

Mathematical & Computational Biology Seminar

Organizer: Valerie Hower

Wednesday, 2:00–3:00pm, 939 Evans

Sept. 9 **Peter Kim**, University of Utah

Questioning the T cell proliferation program

The current paradigm for primary T cell responses is that each effector T cell independently commits to an autonomous developmental program. This concept is based on several experiments that have demonstrated that the dynamics of a T cell response is largely determined shortly after initial antigen exposure and does not depend greatly on the level and duration of antigen stimulation. An additional experimental study has also shown that T cell responses are robust to large variations in the initial concentration of antigen-specific T cells. A principal question of this presentation is, Does the current paradigm of autonomous T cell programs capture the observed robustness of the T cell response?

Various mathematical models have already corroborated the first result that programmed T cell responses generate dynamics that are insensitive to the nature of antigen stimulation. However, this paper proposes that programmed responses do not adequately explain the robustness of T cell dynamics to variations in antigen-specific precursor frequency. As an alternative, this work studies the hypothesis that the dynamics of a primary T cell response may also be governed by a feedback loop involving adaptive regulatory cells rather than by intrinsic developmental programs.

We formulate two mathematical models based on T cell developmental programs. In one model, effector cells undergo a fixed number of divisions before dying. In the second model, effector cells live for a fixed time during which they may divide. The study of these models suggests that developmental programs are not sufficiently robust, since they produce an immune response that directly scales with precursor frequencies. Consequently we derive a third model based on the principle that adaptive regulatory T cells develop in the course of an immune response and suppress effector cells. Our simulations show that this feedback mechanism responds robustly over a range of at least four orders of magnitude of precursor frequencies.

We conclude that the current paradigm does not capture the observed robustness of T cell responses to variations in initial T cell concentrations and propose an alternative mechanism in which the primary T cell response is governed by an emergent group dynamic and not by individual T cell behavior.