A Cellular Automata Model of Dissolution

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INTRODUCTION

The dissolution of a drug into aqueous body fluids is an essential step in the absorption into the body and the generation of clinical efficacy. Some process must occur which separates parts of an aggregate of molecules into smaller parts, perhaps ultimately single molecules, so that the appropriate chemical reactions may occur. The characteristics of this process and the rate at which change occurs depend upon the intrinsic attributes of the molecule and the water in its presence. The process is dynamic and it is coupled with water which is also a dynamic system. It is this recognition of water and solution attributes that has led us to study these systems by attempting to model them with non-linear dynamics using cellular automata.

Cellular Automata

Cellular automata (CA) is a method of dynamic synthesis, modeling the emergent behavior of a complex system (1). In contrast to molecular dynamics, the elements of a CA model experience transactions as a result of rules rather than physical forces. The elements of a CA model are represented by spaces called cells on a grid. Each element has a state epitomizing its existence. Each responds to its immediate neighbor cells according to rules, expressed as transition functions. Space and time are independent and discreet. At each interval, each cell computes its state and trajectory, thus the cellular automata is local, there is no action at a distance. We use an asynchronous series of computations until all cells have computed. This configuration constitutes one iteration and is a unit of 'time'. The same rules apply to the same type of cell, thus they are uniform. The rules are based upon probabilities selected for each transition function leading to a cellular automata which is stochastic. The configurations and the dynamics are not uniquely specified by the initial conditions but constitute a model of the emergent attributes in a complex system. Prediction of any configuration is not directly possible (it is not deterministic) but requires the actual running of the dynamics in order to study the system and derive some understanding.

In our first study (2) we showed that a single rule, governing the probability of water cluster breakup, produced dynamic simulations of emergent behavior characteristic of some of the properties of water. In a second study (3), we varied a second rule governing the probability of a water molecule joining a neighbor. By exploring the influence of these rules for water and solute molecules, we were able to simulate the dynamic configurations mirroring the water temperature influence on solute solubility, the influence of concentration of solute on water cluster disruption, and the influence of solute self-association on water structure. This latter result is a proposed model of the hydrophobic effect. A third study (4) has elaborated on this simulation. We turn our attention to this study to the cellular automata simulation of the dissolution process.

Our objective in this study is to synthesize, using cellular automata dynamic modeling, various configurations representing the disruption of a crystal, the dissolution of the particles, and their diffusion in the solvent. We are interested in this study to demonstrate whether these simulations can produce dynamic events equatable with experience, and to discover the influence of parameters on the recorded attributes.

METHOD

This study uses the same general conditions and parameters as described earlier (4). A solute, coded L in our parameter symbols is entered as a block of cells 10 × 10 in the center of the grid. The parameters for water are $P_B(W) = 0.30$, $J(W) = 1.0$. The solute-related parameters are listed in table I. The attributes recorded after a certain number of iterations include the following:

$f_0(L)$ The fraction of solute-occupied cells not bound to any other solute-occupied cells.

T(L) The average number of solute-solute tesselations.

D(L) The average distance of all solute-occupied cells from the center of the solute block.

As in an earlier study (4) we equated the $f_0(L)$ with the extent of solubility. The T(L) value is used as an indicator of the degree of disruption of the solute block, while the D(L) value encodes the extent of diffusion of the average solute-occupied cell.

RESULTS

Influence of Transition Parameters

We have generated values of the three attributes, [T(L), $f_0(L)$ and D(L)] every 100 iterations. The influence of each of the four transition parameters on the attributes are shown for 5000 iterations in Table I and described in the following summaries.

The T(L) Attribute

We interpret the T(L) attribute as reflecting the extent of disruption of the solute block. Upon block disruption the number T(L) decreases. With reduced fragment size after disruption there is also a decrease in T(L). The attribute values for the 16 parameter sets at 5000 iterations are shown in Table I for comparison. The $P_B(L)$ rule has the greatest influence on the decrease in the average number of tesselated faces, T(L), both in the original block and in separated solute fragments. Secondarily, the $P_B(WL)$ is influential in

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Table I. Attributes From Several Parameter Sets (5000 iter.)

Parameter Set	P_B(L)	P_B(WL)	J(L)	J(WL)	T(L)	f_0(L)	D(L)
1	0.1	0.7	16	0.06	3.512	0	4.96
2	0.1	0.1	16	0.06	3.405	0	5.02
3	0.1	0.1	16	16	2.920	0.09	5.39
4	0.1	0.1	0.06	16	2.600	0.14	5.53
5	0.7	0.7	16	0.06	2.353	0.14	7.86
6	0.1	0.1	0.06	0.06	2.093	0.13	6.22
7	0.1	0.7	0.06	0.06	1.658	0.10	8.69
8	0.7	0.1	16	0.06	1.631	0.26	7.62
9	0.7	0.1	16	16	1.095	0.46	6.80
10	0.7	0.1	0.06	16	0.722	0.58	6.97
11	0.1	0.7	16	16	0.563	0.57	17.01
12	0.7	0.7	0.06	0.06	0.421	0.65	17.49
13	0.7	0.1	0.06	0.06	0.305	0.74	8.80
14	0.1	0.7	0.06	16	0.172	0.84	23.63
15	0.7	0.7	16	16	0.129	0.88	25.76
16	0.7	0.7	0.06	16	0.043	0.96	26.02

the decrease of the T(L) attribute. The two joining probabilities have a negligible influence.

The f_0(L) Attribute

We interpret the presence of an unbound solute-occupied cell, f_0(L) as a molecule "in solution". From table I we extract the information that the breaking probability rules P_B(WL) and P_B(L) dominate the influences of the f_0 (L) values. The P_B(L) rule has a somewhat greater influence. The joining parameters J(WL) and J(L) play a negligible role. The higher the probability of breaking a solute-solute or solute-water tessellation, the greater the fraction of solutes not bound to other solutes, f_0(L).

The D(L) Attribute

This attribute is the average distance that each solute-occupied cell has traveled from the center of the original block. The breaking probabilities P_B(WL) and P_B(L) dominate the influences of the rules with the P_B(WL) rule having the greatest effect. The joining parameters have a minor influence. From Table I we see the influence of P_B(WL) on the D(L) for several high and low values. High P_B(WL) values lead to greater diffusion, recorded as higher D(L) values. High P_B(WL) values are characteristics of non-polar solutes (3,4) thus the simulation reveals that these types of solutes have a greater propensity then polar solutes to diffuse in water.

The Effect of P_B(W) Change on the Attributes

The transition function associated with the water temperature has been shown to influence the solubility of solutes (3). We can test this influence on the solute block attributes by changing the P_B(W) for water, held constant in this study up to now. Increasing the P_B(W) value, corresponding to raising the temperature, leads to the emergence of lower T(L) values and higher f_0(L) and D(L) values. This corresponds in our model to greater solute block disruption, greater solubility and more extensive diffusion. Figure 1 shows the water temperature influence on the solubility, f_0(L), over the first 8000 iterations.

Information from the Simulation Graphics

At the onset of most of the syntheses, cavities from the water network penetrate and move about the solute block. This surprising observation reveals the cavities acting as "particles" in the case of a large variety of parameters. Very few water molecules penetrate the block of solute. An example is shown in Figure 2. Several of the parameter sets do not reveal any significant amount of disintegration after 8000 iterations, as found for sets 1 and 2 in Table I. Others calve off a few solute cells and then reattach to the solute block. These do not migrate very far from the solute block after several thousand iterations. Examples include parameter sets 4, 5, 6, 9, 10. Other parameter sets produce configurations in which there is extensive penetration of the surface or the interior of the solute block, mostly by water cavities. Parameter set 14 produces an early configuration in which single solute cells break away from the solute block and move into the water domain very rapidly, a configuration that may be associated with a highly soluble substance. Figure 3 shows this configuration.

DISCUSSION

We have conducted a series of studies on a molecular system modeling the disruption, dissolution and diffusion of the ingredients of a block of solute in water. The dynamic modeling was carried out using cellular automata. The state values and transition functions used were comparable to those used in our earlier experiments (2-4). By systematically varying the transition functions governing solute-solute and water-solute encounters, we can define most of the parameter space. This reveals richly varying sets of attributes

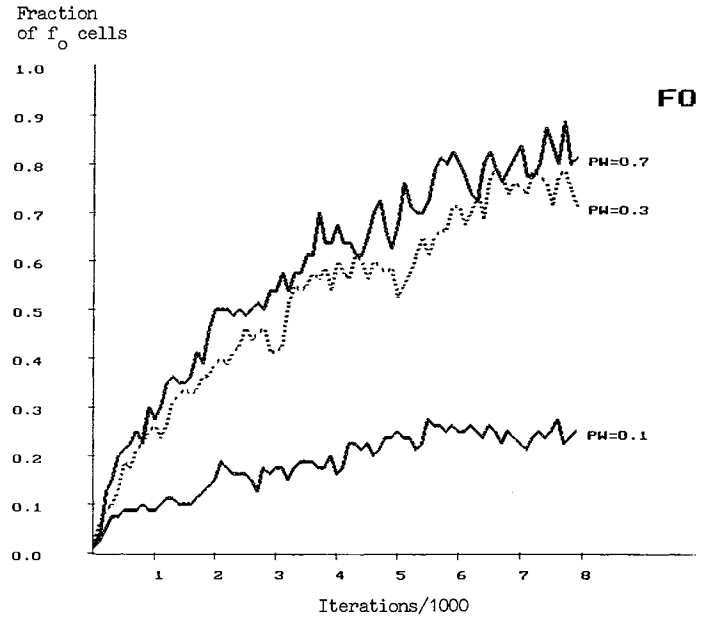

Fig. 1. The f_0 values over 8000 iterations of a parameter set defined in the text. The three curves represent these values for different $P_B(W)$ values.

modeling conditions ranging from rapidly disrupting to virtually inert solute block behavior; soluble to insoluble condition; and highly condensed to largely diffused status.

The dynamics reveal a dominant influence of the breaking probabilities between two solute molecules on the extent and rate of solute block disruption. This probability bears a relationship to factors influencing the melting point. The melting point and the heat of fusion are frequently used as parameters in empirical equations modeling solubility. The configurations interpreted as the emergent property of solubility are influenced by both breaking probabilities. The extent of the migration of solute molecules from the disrupted solute block is largely dependent on the solute-water breaking probability. From earlier studies (4) we relate this probability to emergent properties of polarity-nonpolarity of a solute. High probabilities are associated with nonpolar sol-

Fig. 2. Configuration of parameter set 5 after 500 iterations showing cavities permeating the solute block.

Fig. 3. Configuration of parameter set 14 after 300 iterations showing the direct diffusion of unbound solute cells away from the solute block.

utes and give rise to the hydrophobic effect. Low values of this transition lead to simulations characteristic of polar solutes. Our solute diffusion model leads to the inference that nonpolar solutes diffuse through water more rapidly and extensively than polar solutes when comparing molecules of equal size and shape. Diffusion is generally believed to be dependent upon size; there being little attention paid to polarity, hence a paucity of data. Support for our finding can be derived from some comparative diffusion data described by Sawyer and Roberts (5).

The effect of changing the water-water breaking probability, corresponding to changing the water temperature (2), while holding all other parameters constant was simulated. The effect of increased water "temperature" produces a greater disruption of the solute block and an increase in the solubility, measured by an increase in the $f_0(L)$ value. This corresponds to the general observation of increased solubility with higher solvent temperature.

Regrettably, in the printed media we cannot exhibit the dynamics as they unfold. We can only show tabular data, plots, and frozen images of configurations. These do give some useful information derived from our models. We can see that the processes encoded by the attribute values are not a single phenomenon, but many possible scenarios in which breaking probabilities of water-solute and solute-solute are highly influential. The classical model of a diffusion zone formed around the crystal followed by the steady exchange of these zone molecules with the bulk phase, is just one of many models created by the dynamics.

An interesting emergent configuration is the predominant occurance of the penetration of the solute block by water cavities rather than by water molecules. These cavities, behaving as a "particle," roam through the block accompanied by the breaking of the solute-solute tessellations. This coincides with the disruption of the block. If we reflect on this observation, it is conceivable that a water cavity "particle" would have no attractive or repulsive behavior relative to a solute molecule. Thus it would be expected that it could move about the block unrestrained, whereas a water molecule would be governed by the rules relating it to itself and to the solute. Whether or not this cavity behavior has any basis in fact remains to be explored. If there is any validity to this model, then there is some obvious practical value that may be derived.

We propose that the processes experienced by a solute block in a solvent are emergent properties associated with a complex system. The ingredients of such a complex system are the molecules which may be defined by electronic and topological characteristics. We cannot, however, dissect this complex system to this level and study these ingredients individually to derive much understanding of the emergent properties. We must employ representations of molecules that epitomize their participation at the molecular system level. The use of rules allows us to include these ingredients in a dynamic synthesis leading to the emergent behavior described here. It is hoped that cellular automata models may prove to be of value in understanding some of the dynamic behavior of water and solutions.

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