

Mathematical Biology: My Personal Journey

Urszula Ledzewicz



One of the amazing things I learned about mathematical biology is that one can join this friendly crowd of wonderful people at almost any stage of one's career. As long as you can bring to the table some tools, which can help in understanding the problems that the discipline is struggling with, you will be welcomed with open arms. My good friend, Antonio Fasano from the University of Florence who joined mathematical biology from physics once said (a phrase I often like to quote) that we all have our "toys", which we like to play with and apply to the biological models.

In my case, it took a long time before my toys were used. I came to the United States from Poland known to be "the land of Banach", where most Ph. D.'s in mathematics are very abstract and theoretical. I would still be working on Banach spaces today, had I not met a smart German guy from my field, Heinz Schattler. Once I realized how much I can learn from him and how much time we will have to spend together to accomplish it, marriage was the only reasonable option!

Thus we became spouses/ collaborators and it is hard to believe that it still is working twenty years later. Now, where is the mathematical biology? you ask? Be patient, the best is still yet to come. And it came in the person of our colleague Andrzej Swierniak. In 1996, already established in our field, Heinz and I organized a session at the Second World Congress of Nonlinear Analysts in Athens and invited Andrzej as one of the speakers. He brought a fresh breeze of biology into our highly abstract session by talking about compartmental models for chemotherapy. What attracted us to these problems was that they were not fully solved and

the tools of the geometric optimal controls seemed to be particularly a good fit to answer some of these questions. Once we got started, there was no way out and the rest was history.

The next stepping-stone was a workshop on cancer modeling in 2003 organized by Avner Friedman and Marek Kimmel at the then newly founded MBI at Ohio State University in Columbus. The workshop was a great eye opener for us, aside from the embarrassment of being the only speakers with handwritten slides; we had a great time and learned a lot! We saw how mathematicians and biologists interact (and "fight" in a positive sense). The heated discussions were sometimes longer than the talks, something we have never seen at our optimal control meetings. Overall, the excitement of that crowd was absolutely contagious. I loved it and I wanted to be "in". Heinz had no choice but to follow along!

Now, more than 100 workshops /conferences/ seminars (hard to believe, but I just counted), over 80 publications and numerous NSF grants later (many thanks to the NSF for all the support!), we reflect back on some of the more special moments. Like in 2009 during the workshop on cancer modeling organized in the beautiful Estoril by Adélia Sequeira over the fish dinner, I got an idea to put together a similar workshop in Tel Aviv with Eugene Kashdan. Heinz's shy comments - that it would be somewhat crazy to organize an event in a country I have not been to, with the guy I have only just met - convinced me to go ahead! With the help of some friends like Avner Friedman and Aziz Yakubu it worked out great. When Avner and Aziz told me shortly after about this amazing scientific and educational place in Muizenberg, South Africa called AIMS on the beach I knew that we just found a place for the sequel. Again I was working in an unknown territory (thanks Google Earth!), but with the help of my co-organizer Jacek Banasiak, placing the workshop in South Africa turned out to be very rewarding.

While involved in the bio-math events, we still remain quite active in our original field of optimal control and try to recruit some of our colleagues to mathematical biology by showing them how much we enjoy it, but also that there are interesting problems out there waiting to be resolved. We can report some success here like recruiting our friend Helmut Maurer, a numerical guru, whose simulations of our results were found particularly attractive by graduate students. Work with them on the bio-math topics has

been particularly rewarding and we think we managed to “infect” a number of them with the enthusiasm for continuing the research in this field.

Working on the boundary of two disciplines has a lot of advantages. You have twice as many collaborators and friends (hopefully not twice more enemies), twice more conference invitations (hopefully with all expenses covered) and it is easier to impress people (not a weak point). We have been extremely fortunate with all the categories, particularly with collaborators who became friends and the other way around. Some collaborations could make a full story by themselves. I still recall waiting in the hotel in Milan for Alberto d’Onofrio from the European Institute of Oncology with whom we had collaborated earlier through e-mails for a couple of years and wondering how he looked like which felt like a blind date (no Facebook at that time). On the other hand, Ami Radunskaya, whom I invited to a conference in Marrakech in 2006, on the way to Morocco, picked me from a huge crowd of people while connecting through Heathrow airport saying, “the way you are dressed, you must be Urszula!” Till today, I still wonder how I should read this. My friendship with Ami led to a workshop in Dunedin, the most southern tip of New Zealand, in 2007 where we were lured by the promise to see penguins on the beach. But any time we went, we were far too noisy... Finally we saw them five years later during our Cape Town workshop!

As for our research in math biology, it actually also had its own interesting journey. Our very first result was to show that for the cell-cycle specific chemotherapy model it is optimal to apply the drug protocols following so called “bang-bang controls”, i.e., apply what in medical terms is called MTD (maximum tolerable dose) with rest-periods. We were very proud of this little, but very nice result, which, in principle, confirmed what is the common medical practice. Later, when we started working on more complex models that involved drug resistance, angiogenic signaling and combination treatments including radio-, chemo or immunotherapy, etc., more complicated solutions started appearing where the drug is given differently than as MTD and followed analytically or numerically calculated protocols of varying lower doses, which, in control theory, are called “singular controls”. Although these were nice mathematical results, we were not very convinced about their medical relevance, since we did not think

that anybody would administer drugs this way. Then it happened! We were both invited to a medical workshop on Tumor Metronomics to Tufts Medical School organized by Philip Hanhfeldt and his MD collaborator Giannoula Klement. We were included precisely because they thought that our low dose solutions could shed some light on the Metronomic chemotherapy, which is becoming more and more of interests to the medical community. In a heartbeat we joined the amazing crowd of biologists, MDs and mathematicians who fight for the chance to develop low cost therapies that can be of crucial importance in providing treatments in many underdeveloped countries where fancy, expensive, new drugs are simply not an option. I am writing this story here in Sydney (as you see from my photo, it is summer down here!) a day after Eddy Pasquier, from the Children Cancer Institute Australia, and I jointly held a lively discussion panel on Metronomics at the Workshop on Tumor Immune System Dynamics organized by our friends Amina Eladdadi, Peter Kim, and Dann Mallet. We have even made plans for a full Metronomics workshop in some nice country, which I will still keep as a secret since we do not want to scare our friends in the funding agencies. So the journey continues and it is becoming more exciting than ever with more new friends and more challenges lying ahead...

Selected Publications

(Full list: www.siue.edu/~uledzew)

- (with H.Schaettler), Geometric Optimal Control, Theory, Methods and Examples, *Springer-Verlag*, 2012 (640 pages).
- (with H. Schaettler), Optimal and suboptimal protocols for a class of mathematical models of tumor anti-angiogenesis, *J.Theor. Biol.*, 252, 2008, pp.295-312
- (with A. d’Onofrio and H. Schaettler), Tumor Development under Combination Treatments with Anti-Angiogenic Therapies, in *Mathematical Methods and Models in Biomedicine*, Springer-Verlag, (editors: U. Ledzewicz, H. Schaettler, A.Friedman, E.Kashdan), October 2012, pp.311-337.
- (with H. Schaettler), Multi-Input Optimal Control Problems for Combined Tumor Anti-Angiogenic and Radiotherapy Treatments, *J. Opt. Theor. Appl.*, (2012), Vol.153, pp.195-224, 10.1007/s10957-011-9954.
- (with M. Faraji and H. Schaettler), Optimal Controls for Mathematical Model of Tumor Immune Interactions under Targeted Chemotherapy with Immune Boost, special issue of *Discrete and Continuous Dynamical Systems*, Series B (A. Eladdadi et al. editors), Vol.18, June 2013, to appear.