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CELL SYSTEMS INITIATIVE

A Model for a Network of T- cell Signaling in Presence of Antigen Presenting Cells (APC)

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Abstract

To understand the adaptive immune system, it is necessary to develop biochemical networks of immunological function based on exploring molecular interactions in cells. Despite substantial progress made in recent years toward elucidating the processes involved in T cell signal transduction, there remains a lack of complete understanding due to the nonlinear, multiscale nature of the complicated biochemical networks. Through stochastic analysis of a mathematical model we are attempting to synthesize and understand the adaptive immune system. Our model couples two submodels. The first submodel handles the two-dimensional surface contact between an APC and a T cell, and is simulated with a modified minimal process (Gillespie) algorithm suitable for reaction-diffusion. The second submodel embodies early T cell signal transduction events within the cell and is simulated using the SigTran stochastic toolkit. Features include models of TCR triggering by kinetic segregation, bystander TCR triggering, cell adhesion, CD28 costimulation of engaged and non-engaged TCRs, activation of transmembrane adaptor proteins such as TRIM and LAT as well as immunological synapse formation. Our simulation results indicate how T cells integrate positive and negative signal amplification and regulation loops, due to APC interaction, which lead to the production and regulation of p27kip1 – an important protein involved in T cell proliferation.

Introduction

The importance of T lymphocytes in the immune system has been known for more than three decades. However, it has only been approximately a decade since cell biologists have realized the importance of molecular interactions in developing biochemical networks of immunological function. Exploring such networks will lead to new technological breakthroughs with biomedical applications to drug delivery and genetic engineering.

A major focus of recent studies in this area has been to clarify the intersecting and diverging branches of antigen-receptor signaling pathways, to provide a better understanding of how distinct immune outcomes are regulated. CD4 positive T cell (TC) and Dendritic cells (DC) are two classes of cells in the adaptive immune response which play key roles in protecting higher organisms from external (pathogens) or internal (cancer) threats [1] . Intracellular communication between these cell types involves interaction of surface molecules such as TCR, CD4 and CD28 receptors on the T-cell with MHC II-peptide complexes and CD80 and CD86 ligands on the DC. When TCR and CD4 molecules come in contact with MHC II-peptide on the DC one class of signals is generated, while a secondary and apparently distinct class of signals is produced when CD28 receptors encounter CD80 or CD86 ligand.

Despite substantial progress made in the last half a decade toward elucidating the processes involved in T cell signal transduction, there remains a lack of complete understanding due to the nonlinear, multiscale nature of the complicated biochemical network. Also, the study of T cell activation remains challenging since T cell activation is considered one of the most complicated and poorly understood signaling processes to be found within in any cell line. The additional challenge with TC-DC systems is the requirement of bringing two cells from different lines together with the requirement that there is subsequent partial or complete T cell activation.

Consequently there has been an emerging need for mathematical analysis to understand the complete process by gathering pieces of information and linking them together with proper hypotheses and assumptions (ref). Our work focuses on the stochastic analysis and its need over the popularly used deterministic approach by analyzing the effect followed by one TCR-pMHC binding on the initial cytoplasmic signaling molecules Ick of Src family and ZAP70 of Src and PTK families respectively.

Model Description

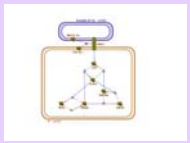

Figure 1 : Schematic representation of simplified model of signal transduction event followed by the TCR engagement with p-MHCII

When TCR binds to a MHC II peptide, there is a cascade of biochemical reactions which transduces and amplifies signals from transmembrane molecules to the cytoplasmic molecules and eventually to the nulceus. As a first attempt to model this complicated network of biochemcial processes [2] we considered one simple process which is involved in the initial signaling event (Fig. 1). The first signaling events is characterised by the recruitment of Lck near the transmembrane molecule of TCR, which then phosphorylates the ITAM residues, resulting in the recruitment and activation of ZAP70. After ZAP70 binds to ITAM, it becomes tyrosine phosphorylated as a result of both auto and trans phosphorylation by Lck. The term Phosphatase represents the process of de-phosphorylation of activated Lck (Lcka) and ZAP70 (ZAP70a).

Results

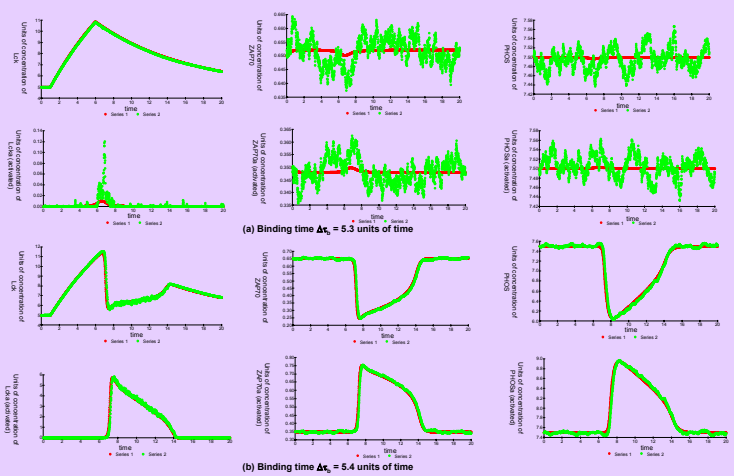

Figure 3 : Graphs of units of concentrations of Ick, ZAP70 and Phosphatase with time showing comparisons of deterministic model (———) with stochastic simulation (.....) for binding time, $\Delta\tau_b$ = (a) 5.3 and (b) 5.4 units time

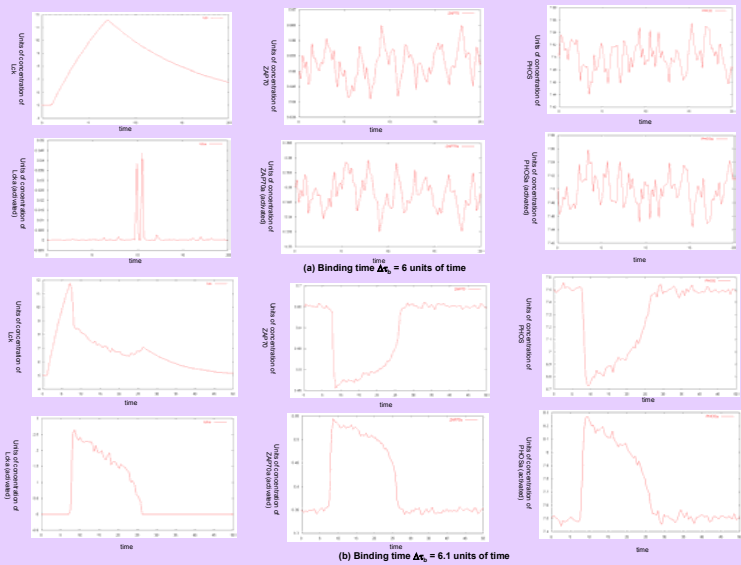

Figure 4 : Plots showing results of stochastic simulation of the model when there is 1/6th amount of total number of complexes present in the system than in Figure 3 with binding time (a) $\Delta\tau_b$ = 6 and (b) $\Delta\tau_b$ = 6.1 unit times

Method of Solution

To solve the simplified model as described by Fig. 1 we had considered stochastic approach based on the idea developed by Firth and Bray (1998) [3] which is described schematically in Fig 2 .

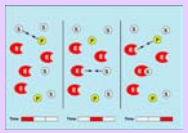

Figure 2: Schematic of three iteration steps of the StochSim algorithm. In this highly simplified diagram, the system contains four molecules of an enzyme E, four molecules of its substrate S, and two molecules of the enzyme product, P. In the first step the program happens to choose one S and one P. Referring to a look-up table, it finds that these two molecules cannot react, and so proceeds to the next iteration. In the second time step, one E and one S are selected. The look-up table reveals that these two can react, and gives a probability for this to happen. In this case the program decides (on the basis of a random number) that the reaction does in fact occur, and creates an enzyme substrate complex ES - the first stage of the enzyme-catalysed reaction. In the third iteration, ES has replaced the previously separate E and S, and a new selection is made.

http://www.zoo.cam.ac.uk/comp-cell/StochSim.html

Simulations are done with the software SigTran (http://csi.washington.edu/teams/modeling/software/index.html) which is developed to address the problems of cell signal transduction. The recruitment of the Lck is governed by the parameter $\Delta\tau_b$, which represents the binding time of the TCR and MHC.

Conclusions

A simple model, involving very initial signal transduction events, has been analysed with both deterministic and stochastic approaches. The stochastic approach is more appropriate since the number of molecules in activated states can be less than ***ten***, which violates the basic assumptions on which deterministic approach is valid. Our results show that

- The switch-like behavior which is observed at $\Delta\tau_b$ = 5.4 in deterministic approach (Fig.3) has shifted to $\Delta\tau_b$ = 6.1 in stochastic approach (Fig. 4).
- The window of activation for the activated Lck (Lcka) remains for 7.9 units time in deterministic approach while increasing to 18.66 units time in case of stochastic modeling.
- Though recruitment of Ick during the binding of TCR complex is similar, rising to a peak of about 12 unit of concentration during the switch-like behavior in both approaches (Figs. 3(b) and 4(b)), activated Lck in stochastic approach rises to almost half of the deterministic value.

These observations show that smaller number of complexes present in the system can lead to longer period of activated Lck leading to the conclusion that Stochastic approach is a more natural way of analysing these signal transduction processes.

Acknowledgement

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Work in Progress

•Stochastic analysis of the cell signaling process

• Effect of spatial distribution of receptor and ligand engagements in the intracellular signaling process

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