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Positive feedback in NF-κB signaling

NF-κB is a key transcription factor controlling immune responses, such as inflammation, proliferation and apoptosis. Its regulatory system is tightly controlled by several feedback loops. The two negative loops mediated by NF-κB inducible inhibitors, IκBα and A20, provide the oscillatory responses to the tonic TNFα stimulation, in which NF-κB translocates in and out of the nucleus with period of about 100 min. These oscillations maintain NF-κB phosphorylation, and are indispensable for NF-κB dependent signalling. Here, we explore the role of the feedback loop mediated by the NF-κB inducible cytokine TNFα, which is secreted by the activated cells and can bind TNFα membrane receptors of the neighboring cells, or of the same cell that give rise to the positive feedback regulation. This positive feedback is negligible in most of cell lines, but may become, as suggested by our study, dominant in immune cells like monocytes or macrophages that have a high level of TNFα expression.

The proposed stochastic model pursues our earlier studies [1-2], by including the positive feedback loop regulation. The bifurcation analysis performed for the deterministic approximation of the stochastic model, revealed that for a broad range of the bifurcation parameter (rate of TNFα synthesis) the limit cycle and stable steady state coexist. As a result single cells stochastic trajectories may jump between these two attractors. Such jumps correspond to the spontaneous activatory – inactivatory transitions. In the stochastic model the bifurcation parameter controls the *on* and *off* rates and the probability that cell is in the oscillatory state. Interestingly, even in the parameter range in which the limit cycle oscillations of the deterministic approximation are not present, the spontaneous activation probability is not zero. The model satisfactorily reproduces single cell kinetic of SK-N-AS cell [3], which exhibit spontaneous activation in the absence of TNF stimulation.

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References

[1] Lipniacki, T., Puszynski, K., Paszek, P., Brasier, A.R., Kimmel, M., 2007. Single TNFα trimers mediating NF-κB activation: Stochastic robustness of NF-κB signaling. BMC Bioinformatics **8**, 376.

[2] S. Tay, J. Hughey, T. Lee, T. Lipniacki, M. Covert, S. Quake., *Single-cell NF-κB dynamics reveal digital activation and analogue information processing* Nature. **466** 267-271.

[3] Turner DA, Paszek P, Woodcock DJ, Nelson DE, Horton CA, Wang Y, Spiller DG, Rand DA, White MR, Harper CV., *Physiological levels of TNFα stimulation induce stochastic dynamics of NF-κB responses in single living cells* J Cell Sci. **123** 2834-43.