From a quantum mechanical description of the assembly processes in microtubules to their semiclassical nonlinear dynamics

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ABSTRACT

In this paper a quantum mechanical description of the assembly/disassembly process for microtubules is proposed. We introduce creation and annihilation operators that raise or lower the microtubule length by a tubulin layer. Following that, the Hamiltonian and corresponding equations of motion are derived that describe the dynamics of microtubules. These Heisenberg-type equations are then transformed to semi-classical equations using the method of coherent structures. The latter equations are very similar to the phenomenological equations that describe dynamic instability of microtubules in a tubulin solution.

1. Introduction

In most multicellular organisms, the interior of each cell is spanned by a dynamic network of molecular fibers called the cytoskeleton (‘skeleton of the cell’). The cytoskeleton gives a cell its shape, acts as a conveyor for molecular transport, and organizes the segregation of chromosomes during cell division, amongst many other activities. The complexity and specificity of its functions has given rise to the theory that along with its structural and mechanical roles, the cytoskeleton also acts as an information processor (Albrecht-Buehler 1985), or simply put the “cell’s nervous system” (Hameroff 1987). Microtubules are the cytoskeleton’s most studied components, and over the years many models of microtubular information processing have been proposed. A microtubule is a hollow cylinder, a rolled-up hexagonal array of tubulin dimers arranged in chains along the cylinder (‘protofilaments’). Within cells, microtubules come in bundles held together by ‘microtubule associated proteins’ (MAPs). The geometry, behavior and exact constitution of microtubules varies between cells and between species, but
an especially stable form of microtubule runs down the interior of the axons of human neurons. Conventional neuroscience at present ascribes no computational role to them, but models exist in which they interact with the membrane’s action potential (Brown & Tuszyński 1997; Priel et al 2006).

Microtubules are very dynamic bio-polymers that simply lengthen and/or shorten repeatedly at the macroscopic level during a course of time. At the microscopic level, however, several biochemical reactions are taking place in order for an individual microtubule to undergo an assembly or disassembly process. This dynamical behavior of microtubules (so-called dynamic instability) has attracted many investigators for decades to examine microtubules’ behavior in many aspects. See section 2 for further details.

Though there is no systematic description for the microtubule’s assembly/disassembly process at the microscopic level, several theoretical models are proposed to describe the macroscopic lengthening/shortening of microtubules using nonlinear classical equations (Dogterom & Leibler 1993; Dogterom et al 1995; Bicout 1997; Dogterom & Yurke 1998; Bicout & Rubin 1999). In spite of their agreement with experimental results, the latter studies are more or less phenomenological. Therefore, several features of the microtubule’s assembly/disassembly process might not be captured.

In this paper, we propose a systematic model for the microtubule’s assembly/disassembly process at the microscopic level using a first-principles quantum mechanical approach. In this model we consider an individual microtubule with length \( L \) consisting of \( N \) tubulin layers viewed here as a quantum state \( |N\rangle \). The state can be raised/lowered by creation/annihilation operator (i.e. polymerization/depolymerization process) to \( |N + 1\rangle / |N - 1\rangle \) state. The corresponding microtubule is then longer/shorter by one tubulin layer from the original one. Based on the chemical binding reactions that are taking place during microtubule polymerization, a quantum mechanical Hamiltonian for the system is proposed. Equations of motion are then derived and transformed from the purely quantum mechanical description to a semi-classical picture using the method of coherent structures. The resulting nonlinear field dynamics is richer than the previous phenomenological descriptions and includes both localized energy transfer and oscillatory solutions.

2. Microtubule assembly background

A very rigid and typically several micrometers long rod-like polymer plays an essential role during cell division. The so-called microtubule (MT) is assembled by tubulin polymerization in a helical lattice. These protein polymers are responsible for several fundamental cellular
processes, such as locomotion, morphogenesis, and reproduction (Alberts et al 1994). It is also suggested that MTs are responsible for transferring energy across the cell, with little or no dissipation.

Both *in vivo* and *in vitro* observations confirmed that an individual microtubule switches stochastically between assembling and disassembling states that makes MTs highly dynamic structures (Mitchison & Krischner 1984a,b). This behavior of MTs is referred to as dynamic instability. Dynamic instability of microtubules is a nonequilibrium process that has been subject of extensive research for the past two decades. It is generally believed that the instability starts from the hydrolysis of guanosine triphosphate (GTP) tubulin that follows by converting GTP to guanosine diphosphate (GDP). This reaction is exothermic and releases $\sim 8kT$ energy per reaction (Walker et al 1989), i.e. approximately $0.22$ eV per molecule (Engelborghs et al 1989). Here $k$ is the Boltzmann’s constant and $T$ is the temperature. Since GDP-bound tubulin favors dissociation, an MT enters the depolymerization phase as the advancing hydrolysis reaches the growing end of an MT. This phase transition is called a catastrophe. As a result of this transition, MTs start breaking down, releasing the GDP-tubulin in the solution. In the solution, however, reverse hydrolysis takes place and polymerization phase of MTs begins. The latter phase transition which comes after a catastrophe is called a rescue. Therefore, MTs constantly fluctuate between growth and shrinkage phases.

Interestingly, Odde et al (1995) studied experimentally and theoretically MTs’ assembly to extract their catastrophe kinetics. They proposed that a growing MT may remember its past phase states by assessing growth of both plus and minus ends of several individual MTs. Their results showed that while the minus end growth time follows an exponential distribution, the plus end fits a gamma distribution. The exponential (gamma) distribution suggests a first (non-first) order transition between growing and shrinking phases. Statistically, the exponential distribution represents that the new state happens independently of the previous state. As a result, an MT with first order catastrophe kinetics does not remember for how long it has been growing. In contrast, the catastrophe frequency of an MT with non-first order kinetics would depend on its growth phase period. The gamma distribution suggests that the catastrophe frequency is close to zero at early times, increases over time and reaches asymptotically a plateau. This is consistent with observations that the catastrophe events are more likely at longer times. Odde et al (1995) concluded that such behavior implies that a ‘crude form of memory’ may be built in MT’s dynamic instability. As a result, a microtubule would go through an ‘intermediate state’ before a catastrophe event takes place.

The dynamics of transitions between growing and shrinking states is still a subject of controversy. It is suggested that a growing MT has a stabilizing cap of GTP tubulin at the end which keeps it from disassembling (Mitchison & Krischner 1984a,b). Whenever MT loses its
cap, it will undergo the shrinking state. Several theoretical and experimental studies have been devoted to the cap model. For the purpose of this paper, we emphasize the link between GTP hydrolysis and the switching process from growing to shrinking of an MT. GTP hydrolysis is a subtle biochemical process that carries a quantum of a biological energy and thus allows us to make a link between quantum mechanics and polymer dynamics. We return to this theme later in the paper but first discuss the statistical methods used in this area.

2.1. Ensemble dynamics of microtubules

As we discussed earlier the MT dynamical instability has been the subject of numerous studies. Although the dynamical instability of MTs is a nonlinear and stochastic process, investigators modeled their averaged behaviors using a simple model. Introducing $p_g(x,t)$ and $p_s(x,t)$ as the probability density of a growing and shrinking tip, respectively, of an MT with length $x$ at time $t$, Dogterom & Leibler (1993) proposed the following equations for the time evolution of an individual MT:

$$\partial_t p_g = -f_{gs} p_g + f_{sg} p_s - v_g \partial_x p_g, \quad (1)$$
$$\partial_t p_s = f_{gs} p_g - f_{sg} p_s - v_s \partial_x p_s. \quad (2)$$

Here $f_{gs}$ and $f_{sg}$ are the transition rates from a growing to a shrinking state and vice versa. The average speeds of the MT in the assembly and disassembly states are given by $v_g$ and $v_s$, respectively. See also Bicout (1997), Dogterom & Yurke (1998) and Bicout & Rubin (1999).

Random fluctuations about the MT’s tip location can be also modeled by adding a diffusive term in the above equations:

$$\partial_t p_g = -f_{gs} p_g + f_{sg} p_s - v_g \partial_x p_g + D_g \partial_x^2 p_g, \quad (3)$$
$$\partial_t p_s = f_{gs} p_g - f_{sg} p_s - v_s \partial_x p_s + D_s \partial_x^2 p_s, \quad (4)$$

where $D_g$ and $D_s$ are the effective diffusion constants in the two states (Flyvbjerg et al 1994, 1996).

Equations (3) and (4) describe the overall dynamics of an individual MT without considering the dynamics of GDP and GTP tubulin present in the solution. It is clear that the MTs are growing faster in the area with a higher concentration of GTP tubulin. Using this fact, Dogterom et al (1995) generalized the above model by incorporating the tubulin dynamics. They added two more equations to the above system:

$$\partial_t c_T = -v_g s_0 p_g + k_{CD} + D \nabla^2 c_T, \quad (5)$$
$$\partial_t c_D = v_s s_0 p_s - k_{CD} + D \nabla^2 c_D. \quad (6)$$
where $c_T$ and $c_D$ are average concentrations of GTP and GDP tubulin, respectively. $D$ is the diffusion coefficient, $k$ is the rate constant and $0 \leq s_0 \leq 1$. In view of the link to quantum transitions between GDP and GTP at the root of this problem we now introduce a method that allows a smooth transition from quantum to classical (nonlinear) dynamics of MT assembly/disassembly process.

### 2.2. Method of Coherent Structures

The method we use here is called the Method of Coherent Structures (MCS) which has been developed in a number of papers and articles (Tuszynski & Dixon 1989a,b,c,d; Dixon & Tuszynski 1990a,b; Tuszynski et al 1994) and is essentially semiclassical in nature. The treatment is quantitative in that important terms which are retained are calculated exactly and those which are very small but nevertheless significant are discussed at a later stage and their effect estimated. The motivation for the method and a derivation of the dynamical field equation are presented by Tuszynski & Dixon (1989a) and a discussion of the types of classical field solutions is presented by Tuszynski & Dixon (1989b). A fuller version has been published in the review paper by Tuszynski et al (1994) whereas a very brief overview is given by Tuszynski & Dixon (1989c). It has been successfully applied to the phenomenon of superconductivity (Tuszynski & Dixon 1989d; Dixon & Tuszynski 1990a) and when combined with topological arguments yields, for example, the correct temperature dependence of the critical current density in low temperature superconductors. One can also obtain from MCS the position of phase boundaries in metamagnets where previously only elaborate numerical techniques could provide this information (Dixon & Tuszynski 1990b). Spatial correlations are fully incorporated using a renormalization technique and quantum fluctuations have been included also. It has been demonstrated that even when the method is generalized to include spin-dependent fields, the equation of motion for the field is of the same form (Dixon & Tuszynski 1991) and the classical field equation is also of the same form for both Boson and Fermion particles. This does not mean that the Fermionic character of the electrons disappears because the statistics of the particles reappear in the choice of the classical field which satisfies the physical boundary conditions on the charge density. The method is basically non-relativistic although it could be readily generalized but here we use the non-relativistic version.

The starting point in the MCS is to write a generic form of second-quantized Hamiltonian using one particle state annihilation and creation operators:

$$ H = \sum_k \hbar \omega_k q_k^+ q_k + \sum_{k, l, m} \hbar \Delta_{k, l, m} q_k^+ q_l^+ q_m q_{k+l-m}, \quad (7) $$

where the vectors $k$, $l$ and $m$ are shorthand labels for quantum numbers of a complete orthonor-
mal set of particle functions in the usual way and we use the linear momentum conserving form for the two-body interaction. Depending on the system studied, using Fermi-Dirac or Bose-Einstein statistics one can derive the Heisenberg’s equation of motion:

$$i\hbar \partial_t q_k(r, t) = [H, q_k(r, t)]. \quad (8)$$

Now both sides of Eq. (8) are multiplied by $\Omega^{-1/2} \exp(-i\eta \cdot r)a_\eta(t)$ and summed over $\eta$. At the same time the matrix elements $\omega_k$ and $\Delta_{k, l, m}$ are each expanded to second order in the deviations from the point $(k_0, l_0, m_0)$. After a considerable amount of algebra and a series of transformations we find

$$i\partial_t \psi = \mu_0 \psi + i\mu_1 \cdot \nabla \psi - \frac{1}{2} \sum_{i,j} (\mu_2)_{ij} \partial^2_{x_i x_j} \psi + \mu_3 \psi^+ \psi \mu_4 \cdot \psi^+ \nabla \psi + i\mu_5 \cdot \psi^+ (\nabla \psi) \psi + i\mu_6 \cdot (\nabla \psi^+) \psi \psi + \text{higher order terms}, \quad (9)$$

where

$$\psi(r, t) = \Omega^{-1/2} \sum_{\eta} \exp(-i\eta \cdot r)a_\eta(t). \quad (10)$$

Here $\mu_i$ or $\mu_i$ are constant parameters, determined by matrix elements $\omega_k$ and $\Delta_{k, l, m}$ and their derivatives calculated at point $(k_0, l_0, m_0)$. To convert Eq. (9) to a PDE in a C-number field, rather than an operator, in MCS the center of expansion $(k_0, l_0, m_0)$ is selected to be a critical or fixed point of the system. The reason for this is that close to a critical point it is an excellent approximation to replace the full quantum field, $\psi(r, t)$, by a classical component, $\psi_c$ (Ma 1976; Jackiw 1977; Amit 1978):

$$\psi(r, t) = \psi_c(r, t) \hat{1} + \hat{\phi}(r, t), \quad (11)$$

where $\hat{1}$ is the unit operator in Fock space, $\psi_c$ is a c-number field, $\hat{\phi}$ is a quantum mechanical operator with magnitude about $|\hat{\phi}| \sim \hbar |\psi_c|$ (Dixon & Tuszynski 1995). See Tuszyński et al (1997) for details.

In the next section we apply the MCS method to study the dynamic instability of an individual microtubule.

3. A quantum mechanical picture of the microtubule assembly processes

3.1. Particle states

For simplicity, we consider that MT polymerization to be a 1D process. Consider an individual microtubule in a free tubulin solution containing a large number of GTP-tubulin, GDP-tubulin
and a pool of free GTP molecules. In this solution several processes take place (as well as their reverse reactions):

(i) creating GTP molecules from GDP molecules:

\[ \Delta_1 + \text{GDP} \rightarrow \text{GTP}. \]  

(ii) generating tubulin GTP from tubulin GDP:

\[ \Delta_2 + \text{T}_{\text{GDP}} \rightarrow \text{T}_{\text{GTP}}, \]  

(iii) growth of an MT:

\[ \Delta_3 + \text{MT}_{N-1} + \text{T}_{\text{GTP}} \rightarrow \text{MT}_N, \]  

(iv) shrinkage of an MT:

\[ \text{MT}_N \rightarrow \text{MT}_{N-1} + \text{T}_{\text{GDP}} + \Delta_4. \]  

Note that experimental studies determined the values of the free energies for these reactions as: \( \Delta_1 \approx 220 \text{ meV}, \Delta_2 \approx 160 \text{ meV} \) and \( \Delta_3 \approx \Delta_4 \approx 40 \text{ meV} \) (Caplow et al 1994). These free energies are clearly above the thermal energy at room temperature \( (kT \approx 26 \text{ meV}) \) and they are within a quantum mechanical energy range that corresponds to the creation of one or a few chemical bounds. Therefore, one may need to consider each chemical reaction as a quantum mechanics process.

In this paper, in order to simplify the problem we combine the above processes into two fundamental reactions:

(i) growth of an MT by one dimer by adding of one tubulin layer in an endothermic process:

\[ \Delta + \text{MT}_{N-1} + \text{T}_{\text{GTP}} \rightarrow \text{MT}_N, \]  

(ii) shrinkage of an MT by one dimer due to the removal of one layer of \( \text{T}_{\text{GDP}} \) dimer in an exothermic process:

\[ \text{MT}_N \rightarrow \text{MT}_{N-1} + \text{T}_{\text{GDP}} + \Delta, \]  

where \( \Delta \) is the energy of the reaction. In order to derive a quantum mechanical description of mechanisms (i) and (ii), we first need to introduce quantum states of MT, tubulin and heat bath:

- \( |N\rangle \) is the state of a microtubule with \( N \) dimers (both GTP and GDP tubulins).
- \( |N_T\rangle \) is the state of a tubulin, \( \text{T}_{\text{GTP}} \) or \( \text{T}_{\text{GDP}} \).
- \( |\tilde{N}\rangle \) is the GTP hydrolysis energy state.
Then, the relevant second quantization operators would be:

\[ a^\dagger = |N + 1\rangle\langle N|, \]
\[ a = |N - 1\rangle\langle N|, \]
\[ b^\dagger = |N_T + 1\rangle\langle N_T|, \]
\[ b = |N_T - 1\rangle\langle N_T|, \]
\[ d^\dagger = |\tilde{N} + 1\rangle\langle \tilde{N}|, \]
\[ d = |\tilde{N} - 1\rangle\langle \tilde{N}|, \]

Here \( b/b^\dagger \) and \( d/d^\dagger \) are annihilation/creation operators of tubulin and energy quanta, respectively. The operators \( a/a^\dagger \) are lowering/raising the number of tubulin layers that constructed a MT. Following Tuszyński & Dixon (2001), one can express the above processes using creation and annihilation operators (18)-(23):

\[ a^\dagger b d : \Delta + MT_{N-1} + T_{GTP} \rightarrow MT_N \]
\[ d^\dagger b^\dagger a : MT_N \rightarrow MT_{N-1} + T_{GDP} + \Delta \]

Operators (24) and (25) describe an MT’s growth and shrinkage by one layer, respectively. Realistically, the polymerization or depolymerization process may happen repeatedly before reversing the process. This can be extended within our model by constructing product operators, i.e. \( (a^\dagger b d)^n \) and \( (d^\dagger b^\dagger a)^m \), where \( m \) and \( n \) are the number of growing or shrinking events in a sequence, respectively.

### 3.2. The Hamiltonian

Based on the mechanisms in (24) and (25), the Hamiltonian for interacting microtubules with \( T_{GTP}/T_{GDP} \) tubulins can be written as

\[
H = \sum_k \hbar \omega_k a_k^\dagger a_k + \sum_m \hbar \varpi_m b_m^\dagger b_m + \sum_l \hbar \sigma_l d_l^\dagger d_l + \sum_{k,m} \hbar (\Delta_{k,m} a_k^\dagger b_m d_{k-m} + \Delta_{k,m}^* d_{k-m}^\dagger b_m^\dagger a_k),
\]

where \( \omega, \varpi, \hat{\Delta} \) and \( \Delta \) are constants in units of energy. However, an intermediate transition between a microtubule in a growing phase and a microtubule in a shrinking phase must also be taken into account. A growing/shrinking microtubule may change its state quickly or after several steps to a depolymerizing/polymerizing state and then may change back to polymerizing/depolymerizing state. Experimentally, the transition of microtubules from the growing...
to the shrinking phase is quantified by the catastrophe rate \( f_{\text{cat}} \) and the transition from the shrinking to the growing phase is expressed by the rescue rate \( f_{\text{res}} \) in which \( f_{\text{res}} < f_{\text{cat}} \). As we discussed earlier, these transitions can be represented by a combination of creation and annihilation operators as the \( n^{\text{th}} \) power of the reaction in (24) and (25):

\[
H = \sum_k \hbar \omega_k a_k^{\dagger} a_k + \sum_m \hbar \omega_m b_m^{\dagger} b_m + \sum_l \hbar \sigma_l d_l^{\dagger} d_l
\]

\[
+ \sum_{n=1}^{\infty} \sum_{l_n, \tilde{m}_n, \tilde{l}_n-1} \hbar [\Delta_{k_n, \tilde{m}_n, \tilde{l}_n} l_n + \Delta_{k_n, \tilde{m}_n, \tilde{l}_n}^* c_{k_n, \tilde{m}_n, \tilde{l}_n}],
\]

(27)

where

\[
c_{k_n, \tilde{m}_n} = (a_{k_1}^{\dagger} b_{m_1} d_1)(a_{k_2}^{\dagger} b_{m_2} d_1) \ldots (a_{k_n}^{\dagger} b_{m_n} d_1).
\]

(28)

Here \( \tilde{k}_n = \{k_1, k_2, \ldots, k_n\} \) is a collection of indices and \( \sum_{k_n} = \sum_{k_1} \sum_{k_2} \ldots \sum_{k_n} \). We note that the momentum conservation for the last two terms in the Hamiltonian (27) requires that

\[
l_n = \sum_{i=1}^{n} k_i - \sum_{i=1}^{n} m_i - \sum_{i=1}^{n-1} l_i.
\]

(29)

Therefore, the first \( n - 1 \) of \( l \) will be free and summed in the Hamiltonian (27).

In Bose-Einstein statistics the creation and annihilation operators satisfy

\[
[q_k, q_m^{\dagger}] = \delta_{km}, \quad [q_k^{\dagger}, q_m^{\dagger}] = 0 = [q_k, q_m],
\]

(30)

where \([A, B] = AB - BA\) is the Dirac commutator and \( q = a, b, \) and \( d \). Since these operators mutually commute, the \( c_{k_n, \tilde{m}_n, \tilde{l}_n}, \) Eq. (28), can be rewritten as

\[
c_{k_n, \tilde{m}_n, \tilde{l}_n} = a_{k_1}^{\dagger} a_{k_2}^{\dagger} \ldots a_{k_n}^{\dagger} b_{m_1} b_{m_2} \ldots b_{m_n} d_1 d_2 \ldots d_n = a_{k_n}^{\dagger} b_{m_n} d_{l_n},
\]

(31)

where \( l_n \) is given by Eq. (29).

4. Derivation of the equations of motion

The Heisenberg’s equation of motion for a space- and time-dependent operator \( q(r, t) \) reads as

\[
\dot{q}(r, t) = \frac{i}{\hbar} [H, q(r, t)],
\]

(32)

where \( H \) is the Hamiltonian. Before finding equations of motion, one needs to calculate the commutation relation \([q_{\eta}, q_{k_n}^{\dagger}]\) that is

\[
[q_{\eta}, q_{k_n}^{\dagger}] = [q_{\eta}, q_{k_1}^{\dagger} \ldots q_{k_n}^{\dagger}] = \delta_{\eta,k_1} q_{k_2}^{\dagger} q_{k_3}^{\dagger} \ldots q_{k_n}^{\dagger} + \delta_{\eta,k_2} q_{k_1}^{\dagger} q_{k_3}^{\dagger} \ldots q_{k_n}^{\dagger} + \ldots + \delta_{\eta,k_n} q_{k_1}^{\dagger} q_{k_2}^{\dagger} \ldots q_{k_{n-1}}^{\dagger}.
\]

(33)
Since all $k_1, k_2, \ldots, k_n$ are dummy indices one can write Eq. (33) as
\[ [q_\eta, q^\dagger_{k_\eta}] = n \delta_{\eta,k_a} q^\dagger_{k_{n-1}}, \]
where $k_a$ is chosen for simplicity. Using Eq. (34) we can find the commutation relations between $a_\eta$ and $b_\eta$ operators with $c_{k_a m_n l_n}$ and $c^\dagger_{k_a m_n l_n}$ operators as
\begin{align*}
[a_\eta, c^\dagger_{k_a m_n l_n}] &= [a_\eta, a^\dagger_{k_b} b_{m_n} d_{l_n}] = n \delta_{\eta,k_a} a^\dagger_{k_{n-1}} b_{m_a} d_{l_n}, \\
[b_\eta, c_{k_a m_n l_n}] &= [b_\eta, d^\dagger_{l_n} b^\dagger_{m_n} a_{k_a}] = n \delta_{\eta,m_a} b^\dagger_{m_{n-1}} a_{k_{n-1}}.
\end{align*}
However, the commutation relation between $d_\eta$ operator and $c^\dagger_{k_a m_n l_n}$ will be
\[ [d_\eta, c^\dagger_{k_a m_n l_n}] = [d_\eta, d^\dagger_{l_n} b^\dagger_{m_n} a_{k_a}] = (n - 1) \delta_{\eta,1_{n-1}} d^\dagger_{l_n-2} d^\dagger_{l_n} + \delta_{\eta,1_n} d^\dagger_{l_{n-1}} b^\dagger_{m_n} a_{k_a}. \]
where $1_n$ is given by Eq. (29). Therefore, the equation of motion for $a_\eta$, $b_\eta$ and $d_\eta$ operators can be derived from Hamiltonian (27) as
\begin{align*}
i \partial_t a_\eta &= \omega_\eta a_\eta + \sum_n \sum_{k_{n-1} m_n l_n} n \Delta \eta_{k_{n-1} m_n l_{n-1}} a^\dagger_{k_{n-1}} b_{m_n} d_{l_n} + \sum_{n=1}^N \delta_{\eta,1_n} d^\dagger_{l_{n-1}} b^\dagger_{m_n} a_{k_n}, \\
i \partial_t b_\eta &= \omega_\eta b_\eta + \sum_n \sum_{k_{n-1} m_n l_{n-1}} n \Delta \eta_{k_{n-1} m_n l_{n-1}} d^\dagger_{l_n-2} d^\dagger_{l_n} + \sum_{n=1}^N \delta_{\eta,1_n} d^\dagger_{l_{n-1}} b^\dagger_{m_n} a_{k_n}, \\
i \partial_t d_\eta &= \sigma_\eta d_\eta + \sum_n \sum_{k_{n-1} m_n l_{n-2}} (n - 1) \Delta \eta_{k_{n-1} m_{n-1} l_{n-1}} d^\dagger_{l_n-2} d^\dagger_{l_n} + \sum_{n=1}^N \delta_{\eta,1_n} d^\dagger_{l_{n-1}} b^\dagger_{m_n} a_{k_n}.
\end{align*}
Equations (38)-(40) describe the dynamics of an MT in a quantum manner. Since MTs are overall classical objects, we need to ensemble average over all possible states to obtain effective dynamical equations.

5. Classical equations of motion

Fourier transforming of $a_\eta$, $b_\eta$ and $d_\eta$ operators over all states, one can find
\begin{align*}
\psi(r,t) &= \Omega^{-1/2} \sum_\eta \exp(-i\eta \cdot r) a_\eta(t), \\
\chi(r,t) &= \Omega^{-1/2} \sum_\eta \exp(-i\eta \cdot r) b_\eta(t), \\
\phi(r,t) &= \Omega^{-1/2} \sum_\eta \exp(-i\eta \cdot r) d_\eta(t),
\end{align*}
where $\Omega$ is the volume over which the members of the plane wave basis are normalized (Tuszynski & Dixon 1989a; Dixon & Tuszynski 1995). Here $\psi(\mathbf{r}, t)$, $\chi(\mathbf{r}, t)$, and $\phi(\mathbf{r}, t)$ are corresponding field operators for the quantum operators $a_\eta$, $b_\eta$ and $d_\eta$, respectively. The derivation of the equation of motion for the field operators are given in Appendix. The final form of the equations of motion is found to be

$$
\partial_t \psi = A_0 \psi + A_1 \cdot \nabla \psi + D_0 \nabla^2 \psi + \sum_{n=2}^{\infty} (A_2^{(n)} \psi^+) \psi^{+n-2} \chi^n \phi^n , \quad (44)
$$

$$
\partial_t \chi = B_0 \chi + D_1 \nabla^2 \chi + \sum_{n=1}^{\infty} (B_1^{(n)} \psi) \psi^{n-1} \chi^{+n-1} \phi^{+n} , \quad (45)
$$

$$
\partial_t \phi = C_0 \phi + D_2 \nabla^2 \phi + \sum_{n=1}^{\infty} (C_1^{(n)} \psi) \psi^{n-1} \chi^n \phi^{+n-1} , \quad (46)
$$

where $n$ represents the degree of nonlinearity and $A_i$, $B_i$, $C_i$ and $D_i$ are constants and given in Appendix. We obtain the general equations of motion for the system in terms of coupled nonlinear partial differential equations (PDE’s) that describe the MT field, the tubulin field and GTP field, respectively.

In this paper we are primarily interested in the dynamics of MTs. Following Eq. (44), the dynamical equations for growing and shrinking states of an MT up to $n = 3$ can be written as

$$
\partial_t \psi = A_0 \psi + A_1 \cdot \nabla \psi + D_0 \nabla^2 \psi + (A_2^{(2)} \psi^+) \chi^2 \phi^2 + (A_2^{(3)} \psi^+) \psi^+ \chi^3 \phi^3 . \quad (47)
$$

Here $\psi^+/\psi$ represent the growing/shrinking state of the MT. Furthermore, the dynamics of the tubulin, $\chi$, and energy of the system, $\phi$, are also determined by

$$
\partial_t \chi = B_0 \chi + D_1 \nabla^2 \chi + (B_1^{(1)} \psi) \phi^+ , \quad (48)
$$

$$
\partial_t \phi = C_0 \phi + D_2 \nabla^2 \phi + (C_1^{(1)} \psi) \chi^+ , \quad (49)
$$

where, for simplicity, we just keep the $n = 1$ term.

It is clear that the system of equations (47)-(49) is very similar to the phenomenological system of equations (3)-(6) which has been extensively studied in the nonlinear physics literature. A vast array of mathematical methods of finding their solutions can be found in the monograph by Dixon et al (1997). Among them one can expect to find localized (solitonic) and extended (traveling wave) solutions. The latter ones may have the meaning of coherent oscillations observed experimentally for high tubulin concentrations by Mandelkow et al (1989).
6. Discussion

In our model, the basic structural unit is the tubulin dimer. Each dimer exists in a quantum mechanical state characterized by several variables even in our simplified approach. Each microstate of a tubulin dimer is sensitive to the states of its neighbors. Tubulin dimers have both discrete degrees of freedom (distribution of charge) and continuous degrees of freedom (orientation). A model that focuses on the discrete will be an array of coupled binary switches (Rasmussen et al 1990; Campbell 2001), while a model that focuses on the continuous will probably be an array of coupled oscillators (Samsonovich et al 1992; Brown & Tuszynski 1997).

In the present paper we have focused on tubulin binding and GTP hydrolysis as the key processes determining the states of microtubules. These are also the degrees of freedom that are most easily accessible to experimental determination. In this paper we have shown how a quantum mechanical description of the energy binding reactions taking place during MT polymerization can be led to nonlinear field dynamics with very rich behavior that includes both localized energy transfer and oscillatory solutions.

We have demonstrated here that the assembly process can be described using quantum mechanical principles applied to biochemical reactions. This can be subsequently transformed into a highly nonlinear semi-classical dynamics problem. The gross features of MT dynamics satisfy classical field equations in a coarse-grained picture. Individual chemical reactions involving the constituent molecules still retain their quantum character. The method of coherent structures allows for a simultaneous classical representation of the field variables and a quantum approach to their fluctuations. Here, the overall MT structure (and their ensembles) can be viewed as a virtual classical object in (3+1) dimensional space. However, at the fundamental level of its constituent biomolecules, it is quantized as are true chemical reactions involving its assembly or disassembly. Whether this process can be implicated in nonlinear computation or information processing by neurons is an open question. The main problem of quantum computation is decoherence: the loss of entanglement from within the quantum computer into its environment. If there is no entanglement left, there is no quantum parallelism, only a stochastic process with no advantage over classical computation (Aharonov & Ben-Or 1996). The best-known model of quantum computation in the microtubule Hameroff & Penrose (1996) is a quantized cellular automaton model, with the additional postulate that state reduction occurs spontaneously (Penrose 1994). Its decoherence timescale has been estimated at $10^{-5}$ to $10^{-4}$ seconds without shielding of the microtubule, and $10^{-2}$ to $10^{-1}$ seconds with shielding by an actin gel present in the cell (Hagan et al 2000). However, the original classical model has been criticized as unrealistic (Brown & Tuszynski 1997), and the proposed alternative (a continuum model) decoheres much more rapidly (Tegmark 2000), suggesting that it can only function classically. In our approach the route taken is opposite since we started with individual tubulin quantum microstates to arrive at classical, nonlinear but coherent (and stable) macro-states of
a microtubule.

Interestingly, using a simplified model of the dimer as a double potential well, the conductivity of the microtubule was recently calculated (Brown & Tuszynski 2001). For a micron-long microtubule, the predicted value falls into the ‘good intrinsic semiconductor’ regime, and even reaches the semi-metallic regime at high electron concentrations. The length of a microtubule is directly proportional to its resistance via Ohm’s law hence there exists a direct link between conductive properties of microtubules and their length which is seen in our model as the average of a mesoscopic state (probability density wave).

The search is still on for a realistic model of quantum computation in the microtubule, one that is grounded in the 1998 atomic structural data. If such a model is found, many more questions will be raised:

*How do separate microtubules become entangled?* It seems unlikely that quantum coherence would be limited to individual microtubules. One possibility is that electrons or quasiparticles tunneling through MAPs cause associated microtubules within the same cell to become entangled. A less likely possibility is that electromagnetic fields generated by individual microtubules do the trick. Looking beyond the single cell, it has been proposed that electrons could even tunnel from one cell to the next through a gap junction, a transient fusion of the membranes of neighboring cells (Woolf & Hameroff 2001).

In our model, an ensemble of MT's can become a higher level coherent structure if the tubulin density is sufficiently high to result in significant correlations between individual MT’s and their interactions leading to the experimentally observed synchronization of MT assembly and coherent oscillations in the assembled tubulin mass (Mandelkow et al 1989).

Finally, contact must eventually be made with experiment. A starting point would be to learn more about electron motion in microtubules. Becker et al (1975) demonstrated the existence of fluorescent resonant energy transfer between aromatics in adjacent tubulins, and between microtubules and membranes. Such exchanges might serve to power the motion of electrons through the aromatic lattice without dissipation of energy. A new generation of such experiments, under varied conditions of pH, MAP attachment, and so forth, could be very helpful both in building and testing models.

On the computational side, it has been suggested that the principal output of microtubules takes the form of highly symmetrical MAP attachment patterns (Samsonovich et al 1992; Woolf & Hameroff 2001) which determine subsequent cytoskeletal growth and behavior. In this case, progress in understanding microtubular computation will be measured by the ability to interpret and predict these outputs. If microtubules are indeed information processors, it seems likely that a long period of trial and error will be necessary before we truly learn how they work.
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Appendix A. Derivation of equation of motion for the field operators

Multiplying both sides of Eq. (38) by \( \exp(-i\eta \cdot r) \), dividing by \( \Omega^{1/2} \) and summing over \( \eta \), one finds

\[
i\hbar \psi = \Omega^{-1/2} \left[ \sum_{\eta} \omega_{\eta} \exp(-i\eta \cdot r)a_{\eta} \\
+ \sum_{n} \sum_{\eta} \sum_{k_{n}m_{n}l_{n-1}} n \Delta_{\eta k_{n-1}m_{n}l_{n-1}} \exp(-i\eta \cdot r) a_{k_{n-1}}^{\dagger} b_{m_{n}} d_{l_{n-1}} d_{\eta + \sum_{j=1}^{n} (k_{j} - l_{j}) - \sum_{j=1}^{n-1} m_{j}} \right].
\]

(A.1)

Changing \( \eta \rightarrow \eta - \sum_{j=1}^{n-1} (k_{j} - l_{j}) + \sum_{j=1}^{n} m_{j} \) in the second term of Eq. (A.1), one finds

\[
i\hbar \psi = \Omega^{-1/2} \left[ \sum_{\eta} \omega_{\eta} \exp(-i\eta \cdot r)a_{\eta} \\
+ \sum_{n} \sum_{\eta} \sum_{k_{n}m_{n}l_{n-1}} n \Delta_{\eta - \xi k_{n-1}m_{n}l_{n-1}} \exp(-i\eta \cdot r + i\sum_{j=1}^{n-1} (k_{j} - l_{j}) - i\sum_{j=1}^{n} m_{j} \cdot r) \\
\times a_{k_{n-1}}^{\dagger} b_{m_{n}} d_{l_{n-1}} d_{\eta} \right],
\]

(A.2)

or

\[
i\hbar \psi = \Omega^{-1/2} \left[ \sum_{\eta} \omega_{\eta} \exp(-i\eta \cdot r)a_{\eta} + \sum_{n} \sum_{\eta} \sum_{k_{n}m_{n}l_{n-1}} n \Delta_{\eta - \xi k_{n-1}m_{n}l_{n-1}} \right.
\]
\[
\times e^{-i\eta \cdot r} d_{\eta} e^{ik_{n-1} \cdot r} a_{k_{n-1}}^{\dagger} e^{-i\bar{m}_{n} \cdot r} b_{\bar{m}_{n}} e^{-i\bar{l}_{n-1} \cdot r} d_{l_{n-1}} \right],
\]

(A.3)

where \( \xi = \sum_{j=1}^{n-1} (k_{j} - l_{j}) - \sum_{j=1}^{n} m_{j} \). Here, for example, \( \exp(-i\bar{k}_{n} \cdot r) = \exp(-i\bar{k}_{1} \cdot r) \exp(-i\bar{k}_{2} \cdot r) \ldots \exp(-i\bar{k}_{n} \cdot r) = \exp(-i \sum_{j=1}^{n} k_{j} \cdot r) \). Our goal is now to rewrite Eq. (A.3) in terms of field operators, \( \psi, \chi, \phi, \) and their derivatives. This can be done in a straightforward manner provided the dispersion matrix elements \( \omega_{\eta} \) and \( \Delta_{\eta - \xi k_{n-1}m_{n}l_{n-1}} \) which are generally function \( \eta, k_{i}, m_{i}, \) and \( l_{i} (1 \leq i \leq n) \) are known. Unfortunately, such information is very model dependent. Therefore, the simplest way that also keeps the generality of the problem is to Taylor expand
these matrix elements about some point \((\eta_0, k_{0i}, m_{0i}, l_{0i})\) in the space spanned by \(\eta, k_i, m_i\) and \(l_i\) (Tuszynski & Dixon 1989a; Dixon & Tuszynski 1995).

Expanding \(\omega_\eta\) to all orders, one finds

\[
\omega_\eta = \omega_0 + \sum_{s=1}^{\infty} (\eta - \eta_0) \cdot \nabla_\eta \frac{s\omega_0}{s!}.
\]

(A.4)

where \(\omega_0 = \omega_{\eta_0}\). Furthermore, for any function \(f(\eta, \hat{k}_n, \hat{m}_n, \hat{l}_n) = \Delta_{\eta_0} \hat{k}_n \hat{m}_n \hat{l}_n\) we can write

\[
f(\eta, \hat{k}_n, \hat{m}_n, \hat{l}_n) = f_0 + (\eta - \eta_0) \cdot \nabla_\eta f|_0 + \sum_{j=1}^{n} (k_j - k_{0j}) \cdot \nabla_{k_j} f|_0
\]

\[
+ \sum_{j=1}^{n} (m_j - m_{0j}) \cdot \nabla_{m_j} f|_0 + \sum_{j=1}^{n} (l_j - l_{0j}) \cdot \nabla_{l_j} f|_0 + \ldots,
\]

(A.5)

where \(sC_r\) are binomial coefficients. Here, for example, \(\nabla_m f\) means \(\hat{i}\partial_{m_x} f + \hat{j}\partial_{m_y} f + \hat{k}\partial_{m_z} f\) where \(\hat{i}, \hat{j}\) and \(\hat{k}\) are unit vectors in the \(m_x, m_y\) and \(m_z\) directions, respectively, and \(\nabla_m f|_0\) is the value of the gradient at point \((\eta_0, k_0, m_0, l_0)\).

Using Eqs. (A.4) and (A.5), Eq. (A.3) can be written as

\[
i\partial_t \psi = \lambda_0(\omega) \psi + i\lambda_1(\omega) \cdot \nabla \psi - \frac{1}{2} \sum_{i,j}[\lambda_2(\omega)]_{ij} \partial_{x_i x_j}^{2} \psi + \sum_{n} n\Omega^{(3n-1)/2} \Lambda_1^{(n)} \psi^{n+1-\chi n \phi^n}
\]

\[
+ \sum_{n} n\Omega^{(3n-1)/2} \left( \psi^{n+1-\chi n \phi^n} \nabla_{\eta} f|_0 \cdot \nabla \phi + \nabla_{k_j} f|_0 \cdot \nabla \phi + \psi^{n+2-\chi n \phi^n} \right),
\]

(A.7)

where

\[
\lambda_0(\omega) = \omega_0 - \eta_0 \cdot \nabla_\eta \omega|_0 + (1/2) \sum_{i,j} \eta_{0i} \eta_{0j} \partial_{\eta_0}^2 \omega|_0,
\]

(A.8)
Similarly, using Eqs. (39) and (40), one can write equations of motion for $\chi$ and $\phi$ as

\[ i \partial_t \chi = \lambda_0(\bar{\omega}) \chi + i \lambda_1(\bar{\omega}) \cdot \nabla \chi - \frac{1}{2} \sum_{i,j} [\lambda_2(\bar{\omega})]_{ij} \phi^2_{i,j} \chi + \sum_n n \Omega^{(3n-1)/2} \Lambda_2^{(n)} \psi^n \chi^{n+1} \phi^n \]

\[ + \sum_n n \Omega^{(3n-1)/2} \left( \psi^n \chi^{n+1} \phi^{n+1} \right) \]

\[ + \sum_{j=2}^{n-1} \psi^n \nabla_{m_j} f_0 \cdot \nabla \chi^{n+1} \phi^n \]

\[ + \sum_{j=1}^{n} \psi^n \nabla_{l_j} f_0 \cdot \nabla \phi^{n+1} \phi^n \]

\[ + \sum_{j=2}^{n-1} \psi^n \nabla_{m_j} f_0 \cdot \nabla \chi^{n+1} \phi^n \]

\[ + \sum_{j=1}^{n} \psi^n \nabla_{l_j} f_0 \cdot \nabla \phi^{n+1} \phi^n \]

\[ + \sum_{j=2}^{n-1} \psi^n \nabla_{m_j} f_0 \cdot \nabla \chi^{n+1} \phi^n \]

\[ + \sum_{j=1}^{n} \psi^n \nabla_{l_j} f_0 \cdot \nabla \phi^{n+1} \phi^n \]

\[ (A.12) \]

\[ i \partial_t \phi = \lambda_0(\sigma) \phi + i \lambda_1(\sigma) \cdot \nabla \phi - \frac{1}{2} \sum_{i,j} [\lambda_2(\sigma)]_{ij} \phi^2_{i,j} \phi + \sum_n n \Omega^{(3n-1)/2} \Lambda_3^{(n)} \psi^n \chi^{n+1} \phi^{n+1} \]

\[ + \sum_n n \Omega^{(3n-1)/2} \left( (n-1) \psi^n \chi^{n+1} \phi^{n+1} \right) \]

\[ + \sum_{j=1}^{n} \psi^n \nabla_{l_j} f_0 \cdot \nabla \phi^{n+1} \phi^n \]

\[ + \sum_{j=1}^{n} \psi^n \nabla_{l_j} f_0 \cdot \nabla \phi^{n+1} \phi^n \]

\[ + \sum_{j=1}^{n} \psi^n \nabla_{l_j} f_0 \cdot \nabla \phi^{n+1} \phi^n \]

\[ + \sum_{j=1}^{n} \psi^n \nabla_{l_j} f_0 \cdot \nabla \phi^{n+1} \phi^n \]

\[ (A.13) \]

where

\[ \Lambda_2^{(n)} = f_0 - \eta_0 \cdot \nabla \eta f_0 - \sum_{j=1}^{n} k_{0j} \cdot \nabla_{k_j} f_0 - \sum_{j=1}^{n} m_{0j} \cdot \nabla_{m_j} f_0 - \sum_{j=1}^{n-1} l_{0j} \cdot \nabla_{l_j} f_0. \]

\[ \Lambda_3^{(n)} = f_0 - \eta_0 \cdot \nabla \eta f_0 - \sum_{j=1}^{n} k_{0j} \cdot \nabla_{k_j} f_0 - \sum_{j=1}^{n} m_{0j} \cdot \nabla_{m_j} f_0 - \sum_{j=1}^{n-1} l_{0j} \cdot \nabla_{l_j} f_0. \]

\[ (A.14) \]

\[ (A.15) \]

Simplifying the equations of motion as

\[ \partial_t \psi = A_0 \psi + A_1 \cdot \nabla \psi + D_0 \nabla^2 \psi + \sum_n (A_2^{(n)} \psi^+) \psi^{n+2} \chi^n \phi^n, \]

\[ \partial_t \chi = B_0 \chi + D_1 \nabla^2 \chi + \sum_n (B_1^{(n)} \psi) \psi^{n+1} \chi^{n+1} \phi^n, \]

\[ \partial_t \phi = C_0 \phi + D_2 \nabla^2 \phi + \sum_n (C_1^{(n)} \psi) \psi^{n+1} \chi^{n+1} \phi^n, \]

\[ (A.16) \]

\[ (A.17) \]

\[ (A.18) \]
where

\[ A_0 = -i\lambda_0(\omega), \quad A_1 = \lambda_1(\omega), \quad A_2^{(n)} \psi^+ = -in\Omega \frac{2n-1}{2} (\Lambda_1^{(n)} + \sum_{j=1}^{n-1} \nabla_{k_j} f|_0 \cdot \nabla)\psi^+, \quad (A.19) \]

\[ B_0 = -i\lambda_0(\varpi), \quad B_1^{(n)} \psi = -in\Omega \frac{2n-1}{2} (\Lambda_2^{(n)} + \sum_{j=1}^{n} \nabla_{k_j} f|_0 \cdot \nabla)\psi, \quad (A.20) \]

\[ C_0 = -i\lambda_0(\sigma), \quad C_1^{(n)} \psi = -in\Omega \frac{2n-1}{2} (\Lambda_3^{(n)} + \sum_{j=1}^{n} \nabla_{k_j} f|_0 \cdot \nabla)\psi, \quad (A.21) \]

\[ D_0 = 2i\lambda_2(\omega), \quad D_1 = 2i\lambda_2(\varpi), \quad D_2 = 2i\lambda_1(\sigma), \quad . \quad (A.22) \]

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