Modèles numériques et analytiques d'invasion cellulaire à 1D avec et sans interactions de contact

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E. Fabiani[12] encadré par C. Deroulers[12]

[1]IMNC – UMR 8165, 91405 Orsay, France
[2]Université Paris Diderot, 75013 Paris, France

Numerical and analytical models of 1D cell invasion with and without contact interactions

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Scientific context and main issues

1) Brain tumors : key figures
2) Biological issues

A discrete approach

1) Introduction to cellular automata
2) 1D cell invasion model

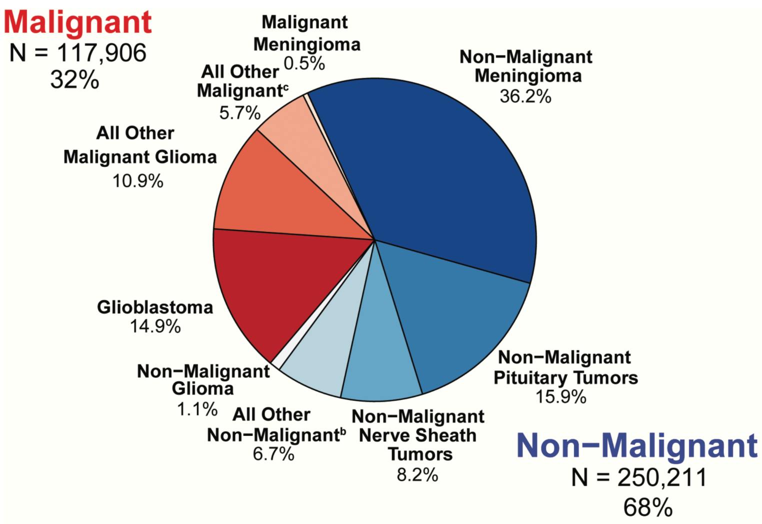
A continuous approach

1) Master equations
2) Analytical 1D model

Results et perspectives

1) Comparison of models
2) Towards a 2D model

74,000 cases diagnosed in US/y



Q. Ostrom & al, 2016

Brain tumors : key figures

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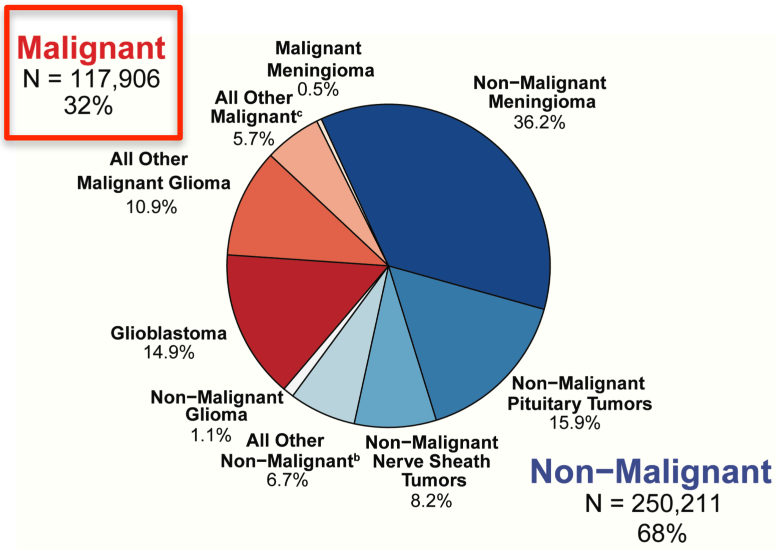


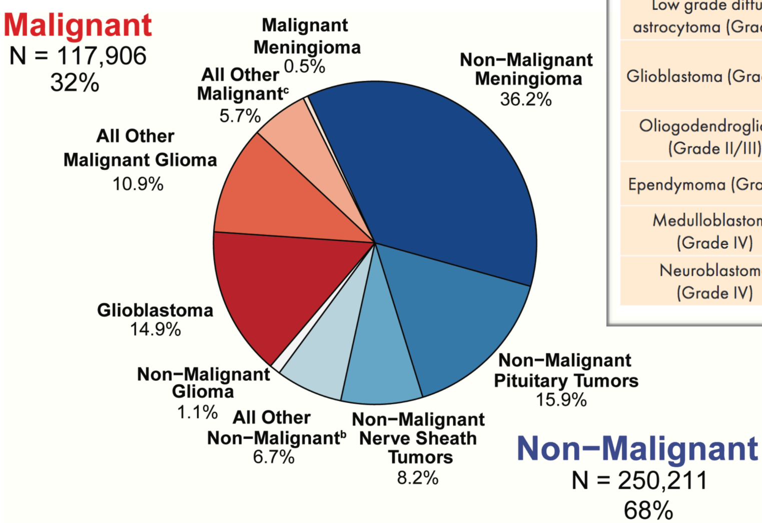
Q. Ostrom & al, 2016

23,700 malignant cases/y

Brain tumors : key figures

Survival rate

74,000 cases diagnosed in US/y



Q. Ostrom & al, 2016

Tumour (WHO Grade)	Typical location	Age at clinical manifestation (% of cases)			Five-year survival (% of patients)	Genetic alterations
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WHO, 2014

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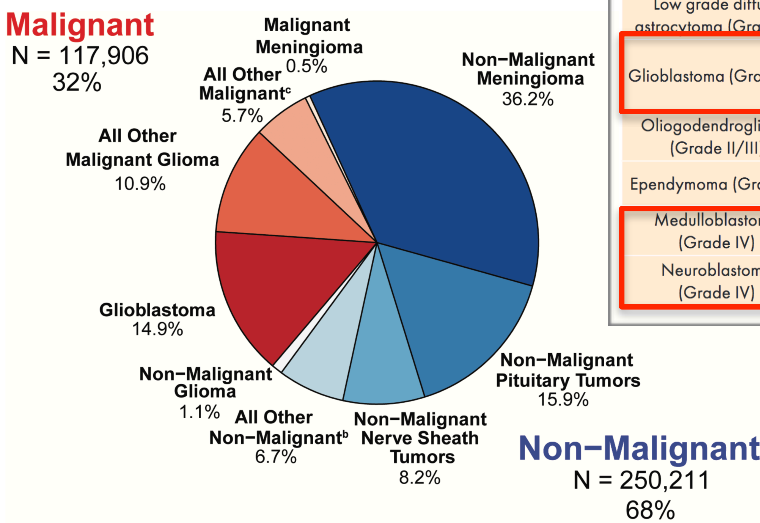

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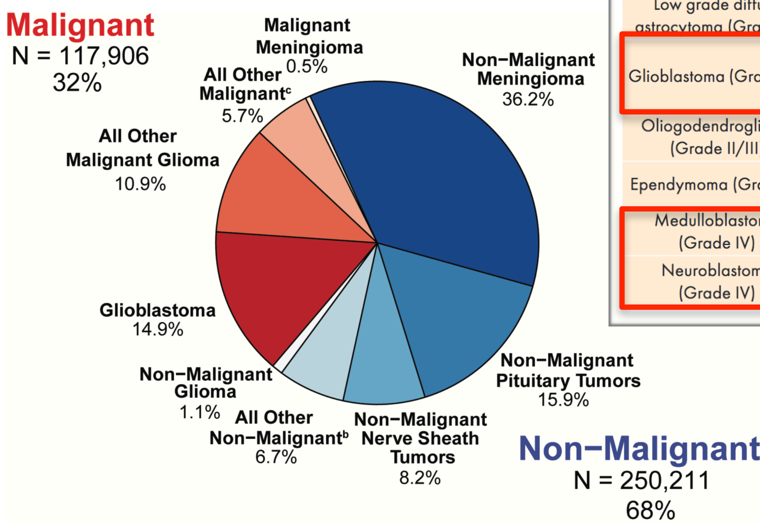

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WHO, 2014

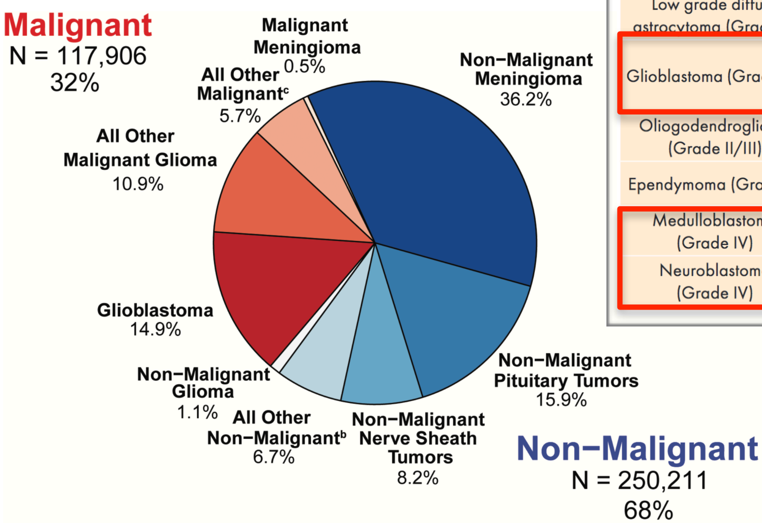
Note :

- Low grades : I & II
  can lead to recurrences
  can mutate to higher grades
  (anaplastic transition is systematic for grade II)

- High grades : III, IV
  are more agressive and fast-growing

Brain tumors : key figures

74,000 cases diagnosed in US/y



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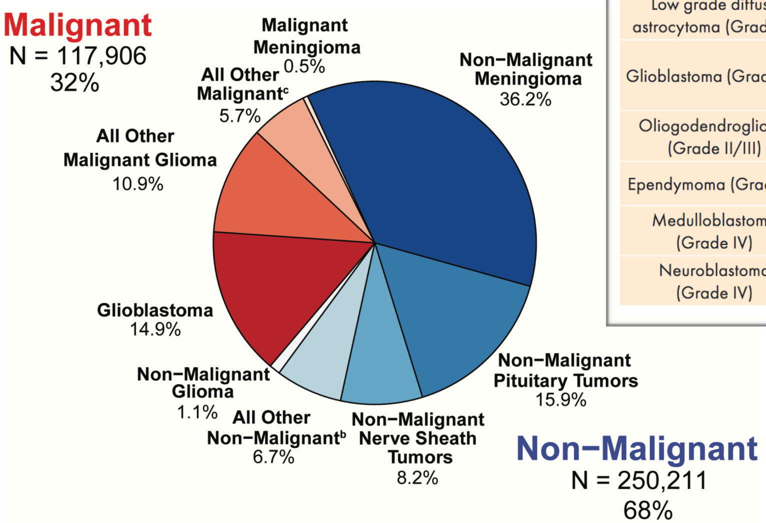

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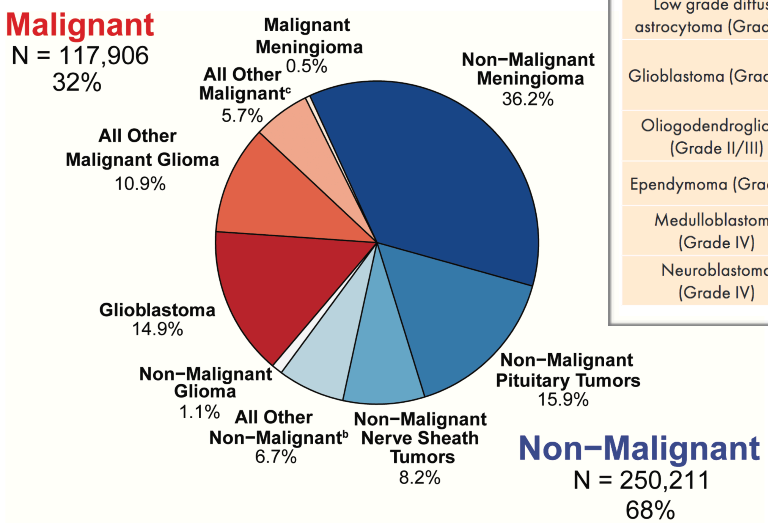
Therapy

Diagnostic :

- Radiographical (CT scan, MRI)
- Histological (biopsies)

Brain tumors : key figures

74,000 cases diagnosed in US/y



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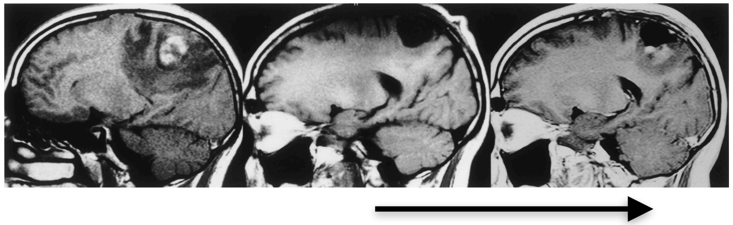
Therapy

Primary brain tumor — After surgery — Secondary brain tumor

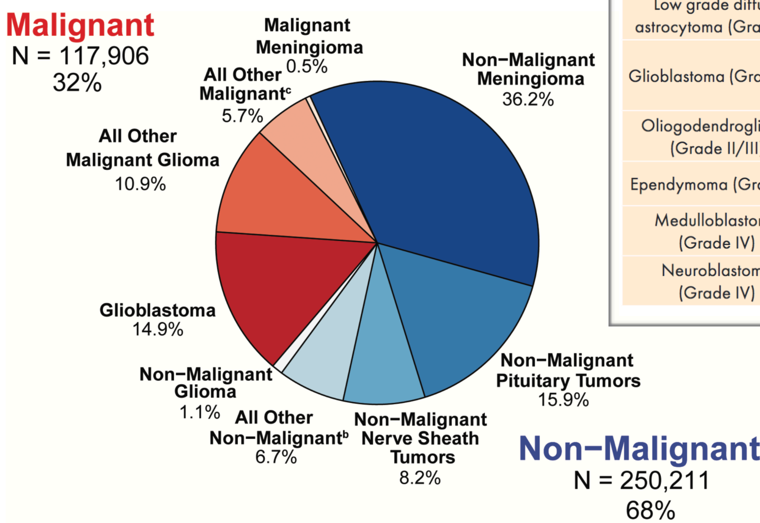


12 months

Giese & al, 2003

Brain tumors : key figures

74,000 cases diagnosed in US/y



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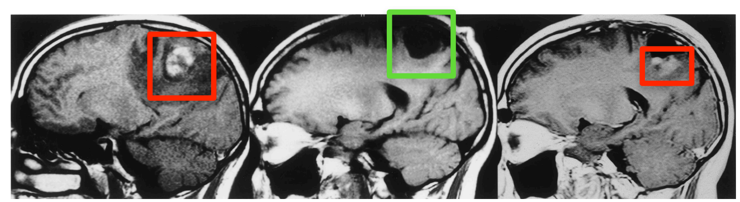

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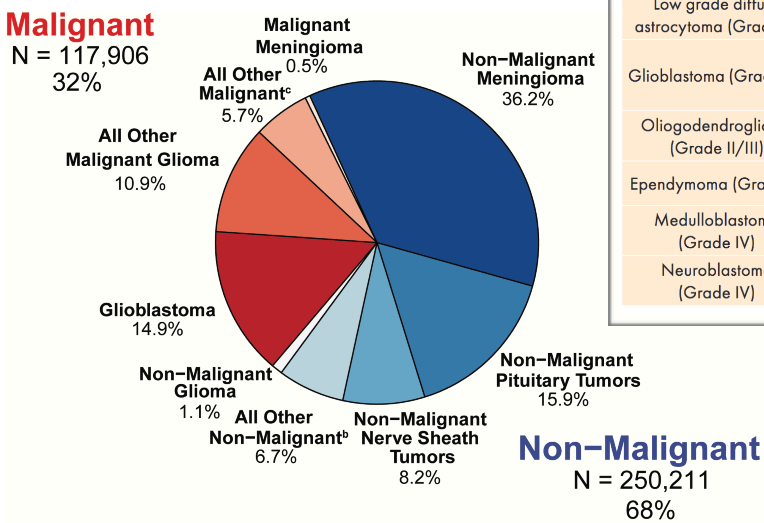

Q. Ostrom & al, 2016

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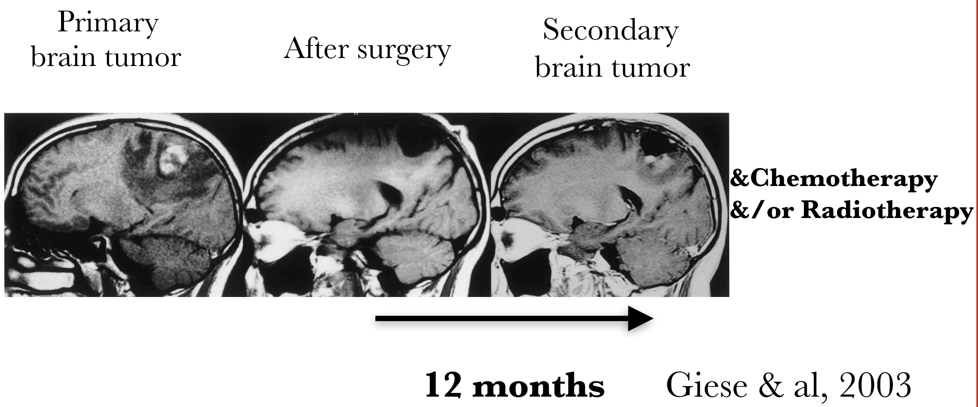

Giese & al, 2003

Biological issues

Why are those figures so bad ?

- Treatments are hardly efficient

  The image resolution is not accurate enough thus the surgeon cannot delineate the perimeter of the tumor for the resection

- Impossibility of removing the totality of the tumor (more would risk to make the patient lose his essential functions : speech, mobility, behavior)

- Left cells systematically causes **recurrences**

Why is there a tumor « growth » ?

Many complex phenomenon appearing:

- Migration
- Proliferation
- Neo-angiogenesis

Which leads to **invasion of the healthy tissue**

One major question for the surgeon :

To which distance the most advanced cells came ?

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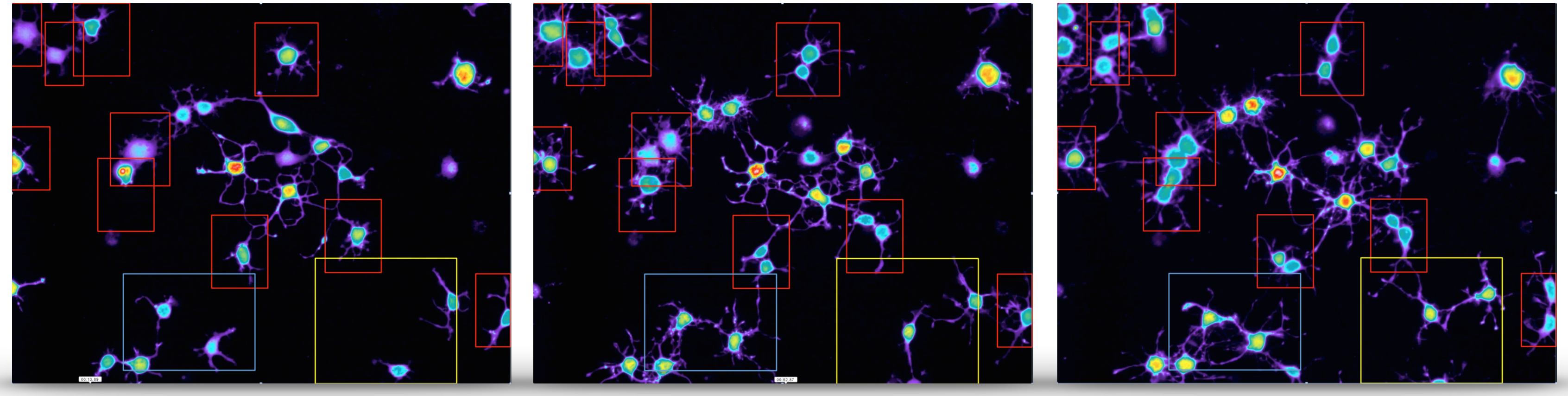
My project aims to develop mathematical models to answer this question

Phenomenons observed during growth

OPC migration
microscope
movie

Phenomenons observed during growth



Experiment of a culture of mice OPC in vitro, O. Seksek, IMNC, 2016

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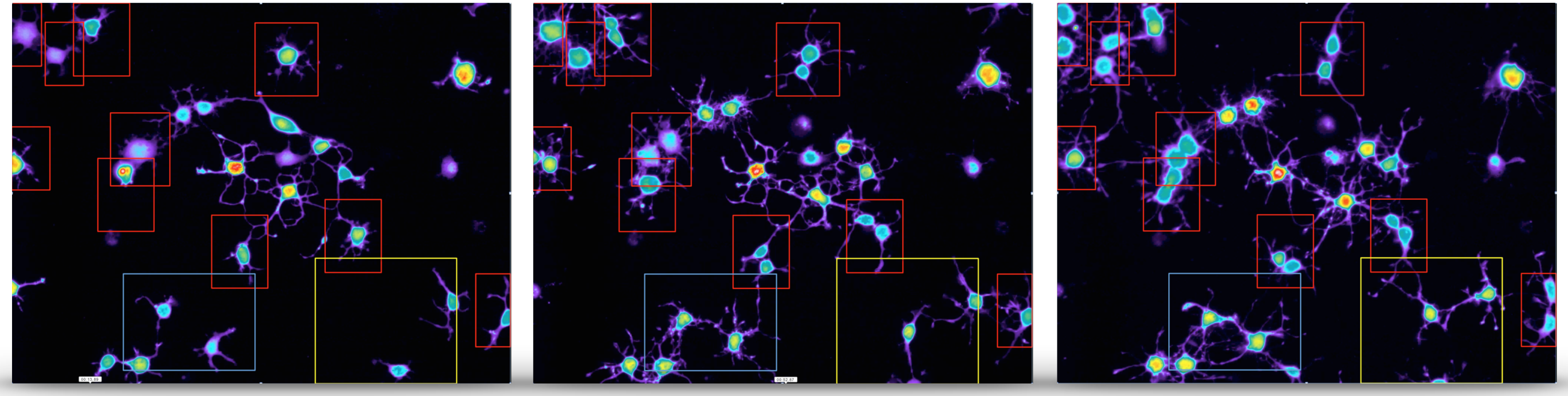

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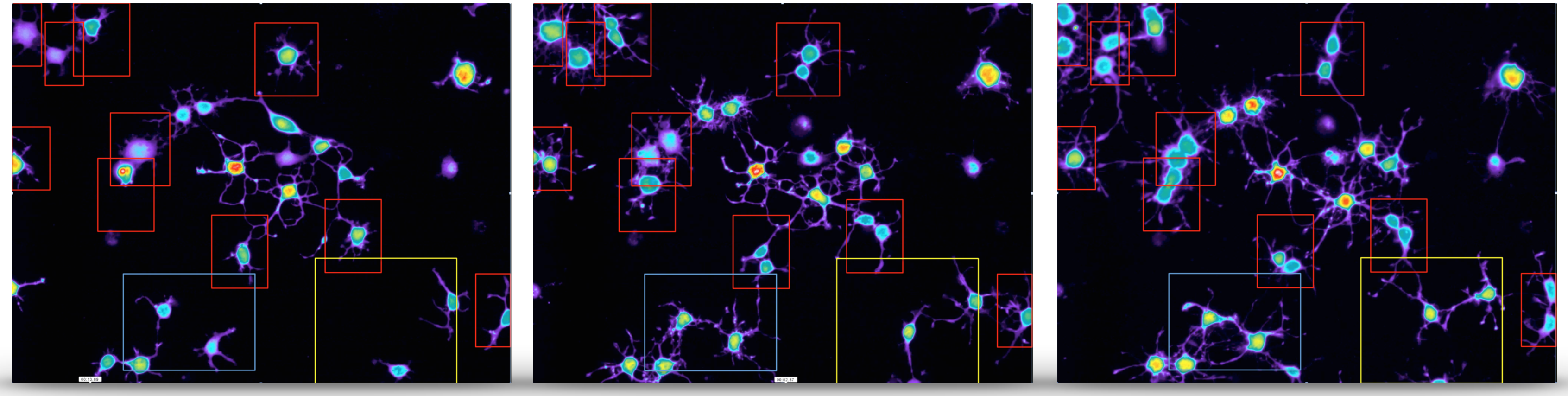

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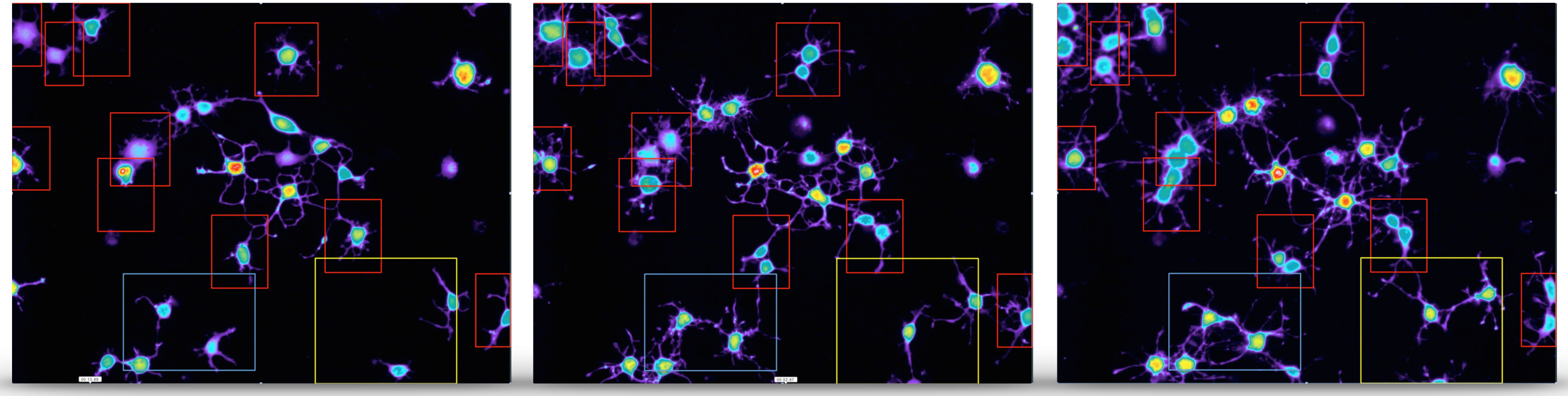

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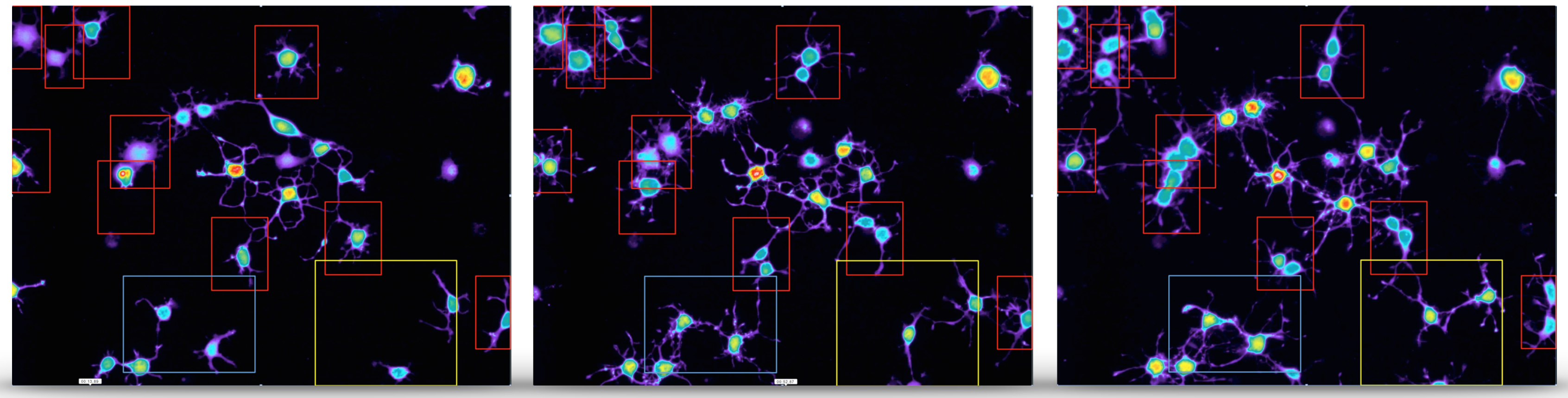

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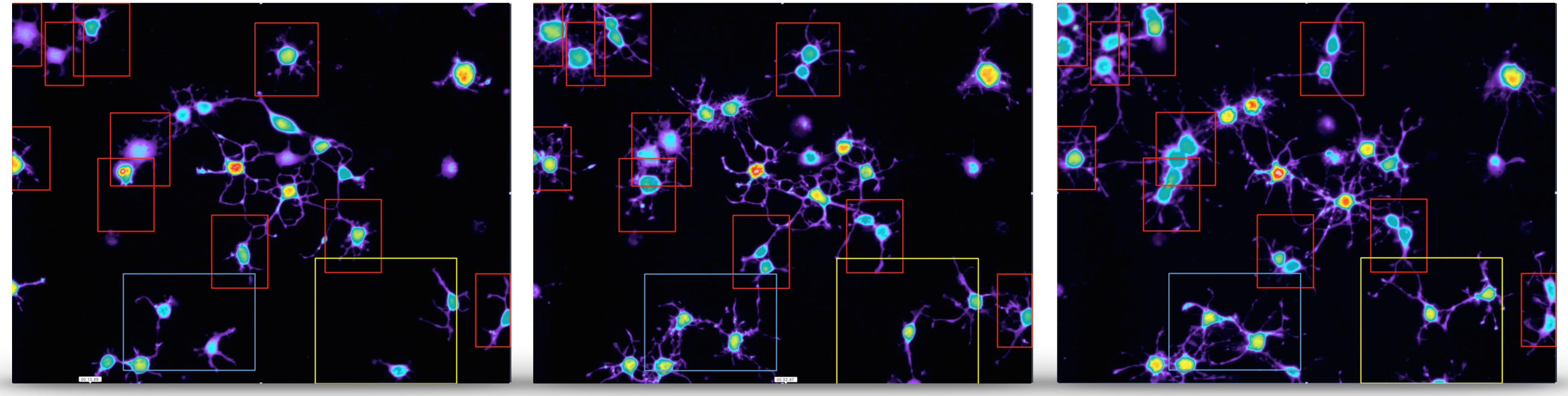

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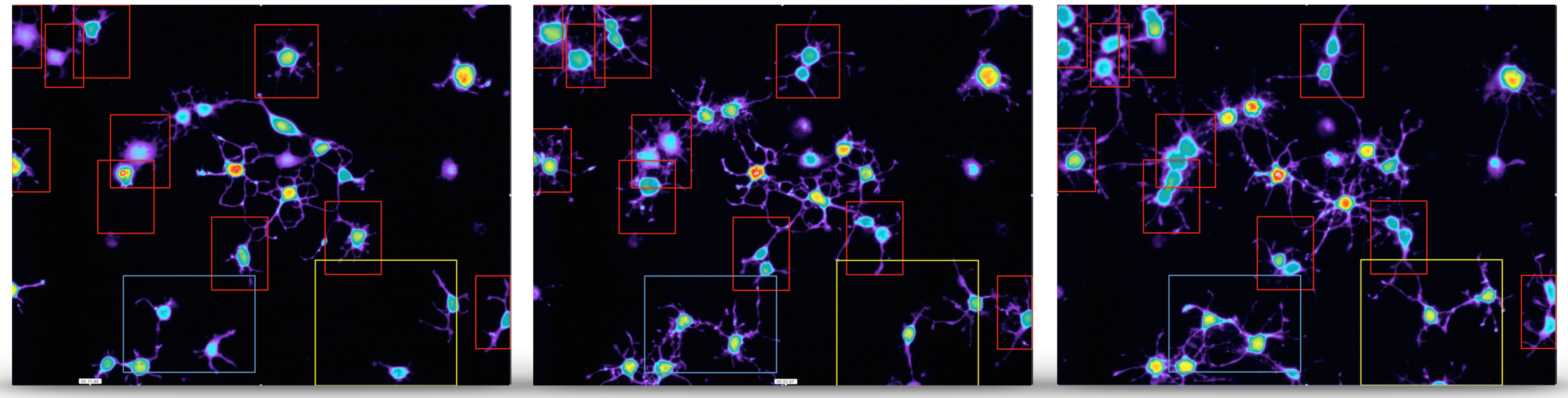

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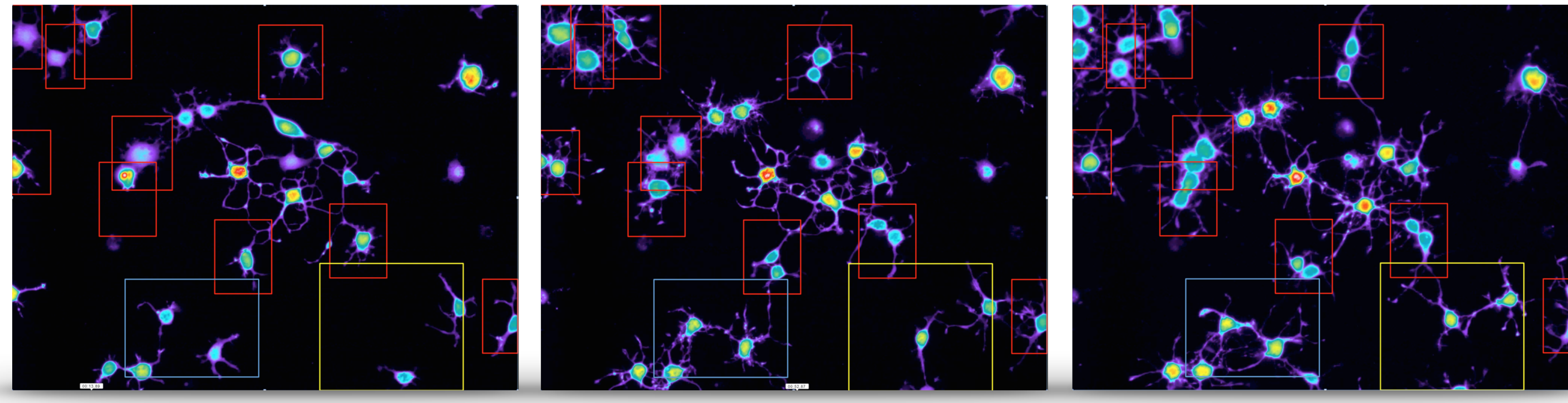

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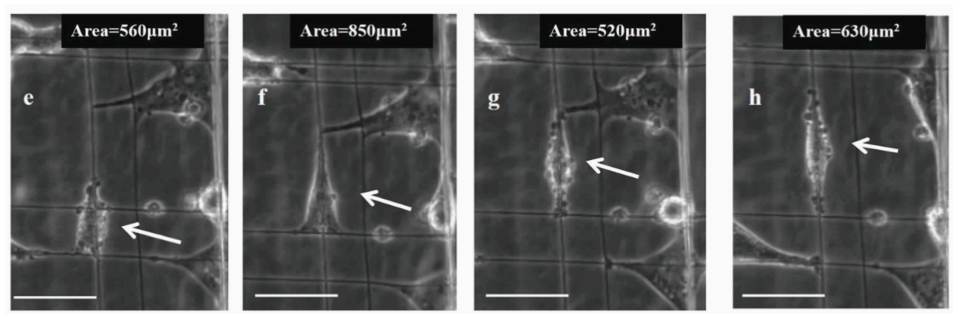
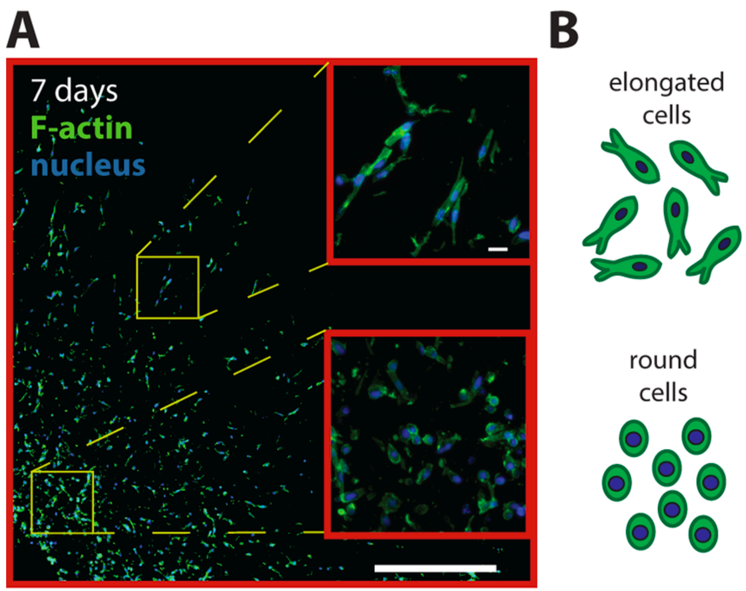


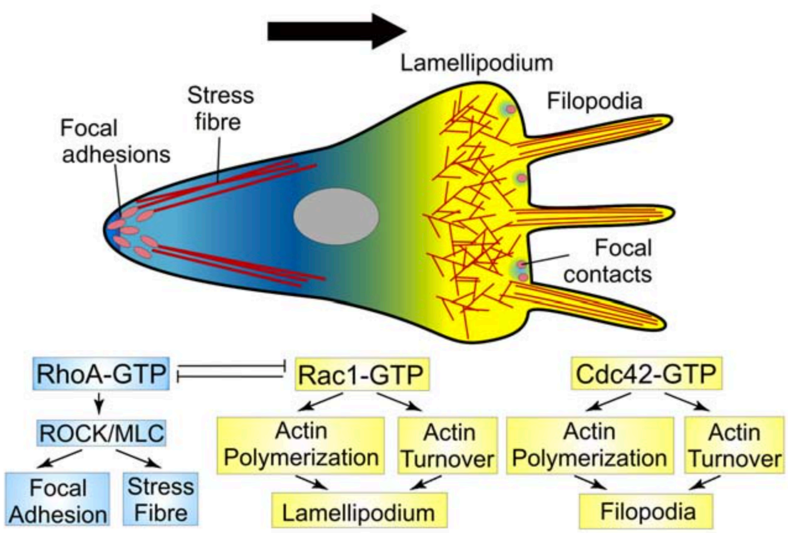
Puja Sharma & al, 2013

Phenomenons observed during growth

Elongated/Round cells in center/periphery



A. Jimenez Valencia & al, 2015



R. Mayor & C. Carmona-Fontaine, 2010

Mathematical models ?
1) Cellular automata
2) Probabilistic theoretical resolution

Cellular automata

<u>« Game of Life »</u>

John H. Conway, 1970

Definition :

Discrete time-depending system of cells/box in a fixed number of states, evolving by iterations according to trivial rules.

Often characterized by the simplicity of its starting rules and the complexity of emergent phenomenon it can gives.

Cellular automata

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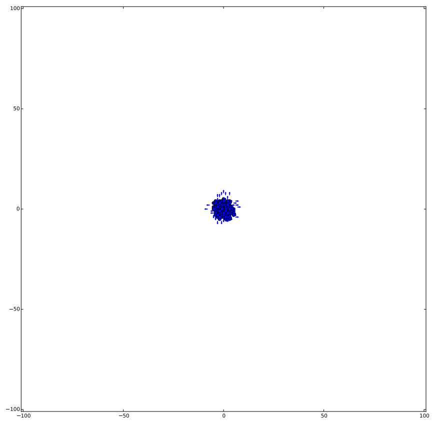
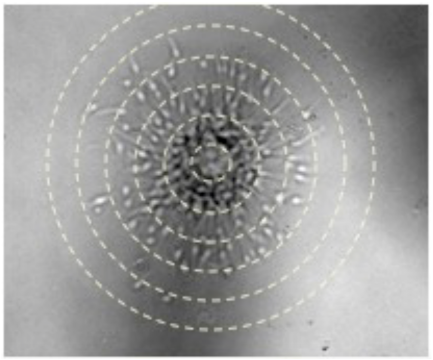
We use it to model cell cultures





2D Cell culture on homogeneous substrate for a spheroïd analysis

Cellular automata

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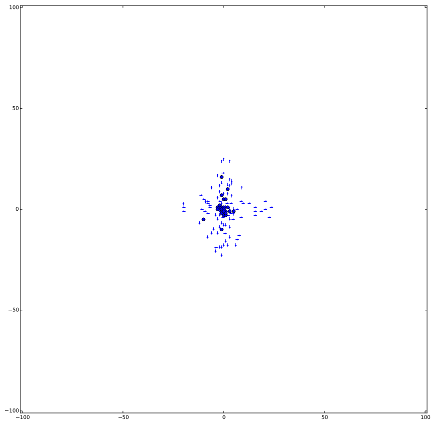

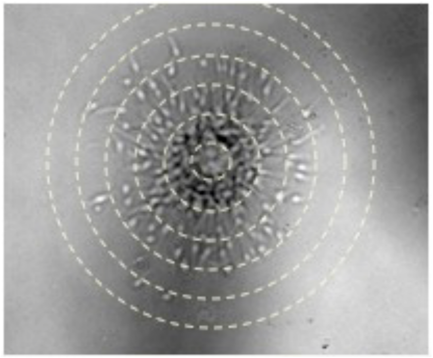

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Introduction to cellular automata

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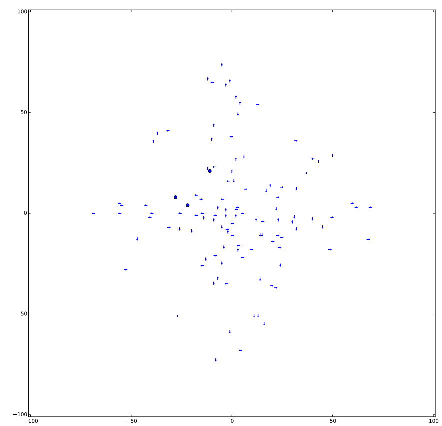

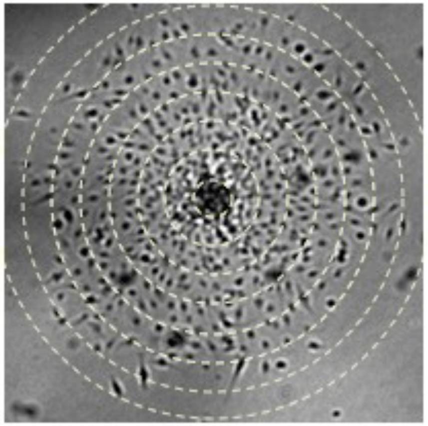

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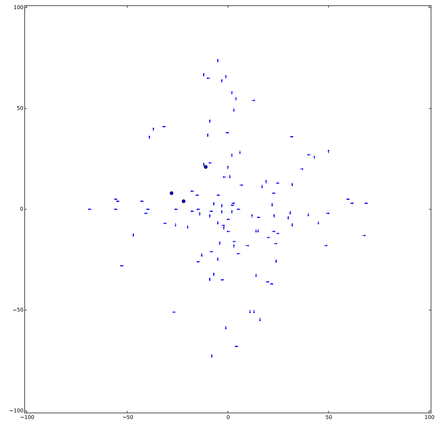
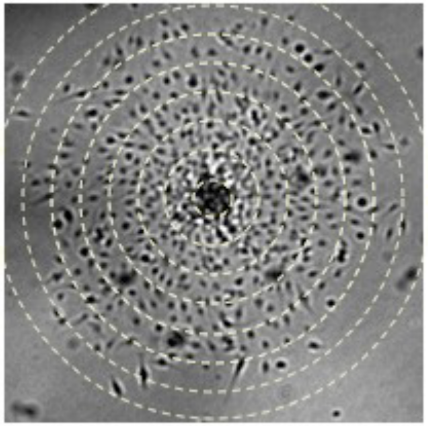


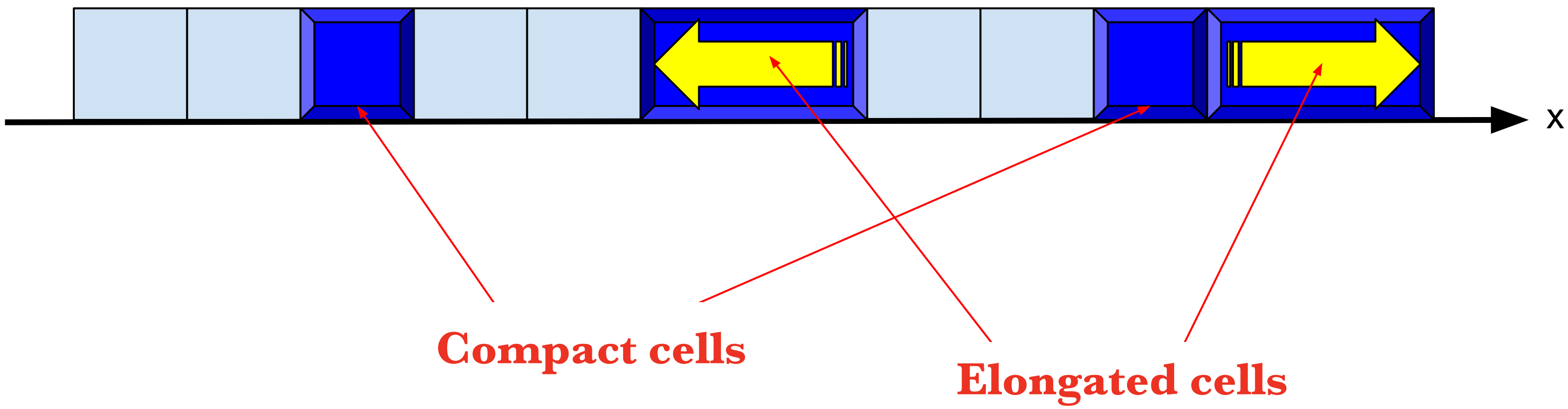


2D Cell culture on homogeneous substrate for a spheroïd analysis

1D cell automata with exclusions

L : number of boxes

$$\begin{cases} \Gamma & = t_{c \to e} \text{ : transition rate Compact} \longrightarrow \text{Elongated} \\ \Lambda & = t_{e \to c} \text{ : transition rate Elongated} \longrightarrow \text{Compact} \end{cases}$$



- ☞ One cell but 3 possibles states
- ☞ Only polarized cell can jump in their polarized direction
- ☞ Polarized cells can retract
- ☞ Compact cells can extend

☞ If there is contact interactions :

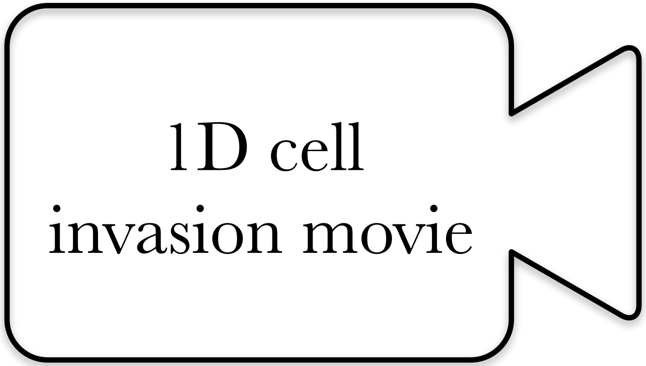
no possible overlap !

1D cell invasion model

1D cell automata with exclusions

L : number of boxes

$$\begin{cases} \Gamma & = t_{\mathrm{c}\to\mathrm{e}} \text{ : transition rate Compact} \longrightarrow \text{Elongated} \\ \Lambda & = t_{\mathrm{e}\to\mathrm{c}} \text{ : transition rate Elongated} \longrightarrow \text{Compact} \end{cases}$$



1D cell invasion model

1D cell automata with exclusions

<u>We average over Ns = 100000 simulations of this stochastic process</u>

Evolution of the density profile with time :

-7 cells at the center of the system

$-t_{C \rightarrow E} = 0.3$

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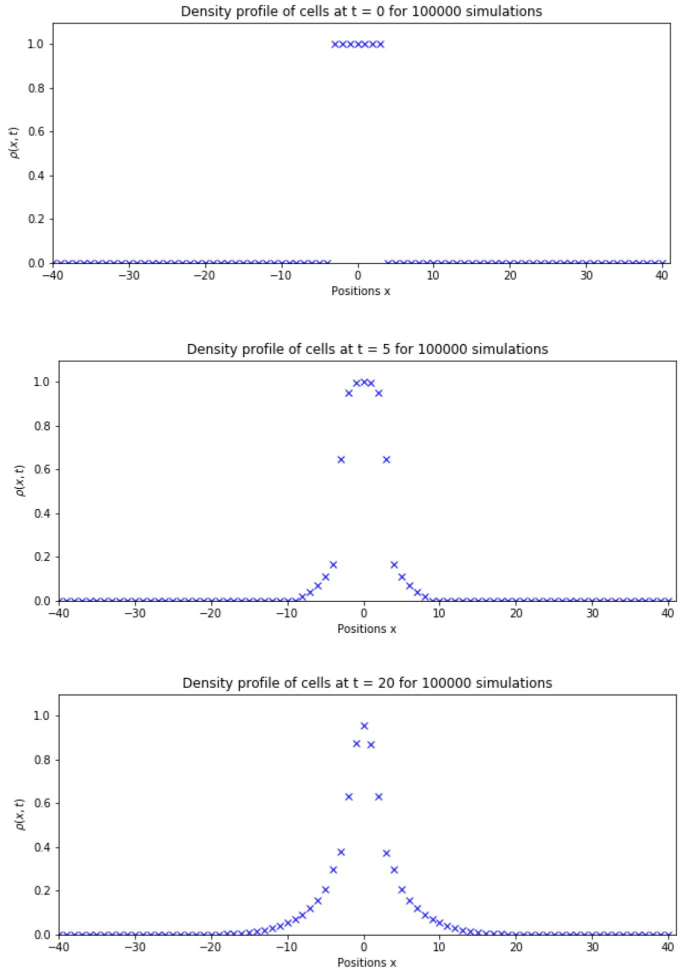

1D cell automata with exclusions

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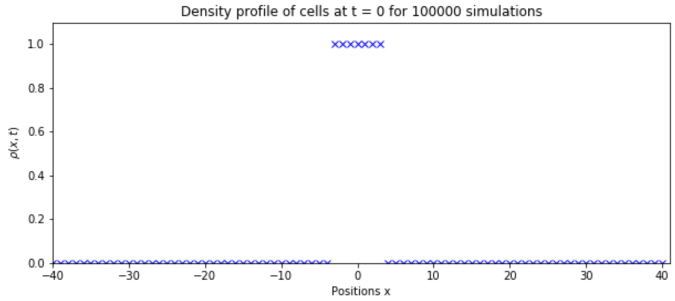
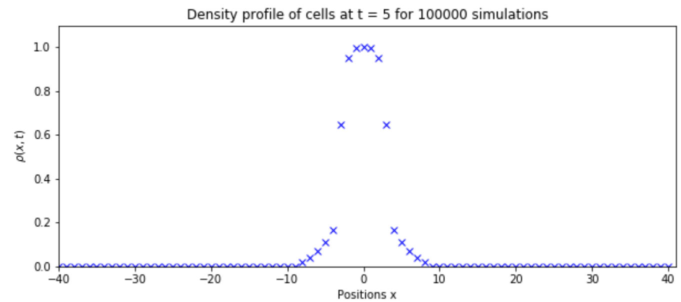
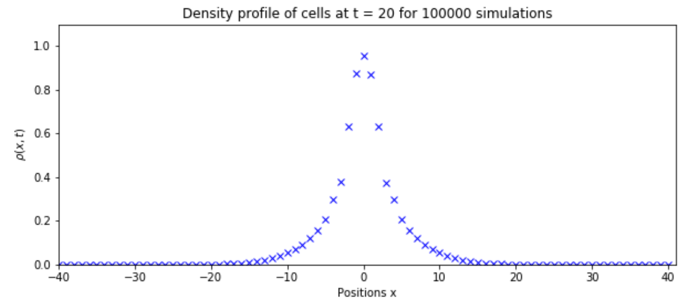
Diffusion process ?







1D cell automata with exclusions

L : number of boxes

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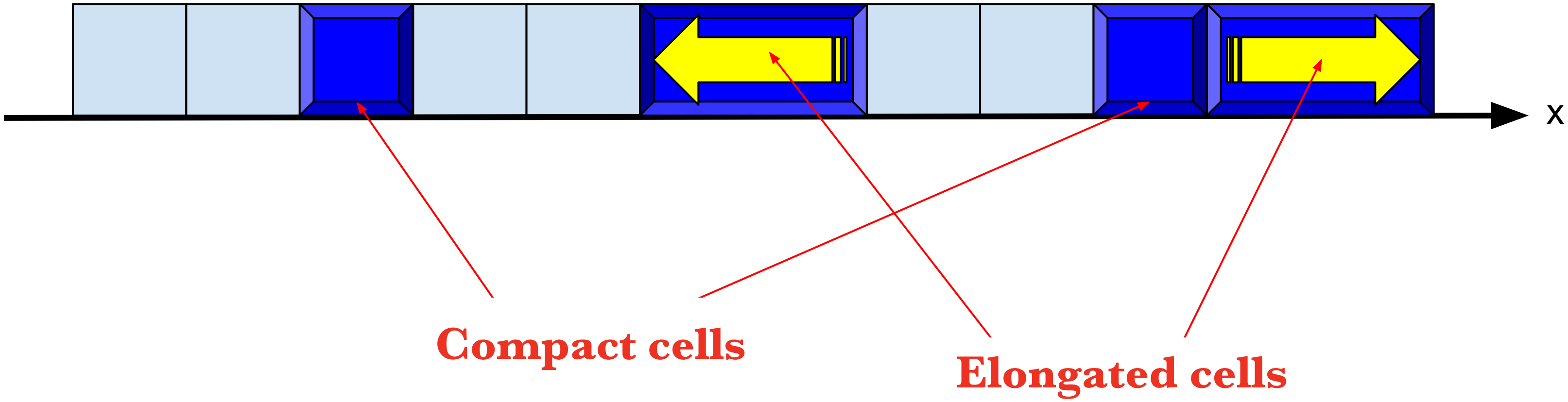
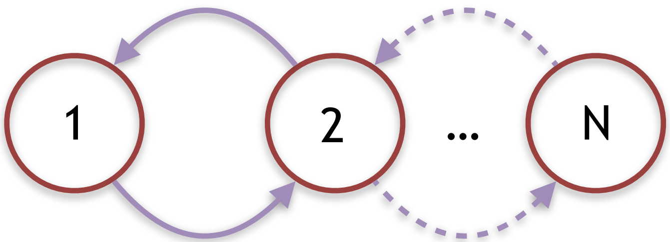


Let's derive this discrete model to an analytical approximated model

Master Equations



Definition :

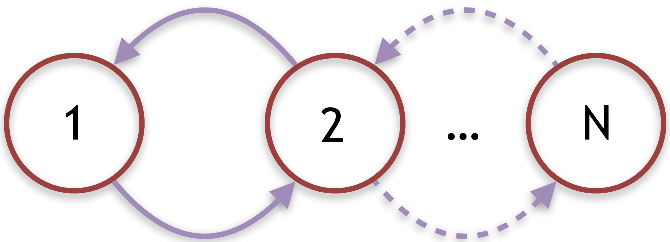
Equations from a Markov process diagram describing N states evolution with continuous time

$$\frac{dP_i}{dt} = \sum_{l \neq i}^{N} (\Gamma_{il} P_l - \Gamma_{li} P_i)$$

Γ : transition rate

P : probability density

Master Equations



Definition :

Equations from a Markov process diagram describing N states evolution with continuous time

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Input terms   Output terms

Γ : transition rate

P : probability density

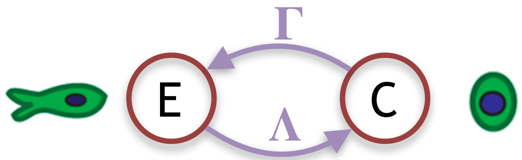
1D analytical model without exclusions

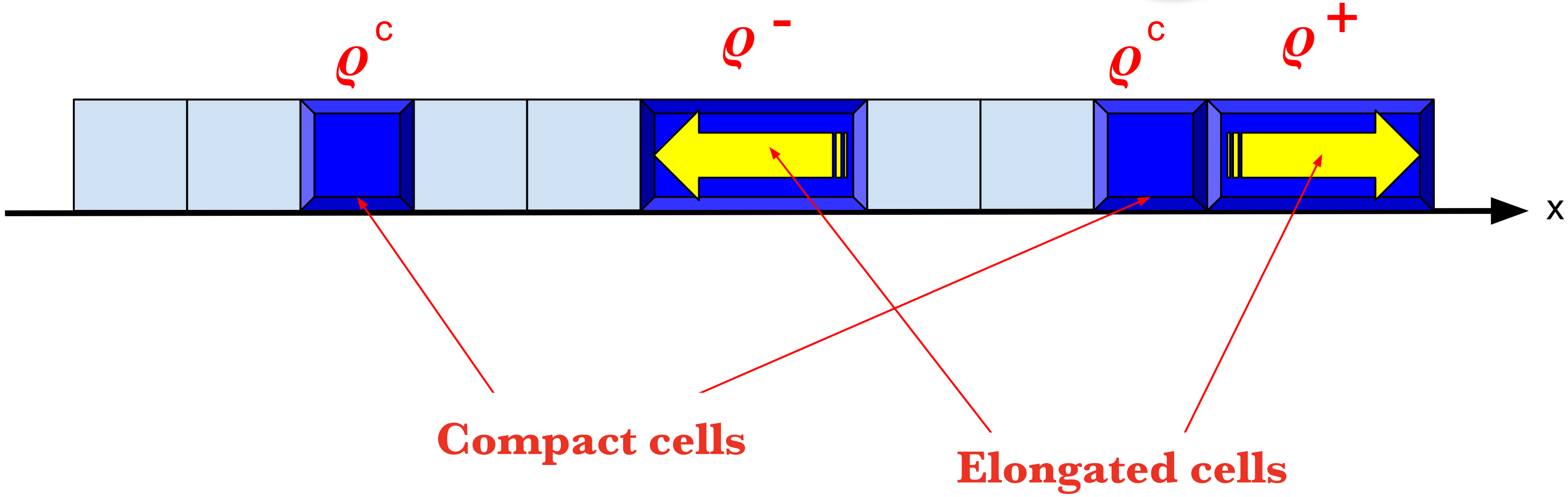
a : lattice step

ρ : local density

$$\begin{cases} \Gamma = t_{c \to e} & \text{: transition rate Compact} \longrightarrow \text{Elongated} \\ \Lambda = t_{e \to c} & \text{: transition rate Elongated} \longrightarrow \text{Compact} \end{cases}$$

$\rho^c + \rho^+ + \rho^- = \rho^{tot}$: total cell density





Reminder : Can we find the diffusive behavior ?

Analytical model

1D analytical model without exclusions

a : lattice step

ρ : local density

$$\begin{cases} \Gamma & = t_{\mathrm{c}\to\mathrm{e}} \text{ : transition rate Compact} \longrightarrow \text{Elongated} \\ \Lambda & = t_{\mathrm{e}\to\mathrm{c}} \text{ : transition rate Elongated} \longrightarrow \text{Compact} \end{cases}$$

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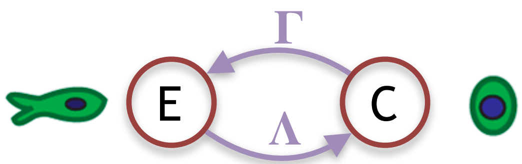

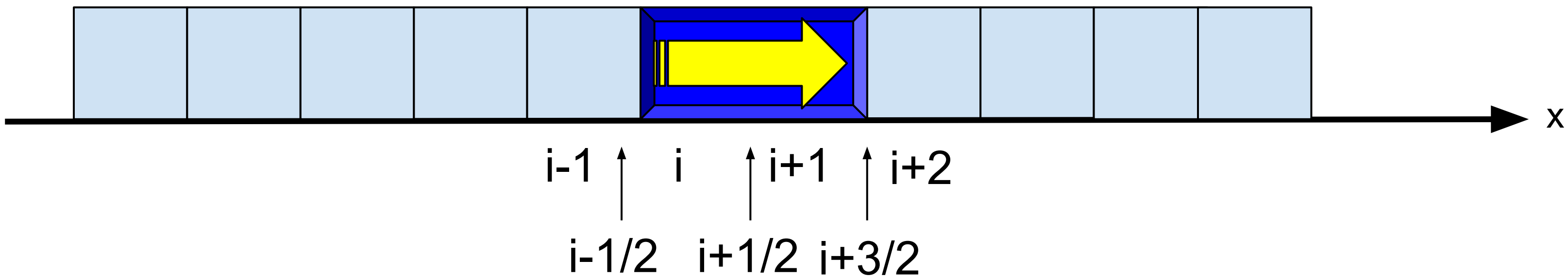

$$\partial_t \rho^{+}_{i+\frac{1}{2}}(t) = \ ?$$

Analytical model

1D analytical model without exclusions

a : lattice step

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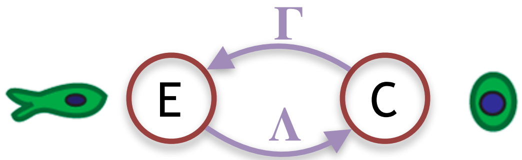

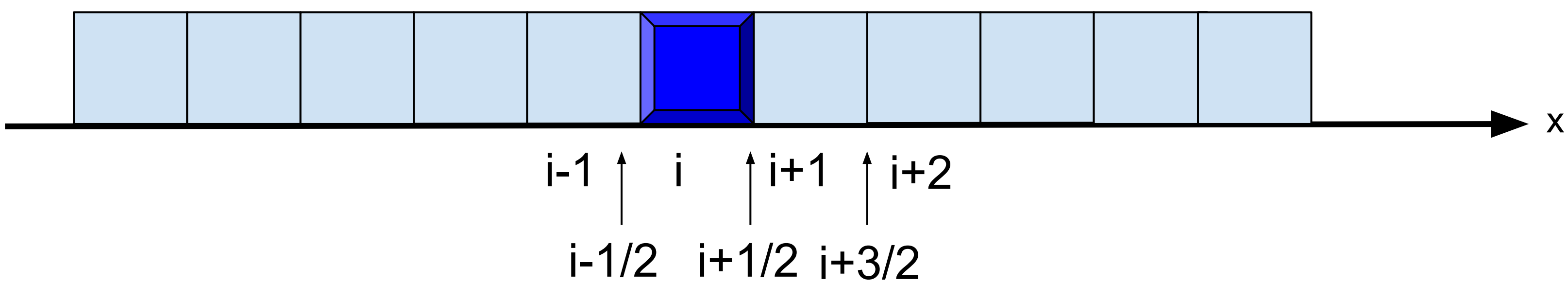

$$\partial_t \rho^{+}_{i+\frac{1}{2}}(t) =$$

1D analytical model without exclusions

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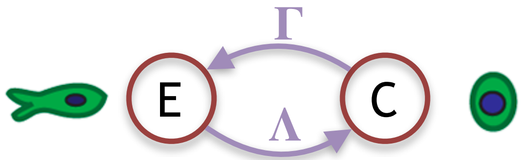

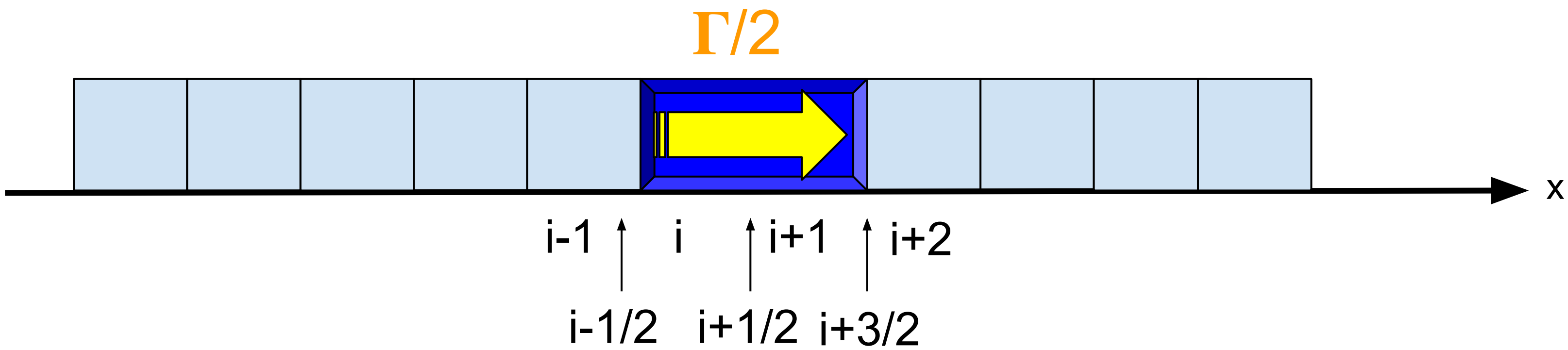

$$\partial_t \rho^+_{i+\frac{1}{2}}(t) = \Bigg(\frac{\Gamma}{2} \rho^c_i(t)$$

Analytical model

1D analytical model without exclusions

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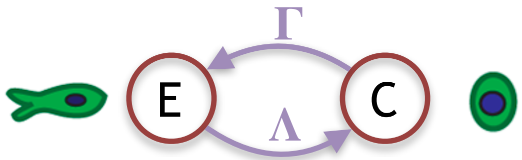
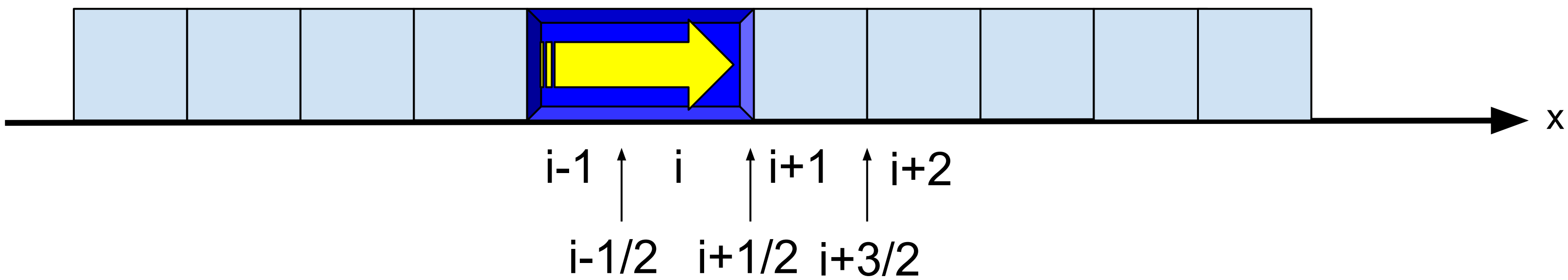
$\rho^{c}+\rho^{+}+\rho^{-} = \rho^{tot}$: total cell density





$$\partial_t \rho^{+}_{i+\frac{1}{2}}(t) = \left(\frac{\Gamma}{2} \rho^{c}_{i}(t) \right.$$

Analytical model

1D analytical model without exclusions

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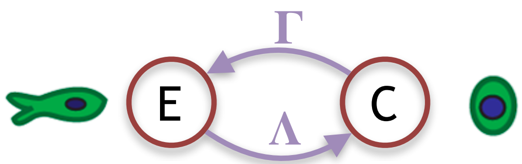

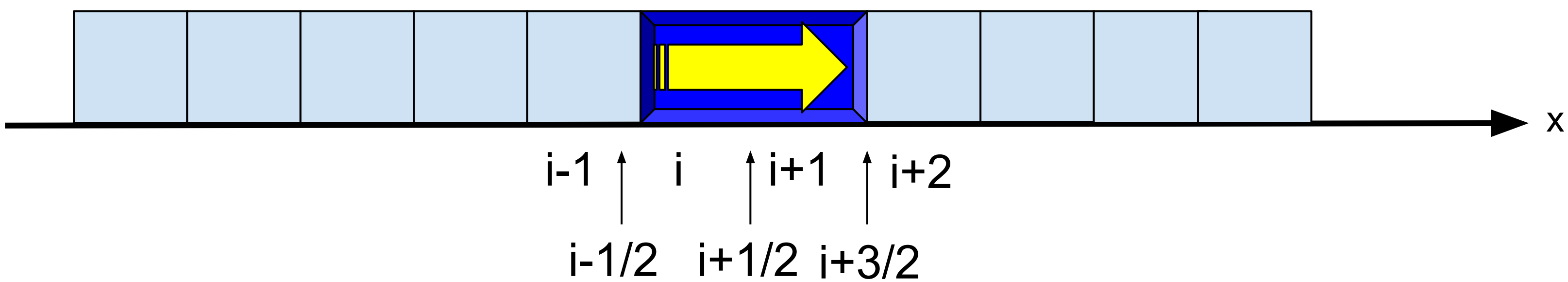

$$\partial_t \rho^+_{i+\frac{1}{2}}(t) = \left(\frac{\Gamma}{2} \rho^c_i(t) + \rho^+_{i-\frac{1}{2}}(t) \right)$$

1D analytical model without exclusions

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$$\begin{cases} \Gamma = t_{\mathrm{c}\rightarrow\mathrm{e}} & \text{: transition rate Compact} \longrightarrow \text{Elongated} \\ \Lambda = t_{\mathrm{e}\rightarrow\mathrm{c}} & \text{: transition rate Elongated} \longrightarrow \text{Compact} \end{cases}$$

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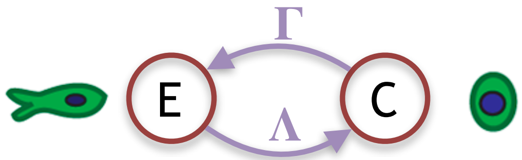

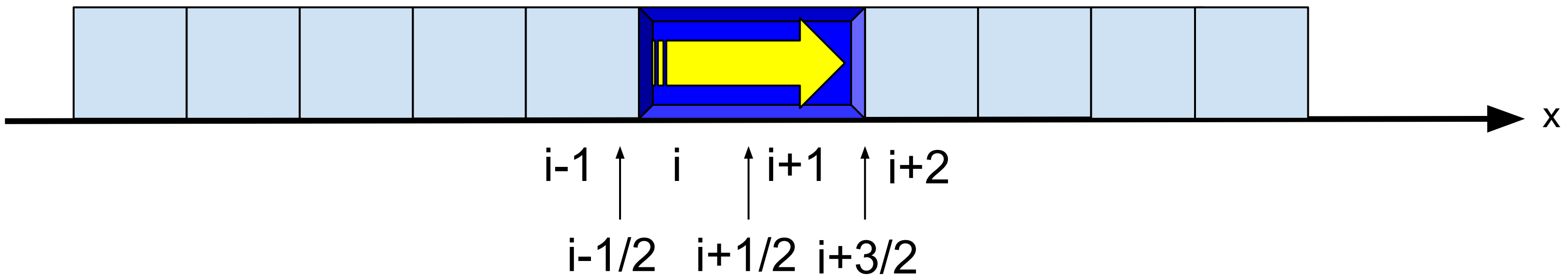

$$\partial_t \rho^{+}_{i+\frac{1}{2}}(t) = \left(\frac{\Gamma}{2}\rho^{c}_{i}(t) + \rho^{+}_{i-\frac{1}{2}}(t)\right) - \rho^{+}_{i+\frac{1}{2}}(t)$$

Analytical model

1D analytical model without exclusions

a : lattice step

ρ : local density

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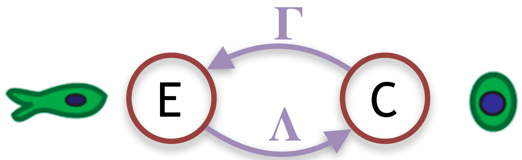

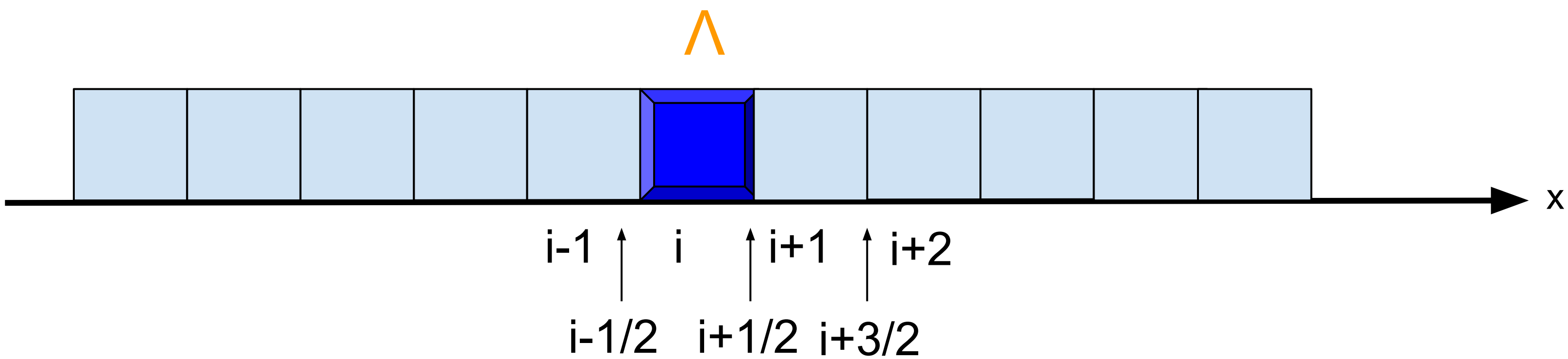

$$\partial_t \rho^{+}_{i+\frac{1}{2}}(t) = \left(\frac{\Gamma}{2}\rho^{c}_{i}(t) + \rho^{+}_{i-\frac{1}{2}}(t)\right) - \rho^{+}_{i+\frac{1}{2}}(t)\,(1+\Lambda)$$

1D analytical model without exclusions

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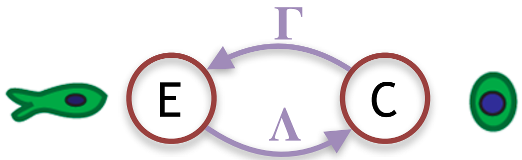
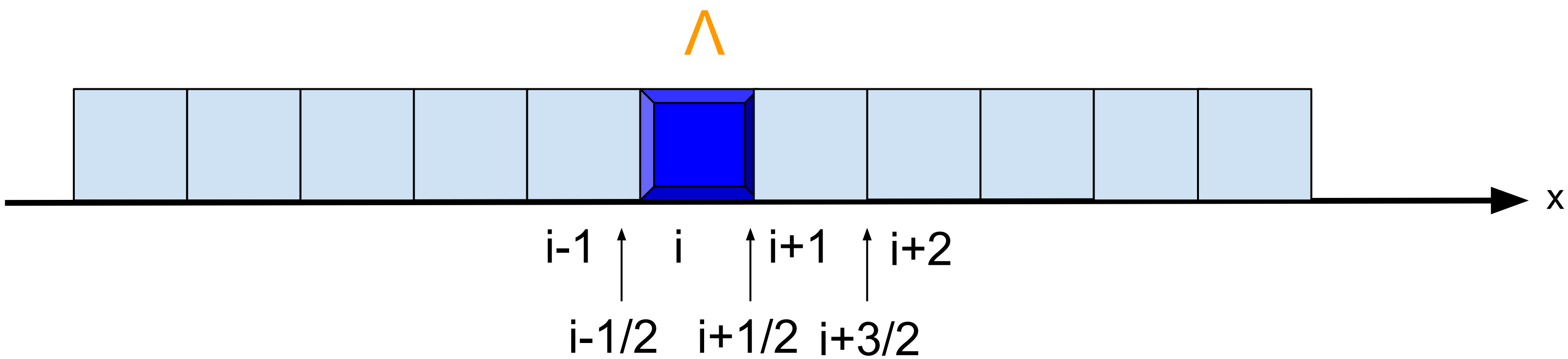




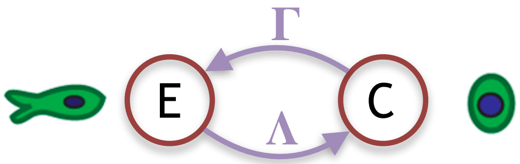
$$\partial_t \rho^{+}_{i+\frac{1}{2}}(t) = \left(\frac{\Gamma}{2}\rho^{c}_{i}(t) + \rho^{+}_{i-\frac{1}{2}}(t)\right) - \rho^{+}_{i+\frac{1}{2}}(t)\,(1+\Lambda)$$

Analytical model

1D analytical model without exclusions

For ρ^c :

$$\partial_t \rho_i^c(t) = -\Gamma \rho_i^c(t) + \Lambda \left(\rho_{i-\frac{1}{2}}^-(t) + \rho_{i+\frac{1}{2}}^+(t) \right)$$



Supposing there is a continuous function $\tilde{\rho}^c$ regular enough, the hydrodynamic limit gives :

$$\partial_t \rho^c = \Lambda \left(\rho^+ + \rho^- + \frac{1}{2} a \partial_x (\rho^+ - \rho^-) + \frac{a^2}{8} \partial_{xx} (\rho^+ - \rho^-) \right) - \Gamma \rho^c + (a^3)$$

1st Master Equation for $\rho^c(x,t)$

1D analytical model without exclusions

3 populations = 3 equations

$$\partial_t \rho^c = \Lambda\left(\rho^+ + \rho^- + \frac{1}{2}a\partial_x(\rho^+ - \rho^-) + \frac{a^2}{8}\partial_{xx}(\rho^+ - \rho^-)\right) - \Gamma\rho^c + \mathcal{O}(a^3)$$

$$\partial_t \rho^+ = \frac{\Gamma}{2}\rho^c - a\frac{\Gamma}{4}\partial_x\rho^c + \frac{a^2}{16}\rho^c - \Lambda\rho^+ - \frac{a^2}{2}\partial_{xx}\rho^+ + \mathcal{O}(a^3)$$

$$\partial_t \rho^- = \frac{\Gamma}{2}\rho^c + a\frac{\Gamma}{4}\partial_x\rho^c + \frac{a^2}{16}\rho^c - \Lambda\rho^- + \frac{a^2}{2}\partial_{xx}\rho^- + \mathcal{O}(a^3)$$

Master Equations (x,t)

1D analytical model without exclusions

Note : We have defined $\rho^c+\rho^++\rho^- = \rho^{tot}$: total cell density

$$\partial_t \rho^c = \Lambda \left(\rho^+ + \rho^- \right) - \Gamma \rho^c$$

$$\partial_t \rho^+ = \frac{\Gamma}{2} \rho^c \quad - \Lambda \rho^+$$

$$\partial_t \rho^- = \frac{\Gamma}{2} \rho^c \quad - \Lambda \rho^-$$

$$\partial_t \rho^{tot} = 0 + \mathcal{O}(a)$$

➡ *Conservation equation*

1D analytical model without exclusions

3 populations = 3 equations

$$\partial_t \rho^c = \Lambda\left(\rho^+ + \rho^- + \frac{1}{2}a\partial_x(\rho^+ - \rho^-) + \frac{a^2}{8}\partial_{xx}(\rho^+ - \rho^-)\right) - \Gamma\rho^c + \mathcal{O}(a^3)$$

$$\partial_t \rho^+ = \frac{\Gamma}{2}\rho^c - a\frac{\Gamma}{4}\partial_x\rho^c + \frac{a^2}{16}\rho^c - \Lambda\rho^+ - \frac{a^2}{2}\partial_{xx}\rho^+ + \mathcal{O}(a^3)$$

$$\partial_t \rho^- = \frac{\Gamma}{2}\rho^c + a\frac{\Gamma}{4}\partial_x\rho^c + \frac{a^2}{16}\rho^c - \Lambda\rho^- + \frac{a^2}{2}\partial_{xx}\rho^- + \mathcal{O}(a^3)$$

Master Equations (x,t)

Analytical model

1D analytical model without exclusions

At long time scale *t* from the balance of different populations

$$0 = \Lambda \left(\rho^+ + \rho^- + \frac{1}{2} a \partial_x (\rho^+ - \rho^-) + \frac{a^2}{8} \partial_{xx} (\rho^+ - \rho^-) \right) - \Gamma \rho^c + \mathcal{O}(a^3)$$

$$0 = \frac{\Gamma}{2} \rho^c - a \frac{\Gamma}{4} \partial_x \rho^c + \frac{a^2}{16} \rho^c - \Lambda \rho^+ - \frac{a^2}{2} \partial_{xx} \rho^+ + \mathcal{O}(a^3)$$

$$0 = \frac{\Gamma}{2} \rho^c + a \frac{\Gamma}{4} \partial_x \rho^c + \frac{a^2}{16} \rho^c - \Lambda \rho^- + \frac{a^2}{2} \partial_{xx} \rho^- + \mathcal{O}(a^3)$$

1D analytical model without exclusions

At long time scale *t* from the balance of different populations

$$0 = \Lambda\left(\rho^+ + \rho^-\right) - \Gamma\rho^c + \mathcal{O}(a^1)$$

$$0 = \frac{\Gamma}{2}\rho^c - \Lambda\rho^+ + \mathcal{O}(a^1)$$

$$0 = \frac{\Gamma}{2}\rho^c - \Lambda\rho^- + \mathcal{O}(a^1)$$

$$S = \rho^+ - \rho^-$$

$$U = \rho^+ + \rho^- - \frac{\Gamma}{\Lambda}\rho^c$$

$$\rho^{tot} = cte$$

1D analytical model without exclusions

At long time scale *t* from the balance of different populations

$$0 = \Lambda\left(\rho^{+} + \rho^{-}\right) - \Gamma\rho^{c} + \mathcal{O}(a^{1})$$

$$0 = \frac{\Gamma}{2}\rho^{c} - \Lambda\rho^{+} + \mathcal{O}(a^{1})$$

$$0 = \frac{\Gamma}{2}\rho^{c} - \Lambda\rho^{-} + \mathcal{O}(a^{1})$$

$$S = \rho^{+} - \rho^{-}$$

$$U = \rho^{+} + \rho^{-} - \frac{\Gamma}{\Lambda}\rho^{c}$$

$$\rho^{tot} = cte$$

$$\partial_t \rho^{tot}(x,t) = \nabla^2 D_{\text{eff}}\,\rho^{tot}(x,t)$$

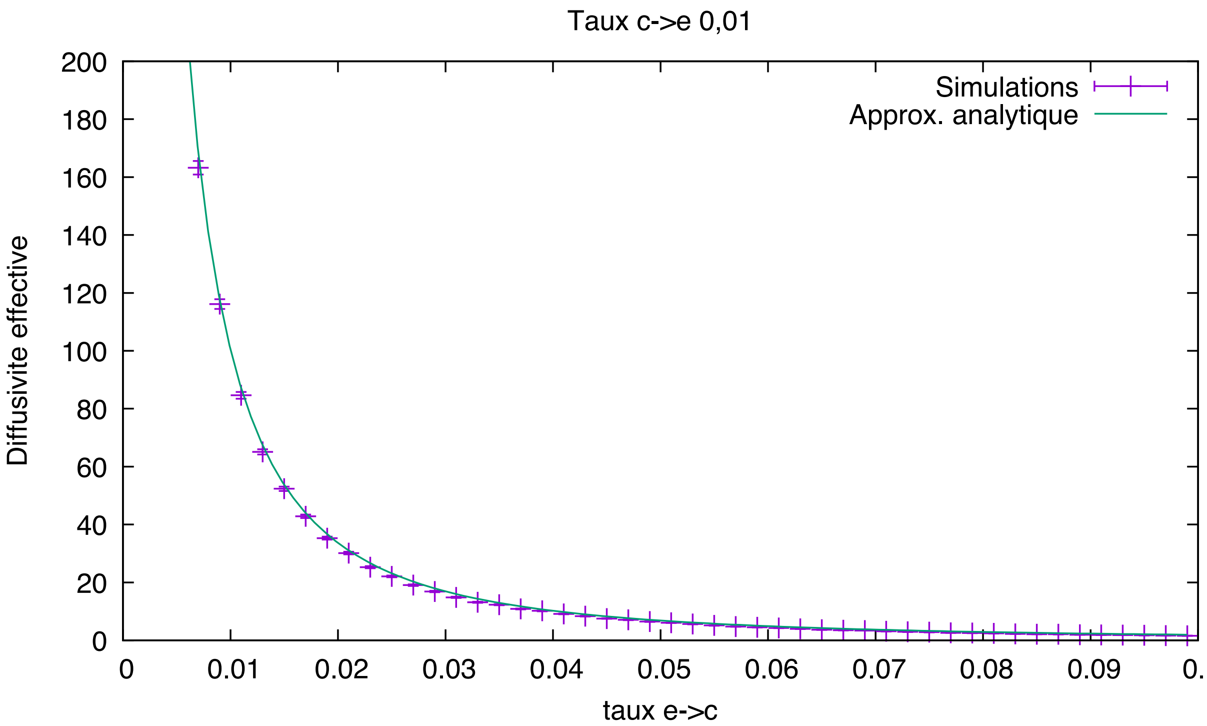
1D analytical model without exclusions

$$\partial_t \rho^{tot}(x,t) = \nabla^2 D_{\text{eff}} \rho^{tot}(x,t)$$

$$D_{\text{eff}}(t_{c\to e}, t_{e\to c}) = \frac{\frac{1}{2} + \frac{1}{t_{e\to c}}}{1 + \frac{t_{e\to c}}{t_{c\to e}}}$$

Compared with :

$$2 \times d \times D_{simulation} \times t = \langle x^2(t) \rangle$$



1D analytical model without exclusions

$$\partial_t \rho^{tot}(x,t) = \nabla^2 D_{\text{eff}} \rho^{tot}(x,t)$$

$$D_{\text{eff}}(t_{c\to e}, t_{e\to c}) = \frac{\frac{1}{2} + \frac{1}{t_{e\to c}}}{1 + \frac{t_{e\to c}}{t_{c\to e}}}$$

Compared with :

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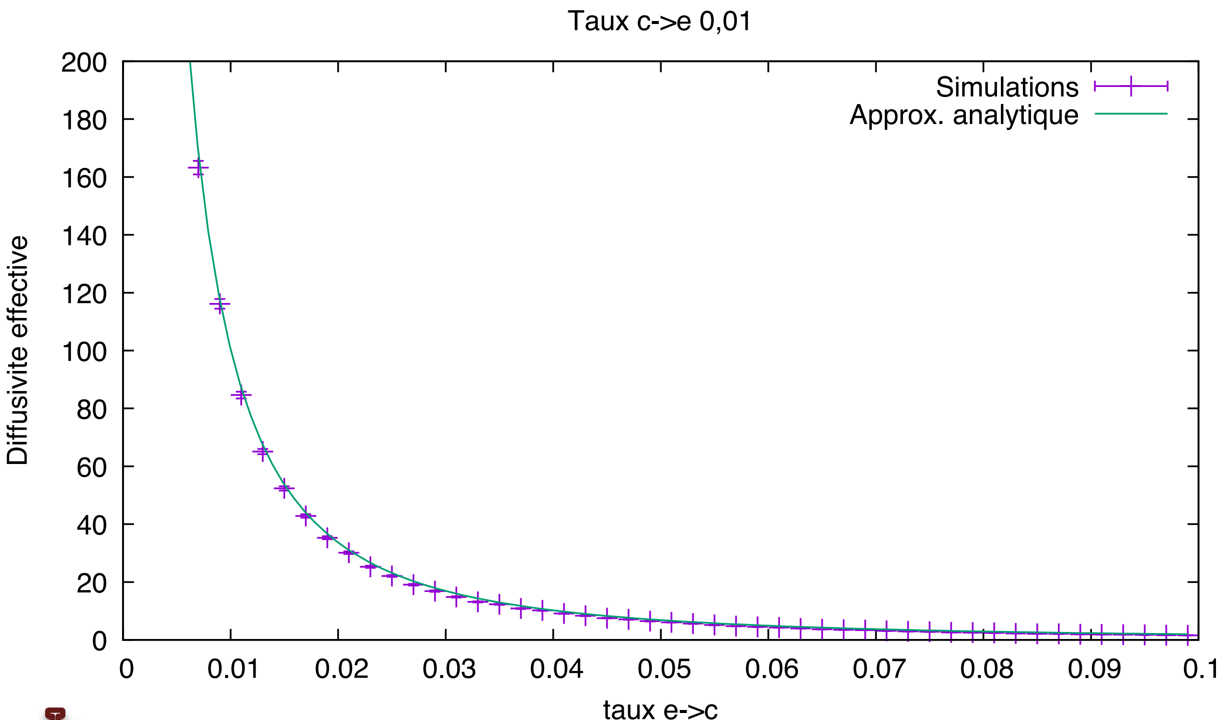


The analytical model is a good approximation at low density !

Hours vs instantly

1D comparison with exclusions

~~$$\partial_t \rho^{tot}(x,t) = \nabla^2 D_{\text{eff}} \rho^{tot}(x,t)$$~~

Adding contact interactions

$$\partial_t \rho^{\text{tot}}(x,t) = \nabla\left(D_{\text{eff}}^{1\text{D}}[\rho^{\text{tot}}(x,t)]\nabla \rho^{\text{tot}}(x,t)\right)$$

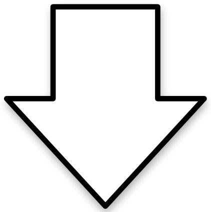
Using the same derivation techniques

$$\partial_t \rho^+_{i+\frac{1}{2}}(t) = \left(\frac{\Gamma}{2}\rho^c_i(t) + \rho^+_{i-\frac{1}{2}}(t)\right)\left(1 - \rho^c_{i+1}(t) - \rho^+_{i+\frac{3}{2}}(t) - \rho^-_{i+\frac{3}{2}}(t)\right)$$
$$- \rho^+_{i+\frac{1}{2}}(t)\left(1 + \Lambda - \rho^c_{i+2}(t) - \rho^+_{i+\frac{5}{2}}(t) - \rho^-_{i+\frac{5}{2}}(t)\right)$$

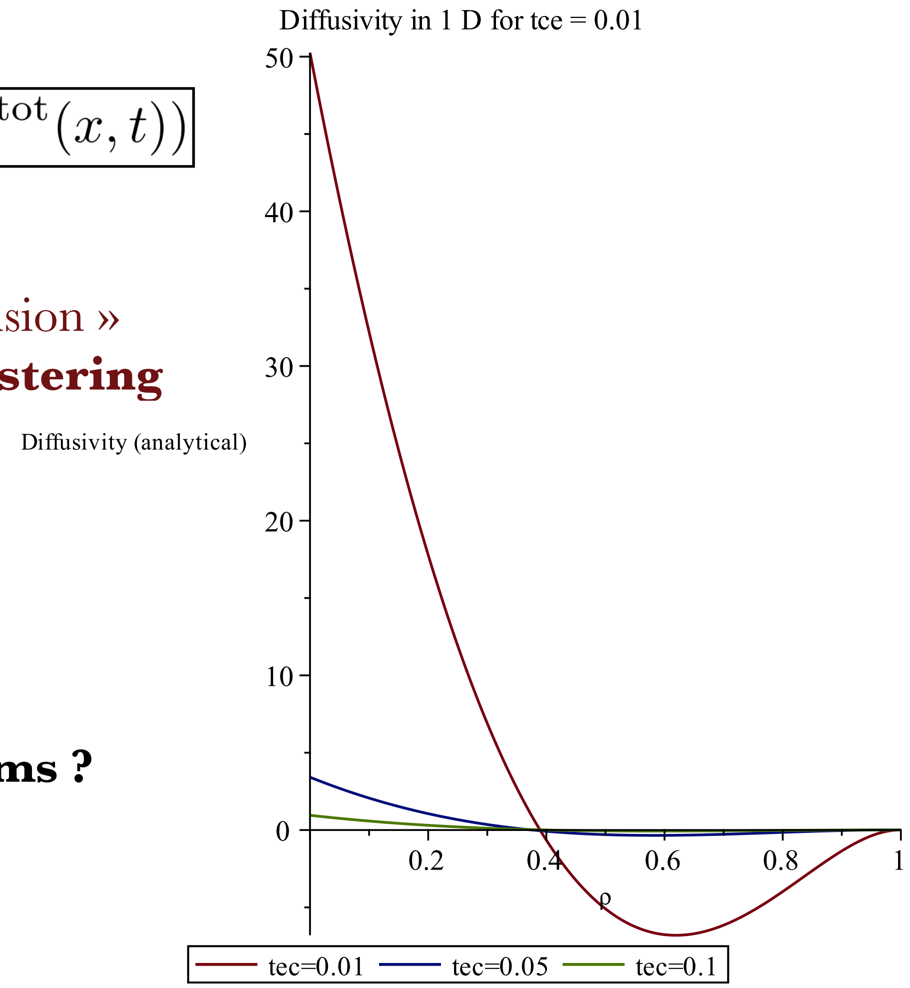
1D comparison with exclusions

$$\partial_t \rho^{\text{tot}}(x,t) = \nabla(D_{\text{eff}}^{1D}[\rho^{\text{tot}}(x,t)]\nabla\rho^{\text{tot}}(x,t))$$

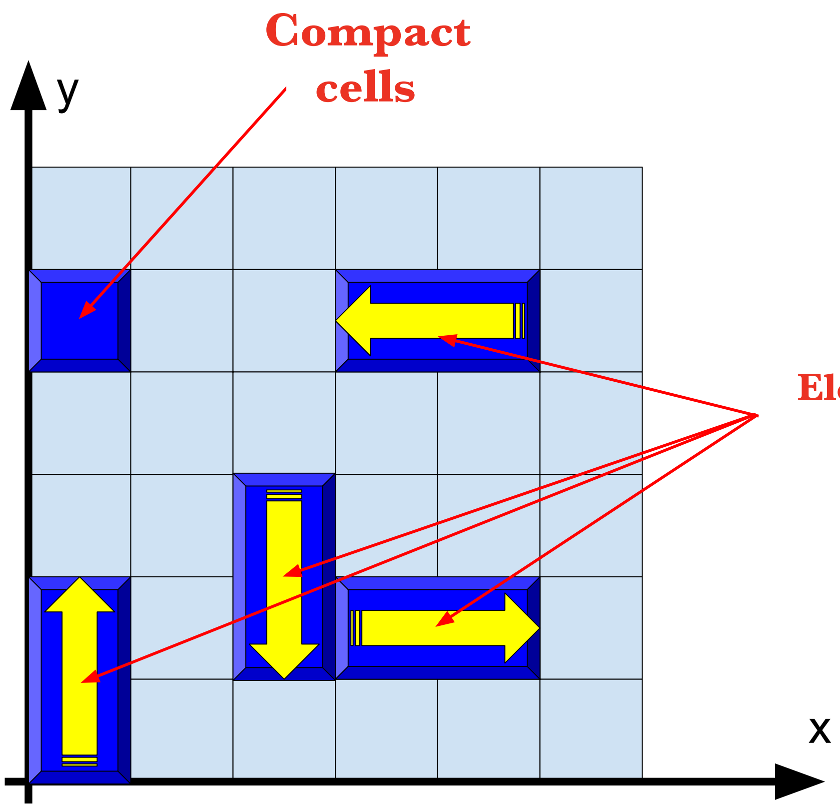
Some regimes tends to have « anti-diffusion » which can be interpreted as **cellular clustering**

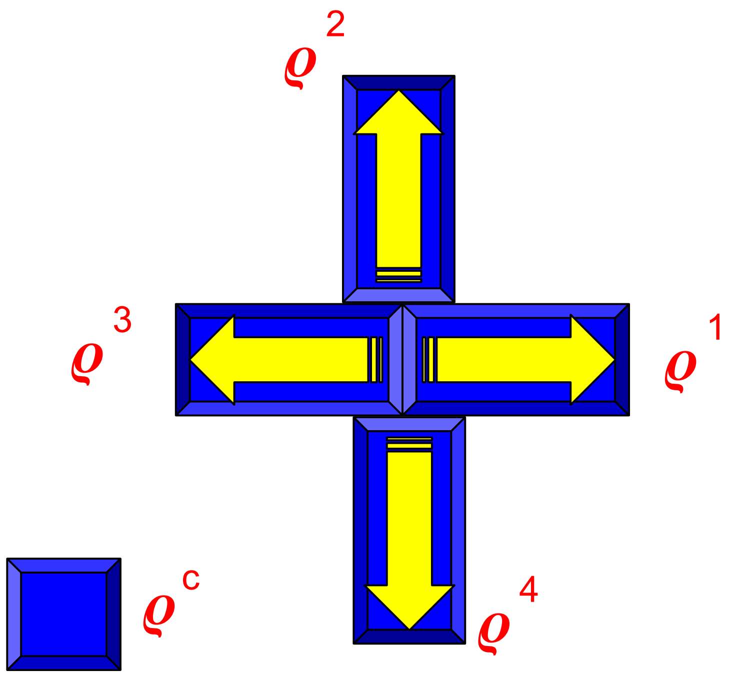


Better visualization in 2D systems ?



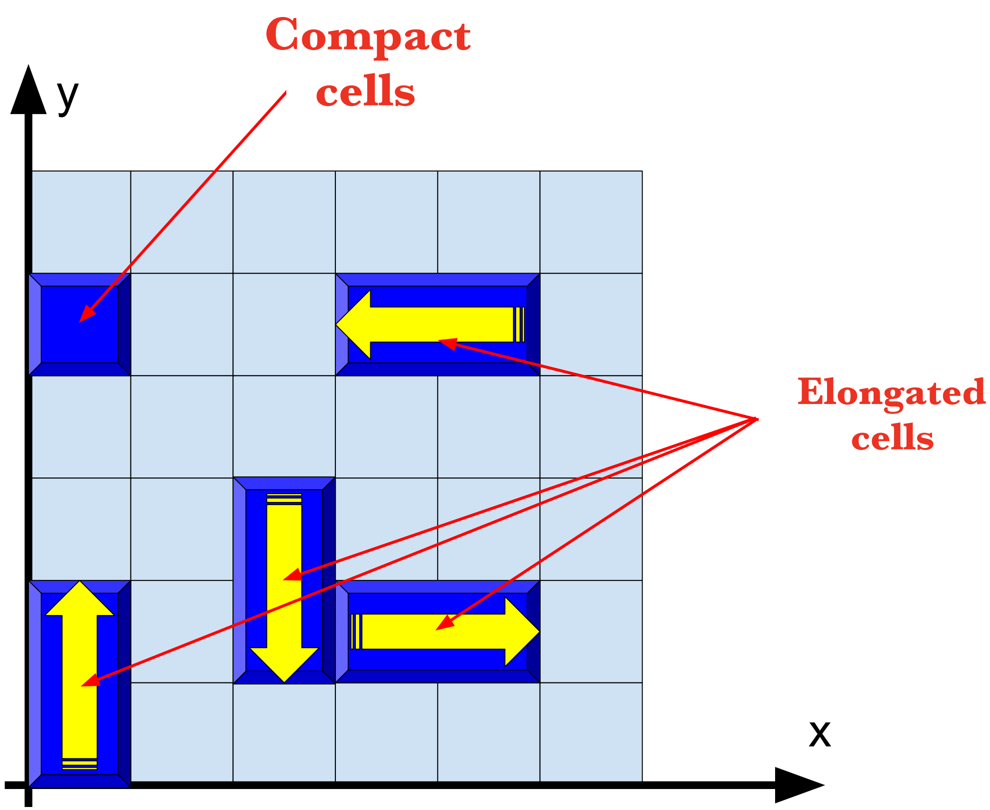
2D cell automata with exclusions

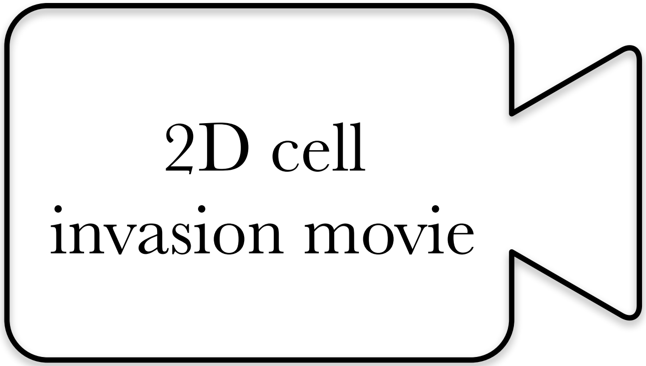




Towards a 2D model with contact interactions

2D cell automata with exclusions





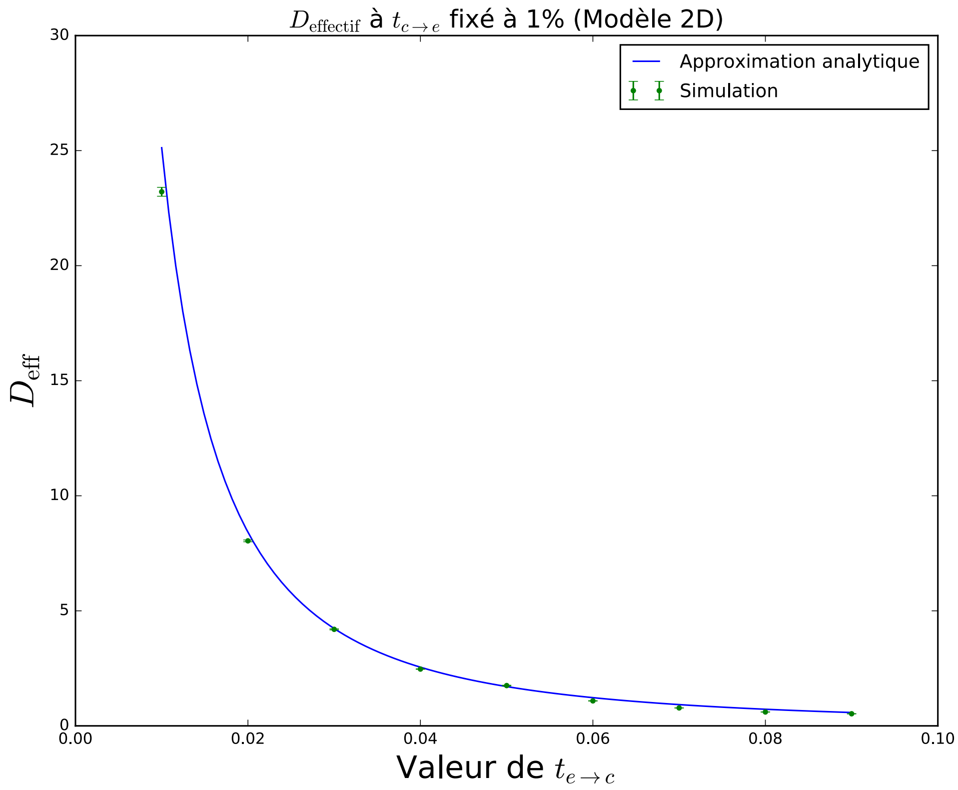
2D cell automata without exclusions

$$\partial_t \rho^{tot}(x,t) = \nabla^2 D_{\text{eff}} \rho^{tot}(x,t)$$

$$D^{2\text{D}}_{\text{eff}}(t_{c\to e}, t_{e\to c}) = \frac{1}{2}\frac{\frac{1}{2} + \frac{1}{t_{e\to c}}}{1 + \frac{t_{e\to c}}{t_{c\to e}}} = \frac{D^{1\text{D}_{\text{eff}}}}{2}$$

à comparer avec:

$$2 \times d \times D_{simulation} | \times t = \langle x^2(t) + y^2(t) \rangle$$



2D cell automata without exclusions

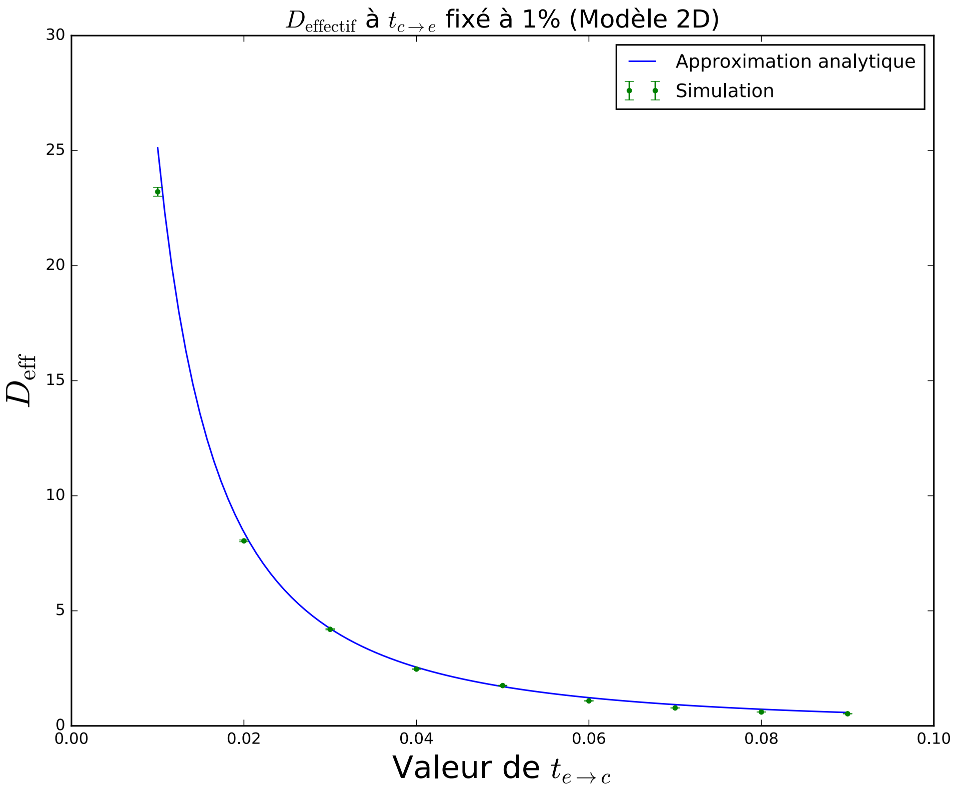
$$\partial_t \rho^{tot}(x,t) = \nabla^2 D_{\text{eff}} \rho^{tot}(x,t)$$

$$D^{2D}_{\text{eff}}(t_{c\to e}, t_{e\to c}) = \frac{1}{2} \frac{\frac{1}{2} + \frac{1}{t_{e\to c}}}{1 + \frac{t_{e\to c}}{t_{c\to e}}} = \frac{D^{1D_{\text{eff}}}}{2}$$

à comparer avec:

$$2 \times d \times D_{simulation} \times t = \langle x^2(t) + y^2(t) \rangle$$

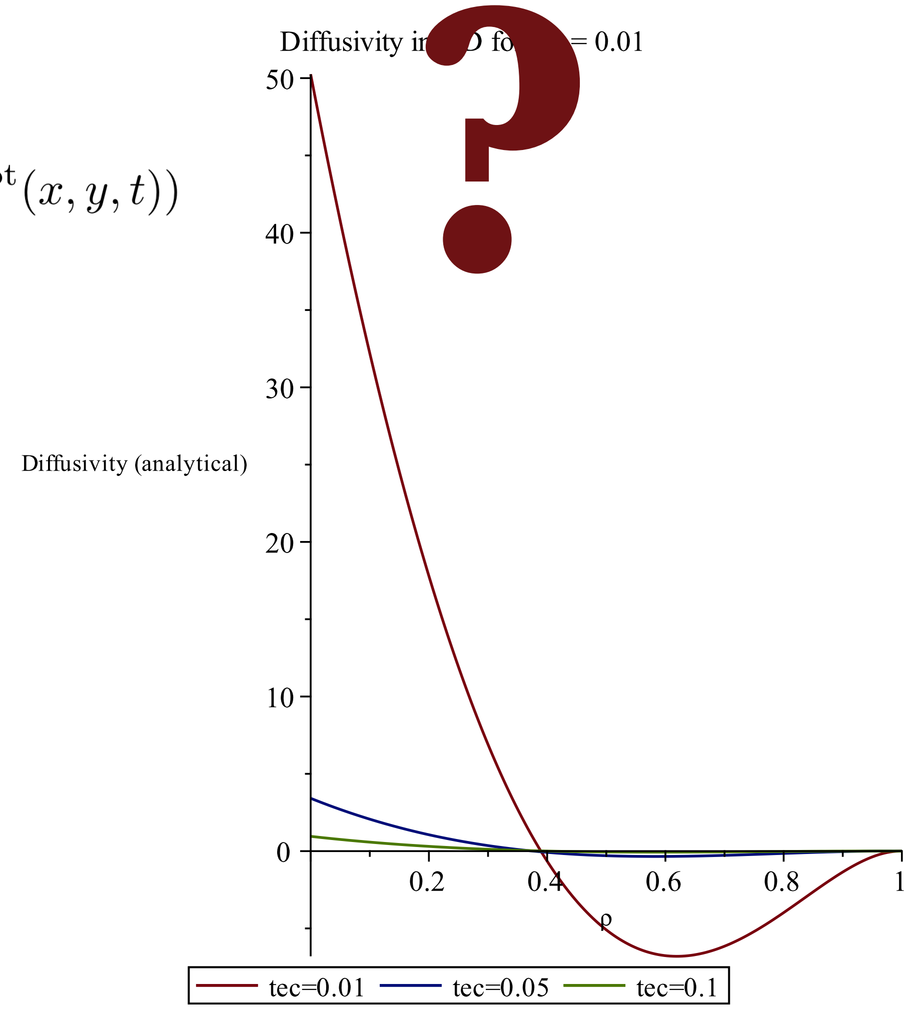
Still a good approximation at low density !



2D comparison with exclusions

$$\frac{\partial \rho^{\text{tot}}}{\partial t}(x,y,t) = \nabla(D_{\text{eff}}^{2\text{D}}[\rho^{\text{tot}}(x,y,t)]\nabla\rho^{\text{tot}}(x,y,t))$$

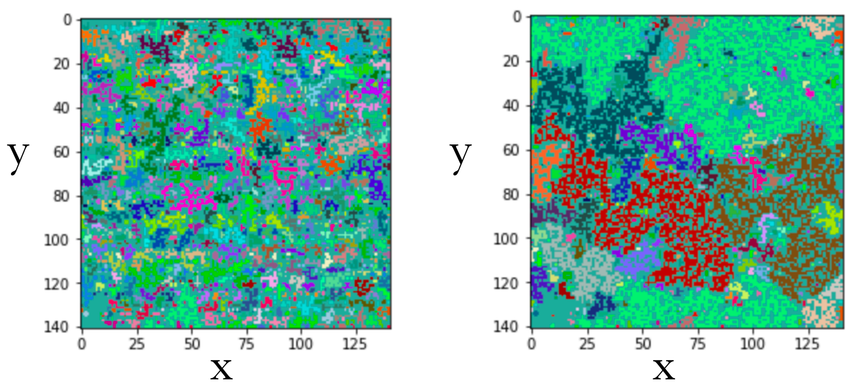
Cellular clustering ?



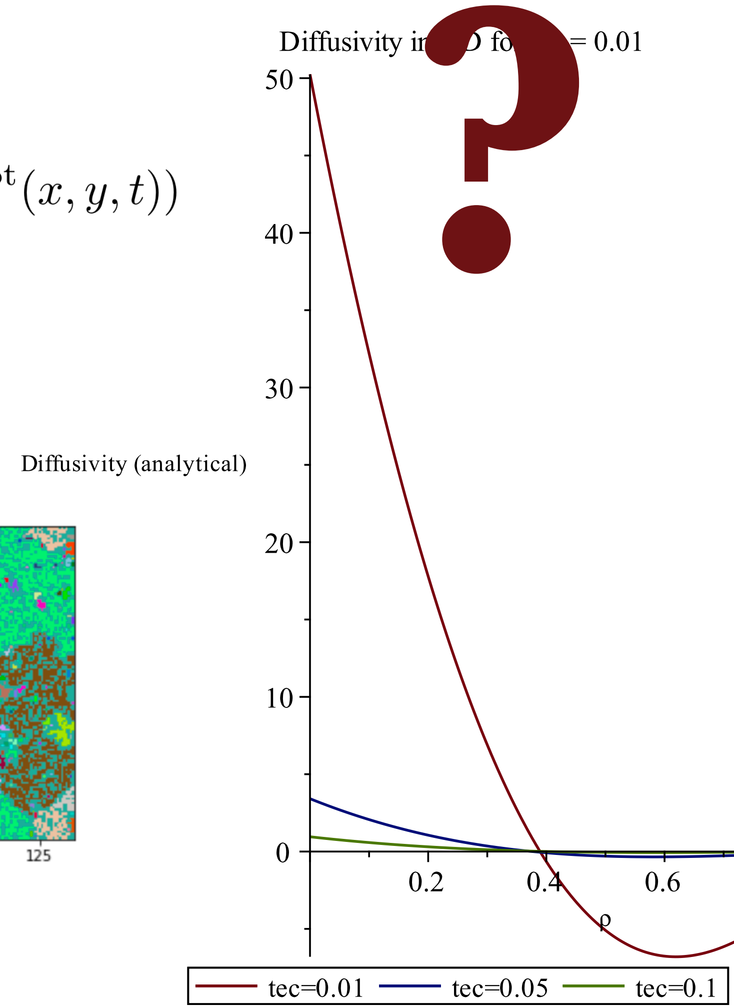
2D comparison with exclusions

$$\frac{\partial \rho^{\text{tot}}}{\partial t}(x,y,t) = \nabla(D_{\text{eff}}^{2D}[\rho^{\text{tot}}(x,y,t)]\nabla \rho^{\text{tot}}(x,y,t))$$

Cellular clustering ?



Time t

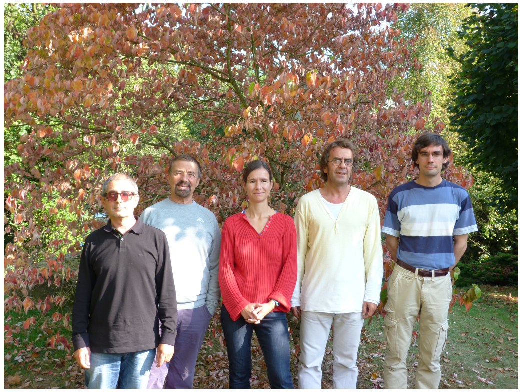


Thanks to all collaborators

In2p3, IMNC

MSB team

- Christophe Deroulers
- Mathilde Badoual
- Roland Mastrippolito
- Basile Grammaticos
- Alfred Ramani



Collaboration with APHP

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imagerie et modelisation en neurobiologie et cancerologie

Thank you for your attention

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