Modeling tumor development in liver

Séminaire des doctorants
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BANG, Inria
November 15th 2011
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:**

1. DNA mutations
2. Aggressive Cell
3. Disorder in tissue
4. Organ not functional
5. Disease or death

*Our purpose is to help to understand part of the mechanisms.*
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 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 is the science field that deals with different biology scales and tries to link them together – using physical and chemical laws.

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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

- Experiment
- Data analysis
- Quantitative modeling
- Model prediction

Pilote experiment that gives the main idea
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

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

Effective friction constant $\times$ 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?
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

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<th>Property</th>
<th>Well-differentiated</th>
<th>Poorly-differentiated</th>
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<td>Size (observation)</td>
<td>bigger</td>
<td>Smaller</td>
</tr>
<tr>
<td>Adhesion (quantified)</td>
<td>Yes</td>
<td>No</td>
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Those differences are not able alone to explain the well-differentiated phenotype.
The liver model: building blocks

Tumor Cells
With different phenotypes
- Rates: Proliferation/death
- Physic: Adhesion, motility, ...
- Mechanisms: cell-cycle, ...

Vascular System
With different components
- sinusoids
- portal veins
- central veins
- Bile duct

Hepatocytes
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).

This situation is not observed in experiments.
Scenario 2: resistant vasculature

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

This situation is observed in well differentiated tumors.
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.
Tumor’s Vessel Digestion

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

Endothelial Cell Density:

Endothelial Cells are destroyed before being killed by SEC.

From a simulation with vessel desctruction.
Scenario 3: vasculature destruction

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

This situation is observed in poorly differentiated tumors
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