Chemical biology: information, mesoscale science and the engineering ethos

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If you live on the frontier long enough civilization might catch up with you if you are not careful and are not prepared to move on. I have spent the past two and a half decades working at one or more of the interfaces between chemistry and biology, first in the Chemistry and Biology Departments at Massachusetts Institute of Technology (MIT) then for the past 11 years in the Biological Chemistry and Molecular Pharamacology Department, created by a fusion of two pre-existing departments, at Harvard Medical School. My research group has addressed problems in biological catalysis and molecular medicine, using whatever input we can assimilate from synthetic and medicinal chemistry, structural biology, experimental therapeutics, and molecular microbiology. First, chemical colleagues were suspicious that I wasn't a real chemist, whereas from the biology side my scientific dialect was not biological enough. Then the chemistry–biology interface became more fashionable and activities got renamed, always an upscale sign, for example to chemical biology. Now we should worry about whether this frontier is closing and we should be finding the new ones that are opening.

On the other hand, "there are no boring problems only boring people" a mentor once related scarily to me. There are, of course, always challenges and opportunities at the interstices of well-defined, even vital, disciplines, provided we have the right ways to look at problems. For chemists and biologists who regularly use chemical intuitions to analyze biological logic, in the contemporary ferment enriched by the massive increases in genomic information there are three currents that swirl to the surface that will percolate through many of the future efforts of chemical biologists and biological chemists.

Interdisciplinarity and information

It is a definitional truism that biochemistry/chemical biology is an interdisciplinary effort and this is not a novel perception as biochemistry departments have already existed for many decades. On the other hand, the discipline has now circled back and caught fresh currency in Chemistry Departments, evinced at least anecdotally by name changes in the Chemistry Departments at the University of Colorado, Boulder and at Harvard, that reinforce chemical biology as a legitimately central focus of chemistry faculty and students. Reciprocally, most research-active cell and molecular biologists name interdisciplinary approaches as the core of the paradigm for future projects and have begun to search for substantively broader definitions of what talents will be essential in research-vigorous departments. Most notably, many would now trade for applied mathematicians, computer scientists, bioinformation experts, even some types of engineers. There is developing consensus that such colleagues are no longer peripheral elements in biologists' futures even if there is no easy plan for how to reshape Biology Department boundaries for such a seamless intellectual continuum.

What is clear in this continuum is that chemical biology/biological chemistry efforts are going to be an information-driven science. The most obvious new intellectual activity that has firmly and vigorously invaded the biology community in the mid/post genomics era is the torrent of information from DNA sequencing. By and large, biologists and chemists are amateurs, not only in gathering and processing information but also in algorithm development and evaluation to assess and order such information. Like quondam definitions of morality, I and most of my colleagues might have trouble defining (relevant) informatics but we know it when we see it and need it. It is painfully obvious that most current investigators need broadened training and retraining in informational sciences to cope with both the biological and chemical attributes of their inquiries.

Take the combinatorial chemical library phenomenon as an example. Given the promise and partial reality of hundreds of thousands of molecules in synthetic, directed libraries along with the rapid advances in automation and miniaturization of assays, high-throughput screens look to provide high-affinity ligands for almost any biological target of interest. At the very least this would advance chemogenetics approaches to an equal footing with 'knockouts' to test the function of any biological target in any desired milieu. Most biochemists and more biologists will find it difficult to evaluate *ab initio* the quality of these molecular libraries, but almost all will want library cards from their chemical colleagues. The criteria for library design, such as the use of high quality molecules with high functional group density and architectural complexity, reminiscent of therapeutically important natural products, will remain frontier efforts for synthetic and natural product chemists, at least in the short term.

Systems approaches and mesoscale science

As increases in information about molecules, both small molecules as noted above and also biological macromolecules such as genes, RNAs, and proteins, careen along exponentially, there is a parallel fixation of biochemical and biological scientists on systems approaches as a central manifestation of their interdisciplinary foci. This encompasses, for example, both genome and proteome elucidations, as well as contemporary approaches to defining programs of development or programmed cell death, plasticity of the nervous system, and pharmacogenetics and predictive medical therapies targeted to individual genotypes. This systems bias also undergirds such superficially disparate efforts as cataloging gene activity temporally and spatially through RNA transcriptional profiling or SELEX enrichments for tightbinding or catalytic RNAs as well as plans to assess the family of all common protein folds both by predictive algorithms and high-throughput X-ray crystallographic consortia. Systems thinking is a pervasive modern condition in this set of scientific interfaces despite the lack of any formal training of chemists and biologists in any of the paradigms of systems dynamics, decision theories or artificial intelligence. These are skill sets that will be central intellectual tools for the next generation of chemical biologists/biological chemists.

Systems approaches and interdisciplinary inputs already have two consequences that will probably intensify and help move the frontiers. The first is, arguably, that research at the chemistry–biology interface is going, or has already gone, mesoscale and the second is the integration of the engineering ethos into these branches of science. Historically, the academic life sciences research model enabled by National Institutes of Health (NIH) support and especially embraced in the embraced in the individual investigator-initiated research paradigm of the National Institute of General Medical Sciences (NIGMS) has been to people the frontier individually, lab by lab, principal investigator by principal investigator. At my university there has been an oft-quoted institutional aphorism: "every tub on its own bottom". This competition-based, peer-reviewed, individual-centered meritocracy should, and will, persevere but lessons from experimental physics and even astronomy have ever more currency. The ongoing genome efforts and incipient proteome activities are biological inquiries practiced in a different way, with dozens of scientists contributing to, and required for, the overlapping and complementary skill sets for these informationally expansive tasks. This Manhattan project mentality might not be a one-time event that will pass from the scene when genome victory is declared. It is equally likely that this effort will have helped transform many of the norms for self-organization of life sciences research. Consortia of scientists are most probably required to implement functional genomics, to incorporate synthetic chemistry, chip design, high-throughput screens and sophisticated analytical and informational science to span approaches such as cryoelectron-microscopic imaging, microfluidics-based analysis of cell function, tandem mass spectrometry to detect minute quantities of thousands of proteins in a microliter of biological fluid and neural network analysis. The biotechnology and research-intensive pharmaceutical companies acting to functionalize genomics are already organized into, and operating within, such mesoscale matrices.

If a consortium, academic, industrial or mixed, wants to study all the attributes of one or more G-protein-coupled signal transduction signaling systems, a plethora of expertise will be required. Initial recognition of ligands at cell surfaces to anastomosing pathways that integrate and diverge through the many transient protein complexes in the cytoplasm to the combinatoric multitudes of transcriptional readouts from specific gene activation in the nucleus suggest a call for mesoscale collections of life scientists. The technology for planning and executing experiments may demand such cooperation on several counts, including cost, availability and competence. For example, affymetrix chips and Fourier transform MS–MS mass spectrometers could be so expensive, to say nothing of the 1 Gigahertz NMR instruments, that they exacerbate a 'haves and have nots' differential accessibility to research resources for frontier biomedical science.

An engineering ethos

The preceding comments raise the explicit recognition that systems focus and interdisciplinarity, among chemical biologists in particular and life scientists in general, are key defining elements of an engineering ethos. When molecules were the primary focus of this scientific microcommunity it might have been acceptable to define engineering and engineers as peripheral to core activity in chemistry and biology. Now, the pervasive metaphors of molecular machines in cells and the notions of reagents, from high-affinity ligands to knockout mice, as molecular tool kits to take apart and rebuild the processes of the cell, from cell-cycle control to chromosome condensation and translocation, to molecular motors, to the assembly and control of ribosomes, proteasomes and splicesomes, illustrate how widespread the nanoscale engineering paradigm has become in our thinking. *Inter alia* this should place at this frontier research-driven engineering institutions such as MIT, CalTech and Carnegie–Mellon in a catalytically central role, not only to redefine the patterns of collaborations with Chemistry and Biology Departments but also to help educate and train new variants of chemical biologists who appreciate mesoscale science explicitly. This agenda is separate from and complementary to the canonical view that most chemists and biologists have of bioengineering efforts.

Among the challenges that follow are the attendant questions of how academic scientists restructure departmental

organizations to incorporate nontraditional skill sets into both their faculty and students. Fruitful redefinition of core knowledge sets almost always starts with graduate education and radiates downwards, so new initiatives in graduate training, including novel coalitions and definitions of training grant programs, might be worth careful attention. Because chemists and biologists in academic centers over the past forty years have had little real impetus or experience in working in consortia or mesoscale group enterprises the challenges for self-organization will be interesting and varied. Enlightened scholarship and appreciation of the changing patterns at the frontiers by the leadership at NIH and by such organizations as the Howard Hughes Medical Institute and the Wellcome Trust will be crucial in helping to catalyze these changes, as they have been in the past.