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A Probabilistic Simulator for Population Dynamics of Quasispecies

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Abstract: We constructed a probabilistic simulator that allows all the events in population dynamics such as death, birth, mutation, and suppression/stimulation to be written with probabilistic rules. The simulator also facilitates a lattice used for expressing distribution and diversity (number of distinct strains) of quasispecies. The simulator is used to investigate the diversity threshold of in HIV and T-cell interaction.

Keywords: probabilistic simulation, population dynamics, lattice model, diversity threshold, mutation

I. INTRODUCTION

The immune system is a complex system, and it exhibits a complex behavior that can be modeled by a non-linear differential equations.

The antigenic diversity threshold theory by Nowak and May [1, 2] also involves such a complex behavior, giving a threshold. The theory determines a threshold of diversity of HIV (human immunodeficiency virus) strains when the threshold is breached, T-cells are unable to cope with HIV and it will progress to AIDS (acquired immune deficiency syndrome).

HIV is a retrovirus, which mutates with a high error rate during proliferation. Hence, diversity of HIV increases in vivo even if it started with a single wild type.

Since the mutation is intrinsically a probabilistic event, many probabilistic extensions of the population dynamics have been studied. However, we treated not only mutation but all the other events such as birth, death, stimulation/inhibition, as stochastic events for simplicity and uniformity. This uniform treatment of population dynamics is one feature of our approach, and we consider this uniform stochastic treatment allows natural modeling for a simulation of biological events. Another feature of our approach is that it facilitates two lattice spaces: one for HIV and another for T-cell.

We describe the probabilistic simulator demonstrating how the deterministic models can be mapped to the probabilistic model. We verified its performance by comparing the results by the probabilistic simulation with these by the conventional the deterministic model.

II. THE PROBABILISTIC SIMULATOR

For the immune reactions involving T-cell receptors, diversity plays an important role similarly to those involving antibodies. The immune system can deal with unknown antigens by the diversity. The pathogen such as retroviruses that mutate with a high error rate also uses diversity to escape from the immune system.

The dimension of deterministic model becomes higher as the model involves higher diversity. It is often difficult to build the mutation into the differential equation.

We transformed the deterministic model to a stochastic model by regarding every change in the population as a stochastic event described by a transition rule. Thus, the deterministic differential equations must be transformed to a Markov chain at first.

1. The probabilistic model

The Nowak-May model describes an interaction between T-cells and HIVs. The model is described by N variables of HIV distinct strains and N variables of T-cell each of which specifically interacts with the corresponding strain of HIV as in (1).

$$\begin{aligned} \dot{v}_i &= v_i(b_i - p_i x_i) \\ \dot{x}_i &= k_i v_i - u_i\left(\sum v_i\right)x_i \end{aligned} \tag{1}$$

A variable v_i is a population of HIV and x_i is that of helper T-cells that remove v_i specifically (i=1, 2,$\cdots$, N). The parameters are nonnegative real numbers as shown in the following.

b_i: Replication rate of v_i

p_i: Rate of elimination of v_i by x_i

k_i: Rate of stimulation of x_i by v_i

u_i: Rate of depletion of x_i by HIV

This model is transformed to a stochastic model with a set of transition rules as shown in Table 1. Transition rate r_k is based on the equation (1). However, when HIV proliferates, the mutation occurs at the rate of mutation rate μ ($0 \leqq \mu \leqq 1$), and a new HIV strain v_j ($i \neq j$) is mutated from v_i.

Table 1. State transition rule transformed from Nowak-May model

k	Transition rule	Transition rate r_k	Event
1	$v_i \rightarrow v_i + 1$	$(1-\mu)b_i v_i$	HIV proliferation
2	$v_i \rightarrow v_i - 1$	$p_i v_i x_i$	HIV removal
3	$x_i \rightarrow x_i + 1$	$k_i v_i$	T-cell stimulation
4	$x_i \rightarrow x_i - 1$	$u_i (\sum v_i) x_i$	T-cell inhibition
5	$v_i \rightarrow v_{N(i)} + 1$	$\mu b_i v_i$	HIV mutation

The events occur obeying the *Poisson process*, and hence intervals t between the consecutive events must follow the probability density function as in (2).

$$f(t) = r\exp(-rt)$$
$$r = \sum r_k \qquad (2)$$
$$p_k = r_k / r$$

The expression (2) shows that event k occurs with a probability p_k in state transitions. The interval t is calculated for each variable as in Fig.1. At each occurrence time, the state transition takes place.

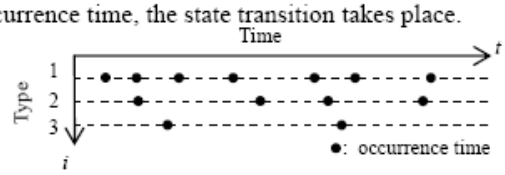

Fig.1. Time distribution for each variable

2. Lattice space

We use two two-dimensional lattice spaces of size N ($=m \times n$) as in Fig.2. One is for HIV strains with different parameters (b_i, p_i). Another is for T-cells, with parameters (k_i, u_i) that react specifically to a strain (b_i, p_i).

A strain i changes to either of four neighborhoods with an equal probability when the strain mutated.

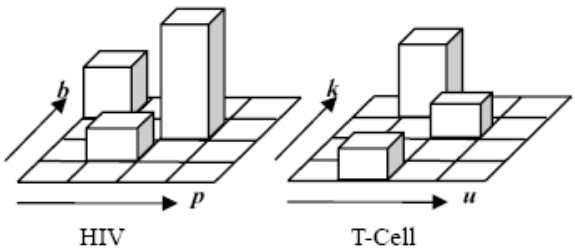

Fig.2. Two lattice spaces, each lattice shows distinct strains.

3. The implementation of simulator

Fig.3 shows a screenshot of the two lattice spaces in a simulation. The size of the lattice is set to the number of HIV strains, and the color of each lattice indicates the population density of the corresponding strain.

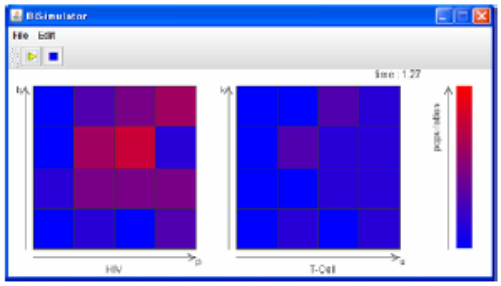

Fig.3. A screenshot of lattice spaces

The simulator is composed of three modules (Fig.4). The user-interface module passes parameters to the simulator module and gets results from the simulator. The simulator module realizes a Monte Carlo simulation for stochastic models. The model module handles the state transition rules describing a Markov chain. Any simulation must be preceded by the compilation of a Markov chain from a deterministic model.

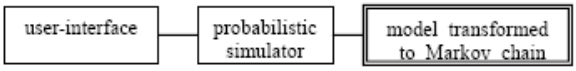

Fig.4. Composition of the simulator, model module and user-interface

III. SIMULATION EXAMPLES

To demonstrate the probabilistic simulation, we compared the results with those by the deterministic simulation. The model used for the comparison is the Nowak-May model and the Lotka-Volterra model. The Runge-Kutta method (RK4) is used in the deterministic simulation.

1. Nowak-May Model

The state transition rules of the Nowak-May model are shown in Table 1. The diversity threshold condition of the model follows:

$$D \equiv \sum \frac{b_i u_i}{p_i k_i} < 1 \quad . \qquad (3)$$

This D indicates the antigenic diversity. In this model, the immune system cannot suppress HIV when the threshold is exceeded, and the population of HIV becomes out of control. To verify the threshold

condition, we conducted simulations for the following three cases: D < 1, D > 1, and D = 1.

A. HIV diversity below the threshold

The case when the diversity D is less than the threshold (D<1) is presented in this section. Table 2 lists parameters for the simulations.

Table 2. Condition of the simulation in the case D<1

Lattice space	4×4
Initial population of T-cells	0
Initial population of HIV each variable species	10
Mutation rate	0

Fig.5 compares the results by the simulator with those by the RK4. The figure plots total population of HIV and T-cell when time develops.

The population of HIV decreases in RK4 because the diversity is below the threshold. The phenomenon that HIV is suppressed by the immune system can be observed similarly in the probabilistic simulation.

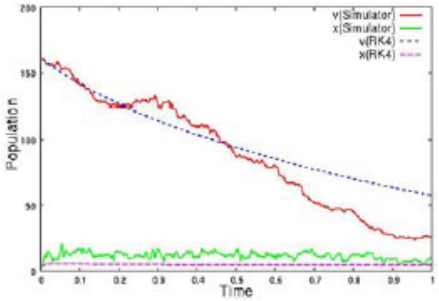

Fig.5. Time evolution of T-cell and HIV population (D<1)

B. HIV diversity over the threshold

The case when the diversity D is greater than the threshold (D>1) is plotted in Fig. 6. The parameters for simulation are the same as those in Table 2 except the lattice space has the size 4×6.

In this case also, the results by the probabilistic simulator qualitatively match well with those by RK4. The population of HIV is increasing and will explode eventually.

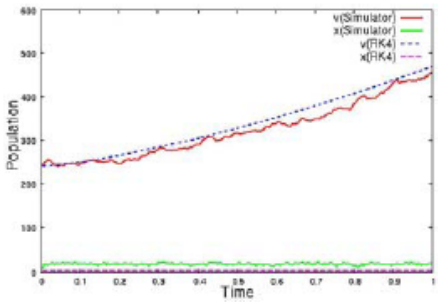

Fig.6. Time evolution of T-cell and HIV population (D>1)

C. HIV diversity near the threshold

The case when the diversity D equal the threshold (D=1) is presented in this section. The parameters for simulation are the same as those in Table 2 except lattice space that is 4×5. Fig.7 compares the results by the simulator with those by the RK4.

The population of HIV is kept almost constant in the result of RK4. On the other hand, HIV is suppressed by the T-cells in the probabilistic simulator. Further, fluctuation in HIV total population is also observed during decay of HIV.

There is another marked difference between the original model by a differential equation and the transformed model by a Markov chain (other than the obvious difference of stochastic and deterministic). The Markov chain model uses integers for population, while the differential equation uses real numbers for population density. The qualitative difference between the results by the simulator and those by RK4 observed in this simulation (Fig. 7) may be caused by this difference. Although when the population density of T-cell is evaluated as 0.1 in RK4, the population can be counted as 1 in the simulator (the Markov chain). Thus, the suppression from T-cells is evaluated higher in the simulator than the suppression in RK4. With only simulation results, however, we are not able to conclude which reflects the reality more faithfully. Nevertheless, the probabilistic simulator seems to provide an instance that could have occurred in reality.

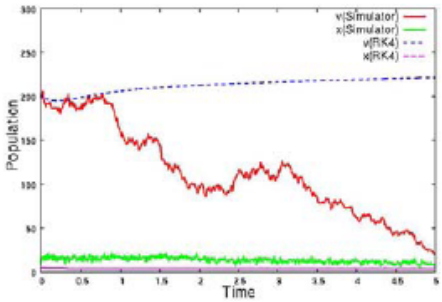

Fig.7. Time evolution of T-cell and HIV population (D=1)

D. Mutation

This section presents a case when the mutation occurs during the interaction. Since the deterministic simulation does not allow mutation, we do not have the result by RK4 unlike the proceeding section. Fig.8 plots total population of HIV and T-cell when time develops.

The parameters are the same as those in the section C above except the mutation rate is 0.5. HIV is suppressed by the immune system with the parameters

in section C. The phenomenon that the immune system cannot suppress HIV due to the diversity increase by mutation can be observed.

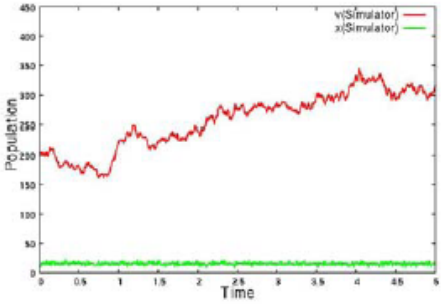

Fig.8. Time evolution of total population of HIV and T-cell

2. Lotka-Volterra Model

The Lotka-Volterra model is described by nonlinear differential equations as in (4). The equations express stimulation and suppression between the predator and prey [5, 6].

$$\begin{aligned} \dot{x} &= x(a - by) \\ \dot{y} &= -y(c + dx) \end{aligned} \tag{4}$$

A variable x is the population of the predator and y is that of the prey. The parameters a, b, c and d are nonnegative real numbers. Table 6 lists the state transition rules transformed from the equations (4).

Table 6. Transition rules transformed from Lotka-Volterra model

k	Transition rule	Transition rate r_k	Event
1	$x \rightarrow x+1$	ax	Increase of prey
2	$x \rightarrow x-1$	bx	Decrease of prey
3	$y \rightarrow y+1$	dy	Increase of predator
4	$y \rightarrow y-1$	cy	Decrease of predator

A.Result

Table 7 lists parameters for the simulations. The parameters a, b, c and d are as follows: a=5, b=0.05, c=5, and d=0.01.

Table 7. Condition of the simulation

Lattice space	1×1
Initial population of the predator	200
Initial population of the prey	50
Mutation rate	0

Fig.9 compares the probabilistic simulation with the deterministic one by the RK4. The figure plots the population of the predator and the prey when time develops. In both probabilistic and deterministic simulations, the populations of the predator and prey oscillate. We should note, however, there is the case when the simulator result gives increasing amplitude of the oscillation, while RK4 gives a fixed one.

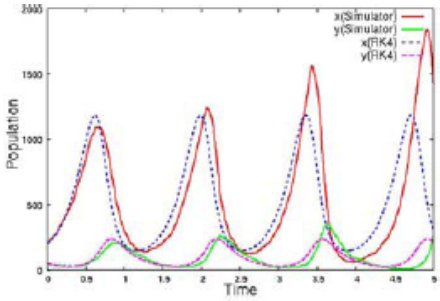

Fig.9. Time evolution of the predator and the prey

IV. CONCLUSION

We have constructed a probabilistic simulator that allows a probabilistic simulation required for a Markov chain transformed from a deterministic differential equation. Probabilistic simulation can involve an intrinsically stochastic event such as mutation in population dynamics of quasispeacies.

We observed that probabilistic simulations can generate results qualitatively similar to those by the deterministic simulations. However, some differences caused by the difference between discrete and continuous values in populations are also observed.

Acknowledgements

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