Dynamic HIV/AIDS Parameter Estimation With Application to a Vaccine Readiness Study in Southern Africa

R. A. Filter*, X. Xia, *Senior Member, IEEE*, and C. M. Gray

***Abstract*—This paper proposes a procedure of parameter estimation for all parameters of the three-dimensional HIV model. The least square based procedure uses standard optimization routines to allow parameter extraction for individual patients. It is shown how additional information from outside a measurement dataset can be included in the estimation routine to increase the reliability and accuracy of parameter estimates. A dataset from 44 patients of Southern Africa is analyzed to find the set point and the time until set point for these patients together with an estimate of the model parameters with confidence intervals for the cohort. The procedure is also applied to a long-term dataset of the HIV/AIDS progression to find possible variations in parameters.**

***Index Terms*—Bioengineering and medical systems, HIV/AIDS physical parameters, parameter estimation, parameter variation, set point estimation.**

I. Introduction

A MODEL that describes the interaction of HIV with the patients immune system and the influence of drugs on the virus can be a helpful tool to decide on treatment strategies in HIV/AIDS patients. One such model is the three-dimensional (3-D) model described in [1] and [2]. Highly active antiretroviral therapy (HAART) in combination with mathematical modeling has helped to reshape the perception of the disease [3]–[5]. To use this model as a tool for treatment decisions, model parameters must be determined from measurements that are acquired on equipment that is accessible to local health services. Since all parameters of the 3-D model can be determined from CD4$^+$T cell levels and viral load in blood [6] (as opposed to higher dimensional models [7]), this model is a good starting point for practical applications.

The viral load in HIV patients may be a critical endpoint in vaccine trials by which to judge efficacy [8]. The 3-D model is used in this context to estimate the set point viral load. This paper presents a procedure that can be used to extract all six model parameters of the 3-D model on a per-patient basis. In situations where it is not possible to extract all six, the procedure can accommodate generalizations of some parameters. This flexibility is achieved by implementing an estimation routine that combines standard optimization methods with a customizable least square (LSQ) based cost function.

The results are presented in three parts. First the basis of the estimation procedure is described. Secondly the procedure is validated with generated data and published parameter estimates. After validation, the estimation of viral set point and parameters for a cohort of patients from a HIV/AIDS vaccine readiness trial is presented. This is followed by an application where the procedure is applied to long-term data to extract possible variations of parameters. Finally conclusions from the results and impetus for further research are presented.

Manuscript received November 22, 2003; revised October 10, 2004. This work was presented in part at the 13th IFAC conference on System Identification and Control, Rotterdam, The Netherlands, 2003. *Asterisk indicates corresponding author.*

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Digital Object Identifier 10.1109/TBME.2005.844274

II. Procedures

A 3-D model of HIV/AIDS, considered here, consists of three variables: the population sizes of uninfected cells (T), infected cells (T^*), and free virus particles (v). Free virus particles infect uninfected cells at a rate proportional to the product of their abundances, βvT. The rate constant, β, describes the efficacy of this process. Infected cells produce free virus particles at a rate proportional to their abundance, kT^*. Infected cells die at a rate δT^*, and free virus particles are removed from the system at a rate cv. By assuming a constant production rate, s and death rate dT for the uninfected cells, the 3-D model of virus dynamics is obtained [1], [2]

$$\begin{cases} \dot{T} = s - dT - \beta Tv, \\ \dot{T}^* = \beta Tv - \delta T^*, \dot{v} = kT^* - cv \end{cases}. \tag{1}$$

Furthermore, for the purpose of estimating model parameters, it is assumed that plasma viral load, v and CD4$^+$T cell count, T are measured, in accordance with the current prevailing medical practice [9].

In the following sections, $\chi = [s\ d\ \beta\ \delta\ c\ k]^T$ is the vector of model parameters, and $\hat{\chi} = [\hat{s}\ \hat{d}\ \hat{\beta}\ \hat{\delta}\ \hat{c}\ \hat{k}]^T$ the estimate of these parameters. The state vector $\vec{x}(t) = [T(t)\ T^*(t)\ v(t)]^T$, and the initial state vector $\vec{x}_0 = [T_0\ T_0^*\ v_0]^T$.

A. Cost Function Overview

As with the method considered in [10], this method is in essence least square (LSQ) based, but with two important differences. Firstly, derivative estimation is only present in the controlled environment of the numerical ordinary differential equation (ODE) solver. Secondly, the cost function is not limited

to the LSQ distance, but can be expanded with penalty terms to increase the accuracy of parameter estimation.

The Nelder-Mead Simplex search method is used as the optimization routine[1] and the steps in the cost function are as follows.

1) The function receives a list of data points for the CD4$^+$T cell and the virus count with their respective time points. Together with these, $\hat{\chi}$ is also passed to the function.
2) When constraints are specified for χ, they are enforced at this point. If constraints are not met, a simplified cost is returned.
3) The function uses $\hat{\chi}$ and solves the dynamic model of (1). This is done within the framework of a pre-existing numerical ODE solver.
4) The differences between each data point and its predicted value are squared and summed.
5) Any additional penalty terms are calculated and added to the total cost, which is returned to the optimizing function.

At each iteration of the search, the cost function is called by the optimization routine, until the pre-set tolerance is met. Since the numerical solution of the ODE can be time consuming, it is desirable to keep its evaluation to a minimum, thus a simplified cost is returned at Step 2), if any of the constraints are not met. Clearly this method is not prone to the derivative estimation error, as is the LSQ method considered in [10].

Apart from the problem of derivative estimation, a second drawback in the pure LSQ method is that the equations that are fitted to the data, contain product terms of CD4$^+$T cell and virus counts. This forces the data vectors to be of equal length for proper estimation. Since the cost function does not require any product terms, this constraint on the length of CD4$^+$T cell and virus data vectors can be dropped.

The basic cost for a nominal set of parameters, $\hat{\chi}$, and initial conditions, $\hat{\vec{x}}_0$, is computed by generating $\hat{T}$ and $\hat{v}$ with a numerical ODE solver. Together with N measurements of T and K measurements of v, at time $t_1, \ldots, t_N$, and $\tau_1, \ldots, \tau_K$ respectively, the basic cost function is defined as

$$J_w = \sum_{n=1}^{N} \frac{(\hat{T}(t_n) - T_n)^2}{N \operatorname{mean}(T_n)} + \sum_{k=1}^{K} \frac{(\hat{v}(\tau_k) - v_k)^2}{K \operatorname{mean}(v_k)}. \quad (2)$$

From [11], it is known that the viral load tests are log based. Also for the experiments performed in [2], the virus data is fitted to the least square of logarithmic distance. Thus, following the scheme in [12, p. 444], the basic cost is modified to incorporate logarithmic distance for the virus data points

$$J_l = \sum_{n=1}^{N} \frac{(\hat{T}(t_n) - T_n)^2}{\operatorname{mean}(T_n) N} + \sum_{k=1}^{K} \frac{(\log \hat{v}(\tau_k) - \log v_k)^2}{\operatorname{mean}(\log v_k) K}. \quad (3)$$

In both cases data vectors are weighted by their mean value and length. For group analysis it is useful to use the means of the cohort data to allow better comparison between patients. Standard procedures apply when adding individual weights to samples. If detailed information is available about the variances in data points, this information can be incorporated as in [12, pp. 448–449].

[1]Successful estimation is not dependent on the chosen search method but, due to abrupt changes in the cost landscape, it is desirable to start with a search method that does not rely on a smooth cost function. At the solution point of the initial search, one can switch to a different algorithm.

B. Penalty Terms and Additional Refinements

When a dataset does not contain enough information for parameter estimation on its own, it might yet be possible to extract key parameters when prevailing circumstances are known. In these situations the addition of custom penalty terms to the cost function is helpful, since the penalty terms allow outside knowledge of the dataset to be incorporated into the parameter estimation cycle. Refinements in the cost function are incorporated at steps 2) and 5) above. Common refinements for this paper are as follows.

- *Enforcing limits:* This is done at Step 2), before the intensive calculations in the cost function, by checking parameters against a predefined range and correcting any parameters that do not fall within the specifications.[2] A second option is to add parameter limits to the cost value at Step 5). This allows for weighted penalties where parameter limits are not well defined. The second option is not desirable for hard limits, since the computationally intensive ODE will be solved even when the parameters fall outside the prescribed limits.
- *Prior knowledge of parameters:* When a parameter is known from another source (e.g., experiment, assumption or literature), this knowledge is incorporated at Step 2). Here the optimization routine can be instructed not to search for fixed parameters.
- *Prevailing conditions:* When prevailing conditions (e.g., a patient is in steady state before initiation of therapy) for a dataset are known, these conditions are added by means of an additional term in Step 5). This term must be scaled to ensure its proper influence.

As an example, consider the experiment described in [2, pp. 16–19] (originally published in [13]). In this experiment key assumptions were made to extract two of the six parameters. Firstly each patient was assumed to be at steady state (set point has been reached) before initiation of therapy. This is a prevailing condition for that experiment, since the author had access to viral load data before the experiment, which indicated that the viral loads were in steady state. Second, in [1, p. 32] it is stated that infected cells live longer than free virus. This information is reflected in J_r by adding two terms to the cost

$$J_r = J + k_1 \max\left(\frac{d\hat{v}_s}{dt}, 0\right) + k_2 \max(\hat{\delta} - \hat{c}0) \quad (4)$$

where J is either J_w or J_l, $\hat{v}_s$ is the vector of computed viral loads returned by the ODE solver and truncated after a few days, and the scaling constants k_1 and k_2 are chosen such that any violation of the prevailing conditions result in a marked increase of the cost function.

The first refinement term is the maximum numerical derivative of $\hat{v}_s$, which corresponds to the knowledge that the patient is in steady state before initiation of therapy. As alternative for this term, the positive numerical derivatives can be summed, subject

[2]In contrast to `fminsearch` in Matlab, some solvers allow constraints to be placed separately from the main cost function. When available, this option should be used to place hard limits on the parameters.

to the proper adjustment of the scaling constant k_1. In either case, no positive derivative should be allowed initially for the viral load. An intuitive way to see this is to note that therapy results in a decline of virions, thus, an increasing virion count could only be the result of fluctuations before therapy, which is not possible since the patient was in steady state at the start of therapy. The second refinement term corresponds to the statement that the average infected CD4$^+$T cell lives longer than free virions.

Other refinements and performance enhancements are possible: One can limit the range of set points before the computationally intensive ODE solver to increase performance (i.e., check that $\text{set point} \leq 0$ at Step 2) for experiments where one assumes 100% effective HAART).

At times, it may be advantageous to dictate the search order of parameters. Parameters with low variation between patients (as the results for c and δ in [2] indicate) are then introduced into the search at a later stage. For instance, c and δ can be fixed at initial values during the first stage of the search until a preset tolerance is met. The search is then continued, this time allowing all parameters to vary.

III. Verification of Method

A. Generated Data

First, the described procedure is checked against generated, well-posed data, exceeding all requirements of [6]. The test-set is generated with the aim to accommodate the range of parameters described in literature [1], [2], [14]–[19]. Some parameters vary considerably among authors—here the choice is biased toward [1] and [2]. Parameter and set point variations are discussed further in [18] and [19].

1) Generated Data With a Random Component: As a starting point, a dataset is generated for $\chi = [10\ 0.01\ 5 \times 10^{-6}\ 0.5\ 3.0\ 1000]^T$, $\vec{x}_0 = [1000\ 1\ 100]^T$, and $t = 0, 1, 2, \ldots, 99, 100$. Without any random component, the estimation routine achieves a near-perfect estimation of parameters (results not shown). A random component with a $\log_{10}$-normal variance of 0.6 in the virus and a normal variance of 50 in the CD4$^+$T cell count, is added to the data to simulate inaccuracies in measurements [11].

The first estimate of parameters is made without any assumptions added to the cost function. The result is shown in Fig. 1, which corresponds to $\hat{\chi} = [10.2\ 0.011\ 7.5 \times 10^{-6}\ 4.22\ 0.45\ 831.23]^T$. Note that $\hat{\delta} = 4.22$ and $\hat{c} = 0.45$ are not correctly estimated. Their values should be exchanged, since the original data has as basis $\delta = 0.5$ and $c = 3$. This difference can be seen in the number of infected cells in Fig. 1, but not in the CD4$^+$T cell or virus counts. The exchange of δ and c reflects the fact that the CD4$^+$T cell and virus counts of (1) are symmetric with respect to δ and c [1]. Since the infected cell count is not available to the estimation routine when determining the parameters, the cost function has to be augmented with the knowledge that $\delta < c$ to correct this exchange. This addition to the cost function was described in Section II.B.

After adding the relevant penalty terms to the cost function, a second estimation is performed. Fig. 2 shows the result. The CD4$^+$T cell and the viral levels are nearly identical in Figs. 1 and 2, but the predicted levels for infected CD4$^+$T cells differ. The infected cell levels are not available as a measurement in practice, but since the data for this test-case is generated from (1), a comparison is possible. In both Figs. 1 and 2 the expected level of infected CD4$^+$T cells is given by the dashed line. Only in Fig. 2 does the predicted level (solid line) match the expected level.

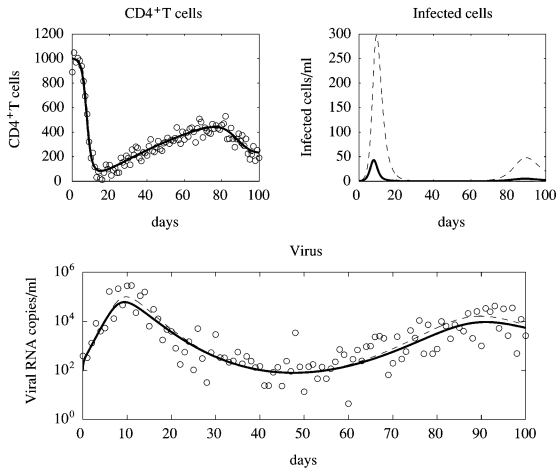

Fig. 1. Estimate of parameters on noisy data, without penalty term assumptions added to the cost function. Note the difference of infected cell levels between the original parameter simulation (dashed) and the estimated parameter simulation (solid). Compare Fig. 2.

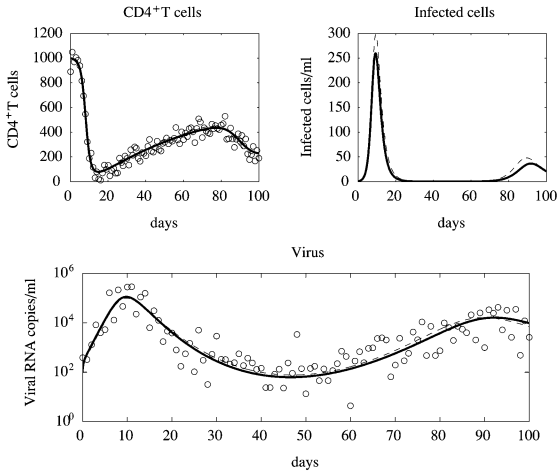

Fig. 2. Estimate of parameters on noisy data with a penalty term, assuming that $\delta < c$, added to the cost function. Note the similarity of infected cell levels for the original parameter simulation (dashed) and the estimated parameter simulation (solid). Compare Fig. 1.

The second parameter estimate is unchanged from the first estimation, except that $\hat{\delta}$ and $\hat{c}$ are exchanged, i.e., $\hat{\chi} = [10.7\ 0.015\ 4.5 \times 10^{-6}\ 0.58\ 2.05\ 896.49]^T$. Note that the order of $\hat{\delta}$ and $\hat{c}$ is correct. The correct estimation is a direct result of the addition of the penalty term, $k_2 \max(\hat{\delta} - \hat{c}, 0)$, to the cost function which implies that $\delta < c$. It is clear that the estimation procedure responds correctly when outside knowledge is added. The next section investigates if the estimation is still reasonable with less data-points.

2) A Dataset With Reduced Number of Data Points: The theoretical limit for the minimum number of data points for an estimation of parameters, under conditions of persistent excitation,

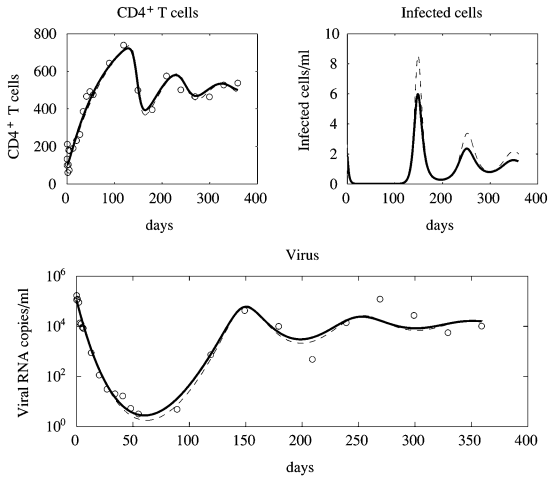

Fig. 3. Estimate for dataset with reduced number of points. Original parameter simulation—dashed; Estimated parameter simulation—solid.

was derived in [6]. It becomes increasingly hard to meet all conditions of identifiability in practical situations. To ensure that sample data complies with identifiability requirements, a time schedule can be set up that allows some flexibility in sampling intervals without jeopardizing parameter identifiability after the initiation of HAART [16], [17]. Before such a time schedule for measurements can be finalized, its viability for model identification has to be determined. As an example, to show the applicability of the proposed procedures, a dataset is created with $\chi = [10\,0.01\,8\times10^{-7}\,0.5\,3.2\,4000]^T, \vec{x}_0 = [100\,2.8\,112\,500]^T$ and the time points taken from the schedule as in Fig. 3.

The proposed schedule is intended for use after initiation of HAART, thus the initial CD4$^+$T cell level is chosen to be $T_0 = 100$ and v_0 is chosen near the set point value of χ with $\beta = 8 \times 10^{-6}$ and $k = 18\,200$ according to [1]

$$v_s = \left(\frac{ks\beta}{\delta dc} - 1\right)\frac{d}{\beta}. \tag{5}$$

After determining the viral point, β is lowered to $\beta = 8\times10^{-7}$, and k is lowered to $k = 4000$ corresponding to the assumption that HAART in this case is 90% effective in reducing β and about 80% effective in reducing k. A random component is added to both the CD4$^+$T cell and virus counts, as with the previous dataset. The estimate corresponding to Fig. 3 gives $\hat{\chi} = [11.2\ 0.012\ 7.4 \times 10^{-7}\ 0.499\,51\ 3.89\ 5156]^T$. The assumption that the patient is in steady state was not added to the estimation procedure, since this assumption is only made to approximate a value for v_0. If such information is available, the accuracy of estimation can be increased.

B. Reproducing a Published Experiment

In this section, the parameter estimation of c and δ for three patients in ([2, pp. 16–19] (originally published in [13]) is repeated. The patients under consideration were treated with protease inhibitors, allowing for additional assumptions to be made about the system. By fitting a reduced system to sample data it was possible to estimate both c and δ. Here the estimation is repeated, but instead of reducing the system equations, the assumptions are added directly to the cost function through penalty terms, as described in Section II-B. The same two parameters as in the experiment are estimated and all assumptions described in the experiment are included in the repeated estimate. This is done to verify that the procedure correctly handles the addition of custom penalty terms to the cost function. The results are compared in Table I.

TABLE I
COMPARISON OF RESULTS WITH A PUBLISHED EXPERIMENT. THE HALF-LIFE FOR c IS COMPUTED AS $t_{c(1/2)} = (\ln 2/c)$ AND SIMILARLY FOR δ

Patient number	Method	Virus clearance $\hat{c}$ (day^{-1})	Virus clearance $t_{c\frac{1}{2}}$ (days)	Infected cell loss $\hat{\delta}$ (day^{-1})	Infected cell loss $t_{\delta\frac{1}{2}}$ (days)
104	published	3.7	0.2	0.5	1.4
	initial cost function	2.03	0.34	0.51	1.36
	$\vec{x}_0$ *fixed*	*3.40*	*0.20*	*0.50*	*1.38*
105	published	2.1	0.3	0.5	1.3
	initial cost function	0.66	1.05	0.66	1.05
	$\vec{x}_0$ *fixed*	*2.22*	*0.31*	*0.45*	*1.54*
107	published	3.1	0.2	0.5	1.4
	initial cost function	2.07	0.33	0.50	1.39
	$\vec{x}_0$ *fixed*	*3.07*	*0.23*	*0.49*	*1.41*

The small data window for this experiment does not allow clear information to be found about the initial conditions. A dependence on $\vec{x}_0$ is to be expected [1], and from the results it is evident that the estimation of c, and to a lesser degree, of δ, is dependent on outside information about the initial level of the virus concentration.[3] When this information is added to the estimation procedure through $\vec{x}_0$, the results compare very well with those published in [2] and [13].

IV. APPLICATIONS IN HIV/AIDS RESEARCH

A. Results From a Vaccine Readiness Trial

This subsection describes the extraction of parameters for patients who took part in an HIVNET 28 vaccine readiness study. As described in [8], viral load may be a critical endpoint in vaccine trials by which to judge efficacy. It is important to define viral dynamics in unvaccinated infected individuals, especially in non-B subtype infections where little information is available. The main aim was to determine the set point for these patients. Also, the time from seroconversion to reach this set point is of interest for the trial.

1) Study Population: Fifty-one individuals with recent HIV-1 infection were recruited from four countries in southern Africa. Details of the cohort are given in [8] and sample data for four patients is shown in Table II.

2) Outline of Procedure: The minimum requirement for estimation of parameters is five viral load and four CD4$^+$T cell measurements [6]. Thirty-four of the fifty-one participants had enough samples $(5 + 4)$ to meet the minimum requirements. For these patients the estimation routine was initiated with initial $\hat{\chi}$ as in Section III-A. After the first iteration of parameter estimates, the model curves were plotted and examined for each patient. For patients where the initial fit was not deemed adequate, the parameters were adjusted manually. The parameters found in this manner were then averaged out for all patients and

[3]An estimate for $\vec{x}_0$ can be found by keeping all parameters at the values published in [2] and instructing the optimization routine to search for the initial values that minimize the cost function.

TABLE II
DATA POINTS FOR FOUR PATIENTS OF THE HIVNET 28 STUDY

Patient ID	days since seroconversion	viral load copies/ml	cd4 cells copies/μl
P536000015	391	46 699	
(5+4 samples)	426	24 463	187
	503	62 364	136
	573	25 079	193
	636	29 821	143
P536000080	170	3 239	
(5+4 samples)	247	5 810	451
	317	6 002	437
	366	20 439	455
	457	9 638	524
P541000228	422	27 941	
(5+4 samples)	506	50 295	409
	597	34 909	312
	723	33 575	308
	786	18 748	250
P541000242	411	67 813	
(4+3 samples)	474	11 569	
	586	39 887	186
	685		178
	775	19 359	272

used as the new starting point for the final computer based parameter search.

Once the parameters for each patient had been estimated, the set point was calculated using (5). The fluctuations in the modeled viral load were analyzed in each patient to find the elapsed time from seroconversion where the set point is reached. The time from seroconversion to the point where the fluctuations fall within 0.5 of the $\log_e$ values of the set point is taken as an estimate for the time to reach set point.

3) Patients With Insufficient Data Points: Of the seventeen remaining patients, seven did not have enough data to be useful for this study. The other ten patients had insufficient data points for a complete evaluation of parameters on their own, but allowed first order estimates in the context of the cohort. For these patients, the assumption was made that c does not differ significantly from the other patients in the cohort [2]. For a discussion of identifiability in situations where key parameters are fixed, see [6]. To solve the estimate of set point for patients with less measurements (say, $4+3$ as for P541 000 242), the clearance rate constant of the virus, c, was fixed at the average value of the participants with five viral load and four CD4$^+$T cell $(5+4)$ measurements. After one initial estimation run, these estimated parameters were used as the initial point to do a second iteration where c was allowed to vary. Thus, by adding these ten patients to the initial group, parameters were estimated for forty-four of the fifty-one participants.

4) Parameter Ranges and Assumptions: Even though the minimum requirements for parameter estimation were met, estimation is still subject to the following assumptions:

- Patients are in the early stages of infection, based on the enrolment data. The midpoint between the last HIV-negative sample and first positive sample is taken as an estimate to the time of seroconversion.
- The initial CD4$^+$T cell concentration does not exceed 1200 copies per microliter, based on the data from healthy patients with similar background.

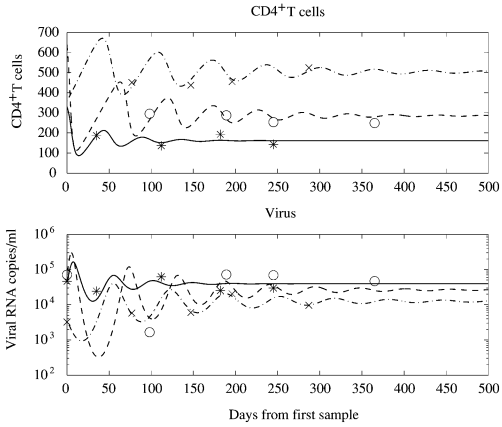

Fig. 4. Model result for three patients with $(5+4)$ samples. See Table II.

TABLE III
PARAMETER ESTIMATES FOR THREE PATIENTS THAT MEET THE IDENTIFIABILITY REQUIREMENT

Pnr	536000015	536000080	541000228
s	3.25	7.88	8.45
d	1.06×10^{-05}	0.00811	0.00822
β	5.38×10^{-07}	7.96×10^{-07}	7.58×10^{-07}
δ	0.16	0.38	0.67
c	0.58	0.69	0.85
k	1016.9	688.5	2548.2
v_s	36847	10439	26551
days to set point	449	335.5	573.5

- Initial values for the viral load coincide with the first viral load measurement.
- Patients do reach a steady-state in viral load.
- Fluctuations due to factors outside the model are of a lesser degree in viral load than in CD4$^+$T cell count.
- The order of c and d is not dictated in this instance of the cost function, but corrected after estimation.
- The model parameters for patients in this cohort allow a common initial parameter set to be found from where the search procedure is drawn to a global minimum in the cost function of individual patients.
- The parameters published for subtype-B infection are close enough to such a common point to be used in the first iteration of the parameter search.
- The bias introduced by human intervention in deciding on the initial point is negligible.

5) Study Results: Fig. 4 shows model predictions compared to the data-points $(5+4)$ of the three patients in Table III. (P536 000 015 solid-marked *, P536 000 080 dotted-marked o, P525 000 171 dash-dot-marked x). Fig. 5 gives a detailed view for P541 000 242 $(4+3$ points). The markers indicate data points and the corresponding model prediction is shown by the solid line. The set point estimate is indicated by a dashed line, and the time to set point is taken at the point where the modeled viral load falls between the dotted lines.

Table III shows the parameter estimates for the three sample patients that meet the minimum requirements for estimation. From the final estimation, we have the following

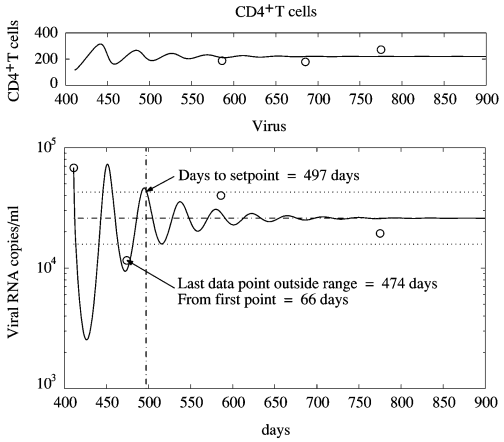

Fig. 5. The model and the original data for P541 000 242. Different definitions for the time to set point are shown.

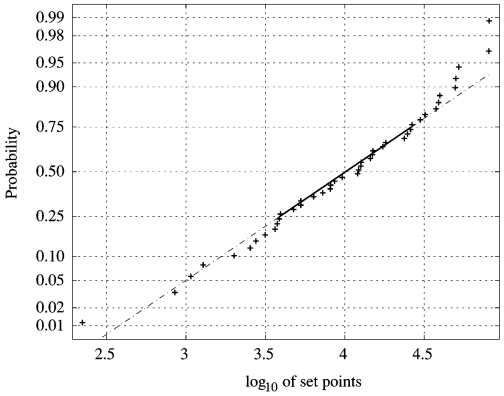

Fig. 6. Normal probability plot of set point estimations.

median estimate of parameters: $\hat{\chi} = [7.48\ 0.000\,85\ 1.4 \times 10^{-6}\ 0.80\ 1.56\ 2834]^T$.

The normal probability plot of $\log_{10}$ set point estimations for all patients in Fig. 6 gives a visual indication that the estimates follow a log-normal distribution. The Bera-Jarque parametric hypothesis test of composite normality confirms this at a significance level of 0.298.

The calculated median time to set point was 16.57 months (497 days) and the $\log_{10}$ based median of the calculated set point distribution was 4.08 (12143 RNA copies/ml). In three participants the parameter estimates indicated continuous variation of viral load, indicating that no set point was reached within the modeled time-frame.

6) A Note About Confidence Intervals: The main aim of the data analysis for the vaccine readiness trial is to determine a benchmark point for patients from southern Africa [8]. It turns out that the set point estimation is robust against variations in the parameter estimates for this dataset. The set point distribution is log-normal with median value of $10^{4.084}$. The mean $\log_{10}$ value is 3.99 with a standard deviation of 0.56, and 95% confidence interval of [3.82, 4.16] for the mean, and [0.46, 0.71]$ for the standard deviation [12].

For the estimation of days to set point, the definition has a direct influence on the result. Since the simulated curve from the ODE solver is used to determine the point at which a patient reaches set point, the estimation is bound to be higher as when the samples are used for this estimation. As an illustration of this, one can look at Fig. 5. The definition used for this study gives 497 days to reach set point. If the definition is taken as the last data point outside the prescribed range it is 474 days. Both definitions are influenced by the estimate of the time from seroconversion. For the definition in this paper, the mean days to set point is 508 days, with a standard deviation of 187. The 95% confidence interval is [449, 567] for the mean and [153, 239] for the standard deviation.

For the parameter estimates it is harder to analyze the results. The confidence intervals for each parameter, assuming a normal distribution, can be easily determined for a group of patients [12], but such closed form equations are not defined for individual patients. Worse still, for nonlinear models the parameter estimates are not in general unbiased [12].

The Bera-Jarque test for composite normality ($\alpha = 0.05$, $p_s = 0.3$) indicates that, of all the parameter estimates for the group, only d might be considered to come from a normal distribution. Whereas the same test ($\alpha = 0.05, [p_s\ p_d\ p_\beta\ p_\delta] = [0.86\ 0.09\ 0.30\ 0.18]$) indicates that s, d, β, and δ might be taken as log-normal. Based on this information, it is reasonable to follow the scheme in [12, p. 444], where a logarithmic transformation is applied to parameters in order to stabilize the random variation, without linearizing the model. In this way one can find the mean values for $\log_{10}(\hat{\chi})$ to be $[0.8656\ -4.1501\ -5.8128\ -0.131\,32\ 0.225\,51\ 3.3329]$, which corresponds to a mean value of $[7.34\ 7.08 \times 10^{-5}\ 1.54 \times 10^{-6}\ 0.739\ 1.681\ 2153]$ for $\hat{\chi}$. The 95% confidence interval for the mean is

$$\begin{bmatrix} 6.28 & 1.41 \times 10^{-5} & 1.22 \times 10^{-6} & 0.629 & 1.435 & 1606 \\ 8.58 & 0.000\,355 & 1.94 \times 10^{-6} & 0.868 & 1.969 & 2885 \end{bmatrix}$$

and the $\log_{10}$ based standard deviation for the parameters is $[0.223\,01\ 2.3026\ 0.334\,26\ 0.229\,66\ 0.226\,19\ 0.418\,46]$.

B. Parameter Variation From Infection to the Onset of AIDS

To get an indication of the variation of parameters over the course of the disease, a dataset from [5] is considered here. In the early stages after infection, the variation in both CD4$^+$T cell and virus levels is clear. This is followed by a period of relative stability and finally, at about 3000 days, the levels indicate progression from steady state to AIDS. A normalized version of the dataset is displayed in Fig. 7 together with each parameter estimate, to give a visual reference of disease progression. This dataset is used in [14] as a benchmark to compare compliance of different HIV/AIDS models to real data.

One concern in [14] is that the model (1) does not track the data from infection until the onset of AIDS with a single set of parameters. It was noted that patients' parameters change during the course of the disease [20]. By estimating parameters from infection to the onset of AIDS our study offers a simulated confirmation of this.

The dataset is interpolated and the parameters are estimated for a fixed data window, which is moved over the data at fixed increments. Large time difference between measurements, combined with interpolation, result in erratic estimates if a perfect fit of the curve is searched for at each point. To prevent this, the estimation procedure exits with a higher tolerance

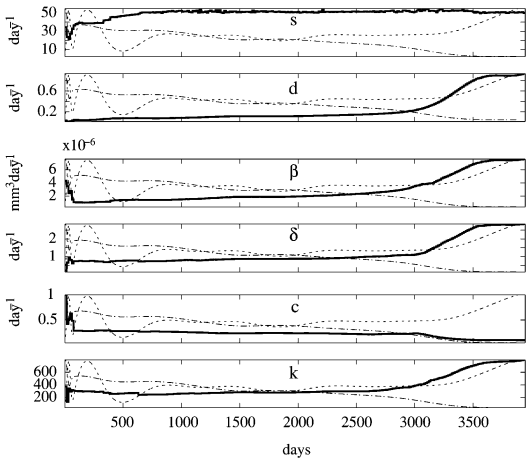

Fig. 7. The progressive estimate of parameters over the course of HIV/AIDS. The estimate for each parameter is represented by a solid line. s is limited to 50. The dash-dot line shows a normalized CD4$^+$T cell count and the dotted line shows the normalized virus level. The normalized levels are shown as a visual reference of disease progression and are not part of the parameter estimate.

for error. Fig. 7 shows the result for a window size of 60 days, with estimates made 15 days apart. On each graph, the normalized CD4$^+$T cell and virus loads are plotted to give a visual reference of the disease progression.

Instead of averaging the estimation over a few windows, the search tolerance is increased and each subsequent search is initialized with $\hat{\chi}$ from the previous window. This allows for continuity of parameters. Intuitively this scheme corresponds to the assumption that parameters vary smoothly over time as the disease progresses. Thus the estimation procedure factors the results from the previous window into the next estimation, resulting in an estimate, $\hat{\chi}$, that is a modification of the previous window's $\hat{\chi}$. Each modification is just enough to ensure that the cost value changes by less than the specified tolerance. In conclusion one can see that, at each point, the estimated line is fitted to the interpolated data, and estimation stops as soon as a *possible* (as opposed to a locally *near optimal*) solution is found. An intuitive description of this procedure would be that the parameter estimate for each window is the "nearest plausible neighbor" to the estimate of the bordering windows.

In Fig. 7, the increase in $\hat{s}$ is halted by the assumption that $s \leq 50$. Most estimations tend toward unreasonable values with the onset of AIDS at about 3000 days. The estimations $\hat{\delta}$, $\hat{c}$, and $\hat{k}$ stay fairly constant until the onset of AIDS, whereas the estimations for $\hat{s}$, $\hat{d}$, and $\hat{\beta}$ show a steady increase, even before the onset of AIDS.

V. Conclusion

By designing and implementing a custom cost function, a diverse base of information from outside the basic dataset can be used to extract model parameters for the 3-D HIV/AIDS model. This method can identify parameters in situations where an orthodox LSQ method would fail. Together with the advantage of higher quality estimates in situations where the data is well-posed, the developed method can use information from outside the dataset to provide reasonable estimates for data that cannot be used with a pure LSQ method. The presented method is a step forward in the effort to supply patients with individualized parameter estimation. The estimates made in literature were for at most two parameters per dataset, whereas the procedures described in this paper can estimate all six parameters. It should be noted that the conditions for successful estimation, as described in [6], still apply if no external information is available to support the basic LSQ cost function.

A standard table that is proposed for data acquisition in hospitals and clinics is considered here. The results show that the table would allow enough information to extract a good estimation for the parameters of the 3-D HIV/AIDS model.

Many experiments in literature have data windows that are too small to make definite conclusions about the parameters from the published data alone. To compare results, external knowledge from articles, or the description of the experiment, can be included in the cost function of the estimation routine. Comparison with a published experiment shows that it becomes increasingly hard to coordinate assumptions and implicit information when analyzing real data.

Parameter variations during the course of HIV/AIDS are still not well understood and the basis of their variation needs to be found. One reason for this poor understanding is the lack of high quality data. The results show that parameters may vary considerably over the course of HIV/AIDS. The data points for the analysis of parameter variation are too sparsely sampled to draw quantitative conclusions, rather the results show that parameters vary over time and that, qualitatively, parameters may vary as presented here. For example, since there is a steady decline in CD4$^+$T cell levels in the dataset and the results show a corresponding increase in s, this observation lends support to the use of a density based proliferation term that is commonly used in conjunction with s [2], [19].

The procedure described in this paper was used successfully to analyze the data from the HIVNET 28 vaccine readiness trial. Despite the sparse data available per patient, the datasets complied with the minimum identifiability requirements, to allow the extraction of the average set point and time from seroconversion until this set point is reached. Both results are important to form a benchmark for the study of vaccination since one outcome of the vaccine trial is to achieve a lower set point viral load. The time it takes for patients to reach a steady state gives a good indication of the period for which patients should be monitored to ensure that some samples are taken when the patient has reached a set point. The results show that after approximately 17 months from seroconversion, oscillations in viremia flattened to a $\log_{10}$ based median set point of 4.08, appearing no different from reported studies in subtype B HIV-1 infected male cohorts [8], [21]–[23]. Together with these main outcomes, initial estimates for parameters are also presented.

From the analysis of confidence intervals for set point, days to set point and the individual parameters it was seen that the set point is robustly estimated, achieving the main goal of the analysis. The estimate of time until set point is dependent on its definition, and is also more sensitive to changes in parameter estimation. For the group of patients statistical confidence intervals for the parameter estimates can be generated. As a result of sparse data, isolated parameter estimates for individual patients of the HIVNET 28 study would result in large confidence

intervals. An ad hoc approach of confidence analysis must be followed to determine confidence intervals for patients in isolation and such approach needs to be addressed in further research. Since patients for the study were selected subject to well defined constraints [8], this allowed for specific conditioning of the estimation routine and a clear layout of assumptions for the group. When estimates for the cohort are combined, the data allows a meaningful first estimate of parameters of the 3-D HIV/AIDS model for patients from southern Africa.

REFERENCES

[1] M. A. Nowak and R. M. May, *Virus Dynamics: Mathematical Principles of Immunology and Virology*. Oxford, U.K.: Oxford Univ. Press, 2000.

[2] A. S. Perelson and P. W. Nelson, "Mathematical analysis of HIV-1 dynamics in vivo," in *SIAM Rev.*, vol. 41, Jul. 1999, pp. 3–44.

[3] D. D. Ho *et al.*, "Rapid turnover of plasma virions and CD4 lymphocytes in HIV-1 infection," *Nature*, vol. 373, pp. 123–126, 1995.

[4] X. Wei *et al.*, "Viral dynamics in HIV-1 infection," *Nature*, vol. 273, pp. 117–121, 1995.

[5] A. S. Fauci, G. Pantaleo, S. Stanley, and D. Weissman, "Immunopathogenic mechanisms of HIV infection," *Ann. Intern. Med.*, vol. 124, pp. 654–663, 1996.

[6] X. Xia and C. H. Moog, "Identifiability of nonlinear systems with applications to HIV/AIDS models," *IEEE Trans. Autom. Control*, vol. 48, no. 2, pp. 330–336, Feb. 2003.

[7] A. M. Jeffrey, X. Xia, and I. Craig, "Identifiability of an extended HIV model," presented at the 5th IFAC Symp. 2003 Modeling and Control in Biomedical Systems, Melbourne, Australia, Aug. 21–23, 2003.

[8] C. M. Gray, C. Williamson, A. Puren, M. Paximadis, X. Xia, R. Filter, L. Zijenah, H. Cao, L. Morris, E. Vardas, M. Colvin, G. Gray, J. McIntyre, S. Allen, D. Katzenstein, M. Mbizo, N. Kumwenda, T. Taha, S. A. Karim, J. Flores, and H. W. Sheppard, "Viral dynamics, CD4 counts and human leukocyte antigen types in subtype C human immunodeficiency virus type 1-infected individuals from Southern Africa: Significance for vaccine trials," in *AIDS Research and Human Retroviruses*, 2004.

[9] Panel on Clinical Practices for Treatment of HIV Infection. (2001, Aug.) Guidelines for the Use of Antiretroviral Agents in HIV-Infected Adults and Adolescents. [Online]. Available: http://www.hivatis.org

[10] X. Xia, "Estimation of HIV/AIDS parameters," *Automatica*, vol. 39, pp. 1983–1988, 2003.

[11] Guidelines for Laboratory Test Result Reporting of Human Immunodeficiency Virus Type 1 Ribonucleic Acid Determination, CDC Working group. (2001, Nov.). [Online]. Available: http://www.cdc.gov/

[12] D. Brown and P. Rothery, *Models in Biology: Mathematics, Statistics and Computing*. Chinchester, U.K.: Wiley, 1993.

[13] A. S. Perelson, A. U. Neumann, M. Markowitz, J. M. Leonard, and D. D. Ho, "HIV-1 dynamics in vivo: Virion clearance rate, infected cell life-span, and viral generation time," *Science*, vol. 271, pp. 1582–1586, 1996.

[14] D. J. Covert and D. Kirschner, "Revisiting early models of the host-pathogen interactions in HIV infection," *Comments Theoretical Biol.*, vol. 5, no. 6, pp. 383–411, 2000.

[15] R. V. Culshaw and S. Ruan, "A delay-differential equation model of HIV infection of $CD4^+$ T-cells," *Mathematical Bios.*, vol. 165, pp. 27–39, Feb. 2000.

[16] A. M. Jeffrey and X. Xia, "Estimating the viral load response time after HIV chemotherapy," presented at the Africon'02 Control Conf., George, South Africa, Oct. 3–5, 2002.

[17] A. M. Jeffrey, X. Xia, and I. Craig, "When to initiate HIV therapy: A control theoretic approach," *IEEE Trans. Biomed. Eng.*, vol. 50, no. 11, pp. 1213–1220, Nov. 2003.

[18] V. Müller, A. F. M. Marée, and R. J. D. Boer, "Small variations in multiple parameters account for wide variations in HIV-1 set points: A novel modeling approach," in *Proc. Roy. Soc. Lond. B. Biol. Sci.*, vol. 268, 2001, pp. 235–242.

[19] D. S. Callaway and A. S. Perelson, "HIV-1 infection and low steady state viral loads," *Bull. Math. Biol.*, vol. 64, pp. 29–64, 2002.

[20] D. C. Douek *et al.*, "Changes in thymic functions with age and during the treatment of HIV infection," *Nature*, vol. 396, pp. 690–695, 1998.

[21] J. W. Mellors, C. R. Rinaldo Jr., P. Gupta, R. M. White, J. A. Todd, and L. A. Kingsley, "Prognosis in HIV-1 infection predicted by the quantity of virus in plasma," *Science*, vol. 272, pp. 1167–70, 1996.

[22] J. W. Mellors *et al.*, "Plasma viral load and CD4+ lymphocytes as prognostic markers of HIV-1 infection," *Ann. Intern. Med.*, vol. 126, pp. 946–954, 1997.

[23] T. W. Schacker, J. P. Hughes, T. Shea, R. W. Coombs, and L. Corey, "Biological and virologic characteristics of primary HIV infection," *Ann. Intern. Med.*, vol. 128, pp. 613–620, 1998.

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