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Editorial

It happened fifty years ago...

In 1967 there were no cell phones, personal computers, compact discs, or the Internet. The students who would one day usher in the era of social media were not yet born. Driverless cars were laughable science fiction. No person had set foot on the moon. Nonetheless, 1967 was an eventful year. The first Boeing 737 took its maiden flight and the first gas was pumped out of the North Sea. The Cold War and the Vietnam War weighed heavy on many a mind. It was the year when Israeli and Arab forces fought the Six-Day War, South Yemen became independent of the United Kingdom, Shah Mohammad Reza Pahlavi of Iran was crowned, and Nicolae Ceaușescu became the leader of Romania. It was the year when Thurgood Marshall was sworn in as the first African American U.S. Supreme Court justice, and a movie actor named Ronald Reagan was inaugurated as the new governor of California. It was the year when the Beatles released *Sergeant Pepper's Lonely Hearts Club Band,* the soundtrack for the Summer of Love, and the musical *Hair* opened off Broadway. *Bonnie and Clyde* and *The Graduate* were released. It was the year when pulsars and quarks were discovered, and the light-emitting solid-state diode was first reported. 1967 was the year of the first heart transplant and of the first use of an intra-aortic balloon pump for a myocardial infarction. The first artificial DNA molecule was synthesized and mouse and human cells were fused for the first time. Chimpanzee Washoe began to learn sign language.

1967 was also the year when Richard Bellman worked with the Elsevier publishing company to launch *Mathematical Biosciences*. Bellman was an applied mathematician who had pioneered dynamic programming techniques and made major contributions to control theory. Although very successful, he left safe ground by advocating the use of tools from mathematics and engineering in two areas that had traditionally stayed away from them: biology and medicine. Thus, he started the preface to the first issue of *Mathematical Biosciences* with the innocuous assertion that "the frontiers of contemporary science lie in the fields of biology and medicine," but quickly infused his bold vision that "progress calls for the full power of modern mathematics and modern computers combined with the striking capability now available for experimentation."

Bellman's preface to the journal could easily have been written today, but it was revolutionary then. In fact, the successful pioneers of biomathematics, including Bellman himself, only started working on biological applications after they had established themselves in other areas of mathematics (and received tenure). Today's students have a choice among numerous graduate programs catering in some way to biomathematics; in 1967; even the term 'applied mathematics' was a frowned upon among 'real' mathematicians. Today, mathematical biology, biomathematics, and systems biology are well-accepted subfields of biology, but when *Mathematical Biosciences* was first published, only two other journals covered the field. Today's research in biomathematics is supported by public funding agencies across the world. Looking at the U.S. as an example, the National Sciences Foundation maintains a Mathematical Biology program, the National Institutes of Health have a study section on Modeling and Analysis of Biological Systems, and numerous other agencies encourage the use of mathematics and computing in biology and medicine. In 1967, pioneers like Bellman, Bremermann, Garfinkel, Mesarović, Rashevsky, Rosen, Savageau, Segel, von Bertalanffy, and Winfree were by and large lone individuals with but a few true peers. Associations like the *Society for Mathematical Biology*, the *International Society for Computational Biology*, and the *SIAM Life Sciences Activity Group* were founded much later. While most scientists considered mathematical and computational biology too mathematical for biologists and too biological for mathematicians, Bellman and his fellow pioneers believed so strongly and genuinely in the value and necessity of this newly emerging field that they were willing to risk their time and reputation.

Much has happened since these early days, but much more lies before us. If we believe in current trends, we should expect a glorious future. Maybe we will create effective models of entire organisms. Maybe we will begin to understand the underlying design and operating principles with which nature solves recurring tasks. Maybe we will fathom crisp or fuzzy biological theories at the horizon. So, at the fleeting moment between past and future, the mile marker of the 50th anniversary of *Mathematical Biosciences* gives us reason to pause and ponder, and to celebrate the enormous advances in our field of endeavor as they are evident in the increasing numbers of practitioners, scientific articles, books, journals and conferences, but maybe even more importantly in the growing acceptance of mathematical and computational approaches among today's researchers in biology and medicine.

This special issue of *Mathematical Biosciences* celebrates the semicentennial of the journal and the blossoming of Bellman's futuristic vision, which is still guiding the journal today. It was not easy to decide on the best manner of making this special issue representative of past successes and today's state of the art. Should the volume offer a smorgasbord of diverse biological topics in which mathematics has played an important role? Should it make predictions about future growth areas? Should it reprint the most cited articles published by the journal over the years? In the end, we realized that it is the members of our editorial board who

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are the best, superb reflection of what our readers consider to be the most important topics in mathematical biology. They represent the collectively expertise and wisdom of mathematics in biology and witness how the field is unfolding on a daily basis.

Guided by this appreciation, we decided to request contributions from the journal's current editors on any topics of their choice. The result is a unique collection of articles representing diverse areas in biomathematics. Some of these are reviews or perspectives while others describe original, cutting-edge research. The contributions span a range of topics, and we decided to organize them coarsely by the scale of their application, from molecules to populations, and finish the special issue with some new methodological advances.

Thus, beginning at the molecular scale, Santiago Schnell and colleagues investigate ligand-receptor binding and characterize the validity and accuracy of the so-called pseudo-first-order approximation of the process. Bridging the molecular and organismal scales, Anmar Khadra and collaborators propose a bistable switch mechanism through which the actions of the immune system distinguish between healthy and autoimmune states. Johnny Ottesen and a colleague focus fully on the physiological scale of the human organism. They describe patient-specific modeling of the endocrine stress-response system and associated disorders that contribute to clinical depression. Several contributions focus on the much larger scale of populations. Mick Roberts studies epidemiological models whose parameters are subject to random fluctuations. In a similar context, Theodore Kypraios and colleagues review stochastic models of epidemics and provide a tutorial to Bayesian inference for such models using approximate Bayesian computation. Jorge Velasco-Hernández and collaborators continue the theme of epidemiology, investigating the spread of Dengue fever when two serotypes of the virus are present in the population, along with the effectiveness of different vaccination scenarios. Abba Gumel and collaborator discuss the spread of malaria, using a non-autonomous age-structured model to investigate how variations in temperature and rainfall affect the transmission of the disease. Also addressing structure within a disease population, Zhilan Feng and collaborators focus on meta-population models with multi-level mixing that assume preferential contacts between family members. Finally, three articles address methodological issues. Richard Bertram and Jonathan Rubin review methods of analysis for biological models with multiple time scales and highlight some unusual behaviors that can occur in such models. Santiago Schnell and colleagues review how timescales can be estimated in nonlinear dynamical systems. Last but not least, Eberhard Voit and a colleague propose a novel method for the data-based design and analysis of nonparametric, nonlinear compartment models.

We hope you will enjoy this special 50th anniversary issue of the journal and join us as we embark on the next fifty years of *Mathematical Biosciences*.

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