Dynamical modeling and data analysis of HIV infection with infection-age, CTLs immune response and delayed antibody immune response

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1 Model discretization method

We employ the classical Iannelli (1996) finite-difference method with enhanced second-order accuracy (marginally superior to conventional Euler differencing) to discretize PDE System (1.1), utilizing Crank-Nicolson-type central finite-difference advancement within the linearized prediction-correction algorithm. Essentially, explicit difference methods are typically applied to dynamic problems due to their step size constraints and favorable convergence properties.

Denote,

$$V = \int_0^{+\infty} r(a)y(t,a)da, C = \int_0^{+\infty} \eta(a)y(t,a)da, Z = \int_0^{\tau^*} f(\tau)e^{-m\tau}v(t-\tau)z(t-\tau)d\tau.$$

Define the maximum time for data fitting as T_0, choose a positive integer N, and let $\Delta t = \frac{T_0}{N}$ be the time discretization parameter and $M = [\sup\{a : y_0(a) \neq 0\}/\Delta t + 0.5]$ be the number of steps necessary to cover the support of the initial datum $y_0(a)$. For $t^n = n\Delta t$, $0 \leq n \leq N$, and $a_j = j\Delta t$, $0 \leq j \leq n + M$. We define $x^n \approx x(t^n)$, $y_j^n \approx y(a_j, t^n)$, $v^n(\theta) \approx v(\theta, t^n)$, $c^n \approx c(t^n)$ and $z^n(\theta) \approx z(\theta, t^n)$,

For $n = 0$,

$$x^0 = x_0,\ y_j^0 = y_0(a_j),\ v^0(\theta) = v_\theta^0,\ c^0 = c_0,\ z^0(\theta) = z_\theta^0,\ j \in [0, M],\ \theta \in [-\tau^*, 0],$$

$$V^0 = \frac{1}{2}\gamma(a_0)y_0^0\Delta t + \sum_{j=1}^{M}\gamma(a_j)y_j^0\Delta t,$$

$$C^0 = \frac{1}{2}\eta(a_0)y_0^0\Delta t + \sum_{j=1}^{M}\eta(a_j)y_j^0\Delta t,$$

$$Z^0 = \sum_{\tau=0}^{\tau^*} f(\tau)e^{-m\tau}v^{-\tau}z^{-\tau}\Delta t.$$

For $n = 1$,

$$\begin{aligned}
\frac{x^1 - x^0}{\Delta t} &= b - \beta x_0 v_0 - \delta_1 x_0,\\
\frac{y_j^1 - y_{j-1}^0}{\Delta t} &= -\sigma(a_j)y_j^1 c^0 - \delta_2(a_j)y_j^1,\\
\frac{v^1 - v^0}{\Delta t} &= V^0 - \mu v^0 z^0 - \delta_3 v^0,\\
\frac{c^1 - c^0}{\Delta t} &= c^0 C^0 - \delta_4 c^0,\\
\frac{z^1 - z^0}{\Delta t} &= \rho Z^0 - \delta_5 z^0,\\
V^1 &= \frac{1}{2}\gamma(a_0)y_0^1\Delta t + \sum_{j=1}^{M}\gamma(a_j)y_j^1\Delta t,\\
C^1 &= \frac{1}{2}\eta(a_0)y_0^1\Delta t + \sum_{j=1}^{M}\eta(a_j)y_j^1\Delta t,\\
Z^1 &= \sum_{\tau=0}^{\tau^*} f(\tau)e^{-m\tau}v^{1-\tau}z^{1-\tau}\Delta t,\\
y_0^1 &= \beta x_0^1 v_0^1.
\end{aligned}$$

For $n \geq 2$,

$$\begin{aligned}
\frac{x^n - x^{n-2}}{2\Delta t} &= b - \beta \frac{x^n + x^{n-2}}{2} \frac{v^n + v^{n-2}}{2} - \delta_1 \frac{x^n + x^{n-2}}{2}, \\
\frac{y_1^n - y_0^{n-1}}{\Delta t} &= -\sigma(a_1) y_1^n c^n - \delta_2(a_1) y_1^n, \\
\frac{y_j^n - y_{j-2}^{n-2}}{2\Delta t} &= -\sigma(a_j) \frac{y_j^n + y_{j-2}^{n-2}}{2} \frac{c^n + c^{n-2}}{2} - \delta_2(a_j) \frac{y_j^n + y_{j-2}^{n-2}}{2}, j \geq 2, \\
\frac{v^n - v^{n-2}}{2\Delta t} &= V^{n-1} - \mu \frac{v^n + v^{n-2}}{2} \frac{z^n + z^{n-2}}{2} - \delta_3 \frac{v^n + v^{n-2}}{2}, \\
\frac{c^n - c^{n-2}}{2\Delta t} &= \frac{c^n + c^{n-2}}{2} C^{n-1} - \delta_4 \frac{c^n + c^{n-2}}{2}, \\
\frac{z^n - z^{n-2}}{2\Delta t} &= \rho Z^{n-1} - \delta_5 \frac{z^n + z^{n-2}}{2}, \\
V^n &= \frac{1}{2} \gamma(a_0) y_0^n \Delta t + \sum_{j=1}^{M} \gamma(a_j) y_j^n \Delta t, \\
C^n &= \frac{1}{2} \eta(a_0) y_0^n \Delta t + \sum_{j=1}^{M} \eta(a_j) y_j^n \Delta t, \\
Z^n &= \sum_{\tau=0}^{\tau^*} f(\tau) e^{-m\tau} v^{n-\tau} z^{n-\tau} \Delta t, \\
y_0^n &= \beta x_0^n v_0^n.
\end{aligned}$$

For any ϑ, $\vartheta \in (-\tau^*, 0)$, $z^\vartheta = z^0$.

2 Parameter estimation and data simulation

The probability distribution $f(\tau)$ is chosen to be the Erlang distribution function as follows:

$$f(\tau) = \frac{\tau^{n-1}}{(n-1)! b^n} e^{-\frac{\tau}{b}}.$$

And we set $n = 9, b = 5$.

We assume that the age-dependent strength of the CTLs killing the infected cells $\sigma(a)$ will decrease with the increase of infection age. With reference to the selection of Edmunds et al. , $\sigma(a)$ declines after the age a_1, in a non-linear fashion and can be empirically described by the following expression:

$$\sigma(a) = \begin{cases} 0.05, & 0 \leq a < a_1, \\ \exp(-p_1 a^{p_2}), & a \geq a_1, \end{cases}$$

where, 0.05 indicates CTLs effectiveness. And we set $p_1 = 2.99573227, p_2 = 1.0014, a_1 = 3$, again, we assume $a_2 = a_3 = 3$. The values of other parameters, initial conditions and thersholds of the model are shown in Table 1-4.

The onset time of ART treatment varies for each patient, and the parameters differ before and after treatment. Therefore, we use subscripts 1 and 2 to denote the pre-treatment and post-treatment parameters, respectively.

Table 1 Parameters, initial value, thersholds and equilibrium states of our system (Patient ID: 900).

Parameter	Definition	Value
$b \in [1, 10](mm^{-3}d^{-1})$	Recruitment rate of uninfected cells	9.8693
$\beta_1 \in [10^{-5}, 0.5](mm^3d^{-1})$	Infection rate	1.3329×10^{-11}
$\beta_2 \in [10^{-5}, 0.5](mm^3d^{-1})$	Infection rate	3.4481×10^{-7}
$\mu \in [0.001, 1](d^{-1})$	The rate of neutralization of free viruses by antibodies	0.0001
$\eta(a) \in [0.001, 1](d^{-1})$	The rate of CTLs proliferate in response to antigenic stimulation	0.2283
$\rho \in [0.001, 1](d^{-1})$	Generation rate of antibodies	0.0013
$\delta_1 \in [0.007, 0.1](d^{-1})$	Death rate of uninfected cells	0.0185
$\delta_0 \in [0.26, 0.68](d^{-1})$	Death rate of infected cells	0.1573
$p_3 \in [0.01, 10]$	Strength coefficient	1.5321
$p_4 \in [10^{-5}, 10]$	Strength coefficient	0.0901
$\delta_3 \in [2.06, 3.81](d^{-1})$	Clearance rate of virus	2.1359
$\delta_4 \in [0.001, 0.15](d^{-1})$	Depletion rate of CTLs	0.001
$\delta_5 \in [0.05, 0.15](d^{-1})$	Depletion rate of antibody	0.0553
$\gamma_{01} \in [0.5, 3.125](d^{-1})$	The rate of infected cells produce new viruses	1.6926
$\gamma_{02} \in [0.5, 3.125](d^{-1})$	The rate of infected cells produce new viruses	0.0010
$p_5 \in [0.01, 10]$	Strength coefficient	0.1181
$p_6 \in [10^{-5}, 10]$	Strength coefficient	1.0000×10^{-5}
$m \in [0.001, 100]$	Strength coefficient	0.0014
$\tau \in [6, 84]$	Strength coefficient	59.2580
$x(0) \in [1, 100]$	Initial value of uninfected cells	481.6703
$y_1(0) \in [0, 300]$	Initial value of infected cells at infection age 1	132.1121
$y_2(0) \in [0, 300]$	Initial value of infected cells at infection age 2	10.8803
$y_3(0) \in [0, 300]$	Initial value of infected cells at infection age 3	0.0062
$y_4(0) \in [0, 300]$	Initial value of infected cells at infection age 4	279.7810
$y_5(0) \in [0, 300]$	Initial value of infected cells at infection age 5	4.2274×10^{-23}
$v(\theta) \in [2, 10^6]$	Initial value of viruses	75.7495
$c(0) \in [2, 1500]$	Initial value of CTLs	1118.3525
$z(\theta) \in [2, 1500]$	Initial value of antibody	4.4682
$\mathcal{R}_1$	Threshold value	1.5863×10^{-10}
$\mathcal{R}_2$	Threshold value	1.5863×10^{-10}
$\mathcal{R}_3$	Threshold value	1.5863×10^{-10}
$\mathcal{R}_4$	Threshold value	2.3728×10^{-5}

References

Iannelli, Mimmo and Loro, Roberto and Milner, Fabio A and Pugliese, Andrea and Rabbiolo, Guglielmo. Numerical analysis of a model for the spread of HIV/AIDS. *SIAM Journal on Numerical Analysis*, 1996, **33**: 864–882.

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Table 2 Parameters, initial value, thersholds and equilibrium states of our system (Patient ID: 1092).

Parameter	Definition	Value
$b \in [1, 10](mm^{-3}d^{-1})$	Recruitment rate of uninfected cells	8.0678
$\beta_1 \in [10^{-5}, 0.5](mm^3d^{-1})$	Infection rate	1.0000×10^{-11}
$\beta_2 \in [10^{-5}, 0.5](mm^3d^{-1})$	Infection rate	4.4119×10^{-7}
$\mu \in [0.001, 1](d^{-1})$	The rate of neutralization of free viruses by antibodies	0.0002
$\eta(a) \in [0.001, 1](d^{-1})$	The rate of CTLs proliferate in response to antigenic stimulation	0.2056
$\rho \in [0.001, 1](d^{-1})$	Generation rate of antibodies	0.0030
$\delta_1 \in [0.007, 0.1](d^{-1})$	Death rate of uninfected cells	0.0076
$\delta_0 \in [0.26, 0.68](d^{-1})$	Death rate of infected cells	0.2619
$p_3 \in [0.01, 10]$	Strength coefficient	1.2150
$p_4 \in [10^{-5}, 10]$	Strength coefficient	0.2351
$\delta_3 \in [2.06, 3.81](d^{-1})$	Clearance rate of virus	2.0602
$\delta_4 \in [0.001, 0.15](d^{-1})$	Depletion rate of CTLs	0.0011
$\delta_5 \in [0.05, 0.15](d^{-1})$	Depletion rate of antibody	0.0500
$\gamma_{01} \in [0.5, 3.125](d^{-1})$	The rate of infected cells produce new viruses	2.9787
$\gamma_{02} \in [0.5, 3.125](d^{-1})$	The rate of infected cells produce new viruses	0.0256
$p_5 \in [0.01, 10]$	Strength coefficient	0.1588
$p_6 \in [10^{-5}, 10]$	Strength coefficient	1.1206×10^{-5}
$m \in [0.001, 100]$	Strength coefficient	0.001
$\tau \in [6, 84]$	Strength coefficient	8.8609
$x(0) \in [1, 100]$	Initial value of uninfected cells	1.0843
$y_1(0) \in [0, 300]$	Initial value of infected cells at infection age 1	125.5061
$y_2(0) \in [0, 300]$	Initial value of infected cells at infection age 2	27.4577
$y_3(0) \in [0, 300]$	Initial value of infected cells at infection age 3	0.0024
$y_4(0) \in [0, 300]$	Initial value of infected cells at infection age 4	212.5744
$y_5(0) \in [0, 300]$	Initial value of infected cells at infection age 5	1.5833×10^{-20}
$v(\theta) \in [2, 10^6]$	Initial value of viruses	262.6280
$c(0) \in [2, 1500]$	Initial value of CTLs	7.6450
$z(\theta) \in [2, 1500]$	Initial value of antibody	2.0474
$\mathcal{R}_1$	Threshold value	5.7470×10^{-10}
$\mathcal{R}_2$	Threshold value	5.7470×10^{-10}
$\mathcal{R}_3$	Threshold value	5.7461×10^{-10}
$\mathcal{R}_4$	Threshold value	0.0079

Table 3 Parameters, initial value, thersholds and equilibrium states of our system (Patient ID: 1430).

Parameter	Definition	Value
$b \in [1, 10](mm^{-3}d^{-1})$	Recruitment rate of uninfected cells	9.9932
$\beta_1 \in [10^{-5}, 0.5](mm^3d^{-1})$	Infection rate	1.2793×10^{-11}
$\beta_2 \in [10^{-5}, 0.5](mm^3d^{-1})$	Infection rate	2.6972×10^{-7}
$\mu \in [0.001, 1](d^{-1})$	The rate of neutralization of free viruses by antibodies	0.0006
$\eta(a) \in [0.001, 1](d^{-1})$	The rate of CTLs proliferate in response to antigenic stimulation	0.1232
$\rho \in [0.001, 1](d^{-1})$	Generation rate of antibodies	0.0014
$\delta_1 \in [0.007, 0.1](d^{-1})$	Death rate of uninfected cells	0.0119
$\delta_0 \in [0.26, 0.68](d^{-1})$	Death rate of infected cells	0.1587
$p_3 \in [0.01, 10]$	Strength coefficient	1.6204
$p_4 \in [10^{-5}, 10]$	Strength coefficient	0.0532
$\delta_3 \in [2.06, 3.81](d^{-1})$	Clearance rate of virus	2.0723
$\delta_4 \in [0.001, 0.15](d^{-1})$	Depletion rate of CTLs	0.001
$\delta_5 \in [0.05, 0.15](d^{-1})$	Depletion rate of antibody	0.0516
$\gamma_{01} \in [0.5, 3.125](d^{-1})$	The rate of infected cells produce new viruses	2.9622
$\gamma_{02} \in [0.5, 3.125](d^{-1})$	The rate of infected cells produce new viruses	0.0179
$p_5 \in [0.01, 10]$	Strength coefficient	0.0010
$p_6 \in [10^{-5}, 10]$	Strength coefficient	1.0571×10^{-5}
$m \in [0.001, 100]$	Strength coefficient	0.0011
$\tau \in [6, 84]$	Strength coefficient	6.0424
$x(0) \in [1, 100]$	Initial value of uninfected cells	98.8155
$y_1(0) \in [0, 300]$	Initial value of infected cells at infection age 1	190.0318
$y_2(0) \in [0, 300]$	Initial value of infected cells at infection age 2	10.3381
$y_3(0) \in [0, 300]$	Initial value of infected cells at infection age 3	0.0023
$y_4(0) \in [0, 300]$	Initial value of infected cells at infection age 4	214.4760
$y_5(0) \in [0, 300]$	Initial value of infected cells at infection age 5	9.1036×10^{-26}
$v(\theta) \in [2, 10^6]$	Initial value of viruses	234.6306
$c(0) \in [2, 1500]$	Initial value of CTLs	589.2103
$z(\theta) \in [2, 1500]$	Initial value of antibody	2.9276
$\mathcal{R}_1$	Threshold value	5.1016×10^{-9}
$\mathcal{R}_2$	Threshold value	1.6509×10^{-9}
$\mathcal{R}_3$	Threshold value	5.0781×10^{-9}
$\mathcal{R}_4$	Threshold value	1.8863

Table 4 Parameters, initial value, thersholds and equilibrium states of our system (Patient ID: 2823).

Parameter	Definition	Value
$b \in [1, 10](mm^{-3}d^{-1})$	Recruitment rate of uninfected cells	8.5859
$\beta_1 \in [10^{-5}, 0.5](mm^3d^{-1})$	Infection rate	1.1710×10^{-11}
$\beta_2 \in [10^{-5}, 0.5](mm^3d^{-1})$	Infection rate	2.0809×10^{-7}
$\mu \in [0.001, 1](d^{-1})$	The rate of neutralization of free viruses by antibodies	0.0003
$\eta(a) \in [0.001, 1](d^{-1})$	The rate of CTLs proliferate in response to antigenic stimulation	0.2335
$\rho \in [0.001, 1](d^{-1})$	Generation rate of antibodies	0.0019
$\delta_1 \in [0.007, 0.1](d^{-1})$	Death rate of uninfected cells	0.0086
$\delta_0 \in [0.26, 0.68](d^{-1})$	Death rate of infected cells	0.1554
$p_3 \in [0.01, 10]$	Strength coefficient	1.5322
$p_4 \in [10^{-5}, 10]$	Strength coefficient	0.0994
$\delta_3 \in [2.06, 3.81](d^{-1})$	Clearance rate of virus	2.0600
$\delta_4 \in [0.001, 0.15](d^{-1})$	Depletion rate of CTLs	0.0010
$\delta_5 \in [0.05, 0.15](d^{-1})$	Depletion rate of antibody	0.0501
$\gamma_{01} \in [0.5, 3.125](d^{-1})$	The rate of infected cells produce new viruses	2.4384
$\gamma_{02} \in [0.5, 3.125](d^{-1})$	The rate of infected cells produce new viruses	0.0182
$p_5 \in [0.01, 10]$	Strength coefficient	0.1324
$p_6 \in [10^{-5}, 10]$	Strength coefficient	1.3573×10^{-5}
$m \in [0.001, 100]$	Strength coefficient	0.0013
$\tau \in [6, 84]$	Strength coefficient	76.7850
$x(0) \in [1, 100]$	Initial value of uninfected cells	29.5948
$y_1(0) \in [0, 300]$	Initial value of infected cells at infection age 1	147.6816
$y_2(0) \in [0, 300]$	Initial value of infected cells at infection age 2	9.6218
$y_3(0) \in [0, 300]$	Initial value of infected cells at infection age 3	0.0057
$y_4(0) \in [0, 300]$	Initial value of infected cells at infection age 4	240.4713
$y_5(0) \in [0, 300]$	Initial value of infected cells at infection age 5	3.5201×10^{-23}
$v(\theta) \in [2, 10^6]$	Initial value of viruses	58.8445
$c(0) \in [2, 1500]$	Initial value of CTLs	13.8064
$z(\theta) \in [2, 1500]$	Initial value of antibody	5.36836
$\mathcal{R}_1$	Threshold value	3.0529×10^{-9}
$\mathcal{R}_2$	Threshold value	3.0529×10^{-9}
$\mathcal{R}_3$	Threshold value	3.0529×10^{-9}
$\mathcal{R}_4$	Threshold value	1.8593×10^{-5}