

Robustness of stochastic signal processing in NF- κ B pathway controlled by interlinked positive and negative feedback loops

Tomasz Lipniacki

Institute of Fundamental Technological Research, Warsaw, Poland

The NF- κ B regulatory network controls innate immune response by transducing variety of pathogen-derived and cytokine stimuli into well defined single-cell gene regulatory events. We analyze the network by means of the model combining a deterministic description for molecular species with large cellular concentrations with two classes of stochastic switches: cell-surface receptor activation by TNF α ligand, and I κ B α , A20 and TNF α genes activation by NF- κ B molecules. Both stochastic switches are associated with amplification pathways capable of translating single molecular events into tens of thousands of synthesized or degraded proteins. The pathway dynamic is controlled by interlinked positive and negative feedback loops. The two negative feedback loops are mediated by NF- κ B inhibitors I κ B α and A20 (Hoffmann et al. 2002 and Lipniacki et al. 2004) allow for oscillatory responses to tonic stimulation. The positive feedback loop, introduced in this study, via TNF α autocrine regulation, is important in TNF α secreting cells (like monocytes) and allows for long lasting NF- κ B oscillations in response to pulse stimulation, which in turn may be helpful in defining cell fate decisions. Also in response to LPS and viral RNA cells produce and secrete TNF α transmitting signal to NF- κ B module, which makes the TNF α a linker of innate immune responses.

We show that at a low TNF α dose only a fraction of cells are activated, but in these activated cells the amplification mechanisms assure that the amplitude of NF- κ B nuclear translocation remains above a threshold (Lipniacki et al. 2007). Similarly, the lower nuclear NF- κ B concentration only reduces the probability of gene activation, but does not reduce gene expression of those responding. These two effects provide a particular stochastic robustness in cell regulation, allowing cells to respond differently to the same stimuli, but causing their individual responses to be unequivocal. Both effects are likely to be crucial in the early immune response: Diversity in cell responses causes that the tissue defense is harder to overcome by relatively simple programs coded in viruses and other pathogens. The more focused single-cell responses help cells to choose their individual fates such as apoptosis, proliferation or differentiation. The model supports the hypothesis that binding of single TNF α ligands is sufficient to induce massive NF- κ B translocation and activation of NF- κ B dependent genes.

Hoffmann, A., Levchenko, A., Scott, M.L., & Baltimore, D., The I κ B-NF κ B signaling module: temporal control and selective gene activation. *Science* 2002, **298**:1241-1245.

Lipniacki T, Paszek P, Brasier AR, Luxon B, Kimmel M: Mathematical model of NF- κ B regulatory module. *J Theor Biol* 2004, **228**:195-215.

Lipniacki, T., Puszynski, K., Paszek, P., Brasier, A. R., Kimmel, M. Single TNF α trimers mediating NF- κ B activation: Stochastic robustness of NF- κ B signaling. *BMC Bioinformatics* 2007, **8**:736-756.