Phase transition analysis of the dynamic instability of microtubules

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Abstract

This paper provides the phase transition analysis of a reaction diffusion equations system modelling the dynamic instability of microtubules (MTs). For this purpose, we have generalized the macroscopic model studied by Mourão \textit{et al} (2011 \textit{Comput. Biol. Chem.} \textbf{35} 269–81). This model investigates the interaction between the MT nucleation, the essential dynamics parameters and extinction, and their impact on the stability of the system. The considered framework encompasses a system of partial differential equations for the elongation and shortening of MTs, where the rates of elongation as well as the lifetimes of the elongating shortening phases are linear functions of GTP-tubulin concentration. In a novel way, this paper investigates the stability analysis and provides a bifurcation analysis for the dynamic instability of MTs in the presence of diffusion and all of the fundamental dynamics parameters. Our stability analysis introduces the phase transition method as a new mathematical tool in the study of MT dynamics. The mathematical tools introduced to handle the problem should be of general use.

Keywords: dynamic instability, microtubules, phase transition, bifurcation, diffusion

Mathematics Subject Classification: 35K57, 37G35, 70K50, 92B05, 92C37

1. Introduction

Microtubules (MTs) are natural rigid structural polymers constructed from subunits made of the protein tubulin [DVMW]. They exist inside living eukaryotic cells and participate in many functions of the cell, including mitosis [AJLR], axon formation in neurons [SO], and
signaling [EM]. MTs are also play an important role in important diseases, such as Alzheimer’s disease [BVT] and Parkinson’s disease [F]. MTs within cells are typically initiated from a complex of proteins that form a nucleation template. Polymerization proceeds at a rate that is dependent upon the concentration of free tubulin subunits [MSS]. Over time, MTs stochastically switch between states of polymerization and depolymerization, a process that is termed dynamic instability [SKE, MK, DM]. Switching frequencies are regulated during certain cellular transitions to modify the length distribution and density of the polymer array. The mechanisms governing dynamic instability are still an active subject of both experimental and theoretical research [YBZS].

There are several analytical models describing how the major factors leading to dynamic instability (i.e. growth and shortening velocities, together with catastrophe and rescue frequencies) will create a steady state system of polymers under various conditions [YBZS]. In this work, we advance these analyses of MT dynamics by extending the analytical methods to go through bifurcation analysis associated with the fundamental dynamics parameter, nucleation, extinction and diffusion. The phase transition is investigated in greater detail with particular attention paid to bifurcation points and dynamic parameters.

Mourão et al [MSS] studied the interaction between the MT nucleation and dynamics parameters, using macroscopic Monte Carlo simulations to study the contribution of these parameters in the underlying MT array morphology (i.e. polymer density and length distribution). They found that, in addition to the well-characterized steady state achieved between free tubulin subunits and MT polymer, MT nucleation and extinction constitute a second, interdependent steady state [MSS]. Their study also shows that the magnitude of both nucleation and extinction rate additively impacts the final steady state free subunit concentration and, consequently, the nucleation template number plays a defining role in shaping the MT length distribution and polymer density [MSS].

Tubulin diffusion is slow and this slowness causes a fast dephasing in the growth dynamics, unbounded growth of some MTs, and morphological change towards creating bounded short MTs in the nucleation centre and unbounded long MTs with narrowly distributed lengths [DYH]. The competition between the rate of the tubulin’s assembly and the tubulin’s diffusion rate is characterized the transition from unbounded to bounded growth. The present study considers the impact of the tubulin’s diffusion coefficient along with other dynamic parameters on the dynamic instability.

In this paper, we will study the formation and dynamic instability of MTs by modifying the macroscopic mathematical model of Mourão et al. We will consider generalized concentration-dependent model for MT growth and shrinkage, and we will also include the diffusion effect.

There are in fact three types of phase transition: continues (type I), jump type II) and mix (type III). The mathematical framework that we will follow here is established in the recent work of Ma and Wang (see [MW13]). Our study of the asymptotic behaviour of the solutions around a bifurcation point is based on a new centre manifold reduction procedure developed in [MW05] and [KWY]. The key element here is a more precise approximation of the reduced centre manifold equations. This method will furnish us with a comprehensive set of reduced equations and certain transition numbers. The behaviour of transition numbers will determine the whole dynamic of the system near the critical bifurcation parameter.

The rest of this paper is organized as follows: the mathematical model is presented in section 2. In section 3, the formation process is discussed and some classic conclusions are derived. Our main results are presented and proved in section 4, where we derive the phase transition properties in two main scenarios.
2. Macroscopic model for MT dynamics with diffusion

Following Mourão et al.’s macroscopic model for MT dynamics, we consider the following generalized concentration-dependent model for MT growth and shrinkage, which includes the diffusion effect:

\[
\begin{align*}
\frac{\partial M_g}{\partial t} &= -P_{gs}M_g + P_{sg}M_s + N + D_1 \Delta M_g \\
\frac{\partial M_s}{\partial t} &= P_{gs}M_g - P_{sg}M_s - E + D_2 \Delta M_s \\
\frac{\partial D_f}{\partial t} &= -V_gM_g + V_sM_s - N + E + D_3 \Delta D_f.
\end{align*}
\]

In these equations \(M_g\) and \(M_s\) represent the number of growing/shrinking MTs; \(D_f\) is the free tubulin concentration. The constants \(N\) and \(E\) show the nucleation and extinction rate and, in general, it is assumed that they are linearly dependent on the concentration of free proteins \(D_f\) [MSS]. The two frequencies \(P_{gs}\) and \(P_{sg}\) are catastrophe and rescue frequencies, and they are linearly dependent on \(D_f\), that is, \(P_{gs} = -k_7 D_f\) and \(P_{sg} = k_5 D_f\), where \(k_5\) and \(k_7\) are constants. The two rates \(V_g\) and \(V_s\) stand for growth and shrinkage rate with linear dependency on tubulin concentration, that is, \(V_g = k_3 D_f\) and \(V_s = C_1\), where \(k_3\) is a constant [MSS]. \(D_1\), \(D_2\) and \(D_3\) are the diffusion rates. Substituting these parameters in (2.1) will result the following system:

\[
\begin{align*}
\frac{\partial M_g}{\partial t} &= -k_7 D_f M_g + k_5 D_f M_s + k_1 D_f + D_1 \Delta M_g \\
\frac{\partial M_s}{\partial t} &= k_7 D_f M_g - k_5 D_f M_s - E + D_2 \Delta M_s \\
\frac{\partial D_f}{\partial t} &= -k_3 D_f M_g + V_s M_s - k_1 D_f + E + D_3 \Delta D_f.
\end{align*}
\]

Therefore we consider the system (2.2) on the spatial domain \(\Omega = (0, \ell)\); and we let

\[
\begin{align*}
f_1 &= f_1(M_g, M_s, D_f) = k_7 D_f M_g + k_5 D_f M_s + k_1 D_f, \\
f_2 &= f_2(M_g, M_s, D_f) = -k_7 D_f M_g - k_5 D_f M_s - E, \\
f_3 &= f_3(M_g, M_s, D_f) = -k_3 D_f M_g + C_1 M_s - k_1 D_f + E.
\end{align*}
\]

We also assume the system (2.2) is supplemented with usual initial condition and either Dirichlet boundary conditions

\[
(M_g, M_s, D_f)(0) = (M_g, M_s, D_f)(\ell) = 0;
\]

or Neumann boundary conditions

\[
\frac{\partial}{\partial x}(M_g, M_s, D_f)(0) = \frac{\partial}{\partial x}(M_g, M_s, D_f)(\ell) = 0.
\]

3. Early formation stage

Formation of MT is the result of a balance between different components of the system (2.2). Like many other pattern forming systems, one naturally assumes that this stage of equilibrium has merged from an earlier state as a result of an initial instability. Spatiotemporal pattern formation occurs due to instabilities of a homogeneous state and is controlled by nonlinearities of the system. In this regard, an extensive study of mathematical and physical phenomena of pattern formations can be found in many references such as [CH] and references therein. The early behaviour of the system can be finely approximated by the linearized system of (2.2).
therefore will focus here on the linearized system considering the background uniform steady state solution (3.1). It is easy to see that

\[ M_g = \frac{k^2 C_1}{K_1}, \quad M_s = \frac{k_1 k_3 E}{K_1}, \quad D_f = \frac{E}{k_1}, \]  

where \( K_1 = C_1 k_1 k_7 - k_3 k_5 E \), is the uniform steady state solution of the equation (2.2). This steady state solution of the system remains always positive if all the parameters are positive and also

\[ K_1 > 0. \]  

We will keep this assumption throughout this paper since we are interested in the realistic situation.

We note that the system of equations (2.2) defines an abstract evolution equation for a vector-valued function

\[ w(t) = \begin{pmatrix} M_g(\cdot, t) \\ M_s(\cdot, t) \\ D_f(\cdot, t) \end{pmatrix}, \quad t \geq 0. \]  

Now let \( \delta : \text{dom}(\delta) \to H \) be defined by the expression

\[ \delta = -\Delta I = \begin{pmatrix} -\Delta & 0 & 0 \\ 0 & -\Delta & 0 \\ 0 & 0 & -\Delta \end{pmatrix}. \]  

where

\[ \text{dom}(\delta) = H_1 = \{ w \in (H^2(\Omega))^3 : w = 0 \text{ on } \partial \Omega \} \]  

when (2.2) is considered with (2.4). Note that \( H^2(\Omega) \) is the usual Sobolev space.

Here we define a new set of conditions, called the zero average condition, as follows

\[ \int_\Omega w_i = 0 \quad \text{for } i = 1, 2, 3; \]  

and we consider (2.2) with (2.5) and (3.6):

\[ \text{dom}(\delta) = H_1 = \{ w \in (H^2(\Omega))^3 : \frac{\partial w_i}{\partial x} = 0 \text{ on } \partial \Omega \text{ and } \int_\Omega w_i = 0 \text{ for } i = 1, 2, 3 \}. \]  

Also let \( A \) and \( D \) be the linear operators in \( H \) represented by the constant matrices

\[ A = \begin{pmatrix} -\frac{k_7 E}{k_1} & \frac{k_5 E}{k_1} & 0 \\ \frac{k_7 E}{k_1} & -\frac{k_5 E}{k_1} & -\frac{k_3 E}{k_1} \\ \frac{k_7 E}{k_1} & \frac{k_5 E}{k_1} & -\frac{k_3 E}{k_1} \\ \frac{k_5 E}{k_1} & -\frac{k_3 E}{k_1} & -\frac{k_1}{C_1} \end{pmatrix}, \quad D = \begin{pmatrix} d_1 & 0 & 0 \\ 0 & d_2 & 0 \\ 0 & 0 & d_3 \end{pmatrix}. \]  

with \( K_2 = k_1 (1 + \frac{C_1 k_5}{k_1}) > 0 \). Without loss of generality we can assume \( k_1 = 1, E = 1 \). And we let \( \kappa = (k_3, k_5, k_7) \) and \( d = (d_1, d_2, d_3) \).

Now the linearized equation looks like

\[ w_\lambda = L_\lambda w. \]  

where

\[ L_\lambda = -\delta D + A. \]
where \( \lambda = (\kappa, d) \) presents all the control parameters. Next, let \( F = F_\lambda : H \rightarrow H \) represent the nonlinear terms of the Taylor expansion of \( f = (f_1, f_2, f_3) \) about the steady state \((3.1)\); that is

\[
F(w) = \begin{pmatrix} k_5 M_i D_f - k_7 M_j D_f \\ -k_5 M_i D_f + k_7 M_j D_f \\ -k_3 M_k D_f \end{pmatrix}.
\] (3.10)

Finally, then equation \((2.2)\) corresponds to the abstract evolution equation

\[
\frac{dw}{dt} = L_\lambda w + F_\lambda(w)
\] (3.11)

for \( w(t) \) in \( H, t > 0 \).

3.1. Onset of instabilities

It is logical to analyse the early behaviour of the system by looking at conditions which make some Fourier modes of the solution of \((2.2)\) to become unstable. Here we will calculate the eigenvalues and eigenfunctions of \( L_\lambda \) in \( H_1 \). To this end, assume \((\rho_m, e_m)\) denote the solution to the eigenvalue problem

\[
-\Delta e = \rho e.
\]

Then the eigenvalues of \( L_\lambda \) are that of its \( m \)-th-component

\[
E_m = E(\kappa, d) = \begin{pmatrix} -k_7 - d_1 \rho_m & k_5 & 0 \\ k_7 & -k_5 - d_2 \rho_m & 1 \\ -k_3 & C_1 & -K_2 - d_3 \rho_m \end{pmatrix}.
\] (3.12)

Assume \( \sigma_{mi} \) for \( m \in \mathbb{N} \) and \( i = 1, 2, 3 \) represent eigenvalues of \( E_m \); we denote the corresponding eigenvectors by \( \omega_{ki} \). By a straightforward calculation we have

\[
\omega_{mi} = \begin{pmatrix} k_5 \\ (d_1 \rho_m + k_7 + \sigma_{mi}) (d_2 \rho_m + k_5 + \sigma_{mi}) - k_3 k_7. \end{pmatrix}
\] (3.13)

It is obvious that \( \sigma_{ki} \)’s are eigenvalues of \( L_\lambda \) and the corresponding eigenfunctions are given by \( w_{ki} = \omega_{ki} e_k \). It is easy to verify that the conjugate operator has the same eigenvalues with eigenfunctions \( w_{ki}^* = \omega_{wi}^* e_k \), where \( \omega_{wi}^* \) are eigenvectors of \( E_m^* (\kappa, d) \), and we have

\[
\omega_{mi}^* = \begin{pmatrix} C_1 k_7 - (d_2 \rho_m + k_5 + \sigma_{mi}) k_3 \\ (d_1 \rho_m + k_7 + \sigma_{mi}) C_1 - k_3 k_5 \\ (d_2 \rho_m + k_5 + \sigma_{mi}) (d_1 \rho_m + k_7 + \sigma_{mi}) - k_3 k_7 \end{pmatrix}.
\] (3.14)

Now we assume

\[
\Lambda_k = \{(\kappa, d) | det(E_k(\kappa, d)) = 0\}.
\]

We note that

\[
\frac{\partial \Lambda_k}{\partial (\kappa, d)} \neq 0.
\]

If we assume

\[
k_5 K_2 \neq C_1 \quad \text{and} \quad C_1 \neq d_2 d_3 \rho_1^2 + d_2 K_2 \rho_1.
\] (3.15)

Therefore \( \Lambda_k \) divides the space to two distinct regions which we denote by \( \Lambda^- \) and \( \Lambda^+ \). We then have the following lemma:
Lemma 3.1 (Exchange of stability). If the following condition is satisfied
\[ k_2 k_1 C_1 > 0, \] (3.16)
then we will have
\[ \sigma_{11}(\kappa, d) \begin{cases} < 0 & \text{if } (\kappa, d) \in \Lambda^-, \\ = 0 & \text{if } (\kappa, d) \in \Lambda^0, \\ > 0 & \text{if } (\kappa, d) \in \Lambda^+. \end{cases} \] (3.17)
and also we have
\[ \sigma_{12}(\kappa, d), \sigma_{13}(\kappa, d) < 0 \text{ if } (\kappa, d) \in \Lambda_0^0; \]
moreover, for \( m > 2 \) and \( i = 1, 2, 3 \) we have
\[ \sigma_{mi}(\kappa, d) < 0 \text{ if } (\kappa, d) \in \Lambda_0^0. \]

Proof. Assume the characteristic polynomial of is given by
\[ \sigma^3 + p_m^m \sigma^2 + p_1^m \sigma + p_0^m = 0. \]
We note that
\[ \prod_{i=1}^{3} \sigma_{mi} = -p_0^m = \det(E_m). \]
It can be easily check that
\[ \sum_{i=1}^{3} \sigma_{mi} = -p_2^m = \text{trace}(E_m) < 0 \text{ for all } m \in \mathbb{N}. \] (3.18)
Also, by (3.16) we will have
\[ \sum_{i,j=1}^{3} \sigma_{mi} \sigma_{mj} = p_1^m < 0 \text{ for all } m \in \mathbb{N}. \] (3.19)
Now, on \( \Lambda_0^0 \) we have \( \prod_{i=1}^{3} \sigma_{ii} = 0 \). By (3.18) and (3.19) only one of these eigenvalues must be zero on \( \Lambda_0^0 \). We denote this critical eigenvalue by \( \sigma_{11} \). Since \( \sigma_{11} \) depends continuously on the control parameter, it changes sing when the control parameter crosses \( \Lambda_0^0 \). We denoted the two distinct regions by \( \Lambda_-^0 \) and \( \Lambda^+_0 \). Moreover, by (3.18) and (3.19), the other two eigenvalues have to be negative. That is
\[ \sigma_{12}(\kappa, d) < 0, \sigma_{13}(\kappa, d) < 0 \text{ if } (\kappa, d) \in \Lambda^0. \]
To prove the last claim, we should note that
\[ E_m(\kappa, d) = E(\rho^m, \kappa, d) = E(\rho_1, \kappa, \rho_1 \rho_m^{-1} d) = E_1(\kappa, \rho_1 \rho_m^{-1} d). \] (3.20)
Also by (3.16) the determinant of the matrix \( E(\rho) \) is decreasing in \( \rho \). Therefore, for \( (\kappa^0, d^0) \in \Lambda_0^0 \), we will have
\[ \det(E_m(\kappa^0, d^0)) < \det(E_1(\kappa^0, d^0)) = 0. \]
Hence from (3.20) we can conclude \( (\kappa^0, \rho_1 \rho_m^{-1} d^0) \in \Lambda^- \). This obviously means that all the eigenvalues of \( E_1(\kappa^0, \rho_1 \rho_m^{-1} d^0) \) are negative; hence all the eigenvalues of \( E_m(\kappa^0, d^0) \) for \( m > 1 \) are negative. This completes the proof. □
4. Transitions

In the previous section we introduced the threshold of instabilities for the system (2.2). Lemma 3.1 states that when the control parameter of the system $\lambda$ crosses the instability threshold, the system undergoes a change of stability. When $\lambda$ is near the instability threshold, one Fourier mode of the solution, called the principal mode, becomes unstable. This should eventually lead the solution to a stable situation. However, this is not clear from the linear analysis. It is known that any type of pattern formation is due to the presence of nonlinear components in the system.

In order to study the transitions of the nonlinear system (2.2), we will study the qualitative behaviour of its solutions when $\lambda$ stays close enough to the instability threshold $\Lambda^0$. Consider the system

$$w_t = L_\lambda(w) + F_\lambda(w).$$

(4.1)

we aim to drive a transition number $b_\lambda$ which will provide comprehensive information about transitional behaviour of the solutions at $\lambda$. Based on the centre manifold theorem, for any control parameter $\lambda$ in the vicinity of $\Lambda^0$, we have

$$w = yw_{11} + \Phi(y),$$

(4.2)

where $w$ is the solution (2.2), $w_{11}$ is the principal mode and $y$ is its amplitude. The error term in fact depends on the leading amplitude $y$.

**Theorem 4.1.** Consider the system of equations (4.1) with (2.4). If $\lambda$ is close to the critical parameter $\lambda_0 \in \Lambda^0$, and all components $\lambda_0$ satisfy conditions (3.2), (3.15),(3.16), and $d_2 > d_1$, then the following assertions hold true.

1. (4.1) has a mixed transition from $(0, \lambda_0)$. More precisely, there exists an open neighbourhood $U$ of $w = 0$ such that $U$ is separated into two disjoint open sets, $U_1^\pm$ and $U_2^\pm$, by the stable manifold $\Gamma$ of $w = 0$ with codimension one in $H$.

2. (4.1) bifurcates from $(0, \lambda_0)$ to a unique saddle point $w^\lambda$ (with Morse index one) on $\lambda \in \Lambda^-$, and to a unique attractor $w^\lambda$ on $\lambda \in \Lambda^+$.

(a) $U = U_1^+ + U_2^-$
(b) the transition in $U_1^+$ is jump, and
(c) the transition in $U_2^-$ is continuous. The local transition structure is as shown in figure 1.

3. (4.1) bifurcates in $U_2^+$ to a unique singular point $w^\lambda$ for $\lambda \in \Lambda^+$, which is an attractor such that for any $\varphi \in U_2^+$ we have

$$\lim_{t \to \infty} ||w(t, \varphi) - w^\lambda||_H = 0$$

4. (4.1) bifurcates for $\lambda \in \Lambda^-$ to a unique saddle point $w^\lambda$ with the Morse index one.

5. Near $\lambda_0$, the bifurcated singular points $w^\lambda$ can be expressed as

$$w^\lambda = \frac{-\sigma_{11}(\lambda)}{\alpha} w_{11} + o(|\sigma_{11}(\lambda)|).$$

where $w_{11}$ is given in (3.13).

**Proof of theorem 4.1.** For $\lambda$ close to $\lambda_0 \in \Lambda^0$, we project the system to its first eigenspace; therefore,

$$\{w_1, w_{11}\} = \{L_\lambda(w) + F_\lambda(w), w_{11}\} = \{L_\lambda(w), w_{11}\} + \{F_\lambda(w), w_{11}\}.$$

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where \( (\cdot, \cdot) \) is the inner product in \( L^2(\Omega) \). We note that
\[
(w_{11}, w_{11}^*) = \frac{dy}{dt} (w_{11}, w_{11}^*) \quad \text{and} \quad \langle L_\lambda(w), w_{11}^* \rangle = \sigma_{11}(\lambda) (w_{11}, w_{11}^*)
\]
By the classic centre manifold theorem, we can easily see that
\[
\langle F_\lambda(w), w_{11}^* \rangle = y^2 \langle F_\lambda(w_{11}), w_{11}^* \rangle + o(|y|^2).
\]
Therefore we can easily drive the following reduced centre manifold equation at \( \lambda_0 \)
\[
\frac{dy}{dt} = \alpha(\lambda_0) y^2 + o(y^2);
\]
where \( \alpha(\lambda_0) = \frac{\langle F_\lambda(w_{11}, w_{11}^*) \rangle}{(w_{11}, w_{11}^*)} \) is a constant. It is a straightforward calculation to see
\[
\alpha(\lambda_0) = \frac{\langle F_\lambda(w_{11}), w_{11}^* \rangle}{(w_{11}, w_{11}^*)} = \frac{\int L_\lambda(\omega) \cdot \omega^*}{\int \omega \cdot \omega^*} = \frac{8}{3\pi} \frac{\int \omega \cdot \omega^*}{\omega^*} = \frac{8}{3\pi} \frac{\int \omega \cdot \omega^*}{\omega^*} = \frac{8}{3\pi} \frac{\int \omega \cdot \omega^*}{\omega^*}
\]
is nonzero (in fact, negative) if \( d_1 > d_2 \). For the sake of simplicity in notations, we drop the indices and simply write \( \omega = \omega_{11} \) and \( \omega^* = \omega_{11}^* \). Now when \( \lambda \) lies near \( \lambda_0 \), the reduced centre manifold equation is approximated as
\[
\frac{dy}{dt} = \sigma_{11}(\lambda) y + \alpha(\lambda) y^2 + o(y^2)
\]
where
\[
\lim_{\lambda \to \lambda_0} \alpha(\lambda) = \alpha(\lambda_0) < 0.
\]
If the solutions are regular, one can approximate the solution of the above equation with
\[
\frac{dy}{dt} = \sigma_{11}(\lambda) y + \alpha(\lambda) y^2.
\]
A simple examination of the asymptotic behaviour of this last equation shows that the only non-trivial steady state solution is
\[
y = -\frac{\sigma_{11}(\lambda)}{\alpha(\lambda)^*},
\]
which is an attractor when \( \sigma_{11}(\lambda) > 0 \) and is a repeller when \( \sigma_{11}(\lambda) < 0 \). □

When the system (2.2) is considered with the Neumann boundary conditions, driving a feasible expression from
\[
\frac{\langle F_\lambda(y w_{11} + \Phi(y)), w_{11}^* \rangle}{\langle w_{11}, w_{11}^* \rangle}
\]

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure1.png}
\caption{Topological structure of the dynamic bifurcation of the (4.1) equation with (2.4). The horizontal line represents the centre manifold.}
\end{figure}
is not as easy anymore. In this case,
\[ \langle F_\lambda(y_{w11}), w^*_{11} \rangle = 0; \] (4.3)
therefore, we have to proceed to another stage of higher order approximation. The difficulty lies in driving a good approximation of \( \langle F_\lambda(y_{w11} + \Phi(y)), w^*_{11} \rangle \). To overcome this difficulty, one normally resorts to a simple Taylor approximation of the implicit centre manifold function. However, we will use another approximation method suggested by Ma and Wang [MW05]. Using their approach will lead us to the following approximation:
\[ \langle F_\lambda(w), w^*_{11} \rangle \langle w_{11}, w^*_{11} \rangle = b_\lambda y^3 + o(|y|^3). \]
where \( b_\lambda \) is the transition number which we will drive later. Therefore the transition equation near the threshold of instabilities reads as
\[ \dot{y} = y\sigma_{11} + b_\lambda y^3 + o(|y|^3). \]
This suggest the existence of a pitchfork bifurcation as the control parameter \( \lambda = (\kappa, d) \) crosses the critical threshold \( \Lambda^0 \). We have the following theorem.

**Theorem 4.2.** Consider the system (4.1) with (2.5) and (3.6). If \( \lambda \) is close to the critical parameter \( \lambda_0 \in \Lambda^0 \), and all components of \( \lambda_0 \) satisfy conditions (3.2), (3.15), and (3.16), then the following assertions hold true.

**Case 1.** If \( b_\lambda < 0 \), the transition of (4.1) over \( \lambda_0 \) is continuous (type I); moreover,

(1) the trivial solution \( w_{\lambda_0} = 0 \) is a locally asymptotically stable equilibrium point of the system (4.1) at \( \lambda_0 \);

(2) after bifurcation, the solution \( w \) of the system (4.1) will asymptotically tend to either \( w^*_\lambda \) or \( w^-\lambda \), where
\[ w^\pm_\lambda = \pm(\sigma_{11} / |b_\lambda|)^{1/2} w_{k1} + \epsilon_\lambda, \] (4.4)
where \( ||\epsilon_\lambda||_H = o(\sigma_{11}^{1/2}) \). (see figure 2)

**Case 2.** If \( b_\lambda > 0 \), the transition of (4.1) over \( \lambda_0 \) is a jump (type II). The steady state solutions are metastable after bifurcation. In this case, points \( w^*_\lambda \) and \( w^-\lambda \) will be repellors.

**Case 3.** If \( b_\lambda = 0 \), the transition of (4.1) over \( \lambda_0 \) is mixed (type III).
The calculation of the parameter $b_\lambda$ becomes, therefore, very crucial. This calculation is lengthy and tedious, but it can reveal valuable information regarding the number of the steady state solution and the type of the bifurcation and transition.

Before we proceed with the proof of theorem 4.2, we state a lemma due to Ma and Wang, but we refer the reader to [MW05] for a proof.

**Lemma 4.1 (Approximation of the centre manifold function).** Assume $w = \sum_{I \in C} y_I w_I + \Phi$ is the solution of (4.1) where $C$ is the set of critical indices. Define

$$E_1 = \text{span}\{w_I | I \in C\}, E_2 = E_1^\perp, \mathcal{L} = L_\lambda|_{E_1};$$

and let $\mathcal{P}_2 : H \rightarrow E_2$ be the Leray projection. Then

$$-\mathcal{L}^{-1}(\Phi(y)) = \mathcal{P}_2\left(F\left(\sum_{I \in C} y_I w_I\right)\right) + o(|y|^2) + O(|\sigma_\lambda||y|^2).$$

**Proof of theorem 4.2.** We note that

$$\langle F_\lambda(w), w^*_1 \rangle = \langle F_\lambda(w), e_1^*_{11} \rangle = \langle F_\lambda(w), e_1 \rangle \cdot \omega^*_{11}.$$ 

We write $\langle F_\lambda(w), e_1 \rangle$ just for simplicity, but we really take the $L^2$-inner product of each component of $F_\lambda(w)$ with $e_1$. We have

$$w = y w_{11} + y_{12} w_{12} + y_{13} w_{13} + \sum_{i > 1} y_{1i} w_{1i}.$$ 

There exist a finite set of indices $\mathcal{I}$ so that we have

$$\langle F_\lambda(w), e_1 \rangle = \left\langle F_\lambda\left(\sum_{I \in \mathcal{I}} y_{1i} w_{1i}\right), e_1 \right\rangle.$$ 

It is easy to see that here $\mathcal{I} = \{2\}$. For the sake of simplicity in notations, again let $\omega = \omega_{11}$ and $\omega^* = \omega^*_{11}$. Let us define

$$B^j(I) := \langle e_i^2, e_1 \rangle \sum_{j=1}^3 b_{1j}^j y_{1j} = \langle e_1^2, e_1 \rangle b_j^1 y_I$$ 

where

$$b_j^1 = (b_{11}^j, b_{12}^j, b_{13}^j), y_I = (y_{11}, y_{12}, y_{13})^T$$

with $b_{1j}^1 = (\omega^1 \omega_{1j}^3 + \omega^3 \omega_{1j}^1)$. Now let us also define

$$B := \begin{bmatrix} k_3 B^2(2) - k_1 B^1(2) & k_3 B^3(2) \\
-k_3 B^2(2) + k_1 B^1(2) & -k_3 B^3(2) \end{bmatrix}.$$ 

It is a straightforward calculation to see that

$$\dot{y} = B^T \omega^* y + o(|y|^3).$$

By lemma (4.1) we can see that

$$y_{1i} = (-\sigma_{1i} \{w_I, w_{1i}\}^{-1} \{F(y w_{11}), w_{1i}\} + o(|y|^2)$$

$$= (-\sigma_{1i} \{e_1, e_1\} \omega_{1i} \cdot \omega_{1i}^* \{e_1^2, e_1\} F(\omega) \cdot \omega_{1i}^* y^2 + o(|y|^2).$$

(4.5)
Therefore, 
\[ y_I = \frac{-\langle e_{1}, e_{I} \rangle}{\langle e_{I}, e_{I} \rangle} \text{diag}[\sigma_{I1}, \omega_{I1} \cdot \cdot \cdot]^{-1} [\omega_{I1}^{\ast} \cdot \omega_{I2}^{\ast} \cdot \omega_{I3}^{\ast}]^{\top} F(\omega) y^2 + o(|y|^2), \]
where by \( \text{diag}[\sigma_{Ii}, \omega_{Ii} \cdot \cdot \cdot] \) we mean a diagonal matrix with diagonal elements \( \sigma_{Ii}, \omega_{Ii} \cdot \cdot \cdot \) for \( i = 1, 2, 3 \). Consequently, we will have 
\[ B^\top(I) = \frac{-\langle e_{1}^{2}, e_{I} \rangle}{\langle e_{I}, e_{I} \rangle} b_{I} \text{diag}(\sigma_{I1}, \omega_{I1} \cdot \cdot \cdot)^{-1} [\omega_{I1}^{\ast} \cdot \omega_{I2}^{\ast} \cdot \omega_{I3}^{\ast}]^{\top} F(\omega) y^2 + o(|y|^2). \]

Note that 
\[ \frac{\langle e_{1}^{2}, e_{I} \rangle}{\langle e_{I}, e_{I} \rangle} = \frac{\ell}{8}, \]
and 
\[ F(\omega) = \begin{bmatrix} k_{5} \omega_{1}^{2} \omega_{3}^{2} - k_{7} \omega_{1} \omega_{3}^{3} \\ -k_{5} \omega_{1}^{2} \omega_{3}^{2} + k_{7} \omega_{1} \omega_{3}^{3} \\ -k_{5} \omega_{1}^{2} \omega_{3}^{3} \end{bmatrix}. \]

**Remark 4.1.** In the proof of theorem 4.2, the parameter \( b_{\lambda} \) is given as an algebraic expression. However, its expression is large; consequently any quantitative calculation requires a long calculation which is trivial yet tedious. We remark that \( b_{\lambda} \) can be substantially simplified by assuming 
\[ C_{1}k_{7} = k_{5}(k_{5} + \rho d_{2}) \]  
(4.6)
It can be easily verified that under the assumption (4.6), we will have 
\[ B^\top \omega^\ast = k_{5} \left( \omega_{1}^{2} - \omega_{2}^{2} \right) \left( B^{2}(2) + B^{3}(0) \right) = -\frac{k_{5}k_{7} \rho}{k_{7}} (k_{5}d_{1} + k_{7}d_{2} + d_{1}(d_{2} \rho)) B^{2}(2). \]  
(4.7)
where \( \rho = \rho_{11} \).

**5. Conclusion**

From the biological point of view, the above results show the complex nature of the formation and phase transition of MTs in the competition of nucleation rate, extinction rate and the dynamic instability fundamental growth, shrinkage and stochastic switching process as well as the concentration dependency of the dynamic instability parameters. In the large-scale, the nucleation rate is depending on the number of free templates in the given geometry and the time interval, and also on the concentration dependent expected frequency of nucleation at each unoccupied template over a unit time interval [MSS]. In general, the mechanisms regulating microtubule nucleation in vivo have not been explicitly determined and it is not known how the number of templates are identified and activated [ARSA]. This shows the necessity for multi-state models to include the timing of the nucleation process with regard to dynamic instability and diffusion, as well as including more complex boundary conditions describing the nucleation in the templates, diffusion, and dynamic instability processes in two or three dimensions. A numerical simulation of the current study as well as stability analysis of the more complex boundary conditions are in progress. It is our hope that this work will open the way to the study of more complicated and realistic biological models with a systematic study across physical parameters.
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References

[ARSA] Aldaz H, Rice L M, Stearns T and Agard D A 2005 Insights into microtubule nucleation from the crystal structure of human gamma-tubulin Nature 435 523–7

[AJLR] Alberts B, Johnson A, Lewis J and Raff M 2007 Molecular Biology of the Cell (New York: Garland Science)

[BVT] Ballatore C, Virginia M Y L and Trojanowski J Q 2007 Tau-mediated neurodegeneration in Alzheimer’s disease and related disorders Nature Rev. Neurosci. 8 663–72

[MSS] Mourão M, Schnell S and Shaw S L 2011 Macroscopic simulations of microtubule dynamics predict two steady-state processes governing array morphology Comput. Biol. Chem. 35 269–81

[CH] Cross M C and Hohenberg P C 1993 Pattern formation outside of equilibrium Rev. Mod. Phys. 65 851–1123

[DM] Desai A and Mitchison T J 1997 Microtubule polymerization dynamics Annu. Rev. Cell Dev. Biol. 13 83–117

[DL] Dogterom M and Leibler S 1993 Physical aspects of the growth and regulation of microtubule structures Phys. Rev. Lett. 70 1347–50

[DVMW] Verma D S, Mitchison T J and Walczak C E 1999 Kin I kinesins are microtubule-destabilizing enzymes Cell 96 69–78

[DYH] Deymier P A, Yang Y and Hoying J 2005 Effect of tubulin diffusion on polymerization of microtubules Phys. Rev. E 72 021906

[EM] Etienne-Manneville S 2010 From signaling pathways to microtubule dynamics: the key players Curr. Opin. Cell Biol. 22 104–11

[F] Farrer M J 2006 Genetics of Parkinson disease: paradigm shifts and future prospects Nature Rev. Genetics 7 306–18

[IB] Bena I 2006 Dichotomous Markov noise: Exact results in out-of-equilibrium systems Int. J. Mod. Phys. B 20 2825–88 (arXiv:cond-mat/0606116)

[KM] Kueh H Y and Mitchison T J Structural plasticity in actin and tubulin polymer dynamics Science 325 960–3

[KWY] Kaper, Hans G, Wang S and Yari M 2009 Dynamical transitions of Turing patterns Nonlinearity 22 601–26

[MK] Mitchison T and Kirschner M 1984 Dynamic instability of microtubule growth Nature 312 237–42

[MW13] Tian Ma and Shouhong Wang 2013 Phase Transition Dynamics (Berlin: Springer)

[MW05] Tian Ma and Shouhong Wang 2005 Bifurcation Theory and Applications (Nonlinear Science) (Singapore: World Scientific)

[SKE] Shaw S L, Kamyar R and Ehrhardt D W 2003 Sustained microtubule treadmilling in Arabidopsis cortical arrays Science 300 1715–8

[SO] Seetapun D and Odde D J 2010 Cell-length-dependent microtubule accumulation during polarization Curr. Biol. 20 979–88

[YBZS] Yarahmadian S, Barker B, Zumbrun K and Shaw S L 2011 Existence and stability of steady states of a reaction convection diffusion equation modeling microtubule formation, J. Math. Biol. 63 459–92