Quantitative biology: where modern biology meets physical sciences

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ABSTRACT **Quantitative methods and approaches have been playing an increasingly important role in cell biology in recent years. They involve making accurate measurements to test a predefined hypothesis in order to compare experimental data with predictions generated by theoretical models, an approach that has benefited physicists for decades. Building quantitative models in experimental biology not only has led to discoveries of counterintuitive phenomena but has also opened up novel research directions. To make the biological sciences more quantitative, we believe a two-pronged approach needs to be taken. First, graduate training needs to be revamped to ensure biology students are adequately trained in physical and mathematical sciences and vice versa. Second, students of both the biological and the physical sciences need to be provided adequate opportunities for hands-on engagement with the methods and approaches necessary to be able to work at the intersection of the biological and physical sciences. We present the annual Physiology Course organized at the Marine Biological Laboratory (Woods Hole, MA) as a case study for a hands-on training program that gives young scientists the opportunity not only to acquire the tools of quantitative biology but also to develop the necessary thought processes that will enable them to bridge the gap between these disciplines.**

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What does a mathematician looking at bacterial division under a microscope have in common with a biologist programming a stochastic simulation of microtubule growth? For one, both can be found at the Physiology Course at the Marine Biological Laboratory (MBL) in Woods Hole, MA, which brings together graduate students and young postdocs who have a passion for quantitative biology. Students enter the course with a wide array of scientific backgrounds, including chemistry, molecular biology, mathematics, and theoretical physics. Although at first hesitant to step outside their comfort zones, students leave the course confident and courageous in their abilities to work across traditional academic boundaries. Having experienced this transformation ourselves as participants in the 2014 Physiology Course, we wanted to share some of our insights and how they have influenced our perspectives on the present challenges and exciting future of quantitative cell biology.

"When you cannot express [what you are speaking about] in numbers, your knowledge is of a meager and unsatisfactory kind; it may be the beginning of knowledge, but you have scarcely, in your thoughts, advanced to the stage of science." The need for quantification in the life sciences could not have been better worded than it is in this quote from Lord Kelvin. One of the key take-home messages from the course has been the crucial need for advancement of quantitative cell biology, which uses accurate measurements to refine a hypothesis, with the aim of comparing experimental data with predictions generated by theoretical models. We strongly believe that quantitative approaches not only aid in better addressing existing biological questions but also enable the formulation of new ones.

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Abbreviations used: MBL, Marine Biological Laboratory; SLB, supported lipid bilayer.

The present time is particularly ripe for implementing quantitative approaches in cell biology, due to the wealth of data available and the depth of control we now have over many experimental systems. In the past 20 years, we have sequenced the human genome, broken the diffraction limit in microscopy, and begun to explore the possibilities of the micron-scaled experiments with microfluidics. With these tools in hand, the means to obtain quantitative data are not limited to a select few model systems; this level of experimental detail allows us to craft theoretical models that not only fit the data but have real predictive power. We can then return to our respective experimental systems with new hypotheses and interrogate them anew, reaping the benefits of an approach that has benefited physicists for decades.

Building quantitative models in biology has been a powerful approach that has often revealed counterintuitive phenomena and insights while at the same time leading to novel research directions. This is of particular importance today, as experiments are becoming increasingly expensive and are rapidly accumulating vast amounts of data. It is now possible to perform "virtual" preliminary experiments in silico using quantitative models and pre-existing data and only then move to "real" laboratory experiments to test the developed hypotheses. Researchers trained this way can perform more focused experiments instead of adopting the traditional exploratory mode in the lab, saving both time and resources. However, we recognize that a majority of biology graduates have not been rigorously trained in the mathematical and physical sciences. Similarly, many physics graduates often remember their introductory biology classes simply for the rote memorization of protein names and signaling pathways, leading to the wrong assumption that biology is all about remembering three-letter abbreviations such as WNT, MYC, and so on. This can often create a misleading picture of biology.

These challenges could be overcome by finding a common language between biologists, physicists, and mathematicians. A simple example of this is the word "model." The same word can mean very different things to scientists depending upon their training: to a physicist it refers to quantitative visualization of a process via certain well-defined mathematical parameters; a biologist, on the other hand, might use the word to refer to a schematic depiction (also called a cartoon) of a biochemical reaction. We aim to reduce this gap between biological and physical sciences and bring these two communities together.

One way to train young scientists in such an approach is to provide opportunities for hands-on engagement with the methods and thought processes necessary to partake in both fields. The MBL Physiology Course is an excellent case study for a training program that gives young scientists the building blocks and community necessary for success in bridging quantitative/physical sciences and biology. The course starts with a weeklong boot camp designed to bring students of different backgrounds up to speed on basic tools in quantitative biology. Students purify proteins, program in MATLAB, and build microscopes. The most important skill that biologists acquire is not simply learning how to write lines of MATLAB code, but rather phrasing biological phenomena in mathematical terms through equations and simulations. Building confocal microscopes and optical tweezers on a bare optical table creates trust in the tools we depend on to acquire quantitative data. Physicists, on the other hand, learn to purify motor proteins like kinesins and dyneins from native sources (squid), in the process coming face-to-face with the natural context of the biological questions that they are addressing.

This interdisciplinary approach helps students from diverse backgrounds develop a common language. After the boot camp, students work together on three 2-week-long research projects under the guidance of leading scientists. Projects range from studying the spatial organization of the human oral microbiome and observing the development of the *Caenorhabditis elegans* embryo all the way to performing computational simulations of cytoskeletal polymers. By working together in a highly informal and stimulating environment, physicists learn to appreciate biological problems and biologists begin to see biological phenomena in a new light as a result of the novel physical tools and methodologies they learn from their peers. As an example, course participants Rikki Garner and Daniel Feliciano successfully collaborated to study how competition between two highly processive microtubule motors that work in opposition controls microtubule length. While Rikki (mentored by Jané Kondev) tackled the question theoretically using a random walk model, Daniel, under the mentorship of Joe Howard, carried out the experimental measurements via an in vitro assay to test Rikki's predictions. Other examples of quantitative and biological expertise coming together to address biological questions include studying the displacement and

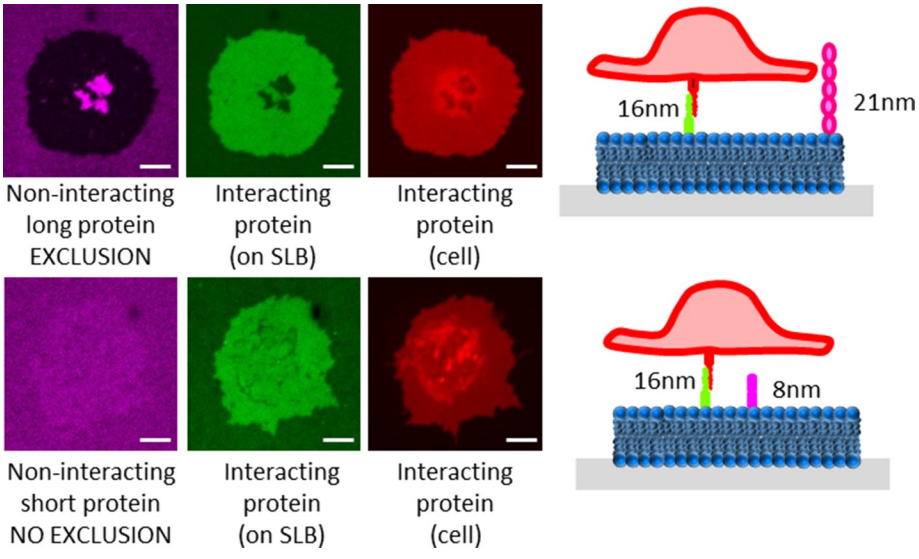

FIGURE 1: Proteins are organized based on size at the membrane interface. The membrane interface between a cell and a supported lipid bilayer (SLB) was formed by the interaction of synthetic adhesion molecules, one protein (bound to the membrane via a His-tag) and another protein that interacts and binds with the membrane-bound protein (expressed in the S2 cells). Note that the long noninteracting protein (21 nm, magenta colored) but not the shorter noninteracting protein (8 nm, magenta colored), which is bigger than the synthetic interacting dimer (16 nm, red–green colored) is excluded from the cell–SLB interface. Both of these noninteracting proteins are bound to the SLB and do not interact with the cell. Scale bar: 10 μm. (Prepared by L.Z. and Nan Hyung Hong under the guidance of Matt Bakalar, Eva Schmid, and Dan Fletcher.)

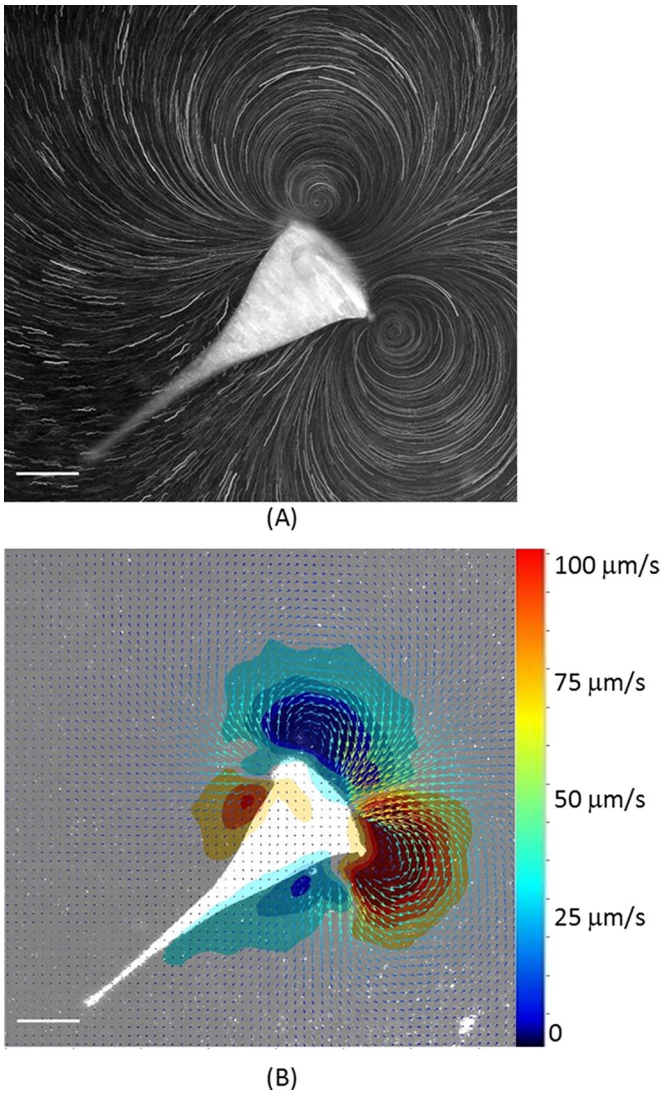

FIGURE 2: *Stentor coeruleus* is a giant single-celled organism that feeds by creating flow vortices in water and directing prey into its oral opening using this flow. (A) Maximum intensity projection of time-lapse images showing flow fields in the feeding flow generated by *S. coeruleus*. The flow is generated by the coordinated ciliary beating of the mouth cilia. (B) Flow velocity and flow directions were quantified by the particle image velocimetry method. The circularity of flow has also been indicated—the blue cloud around the oral cilia indicates clockwise flow, and red indicates anticlockwise flow. Scale bar: 100 µm. (Prepared by S.S. under the guidance of Mark Slabodnick, Tatyana Makushok, and Wallace Marshall in collaboration with Jack Costello, Providence College.)

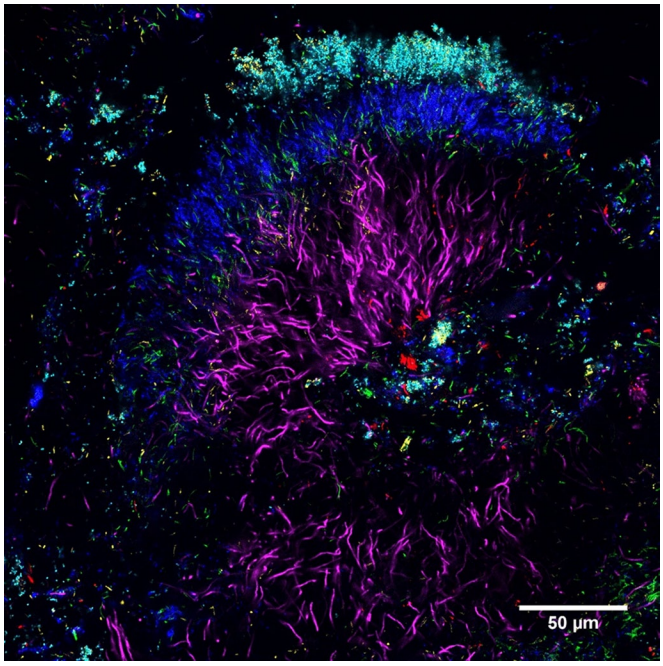

FIGURE 3: Spatial organization of complex microbial communities in an oral plaque sample taken from a volunteer as seen by combinatorial labeling and spectral imaging–fluorescent in situ hybridization (CLASI-FISH). Microbes seen here are *Corynebacterium* (pink), Neisseriaceae (blue), *Fusobacterium* (green), Pasteurellaceae (yellow), *Streptococcus* (cyan), and *Actinomyces* (red). (Prepared by Bryan Weinstein, Lishibanya Mohapatra, and Matti Gralka under the guidance of Blair Rossetti, Jessica Mark Welch, and Gary Borisy.)

transport of proteins at the interface between cells and synthetic supported lipid bilayers (Figure 1), observing and quantifying the cytoplasmic streaming as well as the filter-feeding flow vortices in the giant single-celled organism *Stentor coeruleus* (Figure 2), and imaging the spatial organization of complex oral microbial communities (Figure 3).

An invaluable aspect of the course is the informal nature of the interaction. There are a wide variety of morning seminar speakers, and in the question-and-answer sessions following the talks, the speakers discuss not only science but also the successes and failures they experienced while moving across the boundaries of biological and physical sciences. The interactive and collaborative nature of the course encourages students to not just learn from one another but to actually teach one another. "Chalk talks" and interactions happen spontaneously and are the strongest indication of the richness of the intellectual exchange among members of the community. Prime examples in the 2014 course are the chalk talks on Python (Bryan Weinstein), Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR) cloning (Dan Dickinson), and the basics of microfluidics (Sindy Tang).

Although we have benefited immensely from this interdisciplinary course, we understand that it might not be feasible for all graduate students to participate in such courses. Nevertheless, we believe that the scientific community should work together to replicate elsewhere, at least partially, the strengths of this course to allow students to benefit from this approach. Students should be encouraged to host and attend seminars from speakers with diverse backgrounds, which will expose them to research areas different from their own. Biology students should also be exposed to mathematical and statistical instruction early in their research careers, preferably at the undergraduate level, to enable them to build strong foundations. Students should also be encouraged to participate in short-term, low-pressure interdisciplinary collaborations to broaden their understanding and initiate interactions with other fields. Short summer/winter schools—for example, the physical biology of the cell courses at Cold Spring Harbor and the International Centre for Theoretical Physics (Italy)–International Centre for Theoretical Sciences (India) Winter School on Quantitative Systems Biology, 2013, in Bangalore, India—can serve as the perfect stage for this.

In conclusion, we expect that quantitative approaches will be indispensable for better addressing biological questions in the future. Our experience is that combining traditional experimental cell biology with quantitative thinking leads to hitherto unknown scientifically rich domains, and we ourselves have found this

FIGURE 4: Participants in the 2014 Physiology Course at the MBL at Woods Hole.

exploratory journey to be both achievable and rewarding. Although bridging the gap may appear to be difficult at times, it is extremely satisfying when accomplished, and doing it within a highly motivated and supportive community is what makes the connection possible and extremely useful.

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