Institute of Natural Sciences, SJTU

Winter School on "Mathematical Models of Tumour and Disease"

From single-cell molecular to cell-populational phenotypically structured models to optimise cancer therapeutics

I. Models of cancer growth and therapy

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IUC INSTITUT UNIVERSITAIRE DE CANCÉROLOGIE FACULTÉ DE MÉDECINE PIERRE & MARIE CURIE

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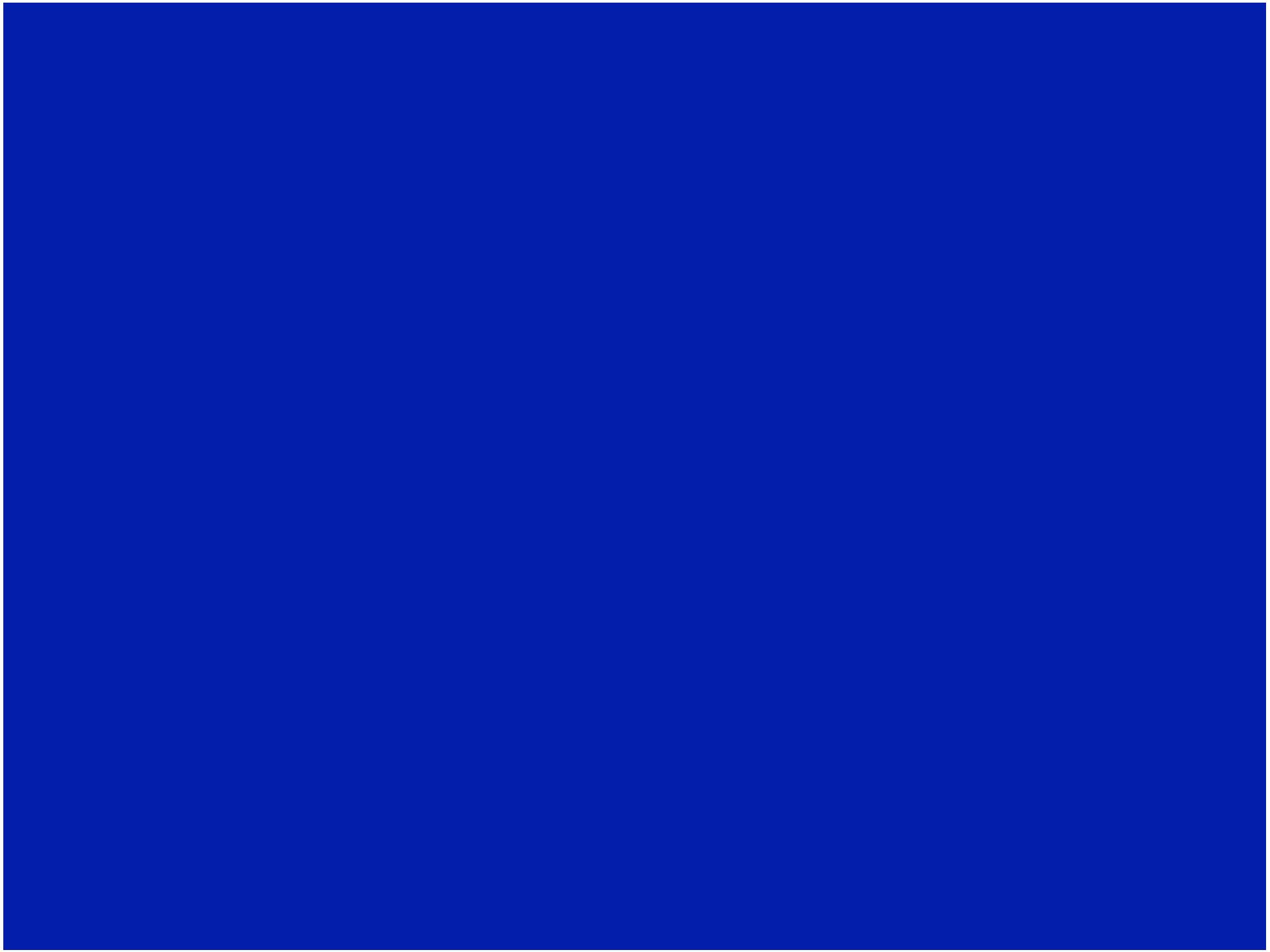
Mamba MODELLING AND ANALYSIS FOR MEDICAL AND BIOLOGICAL APPLICATIONS



A general framework to optimise cancer therapeutics: designing mathematical methods along 3 axes

- Modelling the behaviour of growing cell populations on which anticancer drugs act (the targeted cell populations): proliferating tumour and healthy cell populations, including representing functional (not necessarily molecular) targets for pharmacological control

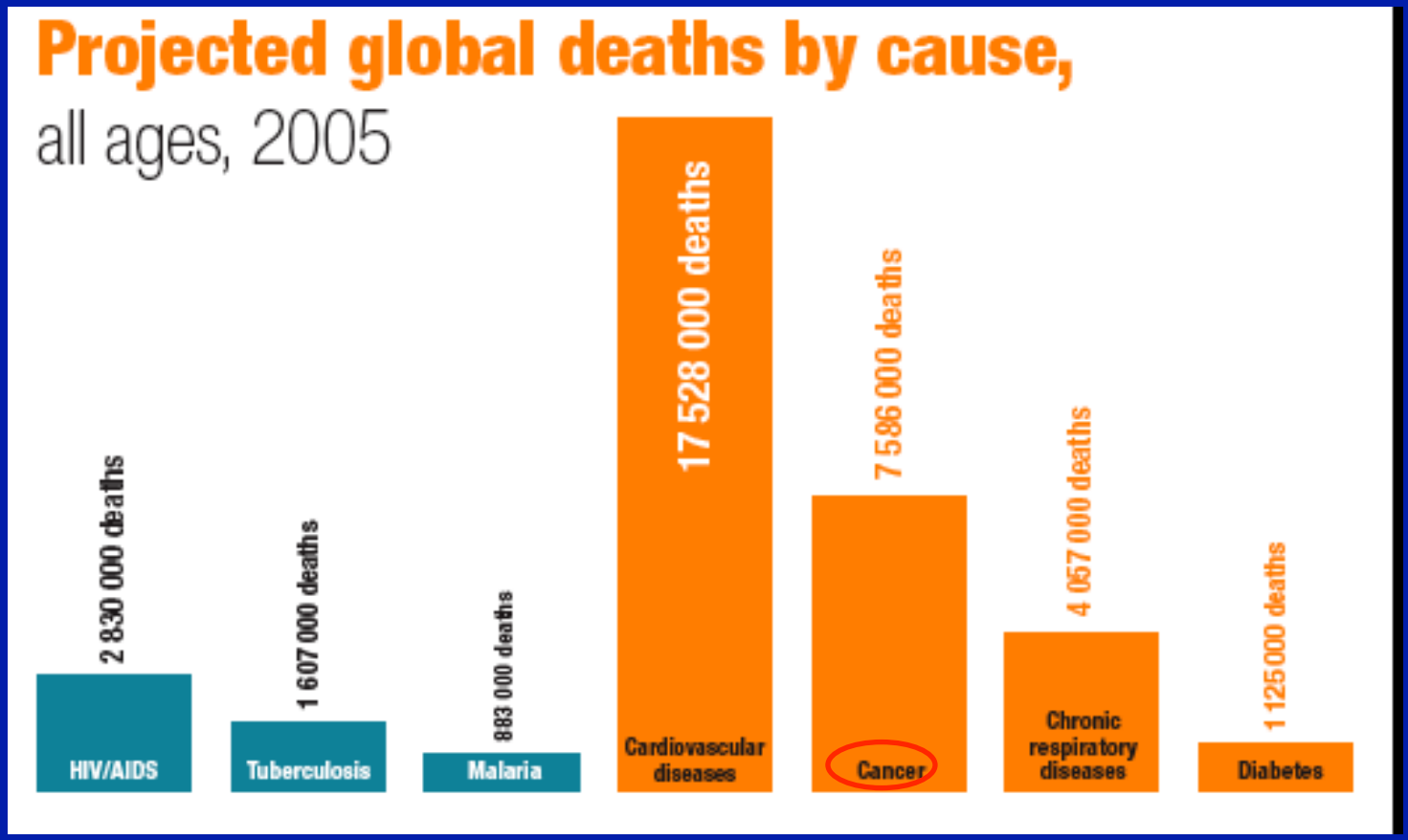
- Modelling the external control system, i.e., fate of drugs in the organism and their effects on healthy and tumour cell populations either by molecular PK-PD (pharmacokinetics-pharmacodynamics) models or merely at the level of their functional targets, by their effects on proliferation, death, differentiation

- Optimising therapeutic controls: dynamically (=time-varying) optimised control of theoretical drug delivery flows representing time-dependent objectives and constraints, making use of known or hypothesised differences between cancer and healthy cell populations

Choosing the constraint to be represented determines the model of proliferation used to optimise drug delivery, aiming to avoid the two main pitfalls of pharmacotherapy:

- *Toxicity issues.* Limiting toxic side effects to preserve healthy cell populations leads to representing proliferating cell populations by ordinary differential equations, or by age-structured models: physiologically structured partial differential equations
- *Drug resistance issues.* Limiting emergence of drug-resistant cell subpopulations in tumour tissues leads to using (evolutionary) phenotypic trait-structured proliferation: physiologically structured evolutionary integro-differential equations
- In fact, one should consider the two issues simultaneously, i.e., two similarly structured cell populations, healthy and cancer, with different characteristics w.r.t. to drug effects and to evolution towards resistance: phenotypic stability of healthy cell populations vs. plasticity of cancer cell populations

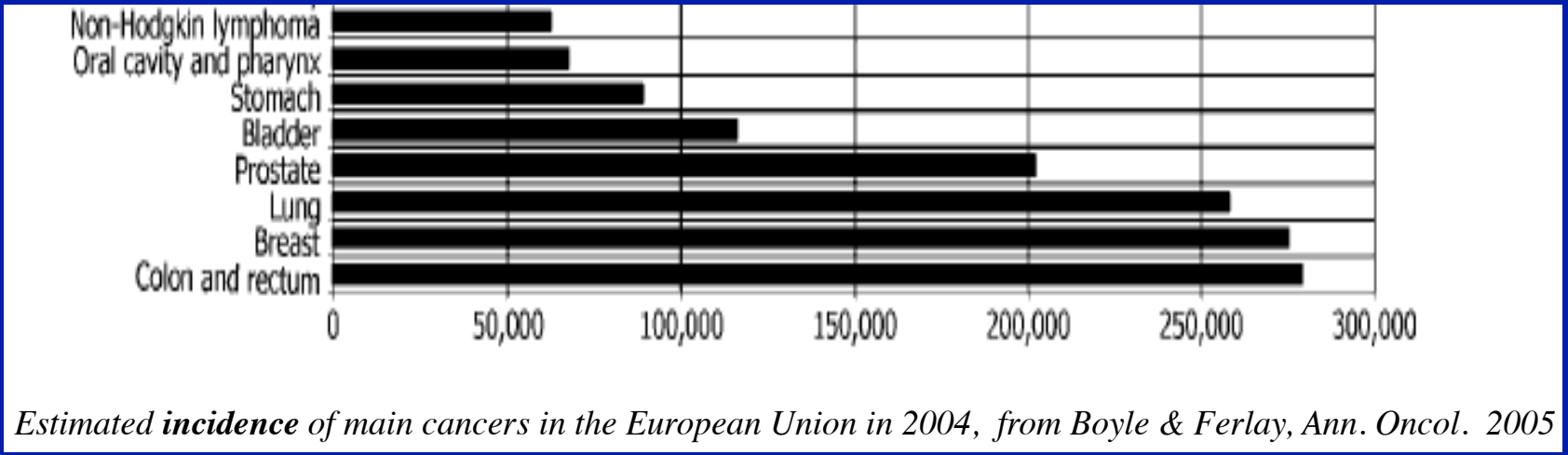
Relative importance of cancer as one of the major killer *chronic* diseases worldwide



WHO source (2005): http://www.who.int/chp/chronic_disease_report/full_report.pdf

Cancer, a major public health problem in Europe

2 major killers in Western Europe:
Cardio-vascular diseases: 35% of deaths by disease, and Cancer: 25%
(precise data according to zones and countries: http://www.euro.who.int)

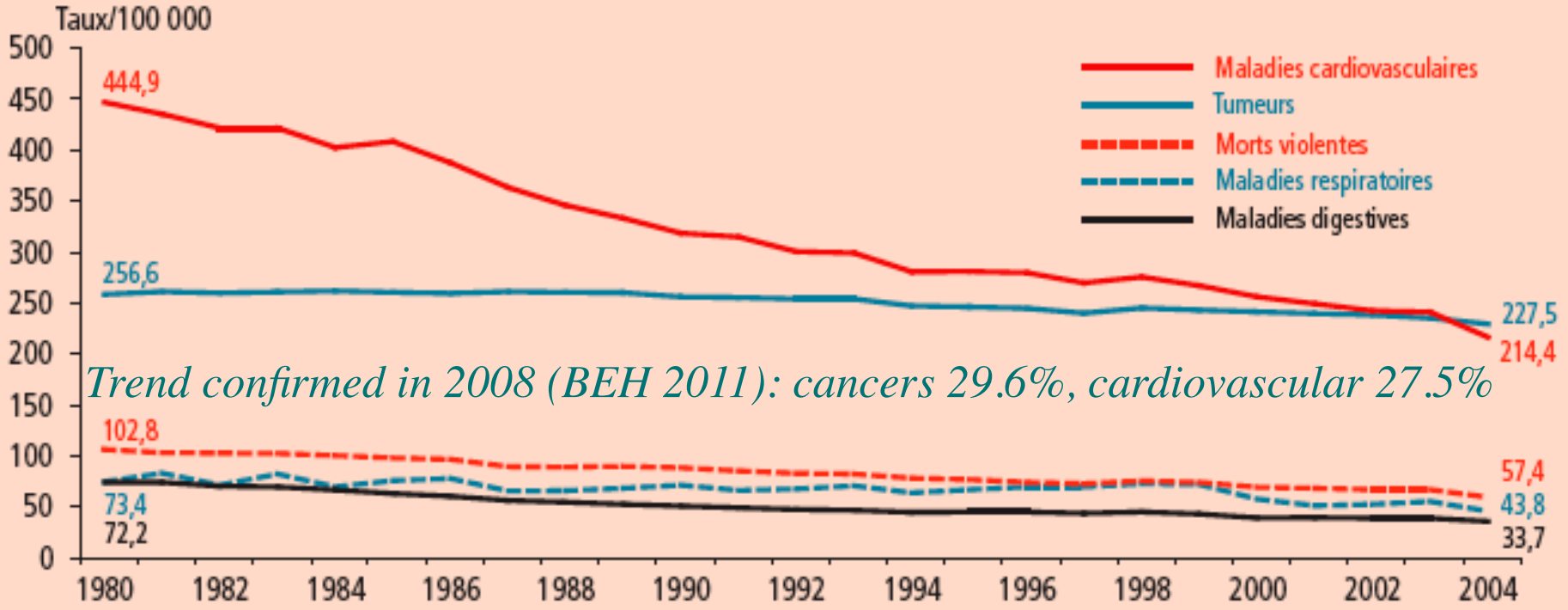


*Estimated **incidence** of main cancers in the European Union in 2004, from Boyle & Ferlay, Ann. Oncol. 2005*

Background: basic facts about cancer

In France, cancer (now 1st) and cardiovascular diseases (2nd) are by far the 2 major killers among *all diseases*

Figure 2 **Evolution des taux* de décès par grande catégorie de causes de décès, 1980-2004, France métropolitaine, deux sexes / *Figure 2 Trends in death rates by main category of causes of death, 1980-2004, Metropolitan France, both sexes***



Trend confirmed in 2008 (BEH 2011): cancers 29.6%, cardiovascular 27.5%

* Taux de décès standardisés pour 100 000.

Bulletin Épidémiologique Hebdomadaire (BEH) de l'INVS, 18/09/2007

(*Bulletin available online*: http://www.invs.sante.fr/beh/2007/35_36/index.htm)

Background: basic facts about cancer

The same trend (Cancer 1st) is also true in the USA

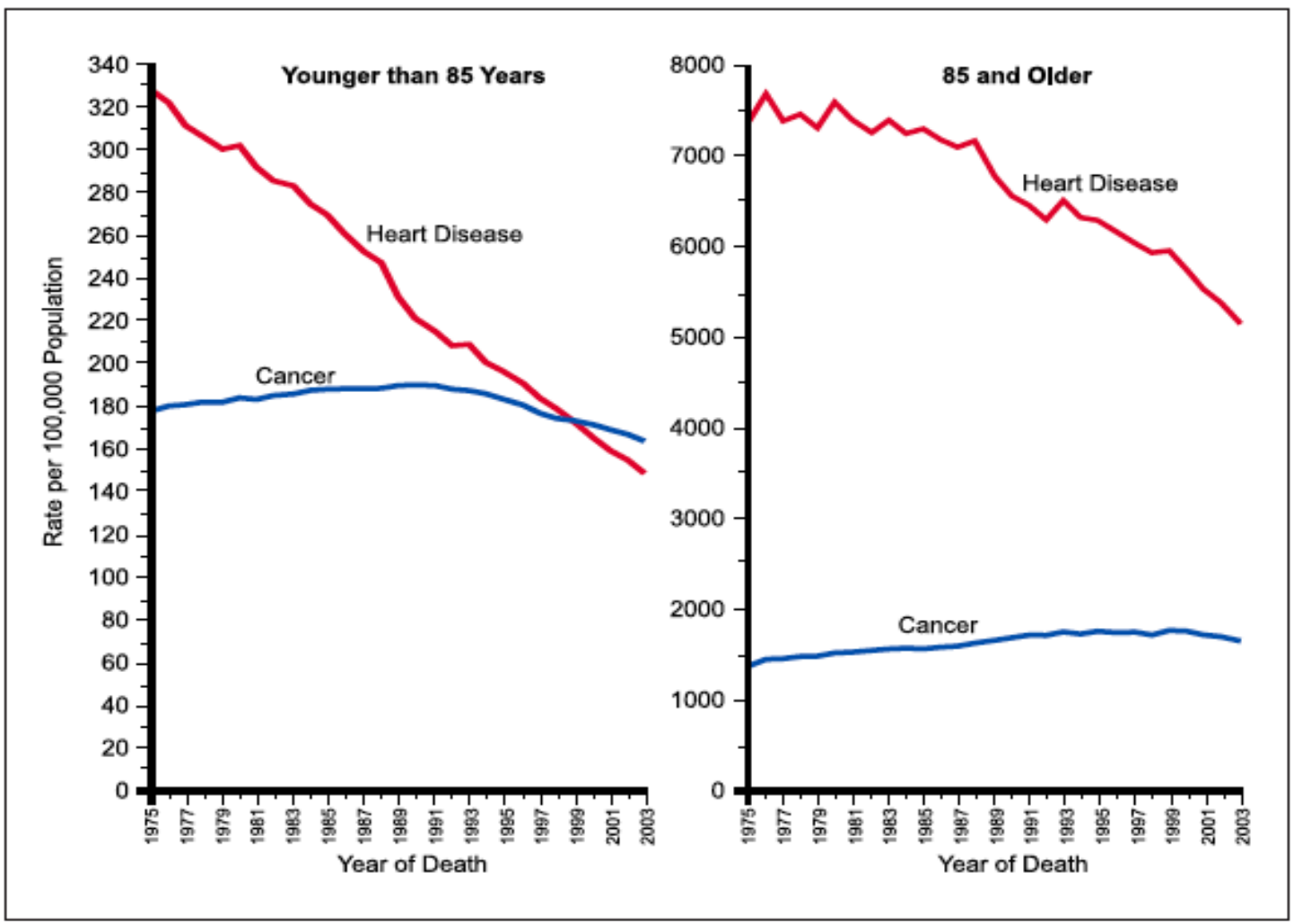


FIGURE 6 Death Rates* From Cancer and Heart Disease for Ages Younger Than 85 and 85 and Older.
*Rates are age-adjusted to the 2000 US standard population.
Source: US Mortality Public Use Data Tapes, 1960 to 2003, National Center for Health Statistics, Centers for Disease Control and Prevention, 2006.

(from Jemal et al., *CA Cancer J Clin 2007)*

Background: basic facts about cancer

Persistence of a very slow decrease in cancer mortality in the US

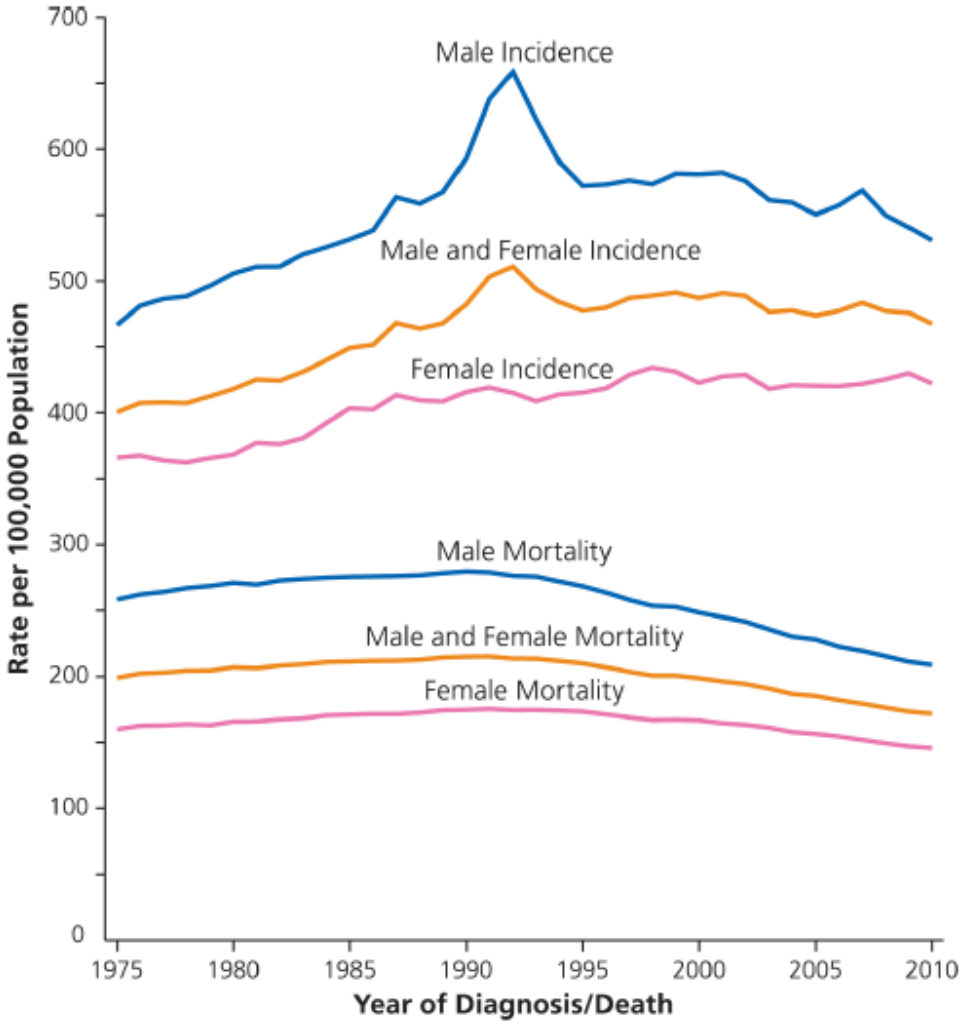


FIGURE 2. Trends in Cancer Incidence and Death Rates by Sex, United States, 1975 to 2010.
Rates are age adjusted to the 2000 US standard population. Incidence rates are adjusted for delays in reporting.

From Siegel et al., Cancer statistics 2014 CA Cancer J Clin 2014

Tissues that may evolve toward malignancy

…are the tissues where cells are committed to fast proliferation
(fast renewing tissues):

- epithelial cells+++, i.e., cells belonging to those tissues which cover the free surfaces of the body (namely *epithelia*): gut (colorectal cancer), lung, cervix, glandular coverings (breast, prostate), skin,…

- liver cells in situations where the liver is called for renewal (e.g., surgery) or, in pathology, hepatocellular carcinoma

- cells belonging to the different blood lineages, daily produced in the bone marrow: liquid tumours, or malignant haemopathies

- others (rare: gliomas, sarcomas, neuroblastomas, dysembryomas…)

Natural history of cancers: from genes to bedside

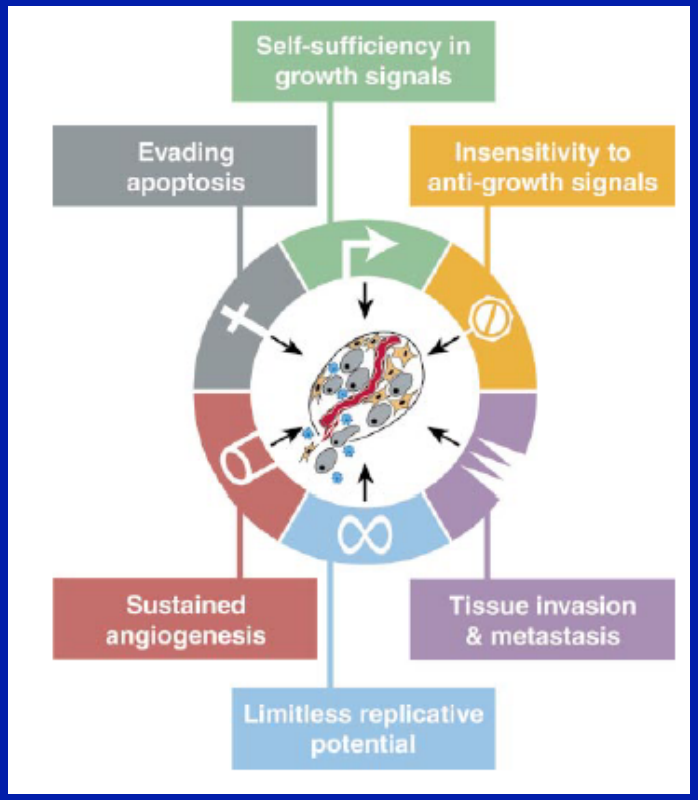
Gene mutations: an evolutionary process which may give rise to abnormal DNA when a cell duplicates its genome, due to defects in tumour suppressor or DNA repair (BER, NER) genes *(Yashiro et al. Canc Res. 2001; Gatenby & Vincent, Canc. Res. 2003)*

Resulting genomic instability allows malignant cells to escape control on proliferation at different levels: subcellular, cell, tissue and whole organism:

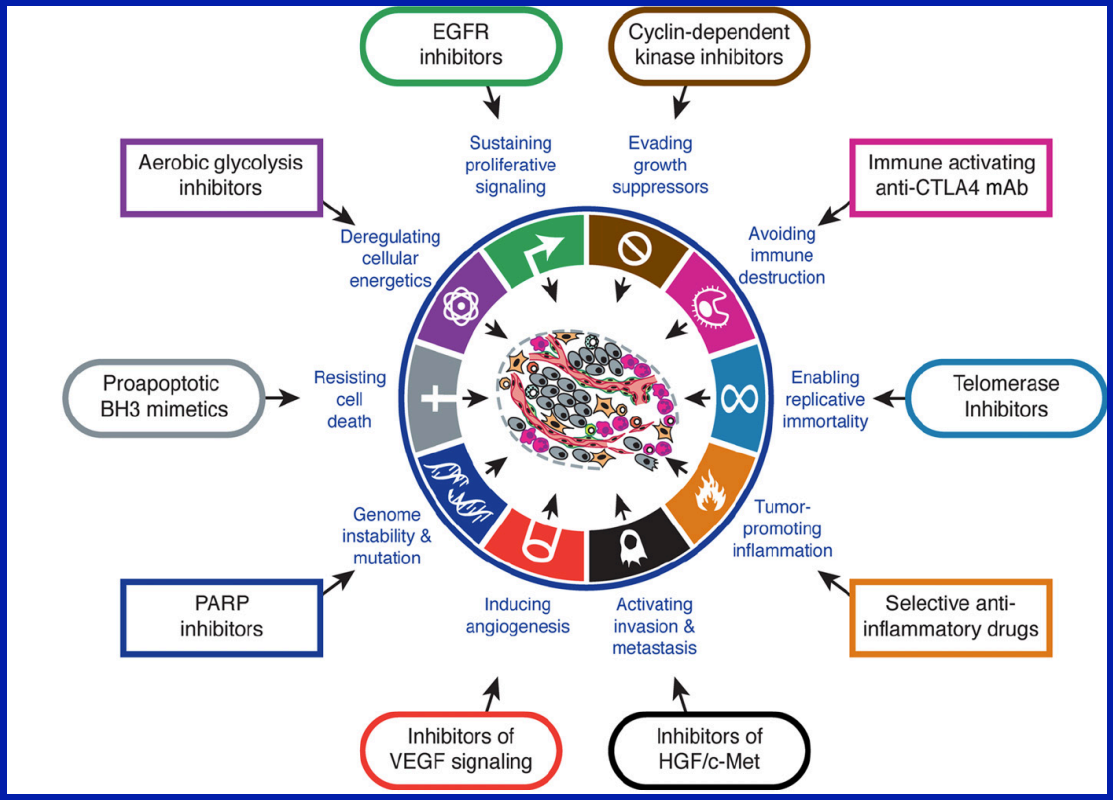
- Control on entry in the cell cycle for quiescent (=non-proliferating) cells
- Control on cell cycle phase transitions and apoptosis for proliferating cells
- Normal inability to use anaerobic glycolysis (selective advantage for cancer cells)
- Contact inhibition by surrounding cells (cell adhesion, cell density pressure)
- Normal inability to stimulate new blood vessels from the vascular neighbourhood
- Normal linking to the extracellular matrix (ECM) fibre network and basal membranes
- Recognition (friend or foe) by the immune system

Cancer invasion is the macroscopic result of breaches in these control mechanisms

Evading proliferation and growth control mechanisms



(Hanahan & Weinberg, Cell 2000)

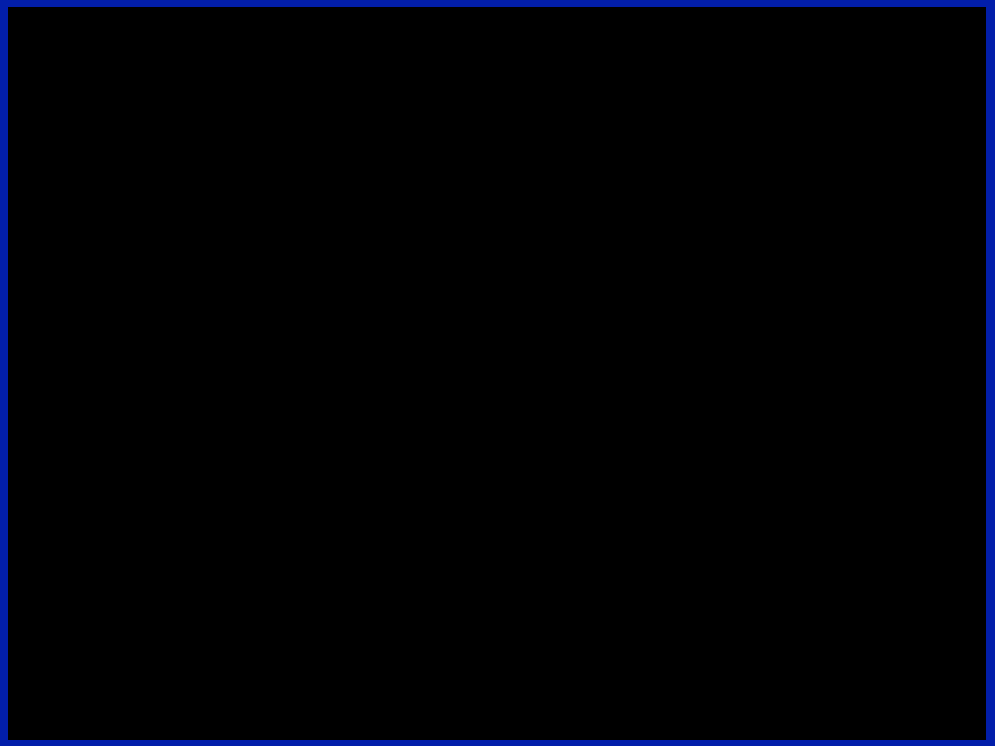


(Hanahan & Weinberg, Cell 2011)

…but just what is cell proliferation?

Background: basic facts about cancer

Cell population growth in proliferating tissues



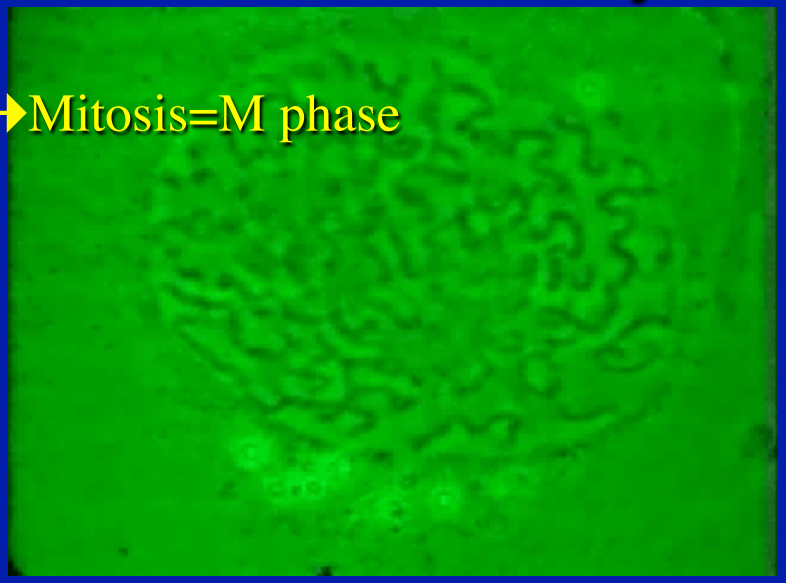
(from Lodish et al., Molecular cell biology, Nov. 2003)

One cell divides in two: a controlled process at cell and tissue levels

Background: basic facts about cancer

At the origin of proliferation: the cell division cycle

S:=DNA synthesis; G_1,G_2:=Gap1,2; M:=mitosis → Mitosis=M phase



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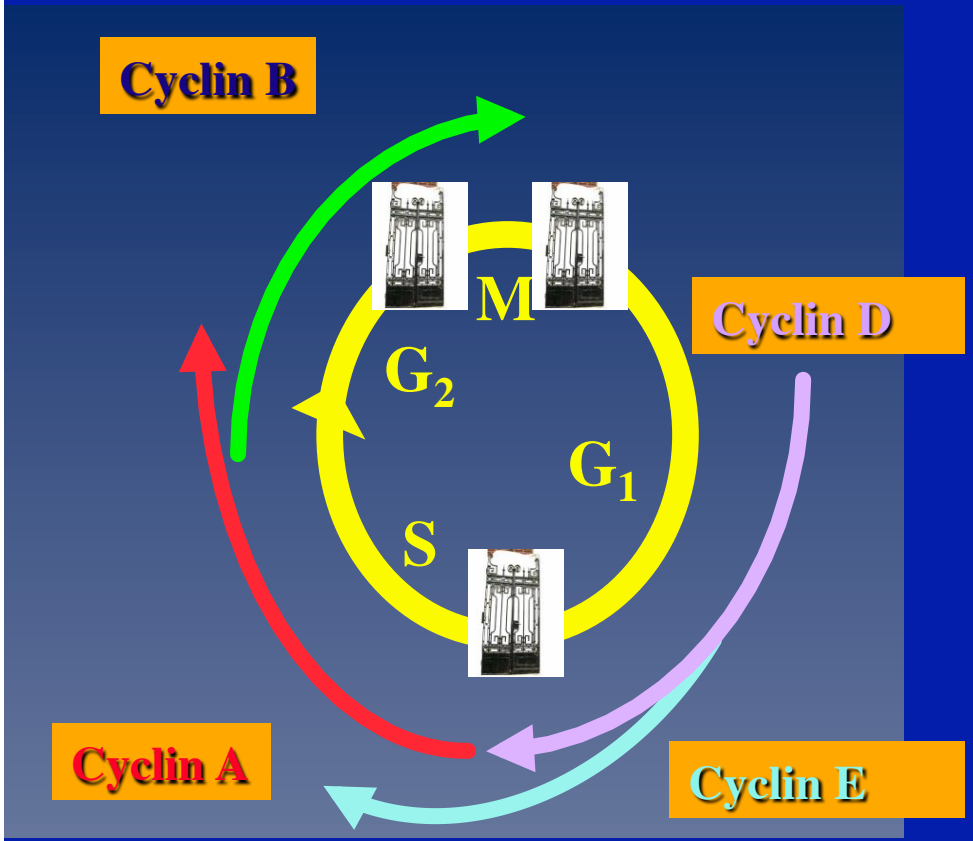


Physiological or therapeutic control exerted on:

- transitions between *cell cycle phases* (G_1/S, G_2/M, M/G_1)
- death rates (apoptosis or necrosis) inside cell cycle phases
- velocity of progression of cell populations in cell cycle phases

Background: basic facts about cancer

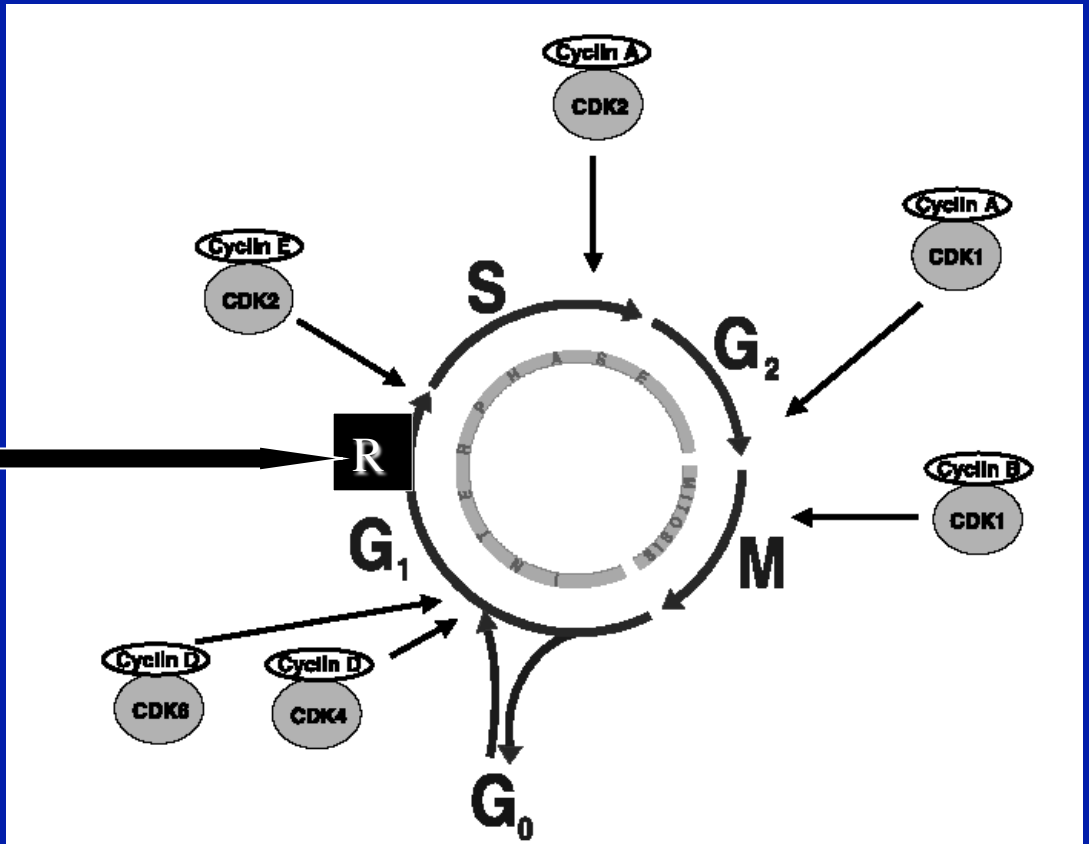
Proliferating and quiescent cells

after R:
mitogen-independent progression through G_1 to S (no way back to G_0)

Restriction point (in late G_1 phase)

(Pardee 1974
Zetterberg & Larsson 1985)

before R:
mitogen-dependent progression through G_1 (possible regression to G_0)



From Vermeulen et al. Cell Prolif. 2003

Most cells do not proliferate physiologically, even in fast renewing tissues (e.g. gut)

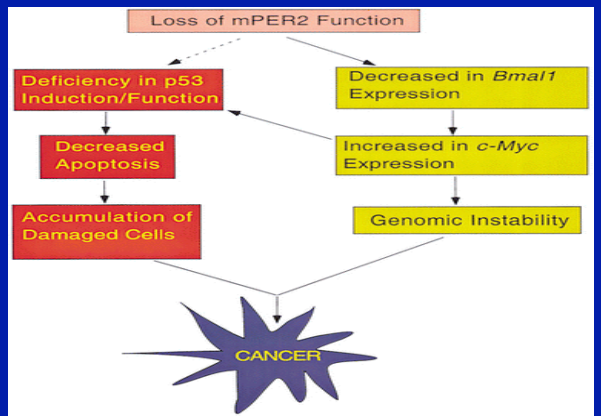
Exchanges between proliferating (G_1SG_2M) and quiescent (G_0) cell compartments are controlled by mitogens and antimitogenic factors in G_1 phase

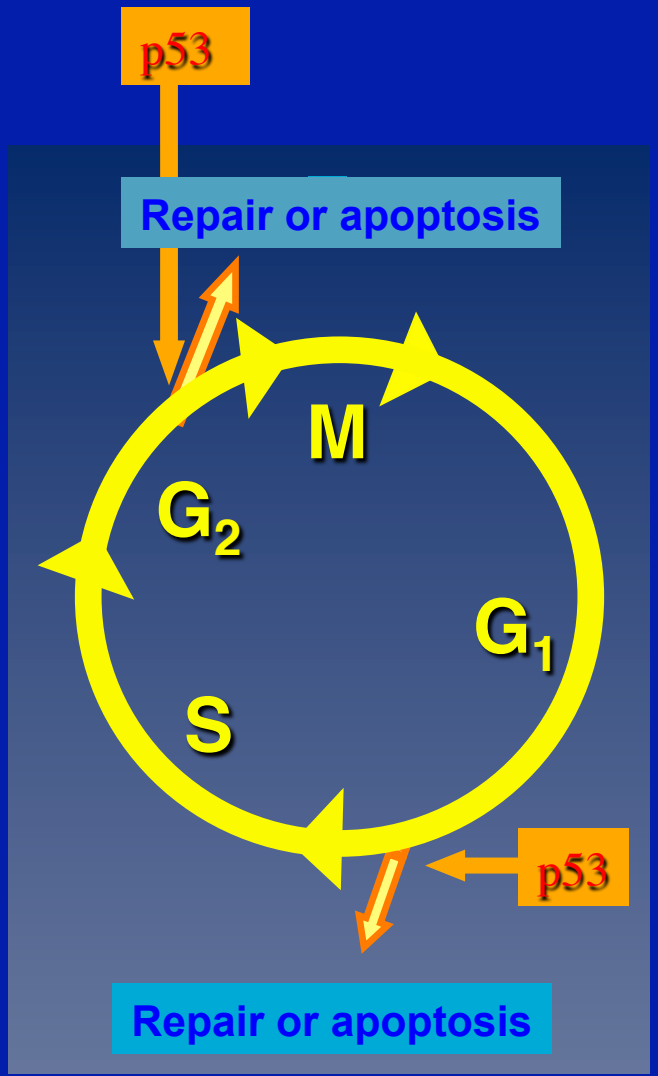
Phase transitions, apoptosis and DNA repair

- Sensor proteins, e.g. p53, detect defects in DNA, arrest the cycle at G_1/S and G_2/M phase transitions to repair damaged fragments, or lead the whole cell toward controlled death = apoptosis

- p53 expression is known to be down-regulated in about 50% of cancers

- Physiological inputs, such as circadian gene PER2, control p53 expression; circadian clock disruptions (*shiftwork*) may result in low p53-induced genomic instability and higher incidence of cancer



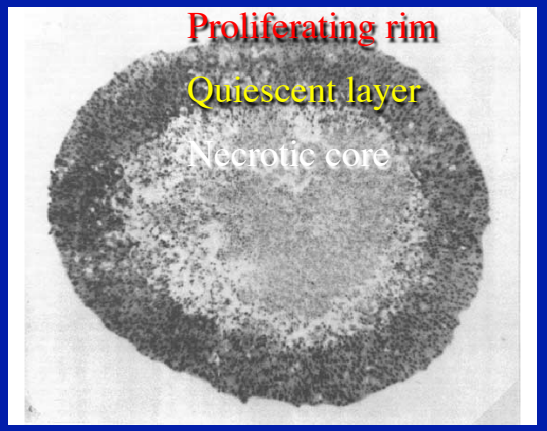


(Fu & Lee, Nature Rev. 2003)

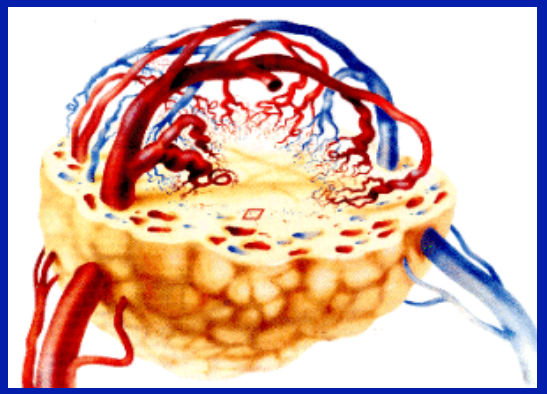
Background: basic facts about cancer

Invasion: local, regional and remote

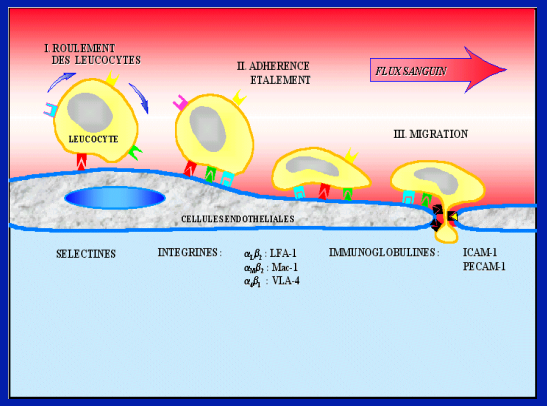
1) Local invasion by tumour cells implies loss of normal cell-cell and cell-ECM (extracellular matrix) contact inhibition of size growth and progression in the cell cycle. ECM (fibronectin) is digested by tumour-secreted matrix degrading enzymes (MDE=PA, MMP) so that tumour cells can move out of it. Until 10^6 cells (1 mm δ) is the tumour in the *avascular stage*.



2) To overcome the limitations of the avascular stage, local tumour growth is enhanced by tumour-secreted endothelial growth factors which call for blood vessel sprouts to bring nutrients and oxygen to the insatiable tumour cells (*angiogenesis*, vasculogenesis)



3) Moving cancer cells can achieve intravasation, i.e., *migration* in blood and lymph vessels (by diapedesis), and extravasation, i.e. evasion from vessels, through vascular walls, to form new colonies in distant tissues. These colonies are called metastases.



(Images thanks to A. Anderson, M. Chaplain, J. Sherratt, and Cl. Verdier)

Interactions with the immune system

Tumours are antigenic, i.e., recognisable as foes by the immune system:

Innate immunity: (non specific)
Cytokines, macrophage-produced molecules to protect intact cells (e.g. interferon)

NK Lymphocytes = cells which sense foe antigens (receptors are modifications of cytoskeleton), migrate into blood and tissues to kill antigenic cells

Adaptive immunity: *B Lymphocytes* produce specific antibodies (immunoglobulins)
(specific: immune memory)

Helper T-Lymphocytes produce cytokines (e.g. interleukins) which boost the immune response

Cytotoxic T-Lymphocytes kill specific antigenic cells

(after P. Lollini, 2005)

I. Mathematical models of healthy and cancer tissue growth

Mathematical models of tumour growth and therapy

A great variety of models, depending on what one intends to describe

- In vivo (tumours) or in vitro (cultured cell colonies) growth? In vivo (diffusion in living organisms) or in vitro (constant concentrations) growth control by drugs?
- Scale of description for the phenomenon of interest: subcellular, cell, tissue or whole organism level? … may depend upon therapeutic description level
- Is space a relevant variable? [Not necessarily!] Must the cell cycle be represented?
- Are there surrounding tissue spatial limitations? Limitations by nutrient supply or other metabolic factors?
- Is loco-regional invasion the main point? Then reaction-diffusion equations (e.g. KPP-Fisher) are widely used, for instance to describe tumour propagation fronts
- Is cell migration to be considered? Then chemotaxis [=chemically induced cell movement] models (e.g. Keller-Segel) have been used

A reference: A. Friedman. 'A hierarchy of cancer models and their mathematical challenges', DCDS-B 2004

Ordinary differential equations

Models of tumour growth 1

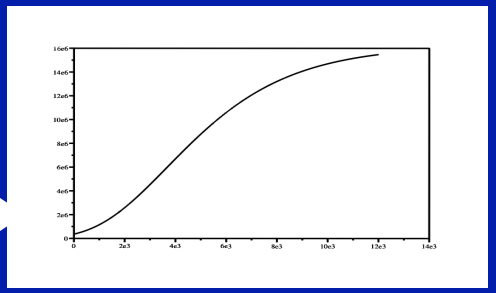
Macroscopic, non-mechanistic models: the simplest ones: exponential, logistic, Gompertz

$$\frac{dx}{dt} = kx \quad (exponential)$$

$$\frac{dx}{dt} = kx(1-x) \quad (logistic)$$

$$\frac{dx}{dt} = kx \ln\left(\frac{x_{max}}{x}\right) \quad (Gompertz)$$

x= tumour weight or volume, proportional to the number of cells, or tumour cell density



Exponential model: relevant for the early stages of tumour growth only

[Logistic and] Gompertz model: represent growth limitations (S-shaped curves with plateau=maximal growth), due to mechanical pressure or nutrient/space scarcity

[Used to describe therapeutic control by adding a drug action term $-\varphi(d, x)$ *on the RHS*]

Models of tumour growth 2: Gompertz revisited

ODE models a) with 2 cell compartments, proliferating and quiescent,
or b) varying the tumour carrying capacity x_{max} in the original Gompertz model

$$\frac{dP}{dt} = [\beta - \mu_p - r_0(N)]P + r_i(N)Q \quad (1)$$

$$\frac{dQ}{dt} = r_0(N)P - [r_i(N) + \mu_q]Q \quad (2)$$

$$N = P + Q, \quad P_0 + Q_0 = 1$$

(Gyllenberg & Webb, Growth, Dev. & Aging 1989; Kozusko & Bajzer, Math BioSci 2003)

Avowed aim: to justify global Gompertz-like growth

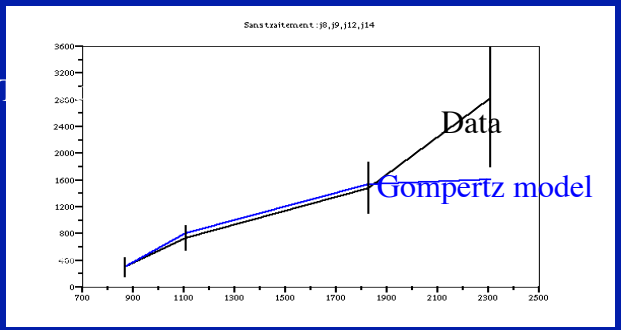
However, a lot of cell colonies and tumours do not follow Gompertz growth

Refinements: Hahnfeldt et al., Canc. Res 1999; Ergun et al., Bull Math Biol 2003

$$\dot{p}_t = -\lambda p_t \ln\left(\frac{p_t}{e_t}\right)$$

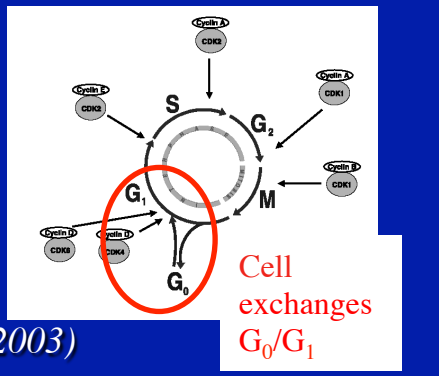
$$\dot{e}_t = be_t^{2/3} - de_t^{4/3}$$

Example of non-Gompertz tumour growth:
(GOS) in a population of mice, laboratory data



a) ODE models with 2 exchanging cell compartments, proliferating (P) and quiescent (Q)

$$\begin{aligned}\frac{dP}{dt} &= [\beta - \mu_p - r_0(N)]P + r_i(N)Q \\ \frac{dQ}{dt} &= r_0(N)P - [r_i(N) + \mu_q]Q \\ N &= P + Q, \quad P_0 + Q_0 = 1\end{aligned}$$



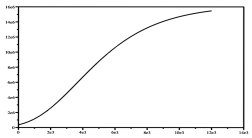
Cell exchanges G_0/G_1

(Gyllenberg & Webb, Growth, Dev. & Aging 1989; Kozusko & Bajzer, Math BioSci 2003)

where, for instance:

$$r_0(N) = \frac{\alpha N^\gamma}{K^\gamma + N^\gamma}, \quad r_i(N) = \frac{\beta L^\delta}{L^\delta + N^\delta}$$

r_0 representing here the rate of inactivation of proliferating cells, and r_i the rate of recruitment from quiescence to proliferation



Initial goal: to mimic Gompertz growth

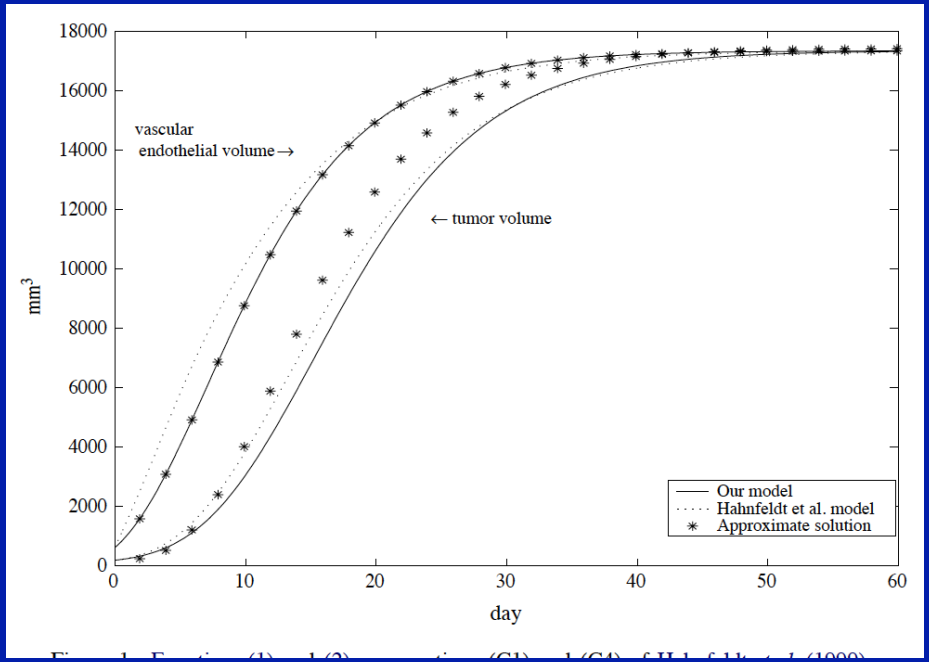
$$\frac{dx}{dt} = kx \ln\left(\frac{x_{max}}{x}\right)$$

b) ODE models with varying carrying capacity

$$\dot{p}_t = -\lambda p_t \ln\left(\frac{p_t}{e_t}\right)$$

$$\dot{e}_t = b e_t^{2/3} - d e_t^{4/3},$$

Hahnfeldt et al., Cancer Res. 1999
Ergün et al., BMB 2003



Used by U. Ledzewicz et al. to optimise combined delivery of cytotoxic and antiangiogenic drugs, acting on p_t and e_t, respectively

Models of tumour growth 3

Physical laws describing macroscopic spatial dynamics of an *avascular* tumour

- Fractal-based phenomenological description of growth of cell colonies and tumours, relying on observations and measures: roughness parameters for the 2D or 3D tumour

Findings: - all proliferation occurs at the outer rim
- cell diffusion *along* (not from) the tumour border or surface
- *linear growth of the tumour radius* after a critical time (before: exponential)

(A. Bru et al. Phys Rev Lett 1998, Biophys J 2003)

Individual-based (=agent-based) models:
- cell division and motion described by stochastic algorithm then continuous limit
- permanent regime = KPP-Fisher-like (also linear growth of the tumour radius)

(D. Drasdo, Math Comp Modelling 2003; Phys Biol 2005)

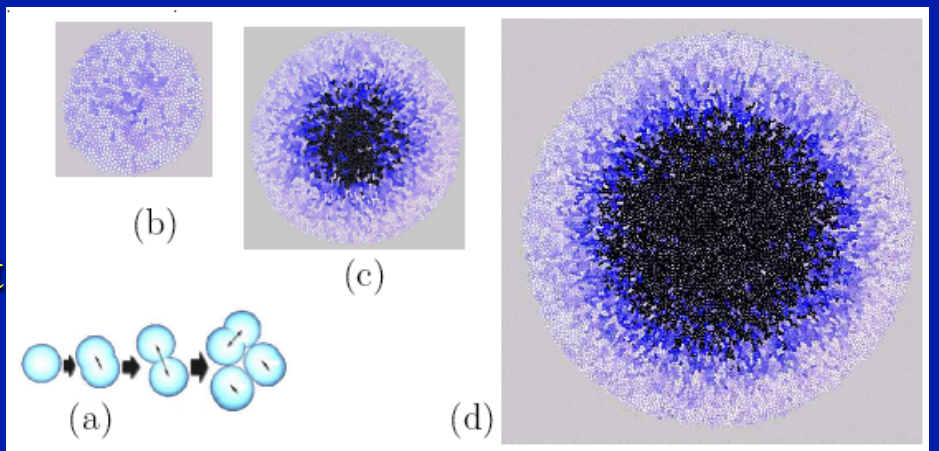


Fig. 1. Typical simulation scenario in the off-lattice model starting from (a) a single cell to (a) three cells and aggregates of (b) $N = 100$, (c) $N = 1000$, and (d) $N = 10000$ cells. (Further

Partial differential equations

Models of tumour growth 3

Mechanical models of macroscopic spatial dynamics involving pressure

Multiphase models with moving boundaries:
proliferating cells, quiescent cells, necrotic cells, surrounding healthy cells…

(see Preziosi et al.)

Simplified models with only intra-tumour cell pressure p and cell velocity $\underline{v}$:

$$\nabla \cdot \underline{v} = s_0 H(p_0 - p)$$
$$\underline{v} = -\mu \nabla p,$$

(from H. Byrne & D. Drasdo JMB 2009)

where $H(p_0 - p)$ denotes the Heaviside step function

Simplified models involving pressure p and nutrient concentration c *(ρ=cell density)*:

$$\begin{cases} \partial_t \varrho - \operatorname{div}(\varrho \nabla p) = \varrho\, \Phi(p, c), \\ \partial_t c - \Delta c = -\varrho\, \Psi(p, c), \\ c(x,t) \to c_B > 0 \qquad \text{as} \quad |x| \to \infty \end{cases}$$

(from Perthame-Quiroz-Vazquez Arch Rat Mech Anal 2014)

$$\partial_p \Phi < 0, \qquad \partial_c \Phi \geq 0, \qquad \Phi(p_M, c_B) = 0,$$
$$\partial_p \Psi \leq 0, \qquad \partial_c \Psi \geq 0, \qquad \Psi(p, 0) = 0.$$

Partial differential equations

Models of tumour growth 4

Macroscopic reaction-diffusion evolution equations (travelling wave fronts)

1 variable c = density of tumour cells): KPP-Fisher equation

$$\frac{\partial c}{\partial t} = \nabla.(D(x)\nabla c) + \rho c(1-c)$$

$D(x)$ = diffusion (motility) in [brain] tissue, ρ (reaction)=growth of tumour cells

1D x and c instead of $c(1\text{-}c)$: used to represent [brain] tumour radial propagation

(K. Swanson & J. Murray, Cell Prolif 2000; Br J Cancer 2002; J Neurol Sci 2003)

2 or more variables: ex.: healthy cells N_1, tumour cells N_2, excess H^+ ions L

$$\frac{\partial N_1}{\partial t} = r_1 N_1\left(1-\frac{N_1}{K_1}-\alpha_{12}\frac{N_2}{K_2}\right) - d_1 L N_1 \quad (1)$$

$$\frac{\partial N_2}{\partial t} = r_2 N_2\left(1-\frac{N_2}{K_2}-\alpha_{21}\frac{N_1}{K_1}\right) + \nabla.\left(D_2\left(1-\frac{N_1}{K_1}\right)\nabla N_2\right) \quad (2)$$

$$\frac{\partial L}{\partial t} = r_3 N_2 - d_3 L + D_3\nabla^2 L \quad (3)$$

(Gatenby & Gawlinski, Canc. Res. 1996)

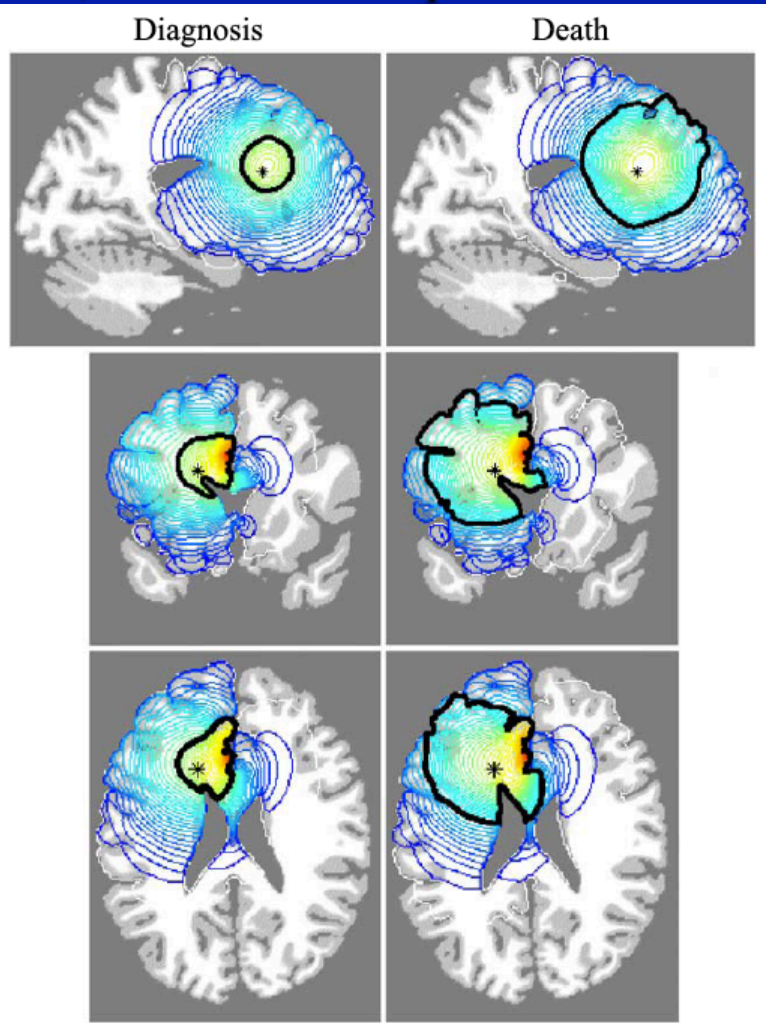
Prediction: interstitial cell gap between tumour propagation and healthy tissue recession fronts

PDE models of tumour growth: invasion

Macroscopic reaction-diffusion equations to represent invasion front

1-dimensional variable c = density of tumour cells): KPP-Fisher equation

$$\frac{\partial c}{\partial t} = \nabla.(D(x)\nabla c) + \rho c(1-c)$$



$D(x)$ = diffusion (motility) in brain tissue, ρ(reaction)=growth of tumour cells, x spatial variable (1-d, 2-d or 3-d) and c: density of tumour cells, used to represent brain tumour radial propagation from a centre. If $D(x) = D$, then v= 2.sqrt(ρD) is the front propagation speed

(K. Swanson & J. Murray, Cell Prolif 2000; Br J Cancer 2002; J Neurol Sci 2003)

Partial differential equations

[Competition for space]

PDE models of tumour growth: invasion as competition

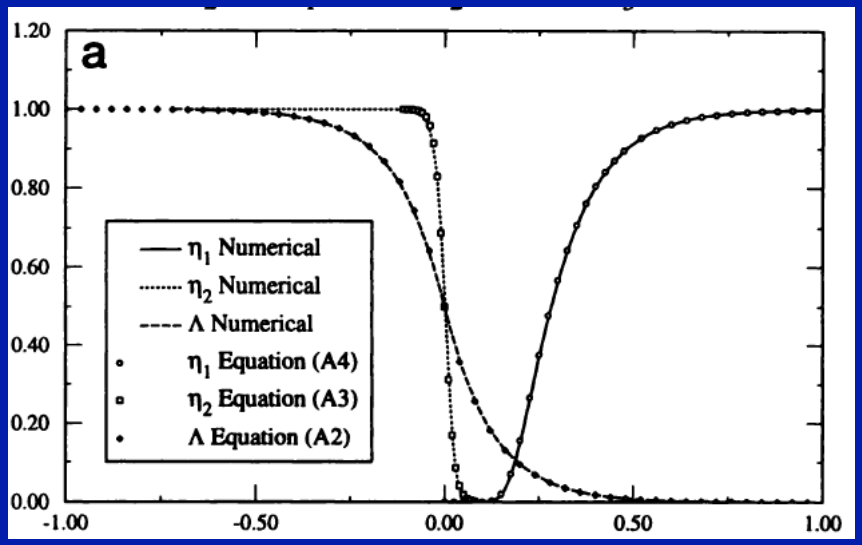
Macroscopic reaction-diffusion equations to represent invasion / recession fronts

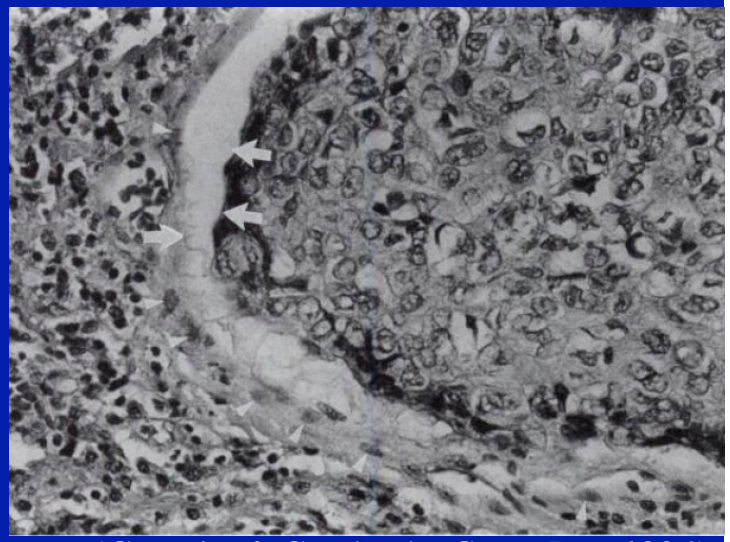
2 or more variables: ex.: healthy cells N_1, tumour cells N_2, excess H^+ ions L

$$\frac{\partial N_1}{\partial t} = r_1 N_1 \left(1 - \frac{N_1}{K_1} - \alpha_{12}\frac{N_2}{K_2}\right) - d_1 L N_1 \quad (1)$$

$$\frac{\partial N_2}{\partial t} = r_2 N_2 \left(1 - \frac{N_2}{K_2} - \alpha_{21}\frac{N_1}{K_1}\right) + \nabla.\left(D_2\left(1 - \frac{N_1}{K_1}\right)\nabla N_2\right) \quad (2)$$

$$\frac{\partial L}{\partial t} = r_3 N_2 - d_3 L + D_3 \nabla^2 L \quad (3)$$





(Gatenby & Gawlinski, Canc. Res. 1996)

Prediction: interstitial cell gap between tumour propagation and healthy tissue recession fronts

PDE models for moving tumour cells in the ECM

Chemotaxis: chemo-attractant induced cell movements

Keller-Segel model

$$\frac{\partial p}{\partial t} = \Delta p - \mathrm{div}\big(p\chi(w)\nabla w\big),$$
$$0 = \Delta w + (p - 1).$$

p = density of cells
w = density of chemoattractant

(Originally designed for movements of bacteria, with w=[cAMP])

(Keller & Segel, J Theoret Biol 1971)

Anderson-Chaplain model for local invasion by tumour cells in the ECM

$$\frac{\partial n}{\partial t} = \overbrace{D_n\nabla^2 n}^{random\ motility} - \overbrace{\chi\nabla.(n\nabla f)}^{haptotaxis} \quad (1)$$

$$\frac{\partial f}{\partial t} = -\overbrace{\delta m f}^{degradation} \quad (2)$$

$$\frac{\partial m}{\partial t} = \overbrace{D_m\nabla^2 m}^{diffusion} + \overbrace{\mu n}^{production} - \overbrace{\theta u m}^{neutralisation} - \overbrace{\lambda m}^{decay} \quad (3)$$

$$\frac{\partial u}{\partial t} = \overbrace{D_u\nabla^2 u}^{diffusion} + \overbrace{F(m,f)}^{production} - \overbrace{\theta u m}^{neutralisation} - \overbrace{\varepsilon u}^{decay} \quad (4)$$

n = density of cells

f = ECM density

m = MDE (tumour metalloproteases)

u = MDE inhibitor

(Anderson & Chaplain, Chap 10 in Cancer modelling and simulation, L. Preziosi Ed, Chapman & Hall 2003)

Integro-differential models

Models of tumour growth 5

Models of Lotka-Volterra type, phenotype-structured, with built-in growth limitation

$$\frac{\partial}{\partial t}n(x,t) = \overbrace{\frac{\theta}{1+\alpha c_2(t)}\left(\int r(y)M(y,x)n(y,t)dy - r(x)n(x,t)\right)}^{\text{mutations and renewal}} + \underbrace{\left(\frac{r(x)}{1+\alpha c_2(t)} - d(x)I(t)\right)n(x,t)}_{\text{growth with cytostatic therapies and death}} - \underbrace{c_1(t)\mu(x)n(x,t).}_{\text{effect of cytotoxic therapies}}$$

(mentioned in Billy & JC, DCDS-B 2013); see also Delitala & Lorenzi's papers

or:

$$\partial_t n(t,x,y) = \left[\frac{r(x,y)}{1+\mu_2(x,y)c_2(t)} - d(x,y)I(t) - \mu_1(x,y)c_1(t)\right]n(t,x,y)$$

(mentioned in Billy & JC, DCDS-B 2013; see here on Thursday; see also Delitala & Lorenzi's papers)

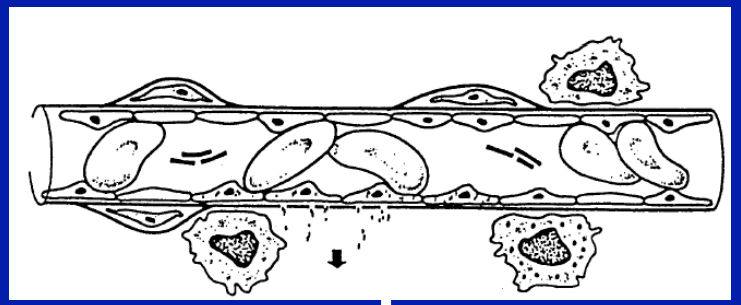
where $I(t) = \int_0^1 \int_0^1 n(x,y,t)\,dx\,dy$ is the total cell population or, more generally, a *[total]* cell population-dependent environment variable = growth limitation

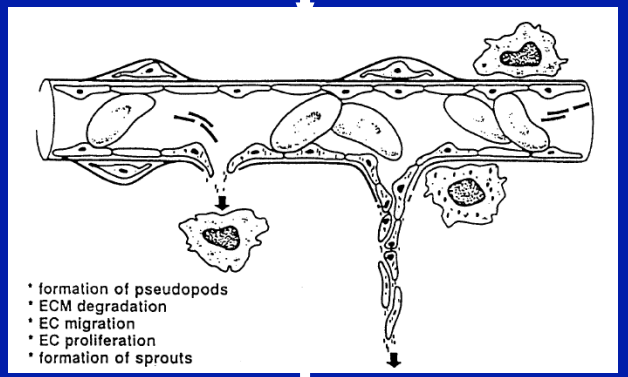
Partial differential equations

Models for angiogenesis

VEGF-induced endothelial cell movements towards tumour

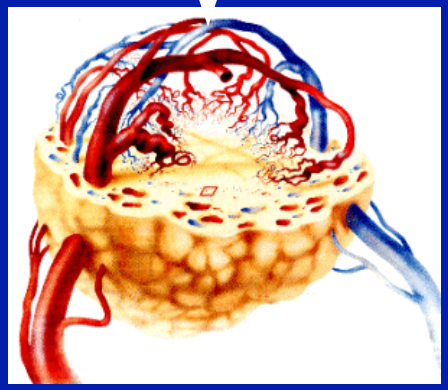
- Biochemical enzyme kinetics
- Chemical transport (capillary and ECM)
- “Reinforced random walks”
- Cell movements in the ECM





Models by Anderson and Chaplain, Levine and Sleeman

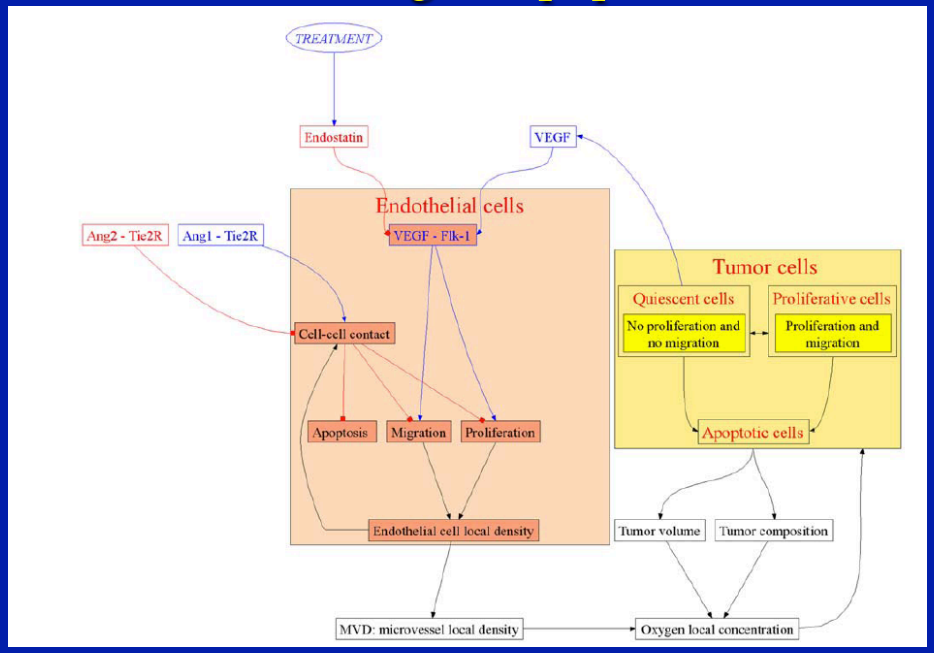
(Levine & Sleeman,Chap. 6 in Cancer modelling and simulation, L. Preziosi Ed, Chapman & Hall 2003)



Partial differential equations

A multiscale angiogenesis model

Interacting cell populations



Proliferating cancer cell population

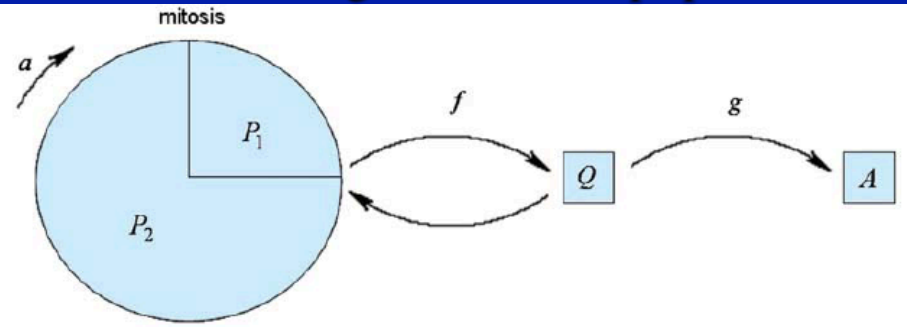


Fig. 4. Schematic representation of our age-structured cell cycle regulation model. We took into account two proliferative phases P_1 and P_2, one quiescent phase Q, and one apoptotic phase A. At the end of the P_1 phase, environmental conditions are checked; this checking is modeled through functions f and g. In a context of overpopulation or hypoxia, proliferative cells become quiescent (through function f). If the hypoxic stress is too high, cells can become apoptotic (through function g). If the environmental conditions become more favorable, quiescent cells can revert to the proliferative phase. We suppose that mitosis occurs at the end of the P_2 phase, leading to the generation of new cells.

Coupling by oxygen concentration, acting on actual commitment of cells into the division cycle (passing the restriction point)

Aim: assessment of an antiangiogenic treatment by endostatin

F. Billy et al., J. Theor. Biol. 2009

Hybrid modelling: PDEs, ODEs and Cellular Automata

- PDEs for the diffusion of molecules in the interstitial medium: oxygen, nutrients, growth factors and drugs in space-structured tissues

- ODEs for intracellular metabolism and PK-PD (pharmacokinetics-pharmacodynamics in single cells, the targets of drugs)

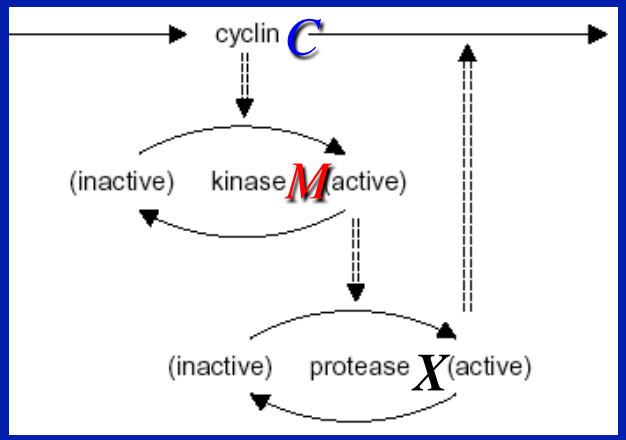
- Cellular Automata or Agent-Based Models (ABMs) to build a tissue from single cells (=the individual agents)

Many examples of such models exist in the scientific literature
A recent one: Robertson-Tessi et al., Cancer Research 2015

Modelling the cell cycle 1 (single-cell models)

Ordinary differential equations to describe progression in the cell cycle

A. Golbeter's minimal model for the « mitotic oscillator »



$$\frac{dC}{dt} = v_i - k_d C - v_d X \frac{C}{K_d + C}$$

$$\frac{dM}{dt} = v_1 \frac{C}{K_c + C} \frac{(1 - M)}{K_1 + (1 - M)} - V_2 \frac{M}{K_2 + M},$$

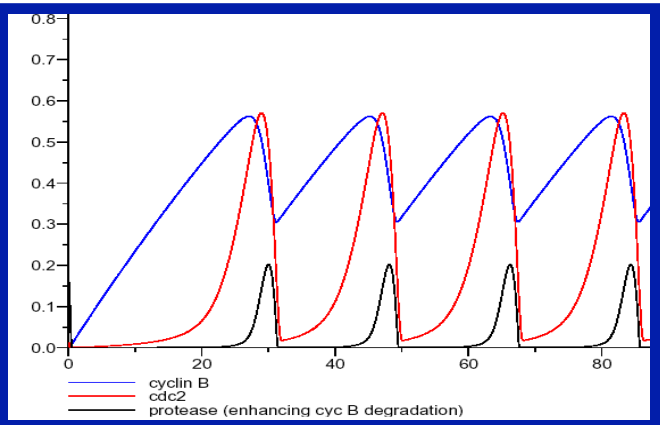
$$\frac{dX}{dt} = v_3 M \frac{(1 - X)}{K_3 + (1 - X)} - V_4 \frac{X}{K_4 + X}.$$

C = cyclin B, M = Cyclin-linked cyclin dependent kinase, X = anticyclin protease

Switch-like dynamics of kinase cdk1, M

Adapted to describe G_2/M phase transition, which is controlled by Cyclin B

(A. Goldebeter Biochemical oscillations and cellular rhythms, CUP 1996)



Ordinary differential equations

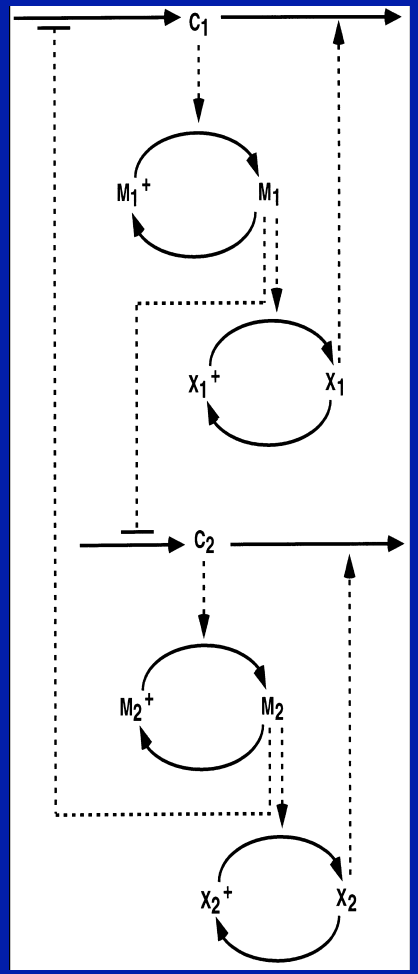
Including more phase transitions in the cell cycle model?

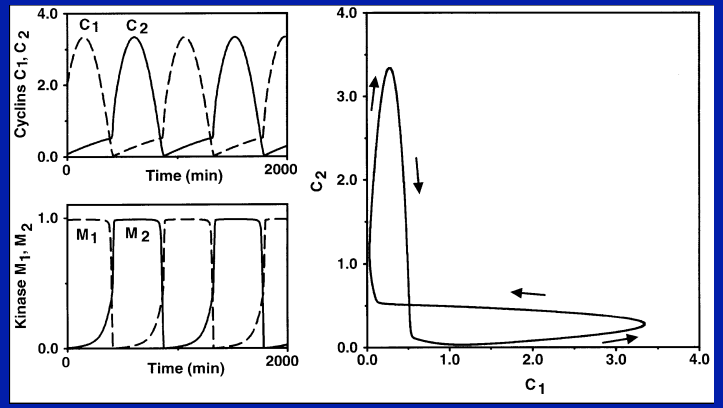
Hint: an existing model for G_1/S and G_2/M synchronisation

(recalling the minimum mitotic oscillator *(C, M, X)* by A. Goldbeter, 1996, here duplicated to take into account synchronisation between G_1/S and G_2/M transitions)

i=1: G_1/S

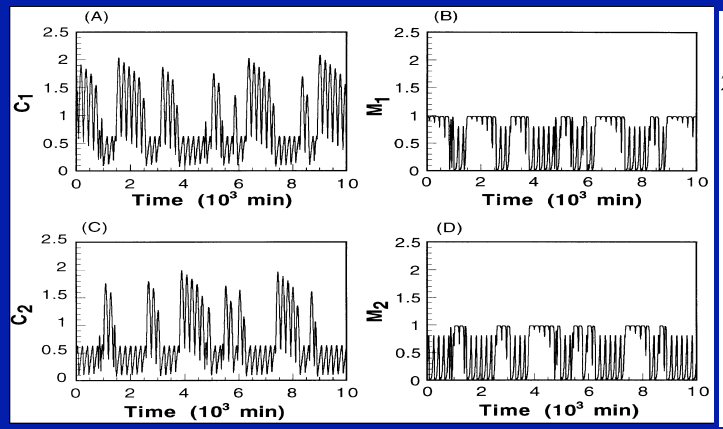
i=2: G_2/M

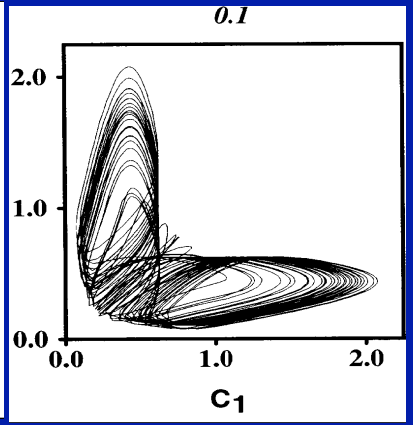




C_i=Cyclin
M_i=CDK
X_i=Protease

Changing the coupling strength may lead to:

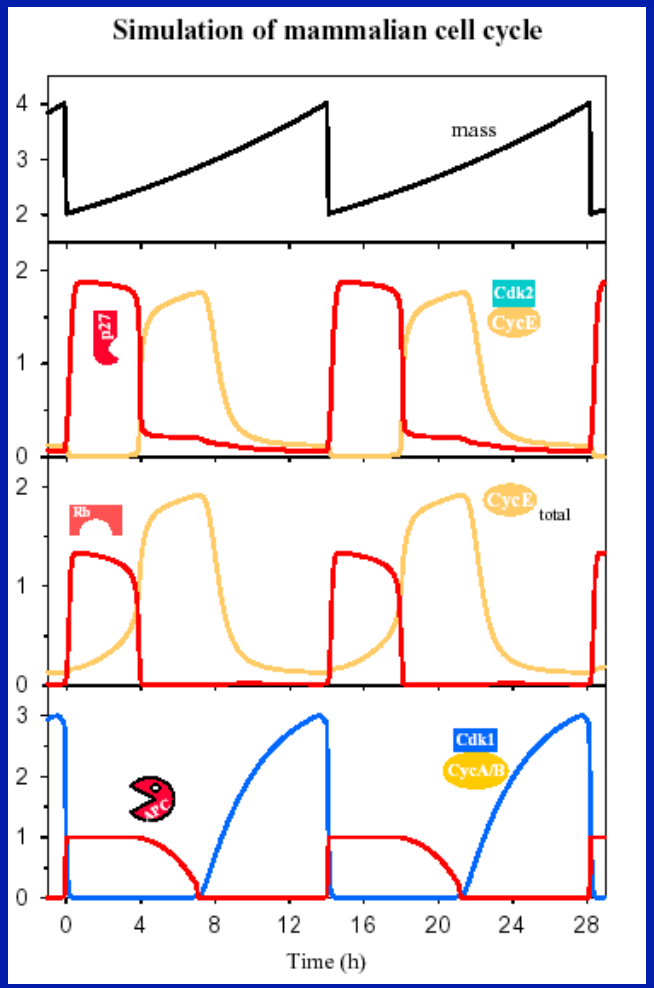




Romond, Gonze, Rustici, Goldbeter, Ann NYAS, 1999

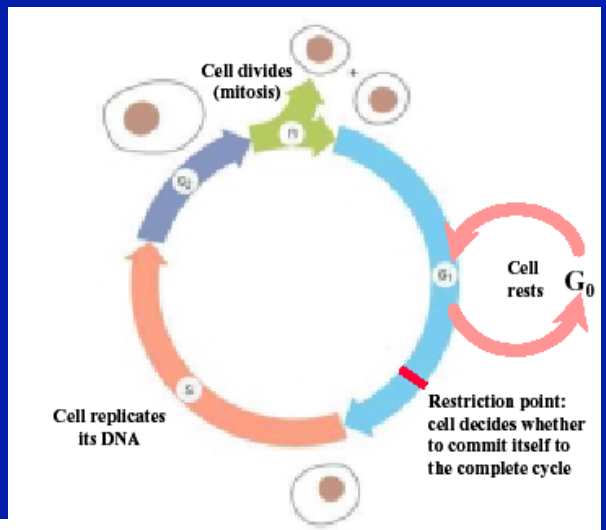
Modelling the cell cycle 2 (single-cell models)

Detailed ODE models to describe progression in the cell cycle



Phase transitions:
-G_1/S
-G_2/M
-Metaphase/anaphase

…due to steep variations of Cyc-cdk concentrations (bifurcation parameter=cell mass)



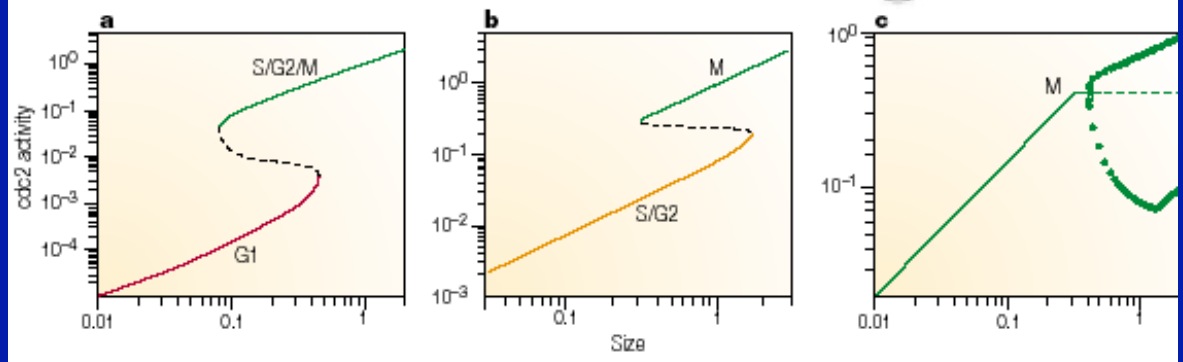


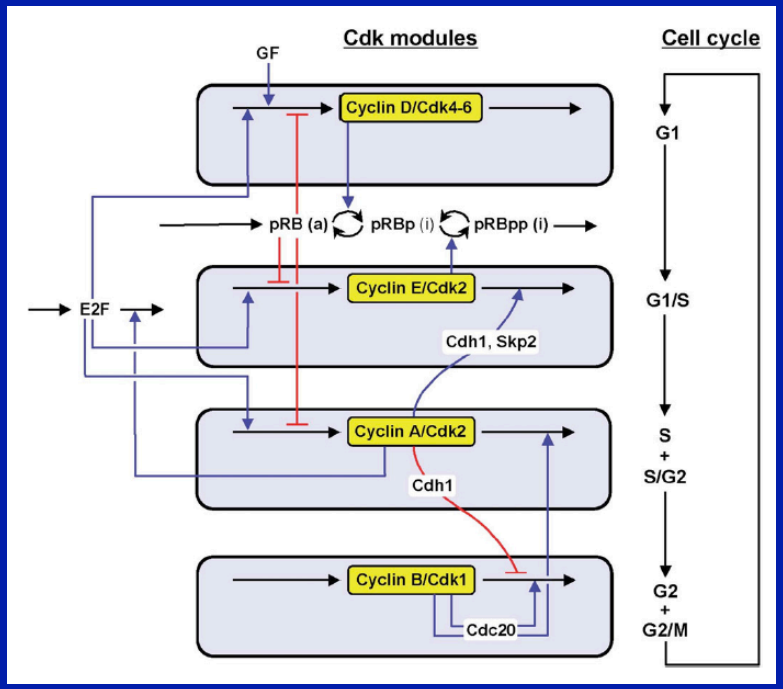
Figure 5 | **Bifurcation diagrams for the three control modules of the cell cycle.** The activity of cdc2–cdc13 dimers (an indicator of the state of the control system) is plotted against 'size' (the number of ribosomes per nucleus, an indicator of cell growth and division). All variables are expressed in arbitrary units. For each value of size, we compute the steady-state activity

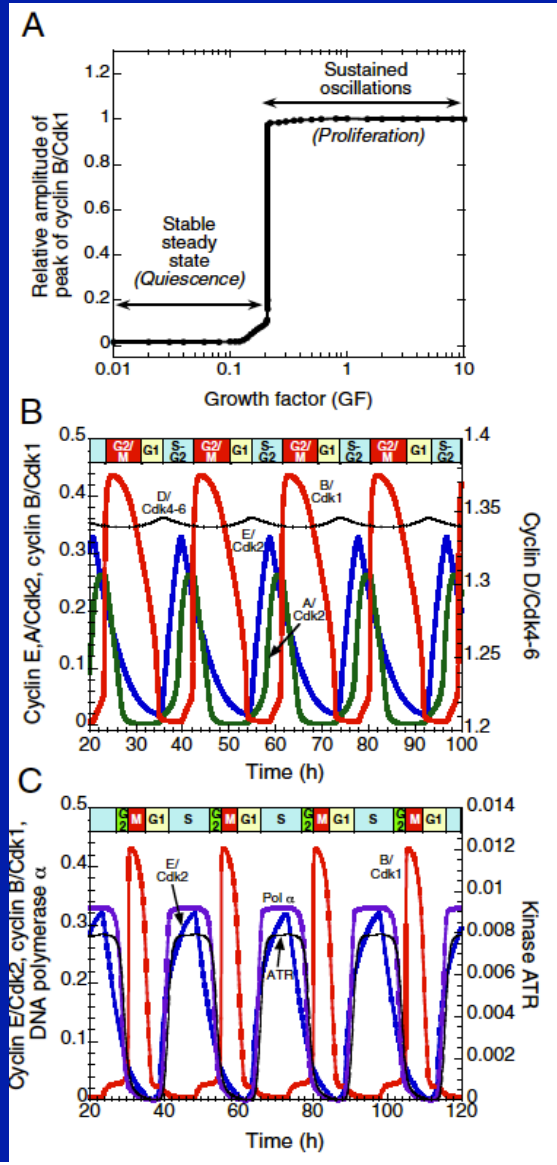
(Novak, Bioinformatics 1999)

(Tyson, Chen, Novak, Nature Reviews 2001)

Modelling the cell cycle 2: single cell (continued)

Even more detailed ODE models to describe progression in the cell cycle





39 variables. Growth factor, rather than cell mass
(as was the case in models by Tyson, Chen & Novak)
is the driving parameter for bifurcations

A simplified model has been proposed, with 5 variables

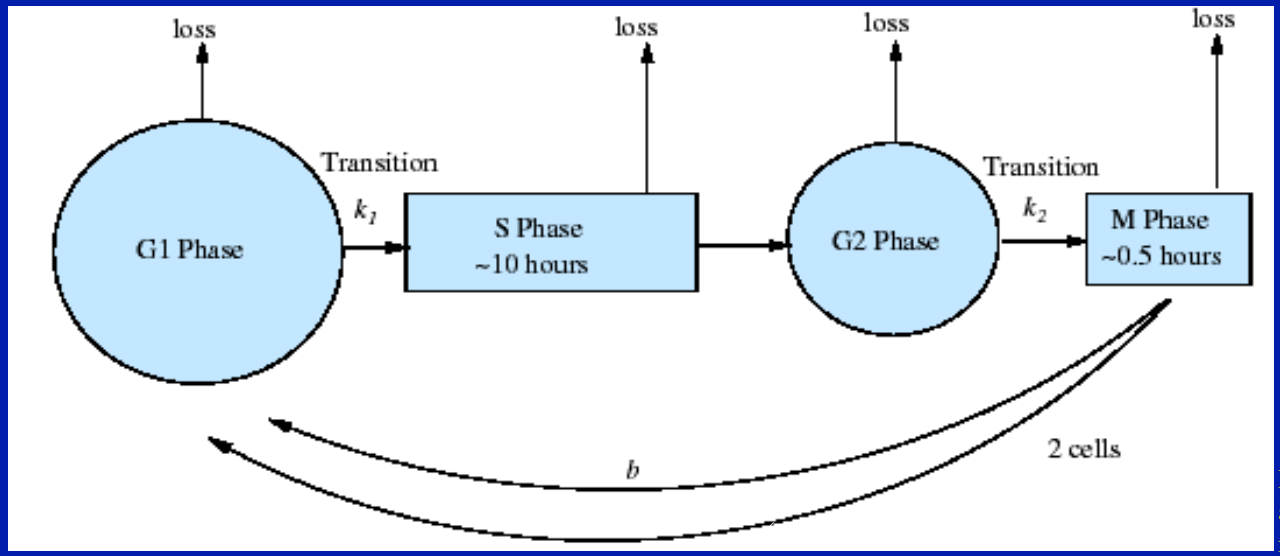
C. Gérard & A. Goldbeter, PNAS 2009; Interface Focus 2011

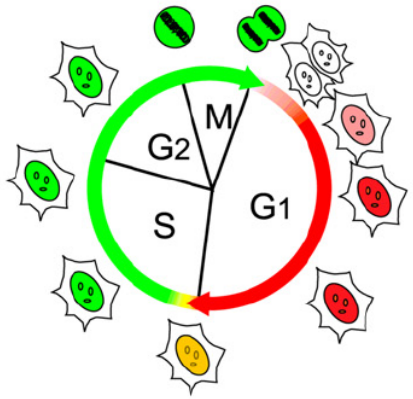
C. Gérard, D. Gonze & A. Goldbeter, FEBS Journal 2012

Partial differential equations

Modelling the cell cycle 3

Transport equations for age-structured cycling cell populations





FUCCI staining *(Sakaue-Sawano Cell 2008)* allows to quantify proliferating cell population repartition according to cell cycle phases

In each phase i , a Von Foerster-McKendrick-like equation:

$$\frac{\partial}{\partial t} n_i(t,a) + \frac{\partial}{\partial a}[v_i(a) n_i(t,a)] + d_i(t,a) n_i(t,a) + K_{i\to i+1}(t,a) n_i(t,a) = 0$$

$$v_i(0) n_i(t, a=0) = \int_{\alpha \geq 0} K_{i-1\to i}(t,\alpha)\, n_{i-1}(t,\alpha)\, d\alpha$$

$$K_{i\to i+1}(t,a) = \psi(t) \mathbf{1}_{a \geq a_i}(a)$$

n_i:=cell population density in phase i
d_i:=death rate

$K_{i->i+1}$:=transition rate (with a factor 2 for $i=1$)

d_i, $K_{i->i+1}$ constant or periodic w. r. to time t ($1 \leq i \leq I$, $I+1=1$)

Death rates d_i and phase transitions $K_{i->i+1}$ are targets for physiological (e.g. circadian) and therapeutic (drugs) control

(JC, B. Laroche, S. Mischler, B. Perthame INRIA research report 4892, 2003)

General case (N phases): by the Krein-Rutman theorem (infinite-dimensional form of the Perron-Frobenius theorem), there exists a nonnegative first eigenvalue λ and, if $\widetilde{N}_i(t,a) = e^{-\lambda t} n_i(t,a)$, N_i, bounded solutions to the problem *(here $v_i(a)=1$)* :

$$\begin{cases} \frac{\partial}{\partial t} N_i(t,a) + \frac{\partial}{\partial a} N_i(t,a) + [d_i(t,a) + \lambda + K_{i\to i+1}(t,a)] N_i(t,a) = 0, \\ N_i(t,a=0) = \int_{\alpha\geq 0} K_{i-1\to i}(t,\alpha)\, N_{i-1}(t,\alpha)\, d\alpha, \quad 2 \leq i \leq I \\ N_1(t,a=0) = 2\int_{\alpha\geq 0} K_{I\to 1}(t,\alpha)\, N_I(t,\alpha)\, d\alpha, \quad \text{with} \sum_{i=1}^{I} \int_{a\geq 0} N_i(t,a) da = 1 \end{cases}$$

with a real number ρ such that the asymptotics of $\widetilde{N}_i(t,a) = e^{-\lambda t} n_i(t,a)$ follow:

$$\int_{\alpha\geq 0} \left| \widetilde{N}_i(t,\alpha) - \quad \rho.\ N_i(t,\alpha) \right| \varphi_i(t,\alpha) d\alpha \to 0 \quad \text{as} \quad t \to \infty$$

(the weights φ_i being solutions to the dual problem); this can be proved by using a generalised entropy principle (GRE). Moreover, if the control (d_i or $K_{i->i+1}$) is constant, or if it is periodic, so are the N_i, with the same period in the periodic case.

Ph. Michel, S. Mischler, B. Perthame, C. R. Acad. Sci. Paris Ser. I (Math.) 2004; J Math Pures Appl 2005
Ph. Michel, B. Perthame, C. R. Acad. Sci. Paris Ser. I (Math.) 2006; Proc. ECMTB Dresden 2005, Birkhäuser 2007

JC.

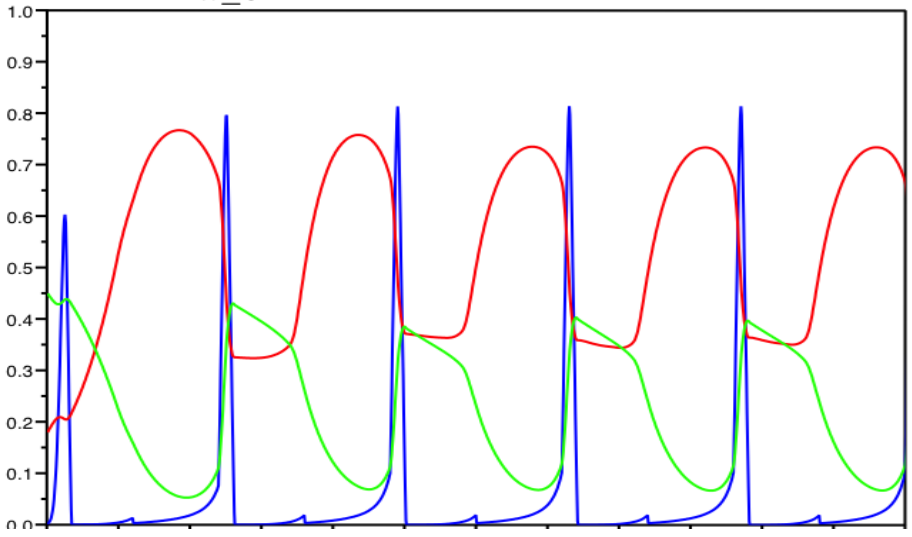
Partial differential equations

λ: a growth exponent governing the cell population behaviour

In summary: proof of the existence of a unique growth exponent λ, the same for all phases i, such that the $\widetilde{N}_i(t,a) = e^{-\lambda t} n_i(t,a)$ are bounded, and asymptotically periodic if the control is periodic

Example of control (periodic control case): 2 phases, control on G_2/M transition by 24-h-periodic CDK1-Cyclin B (from A. Goldbeter's minimal mitotic oscillator model)

$$\mathcal{N}_i^{tot}(t) = e^{-\lambda t} \int_{\alpha \geq 0} n_i(t,\alpha) d\alpha, \quad i = 1,2$$



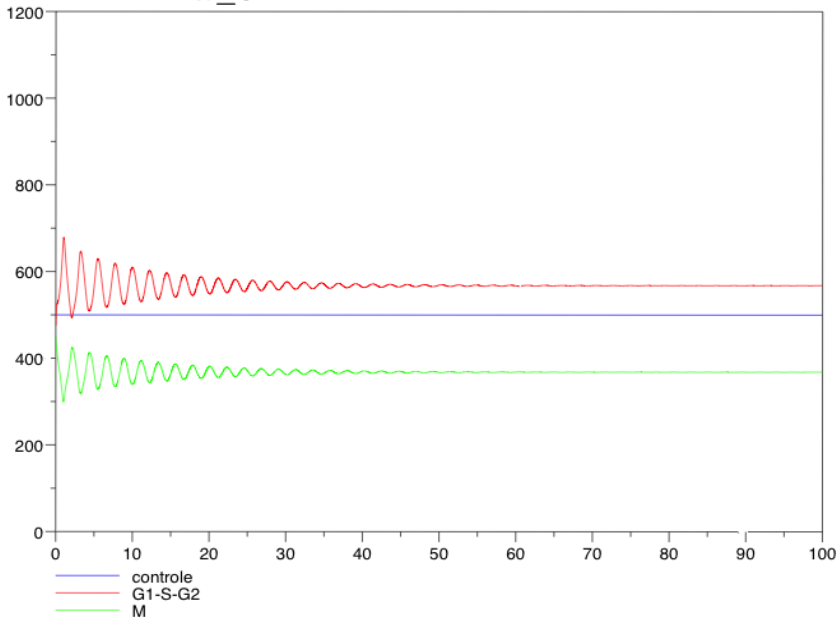
ψ=CDK1 All cells in G1-S-G2 (phase i=1) All cells in M (phase i=2)

"Surfing on the exponential growth curve"

(= the same as adding an artificial death term +λ to the d_i)

Details (1): 2 phases, no control on G_2/M transition

$$\mathcal{N}_i^{tot}(t) = e^{-\lambda t} \int_{\alpha \geq 0} n_i(t,\alpha) d\alpha, \quad i = 1,2$$

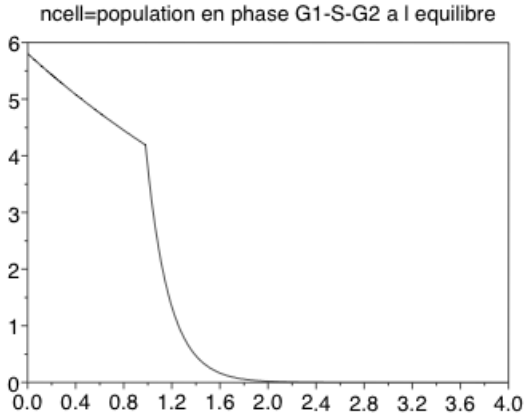


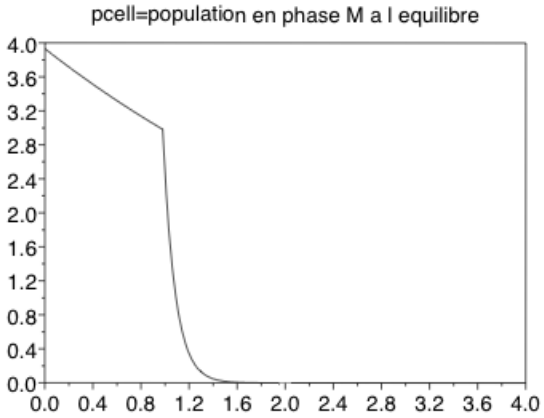
The total population of cells

$$\int_{\alpha > 0} n_i(t,\alpha) d\alpha, \quad i = 1,2$$

inside each phase follows asymptotically an exponential behaviour

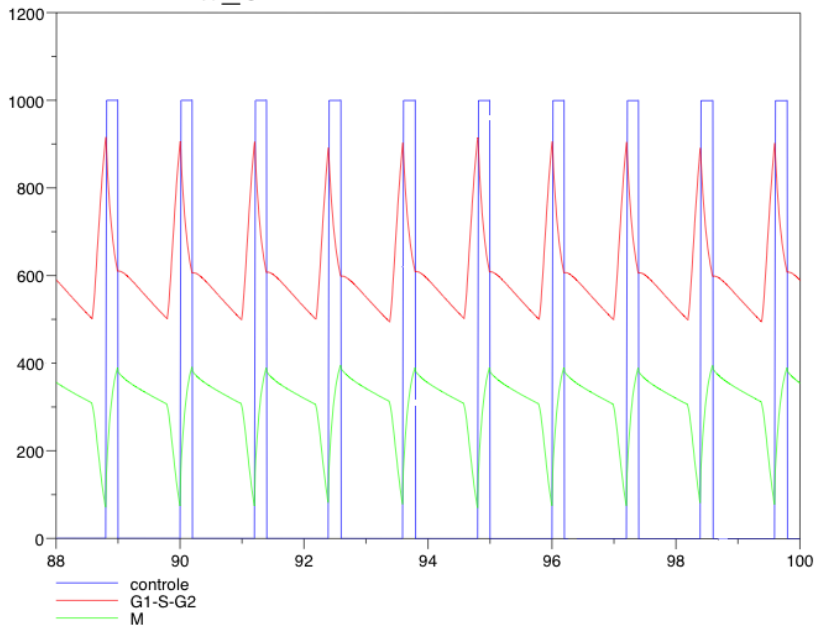
Stationary state distribution of cells inside phases according to age *a*: *no control, hence exponential decay*





Details (2): 2 phases, periodic control ψ on G_2/M transition

$$\mathcal{N}_i^{tot}(t) = e^{-\lambda t} \int_{\alpha \geq 0} n_i(t,\alpha) d\alpha, \quad i = 1,2$$

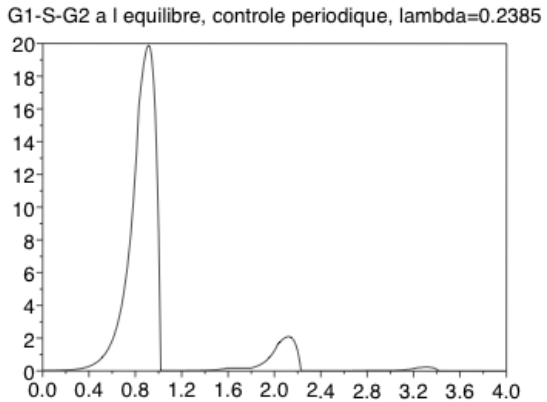


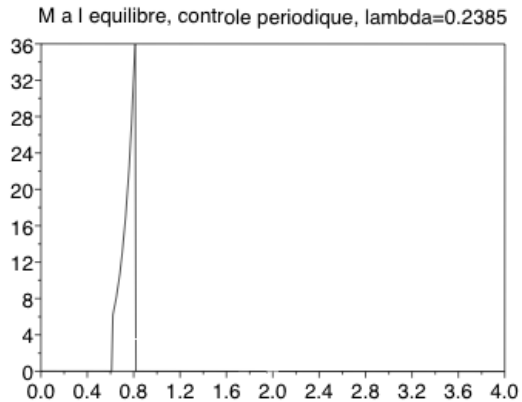
The total population of cells

$$\int_{\alpha > 0} n_i(t,\alpha) d\alpha, \quad i = 1,2$$

inside each phase follows asymptotically an exponential behaviour *tuned by a periodic function*

Stationary state distribution of cells inside phases according to age *a: sharp periodic control, hence sharp rise and decay*





Partial differential equations

The simplest case: 1-phase model with division

$$\frac{\partial}{\partial t}n(t,a)+\frac{\partial}{\partial a}[n(t,a)]+[d(t)+K(t,a)]\,n(t,a)=0$$

$$n(t,a=0)=2\int_{\alpha\geq 0}K(t,\alpha)\,n(t,\alpha)\,d\alpha$$

$$\text{where } K(t,a)=K_0\psi(t)\mathbb{1}_{[a^*,+\infty[}(a)$$

$$\text{and } \psi(t)=\mathbb{1}_{[0,\tau[}(t),\ 1\text{-periodic}$$

(Here, $v(a)=1$, a^* is the cell cycle duration, and $\tau(<1)$ is the time during which the 1-*periodic control* ψ is actually exerted on cell division)

Then it can be shown that the eigenvalue problem:

$$n(t,a)=e^{\lambda t}N(t,a)$$

$$\int_{\alpha\geq 0}N(t,a)da=1$$

$$\frac{\partial}{\partial t}N(t,a)+\frac{\partial}{\partial a}[N(t,a)]+[\lambda+d(t)+K(t,a)]\,N(t,a)=0$$

$$N(t,a=0)=2\int_{\alpha\geq 0}K(t,\alpha)\,N(t,\alpha)\,d\alpha$$

has a unique positive 1-*periodic* eigenvector N, with a positive eigenvalue λ, solution, if $d(t)=d$, $K(t,a)=K(a)$ of Lotka's (=Euler's) equation: $\frac{1}{2}=\int_0^{+\infty}f(x)e^{-\lambda x}dx$, where $f(x)=K(x)e^{-\int_0^x K(y)dy}$ is a p.d.f. if $\int_0^{+\infty}K(x)dx=+\infty$

Partial differential equations

Experimental measurements to identify transition kernels K_{i_i+1}

(and simultaneously experimental evaluation of the first eigenvalue λ)

In the simplest model with d=0 (one phase with division) and assuming K=$K(x)$ (instead of indicator functions $\mathbb{1}_{[a^*,+\infty[}$, experimentally more realistic transitions):

$$\begin{cases} \frac{\partial}{\partial t}n(t,x) + \frac{\partial}{\partial x}n(t,x) + K(x)n(t,x) = 0, \\ n(t,0) = 2\int_0^\infty K(x)n(t,x)dx. \end{cases}$$

Whence (by integration along characteristic lines):

$$n(t+x,x) = n(t,0)e^{-\int_0^x K(y)dy}$$

Which can be interpreted as: if τ is the age in phase at division, or transition, then

$$P(\tau > x) = e^{-\int_0^x K(y)dy} \quad \text{with} \quad \int_0^\infty K(x)dx = +\infty$$

With probability density (experimentally identifiable):

$$f(x) = K(x)e^{-\int_0^x K(y)dy} \quad \text{i.e.,} \quad K(x) = \frac{f(x)}{\int_x^\infty f(y)dy}$$

Experimental parameter identification for this cell cycle model with 2 phases: G1 and S-G2-M using *FUCCI reporters*

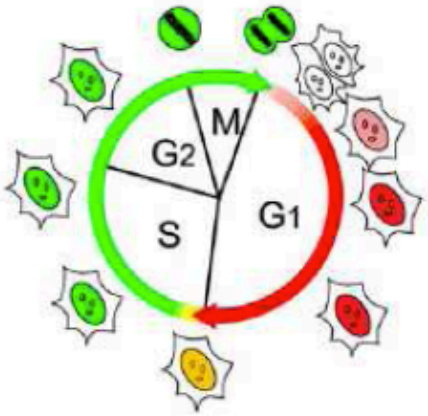
FUCCI=Fluorescent Ubiquitination-based Cell Cycle Indicator

Cells:

NIH 3T3 of a common population

(*mouse embryonic fibroblasts*)

without preliminary synchronization



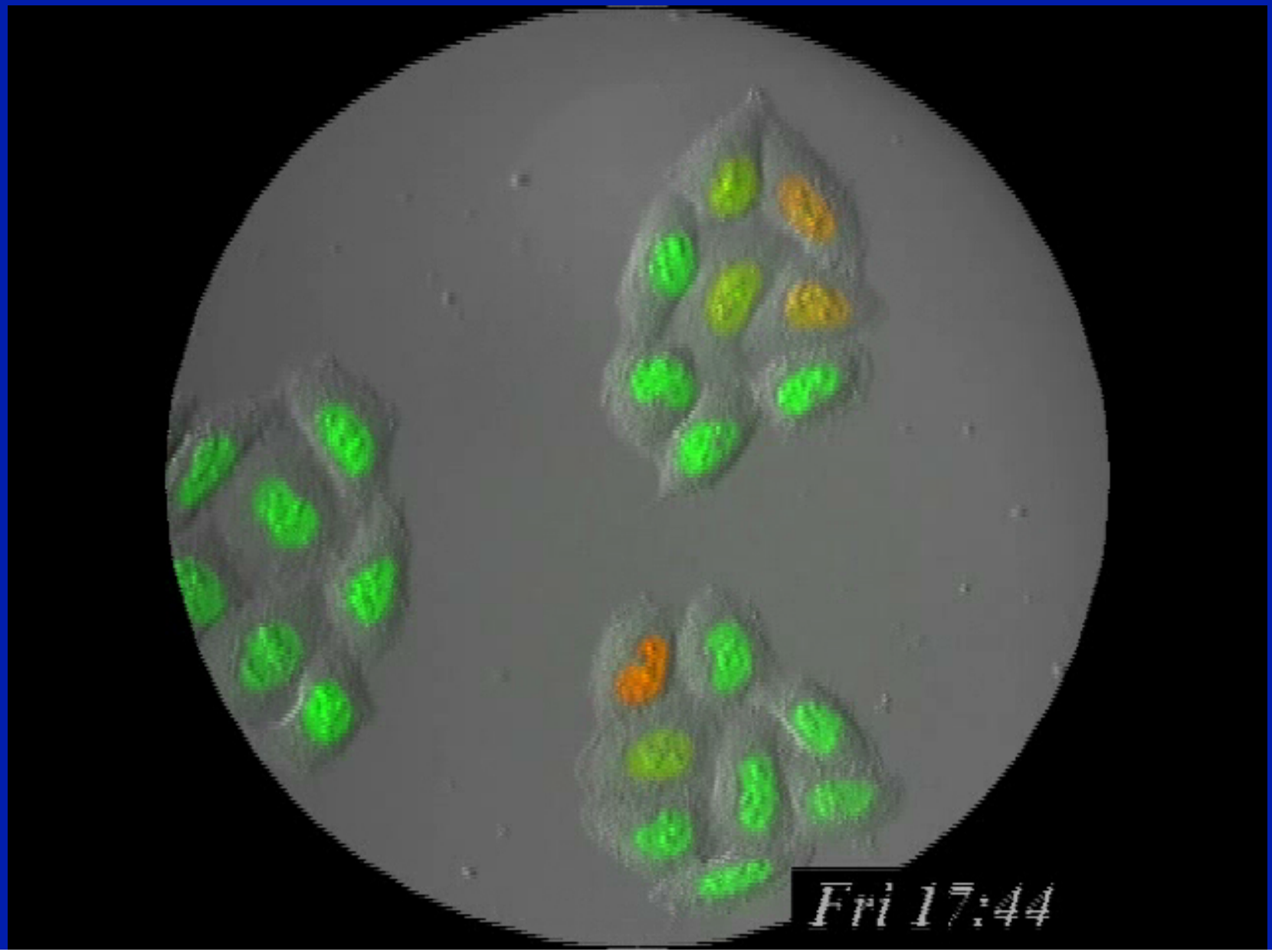
from Sakaue-Sawano et al.
Cell 2008, 132, 487–498

Measures: for each individual cell:

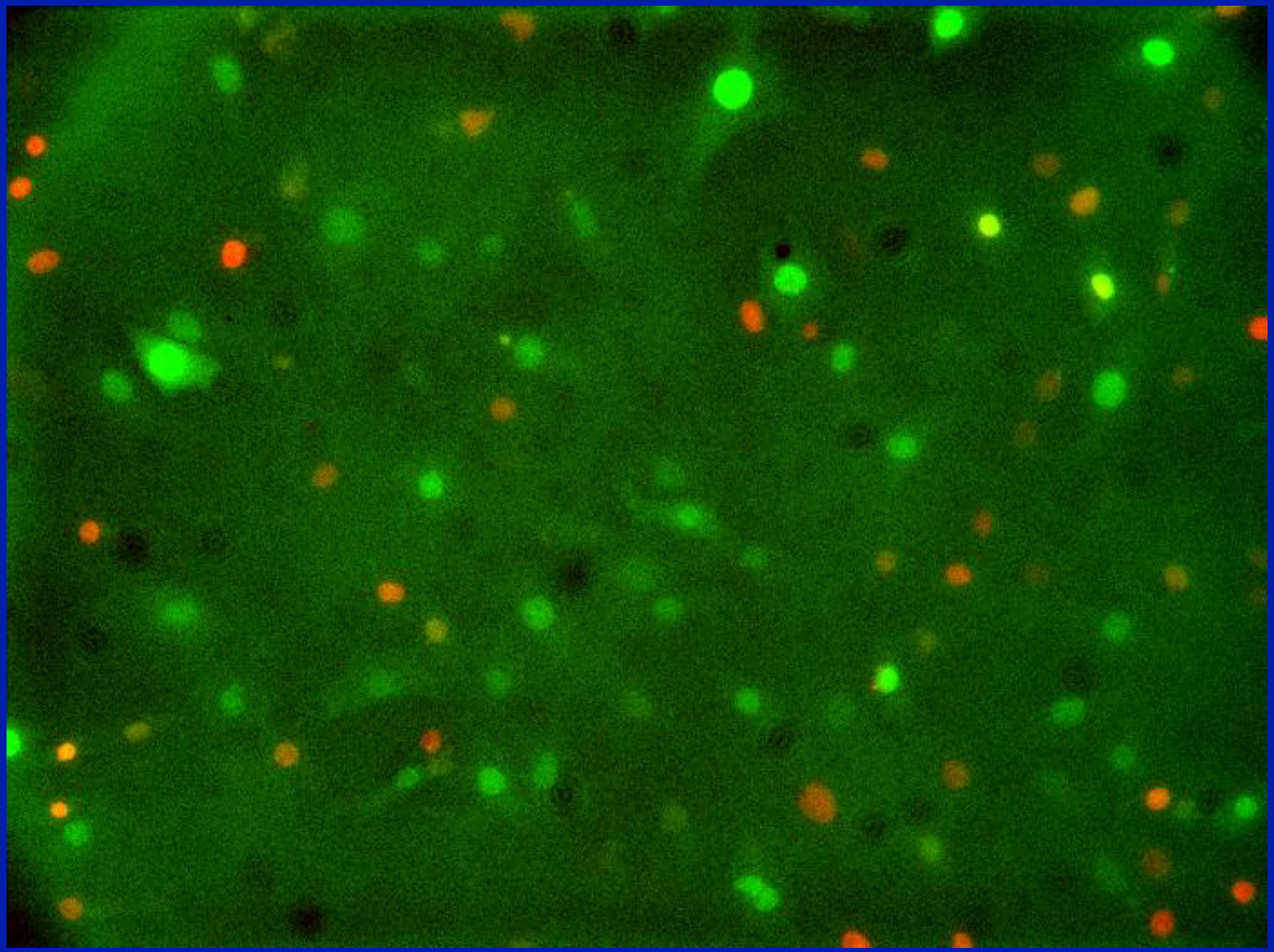
red and green fluorescence time recording

- ⇝ every 15 min
- ⇝ approx. 150 measures for each cell

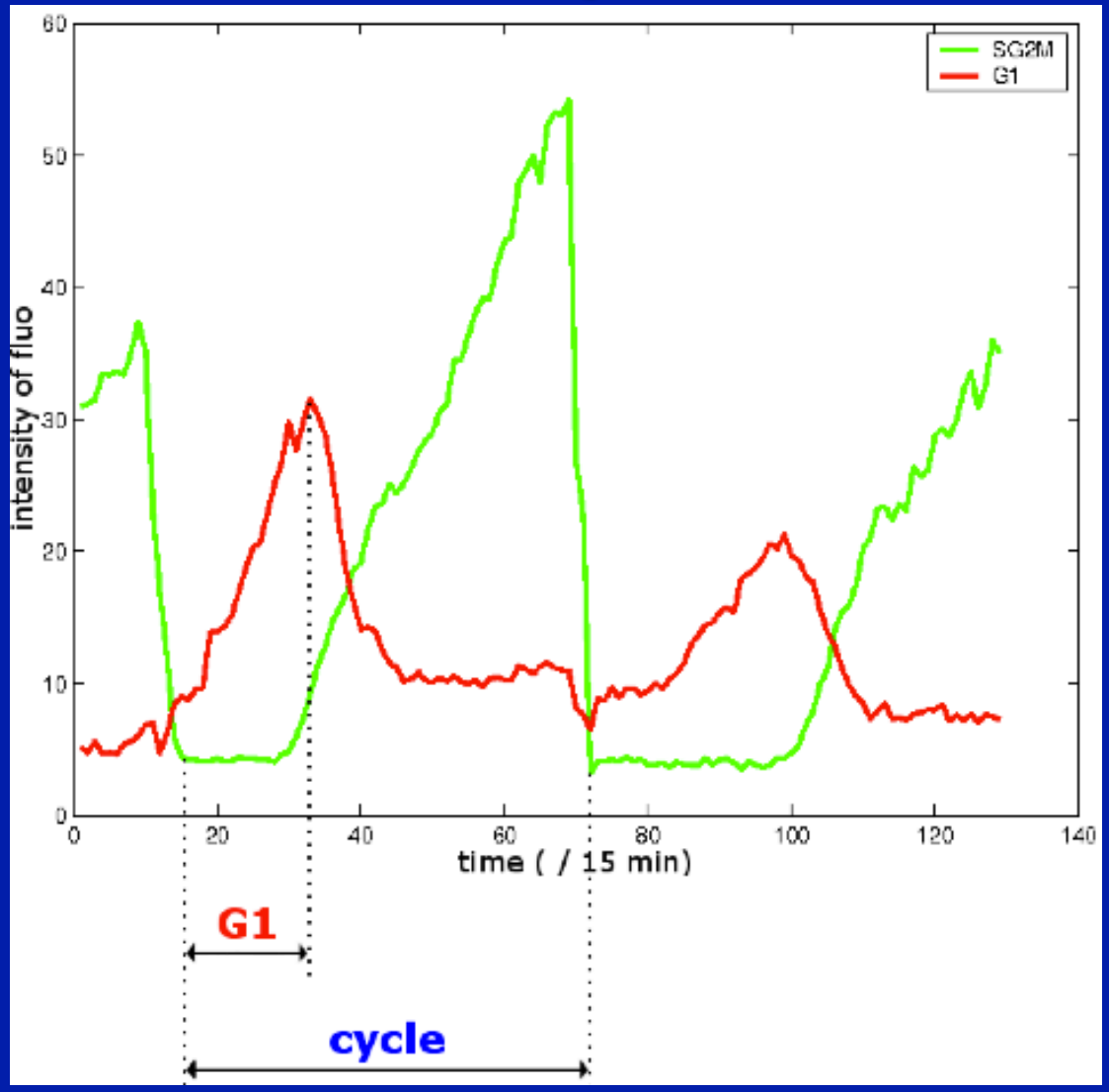
FUCCI: a movie (Sakaue-Sawano 2008), HeLa cells



Another FUCCI movie (C. Feillet, IBDC Nice), NIH3T3 cells



FUCCI reporters + individual cell tracking (non trivial…):
Measuring time intervals: G_1 and total division cycle durations

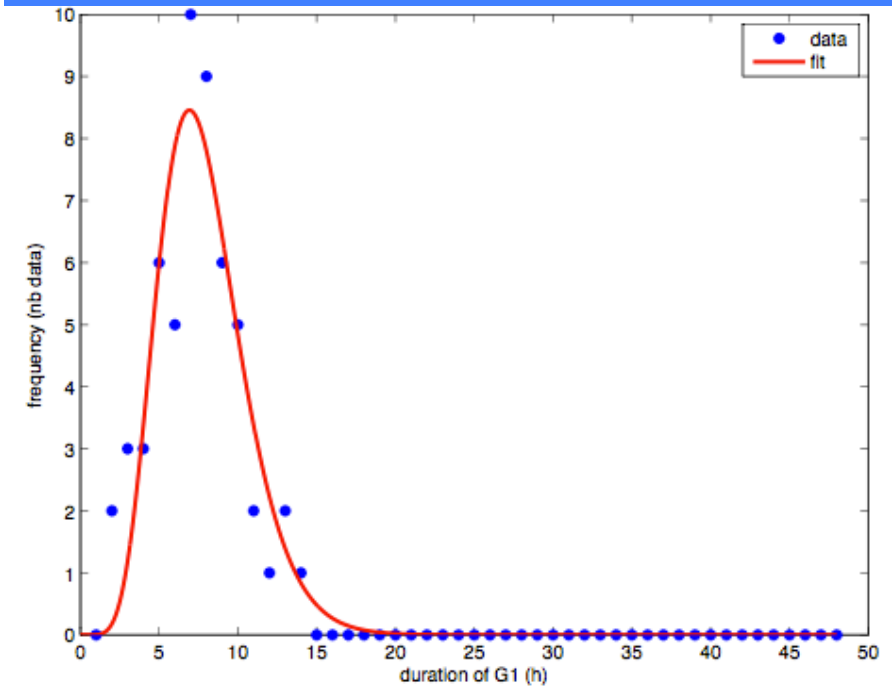


Data from Bert van der Horst's lab, Erasmus University, Rotterdam, processed by Frédérique Billy at INRIA

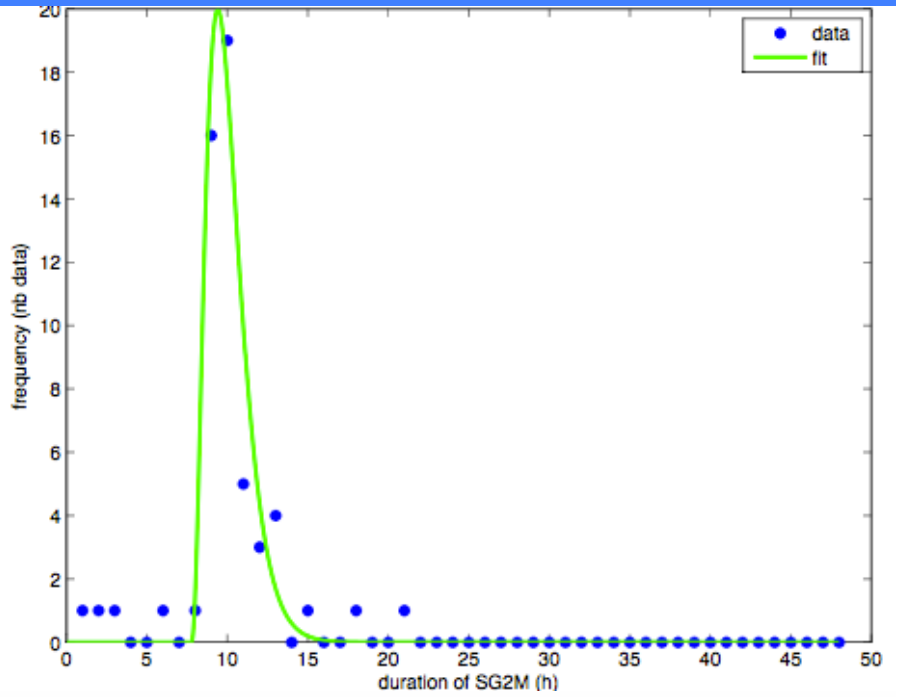
Phase durations (hence transitions, using $K(x) = \frac{f(x)}{\int_x^\infty f(y)dy}$) in age x
Pdfs *f(x)* fitted from data on 50 NIH 3T3 proliferating cells

(mouse embryonic fibroblasts)

Density of duration of G1 phase



Density of duration of SG2M



FUCCI data in NIH3T3 cells, that are healthy mouse fibroblasts tracked in liquid medium

Fitting probability density functions to data and computing λ:
Gamma p.d.f.s were best fits and yielded simple computations

$$f_i(x) = \frac{1}{\Gamma(\alpha_i)}(x-\gamma_i)^{\alpha_i-1}\beta_i^{\alpha_i}e^{-\beta_i(x-\gamma_i)}\mathbb{1}_{[\gamma_i;+\infty[}(x) \qquad i=1,2, \quad \text{where}$$

$$\alpha_1 = 8.28,\ \beta_1 = 1.052h^{-1},\ \gamma_1 = 0h,\ \alpha_2 = 3.42,\ \beta_2 = 1.47h^{-1},\ \gamma_2 = 7.75h$$

2-phase Lotka's equation simply reads:

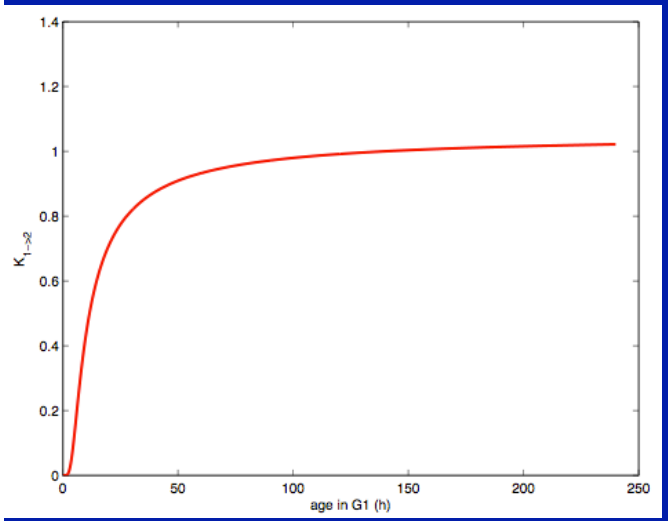
$$\left(1+\frac{\lambda}{\beta_1}\right)^{\alpha_1}\left(1+\frac{\lambda}{\beta_2}\right)^{\alpha_2}e^{\lambda(\gamma_1+\gamma_2)} = 2$$

... which yields here $\lambda = 0.039\ h^{-1}$

(and yields mean doubling time T_d=17.77 h, and mean cell cycle time T_c =17.95 h)

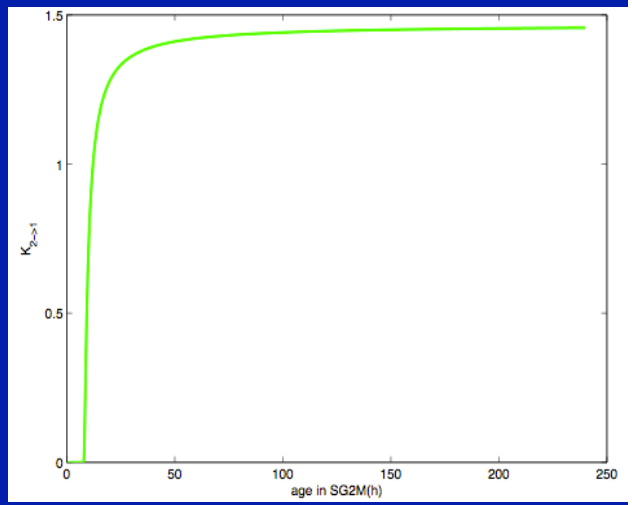
(Billy et al., Math. Comp. Simul. 2014)

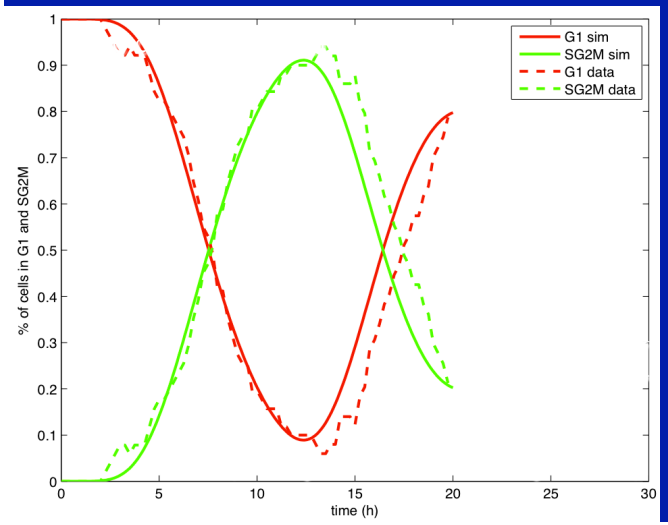
Phase transitions w.r.t. age x: Transition rates $K(x)$ from pdfs $f(x)$ on NIH 3T3 healthy cells and resulting population evolution without control on transitions

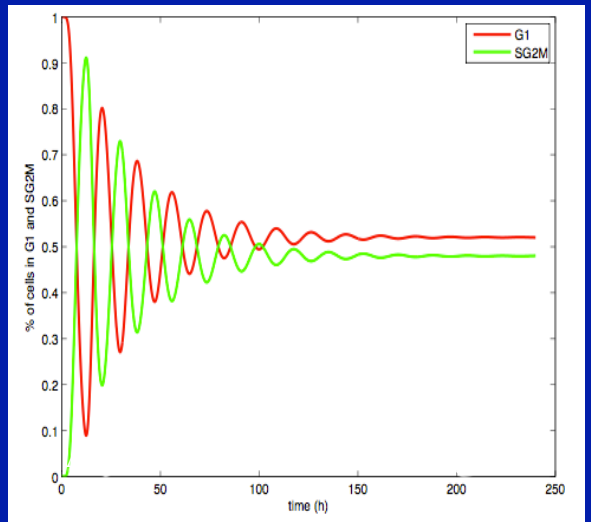


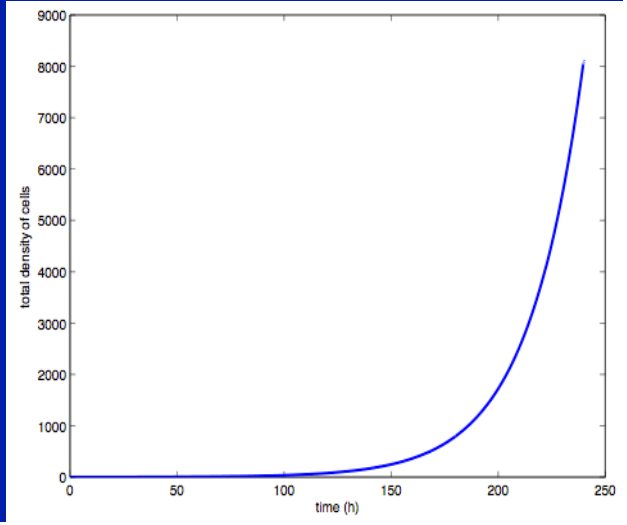
Recalling that in the model
f = p.d.f. of phase duration time
and K = phase transition kernel:

$$K_{i\to i+1}(x) = \frac{f_i(x)}{1 - \int_0^x f_i(\xi)d\xi}$$









More single cell data to build population data from IBDC (F. Delaunay, C. Feillet) in Nice

- 117+150 single NIH3T3 cell data stained by FUCCI, plus a RevErb-α track
- 117 in 10% *Fetal Bovine Serum (FBS), rich in growth factors,* and 150 in 15% FBS (150 out of many; only the ones with a robust RevErb-α circadian clock were kept as mere indicators of good health)
- Results: evaluation of phase transition rates in a 2-phase model of the cell cycle in the two concentration media
- Increasing FBS from 10 to 15% reduces standard deviation of both phase durations, suggesting increased synchrony between cell cycle phases
- Good agreement of the model behaviour with the data, evidencing higher velocity v in cell cycle progression with 15% FBS
- v: 15% FBS cell population grows approximately 10% faster than the 10% FBS

More on FUCCI to identify cell cycle phase durations: Effects of growth factors on NIH3T3 cell populations

117 cells
in 10% FBS

150 cells
in 15% FBS

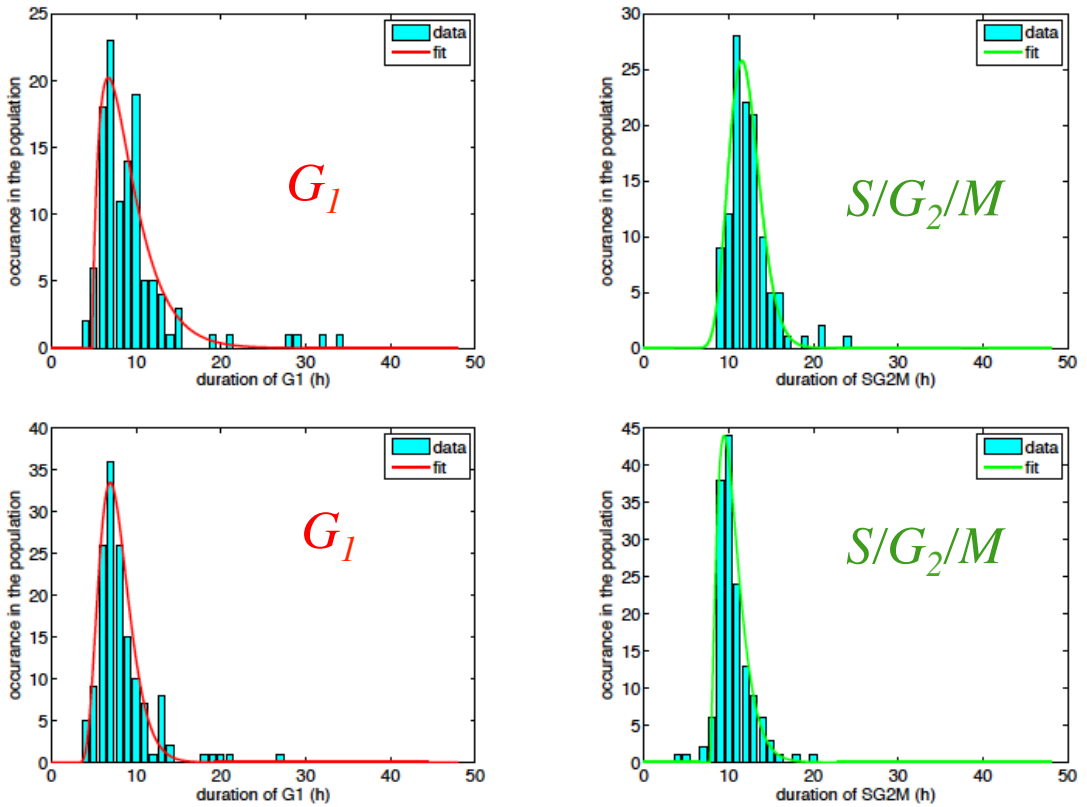


FIGURE 3. Gamma laws (solid line) (multiplied by a coefficient equal to the total number of data) that fit experimental data (bars) for the distribution of the duration of phases G_1 (left) and $S/G_2/M$ (right), for the two experimental conditions i.e., 10% FBS (top) and 15% FBS (bottom).

F. Billy et al. Math BioSci Eng 2013

Descriptive statistics: influence of growth factors on m and sd

	10% FBS		15% FBS	
	mean (h)	sd (h)	mean (h)	sd (h)
G_1	9.3	4.9	8.2	3.3
$S/G_2/M$	12.1	2.5	10.4	2.1
cycle	21.4	5.5	18.6	4.1

TABLE 1. Mean and standard deviation (sd) (in hours) of the duration of the phases G_1 and $S/G_2/M$ and of the cell cycle for two experimental conditions (culture medium composed of 10% of FBS or of 15% of FBS).

Coefficient of variation (sd/m)

G_1: 0.53 / 0.40

$S/G_2/M$: 0.21 / 0.20

	10% FBS		15% FBS	
	G_1 $(i=1)$	$S/G_2/M$ $(i=2)$	G_1 $(i=1)$	$S/G_2/M$ $(i=2)$
α_i	1.80	16.96	5.68	2.71
β_i	0.43h^{-1}	2.22h^{-1}	1.23h^{-1}	1.01h^{-1}
γ_i	4.83h	4.37h	3.13h	7.77h

TABLE 2. Parameters used to fit experimental data of the distribution of the durations of phases G_1 and $S/G_2/M$ in the population by Gamma laws, for the two experimental FBS supplementation of the medium (10% FBS and 15% FBS).

$$m = \frac{\alpha}{\beta} + \gamma \qquad sd = \frac{\sqrt{\alpha}}{\beta}$$

	10% FBS		15% FBS	
	m (h)	sd (h)	m (h)	sd (h)
G_1	9.0	3.1	7.7	1.9
$S/G_2/M$	12.0	1.9	10.5	1.6

TABLE 3. Mean (m) and standard deviation (sd) (in hours) of the Gamma distributed duration of the phases G_1 and $S/G_2/M$ for two experimental conditions (culture medium composed of 10% of FBS or of 15% of FBS), according to the parameters mentioned in Table 2.

Coefficient of variation (sd/m)

G_1: 0.34 / 0.25

$S/G_2/M$: 0.16 / 0.15

F. Billy et al. Math BioSci Eng 2013

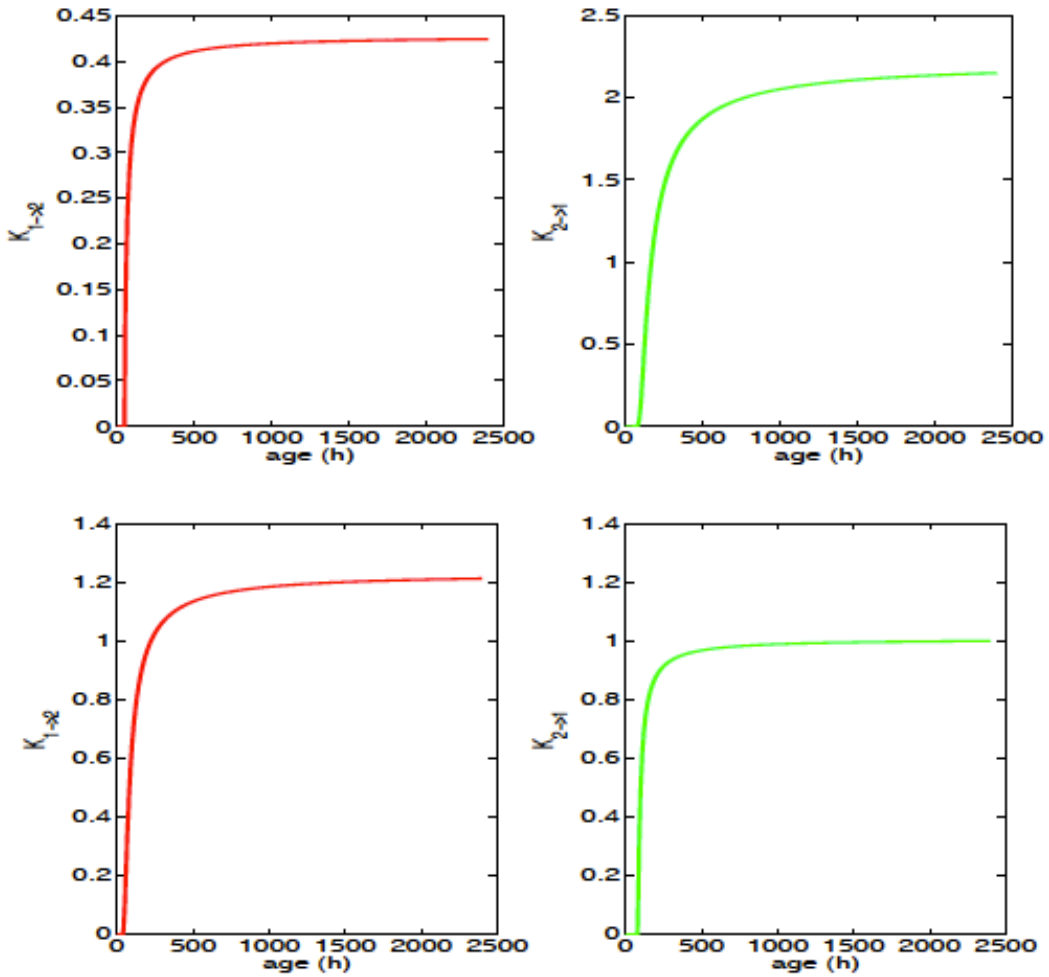


FIGURE 4. Transition rates from G_1 to $S/G_2/M$ (left) and from $S/G_2/M$ to G_1 (right) for the two experimental conditions, i.e. 10% FBS (top) and 15% FBS (bottom). These rates are functions of age of cells in the phases only.

(F. Billy et al., Math Biosci. Eng. 2013)

Taking into account different progression velocities in the cycle

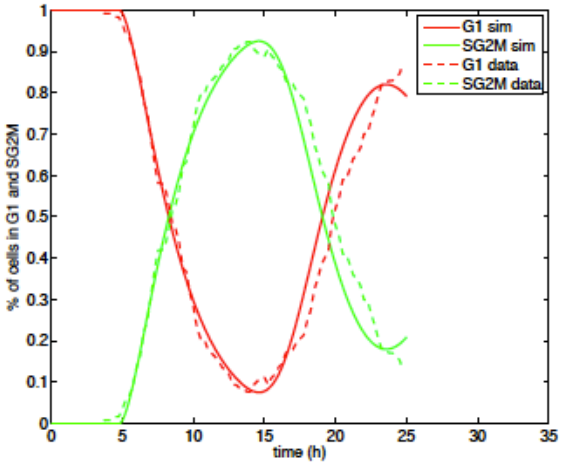
- The complete model, with speed of progression v (in age x w.r.t. time t):

$$\begin{cases} \dfrac{\partial}{\partial t} n_i(t,x) + \dfrac{\partial}{\partial x}\left(v_i(x)\, n_i(t,x)\right) + \left(d_i(t,x) + K_{i\to i+1}(t,x)\right) n_i(t,x) = 0 \\ n_i(t,x=0) = \displaystyle\int_{\xi\geq 0} K_{i-1\to i}(t,\xi)\, n_{i-1}(t,\xi)\, d\xi \quad 2 \leq i \leq I \ , \\ n_1(t,x=0) = 2\displaystyle\int_{\xi\geq 0} K_{I\to 1}(t,\xi)\, n_I(t,\xi)\, d\xi \ . \end{cases}$$

- ... or, choosing a constant speed v independent of age x and phase i:

$$\begin{cases} \dfrac{\partial}{\partial t} n_i(t,x) + v\, \dfrac{\partial}{\partial x} n_i(t,x) + \ K_{i\to i+1,10\%}(x)\ \ n_i(t,x) = 0 \qquad i = 1,2 \\ n_2(t,x=0) = \displaystyle\int_{\xi\geq 0} K_{1\to 2,10\%}(\xi)\, n_1(t,\xi)\, d\xi \ , \\ n_1(t,x=0) = 2\displaystyle\int_{\xi\geq 0} K_{2\to 1,10\%}(\xi)\, n_2(t,\xi)\, d\xi \ , \end{cases}$$

Results: better fit with evaluation of varying speed v



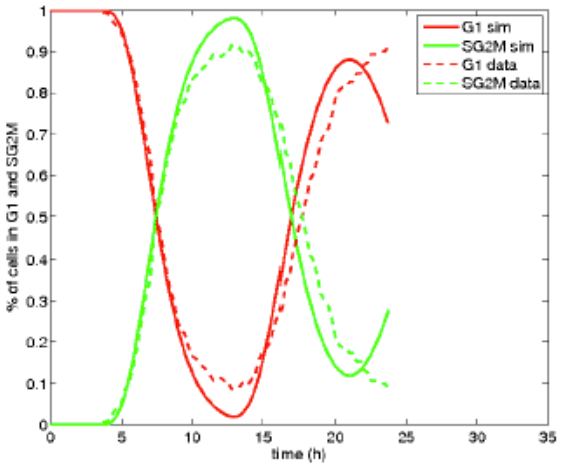


FIGURE 5. Time evolution of the percentages of cells in G_1 (red or deep grey) and $S/G_2/M$ (green or light grey) phases from biological data (dashed line) and from numerical simulations (solid line), in the case of 10% FBS (top) and 15% FBS (bottom). Our model results in a good approximation of the biological data.

Setting free the parameter v = speed of progression in the cell cycle for 15% FBS cells (with basis v=1 in the 10% FBS cell population) yielded v=1.095 in the 15% FBS cell population and better fit of model to experimental data (with T_d=15.4 h instead of 18.1 h in 15% FCS compared with T_d=20.8 h in 10% FCS)

v=1.095 in 15% FCS

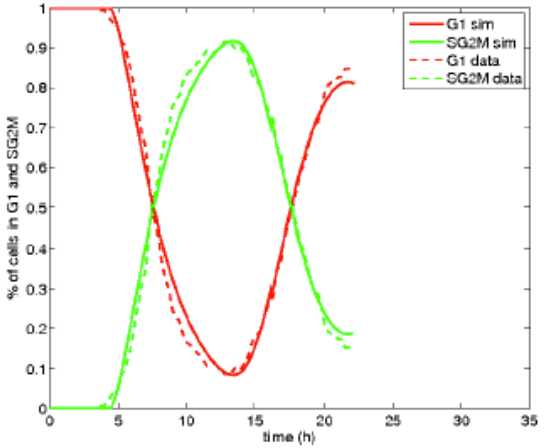
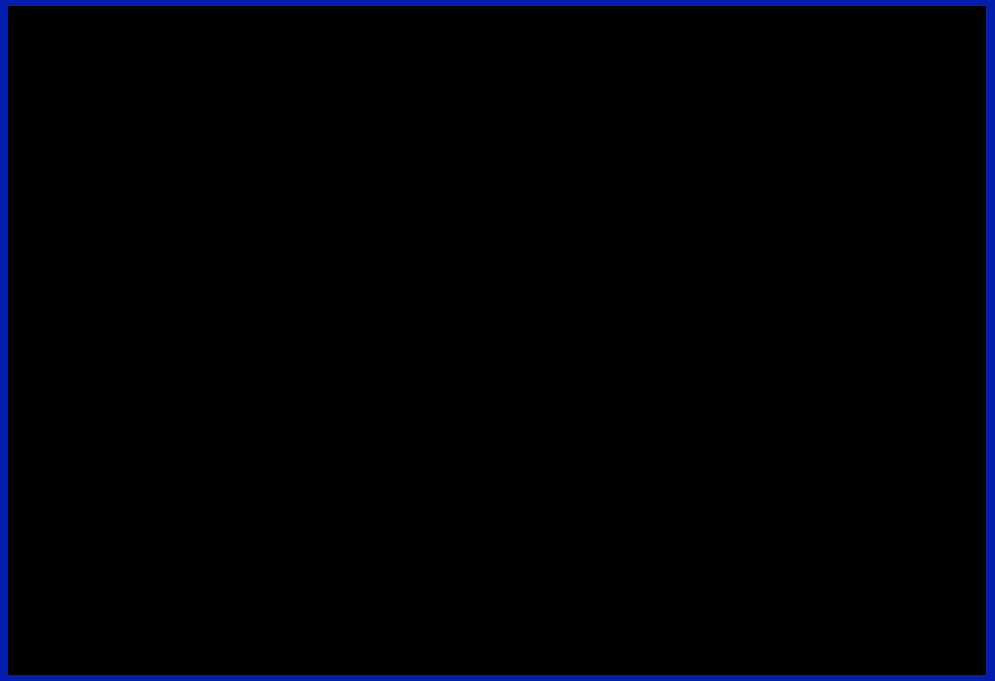


FIGURE 7. Time evolution of the percentages of cells in G_1 (red or deep grey) and $S/G_2/M$ (green or light grey) phases from biological data in the case of 15% FBS (dashed line) and from numerical simulations (solid line) resulting from Equations (13) for $v = 1.095$. Our model results in a good approximation of the biological data.

(F. Billy et al., Math Biosci. Eng. 2013)

A possible application to the investigation of synchronisation between cell cycle phases



(from Lodish et al., Molecular cell biology, Nov. 2003)

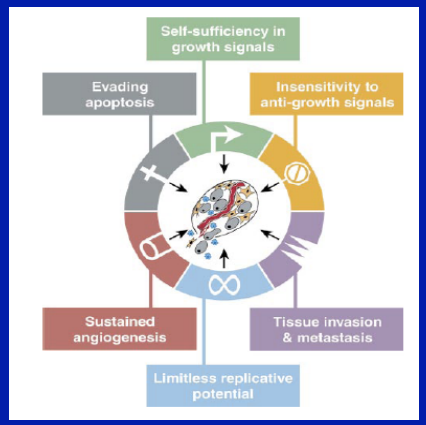
One cell divides in two: a physiologically controlled process at cell and tissue levels in all healthy and fast renewing tissues (gut, bone marrow) that is *disrupted in cancer:*

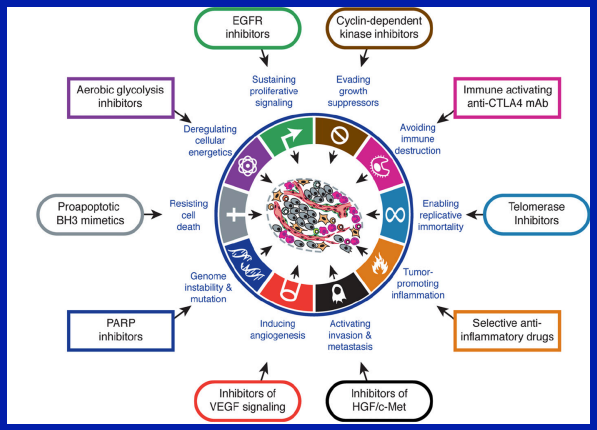
Is cell cycle phase synchronisation a mark of health in tissues?

A working hypothesis that could explain differences in responses to drug treatments between healthy and cancer tissues

Healthy tissues, i.e., cell populations, would be well synchronised w. r. to proliferation rhythms and w. r. to circadian clocks, whereas…

...tumour cell populations would be desynchronised w. r. to both, and such proliferation desynchronisation would be a consequence of an escape by tumour cells from central circadian clock control messages, just as they evade most physiological controls, cf. e.g., Hanahan & Weinberg:





Question:
is cell cycle phase desynchronisation another hallmark of cancer ***in cell populations****?*

A mathematical result: λ increases with desynchronisation

where desynchronisation is defined as a measure of phase overlapping at transition

Proliferation, as measured by the Malthus growth exponent, or first eigenvalue, increases with overlapping between cell cycle phases

i.e., the less synchronised phases are, the faster is proliferation

(NB: so far, this has not been extended to the periodic control case, i.e., phase transitions have been assumed to be uncontrolled)

i.e.,for a given family (f_i) of p.d.f.s with second moment σ_i, λ is increasing with each σ_i

Proposition 1. *Soit f_i, $1 \leq i \leq I$, une famille de fonctions de densité sur $\mathbb{R}_+$. Les taux de transition associés $K_{i\to i+1}$ sont ainsi donnés par (voir (2)) :*

$$K_{i\to i+1}(x) = \frac{f_i(x)}{\int_x^{+\infty} f_i(x')dx'} = \frac{f_i(x)}{1 - \int_0^x f_i(x')dx'}$$

En supposant $d_i = 0$ $(1 \leq i \leq I)$, la première valeur propre du système (1) $\lambda > 0$ est donnée par (voir [1]) :

$$\frac{1}{2} = \prod_{i=1}^{I} \int_0^{+\infty} f_i(x) e^{-\lambda x} dx$$

Pour $1 \leq i \leq I$, on pose $e_i = \int_0^{+\infty} x f_i(x)dx$ et $\sigma_i^2 = \int_0^{+\infty} x^2 f_i(x)dx - e_i^2$, et on suppose que les $e_i > 0$ sont constants. Soit $j \in \{1, ..., I\}$. On suppose que les σ_i^2 $(1 \leq i \neq j \leq I)$ sont constants.

Alors λ est croissante avec σ_j^2.

(Thomas Ouillon's INRIA internship report 2010, also shown in Billy et al., Math. Comp. Simul., 2014)

Simple age-structured PDE models representing exchanges between proliferation and quiescence

$$\frac{\partial}{\partial t}p(t,x) + \frac{\partial}{\partial x}p(t,x) + [K(x) + \gamma(t)]p(t,x) = 0$$

$$\frac{\partial}{\partial t}q(t,x) + \frac{\partial}{\partial x}q(t,x) + [\beta(t) + \delta(t)]q(t,x) = 0$$

$$\text{with :}$$

$$p(0,x) = p^0(x),$$

$$q(0,x) = q^0(x),$$

$$p(t,0) = \beta(t)\int_0^\infty q(t,\xi)d\xi,$$

$$q(t,0) = 2\int_0^\infty K(\xi)p(t,\xi)d\xi$$

p=density of proliferating cells; *q*=density of quiescent cells; γ,δ=death terms;
K=term describing cells leaving proliferation to quiescence, due to mitosis;
β=term describing "reintroduction" (or recruitment) from quiescence to proliferation

Delay differential models with two cell compartments, proliferating (P)/quiescent (Q): *Haematopoiesis models*

(obtained from the previous model with additional hypotheses and integration in x along characteristics)

$$\frac{dP}{dt} + \gamma P - \beta(Q(t))Q(t) + \beta(Q(t-\tau))e^{-\gamma\tau}Q(t-\tau) = 0$$

$$\frac{dQ}{dt} + [\beta(Q(t)) + \delta]Q - 2\beta(Q(t-\tau))e^{-\gamma\tau}Q(t-\tau) = 0$$

$$\text{where } \beta(Q) = \frac{\beta_0\theta^n}{\theta^n + Q^n}$$

(delay τ = cell division cycle time)

(from Mackey, Blood 1978)

Properties of this model: depending on the parameters, one can have positive stability, extinction, explosion, or sustained oscillations of both populations

(Hayes stability criteria, see Hayes, J London Math Soc 1950)

Oscillatory behaviour is observed in *periodic Chronic Myelogenous Leukaemia* (*CML*) where oscillations with limited amplitude are compatible with survival, whereas explosion (blast crisis, alias acutisation) leads to *AML* and death

(Mackey and Bélair in Montréal; Adimy, Bernard, Crauste, Pujo-Menjouet, Volpert in Lyon)

From Adimy, Crauste, ElAbdllaoui J Biol Syst 2008 (see also: Özbay, Bonnet, Benjelloun, JC MMNP 2012)

Modelling haematopoiesis for *Acute Myeloblastic Leukaemia* (AML)

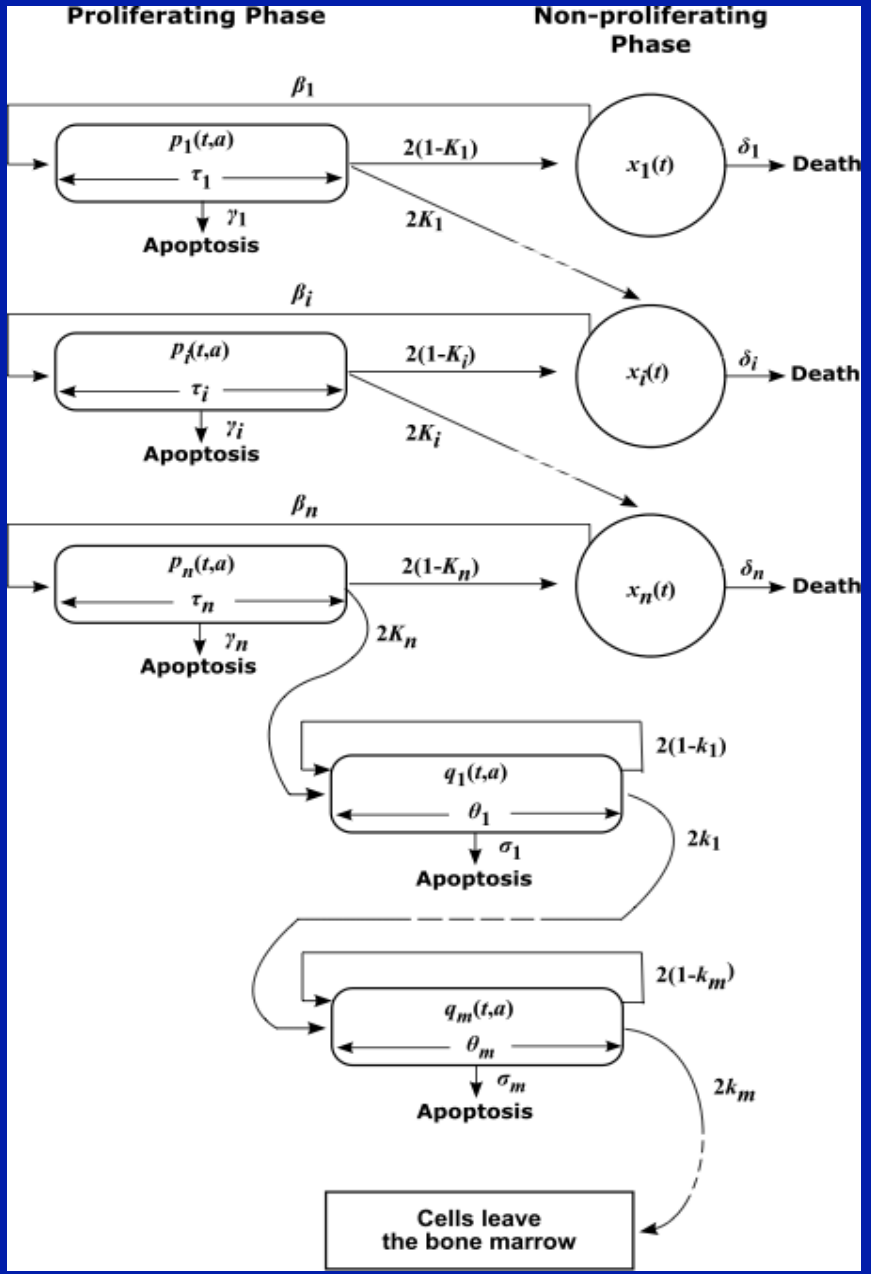
…aiming at *non-cell-killing therapeutics* by inducing *re-differentiation of cells using molecules (e.g. ATRA) enhancing differentiation rates represented by K_i terms*

$$\begin{aligned}
&\frac{\partial r_i}{\partial t} + \frac{\partial r_i}{\partial a} = -(\delta_i + \beta_i)\, r_i, && a > 0,\ t > 0,\\
&\frac{\partial p_i}{\partial t} + \frac{\partial p_i}{\partial a} = -(\gamma_i + g_i(a))\, p_i, && 0 < a < \tau_i,\ t > 0
\end{aligned}$$

where r_i and p_i represent resting and proliferating cells, respectively, with reintroduction term $\beta_i = \beta_i(x_i)$ positive decaying to zero, with population argument: $x_i(t) := \int_0^{+\infty} r_i(t,a)da$

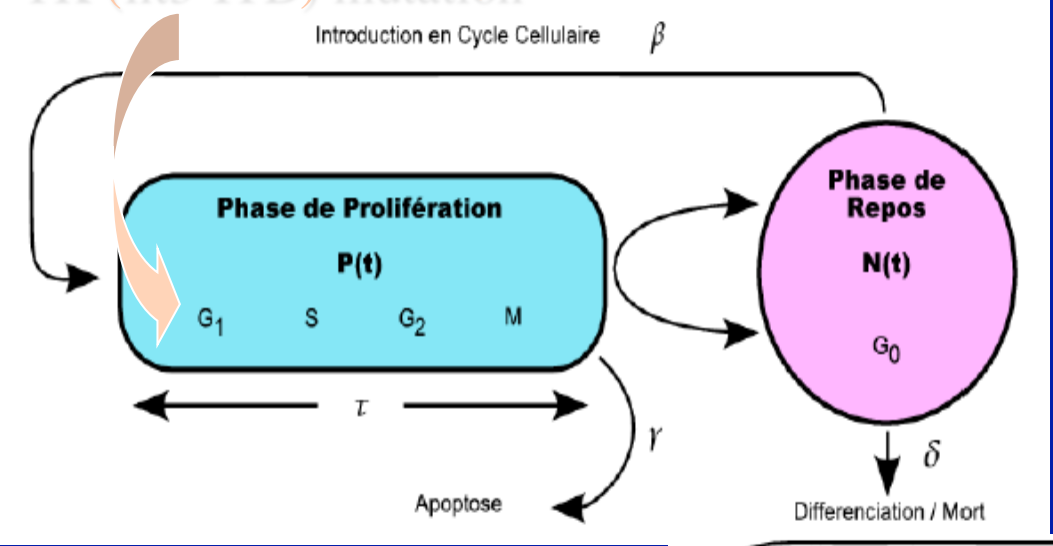
and boundary conditions:

$$\begin{cases}
r_1(t,0) = 2(1-K_1)\displaystyle\int_0^{\tau_1} g_1(a)p_1(t,a)da,\\
r_i(t,0) = 2(1-K_i)\displaystyle\int_0^{\tau_i} g_i(a)p_i(t,a)da\\
\qquad\qquad +2K_{i-1}\displaystyle\int_0^{\tau_{i-1}} g_{i-1}(a)p_{i-1}(t,a)da, \qquad i \geq 2,\\
p_i(t,0) = \displaystyle\int_0^{+\infty} \beta_i(x_i(t))r_i(t,a)da = \beta_i(x_i(t))x_i(t), \quad i \in I_n,\\
\lim\limits_{a\to+\infty} r_i(t,a) = 0.
\end{cases}$$



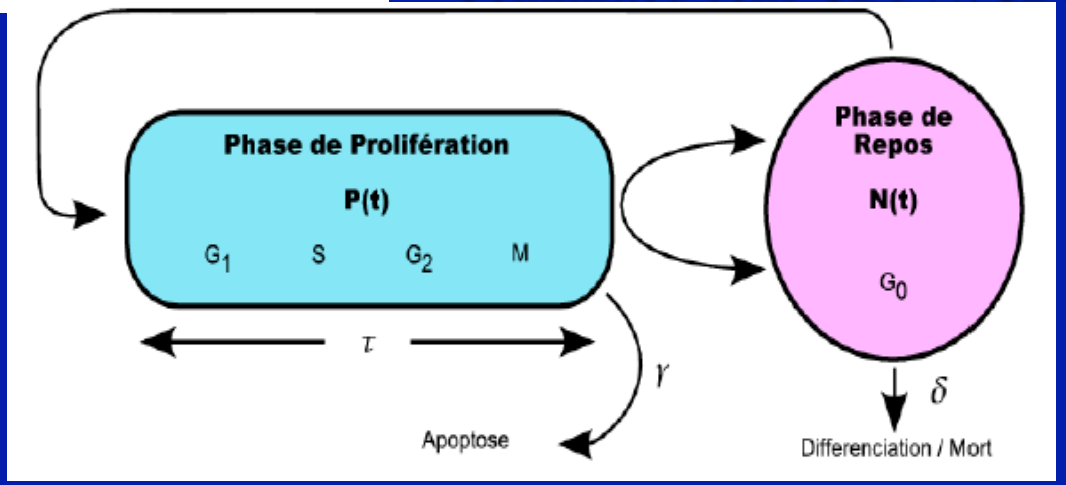
Modelling leukaemic haematopoiesis (Mackey/Adimy) : proliferation advantage?

TK (flt3-ITD) mutation



'Stem-like' cells CD34+/CD38-

Committed cells CD34+/CD38+



Blood/ bone marrow sampling in AML patients
Cell sorting (magnetic beads)

FACS for cell cycle phases
Self-renewal: critical penomenon
Measuring apoptosis and cell division in each population should lead to model identification

An age[a]-and-cyclin[x]-structured PDE model with proliferating and quiescent cells

(exchanges between *(p)* and *(q)*, healthy and tumour tissue cases: G_0 to G_1 recruitments G from q to p differ)

$$\begin{cases} \dfrac{\partial}{\partial t}p(t,a,x) + \dfrac{\partial}{\partial a}\left(\Gamma_0 p(t,a,x)\right) + \dfrac{\partial}{\partial x}\left(\Gamma_1(a,x)\,p(t,a,x)\right) = \\ -\left(L(a,x) + F(a,x) + d_1\right)p(t,a,x) + G\left(N(t)\right)q(t,a,x), \\ \dfrac{\partial}{\partial t}q(t,a,x) = L(a,x)\,p(t,a,x) - \left(G\left(N(t)\right) + d_2\right)q(t,a,x). \end{cases}$$

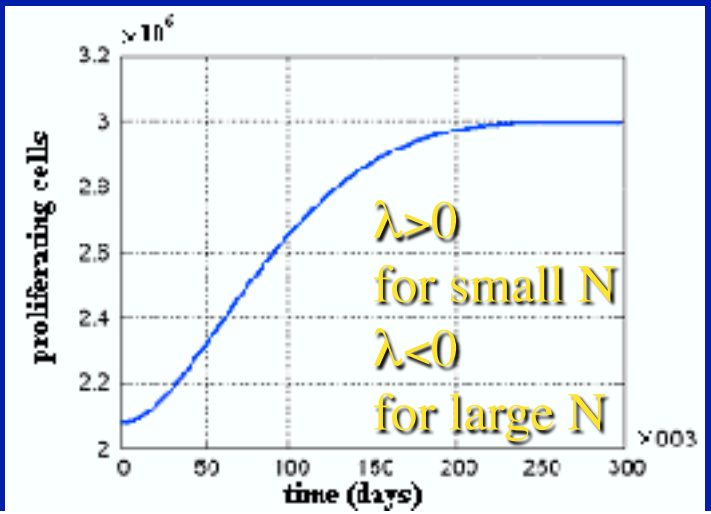
N=p+q: total number of cells
L: leak term from *p* to *q*
F: mitosis

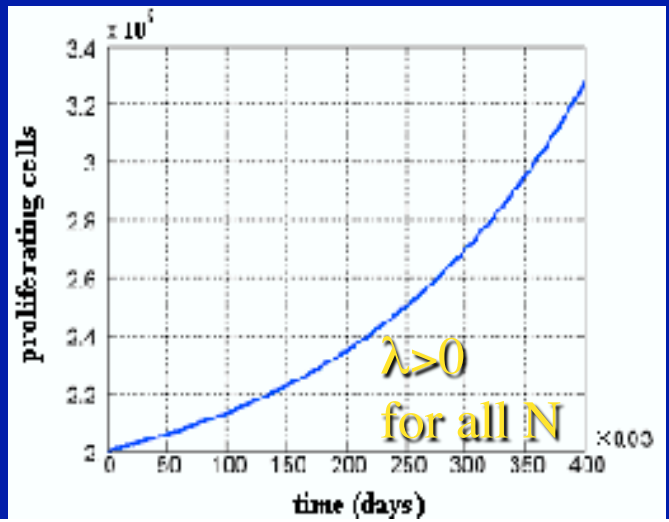
$$G(N) = \frac{\alpha_1\theta^n}{\theta^n + N^n}$$

Healthy tissue recruitment *G*: homeostasis

$$G(N) = \frac{\alpha_1\theta^n + \alpha_2 N^n}{\theta^n + N^n}$$

Tumour recruitment *G*: *(α_2>0)* exponential growth





F. Bekkal Brikci, JC, B. Ribba, B. Perthame J Math Biol 2008; Math Comp Mod 2008; M. Doumic-Jauffret, MMNP 2007

Age[a]-and-cyclin[x]-structured PDE model, continued

Note that if one sets $\lambda_1=0$ and $n=1/k$, k integer, then one can obtain t^k power-law growth

$$G(N) = \frac{\alpha_1 \theta^n}{\theta^n + N^n}$$

Healthy tissue recruitment G: homeostasis

$$G(N) = \frac{\alpha_1 \theta^n + \alpha_2 N^n}{\theta^n + N^n}$$

Tumour recruitment G: ($\alpha_2>0$) exponential growth

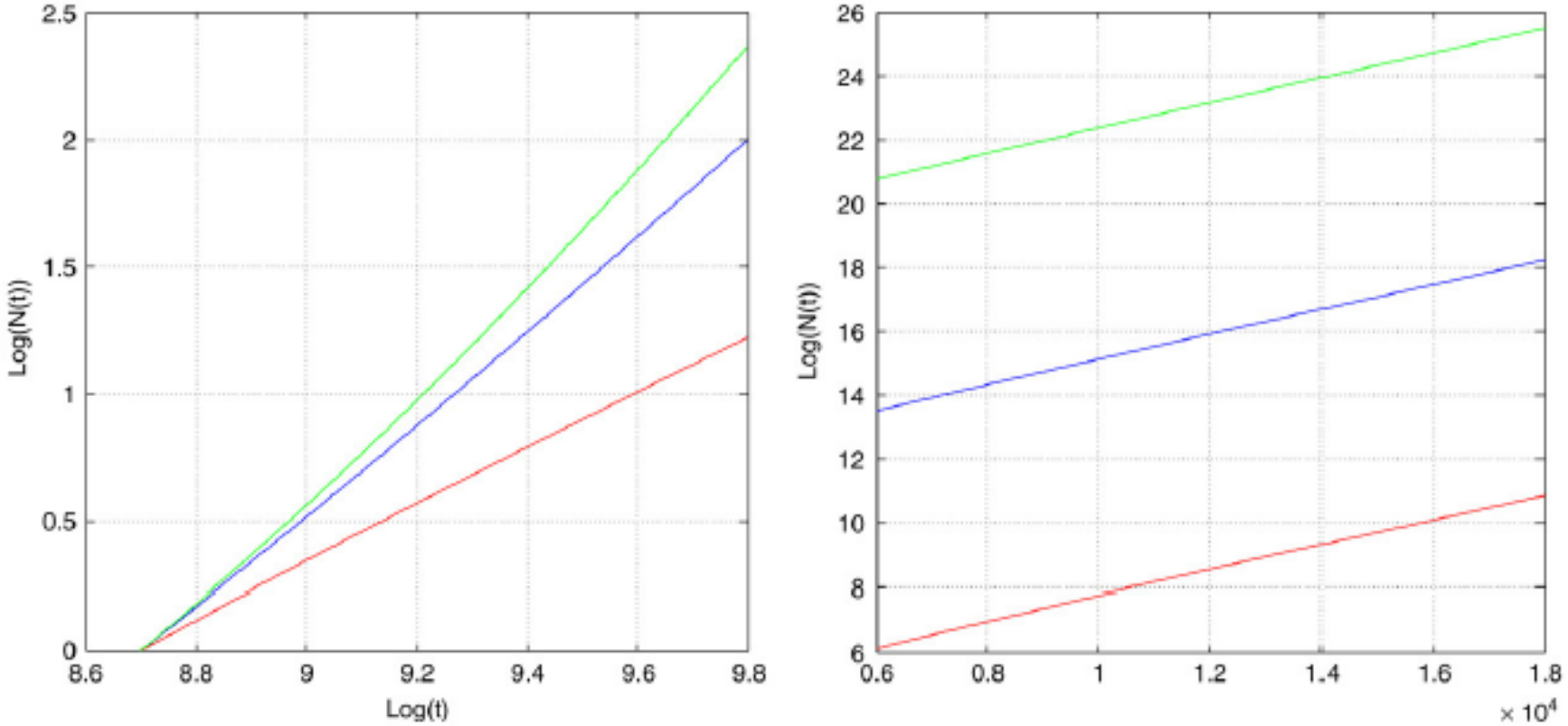


Fig. 5. Evolution of the total cell population $\int_0^{+\infty}\int_0^{+\infty} q(t,a,x)\mathrm{d}a\mathrm{d}x + \int_0^{+\infty}\int_0^{+\infty} p(t,a,x)\mathrm{d}a\mathrm{d}x$ for a tumoral tissue with different values of $n = 1$ (lower curves), $n = 1/2$ (medium), $n = 1/3$ (upper). Left: With polynomial growth, $\lambda_1 = 0$, and a log–log scale (this shows the different power laws). Right: With exponential growth, $\lambda_1 > 0$, and a Log scale (this shows that n does not influence the exponential law).

(Bekkal Brikci et al., Math Comp Modelling 2008)

To conclude this first part on models, quoting Aristotle:

ἔοικε δ΄ ὅ τε λόγος τοῖς φαινομένοις μαρτυρεῖν, καὶ τὰ φαινόμενα τῷ λόγῳ

i.e., "It is appropriate to the model to testify for the phenomena, and to the phenomena for the model"

(in Aristotle's *Περί Ουρανού [Sky], from which I freely translate λόγος by model)*