On Computer Simulation Methods Used To Study Models of Two-Component Lipid Bilayers†

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ABSTRACT: We show that the use of a computer simulation method introduced to calculate the equilibrium thermodynamic properties of a model of a two-component lipid bilayer membrane [Freire, E., & Snyder, B. (1980) *Biochemistry 19*, 88–94] is incorrect. This is done by comparing the method to that of Metropolis, which has been proven to generate equilibrium distribution of that model, and by showing that back-processes have been omitted in the implicit master equation of Freire and Snyder. We have illustrated this explicitly by first generating distributions according to the method of Freire and Snyder and then allowing the system to relax via the Kawasaki method, which uses the technique of Metropolis. We show that relaxation to a different distribution occurs. We also remark that the cluster distributions generated by the Freire–Snyder method are substantially different from those occurring in equilibrium distributions. Thus, conclusions about equilibrium thermodynamic properties such as specific heats and transition enthalpies or about transport properties or cluster properties at equilibrium cannot be drawn from the results obtained by using this method. Finally, we point out that the method of Freire and Snyder is appropriate to so-called aggregation models, which have been used to study irreversible growth; and we suggest biological systems that might be simulated by their method.

Computer simulation is a powerful technique for unravelling the properties of cooperative systems (Binder, 1979), and in recent years it has been used to study two-component bilayer membranes. In a series of papers (Freire & Snyder 1980a,b; Snyder & Freire 1980), results for equilibrium thermodynamic properties of lipid A–lipid B and lipid–cholesterol bilayers were presented. Freire & Snyder (1982) later extended their models to include the study of equilibrium properties of lipid–protein bilayer membranes. In these papers, they calculated enthalpy changes and properties of clusters and correlated lateral diffusion in a lipid bilayer to the onset of a static percolating cluster.

The intention of this paper is to show that the, seemingly reasonable, simulation method used by them does not yield equilibrium distributions, and therefore cannot be used to calculate equilibrium properties, of their model. We shall do so by relating their model of a lipid A–lipid B bilayer to the Ising model and show that their simulation method is different from a simulation method that can be proven to yield equilibrium properties of the Ising model. We shall also give explicit numerical examples to show that distributions generated by their method relax to different distributions when the correct simulation is used. It should be clearly understood that we are not commenting upon their model of a two-component bilayer. We are showing that their simulation method cannot be used to calculate the equilibrium thermodynamic properties of it. In doing this, we shall refer to Freire & Snyder (1980a) since that is where the model is presented in detail, though our remarks apply to all four papers.

The plan of this paper is (i) to show that the model of a lipid A–lipid B bilayer (Freire & Snyder, 1980a) is isomorphic (i.e., mathematically equivalent) to an Ising model, (ii) to review the only simulation algorithm (Metropolis et al., 1953) that has been proven to yield equilibrium thermodynamic properties of this model and to summarize the two methods by which the Metropolis algorithm has been implemented, (iii) to explain how the Freire–Snyder method differs from them, (iv) to present numerical examples to show that distributions generated by the Freire–Snyder method are not equilibrium distributions, and (v) to identify the kind of system that the Freire–Snyder method does simulate and to suggest systems of biological interest that might be studied by their method.

We thus show that conclusions about the equilibrium thermodynamic properties of their model such as specific heats and transition enthalpies or about transport properties or cluster properties of equilibrium cannot be drawn from the results obtained by using this method. We close by discussing whether their results are "sufficiently close" to the correct results and how this could be ascertained.

Simulation Methods Applied to Ising-Type Models

Freire & Snyder (1980a) considered two-component lipid bilayer membranes, in particular DMPC–DPPC, DMPC–DSPC, and DPPC–DSPC bilayers. We are thus concerned with a system that is prepared with a given concentration of molecules of type B, the remainder being of type A. Experimentally, this is brought to equilibrium at temperature T when measurements are performed to determine thermodynamic quantities. The plane of half of the bilayer is represented by a triangular lattice, each site of which is occupied by a lipid of either type A or type B. For a given distribution of A and B molecules on the lattice, the energy was assumed to be [Freire & Snyder (1980a) eq 3 and 4]

$$E = \frac{z}{2}(E_{AA}N_A + E_{BB}N_B) + \Delta E_m N_{AB}$$
$$\Delta E_m = E_{AB} - \frac{1}{2}(E_{AA} + E_{BB}) \quad (1)$$

where N_A and N_B are the numbers of A and B molecules, N_{AB} is the number of A–B nearest neighbors and z represents the total number of nearest neighbors to a site, which for a triangular lattice is $z = 6$. This energy can be obtained from the following Hamiltonian operator (operators are denoted in boldface)

$$\mathbf{H} = \frac{1}{2}\sum_{\langle ij \rangle}(E_{AA}\mathbf{L}_{Ai}\mathbf{L}_{Aj} + E_{BB}\mathbf{L}_{Bi}\mathbf{L}_{Bj} + 2E_{AB}\mathbf{L}_{Ai}\mathbf{L}_{Bj}) \quad (2)$$

where $\mathbf{L}_{Ai}$ and $\mathbf{L}_{Bj}$ are projection operators for lipids of types

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0006-2960/84/0423-3227$01.50/0

A and B at sites i and j, respectively, and $\langle ij \rangle$ indicates a sum over nearest neighbors. Thus, if site i is occupied by an A, then the eigenvalue of $\mathbf{L}_{Ai}$ is 1 and that of $\mathbf{L}_{Bi}$ is 0, while if it is occupied by a B, the corresponding eigenvalues are 0 and 1. When one makes the following transformation to the spin operator σ_i

$$\mathbf{L}_{Ai} = \frac{1}{2}(1 + \sigma_i) \qquad \mathbf{L}_{Bi} = \frac{1}{2}(1 - \sigma_i) \tag{3}$$

$\mathbf{H}$ becomes

$$\mathbf{H} = E_0 - \frac{\Delta E_m}{4}\sum_{\langle ij \rangle}\sigma_i\sigma_j + h\sum_i \sigma_i \tag{4}$$

$$E_0 = \frac{Nz}{8}(E_{AA} + E_{BB} + 2E_{AB}) \qquad h = \frac{z}{4}(E_{AA} - E_{BB})$$

This is the Hamiltonian function of an Ising model in an external field, h [for a readable historical review, see Brush (1967)]. As originally presented, an Ising model is a model of a solid composed of ions or atoms each having two quantum mechanical magnetic states ("spin $-\frac{1}{2}$" states). The quantum mechanical magnetic moment ("spin") of a particular ion is represented by a spin variable, σ, which can take on two values: "spin-up" with $\sigma = 1$ or "spin-down" with $\sigma = -1$. The spins occupy lattice sites and interact, in a particular way, with each other and with an applied magnetic field. It has been long known that this model is equivalent to a simple model of a liquid–gas transition ("lattice gas") or a two-component alloy ("A–B alloy") [e.g., see Huang (1963)]. In the latter case, if $\sigma = 1$ corresponds to an A, then the concentration, c, of B is

$$c = \langle \mathbf{L}_B \rangle = (1/2)(1 - \langle \sigma \rangle) \tag{5}$$

The relation between the average of $\sigma_i\sigma_j$, $\langle \sigma_i\sigma_j \rangle$, and N_{AB} is given in the Appendix. $\langle \sigma_i\sigma_j \rangle$ is clearly proportional to the average energy of interaction of the A–B system.

In order to perform a computer simulation of the Ising model to obtain numerical results for its equilibrium thermodynamic properties, a formalism is needed that can be shown to lead to an equilibrium distribution, i.e., to a minimum of the free energy. If $p(\sigma_1, \sigma_2, ..., \sigma_N, t)$ is the probability of finding sites 1, 2, ..., N to have spin variables $\sigma_1, \sigma_2, ..., \sigma_N = \{\sigma\}$ at time t, than a master equation can be written down that gives an expression for $(dp/dt)(\{\sigma\}, t)$ in terms of probabilities for transitions into and out of the state defined by these values of the spin variables [see, e.g., Binder (1979)]. The master equation is

$$\frac{dp}{dt}(\{\sigma\}, t) = -\sum_{\{\sigma'\}} W(\{\sigma\}\rightarrow\{\sigma'\})p(\{\sigma\}, t) + \sum_{\{\sigma'\}} W(\{\sigma'\}\rightarrow\{\sigma\})p(\{\sigma'\}, t) \tag{6}$$

where $W(\{\sigma\}\rightarrow\{\sigma'\})$ is the transition probability from the state defined by $\{\sigma\}$ to that defined by $\{\sigma'\}$ in unit time and where we make no restrictions on the states $\{\sigma\}$ and $\{\sigma'\}$. Let the transition probability be defined by

$$W(\{\sigma\}\rightarrow\{\sigma'\}) = (1/\alpha)\exp(-\Delta E/k_BT) \tag{7}$$

if $\Delta E > 0$ and $= 1/\alpha$ otherwise where α is an arbitrary time-scale factor that is usually set equal to unity and ΔE is the difference in energy between the states defined by $\{\sigma\}$ and $\{\sigma'\}$ (see below). Then, this transition probability leads to the condition

$$\lim_{t\rightarrow\infty} \frac{dp}{dt}(\{\sigma\}, t) = 0 \tag{8}$$

The system is then said to be in thermal equilibrium, the subsequent states of the system are equilibrium configurations, and the system is ergodic [Metropolis et al., 1953; Binder, 1979 (note the comments on p 5)]. The simulation of the Ising model proceeds as follows. Let a state of the system be given by the distribution $\{\sigma_1, \sigma_2, ..., \sigma_N\}$. Select a site, say i, with spin variable σ_i and calculate the energy of that site through its interaction with its nearer neighbours as well as its "field" energy determined by h. Let this be $E_i(\sigma_i)$. Change σ_i to $-\sigma_i$ and calculate $E_i(-\sigma_i)$. Define $\Delta E_i = E_i(-\sigma_i) - E_i(\sigma_i)$. If $\Delta E_i < 0$, then change the value of the ith spin variable from σ_i to $-\sigma_i$. If, however, $\Delta E_i > 0$, then select a number r randomly in the interval (0, 1). If $r < \exp(-\beta\Delta E_i)$ where $\beta = 1/(k_BT)$, then change σ_i to $-\sigma_i$. If $r > \exp(-\beta\Delta E_i)$, leave the spin variable, σ_i, unchanged. Select another site and repeat the procedure. Define a "step" by selecting each site once and only once. The system will then approach equilibrium if and only if a sufficient number of steps are performed. This method, which allows reversible processes, simulates a system that is in thermal and diffusive contact with a heat reservoir [see, e.g., Binder (1979) and references cited therein] and thus generates an equilibrium distribution of states.

For example, if site i has spin variables σ_i and its six nearest neighbors (1, 2, ..., 6) have variables $\sigma_1, \sigma_2, ... \sigma_6$, then from eq 4

$$E_i(-\sigma_i) - E_i(\sigma_i) = \Delta E_m\sigma_i(\sigma_1 + \sigma_2 + ... + \sigma_6) - 2h\sigma_i \tag{9}$$

Thus, if $\sigma_i = 1$ (a type A) and k of the nearest neighbors of the type B ($\sigma = -1$), then $E_i(-1) - E_i(1) = z\Delta E_m - 2h - 2k\Delta E_m$. If, on the other hand, $\sigma_i = -1$, then evidently $E_i(1) - E_i(-1) = -z\Delta E_m + 2h + 2k\Delta E_m$. It is important to realize that in order to approach equilibrium here, not only must spin variables undergo transitions $1 \rightarrow -1$ (A $\rightarrow$ B) but also $-1 \rightarrow 1$ (B $\rightarrow$ A). This brief description of the Metropolis method cannot do justice to some of the subtleties involved, and the reader should consult Binder (1979). However, the main point is that the simulation from an arbitrary initial state is governed by a master equation (6), which leads to the eventual generation of equilibrium states.

If however, we wish to consider the system only in thermal contact with a reservoir, then the simulation of the model proceeds as follows (Kawasaki method; Kawasaki, 1972). The system is prepared in an initial state compatible with the required concentration of 1 and -1. Let a state of the system be given by the distribution $\sigma_1, \sigma_2, ..., \sigma_N$, where σ's are selected such that the desired concentration is achieved. Select a site say i, with spin variable σ_i and an arbitrary nearest neighbor j with spin variable σ_j and calculate the local energy of the system involving these two spin variables. This calculation includes the interaction energy between the two spin variables σ_i and σ_j and, in addition, the interaction energies due to their nearest neighbors as well as their "field" energies determined by h. Let this be $E(\sigma_i\sigma_j)$. Interchange σ_i and σ_j, and now calculate $E(\sigma_j\sigma_i)$ and define $\Delta E_{ij} = E(\sigma_j\sigma_i) - E(\sigma_i\sigma_j)$. If $\Delta E_{ij} < 0$, then leave σ_i and σ_j interchanged. If, however, $\Delta E_{ij} > 0$, then select a number r randomly in the interval (0, 1) and for $r < \exp(-\beta\Delta E_{ij})$ leave σ_i and σ_j interchanged. If $r > \exp(-\beta\Delta E_{ij})$ return σ_i and σ_j to their original positions on the lattice.

For example, let site i have spin variable σ_i, site j have spin variable σ_j, and the eight nearest neighbors surrounding these two sites, 1, 2, ..., 8, have spin variables $\sigma_1, \sigma_2, ..., \sigma_8$. Then, ignoring E_0

$$E(\sigma_i\sigma_j) = \frac{-\Delta E_m}{2}[\sigma_i\sigma_j + \sigma_i(\sigma_1 + \sigma_2 + \sigma_6 + \sigma_7 + \sigma_8) + \sigma_j(\sigma_2 + \sigma_3 + \sigma_4 + \sigma_5 + \sigma_6)] + h(\sigma_i + \sigma_j)$$

$$E(\sigma_j\sigma_i) = \frac{-\Delta E_m}{2}[\sigma_i\sigma_j + \sigma_j(\sigma_1 + \sigma_2 + \sigma_6 + \sigma_7 + \sigma_8) + \sigma_i(\sigma_2 + \sigma_3 + \sigma_4 + \sigma_5 + \sigma_6)] + h(\sigma_i + \sigma_j) \quad (10)$$

$$\Delta E(\sigma_i\sigma_j) = \frac{-\Delta E_m}{2}[(\sigma_j - \sigma_i)(\sigma_1 + \sigma_2 + \sigma_6 + \sigma_7 + \sigma_8) + (\sigma_i - \sigma_j)(\sigma_2 + \sigma_3 + \sigma_4 + \sigma_5 + \sigma_6)]$$

Thus if $\sigma_i = 1$ (type A) and $\sigma_j = -1$ (type B), then these two lipids will interchange with certainty if the overall energy of the system is lowered, but there is still a non-zero probability of interchanging the two lipids if the energy is increased, and this probability is proportional to the Boltzmann factor. This transition probability in the master equation leads to the equilibrium states of a system in thermal contact only with a heat reservoir from any initially prepared state [see, e.g., Binder (1979) and references cited therein].

Let us now see how the method of Friere and Snyder simulates the Ising system of (1) or (4). All sites of the lattice are initially assigned $\sigma_1 = \sigma_2 = \ldots = \sigma_N = 1$; i.e., all sites are occupied by A lipids (this initial choice is frequently made in the Metropolis method, but the results must be independent of the choice of initial state). All sites are assigned sequential intervals of 1 on the interval $[0, N]$. A number r is selected randomly in the interval $[0, N]$, and the site, say i, into whose interval r falls is thus selected, and its spin variable of $\sigma_i = 1$ is changed to $\sigma_i = -1$ (an A is replaced by a B). The interval associated with site i is now changed from 1 to 0 in order to ensure that is will never be selected again. The intervals associated with each of the six nearest neighbors to site i are changed from 1 to $\exp(\beta\Delta E_m)$, while the remainder retain their initial intervals of 1. A number r is again selected randomly in the interval $[0, N - 7 + 6\exp(\beta\Delta E_m)]$, and the site in whose interval r falls has its spin variable changed from 1 to -1 (an A is replaced by a B). As the simulation proceeds, sites with $\sigma = 1$ (occupied by an A lipid) with k nearest-neighbor sites with $\sigma = -1$ (k nearest-neighbor B's) are assigned an interval $\exp(k\beta\Delta E_m)$.[1] A number, r, is randomly selected in the interval $(0, M)$ where M is the sum of the intervals associated with the sites. The site in whose interval r falls is thus selected next for having A replaced by B. This procedure is repeated until a sufficient number of B's have replaced A's to yield a B concentration equal to a predetermined value c. It should be noted that the energy that appears in the exponential here is only the interaction energy and the field energy, h, present in the Metropolis simulation, is absent. If, however, back-processes ($-1 \rightarrow 1$) were omitted from the Metropolis simulation, then $z\Delta E_m - 2h$ would be common to all exponentials and could, therefore, be omitted, thus yielding the exponential used by Freire and Snyder.[1] Such a simulation does not lead to equilibrium of the Ising model of (1) and (4) since this method is essentially irreversible. Although A's may be replaced by B's no B can ever be replaced by an A and so there is no allowance for the system to relax to equilibrium.

From the resulting distribution of B's, quantities such as cluster distributions and the average of N_{AB} are calculated. The entire simulation is repeated a sufficient number of times to obtain convergent averages. It is essential to realize that a regeneration of a distribution and the resulting averages over a number of states which are *not at equilibrium* does not give the same results as generating a distribution and allowing it to come to equilibrium and then taking the averages of the equilibrium distributions. The essential feature of the method of Freire and Snyder is that their implicit master equation cannot yield the condition $(dp/dt) = 0$ since only the first term of the right-hand side of eq 6 is present. The reason why both processes, A $\rightarrow$ B and B $\rightarrow$ A, must be explicitly included in a simulation is summarized by Binder (1979; section 1.2.1).

In order to give examples to show that the method of Freire and Snyder does not lead to equilibrium, we performed a number of simulations. We first performed the simulation

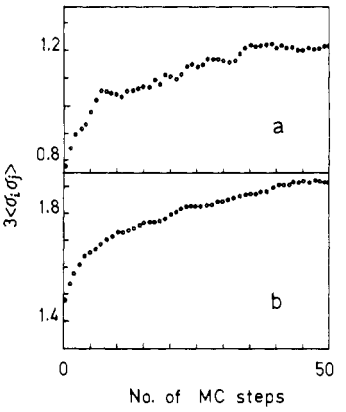

FIGURE 1: $3\langle\sigma_i\sigma_j\rangle$ as a function of a Monte Carlo step where i and j are nearest-neighbor sites. Here we have used $P = \exp(\beta\Delta E_m)$ to generate the starting configurations according to the Freire–Snyder simulation before allowing the system to relax via the Kawasaki method (see text and footnotes). (a) $\beta\Delta E_m = 0.5$; (b) $\beta\Delta E_m = 1.0$. $\langle\sigma_i\sigma_j\rangle$ is proportional to N_{AB} (see Appendix).

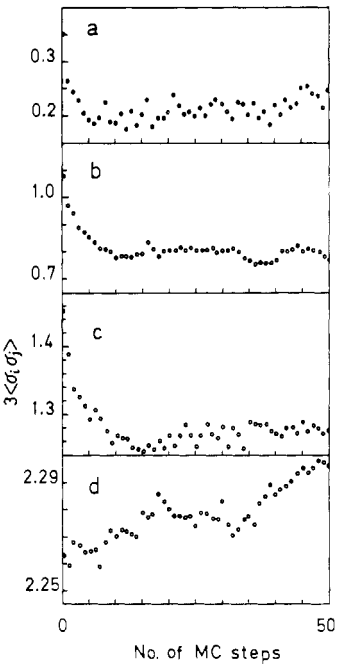

FIGURE 2: $3\langle\sigma_i\sigma_j\rangle$ as a function of a Monte Carlo step where i and j are nearest-neighbor sites. Here we have used $P = \exp(2\beta\Delta E_m)$ to generate the starting configurations according to the Freire–Snyder simulation before allowing the system to relax via the Kawasaki method (see text and footnotes). In the results here and those of Figure 1, the energies involved in the Kawasaki method are the same: (a) $\beta\Delta E_m = 0.125$; (b) $\beta\Delta E_m = 0.35$; (c) $\beta\Delta E_m = 0.5$; (d) $\beta\Delta E_m = 1.0$. $\langle\sigma_i\sigma_j\rangle$ is proportional to N_{AB} (see Appendix). The simulations here and in Figure 1 were performed on triangular lattices with 10 000 sites. The values of $\beta\Delta E_m$ correspond to $P = 1.28$, 2.01, 2.72, and 7.39, respectively. At 25 °C, these correspond to $\Delta E_m = 74$, 207, 296, and 592 cal/mol [the trans–gauche energy difference is ~500 cal/mol (Flory, 1969)].

[1] In fact, an interval of $\exp(2k\beta\Delta E_m)$ was used. (Brian Snyder brought this to our attention.) In this regard, it should be noted that the definition of P in Freire & Snyder (1980a) should be $P = \exp(2\beta\Delta E_m)$ and not $P = \exp(\beta\Delta E_m)$. When this change is made, our calculation of the nonideality parameter, ν, of Freire & Snyder (1980a), before the system is allowed to relax via the Kawasaki method, agrees with the values of ν calculated by Freire & Snyder (1980a) (see Appendix).

according to the procedure of Freiere and Snyder for a selected value of ΔE_m. B's were added to the lattice, thereby replacing A's, until a preselected concentration was obtained, and the energy was calculated. The distribution was then allowed to relax according to the Kawasaki method outlined above, and the value of $3\langle\sigma_i\sigma_j\rangle$, where i and j are nearest-neighbor sites, was recorded as a function of a Monte Carlo step. In order to perform the Kawasaki simulation, it was necessary to choose E_{BB} and E_{AB} in terms of E_{AA}, and we chose $E_{BB} = -E_{AB} = E_{AA}$.

In passing, it might be remarked that a choice only of ΔE_m does *not* uniquely define the average of N_{AB}. This is seen in (4) where it is clear that there are *two* variables, ΔE_m and h.

Figure 1 shows typical results of single simulations if we used the method of Freire and Snyder with $\exp(k\beta\Delta E_m)$, while Figure 2 shows the results if instead we used $\exp(2k\beta\Delta E_m)$ (see footnote 1). These were carried out on lattices with 10000 sites. In both cases, the Kawasaki simulations are identical; i.e., in the second case the Kawasaki simulation uses ΔE_m, as in the first case, and not $2\Delta E_m$. It can be seen from the relaxation observed that the distributions yielded by the Freire–Snyder method are not equilibrium distributions, because the system relaxes to a different value of N_{AB} as soon as the A's and B's are allowed to redistribute themselves. Although we have plotted single simulations, we did in fact perform four or five simulations for each case, and no differences of any significance were seen. Thus, this shows explicitly that the Freire–Snyder method does not yield the equilibrium properties of the Ising-type model that they have proposed (Freire & Snyder 1980a).

The particular values of the parameters shown here are (concentration, $\beta\Delta E_m$) (0.5, 0.125), (0.45, 0.35), (0.45, 0.5), and (0.45, 1.0). These correspond to values of $P = \exp(2\beta\Delta E_m)$ of 1.28, 2.01, 2.72, and 7.39, respectively. The first three are within the range of P values used by Freire & Snyder (1980a). For a temperature of 25 °C, these correspond to ΔE_m values of 74, 207, 296, and 592 cal/mol. These are typical of the energies of lipid A–lipid B bilayers since the energy to form a single gauche bond on an isolated hydrocarbon chain is ~500 cal/mol (Flory, 1969).

Discussion and Conclusions

From the descriptions above, it can be seen that the simulation method of Freire and Snyder is quite unlike that of Metropolis et al. (1953) or that of Alexandrowicz (1972), the latter having been proposed as an alternative to the Metropolis method [see, e.g., Binder (1979)]. The principal objection to their method as a means of obtaining information about equilibrium properties of Ising-type models is that their underlying master equation does not allow the transition B → A (−1 → 1) to occur and is based only on the transition A → B (1 → −1). Alternatively, we may consider their system as being in an initial state with a given concentration that is not allowed to relax to equilibrium. We showed this by explicitly carrying out simulations following their method, for both $\exp(k\beta\Delta E_m)$ and $\exp(2k\beta\Delta E_m)$ (see footnote 1), and then allowing the resulting distribution to relax via a Kawasaki simulation, which has been proven to lead to equilibrium configurations for Ising-type models. The fact that we observed relaxation to a different value of the spin-pair correlation function shows that the distributions generated by the Freire–Snyder method are not equilibrium distributions and, therefore, cannot be used to calculate equilibrium properties.

It should be noted that if ΔE_m is made sufficiently large, then for a small number of Kawasaki Monte Carlo steps no relaxation might be observed. The reason is not that the system is near equilibrium but that the system is locked into a nonequilibrium distribution by a high energy barrier. This can be seen either by increasing the temperature, T, allowing it to relax, and then slowly reducing the temperature to its initial value or by allowing the exchange of spin variables, which are further apart than nearest neighbors.

One can, however, ask the following question: If their method does not simulate the two-component systems described at the beginning of section 2, then what two-component system does it simulate? The answer is that it simulates a so-called aggregation model (Stanley, 1984). One example of such a physical system might be as follows. Monomers (B molecules) are deposited irreversibly onto a two dimensional substrate. The probability of forming B–B bonds leading to polymer formation will be determined by some interaction energy, E_I, and polymers will tend to form if E_I is attractive ($E_I > 0$) while monomers will predominate if $E_I < 0$. Such a model has obvious applications to the study of molecules binding to cell surfaces under a variety of conditions. In this regard, it is clear that energies and degeneracies involving single A and B molecules could be introduced, which could open the way to a rich variety of phenomena.

Aggregation models can display cluster distribution functions quite different from those of Ising-type models. If we let $N(s)$ represent the number of clusters of B's containing s B molecules, then for an Ising model (where B's correspond to spins $\sigma = -1$) it can be proven that $N(s)$ falls off at least as fast as $s^{-\tau}$ ($\tau \approx 2$) for large s values (Stauffer, 1979). The cluster distributions generated by the Freire–Snyder method do not display this property. We have carried out an analysis of the cluster distribution function for this model, and the results will appear elsewhere (N. Jan, T. Lookman, and D. A. Pink, unpublished results).

It might be noted that for $\beta\Delta E_m = 0$, the Freire–Snyder method correctly simulates random percolation. Since the random percolation model is equivalent to the Ising model at $T = \infty$, then the Freier–Snyder method correctly simulates their model when $\beta\Delta E_m = 0$. However, it should be borne in mind that random percolation is also correctly simulated by other irreversible methods.

Finally, the question might be raised as to whether it is, perhaps, only of abstract interest if the two-component system described here is simulated correctly or not. In response, some comments could be made: (i) Reliable computer simulation of an Ising model using the Metropolis algorithm to really quite easy on 16-bit, and in some cases even 8-bit, machines.[2] (ii) Cooperative systems of biological interest that are made up of units that can exist in a number of states can be represented by Ising-type models [e.g., Changeux & Rubin (1968)]. For a review of such applications, see Thompson (1972). It is essential in studying equilibrium phenomena to *know* that ones simulation will lead to equilibrium. (iii) The only way, at present, to test whether the numbers that emerge from an application of the Freire–Snyder method give a result, albeit incorrect, but "sufficiently close" in some undefined sense to the correct result, is to actually perform the Metropolis simulation and compare the two results. This being so, one may as well use the Metropolis method in the first place. For the first three cases shown in Figure 2, the numbers obtained for ν by using the correct simulation procedure differ from those reported by Freire & Snyder (1980a) by ~7, ~14, and ~10%, respectively. Are these errors "sufficiently small"? It is not the intent of this paper to answer this question because

[2] We will supply a Monte Carlo routine (Glauber and/or Kawasaki dynamics) to anyone on request.

it depends upon what quantity one is interested in. The purpose of this paper has been to distinguish between a simulation of equilibrium behavior that is in accord with the laws of thermodynamics and another that is not.

Added in Proof

We repeated the simulations for values (concentration; $\beta\Delta E_m$) of (0.5; 0.35), (0.5; 0.5), and (0.5; 1.0), which are identical with those used by Freire & Snyder (1980a). The equilibrium values of ν differed from those obtained by the Freire–Snyder method by about 12, 6–12, and 14%, respectively.

Acknowledgments

We have enjoyed stimulating arguments with Rodney Biltonen, whose talk at the Summer School on the Physics of Monolayers, Bilayers, and Biological Membranes (Antigonish, July 1982) originally interested us in this problem, and Gene Stanley, whose talk at the Summer School made us aware of properties of clusters. D.A.P. expresses his thanks to Rodney Biltonen and Joseph Larner (Department of Pharmacology, University of Virginia) for a very enjoyable visit during the spring of 1983. We are grateful to Dietrich Stauffer (Universität zur Köln) and Brian Snyder for discussions on the subject of this paper. Leo McDonald helped with the writing of the programs used here, the calculations were carried out at the computer centre, St. Francis Xavier University, and we thank Bonnie Quinn for her cheerful assistance. Finally, Vickie Loeser and Sheila McCabe typed the manuscript for us, for which we are grateful.

Appendix

Relation between N_{AB}, $\langle\sigma_i\sigma_j\rangle$, and the Nonideality Parameter. The relations between N_{AB}, the number of A–B nearest neighbors, and $\langle\sigma_i\sigma_j\rangle$, where i and j are nearest-neighbor sites, is easily calculated:

$$N_{AB} = N(\langle L_{iA}L_{jB}\rangle + \langle L_{iB}L_{jA}\rangle) = \frac{N}{2}(1 - \langle\sigma_i\sigma_j\rangle) \qquad \text{(A1)}$$

For an ideal mixture, $N_{AB}(\text{ideal}) = 2Nc(1-c)$ where c is the concentration of B's. We thus relate the nonideality parameter to $\langle\sigma_i\sigma_j\rangle$ by

$$\nu = \frac{1 - \langle\sigma_i\sigma_j\rangle}{4c(1-c)} = \frac{1 - \langle\sigma_i\sigma_j\rangle}{1 - \langle\sigma\rangle^2} \qquad \text{(A2)}$$

When $\beta\Delta E_m = 0.5$, $P = \exp(2\beta\Delta E_m) = 2.72$, while for $\beta\Delta E_m = 1.0$, $P = 7.39$ [see footnote 1 for the correct definition of P used by Freire & Snyder (1980a)]. An inspection of their Figure 1 (Freire & Snyder, 1980a) shows that, for $c = 0.5$

$$P = 2.72,\ \nu = \sim 0.51 \qquad P = 7.39,\ \nu = \sim 0.25 \qquad \text{(A3)}$$

The simulations reported here were performed 5 times for each value of $c = 0.45$, close enough to their concentration for a comparison to be made, before the system was allowed to relax via the Kawasaki method and to come to equilibrium. From an average over five runs, we obtained, in agreement with (A3), before allowing relaxation

$$\begin{aligned} P &= 2.72,\ \langle\sigma_i\sigma_j\rangle = 0.487,\ \nu = 0.519 \\ P &= 7.39,\ \langle\sigma_i\sigma_j\rangle = 0.758,\ \nu = 0.244 \end{aligned} \qquad \text{(A4)}$$

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