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# Mathematical Biology: A Personal Journey

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I've always loved watching the patterns of change: how a fern unfolds, how the sky changes as the sun sets, how a fugue evolves. I've always loved the patterns in numbers: how they pile up in a particular way as they are added together, how simple geometric shapes can be scaled and glued together to make organic fractals, how simple rules applied repeatedly can result in fabulously intricate constructions. I can point to some early milestones and guides along my current journey: my father brought home conic sections for us to play with, instead of the usual rectangular blocks; I found a slide-rule gift-wrapped under the tree one Christmas; my uncle Jack told me about Scriabin's fascination with color, number and musical tones. I asked myself: can numbers describe everything? Are music, mathematics, growth and evolution articulations of the same laws? These questions led me first to a serious love affair with music, a ten-year career as a profes-

sional 'cellist, then an undergraduate math degree at Berkeley, followed by a Ph.D. from Stanford in ergodic theory. Eventually I found myself as an Assistant Professor at Pomona College where I tried to fill the shoes of my mentor, Ken Cooke, a pioneer in mathematical biology.

One of the classes I taught that first year was "Mathematical Modeling". I asked Ken Cooke, my mentor and the wonderful mathematician whose shoes I would try to fill, "What am supposed to do in this class?" He gave me plenty of concrete advice, but warned me that "you'll see: mathematics can be used to solve just about everything". I learned along with the students, who modeled swimming fish, the collapse of civilizations and segregation in churches.

My department chair walked into my office one day: "We just got a call from an alum, Tom Starbird<sup>1</sup>. His oncologist needs an explanation of chaos theory." New at the job and eager to please, I hiked it over to St. Vincent's Hospital in downtown L.A. where a dozen doctors in white lab coats were gathered in the basement cafeteria grappling with a paper describing a mathematical model of cancer growth. They were stumped by descriptions of growth dynamics that deviated from the simple exponential growth models they had learned in medical school. Eager learners, they quickly picked up the ideas of self-limiting growth and competition models. Won over by the group's enthusiasm, I joined M.O.M. (Mathematics Of Medicine), a study group led by Dr. Charles Wiseman, and fairly soon we came up with our own mathematical models of tumor growth. We met monthly for over eight years; along the way we explored scaling laws (using data from Chuck Wiseman's nephew's pet lizards), model selection, Bayesian analysis, agent-based models, network analysis and experiments on binding kinetics. In 1999 I asked my colleague from Harvey Mudd College, Lisette de Pillis, to join us. I believed that Lisette's numerical expertise would be valuable in implementing and analyzing mathematical models of cancer dynamics. I was right: we have been close collaborators ever since.

From the outset, the focus of M.O.M. was the relatively new field of immunotherapy: harnessing the immune system to fight a tumor. I knew that

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<sup>1</sup>Math major, Pomona College, Ph.D. in mathematics from UC Berkeley, followed by a long and distinguished career at NASA's Jet Propulsion Laboratory.

our models would be meaningless unless we could communicate with medical practitioners outside of M.O.M. We decided to present our latest model at the Society for Biotherapy's annual meeting. At this conference I met James Mulé, now a Vice President of Applied Science at Moffitt Cancer Center. Through his encouragement, I began to believe that we mathematicians *can* make a real contribution to the development of clinically relevant treatments. Moffitt now has an Integrated Mathematical Oncology Center, populated by math biologists. Way to go, Jim! Around this time (2005), we were also able to publish one of our models of tumor-immune interactions in *Cancer Research*, "the most frequently cited cancer journal in the world"<sup>2</sup>. In this paper, we present a model that Chuck Wiseman has dubbed the "DePillis-Radunskaya Law". I am proud of this paper because, despite the differences in communication styles between the mathematics world and the medical world, we persisted in our attempts to adapt, and were ultimately successful in appeasing the referees. Since 2009 *Cancer Research* makes an intentional effort to publish articles in *Mathematical Oncology*. Way to go, *Cancer Research*!

A few years earlier, personal reasons led me to New Zealand. I immediately fell in love with Aotearoa, the "Island of the Long White Cloud", and decided to spend my next sabbatical there. And so began a fruitful collaboration with Professor Sarah Hook, an Immunologist at the University of Otago. Sarah has taught me about the deep mysteries of the immune system, and the difficulty in finding a quantitative description of the complex immune cascade. We have worked together for the past 10 years on models of immune kinetics, and on the design of effective cancer vaccines. In 2007, Sarah and I organized a workshop at Otago focusing on articulating and solving mathematical problems in biomedicine. This workshop has led to many new collaborations, most recently studying the delivery of drugs through the blood-brain barrier. My new collaborators include pharmacologists, neurologists, biochemists and hematologists. I have spent two sabbaticals at Otago, and during each visit I discover new questions in biology and medicine that can be attacked with a mathematical toolbox.

I am attracted to mathematical biology because it is collaborative and interdisciplinary by necessity. I am constantly learning new things and meeting people in fields I know very little about. While I started out in dynamical systems, I have had to learn programming, statistics, and machine learning. I use stochastic, deterministic, continuous and discrete models. I use ODEs, PDEs and DDEs - whatever it takes. I love brainstorming with colleagues about approaches to a problem, and then implementing some of those approaches. I want to share this excitement with everyone, so I spend a significant amount of time working with younger mathematicians. I am fortunate to work each year with talented undergraduate researchers: many of them are motivated by the biological problems to learn new mathematics. One of the most rewarding experiences I have had was organizing WhAM!, a workshop for Women in Applied Mathematics (the "h" is silent). This five-day workshop was supported by the Institute for Mathematics and its Applications (IMA) in 2013. My co-organizer, Trachette Jackson, and I brought together 47 women mathematicians to work on 9 problems in biology and medicine. A monograph containing results from the workshop has just been released by Springer<sup>3</sup>. The feedback from the group was: "fun and fruitful". Since then, two more WhAM! workshops have been held, and I hope that there will be many more.

Most problems in mathematical biology are hard. There is too much data, but not enough of the right kind. The questions are too big, and the tools too clumsy. There is a huge gap between the vocabulary of the biologist or the clinician, and that of the mathematician. There are unavoidable uncertainties and as many variants as there are individuals. But these challenges make our lives more exciting: there are so many problems, so many things to try! I encourage you to sit down with a biologist or a doctor, particularly someone who insists that they "forgot all the maths they ever knew". Take your time: you will both come out the wiser. I am grateful to those who had patience with me.

For more information see  
<http://pages.pomona.edu/~aer04747>

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<sup>2</sup><http://cancerres.aacrjournals.org/site/misc/about.xhtml>, August, 2015

<sup>3</sup>*Applications of Dynamical Systems in Biology and Medicine*, Springer (2015) ISBN: 9781493927821