Impact of migration/proliferation plasticity on tumor development

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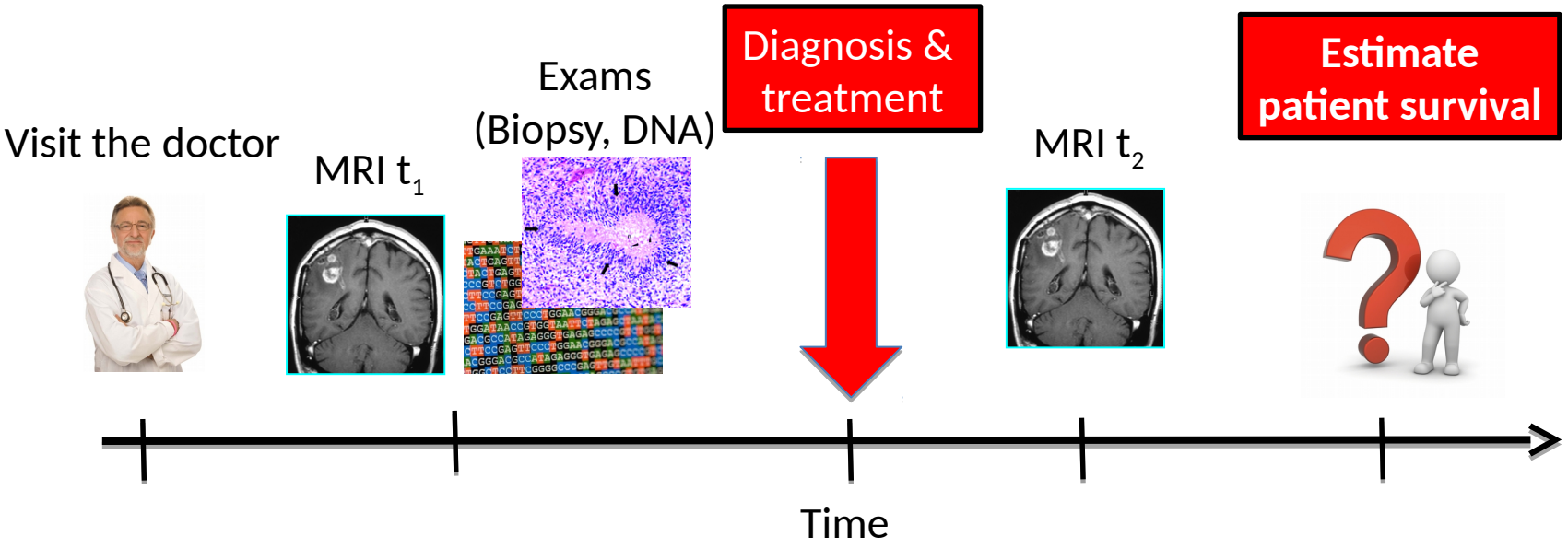
Cancer in clinics



Fact: Sparse data in time.

Diagnosis: Select treatment upon lesion's **past**

Survival: Predict the **future**

Problem: Restricted mechanistic understanding of causalities

Cells as football players

Past

Future

True positive

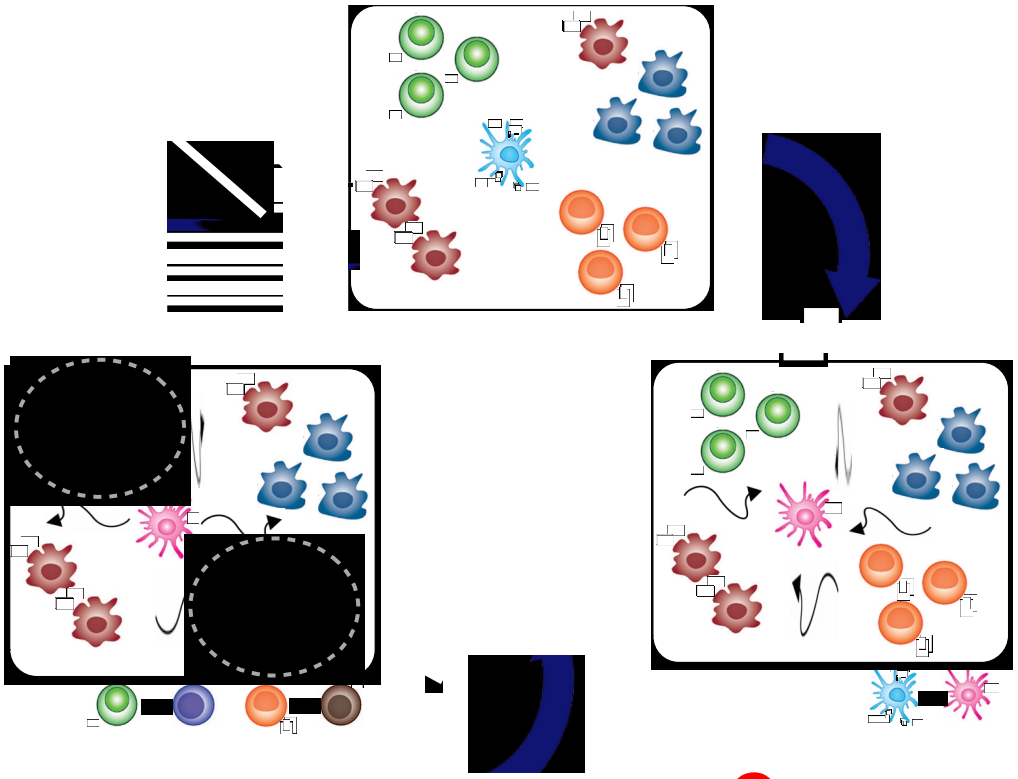
DIAGNOSIS

False negative

PREDICTION

False positive

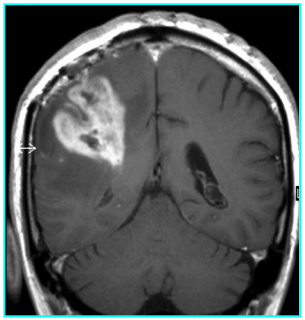
Cancer cell decision-making



Dynamic dialogue between cancer cell and its microenvironment is **complex**

Emergent organization structures

Cancer

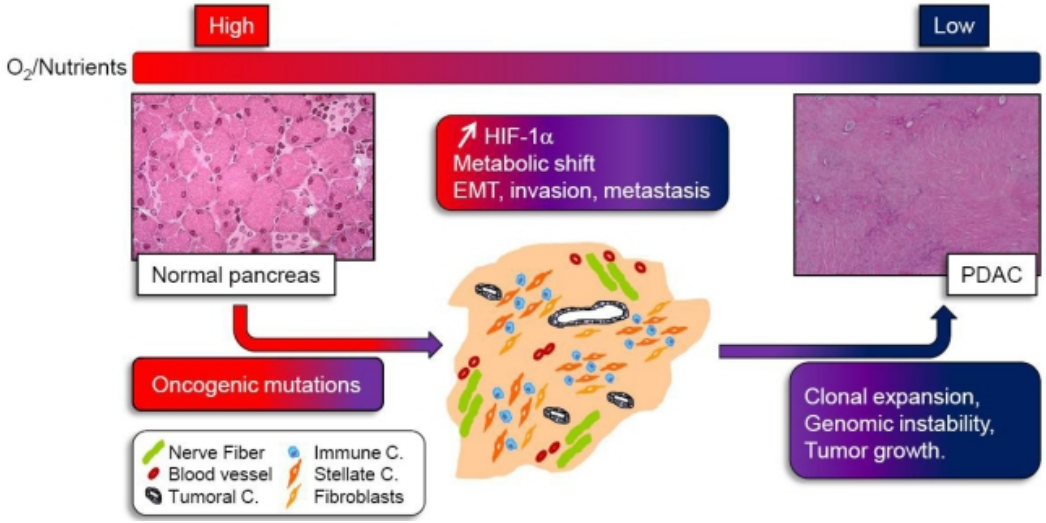


"Cancer is no more a disease of cells than a traffic jam is a disease of cars. A lifetime of study of the internal-combustion engine would not help anyone understand our traffic problems. "
- D. W. Smithers (1962)

Phenotypic plasticity

Phenotypic plasticity := ability of a cell to **reversibly decide** over its phenotype in response to changes in the micro-environment

- Epithelial-Mesenchymal Transition
- Shift to anaerobic, glycolytic metabolism (Warburg effect)



Vasseur S, Tomaisni R, Tournaire R, Iovanna LJ . Hypoxia induced tumor metabolic switch contributes to pancreatic cancer aggressiveness. Cancers 2010; 2(4):2138-52.

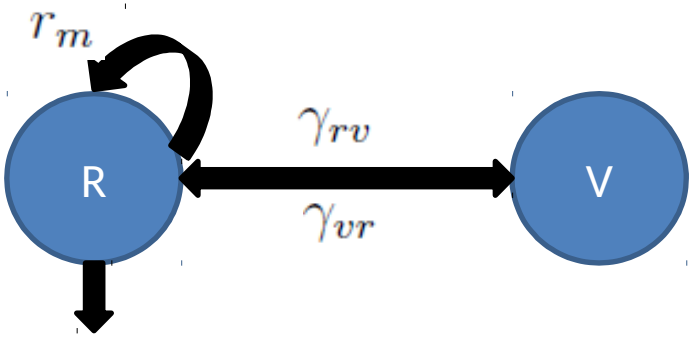
Phenotypic plasticity: “Go or Grow”

Tumor cells (*glioma*) employ a particular **decision mechanism** depending on local information (resources):

“Go or Grow” or **migration/proliferation dichotomy**

PAY-OFF

More proliferation, less migration and vice versa



The menu

1. Can we identify the “Go or Grow” mechanism and its functional dependencies from experimental set-ups?

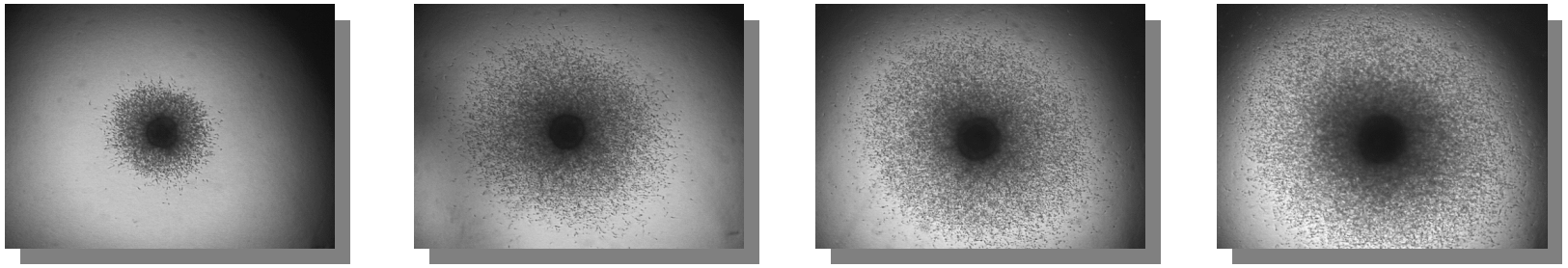
2. How “Go or Grow” influences glioma tumor initiation and persistence?

1. Identification

Experimental data

Stein et al., Biophysical Journal (2007)

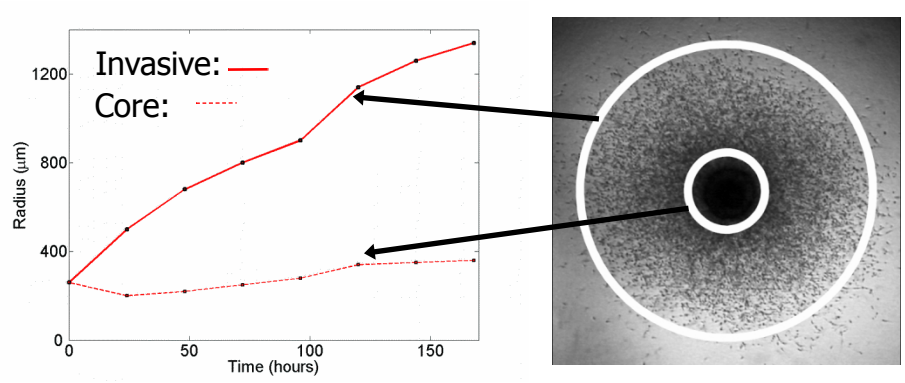
- Multicellular glioma spheroids are implanted in collagen gel and grow for 7 days
- Cells are shed from the spheroid and invade the collagen



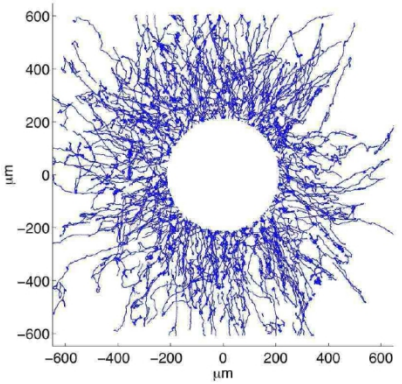
day 1 day 3 day 5 day 7

Observations:

- The core and invasive radii expand with different speeds
- At early stages of the experiment, cells move away from the core with high radial persistency



Time evolution of the core and invasive radii

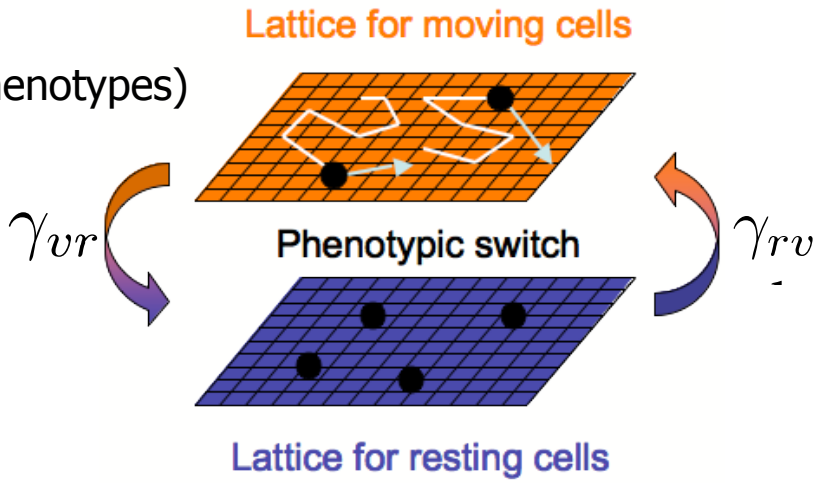


Evidence of radial persistency (t=24h)

The model

Lattice Gas Cellular Automaton

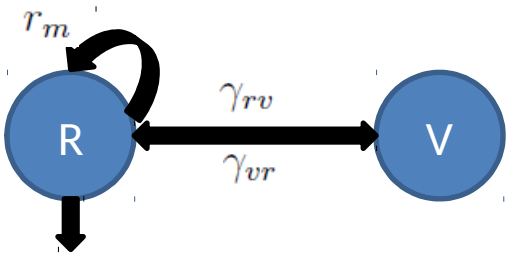
State space: Two glioma cell populations (phenotypes) *resting* and *moving*



Dynamics: **Control model**

r_m: proliferation rate

Dynamics/Rules	**CA Rules**
Proliferation	both populations
Motion	random walk
Phenotypic switch	constant rate



M. Tektonidis, H. Hatzikirou, A. Chauviere, M. Simon, A. Deutsch
Identification of intrinsic cellular mechanisms for glioma tumor invasion.
JTB, 2011

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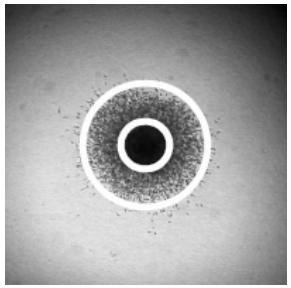
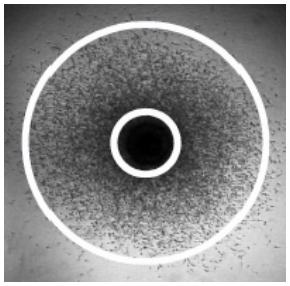
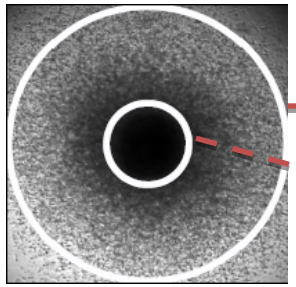


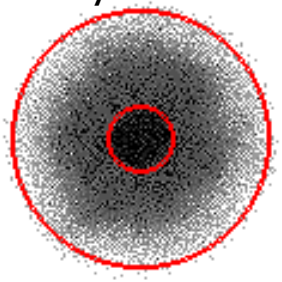
day 1

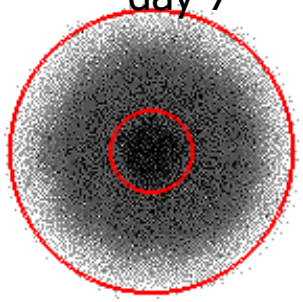


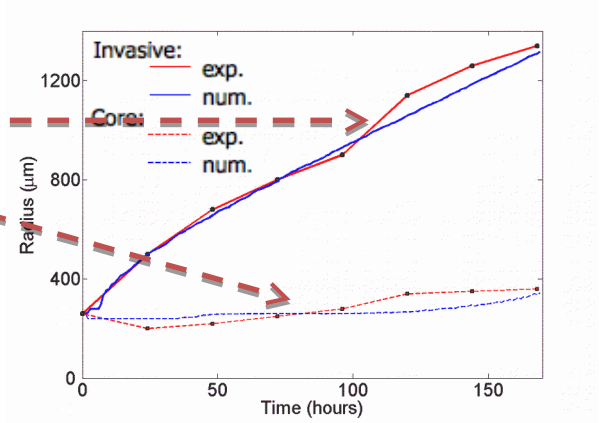
day 5



day 7







Front divergent behavior

What are the responsible mechanisms?

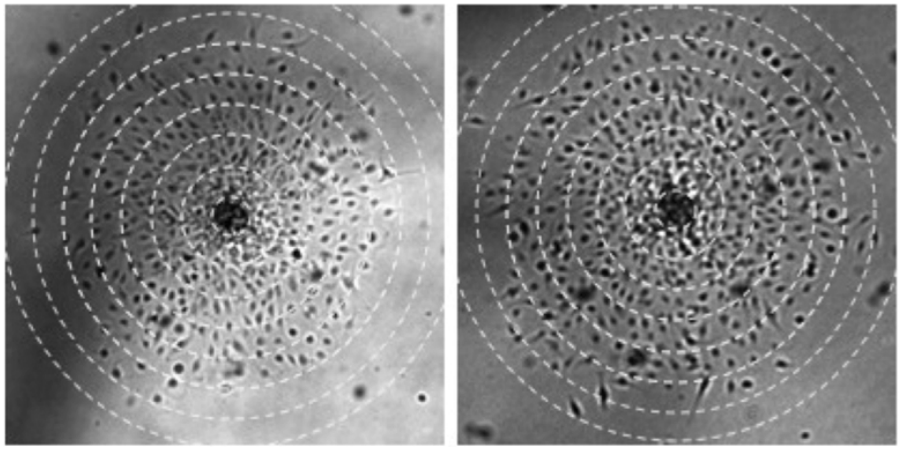
Go or Grow depends on local cell density ☺

… but exact density dependency is not conclusive ☹

Verification

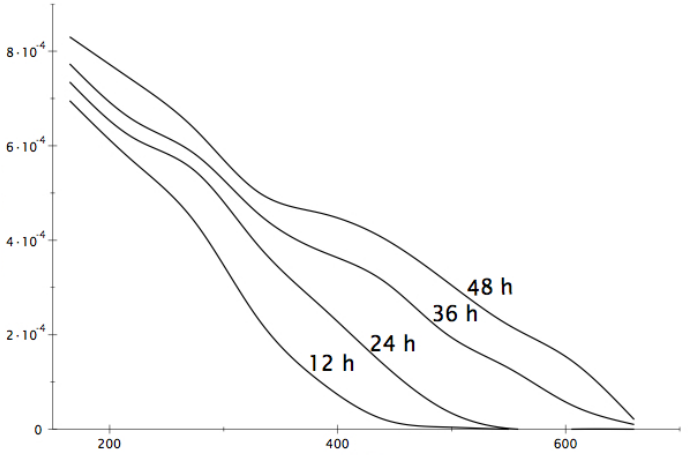
A. Chauviere ,H. **Hatzikirou**, A. Deutsch. Anomalous dynamics of glioma invasion. (in preparation)

2D experimental data (no proliferation)



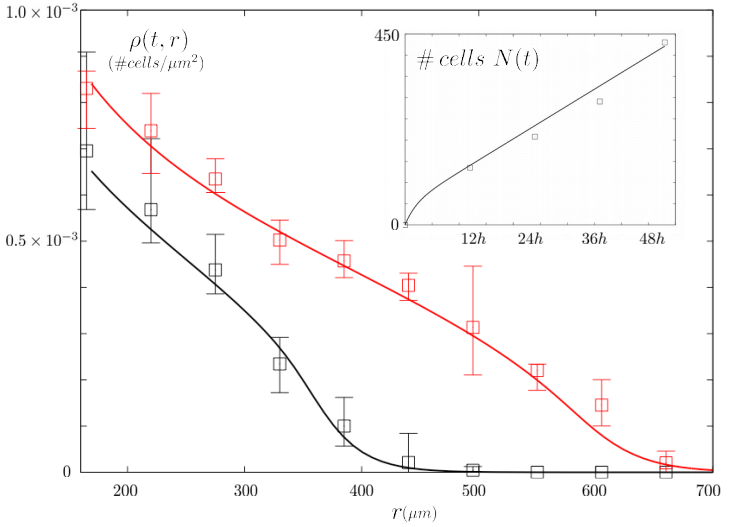
t=36h t=48h

Aubert et al., Phys. Biol. (2006)



Radial density profiles

"Go or Grow" → **"Go or Rest"**



- The phenotypic switch depends on **local information** (tumor cell density)
- Front divergent behavior and non-trivial density profiles are result of **anomalous diffusion**

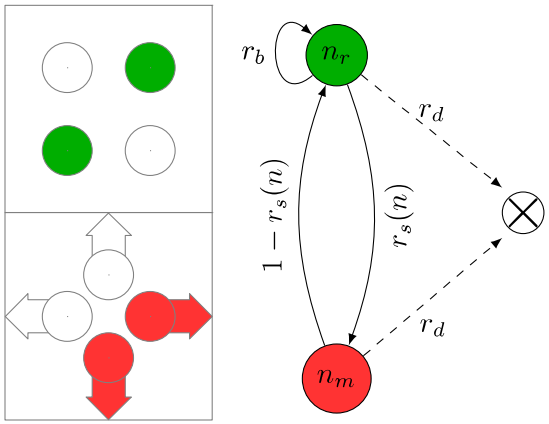
$$\langle x^2 \rangle(t) \propto t^{\theta} \quad \text{with} \quad \theta \neq 1$$

2. Impact on tumor initiation and persistence

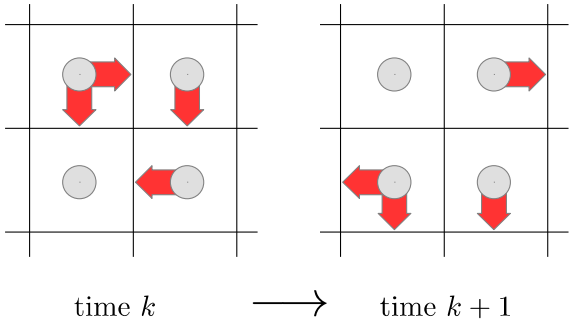
K. Boettger, **H. Hatzikirou**, A. Voss-Boehme, A. Cavalcanti, M. A. Herrero, A. Deutsch
An emerging Allee effect is critical for tumor initiation and persistence, Plos Comp Biol, 2015 (accepted)

Density–dependent migration/proliferation

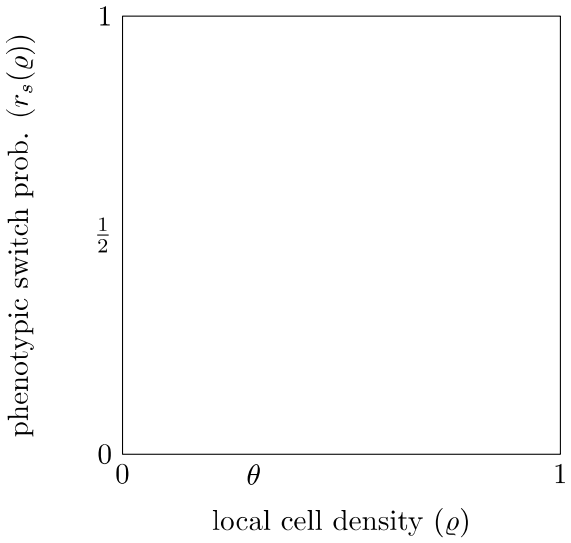
(a) cell reactions



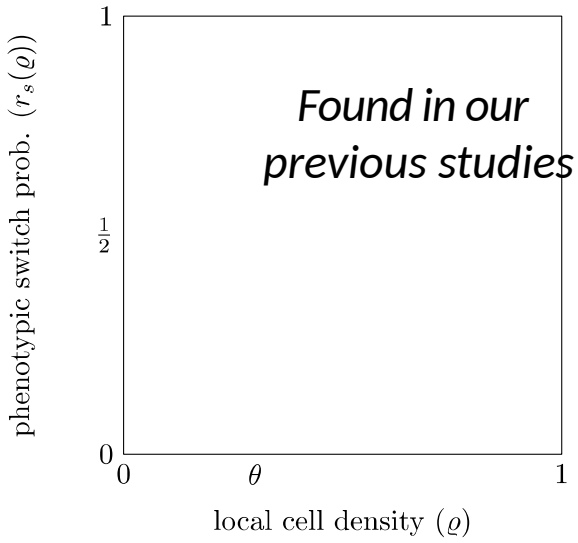
(b) cell propagation



(c) switching (attractive)



(d) switching (repulsive)



Mean-field analysis

Assumption 1: Mean-field assumption $\mathrm{E}[N_t^2] = \mathrm{E}[N_t]^2$

Assumption 2: Switching dynamics are faster than cell migration and proliferation

Mean-field equation:

$$\boxed{\partial_t \rho = \partial_x \left(D(\rho) \partial_x \rho \right) + F(\rho)}$$

Reaction term:

$$F(\rho) = R_b r_s(\rho) \rho \left(1 - \rho\right) - R_d \rho$$

$$r_s(\varrho) = \frac{1}{2}(1 + \tanh(\kappa(\varrho - \theta))), \quad \varrho \in [0, 1].$$

Switching function

Diffusion term:

$$D(\rho) = D\left(\frac{1 - r_s(0)}{2} - r_s'(0)\rho - \frac{3}{2} r_s''(0)\rho^2 \right), \quad \rho \ll 1$$

The system exhibits **bistability** for ρ=0 and ρ=ρ* <1:

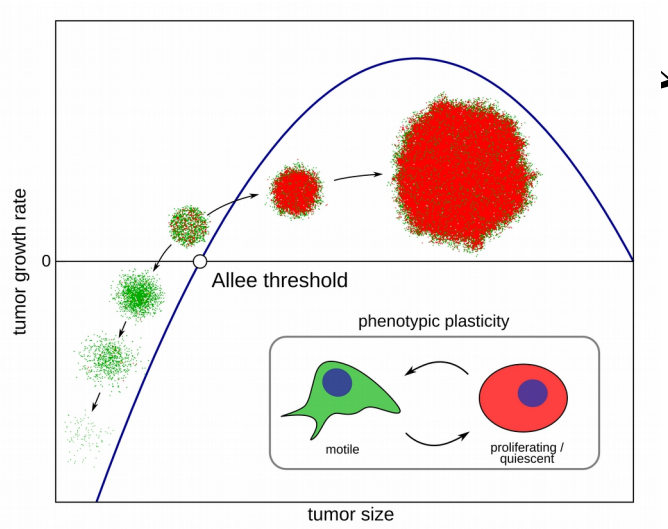
(i) Adhesive case $\kappa > 0$

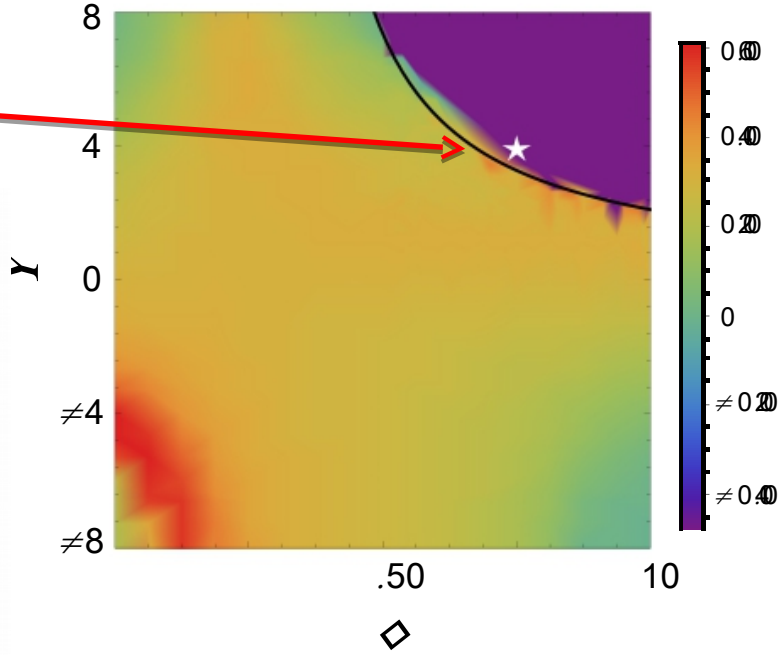
(ii) $r_s(\varrho) r_b < r_d$

Emergent population dynamics

Total population gr tw har te of theer sting cell population depends on the phenotypic sw tch pa ar meter κ da ✓:

$$r_s(\rho) < \frac{r_d}{r_b}$$ (Allee effect)





- er pulsive case ($\kappa < 0$): population always pe r ists
- atta r ctive case ($\kappa > 0$): either su r ival or extinc ion fo pop ia no

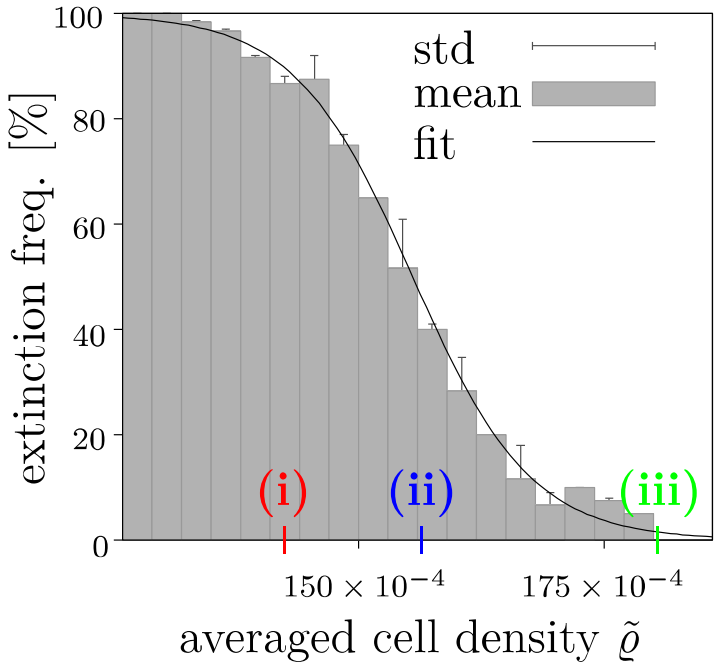
Critical behavior

Extinction

Growth

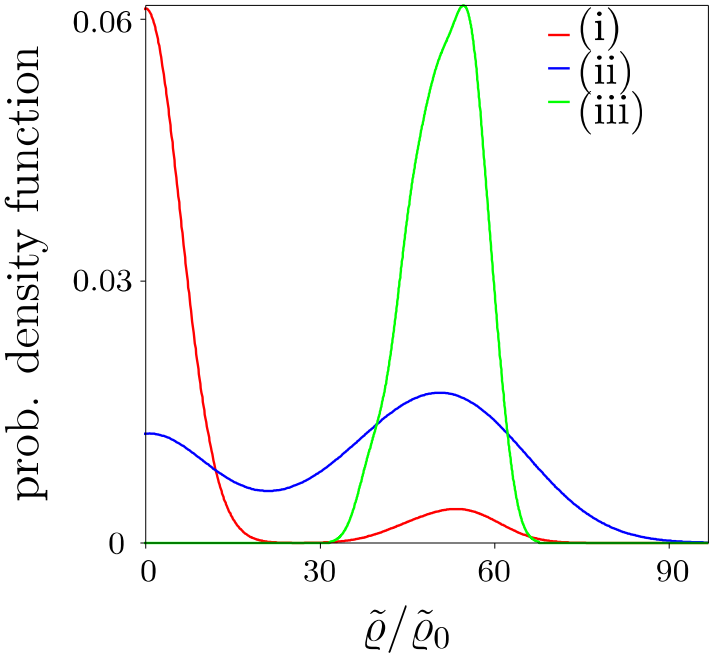
Identical initial condition and parameters for both simulations

Extinction of small tumors



Stochastic fluctuations lead to extinction or growth given a fixed small initial condition.

$\tilde{\varrho} = |\mathcal{L}|^{-1} \sum_{\mathbf{r} \in \mathcal{L}} \varrho(\mathbf{r})$



Low-density initial populations in the critical regime show bimodal stationary size distribution, indicating the possibility of either population extinction or persistence.

And what about real tumors?

Fact: Low-grade cell line cultures, *in vivo* and *in vitro*, have low chances of persistence and low reproducibility.
On the contrary, tumor establishment in high-grade cell lines is repeatedly observed.
[Huszthy et al. Neuro Oncol 2012; Tilkorn et al. Anticancer Res 2011]

Potential explanation: Allee effect for low grade tumors. Tumor initiation depends on stochastic fluctuations and initial cell density.

Conjecture on tumor progression:
The sign of parameter κ defines tumor malignancy (*ongoing work*)

WHO grade	*cellular density*	*mitotic activity*	*spread*	*others*
II	low	no/rare	low (diffuse infiltrative)	
III	increased	high	medium	nuclear polymorphism
IV	high	brisk	high (widely infiltrative)	cellular and nuclear anaplasia, microvascular proliferation, necrosis, vascular thrombosis

Ευχαριστώ!