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LETTER TO THE EDITOR

Finding your inner modeler: An NSF-sponsored workshop to introduce cell biologists to modeling/computational approaches

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ABSTRACT

In classical Cell Biology, fundamental cellular processes are revealed empirically, one experiment at a time. While this approach has been enormously fruitful, our understanding of cells is far from complete. In fact, the more we know, the more keenly we perceive our ignorance of the profoundly complex and dynamic molecular systems that underlie cell structure and function. Thus, it has become apparent to many cell biologists that experimentation alone is unlikely to yield major new paradigms, and that empiricism must be combined with theory and computational approaches to yield major new discoveries. To facilitate those discoveries, three workshops will convene annually for one day in three successive summers (2017–2019) to promote the use of computational modeling by cell biologists currently unversed in its utility or unsure how to apply it. The first of these workshops was held at the University of Illinois, Chicago in July 2017. Organized to facilitate interactions between traditional cell biologists and computational modelers, it provided a unique educational opportunity: a primer on how cell biologists with little or no relevant experience can incorporate computational modeling into their research. Here, we report on the workshop and describe how it addressed key issues that cell biologists face when considering modeling including: (1) Is my project appropriate for modeling? (2) What kind of data do I need to model my process? (3) How do I find a modeler to help me in integrating modeling approaches into my work? And, perhaps most importantly, (4) why should I bother?

A unique workshop entitled “Finding your inner modeler” was held at the University of Illinois at Chicago (UIC) on July 13, 2017. Funded by the Molecular and Cellular Biosciences (MCB) Division of the National Science Foundation (NSF), this was the first in a series of three one-day workshops with the second and third meetings in the summers of 2018 and 2019. The hundred and five attendees of the first workshop spanned the gamut from undergraduate students to senior professors; ~2/3 identified as cell biologists and ~1/3 as computational/modeling scientists.

An overall goal of this workshop series is to demonstrate that the traditional discipline of Molecular and Cellular Biology—in which cellular processes are explored empirically and one experiment at a time—can be combined with the relatively new discipline of Systems Biology—a synthesis of biology, mathematics, chemistry, physics, engineering, and computer science—to discover the deep organizing principles that govern cellular and organismal life. Such a synthesis of bench science and computational approaches is likely to provide paradigm-shifting insight into the profoundly complex and dynamic molecular systems that underlie cell structure and function. Another expected outcome is to shift emphasis from qualitative “cartoon” models to quantitative computational models of biological processes. Only integrating both, experimental research and modeling methods, will expand our understanding of how molecular mechanisms interact in space and time to produce emergent cellular phenomena.

These workshops are designed to facilitate collaborations between cell biologists and systems biologists, and to provide support as they form long-term working pairs. To our knowledge, this was the first workshop with the express purpose of edifying traditional cell biologists (that is, those with little or no relevant modeling experience) as to why, when, and how to employ computational modeling in their research. As Dr. Richard Cyr, an NSF Molecular and Cellular Biology Program Director who attended the workshop, noted, “Many researchers want to learn how to apply them (modeling/computational approaches) to their research in a meaningful way, but are unaware of the new tools that are available and where they can begin their modeling efforts.” In addition, as reiterated by the organizer of this workshop series, Dr. David Stone (University of Illinois at Chicago). A primary goal of this workshop is to target classical cell biologists who have no experience with computational modeling, and provide them with information that will help them use computational approaches in their research.

For a detailed schedule of the workshop, go to https://pages.wustl.edu/haswell/finding-your-inner-modeler. You also can view a video of the presentations at: https://www.youtube.com/watch?v=RumbZBB5WCw. For those interested in finding an interdisciplinary collaborator, please sign up and explore at the
workshop’s collaborator-matching website: compmodelmatch.org. This scientific “dating” service is designed to “connect researchers to accomplish great things”. One need not have participated in the first workshop to use the website or to apply for upcoming workshops. For any additional information, please contact Dr. David Stone at dstone@uic.edu.

In the first Keynote address, Dr. Wallace Marshall (University of California, San Francisco) elegantly dispelled the myth that modeling is difficult by describing how simple linear models can be utilized to understand the regulation of flagellar length in the green algae Chlamydomonas. One of his key points, which was echoed by other presenters, was that the “purpose of the model is to disprove the model”; that is, producing a model is not an end in and of itself, but is just one step towards greater understanding of the biological process under investigation. He further stressed that, while collaborations are good and to be encouraged, it is optimal for both collaborators to acquire at least a basic understanding of the other discipline in order to “break the culture of dependency” between biologists and modelers.

A second Keynote address was equally dynamic despite being delivered remotely from the Marine Biological Laboratory at Woods Hole. Dr. Rob Philips (California Institute of Technology) discussed the value of doing “Figure 1 theory”, where the model drives the design of experiments, rather than “Figure 7 theory” that only interprets the already available data. He also argued that one of the fundamental goals of systems biology is the search for “sameness”, which he believes will ultimately allow the description of common underlying principles governing all biological systems. He further emphasized the need for maximal simplicity when developing a model/computational description of biological mechanisms, championing the notion that we first need to invoke basic principles of physics and chemistry before seeking more complex explanations.

The workshop featured three “Collaborative Pair Talks” designed to familiarize attendees with modeling possibilities and to showcase successful collaborations between cell biologists and computational modelers. These talks were presented in tandem by pairs, each including a traditional cell biologist and a modeler, that were already engaged in ongoing collaborative projects. Dr. Mary Baylies (Memorial Sloan-Kettering Cancer Center) and Alex Mogilner (New York University) described the biological background and computational approaches they are using to model the positioning and size-scaling of nuclei in multi-nucleated muscle cells [3,4 and unpublished]. Their goal is to predict and test physiological factors that influence these parameters and thereby influence muscle fiber size. Both stressed that making many models and then seeing what fits the data is essential for a useful predictive model. Drs. Angela DePace (Harvard University) and Max Staller (now at Washington University in Saint Louis), described the measuring and modeling of enhancer functions during Drosophila embryo development.5,6 They stressed three key points: modeling done prior to initiation of experiments can suggest which experiments should be done; proving a model wrong can be as useful as proving it right; and models can be right for the wrong reasons. Drs. Patrick Robison and Vivek Shenoy (both at University of Pennsylvania), described how modeling mechanical forces can be used to explain how microtubules regulate the contractibility of cardiac myocytes.7 Their comment that the development of their collaboration often felt like a “professional dating” experience elicited laughter from the audience, but also showcased the often difficult task of finding a suitable partner for modeling projects. There also were many nods in the audience in response to a quote attributed to Richard Feynman that “People who wish to analyze nature without mathematics must settle for a reduced understanding”. These three talks successfully illustrated the many ways that molecular research can benefit from a collaborative modeling/computational insight to illuminate a biological problem.

In an engaging and informative presentation entitled “How modeling plays in review panels – do’s and don’ts”, Dr. Cyr explained that MCB sees major discoveries as increasingly dependent on the synergism between cell biology and computational modeling. He stressed that MCB solicits and supports proposals that combine molecular and computational methods, and that engage in multidisciplinary research at the interface of biology, physics, maths, computer sciences, and engineering. The current MCB Program Solicitations (e.g., NSF 17-589) is unambiguous in its call for quantitative, predictive, and theory-driven research, and the forthcoming solicitation (expected late in this calendar year) will stress these areas as well. Dr. Cyr also emphasized the need for true integration of cellular and modeling approaches within proposals, warning against “tacked on” modeling aims that are almost uniformly panned by NSF reviewers when making funding recommendations. For more information about how to best use computational modeling in your next MCB project proposal, Dr. Cyr invites you to contact him at RCYR@nsf.gov.

After a group lunch, the workshop reconvened with a Panel Questions and Answers session, featuring Drs. Richard Cyr (NSF), Patrick Robinson (University of Pennsylvania), Elizabeth Haswell (Washington University in St. Louis), Carlos Lopez (Vanderbilt University), Alex Mogilner (New York University), Marcos Sotomayor (Ohio State University), Shelby Wilson (Morehouse College) and Leslie Loew (University of Connecticut). The panel answered questions from the audience that ranged from the all-important “how do you know when your project could benefit from a modeling approach?” to practical advice on “how do you convince a reluctant graduate student to dive into a collaborative modeling project?”. All questions elicited lively discussion between members of the audience and the panelists.

Next, the director of the Virtual Cell project,8 Dr. Leslie Loew (University of Connecticut), described the modeling and analysis software available at vcell.org, and enumerated the various modeling capabilities (PDE, ODE, stochastic, spatial stochastic and network-free NFSSim) provided free at this site. Dr. Loew stressed the utility of using individual VCell modules to build more complex networks, and the potential of sharing computational models within the scientific community via VCell.

The afternoon session concluded with a two-hour network-building “workshop within a workshop”. In this session, two pre-selected cell biologists were partnered with an expert computational modeler. Each pair of collaborators had
40 minutes to translate the cell biologist’s qualitative/cartoon model of their biological process into a formal network diagram, and to develop and describe the steps required to ultimately generate a quantitative and predictive computational model. These unrehearsed first meetings between possible interdisciplinary collaborators showcased the kind of experimental biological parameters that would be needed to initiate a modeling approach, and described some of the computational methods that could be used to develop robust models. In addition, they beautifully illustrated the back-and-forth negotiations and information exchanges that take place during new collaborations, as well as the more synergic interactions that take place when one (or both) of the collaborators has acquired a certain level of understanding of the other discipline. These sessions were extremely instructive for the participants as well as for the audience.

The two future workshops to be held in summer 2018 and 2019 are designed to further enhance the use of computational modeling by traditional cell biologists by demonstrating its utility, by explaining how computational models are built and how their output is appropriately interpreted, and by debunking widespread misconceptions about these and related topics. The future of Cell Biology lies at the nexus of experimental research and modeling methods, both of which will be needed to answer the fundamental questions of how cellular bits and pieces interact in space and time to integrate all the cell processes that together sustain life. We hope that you will consider joining this new scientific frontier, and we’ll see you at the next workshop!

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No potential conflicts of interest were disclosed.

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