Advances in Modeling the Dynamics of HIV Infection with Conformon-P Systems

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Summary. Further results on the study of the dynamics of HIV infection with grids of conformon-P systems are reported. This study clearly shows a subdivision in two main phases, the first faster than the second, of the mechanism at the base of the considered dynamics.

1 Introduction

The infection by the human immuno-deficiency virus (HIV), the cause of acquired immunodeficiency syndrome (AIDS), has been widely studied both in the laboratory and with computer models in order to understand the different aspects that regulate the virus-host interaction.

Several mathematical models have been proposed (for example [12, 18, 10]) but all of them fail to describe some aspects of the infection. The recent model reported by Dos Santos & Coutinho in [14], based on cellular automata, clearly shows the different time scales of the infection and has a broad qualitative agreement to the density of healthy and infected cells observed *in vivo*. However, in [15] it is noted that this qualitative agreement is reached only if some parameters are chosen in a small interval. If some of the parameters are chosen outside this interval, then the model of [14] does not follow the dynamics of what is observed *in vivo*.

In the present paper we continue our study on the modeling of the dynamics of HIV infection with grids of conformon-P systems started in [2]. There our model proved to be robust than the cellular automata model of [14] to a wide range of conditions and parameters, with more reproducible qualitative agreement to the overall dynamics and to the densities of healthy and infected cells observed *in vivo*.

2 The Modeling Platforms

2.1 Cellular automata

Cellular Automata (CA) are a regularly used platform for modeling, and are increasingly explored as modeling tools in the context of natural phenomena that exhibit characteristic spatiotemporal dynamics [16, 3]. Of interest here, for example, are their use in modeling the spread of infection [1, 11, 14, 10, 17].

A CA consists of a finite number of cells (invariably arranged in a regular spatial grid), each of which can be in one of a finite (typically small) number of specific states. In the usual approach, at each time step t the status of the CA is characterized by its state vector; that is, the state of each of the cells. In the simplest type of CA, the state vector at time $t + 1$ is obtained from that at time t by the operation of a single rule applied in parallel (synchronously) to each cell. The rule specifies how the state of a cell changes as a function of its current state and the states of the cells in its neighborhood (see Figure 4). In many applications, including that addressed here, it is appropriate for the rule to be probabilistic.

The straightforward nature of the time evolution of a CA, combined with its emphasis on local interactions, has made it an accessible and attractive tool for modeling many biological processes.

2.2 Conformon-P systems

Conformon-P systems (cP systems) [5] have been introduced as a novel computational device (*P systems* are the chief systems arising in the emerging research area of *Membrane Computing* [13]) whose early inspiration comes from a theoretical model of the living cell.

CP systems are defined in an extremely simple way that does not limit either their computational power, or their modeling capabilities. As a variant of P systems, they capture the dynamics of interacting processes in a novel way, using constructs that characterize the flow of information between regions in a range of cell-like topological structures. Moreover, their definition allows them to model different kinds of process (a compartment defines locality in general, it is not necessarily a membrane compartment in a cell) and to integrate several degrees of abstraction in the same system.

P systems are well-defined models of parallel computational systems that have a rich and growing base [19] of theoretical understanding of their properties.

A cP system has conformons, a name-value pair, as objects. If V is an alphabet (a finite set of letters) and $\mathbb{N}_0$ is the set of natural numbers (with 0 included), then we can define a conformon as $[\gamma, a]$, where $\gamma \in V$ and $a \in \mathbb{N}_0$, we will say that γ is the *name* and a is the *value* of the conformon $[\gamma, a]$. If, for instance, $V = A, B, C, \ldots, Z$, then $[A, 5], [C, 0], [Z, 14]$ are conformons, while $[AB, 21], [C, -15]$, and $[D, 0.5]$ are not.

Two conformons can interact according to an *interaction rule*. An interaction rule is of the form $\gamma \xrightarrow{n} \beta$, where $\gamma, \beta \in V$ and $n \in \mathbb{N}_0$, and it says that a conformon

with name γ can give n from its value to the value of a conformon having name β. A rule can be applied only if the value of the conformon with name γ is greater or equal to n. If, for instance, there are conformons $[G, 5]$ and $[R, 9]$ and the rule $G \xrightarrow{3} R$, the application of r leads to $[G, 2]$ and $[R, 12]$.

The (membrane) compartments present in a cP system have a label (it is a name which makes it easier to refer to a compartment), every label being different. Compartments can be unidirectionally connected to each other and for each connection there is a *predicate*. A predicate is an element of the set $\{\geq n, \leq n \mid n \in \mathbb{N}_0\}$. Examples of predicates are: $\geq 5, \leq 2$, etc.. A connection and its predicate are referred as *passage rules*. If, for instance, there are two compartments (with labels) m_1 and m_2 and there is a passage rule from m_1 to m_2 having predicate ≥ 4, then conformons having value greater or equal to 4 can pass from m_1 to m_2. In a time unit any number of conformons can move between two connected membranes as long as the predicate of the passage rule is satisfied. Notice that we have *unidirectional passage rules* that is: m_1 connected to m_2 does not imply that m_2 is connected to m_1. Moreover, each passage rule has its own predicate. If, for instance, m_1 is connected to m_2 and m_2 is connected to m_1, the two connections can have different predicates.

A simple cP system is illustrated in Figure 1.

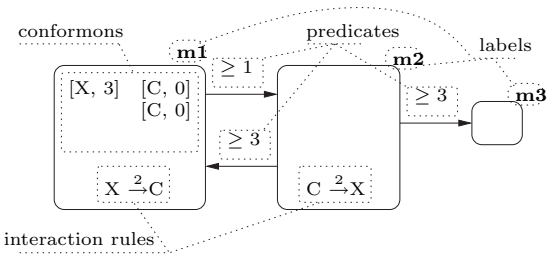

Fig. 1. A cP system

CP systems do not work under the requirement of maximal parallelism, typical to the majority of the models of P systems. When used as modeling platform cP systems can be classified as stochastic descriptive dynamic discrete model based on a discrete spatial heterogeneity. CP systems have been successfully used to model biological processes [7, 2].

A *grid of cP systems* (Figure 2) is composed by *cells*, each cell being a simple conformon-P system connected to some other cells, the *neighborhood* of the cell.

Ongoing research is establishing the computational properties of (models of) cP systems [8, 9, 5, 6, 4].

CP systems can contain *modules*: groups of membranes with conformons and interaction rules able to perform a specific task. The task performed by a module

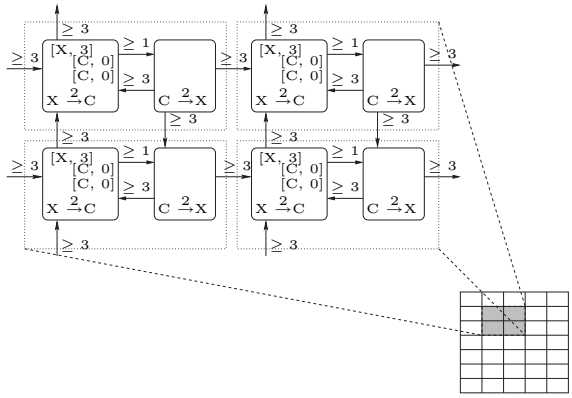

Fig. 2. A grid of cP systems

can be considered atomic (i.e., completed in one time unit) in the context of the cP system containing it. Modules allow cP systems to be scalable.

Some modules are: *Splitter*, *Separator*, *Decreaser/Increaser* [5]. The combination of Separators and Decreaser/Increaser allows us to define *strict interaction* rule: $\gamma^{(a)} \xrightarrow{c} \beta_{(b)}$ where $\gamma, \beta \in V,\ a, b, c \in \mathbb{N}_0$, meaning that a conformon with name γ can interact with β passing just c only if the value of γ and β before the interaction is a and b respectively. Notice that in a strict interaction just c is passed even if the value of γ could be decreased by any multiple of c. Interactions of the kind $\gamma \xrightarrow{c} \beta_{(b)}$ (before the interaction γ can have any value while β has b as value) and $\gamma^{(a)} \xrightarrow{c} \beta$ (before the interaction γ has a as value while β can have any value) can be defined, too.

3 The Process and the Models

The dynamics observed in HIV infections can be divided into three phases. Initially the amount of virus in the host grows in an exponential way, then the viral load drops to what is known as the "set point". Finally the amount of virus in the host increases slowly, accelerating near the onset of AIDS. The first two phases occur in the first weeks following the infection; the third phase can last years. This is plotted in Figure 3 where each unit in the x axes represent a week in time.

In [14] this process was modeled with a CA in which each cell could be in any of four possible states: *healthy*, *A-infected*, *AA-infected*, and *dead*. In the (random) initial configuration a cell had probability p_{HIV} to be *A-infected*, otherwise it is *healthy*.

The rules used in [14] are:

1. if an *healthy* cell has at least one *A1-infected* neighbor, then it becomes *A1-infected*;

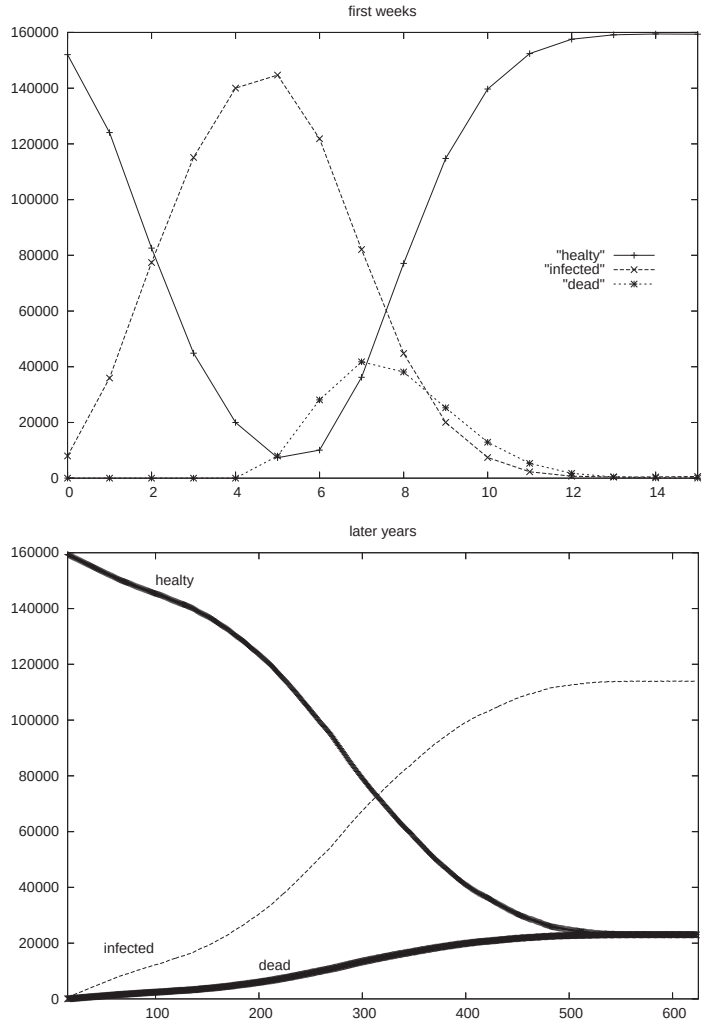

Fig. 3. Typical dynamics of HIV infection.

2. if an *healthy* cell has not *A1-infected* neighbors but it has at least R *A2-infected* neighbors, then it becomes *A1-infected*;
3. an *A1-infected* cell becomes *A2-infected* after τ time steps;
4. *A2-infected* cells become *dead* cells;
5. *dead* cells can become (be replaced by) *healthy* cells with probability p_{repl};
6. newly introduced *healthy* cells can become *A1-infected* with probability p_{infec}.

The biological reasoning behind these rules is explained in [14]. Essentially, rules 1 and 2 model the basic spread of viral infection from cells to neighboring

cells; rules 3-5 model the short life of an infected cell, and rule 6 models the body's continual replenishment of new healthy cells but maintaining a small probability of infection.

In [14] the following parameters were chosen: $p_{HIV} = 0.05, p_{repl} = 0.99, p_{infec} = 10^{-5}, R = 5$ and $\tau = 4$. They experimented with grids of size ranging from 300×300 to 1000×1000, and the averaged results of 500 simulations reported in [14] on toroidal grids ranging from 700×700 show a qualitative agreement to the density of healthy and infected cells observed *in vivo*.

In [15] it is shown that this qualitative agreement is reached only for values of the parameters close to the ones just indicated. If either $p_{HIV} < 10^{-2}$ or p_{infec} is chosen in the range 10^{-2} to 10^{-4}, then the CA model of [14] does not follow the dynamics of what is observed *in vivo*.

3.1 The CA model

3.2 The grid of cP system model

The main difference that our model has in respect to the one reported in [14] is that the interaction rules are divided in two subsets:*part 1* and *part 2* (see Appendix A). The rules in the two subsets differ in the probabilities associated to them.

Other differences as, for instance, the presence of *pre-dead* cells, exist in order to simulate in terms of operations in a cP system some instructions of the CA presented in [14].

Each cell can be in one of five states: *1-healthy*, *A-infected*, *AA-infected*, *pre-dead*, and *dead* (in respect to the rules in *part 1*) identified by the presence of the conformons: $[H, 1], [A, 1], [AA, 1], [PD, 1]$, and $[D, 1]$ respectively. If, for instance, a cell is in an *healthy* state, then it will contain $[H, 1], [A, 0], [AA, 0], [PD, 0]$, and $[D, 0]$ (similarly for the other cases). In the initial configuration, each cell contains the conformons $[R, 1], [V, 10], [E, 0]$, and $[W, 0]$ are present in an unbounded number of copies.

In the following we consider and describe the rules in *part 1*.

If a cell is *A-infected*, then it can generate $[V, 11]$ (meaning: if a cell is *A-infected* it can generate a virus). This is performed by the rules:

$$\textbf{1: } R \xrightarrow{1} A_{(1)} \qquad\qquad \textbf{2: } A^{(2)} \xrightarrow{1} V_{(10)}$$

Notice that $[V, 10]$ does not represent a virus, but $[V, 11]$ does.

$[V, 11]$ conformons can pass from a cell to any other in its neighborhood (meaning: viruses can spread between cells).

An *1-healthy* cell can become *A-infected* if it contains a virus. This is performed by the rules:

$$\textbf{3: } V \xrightarrow{11} H_{(1)} \qquad \textbf{4: } H^{(12)} \xrightarrow{12} A_{(0)} \qquad \textbf{5: } A^{(12)} \xrightarrow{11} W_{(0)}$$

An *AA-infected* cell can generate $[E, 1]$ conformons. These conformons can pass to other cells and interact such that $[E, 4]$ conformons are created. When a $[E, 4]$ conformon is present in an *healthy* cell, then it can become *A-infected*.

This process mimics rule II in Section 3 and it is performed by:

$$\textbf{6: } R \xrightarrow{1} AA_{(1)} \quad \textbf{7: } AA^{(2)} \xrightarrow{1} E_{(0)} \quad \textbf{8: } E^{(1)} \xrightarrow{1} E_{(1)} \quad \textbf{9: } E^{(2)} \xrightarrow{2} E_{(2)}$$
$$\textbf{10: } E \xrightarrow{4} H_{(1)} \quad \textbf{11: } H^{(5)} \xrightarrow{5} A_{(0)} \quad \textbf{12: } A^{(5)} \xrightarrow{4} W_{(0)}$$

and by the fact that $[E, 1]$ can pass from one cell to any other in its neighborhood. From the rules 7, 8, and 9 it should be clear that only $[E, 1]$, $[E, 2]$, and $[E, 4]$ can be present in the system. Because of rule 6 an *AA-infected* cell can generate $[E, 1]$. When two $[E, 1]$ are present in the same cell they can interact to create $[E, 2]$ (rule 8) and two $[E, 2]$ present in the same cell can interact to create $[E, 4]$ (rule 9). If the creation of $[E, 4]$ took place in an *healthy* cell, then this cell can become *A-infected* (rules 10, 11 and 12).

An *A-infected* cell can become *AA-infected* by the application of the rule:

$$\textbf{13: } A^{(1)} \xrightarrow{1} AA_{(0)}$$

An *AA-infected* cell can become *dead*. Before doing so it goes into the *pre-dead* state in which the $[V, 11]$, $[E, 1]$, $[E, 2]$, and $[E, 4]$ conformons present in it are removed. This is performed by the rules:

$$\textbf{14: } AA^{(11)} \xrightarrow{1} PD_{(0)} \quad \textbf{15: } V^{(11)} \xrightarrow{1} PD_{(1)} \quad \textbf{16: } E \xrightarrow{1} PD_{(1)} \quad \textbf{17: } E \xrightarrow{2} PD_{(1)}$$
$$\textbf{18: } E \xrightarrow{4} PD_{(1)} \quad \textbf{19: } PD^{(1)} \xrightarrow{1} D_{(0)} \quad \textbf{20: } PD^{(2)} \xrightarrow{1} W_{(0)} \quad \textbf{21: } PD^{(3)} \xrightarrow{2} W_{(0)}$$
$$\textbf{22: } PD^{(5)} \xrightarrow{4} W_{(0)}$$

A *dead* cell can become *2-healthy* cell by the application of the rule

$$\textbf{23: } D^{(1)} \xrightarrow{1} H2_{(0)}$$

The R and W conformons do not have a direct relationship with any aspect of HIV infection. In broad terms, the R conformons can be regarded as 'food' molecules needed by a cell in a certain state to perform an action (for instance, if *A-infected* to generate a virus). The W conformons can be regarded as 'waste' molecules, to which some conformons can pass part of their value. As W conformons only receive values from other conformons, their initial value is not relevant for the simulation.

The state *2-healthy*, together with *A2-infected*, *AA2-infected*, *2-pre-dead*, and *2-dead* are managed by the rules in *part 2*. The rules in *part 2* are similar to the ones in *part 1* but they have $H2$ instead of H, $A2$ instead of A, $AA2$ instead of AA, $PD2$ instead of PD, and $D2$ instead of D.

In the diagrams related to the grid of cP systems the curve of *healthy* cells is obtained adding up the number of H and $H2$ cells; the curve of *infected* cells is obtained adding up the number of A, AA, $A2$ and $AA2$ cells; the curve of *dead* cells is obtained adding up the number of D, PD, $D2$ and $PD2$ cells.

The interaction rules indicated in Appendix A can be logically divided in two sets: *state-change* and *internal dynamics*. The *state-change* rules allow the cells to pass from a state to another. For instance, rule 4 is a state change rule as when

it is applied in a cell the state of the cell passed from *1-healthy* to *A-infected*. The *state-change* rules are: 4, 11, 13, 14, 19, 23, 27, 32, 34, 35, 40 and 44.

The remaining rules belong to *internal dynamics* as they do not directly effect the state of a cell.

Differently than what done in [2], in the present study the probabilities associated to the *internal dynamics* rules in phase 1 are equal to the ones in phase 2. The probabilities of the *state-change* rules in phase 1 are higher than then ones in phase 2.

Considering what we said in Section 3, rules in *part 1* model the behavior of the first two phases of the dynamics of HIV infection, while rules in *part 2* model the behavior of the third phase.

4 Experiments and Results

The simulations performed with the cP system were based on a toroidal 50×50 grid, using a Moore neighborhood (considering Figure 4 the black cell can pass conformons to any grey cell) and with $p_{HIV} = 0.05$.

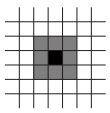

Fig. 4. The Moore neighborhood.

All the 10 simulations (with different random number sequences) run for 16000 iterations and they all show a dynamics very similar to the one observed *in vivo*. A typical outcome is depicted in Figure 5.

This outcome (even if run for only one kind of neighborhood and one values of p_{HIV}) fits the dynamics observed *in vivo* better than the outcomes reported in [2]:

- the tempo of the dynamics is constant during the simulation. In [2] the dynamics was 'too fast' in the later years (or 'too slow' in the first weeks). In the present study 1 year corresponds to 1560 iterations. This means that phase I and phase II (both taking place in at most 10 weeks) should correspond to 300 iterations. In this way the 16000 iterations of out tests corresponds to a bit more than 10 years.
- the percentage of *healthy* and *infected* cells in phase III is closer to what observed *in vivo* than what reported in [2].
- the dynamics of *healthy* and *infected* cells in phase III is not flat as in [2] but shows a concavity similar to the one observed *in vivo*.

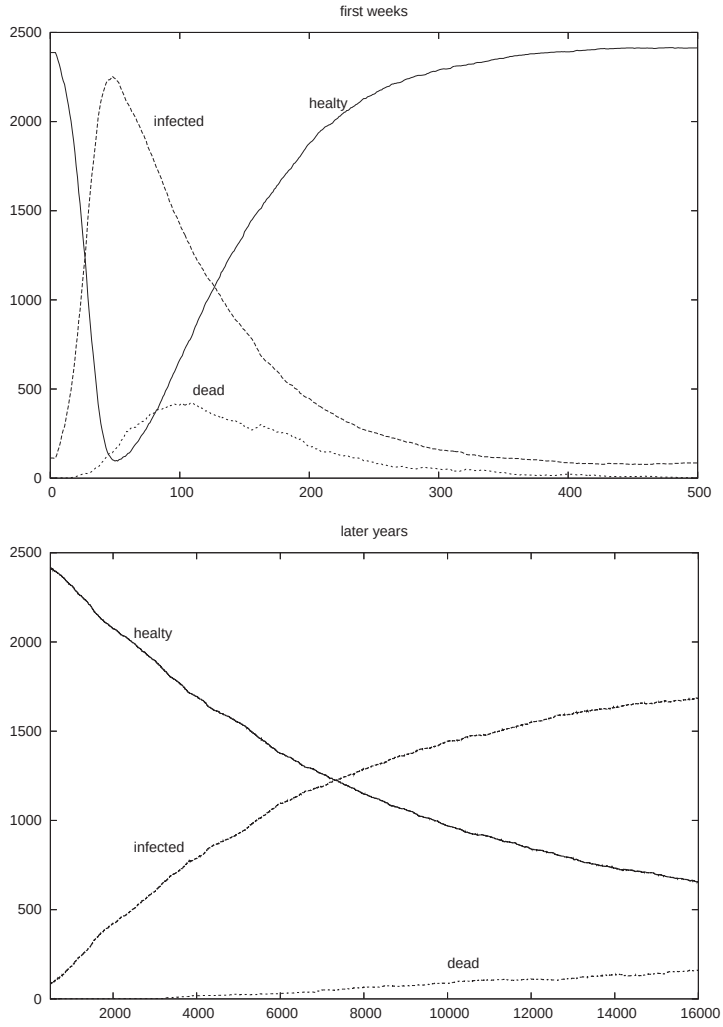

Fig. 5. Typical outcome for grids of cP systems.

There are two major differences between the dynamics obtained by us and the one observed *in vivo*:

in phase III the number of *healthy* cells should become equal to the one of *dead* cells;

the curves followed by the number of *healthy* and *infected* cells in phase III do not change concavity.

5 Final Remarks

We consider the reported study still in its initial phases. In the future we will try to better fit the dynamics obtained with grids of cP system to what observer *in vivo* and we will run the tests on different neighborhoods and different values of p_{HIV} (as done in [2]).

Some results obtained by us indicates that the E conformons play a negligible role in the whole dynamics. On this base we will try to simply our model in the number of interaction rules and conformons present in it.

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A Rules, links, and probabilities

part 1			*part 2*		
label	**rule**	**prob.**	**label**	**rule**	**prob.**
1	$R \xrightarrow{1} A_{(1)}$	0.7071	**24**	$R \xrightarrow{1} A2_{(1)}$	0.7071
2	$A^{(2)} \xrightarrow{1} V_{(10)}$	0.7071	**25**	$A2^{(2)} \xrightarrow{1} V_{(10)}$	0.7071
3	$V \xrightarrow{11} H_{(1)}$	0.79	**26**	$V \xrightarrow{11} H2_{(1)}$	0.79
4	$H^{(12)} \xrightarrow{12} A_{(0)}$	0.79	**27**	$H2^{(12)} \xrightarrow{12} A2_{(0)}$	0.0001
5	$A^{(12)} \xrightarrow{11} W_{(0)}$	0.79	**28**	$A2^{(12)} \xrightarrow{11} W_{(0)}$	0.79
6	$R \xrightarrow{1} AA_{(1)}$	0.7071	**29**	$R \xrightarrow{1} AA2_{(1)}$	0.7071
7	$AA^{(2)} \xrightarrow{1} E_{(0)}$	0.7071	**30**	$AA2^{(2)} \xrightarrow{1} E_{(0)}$	0.7071
8	$E^{(1)} \xrightarrow{1} E_{(1)}$	0.07071			
9	$E^{(2)} \xrightarrow{2} E_{(2)}$	0.07071			
10	$E \xrightarrow{4} H_{(1)}$	0.79	**31**	$E \xrightarrow{4} H2_{(1)}$	0.79
11	$H^{(5)} \xrightarrow{5} A_{(0)}$	0.79	**32**	$H2^{(5)} \xrightarrow{5} A2_{(0)}$	0.0001
12	$A^{(5)} \xrightarrow{4} W_{(0)}$	0.79	**33**	$A2^{(5)} \xrightarrow{4} W_{(0)}$	0.79
13	$A^{(1)} \xrightarrow{1} AA_{(0)}$	0.04	**34**	$A2^{(1)} \xrightarrow{1} AA2_{(0)}$	0.0001
14	$AA^{(11)} \xrightarrow{1} PD_{(0)}$	0.1	**35**	$AA2^{(11)} \xrightarrow{1} PD2_{(0)}$	0.00075
15	$V^{(11)} \xrightarrow{1} PD_{(1)}$	0.7071	**36**	$V^{(11)} \xrightarrow{1} PD2_{(1)}$	0.7071
16	$E \xrightarrow{1} PD_{(1)}$	0.7071	**37**	$E \xrightarrow{1} PD2_{(1)}$	0.7071
17	$E \xrightarrow{2} PD_{(1)}$	0.7071	**38**	$E \xrightarrow{2} PD2_{(1)}$	0.7071
18	$E \xrightarrow{4} PD_{(1)}$	0.7071	**39**	$E \xrightarrow{4} PD2_{(1)}$	0.7071
19	$PD^{(1)} \xrightarrow{1} D_{(0)}$	0.2	**40**	$PD2^{(1)} \xrightarrow{1} D2_{(0)}$	0.001
20	$PD^{(2)} \xrightarrow{1} W_{(0)}$	0.7071	**41**	$PD2^{(2)} \xrightarrow{1} W_{(0)}$	0.7071
21	$PD^{(3)} \xrightarrow{2} W_{(0)}$	0.7071	**42**	$PD2^{(3)} \xrightarrow{2} W_{(0)}$	0.7071
22	$PD^{(5)} \xrightarrow{4} W_{(0)}$	0.7071	**43**	$PD2^{(5)} \xrightarrow{4} W_{(0)}$	0.7071
23	$D^{(1)} \xrightarrow{1} H2_{(0)}$	0.1	**44**	$D2^{(1)} \xrightarrow{1} H2_{(0)}$	0.001

Links:
$[V, 11]$ can pass with probability 1 from any cell to any of its neighbors; $[E, 1]$ can pass with probability 0.01 from any cell to any of its neighbors.