Complexity miniproject proposal

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The effect of phosphatase SHP-1 on T cell triggering

Background to project: The immune system has to achieve an extraordinary task: to recognize and eliminate and extremely diverse universe of proteins (antigens) that could be deleterious for the host. An important feature of the immune system is the ability to distinguish harmless self-antigens from those derived from foreign organisms such as viruses. Hence, immune recognition must be highly specific in order to avoid autoimmune disorders. Unlike the innate immune responses, the adaptive response comprises numerous antigen-specific recognition events. B and T lymphocytes are the two main cellular components of the adaptive immune system. T cells are not able to respond to soluble antigens like B cells do and need a specialized molecular system for antigen recognition. The T cell receptor (TCR) is a complex of membrane proteins that participates in the activation of T cells in response to antigen peptides. Peptides are protein fragments which undergo intracellular degradation by antigen presenting cells (APCs) such as macrophages and are presented in complex with MHC molecules (pMHC) to T cells on the surface of the APC. TCR-pMHC engagement then initiates signalling cascades which regulate the development and function of T cells.
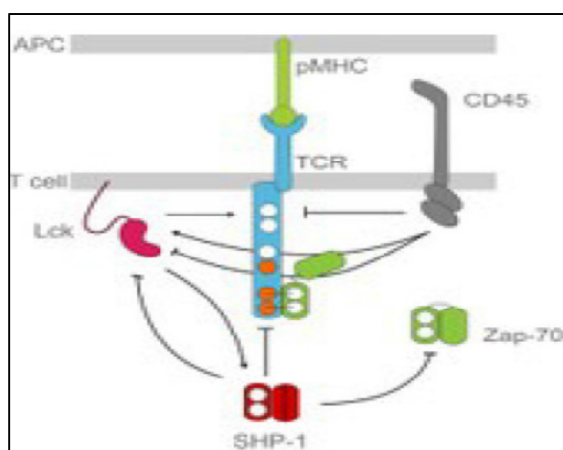
It is unclear how a limited pool of $\sim10^8$ human TCRs can provide effective immunity to a much larger number of pMHCs that could be produced from 20 amino acids and presented by MHC molecules ($\sim10^{15}$ different pMHCs). This discrepancy suggests that even if TCRs are highly specific, TCR recognition cannot be one-to-one and a single TCR can respond to a large number of pMHCs. T cell antigen recognition can be expressed in terms of *functional sensitivity* (or TCR triggering rate), which can be viewed as the rate by which a single pMHC ligand elicits TCR triggering. Such ligands capable of TCR triggering are termed agonists. Functional sensitivity depends, among others, on the TCR/pMHC on-rate, off-rate, TCR and pMHC populations. For the vast majority of ligands the functional sensitivity is really small and only for a minute fraction, is the functional sensitivity high.


As shown in the Figure to the left (with kind permission from Dr. Omer Dushek, Oxford), there are myriad molecules involved in T cell activation. The most common mechanism for activation and regulation of these molecules is via phosphorylation or dephosphorylation by protein tyrosine kinases (PTK) such as Lck and Zap-70, and phosphatases (PTP) such as CD45 and Shp-1. PTKs phosphorylate tyrosines that are part of ITAMs (immunoreceptor tyrosine-based activation motifs) found in the tails of the TCR/CD3 complex (orange circles in the Figure). Negative regulation of TCR signalling is also important to avoid hyperactivation. This can be achieved, in part, by inhibiting Lck activation by tyrosine phosphatase Shp-1. Studies have shown that Shp-1 is a mediator of a *negative feedback*; activated Lck induces Shp-1 phosphorylation, then phosphorylated Shp-1 binds to Lck and inactivates it. Moreover, stronger Lck activation promotes more rapid Shp-1 phosphorylation and binding to TCR. The goal of this project is to investigate the *effect of phosphatase Shp-1 on the TCR triggering rate* while taking into account TCR, pMHC and Shp-1 populations.

Programme of work: The mathematical model we aim to develop builds on classical models of TCR triggering. The Shp-1-TCR-pMHC kinetics is shown below in Figure A. The four possible binding states are assumed to be in kinetic equilibrium. The TCR-

pMHC bound states in Figure B are further subdivided into *n* states depending on the number of phosphorylated ITAMs (grey circles in the Figure), resulting in a Markov chain. The TCR is triggered when all ITAMs are phosphorylated, but the phosphorylation is dampened by Shp-1. Although agonists induce Shp-1 phosphorylation, but Shp-1 recruitment to the TCR is not rapid, it is reasonable to assume that Ship-1 is recruited at a rate proportional to the TCR triggering rate. Hence, *d/dt Shp = F(W(t)) - c Shp*, where *W* is the TCR triggering rate, which depends on the TCR, pMHC and Shp-1 densities and is obtained by calculating the TCR triggering probability based on Figure B.
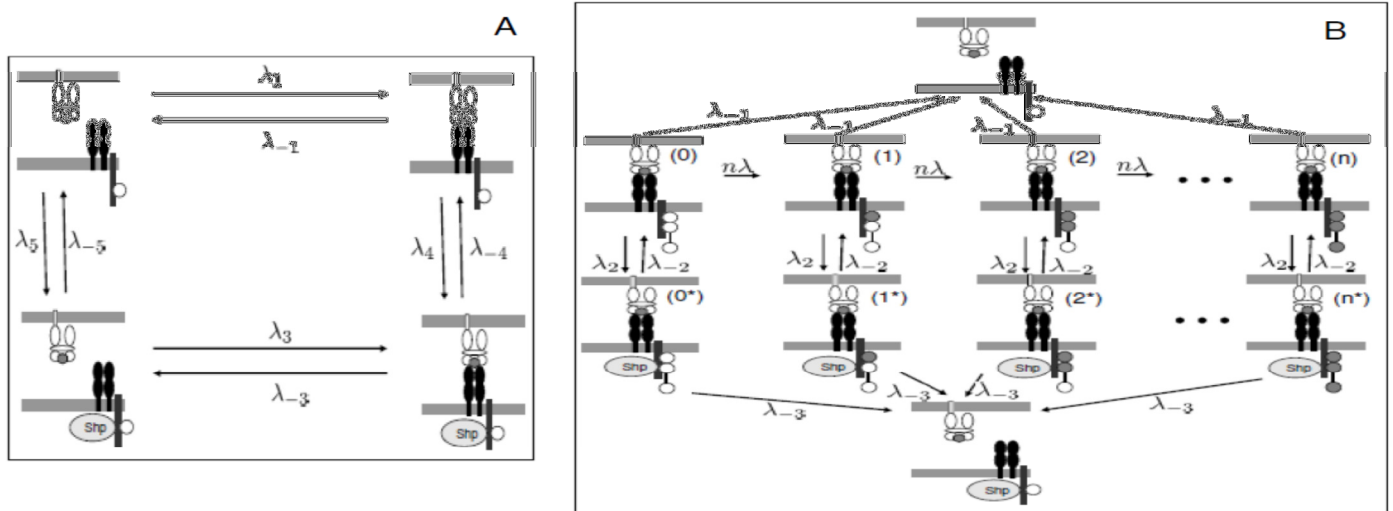
The main assignment is to implement numerical simulations of the model (ODE modulated by continuous Markov chain) and to characterise the inhibitory effect of Shp-1 on TCR triggering. This requires deriving the transition matrix for the Markov chain based on Figure B. Time permitting, the student will also perform ***qualitative fitting*** of the model to published Shp-1 data and explore how ***stochastic fluctuations*** in population sizes influence T cell signalling.

Skills to be learned: Analysis and performing simulations of the model, possibly including stochastic simulations. Relating results to experimental studies.

Resources required: Literature is available and the use of MATLAB is recommended.

Scope for extension to a PhD project: The project is co-supervised by Dr. Hugo A. van den Berg. Warwick has active collaboration with immunologists at Cardiff and Bristol whose experimental methods could benefit from the model built in the proposed project. Such a PhD project may involve extension of the model to TCR degeneracy and developing bioinformatics approaches using peptide libraries, for example. Moreover, the role of Shp-1 is not limited to TCR activation alone, but is also a therapeutic target for certain cancers and has important functions in other biological processes such as phagocytosis, which could be pursued in other modelling studies.

References:

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