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## Mathematics of the NFAT signalling pathway

NFAT (nuclear factor of activated T cells) is a transcription factor which plays an important role in various signalling pathways. One of these contributes to transmitting the information that an antigen has been encountered from the T cell receptor to the nucleus. This causes the transcription of the interleukin 2 (IL-2) gene, a key early event in T cell activation. In more detail, the recognition of an antigen by the T cell receptor, combined with a suitable costimulatory signal, leads to a flux of  $\text{Ca}^{2+}$  into the cytosol and the dephosphorylation of NFAT by calcineurin. The NFAT then moves into the nucleus and can take part in transcription.

The process just described has been modelled mathematically by Salazar and Höfer [1]. In the resting cell NFAT is phosphorylated at thirteen sites and the sequential dephosphorylation at these sites leads to a digital effect in an individual cell. Thus after activation almost every cell either produces IL-2 at a maximal rate or produces almost none. The model uses a system of 56 ordinary differential equations with 134 parameters, where the unknowns are the concentrations of different phosphorylation states of NFAT in the cytosol and in the nucleus. The analysis of [1] is based on an examination of a certain steady state of this system for each choice of the parameters. In [2] a more global understanding of the system was obtained. It was shown that the steady state of the system considered in [1] is the only one for a given choice of the parameters and that all other solutions converge to the steady state.

These results were proved using the Deficiency Zero Theorem of Chemical Reaction Network Theory (CRNT). Apart from the interest in understanding this particular system this is an example of the power of CRNT for obtaining rigorous mathematical results about large systems of ordinary differential equations containing many parameters of the kind which often come up in modelling biological systems. In [2] it was also examined what happens when the constant concentration of calcineurin in the model of [1] is replaced by the time-dependent concentration coming from a dynamical model of the calcium influx. Parameters were identified for which the calcineurin concentration tends to a constant and the analysis of the more complicated model can be reduced to that of the previous case.

### *References*

- [1] Salazar, C. and Höfer, T. 2003 Allosteric regulation of the transcription factor NFAT1 by multiple phosphorylation sites: a mathematical analysis. *J. Mol. Biol.* 327, 31–45.
- [2] Rendall, A. D. 2012 Mathematics of the NFAT signalling pathway. Preprint arXiv:1201.1094