

Improving Data Fitting of a Signal Transduction Model by Global Sensitivity Analysis

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Abstract— Based on a simplified model of the (TNF- α mediated) I κ B α -NF- κ B signal transduction pathway, global sensitivity analysis has been performed to identify those parameters that exert significant control on the system outputs. The permutation operation in Morris method is modified to work for log-uniform sampling parameters. The identified sensitive parameters are then estimated using multivariable search such that the output of the model matches experimental data representing the nuclear concentration of NF- κ B. Such parameter tuning leads to much better agreement between the model and the experimental time series relative to those previously published. This shows the importance of global sensitivity analysis in Systems Biology models.

I. INTRODUCTION

With the development of systems biology [1-3], mathematical modeling and dynamic simulation are playing increasingly important roles in the study of signal transduction and other pathways. Well-developed mathematical models can be used to explain and predict the dynamics of biochemical networks [4, 5]. Building such a model includes model structure development, parameter estimation and model validation. In general, it is difficult to formulate a suitable model structure, not least since signal transduction pathways almost always have complex nonlinear dynamics, and most models are severely underdetermined. Once a reasonable structure of a small part of a biochemical system is established, it is then necessary (i) to construct an objective function reflecting the ‘purpose’ of the investigation (whether to explain a piece of biology or for the purposes of metabolic engineering) and (ii) to determine with which parameters and within what boundaries the manipulations can be made [6]. A particular issue with systems biology is that it is the parameters that control the variables and not the other way around, while omics measurements usually determine only the variables (e.g. the metabolic fluxes and concentrations in metabolism / metabolomics) [7]. Going from the variables to the parameters involves solving an inverse or system identification problem [8], and this is

typically very hard as these problems are again often heavily underdetermined, even if the structural model is correct [9-12].

A common approach to decide the values of parameters is to find them from published literature. An alternative approach, more typically only for fairly small systems, is to measure each and every parameter, which is almost always impossible. For poorly determined or unknown parameters in the model, the third approach is to estimate the parameters by fitting the output of the system variables to the measurement profiles, using parameter estimation techniques.

The optimization of parameters for the fitting problems in biochemical systems is stated as a nonlinear programming (NLP) problem subject to nonlinear differential-algebraic constraints. Both deterministic and stochastic optimization methods have been explored in various cases [6, 11, 13]. However, sometimes even when a suitable fitting strategy is implemented, satisfactory resolution might still be difficult to obtain (e.g. as in [14]). This may be caused by an inappropriate model structure and/or experimental error. Even if both the model structure and experiments are well designed, there will be inaccuracies in the ‘known’ parameter values. For a simple module of a signal transduction pathway, there are normally dozens or even hundreds of parameters. Although it is possible to reset all their values during the fitting process, a much more suitable strategy is to reset those parameters that have significant effects on the system output while keeping the rest constant.

Sensitivity analysis is a good way to compare the different contribution(s) of parameters to the system output(s). It is the study of how variation in the output of a statistical model can be apportioned, qualitatively or quantitatively, to different sources of variation. It should be considered a pre-requisite for mathematical model building in any scientific discipline where modeling takes places [5, 15]. Sensitivity analysis has been applied in many areas including the signal transduction pathway systems [16-18], but most focus has been on local sensitivity analysis. Local sensitivity analysis is problematic when a most likely value cannot be reliably determined [19], and it cannot provide the real variation of the model output with respect to each parameter within its boundary. For a rather nonlinear model of signal transduction pathway, global sensitivity analysis should be performed. There is a vast literature on numerical methods and applications of global sensitivity analysis (for a review see [15, 20, 21]), among them the Morris method [22] is a screening method which is computationally cheap compared to Monte Carlo type

This work was supported by the UK Biotechnology and Biological Science Research Council (BBSRC), and the Outstanding Overseas Chinese Scholars Fund of Chinese Academy of Sciences (2004-1-4)

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methods. It deals efficiently with models with a large number of input factors and can rank them in the order of their importance, but does not quantify by how much a given factor is more important than another. In this work, a modified Morris method is used to evaluate the global sensitivities of an I κ B-NF- κ B signal transduction model, based on which some sensitive parameters are re-estimated.

II. AN I κ B α -NF- κ B SIGNAL TRANSDUCTION MODEL

The transcription factor NF- κ B regulates numerous genes that play important roles in inter- and intra-cellular signaling, 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. Five related mammalian gene products participate in NF- κ B functions (RelA/p65, cRel, RelB, p50, p52) and the predominant species in many cell types is a p65:p50 heterodimer [14].

Activation of most forms of NF- κ B is largely controlled by three I κ B isoforms (I κ B α , - β , and - ϵ) that bind to NF- κ B, preventing its association with DNA and causing its localization in the cytoplasm. Signals from various stimuli are transduced so as to activate the I κ B kinase (IKK) complex, which phosphorylates each I κ B isoform, leading to their ubiquitination and proteolysis. I κ B degradation allows NF- κ B to translocate to the nucleus and to bind DNA. I κ B α synthesis is controlled by a highly NF- κ B-responsive promoter causing autoregulation of NF- κ B signalling. In this model (and experimentally) there are significant oscillations in the concentration of NF- κ B in the nucleus (NF- κ Bn) [14, 17].

In the mathematical model of I κ B-NF- κ B signal pathway provided by Hoffmann *et al.* [14], the rates of transcription and translation of I κ B isoforms and the rate of I κ B-NF- κ B nuclear export and NF- κ B nuclear import are unknown. TNF α stimulation of fibroblasts that contained only the I κ B α isoform resulted in a highly oscillatory NF- κ B response, with four peaks over the course of the 6-hour experiment [14]. The authors utilized both a steepest gradient descent (GD) method and genetic algorithm (GA) separately to estimate the parameter values. However, the resulting model failed to describe faithfully the overall shape and frequency of the oscillations of NF- κ Bn measured in cells with only I κ B α isoform. A random search method was then used to improve the fitting quality regarding the frequency and the amplitude of oscillations (shown in Fig. 1, see supplementary material to [14]). However, neither result is satisfactory. Note that the measurement of ensembles of cells also leads to inaccuracies that are not observed when single-cell measurements are used [23].

For such a nonlinear model, likely with many local minima, the parameter estimation is not an easy job. Nevertheless, good results are expected when both local and global optimization methods are implemented. It is assumed that this model structure is reasonably reliable [14, 23]. A possible problem causing the mismatch of data fitting might then be that some parameters cited directly from literature should be further estimated.

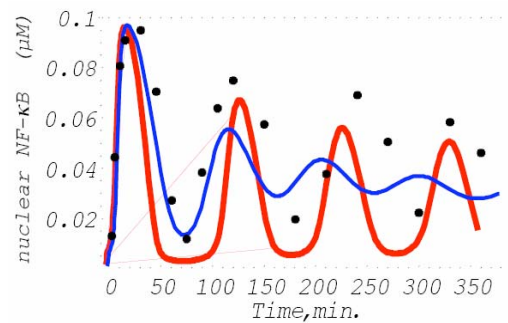


Fig. 1. Comparison of the fitting methods applied to the oscillatory NF- κ B activation profile in I κ B β -/- I κ B ϵ -/- cells. The experimental data are shown as black filled circles; the “semi-quantitative” fit is shown in red and the result of random search fitting in blue (See Fig. S1 in the supplementary material to [14]).

TABLE I LIST OF REACTIONS AND PARAMETERS OF THE I κ B α -NF- κ B COMPUTATIONAL MODEL

Reactions	Parameter values	Units
$I\kappa B\alpha + NF - \kappa B \rightarrow I\kappa B\alpha - NF - \kappa B$	k1 30	$\mu M^{-1} min^{-1}$
$I\kappa B\alpha - NF - \kappa B \rightarrow NF - \kappa B + I\kappa B\alpha$	k2 6e-5	min^{-1}
$IKK I\kappa B\alpha + NF - \kappa B \rightarrow IKK I\kappa B\alpha - NF - \kappa B$	k3 30	$\mu M^{-1} min^{-1}$
$IKK I\kappa B\alpha - NF - \kappa B \rightarrow NF - \kappa B + IKK I\kappa B\alpha$	k4 6e-5	min^{-1}
$IKK I\kappa B\alpha - NF - \kappa B \rightarrow NF - \kappa B + IKK$	k5 1.221	min^{-1}
$I\kappa B\alpha - NF - \kappa B \rightarrow NF - \kappa B$	k6 6e-5	min^{-1}
$NF - \kappa B \rightarrow NF - \kappa B_n$	k7 5.4	min^{-1}
$NF - \kappa B_n \rightarrow NF - \kappa B$	k8 0.0048	min^{-1}
$I\kappa B\alpha_n + NF - \kappa B_n \rightarrow I\kappa B\alpha_n - NF - \kappa B_n$	k9 30	$\mu M^{-1} min^{-1}$
$I\kappa B\alpha_n - NF - \kappa B_n \rightarrow NF - \kappa B_n + I\kappa B\alpha_n$	k10 6e-5	min^{-1}
$source \rightarrow I\kappa B\alpha_{-i}$	k11 9.24e-5	$\mu M^{-1} min^{-1}$
$NF - \kappa B_n + NF - \kappa B_n \rightarrow I\kappa B\alpha_{-i} + NF - \kappa B_n + NF - \kappa B_n$	k12 0.99	$\mu M^{-1} min^{-1}$
$I\kappa B\alpha_{-i} \rightarrow sink$	k13 0.0168	min^{-1}
$IKK + I\kappa B\alpha \rightarrow IKK I\kappa B\alpha$	k14 1.35	$\mu M^{-1} min^{-1}$
$IKK I\kappa B\alpha \rightarrow IKK + I\kappa B\alpha$	k15 0.075	min^{-1}
$I\kappa B\alpha_{-i} \rightarrow I\kappa B\alpha + I\kappa B\alpha_{-i}$	k16 0.2448	min^{-1}
$I\kappa B\alpha \rightarrow sink$	k17 0.00678	min^{-1}
$I\kappa B\alpha \rightarrow I\kappa B\alpha_{(import)}$	k18 0.018	min^{-1}
$I\kappa B\alpha_n \rightarrow I\kappa B\alpha_{(export)}$	k19 0.012	min^{-1}
$IKK + I\kappa B\alpha - NF - \kappa B \rightarrow IKK I\kappa B\alpha - NF - \kappa B$	k20 11.1	$\mu M^{-1} min^{-1}$
$IKK I\kappa B\alpha - NF - \kappa B \rightarrow IKK + I\kappa B\alpha - NF - \kappa B$	k21 0.075	min^{-1}
$I\kappa B\alpha_n - NF - \kappa B_n \rightarrow I\kappa B\alpha - NF - \kappa B_{(export)}$	k22 0.828	min^{-1}
$IKK \rightarrow sink$	k23 0.0072	min^{-1}
$IKK I\kappa B\alpha \rightarrow IKK$	k24 0.2442	min^{-1}

In order to improve the output fitting of this model to the experimental data, we reconstruct the simplified I κ B α -NF- κ B computational model with I κ B β and I κ B ϵ knock out. This reduced model contains 24 reactions (shown in Table I with the nominal value of each parameter given [14, 24, 25]) and 12 species with their initial concentrations listed in Table II.

TABLE II INITIAL CONCENTRATION OF REACTION SPECIES

	Species	Initial concentration
1	IκBa, x_1	0
2	NF-κB, x_2	0.1
3	IκBa-NF-κB, x_3	0
4	IKKIκBa, x_4	0
5	IKK-IκBa-NF-κB, x_5	0
6	IKK, x_6	0 (increased to 0.1 after equilibrium)
7	NF-κB _n , x_7	0
8	IκBa _n , x_8	0
9	IκBa _n -NF-κB _n , x_9	0
10	Source	1 (constant)
11	IκBa _i , x_{10}	0
12	sink	0 (constant)

The system model can be described by the following ordinary differential equations (ODEs):

$$\begin{aligned}
\dot{x}_1 &= -(k_{17} + k_{18})x_1 + k_2x_3 + k_{15}x_4 + k_{19}x_8 + k_{16}x_{10} - k_1x_1x_2 - k_{14}x_1x_6 \\
\dot{x}_2 &= -k_7x_2 + (k_2 + k_6)x_3 + (k_4 + k_5)x_5 + k_8x_7 - k_1x_1x_2 - k_3x_2x_4 \\
\dot{x}_3 &= -(k_2 + k_6)x_3 + k_{21}x_5 + k_{22}x_9 + k_1x_1x_2 - k_{20}x_3x_6 \\
\dot{x}_4 &= -(k_{15} + k_{24})x_4 + k_4x_5 + k_{14}x_1x_6 - k_3x_2x_4 \\
\dot{x}_5 &= -(k_4 + k_5 + k_{21})x_5 + k_3x_2x_4 + k_{20}x_3x_6 \\
\dot{x}_6 &= (k_{15} + k_{24})x_4 + (k_5 + k_{21})x_5 - k_{23}x_6 - k_{14}x_1x_6 - k_{20}x_3x_6 \\
\dot{x}_7 &= k_7x_2 - k_8x_7 + k_{10}x_9 - k_9x_7x_8 \\
\dot{x}_8 &= k_{18}x_1 - k_{19}x_8 + k_{10}x_9 - k_9x_7x_8 \\
\dot{x}_9 &= -(k_{10} + k_{22})x_9 + k_9x_7x_8 \\
\dot{x}_{10} &= k_{11}S - k_{13}x_{10} + k_{12}x_7^2
\end{aligned} \tag{1}$$

III. GLOBAL SENSITIVITY ANALYSIS

A. The Method of Morris

The Morris method can investigate the model over a global range, i.e. the input parameters are varied over the whole range of their possible values. It is very effective in identifying inputs which are not influential, and is thus very useful for model simplification. It is based on what is called an elementary effect (EE). Through a pre-defined sampling strategy, a certain number of elementary effects are obtained for each factor (i.e. parameter) [22].

In the Morris method, it is supposed that a finite distribution of elementary effects associated with each input, denoted by F_i , can be estimated. Two sensitivity measures were proposed for each factor: μ , an estimate of the mean of the distribution F_i , and σ , an estimate of the standard deviation of F_i . These two measures will be used as indicators of which inputs should be considered important. A large value of μ indicates an input factor with an important overall influence on the output. A large value of σ indicates an input whose influence is highly dependent on the values of other inputs or whose effect is highly nonlinear.

The sampling strategy in Morris method has a large value of 'economy', which is defined as the number of elementary effects produced by the design divided by the number of

experimental runs necessary to produce them [22]. The larger the value of the economy for a particular design or method is, the better it is in terms of providing information for sensitivity.

Consider a model for which the output y is a deterministic function of k input factors (parameters), i.e., $y = f(x_1, \dots, x_k)$. Assume that each x_i is scaled in the interval $[0, 1]$ and may take on values from $\{0, 1/(p-1), 2/(p-1), \dots, 1\}$. The region of interest, ω , is then a k -dimensional p -level grid. Denote $x = [x_1 \ x_2 \ \dots \ x_k]^T$, the EE of the i th input is defined as

$$EE_i(x) = \frac{f(x_1, x_2, \dots, x_{i-1}, x_i + \Delta, x_{i+1}, \dots, x_k) - f(x)}{\Delta} \tag{2}$$

where $x \in \omega$, $x_i \leq 1 - \Delta$. Δ is a predetermined multiple of $1/(p-1)$. It will be convenient to restrict attention to the case in which p is even and $\Delta = p/[2(p-1)]$.

In principle, producing a value for F_i requires random selection of a value of each x_i ($i = 1, 2, \dots, k$) from the grid and evaluation of y twice, one at the selected k values, the other at the values after increasing x_i by the quantity Δ . The difference between these two runs yields one elementary effect. The calculation will be repeated r times to produce a random sample of r elementary effects for F_i . The computational steps can be implemented as follows:

- 1) Prepare matrices J, B as follows:
 - $J \in \mathbf{R}^{(k+1) \times k}$ is a matrix of 1's;
 - $B \in \mathbf{R}^{(k+1) \times k}$ is a strictly lower triangular matrix of 1's.
- 2) Prepare matrices x^* , D^* , P^* as follows:
 - $x^* \in \mathbf{R}^{1 \times k}$ is a base vector for which each element is randomly assigned a value from $\{0, 1/(p-1), 2/(p-1), \dots, 1-\Delta\}$, each with equal probability;
 - $D^* \in \mathbf{R}^{k \times k}$ is a diagonal matrix in which each element is either +1 or -1 with equal probability;
 - $P^* \in \mathbf{R}^{k \times k}$ is a random permutation matrix in which each column contains one element equal to 1 and all others equal to 0 and no two columns have 1's in the same position, and each such matrix P^* has an equal probability of selection.
- 3) The random orientation of B is given by

$$B^* = (J_{k+1,1}x^* + (\Delta/2)[(2B - J_{k+1,k})D^* + J_{k+1,k}])P^* \tag{3}$$

B^* represents the design matrix and provides one elementary effect per input, which is randomly selected. Any two neighboring rows in B^* only differ in one column (e.g., the j th column) by Δ , i.e.

$$B^*(i,:) - B^*(i+1,:) = \begin{bmatrix} 0 & \dots & 0 & \Delta & 0 & \dots & 0 \\ \underbrace{\hspace{1.5cm}}_{(j-1) \text{ 0's}} & & \underbrace{\hspace{1.5cm}}_{(k-j) \text{ 0's}} \end{bmatrix} \tag{4}$$

- 4) The EE for the j th factor is calculated as

$$EE_j = \frac{f(B^*(i,:)) - f(B^*(i+1,:))}{\Delta} \tag{5}$$

Run step 4) from $i=1$ to k so as to obtain all the elementary effects for the k input factors.

- 5) If a sample of r effects is required, repeat steps 2) to 4) r times and obtain r EEs for each input factor.
- 6) Take the average μ and standard deviation σ out of r local measures of EEs for each F_i . Identify the significant factors through the μ - σ plane.

It can be noted that under this sampling scheme, all $r \times k$ elementary effects are independently produced.

B. Modification of Morris Method and its Application to an $\text{IkB}\alpha$ -NF- κB model

Applying this global sensitivity analysis method to a ‘real’ system such as $\text{IkB}\alpha$ -NF- κB signal transduction pathway model, some issues should be considered.

The first is to give an appropriate parameter range for analysis, which might be different, for each input factor. The ranges of parameters can be constrained by the literature or by simulation results from which one can make sure that out of these ranges, the system will be either biologically meaningless or too stiff to be solved with common mathematical methods. For biological networks, the possible range of a parameter is normally considered to be of several orders, therefore the p -level grid should better be log-uniformly distributed within the range. It should be noted that the orientation matrix B^* in (3) only applies to the case that the input factors are defined in the same intervals and are uniformly distributed inside. For real systems with different parameter ranges and log-uniform distributions, Δ should be rescaled subsequently to be $\tilde{\Delta} = \Delta \times (\log ub_i - \log lb_i)$ with lb_i and ub_i being the lower and upper bounds of the i th parameter range. Then the base vector x^* changes to $\tilde{x}^* = \{0, 1/(p-1), 2/(p-1), \dots, 1-\Delta\} \times (\log ub_i - \log lb_i) + \log lb_i$. Accordingly, the orientation matrix B^* should be formulated as

$$\tilde{B}^* = J_{k+1,1} \tilde{x}^* + (\tilde{\Delta}/2)[(2B - J_{k+1,k})D^* + J_{k+1,k}]P^* \quad (6)$$

Note that in (6) the permutation operation is only performed in the second term. This is to make sure that in each row of the \tilde{B}^* matrix, the input labels can be kept as that in \tilde{x}^* , rather than a random shuffling sequence.

The second consideration is to choose proper variables and define the output function y used in the calculation of EEs in the dynamic system of interest. The purpose of our sensitivity analysis is to identify significant parameters to enhance the accuracy of parameter estimation. Because the parameter estimation is based on the experimental data of NF- κB in nucleus (NF- κBn), we consider here only the behavior of NF- κBn . When implementing local sensitivity analysis, Ihekwa *et al.* focused on several characteristics that could be used to represent the system output, such as the time, amplitude or period of the peaks in the oscillation profile of NF- κBn [17, 26]. However, all these characteristics are of course only a partial expression of the output. Sensitivity analysis based on incomplete expression of the system might

be inaccurate or even misleading. In this case, the complete set of data in the time response curve of NF- κBn is taken into account. Then in the calculation of an EE, y is formulated as a Euclidean distance, i.e. ,

$$EE_i(x) = \frac{\sqrt{\sum_l [f_l(x_1, x_2, \dots, x_{i-1}, x_i + \tilde{\Delta}, x_{i+1}, \dots, x_k) - f_l(x)]^2}}{\tilde{\Delta}} \quad (7)$$

l stands for the sampling index in the concentration profile.

In the global sensitivity analysis of the simplified $\text{IkB}\alpha$ -NF- κB model, the lower bound (lb) is set to be 1/100 of the nominal value, and the upper bound (ub) 100 times of the nominal value. The sampling is based on the logarithmic value of the input space. For the choice of the number of levels, p , and the number of EEs, r , some works have demonstrated that $p=4$ and $r=10$ produce satisfactory results for general systems [27-29]. In our experiment, the parameter range is quite large, therefore p is set to be 10. Simulation shows that when $p=10$, r should be larger than 40 to make the results convergent. So the two parameters are set to be $p=10$ and $r=100$. The means and standard deviations of the elementary effects for the 24 parameters are displayed in Fig. 2.

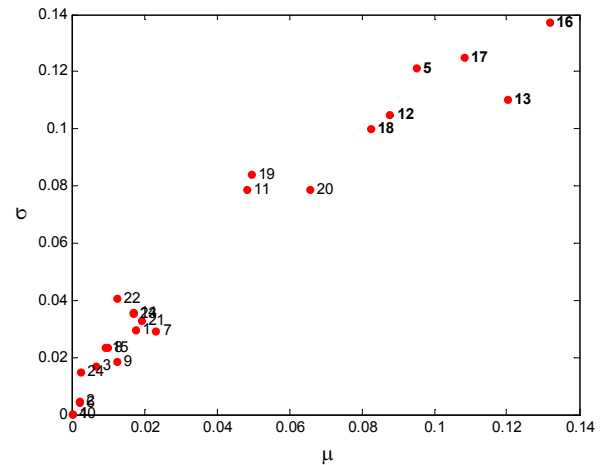


Fig. 2. The Morris sensitivity analysis result of the $\text{IkB}\alpha$ -NF- κB model. The abscissa indicates the mean of the element effects for each parameter while the ordinate represents the standard deviation.

The following parameters are identified to be relatively important from the $\mu - \sigma$ plane in Fig.2:

- k5: IKK $\text{IkB}\alpha$ -NF- κB catalysis rate
- k12: $\text{IkB}\alpha$ inducible mRNA synthesis rate.
- k13: $\text{IkB}\alpha$ mRNA degradation rate
- k16: constitutive $\text{IkB}\alpha$ translation rate
- k17: constitutive $\text{IkB}\alpha$ degradation rate
- k18: $\text{IkB}\alpha$ nuclear import rate

Comparing with the local sensitivity analysis results for the complete IkB -NF- κB model with three IkB isoforms ($\text{IkB}\alpha$, $-\beta$, and $-\epsilon$) in [30], here 5 out of the 6 identified sensitive parameters, i.e., k5, k12, k13, k16 and k18, are also within the top 8 sensitive parameters in the local analysis of the complete model. This shows that there are close links between global

and local sensitivity analysis although the results are not exactly the same.

IV. ESTIMATION OF SENSITIVE PARAMETERS

Parameter estimation of nonlinear dynamic systems typically seek to minimize a cost function that measures the distance between the model output and the given experimental data set, subject to the dynamics of the systems (acting as a set of differential equality constraints) plus possibly other algebraic constraints [11]. In this work, the reduced model with 24 reactions is described as ODEs in Eqn. (1). As can be seen from Table I, the parameters span several orders of the magnitude, which makes the ODEs stiff and increase the computational load for solving those ODEs. If a global optimization method, e.g. a genetic algorithm, is applied, numerous function evaluations are needed and the complete calculation will be expensive. When using traditional local optimization methods such as the Levenberg-Marquardt method, due to the existence of the local minima, the nonlinear regression must be implemented from many starting points to adequately explore the parameter space.

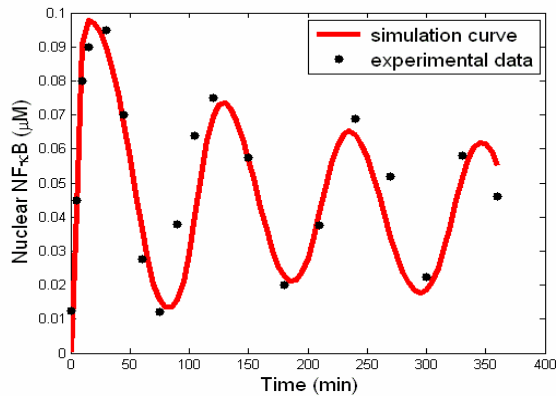


Fig. 3. The fitting result of NF-κB in the $I\kappa B\alpha$ -NF-κB model. The experimental data are shown as black dots; the best solution from the fitting is shown in the red curve.

In adjusting the parameters, we implement a randomized multi-shoot Levenberg-Marquardt optimization method to minimize the Euclidean difference between the predicted and actual responses, i.e., the concentration profiles of NF-κB in the nucleus, in this $I\kappa B\alpha$ -IKK-NF-κB model. Given the scan range for each parameter, the starting point for the optimization is randomly generated from the input space. Then the Levenberg-Marquardt method is used to search for the optimal solution. The searching iteration will repeat with different initial points until a satisfactory result is obtained.

TABLE III THE ESTIMATED VALUES OF UNKNOWN AND SENSITIVE PARAMETERS IN THE $I\kappa B\alpha$ -IKK-NF-κB MODEL

	k5	k11	k12	k13	k16	k17	k18
new	1.022	6.7e-5	0.97	0.0267	0.201	5.8e-3	7.5e-3
old	1.221	9.25e-5	0.99	0.0168	0.245	6.8e-3	0.018

Due to the nonlinear characteristics of this kind of ODE systems, the estimated values of parameters need to be analyzed carefully even for the best fitting solution. For this

model, in addition to the 6 sensitive parameters identified in section III, parameter k11 is also estimated as it is regarded as unknown in literature [14]. After the best fitting solution is obtained, the simulation results of all the outputs are observed and compared with the preceding description of the behavior in literature [14, 23, 24]. The best fitting results of the concentration profile of nucleus NF-κB is shown in Table III and Fig.3. In Table III., the parameter values in the ‘new’ row are the estimated values, while those in the ‘old’ row are parameters taken from literature.

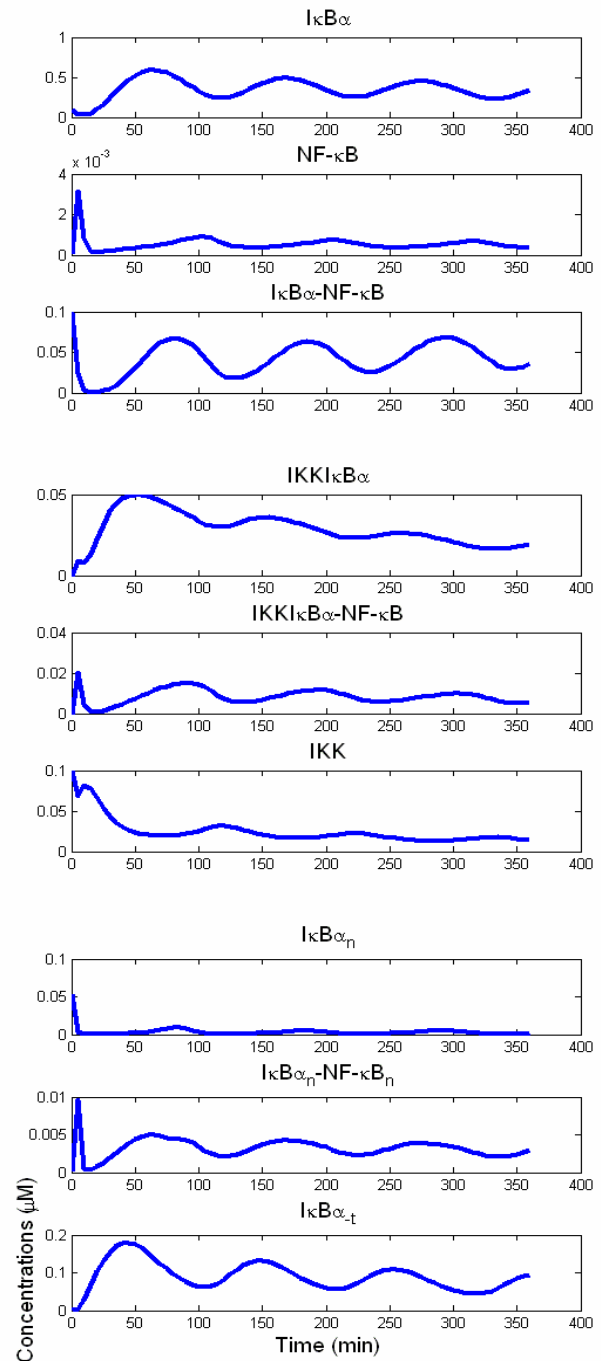


Fig. 4. Simulation time courses of all species based on the new values of parameters in the $I\kappa B\alpha$ -NF-κB model.

Comparing Fig.3 with Fig.1, it can be clearly seen that the fitting performance has been improved with the new set of estimated parameters. The simulation outputs of all the variables in the simplified model are shown in Fig. 4. It can be seen that each species profile is biologically reasonable, and that the changes required to the parameters are comparatively small in size, as is often the case in biology [31].

V. CONCLUSIONS

In this work, we have analyzed a simplified model of the NF- κ B signaling pathway containing 12 species (including the source and sink) in terms of the sensitivity of the concentration of the nuclear NF- κ B to each of the 24 reaction parameters of the model. Using the Morris method to perform global sensitivity analysis, the most sensitive parameters in the I κ B α -NF- κ B model are identified to be constitutive I κ B translation rate, I κ B mRNA degradation rate, IKK1 κ B α -NF- κ B catalysis rate, the constitutive I κ B degradation rate, I κ B α inducible mRNA synthesis rate and I κ B α nuclear import rate. Improved fitting to the experimental data is obtained simply by resetting the values of these sensitive parameters and the I κ B α mRNA synthesis rate, often by comparatively small amounts. This illustrates the importance of focusing on the most sensitive parameters of a complex system when seeking to improve the fit of a model to experimental.

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