Workshop on Mid-Scale Instrument Development for the Chemical Sciences

Paul W. Bohn – University of Notre Dame
Marcos Dantus – Michigan State University

Executive Summary

The Workshop on Mid-Scale Instrument Development for the Chemical Sciences was organized to address the need and potential for mid-scale instrument development in the chemical sciences. The workshop, organized as a complement to the Workshop on Mid-Scale Instrumentation for the Chemical Sciences held Sept. 29-30, 2016, targeted the support of activities in the design, development, testing and characterization of chemical instrumentation of a scale and complexity that cannot be addressed through existing programs of instrument support from federal agencies. These needs have been met, up to the $4 million level, through the National Science Foundation's (NSF) Chemistry Division, using the agency's Major Research Instrumentation (MRI) program. Support for instrument development on a grander scale, up to ~$120 million, has not been available, and has seldom been sought by chemists. The workshop thus assessed the needs and opportunities for instrument development on the mid-scale level that could impact the entire chemical sciences community, and closely associated industries (fuels, energy, commodity materials and medicine) in the U.S. and the world.

Strong motivation for mid-scale instrument development arises from NSF's 10 Big Ideas for Future Investments, many of which pertain to the chemical sciences, and the solutions to which would be transformative. Thus, a key objective of the workshop was to bring together research leaders in the chemical sciences with a specific interest and expertise in the development of advanced instrumentation. Over the course of two days, these leaders considered the impact of new initiatives in mid-scale instrument development on overarching challenges in modern chemical sciences by: (1) Defining national needs in the chemical sciences for mid-scale instrument development; (2) Organizing needs assessments around chemical grand challenge problems; and (3) Raising community awareness regarding mid-scale instrument development.

The workshop was organized around grand challenge goal setting, refinement, and ultimate identification of three examples of transformational projects that embody the kinds of problems that can only be solved by mid-scale instrument development. A series of eight grand challenge talks delivered by experts addressed specific problems where the development of new instrument capacity could catalyze transformative change. Prior to the meeting, workshop participants proposed 33 "transformative instrument development" concepts. Informed by the participants' grand challenge talks, these concepts were then refined through a down-selection and aggregation process into eight overarching thematic concepts for further fine-tuning. From these eight concepts emerged three key examples of instrument-dependent scientific problems with the potential to revolutionize the chemical sciences.

(1) High-Flux Ion Sources to Transform Synthetic Chemistry. For two centuries, synthetic chemistry has largely proceeded by condensed phase molecular manipulations. Now there is an opportunity to completely transform the way we execute synthetic reactions by carrying them out with ions in low-density media. This approach will yield unique chemical products with exquisite isotopic control and purity and with minimal need for purification. Turning these opportunities into reality will require the development of new high-flux ion sources capable of implementing ion-based synthetic chemistry at the molecular scale.

(2) Mapping the Dark Molecules of Life. Presently, less than 1% of the compounds associated with life are known. The myriad of unknown molecules, the so-called “Dark Molecules,” are critical determinants of biological function, and are therefore relevant to health and disease. These molecules include many proteins, both native and modified, and unknown endogenous (metabolites and lipids) and exogenous (compounds we are exposed to since birth) small molecules in living organisms that have yet to be structurally assigned. Identifying and mapping the interactions of these Dark Molecules of Life will require transformational developments in high-performance analytical instruments, such as high-resolution nuclear magnetic resonance (NMR) and high-resolution mass spectrometry (MS) with a variety of different activation sources.

(3) Quantum-Level Prediction and Control of Chemical Reactivity. A significant amount of the world’s energy budget is spent on the production of commodity chemicals. Efficiency improvements of just a few percent could have tremendous impact. However, such modest improvements are hard to come by, because chemistry is heterogeneous both in space and time, and reactions are rare events in which reagents and catalysts interact for only a brief moment at the “right” configuration. Recent developments in laser control, and in particular the preparation of linked quantum pairs known as “entangled photons,” open the door to new highly sensitive modes of probing and controlling molecular reactivity in space and time. Together with advances in the accuracy and speed of molecular electronic structure calculations, capable of modeling the chemical structure of reagents as they transition through intermediate configurations on their way to become products, our understanding of chemical reactions and how to accelerate them efficiently will emerge. This project, combining advanced laser measurements and computation, will accelerate developments aimed at significantly reducing the energetic and environmental footprint associated with the production of commodity chemicals.

I. Workshop Organization and Activities

Evaluating Project Concepts for the Development of Mid-Scale Instruments for the Chemical Sciences

Bringing together three-dozen chemical science luminaries (**Appendix A**) *and asking them to dream up blue-sky ideas for the development of mid-scale chemistry instrumentation resulted in many creative, scientifically compelling project concepts. The concepts varied in their potential societal impact, readiness for implementation, and novelty. Figuring out which ideas maximized the combination of these factors in the course of a two-day workshop was a challenge. Below is a description of how the ideas were presented, evaluated, combined and ultimately narrowed down into the list of three main example concepts detailed in* ***Section II*** *of this report.*

In the weeks leading up to the workshop, each participant was asked to submit two proposals (**Appendix B**) to a webpage in order to frame the workshop agenda (**Appendix C**). Rather than requesting page-long blocks of text to describe each idea, the workshop organizers asked for proposals in the form of quad charts. As the name suggests, quad charts (**Figure 1**) were broken into four sections (Science Challenges, Broader Impacts, New Ideas, Resources), each of which was physically placed in a separate quadrant on a single slide. Again, because the goal was to solicit concepts, not fleshed out proposals, each quadrant consisted of a varying mixture of bullets, pictures and diagrams.

A total of 33 quad charts/concept documents (**Appendix D**) and 12 scientific priorities for instrument development (**Appendix E**) were submitted. Workshop participants were encouraged to review each of the other participants' quad charts ahead of the workshop. These initial concepts were important - both in and of themselves, *i.e.* at some level all were appropriate to direct the efforts of mid-scale instrument development – as well as providing a starting point for an organized evaluation process to identify strong themes that could serve as examples of viable mid-scale instrument development projects.

The two-day workshop was organized around a kickoff event, four concept elaboration sessions, two intensive small-group breakout sessions, and a series of discussions involving all of the workshop attendees. The kickoff event included a presentation by Albert Lazzarini, Deputy Director of the LIGO Laboratory. The goal of this event was to inspire mid-scale instrument development in a community of chemists, to whom projects of the size and scope traditionally associated with astronomy are generally foreign. Concept elaboration sessions consisted of pairs of participants presenting 30-minute talks about specific project proposals. The four session topics were inspired by NSF's "10 Big Ideas For Future Investments":

- Thinking Big
- Disruptive Technologies and "Impossible" Measurements
- The Quantum Leap
- Understanding the Rules of Life

The first presentation in each pair was chosen to encourage "thinking big" and "thinking outside the box." The second presentation in each pair was chosen to highlight research areas within the 10 Big Ideas where chemists could make significant contributions. Each presentation was followed by a short question and answer period, and a 30-minute mini-panel discussion in which the entire workshop was encouraged to debate the merits, practicality and potential outcomes of

the pair of presented concepts.

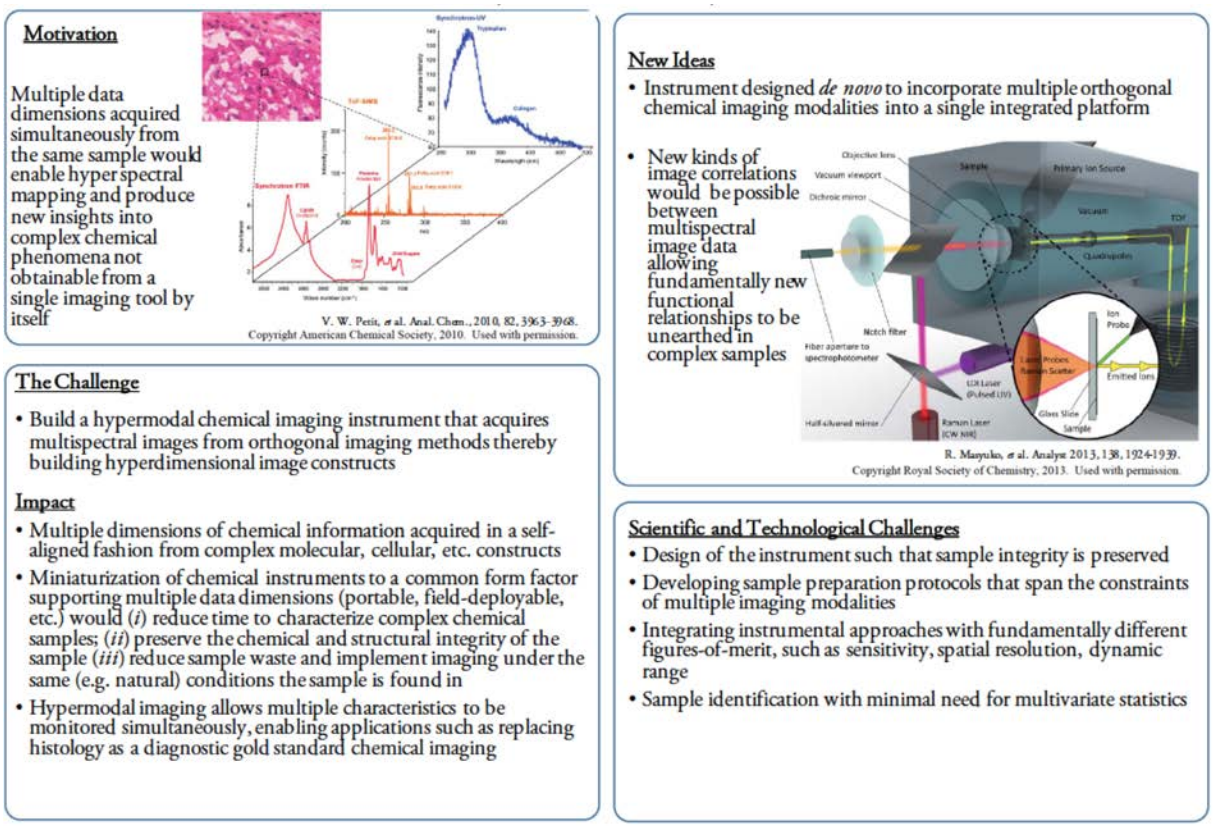


Figure 1. Example of pre-meeting quad chart used to solicit project concepts.

Two breakout sessions, one on the first day and another on the second day, were organized to provide a mechanism for the attendees to focus on and elaborate upon the ideas presented in the pre-workshop documents and in the concept elaboration sessions. In addition, the breakouts gave participants the opportunity to discuss in general the needs of the chemistry community for new mid-scale instrumentation and to consider the idea proposals in detail.

During the first breakout session on Day 1 of the workshop, participants divided into four groups, each of which met in a different conference room and had an assigned leader and reporter (**Appendix F**). The participants were asked to consider the full range of project concepts in the context of four questions:

- How would mid-scale instrument development transform our capabilities to **measure and analyze** chemical systems at **molecular and nanoscale levels**?
- How would mid-scale instrument development transform our capabilities to **create** new chemical systems to achieve **new atomic, molecular, and supermolecular arrangements of matter with transformative properties**?
- How would mid-scale instrument development transform our capabilities to **measure and analyze biomolecular systems** with an emphasis on relating biomolecular information to form and function?
- How would mid-scale instrument development transform our capabilities to **create new biomolecular systems with transformative properties**, including those not found in nature?

By keeping in mind the various proposed concepts in their attempts to formulate answers to these questions, the workshop participants primed themselves to think critically about which concepts were most likely to deliver significant scientific breakthroughs. In addition, the participants were asked to think about how the instrument development ideas were positioned along the three dimensions of risk, complexity and impact. They then sorted and consolidated the conceptual ideas and identified and organized the eight most compelling project concepts.

Following the first breakout session, each of the four group reporters gave a 10-minute summary presentation to the rest of the participants. The remainder of the first day and the early portion of Day 2 were devoted to further refining the ideas.

During the second breakout session on Day 2 of the workshop, most of the attendees were assigned to one of four groups. Each of the four groups evaluated two related project concepts (for a total of eight) along four dimensions:

- Science Challenges
- Broader Impacts
- New Ideas
- Required Resources

A dedicated discussion leader and a reporter were assigned to each pair of project concepts. Each of the four groups spent 15 minutes with the concept leader and reporter exploring ways to further "elaborate" the pair of concepts before rotating through discussions of each of the other concept pairs. This refinement process provided a unique opportunity to have the entire range of experts consider each of the ideas and suggest improvements.

Following the breakout session, the reporters assigned to each of the four concept pairs gave 10-minute summary presentations to the entire workshop. This was followed by extended, in-depth discussion of each of the eight conceptual ideas by all of the attendees.

At the end of the workshop, attendees were asked to vote for the three project concepts they felt were most promising. The votes submitted were then tallied and the results presented to the entire group. Attendees then discussed which of the concepts would benefit by being combined together into broader concepts. The result of this process was three project concepts that stood above the others:

- High-Flux Ion Sources
- Mapping the Dark Molecules of Life
- Quantum-Level Prediction and Control of Chemical Reactivity

Each of these concepts is described in detail in **Section II** of this report.

II. Three Transformative Ideas for Mid-Scale Instrument Development

The objective of the workshop, beyond assessing the chemical science community's appetite for support of mid-scale instrument development, focused on the identification of a small set of exemplary problems that (a) cannot be accomplished within currently available funding structures, and (b) have the potential to transform the way chemistry is performed and understood. The first criterion was understood in the context of two existing programs: the Major

Research Instrumentation (MRI) and the Centers for Chemical Innovation (CCI) programs. Projects were judged to be outside of the focus of the MRI program for reasons of scale and scope, since the MRI program is capped at $4M, and the workshop focused on ideas beyond this range. The CCI program supports "……research centers focused on major, long-term fundamental chemical research challenges." As such, CCI efforts may include elements of instrument development, but the larger focus is on fundamental advances in understanding that may, for example, integrate efforts across theory, synthesis, and characterization. For this reason, projects that are specifically and solely dedicated to the development of new chemical instrumentation, are unlikely be competitive in this context. Finally, it is important to note that scale and scope alone do not necessarily justify mid-scale instrument development. Rather, the workshop focused its attention to those projects that, due to their inherent complexity and risk, fell outside of current programmatic parameters.

Beginning with a set of 33 initial "transformative instrument development" ideas, developed by the workshop participants prior to the workshop, a series of talks focused on chemical grand challenges were used to focus the discussion and facilitate the consolidation of these initial ideas into eight global themes for further refinement. These eight themes were vigorously and critically evaluated by all the participants, and from them emerged three instrumentation-dependent scientific problems that serve as examples of instrument development projects with the potential to transform the molecular sciences. The funding required to make each of these projects come to life ranges from $12 million to $30 million for a canonical five-year effort. The projects put forward here are examples of instrument development initiatives that (a) could not be accomplished under the aegis of existing programs (scale and scope); (b) are well-poised to catalyze transformative change in the way chemistry is understood and performed; and (c) have strong potential for wider societal benefits.

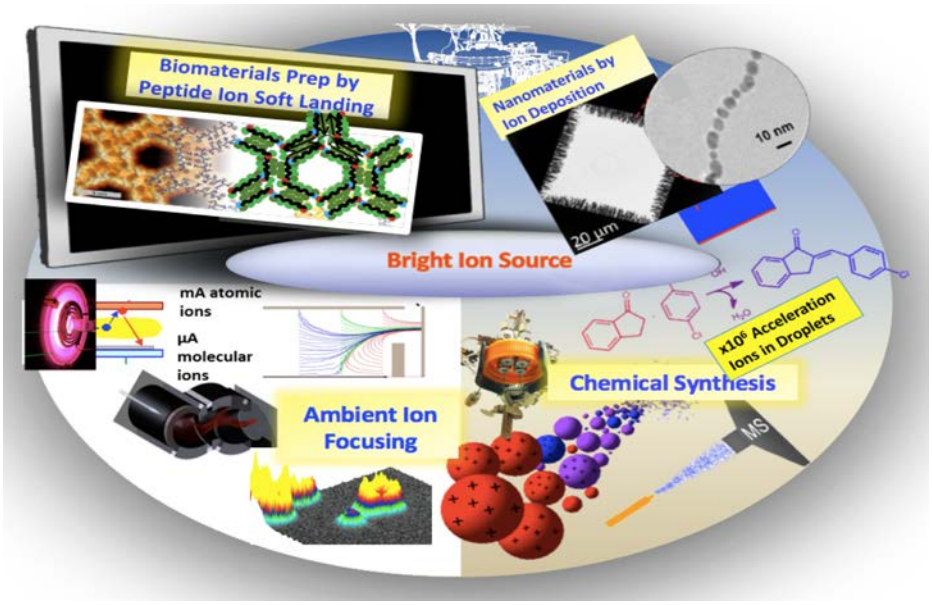


Figure 2. High Flux Ion Source

II.A. High-Flux Ion Sources for Transformative Synthetic Chemistry

Summary and Rationale: A High-Flux Ion Source, *viz.* **Figure 2**, would impact molecular synthesis, surface tailoring and nanomaterial preparation. The key focus would be to accelerate organic synthesis in charged droplets, to facilitate ion soft landing to create new catalysts and biomaterials, and to open new routes to nanomaterial preparation using high-flux selective-ion beams. In addition to these key drivers, a High-Flux Ion Source would enable non-nuclear isotope preparation, non-lithographic methods of device fabrication, and new forms of microscopy and ion spectroscopy. While this special instrument would be chemistry-centered, strong interactions with engineering and other sciences are expected in the development and

applications of the High-Flux Ion Source.

Transformative approaches to molecular synthesis and materials fabrication are envisioned based on direct use of precursor molecular ions, ionic clusters and charged droplets. The High-Flux Ion Source would provide high fluxes of charged microdroplets with tunable ion content – a special environment, known to strongly accelerate reaction velocities and with the potential to make new products available. High fluxes of mass-selected ions would be produced such that they could be landed on surfaces to create new biomaterials, custom-designed catalysts and surface coatings. High fluxes of charged microdroplets would be employed in nanomaterials preparation.

Scientific Impact: The High-Flux Ion Source facility would be based on atomic-to-molecular ion conversion. Multiple beam lines/trapped ion sources would be constructed to produce high fluxes of ions at different energies and ion currents. Atomic ion beams would be used for physical processes (depth profiling, implantation). The beams would also be used for conversion into molecular ions by sputtering, relay spray and charge transfer. High fluxes of molecular ions would be mass analyzed and, depending on the end-use, provided at low (eV) to high (keV) translational energies.

Chemical synthesis is an area in which there are great opportunities to incorporate recent dramatic changes in technology, such as the adoption of "flow chemistry" strategies. Further advances in synthesis are surely on the horizon if we can collect and incorporate new ways to think about and realize chemical transformations. The High-Flux Ion Source offers the prospect of substantial new approaches to chemical synthesis, including the synthesis of libraries of compounds in an automated, efficient manner. These approaches would completely revamp the concept of plant-scale reaction engineering, making possible heretofore difficult-to-achieve transformations.

Broader Impact: Synthesis is both an infrastructure and a front-line societal tool. Drug discovery and development, reading/writing and ion tagging, ion spectroscopy, catalyst and biomaterials production, forensics, diagnostics and point-of-care clinical tools are all potential applications of the new technologies that would emanate from the High-Flux Ion Source. A successful facility would energize and enable new single-investigator programs in analytical, surface and synthetic chemistry. In addition, there would be substantial impact on STEM education. The Venn diagram overlap of accomplished synthetic chemists and engineers is small. The High-Flux Ion Source would enable the *training and education of scientists to fill in this gap.* A highly important impact would be on education in synthetic chemistry – for example, the ability to synthesize a whole series of substituted aromatic compounds in a few minutes could potentially transform instruction in synthetic chemistry and drive home the principles of molecular transformations in a context that students will enjoy[1, 2]. Finally, mission-oriented agencies will likely find this an attractive area in which to invest, given the STEM-wide applicability of materials and molecular synthesis. For example, the energy-related impacts of the proposed High-Flux Ion Source raise the possibility of a DOE partnership.

II.B. Mapping the Dark Molecules of Life

Summary and Rationale: Understanding life is a fundamental quest for humankind, and life is, at its core, the interplay among special suites of "active" chemicals. The Human Genome Project has given us the blueprints of life, but actually understanding them will require enormous effort. Genes contain the instructions for making proteins, but each protein is produced in many different forms, or proteoforms, that vary widely in their function[3]. The families of proteoforms

derived from a given gene comprise the functional underpinnings of biological systems[4]. For example, many proteoform families drive metabolic processes involving tens of thousands of small molecules – collectively known as the metabolome – whose roles are similarly essential to life.

Remarkably, the identities of a large number of these critical proteins and metabolite molecules are still hidden from view. In analogy to the exploration of the universe, we refer to the vast families of molecules that have yet to be discovered as the Dark Molecules of Life. Existing technologies for proteomic analysis, although extremely powerful, are not yet able to reveal the identities of the various proteoforms present. Similarly, only a relatively small fraction of the detectable small endogenous molecules comprising the metabolome have known structures[5], the vast remainder of which constitute the "Dark Metabolome." Similar complexity is found when interrogating small molecules of exogenous origin that become incorporated in an organism through life-long exposure (*i.e.* the "exposome"). Revealing the identities of these critical molecules represents the next essential milestone in truly understanding life.

Scientific Impact: The twin mysteries posed by dark proteoforms and the dark metabolome can be attacked with a two-pronged initiative. One aspect of the problem could be addressed by building a Proteoform Atlas, *viz.* **Figure 3**, which would contain all of the proteoforms that are expressed in living systems. The second aspect would be addressed by a similar map containing families of small molecule metabolites related to a specific cell or disease. The challenges outlined here would require parallel transformative developments in instrumentation – especially new, high-performance mass spectrometers and magnetic resonance spectrometers as well as "fused" analytical technologies for high-throughput structural determinations of small-molecule metabolites. Similarly, both of these refractory grand challenge problems demand that new informatics and data mining strategies be developed in parallel with the new instrumentation.

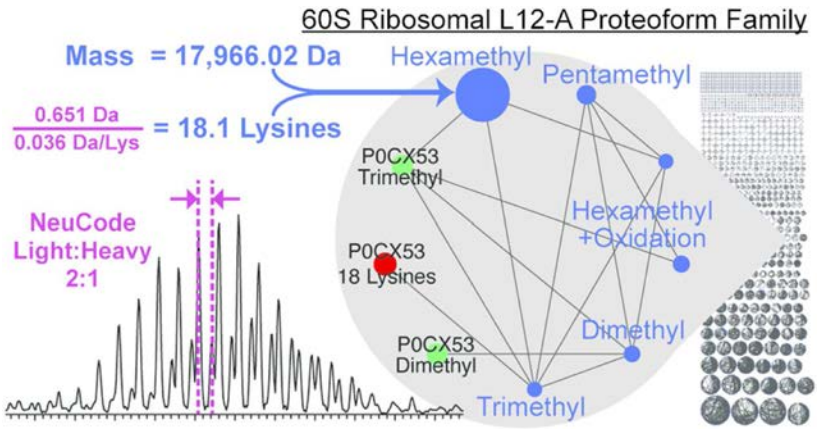


Figure 3. The Proteoform Atlas

In addition, there is a dark proteome – composed of proteins or protein domains that have no stable structure in isolation, but which can take on multiple structures when bound to specific targets. These intrinsically disordered domains have been found to have many of the post-translational modifications that give rise to proteoforms. Consequently, the combined efforts of ultra-high-field mass spectrometry and NMR spectroscopy are ideal for the characterization of proteoforms, the nascent structure of intrinsically disordered protein domains and the multiple structural forms with their binding partners.

The key technological hurdles to addressing these critical problems at the intersection of chemistry and biology lie in developing advanced instrumentation with the requisite sensitivity, mass and nuclear spectral resolution and ability to manipulate molecules for detection. Some of these performance metrics can be achieved by novel instrument design – for example, the

ability to break strong chemical bonds while leaving intact weaker bonds associated with post-translational modifications. Other metrics would benefit from improvements in underlying capabilities, such as higher magnetic fields that are becoming available with the development of high-temperature superconductors. NMR instruments, in particular, would benefit from increasing field strength in dispersion, *i.e*. the separation of NMR resonances. Even more significantly, NMR instruments would benefit in accessing nuclei (*e.g*. ^{17}O, ^{25}Mg, ^{33}S, ^{39}K, ^{43}Ca …) that have only rarely been observed, because of very poor sensitivity and broad spectral linewidths. As an example, ^{17}O is a particularly appealing target nucleus, because the O atoms that lie at the sites where much biological chemistry occurs could be directly observed for the first time. In addition, the functional metal sites of metalloproteins could be characterized by NMR for the first time. ^{33}S has high natural abundance and would be a game changer for proteoform studies through the less-explored chemical moieties, such as disulfide linkages in tertiary structures and methionine groups that frequently determine tertiary and quaternary structure. Extending the boundaries of NMR capabilities could be accomplished by pushing magnet construction to higher field strength and larger bore diameters – the combination constituting a powerful enabler for our ability to explore and map the Dark Molecules of Life. Together, these efforts would reveal the hitherto hidden identities of the central molecular players that comprise living systems, and thereby enable tremendous advances in humankind's ability to understand the functioning of life itself.

II.C. Quantum-Level Prediction and Control of Chemical Reactivity – The Quantum Explorer

Summary and Rationale: An instrument where measurement, prediction and control of chemical reactivity is sped up many orders of magnitude by closing the gap between experiment and computation could transform the chemical sciences and related industries and significantly reduce their economic and environmental footprint. Taking advantage of unprecedented control over wavelength, phase, duration and quantum entanglement of photons[6,7] would allow chemists to characterize and exploit the rare, far-from-equilibrium events in which reagents and catalysts interact at the "right" configuration to yield a desired product. The experimental data obtained would inform quantum-level descriptions of chemical structure and reactivity, resulting in models that can be used to computationally and experimentally achieve leaps in efficiency that have eluded conventional efforts.

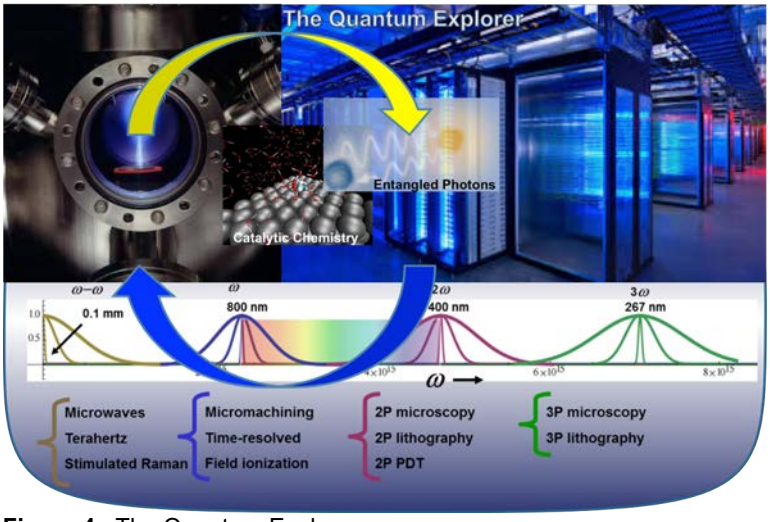


Figure 4. The Quantum Explorer.

Often, years pass between observation and understanding, because the observations are carried out by separate instruments. Improvements in chemical processes are tied to empirical observation that should ideally be guided by theoretical models. The 21st century offers the possibility of a quantum-level description of chemical structure and reactivity on a timescale, and with a precision that approaches that of experimentation[8]. This new level of understanding arises from developments in laser technology including the preparation of new non-classical forms of light that can

completely alter how matter responds to radiation[9], and from computational models capable of achieving near experimental accuracy. Together these capabilities portend a paradigm shift in our understanding of how to predict and control chemical reactivity. The instrument capable of accomplishing such tight coupling between prediction and quantum-level control of chemical reactivity is the Quantum Explorer, *viz.* **Figure 4**.

Scientific Impact: Successful realization of the Quantum Explorer would enable the autonomous exploration, prediction, and control of chemical reactivity at the quantum level by exploiting and combining two key advances: the use of non-classical light not only as a probe but as a reagent, and the development of quantum-level theories capable of exploring structures far from equilibrium. The Quantum Explorer would realize improvements in chemical reactivity by taking advantage of new photon sources to probe the chemical reaction under consideration. This information would then be used to optimize quantum calculations of the reactants and products. Mechanisms for the reaction would be simulated, and hypotheses formulated and tested experimentally by the newly prescribed experimental measurements. Through this close and information-rich feedback loop between computation and experimental measurement, more efficient reactions can be developed. Enhanced quantum-level predictability and controlled improvements of chemical reactions have the potential for improvements on the days-to-weeks timescales for the kinds of systems where change has traditionally happened only after decades.

Principal Scientific Challenges: Chemistry is heterogeneous both in space and time, and reactions are rare events occurring against a large background. In the face of this sparse reaction environment, achieving predictability and control over chemical reactivity will require wholly new kinds of experimental measurements that yield rich data sets. These data, in turn, will become input for state-of-the-art quantum-level computation of chemical structure and dynamics. The required triggering and probing of reactions in space and time will require high-intensity non-classical quantum light pulses with frequency, time, phase and amplitude control. Complementing these experimental advances, computational advances are necessary to complete the transition from predicting static equilibrium structures to predicting the dynamic transient far-from-equilibrium configurations responsible for the transformation of reagents into products.

Broader Impact: Chemistry is the science of the material world. It is critical for the production of food, medicine and the building blocks underlying all of the materials used by society. Unfortunately, these benefits often come at significant costs, both in terms of energy use and damage to the environment. The Quantum Explorer has the potential to transform chemical reactivity by making it possible to discover new catalysts that could reduce the footprint of the chemical industry. One example is ammonia, which, as a key precursor to fertilizers, helps feed the world population. This commodity chemical is produced in half-billion ton quantities using the Haber-Bosch process introduced in 1913. Given that up to 2% of the world's annual energy supply is used for producing ammonia, a modest improvement in efficiency realized by the Quantum Explorer could have a major monetary, energy, and pollution impact. The Quantum Explorer could also hasten scientific progress by drastically reducing the time between experimentation and calculation, and shorten the time between prediction and confirmation from decades to days.

The ambitious instrumentation being envisioned would require several advances, including:

- The development of computer-controlled sources of light

- The development of high-flux sources of entangled photons
- The capture of rich spectroscopic data providing electronic and vibrational energies of reagents
- Transition states and products, to be fed into computer programs
- The development of new algorithms that will turn data into information to test computer predictions of chemical reactivity

STEM education would be inspired by the conception, design and construction of the technologies needed to accomplish these objectives. In addition, advances from single-investigator programs would help guide the types of projects addressed through instrument development.

III. Conclusions

1. Mid-Scale Instrument Development Focused in the Chemical Sciences. The workshop identified a need - as evidenced by strong interest of the participants - to develop novel chemical instrumentation that cannot now be encompassed within existing programs.

The activities sponsored by the workshop, as well as the many informal communications received from interested non-attendees, make it abundantly clear that there is substantial interest in pursuing instrument development projects in the mid-scale range that could transform the chemical sciences and associated industries. The workshop attendees explicitly considered both scenarios where additional new resources could be brought to bear in support of mid-scale instrument development and where it would be supported by reallocation of existing resources. The workshop participants and organizers concluded that there is a need for new resources to support Mid-Scale Instrument Development. However, even absent new resources, the need is sufficiently well demonstrated that alternative strategies to support the development of mid-scale instrumentations in Chemistry would serve the community well. Workshop attendees remarked that the transformative mid-scale projects being considered would likely garner support from multiple funding agencies, universities, and industries.

2. Scale and Scope of Instrument Development Efforts. Efforts to address Mid-Scale Instrument Development in the chemical sciences should anticipate either: (a) instrument development efforts that result in demonstration vehicles that can then be replicated and used in other laboratories or by industry; or (b) instrument development efforts that produce a single unique instrument with the intent that eventually the instrument is shared by the community. Implicit in the example projects identified and discussed in **Section II A-C** are chemical problems that span both of these possibilities, and the workshop produced a strong sentiment that both types of development activities would be beneficial to the field.

3. Transformative Potential and Grand Challenge Problems. The sense of the workshop is that Mid-Scale Instrument Development efforts should be guided by the absolute criteria that all projects: (a) demonstrate a potential for transformative change to chemical sciences, broadly construed, and (b) address grand challenge problems in chemistry. In support of this, ample evidence from the concepts developed and elaborated during the workshop suggests that there are a number of potential instrument development ideas that meet these criteria. In addition, these criteria can loosely be associated with the standard NSF evaluation metrics of intellectual merit and broader impact. However, there was a strong sense in the workshop that the scale and scope of mid-scale instrument development dictates that only the most meritorious ideas –

ones with truly transformative potential and the capacity to address truly critical challenges facing the chemical sciences – are best poised to serve the community.

4. High-Risk and Mid-Scale Instrument Development Efforts: The workshop recognized that Mid-Scale Instrument Development in the Chemical Sciences would necessarily involve projects with significant risk, complexity, and impact. A need exists for avenues to support high-risk/high-reward projects that would otherwise not come to fruition without this type of funding. Mid-scale instrument development projects with transformative potential for chemistry may well involve the creation of instruments with sufficient complexity and future-looking capabilities that they would be considered too risky and thus not fundable through conventional funding venues. As made clear in LIGO Deputy Director Albert Lazzarini's presentation that kicked off the workshop, significant funding is required to develop instrumentation with these characteristics.

IV. Summary

The Workshop on Mid-Scale Instrument Development for the Chemical Sciences assessed the needs and opportunities for advanced instrumentation to inform, educate, and impact the entire chemical sciences community of researchers and educators in the U.S. Over two days, nearly 50 workshop attendees and government agency observers exhaustively debated and elaborated 33 initial "transformative instrument development" concepts – informed by the grand challenge talks – into eight overarching thematic ideas for further refinement, and from these eight thematic ideas emerged three key examples of instrumentation-dependent scientific problems with the potential to transform the molecular sciences: High-Flux Ion Sources, Mapping the Dark Molecules of Life, and Quantum Level Prediction and Control of Chemical Reactivity. The activities engaged by the workshop attendees made it abundantly clear that there are significant opportunities for mid-scale instrument development in chemistry.

Based on these ideas and the surrounding intellectual challenges, four critical conclusions were reached: (1) There is broad support in the community for the development of novel chemical instrumentation that cannot now be encompassed within existing programs; (2) The community would be well-served by considering both (a) instrument development efforts that result in demonstration vehicles with the expectation that successful demonstrations would lead to wide-spread deployment supported by mission-oriented agencies and the private sector; and (b) instrument development efforts that produce a single unique instrument with the expectation that the instrument be shared by the community; (3) The community's interests are best-served by considering the absolute criteria that all mid-scale instrument development projects should (a) demonstrate a potential for transformative change to chemical sciences, broadly construed, and (b) address grand challenge problems in chemistry. From among this group of qualifying concepts, the most meritorious should be strongly supported. (4) Efforts to support Mid-Scale Instrument Development in the chemical sciences must necessarily take into account the risk and complexity of projects, as well as their potential societal impact. There is a substantial need for support mechanisms for scientifically meritorious projects characterized by a sufficient level of risk and complexity that they would go unfunded without mid-scale support.

V. Acknowledgment

This workshop was supported by the National Science Foundation through grant NSF1642322. The opinions expressed in this document reflect those of the workshop participants and not necessarily those of the National Science Foundation.

Appendix A – Workshop Attendees

Workshop Participants	Institution
Baig, Nameera	Univ. of Notre Dame
Baker, Lane	Indiana Univ.
Barty, Christopher	Lawrence Livermore National Lab
Belkacem, Ali	Lawrence Berkeley National Lab
Bohn, Paul	Univ. of Notre Dame
Buchanan, Michelle	Oak Ridge National Lab
Buratto, Steve	UC-Santa Barbara
Centurion, Martin	Univ. of Nebraska
Cicerone, Marc	National Institute of Standards & Technology
Cooks, Graham	Purdue Univ.
Cross, Tim	Florida State Univ.
Dantus, Marcos	Michigan State Univ.
Dunn, Bob	Univ. of Kansas
Engel, Greg	Univ. of Chicago
Fell, Nick	Army Research Lab
Fernandez, Facundo	Georgia Inst. of Technology
Garrett, Bruce	Pacific Northwest National Lab
Goodson III, Theodore	Univ. of Michigan
Hayes, Sophia	Washington Univ.
Hendrickson, Chris	National Magnet Lab
Jimenez, Ralph	Univ. of Colorado - JILA
Kleiman, Valeria	Univ. of Florida
Larive, Cindy	UC-Riverside
Laskin, Julia	Pacific Northwest National Lab
Lazzarini, Albert	California Institute of Technology
Manicke, Nick	Indiana Univ. - Purdue Univ. at Indianapolis
Minteer, Shelley	Univ. of Utah
Nairat, Muath	Michigan State Univ.
Pellegrino, Paul	Army Research Lab
Perry, Joseph	Georgia Inst. of Technology
Rolison, Debra	Naval Research Lab
Shafaat, Hanna	Ohio State Univ.
Smith, Lloyd	Univ. of Wisconsin
Soper, Steve	Univ. of Kansas
Weiss, Paul	UCLA
Woodbury, Neal	Arizona State Univ.

Appendix B – Pre-Workshop Charge to Participants

NSF Mid-Scale Instrument Development Workshop ($5 - $125M)
Charge to Participants
NSF Sponsored Workshop Arlington, VA

Dear Participant,

As we consider instrumentation that will revolutionize chemistry five to ten years from now, we can (a) extrapolate on what is already available, augmented by technologies that are advancing at a very fast pace, or (b) we can consider developments *that can only take place provided a significant amount of resources (human and monetary) are invested*.

The purpose of this workshop is to consider how a bold initiative—if funded at the $5-125M level—could make a quantum leap over technology that would naturally evolve during the next five to ten years.

Justifying the need for a mid-scale instrument development investment will require identification of societal needs, overarching benefits to society, solution to presently intractable scientific and technological problems, overcoming global technical challenges, and exploration of radically new paradigms in chemistry. We recommend you download the document "10 Big Ideas for Future NSF Investments."

In preparation for our meeting, we ask that you create a list of five priorities that could justify a considerable investment in instrument development. We then would like you to explore two of those priorities in depth. Using a single PowerPoint slide, along the lines of a DARPA quad-chart, explain: (a) The priority; (b) The new concepts to be explored; (c) The benefits that would stem from the proposed project; and (d) The resources that would be needed. At this point, we are only interested in bullets without technical detail or narrative. We are not writing the proposals; our goal is to identify the need for mid-scale investment in instrument development for the chemical sciences and the overall enthusiasm from the chemical sciences community.

A successful outcome from this workshop will be a document outlining a set of high priority scientific objectives with the *potential to transform the chemical sciences*. Such a document will likely be used by one or more agencies to prioritize funding. Perhaps one or more agencies (industries?) will also partner and call for proposals to fund one or more mid-scale instrument development projects.

We hope you can submit your list of priorities and your two quad-charts by October 27th. Analysis of the priority lists will allow us to identify general areas of interest. We will use this information to fine-tune the organization of the workshop.

Note on intellectual property: Recommendations made to federal agencies should be considered public documents and will likely be generally accessible to the public. Please do not include restricted or confidential information. At the workshop, we plan to have an open and free-flowing discussion. Given the number of creative minds that will be assembled, an invention worth patenting may take place. There will be approximately one month between the end of the

workshop and the completion of the final document during which all rightful contributors to the invention will have an opportunity to file a patent.

We look forward to seeing you in Arlington this November,

Marcos Dantus and Paul Bohn

Appendix C – Final Agenda

NSF Mid-Scale Instrument Development Workshop - Final Agenda

Day 0 (Westin) November 6, 7:00 - 9:00 pm

(check at hotel for room assignment)

Registration and Kickoff Meeting

Intro: M. Dantus and P. Bohn (15 min)
Kickoff Lecture: Albert Lazzarini, LIGO (30 min)
Review of proposed ideas: Dantus/Bohn (30 min)
Logistics/Agenda (15 min)

Day 1 (NSF Stafford II-Room 555)- November 7

Continental Breakfast 8:00 - 8:30 am

Session 1: Thinking Big – M. Dantus

Opening Remarks: A. Wilson, Chemistry Division, NSF
Lecture 1 (invited): 8:40 - 9:10 am – G. Cooks
Lecture 2 (invited): 9:10 - 9:40 am – C. Barty
Mini-Panel (Cooks/Barty): 9:40 - 10:10 am

Break 10:10 - 10:30 am

Session 2: Disruptive Technologies and "Impossible" Measurements – P. Bohn

Lecture 3 (invited): 10:30 - 11:00 am – L. Smith
Lecture 4 (invited): 11:00 - 11:30 am – P. Weiss
Mini-Panel (Smith/Weiss): 11:30 - 12:00 pm

Working Lunch 12:00-1:00 pm

Clustering the submitted ideas

Breakout Session 1: 1:00 - 2:00 pm

(~8 participants for each of 4 breakout groups)
Discussion Leaders/Reporters: F. Fernandez/H. Shafaat, C. Larive/P. Pellegrino, S. Minteer/L. Baker, D. Rolison/J. Perry

Reports from Breakout Sessions: 2:00 - 2:50 pm (4 reports, 10 minutes each)

Break 2:50 - 3:10 pm

Session 3: The Quantum Leap – N. Fell

Lecture 5 (invited): 3:10 - 3:40 pm – G. Engel
Lecture 6 (invited): 3:40 - 4:10 pm – M. Buchanan
Mini-Panel (Engel/Buchanan): 4:10 – 4:40 pm

Summary and Evening Thoughts: 4:40 - 5:00 pm

Dinner 6:00 - 8:00 pm

Day 2 (NSF Stafford II-Room 555) - November 8

Continental Breakfast 8:00 - 8:30 am

Session 4: Understanding the Rules of Life – J. Laskin

Lecture 7 (invited): 8:30 - 9:00 am – M. Cicerone
Lecture 8 (invited): 9:00 - 9:30 am – T. Goodson
Mini-Panel (Cicerone/Goodson): 9:30 - 10:00 am

Vision and Summary 10:00 - 10:30 am

F. Crim – MPS, NSF 10:10 - 10:30 am

Break 10:30 - 10:50 am

Logistics/Agenda 10:50 - 11:00 am

Breakout Session 2: Project Refinement 11:00 - 12:00 pm

(~ 8 participants for each of 4 break-out groups)
Participants rotate and contribute to each group
Discussion Leaders/Reporters: N. Manicke/R. Dunn, V. Kleiman/S. Soper, R. Jimenez/S. Buratto, N. Woodbury/C. Hendrickson

Working Lunch 12:00 - 1:00 pm

Further refinement of projects and preparation of reports

Reports from Breakout Sessions: 1:00 - 1:50 pm (4 reports, 10 minutes each)

Closing Session: 1:50 - 3:00 pm

Summary and discussion of broader impacts, buy-in from other agencies and industry (Moderators – P. Bohn/M. Dantus)

Adjourn 3:00 pm

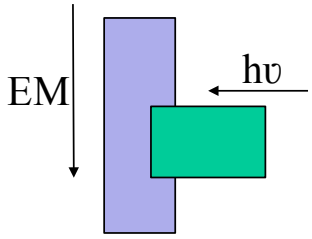
Appendix D – Participant Pre-Workshop Instrument Development Concepts

CryoTEM/Correlative Super Resolution Light Microscopy

Objective

(1) To bring the recent revolution in protein structure determination by TEM to chemical/macromolecular structures

(2) To combine super resolution optical techniques with cryotransmission electron microscopy; this has advantages for chemistry, materials and biology



Approach:

An emerging/emerged tool in structural biology is the electron microscope, which can now provide 3D structural information of individual proteins, without the need to obtain single crystals.

Chemical systems might also benefit from similar approaches as the technology improves. The ability to study self assembled structures, higher order structures and the interaction of chemicals (drugs, exposure to compounds) with biological entities is sought.

Correlating super resolution optical techniques with high resolution cryoTEM in single measurement platforms could enable addition of chemical information to such high resolution images.

Key Milestones

- Develop a center with appropriate instrumentation as a national clearing house for this approach, focused on chemistry/materials
- *Requires some instrumental advances/work yet
- Pricetag for present high end cryoTEM with necessary camera ($3-6M) (no optical component)

Distributed Sensor Network

Objective

A multi-sensor network that can be distributed universally to monitor air/water quality, exposure events, integrate point of care readout for human health

Approach:

Network to coordinate data from multiple sources and to extract and relay meaningful values

System would have to continually grow/evolve. But in reality would be one large instrument with a nearly infinite array of detectors that could be plugged into it.

Would require significant computational resouces, but could be built to adapt to advances in sensors as they evolve

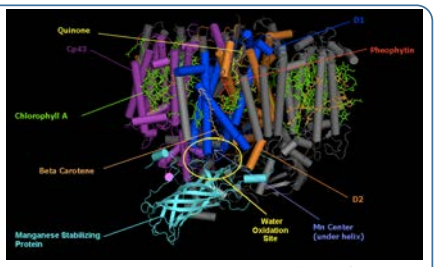
Blue sky- could be the ability to rapidly screen organisms for genetic manipulation and possibility of deploying counter measures. (CRISPR/antiCRISPR)

Key Milestones

- Put network in place
- Pair with computational people
- Really advanced sensors might not be here yet
- Could spend as much as one wanted on this. ($200M might not be enough)

Reconfigurable Supermolecular Machines
(Bohn - Notre Dame)

Motivation



Nature uses multi-molecular architectures to control cellular function which have the following characteristics:

- multiple sensor elements and fuzzy logic
- multi-step signaling cascades and signal amplification
- high-precision spatial organization to control reaction dynamics
- multiple-redundancy

The Dream

- Build highly functional "reconfigurable" molecular machines with multiple sub-units to accomplish context-specific chemical transformations

Impact

- Numerous technological problems share a common theme - measurements of a complex molecular environment are assessed by a human and used to generate a molecular response
- Functional molecular machines would integrate the assessment (measurement) and response (synthesis) functions into a single highly engineered architecture capable of responding to its surroundings in a context-specific manner
- Possible applications include continuous monitoring of molecular markers of human health linked to *in situ* therapeutic release on-demand

New Ideas

- Assembly utilizes the HARP principle: **H**ierarchical – different design elements and construction principles at different scales; (*b*) **A**lgorithmic – genetic algorithms with fitness functions derived from microscale descriptions; (*c*) **R**econfigurable – evolution through multiple generations conforming to reconfigurable structural principles; and (*d*) **P**recise – with spatial and orientational registration of nodes held to atomic-scale tolerances over μm-scale final assembly specifications
- Instruments would be constructed by spatially and temporally controlled reactions in "inaccessible" locations using non-contact control mechanisms, *e.g.* field-directed chemistry
- Multi-molecular assemblies fabricated so that they can "reconfigure" themselves - changing their spatial organization in response to the environmental context
- Spatial organization of the multi-molecular architectures will control the synthesis of new molecules that can either be incorporated into the growing assembly or shipped to a remote location as cargo

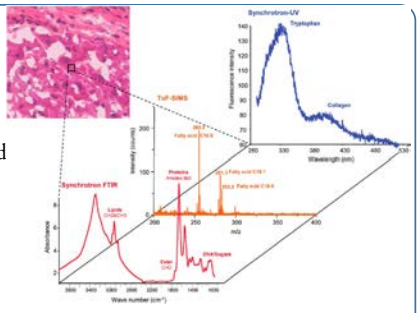
Scientific and Technological Challenges

- Building super molecular architectures with sub-nanometer precision of molecular placement and orientation
- Developing built-in error-correcting functionality
- Linking measured environment features to synthetic feedstocks and reaction pathways
- Developing self-reconfiguring architectures to shift reaction products based on context cues
- Organizing and managing a geographically distributed team of researchers around core scientific and technical goals

Integrated HyperModal Chemical Imaging
(Bohn - Notre Dame)

Motivation

Multiple data dimensions acquired simultaneously from the same sample would enable hyper spectral mapping and produce new insights into complex chemical phenomena not obtainable from a single imaging tool by itself



V. W. Petit, *et* al. Anal. Chem., 2010, 82, 3963–3968.

The Challenge

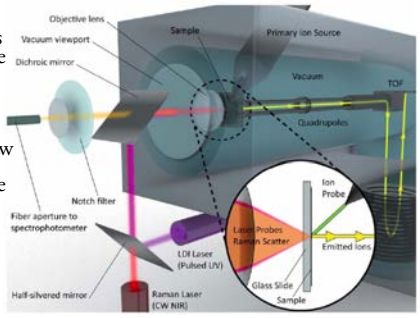
- Build a hypermodal chemical imaging instrument that acquires multispectral images from orthogonal imaging methods thereby building hyperdimensional image constructs

Impact

- Multiple dimensions of chemical information acquired in a self-aligned fashion from complex molecular, cellular, etc. constructs
- Miniaturization of chemical instruments to a common form factor supporting multiple data dimensions (portable, field-deployable, etc.) would (*i*) reduce time to characterize complex chemical samples; (*ii*) preserve the chemical and structural integrity of the sample (*iii*) reduce sample waste and implement imaging under the same (e.g. natural) conditions the sample is found in
- Hypermodal imaging allows multiple characteristics to be monitored simultaneously, enabling applications such as replacing histology as a diagnostic gold standard chemical imaging

New Ideas

- Instrument designed *de novo* to incorporate multiple orthogonal chemical imaging modalities into a single integrated platform
- New kinds of image correlations would be possible between multispectral image data allowing fundamentally new functional relationships to be unearthed in complex samples



R. Masyuko, *et* al. Analyst 2013, 138, 1924-1939.

Scientific and Technological Challenges

- Design of the instrument such that sample integrity is preserved
- Developing sample preparation protocols that span the constraints of multiple imaging modalities
- Integrating instrumental approaches with fundamentally different figures-of-merit, such as sensitivity, spatial resolution, dynamic range
- Sample identification with minimal need for multivariate statistics

Operando X-Ray Microscopy via X-Ray Raman, XRD and XANES

Steve Buratto UC Santa Barbara

Objective

Develop x-ray Raman scattering, x-ray diffraction and x-ray absorption tomography for imaging objects with sub-micron spatial resolution and chemical contrast..

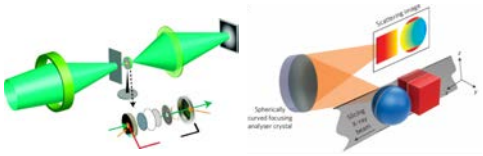
Imaging must be possible under ambient conditions.

Imaging must also be possible under reactive conditions (i.e. operando studies)

Ideally both light elements (C, N, S, P, O) and heavy elements (metals) should provide image contrast.

X-ray imaging methods will be based on synchrotron radiation and will require the highest intensity sources possible.

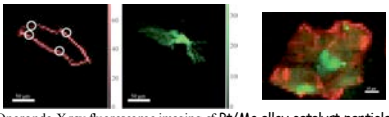
1. Price, SWT; Geraki, K; Ignatyev, K; Witte, PTW; Beale, AM; Mosselmans, JFW *Angew. Chem. Int. Ed.* **2015**, 54, 9886 –9889.



X-Ray Imaging Methods: X-ray absorption or fluorescence tomography (left) and inelastic X-ray scattering tomography (right)

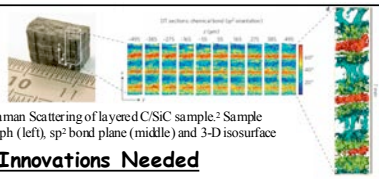
2. Huotari, S; Pylkkanen, T; Verbeni, R; Monaco, G; Hamalainen, K *Nature Materials* **2011**, 10 489–493 .

Applications:



Operando X-ray fluorescence imaging of Pt/Mo alloy catalyst particle show the spatial distribution of Pt (red) and Mo (green).[1]

1. Operando imaging of nanoparticle catalysts (above).
2. Operando imaging of batteries and battery materials.
3. X-ray imaging of soft tissue (e.g. tumors, amyloid plaques and cells).
4. Direct tomography with chemical bond contrast (next panel).



X-ray Raman Scattering of layered C/SiC sample.[2] Sample photograph (left), sp^2 bond plane (middle) and 3-D isosurface (right)

Key Innovations Needed

- Fundamental understanding of ineleastic x-ray scattering for light atoms using hard x-rays (experiments and modeling)
- Continued development of sensitive x-ray detectors.
- Continued development of brighter x-ray sources.
- Better algorithms for computing 3-D image data.

AFM-IR and Photoinduced Force Microscopy (PiFM) for Chemical Imaging at the 1 nm Length Scale

Steve Buratto UC Santa Barbara

Objective:

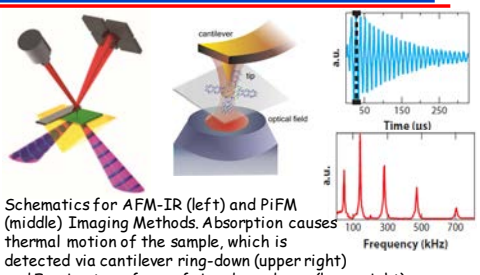
In either AFM-IR or PiFM (see upper right panel) the sample absorbs light. The absorption causes thermal motion of the sample that must be detected by the tip. Sensitive detection is key.

Develop photothermal atomic force microscopy methods for measuring the infrared spectrum of thin film samples using direct IR absorption or Raman scattering.

Performance goals are 1 nm spatial resolution and single molecule sensitivity.

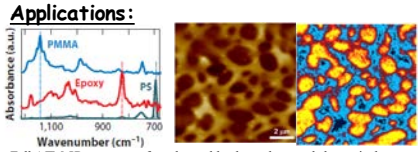
Technologies include high Q cantilevers, super-sharp AFM tips with radius of curvature < 5 nm, dual channel heterodyne detection, and high intensity IR sources.

1. Centrone, A., *Annu. Rev. Anal. Chem.* **2015**, 8:101–126
2. Jahng, J; et. al. *Acc. Chem. Res.* **2015**, 48, 2671−2679



Schematics for AFM-IR (left) and PiFM (middle) Imaging Methods. Absorption causes thermal motion of the sample, which is detected via cantilever ring-down (upper right) and Fourier transform of ring down decay (lower right).

Applications:

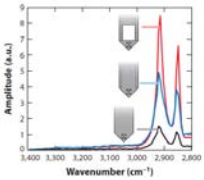


Full AFM-IR spectrum of a polymer blend sample recorded at a single spot. [1] AFM-IR chemical map at 3026 cm^{-1} a polymer blend sample (PS/PMMA); Topography (middle) and IR absorbance (right; PS is yellow). [2]

1. Chemical imaging of polymer blends (e.g. bulk heterojunction organic photocells).
2. Chemical imaging of electrode materials for batteries and fuel cells.
3. Spectroscopic imaging of bio-aggregates of proteins, enzymes and nucleic acids.

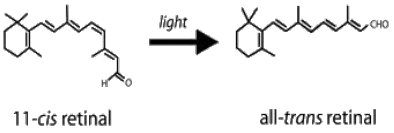
Key Innovations Needed

- New higher Q cantilevers with high sensitivity to thermal motion (see example on the right).
- Development of novel heterodyne detection schemes to measure the amplitude of the cantilever motion.
- Development of super-sharp tips based on carbon nanotubes for high resolution imaging.
- Development of accurate models to describe the thermal motion of thin films and how this motion is translated to the cantilever.



AFM-IR spectra of an ethylene acrylic acid polymer film [1] obtained with rectangular Si cantilever (bottom, black), paddle probe (middle, blue), and modified paddle probe (top, red).

High-resolution ultrafast electron diffraction for molecules in the gas phase and in solution



Example: cis-trans isomerization in retinal takes place on the femtosecond scale.

A new instrument to measure transient molecular structures on the time scale of 30 fs and determine atomic positions with picometer precision.

New concepts

The new device will require:

- High current laser-driven electron gun.
- Compression of highly-charged electron pulses to < 30 fs.
- Suppression of timing jitter between the laser and electron pulses.

Benefits

- Capturing detailed atomic resolution images of transient molecular states during chemical reactions in isolated molecules and in solution.
- Currently, in many cases the intermediate structures cannot be measured and are only known from simulations.

Resources needed

- Implementation of the technology to combine a high repetition rate electron gun, a high repetition rate high-power laser, electron pulse compression and single-shot timing jitter correction.
- Development of methods for delivery of molecules in gas phase and solution.

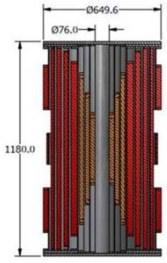
Chemical Kinetics: 1.4 GHz NMR Magnet

The Priority:

• To engineer and construct a 1.4 GHz (32.8 T) high homogeneity NMR magnet.

• Exploiting the revolution in High-Temperature Superconducting (HTS) materials.

• Such a development will leap-frog over the 1.2 GHz (28.1 T) magnets proposed by Bruker.



New Concepts:

• The route to ^{1}H frequencies > 1 GHz is through using the cuprate HTS materials made of REBCuO and Bi-Sr-Ca-CuO (2212 and 2223) that will superconduct to fields >>60 T.

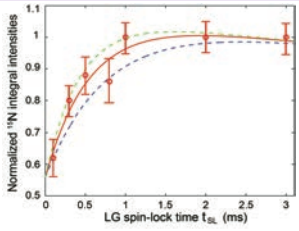
• Prototype magnets made at the MagLab have now generated more than 40 T, making a 1.4 GHz magnet now conceivable.

• Prototype triple resonance NMR Probes made at the NHMFL for a ^{1}H frequency of 1.5 GHz will be tested in the NHMFL's 36T Series Connected Hybrid (Resistive & Superconducting) magnet.

Benefits:

• Structure & dynamics in complex heterogeneous environments, such as cellular membranes.

• In-cell characterization of protein functional mechanisms through structure, dynamics and kinetic characterizations.



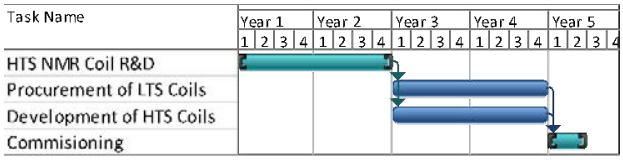
Normalized dipolar-dephased ^{15}N integral intensities illustrating a water/His37 H^+ kinetic rate of k_{1M}=1750 s^{-1} for the M2 H^+ channel.

Resources:

• The NHMFL is now testing a 32 T all superconducting magnet for condensed matter physics using REBCO tape.

• R&D is expected to cost ~$15M.

• Design & Construction is expected to cost another ~$15M.



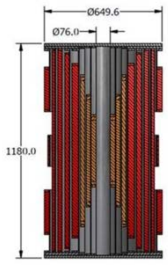
Functional Mechanisms: 1.4 GHz NMR Magnet

The Priority to achieve the science:

• To engineer and construct a 1.4 GHz (32.8 T) high homogeneity NMR magnet.

• Exploiting the revolution in High-Temperature Superconducting (HTS) materials.

• Such a development will leap-frog over the 1.2 GHz (28.1 T) magnets that Bruker Instruments proposed by Bruker.



New Concepts:

• The route to ^{1}H frequencies > 1 GHz is by using the cuprate HTS made of REBCuO and Bi-Sr-Ca-CuO (2212 and 2223) that will superconduct to fields >>60 T.

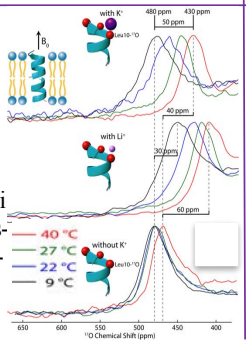
• Prototype magnets made at the MagLab have now generated more than 40 T, making a 1.4 GHz magnet now conceivable.

• Prototype triple resonance NMR Probes made at the NHMFL for a ^{1}H frequency of 1.5 GHz will be tested in the NHMFL's 36T Series Connected Hybrid (Resistive & Superconducting) magnet.

Benefits: ^{17}Oxygen Spectroscopy – the site of so much chemistry!

• Cation solvation by physiological channels for achieving functional selectivity via high resolution ^{17}O NMR with ultra-high magnetic fields.

• Anisotropic ^{17}O spectra of Gramicidin A in hydrated lipid bilayers illustrating dramatic sensitivity to different cations and to sample temperature when cations are bound.

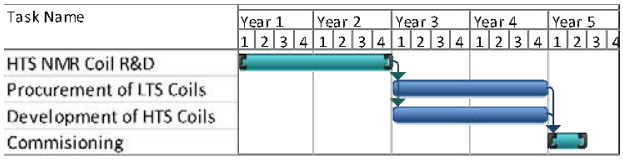


Resources:

• The NHMFL is now testing a 32 T all superconducting magnet for condensed matter physics using REBCO tape.

• R&D is expected to cost ~$15M.

•Design & Construction is expected to cost another ~$15M.



Opening the Periodic Table: 1.4 GHz NMR Magnet

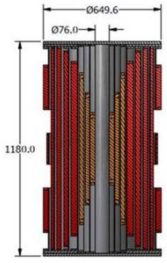
NATIONAL HIGH MAGNETIC FIELD LABORATORY

The Priority:

• To engineer and construct a 1.4 GHz (32.8 T) high homogeneity NMR magnet.

• Exploiting the revolution in High-Temperature Superconducting (HTS) materials.

• Such a development will leap-frog over the 1.2 GHz (28.1 T) magnets that Bruker Instruments proposed by Bruker.



New Concepts:

• The route to ^{1}H frequencies > 1 GHz is by using the cuprate HTS made of REBCuO and Bi-Sr-Ca-CuO (2212 and 2223) that will superconduct to fields >>60 T.

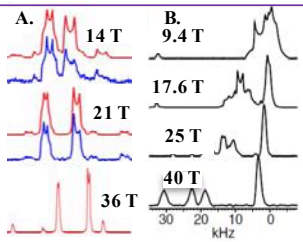
• Prototype magnets made at the MagLab have now generated more than 40 T, making a 1.4 GHz magnet now conceivable.

• Prototype triple resonance NMR Probes made at the NHMFL for a ^{1}H frequency of 1.5 GHz will be tested in the NHMFL's 36T Series Connected Hybrid (Resistive & Superconducting) magnet.

Benefits: Quadrupolar Spectroscopy – opening the Periodic Table.

• Dramatic resolution & sensitivity enhancement as a function of field.

• Most nuclei are Quad-rupoles that have been difficult or nearly impossible to observe at current field strengths.



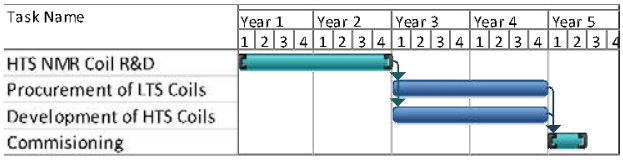
(A) ^{17}O NMR of Salicylic Acid (14T/15k scans; 21T/1k scans; 36T simulation, 128 scans expected) & (B) ^{27}Al NMR of $9Al_2O_3 + 2B_2O_3$.

Resources:

• The NHMFL is now testing a 32 T all superconducting magnet for condensed matter physics using REBCO tape.

• R&D is expected to cost ~$15M.

•Design & Construction is expected to cost another ~$15M.



Reach out and 'grab' the molecules (*Dantus*)

Haptic macro-to-nanorobotic hands can play with molecules!

New Ideas Developed:

- Nano-hands
- Photonic and electronic control of nano actuators and sensors.
- Haptic feedback allows user to interact with the molecular world.
- Exploration and control of molecules, nanoparticles and organelles in the living cell.
- First step for a nano-factory capable of building nano-bots.

Problem

- The closest we get to interact with molecules is through a scanning tunneling microscope or an atomic force microscope. There is no present instrument that allows one to "manipulate" molecules taking advantage of the multidimensionality of our hands.

Impact

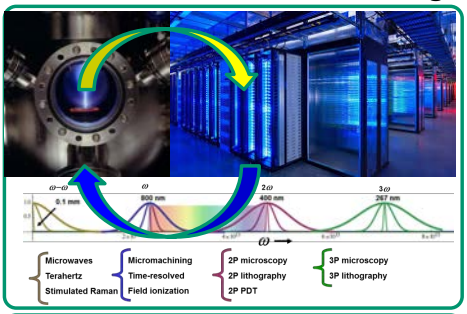
- Hundreds of molecular interactions and reactions in a living cell are known only from isolated measurements. Being able to "hold" molecules would allow unprecedented ability to confirm concepts we have about protein folding, intermolecular interactions, conformations, orientations, molecular motors and forces.
- Nano-bots will be built by nano-hands

Resources needed

- Nanofab facility and development of opto-electronic actuators
- Micro electronic development of the "hand"
- Electronics facility providing nano-to-macro control
- Materials, Spectroscopy, and AFM research
- Computer programing and development
- Development of the microscope platform

Equipment, Materials, Supplies and Support for 24 scientists

Deep-learning molecular quantum dynamics with universal fs light source (*Dantus*)



New Ideas:

- New quantum electronic structure programs will prescribe spectroscopic measurements, interpret the results and refine the calculations themselves.
- Development of a laser capable of emitting on demand femtosecond laser pulses at wavelengths raging from microwaves to x-rays.
- Development of autonomous 'chemical explorer' programs that request the experiments form the automated spectrometers, interpret the data, and confer with electronic structure calculations. This process can iterate to achieve a desired goal such as controlling a chemical outcome, refining the structure of a transition state, or explore the chemical landscape of another planet.

Problem

- Going from measurement to theory can take years.

Impact

- There is potential to shorten the time it takes to fully understand and control the quantum dynamics of polyatomic molecules by three or more orders of magnitude. This process will greatly improve electronic structure calculations and dynamics simulations.
- Quantum electronic structure calculations (energy and time resolved), need experimental spectroscopic refinement.
- Opens the possibility for autonomous chemistry explorers that can operate in remote locations including other planets.

Resources needed

- Spectroscopy development
- Electronic structure development
- Computer programing and development
- Development of the laser spectroscopy system
- Close collaboration from all partners

Equipment, Materials, Supplies and Support for 16 scientists

Nanometric/single molecule MRI

Potential new scanning probe technique?

New Ideas

-NMR is arguably the most important chemistry tool invented
-The ability to apply these measurements at the nanometric or single molecule level would open vast new areas of research.

Impact
-interface properties
-material properties
-reaction mechanisms at interfaces
-catalytic mechanisms
-Membrane protein structure

Buy-in opportunities

-NIH: significant biological applications are envisioned
-DOE: materials, catalyst, and energy related applications at surfaces will all be applicable.

Enabling tools for Quantum (non-binary) computing

Need for new tools to test these ideas.

Impact

-Calculations/simulations in chemistry are often limited by the size of the system.
-New computing approaches that enable a leap in performance are required to enable more accurate simulations of real chemical/biological systems.
-MD trajectories in realistic biological models
-electronic structure in extended systems

New Ideas

-The idea of quantum computing has been around for some time.
-The advance of this approach is limited by the lack of experimental tools to create and read the quantum states enabling large scale computing.
-NMR approaches are largely used now, but advances in light based approaches may offer new opportunities.
Buy-in opportunities

-NIH: This approach will be especially important for large biomolecules.
-DOE: large scale simulations in extended materials.
-NSA: cybersecurity

High Concentration Contrast Detection at Range (Finding the needle in a stack of needles)

Priority

- Inability to detect target molecules in environment with much larger amount of background
- Ratios of target to background in excess of 10^{12} when the background responds to probe method
- Additional challenge of performing the analysis at ranges of >1m and on surfaces

Benefits

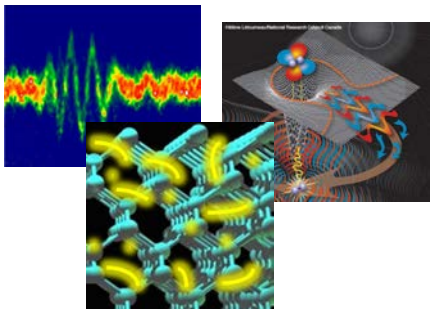
- Applications enabled include
  - Trace detection of WMD & explosives in real environments (public transportation, Army Field applications)
  - Following biomolecular processes in living systems
  - Detecting human presence in real environments
- Significant increases in ability to understand and monitor complex systems in situ and at range

New Concepts

- Optical Spectroscopy with extremely high QE detectors and high throughput, high resolution wavelength selection
- Chromatography with high resolution, rapid separations with dramatically reduced band broadening and lower material loss in the column
- Portability of systems using emerging technologies such as fs pulse shaping and other large scale new techniques

Resources

- Multi-disciplinary teams combining chemistry, physics, and engineering to address range of challenges
- Funding ~$50M over several years
- Scheduling
  - CY17 planning & CFP
  - CY18 – Teams form and identify critical scientific issues
  - CY18-20 – Teams perform research to enable engineering of demonstrations of pertinent capabilities



CONCEPT

Creation of user facility capable of probe fundamental levels of chemical reactions at molecular and sub-molecule timescales

- Attosecond laser for electron dynamic studies
- Femtosecond laser facility for molecular vibration/rotation studies
- Pump-probe studies using ps-fs-as configurations
- Companion Mass spectrometry for product and dark state attributions
- X-ray generation complimentary to Advanced Photon Source

IMPACT

Facility will provide a medium to large scale facility dedicated to light-matter interactions specifically for study of fundamental chemistry & material science

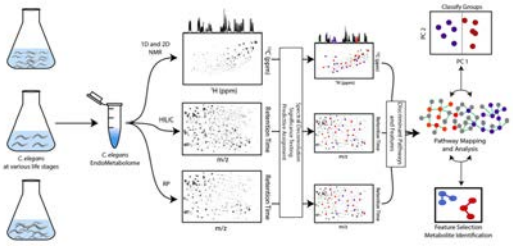
- Discover "hidden" mechanisms for certain reaction only seen at attosecond & femtosecond scales
- Examination and possible creation of new compounds based on this knowledge for combustion, energetics
- Open up this type of science to a much larger community of scientist that are "costed-out"
- Possibly open up new avenue of scientific study that finally uses light to drive reaction chemistry

SCHEDULE

Facility should be centrally located within Continental US, which accessible to transportation hub

- Creation of master development plan including budget in CY17 (expected to push $125M bound)
- Site selection and negotiation CY 2017/8
- Contracting, construction and installation CY2018/9
- Full staffing, operational drill and soft-opening in late CY19
- Beamlines open and in full operation for experimentation in CY20

Quantitative Phenotyping of the Integratome



"Fusion of Multiplatform Phenotyping Data"

Technology

- Multi-omics platforms (Genomics, transcriptomics, epigenomics, proteomics, metabolomics (metabolome, exposome, microbiome, lipidome).
- HRAM-MS^n, HR-NMR, next gen gas-phase and liquid phase separations. "Discovery" 3D MS/MRI imaging (volume/surface).
- Single omics not sufficient
- "Big data ceiling"

Schedule

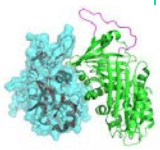
- Development of 4 transformative technologies. Both hardware and software.
- First test beds @ year 2-3
- Engineering/Science partnership
- At least one technology in partnership with instrument manufacturer.

Funding ($M)

- $15-20M/5 years
- Leverage NSF HP computing infrastructure
- Married to "deep machine learning" methods (model high level abstractions in data by using deep graphs with multiple processing layers, composed of multiple linear and non-linear transformations)
- Innovation component
- High-risk/High-reward subprogram.

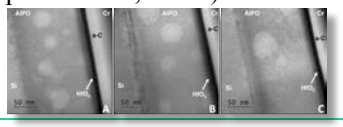
Next Generation NMR - Sophia Hayes, Washington University

Priority



Instrumentation development for

- "Ultra" high field NMR (> 1GHz)
- Surface-sensitive NMR (through dynamic nuclear polarization, DNP)



New Concepts to be Explored

Ultra-high field NMR: new designs for magnets incorporating high Tc superconductors (HTS) for ultra-high field NMR (>1.2 GHz)

Dynamic nuclear polarization: a field in its "infancy" – new developments in gyrotrons (in nuclear science) allow for entirely new realization of pulsed EPR – coupled to NMR

Benefits

- *Sensitivity of NMR would be boosted*, to pursue structures of surfaces—catalysts, active sites, protein-complexes, etc.
- *New nuclei not currently accessible* (spin-1/2 and quadrupolar) could be studied
- *Quadrupolar nuclei require* multiple high magnetic fields.
- Development in HTS can *reduce U.S. reliance on liquid He for ALL magnets*—affects the strategic supply.

Resources Needed

Interdisciplinary teams must be brought together—RF and microwave engineers together with chemists to help design hardware around application needs

Decade-long investments in the long term to support cryogenic engineering, HTS materials, gyrotron (maser) development—areas often NOT in chemistry.

Functional imaging of heterogeneous biological elements (enzymes, complexes, or organisms) in reaction networks

The priority	**Benefits**
Understanding interactions & functions within biomolecular networks & microbial communities	Efficient, environmentally-positive production of fuels, materials & pharmaceuticals
New concepts to be explored Methods for *in situ* microscopic analysis of cellular & molecular structure Explore cellular behavior beyond current frontiers of space & time Models of networks spanning molecular to cellular scales	**Resources needed** Regional centers ($25M scale?) providing suites of new technologies for multi-spatial & temporal scale, non-destructive imaging accessible to graduate students, postdoctoral researchers and industry

R. Jimenez (JILA/NI

Nanoassemblies of atomic, molecular & biomolecular components: pushing the envelope on speed of assembly & multifunctionality of characterization	
The priority Surmounting the obstacles to realizing the promise of dynamic nanotechnology by learning to assemble, harness & amplify the output of multiple molecular machines	**Benefits** Nanomachines for healthcare, environmental remediation, and threat detection
New concepts to be explored Understanding spatiotemporal reaction kinetics Effective function without high spatial precision assembly? Combined imaging/manipulation employing AFM, chemically-specific & electron imaging techniques for dynamic *in situ* measurements	**Resources needed** Regional centers ($25M scale?) developing new technology for assembly & characterization of molecular machines Facilities accessible to graduate students, postdoctoral researchers & industry

R. Jimenez (JILA/NI

New methods/instrumentation for increasing NMR sensitivity

Needs - Robust instrumentation for increasing nuclear polarization (e.g. DNP)

- Instruments designed to increase the efficiency of polarization transfer
- Use ultra low temperatures to increase the polarization lifetimes in solids
- More efficient dissolution DNP methods that can hold on to polarization longer

Benefits

- Methods like DNP and para-hydrogen can greatly increased NMR sensitivity
- Currently seems to hold the best promise for solid state and gas phase measurements (Xe), solution polarization is fairly rapidly lost.
- DNP instrumentation is expensive and not universally available. This is a relatively new area that is not yet mature.

New Concepts

- Combination of ultra high field NMR and DNP magnets will increase polarization/sensitivity
- Development of NMR probes that could hold polarized solid state samples at ultra low temperatures while spinning at high speeds
- For solution state DNP, develop chemical strategies to slow T1 relaxation processes so that the polarization is retained for longer times.

Resources

- Both technological and chemistry breakthroughs needed.
- Could be one or two regional NMR centers focused on DNP developments and applications.

Bright Ion Source

The priority

A one-of-a-kind capability for preparation and delivery of well-defined high flux (1 μA – 1 mA) ion beams with controlled kinetic energy (eV to keV) and spatial focusing to multiple end stations simultaneously for molecular printing and 3D nanofabrication

New Concepts that Will be Explored

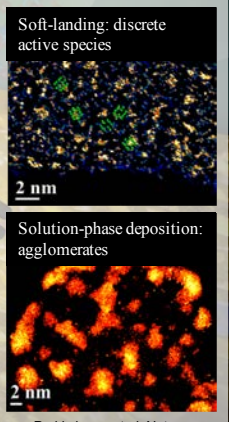
- How to design and modify materials using intense beams of complex ions
- Accelerated synthesis in microdroplets
- How to direct bottom-up assembly of hierarchical materials/mesoscale architectures with precise control of composition and spatial localization
- Understanding and predicting structure-property relationships of unique nanomaterials prepared with atom-by-atom precision

Impact

- New era in materials synthesis
- Development of new classes of materials with unique properties through 2D and 3D printing of complex ions
- Reverse design of materials starting with a set of desired properties
- Focused ~~ion~~ beams of complex ions for direct "writing" on surfaces with nanometer precision

Resources

Design and construction of a high-flux ion source (>1000 brighter than existing systems) and multiple end stations for mass/shape selection, transformation (ion-molecule, ion-ion chemistry), focusing down to ~50 nm.



Prabhakaran et al. Nat. Commun., 2016, 7, 11399

Measuring Chemical Exposure

Priority: • Development of the chemical instrumentation required to measure human chemical exposure on a large scale (many people) routinely (time resolved measurements). • Chemical exposure here includes both intentional (such as therapeutic drugs) or unintentional (such as environmental). • Technology exists to make all these measurements, but in practice such an undertaking is impossible due to the time required to perform a single measurement and the centralization of chemical instrumentation is another major barrier	Concepts: • Sample collection, automatic and/or passive sample preparation, and separations must be streamlined • Development of portable but highly informing detection methods (MS, spectroscopic, ion mobility) • Data analysis and method development are major bottlenecks
Benefits: • Potentially huge impact on human health • Enable better understanding of the role of environmental chemical exposure on mankind • Instrumentation developed will enable more chemical measurement across many fields	Resources: • Requires chemists, engineers (electrical, mechanical, software), novel materials

MS as an Enabling Technology for Nanomaterials

Priority:
- NMR and other spectroscopic techniques are useful for characterization of nanomaterials. However, such approaches give an average over the population
- MS approaches can help fill this gap
- MALDI-TOF is routinely used to measure nanoparticles. However, the information content from this experiment is limited.

Concepts:
- Use of trapping type MS over an extended and wide m/z range to allow manipulation of nanomaterials
- Control over charge state to favorably manipulate m/z
- Various excitation methods to glean information about structure and composition
- Unconventional detection methods
- Recovery of trapped nanomaterials from the MS

Benefits:
- Potential for routine and complete characterization of nanomaterials with molecular resolution
- Potential for an alternative method for nanomaterial purification

Resources:
- Parallel efforts will be required in instrumentation, ion activation and fragmentation, and ionization

Instrumentation for Nanoscale Resolution of Catalytic Characterization

The priority:
Advances in **simultaneous** surface characterization, chemical perturbation (optical or electrochemical), chemical analysis and microscopy

New Concepts to be Explored: For instance, in-situ electrochemical TEM has provided the ability to see how catalysts change structure with time, but without the ability to probe the products being formed at those changing active sites (i.e. we now know the catalysts are changing and heterogeneous, but we don't know how that is changing the catalysis chemistry occurring).

Benefit that would stem from the proposed project:
Better understanding of structure/function relationships in heterogeneous catalysis

Resources Needed:

- Instrumentation for combining techniques that haven't been combined before.

Instrumentation for Interrogating Biofilms

The priority:
Biofilms are important in infections, biocorrosion, wastewater treatment, and many other applications. However, there are not comprehensive techniques for evaluating biofilm formation and aging directly.

New Concepts to be Explored:
There is a large debate about how electron transport occurs in biofilms and although scientists have many indirect or ex-situ techniques for getting information, there is no in-situ method for evaluating this phenomena.

Benefit that would stem from the proposed project:
In-situ evaluation of drug effects on prevention, formation, and sustainability of biofilms
Understanding mechanisms of biocorrosion and BES systems for minimizing biocorrosion and improving the efficiency of BES systems

Resources Needed:
- New bioanalytical tools for studying transport of molecules and electrons through biofilms without killing cells: including microscopy and spectroscopy.

U.S. NAVAL RESEARCH LABORATORY

Improve catalysis

Study (architectured) wild-type not model catalysts

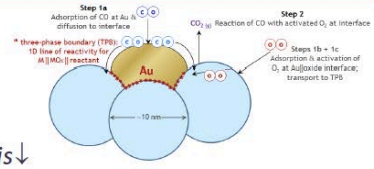
S&T Challenge

Transforming $10T/year catalysis from a world of congested reaction zones with ad-hoc transport functionality requires characterizing multiphase reactions in nano/mesoscale + disordered + non-flat interphases with matter undergoing x–y–z–t fluctuations

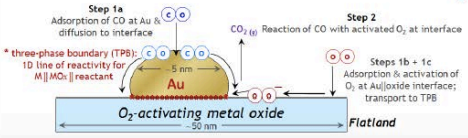
Characterization Challenge

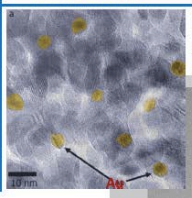
- Multicomponent, multifunctional, interdependent (and yes, disorder-containing) entities: Analyze that!
- Real surfaces are a mess, but that's what matters!
- Multimodal/temporal analyses required to characterize reality @ work generates too much data

this→



not this↓

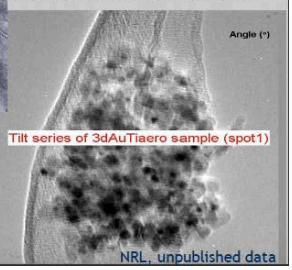




… not just a cartoon …

Pietron, Stroud, Rolison: *Nano Lett.* **2** (2002) 545; U.S. Patent **6,824,776**

Image TPBs via 3D electron tomography



U.S. NAVAL RESEARCH LABORATORY

Improve electrochemical energy storage

Study optimally wired electronic+ionic+molecular transport

S&T Challenge

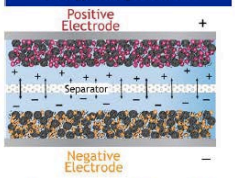
When asked to name the three greatest challenges in sustainability, Paul Anastas ("Father of Green Chemistry") named only two, the second being energy storage (March 2012, San Diego, RSC dinner)

. . . ' cause the sun doesn't shine at night & the wind doesn't always blow . . .

Characterization Challenge

- Multicomponent, multifunctional, interdependent (and yes, disorder-containing) entities: Analyze that!
- Real surfaces are a mess, but that's what matters!
- Multimodal/temporal analyses required to characterize reality @ work generates too much data

Cell construction in traditional energy-storage devices



Doubling the performance of batteries every 10 years—making them the old masonry way will not get the job done!

Moore's Law Meets Batteries: $\frac{1}{2}^n$
where n = # of transport functions

Computation	n = 1	50%/year
Energy Storage	n = 3	12.5 %/year

Rolison & Nazar, *MRS Bull.* **36** (2011) 486

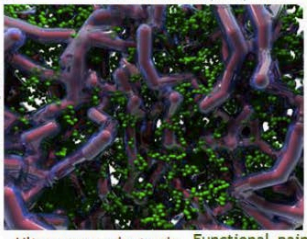
Analyze this!

Long, Dunn, Rolison, White *Chem. Rev.* **104** (2004) 4463

Nanoscale functionalization

Wired ion/electron transport in 3D

100s of µm

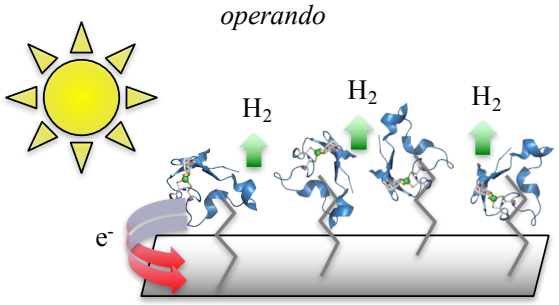


Ultraporous electrode architecture
$\sigma > 10$ S cm^{-1}

Functional paint ~10-nm thick

The Priority

Characterization of devices for energy capture and storage across multiple time- and length-scales *in operando*



New Concepts to be Explored

- Molecular-level information on large/complex systems
- Studying reactivity of molecules and surfaces with high spatial and temporal resolution
- How do molecules interact with surfaces?
- How do large molecules (proteins) or even organisms (biofilms) interact with surfaces?
- How do those interactions change activity?

Benefits from Proposed Project

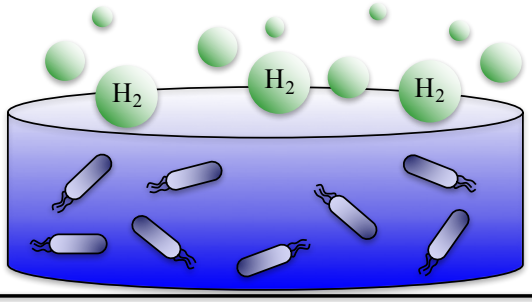
- Understand how multiple components work together
- Identify failure sites for multicomponent systems
- Enhance robustness
- Increase efficiency of solar capture devices
- Better integrate high-activity molecules / enzymes into material systems for industrial application

Resources Needed

- Imaging facilities coupled to optical equipment for high-resolution experiments
- Wide energy ranges for spectroscopy to look at different components of the system / different degrees of freedom (from radio waves to X-rays)
- High sensitivity instrumentation to identify low-frequency / slow occurances (to ID nonproductive pathways)
- Integrated materials / synthetic / molecular/ biological sample facilities

The Priority

Targeted metabolic engineering of model organisms for "green" materials (fuels, plastics, etc.)



New Concepts to be Explored

- How to make industrially-relevant chemicals cheaply (need to optimize separation approaches)
- Installing genetic machinery into inexpensive organisms (*E. coli*)?
- Strengths of *in vitro vs. in vivo* systems
- Can we optimize systems *in vitro* for "green" synthesis and identify mechanisms?
- Do they stay optimized *in vivo*?
- What are most valuable targets?

Benefits from Proposed Project

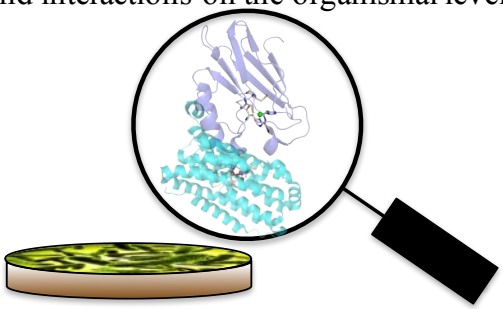
- Route to "green" plastics
- Easily separable fuels
- Molecular-level insight into catalytic processes
- Addresses gene-to-phenotype "Big Idea"
- Understanding how *in vitro* mechanisms translate into *in vivo* activity

Resources Needed

- Lab-to-plant scalable facilities
- Molecule-to-organism biological facilities
- Integrated physical characterization systems with large-scale biological and chemical synthetic facilities
- Characterization across many different scales

The Priority:

Understanding protein structure, function, and interactions on the organismal level



New Concepts to be Explored

- Non-invasive and non-perturbative methods for looking at cells
  - Bacterial species
  - Microorganisms (yeast, protozoa)
  - Human cells
- High-sensitivity probes
- High-resolution, harmless imaging methodology Quantifying the impact of current "tools" (e.g., GFP-tagging) on activity
- Do things "look" and behave the same *in vivo* as they do *in vitro*?

Benefits from Proposed Project

- Understanding how molecules interact under biologically relevant conditions
- Deriving molecular-level systems-biology information
- Learning how drugs impact systems at the molecular level
- Identifying new drug targets
- Watching temporal evolution of a system over many timescales

Resources Needed

- Imaging and optical facilities in conjunction with biology and chemistry facilities
- Methods development for non-invasive probes
- Model cell lines
- Cryo- and warm microscopy coupled together to get structure-function information

Programmable Molecular and Material Systems

Priorities

- Designing molecular and material structure systematically
- Modular components capable of computational directed programmed assembly
- Diverse functional capability in molecular recognition, catalysis, optical and electronic properties
- Interface with human technology

New Concepts

- Biology depends on folding rules created via evolution – messy and hard to compute
- However, biology shows us that combinations of simple building blocks can give rise to almost any structure and function
- Combine top-down and bottom up approaches to design complexity

Benefits

- Reduce molecular and material function design to a simple rule based approach
- Equivalent to the analog to digital transition in electronics
- Build systems to interface with our electronic/optical technologies

Resources

- Massively high throughput synthesis systems
- Massively high throughput structure analysis
- Massively high throughput functional analysis
- Major computational capability
- Electronic and optical platforms for developing interfaces

NSF Mid-Scale Instrument Development Workshop, N. Woodbury

Multi-scale Structural Integration: the structure of a cell at atomic resolution

Priorities

- Combining structural methods at different scales
- High resolution structures of complex heterogeneous systems
- Dynamic as well as static information
- Building predictive models for the behavior of these systems

New Concepts

- Structural relationships in complex heterogeneous systems are statistical rather than stoichiometric
- Living things are resilient because they are heterogeneous and dynamic
- Non specific interactions in biology are actually carefully defined in the crowded environment of the cell

Benefits

- Understanding the origins of emergent phenomena in complex systems
- Predicting how changes at one scale will effect function at another

Resources

- Groups of multiscale structural instruments in one place
- High throughput structural approaches
- Dynamic structural approaches
- Approaches for analyzing individual cells at multiple scales
- Large scale computational modeling capabilities 1-2 orders of magnitude beyond current

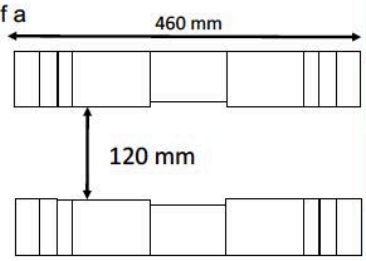
NSF Mid-Scale Instrument Development Workshop, N. Woodbury

NATIONAL HIGH MAGNETIC FIELD LABORATORY

28 Tesla FT-ICR Magnet

The Priority:

- Design and construction of a compact 28 T FT-ICR magnet.
- Exploits the revolution in High-Temperature Superconducting (HTS) materials.
- Surpasses today's 21 T.

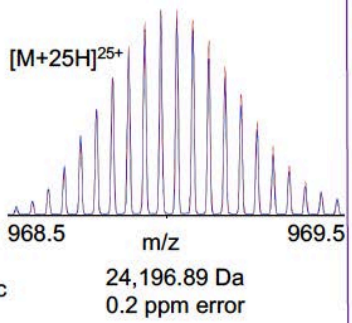


New Concepts:

- The route to superconducting magnets >23.5 T uses the cuprate HTS made of REBCuO and Bi-Sr-Ca-CuO (2212 and 2223) that will superconduct to fields >>60 T.
- Prototype magnets made at the MagLab have now generated more than 40 T, making a large bore 28 T ICR magnet conceivable.
- Use of novel no-insulation REBCO wire technology for compact, high field magnet design.

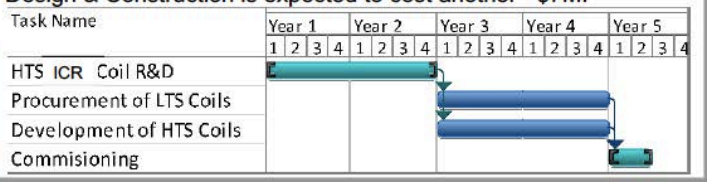
Benefits:

- Ultrahigh mass resolving power for small and large molecules (>100 kDa).
- Ultrahigh mass accuracy (ppb).
- Precise analysis of complex mixtures (e.g., proteins, metabolites, dissolved organic matter, petroleum).



Resources:

- The NHMFL is now testing a 32 T all superconducting magnet for condensed matter physics using REBCO tape.
- R&D is expected to cost ~$7M.
- Design & Construction is expected to cost another ~$7M.



Appendix E – Participant Pre-Workshop Instrument Development Priorities

S. Buratto

- Operando X-Ray Imaging via X-Ray Raman Scattering, XRD and XANES.
- AFM-IR and Photo-induced Force Microscopy (PiFM) for Chemical Imaging at the 1 nm Length Scale.
- High Spatial Resolution Imaging Coupled with Mass Spectroscopy. In this idea a thin-film sample is ionized from ambient conditions using a spatially resolved ionization source such as an AFM tip (using thermal desorption/ionization) or an NSOM probe (photoionization). A microscopy image is recorded and interleaved with a chemical map.
- Ion Soft Landing of Shape-Selected Bioaggregates and Biocomplexes. In this idea a biosample is introduced to an ion mobility mass spectrometer for shape selection. The output of the IM-MS instrument is then soft-landed on a surface for further analysis such as scanned-probe microscopy and spectroscopy. In this way it will be possible to analyze a sample of the same shape rather than a distribution.

T. Cross

- Macromolecular Functional Mechanisms – Understanding how macromolecular systems function in complex environments: High Magnetic Fields for Quadrupolar Nuclei in combination with other technologies.
- Macromolecular Chemical Kinetics – Explaining kinetic rates in complex systems and environments: from structure and dynamics to kinetic understanding: High Magnetic Fields for ^{1}H Detection, Sensitivity, Dispersion, etc. in combination with other technologies.
- Exploring Previously Hidden Chemistry – Opening the Periodic Table for characterization by ultra-high field NMR: ^{7}Li, ^{9}Be, ^{11}B, ^{17}O, ^{23}Na, ^{25}Mg, ^{27}Al, ^{33}S, ^{35}Cl, ^{39}K, ^{43}Ca, ^{45}Sc, ^{47}Ti, ^{51}V, ^{53}Cr, ^{55}Mn ^{59}Co, ^{61}Ni, ^{63}Cu, ^{67}Zn, ^{71}Ga, ^{73}Ge, ^{75}As, ^{81}Br, ^{83}Kr, ^{87}Rb, ^{87}Sr, ^{91}Zr, ^{93}Nb, ^{95}Mo, ^{101}Ru, ^{105}Pd…
- Surface Science – NMR under transition from bulk samples to catalytic surfaces: Combining electron and nuclear spin resonance through Dynamic Nuclear Polarization for orders of magnitude of sensitivity.
- Biochemistry in Life Processes – Macromolecules, complexes, crowding, membrane and membraneless compartmentalization: Integrated technologies for a view of life.

N. Fell/P. Pellegrino

- Detection & identification of low concentration target molecules in the presence of a large background
    - Need for high degree of sensitivity and specificity simultaneously in real-time
    - Optical spectroscopy – Need for highly sensitive detectors with high spectral resolution wavelength selection along with very low losses in the wavelength separation process. Laser power cannot be increased to increase sensitivity or optical damage to the target molecules will result.
    - Chromatography – Need for high-resolution separations with minimal band broadening, minimal loss of analyte in the column, and high sensitivity detection.
    - Will advances in signal processing algorithms help to solve this challenge?

    - Example applications – WMD trace detection of threat materials and their precursors in both military and public transportation security scenarios; detecting signs of human presence in areas, buildings, caves, or at disaster scenes; monitoring levels of biomolecules inside cells in a dynamic way to follow intracellular processes.
- High-sensitivity trace detection on surfaces at extended ranges in real-time
    - Need for high degree of sensitivity, specificity, and discrimination simultaneously at stand-off ranges in real-time
    - Example applications – Screening for WMD components and precursors at checkpoints and public transportation hubs, determining whether a decontamination process has been successful. Is a "cleaned" container really clean?
- Control of chemical synthesis and degradation
    - At attosecond and femtosecond timeframes, the potential to control, direct, and understand both the molecular and electronic dynamics that result in synthesis and degradation of materials
    - Example applications – Better energetic materials: more bang for the mass; better control of synthesis and potential to create previously unknown/intractable chemical structures; understanding combustion to make better more efficient, greener fuels
- Structure determination of non-crystalline proteins and other biomolecules
    - One issue is the sensitivity of traditional structural determination tools.
    - Another issue is the time-domain variance between the measurements and the motions of the molecules that are being measured.

  Need faster response time in measurements that are faster than the motions of the molecules without resorting to cooling them to extremely low temperatures.

S. Hayes

- Reactions on surfaces – catalysis, electrochemical charge/discharge, biomineralization, enzymatic catalysis
- The structure at interfaces – semiconductor devices, biomineralization, solid-liquid interfaces, polymorphs, membrane proteins
- Computation of NMR tensors from crystalline and eventually non-crystalline structures opens up increasing numbers of NMR-active isotopes – beyond ^{1}H, ^{13}C, ^{15}N…

R. Jimenez

- Instruments for probing quantum systems: effects of disorder & fluctuations on emergent properties
- Nanoassemblies of atomic, molecular & biomolecular components: pushing the envelope on speed of assembly & multifunctionality of characterization
- Structure and dynamics of excited-state molecular systems via time-resolved x-ray diffraction & absorption measurements: applications to energy storage and display technologies
- Functional imaging of heterogeneous biological elements (enzymes, complexes, or organisms) in reaction networks
- Integration of instrumentation & materials for molecular memory to meet mankind's information storage and high-bandwidth data access demands.

C. Larive

- Robust, efficient and affordable instrumentation to enhance NMR sensitivity for all nuclei (*e.g.* higher-field magnets, DNP, better probes).
- "Molecular Tricorder" that could operate like a handheld XRF detector but give molecular identity and concentrations for environmental and point-of-care healthcare.
- Understanding the intersection of climate change, weather and air pollution. What impact will Artic melting and increased desertification have on regional air quality, especially particulates?
- Instrumentation for determining long range atomic/molecular structure for nanoscale materials and correlating structure with properties.

N. Manicke

- Detection of large molecules with improved specificity and sensitivity. Immunoassays are still the best we have, but the limited multiplexing and the lack of specificity limit their application. MS approaches have been plagued by poor reproducibility, laborious sample preparation, and inadequate sensitivity toward intact proteins.
- Ion mobility and differential mobility are promising approaches to increase the data dimensionality. The inability to control selectivity in ion mobility and differential mobility limits their utility for separations compared to chromatography.
- Instrumentation prototyping facilities, with machining, 3D printing, electronics, and fabrication capabilities.

D. Rolison

- Characterizing disordered/amorphous materials – still not our finest hour: *". . . materials are discussed with reference to the presence of disorder in an idealized ordered material, as opposed to order in an otherwise chaotic material. This bias toward the ordered end of the order-disorder scale is probably influenced by the structure-characterization tools at our disposal" – Eckert, Stucky, Cheetham (1999)*
- The molecular era is so 20th Century: Multicomponent, multifunctional, interdependent (and yes, disorder-containing) entities. Analyze that!
- Are nanostructured pore-solid multifunctional architectures that entrain biomolecules an instrument? *Incorporate optical/electrical/magnetic elements as part of the nanostructured architecture in order to monitor/stimulate/control biomolecular events*
- Real surfaces are a mess, but that's what matters! *"Surfaces, where 3D periodicity is forcibly truncated and disorder and reconstructed domains predominate, dictate much of the technological relevance of functional materials" – Rolison (2016)*
- Multimodal/temporal analyses required to characterize disorder/real surfaces/microheterogeneous media generate too much data. *Devise AI that automates collection, data deconstruction and iterative re-analysis*

H. Shafaat

- Developing distributed systems for "green" energy storage and utilization
- Understanding how these energy capture and storage devices work across multiple time- and length-scales *in operando*

- Targeted metabolic engineering of model organisms for “green” materials (fuels, plastics, etc.)
- Understanding protein structure, function, and interactions on the organismal level => Non-invasive/non-perturbative *in vivo* molecular characterization (bacterial/microorganisms/human cells)
- High-throughput automated synthesis, on-line structure determination, and screening for drug discovery

L. Smith

- Single-molecule mass spectrometry (Can anyone think of a fundamental reason to NOT be able to determine the mass of a single molecule?)
- Single-cell proteomics
- Determination of the proteoform-one: compile a database of all of the protein forms in human (and other organisms)
- Automate small-molecule structural determinations (1/2 of all metabolites detected are of unknown structure)
- Gas-phase gene assembly: purify short ssDNAs, assemble them into genes, soft-landing to collect
- Image and identify all of the molecules in a cell (akin to atom-probe tomography for 3D localization of every atom in a sample)
- High-resolution 3D structures of single macromolecules
- Protein sequencing (with PTM localization) through nanopores (this is underway folks!)

N. Woodbury

- Bio-electronic interfaces
- Monitoring and controlling heterogeneous systems
- Multi-scale structural integration (atomic-resolution structures of whole cells)
- Understanding hard/soft matter interfaces
- Programmable molecular and material systems

Appendix F – Breakout Session Organization and Charge

Breakout Sessions

NSF Planners have identified 10 "Big Ideas" (see nsf_big_ideas.pdf). Of these ideas, six (1-6) are focused on research and four (7-10) on process. Chemistry-Based Instrument Development could potentially address all 10 Big Ideas. Note that the lack of precise definition is intended to bring out creativity in proposals.

1. The Quantum Leap: Leading the Next Quantum Revolution
   By exploiting interactions of these quantum systems, next-generation technologies for sensing, computing, modeling and communicating will be more accurate and efficient. It will address fundamental questions about quantum behavior and the manipulation of quantum systems.
2. Understanding the Rules of Life: Predicting Phenotype
   The universally recognized biggest gap in biological knowledge is our inability to predict an organism's observable characteristics – its phenotype – from what we know about its genetics and environment.
3. Work at the Human-Technology Frontier: Shaping the Future
   This initiative will tackle pressing research challenges at the human-technology frontier about the changing ways we produce goods, provide services, and collaborate with our colleagues.
4. Harnessing Data for 21st Century Science and Engineering
   This initiative will support basic research in math, statistics and computer science that will enable data-driven discovery through visualization, better data mining, machine learning and more.
5. Windows on the Universe: The Era of Multi-messenger Astrophysics
   [Electromagnetic radiation, particles such as neutrinos and cosmic rays and gravitational waves] will provide unique insights into the nature and behavior of matter and energy and help to answer some of the most profound questions before humankind, such as how the universe began and why it is accelerating.
6. Navigating the New Arctic
   The National Science Foundation (NSF) proposes to establish an observing network of mobile and fixed platforms and tools across the Arctic to document these rapid biological, physical, chemical and social changes, leveraging participation by other federal agencies.
7. NSF INCLUDES: Enhancing Science and Engineering through Diversity
8. NSF 2050: The Integrative Foundational Fund
9. Mid-scale Research Infrastructure
10. Growing Convergent Research at NSF

Charge to Breakout Sessions

Breakout Session Questions - Day 1

Consider one or more of the NSF 10 Big Ideas and the submitted concepts to propose mid-scale instrument development programs aimed at the following questions. Each group is identified with Discussion Leader/Reporter.

1. **Measurement/analysis (molecular/nano)** – Rolison/Perry. How would a mid-scale instrument development program transform our capabilities to characterize chemical systems – with an emphasis on fundamental properties, such as size/scale, spatial and temporal resolution, and chemical information? Illustrate the answers with a minimum of two specific examples.
2. **Synthesis/production (molecular/nano)** – Minteer/Baker. How would a mid-scale instrument development program transform our capabilities to create new chemical systems – with an emphasis on the ability to achieve new atomic, molecular, and supermolecular arrangements of matter with transformative properties? Illustrate the answers with a minimum of two specific examples.
3. **Measurement/analysis (bio-related)** – Fernandez/Shafaat. How would a mid-scale instrument development program transform our capabilities to characterize biomolecular systems, such as molecules, complexes and supermolecular assemblies – with an emphasis on relating biomolecular information to form and function? Illustrate the answers with a minimum of two specific examples.
4. **Synthesis/production (bio-related)** - Larive/Pellegrino. How would a mid-scale instrument development program transform our capabilities to create new biomolecular systems with transformative properties, including those not found in nature? Illustrate the answers with a minimum of two specific examples.

Breakout Session Questions - Day 2

Attendees will be broken into four groups. Each group will consider two projects (total of eight) arising out of the Day 1 Breakouts and Discussion. Discussion leader and reporter will remain "fixed" with one set of projects, while all other attendees will rotate (Manicke/Dunn – Group 1, Kleiman/Soper – Group 2, Jimenez/Buratto – Group 3, Woodbury/Hendrickson – Group 4). Participants will have 15 minutes to "improve" each project - in particular their fit and impact on scientific merit (including one or more of the six research Big Research Ideas) and broader impacts (including one or more of the four Big Process Ideas). For broader impacts consider buy-in from other agencies (principally, but not solely, DOE, DOD, NIH) and from the private sector.

At 15-minute intervals the groups (excluding discussion leader and reporter) will rotate to another set of projects and do the same with those projects. The goal of this breakout is to ensure each project has been augmented as much as possible in a short time.

At the end we will be able to present a maximum of eight very significant and well-vetted projects.

Breakout Groups – Day 1

Measurement/analysis (molecular/nano) – (Rolison/Perry) Barty, Weiss, Bohn, Dunn, Engel, Fell, Garrett

Synthesis/production (molecular/nano) – (Minteer/Baker) Belkacem, Buratto, Laskin, Dantus, Kleiman, Hendrickson, Goodson

Measurement/analysis (bio-related) – (Fernandez/Shafaat) Woodbury, Soper, Centurion, Cicerone, Cross, Jimenez

Synthesis/production (bio-related) – (Larive/Pellegrino) Buchanan, Smith, Manicke, Cooks, Hayes

Breakout Groups – Day 2

Group 1 – (Manicke/Dunn) Rolison, Garrett, Minteer, Goodson, Shafaat, Cross, Ando

Group 2 – (Kleiman/Soper) Perry, Fell, Baker, Dantus, Centurion, Cicerone, Buchanan

Group 3 – (Jimenez/Buratto) Barty, Engel, Belkacem, Laskin, Larive, Cooks

Group 4 – (Woodbury/Hendrickson) Weiss, Bohn, Fernandez, Hayes, Pellegrino, Smith

Discussion Lead/Reporter	11:00-11:15	11:15-11:30	11:30-11:45	11:45-12:00
Manicke/Dunn	Group 1	Group 4	Group 3	Group 2
Kleiman/Soper	Group 2	Group 1	Group 4	Group 3
Jimenez/Buratto	Group 3	Group 2	Group 1	Group 4
Woodbury/Hendrickson	Group 4	Group 3	Group 2	Group 1

All participants (excepting the discussion leaders and reporters) will have the opportunity to address all of the ideas brought forth from the first day.

References

[1] Bain, R.M., Pulliam, C.J., Raab, S.A., Cooks, R.G. On-Line Synthesis and Analysis by Mass Spectrometry. *J. Chem. Ed.* **2015**, 92, 2146-2151.

[2] Bain, R.M., Pulliam, C.J., Yan, X., Moore, K.F., Muller, T., Cooks, R.G. Mass Spectrometry in Organic Synthesis: Claisen-Schmidt Base-Catalyzed Condensation and Hammett Correlation of Substituent Effects. *J. Chem. Ed.* **2014**, 91, 1985-1989.

[3] Smith, L., Kelleher, N. Consortium for Top Down Proteomics. Proteoform: a single term describing protein complexity. *Nature Methods* **2013**, 10, 186-187.

[4] Shortreed, M., Frey, B., Scalf, M., Knoener, R., Cesnik, A., Smith, L. Elucidating Proteoform Families from Proteoform Intact Mass and Lysine Count Measurements. *J. Proteome Res.* **2016**, 15, 1213-1221.

[5] da Silva, R., Dorrestein, P., Quinn, R. Illuminating the Dark Matter in Metabolomics. *Proc. Nat. Acad. Sci. USA* **2015**, 112, 12549-12550.

[6] Walowicz K.A., Pastirk I., Lozovoy V.V., Dantus M. Multiphoton intrapulse interference. 1. Control of multiphoton processes in condensed phases. *J. Phys. Chem. A*. **2002**, 106, 9369-73.

[7] Pe'er, A., Dayan, B., Friesem, A.A., Silberberg, Y. Temporal Shaping of Entangled Photons. *Phys. Rev. Lett.* **2005**, 94, 073601.

[8] Wang L.P., Titov A., McGibbon R., Liu F., Pande V.S., Martínez T.J. Discovering chemistry with an ab initio nanoreactor. *Nature Chem.* **2014**, 6, 1044-8.

[9] Upton L., Harpham M., Suzer O., Richter M., Mukamel S., Goodson III T. Optically excited entangled states in organic molecules illuminate the dark. *J. Phys. Chem. Lett.* **2013**, 4, 2046-52.