INTERNATIONAL CONGRESS OF IMMUNOGENOMICS AND IMMUNOMICS

IMMUNOLOGY FOR THE 21st CENTURY
Join us, share ideas and accelerate your research
Immunogenomics + Immunoproteomics + Immunoinformatics
= IMMUNOMICS

A joint meeting of the
2nd Basic and Clinical Immunogenomics
and
3rd Immunoinformatics (Immunomics) Conferences

October 8-12, 2006 - Budapest, Hungary

Organized by
Hungarian Society for Immunology
International Immunomics Society
Hungarian Academy of Sciences

Main patrons:

Prof. Dr. Szilveszter E. Vizi, President of Hungarian Academy of Sciences

Dr. Kalman Kovacs, Senior State Secretary of the Ministry of Environment and Water

Prof. Dr. Tivadar Tulassay, Rector of Semmelweis University

Erik Bogsch, Managing Director of Gedeon Richter Ltd.

P-1-20

STOCHASTIC SIMULATION OF T-CELL ACTIVATION

W. Schreiner, M. Cibena, M. Berger and R. Karch

Core Unit for Medical Statistics and Informatics, Medical University of Vienna, Vienna, Austria
E-mail: office-bcb@meduniwien.ac.at

The interface between an antigen presenting Cell (APC) and a T-Cell is modeled as a two dimensional area. The APC is furnished with MHC molecules, either carying self epitops (sMHCs) or pathogen epitops (pMHCs). Likewise the T-Cell surface holds T-Cell receptors (TCRs). The sizes of APC and TC are scaleable, while densities of MHCs and TCRs are kept constant. Both TCRs and MHCs are stochastically moved (brownean motion) at each simulation time step. Position increments are randomly chosen from a uniform distribution so as to yield realistic diffusion coefficients. In order to emulate contact areas larger than actually simulated, periodic boundary conditions (PBC) are applied: periodic "pseudo"-copies of the contact area are added as virtual neighbor cells. Distances between interaction partners (MHC-TCR, TCR-TCR) are computed as the shortest distance to either the real neighbor or to one of it's images. Thus the system may be finite without actually having borders. As in reality, the T-Cell surface is simulated to creep across the APC at a physiologically scaled velocity the creeping velocity being scaled appropriately.

The interaction between the TC and the APC is modeled in a multi particle stochastic simulation, implemented in Java. We consider interactions between MHC molecules loaded with self peptides (non-agonist) or pathogen peptides (agonist) as well as several types of interactions between the population of TCRs themselves. Types of such interactions are mutual inhibition and mutual protection. TCR activation is modeled to run through several levels, transitions occurring on a stochastic basis according to statistical models of live time. The parameters of these models are derived from the presence of either pMHC or sMHC as well as the mutual interactions with neighbor TCRs.

The readout from the simulation is the number of activated TCRs over time. Currently we are investigating the impact of simulation parameters on cooperative mechanism among TCRs in detecting a small number of pMHCs within a pool of numerous sMHCs.

The main goal of this work is the investigation of possible mechanism for the receiver operating characteristics (ROC) of immune detection.

Stochastic simulation of T-Cell Activation

W. Schreiner, M. Cibena, M. Berger, R. Karch

Core Unit for Medical Statistics and Informatics (MSI), Medical University of Vienna, Austria

eMail: wolfgang.schreiner@meduniwien.ac.at
http://www.meduniwien.ac.at/msi/biosim/

Introduction

The interface between an antigen presenting Cell (APC) and a T-Cell is modeled as a two dimensional area. The APC is furnished with MHC molecules, either carying self epitops (sMHCs) or pathogen epitops (pMHCs). Likewise the T-Cell surface holds T-Cell receptors (TCRs). In the model the sizes of APC and TC are scaleable, while densities of MHCs and TCRs are kept constant. Both TCRs and MHCs are stochastically moved (brownean motion) at each simulation time step. Position increments are randomly chosen from a uniform distribution so as to yield realistic diffusion coefficients.

Methods

In order to emulate contact areas larger than actually simulated, periodic boundary conditions (PBC) are applied: periodic "pseudo"-copies of the contact area are added as virtual neighbor cells. Distances between interaction partners (MHC-TCR, TCR-TCR) are computed as the shortest distance to either the real neighbor or to one of it's images. Thus the system may be finite without actually having borders. As in reality, the T-Cell surface is simulated to creep across the APC at a physiologically scaled velocity the creeping velocity being scaled appropriately.

In order to speed up computation we used 'neighbourhood tables' (NHT). The whole interface aerea is decomposed into squares with a sidelength of the maximum interaction radius. Therefore every neighbour molecule to which an interaction is possible can be found in either the square itself or one of the eight neighbour squares. The computational load to check all neighbour molecules B of one given molecule A only increases with interaction radius and with molecule densitiy. The total load thus increaes with O(n) rather than $O(n^2)$.

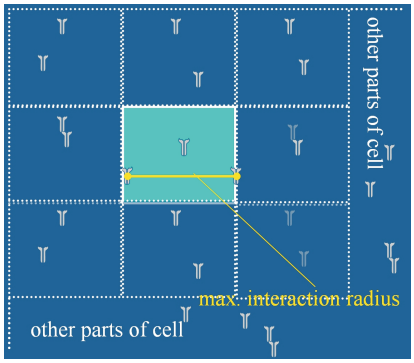


Figure 1: Neighbourhood tables reduce the computational load for evaluating molecular interactions.

The interaction between the TC and the APC is modeled in a multi particle stochastic simulation, implemented in Java. We consider interactions between MHC molecules loaded with self peptides (non-agonist) or pathogen peptides (agonist) as well as several types of interactions between the population of TCRs themselves. Types of such interactions are mutual inhibition and mutual protection. TCR activation is modeled to run through several levels, transitions occurring on a stochastic basis according to statistical models of live time. The parameters of these models are derived from the presence of either pMHC or sMHC as well as the mutual interactions with neighbor TCRs.

For details of software implementation see our poster by Michael Cibena et al.

Results

The readout from the simulation is the number of activated TCRs over time. Currently we are investigating the impact of simulation parameters on cooperative mechanisms among TCRs in detecting a small number of pMHCs within a vast pool of sMHCs.

Figure 2a: Varying HalfTimes for MHC-Docking

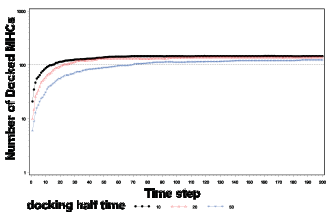


Figure 2b: Lifetime of TCR Stages

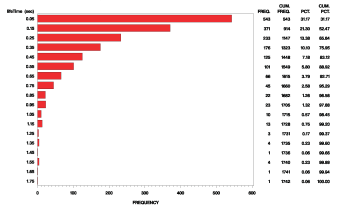


Figure 2c:Dissociation MHC - TCR

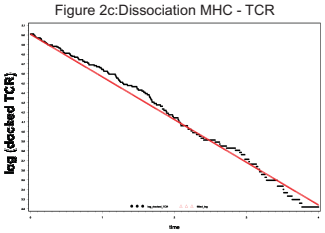
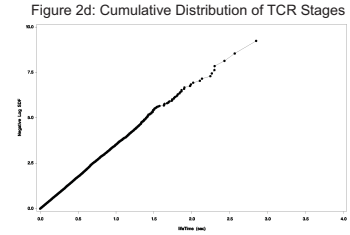


Figure 2d: Cumulative Distribution of TCR Stages



Prospects

As a further refinement we consider replacing stochastic diffusion of molecules by 'biased stochastics' so as to incorporate the influence of lipid rafts within cellular membranes. It has often been argued that borders of lipid rafts - due to the change in molecular composition - provide an optimum site for inforced molecular encounter. This is seen as a prerequisite for the formation of immunological synapses.

The main goal of this work is the investigation of possible mechanisms underlying the receiver operating characteristics (ROC) of immune detection.

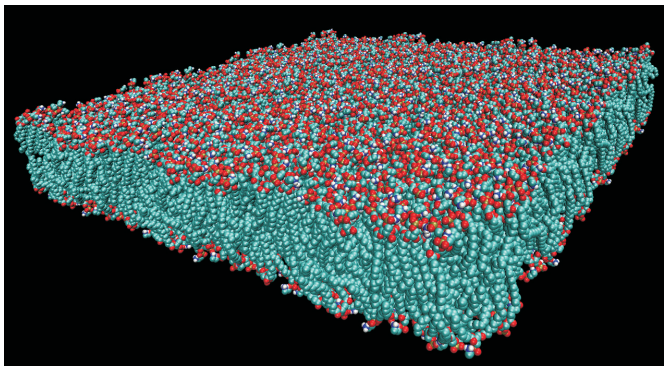


Figure 3: Cellular membrane simulated as lipid bi-layer. Varying lipid density generates fluctuating patterns of membrane composition (lipid rafts), which are considered to play an esential role in triggering immune response.

This pilot project is carried out in the context of the Austrian Grid Consortium, whose activities are also of relevance to Research/Education-application support.

This work is supported in part by the Austrian Grid Project of the Austrian Ministry of Education, Science and Culture (contract no. GZ 4003/2-VI/4c/2004).

MEDICAL UNIVERSITY OF VIENNA

AUSTRIAN GRID