Modélisation multi-agents et aide à la compréhension de phénomènes physiologiques

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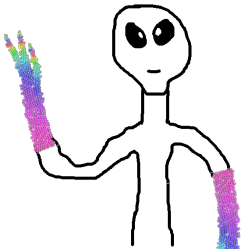

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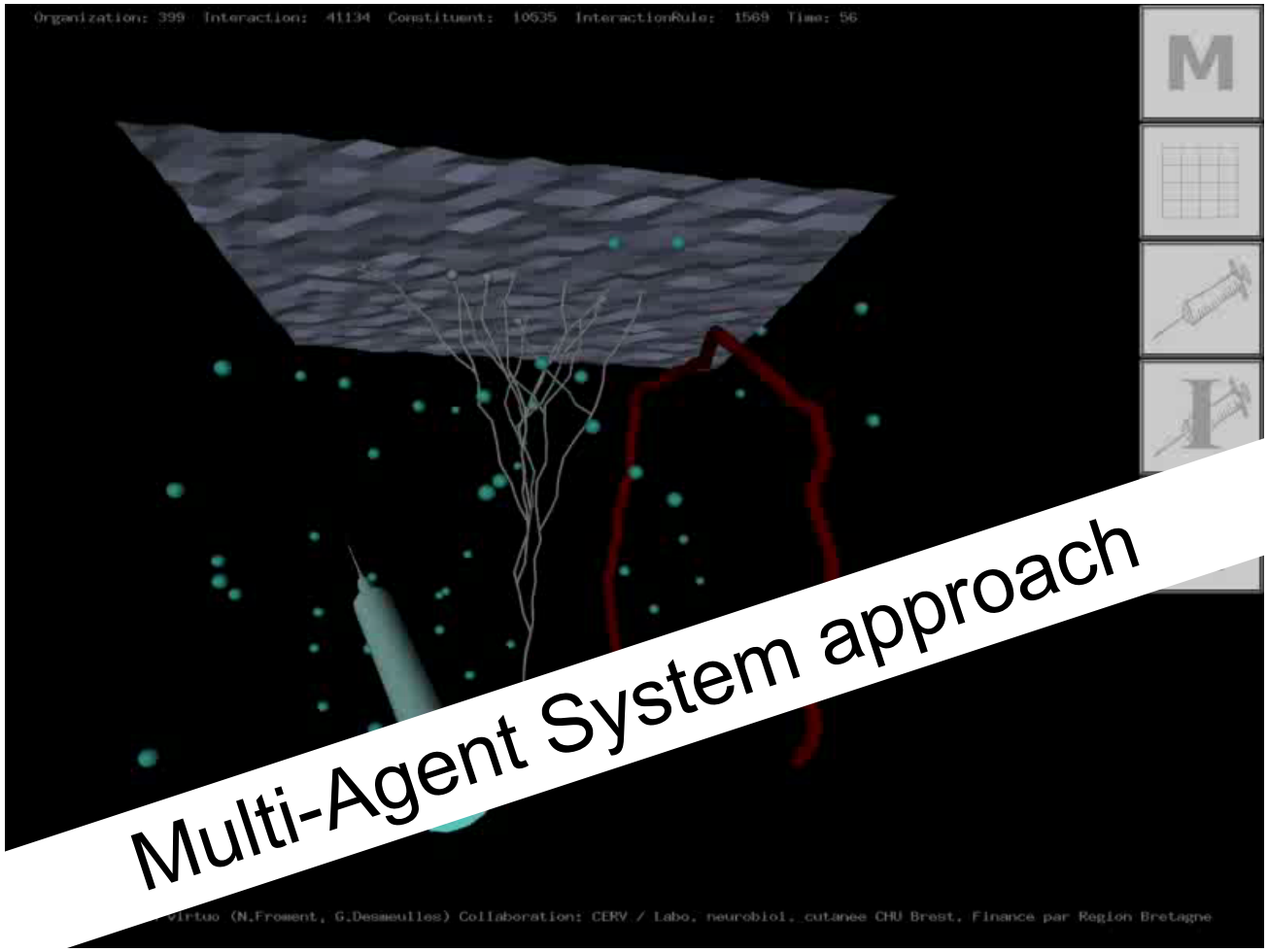
Université de Brest

IHSEV, Lab-STICC

Virtual Reality ➔ Virtual Biology



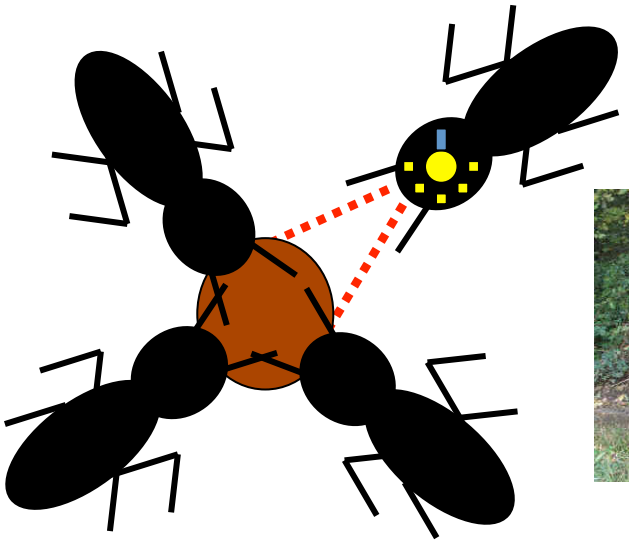
Interaction between virtual cells and/or molecules

Multi-Agents systems properties

Agent : perception-decision-action

Multi-agents System :

- auto-organisation
- emergence
- robustness
- adaptability



Models' autonomy

Road map

- ☑ Multi-Agents Systems (MAS)
- ❑ « in virtuo » experiments
- ❑ Modelisation and simulation of human physiological systems
- ❑ Multiple myeloma simulation
- ❑ Towards morphogenesis…

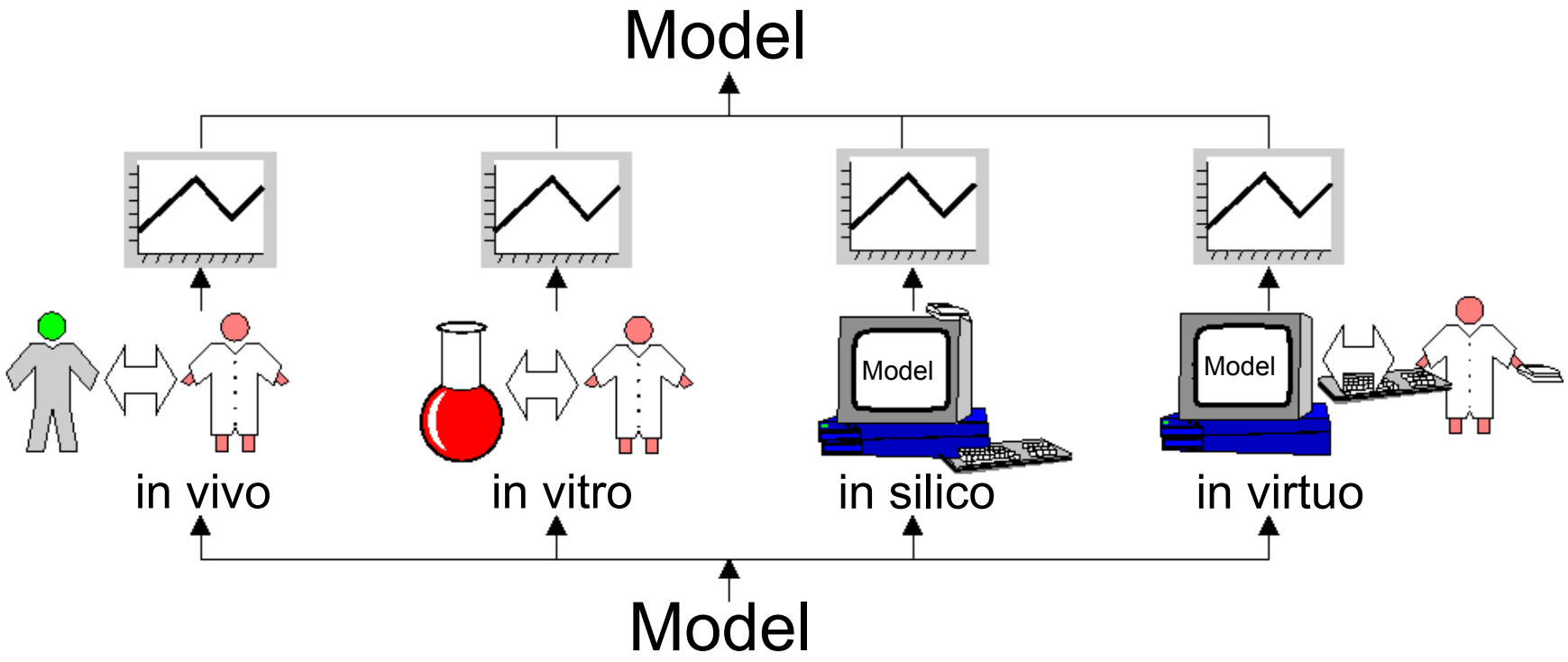
… and tumor growth?

« in virtuo » Experiments

Interdisciplinary stories

- 1997 : CHU de Brest, Immunology
  Pr. Pierre Youinou
- 1998 : CHU de Brest, Hematology
  Pr. Jean-François Abgrall
- 2001 : INSERM Nantes U 463, Cancerology
  Pr. François-Régis Bataille
- 2002 : CHU de Brest, Allergology/Dermatology
  Pr. Laurent Misery
- …
- 2009 : IMTh, Lyon
- …
- 2014 : LaTim, Brest
  DR. Dimitris Visvikis

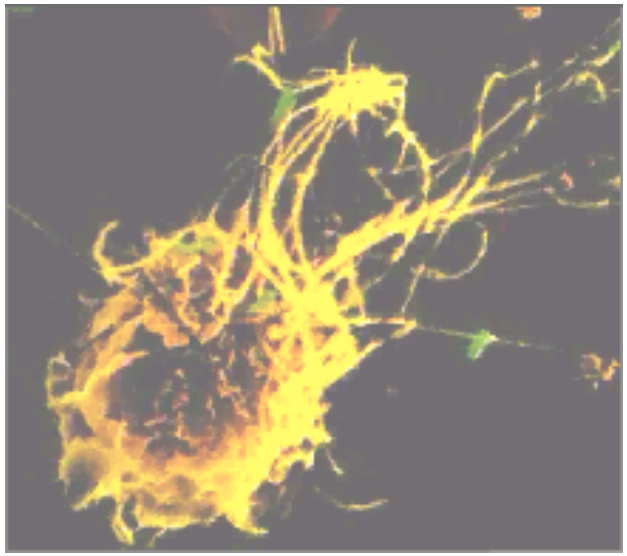
« in virtuo » Experiments



« in virtuo » Experiments

Agent

Multi-agents system



Cell

Multi-cellular system

Road map

- ☑ Multi-Agents Systems (MAS)
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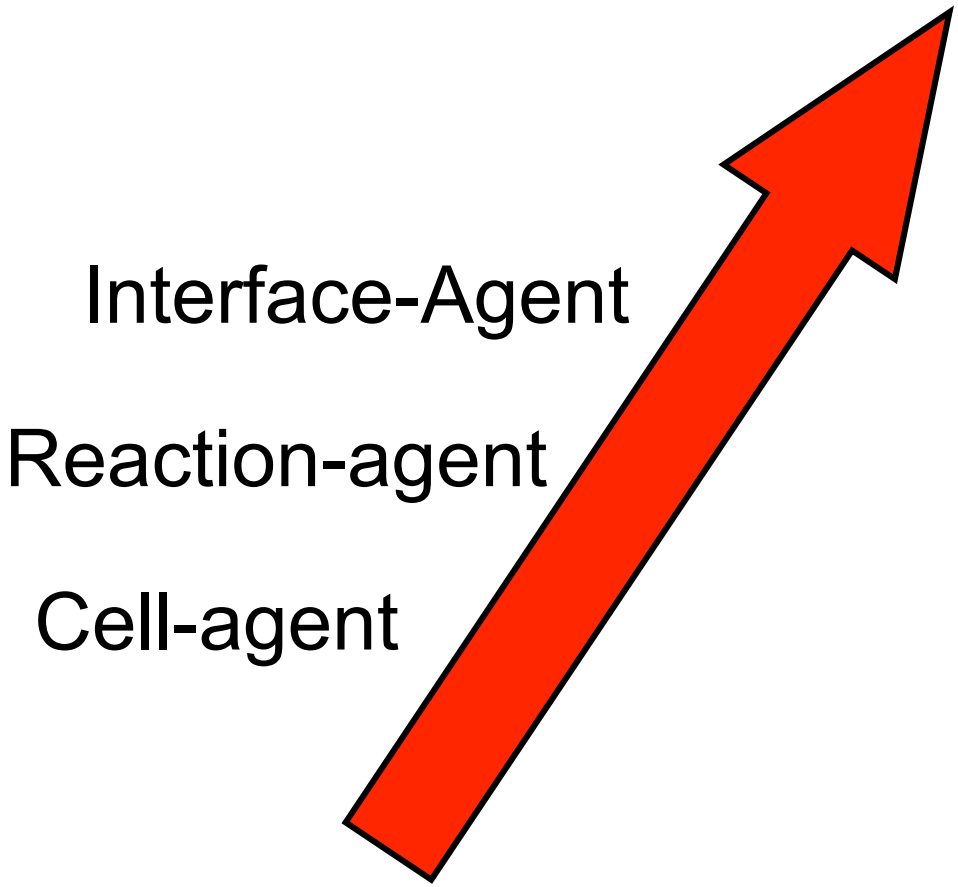
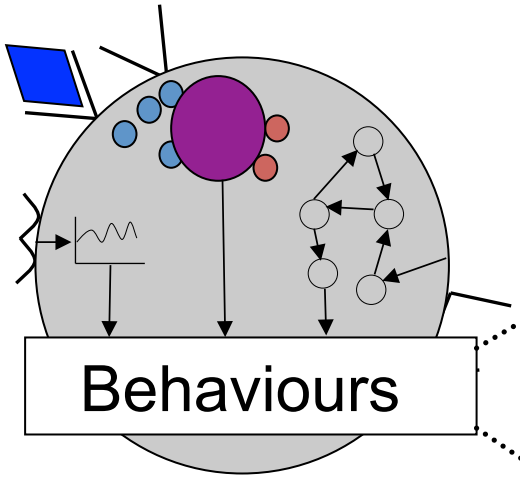
Modelisation and simulation of human physiological systems



Cell-agent model



Basic behaviours

- Mitosis
- Activation
- Internalisation
- Expression of receptor
- Apoptose

Model of located agents with complex behaviors

Cell-agent model: An example of application

Simulation of physiologic coagulation:

Cell

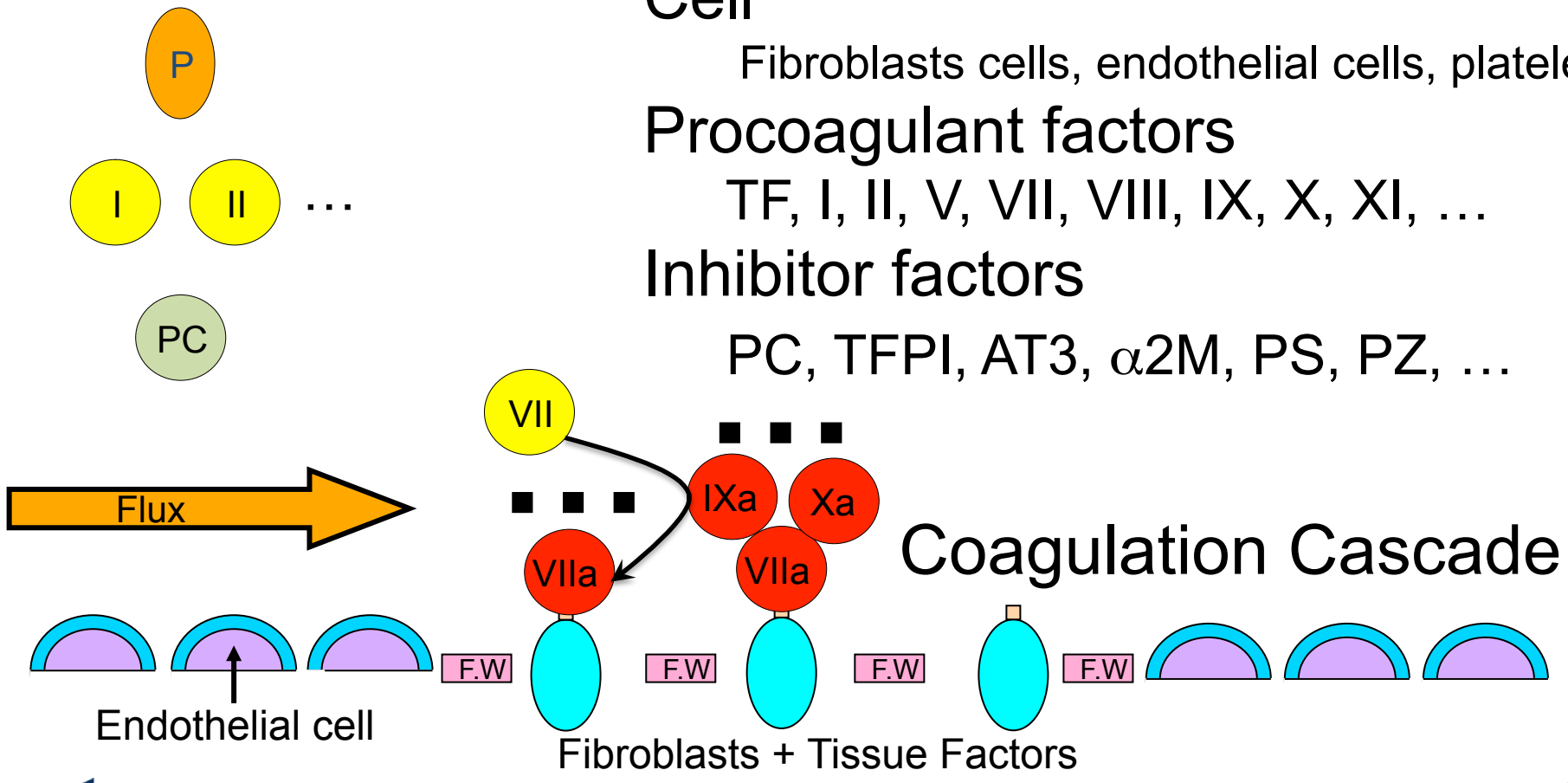
Fibroblasts cells, endothelial cells, platelets

Procoagulant factors

TF, I, II, V, VII, VIII, IX, X, XI, …

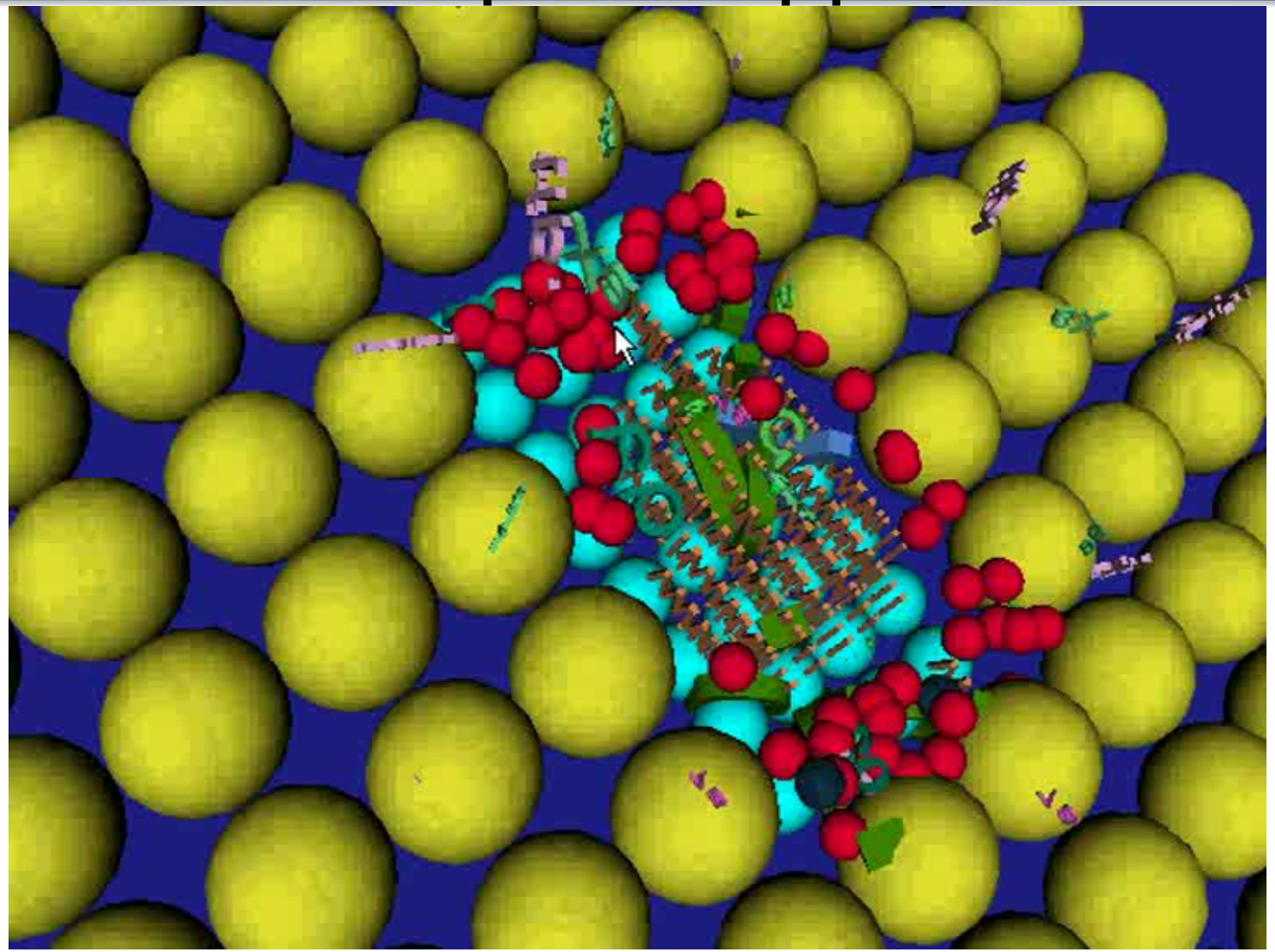
Inhibitor factors

PC, TFPI, AT3, α2M, PS, PZ, …



Coagulation Cascade

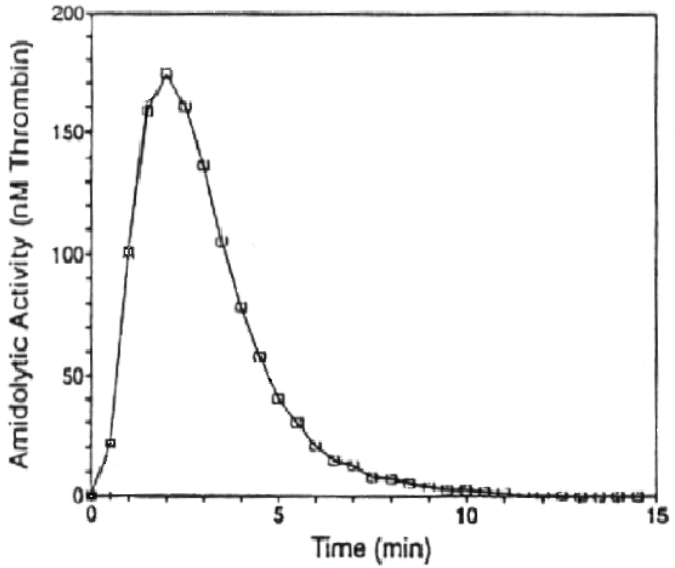
Cell-agent model: An example of application



Cell-agent model: An example of application

Elements of validation of the coagulation multiagents model :

- Comparison with Biological experiment



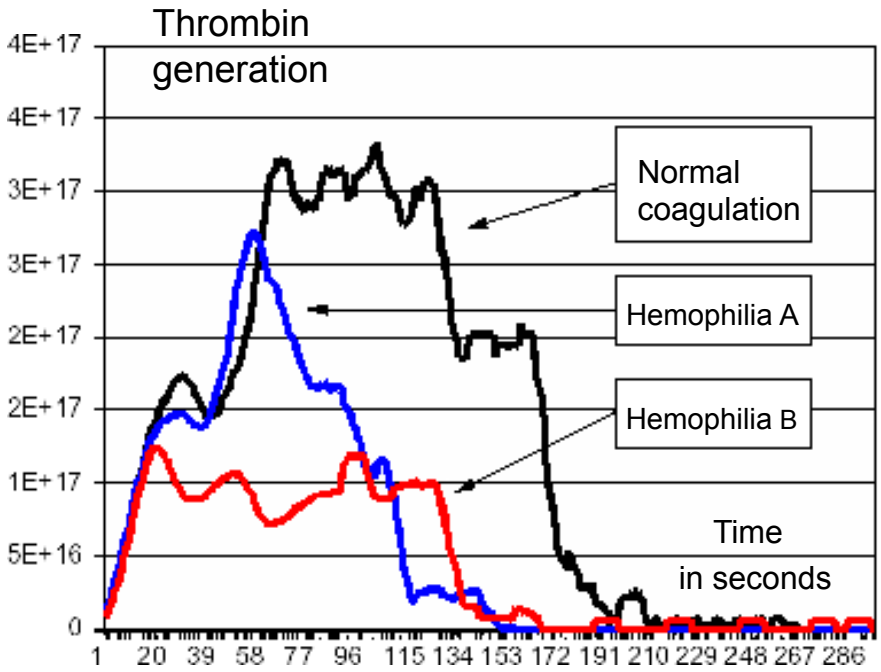
Curve of thrombin Generation [Hemker, 1995]

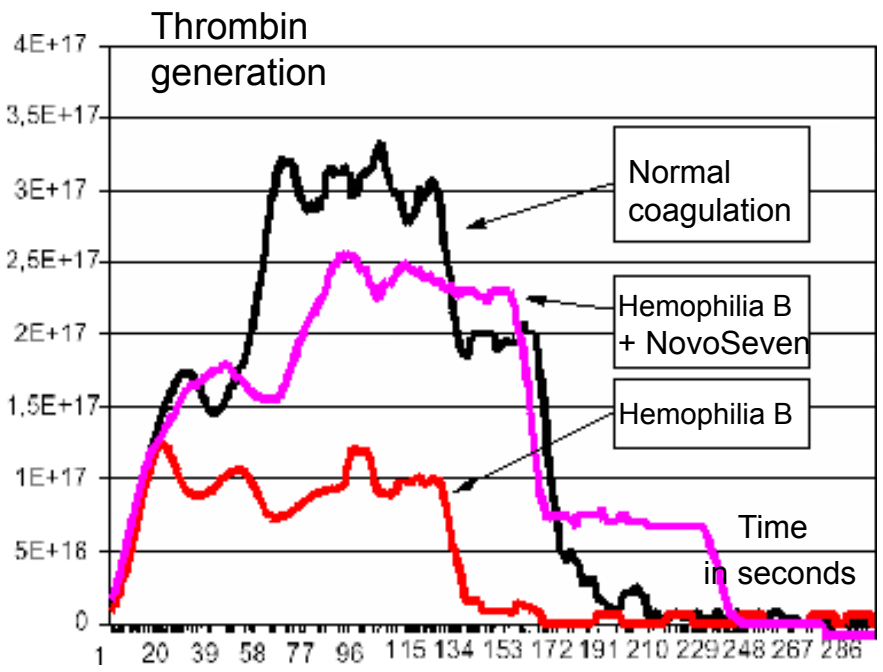
- Conerence with respect to pathologies

Cell-agent model: An example of application

Simulation of physiologic coagulation:

Healthy patient, hemophiliac, hemophiliac with treatment





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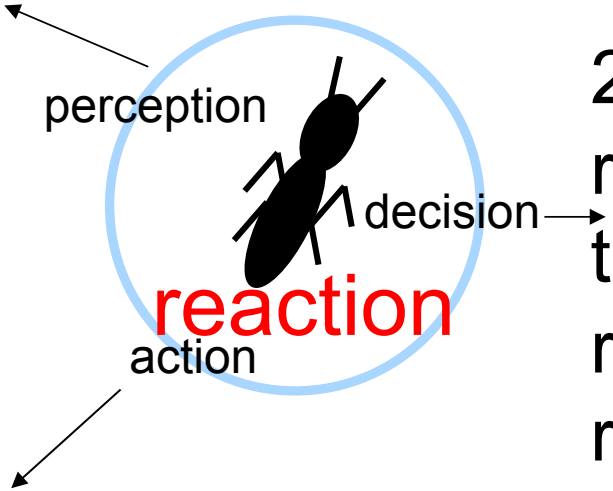
Modelisation and simulation of human physiological systems

Reaction-agent model

- « microscopic » level: agent = cell/molecule
- « macroscopic » level: agent = reaction

1: reading of the concentrations in reactants



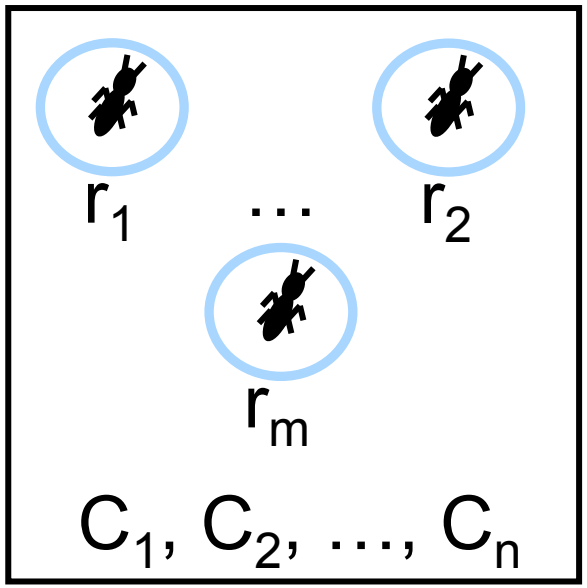
2: calculation the reaction speed and then the quantity of reactant to be reacted

3: consequently, modification of the concentrations in reactants and products

Reaction-agent model

Spatial indiscernibility

Non located agents



Chemical reactor

Reaction-agent model

$$d[S_1]/dt = -kcat_1[E_1][S_1]/(Km_1+[S_1]) - kcat_3[E_1][S_1]/(Km_3+[S_1])$$

$$d[S_2]/dt = +kcat_2[E_2][S_2]/(Km_2+[S_2])$$

$$d[P_1]/dt = -kcat_1[E_1][S_1]/(Km_1+[S_1]) - kon_3[P_1][P_2] + kcat_3[E_1][S_1]/(Km_3+[S_1])$$

$$d[P_2]/dt = +kcat_2[E_2][S_2]/(Km_2+[S_2]) - kon_3[P_1][P_2]$$

$$d[P_1P_2Complex]/dt = kon_3[P_1][P_2]$$

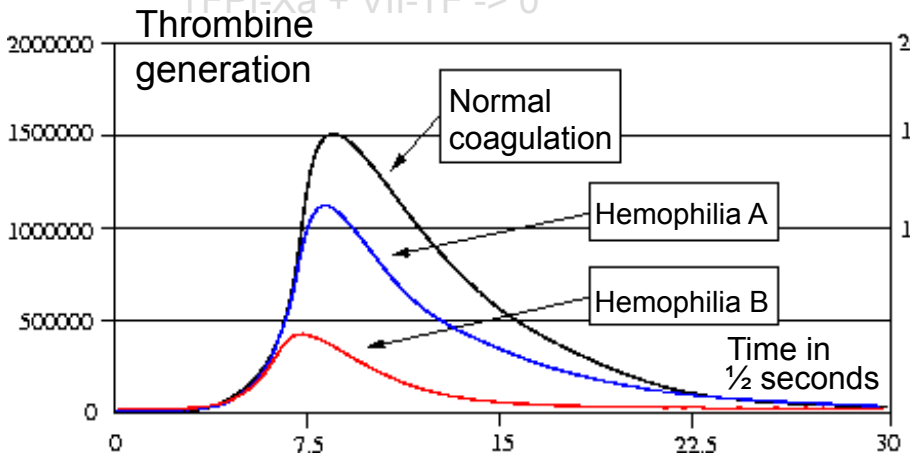
$$E_1 + S_1 \rightarrow E_1 + P_1$$
$$E_2 + S_2 \rightarrow E_2 + P_2$$
$$P_1 + P_2 \rightarrow P_1P_2Complex$$
$$E_3 + S_1 \rightarrow E_3 + P_1$$

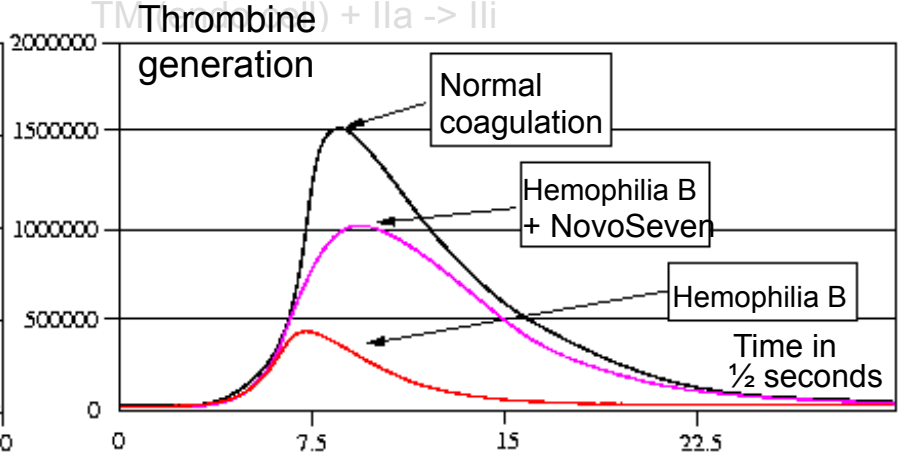
```
new EnzimaticReaction(plasma, E1, S1, P1, kcat1, Km1);
new EnzimaticReaction(plasma, E2, S2, P2, kcat2, Km2);
new ComplexFormationReaction(plasma, P1, P2, P1P2Complex, kon3);
new EnzimaticReaction(plasma, E3, S1, P1, kcat3, Km3);
```

Reaction-agent model: An example of application

Simulation of physiologic coagulation:

Healthy patient, hemophiliac, hemophiliac with treatment

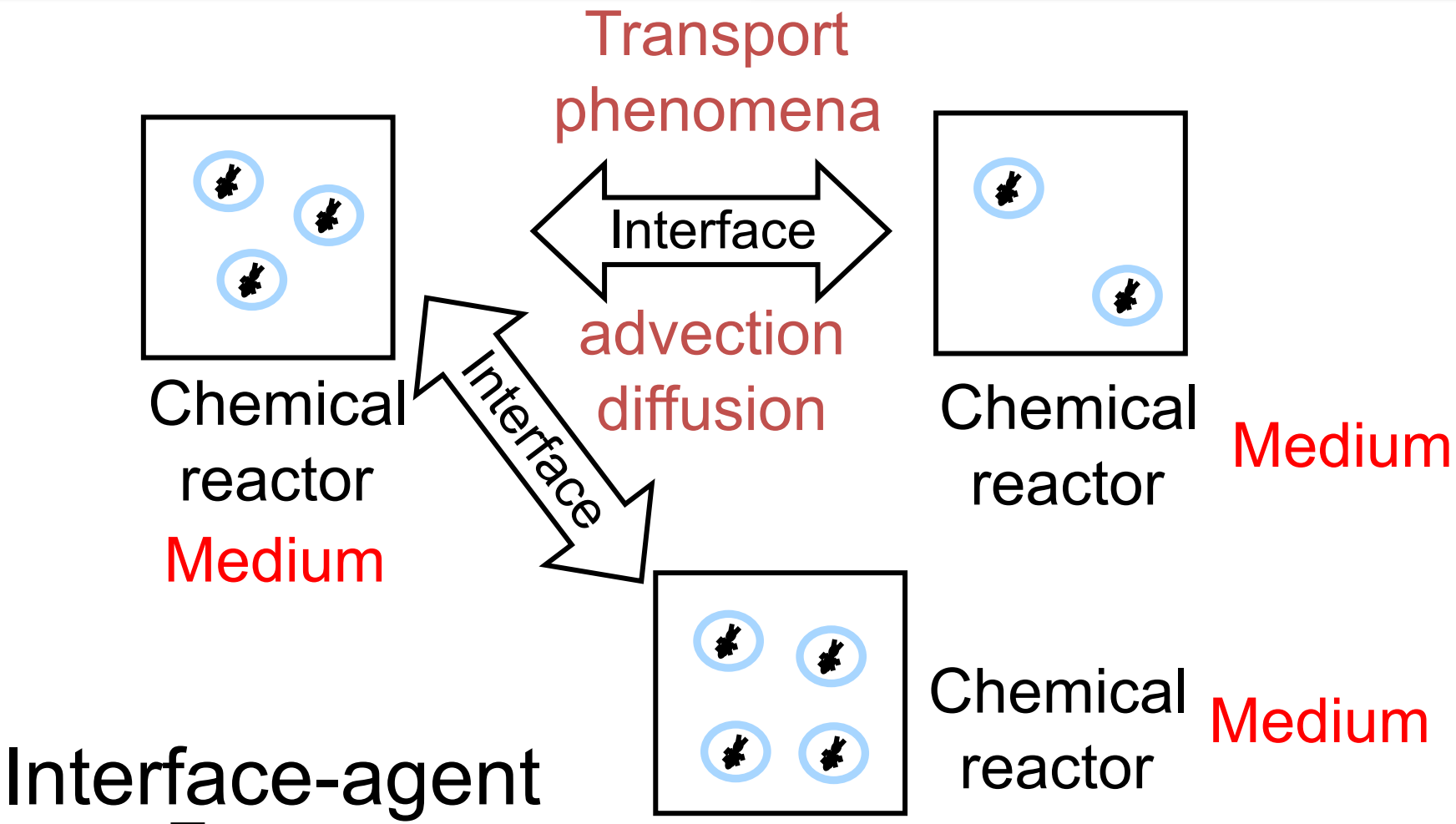




42 reactions

Modelisation and simulation of human physiological systems

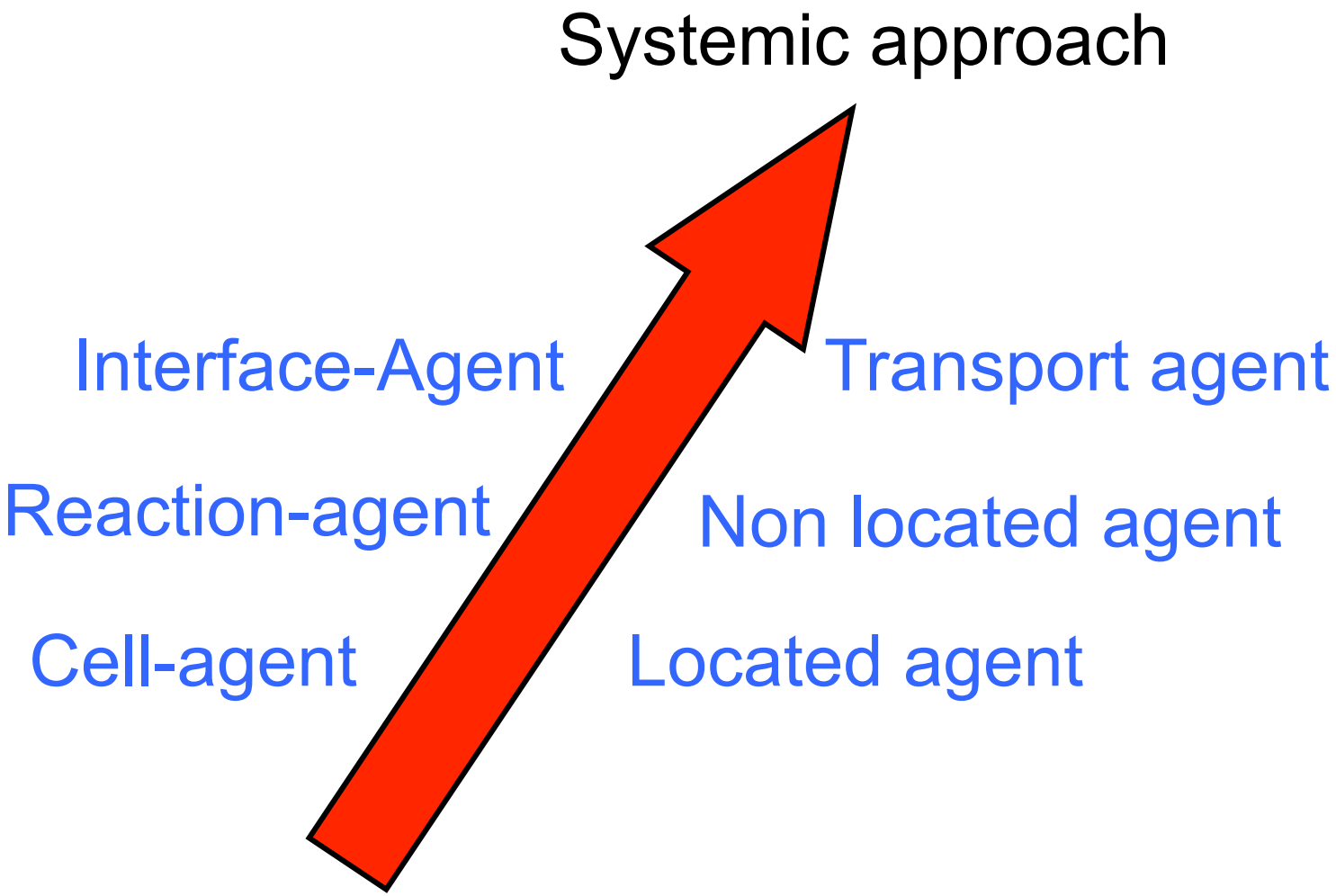
Interface-agent model:



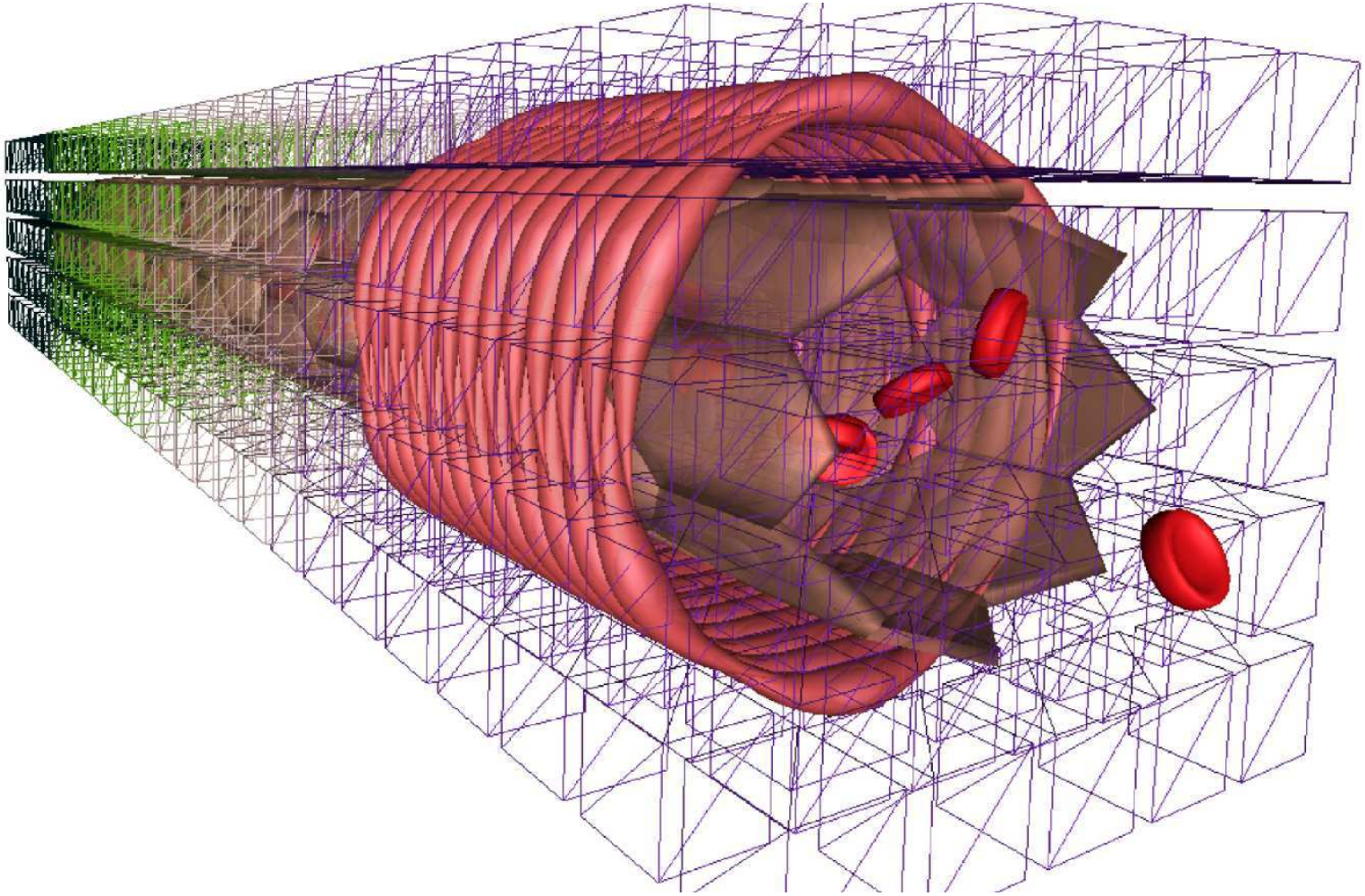
Interface-agent

↳ Interaction between mediums

Modelisation and simulation of human physiological systems

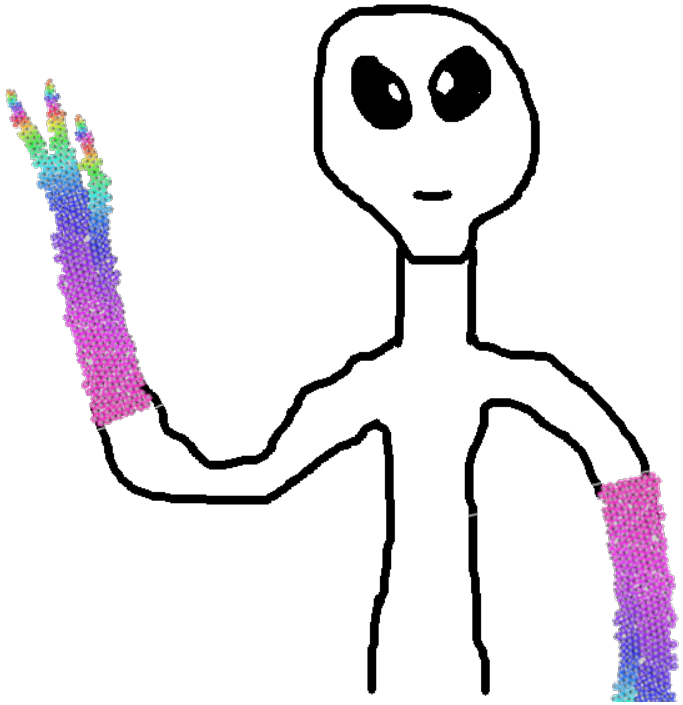


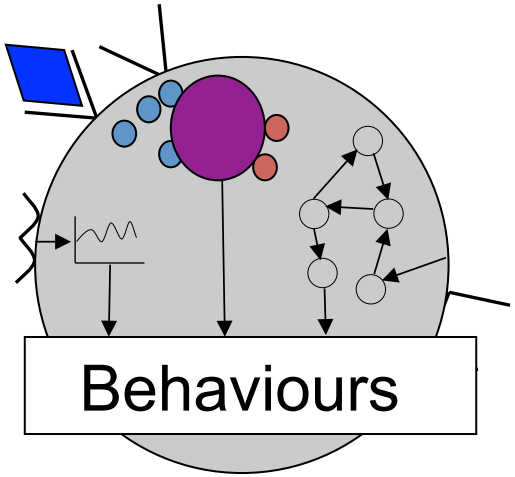
Modelisation and simulation of human physiological systems



Modelisation and simulation of Multiple Myeloma

Vincent, you didn't talk about cancer today !!





Cell-agent model

↳ Internal machinery

Road map

- ☑ Multi-Agents Systems (MAS)
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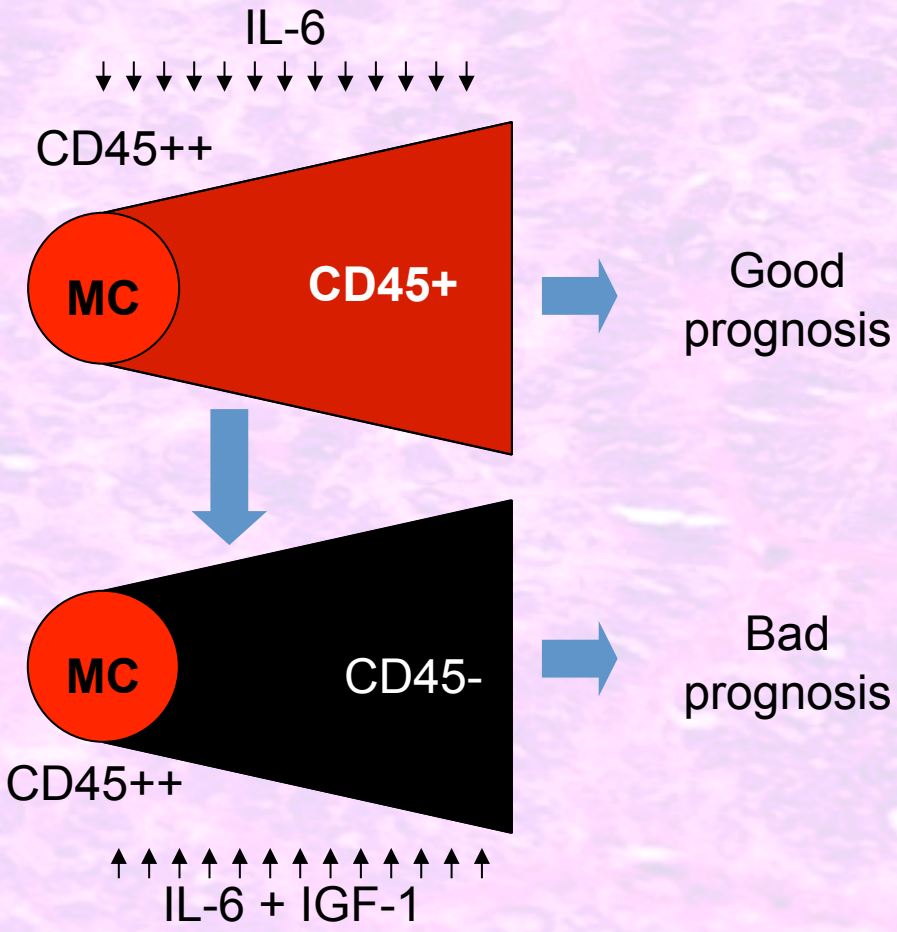
- ❑ Multiple myeloma simulation
- ❑ Towards morphogenesis…

… and tumor growth?

Modelisation and simulation of Multiple Myeloma

Collaboration
INSERM Nantes U 463,
Pr. F.R. Bataille



Modelisation and simulation of Multiple Myeloma

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INSERM Nantes U 463,
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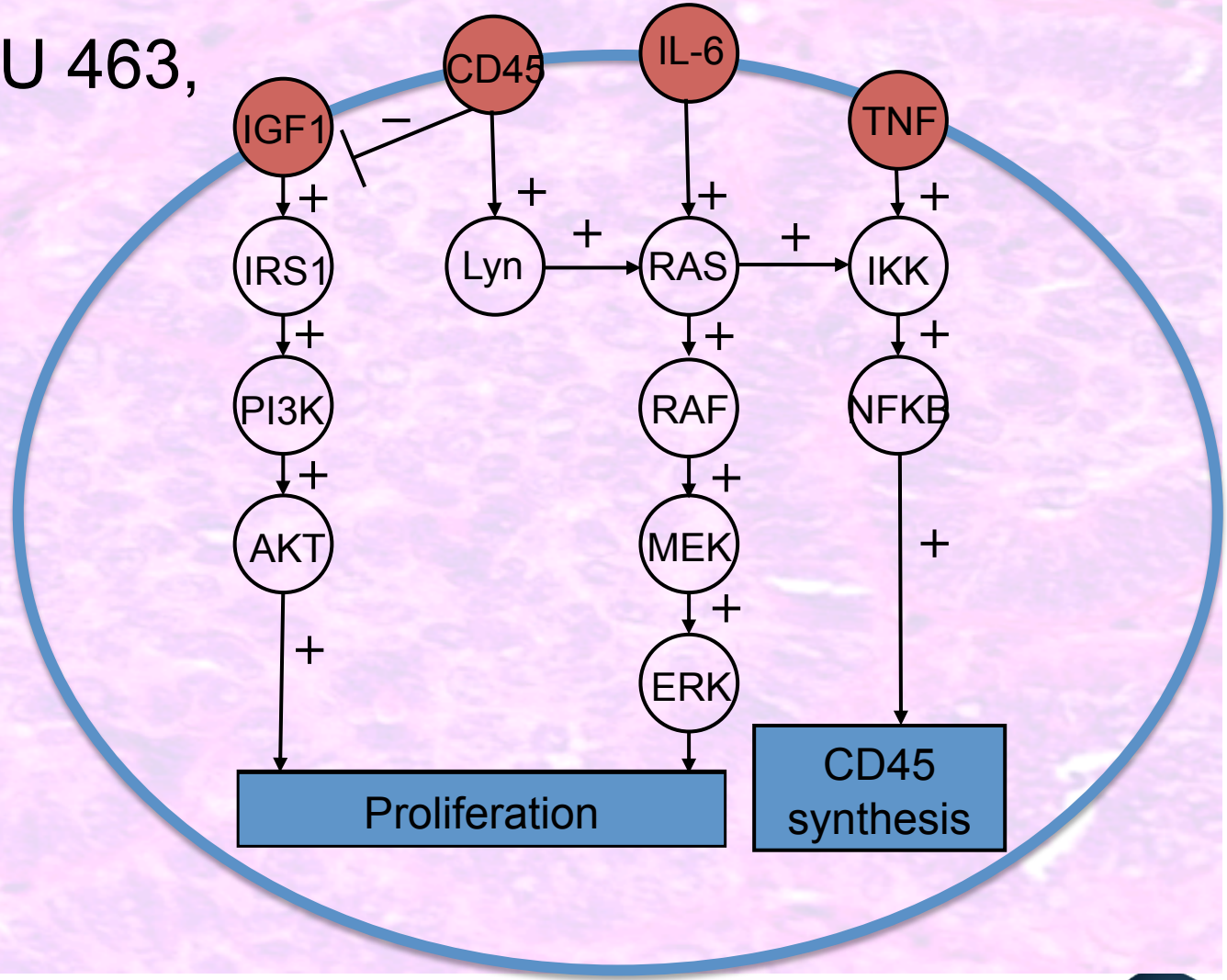

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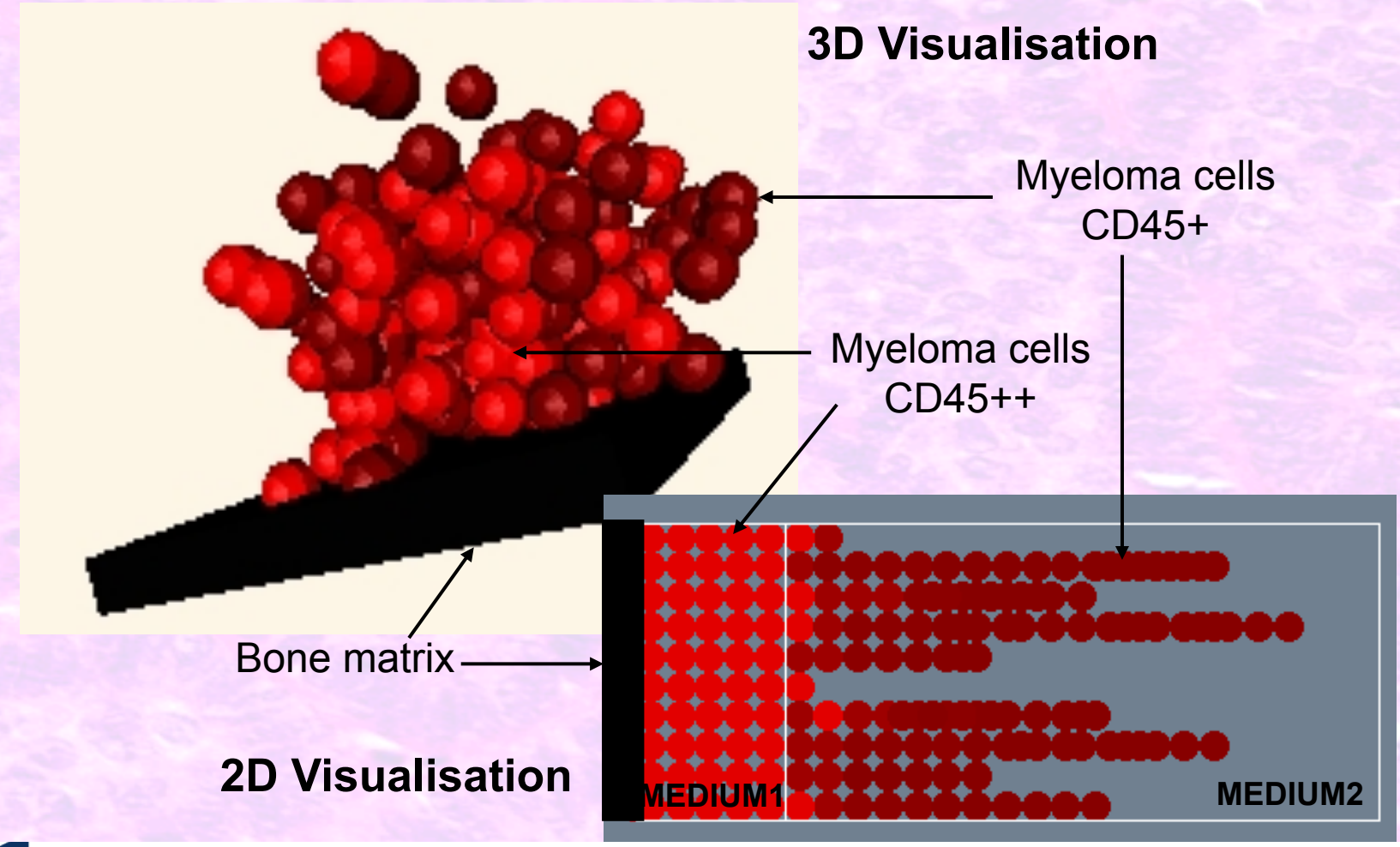
Collaboration INSERM Nantes U 463, Pr. F.R. Bataille



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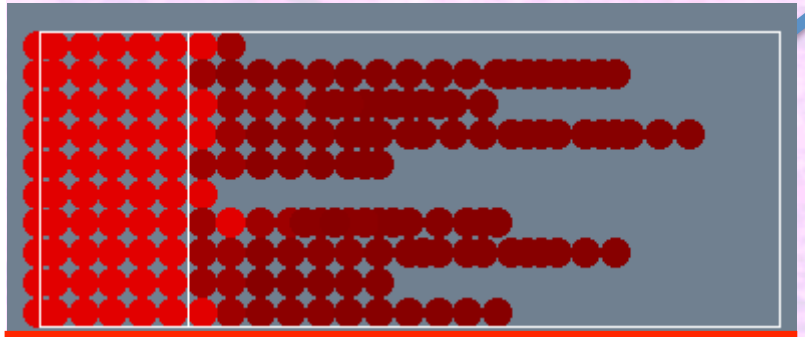
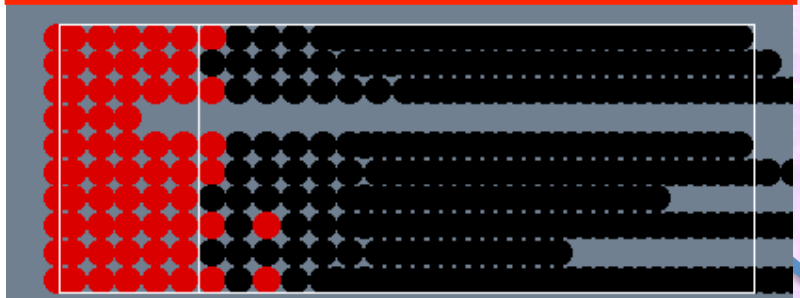
Modelisation and simulation of Multiple Myeloma

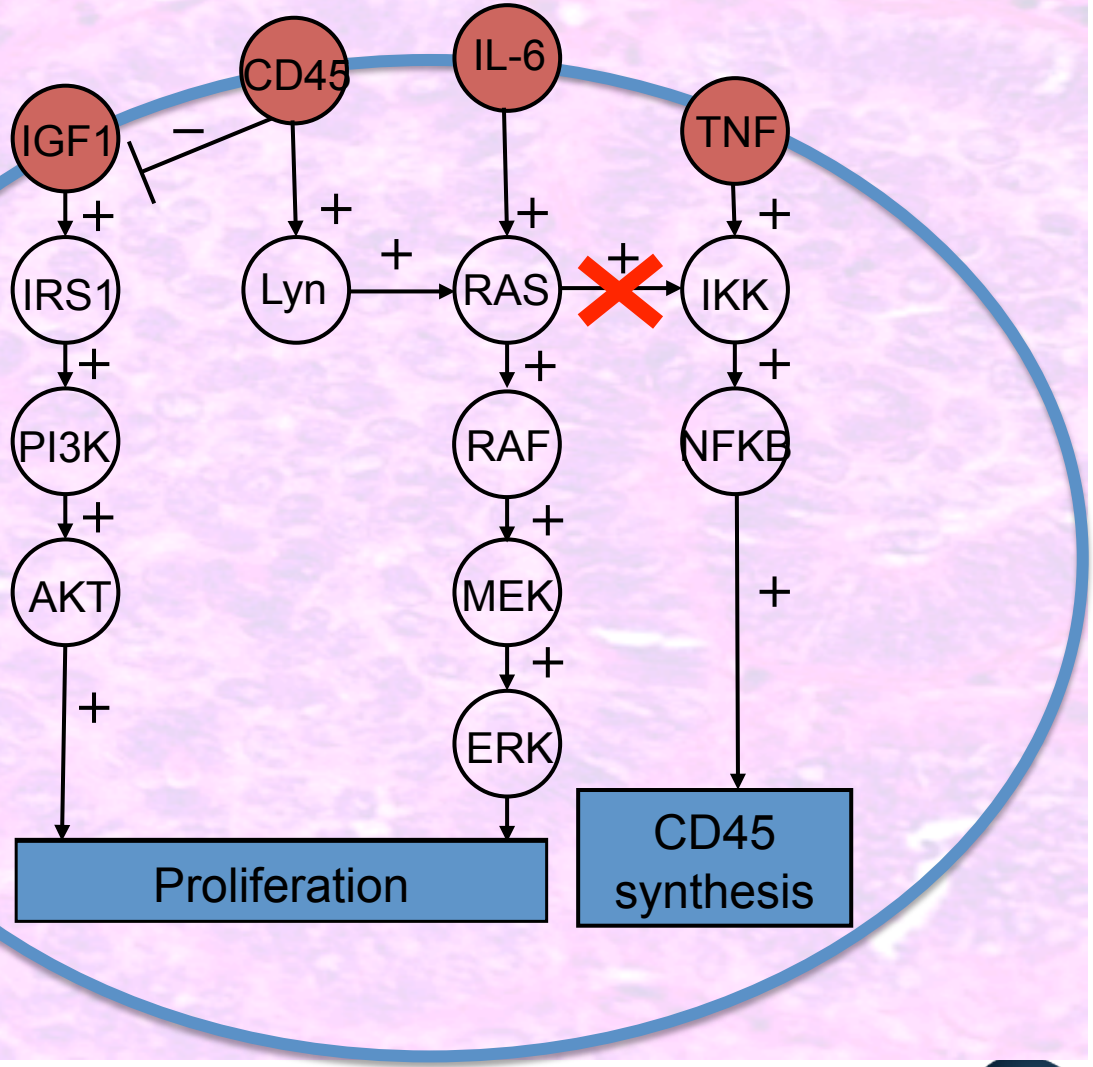
Collaboration
INSERM Nantes U 463,
Pr. F.R. Bataille



Without RAS mutation



With RAS mutation



Road map

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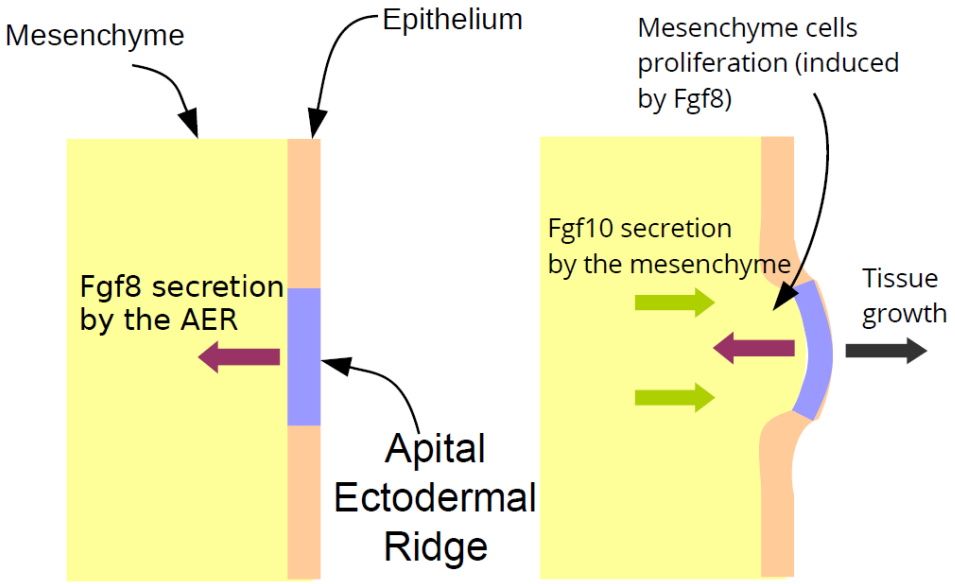
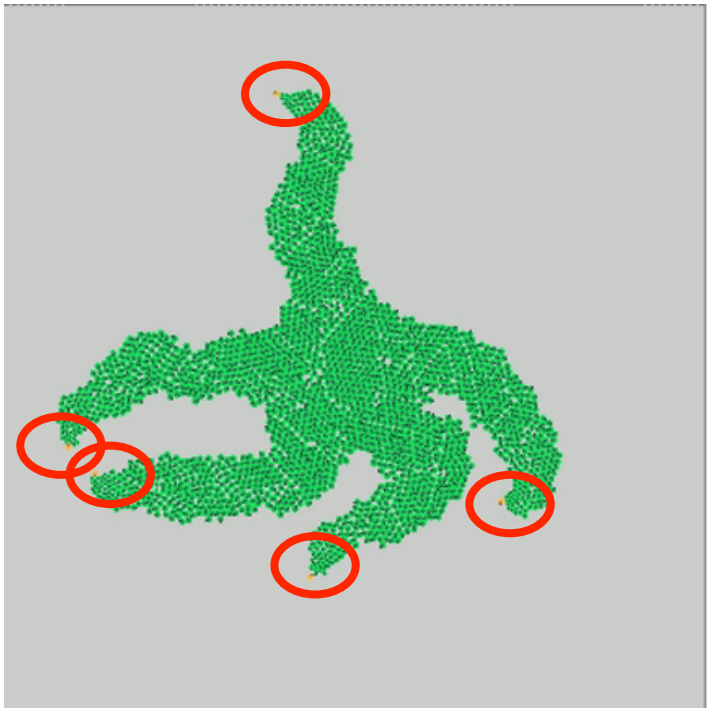
… and tumor growth?

Towards morphogenesis: Starfish growth (1/2)

a simplified model



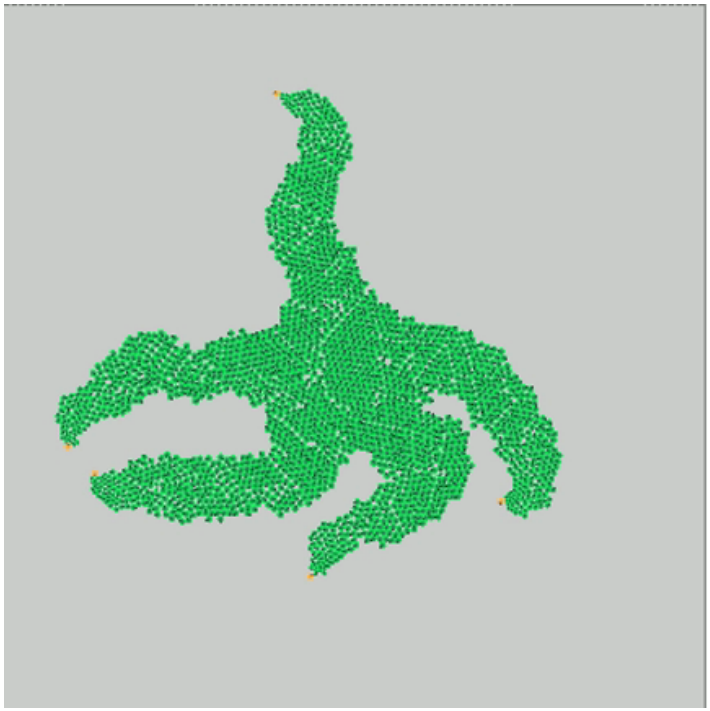


- AER Cells secrete Fgf8 molecules
- Fgf8 molecules induce mesenchyme cells proliferation
- Mesenchyme cells response to Fgf8 by secreting Fgf10 molecules
- Fgf10 molecules maintain Fgf8 secretion

Problem: we put the right cells at the right places….

Towards morphogenesis: Starfish growth (2/2)

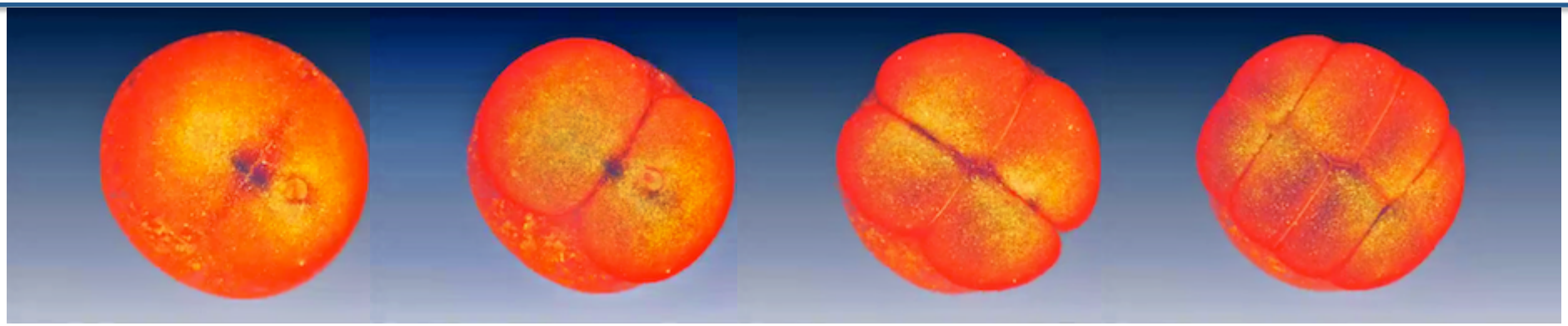
What is the « program » ?



...

Towards morphogenesis modeling..?(1/2)

occidentale



Early zebrafish embryo, from [N. Olivier et al, 2010]

During early embryogenesis, we can see (probable) :

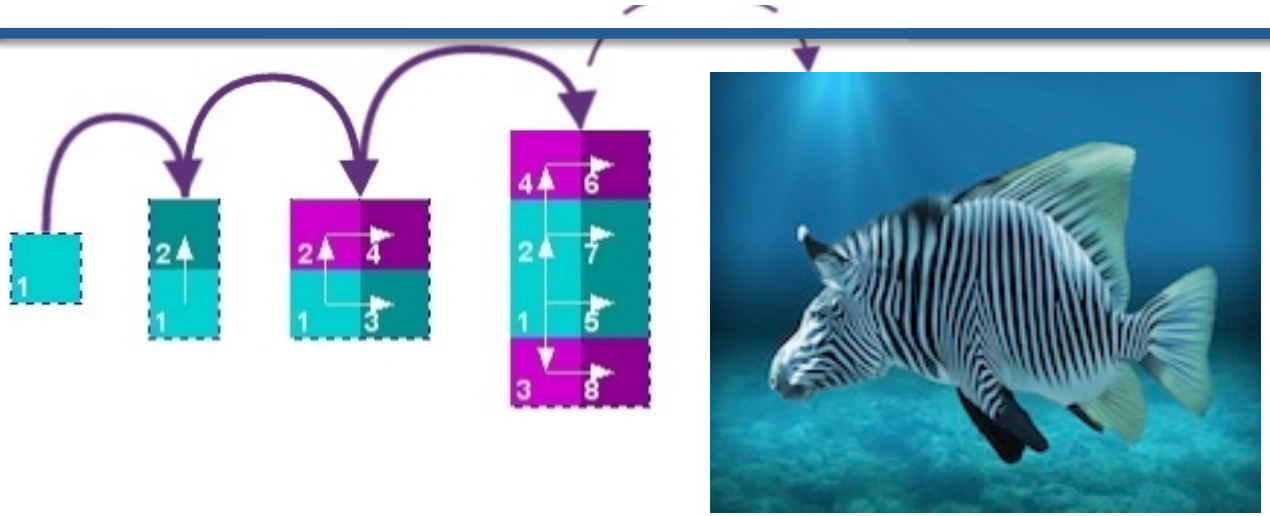
- Geometric segmentation
- Deterministic process

What is the program within cells that controls their placement and their differentiation at the early embryogenesis ?

...

Towards morphogenesis modeling..?(1/2)

occidentale



Idea:

- Find a mathematical model of a well-guided morphogenesis
- Generate, from a single cell, all early tissues and the associate programs

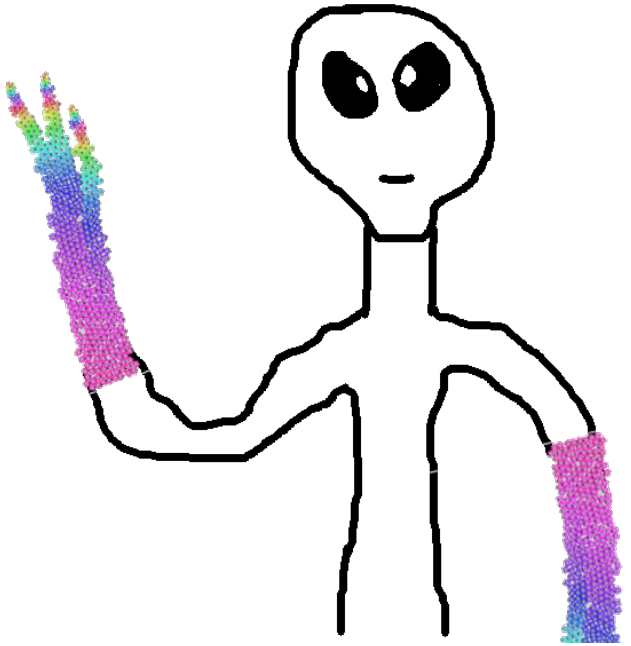
Problem:

- Huge number of possibilities ! ➔ viability theory (J.P. Aubin)

And now:

- Cancer growth modeling ! ➔ collaboration LaTIM (Dimitris)

Thank you



Abdoulaye, Alexandra, Anne, Dimitris, François, François, François-Régis, Gabriel, Gireg, Jacques, Jean-François, Jérémy, Karine, Laurent, Laurent, Mikaël, Michaël, Nicolas, Pascal, Pascal, Sébastien, Sébastien, Séna