Fuzzy Approach to Regulate S-type Biological Systems

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ABSTRACT
It is important to regulate biological systems to return to nominal steady states such that systems are able to maintain normal functions. S-type biological systems (S-systems) are described as power-law-based differential equations which are able to show nonlinear interactive strength between constitutes and as a result, S-system becomes the most potential model for large-scale systems. Biological systems always possess a lot of uncertainties and noises. Fuzzy sets and models are able to describe, recognize and manipulate data that are vague and lack certainty. However, biological systems are different from electromechanical systems that allow various types of time-varying signals as system inputs. Therefore, step functions are used as fuzzy outputs to denote constant concentration and the firing strength of each fuzzy rule is the blending or allocating ratio. A cascade pathway is concerned and an exponentially decaying model is used to describe the functional degradation phenomenon. Dry-dlab experiments are carried out in five different situations. Simulation results show that the proposed seven-rule fuzzy logic controllers are able to find out the nominal values of independent variables and force systems to return to their nominal steady states. The larger the nominal values are the longer the time to reach targets.

Keywords
Fuzzy logic control, systems biology, computational biology

1. INTRODUCTION
Generalized Michaelis-Menten kinetics describes physically interactive kinetics between constitutes (proteins, genes and metabolites). S-systems (S-type biological systems) in Eq. (1) show net interactive strength between constituents.

\[ \dot{x}_i = v_i^+ - v_i^- = \alpha \prod_{j=1}^{n+m} g_{ij} x_j^{\beta_i} - \beta_i \prod_{j=1}^{n+m} h_{ij} x_j^{\gamma_i}, i = 1, ... n \]

where \( g_{ij} \) and \( h_{ij} \) denote the net interactive strength from \( x_j \) on \( x_i \), \( \alpha \) and \( \beta_i \) are the rate constants. The \( x_n, i = 1, ... n \) are dependent variables and \( x_{n+1}, ... x_{n+m} \) are independent variables, the values of which remains constant during a period of an experiment. These two well-known biological systems are both based on biochemistry system theory and described as highly nonlinear differential equations. The modelling of generalized Michaelis-Menten systems is a bottom-up process. System is gradually constructed from small systems [1] to medium-scaled systems [2] and then expanded to large systems [3]. Parameters are estimated through doing experiments over and over again and a large amount of experimental data are used. The modelling of S-systems is a top-down process and parameters are estimated through computational approaches. Good generalization properties let S-system become the most potential model for large-scale systems. Liu and coworkers used the S-system to describe p53 signaling pathway mechanism [4]. S-system modelling is a multi-objective multi-constraints optimization problem. Various intelligently computational technologies were recently developed to achieve S-system modelling [5-11].

There exist too many uncertainties and noises in a biological system. Luo and An reviewed fuzzy theory in four kinds of biomedical science (device control, biological control, classification and pattern recognition, and prediction and association) [12]. Komiyama and coworkers did a deep-review on DNA nano architectonics and cell-macromolecular nano architectonics [13]. They emphasized that many biological mechanisms (for example, hydrophobic effects and electrostatic interactions) exist rather fuzzy molecular interactions. So, exact or optimal methods have considerable limitations in this field. Fuzzy logic comes from an observation that the thinking of people is always based on imprecise and non-numerical information. Fuzzy sets and models are able to describe, recognize and manipulate data that are vague and lack certainty. The use of linguistic variables and imprecise relationship let fuzzy set theory have great potential in analyzing biological data, modeling biological systems and solving a wide range of biological problems. Abyad and coworkers used the T-S fuzzy model to describe a biomass growth process, a growing population of microorganisms through substrate consumption [14]. Bordón et al. used fuzzy logic to describe a three-gene repressor of unknown kinetic data [15]. Liu and coworkers reviewed three kinds of fuzzy Petri nets for biological system modelling and discussed modelling capacities and applications [16]. They integrated continuous Petri nets with fuzzy inference system and proposed a workflow for modelling and analyzing biological systems [17]. Zhu and coworkers combined fuzzy neural network inverse system methods and decoupling control technologies to achieve the control of marine alkaline protease MP (a kind of extracellular enzyme) [18]. Adaptive neural-fuzzy modeling technique was previously proposed to identify biological systems and discussed the scalability of the proposed method [19].

Biological systems always possess a good regulation mechanism to maintain a system within certain limits. When systems are in a bad situation (for example, modelable experimental variables denoted as independent variables decay with time) the regulation mechanism fails to work and systems are not able to return to nominal states (steady states). In this study, fuzzy logic controllers are used to regulate biological systems back to their nominal states.

2. METHODS
When individuals get sick the dynamic behavior of underlying systems go far from their nominal states (steady states). Systems can not automatically return back to their nominal states and additional treatments are required.
Exponentially decaying model
The degradation of body functional changes the environment of biological systems and makes system loss the regulation ability. When medicines are administered intravenously, the concentration decreases as due to liver metabolism and kidney filtration (clearance of liver and kidneys). In these situations, system inputs (independent variables, modelled experimental variables) cannot remain at a constant value and will continually decrease as time goes (time-varying input). In this study, an exponential function \( r = r_0 e^{at} \) is used to describe the decaying phenomenon, where \( r_0 \) is a starting value of concentration of independent variables, \( e \) is the Euler’s constant and \( a \) is a negative constant that determines the rate of decay [21]. (The exponentially decaying model is always used in biology and radioactive isotopes to estimate the half-life, the time for a substance to exponentially decay to half of its original quantity.) The exponentially decaying model is expressed as block diagrams in the Simulink environment, as shown in Fig. 1.

Prototype of biological fuzzy control
When system states are out of suitable living environments, fuzzy control is used to drive systems back to nominal states. However, biological systems are different from electromechanical systems that allow various types of time-varying signals system inputs (impulse, exponentially signals...). A fuzzy model prototype is proposed: Eq. (2) describes the ith rule of the used fuzzy controller, where \( x \) and \( y \), respectively, denote the linguistically input and output variables, \( A_{1i} \), \( B_{1i} \) are fuzzy sets and the fuzzy set \( C_i \) denotes a set function. The firing strength of each fuzzy rule (denoting the degree to which the rule matches the inputs) is considered as a blending or allocating ratio of the fuzzy sets \( C_i \), \( i = 1, \ldots, n \). The fuzzy logic block in Simulink toolbox, as shown in Fig. 2, is then used to build up the fuzzy controller.

\[ R^i: \text{If } x_1 \text{ is } A_{1i} \text{ and } x_2 \text{ is } B_{1i}, \text{ then } y = C_i, i = 1, \ldots, n. \]  

Simulink-based dynamic behavior
Simulink is a toolbox of Matlab (MATrix LABoratory, a software developed by The MathWorks Company). In the Matlab/Simulink software environment, locally dynamic behavior is treated as a block. The dynamic behavior of asystenm is obtained through a connection of blocks. Blocks are further grouped into a subsystem (a module) which is composed of a set of connected blocks. In this way, a large-scale system can be shown as a concise diagram. In addition to achieve the prediction of dynamic behavior of biological systems in various modellable experimental environments (denoted as input signals), the Simulink environment further provides people more conducive way on the modification and maintenance of individual modules and the modification of interaction between modules.

3. RESULTS AND DISCUSSION
A small S-type system is considered to describe the proposed fuzzy approach clearly. Figure 3 is a cascade pathway [22]. The source \( x_4 \) is an independent variable which generates mid-product \( x_1 \). The generation reaction is inhibited by both \( x_2 \) and \( x_3 \). The \( x_1 \) induces the generation of mid-product \( x_2 \) which further induces the generation of the final product \( x_3 \).

The corresponding S-type biological systems (called S-systems in biology fields) is

\[ x_1 = 10x_2, x_2 = x_3 - 5x_1, \]
\[ x_2 = 2x_4^0.5 - 1.44x_5^0.5, \]
\[ x_3 = 3x_5^0.5 - 7.2x_5^0.5. \]

The values of exponent order and rate constants are cited from Tsai and Wang’s paper [22]. In normal situations, the concentration of the independent variable \( x_4 \) always keeps constant throughout experiment. A situation is considered in which systems experience functional degradation that leads to the value of source constant \( x_4 \) decreasing from time to time. The exponentially decaying model in Sec. 2 is used to describe this phenomenon: \( x_4 = r_0 e^{at} \) were \( r_0 \) is the nominal value of \( x_4 \).

Nominal steady state estimation (target states)
At equilibrium the net flux \( \dot{y}^i = \dot{y}_i^u \). (The upper bar denotes equilibrium). Equation (1) becomes an algebraic equation in Eq. (4) through setting \( g = \ln x_i, h_i = g_i - h_i, C_{Bi} = \ln(2^C) \) and letting matrices \( b = [\alpha \beta]_{i=1,n} \). \( \tilde{y}_d \) and \( \tilde{y}_i = [y_i]_{i=1,n} + [y_i]_{i=1,n+1,m} \) and \( A_{1i} = [g_i h_i]_{i=1,n,j=1,n+1,m} \) and \( A_d = [g_i h_i]_{i=1,n,j=1,n+1,m} \).

\[ A_{1i} \tilde{y}_d + A_{1i} \tilde{y}_i = b. \]

The steady state values are estimated: \( \tilde{y}_d = A_{1i} \tilde{y}_d + b - (A_{1i} A_{1i}) \). \( Y_i \), where \( A_{1i} \) is the inverse or the pseudoinverse of \( \tilde{y}_d \). In this case, \( n = 3, m = 1, A_{1i} = [0.5 \ -0.5 \ 0], A_{1i} = [0.5 \ -0.5 \ 0]. \)

Fuzzy logic control
Fuzzy controller is developed to regulate the system back to
the equilibrium state $X_0 = [x_1, x_2, x_3]^T$ in the case of the independent variable $x_4$ exponentially decaying with time ($x_4 = r_0 e^{-0.2t}$). In order to solve this issue the independent variable $x_4$ is treated as a system input. The problem becomes a regulator problem. A fuzzy controller is then constructed to force all of the errors, $e_i = x_i - x_i^o$, $i = 1, ... 3$, to reach zero. Since the concentration of $x_1$ and $x_3$ is related to the concentration of $x_2$. For simplification the $x_2$ is used as a target to follow: $e_2 = x_2 - x_2^o$. Table 1 and Eq. 5 show the seven rules of the proposed fuzzy controller. The used membership functions for the input variable $e$, the input variable $\dot{e}$ and the output variable $u$, are, respectively, shown in the upper figure, middle figure and down figure of Fig. 4.

$$R^1: \text{If } e \text{ is } Z, \text{ then } u = Z,$$

$$R^2: \text{If } e \text{ is } P \text{ and } \dot{e} \text{ is } P, \text{ then } u = NN,$$

$$R^3: \text{If } e \text{ is } P \text{ and } \dot{e} \text{ is } Z, \text{ then } u = N,$$

$$R^4: \text{If } e \text{ is } P \text{ and } \dot{e} \text{ is } N, \text{ then } u = N^-$$

$$R^5: \text{If } e \text{ is } N \text{ and } \dot{e} \text{ is } P, \text{ then } u = P^+,$$

$$R^6: \text{If } e \text{ is } N \text{ and } \dot{e} \text{ is } Z, \text{ then } u = P,$$

$$R^7: \text{If } e \text{ is } N \text{ and } \dot{e} \text{ is } N, \text{ then } u = PP.$$  

**Table 1. Fuzzy rules**

<table>
<thead>
<tr>
<th>$e$</th>
<th>$\dot{e}$</th>
<th>$P$</th>
<th>$Z$</th>
<th>$N$</th>
<th>$P^+$</th>
</tr>
</thead>
<tbody>
<tr>
<td>P</td>
<td>P</td>
<td>P</td>
<td>$N$</td>
<td>$Z$</td>
<td>$P$</td>
</tr>
<tr>
<td>Z</td>
<td>Z</td>
<td>N</td>
<td>Z</td>
<td>$P$</td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>$N^-$</td>
<td>Z</td>
<td>$Z$</td>
<td>$P$</td>
<td></td>
</tr>
</tbody>
</table>

Figure 5 shows the scheme for fuzzy logic control of the cascade pathway. The two subsystem blocks with $x_4$ input node and $x_1$, $x_2$, $x_3$ output nodes are the cascade pathway system block. Figure 6 is the detailed signal flow of this block. In Fig. 5 the upper figure denoted by dashed red line simulates the dynamic behavior of the system with an exponential input (original systems). The down figure runs the dynamic behavior of the closed-loop fuzzy-logic controlled system. The experimental condition is set at $r = 0.2e^{-0.2}$ where the nominal value of the independent variable is $x_4 = r_0 = 3$. At this case ($x_4 = 3$), the target steady states are estimated through Eq. (4): $\hat{x} = [1.548, 29.86, 85.185]^T$. In Fig. 5, the “Interpreted MATLAB Fcn” block (the bottom box in the middle) carries out steady state estimation. For clear comparison, the target values and the simulation results are displayed in the lower right corner of Fig. 5 and the target values is marked by a dashed blue block. The results show that the proposed controller is able to perfectly regulate the system back to the target steady state.

The Rule Viewer in fuzzy logic control subsystem supports people real-time view the inference process. Figure 7 is the final result shown in the Rule Viewer. The estimated error $e_2 = x_2 - x_2^o = 0.0168$, the estimated error derivative $\dot{e}_2 = \dot{x}_2 - \dot{x}_2^o = -0.00272$ and the estimated independent variable $x_4 = u(t) = 3$ which reach the nominal value ($r_0 = 3$). Figure 8 shows the dynamic behavior of the system states $x_1$ (purple), $x_2$ (red) and $x_3$ (blue). The states of the original system are denoted as dashed lines, that of the controlled system are denoted as solid lines and green solid lines show the target values. The controlled system reaches the target at around 22.5 seconds.

Additional experiments are conducted at $r_0 = 0.75, 1, 1.5, 2$. The simulation results for these four experiments are shown in Table 2. The detailed results are shown in the supplementary file. The time for the controlled system to reach the target values is around 6 seconds, 7 seconds, 11 seconds and 15 seconds for $r_0 = 0.75, 1, 1.5, 2$, respectively. All of the simulation results show that the proposed fuzzy logic controllers are able to force the system back to nominal steady states. The bigger the non nominal value of the independent variable is the longer the time to reach the target becomes.
Fig 5: Scheme for fuzzy Logic Control of the cascade pathway in Eq. (3). The right down table shows the estimated values (upper three rows) and the target values (down three rows).

Fig 6: Block diagrams of the cascade system in Eq. (3).
Fig 8: The dynamic behavior system states $x_1$ (purple), $x_2$ (red) and $x_3$ (blue). The states for the original system are denoted as dashed lines, that for the controlled system are denoted as solid lines and the target states are shown in green solid lines.

Table 2. Simulation results for $x_4 = r_0 e^{-0.2t}$ with $r_0 = 0.75, 1, 1.5, 2, 3.$

<table>
<thead>
<tr>
<th>Estimated input $u(t)$</th>
<th>0.75</th>
<th>1</th>
<th>1.5</th>
<th>2</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Regulating time $t_x$</td>
<td>6</td>
<td>7</td>
<td>11</td>
<td>15</td>
<td>22.5</td>
</tr>
<tr>
<td>Target states $x$</td>
<td>1.835</td>
<td>5.509</td>
<td>5.229</td>
<td>8.296</td>
<td>15.48</td>
</tr>
<tr>
<td>Estimated states $x_{es}$</td>
<td>1.835</td>
<td>5.509</td>
<td>5.229</td>
<td>8.296</td>
<td>15.48</td>
</tr>
<tr>
<td>Error $e$</td>
<td>-8.34 x 10^{-6}</td>
<td>0.000373</td>
<td>0.00396</td>
<td>0.0124</td>
<td>0.0168</td>
</tr>
<tr>
<td>Error derivative $e'$</td>
<td>4.63 x 10^{-6}</td>
<td>0.000166</td>
<td>-0.00128</td>
<td>-0.00034</td>
<td>-0.00272</td>
</tr>
</tbody>
</table>

4. CONCLUSION
The degradation of biological functions changes the environment of organisms as a result, organism loses regulation ability. For S-type biological systems, modellable experimental environments are denoted as independent variables, the values of which remain constant throughout an experiment. Time-varying independent variables are concerned to describe this kind of degradation phenomenon. A fuzzy logic controller is then proposed to regulate systems to target states, and estimate the nominal values of independent variables. Simulation results show that the proposed controller is able to not only successfully force systems to target states but also find out the nominal values of independent variables. This research initiates the application of fuzzy logic control in S-type biological systems. Follow-up research will apply fuzzy logic control to systems with generalized Michaelis-Menten kinetics, and develop various fuzzy compensators or fuzzy estimators to deal with noise-contaminated biological systems.

5. ACKNOWLEDGMENTS
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6. REFERENCES


