Abstract

T-cell is a major component in the vertebrate immune system which eradicates other infected cells through an interaction mediated by the binding of the T -cell receptor (TCR) to antigenic peptide derived from the infectious pathogens. The peptides are presented to the T-cell on the MHC (I / II) molecule on the cell surface of an Antigen Presenting Cell (APC). The complex of molecules contained in T - cell, antigenic peptide and the MHC are commonly known as the T - cell pMHC complex. The interaction between T-cell and pMHC complex may ultimately lead to activation of T-cell characterized by secretion of cytokines and / or cell proliferation and differentiation.

Main objectives of the present project are,

1. to build up a simple stochastic model to investigate interactions between T-cells and APC,

2. to estimate the free energy of the T-cell and APC interaction via Monte-Carlo simulation techniques in statistical physics and,

3. to compare the behaviour of the reported model with the experimental data; in particular , we shall compare the predictions of the model proposed in chapter 3

with these experimental results for assessing the effect of TCR - microclustering on T-cell activation.

Summary of the research are following:

- We discuss about Random Energy Model for interaction between T-cell and APC system and estimate the free energy of the Random Energy Model via Monti-Carlo simulation techniques. We consider a sample space -1, 1 of interaction events, where '-1' (respectively '1') corresponds to an unfavorable (respectively favorable) interaction between the T-cell and APC and propose the Hamiltonian model for the binary sequences of interactions between T-cell and APC system. The plots of the specific free energy with respect to inverse temperature. As N (bit sequence of pathogen)increases, free energy converges quickly into its theoretical limit.

- Secondly, we discuss about T-cell receptor clusters and T-cell activation. A Hamiltonian Model for the interactions between T-cell and APC system has been developed and the free energy is calculated with respect to the generation time. We also investigate the effect on the free energy from the interaction between clusters, number of clusters, standard deviation the distribution of energies associated with the interactions between the T-cell and APC, and generation time. According to the results, the duration of the time required for the T-cell to get into 'activated' state does not depend on the number of clusters, cluster size, or interaction between clusters. For low values of the standard deviation of the distribution, no change in the time duration required for T-cell activation can be observed as generation time is varied. For

high values of the standard deviation of the distribution, the interactions between the T-cell and APC will be unstable. Also we observed a discontinuity in the first derivative of free energy with respect to $\tilde{T}$ (generation time) at $\tilde{T} = T_c(= 0.163)$. Here, free energy increases up to T_c and after that ($\tilde{T} \geq T_c$) free energy remains constant indicating a phase transition in the T-cell APC system.

- Coombs et.al report that clustering of TCR does not amplify signaling through increased local density of TCR [9]. Non-dependency of the number of clusters or cluster size on the duration of time required for activation is indeed a result which has not been anticipated prior to simulation done in this study.

  Silvias et.al [28] studied the role of micrometer - scale clustering of TCRs at the T cell - APC interface. They also report that extensive TCR clustering is not required for efficient T cell stimulation, indicating that very few pMHC complexes are needed to trigger a T-cell.

  Deem et.al have considered these in six subdomains of TCR molecule, TCR - pMHC molecule at sequence space level. Thus the free energy functional in Deem's model is composed of the interactions within above subdomains and between subdomains of the the TCR and also indirect and direct interaction between T- cell and pMHC. The destruction of a pathogen by an APC, under the influence of specific TCR is known as a specific lysis. Specific lysis exhibits a switch like behaviour in response to the ration of effector cells. The lysis initiates only when the effector target ratio exceeds threshold and, this saturates as the effector ratio further increases.