Modeling the Oscillatory Response of the NF-κB Signaling Pathway

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***Short Abstract* — The negative feedback architecture of the NF-κB signaling pathway has been shown to produce damped oscillations in NF-κB nuclear-cytoplasmic localization. Beginning with a previously reported large-scale model describing the response of the NF-κB signaling network to external perturbation, we have formulated a simplified nonlinear model consisting of the essential components of the signaling pathway. We have demonstrated that results from the reduced model are in excellent agreement with experiments. Furthermore, we have utilized the reduced model to gain insight into how the NF-κB signaling network may have evolved to produce a robust cellular response in a noisy environment.**

***Keywords* — Stochastic gene regulation, NF-κB signaling pathway, Negative feedback**

I. INTRODUCTION

THE NF-κB signaling network plays an essential role in mitigating many important cellular processes including inflammation, the immune response, and apoptosis [1]. NF-κB activity is controlled by inhibitor IκB proteins (IκBα, -β, -ε) that bind to NF-κB holding it in the cytoplasm. IκB proteins are degraded in response to cell stimulation allowing free NF-κB to translocate into the nucleus and activate genes including IκBα and IκBε. The negative feedback architecture of NF-κB regulation has been shown to generate damped intracellular oscillations for certain input signals [2,3]. Recent work has shown that removal of IκBε negative feedback loops leads to an increase in the number of oscillatory cycles of nuclear NF-κB activity [4], suggesting that this loop serves to stabilize the system by reducing undesirable oscillations.

II. METHODS

Beginning with a previously reported large-scale model describing the response of the NF-κB signaling network to external perturbation [2], we formulate a simplified nonlinear model consisting of the essential components of the system. We demonstrate that results from the reduced model are in excellent agreement with experiments.

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Next, we hypothesize that the architecture of the NFKB signaling network evolved in two main steps from a simple network with no feedback into a network with two antiphase negative feedback loops. Using our reduced model, we show that a signaling network without feedback is much less sensitive than a network with negative feedback. Although negative feedback results in increased sensitivity, chronic stimulation of a network with negative feedback produces pronounced oscillations in nuclear NFKB levels. We suggest that oscillations are detrimental to cellular behavior and the single feedback network evolved into a more complicated dual-feedback network in order to provide a mechanism for diminishing oscillations. We show that the addition of a second negative feedback loop out of phase with the first feedback loop results in less pronounced oscillations.

Finally, we introduce a stochastic version of the reduced model to allow us to analyze the effect of noise on the signaling pathway by comparing results from the deterministic model with results from the stochastic model. We utilize the stochastic model to gain insight into how the architecture of the NF-κB network may have evolved to provide a robust cellular response in a noisy environment.

III. CONCLUSION

We conclude with new testable predictions that arise from the modeling.

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