Modeling tumor development in liver

Séminaire des doctorants

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BANG, Inria

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INVENTEURS DU MONDE NUMÉRIQUE

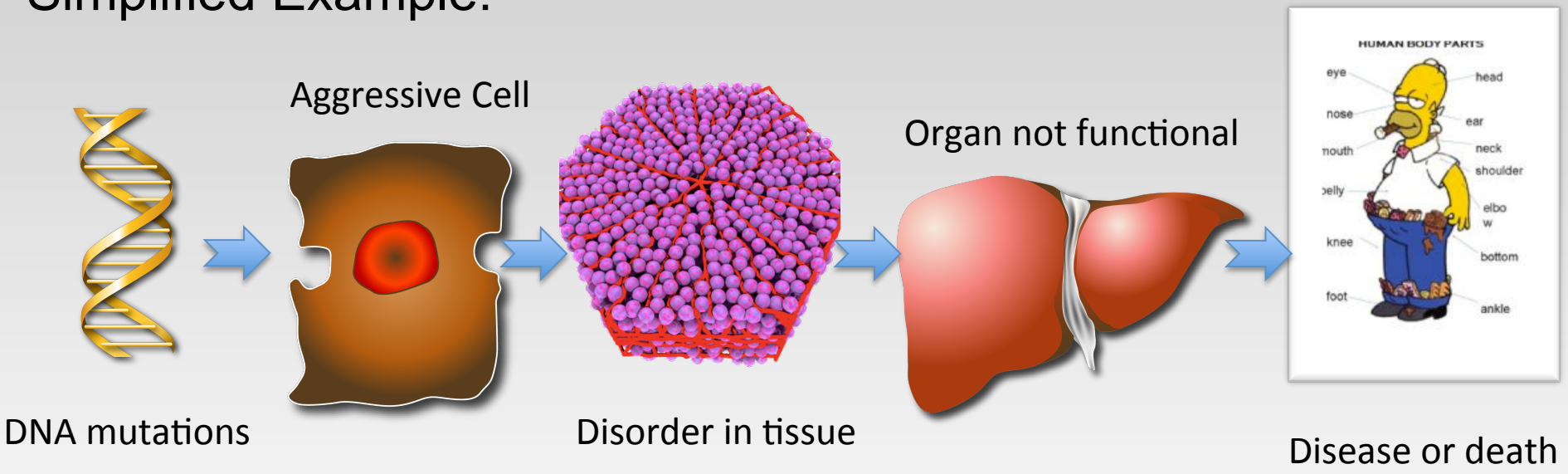
Outline

1. Cancer
2. Systems Biology
3. Mathematical description
4. Application to liver tumor
5. Conclusion

What is cancer?

Definition: Cancer is an abnormal cell proliferation caused by genetic mutations.

Simplified Example:



Our purpose is to help to understand part of the mechanisms.

Cancer over the world

Data from 2008:

1. Cancer is the leading cause of death worldwide.
2. Liver cancer is the 3rd most killer (700 000 death per year)
3. Among liver cancers, hepatocellular carcinoma (HCC) is the most frequent.

Different liver diseases are responsible for HCC:

- Hepatitis B,C
- Alcoholism
- Aflatoxin B1

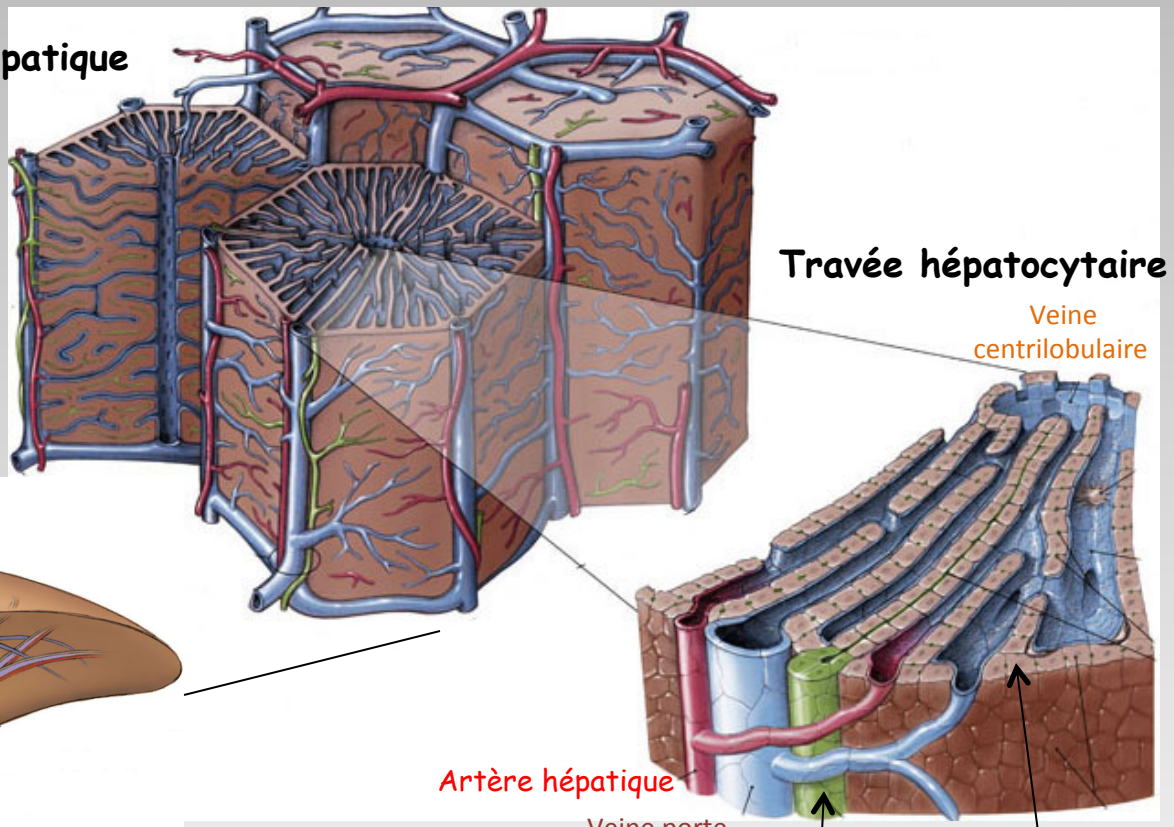
Studying cancer is critical health issue and of course an important economic issue.

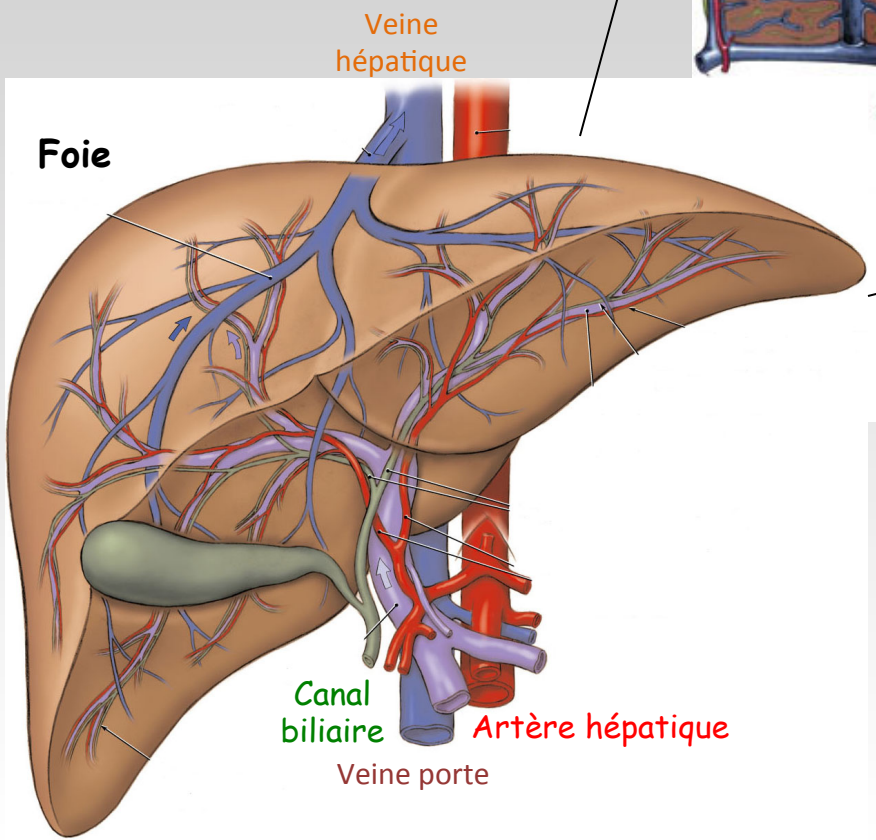
Source: World Heath Organization (WHO)

Liver: an adaptated architecture to its function

Liver function is to filter the blood:

- to remove raw materials
- to deliver important molecules





Liver cells (hepatocytes) are organized to optimize those functionalities.

Systems Biology

Systems biology is the science field that deals with different biology scales and tries to link them together – using physical and chemical laws.

Information	Scale
Gene mutation	Molecule
Derivation of cell phenotype	Cell
Modification in lobule architecture	10^4 cells
Global effect on liver	Tissue
Impact on metabolism	Human Body

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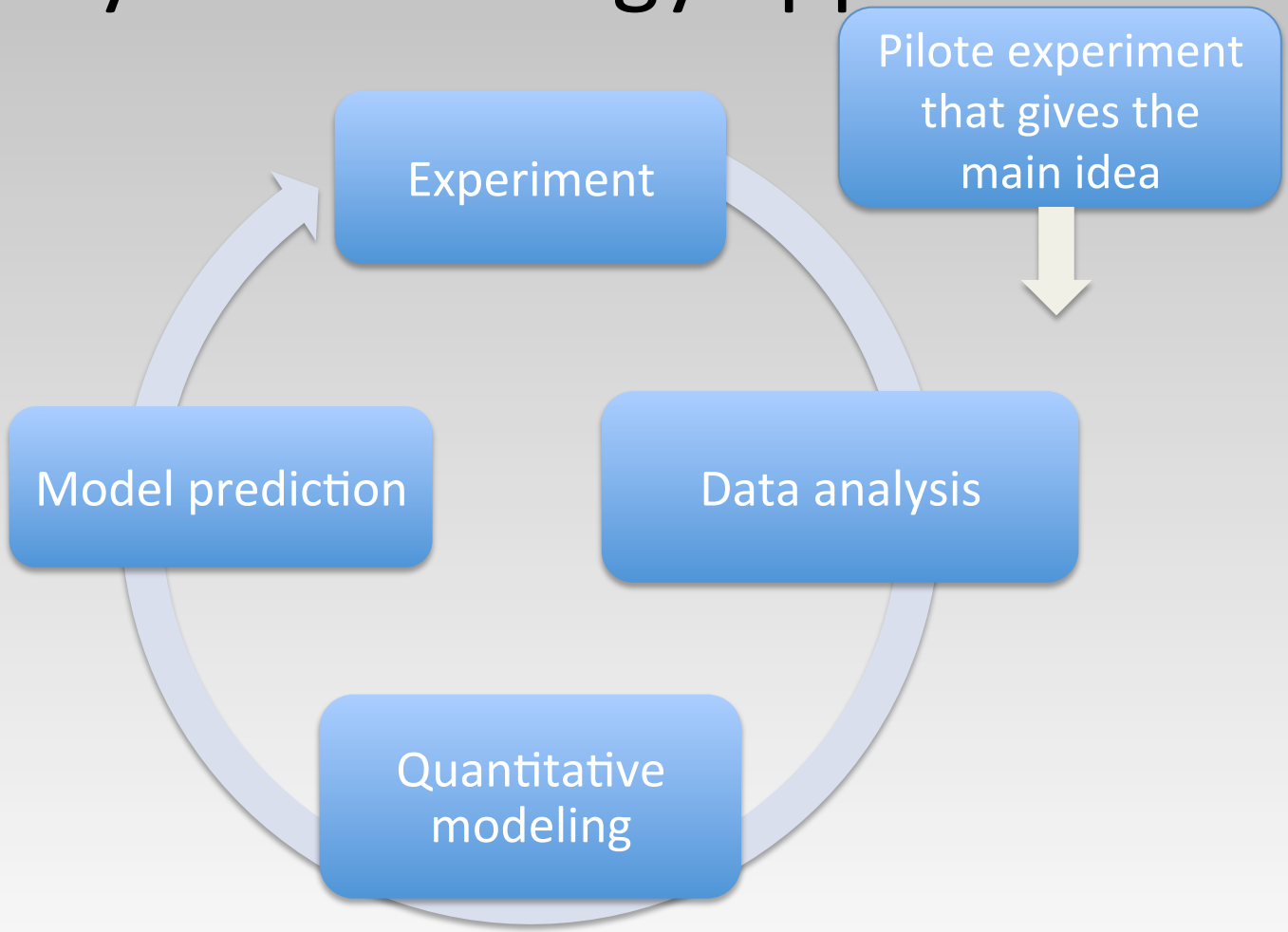
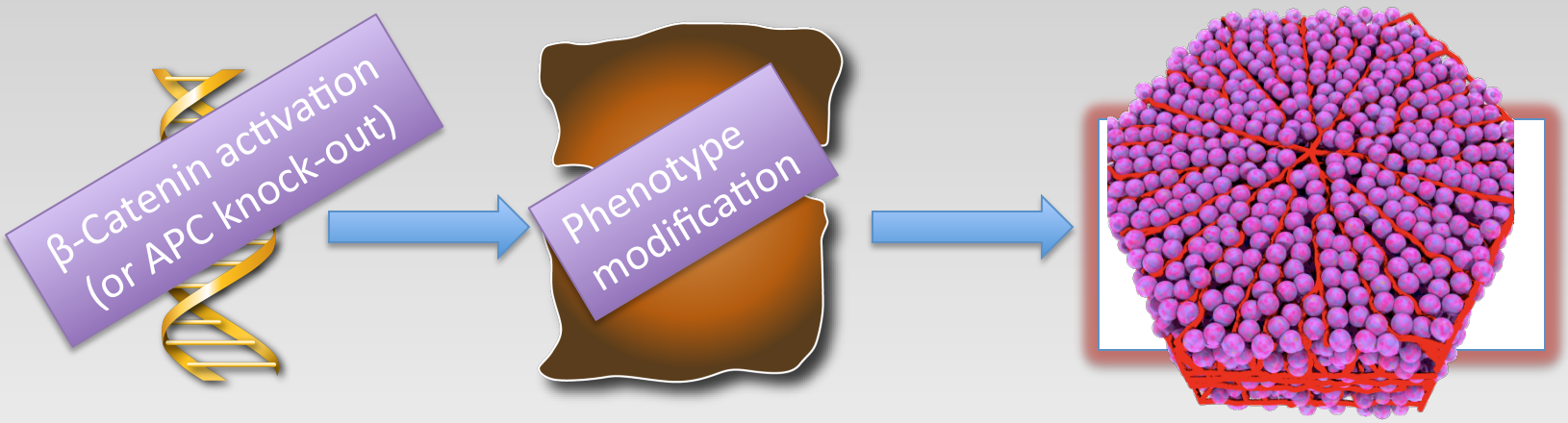
Our expertise is the cell-scale (from 1 to 100 000 cells) and its physical interactions (modeled by Agent-Based model)

Philosophy ?
A systems biology approach



Simulation Principle

1. Simulate cancer in a “in real” situation with different parameters and properties
2. Select plausible results
3. Understand cancer mechanisms



Examples of cell parameters and properties we can change:

- Proliferation rate
- Death rate
- Vessel stiffness (blood vasculature flexibility)
- Etc.

Cell interactions mathematical description

How does cell *i* move and how it interacts with cells j?

Langevin equation for cells motion

$$\gamma \mathbf{v}_i(t) + \sum_j \Gamma_{ij}(\mathbf{v_i} - \mathbf{v_j}) = \sum_j \mathbf{F_{ij}}(t) + \xi_i(t)$$

t = time

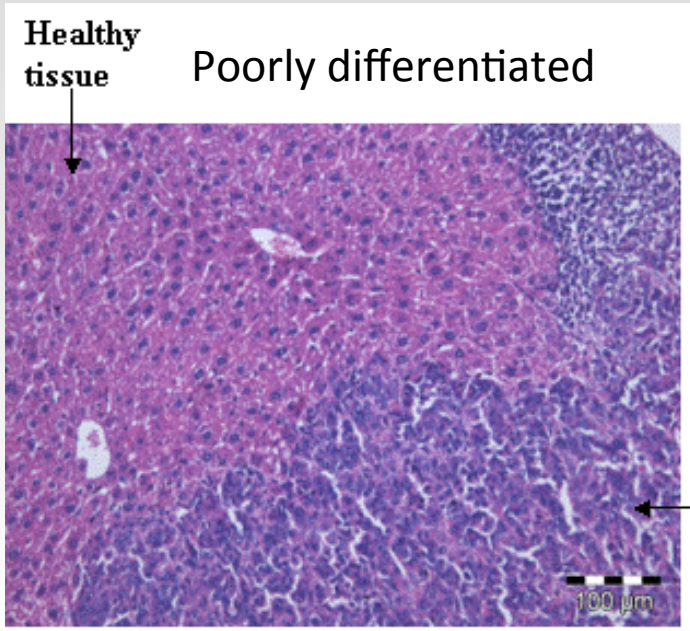
Effective friction constant × velocity + friction between cells = forces (cell/cell, cell/substrate) + Active migration

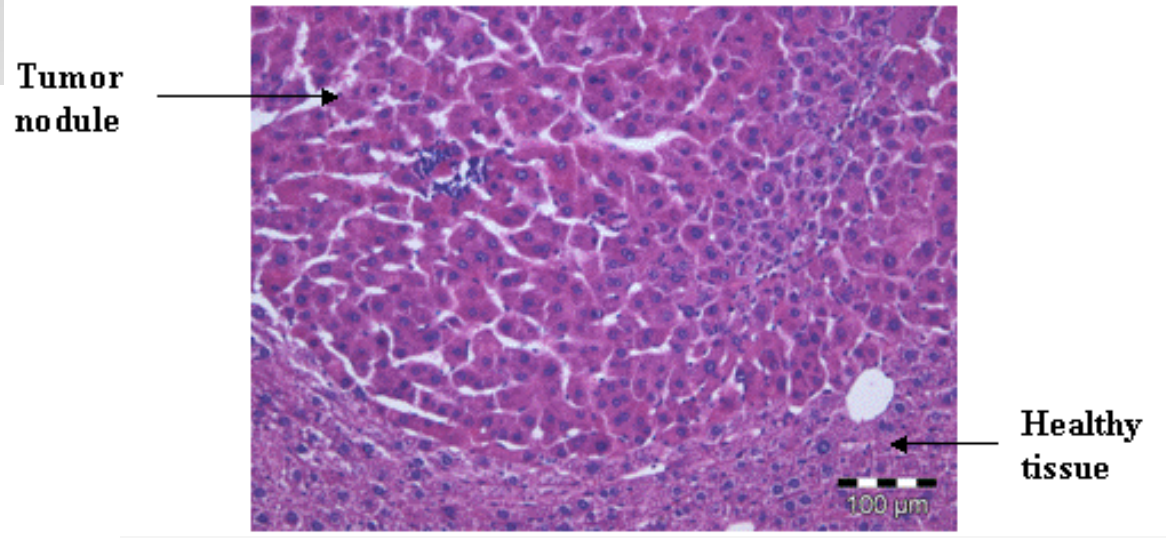
Blood vessels (small + large) modelled as semi-flexible chain of spheres linked by springs

Application to HCC

In experiments we observed two phenotypes: well-differentiated and poorly-differentiated.

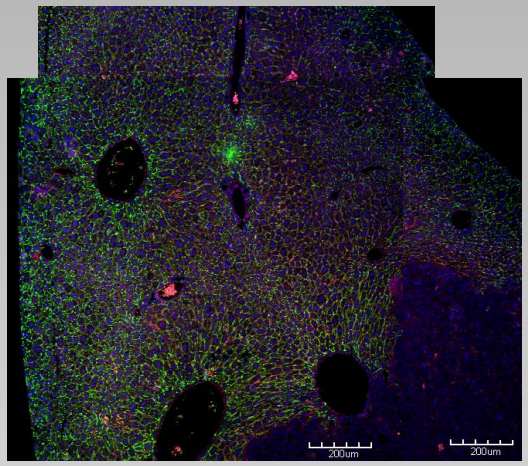
What are the relevant and minimal changes that could explain both phenotypes?

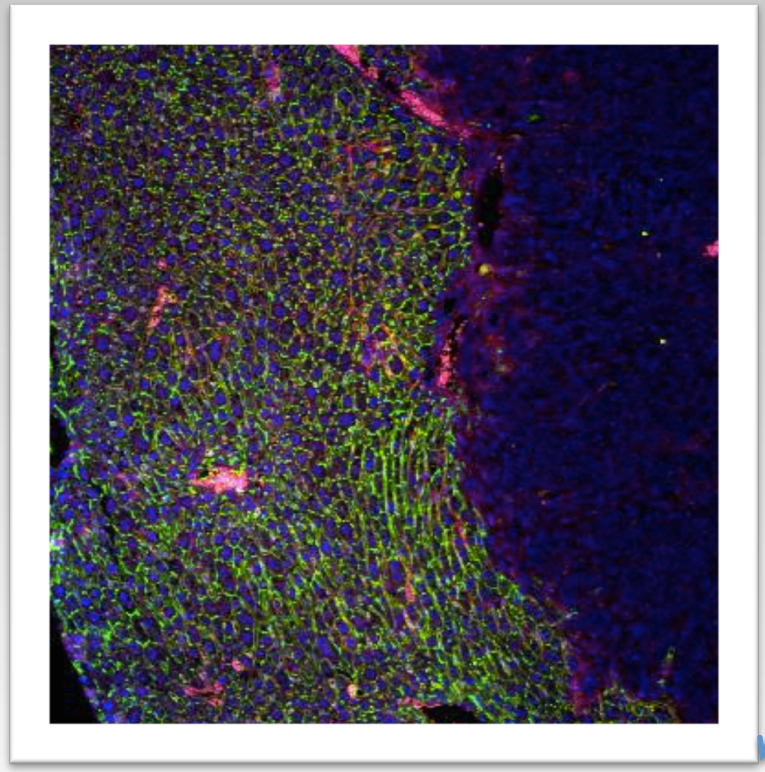


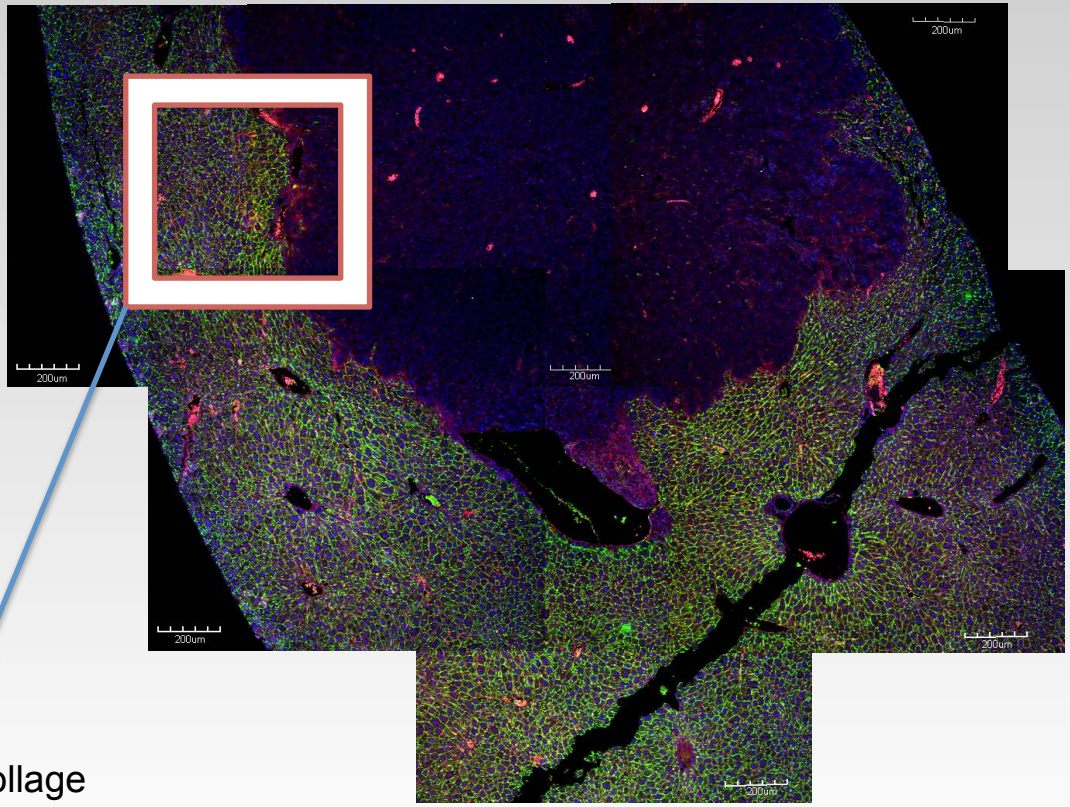


Well differentiated tumor

Poorly differentiated

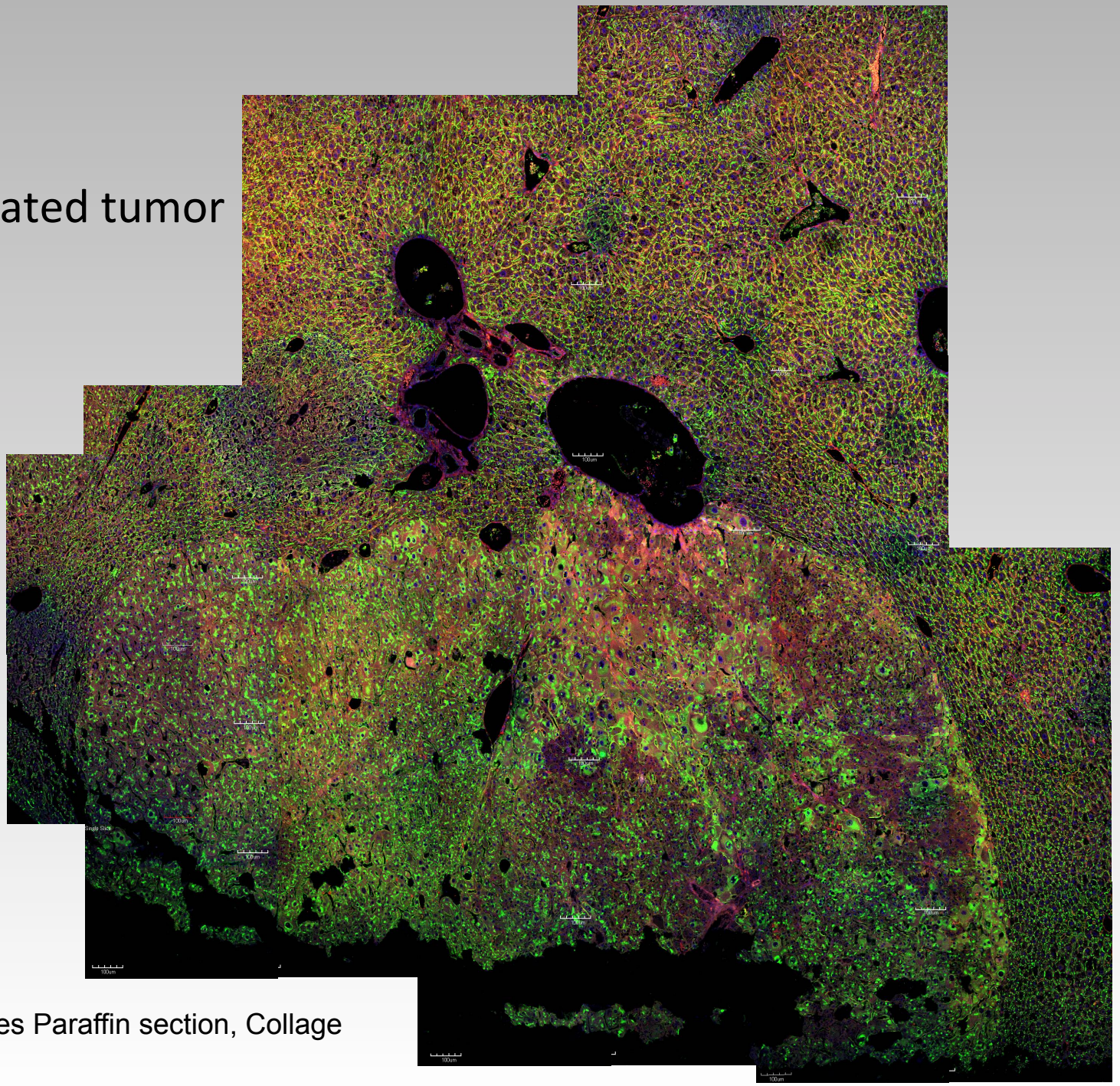






Sabine Colnot - samples Paraffin section, Collage and staining IFADO

Well differentiated tumor



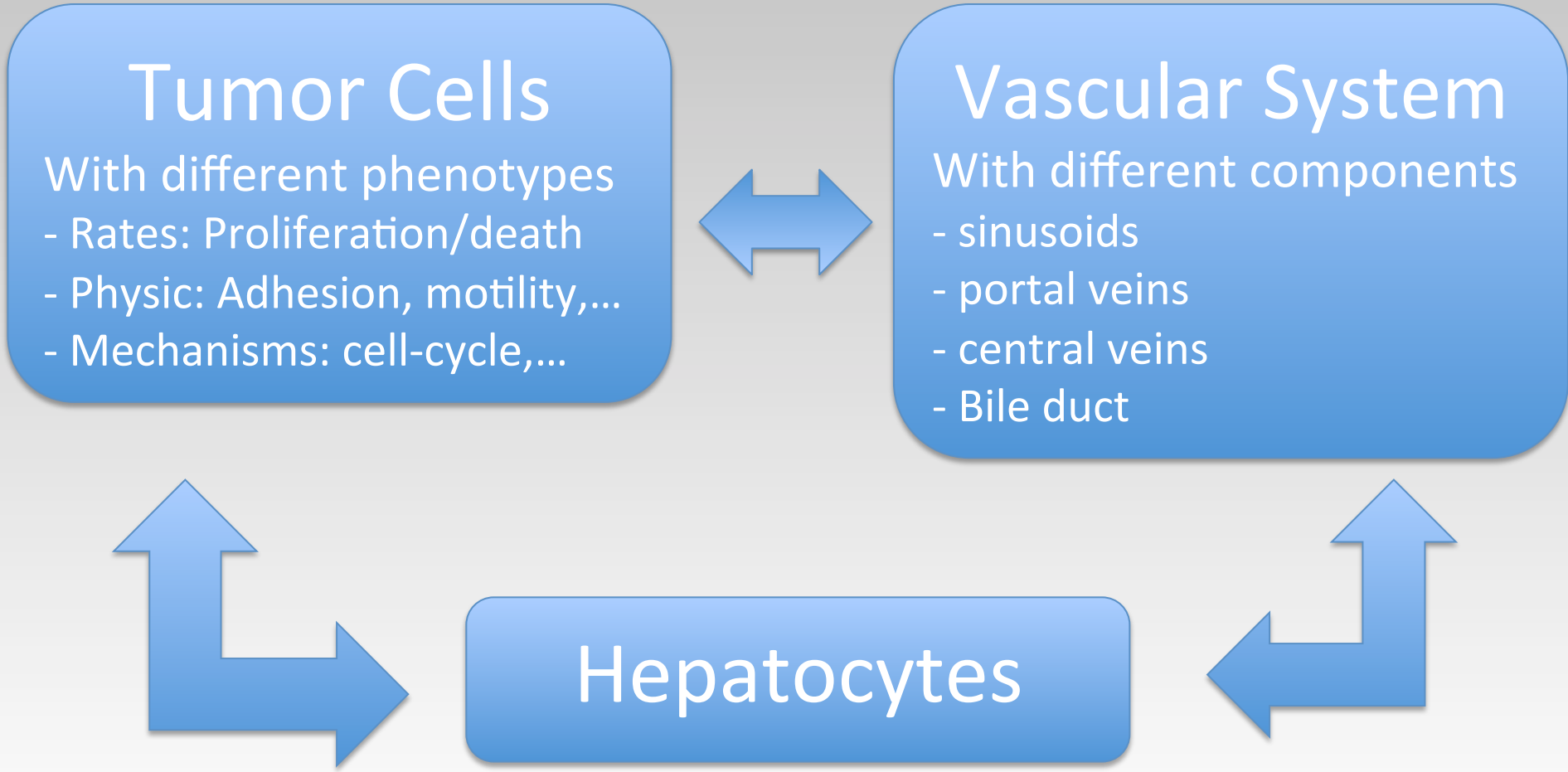
Sabine Colnot - samples Paraffin section, Collage and staining IFADO

Comparison of phenotypes

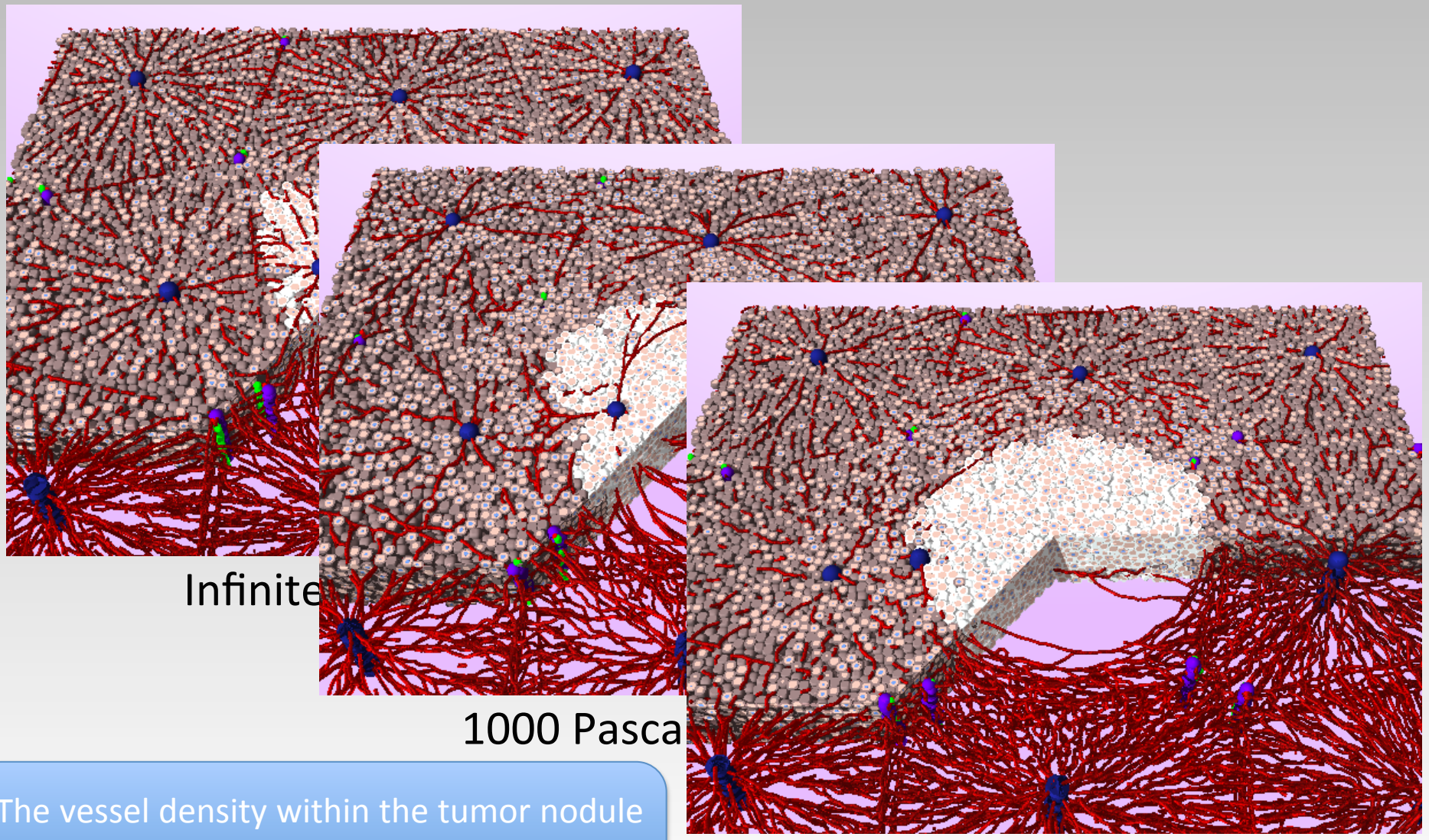
Property	Well-differentiated	Poorly-differentiated
Size (observation)	bigger	Smaller
Adhesion (quantified)	Yes	No

Those differences are not able alone to explain the well-differentiated phenotype

The liver model: building blocks



Vessel stiffness analysis



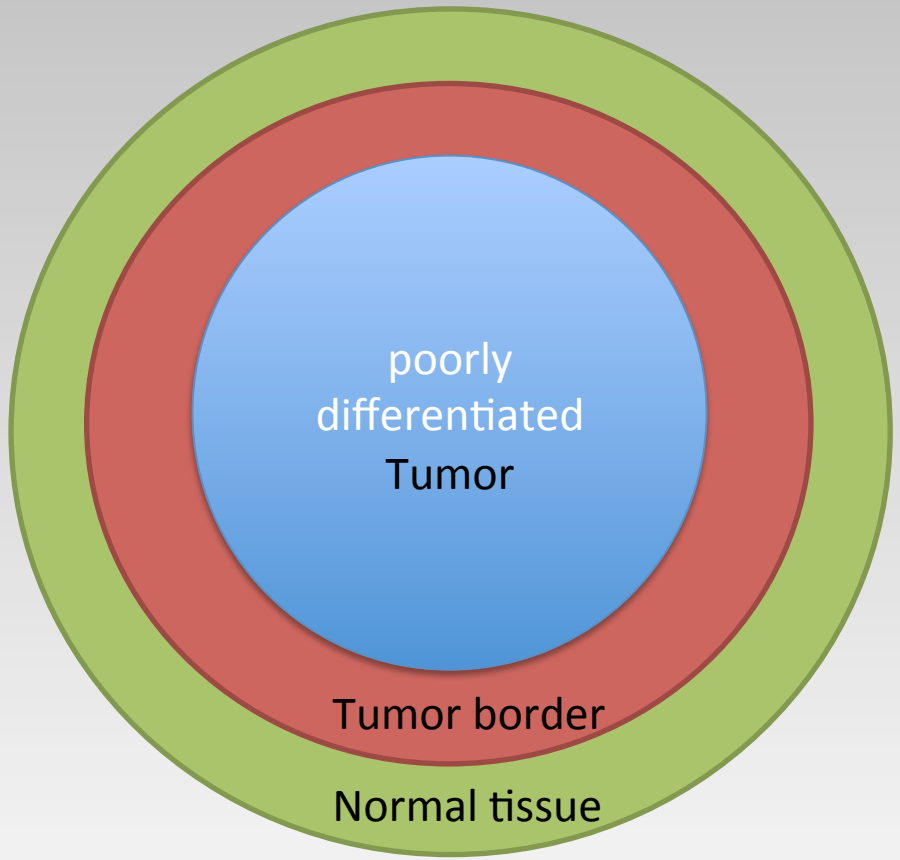
Infinite

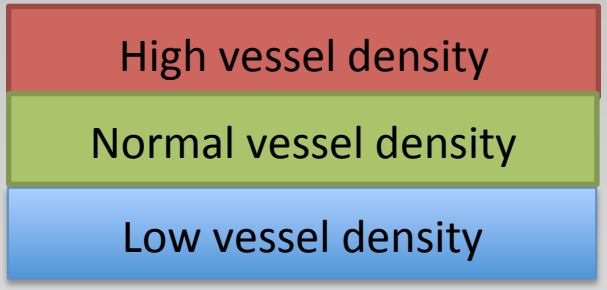
1000 Pasca

20 Pascal stiffness

The vessel density within the tumor nodule is correlated with the ability of the tumor to push the vessels away.

Scenario 1: unrestricted proliferation

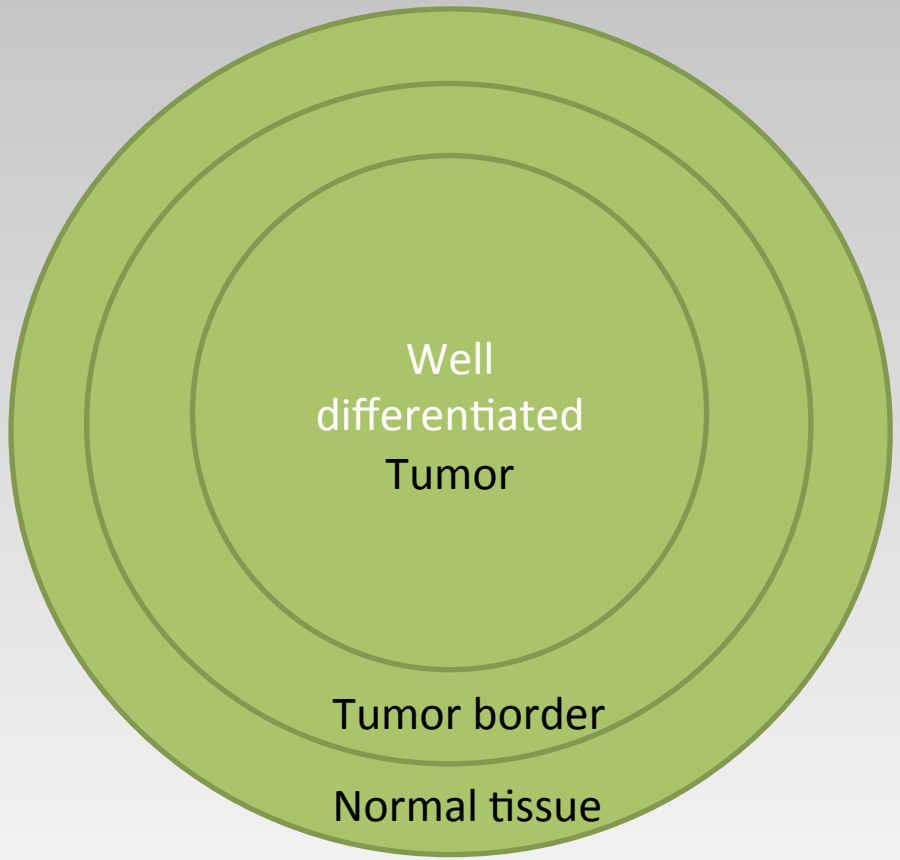




Tumor cells elevate their critical pressure at which they enter quiescence above the value at which vessels can be pushed aside (without dying).

<u>This situation is not observed in experiments</u>

Scenario 2: resistant vasculature



High vessel density

Normal vessel density

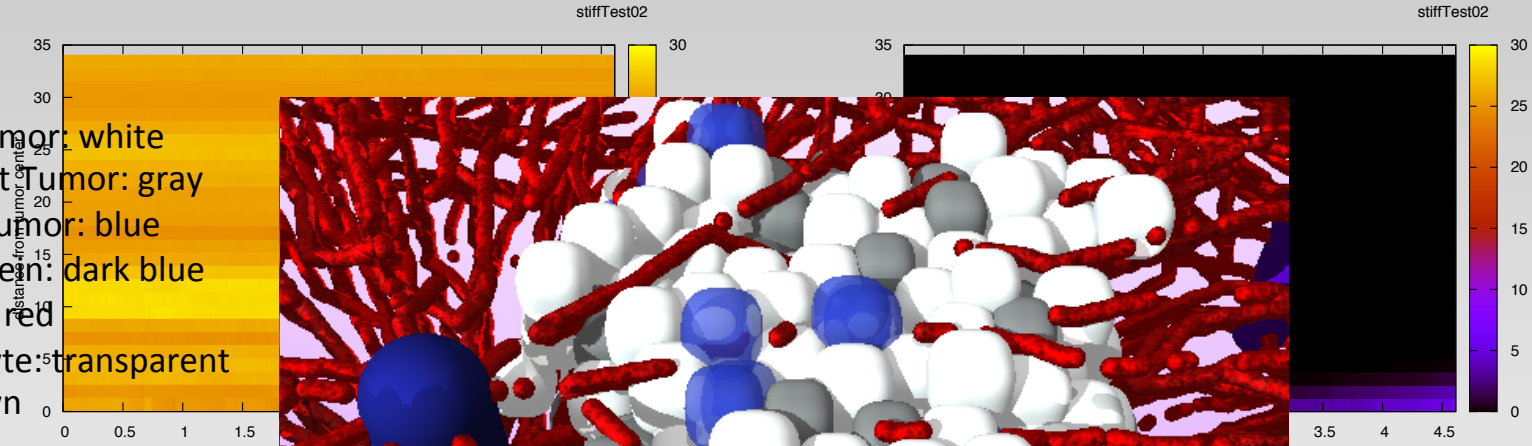
Low vessel density

Tumor cells replace healthy cells without destructing the liver vasculature. Cells are said well differentiated because they behave almost like normal hepatocytes

<u>This situation is observed in well differentiated tumors</u>

High Vessel Stiffness

- The tumor grows and finds its path around the vessel. When there is no more free spaces, the tumor has to kill its surrounding healthy hepatocytes.



Active Tumor: white
Quiescent Tumor: gray
Mitotic Tumor: blue
Central Vein: dark blue
Sinusoid: red
Hepatocyte: transparent and brown

Endothe
remains

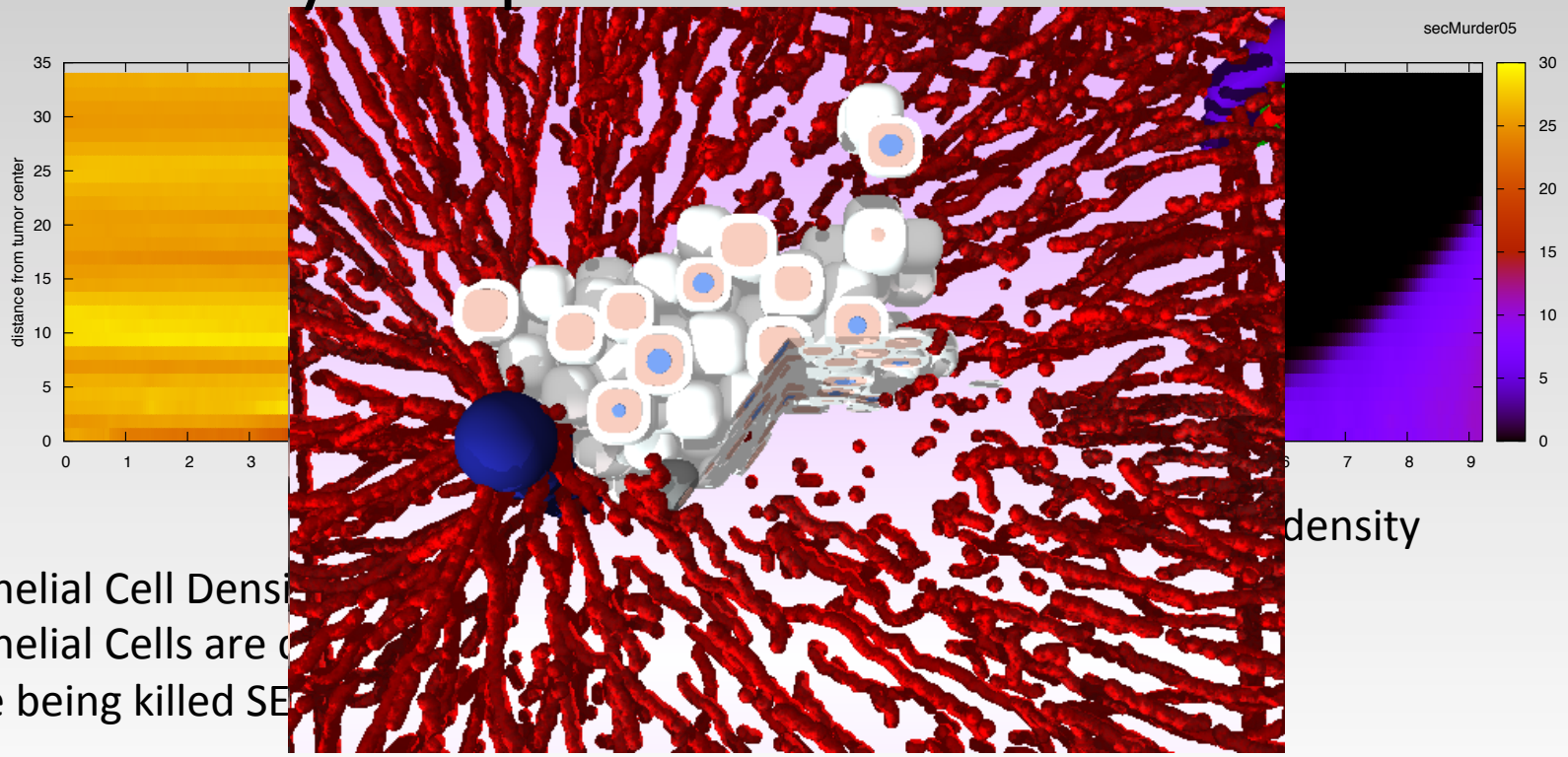
ensity

Full environment with a cut in visualization

Only Tumor cells and vasculature

Tumor's Vessel Digestion

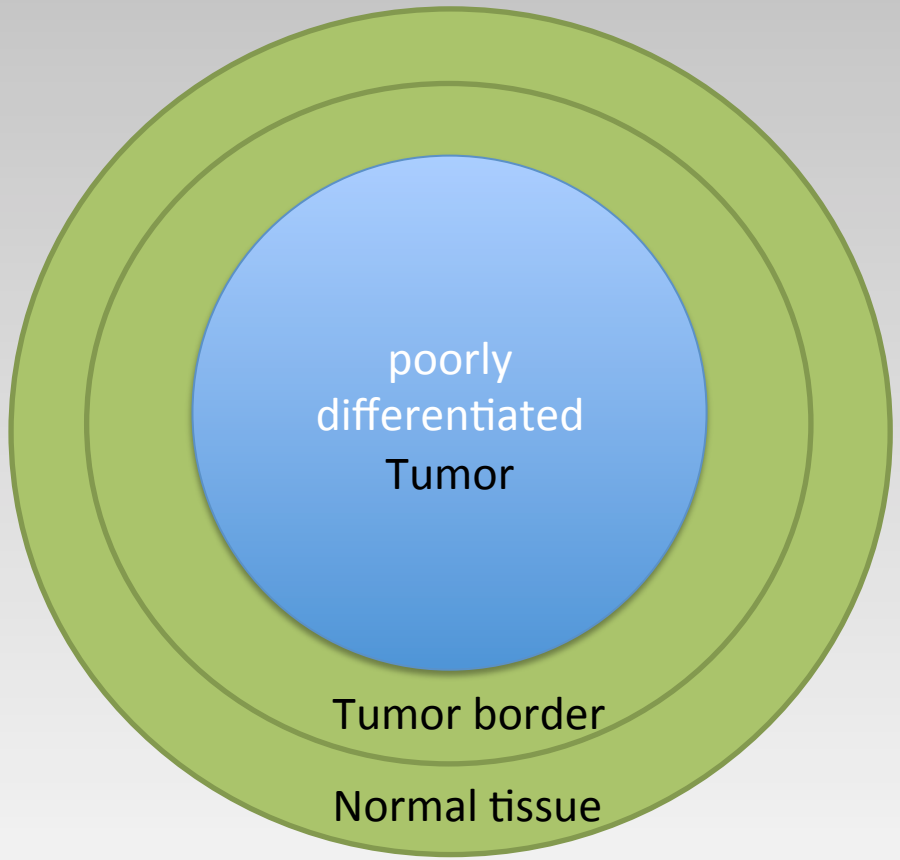
- The tumor growths and destroys the blood vessel by compression.



Endothelial Cell Densi
Endothelial Cells are
Before being killed SE

From a simulation with vessel desctruction

Scenario 3: vasculature destruction



High vessel density

Normal vessel density

Low vessel density

Tumor cells may secrete proteolytic enzymes, weakening the cell-cell contacts of endothelial cells to eventually destructing them.

<u>This situation is observed in poorly differentiated tumors</u>

Conclusion

- Biomechanical effects alone can reproduce most of the different observed phenotypes
- The model is able to reproduce biological data and to confirm or invalidate some assumptions on the tumor cell phenotype
- Thanks to exchange with biologist the model is more and more precise and realistic
- At the same time, biologists used our results to make new assumptions and experiments

We are currently analyzing simulation with asymmetric liver cells

Thank you