

MARKOV CELLULAR AUTOMATA MODELS FOR CHRONIC DISEASE PROGRESSION

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ABSTRACT. We analyze a Markov cellular automaton that models the spread of viruses that often progress to a chronic condition, such as human immunodeficiency virus (HIV) or hepatitis C virus (HCV). We show that the complex dynamical system produces a Markov process at the later stages, whose eigenvectors corresponding to the eigenvalue 1 have physical significance for the longterm prognosis of the virus. Moreover we show that drug treatment leads to chronic conditions that can be modeled by Markov shifts with more optimal eigenvectors.

1. INTRODUCTION

When studying an extremely complex system it is frequently useful to develop a model which explains or illuminates statistical properties of the process rather than to follow the individual behavior of each of 10^{12} or more particles interacting with others nearby. This is the case for immunology and virology studies of diseases with underlying mechanisms often too complicated to model precisely; this statistical or global dynamics approach has been used by many authors [1, 6, 7, 8, 10, 11, 14, 13, 15, 18, 19, 24, 25, 35, 36, 37]. In this paper we discuss Markov cellular automata models as a noninvasive method for analyzing some aspects of chronic diseases. Cellular automata (CA) models used in the study of immune responses have been used for decades (eg., see the references listed above which also contain references to earlier studies). The authors (and Burkhead) introduced the use of Markov CAs to model end stage virus dynamics in [1], and in this paper we expand the analysis to show it applies quite generally to chronic diseases.

In [37] a mathematical model for the spread of human immunodeficiency virus (HIV) within a lymph node was presented and studied; the paper [1] gives a rigorous mathematical study showing that the model simulates, with robustness in parameter changes, the timing of the virus spread up to the terminal stages when AIDS sets in. The model works roughly as follows. An initial infection is simulated by introducing a random sprinkling of infected lymph cells (1's) into a grid of healthy cells (0's), with a density determined by clinical data [27]. At each time step one of three possible CAs is applied with certain data-driven probabilities and independently chosen at each site. Of the 3 CAs, labelled \mathcal{N} , \mathcal{C} , and \mathcal{D} , the CA \mathcal{N} reflects the usual course of a disease such as a flu-virus, with the immune response fighting off the virus (and this CA receives the highest probability), \mathcal{C} reflects that

there are reservoirs of infected cells lying dormant that somewhat randomly (and rarely) spring to action, and the third, \mathcal{D} represents the possibility that a depleted cell site remains in that state, instead of being replaced immediately by a healthy cell.

In [1] we established that once enough time has elapsed the more orderly view of the course of the disease disappears, and the state of a cell in the lymph node (or site of cells as in [1]) seems to evolve in a more random way that only depends on its current state. In the intervening years, many authors have worked on the model [26, 25, 18, 6, 7], inserting drugs into the model; this was also done in Section 6 of [1]. Most of the newer mathematical models are far more complicated than the original one.

In this paper we generalize the model to chronic diseases caused by persistent virus activity, by turning our focus to the later stages and providing a Markov model whose mathematical analysis can be done using some fundamental theorems in ergodic theory.

By analyzing the eigenvectors of an associated matrix we obtain results about limiting percentages of cells at certain stages of infection. For the HIV application we focus on the CD4 cell counts because according to a large study using collaborative data involving over 75,000 HIV-infected adults ([22], p. 7):

In all these studies, CD4 cell count was the strongest prognostic factor for disease progression; viral load was at best only weakly predictive of progression in models with time updated CD4 cell counts.

Often drugs are not introduced until the HIV has been present for some time and the CD4 count is already low; eg. the levels remaining in the system used in [22] are 20%, 30%, and 50% of the healthy CD4 count, for drug treatment to be deemed essential, recommended, or worth considering, respectively. Therefore according to [1] the three CAs have been interacting long enough that the big picture is somewhat random and the Markov model can be used.

In the case of other chronic diseases, we use a configuration of the dynamical system to represent the cells (or cell sites) of the organ most affected by the virus. For example in the case of hepatitis C virus (HCV) we use liver cells [32], and to apply the model to the human papilloma virus (HPV), a point in the math model would represent a configuration of epithelial cells [5].

One important advantage of this approach is that the math model is based on a Markov shift whose associated eigenvectors, coming from an invariant measure, represent the longterm and limiting percentages of healthy and infected cells in patients. We showed in [1] that without drugs the final limiting CD4 count is barely above 14% which is well below the medically determined 20% AIDS-defining cut-off [21]. Secondly when drugs are introduced we can show how this affects the underlying Markov shift, the incidence matrix

along with its dominant eigenvector, and the invariant probability measure, and estimate the new limiting healthy CD4 cell percentages. The model reflects the findings of the longitudinal cohort study done in [22]: namely patients with a lower beginning CD4 count are helped more, while patients with a moderately high starting CD4 level are only helped a little. The basic theory of irreducible Markov shifts reveals a parallel phenomenon, that with probability one, every starting distribution vector, when acted on by the same Markov shift, approaches the same limiting distribution. A conclusion to be drawn from this mathematical model is that drug intervention should occur before the end stages.

Before the Markov stage has been reached, from [37] and [1] we know that the stochastic cellular automaton (SCA) models control the dynamics, and in that scenario the “healthy recovery model” (\mathcal{N} described above and defined in Section 2.2 showing normal immune response) is the one that prevails. In that setting, before going over the threshold into the Markov dynamics, complete recovery is a mathematically possible outcome, which is seen in some potentially chronic diseases such as HCV.

In the clinical setting, drug toxicity and reduction in drug effectiveness over time inhibit the search for a cure [30, 31], and in our model, the measures used to model the dynamics suggest that the optimal outcomes can be reached before this occurs (see Figure 9), reinforcing the idea that early drug intervention is best. Despite many disadvantages of an early rigorous drug treatment such as the potential for pill fatigue and short- term and long-term toxicity this hypothesis has been shown to have definite advantages in some patients ([3],[16]).

This paper is organized as follows. In Section 2 we give some mathematical definitions for the model. Since we discuss limiting behavior it is necessary to have a metric; that is, a notion of what it means for one configuration of the system to approach a limit. We also describe briefly the original model used in [37] and [1] to explain the dynamics of HIV in a lymph node. In Section 3 we turn to the Markov model which simulates the chronic stages of HIV and give a brief mathematical description of how it works. Section 4 describes how the math model shows the effects of drug therapy and gives some rigorous results about limiting behavior of the cell dynamics. We apply the analysis in Section 5 to model the chronic hepatitis C dynamics using Markov CAs.

2. PRELIMINARIES

We introduce the basic mathematical building blocks for the models studied in this paper, including the metric used to discuss limiting behavior. We refer the reader to the original SCA model appearing in [37] and worked on rigorously in [1] for more details. One outcome of the study in this paper is that despite the fact that many complicated models exist in the literature, the chronic stage of viral disease can be studied using a simple Markov

model. Moreover, our current analysis of the model is independent of the dimension used to represent the organ (which is typically 2 or 3).

2.1. Mathematical background and notation. We begin by giving the mathematical setup for a cellular automaton (CA). Let \mathcal{A} denote a finite state space $\mathcal{A} = \{0, 1, \dots, m\}$. State 0 represents a healthy cell site in an organ, and states 1 through $m - 2$ represent infectious cells able to infect neighboring cells. State $m - 1$ represents an infected cell whose ability to infect a neighboring cell has weakened so that a healthy cell needs many of these surrounding it (a parameter which we usually set to be 4) before it gets infected; that is, $m - 1$ is an infected and very weakly infectious cell. State m is a depleted (dead) cell; for our examples we use $m = 6$.

We find that modeling in two dimensions captures most of the dynamics; this corresponds to thinking of a lymph node as a sort of cylinder. All of the math analysis that follows can be done for dimension $d = 3$ as well, but the analysis is the same. However using $d = 2$ makes the concepts and notation easier to explain in this paper; moreover when we switch to the Markov model in Section 3 the dimension is irrelevant. We define the space of vectors $\mathbb{Z}^2 = \{\vec{i} = (i, j), i, j \in \mathbb{Z}\}$. It is useful to picture \mathbb{Z}^2 as a lattice of integers in the plane (or on a surface, by identifying edges of a polygon in the plane). On \mathbb{Z}^2 we define length as: $\|\vec{i}\| = \max\{|i|, |j|\}$, the larger absolute value of the two indices.

We define a CA on the space: $X = \mathcal{A}^{\mathbb{Z}^2}$, which we should think of as the integer lattice \mathbb{Z}^2 with a coordinate from the state space \mathcal{A} placed at each (i, j) coordinate in the lattice. Since each location (i, j) is assigned exactly one state from \mathcal{A} , mathematically we define X as the space of functions from \mathbb{Z}^2 to \mathcal{A} . In this way each for each $x \in X$ and $\vec{i} = (i, j) \in \mathbb{Z}^2$ we write $x_{(i,j)}$ to denote *the coordinate of x at \vec{i}* , with $x_{(i,j)} \in \{0, \dots, m\}$.

Let $E \subset \mathbb{Z}^2$ be any finite set; by x_E we denote the block of coordinates $\{x_{\vec{i}}, \vec{i} \in E\}$, so $x_E \in \mathcal{A}^{|E|}$ where $|E|$ is the cardinality of E . We define a neighborhood of radius $k \in \mathbb{N} \cup \{0\}$ about $(0, 0) \in \mathbb{Z}^2$, by $N_k = \{\vec{i} = (i, j) : |i|, |j| \leq k\} = \{\vec{i} : \|\vec{i}\| \leq k\}$. Note that $|N_k| = (2k + 1)^2$; it is just pairs of integers (i, j) with $|i| \leq k$ and $|j| \leq k$.

If u is a fixed $(2k + 1)^2$ square pattern of symbols from \mathcal{A} , centered at $(0, 0) \in \mathbb{Z}^2$, then $B_u = \{x \in X : x_{N_k} = u\}$ is the *u -cylinder of radius k* (centered at $(0, 0)$). B_u is precisely the set of points from X whose central block of coordinates extending out k units in each direction coincides with the fixed pattern u . These form a basis for the topology on X .

The shift map on X corresponds to sampling different areas in the same affected organ (lymph node, liver, etc) and expecting the outcome to be more or less independent of the precise location of the sample. We define the shift maps on X as follows:

$$\forall \vec{i} = (i, j) \in \mathbb{Z}^2, \sigma_{\vec{i}}(x)_{(k,l)} = x_{(i+k, j+l)}.$$

In order to discuss continuity of $\sigma_{\vec{r}}$ we need to recall the classical metric on X . For any pair of points $x, v \in X$, $d_X(x, v) = \frac{1}{2^k}$ where $k = \min\{m : x_{N_m} \neq v_{N_m}\}$; X is compact with respect to the metric topology. This metric topology makes the points x and v close to each other if and only if their central blocks of coordinates agree; i.e., x and v look the same when restricted to N_k for some $k \in \mathbb{N}$.

We start with the mathematical definition of a CA, but immediately follow it by an equivalent more practical one.

Definition 2.1. A **2-dimensional cellular automaton (CA)** is a continuous transformation $F : X \rightarrow X$ such that for every $\vec{r} \in \mathbb{Z}^2$, $F \circ \sigma_{\vec{r}} = \sigma_{\vec{r}} \circ F$.

It is well-known that each CA is characterized by a local rule using the definition of continuity in the metric topology on X . In the next theorem the letter r represents the radius of the local rule.

Theorem 2.2. [12] The map F on X is a CA if and only if there exists an integer $r \geq 0$ and a map $f : \mathcal{A}^{(2r+1)^2} \rightarrow \mathcal{A}$ such that for every $x \in X$,

$$(2.1) \quad F(x)_{\vec{r}} = f(x_{N_r + \vec{r}}).$$

The map f that appears in (2.1) is the *local rule* for the CA F as it describes it completely. To summarize, a CA is a map or rule that updates each coordinate in X at each time step by looking only at nearby coordinates. If F is a CA, we iterate F using the notation $F^k(x) = F \circ \dots \circ F(x)$ to denote composition with itself k times.

2.2. Using CAs to model the immune response to a virus. We describe a 2-dimensional CA, which we denote by \mathcal{N} for “normal immune response”, and which is shown in Fig. 1. It is a single CA where white represents 0, healthy cells; light blue (gray) cells represent state 1, the initial infection, as shown in the first frame. Each frame is labelled by 4 pieces of data in brackets above the frame. The first entry is the time step, showing how many increments of time have passed. The next 3 entries show percentages of cells in healthy (0), infected (1 – 5), and depleted (6) states respectively. One increment of time varies according to the virus. The blue (gray) gets darker as time passes showing the passage of time as a higher numbered state, revealing the spread of the virus; the darker color represents the next generation of the (often mutated) virus infected cells. In a healthy individual with a functioning immune system, after a time the infected cells die and are replenished by healthy ones at a rate faster than the infection. Therefore we see a return to all 0’s after a few more iterations. The local rule ν that defines the CA \mathcal{N} is given here.

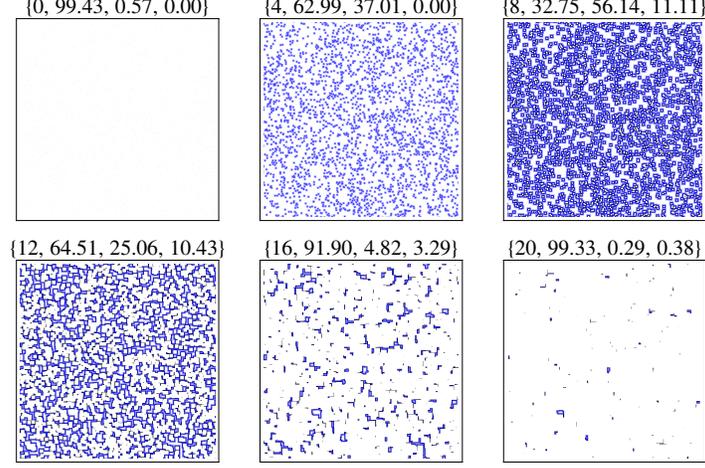


FIGURE 1. The CA \mathcal{N} represents a normal immune response to a virus, where infected cells are replenished by healthy ones and the virus is eradicated

Local rule for \mathcal{N} . Consider the state space $\mathcal{A} = \{0, 1, \dots, 6\}$ and define the local rule $\nu : \mathcal{A}^{3 \times 3} \rightarrow \mathcal{A}$ as follows:

$$\nu \begin{pmatrix} * & * & * \\ * & 0 & * \\ * & * & * \end{pmatrix} = \begin{cases} 1 & \text{if at least one } * \text{ is } 1, 2, 3, \text{ or } 4, \text{ or if at least } 4 \text{ } * \text{'s are } 5 \text{'s} \\ 0 & \text{otherwise} \end{cases},$$

$$\nu \begin{pmatrix} * & * & * \\ * & a & * \\ * & * & * \end{pmatrix} = a + 1 \text{ for } 1 \leq a \leq 5,$$

$$\nu \begin{pmatrix} * & * & * \\ * & 6 & * \\ * & * & * \end{pmatrix} = 0$$

The CA \mathcal{N} occurs most of the time in the stochastic model discussed in [37] and [1]. Using the metric defined above, we showed in [1] that: $\lim_{k \rightarrow \infty} \mathcal{N}^k(x) = \bar{0}$ for every initial configuration $x \in X$ consisting of 0's and 1's, where $\bar{0}$ denotes the point with a zero in every coordinate. That is, initial infections are repaired by the normal immune response.

Similarly we use two small variations on this CA to represent the dynamics if the immune system is compromised or if the virus mutates too fast for it to be eradicated. We call the two other CAs \mathcal{C} for compromised response and \mathcal{D} for depleted response; we define them by their local rules, c and d respectively. Using the same state space \mathcal{A} , we define the local rules c, d :

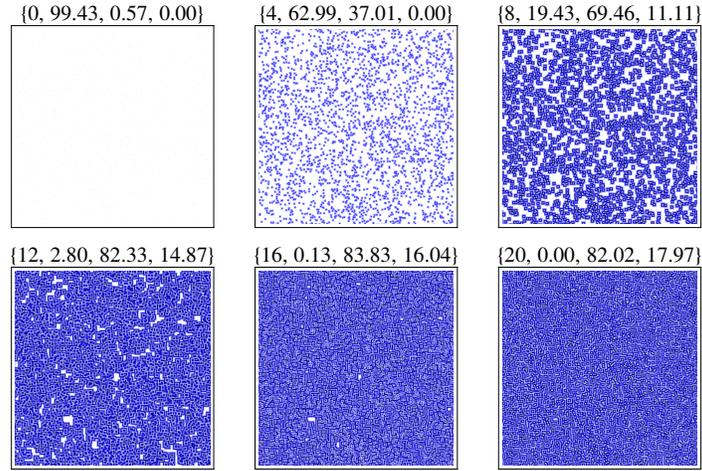


FIGURE 2. The CA \mathcal{C} has cycles of cell infection that repeat over and over when the virus cannot be completely removed from the system

$\mathcal{A}^{3 \times 3} \rightarrow \mathcal{A}$ by:

$$c, d \begin{pmatrix} * & * & * \\ * & a & * \\ * & * & * \end{pmatrix} = \nu \begin{pmatrix} * & * & * \\ * & a & * \\ * & * & * \end{pmatrix} \text{ for any } a \neq 6,$$

while

$$c \begin{pmatrix} * & * & * \\ * & 6 & * \\ * & * & * \end{pmatrix} = 1, \quad d \begin{pmatrix} * & * & * \\ * & 6 & * \\ * & * & * \end{pmatrix} = 6.$$

Denote by $\mathcal{N}, \mathcal{C}, \mathcal{D} : \mathcal{A}^{\mathbb{Z}^2} \rightarrow \mathcal{A}^{\mathbb{Z}^2}$ the CA with local rule ν, c , or d , respectively.

Figs. 2 and 3 show the dynamics of \mathcal{C} and \mathcal{D} ; we proved in [1] that: $\lim_{k \rightarrow \infty} \mathcal{D}^k(x) = \bar{6}$ for every initial configuration $x \in X$ consisting of 0's and 1's, where $\bar{6}$ is the point with all 6's. When an otherwise healthy person is infected with HIV, we combine these CAs randomly, using the rule \mathcal{N} slightly less than 99% of the time, to form a stochastic CA. The probabilities chosen for the model are data-driven. This is explained in detail in a variety of papers (see in particular [1] or [11]).

3. MARKOV CELLULAR AUTOMATA USED TO MODEL CHRONIC VIRAL DISEASE

We now turn to a mathematical analysis of the event that the immune system does not clear out the infection and therefore there is not convergence to the healthy state. Specifically we look at the dynamics of a chronic illness such as HIV or hepatitis C and describe a model for the limiting viral presence in the lymph node or liver, with and without drug intervention.

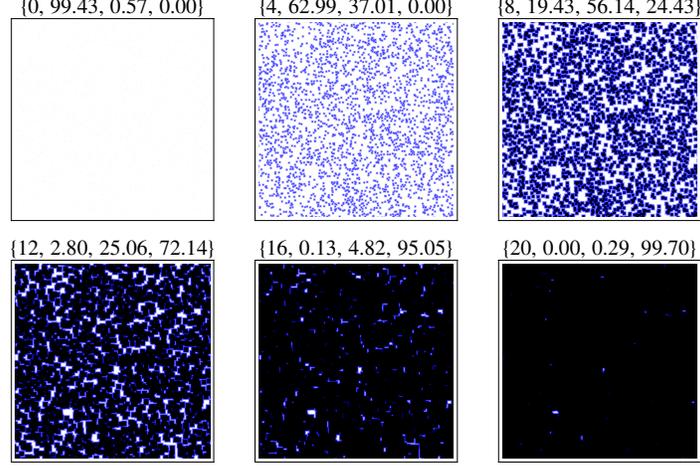


FIGURE 3. The CA \mathcal{D} represents the weakening of the immune system so that cells are not replenished

We describe a dynamical system on $X \subseteq \mathcal{A}^{\mathbb{Z}^2}$, a CA of radius 0, determined by a constant rule at each $\vec{i} \in \mathbb{Z}^2$. Our claim is that this SCA provides an excellent simple model for the virus dynamics after the original SCA has been iterated so many time steps that there are no longer coherent areas of healthy and unhealthy cells. Under the assumption of no drug intervention, the SCA model given by \mathcal{N}, \mathcal{C} , and \mathcal{D} , gives rise to an incidence matrix $B = (B_{ij}), i, j = 0, 1, \dots, 6$, where $B_{ij} = 1$ if a cell can go from state i to state j in one time step, and 0 otherwise. In Fig. 4 we show the incidence graph which determines the matrix in (3.1) (and vice versa). The directed graph in Fig. 4 has vertices representing the possible states in $\mathcal{A} = \{0, 1, 2, 3, 4, 5, 6\}$ and vertices i and j are connected by a directed edge if a cell in state i can transition to state j in one time step of the stochastic CA. Details are given in [1].

The corresponding incidence matrix is given by:

$$(3.1) \quad B = \begin{pmatrix} 1 & 1 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 1 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 1 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 1 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 1 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 1 \\ 1 & 1 & 0 & 0 & 0 & 0 & 1 \end{pmatrix}$$

The graph or the matrix B defines a subshift (of finite type), $\Sigma_B \subseteq \mathcal{A}^{\mathbb{Z}}$, given by $\Sigma_B = \{\alpha = \dots a_{-1}a_0a_1\dots \in \mathcal{A}^{\mathbb{Z}} : B_{a_i a_{i+1}} = 1\}$. The natural dynamical system to consider on Σ_B is the shift s ; namely $s(\alpha)_i = \alpha_{i+1}$. This shift will be used as the local rule in the Markov CA.

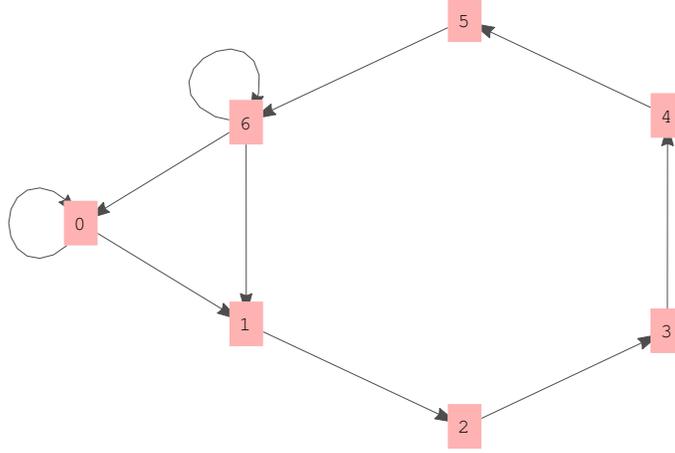


FIGURE 4. The incidence matrix used to determine Σ_B , assuming no drug intervention

Definition 3.1. We define a (topological) Markov CA as follows: using the state space $\mathcal{A} = \{0, 1, \dots, 6\}$ define the local rule $m : \mathcal{A}^{3 \times 3} \rightarrow \mathcal{A}$ as follows:

$$m \begin{pmatrix} * & * & * \\ * & a & * \\ * & * & * \end{pmatrix} = s(\alpha)_0$$

for all $a \in \mathcal{A}$ and any $\alpha \in \Sigma_B$ with $\alpha_0 = a$. We write M for the Markov CA with local rule m .

We note that this is a rule of radius 0 since the state of a cell at time $t + 1$ depends only on its state at time t and not on the states of any of its neighbors. On the other hand we have that M is actually an SCA because if $\alpha, \beta \in \Sigma_B$ with $a = \alpha_0 = \beta_0$, then $s(\alpha)_0$ might not be the same as $s(\beta)_0$, for example if several successor states are allowed after a . More precisely we look at a larger space by placing a copy of Σ_B at each coordinate $(i, j) \in \mathbb{Z}^2$; we denote the space by $\bar{\Sigma}_B = (\Sigma_B)^{\mathbb{Z}^2}$. Then for $(i, j) \in \mathbb{Z}^2$, $k \in \mathbb{N} \cup \{0\}$, $\bar{y} \in \bar{\Sigma}_B$ can be written as $\bar{y} = \{y_k^{(i,j)}\}$, $X = \{y_0^{(i,j)}\} = \{x_{(i,j)}\} \subseteq \mathcal{A}^{\mathbb{Z}^2}$ and the SCA as $M(x)_{(i,j)} = y_1^{(i,j)} \in \mathcal{A}$. With this notation, if $\alpha \in \Sigma_B$ is the sequence located at a fixed (i_0, j_0) , then $s(\alpha)_0 = y_1^{(i_0, j_0)}$. We next add a measure to finish the construction.

3.1. An invariant probability measure for a topological Markov CA. Given an incidence matrix such as B in (3.1) above, we define a Markov probability measure μ on Σ_B as follows. Assume we have a probability vector $p = (p_0, \dots, p_6)$; this means $p_k \geq 0$ and $\sum_k p_k = 1$. In addition we have a stochastic matrix $P = (p_{ij})_{i,j=0,\dots,6}$; by definition, $p_{ij} \geq 0$ and all row sums

are 1; we also assume that

$$(3.2) \quad pP = p.$$

From the pair (p, P) we define a measure μ on Σ_B by setting, for each finite sequence c_0, c_1, \dots, c_m ,

$$\mu(\{\alpha : a_k = c_k, k = 0, \dots, m\}) = p_{c_0} \cdot p_{c_0 c_1} \cdots p_{c_{m-1} c_m}.$$

We call (s, μ) the (p, P) -Markov shift, and note that μ is invariant for s on Σ_B .

The matrix P is *irreducible* if for each pair $i, j \exists l > 0$ such that $(P^l)_{ij} > 0$. That Markov measures can be found for any irreducible P follows from the following result (cf. [34]).

Theorem 3.2. (Perron-Frobenius Theorem) Let P be an irreducible stochastic matrix. Then 1 is an eigenvalue of P such that:

- (1) 1 is a simple root of the characteristic polynomial of P ,
- (2) 1 has strictly positive right and left eigenvectors,
- (3) these eigenvectors are unique up to a constant multiple,
- (4) $1 \geq |\beta|$ for all other eigenvalues β of P .

We note that the vector p satisfying Eqn (3.2) is the left eigenvector for the eigenvalue 1 and satisfies the conclusions of the Perron-Frobenius Theorem.

Since the space X on which the CA is acting is isomorphic to $(\Sigma_B)^{\mathbb{Z}^2}$ in an obvious way, we therefore use the product measure obtained by using μ as each factor measure. We call the resulting measure $\bar{\mu}$ and it follows from the construction that $\bar{\mu}$ is invariant for the Markov CA M .

3.2. A medical interpretation of the measure on the Markov CA.

The left eigenvector for the left eigenvalue 1 for P , the probability vector p , represents the probability that if we sample a cell randomly from a lymph node, then the cell will be in state $a \in \{0, 1, \dots, 6\}$. The stochastic matrix P represents the probability that if a cell is currently in state i , then with probability p_{ij} after one time step it will be in state j . Recall that only 0 represents a healthy cell, so that the first entry in p , p_0 , is the expected proportion of healthy cells overall. The other entries of p are not as important because all the other states represent either infected or dead cells. It is therefore the leading term of the invariant vector p we would like to understand and control if possible.

A theorem from ergodic theory, Theorem 3.5 below, gives us a tool for finding that leading entry. Markov measures lead to understandable longterm behavior of a shift map, and they give information that is easy to estimate, as is shown in the next result.

Lemma 3.3 ([34], Lemma 1.18). Let P be a stochastic matrix, having a strictly positive probability vector, p , with $pP = p$. Then

$$Q = \lim_{N \rightarrow \infty} \frac{1}{N} \sum_{n=0}^{N-1} P^n$$

exists. The matrix Q is also stochastic and $QP = PQ = Q$. Any eigenvector of P for the eigenvalue 1 is also an eigenvector of Q and $Q^2 = Q$.

The notion of an ergodic measure is important and reflects the indecomposable nature of the dynamical system; this corresponds to the fact that a virus spreads throughout a lymph node over time, and is not contained in one region. The Markov shifts we use in our model are mixing and have positive entropy, but we do not study the consequences of those properties here; some of these properties are discussed in [1].

Definition 3.4. We say that the shift s is ergodic on Σ_B with respect to an invariant probability measure μ if: $s^{-1}A = A$ for some measurable set $A \subset \Sigma_B$ implies that $\mu(A) = 0$ or $\mu(A) = 1$.

Theorem 3.5 ([34]). Consider the (p, P) Markov shift s on Σ_B . Assume that $p_i > 0$ for each i where $p = (p_0, \dots, p_6)$. Let Q be the matrix obtained in Lemma 3.3. Then the following are equivalent:

- (1) s on Σ_B is ergodic with respect to the measure μ determined by (p, P) .
- (2) All rows of the matrix Q are identical and each row is p .
- (3) Every entry in Q is strictly positive.
- (4) P is irreducible.
- (5) 1 is a simple eigenvalue of P with eigenvector p .

For a patient with HIV, the analysis given in [1] gives rise to a matrix P with a set of parameters chosen that are well supported by the data available. We give a brief explanation of how we determine the entries in P . We associate transition probabilities to the edges of the graph based on the local rules. Since each rule ν, c, d has the rules $1 \rightarrow 2, 2 \rightarrow 3, 3 \rightarrow 4, 4 \rightarrow 5$, and $5 \rightarrow 6$, for all $j \in \{1, 2, 3\}$, these directed edges each have weight 1. The directed edges incident to 6 are weighted according to the probability of using ν, c , or d when the site is in state 6. Therefore we weight the edge $6 \rightarrow 0$ with p_1 , $6 \rightarrow 1$ with p_2 , and $6 \rightarrow 6$ with p_3 , using the values $p_1 = .98999, p_2 = 9.9 \times 10^{-6}$, and $p_3 = .01$ arrived at using the biological analysis in [1]. Finally, the weights of edges incident to 0 are determined by counting how many of the 7^8 total 3×3 patterns with a center 0 update to 0 and how many update to 1. The transitions are the same under each local rule, (but can change across the board according to some parameter changes). We compute the number of patterns which update to 0. For this to be the case, none of the 8 neighbors can have value 1, 2, 3, or 4, and so each neighbor must have value 0, 5, or 6. Further, there must be no more than four 5's and so we have $z = \sum_{k=0}^3 \binom{8}{k} 2^{8-k} = 4864$ of the 3×3 patterns with a center 0 which update to 0. Thus $0 \rightarrow 0$ has weight $\frac{z}{7^8} = \frac{4864}{5764801} \approx 0.000843741$ and $0 \rightarrow 1$ has weight $1 - \frac{z}{7^8}$.

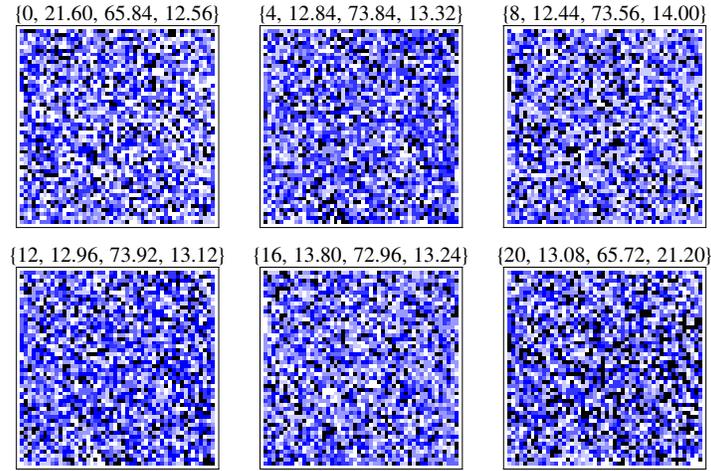


FIGURE 5. This Markov SCA shows the end stages of HIV, modeled by a Markov process; if at time 0 there are 20 – 25% of healthy cells, then very soon less than 16% of the cells are healthy

$$(3.3) \quad P = \begin{pmatrix} 8.43741 \times 10^{-4} & 0.999156 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 1 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 1 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 1 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 1 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 1 \\ .98999 & 9.9 \times 10^{-6} & 0 & 0 & 0 & 0 & .01 \end{pmatrix}$$

For this matrix a standard programming technique gives an accurate approximation to the vector, namely

$$(3.4) \quad p = (0.142753, 0.142634, 0.142634, 0.142634, 0.142634, 0.142634, 0.144075)$$

satisfying: $pP = p$ and $\sum_{k=0}^6 p_k = 1$. Therefore we can look at the first entry in this vector and see that if untreated, the healthy cells would drop to around 14% of the original healthy CD4 cell count. And further time increments would not change this percentage, by Theorem 3.5. However a patient has AIDS at 20% and is unlikely to survive long enough for the levels to reach this limiting value.

An important consequence of ergodicity is that for a set of initial values of full measure in $\mathcal{A}^{\mathbb{Z}^2}$, (which correspond to a large set of arbitrary points in time and space in which we start sampling the CD4 cells in a lymph node), after the system has entered its Markov stage and as time passes, the percentage of each state will approach their respective limiting values.

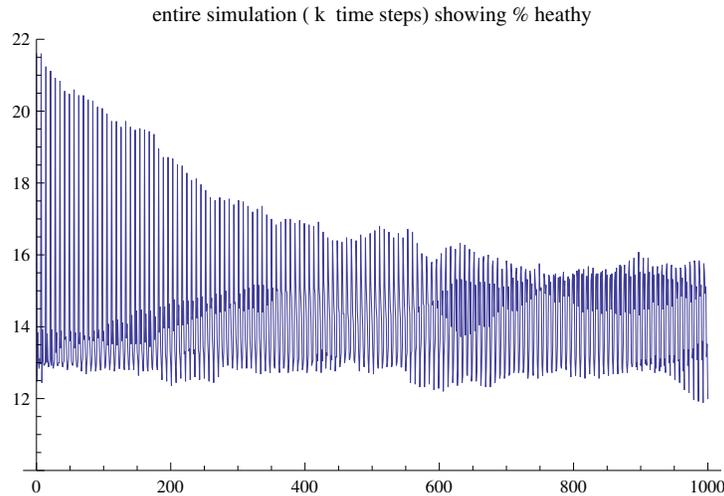


FIGURE 6. The graph shows that if at time 0, 20% of the cells are healthy, over time the percentage fluctuates around the limiting percentage of $\approx 14.3\%$

Fig. 6, obtained by 1000 iterations of the Markov model, shows that there is some fluctuation about the limiting value. However in the case of an untreated patient the limit is medically unlikely to be reached because the immune system is usually fatally compromised before that time.

We now turn to a discussion of how the drug intervention protocols developed over the past years have outcomes that are corroborated by this model, and with survivable limits for the percentages of healthy cells.

4. DRUG INTERVENTION IN THE MODEL

In this section we analyze how the limiting value of the percentage of healthy CD4 cells increases under a drug regimen such as cART (combination antiretroviral therapy) [22] or HAART (highly active antiretroviral therapy) [26]. While it is desirable for the drugs to prevent infectivity in all cells attacked by the virus, so far this has remained elusive [31]. However it is fairly well accepted by now that for an enzyme inhibitor such as a reverse transcriptase inhibitor (RTI) or a protease inhibitor (PI), the IC50 (the concentration of a drug needed to produce 50% of the maximal inhibitory effect in vitro) can be calculated and realized in the drug applications [23, 31].

Due to the types of drugs administered we have a new incidence matrix for the underlying dynamical system, which we now explain. The reverse transcriptase inhibitor (RTI) prevents the virus from replicating; put simply in the incidence graph below, either an uninfected cell remains uninfected because the transcription has been prevented, (state 0 stays at state 0 even if the cell is touching an infected one), or it becomes infected and goes through

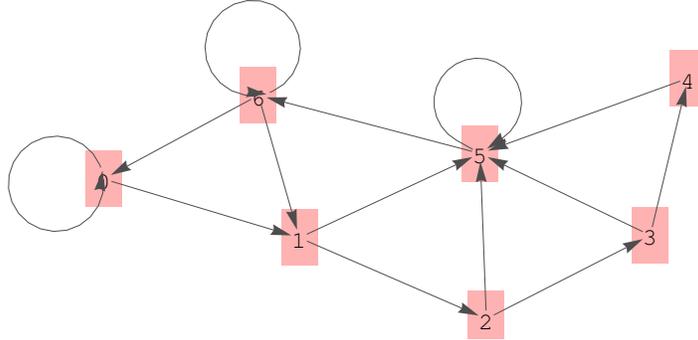


FIGURE 7. The incidence graph used to determine Σ_{BD} , assuming drug therapy has been started

the usual infection cycle. The effect of the RTI drug is modeled by choosing appropriate probabilities for the top row of the matrix; the incidence matrix does not change.

The protease inhibitor (PI) drug therapy causes immature non-infectious virions to be formed instead of active ones; this takes place after transcription, and therefore after the cell is infected. Hence the CD4 cell is itself infected and will be depleted, but nearby cells will likely not become infected; the drug works by interfering with the process of forming new virions. In the model we add the incidence relations $j \mapsto 5$ for $j = 1, \dots, 5$; recall that a cell in state 5 is only mildly infectious, and is soon going to die. If a PI is effective at any one of the already infected states, 1 – 3, then at the next time step the cell will be producing weakened and mostly non-infectious cells. Since it is difficult to say if cells last in that state for a while, we assign probabilities of 50% to each event of remaining another time step in that weakened state (5) or dying off (6). More precisely, instead of mutating through many generations of new virions and infected cells, the cell site is infected but is not producing infectious cells. This is shown by the graph in Fig. 7 sending an infected state 1 – 3 to 5 as a possibility since 5 is the “cell is not infectious but will be depleted soon” state. The new incidence graph is therefore shown in Fig. 7. We note that a depleted or dead cell can, as before, be replaced by a healthy or infected cell, or just not be replaced immediately.

The corresponding incidence matrix is:

$$(4.1) \quad BD = \begin{pmatrix} 1 & 1 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 1 & 0 & 0 & 1 & 0 \\ 0 & 0 & 0 & 1 & 0 & 1 & 0 \\ 0 & 0 & 0 & 0 & 1 & 1 & 0 \\ 0 & 0 & 0 & 0 & 0 & 1 & 0 \\ 0 & 0 & 0 & 0 & 0 & 1 & 1 \\ 1 & 1 & 0 & 0 & 0 & 0 & 1 \end{pmatrix}$$

Using some conservative estimates from [31] and [23] we assume that the drugs are each better than 50% effective but not 100% effective in their inhibitory effects. We assume each of the types of drugs is successful 55% of the time for this next calculation. The probabilities of the bottom line of the matrix are unaffected by the drugs in this model. Then the stochastic matrix for determining the limiting values becomes, using the algorithm of [1] and rounding off:

$$(4.2) \quad PD = \begin{pmatrix} .8338 & .1662 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & .45 & 0 & 0 & .55 & 0 \\ 0 & 0 & 0 & .45 & 0 & .55 & 0 \\ 0 & 0 & 0 & 0 & .45 & .55 & 0 \\ 0 & 0 & 0 & 0 & 0 & 1 & 0 \\ 0 & 0 & 0 & 0 & 0 & .5 & .5 \\ .98999 & 9.9 \times 10^{-6} & 0 & 0 & 0 & 0 & .01 \end{pmatrix}.$$

The left eigenvector for PD corresponding to the eigenvalue 1 given in (4.2) is approximately

$$p_D = (0.5587, 0.0928, 0.0418, 0.0188, 0.0085, 0.1857, 0.0938),$$

(compare with Eqn (3.4)) which shows that in the limit, in ideal conditions more than 55% of the CD4 cells could be fully functioning because they are healthy at state 0. Figures 8 and 9, generated by running the Markov model, show that the same limit is reached with different starting levels of healthy cells. That is to say, these simulations reveal that assuming other causes of death are minimized, a person lives chronically with the disease as long as the drugs are taken at the appropriate regular intervals and at therapeutic doses; this has been corroborated by large clinical studies [22, 29].

The leading entry in the stochastic eigenvector for the eigenvalue 1 shows that the percentage of healthy (state 0) cells is within a much safer range to ward off most opportunistic infections. According to many recent studies, [23]

Antiretroviral therapy has changed human immunodeficiency virus type 1 (HIV-1) infection from a death sentence to a treatable chronic illness.

We prove below that as long as there is some uncertainty about the ability of a dormant virus to reactivate, the longterm effectiveness of any given drug

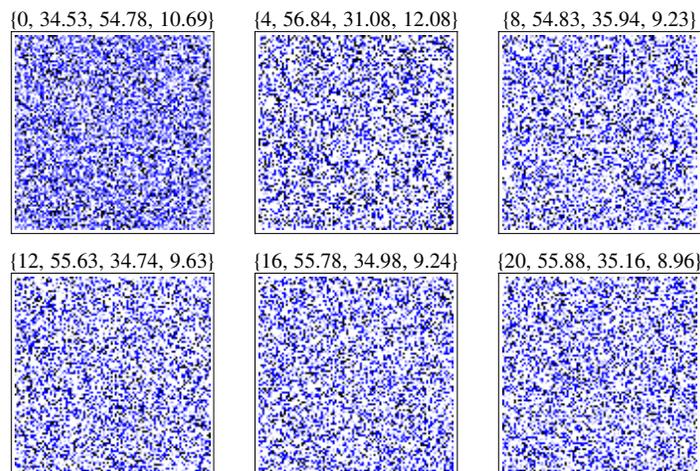


FIGURE 8. When drugs are introduced during the chronic stage of HIV, the Markov process shows that a much larger percentage of the cells are healthy at any given time

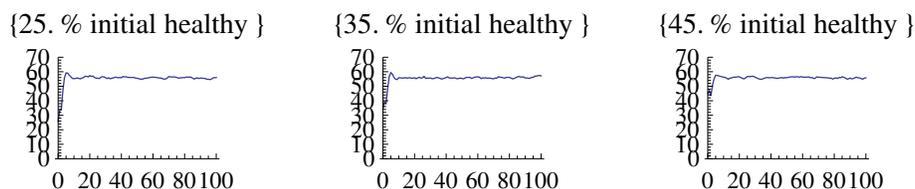


FIGURE 9. If at the time drug therapy is initiated, 25%, 35% or 45% of the cells are healthy, respectively, over time the percentage fluctuates around the limiting percentage of $\approx 60\%$

does not change too much. If we assume that E_2 denotes the effectiveness of the PI drug, then if the drug treatment starts when the viral spread has already entered the Markov stage there are limits (upper and lower bounds) to how much of the CD4 supply can be restored.

This shows the benefits of the combined drug therapy [26] as well as supports the studies showing advantages to starting the drug treatment early [3, 16].

4.1. Mathematical justification. We express the stochastic matrix for the Markov drug model more generally as follows:

Let

$$(4.3) \quad G = \begin{pmatrix} E_1 & 1 - E_1 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 1 - E_2 & 0 & 0 & E_2 & 0 \\ 0 & 0 & 0 & 1 - E_2 & 0 & E_2 & 0 \\ 0 & 0 & 0 & 0 & 1 - E_2 & E_2 & 0 \\ 0 & 0 & 0 & 0 & 0 & 1 & 0 \\ 0 & 0 & 0 & 0 & 0 & .5 & .5 \\ .98999 & 9.9 \times 10^{-6} & 0 & 0 & 0 & 0 & .01 \end{pmatrix},$$

where E_1 is a function of the effectiveness of the RTI given in ([1], Section 6), and E_2 denotes the effectiveness of the PI. Clearly if the virus cannot replicate, i.e., if the RTI is completely effective, then cells cannot be infected and the system returns to normal. Due to the high rate of mutation of virus present in chronic illness, this is not to be expected. However the mathematical interpretation is in the following lemma. We define the vector $\vec{e} = (1, 0, 0, 0, 0, 0, 0)$.

Lemma 4.1. If $E_1 = 1$, then for every value of $E_2 \in (0, 1)$, G is not irreducible, and we have $\vec{e}G = \vec{e}$.

In other words the state of 100% healthy cells is a fixed vector for G (under left multiplication). Moreover the healthy configuration $\bar{0}$ is a point of equicontinuity for the Markov CA M .

Proof. Let $G_{(i,j)}^n$ denote the $(i, j)^{th}$ entry of the matrix G^n . It is easy to see that for any $n \in \mathbb{N}$, $G_{(1,j)}^n = 0$ for $j > 1$ since from a healthy state you never get to any other state. Therefore G is not irreducible; it is also easy to verify that the vector \vec{e} is fixed by G so is a left eigenvector corresponding to the eigenvalue 1. To show that $\bar{0}$ is an equicontinuity point, we use the notation given in Section 2.1. Given any $\epsilon = 2^{-k} > 0$, we consider any configuration x ϵ -close to $\bar{0}$, which means a central block of x is all 0's when restricted to N_k . Choosing $\delta = \epsilon$, independent of the x chosen, $M^j(x)$ stays ϵ -close to $M^j(\bar{0})$ for all $j \in \mathbb{N}$ (since the central coordinates remain 0's). Therefore $\bar{0}$ is a point of equicontinuity. \square

We will assume the hypotheses of Lemma 4.1 are never satisfied due to the ability of a persistent virus to mutate quickly to a drug resistant form and the presence of viral reservoirs [27]; therefore $E_1 < 1$. We now turn to E_2 for a similar analysis. In the next result we show mathematically that assuming an upper bound on E_1 , say $E_1 \leq L < 1$, no matter how effective E_2 , a large percentage of healthy cells is never achieved.

Proposition 4.2. Given G as in (4.3), let $w = (h, i_1, i_2, \dots, d)$ denote the left probability eigenvector for G for the eigenvalue 1. Then $0.46 < h < .61$.

Proof. Set $p_1 = .98999, p_2 = 9.9 \cdot 10^{-6}, p_3 = .01$ as in the bottom row of G . Since the matrix G is sparse, it is not hard to solve for and verify directly

that the vector: $v = (\alpha p_1 / (1 - E_1), (p_1 + p_2)\alpha, (1 - E_2)(p_1 + p_2)\alpha, (1 - E_2)^2(p_1 + p_2)\alpha, (1 - E_2)^3(p_1 + p_2)\alpha, 2(p_1 + p_2)\alpha, \alpha)$ satisfies $vG = v$ for any nonzero choice of α ; therefore this is a left eigenvector for G corresponding to the eigenvalue 1. So we assume $\alpha = 1$, write $x = E_2$, and we see that the first entry of the probability eigenvector, $w = v / \sum_{i=0}^6 v_i$ depends on x . Summing the v_i 's gives the desired entry

$$h = \frac{p_1}{1 - E_1} \frac{1}{1 + (p_1 + p_2)(6 - 6x + 4x^2 - x^3) + \frac{p_1}{1 - E_1}}.$$

We assume throughout that $p_1 + p_2 = .99$, and while E_1 might vary, we assume for now it is the number computed above, say .8338, so that we now have:

$$h = h(x) = \frac{5.95662}{6.95662 + .99(6 - 6x + 4x^2 - x^3)}.$$

A calculus exercise shows that $q(x) = 6 - 6x + 4x^2 - x^3$ decreases monotonically from 6 to 3 as x goes from 0 to 1, so substituting in these values, the range for h , the percentage of healthy cells, is: $0.461874 \leq h \leq 0.600065$. \square

Remarks 4.3. If we write $\beta = \frac{p_1}{1 - E_1}$, then Proposition 4.2 shows that

$$h = \frac{\beta}{1 + \beta + .99q(E_2)},$$

with $3 \leq q(E_2) \leq 6$. Clearly for each $p_1 > 0$

$$\lim_{E_1 \rightarrow 1} \beta = \infty, \quad \text{so} \quad \lim_{E_1 \rightarrow 1} h = 1$$

for every $x \in [0, 1]$ which is consistent with Lemma 4.1.

5. THE MARKOV MODEL APPLIED TO CHRONIC HEPATITIS C

There are other chronic viral infections that can be studied using this Markov model; we focus on the hepatitis C virus (HCV) in this section. While many changes in the parameters of the model need to be made for the model to be consistent with the existing data on the course of the disease, we give an idea here of the connections between dynamics of the persistent viral levels of HCV and the Markov model developed above.

According to the Center for Disease Control, the hepatitis C virus (HCV) is a major health problem in the U.S. and worldwide. In the United States, around 3.2 million people are believed to be infected with chronic HCV and 12,000 each year die from it [2]. While some cases of HCV infection clear up on their own, around 75 – 85% of the instances of HCV infection become chronic cases [2, 17]; i.e., the virus persists in the system, sometimes causing no symptoms while still able to be spread. However 60 – 80% of the people who get infected with HCV develop chronic liver disease [32]. As is the case for HIV, in the early stages of HCV infection many of the patients

show a typical “yo-yo” pattern of high to low viral infection [28], and this is captured by the stochastic CA (SCA) model discussed in [1].

Some trials of the SCA model result in chronic infection while occasionally the virus is eradicated [1]; in the model the probability of a chronic infection depends on the parameters chosen for the model which in turn are determined by available data. At the acute stage of the infection (as represented in the SCA model and each of the component CA models) the immune response is operating; therefore it is difficult to predict at this early stage in which patients the infection will persist [17, 28]. This uncertainty in outcome is reflected in the stochastic nature of the model; i.e., the SCA provides a much better model than a single CA. A CA model of hepatitis B was described in [35] which is similar to the SCA HIV model given in [37] and [1].

It is not fully understood what causes 15 – 20% of the people infected with HCV to spontaneously be cured, or at least to go to an undetectable viral level, but many believe this early viral clearance is due to a strong and fast initial CD4 cell response against the virus (see [28] and the multiple studies referenced there). The progression of the virus has some similarities to that of HIV, so the SCA model, suitably adapted through parameter choices, does a good job of simulating the dynamics of this disease. We direct our focus here on the chronic stage, the most common outcome of HCV infection; since chronic hepatitis C is most likely to end up in fibrosis or cirrhosis of the liver [33], understanding the dynamics is worthwhile. Our Markov model is consistent with the hypothesis that it is not a lack of an immune response from the start that causes chronic HCV presence, but rather a fast tapering off of the response which leaves viral levels at low and sometimes undetectable levels. These levels keep the person asymptomatic and relatively healthy for long periods of time while still able to spread the virus. This dynamic is evident in the model whose outcome is supported by Theorem 3.5.

The space $X = \mathcal{A}^{\mathbb{Z}^2}$ in this setting represents hepatocytes, or more precisely, configurations of sites of liver cells, as these are the cells that host the HCV virus. We call state 0 cells “healthy” hepatocytes. All other states represent various stages of infected sites or 6 (depleted cells). The progression from state 1 (newly infected) to state r , with r varying from 2 to 6, depends on the precise time scale used for the model. The precise number of states in a good Markov CA model of persistent HCV depends on the data-driven parameters; the viral dynamics are on a much shorter time scale than for HIV [20] but they have many similarities in terms of the viral dynamics. An example of how they differ in timing is if HCV persists in the blood after 3 months or more, then chronic hepatitis is diagnosed. A similarity is that like HIV, HCV mutates quickly; drug resistant mutations have been observed as early as 2 days after the first administration of the drug, making treatment difficult [9] and combination therapies desirable [4].

If we use the same parameters in the stochastic matrix P as for the HIV setting, that is the matrix given in (3.3) before drugs are introduced, *keeping in mind that we are only doing this at the third stage of the model when the length of one time step and the time to this stage are no longer relevant*, then we see that only around 14% of the healthy liver cells remain from the beginning of the infection. This could be enough to keep the infection from quickly destroying more liver cells but not enough to eradicate the virus. In other words, while the precise parameters could shed more light on the best treatment, the dynamics show that the steady state will not allow the immune system to completely eliminate the viral presence. Many studies give data to support this hypothesis, such as [17] and the references therein. Again the Markov model shows that a drastic intervention is needed, one that upsets the stochastic nature of the dynamics, to set the longterm prognosis of the patient on a new course.

Indeed in [20] it is noted that the most effective drug treatment seems to speed up the death of an infected cell, and this would lead to an incidence matrix such as the one in (4.1); in addition due to the efficacy of the drugs we expect to see (4.2) also apply to the HCV setting. Finally, though drug treatment brings the virus to undetectable quantities in the blood, it is widely assumed that the HCV persists and measurable quantities of the virus return in more than 50% of the patients. If the dynamics of HCV and HIV are as similar as they seem to be, continuing drug therapy for a patient carrying chronic HCV might be appropriate until new drugs assure the eradication of the virus from the liver. Since the drugs can have adverse side effects, this leaves the problem of calibrating the minimum effective dosage. A careful assessment of drug efficacy plugged into the Markov CA from Section 4 can help tackle this problem.

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