# IL-2 couples T lymphocytes in their activation: from single cell to population

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***Short Abstract* — The interleukin-2 (IL2) mediated feedback pathway integrates the responses of activated T-cells affecting decisions on the population level. We study this circuit on the scale of the single T-cell as well as that of the whole population. On the single cell level we quantitatively measure and model the binding of IL2 to its receptor (IL2r) over short time scales and the effect of this on the production of both IL2 and IL2r. We link this microscopic behavior to global group decisions using *in-vitro* cultures along with computer simulations.**

***Keywords* — interleukin-2, T-lymphocytes, quorum-sensing, cell heterogeneity, modeling and experimental testing.**

## I. BACKGROUND

DURING the course of an infection a handful of T-cell clones can proliferate to compose 10% of the total T-cell population. This robust expansion (by factors up to $10^5$) implies error-correction on the activation of every individual T cell. For that purpose, the immune system relies on signaling feedbacks between large number of cells (through intricate signals emanating from chemokines, cytokines as well as cell-contacts with rich spatio-temporal dependence). A major player in this feedback loop is the Interleukin-2 (IL2) cytokine [1]: after recognizing antigen, T-cells produce and secrete IL2 while expressing its high affinity receptor, IL2r-□, on their surface. Activated T-cells must compete [2] for the IL-2 released into the extracellular medium as it is crucial for survival and proliferation [3]. Signaling through the IL-2 receptor further induces upregulation of IL2r-□ expression but down-regulation of IL2 expression [4]. Thus the IL-2 feedback circuit induces complex coupling among T-cell populations that is crucial to decide between proliferation or death. Fortunately, teasing out the quantitative intricacies of these competing feedbacks can be done with in-vitro experiments.

## II. RESULTS

Expression of the IL2r components can vary by a factor of 1000 within a clonal population of T-cells undergoing activation. In order to understand how such a diverse population of cells shares IL2 growth factor, we probed how the expression levels of three different components of the IL2r modulate a cell's affinity to IL2. We first developed a single cell assay monitoring T cell's response to IL-2 (by phospho-STAT5 accumulation) in conjunction with the expression levels of surface receptors [5, 6]. The relation between receptor levels and affinity was modeled using coupled reaction-diffusion equations. The IL2-IL2r detection system proved to be subtler than expected. Whereas biochemical measurements had reported an average affinity for IL2-IL2-r interaction around 10pM [5, 6], we found that individual cells can vary their affinity for IL2 from 0.1pM to 100pM depending on the densities of receptor units on the cell's surface. Hence, every individual T cell will operate as its own IL2 sensor with varied threshold. We also found that the ability of cells to deplete IL-2 from the external pool is linearly related to this highly variable affinity. From these findings we derive rules that link a cell's affinity with its ability to deprive neighboring cells of IL2. We verified these rules, *in-vitro*, by testing how the behavior of T-cells of different affinities couples through competition for a limited number of IL2 molecules.

## III. CONCLUSION

We are integrating quantitatively how T lymphocytes produce IL2, express the high-affinity IL2r and scavenge extracellular IL2 to derive a theoretical model for the response of a population of T cells based on individual cell behavior. Our model has important implications for the role of regulatory T cells in differentially controlling T cell activation.

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