Interactions and co-evolution between viruses and immune systems

viralimmune24

Activity report

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Abstract

The goal of this program was to make progress on the problem of viral-immune interactions by bringing together two broad communities of biology-minded physicists and biologists who don't usually meet: quantitative immunology and viral evolution. Challenges range from the molecular scale, with the formidable problem of predicting binding specificity between immune receptors and their targets derived from pathogens, to the population scale, with complex patterns of co-evolution and the integration of epidemiological modeling.

The program achieved this goal by helping start new collaborations across these communities, as well as between theorists and experimentalists. Specifically, several projects were started to leverage the tools of machine learning to make progress on the specificity problem through structural modeling, and how to test the resulting prediction experimentally, both in the context of T and B-cell receptors (antibodies). Participants also worked on and discussed models of in-host immune and viral dynamics, gaining insight into the processes of the immune response and affinity maturation to better understand the specificity, diversity, and efficacy of immune memory. Participants also worked on detecting signatures on the immune repertoire of past challenges and how to analyse repertoire data to decipher and decode viral specificity. Vigorous discussions challenged the view that neutralizing antibodies found in sera were the only determinant of protection against future infections. Efforts were made to use large viral databases to infer molecular processes of their evolution driven by the reaction of the immune system. Finally, modeling efforts to integrate existing information into predictive models for the evolution of viral strains was pursued.

Program organization

The program lasted 3 weeks, equivalent to 14 working days. At the beginning of each week, we asked each participant to introduce themselves using slides, tell others what they work on, what they hope to achieve, and what their interests are to foster informal conversations.

We shared those slides with the program participants so that people who didn't overlap on their first week still got to know each other.

We had two talks each morning, with an 1h15 time slot and instructions to prepare for 45 minutes to allow for plenty of questions. Talks led to lively discussions, and rarely went over the allotted time, providing the right balance between concision and the ability to delve into more technical questions. There were a total of 26 such talks. Aleksandra Walczak gave a more physics-oriented chalkboard talk on the second Monday to present our community to the KITP.

In addition, on the second Friday we had an exceptional 1-day symposium in the honor of Anton Zilman, who passed away this year and was supposed to come to this program. This day was packed with 5 interesting talks on quantitative immunology and finished off with a barbecue at the residence.

Afternoons were left free for discussions, and were heavily used for that, as testified by the fact that most meeting spaces were occupied by our program members. Many participants mingled for informal discussions over the daily 3:15pm tea time, and lingered after to continue talking science. We left participants to self-organize into groups of conversation, rather than to organize topical sessions. Our program included a large number of affiliates (9) and postdocs, who also participated actively in many of these working groups.

We organized a barbecue every week at the residence. Some participants spontaneously stepped in to help with the costs and organization. These barbecues helped cement the community and fostered more informal contacts between the participants. In addition, our program was lucky to overlap with the traditional soccer game followed by a family picnic at KITP. Although our program lost the game, all participants were enthusiastic and engaged. It also gave opportunities to exchange with other members of the KITP community. Finally, on the Sunday of the second week-end, we organized and invited everyone to a hike in memory of Anton Zilman, who particularly enjoyed this activity.

Goal and achievements

The workshop covered three main areas: (1) co-evolution between viruses and immune system, with a focus on how immune interactions impose selective pressure on viruses; (2) immune repertoires, and how they respond and self-organize to immune challenges; (3) immune-pathogen molecular interactions, which poses a big challenge from the point of view of protein-protein interactions and has links to AI and disordered systems. Below we list the discussion, work, and collaboration that took place in these three areas.

Viral Evolution

Haddox and Neher collaborated on SARS-CoV-2 mutation rates, identifying variability influenced by genomic and structural contexts. They also worked on clonal interference and selective pressures during immune evasion.

Meijers and Lässig discussed with Nourmohammad and Visani to study influenza antigenicity, cross-neutralization ability of sera, and SARS-CoV-2 evolution, using machine learning. Collaborations included combining genetic and phenotypic data to predict mutation effects.

Starr discussed ongoing work on a joint collaboration with Matsen and Haddox on parameterizing selection factors to predict antibody evolvability based on primary sequence.

Cobey worked with Mora and Walczak on an ongoing collaboration to study an influenza cohort through the analysis of the donors' immune repertoire, to gain insight into the determinants of protection as a function of infection and vaccination history.

Ukogu, Nourmohammad, Mora and Walczak collaborated on a new model of interaction between microbiome and the immune system, as another example of co-evolution between the immune system and microbes.

Matsen and Mora brainstormed ideas about fitting arbitrary tree distribution in a non-parametric way, with applications to viral evolution or B cell affinity maturation.

Desai has established a new collaboration with Lassig and Meijers. They are working together to use methods Desai's lab has developed to construct large libraries of specific protein variants to construct and measure binding affinities of libraries of influenza hemagluttinin sequence variants that his group will use to parameterize their predictive models of influenza evolution.

Immune Repertoires and Dynamics

Victora, Mora, and Walczak, along with Abatte and Mazzolini from the Walczak-Mora lab and Rezende de Castro from the Victora started a new collaboration to characterize a new mouse model for studying a minimal and reproducible repertoire. This effort is key to understanding variation and reliability of the immune response against viruses.

Abatte, Mazzolini, Ruiz Ortega, Mora and Walczak resumed discussions on a project for building a computational model of baseline B cell repertoires that take into account its lineage structure and hypermutations.

G Altan-Bonnet expanded collaborations with Nourmohammad to model in vivo T cell differentiation. Insights from these projects were integrated into his study of cancer immunotherapy, focusing on TCR identity and differentiation state.

Ukogu, Nourmohammad, Mora and Walczak continued their collaboration on understanding adaptation and tolerance to self using tools from dynamical systems.

Tsang, in collaboration with G Altan-Bonnet, contributed to revising a manuscript on hematopoiesis dynamics. These discussions highlighted variability in the hematopoietic process across species.

DeWitt, with Victora, Matsen, and Starr, worked on modeling B cell receptor selection in germinal centers. The team focused on replaying antibody evolution to understand the

constraints shaping receptor diversity. DeWitt talked with Aragon on the correspondence between different mathematical frameworks for describing B cell evolutionary trees.

Höfer analyzed CD8 T cell lineage trees with Veit Busch, focusing on memory-effector bifurcation mechanisms. Discussions with G Altan-Bonnet on mouse hematopoiesis led to a collaborative project on clone size distributions.

Zarnitsyna collaborated with Borghans and others on immune response modeling for influenza, aiming to quantify host-viral interactions and immune escape mechanisms. She hopes to collaborate on a manuscript with Dr. Molina-Paris and Dr. Bravi, and plans to submit a joint grant application with them.

Matsen collaborated with Tiffeau-Mayer on extending repertoire analyses to B cells.

Immune-pathogen interactions

Bradley initiated a project with Tiffeau-Mayer on analyzing patterns of SARS-CoV-2 antibody sequence, structure, and binding. Discussions included Cvijovic and DeWitt, with potential follow-ups on antibody evolution.

Bravi worked on computational methods for predicting binding properties of immune proteins, leveraging workshop discussions to identify relevant datasets and literature. She also planned joint NIH and EU grant applications.

Tsang and Wang discussed developing generative models for T cell epitopes. Their collaboration aimed to link allelic polymorphisms to antibody binding stability and library screening data.

Wu worked with Wang on a paper in revision on antibody evolution. Wu and Nourmohammad have discussed several plans to write grant proposals together on T cell epitopes.

Minervina collaborated with Walczak, Mora, on modifying TCR specificity in vitro and with Bradley on applying AlphaFold2 for structural predictions of unresolved TCR-pMHC cases. Minervina, Nourmohammad and Visani are working on a paper on testing predictions of TCR-pMHC specificity using AI.

Visani and Nourmohammad started discussions with Thorp and Phillips on designing broadly neutralizing antibodies.

Desai had discussions about a potential collaboration with Gabriel Victora. Victora is planning to provide a large set of ~10,000 sequences from his germinal center B cell sequencing project, and Desai will attempt to construct these sequences and measure binding affinities to the relevant antigen (chicken immunoglobulin).

G Altan-Bonnet had discussions about models of TCR antigenicity with Bradely, Nourmohammad, Mayer, Elhanati, which he will use to design future experiments in his group.

Efforts to increase diversity

We actively sought to recruit women and other underrepresented minorities, personally reaching out to encourage their participation. As a result, out of 54 total participants, 19 were women researchers, 9 were junior faculty members, and 19 were early-career scientists, including postdoctoral fellows and graduate students. In addition, we worked to ensure that our speaker lineup reflected the diversity of our attendees. Of the 33 presentations, 14 were delivered by women, and 11 were given by junior faculty members or postdocs.

Our meeting was on an interdisciplinary topic, and we advertised it widely across multiple different communities. As a result, participants represented a broad range of expertise, including physics, mathematics, computer science, immunology, infectious disease, virology, and biochemistry. This fostered a rich interdisciplinary dialogue among attendees.

We found that the extra support for families specifically helped to attract women and participants with young families since several participants brought their children and spouses. We did have an issue finding local childcare for participants with very young children, and those participants either could not attend or had to stay for a shorter duration of time.

Suggestions

The program went very smoothly with no incidents or complaints, and good feedback about logistics and organization.

An area of improvement could be to streamline the conditions and timeline for the admission of affiliates. Some affiliates were not notified until very late, making it difficult for them to organize their trip and in particular their housing, which is not provided by KITP. We would have preferred if applications for affiliates would close shortly after the main participants have been invited.

The difficulty to obtain childcare in the Goleta/SB area during the program has prevented a participant from staying as long as she would have wanted. Any progress in this area would be welcome.

Conclusion

The feedback we got from participants was overall very positive, one senior participant calling it the most productive and professionally rewarding she could remember, and many more citing the positive impact it had on their career. Many participants highlighted that informal discussions and in-depth brainstorming sessions helped them refine and inform their research program, and envisage new directions and collaborations. Many also report making progress on existing collaborations and on writing or finalizing papers. The many

junior researchers who participated benefited greatly from their time at KITP, allowing them to talk at length with senior researchers.

While previous programs had covered microbial evolution and the immune system separately, we hope that this program has helped build bridges between the two communities, and create a new one on the topic of immune-pathogen co-evolution. The many contacts and new collaborations started between the participants are encouraging and hold promise for the future development of this emergent field.