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Department of Mathematics
University of Florida
Gainesville, FL 32611



UFCTI 2002

The University of Florida Conference on Theoretical Immunology

Sponsors:

The National Science Foundation
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Department of Mathematics

Organizers:

Sergei S. Pilyugin(pilyugin@math.ufl.edu)

Conference web page:

<http://www.math.ufl.edu/~pilyugin/Conf2002/conference.html>

Conference schedule

Monday, May 27, 2002

- 9:00–9:30 Welcome address
- 9:40–10:40 **Lee Segel**
Distributed feedbacks: Towards multiple conflicting goals in the immune system
- 10:50–11:20 **Daniel Coombs**
The roles of serial engagement and kinetic proofreading in peptide-induced T-cell activation
- 11:30–12:00 **Discussion session**
- 12:00–2:00 **Lunch break**
- 2:00–3:00 **Nigel Burroughs**
Driving segregation in immunological synapse
- 3:10–3:40 **Mark Alber**
A cellular automata model for TCR signal integration
- 3:50–4:20 **Aranca Casal**
A stochastic cellular automata model for TCR microcluster formation
- 4:30–5:00 **Discussion session**

Tuesday, May 28, 2002

- 9:00–9:30 **Miriam Nuno**
- 9:40–10:40 **Rob De Boer**
Estimating average cellular turnover from BrdU measurements
- 10:50–11:20 **Roland Regoes**
Target cell limitation versus immune control in primary SIV infection
- 11:30–12:00 **Daniel Coombs**
Optimal viral production scheduling
- 12:00–2:00 **Lunch break**
- 2:00–3:00 **Rustom Antia**
Modeling immune responses
- 3:10–3:40 **Vitaly Ganusov**
Evolution of microparasites and the maintenance of parasite virulence: a within-host approach
- 3:50–4:20 **Dominik Wodarz**

4:30–5:00 **Discussion session**

Tuesday, May 28, 2002

9:00–9:30 **Discussion session: Mee Choi**

9:40–10:40 **Olga Smirnova**

Autoimmunity dynamics in irradiated mammals: Mathematical modeling

10:50–11:20 **Yoram Louzoun**

Comprehensive Analysis of B cell L chain rearrangement

11:30–12:00 **Discussion session**

12:00–2:00 **Lunch break**

2:00–5:00 **Discussion session**

All talks and discussion sessions are held in the Atrium (339 Little Hall) on the third floor of the mathematics department building.

Conference abstracts

A cellular automata model for TCR signal integration

Mark Alber, Department of Mathematics, University of Notre Dame

Cenk Sumen, Hughes Medical Institute, Stanford University School of Medicine

Elena Nabieva, Department of Computer Science, Stanford University

Helen Moore, Department of Mathematics, Stanford University

Mark Davis, Hughes Medical Institute, Stanford University School of Medicine

Abstract

T cells play a central role in orchestrating the adaptive immune response. Specificity of T cells is defined by each cell expressing a unique population of T cell receptors (TCR) which interact with specific peptide-MHC (pMHC) complexes. As a T cell interacts with another cell, it needs to quickly survey the surface of the other cell and make a decision within seconds whether to move on or to sustain the interaction with the possibility of subsequent activation. During this brief moment, TCRs on the T cell interact with numerous different pMHC complexes with a wide range of affinities - the T cell must integrate these data into a decision. Over the past decade, the nature of the interaction between several pairs of TCR-pMHC have been elucidated. However, a critical question remains: how does a T cell integrate the varied signals it receives from different TCR-pMHC interactions leading to TCR triggering? We envisioned that TCRs on a T cell surface are governed by local rules as to their movements and interactions, and therefore may be well modeled using cellular automata (CA) methodologies. Furthermore, interactions between a TCR and a pMHC are probabilistic events, and therefore are suitable for modeling with Monte Carlo simulation. The model described in this paper examines the molecular events in the space delineated by the interacting membranes of a T cell and an APC (antigen-presenting cell) e.g., a B cell or a macrophage or a target cell. The initial phase of the model, simulating the earliest events in T cell activation, deals with TCRs interacting with pMHCs and the formation of microclusters. Subsequent phases will consider synapse maturation, signal stabilization, as well as the role of accessory molecules (e.g., CD4, CD8, CD28, and LFA-1).

Conference abstracts

Modeling immune responses

Rustom Antia, Department of Biology, Emory University

Carl T. Bergstrom, Department of Zoology, University of Washington

Sergei S. Pilyugin, Department of Mathematics, University of Florida

Susan M. Kaech, Vaccine Research Center, Emory University

Rafi Ahmed, Vaccine Research Center, Emory University

Abstract

We describe how recent experimental results showing that brief stimulation with antigen is sufficient to cause antigen-specific T cells to undergo sustained proliferation force us to revise existing models for the generation of immune responses. We use the revised simple models together with experimental results to better understand the dynamics of generation of immune responses.

Conference abstracts

Estimating average cellular turnover from BrdU measurements

Rob J. De Boer, Department of Theoretical Biology, Utrecht University
Hiroshi Mori, Aaron Diamond AIDS Research Center, The Rockefeller University
David D. Ho, Aaron Diamond AIDS Research Center, The Rockefeller University
Alan S. Perelson, Theoretical Division, Los Alamos National Laboratory

Abstract

Cellular turnover rates in the immune system can be determined by labeling dividing cells with 5-bromo-2'-deoxyuridine (BrdU) or deuterated glucose (^2H -glucose). To estimate the turnover rate from such measurements one has to fit a particular mathematical model to the data. The biological assumptions underlying various models developed for this purpose are controversial. Here we fit a series of different models to BrdU data on CD4+ T cells from SIV⁻ and SIV⁺ rhesus macaques. We first show that the parameter estimates obtained using these models depend strongly on the biological assumptions of the model. To resolve this lack of generality we introduce a new parameter for each model, the “average turnover rate”, defined as the cellular death rate averaged over all sub-populations in the model. We show that very different models yield similar estimates of average turnover rate, i.e., about 1% per day in uninfected monkeys, and about 2% per day in SIV-infected monkeys. Thus, we show that one can use BrdU data from a possibly heterogeneous population of cells to estimate the average turnover rate of that population in a robust manner. This resolves a controversy about the appropriateness of current models and the parameter estimates they have provided.

Conference abstracts

Driving segregation in the immunological synapse

Nigel Burroughs, Mathematics Institute, University of Warwick

Christoph Wulfig, Center for Immunology, UT Southwestern Medical Center, Texas

Abstract

The accumulation of receptors and associated signaling molecules in specific geometrical patterns at the T cell/APC interface during T cell activation is a major element in the regulation of the efficiency of T cell activation. While it is intriguing that receptors mostly segregate according to their sizes the mechanism of receptor localisation at the interface is unknown. Here we present results derived from a mathematical model of receptor localisation based on bond length differences. We show that receptor segregation according to receptor-ligand size into distinct microdomains is energetically favorable, i.e. the free energy attributable to bond length differences is significant in cell:cell contact dynamics. Further, segregation requires seeding of the microdomains by membrane heterogeneity, possibly implicating lipid rafts in the process, and aggregation of these microdomains into cSMAC and pSMAC requires cytoskeletal receptor transport. The model establishes five criteria for successful receptor localization: sufficiently high membrane tension, membrane heterogeneity, cytoskeletal transport, tolerances of receptor and ligand densities, and TCR mediated control of bond affinities (LFA1).

Conference abstracts

A stochastic cellular automata model for TCR microcluster formation

Aranca Casal, Department of Hematology, Stanford University

Peter Lee, Department of Hematology, Stanford University

Mark Alber, Department of Mathematics, University of Notre Dame

Abstract

In this paper, we propose a model for microcluster formation by a T cell that encounters an antigen-presenting cell (APC). The model consists of a cellular automata which approximates the interface between a T cell and an APC. The TCR's and MHC's move and interact based on biologically motivated local rules. Each outcome is assigned particular probability. Running the stochastic model for 1 minute relative time yields the net result of microcluster formation, a stage prior to synapse formation.

Conference abstracts

The roles of serial engagement and kinetic proofreading in peptide-induced T-cell activation

Daniel Coombs, Theoretical Division, Los Alamos National Laboratory
Carla Wofsy, Theoretical Division, Los Alamos National Laboratory
Byron Goldstein, Theoretical Division, Los Alamos National Laboratory

Abstract

The activation of a T-cell requires the formation of a long-lived attachment to an antigen-presenting cell (APC). APCs present peptide on their surfaces, held by a major-histocompatibility complex (MHC). A given T-cell carries receptors (TCRs) specific for a particular MHC-peptide group, along with other less specific adhesion and costimulatory molecules. The stable region of close apposition (immunological synapse) may facilitate signal transduction, by concentrating the TCR and MHC-peptide together and allowing long-lived bond formation. A TCR will become activated if it can form a sufficiently long-lived bond to allow multiple biochemical changes to occur (the kinetic proofreading hypothesis).

We have developed a mathematical model to examine the TCR-MHC-peptide interaction within the stable region and use it to study (1) the competing effects of serial engagement (sequential activation of TCR by one MHC-peptide) and kinetic proofreading, and (2) the possible role of TCR oligomerization in activation of T-cells. In conjunction with the model, recent experimental data indicates that activated TCR must remain active for a period after dissociation from MHC-peptide. Recent extensions of the model to deal with other situations will also be presented.

Conference abstracts

Optimal viral production scheduling

Daniel Coombs, Theoretical Division, Los Alamos National Laboratory
Alan Perelson, Theoretical Division, Los Alamos National Laboratory

Abstract

Viruses reproduce by multiplying within host cells. We will consider the evolutionary fitness of the virus to be defined by the number of times it can reproduce during the lifetime of the host cell. However, the death of the host cell will generally be hastened by the infection, either because essential resources are redirected toward virion production, due to the toxicity of virally encoded products, or by immune system responses to the infected cell. In general, therefore, the virus must make a trade off between current and future production to maximise its fitness. We present a general mathematical model for this scenario which may be adapted to many host-parasite systems, and use it to examine the optimal virus production scheduling problem from the perspective of the virus.

Conference abstracts

Evolution of microparasites and the maintenance of parasite virulence: a within-host approach

Vitaly V. Ganusov, Department of Biology, Emory University

Carl T. Bergstrom, Department of Zoology, University of Washington

Rustom Antia, Department of Biology, Emory University

Abstract

One of the major conclusions of the theoretical analysis on the evolution of microparasites and maintenance of parasite virulence is that in the presence of a trade-off between transmissibility of a parasite and its virulence (or/and host recovery rate and virulence), the parasite will evolve towards some intermediate level of virulence ("adaptive theory of the parasite evolution"). Moreover, the exact level of virulence evolved depends critically on the shape of the trade-off(s).

If the exact nature of such trade-offs is unknown how should we proceed? Can any general conclusion be made regarding how a particular parasite will evolve if the knowledge of trade-offs of any kind is lacking? With a help of simple mathematical models we demonstrate that depending on fine details of the within-host dynamics of the evolving parasite and the host immune system, parasites may evolve any level of host mortality (i.e., virulence) depending on a particular set of model assumptions.

For example, if the rate of parasite transmission from infected hosts saturates at densities which are much lower than the lethal density at which the parasite kills the host, the optimal parasite (i.e., obtaining maximum transmission during the infection) will on average cause little damage to its hosts (case mortality $\sim 1 - 3\%$). On the other hand, if host mortality during infection is determined by the depletion of host resources below some critical density and the rate of the resource turnover is small, then the optimal parasite will be very virulent (case mortality $\sim 90\%$).

Our analysis suggests that no general conclusion can be made regarding what level of virulence a given parasite will evolve unless details of the within-host dynamics of the parasite and the pattern of parasite transmission from infected hosts are well (i.e., quantitatively) understood.

Conference abstracts

Comprehensive analysis of B cell L chain rearrangement

Yoram Louzoun, Department of Molecular Biology, Princeton University

Abstract

We present a comprehensive analysis of the B cell receptor L chain rearrangement. We use a vast array of observation and detailed probabilistic model to analyze each step in the L chain rearrangement process. We use the ratio between $\kappa\kappa-$ and $\kappa\kappa0$ to estimate the rearrangement rate in the V_κ allele and the probability to switch from one allele to the other. We then conclude from the distribution of J_κ genes usage that the J rearrangement is partly sequential. We set the λ rearrangement rate and the time window from rearrangement with data from κ deleted mice and from the $\kappa : \lambda$ expression ratio. We use these results to provide a new explanation for haplotype inclusion, and the distribution of $\kappa\kappa$ and $\kappa\lambda$ double expressers in normal and 3H9 transgenic mice. We then focus on the population of double expressers to show that the amount of each L chain expressed on the surface of the double expressers is different. We analyze the surface dynamics of the receptor-antigen interactions to propose new mechanisms of tolerance. These results are used to study the effects modulating antibody diversity.

Conference abstracts

Target cell limitation versus immune control in primary SIV infection

Roland R. Regoes, Department of Biology, Emory University

Rustom Antia, Department of Biology, Emory University

Mark B. Feinberg, Emory/Atlanta Center for AIDS Research

Silvija I. Staprans, Emory/Atlanta Center for AIDS Research

Abstract

The virus load in primary HIV infection is characterized by a steep initial increase, a peak at two or three weeks after infection, and a postpeak decline to the so-called viral setpoint. It is hypothesized that the postpeak decline could be driven by target cell limitation, or by specific cellular immune responses to the virus, or both. Since the viral setpoint is one of the best correlates of disease progression, an understanding of the factors governing primary HIV infection is crucial for the design of rational treatment and vaccination strategies.

We investigated the factors governing primary SIV infection, analysing an extensive dataset which contains frequent virus load and immune cell measurements obtained from eight SIV-infected rhesus macaques. In this dataset, four of the eight animals were treated with a costimulatory blocker that "knocked out" specific immune responses.

We approach our question by fitting two simple mathematical models to the viral load, one that describes the interaction between the virus and its target cells only, and an extended model which additionally takes into account the inhibitory effect of specific immune responses. Comparing the goodness of fits of these two models enables us to determine whether specific immune responses play a significant role in primary infection. As expected, the treated animals (with negligible specific immune responses) are fitted well without taking specific immune responses into account. In the untreated animals, however, we show that neither target cell limitation nor specific CTL responses are sufficient to explain the pattern of primary SIV replication. We hypothesize further that cytokine production by specific CD4 T cells may have to be invoked to fully account for the post peak decline of the viral load.

Conference abstracts

Distributed feedbacks: Toward multiple conflicting goals in the immune system

Lee A Segel, Department of Computer Science and Applied Mathematics, Weizmann Institute, Rehovot, Israel

Abstract

Evidence for the following scenario will be presented. It is useful to regard the immune system as having short term goals – which are overlapping and even contradictory. Sensors monitor progress toward the goals. Information from sensor readings is broadcast to the system via "vectors" of signaling chemicals (cytokines). Sensors drive "distributed feedbacks" that

- (i) improve the performance of a given type of effector cell;
- (ii) cause the preferential amplification of more potent effectors; and thus, more generally,
- (iii) in some sense improve goal achievement.

Conference abstracts

Autoimmunity dynamics in irradiated mammals: Mathematical modeling

Olga A Smirnova, Research Center of Spacecraft Radiation Safety, Moscow

Abstract

Mathematical models describing an autoimmune reaction in mammals exposed to acute and chronic radiation are developed. They proceed from the current immunological concept concerning the important role of immunosuppression function of thymus in maintenance of autotolerance as well as from radiobiological theories and experimental data. The models comprise the systems of nonlinear differential equations. The concentrations of target-cells of autogenous tissue, of T-lymphocytes-killers, and of T-lymphocytes-suppressors are the dynamical variables in these equations whereas the radiation dose and dose rate are variable parameters in them. The models are investigated by making use of the methods of the quantitative theory of differential equations, bifurcation theory and by a computer. The models reproduce the well-known fact that radiation-induced autoimmunity is directed against the tissues most sensitive to radiation. Depending on the value of the dose and dose rate the models describe different dynamical regimes which are observed in experiments: complete restoration of target-tissue after low dose acute irradiation, slight damages of target-tissue under low dose rate chronic irradiation, cyclic autoimmune processes at moderate doses and dose rates, and irreversible injury of all the target-tissue cells under high level exposures. A simple formula for calculating dangerous dose rates of chronic irradiation, which involves some immunological and radiobiological parameters, is obtained. The modeling results elucidate the origin of radiation-induced autoimmunity and allow to make some predictions, in particular, about the effectiveness of shielding the thymus to prevent autoimmune diseases.

References:

Smirnova O. A., Mathematical modeling of the effect of ionizing radiation on the immune system of mammals, *Physics of Particles and Nuclei*, American Institute of Physics, 1996, v. 27, No. 1, p. 100-120.