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Core network identification using parametric sensitivity and multi-way principal component analysis in NFkB signaling network

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ABSTRACT

Biochemical networks are complex in nature. It is desirable that the key features be captured and analyzed using a core-network. In this work, a hierarchical core-network identification procedure was developed using parametric sensitivity and multi-way principal component analysis. The procedure was applied to the intracellular IKK to NFkBn (NFkB in nucleus) signaling transduction network to identify the key reactions in the network. We found that the key internal feedback control of IKK to NFkBn signaling transduction is through IkBa. The key reactions governing initial signal transduction are the phosphorylation of IkBaNFkB by IKK outside the nucleus, subsequent dissociation to release NFkB, and the transport of NFkB into the nucleus. Similar reactions involving IkBe and IkBb are only important when the IKK stimuli are relatively large. Moreover, this signal transduction network is able to damp the initial NFkBn response to IKK stimulus and transform large stimulus into delayed and sustained response. Such damping effect is present with only IkBa feedback loop is included, but IkBe and IkBb are responsible for transforming large stimulus into sustained response. Furthermore, the alternative pathway of formation of IKK-IkBa and trimerization of NFkB is responsible for a secondary buildup of IKK at large stimulus.

1. Introduction

Mathematical modeling of biological processes, a critical tool in system biology, is indispensable in advancing our knowledge of biological network systems [1–3]. However, such studies inevitably produced complex biochemical networks involving a large number of reactions and species, modeled by equations involving a large number of parameters and variables. Sensitivity analysis is usually applied to analyze how sensitive a system is with respect to the change of parameters [4]. It is an important tool to identify those key reactions and species, *i.e.* a core-network that capture the essential characteristics of the system [5]. For example using the Monte Carlo method, Cho *et al.* employed multi-parametric global sensitivity analysis on the TNFa-mediated NFkB signal transduction pathway for experimental design [6]. Schwacke and Voit presented a Taylor integration method for the efficient computation of time dependent sensitivities for generalized mass action systems, then investigated the effects of different initial species concentrations on the system dynamics [7]. Eissing *et al.*, employed local sensitivity analyses of a characteristic steady state behavior for all states and parameters to provide an overview for the whole system of signal transduction pathway of receptor-induced apoptosis [8]. Yue *et al.*, performed lumped dynamic sensitivity analysis on a model of the IκB-NFkBn signal pathway system and find that only 8 out of the 64 parameters in the model have major influence on the nucleus NFkB oscillations [9]. A lumped index over a time course is usually used to identify the key reactions. Such an approach may not be most desirable to capture the key features of a dynamic process.

Inflammation is an important mechanism for a biological entity to defend against external stimulus. One of the key transcription factors affecting inflammation response is the nucleus factor NFkB. NFkB is a dimer made up of one of the five protein subunits. In addition to inflammation, it is also considered very important in virus infection, immunity deceases, cancer, arthritis, *etc.* [10]. Hence its regulation and control have been studied extensively. Several reports have developed complex kinetic models describing the signal transduction process for inducing NFkBn [11–17].

One of the commonly employed methods for feature extraction of time profile data is the multi-way principal component analysis (MPCA) method proposed by Nomikos and McGregor [18]. In this

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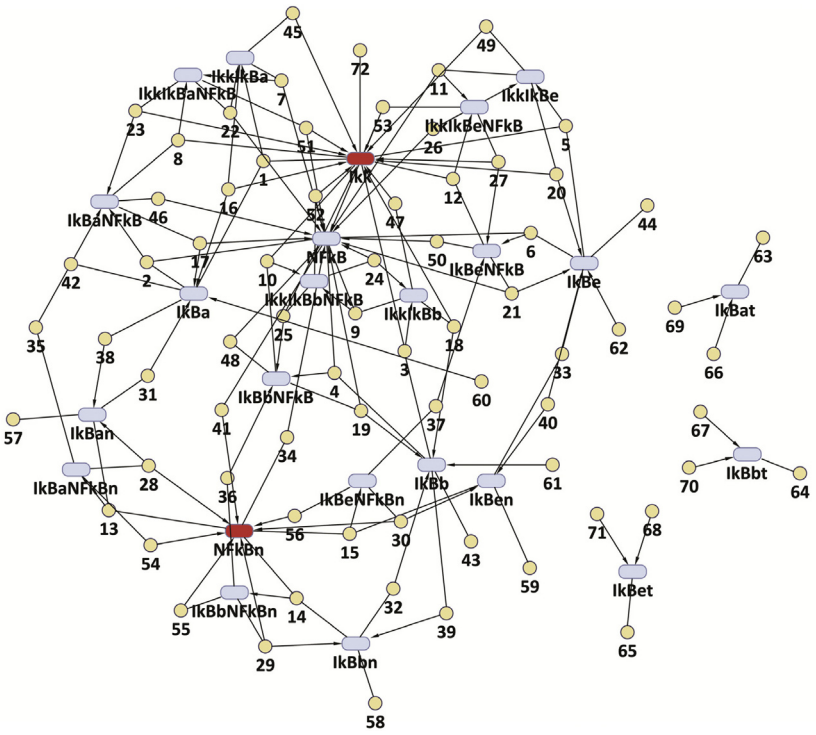

Fig. 1. Full network of IKK to NFkBn signaling model proposed by Kearns *et al.* [12]. It contains 72 reactions and 24 species.

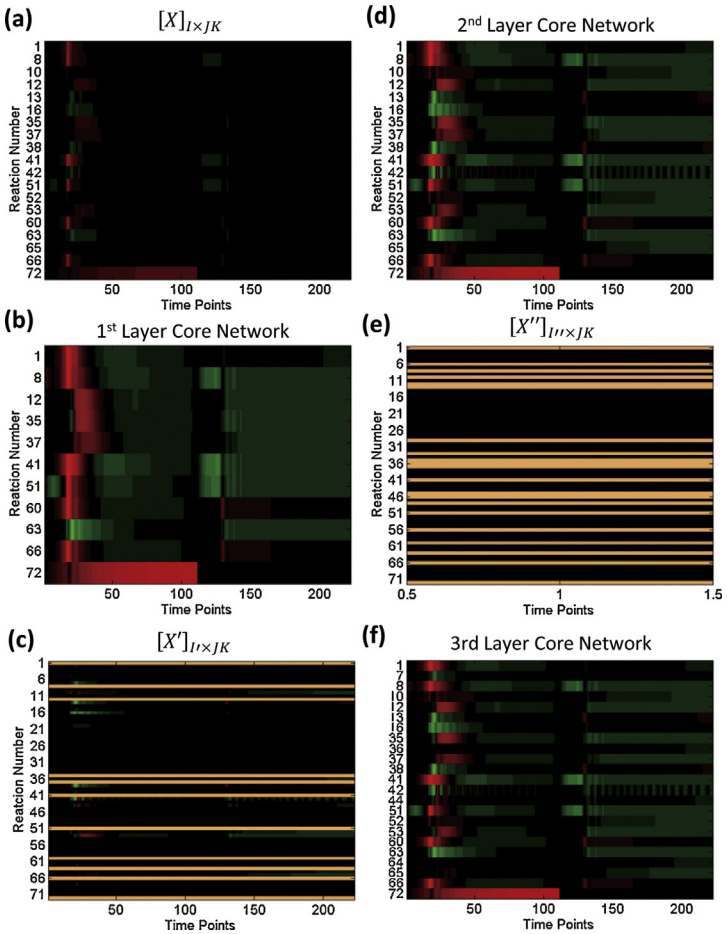

Fig. 2. Hierarchical identification procedure: (a) difference between reference and perturbed profiles $[X]_{I\times JK}$ of all reactions, (b) sample profile of 1st level core-network, (c) difference between reference and perturbed profiles, reactions of 1st level core network marked in orange, (d) sample profile 1st and 2nd levels core-network, (e) difference between reference and perturbed profiles, reactions of 1st and 2nd level core network marked in orange, (f) sample profile 1st, 2nd, and 3rd levels core-network.