Stochastic Robustness of NF-κB signaling

T. Lipniacki[1], K. Puszynski[2], P. Paszek[3], A.R. Brasier[4] and M. Kimmel[5]

***Short Abstract* — The role of stochasticity in NF-□B pathway is studied using a mathematical model. We found that at low TNF□ dose, population of cells splits into subpopulations of responding and non-responding cells, and that TNF□ dose rather regulates fraction of responding cells than the amplitude of individual cell responses. This may be important for proper immune responses helping cells to decide their individual fates such as proliferation or apoptosis.**

***Keywords* — Stochastic modeling, robustness, innate immunity, NF-□B, TNF□.**

THE NF-□B regulatory network controls innate immune responses by transducing variety of pathogen and cytokine stimuli into well defined single-cell gene regulatory events. Our analysis of the system is based on the two-feedback loop stochastic model of the NF-□B pathway, which combines the signal transduction cascade that connected cell surface receptors with NF-□B core regulatory module, **Fig. 1A** [1]. In short the action of regulatory pathways may be summarized as follows: The binding of TNF□ trimer initiates formation of an active receptor complex. The active receptors activate the IKKK kinase, which in turn activates the IKK kinase. Active IKK binds transiently to cytoplasmic (NF-□B|I□B□) complex and phosphorylates I□B□ initiating its degradation. Released NF-□B enters the nucleus to induce transcription of its two inhibitors: I□B□ and A20.

We identified two stochastic switches key to the NF-□B pathway regulation: activation of A20 and I□B□ genes due to binding of NF-□B molecules to the gene promoters and activation of TNFR1 receptors due to binding TNF□ trimers. Both switches are associated with amplification pathways capable to transmitting single molecular events into tens of thousands of synthesized or degraded proteins. The mathematical representation of the model consists of 15 ordinary differential equations coupled with stochastic process that controls gene and receptors activation. The single cell numerical simulations were performed to analyze the individual cell responses to persistent stimulation in a board range of TNF□ doses, **Fig. 1B**.

At high TNF□ dose (above 1ng/ml) the receptor activation rate is high and most of cells are activated in the first few minutes of the TNF□ stimulation. As a result, the first peak of nuclear NF-□B is well synchronized among cells, in accordance with experiment [2]. Synchronization of subsequent peaks decreases due to the stochasticity in cell regulation. For low dose (0.1 and 0.3 ng/ml) the activation of each cell typically results from the activation of single receptors and thus the first peak waiting time varies between cells. As a result NF-□B oscillations are not synchronized.

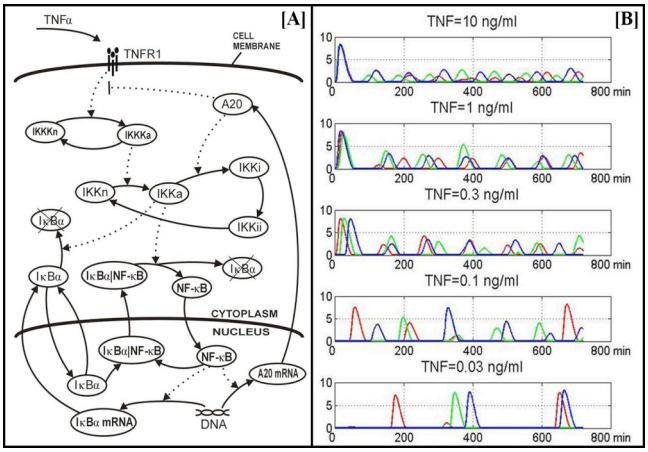

Fig 1. [A] Diagram of NF-□B regulatory pathway. [B] Amplitude of NF-□B oscillations obtained single cell simulations for five TNF□ doses. Each cell is marked by different color.

Stochastic receptor activation leading to the massive NF-□B nuclear translocation and stochastic gene activation leading to bursts of proteins provides a particular "stochastic robustness" in cell regulation, which assures the minimal responses to the signals. Decreasing magnitude of the signal reduces mostly the probability of the response. If the TNF□ signal is low, some cells respond by a massive NF-□B translocation, whereas some do not respond at all. It helps to avoid ambiguity, such as when small nuclear concentration of NF-□B leads to activation of the undefined fraction of NF-□B responsible genes. Stochastic robustness allows cells to respond differently to the same stimulation, but makes their individual responses better defined.

REFERENCES

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[1]Inst. of Fundamental Tech. Research, Poland. E-mail: tlipnia@ippt.gov.pl

[2]Silesian Univer. of Tech., Poland. E-mail: krzysztof.puszynski@polsl.pl

[3]University of Liverpool, U.K. E-mail: p.paszek@liverpool.ac.uk

[4]UTMB, USA. E-mail: arbrasie@utmb.edu

[5]Rice University, USA. E-mail: kimmel@rice.edu