On the Theory of Ion Transport Across the Nerve Membrane, VII. Cooperativeity Between Channels of a Large Square Lattice

(computer simulation/Ising kinetics/Adam model/correlation functions/phase transition)

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ABSTRACT The exact kinetics of a 10 x 10 Ising system (periodic boundary conditions) with two-state channels arranged in a square lattice was studied by computer simulation. With all three values of the cooperativity parameter used, no induction in the K+ current curve was obtained. This confirms one of our previous conclusions concerning K+ channels in the squid axon membrane: models with interacting channels arranged in a two-dimensional lattice (Adam’s model) are apparently excluded. Other topics included: equilibrium properties; short-range pair correlation functions; phase transition.

In a previous paper (1), we investigated the exact kinetics of 2 x 2, 2 x 3, and 3 x 3 square Ising lattices with periodic boundary conditions to simulate Adam’s model (2, 3) of a two-state (open and closed) K+ channels arranged in a two-dimensional lattice with nearest-neighbor interactions between channels. It was shown that this model failed to generate induction or satisfactory superposition behavior, and therefore is presumably not applicable to K+ transport across the nerve membrane. However, it is possible that one could be misled in the representation of a very large patch of channels by such small numbers as above. In this paper, we report the calculation of the kinetics of a much larger lattice, 10 x 10 with periodic boundary conditions, in order to extend the generality of the conclusion reached before with respect to induction behavior.

A system containing z channels in a lattice, each of which may be open or closed, has 2^z possible system states. In order to study the exact kinetics of this system with z = 100, a tremendous number of first-order differential equations would have to be solved. The formal matrix diagonalization method used before (1, 4) is not feasible in this case; both the computing time and computer memory needed would be too large. Therefore, the calculations were performed on a computer by Gordon’s dynamic simulation (Monte Carlo) method (5). To check the program, the empirical results so obtained were first compared with some of the known exact properties of an infinite Ising system at equilibrium. The kinetics at three cooperativity strengths, s = 0.7, 0.5, and 0.4, was then investigated.

We refer the reader to similar work by Ogita et al. (6) in which Markov chains generated in discrete time steps were used to simulate the kinetics of an Ising system. However, their method is less efficient than the present procedure (5).

THE MODEL AND SIMULATION

Consider a 10 X 10 square lattice in which each site (channel) has four nearest neighbors. Each channel can be in one of two states, i (closed) and ii (open). The first row of the lattice is considered to be adjacent to the last row and the first column is considered to be adjacent to the last column (periodic boundary conditions). The notation for rate constants and nearest-neighbor interaction energies is the same as in the asymmetric (Adam) Schemes 8, 9, and 10 of ref. 1. Thus, the rate constants for the change in state of some particular channel are

\[ (i \rightarrow i) k_{i2} = \alpha z N_i \]  
\[ (ii \rightarrow i) k_{ii} = \beta \]

where \( N_i \) is the instantaneous number of nearest neighbors to the particular channel that are in state \( i \) (0 ≤ \( N_i \) ≤ 4) and

\[ s = e^{\alpha z k T}, w = w_1 + w_2 - 2w_3 \]

Here \( w_1 \) is the \( i - i \) pair interaction energy, etc. Of course \( N_i \) fluctuates with time, but this is taken into account in the following procedure.

A state of the entire system is determined by the configuration (i.e., specification of state \( i \) or \( ii \) for each channel) of the lattice. When the system is in any given state, \( i, x \) possible events may occur, yielding a transition to a different system state \( m \), by changing the state \( i \) or \( ii \) of some one channel in the lattice. Eqs. 1 and 2, together with the complete configuration of the lattice, provide the \( x \) rate constants that are operative here. We follow Gordon (5) in using a random number generator to decide which event actually occurs and in assigning a mean time interval \( \langle \Delta t \rangle \) to the event.

If some property of the system \( X \) (e.g., the number of open channels) has the value \( X_1 \) in system state \( i \), then at equilibrium \( (t \to \infty) \) the mean value of \( X \) is the time average

\[ \bar{X} = \sum_i X_i \langle \Delta t \rangle / \sum_i \langle \Delta t \rangle \]

where the sum is over a consecutive sequence of a very large number (e.g., tens of thousands) of system states.

If the system is not at equilibrium, we could follow by computer the event by event values of \( X_1 \) and \( \langle \Delta t \rangle \), and thus be able to plot \( X(t) \). However, this is inconvenient and unnecessarily detailed. Instead, we can group together a consecutive sequence of a relatively small number of system states (say of order 10 or 100) and assign an average \( \bar{X} \) from Eq. 3 to the time interval \( \sum \langle \Delta t \rangle \), thus giving \( \bar{X}(t) \). This can be done (see below for examples) with either a fixed number of consecutive system states per averaging step or a fixed time interval \( \sum \langle \Delta t \rangle \) per averaging step. The latter procedure
is generally more convenient because what we are primarily interested in is a further average of the function \( \bar{X}(t) \) over a large number of "runs" (this is equivalent to averaging over an ensemble of identical patches of channels, each with \( x = 100 \)). Clearly, the "fixed time" procedure makes the latter averaging easier and produces points \( \bar{X}(t) \) equally spaced along the time axis.

In this study, the state variables of the system of particular interest are the fraction of open channels \( p \) (the fraction of channels in state \( \bar{i} \)), and the short-range pair correlation functions, \( \langle S_{x,z} S_{x+1,z} \rangle \), \( \langle S_{x,z} S_{x+2,z} \rangle \), \( \langle S_{x,z} S_{x+1,z+1} \rangle \), and \( \langle S_{x,z} S_{x+1,z-1} \rangle \), where \( y \) and \( z \) denote the coordinates of a channel in the lattice and the values of \( S \) are taken to be \(+1\) for channel state \( i \) and \(-1\) for state \( \bar{i} \). The brackets mean averaging the product over the entire lattice.

CALCULATIONS ON EQUILIBRIUM SPIN SYSTEMS 
AT ZERO MAGNETIC FIELD

Several exact properties of an infinite square Ising-spin system at zero magnetic field have been found by Onsager (7), Kaufman and Onsager (8), Yang (9), and others. After translating (10) some of these results into our notation, comparison with \( 10 \times 10 \) simulated values provides a check on the correctness of the computational algorithms and on the adequacy of representing an infinite lattice by a \( 10 \times 10 \) lattice (with periodic boundary conditions).

Zero magnetic field, \( H = 0 \), in the usual spin system would lead to the result (in our notation) \( \beta = 1/2 \) (averaged over infinite time). It is easy to see, by consideration of detailed balance at equilibrium in Schemes 8 and 9 (1), that the parameter choice (equivalent to \( H = 0 \)) required to produce \( \beta = 1/2 \) is \( \beta/\alpha = s^4 \).

In the special case \( \beta/\alpha = s^4 \), then, we have calculated \( \bar{p} \) and the four shortest-range pair-correlation functions (see above) for a few temperatures in the range \( 0.8 < T/T_c < 1.4 \). A single long simulation run was used for each temperature. The temperature is determined by the value of \( s^4 = e^{\beta/2T} \). The critical value of \( s \) (7) is \( s_c = e^{\beta/2T_c} = \sqrt{2} - 1 = 0.4142 \).

A special comment is required concerning \( \bar{p} \) when \( T < T_c \).

Over infinite time, the computer simulated system would spend equal amounts of time in two different phases with \( \beta \) values of, say, \( \beta' > 1/2 \) and \( 1 - \beta' < 1/2 \), so that the overall \( \bar{p} = \langle \beta'/2 \rangle + [(1 - \beta')/2] = 1/2 \). However, in our calculations the system was started and then remained in the \( \beta' \) phase because of an extremely long nucleation time for the phase transition.

Fig. 1 shows the theoretical \( \bar{p}' \) \( (T < T_c) \) and \( \bar{p} \) \( (T > T_c) \) curves (infinite system), together with computer simulated points \( (10 \times 10 \) system). The \( \beta' \) curve is also the "coexistence curve" (10), in lattice-gas language, or the spontaneous magnetization per spin (10) in a spin system (change the ordinate scale, in this case, from \( 0.5 \leftrightarrow 1.0 \) to \( 0 \leftrightarrow 1.0 \)).

The length of simulation run used for each point varied from 10,000 to 40,000 consecutive events; these numbers are indicated in the figure.

Fig. 2 shows the theoretical correlation function curves and computed points from the same simulation runs as in Fig. 1. The results in both figures indicate that the \( 10 \times 10 \) (periodic boundary conditions) system is a very good approximation to the infinite system. Of course, the scatter of points around the theoretical curves would decrease with increasing lengths of simulation runs.

The computer print-outs for both \( \bar{p}(t) \) and the correlation functions exhibit two kinds of fluctuations: one with small

**Fig. 1.** Mean number of channels in state \( \bar{i} \) (open) at equilibrium with \( \beta/\alpha = s^4 \) (corresponding to zero magnetic field in a spin system). Curves are exact for an infinite system; points are computer simulated for a \( 10 \times 10 \) system by use of a single run of the number of thousands of consecutive events indicated beside each point.

**Fig. 2.** Four shortest-range pair-correlation functions at equilibrium with \( \beta/\alpha = s^4 \) (corresponding to zero magnetic field in a spin system). Curves are exact for an infinite system; points are computer simulated for a \( 10 \times 10 \) system by use of the same runs as in Fig. 1.
amplitude and short period; and another with large amplitude and long period (the amplitude and period of the latter increase when the temperature approaches the critical value). In general, the period of the long $\bar{p}$ fluctuation is longer than those of the pair correlation functions. In fact, as $T \to T_\epsilon^+$, this long $\bar{p}$ period becomes of the same order as the length of the runs used. This accounts for the greater scatter in $\bar{p}$ points.

**CALCULATION OF KINETIC PROPERTIES**

In order to make a comparison with our previous results in Fig. 8 of ref. 1, we calculated $\bar{p}(t)$ starting from a system state with all channels in state 1 ($\bar{p} = 0$) and ending with $\bar{p} \cong 0.895$, thus simulating the depolarization of the $K^+$ channels of a squid axon membrane from a maximally hyperpolarized state to $E_{Na}$ (1). Three values of the cooperativity parameter, $s = 0.7, 0.5$, and 0.4, were used. Note that $s = 0.4$ is below $s_c = 0.4142$.

For each value of $s$, it was first necessary to make several equilibrium runs to determine by interpolation the approximate value of $\beta/\alpha$ that leads to $\bar{p}(\infty) \cong 0.895$.

With these approximate values of $\beta/\alpha$, 100 simulation runs were performed for $s = 0.5$ and 0.7, and 60 runs for $s = 0.4$, to obtain ensemble averaged $\bar{p}(t)$ points from the individual "fixed-time" points $\bar{p}(t)$ obtained from each run. The three sets of $\bar{p}(t)$ points ($s = 100$) are shown in Fig. 3, superimposed on the $s = 4, 6, 9$ curves taken from Fig. 8 of ref. 1. As with $s = 6, 9$ (1), the time scales of the $\bar{p}(t)$ points ($s = 100$) have been adjusted to give approximately the same $t'_{1/2}$ (1) as for $s = 4$ ($t'$ is defined (4) as $(\alpha + \beta)t$).

We used a smaller number of runs for $s = 0.4$ because of the much greater computer time required per run. Ideally, of course, since $s = 0.4$ is so near $s = s_c$, we should have used an appreciably larger number of runs for $s = 0.4$ than for $s = 0.5$ or 0.7. This would have reduced the considerable scatter apparent in the $\bar{p}(t)$ points for $s = 0.4$.

Incidentally, the average number of events per $\bar{p}(t)$ point per run in Fig. 3 is 597 for $s = 0.4$, 162 for $s = 0.5$, and 345 for $s = 0.7$.

The results shown in Fig. 3 for $s = 100$ are approximate in various ways (especially the $\beta/\alpha$ values), as indicated in the above discussion, but they seem to us to be more than adequate to demonstrate the qualitative point of primary interest in this paper: the experimentally observed induction behavior in the $K^+$ current near $t = 0$ (1, 4) is not recovered in a model with cooperative interactions between channels on increasing the size of the patch of interacting channels to a size, which for practical purposes, is essentially infinite. Thus, the conclusions reached in discussing Figs. 6, 7, and 8 of ref. 1 are reinforced here.

Although smooth curves through the three sets of $\bar{p}(t)$ points in Fig. 3 are very similar in shape, the behavior of the individual $\bar{p}(t)$'s from which the average $\bar{p}(t)$'s were derived is quite different. For example, at $s = 0.7$, the change of the lattice with time from the initial to the final configuration is more or less gradual, and the general appearance of $\bar{p}(t)$ does not differ much from one run to another. But at $s = 0.4$, in an individual run, the lattice tends to stay in the initial "dilute" (small $\bar{p}$) configuration for a considerable time and then changes quite suddenly to the final stable "dense" configuration when a large enough fluctuation nucleates the phase transition. The phase transition is a random process and the nucleation times are Poisson distributed.
For somewhat smaller values of \( s \) than \( s = 0.4 \) we would then expect a simple exponential \( \bar{\eta}(t) \) curve. This phenomenon was already encountered (indirectly) with \( x = 4 \) and discussed near the end of ref. 4.

Fig. 4 contains an illustration of the above comments in which, for variety, we have used "fixed number" averaging rather than "fixed time" averaging: each point \( \bar{\eta}(t) \) in the figure is an average over 10 consecutive system states for \( s = 0.7 \) and an average over 300 such states for \( s = 0.4 \). The two time scales used differ by a factor of 1000. In the \( s = 0.4 \) case, note the much shorter mean lifetime of system states after the transition (because of the factor \( s^N \)).

Finally, we supplement the \( \bar{\eta}(t) \) results (\( x = 100 \)) in Fig. 3 with plots in Fig. 5 of the time dependence of the shortest range correlation function obtained from the same computer runs as in Fig. 3, and using the same time scales as in Fig. 3. The \( s = 0.7 \) system has an almost random distribution of channels at \( \bar{\eta} = 0.5 \). The relatively flat correlation function for \( s = 0.4 \) arises because, roughly speaking, what is happening in this case as time passes is random and sudden phase transitions (see above) in the ensemble of 60 systems from a phase with \( \bar{\eta} \approx 1 - 0.895 \) to another with \( \bar{\eta} \approx 0.895 \). But these two phases would have approximately the same value of the correlation function, so this quantity remains roughly independent of time. The argument is not exact because the former phase is not an equilibrium phase while the latter is an equilibrium phase.

The other three correlation functions (not shown) behave in much the same way.