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Interdisciplinary research and education at the biology–engineering–computer science interface: a perspective (reprinted article)

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Progress in the life sciences, including genome sequencing and high-throughput experimentation, offers an opportunity for understanding biology and medicine from a systems perspective. This 'new view', which complements the more traditional component-based approach, involves the integration of biological research with approaches from engineering disciplines and computer science. The result is more than a new set of technologies. Rather, it promises a fundamental reconceptualization of the life sciences based on the development of quantitative and predictive models to describe crucial processes. To achieve this change, learning communities are being formed at the interface of the life sciences, engineering and computer science. Through these communities, research and education will be integrated across disciplines and the challenges associated with multidisciplinary team-based science and engineering will be addressed.

The emerging field of systems biology represents an integration of concepts and ideas from the life sciences, engineering disciplines and computer science. Recent advances in biology, including sequencing the human genome and massively parallel approaches to probing biological samples, have created new opportunities for understanding biological problems from a systems perspective. This new approach emphasizes the functional behavior of collections of components working together and builds upon the more traditional approach of studying the individual roles of single components. Systems modeling and design are well-established in engineering disciplines but, until recently, have been relatively rare in biology. To explore the application of complex systems analysis to biological problems, multidisciplinary teams of biologists, engineers and computer scientists are working together – applying principles and techniques from engineering with concepts and algorithms from computer science to solve problems in biology and medicine. Likewise, through working on biological problems, engineers and computer scientists are creating new knowledge in their own disciplines. To be truly effective, community structures must be built to facilitate the interaction of researchers, educators and students from multiple disciplines. This effort is aimed at integrating multiple interests into one community, a community of practice. In addition, educational programs must be recast to produce a new breed of researcher prepared and suited to working at the interface of multiple disciplines, thereby creating a second type of integration, a new learning community. Several barriers must be overcome to achieve both forms of integration effectively. Progress has been made in building research communities at universities to approach problems in systems biology, and frequently these communities are built around graduate students and their education. Here we discuss challenges to and strategies for integrating students, staff and faculty

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from multiple disciplines to create new learning communities at the interface of biology, engineering and computer science.

A new approach to biology

Rapid progress in biological research now permits probing and perturbing living systems with exquisite control while monitoring their structural, dynamic and functional response through the measurement of up to tens of thousands of components simultaneously. Technological advances have made it clear to many biologists that progress in the life sciences can be accelerated by considering biological problems from the viewpoint of complex systems, where the focus moves to the holistic behavior of the system and the roles of the components are understood in the context of the larger system. Engineers, physicists, computer scientists and others trained in systems research also recognize that the fundamental technologies and emerging mechanistic understanding in biology make it feasible to study the life sciences, including medicine, from a systems perspective and to consider building a synthetic engineering field based on biological substrates ('synthetic biology').

This shift in focus from a component-based to a systems-based approach has important implications for medical research and the profile of diseases that have resisted effective treatment. For diseases where a single, non-essential factor, often a protein, is crucial to disease progression, modern medical research has generally been successful at designing therapeutic agents to interfere with the target and ameliorate disease. In such cases, the focus on individual components in the absence of systems-level understanding is still sufficient to create an effective therapy. By contrast, there is a sense that many of the more complex but common diseases that have been more resistant to therapy, such as cancer, Alzheimer's disease and diabetes, require a systems understanding to combat them effectively. Thus, the paradigms developed through approaching biology from a systems perspective have the potential to revolutionize not only our knowledge of fundamental basic science but also applications to medicine and, additionally, biotechnology.

At MIT, research in systems biology includes levels of abstraction from molecules, cells and tissues through to organisms, populations and ecosystems (Figure 1). Questions being addressed include how cells make decisions based on environmental cues, how 3D architecture and spatial organization modulate the behavior of tissues, how genes are distributed amongst populations and how different species compete and co-exist in the same environment. One theme that unites these diverse questions is the method of addressing them, known as 'the four Ms' – measure, mine, model and manipulate (Figure 2) – which characterizes the body of MIT research in this field. Efforts in measurement emphasize the systematic collection of data and the development of new experimental methods and technologies (e.g. microfabrication). Mining large datasets identifies underlying relationships, which can be captured in predictive models. Finally, design is an important facet of systems biology where the goal is to make rational modifications to biological systems. This type of manipulation provides a forum for testing our understanding and models; moreover, it promises to lead to practical advances in biotechnology and medicine. A key paradigm in this research approach is the interplay between experiment and computation. The strong focus on building and testing detailed, quantitative and predictive computational models of biological systems is a defining feature of the MIT effort, which has been named the Computational and Systems Biology Initiative (CSBi) to indicate the interplay of computation and systems analysis with biology. Models can be built at multiple levels of abstraction, depending on the type of information available and the role of the model (Figure 1) [1]. Such models form the basis of understanding and the foundation for design.

It should be stressed that, in this view, systems biology is a way of thinking, an approach to formulating questions and knowledge and a framework for solving problems. Systems biology is not merely a collection of technologies whose routine application will by themselves be enabling. Likewise, the stress on computation should not be construed as advocating modeling as a replacement for experimentation. Rather, the introduction of a quantitative theoretical and computational component represents a fundamental departure from a more descriptive tradition that has dominated the life sciences.

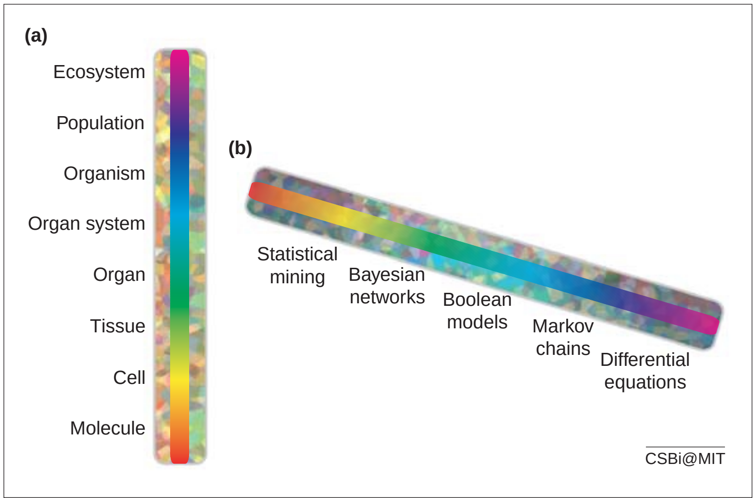

FIGURE 1

Systems biology involves the study at multiple layers of complexity. (a) Complex biological processes can be studied at all levels of abstraction, from molecules to ecosystems. A significant challenge involves bridging insights obtained from multiple levels and constructing models that effectively connect multi-level concepts and observations. For instance, therapeutic drug molecules exert their effect at the molecular level but are effective and safe only if they have the desired effect at the level of the whole individual (organism). **(b)** Modeling tools also span multiple levels of abstraction. Current research efforts span a progression of understanding from phenomenological, statistical relationships to more mechanistic understanding, exemplified by a model based in differential equations [1].

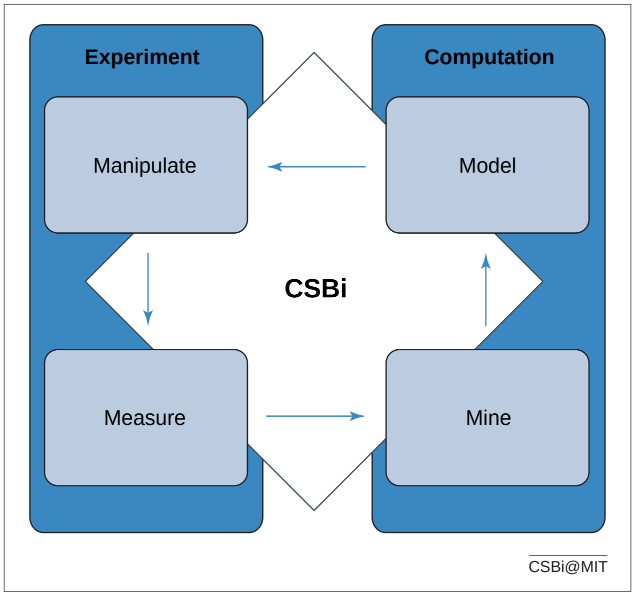

FIGURE 2

Research in systems biology at MIT is characterized by the four Ms – measurement, mining, modeling and manipulation – a research paradigm that consists of iterative cycles of experimentation and computation. Systematic measurement provides sufficient amounts of high quality data that can be mined to determine statistical relationships. Further measurement and analysis permits those relationships to be defined more quantitatively and a series of models can be built. Models then lead to testable hypotheses that can be implemented through experimental manipulation and tested through re-measurement. In iterative cycles, additional data mining and analysis efforts continue to improve the models until they are robust enough to predict outcome.

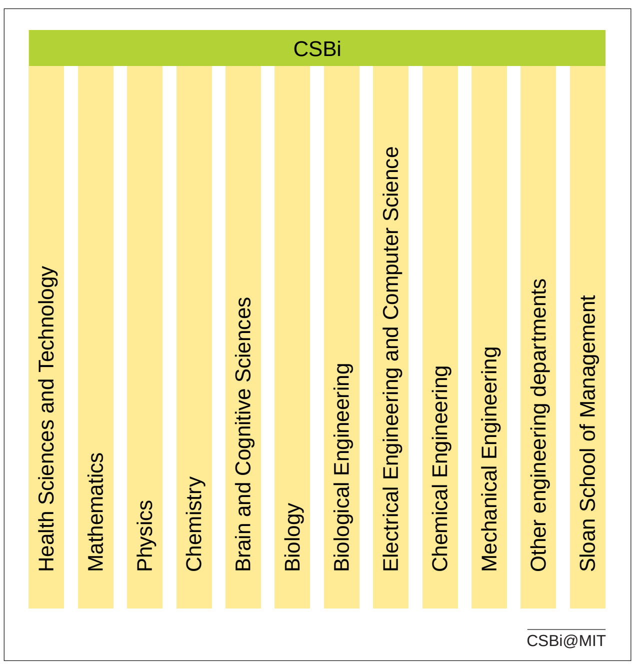

FIGURE 3

Academic departments (yellow) represent vertically integrated structures that are well-suited to disciplinary pursuits but these structures provide limited mechanisms to promote multidisciplinary research and education. At MIT, the Computational and Systems Biology Initiative (CSBi) fulfills a horizontal integrating function by facilitating interactions in research and education activities amongst faculty, students and staff working in a broad range of engineering and science disciplines related to systems biology.

A multidisciplinary research community

The broad scope of problems and approaches relevant to systems biology requires an open community that provides an unimpeded flow of ideas amongst a large number of disciplines and researchers. CSBi at MIT includes faculty, staff and students from a wide range of departments across the campus. Membership in this distributed community is based on self-identified interest in systems biology. Current membership is ~300 students, staff and faculty from 12 academic units in the Schools of Science, Engineering and Management (Figure 3). In addition to biology and brain and cognitive sciences, the systems biology effort includes biological, electrical, chemical, mechanical, civil and other engineering disciplines, computer science, chemistry, physics and mathematics.

Figure 3 illustrates the concept that each of the academic departments forms a vertically integrated structure (like a building) with its own personnel, facilities and educational programs. Significantly, the traditional departmental structure provides rich opportunities for informal interactions and for members to learn together and from one another: departmental retreats, seminar series, co-teaching, co-mentorship of students, thesis committees and student and faculty recruiting are but a few examples. However, a substantial barrier to multidisciplinary research is the absence of a strong mechanism for informal interactions between members of different departments and the corresponding lack of knowledge about each others' teaching and research. To address this issue, CSBi serves a horizontal integrating function by providing a framework for substantial informal interactions amongst researchers and students independent of departmental affiliation, like a common mezzanine connecting occupants of many different buildings. Joint activities in the field of systems biology promoted by CSBi include a seminar series, workshops, symposia, shared research facilities and large-scale research projects, as well as educational, training and outreach activities.

In addition to community-building efforts that bring researchers together, systems biology research also requires access to sophisticated equipment and experimental and computational paradigms that exceed the scale and scope for most individual research groups to own, master and maintain independently. At MIT, shared facilities are being developed in the areas of genomics, proteomics and structure, imaging, microfabrication, high-performance computing, and bioinformatics and modeling. These capabilities provide crucial research resources for conducting experimental and computational studies; the shared facilities also serve as strong community integrators, where researchers with a common interest meet and learn together. This function is strengthened through research staff members who integrate facility activities with individual researchers and their projects. Their role is unlike that of traditional facility staff but rather it represents a new type of career path in an academic environment that requires integration of research and educational activities across multiple disciplines.

Interdisciplinary graduate education

A variety of mechanisms at universities worldwide are addressing the dual challenges of conducting multidisciplinary, and often team-based, research projects in systems biology while also educating a new breed of researcher to assume leadership positions in this emerging field. Notably, Princeton University, led by David Botstein, is experimenting with a new undergraduate curriculum featuring an integrated introduction to mathematics, the physical sciences and biology. Each subject is not taught separately but rather the ideas of each are taught together with examples drawn from biology [2]. At MIT, we are building a systems biology community that includes students enrolled in a wide range of academic departments with an interest in interdisciplinary training, as well as students enrolled in the recently created graduate degree program in the field of Computational and Systems Biology (CSB PhD Program). In a related effort, MIT is launching a new undergraduate major in Biological Engineering.

The graduate CSB curriculum that is being built at MIT serves as an educational counterpart to the research paradigm of the four Ms – measure, mine, model and manipulate (Figure 2). Students in this curriculum are trained to do more than use current technologies; they are empowered to be the developers of the tools, algorithms, techniques and approaches of tomorrow. We are convinced that future research progress depends less on repeated applications of current technologies, but on the development of new ones. Thus, there is a strong emphasis on discovery and understanding of mechanism and underlying principles.

Interdisciplinary graduate courses are being developed that integrate information from different areas (such as several of the four Ms, engineering and biology, or computation and biology) and that are accessible to students from diverse backgrounds. Additionally, these new courses are foundational in that they provide a strong basis from which to build new tools and technologies. Examples include a new computational biology and bioinformatics class that takes a holistic view of the field and places equal emphasis on sequence, structure and systems analysis; a second new course that integrates measurement and modeling with a focus on the physics of measurement using modeling as a basis for device development, error analysis and data interpretation; and a third new class that teaches advanced computational algorithms, machine learning approaches and numerical techniques in the context of systems biology research. Taken together, these courses emphasize matchmaking between problems and solutions. There are many problems in biology that are equally interesting to solve and there are many potential approaches to finding solutions from the world of engineering and computer science. However, for certain problem phrasings there are especially efficient approaches available and matching the best available approach with a corresponding and well-articulated problem formulation is an important skill set for interdisciplinary researchers. Cross-training students across multiple disciplines will empower them to make productive matches of problems amenable to efficient solutions.

Systems biology represents a broad field with the opportunity for contributions in a large number of areas, some with direct impact on biology and others using biology to further engineering, other science disciplines or even more remote disciplines, such as the management sciences. As such, the CSB curriculum emerging at MIT does not have a core block of compulsory classes that all students must complete. Rather, each student crafts a program of study most suited to his or her background, interests and research area; a flexible and customized approach is consistent with the current status of systems biology as a field, as opposed to a discipline. For students in the CSB PhD program, a graduate committee works with each student to create a custom program, ensuring sufficient breadth across multiple disciplines while also including sufficient depth in at least one area. Because the number of available classes is large, including diverse subjects from essentially every science and engineering department, this type of guidance ensures that each student develops an appropriately focused program.

At this early stage in the development of systems biology learning communities, students have already started to focus their efforts in several distinct directions. One group of students has built their classroom and research programs around the idea of tool development and deployment, including computational algorithms and techniques, novel and improved experimental approaches, and the development of new devices to make improved measurements on biological systems. At MIT, two areas of particular growth are: (i) a chemistry-based effort to develop new sensing, labeling and imaging agents, and (ii) a device development and instrumentation engineering effort that includes microfabrication and biological microelectromechanical systems (bioMEMS) approaches to improved experimental measurement. Such devices can result in greatly improved experimental control as well as reduced sample sizes. A second group of students is focusing their efforts on foundational biological experimentation and model system definition and development. Research in this area aims to bring forward compelling biological questions and areas to the stage where they are amenable to a systems-level approach. A third and distinct type of student that is emerging is integrative in the sense that one uses current cutting-edge tools to increase our understanding of relatively well developed experimental systems. The challenge here is to learn how to design the best strategies for understanding and discovery given the current state of the art.

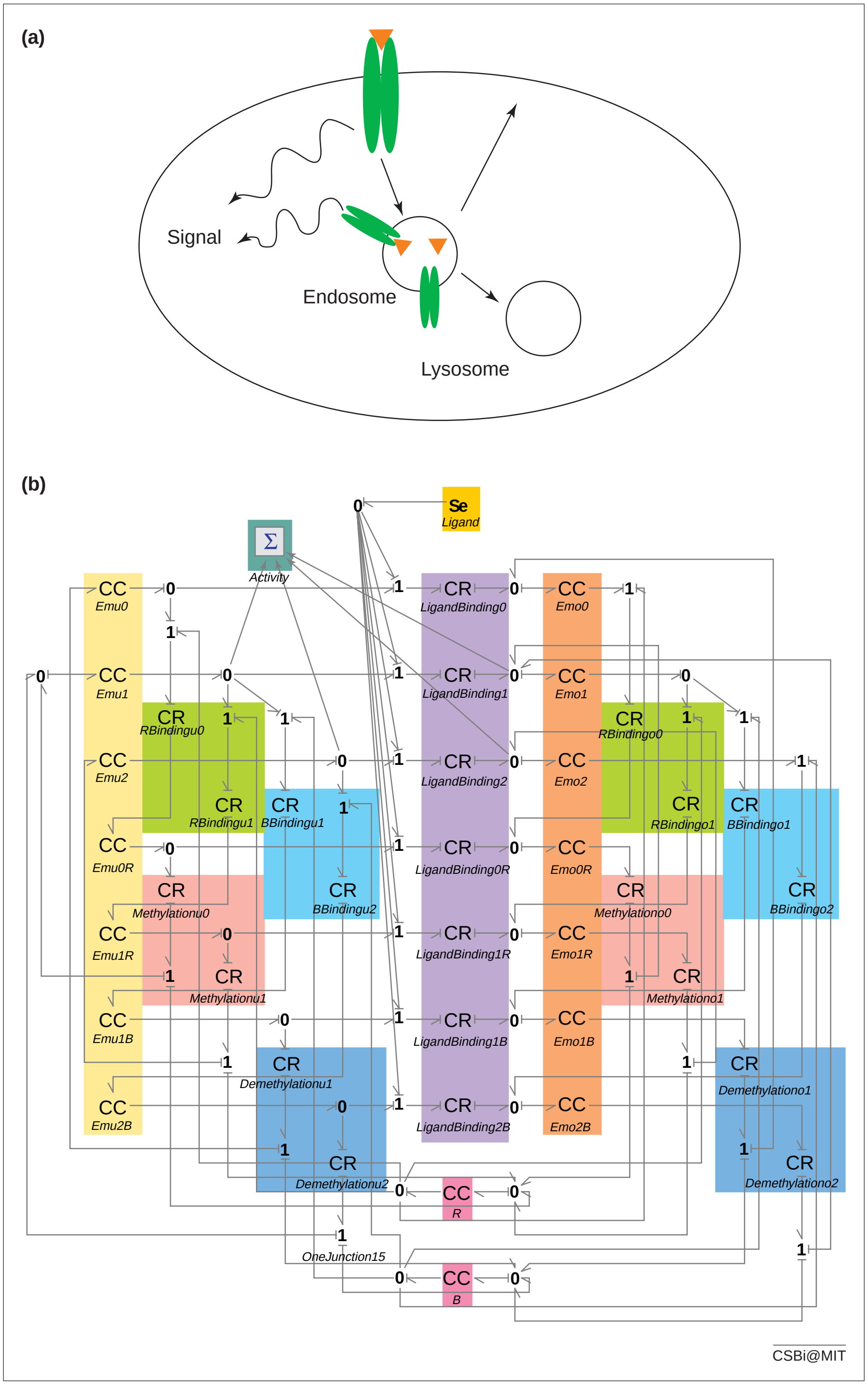

FIGURE 4

Models in biology (a) and engineering (b) tend to have different meanings and uses. Biological models tend to be sketches that illustrate essential ideas and concepts in a qualitative fashion, whereas engineering models tend to include accurate mathematical descriptions sufficient to construct simulations and make quantitative predictions of outcome. This represents just one of the cultural differences between disciplines that can be a barrier to interactions across multiple disciplines. Part **(b)** is courtesy of Michael D. Altman.

At MIT, we are finding that many students are well-suited to and interested in joint mentorship of their PhD research by two faculty members with different backgrounds. By integrating fully into two research groups and learning how each one thinks and approaches problems, these students will be uniquely qualified to tackle non-traditional interdisciplinary research questions on their own. In addition, they will be well positioned to act as integrating agents in the community by serving as communications bridges or translators between two distinct research groups and approaches. Together, the emerging student profiles are beginning to define niches in the educational, cultural and research landscape of modern systems biology; the coming years will further refine the relationships among students, skills, classroom subjects and research areas that will further affect how learning communities in systems biology organize themselves.

Further challenges to multidisciplinary growth

In addition to spanning a broad range of disciplines, systems biology also aims to bridge quantitative and non-quantitative disciplines. Intellectually, there is great disparity between the worlds of engineers and biologists. As one example, from the perspective of a traditional molecular biologist, a model consists of a cartoon-like illustration – a sketch. The graphic illustration is characterized by an informal, qualitative representation of the parts of the model and interconnectivity of the parts, and little information is conveyed as to how they change over time. By contrast, in the world of engineers, standardized language is used to describe the parts of a system and models contain quantitative information about the dynamics and connectivity of the system – essentially a mathematical description (Figure 4). Bridging the two opposing worldviews on what constitutes a model is just one of the key challenges that needs to be addressed when educating the future generation of scientists and engineers at the biology–engineering interface and, in turn, integrating communities of learning.

Scientific and technological aspects are only part of the challenges that need to be addressed when engaging in research and educational efforts at the intersection of disciplines. The 'softer' and often underestimated issues relate to organizational and cultural differences between disciplines. Some of these dissimilarities are profound and are deeply rooted in the cultures of traditional academic disciplines. Some such differences include:

- Long-term versus short-term funding: biology faculty tend to be funded by the National Institutes of Health (NIH) while engineering faculty traditionally receive funding from the National Science Foundation (NSF) and other government agencies, such as the Department of Defense (DoD). To receive NIH funding, an investigator needs a large initial investment but, once funded, research projects are often renewed for many years. By contrast, NSF or DoD funding tends to be more episodic.
- Team-based versus single-investigator-led science: criteria for selecting students and awarding tenure can also differ significantly between engineering and science departments. Many engineering departments have a long-standing tradition of team-based research, while biology departments tend to encourage single-investigator research to better understand the contribution of individual faculty members when deciding on tenure or promotions.
- Real-world versus basic science: at MIT, engineers tend to be motivated by making an impact in the world and they are more likely than their biology colleagues to work on real-world problems, often in collaboration with industry. By contrast, biologists are encouraged to publish their research results in prestigious scientific journals and they are less inclined to choose a research problem based on its relevance to industry or society at large.
- Theoretical versus experimental science: it is not unusual that it takes much longer to obtain a degree in a highly experimental field (e.g. biology) than in a more theoretical field (computer science or mathematics). Moreover, in addition to academic excellence, biology students need to be able to conduct complicated laboratory procedures and work alongside other researchers in large and relatively structured research laboratories. Students in more theoretical fields tend to have more freedom when choosing the place, time and type of their work, and there is little or no focus on manual techniques.

These differences make collaborative research and educational efforts between engineers and biologists a challenging task for faculty, students and administrators. In addition to dealing with the academic demands, students interested in systems biology will need to be able to move smoothly between multiple worlds and cultures. Those who tend to be frustrated or confused by differing or even contradicting views might be lost in the course of their study. By contrast, those students who excel at switching between different environments are likely to become role models for how to work across disciplinary boundaries. At MIT, the latter students often serve as the 'glue' between investigators from different disciplines and they are seen as the mechanism to promote interdisciplinary research and education efforts.

Conclusion

The new and emerging field of systems biology is being defined and pursued by individual researchers, collaborators and multidisciplinary teams. There is a strong sense that the result will change biology and many of the other disciplines involved, including those from engineering and computer science. Although there is a temptation to measure the success of an endeavor by the tools developed and specific knowledge that results, the potential outcome here is much more dramatic – it is nothing less than a casting of biology as a quantitative and predictive discipline through the development of appropriate models to describe all key phenomena.

Academia and industry alike have started to respond to the challenges posed by systems biology. This perspective article has focused on the academic arena, where learning communities are forming to train a new breed of researchers to work effectively on multidisciplinary teams at the interface of biology, engineering and computer science. The characteristics of the emerging systems biology research communities might differ somewhat between academic and industrial settings, but we believe that the type of researcher who will succeed in an interdisciplinary environment and the mechanisms that hold these multidisciplinary communities together, on a fundamental level, will be alike.

When educating future biologists and engineers, the challenge goes far beyond introducing students to the foundations of and latest advances in each others' disciplines. Because systems biology represents a new and more quantitative approach to biology – a new way of asking and answering biological questions and a new way of thinking about them – biologists and their engineering colleagues must function as equal partners. Likewise, biological research has the potential to offer insight into and advance the frontiers of engineering disciplines and computer science. Indeed, at MIT, engineers and computer scientists are not viewed in the limited role of toolmakers that merely enable biologists to collect and analyze data in a more systematic and quantitative manner. We are striving for an equal partnership between quantitative and non-quantitative disciplines. Creating this equal partnership poses an unprecedented challenge and opportunity in the education and research infrastructure. That challenge is being addressed and the opportunity is starting to be fulfilled through the establishment of multidisciplinary learning communities. Such communities are part of a new organizational structure to facilitate the pursuit of interdisciplinary research and educational efforts. There is ample reason to be hopeful that the results of these efforts will be fruitful on many levels [3].

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