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SENSITIVITY ANALYSIS AND EXPERIMENTAL DESIGN OF A STIFF SIGNAL TRANSDUCTION PATHWAY MODEL

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Sensitivity analysis is normally used to analyze how sensitive a system is with respect to the change of parameters or initial conditions and is perhaps best known in systems biology via the formalism of metabolic control analysis [1, 2]. The nuclear factor κB (NF-κB) signalling pathway is an important cellular signalling pathway, of which protein phosphorylation is a major factor controlling the activation of further downstream events. The NF-κB proteins regulate numerous genes that play important roles in inter- and intra-cellular signalling, cellular stress responses, cell growth, survival, and apoptosis. As such, its specificity and its role in the temporal control of gene expression are of crucial physiological interest.

The mathematical model used in this work is the TNFα-mediated NF-κB model provided by Hoffmann *et al*. [3]. In this model (and experimentally) there are significant oscillations in the concentration of NF-κB in the nucleus (NF-κB$_n$) [3-5]. The dynamics of the system is described by a set of ordinary differential equations (ODEs) with given initial conditions. As this system involves a large number of reactions and the parameters span several orders of magnitude, the ODEs turn out to be nonlinear and stiff. The direct differential method (DDM) is used to calculate the local sensitivities as a function of time. Relative sensitivity coefficients are used for parameter ranking and experimental design. In order to consider the complete dynamics of the oscillation system, two performance indices are proposed for analysis. One is to use a single variable (nuclear NF-κB) to form the L^2-norm performance, the other is to include all species concentration profiles to formulate the Euclidean-norm function. For this system, the local sensitivity analysis using nuclear NF-κB only and all species produce consistent results (see fig 1 (a) and (b)).

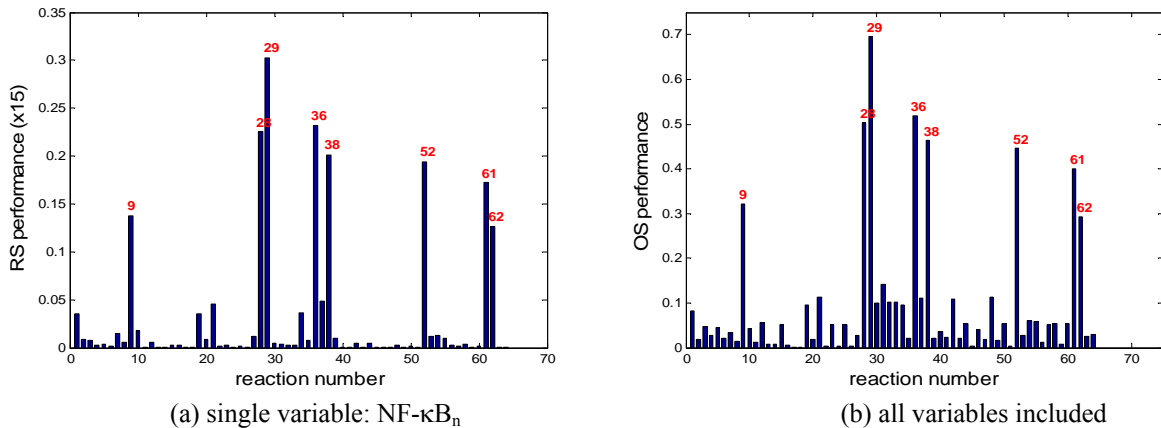(a) single variable: NF-κB$_n$ (b) all variables included
Figure 1. Relative sensitivity indices with single variable and multiple variables

The Morris method [6] is used to investigate the global sensitivity of the system. It is supposed that a finite distribution of elementary effects associated with each input can be estimated. Two sensitivity measures were proposed for each factor: μ, an estimate of the mean of the distribution, and σ, an estimate of the standard deviation of the distribution. These two measures are used as indicators of which inputs should be considered important. Modifications to the original Morris method is proposed to deal with the case that the parameters are within wide and different intervals. Simulation results in terms of μ are given in fig.2 with both wide and narrow ranges being considered. It can be seen that when the parameter range is very small, global analysis makes similar results as that of the local analysis (see fig.1 (a) and fig2. (a)). However, when the analysis range is large, it produces a different sensitivity pattern from the local analysis (see fig.1 (a) and fig2. (b)). This is because global sensitivity analysis can provide information on interactions between parameters and also reveal the non-linear effects from simultaneous parameter variation while local sensitivity analysis can't.

Optimal experimental design on the IKK activation intensity is then performed based on sensitivity analysis. Under the assumption of uncorrelated measurement noise with zero-mean Gaussian distribution, the information content of measurements can be quantified by the Fisher information matrix (FIM) [7, 8]. In general, the smaller the joint confidence intervals for the estimated parameters are, the more information is

contained in the measurements. The FIM is formulated from the sensitivity matrix. Along with the Cramer-Rao theorem, the FIM is used to determine the optimal step input signal such that the estimated parameters have the minimum variance. Taking IKK as the step input and nuclear NF-κB as the system output, four commonly used optimal design criteria, i.e., A-optimal, D-optimal, E-optimal and the modified E-optimal design, are used for calculation. Simulation shows that the optimal initial concentration of IKK is $0.1\,\mu M$ under the modified E-optimal design, and it is $0.06\,\mu M$ under the other three optimal designs. The 95% confidence intervals of these two results are illustrated in fig.3 when two sensitive parameters are considered each time. It can be seen that the optimal input amplitude should be $0.06\,\mu M$ because its confidence interval ellipsoid is smaller.

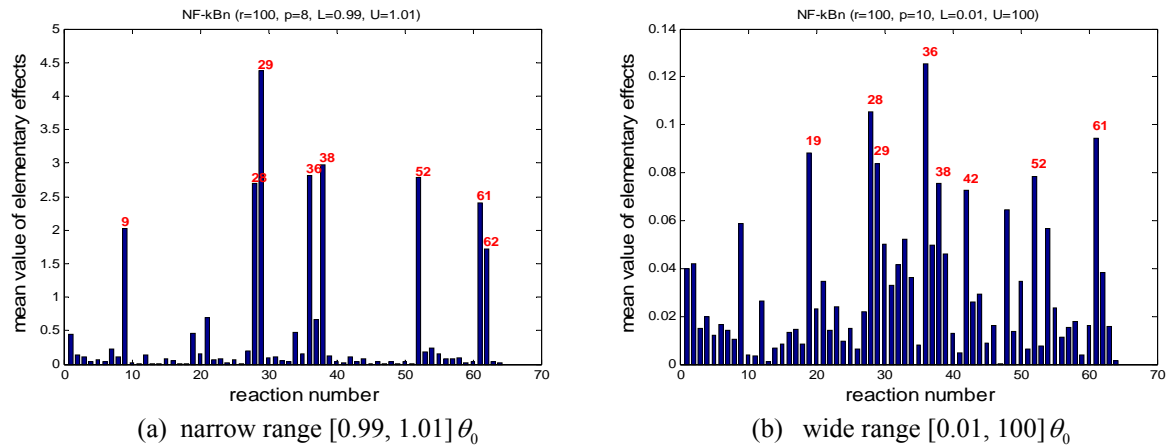(a) narrow range $[0.99, 1.01]\,\theta_0$ (b) wide range $[0.01, 100]\,\theta_0$

Figure 2. Global sensitivity analysis results in terms of the mean value of the elementary effects in Morris method (θ_0 stands for nominal value in simulation)
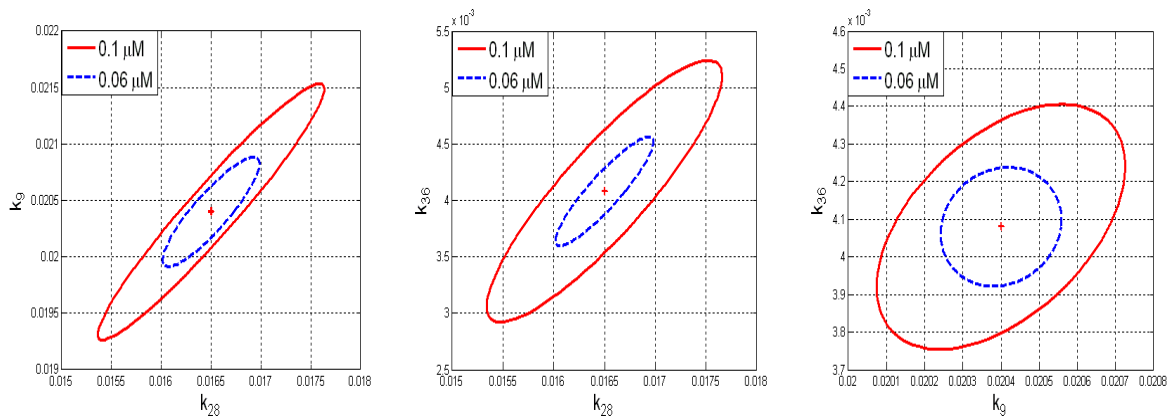

Figure 3. Confidence intervals of two different amplitudes of the step input

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