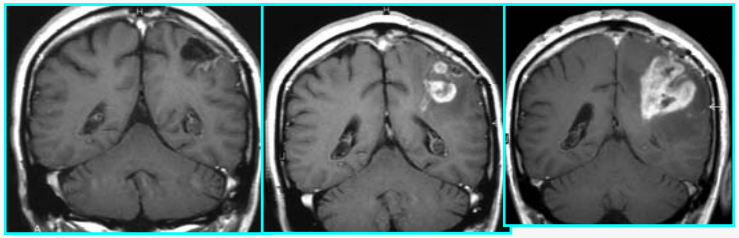
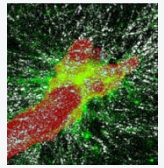
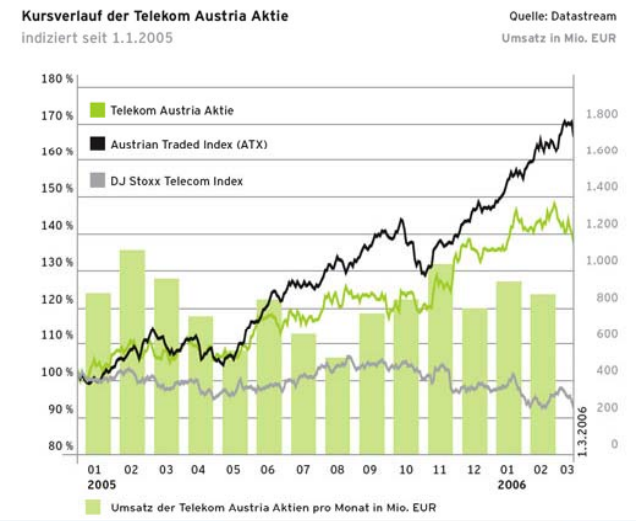
Weather

Cancer





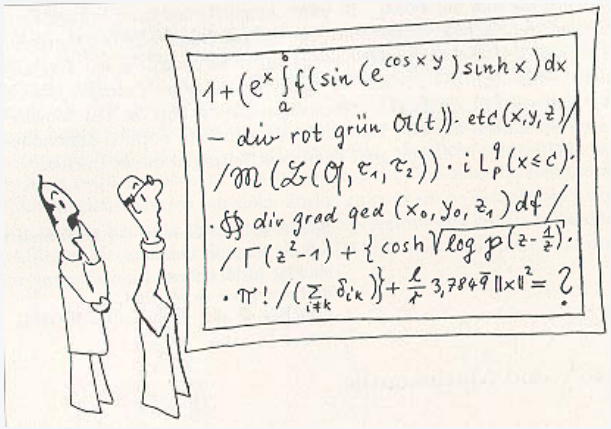
Financial markets

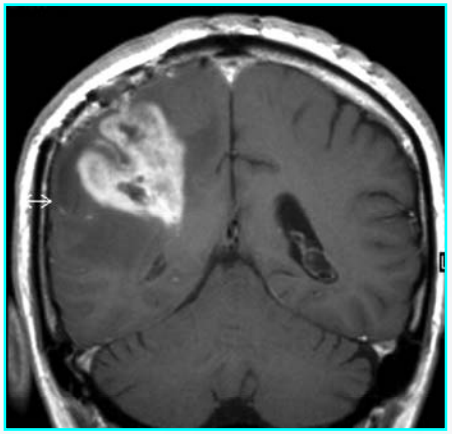


Problem:

- Wanted: prediction
- But: difficult
- Why?

  → Complex systems, i.e. many „agents“, feedback dynamics


1+(e^x ∫_a^b f(sin(e^{cos x y}) sinh x) dx
– div rot grün Ol(t)) · etc(x,y,z)
/m(Z(Ol, τ1, τ2)) · i L_p^q(x≤c)
· ∯ div grad ged (x0, y0, z1) df
/Γ(z²−1) + {cosh √log p(z−½)
· π! /(Σ_{i≠k} δik)} + ℓ/r 3,7849 ||x||² = ?



?

TECHNISCHE UNIVERSITÄT DRESDEN

Analyzing emergent behaviour in cellular automaton models of cancer invasion

NanoSeminarSeries

October, 22 2009

TU Dresden

Andreas Deutsch (Andreas.Deutsch@tu-dresden.de)

ZIH
Center for Information Services & High Performance Computing

Outline

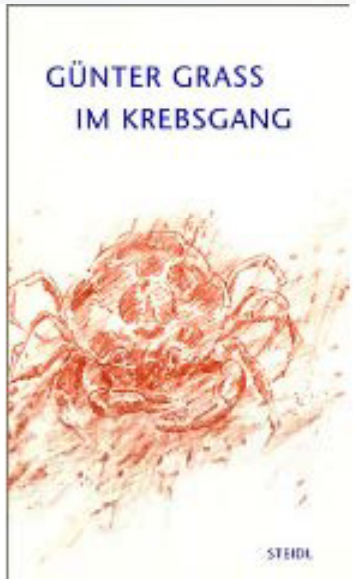
- What is cancer?
- Why mathematical models?
- **Lattice-gas cellular automaton:** idea
- **Glioma:**
  - invasion speed, how to detect invisible cells?
  - how to identify cellular mechanisms?
  - emergence of invasion?
  - prediction?
- **Outlook:**
  Computer simulation of tumour growth: can it help?

What is cancer?

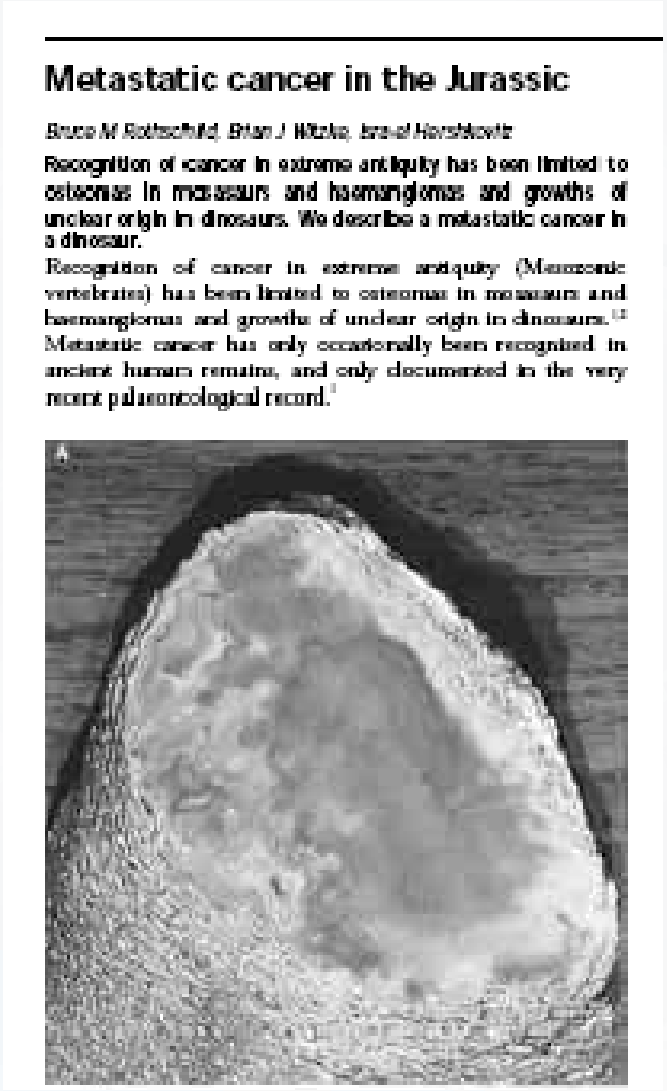
Cancer is a group of more than 100 diseases that develop across time and involve the uncontrolled division of cells.

Etymology:

Gk. karkinoma „a cancer,"
from karkinos "crab„
Lt.: tumre „to swell“ .



(crabwalk)



Metastatic cancer in the Jurassic

Bruce M Rothschild, Brian J Witzke, Israel Hershkovitz

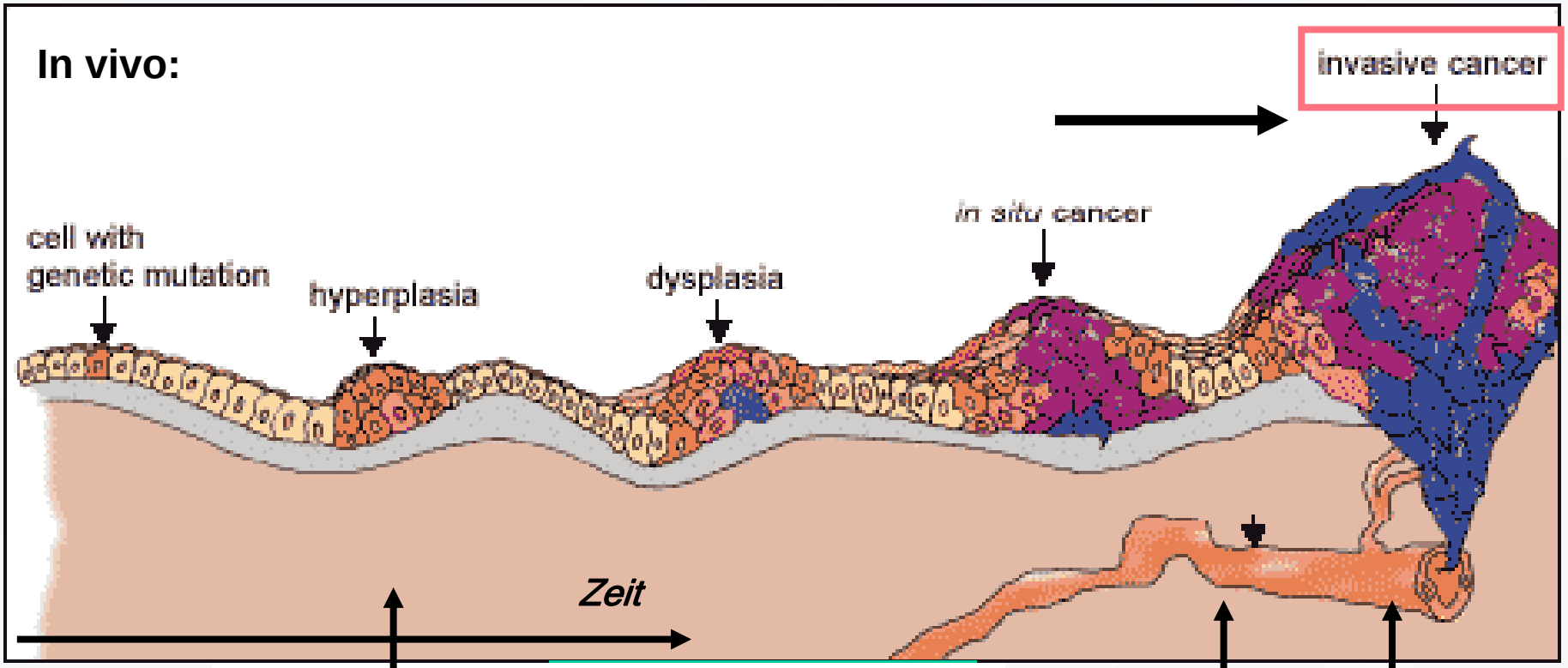
Recognition of cancer in extreme antiquity has been limited to osteomas in mosasaurs and haemangiomas and growths of unclear origin in dinosaurs. We describe a metastatic cancer in a dinosaur.

Recognition of cancer in extreme antiquity (Mesozoic vertebrates) has been limited to osteomas in mosasaurs and haemangiomas and growths of unclear origin in dinosaurs.[1,2] Metastatic cancer has only occasionally been recognised in ancient human remains, and only documented in the very recent palaeontological record.[3]

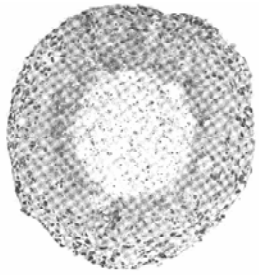
THE LANCET • Vol 354 • July 31, 1999

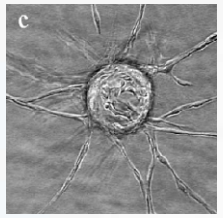
Tumor development

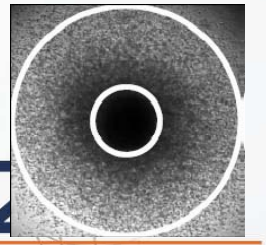
In vivo:



In vitro:







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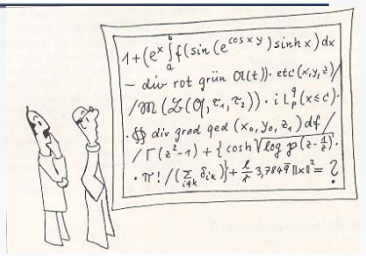
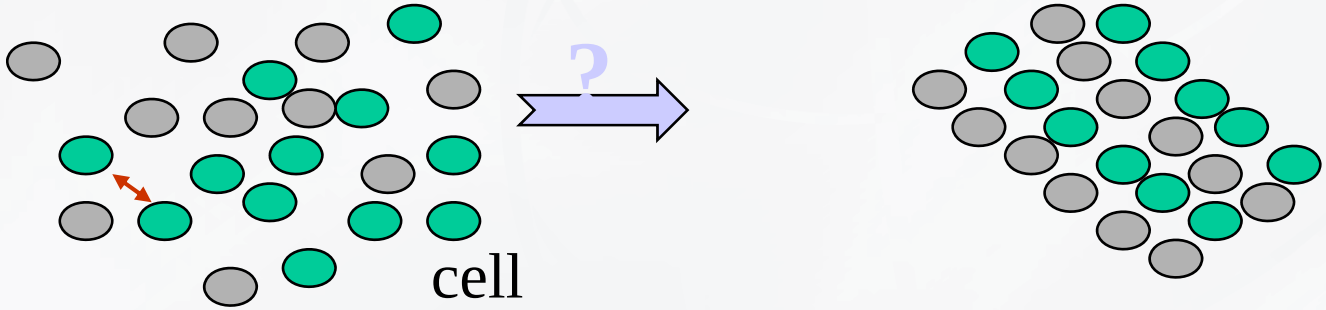
Why mathematical models and computer simulation?



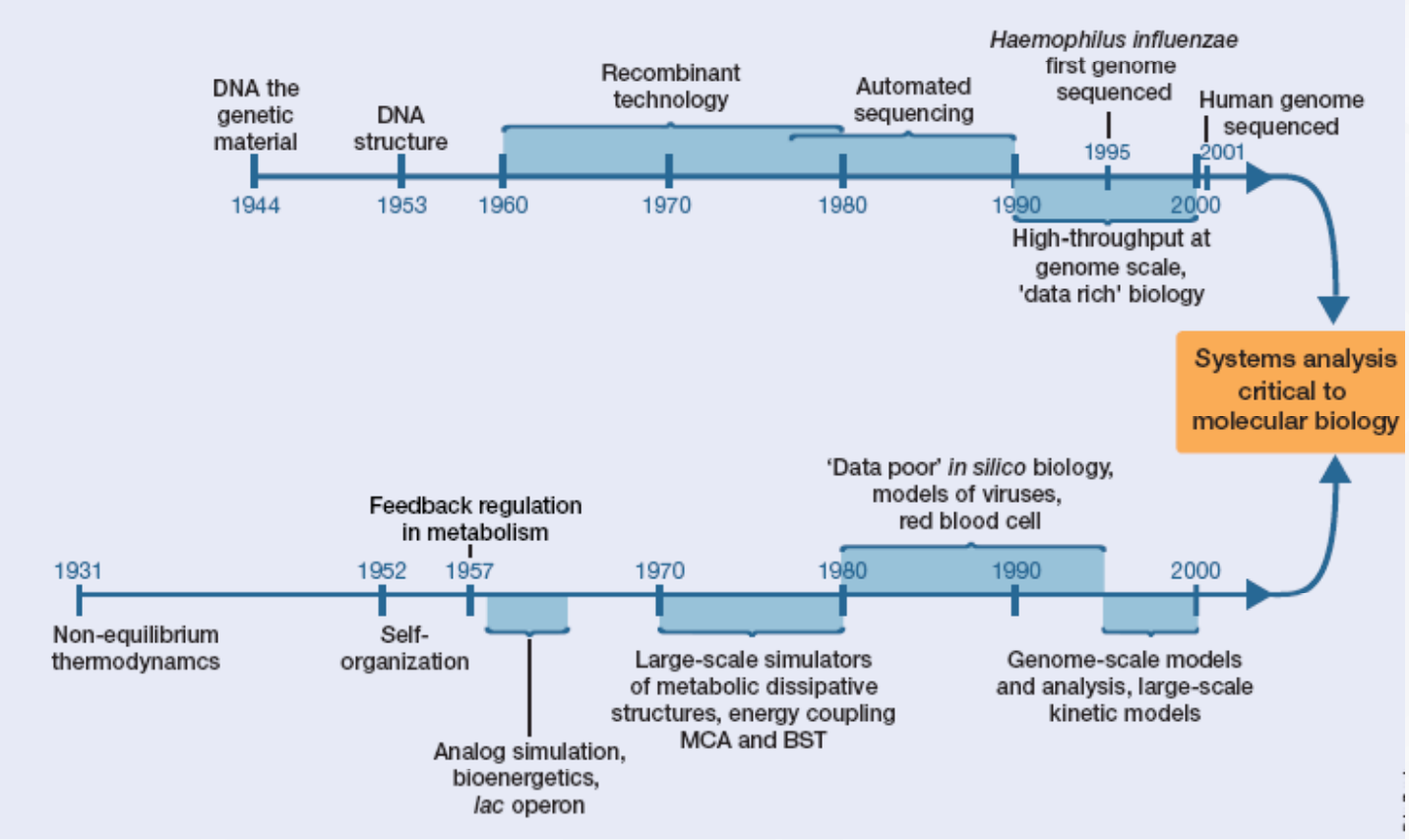
Mathematical models can help to explain emergent (*cooperative) behavior*

Cancer development and invasion:
collective, emergent phenomenon arising from the interplay of healthy, malignant and cells of the immune system.



WHAT ARE THE RULES?

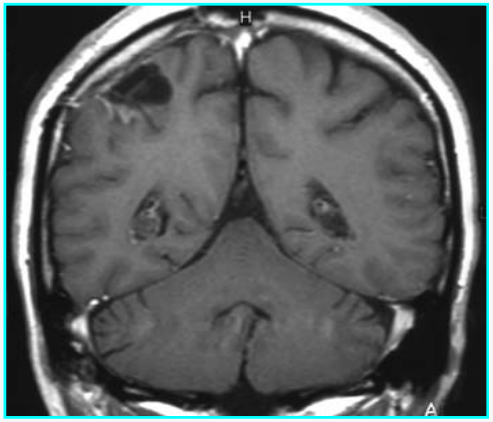
Systems analysis of biological systems



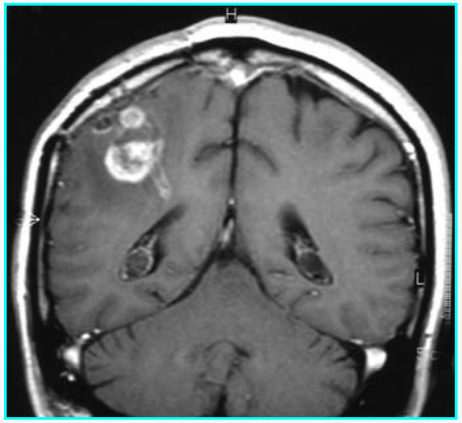
From: Westerhoff/Palsson, Nature Biotech. 22 (10), 2004

Glioma invasion: biomedical problem

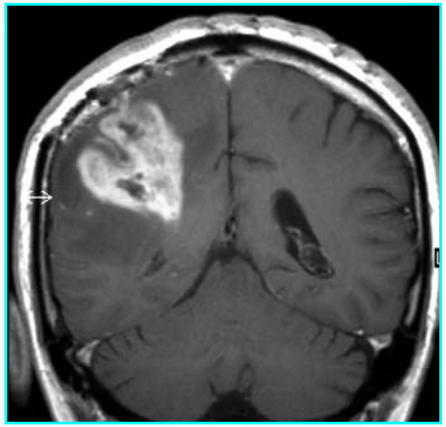
- **Glioblastoma multiforme (GBM):** most frequent and malignant primary brain tumour



t= 0 months



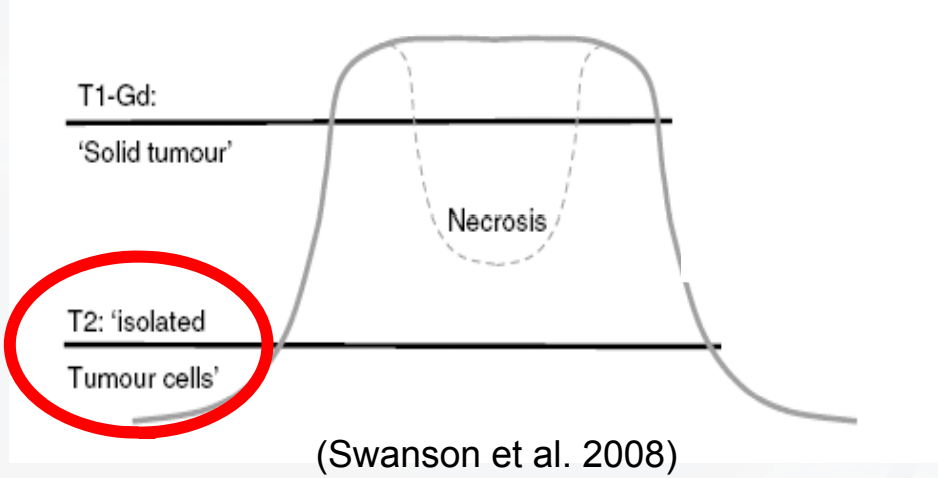
t= 3 months



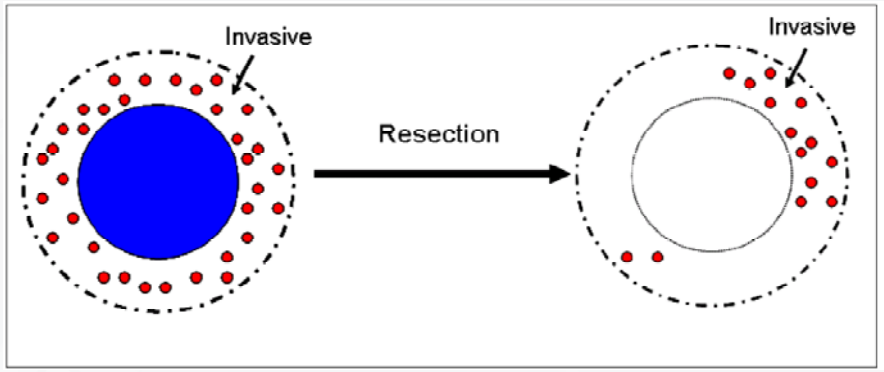
t= 6 months

- **Current imaging techniques:** identify max. 90% of glioma
- **Usual therapy:** resection followed by chemotherapy. Tumour recurrence is almost sure (see figure) due to the „invisible“part

How can we identify the “invisible” tumor cells?



(Swanson et al. 2008)

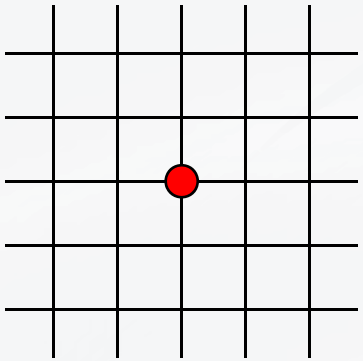


Isolated invasive tumor cells at the tumor’s front cannot be captured by imaging techniques

These cells usually are not removed by resection

Model: Cellular automaton

- **Lattice:**



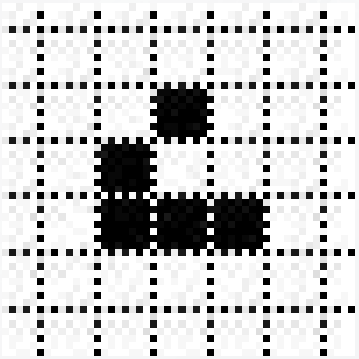
- **Time:** $t = 0,1,2,...$
- **State Space:** $S = \{s_1, s_2, ... \}$
- **Dynamics: rules**
- **Roots:** **J. v. Neumann, S. Ulam: self-reproducing systems,**
  J. Conway: Game of Life

Game of life

The rules:

1. ***Survival***, if living cell has 2 or 3 neighbours,
2. ***Death***, if living cell has less than 2 or more than 3 neighbours ,
3. ***Birth***, if dead cell has precisely 3 living neighbours.

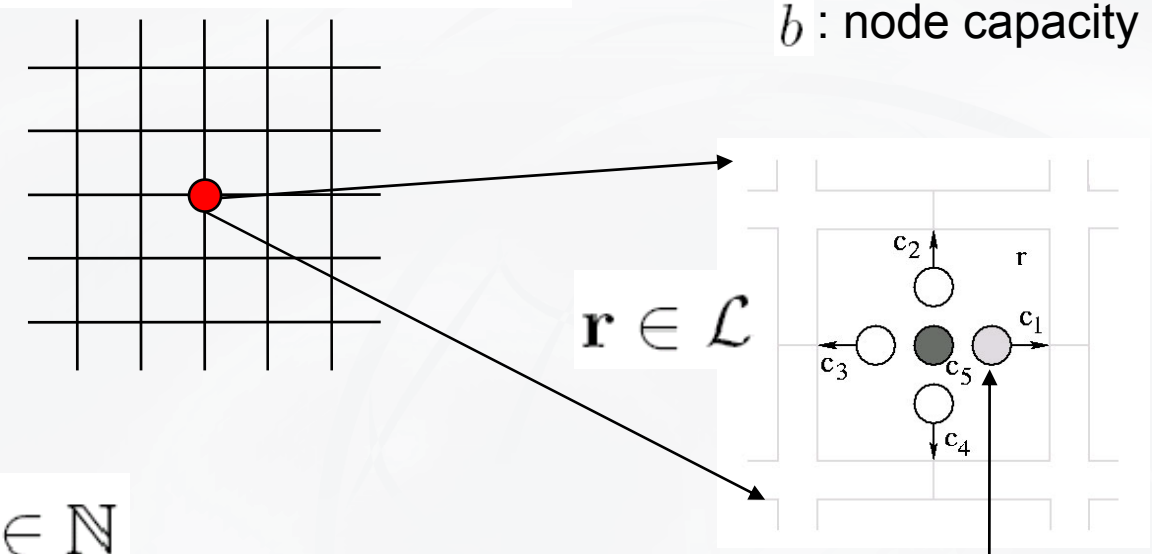
Simulation:



Lattice-Gas Cellular Automata (LGCA)

$$\mathcal{L} = L_1 \times ... \times L_d \subset \mathbb{Z}^d$$

$\tilde{b}$: node capacity



- **Lattice**

$(d = 2)$

- **Time** $k \in \mathbb{N}$

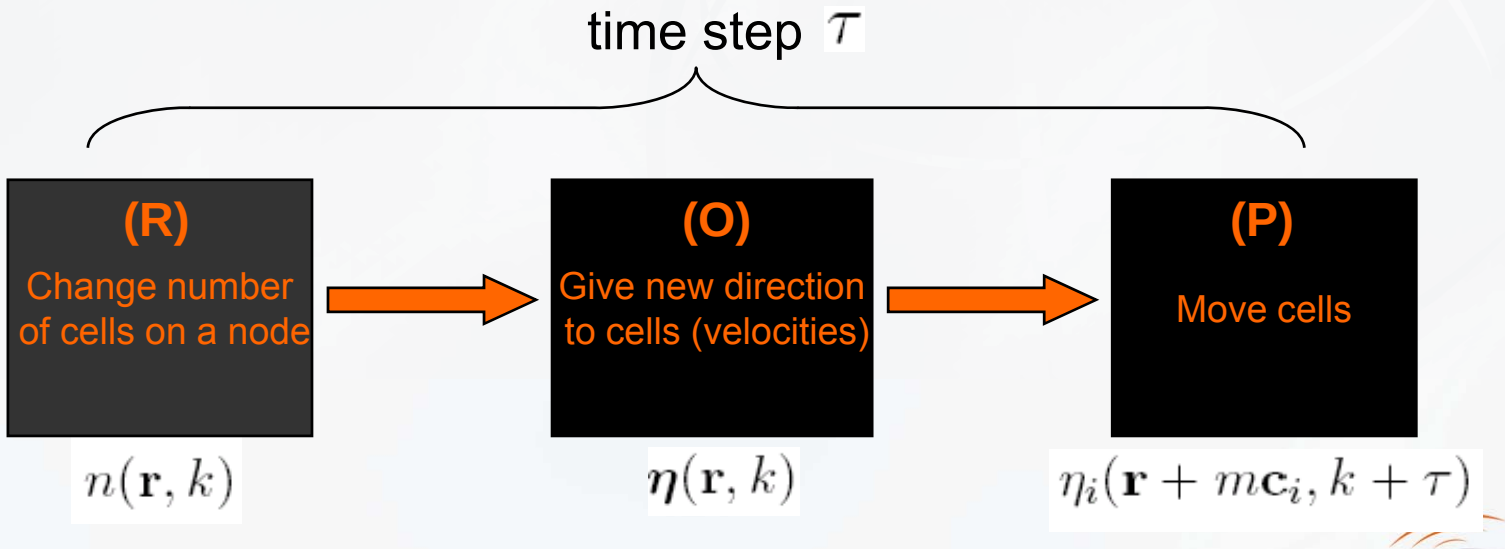
- **State Space** $\mathcal{E} = \{0, 1\}^{\tilde{b}}$

- **Exclusion principle:**
Each channel is occupied by at most one cell

LGCA Dynamics

The temporal dynamics of the LGCA is defined by the application of three operators: **propagation (P)**, **re-orientation (O)**, **cell kinetics (R)**

$$\eta_i(\mathbf{r}, k) \rightarrow \eta_i^{\mathrm{R}\circ\mathrm{O}\circ\mathrm{P}}(\mathbf{r}, k)$$

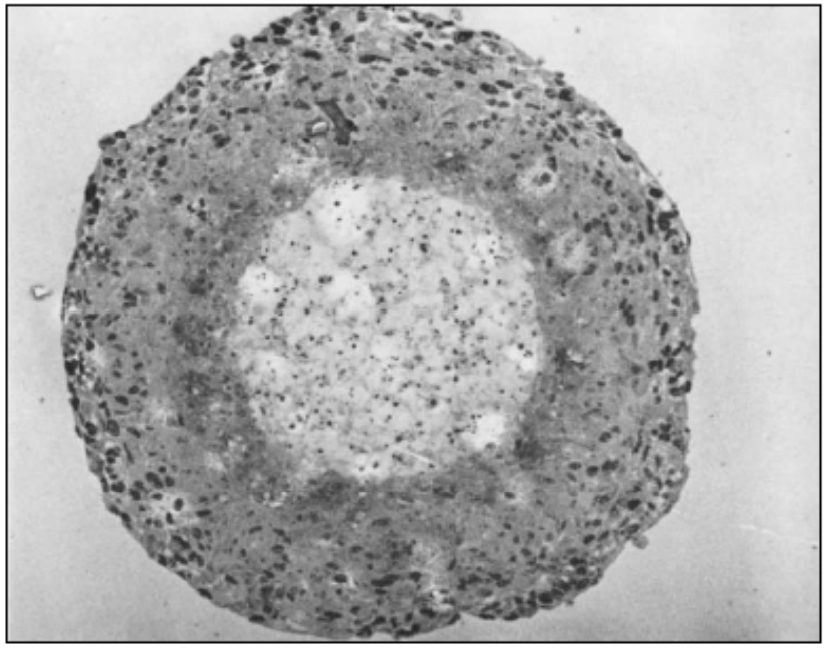


Cell kinetics

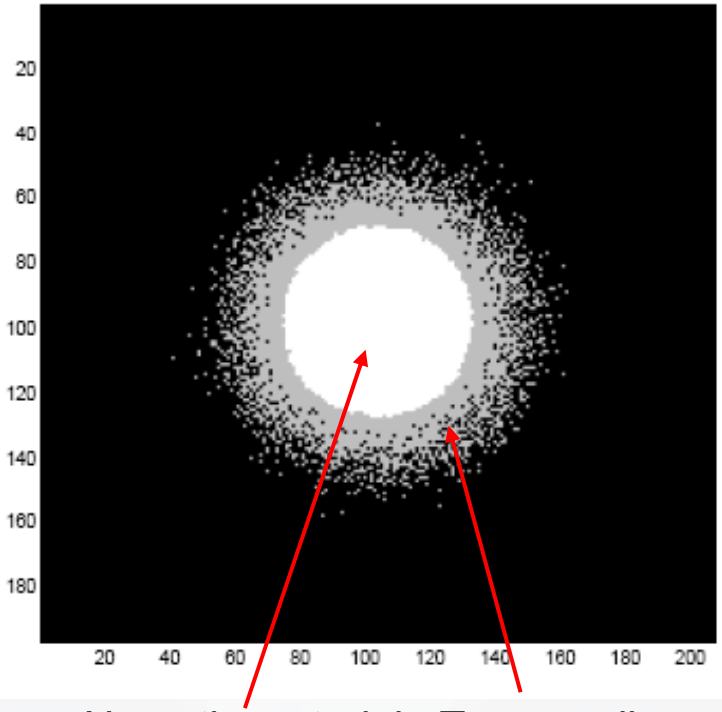
- Stochastic birth/death process of tumor cells
- Birth (mitosis): occurs with a rate r_M and depends on local node density threshold θ_M
- Death (necrosis): occurs with a rate r_N and depends on local node density threshold θ_N
- **Markov process** with transition probabilities:

$$\mathbb{P}(n \to n^{\mathrm{R}}) = \begin{cases} r_M \mathbb{P}(n \leq \theta_M),\ n^{\mathrm{R}} = n+1 \\ r_N \mathbb{P}(n \geq \theta_N),\ n^{\mathrm{R}} = n-1 \\ 1 - r_M \mathbb{P}(n \leq \theta_M) - r_N \mathbb{P}(n \geq \theta_N),\ n^{\mathrm{R}} = n \end{cases}$$

Simulation



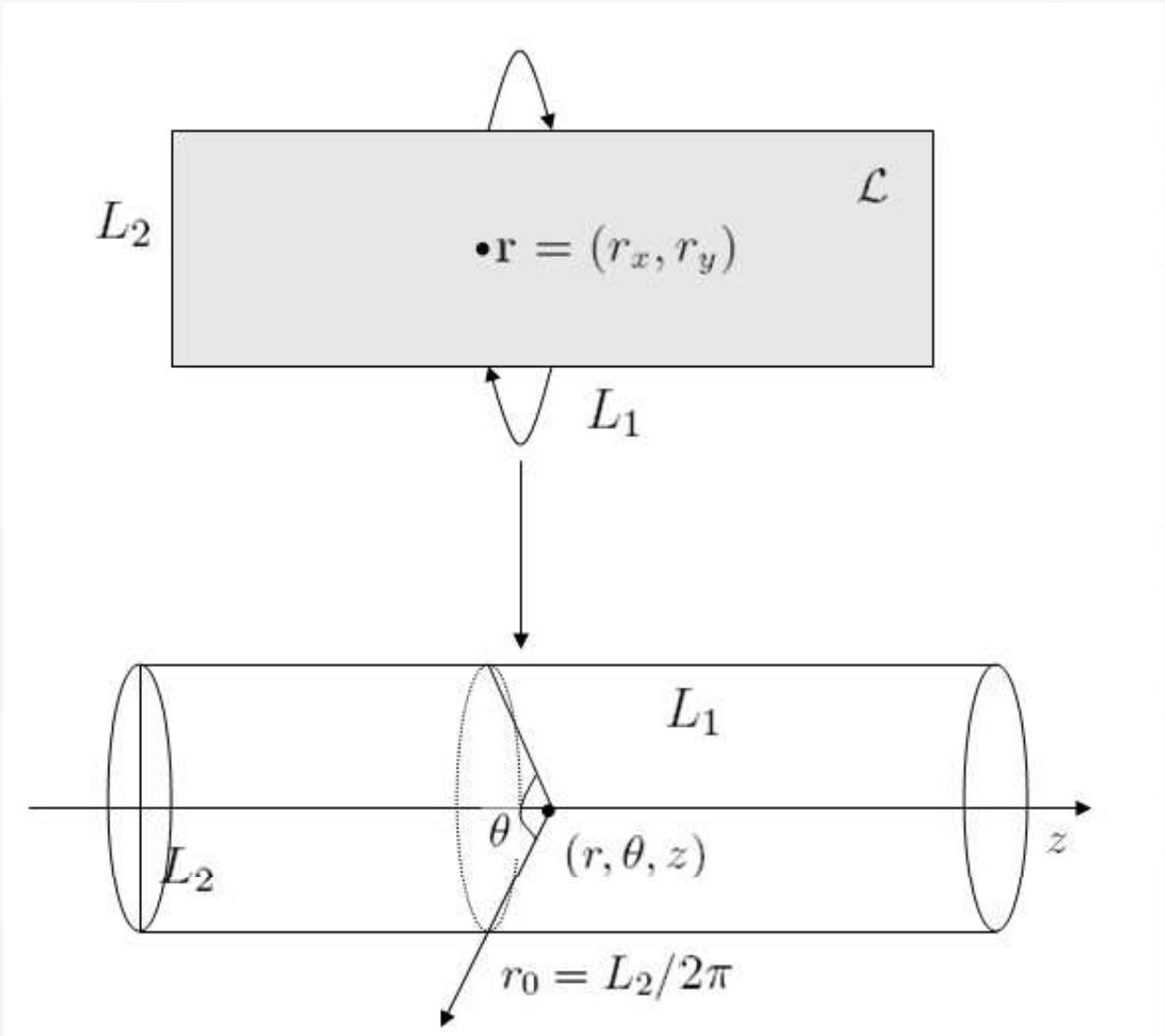
Experiment
Folkman, J. and
Hochberg, M., (1973)



Simulation
I.C.: A disc of cells in the center of the lattice

To study the front dynamics, we simplify the 2D simulation geometry as…

„Tube“ simulations

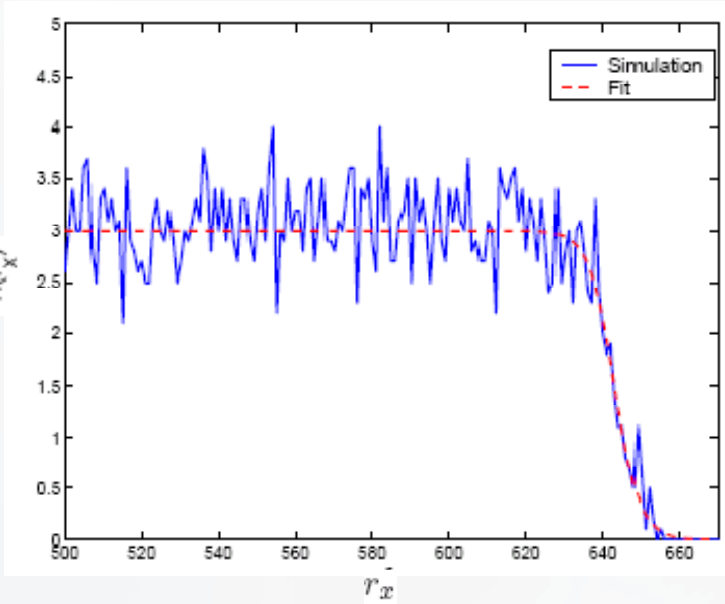


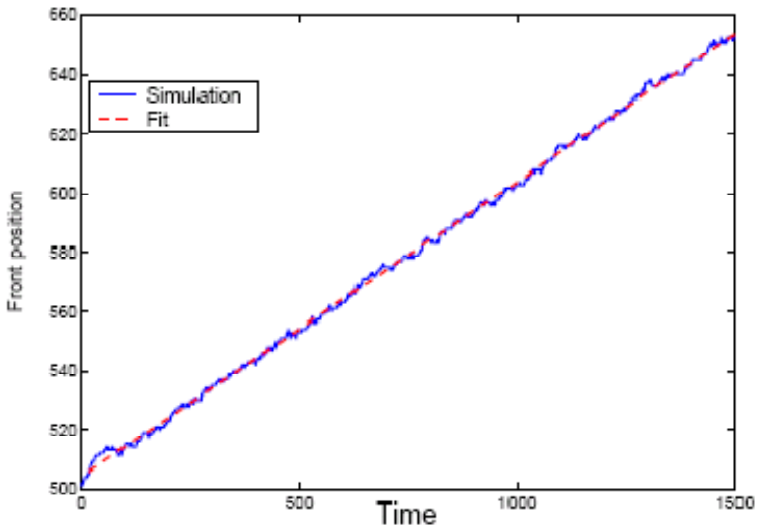
B.C.:
L_1-axis: No flux
L_2-axis: Periodic

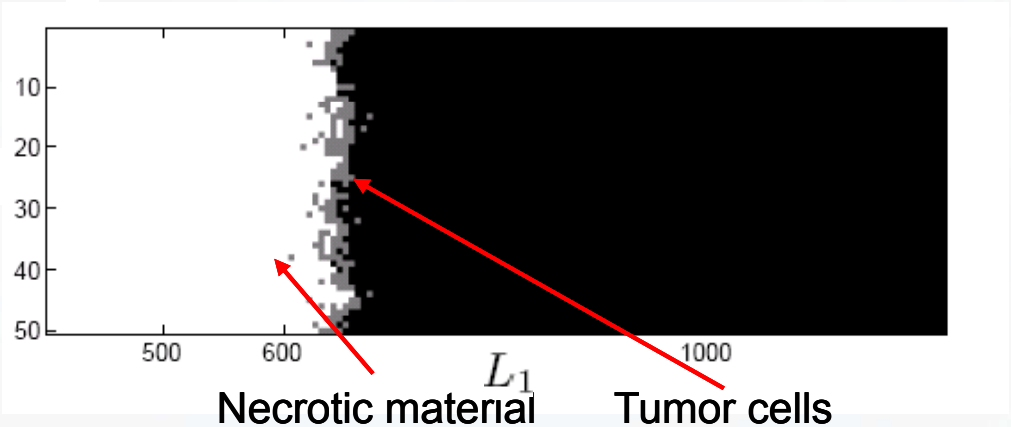
„Tube“: Simulating in cylindrical coordinates

Remark:
„Infinetely“ long tube

Traveling front



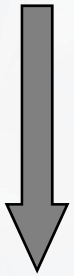




I.C.: A thin stripe of tumor cells at the beginning of L_1 axis

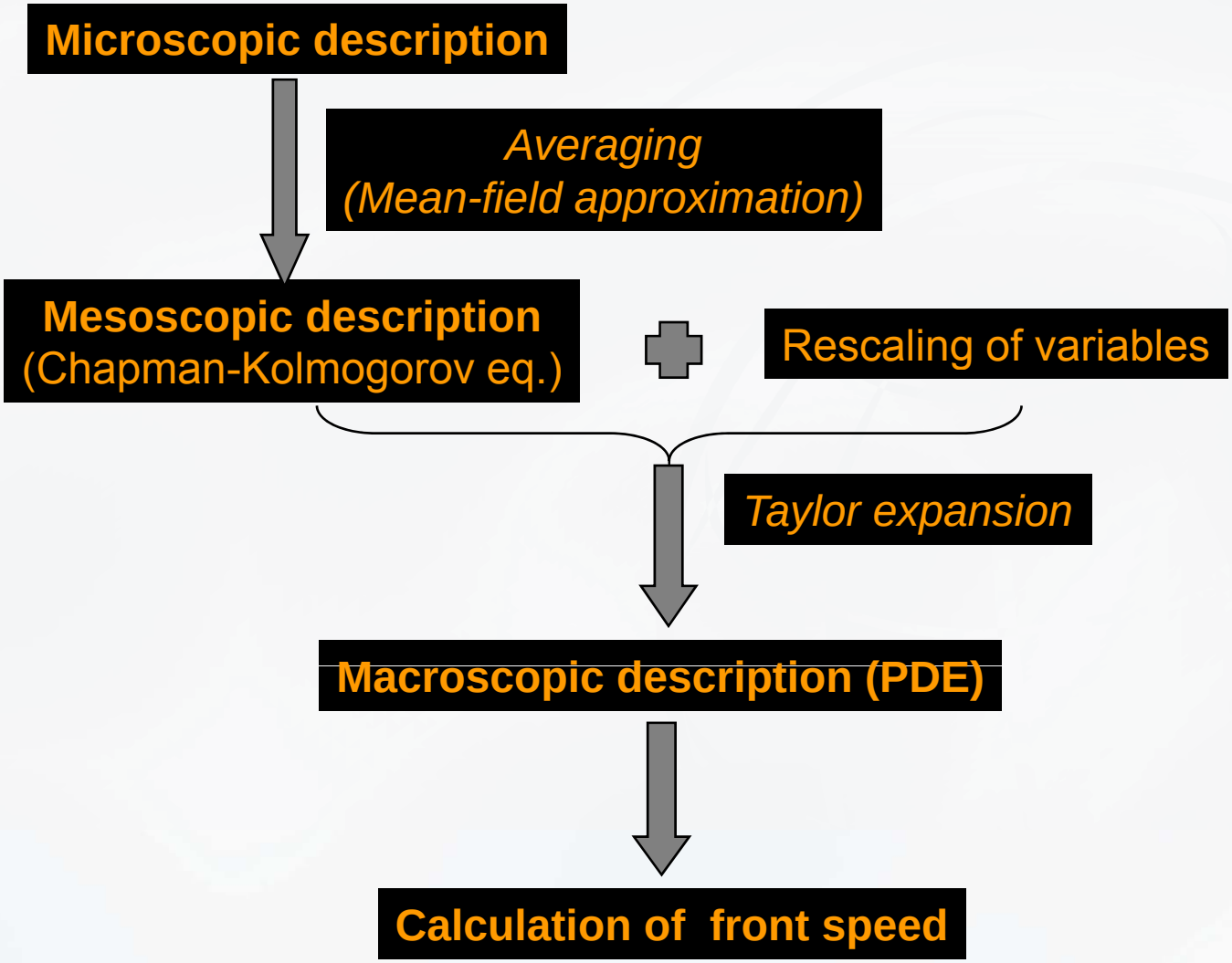
Observations

- The „tube“ geometry allows for a 1D reduction of the system
- The front is well-defined as the mean position of the foremost cell
- The front relaxes to a time-invariant shape, which moves uniformly
- The front can be viewed as the macroscopic manifestation of the collective cell dynamics



For the analysis of the front dynamics, we derive a macroscopic description of our system

Analysis strategy



Macroscopic description (PDE)

- Using Taylor expansion, in combination with the scaling argument, we derive a macroscopic description of our system (PDE):

$$\partial_t \rho = \frac{m^2}{\tilde{b}\tau}\nabla^2\rho + \frac{1}{\tau}F(\rho)$$

B.C.:
x-axis: No flux
y-axis: Periodic

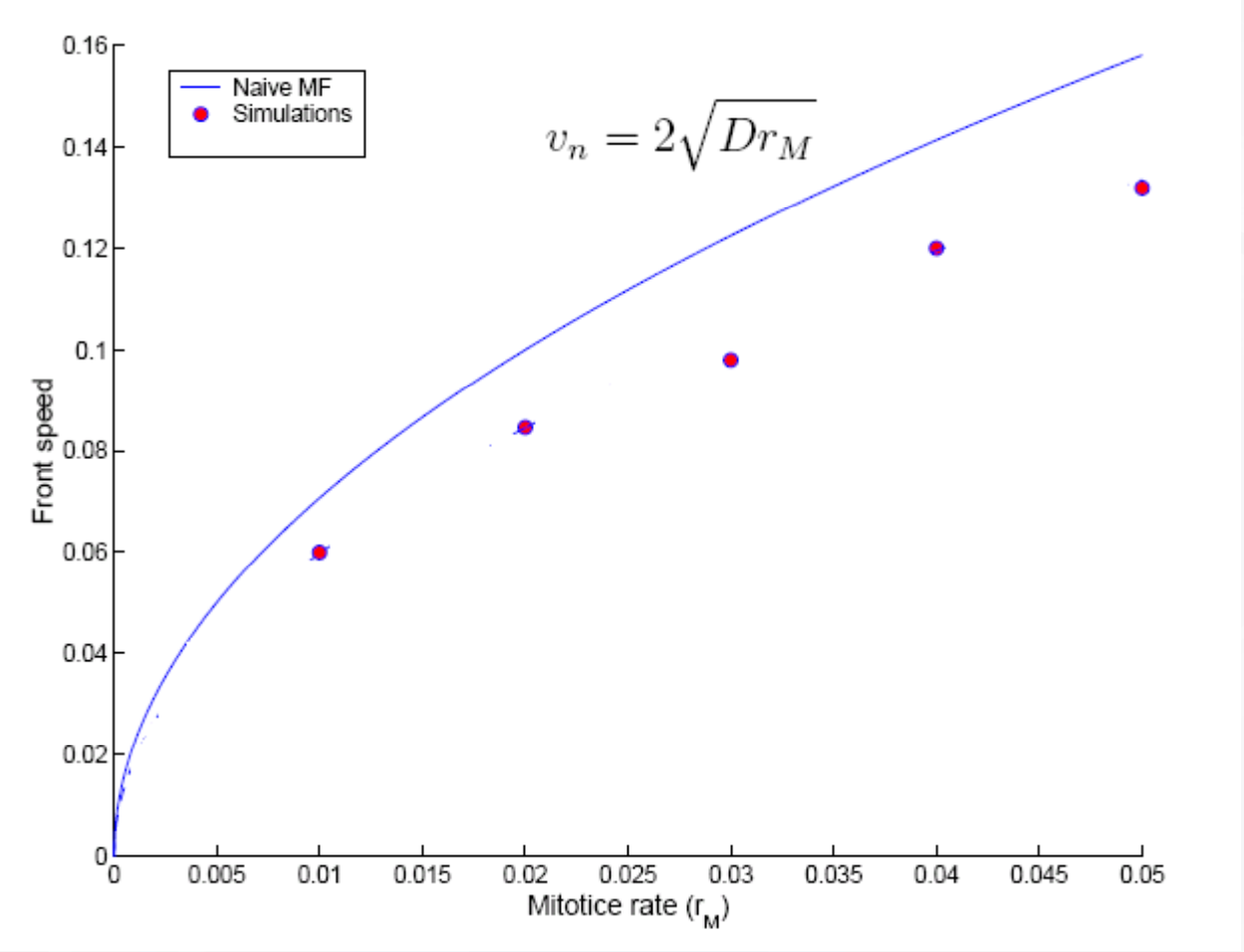
Diffusion coefficient: $D = \frac{m^2}{\tilde{b}\tau}$

- The above macroscopic description is valid for small mitotic rates

$$r_M \ll 1$$

- **Remark**: The reaction term F(ρ) is a $\tilde{b}$ -th order polynomial for the variable ρ, where the first order term is multiplied by the birth rate r_M

Front speed vs simulations



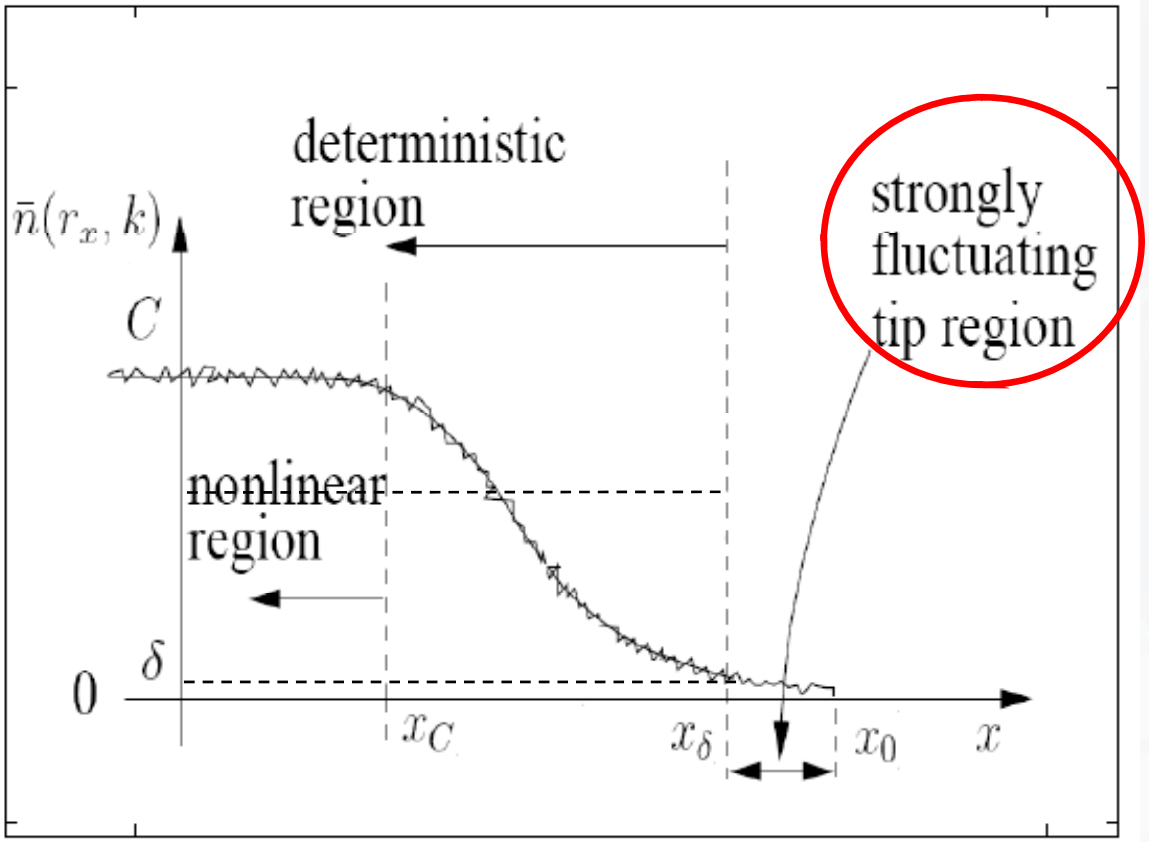
The analytical front speed **overestimates** the values observed in simulations!!

Refined macroscopic analysis: Cut-off description

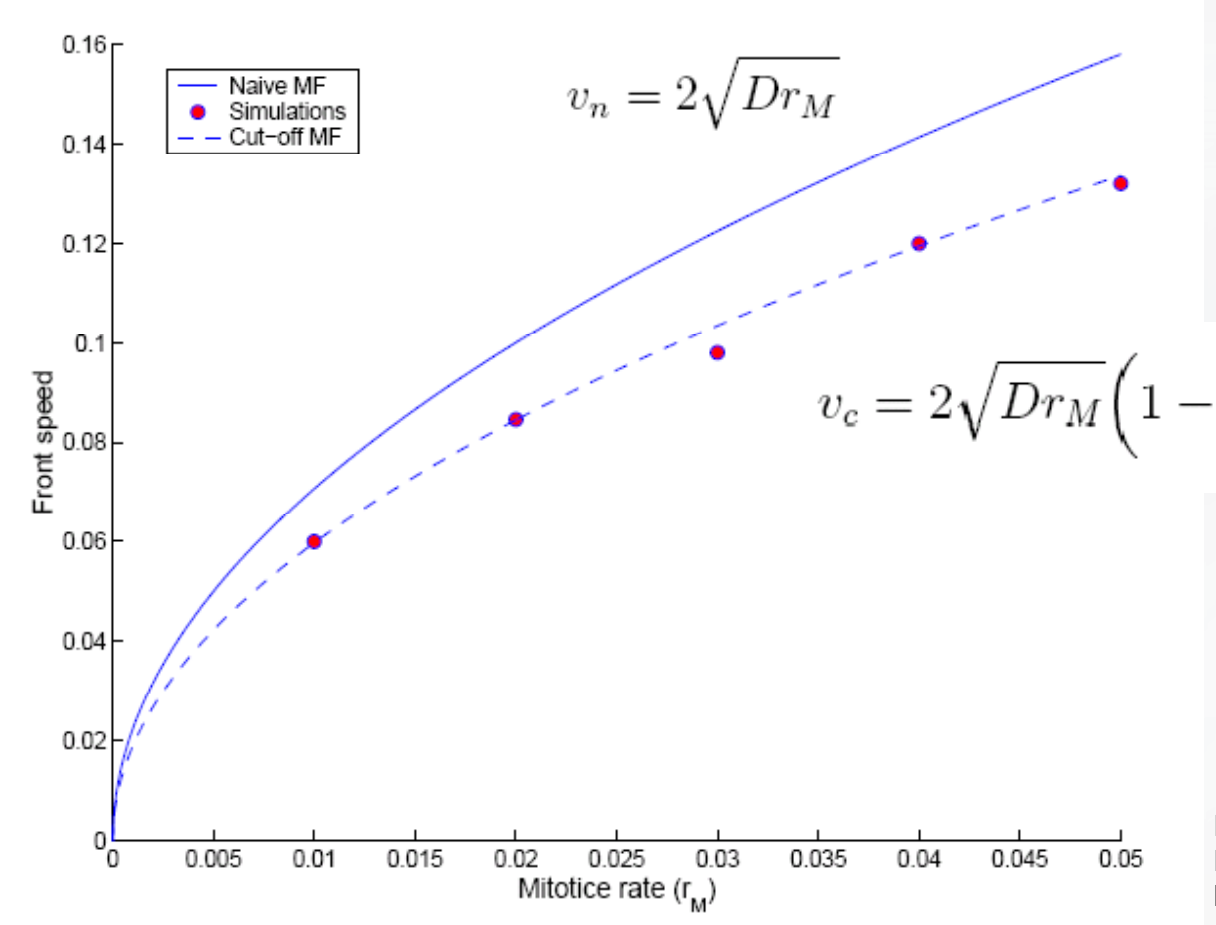
Refined macroscopic description of **our LGCA**:

$$\partial_t \rho = D \nabla^2 \rho + \frac{1}{\tau} F(\rho) \Theta(\rho - \delta)$$

cut-off



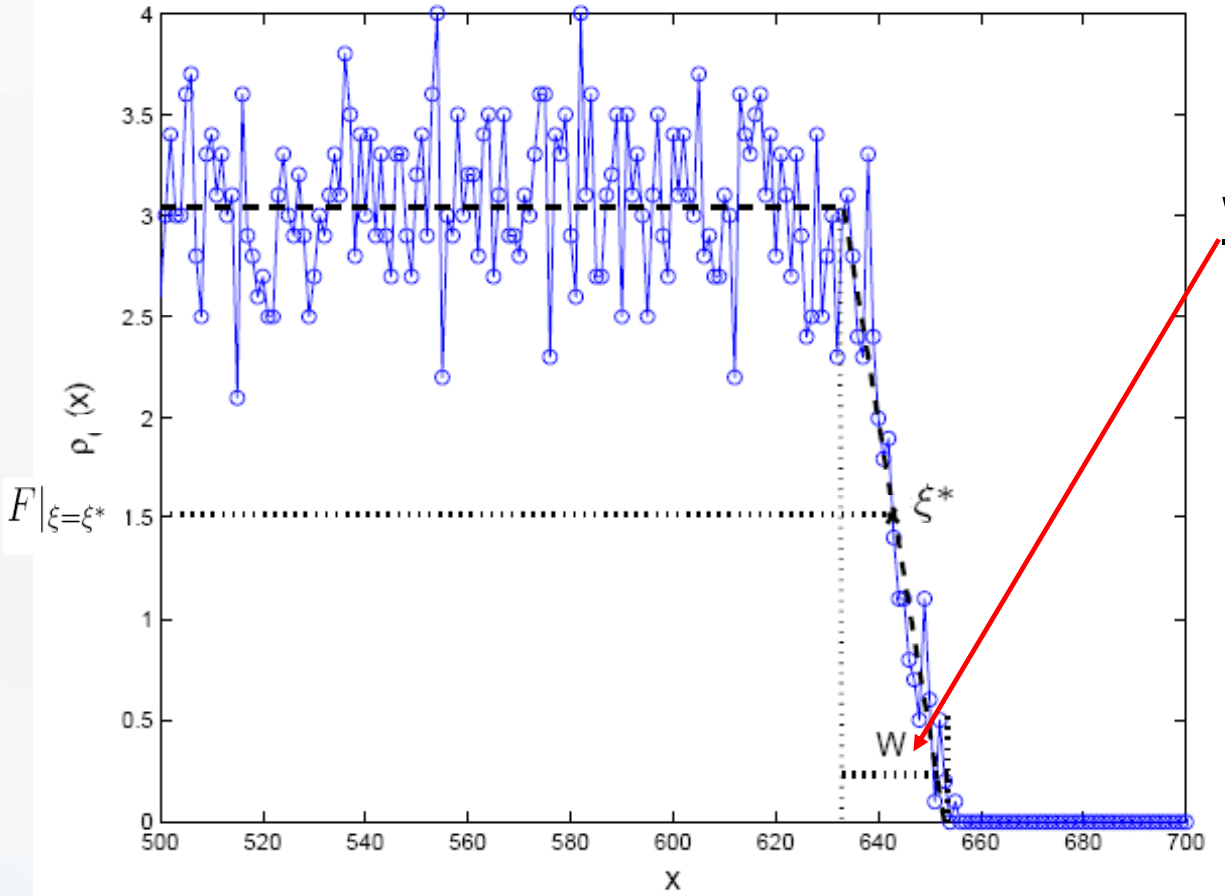
Front speed vs simulations (rev.)



Brunet and B. Derrida.
J.Stat. Phys., 2001

H. Hatzikirou et al.
Prediction of traveling front behavior in a lattice-gas cellular automaton
model for tumor invasion. Comput. Math. Appl., 2009

Invasive zone width



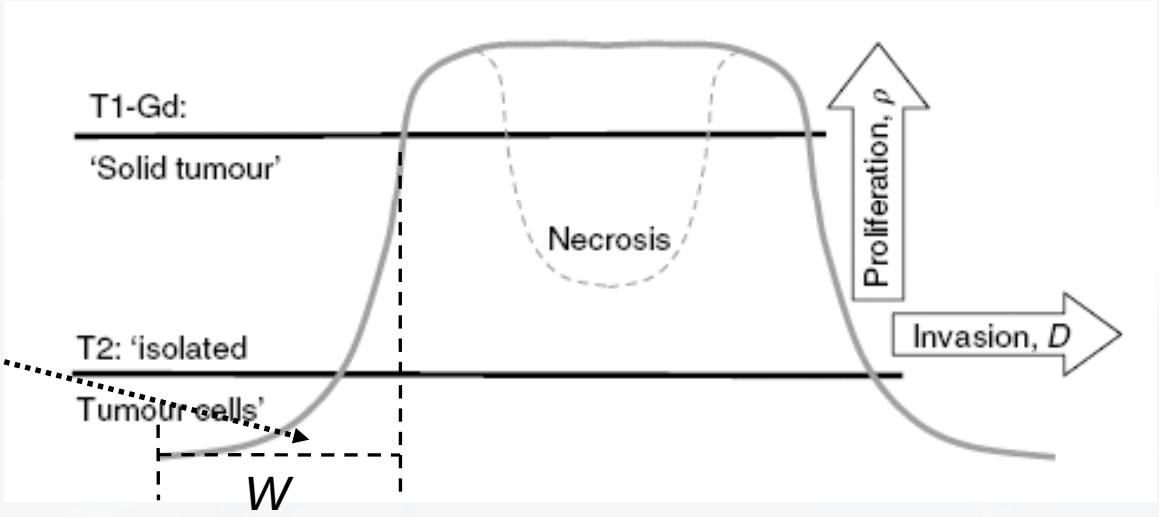
Width of invasive zone

$$W = \frac{v}{F|_{\xi=\xi^*}}$$

H. Hatzikirou et al.
Prediction of traveling front behavior in a lattice-gas cellular automaton model for tumor invasion. Comput. Math. Appl., 2009

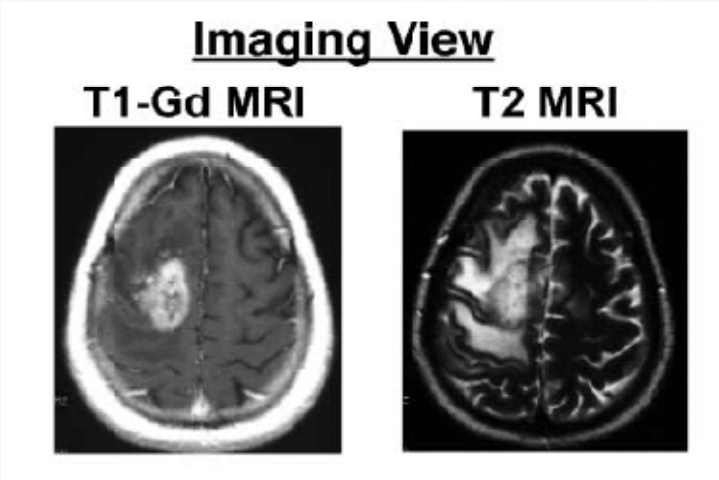
Answer to the “invisible cell” problem

Invasive zone



(Swanson et al. 2008)

- Discrete models can reveal the “hidden” front edge
- We can analytically estimate the “invisible” part of the tumor



Can computers/simulations help?

- **Organization principles** of cancer growth
- Simulation of **treatments**
- **Carcinogenesis**: evolutionary models (mutations, microenvironment)
  → *Game-theoretic perspectives on somatic cancer evolution, D. Basanta, AD, 2008*
- **Pattern recognition**: cancer surface, scaling analysis
- **Genetic analysis**: bioinformatics → cancer genes

Modeling pattern formation of interacting cell systems with CA

- ***Self-organization***:
  single cell behavior → cooperative behavior
- ***Simulations & analysis***:
  mean-field analysis, linear stability analysis...
- ***Interactions***:
  local (e.g. adhesion, contact inhibition) and nonlocal (e.g. chemotaxis)
- ***Resolution***: cell size and the fastest biological process to be modeled determine the spatio-temporal resolution
- Effect of **fluctuations**
- **Microscopic/macroscopic observables**
- ***Algorithm***: parallel (large cell no.)

Cellular Automaton Modeling of Biological Pattern Formation

Characterization, Applications, and Analysis

Andreas Deutsch and Sabine Dormann

This book focuses on a challenging application field of cellular automata-pattern formation in biological systems, such as the growth of microorganisms, dynamics of cellular tissue and tumors, and formation of pigment cell patterns. These phenomena, resulting from complex cellular interactions, cannot be deduced solely from experimental analysis, but can be more easily examined using mathematical models, in particular, cellular automaton models.

While there are various books treating cellular automaton modeling, this interdisciplinary work is the first one covering biological applications. The book is divided into three parts: Part I deals with general principles, theories, and models of pattern formation; Part II examines cellular automaton modeling; and Part III explains various applications. The models and analytic techniques described may be extended to other exciting applications in biology, medicine, and immunology.

Key topics and features:

- Provides an introduction and historical account of the principles of biological pattern formation (morphogenesis)
- Gives an overview of mathematical modeling approaches to morphogenesis, and an introduction to cellular automata and analytic techniques
- A supplementary web-based Java applet—*Cellular Automaton Simulator*—enables interactive simulation of various cellular automaton applications described in the book; available on the internet at: www.biomodeling.info
- Self-contained presentation is accessible to a broad audience; only basic calculus and linear algebra are required
- Careful balance of theory, models, and applications useful to both experimentalists and theoreticians
- Includes suggestions for further research topics

The book is aimed at researchers, practitioners, and students in applied mathematics, mathematical biology, computational physics, bioengineering, and computer science interested in a cellular automaton approach to biological modeling. The book's accessible presentation and interdisciplinary approach make it suitable for graduate and advanced undergraduate courses and seminars in mathematical biology, biomodeling, and biocomputing.

ISBN 0-8176-4281-1

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Dormann

Cellular Automaton Modeling of Biological Pattern Formation

Modeling and Simulation in Science, Engineering and Technology

Cellular Automaton Modeling of Biological Pattern Formation

Characterization, Applications, and Analysis

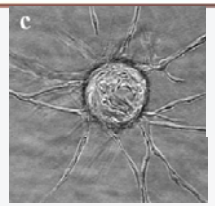
Andreas Deutsch
Sabine Dormann

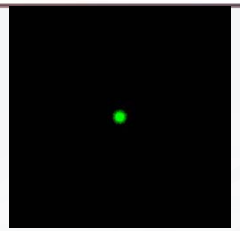
BIRKHÄUSER

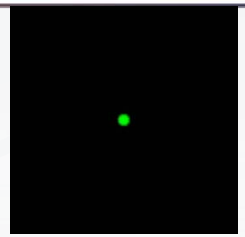
In: Modelling and Simulation in Science, Engineering and Technology, Series editor: N. Bellomo 2005

Outlook

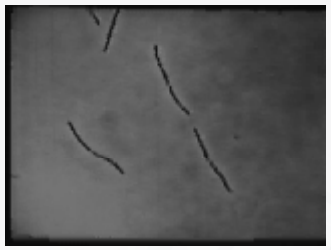
- ***Angiogenesis***

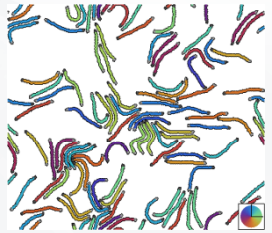






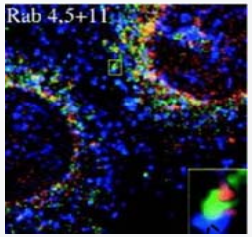
- ***Pattern formation:*** *Microorganisms*

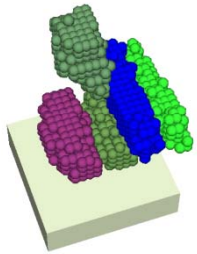




- **Biological development:**
  regeneration of corals,
  myotome formation

- ***Intracellular pattern formation:***
  endocytosis
  (Mol. Syst. Biol. 2008)





- **Mathematical analysis:**
  comparison of cell-based
  models

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