Roles of two coupled negative feedback loops on dynamic patterns of NF-κB signaling

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Short Abstract — **Current mathematical models of NF-κB signal transduction rely on parameterization, followed by numerical simulation, of a set of differential equations and do not fully explain the governing principles for dynamic patterns of NF-kB response, which are presumably responsible for the pleiotropism of NF-κB signaling. We have constructed a hybrid NF-κB model from previously published components and used sensitivity analysis to derive a minimal model consisting of two coupled negative feedback loops involving IκB and A20. We predict a dose-response curve with sigmoidal shape, the existence of A20-driven Hopf-bifurcations, and deduce a statistical ensemble that categorizes dynamic patterns of NF-κB signaling response.**

Keywords — **NF-κB signal transduction, sensitivity analysis, mathematical analysis, statistical ensemble of dynamic patterns.**

NF-κB is a stimulus-responsive pleiotropic transcription activator, which plays significant roles in various parts of the immune system [1]. NF-κB shuttling between nucleus and cytoplasm is regulated by IKK-NFκB-IκB, which consists of three proteins IκB, IKK (IκB kinase), and NF-κB [1,2]. Upon stimulus, NF-κB is freed up to shuttle into the nucleus, initiating transcription of target genes responsible for inflammatory cytokines, anti-apoptic molecules, and NF-κB signal termination.

Using both computational models and experiments, Hoffmann et al [2] demonstrated that IκBα is responsible for strong negative feedback and for sustained oscillatory shuttling of NFκB, whereas IκBβ and IκBε reduce oscillation magnitudes. Lipniacki et al [3] introduced A20 as an additional negative feedback component in their computational model, reproducing NF-κB signaling response experimentally observed in A20-deficient cells. Using a minimal model with negative feedback provided solely by IκB, Krishina et al [4] showed robustness of the NFκB oscillatory shuttling pattern across a range of parametric variations, primarily due to the saturated degradation rate of IκB. However, the analyses of neither the minimal model [4] nor the full NFκB reaction networks [2,3] fully elucidate the governing principles of two coupled negative feedback loops on dynamic patterns of NFκB response.

We combined features of these several models [2,3] to build a hybrid network of the IKK-NFκB-IκB signaling module, which when translated to a set of nonlinear differential equations, contains 70 kinetic rate variables. Using Latin hypercube sampling techniques, we generated several thousand sets of kinetic parameters in biologically feasible ranges for the model and numerically integrated the equations to generate temporal response profiles. We then calculated correlation coefficients between individual kinetic parameter and dynamic characteristics of NFκB profiles, and were able to identify a dozen kinetic parameters that significantly influence the NFκB temporal evolution.

Using the results of the sensitivity analysis and additional heuristic singular perturbation approximations, we derived a minimal model with IKK, NF-κB, and two coupled negative feedback loops of IκB and A20. To understand the roles of these feedback loops on the dynamic patterns of NF-κB shuttling between nucleus and cytoplasm, we analyzed the minimal model, predicting that (1) a limit cycle of NF-κB shuttling can exist only if a negative regulator A20 is present, and (2) there are only four basic dynamic patterns of NF-κB shuttling. The underlying principle for the latter can be understood by simple inequality relations between the relaxation times of four biochemical species in the minimal model. We also predict (3) that the shape of the dose-response curve of NF-κB signaling, e.g., LPS versus overnight production of TNF-α, should be sigmoidal, based on steady state analysis of the minimal model and numerical simulations of the full NF-κB biochemical reaction network. Lastly, taking into account the heterogeneous state of cells arising from various sources, we observe (4) that the dynamic patterns of NF-κB signaling should be represented not by a single NF-κB temporal profile but by its statistical distribution and present such a distribution for the wild type and various mutants.

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