ЖЭТФ, 2007, том 132, вып. 4 (10), стр. 978–983 

# KINETIC MODEL OF HIV INFECTION

***V. P. Zhdanov*** [a,b*]

[a] *Department of Applied Physics, Chalmers University of Technology S-41296 Göteborg, Sweden*

[b] *Boreskov Institute of Catalysis, Russian Academy of Sciences 630090, Novosibirsk, Russia*

Received April 23, 2007

The recent experiments clarifying the details of exhaustion of the CD8 T cells specific to various strains of human immunodeficiency virus (HIV) are indicative of slow irreversible (on the one-year time scale) deterioration of the immune system. The conventional models of HIV kinetics do not take this effect into account. Removing this shortcoming, we show the likely influence of such changes on the HIV escape from control of the immune system.

PACS: 87.18.-h, 87.19.Xx, 87.10.+e

## 1. INTRODUCTION

The kinetics of interaction of viruses and cells have long attracted attention of mathematicians and physicists interested in theoretical biology and biophysics [1]. During several decades, the theoretical works in this field were almost exclusively focused on the interplay of ensembles of virions and cells. The numerous models belonging to this class (see reviews [2, 3] and recent examples including a multi-variable analysis of temporal HIV kinetics [4–6] and simulations of spatio–temporal kinetics [7]) are essentially extracellular in the sense that the intracellular processes (such as virus genome replication, synthesis of viral proteins, and assembly of new virions) are not described explicitly. The models of intracellular viral kinetics are now available as well, including the analysis of specific systems [8, 9] (we note that Ref. [8] is focused on HIV) and generic simulations treating primarily stochastic effects [10, 11]. The gap between the extracellular and intracellular models was recently bridged in Ref. [12]. In addition to Refs. [1–12], it is appropriate to mention reviews [13] of the applications of kinetic models and bioinformatics to assisting the design of anti-HIV therapies.

In this work, focused on the kinetics of chronic HIV infection, we briefly discuss available extracellular models (Sec. 2), outline some relevant recent experimental results indicating the novel factors (Sec. 3), and, introducing the related modifications into the theory (Sec. 4), show the corresponding results clarifying the likely details of the HIV escape from control of the immune system (Secs. 5 and 6).

## 2. CONVENTIONAL MODELS

The immune system, defending us of viruses, bacteria, fungi, and other pathogenic agents (referred to as antigen) includes a variety of cells and numerous regulatory and effector molecules (see, e.g., review [14] oriented to physicists). The key class of cells includes white blood cells, known as lymphocytes (these cells are created in the bone marrow), and can be subdivided into B cells, secreting antibodies (protective molecules), and T cells or, more specifically, helper T cells and effector (or cytotoxic) T cells, promoting the growth and differentiation of B cells and killing infected cells, respectively. In the case of HIV infection, the virus is well known to mutate and, accordingly, there are typically a few HIV quasispecies simultaneously.

At present, a full-scale description of the immune system including all the species is impossible because the available information is far from being complete. For this reasons, the kinetic models of HIV infection are focused on the generic factors. To illustrate the

*E-mail: zhdanov@fy.chalmers.se

type of the models used now, it is instructive to introduce deterministic kinetic equations

$$\frac{dv_i}{dt} = r_i v_i - p_i v_i x_i + \sum_{j \neq i} (\kappa_{ji} v_j - \kappa_{ij} v_i), \qquad (1)$$

$$\frac{dx_i}{dt} = k_i v_i - \lambda_i x_i - \mu_i v x_i \qquad (2)$$

corresponding to the model representing a hybrid of the models proposed in Refs. [3] and [6].

Equation (1) describes evolution of the HIV-quasispecies concentrations $v_i$, where $1 \leq i \leq n$ and $n$ is the total number of the virus strains ($n$ should be sufficiently large such that the results are insensitive to $n$; in different works, $n$ is typically in the range from 10 to about $10^4$). The first term takes viral replication into account ($r_i$ is the replication rate constant). The second term is related to suppression of the viral population due to immune response (the rate constant $p_i$ characterizes the efficacy of the strain-specific immune responses $x_i$). The rate of elimination of HIV-quasispecies is assumed to be proportional to $v_i x_i$ [3] (see Ref. [6] for a more complex expression). The third and fourth terms take mutation of strains into account ($\kappa_{ij}$ is the mutation rate constant).

Equation (2) defines evolution of the strain-specific immune responses $x_i$. The first term in the right-hand side of this equation represents the rate at which the response is evoked ($k_i$ is the corresponding rate constant). The second term takes relaxation of the immune system into account ($\lambda_i$ is the relaxation rate constant). The third term corresponds to the impairment of the immune system due to interaction with virus ($\mu_i$ is the corresponding rate constant). The rate of impairment is assumed to be proportional to the total virus concentration $v \equiv \sum_{i=1}^{n} v_i$ [3] (see Ref. [6] for a more complex expression).

The model introduced above represents one class of extracellular models. For extracellular models explicitly taking helper (CD4+) T cells into account and for combined models, see, e.g., Refs. [2, 4, 15] and [16], respectively. With an appropriate choice of the parameter values, the conventional models like that introduced above are well known [3, 6] to be able to describe the first stages of the HIV infection including a rapid increase in the viral load at the beginning of verimia, followed by a sharp decline due to immunological control and a long period of latency. The model in [6] also describes a subsequent (after 6–10 years) increase in the viral load corresponding to the onset of AIDS. But this does not mean that such models are fully sufficient in order to understand what happens in reality, at least conceptually.

## 3. RECENT EXPERIMENTS

HIV predominantly infects helper (CD4+) T cells [14]. In addition, during persistent infections in general [17, 18] and HIV infection in particular [19–21], the effector (CD8+) T cells gradually dwindle in number and lose the ability to kill cells and to make cytokines. This seems to be related to exhaustion of the memory CD8 T cells [17, 19] (exhausted cells are characterized by the abundance of surface-receptor protein called programmed death-1, PD-1).

Recent studies of HIV-infected patients [19, 20] show that both the proportion of cytotoxic T cells expressing PD-1 and the level of PD-1 on the cell surface correlate with the viral load in the blood plasma — currently, the best indicator of disease progression. Specifically, the PD-1 expression was examined on HIV-specific CD8 T cells [19], using histocompatibility complex class I tetramers specific for frequently targeted epitopes (i.e., for the parts of an antigen molecule to which an antibody attaches itself). The measurements were performed inspecting infected people who were naive to anti-HIV treatments and also people after initiation of the therapy (on the one-year time scale). The latter resulted in a dramatic decline of detectable plasma viral load, coincident with a decrease in PD-1 expression. In the context of our presentation, it is of interest that the decrease was different for different cells. For some of them (e.g., for those marked by tetramer B*0801 EI8), it followed the decline of viral load. For others (e.g., for those marked by tetramer B*4201 TL9), it was rather small. One of the likely interpretations of these observations is that during chronic infection, the HIV induces irreversible changes in the immune system in the sense that on the one-year time scale, the system is not able to completely recover even after an appreciable decline of viral load.

## 4. UPDATED MODEL

Although the conventional models do not explicitly describe exhausted memory CD8 T cells, it may be argued that the corresponding deterioration of the immune system related to their generation could be implicitly taken into account by the last term, $\mu_i x_i v$, in the right-hand side of Eq. (2) (this is the only relevant term in Eqs. (1) and (2) unless we modify them).

To some extent, this argument is correct, but not completely. For example, if we assume that at some moment the virus is completely eliminated (hypothetically) or its load is appreciably reduced (this can be done in reality), the recovery of the immune system is described by $dx_i/dt = -\lambda_i x_i$ (cf. Eq. (2)). This means that the corresponding time scale is $\approx 1/\lambda_i$. Typically, $\lambda_i \approx 0.01$–$0.03$ days$^{-1}$ (such values, used, e.g., in Ref. [6], can be validated taking into account that the models should reproduce termination of the growth of the viral population after the first few weeks after infection). Therefore, the recovery time scale is expected to be about one or two months. This value is much shorter than the one-year (or longer) time scale characterizing the irreversible changes discussed above. For these reasons, we believe that Eqs. (1) and (2) should be revised.

The presence of exhausted cells indicates that the potential for generation of functional effector cells is somehow reduced on the long-term scale (one of the likely reasons of this effect is the virus-related destruction of the niches of stem cells involved into the function of the immune system). The most natural way to incorporate this effect into the model is to introduce an additional equation describing slow reduction of $k_i$ in Eq. (2) due to the irreversible influence of virus on the immune system. This reduction explicitly takes into account that the rate of production of functional effector cells becomes lower and implicitly describes the increase in the population of exhausted cells. The variation of other constants is less appropriate. For example, $r_i$ can hardly be changed, because this constant corresponds to replication of virions after infection of healthy cells, and its relation to the deterioration of the immune system is accordingly less explicit compared to that of $k_i$.

The simplest relevant phenomenological equation for $k_i$ is

$$dk_i/dt = -\gamma_i v(k_i - k_i^{min}), \tag{3}$$

where $\gamma_i$ is the corresponding rate constant and $k_i^{min}$ is the minimal value of $k_i$. This equation implies that the rate of deterioration of the immune system is proportional to the viral load. For chronic infection, we should typically have $\gamma_i v \ll \lambda_i$ because the degradation of the immune system is slow.

Equations (1)–(3), representing the model we suggest, can be analyzed analytically in the mean-field approximation (Sec. 5) or numerically (Sec. 6). Both these approaches indicate that if $k_i^{min}$ are close to $k_i(0)$, the model predicts an asymptotic (as $t \to \infty$) transition to a final stable steady state. This solution corresponds to rare cases where the immune system is able to co-exist with virus. If $k_i^{min}$ are appreciably smaller than $k_i(0)$, the analysis indicates that there is no steady state with finite virus concentration. Under such circumstances, Eqs. (1)–(3) predict unlimited growth of the virus concentration during a finite time interval. This means that the virus population escapes control by the immune system.

## 5. MEAN-FIELD AND STEADY-STATE APPROXIMATIONS

The mean-field approximation allows describing chronic HIV infection including the HIV escape from control of the immune system. In this approximation, we consider the scales of the values of the parameters $r_i$, $p_i$, $k_i$, $\lambda_i$, $\mu_i$, $\gamma_i$, and $k_i^{min}$ to be the same for all different virus strains and drop the subscript $i$ accordingly. In addition, taking into account that the degradation of the immune system is slow, we use the steady-state approximation for Eqs. (1) and (2). We then have

$$rv_i - pv_i x_i + \kappa(v - nv_i) = 0, \tag{4}$$

$$kv_i - \lambda x_i - \mu v x_i = 0, \tag{5}$$

$$dk/dt = -\gamma v(k - k_{min}). \tag{6}$$

To proceed, we replace $v_i$ in the second term of Eq. (4) by the average value, i.e., by $v/n$. Then the summation of all the equations (4) yields

$$x = nr/p, \tag{7}$$

where $x = \sum_i x_i$.

After summation of all the equations (5), we obtain

$$kv - \lambda x - \mu v x = 0. \tag{8}$$

Substituting expression (7) in this equation results in

$$v = \frac{nr\lambda}{p(k - k_{cr})}, \tag{9}$$

where $k_{cr} \equiv nr\mu/p$ is the critical $k$ value defining the condition of the existence of the steady state. Substituting the last expression in Eq. (6), we have

$$\frac{dk}{dt} = -\frac{nr\gamma\lambda(k - k_{min})}{p(k - k_{cr})}. \tag{10}$$

Equation (7) indicates that $x$ should be constant under steady-state conditions. With decreasing $k$, this can be reached if $v$ increases (see Eq. (9)). This results

in a further decrease in $k$ (see Eq. (10)). Due to this feedback, Eq. (10) may predict collapse of the immune system. Specifically, the solution of Eq. (10) depends on the relation between $k_{cr}$ and $k_{min}$.

If $k_{cr} < k_{min}$, Eq. (10) asymptotically (as $t \to \infty$) describes a transition from the initial state (with $k(0) > k_{min}$) to the final stable steady state with the virus concentration given by

$$v = \frac{nr\lambda}{p(k_{min} - k_{cr})}. \tag{11}$$

As already noted, this solution corresponds to rare cases where the immune system is able to coexist with virus.

If $k_{cr} > k_{min}$, there is no steady state with a finite virus concentration and the virus population eventually escapes control by the immune system. To illustrate this regime explicitly, it is instructive to analyze the situation with $k_{min} = 0$. In this case, after elementary integration, Eq. (10) yields

$$k(0) - k(t) + k_{cr} \ln \frac{k(t)}{k(0)} = at, \tag{12}$$

where $a \equiv nr\gamma\lambda/p$. This equation shows that the time interval corresponding to the collapse of the immune system (this happens when $k(t)$ reaches $k_{cr}$) is given by

$$\Delta t = \frac{1}{a}\left(k(0) - k_{cr} + k_{cr} \ln \frac{k_{cr}}{k(0)}\right). \tag{13}$$

For the virus concentration, Eq. (9) can be rewritten as

$$v = \frac{v_0 k_{cr}}{k(t) - k_{cr}}, \tag{14}$$

where $v_0 \equiv nr\lambda/pk_{cr}$.

Typical dependences of $k$ and $v$ on time, calculated using Eqs. (12) and (14), are exhibited in Fig. 1. The virus concentration is seen to be nearly constant during a long period (up to $\approx 0.9\Delta t$), and then (at $0.9\Delta t < t < \Delta t$) the virus spirals out of control. We note that the growth of $v$ is far from purely exponential, because the induction phase is very long and the collapse is reached during a final time interval. Choosing $a$ in Eq. (13) such that $\Delta t \approx 10$ years, we can use Eq. (14) to describe typical real runs of persistent HIV infection.

## 6. NUMERICAL CALCULATIONS

Taking into account that the accuracy of the mean-field and steady-state approximations is open for debate, we present results of numerical calculations (with

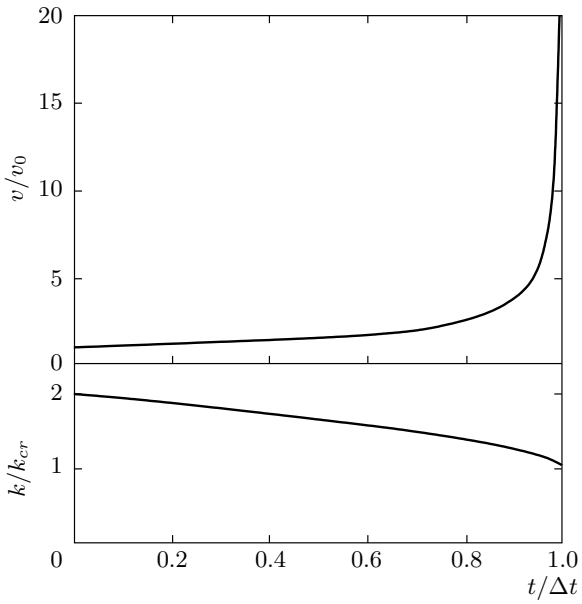


**Fig. 1.** Virus population $v$ and the parameter $k$ characterizing the efficacy of the immune system, as a function of time according to Eqs. (12) and (14) with $k(0)/k_{cr} = 2$

$k_i^{min} = 0$) illustrating the HIV escape from control of the immune system.

In general, the number of variables and kinetic parameter values in Eqs. (1)–(3) may be huge (up to about $10^5$ [6]) and their choice may reflect many real details. To not obscure the main message, we use a relatively simple procedure of the specification of the values of the model parameters and show that even in this case, the model behavior is very robust.

To specify the kinetic parameters, we first note that the concentrations $v_i$ and $x_i$ can be normalized to arbitrarily chosen concentrations and can therefore be dimensionless. With this choice used here, the dimension of all the rate constants should be day$^{-1}$. The values of the kinetic parameters should be distributed in a relatively wide range and chosen such that the model reasonably describes all the stages of the infection on the time scale corresponding to reality. In our calculations, we use $n = 10$ and distribute the kinetic parameter values at random as follows: $r_i$ is in the range from 0.2 to 0.4 day$^{-1}$, $p_i$ is in the range from 2 to 4 day$^{-1}$, $\kappa_{ij}$ is in the range from 0 to 0.01 day$^{-1}$, $k_i(0)$ and $\lambda_i$ are in the range 0.01 to 0.02 day$^{-1}$, $\mu_i$ is in the range from 0.001 to 0.002 day$^{-1}$, and $\gamma_i$ is in the range from $10^{-4}$ to $2 \cdot 10^{-4}$ day$^{-1}$. The initial conditions for Eqs. (1) and (2) are $v_i(0) = 0.01$ and 0 for $i = 1$ and $i > 1$, respectively, and $x_i(0) = 0$ for $i \geq 1$.

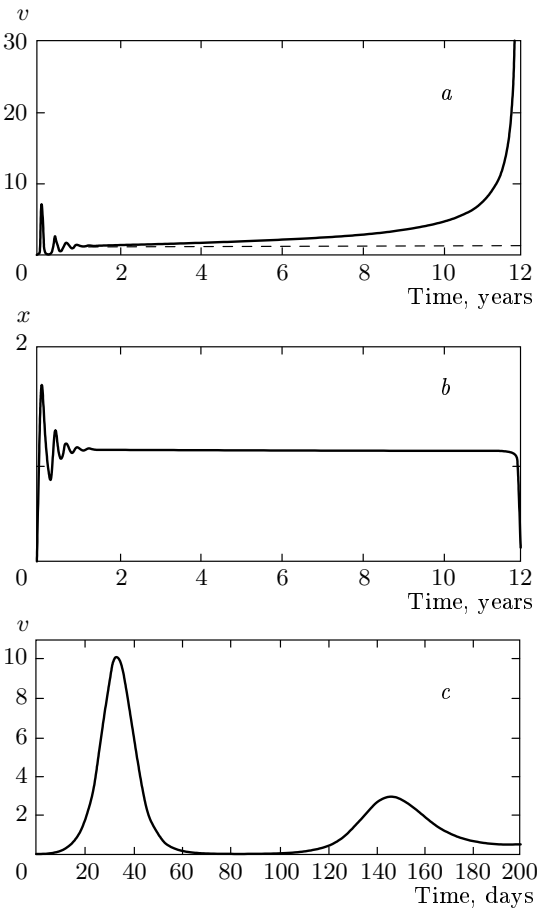


**Fig. 2.** Virus population ($a$) $v = \sum_i v_i$ and immune response ($b$) $x = \sum_i x_i$ as a function of time. Panel $c$ shows the virus population during the first 200 days in more detail. The solid lines correspond to Eqs. (1)–(3). For comparison, the dashed lines show the kinetics predicted by Eqs. (1) and (2) in the case where the rate constants $k_i$ are independent of time. We note that during the first 200 days, the solid and dashed lines practically coincide. For this reason, the dashed lines are nearly or completely invisible on panels $b$ and $c$

The viral kinetics obtained by integrating Eqs. (1)–(3) with the parameters specified above, are shown in Fig. 2. The model is seen to reproduce all the stages of the HIV infection including (i) a rapid increase in the viral load at the beginning of verimia (during the first six weeks), (ii) a sharp decline due to immunological control (week 7), (iii) a long period (about ten years) of latency, and (iv) a subsequent (after 10 years) increase in the viral load corresponding to the onset of AIDS.

For comparison, we also show in Fig. 2 the kinetics predicted by Eqs. (1) and (2) in the case where the rate constants $k_i$ are independent of time. In this case, as expected, the model describes only stages (i)–(iii).

## 7. CONCLUSION

We have proposed a new model of the kinetics of HIV infection. In addition to the conventional ingredients, it accounts for slow irreversible (on the one-year time scale) changes in the immune system related to its interaction with virus. Our analysis shows that the model reasonably describes all the stages of the HIV infection even with the simplest choice of the parameter values. Specifically, we show that the slow irreversible changes in the immune system may play a key role in the HIV escape from control of the immune system. If necessary, we can increase $n$ and/or specify the parameter values in more detail, e.g., introduce correlations of the mutation rate constants. Such modifications do not change our conclusions. As already noted, the behavior of the model is fairly robust.

Physically or chemically, the viral kinetics (Figs. 1 and 2) predicted by our model represents an example of kinetic explosion. In different systems, the driving forces behind kinetic explosion are different, and hence the corresponding equations are usually far from universal. For comparison, we mention the analysis of the kinetics of "explosions" in heterogeneous catalytic reactions [22].

Finally, it is appropriate to recall that 25 years after the start of the HIV epidemic, the world is still contending with more than 27 million HIV-related deaths to date, and an estimated 4.9 million new infections each year [23]. Since the first observations of HIV, the experiments, simulations, and trials to design the corresponding therapies are primarily focused on HIV mutations. There is no doubt that this key feature of HIV should be explored, described, and treated in detail. On the whole, however, the HIV escape from control of the immune system seems to result from a complex interplay of various factors including slow degradation of the system. Our goal was to articulate and illustrate this point by using a generic model. The key new ingredient of our model (Eq. (3)) was introduced phenomenologically. The scrutiny of biochemistry and/or biophysics behind this equation is of high interest.

This work is a part of the FP6-project STREP NANOCUES funded by the European Commission and is partially funded by the Chalmers Bioscience Program, the Swedish Science Council, and the Foundation for Strategic Research.

## REFERENCES


1. M. A. Nowak and R. M. May, *Virus Dynamics. Mathematical Principles of Immunology and Virology*, Oxford Univ. Press, Oxford (2000).
2. A. S. Perelson, Nature Rev. Immun. **2**, 28 (2002).
3. D. Wodarz and M. A. Nowak, BioEssay **24**, 1178 (2002).
4. J. M. Murray and A. S. Perelson, Multiscale Model. Simul. **3**, 300 (2005).
5. S. Iwami, S. Nakaoka, and Y. Takeuchi, Physica D **223**, 222 (2006); F. Bagnoli, P. Lio, and L. Sguanci, Physica A **366**, 333 (2006).
6. G. Y. Wang and M. W. Deem, Phys. Rev. Lett. **97**, 188106 (2006).
7. M. C. Strain, D. D. Richman, J. K. Wong, and Levine H, J. Theor. Biol. **218**, 85 (2002); G. A. Funk, V. A. A. Jansen, S. Bonhoeffer, and T. Killingback, J. Theor. Biol. **233**, 221 (2005); C. Beauchemin, J. Theor. Biol. **242**, 464 (2006).
8. B. Reddy and J. Yin, AIDS Res. Human Retrovir. **15**, 273 (1999).
9. Y. Sidorenko and U. Reichl, Biotech. Bioing. **88**, 1 (2004).
10. R. Srivastava, L. You, J. Summers, and J. Yin, J. Theor. Biol. **218**, 309 (2002).
11. V. P. Zhdanov, J. Phys. A **37**, L63 (2004); Biosystems **77**, 143 (2004); Phys. Biolog. **2**, 46 (2005).
12. E. L. Haseltine, J. B. Rawlings, and J. Yin, Comput. Chem. Eng. **29**, 675 (2005).
13. F. Castiglione and A. Liso, Immunopharm. Immunotox. **27**, 417 (2005); T. Lengauer and T. Sing, Nature Rev. Microbiol. **4**, 790 (2006).
14. A. S. Perelson and G. Weisbuch, Rev. Mod. Phys. **69**, 1219 (1997).
15. R. J. De Boer and A. S. Perelson, J. Theor. Biol. **190**, 201 (1998).
16. N. I. Stilianakis, K. Dietz, and D. Schenzle, Mathem. Biosci. **145**, 27 (1997).
17. D. L. Barber, E. J. Wherry, D. Masopust, B. G. Zhu, J. P. Allison, A. H. Sharpe, G. J. Freeman, and R. Ahmed, Nature **439**, 682 (2006).
18. M. A. Williams and M. J. Bevan, Nature **439**, 669 (2006).
19. C. L. Day, D. E. Kaufmann, P. Kiepiela, J. A. Brown, E. S. Moodley, S. Reddy, E. W. Mackey, J. D. Miller, A. J. Leslie, C. DePierres, Z. Mncube, J. Duraiswamy, B. G. Zhu, Q. Eichbaum, M. Altfeld, E. J. Wherry, H. M. Coovadia, P. J. R. Goulder, P. Klenerman, R. Ahmed, G. J. Freeman, and B. D. Walker, Nature **443**, 350 (2006).
20. S. Rowland-Jones and T. Dong, Nature **443**, 282 (2006).
21. L. Trautmann, L. Janbazian, N. Chomont, E. A. Said, S. Gimmig, B. Bessette, M. R. Boulassel, E. Delwart, H. Sepulveda, R. S. Balderas, J. P. Routy, E. K. Haddad, and R. P. Sekaly, Nature Med. **12**, 1198 (2006).
22. R. G. Sharpe and M. Bowker, J. Phys.: Condens. Matter **7**, 6379 (1995).
23. M. Altfeld and T. M. Allen, Trends Immun. **27**, 504 (2006).