Multi-scale modelling and simulation of avascular tumour growth

A study of the role of the micro-environment in the metastatic escape

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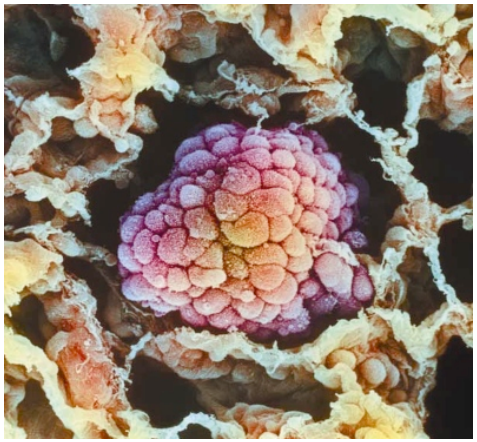


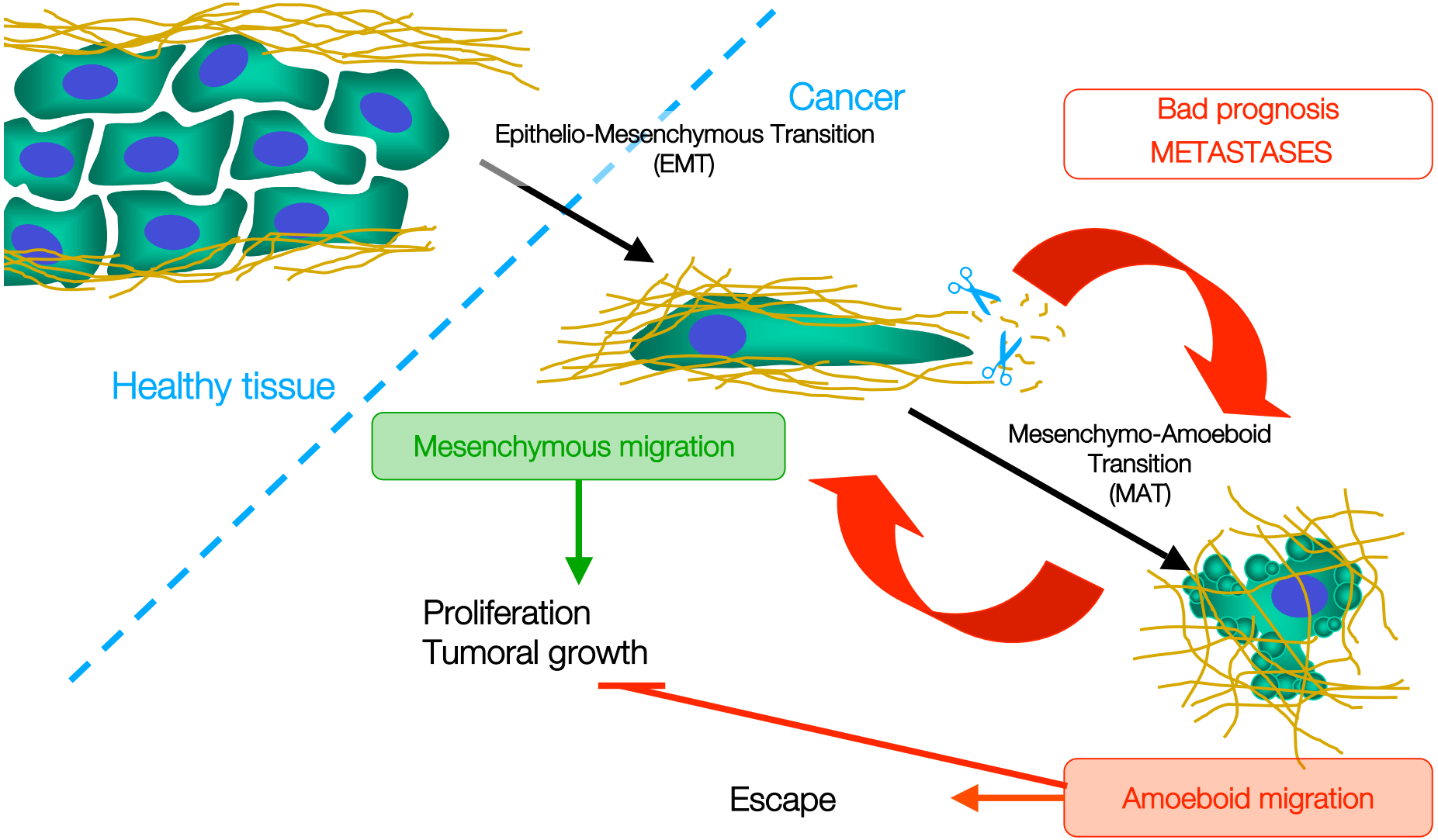
lung cancer metastasis

Outline

- Presentation of the biological model
- Modelling issues
- A first naive approach
- A hybrid multi-scale approach
- Current modelling issues

Current knowledge – metastasis and cellular migration

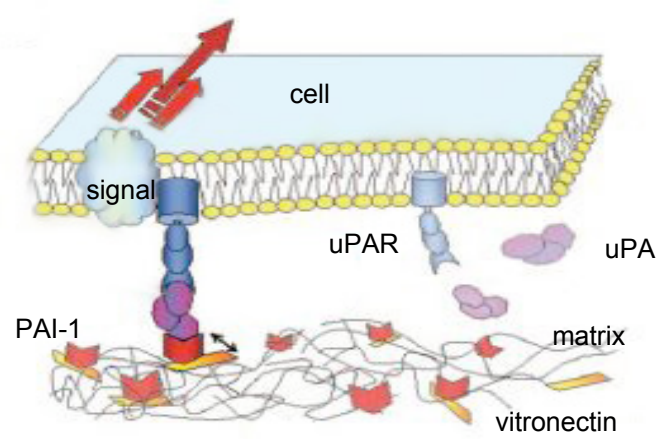
Transitions of the cellular migration mode during the cancerous process



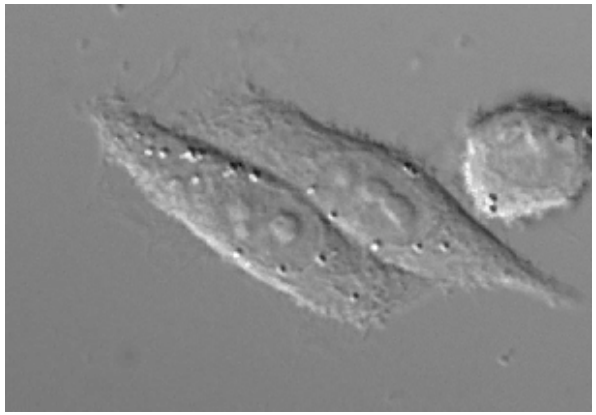
Metastases and cellular microenvironment

The environment is capable of inducing a metastatic behaviour

- Matrix-bound PAI-1 = inducer of cancerous migration
  - Molecular interface between matrix and cells
  - Migration parameters modulator
  - Factor of bad prognosis
- Matrix-bound PAI-1 = signal
  - Activation of the RhoA/ROCK GTPase pathway
  - Reorganisation of the actin cytoskeleton (rings)
  - « Blebbing » process

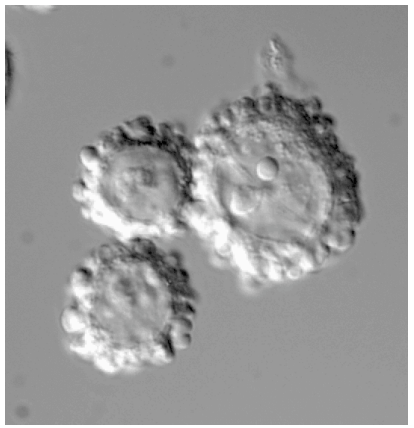


Collagen



[Malo et al. 2005]

PAI-1



[Malo et al. 2005]

« blebbing »

Issues addressed

- Biological issues
  - Understand the role of PAI-1 in the metastatic escape
  - Understand the interactions between cells and their micro-environment

- Modelling issues
  - Model the proliferation process (tumoral growth)
  - Model the PAI-1 endocytosis and exocytosis processes
    - formation of a PAI-1 ring around the tumour

The different states of PAI-1

- Different types of PAI-1
  - Soluble Form

Produced by the cells

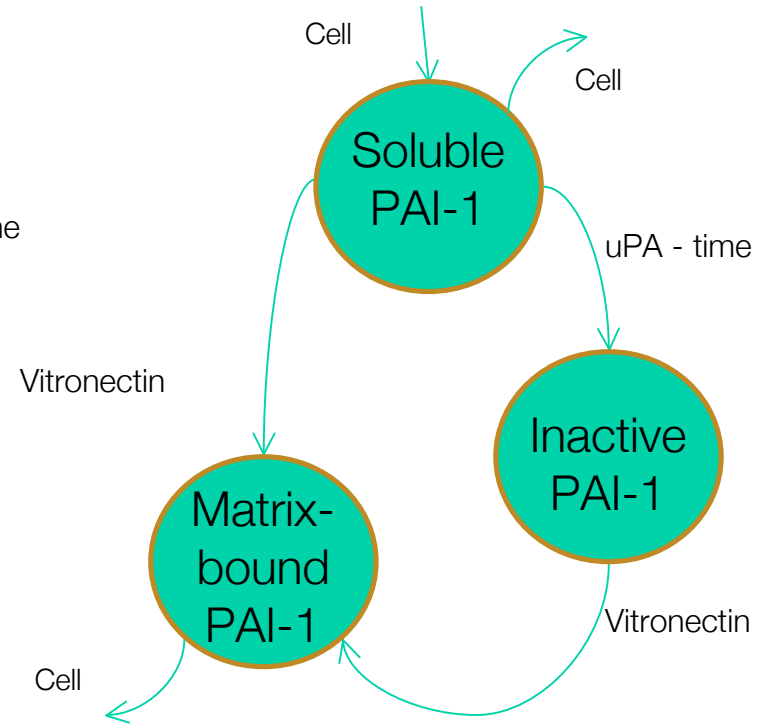
Possible link to uPa/uPar receptors (simplification) on the membrane
→ Internalisation, no propulsion effect
Possible link to the vitronectin on the extra-cellular matrix
→ Switch to matrix-bound state
Loose of activity
→ Switch to inactive state

  - Inactive Form

Possible link to the vitronectin on the extra-cellular matrix
→ Switch to matrix-bound state, reactivation

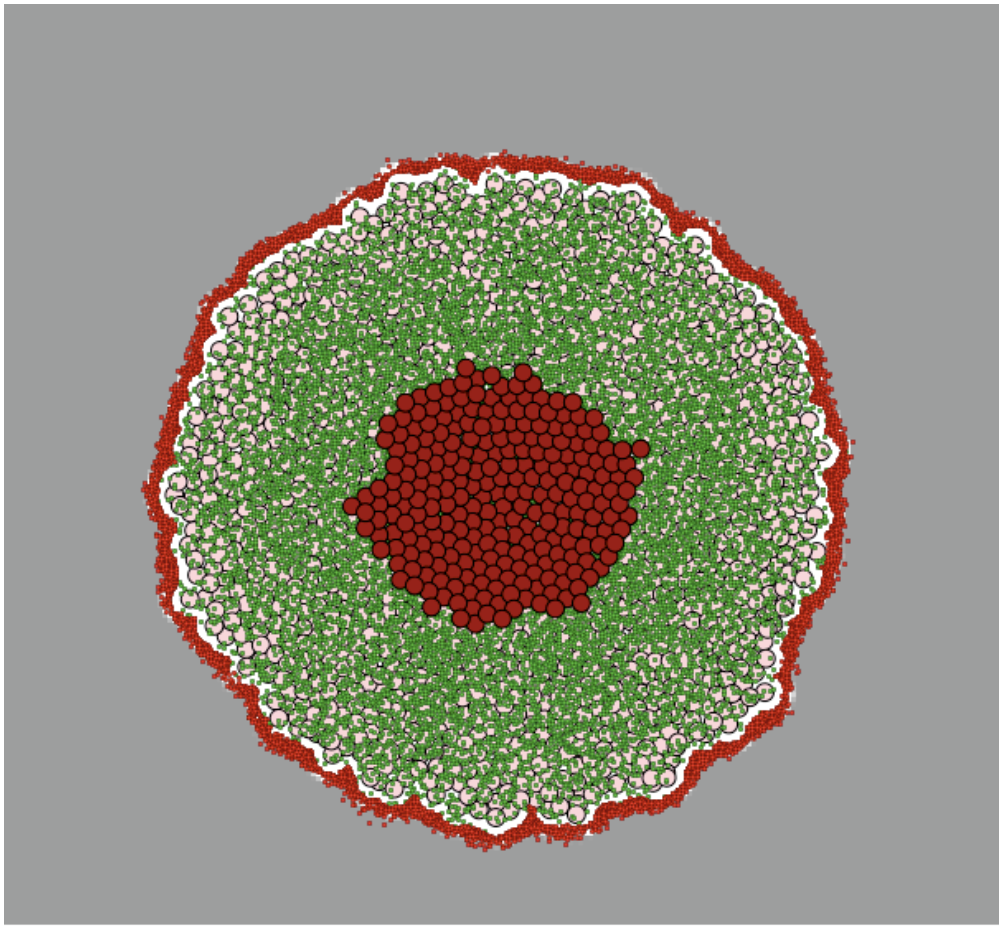
  - Matrix-bound Form

Possible link to uPa/uPar receptors (simplification) on the membrane
→ Internalisation, propulsion effect



Modelling

- Environment
  - matrix / vitronectin
- Agents
  - cells
    - proliferating
    - quiescent
    - necrosed
  - molecules
    - soluble PAI-1
    - matrix-bound PAI-1

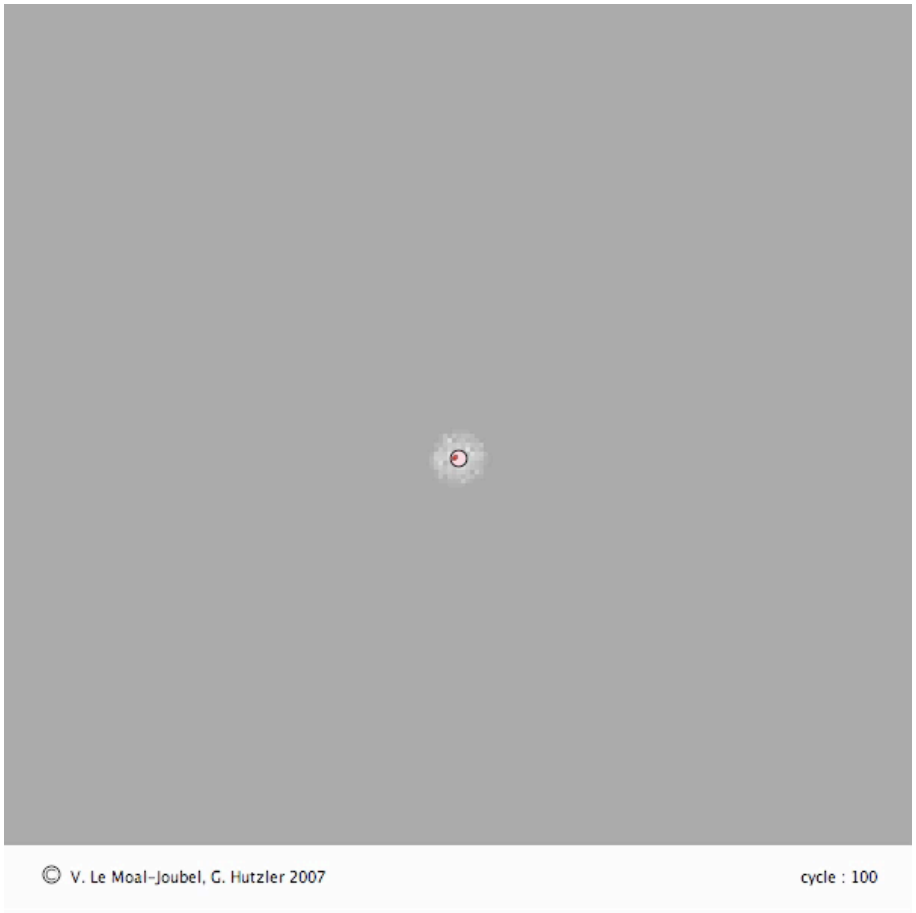


Behaviour of the agents

- Cell
  - Division
    - Local movement
    - Repulsive movements between cells
  - Links with PAI-1
    - Production of soluble PAI-1
    - Internalisation of surrounding PAI-1
  - Metabolism
    - Proliferating / quiescent / necrosed life cycle
  - Matrix degradation
- Soluble PAI-1
  - Pseudo-brownian movement
  - Possible inactivation
- Matrix-bound PAI-1
  - No behaviour

First results (1/4)

Tumour growth



Proliferating cell

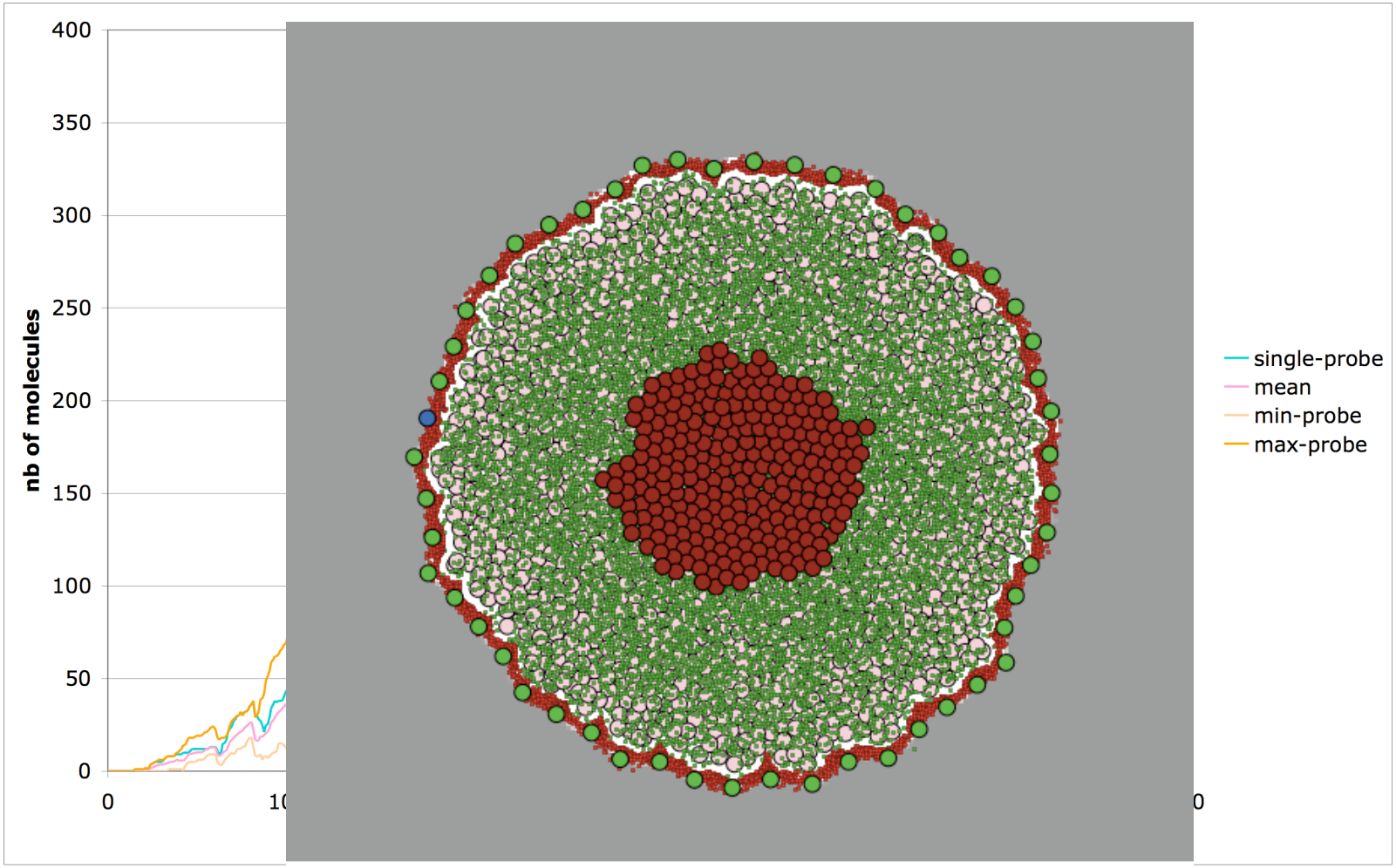
Necrosed cell

Soluble PAI-1

Matrix-bound PAI-1

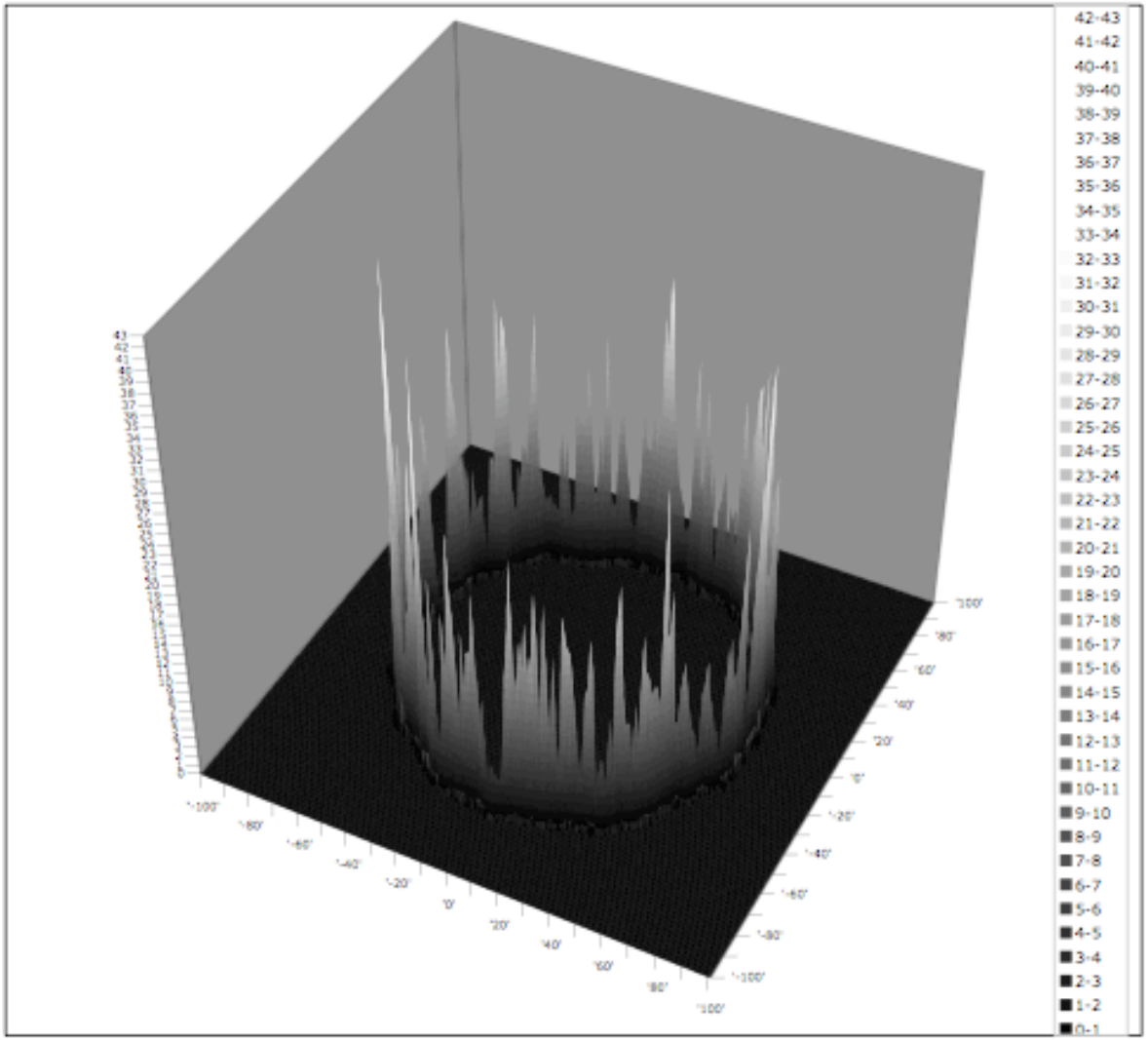
First results (2/4)

Available matrix-bound PAI-1 around the tumour



First results (3/4)

Available matrix-bound PAI-1 around the tumour

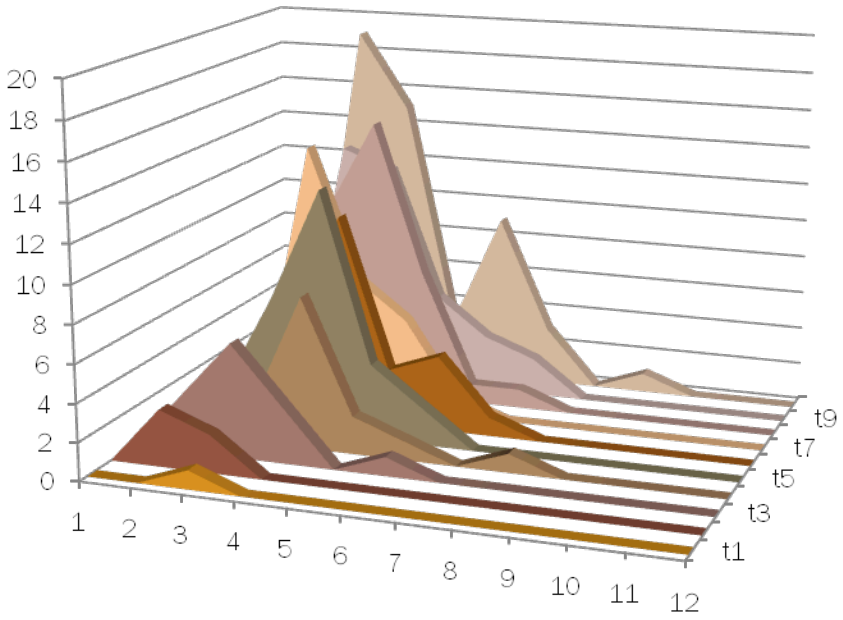


[Malo et al. 2009, Math.Pop Studies]

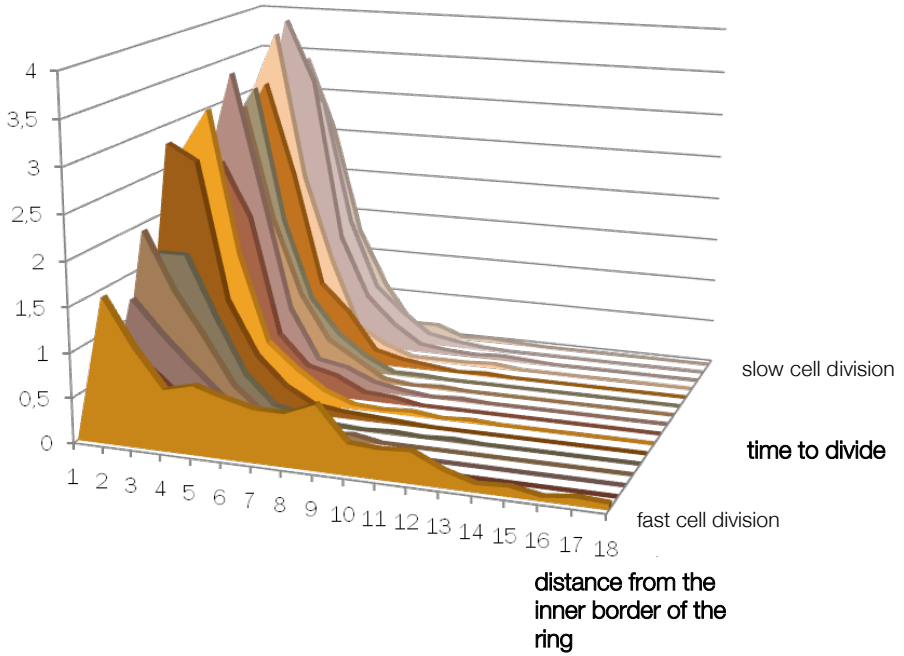
First results (4/4)

Characterization of the PAI-1 ring

Along time



Depending on cell division time



Conclusion

- Very simple model...
  - approximate tumoral growth
  - approximate diffusion of the molecules
  - no mechanical constraints on the growth of the tumour
  - no realistic diffusion of the nutrients
  - rigid cells
  - 2D
  - etc.
- ...but some qualitatively satisfying results
  - constitution of a matrix-bound PAI-1 ring
  - characterisation of the ring
  - compatible with the metastatic escape of some cells (but not all)

Towards a multi-scale hybrid model

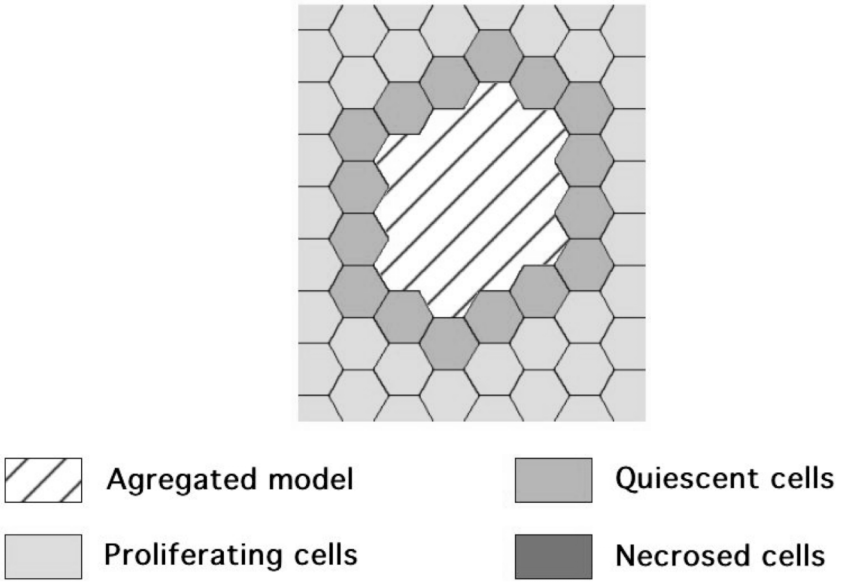
- Problem
  - tumoral growth leads to
    - thousands of cells
    - hundreds of thousand of molecules
  - impossible to simulate big tumours
  - impossible to add much details

- But...
  - not necessary to model PAI-1 molecules or cells at the individual level inside the tumour
  - the zone of interest is at the interface between the tumour and the extra-cellular matrix

- Proposal = aggregated model inside the tumour that contains
  - a number of active / inactive PAI-1 molecules
  - a number of necrosed / quiescent cells

Definition of the aggregated model

- Spatial extension



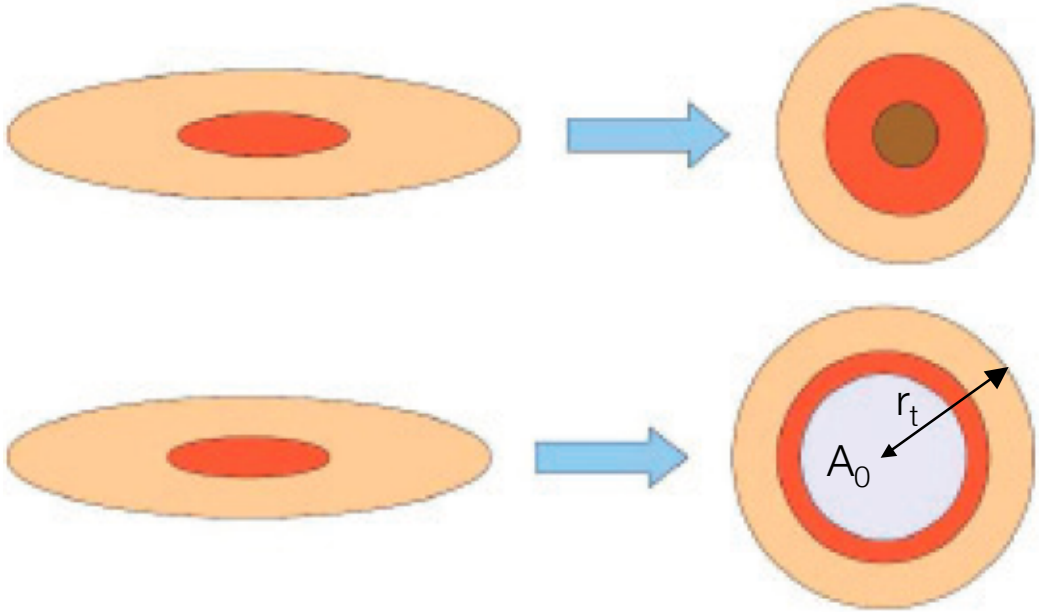
- Parameters
  - n_c, the number of quiescent cells
  - n_n, the number of necrosed cells
  - n_a, the number of active PAI-1 molecules
  - n_i, the number of inactive PAI-1 molecules

Update of the aggregated model

- Internal dynamics
  - update the number of quiescent and necrosed cells
  - update the number of active and inactive molecules
- Molecular exchanges
  - internalize individual PAI-1 molecules that collide the aggregated model
  - externalize the appropriate quantity of active and inactive PAI-1 molecules as individual agents
- Cell-cell interactions
  - repulse the neighbouring cells when the density of cells inside the aggregated model implies a compression of the cells
  - update the frontiers of the aggregated model

Internal dynamics

- update the number of quiescent and necrosed cells
  - cells too far away from the surface of the tumour become necrosed
  - depends on the size and shape of the tumour



$$n_n = (r_t - D_n)^2 - \frac{A_0}{\pi}$$

$$n_c = n_s - n_n$$

Internal dynamics

- update the number of active and inactive molecules
  - quiescent cells produce and internalize molecules
  - molecules become inactive after age i_{max}
  - depends on n_c the number of quiescent cells, and the mean number of receptors on their membrane

estimated number of internalized molecules $$\Delta_a = n_a(1 - P_{still})$$

estimated number of inactive molecules $$n_i' = n_i + n_{a,i_{max}}$$

estimated number of active molecules at age *i* $$n'_{a,i} = n_{a,i-1} - \frac{\Delta_a}{i_{max}} \quad \text{for } i = i_{max} \text{ down to } 1$$

estimated number of produced molecules $$n_0 = P_g n_c$$

Molecular exchanges

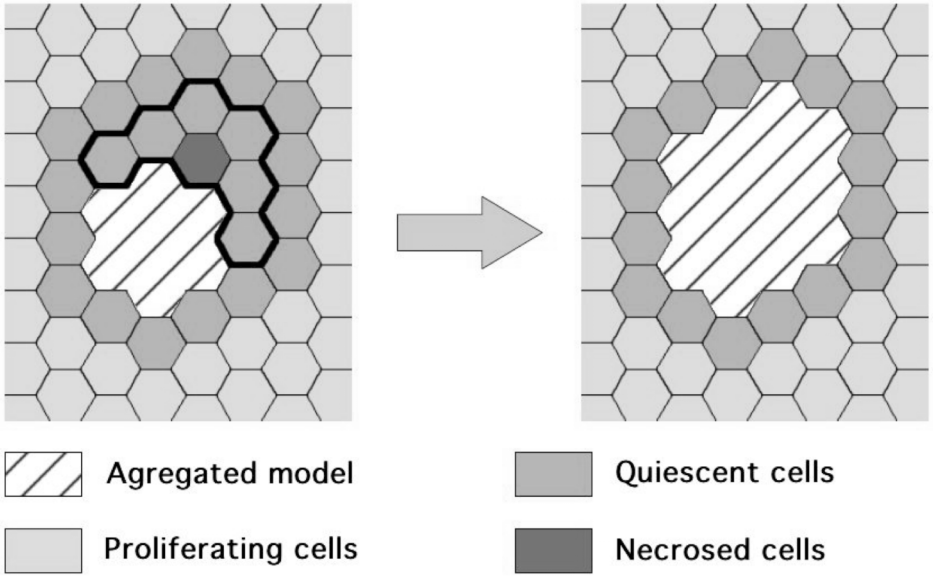
- compute the exchanges between the aggregated and the agent models
  - individual molecules bumping into the frontier of the aggregated model are integrated
  - molecules are externalized
  - depends on the molecular « pressure » inside the aggregated model

$$p = \frac{nRT}{V} = \alpha \frac{n}{V}$$

$$n_g = \alpha \frac{n_a + n_i}{r_c \sqrt{\frac{A_0}{\pi} + n_s}}$$

Cell-cell interactions

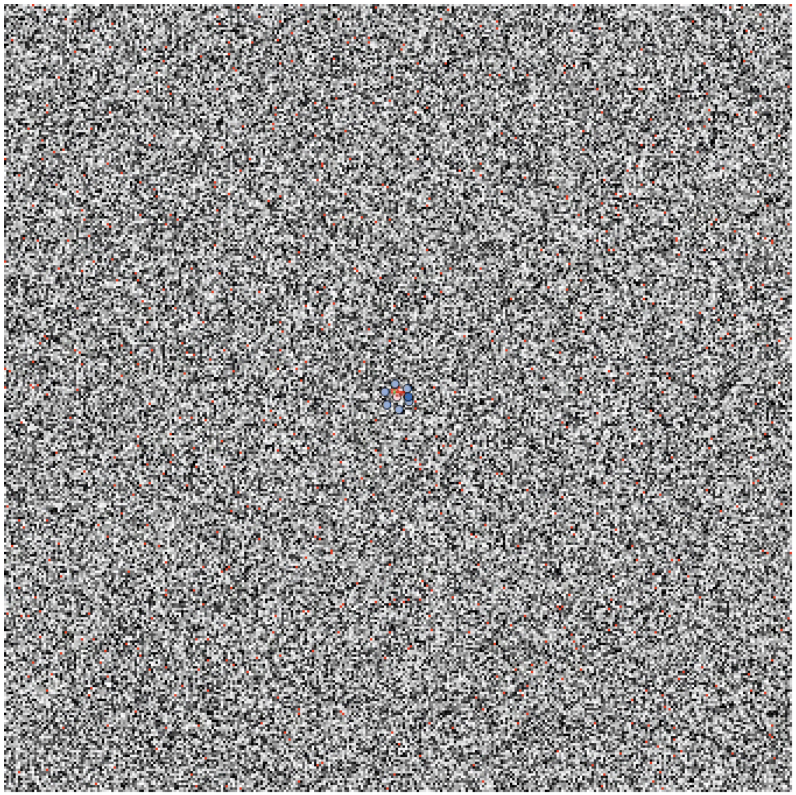
- update of the spatial extension of the aggregated model



- repel quiescent cells at the border when the volume V_0 of the virtual cell a the core of the tumour is negative

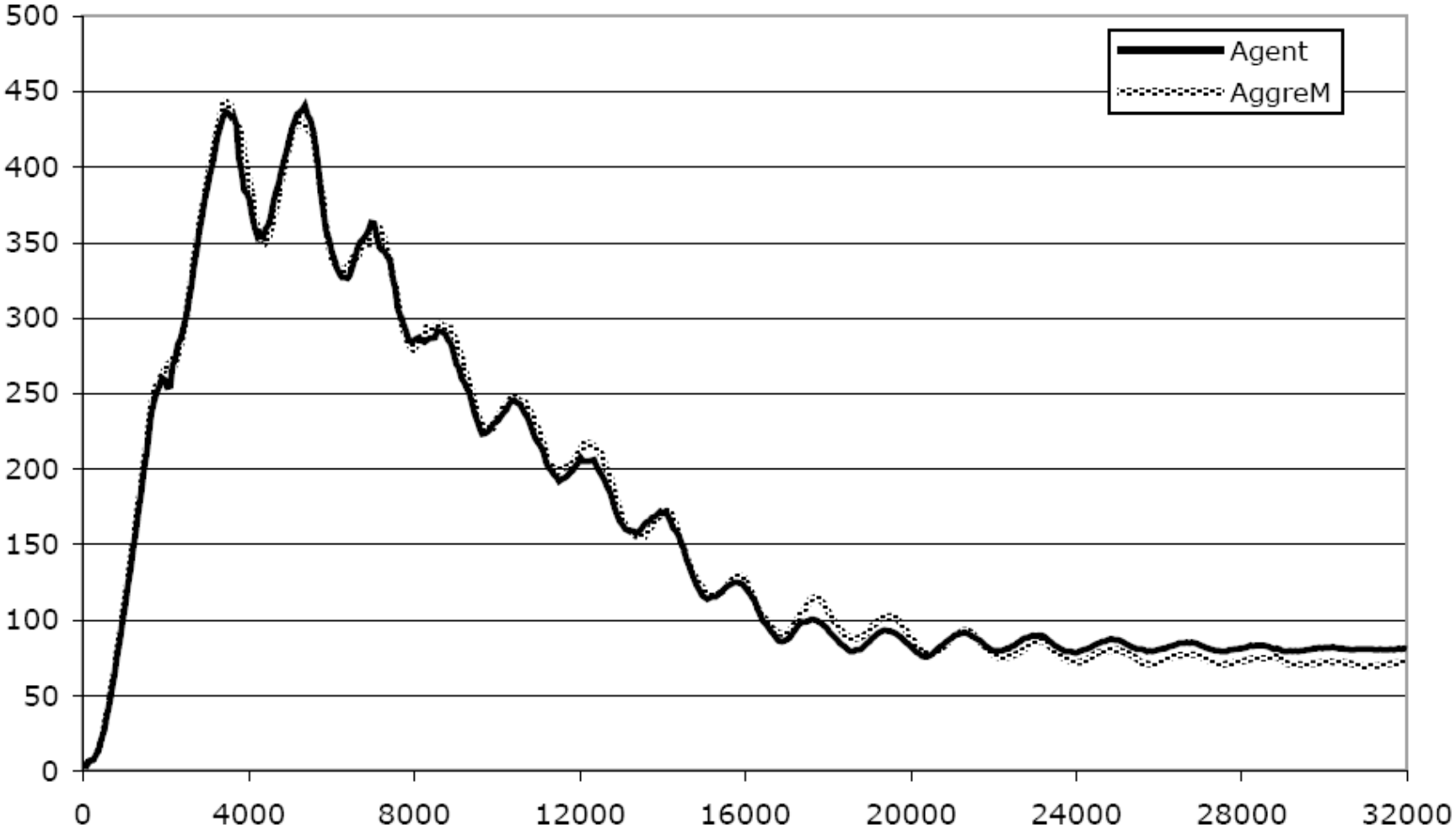
First results

- growth of the tumour
  - qualitatively and quantitatively equivalent
  - computationally much more efficient

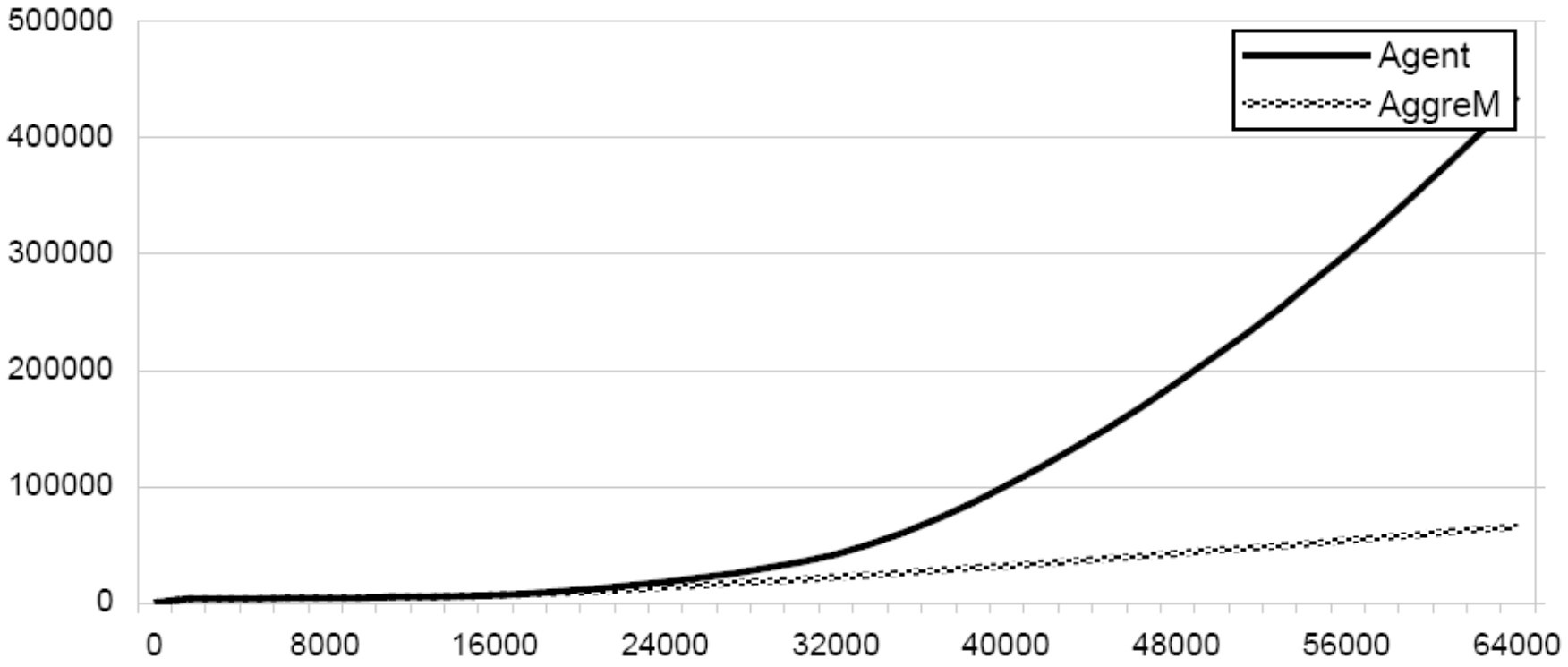


[Lepagnot & Hutzler 2009, JBPC]

Mean number of matrix-bound PAI-1 molecules



Comparison of computing power needed



Perspectives: from a biological point of view

Aim = gain insight on the conditions / specific topological configurations that can lead to the metastatic escape

- Calibrate / validate the model
  - need to validate with respect to the literature on avascular tumour growth
  - go 3D
- Better take into account the external constraints on the tumour growth
  - mechanical constraints because of external tissues
  - chemical constraints because of nutrients diffusion
- Add cell deformation and adhesion mechanisms
  - very different geometries between mesenchymal and amoeboid cells
  - different adhesion forces between the two

Perspectives: from a computer modelling point of view

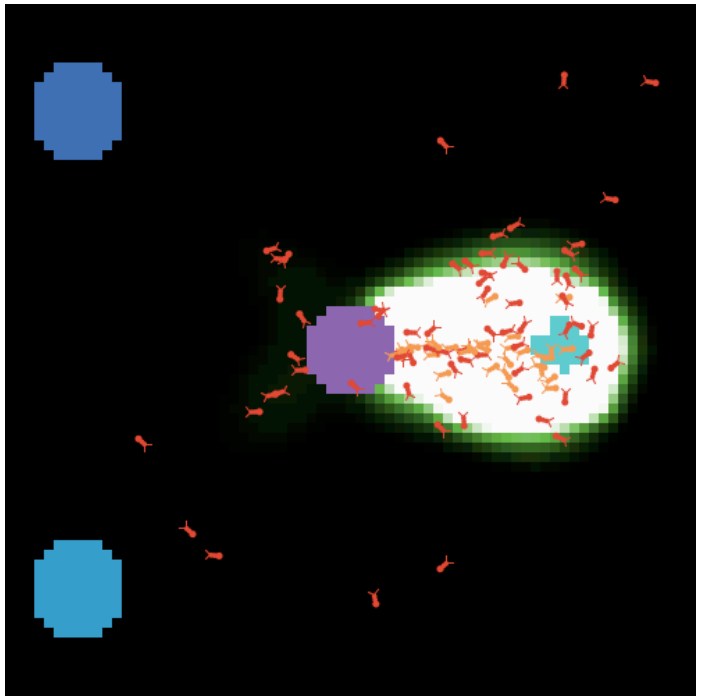
- A single modelling formalism is not enough
  - Need to couple Agent-based models, Ordinary and Partial-Differential Equations, Cellular Potts Models, other models...
- The most suited formalism may vary...
  - Along time
    - Individual-Based Modelling may be most suited when the tumour is small
    - Global models may be more suited when tumours become big enough
  - In space
    - The inner part of the tumour doesn't need much details
    - The outer part has to be described with much more details
  - Depending on the entities that are modelled
    - Large homogeneous populations may be described with global models
    - Populations with specific spatial distribution have to be modelled individually

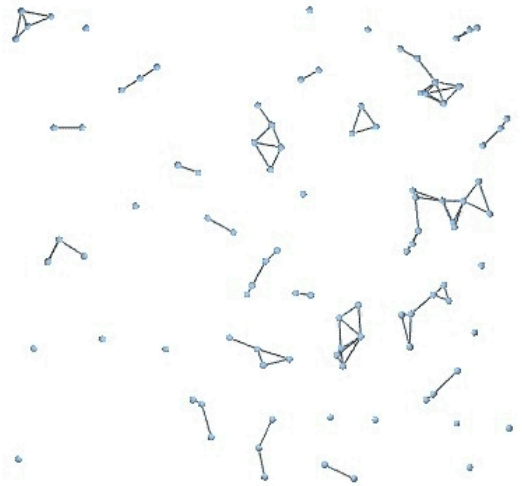
Perspectives: from a computer modelling point of view

- The global structures to take into account are not necessarily known beforehand: need to develop new tools to
  - Detect and characterize the structures that are created during the simulation
  - Automatically reify these structures as global models, coupled to the other parts of the simulation
  - Interactively zoom on some parts of the simulation
  - Calibrate and validate these hybrid simulations

Perspectives: from a computer modelling point of view

- Construction and analysis of the interaction network
  - interactions between the agents modelled as a dynamical graph
  - global statistical measures on the graph to detect structuring phenomena
  - clustering algorithms to detect groups of agents
  - characterization of the properties of the group





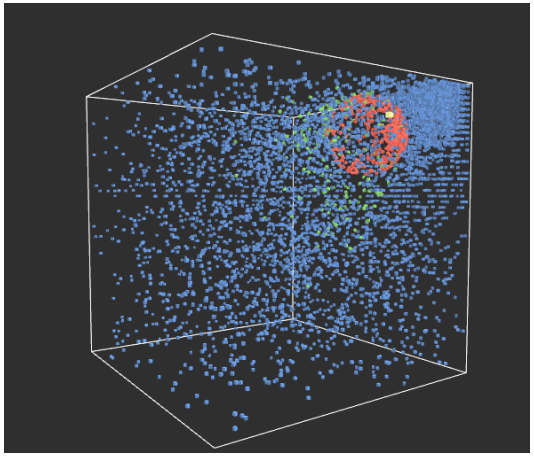
[Moncion et al. 2010, JBPC]

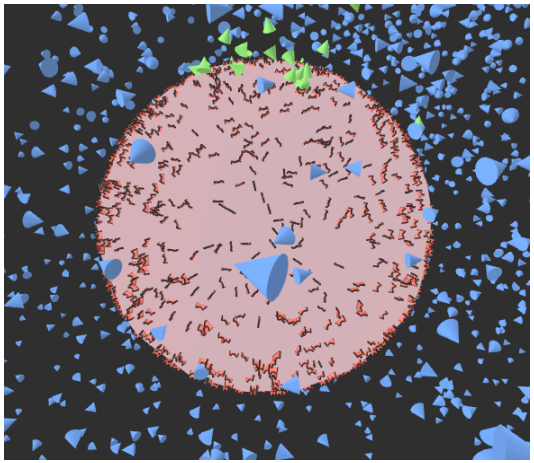
Perspectives : from a computer modelling point of view

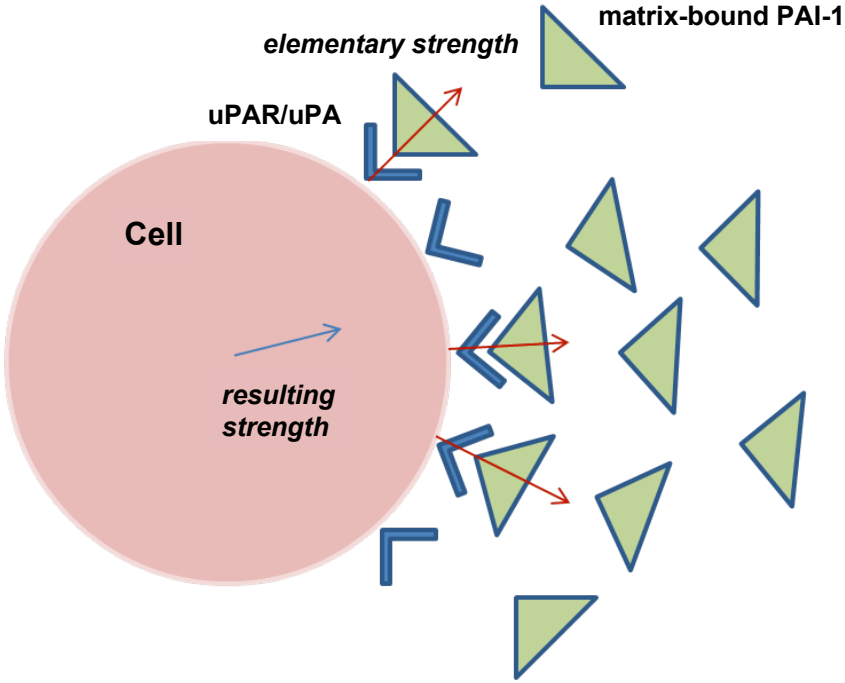
- Need to develop new tools to
  - reify the group in the graph as a single node and study the interactions between the group and the individual agents
  - characterize a group's behaviour and conditions of existence
  - reify the group in the simulation as a single agent
    - control the behaviour and interactions of that agent
    - control the conditions of existence of that agent

PAI-1 and metastatic escape

- The cell can go its way through the extra-cellular matrix thanks to the PAI-1m/uPA/uPAR matricial bridge
  - New model taking into account the dynamics implied by this behaviour







Migration through the PAI-1 ring