Modelling competition between cancer cells and healthy cells

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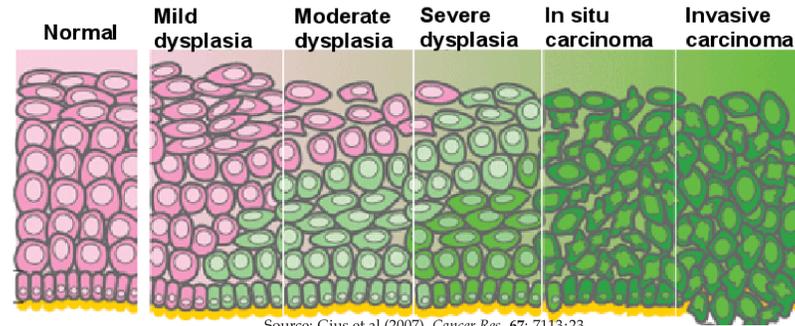[2]Centrum voor Wiskunde en Informatica (CWI)

Background

- Study **cancer** cells and **normal** cells in one tissue

- At some point cancer cells may take over the normal cells by **competition**

- Question: which physical **properties** of cells influence competition between cell types?

- Highly relevant for **initial stages** of cancer

- Main **properties** of interest:
  - Cellular **rigidity** (λ)
  - Cellular **adhesion** (J):
    Homogeneous ($J_{g,g}$): to cells of the same type
    Heterogeneous ($J_{g,b}$): to cells of the other type
    A low J means high adhesion

Aim:

To gain insight in which physical **properties** of cells influence **competition** and make one cell type take over at cost of the other

Normal — Mild dysplasia — Moderate dysplasia — Severe dysplasia — In situ carcinoma — Invasive carcinoma

Source: Gius et al (2007). *Cancer Res.* **67**: 7113:23

Approach

Two **models**, a competitive **Lotka-Volterra (LV)** model and a **spatial model** are used for:
1. **Comparison**: advantages of the more sophisticated spatial model over the simpler LV model
2. **Insight**: the LV model is used to better understand the spatial model

Characteristics of both models:
- Two cell types (50% green and 50% blue initially)
- Individual cells or cells as a population **grow**, **die** and **compete** for space.
- The main properties of interest are defined by parameters and may differ between cell types

Competitive Lotka Volterra Model

- **Ordinary Differential Equations (ODEs)**
- Two cellular populations: g and b
- Populations **grow**, **shrink** and **compete** with eachother.
- Deterministic
**Lotka-Volterra** based model with logistic growth and interaction term.

$$\frac{dg}{d\tau} = \Gamma_1(1 - \alpha_1 g - \beta_1 b)g$$

$$\frac{db}{d\tau} = \Gamma_2(1 - \alpha_2 b - \beta_2 g)b.$$

α = how much are cells hindered by own cell type
β = how much are cells hindered by other cell type

Competitive Spatial Model

- **Cellular Potts Model (CPM)**
- Cell-based: cells modelled as set pixels on a grid
- Individual cells grow, divide, die and compete
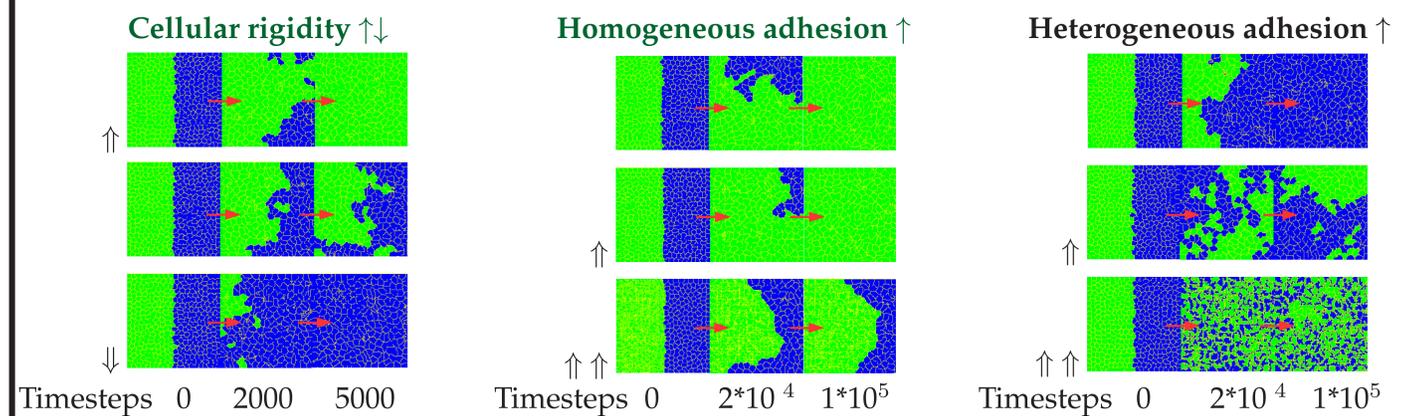- Several dimensions: volume, shape and rigidity of individual cells can be incorporated
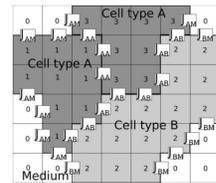
Source: Voss-Böhme A (2012). *PLoS ONE* 7(9): e42852

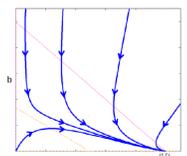- Energy (H) minimized; stochastic movement
- $H = H_{adhesion} + H_{volume}$

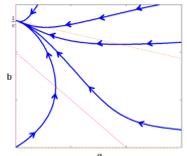## Results - Spatial Model - Rigidity, cohesion and heterogeneous adhesion

CPM Time Lapse

Cellular rigidity ↑↓   **Homogeneous adhesion ↑**   **Heterogeneous adhesion ↑**

Timesteps 0   2000   5000   Timesteps 0   2*10^4 1*10^5 Timesteps 0   2*10^4 1*10^5

Results - Competitive LV Model

Cellular rigidity ↑   **Cohesion ↑**

$\beta_2 > \alpha_2 = \alpha_1 > \beta_1$ $\alpha_1 > \alpha_2 = \alpha_1 > \beta_1$

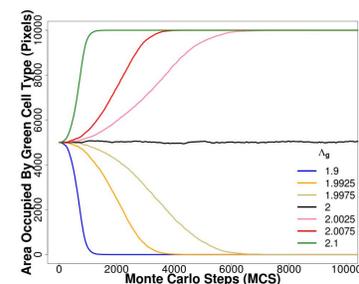**Cellular rigidity ↓**   **Het. adhesion ↑**
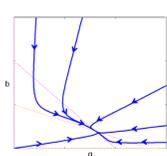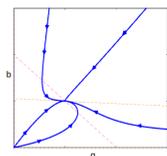
$\beta_1 > \alpha_2 = \alpha_1 > \beta_2$ $\beta_1 > \alpha_2 > \beta_1 = \beta_2$

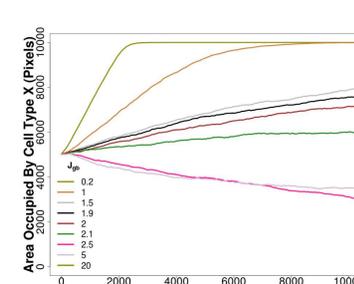## Spatial model shows complex interaction between rigidity and cohesion

Cellular rigidity   **Homogeneous adhesion**   **Cellular rigidity & adhesion**

Most rigid cell type wins.   Moderately adhesive cell type (low J) wins.   **High** rigidity both cells: nonadhesive cells win

Graphs represent the area occupied by the green cell type over time for different parameters.

Conclusions

- Both models show that increasing **rigidity** of cells is an advantage in cellular competition

- Increasing **homogeneous adhesion** is in general a competitive advantage.
  However: when homogeneous adhesion is **too strong**, cell types hardly interact

- Increasing **heterogeneous adhesion** inhibits the **coherence** of cells of the same type and thereby also hinders competition

- There is an interesting **interaction** between **rigidity** and **cohesion**

- Adhesive properties are important to induce and to win the competition.