Collective Decision Making in T Cells

Yaron E. Antebi, Shlomit Reich-Zeliger, Nir Waysbort and Nir Friedman

***Short Abstract* — The exchange of signals between T cells has an important role in the regulation of their activity. Transmitted signals can be used by cells to make decisions collectively based on the state of other cells in the population. We study two examples in T-cell activation and differentiation that exhibit intercellular feedback, and show how the outcome of cell decisions can change significantly due to intercellular communication. We analyze the role of communication in regulating cell response using both quantitative experiments and mathematical modeling of the intercellular interaction network.**

***Keywords* —Intercellular Feedback, T Cells, Decision Making, Mathematical Models**

I. Introduction

THE immune system is composed of many individual cells that must operate in synchrony to produce a beneficial response against a variety of possible threats. A main regulatory mechanism of a developing immune response is provided by small secreted proteins, called cytokines, which allow for intercellular communication. This sharing of information allows cells to make decisions based on the state of the system rather than that of a single cell. In our research we focus on several examples of cytokine mediated regulatory mechanisms that function in the helper T-cell (Th), whose role is to direct the immune response in the desired course by affecting responses of other cells.

The studied system contains positive and negative feedbacks both at the intra- and inter-cellular level. To analyze the relative importance of the different components affecting the behavior of the cells we employ mathematical modeling and numerical simulations of specific experimental settings. Quantitative experiments are performed to evaluate unknown parameters and to verify model predictions.

II. T-Cell Activation

Upon receiving an activation signal from the T-cell receptors, T-cells secrete interleukin-2 (IL-2) [1], a vital cytokine needed for T-cell proliferation. The secreted cytokine can then be sensed by other cells, thus transmitting information between activated T-cells. Binding of IL-2 to its receptors further increases the sensitivity of the cell, due to a positive feedback loop that up regulates the number of receptors [2]. Additionally, this increase in the number of receptors causes faster depletion of the cytokine level available to other cells due to internalization of bound receptors, resulting in a competitive population dynamics.

We compose available data into a mathematical model, describing the behavior of a single cell. Analysis of the equations predicts hysteresis in the response of the cells to varying levels of IL-2 signal. We experimentally measure the response function of activated T-cells in vitro, to evaluate model parameters and test its predictions. Next, we use the single cell model to build a master equation describing the dynamics of a heterogeneous population of interacting cells.

III. T-cell Differentiation

After activation, T-cells start to differentiate into one out of few possible effector lineages, each invoking a specific immune response [3]. This decision is influenced by the spectrum of cytokine signals the cells sense. However, the cell actively alters the signals by producing cytokines and regulating expression levels of relevant cytokine receptors, thus communicating its current state to other cells.

IL-12 and IL-4 direct differentiation into the main fates of Th cells, Th1 and Th2, respectively. By exposing cells to varied combinations of the two cytokines we experimentally map the "decision phase space". We measured, at the single cell level, eight parameters relating to the differentiation process, whose statistical dependence can be translated to the network describing the system [4]. We also map this decision space for cytokine knock-out mice where communication is disrupted, thus elucidating its specific roles.

We incorporate our experimental results and other known data into a cellular automata based simulation. Each cell is simulated as a node on a dynamic network, whose links describe the propagation of intercellular cytokine signals. The intracellular protein network for each node is realized as an automaton with cytokines levels as inputs and their secretion rates as output. By varying model parameters and comparing to experimental results we can gain insight into the significance of the various components driving the differentiation process.

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[1]Department of Immunology, Weizmann Institute of Science, Rehovot Israel. E-mail: ayaron@weizmann.ac.il

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