Information Processing in the NF-κB Pathway

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***Short Abstract* — We combined experimentation with mathematical modeling to elucidate how information about TNF concentration is turned into a binary decision in the NF-κB pathway. Using Kolmogorov-Smirnov distance, we quantified the ability of a cell to discern 8 TNF concentrations at each step of the pathway. Discernibility of low TNF concentrations is restricted by noise at the TNF receptor level, whereas discernibility of high TNF concentrations is restricted by saturation/depletion of downstream signaling components. The impact of co-stimulation with a translation inhibitor shows that the NF-κB network not only relays ~1 bit of information to coordinate expression of early genes, but also over a longer time course integrates information about other stimuli.**

I. Background

BINARY cell fate decisions result from integration of information obtained from several sources and subsequent information processing. These processes should be distinguished from trivial information decay to ultimately 1 bit just by noise.

A key pathway of innate immunity, the NF-κB pathway, is known to transmit merely 1 bit of information about the level of a biochemical stimulus [1,2]. Here, we analyze how information transmitted through subsequent steps of the signaling cascade from TNF receptor (TNFR) to NF-κB is reduced or turned into a binary decision [3]. We employ our recently calibrated [4] mathematical model of the NF-κB network and focus on the first pulse of NF-κB nuclear translocation. In addition to estimating upper bound of mutual information (max MI), we quantify the ability of the system to discern the neighboring concentrations of a stimulus ("dose discernibility") at each step of the core pathway by means of the Kolmogorov–Smirnov (KS) distance, a measure of distance between two probability distributions.

II. Results

A. Transmission of information and dose discernibility are reduced by extrinsic noise

The model system simulated stochastically without extrinsic noise transmits about 1.3 bit of information about TNF concentration. When extrinsic noise, associated with heterogeneity in the levels of TNF receptor and total NF-κB, is considered, both dose discernibility and max MI are reduced; the latter, to ~1 bit.

B. Mutual information and dose discernibility decrease as the signal propagates through the pathway

Information transmission at low TNF concentrations is mostly limited by molecular noise at the TNFR level, whereas at high TNF concentrations it is mostly limited by saturation of active IKK. As a result, the highest discernibility of adjacent TNF doses by NF-κB is observed at intermediate TNF doses: between 0.03 and 0.3 ng/ml.

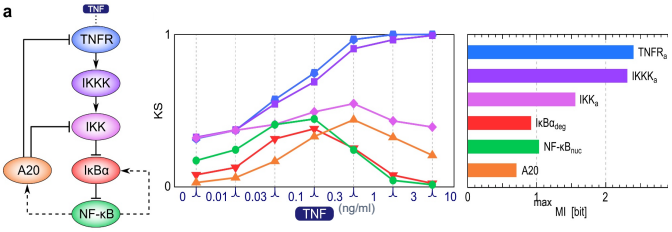

Figure 1. When passing through the NF-κB pathway (**A**), dose discernibility (**B**) and mutual information (**C**) are reduced.

C. NF-κB network can integrate signals from different sources over time

Cycloheximide (CHX) that blocks the synthesis of NF-κB inhibitors, IκBα and A20, allows NF-κB to remain in the nucleus for at least two hours. Responses to the combined lipopolysaccharide (LPS) + CHX stimulation, although almost indistinguishable from responses to pure LPS at 30 min, are clearly distinct at 120 min. This shows that LPS-stimulated cells are able to integrate additional signal from CHX over a longer time course.

III. Conclusion

The NF-κB system should be perceived as a feedback-controlled decision-making module rather than a simple information transmission channel.

References

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