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Some state space models of HIV pathogenesis under treatment by anti-viral drugs in HIV-infected individuals

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Abstract

In this paper we have extended the model of HIV pathogenesis under treatment by anti-viral drugs given by Perelson et al. [A.S. Perelson et al., Science 271 (1999) 1582] to a stochastic model. By using this stochastic model as the stochastic system model, we have developed a state space model for the HIV pathogenesis under treatment by anti-viral drugs. In this state space model, the observation model is a statistical model based on the observed numbers of RNA virus copies over different times. For this model we have developed procedures for estimating and predicting the numbers of infectious free HIV and non-infectious free HIV as well as the numbers of different types of T cells through extended Kalman filter method. As an illustration, we have applied the method of this paper to the data of patient Nos. 104, 105 and 107 given by Perelson et al. [A.S. Perelson et al., Science 271 (1999) 1582] under treatment by Ritonavir. For these individuals, it is shown that within two weeks since treatment, most of the free HIV are non-infectious, indicating the usefulness of the treatment. Furthermore, the Kalman filter method revealed a much stronger effect of the treatment within the first 10 to 20 h than that predicted by the deterministic model.

Keywords: Actively infected T cells; Extended Kalman filter; Infectious free HIV; Non-infectious free HIV; Protease inhibitor; Stochastic differential equations

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1. Introduction

To study the dynamics of the HIV pathogenesis under treatment by anti-viral drugs and to estimate some key parameters, Perelson et al. [1] have recently proposed a mathematical model for the HIV pathogenesis under treatment by protease inhibitors. They have used this model to estimate the turnover rate of free HIV and the death rate of the actively HIV-infected $CD4^+$ T cells. In this paper we will extend the Perelson et al. model into a stochastic model. By using this stochastic model as the stochastic system model, we will develop a state space model for HIV-infected individuals under treatment by protease inhibitors. The observation model in this state space model is based on the observed RNA virus copies over time and/or the observed total number of $CD4^+$ T cell counts over time depending on the types of available observed data. In this paper we will consider discrete time since only discrete time model will be used in computer Monte Carlo studies; however, we will take 1 h as one time unit so that it provides a close approximation to the continuous-time model as described in [1].

In Section 2, we will describe how to derive stochastic models for the HIV pathogenesis at the cellular level in HIV-infected individuals under treatment by an anti-viral drug. Using results from Section 2, in Section 3 we will derive some state space models for HIV pathogenesis at the cellular level in HIV-infected individuals using data from RNA virus load and/or the total number of $CD4^+$ T cell counts. As an application of our models, in Section 4 we will apply the results of our model to some data given in [1]. In Section 5, we will generate some Monte Carlo studies through computer to assess the efficiency and usefulness of the extended Kalman filter method. Finally in Section 6, we will draw some conclusions and discuss some relevant issues regarding state space models.

2. A stochastic model for the HIV pathogenesis under treatment by antiviral drugs

To develop a stochastic model for the HIV pathogenesis under treatment by antiviral drugs, note first that there are two categories of anti-viral drugs for treating HIV-infected patients. Category 1 drugs attack the virus by damaging the reverse transcriptase of HIV, thus blocking the reverse transcription from RNA to DNA of HIV inside the T_4 cells (referred to as T cells). AZT, DDC, 3TC and DDI are examples of this type of drugs. Category 2 drugs attack the HIV through the inhibition of protease of HIV to reduce the generation of infectious free HIV at the death of actively infected T_4 cells (referred to as T^* cells). This latter group of drugs are called protease inhibitors. Thus, under treatment by Category 1 drugs, the attacked HIV are defective in reverse

transcriptase so that they cannot successfully infect the T cells; however, the damaged free HIV can still enter the T cells so that they are removed from the pool of free HIV. On the other hand, under treatment by protease inhibitors, most of the released free HIV by the death of the T^* cells are non-infectious.

Let $T(t), T^*(t), V_1(t)$ and $V_0(t)$ denote the numbers of T cells, T^* cells, infectious free HIV and non-infectious free HIV at time t respectively. (Following Perelson et al. [1] we will ignore the path involving latently infected T_4 cells as the number of free HIV from this path is very small.) To develop a stochastic model for the HIV pathogenesis under treatment by anti-viral drugs, consider a situation in which a combination of a Category 1 drug (called drug 1) and a protease inhibitor (drug 2) is used to treat a HIV-infected individual. In this section we will derive stochastic differential equations for this process under the assumption that drug resistance of HIV to the anti-viral drugs has not yet been developed.

2.1. Some biological consideration

To develop a stochastic model for the HIV pathogenesis under treatment by anti-viral drugs, we summarize some relevant biological observations and describe some basic stochastic modeling procedures in the following:

(a) New normal T_4 cells (i.e. T cells) are produced by precursor cells in the bone marrow. These cells move to the thymus to mature before moving to other sites through the blood stream. In the absence of HIV, these cells are produced at constant rates; however, in the presence of free HIV, these rates are decreasing functions of the number of free HIV since free HIV can also infect the precursor stem cells [2–5]. In this paper we will model this process by a discrete-time pure birth process with rate $s(t)$. That is, the probabilities that there are one or zero T cells generated by precursor stem cells in the bone marrow and thymus during $(t, t+1]$ are $q_{TP}(t) = 1 - \exp\{-s(t)\}$ and $1 - q_{TP}(t)$ respectively (see Remark 1). (For small $s(t), q_{TP}(t) \simeq s(t)$.) Following [3] and [5] we will assume $s(t)$ as $s(t) = s\theta/(\theta + V_1(t))$, unless otherwise stated.

Remark 1. The rate $s(t)$ is the hazard function at time t. Thus, the probability that the event occurs after time t is $\exp\{-\int_0^t s(u)\mathrm{d}u\}$. Since the time unit is one h which is very small, the conditional probability that the event occurs during $(t, t+1]$ given no event at time t is

$$\left\{\exp\left\{-\int_0^t s(u)\mathrm{d}u\right\} - \exp\left\{-\int_0^{t+1} s(u)\mathrm{d}u\right\}\right\}\left[\exp\left\{\int_0^t s(u)\mathrm{d}u\right\}\right]$$

$$= \left\{1 - \exp\left\{\int_0^t s(u)\mathrm{d}u - \int_0^{t+1} s(u)\mathrm{d}u\right\}\right\} \simeq 1 - \exp\{-s(t)\} \simeq s(t).$$

(b) Following Perelson et al. [1] we will ignore the path involving latently infected T cells since the number of free HIV produced by this path is very small. In this paper we will thus assume that free HIV infect mainly activated T cells to yield actively HIV-infected T cells (to be referred to as T^* cells). This infection process occurs by law of random mass interaction. Let $k_1(t)$ be the infection rate at time t. Then, given $T(t)$ T cells at time t, the probability that a free HIV will infect a T cell during $(t, t+1]$ is $q_{VI}(t) = 1 - \exp\{-T(t)k_1(t)\} \simeq T(t)k_1(t)$ for small $T(t)k_1(t)$.

(c) T cells have finite life span so that with positive probability they will die or be removed over the time span. On the other hand, in the presence of antigen and free HIV, T cells are stimulated to proliferate stochastically to activate the immune system. We will model this by a discrete-time stochastic birth and death process with birth rate $b_T(t)$ and death rate $d(t) = \mu_1$, independently of the infection process of T cells by free HIV. That is, the probabilities that each T cell at time t will give rise to 2 T cells, 0 T cells and 1 T cell by the proliferation and death process are given respectively by $q_{T2}(t) = 1 - \exp\{-b_T(t)\}, q_{T0}(t) = 1 - \exp\{-d(t)\}$ and $q_{T1}(t) = 1 - q_{T2}(t) - q_{T0}(t)$. For small $b_T(t)$ and $d(t), q_{T2}(t) \simeq b_T(t), q_{T0}(t) \simeq d(t)$ and $q_{T1}(t) \simeq 1 - [b_T(t) + d(t)]$. (Since the time unit one h is very small, one may assume $0 \leqslant q_{T1}(t) \simeq 1 - [b_T(t) + d(t)] \leqslant 1$.) Following Kirschner and Webb [6], we will assume $b_T(t)$ as $b_T(t) = \gamma V(t)/[\theta_v + V(t)]$, where $V(t) = V_0(t) + V_1(t)$.

(d) Because of cytopathic effects or apoptosis [2,5,7], the T^* cells are short lived with life span much shorter than that of T cells (average life span is 2.66 days; see Ref. [1]) and thus will die upon activation. Thus, unlike the T cells, it is not unrealistic to assume that T^* cells would not proliferate by activation. This latter assumption has also been made in the literature [1,3,5,6].

Similarly, it has been documented that free HIV are short lived with life span much shorter than that of T^* cells (the average life span of free HIV is 0.3 days; see Refs. [1,8,9]). Furthermore, the HIV viral clearance rate is not affected by disease status although advanced disease is associated with higher virus load [8,10]. Hence one may assume that the death and removal rate of free HIV is fairly constant.

(e) At the death of T^* cells, free HIV will be released. Let $N_j(t)$ be the number of free HIV released by the death of the jth T^* cell at time t. Let $D_{T^*}(t)$ be the total number of death of T^* cells at time t. Then one may assume that given $D_{T^*}(t)$, the $N_j(t), j = 1, \ldots, D_{T^*}(t)$ are independently and identically distributed (iid) random variables with mean $N(t)$ and variance $\sigma_N^2(t)$. Following Refs. [11,12], we will assume $N(t)$ as an exponential increasing function of t given by $N(t) = N_0 \exp(-\beta_1 t) + \beta_2\{1 - \exp(-\beta_1 t)\}$ unless otherwise stated.

(f) Under treatment by Category 1 drugs, the damaged free HIV are defective in reverse transcriptase so that these HIV cannot successfully infect T cells; however, these HIV can still enter T cells and hence will be removed from the pool of free HIV. On the other hand, under treatment by protease

inhibitors, most of the released free HIV at the death of T^* cells are non-infectious. To model this, we let $h_1(t)$ be the probability that a free HIV is affected by Category 1 drugs during $(t, t+1]$ and let $\omega(t)$ be the expected proportion of non-infectious free HIV released by the death of a T^* cell at time t. Then $h_1(t)$ is a non-negative function of the dose $d_1(t)$ of Category 1 drugs at time t with the constraint $h_1(t) = 0$ if $d_1(t) = 0$. From this, the expected number of free HIV which are defective in reverse transcriptase due to treatment by Category 1 drugs during $(t, t+1]$ is $h_1(t)V_1(t)$. Similarly, given $D_{T^*}(t)$ deaths of T^* cells at the time t, the expected total number of non-infectious free HIV released by the deaths of T^* cells is $\omega(t)N(t)D_{T^*}(t)$.

(g) Given $X(t) = \{T(t), T^*(t), V_0(t), V_1(t)\}$, conditionally the above processes are assumed to be independently distributed of one another.

2.2. The stochastic difference equations for the numbers of different types of $CD4^+$ T-cells and free HIV

Given the above biological specifications and assumptions, one may readily derive stochastic difference equations for the numbers of different types of $CD4^+$ T-cells and free HIV per $dm^3 = 10^6 \times mm^3$ volume. (We assume dm^3 rather than mm^3 as volume unit because the number of viruses has to be taken integers; see Ref. [12] for detail.)

To proceed, let $S(t)$ be the number of new T cells generated by the precursor stem cells in the bone marrow and thymus during $(t, t+1]$, $F(t)$ the number of T cells infected by HIV during $(t, t+1]$ to become T^* cells, and $B_T(t)$ and $D_T(t)$ the respective number of birth and death of T cells generated by the stochastic proliferation through stimulation by antigens and free HIV and by death during $(t, t+1]$. Let $D_{T^*}(t), D_{V0}(t)$ and $D_{V1}(t)$ denote the numbers of death or removal of T^* cells, non-infectious free HIV and infectious free HIV during $(t, t+1]$ respectively. Let $R(t)$ be the number of free HIV which are defective in reverse transcriptase due to treatment by Category 1 drugs during $(t, t+1]$ and $M_j(t)$ the number of non-infectious free HIV released by the death of the jth T^* cell at time t due to treatment by protease inhibitors. Then, by taking into account the input and output of the state variables, we have the following stochastic difference equations for $T(t)$,$T^*(t)$, $V_0(t)$ and $V_1(t)$:

$$T(t+1) = T(t) + S(t) + B_T(t) - D_T(t) - F(t), \tag{1}$$

$$T^*(t+1) = T^*(t) + F(t) - D_{T^*}(t), \tag{2}$$

$$V_0(t+1) = V_0(t) + \sum_{j=1}^{D_{T^*}(t)} M_j(t) + R(t) - D_{V_0}(t), \tag{3}$$

$$V_1(t+1) = V_1(t) + \sum_{j=1}^{D_{T^*}(t)} [N_j(t) - M_j(t)] - R(t) - F(t) - D_{V_1}(t). \tag{4}$$

To specify the probability distribution of the random variables in Eqs. (1)–(4), denote by $\boldsymbol{M}_1 = [B_T(t), D_T(t)]$ and $\boldsymbol{M}_V = [F(t), R(t), D_{V_1}(t)]$. From the above results, the conditional distributions of these variables given the numbers $X(t)$ at time t are given by

- $S(t) \mid V_1(t) \sim$ Point Binomial with mean $q_{TP}(t) \simeq s(t)$
- $\boldsymbol{M}_1 \mid T(t) \sim$ Multinomial $[T(t); q_{T2}(t) = 1 - \exp\{-b_T(t)\} \simeq b_T(t), q_{T0}(t) = 1 - \exp\{-\mu_1\} \simeq \mu_1]$
- $\boldsymbol{M}_V \mid X \sim$ Multinomial $[V_1(t); q_{VI}(t) = 1 - \exp\{-k_1 T(t)\} \simeq k_1 T(t), h_1(t), q_{VD}(t) = 1 - \exp\{-\mu_V\} \simeq \mu_V]$
- $D_{T^*}(t) \mid T^*(t) \sim$ Binomial $[T^*(t), q_{T^*0}(t) = 1 - \exp\{-\mu_2\} \simeq \mu_2]$
- $D_{V0}(t) \mid V_0(t) \sim$ Binomial $[V_0(t), q_{VD}(t) = 1 - \exp\{\mu_V\} \simeq \mu_V]$
- $M_j(t) \mid N_j(t) \sim$ Binomial $[N_j(t), \omega(t)]$.

Further, given $X(t)$, conditionally $S(t), \boldsymbol{M}_1, \boldsymbol{M}_V, D_{T^*}(t)$ and $D_{V_0}(t)$ are independently distributed of one another and are independently distributed of the $N_j(t)$'s. Also, given $D_{T^*}(t)$, the $N_j(t), j = 1, \ldots, D_{T^*}(t)$, are independently and identically distributed with mean $N(t)$ and variance $\sigma_N^2(t)$.

Let $\boldsymbol{\varepsilon}(t) = [\varepsilon_1(t), \varepsilon_2(t), \varepsilon_3(t), \varepsilon_4(t)]^T$ denote the vector of random noises for the deviation from the respective conditional mean numbers. From the above distribution results, one may readily derive the conditional means of the random variables in the above equations. Then, by subtracting these conditional means from the respective random variables in the above equations and noting that the time unit of one h is very small, we obtain

$$\begin{aligned}
\varepsilon_1(t) &= [S(t) - s(t)] + [B_T(t) - T(t)b_T(t)] - [F(t) - T(t)V_1(t)k_1] \\
&\quad - [D_T(t) - T(t)\mu_1],
\end{aligned}$$

$$\varepsilon_2(t) = [F(t) - T(t)V_1(t)k_1] - [D_{T^*}(t) - T^*(t)\mu_2],$$

$$\begin{aligned}
\varepsilon_3(t) &= \left[\sum_{j=1}^{D_{T^*}(t)} M_j(t) - \omega(t)N(t)T^*(t)\mu_2\right] + [R(t) - V_1(t)h_1(t)] \\
&\quad - \left[D_{V_0}(t) - V_0(t)\mu_V\right],
\end{aligned}$$

$$\begin{aligned}
\varepsilon_4(t) &= \left\{\sum_{j=1}^{D_{T^*}(t)} [N_j(t) - M_j(t)] - [1 - \omega(t)]N(t)T^*(t)\mu_2\right\} \\
&\quad - [R(t) - V_1(t)h_1(t)] - [F(t) - T(t)V_1(t)k_1] - [D_{V_1}(t) - V_1(t)\mu_V].
\end{aligned}$$

Then, Eqs. (1)–(4) are equivalent to the following stochastic difference equations:

$$T(t+1) - T(t) = s(t) + [b_T(t) - \mu_1]T(t) - k_1 T(t)V_1(t) + \varepsilon_1(t), \tag{5}$$

$$T^*(t+1) - T^*(t) = k_1 V(t)T(t) - \mu_2 T^*(t) + \varepsilon_2(t), \tag{6}$$

$$V_0(t+1) - V_0(t) = \omega(t)\mu_2 N(t)T^*(t) + h_1(t)V_1(t) - \mu_V V_0(t) + \varepsilon_3(t), \tag{7}$$

$$\begin{aligned} V_1(t+1) - V_1(t) = {} & [1-\omega(t)]\mu_2 N(t)T^*(t) - k_1 V_1(t)T_1(t) - h_1(t)V_1(t) \\ & - \mu_V V_1(t) + \varepsilon_4(t). \end{aligned} \tag{8}$$

In Eqs. (5)–(9), given $X(t)$ the random noises $\varepsilon_j(t), j = 1,2,3,4$ have expectation zero. It follows that the expected value of $\boldsymbol{\varepsilon}(t)$ is $\mathbf{0}$. Using the basic formulas $\mathrm{Cov}(X,Y) = \mathrm{E}\{\mathrm{Cov}[(X,Y) \mid Z]\} + \mathrm{Cov}[\mathrm{E}(X \mid Z), \mathrm{E}(Y \mid Z)]$, it is also obvious that elements of $\boldsymbol{\varepsilon}(t)$ are uncorrelated with elements of $X(t)$ as well as with elements of $\boldsymbol{\varepsilon}(\tau)$ for all $t \neq \tau$. Further, because the random noises are basically linear combinations of binomial and multinomial random variables, the variances and covariances of elements of $\boldsymbol{\varepsilon}(t)$ can easily be derived. Because we need these variances and covariances in computing Kalman filter estimates, we give these variances and covariances in Appendix A.

3. A state space model for the HIV pathogenesis under treatment by anti-viral drugs

The state space model consists of a stochastic system model which is the stochastic model of the system and an observation model which is a statistical model based on some data to relate the observed data to the system. Thus, the state space model has significant advantages over both the stochastic model and the statistical model alone since it combines information from both models. For the state space model of the HIV pathogenesis under treatment by anti-viral drugs, the stochastic system model is the stochastic model given by the stochastic difference Eqs. (5)–(8) of Section 2.2. Let $Y(j)$ be the observed total number of RNA virus load at time t_j. Then the observation model based on RNA virus load is given by

$$Y(j) = V_0(t) + V_1(t) + e(j) = \underset{\sim}{H}^T(t)\underset{\sim}{X}(t) + e(j), \quad j = 1, \ldots, n, \tag{9}$$

where $H(t) = (0,0,1,1)^T$ and where $e(j)$ is the random error associated with measuring $Y(j)$. (If $\mathrm{CD4}^+$ T cell counts at different times are available, then the observation model will contain some additional equations involving observed $\mathrm{CD4}^+$ T cell counts.)

In Eq. (9), one may assume that $e(j)$ has expected value 0 and variance σ_j^2 and are uncorrelated with the random noises of Eqs. (5)–(8) of Section 2.2.

In the above state space model, the system model is nonlinear. Also, unlike the classical discrete-time Kalman filter model, the above model only has

observations at times $t_j, j = 1, \ldots, n$. (This is the so-called missing observations.) For non-linear models, the standard approach in the literature is to approximate non-linear functions by linear functions (see Refs. [13,14]). These are called the extended Kalman filters. In the above model, since the infection rate is very small, one would expect that this model can be closely approximated by an extended Kalman filter model. This has in fact been confirmed by some Monte Carlo studies given in Section 5; see also [15,16]. In this paper we will thus use the extended Kalman filter model to derive the estimates and the predicted numbers of the state variables $\{T(t), T^*(t), V_0(t), V_1(t)\}$. To handle the problem of missing observation, we will first derive Kalman filter models at time points $t_j, j = 0, 1, \ldots, n$ and then use the stochastic system model to derive results at time points where there are no observations. Since the extended Kalman filter is basically a linear Kalman filter, to obtain general theories for our model we will first derive results for discrete-time linear Kalman filter models. Then we will apply these results to the non-linear extended Kalman filter models.

To proceed, consider the state space model with stochastic system model given by Eq. (10) and with observation model given by Eq. (11), where $F(t+1, t)$ and $H(j)$ are non-stochastic transition matrices

$$\underset{\sim}{X}(t+1) = F(t+1, t)\underset{\sim}{X}(t) + \underset{\sim}{\epsilon}(t+1), \tag{10}$$

for $t = 0, 1, \ldots$ with $t_0 = 0$ and $t_{n+1} = \infty$;

$$\underset{\sim}{Y}(j) = H(j)\underset{\sim}{X}(t_j) + \underset{\sim}{e}(j), \quad j = 1, \ldots, n, \tag{11}$$

where $\mathrm{Cov}(\underset{\sim}{\epsilon}(t), \underset{\sim}{e}(j)) = 0$, $\mathrm{Cov}(\underset{\sim}{\epsilon}(t), \underset{\sim}{\epsilon}(\tau)) = \delta_{t\tau} V_X(t)$, $\mathrm{Cov}(\underset{\sim}{e}(j), \underset{\sim}{e}(u)) = \delta_{ju}\Sigma_j$, $\mathrm{Cov}(\underset{\sim}{\epsilon}(t), \underset{\sim}{X}(t)) = 0$ and $\mathrm{Cov}(\underset{\sim}{X}(t), \underset{\sim}{e}(j)) = 0$ with δ_{ju} being the Kronecker's δ.

In the extended Kalman filter model, the transition matrix $F(t+1, t)$ is then defined by the matrix of the first derivatives of the non-linear functions defining the stochastic system model. (In this paper we will use the notation $F(t \mid t_j)$ in the extended model as given in Theorems 3.3 and 3.4.)

Let $\hat{X}(t)$ be a predictor or estimator of $X(t)$ with residual $\hat{\epsilon}(t) = \hat{X}(t) - X(t)$. Define $\underset{\sim}{\hat{X}}(t)$ as an unbiased predictor or estimator of $X(t)$ if $\underset{\sim}{E}\hat{\epsilon}(t) = 0$. Suppose that $X(\underset{\sim}{0} \mid 0)$ is an unbiased estimator for $X(0)$ and that the covariance matrix of $\hat{\epsilon}(\underset{\sim}{0} \mid 0) = \hat{X}(0 \mid 0) - X(0)$ is $P(0 \mid 0)$. Then, starting with $\hat{X}(0 \mid 0)$, the following two subsections provide some optimal methods for estimating and predicting $\underset{\sim}{X}(t)$ for the state space model given by Eqs. (10) and (11).

3.1. Estimating $\underset{\sim}{X}(t)$ given data $D(j) = \{\underset{\sim}{Y}(u), u = 1, \ldots, j\}, t_j \leqslant t < t_{j+1}$

Let $\underset{\sim}{\hat{X}}(t \mid j)$ be a predictor (or estimator) of $\underset{\sim}{X}(t)$ given data $D(j)$ with residual $\underset{\sim}{\hat{\epsilon}}(t \mid j) = \underset{\sim}{\hat{X}}(t \mid j) - \underset{\sim}{X}(t)$. Denote the covariance matrix of $\underset{\sim}{\hat{\epsilon}}(t \mid j)$ by $\underset{\sim}{Q}(t \mid j)$.

To derive the optimal $\hat{X}(t \mid j)$, define $F(s,s) = I$ and $F(t,s) = \prod_{r=s}^{t-1} F(r+1,r)$ for $t > s$. Write $\hat{X}(t_j \mid \tilde{j}) = \hat{u}(j \mid j)$ and $Q(t_j \mid j) = P(j \mid j)$. Then, we have the following theorem which provides the optimal estimator and predictor of $X(t)$ given $D(j)$.

Theorem 3.1. *Starting with $\hat{u}(0 \mid 0)$ with $P(0 \mid 0)$ as the covariance matrix of $\hat{\epsilon}(0 \mid 0)$, if $t_j \leqslant t \leqslant t_{j+1}$, the linear, unbiased and minimum variance predictor (or estimator) of $X(t)$ given data $D(j)$ are given by the following recursive equations*:

(i) *For $t_j \leqslant t < t_{j+1}$, $j = 0, 1, \ldots, n (t_0 = 0, t_{n+1} = \infty)$,*

$$\hat{X}(t \mid j) = F(t, t_j)\hat{u}(j \mid j),$$

where $\hat{u}(j \mid j)$ is given in (iii).

(ii) *For $t_j \leqslant t < t_{j+1}$, $\quad j = 0, 1, \ldots, n$,*

$$Q(t \mid j) = F(t, t_j)P(j \mid j)F(t, t_j)^T + V_0(t, t_j),$$

where $P(j \mid j)$ is given in (iii) *and $V_0(t, t_j)$ is given by: $V_0(t, t_j) = 0$ if $t = t_j$ and*

$$V_0(t, t_j) = \sum_{r=t_j+1}^{t} F(t,r)V_X(r)F^T(t,r) \quad \text{if} \quad t > t_j.$$

(iii) *Denote by $\hat{X}(t_{j+1} \mid j) = \hat{u}(j+1 \mid j)$ and $Q(t_{j+1} \mid j) = P(j+1 \mid j)$. Then $\hat{u}(j+1 \mid j+1)$ and $P(j+1 \mid j+1)$ are given recursively by*

$$\hat{u}(j+1 \mid j+1) = \hat{u}(j+1 \mid j) + K_{j+1}\{Y(j+1) - H(j+1)\hat{u}(j+1 \mid j)\},$$

and

$$P(j+1 \mid j+1) = [I - K_{j+1}H(j+1)]P(j+1 \mid j),$$

where

$$K_{j+1} = P(j+1 \mid j)H(j+1)^T[H(j+1)P(j+1 \mid j)H^T(j+1) + \Sigma_{j+1}]^{-1}.$$

Proof. We give the proof in the Appendix B. Theorem 3.1 has been referred to in the literature as forward filtering.

3.2. Estimating $X(t)$ given $D(n) = \{Y(r), r = 1, \ldots, n\}, t \leqslant n$

Let $\hat{X}(t \mid n)$ denote an estimator of $X(t)$ given data $D(n)$. Let $Q(t \mid n)$ denote the covariance matrix of the residual $\epsilon(t \mid n) = \hat{X}(t \mid n) - X(t)$. Assume the same notation in Theorem 3.1. Then we have the following theorem providing the optimal estimator $\hat{X}(t \mid n)$ of $X(t)$ given data $D(n)$.

Theorem 3.2. *Starting with $\hat{X}(0 \mid 0) = \hat{u}(0 \mid 0)$ as an unbiased estimator of $X(0)$ with $P(0 \mid 0)$ as the covariance matrix of the residual $\hat{\epsilon}(0 \mid 0)$, if $t_j \leqslant t < t_{j+1}$ with*

$0 \leqslant j \leqslant n$, the linear, unbiased and minimum varianced estimators of $\underset{\sim}{X}(t)$ given data $D(n)$ are given by the following recursive equations:

(i) *For $t_j \leqslant t < t_{j+1}, j = 0, 1, \ldots, n$,*

$$\underset{\sim}{\hat{X}}(t \mid n) = F(t, t_j)\underset{\sim}{\hat{u}}(j \mid n),$$

where $\underset{\sim}{\hat{u}}(0 \mid n) = \underset{\sim}{\hat{u}}(0 \mid 0)$ and for $(1 \leqslant j \leqslant n), \underset{\sim}{\hat{u}}(j \mid n)$ is given in (iii).

(ii) *For $t_j \leqslant t < t_{j+1}, j = 0, 1, \ldots, n$*

$$Q(t \mid n) = F(t, t_j)P(j \mid n)F^T(t, t_j) + V_0(t, t_j),$$

where $P(0 \mid n) = P(0 \mid 0)$ and for $(1 \leqslant j \leqslant n), P(j \mid n)$ is given in (iii).

(iii) *For $j = 1, \ldots, n, \underset{\sim}{\hat{u}}(j \mid n)$ and $P(j \mid n)$ are given by the following recursive equations, respectively*:

$$\underset{\sim}{\hat{u}}(j \mid n) = \underset{\sim}{\hat{u}}(j \mid j) + A_j\{\underset{\sim}{\hat{u}}(j+1 \mid n) - \underset{\sim}{\hat{u}}(j+1 \mid j)\}$$

and

$$P(j \mid n) = P(j \mid j) - A_j\{P(j+1 \mid j) - P(j+1 \mid n)\}A_j^T,$$

where, with $R(j+1, j) = F(t_{j+1}, t_j)$,

$$A_j = P(j \mid j)R(j+1, j)^T P^{-1}(j+1 \mid j).$$

Proof. We give the proof in the Appendix B.

Theorem 3.2 has been referred to in the literature as the smoothing procedure. This has also been referred to as backward filtering.

Notice that results of the above theorems are basically results from linear least square methods. Hence, results of the above two theorems may be considered as extensions of the Gauss–Markov theorems in linear least square models.

To derive results for the state space model in Section 3, we write Eqs. (5)–(8) and Eq. (9), respectively, as

$$\underset{\sim}{X}(t+1) = \underset{\sim}{f}[\underset{\sim}{X}(t)] + \underset{\sim}{\epsilon}(t+1)$$

for $t = 0, 1, \ldots,$ and

$$Y(j) = \underset{\sim}{H}^T\underset{\sim}{X}(t_j) + e(j), \quad j = 1, \ldots, n,$$

where $\underset{\sim}{H} = (0, 0, 1, 1)^T$.

Given that the above state space model can be closely approximated by the extended Kalman filter model, then one may use the procedures given in Chapter 6 of Ref. [13] and Chapter 9 of Ref. [14] in connection with Theorems 3.1 and 3.2 to derive approximate optimal estimators of $\underset{\sim}{X}(t)$. The basic idea is to expand $\underset{\sim}{f}[\underset{\sim}{X}(t)]$ in Taylor series with respect to $\underset{\sim}{\hat{X}}(t \mid j)$ up to the first order and then take conditional expectation given data. Since the basic procedures are given in Refs. [13,14], we summarize without proof the results in the following two theorems.

Theorem 3.3. *Starting with* $\hat{\underset{\sim}{X}}(0 \mid 0) = \hat{\underset{\sim}{u}}(0 \mid 0)$ *with* $P(0 \mid 0)$, *if* $t_j \leqslant t$, *the linear, unbiased and minimum variianced predictors of* $\underset{\sim}{X}(t)$ *given data* $D(j)$ *are closely approximated by the following recursive equations*:

(i) *For* $t_j \leqslant t < t_{j+1}, j = 0, 1, \ldots, n$ $(t_0 = 0, t_{n+1} = \infty)$,

$$\hat{\underset{\sim}{X}}(t+1 \mid j) = \underset{\sim}{f}[\hat{\underset{\sim}{X}}(t \mid j)],$$

where $\hat{\underset{\sim}{X}}(t_j \mid j) = \hat{\underset{\sim}{u}}(j \mid j)$ *is given in* (iii).

(ii) *For* $t_j \leqslant t < t_{j+1}, j = 0, 1, \ldots, n$,

$$Q(t+1 \mid j) = F(t \mid t_j) Q(t \mid j) F(t \mid t_j)^T + V_0(t+1, t_j),$$

where $F(t \mid t_j) = (\frac{\partial}{\partial X^T} \underset{\sim}{f}(X))_{X = \hat{\underset{\sim}{X}}(t \mid j)}$ *with* $Q(t_j \mid j) = P(j \mid j)$ *being given in* (iii).

(iii) *Denote by* $\hat{\underset{\sim}{X}}(t_{j+1} \mid j) = \hat{\underset{\sim}{u}}(j+1 \mid j)$ *and* $Q(t_{j+1} \mid j) = P(j+1 \mid j)$. *Then* $\hat{\underset{\sim}{u}}(j+1 \mid j+1)$ *and* $\tilde{P}(j+1 \mid j+\tilde{1})$ *are given by the following recursive equations respectively*:

$$\hat{\underset{\sim}{u}}(j+1 \mid j+1) = \hat{\underset{\sim}{u}}(j+1 \mid j) + K_{j+1}\{Y(j+1) - h[\hat{\underset{\sim}{u}}(j+1 \mid j)]\},$$

and

$$P(j+1 \mid j+1) = [I - K_{j+1} \underset{\sim}{H}^T] P(j+1 \mid j),$$

and

$$K_{j+1} = P(j+1 \mid j) \underset{\sim}{H} [\underset{\sim}{H}^T P(j+1 \mid j) \underset{\sim}{H} + \sigma_{j+1}^2]^{-1}.$$

To implement the procedures in Theorems 3.1 and/or 3.3, one starts with $\hat{X}(0 \mid 0) = \hat{u}(0 \mid 0)$ and $P(0 \mid 0)$. Then by (i) and (ii) of the respective theorems, one derives $\hat{X}(t \mid 0)$ and $Q(t \mid 0)$ for $t_0 \leqslant t \leqslant t_1$ and derives $\hat{u}(1 \mid 1)$ and $P(1 \mid 1)$ by (iii) of the respective theorems. Repeating these procedures one may derive $\hat{X}(t \mid j)$ and $Q(t \mid j)$ for $t_j \leqslant t < t_{j+1}, j = 0, 1, \ldots, n$. These procedures are referred to as forward filtering procedures. Note that in implementing the procedures in Theorem 3.1, we will need the variances and covariances of the random noises as given in Section 2. For computing these estimates, we estimate the variances and the covariances by using formulas given in Section 2 with the means of the state variables being replaced by the one-step ahead prediction of these variables.

Theorem 3.4. *Starting with* $\hat{X}(0 \mid 0) = \hat{u}(0 \mid 0)$ with $P(0 \mid 0)$, *if* $t_j \leqslant t < t_{j+1}$ *with* $0 \leqslant j \leqslant n$, *the linear, unbiased and minimum varianced predictors of* $\underset{\sim}{X}(t)$ *given data* $D(n)$ *are given by the following recursive equations respectively*:

(i) *For* $t_j \leqslant t < t_{j+1}, j = 0, 1, \ldots, n$ *with* $t_0 = 0$ *and* $t_{n+1} = \infty$,

$$\hat{\underset{\sim}{X}}(t+1 \mid n) = \underset{\sim}{f}[\hat{\underset{\sim}{X}}(t \mid n)],$$

where $\hat{\underset{\sim}{u}}(0 \mid n) = \hat{\underset{\sim}{u}}(0 \mid 0)$ *and for* $1 \leqslant j \leqslant n, \hat{\underset{\sim}{X}}(t_j \mid n) = \hat{\underset{\sim}{u}}(j \mid n)$ *is given in* (iii).

(ii) *For* $t_j \leqslant t < t_{j+1}, j = 0, 1, \ldots, n$,

$$Q(t+1 \mid n) = F(t \mid t_j) Q(t \mid n) F(t \mid t_j)^T + V_0(t+1, t_j),$$

where $F(t \mid t_j) = (\frac{\partial}{\partial X^T} f(X))_{X=\hat{X}(t \mid n)}$ *and where* $Q(0 \mid n) = P(0 \mid 0)$ *and for* $1 \leqslant j \leqslant n, Q(t_j \mid n) = P(j \mid n)$ *is given in* (iii).

(iii) *For* $j = 1, \ldots, n, \hat{u}(j \mid n)$ *and* $P(j \mid n)$ *are given by the following recursive equations respectively*:

$$\hat{u}(j \mid n) = \hat{u}(j \mid j) + A_j\{\hat{u}(j+1 \mid n) - \hat{u}(j+1 \mid j)\}$$

and

$$P(j \mid n) = P(j \mid j) - A_j\{P(j+1 \mid j) - P(j+1 \mid n)\}A_j^T,$$

where, with $G(j+1, j) = F(t_{j+1} \mid t_j)$,

$$A_j = P(j \mid j) G(j+1, j)^T P^{-1}(j+1 \mid j)$$

and where $P(j \mid j)$ *and* $P(j+1 \mid j)$ *are given in Theorem* 3.3.

To implement the procedures in Theorems 3.2 or 3.4 to derive $\hat{X}(t \mid n)$ for $t_j \leqslant t < t_{j+1}$, one first derive $\hat{X}(t \mid j)$ for $t_j \leqslant t$ by using formulas in Theorem 3.1 or Theorem 3.3 (forward filtering). Then one goes backward from n to 1 to derive the estimates given data D(n) for $t_j \leqslant t < t_{j+1}$ by using formulas in Theorem 3.2 or Theorem 3.4. These are the backward filtering procedures.

4. An illustrative example

To illustrate the application of the model in Section 3, we consider the study by Perelson et al. [1]. In this study, Ritonavir (a protease inhibitor) has been applied to five HIV-infected individuals at 15 times in two weeks. In Section 2, we have extended the deterministic model of Perelson et al. [1] into a stochastic model. ($h_1(t) = 0$ corresponds to the model under treatment by protease inhibitors.) Since the data in Perelson et al. [1] are the RNA virus load at different times, the state space model based on the observed RNA virus load in Section 3 is then applicable to the data sets in [1].

Given in Table 1 are the data sets from patient Nos. 104, 105 and 107 extrapolated from Fig. 1 of [1]. (Since we do not have the actual data, we can only extrapolate the data from the published figures in [1].) Further, $\{V_0(0) = 0, V_1(0) = 9.8 \times 10^4/\text{mm}^3, T(0) + T^*(0) = 2/\text{mm}^3\}$ for patient No. 104, $\{V_0 = 0, V_1(0) = 6.43 \times 10^5/\text{mm}^3, T(0) + T^*(0) = 11/\text{mm}^3\}$ for patient No. 105 and $\{V_0 = 0, V_1(0) = 7.7 \times 10^4/\text{mm}^3, T(0) + T^*(0) = 412/\text{mm}^3\}$ for patient No. 107. Thus, under steady-state condition, one has the basic relationship $k_1 T(0) V_1(0) = T^*(0)\mu_2 = (2 - T(0))\mu_2$ for patient No. 104, $k_1 T(0) V_1(0) = T^*(0)\mu_2 = (11 - T(0))\mu_2$ for patient No. 105 and $k_1 T(0) V_1(0) = T^*(0)\mu_2 = (412 - T(0))\mu_2$ for patient No. 107. The estimates of the parameters for these

Table 1
Number of observed RNA virus copies per mm^3 for patient Nos. 104, 105 and 107

Time (h)	Patient 104	Patient 105	Patient 107
0	52000	643000	77000
2	94000	1000000	250000
4	180000	2200000	300000
6	175000	1000000	240000
12	110000	2200000	250000
18	110000	1800000	190000
24	100000	3000000	200000
30	110000	2200000	190000
36	57000	1200000	130000
42	60000	1000000	140000
48	55000	900000	150000
72	34000	700000	52000
96	22000	500000	48000
120	20000	250000	28000
144	18000	150000	14000
168	3000	480000	9800

patients are given in Table 2. In Table 2, s was estimated by $s = \mu_1 \times 10^3$ since there are approximately 10^3 normal $CD4^+$ T cells per mm^3 of blood and there are no proliferation and no HIV infection in the absence of HIV and other stimulation and since $T(t+1) - T(t) \simeq 0$ under steady state condition; the parameters values of $\{\mu_i, i = 1, 2, \mu_V\}$ were taken from Refs. [1,3,5] whereas the estimates of the parameters $\{\gamma, k_1, \omega, \theta, N_0\}$ were derived by applying nonlinear optimal procedures from programs in IMSL as in Refs. [12,15].

Given in Fig. 1 are the fitted curves for patient Nos. 104, 105 and 107. Given in Fig. 2 are the curves of the estimated numbers of un-infected T cells and actively infected T cells for these patients. Given in Fig. 3 are the curves of the estimated total numbers of infectious free HIV and non-infectious free HIV for these patients.

From Figs. 1–3, the following results have been observed:(i) From Fig. 1, it appeared that the Kalman filter estimates fitted to the observed data much better than the estimates by the deterministic model which is obtained by ignoring the random noises in the system model. The Kalman filter estimates of the total numbers of HIV have traced the observed numbers closely; on the other hand, the estimated numbers by the deterministic model appeared to draw a smooth line across the observed numbers. Thus, while results from the deterministic model are useful to study the trend and behavior of the HIV epidemic, it can not trace the ups and downs of the observed numbers, presumably due to random disturbances.

(ii) From Fig. 3, we observed that for the infectious HIV, there were little differences between Kalman filter estimates and estimates by the deterministic

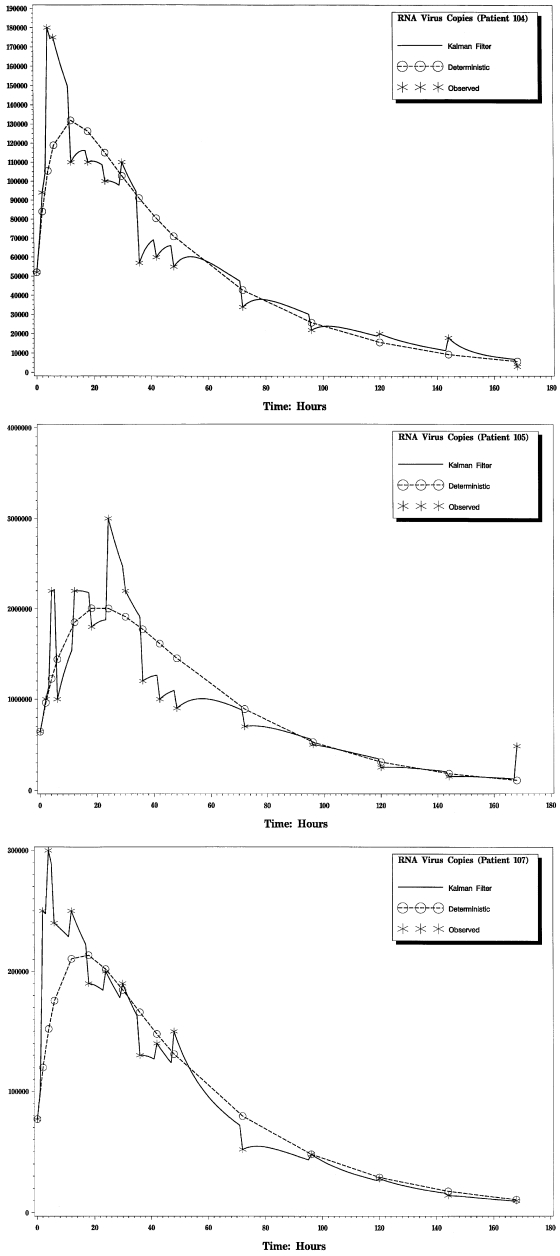

Fig. 1. Plots showing the observed number of RNA virus copies, the Kalman filter estimates and the estimates by the deterministic model for patient Nos. 104, 105 and 107.

Table 2
Estimates of parameters for patient Nos. 104, 105 and 107

Parameters (unit)	Patient 104	Patient 105	Patient 107
μ_1(/day)	2.0E−2	2.0E−2	2.0E−2
μ_2(/day)	0.5000	0.5000	0.5000
μ_V(/day)	3.6792	2.0600	3.0889
N_0	618373	1859755	35170
k_1(/day/mm^3)	5.1989E−5	0.7922E−6	0.7922E−6
γ(/day)	2.3757E−2	0.2431E−2	0.2400E−2
ω	0.91706	1.0000	1.0000
s(/day/mm^3)	20	20	20
θ(/day/mm^3)	0.4571E−3	0.6846E−2	0.9076E−1

model, presumably due to the relative smaller numbers. On the other hand, for the non-infectious HIV, there appeared to have significant differences between the Kalman filter estimates and the estimates by the deterministic model, especially before 60 h since treatment began. It appeared that for patient No. 104, the Kalman filter estimates were considerably larger than the corresponding estimates by the deterministic model before 10 h since treatment, but the opposite is true during the period 15–50 h since treatment. On the other hand, for patient No. 107, the Kalman filter estimates are considerably larger than the corresponding estimates by the deterministic model before 20 h since treatment. Thus, for patient Nos. 104 and 107, the Kalman filter estimates have revealed a much stronger effect of treatment within the first 10 and 20 h respectively. Note that for all patients, the curve of the Kalman filter estimates of non-infectious HIV appeared to be consistent with the pattern of the total actually observed numbers of HIV as revealed in Fig. 1.

5. Some Monte Carlo studies

To justify and confirm the usefulness of the extended Kalman filter method for the state space model in Section 3, in this section we generate some Monte Carlo studies through computer by using the model in Sections 2 and 3. The parameters of this model were taken from those of the estimates of patient No. 104 given in Table 2 but with $T(0) + T^*(0) = 20/\text{mm}^3$ and $T(0) = 1/\text{mm}^3$.

To generate the numbers of T cells, T^* cells, V_0 free HIV and V_1 free HIV by computer for the model in Section 2, we use the distribution theories given in Section 2. Thus, we use a point binomial generator with means $s(t)$ to generate $S(t)$ and use a binomial generator to generate $D_2(t)$ by assuming $D_2(t) \sim B[T^*(t); \mu_2]$ for given $T^*(t)$. Given $\{T(t), V_0(t), V_1(t)\}$, we generate $[B_T(t), D_T(t)]$ from the multinomial distribution, Mult $[T(t); b_T(t), \mu_1]$, where $b_T(t) =$

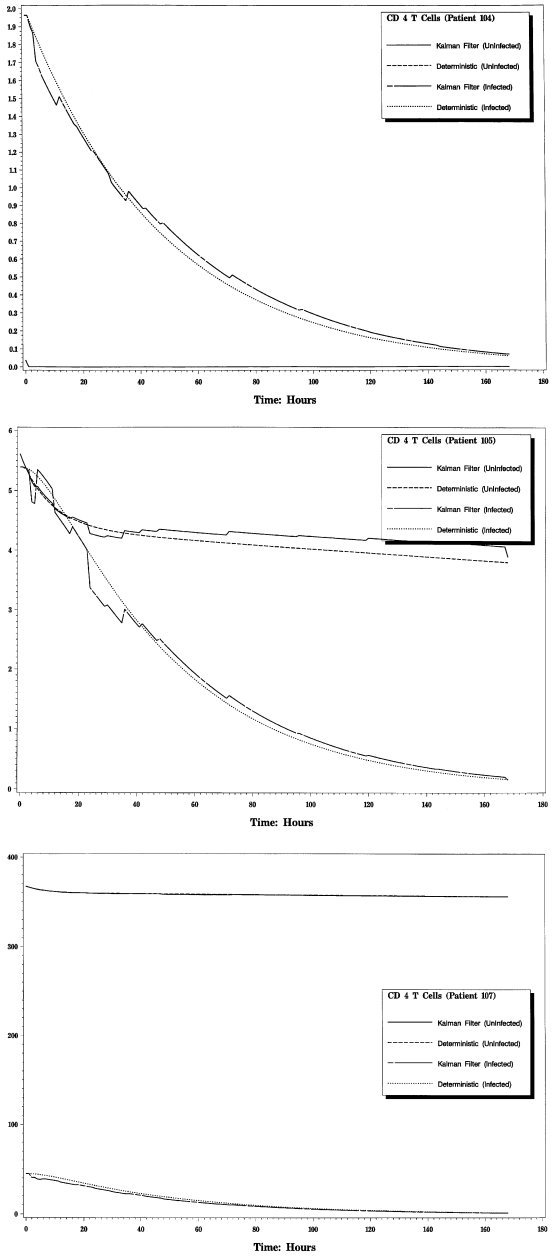

Fig. 2. Plots showing the Kalman filter estimates of the uninfected as well as infected CD4 *T* cells and the estimates of these cells by the deterministic model for patient Nos. 104, 105 and 107.

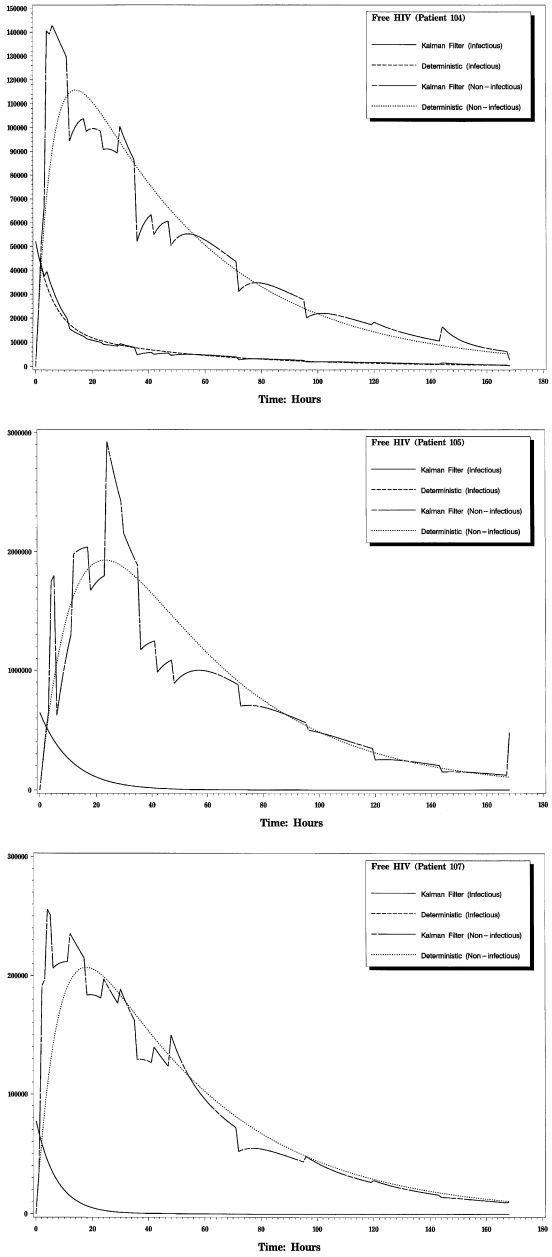

Fig. 3. Plots showing the Kalman filter estimates of the infectious and non-infectious free HIV and the estimates by the deterministic model for the patient Nos. 104, 105 and 107.

$\gamma V(t)/[\theta_V + V(t)]$ with $V(t) = V_0(t) + V_1(t)$; given $\{V_1(t), T(t)\}$, we generate $[F(t), D_{V1}(t)]$ from the multinomial distribution, Mult$[V_1(t); k_1 T(t), \mu_V]$. Similarly, given $V_0(t), D_{V_0}(t)$ is generated from the binomial distribution, $B[V_0(t); \mu_V]$. Then Eqs. (1)–(4) were used to generate $T(t+1), T^*(t+1), V_1(t+1)$ and $V_0(t+1)$ from $X(t)$. For generating these random variables, all the random generators are taken from the IMSL [18] library functions. The time unit for generating these random numbers is one h.

To generate the observation model, we add some Gaussian noises to the total number of the generated free HIV to produce $Y(j) = Y(t_j)$. That is, we generate $Y(t_j)$ by the equation

$$Y(j) = V(t_j) + e(j), \tag{12}$$

where the $V(t_j)$s are generated as given above and $e(j)$ is assumed as a Gaussian variable with mean 0 and variance $\sigma_j^2 = V(t_j)\sigma^2$ with $\sigma^2 = 4$.

Given the above setup with the parameter values in Table 2, one can readily generate the observed $Y(j) = Y(t_j)$s. Given in Table 3 are one set of the generated $Y(j)$s. We have repeated the experiments 200 times. We now illustrate the results with the generated data in Table 3. Similar results have been obtained by using other generated data sets.

Given in Table 4 are the generated numbers and the corresponding Kalman filter estimates of the T cells, $T^{(*)}$ cells and free V_1. Given in Fig. 4 are the plots of the generated numbers of the non-infectious free HIV (i.e V_0) and the corresponding Kalman filter estimates. To illustrate the usefulness of the state space model and the impacts of ignoring the observation model, we have also given the estimates by the deterministic model in Table 4 and plotted the curves of the deterministic model in Fig. 4 along with the Kalman filter estimates and the generated numbers. From these Monte Carlo studies, we have observed the following results:

(1) In the estimation of the numbers of T cells, T^* cells, V_0 free HIV and V_1 free HIV, the estimates by the extended Kalman filter method appear to trace the generated numbers very closely. These results suggest that in estimating

Table 3
Computer generated total numbers of HIV at 16 time points

Time (h)	RNA copies mm^3	Time (h)	RNA Copies mm^3
0	52000	36	95320
2	79742	42	77322
4	94515	48	74642
6	124585	72	45710
12	148138	96	22906
18	131254	120	14273
24	111024	144	10726
30	99262	168	5155

Table 4
The generated numbers of T, $T^{(*)}$, V_1 and the corresponding Kalman filter estimates and the estimates by the deterministic model

t	Infectious HIV				Infectious HIV			
	(1)	(2)	(3)	(4)	(1)	(2)	(3)	(4)
0	3.632E − 01	3.632E − 01	3.632E − 01	3.632E − 01	1.964E + 01	1.964E + 01	1.964E + 01	1.964E + 01
2	4.291E − 03	4.079E − 03	4.549E − 03	2.812E − 03	1.960E + 01	1.960E + 01	1.934E + 01	1.926E + 01
4	3.044E − 04	2.481E − 04	3.057E − 04	1.585E − 04	1.840E + 01	1.843E + 01	1.869E + 01	1.847E + 01
6	4.720E − 05	3.583E − 05	5.208E − 05	2.527E − 05	1.742E + 01	1.743E + 01	1.769E + 01	1.771E + 01
12	1.781E − 06	1.231E − 06	2.121E − 06	1.112E − 06	1.509E + 01	1.516E + 01	1.529E + 01	1.561E + 01
18	3.550E − 07	1.772E − 07	2.995E − 07	2.080E − 07	1.370E + 01	1.372E + 01	1.346E + 01	1.375E + 01
24	1.333E − 07	6.542E − 08	6.922E − 08	6.987E − 08	1.212E + 01	1.213E + 01	1.195E + 01	1.212E + 01
30	9.977E − 08	2.673E − 08	1.807E − 08	3.236E − 08	1.087E + 01	1.086E + 01	1.057E + 01	1.068E + 01
36	7.526E − 08	1.770E − 08	6.311E − 09	1.876E − 08	9.656E + 00	9.542E + 00	9.194E + 00	9.416E + 00
42	4.092E − 08	1.099E − 08	0.000E + 00	1.306E − 08	8.545E + 00	8.476E + 00	8.169E + 00	8.298E + 00
48	3.286E − 08	5.216E − 09	2.980E − 09	1.065E − 08	7.790E + 00	7.657E + 00	7.094E + 00	7.314E + 00
72	2.281E − 08	1.216E − 08	3.343E − 09	1.404E − 08	4.577E + 00	4.570E + 00	4.198E + 00	4.412E + 00
96	4.527E − 08	3.352E − 08	0.000E + 00	4.220E − 08	2.621E + 00	2.766E + 00	2.556E + 00	2.662E + 00
120	1.866E − 07	7.063E − 09	0.000E + 00	1.738E − 07	1.721E + 00	1.707E + 00	1.547E + 00	1.606E + 00
144	8.584E − 07	5.186E − 08	3.410E − 07	8.705E − 07	1.011E + 00	1.036E + 00	9.249E − 01	9.691E − 01
168	3.395E − 06	2.044E − 07	0.000E + 00	5.036E − 06	6.467E − 01	6.318E − 01	5.589E − 01	5.847E − 01
t	Infectious HIV				Uninfectious HIV			
	(1)	(2)	(3)	(4)	(1)	(2)	(3)	(4)
0	5.200E + 04	5.200E + 04	5.200E + 04	5.200E + 04	0.000E + 00	0.000E + 00	0.000E + 00	0.000E + 00
2	4.064E + 04	3.963E + 04	4.079E + 04	4.115E + 04	2.482E + 04	2.602E + 04	3.882E + 04	4.284E + 04
4	3.198E + 04	3.399E + 04	3.232E + 04	3.326E + 04	8.259E + 04	8.034E + 04	6.193E + 04	7.226E + 04
6	2.791E + 04	2.909E + 04	2.791E + 04	2.744E + 04	1.112E + 05	1.098E + 05	9.683E + 04	9.164E + 04
12	1.651E + 04	1.871E + 04	1.876E + 04	1.743E + 04	1.312E + 05	1.288E + 05	1.294E + 05	1.147E + 05
18	1.111E + 04	1.177E + 04	1.331E + 04	1.288E + 04	1.020E + 05	1.014E + 05	1.184E + 05	1.136E + 05
24	9.109E + 03	9.867E + 03	1.011E + 04	1.043E + 04	9.905E + 04	9.851E + 04	1.012E + 05	1.048E + 05

Table 4 (Continued)

t	Infectious HIV				Infectious HIV			
	(1)	(2)	(3)	(4)	(1)	(2)	(3)	(4)
30	5.864E + 03	7.978E + 03	8.519E + 03	8.858E + 03	8.632E + 04	8.431E + 04	9.029E + 04	9.404E + 04
36	7.221E + 03	7.546E + 03	8.005E + 03	7.682E + 03	8.228E + 04	8.200E + 04	8.708E + 04	8.350E + 04
42	5.706E + 03	6.454E + 03	6.481E + 03	6.725E + 03	7.159E + 04	7.084E + 04	7.113E + 04	7.383E + 04
48	4.547E + 03	5.098E + 03	6.213E + 03	5.910E + 03	5.671E + 04	5.617E + 04	6.850E + 04	6.515E + 04
72	4.478E + 03	3.910E + 03	3.802E + 03	3.559E + 03	4.266E + 04	4.322E + 04	4.203E + 04	3.934E + 04
96	2.315E + 03	2.173E + 03	1.910E + 03	2.147E + 03	2.378E + 04	2.402E + 04	2.111E + 04	2.374E + 04
120	1.088E + 03	9.848E + 02	1.193E + 03	1.295E + 03	1.081E + 04	1.089E + 04	1.319E + 04	1.432E + 04
144	6.750E + 02	7.434E + 02	8.754E + 02	7.815E + 02	8.280E + 03	8.220E + 03	9.679E + 03	8.641E + 03
168	4.165E + 02	3.526E + 02	4.327E + 02	4.715E + 02	3.879E + 03	3.899E + 03	4.785E + 03	5.213E + 03

(1) = generated number, (2) = extended Kalman filter estimates, (3) = quadratic Kalman filter estimates, (4) = deterministic model.

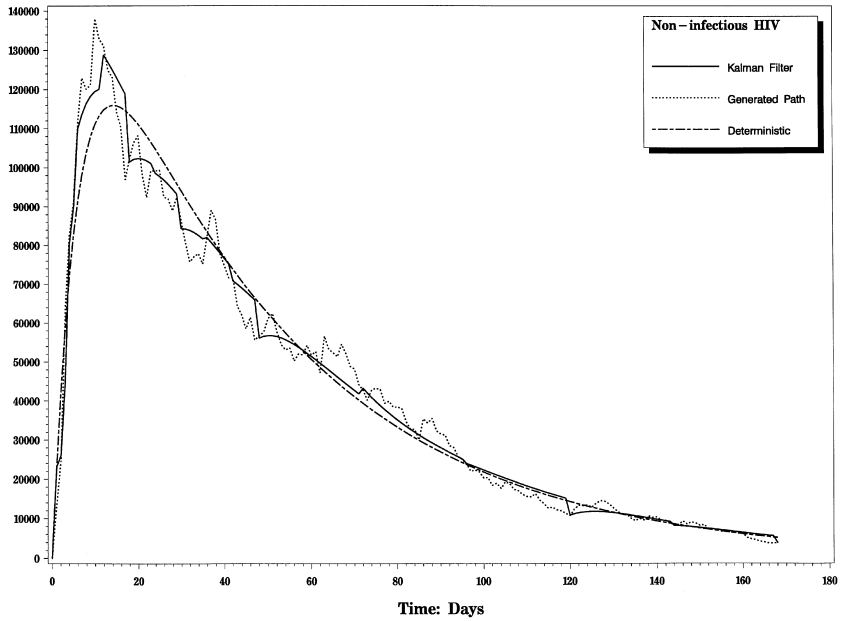

Fig. 4. Plots showing the generated numbers of non-infectious free HIV, the corresponding Kalman filter estimates and the estimates by the deterministic model.

these numbers, one may in fact use the extended Kalman filter method as described in Section 3. Similar results have also been obtained by Tan and Xiang [16] in other models of similar nature.

(2) As shown in Table 4 and in Fig. 4, the estimates by using the deterministic model seem to draw a smooth line across the generated numbers. Thus, although results of deterministic model cannot trace the ups and downs of the generated numbers presumably due to the randomness of the state variables, they are still quite useful in assessing the behaviour and trend of the process. This result appears to be a logical consequence of two interacting factors: (a) Since the numbers of the T^* cells and free HIV are quite small in the early stage, randomness of the state variables would have an important impacts on the process, and (b) The solutions of deterministic differential equations are usually smooth and are continuous functions of time. These results suggest that in estimating the numbers of T cells and free HIV, it is important to adopt the stochastic model and the state space model.

(3) As shown in Table 4 and Fig. 4, for the numbers of T cells and V_1 free HIV, there are little differences between the Kalman filter estimates and the estimates by the deterministic model, presumably due to the small numbers of these cells. For the non-infectious free HIV (i.e. V_0), however, there are significant differences between the Kalman filter estimates and the estimates by

using the deterministic model. It appears that the Kalman filter estimates have revealed a much strong effects of the treatment at early times (before 10 h) which could not be detected by deterministic model.

6. Conclusions and discussion

In this paper we have developed a state space model for the HIV pathogenesis at the cellular level under treatment by anti-viral drugs in HIV-infected individuals. In this state space model, the stochastic system model is the stochastic model of HIV pathogenesis which is an extension of the deterministic model of Perelson et al. [1] whereas the observation model is a statistical model based on the numbers of RNA virus copies per unit volume of blood measured at different times. Because the state space model combines information from both the stochastic model and the statistic model, it is advantageous over both of these models alone in many aspects. Comparing with the stochastic model, the state space model not only takes into account the basic biological mechanism of the process as does the stochastic model but also make full use of available data to validate and upgrade the stochastic model. Comparing with the statistic model, the statistical model based on RNA virus copies at different times does not take into account the dynamic aspects of the epidemic process and can only be used to monitor the trend and changes of the total number of free HIV over the time course; it can not monitor the trend and the changes of different types of free HIV (infectious and non-infectious free HIV) and if data on CD4 T cell counts are not available, it also can not monitor the trend and changes of the numbers of CD4 T cells. On the other hand, the state space model can be used not only to monitor the trend and changes of the total number of free HIV over the time course, but also the numbers of infectious and non-infectious free HIV as well as the numbers of the uninfected T cells and actively infected T cells over the time course. This latter result is especially important since under treatment by anti-viral drugs a large number of free HIV are non-infectious [7].

The state space model we have developed in Section 3 is a nonlinear model with missing observations. General theories for such models are still non-existent. We note, however, that since the HIV infection rates are usually very small, the model of Section 3 can be closely approximated by an extended Kalman filter model. (The closeness of this approximation has been confirmed by some Monte Carlo studies in Section 5.) By using the extended Kalman filter as an approximation, in this paper we have thus developed some optimal procedures to estimate the numbers of different T cells and the numbers of non-infectious free HIV and infectious free HIV over the time course.

To illustrate the application of the state space model given in Section 3, we have applied the model to the data sets of three patients given in Ref. [1] under

treatment by a protease inhibitor. The numbers of RNA virus copies per unit volume of blood of these patients have been taken at 15 occasions within two weeks. By using these data sets we have developed a state space model for each of these patients and have obtained Kalman filter estimates of the numbers of non-infectious free HIV and infectious free HIV as well as the numbers of different types of T cells over the time course. Our Kalman filter estimates showed clearly that within two weeks most of the free HIV are non-infectious. Further, there are significant differences between the Kalman filter estimates and the estimates by the deterministic model within the first 10 h for patient No. 104 and within the first 20 h for patient No. 107. It appeared that for patient No. 104 within the first 10 h and for patient No. 107 within 20 h, the Kalman filter estimates of the number of non-infectious free HIV are considerably greater than the corresponding estimates by the deterministic model. This is equivalent to saying that the Kalman filter estimates have revealed a much stronger effect of the treatment for patient No. 104 within the first 10 hours and for patient No. 107 within the first 20 h than that by the deterministic model.

By using the stochastic model in Section 2 and the state space model in Section 3, in this paper we have also generated some Monte Carlo studies to assess the efficiency and usefulness of the extended Kalman filter methods. Our numerical results have shown clearly that the estimates by the extended Kalman filter method can trace the generated numbers very closely in most of the cases. These results suggest that the extended Kalman filter estimates would provide very close approximation to the true numbers, presumably due to the fact that the HIV infection rate is usually very small. On the other hand, results by the deterministic model appears to draw a smooth line across the generated numbers, suggesting that there are significant differences between results of state space model and results of deterministic model. It is to be noted, however, results of deterministic models are still useful in monitoring the trend and behavior of the HIV epidemic process.

From the above analysis, it is obvious that the state space models as given in Section 3 are useful for monitoring the dynamic behavior of the HIV process at the cellular level under treatment by anti-viral drugs in HIV-infected individuals and for assessing the efficiencies and usefulness of the treatment. By applying the method of machine learning to the estimates of the numbers of non-infectious free HIV and infectious free HIV as well as the numbers of actively infected CD4 T cells, it may also be possible to develop some optimal treatment protocols through state space models; see Ref. [19]. This, of course, would require further extensive research. To make the model more useful, it is also necessary to extend the model to more general situations involving the development of drug resistance of HIV to these drugs. Further work in this direction and other extensions are definitely needed.

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Appendix A. The variances and covariances of the random noises

$$
\begin{aligned}
Q_{11}(t) &= \mathrm{VAR}[\varepsilon_1(t)] \\
&= \mathrm{E}\{q_{TP}(t)[1-q_{TP}(t)] + [q_{T2}(t)+q_{T0}(t)]q_{T1}(t)T(t) \\
&\quad + q_{VI}(t)[1-q_{VI}(t)]V_1(t)\},
\end{aligned}
$$

$$
Q_{12}(t) = \mathrm{COV}[\varepsilon_1(t),\varepsilon_2(t)] = -q_{VI}(t)[1-q_{VI}(t)]\mathrm{E}[V_1(t)],
$$

$$
Q_{13}(t) = \mathrm{COV}[\varepsilon_1(t),\varepsilon_3(t)] = 0,
$$

$$
Q_{14}(t) = \mathrm{COV}[\varepsilon_1(t),\varepsilon_4(t)] = q_{VI}(t)[1-q_{VI}(t)]\mathrm{E}[V_1(t)],
$$

$$
Q_{22}(t) = \mathrm{VAR}[\varepsilon_2(t)] = \mathrm{E}\{q_{VI}(t)[1-q_{VI}(t)]V_1(t) + \mu_2[1-\mu_2]T^*(t)\},
$$

$$
Q_{23}(t) = \mathrm{COV}[\varepsilon_2(t),\varepsilon_3(t)] = -\omega(t)\mu_2[1-\mu_2]N(t)\mathrm{E}T^*(t),
$$

$$
Q_{24}(t) = \mathrm{COV}[\varepsilon_2(t),\varepsilon_4(t)] = [1-\omega(t)]\mu_2[1-\mu_2]N(t)\mathrm{E}T^*(t),
$$

$$
\begin{aligned}
Q_{33}(t) &= \mathrm{VAR}[\varepsilon_3(t)] \\
&= \omega(t)\{[1-\omega(t)]N(t) + \omega(t)[\sigma_N^2(t) + (N(t))^2]\}\mu_2[1-\mu_2]\mathrm{E}T^*(t) \\
&\quad + \mathrm{E}\{h_1(t)[1-h_1(t)]V_1(t) + \mu_V[1-\mu_V]V_0(t)\},
\end{aligned}
$$

$$
\begin{aligned}
Q_{34}(t) &= \mathrm{COV}[\varepsilon_3(t),\varepsilon_4(t)] \\
&= \omega(t)[1-\omega(t)]\{(N(t))^2 + \sigma_N^2(t) - N(t)\}\mu_2[1-\mu_2]\mathrm{E}T^*(t) \\
&\quad - h_1(t)[1-h_1(t)]\mathrm{E}V_1(t),
\end{aligned}
$$

$$
\begin{aligned}
Q_{44}(t) &= \mathrm{VAR}[\varepsilon_4(t)] \\
&= \mathrm{E}\{[\mu_V(1-\mu_V) + h_1(t)(1-h_1(t)) + q_{VI}(t)(1-q_{VI}(t))]V_1(t)\} \\
&\quad + [1-\omega(t)]\{N(t)\omega(t) + [1-\omega(t)][\sigma_N^2(t) \\
&\quad + (N(t))^2]\}\mu_2[1-\mu_2]\mathrm{E}T^*(t),
\end{aligned}
$$

Appendix B. Proof of Theorems 3.1 and 3.2

In Theorems 3.1 and 3.2 the basic idea is that at the time points $t = t_j$ $(j = 0, 1, \ldots, n)$, we reduce the model into a standard discrete-time linear Kalman filter model and then apply results available from the literature [13,14,17]; for time t in $t_j < t < t_{j+1}$, since observed data are not available, we use stochastic system equations and take conditional expectations on the given data. These are the basic procedures we use to prove these theorems.

To proceed, let $\underset{\sim}{\epsilon}_j(t) = \Sigma_{r=t_j+1}^{t} F(t,r)\underset{\sim}{\epsilon}(r)$ for $t > t_j$. (As a conventional notation, $\Sigma_{r=t_j+1}^{t_j}$ is defined as 0 or zero vector.) Then, $\mathrm{E}\,\underset{\sim}{\epsilon}_j(t) = \underset{\sim}{0}$ and the covariance matrix of $\underset{\sim}{\epsilon}_j(t)$ is $V_0(t,t_j)$ as given in Theorem 3.1. For $t_j \leqslant t \leqslant t_{j+1}$, from Eq. (10) we obtain

$$\underset{\sim}{X}(t) = F(t,t-1)\underset{\sim}{X}(t-1) + \underset{\sim}{\epsilon}(t) = \ldots = F(t,t_j)\underset{\sim}{X}(t_j) + \underset{\sim}{\epsilon}_j(t) \tag{B.1}$$

Put $\underset{\sim}{X}(t_j) = \underset{\sim}{u}(j), R(j+1,j) = F(t_{j+1},t_j)$ and $\underset{\sim}{\epsilon}_j(t_{j+1}) = \underset{\sim}{\zeta}(j+1)$.

Then $$\underset{\sim}{u}(j+1) = R(j+1,j)\underset{\sim}{u}(j) + \underset{\sim}{\zeta}(j+1). \tag{B.2}$$

Obviously, $E\zeta(j+1) = 0$ and the covariance matrix of $\underset{\sim}{\zeta}(j+1)$ is $V_0(t_{j+1},t_j) = V_u(j+1)$. Further, the $\underset{\sim}{\zeta}(t+1)$'s are uncorrelated with $\underset{\sim}{e}(j)$ for all t and j. Combining with the following observation equation, we have then a discrete-time linear Kalman filter model as given in standard texts such as Refs. [13,14] and [17]

$$\underset{\sim}{Y}_{j+1} = H(j+1)\underset{\sim}{u}(j+1) + \underset{\sim}{e}(j+1). \tag{B.3}$$

Part (iii) of Theorems 3.1 and 3.2 then follow from basic results as given in the literature [13,14,17].

To prove (i) and (ii) of Theorems 3.1 and 3.2, for $t_j \leqslant t \leqslant t_{j+1}$, write $X(t)$ as a linear function of $X(t_j)$ as given in Eq. (B.1). Then the residual $\underset{\sim}{\hat{\epsilon}}(t \mid j) = \underset{\sim}{\hat{X}}(t \mid j) - X(t)$ can be expressed as

$$\underset{\sim}{\hat{\epsilon}}(t \mid j) = F(t,t_j)\,\underset{\sim}{\hat{\epsilon}}_u(j \mid j) - \underset{\sim}{\epsilon}_j(t),$$

where $\underset{\sim}{\hat{\epsilon}}_u = \underset{\sim}{\hat{u}}(j \mid j) - \underset{\sim}{u}(j)$.

Obviously, the covariance matrix of $\underset{\sim}{\hat{\epsilon}}(t \mid j)$ is $Q(t \mid t_j) = F(t,t_j)P(j \mid j)F(t,t_j)^T + V_0(t,t_j)$ as given in (ii) of Theorem 3.1. Similarly one proves (ii) of Theorem 3.2.

To prove (i) of Theorem 3.1, let $\underset{\sim}{\hat{X}}^*(t \mid j)$ be a linear unbiased predictor of $X(t)$ given data $D(j)$, where $t_j < t < t_{j+1}$. Then, by Eq. (B.1), $\underset{\sim}{\hat{X}}^*(t \mid j) = F(t,t_j)\,\underset{\sim}{\hat{u}}^*(j \mid j)$, where $\underset{\sim}{\hat{u}}^*(j \mid j)$ is an unbiased estimator of $\underset{\sim}{X}(t_j) = \underset{\sim}{u}(j)$ and is a linear function of elements of $D(j)$. Let $Q^*(t \mid j)$ be the covariance matrix of $\underset{\sim}{\hat{\epsilon}}^*(t \mid j) = \underset{\sim}{\hat{X}}^*(t \mid j) - \underset{\sim}{X}(t)$ and $P^*(j \mid j)$ the covariance matrix of $\underset{\sim}{\hat{\epsilon}}_u(j \mid j)$. Then,

$$Q^*(t \mid j) = F(t, t_j)P^*(j \mid j)F^T(t, t_j) + V_0(t, t_j).$$

But by (iii) of Theorem 3.1, $P^*(j \mid j) - P(j \mid j)$ is positive semi-definite. It follows that $Q^*(t \mid j) - Q(t, t_j) = F(t, t_j)\{P^*(j \mid j) - P(j \mid j)\}F^T(t, t_j)$ is positive semi-definite. This proves (i) of Theorem 3.1. Similarly one proves (i) of Theorem 3.2.

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