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Chaos synchronization and Nelder-Mead search for parameter estimation in nonlinear pharmacological systems: estimating tumor antigenicity in a model of immunotherapy

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Abstract

In mathematical pharmacology, models are constructed to confer a robust method for optimizing treatment. The predictive capability of pharmacological models depends heavily on the ability to track the system and to accurately determine parameters with reference to the sensitivity in projected outcomes. To closely track chaotic systems, one may choose to apply chaos synchronization. An advantageous byproduct of this methodology is the ability to quantify model parameters. In this paper, we illustrate the use of chaos synchronization combined with Nelder-Mead search to estimate parameters of the well-known Kirschner-Panetta model of IL-2 immunotherapy from noisy data. Chaos synchronization with Nelder-Mead search is shown to

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Declarations of Interest

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provide more accurate and reliable estimates than Nelder-Mead search based on an extended least squares (ELS) objective function. Our results underline the strength of this approach to parameter estimation and provide a broader framework of parameter identification for nonlinear models in pharmacology.

Keywords

Chaos synchronization; Parameter estimation; Nonlinear models; Parameter identifiability; Immunotherapy

1. Introduction

The past quarter century in anti-cancer treatment has seen remarkable transitions in both our ability to mitigate cancers through traditional chemotherapy and in the development of new treatment modalities, primarily dominated by targeted treatments and immunotherapeutics [1, 2]. These latter approaches, broadly focused on stimulating or modulating innate and adaptive immunity to induce greater anti-tumor effects [1], have garnered a great deal of interest and have demonstrated significantly improved patient progression-free survival [3]. Immunotherapies may be generally combined with traditional (cytotoxic) chemotherapies [1] and there is an ongoing need for rational treatment design. Given the complex nature of the immune system, tumor growth and metastasis, and their manipulation and control via xenobiotics, therapeutic optimization supported by mathematical modeling of the interplay between tumors and the immune system should be employed to better understand these interactions and to guide the delivery of therapeutics.

There is a great deal of interest within the biomathematical community in addressing immunotherapy via semi-mechanistic and mechanistic models of immunotherapy [4-8]. Recent reports also endeavor to predict robust therapy designs through the combination of immunotherapy models and statistical approaches [9]. One of the best-known models is the Kirschner-Panetta (KP) model [10], developed to address interleukin-2 (IL-2) immunotherapy (deemed the first effective immunotherapy for human cancer" [11]). In [10], non-dimensionalization, and stability and bifurcation analyses were undertaken to understand the dynamics of these three interacting populations. The trivial steady-state was shown to always be unstable; the parameter denoting tumor antigenicity was explored to determine the stability of the other positive steady-states.

The primary purpose of disease models and their interaction with pharmacological models is to achieve therapeutic optimization. Modeling efficacy depends upon the ability to accurately identify and quantify model parameters. However, achieving effective therapy for cancer is complicated by a fundamentally evolutionary process. Within the genetically heterogeneous tumor, response to therapeutic intervention is characterized by the simultaneous decline of treatment sensitive cancer cells and the growth of resistant ones. If treatment-sensitive cells are responsible for suppressing the growth of resistant cells, then treatment is, in effect, selecting resistant cells for survival.

Accordingly, tumor heterogeneity presents a daunting problem of efficiency and efficacy in experimental design. Based on experience with evolutionary dynamics in fields other than cancer, there is a strong suggestion that mathematical modeling can hold the key for effective hypothesis generation and testing, with much of that interest related to the immune system response to an antigenic tumor cell and to efforts enhancing that response. In the course of these studies, currently and over the past two decades, significant attention has been paid to nonlinear dynamical chaotic systems, employing variations in logistic equations familiar to population models (e.g. Kuznetsov et al. (1994) [12], Galindo et al. (2015) [13]).

Our ultimate goal is therefore to develop modeling approaches consistent with the complex evolutionary dynamics of cancer and cancer therapy. This approach is applicable to all forms of cancer therapy – cytotoxic, target, immune, and radiation. In this work, we address parameter estimation for the KP model. While the KP model is significantly distant from the parameterization necessary for optimization of therapy, the goal of this study is to introduce a more general discussion of global parameter estimation techniques and their use for quantitative systems pharmacology models in general. We will show that the parameters of KP model are locally identifiable, which is in accordance with the multiple solutions exhibited in [10]. Although chaos synchronization is primarily established to closely track chaotic systems, an ancillary outcome of the approach is the ability to perform global parameter estimation. In this vein, we will next demonstrate the superior performance of chaos synchronization combined with Nelder-Mead search over the widely used extended least squares method when estimating parameters in this nonlinear dynamic model.

2. Modeling tumor-immune system interactions: The Kirschner-Panetta model

The KP model describes the dynamics of tumor-immune system interactions by accounting for activated immune cells called effector cells (E), tumor cells (T), and IL-2 (I_L) as follows

$$\frac{dE}{dt} = cT - \mu_2 E + \frac{p_1 E I_L}{g_1 + I_L} + s_1 \quad (1)$$

$$\frac{dT}{dt} = r_2(1 - bT)T - \frac{aET}{g_2 + T} \quad (2)$$

$$\frac{dI_L}{dt} = \frac{p_2 ET}{g_3 + T} - \mu_3 I_L + s_2, \quad (3)$$

with initial conditions $E(0) = E_0$, $T(0) = T_0$, and $I_L(0) = I_{L0}$. Here c denotes the antigenicity of the tumor, the term $\frac{p_1 E I_L}{g_1 + I_L}$ models the stimulation of effector cells by IL-2, s_1 represents

the external source of effector cells (treatment term), $r_2(1 - bT)T$ represents the (logistic) growth of tumor cells (which can be modified to be exponential or Gompertzian growth), a denotes the loss of tumor cells by interactions with the immune system (a saturable effect hence the Michaelis-Menten term $\frac{aET}{g_2 + T}$), $\frac{p_2 ET}{g_3 + T}$ models the stimulation of IL-2 by the effector cells, μ_3 denotes the IL-2 degradation rate, and finally s_2 denotes an additional treatment term for the external input of IL-2 [10]. As in [10], we explore the steady states without treatment terms thus, in what follows, we set $s_1 = s_2 = 0$.

In [10], parameter values for Eqs. (1) and (2) were primarily obtained from [12] and [14], though it is stated that when large ranges in estimates existed, "...we chose values most appropriate for this model," [10] without explanation as to how "appropriate" was defined. We will demonstrate below a more systematic approach to the estimation of certain parameter values in this model. The parameter values used by Kirschner and Panetta [10] are presented in Table 1.

3. Systematic methods for estimating model parameters

3.1. Model identifiability

We started by analyzing the structural identifiability of the KP model using the GenSSI software [15]. This MATLAB [16] tool assesses structural identifiability for parameters of a nonlinear system generated by successively computing the Lie derivatives of the functions f and g in the direction of the output h defined by the model system given by

$$\dot{x}(t) = f(x(t), p) + g(x(t), p)u(t) \quad (4)$$

$$y(t, p) = h(x(t), p), \quad (5)$$

subject to the initial conditions $x(t_0) = x_0(p)$. Here p represents a vector of system parameters, $x(t) \in \mathbb{R}^n$ denotes a vector of state variables, $u(t) \in \mathbb{R}^m$ denotes a vector of input (control) variables, and $y(t, p) \in \mathbb{R}^r$ denotes a vector of output variables [15]. We observed that all parameters of KP model are structurally locally identifiable. This is reasonable in view of the multiple solutions discussed in the bifurcation analysis [10].

We believe that there is rationale for obtaining the other parameters from the literature, *in vitro* studies using donor peripheral blood mononuclear cells (PBMCs), or xenograft studies in humanized mice sampled via microdialysis or imaging. Accordingly, based on the possibility of such these studies and the results of the structural identifiability analysis with GenSSI, we proceeded by estimating the parameters r_2 , b , and c with all other parameters held fixed in the system given by Eqs. (1)-(3).

3.2. Chaos synchronization

Chaotic systems are dynamical systems that are exponentially sensitive to initial conditions. As a result, two identical chaotic systems starting with nearly the same initial conditions can have exponential separation of trajectories with time [17]. According to [17], “synchronization of chaos refers to a process wherein two (or many) chaotic systems (either equivalent or nonequivalent) adjust a given property of their motion to a common behavior due to a coupling or to a forcing (periodical or noisy)”.

In this example, we implemented a unidirectional coupling scheme using an adaptive chaos synchronization method [18]. The driver system has exactly the same form as the model system given in Eqs. (1)-(3). It is assumed that the system’s experimental output is available as time series for all variables (i.e. there are experimental measurements for tumor cells, effector cells, and IL-2 values at different time points). From our initial analyses, we found we were able to uniquely estimate r_2 and b using an approach to adaptive chaos synchronization developed by Huang [18]. Through bifurcation analysis, Kirschner and Panetta [10] found that the value of the antigenicity parameter c is critical for controlling the ultimate behavior of the system in Eqs (1)-(3) by demonstrating that different values of c result in significantly different response patterns. Moreover, c enters the system in a linear fashion. Thus, chaos synchronization according to [18] was applied solely to estimate the antigenicity parameter c .

To estimate the unknown parameters that enter the system model in a linear fashion, we defined a receiver system whose governing equations are identical to the driver system, although corresponding parameter values are not necessarily the same. The evolution of the receiver system is guided by the driver trajectory by means of the driving signal. These parameters are initialized to arbitrary initial values and their values are updated iteratively until complete synchronization is obtained [18]. A linear adaptive feedback, given by the following equations, is used to control the receiver system

$$\frac{dE}{dt} = cT - \mu_2 E + \frac{p_1 E I_L}{g_1 + I_L} + \epsilon_E(t)(E(t) - E_o(t)) \quad (6)$$

$$\frac{dT}{dt} = r_2(1 - bT)T - \frac{aET}{g_2 + T} + \epsilon_T(t)(T(t) - T_o(t)) \quad (7)$$

$$\frac{dI_L}{dt} = \frac{p_2 ET}{g_3 + T} - \mu_3 I_L + \epsilon_{I_L}(t)(I_L(t) - I_{L_0}(t)), \quad (8)$$

where the difference between the observed and predicted output ($E(t)$, $T(t)$, $I_L(t)$) is defined as the synchronization error denoted by e_i and ϵ_j denotes the feedback strength.

The feedback strength ε_j is adapted according to the following nonlinear update law:

$$\frac{d\varepsilon_E(t)}{dt} = -\Gamma \left(\varepsilon_{E_i} \right)^2 \quad (9)$$

$$\frac{d\varepsilon_T(t)}{dt} = -\Gamma \left(\varepsilon_{T_i} \right)^2 \quad (10)$$

$$\frac{d\varepsilon_{I_L}(t)}{dt} = -\Gamma \left(\varepsilon_{I_{L_i}} \right)^2. \quad (11)$$

Here, Γ is a tuning parameter that affects the rate of convergence. Like the delta-rules encountered in machine learning, the parameters are adapted as follows:

$$\frac{dc(t)}{dt} = -\delta \varepsilon_{E_i} dF, \quad (12)$$

where $dF = y$, the vector of output values (Eq. 5), and δ denotes a tuning parameter that determines the rate of convergence. Note that though the tumor antigenicity parameter c is constant in Eq. (6), its values fluctuates during the optimization within the chaos synchronization scheme, hence the additional dependency on time in Eq. (12). In what follows, the values of Γ and δ were fixed to be 100 and 0.01, respectively. Theoretically, the receiver system should track the driver system accurately for any value of Γ and γ , however the rate of convergence of parameters, especially for noisy data, is a central issue in chaos synchronization. For densely sampled noiseless data, if all other parameter values are known, the method from [18] guarantees convergence for all values of c , irrespective of how far from nominal they are. However, it is difficult to relate the basin of attraction to the qualitative behavior of the system given that the basin of attraction is uncertain since the data are noisy, denoised via truncation of a wavelet series, sparsely sampled, interpolated (via piecewise cubic Hermite interpolating polynomials-*pchip*-or another interpolation algorithm), and/or discretized via the solver's mesh. Therefore, the values of Γ and δ were chosen such that even for noisy systems, the parameters converge to their nominal value within 1000 days.

Equations (6)-(12) were solved in MATLAB (version 2017a) using the *ode23* solver with an initial value of $\varepsilon=0.1$. From our initial analysis, we observed that the adaptive chaos synchronization method [18] accurately identified the linear parameters in the KP model. Nelder-Mead search was used in combination with chaos synchronization to further estimate the parameters that enter the model in a nonlinear fashion, namely r_2 and b .

3.3. Nelder-Mead search

An initial analysis indicated that coarse-to-fine grid search did not perform adequately estimate nonlinear parameters for the KP model (results not shown) hence we used the more robust Nelder-Mead search method via the *fminsearch* function in MATLAB. The *fminsearch* function finds the minimum of an unconstrained multivariable function using a derivative-free method [19]. The Nelder-Mead method is almost invariably applied to nonlinear optimization problems for which the derivatives may be unknown [19]. The inputs to *fminsearch* were the initial values of the parameter to be estimated and a function f_{NM} that solves the differential equation of interest and minimizes the objective function (the root mean square error (RMSE) between the predicted and observed state variables). Within f_{NM} , we invoke the adaptive chaos synchronization function that predict the value of the antigenicity parameter c and predicts the volume of tumor cells, effector cells, and the concentration of IL-2. The *fminsearch* function then predicts the values of the growth rate r_2 and b , the inverse of carrying capacity, as part of the overall scheme to minimize the RMSE between the observed and the predicted outputs. The workflow is illustrated by Figure 1.

We compared the results obtained from adaptive chaos synchronization with Nelder-Mead search to the results from a well established method [20] that uses extended least squares (ELS) objective value function with Nelder-Mead search. The objective value function for ELS is given by:

$$obj_{ELS}(\theta, \sigma) = \sum_{n=1}^n \left[\frac{(C_i - M(\theta, t_i))^2}{V(\theta, \sigma, t_i)} + \ln V(\theta, \sigma, t_i) \right],$$

where $V(\theta, \sigma, t_i)$ is a variance model (taken here to be a proportional model of residual unexplained variance), C_i represent the observed data, $M(\theta, t_i)$ represent the predicted data, θ denotes the vector of parameters of the model, and σ denotes the standard deviation [20]. An overview of the various estimation techniques explored in this work is summarized in Figure 2. Note that for noiseless data, the ELS method coincides with ordinary least squares and that to use the ELS method on noiseless data is a misspecification of the model as stochastic rather than deterministic. It should be noted that in the presence of noise, ELS performs better than RMSE due to the weighting scheme implemented in ELS. This is important for nonlinear dynamic systems since they have been shown to have multiple minima.

3.4. Processing noisy data

To evaluate a noisy system, simulated noisy data were generated from a normal distribution with mean equal to the mean values of the experimental state variables obtained by solving Eqs. (1)-(3), and standard deviation equal to 20% of the experimental system state variables using the *randn* function in MATLAB. To process and extract information from this data, we first reduced the noise using a noise filter, knowing that the CS method according to Huang [18] is robust to a modest level (typically a few percent) of noise. The densely sampled noisy data were denoised by the MATLAB function *wden* using a symmlet basis expanded to level 4 and MINIMAXI thresholding rule. This function performs an automatic denoising process

of a one-dimensional signal using wavelets and input options can be changed depending on the noise level. This filtering approach preserves geometric information at multiple scales [21-23].

4. Results

The KP model was first analyzed by an ELS objective function with parameters estimated according to Nelder-Mead search because gradient-based methods are often trapped in local minima. When the estimated parameters are very close to their nominal values, this method performed well for both parameter estimation and system tracking, as shown in Figure 3. We next analyzed the case where the initial estimate of the critical controlling parameter c was changed to 0.06 from its previous value of 0.05, with the initial estimates of all other parameters fixed at their previous values (see Table 2). We observed that for this set of initial estimates the ELS method with Nelder-Mead search did not provide reliable results as the parameter estimates were far from actual values and the predicted profile was not accurate. These discrepancies are illustrated by Figure 4.

In a second analysis, the KP model was analyzed using CS and Nelder-Mead search for the same set of initial estimates ($r_2 = 0.2$, $b = 2e - 9$, $c = 0.06$). We found that the combination of CS and Nelder-Mead search was able to properly track the system (see Figure 5, where the left panel displays noiseless data and the right panel displays noisy data that has been de-noised via wavelet filtering) and that the parameters estimated using this method had considerably lower percentage errors when compared to the estimates using ELS and Nelder-Mead search, as listed in Table 3. In both Figures 4 and 5, despite the presence of noise, the CS method is capable of closely tracking the data. This agrees with the notion that noise can improve the synchronization of coupled systems by improving the coupling strength due to the phenomenon of stochastic resonance [24].

To assess the impact of sampling density on parameter estimates, we next analyzed the model with sparser samples over a range of time intervals. To improve the accuracy of estimates, we used *pchip*, a well-known method for approximating monotone intervals in data using piecewise cubic Hermite polynomials that are only locally sensitive to changes in data [25]. For each of the time intervals (two cases of sampling every 100 days for 1000 days total and two cases of samples taken every 30 days over a period of 360 days), the data were interpolated at one-day intervals; the resulting interpolations are shown in Figure 6. As reflected in Table 4, in both the noiseless and noisy cases sparse sampling cases, CS performed more accurately than ELS on densely sampled data (see Table 2).

Finally, we explored how perturbations to initial values affect final parameter estimates on a sparsely sampled case (13 samples total-samples taken every 30 days for 360 days). We observed no effect from perturbations to initial values on the estimated value of c (estimated via CS), whereas there were moderate impacts to the final estimates of r_2 and b provided by Nelder-Mead search (Table 5).

5. Discussion

The KP model (Eqs. (1)-(3)) describing tumor immune modulation by IL-2 provides a useful test case in the assessment of optimization methods for systems exhibiting nonlinear dynamics. In this paper, we demonstrated that extended least squares (a first order approximation to the maximum likelihood method for models with normally-distributed errors) is very poorly suited for both tracking the evolving nonlinear dynamical system and estimating its parameters, particularly when initial parameter values were not extremely close to the nominal values. Fixing all other parameters, even a small deviation of c (tumor antigenicity) from its true value of 0.05 to 0.06 was sufficient to illustrate the point. This is by contrast with the implementation of CS in conjunction with Nelder-Mead search and RMSE as the objective function, which was able to track the evolving system and estimate its parameters accurately. Using CS, we estimated c with an adaptive feedback control, making the system asymptotically stable with time, that is that the driver and receiver outputs eventually completely overlap each other as time increases. Thus, unlike the previous ELS method, we did not encounter instability.

In our analyses, we observed that the adaptive chaos synchronization method properly tracks the system and that the parameter estimates have reduced percentage error when compared to parameters estimated using ELS (compare the results in Table 3 and Figure 4 to the ELS predictions in Table 2) for both noiseless and noisy data. Additionally, Nelder-Mead with CS on sparsely sampled data (Table 4) outperforms ELS applied to dense data and is only moderately impacted by perturbations to initial values (Table 5). In summary, for all of the cases we analyzed, the adaptive chaos synchronization method converged close to the global minimum while the ELS method failed to do so. CS with Nelder-Mead search is therefore more robust to the effects of noise and small perturbations of initial estimates by comparison with ELS for our example and can also work well for the cases when the data are sparsely sampled.

It should be noted that the CS method was not initially established for parameter estimation. The approach was originally designed for tracking a noiseless system that evolves with time, irrespective of chaos or nonlinear dynamics. The asymptotic determination of linear parameters is a supplemental effect of the approach made possible by leveraging the invariance principle of ordinary differential equations to establish a system that has a driver and a receiver tracking the driver system exactly [18]. The CS system method outlined here assumes a deterministic system. It is not possible to define standard errors for parameter estimates from this CS approach because this CS method assumes that the denoised system is deterministic and does not provide any stochastic component. Thus, even though there may be oscillations in the estimated parameters about the steady-state solution of the ODEs associated with the CS system, this is not equivalent to uncertainty rather the nonlinear dynamics. While one can report a range or distribution reflecting possible parameter values at the solution, this is not strictly analogous to the parameter uncertainty that would be obtained using a Fisher information matrix approach or non-parametric bootstrap.

In conclusion, the use of CS is emphasized as a useful methodology using the KP model as an example, not to suggest that the KP system will provide new clinical insight or assist with

precision medicine, rather to highlight how the CS can solve systems, provide accurate parameter estimates, and successfully track the evolution of a nonlinear dynamical system. There are, however some significant limitations with the present implementation of this approach. This analysis illustrates using samples of tumor size, effector cell, and IL-2 concentrations at ten-day intervals to provide an accurate assessment of the system, although we analyzed the noiseless case where data were sampled at 60 day intervals for which CS with Nelder-Mead search was highly accurate with final parameter estimates of $r_2 = 0.2021$, $b = 2.18e - 9$, $c = 0.0335$. We understand that the above sampling time requirement is unlikely to be a reasonable interval in a clinical trial or in clinical practice.

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Figure 1:

Schematic tracing the general approach to chaos synchronization and Nelder-Mead search for parameter estimation. First, parameters that are in nonlinear combinations are initialized. These parameters are estimated using Nelder-Mead search with root mean square error (RMSE) chosen as objective function. These estimates are passed to the Nelder-Mead function, inside which linear parameters are initialized. Chaos synchronization is then performed on the whole parameter set to estimate linear parameters and to predict the outputs ($E(t)$, $T(t)$, $I_L(t)$). The time series of predictions is compared with the respective observations and the corresponding RMSE stored. The procedure is repeated until convergence of the Nelder-Mead search function to within a specified tolerance (default tolerance of $1e-4$). Final estimates correspond to the set of parameters with lowest RMSE.

Figure 2:
Decision tree for the estimation of nonlinear parameters in the Kirschner-Panetta model [10].

Figure 3:

ELS provides accurate fits when initial estimates are close to actual values. Noiseless data are sampled at ten-day intervals. We obtained fits for initial values of $r_2 = 0.2$, $b = 2e - 9$, $c = 0.05$.

Figure 4:

The ELS method does not provide sufficient accuracy when the initial parameter estimates are not extremely close to their nominal values. We obtained fits using ELS for initial estimates that were tweaked from those used in Figure 3, namely $r_2 = 0.2$, $b = 2e - 9$, $c = 0.06$. a) Data are sampled every ten days and are noiseless. b) Data are sampled every ten days and with 20% proportional error. It should be noted that filtering of noisy data can produce slightly negative parameter values in the initial phase. These initial fluctuations do not impact on the final estimates as parameter estimation was performed solely on the trailing phase. Thus, we opted to keep the biologically implausible values in the initial phase over artificially forcing any negative value to zero.

Figure 5:

CS with Nelder-Mead search is more reliable and accurate than ELS with Nelder-Mead search, for our example. We fitted parameters by chaos synchronization for the same set of initial estimates used to generate Figure 3 ($r_2 = 0.2$, $b = 2e - 9$, $c = 0.06$). a) Noiseless data are sampled at ten day intervals. b) Noisy data (20% proportional noise) are sampled at ten day intervals. As in Figure 4, negative values in the initial phase resulting from the filtering of noisy data were retained as they do not impact on final parameter estimates.

Figure 6:

Sparse data are accurately recapitulated via *pchip* interpolation. For two sparse datasets- sampling every 30 days for 360 days total and sampling every 100 days for 1000 days total- we applied *pchip* to densify the time courses before performing ELS and CS to obtain parameter estimates.

Table 1:

Parameter values for the KP model as defined in [10]. Unless stated, all parameter values in the present study are per original KP study. Conc=concentration.

Parameter	Definition	Value	Units
c	Tumor antigenicity	0 - 0.05	days ⁻¹
μ_2	Effector cell half-life	0.03	days ⁻¹
p_1	Maximal stimulation of effector cells by IL-2	0.1245	days ⁻¹
g_1	Half-effect conc. effector cell stimulation by IL-2	2×10^7	volume
g_2	Half-effect conc. tumor cell loss via immune interactions	1×10^5	volume
r_2	Maximal tumor cell growth	0.18	days ⁻¹
b	Inverse carrying capacity of tumor cells	1×10^{-9}	volume ⁻¹
a	Rate of tumor cell loss by immune interactions	1	days ⁻¹
μ_3	IL-2 degradation rate	10	days ⁻¹
p_2	Maximal stimulation of IL-2 by effector cells	5	days ⁻¹
g_3	Half-effect conc. IL-2 stimulation by effector cells	1×10^3	volume

Table 2:

Final parameters estimates for noiseless or noisy data obtained by extended least squares (ELS) or chaos synchronization (CS). The nominal value represents the value of the parameter used to generate the data; the initial estimate represents the initial value provided to the Nelder-Mead and CS functions. Data were sampled at ten-day intervals in both cases. The parameter c , in the case of the chaos synchronization method, was estimated according to the median value of the time series of parameter c over the time range of 500 to 1000 days; this range was chosen to avoid transients.

			<i>Noiseless</i>		<i>Noisy</i>	
Parameter	Initial Estimate	Nominal Value	ELS	CS	ELS	CS
r_2	0.2	0.18	1.18	0.2053	0.627	0.1823
b	2e-9	1e-9	7.4e-9	1.87e-9	0	2.04e-9
c	0.06	0.035	42.5	0.0326	6.1	0.0355

Table 3:

CS with Nelder-Mead search reduces the bias according to percentage errors in the parameter estimation. Percentage errors for the final parameter estimates are provided in Table 2.

	<i>Noiseless</i>	<i>Noisy</i>
Parameter	Bias (%)	Bias (%)
r_2	14.05	1.27
b	87	104
c	6.85	1.42

Table 4:

Analyzing sparse samples. Sparsely sampled noiseless and noisy data was densified using pchip (interpolated every day) and Nelder-Mead and CS were used to estimate parameter values. Nelder-Mead with CS outperforms ELS on densely sampled data (Table 2).

Sampling Interval (Days)	Total Time (Days)	Samples (Number)	Proportional Error (%)	r_2	b	c
100	1000	11	0	0.209	2.25E-09	0.0252
30	360	13	0	0.192	2.09E-09	0.0329
100	1000	11	20	0.203	2.08E-09	0.0252
30	360	13	20	0.1422	2.57E-09	0.035

Table 5:

Effect of perturbations on the initial parameters values. Initial estimates for all three parameters were varied by 50%, 100%, and 200% before Nelder-Mead and CS were applied. No effect was observed on the final estimate for the tumor antigenicity parameter c estimated using CS. Values of r_2 and b provided by Nelder-Mead search fluctuated slightly as the perturbation to the initial estimate was increased.

Perturbation to Initial Value	r_2	b	c
50%	0.1927	1.94E-09	0.329
100%	0.1929	2.83E-09	0.329
200%	0.1931	4.78E-09	0.329