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A cellular automata model of an anticipatory system

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An anticipatory system has been modeled using the dynamic characteristics of cellular automata. Rules governing the steps in an enzymatic conversion of substrates to products are operative in the system. A concentration of an intermediate product influences the creation of a supplemental enzyme that enhances the competence of an enzyme down stream. This anticipation of the future event creates a condition in which the concentration of a later substrate is suppressed, a property characteristic of the system. The model presents a useful opportunity to study a variety of aspects of this fascinating phenomena. © 2000 by Elsevier Science Inc.

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INTRODUCTION

It is taken to be a natural law that the change of state of a system may depend upon the states of other systems and possibly past states if there is a "memory", but it cannot depend upon a future state. This is the essence of causality in science. Rosen[1] has addressed this issue by relegating the influence of future events to an anticipatory model containing predictions built into the system. A classic repository of an anticipatory system is the human mind, rich with models of future events influencing choices and decisions. Rosen[2] remarked on the ubiquitousness of these systems, especially in biochemical pathways. These systems contain predictive models, enabling them to change state in response to the anticipation of future events in the pathways.

A general example of this phenomenon is found in the forward activation of an enzyme by the presence of a substrate upstream to the focus of the change. An initial substrate, S_0, in the scheme in Figure 1, is a predictor of the role played by an enzyme, e_3, further downstream in the biochemical pathway. The substrate, S_0, predicts and preadapts the system to exhibit a state due to a change in the competence of enzyme, e_3. A property that emerges is the change in the concentration of the substrate, S_3, when the competence of e_3 to function at a higher level is stimulated in the forward activation.

For many years, biochemists have been interested in simulating these pathways, producing a number of systems summarized by Fell,[3] including work by Trakhtenbrot[4] and Tsoukalas.[5] Prideaux[6] has recently examined a biochemical pathway in which feed forward activation is exhibited by fructose-1,6-biphosphate on the enzyme, pyruvate kinase (PK) in the glycolysis biosynthetic pathway shown in Figure 2. In this feed-forward activation system, the upstream substrate, F16BP, activates the downstream enzyme, PK. The property emerging from this anticipatory system is the diminished buildup of phosphoenolpyruvate (PEP). Prideaux modeled this system using an electrical network analog called PSpice. The results revealed the decline of the PEP concentration as the downstream flow reached this substrate. The forward activation of the PK enzyme had anticipated the formation of PEP in the model.

A recent study reported a simple enzyme-controlled reaction using cellular automata to model the dynamic events.[7] This model reproduced the Michaelis-Menten model and gave good Lineweaver-Burk plots of the data. The validity of the model in these studies encouraged us to use cellular automata in the modeling of an anticipatory system such as the type shown in Figure 2.

THE CELLULAR AUTOMATA MODEL

Cellular automata are dynamic computational systems that are discrete in space, time, and state whose behavior is specified completely by rules governing local relationships. They are an attempt to simplify the often numerically intractable dynamic phenomena into a set of simple rules that mirror intuition and that are easy to compute. As an approach to the modeling of

Color plates for this article are on page 61.

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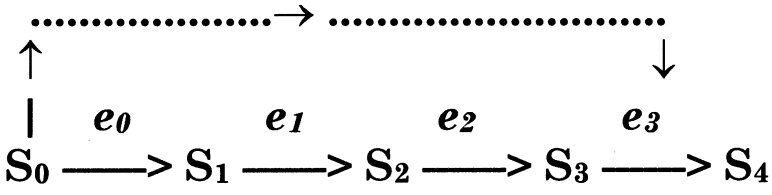

Figure 1. Anticipatory feed-forward biochemical system.

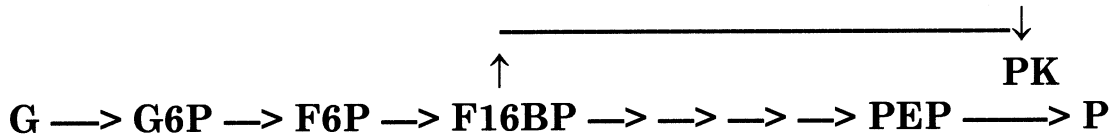

Figure 2. Fructose/pyruvate kinase feed-forward activation system. The multiple arrows imply a sequence of reactions in the system.

emergent properties of complex systems, it has a great benefit in being visually informative of the progress of dynamic events. From the early development by von Neumann,[8] a variety of applications ranging from gas phenomena to biological applications have been reported.[9–11]

Our model is composed of a grid of spaces called cells on the surface of a torus to remove boundary conditions. Each cell i has four tessellated neighbors, j, and four extended neighbors, k, in what is called an extended von Neumann neighborhood, shown in Figure 3. Each cell has a state governing whether it is empty or is occupied by a molecule. The contents of a cell move, join with another occupied cell, or break from a tessellated relationship according to probabilistic rules. These rules are established at the beginning of each simulation.

The first of two trajectory or interaction rules is the breaking probability, P_B. This is the probability for a molecule at i bonded to molecule j to break away from another at j when there is exactly one occupied j cell (Figure 1). The value for P_B lies in the closed unit interval. If molecule i is bonded to two other cells, j′ and j″, the simultaneous breaking away of cell i is $P_B/2$. If cell i is bonded to three other molecules at j′, j″, and j‴, the simultaneous breaking away cell i is $P_B/3$.

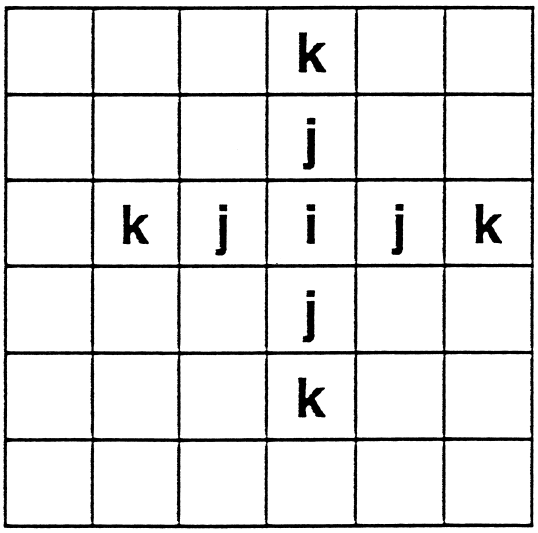

Figure 3. Extended von Neumann neighborhood showing the reference cell, i, the four tessellated neighbors, j, and the tessellated neighbors beyond j, labeled k.

The second trajectory parameter, J, describes the movement of a molecule at i toward or away from the particle at a k cell in the extended von Neumann neighborhood, Figure 1d, when the intermediate j cell is vacant. J is a positive real number. When $J = 1$, it indicates that the particle, i, has the same probability of movement toward or away as for the case when k is empty. When $J > 1$, it indicates that i has a greater probability of movement toward an occupied cell k than when k is empty. When $J < 1$, it indicates that i has a lower probability of such movement.

The rules are applied one after another to each cell at random, the complete application of the rules to all cells constituting one iteration. The rules are applied uniformly to each cell type and are local; thus, there is no action at a distance. Our cellular automata model is kinematic, asynchronous, and stochastic. The initial configuration is random; hence, it does not determine the ultimate configuration. The same initial set of rules do not yield the same system configuration after a certain number of iterations, except in some average sense. The configurations achieved after many iterations reach a collective organization that possesses a relative constancy in appearance and in reportable counts of attributes. What we observe and record from the cellular automata models are emergent attributes of a complex system. Kier et al.[12–16] used cellular automata to advance our understanding of solution phenomena, including solubility, oil-water partitioning, micelle formation, aqueous diffusion, and acid dissociation.

THE MOLECULAR SYSTEM

It must be made clear just what the cells, the configurations generated, and the cellular automata models represent. This is important in order to derive any understanding of the results of a cellular automata study and to dispel misunderstanding based on direct comparisons with molecular methods. A cell with a state value encoding occupation by a particular object is not a model of a molecule with specified electronic and steric features. These attributes are considered to be subsumed into the rules. The molecular system is intermediate between molecular level and bulk phase models of systems and may be modeled with molecular dynamics or cellular automata. Molecular level phenomena are modeled with molecular orbital theory, topo-

logical indices, or fragment methods. At the bulk level, we use descriptions based on statistical and thermodynamic methods. Many solution phenomena might be profitably studied using molecular system models in order to understand the processes whereby single molecules achieve the configurations measured as bulk properties.

THE ANTICIPATORY MODEL

The anticipatory model we employ in this study reflects the characteristics shown in the general reaction in Figure 1 and the typical reaction in Figure 2. The substrate/product molecules are labeled A, B, C, D, and E. The enzymes catalyzing the reactions are labeled e_x, where x is the number of the substrate in the system. The first scheme in the model is the conversion of A to B, assumed to be an irreversible second order reaction.

The rules governing the initial encounter, $P_B(Ae_1)$ and $J(Ae_1)$, are set at the beginning of each of three simulations. The concentrations of A in three separate studies are, respectively, 50, 100, and 200 cells in a grid of 2500 cells. The conversion probability, P_C, of Ae_1 to Be_1 is chosen to be 0.2.

The next step in the reaction is modeled as in Scheme 2:

$$A + e_1 \longrightarrow Ae_1 \longrightarrow Be_1 \longrightarrow B + e_1 \qquad \text{(Scheme 1)}$$

$P_B(Ae_1) = 1.0$ $\quad P_C = 0.2$ $\quad P_B(Be_1) = 1.0$

$J(Ae_1) = 1.0$ $\quad J(Be_1) = 0.0$

$$B + e_2 \longrightarrow Be_2 \longrightarrow Ce_2 \longrightarrow C + e_2 \qquad \text{(Scheme 2)}$$

$P_B(Be_2) = 1.0$	$P_C = 0.1$	$P_B(Ce_2) = 1.0$
$J(Be_2) = 1.0$		$J(Ce_{2,4}) = 0.0$
$P_B(Be_{2,4}) = 1.0$	$\dashrightarrow Ce_{2,4} \dashrightarrow$	$C + e_{2,4}$
$J(Be_{2,4}) = 1.0$	$P_C = 0.1$	$P_B(Ce_{2,4}) = 1.0$
		$J(Ce_{2,4}) = 0.0$

If the system is not an anticipatory one, the conversion of Be_2 to Ce_2 would follow only one route with a P_C value of 0.2. If the system is anticipatory, as shown above, there are two paths for the conversion of Be_2. We have elected to set these conversion probabilities equal as shown. The formation of $e_{2,4}$ represents an enzyme that may function on substrates B or D. Thus, the available enzyme to convert B to C is the same for an anticipatory or nonanticipatory system. In the case of an anticipatory system, above, there is formed, in advance of the creation of substrate, D, an enzyme, $e_{2,4}$, that will enhance the reaction of D and e_4 to form product E. Substrate B serves as a predictor of the concentration of D, reducing its accumulation, relative to that in a nonanticipatory system.

The next step in the sequence is Scheme 3.

This is an intermediate step in the pathway. It remains intact whether there is a feed-forward process or not. The next step in the process is the focal point of the anticipatory feature of the pathway, shown in Scheme 4.

The substrate D is confronted with an enhanced competence of its specific enzyme, modeled by e_4 and $e_{2,4}$ facilitating the conversion of D to E. The decrease in the concentration of D is the property of the anticipatory system that is created by the feed-forward influence of $e_{2,4}$.

THE CELLULAR AUTOMATA RULES

The studies are conducted in a grid of 50 × 50 cells. The initial concentrations of substrate A in the three studies are 50, 100and 200 cells, respectively. The concentrations of enzymes e_0, e_1, e_2, e_3, and e_4 are collectively 10% of the initial concentration of A in each of the three concentration-varying studies. All substrates (products) move with a probability of one through the grid. They do not join with each other or with any other substrate or product. They may join only with the enzyme specific for them, as shown in the

$$C + e_3 \longrightarrow Ce_3 \longrightarrow De_3 \longrightarrow D + e_3 \qquad \text{(Scheme 3)}$$

$P_B(Ce_3) = 1.0$ $\quad P_C = 0.2$ $\quad P_B(De_3) = 1.0$

$J(Ce_3) = 1.0$ $\quad J(De_3) = 0.0$

$$D + e_4/e_{2,4} \longrightarrow De_4/e_{2,4} \longrightarrow Ee_4/e_{2,4} \longrightarrow E + e_4/e_{2,4} \qquad \text{(Scheme 4)}$$

$P_B(De_4/e_{2,4}) = 1.0$ $\quad P_C = 0.2$ $\quad P_B(Ee_4/e_{2,4}) = 1.0$

$J(De_4/e_{2,4}) = 1.0$ $\quad J(Ee_4/e_{2,4}) = 0.0$

schemes above. The enzymes, *ex*, move with a probability of 0.7. They do not join with themselves or with any other species of catalyst. They join only with their specific substrates. All conditions are the same for the anticipatory model and the nonanticipatory model except for the formation of $e_{2,4}$ and the concentrations of e_2, which, in the anticipatory model, are one half those in the nonanticipatory model. The $e_{2,4}$ concentration in that scheme makes up the other half of the enzyme available to catalyze substrate B to C. In addition, the enzyme $e_{2,4}$ is available to catalyze substrate D to E, and this produces the increase in the competence of the enzyme for this conversion.

RESULTS AND DISCUSSION

The dynamics reveal concentrations over time in each study, influenced by the presence or absence of a feed-forward or preadaption state in the system. The concentrations are derived from the average values from 20 runs for each study. In Color Plates 1a, 2a, and 3a are shown the plots for each concentration as a result of the dynamics of a system in which no anticipatory condition exists. This is the expected irreversible second order enzymatic pathway. The concentration of A steadily diminishes as successive concentrations of B, C, and D rise and fall at the same levels. The concentration of E rises at the end of the run, eventually becoming the only ingredient in the system. The maximum concentration of D is approximately 0.25 in each case.

In contrast, with an anticipatory or feed-forward step in the system, as seen in Color Plates 1b, 2b, and 3b for each concentration, there is created an additional amount of enzyme specific for substrate D. This enzyme, $e_{2,4}$, is available at a future time to catalyze the conversion of D to E. This creates a property of the system in which the concentration of ingredient D is not allowed to accumulate to its normal level. The concentration of D in each case is approximately 0.13, about one half of the D concentrations for the unanticipatory models. The concentration of B therefore serves as a predictor of the concentration of D at a later time. This is the anticipatory nature of the system that we model in this study. The success of the use of cellular automata to model an anticipatory system in such a simple and straight-forward manner lends credence to the belief in the general value of the method to study these dynamic systems.

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