Parameter estimation from experimental laboratory data of HSV-1 by using alternative regression method

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Abstract In this paper, an estimation of model parameters is performed by using the Alternative Regression (AR) approach on an experimental data set of Herpes Simplex Virus type-1 (HSV-1) infection with innate immune response. Throughout the specified course of time, the measurements of monocytes, neutrophils, and viral load were obtained from the corneas of infected mice. C57BL/6 (B6) mice were used at Oakland University, Department of Biological Sciences, and the outcome measurements were divided into training and testing data sets. The HSV-1 nonlinear dynamic model is proposed based on the observed data patterns and biological system information. The simulation results of the proposed model showed that they consistently fit the experimental data set. In addition, the sensitivity test and model validation diagnostics are considered to determine the most significant key parameters that affect the dynamics of the HSV-1 system.

Keywords Biochemical system theory · HSV-1 experimental data set · Nonlinear HSV-1 model · Smoothing algorithm · Alternative regression method · HSV-1 parameter estimation

Introduction

An important mission in computational biology is the conversion of biological system interactions into computational models. This conversion requires data observations, biological knowledge about system dynamics, nonlinear mathematical representations, and finding suitable estimation techniques (Voit and Chou 2010). Moreover, these computational models may involve assumptions, simplifications, and evaluation of the performance of the proposed model based on the actual experimental data (Chou and Voit 2009). The mathematical formulation may fail to provide good representations in the absence of important dynamic factors. Therefore, biochemical system theory has been used to investigate the biological interactions (Voit and Chou 2010; Chou and Voit 2009; Savageau 1969) and has supplied important information and an efficient framework for symbolizing the dynamics of biological systems. Also, estimation methods based on optimization are used to diminish the error between the mathematical model and experimentally-observed data. In the literature (Lowe and Zohdy 2009; Ueda et al. 2002; Sugimoto et al. 2005; Zohdy et al. 1995; Nakatsui et al. 2003; Kikuchi et al. 2003; Maki et al. 2002; Almeida and Voit 2003; Tsai and Wang 2005; Matsubara et al. 2006; Polisetty et al. 2006), many estimation methods based on direct estimation of parameter values were introduced. These methods consumed a large amount of time and added complexity in general. Therefore, in (Chou et al. 2006), the AR method is proposed to estimate the parameters of biochemical systems. The advantage of using the AR is the reduction of the nonlinear differential equations into iterative linear regressions by performing logarithmic transformations and replacing the derivatives with estimated slopes that were calculated from observed

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measurement data (Vilela et al. 2008). In this study, a new HSV-1 nonlinear dynamic model is proposed. This model is based on the available laboratory information on HSV-1 virus interactions with innate immune system response and additional assumptions are considered to fill the gap of missing data. The model's parameters are estimated by using the AR, and the results showed that the new model consistently fits the experimental data. In addition, sensitivity test and model validation are also considered to find the most important key parameters and illustrate the performance of the proposed model.

HSV-1 collection data procedures

In this study, we used an experimental data set that was collected at Oakland University's Department of Biological Sciences for HSV-1 with innate immune response. The total experimental procedures completely adhered to the Association for Research in Vision and Ophthalmology (ARVO) statement for the use of animals. Furthermore, the experimental procedures were done according to the rules and regulations of the Institutional Animal Care and Use Committee (IACUC) of Oakland University. This experimental data set was taken from C57BL/6 (B6) mice that were bought from Jackson Lab (Bar Harbor, Maine), accommodated in the animal facility at Oakland University, and anesthetized by intraperitoneal injections of Avertin. After the injection, an infectious dose of plaque-forming units (PFU) of HSV-1 was applied to one eye of each mouse. This procedure was followed by a gentle massage over the eyelids. Then, an observation of the weight, eyelid inflammation, encephalitis, and food consumption of each mouse was done daily. The HSV-1 RE virus that was used for this study was acquired from Hendricks Lab at the University of Pittsburgh School of Medicine in Pittsburgh, Pennsylvania. Also, flow cytometry was used to determine the influx of monocytes and neutrophils in the infected corneas of the mice. Furthermore, plaque assay was used to determine the viral load in infected corneas (Twardy et al. 2011). The data set of HSV-1 with innate immune response was divided into three phases. The first phase was assigned for day (0), where there was no infection in the cornea, the second phase (pre-clinical) was assigned from day (1) until day (6), and the third phase (clinical) was assigned for day (10), day (13), and day (15). Testing procedures for the experimental data set started with the collection of four infected corneas for each data time point, and, to obtain one test sample, the collected corneas were pooled and digested in 2 mg/ml of collagenase type IV (Sigma-Aldrich Co.) and 0.05 mg/ml of Deoxyribonuclease I (DNase I) in Roswell Park Memorial Institute medium 1,640 (RPMI) for 90 min at 37 °C.

After that, the homogenized procedure (trituration) was applied to achieve a single cell suspension. The suspension was passed into a 40 μ cell strainer and washed in RPMI medium. Then, the influx of monocytes and the influx of neutrophils were determined by using different antibodies for cell surface staining. The following antibodies were used: CD45, CD11b, F480, and Ly6G + (BD Pharmingen, San Diego, CA) in FACS buffer (Phosphate Buffered Saline (PBS), +2 % Fetal Bovine Serum (FBS), and +0.1 % sodium azide). At the final stage of staining, monocytes cells and neutrophils cells were fixed in 1 % paraformaldehyde, and samples were acquired on a FACS canto II flow cytometer. Data measurements were analyzed using software (Flowjo v8.7.1, TreeStar, Ashland, OR). The testing procedures for the experimental data are described in Fig. 1.

Assumption on HSV-1 model from biochemical knowledge

The proposed model for HSV-1 is derived from the experimental data measurements that represent the dynamics of the HSV-1 virus and the innate immune response. Also, the structure of the biochemical system is considered and modified in light of HSV-1 dynamics. The proposed model used in this study consists of three state variables: x_1 , x_2 , and x_3 , representing the HSV-1 virus, monocytes, and neutrophils, respectively. The HSV-1 virus is assumed to produce at rate α_1 and is killed by the effect of monocytes and neutrophils at rate β_1 , the monocytes are assumed to produce by the stimulation of the virus at rate α_2 and die at rate β_2 , and the neutrophils are also assumed to produce by the provocation of the virus at rate α_3 and die at rate β_3 . The parameters g and h represent the kinetic orders of the system where g_{11} , h_{11} , h_{12} and h_{13} are the kinetic orders of the first state, g_{21} , g_{22} , and h_{22} are the kinetic orders of the second state, and g_{31} , g_{33} , and h_{33} are the kinetic orders of the third state. The HSV-1 system of

Fig. 1 Testing procedures for the experimental data

equations can be explicitly written as in Eq. (1) and demonstrated in Fig. 2.

$$\begin{aligned}\dot{x}_1 &= \alpha_1 x_1^{g_{11}} - \beta_1 x_1^{h_{11}} x_2^{h_{12}} x_3^{h_{13}} \\ \dot{x}_2 &= \alpha_2 x_1^{g_{21}} x_2^{g_{22}} - \beta_2 x_2^{h_{22}} \\ \dot{x}_3 &= \alpha_3 x_1^{g_{31}} x_3^{g_{33}} - \beta_3 x_3^{h_{33}}\end{aligned}\quad (1)$$

Preprocessing of experimental data using information theory

Rate of change approximation

The idea behind the rate of change approximation is splitting the ordinary differential equations (ODEs) into sets of separate algebraic equations, and then calculating the slopes from measurement data to approximate the derivatives (Voit and Almeida 2004). There are two advantages of using this approximation: the first is that the analysis of algebraic equations becomes an easy problem, and the second is that the computational effort for parameter estimation is reduced compared to the numerical integrations. The proposed model and its derivative approximation can be expressed as a general formula of the S-system as shown in Eqs. (2) and (3), where S stands for synergism and saturation (Voit and Ferreira 2000) of the HSV-1 dynamic model.

$$\dot{x}_i = \alpha_i \prod_{j=1}^n x_j^{g_{ij}} - \beta_i \prod_{j=1}^n x_j^{h_{ij}}, \quad i = 1, 2, \dots, n \quad (2)$$

$$\begin{aligned}s_i(t_k) &= \alpha_i \prod_{j=1}^n x_j^{g_{ij}}(t_k) - \beta_i \prod_{j=1}^n x_j^{h_{ij}}(t_k) \quad i = 1, 2, \dots, n \\ k &= 1, 2, \dots, N\end{aligned}\quad (3)$$

where $s_i(t_k)$ represents the slopes, n represents the total number of state variables within the system. Since the proposed model had three states, $n = 3$. N represents the time points of the measurements, in this case, $N = 11$.

Fig. 2 HSV-1 proposed model

Smoothing algorithm

The smoothing algorithm is used to reduce the noise in the measurements before calculating the slopes. The task was proposed in Whittaker's smoother (Whittaker 1923) and extended in (Eilers 2003) as a minimization of the Q function shown in Eq. (4):

$$Q = \sum_{i=1}^N (\gamma_i - z_i)^2 + \lambda \sum_{i=1}^{N-d} (\Delta z_i)^2 \quad (4)$$

where γ is the noisy time series, z is the smoothed series, N are the noisy data points, λ is the weighing of the filter's residuals, Δz_i is the difference between two consecutive points, e.g. $\Delta z_i = (z_{i+1} - z_i)$, and d is the order of the filter. The first term in the right hand side of Eq. (4) measures the fidelity of the data and the second term measures the smoothness of the output data (Vilela et al. 2007). Equation (4) can be rewritten in matrix form as:

$$Q = |\gamma - z|^2 + \lambda |Dz|^2 \quad (5)$$

such that $|\gamma - z|^2 = \sum_{i=1}^N (\gamma_i - z_i)^2$, $|Dz|^2 = \sum_{i=1}^{N-d} (\Delta z_i)^2$, where D is a matrix with dimension $(N - d) \times N$. Therefore, the smoothing series z is calculated from Eq. (5) by minimizing Q as:

$$z = (I + \lambda D^T D)^{-1} \gamma \quad (6)$$

where I is an identity matrix with the same dimension of noisy data points.

Since the parameters λ and d play an important role in obtaining the smoothing signal, the Cross Validation Error (CVE) is used in (Eilers 2003). But, the problem of using CVE in Whittaker's smoother is the sensitivity to the signal scaling, which means that the smoother algorithm is not adaptive, and consequently the parameters λ and d are not optimized. Therefore, Renyi's second entropy equation is introduced in (Vilela et al. 2007) as:

$$H_{R_2}(\gamma) = -\log(V(\gamma)) \quad (7)$$

where $V(\gamma)$ refers to Information Potential (IP) as:

$$V(\gamma) = \frac{1}{N^2} \sum_{i=1}^N \sum_{j=1}^N k_{2\sigma}(\gamma_j - \gamma_i) \quad (8)$$

where $k_{2\sigma}$ is the Gaussian kernel with size σ . With minimizing the Renyi's second entropy of cross validation error, the parameters λ and d are optimized.

In this study, the reformulated Whittaker's smoother package (Vilela et al. 2007) that deals with nonstationary noise in time series data is used. This reformatted smoothing is an effective tool for extracting the signal from different noise structures, and it's based on Whittaker's smoother (Whittaker 1923) and Eilers's extension (Eilers 2003).

Alternative regression for HSV-1 parameter estimation

Parameter estimation of biological systems has been a challenging topic for many researchers. (Tucker et al.

2007) used a constraint propagation to estimate the parameters for a generalized mass action, (Ho et al. 2007) used an intelligent two stage evolutionary algorithm for genetic networks, (Wang et al. 2010) used a unified approach to estimate gene regulating networks using the S-system structure, and (Kikuchi et al. 2003) used a genetic algorithm and S-system to estimate the parameters of a dynamic system.

The aforementioned methods are slow and complex to implement. Therefore, (Chou et al. 2006) proposed an efficient and fast estimation algorithm compared with other methods. This method was used to estimate the parameters of the biochemical system networks. The advantage of this technique is that it transforms the computation into an iterative linear regression. This estimation algorithm can be described as follows:

- The first phase of the algorithm can be explained as:
- The second phase of the algorithm can be described as:

The algorithm iterates between two phases until the parameters' values converge.

HSV-1 experimental data fitting using alternative regression

Both the AR method and the smoothing algorithm were applied to the experimental data set of HSV-1 infection with innate immune response. The data was divided into training and testing data sets as shown in Tables 1 and 2. The training and testing data sets were based on the measurements of viral load, monocytes, and neutrophils during the pre-clinical and clinical phases. In order to fill the gaps between the day (10) and day (13) data time points and between the day (13) and day (15) data time points during the clinical phase, we used an interpolation for the measurements of monocytes and neutrophils, and we assumed that the measurements of the viral load were below the limit of detection. The predicted performance of the developed model that showed the interaction between the HSV-1 virus and innate immune system response is shown in Fig. 3. Furthermore, the estimated parameters of the HSV-1 model are presented in Tables 3, 4, and 5. Equation (1) can be written with model parameter values and initial conditions as:

$$\begin{aligned}\dot{x}_1 &= 76.2132x_1 - 75.4034x_1^{0.9987}x_2^{-0.0018}x_3^{0.0138}; \quad x_1(0) = 3.3 \\ \dot{x}_2 &= 15.4098x_1^{0.0002}x_2^{1.98} - 15.0001x_2^2; \quad x_2(0) = 2 \\ \dot{x}_3 &= 15.1809x_1^{-0.0007}x_3^{1.9919} - 15.000x_3^2; \quad x_3(0) = 2\end{aligned}\quad (9)$$

From these equations, we noticed that the kinetic order of the production rate with respect to viral load for the second state and the third state is fairly small. Therefore, Eq. (9) can be approximated as:

Table 1 Training set for viral load, monocytes, and neutrophils

Viral load (log10)	Monocytes (log10)	Neutrophils (log10)
5.77	2.48	2.56
5.57	3.4	3.41
5.16	3.91	3.28
4.9	3.77	3.72
4.16	3.84	3.32
3.92	3.7	3.26
0.48	3.89	4.51
0.48	3.85	4.65
0.48	3.8	4.76

Table 2 Testing set for viral load, monocytes, and neutrophils

Viral load (log10)	Monocytes (log10)	Neutrophils (log10)
0.48	3.79	4.84
0.48	3.78	4.91

Fig. 3 Estimation performance for nonlinear HSV-1 proposed model with $x_1(0) = 3.3, x_2(0) = 2, x_3(0) = 2$

Table 3 Estimated parameters for the viral load

Parameters	Estimated value
α_1	76.2132
β_1	75.4034
g_{11}	1.0000
h_{11}	0.9987
h_{12}	-0.0018
h_{13}	0.0138

Table 4 Estimated parameters for the monocytes

Parameters	Estimated value
α_2	15.4098
β_2	15.0001
g_{21}	0.0002
g_{22}	1.9800
h_{22}	2.0000

Table 5 Estimated parameters for the neutrophils

Parameters	Estimated value
α_3	15.1809
β_2	15.000
g_{31}	-0.0007
g_{33}	1.9919
h_{33}	2.0000

$$\begin{aligned}\dot{x}_1 &= 76.2132x_1 - 75.4034x_1^{0.9987}x_2^{-0.0018}x_3^{0.0138}, \quad x_1(0) = 3.3 \\ \dot{x}_2 &= 0.4097x_2^2; \quad x_2(0) = 2 \\ \dot{x}_3 &= 0.1809x_3^2; \quad x_3(0) = 2\end{aligned}\quad (10)$$

Fig. 4 Sensitivity effect ($\alpha_1^+ = 76.2894$) on nonlinear HSV-1 proposed model with $x_1(0) = 3.3, x_2(0) = 2, x_3(0) = 2$

Fig. 5 Sensitivity effect ($\beta_1^+ = 75.4788$) on nonlinear HSV-1 proposed model with $x_1(0) = 3.3, x_2(0) = 2, x_3(0) = 2$

Sensitivity test and performance measure of the HSV-1 dynamic model

In this paper, the dynamic behavior of the model is evaluated by testing the sensitivity and the performance of the model. The sensitivity evaluation was done by changing each parameter individually. It was found that some parameters had larger effects on the dynamics of the system than others did. The simulations in Figs. 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14 and 15 show the sensitivity of the predicated system to the variations in several parameters. For the performance measure, the Root Mean Square error (RMSError) was calculated for each state and is illustrated in Tables 6, 7, and 8. For the sensitivity analysis, we examined the sensitivity of the proposed model to specific parameters including: the production rate of viral load (α_1), the death rate of viral load (β_1), the production rate of monocytes (α_2), the death rate of monocytes (β_2), the production rate of neutrophils (α_3), and the death rate of neutrophils (β_3). This is because early sensitivity tests showed that α_2 and β_2 were important to reveal the role of innate immune responses in controlling the virus dynamics (Figs. 6, 7, 12, 13). An increased value of the death rate of monocytes called (β_2^+) can yield a quick decline of viral load during the pre-clinical phase. However, this will decrease the number of monocytes cells during the clinical phase (Fig. 7). For a decreased value of the production rate of monocytes called (α_2^-), a behavior which is similar to β_2^+ appeared (Fig. 12). Moreover, increased values of the

Fig. 6 Sensitivity effect ($\alpha_2^+ = 15.4252$) on nonlinear HSV-1 proposed model with $x_1(0) = 3.3, x_2(0) = 2, x_3(0) = 2$

Fig. 7 Sensitivity effect ($\beta_2^+ = 15.0151$) on nonlinear HSV-1 proposed model with $x_1(0) = 3.3, x_2(0) = 2, x_3(0) = 2$

death rate of viral load and the production rate of neutrophils called β_1^+ and α_3^+ can cause fast decline of viral load between the phases. However, this will increase the number of neutrophils cells during the clinical phase (Figs. 5, 8). Decreased values of the death rate of viral load and the

Fig. 9 Sensitivity effect ($\beta_3^+ = 15.015$) on nonlinear HSV-1 proposed model with $x_1(0) = 3.3, x_2(0) = 2, x_3(0) = 2$

production rate of neutrophils called β_1^- and α_3^- can have a significant impact on HSV-1 dynamics (Figs. 11, 14). In the same way that increased values of β_1^+ and α_3^+ cause a decline of viral load, decreased values of the production rate of viral load and the death rate of neutrophils called

Fig. 8 Sensitivity effect ($\alpha_3^+ = 15.1962$) on nonlinear HSV-1 proposed model with $x_1(0) = 3.3, x_2(0) = 2, x_3(0) = 2$

Fig. 10 Sensitivity effect ($\alpha_1^- = 76.1370$) on nonlinear HSV-1 proposed model with $x_1(0) = 3.3, x_2(0) = 2, x_3(0) = 2$

α_1^- and β_3^- can also be significant in reducing the viral load (Figs. 10, 15). Increased values of the production rate of viral load and the death rate of neutrophils called α_1^+ and β_3^+ can also cause similar response as β_1^- and α_3^- (Figs. 4, 9).

Fig. 11 Sensitivity effect ($\beta_1^- = 75.328$) on nonlinear HSV-1 proposed model with $x_1(0) = 3.3, x_2(0) = 2, x_3(0) = 2$

Fig. 12 Sensitivity effect ($\alpha_2^- = 15.3944$) on nonlinear HSV-1 proposed model with $x_1(0) = 3.3, x_2(0) = 2, x_3(0) = 2$

Discussion

In this study, a comparison of the model's prediction with the experimental data was investigated through examination of the relative roles of monocytes and neutrophils (innate immune response) in controlling the viral load

Fig. 13 Sensitivity effect ($\beta_2^- = 14.9851$) on nonlinear HSV-1 proposed model with $x_1(0) = 3.3, x_2(0) = 2, x_3(0) = 2$

Fig. 14 Sensitivity effect ($\alpha_3^- = 15.1657$) on nonlinear HSV-1 proposed model with $x_1(0) = 3.3, x_2(0) = 2, x_3(0) = 2$

Fig. 15 Sensitivity effect ($\beta_3^- = 14.985$) on nonlinear HSV-1 proposed model with $x_1(0) = 3.3, x_2(0) = 2, x_3(0) = 2$

Table 6 The performance measure for viral load (x_1)

Time measurement (m)	Experimental value (x_1)	Estimated value ($\hat{x}_1$)	$(x_1 - \hat{x}_1)^2$
Day (1)	5.77	4.25	2.31
Day (2)	5.57	4.98	0.35
Day (3)	5.16	5.32	0.03
Day (4)	4.9	5.22	0.10
Day (5)	4.16	4.75	0.35
Day (6)	3.92	4.04	0.01
Day (10)	0.48	1.12	0.41
Day (11.5)	0.48	0.51	0.0009
Day (13)	0.48	0.18	0.09
Day (14)	0.48	0.08	0.16
Day (15)	0.48	0.03	0.20

$$RMSError = \sqrt{\frac{\sum_{i=1}^m ((x_1)_i - (\hat{x}_1)_i)^2}{m}} = 0.6038$$

(HSV-1). Our results showed that the proposed model, which was based on parameters that were estimated using the alternative regression method, consistently fit the experimental data set. Moreover, preprocessing of experimental data, sensitivity analysis, and performance measure were conducted. The preprocessing stages for the experimental time series data were applied to compensate for noisy measurements, to provide a robust and adaptive solution for signal extraction, and to reduce the time-consuming nature of the numerical integrations. The AR that

Table 7 The performance measure for monocytes (x_2)

Time measurement (m)	Experimental value (x_2)	Estimated value ($\hat{x}_2$)	$(x_2 - \hat{x}_2)^2$
Day (1)	2.48	2.82	0.12
Day (2)	3.40	3.45	0.0025
Day (3)	3.91	3.75	0.03
Day (4)	3.77	3.86	0.0081
Day (5)	3.84	3.89	0.0025
Day (6)	3.70	3.90	0.04
Day (10)	3.89	3.86	0.0009
Day (11.5)	3.85	3.84	0.0001
Day (13)	3.80	3.80	0
Day (14)	3.79	3.78	0.0001
Day (15)	3.78	3.74	0.0016

$$RMSError = \sqrt{\frac{\sum_{i=1}^m ((x_2)_i - (\hat{x}_2)_i)^2}{m}} = 0.1368$$

Table 8 The performance measure for neutrophils (x_3)

Time measurement (m)	Experimental value (x_3)	Estimated value ($\hat{x}_3$)	$(x_3 - \hat{x}_3)^2$
Day (1)	2.56	2.34	0.05
Day (2)	3.41	2.66	0.56
Day (3)	3.28	2.95	0.11
Day (4)	3.72	3.20	0.27
Day (5)	3.32	3.39	0.0049
Day (6)	3.26	3.55	0.08
Day (10)	4.51	4.05	0.21
Day (11.5)	4.65	4.29	0.13
Day (13)	4.76	4.62	0.02
Day (14)	4.84	4.91	0.0049
Day (15)	4.91	5.28	0.14

$$RMSError = \sqrt{\frac{\sum_{i=1}^m ((x_3)_i - (\hat{x}_3)_i)^2}{m}} = 0.3790$$

was used to estimate the parameters of the model is fast and effective; however, it was difficult to find suitable initial guesses and initial conditions to make the parameters converge. The sensitivity of the proposed model was also considered. The simulations showed that the variation in some parameters had a significant impact on the HSV-1 dynamic model and that the variation of other parameters can be important to show the role of innate immune responses in controlling the virus dynamics. This sensitivity analysis should be accounted for in future biological designs. Furthermore, the RMSerrors for viral load, monocytes, and neutrophils are evaluated as: 0.6038, 0.1368, and 0.3790, respectively; this evaluation indicates that the fit between the model and the experimental data is significant and can have future biological implications.

Conclusion and future work

In this paper, the nonlinear HSV-1 dynamic model was proposed, and its parameters were successfully estimated using the AR method. The experimental data set of monocytes, neutrophils, and viral load measurements were introduced and investigated. The pre-processing stages, such as the rate of change approximation and smoothing algorithm, were applied to compensate for noisy measurements and the time consuming nature of the numerical integrations. This data set was divided into training and testing data sets. The HSV-1 proposed model was developed based on the available information, biological interactions between states, and data measurements that were taken from the mice. The experimental data set of HSV-1 was divided into three phases. The first phase consisted of day (0), where no infection was present in the corneas of mice, the second phase was from day (1) until day (6); and the third phase was assigned for day (10), day (13), and day (15). The proposed nonlinear model is dynamic and has three states that represent the viral load, monocyte concentration, and neutrophil concentration. The HSV-1 proposed model successfully fit the experimental data set. For validation of the model, the root mean square performance measure was evaluated for each state variable. In addition, discussion on the sensitivity of estimated parameters was considered to show the significance of some parameters over others. The results show that this proposed model can be used to present important biological factors that explain the HSV-1 dynamics with innate immune responses, to suggest different biological experiment designs, and even to promote drug treatment decisions for HSV-1 infection disease. In future research, stochastic estimation methods can be used to predict the dynamics of the interaction between HSV-1 and innate immune responses based on the available data measurements. Also, experimental data that involve natural killer cells should be considered on the model to investigate different characteristics of the HSV-1 disease.

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