Mathematics inspired by immuno-epidemiology

organized by
Maria Vittoria Barbarossa, Rongsong Liu, and Gergely Roest

Workshop Summary

Background

Immunology and epidemiology are traditionally separate disciplines. In the past, mathematical models have been developed either only for immunological or only for epidemiological aspects of a disease. Whereas epidemiological models consider the spread of the disease at population level [BrauerCCC], mathematical immunology aims to describe the within-host dynamics during and after an infection [Wodarz2007].

Immuno-epidemiology combines individual- and population-oriented approaches, studying the influence of the immune status of single hosts on epidemiological patterns [Hellriegel2001,Mideo2008]. Mathematical models provide an important support for research in this field. The challenge, both from medical and mathematical point of view, is to identify individual features which give information on the immune status of the host, and at the same time are relevant at the population level. The choice of proper mathematical tools in this context is not easy [Gog2015].

Participants

The workshop had 26 participants (10 women): 2 organizers (the third one could not be present in person), 11 applicants, 13 invited participants. Out of these, 23 participants came from North America (USA 17, Canada 5, Mexico 1), 3 from Europe. The group was quite heterogeneous with experts in mathematical modeling, applied analysis, dynamical systems, as well as epidemiologists and immunologists. The group was balanced with 5 graduate students, 4 postdocs, few tenure-track or associate professors, and about 12 senior researchers.

Workshop activities

The meeting followed the AIM-workshop structure with two lectures in the morning (every day from Monday to Thursday), and discussion or working groups in the afternoon.

Monday. The first lecture was delivered by John Glasser, who gave an overview on modeling epidemiology and immunology, with particular focus on vaccination. He reported medical facts and observations about diseases caused by Rubella virus, Measles virus, Bordetella pertussis, Herpes simplex, Herpes zoster and Cytomegalovirus. The lecture stressed factors such as age- and gender-specific immunity. Moreover, mixing models allowing preferential contacts (e.g., with parents, children, grandparents and grandchildren as well as contemporaries) were presented. Among the references for this lecture: [GlasserFeng2010, GlasserFeng2012, FengGlassserPertussis].

Alan Perelson gave a lecture on the complexities of within-host modeling of hepatitis-C virus (HCV) infection. He reviewed within-host models and multiscale models that are being used to study the dynamics of infection and the effects of treatment driven cures [Guedj2013, Rong2013]. In the afternoon participants had speed talks to introduce themselves, their scientific backgrounds and their specific research interests related to this workshop. After a short break we split into groups of 4-5. Research topics for the groups were defined based on participants contributions, submitted together with the applications or in the months ahead the workshop. The organizers proposed working groups taking into account (i) the preferences indicated by the participants during the weeks before the workshop and (ii) a certain heterogeneity, having a balance between younger and more experienced researchers in each group, as well as between different fields. Topics for the working groups were the mathematical modeling of immuno-epidemiology of vector-borne diseases, virus-induced cancer, latent virus infections, waning and boosting of immunity in broad sense, disease outbreaks on networks and host immunity to ticks.

Tuesday. Andrea Pugliese provided an overview on immuno-epidemiological mathematical models. Nested model for host-parasite co-evolution [Gilchrist2002] extended to SIR dynamics [Pugliese2011] show that host heterogeneity determines a decrease in pathogen virulence. Other in-host models for specific and aspecific immune response [Dushoff1996, Pugliese2008] are presented. Structured populations by the level of immunity (cf. [BarbarossaRost2015, BarbarossaRostVaccination]) are written in a simpler form using the age-since-infection as the structuring variables, however this seems to work only when reinfection is excluded [Gandolfi2014]. It remains unclear how to formulate an age-structured model when immunity loss and immune system boosting are considered.

Lauren Childs gave a lecture on malaria, focusing on immunological aspects, waning immunity and susceptibility. It remains unknown which antigens cause a protective immune response against malaria leading to difficultly in measuring immunity and in developing vaccines. Lauren presented several open questions (Which individuals are primarily responsible for malaria transmission? Why does someone develop symptoms and others do not?) and discussion followed. A review on modeling of vector-borne diseases can be found in [Reiner2013]. In the afternoon working groups had a two-hours session, followed by a short presentation and discussion with all participants.

Wednesday. Jane Heffernan presented several methods modeling over many scales. In general, immunological and epidemiological level of a disease run on different time scales and naturally lead to multi-scale approaches. Compartment models with several levels of immunity [Heffernan2009] or with only one compartment for hosts with low immunity [Dafilis2014,Dafilis2014b] can be used to study the effects of waning of immunity and immune system boosting. For the transmission of certain viruses, such as the herpes simplex virus, it is important to consider factors such as age, gender and risk of exposure of each host, yielding models with many compartments [Lou2012].

Jianhong Wu gave a lecture about mathematical modeling of tick-borne diseases, such as Lyme disease. The focus was on the spread of ticks related to climate change [Ogden2014,Wu2013], and very detailed heat maps were presented showing the potential risk of future tick spread in Canada. Consideration on host resistance or immunity to ticks and following discussion were inspired by [Wikel1999]. In the afternoon working groups had a three-hours session.

Thursday and Friday. On Thursday morning, Horst Thieme gave a lecture on several aspects of mathematical immuno-epidemiology. He recalled early models with state-dependent delay for virus latency [Cooke1967, Hoppensteadt1970, Hoppensteadt1971] as well as progression-age structured models for latency and reactivation [Martcheva2003]. Concerning waning immunity due to time since recovery and virus evolution, several works inspired by Pease [Pease1987] were presented [Thieme2002, Inaba1998, Inaba2001, Inaba2002, Ruan2010]. Horst suggested a hybrid model for waning immunity and immune system boosting alternative to the one in [BarbarossaRost2015], in which the immune population is structured by age-since-infection: with some probability, immune hosts either get reinfected or boosted, resetting the clock of the age-since-infection. Examples of models for cross-immunity in vector-borne diseases with two hosts are presented [Mopecha2003]. Jorge Velasco-Hernandez gave a lecture about modeling transmission on networks and in-host / between-hosts models for Dengue fever. He showed data reported in Mexico between 1990 and 2014. These data were clustered to form a network according to a gravity formula which connects two cities depending on the number of reported cases in each city and the geographic distance between the two. The weekly evolution and degree-distribution of the network were studied. The question of how the within-host and between-hosts dynamics affect each other was addressed and a modeling idea to combine slow and fast time scale was presented. On Thursday afternoon working groups had a two-hours session followed by a joint discussion stimulated by the reports of each group. This activity was continued on the following day.

Working Groups Reports

In the following we give a short summary of the results and questions achieved by the working groups during the week.

Working Group 1: Mosquito-borne diseases. The group discussed topics related to vector-borne diseases in general, focusing on Dengue fever. Four viral strains are responsible for Dengue fever, an infection with one strain does not induce immunity to others. In general re-infection is possible, and secondary Dengue cases are more severe than first infections.

Two models were proposed. In the first and simpler approach there is no distinction between strains. Mosquitoes are not included in the model, humans transit sequentially through few stages: Susceptible - Infective (first infection) - Recovered (recovery after first infection) - Infective (second infection) - Recovered (second recovery). A second model, where infection with either one or both of two virus strains is explicitly considered, is proposed, discussing similarities to [FengVelascoDengue].

Both models could be extended with delays to take into account temporary immunity. The first approach could be easily extended to the four strains, while this would be rather cumbersome in the latter approach. The two models are equivalent when all parameters are identical between strains, then comparison between the two approaches is examined when they differ.

It would be possible, though challenging, to formulate an age-structured model for multi-strain infections. Few data on age-specific incidence, however hardly any data at immunological/serological level, are available. A vaccine against Dengue fever is being developed. Questions related to the timing of vaccination are still open: given that it appears

that the vaccine is more effective in hosts that have already been infected once, would it be convenient to vaccinate hosts who already underwent primary infection rather than naive hosts?

Working Group 2: Cancer. The group discussed the interplay of viruses, cancer cells and immune system effectors. Topics were oncogenic viruses (those which induce cancer growth, such as HCV or HPV), as well as oncolytic viruses (which induce regression of cancer, several natural viruses are known). The discussion turned to engineered viruses (which are preferred due to tumor selectivity) and engineered immune system effectors (for improved immune response) and the group work focused on immunotherapy for cancer. Motivated by a recent experiments [Rapoport2015] with modified T-cells, engineered to recognize and kill myeloma cells, the group proposed a compartment model for natural T-cells, engineered T-cells and cancer cells in blood and in the bone marrow.

First comparison with data was performed. Among the goals of the project are the estimation of reliable parameter ranges and a deeper understanding of the in-host dynamics for improved treatments.

Working Group 3: Latent viruses. The work of this group is related to John Glasser's talk on Monday. Several viruses establish latency in sites inaccessible to the host's immune system, reactivating with some frequency, but being controlled for months or years. Multiple reactivations of some viruses (e.g., Varicella zoster) are rare, whereas others are common (e.g., Herpes simplex), although the period between successive reactivations may increase and severity of symptoms decrease. As control undoubtedly is due to immunity, reactivations may be caused by loss of immunity alone or together with immuno-compromising conditions.

From a modeling point of view, the immune and the latent host populations can be structured by the level of immunity, leading to a model with two conveyor belts (one for building up the immunity during infection and one for waning immunity after the infection). Hosts transit from one structured population to the other by some rate which depends only on the level of immunity. Similar approaches in [White1998,Martcheva2006]. Nevertheless, the mathematical analysis and numerical simulation of such a structured model is very hard. The structured model can be simplified to a system of ODEs (somehow related to [Heffernan2009]) for which the basic reproduction number can be computed.

Working Group 4: Waning/boosting of immunity. Immunity can be developed after natural infection or through vaccination. The protection gained from this process can be lost over time, however, and boosted with consecutive exposures and vaccinations [Heffernan2009]. The group worked on modeling the coupling between the waning of immunity and the boosting of the immune system as hosts age. They have developed a system of PDEs to study this process. Hosts have five possible immune levels (naive, low/medium/high immunity, vaccinated), susceptibles and infectives are structured by biological age, similar to [Lavine2011]. Numerical simulation of some preliminary results was performed. The group plans to continue the collaboration applying for an AIM Square.

Working Group 5: Networks. The group aims to link an immunology model with a network epidemiological model. They propose a simple in-host model (immune response and virus). The nodes of the network model represent hosts in the susceptible or in the infected class (several level of immunities are possible). The probability of being infected per contact in each class is a function of the viral load derived from the immunology model. A set of discrete values for the viral load were used to adjust the transmission probabilities.

The group aims to investigate the effect of changes in the immunology model on the network model. Comparison of the mean field model for the network and the corresponding mass action, well-mixed model will be performed. In the future more heterogeneity into the immunology and network models can be included, for example to investigate the impact of clustered immunity levels on the disease spread.

Working Group 6: Host immunity to ticks. The group proposes an immuno-ecological model depicting the interaction of questing nymphs and questing adults sharing a common host, such as a deer. The goal is to determine whether or not the development of a host immune response to ticks has the potential to act as a mechanism for self-regulation of the tick population by decreasing the tick developmental rate and reducing fecundity, and eventually, whether such a regulation can possibly prevent or slow down the spread of a tick-borne disease.

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