CONTINUOUS MODEL FOR MICROTUBULE DYNAMIC INSTABILITY WITH PAUSING

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OBJECTIVES

- Develop and simulate a model for MT dynamics to describe growth, shortening and pause..
- Determine how variations in model parameters, the initial tubulin concentration, and the pausing rate, can alter the parameters that empirically describe MT dynamics (catastrophe frequencies with respect to distance and time).
- Determine the amount of time a MT spends in each of the growing, shortening, and pausing states.

INTRODUCTION

Microtubules (MTs) are protein polymers found in all eukaryotic cells. Made up of protein heterodimers. MTs are important in the sense that:

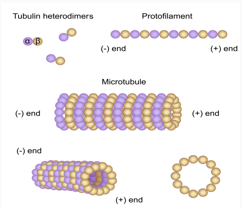

Figure 1: Structure of the Microtubule

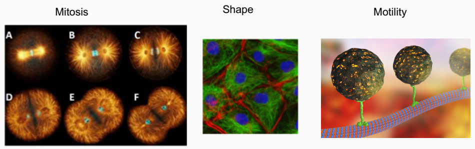

Figure 2: Functions of the Microtubule (MT)

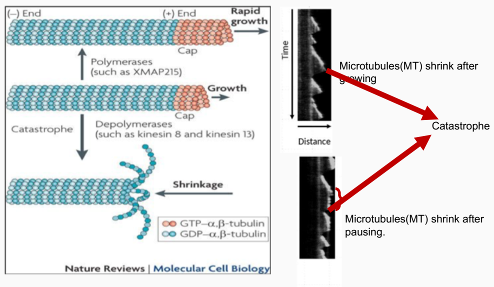

Figure 3: Dynamic instability of Microtubules(MT)

MODEL

Polymerized tubulin

- $u(x,z,t)$: Density of growing MTs of length x and cap size z at time t.
- $v(x,t)$: Density of shrinking of MTs of length x at time t.
- $Q(x^*,z,t)$: Density of pausing MTs of length x^* and cap size z at time time t.

Free tubulin

- $p(t)$: Concentration of GTP(Guanosine triphosphate) tubulin.
- $q(t)$: Concentration of GDP(Guanosine diphosphate) tubulin.

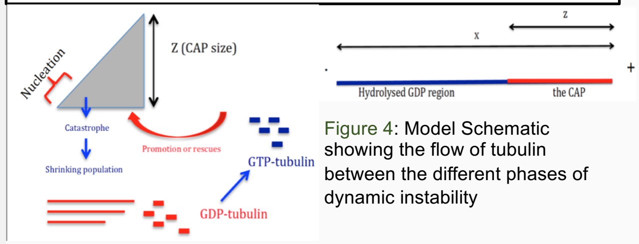

Figure 4: Model Schematic showing the flow of tubulin between the different phases of dynamic instability

Model Equations

$$\frac{\partial u(x,z,t)}{\partial t}+\underbrace{\gamma^{poly}(p(t))\frac{\partial u(x,z,t)}{\partial x}}_{\text{MT growth dependent on GTP}}+\underbrace{(\gamma^{poly}(p(t))-\gamma^{h})\frac{\partial u(x,z,t)}{\partial z}}_{\text{Change in cap size}}=\underbrace{-cu}_{\text{MTs leave to enter pause state}}$$

$$R(t) = \gamma^{p}-\gamma^{h}$$

$$\frac{\partial v(x,t)}{\partial t}-\underbrace{\delta\frac{\partial v}{\partial x}}_{\text{MT shortening}}=-\begin{cases}\lambda v(x,t) & \text{if } R(t)>0 \text{ cap grows}\\ R(t)u(x,0,t) & \text{if } R(t)<0 \text{ cap shrinks}\end{cases}$$

$$\frac{\partial Q(x^*,z,t)}{\partial t}-\underbrace{\gamma^{h}\frac{\partial Q(x^*,z,t)}{\partial z}}_{\text{cap shortening}}=\underbrace{cu}_{\text{MTs enter pausing state}}$$

$$\frac{dp}{dt}=\underbrace{-\gamma^{p}(p(t))\int_0^\infty\int_0^x u(x,z,t)\,dz\,dx}_{\text{loss due to MT growth}}-\underbrace{\mu p^n}_{\text{loss due to nucleation}}+\underbrace{\kappa q}_{\text{exchange from GDP}}$$

$$\frac{dq}{dt}=\underbrace{\delta\int_0^\infty v(x,t)\,dx}_{\text{Tubulin from shrinking MTs}}+\underbrace{\gamma^{h}\int_0^\infty Q(x,0,t)\,x\,dx}_{\text{Tubulin from paused MTs}}\underbrace{-\kappa q}_{\text{loss through pumping.}}$$

Boundary condtions

$u(x,z,0)=0$
$v(x,0)=0$
$Q(x,z,0)=0$

$p(0)=15\mu M$
$q(0)=0$

$$(\text{Tubulin in polymer form} + \text{free tubulin}) = \text{constant}.$$

Boundary Conditions:

Nucleation: $\gamma^{h}u(x,x,t)=\frac{H(p,p_N)\mu p^n\xi(x)}{L^*},\ \ H(p,p_N)=\frac{1}{2}(1+\tanh(c(p-p_N)))$.

Rescue: $R(t)u(x,0,t)=\lambda v(x,t),$ for $R(t)>0$

No flux condition for pausing MTs: $\left.\frac{\partial Q(x,z,t)}{\partial z}\right|_{z=x}=0.$

CONTACT

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RESULTS (CATASTROPHE FREQUENCY)

$$f_c^{time}=\frac{1}{N}\sum_{i=1}^{N}\frac{\int_{I_i}\frac{1}{T_{grow}(t)}\int_0^\infty u(x,0,t)\,dx\,dt}{\int_{I_i}\int_0^\infty u(x,0,t)\,dx\,dt}(\text{for } R(t)<0)\qquad f_c^{\text{pause}}=\frac{\int_0^{T_{\max}}\frac{1}{T_{\text{pause}}(t)}\int_0^\infty Q(x^*,0,t)\,dx^*dt}{\int_0^{T_{\max}}\int_0^\infty Q(x^*,0,t)\,dx^*dt}$$

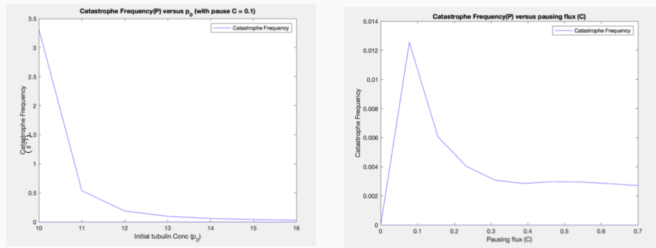

Figure 5: Catastrophe (w.r.t both pausing and growing times) decreases with initial concentration of tubulin and also decreases with the pausing rate.

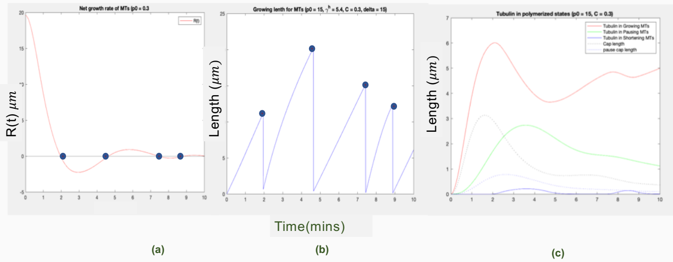

Figure 6: Peeks of the kymograph in (b) correspond to times at which R(t)=0 in (a). (c) shows tubulin in polymerized states

FUTURE WORK

- Reduce model complexity to study the corresponding ODEs which describe the the tubulin in each polymerized compartment and free tubulin (see ODE simulations in Fig. 6(c))
- Simulate the above ODE system to study the stability of the ODEs (identifying stable and/or unstable limit cycles, spirals, nodes)–
- Continue to study how variations in other model parameters affect growth rate and Catastrophe frequencies with respect to distance and compare these to experiments to provide insight into the mechanisms involved in MT pausing
- How much does the incorporation of the catastrophe component change the original catastrophe definition?

REFERENCES

- *Diana White et al.* Exploring the effect of end-binding proteins and microtubule targeting chemotherapy drugs on microtubule dynamic instability (2017)
- *Peter Hinow et al.* Continuous model for microtubule dynamics with catastrophe, rescue, and nucleation processes (2009)