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Figure 1: Functional diagram of $NF-\kappa B$ Biological Module. Extracellular signal stimulus (e.g., cytokines) and intracellular signals (disturbances and stress) activates the $I\kappa B$ kinase (IKK) complex, which then phosphorylate $I\kappa B$ leading to ubiquitation and proteolysis. Freed $NF-\kappa B$ translocates to the nucleus where it starts genes transcription and translation (in cytoplasm), one of which being $I\kappa B$ that enters the nucleus and associates with $NF-\kappa B_n$, thus inhibiting its activity. The formed complex is then transferred to the cytoplasm.

Mathematical Model of $IL-1$ — $NF\kappa B$ Biological Module

Nataša A. Kablar [1] and Vladimir Kvrgić[2]
[1]N. A. Kablar is with Lola Institute and Faculty of Computer Science, 11000 Belgrade, Serbia.
[2]V. Kvrgić is with Lola Institute, 11000 Belgrade, Serbia.

ABSTRACT: In this paper we develop mathematical model of $IL-1$ — $NF\kappa B$ signaling pathway. First, we describe physiology and draw functional diagram, then, based on physiology, we state set of biochemical reactions to describe underlying biochemistry. At last we develop mathematical model. Parameter data are chosen from experimental literature or are assumed (for $IL-1$). For plausable set of parameter data we run simulations.

1 INTRODUCTION

The mathematical modeling of biological processes has become crucial for future developments in biological sciences and medicine [1]. Specifically, mathematical models enable computer simulations of biochemical and signalling networks and provide i) quantitative predictions about their behavior, ii) an understanding of the role of specific biological modules within complex signalling pathways, and ultimately, iii) information for disease treatment and drug discovery.

Biochemical modeling is based on the set of reactions that describe the biochemical process. Applying elementary chemical laws, such as mass action kinetics [2], Michaelis-Menten enzime kinetics [3], enzyme inhibition [3] or Hill's approximation, one can derive a set of ordinary differential equations (ODEs) from the set of biochemical reactions, which describe the dynamic behavour of the process. ODE models are the simplest form of describing a dynamical biochemical process in mathematical terms. From the equations, one can then proceed to determine the equilibrium points, existance of bifurcations, and perform a stability, sensitivity, and/or robustness analysis. These analyses can yield vital information about specific species that are deficient or abundant in the biochemicall process and consequently, information about medical treatments via natural substances and drugs. From a system theory perspective, medical treatments attempt to reestablish "order" to the dynamics of the biological processes.

This paper is devoted to the dynamic modeling and simulation, and analysis, of the so-called $NF-\kappa B$ module. This module consist of the nuclear factor κB, whose primary role is to control a variety of physiological aspects of immune and inflammatory responses. Specifically, the $NF-\kappa B$ is an extremely important biological module that mediates in diseases like cancer, arteriosclerosis, diabetes, allergy, asthma, arthritis, Crohn's disease, multiple sclerosis, osteoporosis, psoriasis, septic shock, and AIDS, and neurodegenerative diseases such as Alzheimer and Parkinson [4]. In this paper, we describe NFκB module's autoregulation mechanism as a negative feedback loop, starting from its activation via phosphorylation by the IκB kinase (IKK) complex to the gene transcription and translation. In addition to the module's dynamical representation as a set of ordinary differential equations, we also provide a biological and medical explanation for its regulatory role and connections to medical diseases such as cancer, Alzheimer, and Parkinson [5].

2 PHYSIOLOGY

Ligand $IL-1$ binds to its receptor $IL-R$. It recruits then adapter protein $MyD88$ and $IRAK$. Their complexes are further recruited with effector protein $TRAF$ to activate IKK, which further activate $NF-\kappa B$.

The physiology of the $NF-\kappa B$ module is shown in Figure 1. The nuclear transcription factor $NF-\kappa B$ is held inactive in the cytoplasm in the form of dimmer $I\kappa B$. $NF-\kappa B$ with $I\kappa B\alpha$ being transcribed by $NF-\kappa B$ itself. The activation of this dimmer through phosphorylation by the IKK molecule leads to ubiquitination and proteolytic degradation of $I\kappa B$. This in turn frees $NF-\kappa B$, which is translocated to the nucleus ($NF-\kappa B_n$) through the nuclear localization signal where it starts the process of gene transcription. $NF-\kappa B$ is a homo- or hetero-dimmer, which in case of mammals consists of a specific combination of five closely-related transcription factor molecules (i.e., $c-Rel$ or Rel, $RelA$ or $p65$, $RelB$, $p50$, and $p52$). These molecules are critical regulators in the development and maintenance of the immune system as well as in the coordinated response to infections. All of these molecules posses Rel Homology

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Figure 2: Functional diagram of NFkB Biological Module. External signal stimulus transduce through several proteins, activating IKK complex (or is activated via internal signals: disturbances or stress) that activates $I\kappa B$. $NF-\kappa B$ complex by phosphorylating $I\kappa B$ that leads to ubiquitination and proteolytic degradation of $I\kappa B$, freeing $NF-\kappa B$ that becomes active and translocates into nucleus where it strats gene transcription further translocated to cytoplasm for gene translation process. Newly formed gens/protein carry certain biological functions, one of them being $I\kappa B$ that enters nucleus where it associates to $NF-\kappa B_n$, thus inhibiting it (i.e., the negative feedback represented by the red line) and forming the $I\kappa B_n.NF-\kappa B_n$ complex. This complex translocates to the cytoplasm where $NF-\kappa B$ is held inactive.

Domain (RHD), which affects their dimmerization, DNA binding, and principal regulatory domain. RHD contains in its C-terminus a nuclear localization sequence that is rendered inactive in non-stimulated cells through binding of specific $NF-\kappa B$ inhibitors such as $I\kappa B$. Binding and transcription of each molecule to DNA leads to the transcription of certain genes/proteins, which at times have opposing biological functions. Among the proteins transcribed are $I\kappa B\alpha$ and its beta and epsilon isoforms. $I\kappa B\alpha$ translocates to the cytoplasm where it inhibits the $NF-\kappa B$ molecule, therefore establishing a negative feedback loop. Beta and epsilon isoforms mainly influence the attenuation of the oscillatory behavior of $NF-\kappa B$ concentrations. Transcribed genes go through process of translation in order to give proteins that will have certain biological function. A functional block diagram of the $NF-\kappa B$ module is shown in Figure 2.

3 BIOCHEMICAL REACTIONS

Underlying biochemistry of model shown in Figure 1 can be described by the following set of biochemical reactions:

$$IL-1+IL-R \underset{d_{14}}{\overset{a_{14}}{\rightleftarrows}} [IL-1.IL-R] \tag{1}$$

$$MyD88+[IL-1.IL-R] \underset{d_{15}}{\overset{a_{15}}{\rightleftarrows}} [MyD88.[IL-1.IL-R]] \tag{2}$$

$$IRAK+[MyD88.[IL-1.IL-R]] \underset{d_{16}}{\overset{a_{16}}{\rightleftarrows}} [IRAK.[MyD88.[IL-1.IL-R]]] \tag{3}$$

$$TRAF6+[IRAK.[MyD88.[IL-1.IL-R]]] \underset{d_{17}}{\overset{a_{17}}{\rightleftarrows}} [TRAF6.[IRAK.[MyD88.[IL-1.IL-R]]]] \tag{4}$$

$$IKK+[TRAF6.[IRAK.[MyD88.[IL-1.IL-R]]]] \underset{d_{18}}{\overset{a_{18}}{\rightleftarrows}} IKK.[TRAF6.[IRAK.[MyD88.[IL-1.IL-R]]]] \tag{5}$$

$$IKK.[TRAF6.[IRAK.[MyD88.[IL-1.IL-R]]]] \overset{k_{19}}{\rightarrow} IKK_P+[TRAF6.[IRAK.[MyD88.[IL-1.IL-R]]]] \tag{6}$$

$$IKK_P+I\kappa B \underset{d_1}{\overset{a_1}{\rightleftarrows}} [IKK_P.I\kappa B] \tag{7}$$

$$[IKK_P.I\kappa B]+NF\kappa B \underset{d_2}{\overset{a_2}{\rightleftarrows}} [[IKK_P.I\kappa B].NF\kappa B] \tag{8}$$

$$[[IKK_P.I\kappa B].NF\kappa B] \overset{k_2}{\rightarrow} IKK_P+NF\kappa B \tag{9}$$

$$I\kappa B+NF\kappa B \underset{d_3}{\overset{a_3}{\rightleftarrows}} [I\kappa B.NF\kappa B] \tag{10}$$

$$[I\kappa B.NF\kappa B] \overset{k_3}{\rightarrow} NF\kappa B \tag{11}$$

$$IKK_P+[I\kappa B.NF\kappa B] \underset{d_4}{\overset{a_4}{\rightleftarrows}} [IKK_P.[I\kappa B.NF\kappa B]] \tag{12}$$

$$IKK_P \overset{k_4}{\rightarrow} sink \tag{13}$$

$$[IKK_P.I\kappa B] \overset{k_5}{\rightarrow} IKK_P \tag{14}$$

$$(source)\ I\kappa B_t+NF\kappa B_n+NF\kappa B_n \overset{k_6}{\rightarrow} I\kappa B_t \tag{15}$$

$$I\kappa B_t \overset{k_7}{\rightarrow} sink \tag{16}$$

$$I\kappa B_t \overset{k_8}{\rightarrow} I\kappa B+I\kappa B_t \tag{17}$$

$$I\kappa B \overset{k_9}{\rightarrow} sink \tag{18}$$

$$I\kappa B \underset{d_{10}}{\overset{a_{10}}{\rightleftarrows}} I\kappa B_n \tag{19}$$

$$NF\kappa B \underset{d_{11}}{\overset{a_{11}}{\rightleftarrows}} NF\kappa B_n \tag{20}$$

$$NF\kappa B_n+NF\kappa B_n \overset{k_{11}}{\rightarrow} I\kappa B_t+NF\kappa B_n+NF\kappa B_n \tag{21}$$

$$I\kappa B_n+NF\kappa B_n \underset{d_{12}}{\overset{a_{12}}{\rightleftarrows}} [I\kappa B_n.NF\kappa B_n] \tag{22}$$

$$[I\kappa B_n.NF\kappa B_n] \overset{k_{13}}{\rightarrow} [I\kappa B.NF\kappa B] \tag{23}$$

4 MATHEMATICAL MODEL

To develop mathematical model let us first introduce set of state variables as given in Table 1.

Table 1 - State Variables

Variable	Specie	Description
x_1 :	IKK_P	
x_2 :	$I\kappa B$	
x_3 :	$[IKK_P.I\kappa B]$	
x_4 :	$NF\kappa B$	
x_5 :	$[[IKK_P.I\kappa B].NF\kappa B]$	
x_6 :	$[I\kappa B.NF\kappa B]$	
x_7 :	$[IKK_P.[I\kappa B.NF\kappa B]]$	
x_8 :	$I\kappa B_t$	
x_9 :	$I\kappa B_n$	
x_{10} :	$NF\kappa B_n$	
x_{11} :	$[I\kappa B_n.NF\kappa B_n]$	
x_{12} :	$IL-1$	
x_{13} :	$IL-R$	
x_{14} :	$[IL-1.IL.R]$	
x_{15} :	$MyD88$	
x_{16} :	$[MyD88.[IL-1.IL.R]]$	
x_{17} :	$IRAK$	
x_{18} :	$[IRAK.[MyD88.[IL-1.IL.R]]]$	
x_{19} :	$TRAF$	
x_{20} :	$[TRAF.[IRAK.[MyD88.[IL-1.IL.R]]]]$	
x_{21} :	IKK	
x_{22} :	$[IKK.[TRAF.[IRAK.[MyD88.[IL-1.IL.R]]]]]$	

Mathematical model is given with:

$$\frac{dx_1}{dt} = -a_1x_1x_2 + d_1x_3 + k_2x_5 - a_4x_1x_6 + d_4x_7 - k_4x_1 + k_5x_3 + k_{19}x_{22}, \tag{24}$$

$$\frac{dx_2}{dt} = -a_1x_1x_2 - d_1x_3 - a_3x_2x_4 + d_3x_6 + k_8x_8 - k_9x_2 - a_{10}x_2 + d_{10}x_9, \tag{25}$$

$$\frac{dx_3}{dt} = a_1x_1x_3 - d_1x_3 - a_2x_3x_4 - k_5x_3, \tag{26}$$

$$\frac{dx_4}{dt} = -a_2x_3x_4 + k_2x_5 - a_3x_2x_4 + d_3x_6 + k_3x_6 - a_{11}x_4 + d_{11}x_{10}, \tag{27}$$

$$\frac{dx_5}{dt} = a_5x_3x_4 - d_2x_5 - k_2x_5, \tag{28}$$

$$\frac{dx_6}{dt} = a_3x_2x_4 - d_3x_6 - k_3x_6, \tag{29}$$

$$\frac{dx_7}{dt} = a_4x_1x_6 - d_1x_7, \tag{30}$$

$$\frac{dx_8}{dt} = k_6 - k_7x_8 - k_8x_8 + k_{11}x_{10}^2, \tag{31}$$

$$\frac{dx_9}{dt} = a_{10}x_2 - d_{10}x_9 - a_{12}x_9x_{10} + d_{12}x_{11}, \tag{32}$$

$$\frac{dx_{10}}{dt} = a_{11}x_4 - d_{11}x_{10} - k_{11}x_{10}^2 + k_{11}x_{10}^2 - a_{12}x_9x_{10} + d_{12}x_{11}, \tag{33}$$

$$\frac{dx_{11}}{dt} = a_{12}x_9x_{10} - d_{12}x_{11} - k_{13}x_{11}. \tag{34}$$

$$\frac{dx_{12}}{dt} = -a_{14}x_{12}x_{13} + d_{14}x_{14} \tag{35}$$

$$\frac{dx_{13}}{dt} = -a_{14}x_{12}x_{13} + d_{14}x_{14} \tag{36}$$

$$\frac{dx_{14}}{dt} = a_{14}x_{12}x_{13} - d_{14}x_{14} \tag{37}$$

$$\frac{dx_{15}}{dt} = -a_{15}x_{15}x_{14} + d_{15}x_{16} \quad (38)$$

$$\frac{dx_{16}}{dt} = a_{15}x_{15}x_{14} - d_{15}x_{16} \quad (39)$$

$$\frac{dx_{17}}{dt} = -a_{16}x_{17}x_{16} + d_{16}x_{18} \quad (40)$$

$$\frac{dx_{18}}{dt} = a_{16}x_{17}x_{16} - d_{16}x_{18} \quad (41)$$

$$\frac{dx_{19}}{dt} = -a_{17}x_{19}x_{18} + d_{17}x_{20} \quad (42)$$

$$\frac{dx_{20}}{dt} = a_{17}x_{19}x_{18} - d_{17}x_{20} \quad (43)$$

$$\frac{dx_{21}}{dt} = -a_{18}x_{21}x_{20} + d_{18}x_{22} \quad (44)$$

$$\frac{dx_{22}}{dt} = a_{18}x_{21}x_{20} - d_{18}x_{22} - k_{19}x_{22} \quad (45)$$

5 MODEL REFINEMENTS

The system of ODES is the simplest mathematical model for the aforementioned biochemical reaction. Simple models provide basic qualitative insights into the biochemical process as they readily identify, for example, the existence of feedback loops. If a quantitative understanding of the process is sought, several refinements can be made to the model to account for phenomena initially left out. For example, transport delay between the cytoplasm and nucleus can be modeled as a pure time delay,leading to a set of functional differential equations, The model should also account for the fact that reactions within the NFκB module often evolve in different time scales. In certain cases, one can use singular perturbation theory [6] to decompose the model into fast and slow subsystems. Fast process, such as transcriptions, will be approximated by algebraic equations, leading to a singular [8] or singular delayed system model. The addition of drugs to the module can also be modeled by assuming the drug between process is very fast and the concentration of certain components increases instantaneously. This approach will lead to an impulsive [9] or singularly impulsive system model [10]. More details are given in [5].

Biochemical reaction models are a subclass of compartmental models [11] since the state variables (change in concentration species) are always nonnegative quantities. As such, their dynamic can also be analyzed using the theory of positive systems [12]. Another model refinement, which is beyond the scope of this paper, is the use of a stochastic model to account for intristic and extrinsic noise effects [7].

6 PARAMETER DATA

Set of parameter data is given in Table 2.

7 INITIAL CONDITIONS

Set of initial conditions is given in Table 3.

Table 2 - Parameter Values

Parameter	Value	Units	Description
a_1	22.5×10^{-3}	$\mu M^{-1}s^{-1}$	association rate
d_1	1.25×10^{-3}	s^{-1}	dissociation rate
a_2	0.5×10^{0}	$\mu M^{-1}s^{-1}$	association rate
d_2	0.5×10^{-3}	s^{-1}	dissociation rate
k_2	2.04×10^{-2}	s^{-1}	reaction rate
a_3	0.5×10^{0}	$\mu M^{-1}s^{-1}$	association rate
d_3	0.5×10^{-3}	s^{-1}	dissociation rate
k_3	2.25×10^{-5}	s^{-1}	reaction rate
a_4	1.85×10^{-1}	$\mu M^{-1}s^{-1}$	association rate
d_4	1.25×10^{-3}	s^{-1}	dissociation rate
k_4	1.2×10^{-4}	s^{-1}	reaction rate
k_5	4.07×10^{-3}	s^{-1}	reaction rate
k_6	1.54×10^{-6}	$\mu M^{-1}s^{-1}$	reaction rate
k_7	2.8×10^{-4}	s^{-1}	reaction rate
k_8	4.08×10^{-3}	s^{-1}	reaction rate

Figure 3: Responses of NFkB Biological Module.

Table 2 - Parameter Values, contd.			
Parameter	**Value**	**Units**	**Description**
k_9	1.13×10^{-4}	s^{-1}	reaction rate
a_{10}	3×10^{-4}	s^{-1}	association rate
d_{10}	2×10^{-4}	s^{-1}	dissociation rate
a_{11}	0.9×10^{-1}	s^{-1}	association rate
d_{11}	0.8×10^{-4}	s^{-1}	disscociation rate
a_{12}	0.5×10^{0}	$\mu M^{-1} s^{-1}$	association rate
k_{11}	1.65×10^{-2}	$\mu M^{-1} s^{-1}$	reaction rate
d_{12}	0.5×10^{-3}	s^{-1}	dissociation rate
k_{13}	1.38×10^{-2}	s^{-1}	reaction rate
a_{14}–a_{18}	0.5×10^{0}	$\mu M^{-1} s^{-1}$	assumed rates
d_{14}–d_{18}	0.5×10^{-3}	s^{-1}	assumed rates
k_{19}	$1.2 * 10\hat{}(-4)$	$\mu M^{-1} s^{-1}$	assumed rate

Table 3 - Initial Values		
Variable	**Specie**	**Initial Value**
$x_{10}:$	IKK	0.1
$x_{20}:$	$I\kappa B$	0
$x_{30}:$	$[IKK.I\kappa B]$	0
$x_{40}:$	$NF\kappa B$	0.1
$x_{50}:$	$[[IKK.I\kappa B].NF\kappa B]$	0
$x_{60}:$	$[I\kappa B.NF\kappa B]$	0
$x_{70}:$	$[IKK.[I\kappa B.NF\kappa B]]$	0
$x_{80}:$	$I\kappa B_t$	0
$x_{90}:$	$I\kappa B_n$	0
$x_{100}:$	$NF\kappa B_n$	0
$x_{110}:$	$[I\kappa B_n.NF\kappa B_n]$	0
$x_{120}:$	$IL-1$	0.15
$x_{130}:$	$IL-R$	0.1
$x_{140}:$	$[IL-1.IL.R]$	0
$x_{150}:$	$MyD88$	0.05
$x_{160}:$	$[MyD88.[IL-1.IL.R]]$	0
$x_{170}:$	$IRAK$	0.05
$x_{180}:$	$[IRAK.[MyD88.[IL-1.IL.R]]]$	0
$x_{190}:$	$TRAF$	0.05
$x_{200}:$	$[TRAF.[IRAK.[MyD88.[IL-1.IL.R]]]]$	0
$x_{210}:$	IKK	0.1
$x_{220}:$	$[IKK.[TRAF.[IRAK.[MyD88.[IL-1.IL.R]]]]]$	0
	source	1
	sink	0

8 SIMULATION RESPONSES

Responses of the NFkB model only (without IL-1 through IKK) for the parameter data given in Table 2, and initial conditions given in Table 3 is shown in Figure 3. Phase portrait of variables of interest is given in Figure 4.

Responses of the model shows that after stimulans of 0.1 $NF\kappa B$ nuclear $NF\kappa B_n$ rise initialy. Since $I\kappa B_t$ is transcribed and produce $I\kappa B$ which neutralize $NF\kappa B_n$ its value shortly drop to 0. $I\kappa B_n$ and $I\kappa B$ are on the elevated value to inactivate $NF\kappa B_n$, after which they will drop to 0 as well.

9 DYNAMICAL ANALYSIS

Once we obtain the mathematical representation of the NFκB biological module dynamics, it can be performed stability and robustness analysis, [5]. This will entail determining equilibrium points and their stability, bifurcation points, and

sensitivity to system parameters. Existing techniques for analysis of nonlinear systems, such as Lyapunov stability, passivity, input-output stability, and perturbation theory [6], is exploited for this purpose, [5]. With the results of this analysis in hand, it is further provided biological interpretation of the NFκ B module [5]. That is, there are identified stimuli and intensity and duration of application necessary for certain gene/protein to be transcribed. The relationship between concentration of NFκB molecule, oscillatory behavior, and the role of the oscillatory state within the biological module and signalling pathway is also discussed. Furthermore, we provided an explanation of the specific role of the NFκB module in mediating certain diseases. This entails discovering signalling pathways of the NFκB module that are related to malfunctions causing specific diseases. Ultimately, this may lead to possible medical treatments for mitigating such diseases.

The overall goal of this work [5] is to illustrate how different fields of research, viz., mathematical modeling of biochemical processes, systems and control theory, and biological sciences, can be combined to study the NFκB Module.

10 CONCLUSIONS

In this paper we discussed NFκB Biological Module. We established mathematical model, simulations, and dynamical analysis directions. At first we gave the set of biochemical reactions that underly the mechanism of this biological module, than we chose the state variables, and then we set mathematical model in form od ordinary differential equations. Further refinements of the model are discussed. For the set of plausable parameter data and initial conditions we run simulations. Interpretations of the results are given, with further medical and biological interpretations given in [5]. We further discussed dynamical aspects of the work, [5]. And we stated block diagram of the system. The overall goal of this paper and work in [5] is to illustrate how different fields of research, viz., mathematical modeling of biochemical processes, systems and control theory, and biological sciences, can be combined to study the NFκB Module.

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