Evolució de la càrrega viral després del tractament. Caiguda bifàsica.

1. Decay characteristics of HIV-1-infected compartments during combination therapy.
   Perelson et al. (1997) Nature
2. Mixed-effects state space models for analysis of longitudinal dynamic systems.
   Liu et al. (2011) Biometrics

Nuria Perez
GRASS, 13 November 2013

Evolució de la càrrega viral després del tractament. Caiguda bifàsica. Decay characteristics of HIV-1-infected compartments during combination therapy. Perelson et al. (1997)

Classical reference

OUTLINE

1 CLINICAL VOCABULARY

Defines the clinical background concepts required to understand the paper

2 METHODOLOGICAL CONCEPTS

Describes several methodological terms needed for the paper understanding

3 THE PAPER ITSELF

Explains the scientific content of the paper

4 REFERENCES

The paper reviewed and other materials that were used

1 CLINICAL VOCABULARY

- HIV-1: Human immunodeficiency virus type 1
- Used as synonymous:
    - Concentrations of HIV-1 in blood plasma
    - HIV-1 RNA concentration in plasma
    - Viral load
    - Plasma viremia
- Peripheral blood mononuclear cells (PBMC)
- Antiretroviral regimen
- Drug resistant virus // Drug resistance

HIV infection markers

- Viral Load (copies/ml)
- CD4 lymphocyte count or $CD4^+$ T-cell count (cells/µl)
- Proviral copy number per 10^6 CD4+T lymfocytes
- What’s desirable:
  - Low values of Viral Load
  - High values of CD4 cells

2 METHODOLOGICAL CONCEPTS:

Non-linear least squares regression

- we measure some observable φ as a function of some independent variable, *x*,
  we have some theoretical function that we expect the observations to obey.
  The function may have parameters in it that we need to determine.
  The process of determining the best values of the parameters that fit the function to the given data is known as ***regression***.
- **Linear Least Squares Regression**
  can be applied to a function in polynomial form, $y(x)=a_0+a_1x+a_2x^2+\ldots+a_nx^m$
  we are looking for the coefficients of the polynomial, a_j given *n* observations (x_i,y_i). We can write this as a set of polynomials or in a matrix form

$$\begin{aligned} y_1 &= a_0 + a_1x_1 + a_2x_1^2 + \cdots + a_mx_1^m \\ y_2 &= a_0 + a_1x_2 + a_2x_2^2 + \cdots + a_mx_2^m \\ \vdots &= \vdots \\ y_n &= a_0 + a_1x_n + a_2x_n^2 + \cdots + a_mx_n^m \end{aligned}$$

$$\underbrace{\begin{bmatrix} 1 & x_1 & x_1^2 & \cdots & x_1^m \\ 1 & x_2 & x_2^2 & \cdots & x_2^m \\ \vdots & \vdots & \cdots & \vdots & \\ 1 & x_n & x_n^2 & \cdots & x_n^m \end{bmatrix}}_{A} \underbrace{\begin{pmatrix} a_0 \\ a_1 \\ a_2 \\ \vdots \\ a_m \end{pmatrix}}_{\phi} = \underbrace{\begin{pmatrix} y_1 \\ y_2 \\ \vdots \\ y_n \end{pmatrix}}_{b}$$

- **Non-linear regression**

For equations which are **originally non-linear in the parameters** but **can be recast in a polynomial form** they can be solved using linear regression.

When it is **not possible to reduce** a problem to a linear one in order to perform regression, we must use nonlinear regression, which involves **solving a system of nonlinear equations** for the unknown parameters.

Non-linear least squares regression

- Regression:

we measure some observable φ as a function of some independent variable, *x*, and we have some theoretical function that we expect the observations to obey. The function may have parameters in it that we need to determine. The process of determining the best values of the parameters that fit the function to the given data is known as *regression*.

- Linear Least Squares Regression

can be applied if we can write our function in polynomial form, $y(x)=a_0+a_1x+a_2x^2+\ldots+a_nx^m$. If we can do this, then we are looking for the coefficients of the polynomial, a_j given n observations (x_i,y_i). We can write this as a set of polynomials or in a matrix form

$$\begin{aligned} y_1 &= a_0 + a_1x_1 + a_2x_1^2 + \cdots + a_mx_1^m \\ y_2 &= a_0 + a_1x_2 + a_2x_2^2 + \cdots + a_mx_2^m \\ \vdots &= \vdots \\ y_n &= a_0 + a_1x_n + a_2x_n^2 + \cdots + a_mx_n^m \end{aligned}$$

$$\underbrace{\begin{bmatrix} 1 & x_1 & x_1^2 & \cdots & x_1^m \\ 1 & x_2 & x_2^2 & \cdots & x_2^m \\ \vdots & \vdots & \cdots & \vdots & \\ 1 & x_n & x_n^2 & \cdots & x_n^m \end{bmatrix}}_{A} \underbrace{\begin{pmatrix} a_0 \\ a_1 \\ a_2 \\ \vdots \\ a_m \end{pmatrix}}_{\phi} = \underbrace{\begin{pmatrix} y_1 \\ y_2 \\ \vdots \\ y_n \end{pmatrix}}_{b}$$

- Non-linear regression

For equations which are originally non-linear in the parameters but can be recast in a polynomial form they can be solved using linear regression.

When it is not possible to reduce a problem to a linear one in order to perform regression, we must use nonlinear regression, which involves solving a system of nonlinear equations for the unknown parameters.

Extension of Linear Least Squares Regression

- Extends linear least squares regression
- The unknown parameters in the function are estimated as in linear least squares regression
- Limitations on the way parameters can be used in the functional part of a nonlinear regression model

Definition of a Nonlinear Regression Model

- a nonlinear model has this basic form

$$y = f(\vec{x}; \vec{\beta}) + \varepsilon$$

- in which
  - the functional part of the model is not linear with respect to the unknown parameters, $\beta_0, \beta_1, \ldots$, and
  - the method of least squares is used to estimate the values of the unknown parameters

- To estimate the unknown parameters of the function it is often much easier to work with models that meet two additional criteria:
  - the function is **smooth with respect to the unknown** parameters, and
  - the **least squares criterion** that is used to obtain the parameter estimates has a **unique solution**

- These last two criteria are not essential parts of the definition of a nonlinear least squares model, but are of practical importance.

Examples of Nonlinear Models

$$f(x;\vec{\beta}) = \frac{\beta_0 + \beta_1 x}{1 + \beta_2 x}$$

$$f(x;\vec{\beta}) = \beta_1 x^{\beta_2}$$

$$f(x;\vec{\beta}) = \beta_0 + \beta_1 \exp(-\beta_2 x)$$

$$f(\vec{x};\vec{\beta}) = \beta_1 \sin(\beta_2 + \beta_3 x_1) + \beta_4 \cos(\beta_5 + \beta_6 x_2)$$

Advantages of Nonlinear Least Squares

- A **broad range of functions** that can be fit.
- Describe models that can no be described with linear models:
  - processes that asymptote have to increase or decrease at a declining rate as the explanatory variables go to the extremes.
- "least squares" procedure, has some of the advantages that linear least squares regression has:
  - Its **efficient use of data**
  - A fairly well-developed theory for computing confidence, prediction and calibration intervals to answer scientific and engineering questions. In most cases the probabilistic interpretation of the intervals produced by nonlinear regression are only approximately correct, but these intervals still work very well in practice.

Disadvantages of Nonlinear Least Squares

- The need to use **iterative optimization** procedures to compute the parameter estimates. With functions that are linear in the parameters, the least squares estimates of the parameters can always be obtained analytically, while that is generally not the case with nonlinear models.
- The use of iterative procedures requires the user to **provide starting values** for the unknown parameters before the software can begin the optimization.
- Disadvantages shared with the linear least squares procedure includes a **strong sensitivity to outliers**.
- In addition there are unfortunately **fewer model validation tools** for the detection of outliers in nonlinear regression than there are for linear regression.

3 STUDY DEVELOPMENT

- 8 naïve infected patients
- Study design:
  - Antiretroviral treatment:
    - 1 PI and 2Nucleoside reverse transcriptase inhibitors (NRTIs): Nelfinavir, zidovudine and lamivudine
  - 4 moths follow-up
  - Viral load measured at weeks: 0, 1, 2, 3, 4, 6, 8, 10, 12, 14, 16
  - Plasma viremia
- Remark: $\log_{10}$Viral load is assessed
- Log_{10} Viral load is fitted using nonlinear least-squares regression
- Infectivity titre of HIV-1 in PBMC is also fitted

Model (I) Kinetic model proposed

Cells

M ---infection--- M* (long-lived cells) → Produce vires with rate p

rate k_M → are lost with with rate μ_M

CD4+T

T ---infection--- T* (long-lived cells) → produce a total of N virions, V,during their lifetime → cleared with rate c

rate k

rate fk → are lost with with rate δ

Latently infected lymphocytes

L → die with a rate constant δ_L

→ activated into productively infected cells with a rate α } rate of loss $\mu_L = \alpha + \delta_L$

Latently infected T cells: $dT^*/dt = kVT + \alpha L - \delta T^*$

Latently infected lymphocytes: $dL/dt = fkVT - \mu_L L$

Long-lived infected cells: $dM^*/dt = k_M VM - \mu_M M^*$

Virions: $dV/dt = N\delta T^* + pM^* - cV$

Model (II): Decay in the level of plasma virus after drug therapy

$$V(t) = V_0[Ae^{-\delta t} + Be^{-\mu_L t} + Ce^{-\mu_M t} + (1 - A - B - C)e^{-ct}] \quad (1)$$

where

$$A = \frac{NkT_0}{c-\delta}\left(1 - \frac{af}{\delta - \mu_L}\right)$$

$$B = \frac{af\delta NkT_0}{\mu_L(\delta - \mu_L)(c - \mu_L)}$$

$$C = \frac{c - NkT_0\left(1 + \frac{af}{\mu_L}\right)}{c - \mu_M}$$

Assumptions: f=0 and c=3 d^{-1}

Fitting plasma viremia data and using least-squares regression the parameters: δ, μ_M and the composite parameter NkT_0 where estimated.

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$$V(t) = V_0[Ae^{-\delta t} + Be^{-\mu_L t} + Ce^{-\mu_M t} + (1 - A - B - C)e^{-ct}] \quad (1)$$

M cells loss rate

where

Loss T* rate

Loss lymphocytes rate

rate of virions clearеance

$$A = \frac{NkT_0}{c - \delta}\left(1 - \frac{af}{\delta - \mu_L}\right)$$

$$B = \frac{af\delta NkT_0}{\mu_L(\delta - \mu_L)(c - \mu_L)}$$

$$C = \frac{c - NkT_0\left(1 + \frac{af}{\mu_L}\right)}{c - \mu_M}$$

Assumptions: f=0 and c=3 d^{-1}

V_0 baseline viral load

T_0 baseline CD4+T cells

Fitting plasma viremia data and using least-squares regression the parameters: δ, μ_M and the composite parameter NkT_0 where estimated.

Results

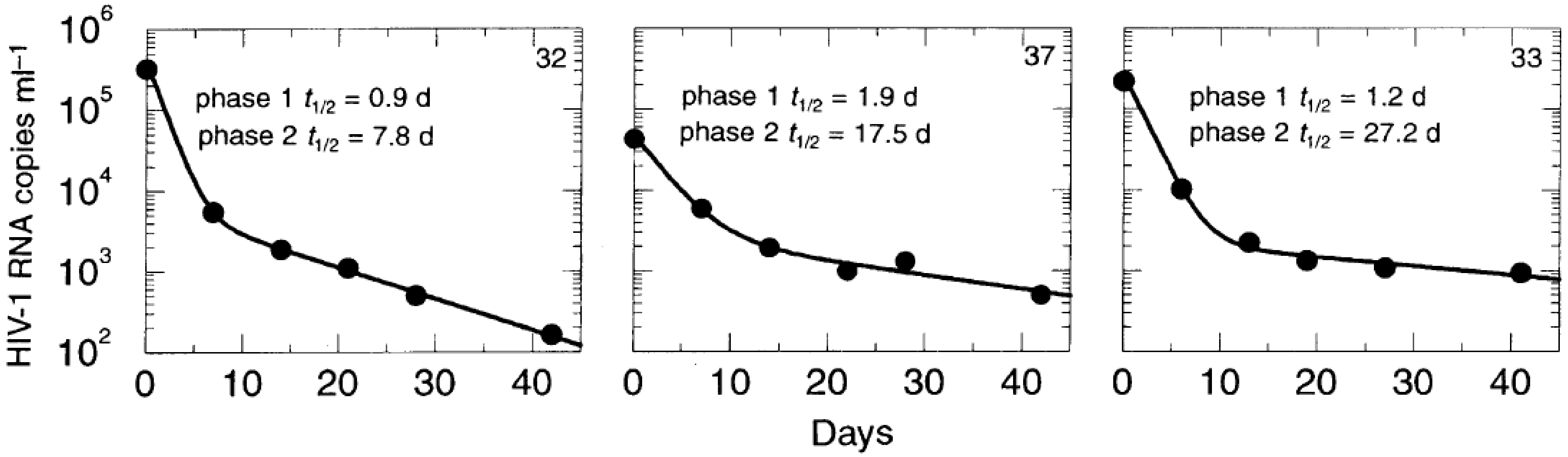


Figure 1 Plasma levels of HIV-1 RNA (filled circles) measured by the bDNA assay for three representative patients during triple therapy, begun on day 0; data points between 100 and 500 copies ml^{-1} were determined using 10 ml plasma. The theoretical curve (solid line) was obtained by nonlinear least-square fitting of the logarithm of equation (1), with $f = 0$, to the logarithm of the data. The parameters δ, μ_M and NkT_0, were simultaneously estimated. The parameter estimates obtained were: patient 32, see Table 1; patient 33, $\delta = 0.57\,\mathrm{d}^{-1}$, $\mu_M = 0.025\,\mathrm{d}^{-1}$, and $NkT_0 = 2.97$; patient 37, $\delta = 0.36\,\mathrm{d}^{-1}$, $\mu_M = 0.040\,\mathrm{d}^{-1}$, and $NkT_0 = 2.80$.

Model (III): The number of PBMC carrying infectious HIV-1

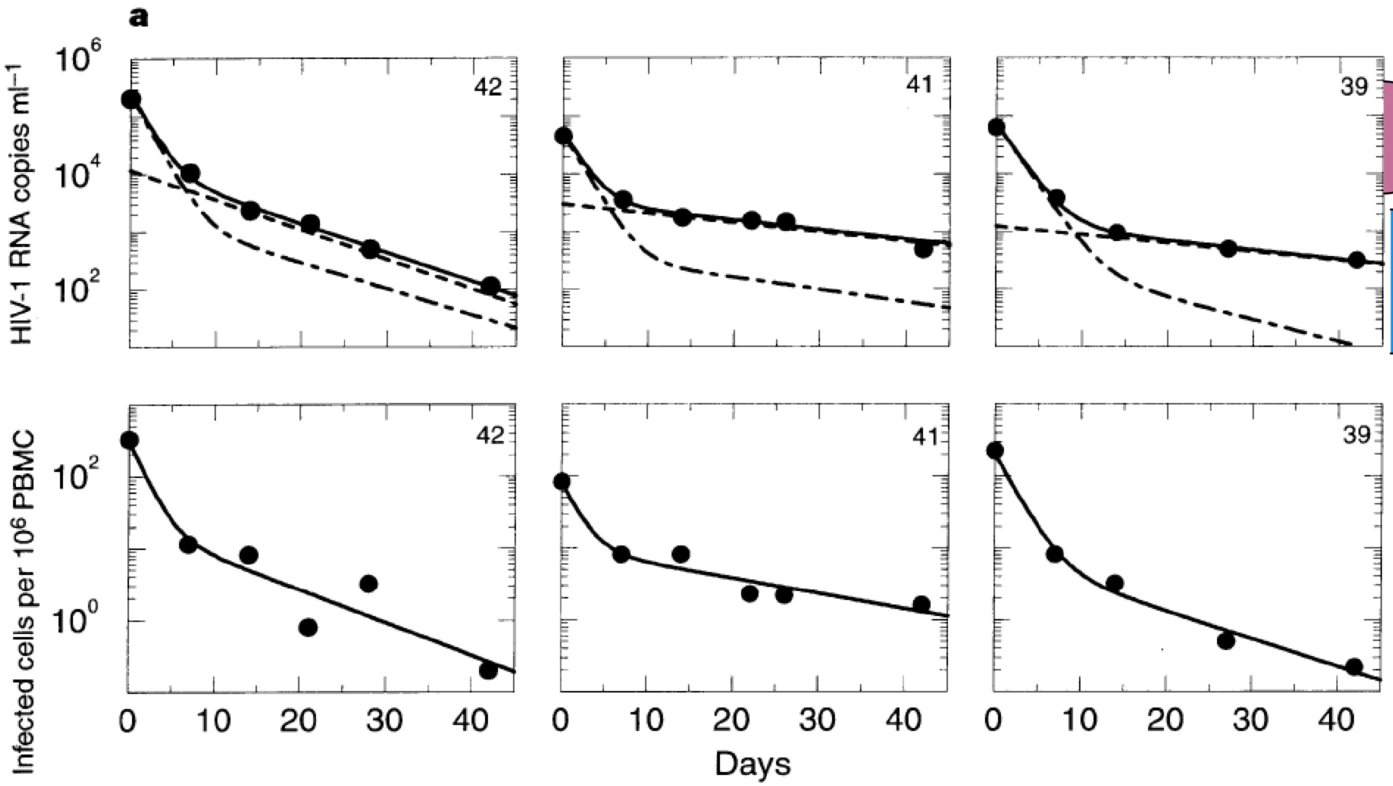
The PMBC infectivity is proportional to I(t)=T*+L(t)

$$I(t) = \frac{kV_0T_0}{\delta}\left[\left(1-\frac{af}{\delta-\mu_L}\right)e^{\underset{\substack{\Uparrow\\ \text{Loss T* rate}}}{-\delta t}} + \frac{f\delta}{\mu_L}\left(1+\frac{a}{\delta-\mu_L}\right)e^{\underset{\substack{\Uparrow\\ \text{Loss lymphocyts rate}}}{-\mu_L t}}\right] \quad (2)$$

Assumptions:

The long-lived, virus-producing cells reside in tissues and that the number of infected CD4+T cells in blood are prorportional to the total number in the body.

Results:
Plasma levels of HIV-1 RNA



1st stage

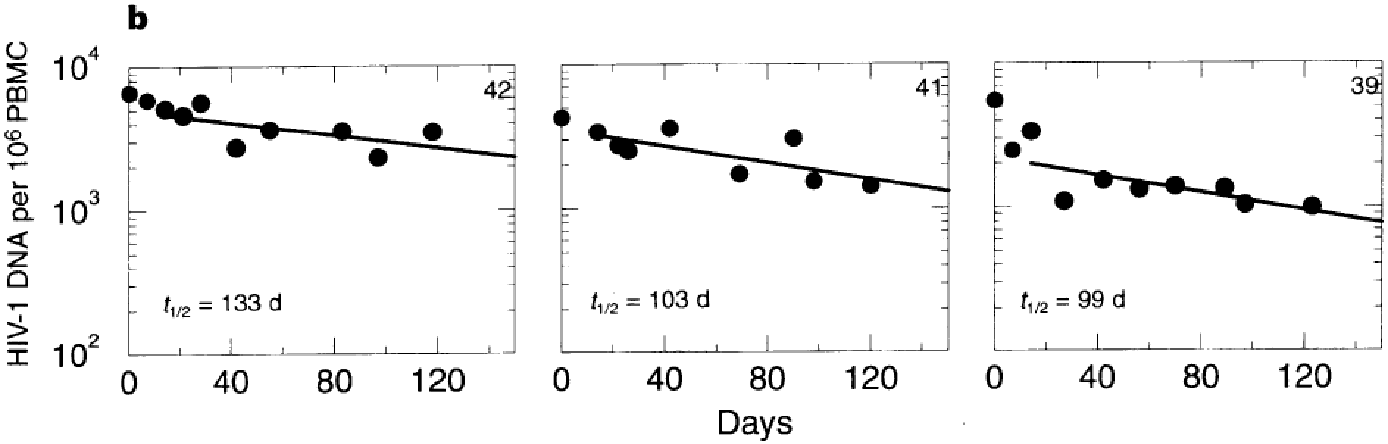
Latently
infected
cells

2nd stage

Long-lived
infected cells

Figure 2 a, Plasma levels of HIV-1 RNA, PBMC infectivity, and **b**, HIV-1 proviral DNA for three representative patients. The theoretical curves (solid lines) were obtained by fitting equations (1) and (2) simultaneously to the data (filled circles). The long-dashed short-dashed line indicates the contribution to the total HIV-1 RNA by pre-existing productively infected T cells plus those generated by the gradual activation of latently infected T cells (the terms $Ae^{-\delta t} + Be^{-\mu_L t}$ in equation (1)); the dashed line indicates the contribution made by long-lived infected cells, M^* (the term $Ce^{-\mu_M t}$ in equation (1)). By day 14, the productively infected CD4$^+$ T cells initially present have substantially decayed, and the remaining productively infected T cells are being generated by activation of laterally infected T cells. As indicated by the long-dashed short-dashed line after day 14, the contribution to the second phase made by latently infected T cells is substantially smaller than the contribution made by long-lived infected cells (dashed line).

Results:
HIV-1 proviral DNA for three representative patients



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Conclusion

- The two phases of decay correspond to two different infected-cell populations
  - 1st phase: rapid elimination of free virus and loss of productively infected cells
  - 2nd phase: loss of long-lived infected cells
- The model assumes that the immune system exerts a constant antiviral effect during treatment

4 REFERENCES

- Perelson AS, Essunger P, Cao Y, Vesanen M, Hurley A, Saksela K, Markowitz M, Ho DD. Decay characteristics of HIV-1-infected compartments during combination therapy. Nature. 1997 May 8;387(6629):188-91.

- Non-linear least squares models:
  - http://itl.nist.gov/div898/handbook/pmd/section1/pmd142.htm
  - http://en.wikipedia.org/wiki/Non-linear_least_squares

Mixed-effects state space models for analysis of longitudinal dynamic systems.

Liu et al. (2011)

Innovative approach

OUTLINE

1 METHODOLOGICAL CONCEPTS

Describes several methodological tools used in the analysis

2 HIV DYNAMIC APPLICATION

Example of application in HIV data

3 References

The paper reviewed

1 METHODOLOGICAL CONCEPTS

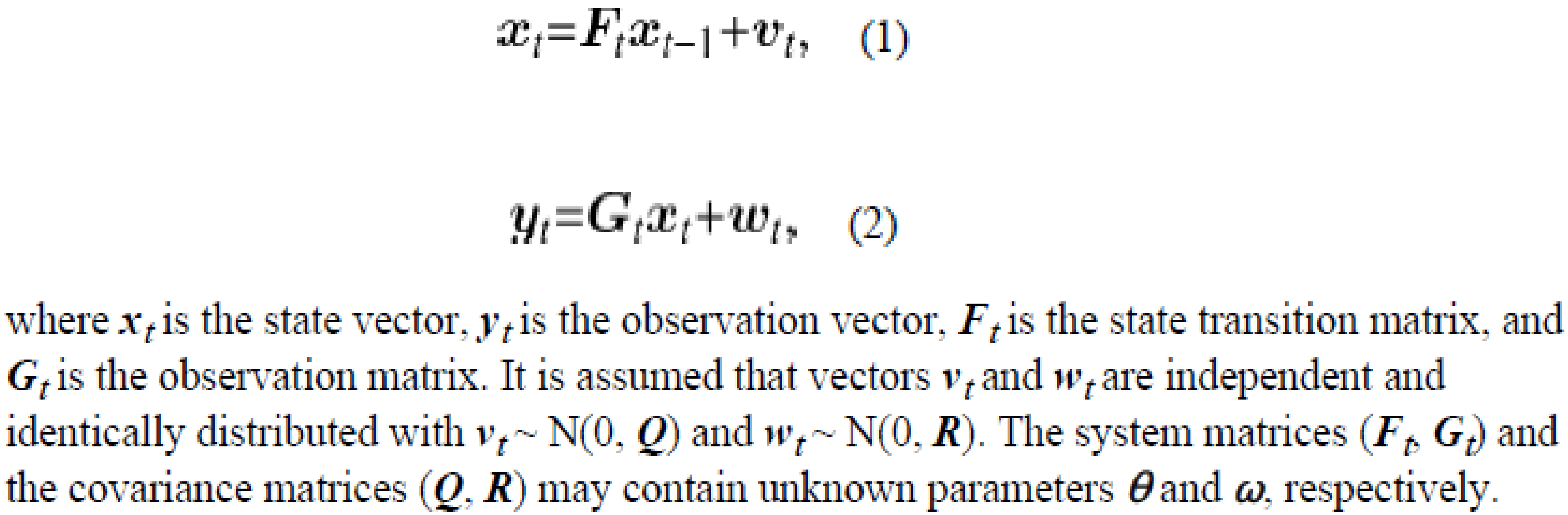
- The authors propose a class of mixed-effects state space models
    - State models used in time series data
    - Linear random-effects model

- Parameters of the model estimated using:
    - Bayesian approaches
    - Maximum likelihood methods

State space model

Consists of an

- state equation: models the process of the states
- observation equation: links the observations to these underlying states



$$x_t = F_t x_{t-1} + v_t, \quad (1)$$

$$y_t = G_t x_t + w_t, \quad (2)$$

where $\boldsymbol{x}_t$ is the state vector, $\boldsymbol{y}_t$ is the observation vector, $\boldsymbol{F}_t$ is the state transition matrix, and $\boldsymbol{G}_t$ is the observation matrix. It is assumed that vectors $\boldsymbol{v}_t$ and $\boldsymbol{w}_t$ are independent and identically distributed with $\boldsymbol{v}_t \sim \mathrm{N}(0, \boldsymbol{Q})$ and $\boldsymbol{w}_t \sim \mathrm{N}(0, \boldsymbol{R})$. The system matrices $(\boldsymbol{F}_t, \boldsymbol{G}_t)$ and the covariance matrices $(\boldsymbol{Q}, \boldsymbol{R})$ may contain unknown parameters $\boldsymbol{\theta}$ and $\boldsymbol{\omega}$, respectively.

- State space models
  - Main goal: estimate the state variables based upon the observations
  - Provides rich covariance structures for y_i
  - Are flexible in the modelling because they treat separatedly the
    - Underlying mechanism (state equation)
    - Observations (observation equation)

Linear random-effects model

- Used for longitudinal studies
- Individuals measured several times over a period of time
- Variations among the observations can be due to:
  - Between-subject variation
  - Within-subject variation

$$\boldsymbol{y}_i = \boldsymbol{x}_i\beta + \mathbf{Z}_i\boldsymbol{b}_i + \boldsymbol{e}_i, \qquad \boldsymbol{b}_i \sim \mathrm{N}(\mathbf{0}, \boldsymbol{D}), \qquad \boldsymbol{e}_i \sim \mathrm{N}(\mathbf{0}, \boldsymbol{\Omega}_i),$$

the random effects $\boldsymbol{b}_i$ and errors $\boldsymbol{e}_i = [e_{i1}, \cdots, e_{in_i}]'$ account for the between-subject and within-subject variation, respectively. Covariance matrix $\boldsymbol{\Omega}_i$ may be diagonal or has a complicated structure (Jones, 1993; Diggle, Liang and Zeger, 1994).

MESSM tool

State space model

+

Linear random-effects model

- State space model approaches the longitudinal dynamic system
- Random-effects are introduced into F_t and G_t to account for between-subjects variation

MESSM specification

$$\boldsymbol{x}_{i,t+1}=\boldsymbol{F}(\theta_i)\boldsymbol{x}_{it}+\boldsymbol{v}_{it}, \quad \boldsymbol{v}_{it}\sim \mathrm{N}(0,\boldsymbol{Q}), \quad (3)$$

$$\boldsymbol{y}_{it}=\boldsymbol{G}(\theta_i)\boldsymbol{x}_{it}+\boldsymbol{w}_{it}, \quad \boldsymbol{w}_{it}\sim \mathrm{N}(0,\boldsymbol{R}), \quad (4)$$

where $\boldsymbol{y}_{it}$ is the $q \times 1$ vector of observations for the ith ($i = 1, \ldots, m$) subject at time t ($t = 1, \ldots, n_i$), $\boldsymbol{x}_{it}$ is the $p \times 1$ state vector, $\boldsymbol{v}_{it}$ is the $p \times 1$ dynamic disturbance vector, and $\boldsymbol{w}_{it}$ is the $q \times 1$ vector of the observation errors. $\{\boldsymbol{v}_{it}\}$ and $\{\boldsymbol{w}_{it}\}$ are assumed to be mutually independent within themselves and independent to each other.

parameters for ***F*** and ***G*** are not necessarily same. They may share some common parameters or may have different parameters. However, for presentation convenience, we use $\boldsymbol{\theta}_i$ to denote all the unknown parameters in both ***F*** and ***G***. Similar handling is applied for $\boldsymbol{\omega}$. Recognized as a vector of individual parameters, $\boldsymbol{\theta}_i$ can be modelled as

$$\theta_i = \theta + \boldsymbol{b}_i, \quad \boldsymbol{b}_i \sim \mathrm{N}(0, \boldsymbol{D}), \quad (5)$$

where $\boldsymbol{\theta}$ is the fixed effect or the population parameter vector ($r \times 1$), and the vectors $\boldsymbol{b}_i$ are the random effects, which are assumed to be i.i.d. random vectors.

MESSM applied to the HIV dynamic model proposed by Perelson et al.

. This model consists of three differential equations describing the interaction between the target cells and HIV infection. It was assumed that the antiviral therapy completely blocked the reproduction of infectious HIV virions, thus the newly produced virions were all noninfectious. The model was written as

$$\frac{dT^*}{dt} = kV_I T - \delta T^*, \quad \frac{dV_I}{dt} = -cV_I, \quad \frac{dV_{NI}}{dt} = N\delta T^* - cV_{NI}, \qquad (6)$$

where V_I, V_{NI}, T and T^* represented the plasma concentrations of infectious viruses, noninfectious viruses, uninfected T-cells, and productively infected T-cells, respectively.

If the total plasma HIV concentration ($V = V_{NI} + V_I$) and T^* observed, a mixed-effects state space model for system (6) could be formulated as

$$\boldsymbol{x}_{it} = \boldsymbol{F}_i \boldsymbol{x}_{i,t-1} + \boldsymbol{v}_{it}, \quad (7)$$

$$\boldsymbol{y}_{it} = \boldsymbol{G} \boldsymbol{x}_{it} + \boldsymbol{w}_{it}, \quad (8)$$

where $\boldsymbol{y}_{it}$ is the observed (T^* V) for the ith patient at time t,

$$\boldsymbol{x}_{it} = \begin{pmatrix} T^*_{it} & V_{I_{it}} & V_{NI_{it}} \end{pmatrix}', \quad \boldsymbol{F}_i = \begin{bmatrix} 1-\delta_i & k_i T_i & 0 \\ 0 & 1-c_i & 0 \\ N_i \delta_i & 0 & 1-c_i \end{bmatrix}, \quad \boldsymbol{G} = \begin{bmatrix} 1 & 0 & 0 \\ 0 & 1 & 1 \end{bmatrix}.$$

The mixed effects $\theta_i = (\ 1-\delta_i \quad k_i T_i \quad N_i \delta_i \quad 1-c_i\ )'$ are assumed to follow

$$\theta_i = \theta + \mathbf{b}_i, \quad \mathbf{b}_i = (\ b_{i1} \quad b_{i2} \quad b_{i3} \quad b_{i4}\ )' \sim \mathrm{N}(\mathbf{0}, \boldsymbol{D}),$$

where $\theta = (\ 1-\delta \quad kT \quad N\delta \quad 1-c\ )' = (\ \theta_1 \quad \theta_2 \quad \theta_3 \quad \theta_4\ )'$ are population parameters.

Estimation of the state variables: individual states

- The estimation of an individual state x_{it} can be classified according to the information available:
  - If $\{y_{i1},..y_{i,t-1}\}$ are observed (one-step-ahead)
  - If $\{y_{i1},..y_{it}\}$ are observed (filtered estimation)
  - If $\{y_{i1},..y_{in_i}\ (n_i>t)\}$ are observed (smoothed estimation)

Kalman filter

- If the parameters θ_i and ω are known in the linear MESSM (3) – (4), then the Kalman filter provides the basic solutions
- It is a recursive algorithm which produces the linear estimators for the state variables
- Under the assumption of normality:
  - the estimators obtained are unbiased and minimize the mean squared error.
  - estimator $x_{it|k}$ is the mean of x_{it} conditional on the data $\{y_{i1}, \ldots, y_{ik}\}$.
  - If the normality assumption does not hold, the Kalman filter may not produce the conditional means of the states →Bayesian approach

Estimation of the state variables: population state variable

- Represents the mean response of all indiviuals at a time t
- Use data to define the pseudolikelihood function
- Find the pameters by the EM algorithm

Parameter estimation

By means of Bayesian tools

Or

Likelihood perspectives

--Data not shown here--

2 HIV DYNAMIC APPLICATION

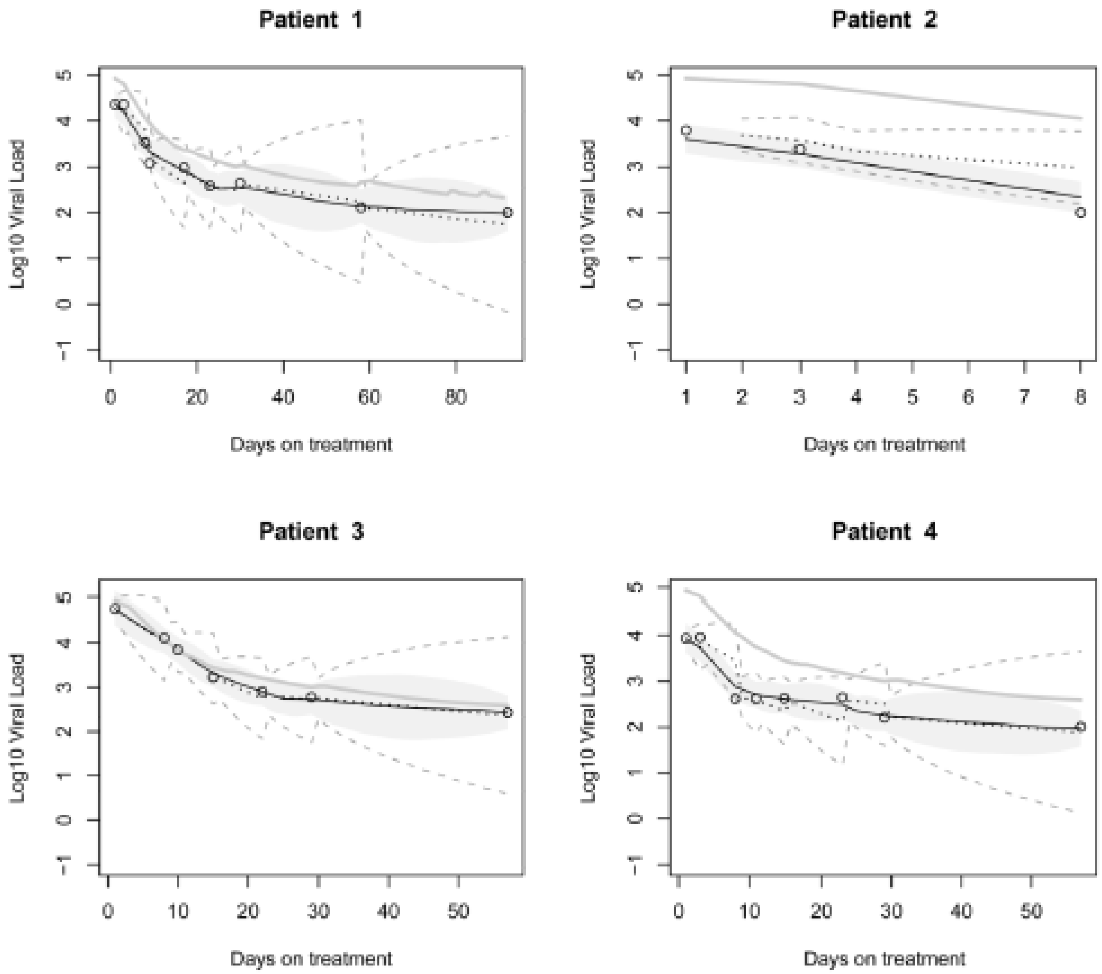
- 53 Infected patients
- Treated with ritonavir, 3TC and AZT
- HIV-1 RNA measured on days: 0, 2, 7,10, 14, 21, 28 adn weeks 8,12,24,48 after treatmetn initiation
- Perelson et al. (1997) suggested a two-phase clearance of viral load.
- Here we considered a time-varying MESSM assuming the rate of clearance changed at the mid-point of week 4 (day 24)

MESSM for HIV dynamic

$$x_{it}=\theta_{it}x_{i,t-1}+v_{it},\ \text{and}$$

$$y_{it}=x_{it}+w_{it},$$

where y_{it} is the base 10 logarithm of the measured viral load from patient i at time t, and x_{it} represents the base 10 logarithm of the actual viral load. θ_{it} indicates the viral clearance rate for patient i at day t ($\theta_{it}=\theta_i^{(1)}$ for $t \leq 23$; $\theta_{it}=\theta_i^{(2)}$ for $t>23$). Here $\theta_i^{(k)}\sim N(\theta^{(k)}, D_k)$ for $k = 1, 2$, and $\theta_i^{(k)}$ are independent. Note that we may use the log-transformation to guarantee θ_{it} to be positive.



Estimation and prediction of viral load for four patients in the HIV dynamic study (four subjects with different number of measurements and different response patterns are selected for illustration). Base 10 logarithm of the **viral loads** are shown in **circles**. The **smoothing estimates using the Gibbs sampler** approach are shown in **black solid** curves, and the 95% error bounds are shown by the shaded grey region. The **one-step-ahead Kalman forecasts** are shown in **black dotted curves**, and the prediction error bounds are in grey dashed curves. The estimates of population state variable are shown as the gray solid curve.

3 REFERENCE

- Liu D, Lu T, Niu XF, Wu H. Mixed-effects state-space models for analysis of longitudinal dynamic systems. Biometrics. 2011 Jun;67(2):476-85.

Thank you!!!