

## A Cellular Automata Model of Water Structuring by a Chiral Solute

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The organization of water around a solute molecule with surface features of varying hydropathic states is studied. A stationary solute molecule and mobile water solvent molecules are modeled using cellular automata dynamics. It is shown that varying hydropathic states of solute molecule surface features influence the relative affinities of water for these features. In the case of a simulated chiral solute, a chiral pattern of associated water molecules binding to the surface is produced. This finding is in agreement with published simulations and circular dichroism measurements. A pattern of water molecules at locations beyond the surface of the solute molecules is detected, evidence of an emergent property in this solvent–solute system.

### INTRODUCTION

The hydrophobic effect is well-known and recognized as an important influence on many biological phenomena. The ability of a solute to organize water in its vicinity is a mechanism often invoked to explain phenomena such as the role of glycopeptides as antifreeze agents in arctic fish, taste persistence after washout, and diffusion controlled enzyme reactions to name a few. Another observation is that chiral solutes have the ability to influence circular dichroism (CD) measurements responding to a chiral pattern of solvent surrounding a chiral solute. A recent study by Fidler et al.<sup>1</sup> focused attention on the nature of the immediate environment of a chiral molecule. Chiral patterns of solvent organization were detected by CD measurements and molecular dynamics simulations as a response to the influence of a chiral solute.

There is a lack of information on the surroundings of a solute in a solvent, particularly water. These are the systems of interest to the biologist. Water and solution phenomena have been targets of our studies over the past decade, where we have used cellular automata dynamics to model and study their emergent properties. In this study we explore the organization of water in close proximity to solutes which have varied surfaces capable of experiencing a solvated-unsolvated equilibrium. We examine the possibility of a chiral pattern of water occurring in direct contact with a chiral solute and the possibility of some solvent organization occurring beyond the immediate solvent–solute contact. We also explore the influence of the relative hydropathic states of fragments of a solute molecule on the water affinities for these molecules and the effect of temperature on the organization of water. These dynamic emergent properties are modeled using cellular automata.

### METHOD AND CONDITION

**Cellular Automata.** Cellular automata are dynamic computational systems that are discrete in space, time, and state and whose behavior is specified completely by rules governing local relationships. They are an attempt to simplify the often numerically intractable dynamic simulations into a set of simple rules that mirror intuition and that are easy to compute. As an approach to the modeling of 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<sup>2</sup> a variety of applications ranging from gas phenomena to biological applications has been reported by Ermentrout and Edelstein-Keshet,<sup>3</sup> Choppard and Droz,<sup>4</sup> and Kier, Cheng, and Testa.<sup>5</sup>

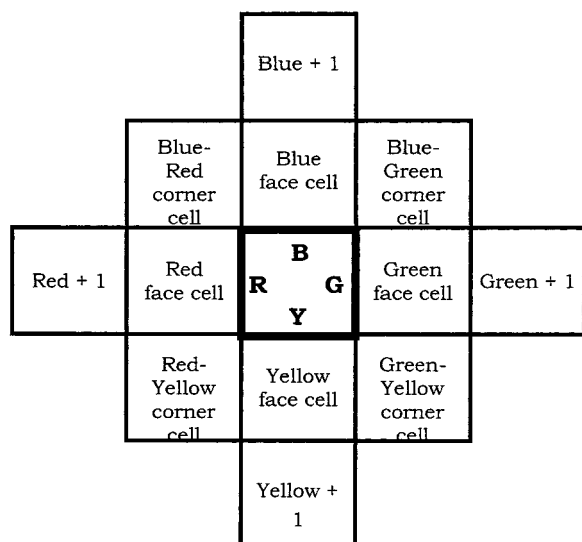
Our model is composed of a grid of square spaces called cells on the surface of a torus to remove boundary conditions. Each cell *i* has four tessellated neighbors, *j*, and four extended neighbors, *k*, in what is called an extended von Neumann neighborhood. Each cell has a state governing whether it is empty or is occupied by a water or other molecular particle. 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 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 conditions are random hence they do not determine the ultimate state of the cells, called the configuration. The same initial conditions do not yield the same set of configurations 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 simulations are emergent attributes of a complex system.

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**Figure 1.** The model used in the studies of a central solute molecule having four faces with different affinities and the nearby space realms which may be occupied with water.

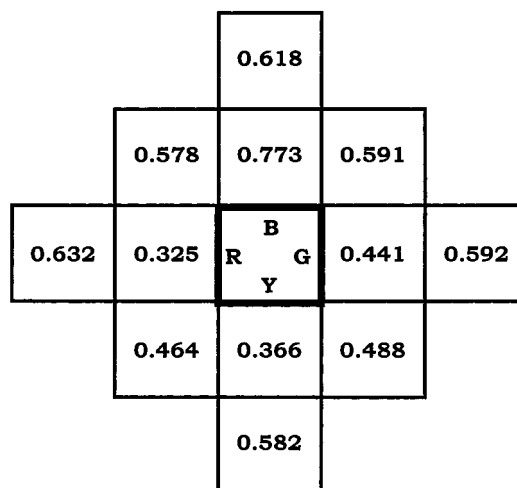
The nature of a cellular automation, representing a molecule in a dynamic simulation, is described with rules of probabilities of movement and/or encounters with other automata. It is a functional description not a conventional structure description in which electrons, atoms, and groups are explicit. These structural features are subsumed into rules governing the affinities of each cell face relative to water cells in their environment. The emergent properties from these encounters portray probable occupancy of positions in relation to other ingredients. The interpretation is meaningful in terms of the movements and encounters experienced by molecules with relative values of properties such as hydropathic state, polarity, temperature, and others. These results provide us with significant insight into the nature of the systems emerging from the dynamic phenomena being modeled.

**The Rules.** Two parameters were adopted in our model to express the probabilities of molecules moving in the grid. The breaking probability,  $P_B$ , is the probability for a molecule at  $i$  to break away from another at  $j$  when there is exactly one occupied  $j$  cell. The value of  $P_B$  lies in the closed unit interval. The second parameter,  $J$ , describes the movement of a molecular particle at  $i$  toward or away from the particle at a  $k$  cell in the extended von Neumann neighborhood (Figure 1) 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.

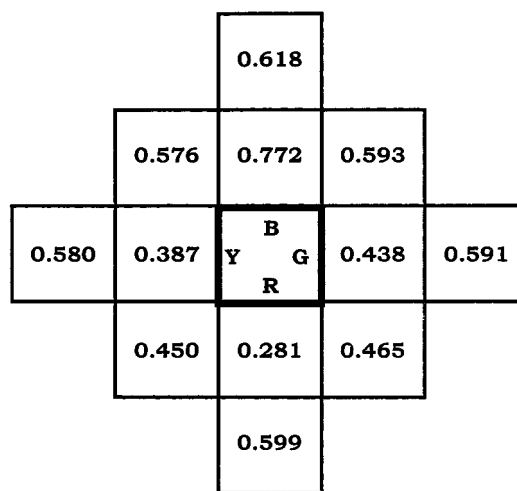
**The Cell Models.** To study a molecule with a variety of surface structural characteristics, we resort to the use of the variegated cell<sup>6,7</sup> where each face of a square cell is endowed with a separate set of joining and breaking probability rules giving each a characteristic hydropathic state. For convenience we color and label each face and assign the rules to reflect its state, as in Table 1. As an example, a cell with these four discrete faces would look like the model in Figure 1. The simulated temperature of the water used in these

**Table 1.** Designations of Solute Molecule Faces with Breaking and Joining Rules Assigned

color code	letter	$P_B$ (WS)	$J$ (WS)	hydropathic state
blue	B	0.10	2.80	hydrophilic
green	G	0.50	0.70	slightly hydrophilic
yellow	Y	0.60	0.50	slightly hydrophobic
red	R	0.95	0.10	hydrophobic



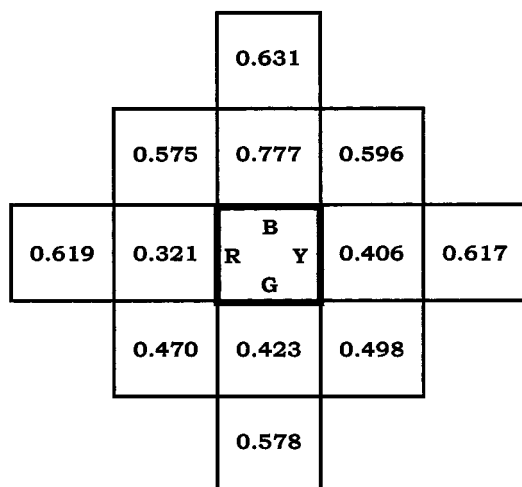
**Figure 2.** A solute molecule modeled at 20 °C in clockwise configuration **BGYR** (see Table 1, with affinities of water for surrounding space realms).



**Figure 3.** A solute molecule modeled at 20 °C in clockwise configuration **BGRY** (see Table 1) with affinities of water for surrounding space realms.

studies is 20 °C with two studies being run at 40 and 80 °C to model the influence of temperature on the water affinities. The water temperature is simulated using  $P_B(W)$  rules for water of 0.20, 0.40, and 0.80. These probabilities have been demonstrated to relate closely to the water temperature.<sup>7</sup> Each study consists of 100 runs, each of 10 000 iterations, totaling 1 000 000 iterations. A measurement is made of the fraction of the time (iterations) that a water molecule is

- (1) bound to each face of the solute cell—designated by a color;
- (2) bound to a cell once removed from a face—designated by a color + 1;
- (3) at the corner of two adjacent faces—designated by the colors of the two corner cells.



**Figure 4.** A solute molecule modeled at 20 °C in clockwise configuration **BYGR** (see Table 1) with affinities of water for surrounding space realms.

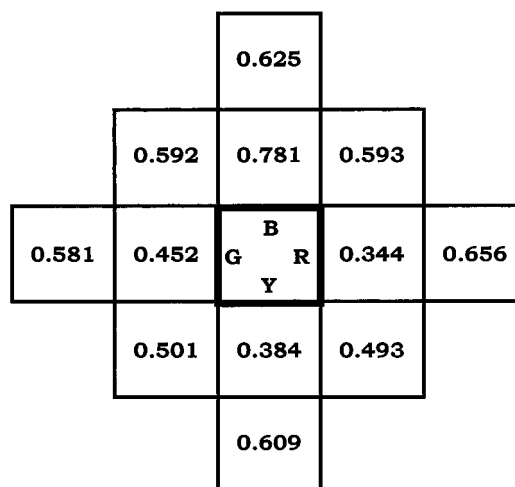
These positions relative to a single solute molecule are shown in Figure 1. This fraction of the time is used as a measure of the affinity of water molecules for the various positions around the central solute cell in each grid. The variation in the affinities is the standard deviation of the mean equal to the standard deviation divided by the square root of the number of iterations. This value is about 0.015 for all studies. The range of affinities between water and a solute molecule surface fragment may be compared to the probability of a water molecule occupying a cell in the grid we use in these studies. This probability is the density of the system, in this case 1100 water molecules in a  $40 \times 40$  cell grid. This reference probability of occupancy is therefore 0.688 in our studies.

The structures of the solute molecules being modeled are designated by letters in the center cell shown in Table 1. From the north face of the cell, around clockwise, the structural features of each solute are illustrated. The solute molecule **BGYR** is shown in Figure 2 with the letters shown in the center of the grid. There are three distinct solute molecule configurations, **BGYR** (Figure 2), **BGRY** (Figure 3), and **BYGR** (Figure 4), each with a mirror image. As an example, the cell designated as **BGYR** (Figure 2) has a mirror image designated as **BRYG** (Figure 5).

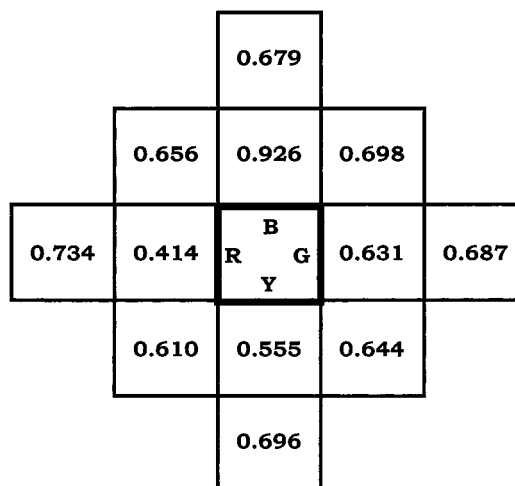
The objective of these simulations is to analyze the water association potential with a solute surface structural feature. These features were selected to impart to the solute molecules a chiral configuration. Our studies were then directed toward the goal of determining if a chiral induction of nearby water could be modeled.

## RESULTS

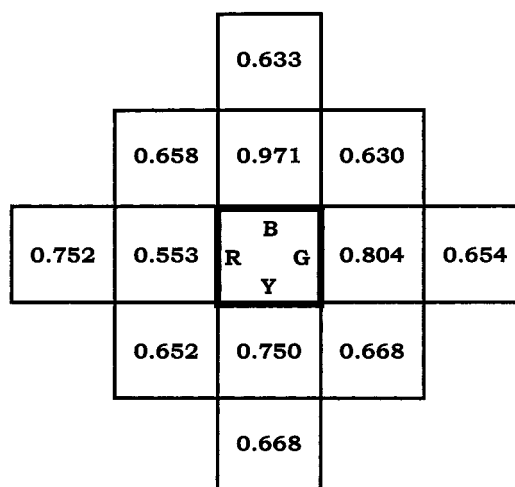
**Water Affinities to a Solute Molecule.** Several studies reveal the pattern of attachment and affinities of water for solute surface features. The fraction of time (iterations) that a water molecule is bound to the face of a solute is recorded from 1 000 000 iterations. These affinities are shown in Figures 2–4 and summarized in Table 2. The affinities of water molecules attaching to the solute molecule cell corners is shown in Figures 2–4 and is summarized in Table 3. The affinities of water molecules occupying the cell once



**Figure 5.** A solute molecule modeled at 20 °C in a configuration mirror image to the solute molecule in Figure 2 with affinities of water for surrounding space realms.

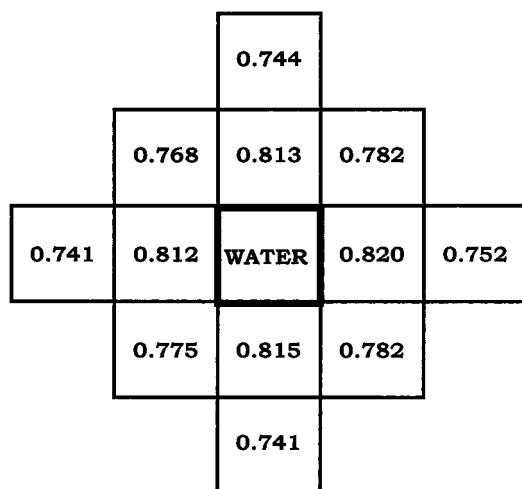


**Figure 6.** A solute molecule simulated at 40 °C in a configuration as in Figure 2, showing the affinities for water in surrounding space realms.



**Figure 7.** A solute molecule simulated at 80 °C in a configuration as in Figure 2, showing the affinities for water in surrounding space realms.

removed from the solute molecule face are shown in Figures 2–4 and are summarized in Table 4. The organization of water molecules around a solute molecule matches the pattern



**Figure 8.** A model of a water molecule surrounded by water molecules simulated at 20 °C with their affinities for surrounding space realms.

**Table 2.** Water Affinities to Solute Faces at 20 °C<sup>a</sup>

face	adjacent faces	opposite face	water affinity
B	R, Y	G	0.777
B	G, R	Y	0.773
B	G, Y	R	0.772
G	B, Y	R	0.441
G	B, R	Y	0.438
G	Y, R	B	0.423
Y	B, G	R	0.406
Y	B, R	G	0.387
Y	G, R	B	0.366
R	B, G	Y	0.321
R	B, Y	G	0.325
R	G, Y	B	0.281

<sup>a</sup> Data taken from Figures 2–4.

**Table 3.** Water Affinities to Corner Cells at 20 °C<sup>a</sup>

corner cells	(J + J)/2	corner affinities
B/G	1.75	0.592
B/Y	1.65	0.586
B/R	1.45	0.577
G/Y	0.60	0.493
G/R	0.40	0.468
Y/R	0.30	0.458

<sup>a</sup> Data taken from Figures 2–4.

**Table 4.** Water Affinities to Cells Once Removed from Solute Faces at 20 °C<sup>a,b</sup>

cell face + 1	affinities
B	0.616
G	0.591
Y	0.581
R	0.619

<sup>a</sup> Data taken from Figures 2–4. <sup>b</sup> In the absence of a solute molecule the average occupancy by a water molecule is 0.688.

exhibited by the chiral isomer. The affinities for solute face, corner, and face + 1 associations with water are shown in the two solute configurations in Figures 2 and 5 and are summarized in Table 5.

The effect of the temperature of water was examined to discover this influence on the affinities of water with the faces of the solute molecule. The water temperatures

**Table 5.** Affinities of the Enantiomeric Solutes **BGYR** and **BRYG** at 20 °C<sup>a</sup>

cell	affinity	
	R	S
<b>B</b> face cell	0.77	0.78
<b>G</b> face cell	0.44	0.45
<b>Y</b> face cell	0.37	0.38
<b>R</b> face cell	0.33	0.34
<b>B/G</b> corner cell	0.59	0.59
<b>G/Y</b> corner cell	0.49	0.50
<b>Y/R</b> corner cell	0.46	0.49
<b>B/R</b> corner cell	0.58	0.59
<b>B+1</b> cell	0.62	0.63
<b>G+1</b> cell	0.59	0.58
<b>Y+1</b> cell	0.58	0.61
<b>R+1</b> cell	0.63	0.66

<sup>a</sup> Data taken from Figures 2 and 5.

**Table 6.** Temperature Effect on Affinity of Water for Solute Molecule Faces

cell	affinities at modeled temperatures		
	20 °C (Figure 2)	40 °C (Figure 6)	80 °C (Figure 7)
<b>B</b> face cell	0.77	0.93	0.97
<b>G</b> face cell	0.44	0.63	0.80
<b>Y</b> face cell	0.37	0.56	0.75
<b>R</b> face cell	0.33	0.41	0.55

**Table 7.** Affinity of Water for Water at 20 °C<sup>a,b</sup>

water position	affinity values
next to faces	0.815
at corners	0.781
face + 1	0.745

<sup>a</sup> Data averaged from Figure 8. <sup>b</sup> In the absence of a solute molecule the average occupancy by a water molecule is 0.688.

simulated were 20, 40, and 80 °C. The results are shown in Table 6. To compare water–solute affinities with water–water affinities we have modeled the association of water molecules with positions around a stationary water molecule at 20 °C. These results are shown in Table 7.

## DISCUSSION

A variegated cell has been created to simulate a molecule with a varied surface in respect to hydrophathic states. These surface features range from hydrophilic (designated blue in Table 1), slightly hydrophilic (green), slightly hydrophobic (yellow), and hydrophobic (red). This stationary solute molecule is allowed to be bathed with water cells for a million iterations. The fraction of the iterations in which each of the solute molecule faces is occupied with a water molecule is recorded as the affinity of water for that face. Other studies observe the affinities for corner cells adjacent to two faces of the solute molecule and cells once removed from each face of the solute. The affinities of water for the solute molecule faces observed in the cellular automata dynamics relate to the parameters chosen for each hydrophathic state of the solute molecule faces as seen in Table 2. There is a modest influence on the affinity observed from the hydrophathic states of the two adjacent solute faces.

The affinity of water for the corner cell, formed by two adjacent faces on the solute molecule, is a direct function of

the average of the  $J$  values of these two faces as seen in Table 3. The correlation between the affinity and this average of  $J$  values is  $r^2 = 0.994$  for the six possible corner cell environments. This result is not a direct consequence of the solute molecule face parameters relating water to solute. It is an effect mediated through the water bound directly to the solute faces that form the corner realm. This is an emergent property of the system. The corner cells simulate the possible location of a second hydration shell associated with a solute molecule.

The affinity of water for the realm of cells once removed from the solute molecule surface is not significantly influenced by the hydropathic state of the solute molecule surface, as is apparent in Table 4. This realm simulates the possible location of a third hydration shell. This implies that the influence of a solute on its hydration sphere may only extend out through two layers of water, corresponding to the result described by Fidler et al.<sup>1</sup>

In the case of a chiral solute molecule, the water organized at each face, corner, and face + 1 realms is virtually the same when compared with the corresponding faces of a mirror image molecule. These results are shown for two mirror images, **BGYR** and **BRYG** in Table 5. This agrees with the findings of Fidler et al.<sup>1</sup> using circular dichroism experiments and molecular dynamics modeling.

The effect of water temperature on the affinities of water at the solute faces was studied and recorded in Table 6. The affinities increase with increasing water temperature for each of the hydropathic states represented in solute molecule **BGYR**. These results correspond to an increase in solubility for any hydropathic state. The hydrophobic faces are seen to exhibit an increased affinity but at a lower level than the more hydrophilic faces of solute molecules. This study presents an insight into why a solute may be more soluble at higher temperatures, namely that there is a higher

probability of water contact with the surface of a solute molecule at higher temperatures, thus a greater chance of isolation from other solute molecules.

In the last study of this project, it was of interest to replace the stationary solute molecule with a water molecule to observe the affinities with nearby water molecules. Table 7 shows these effects. The affinities are greater at the faces, less so at the corner realms and least in the realms once removed from the faces of the reference water molecule. The affinity average of 0.815 for the surface of the central water molecule translates into an average hydrogen bonding per water molecule of 3.26 for a simulated temperature of 20 °C. This is in agreement with experiment and modeling studies.

The studies using cellular automata reveal a coherent pattern of solute organization of nearby water molecules. The chiral pattern of a solute surface is reproduced in the nearby hydration water. The influence of the hydropathic states is direct at the solute surface but produces an emergent property in respect to hydration at more remote realms.

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