An Entropic-Energetic View for the Dynamics of HIV Infection

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We propose a time-based analogy between the thermodynamic behavior of a three-level energy system and the progression of HIV infection described by the evolution of the cell population.[b]

The CA model proposed by R.M. Zorzenon dos Santos et al. [1] is re-examined, from the perspective of the thermodynamic behavior of a three-level energy system. The evolution of the infection happens in the model based on well-defined rules. Therefore, figure 1 shows a simulation of the dynamics of the HIV infection generated from the CA model proposed by the authors, after the occurrence of the primary infection stage. In this model, we assume that each stage of the automata evolution (one week) the macroscopic states are in thermodynamic equilibrium with well-defined energy and entropy. All according to the average populations of CD4+T Cells, defined as healthy, infected and dead states from the CA model. We designed a three-level physical model to describe the dynamics of HIV infection (without treatment), analogous to that proposed as reported in the literature [2], considering the CD4+T cell population is characterized by its three possible states: infected $N_1(t)$, healthy $N_2(t)$ and dead $N_3(t)$. Figure 2 illustrates the energy and transition diagram of the proposed model. The relative values between these energies are fixed from the populations of each state at the threshold of the onset of AIDS, that is, when $n_1^* \sim 0.7$, $n_2^* \sim 0.2$ and $n_3^* \sim 0.1$, respectively, where $n_i = N_i/N$, ($i = 1$, 2, and 3).

In terms of the variables of the HIV infection model, one can write the following equations:

$$n_1(t) + n_2(t) + n_3(t) = 1 \tag{1}$$

$$\mathcal{E}_1 n_1(t) + \mathcal{E}_2 n_2(t) + \mathcal{E}_3 n_3(t) = \mathcal{E}(t) \tag{2}$$

$$\mathcal{S}(t) = -\sum_{i=1}^{3} n_i(t) \log n_i(t) \tag{3}$$

In the equations above $\mathcal{E}(t)$ and $\mathcal{S}(t)$ label the energy (in units of $k_B T$) and the entropy (in units of k_B) per particle at the instant t, respectively.

In our correspondence between the CA model and the 3-level energy model, the transition probabilities $P_{D\to H}$ and $P_{D\to I}$, which represent the reposition of dead cells, are mimicked in the 3-level model by the respective Boltzmann weights, as indicated in the equations:

$$\mathcal{P}_{D\to H} = p_r(1-p_i) \;\propto\; e^{-(\mathcal{E}_2-\mathcal{E}_3)} \tag{4}$$

$$\mathcal{P}_{D\to I} = p_r p_i \;\propto\; e^{-(\mathcal{E}_1-\mathcal{E}_3)} \tag{5}$$

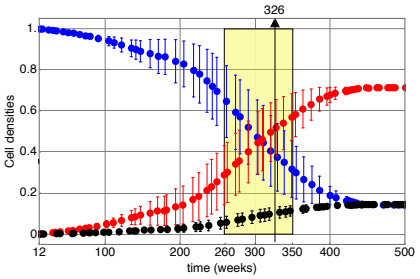
As it can be seen in Figure 2, the direct transition from the infected to the healthy state is absent once this process is prohibited by any mechanism.

In Figure 3, the region of the spectrum with negative energies $\mathcal{E} \sim -1.8$ corresponds to states in which the population of infected cells not yet exceeds that of uninfected cells (healthy + dead), which occurs on average until week 320 after the peak of primary infection. Up to $\mathcal{E} \sim -5.4$, we observed a deterioration in the probability density function $P(\mathcal{E})$. This global behavior shows the highest occupancy in the most negative energy levels, due to the predominance of healthy cells at this stage. In the dynamics of infection, this occurs during the clinical latency period of up to ~ 231 weeks (average). The peak observed around $\mathcal{E} \sim 6.5$ corresponds to the dynamics of the infection in the time interval between 165 and 188 weeks, where the probability of the appearance of compact structures becomes significant [3], which leads the course of the infection to the inexorable beginning of AIDS. Positive energy values indicate the predominance of infected cells (high energies) when the unwanted development of AIDS is established with the collapse of the immune response from week ~ 350 (average).

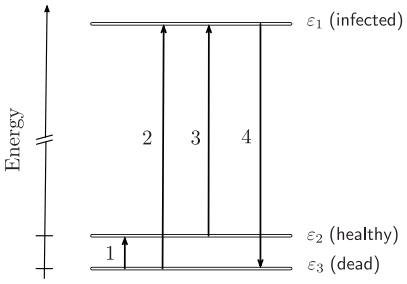
In Figure 4: (i) $10 < t < 200$ weeks corresponding to the clinical latency period, the density of infected cells is low and increases linearly with time; (ii) $200 < t < 450$ weeks corresponding to the onset of AIDS, which is the density of infected cells when the growth rate of them approximately doubles and finally; (iii) $t \geq 450$ weeks, when the infected cell rate reaches its maximum value and becomes stationary. Figure 5 shows the behavior of the entropy of the system as a function of time.

The growth decreases continuously to zero in Figure 4, characterising the instant where the temperature signal change occurs. Subsequently, the entropy in Figure 5 decreases steadily until reaching the steady-state equilibrium value (full establishment of AIDS). The instant the entropy reaches its maximum value marks the change from the regime of positive to negative temperatures as indicated in Figure 3. This value corresponds to negative but close-to-zero energy values. Analysing dynamics of HIV infection (no treatment), we conclude that the dominant state of infected cells is the one where the highest energy level is *populated* with the majority of cells characterizing by negative values of absolute temperature. In these circumstances, the infected state becomes the state of equilibrium of the system.

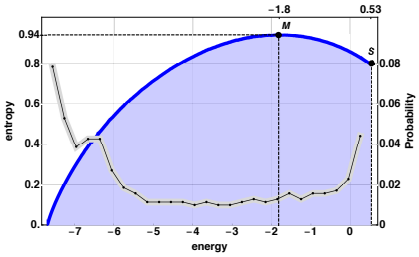
From the temporal evolution of the entropy, we ob-



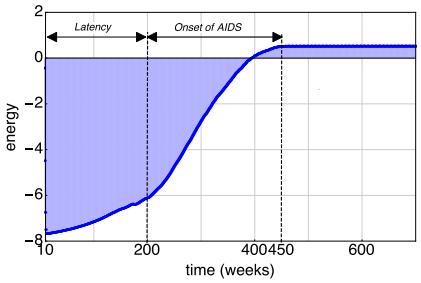
(1) Fractions of CD4 T+ cells healthy (blue), infected (A and B) (red) and dead (black) as a function of time (weeks).



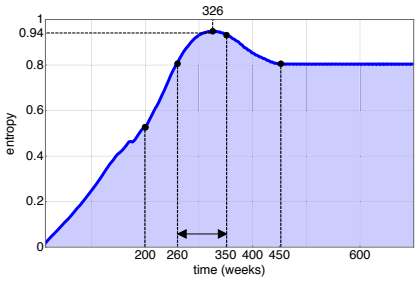
(2) Scheme of the energy levels and the transitions between the states of the three cell populations prescribed by the model: E1 for infected, E2 for healthy and E3 for dead cells respectively. The arrows indicate the direction of possible transitions.



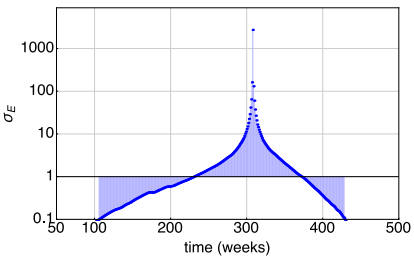
(3) Histogram of the energy distribution (right y-axis) $P(\mathcal{E})$ for energy states with positive ($\mathcal{E} < -1.8$) and negative temperatures ($\mathcal{E} > -1.8$), and time-dependent parametric behavior of entropy as a function of energy (left y-axis).



(4) Energy evolution from 10 to $\sim$ 200 weeks: clinical latency phase. From $\sim$200 to $\sim$450 weeks: development of AIDS.



(5) Entropy evolution (weeks). Interval $(260 - 350)$ weeks is the time lag for occurrence of high fluctuations on cell concentrations.



(6) Semi-log plot of Energy relative error dynamics, same parameters used in Figure 1

served a linear monotonic growth until approximately $t \sim 200$ weeks, when the appearance of partially ordered and compact spatial structures occurs with predominance of sequestering cells over the number of infected cells. With the growth of entropy in the first half of clinical latency, the system information losses are associated with the dynamic correlation losses that happen in $t \simeq 200$ weeks. This loss of correlation can be tracked through the statistical behavior of the dynamics of infection via random matrix (RM) theory [3].

We found in Figure 5 that there is a small region of energy fluctuations with still negative values but corresponding to negative temperatures. In the dynamics of infection, this region corresponds to the time interval between $\sim$260 and $\sim$326 weeks, when the "crossing" of the densities of infected and uninfected cells occurs, as mentioned above. To quantify the energy fluctuations and to establish a criterion specifying the region where absolute inversion occurs between infected and uninfected cell populations, we define the relative deviation $\sigma_{\mathcal{E}}$ as the ratio between the mean square deviation of the energy, $\delta\mathcal{E}$, and its absolute value:

$$\sigma_{\mathcal{E}} = \frac{\delta\mathcal{E}}{|\mathcal{E}|}. \qquad (6)$$

In Figure 6, fluctuations of order 10^3 higher than the absolute value of the energy are responsible for the states in which energy and temperature are both negative. The instants for which $\sigma_{\mathcal{E}} = 1$ correspond to $t = 231$ and $t = 372$ weeks, the beginning and end of the transition, respectively. These values fit the region where the error bars overlap, as shown in Figure 1.

Notes

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b. Original version of this article is Ref. [4]

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