,[15] which calls for major advances in a number of relevant areas, including “Transformative Advances in Imaging Capabilities across Multiple Scales,” “Revolutionary Advances in Models, Mathematics, Algorithms, Data, and Computing,” and “Mastering Hierarchical Architectures and Beyond-Equilibrium Matter.”

We are at an auspicious time to tackle the challenge. For example, the ability to synthesize matter under extreme conditions is making appreciable strides, providing access to *terra incognita* in the phase space of new, metastable compounds.[16] New frameworks for understanding the assembly of crystalline matter,[17] for instance prenucleation[18] and inorganic synthon concepts,[19] offer new ways of thinking about synthesis. Powerful tools for monitoring growth in situ are being used, with new approaches being conceived and developed, to shine light on the atomic-to-mesoscale processes underlying molecular and materials assembly. Computation is already a powerful tool for design in the synthesis laboratory (e.g., the density functional theory–based Materials Project).[20] The sheer complexity of multi-length-scale structures offers an opportunity for increased feedback from exploratory synthesis to computational models. Looking ahead, the use of computational methods in concert with in situ probes would provide a critical tool to guide synthesis, for example, through machine learning. Today's confluence of insight, new tools, and advances in computational methodologies suggests that we are on the cusp of massively expanding the phase space available for exploration and discovery. As a result, work at the base of the new materials pyramid is poised to flourish in a properly nourished ecosystem of academic, national laboratory, and industrial research. It is in such an environment that the time required to move from conceptualizing a new structure to mastering its precise synthesis and/or assembly will be measured in weeks instead of years.

Recognizing both the needs and opportunities for advancing synthesis science, BES organized this workshop on the Basic Research Needs for Synthesis Science for Energy Relevant Technology. The goal of this workshop, and the associated report, was to identify Priority Research Directions (PRDs) that open up new pathways toward realizing these transformative opportunities, specifically the ability to make the molecules and materials that are envisioned herein. The specific charge to the workshop was as follows:

> Identify basic research needs and priority research directions in synthesis science with a focus on new, emerging areas with the potential to leapfrog current capabilities and impact future energy technologies. The workshop will identify the scientific opportunities and new frontiers associated with both existing and novel synthetic processes that will enable predictive synthesis of energy relevant matter via assembly of atoms, molecules, clusters, nanoparticles, and other constituents. This research is essential to realizing the opportunities identified in the recent BES Advisory Committee report *Challenges at the Frontiers of Matter and Energy: Transformative Opportunities for Discovery Science*.[15] This report concluded that further progress towards the transformative opportunities will require specific, targeted investments in synthesis science, specifically the ability to make the materials and architectures that are envisioned.

Workshop Organization

A major consideration in defining the workshop panels was that synthesis is a broad field covering a wide range of molecular and materials systems explored across a diverse set of scientific frontiers important for the development of new energy technologies. Research frontiers of particular relevance include these:

- Achieving new states of matter with novel functions for innovative applications in energy technology by (1) driving synthetic outcomes toward metastable and kinetically stabilized states; (2) enabling discovery of new molecular and materials systems; (3) exploiting weak interactions to control self- and directed-assembly of hierarchical, dynamic and dissipative structures; (4) directing spatial organization over multiple length scales in multi-component systems with control over interface structure and properties; and (5) using extreme conditions of high fields, fluxes, and chemical gradients

- Targeting equilibrium phases of crystalline solids in complex phase diagrams and/or in species in unusual coordination and charge states to enhance energy conversion and transport properties

- Synthesizing matter to function under extreme physical and chemical conditions present during energy generation and storage

- Developing new approaches to and the basic science of scale-up: e.g., massively parallel synthesis routes, self-replication, additive manufacturing

To achieve the workshop goal of defining a small, well-focused set of PRDs despite the breadth of the field, the workshop chairs worked with BES staff to identify a set of common scientific challenges around which the workshop could be organized, rather than specific classes of matter (although in some cases the two were necessarily coupled).

The workshop was organized into five topical panels. The panel on mechanisms of synthesis under kinetic and thermodynamic controls focused on understanding the competing controls of thermodynamics and kinetics underlying synthesis, including how and why inorganic matter assembles, in much the same way that organic chemists use a toolbox of functional groups and their associated reactivity to guide retrosynthetic approaches. The panel on establishing the design rules for supramolecular and hybrid assemblies looked at efforts to predictably connect the design of constituent organic and hybrid building blocks to the structural and functional outcomes of their self-assembly, with a strong focus on understanding the underlying energetic and structural factors controlling pathways and outcomes. The panel on interface-defined matter addressed the challenge of creating hierarchical structures based on an understanding of the interactions and dynamics of ions, molecules, clusters, and particles interacting at interfaces and the relative roles of kinetic stabilization vs. thermal relaxation in creating both equilibrium and nonequilibrium or persistently metastable structures. The panel exploring crystalline matter: challenges in discovery and directed synthesis focused on efforts in solid state synthesis to use equilibrium phase diagrams to predict and realize new compositions and phases of crystalline matter and create a road map for their design and directed synthesis. The panel on emerging approaches to synthesis at all length scales considered novel methods of synthesis and post-synthesis processing, particularly those using unusual or extreme physical or chemical conditions, with a focus on the energetic controls and transfer of mass that underlie such approaches.

Crosscutting panels: In addition to these five topics, the subjects of two crosscutting panels were “Theory and simulation” and “In situ characterization,” which are essential to progress in all five areas. Theory and simulation provide a platform for testing mechanistic models and predicting synthesis conditions and outcomes. In situ characterization provides the data needed to observe synthetic pathways, quantify energetic and kinetic parameters, test predictions, and discover new classes of matter.

Priority Research Directions

Each panel identified a set of important research opportunities within its topical focus area, which are discussed in detail within subsequent chapters of this report. These research opportunities were distilled into four PRDs for realizing the vision of predictive synthesis:

- Achieve mechanistic control of synthesis to access new states of matter.

- Accelerate materials discovery by exploiting extreme conditions, complex chemistries and molecules, and interfacial systems.

- Harness the complex functionality of hierarchical matter.

- Integrate emerging theoretical, computational, and in situ characterization tools to achieve directed synthesis with real-time adaptive control.

Summary

The historical impact of chemistry and materials sciences on society makes a compelling case for developing a foundational approach to synthesis that can quickly predict and discover new molecules and materials and master their synthesis for the rapid deployment of new technologies. Future energy technologies depend upon advances in the science of synthesis. The conversion of sunlight to fuel, efficient electrical energy storage; highly efficient low-temperature catalysis; low-cost separation of rare-earth and precious metals, carbon dioxide, and water; development of quantum information systems; advances in energy efficiency from solid state lighting to high-frequency motors; superconducting materials for the smart electric grid; and lightweight vehicles all require the development of new matter with unprecedented functionality and performance. For all of these technologies, the ability to define the underlying physical and chemical principles of function and establish conceptual designs for new molecules and materials has greatly outpaced the development of synthetic processes that can turn those concepts into reality. The PRDs identified in this workshop hold the promise of enabling the dream of discovering and synthesizing these new molecules and materials on demand by finally realizing the ability to link *predictive design* to *predictive synthesis* based upon an ability to define both where the atoms need to be placed **to achieve the desired function** and how to get them where they need to go **to achieve the targeted structure—**the central goal of the Synthesis Science BRN workshop and this report.

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2. Priority Research Directions

Each of the workshop panels identified a number of emerging research challenges, all of which reflect specific scientific challenges in the respective topical areas. Four unifying themes emerged that were the most compelling and pervasive, crosscutting all panels. These Priority Research Directions (PRDs) are critical to advancing the predictive science of synthesis:

- Achieve mechanistic control of synthesis to access new states of matter
- Accelerate materials discovery by exploiting extreme conditions, complex chemistries and molecules, and interfacial systems
- Harness the complex functionality of hierarchical matter
- Integrate emerging theoretical, computational, and in situ characterization tools to achieve directed synthesis with real-time adaptive control

PRD 1: Achieve mechanistic control of synthesis to access new states of matter

How can we develop a fundamental understanding of the processes by which reactants assemble into products and how they can be controlled? Can we access metastable ordered phases that are formed during synthesis but subsequently dissolve or transform before equilibrium is reached?

The opportunities for generating new molecules and materials are boundless. Combining elements from across the periodic table—each with its own chemical, structural, and electronic signatures—through a selection of synthetic conditions bestows a favored reaction pathway across an energy landscape to an end product. Although this variety of choices provides enormous opportunity, it also leaves an unwieldy collection of options to assess and control. Parameter decisions are often made in the absence of a fundamental understanding of their potential consequences. Therefore, much of the current approach to synthesis relies on intuition-driven methods that are high consumers of energy, resources, and time. This approach has led to critical discoveries of new products with unprecedented structures and functions; but current-day energy demands drive us toward ever more complex molecules and materials and, consequently, the requirement for a more disciplined methodology for producing them. Desperately needed, and currently largely lacking, is a fundamental understanding of the processes by which reactants assemble into products and how they can be controlled.

The common approach to synthesis of a new molecule or material begins with assembling reactants and choosing the synthetic conditions, the details of which are either founded in past experience or based on literature precedent. Knowledge of the reaction pathway itself is based largely, if not solely, on an analysis of the final products. The atomic correlations that develop along the way, the intermediates that form and then redissolve or are modified, and the intricate mechanisms that may have come into play all remain unknown. This lack of awareness of competing mechanisms or transient intermediates represents lost opportunities to improve ways of making known substances, or to glean new insights into ways of creating unknown classes of compounds and materials.

Synthesis by design: How materials form

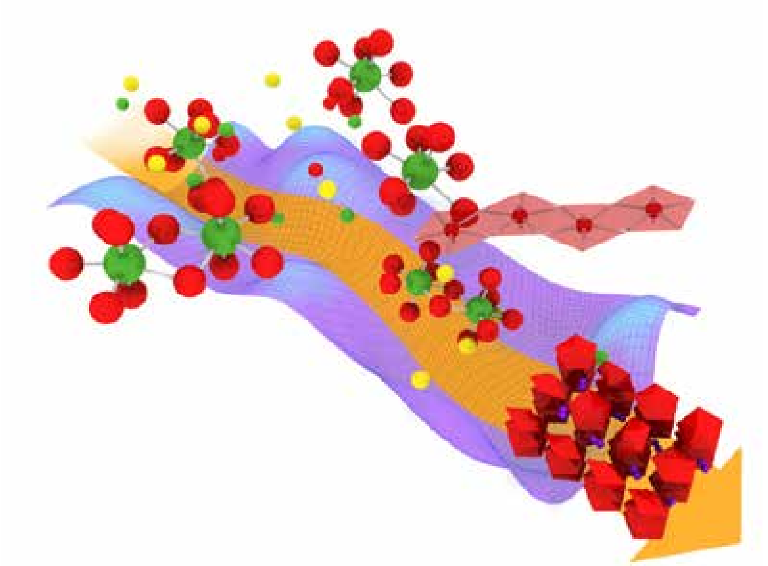


Figure 3. The reaction pathway from reagents to a targeted product can be fraught with false minima and high-energy barriers. The goal of predictive synthesis-by-design capabilities requires a mechanistic knowledge of how molecules traverse an energy landscape and how a reaction can be manipulated to favor a specific outcome. Looked at differently, characterizing pathways through complex landscapes provides an opportunity to synthesize entirely new materials with new properties of importance to energy production, efficient use, and storage. | *Image courtesy of L. Soderholm, Argonne National Laboratory*

The full realization of synthesis-by-design will require amassing information about the molecular-level processes taking place during a variety of reaction types and under various conditions (Figure 3). Success hinges on our ability to define the attributes signaling relevant chemical changes and probe them in situ. Some tools already exist to provide information of this type, but combinations covering the necessary temporal and spatial ranges have yet to be developed. Although challenging in its own right, combining two or more complementary experimental techniques—for example to simultaneously cover molecular, nano, and micro length-scale correlations—has the potential to provide valuable insights into a synthetic pathway. Access to complementary information concerning how and when materials form will underpin a predictive mechanistic understanding of a class of reactions, and it represents a critical component for the validation of new computational strategies to describe synthetic processes, particularly those occurring out of equilibrium (Figure 4).

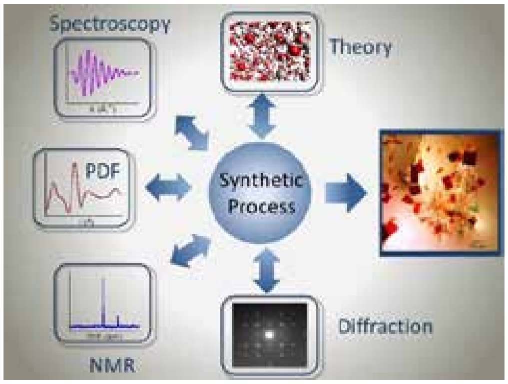


Figure 4. The availability of a complementary suite of experimental data and computational predictions would optimize both the resources and time invested in synthesizing new and targeted materials. Note: PDF = pair distribution function; NMR = nuclear magnetic resonance. | *Image courtesy of L. Soderholm, Argonne National Laboratory*

The full power behind understanding how a reaction proceeds will achieve fruition only with concurrent capabilities to reduce and analyze in situ data, in real time, during the actual course of synthesis. Efforts quantifying the utility of, for example, electronic spectroscopies as probes of reaction pathways are currently particularly underrepresented. For most current experiments, the shear data quantity and the time required to process them prohibit real-time understanding of a reaction as it proceeds. A successful advancement will be to permit the interjection of experimental control at critical points during the reaction. For example, the pathway to a targeted hierarchical structure may first require the formation of individual building units; and their subsequent condensation may require the precisely timed addition of a templating agent. Such a capability requires a wide cadre of experimental, theoretical, and computational tools, each of which contributes its own perspective to the development of the mechanistic route taken during synthesis. From another perspective, a reaction pathway could be tested in real time to determine the underlying forces and conditions dominating the pathway choice; doing so would minimize the need for synthetic arrays in which many tens of samples, all with slightly differing conditions, are left to react. For example, there is no point in adding a templating agent, designed to assemble the building units, if the building units themselves did not form.

The capability to describe how individual reactions proceed is receiving increasing interest within the synthetic community. These efforts are allowing the development and testing of new theories of compounds and materials growth, including how thin films form and clusters assemble. However, much more experience is needed over a wide range of compounds and structures and under a wide range of reaction conditions, before sufficient knowledge will exist to permit robust fundamental insights into the general mechanisms underlying targeted synthesis. Atomic-scale theories need to be linked through the molecular/nanoscale to the mesoscopic for maximum impact.

The progression from the art-of-synthesis into the science-of-synthesis will require a multi-pronged approach to understanding how molecules and materials assemble, in terms of both their mechanism of correlation formation and the factors influencing their reaction pathways. Not to be lost in this search is the opportunity to capture as-yet-undiscovered new molecules and materials that may form during the synthetic process but not survive to the final product. Such a substance may be a critical intermediate in the reaction or a deviation leading away from the desired target. On the one hand, ideas for new structures are increasingly being generated in silico, rendering more critical the ability to understand how to synthesize a designed target. On the other hand, the search for whole new classes of molecules and materials, some of which are yet unimagined, requires a continuation of serendipitous discovery—but one with a rational underpinning that targets kinetically unstable or transient species that form during syntheses.

Discovering new molecules and materials: Intermediates and phase space

Mechanistic studies, coupled with theory and computation, represent one avenue to achieving synthetic control. Another potential methodology, involving total phase awareness, is more focused on the discovery of new-materials classes. Complementing the mechanistic approach described above, this perspective considers intermediates not in terms of defining synthetic pathways and energy landscapes but instead as an avenue to the discovery of new metastable or kinetically stabilized substances. The information sought concerns building an awareness of ordered phases that form during a synthesis but subsequently dissolve or transform before equilibrium is reached or the reaction is stopped. Such transient phases are unobserved in following most current synthetic approaches, which analyze only final products. Access to structural and chemical information through probes applicable for in situ application would not only elucidate how the final compound forms but also reveal any compounds hidden by processes preceding reaction termination.

Because the goal of total phase awareness is to obtain knowledge of all the ordered phases that form during a reaction, experimental protocols are needed that focus on monitoring an ongoing reaction using a structural probe, such as diffraction. Again, the data volume would be excessive, but computational tools to index correlation peaks are currently available. Advancements would include the development of faster data reduction and phase identification. The presence of unknown structures and phases, thus determined, could then be targeted through protocols that arrest the synthetic process before the molecule or material is transformed. Extended opportunities include further analyses of the powder patterns to extract pair correlations that could provide insights into total-phase awareness.

An opportunity arising from in situ phase monitoring lies in the potential not only to streamline the assembly of phase diagrams, but also to extend their utility into multi-variable, metastable phase spaces by incorporating the effects of reaction time and/or synthetic conditions. Such extended-dimensionality diagrams would include both stable and kinetically stabilized structures; they would provide a critical step in merging existing knowledge of phase diagrams with more fine-grained approaches for deriving energy landscapes. The outcome of such a methodology will be critical as the quest for new molecules and materials moves away from thermodynamically stable compounds into those that form far from equilibrium. The availability of new information in this realm will both streamline and transform new materials discovery, design, and synthesis.

PRD 2: Accelerate materials discovery by exploiting extreme conditions, complex chemistries and molecules, and interfacial systems

Materials discovery is crucial for progress in science and technology, but how will the new materials of the future be created? And where should we look for them?

Synthesis is, at its heart, discovery science, and this PRD seeks to enhance the science of materials discovery while remaining realistic about our predictive capabilities.

Extreme conditions: Regions of parameter space where rules are not well developed

A proven strategy to enhance materials discovery is to exploit “extreme conditions,” i.e., push into regions of parameter space that have not been extensively explored and are not well understood. Examples include the use of new crystal growth tools, such as laser diode and high-pressure floating zone furnaces; new fluxes, such as molten alkaline earth metal fluxes for growing oxide crystals;[1] and new deposition tools that go beyond established methods, such as molecular beam epitaxy and pulsed laser deposition. Kinetic control of synthesis using “chimie douce” (soft chemistry, i.e., reactions carried out at modest temperatures) is a promising route to creating new inorganic materials.[2] In contrast to organic chemistry, which employs a set of mechanistic rules for the detailed planning of syntheses, methodologies for inorganic solids are in their infancy. To illustrate this issue, Figure 5 shows a thermodynamic phase diagram (800°C) of carbon, oxygen, and hydrogen—the elemental basis of organic chemistry. At 800°C, the landscape is quite barren; but when you turn down the heat, everything changes. The richness of organic chemistry is due to kinetics, and chimie douce techniques promise to increase the chemical richness on the inorganic side. Mechanochemistry approaches (solid-state synthesis under extreme deformation) allow for access to stable material phase space at lower temperatures and pressures, or to pathways not achievable via standard thermal processes. Electrochemical approaches such as molten salt electrolysis[3] and electrochemically driven insertion reactions[4] are also promising routes to creating new materials. Hand-in-hand with these new tools, cross-cutting efforts in theory, modeling, and in situ characterization are also needed.

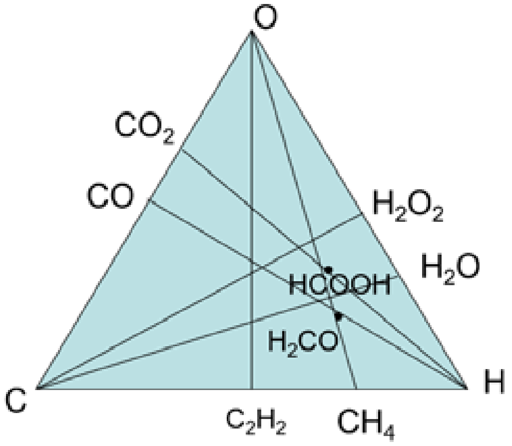


Figure 5. If organic chemists were limited to synthesizing thermodynamically stable compounds, the world of organic chemistry would be a barren one with few compounds inhabiting the C-O-H ternary diagram, shown here at 800°C. Instead, using kinetic stabilization by working at low temperatures enables a richness of compounds synthesized by design. The path forward for solid state syntheses is to find methods that allow an equal richness of kinetically stabilized compounds synthesized by design. **|** *Images courtesy of M. Kanatzidis, Northwestern University*

Complex chemistries and interfaces: Expanding the palette of synthesis

Materials discovery will also be enhanced by increasing our ability to think beyond simple chemistries to master ternary or quaternary systems and beyond. Exploring phase relationships in such chemically complex systems has been a key step in the discovery of a wealth of new materials over the past two decades. Moreover, these complex chemistries have naturally led to materials whose properties arise from compositional and structural factors beyond those of the unit cell. Two triumphs of 20th century materials science were the discoveries that the electrical properties of semiconductors and the mechanical properties of metals are both controlled by imperfections and cannot be engineered with only a unit cell–level of understanding. What other properties of materials are controlled by structures that go beyond the unit cell? One example is thermoelectric materials, in which it has been shown that incorporating nanoscale inclusions can improve performance.[5] Another example is the formation of a skyrmion lattice in helimagnets such as MnSi.[6] The skyrmion lattice is a topologically stable spin state with a characteristic length scale vastly larger than the unit cell.

Among the complex chemistries yielding new states of matter are supramolecular, macromolecular, and hybrid organic–inorganic systems. Exploration of these systems has also revealed a rich store of new structures over the past two decades.[7] The high information content of the building units and the capability they offer to introduce multiple components—including distinct sequences, molecular species, or inorganic nanomaterials—enables a degree of hierarchy not achievable in small molecule or inorganic systems. The emergence of DNA origami[8] as a materials system that can be programmed to produce topologically intricate nanostructures with atomic precision highlights the potential of supramolecular and macromolecular systems for generating complex hierarchical materials. Introducing a commensurate level of sophistication in functionality likely requires the chemical diversity seen in peptides and synthetic foldamer systems, such as peptoids,[9] in which the building blocks are selected from a large library that provides high side-chain diversity. The resulting complexities and preponderance of shallow minima in the energy landscapes associated with folding and assembly define an enormous parameter space for discovery of new structures and functions. However, this diversity comes with the price of lost predictability: not only are equilibrium architectures difficult to predict, but also the final structures may often represent nonequilibrium states of matter. Consequently, hypothesis-driven synthetic efforts will continue to propel new discoveries.

Another route to creating the new materials of the future is to more deeply understand how materials properties can be determined by interfaces and defect populations. This is true for nanomaterials, for porous materials such as zeolites and other framework materials, for hybrid materials, and for heterostructures. An example of an interesting recent development is the creation of electric-double-layer field-effect devices at the interfaces between ionic liquids and crystals.[10] Using this approach, a two-dimensional (2D) electron gas can be created at the interface; and the carrier density of the electron gas can be tuned with a gate voltage to produce an amazing variety of behaviors, such as driving materials through metal-insulator and charge density wave transitions and switching superconductivity on and off. Gate tuning of magnetism is the next step, and this is an active area of investigation around the world.

One emerging research area that encompasses most of these themes is that of van der Waals heterostructures.[11] This area bridges bulk inorganic crystal synthesis and nanoscience. These materials consist of single layers of 2D semiconductors or other 2D crystals mechanically assembled and held together with van der Waals bonding. What is exciting about van der Waals heterostructures is that absolutely new and potentially revolutionary materials can be quickly assembled like stacking Lego bricks. Right now, the materials under study are mostly 2D semiconductors; but in the coming years, they will be expanded to include 2D metals, superconductors, magnets, ferroelectrics, and others. The possibilities for creating new materials are practically limitless. As pointed out by Geim and Grigorieva, “At the time of writing, the dreams of other 2D crystals are relatively more modest.¼ In contrast, van der Waals heterostructures do not lack ambition.”[11]

In light of all these possibilities, it should be stated that exploratory synthesis is essential. Although great strides have been made in recent years in the ability to predict the properties of matter from first principles, rigorous prediction of a synthesis pathway for a given molecule or material has not kept pace. For that reason, we cannot rely on theory alone to drive innovation; and exploratory synthesis will continue to provide the overwhelming majority of new materials for years and perhaps decades to come. Although it is true that exploratory synthesis lacks the mathematical rigor of, say, density functional theory (DFT), it must be kept in mind that it is a rational approach relying on chemical reasoning, rules of thumb, experience, and observation. As noted by H. G. von Schnering, “¼ anyone who wants to harvest in his lifetime cannot afford to wait for the ab initio theory of weather!”[12]

The materials of the future will come from new tools and new ideas. New tools such as the use of extreme conditions will enable discovery; and new ideas such as complex chemistries, information-rich molecules, and interfacial systems will suggest where to look.

PRD 3: Harness the complex functionality of hierarchical matter

Functionality involves hierarchical matter with properties determined across multiple length scales. How can synthesis access multiscale structures to produce desired novel functionality?

The challenge of mastering hierarchy crosscuts all classes of syntheses (Figure 6). In interfacial, supramolecular, biomolecular, and hybrid matter, hierarchy is *the* characteristic feature that leads to function. Nanostructured bulk solids, whether characterized by particles within a matrix or interconnected negative space within an extended framework, use coupling across length scales to create properties not available in homogeneous materials. Indeed, the phenomenon of emergent properties is often a consequence of hierarchical design. Moreover, the concept of hierarchy applies at all length scales of synthesis from atomic to micrometer, Examples include

- interpenetrating patterns of atoms and unit cells in crystalline matter[13]
- multi-layers of distinct two 2D materials in thin films[11]
- 3-dimensional (3D) nanoparticle superlattices[14]
- self-assembled polymeric solids[15]
- topologically complex bulk solids[16]

The approaches to synthesizing hierarchical structures are as varied as the classes they represent. The growth of 2D multilayers follows traditional approaches that go back many decades, such as molecular beam epitaxy;[17] but it also includes more recently developed approaches, such as focused electron beam–induced deposition,[14] that can create 3D structures with sub-nanometer feature sizes. Supramolecular systems, in which the hierarchical nature of the resulting structure is programmed through the structure and functionality of the initial complexes,[15] generally use solvent-based routes that rely on weak interactions to drive self-assembly. Nanoparticle superlattices and nanocomposites are often produced by solvothermal methods,[14] but their architectures depend on the physical shapes of the building blocks, combined with their functionalization. In contrast, nanostructured bulk metals are typically formed by rapid cooling of melts followed by post-solidification processing, such as high shear deformation. Mesoporous and microporous solids often involve solvent-based reactions around a sacrificial structure-directing agent but, in the case of metals, can be generated via a de-alloying process following casting.[16] For all these classes of materials, remarkable structures have already been created; but major gaps in our understanding of the synthetic process limit their complexity, diversity, and scalability. For example, materials that approach the complexity of those produced in living systems, such as enzymes and photosynthetic complexes, lie well beyond our reach.

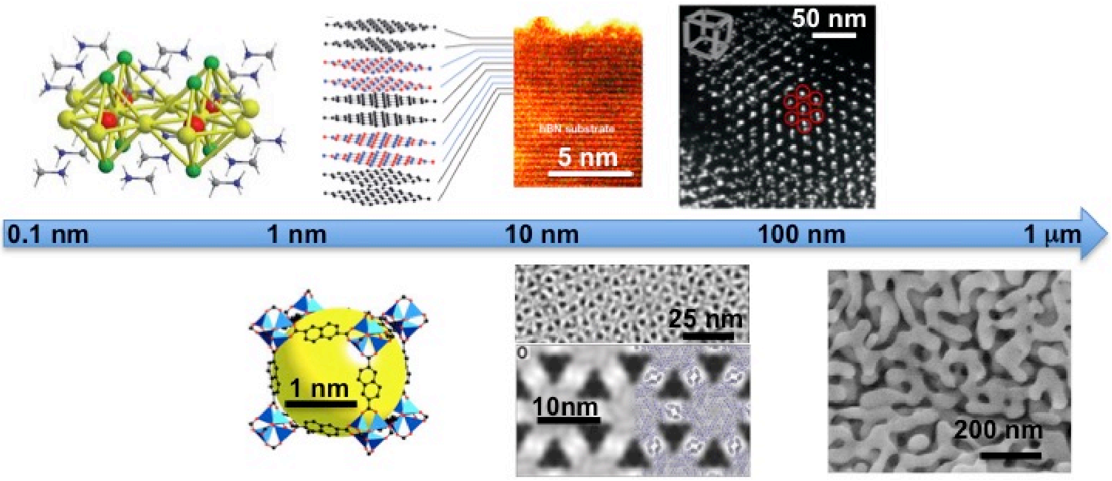


Figure 6. Hierarchical design at all length scales leads to unique structure and function. In this example, hybrid lattices with promise for high-efficiency photovoltaics juxtapose inorganic ions with organic molecules[13] at the shortest length scales, while porous materials useful for high-surface-area catalysts formed through de-alloying exhibit features approaching 1 mm at the longest length scales.[16] Metal-organic frameworks[22] with applications in chemical separations, multilayers of 2D van der Waals solids[11] that can produce a 2D electron gas or control molecular transport, engineered protein lattices[15] that may serve as enzyme arrays or scaffolds for organizing p- and n-type semiconductors, and nanoparticle-DNA superlattices[14] with novel photonic properties span the gap between these limits. *Image courtesy of J. De Yoreo, Pacific Northwest National Laboratory. | [Top left] Reprinted with permission from M. A. Loi and J. C. Hummelen. 2013. "Hybrid Solar Cells: Perovskites under the Sun." Nature Materials 12 [12]: 1087–89. DOI: 10.1038/nmat3815. © 2013 Macmillan Publishers. | [Top center] Reprinted with permission from A. K. Geim and I. V. Grigorieva. 2013. "Van der Waals Heterostructures." Nature 499 [7459]: 419–25. DOI: 10.1038/nature12385. © 2013 Macmillan Publishers. | [Top right] Reprinted with permission from Y. Tian et al. "Lattice Engineering through Nanoparticle-DNA Frameworks." Nature Materials 15 [6]: 654–61. DOI: 10.1038/nmat4571. © 2016 Macmillan Publishers. | [Bottom left] From N. L. Rosi et al. 2003. "Hydrogen Storage in Microporous Metal-Organic Frameworks. "Science 300 [5622]: 1127–29. DOI: 10.1126/science.1083440. Reprinted with permission from the American Association for the Advancement of Science. | [Bottom center] Reprinted with permission from S. Gonen et al. 2015. "Design of Ordered Two-Dimensional Arrays Mediated by Noncovalent Protein-Protein Interfaces." Science 348 [6241]: 1365–68. DOI: 10.1126/science.aaa9897. © 2015 American Association for the Advancement of Science. | [Bottom right] Image courtesy of J. Erlebacher, Johns Hopkins University.*

Mesoscale architectures: Moving beyond the unit cell through interfaces and defects

In most hierarchical structures, dissimilar molecules or materials are juxtaposed; but our ability to predict how the functionalities of one interface control the energy landscape across which the formation of the second takes place, or how two fully formed interfaces interact and assemble, is in its infancy. In all cases, interface formation involves charge and/or mass transport and chemical reactions that are controlled at some level by the symmetry of the interface, its chemical reactivity, and the distribution of defects where mismatches occur, in either structure or chemical potential. The extent to which these factors influence the creation of persistently metastable structures vs. equilibrium states is unclear. A key challenge in the field is to exploit the juxtaposition of dissimilar phases to intentionally create metastable or stable arrays of defects-by-design that would be inaccessible through bulk synthesis methods.

Many of the unique and interesting properties of planar heterostructures result from the interface states created at or in the boundary regions between each constituent. Both advances in traditional methods and the development of new approaches have led to exquisite control over defect structures at interfaces, enabling, for example, creation of ultra-high carrier density 2D conductors.[17] A major gap in our predictive capability for these 2D interfacial systems is understanding how to control the reaction pathway to achieve or avoid thermodynamically stable atomic arrangements while allowing atomic mobility as the desired interleaved structures form.

The extension of interfaces from planar systems to 3D nanostructured matter—such as core-shell nanoparticles, nanoparticle superlattices, highly branched nanowire arrays, and nanocomposites—presents a new set of challenges to predicting pathways and outcomes. The growth and the properties of such materials are largely defined by the structure, interactions, and transport behavior of the interfaces. However, the mechanisms by which these hierarchical structures form are poorly understood because they often involve “nonclassical” processes. That is, in contrast to monomer-by-monomer addition, formation occurs through the assembly of “higher-order” species ranging from multi-ion clusters to fully formed nanocrystals.[18] Quantitative models relating progress along formation pathways to underlying thermodynamic drivers, kinetic constraints, and fundamental materials and solution parameters do not exist.

The challenges are amplified when interfaces are utilized to steer assembly processes. In this approach, the energy landscape that defines the pathway to the product is biased to preferentially form the desired outcome at the interface, often with control over crystal phase and crystallographic orientation. The drivers for solvent and ion structure at interfaces are not understood, nor is how they evolve. The fields and forces at these interfaces, their scaling as assembly proceeds, and their translation into particle motions are unknown. The nanoscale physics and chemistry operating within the interfacial regions between particles that govern alignment and attachment events are poorly understood, as is the size dependence of surface energy, solvation energy, and phase stability. Equally unclear are the roles played by stabilizing ligands, which can profoundly affect shape, faceting, and surface structure by either promoting assembly or presenting barriers to co-alignment and attachment events.

Many microporous and mesoporous materials can also form through complex pathways that nearly all involve assembly, perhaps by molecular clusters, around a sacrificial structure-directing agent.[19] However, it is unclear whether they define minimum energy configurations or kinetic traps for the resulting crystalline frameworks. Moreover, although studies of some porous structures show that the assembly pathway can pass through an amorphous state before producing the first crystal, there is little evidence that such a complex pathway is at work for many structures. Thus, whether hierarchical assembly pathways are general and/or necessary features of porous structures is unknown.

Even within the class of inorganic crystals—which are commonly viewed as bulk single crystals for which perfect ordering is the ultimate goal—new directions leading to hierarchical structure via the distribution of elements across multiple cation sites, interpenetrating sublattices with repeat units much larger than a simple unit cell, and variable lattice parameters are being explored with surprising outcomes.[13] Developing phase diagrams for multicomponent systems; understanding sublattice ordering; and delineating the factors that determine defect distributions during synthesis, both equilibrium factors and kinetic constraints, pose significant challenges for future development of these systems.

Post-synthetic modification (PSM) is an approach to achieving hierarchical design in bulk materials that serves as an alternative to direct synthesis; it often involves extreme conditions of high fields, fluxes, chemical potentials, or forces. PSM can enable the production of materials under conditions where high atomic mobility would prevent the juxtaposition of disparate components or distributions of components, because they are inherently unstable or metastable.[20] Alternatively, metastable phases or distributions of phases can be created through a synthetic process that traps these states. PSM can then serve to create distributions in the former by, for example, inducing phase separation or eliminating a phase (dealloying).[16] Or it can modify the distributions in the latter either via kinetic processes or by inducing an approach toward equilibrium.[19] However, significant unknowns are associated with the scientific underpinnings of PSM. Principally, the equilibrium phase diagrams are poorly constrained for multicomponent systems at extreme conditions. In addition, transformation processes are often driven by far-from-equilibrium conditions so that knowledge of equilibrium states is insufficient to be predictive. Moreover, kinetics and mass transport play a significant role in PSM; consequently, dynamics can largely define the sizes and distributions of constituent elements and phases.

Hybrid systems: Supramolecular, macromolecular and organic-inorganic systems

Supramolecular and hybrid materials provide the ultimate opportunity for the synthesis of hierarchical molecules and materials, because the structural paradigm they represent is inspired by living systems. Here, the power of high-information content encoded into sequence-defined biopolymers (e.g., proteins) leads to folding and/or self-/directed-assembly into functional architectures that exhibit both hierarchy across atomic-to-micron scales and the possibility of multiple functionalities within a single structure.[21] Moreover, this ability to encode information into proteins leads to exquisite control over the configuration of energy maxima and minima underlying the formation of inorganic materials with topologically complex 3D organization[14,22] that may be translatable to engineered arrays of inorganic electron acceptors and donors. The macromolecular nature of the building blocks also creates distinct structural and chemical environments precisely positioned to enable a cascade of catalytic, ion-transfer, or synthetic reactions that, if harnessed, could revolutionize the synthesis of functional molecules and materials, such as catalysis.

There are three major challenges to realizing supramolecular synthetic approaches:

1. Develop libraries of monomeric units that can be assembled end-to-end to produce synthetic linear polymers that are more robust than proteins.

2. Develop a facile synthetic approach that can mimic the function of the ribosome in order to produce the polymers in a sequence-defined manner.

3. Develop the ability to predict both the structures of these polymers from their sequences and the free energy landscape that defines folding into hierarchical units, assembly into functional materials, and control over the formation of inorganic components.

Although numerous polymeric systems are currently being pursued to overcome these challenges,[23] the gap between manmade supramolecular and hybrid structures and those produced by nature remains vast. Hence, so is the potential to advance the complex functions of energy production, transformation, and storage by closing that gap.

PRD 4: Integrate emerging theoretical, computational, and in situ characterization tools to achieve directed synthesis with real time adaptive control

How can characterization, theory, and computation be combined to make the leap from predictive understanding of existing materials to predictive control enabling radically new molecules and materials?

By combining in situ probes to define structures as they form, with theory and modeling to guide synthetic processes on the fly, the science of synthesis is poised to leap from predictive understanding to predictive control. This transformation will dramatically impact the time and energy requirements for developing new molecules and materials, allowing the matter we imagine to become the matter we use.

Recent developments in theory, computation, and in situ characterization have greatly advanced our conceptual understanding of synthetic processes. Physical descriptions of phase separation; crystal growth; macromolecular and nanoparticle self-assembly; solid-solid, solid-liquid, and liquid-liquid interfaces; and defect dynamics have undergone dramatic changes. Computational approaches are becoming powerful enough to predict a number of unknown stable and metastable phases[24] and are making steady progress toward simulating dynamical processes of nucleation, bond formation, growth, self-assembly and transformation.[25-28] Similarly, in situ characterization tools have provided new fundamental insights into the mechanisms and progression of these processes.[29-32] However, current capabilities limit the simultaneous application of theory, computation, and in situ characterization, even for highly idealized synthetic scenarios. Providing a theoretical description of the complex energy landscape inherent to synthetic processes—which are exacerbated by interfaces, defects, and chemical gradients—remains a major challenge. So does the creation of algorithms that can cross time and length scales to predict reaction kinetics and ensemble outcomes with molecular fidelity. Similarly, in situ characterization at the time and length scales relevant to understanding synthetic processes often depends upon specialized equipment available only to those practicing synthesis. It can rarely be applied to realistic environments by persons with knowledge of and control over critical parameters. Moreover, the tremendous mismatch between rates of data generation during in situ characterization experiments and the speed at which simulations of synthetic processes can currently be performed limits the ability to carry out the measurement-analysis-feedback loop critical to predictive control on the fly.

Innovative approaches: Multimodal in situ characterization probes

In situ characterization techniques play an increasingly important role in understanding synthesis for two reasons, both of which have their origins in complexity. First, the targets of synthesis have become more complex. Hierarchical systems like nanoparticle superlattices, core-shell structures, epitaxial multilayers, supramolecular structures and assemblies, hybrid crystal lattices, and nanostructured alloys follow complex formation pathways that are not readily described by simple theories or equilibrium thermodynamic considerations. Consequently, in situ probes that can provide information about pathways and dynamics of formation and/or transformation are critical to developing the mechanistic approach that will lead to an understanding of how to manage and control outcomes. Second, numerous lines of research have shown that, even for simple systems, transient states—both microscopic and macroscopic—often lie on the pathway to final outcomes.[18] In situ methods provide a window onto these metastable precursors and their evolution that are otherwise hidden from view.

X-ray and neutron techniques, environmental transmission electron microscopy (TEM) and scanning probe microscopy (SPM), mass and optical spectroscopy, and nuclear magnetic resonance (NMR) spectroscopy each provide unique in situ information and are all widely used to investigate synthetic processes. For all of these capabilities, there are common challenges that must be addressed before the dream of on-the-fly analyses and prediction can be realized. For microscopy methods, attaining simultaneous atomic-level spatial resolution and millisecond time resolution would allow direct imaging of events that lead to creation of molecules and clusters and the advance of interfaces. Both TEM and SPM are on the threshold of achieving this capability.[33,34] But both have other limitations, such as limited environment of application and—in the case of TEM in liquids—significant electron beam effects, as well as a lack of knowledge of or control over solution composition. Finally, as temporal resolution has increased, as the events being interrogated have become increasingly transient, and as data compression methods have started to become important, achieving streaming data analytics has emerged as a major challenge for these microscopy techniques. Without this analysis, it can be difficult or impossible to judge whether the data stream is sensible or relevant, or how to adjust parameters to make it so.

As with TEM and SPM, the resolution of x-ray imaging methods has steadily improved; and the continued development of x-ray–based coherent diffractive imaging techniques such as ptychography[35] is now pushing resolution to 5 nm. Moreover, near–attosecond time resolution is now possible with x-ray free electron lasers, and preliminary success has been achieved in executing real-time data analysis using links from beam lines to high-performance computing resources (Figure 7). However, as with TEM and SPM techniques, incorporating synthesis reactors that produce realistic and known reaction conditions remains a major challenge, as does implementation of streaming data analytics.

X-ray and neutron sources hold particular promise because the penetrating nature of their beams allows for the construction of elaborate but robust sample holders that can provide a variety of opportunities for in situ studies. Containment cells can be designed to allow in situ studies involving extreme synthetic conditions, including corrosive gases, radioactive and other hazardous chemical reactants, or variable temperature and/or pressure environments such as those encountered in solvothermal syntheses.[36] The combination of this sample-environment flexibility with the range of imaging, scattering, and spectroscopic options provided by these DOE national facilities makes them particularly attractive tools for probing syntheses on-the-fly.

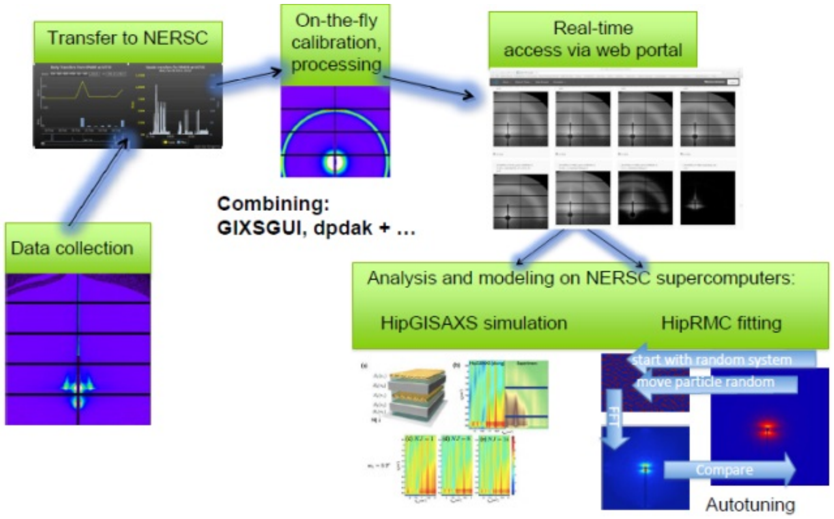


Figure 7. Real-time data analysis and modeling setup that streams grazing-incidence small-angle x-ray scattering (GISAX) data to the high-performance computing resources at the National Energy Research Scientific Computing Center (NERSC). Note: GISXGUI = GISAX graphical user interface; HipRMC = High-performance Reverse Monte Carlo; dpdak and HipGISAXS are the names of software packages. **|** *Images courtesy of S. Billinge, Columbia University*

High-brightness neutron sources cannot reach the temporal and spatial resolution of these other methods. But the high sensitivity of neutron scattering to select chemical species provides vital information missing in x-ray and TEM experiments; and it allows for novel contrast mechanisms, such as labeling of particular locations on a molecule with selective deuteration, or contrast matching in small-angle neutron scattering to separately obtain signals from different parts of a heterogeneous sample.[37] Despite the capacity of spallation sources and their advanced detectors to provide this unique information, the use of neutron scattering for in situ studies of synthesis is in its infancy and will be significantly advanced through coupling to streaming event-based data collection and real-time analysis.

While these imaging and scattering methods deliver an in situ view of the evolving solids, for vapor-solution–based and some melt-based synthesis of matter, NMR and mass spectroscopy fill a crucial gap by providing data on the evolving speciation and structure in vapors and liquids, including at solid interfaces. Here the frontier lies in analyzing liquids. Specialized cells that can go to high temperatures and pressures have dramatically widened the range of systems amenable to NMR analysis. When combined with new pulse combinations and cross-polarization modes, it is now beginning to be used in tracking the evolution of solution and adsorbate species.[38] Similarly, new techniques for using liquid cells in time-of-flight secondary ion mass spectrometry have enabled sampling of solution streams to track solution speciation over time.[39] However, understanding how the measurement method affects the distribution is still under investigation. For both methods, the number of investigations that have attempted to follow synthetic processes is extremely small, and the limits on resolution and detection are uncertain.

No single spectroscopic, scattering, or imaging experiment can provide the information about the structure, chemical composition, and defects of products needed to guide synthesis. Consequently, multimodal approaches to simultaneously follow synthesis reactions using a suite of instruments during the same experiment are needed. Finally, for many of these methods, developing approaches to apply them at extreme conditions of temperature, pressure, fields, and chemical conditions remains an outstanding challenge.

Theory and simulation: Real time interpretation of in situ data to predictively guide the synthesis process

Using the data stream from in situ characterization to guide synthesis on-the-fly requires

1. Theoretical understanding

2. Computational tools that can both interpret the data and make real-time predictions about the impacts of processing parameters on synthetic outcomes, based on a fundamental understanding of underlying mechanisms

Because of the broad range of materials systems that are of interest from the standpoint of energy technology, the inherently mesoscale nature of synthesis, and the high degree of heterogeneity required for advanced functional materials, novel theoretical and computational methods are needed that can predict numerous descriptors of synthetic outcomes for a wide variety of conditions over multiple length and time scales (Figure 8).

To seamlessly cross length and time scales, progress relies on coupling atomistic simulation techniques, such as DFT and molecular dynamics, with advanced sampling methods capable of capturing rare events, e.g., metadynamics or forward-flux sampling, as well as Monte Carlo methods. The development of theory must be emphasized, for there are fundamental aspects of synthesis for which solid theoretical frameworks do not yet exist. The knowledge gaps are particularly severe for condensed matter systems, such as growth from solutions or via solid–solid transformations. For example, for nucleation pathways involving the assembly of polynuclear clusters[18] or for crystal growth processes that proceed by the assembly of primary nanoparticles,[18] the forces between the interacting objects, which drive assembly, are poorly understood. (See the sidebar *Crystallization pathways and the role of intermediates*.) Moreover, those forces depend on the structure of the solvent layer in the intervening region, which is equally ill defined.

Developing computational approaches that can handle the complexities of these systems also presents a major challenge with no obvious general solution at the current time. Consequently, development of multiscale simulations must go hand in hand with advances in theory. Validating computational approaches and the underlying theoretical precepts must be a major focus, because the demand to attain computational efficiency by minimizing atomistic simulations, as well as the degree to which their results are transferred upscale, is inherently at odds with achieving high-fidelity predictions. Identifying specific classes of systems for which robust experimental results can be collected and used to validate theory at different levels of accuracy will be particularly valuable.

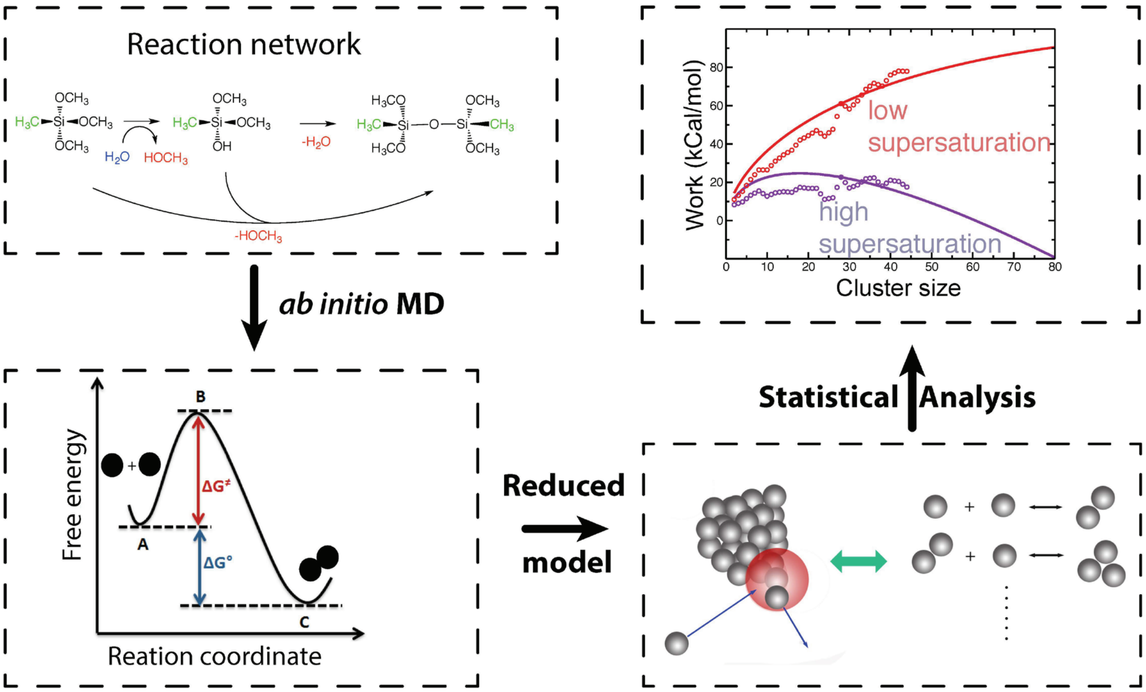
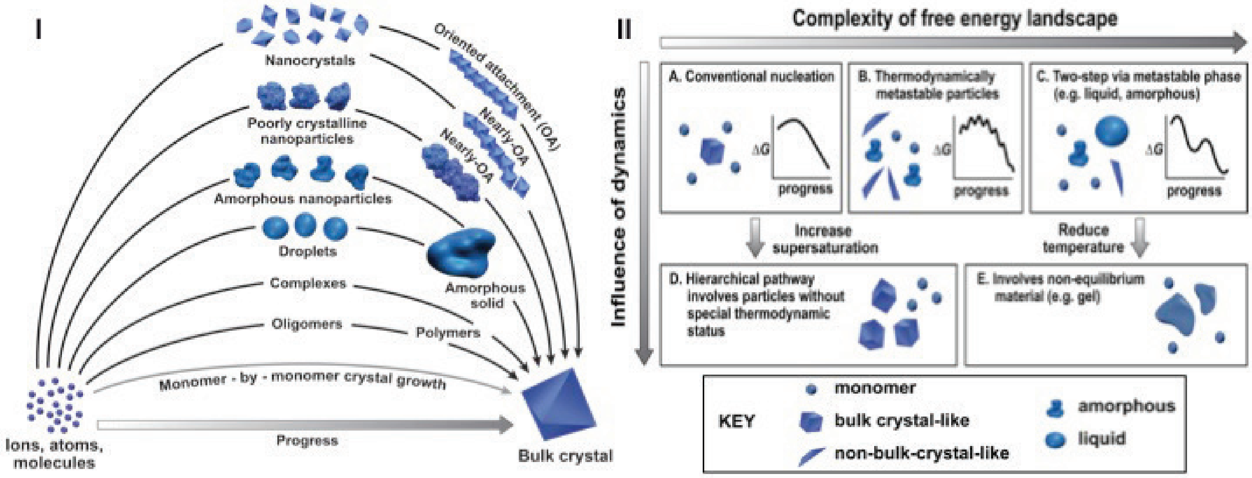


Figure 8. Predicting the outcomes of synthesis, such as rates of nucleation, when pathways exhibit complexities such as chemical reaction networks, requires methods to cross scales from atomistic processes to ensemble behavior. Reaction pathways identified experimentally can be simulated by ab initio methods to produce free energies to develop reduced models for the calculation of rates, and ultimately, the pathways and barriers to nucleation. Note: The symbol ΔG refers to the changes in Gibbs free energy caused by a reaction. | *Images courtesy of C. Mundy, Pacific Northwest National Laboratory*

Even given the capability to simulate synthesis pathways and outcomes, integrating that capability with in situ characterization requires methods of simulating imaging, scattering, and spectroscopy data. Current methods can be used to validate theory in off-line analyses, but realizing the vision of this PRD demands methods that are sufficiently fast and efficient to perform simulations in real time as synthesis and characterization proceed. Such approaches must include ab initio methodologies based on post-DFT methods for samples containing thousands of atoms and calculations of experimental data based on large-scale, coarse-grained molecular dynamics and Monte Carlo methods. The ability to accurately reproduce data sets from multiple characterization techniques would have the added benefit of disentangling sources of signals that are inexorably convoluted in experiments, thereby increasing the extent to which experiments lead to an understanding of underlying mechanisms.

Ideally, one would combine these theory and simulation tools with in situ imaging, scattering, and spectroscopy on two levels. First, the in situ data must be processed in real time to extract the important information, such as the formation rates and spatial distributions of new structures, mass and energy transfer at interfaces, the evolution of order, phase transformations, and defect distributions. Second—using the starting conditions of the synthesis reaction and theories that describe the underlying processes—computational algorithms must exploit the stream of in situ data to extract the key physical parameters needed to predict how the synthesis conditions should be modified to achieve the target structure. Incorporating machine learning algorithms that can draw on the collective knowledge of past synthesis outcomes[40] and simulation results would amplify the power of on-the-fly analysis and prediction.

Crystallization pathways and the role of intermediates

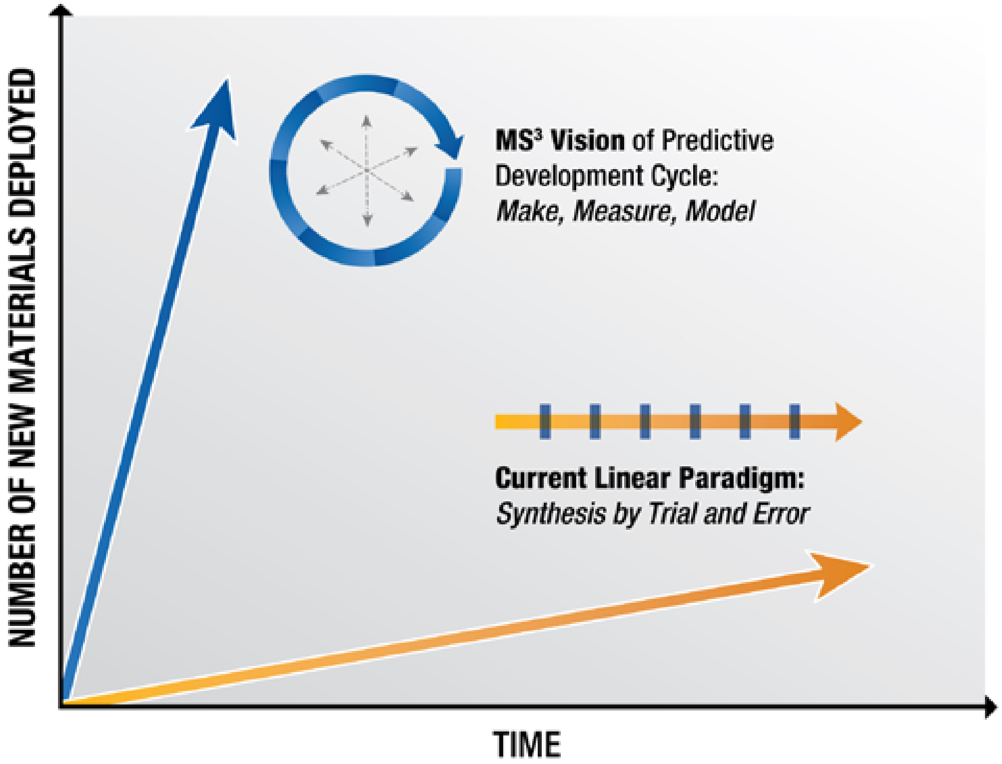


Observations over the past 15 years have revealed a rich set of crystallization pathways marked by transient intermediate states and assembly of complex species. (I). These intermediates can consist of metastable bulk crystalline or amorphous phases, dense liquid droplets, or microscopic states consisting of dynamic molecular clusters. Despite this complexity, a holistic framework rooted in classical concepts of crystallization emerges when coupled effects of complex free energy landscapes and the impact of dynamical factors are considered (II). While the smooth free energy barrier of classical theories leads to direct formation of the final ordered state (II, top left), the introduction of either size-dependent phase stability associated with high surface-to-volume ratios of nanoparticles, or high driving force coupled with the existence of metastable polymorphs, drives two-step pathways characterized by the initial appearance of a bulk precursor phase (II, top right). The creation of micro-states, which represent local minima in free energy stabilized by configurational factors, can also lead to hierarchical pathways; but the transient intermediates do not appear on bulk phase diagrams (II, top middle). In both cases, reducing molecular mobility, e.g., by lowering the temperature, can freeze nonequilibrium states into place for dynamical reasons (II, bottom right). Even when barriers are smooth and pathways direct, a high driving force generates many clusters, which interact to produce kinetically dominated processes of cluster aggregation (II, bottom left). These intermediated states open up opportunities for trapping new states of matter, if these pathways can be predicted and controlled. | *Images courtesy of the American Association for the Advancement of Science*

Summary

Taken together, the fundamental scientific understanding, method development, and discoveries of new molecules and materials that will result from pursuit of these PRDs will address many of the priorities identified in previous Basic Energy Sciences Advisory Committee (BESAC) reports, as well the transformative opportunities called out in the report *Challenges at the Frontiers of Matter and Energy: Transformative Opportunities for Discovery Science*.[41] (See the sidebar *A predictive cycle for energy materials development and deployment*.) In doing so, their achievement will enable the dream of synthesizing matter on demand by finally realizing the ability to link *predictive design* to *predictive synthesis*.

A predictive cycle for energy materials development and deployment



The importance of synthesis science to energy technology, and the intimate link between the two, are reflected in many of the BES Basic Research Needs (BRN) Workshop reports, which highlight synthesis as an enabling capability for solar energy, electrical energy storage, catalysis, solid state lighting, carbon capture, and hydrogen storage. The advances required to realize the synthesis goals cited in these BRN Workshop reports are well summarized in the BESAC report *Challenges at the Frontiers of Matter and Energy: Transformative Opportunities for Discovery Science*, which calls for major advances in *"Mastering synthesis and assembly of hierarchical structures," "In situ characterization … during synthesis and assembly,"* and *"Predictive models, including the incorporation of metastability."*

Developing a science of synthesis that enables predictable, controllable production of materials also emerges from the 2012 report *Materials Genome Initiative for Global Competitiveness*. It highlights the importance of developing advanced materials to address challenges in energy, but noted that *"… the time it takes to move a newly discovered advanced material from the laboratory to the … market place remains far too long"* and *"accelerating this process could … ensure that the Nation remains at the forefront of the … materials marketplace."*

Emphasizing the critical need for strong coupling between prediction, synthesis, and characterization, the report goes on to point out that the lengthy time between materials discovery and commercialization is partly due to dependence *"… on scientific intuition and trial and error experimentation"* with *"… design and testing of materials … performed through time-consuming and repetitive experiment and characterization loops."* **|** *Adapted from the Report of the National Science and Technology Council, Materials Genome Initiative for Global Competitiveness*[42], https://www.mgi.gov/

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3. Mechanisms of Synthesis under Kinetic and Thermodynamic Controls

Materials synthesis involves chemical pathways that take reactants to products, sometimes through very complex and uncharted energy landscapes. Other than empirically, little is known about how to design and construct metastable or hierarchical materials, which may encompass an ensemble of reaction pathways. Chemical pathways are usually traversed with little or no knowledge about deep or shallow energy minima and maxima that can either facilitate or derail a targeted outcome. In the context of crystallization, intermediate clusters, nanoparticles, and aggregates may form during the process, often under kinetic control. These intermediates play roles in material modification, topology, and physical properties of the crystal; consequently, they are scientifically important in their own right. Few experiments probe and study these intermediates in the context of materials assembly. Theory provides some guidance about the pathway to a targeted material, but computations become increasingly difficult for complex systems and do not yet address the full spectrum of synthetic conditions (e.g., solvent choice, temperature, pressure, and effects of other solutes), which can play key roles in successful outcomes. Without computationally aided pathway design, established chemical knowledge and qualitative concepts guide discovery and synthesis of desired materials. Organic chemists apply a toolbox of functional groups and reaction mechanisms to guide synthetic approaches and to produce targeted molecules, prompting the questions: Can the synthesis of inorganic solids that exhibit an astonishing diversity of chemical and structural classes be organized in distinct reaction types so that general synthetic methodologies can be developed? Can research focused on reaction-pathway studies produce a new mechanism-based toolbox to aid targeted synthesis of hierarchical hybrid and inorganic functional materials?

Current Status and Recent Advances

For decades, molecular chemistry has pursued the goal of “synthesis by design.” In many ways, the synthesis of almost any chemically plausible molecule can be addressed through retrosynthetic analysis supplemented with deep mechanistic understanding. This approach began as a black box approach that was subsequently transformed into refined classification schemes of reaction types, mechanisms, chemical signatures, and theoretical frameworks through extensive study. Many synthetic methods were developed by understanding specific chemical reactions delineated through detailed mechanistic studies. Chemical signatures were identified by using in situ approaches to provide a fundamental understanding of the bonding, kinetics, electron transfer, and overall energetics throughout the course of the reaction. For molecular species, this diagnostic approach relied on advancements in x-ray, neutron, and electron scattering; mass spectrometry; and nuclear magnetic resonance, as well as infrared, ultraviolet-visible, and x-ray photoelectron spectroscopies. The thermodynamics of these systems have been systematically investigated and provide a sound understanding and predictive capability for designing novel molecular complexes. Computational efforts came much later and have provided user-friendly interfaces that enable the initial analysis of bond distances and angles, steric strain and hindrance, preferential intermolecular interactions, reaction energies, and intermediate identification.

Defining mechanisms and pathways. Currently, the mechanisms that drive materials assembly and growth throughout the entire reaction pathway are largely ambiguous because of the chemical complexity, infrequent application of diagnostic tools, limited knowledge of the energy landscape, and limited theoretical approaches. While significant efforts were initially established in the 1960s to investigate, for example, zeolite formation mechanisms (important to and led by the petrochemical industry), broader efforts have encountered major roadblocks, and progress has been slow.[1-9] The cause of the first roadblock is that complex materials make use of chemistry that spans the entire periodic table. The constituent elements can encompass different chemical bonding and reactivities, leading to a large number of possible mechanisms and reaction pathways operating during a synthesis. Furthermore, many different polymorphs are often possible for a given composition (see additional discussion below).

The second roadblock is the lack of powerful interrogation tools to develop diagnostic signatures, particularly at the nanoscale and mesoscale. For example, monitoring what happens and how fast it occurs in concentrated solutions or inside vessels placed in high-temperature furnaces is a significant challenge. Many solid-state syntheses require elevated temperatures that may cause blackbody radiation to overwhelm some characterization methods that use low-energy radiation, such as infrared and ultraviolet-visible spectroscopy. Most spectroscopic approaches have been developed with a narrow scope in mind, probing limited aspects, such as strong covalent interactions or specific nuclei; or they focus on simple chemical systems. Consequently, these techniques are not widely applicable to the complex nature of solid-state materials with diverse suites of elements. Third, the overall thermodynamics of reactions and their individual steps are poorly known in most cases, and this is confounded by the many polymorphs and types of reactions possible. Simultaneously, rigorous formalisms for the kinetics of solid-state reactions are problematic because of the interplay of diffusion, dissolution-precipitation, and phase transformation during synthesis and an inability in most cases to identify the operative processes. It is well accepted that in a conceptual generic synthesis (Figure 9) the reaction pathways and outcomes depend on many parameters and cannot be easily predicted. Finally, computational approaches have advanced significantly over the past several decades, but there are still limitations on the size and scope of the material that can be studied, realistic depictions of synthesis conditions, accuracy of the calculated physicochemical properties, and accessible timescales.

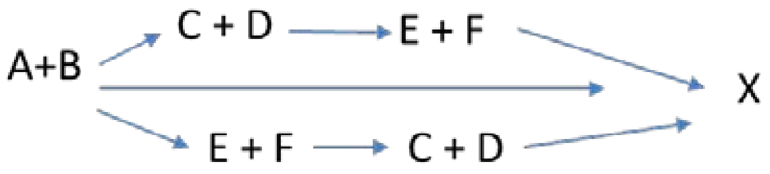

Figure 9. In this generic reaction scheme, reactants A and B combine to create the product X. A variety of pathways can occur during this process, including the formation of metastable phases (C, D, E, and F). Knowledge of the events occurring during synthesis and the relative energetics of species involved in the process have the potential to elevate materials synthesis to unprecedented levels of control. | *Image courtesy of M. Kanatzidis*

In recent years, new scientific horizons have emerged based on the development of novel synthesis and processing tools and integration of powerful analysis methods. A wide range of synthesis tools and techniques are currently employed to produce a wealth of high-quality single-crystal, polycrystalline, hierarchical, and amorphous materials. Indeed, these methods have freed researchers from the "tyranny of equilibrium" in which only the lowest free energy assemblages are accessible, providing a route to kinetically stabilized or even metastable phases synthesized at low temperatures or at high pressures. In addition, these techniques have expanded the ability to synthesize nanoscale crystals of all dimensionalities, including sheets, fibers, nanowires, nanocrystals, thin films, and heterogeneous composite materials. More efforts are being devoted to developing chemical signatures across the periodic table, exploring the energy landscapes in complex materials, and advancing and expanding on existing theoretical approaches. Recent development of in situ analytical, microscopy, and spectroscopy techniques—as discussed in Section 8,Transformative Research Capabilities I: In situ Characterization—provide the capability for detailed mechanistic studies. Advances in thermodynamic measurements allow researchers to follow the energetics of synthesis and phase transformation, providing insight into energy landscapes. Increased computational power and the development of novel theoretical methods are now pushing the limits on the scale and types of systems that can be accurately modeled. Most important, the ability to integrate a multitude of techniques synergistically presents unprecedented opportunities to develop a comprehensive view of and targeted approach to the formation of complex materials. Recent advances in understanding the mechanisms of synthesis under thermodynamic and kinetic controls are highlighted below.

Integration of tools in bulk synthesis and thin films. Powerful experimental tools—including real-time x-ray scattering and diffraction from thin film, powder, and liquid phase samples—have been developed, providing time-resolved information necessary for understanding growth mechanisms and synthesis pathways.[10] The reaction mechanisms and kinetics occurring throughout the synthesis are mostly unknown. A rigorous analysis of observations recorded as a function of different reaction parameters could provide information about the kinetics and insights into the operating reaction mechanisms. For example, solvothermal studies in thioantimonates, such as $[Co(C_6H_{18}N_4)][Sb_2S_4]$, an important catalyst, have demonstrated that diffusion is the rate-limiting step; and at later stages, the derived reaction exponents indicate more complex kinetics and mechanisms (Figure 10).[10,11] When $[Co(C_6H_{18}N_4)][Sb_2S_4]$ was synthesized with elemental cobalt at $T \leq 120°C$, a random dissolution of cobalt influenced the reaction path, which was immediately detected by diffraction experiments. In the beginning, only the (102) reflection of the product $[Co(C_6H_{18}N_4)][Sb_2S_4]$ began to grow and shifted as the reaction proceeded; and in the final stages, all Bragg peaks of $[Co(C_6H_{18}N_4)][Sb_2S_4]$ appeared and grew simultaneously. The interpretation drawn from these observations is that in the early stages, disordered layers of $[Sb_2S_4]^{2-}$ assemble from smaller units that then start to organize to the 3-dimensional long-range crystallized material (Figure 10). This insight is valuable not only because it is an important revelation about the synthesis mechanism, but also because it allows for effective intervention by the synthetic chemist to alter the reaction path or for a theorist to predict the intermediates.

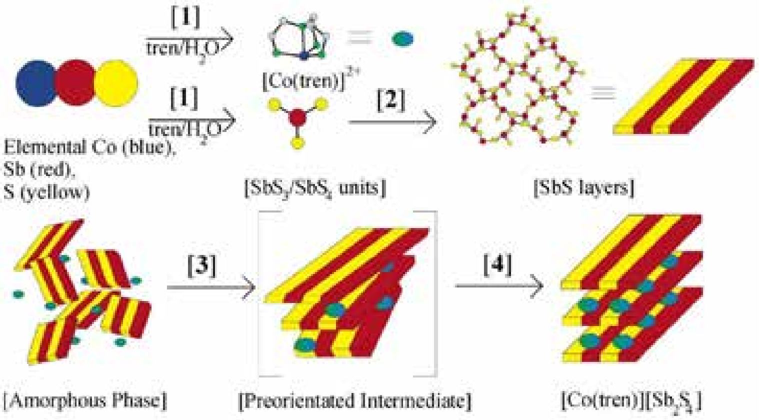

Figure 10. Reaction scheme for the formation of $[Co(tren)][Sb_2S_4]$ derived from studies of in situ energy-dispersive x-ray diffraction and in situ extended x-ray fine absorption spectroscopy, from which information about the reaction can be obtained from the very early stages until products begin to crystallize.[10] **|** *Reprinted with permission from R. Kiebach et al. "Combined In Situ EDXRD/EXAFS Investigation of the Crystal Growth of* $[Co(C_6H_{18}N_4)][Sb_2S_4]$ *under Solvothermal Conditions: Two Different Reaction Pathways Leading to the Same Product." Chemistry of Materials. © 2006 American Chemical Society.*

Understanding the forces driving and controlling crystallization is key to efficient and cost-effective synthesis of new materials, as exemplified by the Yeung et al.[12] study of the crystallization of lithium tartrate metal-organic frameworks (MOFs) via variable-temperature, synchrotron x-ray powder diffraction (Figure 11). From the diffraction data, the temperature-dependent crystallization and interconversion of three different meso-tartrate phases were studied, with particular focus on the intermediate phases and energetics of the reaction. Two intermediates, 1 and 2a, formed along the reaction pathway to the thermodynamic phase 2b. Crystallization data were fit to the Avrami–Erofe'ev expression for crystal growth; and rate constants for nucleation, growth, and dissolution were determined. Arrhenius plots of rate-constant data suggested changes in ligand conformation contributed to the activation energies and the rate-limiting steps in the formation of the MOF materials. This study represents an important example of the energetic and mechanistic details available from synchrotron-based studies.

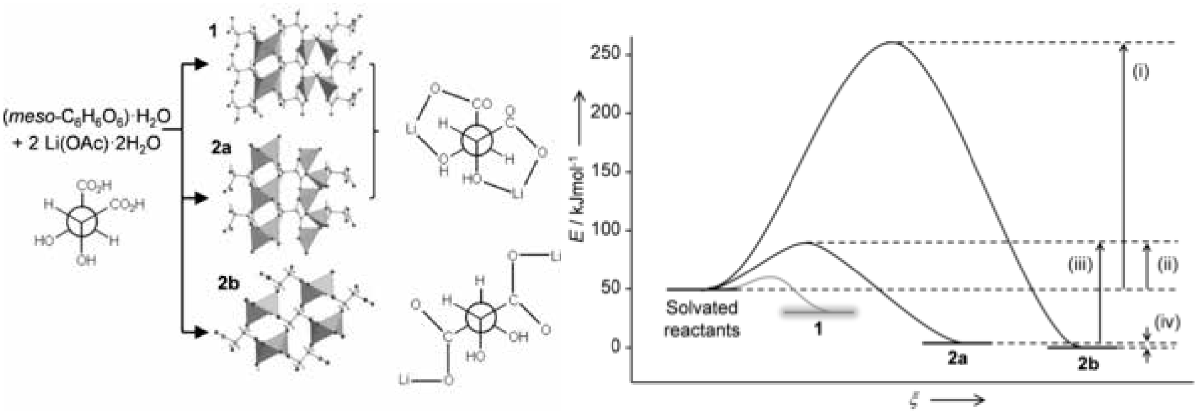

Figure 11. The formation of a MOF material was evaluated using in situ powder x-ray diffraction, and the activation energies were calculated using the Arrhenius plots of rate-constant data.[12] **|** *Reprinted with permission from H.H.M. Yeung et al. "In Situ Observation of Successive Crystallizations and Metastable Intermediates in the Formation of Metal-organic Frameworks. Angewandte Chemie International Edition 55[6]: 2012–16. DOI: 10.1002/anie.201508763. © 2016 John Wiley and Sons.*

In situ energy dispersive x-ray diffraction (EDXRD) has proved to be a useful tool to study the mechanism of solid-state reactions, as demonstrated in the formation of an ordered layered double hydroxide (LDH) from poorly crystalline mixed Al–Mg oxide (calcined at ~400°C) with an MgO-like structure.[13] In this case, EDXRD and successful modeling of the kinetics using the Avrami–Erofe'ev approach led to the insight that the reaction occurs by dissolution of the highly reactive but poorly crystalline oxide followed by crystallization of the LDH from solution.

Sequential deposition techniques such as molecular beam epitaxy, atomic layer deposition, physical vapor deposition, and chemical vapor deposition, and solution methods are powerful approaches to create heterostructures by stacking two or more chemically different layers along a given stacking direction. Many of the unique and interesting properties of heterostructures result from the finite thicknesses of the individual layers and the resulting interfacial states between each constituent. These approaches are powerful because they create designed artificial structures that are inaccessible by bulk synthesis techniques, as exemplified by the synthesis of a family of ordered materials consisting of intergrowth layers of SnSe and MoSe$_2$ (Figure 12).[14] These studies confirm that the structure, order, and thickness of the constituent layers can be controlled by matching structures with that of their precursors.

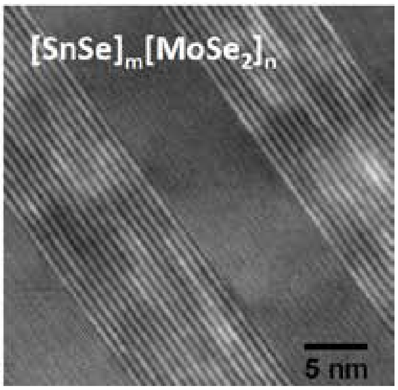

Figure 12. Alternating SnSe/MoSe$_2$ layers define a new phase deposited by a physical vapor deposition method. A bulk composition of layered Sn-Mo-Se phase has not been reported.[14] **|** *Reprinted with permission from M. Beekman et al., "Controlling Size-Induced Phase Transformations Using Chemically Designed Nanolaminates." Angewandte Chemie International Edition 52(50), 13211–14 (2013). DOI: 10.1002/anie.201305377. © 2013 John Wiley and Sons.*

Conceptually, heterostructures provide both experimentalists and theorists with reasonably well-defined targets, in which the interleaved layers are very likely to be at least local free energy minima. Furthermore, these structures enable theorists to explore the expected properties of currently unknown materials with reasonable assurance that the structures could be made. For experimentalists, the challenge is to control the reaction pathway, avoiding more thermodynamically stable atomic arrangements and allowing atoms to diffuse as the desired interleaved structure forms.

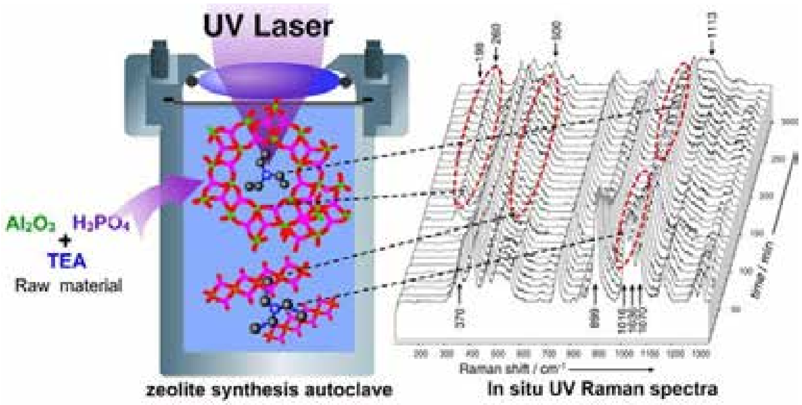

Figure 13. In situ ultraviolet Raman spectroscopy was used to understand the formation of clusters within the AlPO-5 system.[15] | *[Left] "*[*New Accomplishment in Mechanism of Zeolite Synthesis*]*. Dalian Institute of Chemical Physics, Chinese Academy of Sciences. 2009. [Right] Reprinted with permission from F. Faneet al. "In-situ-UV Raman Spectroscopy Study on the Synthesis Mechanism of AlPO-5." Angewandte Chemie International Edition 48[46]: 8602–07. DOI: 10.1002/anie.200903601 © 2009 John Wiley and Sons.*

Bringing molecular-level insights to materials synthesis accelerates the discovery of novel functional materials by reducing reliance on time- and energy-consuming empirical trials. In many cases, mechanistic studies must address molecular, cluster, and nanoscale species in aqueous and non-aqueous solutions. An example of this type of study includes the development of an in situ ultraviolet Raman apparatus by Fan et al.[15] capable of monitoring hydrothermal reactions (Figure 13). During the synthesis of AlPO-5, an aluminophosphate molecular sieve, the bands at 370 and 899 cm^{-1} decrease, signifying the consumption of the octahedrally coordinated Al^{3+} and phosphate ions. With time, bands at 260 and 500 cm^{-1} appear, indicating the formation of clusters and the beginnings of the crystallization process.

Phase diagrams. Binary and ternary phase diagrams are extremely useful to assess the reactivity and solubility of various elements and the thermal stabilities of complex products formed from them. Understanding the phase space where a compound forms allows the synthetic chemist to avoid byproducts, optimize yield, and even grow large single crystals. For instance, very large crystals of the hybridization gap semiconductor $FeGa_3$ (a potential thermoelectric material) can be isolated from gallium-rich solutions of iron and slowly oscillated about the liquidus line to eliminate smaller nuclei and promote large crystal growth.[16] Unfortunately, a major drawback to their applicability is that these diagrams contain only the thermodynamically stable phases that exist at a given temperature and composition, typically at 1 atmosphere of pressure. Information is lacking about metastable or kinetically stabilized phases, such as those accessible only through soft chemistry, other low-temperature methods, or high-pressure synthesis.

Another issue with the use of phase diagrams is published errors, although many errors are gradually being eliminated using improved synthetic techniques. Attention is needed for better characterization of equilibria, improved characterization methods, and advances in computational methods applied to advance predictive modeling. For instance, the barium-germanium system features a rich variety of clathrates and other Zintl phases discovered in the past 15 years.[17-19] The binary phase diagram published in 2008 corrects many errors that were originally reported in 1966.[20] Ba_2Ge and $BaGe_2$ are now known to melt congruently, and the melting point of BaGe (also congruently melting) was corrected from 1115 to 980°C.[20,21] Errors in earlier work may have been caused by the volatility of barium at elevated temperatures or possibly by contamination by hydrides, a common problem for heavy alkaline earth metals. Several phases were also added to the phase diagram, including a-Ba_3Ge_4, Ba_3Ge_4, Ba_6Ge_{25}, $BaGe_5$, and Ba_8Ge_{43}, all of which exist over limited temperature regimes. This indicates that improvements in techniques—such as temperature-dependent diffraction studies, differential scanning calorimetry thermal stability studies, and scanning electron microscope-energy-dispersive spectroscopy analysis of mixed phase products—may enable the discovery of many new compounds. Even with these corrections and additions, metastable high-pressure phases will be absent, such as the two recently discovered $BaGe_3$ variants that are both superconducting.[22,23] The research community is now at the point that nearly all the binary elemental phase diagrams are cataloged (ASM database), along with binary oxides (ACerS database), and have been examined at a course level with density functional theory (e.g., Materials Project, Open Quantum Materials Database, Aflowlib). These phase diagrams contain useful information for crystal growth and often serve as starting points for solid-state synthesis pathways, but no information about kinetically stabilized phases is incorporated.

Energy landscapes and nonclassical nucleation pathways. Since the late 1990s, nanomaterials and nanotechnology have become almost household words, and a huge volume of research has emerged, mainly based on nanomaterials synthesis and properties. Despite this interest, knowledge about the energetic driving forces that make nanomaterials different from bulk materials remain incompletely understood. High-temperature oxide melt solution calorimetry in combination with room-temperature water adsorption calorimetry—on materials including solid oxide fuel cells and catalytic TiO_2—has provided a breakthrough in the experimental determination of nanophase thermodynamics,[24] knowledge critical to effecting targeted syntheses of these materials. The differences in surface energy between polymorphs result in crossovers in the thermodynamic stability of polymorphs at the nanoscale. All nanoparticles are higher in energy, enthalpy, and free energy than their bulk counterparts; but in many systems, especially at temperatures below 200°C–400°C, coarsening does not occur and the particle size distribution remains as obtained in the original synthesis.[25] Under that constraint, the system can minimize its free energy by transforming to a polymorph of lower surface energy.[26,27] For example, there are a myriad of iron-oxide/hydroxide phases, all with different properties, that are stabilized as nanoparticles for use as chemical precursors, as catalysts, or as magnetic phases in applications, including magnetic storage devices. Based on this understanding, the thermodynamically driven crossovers in phase stability can be harnessed to make new phases and structures. Additionally, particle size and morphology can be controlled by additives that affect surface energies, favor a given growth surface, or both. Such effects have been harnessed empirically, but understanding the underlying thermodynamic driving forces is essential to predictive synthesis.

Exploration of the energy landscapes, combined with characterization techniques, has also played an important role in establishing nonclassical routes to nucleation and particle growth. Such routes are underused in conceptualizing a synthesis, largely because the conditions under which they are active have not been sufficiently characterized. Initial evidence of nonclassical nucleation in aqueous solutions was obtained from advances in cryo–transmission electron microscopy capabilities that led to the identification of $CaCO_3$ and Fe(III) oxide/hydroxide precursor clusters dispersed in solution and during the growth process.[28,29] Both of these materials have been used as classical examples for study of nucleation processes. Pair-distribution function analysis has provided evidence for precursor phases for a range of metal hydroxides and carbonates and evidence that structural features may be controlled by counterions present in these solutions.[30-32] Aggregation and self-assembly of $[Ni(quinolone\text{-}8\text{-}thiolate)_2]$ using vapor deposition methods was monitored by high-temperature atomic force microscopy, which indicated that nonclassical pathways were involved in the growth of the molecular crystal.[33] These experimental efforts have been supported by computational studies revealing an evolution of the initial clusters during multistep nucleation processes.[34,35] Carbonate prenucleation clusters[28] have been proposed as precursors because their aggregation leads to an initial amorphous calcium carbonate phase, which is then a precursor to different crystalline polymorphs with downhill transformations on a rich energy landscape controlling biomineralization.[36] There is growing evidence for these precursor-controlled processes for a wide range of solid-state materials. Their detailed mechanisms and energetics have been explored in only a few systems; and even for the most studied compositions, fundamental questions remain.

Computational methods. Traditional electronic structure methods have contributed much to our current understanding of reaction pathways—from gas phase reactivity, to embedded continuum models that aid in understanding the solution-phase stability of reactants and products, to periodic implementations of solids and their interfaces. These are complemented by global energy landscape exploration methods such as a plethora of Monte Carlo–based algorithms or genetic algorithms, for both bulk compounds and nanomaterials.[37,38] For example, so-called global space-group optimization (GSGO) methods now predict both compositions and crystal structures.[39-42] In GSGO and X-GSGO, unstable structures mutate and mate via genetic algorithms to produce stable compositions and crystal structures. In this way, the approach produces energy landscapes and phase equilibria diagrams (Figure 14).[43] Additional computations render results in temperature and pressure space to deliver valuable guides for synthesis work. Massively parallel ab initio and classical molecular dynamics methods have recently been applied to understand molecular and solvothermal synthesis, or the growth of thin films on substrates. The ability to reproduce realistic experimental conditions and timescales, however, remains a significant challenge. When a reasonable reaction path can be discerned, time-accelerated methods can also be employed to effectively pursue rare events that may be critical to targeted design. The correlations between particle interactions and hierarchical characteristics (e.g., fractal dimension, effective diameter, and intermolecular networks) can be simulated using a variety of methods, like the lubrication or flow-discrete element method (LF-DEM). Stokesian dynamics and dissipative particle dynamics are applicable, but they have limited size variation, surface geometry, and contacting interaction flexibility. Commensurate with these exciting theoretical developments are new ways to analyze simulations of complex solutions, interfaces, and solids that enable the identification of correlated phenomena and a more detailed ability to test the separation of length and time scales that often underpin multiscale computational approaches to synthesis. These include graph theoretical techniques, clustering, genetic algorithms, and other data mining methods that can extract more information from simulations than traditionally employed correlation functions.

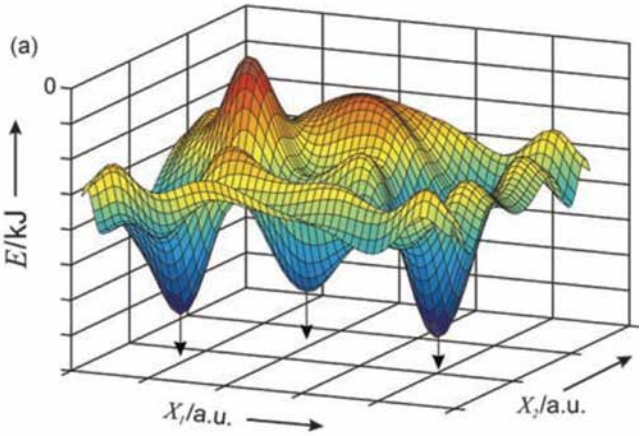

Figure 14. Schematic complex energy landscape highlighting local minima and barriers between them.[43] **|** *Reprinted with permission from J. C. Schon. "Wanderungen in der Energie-Landschaft." Physik Journal 9: 20–22. © 2006 Wiley-VCH Verlag GmbH & Co. KGaA.*

Scientific Challenges and Opportunities

Approaching the long-term goal of "synthesis by design" requires establishing generalized rules for complex materials assembly. These rules will provide road maps for synthesis, analogous to the role played by equilibrium phase diagrams in the synthesis and crystal growth of thermodynamically stable compounds. They will enable a new synthesis science focused on kinetically stabilized and metastable phases. Even the seemingly simple case of thermodynamically stable phases presents major challenges because of large gaps in current knowledge about the nature of intermediate structural building blocks present in a melt, solid state, or vapor reaction. Similar gaps exist in determining how to control these building blocks and precursor phases to produce desired materials.

To delineate the rules for complex materials assembly, it is necessary to characterize the constituent molecular species and understand correlations and dynamics at the growth front as a function of time. To chart assembly, the characterization of liquid, solid, and vapor phases and surfaces is required to identify and develop chemical signatures to support reaction-type systematics. Focused research in this area will ultimately lead to accelerated and more informed exploratory syntheses as a deeper understanding of reaction processes reveals all accessible pathways to a synthetic target. When guided by theoretical and computational input, chemical mechanistic knowledge will have a powerful impact on energy science and technology. An associated outcome of targeted research in this area will be the generation of new databases of reactions; basic reaction mechanisms; and their associated taxonomies, including structural, thermodynamic, and kinetic parameters.

Understanding the mechanisms and thermodynamic driving forces of how solid materials form and transform will allow pathway control to yield synthetic targets. This is a great challenge because of the difficulties in interrogating the synthesis, while not also perturbing the reaction pathway.

The following overarching questions inform a mechanistic understanding of materials synthesis and design:

- Can our understanding of fundamental mechanisms and pathways be improved to purposely build new materials?
- Can the balance between thermodynamic driving forces and kinetic barriers for a specific synthetic pathway to a targeted product be determined? Can such an understanding be used to identify critical points during a synthesis at which pathways to the desired product diverge from those leading to other, less desirable outcomes?
- What kinds of chemical, structural, and spectroscopic signatures could provide insight into reaction mechanisms?
- Can what happens before a structure is assembled, and how the structure has been “chosen” from either a thermodynamic or kinetic standpoint, be observed?
- Can precursors to produce specific materials be proposed?
- Can the short-range order in melts, glasses, and other solutions be harnessed to control crystallization pathways or to apply preassembled but robust constructs to create new materials?
- Can computational methodologies be developed to make robust predictions ensembles of energy landscapes in a realistic synthetic condition and reliably obtain structural features and chemical or physical properties that incorporate robust descriptions of electronic structure across the periodic table (e.g., relativistic treatments)?
- How can experiments to benchmark and confirm computational methodologies be used?

Emerging research challenges. To address the knowledge gaps described above and answer these overarching questions, the panel recommends the following primary emerging research challenge:

Develop a mechanistic understanding of synthesis through quantification of energy landscapes and formation pathways for both stable and kinetically stabilized matter, particularly for complex chemical systems

The pathways through which solid state materials form are typically unknown and complex in their dependence on experimental variables (e.g., temperature, pressure, chemical composition). Compared with the broad, longstanding emphasis on materials discovery and, more recently, computational design, little effort has been directed to determining how materials form. Consequently, limited mechanistic knowledge greatly impedes progress in materials synthesis and processing. Advancing this knowledge will

- transform the discovery of new materials
- create optimized methods for synthesis of materials with targeted properties
- inspire computationally aided synthesis via reactive pathway design

Addressing relevant mechanistic knowledge and research gaps could lead to directed syntheses of new materials with unprecedented and transformative properties. To understand these mechanisms, researchers must address the experimental and computational challenges necessary to construct ensembles of complex energy landscapes that describe the transformation of reactants to products. Conventional approaches must be integrated with new experimental and computational techniques to generate landscapes replete with information and guidance. Such landscapes should portray energy barriers and potential low-energy pathways to aid the process design and synthesis of a targeted material[44] with local minima representing both thermodynamically and kinetically stable phases.[37,38]

Establishing general principles of materials formation for different classes of compounds, reaction types, and reaction conditions will improve synthesis outcomes. Generalizing schemes derived from related reaction mechanisms will enable new predictive capabilities. Organic chemists have long exploited reaction mechanisms and classification schemes to enable targeted and scalable syntheses so that optimal synthetic conditions are routinely proposed and executed based on mechanistic understanding. Duplicating this understanding for materials synthesis will enable both efficient processing vital to today’s technologies and accelerated discovery of previously unknown materials. In this vein, studies of model reaction types offer opportunities to identify and classify mechanisms common to large materials classes. Once precise control of atomic structure, morphology, and defect concentrations is recognized for a prototypical model system, structural derivatives in that class can be synthesized under similar conditions.

In synthesis, intermediates play formative roles and influence rate-limiting and path-directing steps. Systematic understanding of these intermediates will aid the design of synthesis strategies. Hydrothermal methods, metal growth in melts, molecular precursor approaches, post-synthetic transformation of materials, and general reactions of nanoparticles (e.g., oxidation, elimination, addition, and coupling) represent some of the important classes of reactions available for study.

Assessing reaction mechanisms requires both the integration and the development of advanced characterization techniques out to the limits of energy, temporal, and spatial resolution. Common techniques to study reaction pathways include x-ray and neutron diffraction, small and wide-angle x-ray and neutron scattering, x-ray absorption spectroscopy, x-ray photoelectron spectroscopy, near-ambient-pressure x-ray photoelectron spectroscopy, solid-state nuclear magnetic resonance, temperature-programmed desorption, electron microscopy, and numerous optical methods. New techniques are needed that further enable the disentanglement of critical signatures from background information across multiple length and timescales.

Often, theoretical and computational methods aid data interpretation and chemical and structural assignments. Many solid-state, liquid-metal, molten-salt, and solvothermal syntheses use elevated temperatures that will require the development of new characterization techniques. Recent developments in spectroscopy and photonics (e.g., ultrafast coherent spectroscopies and imaging using ballistic photons) enable the extraction of valuable spectroscopic information from complex, opaque media that cannot be used with traditional characterization techniques. Tomographic x-ray, atom probes, and electron microscopy techniques provide spatial resolution across multiple length scales, from atomistic to mesoscale. These data can then be paired with information from computational studies to understand and learn why specific topologies are favored. To realize a robust, validated platform, computational results must reflect and describe observed experimental data, which may require advances in the description of electronic structure, the ability to probe longer time scale phenomena, or the incorporation of more realistic chemical models and synthetic conditions. In this way, researchers will learn how reagents transform into desired materials. Understanding and classifying synthesis and growth mechanisms will revolutionize predictive materials synthesis by providing a theory of materials synthesis, which will be conceptually analogous to those available for constructing organic molecules.

An additional challenge will be to develop databases comprising measurements from numerous techniques and to efficiently analyze all these data as a function of reaction conditions (starting point of synthesis or synthesis steps, pH, concentration, composition, flux, temperature, time, pressure ¼) and across wide length and time scales. The ability to reconcile errors within these data, to learn how data cluster together, and to find patterns across dissimilar chemical systems will be critical in guiding computational efforts and identifying the pathway bottlenecks limiting successful synthesis.

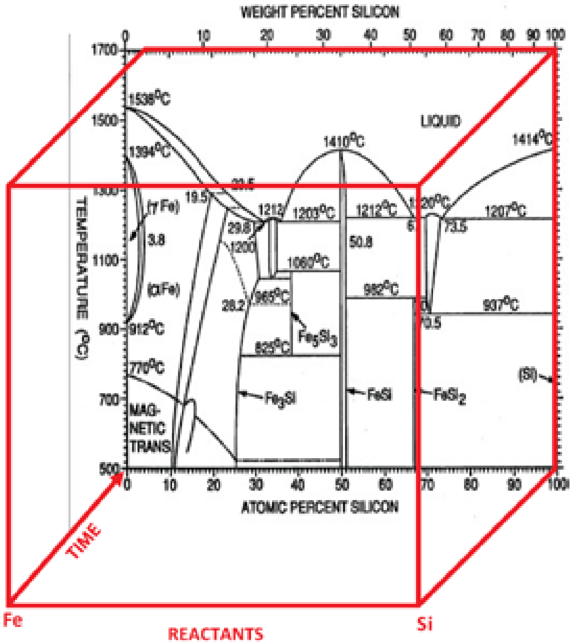

Figure 15. An example of a generic multivariable phase diagram incorporating reaction time to include both stable and kinetically stabilized materials within the illustration. The thermodynamic phase diagram in the end is the equilibrium phase diagram. | *Image courtesy of M. Kanatzidis.*

Materials synthesis involves multiple chemical constituents and process variables, including pressure, temperature, pH, time, particle size, and reactions in all phases of matter. A major deliverable from an energy landscape exploration is the development of multivariable phase diagrams. Whereas traditional phase diagrams include only thermodynamically stable compounds, multivariable phase diagrams are meant to encompass all temporal and compositional phase space, including kinetically stabilized precursors or materials (Figure 15). Their development and use will accelerate exploratory materials discovery and allow the exercise of precise control over atomic structure, morphology, and defect concentration. Advances such as this, brought about by greater understanding of reaction mechanisms, will permit a more efficient approach to the synthesis of new materials for technological use and provide more facile pathways to scale-up reactions with less waste.

One approach to exploring phase space before a system reaches equilibrium is to capture information about all phases that form as intermediates during the course of a synthetic protocol. The process could involve heating a set of reactants to a temperature known to yield a single, well-defined product after cooling. What is missed in this standard synthetic protocol is the formation of any transient or intermediate phases that may form and then disappear as the heating cycle continues. Access to this information through structural probes that could be applicable in situ would not only elucidate how the final materials form but also reveal any interesting phases hidden by the process that precede the final product. Information and insights garnered in this manner, which are related to the synthetic energy landscape, could then be used to redesign the synthesis. In addition, knowing about the transient existence of intermediates would allow a rational development route for their targeted synthesis. In situ observation and knowledge of all phases formed, known as a “panoramic” approach, will require the invention of new in situ structural and spectroscopic tools to observe if and when intermediates form during synthesis. Figure 16 shows one example of such an approach involving the reaction of copper metal in potassium polysulfide fluxes. When run in the conventional manner described above, the only final product isolated is $K_3Cu_8S_6$.[45]

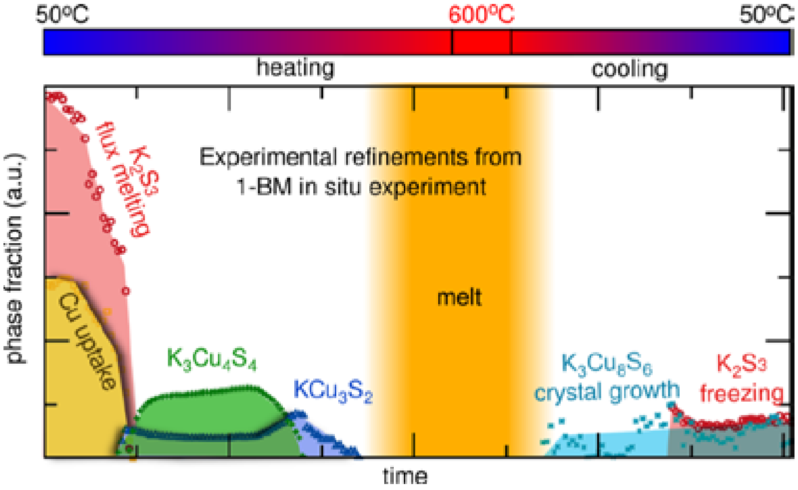

Figure 16. Time sequence in the reaction of Cu + K_2S_3 using in situ synchrotron radiation. The in situ diffraction data reveal that, on heating, the $K_3Cu_4S_4$ and KCu_3S_2 materials form, maximize their yield, and disappear as the temperature increases. When the molten temperature is reached, all phases dissolve; and when the cooling begins, the only compound forming is $K_3Cu_8S_6$, the sole reaction product.[45] **|** *Reprinted by permission from D. P. Shoemaker et al. “In Situ Studies of a Platform for Metastable Inorganic Crystal Growth and Materials Discovery.” PNAS 111[30]: 10922–27. DOI: 10.1073/pnas.1406211111.*

Often, the morphology of a technologically relevant material is as important in determining function as its composition and crystal structure. Understanding how a solid forms will allow us to directly synthesize the material in the required morphology, such as high-quality thin films for semiconductor devices or membranes for gas separation. Similarly, low-dimensional materials (such as quantum dots and layered materials) have important technological applications, including use as emitters in LEDs, phosphors, and transparent conductors. Understanding the mechanism that can terminate the growth of an extended solid to yield lower-dimensional structures will allow systematic leveraging of dimensionality as a tool for accessing new material properties. Mechanistic studies will also provide vital information about how to control dopants, defect types, and their concentrations. Such features are known to dictate the performance of a wide range of energy-related materials, including absorbers for solar cells, electrodes for rechargeable batteries, and phosphors for solid state lighting. Many technologically important materials contain toxic, rare, or expensive elements that hinder their wide-scale usage. Understanding how these derivative materials form will allow researchers to synthesize nontoxic or inexpensive analogues that show similar performance. Knowing which precursors and synthetic conditions will yield analogous materials (with similar properties) will eliminate the massive waste of materials and effort involved with trial-and-error syntheses. It will also enable researchers to target new materials with unprecedented functionality and ultimately provide the basis of new and revolutionary technologies.

Potential for Energy Relevant Technologies

Improvements in synthesis methodologies and techniques enabled by better understanding the mechanisms of materials formation and by establishing rules for complex assembly will have an even wider impact affecting the discovery and synthesis of complex materials with energy relevance. An important barrier to creating new energy technologies or the adoption of many new technologies is a lack of suitable materials that can be inexpensively and sustainably produced. The breakthroughs envisioned by broadly developing a systematic and mechanistic understanding of materials will in many cases influence the emergence of a wider class of materials. Consider that a mechanistic understanding of synthesis will allow the direct design of the most efficient solar energy conversion materials, thermoelectrics, superconductors, fuel production, materials suitable for extreme environments, catalysts, and electrochemical energy storage materials. Understanding and directing the precursors in aqueous or non-aqueous phases can lead to films with high performance with regard to energy conversion and storage properties. With the development of robust monitoring, characterization, and theoretical platforms, we envision a new field that encompasses the science of synthesis with direct and rational strategies for materials design and further development by the technological sector.

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4. Establishing the Design Rules for Supramolecular and Hybrid Assemblies

Self-assembly of macromolecules and hybrid "soft–hard" materials has emerged as a major frontier for the synthesis of hierarchical matter. In some cases, structure results from intra-molecular interactions that cause individual macromolecules to fold into hierarchical geometries, mimicking protein complexes such as enzymes. In others, inter-molecular interactions drive self-assembly into supramolecular structures with long-range order. Unlike most inorganic solids, which form in response to strong bond formation, these self-assembled structures organize through weak forces, often involving a competition between attractive and repulsive interactions that leads to a characteristic length scale of ordering. The inclusion of stronger, direction-specific interactions through functional group design, either intra-molecularly or at interfaces with inorganic materials, can lead to a degree of order approaching that of crystalline solids.

However, the complexity of the building units and the capability to introduce multiple components—including distinct sequences, molecular species, or inorganic nanomaterials—enables a degree of hierarchy not achievable in small molecule or inorganic systems. Taking advantage of these features of supramolecular and hybrid systems requires overcoming two significant challenges. The first is to develop synthetic information-encoded building blocks to enable programmable folding and/or assembly of hierarchical matter. The second is to understand and navigate the energy landscapes leading to folding and assembly to enable the design of those building blocks. The ultimate impact of such advances will be a level of function for synthetic matter rivaling that of living systems (See the sidebar *Nature's Molecular Machines*).[1]

Current Status and Recent Advances

Impressive progress has been achieved in the field of supramolecular and hybrid materials synthesis. Fields engaged in this research range from small-molecule organic, polymer, and inorganic chemistry to molecular and cellular biology, as well as traditional materials science. Subject areas include synthetic host-guest complexes, surfactant assemblies, self-assembled monolayers, liquid crystals, colloidal assemblies, polymeric self-assembly, block copolymer mesophases, crystal engineering, protein complexes, lipid bilayers, DNA assembly, and cellular cytoskeletons and compartmentalization. Synthetic development in small-molecules, polymers, peptides and peptidomimetics, proteins, and inorganic nanoparticles has opened up many new opportunities in hybrid materials (Figure 17).[2]

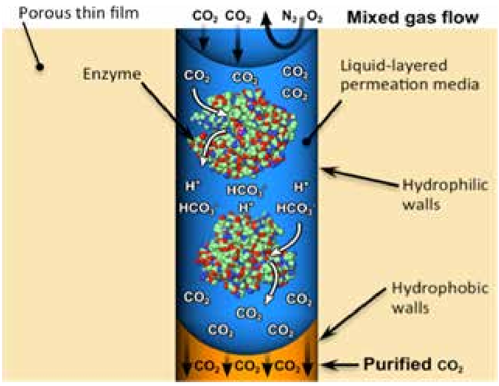
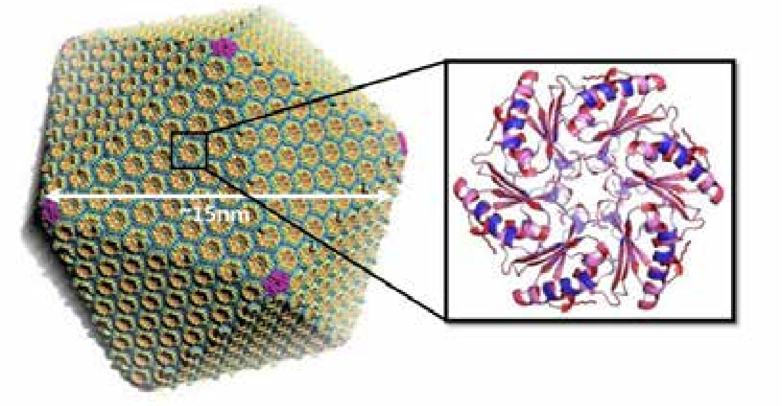


Figure 17. Nano-stabilized enzymatic membrane for CO_2 capture.[2] | *Image courtesy of Sandia National Laboratories*

Developments in organic synthesis have enabled organic chemists to prepare at will any type of molecular organic structure. The tools of organic synthesis have been used to construct a beautiful array of molecular, oligomeric, and polymeric materials, as well as to further engineer the ability of these entities to self-associate into materials with even higher degrees of complexity. For example, pi-conjugated polymers that span the visible spectrum of colors have been synthesized; and recent advances in side-chain and heteroatom engineering have further enhanced the energy-transporting nature of these materials to enable hole mobilities on the order of $10cm^2/(V\text{-}s)$ and organic photovoltaic efficiencies now routinely over 10%. Now it is almost routine practice in many laboratories to synthesize polymers with low polydispersity and controlled composition using free radical polymerization.

Nature’s Molecular Machines



In living systems, cellular functions are carried out by a network of molecular machines primarily composed of proteins. The structural paradigm that enables the remarkable level of function exhibited by these machines is one of hierarchical design. Though similar in dimensions to typical synthetic nanomaterials such as quantum dots and nanowires, these protein-based machines have substructure at the molecular level that is precisely controlled. Moreover, they self-assemble into fibers, sheets, and 3-dimensional multi-protein complexes from which new functions emerge through the cooperative action of the constituent proteins.

The carboxysome, pictured above, provides a beautiful example of this paradigm. The individual proteins fold and assemble into hexameric units, resulting in the creation of a pore at the center. The set of peptide loops that meet around the periphery of this pore define a physical and chemical environment that permits the passage of only certain ions. In this case, the species that passes through the pore is dissolved CO_2 in the form of HCO_3^-. In addition, the hexamers themselves self-assemble into a membrane, which closes to form a shell through the sporadic inclusion of a second pentameric protein complex. Inside the shell, other enzymes process the HCO_3^- ions and, in the end, transform CO_2 into fixed carbon.

The secret to this approach to making functional materials is that the proteins themselves—although composed of nothing more than simple linear polymers—have high information content by virtue of the chemical diversity of the constituent monomers, which come from the library of natural amino acids. The sequence of monomers provides the code for both intra- and inter-protein interactions that result in folding, assembly, and ultimately, the remarkable diversity of function that is Life. **|** *[Left] Adapted with permission from Kerfeld C. A. et al. 2005. “Protein Structures Forming the Shell of Primitive Bacterial Organelles.” Science 309 [5736]: 936-938. DOI. 10.1126/science.1113397. © 2005 American Association for the Advancement of Science.* [1] *[Right] Reprinted with permission from J. N. Kinney et al. 2011. “Comparative Analysis of Carboxysome Shell Protein.” Photosynthesis Research 109[1–3]: 21–32. DOI: 10.1007/s11120-011-9624-6*

The use of macromolecules to fold into or directly assemble structures has relied for decades on macromolecular chain architectures with blocked monomer sequences along the primary chains. Nature has evolved polymer sequence control to the maximum in the form of DNA and proteins, which are carriers of information about structure and ultimately function in biological systems. The sequence control of DNA with computer algorithms has led to unprecedented control of synthetic self-assembled structures and functions. In parallel, activities have intensified in recent years to improve sequence control of polymers from synthetic monomers. Spatial control of monomers has a strong influence over macroscopic material properties, such as the solubility, elasticity, conductivity, and phase behavior of, for example, block copolymers.[3,4] Notable examples of new strategies to achieve unique synthetic sequence-defined materials include novel templated reactions,[5-7] sequential living radical polymerizations with precise monomer reactivity,[8-11] and iterative additions on a liquid[12,13] or solid support[14-17] via orthogonal chemistries. Notable examples of synthetic single polymer chain compartmentalization and folding include single chain intramolecular covalent[18] and noncovalent[19,20] crosslinking. Other notable examples include the assembly of supramolecular polymeric structures formed by the self-assembly of subunits with specific and directional interactions.[21]

Supramolecular chemistry. The ideas of supramolecular chemistry and spontaneous assembly based on molecular geometry, conformational flexibility, and functionality—in conjunction with noncovalent and weak interaction forces that include hydrogen bonding, screened electrostatics, p-p stacking, van der Waals interactions, and coordination bonds—has led to significant advances in the ability to control the assembly and function of supramolecular structures and the fundamental understanding of their structure, order, and dynamics.

In the 1980s, the discovery of Buckminsterfullerenes and the advent of synthesis approaches for narrowly size-dispersed semiconductor quantum dots helped initiate the field of nanotechnology. These accelerated interdisciplinary approaches to colloidal self-assembly in particular, and toward supramolecular assemblies in general, brought together researchers from very different fields and backgrounds. At the start of the 1990s, initial studies pointed to the use of self-assembly by organic molecules to direct the structure of inorganic materials.[22,23] Starting from small-molecule surfactant assemblies, this approach was quickly directed toward macromolecular surfactant and block copolymer self-assemblies and their associated directing of inorganic nanoparticle assembly—thereby increasing accessible structural length scales from tens to hundreds of Å.[24-26] High-temperature transformations of the resulting periodically structured organic-inorganic hybrid materials led to dramatic advances in the field of mesoporous solids (Figure 18)[27] with potential applications in separations, catalysis, and energy devices.

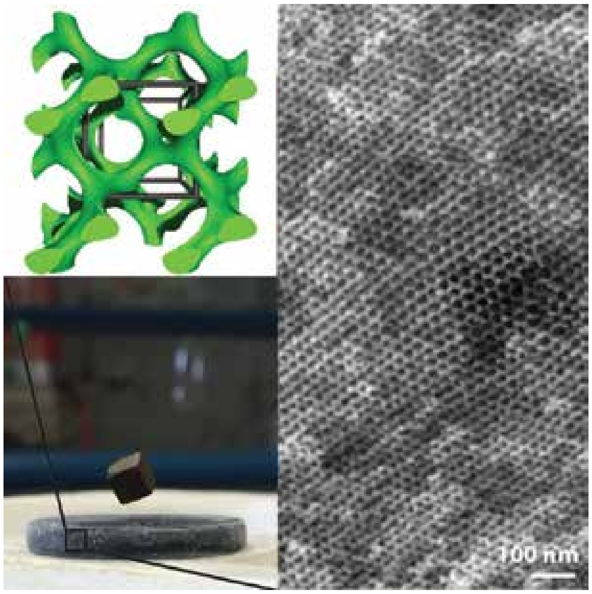


Figure 18. Block copolymer self-assembly directed synthesis of mesoporous gyroidal superconductors.[27] | *From S. W. Robbins et al. "Block Copolymer Self-Assembly–Directed Synthesis of Mesoporous Gyroidal Superconductors." Science Advances 2 [1]: Article ID e1501119. DOI: 10.1126/sciadv.1501119. © 2016.*

Studies starting with all amorphous organic-inorganic hybrids produced mesoporous amorphous solids, such as silica and carbon[28,29] but quickly expanded to polycrystalline mesoporous solids of, for example, transition metal oxides and metals,[30-32] and finally to mesoporous solids of single-crystals.[33] To enable such high-surface-area materials to also provide high fluxes, hierarchical porous materials were developed soon afterward.[34,35]

Recent advances in this field include shape control by direct laser writing of mesoporous materials, as well as the formation of asymmetric membrane structures via a combination of self-assembly and non-solvent–induced phase separation.[36,37]

Hybrid organic-inorganic matter. Developments in inorganic nanoparticle synthesis opened up another opportunity in organic-inorganic hybrid materials. Once nanoparticles are synthesized, their sizes, shapes, ligands, and chemical composition are defined to some extent.[38-42] Various approaches have been developed to control nanoparticle assemblies in 1, 2, and 3 dimensions, such as solvent evaporation,[43] application of external fields, DNA-guided assembly,[44-46] and polymeric template assembly. The co-assembly of organic and inorganic building blocks can be attained by processing them together or in a two-step fashion in which the organic phase acts as a structural framework.[47,48] Nanoparticle superlattices with novel properties have been formed via controlled evaporation or via DNA origami assembly.[49] Polymer-based nanoparticle assembly is compatible with scalable manufacturing. Supramolecular nanocomposites are particularly advantageous for achieving diverse nanoparticle assemblies with very high precision and rapid assembly kinetics.[50,51] Polymers can also be either grafted to or grown from the nanoparticle surface, with the polymeric ligands adding another level of control over nanoparticle assembly.[52]

Aside from organic/inorganic hybrids, a new family of hybrid materials containing synthetic and biological components are equally exciting. With phage displays, peptide libraries are readily available, and peptides have been used as material building blocks.[53,54] Solid-phase synthesis is a mature technique for synthesizing peptides and peptidomimetics with sequence lengths of up to ~70 monomers. With combinatorial synthesis using robots, large libraries containing more than 1000 oligomers can be made at once. Different non-natural amino acids have been designed and synthesized to enhance resistance to proteolysis and modulate backbone structure and assembly.[55]

Developments in synthetic biology allow the incorporation of non-natural amino acids into natural proteins without detrimental effects in the translation process.[55] The chemistry toolbox for site-specific protein modification post-translation is expanding at a rapid rate.[56-61] Computational protein design has traditionally been applied to understanding biology and has only more recently been converging toward materials needs. Through data mining, information on protein backbone and side chain packing can be extracted from protein data banks. De novo protein design has led to numerous building blocks, both peptide- and protein-based, with prescribed assembly behavior.[62-64] Hierarchical assemblies based on peptides forming secondary and tertiary structures have been demonstrated with confirmed crystal structures. More recently, different functionalities such as catalysis and charge transport have been engineered.[65] Synthetic/natural hybrids offer opportunities to combine the advantages of both natural and synthetic building blocks. For example, synthetic polymers can mediate protein/peptide interactions with local media and stabilize proteins in non-natural environments. The polymers also improve protein processability, thereby enabling their incorporation into devices. Protein incorporation diversifies chemical heterogeneity, structural precision, and dynamic responses to external stimuli in a synthetic system.[66] Molecular amphiphiles have been used as active scaffolding for the spatial organization of functional guests, including natural building blocks such as transmembrane proteins.[67]

In situ discoveries. In situ investigations into the assembly of supramolecular and hybrid systems have revealed a number of common features. The emergence of ordered states in these systems typically occurs along hierarchical pathways, where the monomeric units often first form a disordered state before transforming into an ordered state. These two-step pathways were inferred from pioneering studies on globular proteins undergoing crystallization[68,69] and then directly demonstrated at a molecular level using in situ atomic force microscopy to follow the assembly of proteins.[70,71] Since then, two-step pathways have been documented in numerous supramolecular and biomolecular systems.[72-78] In situ studies of such systems also show that the conformational transformations that commonly take place in the transition from solvated monomers to assembled structures are a major factor inhibiting the emergence of order. Finally, once order begins to emerge following condensation, further growth is catalyzed by the presence of ordered domains and proceeds rapidly.[70] In essence, the ordered domains serve as templates to guide the binding of monomers in the correct conformation.

Scientific Challenges and Opportunities

Much of the progress in this field has been the result of intuitive approaches. There is only a rudimentary understanding of the underlying energetic and structural factors controlling assembly pathways and outcomes. In all supramolecular and hybrid systems—except for DNA origami, in which bonds are highly specific and structure exhibits a one-to-one relationship to base-pair sequence[78]—the ability to predict ensemble outcomes of assembly starting from the details of molecular structure is extremely limited. This is particularly true for nonequilibrium approaches to achieve assembly over multiple length scales in multi-component systems. Experimental studies show that the kinetics of assembly and the probability of achieving the ordered state can be tuned through the balance of electrostatic and hydrophobic interactions, and that surfaces can be exploited to both accelerate assembly kinetics and direct it toward a preferred ordered state.[79-82] However, these serve as crude rules of thumb, and true design rules are lacking.

It remains a significant challenge to establish the ability to control molecular assembly beyond the “supramolecular” scale—that is, microscale and mesoscale assemblies guided by molecular and supramolecular design. The ability to control system dynamics and engineer responsive or self-healing properties by design (or conversely, engineer self-destructive properties by design) and ultimately, to achieve transduction between multiple energy currencies (e.g., photonic or thermal attenuation of electrical properties) is important but lacking. Equally important is the ability to rationally control interfacial properties between disparate material sets. For example, a lack of understanding of the composition on a nanoparticle surface in turn leads to persistent difficulties in performing derivatization and functionalization reactions that tailor the interfaces between inorganic and organic materials.[83]

To achieve desired performance and functionality, significant advances are required in the control of the composition and architecture of multiscale functional structures. This is particularly challenging for hierarchically structured materials that are formed via the assembly of disparate components. Complex energy landscapes at multiple length scales involved in the assembly provide an enormous parameter space for the design of the hierarchal structures. This, on the other hand, implies that these assemblies are often in nonequilibrium states of matter; and it is challenging, if not currently impossible, to quantitatively correlate the needed functions with attainable assembled architectures during early stages of the design. Therefore, to establish the scientific basis of assemblies and their pathways, it is desirable to watch the structures and functions evolve in both temporal and spatial dimensions.

The field of supramolecular and hybrid assembly is still only beginning to pursue compartmentalized materials designs and synthesis strategies that enable and exploit the development of chemical potential gradients during both the synthesis and the “operation” of biomimetic materials. The dynamic functionality evident in natural systems requires dissipative assemblies, i.e., energy transfer and consumption and operation under conditions far from equilibrium. For example, the synthesis of composites incorporating switchable, reconfigurable, or ion-selective membrane bound components, scaffolded on cytoskeletal replicas that enable directed energy and materials transfer, would be a first step toward the formation of cell-like constructs, *protocells,* that can autonomically sense and respond to their external environments. Such dynamically responsive materials and assemblies are challenging to design, synthesize/fabricate, and control. They are not based on equilibrium thermodynamic concepts, for which we have sound theoretical frameworks to describe and control material structure and function. But the study of such systems offers substantial opportunities to expand on accessible materials functions, as well as our fundamental understanding of dissipative systems. Simultaneously probing the structural dynamics and functional evolution in the environment in which assemblies are active is critical to deciphering the interactions of the sub-structures and evaluating their correlation with function. There are few capabilities that combine the available characterization probes, even at national user facilities. Significant efforts are needed to bridge multiple probes, for both lab-scale tools and user facilities.

Synthetic/natural hybrid systems that combine the biological and synthetic worlds clearly hold great promise as an interesting new class of materials that mimic natural systems. A fundamental understanding of these hybrid materials is necessary, along with control over their self-assembly, for these building blocks to reach their full potential in biological and nonbiological applications. Developing this understanding requires coordinated efforts from different communities—including biology, biochemistry, biophysics, and polymer science—as well as the combined efforts of synthesis, structural characterization, and simulation. Since many noncovalent interactions at similar energy scales underpin the behavior of hybrid systems, a delicate balance of the various energetic contributions must be achieved. Detailed structural characterization is critical to fully deduce the structure of each component. Scattering is a powerful tool for doing so. A particularly important opportunity lies in the use of resonant soft x-ray scattering techniques in conjunction with neutron scattering techniques, via which chemical information about a multi-component system can be applied to tailor the contrast in the system.[84] This technique is especially applicable to the extraction of structural information in hybrid systems in which the scattering profile is dominated by high-Z components. Research that combines detailed structural characterization with application performance is important for future progress.

Computation and simulation are critically needed to provide guidance toward molecular design and to develop a basic understanding of phase behavior, not only within static 3-dimensional (3D) structures but also in terms of dynamics and kinetic pathways. In the case of block co-polymers, molecular packing theory and kinetic Monte Carlo methods have achieved significant success in relating properties of the molecules, such as hydrophobicity and molecular volume, to the stable phase (e.g., cylindrical or hexagonal).[79-82] However, molecular details are currently absent. In the case of sequence-defined polymers, such as proteins, peptides, and their biomimetic counterparts,[85-89] the incorporation of conformational transformations during assembly has been introduced only at a coarse level.[90] These studies show that self-assembly in supramolecular and hybrid systems can be enabled through manipulating the interplay of interface chemistry, solvent conditions, and polymer sequence; but the ability to predict either the pathways or the outcomes, given these parameters, remains a major challenge. New approaches to supramolecular and hybrid synthesis that lie on the horizon—such as massively parallel synthesis via cellular factories and self-replication—offer the prospects of sustainable, energy-efficient synthesis methods, amplify this challenge.

The challenge to theory and characterization epitomizes the challenge of mesoscale science—self-assembly depends on molecular details of the interactions, but the order emerges through ensemble processes in which the collective behavior imposes a conformation on the individual units. Making the connection from atomistic details to ensemble outcomes computationally, and capturing the dynamics experimentally at the time and length scales of individual units while following the long-range order, both require crossing considerable length and time scales. Consequently, new developments in both theory/simulation and multimodal in situ imaging are needed to make these connections and define the structural pathways and dynamics of assembly. The ultimate goal is to develop a fundamental understanding and quantification of the underlying physical mechanisms that govern assembly, and of the relationships among molecular structures, the interactions driving organization, and the resulting architecture.

To address the challenges described, the panel recommends focusing on two emerging research challenges.

Enable programmable assemblies via the synthesis of information-encoded building blocks

To synthesize functional materials with predictable properties, it is important to design and synthesize individual building blocks, control assembly, and investigate structure–property relationships. For decades, we have been investigating the self-assembly of single types or mixtures of building blocks. The ability to characterize and even predict self-assembled structures from given building blocks experimentally and theoretically is improving. However, the ability to design building blocks, particularly the assembly process itself, is limited. There is typically a large gap between a targeted material and the results experimentally obtained. The ability to readily select building blocks for the assembly of predefined target structures with desired functions is highly challenging. This is particularly true for the generation of hierarchically structured functional materials using multicomponent systems.

To date, the most successful efforts along these lines use DNA as building blocks. A desired 3D DNA structure can be assembled under kinetic and thermodynamic control by simply changing the coded information. DNA hybridization permits significantly diversified bonding types and opens opportunities to control structural diversity in nanoparticle assembly. However, the side chain diversity found in other biopolymers, particularly proteins, is lacking. Hence there is a great need to master the design of building blocks that go beyond DNA-based systems, with the ultimate goal of enabling soft functional materials by design.

In nature, the success of information encoding is obvious, and the genetic information encoded in the DNA sequence determines a cascade of various complicated events. The field of biomineralization provides a multitude of examples of how nature has used encoding to control the chemistry of mineralization by proteins and other biomolecules. If information is embedded into the building blocks, the energy landscapes of interacting components may “encode” a final low-energy (equilibrium) structure. This information-encoding strategy may also allow us to understand and predict intermediate states and realize kinetically trapped states in a rational manner.

New ways are needed to encode information about the desired assembly structure. Improving the ability to synthesize desired assemblies depends on improving the ability to control small-molecule chemistry, the surface chemistry of nanoparticles, and macromolecular sequencing in order to design information-coded building blocks for programmable assemblies. Small molecules represent desirable building blocks from the standpoint of simplicity and, potentially, sustainability in design. Developments in organic chemistry, in particular in total synthesis, make it feasible to synthesize molecules on demand. The vast arsenal of organic synthesis allows for the ability to construct, with atomic precision, a variety of molecular structures with programmed elements consisting of various flavors of interactions, such as hydrogen bonding, van der Waals interactions, and metal coordination complexation. The foremost challenge is to efficiently encode information and function so that the molecules can react and/or organize, either via self-assembly or guided assembly into 1, 2, and 3-dimensional structures by design.

When prescribed information is encoded into a macromolecular strand, complementary segments on a polymeric building block can associate and lead to self-organization across multiple length scales into a desired structure (Figures 19 and 20).[36,91] However, unlike in biomacromolecules, programming information into synthetic macromolecules, by way of sequence and spatial compositional control, remains challenging. Therefore, advances are needed in the synthesis of information-encoded building blocks (synthetic polymers), building block

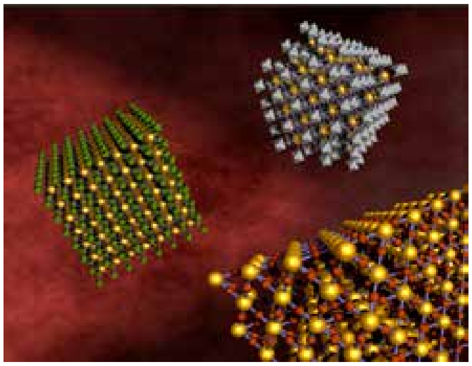


Figure 19. DNA-driven assembly methods enable the by-design creation of large-scale superlattice nanocomposites.[91] | *Image courtesy of Brookhaven National Laboratory*

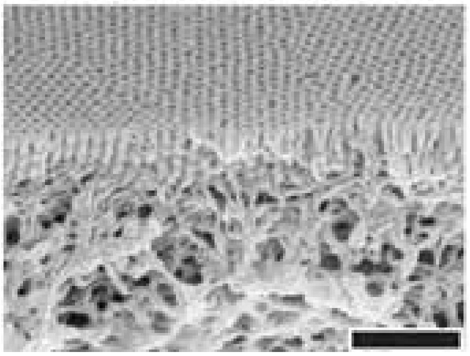


Figure 20. Asymmetric superstructure formed in a block copolymer via phase separation.[36] | *Reprinted with permission from K. V. Peinemann et al. “Asymmetric Superstructure Formed in a Block Copolymer via Phase Separation.” Nature Materials 6 [12]: 992–96. DOI: 10.1038/nmat2038. © 2007 Macmillan Publishers.*

precursor design (monomers), and macromolecular sequence control. This effort will require an enhanced mechanistic understanding of how to encode diverse chemical information into macromolecular chains.

Progress is needed in the synthesis of monomers (i.e., polymer building block precursors) in which controlled polymerization can be driven selectively and orthogonally. Research efforts required to improve this understanding include control over individual monomer reaction kinetics, prediction of monomer-monomer and/or monomer/macromolecule interactions and their effects on subsequent addition kinetics, and enhanced characterization techniques. In particular, there is a need to develop methods to characterize, preferably via nondestructive methods, the spatial composition along a macromolecular chain. Finally, the use of theoretical/computational methods to guide information encoding (i.e., functional groups) along the macromolecular chain toward achieving robust self-assembly will be critical to screen the expansive compositional and sequence space for the most desirable structures. A final challenge is the preparation of these building blocks and their precursors at scale and under environmentally benign synthesis conditions.

In addition to pure synthetic systems, hybrid systems based on natural and synthetic building blocks present new opportunities to meet energy material needs. Natural building blocks such as proteins, organelles, and cells are all encoded with information. For example, in a hybrid polymer-DNA system, the polymer may provide the long-range assembly, while complementary DNA sequences can provide specificity of interactions, enabling the synthesis of multiscale functional structures. In addition, many natural systems provide a source of inspiration, as well as templates of biomolecules such as mineralization proteins that can be coupled with self-assembling organic building blocks to grow inorganic nanocrystals during self-assembly, thereby creating organic/inorganic hybrid materials. Incorporating natural building blocks into synthetic systems may represent a viable path to improve material designability; but it is often limited by challenges of compatibility, stability, and the ability to scale up synthesis. There is a need to take advantage of recent developments in synthetic biology and make these natural building blocks compatible and viable with synthetic materials via, for example, appropriate choices of processing and operation conditions.

Past decades of research into particle (microscale and nanoscale) self-assembly have shown that a rich diversity of periodic structures can be generated.[92] For nanoparticle building blocks, the crystal structures, sizes, and shapes of nanoparticles are readily controllable in many material systems. However, the chemical composition and functionality at surfaces are often complex, difficult to determine, and heterogeneously distributed. This issue is especially problematic in colloidal crystals, in which modern synthesis reagents and protocols lead to complex chemical compositions that are poorly understood and difficult to functionalize precisely. Improved mechanistic understanding of colloidal crystallization reactions is needed so that new synthesis methods can be designed to optimize the size and shape distribution and, especially, the chemical composition.

As discussed in Section 3 of this report, Mechanisms of Synthesis under Kinetic and Thermodynamic Controls, understanding the controls on synthesis pathways is critical to advancing the synthesis of hybrid materials. If nanoparticle formation mechanisms can be understood on a microscopic level, synthesis technology will move beyond the typical synthetic process of Edisonian trial and error to one in which all aspects of nanoparticle composition and structure are controlled by design. The capability to design nanoparticle precursors with well-defined conversion byproducts and reproducible and tunable conversion kinetics is necessary for this purpose. Greater emphasis on systematic studies of colloidal nanocrystal surfaces is needed, especially exchange reactivity and ligand binding thermodynamics. Furthermore, multi-type anisotropic affinities, which have been considered theoretically, would enable the creation of structures with modest complexity and high information content. Thus, different assembled structures could be produced from a single set of diverse building blocks. However, controlling nanoparticle surface chemistry asymmetrically is a significant bottleneck; and design rules that take into account nanoparticle geometry, addressable site locations, and particle details are still to be uncovered. Encoding assembly instructions into building blocks requires theoretical guidance for targeted assembly from those information-rich blocks and new theoretical methods bridging statistical mechanics and information theory.

Identify and navigate energy landscapes to achieve functional hierarchical assemblies

Realizing a materials by design approach to functional hierarchical assemblies on the basis of information-encoded building blocks requires understanding and successfully navigating complex energy landscapes. Such multicomponent synthesis systems may include any combination of organic, inorganic, and biological components, together with single or mixed solvents. And they may require the variation of processing parameters, including concentration, temperature, or pressure. The associated complexity is substantial; and enormous effort is needed to integrate synthesis, characterization, theory, and simulation efforts to build a fundamental understanding of the underlying physical and chemical phenomena that govern supramolecular structure formation and the resulting property profiles.

Although equilibrium morphological considerations have guided most synthesis efforts in the past, future research likely will see increased emphasis on nonequilibrium and dissipative assembly strategies. These should provide access to, for example, hierarchical vascular-like structures that exhibit graded porosity and thereby simultaneously optimize surface area and flow. Compartmentalized structures, as found in biological systems such as cells, are also likely to become more prevalent in research and development efforts as requirements for the multifunctionality of materials steadily increase. The same is true for dynamically responsive, reconfigurable, or self-healing materials, which already are receiving increasing attention.[93] In all of these cases, attaining control over periodic and defect structures, and moving from amorphous to polycrystalline to single-crystal materials, will be at the heart of the successful conversion of materials design principles to established structure-property correlations.

Identifying and navigating the energy landscapes of specific assembly systems will require monitoring of the reaction pathways using a combination of process metrology and characterization capabilities. Supramolecular/ hierarchical systems are multiscale in nature and therefore require measurements that cover length scales from sub-nanometers to millimeters and time scales from 10^{-9} to 10^{5} seconds. Large-scale equipment—such as x-ray and neutron-based scattering and spectroscopy tools available at BES user facilities, as well as advanced laboratory-scale tools such as electron microscopes—does not fully meet these requirements.[94] Therefore, the community needs to continue to explore and stretch the limits of these capabilities, particularly in large-scale facilities. For example, a recent advance in synchrotron technology, the diffraction-limited storage ring, promises 100–1000 times more coherent flux than is available presently. These advances have the potential to revolutionize the understanding and the application of emerging coherence-based x-ray imaging capabilities, such as ptychography and coherent scattering imaging, in which nanometer to even sub-nanometer resolution on macroscopic samples assembled from nanoscopic building blocks will become feasible. A particularly important opportunity lies in the use of resonant soft x-ray scattering in conjunction with neutron scattering techniques, by which chemical information about a multicomponent system can be applied to tailor the contrast in the system.[84] This is especially applicable to extracting structural information in hybrid systems in which the scattering profile is dominated by high-Z components.

Similar to the expansion of techniques, operando measurements—which simultaneously probe structure, dynamics, and functional evolution in the environment in which assemblies are functioning—are critical to deciphering the interactions of substructures and evaluating their correlations with desired functions. Although there has been progress, this area of characterization must be substantially expanded; questions regarding, for example, performance degradation as a result of structural changes under operating conditions are paramount, particularly for applications in energy conversion and storage. Significant efforts are needed to bridge and couple multiple experimental probes, especially including those in large-scale facilities.

Because of the multiple time and length scales involved, theoretical and computational treatments of energy landscapes associated with functional hierarchical assemblies remains a major challenge. Connections between ab initio and coarse-grained models, to understand the microscopic origin of coarse-grained theories, can help guide experiments but are still challenging to establish. Greater efforts should also be placed on theories that investigate the dynamics of self-assembly, especially the formation and dynamics of intermediate states that precede the final structures, with the goal of defining the energy landscapes across which assembly occurs and determining how to successfully navigate them toward desired outcomes.

Potential for Energy Relevant Technologies

Whether in solar cells, electrochemical storage devices (e.g., batteries), or electrochemical conversion devices (e.g., fuel cells), substantial progress is expected to result from overcoming existing barriers through materials synthesis approaches based on supramolecular and hybrid assemblies. The development of electrochemical storage devices provides a clear example. In such devices, shortening the diffusion lengths of charge carriers from the micron scale to the nanoscale is expected to lead to devices with both high energy and high power densities.[95] Ideas for integrated 3D batteries—in which anode, separator, and cathode are not spatially separated into layered architectures but intertwined into triply continuous nano-architectures—were proposed more than a decade ago. But synthesizing/fabricating them is technically extraordinarily challenging.[96] Self-assembly of nanostructured materials is believed to be the only cost-effective approach to realizing them.[96] For electrochemical conversion devices, also, self-assembly is a subject of intense research activity; it provides, for example, access to high-surface-area solids that can function as catalyst supports and to high-surface-area catalysts for oxidation/reduction reactions of fuels. The synthesis of such support or catalyst materials is often based on self-assembly.[97] It will require substantial progress in the understanding of issues including nano-confined nucleation and growth, control of materials interfaces, and material stability under device operating conditions.

Layered and 2D materials are of considerable interest in battery technologies[98] and, increasingly, in various roles in solar devices, from transparent conductors[99] to semiconducting absorbers.[100,101] The physics community has advanced van der Waals heterostructures[102] as a compelling synthetic target with demonstrations of light-emitting diodes,[103] solar cells,[104] and photodetectors.[105,106] Despite these advances, the self-assembly of layered heterostructures by solution-phase approaches is underdeveloped. Nevertheless, there are already some hints that such materials could provide unique advantages in energy conversion and storage devices. For example, a phosphorene-graphene hybrid with high capacity and good cyclability was recently demonstrated as a lithium ion battery anode.[107] Alternating layers of graphene and phosphorene in the anode are thought to help the material preserve its structural integrity during cycling while also altering the energetics of ion intercalation.[108] In another example, the self-assembly of 2D flakes at a liquid-liquid interface led to improved charge transport through assemblies of the flakes, allowing the resulting material to be an effective semiconductor absorber for solar water splitting.[109]

When deposited on a flat substrate (e.g., a conductive substrate), 2D and layered materials typically lie with the basal plane parallel to the substrate. If such materials could be assembled with the basal plane perpendicular to the substrate, transport of all sorts—mass, ion and electron—could be dramatically improved.[110] Few routes now exist to reach this level of control. Given the often large dimensions of such 2D and layered materials, approaches that use external fields to self-assemble them may be necessary. In addition, controlled self-assembly of van der Waals heterostructures remains a particularly outstanding challenge, but perhaps an even bigger opportunity.

Advances in the emerging research challenges identified above will enable the realization of these developments in energy technology. Success in the design of information-encoded building blocks will lead to a suite of new chemical tools and provide new platforms to the scientific community for the development of predictable strategies for assembly. It will lead to the formation of new assemblies and a viable path for the efficient design of targeted functions, thereby solving the reverse design problem. The research directions identified here will also enable the synthesis of reconfigurable and stimuli-responsive matter with unprecedented sensitivity and selectivity. These capabilities can result in the synthesis of synthetic complexes for energy harvesting; enzymes for chemical conversion; and metamaterials with controlled combinations of mechanical, phononic, electronic, and photonic properties that exhibit optimized mulitiscale morphological control for functional and switchable devices.

Although the scientific challenges associated with identifying and navigating energy landscapes to achieve functional hierarchical matter are immense, the potential impact on science in general and on energy technologies in particular cannot be overstated. Because of the complexities associated with controlling structure at multiple length scales and dynamics over a vast expanse of time scales, synthetic approaches to supramolecular structures and materials currently are conducted largely in a trial-and-error fashion, guided by the chemical and physical intuition of the experimentalist rather than by theoretical or computational models. Theoretical and computational efforts are to a large extent focused on understanding structures or properties of molecules and materials after they have been synthesized. At the same time, because of a growing number of chemical components and experimental parameters, synthesis systems and their associated energy landscapes have become so complex that their full experimental assessment is exceedingly time consuming. As a result, individual researchers mostly focus on specific parameter windows without knowing how and where particularly promising compositions or structures might be found.

Advances in the understanding of reaction energy landscapes may change all this. Progress in this field may allow the generation of synthesis roadmaps that experimentalists could follow as guides, at least for specific classes of hierarchical molecules and assemblies. The development of robust multiscale computational tools may simultaneously allow experimentalists to identify regions of interest in synthesis parameter spaces that will accelerate discovery. Associated process metrology may finally provide researchers with on-line information during synthesis procedures to control reactions toward desired outcomes.

Improved understanding of how to design materials could have a significant impact on energy technology. For example, using self-assembled matter as a way to perform cascade reactions or synthesis could revolutionize both how materials are made and the efficiency of chemical conversions. The identification of scalable cell-free synthesis of chemicals by assembling bio- or bio-inspired machineries into robust systems could lead to fully sustainable synthetic processes. The synthesis of metamaterials from supramolecular assemblies with controlled mechanical, electronic, and photonic properties and property combinations could revolutionize energy storage and conversion devices. Finally, employing self-synthesis of energy relevant matter in hybrid synthetic/biological and entirely synthetic systems, by combining self-assembly with self-replication and selection, could move us closer to the idea of completely synthetic “living” systems.

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5. Interface-Defined Matter

The growth and properties of nanostructured matter are largely defined by the structure, atomic/molecular interactions, and transport behavior of the interfaces. A broad range of nanosizes and nanostructured composite materials exhibit emergent properties that arise directly from the creation of either stable or metastable interfaces. The heterogeneities inherent in these materials typically define persistently metastable interfacial structures, which requires creating and maintaining a balance between thermodynamic and kinetic controls. Designed synthesis of these hierarchical structures requires an understanding both of the dynamics of ions, molecules, clusters, and particles interacting at interfaces and of the relative roles of kinetic stabilization and thermal relaxation. Conversely, the ability of interfaces to modify the energy barriers and the relative stability of structures creates new possibilities for directing the synthesis of matter across length scales, provided those thermodynamic and kinetic controls can be defined.

Current Status and Recent Advances

The synthesis of interface-defined matter has significant overlap with the broad field of nanomaterials and thin film synthesis, in part because interfacial area generally increases as size decreases. More distinctions are needed, however, to understand the key issues in the field. Interface-defined matter can be broadly divided into two major research areas: the synthesis of materials with precisely controlled interfaces, and the use of interfaces as a medium to control the progress and topology of a synthetic reaction. To review this broad field briefly, the types of interface-dominated materials for which control of interfacial structure can be enabling are summarized first. In this section, materials are divided by dimensionality as an organization tool. Next, a range of systems with interfaces that provide a key guiding force for synthetic reactions are considered, with the deposition method for each system used to frame the discussion.

Materials with synthetically derived interfaces

Zero-dimensional (0D) and 1-dimensional (1D) materials. The controlled formation of interfaces is key to 0D and 1D systems. Currently, a nearly unlimited range of nanocrystals and nanorods can be created from materials ranging from insulators, to semiconductors, to metals. Dimensions span the range from single nanometers to microns, and a wide range of shapes and aspect ratios can be created. Within colloidal materials, both core-shell structures and superlattices exhibit unique properties not available in homogeneous, dispersed nanoparticles or wires. Superlattices present the added complexity of particle-particle interfaces that are typically mediated by ligands, which have a significant impact on properties. Ligand exchange approaches have led to novel composite materials[1] that can, for example, provide mixed pathways for electron and ion transport. Ligand-free nanocrystals can also be built into nanoporous networks using templating. In the case of nanowires, the same nanoparticle assembly processes that lead to superlattice formation can generate highly branched nanostructures with high optical absorption cross sections and mean-free paths for photo-induced carriers comparable to or larger than the dimensions of individual branches.[2] In isolated nanoparticles, ligand/particle interactions can profoundly affect shape, faceting, and surface structure, and therefore functionality.[3,4]

Two-dimensional (2D) materials. Traditional approaches to the synthesis of multilayered materials through chemical vapor deposition, molecular beam epitaxy, sputtering, and liquid phase epitaxy go back decades[5]; but recent years have seen significant advances in the extent to which smooth interfaces and compositionally complex materials can be synthesized using these and similar deposition methods. For example, atomic layer deposition (ALD) is now used to create atomically sharp interfaces between dissimilar materials.[6] These advances have led to exquisite control over defect structures at interfaces, enabling, for example, the creation of ultra-high-carrier-density 2D conductors at the interfaces between complex oxide insulators.[7]

The discovery of graphene[8] and its electronic properties as a Dirac solid has opened up a new field of research into true 2D materials, such as molybdenum disulfide and graphene oxide.[9] A wide range of synthesis techniques and approaches to postsynthesis processing have been explored, enabling many interesting characteristics exhibited by these materials to be investigated.[10] These include optical properties, selectivity as membranes for molecular separation,[11] electrochemical activity, and high absorptivity.[12,13] In some cases, these methods take advantage of traditional gas phase deposition approaches; but others include controlled exfoliation of single layers,[8] spin coating to make multilayer membranes, sol-gel methods to form high-capacity porous materials,[12,13] post-growth perforation to create atomic-scale transport channels,[14] and use as substrates for the growth of metal and metal oxide nanoparticles for electrode and catalytic materials.[15] The layers can even be restacked to form designed heterostructures that generate novel functionalities, such as topological insulators.[16]

Porous three-dimensional (3D) networks. Microporous and mesoporous materials are hierarchical framework solids exhibiting interconnected negative space on multiple length scales.[17,18] Through host-guest chemistry, these frameworks often present active sites—atomic, molecular, or nanoparticulate—and the sizes and spatial distribution of both the pores and active sites are controlled by the architecture of the framework. Traditional zeolite-type materials[18,19] have been joined, over the past two decades, first by a broad range of mesoporous SiO_2 and similar compounds,[20] then by metal-organic frameworks (MOFs),[21] and more recently by covalent organic frameworks (COFs).[22] Applications such as catalysts, sensors, electrodes, and gas separation membranes have been widely explored. Mesoporous materials have also been broadly used in energy harvesting and storage and in electrocatalysis. While zeolites, MOFs, and COFs are dominated by metal oxide and organic components, mesoporous silicas have expanded to cover metals, semiconductors, and a nearly unlimited array of complex oxides, mostly in nanocrystalline form.

Dense 3D structures. A broad range of nonporous nanostructured organic, organic-inorganic hybrid, and pure inorganic materials can be produced; and in most cases, their functions depend critically on the nature and extent of interfaces within the extended solid. For example, in excitonic solar cells composed of polymers and small molecules, the morphology of different combinations of small molecules, polymers, and inorganic nanomaterial moieties—which defines performance—depends critically on the ability to design organic-organic or organic-inorganic donor-acceptor interfaces to facilitate charge separation and current generation.[23] A broad range of interface-rich inorganic phases can be formed by gas phase deposition, layer-by-layer growth from solution, and phase separation following high-temperature synthesis. Hybrid interface-rich materials can be produced using solution-phase methods that embed nanocrystals in an inorganic matrix, and a limitless array of interface-rich materials can be produced by combining polymeric hosts with colloidal guests of all types.

Interfaces that drive materials formation

Gas phase deposition. Many years of scanning tunneling microscopy and x-ray reflectance studies have revealed in exquisite detail the physics that drive the growth of thin film heterostructures.[24-26] The relative competition between depositional flux and surface mobility, coupled with asymmetries in probabilities of attachment to growing islands, largely determines morphological evolution.[26] Consequently, temperature plays a major role in film quality.

Organic assemblies at interfaces. Graphoepitaxy is the use of nanostructured templates to direct the assembly of block copolymers at interfaces.[27] Directed self-assembly of block copolymers aims to create large-area, defect-free nanopatterns using a combination of substrate topography and chemistry.[28] By matching the periodicity of the substrate to the characteristic length scale of the block copolymer, amphiphilic diblock copolymers can assemble over large areas. Defining the chemistry or the interface can further direct the assembly.

Materials growth from solution. Historically, achieving high-quality complex materials via solution growth was more challenging than by vacuum-based approaches. More recently the inverse situation has arisen from the increasing importance of organic electronics—both organic LEDs and organic photovoltaics—and the increasing focus on roll-to-roll processing of everything from solar cells to batteries and fuel cells. New techniques for printing at the nanoscale and for creating complex precursors[29] that decompose by design have enabled a significant renaissance in this area.[30] In many of these cases, the nature of the surface significantly defines the quality and the morphology of the growing structure, which can be planar or textured in 3D.[31] A key recent example is the hybrid organic inorganic perovskites, which have demonstrated stunning functionality and nearly equivalent structures by solution or vacuum processing.[32,33] In micro- and nano-printing[34] and in roll-to-roll processing,[35] surface preparation and interface structure and morphology define the structure and properties of the grown layer and, increasingly, those of multilayer stacks.[36]

Functionalized substrates, such as self-assembled monolayers of alkanethiols on gold or silanes on silica, have been used to direct the nucleation of a range of crystalline materials.[31,37-42] The chemistry of the substrate can dictate the polymorph, crystallographic orientation, and morphology of the resulting single crystals or films. The substrate can also mediate the transformation of an amorphous precursor to an oriented crystalline film.[31] In all of these studies, the chemical functionality, as well as the structural arrangement of the substrate, is essential for transferring information to the crystals.[31,37-44]

Growth by oriented attachment. In recent years, the process of crystal growth through nanoparticle assembly[43]—particularly oriented attachment—has been explored through molecular dynamics simulations[45,46]; x-ray scattering[47]; and electron microscopy, both cryogenic- and liquid phase transmission electron microscopy (cryo-TEM and LP-TEM).[48-56] Colloidal physics has a long history; but major knowledge gaps exist regarding the impact of anisotropic crystal structure—both directly on the interaction forces between particles and on the forces mediated by the solvent and solvated ions on particle interactions. Such studies suggest that assembly creates a transient state that in turn separates particles by a solvent barrier, beyond which particles attach because of orientation-dependent attractive forces.[50,51]

In situ characterization. There is a significant body of literature on the formation of interface-defined matter for certain classes, particularly vapor-deposited thin films; nanoparticle superlattices; block copolymer films; and, to a lesser extent, branched nanowires and certain porous frameworks, such as zeolites, MOFs, and COFs.

Compared, for example, with thin multilayer films, little is known about the formation of zeolites, MOFs, and COFs, which have attractive properties for both molecular separation and catalysis. As with most solution processes, especially those that take place at elevated temperatures, the pathways are difficult to access. However, some of the first studies to suggest that inorganic systems can follow two-step pathways were performed on zeolites.[57] Ex situ and later cryo-TEM revealed intermediate amorphous or highly disordered precursors that eventually transform into the ordered state.[58,59] Interestingly, the final products may well be thermodynamically unstable and exist only because of so-called structure-directing agents (SDAs), which impact the interfacial properties by stabilizing the porous network against the solvent. On removal from the growth medium, the solvent and SDAs are eliminated.

Theory and simulation. A single common theme that cuts across the contemporary challenges facing interfacial-defined matter is the need to integrate synthesis and modeling, perhaps even as early as in the design stage of synthesis. This is because modeling can offer important insights into interfacial processes.

These include optimal surface structures for catalytic reactions, adsorbate interactions, and a broad range of insights about the electronic structure of materials. Slab calculations with periodic boundary conditions offer the ability to combine high-level quantum calculations with lower symmetry surface structures.[60] Novel methods to decrease the computation time for fully ab initio methods and new ways to perform mixed quantum-classical simulations are allowing increasingly larger interface-defined systems to be explored theoretically.[61] The inherent complexity and low symmetry of interface-defined matter, however, means that fully predicative modeling remains a challenge to the field.

Scientific Challenges and Opportunities

Several common themes cut across the chemical and structural diversity of interfacial phenomena. The ability to predict the formation of interface-defined matter requires computational methods that capture the molecular details of interfacial structure and predict the impact of those interfaces on interfacial energies, long-range ordering, and defect structures. Many interfaces represent persistent metastable states; consequently, equilibrium calculations may fail to predict their formation or the heterogeneous distributions produced. In the case of nanoparticles, organic constituents play a key role in mediating these interactions, even if these represent sacrificial ligands or scaffolds not present in the final, functional product. Thus, organics inject an added level of complexity into simulations of assembly. In all cases, the formation of the interface involves charge, mass transport, or both, as well as chemical reactions that are controlled at some level by the symmetry of the interface and the distribution of defects at which mismatches occur, in either the structure or chemical potential.

For the growth of thin film multilayers, the development and evolution of defect structures at the interfaces of dissimilar materials are still poorly understood and difficult to predict, despite often being the source of functionality. In the case of zeolites, MOFs, and other framework materials, the chemical reaction networks that lead to rather complex growth units and hierarchical unit cells are ill-defined and very difficult to sample.[59] In situ nuclear magnetic resonance spectroscopy may provide a tool for mapping these pathways in the future.[62] For nanoparticle assembly, the structuring of the solvent and ions in the interfacial region between nanoparticles—as well as the nature of the forces that both transiently separate nanocrystals and eventually drive OA events—are poorly understood.[43] Finally, the formation of hierarchical materials, for example through growth of clusters on complex substrates, often depends on the presence of poorly characterized defects. In the case of formation of hierarchical materials through growth of metal clusters and nanoparticles on 2D materials and other substrates, atomic-force microscopy is beginning to provide the kind of information that scanning tunnel microscopy provided for vapor-deposited films in the past.[63] However, the interpretation of results from all in situ techniques requires multiscale computational tools to build a predictive understanding of the nucleation and growth processes.

A key challenge is that synthetic methods with a strong kinetic component, such as solvothermal reactions, templation, or assembly, are hard to control and not necessarily transferrable or scalable. Traditional screening approaches to iteratively improve performance are therefore nonviable. Basic research that addresses the development of virtual screening methods and how to understand surface adhesion is necessary to advance this field further. Modeling and in situ characterization to understand interfacial phenomena controlled by adsorbate-surface, adsorbate-adsorbate, and adsorbent-substrate interactions are needed. Once specific materials are targeted by virtual screening, then robust synthetic approaches that are effective outside equilibrium conditions are needed. Even reactions that are as straightforward as ion exchange are not fully understood. In addition, in many cases, high selectivity is required, as competing cations can be within tenths of angstroms in size difference, have the same oxidation state, and have other similar properties, such as bonding energies.

To address the challenges described, the panel recommends two primary emerging research challenges: (1) Achieve the synthesis of multifunctional hierarchical materials by design with precise control over interfacial structure and composition across all scales and (2) exploit interfaces as drivers of synthesis for both stable and metastable matter by understanding and predicting interface-controlled pathways and barriers.

Achieve synthesis of multifunctional hierarchical materials by design with precise control over interfacial structure and composition across all scales

Nanostructured materials are rich in interfaces, but our current ability to precisely control interfacial structure does not match our ability to manipulate either the atomistic structure of materials or their nanoscale architecture. In this PRD, we describe a number of classes of materials systems in which precise interfacial control could be achieved. These include assemblies of atomistically precise molecular and nanocrystal building blocks, bulk and porous materials with postsynthetic modification, and flexible porous networks. Because of the complexity of molecular interactions at interfaces, theoretical studies are key to designing new materials with optimized interfacial structure.

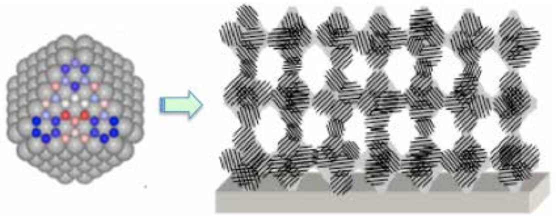

Figure 21. Schematic showing distinct surface sites on a nanocrystal surface (*left*)[64] and their assembly into a large-scale hierarchical structure (*right*)[65] **|** *[Left] From X. Huang et al. "High-performance Transition-metal Doped Pt_3Ni Octahedra for Oxygen Reduction Reaction." Science 348[6240]: 1230–34. DOI: 10.1126/science.1118765. Reprinted with permission from AAAS.* **|** *Reprinted with permission from I. E. Rauda et al. "General Method for the Synthesis of Hierarchical Nanocrystal-Based Mesoporous Materials." ACS Nano 4 [6]: 6386–99. © 2012 American Chemical Society.*

Precise structural and chemical control of interfaces. Precisely controlling the interfacial structure and composition of individual nanoscale or molecular building blocks in large-scale hierarchical 3D networks is critical to developing future generations of materials for energy applications. On a nanoscale surface, there are distinct active sites dependent on local bonding and the coordination environment (Figure 21).[64,65] Consequently, the capability to precisely place individual atoms and functional groups on a building block and to control their distributions in extended hierarchical structures is of paramount importance (Figures 21–22).

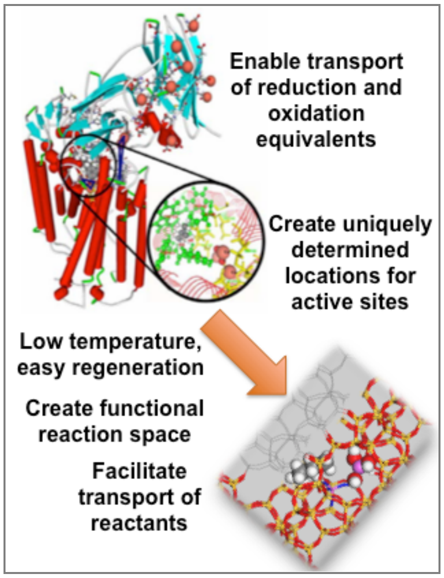

Figure 22. Translating design principles seen in enzymes into inorganic materials could enable synthesis of catalysts that exhibit high activity and selectivity near ambient temperature. **|** *Image courtesy of Bruce Garrett*

To achieve this lofty goal, effective synthesis approaches need to be developed for different reaction environments, including solution-phase, gas-phase, and solid-phase reactions. The synthesized building blocks should possess dimension-dependent corner, edge, and crystal facet sites so surface atoms with controlled coordination numbers and surface energies can show distinctive interfacial properties. Assembly approaches also need to be developed to integrate nanocrystal and molecular building blocks into larger-scale hierarchical network structures with tight control of size, shape, and spacing (Figure 21).[65] Directed interfacial interactions between building blocks—such as corner-corner, edge-edge, or face-face interactions—can be explored not only for the formation of oriented networks of the building blocks but also for tuning the chemical interaction strength between any two building blocks. These would provide a unique way of fabricating functional materials with tunable physical and chemical properties. For example, the controlled assembly of magnetic building blocks may yield a magnetic network with the magnetization direction of each building block aligned in one direction, creating a strongly anisotropic magnetic material.[66] A network of plasmonic nanoparticles may facilitate the tuning of the interparticle spacing to achieve maximum plasmonic absorption at the nanoparticle junctions.[67-69] Similarly, if the building blocks are catalytically active, oriented arrays of these building blocks may become the best type of catalyst system, with the active sites precisely placed to achieve maximal catalytic activity and selectivity.[70]

Biology provides even greater inspiration for creating hierarchical materials with multiple functionalities to enable emergent phenomena that are more than the sum of the actions of individual functionalities.[71] For example, enzymes use the constrained space of active sites, the multifunctionality of active sites, and channels of designed size to transport reactants in order to allow chemical transformations at ambient temperature and pressure (Figure 22). Therefore, achieving predictive design and synthesis of inorganic systems that incorporate these bioinspired principles is promising for translating enzymatic principles to practical catalysts. Highly efficient energy flow or charge transport pathways observed in biological systems[72] may also be adopted and applied directly for applications in solar energy harvesting and electrochemical transformations. The ability to create multifunctional surfaces and interfaces at will and across length scales will pave the way to design robust synthetic materials that will leapfrog current materials to impact future energy technologies.

Synthetic control of interfaces: Postsynthetic modification (PSM). One method of controlling interfaces formed during synthesis is via PSM methods conducted on a metastable phase. PSM enables the transition of a metastable phase into a novel metastable phase via various interface modifications, transformations, and at times destructions. Examples of three innovative methodologies for interface postmodification to synthesize novel metastable materials are described below.

The first innovative method is the creation of new interfaces via phase transformations in existing materials. For example, in an effort to design multifunctional materials, the surface structure and composition of hierarchical structures such as nanoparticle superlattices and composites or nanoporous material have been modified to exhibit enhanced surface area and functionality. The use of post-synthetic etching of zeolites with fluorides (HF and NH_4F) to create mesoporosity via etched interfaces illustrates this approach. The result is an enhancement of catalytic conversion of methanol (Figure 23).[73] In this study, SAPO-34 zeolite crystals were etched in a fluoride medium. The interface between the crystalline domains was dissolved, yielding a hierarchical material with a system of straight intersecting mesopores that improve the access to micropore space. As a result, the cumulative MeOH catalytic conversion over this modified zeolite was improved by nearly 100% versus the parent zeolite.[73]

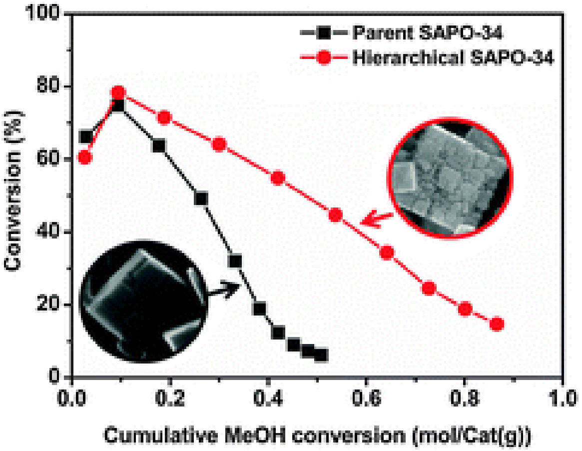

Figure 23. Fluoride-treated zeolites show enhanced catalytic activity compared with the pristine material.[73] | *Reproduced with permission of The Royal Society of Chemistry from X. Chen et al. 2016. "The Preparation of Hierarchical SAPO-34 Crystals via Post-Synthesis Fluoride Etching." Chemical Communications 52 [17]: 3512–15.*

The second innovative method is the chemical modification of interfaces and surfaces for site-specific functionality. In this case, the original interface of a material can be a standard 2D surface or buried interface, or it can be the interior surface of a 3D pore system (e.g., a pore of a MOF, a zeolite, or another mesoporous material). For example, the internal surface of mesoporous titania can be transformed into a multifunctional material through grafting, similar to the addition of light-adsorbing chromophores for dye-sensitized solar cells.[74] This approach may also provide a means of improving poor interfaces, which can be a source of failure as, for example, in the case of Cu_2ZnSnS_4 devices (Figure 24)[75] in which defects at grains and contacts form recombination centers that result in short-circuit currents. A fundamental understanding of how to use PSM via chemical modification to create high-quality interfaces could lead to significant improvements in device performance, such as power conversion efficiency in Cu_2ZnSnS_4 thin film solar cells.

Another example is the chemical modification of 3D pores, including ordered pore systems. In this way, new function can be created in materials by combining disparate properties at the interfaces. For example, covalent bonding between metal centers at MOF internal pore interfaces and trisradical rotaxanes creates an array of artificial molecular switches based on mechanically interlocked molecules within the porous crystalline framework (Figure 25).[76] Once arranged within the pores of the framework, the electronic state of the switches can be altered by the application of an electrochemical potential.

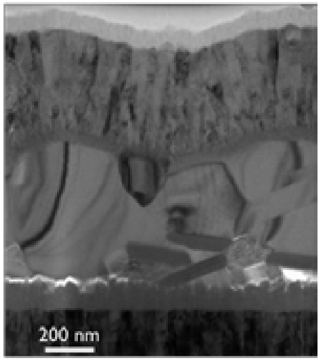

Figure 24. An example of interface failure, here at a Cu_2ZnSnS_4-substrate interface.[75] **|** *Reproduced with permission of AIP Publishing from K. Wang et al. 2011. "Structural and Elemental Characterization of High Efficiency Cu_2ZnSnS_4 Solar Cells." Applied Physics Letters 98 [5].*

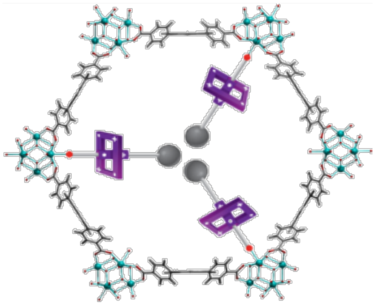

Figure 25. A rotaxane covalently linked to a MOF pore.[76] **|** *Adapted with permission of the National Academy of Sciences from P. R. McGonigal et al. 2015. "Electrochemically Addressable Trisradical Rotaxanes Organized within a Metal-Organic Framework." PNAS 112 [36]: 11161–68. DOI: 10.1073/pnas.1514485112.*

This approach has also produced materials for enhanced separations. In particular, the adsorption of polar molecules on the surface of a MOF at the metal centers enables the transformation of the overall framework from hydrophilic to hydrophobic. This "switching" of the interface enables the design of very specific sorption properties in sorption materials. Two examples include the transformation of hydrophilic Cu-BTC to hydrophobic frameworks: Cu-BTC@ perfluorohexane[77] and Cu-BTC@I_2, which enables enhanced I_2 fission gas sorption from humid streams (Figure 26).[78]

The third innovative method for interface PSM is to use interfaces as templates and scaffolds for enhanced functionality. The synthetic approach then combines the effects of nanoscale architecture, surface area, surface composition, and surface bonding, leading to novel layers and membranes. One biologically inspired example is that of enhanced transport through membranes via biological mimics of porins. In this case, carbon nanotubes are functionalized with lipids; the functionalization of the carbon nanotube allows for its chemical insertion into a biomembrane (Figure 27).[79]

Figure 26. Example of selective sorption in surface functionalized MOFs.[78] **|** *Reprinted with permission from D. F. Sava et al. "Competitive I2 Sorption by Cu-BTC from Humid Gas Streams." Chemistry of Materials, 25 [13]: 2591–96. DOI: 10.1021/cm401762g. © 2013 American Chemical Society.*

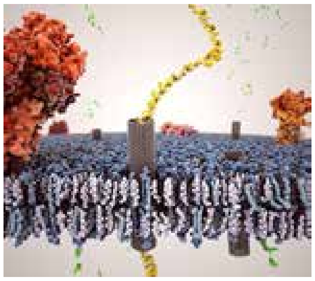

Figure 27. An example of a chemically functionalized carbon nanotube in a lipid membrane.[79] **|** *Image courtesy of Lawrence Livermore National Laboratory*

Synthesis of materials that exhibit stimuli-responsive interfacial properties. Stimuli-responsive materials (SRMs) are a class of materials that adapt to changes in their surrounding environment through structure changes, property changes, or a combination of both. In many cases, these changes are dramatic and are induced through interfacial phenomena such as exposure to small molecules at solid-gas or solid-solution interfaces, light, magnetic field, or change in temperature. SRMs are broad in scope in terms of both their composition and their applications: they cover all classes of materials from organic polymers to composites to purely inorganic solids such as zeolites; they have potential utility in sensors, gas storage, microfluidics and integrated circuits.[80-83] However, despite a growing body of literature on SRMs, there remains a need to design and study whole new classes of SRMs to enable the fabrication of devices based on them. Given the very nature of SRMs and their potential applications, learning how to control interfaces between SRMs and their environment (i.e., how to control stimuli-responsive interfaces) is critical to their design, synthesis, and performance. Several examples of SRMs are discussed below that illustrate their diverse range of composition and applications and why these are critical to understanding interfacial phenomena.

Stimuli-responsive molecularly imprinted polymers (SR-MIPs)[81] combine stimuli-responsive behavior with molecular imprinting. Therefore, these polymers not only respond to external stimuli but also can exhibit molecular recognition when they retain a binding site with a structure similar to that of the imprinting state. The release and adsorption of molecules can be achieved through external stimuli, such as changes in temperature, pH, or light. Figure 28 illustrates how a thermo-responsive polymer loses its ability to bind a molecule when it passes a critical temperature known as the low-critical solution temperature. This binding ability can be regained when the temperature returns below the low-critical solution temperature. Figure 28 [81,84] also illustrates how flexible porous coordination polymers can bend and flex when subjected to pressure changes. Such materials exhibit the regularity of inorganic materials and the flexibility of organic polymers, meaning that they undergo dramatic mechanical transformations when stressed by pressure or temperature. While zeolites can also exhibit flexibility, that seen in coordination polymers can be much greater. The first examples of flexible coordination polymers were discovered in the 2000s,[82,83] but they were considered to be a scientific curiosity. However, it has recently been demonstrated that these systems offer great potential for gas storage, specifically natural gas storage, because they can exhibit a much bigger working capacity than rigid porous materials.[84] Two other examples of SRMs are illustrated in Figure 29. Catalysts based on gold nanorods that are semi-coated with two TiO_2 nanoparticles[85] can exhibit visible light–driven photocatalytic behavior in the context of hydrogen production from water (Figure 29). Materials with wettability that can be chemically controlled are exemplified by hydrogels that exhibit switchable wettability (Figure 29).[80,85] These SRMs have applications in many fields, including microfluidic devices, drug delivery, capture and release of cells, separation of water and oil, and detection of biomolecules.[80] A major challenge to further development of

SRMs is that the specific conditions under which interfacial changes trigger the response to a stimulus occurs is critical to applications, but in general there is very little understanding of the drivers for the response.

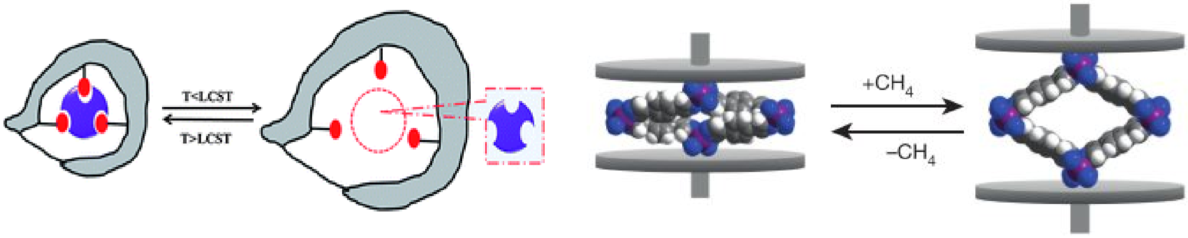

Figure 28. Thermal volume change on analyte binding in a stimuli-responsive molecularly imprinted polymer (*left*).[81] Reversible pressure-induced structural change occurs in a flexible porous coordination polymer (right).[84] **|** *[Left] Reproduced with permission of The Royal Society of Chemistry from S. Xu et al. 2013. “Stimuli-Responsive Molecularly Imprinted Polymers: Versatile Functional Materials.” Journal of Materials Chemistry C 29: 4406–22.* **|** *[Right] Reprinted by permission from J. A. Mason et al. “Methane Storage in Flexible Metal-organic Frameworks with Intrinsic Thermal Management.” Nature 527: 357–61 DOI: 10.1038/nature15732. © 2013 Macmillan Publishers.*

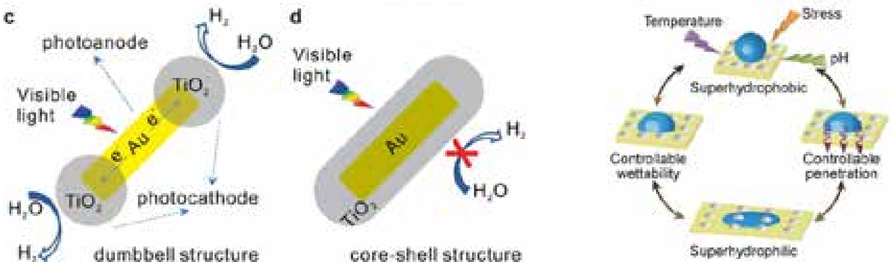

Figure 29. Light-driven surface reactivity in a dumbbell shape nanostructure (left).[85] Stimuli-responsive surface of a hydrogel can enable chemically switchable wetting (right).*[80] **Online Abstract Figure* **|** *([Left] Reprinted with permission from B. H. Wu et al. “Anisotropic Growth of TiO2 onto Gold Nanorods for Plasmon-Enhanced Hydrogen Production from Water Reduction.” Journal of the American Chemical Society 138 [4]: 1114–17. DOI: 10.1021/jacs.5b11341. © 2016 American Chemical Society.* **|** *[Right] Reprinted with permission from X. Huang et al. “Stimuli-Responsive Surfaces for Tunable and Reversible Control of Wettability.” Advanced Materials 27: 4062–68. DOI: 10.1002/adma.201501578. © 2015.*

Synthetic control of interfaces: Iterative synthesis, characterization, and modeling. New approaches to synthetic processes will dramatically accelerate the development of advanced functional materials and interfaces. One critical component is the implementation of synthetic methods that use an iterative synthesis, characterization, and modeling loops. This strategy exploits key synergistic opportunities present only when feedback between these areas is present. In situ characterization techniques that probe the formation of stable and metastable species will provide critical feedback for the optimal conditions to synthesize and isolate desired products. Computational modeling based upon existing materials and interfaces is beginning to be effective at predicting materials and interfaces in silico that have desired properties and can be used to direct the synthesis of new materials and interfaces with improved properties. Two promising examples of the iterative synthesis, characterization, and modeling process that resulted in synthesis of new interface-defined materials with improved properties are highlighted below.

Crystalline nanoporous materials have provided several notable examples of the benefits of the synthesis, characterization, modeling loop; and it is critical for performance to understand and control the interface between the guest and host of such materials. For example, $[Cu(4,4'\text{-bipyridine})_2(SiF_6)]_n$ (SIFSIX-1-Cu) is a MOF that exhibits highly selective CO_2 uptake.[86,87] Computational modeling that revealed the key interactions for the high selectivity also predicted that chemical substitution of the hexafluorometalate (MF_6^{2-}) metal centers would enhance selectivity. When the SiF_6^{2-} was replaced with TiF_6^{2-} or SnF_6^{2-}, the new MOFs exhibited much higher selectivity.[88] As a test of the accuracy of the modeling, the most probable positions of CO_2 adsorbed in the TiF_6^{2-} variant were predicted from simulations and compared with x-ray diffraction measurements. As seen in Figure 30,[89] the agreement between the modeling and experiment is excellent.

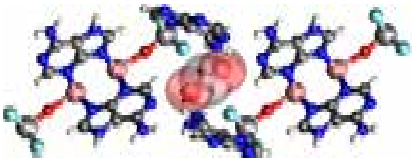

Figure 30. Location of CO_2 in TiF_6^{2+} predicted from simulations (ball and stick) and measured from x-ray diffraction (transparent spheres).[89] **|** *Reprinted with permission from T. Pham et al. "Theoretical Investigations of CO_2 and H_2 Sorption in Robust Molecular Porous Materials." Langmuir 32 [44]: 11492–505. © 2016 American Chemical Society.*

These highly CO_2-selective MOFs can be used for CO_2 capture, but there is a complementary need to design materials for CO_2 conversion. Periodic density functional theory has been used to identify catalytically active functional groups that can be incorporated into MOF linkers for reduction of CO_2 with H_2.[90,91] Calculations identified trends showing how reaction barriers for CO_2 hydrogenation change for relatively simple descriptors. A MOF with the surface-bound catalytic moiety is shown in Figure 31,[90] along with the trend in the barrier for the second step of the $CO_2 + H_2$ à HCOOH reaction. These calculations identified promising candidates, reducing the time needed to develop new materials by focusing on the functional groups with the highest probability of success.

These crystalline materials represent current success stories, but the last example exemplifies a future direction for the field. Interfaces of rigid crystalline materials can now be effectively modeled, but materials with significant conformational flexibility still present a significant challenge. A straightforward example is found in the field of energy conversion based on low-cost organic photovoltaic devices. The functioning of these devices critically depends on the controlled creation of donor-acceptor interfaces that can facilitate excited-state charge transfer in hybrid organic-organic and organic-inorganic materials synthesized by a variety of strategies. Because fullerene derivatives (Figure 32)[92] are spherical, their orientation at donor-acceptor interfaces in current polymer solar cells is invariant and supports isotropic charge transport. Primarily for this reason, fullerene derivatives are the acceptors of choice for most organic photovoltaics. However, a variety of promising new electron acceptors exemplified by DBFI-Ar are highly anisotropic (Figure 32),[93] which suggests that coupling of modeling and characterization with synthesis will be essential to achieving optimal molecular orientations at donor/acceptor interfaces and ideal photo-conversion in next-generation hybrid photovoltaic materials.

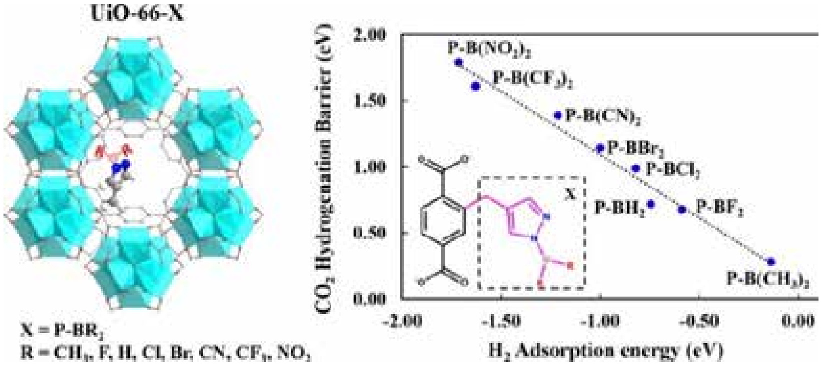

Figure 31. View of UiO-66 with a functional group (ball and stick model) shown bound to a linker (*left*). Results of computational modeling showing the relationship between H_2 binding energy and CO_2 hydrogenation barrier.[90] **|** *Reprinted with permission from J. Y. Ye and J. K. Johnson. "Screening Lewis Pair Moieties for Catalytic Hydrogenation of CO_2 in Functionalized UiO-66." ACS Catalysis 5 [10]: 6219–29. DOI: 10.1021/acscatal.5b01191. © 2015 American Chemical Society.*

Whereas the first emerging research challenge and the examples presented address the importance of interfaces in creating energy-relevant functions, the second challenge focuses on the use of interfaces to drive synthesis:

Exploit interfaces as drivers of synthesis for both stable and metastable matter by understanding and predicting interface-controlled pathways and barriers

Many energy technologies—ranging from catalysts to solar photovoltaics and solid state lighting, to electrochemical devices such as batteries and fuel cells, to smart building materials and advanced structural composites[94-98] —are critically dependent on interfaces for growth, as well as definition of their subsequent function. These technologies require processing of large active areas, necessitating the ability to achieve uniform growth of a range of molecules, crystals, and amorphous solids at interfaces. Interfacial control over synthesis of inorganic, organic, and hybrid matter can create more efficient, higher-yield processing, and it can lead to more reliable and stable materials with enhanced functionality.

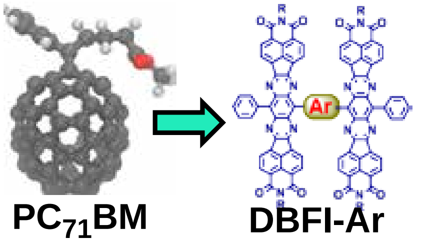

Figure 32. Ball and stick model of PC$_{71}$BM-fullerene (*left*)[92] and the molecular structure of DBFI-Ar (*right*).*[93] | *[Left] Reprinted with permission from M. Williams et al. "Influence of Molecular Shape on Solid-State Packing in Disordered PC$_{61}$BM and PC$_{71}$BM Fullerenes." Journal of Physical Chemistry Letters 5 [19]: 3427–33. © 2014 American Chemical Society. [Right] Reprinted with permission from Y.-J. Hwang et al. "Nonfullerene Polymer Solar Cells with 8.5% Efficiency Enabled by a New Highly Twisted Electron Acceptor Dimer." Advanced Materials 28 [1]: 124–31. © 2016 John Wiley and Sons.*

The first critical interface is the substrate on which functional matter and, ultimately, devices are created through a variety of synthetic approaches ranging from solution growth to vapor deposition to solid-state transformations. The current understanding of the complex interplay between kinetics and thermodynamics of reaction processes at interfaces remains rudimentary. There is a need to bridge this knowledge gap to enable a new generation of materials- and molecules-by-design. Enabling the synthesis of a broad range of materials classes requires a predictive understanding of key aspects of interface-directed growth.

Research needs. Achieving predictive interface-driven synthesis requires a three-pronged approach: (1) the characterization and understanding of the chemistry occurring at interfaces and the subsequent transformation of matter to the final state under actual synthetic conditions; (2) the development of predictive models of the structure, and subsequent assembly and growth of new molecules and materials at the interface, including potential ordering across multiple length scales; and (3) the integration of the knowledge gained from the first two research directions to develop a suite of design rules capable of supporting current and future growth approaches based on interface-driven growth. When successful, this predictive understanding will lead to a transformative leap in the synthesis of new metastable and equilibrium functional matter–enabled through active interfacial control.

Characterize and understand the interface. To predictively direct synthesis at interfaces will require a much higher level of understanding about interfaces than is currently available, including the structure and chemistry of the interface, the surface energy, and defect structures. In addition, a much more complete understanding of the dynamic nature of the interface under actual synthetic conditions (e.g., supersaturated solutions or vapors) is needed to fully understand interfacially induced morphology and electronic structure. This understanding will include the nature of initial precursor-interface interaction; consequently, this will be inherently process dependent. If an in-depth understanding of these interfacial processes can be developed across various synthetic approaches from solution to vacuum, then an additional set of design rules can be established, pointing to an appropriate interface-driven approach to synthesis for a particular functional molecule or material. In many cases, the initial deposition creates metastable structures or phases, which can be used as is or transformed across the energy landscape to produce other metastable and stable phases. These include increasingly ordered phases, so understanding the nature of interface-stimulated transformations is crucial. This question can be as simple as what is the mechanism of induced nucleation at interfacial defects or potentially as complex as how do 3D hybrids grow from templated interfaces. Finally, it will be important to understand the detailed relationship between the interface and the endpoint materials, as this feature will be important in defining the functionality, stability, and reliability of the final material. Achieving this deeper understanding of the static and dynamic nature of reactive interfaces will require the development of new in situ/in operando probes. A number of tools can be envisaged in this role, but they will need to probe both long- and short-range order and defects, as well as the chemical and electronic properties of the interface. In certain cases, an understanding of the mechanical properties of the interface is also desirable. Recently, a number of studies have demonstrated the ability to use in situ techniques, including TEM, Raman, atomic-force microscopy, and x-ray scattering to examine interfacial processes dynamically.

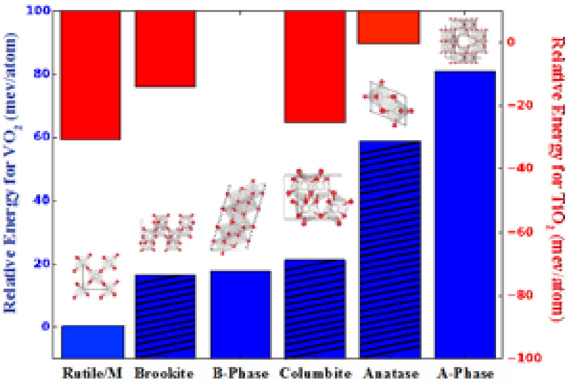

Figure 33. To estimate the accessible window of metastability, the calculated relative formation energies of various polymorphs in TiO_2 (red) and VO_2 (blue) were compared. The lowest-energy structure (anatase for TiO_2 and rutile for VO_2) is used as the reference state. Dashed bars indicate the polymorphs that have not been synthesized.[99] | *Reprinted with permission from H. Ding et al. "Computational Approach for Epitaxial Polymorph Stabilization through Substrate Selection." ACS Applied Materials & Interfaces 8 [20]: 13086–93. DOI: 10.1021/acsami.6b01630. © 2016 American Chemical Society.*

Create predictive computational models of structure, assembly, and growth at interfaces. Recent work has shown there are many interfacial relationships that must be included in the development of a predictive model with broad applicability for the active participation of an interface in synthesis. In many cases, the interface directly acts as a geometric and chemical template during growth, and it is important to capture the topotactic relationships in combination with the active chemical interaction with the precursors. Figure 33 illustrates the energy manifold of polymorphs for VO_2 and TiO_2 showing the known and unknown polymorphs, some of which have potential applications in photocatalysis and smart windows.[99] Templating within a synthetically accessible range may enable the selection of existing or discovery of new functional polymorphs.

Predictive models must directly couple the surface energy landscape with that of growth. The surface modifies the energy landscape of nucleation and growth, can direct the assembly of solution or vapor phase clusters, and can enable transformations of initial solid precursors to a final functional material. To truly develop a model that provides enough understanding to generate predictive design rules requires a detailed dynamic understanding of the coupling, geometrically and chemically, between the interface and desired molecule or material. This task will require building predictive models based on improved interfacial theory and foundational in situ characterization. This information will enable prediction of the assembly and transformation processes during growth. Ultimately this research will lead to the creation of computational models of interface structures, including defects across multiple length scales and their effects on the subsequent order, structurally and electronically, of the synthesized material—including the processes of adhesion, nucleation, growth, and transformation. An example of the potential of such an approach is shown in Figure 34, which illustrates a theoretically informed course-grained model of dynamic self-assembly that was developed to predict pattern formation by a diblock copolymer on a patterned surface.

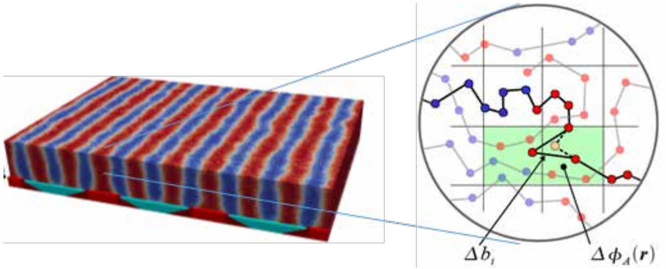

Figure 34. Prediction of block copolymer structure based on coarse grain model of dynamic self-assembly. **|** *Image courtesy of P. Nealey and J de Pablo*

Formulate design rules and innovative approaches for interface-driven synthesis. Once the characterization and modeling described are developed, the community will gain a predictive understanding of the role of interfaces in synthesis that is sufficient to create a set of computationally usable design rules for predicting synthetic outcomes in increasingly complex systems. This knowledge can potentially be applied to direct the formation of new computationally predicted compounds and materials. The outcome not only will enable new forms of matter but also could enable their low-cost processing. This approach potentially can incorporate diverse synthetic methods and precursor chemistries, pointing the way to an optimum synthetic approach and predicting key parameters. The goal is a more universal model of synthesis that includes surface- and interface-driven formation. This understanding will also allow predictive design of complex architectures from surfaces, specifically including the 3D ordering of complex and hybrid materials driven from a 2D interfaces, as shown schematically in Figure 35. Ideally, these models will also permit the design of substrates that significantly enhance the chances of obtaining the predicted outcomes (e.g., new crystalline materials with well-defined textures, new molecular structures, new polymorphs, new hybrids with persistent long-range order). Through the coupling of chemically and structurally selected substrates and precursors (e.g., clusters in solution or vapor) with specific deposition approaches, targeted materials can be obtained via interface-driven transformations of solid-state precursor phases into the desired functional materials. Hence, 2D information can be propagated into 3D materials. Ultimately, this model will require developing a much more thorough and predictive understanding of the interface, including its morphology, surface energy, bond structure, and interactions with ions and precursors arriving from diverse sources.

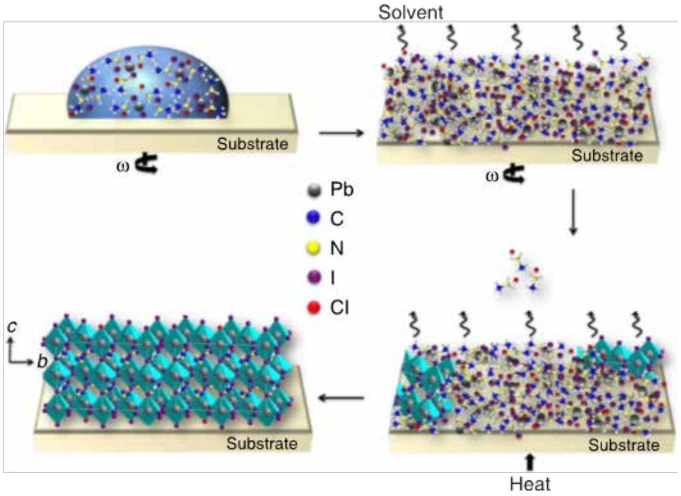

Figure 35. Example of a complex formation process of a hybrid organic-inorganic perovskite thin film. Ion-complexes in solution deposit onto a substrate, solvent evaporation leads to the formation of a crystalline precursor, and a solid-state transformation leads to the desired perovskite.[33] **|** *Reprinted by permission from W. Zhang et al. "Ultrasmooth Organic-Inorganic Perovskite Thin-Film Formation and Crystallization for Efficient Planar Heterojunction Solar Cells." Nature Communications 6, Article ID 6142. DOI: 10.1038/ncomms7142. © 2015 Macmillan Publishers.*

An example of complex growth pathways directed by interfaces has been described for the growth of hybrid methyl ammonium lead iodide films, which have gained interest as photovoltaic materials (Figure 35).[33] Interestingly, solution growth of $CH_3NH_3PbI_3$ thin films and physical vapor deposition growth both produce similar materials with spectacular transport properties. In solution growth, a crystalline solid-state precursor film undergoes structural and chemical transformation to a fully crystallized perovskite thin film. The texture of the film depends on substrate chemistry and structure.

Design rules will also allow a more intimate coupling of morphology and functionality. A potential example is shown in Figure 36,[100] which shows step edges on interface generate dislocation spirals in Bi_2Se_3 with cores that may support topologically protected 1D states,[100] which could substantially improve thermoelectric properties.

Finally, there is the grand challenge of trying to develop design rules for creating materials with less and less long-range order to the limit of the amorphous state. Amorphous materials are of increasing interest as functional materials,[101,102] substrates, and precursors to be transformed into more crystalline materials. While these materials are becoming ubiquitous in everyday life (e.g., in displays for phones and tablets), developing predictive models and design rules for their synthesis remains a significant challenge. Properly designed substrates could play an important role in kinetic stabilization of amorphous phases to prevent transformation to crystalline phases. There is a need, therefore, for a significant improvement in understanding the structure-property relationships and creation of a computational framework for amorphous materials. This is a key step on the way to predictive growth of functional amorphous materials.

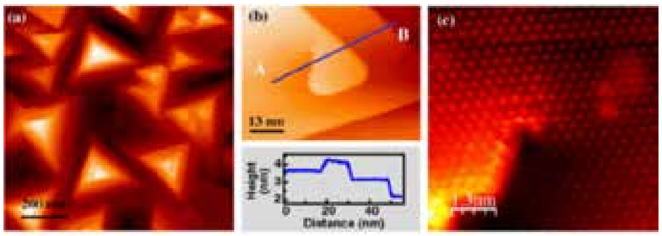

Figure 36. (a) A scanning tunnel microscopy image of a 30 QL Bi_2Se_3 film grown on epitaxial graphene/SiC taken at room temperature, showing the formation of spirals (It = 0.79 nA, Vs = −0.047 V). (b) Close-up view of a spiral, and line profile across AB (It = 1.17 nA , Vs = −1.70 V). (c) Atomic-resolution image of the spiral core taken at 78 K, showing a step originated from the spiral core in the center of the image (It = 1.30 nA, Vs = 1.10 V).[100] | *Reprinted figure with permission from Y. Liu et al. (2012) "Spiral Growth without Dislocations: Molecular Beam Epitaxy of the Topological Insulator Bi_2Se_3 on Epitaxial Graphene/SiC(0001)." Physical Review Letters 108 [11], Article ID 115501. © 2015 American Physical Society.*

Potential for Energy Relevant Technologies

The insights and capabilities that result from overcoming these scientific challenges and realizing the opportunities will provide the foundational science for two technological vectors of importance to energy technology. The first vector is energy relevant functionality, and the second is energy-efficient scalable approaches to the synthesis of complex matter.

Catalysis. The entire field of heterogeneous catalysis—from hydrocarbon cracking to CO_2 reduction to water splitting—is dependent on control over interfacial composition, structure, and surface area. Specific materials systems vary dramatically, encompassing highly ordered microporous materials such as zeolites and MOFs,[17-19,21,22] nanocrystals and nanocrystal arrays,[73] and exfoliated phases.[9,19] Catalysis researchers in these fields share many common synthetic goals. These include (1) precise control of atomic composition, bonding geometries and oxidation states at surfaces to control surface reactivity, selectivity, and efficiency; and (2) a need for the highest possible surface areas to facilitate many slow reactions in parallel. Separation and sequestration are technologies that share many of the same issues.

Energy harvesting. While "interface-defined materials" may initially conjure images of porous or particulate materials like those described earlier, buried interfaces within nanostructured solids play a key role in many energy harvesting technologies. For example, low-cost excitonic solar cells function entirely through networks of buried donor-acceptor interfaces.[103] These interfaces can be organic-organic (e.g., polymer/fullerene photovoltaics), organic-inorganic (e.g., dye sensitized solar cells), or inorganic-inorganic (e.g., quantum dot solar cells). Key synthetic parameters are energy levels at the interfaces (both absolute energies and gradients), electron or hole transfer barriers at those interfaces, and the interfacial area.

Thermoelectrics. Thermoelectric materials, which can be used to convert waste heat to useful energy, present another interesting challenge for interface-defined matter; these materials share some of the same issues as photovoltaics but many opposite constraints. In addition to a high Seebeck coefficient, which is the material-specific property most easily controlled by doping, thermoelectrics require high electrical conductivity and low thermal conductivity.[104] The synthetic challenge is to make solid state interfaces that are invisible to electron flow, allowing current to move freely through the material, but are highly scattering to phonons, producing a low thermal conductivity. Current synthetic methods include the fabrication of multilayer, nanowire, and particulate-derived materials to create functional materials in which buried interfaces play a key role. In a field dominated by reactive interfaces, the need for perfect interfaces in this system stands out.

Electrical energy storage. Interface-defined materials play a key role in electrochemical energy storage. Although batteries are generally considered bulk systems with micron-sized grains, a new generation of interface-defined energy storage materials is appearing in the form of supercapacitors and pseudocapacitors.[105] Traditional electric double layer capacitors (EDLCs) depend almost entirely on the amount of electrifiable interface area exposed to the electrolyte to determine the capacity, with high-surface-area nanomaterials like graphene producing dramatic improvements in energy density.[106-108] EDLCs offer both higher power and longer cycle life than traditional batteries. Pseudocapacitors are redox-based systems, more like batteries, with higher energy densities than EDLCs. Redox reactions in pseudocapacitors generally occur at the surface or in the near-surface regime of a material. In some cases, the capacitive energy storage regime may penetrate several tens of nanometers into a material, resulting in fast cycling of a nanophase system in a process termed “intercalation pseudocapacitance.”[109] Synthetic challenges include simultaneous control of surface area, network connectivity, crystal structure, redox activity, and electrical conductivity.

Purification and separations. Purification of commodities currently uses 10% of the world’s supply of energy, and the percentage is projected to increase if reliance on existing methods like distillation continues. For example, the largest-scale industrial process for an organic commodity is ethylene production (150 million t/y), and removal of acetylene from ethylene is very energy-intensive.[110] Water desalination currently provides water for only 1% of the world’s population; but it has been projected that water scarcity will impact 14% of the world’s population by 2025, dramatically increasing the demand for this energy-intensive process.[111] Postcombustion carbon capture is touted as a solution to greenhouse gas emissions, but current methods based on chemical capture by liquid amines cost ~30% of the energy produced by a power plant.[112] Advanced porous materials offer the potential to significantly reduce energy costs associated with commodity purification by improving selectivity toward the target commodity or its impurities. The potential in this area can be realized only by molecular-level understanding of the forces that define selectivity and by designing new porous materials that offer new benchmarks for selectivity.

Gas storage. Methane (natural gas) is likely to be a source of energy in the future because of its abundance and lower carbon footprint. Natural gas is highly volatile, and current storage and transportation technologies rely on liquefaction or compression, which are both energy-intensive. Adsorbed natural gas offers the possibility of high-energy-density storage at lower pressures; however, problems remain with working capacity and delivery.[113] Hydrogen gas is another important gas storage opportunity, but the problems of uptake and working capacity are exacerbated further because hydrogen is even more volatile than methane. Flexible materials that switch between fully closed (nonporous) and open phases (highly porous) can potentially address some of these problems.[84]

These applications appear disparate, but all require understanding, characterizing, and controlling interfaces, including all or some of the physical, chemical, and electronic properties. The key synthetic challenge of developing predictive methods to control interfacial function remains.

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6. Crystalline Matter: Challenges in Discovery and Directed Synthesis

Crystalline inorganic solids make possible the optical, electronic, and magnetic technologies that drive the 21st century society and economy. As emphasized by the Materials Pyramid (Figure 2), the creation of the materials platforms critical to new applications relies fundamentally on a steady stream of new materials discoveries. Despite considerable effort by solid state chemists, materials scientists, and condensed matter physicists to systematize the understanding of inorganic crystalline matter, there are significant hurdles to clear in both the prediction and the synthesis of new functional materials, even “simple” ones. The most general of these challenges is simply “How do we accelerate the ‘hit’ rate for new functional materials, particularly in systems requiring fine-tuning of structure, dopants, and phase composition?” Corollaries to this central question follow: How can we routinely translate desired electronic, magnetic, optical or mechanical properties into predictable structures and chemistries for new materials? How do we control (or even measure) defects that can create new functionality? Ultimately, how do we link “materials by design” to “synthesis by design?” To address these questions, an organizational framework for new materials creation is proposed that builds around two tightly linked emerging research challenges: exploring hierarchies of crystalline complexity and mastering the science of crystal synthesis. These two directions will draw the roadmap for a broad but deep research portfolio that focuses on designing, discovering, and synthesizing the new functional crystalline solids of the future.

Current Status and Recent Advances

Imagine a world without smartphones, without the internet, or without PCs. Imagine roads without electric cars, hillsides without windmills, hospitals without MRI (magnetic resonance imaging) machines, or store shelves without LED light bulbs. Imagine a world in which these everyday pieces of our 21st century life are simply not possible, or for which other dreamed-of applications are forever out of reach. This imaginary world is a world without crystalline inorganic matter. Crystalline inorganic solids make possible the structural, optical, electronic, and magnetic technologies that move society and the economy forward. Their impact on present-day energy science and technology is inestimable, and they will underpin the enabling technologies of the foreseeable future—technologies like quantum and neuromorphic computing, levitating high-speed trains and superconducting power transmission, low-cost solar energy, solid state refrigerators, or high-capacity lightweight batteries. But delivering these technologies tomorrow depends critically on deploying strategies and new approaches today that will enhance our capacity to discover and to synthesize wholly new crystalline inorganic solids.

Just how many such new inorganic solids might there be? As a measure of the available opportunity space in inorganic crystalline matter, consider the nearly 185,000 entries in the Inorganic Crystal Structure Database, and the 274,000 entries in the Pearson's Crystal Structure Database for Inorganic Compounds. Within each structure type in these databases, there is typically additional scope for compositional variation, so these numbers represent the lower bounds to the total *known* crystalline inorganic materials space available for development into application platforms. Navigating this vast opportunity space relies on hybridizing the disciplines of inorganic chemistry, materials physics, materials science, and condensed matter physics to work in lockstep.

To grasp the potential of the uncharted materials space available, the community must realize that discovery and synthesis of novel materials has as its objective the creation of crystalline matter of a quality sufficient to reveal intrinsic behavior, and ultimately to lead to function. It is by nature a highly experimental enterprise. The state of the art today is highly sophisticated and continually evolving in its quest to create new, high-quality bulk and thin film crystals. The following provides a snapshot of this current state, discussing the meaning and importance of “exploratory synthesis” as well as some of the methodologies, tools, and techniques used in the pursuit of synthesis of new crystalline inorganic matter.

Exploratory synthesis. Exploratory synthesis is a rational, ongoing experimental endeavor that iteratively generates and follows rules of predictive design and assembly—such as known trends upon which the periodic table is organized—to identify promising regions for finding new compounds out of a practically infinitely large chemical search space. In the same way that the discovery of the Higgs particle was not the result of some “accelerator folks getting lucky,” the discovery of new functional materials is not the result of a “fishing expedition” or simply serendipity. Instead, exploratory synthesis consists of both the creation of completely new structures, compositions, or architectures and the targeted discovery of new properties via rational modification of known aristotypes—both approaches following largely empirical rules. (See the sidebar *The Fruits of Exploratory Synthesis*.) Successful examples of such rules include leveraging structurally related series that share a common building block to design libraries of new materials, such as cuprate superconductors[1] or chalcogenide narrow-gap semiconductors:[2] once the key building block (e.g., CuO or BiSe layer) is identified, the door is flung open to creation of a practically limitless number of compounds. A powerful, developing concept exploits molecular assembly of inorganic solids, for example using Cu-OH and Cu-Cl building blocks, called “synthons” or “tectons,”[3] to generate new materials, such as a family of quantum spin liquid candidates (Figure 37).[3] Simple molecular orbital theory combined with chemical principles of electronegativity and bond strength can guide the design and synthesis of materials exemplified by recent hits in thermoelectric compounds[4] or deep ultraviolet laser crystals.[5] Recent successes in designing materials based on the predictions of ab initio density functional theory (DFT) calculations, such as those which led to the design of the battery cathode candidate $Li(Ni_{0.5}Mn_{0.5})O_2$,[6] indicate that such computationally guided searches will increasingly become an asset for exploratory synthesis of inorganic crystalline matter. The impact of predictive design will be facilitated by open access to simulations platforms, such as those being developed by the Materials Project[7] or by the five recently-launched BES Computational Materials Sciences centers.[8]

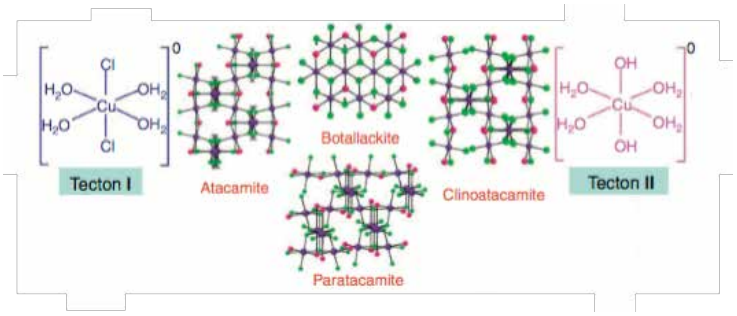
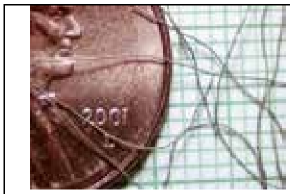
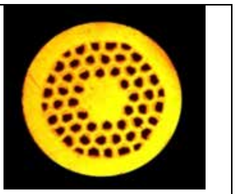


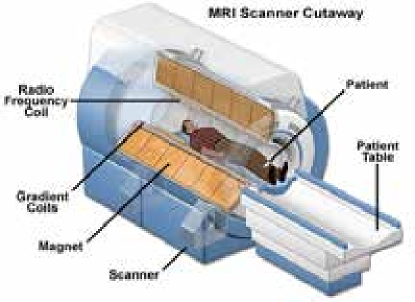
Figure 37. Assembly of quantum spin liquid candidates from building blocks, or tectons.[3] | *Reprinted with permission from M. Singh, J. Thomas, and A. Ramanan 2010. “Understanding Minerals and Materials: A Retrosynthetic Analysis of Copper-Based Solids, ”Aust. J. Chem. 63: 565–572. DOI: 10.1071/CH09427.*

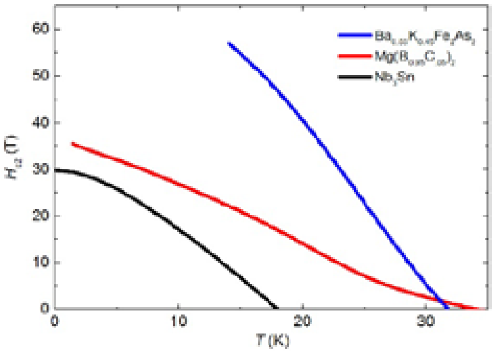
Methods and approaches of exploratory synthesis. The range of synthetic techniques for the discovery and growth of crystalline matter is extensive: solid state synthesis, vapor and solution growth, topotactic synthesis, solvothermal, melt growth, and electrochemical synthesis. For either exploratory or targeted discovery synthesis, however, solid state synthesis is frequently the method of choice for speed, and recent advances in the ab initio determination of crystal structure from powder diffraction data (e.g., simulated annealing[9] and charge-flipping[10]) has narrowed the gap between poly-crystals and single crystals as platforms for discovery of new materials. Solution growth (sometimes referred to as “flux growth”), in which crystals are coaxed to grow from supersaturated liquid solvents (including water), can be equally or in some cases more efficient as a discovery tool in the case of complex materials. Each growth experiment can be thought of as running an “analog computer” that traverses a (frequently unknown) phase diagram, with new crystalline matter as its output.

The Fruits of Exploratory Synthesis









Superconductors are crystalline inorganic materials made special by their property of zero electrical resistance. This is a profoundly useful zero that makes possible the powerful magnetic fields needed in applications ranging from particle accelerators to hospital MRIs. For the past 30 years, the superconductors most commonly used for such applications have been niobium (Nb) -based compounds and alloys that need to be cooled with liquid helium to reach the superconducting state. The technological promise of cheaper, easier-to-make, or even easier-to-cool superconductors, drives a worldwide exploratory quest for new, superior materials.

Indeed, from the discovery of superconductivity in elemental lead over a century ago, the transformative milestones in the field can be traced back to new materials discoveries: Nb in the 1930s, NbN in the 40s, Nb_3Sn in the 50s, and the cuprates in the 80s. In turn, the 21st century opened with the discovery of another class of superconductor, MgB_2, with a T_c of ~40 K in 2001, and 7 years later, of FeAs-based compounds, with T_c values as high as 55 K.

MgB_2 was discovered during a guided exploration of transition metal-magnesium-boron ternary compounds. As the telltale fingerprint of superconductivity emerged at 40 K, it became clear that a simple binary compound was its origin. The basic physics of MgB_2 was understood within a short few months through refined syntheses of high-quality specimens, revealing a tolerance to magnetic fields (measured by a critical field, H_{c2}) that exceeded that of the current industrial gold standard, Nb_3Sn. Over the past 15 years MgB_2 has become an industrial superconductor, with multi-filament wires being wound into the solenoids that provide the fields for prototype MRI units.

The FeAs-based superconductors were found by tracking down a curious, low-T_C superconductivity in a recently discovered class of FeP-based materials. As exploratory syntheses were made, a wide family of FeAs-based materials emerged, including the $BaFe_2As_2$-derived compounds. When the $H_{c2}(T)$ of $(Ba_{0.55}K_{0.45})Fe_2As_2$ was measured, it became clear that these FeAs-based materials might ultimately surpass the application potential of MgB_2, just as MgB_2 has surpassed that of Nb_3Sn.

| [Upper left]P. C. Canfield and S. L. Bud'ko 2002. "Magnesium Diboride: One Year On." Physics World. | [Upper right] Reprinted with permission from Y. Yang et al. "Influence of Twisting and Bending on the Jc and N-Value of Multifilamentary MgB_2 Strands." Physica C: Superconductivity 519: 118–23. © 2015 Elsevier.| [Center] "MRI: A Guided Tour." Magnet Academy, National High Field Magnetic Laboratory. | [Bottom] Courtesy of P. C. Canfield and S. L. Bud'ko, Ames Laboratory.

In the quest to expand the regime of available phase space and to capture the properties of compounds that lie off the equilibrium phase diagram, efforts have turned to exploiting extreme conditions such as high pressure to create metastable bulk materials (for example the multiferroic $FeTiO_3$[11] or the high-temperature superconductors derived from H_2S)[12] or to epitaxially stabilize thin films (for example, the recent discovery of oxide polar metals following a materials-by-design strategy).[13] Other approaches include taming volatility in flux growth (e.g., work on arsenides and related materials)[14] and exploiting extreme oxygen fugacity in floating-zone crystal growth (Figure 38)[15] to expand the phase space of new materials by moving phase lines, or extending doping ranges (e.g., discovery of Brownmillerite

$Ca_2Co_2O_5$, an elusive member of a family of compounds exhibiting significant electronic, magnetic and optical properties).[15] For crystalline films, chemistry-based control of heterostructures using self-limiting techniques, such as atomic layer deposition, has been refined to considerable sophistication and has had an impact on catalysts and solar photovoltaics, among others.[16] High-throughput combinatorial approaches to film growth using pulsed layer deposition (PLD),[17] molecular beam epitaxy (MBE),[18] or sputtering,[19] when paired with high-throughput characterization, have accelerated the discovery of functional materials, such as thermoelectrics[20] or transparent conducting oxides.[21]

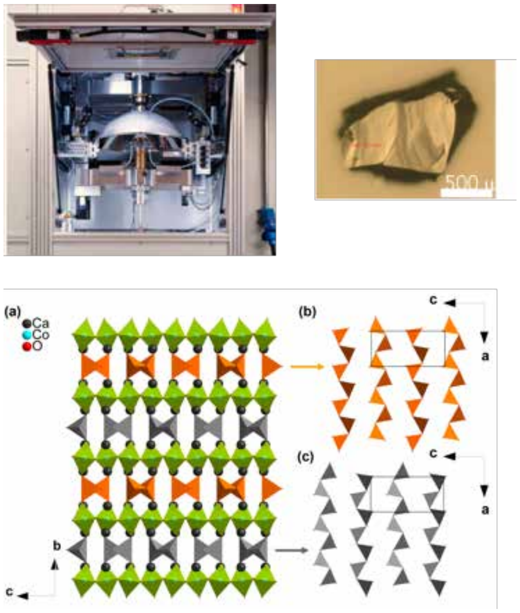


Figure 38. High oxygen fugacity promotes discovery of new crystalline phases, such as the previously unknown ordered Brownmillerite structure $Ca_2Co_2O_5$ grown in a floating-zone optical image furnace capable of operating under 150 bar of oxygen.[15] **|** *Reprinted with permission from J. Zhang et al. "Brownmillerite $Ca_2Co_2O_5$: Synthesis, Stability, and Re-Entrant Single Crystal to Single Crystal Structural Transitions." Chemistry of Materials 26 [24]: 7172–82. © 2014 American Chemical Society.*

In parallel, the desire to understand exactly what is going on during reactions or growth has rapidly become a focus of methodology and technique development because such knowledge offers a pathway to discover new materials in predictable fashion. In the arena of bulk reactions, in situ synchrotron-based studies of compound formation pathways[22] and solution behavior have recently been pursued for main group metal sulfides[23] and transition metal oxide–sulfides.[24] The value proposition here is that actual reaction pathways can be charted and materials discovered that would never be known via traditional approaches. For example, in the case of the Cu:K_2S system, such a "panoramic synthesis" revealed the previously unknown narrow-band semiconductor $K_3Cu_4S_3$.[23] Grey's in situ exploration of metastable solid-solution of Li_xFePO_4 at high discharge rates offers another example of the power of in situ synthesis, this time under driving conditions.[25] In situ growth is not limited to bulk materials, and recent efforts at mounting film growth chambers at beam line end stations has been profitable. For example, the demonstration of "layer-swapping" in MBE growth of layered $SrTiO_3$ homologs was made possible by synchrotron-based mapping of the reaction steps, bolstered by first-principles calculations.[26]

While synthesis is ultimately an experiment-driven activity, theory and computation are streamlining the discovery process of crystalline inorganic materials. For example, understanding the fundamental crystal-chemical factors underlying the suppression of ferroelectricity in most perovskites has led to a design principle, recently experimentally verified, for new classes of polar materials.[13,27] Theoretically predicted topological insulator ternary Heusler compounds created in the laboratory have launched a rapidly growing subfield of condensed matter physics.[28] Genomic approaches (e.g., Materials Project, Aflowlib, Figure 39)[7] are quickly being adapted by synthesis laboratories to accelerate discovery by limiting the search space for experimental testing. Along these lines, theoretically modeled core/shell Pt-Co catalyst particles have been fabricated and show a 300% improvement in specific activity over disordered analogs. Another example is a computationally predicted lithium-ion cathode material that was successfully synthesized in the lab.[6] Ultimately, the purpose of creating new, more powerful theories and simulations such as these is not to replace experimental approaches, but rather to offer "more powerful ways of thinking that lead to new ideas and concepts."[29]

Exploratory synthesis is far from random, and exploratory synthesis delivers new science. Over the next decade, the research community needs to deliberately explore as many promising compositional spaces as possible, using the established, successful approaches discussed above and the new approaches discussed below, to look for stable as well as metastable systems with new and/or enhanced properties. These searches need to be both ambitious and humble. Ambitious in that we need to incorporate as much guidance and insight from theory and simulation as possible to help identify promising regions for exploration; humble in the realization that this is still an exceptionally large phase space and the appreciation that many surprises are yet to be found, often via purely experimental exploration, using the most sophisticated neural network–based search algorithms and tools currently available: the human brain combined with skilled hands.

Figure 39. Web-based, interactive, materials-selections platforms are advancing materials prediction. These interactive websites contribute to the rational screening of known and new materials for energy research. **|** *Image courtesy of J. Mitchell, Argonne National Laboratory.*

Scientific Challenges and Opportunities

Examples of how the discovery of crystalline inorganic compounds open new areas of science and application are not hard to come by: high-T_c superconductivity, the 2-dimensional (2D) electron gas at the $LaAlO_3/SrTiO_3$ interface, hybrid perovskite solar photovoltaic materials, nonlinear optical crystals, graphene and its congeners, multiferroic oxides, topological solids and other quantum materials, and many others. The challenge and opportunity is to enhance the ability to open these new directions, expand conceptual frameworks, and develop the tools needed to create and perfect the growth of such new crystalline matter. The journey begins with identifying promising new materials candidates and structures, followed by harnessing appropriate routes to create them; but for the effort to be successful, a number of questions need to be addressed: If structure and composition guide the choice of synthesis and crystal growth, how do researchers navigate the vast compositional space that lies unexplored? How do they predict what to synthesize? More important, what lies beyond? How many untold thousands of *unknown* structures are waiting, and how can they be found efficiently? Even more critically, how can they be made? Although the ability to predict has massively accelerated with the rise of computation and modeling, much remains to be done in developing complementary methods that reveal how to make these predicted materials in the lab. That is, while many materials can be created in silico, there still are substantial challenges to creating them in silica. These are the questions that must be answered to advance the science of synthesis for crystalline inorganic matter. Doing so will lead to an understanding of not just where to put the atoms for specific functionality, but how to put them there.

These questions define two emerging research challenges for advancing the science of synthesis for crystalline matter: Explore hierarchies of crystalline complexity and master the science of crystal synthesis.

The research community is at an auspicious time to advance these challenges. The discovery of materials in tellurium- and arsenic-based chemistry demonstrates the importance of exploring poorly charted regions of the Periodic Table and provides the tools to do so. The ability to grow materials under extreme conditions is rapidly advancing, providing access to *terra incognita* in the phase space of new, metastable compounds.[2] New frameworks for understanding the assembly of crystalline matter, for instance prenucleation[3] and inorganic synthon concepts,[4] offer new ways of thinking about crystal synthesis. Powerful in situ tools for monitoring growth are shining a light on the synthesis outcomes and assembly pathways. Computation is already providing a powerful tool for materials design in the synthesis laboratory (e.g., the DFT-based Materials Project).[5] The sheer complexity of solid state structures reflects an opportunity for increased feedback from exploratory synthesis to computational models. Looking ahead, we can envision the use of computational methods in concert with in situ probes to guide synthesis, for example, by harnessing machine learning. Today's confluence of insight, tools advances, and computational methodologies means that researchers are on the cusp of massively expanding the phase space available for exploration and discovery. As a result, work at the base of the materials pyramid is poised to flourish in a properly nourished ecosystem of academic, national laboratory, and industrial materials research. It is in such an environment that the time required to move from discovery of a new structure to mastering its growth will be measured in weeks instead of years.

Explore hierarchies of crystalline complexity

Of particular importance is the synthesis of new materials, with novel and complex structural motifs that challenge our existing notions of structural complexity or of periodic order, to deliver targeted functionality. This includes complex bonding arrangements at the unit cell level and extends to defects and structural patterns that cross multiple length scales and dimensions. The widespread outcomes of this discovery research will include taxonomies of new bulk structural and bonding motifs, useful for expanding the palette of computational materials design to new crystalline thin films and heterostructures that express emergent phenomena at their surfaces and interfaces.

Hierarchies at the unit cell level. Curiosity about the crystal chemistry of elements in all their myriad combinations is the keystone of discovery synthesis, the quest for new structures, new building blocks, new solids—both thermodynamically and kinetically stabilized. What are the kinds of crystalline compounds seen in the ternary Na-Ni-In systems explored by Corbett, for example?[30] The answer is surprisingly complex, involving fullerene-like architectures with a level of complexity that even today lies completely outside the realm of structure prediction using state-of-the-art genetic algorithms[31] or particle swarm optimization approaches.[32] Oxypnictides compiled by Jeitschko as crystal chemical curiosities have become famous as the progenitors of the iron-pnictide family of superconductors that has transformed condensed matter physics since 2008.[33] Curiosity-driven empirical synthesis and growth remains a foundational need in inorganic crystalline materials research, to be cultivated[34,35] and advanced using the methods and tools discussed throughout this chapter.

In concert, more directed efforts will increasingly play a role, ranging from "design by Hamiltonian" to database mining. Approaches that rely on fundamental symmetries offer rigorous approaches for structure prediction. For example, the idea that non-symmorphic symmetry can protect the opening of gaps in systems with 2D Dirac cones has led to an experimental realization that includes a novel Dirac material in the layered compound ZrSiS.[36,37] "Toy models" of magnetic exchange can be harnessed to inspire structural design principles, for example, anisotropic bond-directional exchange topologies leading from honeycomb to hyperhoneycomb to hyperkagome structures in iridates.[38-40] The concepts of preserved entropy and fragile magnetism can be used to guide searches for new high-T_c superconductors and quantum critical systems.[41] Examples of computational design include the use of proxies or descriptors obtained from DFT calculations for the screening of, for example, crystalline inorganic phosphor hosts for solid-state lighting applications,[42] or thermoelectric materials.[43] A strategy frequently used to encourage the search for new compositions of matter is to consider the stability—based on high-throughput, 0 K DFT calculations—of new compositions within known structure types. As an example, in a single published study, combined ab initio computation and machine learning predicted more than 200 new ternary oxide compounds as a "carrot" to encourage synthetic realization.[44] Missing are further screening tools to narrow the field even further to those most likely to be synthesized successfully, and methods to extend the technique to metastable phases. A further exciting development is the prediction of completely new extended inorganic structures (i.e., both structure and composition) based on a modular assembly approach to unit cell structure. One embodiment of this strategy, extended module materials assembly,[45] is depicted in Figure 40,[45] which illustrates new structure types with exceedingly complex, hierarchical unit cell designs that can be designed and realized, in this case for application as oxide-ion conductors.

Hierarchies beyond the unit cell. Although the common notion of a crystal is of an infinite, perfectly ordered repetition of a relatively small unit cell, it has been appreciated for the better part of a century that deviations from this perfection are exceptionally useful. Much of the world around us depends on single crystals of “dirty silicon” providing p- and n-doped semiconductors, crystals of “dirty alumina” providing lasers, and imperfections in $Nd_2Fe_{14}B$ allowing it to become the current industrial ferromagnet of choice. Whereas the impurities responsible for the industrial importance of these compounds are small deviations from our sense of crystallinity, rapidly evolving synthetic techniques are providing access to a huge array of new materials that stretch this definition to its limit. Furthermore, the definition of the repeat unit is being modified to reflect a new understanding of periodic order in crystalline materials. It is still true that crystals are thermodynamically stable, repeated units, but they need only be *stable under the conditions from which they are prepared and used*;, and the repeat units can be defined to be *much larger than a simple unit cell*. Powerful new advances in tools such as x-ray diffraction, neutron diffraction, and electron microscopy allow a deeper understanding of the subtle modifications of unit cells and promise to revolutionize our understanding and practice of crystal growth and synthesis.[46] What previously were dismissed as twinning, disorder, or simply “bad crystals” are now recognized as incommensurate lattices, complex defect patterns, and repeat units on the mesoscale of non-ideal crystals.[47]

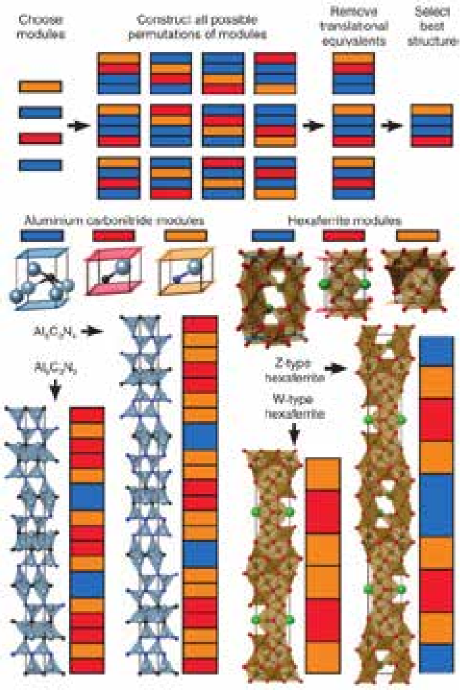


Figure 40. Describing structures based on the stacking of modular units allows unknown structures to be predicted by enumerating the large number of stacking sequences of appropriate modules, and then seeking out symmetry-inequivalent compositions and structures for attempted synthesis. Examples of layered aluminum carbonitride (Al-C-N) compounds for structural applications, and barium hexaferrite (Ba-Fe-O) compounds for oxide ion conduction applications are depicted.[45] **|** *Adapted by permission from M. S. Dyer et al. “Computationally Assisted Identification of Functional Inorganic Materials.” Science 340 [6134]: 847–52. DOI: 10.1126/science.1226558. © 2013 American Association for the Advancement of Science.*

Moving beyond “perfect” crystals, crystals with engineered defects such as grain boundaries, dislocations, and vacancies provide opportunities to tune intrinsic properties of materials for either technological applications or fundamental science. Examples include nitrogen vacancies (point defects) in diamonds that exhibit photoluminescence with long coherence time at room temperature, the generation of dislocations during metal work-hardening processes to increase their mechanical strength, and inclusions of precipitates to efficiently block phonon propagation in thermoelectric materials. Even for quantum materials such as topological insulators, topologically protected edge states are expected at point defects or at dislocation cores.

Bulk materials in which self-organized structures develop across length scales offer a nontraditional synthetic degree of freedom for building functionality. For example, directional solidification has been harnessed to create 1D and 2D structures on the micron scale in both metallic[48,49] and oxide[50] eutectic systems with exquisite uniformity at the micron scale and below (Figure 41).[48,49] Better understanding of thermodynamic and kinetic phase diagrams will make it possible to more fully exploit this methodology for mesoscale engineering. Spontaneous organization of objects at the nanoscale occurs in several

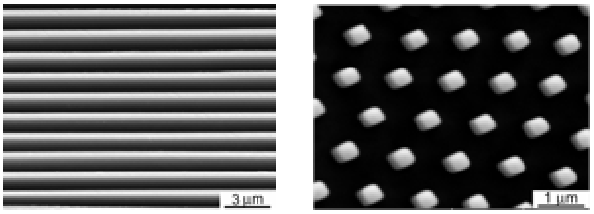


Figure 41. Highly ordered, spontaneously formed eutectic mixtures resulting in a lamellar structure in NiAl-Cr(Mo) (left)[49] and of rod-like structures in a NiAl-Mo (right).[48] **|** *[Left] Image courtesy of Hongbin Bei, Oak Ridge National Laboratory.* **|** *[Right] Adapted with permission from H. Bei et al. "Small-Scale Mechanical Behavior of Intermetallics and Their Composites." Materials Sciences and Engineering A 438 [1]: 218–22. DOI: 10.1016/j.msea.2006.12.185. © 2008 Elsevier.*

transition metal oxide systems. For instance, nano "chessboard superlattices" have been reported in the perovskite $(Nd_{2/3-x}Li_{3x})TiO_3$[51] and in the spinel $ZnMnGaO_4$,[52] the latter reflecting a hierarchical scaling of the Jahn-Teller charge-lattice coupling instability of Mn^{3+} from the atomic to the nanoscale. In the case of the perovskites, phase segregation of the mobile lithium species plays a key role in mesostructure formation. This suggests the possibility of a more general materials synthesis strategy that would hinge on deeper understanding of how to manipulate light ion motion to achieve kinetic control of the end product.

The ordering of defects in single-crystal thin films into hierarchies beyond single point defects often leads to the discovery of ground states not observable in the bulk. For example, epitaxial strain has been used to generate ordered oxygen vacancy structures that, in turn, are thought to lead to long-range ferromagnetic ordering.[53] In other systems, control of dopant ordering on cation sites that is not possible in the bulk has led to novel switching of magnetic behavior in thin-film oxides.[54] Although approaches based on MBE can offer routes to such defect control, the difficulty in precisely positioning defects more generally remains a significant obstacle requiring attention to fully exploit such strategies to realize new materials and properties.

New synthetic methodologies are providing unprecedented ability to modify new low-dimensional materials and multi-domain crystals. These advancements lead to new concepts of the lattice with the isolation of new strained structures across multiple dimensions, as in $LaTiO_3$-$LaNiO_3$-$LiAlO_3$ superlattices and heterogenous oxide interfaces[55,56] (Figure 42).[55] Adjusting the lattice via electric field provides a route to continuously tune the electronic structure of a transition metal center—in a sense an orbital alchemy. Another exciting example is the hybrid perovskite photovoltaics, which change properties dramatically as the dimensionality of the lattice is varied (see the sidebar *Hybrid Organic–Inorganic Crystalline Matter*).[57]

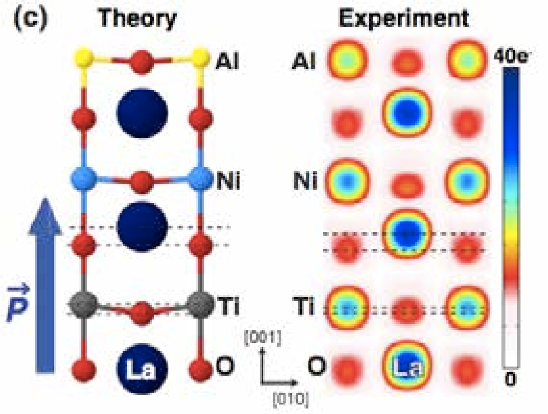


Figure 42. "Orbital alchemy" tunes electronic character of the transition metal to lie between discrete elemental states of Ni and Cu. The electric field of a neighboring $LaTiO_3$ induces this transformation in the $LaNiO_3$ perovskite block.[55] **|** *Reprinted with permission from A. S. Disa et al. "Orbital Engineering in Symmetry-Breaking Polar Heterostructures." Physical Review Letters 114 [2]: 026801. DOI: 10.1103/PhysRevLett.114.026801. © 2015 American Physical Society.*

Despite the critical role that defects and disorder at all hierarchical length scales play in materials properties, the ability to generate, control, and manipulate such features in single crystals and films is inadequate to the task of delivering the full range of potential functionality. This represents a tremendous opportunity for fundamental research with potential payoff across a broad range of applications. One way forward relies on detailed understanding of crystallization pathways. This can be leveraged using, for example, in situ growth techniques that monitor, in real time and in real space, the formation of nucleation sites and propagation of grain growth at a spatial resolution comparable to the relevant length scales. Such information is critical to build understanding of crystallization beyond the classical theories, which often fail to capture the complexity of crystallization processes.[62] Recent advances in nanoscale ptychographic measurement[63] offer promise in this direction and will become more powerful with the advent of coherent x-ray scattering after planned upgrades to synchrotrons. Theoretical calculations that provide the energy levels of various defects in crystals will be valuable complements to such experimental work, as already demonstrated for the topological materials Bi_2Te_3 and SnTe, which are disadvantaged greatly by defect-induced large bulk carrier densities.

Hybrid Inorganic–Organic Crystalline Matter

Hybrid inorganic-organic perovskites have stormed to the forefront of solar photovoltaic (PV) research and applications development. The performance levels for perovskite solar cells already approach those of the highest-performing PV materials systems, and the new materials have the advantage of very simple, near-ambient-temperature processing. Besides PV devices, their reported exceptional light-emission, photoconductive, and other optoelectronic characteristics indicate substantial opportunities for use in a wide range of electronic/energy-related devices.

Several decades of extensive, detailed foundational solid state and materials chemistry research provided an essential foundation for the explosive advances in applications of hybrid perovskites. The first reports of hybrid perovskite structures can be traced back to the late 19th century. However, in the 1990s and 2000s, extensive work focused on elucidating the unprecedented structural, optical, and electrical diversity of Ge^{2+}, Sn^{2+} and Pb^{2+} halide perovskites. These characteristics include an exceptionally strong and tunable absorption spectrum, exciton binding energies that can exceed 250 meV for layered systems, and near-ideal semiconducting transport properties. Detailed structure–property analysis revealed extensive flexibility within the hybrid perovskite family, including the ability to control bonding within the inorganic framework (and therefore the electronic structure) using the choice of organic cation, the flexibility to tailor the effective dimensionality and crystallographic orientation of the inorganic framework, and the possibility of incorporating relatively complex/functional organic cations within the hybrid structures. In the early 2000s, fundamental studies pursued the application of hybrid perovskites to simple proof-of-principle devices, including light-emitting devices (LEDs) and transistors (TFTs). Further, extensive fundamental studies elucidated a range of opportunities for processing the hybrid semiconductors—including traditional solution-processing approaches (e.g., drop casting, spin coating, and spray coating), vacuum evaporation, two-step approaches, and melt processing—that have proved to be enabling for the current generation of PV and optoelectronic innovation.[58-61] **|** *[Left] Reprinted by permission from Macmillan Publishers Ltd: Nature 369[6480]. June 1994.*

Master the science of crystal synthesis

Achieving directed synthesis of functional materials requires an understanding of how to create new, highly controlled crystalline inorganic materials with desired composition, structure, size, and architecture. Scientific challenges underpinning this objective include (1) opening new chemistries for discovery, particularly chemistries at extremes of temperature, pressure, volatility, and reactivity; and (2) learning how to grow tailored bulk and thin film crystals with stringent properties-based criteria in mind.

Harnessing synthesis at extremes. Diamond epitomizes synthesis of crystalline matter under extreme conditions of pressure and temperature (HPHT). While diamond may have initially motivated the development of HPHT techniques, the potential to discover wholly new classes of materials under these conditions has led to an expansion of HPHT synthesis science, with marked success. Superconductors,[64] low-dimensional metals,[65] and multiferroics[11] are but a few of the classes of materials being discovered using high pressure. HPHT also offers a route to control difficult chemistries—for example, the incorporation of fluorine into oxides (e.g., Ruddlesden−Popper–type structures),[66] overcoming the synthetic challenges posed by solid state reaction using fluorinating agents, which produced only low fluorine content or inhomogeneous phases. Spark plasma sintering,[67] a special case of HPHT, is a relatively new entrant that has found success in the synthesis of high-ZT thermoelectrics[68] but promises to be far more broadly applicable as a discovery synthesis tool.

Extreme conditions are not limited to HPHT. The discovery of iron pnictide superconductors less than a decade ago[33] highlighted the need to master highly reactive, highly volatile materials synthesis. Growth involving pnictogens, chalcogens, and the like is challenging owing to the high vapor pressure of these components, their toxicity or in some cases, both. Several other examples of compounds based on volatile or highly reactive elements (nontransition metal nitrides,[69] sulfur-based transition metal compounds,[70] Zn- or Cd-based binary quasicrystals,[71,72] dilute ferromagnets,[72] layered chalcogenides[73]) point to the rich physics to be unveiled by the development of growth techniques at these extreme conditions. In addition, controlling these extreme synthetic parameters opens up new, poorly explored phase spaces.[74]

Rapidly evolving extreme conditions synthetic methods such as hydrothermal (and solvothermal) and liquid metal solvents are promising areas for development, as they eliminate the need for high-temperature stability as a criterion for synthesis.[75-79] These new methods can in some cases free modern crystal materials design from the tyranny of the equilibrium phase diagram, and they are providing access to a vast range of new materials and larger crystals thereof (Figure 43). Examples include new nonlinear optics (KBBF, SBBO),[76] new classes of superconductors (MgB_2,[80] $BaFe_2As_2$,[14] KFe_2Se_2),[81,82] magnetically responsive materials such as magnetocalorics ($Gd_5Si_2Ge_2$),[83] and magnetostrictives (Fe-Ga[84]). Understanding how composition and, particularly, defect behavior evolve across the range of crystal size and under these extreme synthesis conditions is vital, calling for deeper understanding of how to control both intrinsic and extrinsic defects during crystal growth.

Figure 43. RBBF ($RbBe_2BO_3F_2$), a new deep ultraviolet nonlinear optical crystal lasing at 175 nm. RBBF is grown under extreme conditions of hydrothermal synthesis. | *Image courtesy of J. Kolis*

Inevitably, extreme environments pose a challenge to control of experimental conditions and hence to outcomes. Ways to address this challenge include mitigation strategies adapted to existing apparatus or the development of wholly new techniques and tools. As an example of the former approach, combining HPHT growth methods with various metallic and nonmetallic catalysts renders the synthesis of diamond far more tractable, lowering the growth temperature to as low as 600–700°C using germanium.[85] This success naturally poses the question whether similar chemical strategies can be applied more broadly in HPHT synthesis. In the case of refractory materials such as borides and carbides, new furnaces have recently been developed (Figure 44) to allow for flowing inert gas environments and in situ decanting at temperatures up to 1600°C.[86] Extension of this well-established technique to such extreme temperatures will open new chemical phase spaces for discovery synthesis. Chemical and physical vapor transport are effective in the synthesis of layered chalcogenides TX_2 (T=transition metal, X=S, Se, Te, see Figure 44). However, challenges remain because of the chalcogen vapor pressure at high temperatures, and solutions are needed to problems such as chalcogen deficiency and poorly controlled crystal composition if this technique is to be more broadly applied. As discussed elsewhere in this document, the development of in situ or operando monitoring techniques applied to these synthesis modalities is a direction ripe for development, both to control growth and to understand formation pathways.

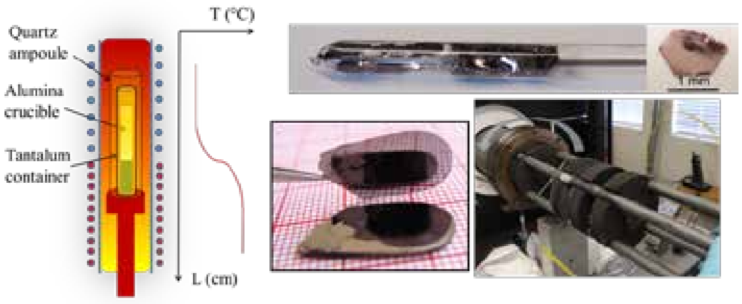


Figure 44. Synthesis of materials under extreme conditions requires new tools capable of controlling these environments. At left is a schematic of an inverted gradient furnace for mitigating the loss of volatile components during growth *(image courtesy of T. Lograsso)*. At right are (counterclockwise from top) crystal of vapor-grown TiSe$_2$ *(image courtesy of E. Morosan)*, Ba$_{0.61}$K$_{0.39}$Fe$_2$As$_2$ grown by the inverted gradient method, and a recently designed centrifugal decanting furnace capable of operation at up to 1600°C *(image courtesy of C. Petrovic)*.

Advancing controlled crystal synthesis. As advocated above, new, clever materials design strategies are essential to guide the function-based discovery and growth of single crystals and films. For instance, better gamma detector crystals can be imagined through dimensional reduction and control of covalency in known semiconductor structures,[87] which systematically modify the bandgap. However, with each materials class comes a unique set of synthetic challenges to delivering crystals of the appropriate composition, homogeneity, uniformity, or dimension to yield the desired functionality. Making these new gamma detector materials work requires developing control of impurities and point defects. There is thus both considerable need and opportunity to develop new, more effective materials and, in concert, the strategies and techniques required for crystal synthesis in both bulk and thin film forms.

Bulk materials. Czochralski,[88] Bridgman,[89] and other industrial, large-yield crystal growth methods have been practiced for nearly a century with minimal changes and have delivered inestimable impacts on science and technology during that time.[90] Although they are highly optimized for commercial crystals, their application to materials discovery and synthesis has been limited, leading to growth typically informed by empirical knowledge and ad hoc implementation. With increasingly sophisticated approaches that inform researchers *where* to put atoms for specific function comes a need to understand *how* to put them there during crystal synthesis; the existing, simple tools for crystal growth are no longer adequate to this task. Progress toward resolving this lack of understanding can begin with reimagining these established techniques.

For example, highly realistic, continuum-level simulations have vastly improved understanding of conditions in classical crystal growth systems.[91] Such knowledge now opens the door to nontraditional approaches, such as the dynamic reconfiguration of applied furnace profiles during Bridgman crystal growth, to better influence outcomes.[92] As another example of such reimagined techniques, the Bridgman process can be literally turned on its head in an inverted gradient approach (with the melt underlying the crystal) to achieve improved compositional uniformity of extremely volatile compounds.[14]

The optical-image floating zone crystal growth method—which relies on the directional solidification of a crystal from a locally heated, liquid "floating" zone suspended by surface tension—is an ideal technique for growing ~cm^3 crystals from a pre-sintered ceramic solid. Replacing the currently used mirrors and lamps with laser diodes will provide significant improvements in focusing, with subsequently greater precision in the control of temperature gradients.[93] Innovations have also allowed for controlled atmospheres at very high pressures (currently 150 bar, but 300 bar arriving in 2017 and 1000 bar prototypes in development) in such furnaces, providing a much richer phase space for solidification conditions to be explored.[15,75,94-98]

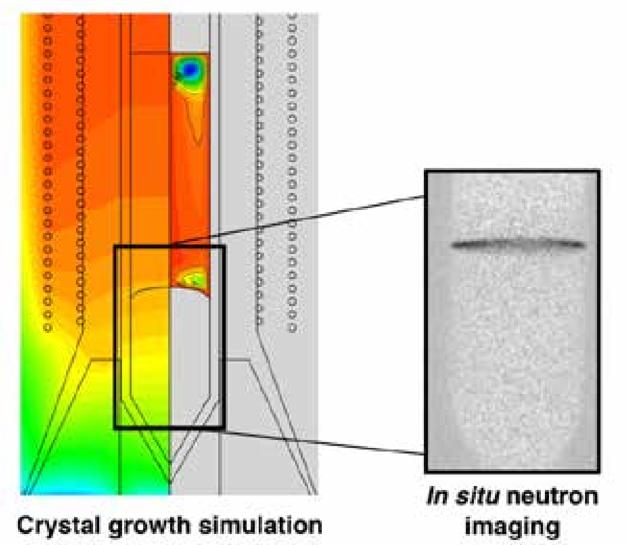


Figure 45. Continuum models of heat and mass flow during Bridgman growth (left) can be monitored in situ using neutron imaging, which shows the melt interface. In the future, feedback control of growth is envisioned. *Image courtesy of J. Derby.* **|** *Reprinted with the permission of Nature Publishing Group from A. S. Tremsin et al. 2017. "Real-Time Crystal Growth Visualization and Quantification by Energy-Resolved Neutron Imaging." Scientific Reports 7 [46275]. DOI: 10.1038/srep46275. Distributed under the terms of the Creative Commons Attribution 4.0 International [CC BY 4.0] License.*

Modern advances toward in situ diagnostics promise to revolutionize our understanding and practice of crystal growth and synthesis. For example, in situ, real-time neutron imaging (Figure 45) is being developed to provide direct observation of large-scale Bridgman crystal growth.[99] When deployed, neutron imaging will enable growers to directly "see" the phase change occurring in processes that have heretofore been carried out blindly. Such developments are synergistic with the computational models mentioned earlier for validation and interpretation, offering a means for feedback, optimization, and on-the-fly changes to parameters to control crystal growth in target compounds that require the most stringent control of purity, homogeneity, or other characteristics. This style of active monitoring with feedback can be extended to other crystal synthesis techniques, such as hydrothermal synthesis, to achieve the goal of optimized synthesis conditions in a complex parameter space.

Finally, solution growth of crystals has historically relied on a set of "usual suspect" solvents, empirically cataloged. Most crystals are grown from a small number of proven low-melting solutions, such as tin and bismuth in the case of intermetallics, or PbO, halides, or carbonates for oxides. Less work has been done developing new solvents, and no modeling of crystal synthesis by solution growth has been used to screen potential candidates for solution materials. A notable exception is the growth of EuO from molten Ba-Mg solutions.[100] A solvent design methodology for tailoring solvents for particular material systems, based on thermochemistry predictions, would be highly beneficial if it were developed.

Indeed, such solvent design is a subset of a larger opportunity that would emerge from new approaches to exploring and presenting phase diagrams. Although expanding the breadth (and improving the accuracy) of traditional thermodynamic equilibrium phase diagrams would be beneficial, the real opportunity lies in moving off equilibrium. Incorporating kinetic behavior and data and temporal information, for instance by extensions of the panoramic synthesis discussed earlier (and more thoroughly in Section 3), would reveal strategies relevant for capturing metastable phases and for designing the synthesis pathways leading to other undiscovered materials.

Thin films. Single-crystal inorganic thin films provide the platform for the stabilization of phases, artificial heterostructures, and interfaces not attainable in bulk systems and are often the platform of choice for applications. Perovskite oxides have recently received the lion's share of attention following decades of refinement of pulsed laser deposition (PLD), chemical vapor deposition (CVD), and MBE techniques that now routinely deliver atomic-scale precision in growth.[101,102] This development comes on the heels of advances in atomic-scale deposition of compound semiconductors in the preceding decades. Other materials opportunities requiring improved crystal synthesis lie on the horizon. In oxides, exciting opportunities can be found by harnessing new crystal structures, such as spinels and garnets, in which multiple cation sites not only provide for a hierarchy of interactions among metal ions but also provide the framework for atomic-level doping of such systems to target specific functionalities—such as ferromagnetism in conjunction with metallicity. By depositing atomic species, MBE is most promising for atomic-scale composition tuning across multiple cation sites in such complex oxide materials. "Designer substrates" may be required to epitaxially stabilize these nonperovskite phases, reflecting a need for synergy between bulk and thin film crystal growth.[103] Figure 46[104] shows a heterostructure prepared on elastic and transparent substrates, leading to band structure engineering for quantum wells and flexible and semi-transparent electronics.[104] For larger-scale production, CVD techniques with similar precision present a formidable challenge. In situ methods for studying film nucleation, secondary phase formation, and plasma time-of-flight studies would help to mitigate some of these challenges. An alternative approach would be to couple physical vapor deposition techniques with high-throughput combinatorial methodologies.

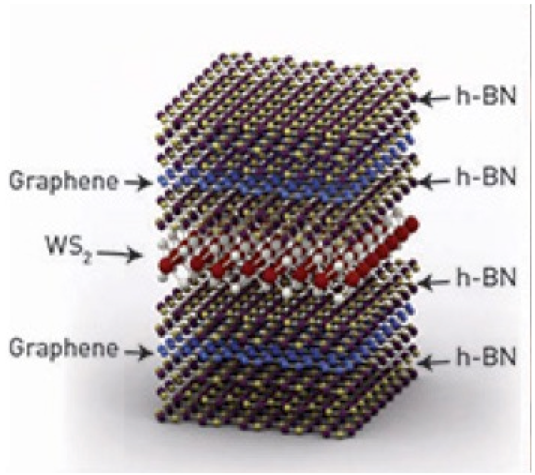


Figure 46. Heterostructure of stacked graphene, transition metal chalcogenide, and hexagonal boron nitride.[104] **|** *Reprinted with permission from F. Withers et al. "Light-Emitting Diodes by Band-Structure Engineering in van der Waals Heterostructures." Nature Materials 14 [3]: 301–06. DOI: 10.1038/nmat4205. © 2015 Macmillan Publishers.*

Looking beyond oxides, hexagonal 2D van der Waals materials such as graphene, boron nitride, and transition metal chalcogenides [e.g., MX_2 (M=Mo, W, X=Se, Te), and M_2X_3 (M=Bi, Sb, X=Se, Te)] offer opportunities for synthesis science to lead the discovery of new phases, such as topological states of matter, and to impact a broad range of functionalities, including thermoelectricity, spin-based electronics, light-matter interactions, and chemical processes (e.g., photoelectric hydrogen production). Looking even further, is it possible to stabilize 2D materials with square symmetry? Can stacking 2D materials with exotic dielectric functions lead to novel optical properties? Can these materials be engineered to have unique functionality beyond electronic–optical or thermoelectric?[105]

Standing in the way of answering these questions is a lack of fundamental understanding of the crystal growth of such 2D films. Specifically, researchers need to understand how to directly grow van der Waals heterostructures with atomic precision and layer number control that rivals that of oxides. Approaches could include strain engineering beyond substrate lattice match, such as strain-induced polymorph formation,[106] laser-induced strain,[107] intercalation,[108-110] and the larger accommodation of film/substrate mismatch due to the weaker van der Waals bonding. Ultimately, crystallization phenomena in 2D van Waals solids must be understood—especially where classical nucleation and growth models do not apply. Tracking of nucleation and growth events by in situ probes—including transmission electron microscopy, low-energy electron microscopy, and spatially resolved spectroscopy for compositional analysis—offers a promising way forward. Finally, surface degradation of these reactive materials and its impact on measured properties must be understood[111] and, if it is undesirable, mitigation strategies developed.

Potential for Energy Relevant Technologies

Crystalline inorganic materials discoveries have historically driven revolutionary changes in the technologies that they underpin: the growth of doped semiconductor crystals led to the transistor age and the modern information technology ecosystem; laser crystals ushered in a revolution in nonlinear optical signal processing for both terrestrial and space-based telecommunications; single-crystal blades transformed jet turbines to operate at temperatures approaching their melting points; vastly improving engine efficiency. The enormous technological impact realized through the discovery of these inorganic crystalline materials of the past presage similar transformative impacts on the energy technologies of tomorrow, in an environment in which directed and discovery synthesis are pursued synergistically. Select possible directions include the following.

Crystalline materials for electrochemical energy storage. Early US leadership in developing lithium-ion batteries[112,113] has taken a back seat in the discovery of new materials, despite the availability of a robust theory base. Current materials and technologies trace their lineage to discoveries of 30+ years ago. There is considerable opportunity for solid state chemistry to expand this narrow phase space. Specifically, beyond–lithium-ion materials, materials for sodium and magnesium, and solid-electrolyte materials (for lithium and non-lithium systems) all need considerable work.

Crystalline materials for efficient solar conversion. Organic-inorganic perovskites excite exceptional technological interest by harnessing complementary properties of organic and inorganic materials within a single molecular-scale composite. Recently, this family has yielded an unprecedented leap in photovoltaic device performance, to power conversion efficiency levels above 22% within the short span of 6 years from the first device demonstration. The recent announcement of high-efficiency (12.5%), stable Ruddlesden-Popper (a layered perovskite homolog) hybrid structures indicate that there may be considerable latitude for crystal engineering of such materials based on known inorganic structural aristotypes.[114]

Crystalline materials for magnetocaloric refrigeration. Caloric materials are poised to revolutionize *all* refrigeration, offering more energy-efficient, potentially more robust, and fluorocarbon-free alternatives.[115-117] However, numerous unanswered questions limit progress toward predictive synthesis of these materials. Where are the guidelines for new materials that exhibit high susceptibilities to external fields? What are the thermodynamic and kinetic origins that underlie the intrinsic responsiveness of these materials? A potential larger arena here is that of *functional intermetallics*.

This is far from an exhaustive list. Looking to the foreseeable future, crystalline inorganic materials will continue to hold a privileged position as platforms for functional materials. Building a broad, solid, and diverse base to the crystalline inorganic materials pyramid must be prioritized if this launching pad for new functional energy materials is to deliver its fullest potential.

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7. Emerging Approaches to Synthesis at All Length Scales

There is a strong impetus to develop creative new approaches for the synthesis of materials to enable the creation of novel phases of bulk materials, nanostructured alloys, and composites that allow control of composition, phase, and morphology from the macro to the atomic scale. This section considers emerging synthesis strategies that can reach new states of matter, exhibit synergistic interactions between multiple classes of materials, or add novel functionality via an internal structural and compositional complexity. To realize these outcomes, three emerging research challenges are identified: synthesis under far-from-equilibrium or extreme conditions, creation of complex hybrid materials, and hierarchical control during materials synthesis and processing.

Current Status and Recent Advances

Utilizing extreme conditions. Novel approaches to synthesis are a current subject of research across a broad range of materials classes. The use of extreme conditions is being explored as a means of synthesizing new phases of nonmolecular solids. The basic idea behind this approach is that extreme conditions can lead to kinetic trapping of atoms and/or molecules in metastable configurations otherwise inaccessible via near-ambient processing conditions. Common examples are the use of very high pressures (including geological conditions) or very low pressures, and/or high temperatures to stabilize these otherwise unstable or metastable phases. For example, a new high-pressure synthetic approach, based on crystal control of organic solid state reactions, has been shown to allow for low-dimensional sp^3-bonded carbon nanothreads, akin to the thinnest possible thread of diamond.[1] This new type of carbon nanomaterial could have superlative properties that include the highest strength-to-weight ratio known, high-temperature superconductivity, and a unique combination of strength, flexibility, and resilience.

Laser processing is a good example of exploiting extreme temperatures to achieve unusual states of matter. This method induces electronic, optical, acoustic, thermal, and other interactions that ultimately result in materials with unique structures and chemistries not accessible through traditional routes.[2] Although this approach has been in use for over 50 years, a clearer understanding of the materials formation and transformation mechanisms during laser processing will result in the development of emerging approaches to laser-based synthesis with full spatial control of materials down to the smallest possible scales for energy applications.[3] Laser-based approaches have been successful in synthesizing nanomaterials and heterogeneous structures with novel properties, yet further development and fundamental understanding is necessary to transition such technologies beyond the research lab.

Whereas high/low pressures and high temperatures have been the most common methods of achieving extreme conditions in the past, more recent approaches define a number of currently active areas of research. Approaches to nonthermal materials synthesis from the gas phase,[4,5] including nonthermal plasmas,[6] magnetron sputtering,[7] flames,[8] and pyrolysis techniques,[9] offer a wide spectrum of novel materials synthesis opportunities that are not accessible through precipitation techniques that operate closer to equilibrium. Material compositions are controlled largely by gas kinetics and surface reaction kinetics, enabling the synthesis of materials far from thermodynamic equilibrium, such as “hyperdoped” semiconductors.[10] Synthesis conditions provide delicate control over the materials microstructure, from amorphous to crystalline.[11] One advantage of gas-phase synthesis is that it does not require the solvents, surfactants, or stabilizing ligands used in solution-phase synthesis approaches.[12] The lack of solvents also enables the use of very high synthesis temperatures, which are crucial for many covalently bonded materials. When coupled with ion soft landing,[13,14] which enables the deposition of mass-selected ionic clusters and nanoparticles onto surfaces at defined coverages and kinetic energies, gas-phase synthesis techniques provide unprecedented control over parameters that determine material performance.

Synthesis from solutions has also proved useful in providing extreme conditions. In particular, the striking finding that solution-phase reactions can be orders of magnitude faster in microdroplets and thin liquid films than in the bulk opens up unique opportunities for materials synthesis in confined environments.[15,16] Examples of emerging applications include preparative-scale synthesis on a short time scale,[17] synthesis with temporal control of reaction intermediates,[18] ambient reactive landing of molecules onto substrates using microsolvated ions,[19] and electrochemical nanoparticle synthesis in charged microdroplets.[20]

Extreme processing in the solid state has offered an alternative means of synthesizing new materials, using the concept of "driven systems." A driven (or open) system represents the case in which a material undergoing reaction or relaxation from an energized state receives a continued input of energy that can expose new kinetic pathways and new structures. The concept was originally utilized for materials undergoing radiation damage. However, the description has more general applications, such as for materials subjected to severe deformation, electrochemical processes, or other fields. A related area is induced alloying or mechanochemical synthesis (transduction), in which methods such as mechanical alloying, cladding, friction stir welding and cold spray deposition are widely used.

In a similar vein to processing in the solid state to obtain new materials, liquid metal dealloying has emerged very recently as a powerful new synthesis method to produce nanocomposite and nanoporous structures for a wide range of applications that exploit ultra-high interface areas.[21,22] This method is similar to electrochemical dealloying but is applicable to a wider range of elements of the periodic table.

For solid state and liquid metal processing, morphological control and phase evolution during phase transformations has been significantly informed by phase field modeling.[23,24] Solidification is the main processing route to produce structural alloys for energy applications ranging from transportation to power generation, yet controlling the solidification process to obtain desired microstructures and optimize materials properties remains a major challenge.

Novel materials and the challenge of stability. Many important materials have been discovered or developed using these extreme methods. For example, numerous materials used in energy harvesting (e.g., shape memory alloys, caloric materials, thermoelectrics) or transformation (soft magnetic alloys, some permanent magnets) are rarely equilibrium, stoichiometric compounds.[25] In fact, it is the defects, interfaces, or nonequilibrium microstructures that are crucial to optimizing the efficiency of these materials. Most discoveries in this class of materials have been in the realm of near-equilibrium processing.[26] Also, severe plastic deformation (SPD) is widely used to produce ultrafine-grain nanostructured materials with superior mechanical properties,[27,28] as well as to produce well-defined radiation-tolerant interfaces in nanocomposite materials.

One of the challenges associated with materials synthesized under extreme conditions is that the materials may lack stability. For example, despite recent advances in nanoscale/nanostructured materials synthesis, and the corresponding transformational property and performance enhancements, the research community has been severely limited by the lack of thermal stability or stability under application conditions (e.g., radiation, mechanical, corrosion) of these materials.[29,30] This barrier prevents scalability without losses in performance due to phase segregation, grain/crystal growth, decomposition, or other thermodynamic/kinetic–driven phenomena. Therefore, a major challenge and opportunity exists in the design of both nanomaterials and their corresponding scalable processing approaches to enable the retention of properties at the scale of applicability.[31]

Exploiting the complexity of living systems. The main objective of using extreme conditions is to achieve new states of matter. In that regard, the biological world offers a rich target for materials development because the extreme complexity of proteins—which comprise the fundamental building blocks of biomolecular materials—confers upon those materials a level of functionality not available in atomic and small-molecule systems. Unfortunately, direct synthesis of biomimetic materials, particularly sequence-defined polymers approaching the size and complexity of proteins, remains an unsolved problem. One approach to overcoming this limitation is to genetically code target proteins into bacterial systems,[32] which can then serve as the factories to produce these complex molecules at scale. The availability of the protein database as a means of identifying basic structural units, and protein engineering software like ROSETTA to design the interfaces between units, has enabled the design and synthesis of large artificial protein complexes, as well as 2-dimensional (2D) and 3D assemblies.[33,34] The use of bacterial cells as factories is also being explored for producing a wide array of chemical compounds and materials through genetic programming to direct the natural metabolic processes of cells toward production of these desirable products.[35]

Emerging characterization tools. Systems under extreme conditions are often, by their nature, difficult to probe with most analytical tools. X-rays and neutrons are among the most useful. In the past decade, the quality of interfaces has improved so much that, over large lateral length scales, the interfaces are perfect (have essentially unit cell perfection). This improvement has greatly enhanced the usefulness of x-ray and neutron reflectometry for materials characterization. However, despite dramatic advances in film growth, it is still difficult to grow high-quality interfaces over areas sufficient to enable inelastic scattering. Recent examples of new growth techniques, including immiscible growth,[36] synthesis of patterned substrates,[37,38] and highly nonequilibrium growth,[39] are providing precisely controlled interfaces grown parallel to the growth direction. This means the interface looks exactly the same at the bottom of the film as at the top, and films of micron or greater thickness can be grown for characterization by neutron scattering.

Scientific Challenges and Opportunities

Many of the scientific challenges associated with the energetic controls and transfer of mass that underlie these novel approaches to synthesis have yet to be explored and must be overcome before their full promise can be realized. The workshop panel identified three emerging research challenges that hold the most promise for transformative advances in the science of synthesis.

Conducting synthesis under far-from-equilibrium or extreme conditions

The use of synthesis in extreme or far-from-equilibrium conditions is being explored (1) to create new materials that cannot be made easily or at all using conventional near-equilibrium methods, and (2) to yield new materials that are robust under the same conditions in which they were made, or similar conditions—for instance, able to withstand environmental extremes in temperature, pressure, or radiation. The distinction must be made between extreme and far-from-equilibrium synthesis. Synthesis under extreme conditions may result in materials that are in equilibrium under such conditions, in which case their stability upon returning to ambient conditions may be an issue. “Far-from-equilibrium” suggests the presence of steep gradients in energy and chemical potential, both in space (e.g., high-temperature gradients) and in time (e.g., rapid inputs of energy via electromagnetic or acoustic waves, chemistry that uses or releases large quantities of energy, or rapid removal of energy via quenching from melt or vapor). In both cases, however, the development of new synthesis methods must include strategies for kinetic trapping of atoms and/or molecules in metastable configurations otherwise inaccessible via near-ambient processing conditions. Synthesis tools in this area include high-energy plasmas, high fields, high pressures and/or temperatures, chemistry in nanoconfinement, extreme mechanical deformation, large undercooling/overheating, and irradiation.

The development of predictive understanding of materials transformation pathways during synthesis, which involves competitive and cooperative nucleation and growth processes on a dynamic energy landscape, is a longstanding and persistent challenge in materials science (Figure 47).[40-42] When large driving forces are present, for example, in the case of highly supercooled liquids, a broad range of nonequilibrium phases and structures often significantly influence (and complicate) the observed behavior.[43] With sufficient cooling, materials can be either nanocrystalline or amorphous.[44] Because devitrification can proceed along complicated pathways that involve multiple stable or metastable crystalline phases,[45] predicting phase selection is a multivariant problem, depending on the initial state of the amorphous material and the heating rates imposed.[46] Quantification of the energetics—even for conceptually simple processes such as diffusive transport—is further complicated by the presence of many transient phases. Their nanoscopic size and short lifetimes, and the possibility that they will be buried inside constituent materials, make their observation and characterization extremely challenging, highlighting the synthesis challenges in this area.

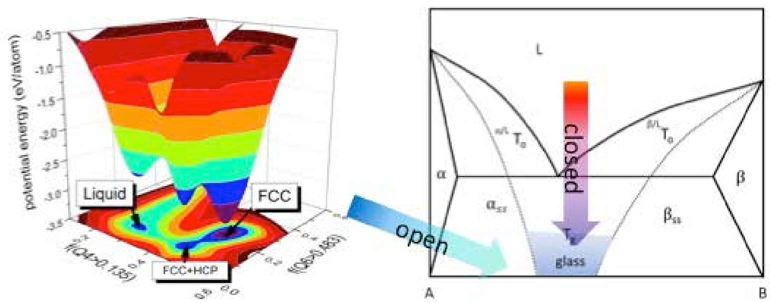

Figure 47. Control and understanding of far-from-equilibrium synthesis will require advanced computational tools combined with in situ characterization to predict complex energy landscapes, as well as differences in pathways for open vs. closed systems. | *Image courtesy of Matt Kramer, Ames Laboratory and John Perepezko, University of Wisconsin.*

Opportunities for synthesis under extreme or nonequilibrium conditions can be found in every phase. For instance, gas-phase materials synthesis methods that are far-from-equilibrium include nonthermal plasmas[47,48] (Figure 48),[47] magnetron sputtering,[7] and pyrolysis.[9,49,50] Those methods offer a wide spectrum of novel materials that are not accessible through precipitation techniques that operate close to equilibrium. The composition and structure of materials made by these methods are largely controlled by rapid gas and surface reaction kinetics, enabling facile synthesis of materials such as hyperdoped semiconductors.[51] Synthesis conditions can also provide delicate control over the materials microstructure from amorphous to crystalline.[52,53] And a particularly attractive feature of gas-phase synthesis approaches is that they do not require the solvents, surfactants, or stabilizing ligands used in solution-phase techniques.[54] Thus they enables the synthesis of high-purity materials at high temperatures and growth rates.

Figure 48. Nonthermal plasmas are gas phase media far-from-equilibrium that, for instance, enable the synthesis of highly luminescent silicon nanocrystals.[6] | *Reprinted with permission from U. R. Kortshagen. "Nonthermal Plasma Synthesis of Nanocrystals: Fundamental Principles, Materials, and Applications." Chemical Reviews 116 [18]: 11061–27. © 2016 American Chemical Society.*

Physical processes underlying gas-phase materials synthesis have been explored within the context of plasma-enhanced chemical vapor deposition, but a general understanding of relevant phenomena beyond the context of thin film growth (e.g., particle nucleation and growth in the gas phase) is still a significant research challenge and opportunity. How can one control the nanomaterials stoichiometry, size distribution, aggregation state, and morphology? How can doping and alloying be controlled during gas-phase synthesis, and which mechanisms determine whether dopants are activated or not? What is the role of surface states, and which strategies can be used to manipulate and/or remediate them? How can the efficiency of nanoparticle and cluster formation be controlled to ensure that the maximum amount of sputtered material is converted into usable nanoparticles at the substrate? Although numerous studies have characterized how experimental parameters influence nanoparticle properties, this information is empirical, and predictive models that would enable the rational design of the synthesized species are lacking. New capabilities are needed for the controlled physical synthesis, mass and size selection, and controlled immobilization of bare clusters and nanoparticles. This is particularly the case for complex binary, ternary, and quaternary compounds and alloy materials that may adopt several different internal mixing patterns, including core-shell, segregated, mixed, and multi-layer motifs.

Moving from the gas phase toward condensed phases, a striking finding—that solution-phase reactions can be orders of magnitude faster in submicron-size droplets and thin liquid films than in the bulk—opens up unique opportunities for materials synthesis in confined environments.[15,16] Physical and chemical processes in such dynamic systems with ultra-short lifespans resulting from rapid evaporation, and steep gradients due to rapidly changing chemical composition, may provide access to products not accessible using traditional bulk synthesis approaches. Examining reaction pathways in such confined environments requires new modeling approaches, and the development of new in situ characterization techniques capable of measuring droplet size and composition beyond the diffraction limit with high temporal resolution in a high-throughput manner. The study of accelerated reactions in microdroplets and thin films is at an early stage. Physical and chemical characterization of small droplets below the diffraction limit in size, with ultra-short lifespans due to rapid evaporation, and rapidly changing chemical composition, is a major analytical challenge. Understanding of the kinetics, mechanisms, and selectivity of reactions in confined environments is needed to transform this emerging technology into a robust tool for materials synthesis.

Laser-based methods can excite a variety of electronic, optical, acoustic, thermal, and other processes that ultimately result in materials with unique structures and chemistries not accessible through traditional routes.[55] Although laser processing has been used for over 50 years, the development of advanced sources, novel beam control methods, and high-resolution characterization has opened the door to new kinds of synthesis that can enable the creation of novel structures and materials with features down to the smallest size scales. In addition, laser-based approaches have been successful in making nanomaterials and heterogeneous structures with novel properties in zero, one, two, and three dimensions.[56]

Understanding chemical and physical processes occurring on time scales ranging from femtoseconds to the continuum during light-matter interactions is necessary for transforming laser processing technology from one relying on a laser as a simple localized source of heating, to one with full spatiotemporal control over the interactions and the resulting transient and permanent modifications to materials. Current and future laser-based applications in materials processing will require advanced feedback and control over the spatial and temporal properties of the incident laser beam. This will require further breakthroughs in sensors, sources, and beam delivery, and approaches to real-time characterization of materials undergoing modification.

Pressure can dramatically alter chemical bonding and induce chemical reactions that are otherwise difficult to achieve; by appropriate consideration of the energy landscape/barriers, such high-pressure transformations can be designed to allow the synthesis of structures stable to quenching to ambient pressure. High-pressure synthesis in a broad range of chemical/materials systems is possible. For example, high-pressure synthesis of a sodium compound, Na_4Si_{24}, followed by subsequent removal of the sodium, resulted in a new semiconducting allotrope of silicon that has a quasi-direct bandgap that falls within the desired range for solar absorption.[57] Another example is the high-pressure synthesis of low-dimensional sp^3-bonded carbon nanothreads from benzene, described earlier.[1] Further development of the organic solid state chemistry underlying the synthesis of nanothreads could allow for a broad range of low-dimensional nanomaterials that have the potential to exhibit best-in-class structural, electronic, vibrational, and thermal properties, ordered at length scales from atomic to macroscopic. The synthesis at 18 GPa of $FeTiO_3$ validated the prediction of multiferroic behavior in the high-pressure form of this compound.[58]

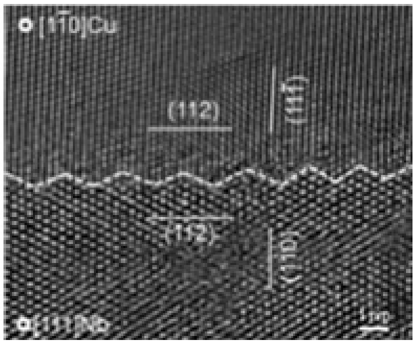

Figure 49. Synthesis of nanolaminates via extreme plastic straining of bimetallic composites can lead to a natural selection of interfaces that possess atomic order.[60] **|** *Adapted with permission from I. J. Beyerlein et al. 2015. "Emergence of Stable Interfaces under Extreme Plastic Deformation." PNAS 111[12]: 4386–90. DOI: 10.1073/pnas.1319436111.*

These studies point to novel routes for material synthesis under extreme environments, in which nanocomposites driven far-from-equilibrium lead to the emergence of low-energy interphase boundaries that are both point defect sinks and morphologically and chemically stable at high temperatures. Such synthesis routes are particularly relevant for the synthesis of damage-tolerant materials. For example, the extreme conditions occurring in SPD can lead to the synthesis of materials designed for tailored response in extreme environments (e.g., high irradiation doses, high stresses, high temperatures). Furthermore, due to the ultrafine-grained nature of materials prepared via SPD, this process may be used to produce well-defined radiation-tolerant interfaces in nanocomposite materials (Figure 49).[28,59,60]

SPD is an example of driven system processing. Although widely used methods such as mechanical alloying, cladding, friction stir welding, and cold spray deposition are examples of driven systems, the fundamental nature of the bonding, and the atomic-scale mixing, examinations have been almost uniformly empirical in nature, limiting their generality. It seems evident that atomic-scale interfacial processes are important, and some mechanisms have been proposed; but a predictive capability is not available, especially to identify new kinetic pathways. Furthermore, understanding the connection between defect-level phenomena and material response is critical for improved synthesis of radiation-tolerant materials, as well as novel metastable structures.[61] Improved interatomic potentials for translational modeling/simulations of such materials over different length scales, including design parameters such as 3D defects (voids, pores, precipitates) and single-atom response, are needed for future development.

Like all far-from-equilibrium or extreme synthesis methods, non-obvious emergent behavior is quite common. For instance, while SPD is used to refine the microstructure and increase the dislocation density in metallic materials, it was recently discovered that SPD via accumulative roll bonding of Cu-Nb nanolaminates can lead to the synthesis of preferred interfaces possessing regular atomic order,[60] and that the atomic structure of these interfaces can be controlled via strain path changes in deformation processing.[62] Roll-bonded Cu-Nb nanolaminates containing such low-energy interfaces were found to be morphologically and chemically stable at high temperatures.[63] Perhaps more important, these materials contain two immiscible materials, with interface structure and length scale at the nanoscale. This unique morphology leads to high densities of internal interfaces that serve as sinks for point defects and consequent radiation damage tolerance.

Extreme synthesis environments include the unusual and complex chemistry of radionuclides, for which synthesis is often complicated by the problem that reactants are decaying into other reactants, sometimes at time scales even faster than microseconds. However, understanding the synthesis and chemistry of such materials is critical for developing advanced waste forms for specific radionuclides with atomic-level control of structure. Also, the ability to tailor the morphology of the resultant materials plays a central role in mitigating the historic legacies, ongoing commercial use in medical imaging and other applications (e.g., thorium), and the continued use of nuclear fission as a source of energy. Early actinides that are the most relevant to these issues are especially hard to regulate during synthesis because of undesired redox changes, and their fundamental coordination chemistry cannot yet be predicted.[64] Hence, true materials design is simply not possible for these radionuclides at this point in time. However, while many of the human-made radionuclides have been available since the late 1940s, the tools for understanding the chemistry and physical properties of these elements have become available only in the last two decades. These new analytical techniques, combined with synthetic methods and theory, will enable the rational design of heavy element materials needed for a future that includes nuclear energy.[65]

Given the variety of methodologies used to induce far-from-equilibrium synthesis of materials, it is instructive to consider the combination of multiple methods to create unique kinetic pathways through the thermodynamic space of materials. For instance, by combining multiple light sources in laser synthesis[66] or combining energetic ion beams with physical vapor deposition,[67] the direct writing of features a few nanometers in size or the fabrication of thin films with user-specified textures and properties is feasible. With better understanding of the underlying physics and chemistry of the far-from-equilibrium synthesis methods, the capability to combine research techniques will enable the production of new materials with desired properties and advanced performance.

Creating complex hybrid materials

There is nascent recognition that a broad spectrum of composite materials can exhibit extraordinary properties when a synergistic interaction between constituent phases or classes of materials is engineered into the composite. A dramatic example is the single-phase intermetallic FeSe, which by itself is an unconventional superconductor with a transition temperature of 9 K. Remarkably, very thin films of FeSe deposited on $SrTiO_3$ or $BaTiO_3$ exhibit transition temperatures near 75 K.[68] Theoretical modeling suggests electron-phonon coupling across the intermetallic/oxide interface is responsible for the synergistic response. A further doubling of the transition temperature is predicted if nanoscale FeSe is confined on both surfaces.[68-71] Ultimately, an unconventional superconductor composite and oxide matrix might be a means to achieve room-temperature superconductivity, which has otherwise proved elusive in single-phase materials. From a synthesis standpoint, this system also represents a challenge in fabricating composite materials containing constituents from more than one class of materials, in this case an intermetallic thin film and an oxide.

Multicomponent, multiphase materials, especially with complex 3D microstructures, are fundamental to the concept of drawing out synergies between materials classes in intimate contact; they have significant impact across the spectrum of materials relevant to basic research challenges for energy. In addition to electronic materials, such synergies can be exploited in, for example, catalysts, capacitive materials, and materials with tailored structure/response behavior. In such cases, we are primarily concerned with multiphase and multiclass composite materials that have constituents (building blocks) individually synthesizable using near-equilibrium approaches, but whose integration into a functional composite is challenging. Examples of complex hybrid materials are illustrated in Figure 50.[72-75]

One of the most important goals of modern materials physics and nanoscience is to control materials and their interfaces to atomic dimensions through controlled synthesis. Because of their reduced dimensionality and/or enhanced interfacial areas, nanocomposite thin films (such as nanoparticles dispersed in a matrix, nanofibers or nanopillars dispersed in a matrix, and nanolaminate or layered heterostructures films or superlattices) have been the model systems to investigate enhanced interface effects on the physical properties of complex materials.[74] Furthermore, a composite, consisting of two or more constituents with different forms and/or elemental compositions, can produce emergent behaviors through coupled competing order parameters. In other words, the physical properties of a nanocomposite are determined by the properties of the constituents and the interactions among them. Epitaxial nanocomposites, in which emergent behaviors can be achieved by interfacing different materials at the nanoscale, provide a new design paradigm to produce enhanced and/or novel properties that cannot be obtained in the individual constituents. Several recent experimental results have shown that new functionalities and emergent behavior in complex materials can be obtained through constituent interactions on the micro-, meso-, and macro-scales.[76] However, empirical rules are currently used to guide research on such materials, and the state of the art remains at the "observation/validation" stage. Development of synthetic strategies (closing the loop of theory/computation, controlled synthesis, and advanced characterization) is needed to synthesize novel materials with entirely new or significantly improved functionalities in such dimensionally variegated materials. Further efforts in this area will lead to tailored, scale-dependent functionality in materials.

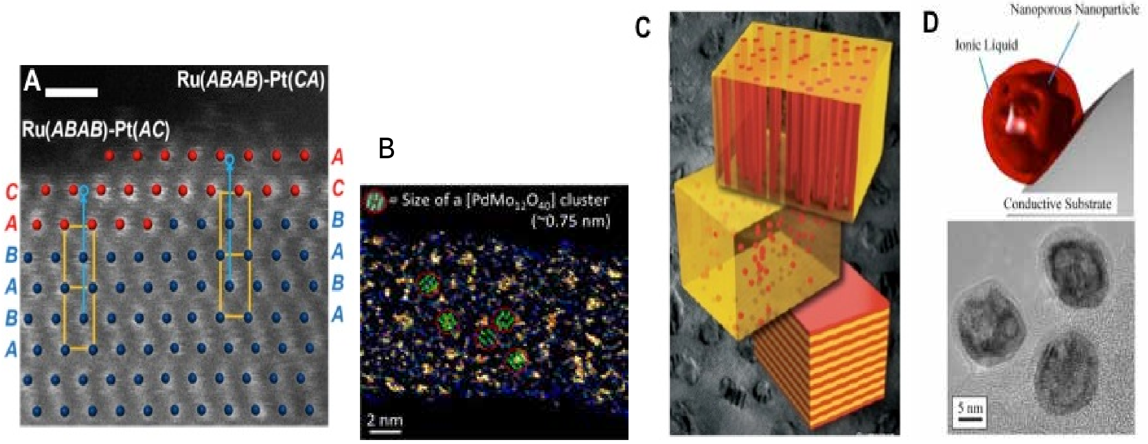

Figure 50. Examples of complex hybrid materials. (A) Atomic ordering of core-shell interface for enhancing catalyst activity and durability, illustrated by a STEM image of a platinum (Pt) bilayer on ruthenium (Ru) core. Ru hcp to Pt fcc structure at their interface;[72] (B) Ion soft landing enhances stability and capacitance of carbon nanotube (CNT) electrodes by uniformly depositing pure redox-active polyoxometalate anions (bright spots) onto CNT.[73] (C) Background: Plan-view transmission electron microscope image of a vertically aligned nanocomposite $LaFeO_3$:$CoFe_2O_4$ film with $CoFe_2O_4$ nanopillars embedded in an $LaFeO_3$ matrix. Nanocomposite architectures: (top) nanowires, nanotubes, or nanoplates dispersed in a matrix; (middle) nanoparticles dispersed in a matrix; (bottom) nanolaminate or heterostructured thin films or superlattices;[74] (D) Fuel cell oxygen reduction electrocatalysts: ionic-liquid impregnated Pt-shell/Pt-Ni core nanoporous nanoparticles.[75] **|** *[A] Reprinted with permission from Y.-C. Hsieh et al. "Ordered Bilayer Ruthenium–Platinum Core-Shell Nanoparticles as Carbon Monoxide-Tolerant Fuel Cell Catalysts." Nature Communications 4 [2466]. DOI: 10.1038/ncomms3466. © 2013 Macmillan Publishers.* **|** *[B] Reprinted with permission from V. Prabhakaran et al. "Rational Design of Efficient Electrode-Electrolyte Interfaces for Solid-State Energy Storage Using Ion Soft Landing." Nature Communications 7 [11399]. DOI: 10.1038/ncomms11399. © 2016 Macmillan Publishers.* **|** *[C] Reprinted from MRS Bulletin 40[9]: cover and front matter, 1–7. Transmission electron microscope image by Aiping Chen; schematic drawing by Chris Sheehan. C.-W. Nan and Q. Jia. 2015. "Obtaining Ultimate Functionalities in Nanocomposites: Design, Control, and Function. 719–723. [D] Reprinted with permission from J. Snyder, K. Livi, and J. Erlebacher. "Oxygen Reduction Reaction Performance of [MTBD][beti]- Encapsulated Nanoporous NiPt Alloy Nanoparticles. Advanced Functional Materials 23 [440]: 5494–501. © 2013 John Wiley and Sons.*

Interface composition control at the atomic scale is particularly important in atomic-scale compositional ordering in catalytic nanoparticles. Obtaining high-activity, high-durability, ultra-low platinum-group metal content catalysts—creating materials with new composition, structure, morphology and new properties—requires addressing challenges in refining synthetic methods, such as atomic-level control of the deposition of monolayer (most often platinum) or multilayer single-metal or heterometallic shells on nanoparticle cores. A range of material classes needs to be used as cores: metals, alloys, intermetallics, oxides, carbides, and nitrides of various shapes, sizes, facets, and compositions, including passivating refractories and their alloys. By controlling both ligand and strain effects through core-shell interactions, highly stable and durable catalysts may be developed. The synthesis of stratified heterometallic (onion shell) nanoparticles offers the potential for catalysts with new properties.[77] Other promising approaches involve surface segregation of modified alloy nanoparticles[78] and nanoparticles obtained by dealloying.[75] The development of catalysts based on non-platinum metals, and nonmetallic catalysts with improved activity and stability, are both a challenge and a major opportunity.[79]

Further enhancements of electrochemically active materials can be achieved by taking advantage of morphological control of multicomponent architectures and surface composition. For instance, nanoparticle catalysts in hydrogen storage structures[80] exemplify a concept in which palladium nanoparticles embedded in an magnesium oxide surface mediate hydrogen transport and storage into an underlying magnesium film. Another example is oxygen reduction reaction catalysts, often synthesized via dealloying of platinum-transition metal alloys,[81] which can form nanoporous nanoparticles. By further impregnating such catalysts with ionic liquids that are both oxophilic (drawing in reactants from the aqueous environment) and hydrophobic (expelling product water), aggregate activity is enhanced through a physical manifestation of Le Chatelier's Principle.[82] Already leading to the most active catalysts for fuel cell oxygen reduction,[83] this concept should be generalizable to more challenging reduction reactions, such as electrochemical reduction of carbon dioxide or even electrochemical reduction of nitrogen to ammonia.

Another new method of making novel nanocomposite materials with precisely controlled uniform distribution of individual building blocks is soft landing of mass-selected ions.[13,14] Ion soft landing enables the deposition of mass-selected complex ionic species (e.g., clusters, nanoparticles, organometallic complexes) onto surfaces at defined coverages and kinetic energies, thereby providing unprecedented control over parameters that determine material performance. For example, soft landing provides accurate control over the size and surface coverage of deposited clusters, which enables emergent mesoscale behaviors such as catalytic and electrochemical activity to be studied precisely as functions of interparticle distance.[84] Recent studies have demonstrated the use of ion soft landing for the controlled design of novel interfaces for fundamental studies in catalysis and energy storage.[85] For example, ion soft landing was used to enhance the stability and capacitance of carbon nanotube (CNT) electrodes by uniformly depositing pure redox-active polyoxometalate anions onto CNTs.[73] Current ion soft-landing capabilities provide access to novel 2D materials of either isolated species or their mesoscale assemblies. Future development of bright ion sources will enhance ion currents by several orders of magnitude and thereby facilitate 3D molecular printing of materials using this technique.

Achieving hierarchical control during materials synthesis and processing

Understanding the synthesis of materials so that structure is controlled at multiple length scales is critical to enhancing and stabilizing materials properties, and it provides motivation to develop methods of synthesis that simultaneously control structure at the atomic, meso, and bulk scales. A longstanding challenge in this area is the development of porous materials (e.g., zeolites, mesoporous carbon) with supported nanoparticle catalysts. In such materials, mesoporosity controls the transport of reactant and products into and out of the active region. Simultaneous structural, compositional, and morphological stability of the surface nanoparticle assembly is required, often in chemically aggressive atmospheres. In this general view, this problem is analogous to synthesizing nanocrystalline metals, where stabilization of the mesoscale grain structure is required for retained functionality. Synthesized materials must exhibit structural and/or phase stability in addition to well-controlled microstructure. Examples of materials considered by the workshop panel are shown in Figure 51.[86-89]

A particularly versatile new method for introducing hierarchical structure and morphological evolution in hard and composite materials is dealloying. In this subtractive approach to synthesis, one component of a uniform solid solution is selectively dissolved out under certain conditions, while the remaining component diffuses to reorganize into a 3D porous phase—a mechanism that does not introduce any new grain boundaries into the parent material.[90] Dealloying via electrochemical dissolution has been used in high-performance electrocatalysis; more recent innovations in this area include multi-step dealloying to produce hierarchical porosity[86] and using metal melts to drive dissolution,[91]or liquid metal dealloying.

Liquid metal dealloying has emerged very recently as a powerful new synthesis method to produce nanocomposite and nanoporous structures from a broader range of elemental precursors (including refractory metals[92] and semiconductors).[93] More broadly, obtaining the desired microstructures and materials properties in alloys through solidification and melting—which remains the main processing route to synthesize structural alloys for energy applications ranging from transportation to power generation—generally represents a challenge. Optimization and fundamental understanding can be informed by phase field modeling;[22] but the parameter space in this area is very large, especially when modifications of material structure and composition via post-processing, such as carburization or nitridization of internal interfaces, are considered.

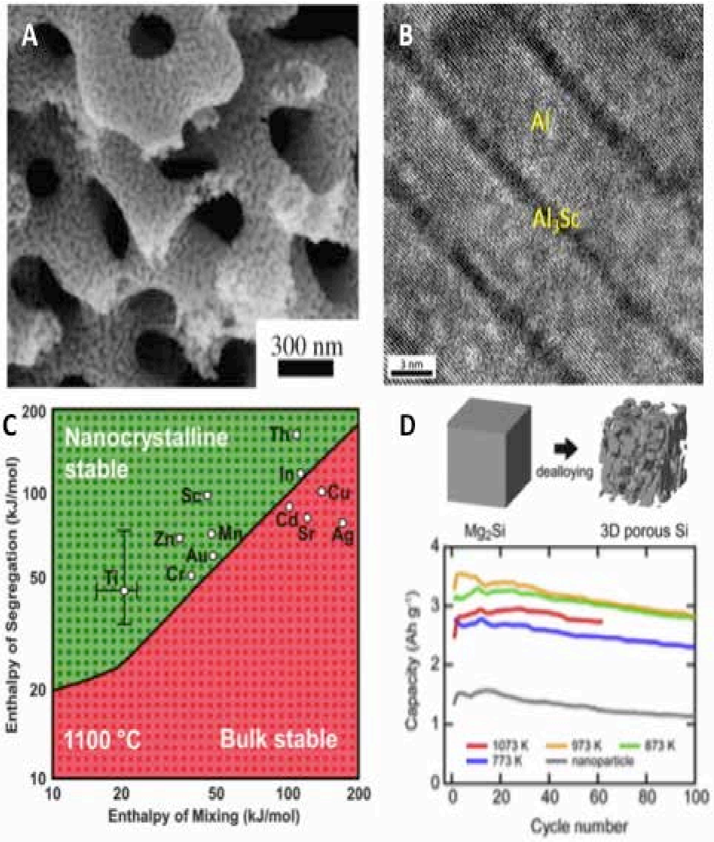

Figure 51. Examples of materials synthesized with controlled hierarchical structure. (A) Bimodal porosity in nanoporous gold formed via a multi-stage dealloying protocol.[86] (B) Nanocomposite thin films, in which the scandium content was tuned beyond that which is available with conventional approaches.[87] (C) Stability map for nanocrystalline tungsten showing which elements segregate to boundaries and suppress grain coarsening.[88] (D) High-surface-area nanoporous silicon for lithium battery anodes formed via dealloying in a metallic melt.[89] | *[A] Reprinted with permission from Z. Qi and J. Weissmuller. "Hierarchical Nested-Network Nanostructure by Dealloying." ACS Nano 7 [7]: 5948–54. © 2013 American Chemical Society.* | *[B] Reprinted with permission from M. A. Phillips et al.* | *"Microstructure and Nanoindentation Hardness of Al/Al_3Sc Multilayers." Acta Materialia 51 [11]: 3171–84. © 2003 Elsevier.* | *[C] Reprinted with permission from T. Chookajorn et al. "Design of Stable Nanocrystalline Alloys." Science 337: 951–54. DOI: 10.1126/science.1224737. © 2012 American Association for the Advancement of Science.* | *[D] Reprinted from Journal of Power Sources 306, T. Wada et al. "Preparation of Three-dimensional Nanoporous Si Using Dealloying by Metallic Melt and Application as a Lithium-ion Rechargeable Battery Negative Electrode," 8–16, 2016, with permission from Elsevier.*

Nanocrystalline metals have been the subject of extensive study because of their extraordinary property improvements compared with their coarse-grained counterparts.[94,95] However, despite recent advances in nanocrystalline materials synthesis and processing, the resultant materials remain severely limited by a lack of thermal stability of the controlling structures and phases. This is manifested in the form of phase segregation, grain/crystal growth, decomposition, and other thermodynamic/kinetic–driven phenomena that prevent scalability without a loss in performance.[96] Thus, the corresponding major scientific challenge is to create disruptive alloy design paradigms and synthesis methods that enable the stabilization or kinetic/thermodynamic trapping of structures and/or phases.[97] Research opportunities point to promising nascent synthesis approaches that enable precision control of interface behaviors, including predictive solute segregation to reduce grain boundary interfacial energy,[88,98] amorphous intergranular regions,[99] immiscible systems,[100] and novel theoretical and modeling approaches.[101]

Potential for Energy Relevant Technologies

Emerging synthesis approaches using far-from-equilibrium conditions and/or unusual chemistries provide access to novel nanomaterials (e.g., metals, metal alloys, metal oxides, carbon), including both amorphous and nanocrystalline materials; 2D and 3D nanostructured patterns; nanocomposites with outstanding mechanical properties and high tolerance to radiation damage; and hierarchical materials with interfaces that are crystallographically, morphologically, and chemically stable under extreme conditions of irradiation, deformation, and temperature. These and other new materials have potential applications in catalysis, nuclear power reactors, energy harvesting and storage, photovoltaics, thermoelectrics, and plasmonics. Understanding of the basic science underlying the control of the composition and mesostructure of materials may enable scalable manufacturing of ultra-high-strength lightweight alloys for transportation, the engineering of high-efficiency nanostructured soft/hard magnets for electric motor components, coatings for environmental and wear resistance, and interface design to control radiation damage and microstructural control during the additive manufacturing of advanced materials. It is recognized that radically new methods of materials synthesis require a fundamental understanding of kinetics and thermodynamics in systems driven far from equilibrium in a dynamic energy landscape, along with new methods of in situ characterization and theory and computational modeling.

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8. Transformative Research Capabilities I: In Situ Characterization

Mechanisms and pathways of synthesis are difficult to determine when the information available is limited to input components and final outcomes (ex situ studies). Attempts to manipulate outcomes by influencing pathways to achieve, for example, trapping of persistently metastable states, require an understanding of those mechanisms and pathways, as well as the underlying kinetic and thermodynamic controls. In situ methods are uniquely suited to deliver this information. Spectroscopic methods can be used to determine the evolution of atomic/molecular structure and bonding of both liquids and solids. Scattering techniques can be employed to follow the development of dimensionality and order. Imaging techniques provide real-space views of synthetic pathways, as well as measurements of rates from which kinetic barriers and free energy landscapes can be extracted. In general, combining different characterization modalities (multi-modal analysis) is actually what is needed to gain a complete understanding. The workshop panel evaluated the challenges and opportunities presented by the use of a wide range of in situ methods and defined a primary research focus area: Identifying and controlling synthesis pathways by using in situ characterization tools that match the length scales, time scales, and sensitivities required to understand mechanisms and predict material outcomes. The role of quasi-real-time analysis and the use of data analytics to control experiments and to mine databases of inputs, intermediates and outputs are also discussed.

Current Status and Recent Advances

Introduction. Recent developments in characterization tools place us on the cusp of transformational breakthroughs in the understanding of materials synthesis. Exciting developments in sources, detector technologies, algorithms, computation, and data handling are providing unprecedented time, energy, spatial, and momentum resolution, with exceptional (approaching single-atom) sensitivity that will allow for a completely new paradigm for predictive materials *discovery* that goes well beyond computational materials *prediction*, which is the current frontier in materials genomics.

X-ray scattering. Synchrotron sources are producing beams of unprecedented power and brightness, and developments in beam line optics are conditioning these beams to micron and nanometer sizes with very high fluxes. Detectors are more sensitive, lower-background, and stable. Crucially, all these developments are being pushed up the electromagnetic spectrum to harder x-rays, which are particularly useful for in situ structural analysis and core-level spectroscopies throughout the periodic table. Small beams with high fluxes allow spatially resolved measurements that allow for nanofluidic reactors for solvothermal syntheses, and synthesis-on-a-chip technologies by which multiple reactor devices are patterned onto a substrate. These technologies are well matched with emerging nanoscale additive manufacturing technologies, such as dip-pen nanolithography and ink-jet printing of reagents, and nanoscale subtractive technologies based on focused ion beams and e-beam lithographic methods. The high throughput enabled by these methods allows for the combination of diffraction with imaging approaches, such as tomographic reconstruction, to obtain structural information in a spatially resolved way, thus allowing synthesis in heterogeneous environments to be studied.

As an example, crystalline species precipitate out of fluxes or solutions under particular reaction conditions. In situ x-ray diffraction (XRD) experiments yield information on the preparation of extended solids with high time resolution that allows for reaction kinetics and for the formation of reaction intermediates to be studied, giving novel insights into the synthesis pathway. Even complex materials such as metal-organic frameworks (MOFs) forming under solvothermal conditions may be studied (Figure 52).[1] In this case, the in situ tool is both diagnostic and predictive. The diagnostic aspect comes in the monitoring of the metastable phases that form before the final product is stabilized. The predictive aspect is in the calculation of activation barriers from the time-dependent x-ray data. Knowing the activation energies would allow directed synthesis of MOFs to be better guided. In addition to water, other solvents used for the growth of crystalline materials can be probed with these methods. Examples of the successful use of situ monitoring include ternary metal chalcogenides from polychalcogenide fluxes.[2]

Nanoparticles and clusters pose particular challenges to in situ characterization since they form quickly, have surface structures that are not easily probed by current techniques, and are mobile in solution. They are amenable to study using atomic pair distribution function (PDF) methods or extended x-ray absorption fine structure (EXAFS) spectroscopy. In situ synthesis has been monitored by PDF,[3] and a combined in situ EXAFS and diffraction study has shown that a partial view of the pre-formed clusters and crystalline phase can be seen in the formation of the organometallic sulfide $[Co(tren)][Sb_2S_4]$ (Figure 10 [Section 3]).[4]

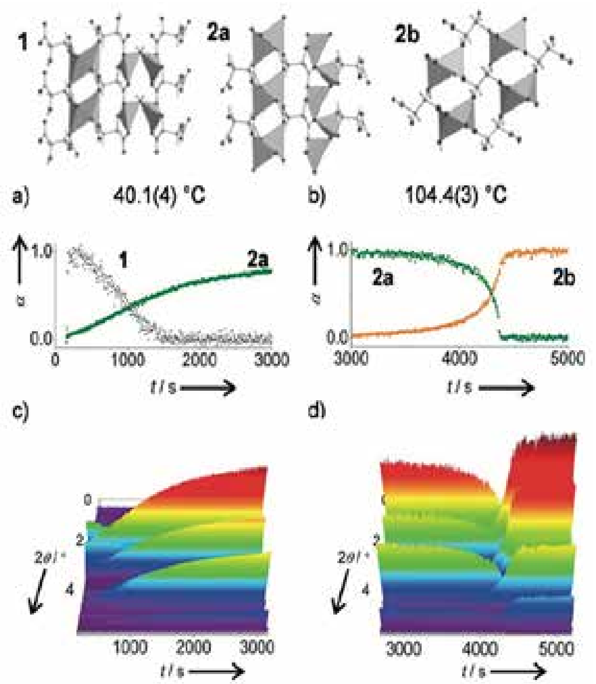


Figure 52. In situ monitoring of hydrothermal synthesis of a metal-organic framework by synchrotron XRD as a function of time.[1] | *Reprinted with permission from H.H.M. Yeung et al. "In Situ Observation of Successive Crystallizations and Metastable Intermediates in the Formation of Metal-organic Frameworks. Angewandte Chemie-International Edition 55[6]: 2012–16. DOI. 10.1002/anie.201508763. © 2016 John Wiley and Sons.*

Understanding changes at nanoparticle interfaces is also in a nascent state: transmission electron microscopy (TEM) alone does not reveal the surface structure of SnO_2 particles, but a comparison of molecular dynamics simulations and PDF data reveals hydroxide termination and aqueous coordination (Figure 53).[5] However, it does so only in the static case—in situ techniques could tie changes in these interfaces to phase selection, growth, and assembly. Increased 3-dimensional (3D) resolution via x-ray and electron imaging techniques could permit the ångstrom-level interrogation of surface structure. Measurement of many discrete particles could be facilitated by automated particle tracking and data tagging with orientation, phase, and reaction conditions. Measurements on longer length scales, such as the evolution of particle size from small-angle neutron scattering/small-angle x-ray scattering (SANS/SAXS); the diffusion behavior from neutron spectroscopy; and interactions with surfaces would provide a broad picture of the processes that drive materials synthesis from solution.

To establish the design rules for assembly at the next length scale on which nanoparticles form superlattices, information about pathways and energy landscapes is needed, requiring observations as structure evolves in both space and time. Scattering-based techniques such as SAXS, WAXS (wide-angle x-ray scattering), SANS, and reflectivity have dominated the characterization of assembly, but to date most measurements have been applied to the final structure; in situ characterization efforts have only recently started. Examples include structural transformation induced by external fields (e.g., solvent, thermal, electric) in block-copolymer films,[6] roll-to-roll printing of organic photovoltaics,[7] spin-coating kinetics of polymer films,[8] 2D superlattice assembly of inorganic colloidal particles or biomimetic blocks (such as microphages) at interfaces,[9,10] and phase transformations of DNA-linked nanoparticles.[11]

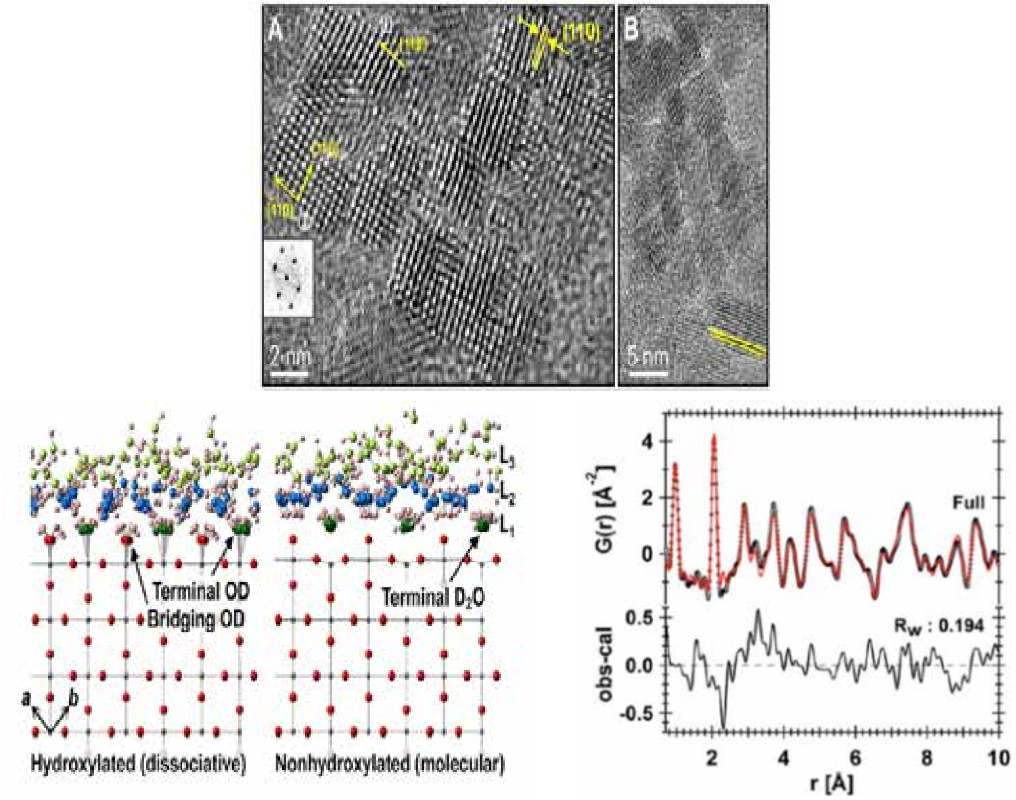


Figure 53. TEM (upper) shows the morphology of SnO_2 nanoparticles, but the surface structure is not apparent until molecular dynamics simulations (lower left) are compared with neutron PDF data (lower right). Surface structure and correlations in the solvents near interfaces are a key interest and require multiple techniques. Combining this information in an in situ experiment would lead to an understanding of how these interface effects can be controlled during reactions.[5] **|** *Reprinted with permission from H.-W. Wang et al. "Structure and Stability of SnO_2 Nanocrystals and Surface-Bound Water Species." Journal of the American Chemical Society 135 [18]: 6885–95. © 2013 American Chemical Society.*

In situ x-ray microscopy is having a direct impact on the characterization of synthetic pathways and processes. Sealed liquid cells are now routinely used for spectromicroscopy measurements, including scanning transmission x-ray microscopy (STXM), and these cells are readily modified to operate as microreactors. Furthermore, the capabilities for flow-through studies are rapidly developing for the study of processes in situ; Commercial instruments have recently entered the market that will facilitate measurements of dynamic processes by providing thermal and electrochemical control of the reaction environment. The high spatial (<30 nm) and spectral resolutions (~0.1 eV) give an unprecedented window into the formation of nanoparticles. A recent study demonstrated a resolution of <5 nm (Figure 54).[12]

Soft x-ray spectroscopies, specifically x-ray absorption (XAS) and atomic emission spectroscopy, are powerful tools for in situ characterization of interfacial structure and bonding. Research reported in the past 2 years has demonstrated that improvements in flux and detector technologies at synchrotron sources, coupled with creative cell design, now extend these measurements to the soft x-ray regime under aqueous environments. As a result, dynamic x-ray spectroscopy measurements of interfacial phenomena may now be conducted for materials containing low- to moderate-Z elements.[13,14] This capability has the potential to enhance the understanding of a wide range of interfacial processes, ranging from catalytic mechanisms to electrode function and from electroplating to synthetic pathways. For example, Bagge-Hansen and co-workers used a fluorescence yield detection mode to identify changes in surface bonding and transient strain gradients in operating porous carbon electrodes.[15] Velasco-Velez et al. used a flow cell and a surface-sensitive electron yield mode of detection to determine the structure of water in close proximity to a polarized gold electrode.[14] Significantly, both of these projects involved tightly coupled experimental and modeling efforts; and it is evident that continued development of advanced modeling will be invaluable in support of future in situ XAS studies.

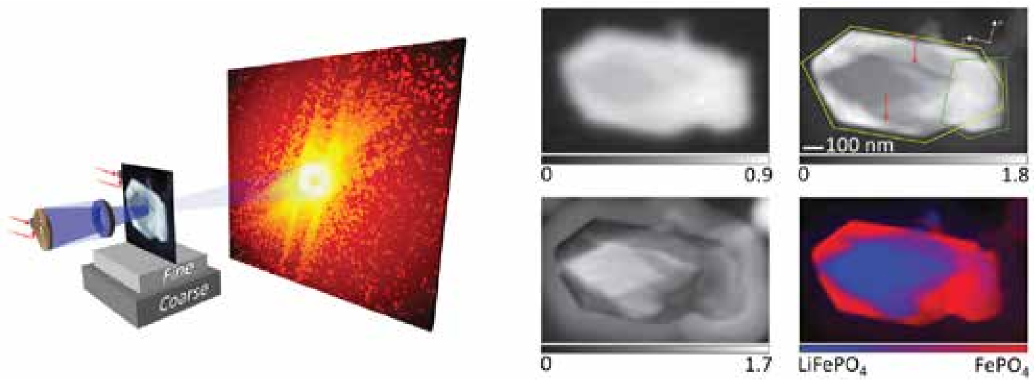


Figure 54. Layout of the soft x-ray microscope at the Advanced Light Source at Lawrence Berkeley National Laboratory (left) and the resulting x-ray micrographs of $LiFePO_4$ particles. (right). The higher resolution of the ptychographic measurement is evident in the top right sub-panel compared with the top left STXM measurement. The lower sub-panels show different information available from analysis of the phase fields of the images.[12] | *Reprinted with permission from D. A. Shapiro et al. "Chemical Composition Mapping with Nanometre Resolution by Soft X-Ray Microscopy." Nature Photonics 8 [10]: 765–69. © 2014 Macmillan Publishers.*

High fluxes of x-rays at modern sources also allow dynamics to be studied on many length scales, from direct atom dynamics (phonons) to motions of large ensembles of atoms using x-ray photon correlation spectroscopy. Measurements with femtosecond time resolution are also possible at x-ray free electron laser (XFELs) facilities such as the Linac Coherent Light Source (LCLS) at the Standard Linear Accelerator Center, which offers energies ranging from ultraviolet to hard x-rays. New sources, the LCLS-II and the proposed LCLS-II-HE, have higher repetition rates with lower flux per pulse and are well suited to time-resolved in situ measurements. The ultra-fast diffraction measurements would reveal the reaction pathways and structures of the intermediates (Figure 55).[16]

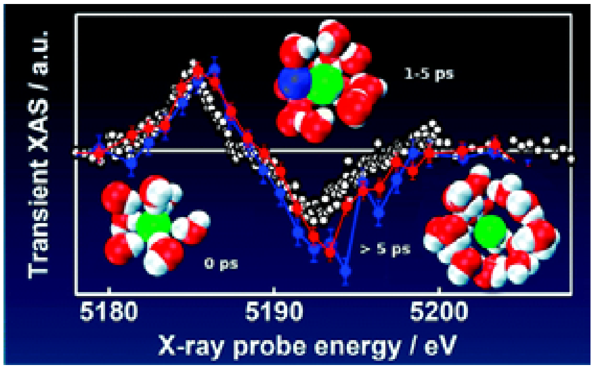


Figure 55. Ultrafast x-ray absorption spectroscopy reveals the changes in solvation of an aqueous iodide as an electron is abstracted. These measurements can now probe transition states and dynamics of species relevant to synthesis. Applying these techniques to in situ reactions, or coupling them to other methods, has tremendous promise but has not yet been demonstrated.[16] | *Reprinted with permission from V.-T. Pham et al. "Probing the Transition from Hydrophilic to Hydrophobic Solvation with Atomic Scale Resolution." Journal of the American Chemical Society 133 [32]: 12740–48. © 2011 American Chemical Society.*

Neutron scattering. The latest generation of spallation-based sources have instruments with very high detector coverage, which, when coupled with streaming event-based data collection, open the door to novel approaches to follow synthesis over time. These have hardly been explored to date. The high neutron sensitivity of certain chemical species provides vital information missing in x-ray and TEM experiments and allows for novel contrast mechanisms, such as the ability to label particular locations on a molecule with selective deuteration or use contrast matching in SANS to separately obtain signals from different parts of a heterogeneous sample. In situ studies of reaction intermediates are now possible, as illustrated in the study of $Li_7La_3Zr_2O_{12}$, in which a surprisingly rich array of intermediates were detected during synthesis (Figure 56).[17,18]

A number of elements of key importance in technology, such as lithium ions and oxides, are best studied by neutrons; therefore, these advances in data collection are particularly encouraging. Note also that neutrons are highly penetrating and can be used to study large samples, or samples in relatively impenetrable environments. Finally, Bragg edge studies can be used to shorten experimental time scales even with the moderate fluxes currently available.

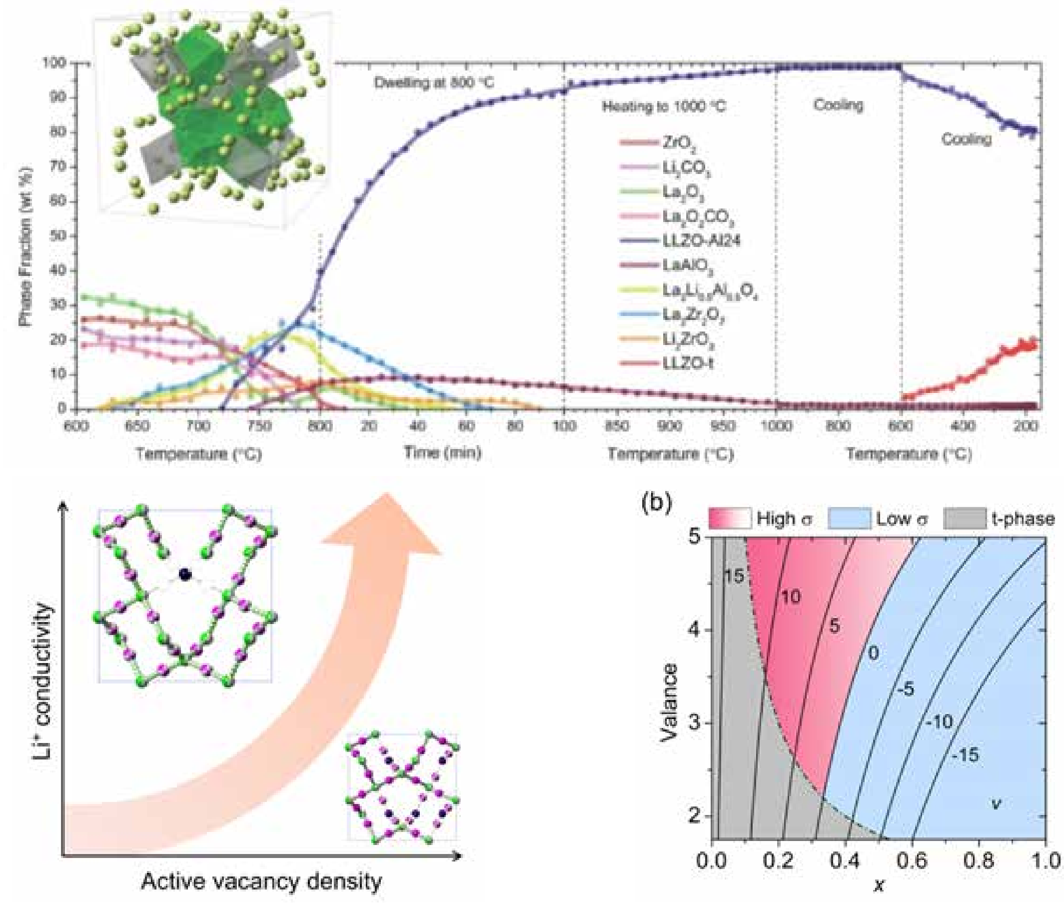


Figure 56. (Top) In situ neutron diffraction reveals the complex synthesis mechanism in doped $Li_7La_3Zr_2O_{12}$ by tracking the phase evolutions.[17] (Lower left) Neutron diffraction uncovers the origin of the high Li+ conductivity that is governed by active vacancy density and accessible transport pathway.[18] (Lower right) The active vacancy density model predicts a tendency toward high ionic conductivity from low dopant content with high valence. | *[Top] Reproduced with permission of The Royal Society of Chemistry from Y. Chen et al. 2015. "A Study of Suppressed Formation of Low-Conductivity Phases in Doped* $Li_7La_3Zr_2O_{12}$ *Garnets by In Situ Neutron Diffraction." Journal of Materials Chemistry A 3: 22868–76.* | *[Lower left] Reprinted with permission from Y. Chen et al. "Origin of High Li+ Conduction in Doped* $Li_7La_3Zr_2O_{12}$ *Garnets." Chemistry of Materials 27 [16]: 5491–94. © 2015 American Chemical Society.* | *[Lower right} Image courtesy of Ke An, Oak Ridge National Laboratory.*

Electron imaging and scattering. Developments in TEM have led to significant capabilities for direct imaging of synthetic processes from the atomic scale to tens of nanometers. For example, imaging of nanowire growth from the gas phase has elucidated the mechanism of vapor-liquid-solid and vapor-solid-solid growth, the existence of both transport-limited and nucleation-limited growth, and the source of faceting and diameter control (see the sidebar *Catalytically Controlled Nanowire Growth*).[19-22] The more recent development of liquid-phase TEM fluid cells with electron transparency has opened a window into the dynamics of materials synthesis from solutions[23] by allowing nucleation, growth, and self-assembly to be controlled by reagent mixing,[24,25] electrodeposition,[26-28] beam-induced deposition,[26,29,30] or thermally triggered reactions[31] (Figure 57).[32-36] Beyond imaging, analyses have also included electron diffraction,[24] Z-contrast imaging,[33] electron energy loss spectroscopy,[37,38] and energy-dispersive x-ray spectroscopy.[39,40]

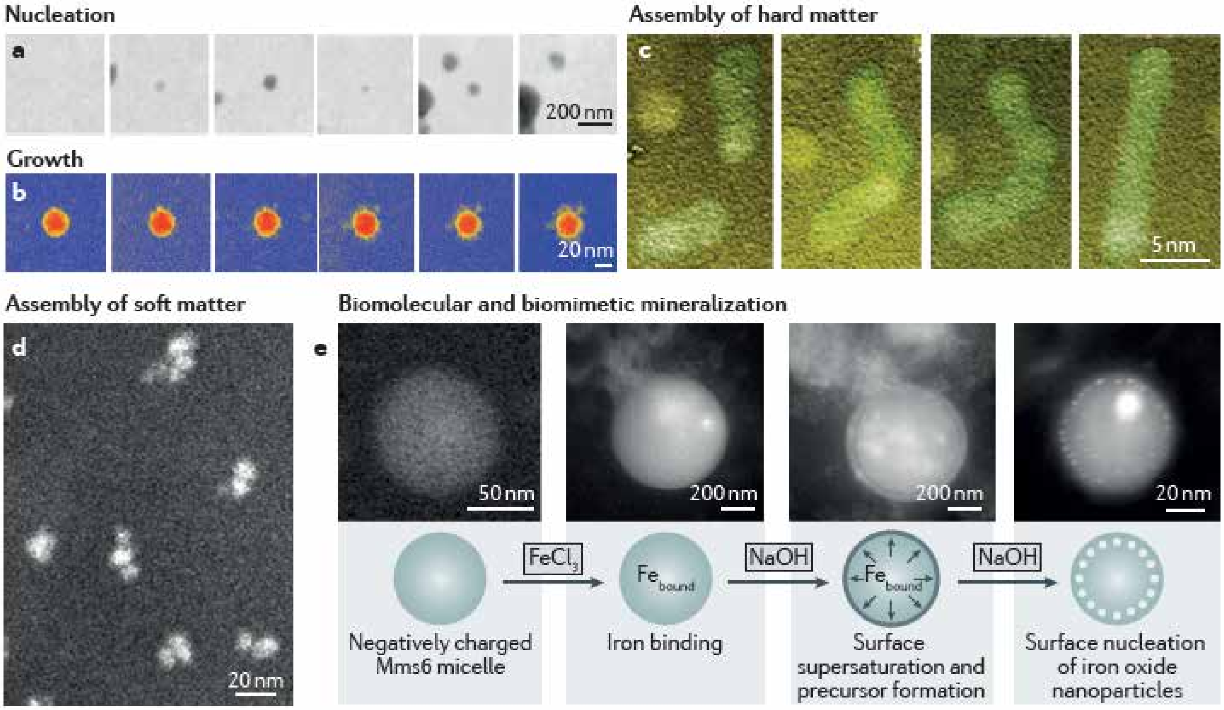
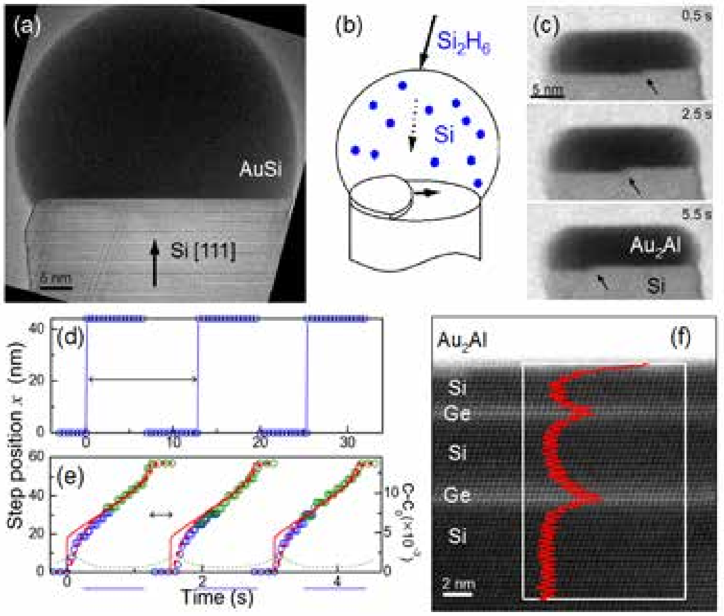


Figure 57. Examples of liquid-phase TEM used to investigate the dynamics of materials formation processes. (a) Gold nanoparticle nucleation.[32] (b) Growth of palladium shells on gold cores.[33] (c) Assembly of Pt_3Fe nanoparticles to form single-crystal nanorods.[34] (d) Assembly of lipid nanodiscs.[35] (e) Biomimetic mineralization of iron oxide by proteins associated with the biological production of magnetite.[36] | *[a] Reprinted with permission from M. H. Nielsen et al. "Investigating Processes of Nanocrystal Formation and Transformation via Liquid Cell TEM." Microscopy and Microanalysis. 20 [2]: 425–36. © 2014 Cambridge University Press. | [b] Reprinted with permission from K. L. Jungjohann et al. "In Situ Liquid Cell Electron Microscopy of the Solution Growth of Au-Pd Core-Shell Nanostructures." Nano Letters 13 [6]: 2964–70. © 2013 American Chemical Society. | [c] Reprinted with permission from H. G. Liao et al. "Real-Time Imaging of Pt_3Fe Nanorod Growth in Solution." Science 336 [1011]: 1011–14. DOI: 10.1126/science.1219185. © 2012 American Association for the Advancement of Science. | [d] Reprinted with permission from J. E. Evans et al. "Visualizing Macromolecular Complexes with In Situ Liquid Scanning Transmission Electron Microscopy." Micron 43 [11]: 1085–90. © 2012 Elsevier. | [e] Reprinted with permission from S. Kashyap et al. "Nucleation of Iron Oxide Nanoparticles Mediated by Mms6 Protein In Situ." ACS Nano 8 [9]: 9097–106. © 2014 American Chemical Society.*

Catalytically Controlled Nanowire Growth



The rational growth of semiconductors nanowires. (a) TEM of Si nanowires grown along a certain direction from a AuSi droplet.[52] (b) Exposure of the droplet with disilane as a gas source for growth of Si nanowires.[52] (c) Time evolution of the vapor-solid-solid growth where arrows indicate the ledge of the growth.[55] (d, e) Step position versus time for growths of Si nanowire growing from different catalysts.[53] (f) Heterostructure of Si/Ge grown from Au_2Al catalyst.[54] **|** *[A] Reproduced with permission of The Royal Society of Chemistry from Y. C. Chou et al. 2016. "Nanowire Growth Kinetics in Aberration Corrected Environmental Transmission Electron Microscopy." Chemical Communications 52[33]: 5686–5689. DOI: 10.1039/c6cc00303f. | [B] Image courtesy of F. M. Ross, IBM Research. | [C] Reprinted with permission from F. M. Ross. 2010. "Controlling Nanowire Structures through Real Time Growth Studies." Reports on Progress in Physics 73[11], Article 114501. DOI: 10.1088/0034-4885/73/11/114501. | [D and E] Reprinted figures with permission from C. Y. Wen et al. (2010) "Step-flow Kinetics in Nanowire Growth." Physical Review Letters 105 [19], Article ID 195502. DOI. 10.1103/PhysRevLett.105.195502. © 2010 American Physical Society. | [F] Reprinted with permission from C.-Y. Wen et al. "Strain and Stability of Ultrathin Ge Layers in Si/Ge/SI Azial Heterojunction Nanowires." Nano Letters 15 [3]: 1654–59. © 2015 American Chemical Society.*

The growth of semiconductor nanowires is an example of how understanding the mechanism of a synthetic process enables control of the outcome. Semiconductor nanowire growth takes place via a nanoscale catalyst whose surface has a high sticking and dissociation probability for reactive precursor gases. For example, an AuSi eutectic droplet can act as the catalyst for the growth of silicon (Si) nanowires from the precursor gas disilane (a, b).[52] As the growth species dissolves into the droplet, it becomes supersaturated and precipitates at the droplet/nanowire interface, creating a long, narrow crystalline structure. Changing the source gas (say, to digermane) changes the nanowire composition, enabling the synthesis of functional structures such as germanium quantum dots within Si nanowires. Imaging this synthetic process via environmental TEM (a, AuSi; c, Au_2Al) shows that material adds to the nanowire layer by layer. However, the step flow kinetics are related to the thermodynamic parameters of the nanowire-droplet system. During growth with liquid catalysts, steps flow rapidly across the growth front with a long incubation time between step flow events (d, AuSi)[53]; i.e., material is added in bursts, even though the arrival rate of Si from the gas phase is constant. During the growth of Si from solid catalysts (e, Cu_3Si),[53] steps flow slowly without much time between flows. A model for this behavior[53] suggests that for growth species that are readily soluble in the catalyst, the supersaturation builds to a high level before overcoming the barrier for step nucleation, at which point there is a sufficient reservoir of the growth species present to complete the layer rapidly (d). However, if the growth species is not readily soluble, the energetically favorable pathway for arriving atoms is immediate incorporation at the growth interface, hence continuous step flow (e). This model suggests that achieving a sharp compositional change requires a low-solubility catalyst. Changing the source gas will then immediately change the composition of the growing nanowire. Observations confirm that step flow dynamics in different catalysts correlate with the abruptness of heterostructure interfaces (f, Si/Ge heterostructure).[54] Such studies enable rational design of catalysts to achieve a desired synthetic structure.[54,55] In situ observations can similarly help to explain the factors that control the crystal phase, allowing superlattices of different crystal structures to be formed in GaAs nanowires.[56] In situ observations can also follow phase transformations in the catalysts, enabling the design of new structures consisting of nanowires with embedded phases of other materials.[57] In all these cases, the ability to control the synthetic structure allows access to new electronic properties.

With a few notable exceptions,[19,41,42] the studies done to date visualize processes with spatial resolutions of 1–10 nm. However, TEM studies involving direct imaging of interfaces, defects, and nanostructures on the scale of individual atoms—defining spatial location, element type, and its oxidation state—show that the spatial regimes of interest lie within the realm of aberration-corrected scanning transmission electron microscopy (STEM).[20-22,43,44] In addition, elucidating 3D structures on scales of from a few nanometers up to microns can be accomplished with tomographic techniques.[45-49] More recently, the development of monochromated electron energy loss spectroscopy has permitted infrared (phonon) spectra to be acquired with high spatial resolution from individual nanostructured interfaces.[50,51] These methods provide proof-of-principle demonstration that the structure and dynamics of bulk material, interfaces, and defects can be characterized with the resolution and sensitivity needed to provide atomistic insights into synthesis mechanisms.

Scanning probe microscopy. Both scanning tunneling microscopy (STM) and atomic force microscopy (AFM) are important tools in understanding the growth of thin films and single crystals. STM has revealed many of the fundamental mechanisms of metal and semiconductor thin film growth from vapor. Research on pure systems like platinum and silicon has detailed the processes of island nucleation, layer-by-layer growth, step edge fluctuations, roughening, and coarsening.[58,59] Investigations of heteroepitaxial systems like germanium on silicon and silver on gold have revealed a rich world of growth phenomena, including wetting transitions, surface alloying, and strain-induced nanoscale patterning.

The need for a conducting substrate prevents the use of STM to investigate the growth of most materials from organic solvents. In contrast, although AFM has slightly poorer resolution than STM, it allows molecular-scale investigation of growth interfaces in situ both when the material is nonconducting and in an aqueous solution,[60] even in hydrothermal conditions.[61] Moreover, it can cover length scales ranging from individual molecules to 100s of micron areas. AFM has been used to probe the growth of single-crystal surfaces from inorganic, organic, and macromolecular species,[60] as well as the self-assembly of supramolecular structures (Figure 58) from polymeric[62] and biological molecules, including proteins[63] and DNA origami.[64] At nanometer length scales, the dynamics of individual atomic steps—including step speed, step fluctuations, and molecular attachment/detachment rates—can all be probed (Figure 59),[61,65] as can the molecule-by molecule assembly of supramolecular structures.[63,64]

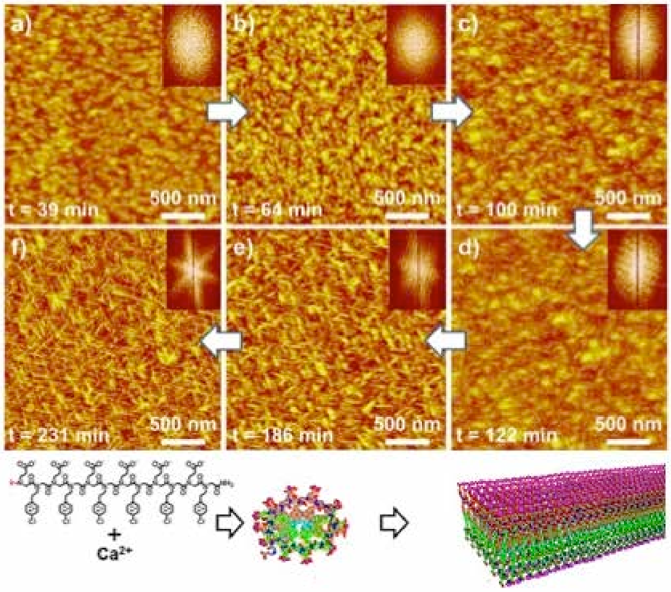


Figure 58. In situ AFM images (upper panel) showing the time evolution of Ca^{2+} complexes of a sequence-defined polymer (peptoid) on a freshly cleaved mica surface at different time points. The inset in each image is a 2D Fourier transform showing the development of six-fold symmetry. Lower panel shows chemical structure of the peptoid and the proposed model of assembly.[62] | *Reprinted with permission from C.-L. Chen et al. "Surface-Directed Assembly of Sequence-Defined Synthetic Polymers into Networks of Hexagonally Patterned Nanoribbons with Controlled Functionalities." ACS Nano 10 [5]: 5314–20. © 2016 American Chemical Society.*

One of the great advantages of AFM is that it allows for both precise control over solution conditions—such as composition, temperature, pH, and flow rate—and changes to the solution during the course of an experiment. This enables direct quantitative comparisons among nucleation, growth, and self-assembly in pure solutions and those containing additives to control these processes.[60] This level of control also ensures that the chemical potential is well defined so that the experimental data can be compared with theoretical analyses and the results of computer simulation.[64–66]

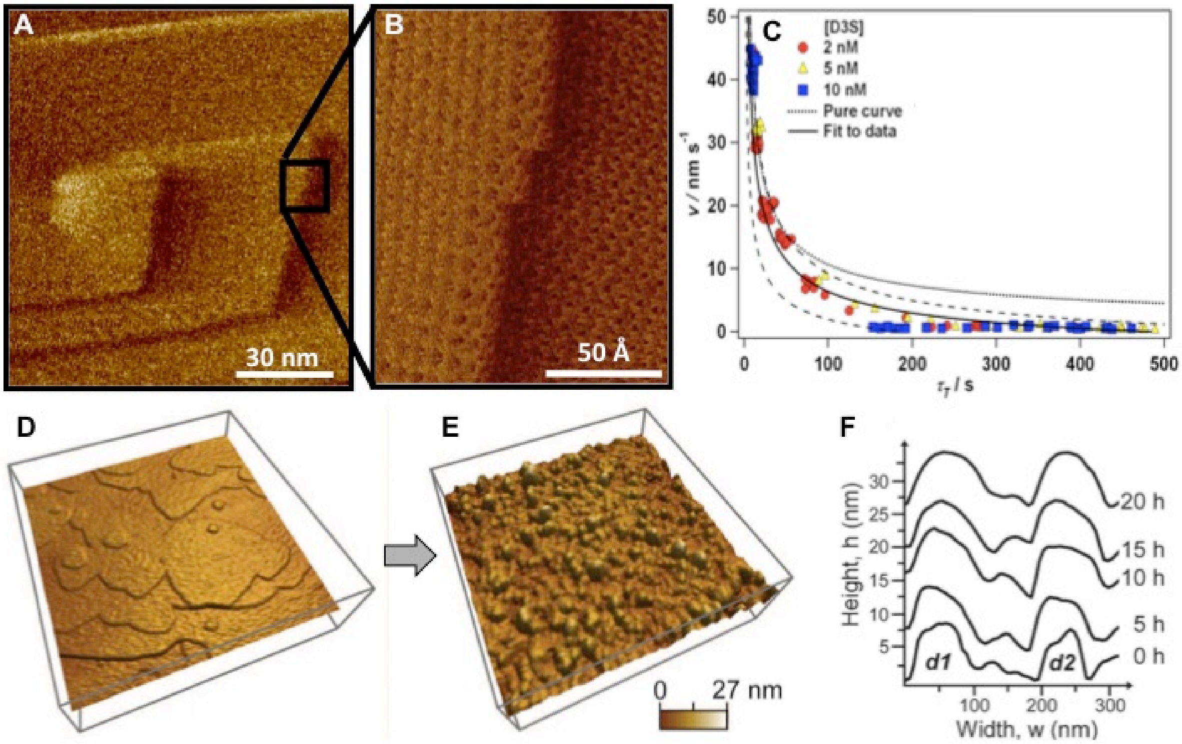


Figure 59. In situ AFM images of crystal faces exhibiting two distinct growth modes. (A, B) Growth of calcium oxalate monohydrate (COM) (010) face on atomic steps. (B) High-resolution image of single atomic kinks along the step. (C) Relationship between step speed and terrace exposure time for COM (-101) face during growth in presence of peptide with the sequence $(DDDS)_6DDD$. Solid curve is fit to data according to a theory that accounts for competition of step advancement with peptide adsorption on terraces with a characteristic adsorption time of ~40 s. Upper dotted curve is the fit to peptide-free data, indicated here as "Pure curve."[65] (D, E) In situ hydrothermal AFM images of particle-mediated growth on the (010) face of the zeolite silicalite-1. (D) Initial surface. (E) After 3 hours at 80°C reveals the attachment of nanoparticles. (F) Height profile at various time intervals showing growth after deposition of particles followed by surface relaxation. The profiles are offset in the y-axis for improved clarity.[61] **|** *Reprinted with permission from A. I. Lupulescu and J. D. Rimer. "In Situ Imaging of Silicalite-1 Surface Growth Reveals the Mechanism of Crystallization." Science 344 [6185]: 729–32. DOI: 10.1126/science.1250984. © 2016 American Association for the Advancement of Science.*

Recent developments in microscope hardware and physical understanding of the response of AFM probes to forces have led to tremendous advances of the method. Both amplitude modulation and frequency modulation of the cantilever are now used to obtain true atomic resolution of crystal surfaces[67] and even to map the hydration structure above the crystal surface.[68] In addition, these developments have led to high-speed scanning, which has decreased image collection times in noncontact image mode by more than factor of 100 to <100 ms.[69] These developments will lead to a deeper understanding of self-assembly, nucleation and growth processes in the years to come.

Light scattering and spectroscopy. Light scattering and spectroscopy reveal information about particle size, lattice vibrational frequencies, and the band structure. In the case of nanocrystals, the size dependence of emission spectroscopy can be used to follow nucleation and growth.[70] Raman and absorption spectroscopy have been effectively used to follow phase evolution during multi-stage nucleation processes.[70,71] The portability of such measurements, including the use of optical fibers to get laser signals into and out of experimental setups, makes these techniques ideal additions to other in situ setups. Although they has not been used extensively, coupled with real-time streaming and multi-modal data analysis, as described below, these capabilities could become standard practice in the future, adding significant information and value to in situ data.

Nuclear magnetic resonance (NMR) and mass spectrometry. In many synthesis processes, the goal is to generate a solid in a gas/vapor or liquid environment. Although there are many techniques for characterizing the solid state interface, characterizing the gas/liquid interface—which actually drives the reaction pathways as much as if not more than the solid—is more complex. Mass spectrometry methods can be used to characterize the residual gases, allowing analysis of at least the before-and-after gases; these are well adapted to in situ operation. Characterizing liquids is more complex, as the structure of the liquid at the interface can be modified by the interface (e.g., by introduction of order and modification of solvation shells and de-solvation processes).

There are special challenges to carrying out NMR in situ; however, the method can provide unique information when used as part of a broader study. The before-and-after liquid can be collected from the reaction and analyzed to provide insights into the overall chemical pathway, but doing so does not answer the question of what the interface does to the liquid.

Multimodal analysis. There is an increasing recognition that no single scattering experiment produces sufficient data to obtain the desired information about the structure, chemical composition, and defects of products during synthesis. When that is the case, it is necessary to obtain measurements from multiple probes, either at different instruments or as simultaneous signals recorded during the same experiment (e.g., x-ray powder diffraction and absorption spectroscopy). Multimodal analysis for synthesis can also include different methods of processing the same data set, rather than monitoring of materials synthesis by two different probes. For example, in work by Martinolich et al.,[72] in situ x-ray total scattering was carried out on a salt-metathesis reaction to prepare superconducting copper sulfides. Performing both Rietveld analysis and PDF analysis provided information on multiple length scales.

In addition to studying materials synthesis simultaneously by two different methods, performing experiments in situ by one technique and ex situ by others can provide powerful information for understanding reaction mechanisms in the formation of extended solids. An example includes work by Haouas et al. in which in situ NMR was combined with ex situ powder XRD and scanning electron microscopy (SEM) to study the crystallization of porous materials based on aluminum trimesates.[73] In situ ^{1}H and ^{27}Al NMR allowed the detection of the aluminum cluster species, such as dimers, that were not only precursors to the various porous framework structures but also a common structural motif; whereas the ex situ experiments revealed various intermediate phases that formed during the synthesis reactions.

Streaming data analysis. Combining the rich multidimensional data coming from in situ experiments with complicated data reduction and analysis schemes such as multimodal analyses will require highly automated and high-throughput streaming data analysis. This technique is not well developed currently, except for a small number of special cases, such as the combination of grazing incidence diffraction with in-line analysis using the SPOT suite software framework running on computing resources at the National Energy Research Scientific Computing Center (Figure 60). However, the emergence of the methods described elsewhere in this section, together with rapidly evolving data analytic methods, means that the benefits to be gained by developing this capability are potentially enormous.

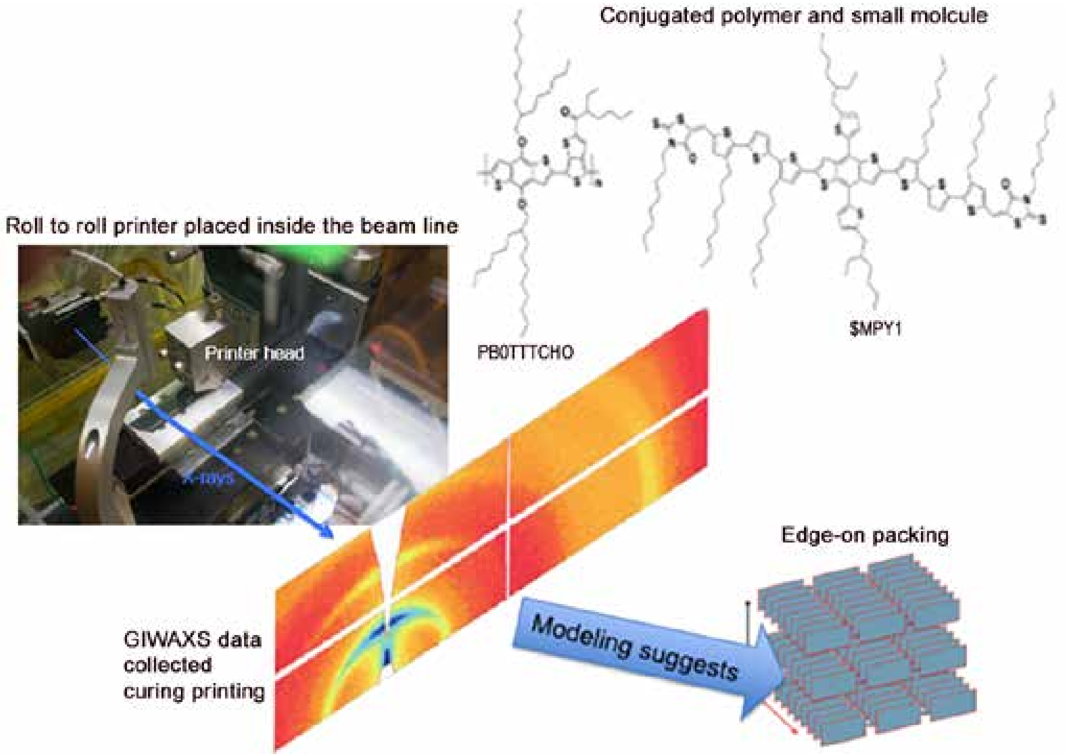


Figure 60. Demonstration of high-throughput in situ characterization of conjugated polymer phase formation. | *Image courtesy of S. Billinge*

Scientific Challenges and Opportunities

The advances in in situ characterization that have taken place over the past two decades have demonstrated the valuable insights into the pathways and dynamics of synthesis. The quantification of rates and dependencies on process parameters has enabled the development and testing of theoretical and computational models. However, major challenges remain that, once overcome, will dramatically expand the impact of in situ characterization on the ability to predict and control synthetic processes.

Mapping metastable phases. Materials synthesis reactions occur by traversing across an energy landscape and crossing activation barriers. Consequently, in situ measurements often reveal novel phases that may be transient or metastable and would have been missed with only ex situ analysis.[2] Thus, these observations reveal both potential obstacles to successful outcomes and the potential for accessing functionally novel materials. The ability to observe pathways and transient states and measure rates enables the determination of the barriers and minima in the landscape. For example, recent in situ XRD studies of MOF formation have shown that the activation barriers can be calculated from time-dependent isothermal data.[1] This capability would augment the quality of work that can be done in user facilities, such as developing specialized stages[74] or combined measurements.[75] Identifying the transition states themselves is becoming possible with ultrafast techniques (TEM and XAS),[16] but these have not yet been applied to synthesis reactions. A variety of in situ techniques are required to (a) locate where these transition states and hidden materials are found and (b) probe them with appropriate spatial, temporal, and energetic probes. Moreover, in situ characterization and computation can work together to map the landscape and identify the structures and lifetimes of these barrier states. Organizing and orienting the collected data in a landscape by maintaining appropriate metadata should accelerate this mapping progress and provide a common interface for theory and computation.

New technologies and multimodalities. In addition to the advances to date, new technologies continue to come on line. Important emerging capabilities include high-pressure neutron diffraction[74] (Figure 61) and NMR; atomic-resolution high-speed AFM; TEM liquid cells instrumented for heating, electrochemistry, and measurement of pH and temperature; dynamic TEM with nanosecond time resolution; nanometer-scale resolution STXM; and on-line furnaces for in situ x-ray and neutron studies of melt-solid interfaces. Accelerating the broad dissemination of this new arsenal of instruments, stages, software, and data management tools that enable researchers to use in situ measurements in their own labs would accelerate both materials discovery and the delineation of synthesis mechanisms.

These approaches can be extended to multimodal and multiscale analyses (Figure 62).[75] Typically, the current approach is to try to overlap two characterization methods. However, in doing so, one or more of the methods is usually sub-optimally sampled (in some cases, all methods are sub-optimally sampled). Also, it must be recognized that overlapping experimental methods is an attempt to sample a smaller and smaller dimensional space with higher spatial/temporal/spectroscopic resolution; for Bayesian methods this is the opposite of what is needed. A far more optimal approach to filling the vast parameter space for synthesis would be to spread the analyses out (and the computations) and be more adept at specifying the connectivity between the conditions for the analyses and simulations. Practically, this is achieved through control of the metadata that is obtained from the system. A complete schema for metadata that provides vectors connecting the different analyses and simulations would permit more optimal use of databases and allow all data generated to contribute to the understanding of underlying mechanisms in a wide range of systems. Without that connectivity, the large extent of such data can be more of an obstacle than an advantage.

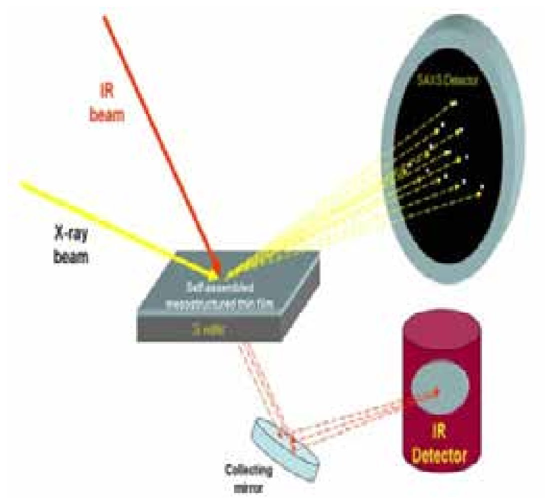


Figure 62. Simultaneous spectroscopy and diffraction provides a method to tie crystalline order to vibrational spectroscopy. Combining such techniques in situ would enable exploratory synthesis to observe new phases and observe correlations in liquids and surfaces that drive phase selection and assembly.[75] **|** *Reprinted with permission from P. Innocenzi et al. "In-Situ Study of Sol-Gel Processing by Time-Resolved Infrared Spectroscopy." Journal of Sol-Gel Science and Technology 48 [1]. © 2008 Springer.*

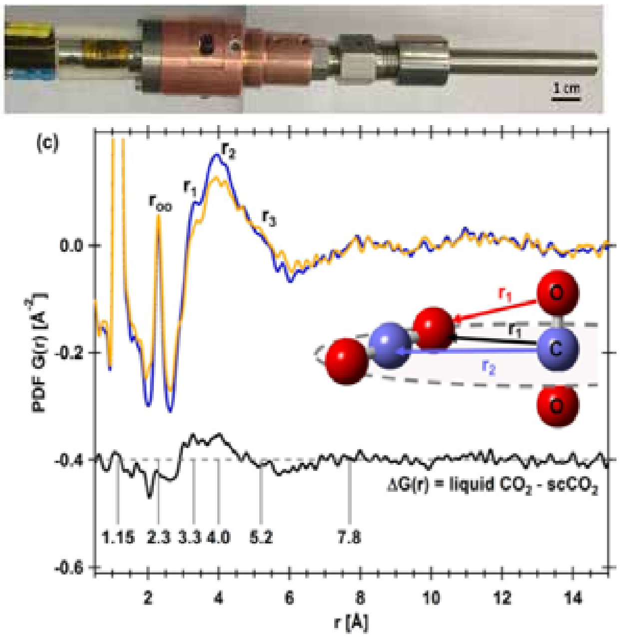


Figure 61. Development of a new capability, such as the high-pressure cell for neutron diffraction (top) leads to the possibility of examining supercritical CO_2 (PDF below) in situ. Developing such environments (in both user facilities and individual laboratories) permits in situ study of entire classes of exploratory reactions that lead to new materials.[74] **|** *Reprinted with permission from H.-W. Wang, V. R. Fanelli, H. M. Reiche, et al. "Pressure/Temperature Fluid Cell Apparatus for the Neutron Powder Diffractometer Instrument: Probing Atomic Structure In Situ." Review of Scientific Instruments 85 [125116]. © 2014 AIP Publishing.*

One advantage of multimodal approaches is that they help to overcome the challenge of matching techniques to time and length scales. Although optical spectroscopy provides an ultrafast measurement capability, the spatial resolution is inadequate to observe individual atomic- or molecular-scale events. In contrast, TEM enables the latter, but with a loss of temporal resolution as well as information on molecular bonding. Even within a single method, multimodal approaches are important to match the spatial and temporal scales to those of the synthetic processes of interest (Figure 63).[76-79] Multimodal approaches might also enable the spatial and temporal resolution to be adaptively changed during measurement, adding an extra dimension of control to extract the maximum benefit for the smallest investment of time, energy, and resources.

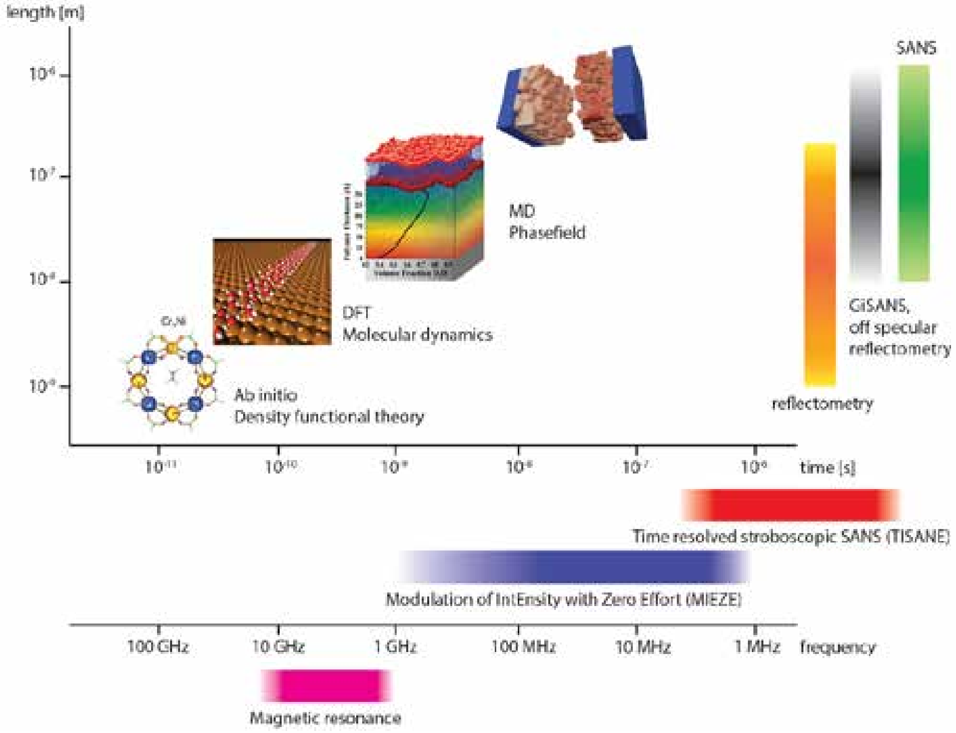


Figure 63. Landscapes of modeling and neutron scattering capabilities relevant to magnetic mesoscale materials. The relationship time to length assumes 100 m/s as representative of the motion of a magnetic domain wall.[76-79] | *Reprinted with permission from v. Bellini and M. Affronte. "A Density Functional Study of Heterometallic Cr-Based Molecular Rings." J. Phys. Chem. B 114[46]: 14797–806 (2010).* | *Reprinted with permission from J. Carrasco et al. 2009. "A One-dimensional Ice Structure Built from Pentagons." Nature Materials 8 [12]: 427–31. DOI: 10.1038/nmat2403. © 2013 Macmillan Publishers. Image courtesy of S. Billinge, M. Fitzsimmons, and A. Michaelides.* | *Reprinted from Biophysical Journal 101 [1], M. S. Jablin et al. "Influence of Lipid Membrane Rigidity on Properties Supporting Polymer,"128–33, © 2011, with permission from Elsevier.* | *Reprinted with permission from Ohlberger et al. "A Model Reduction Framework for Efficient Simulation of Li-ion Batteries," Finite Volumes for Complex Applications, VII. Elliptic, Paarabolic, and Hyperbolic Problems, 695–702. Springer Proc. For math. Stat. 78, Springer , Cham, 2014.*

Pushing the limits of time resolution. Kinetic parameters controlling synthesis are ultimately determined at the atomic and molecular level. Understanding the underlying principles behind the atomistic events controlling nucleation, the evolution of metastable transients, designed persistently metastable structures, and the eventual development of stable functional configurations requires the ability to observe the interfaces in the system (solid-solid, solid-liquid and/or solid-gas) with atomic- and molecular-level spatial resolution on the time scales at which such processes occur. Given the typical energy barriers for atomic-scale diffusion in materials, this time scale is expected to be on the order of milliseconds to nanoseconds, depending on the environmental conditions. Advances in all modalities of imaging that can achieve nanometer to sub-nanometer resolution are required to reach these limits.

Recent developments in frequency modulation-AFM have pushed the spatial resolution down to the atomic level while simultaneously achieving microsecond temporal resolution.[69] Moreover, the sensitivity to forces and stability against thermal noise drift has enabled direct imaging of the hydration layers in solutions overlying crystal surfaces.[80] The challenge now is to push the temporal resolution up by one to two orders of magnitude to achieve resolution of single atomic events at surfaces for a wide variety of systems.

High-temporal-resolution studies in TEM must go beyond the application of standard electron microscopy methods and explore dynamics directly. Ultrafast electron diffraction (UED) is possible with femtosecond time resolution in low-energy systems or in high-electron-energy systems based on accelerators, such as the UED facility at Stanford University. For electron microscopes, two approaches have shown promise in achieving faster time resolution. The first involves using a compressive sensing approach. The second is dynamic TEM (DTEM), which uses pulsed laser systems to produce a short burst of electrons by photoemission.[81-83] The microscope focuses the emitted "pulse" in the traditional way, and images can be obtained with the same temporal resolution as the pulse duration—all normal imaging modes in the TEM are possible. If the photoemission is synchronized with a second laser pulse that stimulates the sample, both nonequilibrium and equilibrium in situ reactions can be initiated and studied with high temporal precision. The DTEM is set up to study interface applications by ensuring each pulse has enough electrons to form a complete image (~10^9 electrons per pulse). This "single-shot" approach means that the process being studied need not be perfectly reversible, allowing for direct observation of the processes underlying synthesis of materials.

Experiments performed using traditional synchrotron sources are capable of monitoring electronic and structural changes with a time resolution of 100 ps or slower. For shorter time scales, emerging opportunities at XFELs may be exploited.[84,85] Experiments performed using the ultra-short and ultra-bright pulses of XFEL sources can probe these changes on a femtosecond time scale (Figure 64).[85] Such ultra-fast x-ray experiments will provide unprecedented insight into the energetic landscapes of important synthetic reactions. Figure 64 highlights a recent key success of an XFEL and provides an example of the challenges associated with extending XFEL science to in situ synthesis.

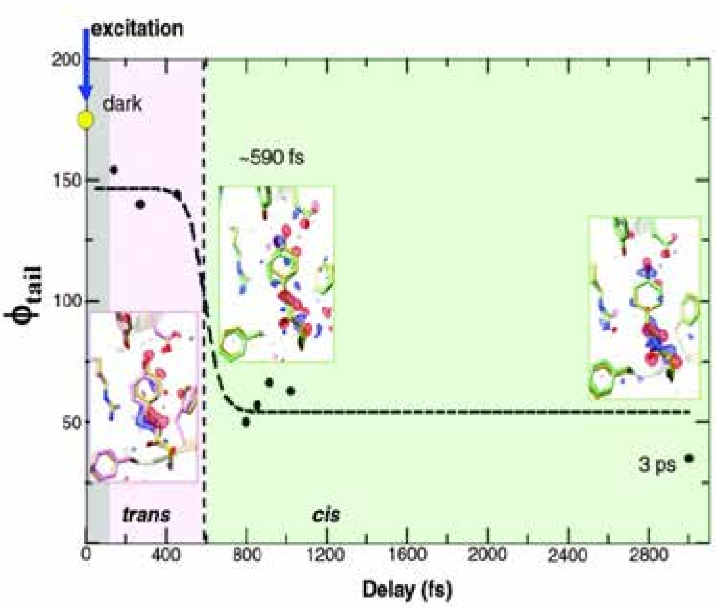


Figure 64. Structural evolution of photoactive yellow protein following photo-excitation determined from time-resolved XRD using an XFEL.[85] | *Reprinted with permission from K. Pande et al. "Femtosecond Structural Dynamics Drives the Trans/Cis Isomerization in Photoactive Yellow Protein." Science 352 [6286]: 725–29. DOI: 10.1126/science.aad5081. © 2016 American Association for the Advancement of Science.*

One of the greatest challenges associated with monitoring the ultra-fast dynamics of chemical reactions is developing a method to initiate the reaction with sufficiently high time resolution. For photochemically driven reactions, this is relatively straightforward, as the synchronization of a sufficiently high time-resolution optical pulse is well established. Kinetic studies of in situ synthesis require the characterization to be performed immediately upon the reaction of the reagents. To reduce the mixing time, which ultimately determines the time resolution of the experiment, devices such as a double-focusing mixing jet have been developed (Figure 65).[86] This device achieves fast, uniform mixing of two solutions with a time resolution of about 250 µs. Future devices that continue to improve upon this design will be used to monitor faster chemical kinetics that can be used to identify key intermediates in synthetic processes.

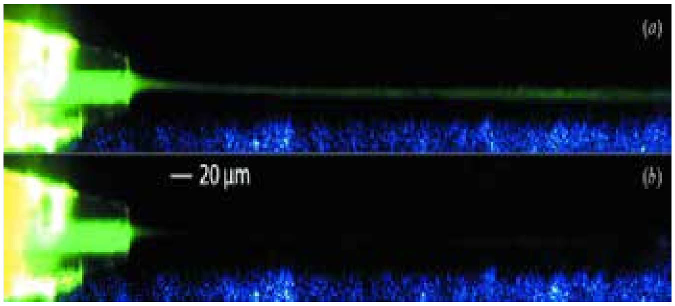


Figure 65. Stream of luminescent dye in a double-focusing mixing jet without (upper) and with (lower) quencher, illustrating the rapidity of mixing with this device.[86] | *Reprinted from D. Wang et al. 2014. Journal of Synchrotron Radiation 21 [6]: 1364–66. Distributed under the terms of the Creative Commons Attribution [CC-BY] License.*

Probe reactions under far-from-equilibrium conditions. Composites of different chemistries, extreme conditions that drive the system far from equilibrium, and so on greatly increase the complexity of the growth process. These challenge the research community to develop better in situ characterization tools that offer opportunities to realize novel structures at all length scales, and in conditions needed to operate under extreme conditions for far-from-equilibrium synthesis conditions. In general, these probes may need to penetrate into high-pressure and high-temperature reaction vessels, vessels that contain plasmas, and so on, or to operate on very fast, irreversible time-scales, for example, under explosive or combustion conditions. In such cases, hard x-rays and neutrons can play an important role, as well as optical spectroscopies.

Data analytics. Data analytics—such as machine learning and image recognition—have revolutionized communications, finance, and commerce and are set to have major impacts in health and infrastructure, not to mention society and politics. These developments are also likely to have a major impact in materials discovery (and implicitly are a major driver for materials genomics). In particular, some of the biggest impacts could be in situations in which there is not a complete and well-developed physics model for the underlying process—for example, materials synthesis. Again, the tools are reaching maturity but their applications to the materials domain are highly limited, presenting a major opportunity.

Analytics may also be used to enhance the performance of a measuring device, enhancing the time resolution and sensitivity appropriate for in situ synthesis. For example, the principles behind high-resolution experimental characterization methods are traditionally governed by the Shannon-Nyquist sampling theory; the signal of interest must be sampled at two times the targeted resolution. Considering all the dimensions in the sampling space needed to completely map synthesis pathways, the challenge to achieving complete in situ characterization for multiple samples and conditions is daunting. Recently, sampling theory has undergone a change in approach with the implementation of compressive sensing and machine learning.[87-91] The goal is not to sample each dimension in smaller and more precise increments, but rather to randomly sample a larger area of phase space and use Bayesian methods to infill the data, as shown in Figure 66[92] for an atomic-resolution STEM image.[91] This approach increases the measurement speed and reduces the required dose. Implementing such approaches to in situ microscopy also has the benefit of limiting the data to be analyzed—the best way to solve the data challenge is not to acquire unneeded data in the first place.

Adaptive and autonomous operation of experiments implies that the outcomes of an experiment are used to intelligently select inputs for the next experiment. For this to happen, raw data must be reduced to a useful processed form on the same time scale as the experiment. In many cases, such as in situ diffraction, this is not currently possible—not because it is computationally infeasible but because the required software and computational hardware infrastructure are not in place. However, there are enormous opportunities in the form of adaptive guided experiments in situ that greatly increase the utilization of x-ray, neutron, and electron beams (scarce resources) and guide experiments to provide the most valuable information possible. Also missing are smart algorithms for adaptively accomplishing data reduction—for example, automatically correcting for shifts in the beam center during the experiment or terminating data collection when the noise level in the data allows the determination of a derived quantity of interest, such as a lattice parameter.

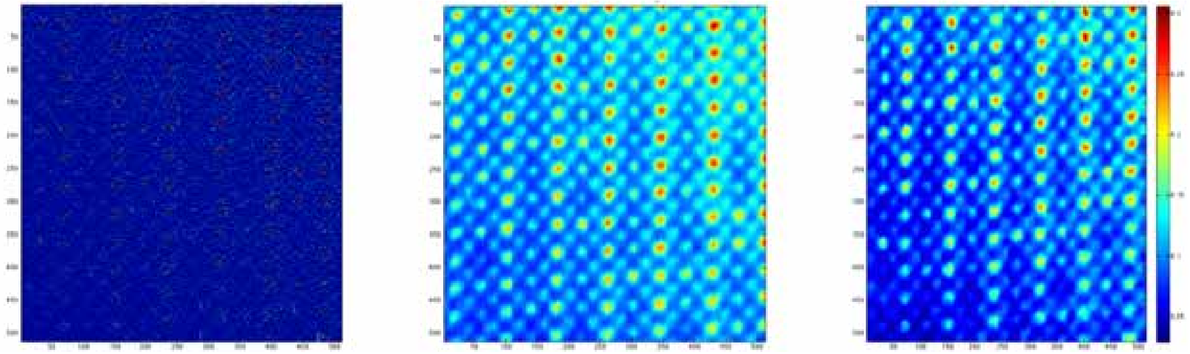


Figure 66. (Left) A randomly rastered STEM image using ~5% of the pixels. (Center) The full image acquired from a precise scan acquiring all the pixels. (Right) The compressive sensing reconstruction of (a) shows very good agreement with the full image.[92] **|** *Image courtesy of Libor Kovarik, Pacific Northwest National Laboratory.*

If the modeling task is straightforward, such as fitting known structural models to data, the computing requirements are not extraordinary. However, if the in situ measured quantity of interest is a material property, it must either be measured directly or computed using expensive forward calculations such as density functional theory or molecular dynamics. If the modeling is to be done using theory in quasi-real time, the computations require large-scale computing capabilities in a high-throughput "on-demand" modality—a definite challenge to existing computational capabilities. Research is needed on (1) algorithms that scale better but still can solve quantum mechanical equations for a quantity of interest more rapidly and (2) finding low-cost "proxy" models, such as empirically derived sets of rate equations. These low-cost models would compute a quantity of interest with sufficient accuracy to have a predictive capability and would do so on the time scale of the experiment. Just as in experimental methods, it is important to match spatial and temporal resolutions to processes of interest, on the theory side, it is important to match accuracy and computational time resolutions to the requirements of the in situ synthesis.

For data to be mined, it is highly important to capture both input-side metadata (process variables from the synthesis method) and experimental output and outcome metadata (raw and processed characterization data). These metadata are used by data mining and machine learning algorithms to seek correlations between input and output. The metadata are difficult to capture, but their capture in a machine-readable format and linked to outcomes is the enabling step in allowing machine learning to work. "Machine readable" implies less about the details of the database platform and more about the organization and labeling of data, which are captured in a schema. Good schemas should be as comprehensive as possible and can be extensible, but it is essential that they capture the dictionary of field keys and relationships between them. These are important in materials synthesis because, to a large extent, they capture the sample definition itself. The sample definition is the set of descriptors that completely (in principle) describe the sample (on the output side) and the set of descriptors that completely (in principle) describe the synthesis steps (on the input side). The schemas are therefore fundamental. Modeling can work quite well with incomplete schemas, minimally a sample name, for example; but it becomes much richer and more powerful the more comprehensive they become. A community effort to develop schemas for material descriptors and for synthesis descriptors would have a potentially dramatic impact. They could allow the capture of metadata in settings ranging from in situ experiments at user facilities built on massive amounts of computer-controlled diagnostic equipment, all the way down to low-tech laboratory experiments in undergraduate laboratories. The low-tech data could be saved in Excel spreadsheets but—if they share the same schema—could be straightforwardly merged into large community-curated online databases. One preliminary example of the power of this approach showed that machine learning algorithms could be trained to surpass humans at predicting synthetic outcomes, given a set of inputs, from just a few thousand examples of synthesis in a well-defined (and low-dimensional) system.[93]

Community databases and community data sharing. To realize these gains from the use of databases, broad community support and adoption is required. There are sociological barriers to be overcome to achieve the needed support, with important issues such as privacy and incentives at the fore. For example, incentives for building a community database include the open sharing of synthetic routes and procedures and the constant refinement of such procedures to produce higher-quality samples. For researchers to receive proper credit for the improvement of synthetic procedures and open publication on the community database, each entry should receive a unique DOI number. This would allow the synthesis route to be cited in peer-reviewed journals with credit to the materials chemist, providing an incentive for the larger community to participate in such a database.

Not only would the original "recipe" of a particular material be included in the database, but also any updates that include critical information that may have been missed in the original work. For example, through hydrothermal routes, Lai et al. prepared a metastable form of iron sulfide known as mackinawite, which is a new superconductor in the iron-based system.[94] However, reproducing the results of the hydrothermal preparation of metastable FeS from the Lai procedure was difficult because of some missing information in the original publication. Borg et al. were able to surmise from the procedure that a base, likely NaOH, was not mentioned in the original recipe; inclusion of such a base indeed led to the preparation of superconducting FeS.[95] This is an example of how such a living synthesis database would be useful to the community interested in preparing iron-based superconductors. Furthermore, machine learning techniques applied to this synthesis and similar hydrothermal routes could have suggested to potentially frustrated chemists the missing parameter, leading to the successful preparation of a metastable compound.

The usefulness of the data in these community databases will be highly dependent on how much data is stored and the quality of the metadata that is captured. Machine learning algorithms can work on incomplete and messy data. However, the precision and accuracy of the predictions will improve with the amount of the data and the data quality. Putting infrastructure in place that helps to capture higher-quality data and metadata, and more of it, will have a huge impact on results. There are a number of directions that may be taken, and all should be pursued. First, software tools are needed for easy capture of high-quality metadata for immediate capture and storage in the community database. If high-throughput, in situ characterization synthesis end-stations are connected to the databases by these tools, then large amounts of high-quality data may be collected. If these are then included in user programs of facilities and made available to the broader community, the impact and community reach will be considerably higher. High-throughput end-stations can include robots for sample manipulation and computer-controlled synthesis capabilities, such as temperature-controlled flow cells, in which input flow rates and compositions and temperatures may be varied, for example.

Making the software and hardware as modular as possible will also enable users to create their own synthesis setups, using well-defined software and hardware interfaces to plug in to the in situ framework so that their metadata and experimental data may flow directly to the community database. Enormous parallelization may also be accomplished without high throughput by making the workflow framework available to users in their own laboratories. The experiments themselves would not be high-throughput, but a large number of laboratories around the country and around the world could all be contributing to (and leveraging results from) the databases.

All of these developments are enormously leveraged by recent developments in cloud computing and the Internet of Things. These will allow measurement devices to be directly connected to wireless internet and from there to the community databases, so that metadata are captured automatically without reliance on users.

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9. Transformative Research Capabilities II: Theory and Simulation

To accelerate the discovery of innovative functional materials, it is not sufficient to compute the properties of the end product; it is critical to simulate and validate the assembly processes that take place during synthesis and fabrication. Currently, theoretical and computational predictions of synthetic processes are in their infancy. Building predictive methods and codes for de novo exploration of synthetic routes requires the development of multiscale approaches that bridge different length and time scales and are capable of describing rare events and out-of-equilibrium processes. It also requires the development of robust validation strategies to establish the "right" level of theory to describe, in an integrated manner, the multitude of chemical and physical properties determining complex synthetic routes.

Current Status and Recent Advances

In the last two decades, most progress in theory and computation has been made in characterizing matter and in predicting its properties. The understanding and prediction of synthetic routes and processes is still an outstanding challenge. However, the progress made in computational characterization will be key to establishing tight connections between theory and experimentation and eventually to building "joint" in situ characterization tools for synthesis. For example, methods to predict the optoelectronic properties of materials—encompassing crystals, disordered systems, and nanostructures, as well as methods to study vibrational spectroscopy and scattering phenomena, are expected to form the basis of the coupling between theory and experiment for in situ characterization of synthesis routes at light sources. These methods include first principles techniques based on density functional theory and post–density functional theory methods based on many body perturbation theory and quantum chemistry, and the analysis and prediction of scattering functions based on classical molecular dynamics and Monte Carlo simulations.

In recent years, a number of groups have reported progress in describing synthesis, with nucleation and assembly processes for several classes of systems[1] serving as illustrative examples. The nucleation of crystals from solution plays a central role in a variety of chemical and engineering processes, and its characterization, especially in the early stages, is challenging from an experimental standpoint. Computationally, molecular simulations have an important role to play in understanding nucleation. Over the years, much attention has been devoted to the study of homogeneous nucleation in simple model systems like Lennard-Jones particles and hard spheres; and more recently, attention has been devoted to computer simulation of nucleation from solutions of organic and inorganic solutes.[2-9] Progress in computer simulation of nucleation relies on coupling of simulation techniques, such as molecular dynamics, with advanced sampling methods capable of capturing rare events. For example, metadynamics methods were recently applied to simulation of urea nucleation from aqueous solutions[10] and forward flux sampling was used to predict nucleation of water nanodroplets, as well as the nucleation and growth of clathrate hydrates.[11]

Several groups have studied the assembly and self-assembly of building blocks, including the interplay between enthalpy and entropy in determining the assembly and packaging of blocks of different shapes and the influence of surfaces in determining block assembly.[12] Those simulations have provided valuable and predictive information about possible synthesis routes in some colloidal materials; however, much work remains to derive simulation parameters for many diverse classes of complex systems (e.g., using ab initio simulations and establishing robust validation strategies and a feedback loop with experiments). The same is true for nucleation processes, which have only been explored for a limited number of systems and often only for models based on empirical force fields.

Scientific Challenges and Opportunities

The main scientific challenge in theory and computation is the development of methods and strategies coupled to experiments that can (1) identify synthetic mechanisms and pathways for solid state, gas-phase, and solution synthesis processes and (2) direct or modify synthetic routes through on-the-fly coupling of theoretical and experimental in situ characterization.

Important examples of systems and phenomena that need to be tackled to advance synthesis science include: the prediction of pathways leading to formation of both crystals (pristine or defective) and amorphous materials; the structure and behavior of liquids and electrolytes with target properties; assembly and dynamics of nanoparticle ensembles composed of building blocks with designer properties; and predictions of surfaces and interfaces that favor specific, desired chemical reactions (e.g., for solar energy conversion processes).

The ability to couple on-the-fly theory and experiments to monitor reactions and synthetic mechanisms and eventually to direct and modify them for given structures will be key to the success of predictive synthesis science. Ideally, the research community will develop imaging techniques that automatically incorporate measurements and simulations at different levels into a flexible tool capable of learning and exploring different synthetic routes.

To meet these challenges, the following capabilities must be developed:

- Novel theoretical and computational methods and codes to access multiple properties and conditions at different length and time scales

- Strategies to validate theory and computation for the description of synthetic processes, including computational techniques to simulate assembly processes out of equilibrium, and theoretical and computational tools to predict properties of building blocks

The recent emphasis on data collection, production, and mining in the computational materials science and chemistry communities has sometimes overshadowed the need to develop theories and computational methods to describe material properties that are not yet accessible by atomistic and first principles computation. Synthesis science is a field with an imperative need to develop novel computational methods to acquire the ability to theoretically and computationally describe new properties of molecules and materials (e.g., chemical reactivity, transport, and dynamical properties) beyond those accessible at present. Novel theoretical and computational methods are required to understand and engineer, at the molecular scale, how to assemble building blocks with designer properties, how to describe pathways at different scales, and how to simulate multiple properties of complex molecules and materials (Figure 67).

The specific theoretical and computational developments that the research community identified as crucial to predicting synthesis, and the properties of materials to target, are described in detail below.

- Improved computational characterization tools, including faster and more efficient simulation methods for scattering and spectroscopy, are prerequisites to couple theoretical and experimental in situ characterization of synthesis pathways within a feedback loop and eventually to build coupled experimental and theoretical imaging tools. These methods include ab initio spectroscopies (encompassing photoemission, vibrational, optical, and x-ray absorption) and scattering techniques for bulk and surfaces, built upon post–density functional theory methods on samples containing thousands of atoms, inclusive of highly correlated materials. Other tools include the calculations of scattering patterns to identify mesoscopic features of materials based on large-scale and coarse-grained molecular dynamics and Monte Carlo methods.

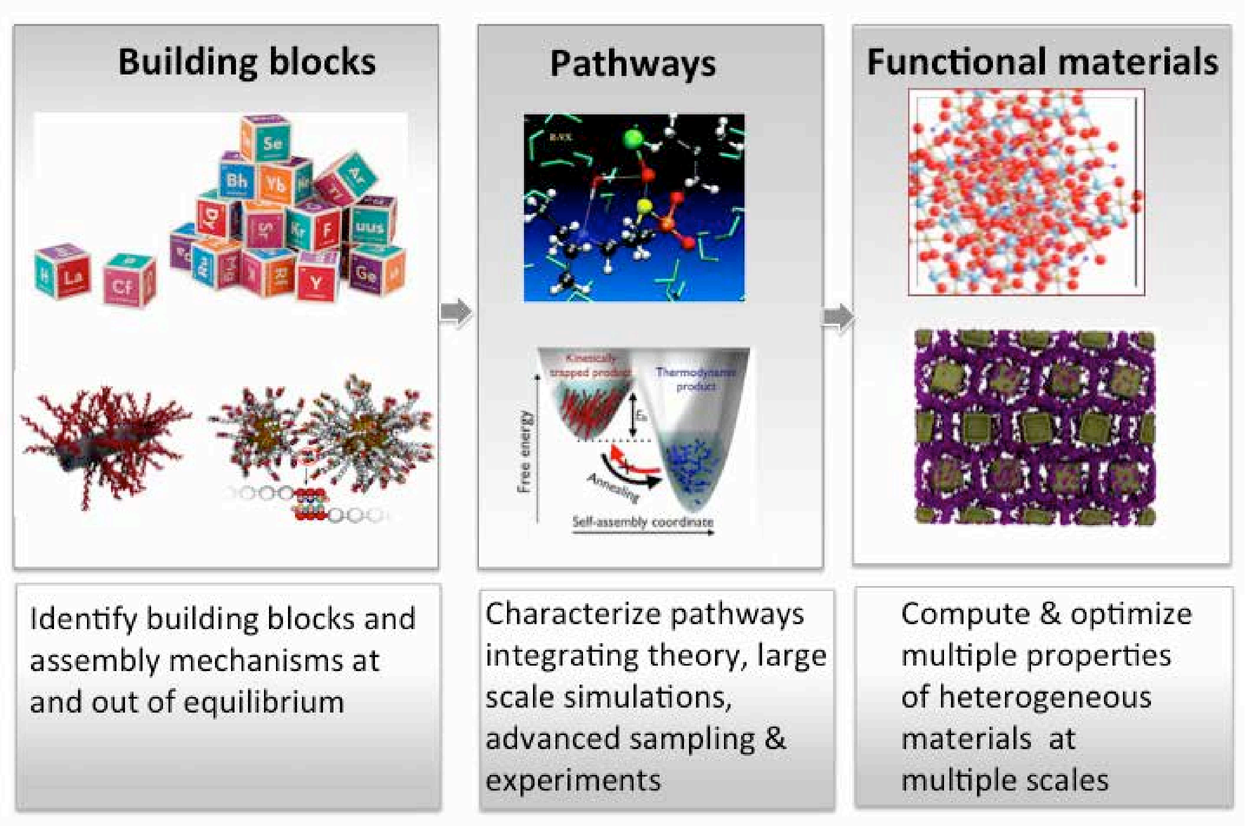


Figure 67. Novel methods are needed to understand how materials development proceeds from building blocks to functional materials with desired properties, through the design and engineering, at the molecular scale, of specific synthetic pathways. **|** *Image courtesy of G. Galli*

- Improved descriptions of interfaces and defects and, more generally, of heterogeneous materials are another prerequisite for in situ characterization. Interfaces affect synthesis at all levels, and their structural and dynamical properties need to be understood in order to develop a fully predictive framework to describe them (e.g., layer-by-layer synthesis and materials assembly from designer building blocks). Consequently, structural models of defective materials must be created and validated with either classical or first principles techniques. In many cases, the coupling of coarse-grained and atomistic simulations using classical potentials and quantum mechanics will be necessary.

- Strategies and possibly automated procedures for validation of theory and computation to describe synthetic processes need to be developed. This includes developing the theory and computation of assembly processes and of building blocks to be assembled. It is anticipated that data on crystalline materials will be particularly useful to validate theories that describe interatomic interactions. The following question will need to be answered for specific classes of materials: What levels of approximations and details are adequate and necessary to develop computational tools to simulate synthetic processes and to develop and validate theories to describe synthesis? Currently, answers to this question are not even available for simple systems that have known synthetic routes and are understood experimentally. The identification of specific classes of systems (e.g., including macromolecular, crystalline, colloidal, liquid, and hybrid systems) for which robust experimental results can be collected and used to validate theory at different levels of accuracy will be particularly valuable.

- Strategies to use theory and computation to disentangle effects that cannot be disentangled experimentally, as they are probed at the same time, will need to be developed; and then descriptors to optimize synthetic processes need to be defined. The identification of descriptors will follow broad and important questions (e.g., solvation as a function of solute size and morphology) involved in specific synthetic processes. The identification of descriptors will rely on the ability to carry out simulations for many different properties (e.g., electronic, mechanical, catalytic, transport, and dynamical properties) for systems of different sizes and morphologies with a controlled level of accuracy. This ability will require carrying out, comparing, and integrating simulations at different levels of theory and for the description of different equilibrium and out-of-equilibrium conditions.

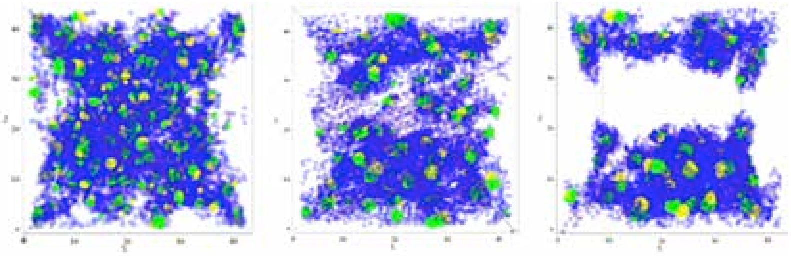
- Strategies to model mechanisms for solid state and solution synthesis need to be developed. At present, these mechanisms are difficult to even identify. Detailed molecular pathways may be identified and have been studied for many systems, but only "average" pathways may be used to describe solid state and solution-based synthetic processes. For molecules (e.g., organic compounds), several packages to plan synthetic experiments are available[13]; however, no such tools exist for condensed phases. The definition of average pathways in the condensed phase, and even the definition of transition states in condensed phases, are open problems. Consequently, the development of techniques to study nonadiabatic processes in the solid state is viewed as particularly important. Likewise, means to identify metastable states and to computationally characterize chemical reactions in condensed states are considered important stepping stones to pursue to achieve predictive synthesis simulations.

- Methods of computing properties and processes that cannot yet be accurately and efficiently computed with atomistic and first principles methods are needed. These include transport properties (i.e., charge, mass, heat); dynamical processes, including rare events; nucleation processes beyond classical nucleation theory, crystallization, precipitation events, including nonclassical particle-based growth pathways; metastable phases composed of complex building blocks and their assembly processes; and conformational transformations, such as macromolecular folding and assembly. Synthesis science requires moving the balance back from the emphasis on "big data" to the need for new theories and computations to access properties the community is not yet able to reliably predict. Big data will eventually have an important role to play in synthesis science, but predictive synthesis calculations first require the development of new theoretical and computational methods and the ability to carry out simulations on new high-performance architectures for multiple, complex, heterogeneous samples.

- Descriptions of materials at different time and length scales (e.g., dynamical simulations integrated with first principles descriptions of interactions; kinetic Monte Carlo integrated with first principles calculations; integration of continuum, mesoscale, and atomistic calculations) need to be integrated. As in many other areas, establishing an effective feedback loop between continuum-to-mesoscale simulations and atomistic simulations is a high priority. This will be accomplished by following well-defined validation strategies devised for specific classes of systems. (See the sidebar *Particle-based simulations of the nonequilibrium mesoscale micro-rheology of charged macromolecules*.)[14-18]

- Strategies for synthetic databases need to be defined and developed. Although synthetic databases remain an elusive concept, a need was identified to retrievably archive, in the public domain, information about what is known not to work and the reasons behind certain synthetic failures. Likewise, the need to incorporate information about failed experiments and, possibly, failed simulations into machine learning procedures that would eventually lead to predictive synthesis science was highlighted. Synthetic databases should be defined with specific machine learning procedures and strategies and will be specific to given classes of systems and synthetic processes.

Particle-based simulations of the nonequilibrium mesoscale micro-rheology of charged macromolecules



Modeling of nonequilibrium transport processes such as electrophoresis, electrochemical reactions in battery charge-discharge cycles, and nonequilibrium complexation of polyelectrolytes and of charged colloids is in its infancy. Dissipative particle dynamics/fluid particle dynamics (DPD/FPD)[14-17] are an attractive set of models to study these processes, because they provide momentum conservation, enabling a correct description of hydrodynamic interactions; and they do not require postulating constitutive equations because the dynamics are included explicitly. A version of DPD[16] with energy conservation, which allows for stochastic heat transfer between neighboring fluid particles, can be generalized to material transport between particles where each fluid particle carries a "load" of ions (protons, cations, anions), and neighboring particles stochastically exchange ionic material and heat proportionally to the difference in (inverse) temperatures and the local chemical potential of the components. Such chemical potentials are functions of the "carrier" particle type (water, oil, or polyelectrolyte segment). The particle-particle conservative forces can be computed in a manner suggested by the "many body" DPD model[17] using a local free energy that includes short range interactions computed from liquid state theory (or from molecular dynamics, Monte Carlo or postulated phenomenologically). Long-range electrostatics can be computed within the conventional particle-mesh method.[18] Heterogeneities of the dielectric permittivity caused by the composition fluctuations can be accounted for within the same method[18] if the composition dependence of the dielectric permittivity is known from elsewhere (dielectric spectroscopy or first principles methods). The figure shows a DPD simulation of the breakup of a gel-forming solution of an AB + ABC copolymer blend with the associated A and C groups. **|** *Image courtesy of V. Pryamitsyn, Northwestern University.*

Summary

The challenges and impacts of predictive synthesis science are hard to overemphasize. Building predictive synthesis capabilities offers tremendous opportunities, including the ability to accelerate the discovery of materials for energy (e.g., catalysts, energy storage, light harvesting, and thermoelectrics), information technology (e.g., spin defects for quantum information technologies), sensors (e.g., scintillators, nanoscale transistors, and plasmonic materials), environmental management (e.g., separation media and waste forms), and many other uses. The development of predictive synthesis science also offers the opportunity to revolutionize the way in which simulations at different scales and with different methods are conducted and integrated, and the way theory, computation, and experimental data are coupled within novel feedback loops. The methods and codes that are currently being developed by the BES Computational Materials Sciences centers (https://science.energy.gov/bes/) are expected to be instrumental to synthesis simulations, as are advances in quantum chemical methods. Advancing the PRDs for the science of synthesis identified in this workshop offers the opportunity to bring together the physics, chemistry, and materials science communities and accomplish a revolution in materials for energy technologies and quantum information systems similar to the one that solid state physics enabled for microelectronics.

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APPENDIX A: WORKSHOP PARTICIPANTS

Basic Energy Sciences Workshop on Synthesis Science for Energy Relevant Technology

Chair: Jim De Yoreo (Pacific Northwest National Laboratory/University of Washington)

Co-chairs: David Mandrus (University of Tennessee/Oak Ridge National Laboratory)
Lynda Soderholm (Argonne National Laboratory)

Basic Energy Sciences Team: Linda Horton, Materials Sciences and Engineering
Arvind Kini, Materials Sciences and Engineering
Raul Miranda, Chemical Sciences, Geosciences, and Biosciences
George Maracas, Scientific User Facilities

Plenary Speakers:

Angela Belcher, Massachusetts Institute of Technology
Paul Canfield, Iowa State University/Ames Laboratory
Anthony Cheetham, University of Cambridge
Tobin Marks, Northwestern University
Kristin Persson, Lawrence Berkeley National Laboratory
George Whitesides, Harvard University

Panel 1: Mechanisms of synthesis under kinetic and thermodynamic controls

Chairs: Tori Forbes, University of Iowa; Mercouri Kanatzidis, Northwestern University

Aurora Clark, Washington State University [b]
Josh Goldberger, Ohio State University
David Johnson, University of Oregon
Hemamala Karunadasa, Stanford University
Doug Keszler, Oregon State University
Susan Latturner, Florida State University
Alexandra Navrotsky, University of California–Davis
Pierre Ferdinand Poudeu, University of Michigan
Raymond Schaak, Pennsylvania State University
J. Christian Schön, Max Planck Institute
Daniel Shoemaker, University of Illinois [a]
Dimitri Talapin, University of Chicago
Richard Wilson, Argonne National Laboratory

Panel 2: Establishing the design rules for supramolecular and hybrid assemblies

Chairs: Ulrich Wiesner, Cornell University; Ting Xu, University of California–Berkeley/Lawrence Berkeley National Laboratory

Chris Alabi, Cornell University
Jeff Brinker, Sandia National Laboratories
Millicent Firestone, Los Alamos National Laboratory
Oleg Gang, Brookhaven National Laboratory
Dale Huber, Sandia National Laboratories
David Kisailus, University of California
Surya Mallapragada, Ames Laboratory/Iowa State
Monica Olvera de la Cruz, Northwestern University [b]
Jonathan Owen, Columbia University
Elena Shevchenko, Argonne National Laboratory

John Tovar, Johns Hopkins University
Scott Warren, University of North Carolina–Chapel Hill
Jiang Zhang, Argonne National Laboratory [a]

Panel 3: Interface-defined matter

Chairs: Sarah Tolbert, University of California–Los Angeles; Mike Zaworotko, University of Limerick

Jason Benedict, University of Buffalo–SUNY
Stacey Bent, Stanford University
Nigel Browning, Pacific Northwest National Laboratory [a]
Lara Estroff, Cornell University
Bruce Garrett, Pacific Northwest National Laboratory
David Ginley, National Renewable Energy Laboratory
Yu Huang, University of California–Los Angeles
Samson Jenekhe, University of Washington
Karl Johnson, University of Pittsburgh [b]
Paul Nealey, Argonne National Laboratory/University of Chicago
Tina Nenoff, Sandia National Laboratories
Fraser Stoddart, Northwestern University
Galen Stucky, University of California–Santa Barbara
Shouheng Sun, Brown University
Mike Ward, New York University

Panel 4: Crystalline matter: Challenges in discovery and directed synthesis

Chairs: Julia Chan, University of Texas–Dallas; John Mitchell, Argonne National Laboratory

Paul Canfield, Iowa State University/Ames Laboratory
Robert Cava, Princeton University
Judy Cha, Yale University
Jeff Derby, University of Minnesot[a]
Craig Fennie, Cornell University [b]
Joseph Kolis, Clemson University
Thomas Lograsso, Ames Laboratory
Dave Mitzi, Duke University
Emilia Morosan, Rice University
Cedomir Petrovic, Brookhaven National Laboratory
Ken Poeppelmeier, Northwestern University
Efrain Rodriquez, University of Maryland [a]
Matthew Rosseinsky, University of Liverpool
Ram Seshadri, University of California–Santa Barbara
Yuri Suzuki, Stanford University
Evan Thomas, University of Dayton

Panel 5: Emerging approaches to synthesis at all length scales

Chairs: Jonah Erlebacher, Johns Hopkins University; Julia Laskin, Pacific Northwest National Laboratory

Radoslav Adzic, Brookhaven National Laboratory
Thomas Albrecht-Schmitt, Florida State University
Craig Arnold, Princeton University
John Badding, Pennsylvania State University
Bruce Clemens, Stanford University
Mike Fitzsimmons, Oak Ridge National Laboratory [a]

Quanxi Jia, Los Alamos National Laboratory
Alain Karma, Northeastern University [b]
Uwe Kortshagen, University of Minnesota
Matt Kramer, Ames Laboratory
Suveen Mathaudhu, University of California–Riverside
Amit Misra, University of Michigan
John Perepezko, University of Wisconsin
Mitra Taheri, Drexel University [a]

Designations *a* and *b* indicate the panels' representatives on the crosscutting panels.

Cross-cutting Panel A: In situ characterization

Chair: Simon Billinge, Columbia University

Nigel Browning, Pacific Northwest National Laboratory
Mike Fitzsimmons, Oak Ridge National Laboratory
Zhang Jiang, Argonne National Laboratory
Efrain Rodriguez, University of Maryland
Daniel Shoemaker, University of Illinois
Mitra Taheri, Drexel University

Cross-cutting Panel B: Theory and simulation

Chair: Giulia Galli, University of Chicago

Aurora Clark, Washington State University
Craig Fennie, Cornell University
Karl Johnson, University of Pittsburgh
Alain Karma, Northeastern University
Jamie Morris, Oak Ridge National Laboratory
Monica Olvera de la Cruz, Northwestern University

Basic Research Needs For Synthesis Science for Energy Relevant Technology

Invited Participants

Radoslav Adzic , Brookhaven National Laboratory
Chris Alabi, Cornell University
Thomas Albrecht-Schmitt, Florida State University
Craig Arnold, Princeton University
John Badding, Pennsylvania State University
Angela Belcher, Massachusetts Institute of Technology
Jason Benedict, University of Buffalo–SUNY
Stacey Bent, Stanford University
Simon Billinge, Columbia University
Jeff Brinker, Sandia National Laboratories
Nigel Browning, Pacific Northwest National Laboratory
Paul Canfield, Iowa State University/Ames Laboratory
Robert Cava, Princeton University
Jeeyoung Cha, Yale University
Julia Chan, University of Texas–Dallas
Anthony Cheetham, University of Cambridge
Aurora Clark, Washington State University
Bruce Clemens, Stanford University

Jim De Yoreo, Pacific Northwest National Laboratory
Jeff Derby, University of Minnesota
Jonah Erlebacher, Johns Hopkins University
Lara Estroff, Cornell University
Craig Fennie, Cornell University
Millie Firestone, Los Alamos National Laboratory
Mike Fitzsimmons, Oak Ridge National Laboratory
Tori Forbes, University of Iowa
Giulia Galli, University of Chicago
Oleg Gang, Brookhaven National Laboratory
Bruce Garrett, Pacific Northwest National Laboratory
David Ginley, National Renewable Energy Laboratory
Josh Goldberger, Ohio State University
Dale Huber, Sandia National Laboratories
Yu Huang, University of California–Los Angeles
Samson Jenekhe, University of Washington
Quanxi Ji, Los Alamos National Laboratory
Zhang Jiang, Argonne National Laboratory
David C Johnson, University of Oregon
Karl Johnson, University of Pittsburgh
Mercouri Kanatzidis, Northwestern University
Alain Karma, Northeastern University
Hemamala Karunadasa, Stanford University
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David Mandrus, University of Tennessee
Tobin Marks, Northwestern University
Suveen Mathaudhu, University of California–Riverside
Amit Misra, University of Michigan
John Mitchell, Argonne National Laboratory
Dave Mitzi, Duke University
Emilia Morosan, Rice University
Jamie Morris, Oak Ridge National Laboratory
Alexandra Navrotsky, University of California–Davis
Paul Nealey, University of Chicago
Tina Nenoff, Sandia National Laboratories
Monica Olvera de la Cruz, Northwestern University
Johnathan Owen, Columbia University
John Perepezko, University of Wisconsin
Kristin Persson, Lawrence Berkeley National Laboratory
Cedomir Petrovic, Brookhaven National Laboratory
Ken Poeppelmeier, Northwestern University

Ferdinand Poudeu, University of Michigan
Efrain Rodriguez, University of Maryland
Matthew Rosseinsky, University of Liverpool
Raymond Schaak, Pennsylvania State University
J. Christian Schön, Max Planck, Stuttgart
Ram Seshadri, University of California–Santa Barbara
Elena Shevchenko, Argonne National Laboratory
Daniel Shoemaker, University of Illinois
Lynda Soderholm, Argonne National Laboratory
Fraser Stoddart, Northwestern University
Galen Stucky, University of California–Santa Barbara
Shouheng Sun, Brown University
Yuri Suzuki, Stanford University
Mitra Taheri, Drexel University
Dimitri Talapin, University of Chicago
Evan Thomas, University of Dayton
Sarah Tolbert, University of California–Los Angeles
John Tovar, Johns Hopkins University
Mike Ward, New York University
Scott Warren, University of North Carolina–Chapel Hill
George Whitesides, Harvard University
Uli Wiesner, Cornell University
Richard Wilson, Argonne National Laboratory
Ting Xu, University of California–Berkeley
Mike Zaworotko, University of Limerick

Basic Research Needs For Synthesis Science for Energy Relevant Technology

Invited Observers

Miriam Deutcsh, National Science Foundation
Ron Faibish, DOE ARPA-E
Gregory Fiechtner, DOE Office of Science, Basic Energy Sciences
Tim Fitzsimmons, DOE Office of Science, Basic Energy Sciences
Rebecca Fushimi, Idaho National Laboratory
Bonnie Gersten, DOE Office of Science, Basic Energy Sciences
Matthias Graf, DOE Office of Science, Basic Energy Sciences
Craig Henderson, DOE Office of Science, Basic Energy Sciences
Linda Horton, DOE Office of Science, Basic Energy Sciences
Igor Kaganovich, Princeton Plasma Physics Laboratory
Helen Kerch, DOE Office of Science, Basic Energy Sciences
Arvind Kini, DOE Office of Science, Basic Energy Sciences
Harriet Kung, DOE Office of Science, Basic Energy Sciences
Young Lee, SLAC National Accelerator Laboratory
Qiang Li, Brookhaven National Laboratory
George Maracas, DOE Office of Science, Basic Energy Sciences
Michael Markowitz, DOE Office of Science, Basic Energy Sciences
Gail McLean, DOE Office of Science, Basic Energy Sciences
Talia Melcer, DOE Office of Science, Basic Energy Sciences
Raul Miranda, DOE Office of Science, Basic Energy Sciences

Nathan Neale, National Renewable Energy Laboratory
Mick Pechan, DOE Office of Science, Basic Energy Sciences
Chuck Peden, DOE Office of Science, Basic Energy Sciences
Mark Pederson, DOE Office of Science, Basic Energy Sciences
Kelly Perry, Oak Ridge National Laboratory, on detail to DOE Office of Science, Basic Energy Sciences
Katie Runkles, DOE Office of Science, Basic Energy Sciences
Thomas Russell, DOE Office of Science, Basic Energy Sciences
Viviane Schwartz, DOE Office of Science, Basic Energy Sciences
Andy Schwartz, DOE Office of Science, Basic Energy Sciences
Michael Sennett, DOE Office of Science, Basic Energy Sciences
Tom Settersten, DOE Office of Science, Basic Energy Sciences
Mark Spitler, DOE Office of Science, Basic Energy Sciences
Thiyaga Thiyagarajan, DOE Office of Science, Basic Energy Sciences
Anthony van Buuren, Lawrence Livermore National Laboratory
John Vetrano, DOE Office of Science, Basic Energy Sciences
Aaron Washington, Savannah River National Laboratory
Tristram West, DOE Office of Science, Office of Biological and Environmental Research
Philip Wilk, DOE Office of Science, Basic Energy Sciences
Lane Wilson, DOE Office of Science, Basic Energy Sciences
H. Felix Wu, DOE Office of Energy Efficiency and Renewable Energy
Xiang Zhang, Lawrence Berkeley National Laboratory

APPENDIX B: WORKSHOP AGENDA

BASIC RESEARCH NEEDS FOR

Synthesis Science for Energy Relevant Technology

Hilton Washington DC: Rockville Hotel and Executive Meeting Center • May 2–4, 2016

Chair: Jim De Yoreo (Pacific Northwest National Laboratory)

Co-chairs: David Mandrus (University of Tennessee/Oak Ridge National Laboratory)
Lynda Soderholm (Argonne National Laboratory)

Monday, May 2, 2016	
7:00 - 8:00 a.m.	Registration and breakfast
Opening Plenary Session—Plaza II and III	
8:00—8:15 a.m.	**BES Welcome and Workshop Charge** Harriet Kung, Associate Director of Science for Basic Energy Sciences
8:15 – 8:30 a.m.	**Chair Welcome** Jim De Yoreo, Pacific Northwest National Laboratory
8:30 – 9:10 a.m.	**Plenary 1: Where Do We Go from Here?** George Whitesides, Harvard University
9:10 – 9:50 a.m.	**Plenary 2: Synthesis as the Heart of New Materials Physics** Paul Canfield, Iowa State University/Ames Laboratory
9:50 – 10:20 a.m.	Break
10:20 – 11:00 a.m.	**Plenary 3: Challenges in Synthesis Science: Rational Creation of New Matter** Tobin Marks, Northwestern University
11:00 – 11:40 a.m.	**Plenary 4: The Increasing Role of Modeling in Guiding Discovery and Synthesis of Novel Functional Materials** Kristin Persson, Lawrence Berkeley National Laboratory
11:40 – 12:20 a.m.	**Plenary 5: Emerging Approaches to Bioinspired Synthesis of Soft and Hybrid Materials** Angela Belcher, Massachusetts Institute of Technology
12:20 – 1:30 p.m.	Working lunch
1:10 – 1:30 p.m.	**Panel introductions: Workshop co-chairs**
1:30 – 5:30 p.m.	**Panel Sessions: Meet in parallel** **Panel 1**: **Mechanisms of Synthesis under Kinetic and Thermodynamic Controls** *Tori Forbes, University of Iowa, and Mercouri Kanatzidis, Northwestern University/Argonne National Laboratory* **Panel 2**: **Establishing the Design Rules for Supramolecular and Hybrid Assemblies** *Ulrich Wiesner, Cornell University, and Ting Xu, Lawrence Berkeley National Laboratory/University of California–Berkeley* **Panel 3**: **Interface-Defined Matter** *Sarah Tolbert, University of California–Los Angeles, and Michael Zaworotko, University of Limerick, Ireland* **Panel 4**: **Crystalline Matter: Challenges in Discovery and Directed Synthesis** *Julia Chan, University of Texas–Dallas, and John Mitchell, Argonne National Laboratory* **Panel 5**: **Emerging Approaches to Synthesis at All Length Scales** *Jonah Erlebacher, Johns Hopkins University, and Julia Laskin, Pacific Northwest National Laboratory*
5:30 – 9:00 p.m.	Working Dinner: Panel discussions (continued); cross-cut panels meet from 8:00 – 9:00

Tuesday, May 3, 2016	
7:30 – 8:30 a.m.	Breakfast
8:30 – 9:10 a.m.	**Plenary 6: Materials Discovery and Energy Science** Anthony Cheetham, University of Cambridge
9:10 – 9:30 a.m.	Break and move to panel sessions
9:30 – 10:10 a.m.	Panels meet for discussion/preparation of preliminary reports
10:10 – 10:20 a.m.	Move to plenary room for panel reports
10:20 – 10:40 a.m.	**Report from Panel 1** Mechanisms of synthesis under kinetic and thermodynamic controls
10:40 – 11:00 a.m.	**Report from Panel 2** Establishing the design rules for supramolecular and hybrid assemblies
11:00 – 11:20 a.m.	**Report from Panel 3** Interface-defined matter
11:20 – 11:40 a.m.	**Report from Panel 4** Crystalline matter: Challenges in discovery and directed synthesis
11:40 – Noon	**Report from Panel 5** Emerging approaches to synthesis at all length scales
Noon – 1:30 p.m.	Working lunch
1:30 – 5:30 p.m.	Panel discussions (continued); cross-cut panels meet
3:00 – 4:00 p.m.	Break
5:30 – 9:00 p.m.	Working dinner: Panel discussions (continued) and preparation for final panel reports
Wednesday, May 4, 2016	
7:00 – 8:00 a.m.	Breakfast
8:00 – 8:30 a.m.	**Report from Panel 1**
8:30 – 9:00 a.m.	**Report from Panel 2**
9:00 – 9:30 a.m.	**Report from Panel 3**
9:30 – 9:45 a.m.	Break
9:45 – 10:15 a.m.	**Report from Panel 4**
10:15 – 10:45 a.m.	**Report from Panel 5**
10:45 – 11:15 a.m.	**Report from cross-cutting panel 1:** In Situ Characterization
11:15 – 11:45 a.m.	**Report from cross-cutting panel 2:** Theory and Simulation
11:45 – Noon	**Closing Remarks** Jim De Yoreo, workshop chair
Noon	**Workshop Adjourned**
1:00 – 5:30 p.m.	Writing (chairs, panel leaders, and designated writers)
5:30 p.m.	Adjourn

Disclaimer