Quantifying cross-talk among Interferon-γ, Interleukin-12 and Tumor Necrosis Factor signaling pathways within a T_H1 cell model: A model-based inference approach

David J. Klinke II[1], Ning Cheng[2], and Emily Chambers[3]

***Short Abstract* — Model-based inference methods, in conjunction with quantitative flow cytometry, can be used to reason about the relative contributions of different putative branches within a signaling network. Here, a cellular model of mouse T_H1 cells was used to quantify the functional response to IL-12, a key cytokine that links innate to adaptive immunity. Our results demonstrate that the response of T helper cells to biochemical cues, as modeled by in vitro culture of the 2D6 cell line, is a dynamic nonlinear process that reflects a hysteresis in response and the engagement of multiple positive and negative feedback mechanisms.**

***Keywords* — CD4+ T cells, Bayesian inference, signal transduction, ordinary differential equations.**

I. Purpose

CELL-MEDIATED immunity is tailored to the perceived threat to the host through the action of $CD4^+$ T helper (T_H) cells [1]. T helper cells recognize particular molecular patterns associated with threat and in response, produce a distinct set of biochemical cues (i.e., cytokines). The fate of $CD4^+$ T cells within the periphery is defined based upon the pattern of cytokines produced by and master regulatory transcription factors expressed within distinct subsets of T_H cells [2]. The particular profile of cytokines produced by T_H cells in response to a particular molecular pattern plays a strong influence on the outcome of the immune response [1], where alternatives include tolerance, resolution, or autoimmunity. However, understanding how biochemical cues present within the periphery regulate T_H cell fate remains a challenge in translating basic knowledge of cellular signaling pathways into practical application of this knowledge, including stem cell engineering, regenerative medicine, and immunotherapy.

Acknowledgements: This work was funded by NSF CAREER Award and NIH grants R56AI076221 and R15CA132124.

[1]Department of Chemical Engineering; Dept of Microbiology, Immunology and Cell Biology; and Mary Babb Randolph Cancer Center, West Virginia University, Morgantown, WV. E-mail: david.klinke@mail.wvu.edu

[2]Department of Chemical Engineering, West Virginia University, Morgantown, WV. E-mail: ncheng@usouthal.edu

[3]Department of Microbiology, Immunology and Cell Biology, West Virginia University, Morgantown, WV. E-mail: echambers@hsc.wvu.edu

Statistical inference for complicated problems related to cell signaling relies on a spectrum of computational tools that vary in their use of prior information. Frequently, the inference problem falls in between the two extremes as there are competing hypotheses proposed regarding the topology of the signaling network. While the lack of parameter values is frequently presented as an obstacle for using quantitative models, the inference problem focuses on whether the structure of the model (i.e., topology) is sufficient to explain the observed data. This implies two things, the inference problem must consider: 1) the specific data under consideration and 2) the uncertainty associated with the model predictions, given the associated uncertainty in the parameter estimates and the proposed topology of the model. Empirical Bayesian methods using in conjunction with quantitative cell signaling models is one solution to this statistical inference problem [3]. It is within this context that we hypothesized that an empirical Bayesian approach for model-based inference could be used to evaluate competing hypotheses regarding how effector T_H1 cells interpret Interleukin-12 (IL-12).

II. Results

We obtained a quantitative 924-point cue-signal-response data set, developed a mathematical model that encoded alternative hypotheses regarding how T_H1 cells orchestrate a cellular response to IL-12, and used an empirical Bayesian approach to reason about the relative importance of alternative pathways and casual implications of the cue-signal-response model. The results clarify the biochemical basis for two emerging concepts regarding cellular decision-making: feedback control and short-term memory.

References

[1] Sher A, Coffman RL (1992) Regulation of immunity to parasites by T cells and T cell-derived cytokines. *Annu Rev Immunol* 10: 385-409.

[2] O'Shea JJ, Paul WE (2010) Mechanisms underlying lineage commitment and plasticity of helper CD4+ T cells. *Science* 327: 1098-1102.

[3] Klinke DJ (2009) An empirical Bayesian approach for model-based inference of cellular signaling networks. *BMC Bioinform* 10: 371.

Nothing should be here on page 2! Please limit your abstract to a single page, and submit it as a one-page editable file (e.g., Word .doc format).