My Journey into Mathematical Biology and Beyond

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I started my career as a physicist, and was fascinated by the analysis of complex systems and emergent phenomena. I already had a couple of papers published, but then had to quit my PhD program due to a problematic pregnancy. After my son was born and all was well, I started looking for a new research topic. Because I was interested in complex systems and algorithms, I broadened my search to also include the chemistry and mathematics departments. In the math department of the Weizmann Institute of Science, I met two mathematical biologists who have influenced my career since: Zvia Agur, who offered me a part-time job so I can try doing math biology and see whether I like it, and the late Lee Segel, who ended up being one of my PhD supervisors.

Moving from physics into biology was not just a matter of overcoming a language barrier - it was a culture shock. Biology in the 1980s was not an exact science, and nobody in biology believes in math - some did not even believe in statistics! I could forget about measuring anything to the seventh decimal point. What was challenging and intriguing, however, was the staggering complexity I discovered. I decided that biology is fractal: no matter what scale you looked at, and you found just as much complexity as in the higher scale. Besides, my field of research was immunology, and the immune system is one of the most complex systems in our body.

My work in the field started with modeling lymphocyte development. Prior to my PhD work, only the pathways of T cell development were known, but there was no quantitative framework within which one could evaluate changes to the dynamics of these pathways in aging or disease. I was the first to create, simulate and tune mathematical and computational models of the population dynamics of T cell development in the thymus. These studies led to the discovery of feedbacks in T cell development, that is, the positive and negative effects exerted by mature T cells on developing thymocytes. Further studies led to the discovery of blind homeostasis in peripheral T cell populations - that is, the fact that the system only "senses" decreases in the total number of T cells, but does not distinguish between decreases in CD4+ and CD8+ T cell numbers. When I presented these studies in conferences in the early 1990's, it became clear that they have serious implications for the dynamics of human immunodeficiency virus (HIV) infection. They explained why pediatric infections, occurring while the thymus is still developing and growing, develop so much faster and are so much more severe than adult infections, and why the CD4:CD8 ratio does not properly recover under antiviral therapies. These conclusions have revolutionized the way the within-host dynamics of HIV infection are treated by modelers - who could no longer ignore the role of the thymus, the feedback from mature T cells (or lack thereof during HIV infection), and the blind homeostasis, in exacerbating the reduction in the CD4:CD8 ratio during the infection.

Further work from my group over the years created the first models for B and NK cell development and maturation, with interesting discoveries. The models were later applied to understand the reasons for reduced lymphocyte production in aging, or the role of key molecules that affect lymphocyte production. Already in the mid 1990's, however, I realized that the unique genetic and cellular processes that create and shape lymphocyte repertoires are even more interesting. I became interested in the process of antigen receptor gene rearrangement, which creates the immensely diverse T and B cell repertoires: I asked how gene segments are chosen for rearrange-

ment and how the structure of the V(D)J segment locus affects the resulting repertoire. The studies of these questions led to the discoveries of DNA order biases in gene segment selection for rearrangement, the delineation of the parameters governing this process, and the formation of a quantitative theory of repertoire selection. All this work - done over several years in Los Alamos, NM and Princeton, NJ - has earned me a tenure-track position in Bar-Ilan University, where I established my research group in 1999. As the systems I studied became more complex and the work had to integrate genetic, molecular, cellular and repertoire-level features, I found myself doing what has later become known as multiscale modeling. Among such models, my group and I developed models for the humoral immune system and isotype class switch recombination. During an immune response, B cell repertoires undergo complex genetic modifications - somatic hypermutation (SHM) of their antigen receptor (immunoglobulin, Ig) variable region gene, accompanied by antigen-driven selection, and isotype class switch recombination (CSR). While the dynamics of the humoral immune response have been extensively modeled prior to my work, I was the first to provide an explanation of the phenomenon of repertoire shift, that is, why secondary (memory) B cell responses are dominated by different clones from those dominating primary responses.

The latter modeling work has sparked my interest in Ig gene lineage-tree based analysis of B lymphocyte clonal dynamics during the response. The idea was suggested by Martin Weigert, my supervisor in Princeton, and my group was the first to develop and test quite a few of the current methods for analysis of the information thus gained. We have applied these methods in studies of the alterations in B cell clonal dynamics in several situations, including aging, chronic inflammation, autoimmune diseases and B cell malignancies. My group also created the first models for the development of natural killer (NK) cell repertoires, from receptor gene expression to selection of functional, non-harmful cells. Going down to the molecular level, we developed the first computer simulations of the dynamics of NK cell immunological synapses.

Thus, over the years, I have carved my "niche" of research - the analysis and modeling of lymphocyte repertoires. The recent development of high-throughput methods for repertoire data collection - from multicolor flow cytometry through single-cell imaging to deep sequencing - presents us now, for the first time, with the ability to analyze and compare large samples of lymphocyte repertoires in health, aging and disease. This has a huge potential for identification of subtle defects or changes in immune function, and developing between vaccines, better interventions in autoimmune diseases and malignancies, and better ways to rejuvenate the immune systems of elderly people. The exponential growth of these datasets, however, challenges the theoretical immunology community to develop methods for data organization and analysis. This task is orders of magnitude more difficult than standard sequencing and genomic analysis. First, there is the repertoire complexity itself, which means that one cannot use "reference genes" in the analysis, and the available computational tools are of no use for theoretical immunologists; research groups must struggle to create the correct experimental controls and computational tools, as in the software tools we developed for Ig gene sequence data analysis. Only a few research groups worldwide currently address these challenges. Thus, a central theme in my research plans is to keep developing these methods, and collaborating with leading groups, in order to remain in the cutting edge of Ig gene research.

When I started working in this area in the beginning of 1991, molecular markers and methods for investigating lymphocyte development and behavior were just being developed, and the human genome project was in its infancy - it has just presented as a possible plan to the US congress. During the years of my work in the field of theoretical immunology, I have seen it grow from a small group of interested individuals to a rich, active and challenging research field, whose members are becoming better integrated within the general immunology community. Theoretical immunology is still growing and has not yet fulfilled its potential, however. Thus, one of my career goals - aside from research - is to continue helping integrate theoretical work within all subfields of immunology. My choices of activities in professional society boards, conference and workshop organization, review and consulting boards reflect this career goal.

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