A Cellular Automata Model of Micelle Formation

Lemont B. Kier,[1,3] Chao-Kung Cheng,[1] Bernard Testa,[2] and Pierre-Alain Carrupt[2]

Received January 5, 1996; accepted June 4, 1996
KEY WORDS: cellular automata; dynamic models; micelle; critical concentration; and complexity.

INTRODUCTION

Amphiphile Structure

Molecules possessing bimodal properties of polarity and hydrophobicity in separated fragments are referred to as amphiphilic. These compounds are prominent in biology as surfactants (bile salts) and components of membranes. A characteristic feature is their propensity to form aggregates known as micelles. Two books on this subject stand out among a large body of literature, (1,2). We have recently modeled water and some solution phenomena with cellular automata using specific rules and initial conditions (3–6). It is our purpose to continue the study of cellular automata models of various solution phenomena such as micelle formation to add to our understanding of the emergent properties and the behavior of complex systems.

Cellular Automata

Cellular automata is a method of modeling the dynamic behavior of collections of molecules in a complex system. Each molecule is represented by a cell on a grid in one or more dimensions. Each cell of a designated type is given a set of rules reflecting its state. Each cell moves and responds to its immediate neighbors according to rules chosen for each category of encounter. These rules take the form of probabilities in our studies; the cellular automata is thus stochastic. Each cell in the grid, in a randomly selected sequence, computes its state, its movement probability, and the consequences of each encounter with a neighbor, according to rules; the cellular automata is thus asynchronous. The rules are local; the influence is only on immediate neighbors. The rules are uniformly applied to all common cells and identical neighbor encounters. Any organization that occurs with the dynamics is not explicitly dependent on initial conditions.

THE AMPHIPHILE MODEL

In our model the cells with designated states corresponding to amphiphiles, A, are endowed with two features intended to represent polar and hydrophobic molecular fragments. We encode this bimodal characteristic into these cells by dividing them into sectors with individual sets of parameters. Three modes of dividing the cells into these sectors are shown in Fig. 1. We employ model b in this study.

Each sector, A_x or A_y, is distinguished in the figure by a shaded or a clear feature respectively. Each sector has its own set of parameters relating it to others of the same type, to the alternate sector type, and to water. In this study we ascribe to sector A_y a hydrophobic character and to A_x a hydrophilic character.

These rule designations are as follows:

$P_B(W)$: probability of a water molecule breaking away from a water cluster

$P_B(A_x)$, $P_B(A_xA_y)$ or $P_B(A_y)$: probability of an amphiphile breaking away from an amphiphile union joined at sectors A_x-A_x, A_x-A_y or A_y-A_y, repectively.

$P_B(WA_x)$ or $P_B(WA_y)$: probability of a water molecule breaking away from an amphiphile molecule in a mixed union of W-A_x or W-A_y.

J(W) joining parameter for two water molecules.

$J(A_x)$, $J(A_xA_y)$ or $J(A_y)$: joining parameter for two amphiphile molecules engaging sectors A_x-A_x, A_x-A_y or A_y-A_y, respectively.

$J(WA_x)$ or $J(WA_y)$: joining parameter for a water and an amphiphile molecule sector.

Low values of P_B and high values of J impart relatively high affinities to the designated ingredients. In contrast, high values of P_B and low values of J impart relatively low affinities to the designated ingredients. When water is one of these designated ingredients, as in $P_B(WA_y)$ and the value is high, we infer that the rule describes a hydrophobic relationship (5). When water is the only ingredient described by such a probability and the value is high, we infer that the system has a relatively high temperature (3).

In this report we vary three of the sets of parameters shown in Table 1. In the first study, we examine the parameter space of the three rules influencing the amphiphile structure and the extent of formation of micelles. In the second study, we compare the concentrations of two distinctly different amphiphiles and their ability to achieve some common level of average cluster size. This study translates into a comparison of what may be interpreted as two relative values of a critical micelle concentration. The third study is an examination of the influence of the change of just the water temperature on the extent of micelle formation.

METHODS

STUDY A: INFLUENCE OF SEVERAL PARAMETERS ON THE MICELLES

The General Model

This study was designed to explore the parameter space of three sets of rules and their influence on micelle formation and properties. Specifically we have varied the WA_x; the A_x; and the A_y rules. We have selected a high and a low value for each of these rules in order to obtain a qualitative understanding of their relative influence on some attributes computed in the

[1] Department of Medicinal Chemistry and Mathematical Sciences, Virginia Commonwealth University, Richmond, Virginia.
[2] Institut de Chimie Therapeutique, Universite de Lausanne, Lausanne, Switzerland.
[3] To whom correspondence should be addressed.

0724-8741/96/0900-1419$09.50/0

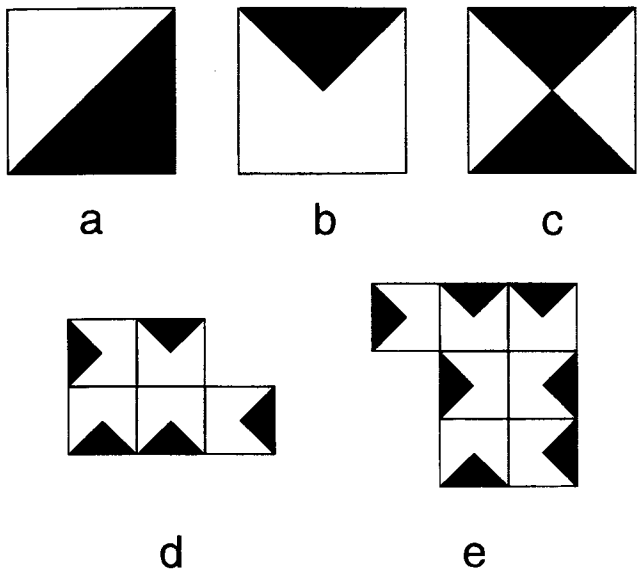

Fig. 1. Kier Chart.

cellular automata dynamics. These attributes are the count of molecules bonded at their y sectors, designated yy, and the average cluster size, S_y, based on the count of adjacent y sectors on attached A_{xy} cells. The concentration of the amphiphile cells among the water cells is 6.7%.

Results from the Parameter Space Study

The predominant influence on the extent of micelle formation is from the parameters related to the breaking and joining rules, $[P_B(A_y), J(A_y)]$, for the hydrophobic fragment of the amphiphiles. The lower the $P_B(A_y)$ value, the more self-association among the y sectors, hence the more hydrophobic is this sector. The consequence of the relatively greater hydrophobicity of the A_y sector (as shown with the first four parameter sets in Table I) is a greater extent of micelle formation and a larger extent of the aggregation. This corresponds to the observation of increased micelle formation with an increase in the nonpolar character of the hydrophobic segment of an amphiphile. It is recognized that this attribute of an amphiphile is the most important one in determining the relative populations and sizes of micelles (1,2).

Table I. Parameter Influence[a] on Micelle Attributes S_Y and YY

	$P_B(A_y)$	$J(A_y)$	$P_B(WA_x)$	$J(WA_x)$	$P_B(A_x)$	$J(A_x)$	Sy	yy
1	0.1	4.0	0.7	0.5	0.3	1.0	3.7	153
2	0.1	4.0	0.7	0.5	0.6	0.5	3.4	150
3	0.1	4.0	0.2	1.0	0.6	0.5	2.7	145
4	0.1	4.0	0.2	1.0	0.3	1.0	2.3	130
5	0.3	1.0	0.7	0.5	0.3	1.0	1.6	75
6	0.3	1.0	0.7	0.5	0.6	0.5	1.5	68
7	0.3	1.0	0.2	1.0	0.3	1.0	1.5	64
8	0.3	1.0	0.2	1.0	0.6	0.5	1.5	60

[a] Using fixed parameters: $P_B(W) = 0.25$, $J(W) = 1.0$ $P_B(WA_y) = 0.9$, $J(WA_y) = 0.25$, $P_B(A_xA_y) = 0.9$, $J(A_xA_y) = 0.25$.

The secondary influence of the $[P_B(WA_x), J(WA_x)]$ sets of parameters is evident from Table I. These rules sets influence the polarity of the hydrophilic fragment of the amphiphile, correspond to the head group. Low values of $P_B(WA_x)$ describe a polar head group, while higher values lead to a head group that can be interpreted as being only modestly polar. The results shown in Table I indicate that a modestly polar head group leads to more and larger micelles than a more polar feature. This result is consistent with experimental observations (7).

STUDY B. THE CRITICAL MICELLE CONCENTRATION

The Model

A common observation of the behavior of amphiphiles in water is the abrupt change in the values of certain solution properties as the concentration is increased. These properties include the surface tension, conductivity, and turbidity. At some approximate concentration, called the critical micelle concentration, c.m.c., there is a change in slope of these values with concentration. These transitions are used to estimate the c.m.c. which is characteristic of the amphiphile structure, its interrelation with itself and with water. This transition occurs when there are sufficient amphiphiles in the solution to form enough aggregates of a critical size to produce a distinct change in these properties. (1,2). Experimental data on the extent of aggregation and the average micelle size are difficult to acquire and are often estimated in calculations.

The attribute, S_y (the average cluster size) is useful in describing the onset of a critical concentration of micelles. The average numerical values of S_y as functions of the concentrations of the amphiphiles in water at standard sets of P_B and J rules is examined. The first rule set, $[P_B(WA_x) = 0.7, J(WA_x) = 0.5]$ corresponds to an amphiphile with a moderately polar head group. The second rule set, $[P_B(WA_x) = 0.2, J(WA_x) = 1.0]$ corresponds to a very polar head group in the amphiphile. These two rule sets were chosen because experimental evidence has shown that amphiphiles of the first type have lower c.m.c. values than those of the second type (7). Our objective is to compare the values of S_y with the concentrations of the amphiphiles in each parameter set study. This attribute value would then correspond to an approximate concentration which we could invoke as being a c.m.c. The amphiphile concentrations ranged from 1.7 to 10.0%.

Results

The values of S_y versus concentration for each parameter set, plotted in figure 2, reveal a change in the relationships. At low concentration values for each parameter set, 1.7 and 3.4%, the average cluster sizes, S_y, are about the same for the parameter sets 1 and 2. Above 3.4% the two curves exhibit distinct slope changes of different magnitudes. The curve for the first set, corresponding to a less polar head group, exhibits a higher slope than the curve for the highly polar head group amphiphile. If we designate some value of S_y above 2.0 as being a critical attribute marking the onset of micelle formation, then it is observed that the concentration leading to this value is lower for the first parameter set. This finding is in agreement with experimental evidence that reveals a lower c.m.c. value for less polar head group amphiphiles (7).

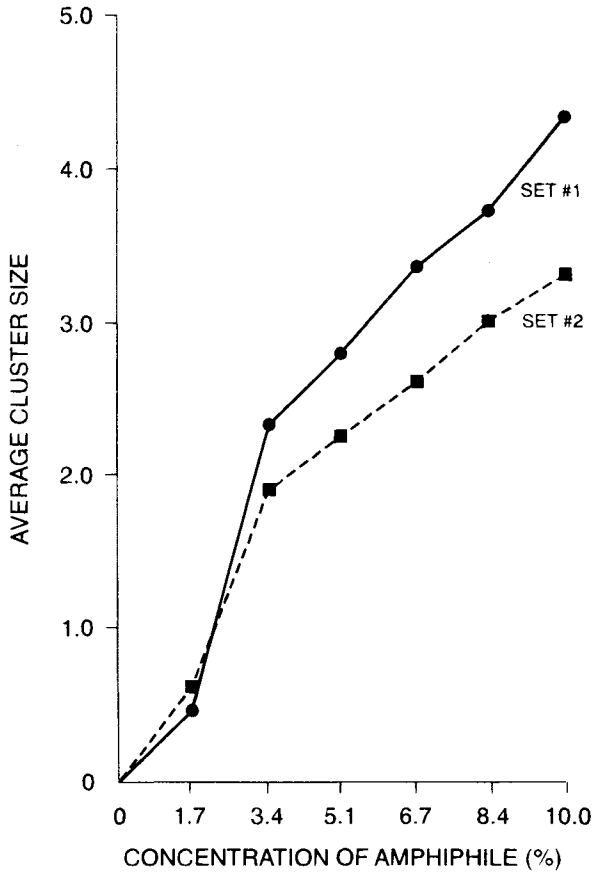

Fig. 2. The average cluster size versus the amphiphile concentration for each of two parameter sets.

STUDY C: EFFECT OF TEMPERATURE ON MICELLE PROPERTIES

The Model

Using rule set number 1 in Table I, we observe the attribute values at several temperatures, simulated by changing the $P_B(W)$ rule. The concentration of amphiphile was held at 6.7% for each simulation. By holding all other rules constant, we observe in Table II the S_y values arising from the simulated water temperature increase.

Table II. Water Temperature Effect on Micelle Formation

$P_B(W)^a$	S_y
0.10	3.00
0.20	3.20
0.25	3.35
0.40	3.25
0.50	3.15
0.55	2.75
0.60	2.70
0.80	2.50

[a] J(W) = 1.

Results

The results in Table II show that there is an increase in the S_y value up to about $P_B(W) = 0.25$. At higher $P_B(W)$ values, the S_y value declines. This finding of a maximum extent of aggregation corresponds to an observation of a sign change in the enthalpy of micellization in the region of 20–30°C (8). In this temperature range, the c.m.c. undergoes a minimum value (9).

DISCUSSION

We have designed a cell for cellular automata dynamic simulations that possesses multi-faceted characteristics. This bimodal cell is intended to model the amphipathic characteristics of amphiphiles in their formation of micelles. The cell is divided into sectors, each with its own set of breaking, P_B, and joining, J, rules, as employed in our earlier studies (3–6,10). In the simulation of the amphiphile, we invoke a non-polar character to one cell sector and a polar character to the other. The dynamics evolve into self-organized systems with characteristics of micelles.

We have found that the predominant influence on the extent of micelle formation is the interrelation between the non-polar sectors of the amphiphiles. The more non-polar an amphiphile sector, the more extensive the micelle formation in agreement with experimental observations. Secondary influence is found to be due to the rules governing the polar sector and the water relationship. Simulations using less polar models for the head group of the amphiphile result in a more extensive micelle formation in agreement with experimental observations. Our dynamic model has led to the finding that the onset of significant micelle formation, the c.m.c., is facilitated by the presence of a relatively less polar head group, in agreement with experience. Finally we have shown that the influence of increasing the water temperature is the increase the extent of micelle formation up to a rule value corresponding to about 25°C for the water. At higher temperature rules, the extent of micelle formation decreases. This follows the observed pattern of a minimum c.m.c. value at about 25°C and a corresponding sign change in the enthalpy of micellization at this temperature.

The dynamic model produces aggregates of amphiphiles consisting of hydrophobic interiors and hydrophilic exteriors closely associated with water. Two examples of these micelle models, extracted from our dynamics, are shown here as d and e in Fig. 1.

These studies lead us to believe that we have created conditions and employed rules in our cellular automata model which give rise to a dynamic model with emergent attributes mirroring some of the characteristics of micelles. This reinforces our belief that cellular automata may afford a method for creating models of dynamic solution phenomena.

ACKNOWLEDGMENTS

The authors thank G. Steyaert and M. Voeffray for helpful discussion. The author (LK) also thanks the, University of Lausanne for support during a summer sabbatical. The cellular automata dynamics were conducted using the program DING-HAO.

REFERENCES

1. C. Tanford. The Hydrophobic Effect: The Formation of Micelles and Biological Membranes, John Wiley & Sons, New York (1980).

2. M. N. Jones and D. Chapman. Micelles, Monolayers and Biomembranes, John Wiley & Sons, New York (1994).
3. L. B. Kier and C. -K. Cheng. A Cellular Automata Model of Water, *J. Chem. Info. Comput. Sci.* **34**:647–652 (1994).
4. L. B. Kier and C. -K. Cheng, A Cellular Automata Model of an Aqueous Solution, *J. Chem. Info. Comput. Sci.* **34**:1334–1337 (1994).
5. L. B. Kier, C. -K. Cheng, B. Testa and P. -A. Carrupt, A Cellular Automata Model of the Hydrophobic Effect, *Pharm. Res.* **12**:615–620 (1995).
6. L. B. Kier and C. -K. Cheng, A Cellular Automata Model of Dissolution, *Pharm. Res.* **12**:1521–1525 (1995).
7. P. Mukerjee and K. J. Mysels. Critical Micelle Concentration Aqueous Surfactant Systems, Nat. Bureau of Standards, Washington, D. C. (1971).
8. L. Espada, M. N. Jones and G. Pilcher, Enthalpy of Micellization. N-Dodecyltrimethyl Ammonium Bromide, *J. Chem. Thermo.* **12**:1–8 (1970).
9. T. Ingram and M. N. Jones, Membrane Potential Studies on Surfactant Solution, *J. Chem. Soc.* **65**:297–304 (1969).
10. L. B. Kier and C. -K. Cheng. In Lipophilicity in Drug Action and Toxicology V. Pliska, B. Testa and H. van de Waterbeemd (eds.) VCH, Weinheim, Germany (1996).