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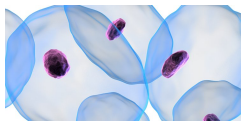

Examining the robustness of adaptive immunological networks in single cells

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Type of thesis: Computational

Required competences: Knowledge of ordinary differential equations (ODEs) and their analysis, ability to simulate systems in MATLAB or Python. These are taught in courses, e.g., SSB30806, SSB31806, BCT20306, BCT31806.

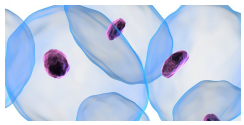
Acquired competences: Simulating stochastic (variable) systems, developing/extending models, analysing system robustness, and potential for parameter estimation compared to real/simulated data.

Date: 22-04-2020

Description

Effector T cells within our body are primed to deal with invading pathogens and viruses. Upon the detection of a foreign presence, ligands on the surface of antigen presenting cells (APCs) interact with T cell receptors (TCRs) on the surface of T cells, triggering a range of intracellular processes. The result of this internal T cell signalling network is the destruction of TCRs from the cell surface and the secretion of, for example, cytokines into the local environment that are used to stimulate other local T cells and eradicate the foreign cellular species. Unpublished data has shown that, over time, the secretion of cytokines by a population of T cells stops after a few hours of constant stimulation regardless of stimulation dose – this is termed T cell adaptation.

Simple 'toy' mathematical models (ODEs) can describe the adaptive behaviour of T cells at population level, for which some phenotypic models have already been obtained. As a starting point to this project, I am interested in understanding whether the adaptive phenotype is seen by single cells within the population; if a cell does not show adaptation, then why not? Is it due to the structure of the signalling network within T cells? Is it due



to the balance of reaction rates of a given system? Could adaptation of single cells be improved through altering the signalling network, including cellular communication, or accounting for the spatial distribution of single T cells?

This style of analysis has previously been used for other small networks that are found in real biology or created using synthetic biology methods (see references for oscillating mechanisms). In principle, the results of this project could help provide a better understanding of population level T cell phenotypes, or to the design of novel, robust, synthetic adaptive circuits.

References

Garcia-Ojalvo J, Elowitz M, Strogatz S (2004) Modeling a synthetic multicellular clock: Repressilators coupled by quorum sensing. *Proc Natl Acad Sci USA* **101:** 10955–10960.

Gonze D, Bernard S, Waltermann C, Kramer A, Herzel H (2005) Spontaneous synchronization of coupled circadian oscillators. *Biophys J* **89:** 120-129.

Trendel NC, Kruger P, Nguyen J, Gaglione S, Dushek O (2019) Perfect adaptation of CD8+ T cell responses to constant antigen input over a wide range of affinity is overcome by costimulation. *bioRxiv* **doi:** 10.1101/535385.