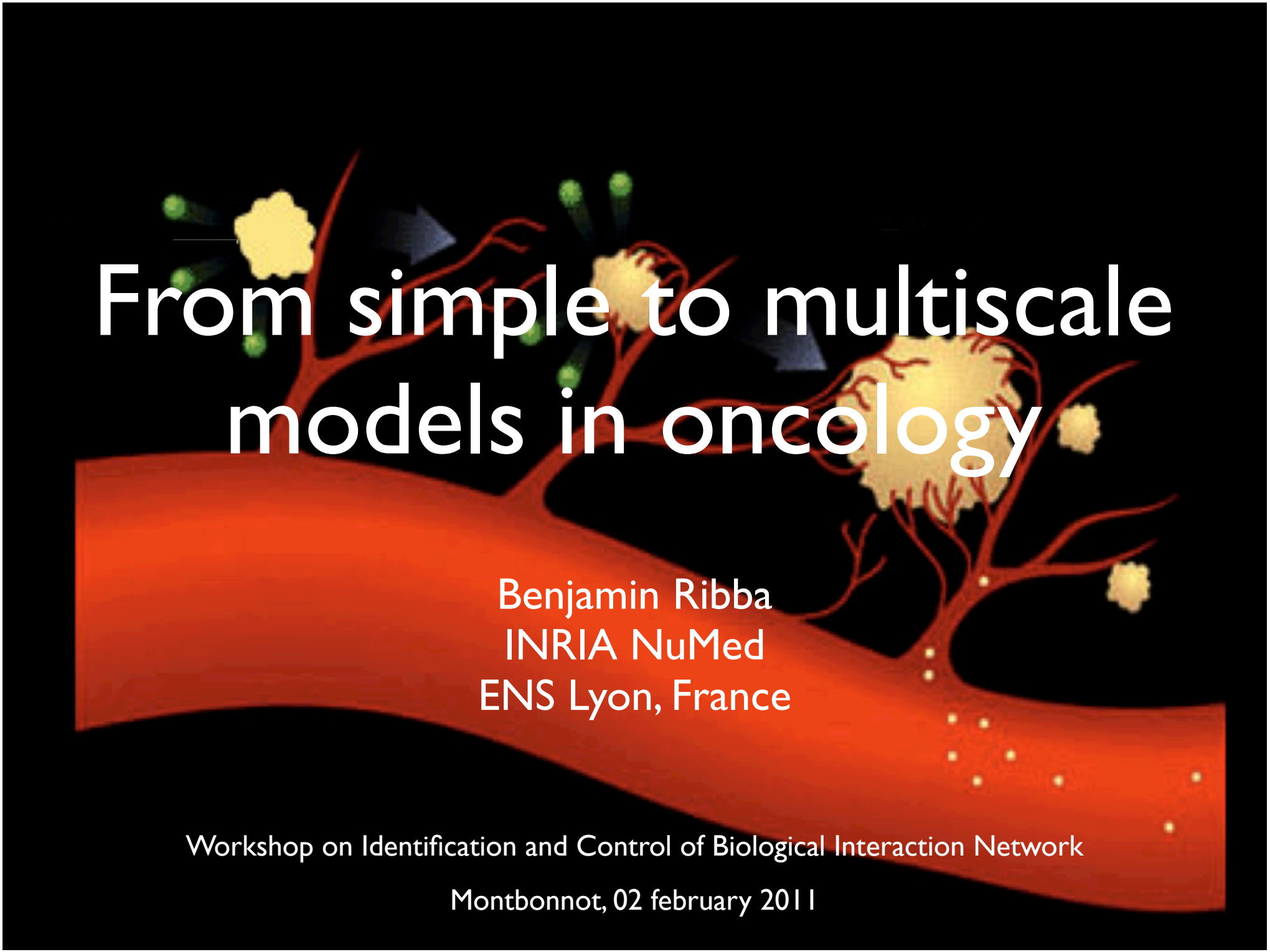


From simple to multiscale models in oncology

Benjamin Ribba
INRIA NuMed
ENS Lyon, France

Workshop on Identification and Control of Biological Interaction Network

Montbonnot, 02 february 2011

General context

- The rate of successful drug development in oncology is about 5%
- Even for compounds entering phase III: 60% of failure rate
- FDA recommends the use of quantitative modeling to improve drug development process
- PK/PD models (modeling and simulation M&S)

Introduction

PK/PD MODELING APPROACH

PK/PD

- Pharmacokinetic (PK)
  - What the body does to the drug: time evolution of drug concentration in plasma
- Pharmacodynamic (PD)
  - What the drug does to the body: time evolution of a disease marker as a function of drug concentration

PK/PD data

- Sparse, especially for clinical data
- Mainly macroscopic measurements such as tumor size
- Carry out the analysis on a population of patients simultaneously and not just on few individuals

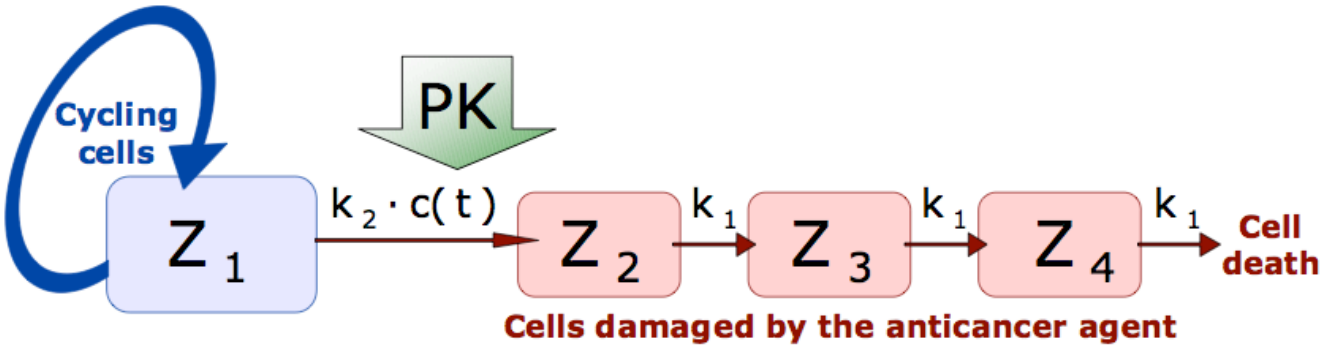
Aims of M&S

- Estimate the different model parameters so that the evolution of the variable best fits the data
- Give an interpretation of the parameters in terms of biological properties of the tumor
- Give to these parameters a clinical interest (prognostics,...)
- Use simulations to explore different strategies

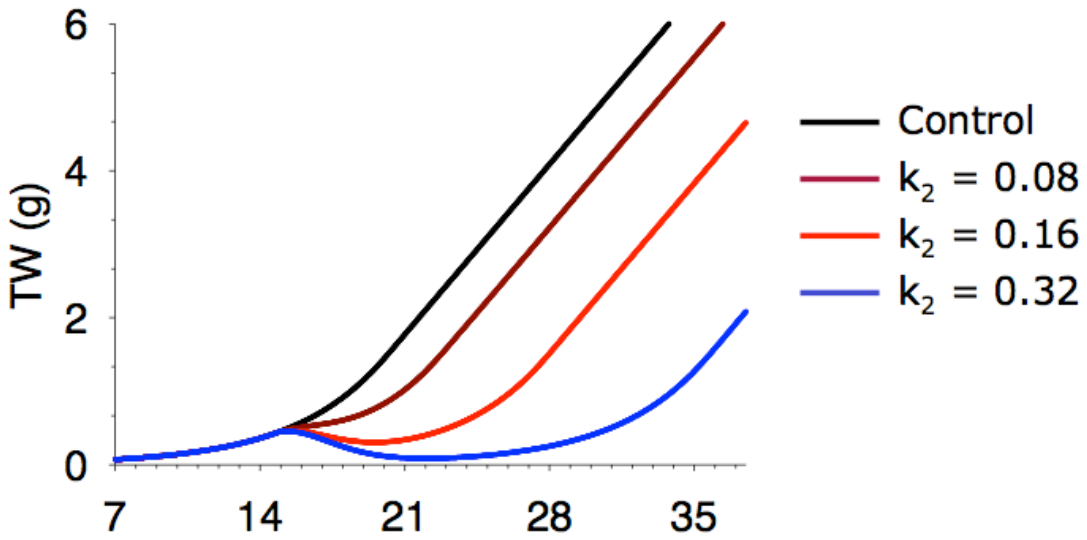
PK/PD model

- Structural part: Simple models of tumor growth have been developed
  - Gompertz-like model or few ODEs
- Statistical part: Population approach or mixed-effect nonlinear regression
- Strong validation with experimental data

TGI model

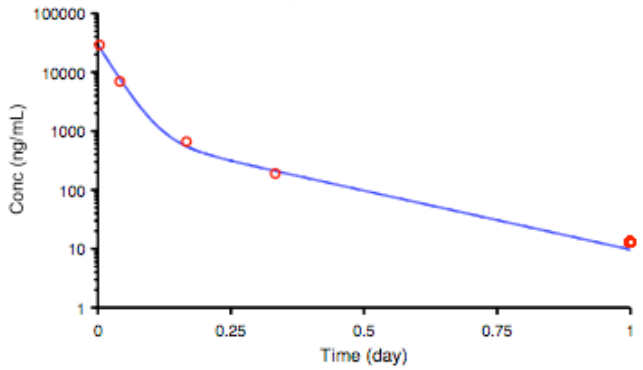


Dependence of the TG kinetics on k_2 (a multiplicative factor representing the drug potency)

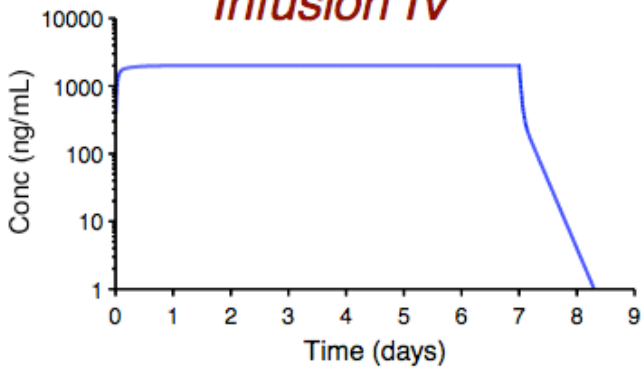


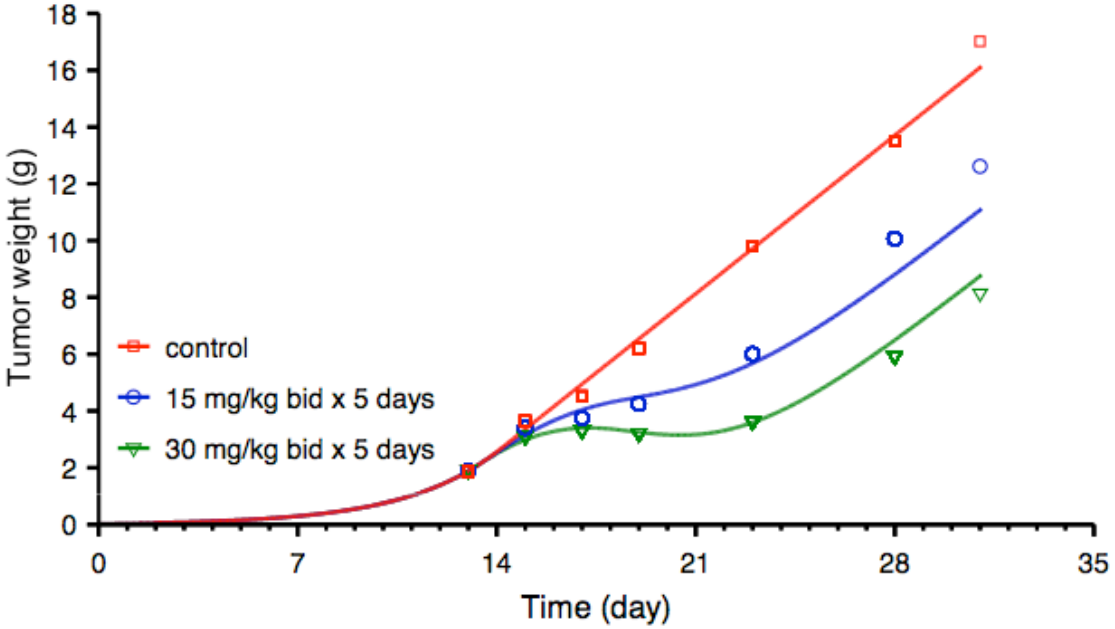
Courtesy **Paolo Magni**

Bolus IV

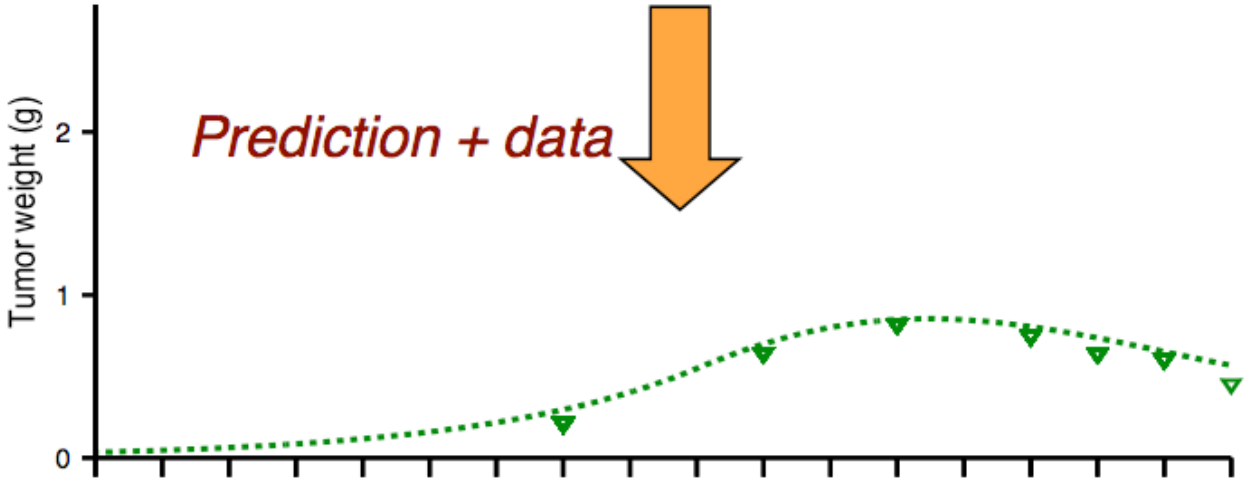


Infusion IV





Prediction + data



Courtesy **Paolo Magni**

Mixed-effect models

- Model complexity is given by the amount of available data
- Allows to quantify the magnitude of inter-individual variability
- Large panels of tools to assess the quality of the model (quantitative approach)
- Not the best tool to study the underlying complex mechanisms of action

Mixed-effect models

Model parameters — Number of individuals

$$y_{ij} = f(x_{ij},\phi_i) + g(x_{ij},\phi_i)\varepsilon_{ij}, \quad 1 \le i \le N; 1 \le j \le n_i$$

Structural model — Error model

Model parameters $\longrightarrow$ $\phi_i = \mu + \eta_i, \quad \eta_i \sim N(0,\Omega), \quad i = 1,\ldots,N,$

Mean value — Inter-individual variability

Full set of parameters $\longrightarrow$ $\theta = (\mu,\Omega,\sigma^2)$

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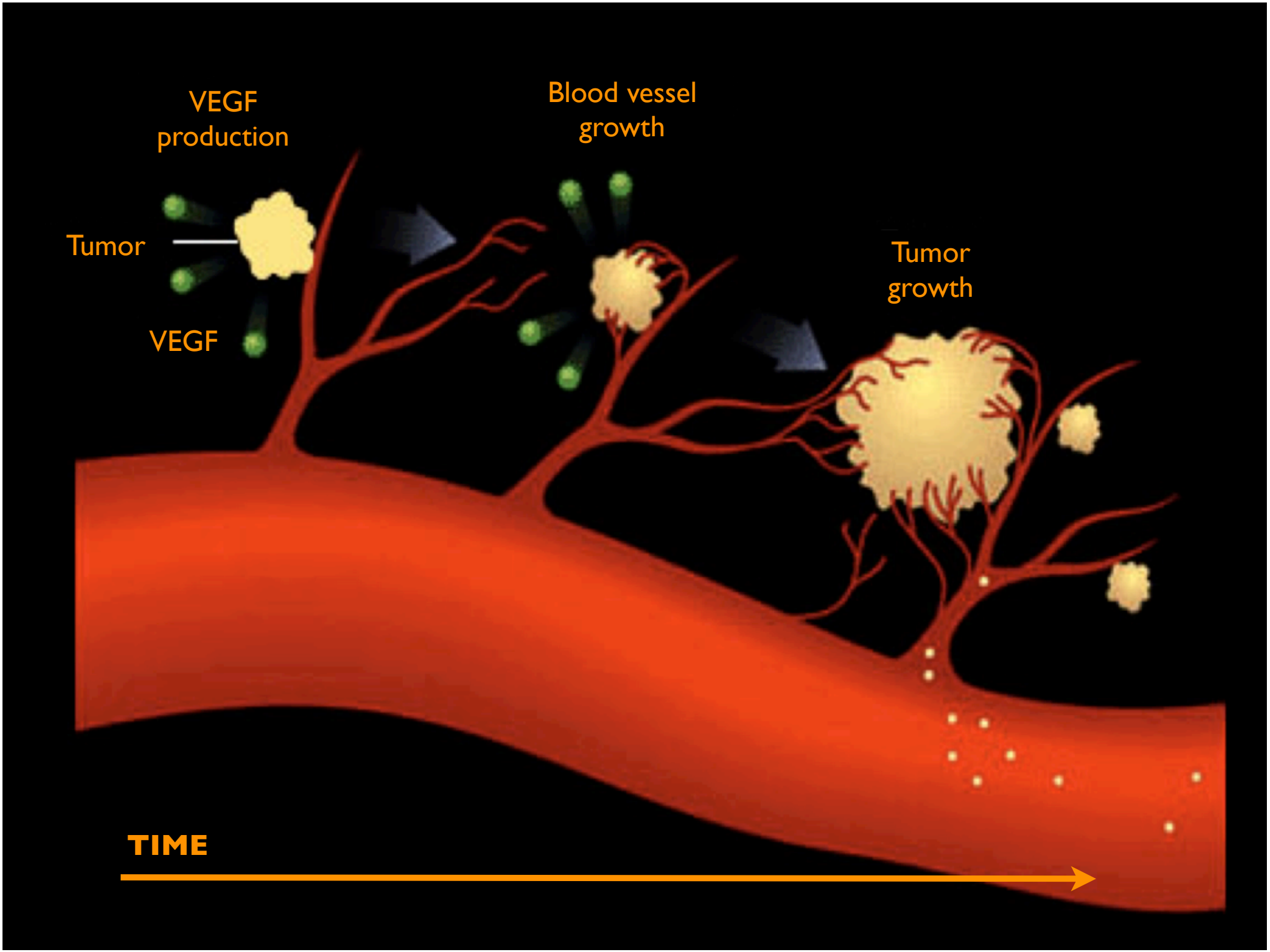
Study case

MODELING THE PROCESS OF ANGIOGENESIS

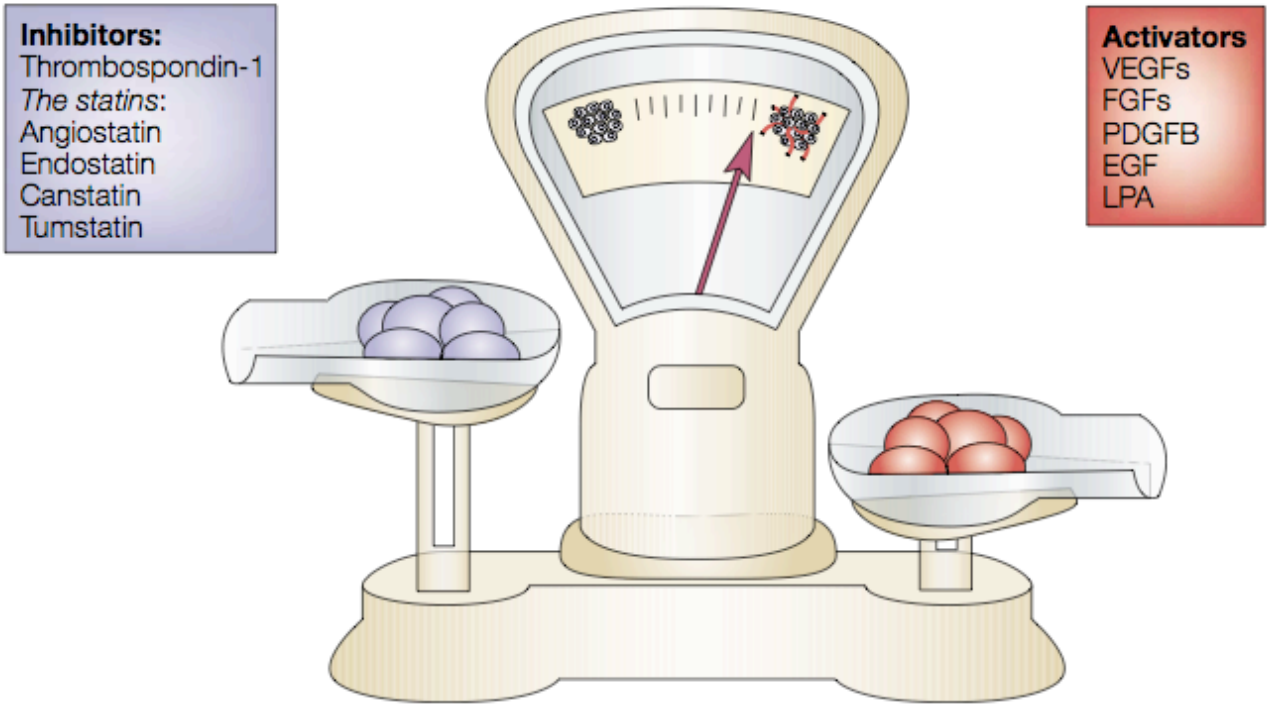

VEGF
production
Blood vessel
growth
Tumor
Tumor
growth
VEGF
TIME

Tumor angiogenesis

- A key process in tumor growth and development proposed by Judah Folkman from Harvard Medical School, since 1970:
  - "*for tumors to develop in size and metastatic potential they must make an* ***angiogenic switch*** *through perturbing the local balance of proangiogenic and antiangiogenic factors*"

Folkman J. **Role of angiogenesis in tumour growth and metastasis**. Semin Oncol 2002

Angiogenic switch



Bergers G and Benjamin LE. **Tumorigenesis and the angiogenic switch**. Nat Rev Cancer 2003

Rational for drug development

- Tumors could be controlled by cutting of their blood supply
- This can be done by:
  - Inhibition of proangiogenic factors
  - Stimulation of endogeneous inhibitors
- Nowadays, around 10 compounds approved by the FDA

Kerbel R and Folkman J. **Clinical translation of angiogenesis inhibitors** . Nat Rev Cancer 2002

The lessons

- High doses are required to destroy the whole vasculature
- High doses may be associated with toxicity profiles
  - FDA approved Avastin for small doses due to cardiac toxicities

Clinical benefit

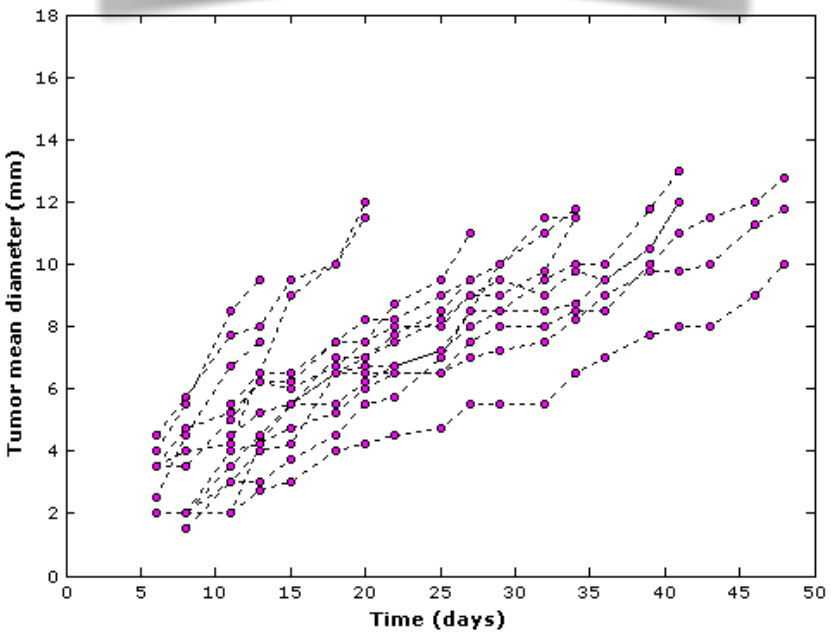
- When used alone, the clinical benefits of antiangiogenic drugs is small
- The combination with chemotherapy and radiotherapy can increase lifespan on average by 2 to 5 months in colorectal cancer, lung cancer, kidney cancer and GIST

Open questions

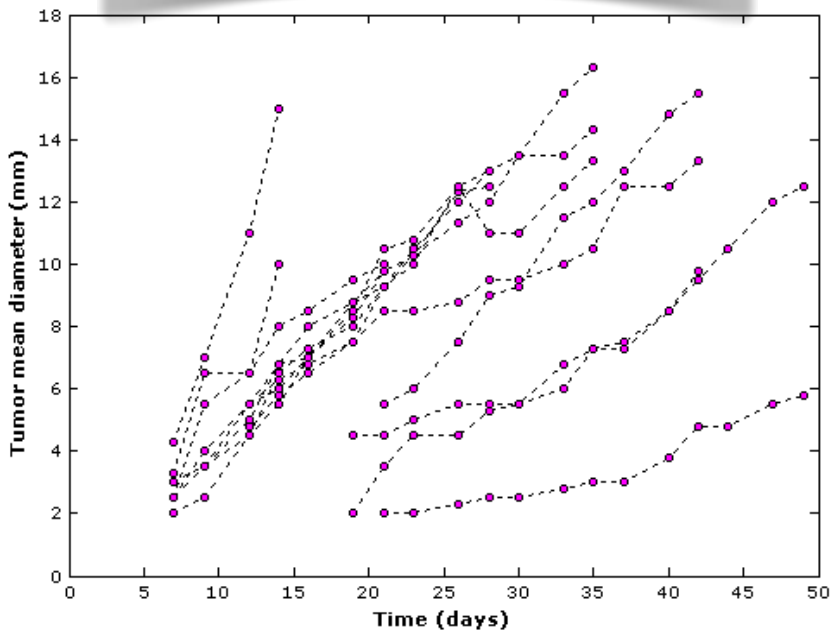
- How long does the window of normalization last?
- When does it open and when does it end?
- How does it link with drug doses and schedules?
- How can we use this knowledge to combine antiangiogenic drugs with conventional therapies

Experimental data

Mean diameter vs time for **HT29** xenografted mice



Mean diameter vs time for **HCT116** xenografted mice



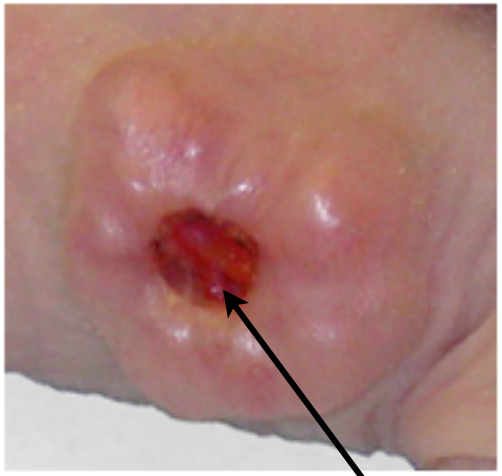
Ribba et al. **A model of vascular tumour growth in mice combining longitudinal tumour size with histological biomarkers.** Eur J Cancer 2010

Histological data

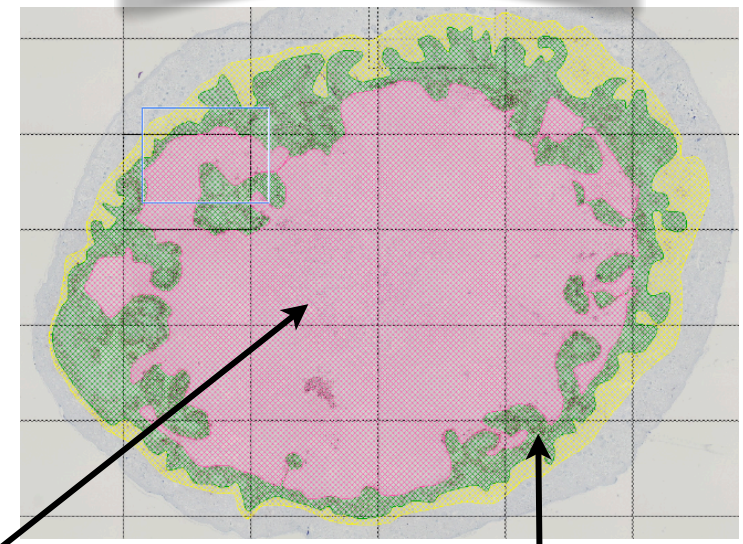
- Hypoxic tissue percentage was assessed using the antibody anti-CA IX, a stable protein whose transcription is induced by HIF
- Necrotic tissue percentage was assessed by staining the same slice with Hematoxylin
- A microscope imaging station with software Histolab was used to quantify the corresponding areas

Histological data

Typical view of tumor shape at day 35



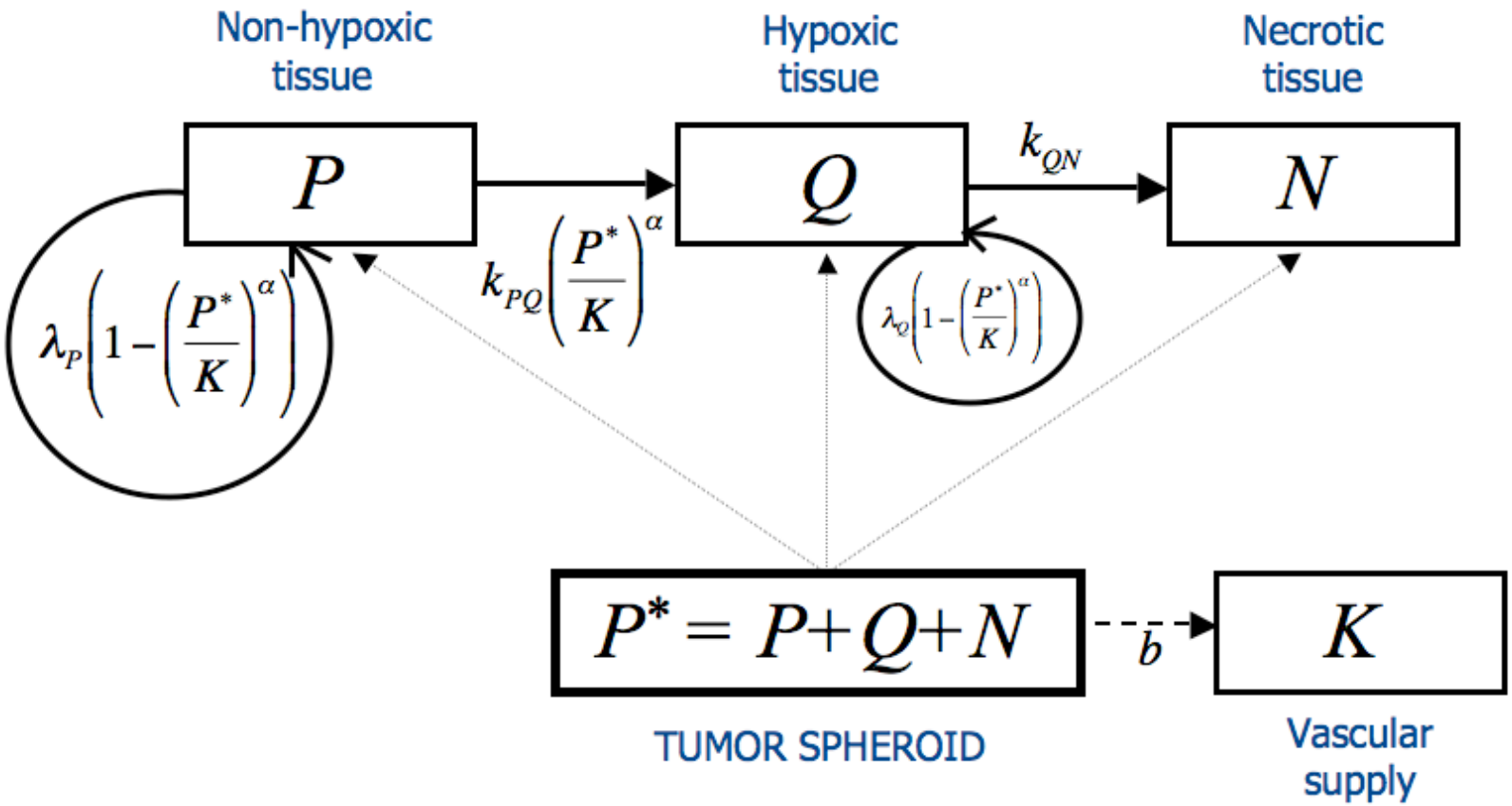
Typical slice view from the imaging station



Necrotic core (staining with Hematoxylin)

Hypoxic tissue (green staining with anti-CAIX)

Model schematic view



Model equations

Non-hypoxic tissue

Hypoxic tissue

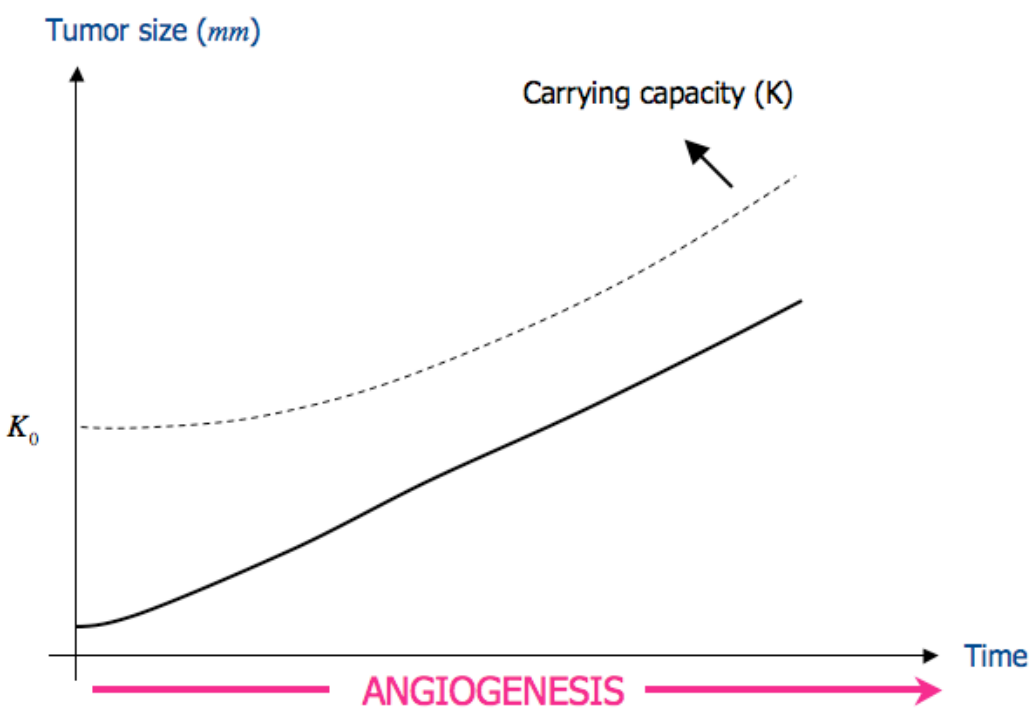
Necrotic tissue

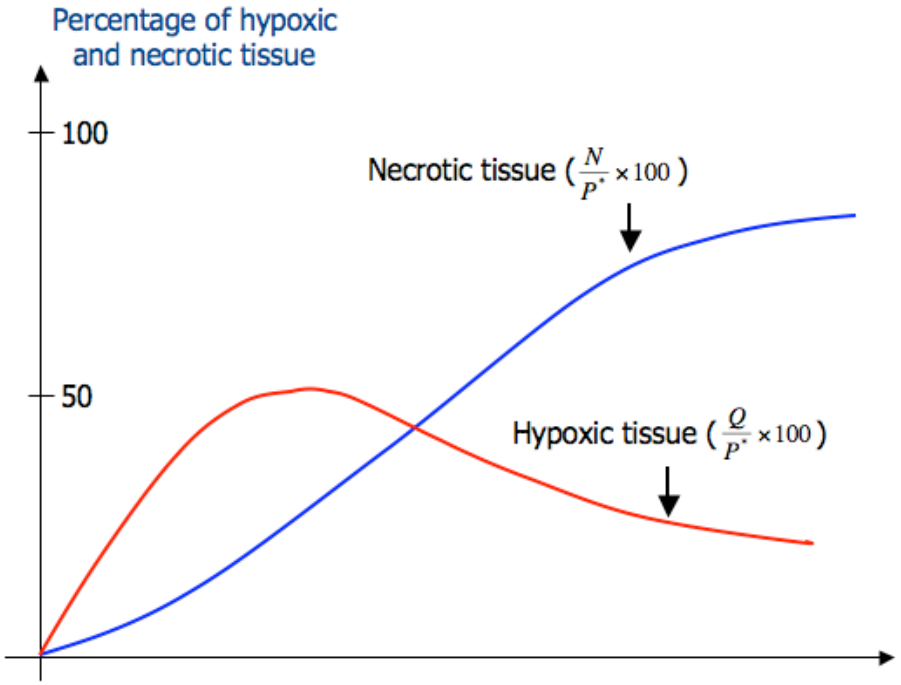
Carrying capacity

Tumor spheroid

$$
\begin{cases}
\dfrac{dP}{dt} = \lambda_P P\left(1 - s^{\alpha}\right) - k_{PQ} P s^{\alpha}, \quad P(t=0) = P_0 \\
\dfrac{dQ}{dt} = k_{PQ} P s^{\alpha} + \lambda_Q Q\left(1 - s^{\alpha}\right) - k_{QN} Q, \quad Q(t=0) = 0 \\
\dfrac{dN}{dt} = k_{QN} Q, \quad N(t=0) = 0 \\
\dfrac{dK}{dt} = b P^{*}, \quad K(t=0) = K_0 \\
P^{*} = P + Q + N \quad \text{and} \quad s = \dfrac{P^{*}}{K}
\end{cases}
$$

Basic simulations

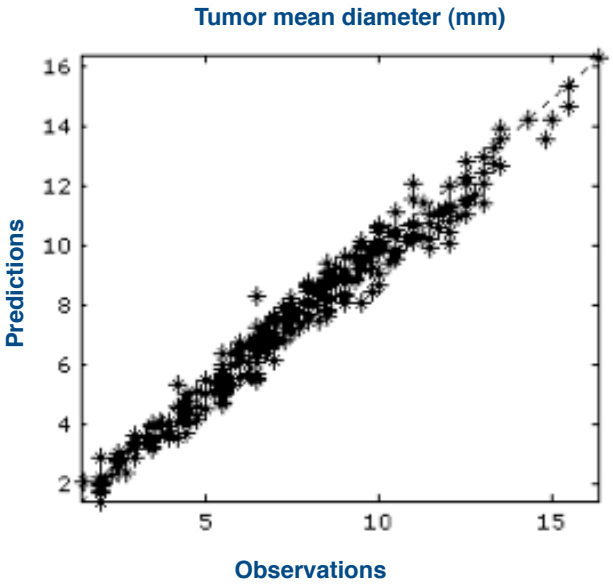


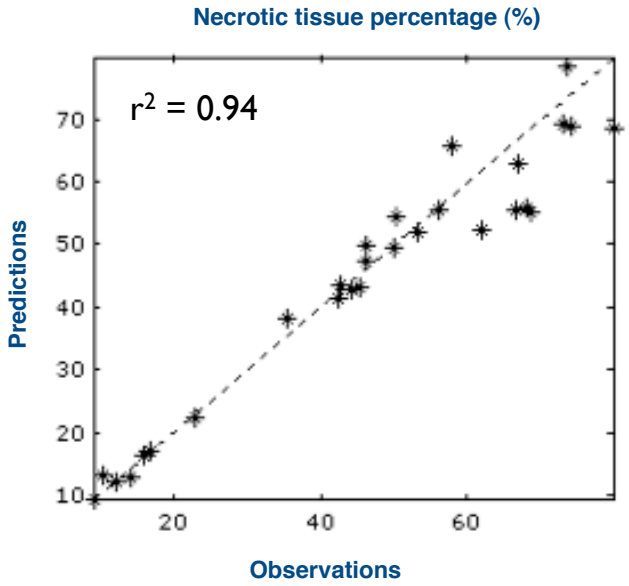


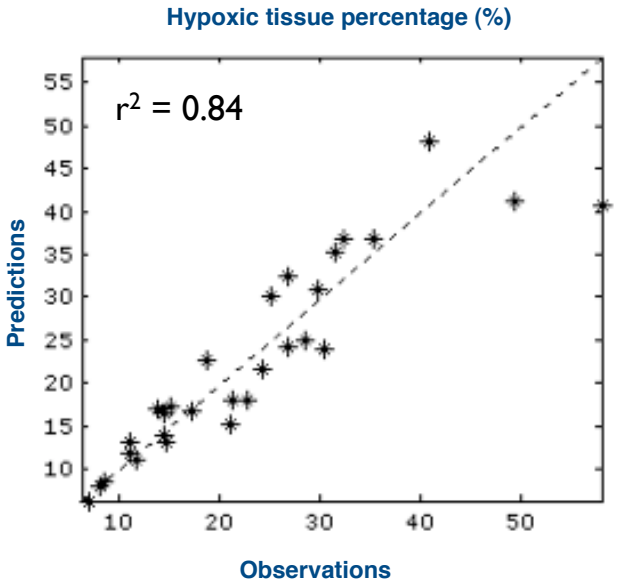
Parameter estimates

Parameter (Unit)	Description	Mean value (SE %)	IAV (SE %)	Shrinkage (%)
$P_0\,(mm)$	Initial tumor size	0.32 (25)	99 (8)	6
$K_0\,(mm)$	Initial carrying capacity	10.4 (58)	52 (20)	2
$\lambda_P\,(d^{-1})$	Growth rate for the non-hypoxic	1.24 (11)	62 (12)	4
$k_{PQ}\,(d^{-1})$	Transfer rate from non-hypoxic to hypoxic tissue compartment	0.06 (12)	46 (35)	3
$\lambda_Q\,(d^{-1})$	Growth rate for the hypoxic tissue	1.43 (20)	65 (18)	1
$k_{QN}\,(d^{-1})$	Transfer rate from hypoxic to necrotic tissue compartment	0.07 (10)	61 (14)	
$b\,(d^{-1})$	Rate of increase of carrying capacity	0.03 (30)	95 (11)	6

Model evaluation







Ribba et al. **A model of vascular tumour growth in mice combining longitudinal tumour size with histological biomarkers.** Eur J Cancer 2010

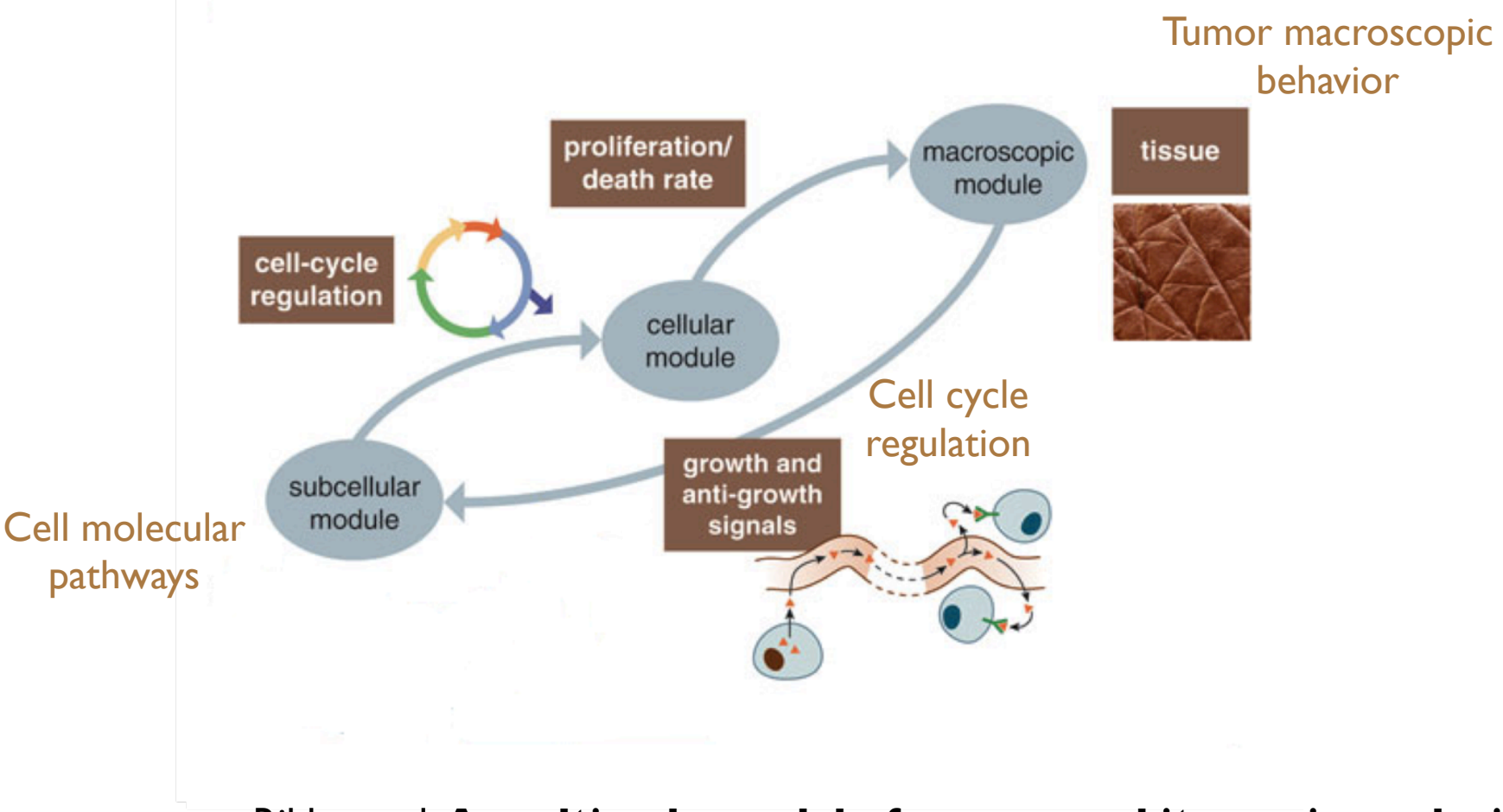
What next...

Towards multiscale and complex models

New drugs

- Recently, development of innovative drugs targeting complex molecular processes involved in tumor growth
- Needs for more complex models integrating such processes
- Needs for complex models to predict the effect of a change in angiogenic factors on the whole tumor system
- We wish to couple PK/PD models to systems biology-like models

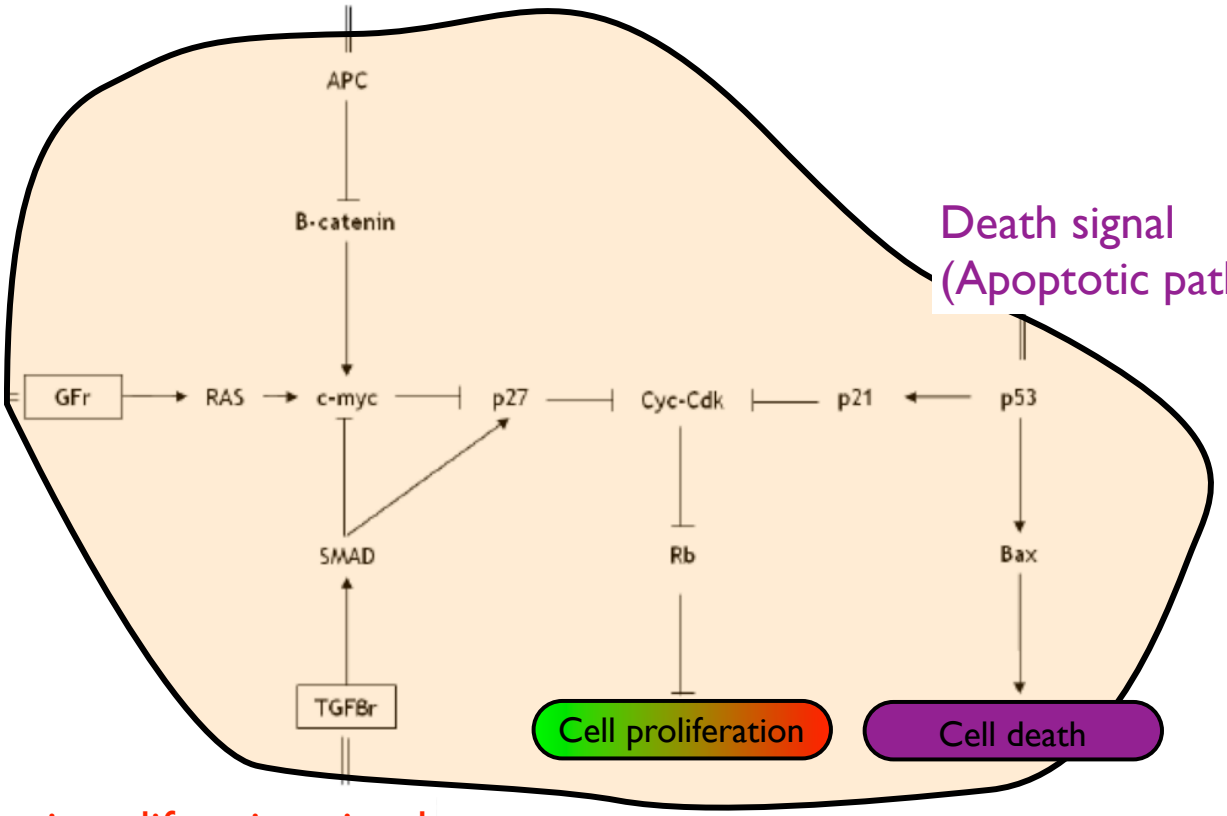
Multiscale approach



Ribba et al. **A multiscale model of cancer, and its use in analyzing irradiation therapies.** Theor Biol Med Model 2006

Cell level

Anti-proliferation signal
(APC pathway - sensitive to overpopulation)



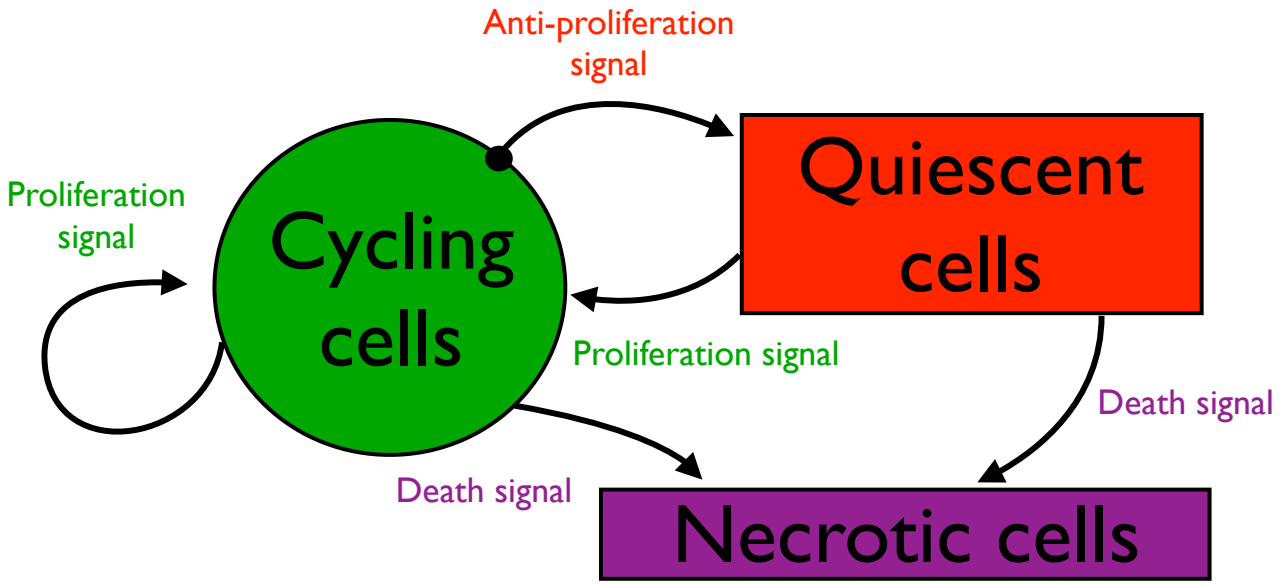
Death signal
(Apoptotic pathway)

Proliferation signal
(MAPK pathway)

Anti-proliferation signal
(TGFβ pathway - sensitive to hypoxia)

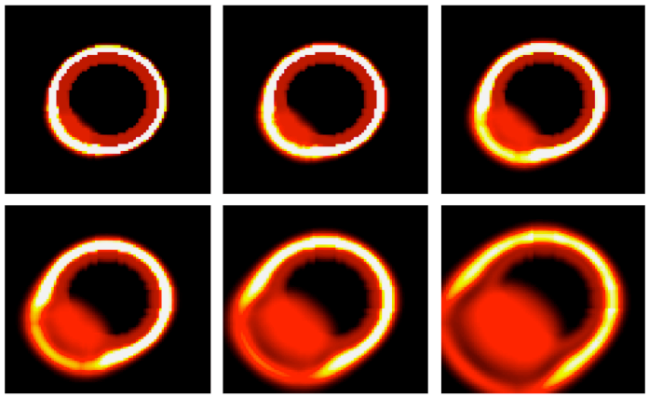
Tissue level

- Describe density of cells in different states (proliferating, hypoxic, necrotic)
- Transitions are function of the outputs of the molecular model

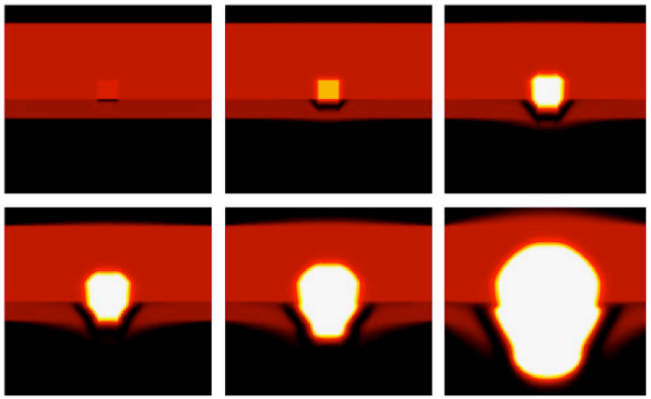


Application

- Process of membrane degradation and invasion of surrounding tissues



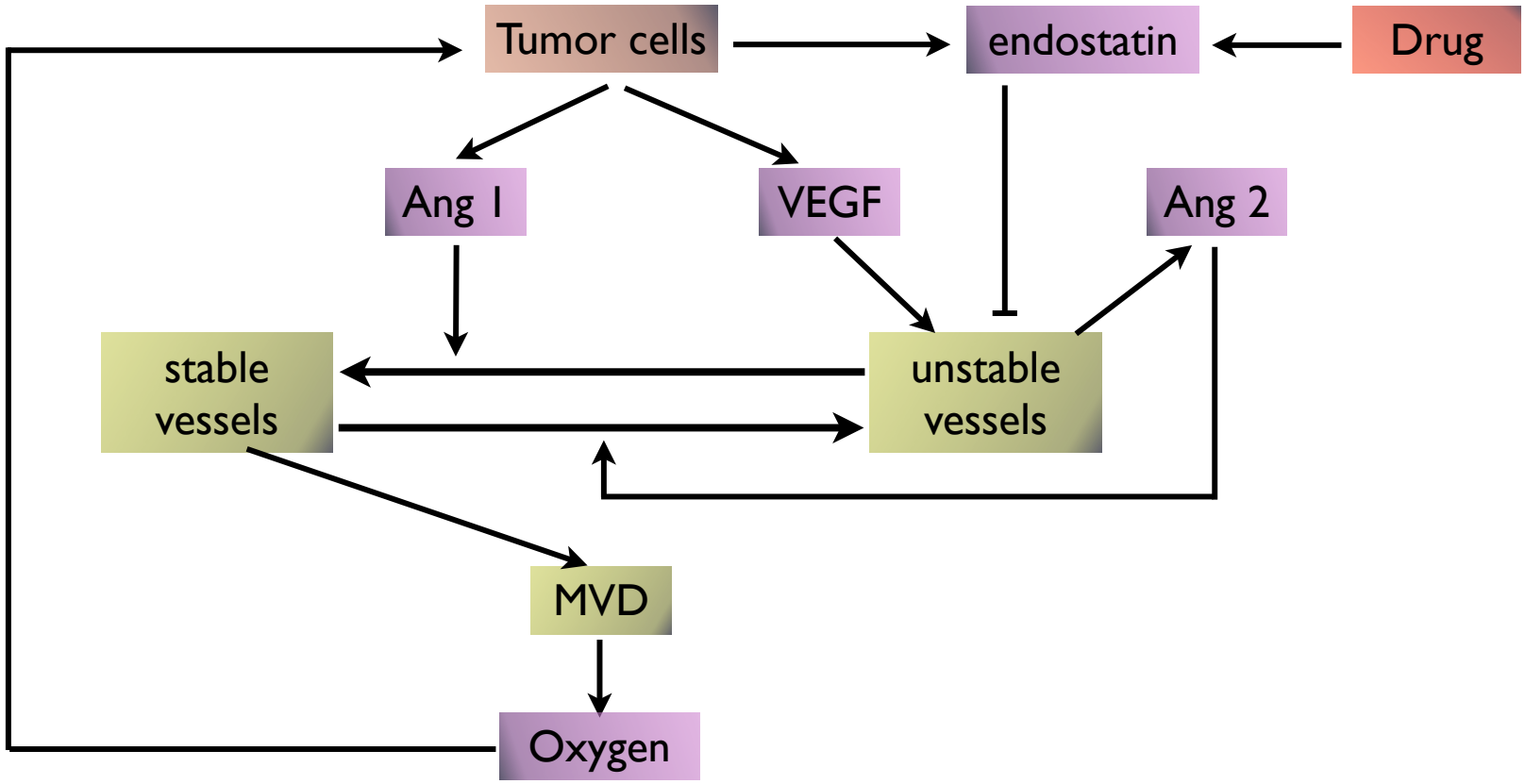
Simulation: Ductal carcinoma *in situ*



Simulation: Invasion of epithelial layer

Ribba et al. **A model of avascular tumor growth to investigate the benefit of anti-invasive agents.** J Theor Biol 2006

Modeling angiogenesis



Billy et al. **A multiscale model of angiogenesis and its use in investigating the efficacy of a new cancer treatment strategy.** J Theor Biol 2009

Main issues

- Multiscale models can integrate a large number of equations
- How to correctly balance *a-priori* information and data-driven knowledge?
- How to efficiently include *a-priori* information?
  - ressource sharing and re-use throughout the community
- How to assess validation in these models?
- How to jump from one scale to the other?

Conclusions

- PK/PD models are powerful tools for drug development
  - mainly because they are simple
- Integrating complex biological network models is the next step
- Needs for new standard and validation methods