A Nobel Prize in *Mathematical* Biology?

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This year both the Nobel Prizes in chemistry and medicine were awarded for advances in *molecular* biology. The Prize in medicine was awarded to Andrew Fire and Craig C. Mello for discovering a mechanism called "RNA interference" (RNAi) by which plants and animals selectively turn off the expression of genes [4]. The discovery is remarkable in many ways. It has opened up completely new approaches to gene therapy, and has transformed biologists understanding of the molecular biology of the cell. The pervasive view of RNA as an unimportant bit player in the drama of molecular biology has been erased forever. Recognizing the impact of RNAi on medicine and biology, the Nobel committee took the unprecedented step of awarding the Prize to Fire and Mello only eight years after they published their work. Award committee member Erna Moller expressed the nature of the work in language usually reserved for mathematical discoveries: "It was like opening the blinds in the morning. Suddenly you can see everything clearly."

Perhaps it comes as no surprise then that Andrew Fire was indeed a student of mathematics in our department (BS 1978, age 19). He also studied biology, and upon graduation decided to pursue a PhD in molecular biology at MIT. His choice of biology after mathematics was not an unusual one; in fact, he is not the first graduate of our department to leave mathematics and subsequently receive a Nobel Prize in medicine. Hamilton O. Smith received a BA in mathematics from our department in 1952, and went on to receive the Nobel Prize for his discovery of restrictions enzymes. He also played a key role in sequencing the first bacterial genome: *Haemophilus influenza*. In his autobiography, Smith recalls that his interest in biology started when his brother showed him a book on mathematical modeling of central nervous system circuits.

Among our faculty, complex analyst Hans Bremermann developed an interest in mathematical biology in the 1960s, and eventually moved to the department of molecular and cell biology where he did pioneering work on mathematical aspects of host-parasite interactions, mechanisms of HIV persistence, and the theory of dreams [1]. There are also many students who received PhD degrees in our department that subsequently distinguished themselves in mathematical and computational biology after leaving mathematics. A prominent example is Phil Green (PhD 1976 with Marc Rieffel) who worked on operator algebras, assuming the position of assistant professor in mathematics at Columbia University upon his graduation from Berkeley. After becoming interested in statistical genetics and attending an intensive summer course on molecular biology, he transferred to the department of pathology at the University of North Carolina on a postdoctoral research grant. He is now professor of genome sciences at the University of Washington where he develops mathematical, statistical and computer methods for analyzing the genomes of humans and other organisms. He is a member of the National Academy of Sciences [2]. David Jaffe (PhD 1987 with Robin Hartshorne) is a leader in developing methods for assembling genomes from data obtained using the sequencing technologies developed, in part, by Hamilton Smith.

The pattern of mathematical training followed by a complete transition to biology was a matter of choice in many of the cases mentioned above, and was justified because the advances in molecular biology required only elementary mathematics, or none at all. For example, Andrew Fire's discovery was based on careful experiments in roundworms, and the ingenuity of the discovery was not mathematical, but in the use of double-stranded RNA to selectively target genes. Nevertheless, as our understanding of biological systems becomes more detailed, mathematics is increasingly playing a central role in biology. In the case of RNAi, mathematics is required in order to design effective therapies, as is demonstrated in the work of Joshua Leonard, a PhD student in chemical engineering at UC Berkeley whom I taught in our course Math 127 (mathematical and computational methods in molecular biology) in 2004. To quote from the abstract in [6]: "The [mathematical] model provides quantitative predictions on how targeting multiple locations in the HIV genome, while keeping the overall RNAi strength constant, significantly improves efficacy." In related work, Christine Heitsch (PhD 2000 with John Rhodes) is using combinatorial methods to study RNA secondary structure [5]. She is now an assistant professor of mathematics at Georgia Tech.

Heitsch is one of a growing number of PhD graduates from our department who work on biology but have chosen to stay in mathematics. Other examples include Sebastian Schreiber (PhD 1995 with Charles Pugh) who is an associate professor of mathematics at the College of William and Mary, and Julie Mitchell (PhD 1998 with Morris Hirsch) who is an assistant professor of mathematics at the University of Wisconsin. Indeed, mathematics students now no longer have to leave mathematics behind in order to contribute to molecular biology. While the connections between mathematics and biology were sporadic in the past, students now benefit from a program that is systematic and exciting. Many members of our faculty actively work on biological problems ranging from population genetics and genomics to carcinogenesis. A group focused on mathematics and computation in biology includes faculty members Steven Evans, Richard Karp, Lior Pachter, John Neu, Rainer Sachs and Bernd Sturmfels [8]. Last year, Nicholas Eriksson was the first student from our department to graduate with a PhD in mathematics together with a designated emphasis in computational biology. The rigorous requirements of the designated emphasis- candidates must complete the standard requirements of their PhD program in addition to taking extra courses and writing an interdisciplinary thesis- is resulting in exciting work in which new biology results are complemented by new contributions to mathematics inspired by biology [7].

In a recent article [3], Joel Cohen argues that "mathematics is biology's new microscope, only better" and that "biology is mathematics' next physics, only better." Despite this optimism, it is too early to predict a Nobel Prize in mathematical biology. However, what is certain is that our undergraduate and PhD students no longer have to choose between mathematics and biology, and can fully embrace the new potent mix of the two sciences. The track record of our former students suggests that we can expect great discoveries from students who are now engaged in *both* the mathematical and biological sciences.

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