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Immigrants in immunology: the benefits of lax borders

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Abstract

The field of immunology has a long history of illuminating fundamental biological processes of critical importance to human health. From an outsider's perspective, the questions are profoundly philosophical and the experimental approaches are elegantly precise. Yet immunology can also appear impenetrable. Here we recount the experience of two graduate students from the fields of ecology and computer science, who have immigrated into immunological terrain attracted by systems-level questions. We argue that such migrations enrich the field of immunology, and that cultural and institutional changes are needed to promote more interdisciplinary explorations.

Border crossing

The last twenty years have witnessed extraordinary innovations in the quantity and complexity of information that can be collected about biological systems. Chief among these has been the revolution in high-throughput sequencing, generating astronomically large datasets that necessitate proficiency in bioinformatics and statistics to handle and analyze the vast amounts of information. The flood of genome sequences has revealed how much animals share in common, including the conservation of their immune systems. In parallel, we're coming to realize the enormous diversity and complexity of microbial life that inhabits the surfaces of all macroscopic organisms. These advances have transformed the nature of questions that can be posed about immunological systems. Rather than studying the interaction of a single immunoglobulin with a single antigen, it is now feasible to determine the entire immunoglobulin repertoire of an animal (for example for the model vertebrate, zebrafish, which has only 300,000 total B cells (Weinstein *et al.* 2009)) and enumerate its corresponding associated microbial communities (Roeselers *et al.* 2011). In other words, we can now study the immune system from a systems biology perspective with a complete catalogue of the component parts.

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We are fascinated by the reciprocal interactions between an organism's immune system and its microbiome, which we approach from the varied perspectives of a graduate student in ecology and evolution (Keaton), a graduate student in computer science (Emily), and a professor in host-microbe systems biology (Karen). Below, we share our individual thoughts on how our backgrounds shape our approaches to immunology and offer advice for lowering the barriers for entering the field of immunology.

Keaton: the immune system as a mediator of species interactions

When I think about the immune system (and exclude the fascinating phenomena of auto-immune disease, allergic reaction, and graft rejection) I think of it as a mechanism for species interaction. This is what, as someone with a background in community ecology, attracted me to studying how the host's immune system influences, and is influenced by, the microbial communities living in, on, and around the host.

When most people think about immunity, they think about fending off germs. Indeed, it's hard to argue that the primary driver behind the evolution of the immune system is anything other than as a defense against pathogens. The Red Queen Hypothesis for the evolution of sex, for example, hinges upon the ability of sexual recombination to maintain MHC diversity for combatting pathogens and parasites (Hartung 1981). From a community ecology perspective, pathogen-host interactions can be modeled almost identically to predator-prey interactions. The immune system, as a whole, is a variable phenotype that can determine the strength of the effect of a pathogen on a host in the same way that thick armor or great speed can mediate the effect of a predator on prey.

Although it's easy to argue that immunity most likely evolved as defense against pathogens, it's more difficult to invoke this argument in explaining the impetus for the evolution of adaptive immunity. One can provide “just so” stories about how vertebrates, being more complex, might have to deal with more pathogens, but the data do not provide strong support for this reasoning. Instead, as Margaret McFall-Ngai (2007) has argued, the vertebrate adaptive immune system may have evolved to manage the significantly more complex commensal microbial communities associated with vertebrates versus invertebrates, communities that confer extraordinary metabolic capacities to adapt to different and changing food sources. By cultivating microbial communities via the immune system, and other mechanisms, the host functions simultaneously as an active community participant as well as the “abiotic” component of the ecosystem, creating a unique situation that is very intriguing to an ecologist.

An obvious extension of the community ecology perspective is to view microbial pathogens as invasive species in the host-microbiota ecosystem. For example, *Salmonella enterica* Serovar Typhimurium thrives on inflammation in the intestine and actually requires it to overcome the competition of the resident microbiota (Stecher 2007; Chung *et al.* 2012). Presumably, *S. enterica* has evolved to stimulate inflammation and withstand this harsh environment that perturbs resident commensals, much as fire-resistant grasses can invade forests by increasing the frequency of fires that remove the trees with which they compete (Brooks and D'Antonio 2004). Unlike the forests, however, a host has a vested interest in

determining which microbial species win ecological competitions. From this perspective, the adaptive immune system can be viewed as playing an active and important role as an ecosystem engineer that shapes the diversity of the gut microbiota (Kawamoto *et al.* 2014). For example, IgA repertoires, in conjunction with TLR5, can pressure bacterial cells to down-regulate production of flagellin, making them less mobile and perhaps shifting the competitive landscape (Cullender *et al.* 2013). From my perspective, ecological concepts like community resistance, competition, invasion biology, and ecosystem engineering, have been useful for framing discussions of pathogen infection and modeling the different roles the immune system can play in the interactions between the host, its microbiota, and pathogens.

These immunological processes are fascinating to me, but as an ecologist attempting to learn immunology, I have been struck by the cultural rigidity with which subdivisions of immunology seem to be maintained—people tend to identify themselves as studying either innate or adaptive immunity, and within adaptive immunity people study either B cells or T cells. While these divisions make sense historically and are often necessary to tackle teaching the complexity of immune systems, when it comes to the burgeoning field of host-microbe interactions, it seems limiting to focus exclusively on a specific cell type in the system, rather like an ecologist only considering the effect that soil pH has on plant communities and ignoring the role of available nitrogen.

Another puzzling limitation in the field, apparent in all immunological textbooks, is the almost exclusive focus on the mouse as a model for human immunology. As an ecologist, I am accustomed to considering organismal diversity, placed within a phylogenetic framework, to understand biological processes. I first assumed that the mouse was featured in my textbooks because it served as an exemplar of all animal immune systems. However, once I started my graduate research on zebrafish immunology, I was shocked to discover how different and diverse adaptive immune systems can be between different vertebrate species, and even between different species of fish (Fillatreau *et al.* 2013). I believe that teaching immunology through the lens of phylogenetic history would better emphasize the fundamental properties of immune systems that are highly conserved and would highlight species-specific specializations to solving common immunological problems.

Emily: the immune system as a selective sampler of sequence space

As a computer scientist, I was drawn to immunology by the computational challenges of analyzing lymphocyte receptor repertoires. At first glance, libraries of B and T cell receptor genes would seem to present challenges similar to the analysis of other sequence data such as 16S ribosomal genes from bacterial communities. Both data types have a skewed distribution where some sequences are very common and others are unique. However, an appreciation of the biological processes behind these skewed distributions dictates different computational approaches. Somatic recombination and hyper-mutation result in the potential for each B or T cell to have a unique receptor gene sequence. Even though this exploration of sequence space is hypothetically limitless, it is constrained by the rate of mutation from the germline sequences and the structural limitations for generating a functional receptor. Knowledge of the germline sequence can be taken into account during gene sequence

clustering, and mutation rates and structure can inform us about the most likely evolutionary trajectories. In light of all this a priori knowledge, “clustering” is an inadequate term to describe the analysis of receptor repertoires. In fact, the goal is not just the grouping of similar sequences, but rather the total reconstruction of the mutation process that led to the observable repertoire (Barak *et al.* 2008). In my own work, I hope to compare the general structures of the B cell receptor repertoires of different vertebrates to deduce the conserved processes of repertoire generation.

I am drawn to the analysis of lymphocyte receptor repertoires not only because of the interesting computational challenges, but also because the analytical approaches I develop could have important clinical applications. Measuring the diversity of patient repertoires is now an important tool in monitoring leukemias, and will likely become a component of diagnosis infectious disease progression. Reconstructing the processes of repertoire creation can be harnessed to design better vaccines. For example, HIV researchers are searching for immunoglobins that are effective at neutralizing the virus but have not undergone extensive somatic hypermutation, reasoning that these ancestral antibodies would be easier to induce via vaccination (Sok, *et al.* 2013).

Analysis of sequence data as complex as lymphocyte receptor repertoires requires competence in basic scripting, command line, and use of online tools. Graduate level immunologists, and biologists more generally, can fall along a spectrum from software consumers to producers, and their educational paths will differ based on their needs and inclinations. I believe that all biology graduate students should have a basic competency in Linux, writing simple scripts in a language like Python or Perl, and the use of statistical software such as MATLAB or R. These skills are essential for the informed use of existing software and to facilitate collaborations with computer scientists. This knowledge could be acquired either through specialized classes offered through biology departments or general computer science courses. Students interested in taking a more active role in software development may decide to take a longer sequence of computer science courses, just as I have chosen to take a more extensive series of biology courses.

Formal training in each other's disciplines can reduce barriers to communication, but we need to find other ways to share ideas through joint conferences and accessible published work. Despite the wealth of interesting immunological questions that would be of interest to bioinformaticians across the discipline, conferences focused in bio-computing are sorely lacking in immunology content. For instance, the latest Association for Computing Machinery Conference on Bioinformatics, Computational Biology, and Health Informatics (ACM BCB) hosted the Immunoinformatics and Computational Immunology Workshop (ICIW 2014), yet the main program did not contain a single immunology talk. This was despite the conference addressing issues that are surely of importance to immunologists; for instance, bridging the gap between research scientists and clinicians. Perhaps for a field as mature as immunology, its own disciplinary conferences satisfy the needs of its constituents, but if this is the case, then immunology conference organizers should make efforts to include computer scientists in their programs. Finally, I would urge immunologists to make their presentations and publications more accessible to outsiders like myself. In particular, I would suggest that they adopt the practice of computer scientists and provide definitions at

the onset of the important components in a study, such as cell types and signaling molecules, just as we would define the variables in a model or algorithm.

Karen: interconnected systems of scientists

Keaton and Emily's perspectives provide compelling arguments for encouraging interdisciplinary research on immunological questions, but how can we encourage these endeavors? As director of a multidisciplinary research center (the Microbial Ecology and Theory of Animals or META Center for Systems Biology at the University of Oregon), I've gained some experience in fostering such collaborations. One can think of the goal as promoting network connectivity within a system of scientists. The first step is to increase the chance encounters of diverse researchers (the nodes of our system). This could be through joint research seminar series, journal clubs, co-instructed classes, or other programmatic activities. These kinds of interdisciplinary activities can sound great on paper, but in order for them to work in practice and achieve the goal of promoting cohesion and interconnectivity, all participants need to acknowledge the challenges and hard work involved in communicating across disciplines. It can be all too easy to dismiss a colleague's ideas when the real problem is differences in conventions or terminology between fields. At META research meetings, we've had to spend time discussing the language we use, reminding ourselves, for example, that the word "niche" can mean very different things to a stem cell biologist versus a microbial ecologist.

In my experience, the best way to solidify nascent connections between scientists established through these kinds of joint activities is through co-mentorship of graduate students or postdocs. In this way, two investigators are forced to learn each other's languages, while mentoring a new scientist, who will become bilingual in the process. Support for such collaborations can be enhanced through training grants or institutional seed grants that require co-mentorship arrangements.

A final recommendation for young immunologists seeking faculty positions is to consider joining non-immunology departments. When viewed through different lenses, the research programs of immunologists can fit into many different types of departments ranging from cell, developmental, structural and evolutionary biology. An investigator who has trained in immunology will maintain her disciplinary ties through the conferences she attends and the paper and grants she reviews, but by embedding herself into a different type of department, she will greatly increase the interconnectivity with colleagues from different disciplines, which will likely foster new and exciting research trajectories.

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Box 1. Recommendations and some tools for ‘border crossing’

For current graduate students who may want to “immigrate” into other fields, for example, immunology students who have an interest in ecology or computer science students with an interest in immunology, there are a number of proactive steps we recommend.

1. We suggest seeking out interdisciplinary conferences, symposia, and workshops as an initial way for graduate students to explore how their current fields intersect with other fields of interest. Such gatherings also tend to be fertile ground for initiating interdisciplinary communication and even collaboration. We also recommend inviting scientists from intersecting fields to speak in your departmental seminar series (faculty especially appreciate invitations from graduate students, and might be more likely to accept your invitation than one from a faculty colleague).
2. Journal clubs are often a great way for graduate students to delve into the literature of a new field where they can get input on and explanations of the research from experts. You might have to traverse administrative or geographic divides to find such gatherings, but journal clubs are typically informal and open to anyone willing to read and discuss the papers.
3. Even if not explicitly stated, many universities will allow graduate students to take classes outside of their department if it will facilitate their dissertation aims, even if it's just to audit the class. Similarly, faculty may wave the prerequisites for graduate students who have a keen interest in a course, but are coming from outside the field.
4. Students who wish to learn a body of material outside of a formal course can often find useful instructional materials online. For example, for students wishing to acquire some basic computational skills, we can recommend two resources. The first is the Unix & Perl Primer for Biologists (Bradnam & Korf 2011), which teaches scripting in a biology-specific context, although many biologists and bioinformaticians have moved away from Perl to Python. The second is Think Python (Downey 2015), which is not specific to biology but aims to teach users to think like a computer scientist—a valuable skill for those who may be interested in creating their own computational tools.