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Fuzzy Modeling of Signal Transduction Networks

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Abstract: This work proposes a fuzzy modeling–based approach for describing signal transduction networks. Many key steps in signal transduction mechanisms have been investigated qualitatively in the literature, however, only little quantitative information is available. Fuzzy models can make use of this situation as fuzzy rules can be based upon the qualitative information that is found in the literature whereas training of the model can be performed with data that is available. This combination of a fuzzy rule set based upon qualitative information with parameters to be determined from data can result in models where fewer parameters need to be estimated than if fundamental or black-box models were used. This work investigates the use of fuzzy modeling to describe an IL-6 signal transduction mechanism as it plays a key role in the body's response to inflammation. The resulting model is capable of capturing the dynamics of key components of the IL-6 signal transduction pathway.

1. INTRODUCTION

Many systems investigated in systems biology are characterized by a lack of quantitative data, yet a significant amount of qualitative knowledge is available. This is a situation which seems ideally suited for fuzzy modeling as the qualitative information can be incorporated into the model building process in the form of linguistic rules, while only parameters of membership functions need to be estimated from (the limited amount of) available data. This situation forms the motivation behind this work as the structure of some signal transduction networks, e.g., the JAK-STAT and the MAPK pathway, is relatively well-known and a significant amount of qualitative information exists, however, very little quantitative data is available. While it is now possible to generate a limited amount of quantitative data using techniques like GFP reporter systems, the amount of information is insufficient to develop or verify a detailed dynamic model of all aspects of the signal transduction pathways. This situation is further exacerbated by the fact that a certain level of measurement error is not avoidable for these experiments (Tahera *et al.*, 2007). The use of fuzzy models for describing signal transduction pathways provides an avenue to address the points mentioned above.

Fuzzy logic is used in this paper to develop a model for IL-6 signal transduction in liver cells. The reasons for choosing this target system are that IL-6 signal transduction plays an important role in the body's response to burn injury or inflammation involving the Acute Phase Response (APR) as well as that mechanisms of IL-6 signal transduction have been extensively studied and the key components of the signal transduction pathway are known. A significant amount of information has been presented in the literature on the structure of IL-6 signal transduction pathways including qualitative information in the form of Western blots (Heinrich *et al.*, 2003; Fasshauer *et al.*, 2004; Lang *et al.*, 2003). However, only a limited number of fundamental models (Schoeberl *et al.*, 2002; Yamada *et al.*, 2003; Singh et al., 2006; Huang et al., 2007) exist due to the limited amount of quantitative data. Additionally, these models contain a large number of parameters which require estimation. This knowledge about the structure of the IL-6 signal transduction pathway will be used for developing the fuzzy model in this work. Furthermore, data provided by the model by Huang et al. (2007) are used for deriving the fuzzy model as (a) it indicates which effect a low/high concentrations of certain proteins and cytokines have on other proteins of the system; and (b) it can be used for training the fuzzy model which has a significantly smaller set of parameters than the original model, and thereby will be easier to adapt to additional experimental data that is collected.

2. PRELIMINARIES

2.1 Fuzzy modeling

Neuro-fuzzy models have found application for describing many different systems over the last few decades. The reasons for this are that fuzzy logic models can be easily interpreted while they also include the learning capabilities of neural networks (Jang, 1995; Kim et al., 1999).

Fuzzy models describing dynamic processes compute the states $x(k+1)$, at a time k+1, from the information of the states $x(k)$ and inputs $u(k)$, at time k,:

$$x(k+1) = f(x(k), u(k)) \tag{1}$$

where $f(\cdot)$ is a fuzzy model with the structure shown in Fig. 1. The values of the inputs, $x(k)$ and $u(k)$, and of the outputs, $x(k+1)$, can be assigned linguistic labels, e.g., 'Very Small' (VS), 'Small' (S), 'Medium' (M), 'Large' (L), and 'Very Large' (VL). Linguistic rules can be formulated that connect the linguistic labels for $x(k)$ and $u(k)$ via an "IF" condition

with a "THEN" part that which determines the resulting linguistic label for $x(k+1)$.

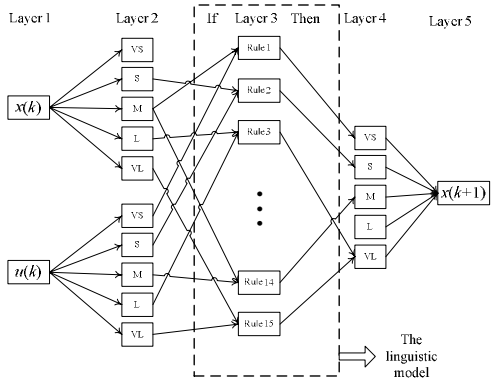


Fig. 1. The fuzzy layer structure

The premise membership functions are the membership functions appearing in the IF-part of the rule in Layer 2 and the consequent membership functions are the membership functions appearing in the THEN-part in Layer 4. These membership functions are of the following form

$$\mu_A(x) = \exp(-\frac{(x-c)^2}{\sigma^2}) \tag{2}$$

where μ_A refers to the degree to which x belongs to the linguistic label A, c represents the center of the membership functions and σ determines the width of the membership functions. The output of each node in layer 2 is the output from the corresponding membership function as given by equation (2). The output of each the nodes in layer 3 is the smallest value of the inputs to that node. The output of layer 4 is the largest value of the inputs to that node. The output of layer 5 is calculated by:

$$O_i^{(5)} = \frac{\sum_{j=1}^{5} O_{i,j}^{(4)} \sigma_{i,j}^{(4)} c_{i,j}^{(4)}}{\sum_{j=1}^{5} O_{i,j}^{(4)} \sigma_{i,j}^{(4)}} \tag{3}$$

where $O_{i,j}^{(4)}$ refers to the output of the node in layer 4, which connects to node i in layer 5 and represent linguistic label j; j=1,2,…,5 represents the five linguistic labels; $\sigma_{i,j}^{(4)}$, $c_{i,j}^{(4)}$ represent the parameters of the membership function of node $O_{i,j}^{(4)}$.

2.2 K-means clustering to obtain parameters *c* of the membership functions

K-means clustering (Kaufman *et al*., 1990) can group data points into several disjoint clusters. The reason for using K-means clustering for determining the center parameter, *c,* of the membership functions is that the centers of the clusters can be used to represent the dynamic characteristics of the data. Taking the normalized data for the concentration of activated transcription factor STAT3 in the nucleus, denoted as $(STAT3N^*)_2$, in Fig. 2.(a) as an example, the data points representing the second peak cannot be distinguished from the data points taken after the 8th hour, i.e., these points would be assigned the same linguistic label. However, if K-means clustering is used to determine the centers, as illustrated in Fig. 2.(b), then different dynamic patterns represented by the second peak and the points after the 8th hour can be described by two different linguistic labels 'B' and 'A' as shown in the figure. Therefore, K-means clustering plays an important role in fuzzy linguistic modeling procedures.

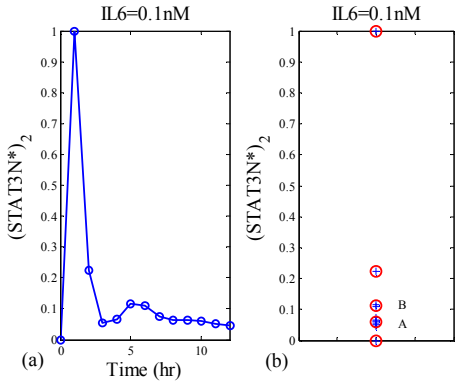


Fig. 2. (a) Dynamics of nuclear STAT3 dimer for stimulation with 0.1 nM of IL-6 and (b) the clusters obtained by K-means clustering

2.3 Algorithm determining linguistic rules

A significant amount of research has been conducted on determining fuzzy rules from data. Sugeno et al. (1993) and Tikk et al. (2002) provide a general procedure to build a linguistic model by clustering data from the system output. Gaweda et al. (2003) proposed to include a linear transformation of the input variables into the model building procedure in order to account for correlation among the inputs. Earlier approaches for minimizing fuzzy rule sets include the work by Wang et al. (1992) who proposed to remove redundant rules.

In addition to linguistic rules which can be determined from a qualitative understanding of the process, input and output data is also required to determine parameters of the membership functions of a fuzzy model. If dynamic behavior is to be described then the states and the inputs at one point in time can serve as input data and the states at the next point in time are the outputs. Accordingly each data point used for determining the model parameters consists of the following triplet ($x(k)$, $u(k)$, $x(k+1)$).

The fuzzy rules are of the form:

IF ($x(k)$ is $A_{x(k)}$) AND ($u(k)$ is $A_{u(k)}$),

THEN ($x(k+1)$ is $A_{x(k+1)}$),

where $A_{x(k)}$, $A_{u(k)}$ and $A_{x(k+1)}$ are the linguistic labels for *x(k)*, *u(k)*, and *x(k+1)*, respectively, generated for the data points.

In order to reduce the number of parameters, a procedure involving the membership functions is used as follows:

$$\mu_{A_{x(k)}}^{x(k)}(x(k)) = \max(\mu_{A_j}^{x(k)}(x(k)), j = 1,2,\cdots,5) ,$$

$$\mu_{A_{u(k)}}^{u(k)}(u(k)) = \max(\mu_{A_j}^{u(k)}(u(k)), j = 1,2,\cdots,5) , \text{ and}$$

$$\mu_{A_{x(k+1)}}^{x(k+1)}(x(k+1)) = \max(\mu_{A_j}^{x(k+1)}(x(k+1)), j = 1,2,\cdots,5) ,$$

where $\mu_b^a(c)$ is the output of the membership function of a for linguistic label b when a=c. In other words, the linguistic label with the largest value for the degree among the five linguistic membership functions is selected.

3. FUZZY MODELING OF IL-6 SIGNAL TRANSDUCTION

In this section a fuzzy model representing the IL-6 signal transduction pathway is developed. In a first step a set of key variables for the signal transduction pathway has to be identified. In a second step, a set of fuzzy rules describing how the inputs and values of these key variables at one point in time affect the system at the next time is developed. Finally, parameters of the membership functions are estimated from data and the model's predictions are evaluated.

3.1 Selection of Input and Output Variables for the Fuzzy Model

The quality of a model is strongly dependent upon the states used to describe a system. In the case of the IL-6 signal transduction model, the state is described by the concentration of several of the key proteins in the signal transduction pathway. Specifically, the concentrations of the following five components (IL-6-gp80-gp130-JAK*)$_2$, SHP2, SOCS3, PP2, and (STAT3N*)$_2$ are chosen as states of the system due to the following reasons: (IL-6-gp80-gp130-JAK*)$_2$ is required for initiating signaling through either JAK-STAT or MAPK. SHP2 is not only one of the main components for initiating the MAPK pathway, but it also acts as an inhibitor for the JAK-STAT pathway. SHP2 dephosphorylates the (IL-6-gp80-gp130-JAK*)$_2$ complex and thereby inhibits phosphorylation of STAT3C and signal transduction through the JAK-STAT part of the pathway. SOCS3 also inhibits signal transduction in the JAK-STAT pathway by inhibiting the phosphorylation of STAT3 in the cytosol. At the same time, SOCS3 is one of the products of the JAK-STAT signaling pathway and acts as a signaling inhibitor. The nuclear phosphatase PP2 causes deactivation of the phosphorylated STAT3 dimer in the nucleus. This deactivation is an important step for returning STAT3 to the cytosol for another phosphorylation-dephosphorylation cycle (Singh *et al*., 2006). (STAT3N*)$_2$ is a transcription factor, which can be measured by Western blots or by analysis of fluorescence images taken from GFP reporter experiments (Huang *et al*., 2007) and is indicative of transcription/translation of important proteins as a result of IL-6 signal transduction.

A summary of the components of x and u from equation (1) is shown in Table 1. The outputs (IL-6-gp80-gp130-JAK*)$_2$, SHP2, SOCS3, PP2, and (STAT3N*)$_2$ at time k+1 will be computed from the input information of IL-6, (IL-6-gp80-gp130-JAK*)$_2$, SHP2, SOCS3, PP2, and (STAT3N*)$_2$ at time k.

Table 1. Description of states and input

Component	Protein/Cytokine
x_1	(IL-6-gp80-gp130-JAK*)$_2$
x_2	SHP2
x_3	SOCS3
x_4	PP2
x_5	(STAT3N*)$_2$
u	IL-6

3.2 Linguistic Modeling for IL-6 Signal Transduction

Data for developing the linguistic structure are taken from information provided in the literature and from simulation results of the model developed by Huang *et al*. (2007). The generated model can then be further refined with additional experimental data. However, one of the advantages of developing this fuzzy model instead of using the model presented by Huang *et al*. (2007) is that the fuzzy model contains a significantly smaller number of parameters that may need to be validated.

A data set is created by hourly recording the values of the states x from simulations of model presented by Huang *et al*., 2007 for six different IL-6 concentrations: 0.001 nM, 0.005 nM, 0.04 nM, 0.1 nM, 0.25 nM, and 0.5 nM. The dynamics of (STAT3N*)$_2$ for stimulation with different IL-6 concentrations ranging from 0.001 nM to 5 nM is shown in Fig. 3. It can be seen that the dynamic profile of the (STAT3N*)$_2$ concentration can vary significantly with the amount of stimulation. For example, for IL-6 concentrations larger than 0.04 nM, the largest value of the concentration appears earlier, the stronger the increase in IL-6. However, for IL-6 concentrations larger than 0.5 nM, the system dynamics shows very little variation due to the fact that the receptors at the cell surface are saturated with IL-6 at this concentration.

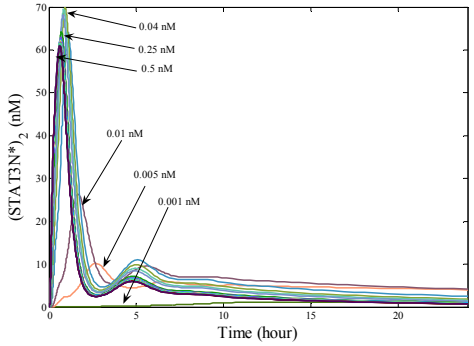


Fig. 3. (STAT3*)$_2$ profile for different IL-6 concentrations

K-means clustering is used to obtain the value of the parameters c of the membership functions. This requires that the data is normalized such that all data points have values

between zero and one. A summary of the results is shown in Table 2. The parameters σ of all membership functions are set to a value of 0.16.

Table 2. Parameters c of membership functions

Linguistic label	$C(u(k))$	$X(k)$ or $X(k+1)$				
		$C(x_1)$	$C(x_2)$	$C(x_3)$	$C(x_4)$	$C(x_5)$
VS	0	0.03	0.17	0.01	0.14	0
S	0.08	0.13	0.69	0.15	0.75	0.05
M	0.2	0.19	0.74	0.23	0.84	0.08
L	0.5	0.34	0.93	0.44	0.89	0.14
VL	1	1	0.99	0.89	0.98	0.80

The linguistic modeling algorithm discussed in Section 2 is used to determine the linguistic rules. The linguistic rules shown in Table 3 are derived from data taken from the literature (Fasshauer *et al.*, 2004; Lang *et al.*, 2003) as well as from data generated by the fundamental model (e.g., see Figure 4 for part of the data set). A description of how the linguistic rules are derived from this information is illustrated for the special case of a stimulation with 0.25 nM of IL-6 in the following.

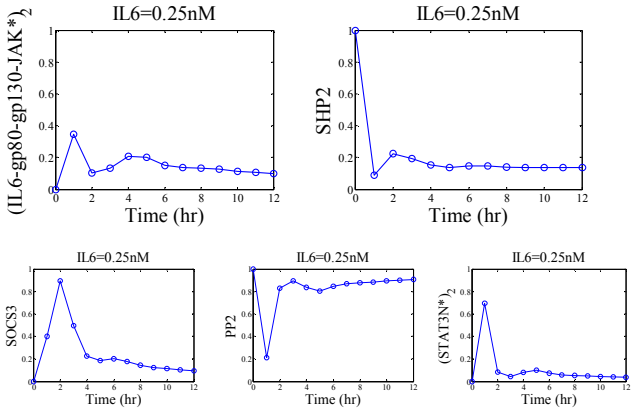


Fig. 4. System behavior for a stimulation with 0.25 nM of IL-6.

The normalized value for IL-6 being equal to 0.25 nM is computed by (0.25 nM - 0.001 nM)/(0.5 nM - 0.001 nM) resulting in a value of 0.5; in this calculation 0.001 nM is the smallest value of the IL-6 concentrations in the data set and 0.5 nM is the largest value. It can be concluded from Table 2 that 0.5 is the center of the linguistic label 'L', i.e., the linguistic label 'L' is assigned to an IL-6 concentration of 0.25 nM. It can be seen in Fig.4 that the normalized values for the $(\text{IL-6-gp80-gp130-JAK}^*)_2$, SHP2, SOCS3, PP2, and $(\text{STAT3N}^*)_2$ concentrations at time zero are 0, 1, 0, 1, and 0, respectively. From Table 2, the center of the linguistic label 'VS' is the closest to the normalized value of the $(\text{IL-6-gp80-gp130-JAK}^*)_2$ concentration of zero and, therefore, the linguistic label 'VS' is assigned to this concentration. Similarly, 'VL' is assigned to the normalized concentration of SHP2 equal to 1, 'VS' is assigned to SOCS3 being equal to 0, 'VL' is assigned to PP2 equal to 1, and 'VS' is assigned to $(\text{STAT3N}^*)_2$ being equal to 0. This description illustrates how the IF-part for Rule 29 in Table 3 was derived. The THEN-part of Rule 29 is constructed by the same procedure applied to the values of the states shown in Fig. 4 at 1 hr. Thus, the entire Rule 29 is constructed from data at 0 hr and 1 hr for an IL-6 concentration of 0.25 nM. The other rules shown in Table 3 are generated by the same procedure for data at different points in time and/or for different stimulation profiles. When several rules have the same IF-part but different THEN-parts, then the rule, whose THEN-part results in the largest change in the states is selected.

Table 3. Linguistic model for IL-6 signal transduction

Rule number	IF						THEN				
	$u(k)$	$X(k)$					$X(k+1)$				
		x_1	x_2	x_3	x_4	x_5	x_1	x_2	x_3	x_4	x_5
1	VS	VS	VL	VS	VL	VS	VS	L	VS	VL	VS
2	VS	VS	L	VS	VL	VS	VS	L	VS	VL	VS
3	VS	S	L	VS	L	S	L	M	VS	M	M
4	VS	L	M	VS	M	M	M	M	S	S	L
5	VS	M	M	S	S	L	S	M	M	M	M
6	VS	S	M	M	M	M	M	M	M	M	M
7	VS	M	M	M	M	M	M	M	S	M	M
8	VS	M	M	S	M	M	M	S	S	M	M
9	VS	M	S	S	M	M	M	S	S	M	M
10	S	VS	VL	VS	VL	VS	VL	VS	M	VS	VL
11	S	VL	VS	M	VS	VL	S	VS	VL	S	L
12	S	S	VS	VL	S	L	S	VS	VL	M	S
13	S	S	VS	VL	M	S	M	VS	L	M	M
14	S	M	VS	L	M	M	L	VS	M	S	L
15	S	L	VS	M	S	L	M	VS	M	S	L
16	S	M	VS	M	S	L	M	VS	M	M	M
17	S	M	VS	M	M	M	M	VS	M	M	M
18	S	S	VS	S	M	M	S	VS	S	M	M
19	M	VS	VL	VS	VL	VS	L	VS	L	VS	VL
20	M	L	VS	L	VS	VL	S	VS	VL	S	L
21	M	S	VS	VL	S	L	S	VS	L	L	S
22	M	S	VS	L	L	S	M	VS	M	M	M
23	M	M	VS	M	M	M	M	VS	M	S	L
24	M	M	VS	M	S	L	M	VS	M	M	M
25	M	S	VS	M	M	M	S	VS	S	M	M
26	M	S	VS	S	M	M	S	VS	S	M	S
27	M	S	VS	S	M	S	S	VS	S	L	S
28	M	S	VS	S	L	S	S	VS	S	L	S
29	L	VS	VL	VS	VL	VS	L	VS	L	VS	VL
30	L	L	VS	L	VS	VL	S	VS	VL	M	M
31	L	S	VS	VL	M	M	S	VS	L	L	S
32	L	S	VS	L	L	S	M	VS	M	M	M
33	L	M	VS	M	M	M	M	VS	S	M	M
34	L	M	VS	S	M	M	S	VS	M	M	M
35	L	S	VS	M	M	M	S	VS	S	L	S
36	L	S	VS	S	L	S	S	VS	S	L	S
37	VL	VS	VL	VS	VL	VS	L	VS	L	VS	VL
38	VL	L	VS	L	VS	VL	S	VS	VL	M	M
39	VL	S	VS	VL	M	M	S	VS	L	L	S
40	VL	S	VS	L	L	S	M	VS	M	M	M
41	VL	M	VS	M	M	M	M	VS	S	M	M
42	VL	M	VS	S	M	M	S	VS	S	M	M
43	VL	S	VS	S	M	M	S	VS	S	L	S
44	VL	S	VS	S	L	S	S	VS	S	L	S

It can be inferred from Table 3, that the fuzzy rules for very small IL-6 concentrations are quite different than those for higher concentrations. This is consistent with the results shown in Fig. 3, as the dynamic behavior of the states for stimulation with IL-6 concentrations below 0.04 nM is significantly different from those for higher IL-6 concentrations.

The parameters of the membership functions of the linguistic model are estimated using a back propagation algorithm (Kim et al., 1999; Jang, 1993). Only the parameters σ of the premise membership functions are estimated, and the parameters σ of the consequent membership functions as well as parameters c are kept constant. The parameters σ of the consequent membership functions are all set to a value of 0.16. Therefore, only 30 parameters need to be estimated which is a significant reduction of the parameters in the

model when compared to the fundamental model presented by Huang *et al*. (2007) which contained 124 parameters.

During the parameter estimation procedure, the parameter vector σ is updated by the following equation:

$$\sigma = \sigma - \eta \sum_{p} \frac{\partial E_p}{\partial \sigma} \tag{4}$$

where η refers to a step-size and E_p is the square of the error between the model output and the actual output for the p_{th} data set. η is updated by the following strategy to increase the rate of convergence:

(1) if $\sum_{p} E$ continuously decreases in four epochs, then adjust η by setting $\eta = 1.001\eta$;

(2) if $\sum_{p} E$ increases and decreases twice in a row then adjust η by setting $\eta = 0.99\eta$.

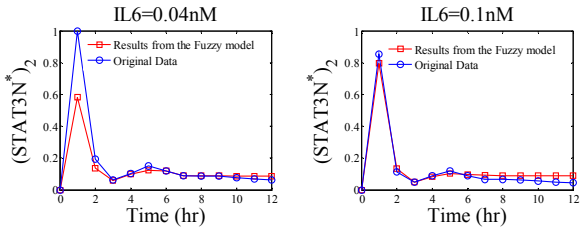
The determined values of σ of the premise membership functions are shown in Table 4.

Table 4. The parameter σ of the premise membership functions

Linguistic label	IF-part					
	$\sigma(u(k))$	$X(k)$				
		$\sigma(x_1)$	$\sigma(x_2)$	$\sigma(x_3)$	$\sigma(x_4)$	$\sigma(x_5)$
VS	0.05	0.35	0.13	0.29	0.19	0.18
S	0.05	0.05	0.07	0.05	0.17	0.08
M	0.05	0.05	0.06	0.05	0.16	0.14
L	0.13	0.05	0.25	0.13	0.16	0.10
VL	0.16	0.19	0.05	0.06	0.19	0.18

The fuzzy model is comprised of the linguistic model shown in Table 3, with values of the centers of the membership functions from Table 2, and the determined values of the parameters σ of the premise membership functions shown in Table 4. This model can be used to compute the dynamic behavior of the model.

A comparison of the dynamic behavior of the fuzzy model with the original training data at different IL-6 concentrations is shown in Fig. 5. Only the results for the profile of $(STAT3N^*)_2$ are shown in this work due to space constraints, however, the profiles of all the components are predicted well by the model. It can be seen in Fig. 5 that the model can correctly reproduce the large peak of the $(STAT3N^*)_2$ concentrations after 1 hr as well as the much smaller peak around 5 hrs. It can also be concluded that the model accuracy at low IL-6 concentrations is not as good as the accuracy at high IL-6 concentrations.



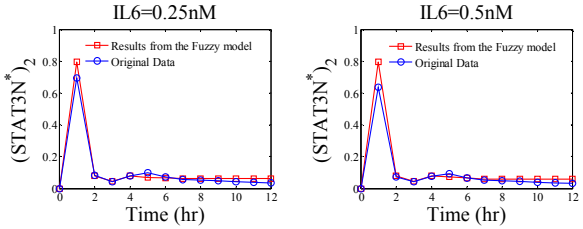


Fig. 5. Comparison of the fuzzy model predictions with the original data set

In addition to being able to reproduce the training data well, the model has to be able to predict the dynamics of the states for values of the states and inputs that were not contained in the training data set. A comparison of some results is shown in Fig. 6 where the model can accurately reproduce the dynamics of the $(STAT3N^*)_2$ concentration.

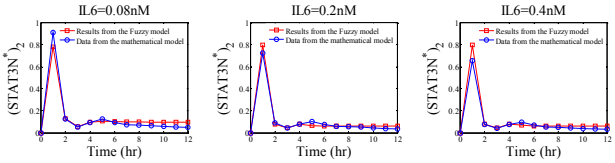


Fig. 6. Comparison of the fuzzy model predictions with a newly generated data set

4. SIMULATION RESULTS AND DISCUSSION

While predicting the dynamic behavior of the $(STAT3N^*)_2$ concentration is one of the key aspects of IL-6 signal transduction, there are other important insights that can be gained by investigating the dynamics of the activated receptor complex $(IL\text{-}6\text{-}gp80\text{-}gp130\text{-}JAK^*)_2$ concentration, and the dynamics of the SOCS3, SHP-2 and PP2 concentrations. In order to investigate these, the simulation results for a stimulation with 0.25 nM of IL-6 are shown in Fig. 7.

It can be concluded that the model is able to describe the main characteristics of the dynamics of IL-6 signaling. These characteristics include the height and location of the two peaks of the receptor complex $(IL\text{-}6\text{-}gp80\text{-}gp130\text{-}JAK^*)_2$ concentration which is caused by the cycling of $(STAT3N^*)_2$ between the cytosol and the nucleus as seen in Fig. 7(a). The magnitude of the decrease in SHP2 as seen in Fig. 7 (b) is also correctly described by the fuzzy model. The correct description of the SHP2 dynamics is important insofar as SHP2 is involved in activating signaling through the MAPK pathway, which then results in reduced signaling through the JAK/STAT pathway. The fuzzy model can also correctly reproduce the peaks of SOCS3 (Fig. 7(c)) and PP2 (Fig. 7(d)), respectively. The SOCS3 dynamics is especially important as SOCS3 acts as a feedback inhibitor for signaling through the JAK/STAT pathway. Another important mechanism is facilitated by the nuclear phosphatase PP2 as it is required for the cycling of STAT3 between the cytosol and the nucleus. The initial drop in the PP2 concentration is a result of the large peak value of nuclear STAT3 that enters the nucleus and reacts with PP2 before it can cycle back to the cytosol. It can be concluded that the fuzzy model is able to capture the

initial changes very well, whereas the model predictions have a small offset after approximately 6 hours. The reason for this is that only slow changes occur at that time and that the chosen set of fuzzy rules is not able to accurately describe small and slow changes. It would be possible to capture this behavior in the model if additional linguistic rules and more model parameters were used, however, the presented model provides a good trade-off between model accuracy and model complexity. This is especially true if it is considered that the initial response of IL-6 signal transduction is more important than small changes in the signaling pathway occurring after prolonged exposure to IL-6.

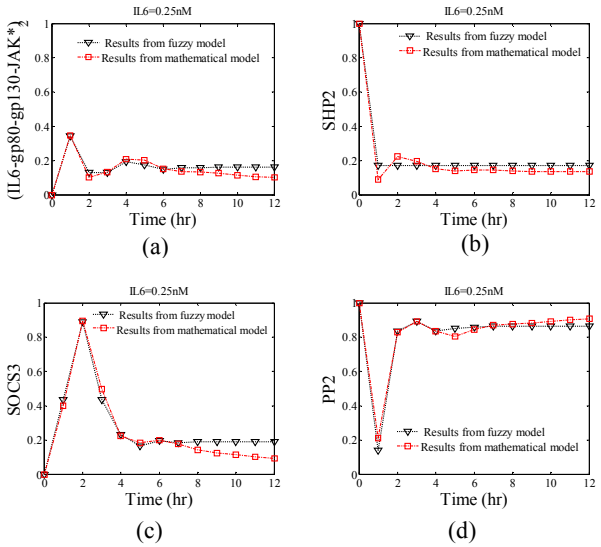


Fig. 7. Simulation results of the fuzzy model for stimulation with 0.25 nM of IL-6

5. CONCLUSION

This paper presented the application of fuzzy modeling to signal transduction pathways. The motivation for using fuzzy models is that a significant amount of qualitative information about signal transduction pathways can be found in the literature, however, a more limited amount of quantitative knowledge exists. The approach presented in this work uses a linguistic model to describe the dynamic behavior of the system as a function of the previous states and current inputs. A K-means clustering algorithm computes the parameter c referring to the center of the membership functions and a back propagation algorithm is used for determining the width parameter σ of the premise membership functions. The technique is illustrated by modeling the dynamics of an IL-6 signal transduction pathway and the results are found to be in good agreement with available data.

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