Helen Moore Interview

Helen Moore *is Associate Director of Quantitative Clinical Pharmacology, Bristol-Myers Squibb in Princeton, New Jersey.*
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Diaz-Lopez: *When did you know you wanted to be a mathematician?*

Moore: I have loved math since I was young. Solving challenging problems gave me a rush. I loved competitions because I got to think about math outside the standard curriculum. My high school, North Carolina School of Science and Mathematics (NCSSM), had an active math club, and we did competitions every other week. I was disappointed to get to college and find out there was only one math competition per year, the Putnam Exam. I started my own math contest my first year in college (University of North Carolina at Chapel Hill), which lasted beyond my graduation. Four contests per semester, a week to solve the problems, with book prizes for top scorers awarded each year by the math department.

Diaz-Lopez: *Who encouraged or inspired you?*

Moore: Although my parents did nothing related to academics or mathematics, they supported my academic endeavors and allowed me to move away from home at the age of sixteen to attend NCSSM. My teachers and classmates at NCSSM provided an enriching experience and continue to do so. Beyond the classes (math, English, physics, Russian, music,…), it was an incredible experience to live with others who loved math and learning. While in graduate school (Stony Brook University), I met a group of women in other departments (physics, astronomy, computer science, and geology) and made great friends. In academic jobs, I would find a "study buddy" to discuss my research/progress with. I co-founded a book group of women scientists that continues today, more than ten years later. Those friendships and others helped me when times were tough.

There were also teachers, before high school, during high school, in college and in graduate school, who encouraged me. If you were ever a teacher of mine and you are reading this, please accept my deep gratitude! I try to honor their contributions by paying it forward. I give a lot of talks to high school and college students about the mathematics used in medicine.

Diaz-Lopez: *How would you describe your research to a graduate student?*

Moore: I am using control theory to optimize combinations of therapies for a model of in-host leukemia-immune dynamics. We have so many therapies we could combine, we can't do all the studies necessary to explore those combinations. For example, suppose there are twelve molecules in development, and we will test one dose level of each. Even if we administer just two molecules at a time, we have twelve choose two, or sixty-six, experiments to run. But in fact, we want to test several dose levels of each molecule, with different intervals between the doses, and we also want to study three molecules at a time. We don't have the time or other resources to run that many studies. So we will use mathematical modeling to help decide which compounds to test together and how much and how often to dose (refer to Figures 1 and 2 for examples).

We (and some other companies) also have a group that builds large ODE systems models (quantitative systems pharmacology, or QSP, models) to identify potential drug targets, to predict toxicity, and to explore mechanistic hypotheses. Semi-mechanistic disease models and model-based meta-analyses are additionally used for prediction purposes. People doing this work often have a math or engineering background, but have also learned a lot about a disease area.

More commonly, others doing quantitative work in biopharma are using more-traditional pharmacometrics: they are fitting nonlinear mixed-effects models to data with various algorithms, testing for covariate relationships with a variety of functional forms, using a Schwarz-Bayesian or other criterion to select a model, bootstrapping parameter estimates, cross-validating model predictions, simulating

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outcomes for different dose regimens, and answering questions that may arise from the internal team or a regulatory agency. Interpreting the quantitative results is important, so pharmacometricians need a good understanding of the techniques behind the results. There are also plenty of technical gaps in the field, and opportunities for numerical and theoretical contributions.

In biopharma, everything we do is driven by questions about treatments. For example, can we improve our predictions of which patients will respond to a particular therapy? At Bristol-Myers Squibb, we are collecting a tremendous amount of data, and using machine learning to make these predictions either before or soon after a patient starts a therapy. Because such questions drive the quantitative approach, modelers at the company need to have broad expertise across areas. The areas that excite me the most include: systems modeling, multi-scale modeling issues, error propagation, numerical analysis, system and parameter identifiability, sensitivity analysis, control theory, fixed and random effects modeling, optimization, statistical modeling, and machine learning.

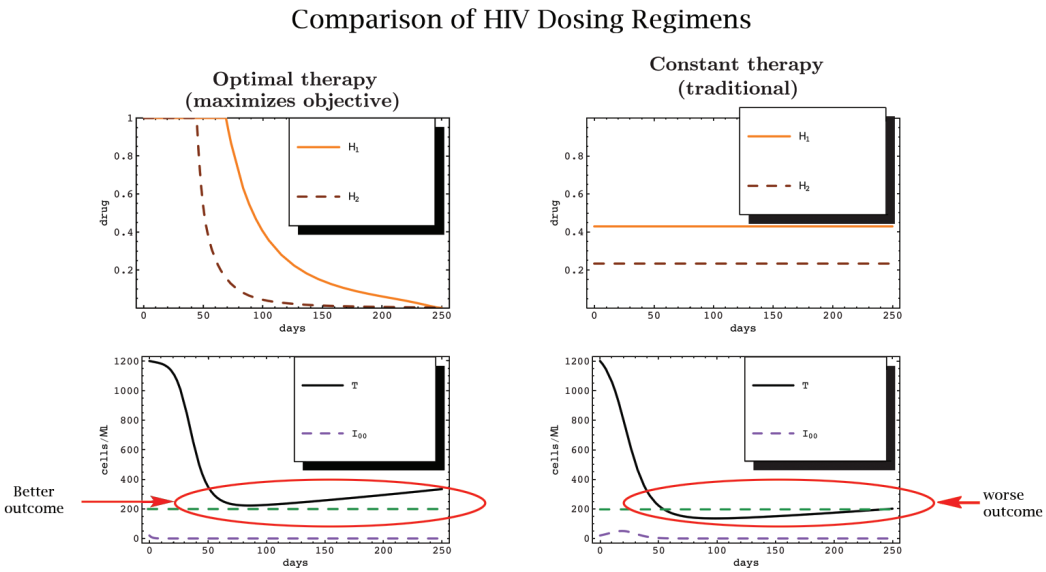

Figure 1. Multi-drug resistance was incorporated in a dynamical system model for HIV-immune cell interactions with five cell populations. Treatment goals were quantified in an objective functional, and control theory applied to this model predicted optimal regimens for combinations of therapies. The upper left shows one of the optimized regimens, and the upper right shows a constant dosing regimen. In the lower panels, the black curves represent a type of healthy immune system T cell ("the good guys"). The purple dashed curves represent cells infected by HIV ("the bad guys"), and are controlled under both regimens. With the optimized regimen, the healthy T cell curve stays above 200 cells/μL, the clinical definition of AIDS, and is 75 percent higher at the end of treatment than the healthy T cell curve on the right resulting from the constant dosing regimen. Please refer to: `www.ams.org/books/conm/410/conm410.pdf` **for additional details.**

Diaz-Lopez: *You have worked in both academia and industry. How do you compare them, and what are the major challenges you have faced in each?*

Moore: In academia, I had a lot of freedom to decide what I would work on. The NSF [National Science Foundation] grant I got was important for my career, because it allowed me to travel to conferences, to buy a computer and software, and to have some time off from teaching. But grants can be time-consuming to apply for and hard to get. Additionally, when I shifted from pure mathematics to applied mathematics, a big challenge was getting enough appropriate data to be able to collaborate well with other academics.

In industry, we have a wealth of data, and decisions about resources are made much more quickly. When I first entered industry, I received modeling project assignments. Although I had flexibility in exactly how I answered the questions asked, I needed to meet the goals and timelines set by others. But now I give internal presentations to explain the ideas I have, and to pitch proposals for ways I could use mathematics to solve high-priority

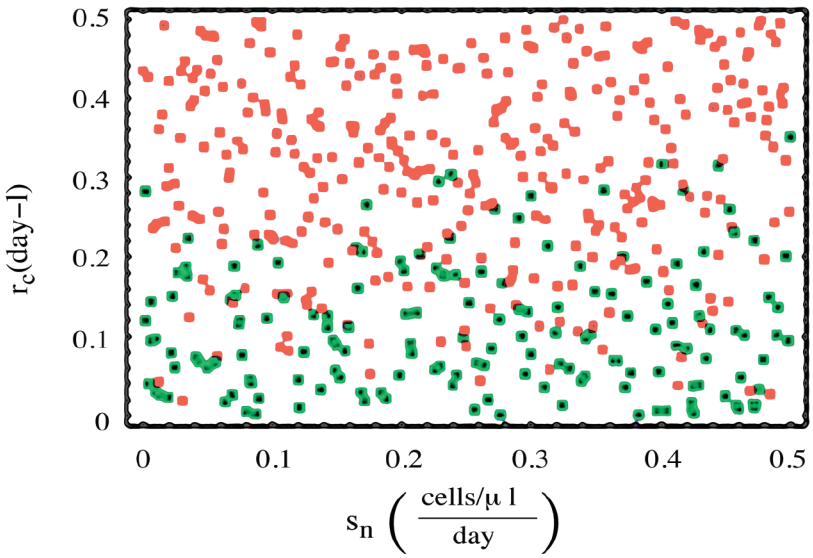

Figure 2. In-host leukemia-immune cell interactions were modeled by a dynamical system with 12 parameters. Five hundred sets of parameter values were selected. The squares in this plot represent the sampled values of the parameters r_c and s_n; their color indicates whether the leukemic cell levels rose above 20,000 cells/μL (orange) or stayed below that (green). The pattern of the colors suggests that changes in r_c values could affect whether the leukemia levels stay below the threshold, and that the value of the parameter s_n does not affect this outcome. Please refer to `www.sciencedirect.com/science/article/pii/S0022519303004454` **for statistical tests of significance.**

questions. My work absolutely must be understood by decision-makers whose expertise is different from my own. I am fortunate to have a manager and others in our department and company who support my ideas.

Companies and groups within them differ in their attitudes toward publications. Generally poster presentations at conferences are valued. However, the only articles I have been able to publish so far while in industry are those I worked on in the evenings and weekends with academic collaborators. I am optimistic that I will have publications based on my industry work in the near future.

Diaz-Lopez: *What advice do you have for graduate students?*

Moore: For someone who wants to do the kind of work I do, I recommend: get a masters degree in statistics along with your PhD in math; learn a programming language such as R or MATLAB; and after finishing your PhD, do a postdoc in an experimental or engineering lab. If there are certain types of jobs you are interested in, look at the current openings to find out exactly which skills and experience companies are looking for. You will need to get both the quantitative/theoretical training plus learn about biology/diseases and have experience putting those together. In my opinion, the connection between mathematical modeling and data is statistics, so statistical knowledge will be expected of a modeler.

Many have said the best way to get a job in industry is to already have a job in industry. A summer internship at a company is a good way to get that industry experience. To look for internships or regular openings, search SIAM [Society for Industrial and Applied Mathematics] Jobs, and look at individual company web sites. You can find lists of biopharma companies by size and region. Some internship and postdoctoral openings get posted to the Society for Mathematical Biology and SIAM Life Sciences email lists. Attend a conference or local meeting in the field you are interested in; in my field that would be the American Conference on Pharmacometrics or one of the affiliated regional meetings. Hand out business cards, post a profile with a photo on LinkedIn, and send link requests to people you meet with a reminder about how you met. You could also work with a recruiter who specializes in your field; you can find one by searching online.

Diaz-Lopez: *All mathematicians feel discouraged occasionally. How do you deal with discouragement?*

Moore: I go running and talk with friends and family. When I lost my husband to cancer, that's how I survived. Now I feel like I can survive anything.

Diaz-Lopez: *If you were not a mathematician, what would you be?*

Moore: I would still want to do something creative; I might be a guitarist/singer/songwriter or a writer.

Diaz-Lopez: *If you could recommend one lecture (book, paper, article, etc.) to graduate students, what would it be?*

Moore: I highly recommend Peter Bonate's book *Pharmacokinetic-Pharmacodynamic Modeling and Simulation*. It is the most mathematically informative work in our field, and Bonate points out "open problems" by discussing strengths and weaknesses of current methods.

Diaz-Lopez: *Any final comment or advice?*

Moore: If you have the desire to help people, working in the biopharma industry is a great opportunity to do that. We could use more people who are really bright and creative, have strong mathematical or quantitative backgrounds, and are willing to learn about and work on problems in biopharma.

Credits

Page 768 photo, courtesy of Helen Moore.

Figure 1 adapted from Gu and Moore, Optimal therapy regimens for treatment-resistent mutations of HIV, *Contemp. Math.* 410 (2006), 139–151.

Figure 2 adapted from Moore and Li, A mathematical model for chronic myelogenous leukemia (CML) and T-cell interactions, *J. Theor. Bio.* 227 (2004), 513–523.

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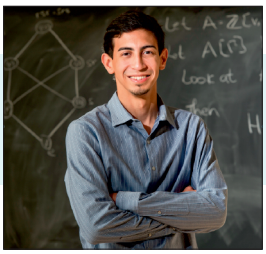

Alexander Diaz-Lopez, having earned his PhD at the University of Notre Dame, is now visiting assistant professor at Swarthmore College. Diaz-Lopez is the first graduate student member of the *Notices* Editorial Board.