Mathematical modeling of the microtubule dynamic instabilities.

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Collaborators

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Microtubules

A therapeutic target in oncology
- MTs play a crucial role in
  - cell division
  - cell migration
  - intracellular transport

- MTs are a favorite target of Microtubule Targeting Agents (MTAs)

- MTAs (taxanes, vinca alkaloids) are successfully used as antimitotic and antiangiogenic agent in cancer treatments but also in neurodegenerative diseases.

- MTs are highly dynamic.
  - The dynamics is complex
  - The dynamics is mandatory to cell division and cell migration.
The role of MTs

- Prometaphase and metaphase. MTs dynamics is increased.
  - Find and capture kinetochore.
  - Chromosome’s congression.

- Anaphase
  Stabilization of MTs
  - Chromosome’s separation.

Roles of MTAs

- Increase or reduction of the dynamics induce mitotic abnormalities and thus apoptosis.

http://www.wadsworth.org
Wikipedia
Growing of MTs induces activation of RAC. $\Rightarrow$ High RAC activity promotes the actine retrograd flow in the lamellipodium.

Shortening of MTs induces activation of RHO. $\Rightarrow$ Presence of RHO promotes contraction of stress fiber at the back of the cell.

MTAs and migration

MTAs reduce endothelial migration even at non-cytotoxic concentration.

$\Rightarrow$ Antiangiogenic effect at low dose.
Microtubules Targetting Agents

Mechanism of action

▶ Destabilizers (Vincristine/Vinblastine)
▶ Stabilizers (Taxol)

Main issues in presence of End Binding proteins (EBs)

▶ Much is known about the action of MTAs on MTs at high doses in the absence and presence of EBs.
▶ At low non-cytotoxic levels of MTAs, the dynamics of MTs depend on whether EBs are present.
▶ It has recently been discovered that EBs sensitize the action of MTAs on MT dynamics in vitro [2, 3] and in vivo [1, 2].

Objectives

Main issues of our collaboration

▸ To describe the dynamics thanks to a mathematical model at a microscopic level.
▸ Better understand the role of each reaction in the dynamics and their synergy.
▸ Better understand the mechanism of action of each family of MTAs.
▸ Better understand the role of EBs, especially in presence of low dose of MTAs.
Microtubule structure

MT in the cell

- MTs are part of the cytoskeleton.
- MTs are characterized by their instabilities.

Protein structure

- Each MT is a long (up to 50\(\mu\)m) hollow cylinder of 25nm diameter built from about 13 protofilaments.
- Each protofilament is composed by an assembly of $\alpha|\beta$ tubulin dimers.
- The assembly is polarized with different dynamics at the + end or - end.
Microtubules instabilities

Dynamics overview

- Phase of growing are followed by phases of sudden shortening called **catastrophe**.
- **Phases of catastrophe** are followed by phases of Rescue
Dynamics of one MT

Protein structure
- Each MT is a long (up to 50µm) hollow cylinder of 25nm diameter built from about 13 protofilaments.
- Each protofilament is composed by an assembly of $\alpha/\beta$ tubulin dimers.
- The assembly is polarized with different dynamics at the + end or - end.
  - + End (tubulin $\beta$): highly dynamic
  - − End (tubulin $\alpha$): link to centrosome in cells

Energetic structure
- Dimers can be in two energy states:
  - GTP: Guanosine triphosphate - active form
  - GDP: Guanosine diphosphate - inactive form
Dynamics of one MT at its + end

Dimers of tubulin
- Dimers can be in two energy states:
  - GTP: Guanosine triphosphate - active form
  - GDP: Guanosine diphosphate - inactive form
- Dimers can be polymerized or not. In fine,
  - GTP polymerized in MTs
  - GDP polymerized in MTs
  - Free GTP
  - Free GDP

- Thanks to EB-GFP fluorescent proteins that bind to GTP-tubulin, are observed
  - A GTP-stabilizing cap
  - The disparition of the cap at the catastrophe

- Four reactions
Deterministic mathematical models

A model of structured population

- Used to follow the mean behavior of a MTs family.

In vitro experiments $\rightsquigarrow$ indicators of the instabilities for the population

- Experiments in cell

$\rightsquigarrow$ MTs tracks captured thanks to PlusTipTracking or Icy software.

Indicators of the instability dynamics

- Growth lifetime, growth distance, growth speed
- Catastrophe frequencies (temporal or spacial)
- Shrinking lifetime, shrinking distance, shrinking rate
- Rescue frequencies (temporal or spacial)
Mathematical challenges

Improve Hinow & al 2009 approach

1. To be able to estimate correctly the indicators of the instability dynamics
2. To take into account aging of MTs.
   - This would enable us to model MTAs.
3. Better represent the depolymerization.
4. To take into account the influence of End Binding Protein (EB1 and EB3) on MTAs efficiency.
   - Fragmentation model.

MTs and migration

3. Take into account MT impact on cell migration.
The unknowns

1. \( u(t, z, x) \) density of MTs with a cap at time \( t \) with a length \( x \) and a cap of length \( z \).
   - Domain: \( \{(t, z, x) \text{ such that } t \geq 0, 0 \leq z \leq x\} \).
   - Boundaries:
     \[
     \begin{align*}
     \Gamma_{nucl} & = \{(t, z, x) \text{ such that } t \geq 0, 0 \leq z = x\} \\
     \Gamma_{cata} & = \{(t, z, x) \text{ such that } t \geq 0, 0 = z \leq x\} \\
     \Gamma_{init} & = \{(t, z, x) \text{ such that } t = 0, 0 \leq z \leq x\}
     \end{align*}
     \]

2. \( v(t, x) \) density of MT in depolymerization at time \( t \) with a length \( x \).
   - Domain: \( \{(t, x) \text{ such that } t \geq 0, 0 \leq x\} \).

3. \( p(t) \) free GTP tubulin available at time \( t \).

4. \( q(t) \) free GDP tubulin available at time \( t \).
Equation for $u$

\[
\partial_t u + (\gamma_{pol}(p(t)) - \gamma_{hydro}) \partial_z u + \gamma_{pol}(p(t)) \partial_x u = 0
\]

This equation reflects:

- Polymerization of MTs with a velocity $\gamma_{pol}$ depending on $p(t)$:

![Graph showing the relationship between $\gamma_{pol}(p)$ and $p$]

- Hydrolysis where $\gamma_{hydro}$ is assumed to be constant.
**Hinow & al 2009 approach**

**Equation for** \( u \)

\[
\partial_t u + \left( \gamma_{pol}(p(t)) - \gamma_{hydro} \right) \partial_z u + \gamma_{pol}(p(t)) \partial_x u = 0
\]

This equation reflects:

- Polymerization of MTs with a velocity \( \gamma_{pol} \) depending on \( p(t) \):
- Hydrolysis where \( \gamma_{hydro} \) is assumed to be constant.

**Boundary conditions for** \( u \)

- On \( \Gamma_{nucl} \), The sign of the entrance flux \( B \cdot \begin{pmatrix} -1 \\ 1 \end{pmatrix} = \gamma_{hydro} > 0 \) is positive
  \[ u(t, x, x) = \mu \Psi(x)p(t)^2. \]

- On \( \Gamma_{cata} \), the sign of the entrance flux \( B \cdot \begin{pmatrix} 0 \\ 1 \end{pmatrix} := R(t) \) depends on the sign of \( R(t) = \gamma_{pol}(p(t)) - \gamma_{hydro} \)
  \[ R(t)u(t, 0, x) = \lambda v(t, x) \text{ if } R(t) > 0 \text{ (Rescue)} \]
Hinow & al 2009 approach

Equation for $u$

$$\partial_t u + \gamma_{pol}(p(t)) \partial_x u + (\gamma_{pol}(p(t)) - \gamma_{hydro}) \partial_z u = 0$$

Equation for $v$

$$\partial_t v - \gamma_{depol} \partial_x v = -\lambda v(R(t) > 0) + R(t)^- u(t, 0, x) = -R(t)u(t, 0, x)$$

- Depolymerization of MTs with a velocity $\gamma_{depol}$ assumed to be constant.
- Catastrophe/Rescue events

Equation for $p$

$$\frac{d}{dt} p = -\gamma_{pol}(p(t)) \int_{0}^{\infty} \int_{0}^{x} u(t, z, x) \, dz \, dx + \kappa q - \mu p^2$$

Equation for $q$

$$\frac{d}{dt} q = \gamma_{depol} \int_{0}^{\infty} v(t, x) \, dx - \kappa q$$
Hinow & al 2009 approach

Conservation of total tubulin

\[
\frac{d}{dt} (L_u(t) + L_v(t) + p(t) + q(t)) = 0
\]

where

- Total length of MTs with cap: \( L_u(t) = \int_0^\infty \int_0^x xu(t, z, x)dz \, dx \)
- Total length of MTs in depol: \( L_v(t) = \int_0^\infty xv(t, x)dz \, dx \)
Aging of MTs

Frequency of catastrophe in vitro increases with age of MT

Gardner & al, Cell 2011

Kymograph of a MT

Visualization of time evolution of the cap of a MT marked thanks to EB protein.

- Stable growth speed away from catastrophe
- Presence of alterations in the cap (all the more evident in presence of MTAs)
  - Change the profile of $\gamma_{hydro}$.

Assumption (A new approach of hydrolysis)

- MTs undergo degradations that stimulates hydrolysis.
  - $\gamma_{hydro}$ may depend on an age of MT.
- Existence of a delay between incorporation in MT and hydrolysis (decoration time).
**A new model of MT instabilities**

A. Barlukova PhD work

### MTs in polymerization

- **Density of the population of MT in polymerization** $u = u(t, a, z, x)$
  - $t$ time, $a$ age, $x$ length, $z$ length of the cap.
- **Density of the population of MT in depolymerization** $v = v(t, a, x)$
  - $t$ time, $a$ age, $x$ length.
- **Amount of Free GTP tubulin** $p = p(t)$
- **Amount of Free GDP tubulin** $q = q(t)$
A new model of MT instabilities

Balance equation for MT in Polymerization $u$

\[
\partial_t u + (\gamma_{pol}(p(t)) - \gamma_{hydro}(a)) \partial_z u + \gamma_{pol}(p(t)) \partial_x u + 1 \times \partial_a u = 0
\]

**Boundary conditions for $u$**

- **Nucleation**, 
  \[u(t, a, x, x) = \psi(x)\Psi(a)\mathcal{N}(p(t)).\]

- **Rescue event**, if the entrance flux 
  \[R(t, a) = \gamma_{pol}(p(t)) - \gamma_{hydro}(a) > 0\]

  \[R(t, a)u(t, a, 0, x) = \lambda\Theta(a) \int_0^{+\infty} (a' > a_{res})v(t, a') \, da'\]

- **Age boundary** 
  \[u(t, 0, z, x) = 0\]
A new model of MT instabilities

Equation for MT in depolymerization $v$

\[
\frac{\partial_t v}{\partial x} - \gamma_{\text{depol}} \frac{\partial_x v}{\partial x} + \partial_a u = I_{u\rightarrow v} - I_{v\rightarrow u}
\]

Depolymerization

where

\[
I_{v\rightarrow u} = \lambda (a > a_{\text{res}}) v(t, a, x)
\]

Rescue event

\[
I_{u\rightarrow v} = \Theta(a) \int_0^{+\infty} R(t, a') \cdot u(t, a', 0, x) \, da'
\]

Catastrophe event
A new model of MT instabilities

A. Barlukova PhD work

Equation for free GTP $p$

$$\frac{d}{dt} p = -\gamma_{pol}(p(t)) \int_{0}^{\infty} \int_{0}^{x} \int_{0}^{\infty} u(t, a, z, x) \, da \, dz \, dx + \kappa q - \mu \mathcal{N}(p)$$

- Recycling
- Nucleation

Equation for free GDP $q$

$$\frac{d}{dt} q = \gamma_{depol} \int_{0}^{\infty} \int_{0}^{\infty} v(t, a, x) \, da \, dx - \kappa q$$

- Recycling
- Depolymerization
Properties of the new model

Conservation of total tubulin

\[
\frac{d}{dt} (L_u(t) + L_v(t) + p(t) + q(t)) = 0
\]

where

- Total length of MTs with cap: \( L_u(t) = \int_0^\infty \int_0^x \int_0^\infty xu(t, a, z, x) da dz dx \)
- Total length of MTs in depol: \( L_v(t) = \int_0^\infty \int_0^\infty xv(t, a, x) da dx \)
In silico indicators of dynamics

Frequency of catastrophe

\[
F_{cat}^{\text{temp}}(t) = \frac{\int_0^\infty \int_0^\infty \chi \frac{1}{a} u(t, a, 0, x) \, da \, dx}{\int_0^\infty \int_0^\infty \chi u(t, a, 0, x) \, da \, dx}, \quad F_{cat}^{\text{spa}}(t) = \frac{\int_0^\infty \int_0^\infty \chi \frac{1}{x} u(t, a, 0, x) \, da \, dx}{\int_0^\infty \int_0^\infty \chi u(t, a, 0, x) \, da \, dx},
\]

\[x_a = \int_0^a \gamma_{pol}(p(t - a + s)) \, ds, \quad \chi = (R(t, a, x, 0) < 0)\]

Frequency of rescue

\[
F_{res}^{\text{temp}} = \frac{\int_0^\infty \int_0^\infty \frac{1}{a} v(t, a, x) \, da \, dx}{\int_0^\infty \int_0^\infty v(t, a, x) \, da \, dx}, \quad F_{res}^{\text{spa}} = F_{res}^{\text{temp}} \gamma_{\text{depol}}
\]

Mean size of the cap and Decoration time

\[
L_{\text{cap}}^{av}(t) = \frac{\int_0^\infty \int_0^x \int_0^\infty z u(t, a, z, x) \, da \, dz \, dx}{\int_0^\infty \int_0^x \int_0^\infty u(t, a, z, x) \, da \, dz \, dx}, \quad T_{\text{deco}}(t) = \frac{L_{\text{cap}}^{av}(t)}{\gamma_{pol}(p(t))}
\]
Numerical approximation

- Explicit Euler scheme in $t$
- Finite volume approach in $z, x$
- Semi-lagrangian in $a$
- Suitable approximation of integral terms to preserve tubulin at the discrete level.
How to calibrate parameters?

$\alpha_{pol}, p_c, p_s, a_c, a_s, \gamma_{hydro}^{young}, \gamma_{hydro}^{new}, \gamma_{depol}, \lambda, a_{res}, \kappa, \mu$

**Observed data**

- Minimal concentration of tubulin required for polymerization $\sim p_c = 2$
- Mean growth speed $\gamma_{pol}(p^\infty) \sim$ mean value of $\sim \gamma_{hydro}$
- Mean shortening speed $\sim \gamma_{depol}$
- On kymograph $\sim a_s, \gamma_{hydro}^{young}, \gamma_{hydro}^{new}$
- Decoration time $\sim a_c$
- Frequence of catastrophe (temporal or spacial)
- Frequence of rescue (temporal or spacial)
- Mean size of the cap

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<table>
<thead>
<tr>
<th></th>
<th>Growth rate (µm/min)</th>
<th>Shortening rate (µm/min)</th>
<th>Catastrophe rate (per min)</th>
<th>Rescue rate (per min)</th>
<th>Catastrophe Fr. (per µm)</th>
<th>Rescue Fr. (per µm)</th>
<th>N (MTs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>3.87 ± 1.00</td>
<td>19.09 ± 16.03</td>
<td>1.72 ± 0.12</td>
<td>2.12 ± 0.29</td>
<td>0.47 ± 0.03</td>
<td>0.12 ± 0.01</td>
<td>62</td>
</tr>
<tr>
<td>Patupilone 1 nM</td>
<td>3.47 ± 0.71</td>
<td>36.36 ± 23.44</td>
<td>1.60 ± 0.12</td>
<td>4.03 ± 0.47</td>
<td>0.47 ± 0.03</td>
<td>0.23 ± 0.02</td>
<td>55</td>
</tr>
<tr>
<td>Patupilone 10 nM</td>
<td>3.67 ± 1.16</td>
<td>21.04 ± 15.95</td>
<td>1.89 ± 0.14</td>
<td>3.44 ± 0.44</td>
<td>0.55 ± 0.04</td>
<td>0.19 ± 0.02</td>
<td>53</td>
</tr>
<tr>
<td>Patupilone 100 nM</td>
<td>2.92 ± 1.42</td>
<td>17.93 ± 12.86</td>
<td>2.07 ± 0.19</td>
<td>3.46 ± 0.58</td>
<td>0.85 ± 0.08</td>
<td>0.22 ± 0.03</td>
<td>30</td>
</tr>
<tr>
<td>Paclitaxel 1 nM</td>
<td>4.13 ± 1.47</td>
<td>17.87 ± 11.24</td>
<td>2.10 ± 0.17</td>
<td>3.79 ± 0.49</td>
<td>0.58 ± 0.04</td>
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<td>Paclitaxel 10 nM</td>
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<td>0.58 ± 0.045</td>
<td>0.33 ± 0.03</td>
<td>38</td>
</tr>
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<td>Paclitaxel 100 nM</td>
<td>5.99 ± 1.54</td>
<td>28.12 ± 25.85</td>
<td>2.96 ± 0.19</td>
<td>4.57 ± 0.50</td>
<td>0.50 ± 0.033</td>
<td>0.18 ± 0.02</td>
<td>50</td>
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</table>
Numerical output of the model

The control test of Pagano & al, 2012

<table>
<thead>
<tr>
<th>Parameter</th>
<th>$p_c$</th>
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<th>$\alpha_{pol}$</th>
<th>$a_c$</th>
<th>$a_s$</th>
<th>$\delta a$</th>
<th>$\gamma_{young}^{hydro}$</th>
<th>$\gamma_{old}^{hydro}$</th>
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<tr>
<td>Values</td>
<td>2</td>
<td>15</td>
<td>32</td>
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<td>In silico</td>
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<td>19 (= $\delta$, fixed)</td>
<td>1.88</td>
<td>0.58</td>
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Global behaviour

In silico kymograph
Numerical output of the model

A. Barlukova PHD work

The control test of Pagano & al, 2012

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Temporal freq of cata  
Spacial freq of cata  
Decoration time
Impact of MTAs: biological data

Destabilizers (Vincristine/Vinblastine)

- Decrease the growth rate and shrinking rate
- Increase rescue frequencies

Florence HUBERT
December 6th 2016
**Stabilizers (Taxol)**

- Decrease growth and shrinking rate
- Decrease rescue frequencies
- Non monotonous behaviour wrt concentration

Derry & al (1995)
Impact of MTAs: biological data

Stabilizers (Taxol)

- Increase growth and shrinking rate
- Increase catastrophe and rescue frequencies
- Non monotonous of the rescue frequency behaviour wrt concentration

with EBs

Pagano & al (2012)
Impact of MTAs: output of the model

Parameter sensibility

Hydrolysis

Influence of $\gamma_{\text{hydro}}$

$a_c = 0.05$, $\gamma_{\text{hydro}}^{\text{old}} = 10.3$

Influence of $a_c$

Ayuna Barlukova PHD work

$\gamma_{\text{hydro}}$ regulates
- $\gamma_{\text{pol}}$
- $a_c$ regulates both
  - $\gamma_{\text{pol}}$
  - $f_{\text{temp}}$
  - $f_{\text{cat}}$
Impact of MTAs: output of the model

Parameter sensibility

Two fundamental parameters: $\gamma_{depol}$ and $a_{res}$

- Influence of $\gamma_{depol}$
- Influence of $a_{res}$

Ayuna Barlukova PHD work

Influence of $\gamma_{depol}$

- Item $\gamma_{depol}$ regulates
  - $f_{temp}$

Influence of $a_{res}$

- $a_{res}$ regulates
  - $f_{temp}$
Impact of MTAs: output of the model

Parameter sensibility

Toward a drug effect: synergy of the parameters

\[ \gamma_{\text{depol}} + a_{\text{res}} \]

\[ \gamma_{\text{depol}} + a_c \]

\[ \gamma_{\text{depol}} + a_c + a_{\text{res}} \]

\[ \sim \sim \text{Taxol effect without EBs} \]

Ayuna Barlukova PHD work
Fragmentation models

To better modelize sudden depolymerization

\[
\partial_t v - \gamma_{\text{depol}} \partial_x v = -R(t)u(t, 0, x)
\]

\[
-\gamma_{\text{depol}} \partial_x v \sim -\gamma_{\text{depol}} \int_0^x k(x, \tilde{x}) v(t, x) \, d\tilde{x} + \gamma_{\text{depol}} \int_x^\infty k(\tilde{x}, x) v(t, \tilde{x}) \, d\tilde{x}
\]

\[
\sim k(x, \tilde{x}) : \text{probability for a MT of size } x \text{ to reach the size } \tilde{x} < x
\]

work with D. White, M. Tournus
Fragmentation models

Shape of the fragmentation kernel: observations from kymograph

\[
k(x, \tilde{x}) = \frac{1}{\sigma \sqrt{2\pi}} e^{-\frac{(x-\tilde{x}-x_0)^2}{2\sigma^2}} \text{ if } x < \tilde{x}
\]

\[
k(x, \tilde{x}) = K(\tilde{x}) = \text{Cte} \text{ if } x > x_0
\]
Fragmentation models

Equation for $u$

$$\partial_t u + \gamma_{pol}(p(t))\partial_x u + (\gamma_{pol}(p(t)) - \gamma_{hydro})\partial_z u = 0$$

Equation for $v$

$$\partial_t v = -R(t)u(t, 0, x) - \gamma_{depol} \int_0^x k(x, \tilde{x})v(t, x) d\tilde{x} + \gamma_{depol} \int_x^\infty k(\tilde{x}, x)v(t, \tilde{x}) d\tilde{x}$$

Equation for $p$

$$\frac{d}{dt} p = -\gamma_{pol}(p(t)) \int_0^\infty \int_0^x u(t, z, x) dz dx + \kappa q - \mu p^2$$

Equation for $q$

$$\frac{d}{dt} q = \gamma_{depol} \int_0^\infty \int_0^x (x - \tilde{x})k(x, \tilde{x})v(t, x) d\tilde{x} dx - \kappa q$$
Consider only size dependance for $u : \sim u(t, x)$
- The model reduces to evolution of $u, p, q$

Model should nevertheless reflects
- The role of the balance between hydrolysis and growth rate.
  - $\gamma_{pol}(p(t)) < \gamma_{hydro} \Rightarrow$ period of catastrophe
  - $\gamma_{pol}(p(t)) > \gamma_{hydro} \Rightarrow$ period of rescue

We introduce a threshold $p_h$ such that $\gamma_{pol}(p_h) = \gamma_{hydro}$
- $p < p_h \Rightarrow$ period of catastrophe
- $p > p_h \Rightarrow$ period of rescue
Fragmentation models

\( \rightsquigarrow \) A simplified model

Equation for \( u \)

\[
\begin{align*}
\partial_t u + \gamma_{pol}(p(t)) \partial_x u &= \\
&= \psi(x)N(p(t)) \\
&- \gamma_{depol}(p(t) < p_h) \int_0^x k(x, \tilde{x}) u(t, x) \, d\tilde{x} \\
&+ \gamma_{depol}(p(t) < p_h) \int_x^\infty k(\tilde{x}, x) u(t, \tilde{x}) \, d\tilde{x}
\end{align*}
\]

Equation for \( p \)

\[
\frac{d}{dt} p = -\gamma_{pol}(p(t)) \int_0^\infty \int_0^x u(t, z, x) \, dz \, dx + \kappa q - \mu p^2
\]

Equation for \( q \)

\[
\frac{d}{dt} q = \gamma_{depol}(p(t) < p_h) \int_0^\infty \int_0^x (x - \tilde{x}) k(x, \tilde{x}) u(t, x) \, d\tilde{x} \, dx - \kappa q
\]
Role of EB proteins

Introduction of EB in the models

- Fragmentation model
  \[ \sim \text{The two populations } u(t, z, x), v(t, x). \]

\[ \begin{align*}
\partial_t u & = \gamma_{pol}(p(t)) \partial_x u + \left( \gamma_{pol}(p(t)) - \gamma_{hydro}(EB^b(t)) \right) \partial_z u = 0 \\
\partial_t v & = R(t) - u(t, 0, x) - \lambda_{EB}(R(t) > 0) v(t, x) \\
& \quad + \left( -v(t, x) \int_0^x k(x, \tilde{x}) d\tilde{x} + \int_x^{+\infty} k(\tilde{x}, x) v(t, \tilde{x}) d\tilde{x} \right) \\
p'(t) & = -\gamma_{pol}(p(t)) I_u(t) + \kappa q(t) - \mathcal{N}(p) \\
q'(t) & = -\kappa q(t) + \int_0^{+\infty} v(t, x) \int_0^x (x - \tilde{x}) k(x, \tilde{x}) d\tilde{x} dx
\end{align*} \]

- Proteins EB = modulation of hydrolysis:

\[ \frac{d}{dt} EB^b = -k_{off} EB^b(t) + k_{on}(u_{cap}(t))(EB^{tot} - EB^b) \]

and

\[ \gamma_{hydro}(EB(t)) = \gamma_1^h + \gamma_2^h EB^b(t), \gamma_{hydro}(EB(t)) = \lambda_1 + \lambda_2 EB^b(t), u_{cap}(t) = \int_0^{+\infty} \int_0^{+\infty} z u(t, z, x) dz dx \]
Role of EB proteins

In vitro findings

- In vitro, EBs are found to increase the catastrophe frequency
  
  Maurer et al., 2014, Mohan et al., 2013

- EBs also found to increase the growth rate of MTs.
- MT length found to be relatively unchanged
  
  Mohan et al., 2013

Output of the model

<table>
<thead>
<tr>
<th>EB concentration (nM)</th>
<th>0</th>
<th>25</th>
<th>50</th>
<th>75</th>
<th>100</th>
<th>125</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\gamma_{pol}$</td>
<td>3.54</td>
<td>3.67</td>
<td>3.76</td>
<td>3.83</td>
<td>3.88</td>
<td>3.94</td>
</tr>
<tr>
<td>$f_{temp}$</td>
<td>1.545</td>
<td>1.595</td>
<td>1.686</td>
<td>1.728</td>
<td>1.764</td>
<td>1.730</td>
</tr>
</tbody>
</table>
Conclusions and perspectives

MTas and aging model

⇒ Go further in the calibration of parameters. Confrontation of the model to a new serie of biological data.

A. Barlukova

Fragmentation model

⇒ Go further in the theoretical study of the model

⇒ asymptotic behaviour

M. Tournus

End binding proteins model

⇒ Go further in the study of the synergy between EB and MTAs.

⇒ Confrontation with a new serie of biological data.

D. White
Thank you very much
Consider a simplified case where MT are structured only by \( t, x \). Let

\[ \gamma_{pol}(t) \]

be the growth speed of MT at time \( t \).

\[ \mathcal{N}(t, x, x + dx) = \int_{x}^{x+dx} u(t, y) dy \sim dx \ u(t, x) \]

Conservation

\[ \mathcal{N}(t + dt, \hat{x}, \hat{x} + dx) = \mathcal{N}(t, x, x + dx) \]

with the new size at \( t + dt \)

\[ \hat{x} = x + \gamma_{pol}(t)dt \]

\[ \hat{x} + dx = x + dx + \gamma_{pol}(t)dt. \]

Thus

\[ dx \ u(t, x) = \left( x + dx - \hat{x} \right) u(t + dt, x + \gamma_{pol}(t)dt) \]

\[ = dx \left( u(t, x) + dt \left( \underbrace{u_t(t, x) + \gamma_{pol}(t)u_x(t, x)}_{=0} \right) \right) + \mathcal{O}(dt^2) \]

\[ = dx \left( u(t, x) + dt \gamma_{pol}(t)u_x(t, x) \right) + \mathcal{O}(dt^2) \]