"Mathematical models and numerical methods in biomedicine", Moscow, Nov. 2016

An evolutionary perspective on cancer, with applications to anticancer drug resistance modelling and perspectives in therapeutic control

Luis Almeida, Rebecca Chisholm, *Jean Clairambault*[†], Alexandre Escargueil, Tommaso Lorenzi, Alexander Lorz, Benoît Perthame, Camille Pouchol, Emmanuel Trélat

Mamba INRIA team & Laboratoire Jacques-Louis Lions, UPMC, Paris

[†] *http : //www.rocq.inria.fr/bang/JC/Jean_Clairambault_en.html*

IUC INSTITUT UNIVERSITAIRE DE CANCÉROLOGIE FACULTÉ DE MÉDECINE PIERRE & MARIE CURIE — UPMC SORBONNE UNIVERSITÉS — JJL cnrs — Inria — PARIS DIDEROT — Mamba MODELLING AND ANALYSIS FOR MEDICAL AND BIOLOGICAL APPLICATIONS

Motivations

- Drug resistance: still a major pitfall of cancer therapeutics
- Accounting for drug resistance in cancer requires considering the level of *cancer cell populations*
- Phenotype heterogeneity in cancer cell populations is likely the main cause of drug resistance
- Heterogeneity in cancer cell populations may be due to *fast backward evolution* ('atavistic theory of cancer')
- We assess it by biological and mathematical models of evolving *heterogeneous* cell populations, structured in traits coding relevant biological variability
- Therapeutic strategies should rely on optimal control algorithms with targets in such models of heterogeneous cell populations

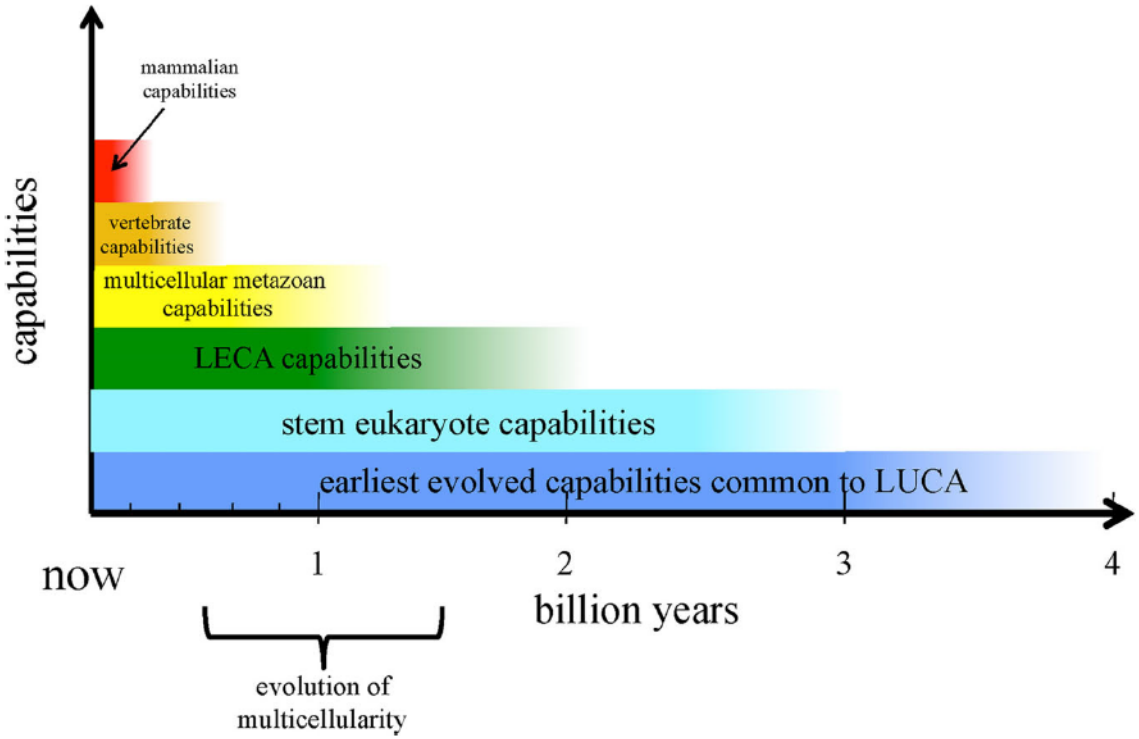
Heterogeneity and plasticity in cancer cell populations

(Summary)

- Intra-tumour heterogeneity, i.e., between-cell variability within cancer cell populations, accounts for drug resistance.
- Added to heterogeneity, evolutionary mechanisms of the great evolution that has designed multicellular organisms, and also smaller windows of evolution on the time scale of human disease, are responsible for drug resistance.
- Plasticity in cancer cells, i.e., partial reversal to a stem-like status in individual cells and resulting adaptability of cancer cell populations, is a backward evolution making cancer cell populations resistant to drug insult.
- Heterogeneity and plasticity are captured by physiologically based mathematical models (PDEs) of cell populations structured in continuous phenotypic variables.
- Such models of cell population dynamics predict drug resistance in cancer; together with optimal control methods, they can help circumvent drug resistance by combined therapeutic strategies, ultimately applied in the clinic.

A possible evolutionary framework (*diachronic view*): the atavistic hypothesis of cancer (1)

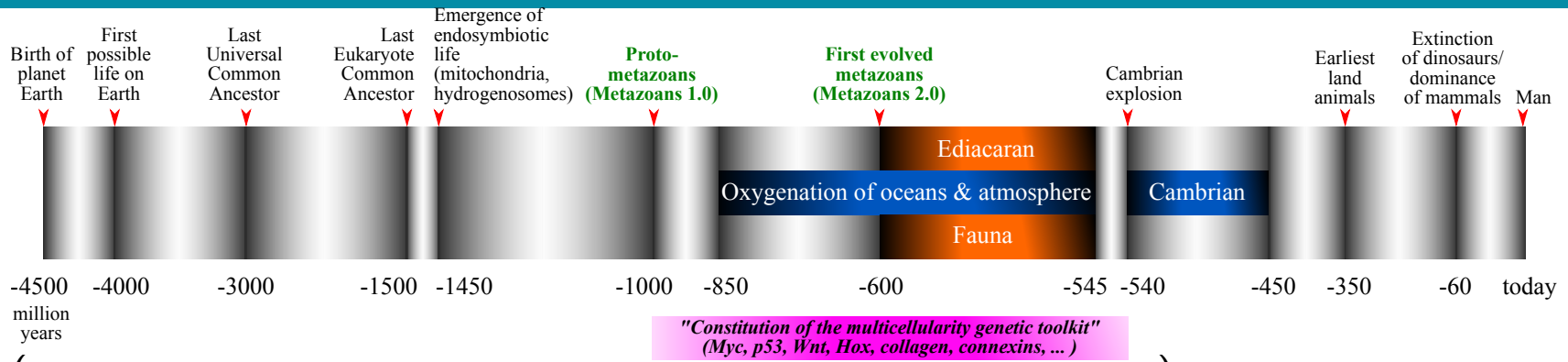
"Nothing in biology makes sense except in the light of evolution" (Th. Dobzhansky, 1973)



"Cancer: more archeoplasm than neoplasm" (Mark Vincent, 2011)

References: *Israel JTB 1996, Davies & Lineweaver Phys Biol 2011, Vincent Bioessays 2011, Lineweaver, Davies & Vincent Bioessays 2014, Chen et al. Nature Comm 2015. Also Wu et al. PNAS 2015 on "cold genes", "hot genes", evolvability and robustness .*

A possible evolutionary framework (*diachronic view*): the atavistic hypothesis of cancer (2)



(*see Chisholm et al. 2016, BBA General Subjects DOI:10.1016/j.bbagen.2016.06.009*)

- The genes that have appeared in the process of development to multicellularity are precisely those that are altered in cancer
- In what order in evolution, from 1) proliferation+apoptosis to 2) cell differentiation +division of work, and to 3) *epigenetic control* of differentiation and proliferation?
- Reconstituting the phylogeny of this 'multicellularity toolkit' should shed light on the robustness or fragility of genes that have been altered in cancer
- Attacking cancer on proliferation is precisely attacking its robustness. It would be better to attack its weaknesses (e.g. absence of adaptive immune response)

Why resistance in cancer, not in healthy, cell populations?

- According to the atavistic hypothesis, cancer is a 'backward evolution' from a sophisticated form of multicellularity (us), in which epigenetic processes control gene regulatory networks of transcription factors: differentiation factors, p53, etc., that physiologically control the basis of cellular life, i.e., proliferation

- We bear in our genomes many attempts of species evolution since billions of years; dead-end tracks ('unused attractors' in S. Huang and S. Kauffman's version of the Waddington landscape) have been silenced (e.g., by epigenetic enzymes, resulting in evolutionary barriers in this landscape), but are still there

- In cancer, global regulations are lost, differentiation is out of control, so that local proliferations without regulation overcome; sophisticated *adaptive epigenetic mechanisms are present, not controlling proliferation, but serving it*

- Primitive forms of cooperation between specialised cells in a locally organised multicellular collection (tumour), with plasticity between them, may be present, exhibiting coherent intratumoral heterogeneity, and escaping external control

- The basic cancer cell is highly plastic and highly capable of adaptation to a hostile environment, as were its ancestors in a remote past of our planet (poor O_2, acidic environment, high UV radiations,...) *and likely presently even more*

Can resistance be assessed by biological experiments? (1)

First hint: cell heterogeneity in Luria and Delbrück's experiment (1943)

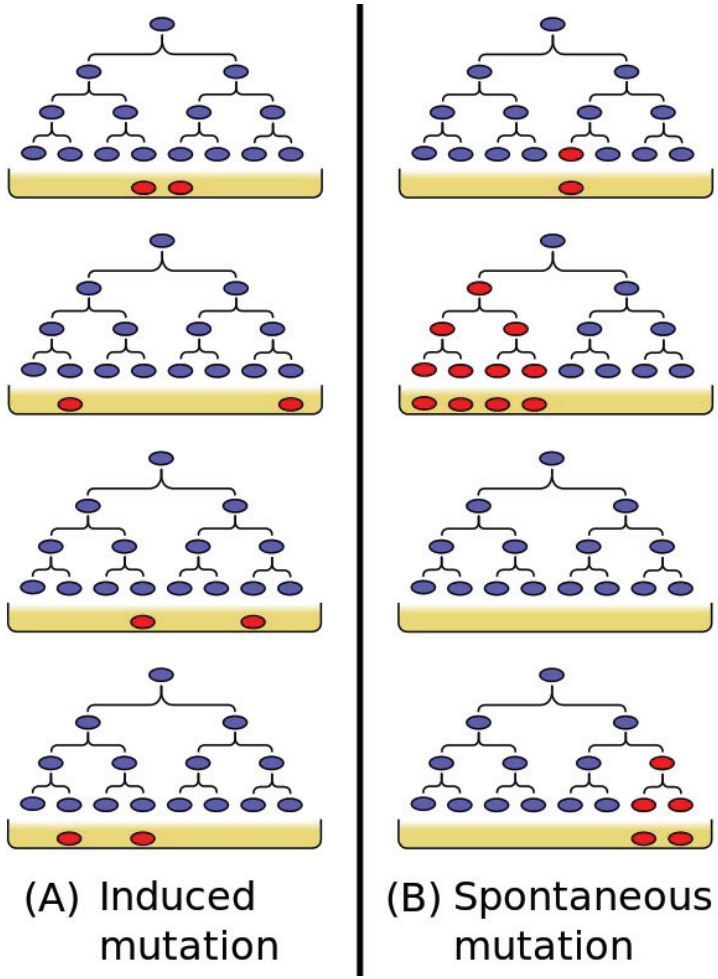
Different Petri dishes, same experimental settings

Bacterial populations firstly proliferating freely, then exposed to a phage environment: some will show resistance to the phages

Question: Is resistance induced by the phage environment, scenario (A)? Or was it preexistent in some subclones, due to random mutations at each generation, and selection by the phages, scenario (B)?

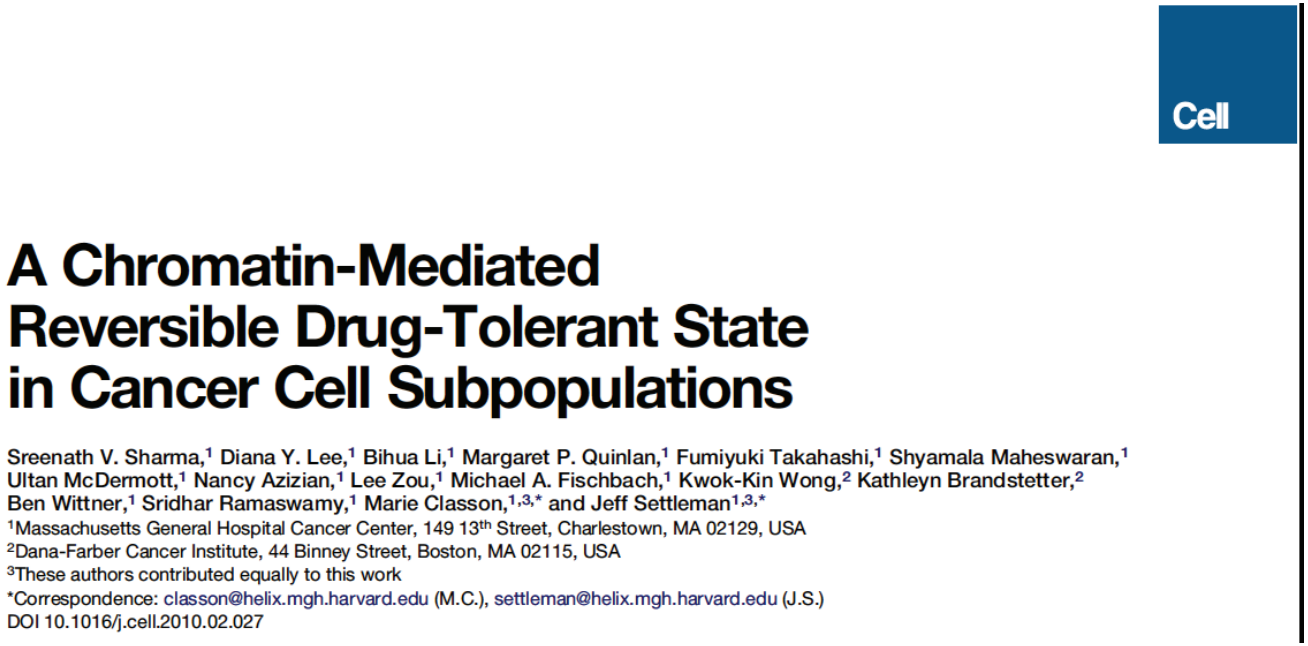
Experiment: the answer is always (B): preexistent mutations before selection

However, bacteria are not cancer cells! In particular, they are far from being able of the same plasticity (no differentiation is available for them)



(*Luria & Delbrück, Genetics, 1943*)

Can it be assessed by biological experiments? (2) Reversible drug resistance of cancer cells in a Petri dish



Cell

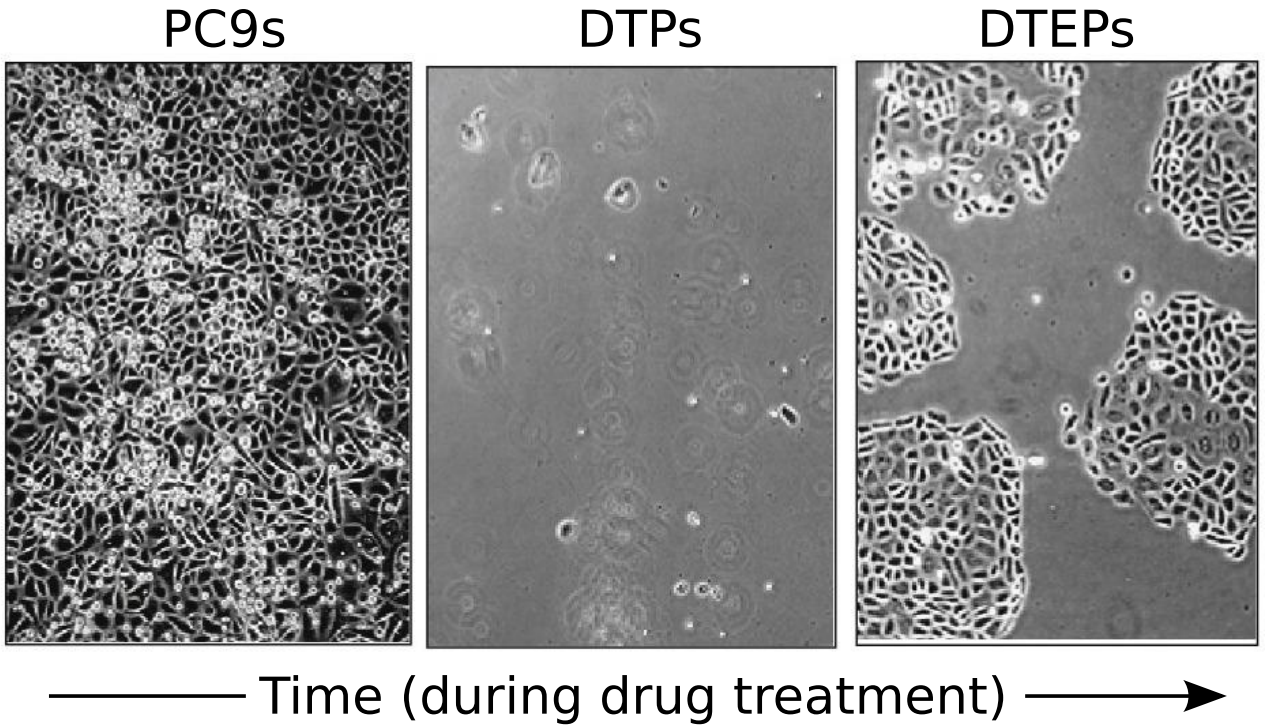
A Chromatin-Mediated Reversible Drug-Tolerant State in Cancer Cell Subpopulations

Sreenath V. Sharma,[1] Diana Y. Lee,[1] Bihua Li,[1] Margaret P. Quinlan,[1] Fumiyuki Takahashi,[1] Shyamala Maheswaran,[1] Ultan McDermott,[1] Nancy Azizian,[1] Lee Zou,[1] Michael A. Fischbach,[1] Kwok-Kin Wong,[2] Kathleyn Brandstetter,[2] Ben Wittner,[1] Sridhar Ramaswamy,[1] Marie Classon,[1,3,*] and Jeff Settleman[1,3,*]
[1]Massachusetts General Hospital Cancer Center, 149 13th Street, Charlestown, MA 02129, USA
[2]Dana-Farber Cancer Institute, 44 Binney Street, Boston, MA 02115, USA
[3]These authors contributed equally to this work
*Correspondence: classon@helix.mgh.harvard.edu (M.C.), settleman@helix.mgh.harvard.edu (J.S.)
DOI 10.1016/j.cell.2010.02.027

- Motivation for math: to account for biological observations of a reversible drug-resistant phenotype in cancer cell populations, *Sharma et al., Cell 2010*
- Underlying hypothesis: epigenetic modifications affect differently survival and proliferation potentials in cancer cell populations exposed to high drug doses
- 2 proposed traits: x, stress survival potential ($\sim$ resistance to apoptosis) and y, proliferation potential ($\sim$ cell division cycle enhancement), both reversible
- A PDE model and an agent-based (AB) model show the same behaviour

Sum-up of the *Sharma et al.* paper

- Population of PC9 (NSCLC) cells under high doses of drugs (e.g., gefitinib)
- 99.7% cells die, .3% survive in this maintained hostile drug environment: DTPs
- In the same hostile environment, 20% of DTPs resume proliferation: DTEPs
- Total reversibility to drug sensitivity is obtained by drug withdrawal, occurring after 9 doubling times for DTPs, and 90 doubling times for DTEPs
- Inhibition of epigenetic enzyme KDM5A blocks emergence of DTPs (*precisely: provokes rapid death of both DTPs and DTEPs, not affecting PC9s*)



(Sharma et al., Cell 2010)

Modelling framework: structured population dynamics

- Description of evolution of a population *in time t and in relevant trait x*
- 'Structure variable' x: trait chosen as bearing the biological variability at stake
- Variable : $n(x,t)$ population density of individuals bearing trait x at time t
- (1) Evolution in numbers of individuals constituting the population

$$t \mapsto \rho(t) = \int_0^1 n(x,t)\, dx \qquad \text{(if, e.g., } x \in [0,1]\text{)}$$

- (2) Asymptotics of distribution of the trait in the population

$$x \mapsto lim_{t \to +\infty} \frac{n(x,t)}{\rho(t)}$$

- Cancer cell populations: (1) tumour growth; (2) asymptotic distribution of trait
- Space is not necessarily a relevant structure variable when studying drug control

2D continuous phenotype-structured PDE model

- Initial (PC9) cancer cell population structured by a 2D phenotype (x, y):
  $x \in [0, 1]$: normalised expression level of survival potential phenotype, and
  $y \in [0, 1]$: normalised expression level of proliferation potential phenotype
  (both biologically relying on, e.g., levels of methylation in DNA and histones)

- Population density of cells $n(x, y, t)$ with phenotypic expression (x, y) at time t satisfies

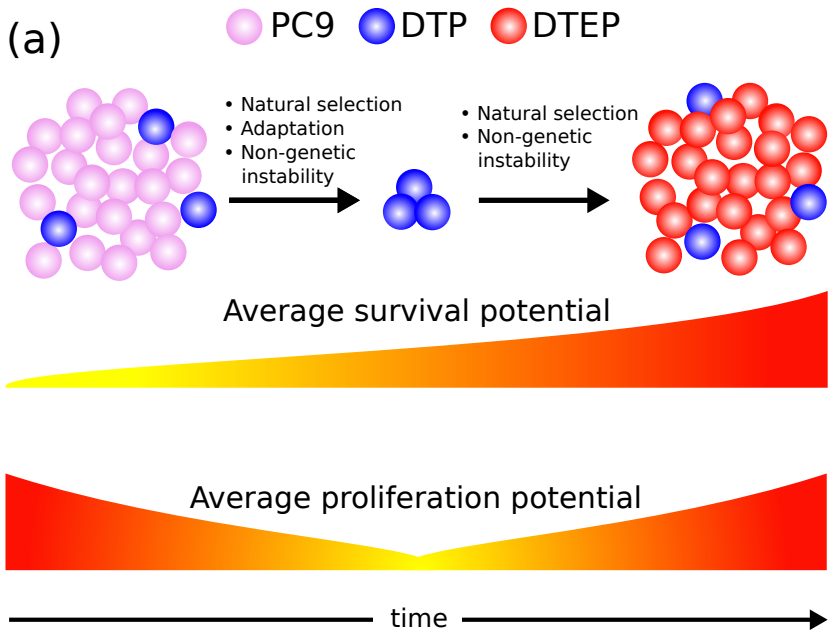
$$\frac{\partial n}{\partial t}(x, y, t) + \underbrace{\frac{\partial}{\partial y}\Big(v(x, c(t); \bar{v})n(x, y, t)\Big)}_{\text{Stress-induced adaptation of the proliferation level}} =$$

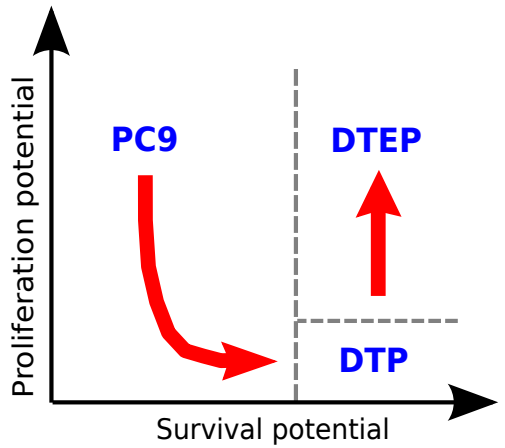
$$\underbrace{\Big[p(x, y, \varrho(t)) - d(x, c(t))\Big] n(x, y, t)}_{\text{Non local Lotka-Volterra selection}} + \underbrace{\beta \Delta n(x, y, t).}_{\substack{\text{Non-genetic} \\ \text{phenotype instability}}}$$

- $\varrho(t) = \int_0^1 \int_0^1 n(x, y, t)\, dx\, dy$, $p(x, y, \varrho(t)) = (a_1 + a_2 y + a_3(1 - x))(1 - \varrho(t)/K)$ and $d(x, c) = c(b_1 + b_2(1 - x)) + b_3$
- The drift term w.r.t. proliferation potential y represents possible (if $v \neq 0$) 'Lamarckian-like', epigenetic and reversible, adaptation from PC9s to DTPs
- $v(x, c(t); \bar{v}) = -\bar{v} c(t) H(x^* - x)$ where $t \mapsto c(t)$ is the drug infusion function
- No-flux boundary conditions

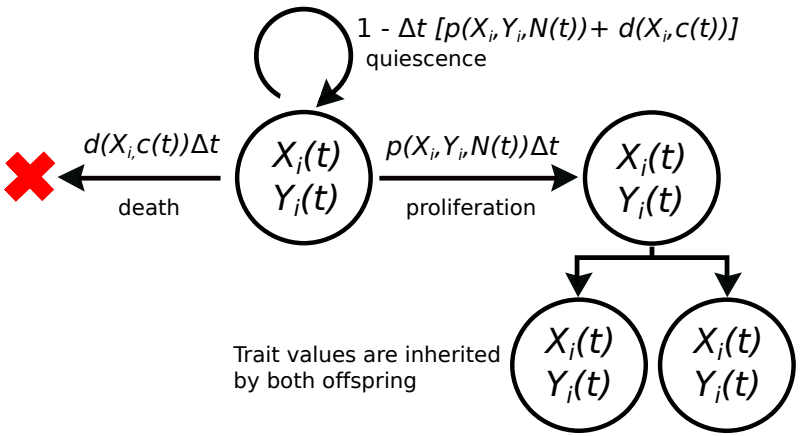
(*Chisholm et al., Cancer Research 2015*)

Agent-based model (ABM)





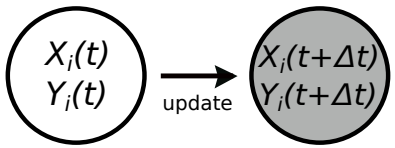
(a) Each cell i undergoes either proliferation, death or remains quiescent:



(b) Each cell i updates its trait values according to the discretised SDEs:

$$X_i(t+\Delta t) = X_i(t) + D\sqrt{\Delta t}\, W_i^1$$

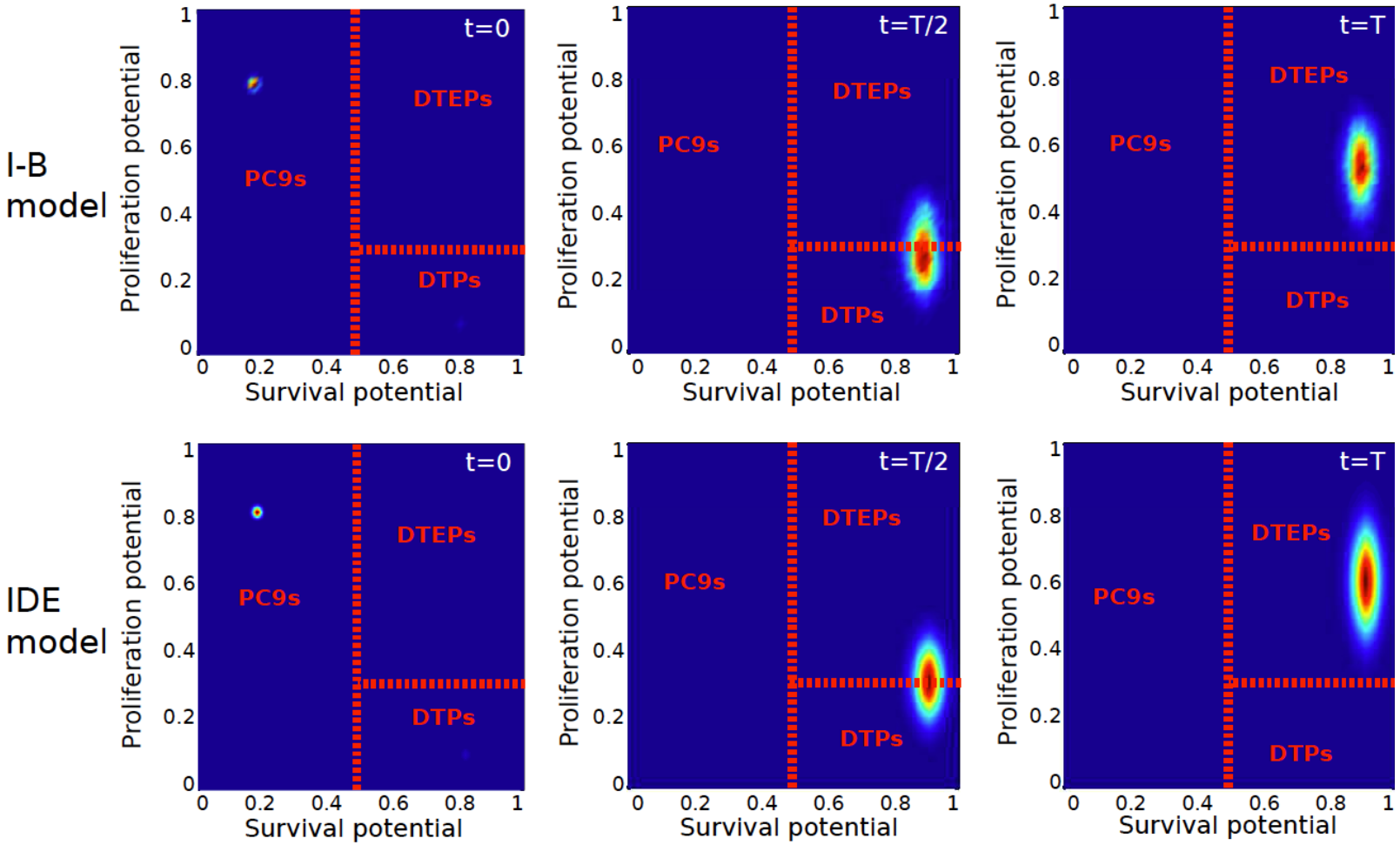
$$Y_i(t+\Delta t) = Y_i(t) + D\sqrt{\Delta t}\, W_i^2 + \Delta t\, v(X_i, c(t))$$



(*Chisholm et al., Cancer Research 2015*)

AB model and IDE model recover phenotype dynamics

e.g., during drug treatment (here, PC9s and DTPs present initially)



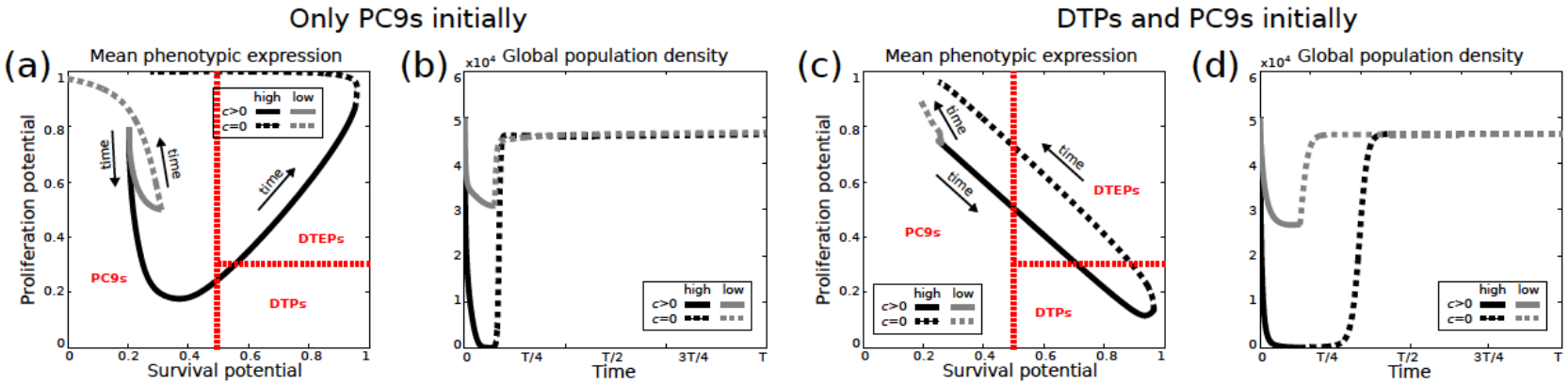
T is the simulation end-time: $0 \leq t \leq T$

(*Chisholm et al., Cancer Research 2015*)

AB model and IDE model recover phenotype dynamics

During drug exposure and after drug withdrawal: total recovery of drug sensitivity (either high or low drug dose):

both models by construction represent *reversible evolution* towards drug resistance

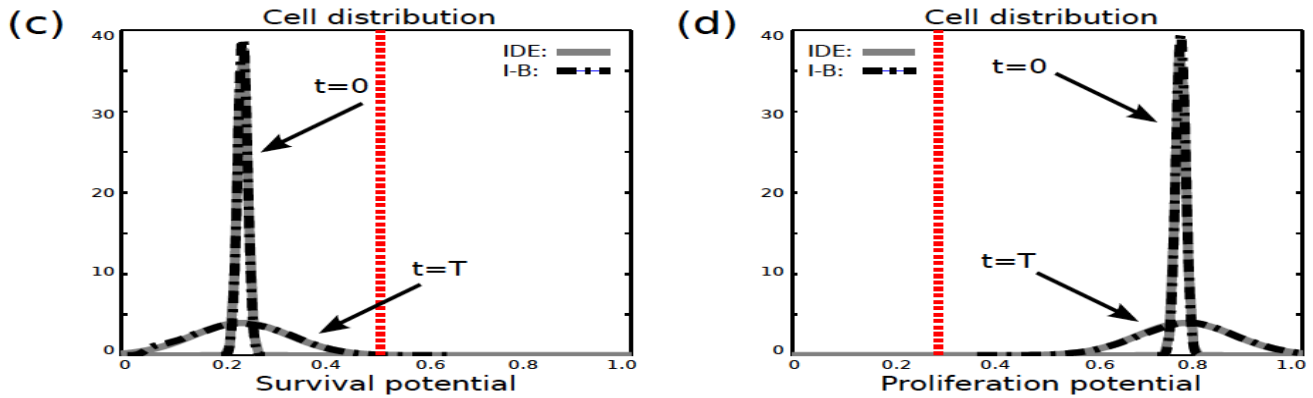


(a), (b) Only PC9s initially, adaptation on $v \neq 0$: *'Lamarckian' scenario*, or Luria-Delbrück scenario (A)

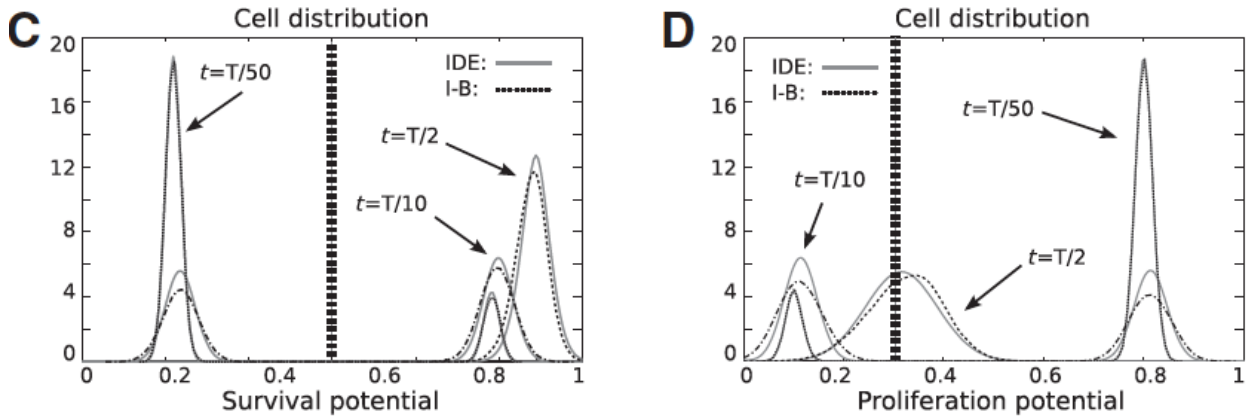
(c), (d) PC9s and DTPs initially, no adaptation $v = 0$: *'Darwinian' scenario*, or Luria-Delbrück scenario (B)

(*Chisholm et al., Cancer Research 2015*)

Phenotype heterogeneity in the cancer cell population

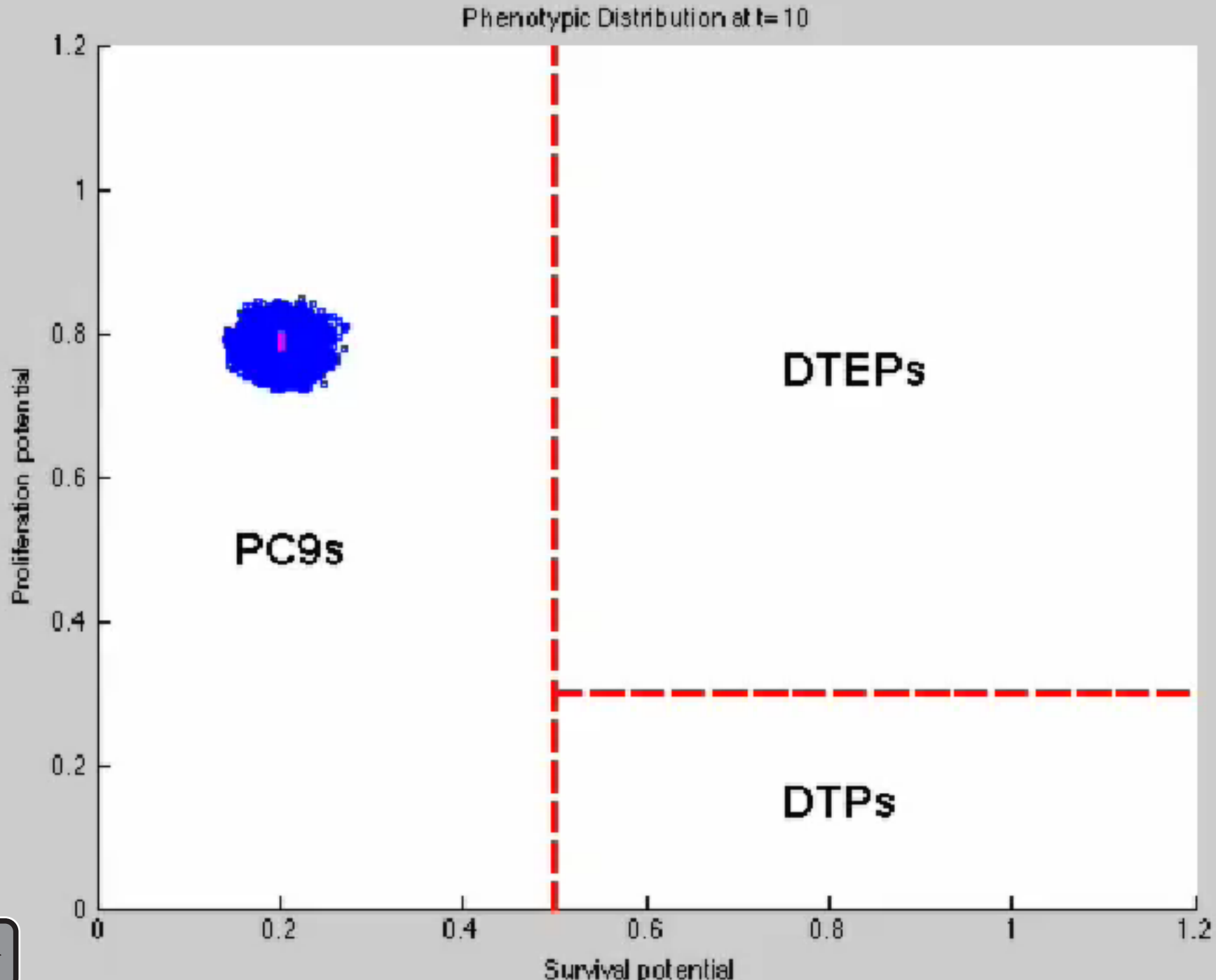


The PC9 cell population becomes more heterogeneous when it is left to evolve in the absence of drug treatment: starting from an initial concentrated phenotype (x_0, y_0), the phenotype (x, y) diffuses in the population according to a Gaussian-like curve. (c) Projection onto the x phenotype axis; (d) Projection onto the y phenotype axis.

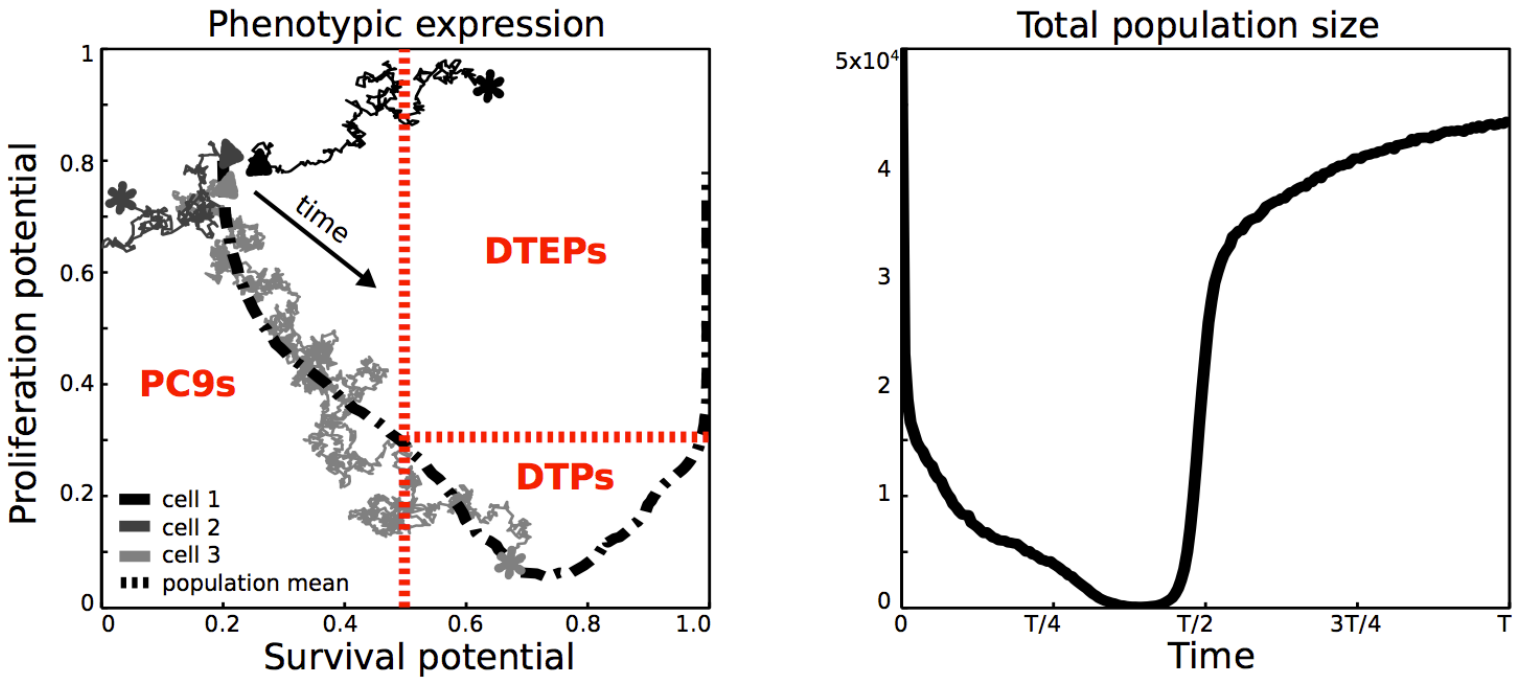


C, **D**: Under drug treatment, heterogeneity persists when phenotypes evolve (here, Darwinian scenario: DTPs are initially present)

(*Chisholm et al., Cancer Research 2015*)


Phenotypic Distribution at t= 10
Proliferation potential
Survival potential
0
0.2
0.4
0.6
0.8
1
1.2
PC9s
DTEPs
DTPs

Individual cell behaviour can be different from the averaged dynamics observed at the population level



- Evolution in the I-B model (here no DTPs initially present, adaptation on): heterogeneity of behaviours in the population of PC9 cells.
- Left: Trajectories of the phenotypic expression of 3 individual cells and mean phenotypic expression of the cell population (dashed line). Triangles: initial phenotype of cells; asterisks: last phenotype expressed by cells before death
- Right: Corresponding global population density as a function of time.

(*Chisholm et al., Cancer Research 2015*)

Use IDE model to address 3 questions

Q1. Is non-genetic instability (Laplacian term) crucial for the emergence of DTEPs?

Q2. What can we expect if the drug dose is low?

Q3. Could genetic mutations, i.e., an integral term involving a kernel with small support, to replace both adapted drift (advection) and non-genetic instability (diffusion), generate similar dynamics?

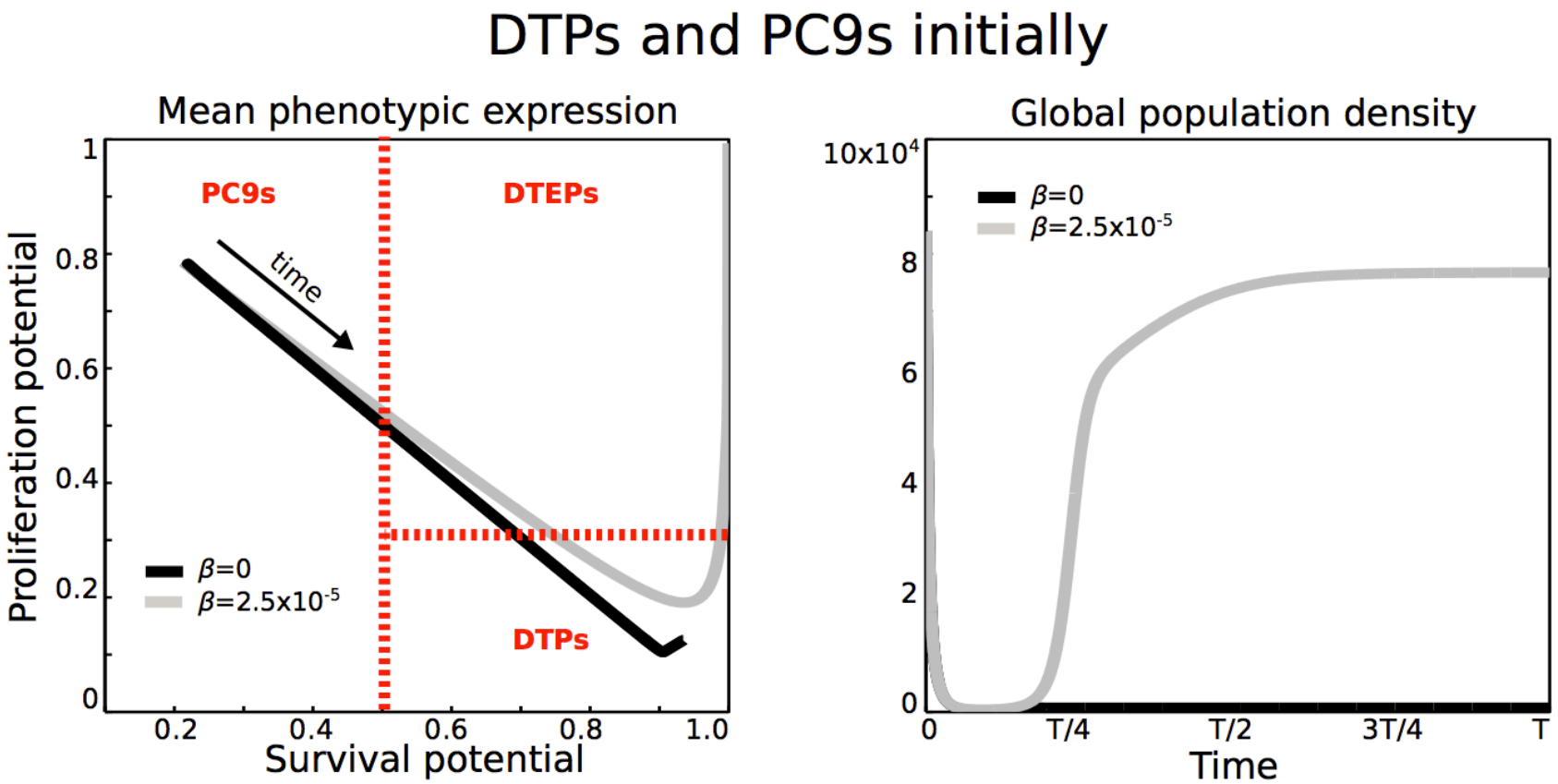
Consider $c(\cdot) = \textit{constant}$ and two scenarios:

(i) (*'Darwinian' scenario (B)*: the biological dogma) PC9s and few DTPs initially, no adaptation ($v = 0$)

(ii) (*'Lamarckian' scenario (A)*: the outlaw) Only PC9s initially, adaptation present ($v \neq 0$)

A1. Non-genetic instability is crucial for the emergence of DTEPs

[*Scenario (B)* PC9s and few DTPs initially present]

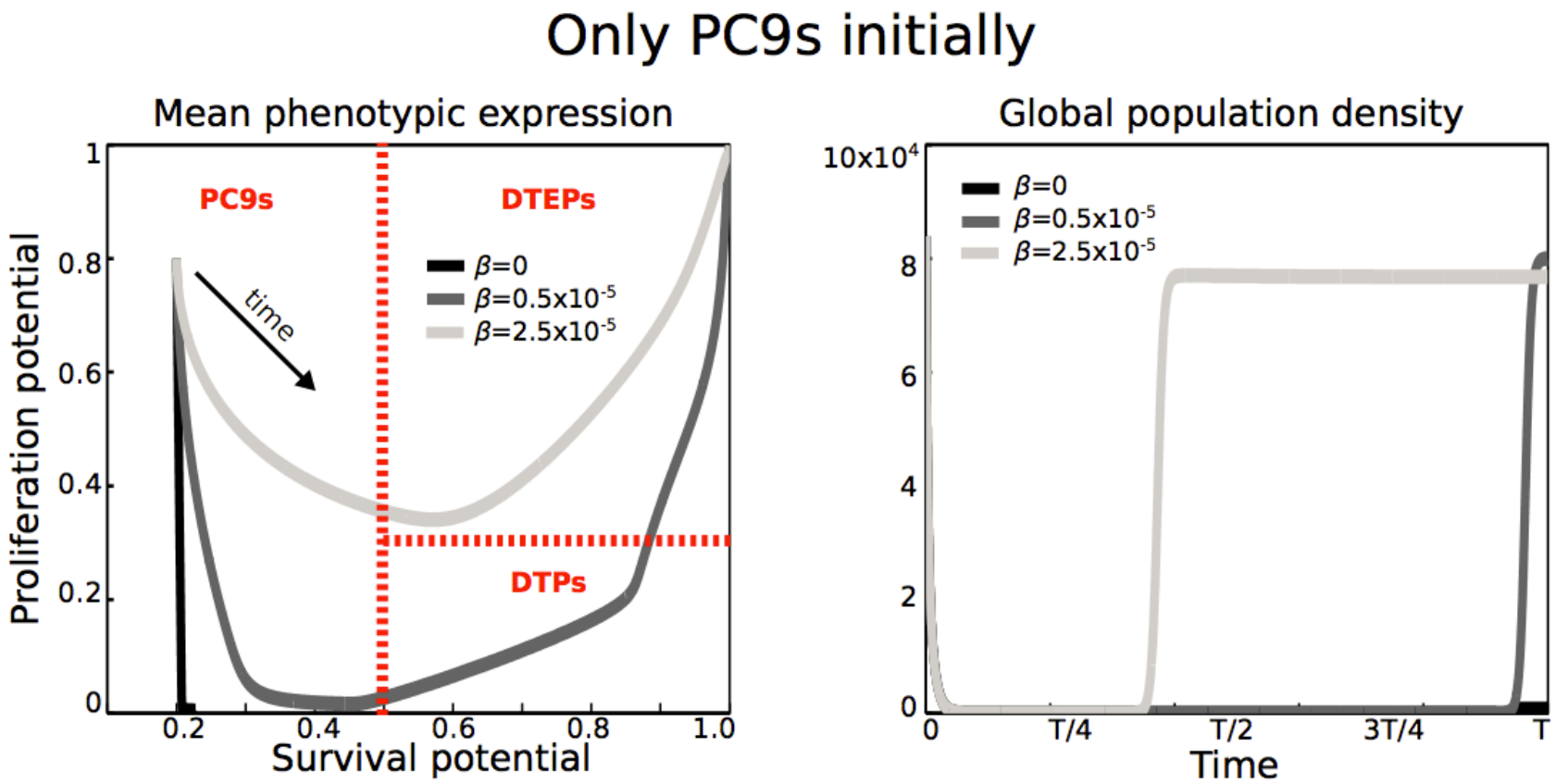


Extinction when $\beta = 0$ (here, adaptation is absent $v = 0$)

(*Chisholm et al., Cancer Research 2015*)

A1. Non-genetic instability is crucial for the emergence of DTEPs

[*Scenario (A)* Only PC9s initially present]



Extinction when $\beta = 0$ (here, adaptation is present $v \neq 0$)

(*Chisholm et al., Cancer Research 2015*)

Q2. What can we expect if the drug dose is low?

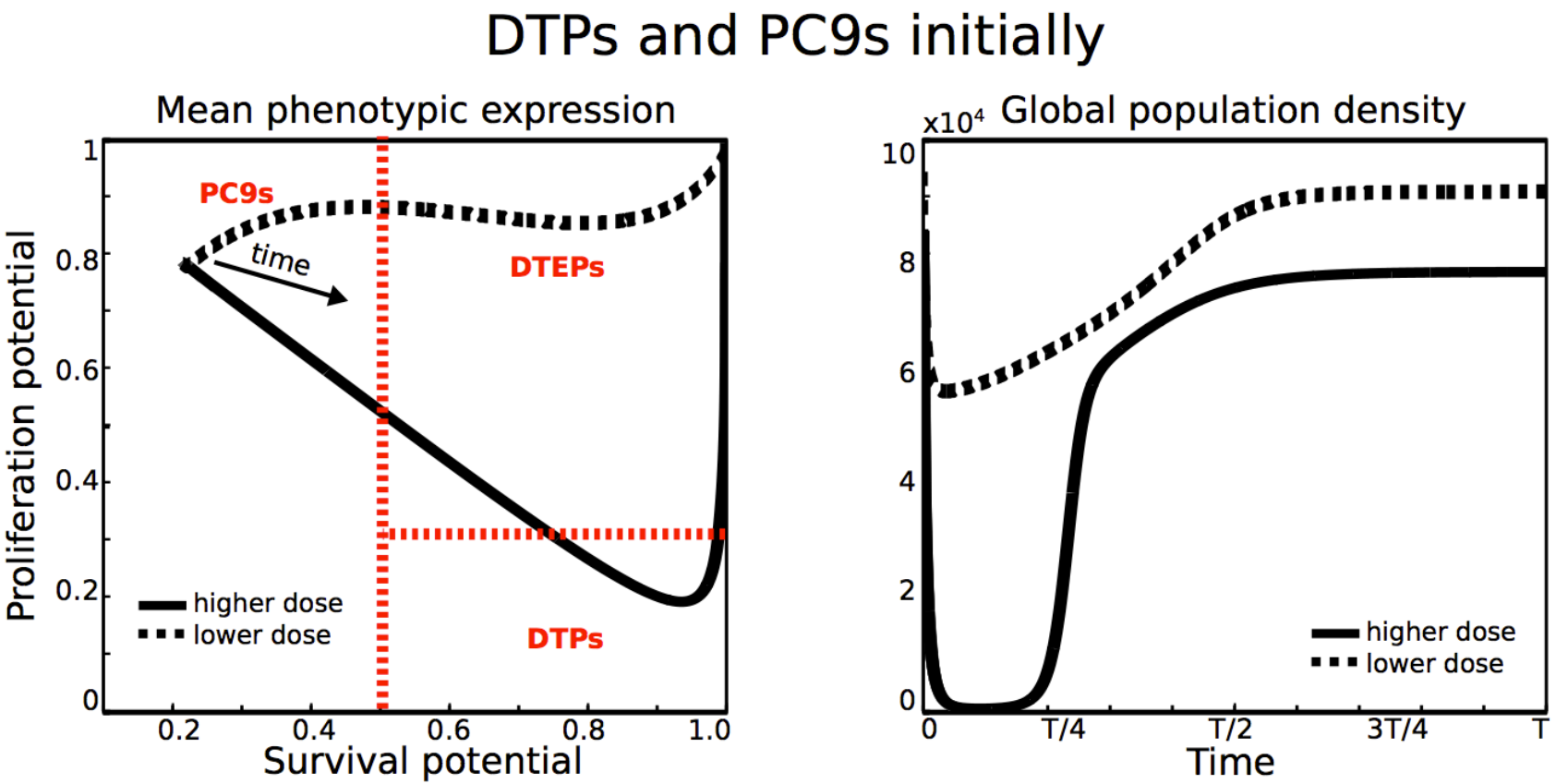
Definition (LC_γ dose)

The drug dose required to kill $\gamma\%$ of the total cell population, in the initial stage of drug therapy, before the population starts to recover

- High c: $c \geq LC_{90}$ dose
- Low c: $c \leq LC_{50}$ dose

A2. High dose of cytotoxic drugs is necessary for the transient dominance of DTPs

[*Scenario (B)* PC9s and DTPs initially present]

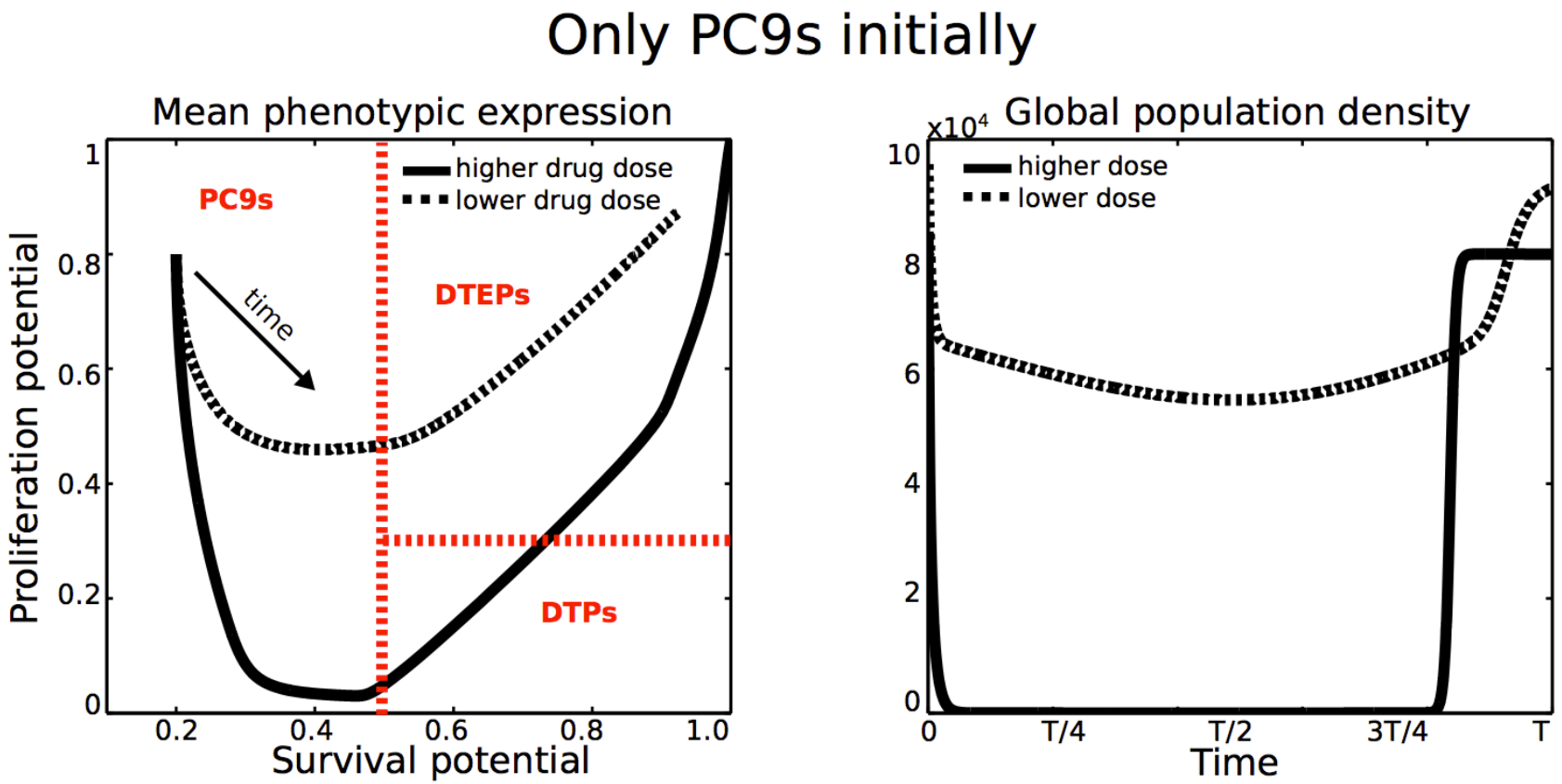


Low drug dose does not let appear DTPs (here, adaptation is absent $v = 0$)

(*Chisholm et al., Cancer Research 2015*)

A2. High dose of cytotoxic drugs is necessary for the transient dominance of DTPs

[*Scenario (A)* Only PC9s initially present]



Low drug dose does not let appear DTPs (here, adaptation is present $v \neq 0$)

(*Chisholm et al., Cancer Research 2015*)

Q3. Could genetic mutations generate similar dynamics?

Consider the pure mutation model (*no diffusion, no stress-induced adaptation drift*)

$$\frac{\partial n}{\partial t}(x,y,t) = \underbrace{\Big[(1-\alpha)p(x,y,\varrho(t)) - d(x,c(t))\Big] n(x,y,t)}_{\text{birth and death term due to sheer selection}} + \underbrace{\alpha \int_0^1 \int_0^1 p(\xi,\eta,\varrho(t)) M(x,y|\xi,\eta;\sigma) n(\xi,\eta,t) d\xi \, d\eta,}_{\text{birth term due to genetic mutations}}$$

where the mutation kernel is defined as,

$$M(x,y|\xi,\eta;\sigma) := C_M e^{-\frac{(x-\xi)^2}{\sigma}} e^{-\frac{(y-\eta)^2}{\sigma}},$$

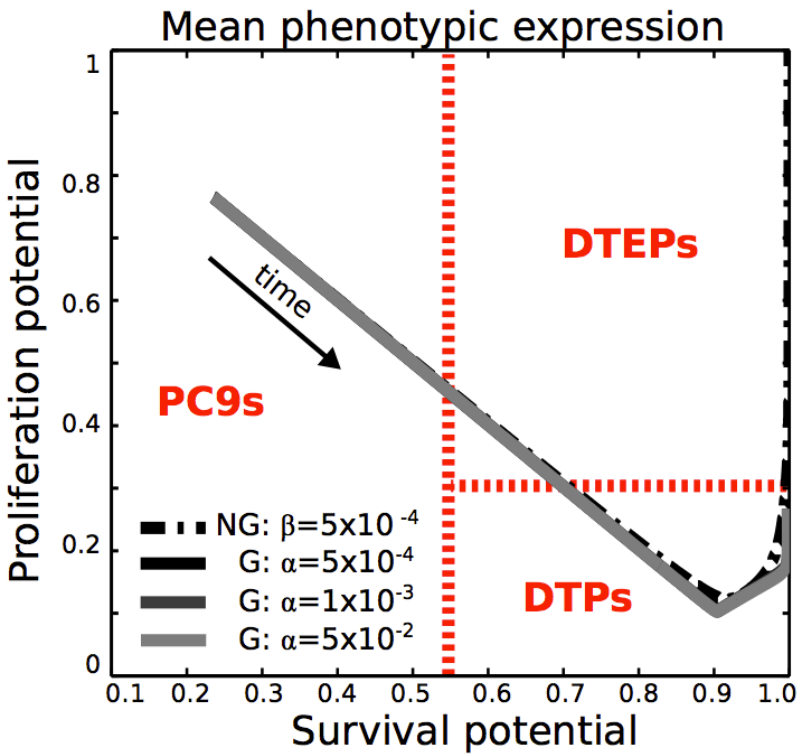
and C_M is a normalisation constant such that

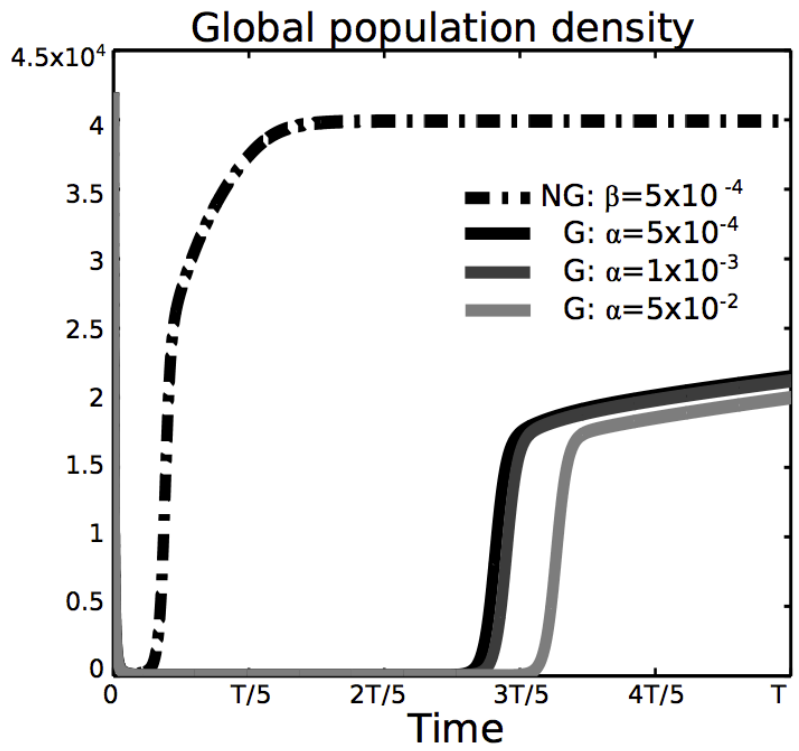
$$\int_0^1 \int_0^1 M(x,y|\cdot,\cdot;\cdot)\mathrm{d}x\mathrm{d}y = 1.$$

A3. Genetic mutations cannot generate similar dynamics

[*Scenario (B)* Initially there are DTPs and PC9s]

- G: only mutations and selection, vs.
- NG: non-genetic phenotype instability and selection





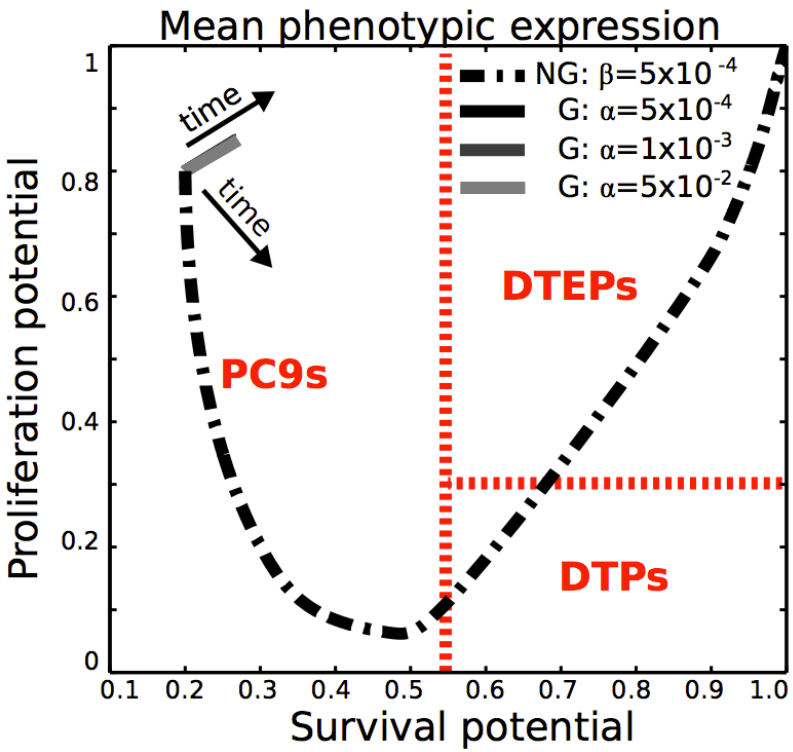
G: mutations do not let occur total recovery (NG: here, adaptation is absent $v = 0$)

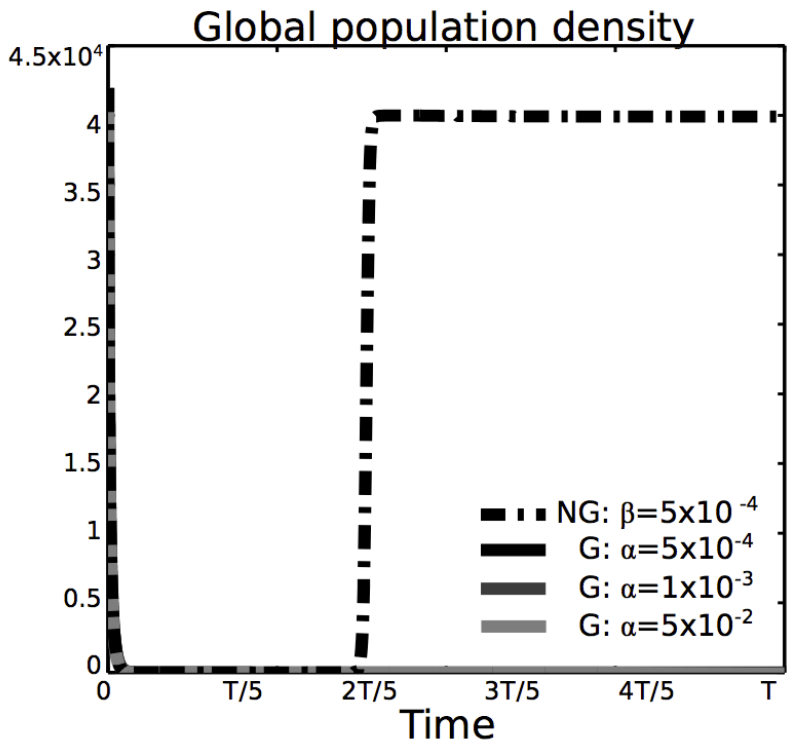
(*Chisholm et al., Cancer Research 2015*)

A3. Genetic mutations cannot generate similar dynamics

[*Scenario (A)* Initially there are only PC9s]

- G: only mutations and selection, vs.
- NG: non-genetic phenotype instability, adaptation and selection





G: total extinction (NG: here, adaptation is present $v \neq 0$)

(*Chisholm et al., Cancer Research 2015*)

Summary of simulation results on the *Sharma et al.* paper

- Both mathematical models (AB, IDE) reproduce the main experimental observations

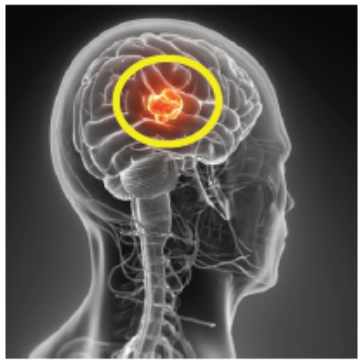
- To see the transient appearance of the DTPs during high-dose drug therapy:

  - If there are **some DTPs** present initially, model explanation requires only
    - non-genetic instability
    - selection
  - If **no DTPs** are present initially, model explanation requires interplay between
    - stress-induced adaptation
    - non-genetic instability
    - selection

- Therapeutic consequences? Not clear yet. Epigenetic drugs? Not many of them exist (in particular no KDM5A inhibitor). Acting on epigenetics by modifying metabolism? Combining cytotoxic (inducing drug resistance) drugs and cytostatic drugs at low doses (in principle not inducing drug resistance)? Might be assessed using this model, not done yet.

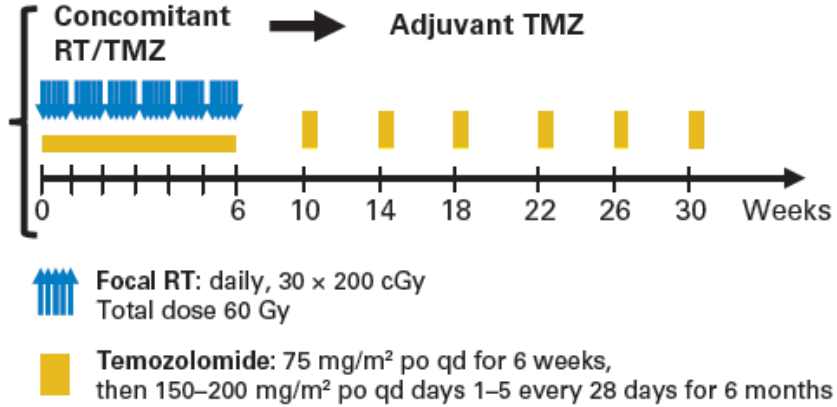
Temozolomide (TMZ) in glioblastoma (GBM)

Treatment



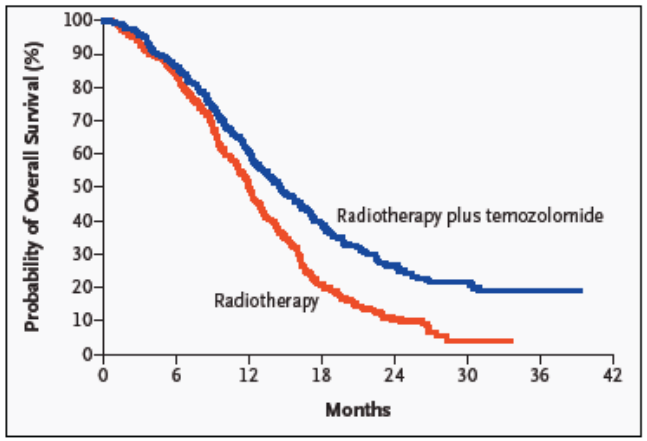
Surgical resection

+



Survival

- Median: 14,6 months
- 5 years: 3%



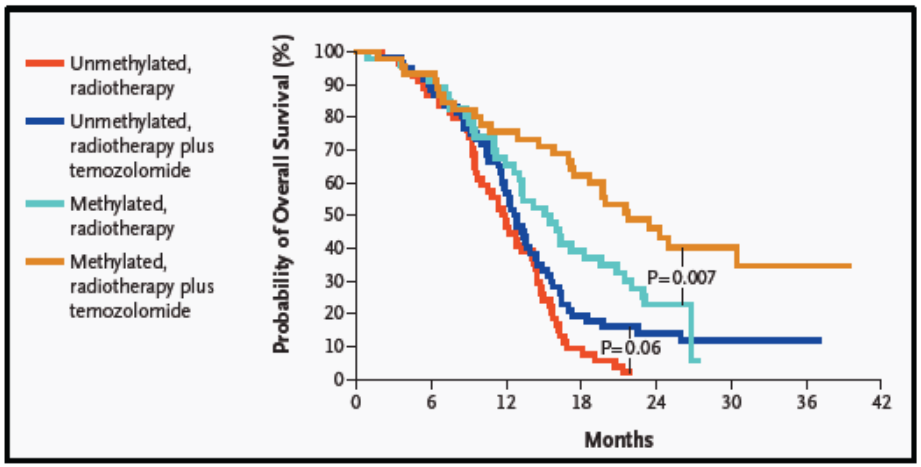
Grossman *et al*, 2009; Stupp *et al 2005;* Preusser, M. *et al*, 2011

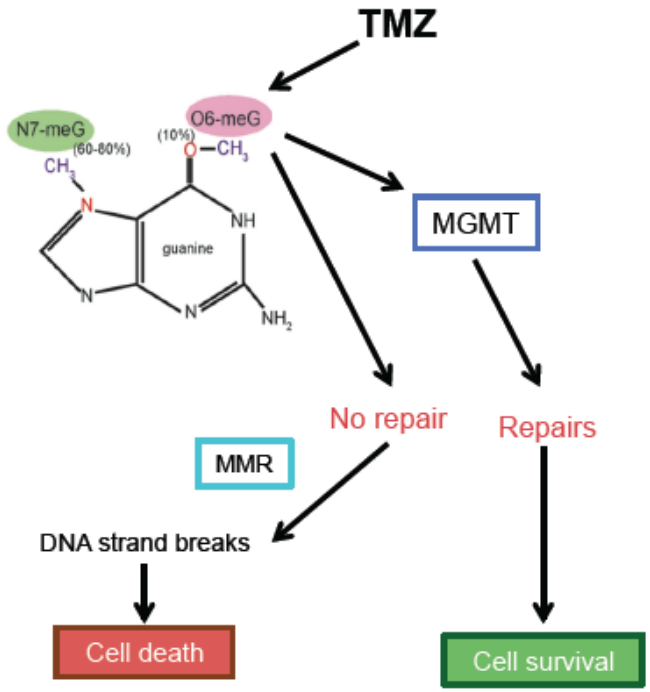
Resistance of GBM cell populations to TMZ

TMZ resistance

Main marqueur of TMZ resistance

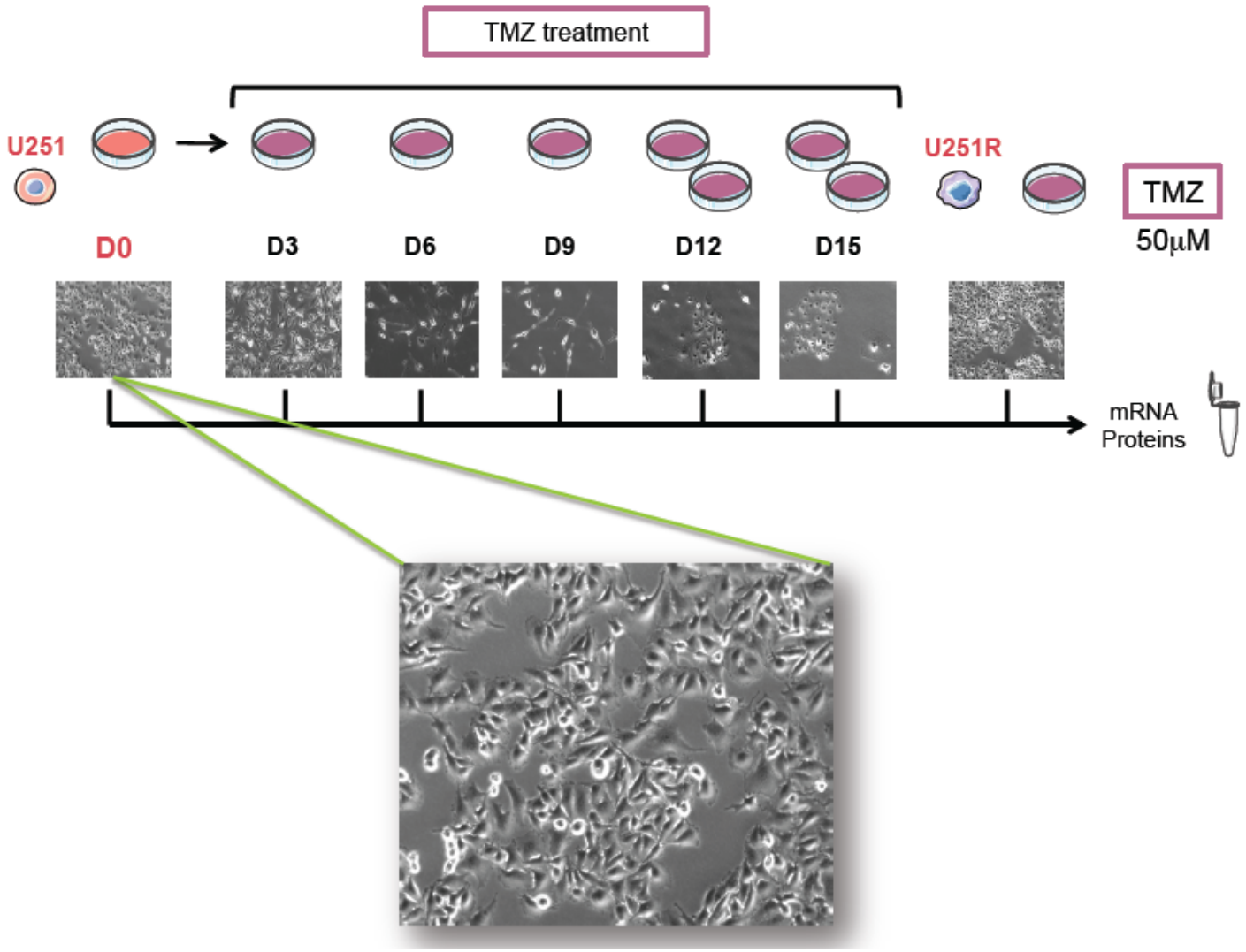
Methylation status of MGMT promoter





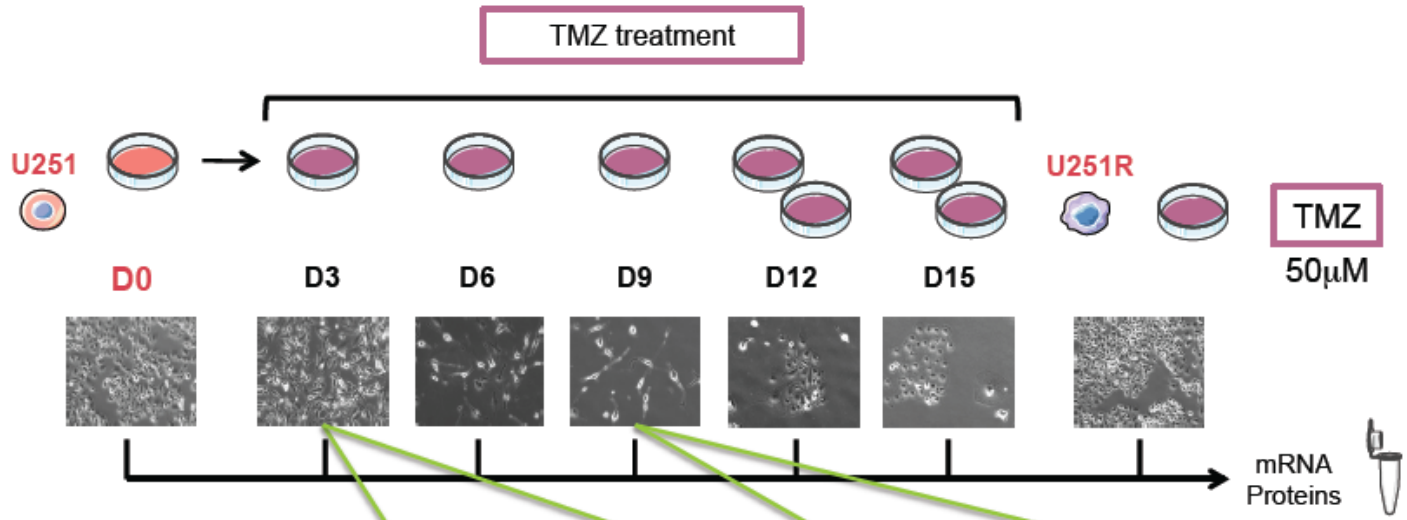
Hegi *et al*, 2005

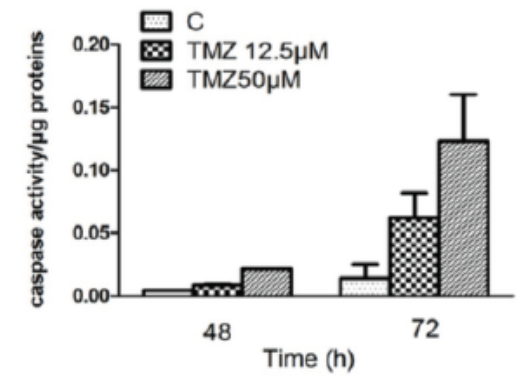
Same observations as in *Sharma et al. Cell 2010*



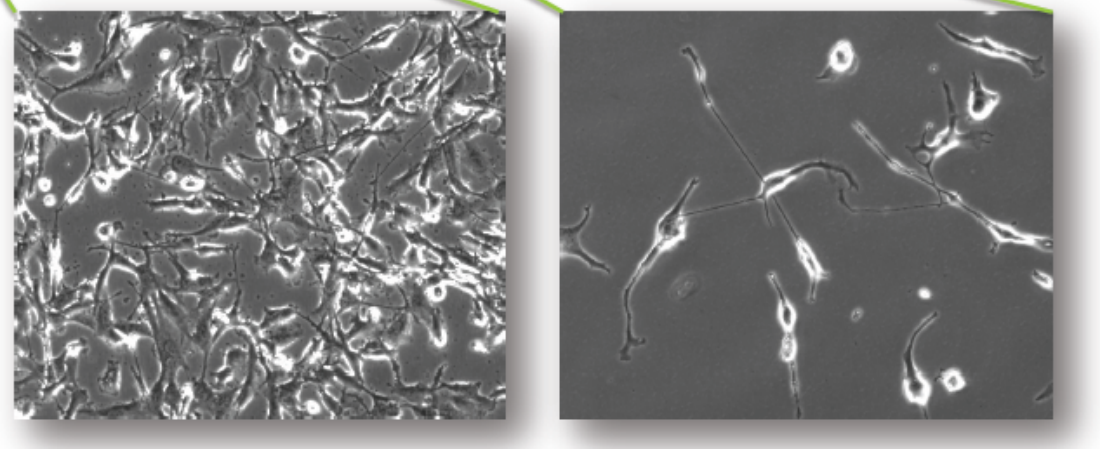
from F. Vallette's INSERM team in Nantes

Same observations as in *Sharma et al. Cell 2010*

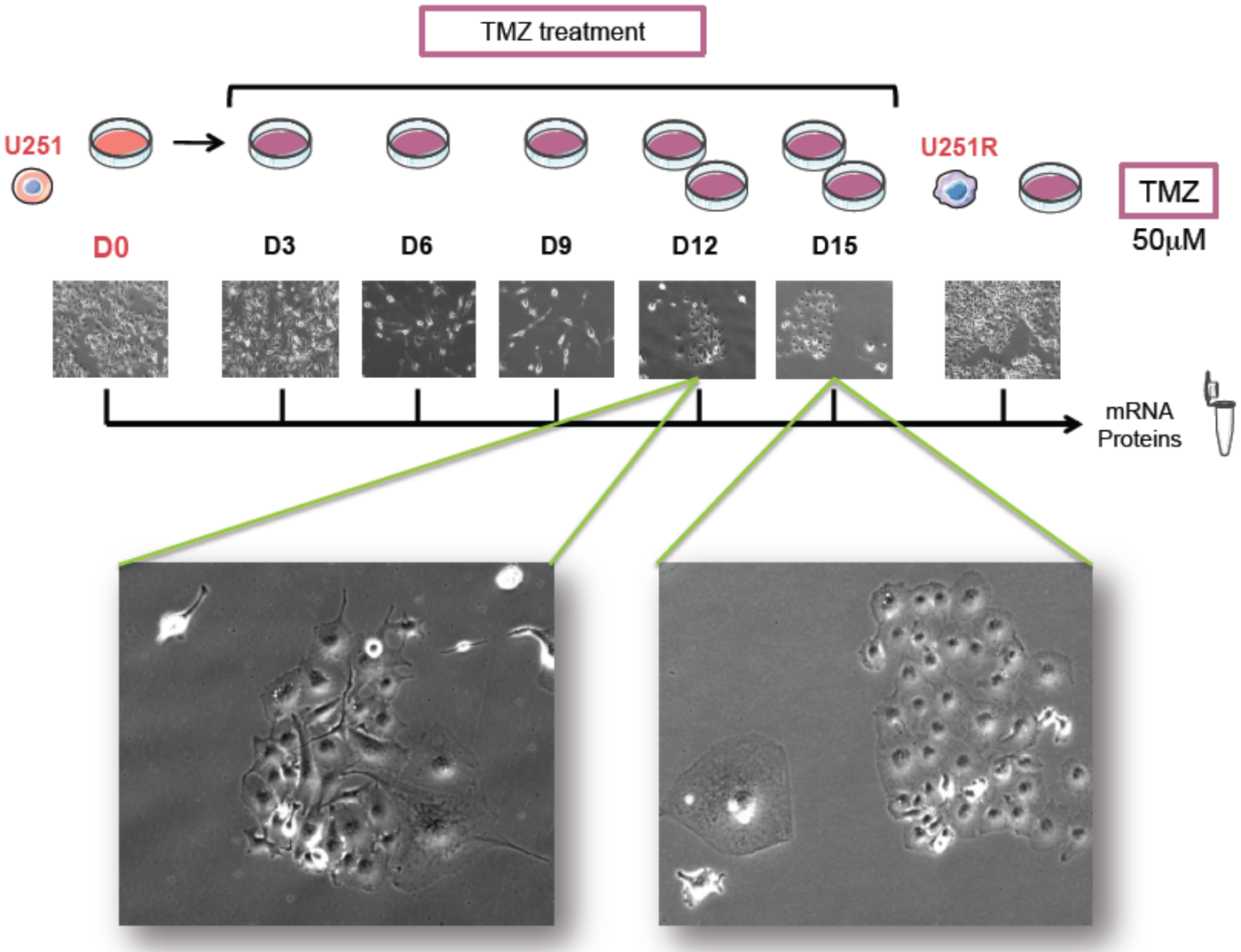




Gratas *et al*, 2014, Oncotarget

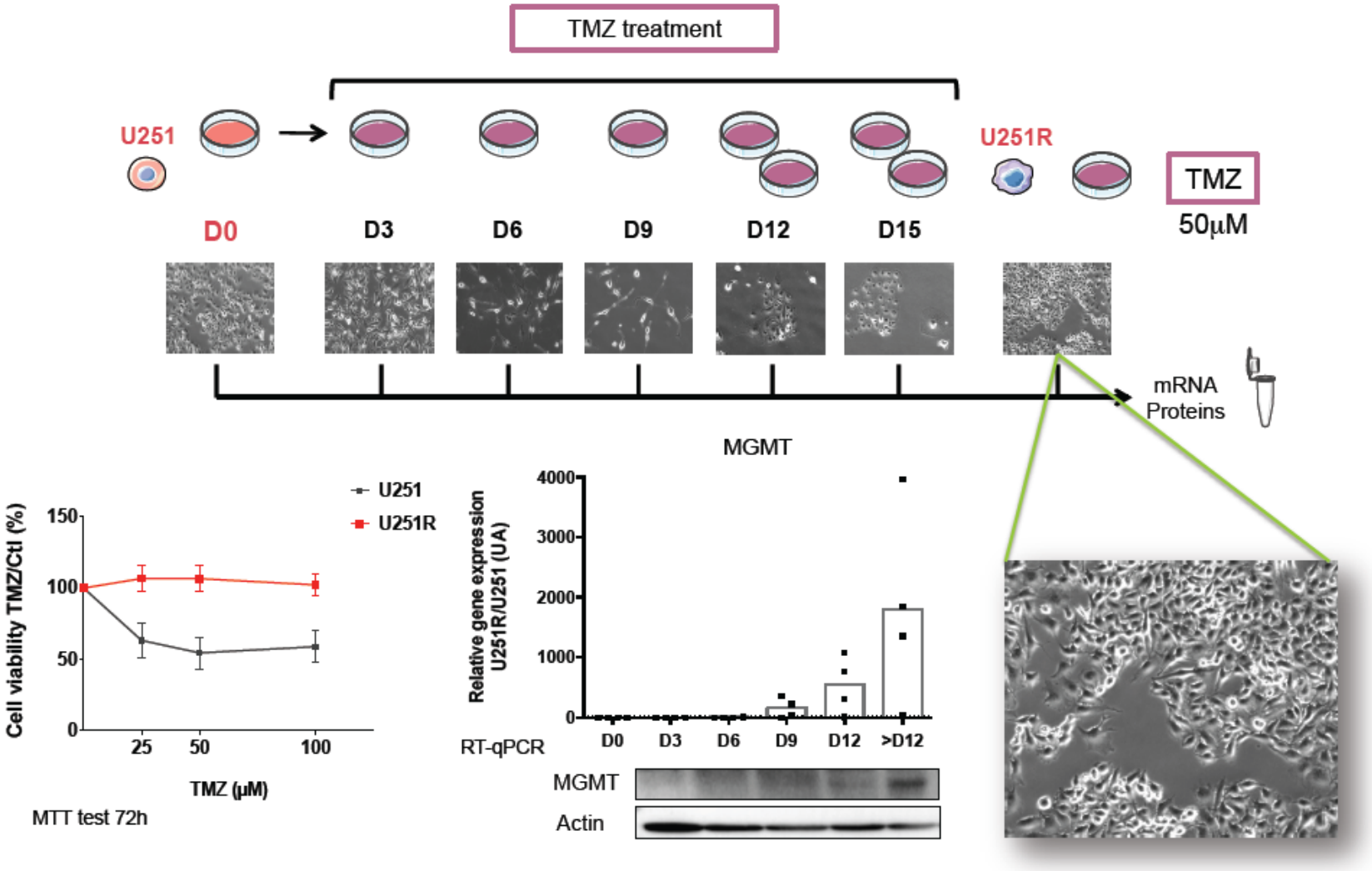


Same observations as in *Sharma et al. Cell 2010*



from F. Vallette's INSERM team in Nantes

Same observations as in *Sharma et al. Cell 2010*



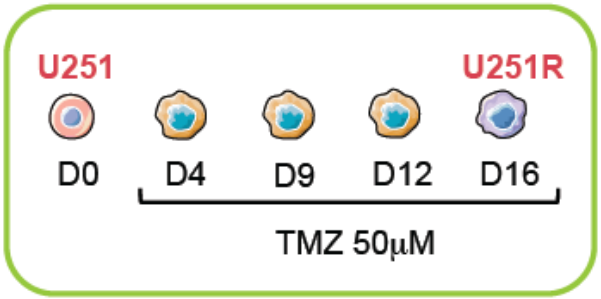
from F. Vallette's INSERM team in Nantes

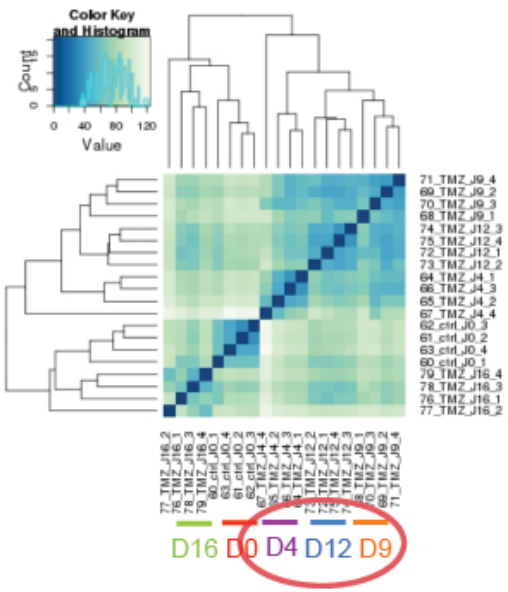
Gene expression followed from D0 to D16

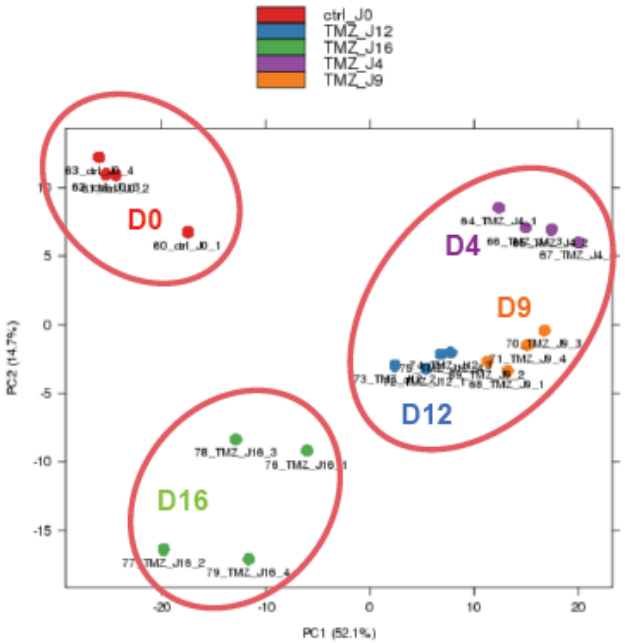
Results: Transcriptomic sequencing

Whole transcriptome sequencing

RNA-Seq





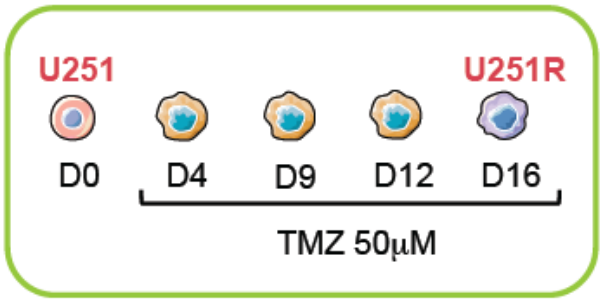


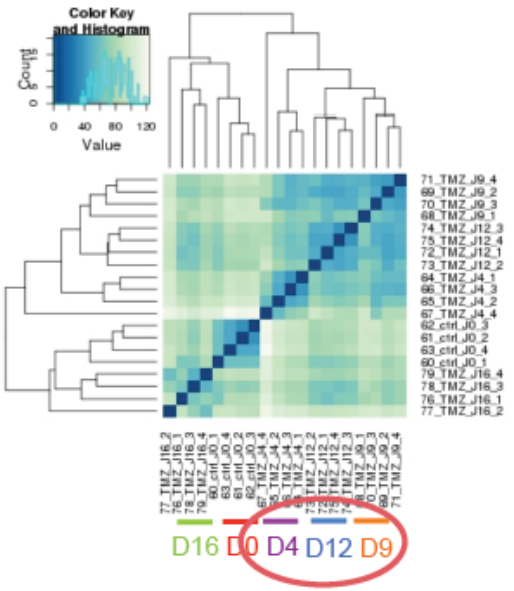
from F. Vallette's INSERM team in Nantes

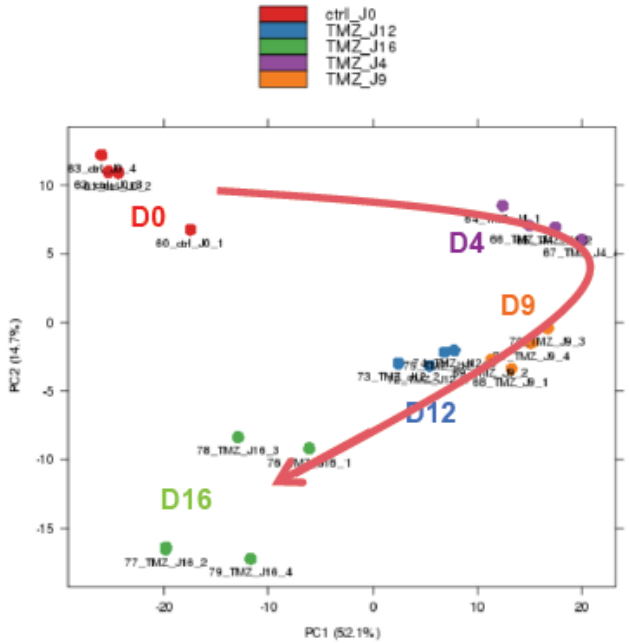
Gene expression followed from D0 to D16

Whole transcriptome sequencing

RNA-Seq







from F. Vallette's INSERM team in Nantes

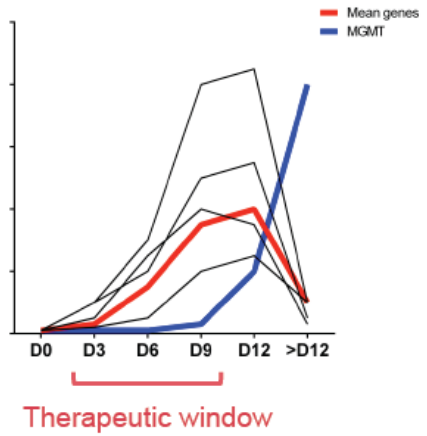
Therapeutic consequences??

Clonal selection or acquired gene expression?

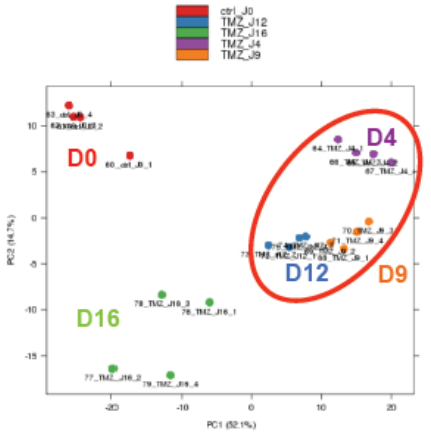
CHI3L1
FAT2
KLK5
HBEGF

➔ Transitory phase

Drug tolerant population



- Stable inhibition of target genes
- Viral barcode library



from F. Vallette's INSERM team in Nantes

Drug effects on cell populations and their optimisation
Model with mutations, one cytotoxic drug: cancer cells

- $x =$ level of expression of a drug resistance phenotype (to a given drug)
- $n_H(x,t)$, $n_C(x,t)$ densities of cell populations (H=healthy, C=tumour)

$$\frac{\partial}{\partial t} n_C(x,t) = \Big[\overbrace{(1-\theta_C)\, r(x)}^{\text{growth}} - \overbrace{d(x)}^{\text{death}} - \overbrace{u(t)\mu_C(x)}^{\text{drug effect}} \Big] n_C(x,t)$$

$$+\theta_C \overbrace{\int r(y) M_{\sigma_C}(y,x) n_C(y,t)\, dy}^{\text{birth with mutation}}$$

- $r(x) =$ basic reproduction rate, $d(x) =$ basic death rate; we assume $r(0) > d(0) > 0, \qquad r'(\cdot) < 0, \qquad r(+\infty) = 0, \qquad d'(\cdot) > 0,$
- $0 \le \theta_{H,C} < 1$ ($\theta_C > \theta_H$) is the proportion of divisions with mutations,
- $\mu_{[H,C]}(x)$ (with $\mu'_C(\cdot) < 0$) represents the phenotype-dependent sensitivity to cytotoxic drug, with concentration $u(t)$, designed to target cancer cells.
- Note: assumptions $r(\cdot) > 0, \mu_C(\cdot) > 0$, $\mu'_C(\cdot) < 0$ and $r'(\cdot) < 0$ (cost of resistance: the higher is x, the lower is proliferation) represent an *evolutionary double bind on resistant cancer cell populations*, *i.e., an evolutionary trade-off between growing (thus getting exposed) and keeping still (thus surviving)*

(Lorz et al., M2AN 2013)

Model with mutations, one cytotoxic drug: healthy cells

$$\frac{\partial}{\partial t} n_H(x,t) = \Big[\overbrace{\frac{1-\theta_H}{\big(1+\rho(t)\big)^{\beta}}\, r(x)}^{\text{growth with homeostasis}} - \overbrace{d(x)}^{\text{death}} - \overbrace{u(t)\mu_H(x)}^{\text{drug effect}} \Big] n_H(x,t)$$

$$+ \frac{\theta_H}{\big(1+\rho(t)\big)^{\beta}} \overbrace{\int r(y) M_{\sigma_H}(y,x) n_H(y,t)\, dy}^{\text{birth with mutation}},$$

where the total population is defined as

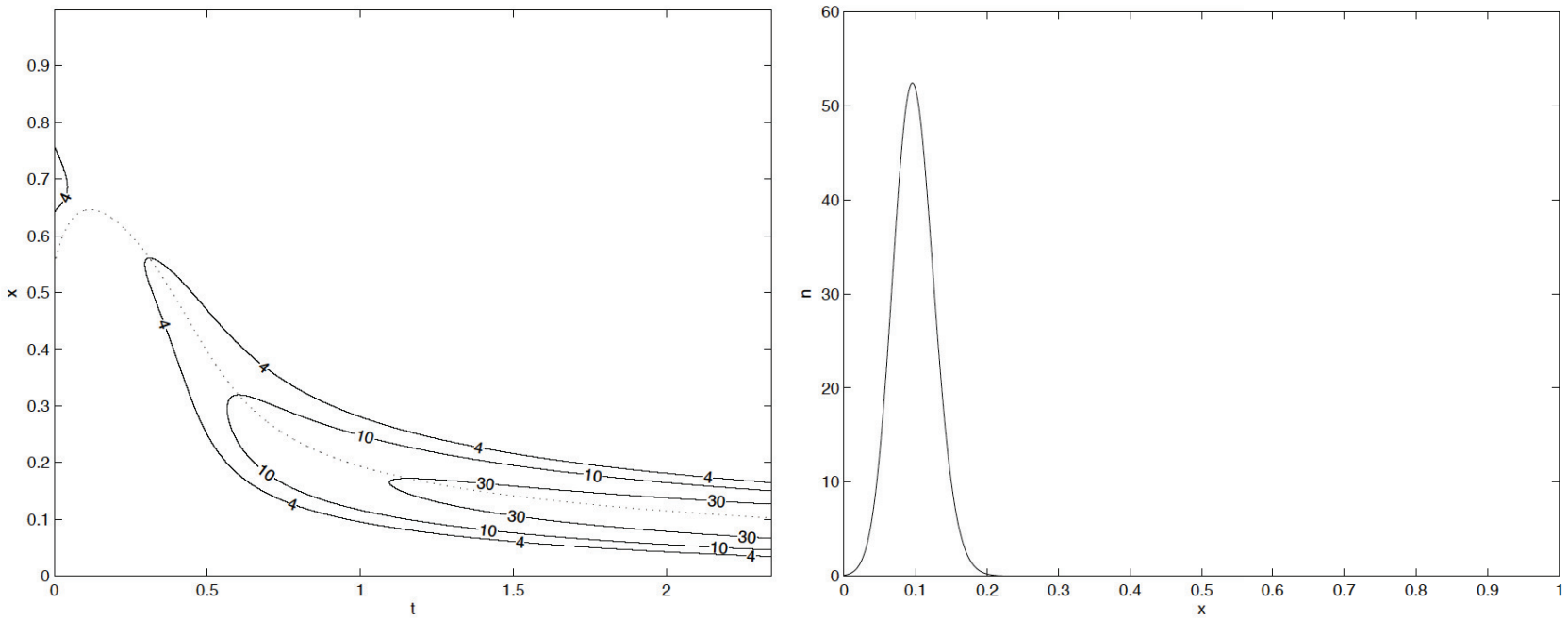
$$\rho(t) = \rho_H(t) + \rho_C(t); \rho_H(t) = \int_{x=0}^{\infty} n_H(x,t)dx; \rho_C(t) = \int_{x=0}^{\infty} n_C(x,t)dx.$$

- $\beta > 0$ to impose healthy tissue homeostasis,
- $u(t)$ denotes the instantaneous dose (concentration) of chemotherapy. We assume in this model that its effect is cytotoxic, i.e., on the death term only.

(Lorz et al., M2AN 2013)

Model with mutations, one cytotoxic drug: illustrations (1)

[Sensitive cell population case: illustration of Gause's exclusion principle]
Theorem: Monomorphic evolution towards drug sensitivity, illustrated here with $\theta_H = 0$, *(no mutations) and* $\mu_H = 0$ *(no drug-induced resistance)*

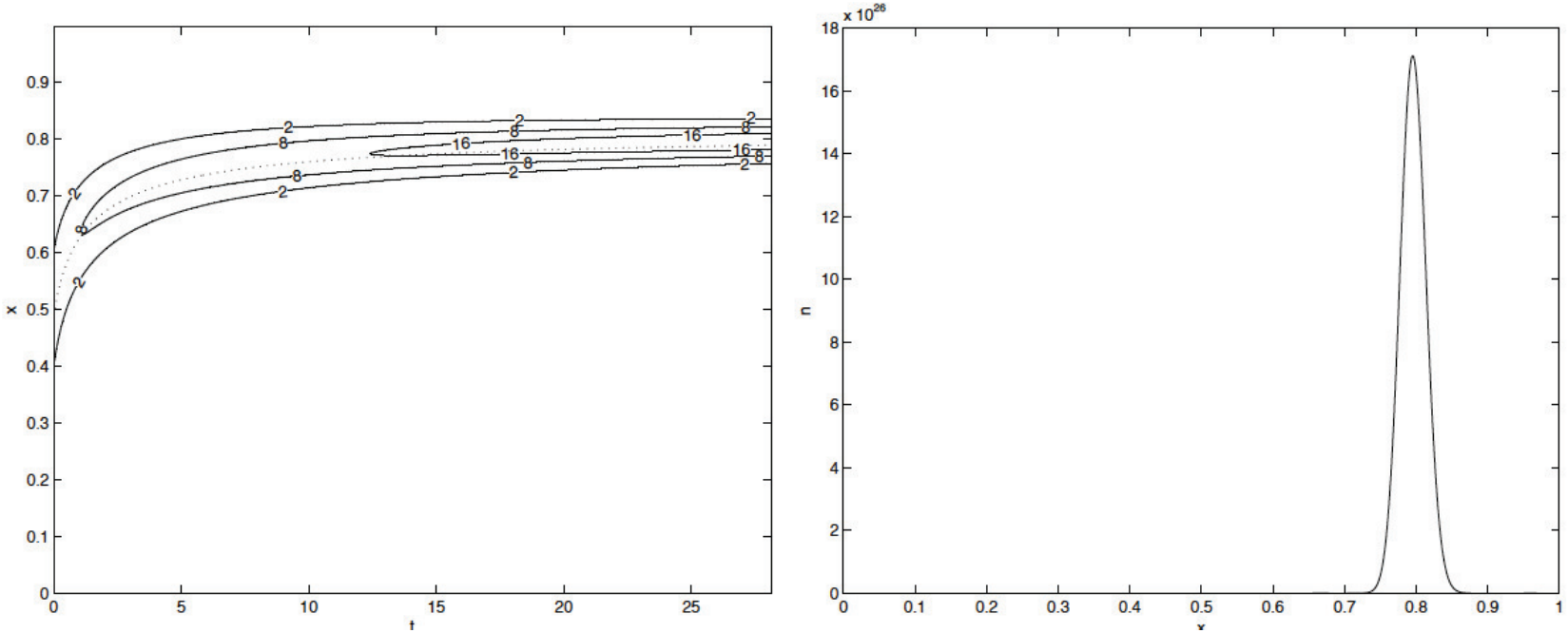


Left panel: starting from a medium phenotype $x = 0.5$, *level sets of a drug-sensitive population in the* (t, x) *plane. Right panel: asymptotic distribution of this drug-sensitive population according to the drug resistance phenotype* x.

(Lorz et al., M2AN 2013)

Model with mutations, one cytotoxic drug: illustrations (2)

[Resistant cell population case: Gause's exclusion principle again]
Theorem: Monomorphic evolution towards drug-induced drug resistance, here with $\theta_C = 0$, $\mu_C(\cdot) > 0, r'(\cdot) < 0, \mu'_C(\cdot) < 0$ *(costly drug-induced resistance),* $u(t) = Cst$



Left panel: starting from a medium phenotype $x = 0.5$*, level sets of a drug- resistant population in the* (t, x) *plane. Right panel: asymptotic distribution of this drug-resistant population according to the drug resistance phenotype* x*.*

(Lorz et al., M2AN 2013)

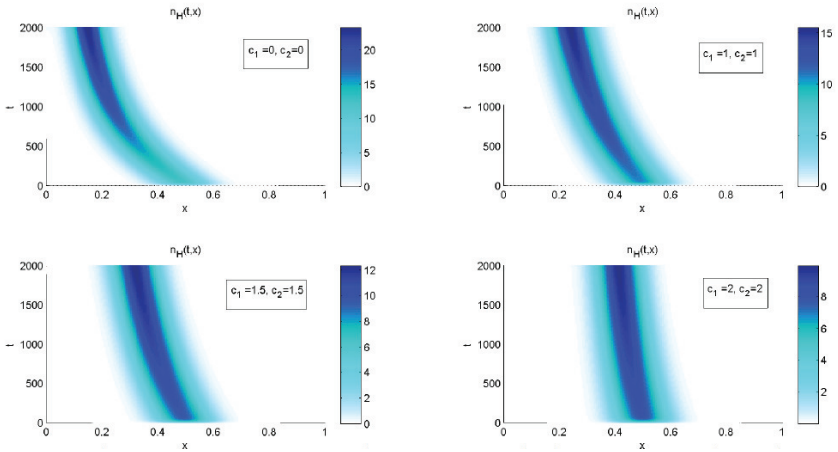
Phenotype-structured non-local Lotka-Volterra model with 2 drugs and one (scalar) resistance phenotype x

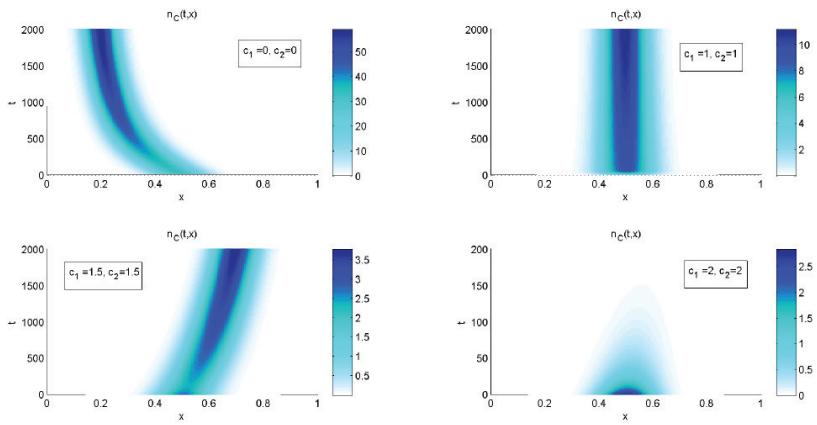
$$\frac{\partial}{\partial t} n_H(x,t) = \left[\frac{r_H(x)}{1 + k_H u_2(t)} - d_H(x) I_H(t) - u_1(t) \mu_H(x) \right] n_H(x,t)$$

$$\frac{\partial}{\partial t} n_C(x,t) = \left[\frac{r_C(x)}{1 + k_C u_2(t)} - d_C(x) I_C(t) - u_1(t) \mu_C(x) \right] n_C(x,t)$$

Environment: $I_H(t) = a_{HH}.\rho_H(t) + a_{HC}.\rho_C(t), I_C(t) = a_{CH}.\rho_H(t) + a_{CC}.\rho_C(t)$,
with $\rho_H(t) = \int_0^1 n_H(x,t)\,dx, \rho_C(t) = \int_0^1 n_C(x,t)\,dx$, u_1 cytotoxic, u_2 cytostatic drugs.

Simultaneous combinations of the 2 drugs, with increasing equal constant doses





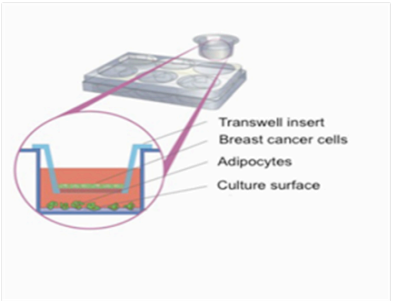
Healthy cells: preserved

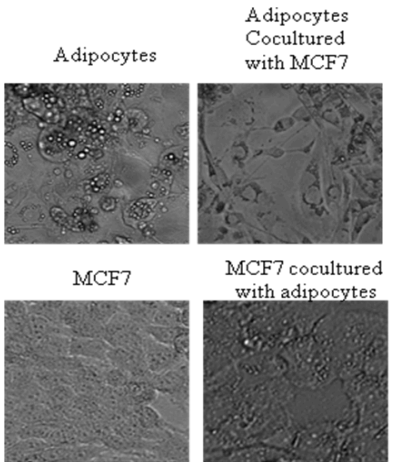
Cancer cells: eventually extinct

(Lorz 2013) "Pedestrian's optimisation"
See also Camille Pouchol's presentation

A different point of view on IDE models: representing mutualistic interactions with the micro-environment

Example: breast cancer cell line MCF7 (n_C) co-cultured with adipocytes (n_A)





Control by drugs: cytostatic $v_r(t)$, cytotoxic $v_d(t)$,
plus blockade of receptors to intercellular soluble factors $\varphi_A(t), \varphi_C(t)$ by other drugs,
e.g., oestrogen receptor blockers $w_{sC}(t)$, antiinflammatory molecules $w_{sA}(t)$

$$\frac{\partial}{\partial t} n_C(u,t) = \left[\frac{r_C}{1+v_r(t)} + \varphi_A(t) \frac{s_C(u)}{1+w_{sC}(t)} - (1+v_d(t)) d_C(u) \rho_C(t) \right] n_C(u,t),$$

$$\frac{\partial}{\partial t} n_A(x,t) = \left[r_A + \varphi_C(t) \frac{s_A(x)}{1+w_{sA}(t)} - d_A \rho_A(t) \right] n_A(x,t).$$

(Works in collaboration with biologists)

What about space? Considering both a (1D) resistance phenotype and (1D) space in a tumour spheroid: equations

We assume that the evolution of functions n, s (nutrients), c_1 and c_2 in a 1D radially symmetric tumour spheroid ($r \in [0,1]$) is ruled by the following set of equations:

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

$$-\sigma_s \Delta s(t,r) + \left[\gamma_s + \int_0^1 p(x) n(t,r,x) dx\right] s(t,r) = 0, \quad (2)$$

$$-\sigma_c \Delta c_1(t,r) + \left[\gamma_c + \int_0^1 \mu_1(x) n(t,r,x) dx\right] c_1(t,r) = 0, \quad (3)$$

$$-\sigma_c \Delta c_2(t,r) + \left[\gamma_c + \mu_2 \int_0^1 n(t,r,x) dx\right] c_2(t,r) = 0, \quad (4)$$

with zero Neumann conditions at $r = 0$ coming from radial symmetry and Dirichlet boundary conditions at $r = 1$

$$s(t,r=1) = s_1, \partial_r s(t,r=0) = 0, c_{1,2}(t,r=1) = C_{1,2}(t), \partial_r c_{1,2}(t,r=0) = 0. \quad (5)$$

For each t, we also define $\rho(t,r) = \int_0^1 n(t,r,x)\, dx$ and $\rho_T(t) = \int_0^1 \rho(t,r) r^2\, dr$

(Lorz et al. BMB 2015)

Tumour spheroid: simulations with constant drug doses (1)

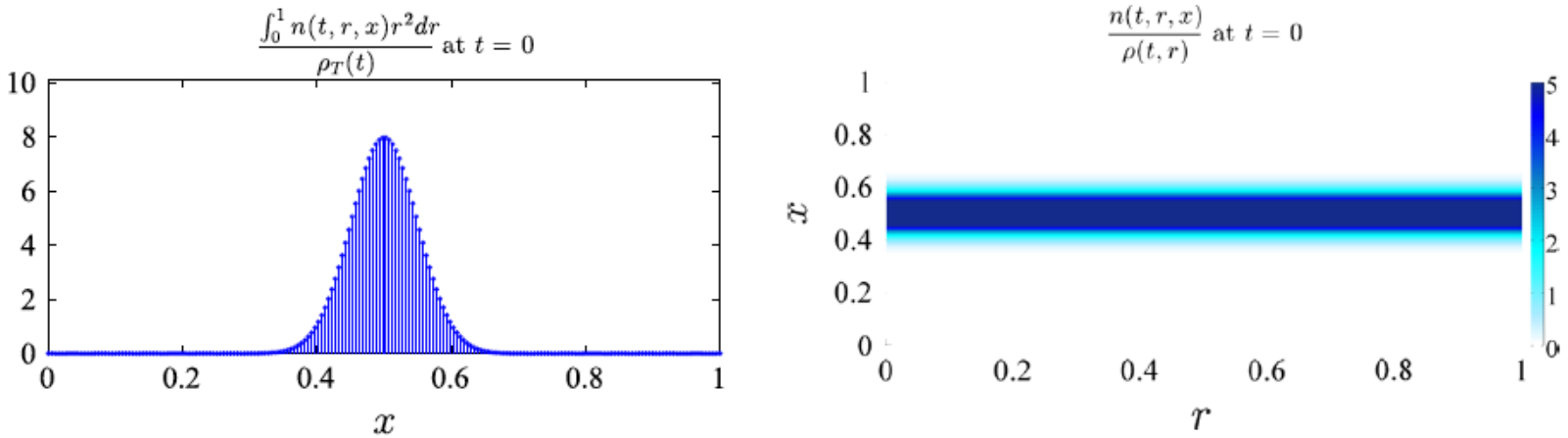
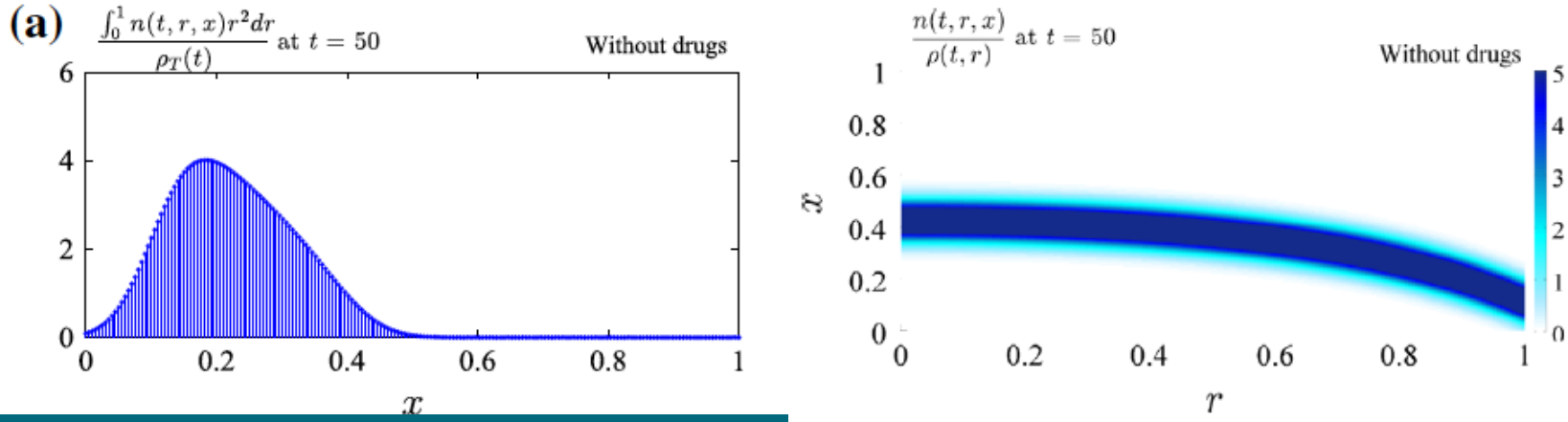
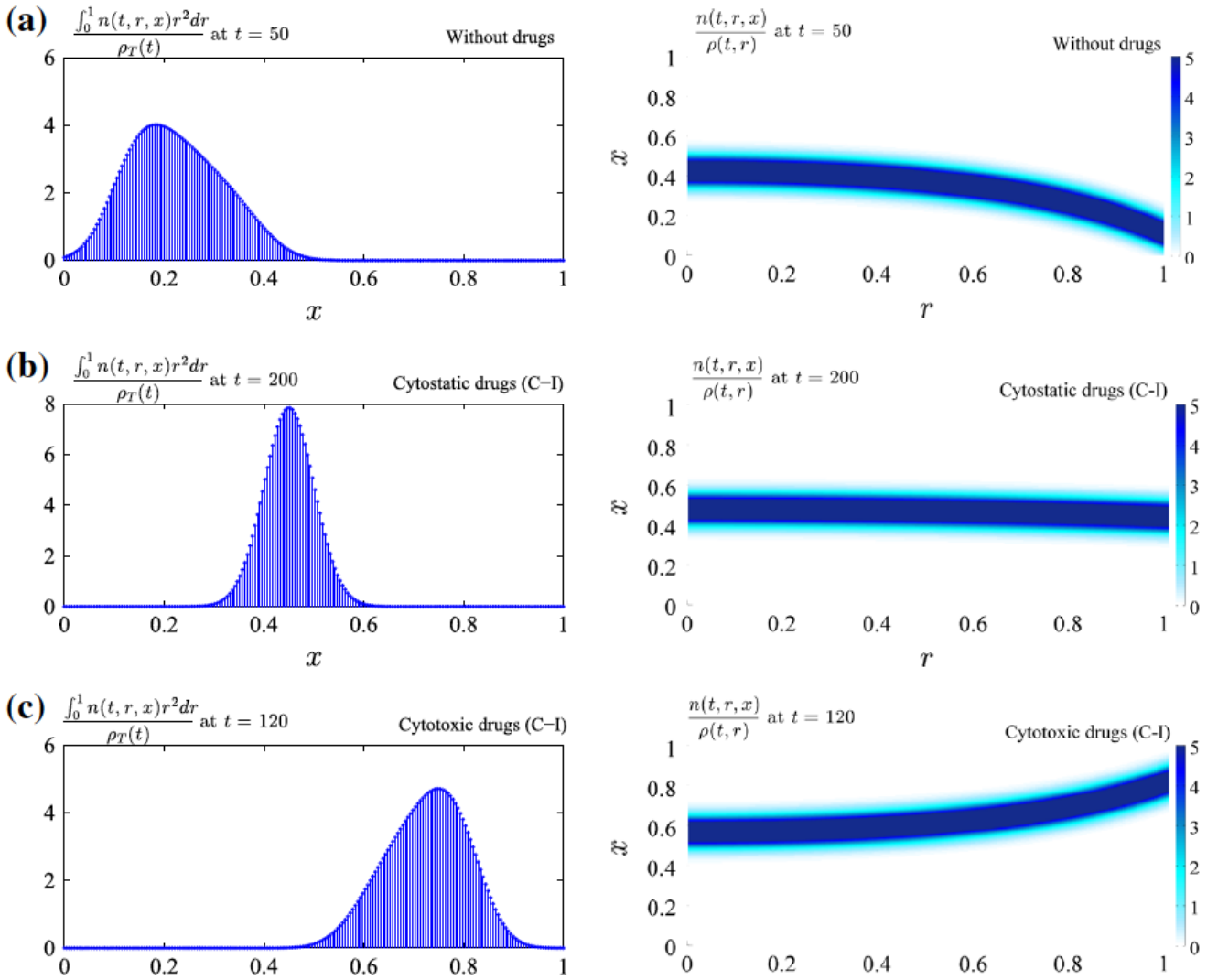


Fig. 1 Initial phenotypic distribution. Plots of $\int_0^1 n(t,r,x)r^2 \mathrm{d}r/\rho_T(t)$ (*left panel*) and $n(t,r,x)/\rho(t,r)$ (*right panel*) at $t=0$. The initial cell population is almost monomorphic

Evolution without drugs: towards sensitive phenotype ($x \to 0$)



Tumour spheroid: simulations with constant drug doses (2)



Cytotostatic c_2 has almost no effect / Cytotoxic c_1 clearly induces resistance

(Lorz et al. BMB 2015)

Tumour spheroid (3): constant or bang-bang control?

Therapeutic strategies c_1/c_2: Constant/Bang-bang vs. Bang-bang/Constant

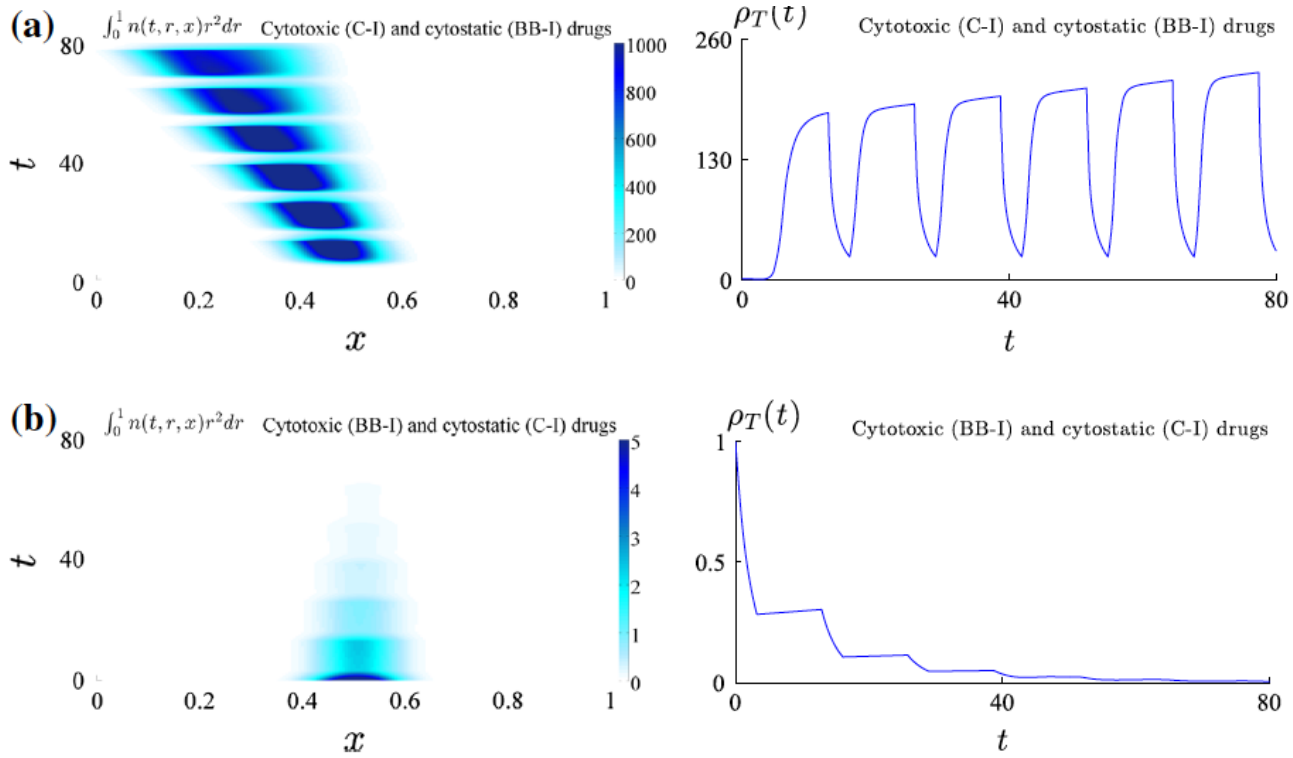
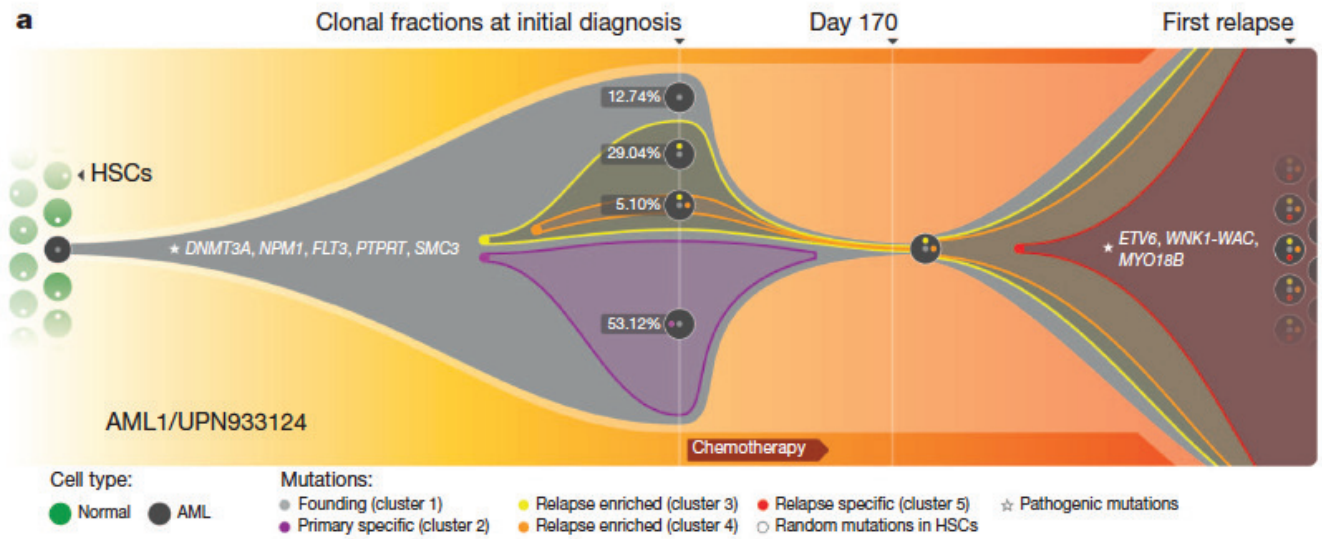


Fig. 11 **a** Cytotoxic (C-I) and cytostatic (BB-I) drugs. Plots of $\int_0^1 n(t, r, x)r^2 \mathrm{d}r$ (*left panel*) and $\rho_T(t)$ (*right panel*). Bang–bang infusion of cytostatic drugs together with constant infusion of cytotoxic drugs weakly affects the dynamics of cancer cells by comparison with the case without therapies, apart from temporary reductions of the global population density. **b** Cytotoxic (BB-I) and cytostatic (C-I) drugs. Plots of $\int_0^1 n(t, r, x)r^2 \mathrm{d}r$ (*left panel*) and $\rho_T(t)$ (*right panel*). Bang–bang infusion of cytotoxic drugs together with constant delivery of cytostatic drugs can push cancer cells toward extinction. The unit of time is days. All values are normalized with respect to the initial global population density

(Lorz et al. BMB 2015)

Limitations of this optimisation procedure, owing to the fact that the trait represents *resistance to only one drug*

- The model assumes *one* trait of resistance corresponding to *one* cytotoxic drug.
- However, overcoming resistance using such strategy may not be successful if too many types of resistance coexist, due to high phenotype heterogeneity.
- Phenotype heterogeneity (e.g., multiclonality) within the tumour may reduce such strategy to nothing, unless a multidimensional phenotype is considered.
- ... Unless also one could act very early to avoid the development of transient drug-resistant cell clones by epigenetic drugs or metabolism-modifying strategies.



(AML relapse, cf. *Ding et al. Nature 2012*)

References

- Chisholm, RH, Lorenzi, T., *JC*. Cell population heterogeneity and evolution towards drug resistance in cancer: biological and mathematical assessment, theoretical treatment optimisation. *BBA General Subjects* 1860:2627-45, 2016.
- Lorenzi, T., Chisholm, RH, *JC*. Tracking the evolution of cancer cell populations through the mathematical lens of phenotype-structured equations. *Biology Direct* 11:43, doi:10.1186/s13062-016-0143-4, 2016.
- Chisholm, RH, Lorenzi, T, Lorz, A, Larsen, AK, Almeida, L, Escargueil, A, *JC*. Emergence of drug tolerance in cancer cell populations: an evolutionary outcome of selection, non-genetic instability and stress-induced adaptation. *Cancer Research*, 75(6):930-939, 2015.
- Lorenzi, T., Chisholm, RH, Desvillettes, L, Hughes, BD. Dissecting the dynamics of epigenetic changes in phenotype-structured populations exposed to fluctuating environments. *Journal of Theoretical Biology*, 386:166-176, 2015.
- Chisholm, RH, Lorenzi, T, Lorz, A. Effects of an advection term in nonlocal Lotka-Volterra equations. *Comm. Math. Sciences*, in press, 2016.
- Lorz, A, Lorenzi, T, *JC*, Escargueil, A, Perthame, B. Effects of space structure and combination therapies on phenotypic heterogeneity and drug resistance in solid tumors. *Bull. Math. Biol.*, 77(1):1-22, 2015.
- Lorz, A, Lorenzi, T, Hochberg, ME, *JC*, Perthame, B. Populational adaptive evolution, chemotherapeutic resistance and multiple anticancer therapies. *ESAIM: Mathematical Modelling and Numerical Analysis (M2AN)*, 47(02):377-399, 2013.
- Lorz, A, Mirrahimi, S, Perthame, B. Dirac mass dynamics in multidimensional nonlocal parabolic equations. *Comm. Part. Diff. Eqs.*, 36(6):1071-1098, 2011.