Dipole interactions in axonal microtubules as a mechanism of signal propagation

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The microtubules (MTs) of nerve cells are stable relative to their counterparts in the rest of the body. This stability allows them to participate in cellular signaling processes. Each of the MT's subunits, dimers of tubulin protein, has an electric dipole moment that contributes to the overall polarity of the structure. We propose that the orientation of the individual dipoles may be flipped due to a conformational change of the tubulin dimer if energy is supplied through guanosine tri-phosphate hydrolysis or via physical interactions. Thus the MT lattice may be viewed as an electric dipole lattice with some overall polarization upon which signals, in the form of dipole patterns, may be propagated through dipole interactions that induce conformational changes. As a nerve impulse propagates along a neuron (nerve cell), the neuronal MTs are subjected to a large transient electric field that interacts with the MT lattices. Based on the recent conjecture of information processing and/or energy transport by MTs, we have used a Monte Carlo technique to model the interactions between the MT's subunits and to investigate the response of the lattice to nerve impulses. Our model of these interactions addresses the problem of thermal fluctuations in the dipole lattice and demonstrates how the nerve impulse may cause a signal to propagate along the MTs within the axon. [S1063-651X(97)07911-7]

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I. INTRODUCTION

Nerve cells are responsible for much of the communication within the body. They may signal other nerve cells or muscle cells in order to produce muscle contraction using nerve impulses. These impulses are commonly referred to as action potentials. The structure of these cells consists of an array of dendrites, which gather input from other neurons; a cell body; and an axon, possibly branched, along which nerve impulses are transmitted to other cells. The axon may project for large distances from the cell body, greater than 1 m in the human spinal cord, and its content is distinct from the cell body. It is generally free of organelles, and filled by microtubules (MTs) and neurofilaments which are jointly known as the cytoskeleton. These filamentous proteins are arranged parallel to the axon. Each neuronal MT is typically about 100 μm long and spans more than 10^5 tubulin subunits. The MTs of the axon have uniform polarity and lie with their positive ends distal to the cell body [1,2]. The network of cytoskeletal tubes is interconnected by high molecular weight proteins known as MT associated proteins (MAPs). Their precise function is not understood but tubulin dimers coassembled with MAPs *in vitro* are polymerized more easily and are more stable than MTs assembled from tubulin in the absence of MAPs [3]. Once the axonal MTs have been assembled, they are post-translationally modified and their properties are changed. These changes to the MTs cause them to become more stable [4,5]. The post-translational, post-MT assembly change has also been frequently studied in the last decade. The transition from newly synthesized tubulin to detyrosinated tubulin within a MT can be used to estimate the age of an individual MT [2].

Additional structural stability allows the neuronal MTs to participate in a capacity greater than their primary cellular function. Their primary function is to act as a cellular backbone, and to serve as railway tracks for vesicle transport by motor proteins. Information processing [6,7] and energy transport [8] have been proposed as secondary MT functions and several models of MT assembly [9,10] have been described. Not only is the tubulin which makes up neuronal MTs specific to humans, but it is also specific to nerve cells and is known to be post-translationally modified. The highly specialized nature of the functional protein suggests that it has been selected to perform a very specific function which we conjecture may be signal transduction. What is known with certainty is that they are assembled from guanosine triphosphate (GTP)-rich tubulin dimers and that this GTP is hydrolyzed rapidly after the addition of the tubulin subunit. What is not yet known is what happens to this energy. We are proposing that some of the energy is stored in the lattice through a conformational change of the protein dimer. The hydrolysis of GTP releases about 4.6 kcal/mol of energy which the lattice could use to flip conformational states of individual tubulin dimers; each flip would require up to 2.0 kcal/mol of energy. (This value is a result of our simulations and based upon our estimated values of the tubulin dimer's dipole strength.) The energy might then propagate along the MT through a sequence of dipole flips as the lattice reorients to accommodate the additional energy. These conformational changes or flips are believed to be the result of a mobile electron. It may be localized at one of two binding sites in the tubulin molecule. Movement of the electron from one binding site to the other causes the tubulin dimer and its electric dipole to reorient. These two states that may be identified by the location of the free electron are the states which we shall hereafter discuss.

Hameroff *et al.* [11] devised a model of MT cellular automata in 1988 inspired by the belief that the cytoskeleton behaves as a cellular nervous system. After all, the cytoskeleton does regulate many complex cell activities such as vesicular transport, mitosis, cell growth, cell shape, and locomotion [12]. Furthermore, Hameroff *et al.* cited numerous indirect indications supporting the hypothesis of information processing by neuronal microtubules. One of these was the

link between MTs and Alzheimer's disease; the link has since been made specific to MAPs [13]. Hameroff *et al.* believed that automata behavior within MTs could explain their capacity for intelligent organization. We feel our model is more physical than that of Hameroff *et al.* One reason is that dipole-dipole interactions are considered. As a result, no overall charge on individual tubulin molecules is required. The three dimensional geometry of the MT lattice is also taken into account in our model; although this has a small effect on dipole-dipole interactions in comparison with the two dimensional geometry of previous modeling, it is crucial when we consider the interaction with external fields like those transient fields of an action potential. Finally, our model incorporates thermal effects. The Hameroff-Rasmussen-Mansson scheme is a zero-temperature model in which signal propagation is an artifact of the model's design. The differences between our model and the Hameroff-Rasmussen-Mansson model will be discussed later.

II. MT LATTICE OF DIPOLES

The MT lattice has been vigorously studied over the past 20 years. In that time, two different lattices have been observed which have become known as the *A* lattice and the *B* lattice [14,15]. *A* lattices with an odd number of protofilaments are distinguished from all other lattices because they are the only ones without a structural discontinuity known as a seam. In all other lattices, the interactions are mixed which means that there are both *A*- and *B*-type lattice interactions in a single MT. It is now known that the number of protofilaments is not only variable from one MT to another, though 13 protofilaments is by far the most frequent *in vivo*, but the protofilament number need not be conserved along the length of an individual MT [16]. The theoretical modeling we have completed considers MTs of various lattice types but does not allow for variation of the lattice type or protofilament number along the length of an individual MT. We are soon hoping to account for dynamic instability [17–19] in the model. The idea of connecting the assembly process with the self-organization process of the dipole lattice is to explore how such a connection may explain the puzzling ensemble dynamics of microtubules grown *in vitro*. This is not so interesting for the information processing model since we believe that only stable microtubules would be important in this regard.

The structure of MTs has been experimentally determined [14]. We model the tubulin molecules as cylinders 5 nm in diameter and 8 nm in height. The dimer may be represented by two equally sized spheres representing the α and β monomers, respectively (Fig. 1). Moving around the MT in a left-handed sense, protofilaments of the *A* lattice have a vertical shift of 4.92 nm relative to their neighbors. In the *B* lattice, this offset is 0.92 nm everywhere but at the seam where it is 4.92 nm.

Our model predicts an organized MT lattice under physiological conditions. The organization of the *B* lattice is of particular interest because while the MT retains a small overall polarization, neighboring protofilaments have opposite polarization directions. We have also studied the self-organizing properties of the various MT lattices both in the presence and absence of static electric fields. The ordered

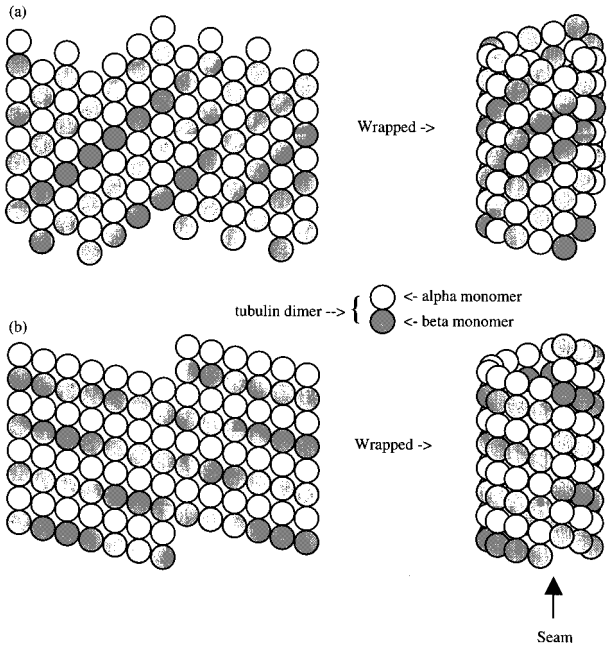

FIG. 1. The two possible MT lattices are depicted. Typical MTs are much longer than these which are shown with a length of only four dimers along each of the 13 protofilaments (columns). (a) The *A* lattice which has helical symmetry. (b) The *B* lattice which has a seam where a line following the α monomers around the MT meets a β monomer. The left-hand side depicts unwrapped MTs as the figures resulting from our simulations are given in a similar manner.

MT lattice and its resultant polarization may be significant given that of the three types of cytoskeletal polymers: actin filaments, intermediate filaments, and microtubules; it is the two polar structures which participate in material transport and cell motility through the use of their respective motor proteins. It is tantalizing to speculate that it might be this polarization which is responsible for guiding the motor proteins, kinesin and dynein, that travel along the MT in opposite directions [20,21]. It would immediately explain why such transport is so efficient because collisions would not occur. The motor proteins would simply have to bind preferentially to a particular conformational state of tubulin.

III. INFORMATION PROCESSING

Let us now return to the primary reason for the development and subsequent extension of the Hameroff-Rasmussen-Mansson model. Namely, could such a MT lattice process information? Consider the MT lattice of dimers in their α or β states as a binary biological computer. The Hameroff-Rasmussen-Mansson model found that signals introduced onto the MT 13*A* lattice would propagate along protofilaments. The propagation was either bidirectional or unidirectional depending upon the choice of flipping force thresholds and whether they were symmetric or not. The model also admitted the possibility of signals which periodically flip back and forth between α and β states but did not move along the protofilaments. The moving patterns of defects were named gliders and the nonpropagating defects were called blinkers.

The other feature of the Hameroff-Rasmussen-Mansson model was its ability to filter input signals. Some would

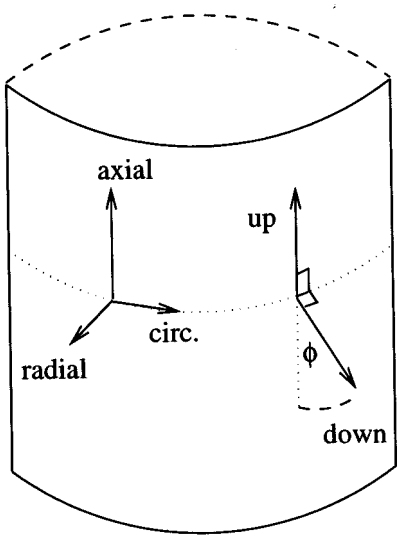

FIG. 2. This view of the outer surface of a MT identifies the directions of fields we may consider. The axial or vertical direction in this diagram points away from the cell body. At the right, the up and down directions which were selected for tubulin's dipole moment are shown ($\phi = 29°$).

propagate, others would be modified and would subsequently propagate, and still others would be annihilated. Thus the cellular automaton model accepted certain patterns and rejected others. We reproduced the results of the Hameroff-Rasmussen-Mansson model before proceeding with our own work. The first modification introduced was simply to replace the discrete charges with dipoles. Some arbitrary torque threshold was required akin to the force threshold of the original model. Despite the relative weakness of dipole interactions, most of the original features of signal transduction were still present in the modified model. The one difference was a shift in the direction of signal propagation from the N-S direction (along the protofilament) to the NW-SE direction (around the helix). Some shortcomings of the model were soon discovered; these have all been addressed in our new model. We will discuss the ramifications of the changes with respect to information processing in the description of the new model which follows and in the results.

IV. NEW MODEL OF DIMER-DIMER INTERACTION

Our new model was inspired by a model introduced by Hameroff *et al.* [11] in 1988. In their cellular automaton model, a discrete charge was associated with each tubulin dimer. In our model, a dipole is associated with each dimer. In this way, there is no net charge on each MT but the structure does have an overall polarization. This polarization may aid in the assembly of the polymer. The electric dipole of the tubulin dimer has two possible orientations depending on the conformational state of the molecule. One orientation is when the dipole points along the protofilament axis, distal to the cell body; this is the *up* state (Fig. 2). We have some freedom to choose the direction of the dipole in the *down* state since the electric dipole has not been measured in each of tubulin's conformational states. We have chosen the *down* state's orientation in a direction which is roughly opposite to the direction of the *up* state but which is 29° from the vertical and points out away from the MT. This choice is based on the geometry of MT ends which are splaying apart during disassembly and of tubulin oligomer rings. Tubulin under these conditions adopts a different conformation [22]. We will comment more on the orientation of the down state later. Our simulations have been carried out with both the tilted, $\phi = 29°$, and nontilted, $\phi = 0°$, down states for comparison. Some degree of tilting is necessary if action potentials are to influence the dipole dynamics because the nontilted dipole is entirely axial and the electric field of the action potential is purely radial. Consequently, there would be no interaction unless one of the states has some radial component.

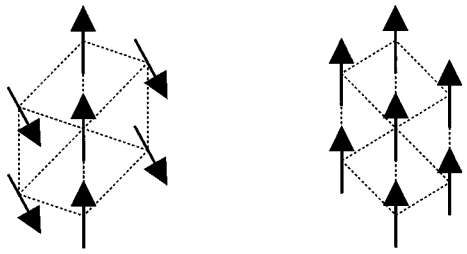

FIG. 3. Nearest-neighbor interactions: Along the protofilament, alignment is preferred so that the negative tails are close to the positive heads. Between protofilaments, the preferred orientation is determined by the vertical offset of the lattice. Left: In the *B* lattice, antialigned protofilaments are preferred. Right: Aligned protofilaments are preferred in the *A* lattice.

The interaction energy between two elementary dipoles is given by the following formula [23]:

$$E_{\text{int}} = \frac{1}{4\pi\epsilon\epsilon_f} \frac{\vec{p}_1 \cdot \vec{p}_2 - 3(\vec{p}_1 \cdot \vec{n})(\vec{p}_2 \cdot \vec{n})}{r^3}, \tag{1}$$

where ϵ is the relative permittivity of the medium, ϵ_f is the permittivity of free space, $\vec{p}_k$ is the kth electric dipole moment, $\vec{n}$ is the normal vector pointing from the position of the first dipole to the second dipole, and r is the distance separating the dipoles. Consider the interaction between dipoles of the MT lattice: from a purely structural point of view, the lattice type may seem insignificant; one does not expect that it will change assembly dynamics much. However, from the point of view of dipole interaction, the lattice type is crucial. In the *B* lattice, dimers are aligned in nearly horizontal rows. As a result, there is a strong interaction between neighboring protofilaments which favors opposite dipole orientations (Fig. 3). In the *A* lattice, the neighboring protofilaments are shifted vertically such that identical orientation of the dipoles is favored. In either case, there is a strong interaction along individual protofilaments which favors similarly oriented dipoles. The effect of the dipole interactions is that the lattice of up and down dipoles will self-organize into an energetically favorable configuration.

Let us consider the statistical mechanics of this system. At high temperatures, the lattice has a random state—each individual dimer can be found in the up or down state in a rather arbitrary fashion. At lower temperatures, the interaction energy dictates the dipole arrangement and the lattice becomes ordered. Our task is to investigate this transition in order to determine the likely state of a MT under physiological conditions.

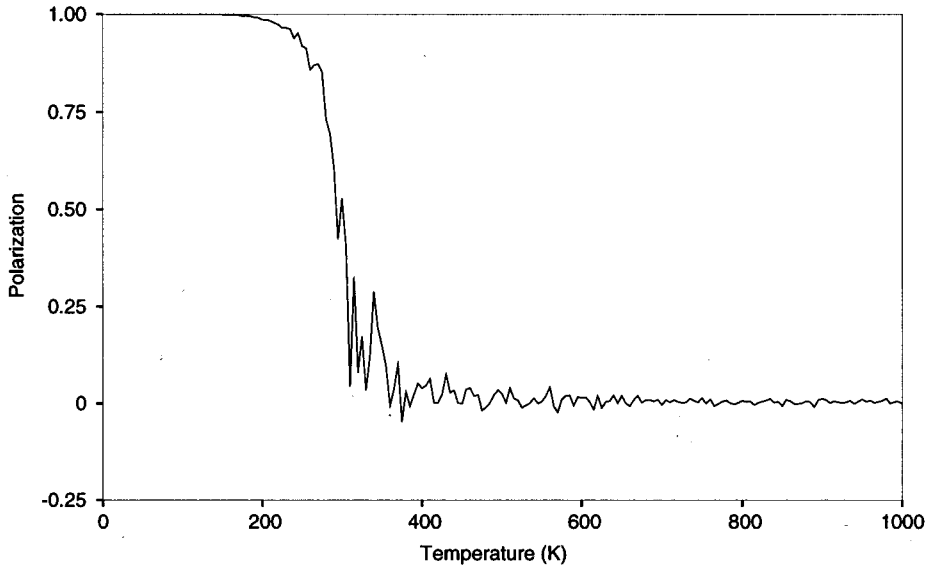

FIG. 4. Ferroelectric transition in the MT lattice: the polarization of the lattice in a microtubule with 13 protofilaments and the *A*-type configuration is shown as a function of temperature.

Monte Carlo simulation

The lattice dynamics are simulated using a standard Monte Carlo technique [24]. For a given time step, the energy of the present state and the opposite state are calculated. Whether a change of state occurs is a random event whose probability is determined by the availability of stored lattice energy, the temperature, and the threshold to reaction. Additional features of the model are (i) the removal of artificial barriers to reaction which were introduced by Hameroff *et al.* [11] in their discrete charge model; and (ii) the removal of the unphysical flip-flop of states which plagued our early attempts at modeling this system.

In our model, the threshold to a dipole flip, in cases where one exists, is simply the maximum interaction energy encountered while turning one dipole in the presence of its nearest neighbors from its present state to the opposite state. The model removes the unphysical flip-flop of states by forbidding nearest neighbors from simultaneously changing states. Thus when the dipole interaction favors paired dipoles and the current state of the neighboring dipoles is up-down, in the next time step, they may be up-down (unchanged), up-up, or down-down but not down-up. When a dipole flips, the change in conformational energy is either removed from or added to the lattice at that location. After the evolution step, energy diffuses to neighboring sites. Our simulations have been carried out with a diffusion constant which is isotropic and small enough that several time steps are required for localized energy to dissipate. Energy is conserved by the lattice in our current model, and the boundary conditions are periodic. None of the energy is returned to the surrounding medium.

There are two numbers which are put into the model by hand. One is the relative permittivity of tubulin, or more precisely that of tubulin in cytosol, ϵ. As an approximation, we are using the value $\epsilon_o = 10$. For comparison, the permittivity of water which is frequency dependent has a value of about 76 for the frequencies of physiological relevance [25]. The dielectric constant of dry tubulin or of tubulin in solution has not been found in the literature. Hasted [25] gives results from some experiments giving permittivities in excess of 100 for some other proteins in solution. However, our choice allows us to compare results with previous modeling attempts. The dynamics of the model are unaffected by the choice of ϵ but it simply scales the temperature. Larger values of ϵ reduce interaction strengths and thereby act like a temperature increase. The other number which is put in by hand is the dipole strength of the conformational states of tubulin. We have chosen the dipole magnitude p by considering the corresponding dipole charge to be an elementary charge in magnitude and the charge separation to be 4 nm which is half of the spacing between neighboring tubulin molecule centers in a MT lattice. This gives a value of $p_o = 6.41 \times 10^{-28}$ C m which is comparable to the measured dipole moments of some other protein molecules [25]. The precise value depends on the pH of the surrounding medium. The following results are derived from these estimates. We shall comment on how changes to these parameters affect the results of our simulations.

V. RESULTS

A. Ordered phases

The behavior of the MT lattice has been simulated for temperatures between absolute zero and 1000 K. The polarization and nearest-neighbor correlation functions have been calculated as a function of temperature. The polarization plot for the MT 13*A* lattice is shown in Fig. 4. The polarization and nearest-neighbor correlation functions are defined, respectively, as

$$P = \frac{1}{N} \sum_{i=1}^{N} p_i , \tag{2}$$

$$\chi_\alpha = \frac{1}{N} \sum_{i=1}^{N} p_i p_{i+\alpha} , \tag{3}$$

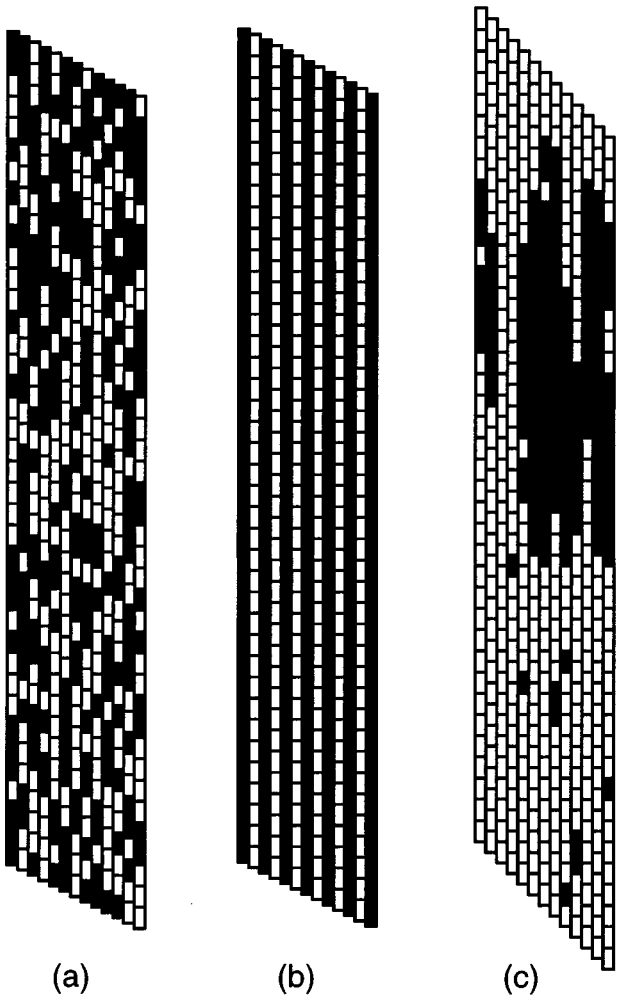

FIG. 5. Portions of three MTs are shown. Light boxes represent the ''up'' state and dark boxes represent the ''down'' state. (a) The *B* lattice above its critical temperature is disordered. (b) The *B* lattice below the critical temperature is ordered. (c) The *A* lattice just below the critical temperature but onto which a large defect has been introduced. Smaller thermal induced defects also dot the structure.

where i is an index labeling the N lattice sites, $p_i = \pm 1$ depending on whether the dimer is in the up or down state, and α describes the nearest-neighbor sites either along the protofilament, or around the protofilament. The existence of an ordered phase is crucial if the MT is to be able to process information. When the lattice is not organized, this signifies that thermal fluctuations dominate over the dipole-dipole interactions and that entropy dominates the lattice. Upon such a background [Fig. 5(a)], any signals which might be emitted would vanish. Our simulations have been carried out by first raising the temperature and then lowering it again. This was done in order to eliminate any sort of hysteresis effects which could have been artifacts of the simulation.

The simulations show that a highly ordered phase exists for both the *A* and *B* lattices at low temperatures. Whether the MT is ordered at physiological temperature depends critically upon p and ϵ since these parameters determine the transition temperature from disorder to order. In the MT *A* lattice with 13 protofilaments, we have found a transition temperature of about 330 K when $p_0^2/\epsilon_o = 12 \times 10^{-56}$ C^2 m^2. In the case where the down state is directly opposite to the up state (the nontilted case), the corresponding transition temperature is slightly higher. This shows that the existence of a transition to order is quite robust but that the transition temperature is sensitive to the specific choice of the down dipole. These temperatures have all been derived based upon our estimates of the dipole moment p and the electric permittivity of tubulin, ϵ, and should be compared to human physiological temperature (310 K, 37 °C). Equation (1) shows how the interaction energy is proportional to p^2/ϵ. Since all transition probabilities in the Monte Carlo simulation obey Boltzmann statistics, they are functions of $E/kT = p^2/\epsilon kT$. This parameter may be used to compare the transition temperature T_c in two systems. Denoting with the subscript o our choices for the parameters p and ϵ,

$$\frac{p^2}{\epsilon kT} = \frac{p_o^2}{\epsilon_o k T_o}, \tag{4}$$

$$T_c = T_c^o \left(\frac{p}{p_o}\right)^2 \left(\frac{\epsilon_o}{\epsilon}\right). \tag{5}$$

This equation demonstrates the scaling of the transition temperature T_c in a MT which is not subject to electric fields. The values p_o and ϵ_o are the values which we have estimated while p and ϵ are the actual values of the dipole moment and permittivity of tubulin. The transition temperature scales directly with the square of p, and inversely with ϵ. The scaling is more complicated in the presence of electric fields. The main result is that the MT could easily exist in an ordered state at physiological temperatures without the application of external fields provided $p^2/\epsilon > 12 \times 10^{-56}$ C^2 m^2.

Our original estimate of p^2/ϵ was about 4×10^{-56} C^2 m^2 which comes within a factor of 3 of what the model requires. We are hopeful that an experimental value for the dipole moment of tubulin will soon be available.

B. Electric fields

The application of an electric field along the length of the MT may serve to order the MT at higher temperatures than without an external field. Consequently, we may be able to relax the requirements on p and ϵ which would be required for our cellular automaton model to predict an ordered lattice under physiological conditions. We hasten to reiterate that at this point, the restrictions are not particularly stringent.

The field is applied in the *up* direction which favors ground state ordering. It is clear that local fields of 10^5 V/m have a significant impact upon MT lattice dynamics. While the effect of the electric field is quite dramatic in the MT 13*A* lattice, for the 13*B* lattice, the effect is greatly reduced because the orientation of the ground state is not ferroelectric [Fig. 5(b)]. A small electric field does lift the degeneracy between the two possible ground state orientations of the MT 13*B* lattice. At the highest field strengths simulated ($\sim 10^6$ V/m), the field was able to defeat the dipole-dipole interactions of the MT 13*B* lattice and caused it to adopt a ferroelectric state.

Such strong electric fields are not the rule in the neurons but strong fields do exist across cell membranes as action potentials pass and may exist during mitosis when the MTs are observed to align themselves in a configuration which is reminiscent of the field lines between a pair of point charges [26]. These fields drop off exponentially with increasing distance from the cell membrane, but would be strong enough to affect MTs and in particular, the protofilaments nearest the membrane. The interaction with steady fields is a logical place to begin in the attempt to model the interaction of dynamic electrical fields like action potentials with the dipoles of the tubulin subunits.

Our modeling has so far made use of axial fields for comparison with previous modeling attempts. When we consider the interaction of a MT lattice with an action potential, we must remember that the electric field on an action potential is radial and not axial. However, the axial field is the simpler field to treat theoretically and should interact in an identical fashion to the radial field provided that the dipole states are not purely axial since the interaction with an electric field may be written as

$$E_{\text{int}}^{(2)} = -\vec{p}\cdot\vec{E}, \tag{6}$$

where $\vec{E}$ is the applied electric field.

C. Propagation of signals

A signal can be recognized as a particular sequence of antialigned dipoles on an otherwise well-ordered lattice. Associated with this signal or defect is some additional energy which is recovered when the antialigned dipole falls back to its original configuration. The energy may diffuse in all directions so with six nearest neighbors, a single defect is not likely to cause neighboring dipoles to flip since they receive only about a sixth of the required energy. However, a larger defect such as a group of three or more dimers might successfully maintain its integrity. This has been observed in our model, larger defects have larger lifetimes.

The interesting question is, how does the MT respond to the presence of defects on the ordered lattice? A defect could arise by GTP hydrolysis to GDP at the exchangeable site upon addition of an additional tubulin subunit or by the less frequent hydrolysis of GTP at the nonexchangeable site [27]. In either case, the energy released might go into changing the conformation of the molecule and its electric dipole.

It is important to note that the conformational state of tubulin is not coupled to GTP hydrolysis. These two events are separate but GTP hydrolysis can easily induce the conformational change. Some authors have directly linked these two events and on occasion have proposed the opposite causality, that the conformation change of tubulin induces GTP hydrolysis [28].

Unlike the Hameroff-Rasmussen-Mansson model, we do not observe the smooth propagation of signals along the MT unless some additional mechanism is added. As it stands, there is nothing to direct the propagation of the defect so it takes a random walk about the MT and its energy is slowly dissipated to the rest of the MT. The efficient propagation of signals could be restored by several mechanisms including (i) the application of an external field which would bias signal propagation; (ii) an asymmetry in the dipole structure which simply makes it more favorable to propagate in a particular direction; or (iii) mechanical stress if dipoles are coupled to a lattice distortion. The second mechanism could be the result of the bonding between tubulin dimers. If the energy deposited by a dipole flip is comparable with the vibrational energy of a particular bond, it is most likely that this energy would be propagated in that direction. The third mechanism would be the result of a piezoelectric effect [29]. There could also be some sort of refractory period which prevents the retrograde propagation of the signal. Since external fields are known to act upon MTs in neurons, the study of these fields and their interaction garners our attention.

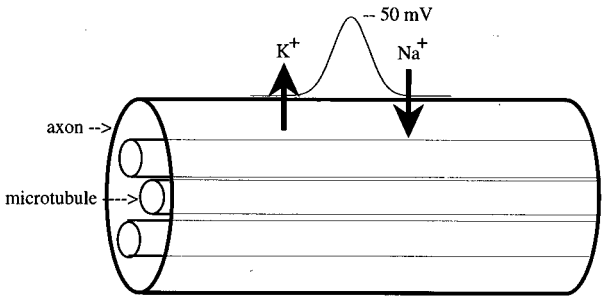

FIG. 6. An action potential moving along an axon containing three MTs. There is an electric field caused by the potential difference once the ions are displaced and a magnetic field caused by the moving ions. The potential difference is typically 50 mV and its magnitude is represented by the curve above the axon. Given the membrane thickness, the transient electric field may be as high as 10^5 V/m within the membrane.

D. Action potentials

As expected, application of a large axial field along the MT causes nearly all dipoles to orient themselves in the direction which most closely follows that of the field. Thus a wave of dipole flips is induced along the MT as the field is translated along the MT. This is similar to what happens as an action potential moves along an axon (Fig. 6). The field affects MTs in the vicinity of the cell membrane. Suppose the field is oriented in a direction which favors an alternate ordering for the lattice, such as is the case in MT, these dipoles will reorient themselves. The field acts like a pump and stores energy in the dimers. Once the field has passed, these dimers may return to their original configuration and release their stored energy. A weaker field does not actually create defects by changing the orientation of dipoles in the ground state, but acts as a bias and directs the movement of existing defects.

When the strength of the interacting action potential is large, such as for those MTs in close proximity to the cell membrane, a wave of structural deformation travels parallel to the action potential along the MT. As the wave reaches the MT end, its effects are unclear. Once the MT relaxes to its ground state structure, energy should once again be available for cellular use if the structural change at the MT terminus is coupled to another cellular structure via a MAP. It might also simply serve as a cellular signal indicating when motor proteins should be activated, MT assembly instructions, or any other host of functions associated with the MT terminal

which could involve signaling another MT or some part of the axon terminal.

VI. DISCUSSION

The results of the Monte Carlo simulation are that the lattice of MT dipoles may be ordered at physiological temperatures. Consequently, we have begun to investigate the response of this system to perturbations which we are calling signals. Once dipole defects have been induced upon the MT lattice, they may propagate along the length of the MT. While some nonlinear effect or external guidance seems to be required, processing of these signals cannot be ruled out. Signal transduction from the distal end of the axon towards the cell body is at least theoretically possible—although unlikely in our opinion. Transduction along the length of the MT is simpler to explain from the proximal end to the distal end though because of the existence of action potentials and the need to explain how a signal may be passed from one MT to another.

Our simulations place a firm limit on the strength of the dipoles required for self-organization. The required dipole strength of about 1×10^{-27} C m is slightly larger than the value which we estimated for tubulin. If the angle between the dipole directions of each of tubulin's conformational states is smaller than predicted, an even larger dipole strength would be required. Should the value for tubulin be smaller than this, information processing must be ruled out. Energy might still be passed along due to the passage of an action potential but it would be marked by the highly ordered configuration of the signal upon the random background. The quantity of energy associated with such an entropic change is much smaller than other values mentioned, about 0.06 kcal/mol.

On the topic of information storage in MTs, the simple introduction of thermal energy seems to have removed the possibility of information storage in MT. The energy involved in flipping the conformation of the dimer would have to be significantly larger for such a form of storage to be possible, not to mention the need for some kind of mechanism which would preserve the integrity of the information.

It is clear that electromagnetic properties are important in cell biology. The intrinsic polarity of MTs also seems to be very important, otherwise one would expect the MTs within the axon to be randomly oriented. Whether the information processing hypothesis proves to be valid or not, the investigations into the interactions between cellular proteins and electromagnetic fields must continue. Our model includes both interactions between individual particles, protein molecules in this case, and an external field, the action potential. We hope it may serve as a starting point for future investigation.

ACKNOWLEDGMENT

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