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An Agent-based Model of T cell Proliferatin Experiments

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Short Abstract: The peripheral T-cell repertoire is maintained in equilibrium by both the production of thymic T-cells and self-renewal in periphery. We present an immune system model based on computational agents to simulate this population dynamics and address the role of self-renewing process in the generation of homeostasis.

Long Abstract:
The peripheral T cell repertoire is maintained by the production of virgin cells in the thymus and by the self-renewal of activated cells in periphery. In a mouse, the peripheral T cell repertoire consist of the order of 108 T cell clones distributed over 106-107 different specificities. These cells constitute an heterogeneous hierarchically organized population, comprising several maturation/differentiation states that have different capacities for clonal expansion and self-renewal. Several studies shown that the relative probability of proliferation, differentiation and death – the cellular events that determine the population's structure as well as its size – are not pre-programmed or fixed; instead, these events are regulated dynamically through the current interaction of lymphocytes with exogenous and/or endogenous antigens, antigen-presenting cells (APC) and each other (Grossman et al., 2004). Despite this complex dynamic structure, the naïve and memory T-cell numbers are kept stable and are maintained independently, under conditions where naïve cells are exported from thymus and memory T cells are generated in the course of an immune response (Freitas & Rocha, 2000).
Several control mechanisms, including competition for growth and viability signals (Callard et al., 2003), elimination or down-regulation of APCs (Sherer & Bonhoeffer, 2005), suppression by specialized regulator T cells (Almeida et al., 2005), as well as homeostatic expansion (Min et al., 2004) appear to be involved in homeostasis regulation. These mechanisms ensure the prevention of excessive expansion and exhaustive differentiation when lymphocyte population is repeatedly or chronically exposed to antigen (Troy & Shen, 2003). Thus, the homeostatic control of cell number provides a basic mechanism that shapes the repertoire of immune competent cells, and therefore, its capacity to respond to exogenous antigens as well as to maintain self-tolerance. It can also enable the re-establishment of the immune system following a disruption and therefore be used in therapeutic strategies to radically modify lymphocyte repertoire, immune responses, autoimmune diseases and allergy.
In this work we present a T cell population dynamic model, focusing on homeostatic proliferation of peripheral T CD4+ cells. This model is based on dynamic cellular automata (DCA) or agent-based modeling. The biological knowledge was obtained from in vivo experiments where monoclonal populations are transferred into RAG-/- or RAG-/-- transgenic mice. An important question we address is the role of homeostatic proliferation in the

generation and robustness of an equilibrium attractor. We also investigate if the attractor will remain stable when a second population is transferred to recipients and whether a phase transition-like phenomena occurs in this immune system dynamics.

Cellular automata (CA) is a multi-object computer simulation tool that captures important features of biological systems - large numbers of homogeneous components (simple finite state machines), extended in space, no central control and limited communication among components. They consist of large numbers of simple identical components with local interactions layered over a lattice or grid. The states or values of the components evolve synchronously in discrete time steps according to identical rules. The value of a particular site is determined by the previous values or states of a neighborhood of sites around it. A key advantage to the DCA modeling processes is that it is very easy to implement and requires remarkably little skill in mathematics or any knowledge of how to formulate or solve time-dependent ODE's, PDE's or SOE's. Furthermore, the DCA approach appears to be much more scalable, visually more realistic and applicable to a much wider range of cellular phenomena than many other simulation methods.

In our model we consider that T cell clones are stimulated to divide by a non-limited immunogenic peptides presented by antigen presenting cells, in an attempt to simulate peripheral CD4+ population dynamics. Several parameters that determined the mature repertoire and its dynamic properties in the model are estimated from biological data. Our model follows the specific assumptions:

i) The model is based on a bi-dimensional lattice (toroid).

ii) All the cells (or agents) that represent the T lymphocytes are identical, except the APC group.

iii) The antigen universe is related to a pre-determined and finite repertoire. In this model we assume that all antigens are ubiquos, making all APC equivalents.

iv) The agents move in a random walk above the lattice.

v) Each cell supports an ilimitate number of Ti co-habitants

vi) Each APC has a limited capacity to accommodate T lymphocytes, implying in a competition for resources supply.

Initially, the tested the global parameters (space, APC number, initial T cell population and epochs number) to establish the best conditions to simulate in vivo transfer experiments. After that, we maintained the same global parameters and changed the local ones, in each experiment, in an attempt to simulate the population dynamic. In a one-population experiment, the T cell number varies between the death of the population and its exponential growth, passing trough a dynamic equilibrium state. Clearly, it is in a close relation to the established local parameters at t=0 (initial T life, life bonus, activation bonus, activation decay, activation saturation, mitosis threshold, refractory epochs and APC capacity). In the two-population experiments, the introduction of a second population, presenting the same or a similar TCR specificity, always provoke a disturbance effect on the first one. This perturbation heavily depends on the size, clonal affinity and time of injection of this second population. We show that this system is able to simulate all the main results related to the T cell competition in homeostatic proliferation experiments. We are now improving the algorithm to introduce different clonal populations, antigens and APCs, to simulate the population dynamic of a normal immune system.