Multiscale modeling of carcinogenesis: Deconvoluting the cancer complexity

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Outline

1- The motivation.

2- Cancer biology in two cartoons.

2.1- Cancer progression.

2.2- The multiple scales of cancer.

3- Multiscale modeling of cancer growth

3.1- Modeling multiple scales.

3.2- A multiscale model for cancer.

3.3- Predicting carcinogenesis.

4- Concluding remarks.

1- The motivation.

The Systems Biology's challenge: how biological functions at different levels of organization are generated from the interactions between molecules?

$$\begin{aligned}\mathcal{L}_{\mathrm{QCD}} &= \bar{\psi}_i \left(i\gamma^\mu (D_\mu)_{ij} - m\,\delta_{ij}\right)\psi_j - \frac{1}{4}G^a_{\mu\nu}G^{\mu\nu}_a \\ &= \bar{\psi}_i(i\gamma^\mu\partial_\mu - m)\psi_i - gG^a_\mu\bar{\psi}_i\gamma^\mu T^a_{ij}\psi_j - \frac{1}{4}G^a_{\mu\nu}G^{\mu\nu}_a,\end{aligned}$$

$\xrightarrow{?}$

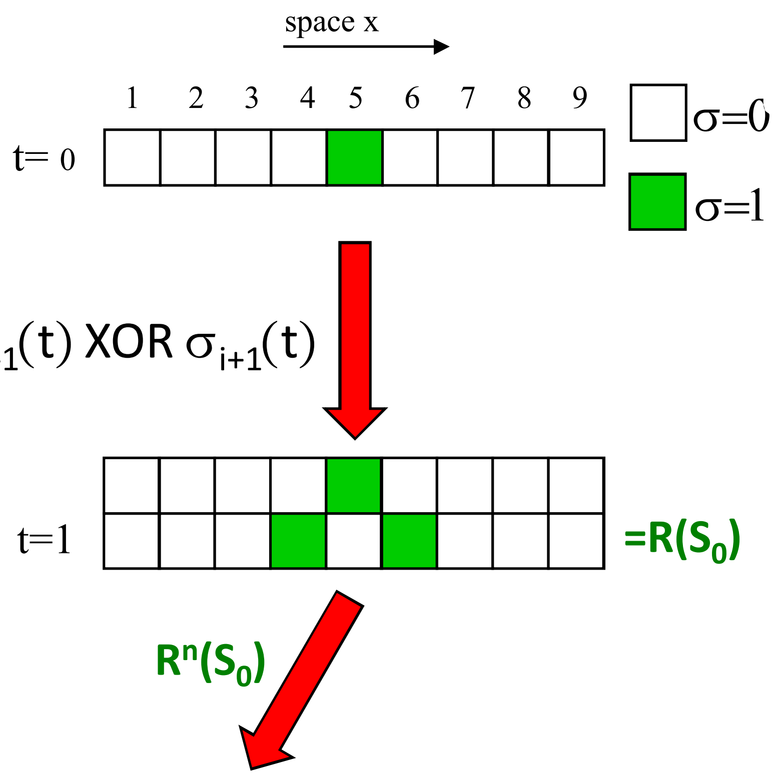
The ability to reduce everything to simple fundamental laws does not imply the ability to start from those laws and reconstruct the universe. (...) The constructionist hypothesis breaks down when confronted with the twin difficulties of scale and complexity.

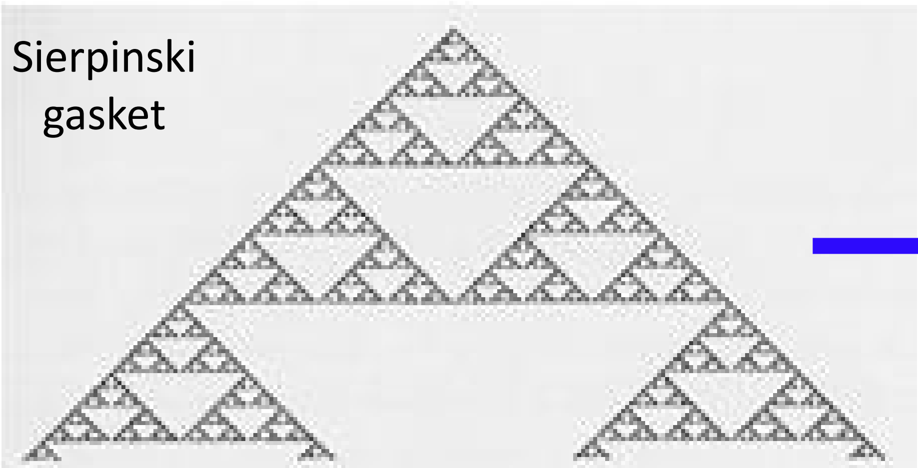
P. W. Anderson, 1972.

How complex patterns can emerge from simple dynamical rules?

Inicial state S_0:

Rule R: $\sigma_i(t+1)=\sigma_{i-1}(t)\ \mathrm{XOR}\ \sigma_{i+1}(t)$





Many particles interacting through simple rules

+

Simple initial state

↓ **successive iterations**

Complex pattern

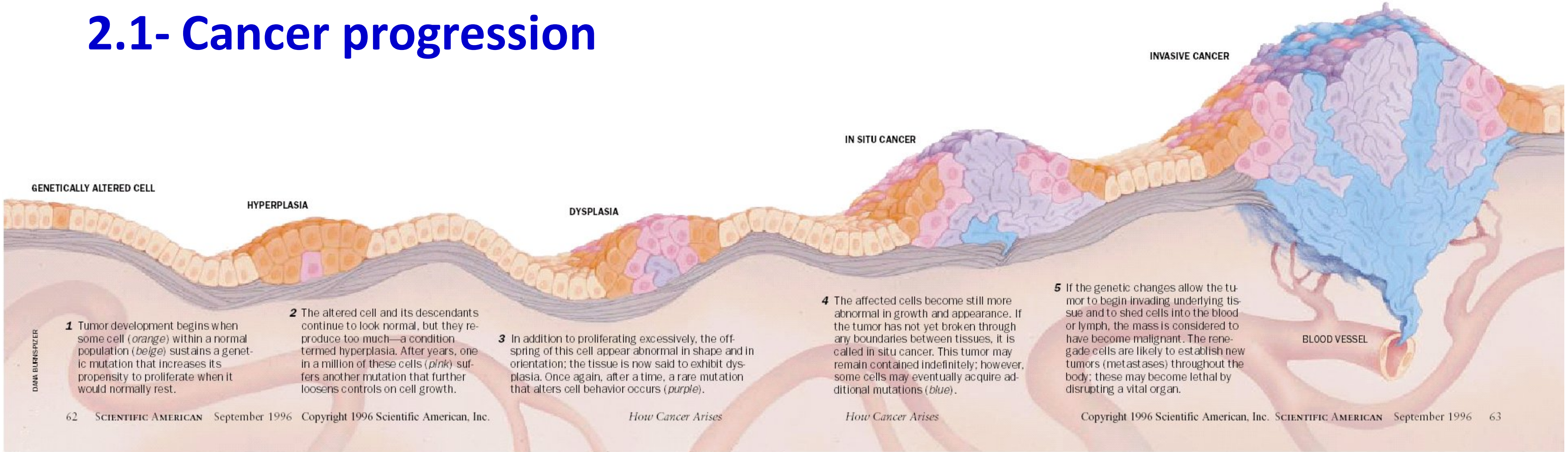
➢ **Lessons from this tale:**

1- The origin of complex patterns in nature is a dynamical problem;

2- In the nonlinear regime even very simple physical systems are able to exhibit complex behaviors;

2- Cancer biology in two cartoons.

2.1- Cancer progression



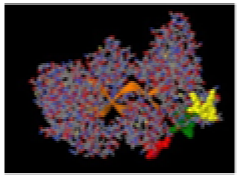
R. Weinberg, Sci. Am. 1996

Constrained growth conditions. → Selection of cells with proliferative advantages. →

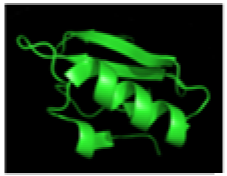
Accumulation of mutations in selected cells. → Additional replication and selection. → Transformed foci with malignant phenotypes, derived from a single cell.

2.2- The multiple scales of cancer

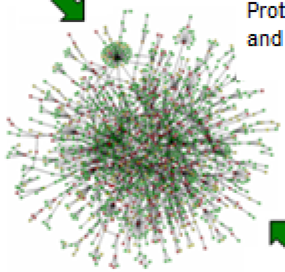
COCIS **15**,18 (2010)



DNA transcription



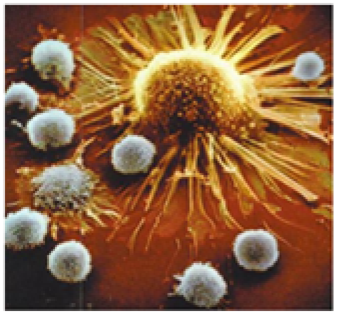
Proteins



Protein-protein interaction
and metabolic networks

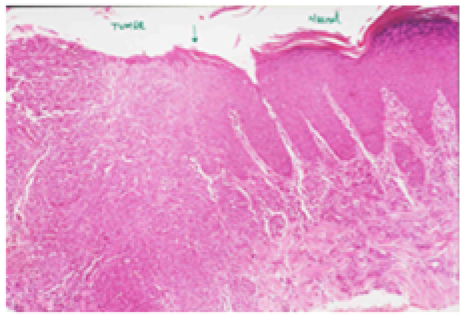
Microscopic scale:

molecular and subcellular processes (mutations, alterations in gene expression, signaling, metabolic pathways, cell cycle etc.)



Mesoscopic scale:

cell-cell and cell-matrix interactions (angiogenesis, immune response, local remodeling of the ECM etc.)



Macroscopic scale:

Processes at the tissue level (difusion of nutrients/GFs, basal membrane breach, cell migration and invasion etc.)

3- Multiscale modeling of cancer growth.

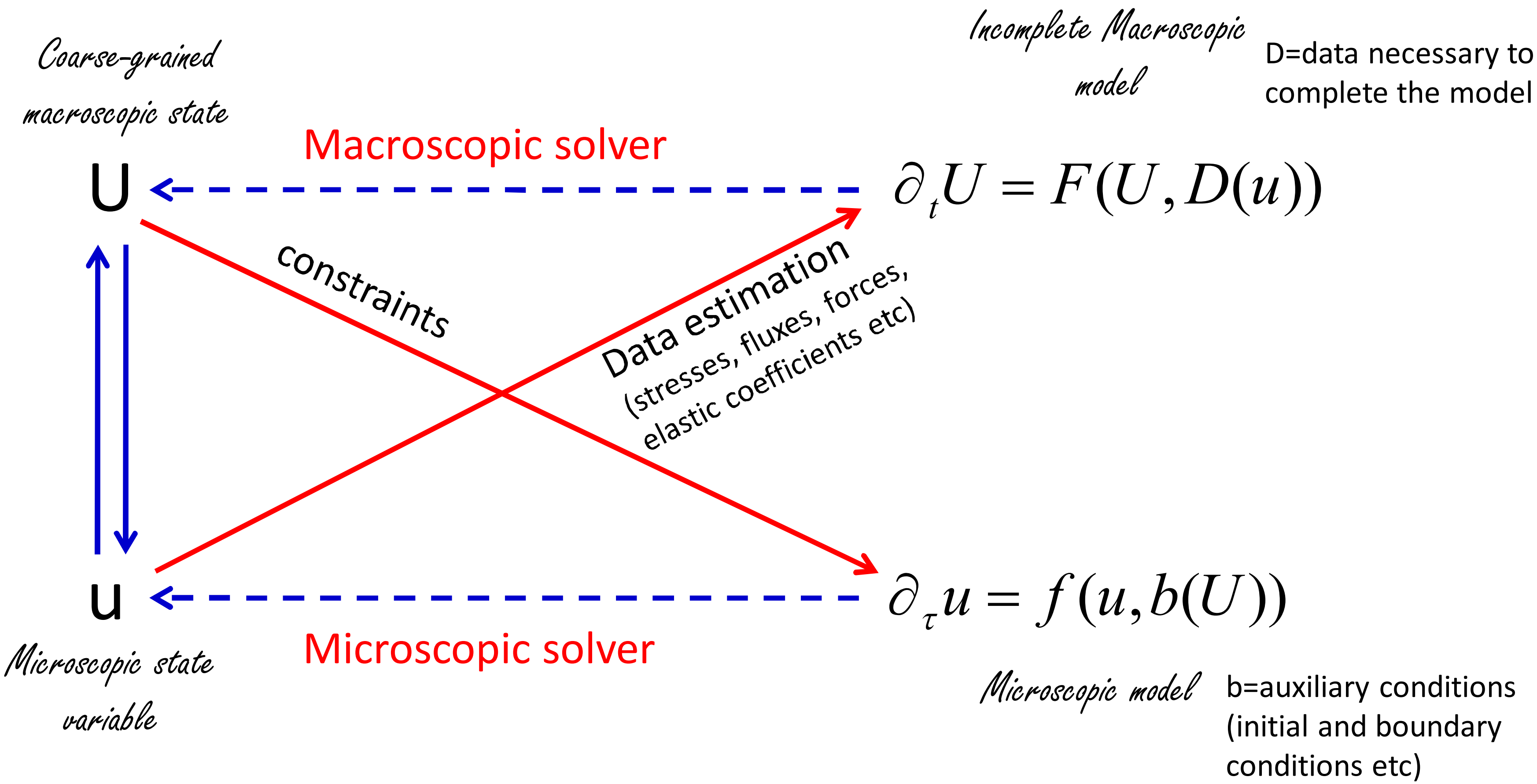
3.1- Modeling multiple scales

Almost all problems in science and engineering are multiscale in nature and we primarily face their macroscopic scales.

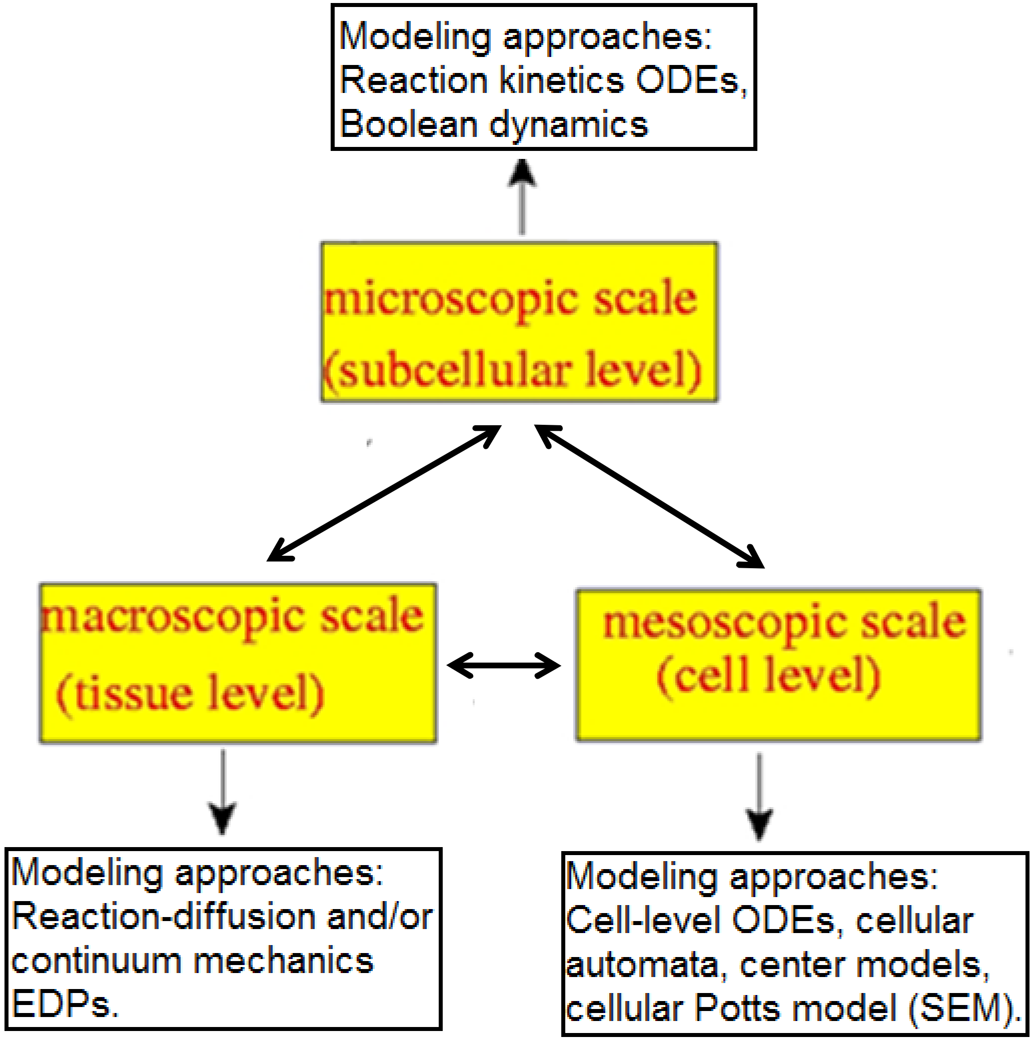
Multiscale mathematics is a systematic approach for integrate models that may be of different nature and applied to different scales, e. g. molecular dynamics at the microscale and continuum mechanics at the macroscale.

Key step: Connecting the outputs of one scale to the inputs of the other scales.

General philosophy: coupling the macro and microscales such that the macrostate provides the environment (constraints) for the micromodel and the micromodel provides the needed constitutive data for the macromodel.



✓The multiscale toolbox:



There is no rule for select an approach!

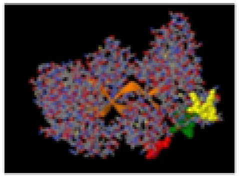
↓

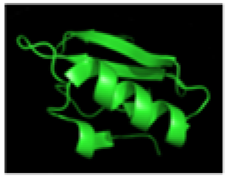
Guiding principles:

- ✓ The question to be addressed;
- ✓ The information that is available for the system;
- ✓ The balance between complexity and the details considered.

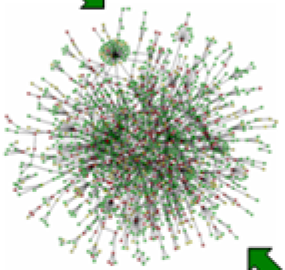
3.2- A multiscale model for cancer.

Microscopic scale:





molecular and subcellular processes



Active (σ=1) or inactive (σ=0) protein .

$$\sigma_i(t+1) = \mathrm{sgn}\left(\sum J_{ij}\sigma_j - \theta_i\right),$$

$$\mathrm{sgn}(x) = \begin{cases} 0, & x \le 0 \\ 1, & x > 0 \end{cases}$$

→ Deterministic Boolean model

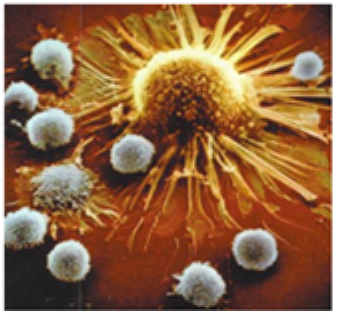
agents performing stochastic actions (replication, death and migration).

$$P_{ação} = f(N, C, \phi, \{\sigma\})$$

→ Stochastic lattice growth model

Mesoscopic scale:

cell-cell and cell-matrix interactions

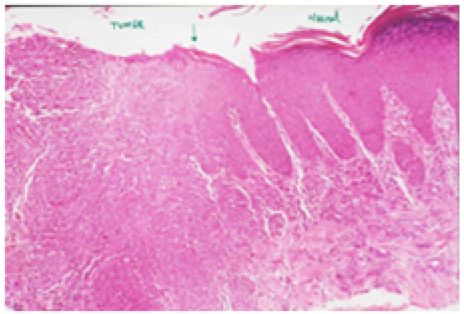


$$\partial_t \phi = \nabla^2 \phi - \alpha^2 N \phi - \lambda \alpha^2 C \phi.$$

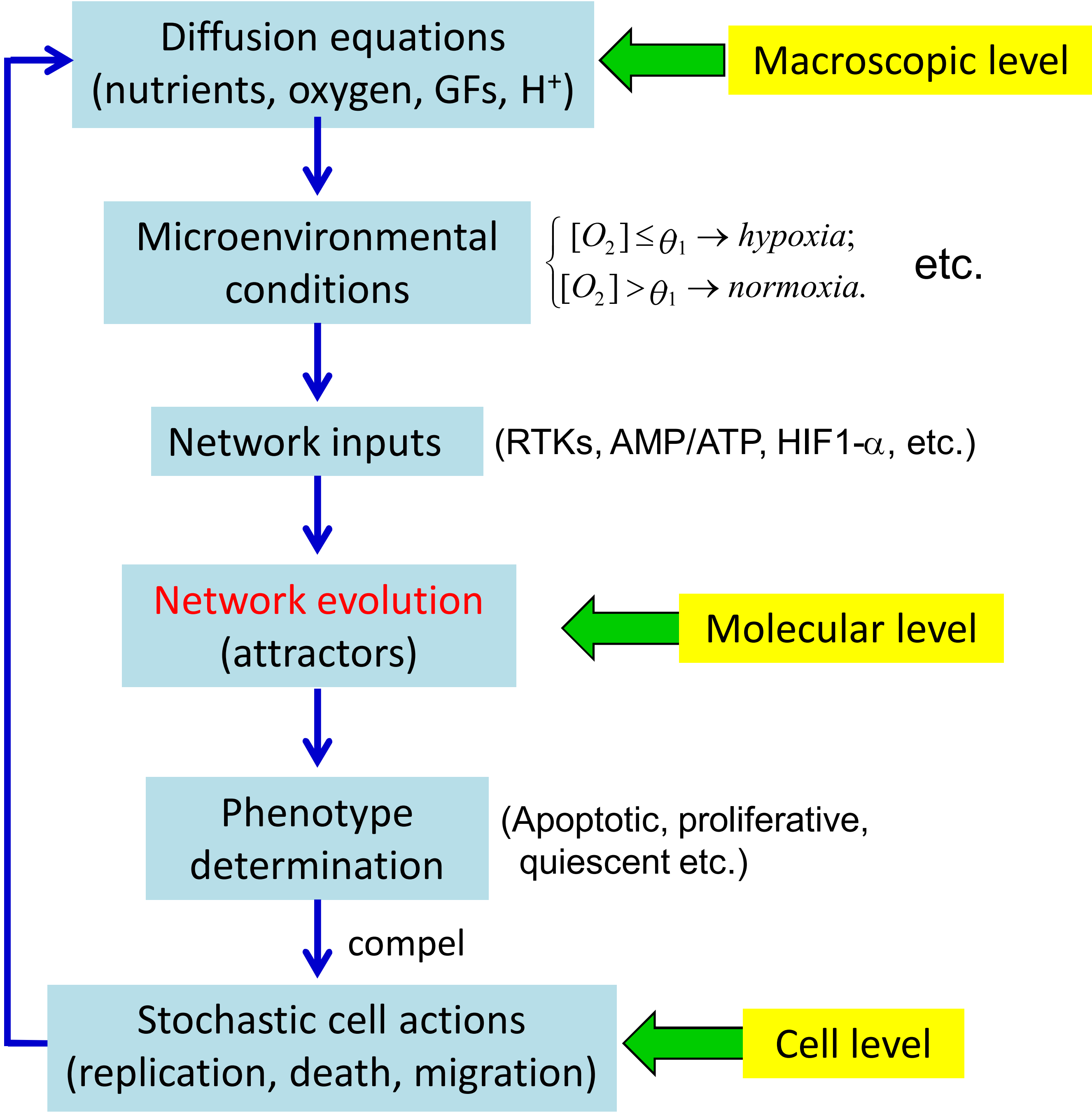
EDPs with stochastic sources/boundaries

Macroscopic scale:

Processes at the tissue level



➢**Flowchart:**


Diffusion equations
(nutrients, oxygen, GFs, H^+)
Macroscopic level
Microenvironmental conditions
$\begin{cases} [O_2] \le \theta_1 \rightarrow hypoxia; \\ [O_2] > \theta_1 \rightarrow normoxia. \end{cases}$
etc.
Network inputs
(RTKs, AMP/ATP, HIF1-α, etc.)
Network evolution
(attractors)
Molecular level
Phenotype determination
(Apoptotic, proliferative, quiescent etc.)
compel
Stochastic cell actions
(replication, death, migration)
Cell level

3.2.1 - Macroscopic scale (Tissue level)

- Tissue: a square lattice fed by a capillary at its bottom edge.
- Nutrientes, oxygen and acid diffuse throughout the tissue.

Glucose:

$$\boxed{\frac{\partial G}{\partial t} = D_G \nabla^2 G - k_G G(\sigma_n + \sigma_t) - \lambda_G k_G G \sigma_g}$$

Oxygen:

$$\boxed{\frac{\partial O}{\partial t} = D_o \nabla^2 O - k_o O(\sigma_n + \sigma_t)}$$

H^+:

$$\boxed{\frac{\partial H^+}{\partial t} = D_H \nabla^2 H^+ + \alpha_H \lambda_G k_G G \sigma_g .}$$

Boundary conditions: fixed supply at the vessel; null flux at the border of the tissue; periodic along the capillary direction.

3.2.2 - Mesoscopic scale (cellular level)

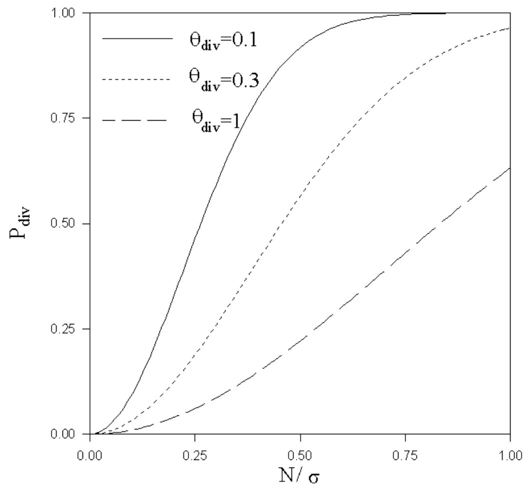
- **Cells** are agents which perform stochastic cell actions: mitotic division, migration and death.

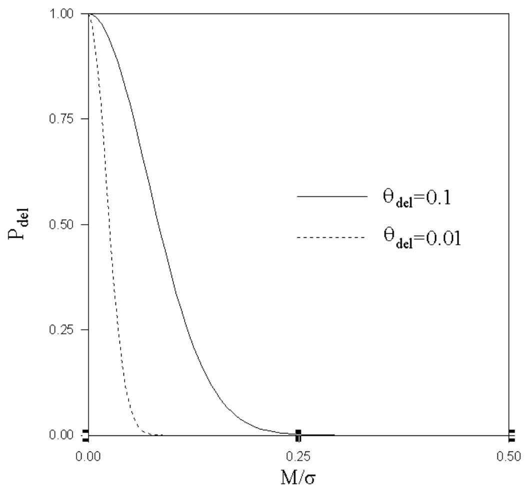
Stochastic cell kinetics connecting the macro and mesoscopic scales

$$P_{div} = 1 - e^{-\left(\frac{\phi_1}{\theta_{div}\sigma_c}\right)^2}$$

$$P_{mov} = 1 - e^{-\sigma_c\left(\frac{\phi_2}{\theta_{mov}}\right)^2}$$

$$P_{del} = e^{-\left(\frac{\phi_2}{\theta_{del}\,\sigma_c}\right)^2}$$





Decision-making is stochastic on the individual cell level.

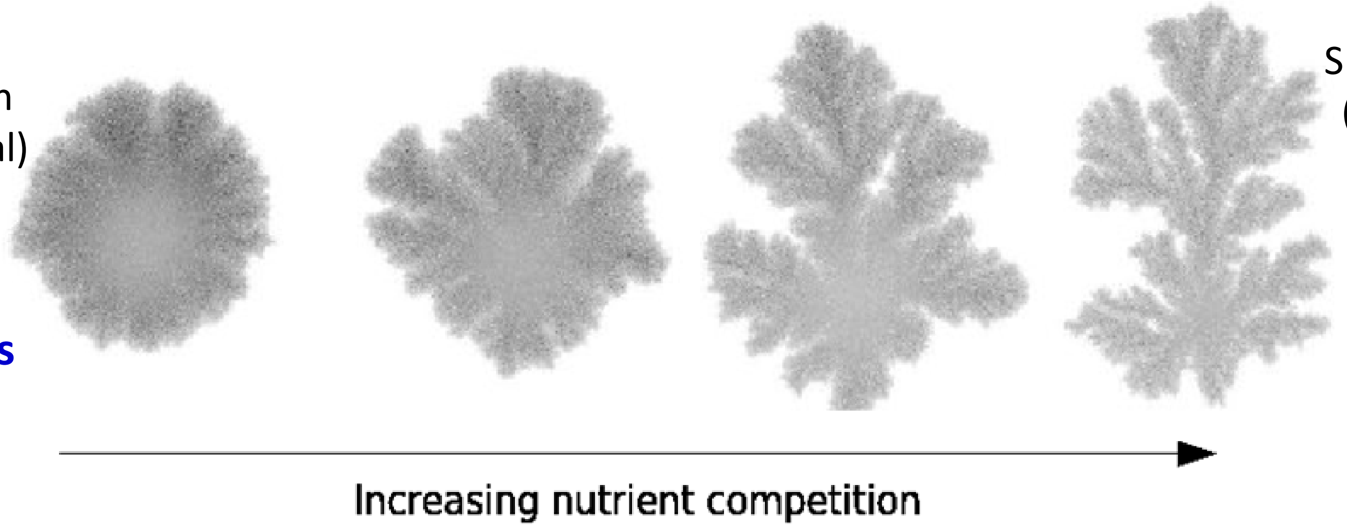
Inicial condition: a single cancer cell in the center of the normal tissue.

➢ Growth patterns

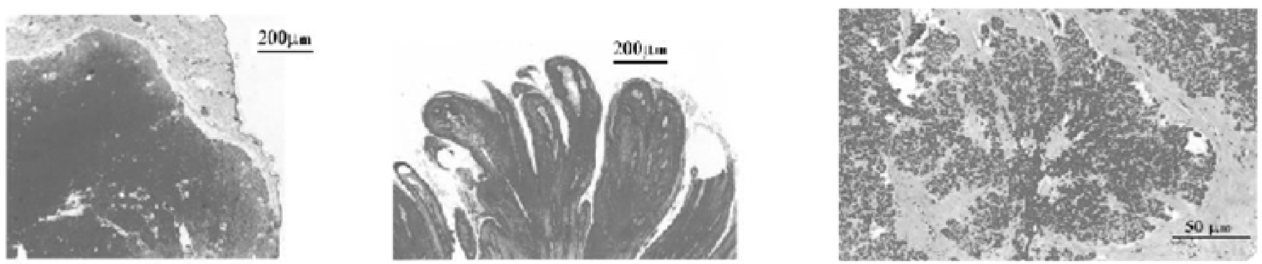
Fast growth (exponencial)

Slow growth (algebraic)

Simulations



Histhological patterns

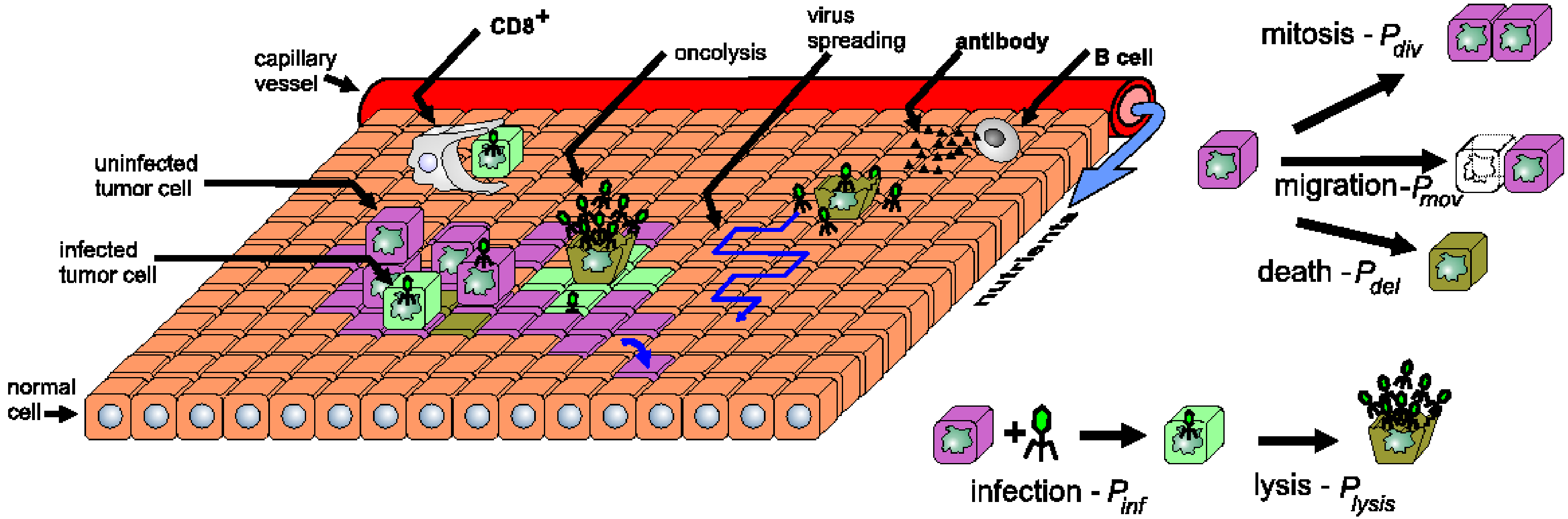


PRE **65**, 021907 (2002);

3.2.3 – Applications in cancer therapy: major results

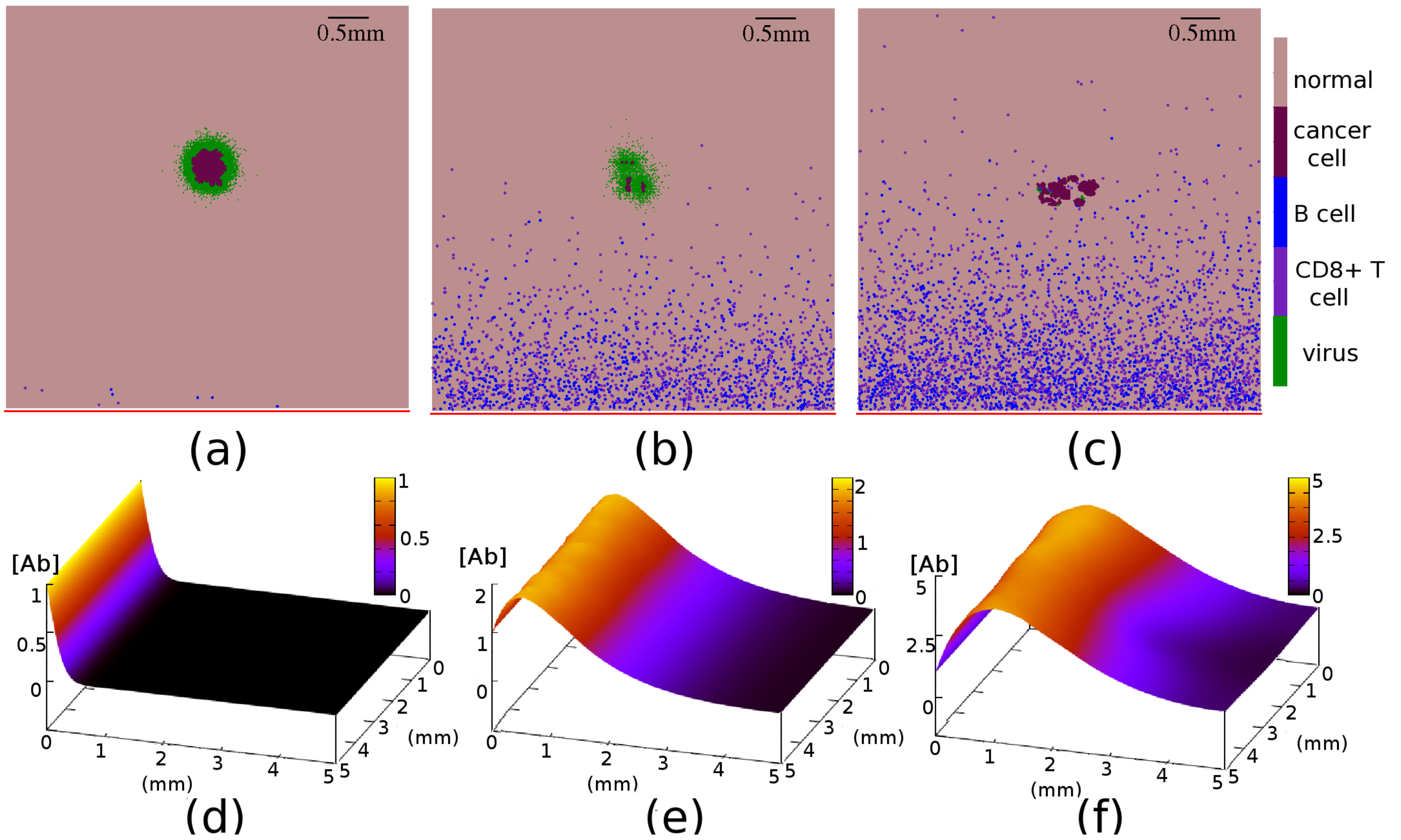
Cancer Res. 2009 & PRE 2013

➢ In silico oncolytic virotherapy

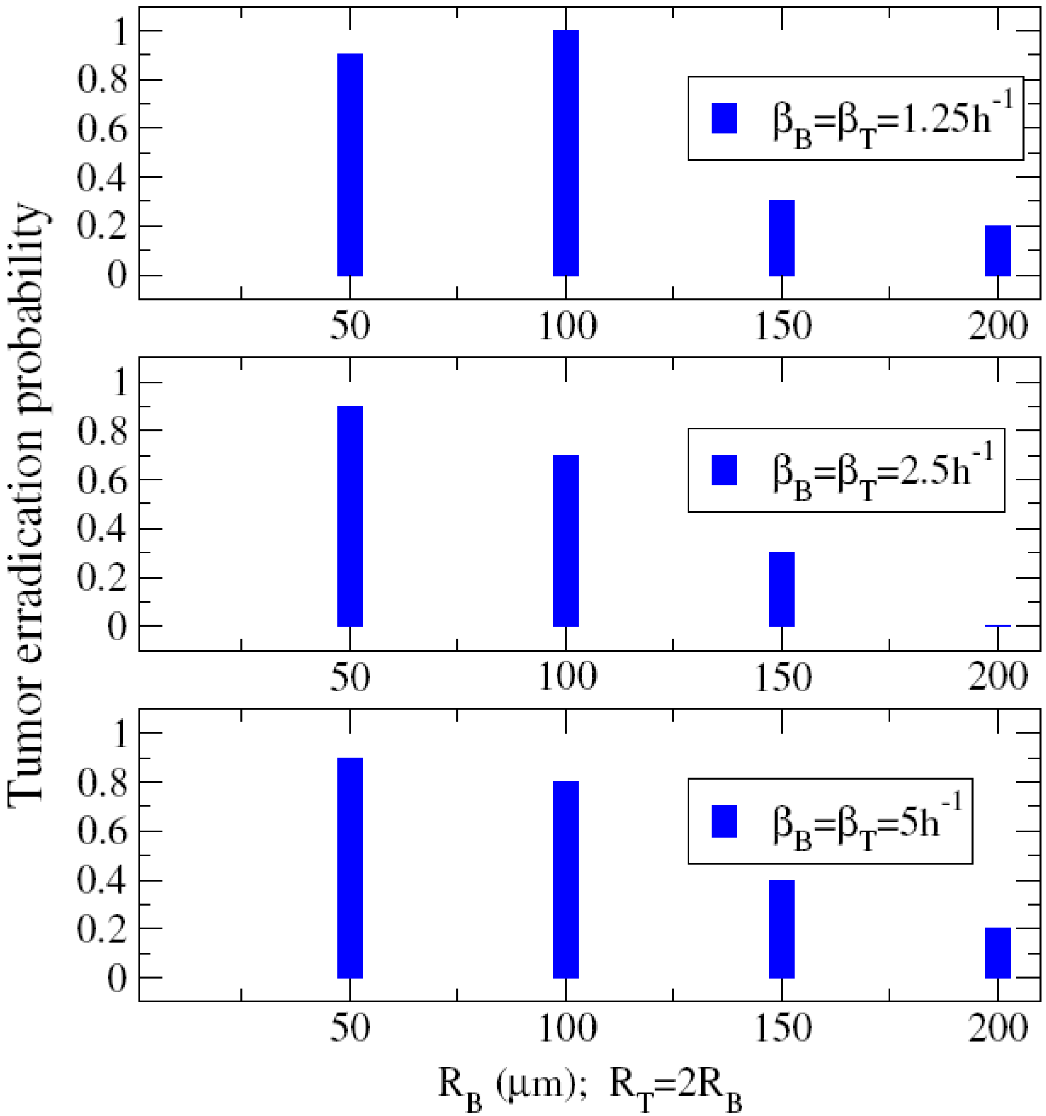


- The optimal traits for oncolytic viruses depends critically on the tumor growth dynamics.
- They do not necessarily include rapid replication, cytolysis and spreading currently assumed as necessary conditions to a successful therapy.
- The antitumor efficacy of a virus is primarily determined by its entry efficiency, its replicative capacity within the tumor, and its ability to spread over the tissue.

Phys. Biol. 2013



The host immune response remove both free virus and their source (infected cancer cells), triggering therapy fail.

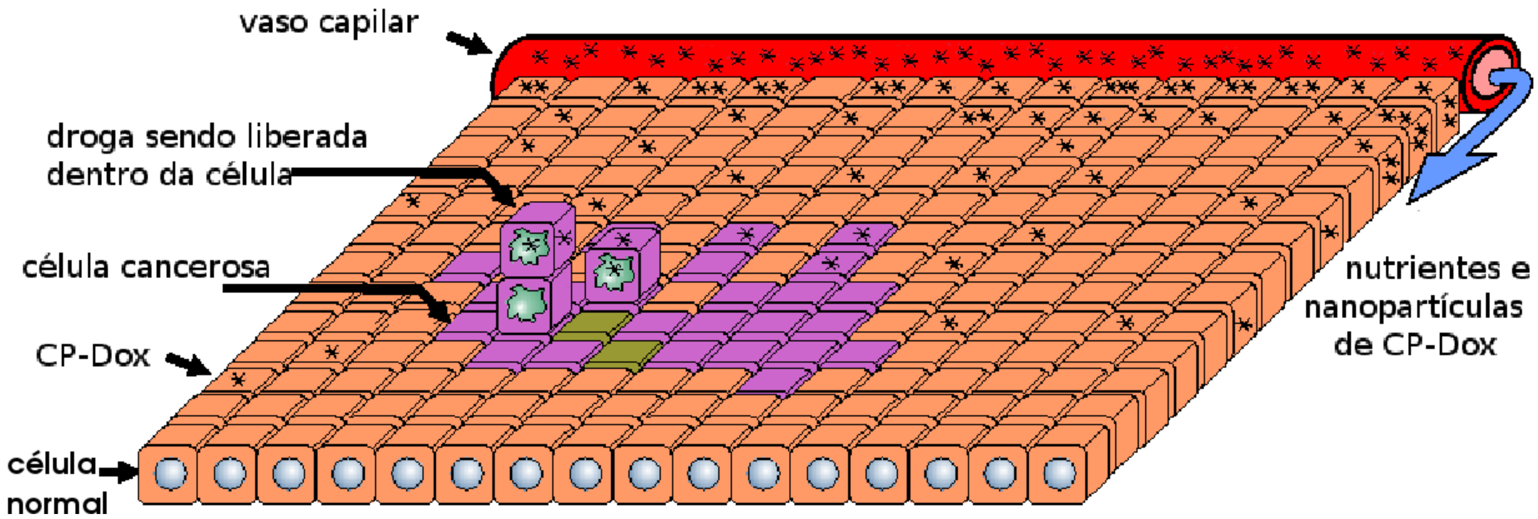


•Reprogramming the immune microenvironment in tumors could substantially enhances the oncolytic virotherapy.

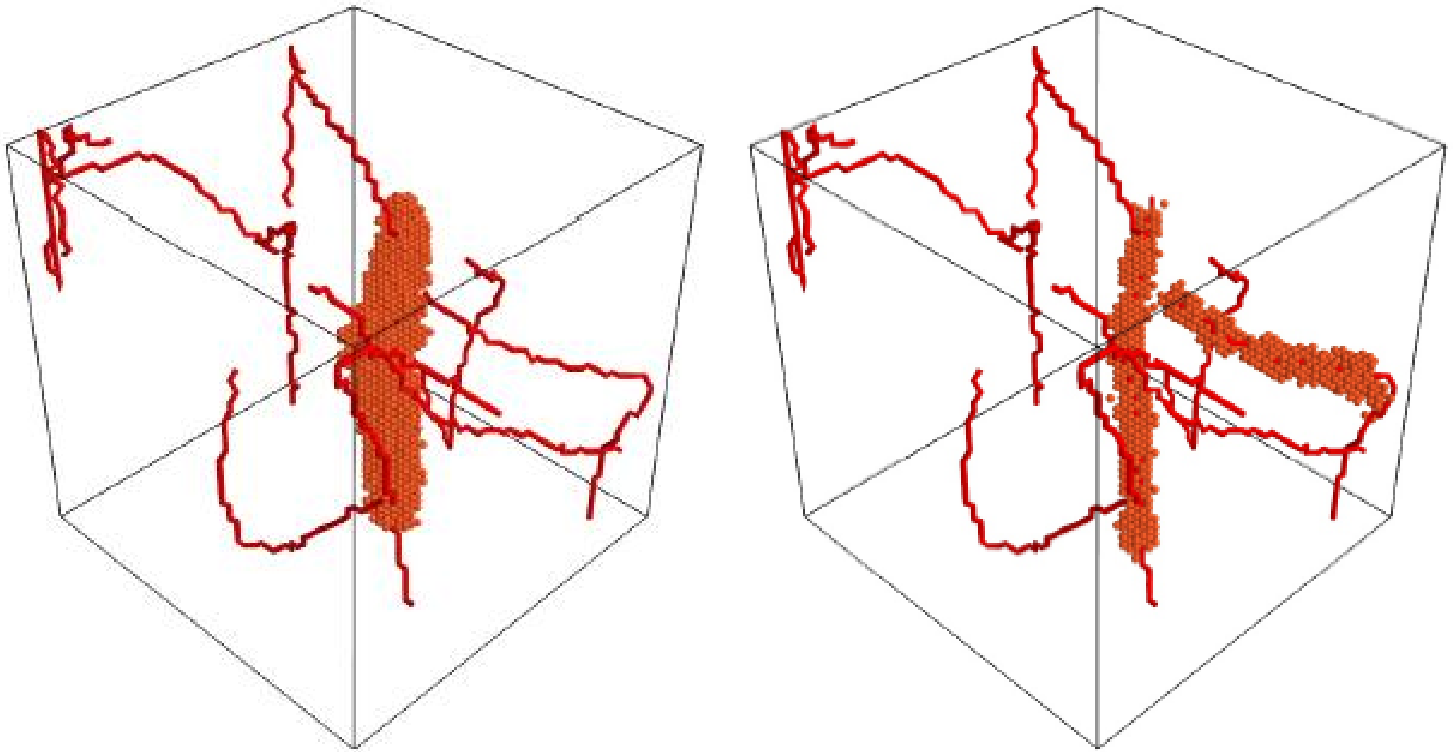
•Promising routes to such reprogramming are either in situ virus-mediated impairing of CD8+ T cells motility or blockade of B and T lymphocytes recruitment.

➢Chemotherapy based on chimeric nanoparticles

Appl. Phys. Lett. 2011



• Cancer chemotherapy using CP-NPs fails primarily due to the small NP endocytic rates. Effective treatments should rely on NPs exhibiting long residence time in the bloodstream, high selectivity for, and large endocytic rates by cancer cells.



Tumor just before the therapy Tumor after therapy, $C_0 = 0.6mM$, $\tau = 4h$.

•Tumor eradication demands either an anticancer drug with a very high endocytic rate (possibly unrealistic) or a combined therapy based on cytotoxic and antiangiogenic agents.

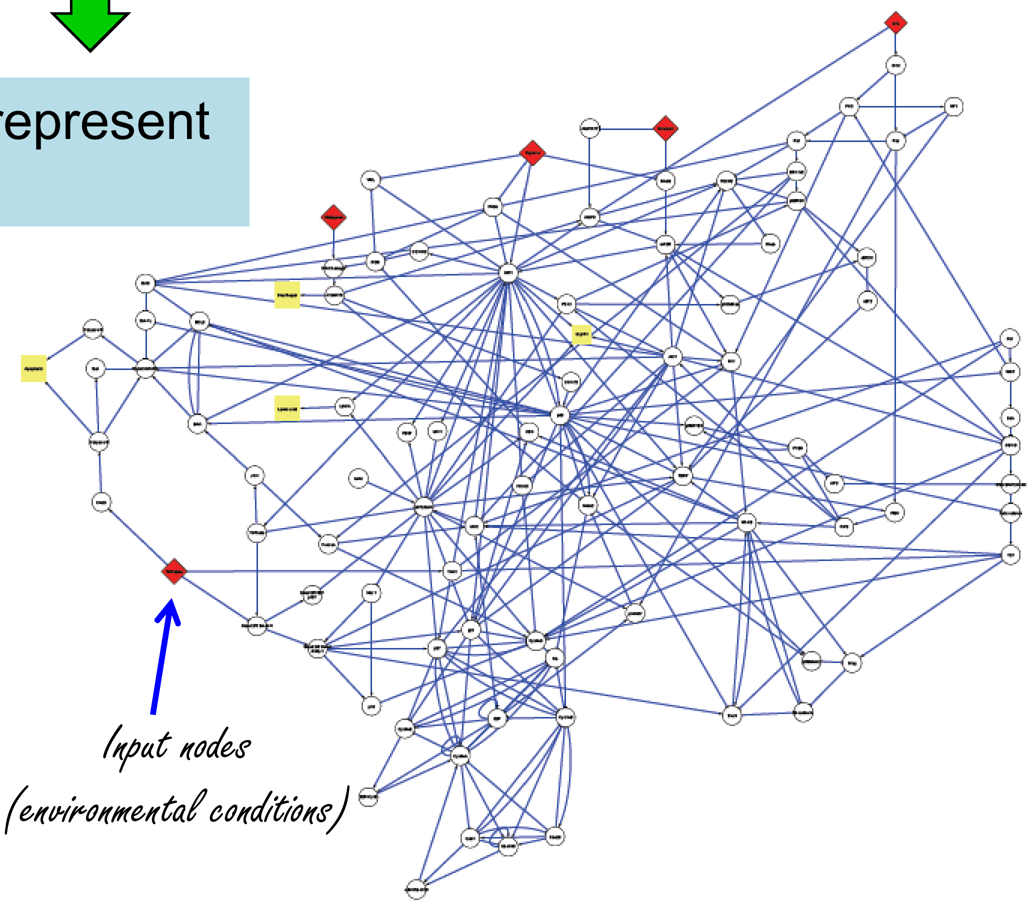
3.2.4 - Microscopic scale (cancer pathways)

PLoS ONE (2013);

- Cancer-related driver mutations affect a dozen or more core signaling pathways that regulate cell death, proliferation and migration.

A natural organizing principle is represent these pathways as a network.

- **The simplified protein interaction network**



Network property	Cancer	Random
nodes	96	96
edges	249	249 ± 12
mean connectivity	2.59	2.59 ± 0.12
shortest path length	3.14	2.91 ± 0.08
clustering coefficient	0.178	0.026 ± 0.005

➢Each protein, a node in the network, is represented by a binary state σ.
$\sigma = 1$ – functionally active protein; $\sigma = 0$ – inactive protein.

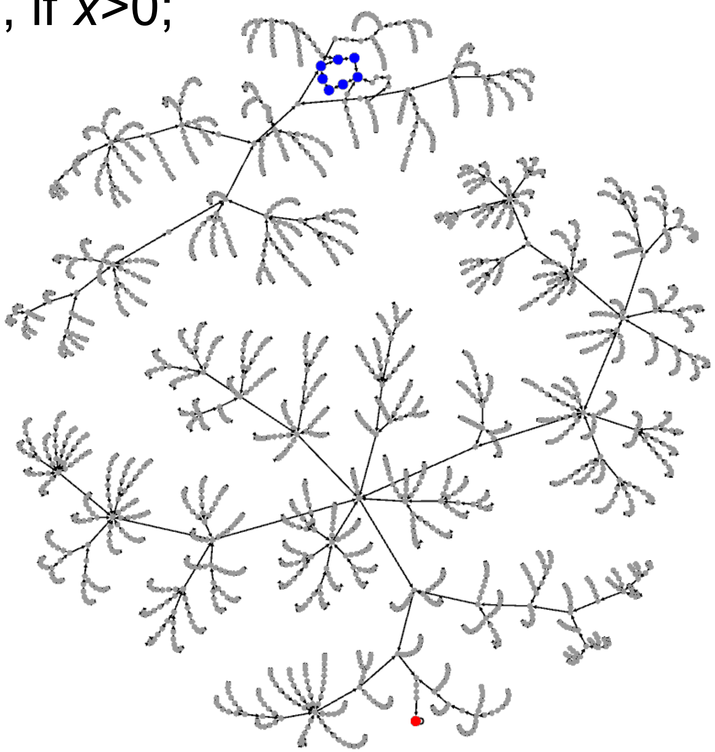
➢ **A Boolean dynamics for protein states:**

$$\sigma_i(t+1) = \mathrm{sgn}\left(\sum_{j=1}^{k_{in}(i)} J_{ji}\sigma_j(t) - \theta_i \right)$$

J_{ji}=interaction from input j on protein i; θ_i=activation threshold of protein i; $sgn(x)$=0, if $x \leq 0$, but $sgn(x)$=1, if $x>0$;

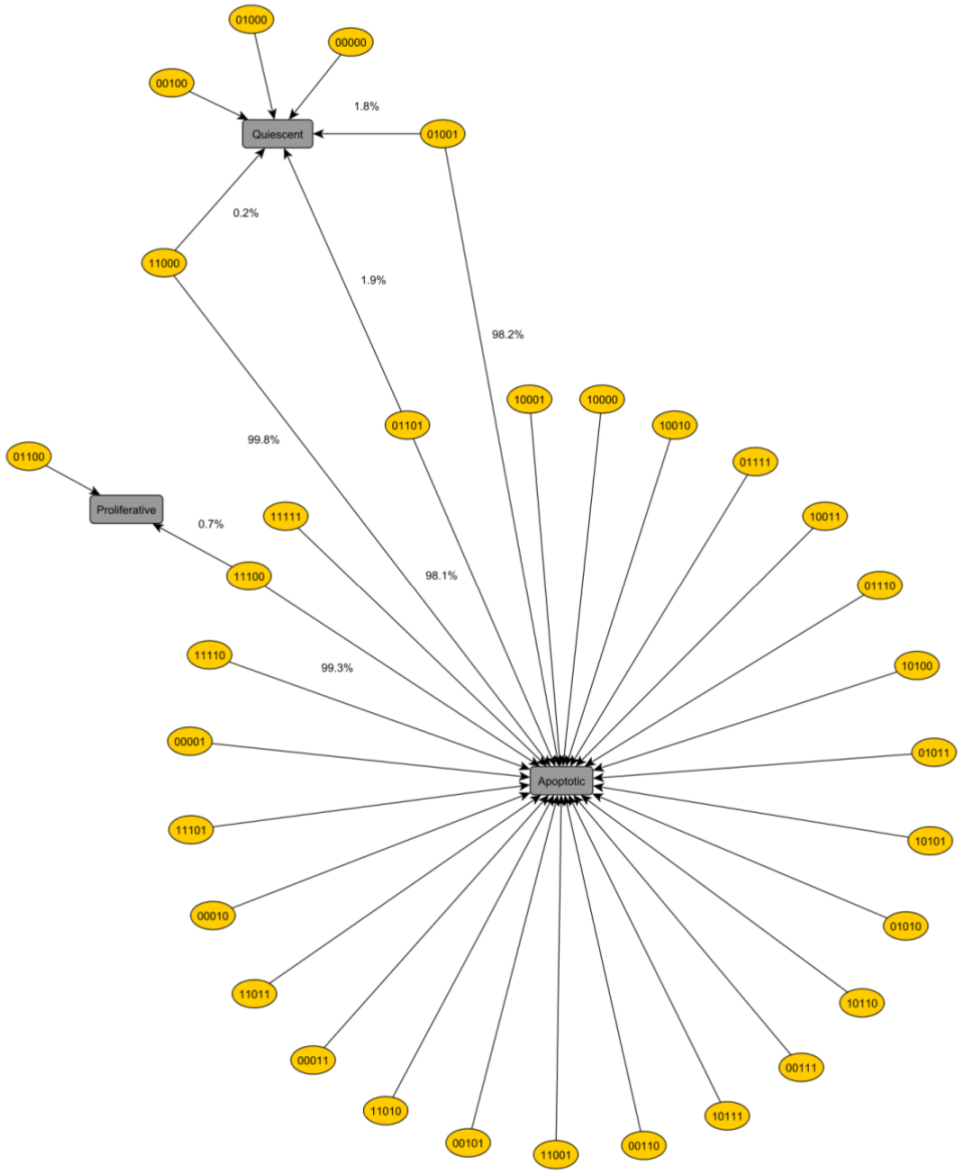
✓ The flow in state-space converges to **dynamical attractors** → dissipative system.

✓ The state-space is organized into a number of basins of attraction.



62 attractors, 47 corresponding to apoptotic, 3 to proliferative and 12 to quiescent phenotypes, which attract *respectively* 87*.4%, 3.1%, and 9.5% of the initial states tested.*

Microenvironmental conditions and network response:



3.3- Predicting carcinogenesis.

3.3.1 – Driver Mutations

Given a microenvironment, which protein mutations transform a formerly quiescent, normal cell into a proliferating one or confers to this cell the ability to evade apoptosis?

Normoxia

Proliferative phenotypes

Protein	mutation	efficacy
Egfr	activation	0.91%
	overexpression	0.91%
Gli	activation	0.08%
	overexpression	0.35%
hTert	activation	0.07%
	overexpression	0.07%
Nf1	deletion	0.03%
Nf-κB	overexpression	0.13%
Pi3k	activation	0.14%
	overexpression	0.73%
Pkc	activation	25%
	overexpression	66%
Pten	deletion	0.51%
Ras	activation	0.16%
Wnt	activation	0.6%
	overexpression	0.6%

Hypoxia

Apoptotic resistant phenotypes

Protein	mutation	efficacy
Akt	overexpression	100%
Bcl2	activation	100%
	overexpression	100%
Bcl-Xl	overexpression	100%
Ikk	overexpression	88, 7%
Nf-κB	activation	91.7%
	overexpression	100%
p53	deletion	100%
Snail	overexpression	83.6%

Have driver nodes special status in network topology?

Akt, Hif1, hTert, Ikk, mTor, Myc, Nf-κB, and p53 → $\left\{ \begin{array}{l} \langle k \rangle = 13.87; \\ \text{centrality } B > 2\langle B \rangle. \end{array} \right.$ ⇒ High connectivity and centrality.

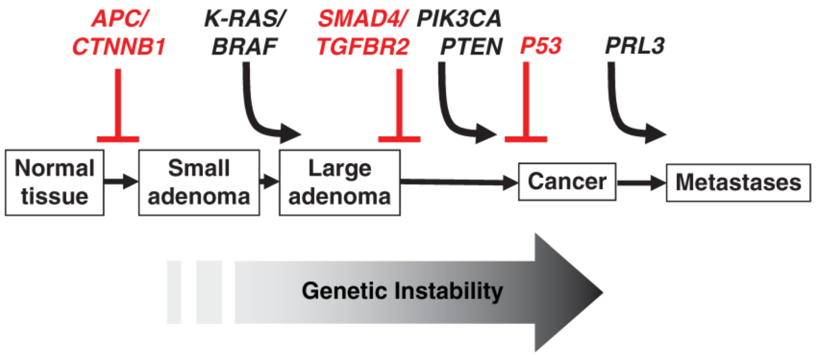
Mdm2 and Pdk1 → $\left\{ \begin{array}{l} \langle k \rangle = 6.5; \\ B \le B < 2\langle B \rangle. \end{array} \right.$ ⇒ Intermediate connectivity and centrality.

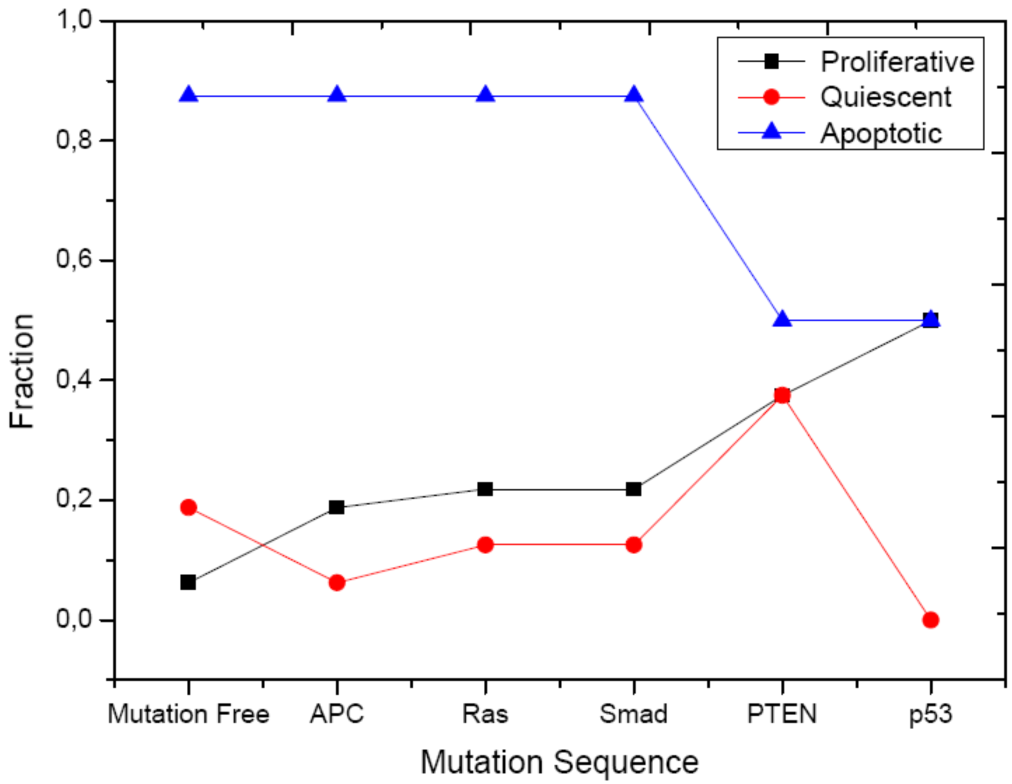
Bcl2,Bcl-xL, Egfr, Gli, Nf1, Phd, Pi3k, Pkc, Pten, Ras, Snail, Vhl, and Wnt → $\left\{ \begin{array}{l} \langle k \rangle = 4.08; \\ B \le \langle B \rangle. \end{array} \right.$ ⇒ small connectivity and centrality.

Driver nodes are not necessarily central in the network topology, but at least they are direct regulators of central components towards which converge or through which crosstalk distinct cancer signaling pathways.

3.3.2 – Carcinogenic routes

- The classical route of colorectal carcinogenesis





- Alternative routes of colorectal carcinogenesis

APC → Ras → Pten p53 ATM (deletion)

PI3K AKT Bcl2 Mdm2 (activation)

4- Concluding remarks

✓ Theoretical multiscale approaches are basic tools in the quest for a quantitative, "ab initio" systems physiology, pathophysiology and for P4 medicine: predictive, preventive, personalized, and participatory.

✓The thought imposed by equation writing will improve understanding of the biological model's assumptions and dynamics.

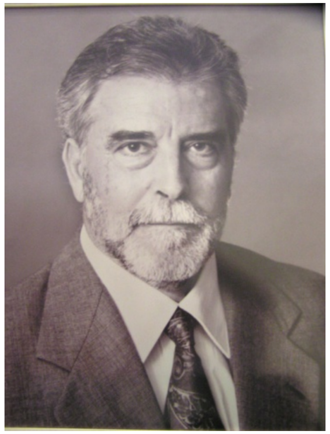
P.Nurse & J. Hayles, Cell **144**, 850 (2011).

✓A functional cell can be created in a laboratory by assembling its parts, even without a detailed understanding of how they engage. But this is not possible in a software.

Mathematics is biology's next microscope, only better.

J. E. Cohen, PLoS Biol. **2**, e439 (2004).

Collaborators



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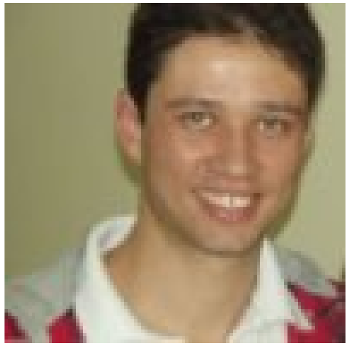

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