Modelling the tumor growth beyond Fickian Diffusion

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Instituto de Matemática Aplicada
a la Ciencia y la Ingeniería

Grupo de Ondas No Lineales y Modelado Matemático Interdisciplinar

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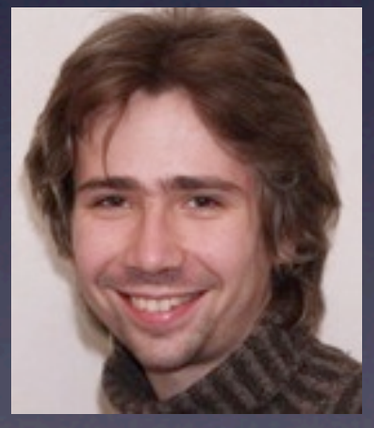

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General Motivation: Mathematical Oncology

"Clinical oncologists and those interested in the mathematical modelling of cancer seldom share the same conference platforms"†

Mechanistic Model

PDEs & Stochastic ODEs

Numerical methods

Improve the model

Results

Do they really have predictive power?

Talking to biologists & clinicians

Applications

Personalized therapies

†R. A. Gatenby & P. K. Maini, Nature **421**, 321 (2003).

Outline of the talk:

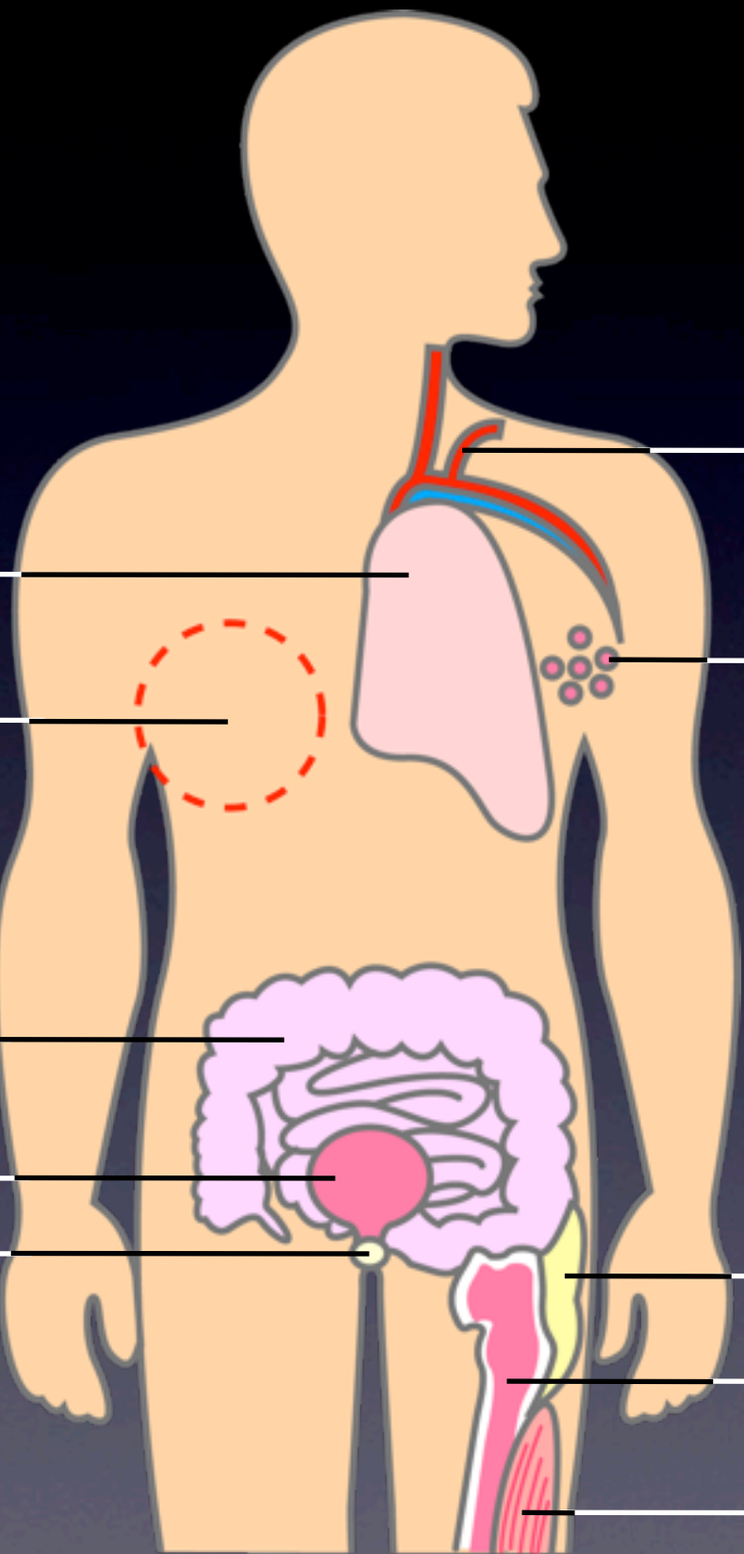
- The Hallmarks of Cancer
- Modelling Tumor Hypoxia
- Time-Delayed Effects due to Cell Migration
- First Steps toward Single-Cell-Based Models

The Hallmarks of Cancer†

- Cancer is a multiscale biological process in which genetic alterations, ocurring at a subcellular level, produce dramatic functional changes at the cellular, tissue and organic levels.
- Tumorigenesis in humans is a multistep process that drives progressive transformation of normal cells into highly malignant derivatives.
- Tumor development is analogous to *Darwinian* evolution, but occurs at a much faster pace.
- There are more than 100 distinct types of cancer, and subtypes of tumors can be found within specific organs.

† D. Hanahan & R.A. Weinberg, Cell **100**, 57 (2000).

Different Kinds of Cancer



Some common carcinomas:

Lung

Breast (women)

Colon

Bladder

Prostate (men)

Leukemias:
Bloodstream

Lymphomas:
Lymph nodes

Some common sarcomas:

Fat

Bone

Muscle

Artwork by Jeanne Kelly. © 2004.

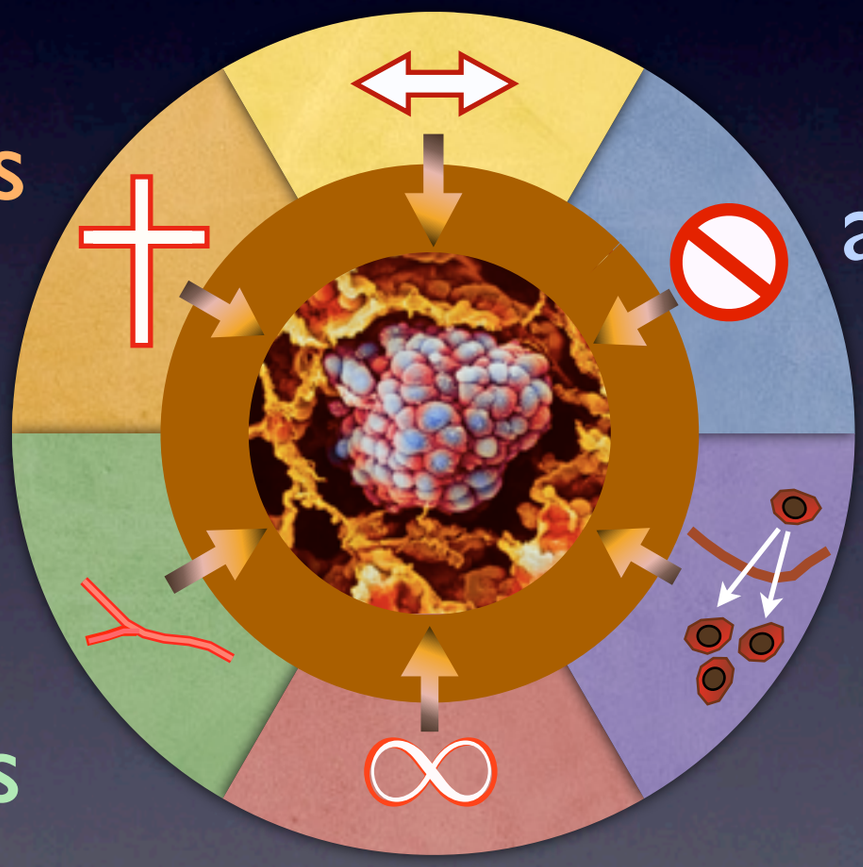
The Hallmarks of Cancer

- Tumor cells manifest six essential alterations:

Self-sufficiency in growth signals

Evading apoptosis

Insensivity to antigrowth signals

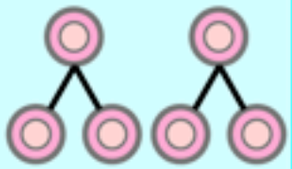
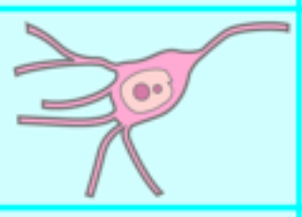
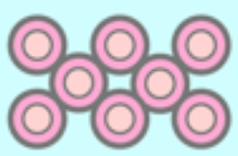


Sustained angiogenesis

Tissue invasion and metastasis

Limitless replicative potential

Cells: Normal vs. cancer

Normal	Cancer	
		Large number of irregularly shaped dividing cells
		Large, variably shaped nuclei
		Small cytoplasmic volume relative to nuclei
		Variation in cell size and shape
		Loss of normal specialized cell features
		Disorganized arrangement of cells
		Poorly defined tumor boundary

Modelling Tumor Growth

Classification:

- As a whole tissue, there are, basically, two distinct stages of tumor growth: avascular and vascular.
- In the avascular phase, the tumor develops via a diffusion-limited mechanism until it reaches a few millimeters in diameter (e.g. multicell spheroids).
- In the vascular phase, the tumor secretes angiogenic factors to induce the formation of a blood vessel network which eventually promotes further tumor progression and metastasis.
- Tumor growth modelling proceeds either from a continuous or discrete (individual-based) approaches.†

†H. Byrne & D. Drasdo, J. Math. Biol. **58**, 657 (2009).

Some references

- Roose, T. and Chapman, S. J. and Maini, P. K. *Mathematical models of avascular tumor growth*, SIAM Review, 49 (2). pp. 179-208 (2007).
- N. Bellomo, N.K. Li, P.K. Maini, *On the foundations of cancer modelling: selected topics, speculations & perspectives*, Math. Mod. Meth. Appl. S. 18, 593-646 (2008)
- *Cancer Modelling and Simulation* (Chapman & Hall/Crc Mathematical Biology & Medicine Series) (Hardcover), Nicola Bellomo Ed. (2003).
- Dominik Wodarz, Natalia L. Komarova, Computational Biology of Cancer: Lecture Notes And Mathematical Modeling, World Scientific (2005).

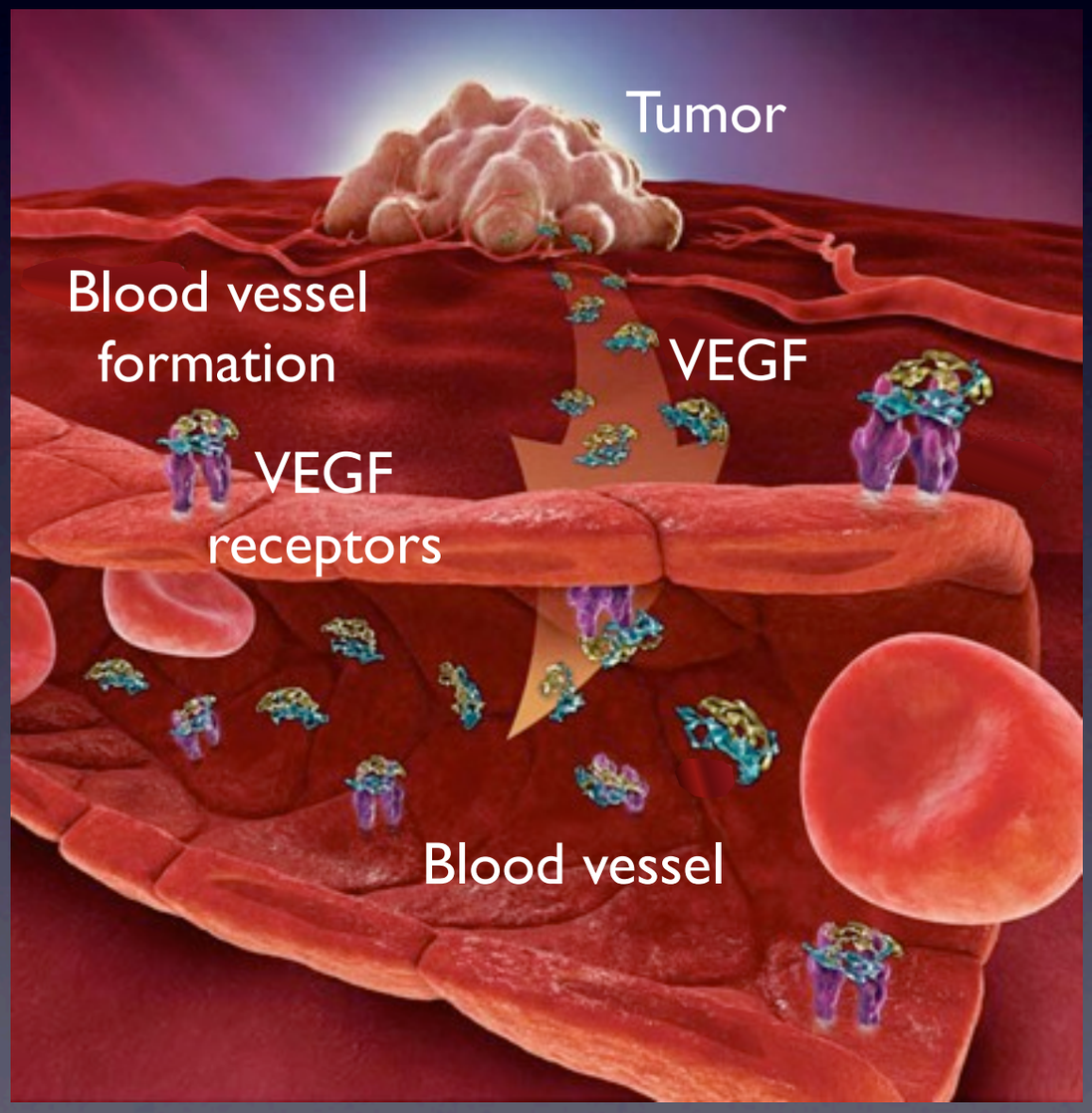
Hypoxia in Tumor Progression†

- Most solid human tumors contain hypoxic (oxygen deficiency) regions, showing a complex time/spatial oxygen distribution (acute and chronic hypoxia).
- In vascularized tumors, hypoxia arises as a consequence of the structural and functional irregularities of the blood vessel network.
- Hypoxic malignant cells can acquire a mutator phenotype: decreased DNA repair, increased mutation rate and chromosomal instability.
- Hypoxic tumors constitute a negative prognostic indicator for cancer patients owing to local radiotherapy resistance and systemic metastases.

† P. Vaupel, The Oncologist **13**, 21 (2008).

Hypoxia in Tumor Progression

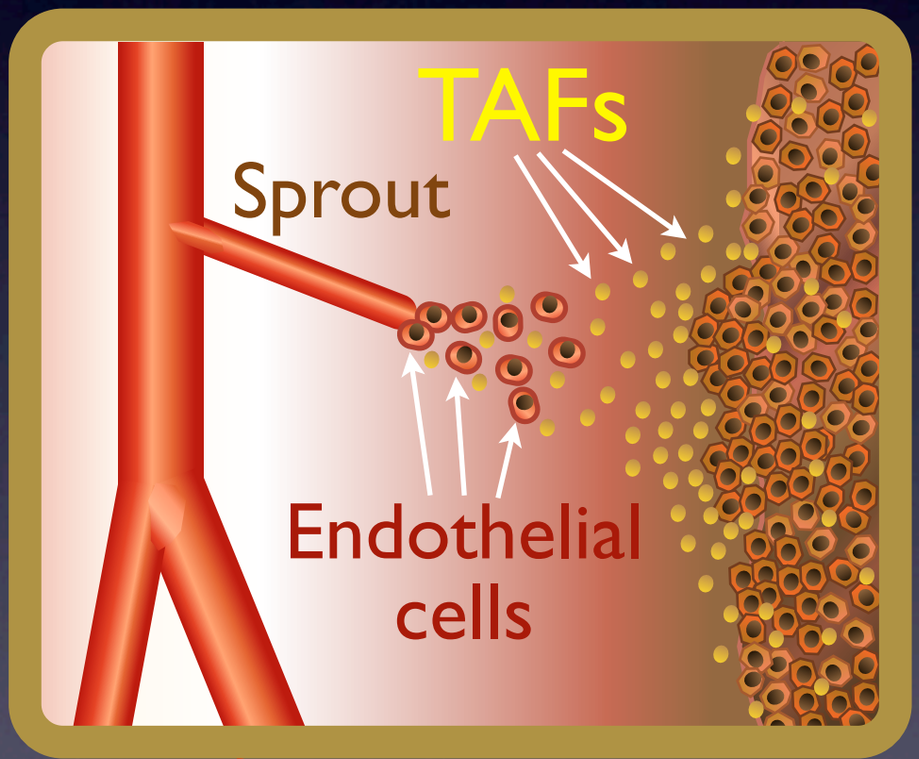
- In order to grow beyond the diffusion-limited phase, tumors require a blood supply. Malignant cells trigger the angiogenic switch.†



† P. Carmeliet, Nature **438**, 932 (2005).

Hypoxia in Tumor Progression

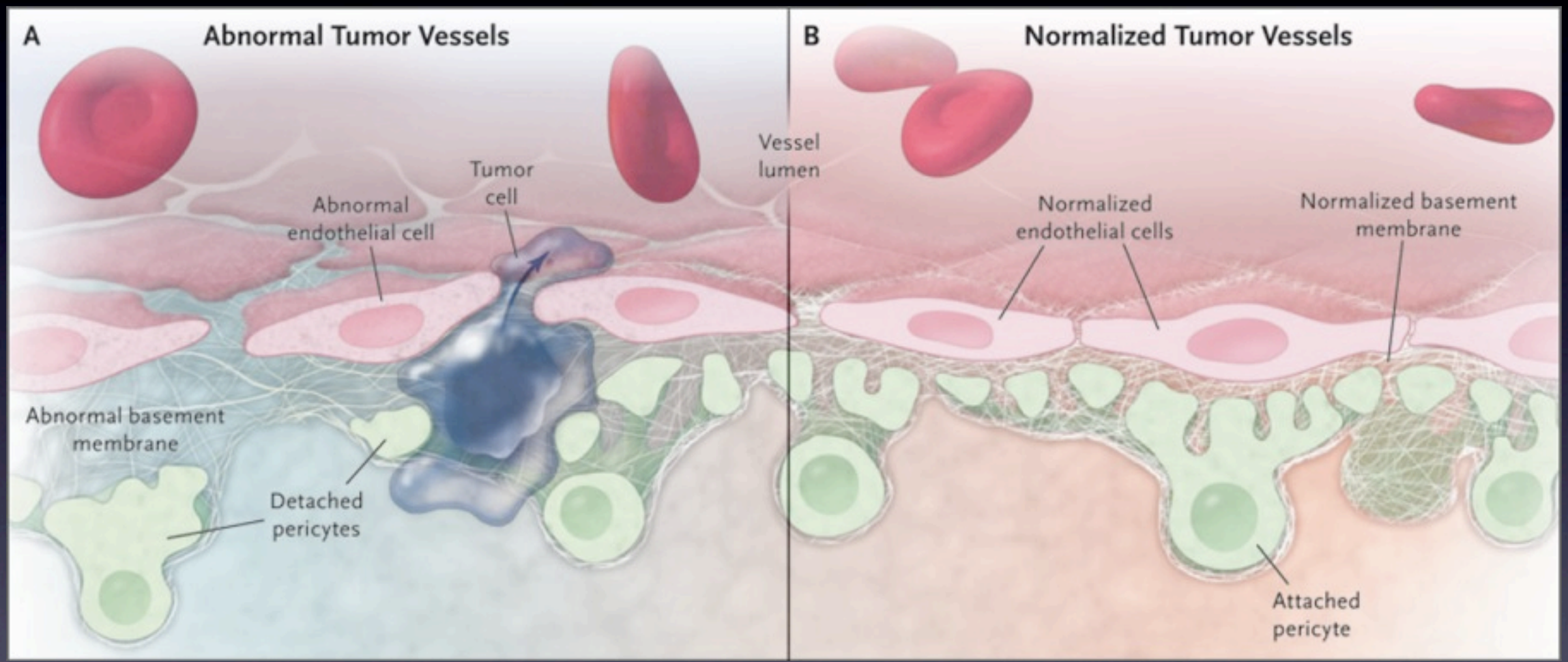
- Tumor cells secrete tumor angiogenic factors (TAF) into the surrounding tissue.
- TAFs diffuse creating a chemical gradient between the tumor and the existing vasculature.



- When TAFs reach neighbor blood vessels induce the migration of endothelial cells towards the tumor.

Hypoxia in Tumor Progression

- One of the targets for tumor theraphy is normalizing the blood vessel vasculature of the tumor area.†

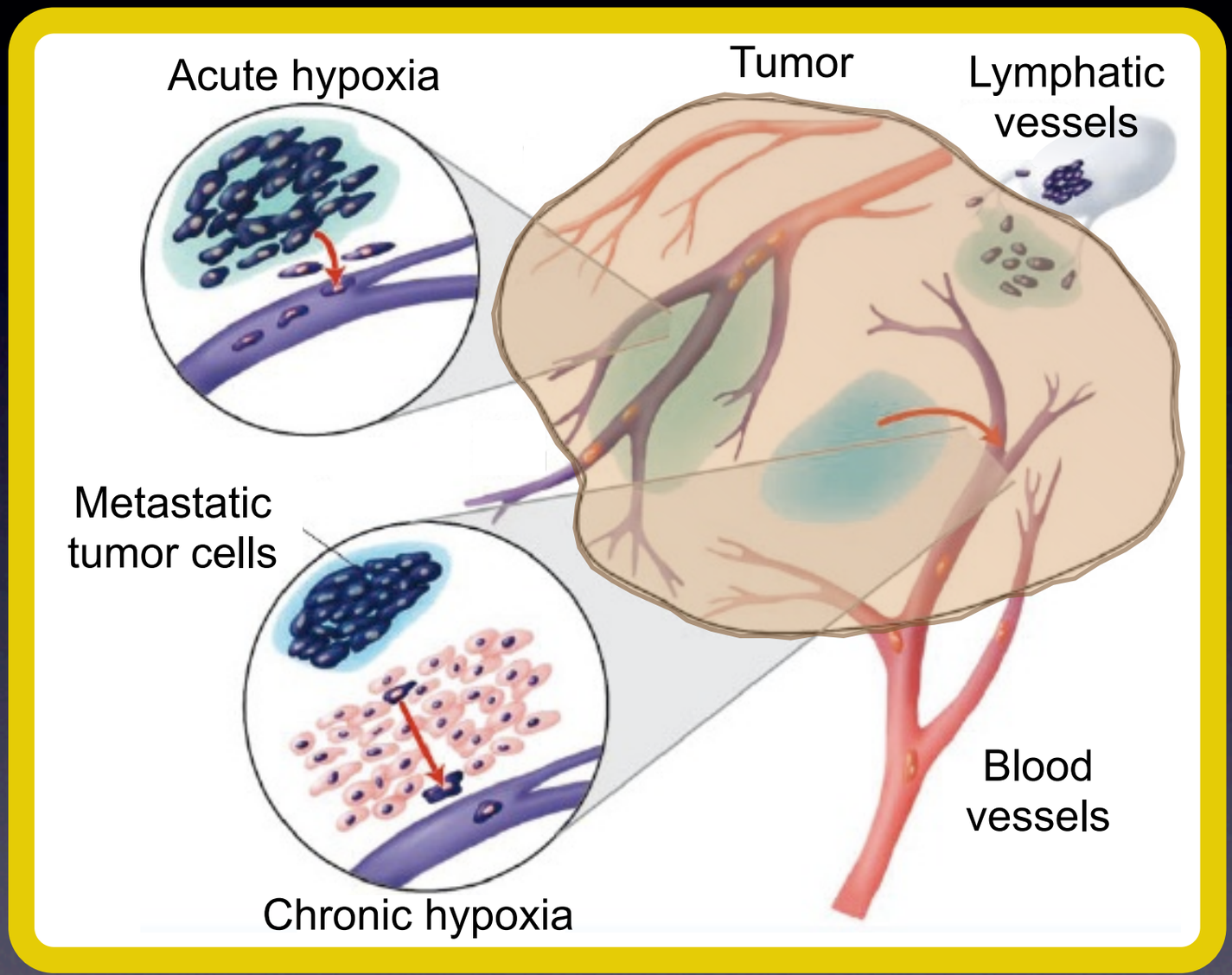


- Normalization would decrease cancer-cell invasion into blood and lymphatic vessels, and thus metastasis.

† R.K. Jain, New Eng. J. Med. **360**, 2669 (2009).

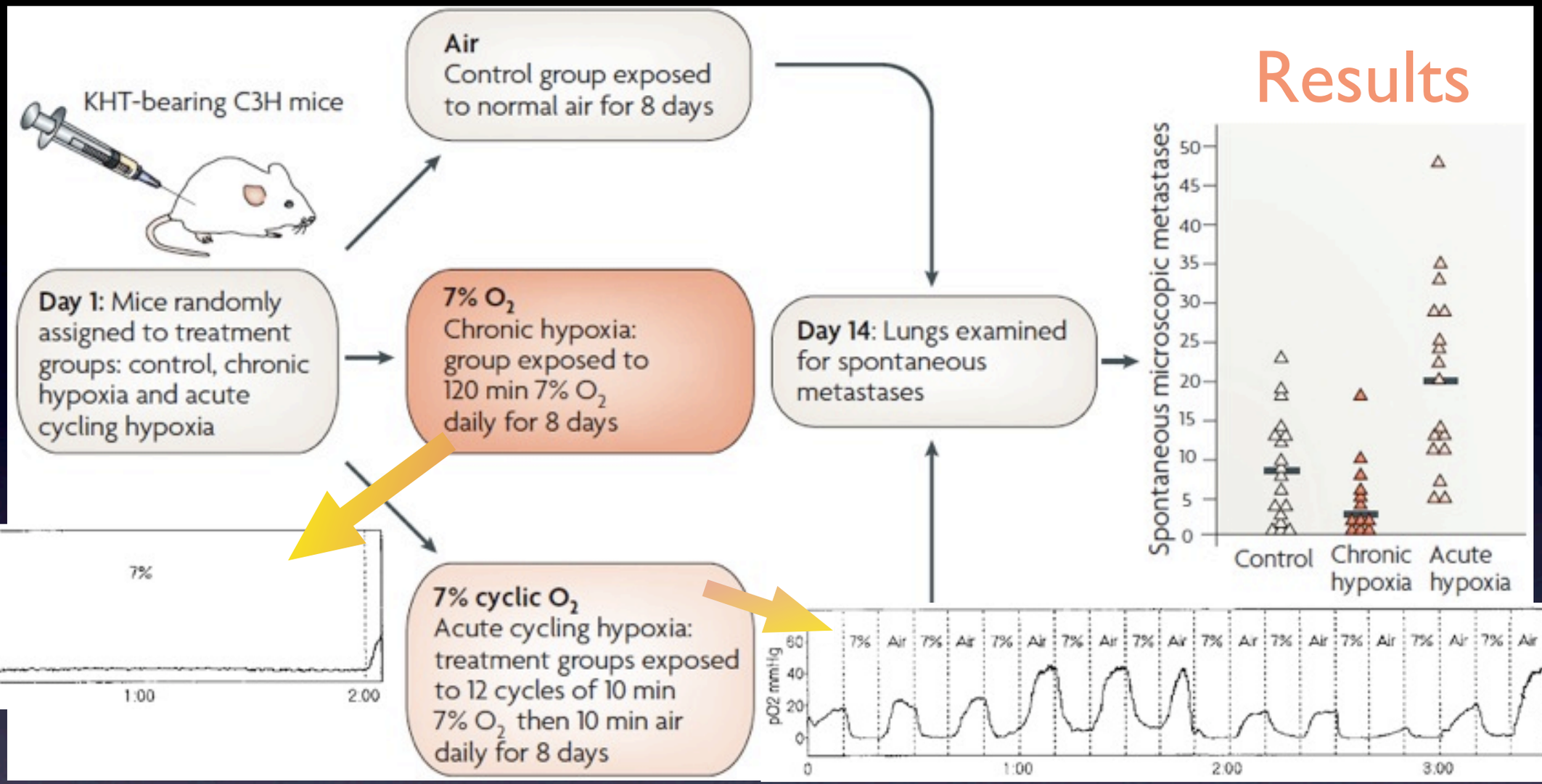
Hypoxia in Tumor Progression

Our Modelling Scenario:



- Tumor cells exposed to acute (fluctuating) hypoxia tend to show more intravasation into blood vessels.

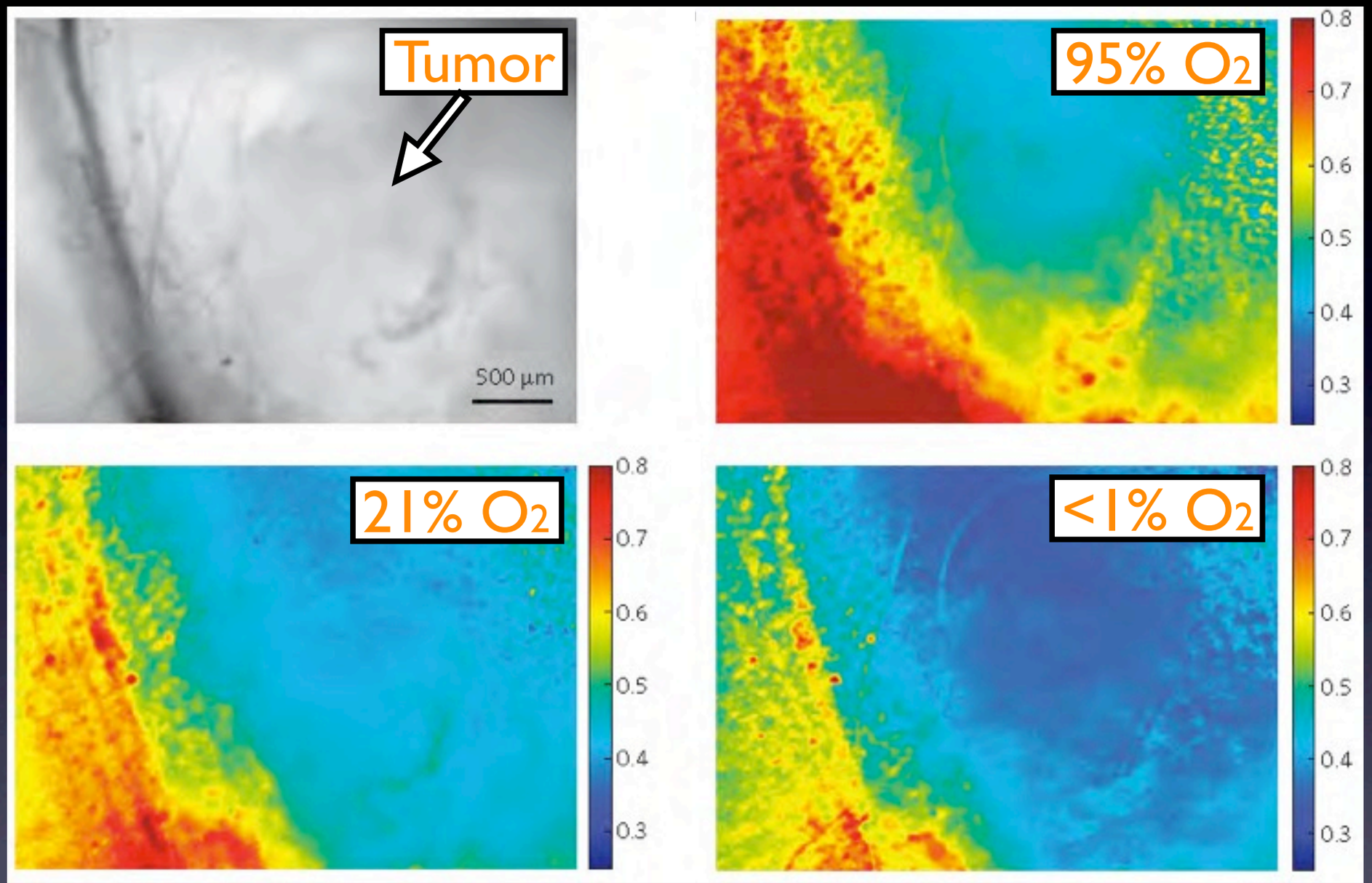
Hypoxia in Tumor Progression



- Induction of acute hypoxia in tumors can increase spontaneous metastases. Tumor-bearing mice were randomly assigned to either control, chronic and cycling hypoxia daily and then evidence of metastasis was scored.†

† R.G. Bristow & R.P. Hill, Nature Rev. Cancer **8**, 180 (2008).

Tumor Hypoxia Imaging using Boron Nanoparticles†



In vivo imaging of a breast cancer mammary carcinoma tumor region in a mouse window chamber.

† C. L. Fraser *et al*, Nature Materials **8**, 747 (2009).

Simplified Model Equations for Tumor Hypoxia

- Three EDPs describe the coupled evolution of normoxic and hypoxic tumor cells with oxygen:

$$\frac{\partial C_{\rm n}}{\partial t} = \underbrace{D_{\rm n}\nabla^2 C_{\rm n}}_{\text{Diff. normoxic c.}} + \underbrace{s_{\rm hn} C_{\rm h}}_{\text{Oxygenation}} - \underbrace{s_{\rm nh} C_{\rm n}}_{\text{Hypoxia}} + \underbrace{\frac{1}{\tau_{\rm P}}\left(1 - \frac{C_{\rm n}+C_{\rm h}}{C^{(\rm M)}}\right) C_{\rm n}}_{\text{Proliferation}}$$

$$\frac{\partial C_{\rm h}}{\partial t} = \underbrace{D_{\rm h}\nabla^2 C_{\rm h}}_{\text{Diff. hypoxic c.}} - \underbrace{s_{\rm hn} C_{\rm h}}_{\text{Oxygenation}} + \underbrace{s_{\rm nh} C_{\rm n}}_{\text{Hypoxia}} - \underbrace{\sigma C_{\rm h}}_{\text{Death by anoxia}}$$

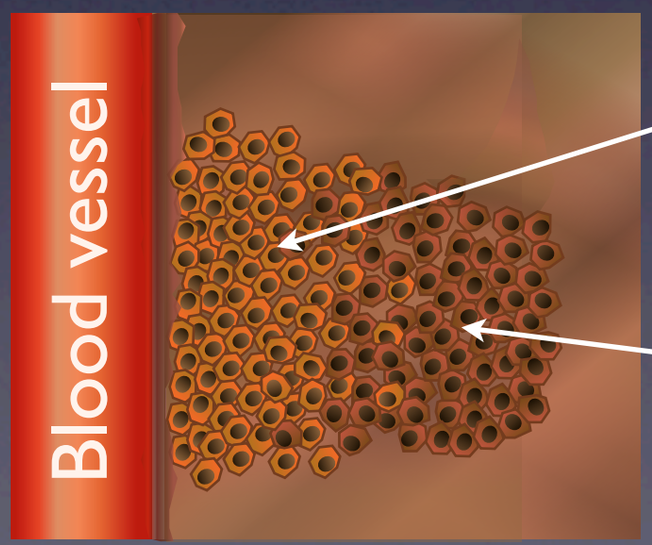
$$\frac{\partial O_2}{\partial t} = \underbrace{D_{O_2}\nabla^2 O_2}_{\text{Diff. oxygen}} - \underbrace{\frac{(\alpha_{\rm n} C_{\rm n} + \alpha_{\rm h} C_{\rm h}) O_2}{O_2^{(\rm T)} + O_2}}_{\text{Oxygen consumption}}$$

$$D_{\rm h} \gg D_{\rm n}$$

where

$$s_{\rm hn} = \frac{1}{\tau_{\rm S}} - s_{\rm nh} = \frac{\int_0^t \chi (O_2 - O_2^{(\rm S)}) e^{-(t-\eta)/\tau_{O_2}} d\eta}{\tau_{\rm S}\tau_{O_2}\left[1 - e^{-t/\tau_{O_2}}\right]}$$

$$\sigma = \frac{\int_0^t \chi (O_2^{(\rm D)} - O_2) e^{-(t-\eta)/\tau_{O_2}} d\eta}{\tau_{\rm D}\tau_{O_2}\left[1 - e^{-t/\tau_{O_2}}\right]}$$



Model Equations for Tumor Hypoxia

- Our set of equations is solved in a square domain of length 1 mm.
- We assume that the surrounding non-malignant tissue does not significantly interact with the tumor cells, although it does consume oxygen.
- Within the time window studied (order of hours), the neighbor blood vessel does not experience relevant changes due to the evolving tumor.
- Here, both normoxic and hypoxic cell populations may transiently coexist in some regions of the tumor. Their total density does not exceed:

$$C_{\mathrm{n}} + C_{\mathrm{h}} < C^{(M)} \simeq 10^6 \ \mathrm{cells/cm}^2$$

Model Equations for Tumor Hypoxia

Boundary conditions:

- For the tumor populations, homogeneous Robin (third type) boundary conditions are imposed at the tumor-blood vessel interface:

$$\frac{\partial C_{\mathrm{n}}}{\partial x} - \frac{v_{\mathrm{n}}}{D_{\mathrm{n}}} C_{\mathrm{n}} = 0\,, \quad \frac{\partial C_{\mathrm{h}}}{\partial x} - \frac{v_{\mathrm{h}}}{D_{\mathrm{h}}} C_{\mathrm{h}} = 0\,,$$

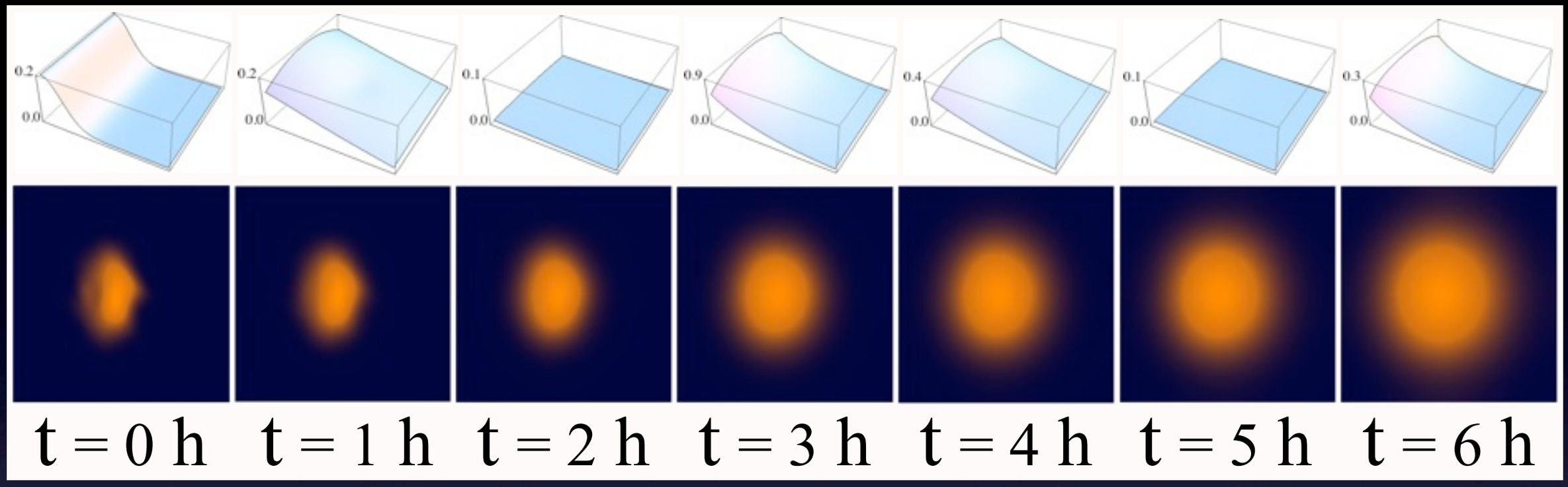
where $v_{\mathrm{n}} \ll v_{\mathrm{h}}$ are the flow velocities of the normoxic and hypoxic cells at the blood vessel wall.

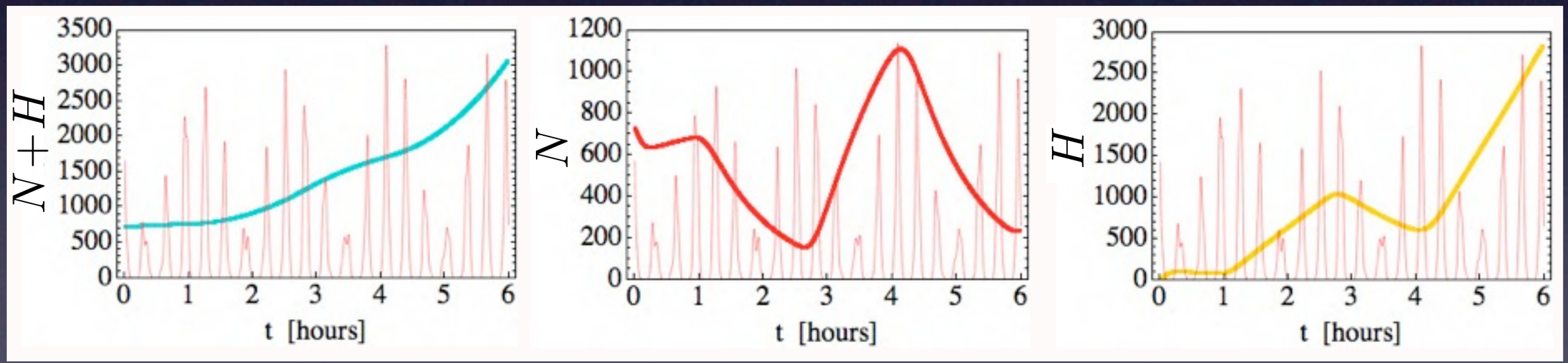
- Oxygen obeys Neumann (second type) boundary conditions at the tumor-blood vessel interface:

$$\frac{\partial O_2}{\partial x} = -\frac{1}{D_{O_2}} J_{O_2}(t)$$

where J_{O_2} is the time-dependent oxygen flux density.

Numerical Simulations of the Model





- The time-scale fluctuations in the oxygen flux from the blood vessel induce a significant growth of hypoxic cells. Even under acute hypoxia the total number of tumor cells increases!

Time-Delay Effects due to Cell Migration

- Purely Fickian diffusion transport assumes that cells continuously move along random directions spending a very small time at every visited point.

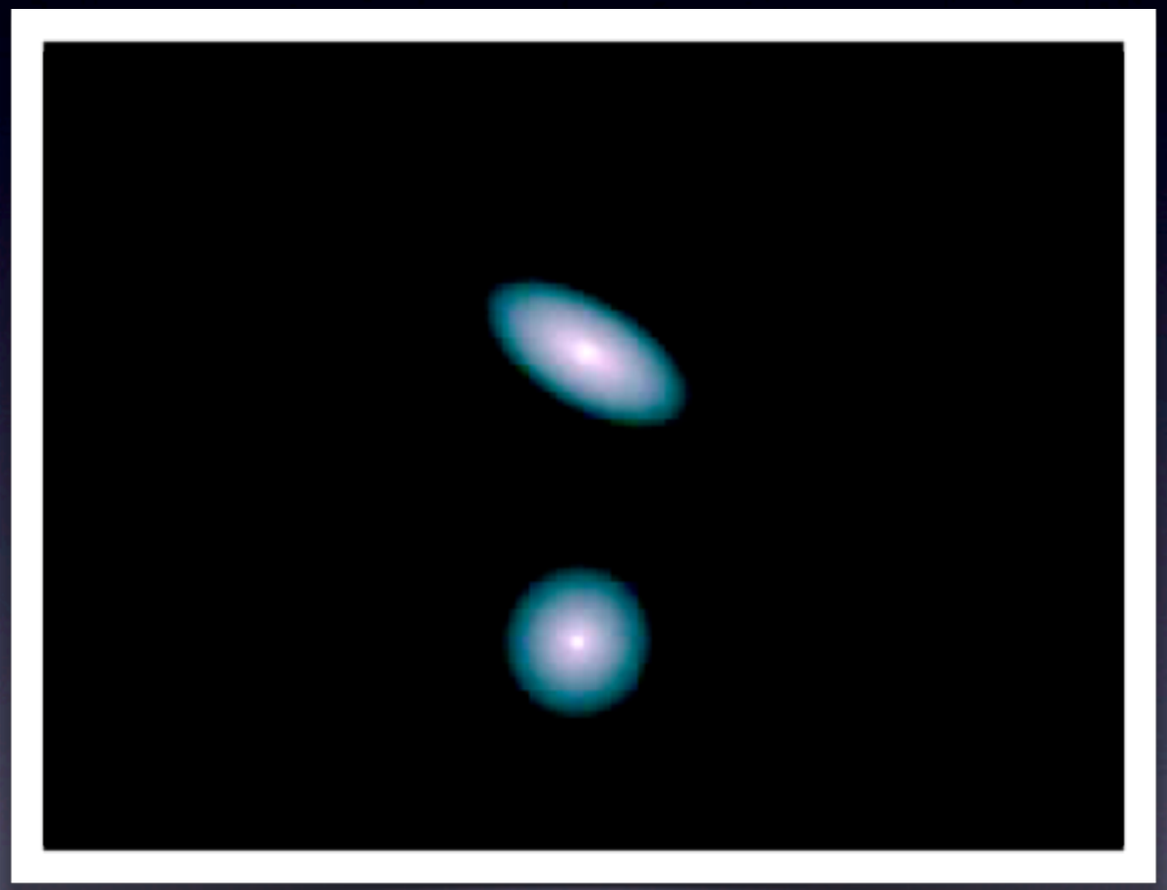
- Tumor cells display a wide movement spectrum, and may remain immobile for a significant amount of time before compelled to migrate to a more favorable location.

- Time-delay effects are expected when comparing the growth of tumor fronts predicted by standard parabolic reaction-diffusion equations with those incorporating the periods in which cells are at rest.

Ok, ¿but is that all we can do?

Many areas of Science studying complex systems tackle them from their very basic constituents

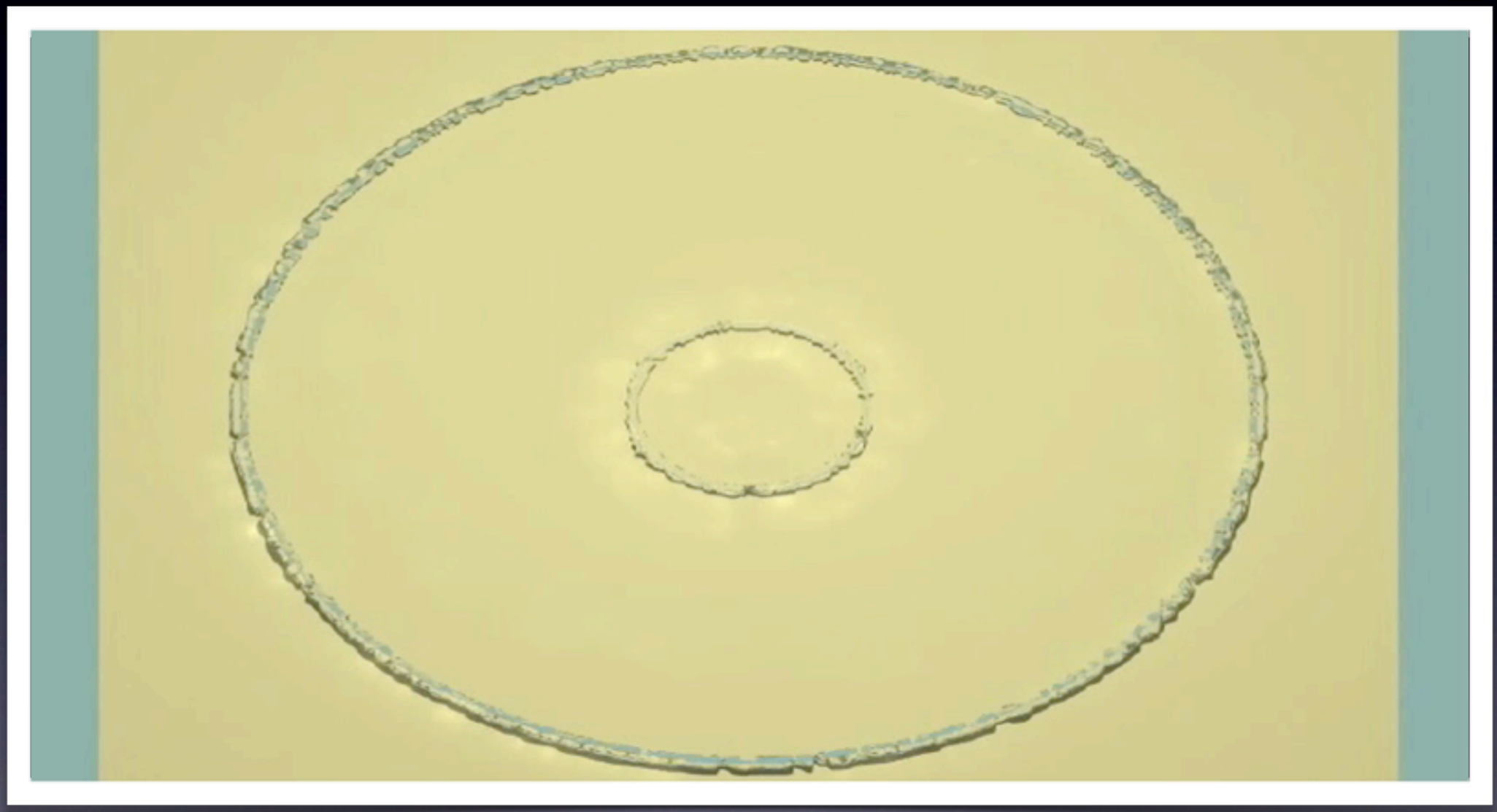
From the very large...



Collision of the Milky Way with Andromeda galaxy

10^8 Stars/Galaxy

... to the very small



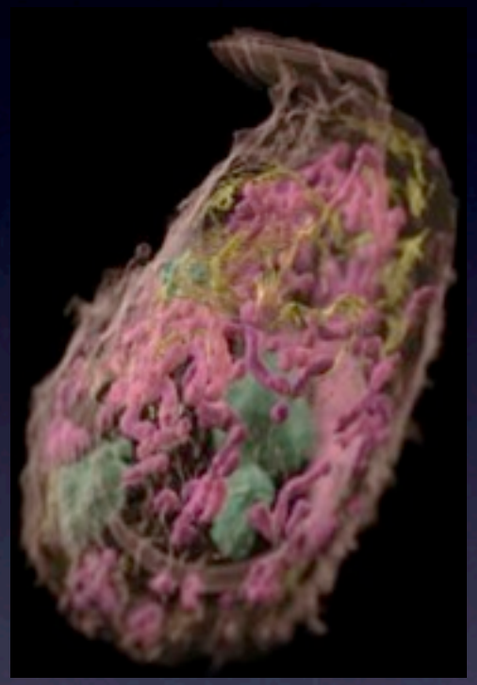
Growth of an ice crystal

Let us make some number estimates ...

- Cells in the human body: 10^{14}
- Neurons in the human brain: 10^{11}
- Large-scale molecular dynamics simulations have already exceeded (e.g. Rayleigh-Taylor instability†): 10^{11}

†http://www.thp.uni-duisburg.de/~kai/index_1.html

Why not simulating the tumor growth, *à la* molecular dynamics simulations, at the single cell level?



Although it is very challenging, it is feasible: using efficient mathematical algorithms and supercomputation

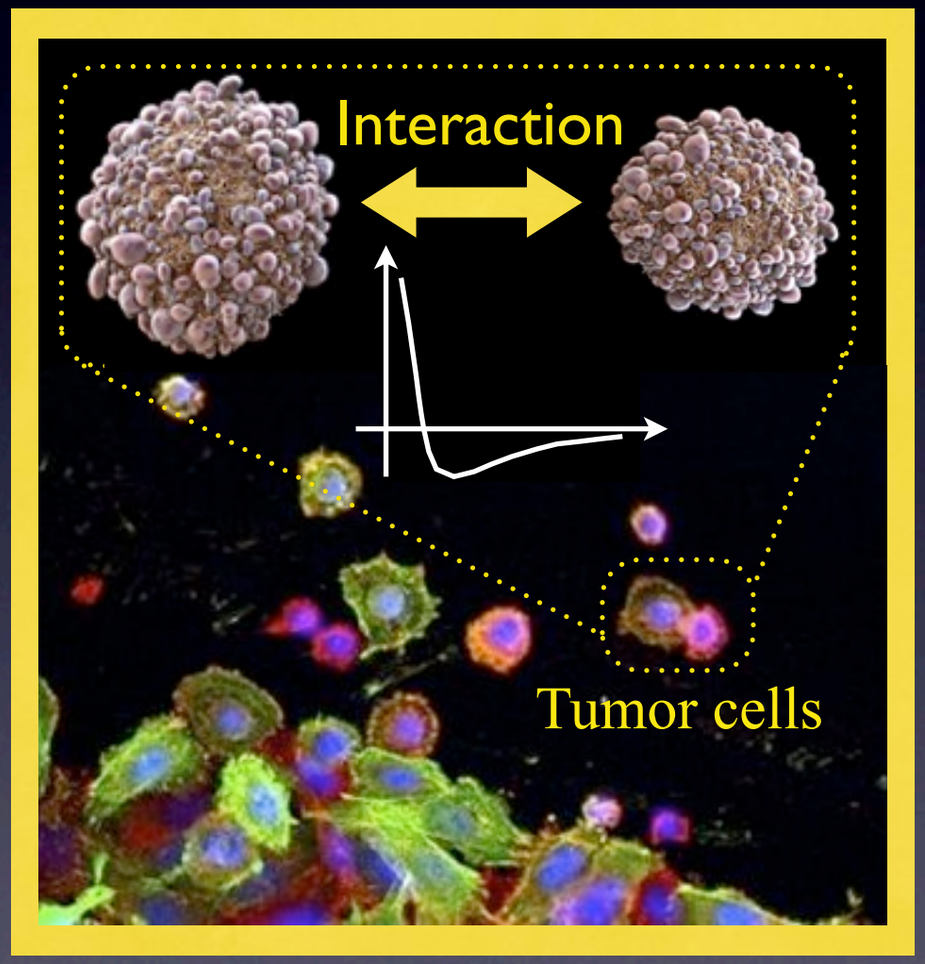
Models of Tumor Cell Dynamics

We can simulate *at the single-cell level* how several tumor cell phenotypes interact and evolve (e.g. cancer stem cells).

Consider a system comprising N tumor cells governed by the following Langevin equations (their velocities):

$$\underbrace{\frac{d\mathbf{v}_k}{dt}}_{\text{Acceleration}} = \underbrace{-\frac{\mathbf{v}_k}{\tau}}_{\text{Friction}} + \underbrace{\boldsymbol{\Gamma}_k}_{\substack{\text{Interaction with} \\ \text{extracellular} \\ \text{matrix}}} + \underbrace{\mathbf{F}_k}_{\substack{\text{Forces} \\ \text{among} \\ \text{cells}}} + \underbrace{\gamma_k \nabla O_2}_{\text{Chemotaxis}}$$

Stochastic force



For each cell $k = 1,\ldots,N$. The number of cells is time dependent!

Models of Tumor Cell Dynamics

Besides cell movement and migration, oxygen and nutrient consumption by the cells has to be included, whose spatio-temporal distributions in the tumor microenvironment exhibit strong fluctuations with phases of acute privation.

To describe hypoxic effects, a PDE is included for the oxygen evolution:

$$\underbrace{\frac{\partial O_2}{\partial t}}_{\text{Evolution}} = \underbrace{D_{O_2}\nabla^2 O_2}_{\text{Diffusion}} - \underbrace{\sum_{k=1}^{N}\alpha_k\delta(\mathbf{r}-\mathbf{r}_k)}_{\text{Cellular consumption}} + \underbrace{S(\mathbf{r},t)}_{\text{External sources}}$$

An appealing feature of single-cell based models is that one may add the internal state of the cell. This corresponds to taking into account the phase of the cell-cycle.

Multiscale Models

Ingredients:

- Model each cell using stochastic ODEs (mechanical interaction and migration).
- Deal with all relevant cell phenotypes (tumor, surrounding non tumor tissues, immune system, etc).
- Model the chemical (continuous) fields (oxygen, glucose, enzymes, pH, TAFs) via PDEs.
- Include the role of therapies and optimization.
- Solve the various complexity levels of the problems using optimized numerical techniques for large-scale simulations (molecular dynamics).

What the clinicians expect from (math) us ...

- Ways to understand what is essential and what it is not in complex biological phenomena.
- Predictive tools
- Personalized treatments
- Quantitative guides for combined therapies
- Quantitative understanding of why in-vitro or animal models fail
- ...

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¡¡Muchas gracias por vuestra atención!!

Modelling the tumor growth beyond Fickian Diffusion

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