Modeling NFAT cycling sensitivity in the cardiac myocyte

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The transcription factor NFAT acts as a signal integrator for a number of signal transduction pathways in cardiac myocytes that initiates gene expression in the disease Pathological Cardiac Hypertrophy[1]. Here we develop a quantitative mathematical model of the cytoplasmic-nuclear-cytoplasmic cycling of NFAT in response to calcium signals in the cardiac myocyte (see Figure 1).

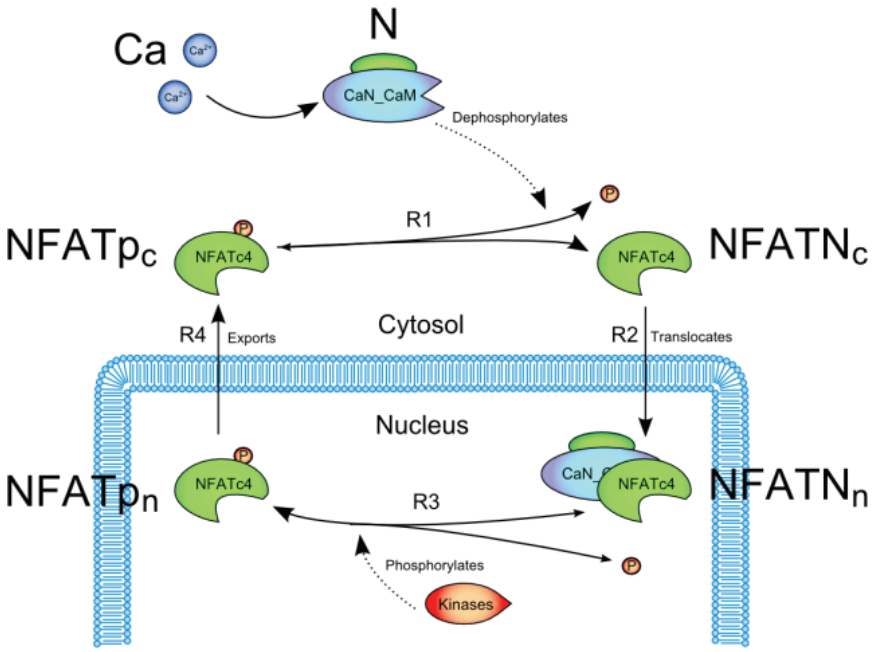

Figure 1: Schematic of the NFAT cycling model.

The model was refined so that output matched experimental myocyte observations and the model also exhibits similar intermediate transient behaviour to that observed in the same pathway component in both BHK and Jurkat T cells. Additionally, the model replicates observed efficient response to an oscillating calcium transient[2], over that of constant calcium for low (<~360 nM) average calcium. One question in understanding calcium handling is whether the system distinguishes between a hypertrophic signal-induced calcium rise, and the background excitation-contraction coupling-driven calcium oscillations present in the cardiac myocyte[3]. We use the model to explore the sensitivity of the system to constant rises in calcium against such a background, showing a surprising sensitivity to the constant calcium signal. Results suggest that hypertrophic signal transduction-induced calcium signals can be easily detected by the NFAT cycling system in the cardiac myocyte, even against calcium oscillations due to beating.

References

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2. Dolmetsch et al. (1998) *Nature* 392(6679):933-936
3. Berridge et al. (2003) *Nature Reviews: Molecular Cell Biology* 4(7):517-529