Final Project for *Statistical Physics in Biology*
Primary authors: **Ming Zheng. Physics**
Correspond to smile321@mit.edu

Identifying Oscillatory Behavior in Master Equations of Microtubules

(Dated: May 18, 2018)

In our class, we took it for granted that the system eventually progresses to the limit of slow and long-wavelength fluctuations, with $\omega \to 0$ and $k \to 0$. Therein, I got my original motivation for writing this particle: whether or not those master equations can–instead of converging to some stable fixed point–be trapped onto the limit cycle and oscillate. The oscillations in master equations would mean that the components (i.e. microtubules of different length) vary against time, which exactly meets the desired dynamic property of microtubules–reduplicative growing and shrinking. My analytical calculation shows that there is no way for the origin model to behavior like a oscillator; However, I built a purely artificial model that is capable of generating limit-cycle oscillations for each independent component, which sheds light on the chances of constructing dynamical switching between growth and catastrophe via Turing-Hopf bifurcation rather than successive tuning of global controlling parameters.

INTRODUCTION

Cells control the dynamics of microtubules (MTs) by tuning the concentration of ATP and ADP in cytoplasm, which further tunes the average drifting speed to be either positive (growing) or negative (shrinking)[1]. Besides, this dynamic is also assisted by the existence of a cap region as well as the intermediate hydrolysis, which inhibit MT from either easy catastrophe or endless growing [2, 3].

However, in addition to adjusting kinetic parameters on and on, there is, by principle, another way of generating dynamical behavior when given a set of fixed kinetic parameters – limit-cycle oscillation. Oscillators are all over the biological systems, especially serving for biological clocks which vary from neuronal oscillations in cortical networks[4] to circadian clocks in cyanobacteria[5]. Oscillators can even be engineered into bacteria through synthetic biology[6].

In this article, I will set out from the simplest version of MT master equations and discuss its possibility of oscillating. If incapable, I will try further modifying the equations in different ways till reaching a functional oscillator. Once achieved, the automatic oscillation of distribution of MTs of different length would mean that the reciprocation of growth and catastrophe can be theoretically realized by intrinsic dynamic properties of the system without any regulation of kinetic parameters. Furthermore, such a mechanism would provide a design principle of oscillator in multi-variable master equations and can be further applied for synthetical networks for dynamic filaments of the cytoskeleton.

MODEL 𝕀

In this article, we think MT filaments can diffuse freely in the solution, surrounded with infinite number of monomers. Those MTs has one end that can either grow or shrink. The master equations for the dynamic behavior of a MT in the continuum limit yield[1]:

$$\begin{aligned}\frac{\partial p_+(z,t)}{\partial t} &= -f_{+-}p_+ + f_{-+}p_- - \frac{\partial}{\partial z}(v_+p_+),\\ \frac{\partial p_-(z,t)}{\partial t} &= +f_{+-}p_+ - f_{-+}p_- + \frac{\partial}{\partial z}(v_-p_-).\end{aligned} \tag{1}$$

By doing Fourier transforming in space and time:

$$p_\pm(z,t) = \int dk d\omega e^{ikz-i\omega t}\tilde{p}_\pm(k,\omega), \tag{2}$$

the coupled master equations become a matrix equation:

$$\begin{pmatrix} i\omega - f_{+-} - ikv_+ & f_{-+} \\ f_{+-} & i\omega - f_{-+} + ikv_- \end{pmatrix}\begin{pmatrix}\tilde{p}_+\\ \tilde{p}_-\end{pmatrix} = 0. \tag{3}$$

If we define

$$\omega \equiv \omega_r + i\omega_i, \tag{4}$$

then by solving the determinant we got two equations (one for the real part and the other one for the imaginary part):

$$\begin{aligned}k^2v_+v_- + (f_{+-}+f_{-+})\omega_i + \omega_i^2\\ + (kv_+ - kv_-)\omega_r - \omega_r^2 = 0,\end{aligned} \tag{5}$$

$$\begin{aligned}f_{-+}kv_+ - f_{+-}kv_- + (kv_+ - kv_-)\omega_i\\ - (f_{+-}+f_{-+}+2\omega_i)\omega_r = 0.\end{aligned} \tag{6}$$

If we further define

$$\nu \equiv \frac{f_{-+}v_+ - f_{+-}v_-}{(f_{+-}+f_{-+})^2} \tag{7}$$

$$\mu \equiv \frac{v_+ - v_-}{f_{+-}+f_{-+}} \tag{8}$$

$$\xi \equiv \frac{v_+v_-}{(f_{+-}+f_{-+})^2} \tag{9}$$

$$\varpi_r \equiv \frac{\omega_r}{f_{+-}+f_{-+}} \quad (10)$$

$$\varpi_i \equiv \frac{\omega_i}{f_{+-}+f_{-+}} \quad (11)$$

then Eq.(5) and Eq.(6) become:

$$\xi k^2 + \varpi_i + \varpi_i^2 + \mu k \varpi_r - \varpi_r^2 = 0, \quad (12)$$

$$\nu k + \mu k \varpi_i - (1+2\varpi_i)\varpi_r = 0, \quad (13)$$

or simply noted as:

$$\xi_k + \varpi_i + \varpi_i^2 + \mu_k \varpi_r - \varpi_r^2 = 0, \quad (14)$$

$$\nu_k + \mu_k \varpi_i - (1+2\varpi_i)\varpi_r = 0, \quad (15)$$

where $\xi_k \equiv \xi k^2$, $\mu_k \equiv \mu k$, and $\nu_k \equiv \nu k$. Owing to Eq.(15), we can substitute ϖ_r in Eq.(14) with the following formula:

$$\varpi_r = \frac{\nu_k + \mu_k \varpi_i}{1+2\varpi_i}, \quad (16)$$

hence we are able to write down the equation of ϖ_i:

$$\varpi_i^4 + 2\varpi_i^3 + \frac{1}{4}(5+4\xi_k+\mu_k^2)\varpi_i^2 + \frac{1}{4}(1+4\xi_k+\mu_k^2)\varpi_i + \frac{1}{4}(\xi_k+\mu_k\nu_k-\nu_k^2) = 0. \quad (17)$$

Here we mainly concern about the solution of ϖ_i since it controls the amplitude of each mode (refer to Eq.(2) and Eq.(4)).

At $k=0$, Eq.(17) can be simplified as:

$$(\varpi_i^3 + 2\varpi_i^2 + \frac{5}{4}\varpi_i + \frac{1}{4})\varpi_i = 0, \quad (18)$$

and the corresponding solutions are

$$\varpi_i^{(1)} = 0,\ \varpi_i^{(2)} = -1,\ \varpi_i^{(3)} = \varpi_i^{(4)} = -\frac{1}{2}. \quad (19)$$

There can only be two non-trivial real eigenvalues regards ϖ_i, since there can only be two independent complex eigenvalues for Eq.(3). This argument can easily be justified by substituting each of the four solutions into Eq.(16), and we can find that $\varpi_i^{(3)}$ and $\varpi_i^{(4)}$ are the two trivial solutions, as the corresponding ϖ_r goes to $\frac{0}{0}$.

At $|k|>0$, let's define the coefficient for the zero order in Eq.(17) as:

$$e_k \equiv \xi_k + \mu_k\nu_k - \nu_k^2, \quad (20)$$

or say:

$$e(k) \equiv (\xi+\mu\nu)k^2 - \nu^2 k^4. \quad (21)$$

According to Vieta's formulas,

$$\varpi_i^{(1)} + \varpi_i^{(2)} + \varpi_i^{(3)} + \varpi_i^{(4)} = -2 \quad (22)$$

$$\varpi_i^{(1)}\varpi_i^{(2)}\varpi_i^{(3)}\varpi_i^{(4)} = \frac{1}{4}e(k) \quad (23)$$

From Eq.(21), we know that if $(\xi+\mu\nu)\le 0$, $e(k)$ will always be negative, which means $\varpi_i^{(1)}$ will always be positive, leading to all modes competing with each other hence no significant oscillation being available. On the other hand, if $(\xi+\mu\nu)>0$, $e(k)$ is positive for 'slowly varying' modes, and finally becomes negative when $|k|$ goes large enough. If we assume that $\varpi_i^{(1)}$ is always larger than $\varpi_i^{(2)}$ (i.e. these two eigenvalues never degenerate), then we can infer that $\varpi_i^{(1)}$ is negative in the long-wavelength limit (i.e. k is close to zero), and finally becomes positive in the short-wave limit (i.e. $|k|\to\infty$). Therefore, the amplitudes of 'slowly varying' modes will always decay with time. Consequently, there is no chance to generate an oscillatory dynamic for the model proposed in Eq.(1).

MODEL Ⅲ

After adding a diffusion term, the modified master equations yield:

$$\partial_t p_+(z,t) = -f_{+-}p_+ + f_{-+}p_- - v_+\partial_z p_+ + d_+\partial_z^2 p_+,$$
$$\partial_t p_-(z,t) = +f_{+-}p_+ - f_{-+}p_- + v_-\partial_z p_- + d_-\partial_z^2 p_-. \quad (24)$$

By doing spatio-temporal Fourier transforming, the coupled master equations become a matrix equation:

$$\begin{pmatrix} i\omega - f_{+-} - ikv_+ - k^2 d_+ & f_{-+} \\ f_{+-} & i\omega - f_{-+} + ikv_- - k^2 d_- \end{pmatrix} \times \begin{pmatrix} \tilde{p}_+ \\ \tilde{p}_- \end{pmatrix} = 0, \quad (25)$$

and the corresponding determinant gives two equations after the similar decomposition upon the circular frequency in Eq.(4):

$$(f_{+-}d_- + f_{-+}d_+ + v_+v_-)k^2 + d_+d_-k^4 + (f_{+-}+f_{-+}+(d_++d_-)k^2)\omega_i + \omega_i^2 + (v_+-v_-)k\omega_r - \omega_r^2 = 0, \quad (26)$$

$$(f_{-+}v_+ - f_{+-}v_-)k + (d_-v_+ - d_+v_-)k^3 + (v_+-v_-)k\omega_i - (f_{+-}+f_{-+}+(d_++d_-)k^2+2\omega_i)\omega_r = 0. \quad (27)$$

If we further define

$$\Xi \equiv \frac{f_{+-}d_- + f_{-+}d_+ + v_+v_-}{(f_{+-}+f_{-+})^2} \quad (28)$$

$$\Gamma \equiv \frac{d_+d_-}{(f_{+-}+f_{-+})^2} \quad (29)$$

$$\Omega \equiv \frac{d_++d_-}{f_{+-}+f_{-+}} \quad (30)$$

$$\Theta \equiv \frac{d_-v_+ - d_+v_-}{(f_{+-}+f_{-+})^2}, \quad (31)$$

combing with definitions from Eq.(7) to Eq.(11), Eq.(26) and Eq.(27) can be expressed as:

$$\Xi k^2 + \Gamma k^4 + (1+\Omega k^2)\varpi_i + \varpi_i^2 + \mu k \varpi_r - \varpi_r^2 = 0, \quad (32)$$
$$\nu k + \Theta k^3 + \mu k \varpi_i - (1+\Omega k^2 + 2\varpi_i)\varpi_r = 0. \quad (33)$$

and can be further simplified as:

$$\phi_k + \sigma_k \varpi_i + \varpi_i^2 + \mu_k \varpi_r - \varpi_r^2 = 0, \quad (34)$$
$$\psi_k + \mu_k \varpi_i - (\sigma_k + 2\varpi_i)\varpi_r = 0. \quad (35)$$

where $\phi_k \equiv \Xi k^2 + \Gamma k^4$, $\sigma_k \equiv 1+\Omega k^2$, and $\psi_k \equiv \nu k + \Theta k^3$. Then, we are able to express ϖ_r in ϖ_i:

$$\varpi_r = \frac{\psi_k + \mu_k \varpi_i}{\sigma_k + 2\varpi_i}. \quad (36)$$

Hence, we got the equation for ϖ_i:

$$\varpi_i^4 + (1+\sigma_k)\varpi_i^3 + (\sigma_k + \phi_k + \frac{1}{4}(\sigma_k^2 + \mu_k^2))\varpi_i^2 + \frac{\sigma_k}{4}(\sigma_k + 4\phi_k + \mu_k^2)\varpi_i + \frac{1}{4}(\phi_k \sigma_k^2 + \mu_k \psi_k \sigma_k - \psi_k^2) = 0. \quad (37)$$

When $k=0$, we still got solutions in Eq.(19), with $\varpi_i^{(1)}$ and $\varpi_i^{(2)}$ being the non-trivial ones.

When $|k|>0$, let's define the zero order coefficient as:

$$g_k \equiv \phi_k \sigma_k^2 + \mu_k \psi_k \sigma_k - \psi_k^2, \quad (38)$$

or more explicitly expressed with $\kappa \equiv k^2$:

$$\begin{aligned} g(\kappa) &\equiv [\Xi - (\nu-\mu)\nu]\kappa \\ &+ [\Gamma - (2\nu - \mu)\Theta + (2\Xi + \mu\nu)\Omega]\kappa^2 \\ &+ [(\Xi\Omega + 2\Gamma)\Omega - (\Theta - \mu\Omega)\Theta]\kappa^3 + \Gamma\Omega^2\kappa^4, \end{aligned} \quad (39)$$

where let's further note

$$c_1 \equiv \Xi - (\nu - \mu)\nu \quad (40)$$
$$c_2 \equiv \Gamma - (2\nu-\mu)\Theta + (2\Xi + \mu\nu)\Omega \quad (41)$$
$$c_3 \equiv (\Xi\Omega + 2\Gamma)\Omega - (\Theta - \mu\Omega)\Theta \quad (42)$$
$$c_4 \equiv \Gamma\Omega^2. \quad (43)$$

According to Vieta's formulas,

$$\varpi_i^{(1)} + \varpi_i^{(2)} + \varpi_i^{(3)} + \varpi_i^{(4)} = -(1+\sigma_k) \quad (44)$$
$$\varpi_i^{(1)}\varpi_i^{(2)}\varpi_i^{(3)}\varpi_i^{(4)} = \frac{1}{4}g_k \quad (45)$$

Due to Eq.(44), there will always be at least one negative ϖ_i. If $c_1 < 0$, then $g_k < 0$ at slow-varying modes, i.e. $\varpi_i^{(1)}$ becomes positive at first (notice that when k varys from zero, $\varpi_i^{(1)}$ initiates from zero while $\varpi_i^{(2)}$ initiates from -1). Because $c_4 > 0$, g_k will finally be positive definite as long as $|k|$ goes large enough; in other words, there will finally be either i.) two negative ϖ_i & two positive ϖ_i, or ii.) four negative ϖ_i (refer to Eq.(45)). Here we still assume that $\varpi_i^{(j)}$ ($j=1,2,3,4$) never cross with each other. Under this assumption: in case i.), one trivial solution (initiated from $-\frac{1}{2}$) also becomes positive, which doesn't make much sense, given that one trivial part would have a positive amplitude; in case ii.), $\varpi_i^{(1)}$ finally become negative again, leaving positive amplitude only maintaining within the slow-varying modes, which indicates a stable temporal oscillation of its length distribution.

Based on all arguments above, one sufficient condition required for oscillatory dynamic is $c_1 < 0$. The explicit expression for c_1 yields:

$$\begin{aligned} c_1 &= \frac{f_{+-}d_- + f_{-+}d_+ + v_+v_-}{(f_{+-}+f_{-+})^2} \\ &- \frac{f_{-+}v_+ - f_{+-}v_- - (v_+ - v_-)(f_{+-}+f_{-+})}{(f_{+-}+f_{-+})^2} \\ &\times \frac{f_{-+}v_+ - f_{+-}v_-}{(f_{+-}+f_{-+})^2} \\ &= \frac{f_{+-}f_{-+}(v_+ + v_-)^2}{(f_{+-}+f_{-+})^4} + \frac{f_{+-}d_- + f_{-+}d_+}{(f_{+-}+f_{-+})^2}. \end{aligned} \quad (46)$$

Given both f_{+-} and f_{-+} are all positive values for a real system and both d_+ and d_- are positive definite, there is no way for c_1 to be smaller than zero, unfortunately.

Now let's check c_2:

$$\begin{aligned} c_2 &= \frac{d_+d_-}{(f_{+-}+f_{-+})^2} \\ &- \frac{2(f_{-+}v_+ - f_{+-}v_-) - (v_+ - v_-)(f_{+-}+f_{-+})}{(f_{+-}+f_{-+})^2} \\ &\times \frac{d_-v_+ - d_+v_-}{(f_{+-}+f_{-+})^2} \\ &+ \frac{2(f_{+-}d_- + f_{-+}d_+ + v_+v_-)(d_+ + d_-)}{(f_{+-}+f_{-+})^3} \\ &+ \frac{(f_{-+}v_+ - f_{+-}v_-)(v_+ - v_-)(d_+ + d_-)}{(f_{+-}+f_{-+})^4} \\ &= 2 \times \frac{f_{+-}f_{-+}(d_+ + d_-)^2 + (f_{+-}d_- - f_{-+}d_+)^2}{(f_{+-}+f_{-+})^4} \\ &+ \frac{(f_{+-}d_- + f_{-+}d_+)(v_+ + v_-)^2}{(f_{+-}+f_{-+})^4} \\ &+ 3\frac{d_+d_-}{(f_{+-}+f_{-+})^2}. \end{aligned} \quad (47)$$

Thus, c_2 is also positive definite.

Now let's check c_3:

$$\begin{aligned} c_3 &= \frac{(f_{+-}d_- + f_{-+}d_+ + v_+v_-)(d_+ + d_-)^2}{(f_{+-}+f_{-+})^4} \\ &+ \frac{2d_+d_-(d_+ + d_-)}{(f_{+-}+f_{-+})^3} - \frac{(d_-v_+ - d_+v_-)^2}{(f_{+-}+f_{-+})^4} \\ &+ \frac{(v_+ - v_-)(d_+ + d_-)(d_-v_+ - d_+v_-)}{(f_{+-}+f_{-+})^4} \\ &= \frac{(f_{+-}d_- + f_{-+}d_+)(d_+ + d_-)^2}{(f_{+-}+f_{-+})^4} \end{aligned}$$

$$+\ \frac{2d_+d_-(d_++d_-)}{(f_{+-}+f_{-+})^3}+\frac{d_+d_-(v_++v_-)^2}{(f_{+-}+f_{-+})^4} \quad (48)$$

Thus, c_3 is also positive definite.

As we can see, g_k will all the way be positive as $|k|$ increases from zero, which means that $\varpi_i^{(j)}$ $(j=1,2,3,4)$ has never surpassed zero, leading to the mode with $k=0$ being the only surviving mode as $t\to\infty$. Accordingly, this system intrinsically prohibits oscillatory dynamics.

Topologically speaking, the regulation network between p_+ and p_- consist of two mutual activations and two self inhibitions, which represents a typical single steady state dynamic (or dual-stable steady state if proper nonlinear terms are incorporated).

MODEL III

In this section, I artificially propose the following mechanism:

$$\begin{aligned}\partial_t p_+(z,t) &= -f_{+-}p_+ + f_{-+}p_- + rp_+p_- \\ &\quad -v_+\partial_z p_+ + d_+\partial_z^2 p_+, \\ \partial_t p_-(z,t) &= +f_{+-}p_+ - f_{-+}p_- - rp_+p_- \\ &\quad +v_-\partial_z p_- + d_-\partial_z^2 p_-. \end{aligned} \quad (49)$$

The additional term "rp_+p_-" can be interpreted as: when a pair of growing and shrinking MTs of the same length juxtapose together, there is some possibility that the shrinking MT will transfer to the growing state.

By comparing Eq.(24) and Eq.(49), we can see that

$$f_{+-}^{eff} = f_{+-} - rp_-^*, \quad (50)$$

where f_{+-}^{eff} is the effective f_{+-} in Eq.(24) at steady state. Consequently, the "f_{+-}" in Eq.(46) could (in principle) be smaller than zero as long as $f_{+-} < rp_-^*$, which results in the chance of $c_1 < 0$.

At the global-uniform steady state, the distribution of growing and shrinking MTs yields the following equations:

$$\begin{cases} f_{+-}p_+^* - f_{-+}p_-^* - rp_+^*p_-^* = 0 \\ p_+^* + p_-^* = 1 \end{cases} \quad (51)$$

where we got:

$$\begin{aligned} p_+^* &= \frac{r - f_{+-} - f_{-+} + \sqrt{(f_{+-}+f_{-+}-r)^2 + 4f_{-+}r}}{2r}, \\ p_-^* &= \frac{r + f_{+-} + f_{-+} - \sqrt{(f_{+-}+f_{-+}+r)^2 - 4f_{+-}r}}{2r}. \end{aligned} \quad (52)$$

To obtain the more specific condition, let's regard r as a tunable parameter, hence:

$$\begin{aligned} \frac{\partial f_{+-}^{eff}}{\partial r} &= \frac{1}{2}\left(\frac{f_{-+} - f_{+-} + r}{\sqrt{(f_{+-}+f_{-+}+r)^2 - 4f_{+-}r}} - 1\right) \\ &= \frac{1}{2}\left(\frac{f_{-+} - f_{+-} + r}{\sqrt{(f_{-+}-f_{+-}+r)^2 + 4f_{-+}f_{+-}}} - 1\right) \\ &< 0. \end{aligned}$$

Consequently,

$$\begin{aligned} \min: f_{+-}^{eff} &= \lim_{r\to+\infty}(f_{+-} - rp_-^*) \\ &= f_{+-} - \lim_{r\to+\infty}\frac{f_{-+}+f_{+-}+r}{2} \\ &\times \left[1 - \left(1 - \frac{1}{2}\frac{4f_{+-}r}{(f_{-+}+f_{+-}+r)^2}\right)\right] \\ &= f_{+-} - \lim_{r\to+\infty}\left(\frac{r}{f_{-+}+f_{+-}+r}\right)f_{+-} \\ &= 0^+. \end{aligned}$$

Therefore, this model still cannot reach the condition of $f_{+-}^{eff} < 0$, thereby oscillation is still forbidden.

MODEL IV

Finally, let's move back to Model II formulized in Eq.(24), except that here we generalize f_{+-} and f_{-+} to be some functions of p_+ and p_-: some cooperative dynamics make the rates of transition between growing and shrinking MTs of specific length to be dependent upon the current concentrations of this length:

$$\begin{aligned}\partial_t p_+(z,t) &= -f_{+-}(p_+,p_-)p_+ + f_{-+}(p_+,p_-)p_- \\ &\quad -v_+\partial_z p_+ + d_+\partial_z^2 p_+, \\ \partial_t p_-(z,t) &= +f_{+-}(p_+,p_-)p_+ - f_{-+}(p_+,p_-)p_- \\ &\quad +v_-\partial_z p_- + d_-\partial_z^2 p_-. \end{aligned} \quad (53)$$

Then in the limit of slow and long-wavelength fluctuations, the transition rates close to the equilibrium state $(p_\pm(z,t) = p_\pm^* + \triangle p_\pm(z,t))$ can be expanded as:

$$f_{\pm\mp}(p_+,p_-) \sim f_{\pm\mp}^0 + f'^{+}_{\pm\mp}\triangle p_+ + f'^{-}_{\pm\mp}\triangle p_-, \quad (54)$$

where $f_{\pm\mp}^0 \equiv f_{\pm\mp}(p_+^*,p_-^*)$, $f'^{+}_{\pm\mp} \equiv \partial_{p_+^*}f_{\pm\mp}$, and $f'^{-}_{\pm\mp} \equiv \partial_{p_-^*}f_{\pm\mp}$. In this case, the evolution dynamic can be described as:

$$\begin{aligned} \partial_t\triangle p_+(z,t) = &- (f_{+-}^0 + f'^{+}_{+-}\triangle p_+^* + f'^{-}_{+-}\triangle p_-^*)(p_+^* + \triangle p_+) \\ &+ (f_{-+}^0 + f'^{+}_{-+}\triangle p_+^* + f'^{-}_{-+}\triangle p_-^*)(p_-^* + \triangle p_-) \\ &- v_+\partial_z\triangle p_+ + d_+\partial_z^2\triangle p_+, \\ \partial_t\triangle p_-(z,t) = &+ (f_{+-}^0 + f'^{+}_{+-}\triangle p_+^* + f'^{-}_{+-}\triangle p_-^*)(p_+^* + \triangle p_+) \\ &- (f_{-+}^0 + f'^{+}_{-+}\triangle p_+^* + f'^{-}_{-+}\triangle p_-^*)(p_-^* + \triangle p_-) \\ &+ v_-\partial_z\triangle p_- + d_-\partial_z^2\triangle p_-. \end{aligned} \quad (55)$$

Notice that $f_{+-}^0p_+^* - f_{-+}^0p_-^* = 0$, so the above equations can be simplified as:

$$\partial_t\triangle p_+(z,t) = -\ (f_{+-}^0 + f'^{+}_{+-}p_+^* - f'^{+}_{-+}p_-^*)\triangle p_+$$

$$
\begin{aligned}
&+ \ (f^0_{-+} + f'^{-}_{-+}p^*_- - f'^{-}_{+-}p^*_+)\triangle p_- \\
&- \ v_+\partial_z\triangle p_+ + d_+\partial_z^2\triangle p_+, \\
\partial_t\triangle p_-(z,t) = &+ \ (f^0_{+-} + f'^{+}_{+-}p^*_+ - f'^{+}_{-+}p^*_-)\triangle p_+ \\
&- \ (f^0_{-+} + f'^{-}_{-+}p^*_- - f'^{-}_{+-}p^*_+)\triangle p_- \\
&+ \ v_-\partial_z\triangle p_- + d_-\partial_z^2\triangle p_-. \qquad (56)
\end{aligned}
$$

Obviously, in this model:

$$
\begin{aligned}
f^{eff}_{+-} &= f^0_{+-} + f'^{+}_{+-}p^*_+ - f'^{+}_{-+}p^*_-, \\
f^{eff}_{-+} &= f^0_{-+} + f'^{-}_{-+}p^*_- - f'^{-}_{+-}p^*_+. \qquad (57)
\end{aligned}
$$

Let's construct $f_{\pm\mp}(p_+, p_-)$ in the following structure:

$$
\begin{aligned}
f_{+-}(p_+, p_-) &= \alpha_1 \times \frac{K^n_{11}}{p^n_+ + K^n_{11}} \times \frac{K^n_{12}}{p^n_- + K^n_{12}}, \\
f_{-+}(p_+, p_-) &= \alpha_2 \times \frac{p^n_+}{p^n_+ + K^n_{21}} \times \frac{p^n_-}{p^n_- + K^n_{22}}. \qquad (58)
\end{aligned}
$$

This kinetics is chosen because many biological processes proceed under cooperative Hill dynamics. Moreover, this mathematical structure automatically satisfies the conditions of $f'^{+}_{+-} < 0$, $f'^{+}_{-+} > 0$, $f'^{-}_{-+} > 0$, and $f'^{-}_{+-} < 0$, which lead to more likely chances of $f^{eff}_{+-} \cdot f^{eff}_{-+} < 0$. I'll further explain in Discussion why this mathematical requirement tends to generate oscillatory behavior.

In practice, let's start with a simplified version:

$$
\begin{aligned}
f_{+-}(p_+, p_-) &= \alpha_1 \times \frac{K^2}{p^2_+ + K^2} \times \frac{K^2}{p^2_- + K^2}, \\
f_{-+}(p_+, p_-) &= \alpha_2 \times \frac{p^2_+}{p^2_+ + K^2} \times \frac{p^2_-}{p^2_- + K^2}. \qquad (59)
\end{aligned}
$$

The Hill index is chosen as $n = 2$ because I want the reaction to have "switch" sensitivity in some degree yet being convenient for mathematical analysis. The half-saturation coefficients are set as identical to reduce parameter dimensions as well as make calculation easier.

At steady state, we have:

$$
p^*_+ = \frac{f^0_{-+}}{f^0_{+-} + f^0_{-+}}, \ p^*_- = \frac{f^0_{+-}}{f^0_{+-} + f^0_{-+}}. \qquad (60)
$$

Tracing back to Eq.(59), we got the constrain conditions for α_1, α_2 and K:

$$
\begin{aligned}
f^0_{+-} &= \frac{\alpha_1}{\left[\frac{1}{K^2}\left(\frac{f^0_{-+}}{f^0_{+-}+f^0_{-+}}\right)^2 + 1\right]\left[\frac{1}{K^2}\left(\frac{f^0_{+-}}{f^0_{+-}+f^0_{-+}}\right)^2 + 1\right]}, \\
f^0_{-+} &= \frac{\alpha_2}{\left[K^2\left(\frac{f^0_{+-}+f^0_{-+}}{f^0_{-+}}\right)^2 + 1\right]\left[K^2\left(\frac{f^0_{+-}+f^0_{-+}}{f^0_{+-}}\right)^2 + 1\right]}; \\
&\qquad (61)
\end{aligned}
$$

Hence, for a given set of $f^0_{\pm\mp}$ and K, we can obtain the corresponding α_1 and α_2. We can also compute four partial derivatives at steady state:

$$
\begin{aligned}
f'^{+}_{+-} &= -\frac{2f^0_{+-}}{p^*_+[(K/p^*_+)^2 + 1]}, \\
f'^{-}_{+-} &= -\frac{2f^0_{+-}}{p^*_-[(K/p^*_-)^2 + 1]}, \\
f'^{+}_{-+} &= +\frac{2f^0_{-+}}{p^*_+[(p^*_+/K)^2 + 1]}, \\
f'^{-}_{-+} &= +\frac{2f^0_{-+}}{p^*_-[(p^*_-/K)^2 + 1]}. \qquad (62)
\end{aligned}
$$

Retrospecting Eq.(57), we can use Eq.(62) to derive:

$$
\begin{aligned}
f^{eff}_{+-} &= f^0_{+-} - \frac{2f^0_{+-}}{(K/p^*_+)^2 + 1} - \frac{2f^0_{+-}}{(p^*_+/K)^2 + 1} \\
&= -f^0_{+-}, \\
f^{eff}_{-+} &= f^0_{-+} + \frac{2f^0_{-+}}{(K/p^*_-)^2 + 1} + \frac{2f^0_{-+}}{(p^*_-/K)^2 + 1} \\
&= 3f^0_{-+}. \qquad (63)
\end{aligned}
$$

Since the perturbing equations in Eq.(56) are linear, the spacial-temporal Fourier transformation into orthorhombic modes in Eq.(2) still works, thus the eigenvalue analyses in Model Ⅲ are still applicable. Therefore, we are able to replace $f_{\pm\mp}$ in Eq.(46) with $f^{eff}_{\pm\mp}$ calculated in Eq.(63):

$$
\begin{aligned}
c_1 &= \frac{1}{(f_{+-} + f_{-+})^4} \times \left[f_{+-}f_{-+}(v_+ + v_-)^2\right. \\
&+ \left.(f_{+-}d_- + f_{-+}d_+)(f_{+-} + f_{-+})^2\right] \\
&= \frac{1}{(3f^0_{-+} - f^0_{+-})^4} \times \left[-3f^0_{+-}f^0_{-+}(v_+ + v_-)^2\right. \\
&+ \left.(-f^0_{+-}d_- + 3f^0_{-+}d_+)(3f^0_{-+} - f^0_{+-})^2\right]. \qquad (64)
\end{aligned}
$$

Typical values of parameters for MTs growing in a tubulin solution of concentration $c \approx 10\mu M$ are $v_+ \approx 2\mu m/min$, $v_- \approx 20\mu m/min$, $f^0_{+-} \approx 0.004s^{-1}$, $f^0_{-+} \approx 0.05s^{-1}$.

As the drift and diffusion in master equations originates from state-transition flux:

$$
v(z) \equiv \int dyyR(y,z), \qquad (65)
$$

$$
d(z) \equiv \frac{1}{2}\int dyy^2R(y,z). \qquad (66)
$$

For MTs, R can be evaluated as $R(y) \sim \frac{v}{s}\delta(y - s)$, where s is the length scale of a MT monomer ($\approx 5nm$); therefore, $d \sim \frac{sv}{2}$, i.e., $d_+ \approx 0.005\mu m^2/min$, and $d_- \approx 0.05\mu m^2/min$.

With those experimental values, we can numerically solve $c_1 = -0.177\mu m^2$ (via Eq.(64)). We finally found a theoretically spontaneous-oscillatory model with a negative c_1!

SIMULATION

Here we only play with dynamics with infinite number of monomers. In this case, the dynamics can be simulated directly with 2-dimension Master equations as described in previous models (Eq.(1), (24), (49), & (53)). The lengths of MTs are discretized to a step length of $\Delta z = 50nm$, spanning from $z_{min} = \Delta z$ ('monomers') to $z_{max} = 50\mu m$. The drift and diffusion rates of change of the probabilities are evaluated as:

$$\frac{\partial p(z,t)}{\partial z} = \frac{p(z+\Delta z,t) - p(z-\Delta z,t)}{2\Delta z} \tag{67}$$

$$\frac{\partial^2 p(z,t)}{\partial z^2} = \frac{p(z+\Delta z,t) + p(z-\Delta z,t) - 2p(z,t)}{\Delta z^2} \tag{68}$$

respectively. To satisfy no-flux boundary conditions, we imaginarily assume there is a probability at $z_l = z_{min} - \Delta z$ with the value $p(z_l,t) = p(z_{min},t)$ as well as a probability at $z_u = z_{max} + \Delta z$ with the value $p(z_u,t) = p(z_{max},t)$ when calculating the first and second order spacial derivatives at boundaries.

For Model $\mathbb{I}$, the parameters are set as typical values under concentration of $c \approx 10\mu M$. For Model $\mathbb{II}$, the additional diffusion coefficients are set as $d_+ \approx 0.005\mu m^2/min$ and $d_- \approx 0.05\mu m^2/min$. For Model $\mathbb{III}$, the additional pair transferring rate is set as $r = 1s^{-1}$. For Model $\mathbb{IV}$, the additional half saturation is set as $K = 0.2$, thus the corresponding maximum rates are $\alpha_1 = 0.102s^{-1}$ and $\alpha_2 = 0.434s^{-1}$ (refer to the constrain relation in Eq.(61)). For Model $\mathbb{I}$, $\mathbb{II}$, & $\mathbb{III}$, simulations initiate from $p_+(z_{min},0) = 1$, progressing with a time step of $\Delta t = 10^{-3}$ and lasting for $5000s$. For Model $\mathbb{IV}$, simulation initiates from the perturbation around the steady state for each independent z: $p_\pm(z,0) = p^*_\pm + noise$ (Note that the overall 'probability' in this case should be conserved to $\frac{z_{max}}{\Delta z}$ rather than 1; Otherwise, the magnitude of K would not match to the steady-state analysis where the probability for each independent z is conserved to 1).

To avoid significant accumulation of numerical residual in the long run, the probability is re-normalized after each step.

RESULTS

In FIG. 1, the time evolution of average length for different models are shown. As we can see, after adding the diffusion term, the average length propagates faster towards the steady state. It seems that Model $\mathbb{IV}$ didn't generate oscillation in terms of the mean length, but I will show later that such a flat line actually consists of many oscillatory components of independent lengths with different phase.

FIG. 2 shows Model $\mathbb{II}$'s dispersion of length distribution against time. This figure presents in concert with our theoretical deduction that only the uniformly distributed state can finally survive, in which MTs of different length share the same probability of existence.

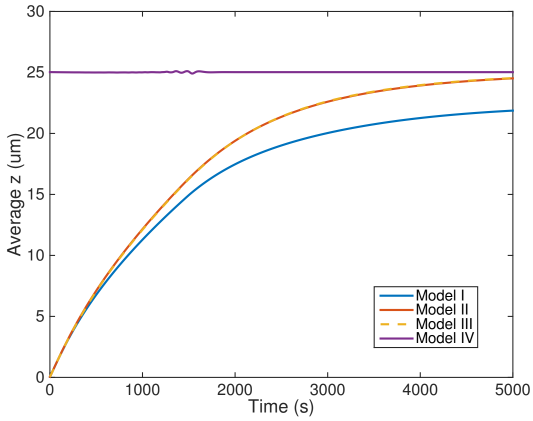

FIG. 1: Time evolution of mean length of different models.

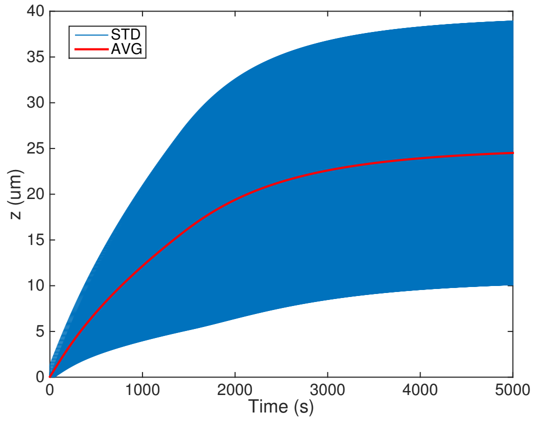

FIG. 2: Dispersion of length distribution of Model $\mathbb{II}$.

FIG. 3 directly justifies Model $\mathbb{IV}$'s capability of generating oscillation. As we can see, the shorter filaments stop oscillating quicker than the longer ones. Additionally, the phases of components of very different lengths seem to be decoupled.

In FIG 4, the global spatio-temporal oscillatory behavior of Model $\mathbb{IV}$ is clearly presented. By mentioning 'spatio-', I refer to the probability distribution of different length here. If we look horizontally, the probability of existence of MTs of any fixed length oscillates against time. If we look vertically, the probability of existence of MTs of different length varies periodically at any fixed time. Therefore, Model $\mathbb{IV}$ successfully generates spatio-temporal periodic distribution of MTs' length, which indicates that MTs act periodic increase and decrease spontaneously without any change of global kinetic parameters.

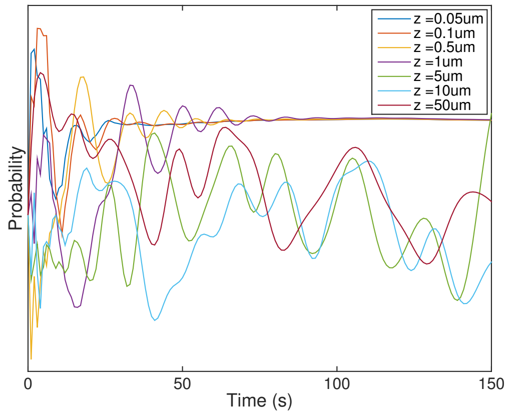

FIG. 3: Trajectories of probability against time of typical lengths in Model 𝕀𝕍.

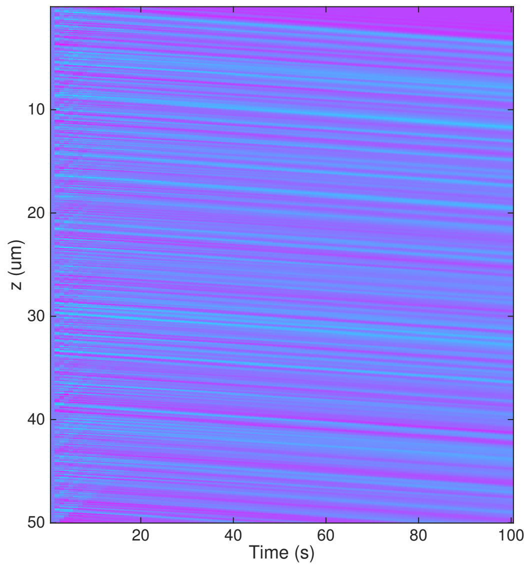

FIG. 4: Spatio-temporal oscillatory pattern of Model 𝕀𝕍. The probability is color-coded, with magenta being the maximum and cyan being the minimum.

DISCUSSION

Topologically speaking, the cross inhibition between two dynamical nodes is a necessity regards linear instability, and it turns out that only two regulatory networks are capable for pattern formation in the two-variable scheme[7]. These two topologies are demonstrated in FIG. 5, which indicates opposite signs between the top-right and bottom-left matrix elements in the Jacobian determinant.

Frankly, Model 𝕀𝕍 is only able to hold the oscillation for the first several hundred seconds and the amplitudes

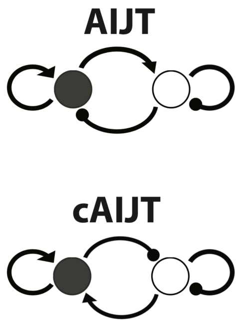

FIG. 5: Two-dimensional Jacobian topologies that are capable for oscillatory behavior. AIJT: Activator-Inhibitor Jacobian Topology; cAIJT: cross Activator-Inhibitor Jacobian Topology.

are weak, this is because it is a linear model and the solidity of linear instability analysis holds only when the system gets very close to the initial steady state at the very beginning. As can be seen from FIG. 4, another spatial uniform mode is spreading from the z^- direction (note the increasing megenta region in the top-right corner of the figure): this argument can be further supported by FIG. 3, where the panels of shorter length lost their oscillatory behavior faster. This problem might be solved by adding some proper nonlinear decay terms in the equations, or we can mathematically make up a $f_{\pm\mp}(p_+, p_-)$ that assure the unique fixed point within the interval of $p_+, p_- \in [0, 1]$.

To summarize, this paper analytically denied the chances of oscillatory behavior for the continuum model introduced in class (Model 𝕀 & 𝕀𝕀), and then investigated two ways of modification upon the reaction part of the master equations (Model 𝕀𝕀𝕀 & 𝕀𝕍), where Model 𝕀𝕍 is able to lead to the oscillatory behavior around the steady state under long-wavelength limitation. More models can also be designed to act as oscillators with the similar numerical requirements, which are equivalent to allowing the distribution of different components to undergo periodic changes.

[1] Dogterom, M. and Leibler, S., *Phys. Rev. Lett.* 70(9),1347 (1993).
[2] Lecture notes of *Statistic Physics in Biology*: 3.1, (2016).
[3] H. Flyvbjerg, T.E. Holy, and S. Leibler, *Phys. Rev. Lett.* 73, 2372 (1994).
[4] Buzski, Gyrgy, and Andreas Draguhn, *Science*. 304.5679 (2004).
[5] Rust Michael J., *et al.*, Science 318.5851 (2007).
[6] Elowitz, Michael B., and Stanislas Leibler. *Nature*, 403.6767 (2000).
[7] Zheng, M. M., Shao, B., & Ouyang, Q. *Journal of theoretical biology*, 408, 88-96 (2016).