Mathematical modeling of the microtubule dynamic instabilities.

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Séminaire du Laboratoire Jacques-Louis Lions

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Collaborators

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- Marie Petit (PhD student)
- Sarah Oddoux (Post-doct)
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.
MT instabilities and cell division

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.

Wikipedia

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

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

MTAs reduce endothelial migration even at non-cytotoxic concentration.

Antiangiogenic effect at low dose.
Microtubules Targetting Agents

Mechanism of action

- Destabilizers (Vincristine/Vinblastine)
  - Decrease the polymer mass
  - Decrease the growth rate
  - Increase catastrophe frequency

- Stabilizers (Taxol)
  - Increase the polymer mass
  - Stabilize MTs

Main issues in presence of 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 micorscosmic 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 µm) hollow cylinder of 25 nm diameter built from about 13 protofilaments.
- Each protofilament is composed by an assembly of α|β 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 α|β tubulin dimers.
- The assembly is polarized with different dynamics at the + end or - end.
  - + End (tubulin β) : highly dynamic
  - − End (tubulin α) : 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

- Biological observations obtained by the use of End Binding GTP proteins:
  - Existence of a GTP-stabilizing cap
  - Disparition of the cap at the catastrophe

- Four reactions
Dynamics of one MT at its + end

Polymerization
- Free GTP can be polymerized at the + end.
  - It creates a GTP stabilizing cap at the + end of the MT.
  - The velocity of polymerization is a increasing function of the free GTP available.

Hydrolysis
- GTP cap can be hydrolyzed into GDP.
  - This reaction induces shortening of the cap.
  - Aging of MTs plays a role in hydrolysis.

Depolymerization (Catastrophy)
- Once the cap is lost the MT depolymerizes suddenly.
  - Free GDP is reintroduced in the media.

Recycling
- Free GDP can be recycled into free GTP.
  - This free GTP is then available for polymerization.
  - Resumption of polymerization is called Rescue.
Some mathematical models

**Stochastic approach**

- Enable to reproduce the dynamics of one protofilament

  Hinow & al 2011

  Approach followed by C. Gomez.

  Possibility to take into account MTAs, EBs.

**Deterministic approach**

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

  Hinow & al 2009

  - Example in cell:
    
    Oddoux & al, Mean parameters obtain thanks to PlusTiptracking software

  - Example in vitro: oscillations observed.

    Petit & al, experiment in progress
Mathematical challenges

**Improve Hinow & al 2009 approach**

1. To be able to estimate correctly the macroscopic indicators of the dynamics as frequency of catastrophe, ...

2. To take into account *adging of MTs*.
   - This would enable us to model MTAs.

**MTs and migration**

3. Take into account MT impact on cell migration.
Hinow & al 2009 approach

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:
     \[
     \Gamma_{nucl} = \{(t, z, x) \text{ such that } t \geq 0, 0 \leq z = x\} \\
     \Gamma_{cata} = \{(t, z, x) \text{ such that } t \geq 0, 0 = z \leq x\} \\
     \Gamma_{init} = \{(t, z, x) \text{ such that } t = 0, 0 \leq z \leq x\}
     \]

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 $t$. 

Florence HUBERT
January 15th 2016
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.
Hinow & al 2009 approach

**Equation for \( u \)**

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

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 \( v \)**

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

This equation reflects:

- 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: \( L_v(t) = \int_0^\infty xv(t, x) \, dz \, dx \)
Adging of MTs

Frequence of catastrophe in vitro increases with age of MT

Gardner & al, Cell 2011

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

- Stable growth speed away from catastrophe
  \( \rightsquigarrow \) Change the profile of \( \gamma_{pol} \).

- Presence of alterations in the cap
  (all the more evident in presence of MTAs)
  \( \rightsquigarrow \) Change the profile of \( \gamma_{hydro} \).

Assumption (A new approach of hydrolysis)

- MTs undergo degradations that stimulates hydrolysis.
  \( \rightsquigarrow \) \( \gamma_{hydro} \) 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

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 $v = v(t, x)$
  - $t$ time, $x$ 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 $u$

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

Boundary conditions for $u$

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

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

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

### Equation for MT in depolymerization \( v \)

\[
\partial_t v - \gamma_{\text{depol}} \partial_x v = -\lambda v \int_a (R(t,a) > 0) \Theta(a) \, da + \int_a R(t,a) - u(t,a,0,x) \, da
\]

- **Depolymerization**
- **Rescue event**
- **Catastrophe event**

### Equation for free GTP \( p \)

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

- **Recycling**
- **Nucleation**

### Equation for free GDP \( q \)

\[
\frac{d}{dt} q = \gamma_{\text{depol}} \int_0^\infty v(t,x) \, dx - \kappa q
\]

- **Depolymerization**
- **Recycling**
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: \( L_u(t) = \int_0^\infty \int_0^x \int_0^\infty x u(t, a, z, x) da dz dx \)
- Total length of MTs in depol: \( L_v(t) = \int_0^\infty x v(t, x) dz dx \)
Properties of the new model

Conservation of total tubulin

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

Frequency of catastrophe

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

\[
x_a = \int_{0}^{a} \gamma_{pol}(p(t - a + s)) \, ds, \quad \chi = (R(t, a, x, 0) < 0)
\]
Properties of the new model

Conservation of total tubulin

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

Mean size of the cap and Decoration time

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

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

\[ \alpha_{pol}, p_c, p_s, a_c, a_s, \gamma_{young}^{hydro}, \gamma_{new}^{hydro}, \gamma_{depol}, \lambda, \kappa, \mu \]

**Observed data**

- Mean growth speed \( \sim \) mean value of \( \gamma_{hydro} \)
- Mean shortening speed \( \sim \) \( \gamma_{depol} \)
- On kymograph \( \sim \) \( \gamma_{pol}(p^\infty), a_s, \gamma_{young}^{hydro}, \gamma_{new}^{hydro} \)
- Decoration time \( \sim \) \( a_c \)
- Frequence of catastrophe (temporal or spacial)
- Frequence of rescue (temporal or spacial)
- Mean size of the cap
- Mean value of the size of MT

Numerical output of the model

A control test

<table>
<thead>
<tr>
<th>Parameter</th>
<th>$p_c$</th>
<th>$p_s$</th>
<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>
</tr>
</thead>
<tbody>
<tr>
<td>Values</td>
<td>2</td>
<td>15</td>
<td>32</td>
<td>6</td>
<td>60</td>
<td>0.06</td>
<td>3.7</td>
<td>4.3</td>
</tr>
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</table>

<table>
<thead>
<tr>
<th>Parameter</th>
<th>$\gamma_{depol}$</th>
<th>$\lambda$</th>
<th>$\mu$</th>
<th>$k$</th>
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<tr>
<td>Values</td>
<td>19</td>
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<td>5.9e-3</td>
<td>2.4</td>
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<tr>
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<th>Growth rate</th>
<th>Shortening rate</th>
<th>Catastrophe Fr (per min)</th>
<th>Catastrophe Fr (per $\mu m$)</th>
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<td>Pagano &amp; al</td>
<td>3.87 ±1</td>
<td>19.09 ±16</td>
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<td>0.47 ±0.03</td>
</tr>
<tr>
<td>In silico</td>
<td>3.23</td>
<td>19 ($= \delta$, fixed)</td>
<td>1.88</td>
<td>0.58</td>
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Global behaviour

In silico kymograph

Link between growth speed, $\gamma_h$, Freq of cata
Numerical output of the model

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<th>$a_s$</th>
<th>$\delta a$</th>
<th>$\gamma_{hydro}^{young}$</th>
<th>$\gamma_{hydro}^{old}$</th>
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Temporal freq of cata

Spacial freq of cata

Decoration time
## Impact of MTAs

### Modification of the parameters

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Control</th>
<th>$\gamma_{pol}$</th>
<th>$\gamma_{av}^{\text{hydro}}$</th>
<th>$\gamma_{av}^{\text{hydro}} - \gamma_{pol}$</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>3.23</td>
<td>3.65</td>
<td>0%</td>
</tr>
<tr>
<td>$a_c = 1.2s \downarrow$</td>
<td>3.43 ↑</td>
<td>6.2%</td>
<td>3.89 ↑ 6.6%</td>
<td>13.4%</td>
</tr>
<tr>
<td>$a_c = 9s \uparrow$</td>
<td>3.13 ↓</td>
<td>-3.1%</td>
<td>3.54 ↓ -3.0%</td>
<td>13.1%</td>
</tr>
<tr>
<td>$a_s = 12s \downarrow$</td>
<td>3.47 ↑</td>
<td>7.1%</td>
<td>3.94 ↑ 7.9%</td>
<td>13.5%</td>
</tr>
<tr>
<td>$\gamma_{old}^{\text{hydro}} = 7.3 \uparrow$</td>
<td>3.53 ↑</td>
<td>9.3%</td>
<td>4.00 ↑ 9.6%</td>
<td>13.3%</td>
</tr>
<tr>
<td>$\gamma_{young}^{\text{hydro}} = 6.7$, $\gamma_{old}^{\text{hydro}} = 7.3 \uparrow$</td>
<td>5.34 ↑</td>
<td>65.3%</td>
<td>6.04 ↑ 65.5%</td>
<td>13.1%</td>
</tr>
<tr>
<td>$a_s = 0.2$, $\gamma_{old}^{\text{hydro}} = 7.3 \uparrow$</td>
<td>5.30 ↑</td>
<td>64.0%</td>
<td>6.0 ↑ 64.3%</td>
<td>13.2%</td>
</tr>
<tr>
<td>$\gamma_{depol} = 9 \downarrow$</td>
<td>2.81 ↓</td>
<td>-13%</td>
<td>3.59 ↓ -1.6%</td>
<td>27.8%</td>
</tr>
<tr>
<td>$\gamma_{depol} = 29 \uparrow$</td>
<td>3.48 ↑</td>
<td>7.7%</td>
<td>3.79 ↑ 3.8%</td>
<td>8.9%</td>
</tr>
<tr>
<td>$\lambda = 10 \uparrow$</td>
<td>2.67 ↓</td>
<td>-17.3%</td>
<td>3.37 ↓ -7.7%</td>
<td>26.2%</td>
</tr>
<tr>
<td>$\lambda = 3 \downarrow$</td>
<td>3.57 ↑</td>
<td>10.5%</td>
<td>3.86 ↑ 5.7%</td>
<td>8.1%</td>
</tr>
<tr>
<td>$\alpha_{pol} = 25 \downarrow$</td>
<td>3.23 ↑</td>
<td>0%</td>
<td>3.65 ↑ 0%</td>
<td>13.0%</td>
</tr>
<tr>
<td>$\alpha_{pol} = 40 \uparrow$</td>
<td>3.23 ↓</td>
<td>0%</td>
<td>3.65 ↓ 0%</td>
<td>13.0%</td>
</tr>
<tr>
<td>$\kappa = 10 \uparrow$</td>
<td>3.22 ↑</td>
<td>0%</td>
<td>3.65 ↑ 0%</td>
<td>13.3%</td>
</tr>
<tr>
<td>$\kappa = 0.5 \downarrow$</td>
<td>3.23 ↓</td>
<td>0%</td>
<td>3.66 ↓ 0%</td>
<td>13.3%</td>
</tr>
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Impact of MTAs

Modification of the parameters

<table>
<thead>
<tr>
<th></th>
<th>$F_{cat}^{temp},[min^{-1}]$</th>
<th>$F_{cat}^{spa},[\mu m^{-1}]$</th>
<th>$L_{cap}^{av},[\mu m]$</th>
<th>$T_{deco},[s]$</th>
</tr>
</thead>
<tbody>
<tr>
<td>control</td>
<td>1.88</td>
<td>0.58</td>
<td>0.45</td>
<td>8.46</td>
</tr>
<tr>
<td>$a_c = 1.2s \downarrow$</td>
<td>3.03 ↑ 61.2%</td>
<td>0.88 ↑ 51.7%</td>
<td>0.25 ↓ -44.4%</td>
<td>4.39 ↓ -48.1%</td>
</tr>
<tr>
<td>$a_c = 9s \uparrow$</td>
<td>1.61 ↓ -14.4%</td>
<td>0.51 ↓ -12%</td>
<td>0.53 ↑ 17.8%</td>
<td>10.20 ↑ 20.6%</td>
</tr>
<tr>
<td>$a_s = 12s \downarrow$</td>
<td>1.89 0.5%</td>
<td>0.54 ↓ -7%</td>
<td>0.46 2.2%</td>
<td>7.96 ↓ -5.9%</td>
</tr>
<tr>
<td>old hydro $\gamma = 7.3 \uparrow$</td>
<td>2.20 ↑ 17%</td>
<td>0.62 ↑ 7%</td>
<td>0.50 ↑ 11.1%</td>
<td>8.44 ↓ -0.2%</td>
</tr>
<tr>
<td>young hydro $\gamma = 6.7 \uparrow$</td>
<td>2.38 ↑ 26.6%</td>
<td>0.45 ↓ -22.4%</td>
<td>0.54 ↑ 20%</td>
<td>6.09 ↓ -28%</td>
</tr>
<tr>
<td>old hydro $\gamma = 7.3 \uparrow$</td>
<td>1.84 ↓ -2.1%</td>
<td>0.35 ↓ -39.7%</td>
<td>0.63 ↑ 40%</td>
<td>7.18 ↓ -15.1%</td>
</tr>
<tr>
<td>$a_s = 0.2 \uparrow$</td>
<td>2.96 ↑ 57.4%</td>
<td>1.05 ↑ 81%</td>
<td>0.33 ↓ -26.7%</td>
<td>6.99 ↓ -17.4%</td>
</tr>
<tr>
<td>$a_{pol} = 29 \uparrow$</td>
<td>1.54 ↓ -18%</td>
<td>0.44 ↓ -24.1%</td>
<td>0.49 ↑ 8.9%</td>
<td>8.49 ↑ 0.4%</td>
</tr>
<tr>
<td>$\lambda = 10 \uparrow$</td>
<td>2.57 ↑ 36.7%</td>
<td>0.96 ↑ 65.5%</td>
<td>0.42 ↓ -6.7%</td>
<td>9.48 ↑ 12%</td>
</tr>
<tr>
<td>$\lambda = 3 \downarrow$</td>
<td>1.54 ↓ -18%</td>
<td>0.43 ↓ -25.9%</td>
<td>0.48 ↑ 6.7%</td>
<td>7.53 ↓ -11%</td>
</tr>
<tr>
<td>$\alpha_{pol} = 25 \downarrow$</td>
<td>1.88 0%</td>
<td>0.58 0%</td>
<td>0.45 0%</td>
<td>8.46 0%</td>
</tr>
<tr>
<td>$\alpha_{pol} = 40 \uparrow$</td>
<td>1.88 0%</td>
<td>0.58 0%</td>
<td>0.46 2.2%</td>
<td>8.46 0%</td>
</tr>
<tr>
<td>$\kappa = 10 \uparrow$</td>
<td>1.88 0%</td>
<td>0.58 0%</td>
<td>0.45 0%</td>
<td>8.47 0.1%</td>
</tr>
<tr>
<td>$\kappa = 0.5 \downarrow$</td>
<td>1.87 -0.5%</td>
<td>0.58 0%</td>
<td>0.46 2.2%</td>
<td>8.45 -0.1%</td>
</tr>
</tbody>
</table>

Florence HUBERT
January 15th 2016
Impact of MTAs

Examples with high growth speed and low propensity of rescue

Test 1

Test 2

<table>
<thead>
<tr>
<th>parameter</th>
<th>$\alpha_p$</th>
<th>$p_c$</th>
<th>$p_s$</th>
<th>$a_c$</th>
<th>$a_s$</th>
<th>$\gamma_{young}$</th>
<th>$\gamma_{old}$</th>
<th>$\mu$</th>
<th>$\lambda$</th>
<th>$\kappa$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test 1</td>
<td>10</td>
<td>2</td>
<td>4</td>
<td>15</td>
<td>60</td>
<td>7.4</td>
<td>7.6</td>
<td>$1.5e-18$</td>
<td>0.136</td>
<td>1.2</td>
</tr>
<tr>
<td>Test 2</td>
<td>11</td>
<td>0.5</td>
<td>4</td>
<td>15</td>
<td>60</td>
<td>7.5</td>
<td>8</td>
<td>$1.5e-18$</td>
<td>0.136</td>
<td>1.2</td>
</tr>
</tbody>
</table>
To go further

To accurately modelize Rescue frequency

- Introduce an age in the population \( v \):

\[ v(t, x) \rightarrow v(t, a, x) \]

To better modelize sudden depolymerization

- Use fragmentation model. Change in equation for \( v \)

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

work with D. White, M. Tournus

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

To accurately modelize Rescue frequency

- Introduce an age in the population $v$:

$$v(t, x) \rightsquigarrow v(t, a, x)$$

To better modelize sudden depolymerization

- Use fragmentation model. Change in equation for $v$

$$-\gamma_{depol} \partial_x v \rightsquigarrow -\gamma_{depol} \int_0^x k(x, \tilde{x}) v(t, x) d\tilde{x} + \gamma_{depol} \int_x^{\infty} k(\tilde{x}, x) v(t, \tilde{x}) d\tilde{x}$$

work with D. White, M. Tournus

$$k(x, \tilde{x}) = K(\tilde{x}) = Cte \text{ if } x < x_0$$
A simplified model

A first step to understand oscillations

- Consider only size dependance for $u: \sim u(t, x)$
- Model should nevertheless reflects
  - the role of the balance between hydrolysis and growth rate. We introduce a threshold $\sim p_h$
    - $p < p_h$ period of catastrophe
    - $p > p_h$ period of rescue
  - the sudden depolymerization during catastrophe time

$\sim$ use of fragmentation terms

$$
\partial_t u + \gamma_{pol}(p(t)) \partial_x u = \psi(x) \mathcal{N}(p(t)) \\
+ (p(t) < p_h) \star \left( -u(t, x) \int_0^x k(x, \tilde{x}) \, d\tilde{x} + \int_x^{+\infty} k(\tilde{x}, x) u(t, \tilde{x}) \, d\tilde{x} \right)
$$

$$
p'(t) = -\gamma_{pol}(p(t)) I_u(t) + \kappa q(t) - \mathcal{N}(p)
$$

$$
q'(t) = -\kappa q(t) + (p < p_h) \int_0^{+\infty} u(t, x) \int_0^x (x - \tilde{x}) k(x, \tilde{x}) \, d\tilde{x} \, dx
$$
A simplified model

A first step to understand oscillations

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- Model should nevertheless reflect
  - the role of the balance between hydrolysis and growth rate. We introduce a threshold $\sim p_h$
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    - $p > p_h$ period of rescue
  - the sudden depolymerization during catastrophe time
  $\sim$ use of fragmentation terms

For a kernel $k(x, \tilde{x}) = K(\tilde{x})$,

\[
I_u' = \mathcal{N}(p(t))
\]
\[
p'(t) = -\gamma_{pol}(p(t))I_u(t) + \kappa q(t) - \mathcal{N}(p)
\]
\[
q'(t) = -\kappa q(t) + (p < p_h)(p_0 - p(t) - q(t))C_K
\]
\[
- (p < p_h)I_u(t)C_K
\]
A simplified model

A first step to understand oscillations

- Consider only size dependance for $u: \sim u(t,x)$
- Model should nevertheless reflects
  - the role of the balance between hydrolysis and growth rate. We introduce a threshold $\sim p_h$
    - $p < p_h$ period of catastrophe
    - $p > p_h$ period of rescue
  - the sudden depolymerization during catastrophe time
  - use of fragmentation terms
- On can prove the existence of bifurcation around a value $p_h^*$

$p_h = 4$

$p_h = 6$
Role of EB proteins

Introduction of EB in the models

\[
\frac{d}{dt} EB^b = -k_{off} E B^b(t) + k_{on}(CAP) E B^{ub} \\
\frac{d}{dt} EB^{ub} = k_{off} E B^b(t) - k_{on}(CAP) E B^{ub}
\]

- Dissociation rate $k_{off}$ is supposed to be constant. Association rate $k_{on}$ is proportional to GTP-tubulin CAP.
- EBs increase the rate of catastrophe by increasing the hydrolysis rate

\[
\gamma_{hydro}(EB(t)) = \gamma_1 + \gamma_2 E B^b(t)
\]
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 (In vitro) have also been found to increase the rescue frequency
  Vitre et al., 2008

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

MTAs and aging model

⇝ How interpret MTAs at high dose (cytotoxic effect)?
⇝ How interpret MTAs at low dose (cytostatic effect)?

A. Barlukova

New model of depolymerization

► Go further in the theoretical study of the model
⇝ Existence, asymptotic behaviour

M. Tournus, D. White

End binding proteins

► Go further in the study of the sinergy between EB and MTAs.

D. White

Migration

► Cell migration modeling in confined domains

CEMRACS 15 work with J. Olivier, O. Theodoly, A. Trescases, M. Jedouaa, I. Khames

► Control the migration of the cells thanks to MT dynamics.

Rémi Tesson PHD work
Thank you very much