Philosophy of Cancer Biology Workshop

Cancer as a default of coherence between tissues in metazoans: what mathematical models should be developed to help prediction, prevention and treatment of cancer, *avoiding drug resistance*?

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

Mamba INRIA team, Laboratoire Jacques-Louis Lions, Sorbonne Université, Paris

Bordeaux, October 2018

[†] *http : //who.rocq.inria.fr/Jean.Clairambault/Jean_Clairambault_en.html*

See also: "Mathematical Challenges in the Analysis of Continuum Models for Cancer Growth, Evolution and Therapy" (Oaxaca, 11/25-30, 2018: https://www.birs.ca/events/2018/5-day-workshops/18w5115)

Motivations from, and focus on, drug resistance in cancer

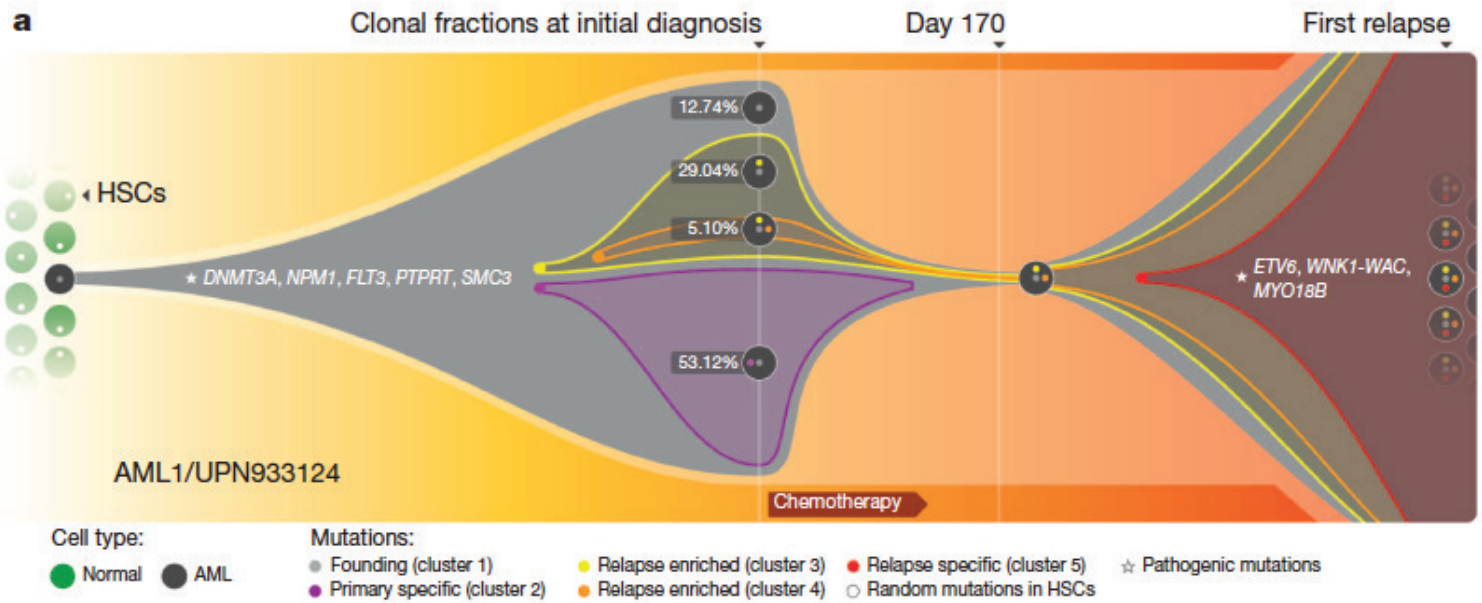
- Intra-tumour heterogeneity, i.e., between-cell phenotypic variability within cancer *cell populations*, is a condition of evolution towards drug resistance in tumours.
- Slow genetic mechanisms of 'the great evolution' that has designed multicellular organisms, together with fast reverse evolution on smaller time windows, at the scale of a human disease, may explain transient or established drug resistance.
- Plasticity in cancer cells, i.e., epigenetic propension to reversal to a stem-like, de-differentiated status, and resulting adaptability of cancer cell populations, makes them amenable to resist abrupt drug insult as extreme stress response.
- Reversible plasticity is captured by mathematical models that incorporate between-cell heterogeneity by making use of continuous phenotypic variables.
- Such models have the advantage of being compatible with optimal control methods for the theoretical design of optimised therapeutic strategies involving combinations of cytotoxic and cytostatic (*and possible epigenetic*) treatments.

Drug resistance: evolutionary bottlenecks in cancer

- Animal genome (of the host to cancer) is rich and amenable to adaptation scenarios that may recapitulate developmental scenarios - resulting in insufficient cohesion of the ensemble - abandoned in the process of evolution from protozoa to metazoa (*Davies & Lineweaver 2011*).

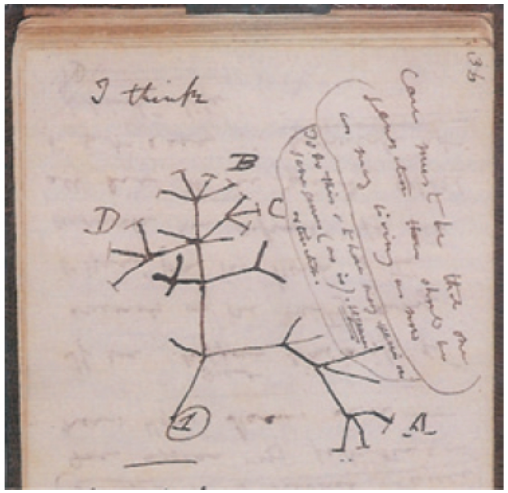
- In cancer populations, enhanced heterogeneity with enhanced proliferation results in a high phenotypic or genetic diversity of proliferating clonal subpopulationss

- So that drug therapy may be followed, after initial success, by relapse due to selection of a resistant clone (*Ding et al. 2012*).

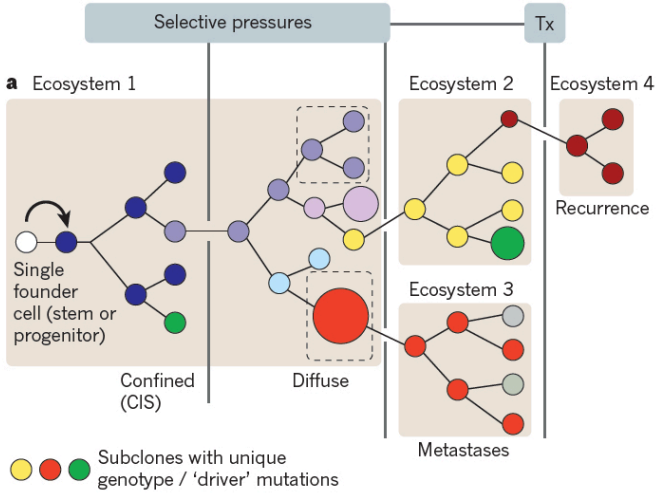


Ding et al. Nature 2012

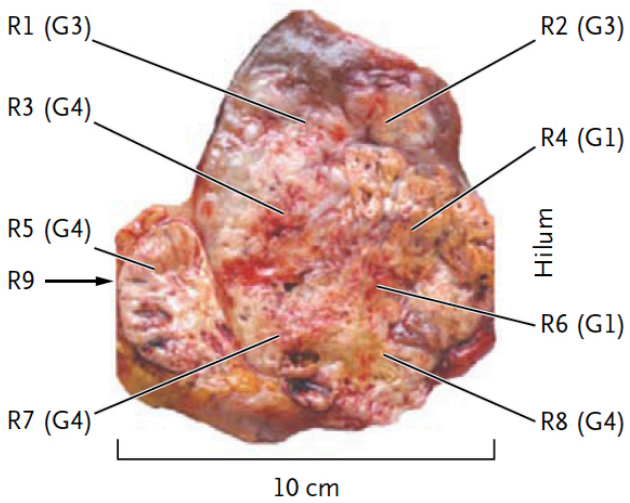
Drug resistance: always mutations and branching?

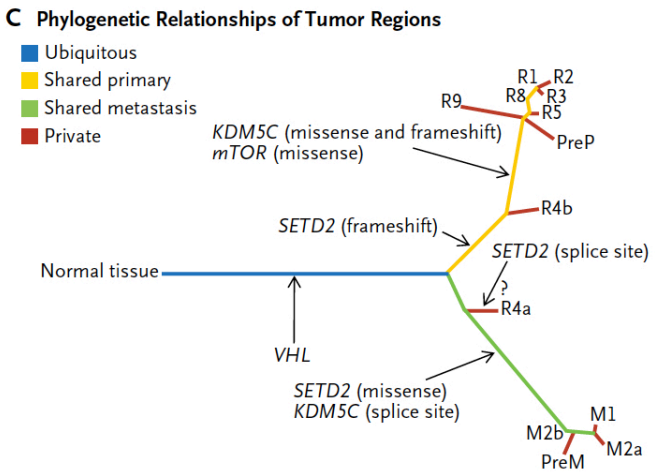


Darwin's notebook 1837



Maley & Greaves Nature 2012

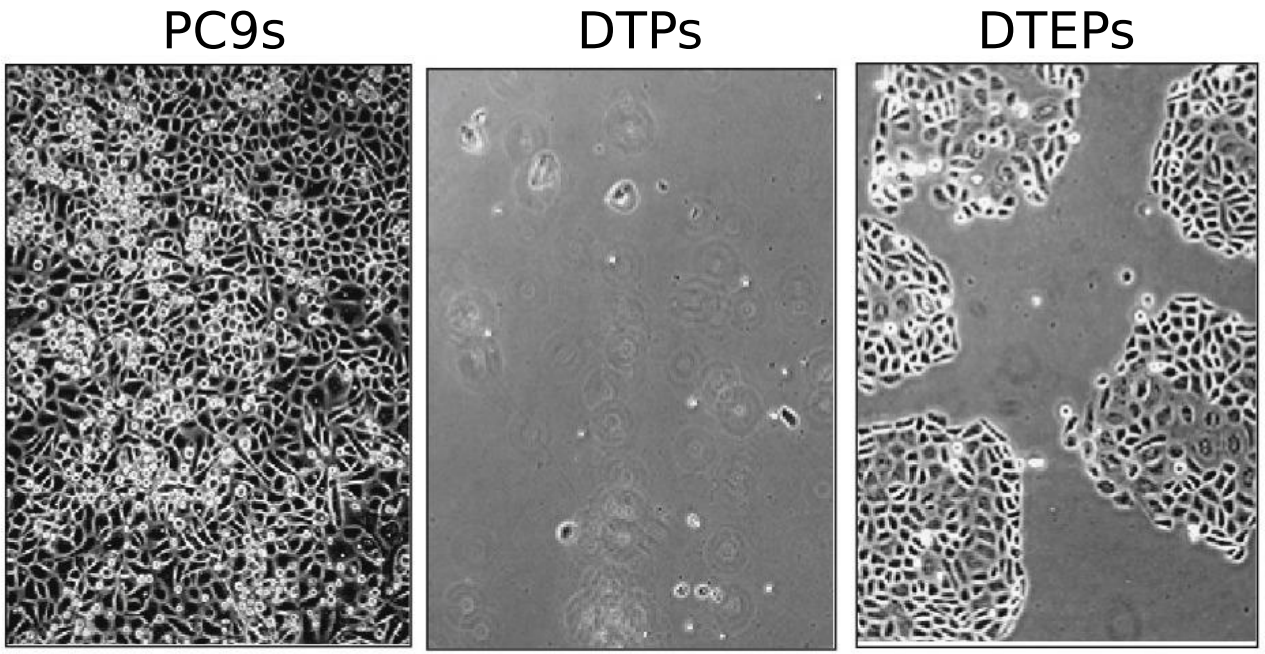




Gerlinger et al. NEJM 2012

An experiment showing reversible drug resistance in cancer

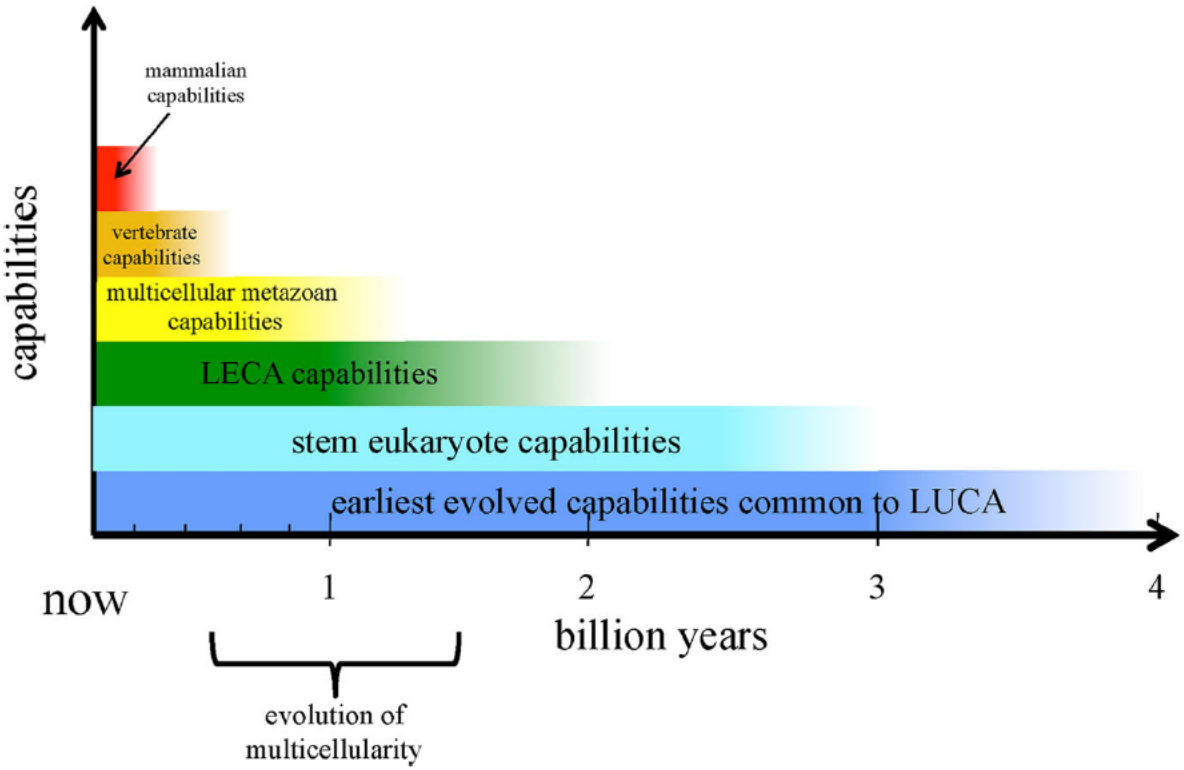
- Population of PC9 (NSCLC) cells under high doses of drugs (e.g., gefitinib)
- 99.7% cells die, .3% survive in this maintained hostile drug environment:
  Drug Tolerant Persisters, DTPs, first-step (transient) surviving population
- In the same hostile environment, 20% of DTPs resume proliferation:
  Drug Tolerant Expanded Persisters, DTEPs, second-step (established) resistant population
- 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



Sharma et al. Cell 2010

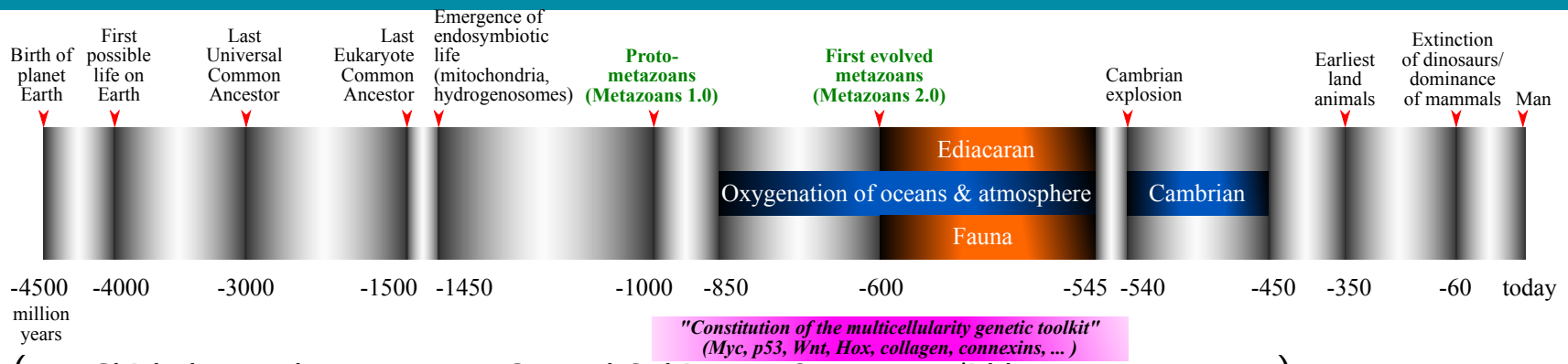
A possible evolutionary framework (*long-term view*): the atavistic hypothesis of cancer (1)

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



"Cancer: more archeoplasm than neoplasm" (Mark Vincent, 2011) More references: *Boveri 1929, Israel JTB 1996, Davies & Lineweaver Phys Biol 2011, Vincent Bioessays 2011, Lineweaver, Davies & Vincent Bioessays 2014, Chen et al. Nature Comm 2015, Bussey et al. PNAS 2017, Cisneros et al. PLoS One 2017, Trigos et al. PNAS 2017*

A possible evolutionary framework (*long-term view*): the atavistic hypothesis of cancer (2)



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

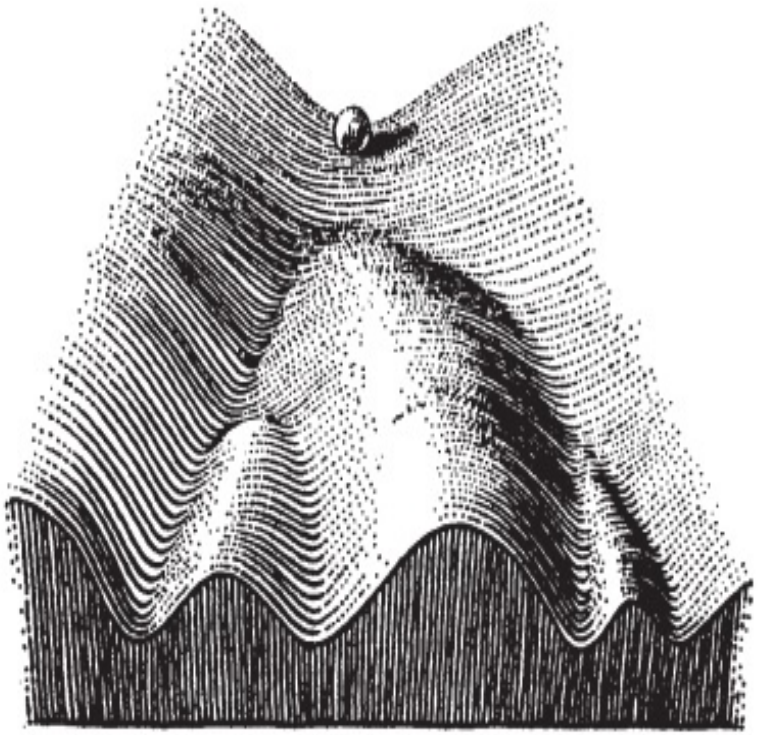
- The genes that have appeared in the process of development to multicellularity are precisely those that are altered in cancer
- In what order in evolution, from 1) proliferation+apoptosis to 2) cell differentiation +division of work, and to 3) *epigenetic control* of differentiation and proliferation?
- 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)

Drug resistance in cancer, not in healthy, cell populations

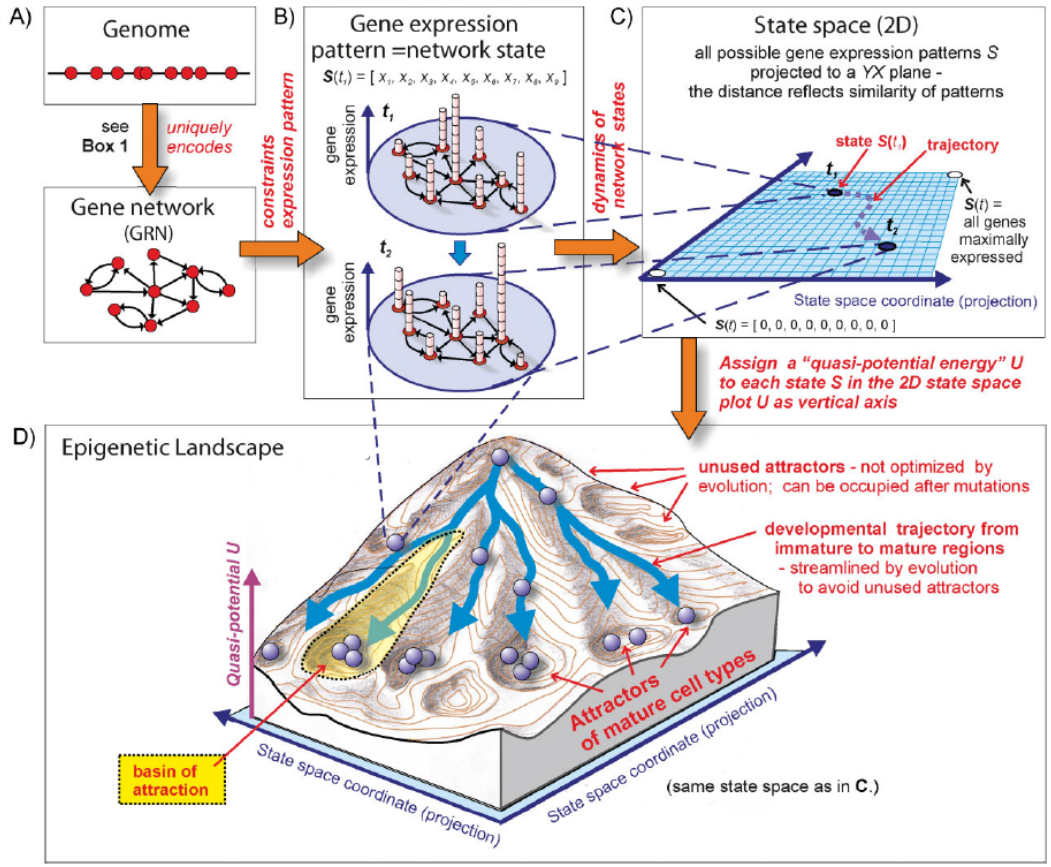
- According to the atavistic hypothesis, cancer is a 'backward evolution' from a sophisticated form of multicellularity (us), in which epigenetic processes control gene regulatory networks of transcription factors: differentiation factors, p53, etc., that themselves physiologically control the basis of cellular life: 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, regulations are lost, *differentiation is out of control (plasticity)*, so that, without regulation, local proliferations overcome; sophisticated *adaptive epigenetic mechanisms are present, not controlling proliferation, but serving it* (by stochastic expression of so-called *cold* genes? cf. Wu et al. PNAS 2015)
- 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*

Another evolutionary framework (*life-term view*): revisiting the Waddington epigenetic landscape

The classic Waddington landscape (1957) for cell differentiation



Waddington landscape revisited by S. Huang (2011, 2012, 2013)



"Nothing in evolution makes sense except in the light of *systems* biology" (S. Huang, 2012)

Simple phenotype-structured population dynamics

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

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

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

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

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

Phenotype-structured non-local Lotka-Volterra models

Questions: what is the asymptotic behaviour ($t \to +\infty$) of

- the total population $\rho(t)$?
- the phenotypes in the population (*i.e.*, possible limits for $\dfrac{n(t,\cdot)}{\rho(t)}$ in $M^1(0,1)$)?

Nonlocal Lotka-Volterra model: $n(t,x)$ density of cells of trait (phenotype) $x \in [0,1]$:

$$\frac{\partial n}{\partial t}(t,x) = \big(r(x) - d(x)\rho(t)\big)\, n(t,x),$$

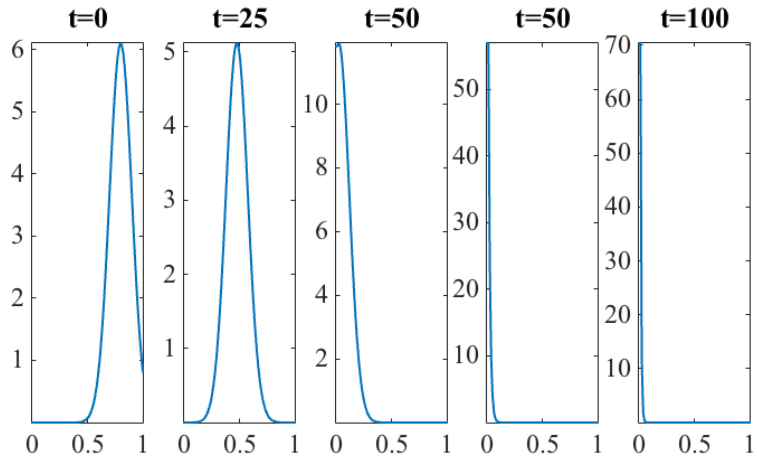
with

$$\rho(t) := \int_0^1 n(t,x)\, dx \quad \text{and} \quad n(0,x) = n^0(x).$$

Firstly (Theorem: convergence in time of $\rho(t)$): ρ converges to $\rho^\infty = \max\limits_{[0,1]} \dfrac{r}{d}$, i.e., to the smallest value ρ such that $r(x) - d(x)\rho \le 0$ on $[0,1]$.

Non-local Lotka-Volterra model: convergence and concentration in x

Secondly (convergence *and concentration in* x): plot of $x \mapsto n(t,x)$ for different t



Theorem

- *ρ converges to ρ^∞, the smallest value ρ such that $r(x) - d(x)\rho \leq 0$ on $[0,1]$.*
- *$n(t,\cdot)$ concentrates on the set $\{x \in [0,1],\ r(x) - d(x)\rho^\infty = 0\}$.*
- *Furthermore, if this set is reduced to a singleton x^∞, then*

$$n(t,\cdot) \rightharpoonup \rho^\infty \delta_{x^\infty} \text{ in } M^1(0,1).$$

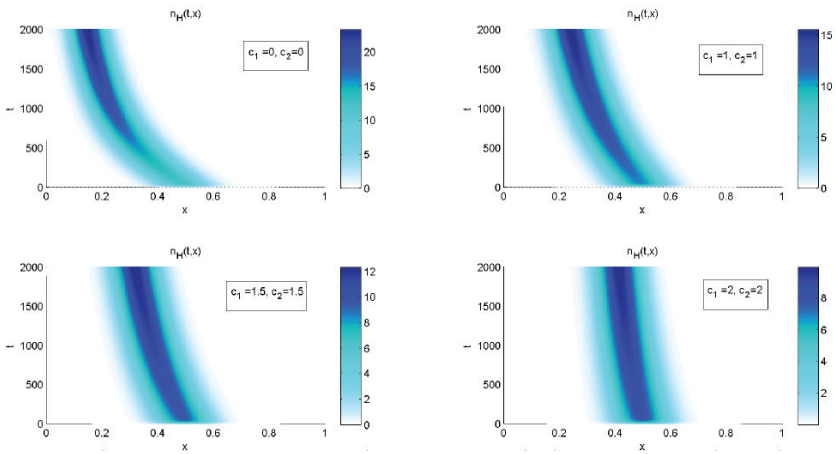
Non-local Lotka-Volterra 2D model (2 populations, n_H, n_C) with 2 different drugs and one resistance phenotype x

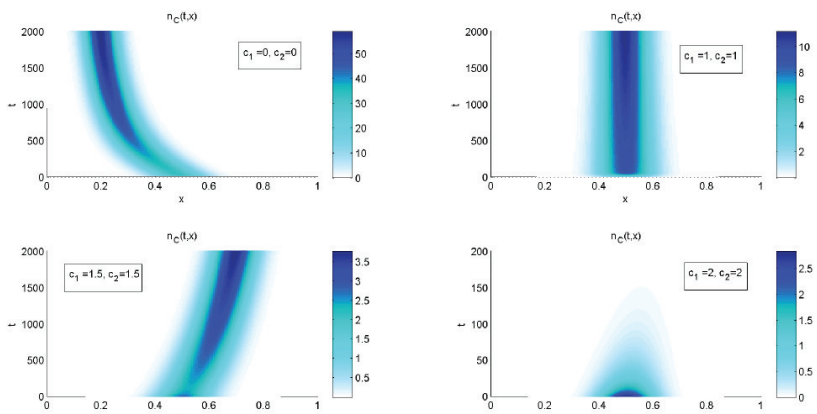
$$\frac{\partial}{\partial t} n_H(t,x) = \left[\frac{r_H(x)}{1 + k_H u_2(t)} - d_H(x) I_H(t) - u_1(t) \mu_H(x) \right] n_H(t,x)$$

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

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 $\rho_H(t) = \int_0^1 n_H(t,x)\,dx$, $\rho_C(t) = \int_0^1 n_C(t,x)\,dx$, u_1 cytotoxic, u_2 cytostatic drugs.

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





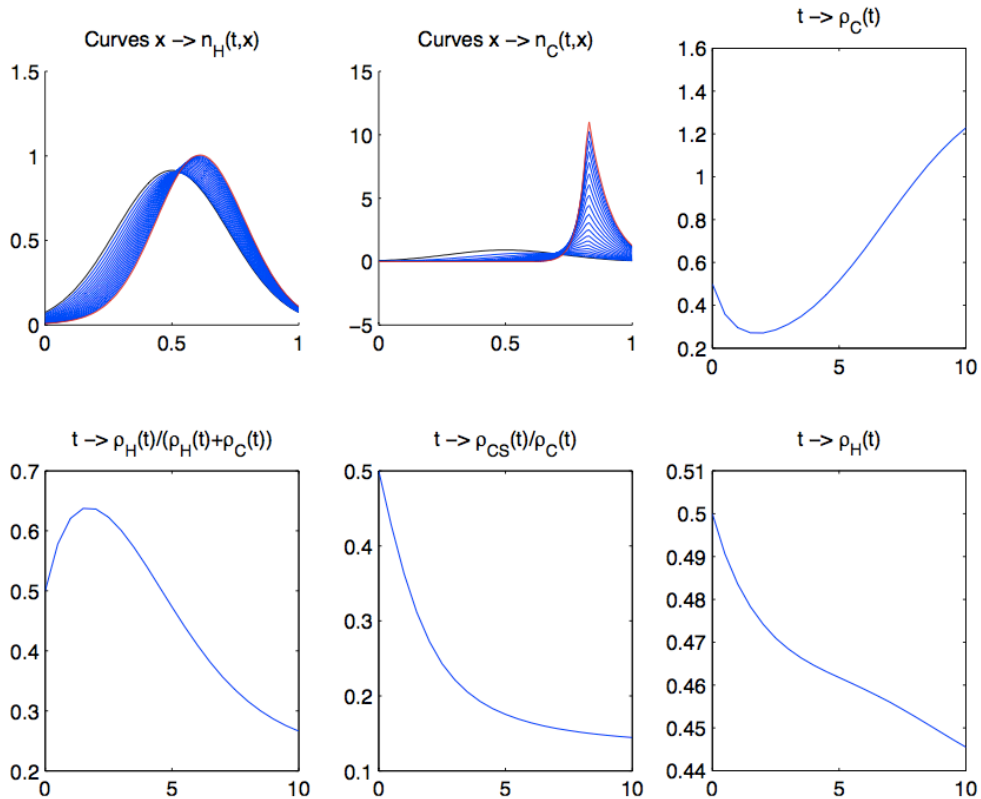
Healthy cells: preserved

Cancer cells: eventually extinct

Proof of concept, or here "Pedestrian's optimisation" *Lorz et al. M2AN 2013*

How to be deleterious by using constant doses of drugs

[We define the population of sensitive cancer cells by $\rho_{CS}(t) := \int_0^1 (1-x)\, n_C(t,x)\, dx$*]*
Simulation with $u_1(t) = \mathrm{Cst} = 3.5$ and $u_2(t) = \mathrm{Cst} = 2$, in time $T = 10$



- Quite small effect of the drug pressure on the phenotype of n_H
- n_C quickly concentrates around a resistant phenotype
- Catastrophic effects on ρ_H, ρ_C and ρ_{CS}.

"What does not kill me strengthens me"

- Note that in the representation of the drug targets on cancer cell populations in the integro-differential equation, with the numerical values chosen for the target functions μ_C and r_C standing for the sensitivities to drugs u_1 and u_2,

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

  the cytostatic drug u_2 *only slows down proliferation* (softly slowing down velocity in the cell division cycle), but does not arrest it, at least at low doses...

- ...whereas the cytotoxic drug u_1 *kills* the cells by increasing the death term, hence it is actually a direct life threat to the cell population, that 'defends itself' (biological bases under assessment...) by increasing its resistance phenotype x

- This resistance-inducing killing effect should be avoided as long as possible in therapeutics. In summary: limit proliferation but do not try too hard to kill cells, lest the cell population should become resistant, but give cytotoxics only at high doses during a short interval of time (MTD), thus avoiding to trigger resistance.

- An alternative to such use of MTD (maximum tolerated dose) towards the end of the chemotherapy course is *metronomics*, that also prevents developing resistance by giving low doses of cytotoxics... expecting that the population, thwarted in its proliferation, will be kept in check by the immune system. This has not been represented in our optimal control perspective thus far (however, see *Cécile Carrère, J Theor Biol 2017*).

Optimal control problem, phenotype-structured IDE model

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 $\rho_H(t) = \int_0^1 n_H(t,x)\,dx, \rho_C(t) = \int_0^1 n_C(t,x)\,dx$.

IDE model with evolution in phenotype x due to effects of cytotoxic drug $u_1(t)$

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

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

$$0 \le u_1(t) \le u_1^{\max}, \qquad 0 \le u_2(t) \le u_2^{\max}$$

Find controls (u_1, u_2) minimising

$$C_T(u_1,u_2) = \rho_C(T) = \int_0^1 n_C(T,x)\,dx$$

under the additional constraints

$$\frac{\rho_H(t)}{\rho_H(t)+\rho_C(t)} \ge \theta_{HC}, \qquad \rho_H(t) \ge \theta_H.\rho_H(0)$$

(the last constraint, with, e.g., $\theta_H = 0.6$, to limit damage to healthy cells)

Optimal control problem: theoretical results

Theorem

(Optimal control theorem)

Under these conditions, the optimal trajectory in large time $T > 0$ consists of 2 parts:

- a long-time part, with constant controls on $[0, T_1]$, at the end of which populations have almost concentrated in phenotype (for T_1 large)
- a short-time part on $[T_1, T]$ consisting of at most three arcs, for $T - T_1$ small:
  1. a boundary arc, along the constraint $\dfrac{\rho_H(t)}{\rho_H(t) + \rho_C(t)} = \theta_{HC}$,
  2. a free arc (no constraint saturating) with controls $u_1 = u_1^{\max}$ and $u_2 = u_2^{\max}$,
  3. a boundary arc along the constraint $\rho_H(t) \geq \theta_H . \rho_H(0)$ with $u_2 = u_2^{\max}$.

Simulations illustrating this theorem

Simulations with $T = 30$
(optimisation using AMPL-IPOPT)

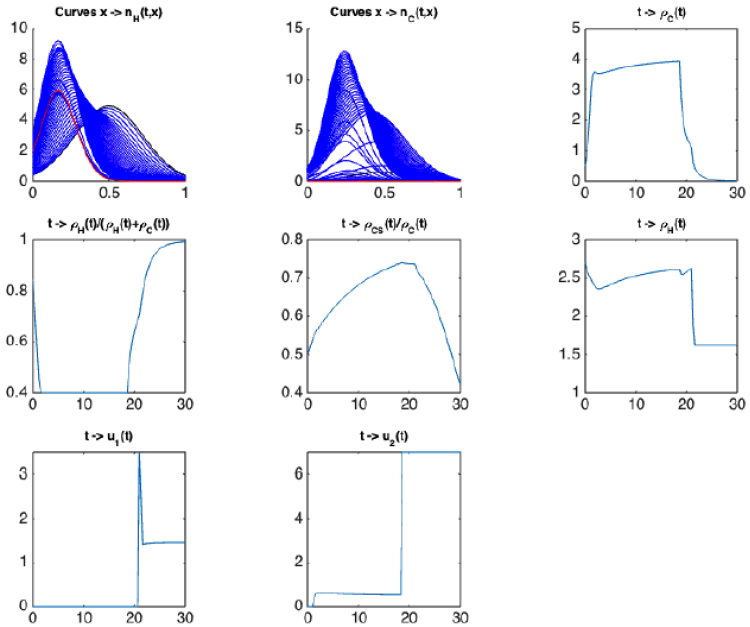


Figure 4: Simulation of (**OCP**) for $T = 30$.

Simulation with $T = 60$
(optimisation using AMPL-IPOPT)

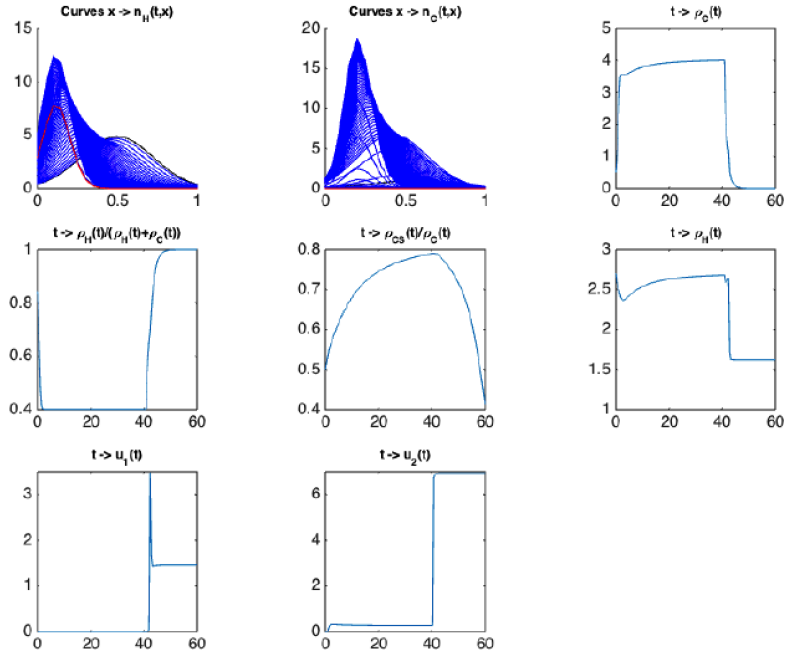


Figure 5: Simulation of (**OCP**) for $T = 60$.

Note that this strategy lets the cancer cell population ρ_C grow initially to an equilibrium level, while increasing the ratio $\dfrac{\rho_{CS}}{\rho_C}$ of drug-sensitive cancer cells, before delivering $u_1 = u_1^{\max}$; only then is the cytotoxic efficacy maximal.

Interpretation

In a first approximation the optimal trajectory is made of 3 parts, the first one with $u_1 = 0$, the 2nd one with $u_1 = u_1^{\max}$, the 3rd one with u_1 slightly lower than $u_1^{\max}$.

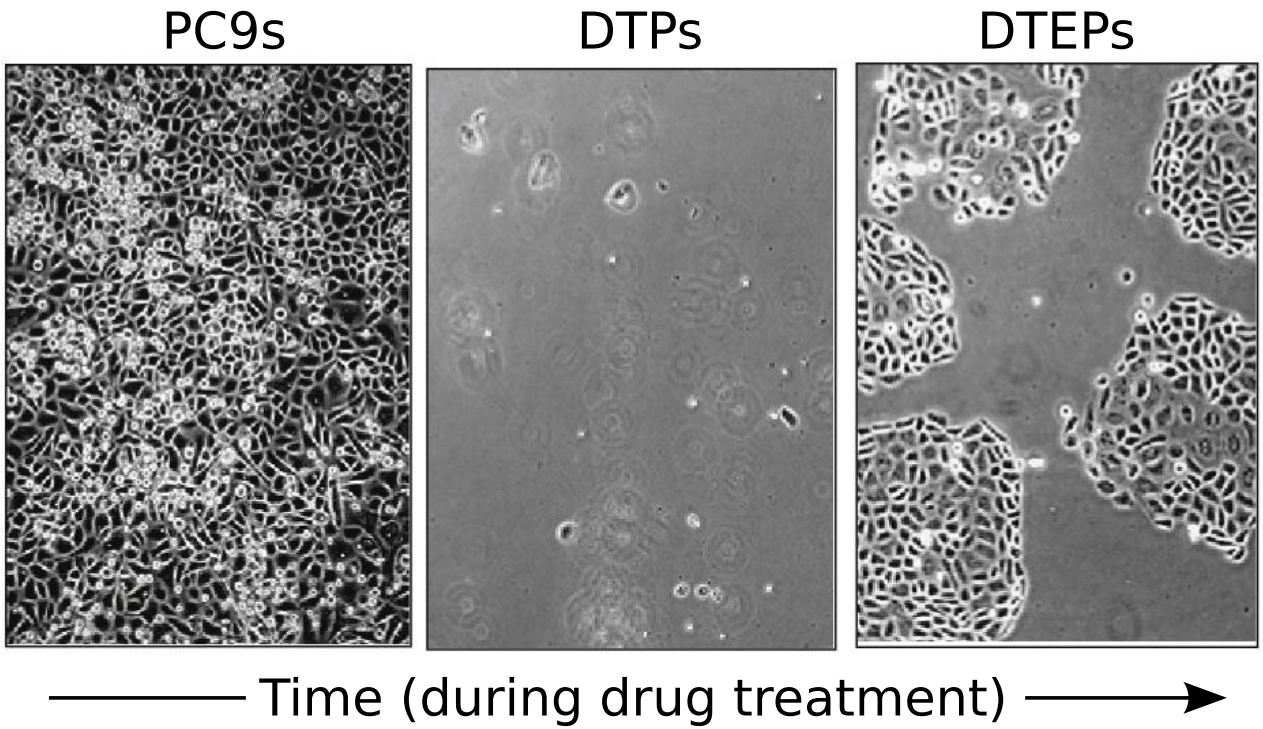
Main idea:

1. Let the system naturally evolve to a phenotype concentration (long-time phase).
2. Then, apply the maximal quantity of drugs, during a short-time phase, in order to eradicate as many tumour cells as possible.

The second short-time phase is all the more efficient as the phenotypes are more concentrated (hence, as the time T is large).

Modelling 2-step evolution towards reversible drug resistance

- 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

Structured cell population: *cell-functional* variables

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

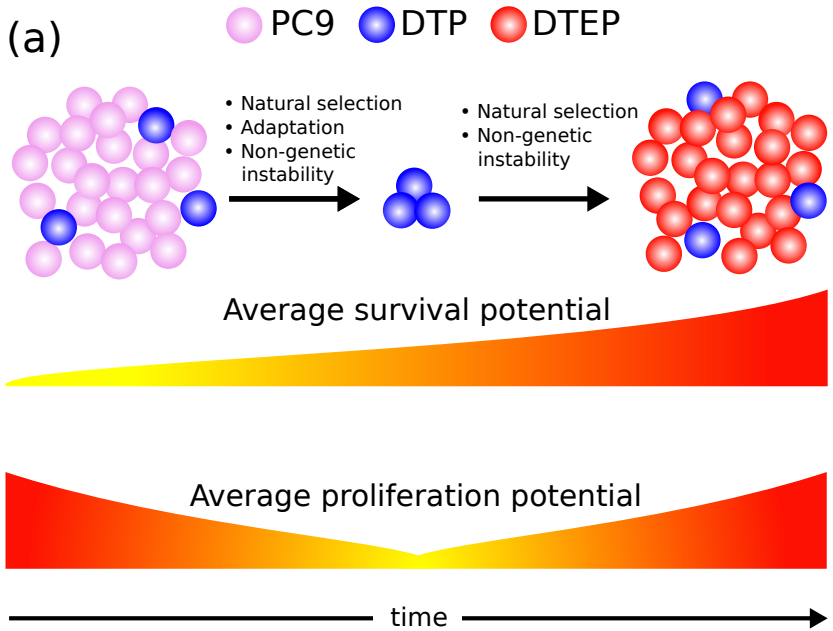
- Population density of cells $n(x, y, t)$ with phenotypic expression (x, y) at time t satisfies

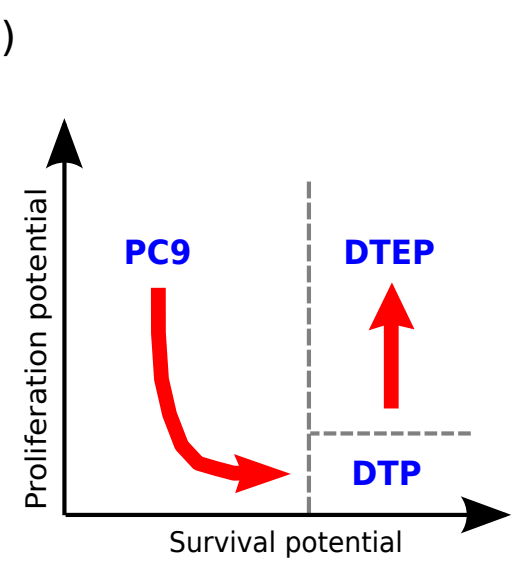
$$\frac{\partial n}{\partial t}(x, y, t) + \underbrace{\frac{\partial}{\partial y}\Big(v(x, c(t); \bar{v})n(x, y, t)\Big)}_{\text{Stress-induced adaptation of the proliferation level}} = \underbrace{\Big[p(x, y, \varrho(t)) - d(x, c(t))\Big] n(x, y, t)}_{\text{Non local Lotka-Volterra selection}} + \underbrace{\beta \Delta n(x, y, t).}_{\text{Non-genetic phenotype instability}}$$

- $\varrho(t) = \int_0^1 \int_0^1 n(x, y, t)\, dx\, dy$, $p(x, y, \varrho(t)) = (a_1 + a_2 y + a_3(1 - x))(1 - \varrho(t)/K)$ 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

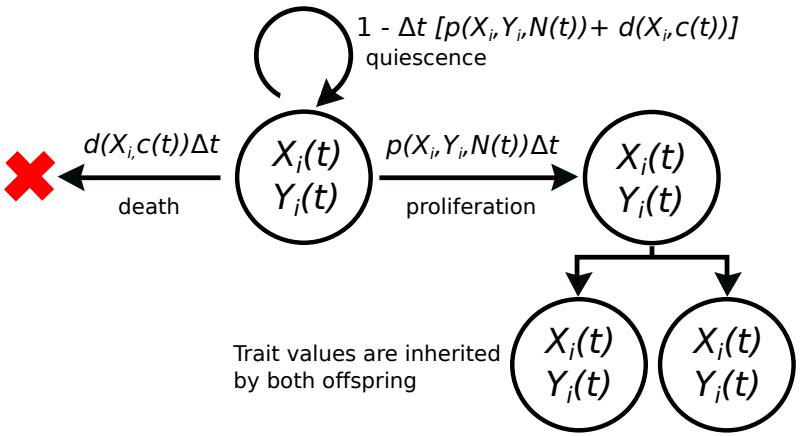
Chisholm et al., Cancer Research 2015

Same framework using an agent-based model (ABM)





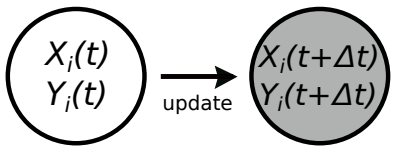
(a) Each cell i undergoes either proliferation, death or remains quiescent:



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

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

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

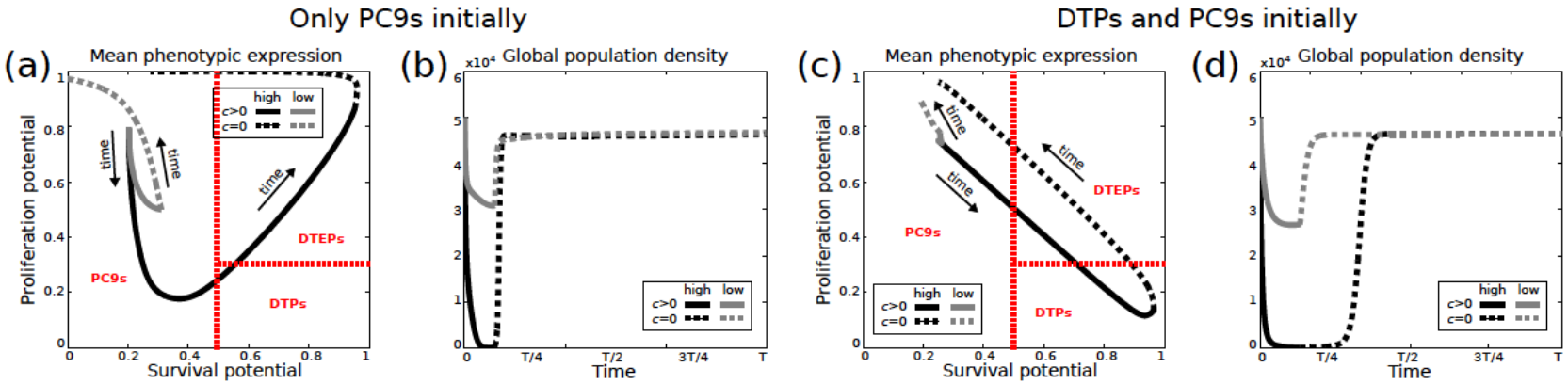


Chisholm et al., Cancer Research 2015

Resensitisation after drug washout is in the model

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

Two scenarios: Lamarckian adaptation, or sheer Darwinian selection of the fittest

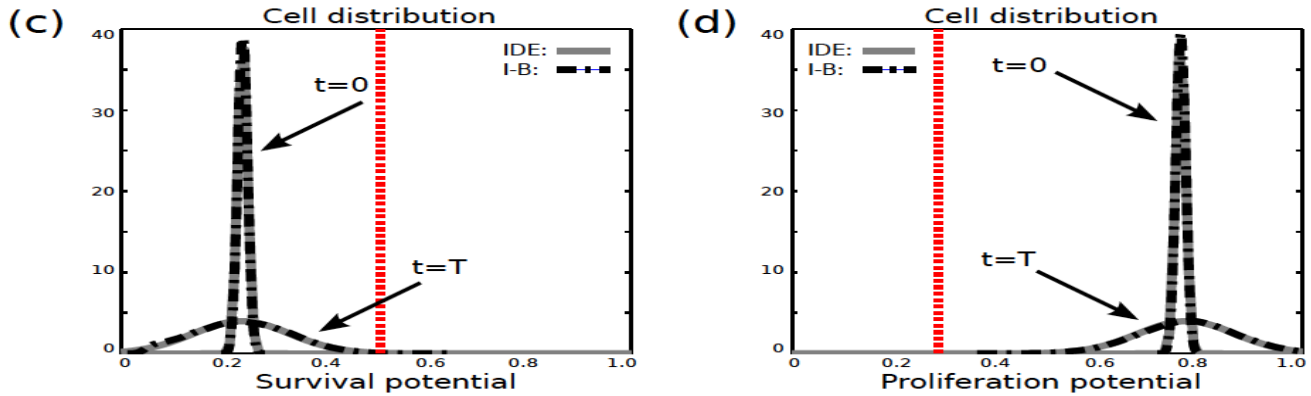


(a), (b) Only PC9s (no DTPs initially), adaptation on ($v \neq 0$): *'Lamarckian' scenario*

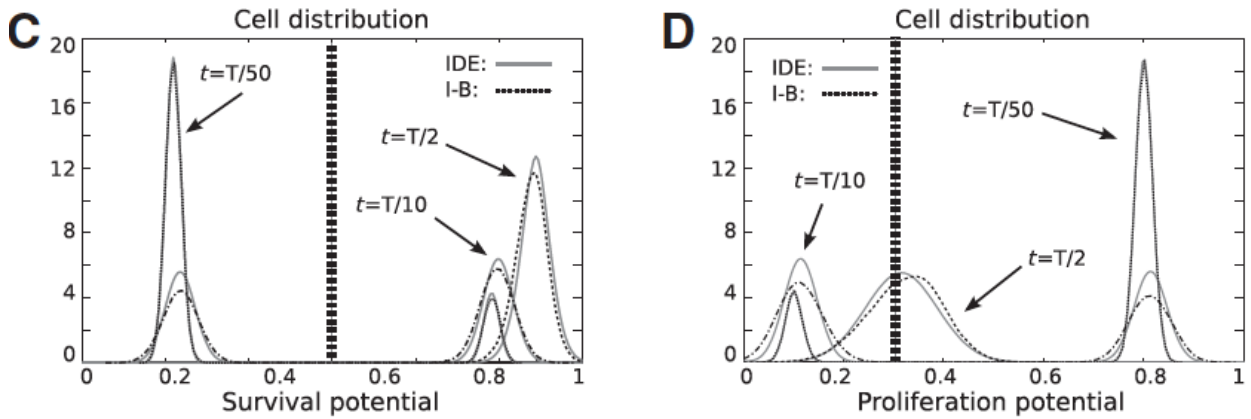
(c), (d) PC9s and DTPs initially, no adaptation ($v = 0$): *'Darwinian' scenario*
(sheer selection of the fittest = DTPs, supposed to be present in the initial population)

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

Use the 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 $c(\cdot) = constant$ and two scenarios:

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

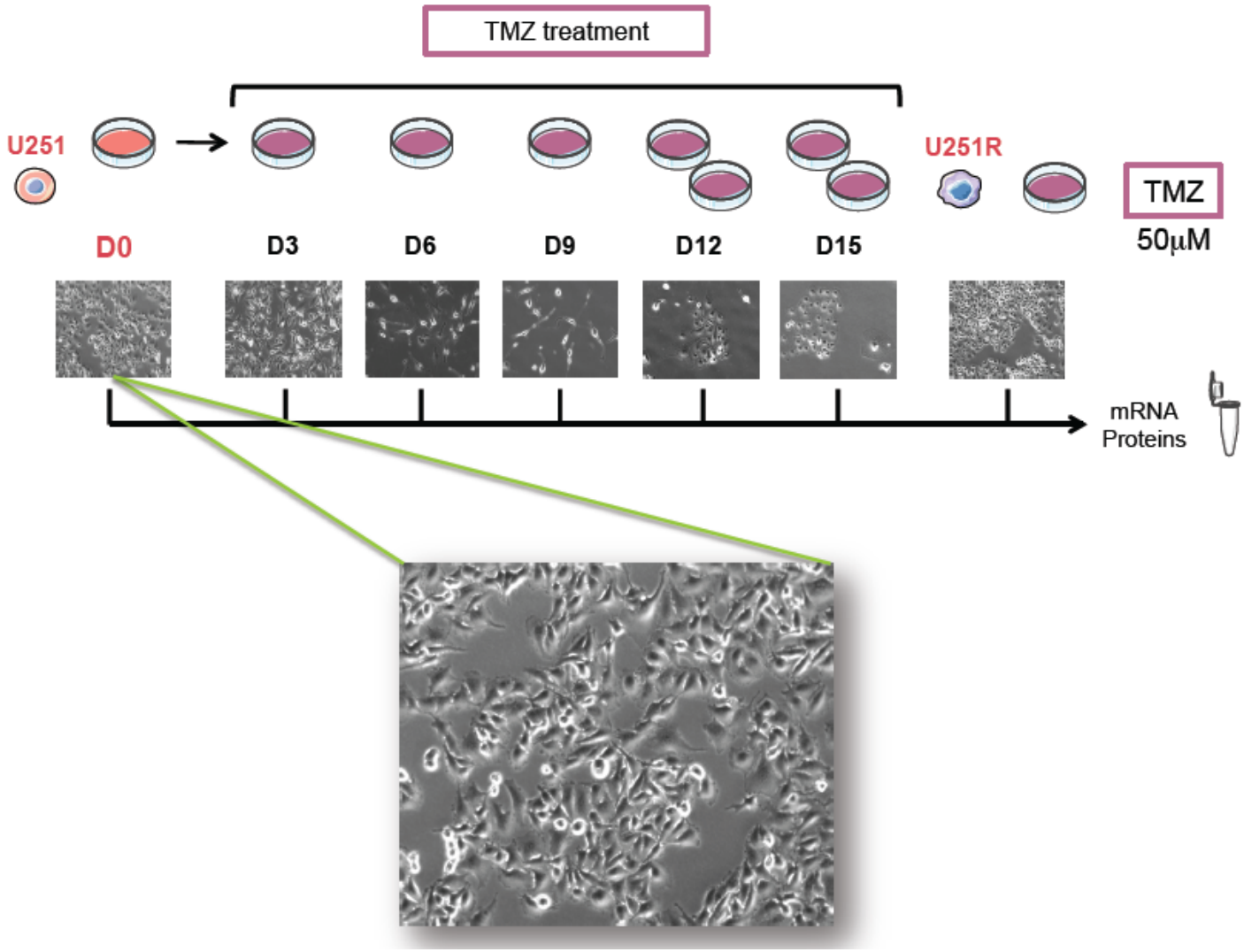
(ii) (*'Lamarckian' scenario (A)*: the outlaw) Only PC9s initially, adaptation present ($v \neq 0$)

To make a long story short, **Q1**. Always yes! Whatever the scenario

Q2. Low drug doses result in DTEPs, but no DTPs

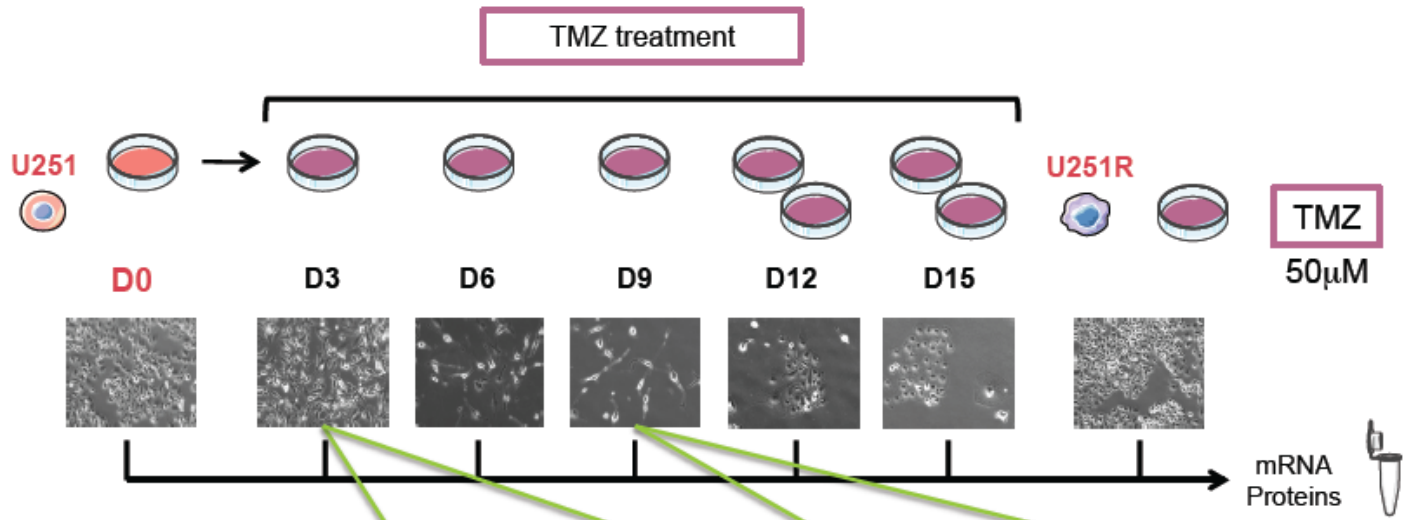
Q3. Never! Whatever the scenario

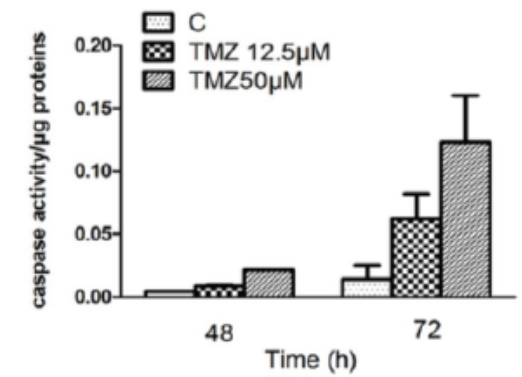
Glioblastoma and temozolomide: as in *Sharma Cell 2010*



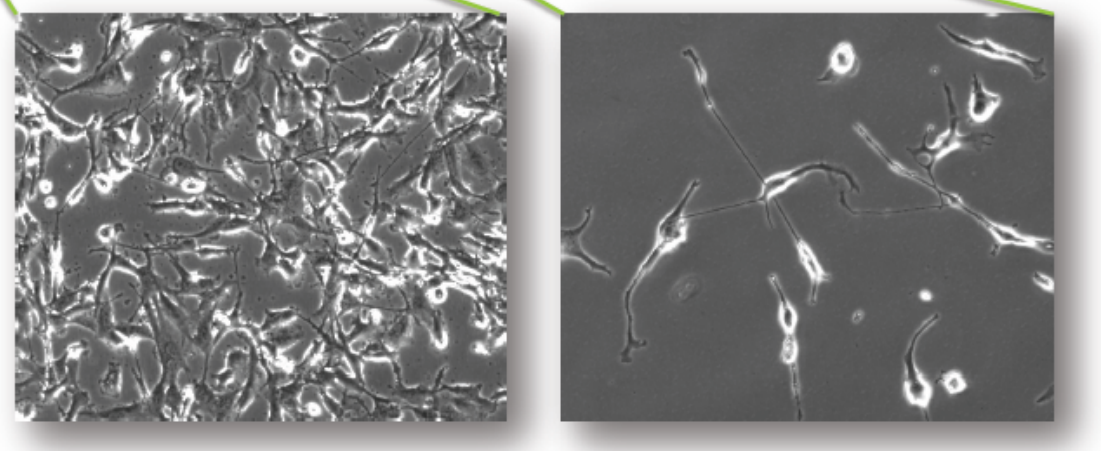
from F. Vallette's INSERM team in Nantes

Glioblastoma and temozolomide: as in *Sharma Cell 2010*



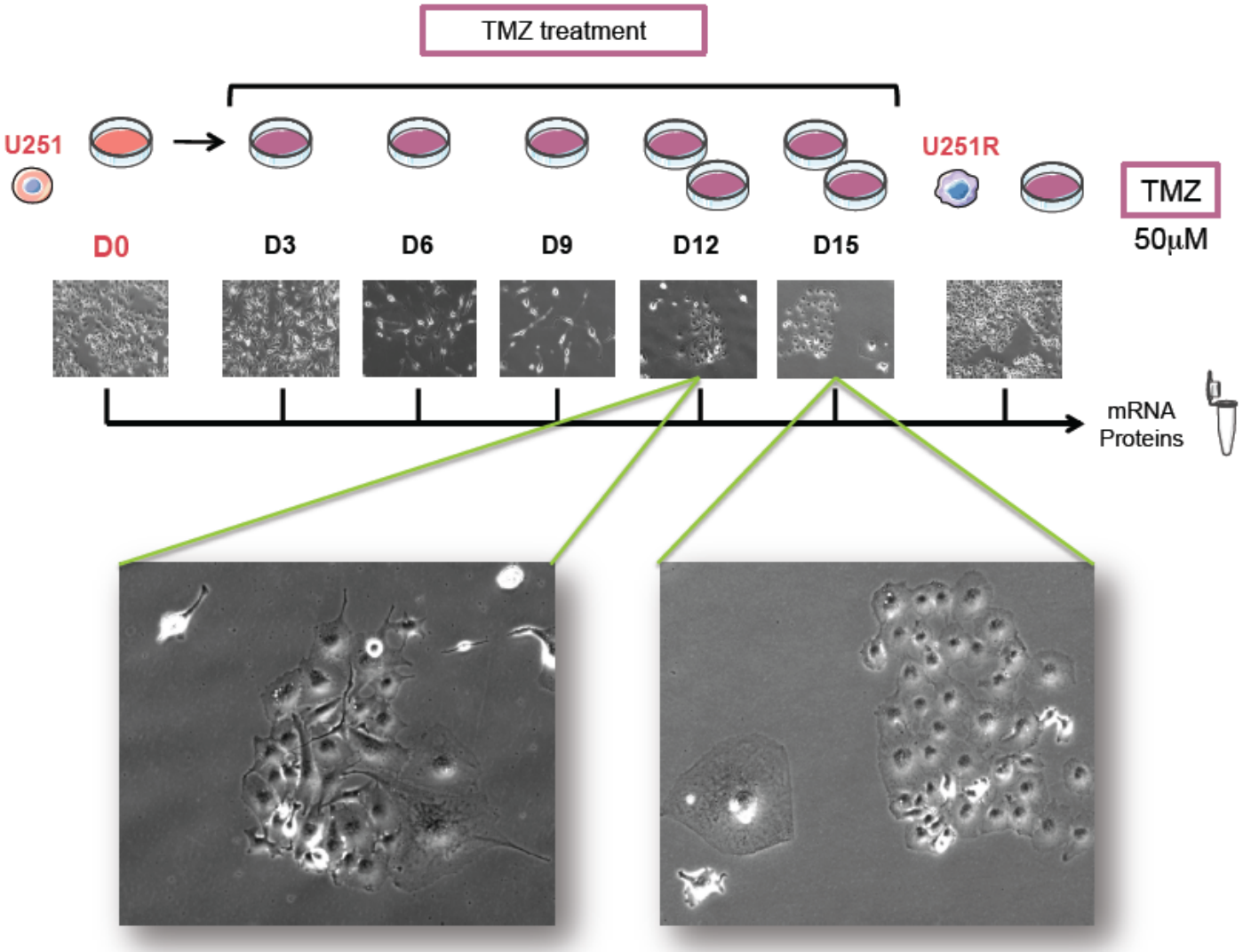


Gratas *et al*, 2014, Oncotarget



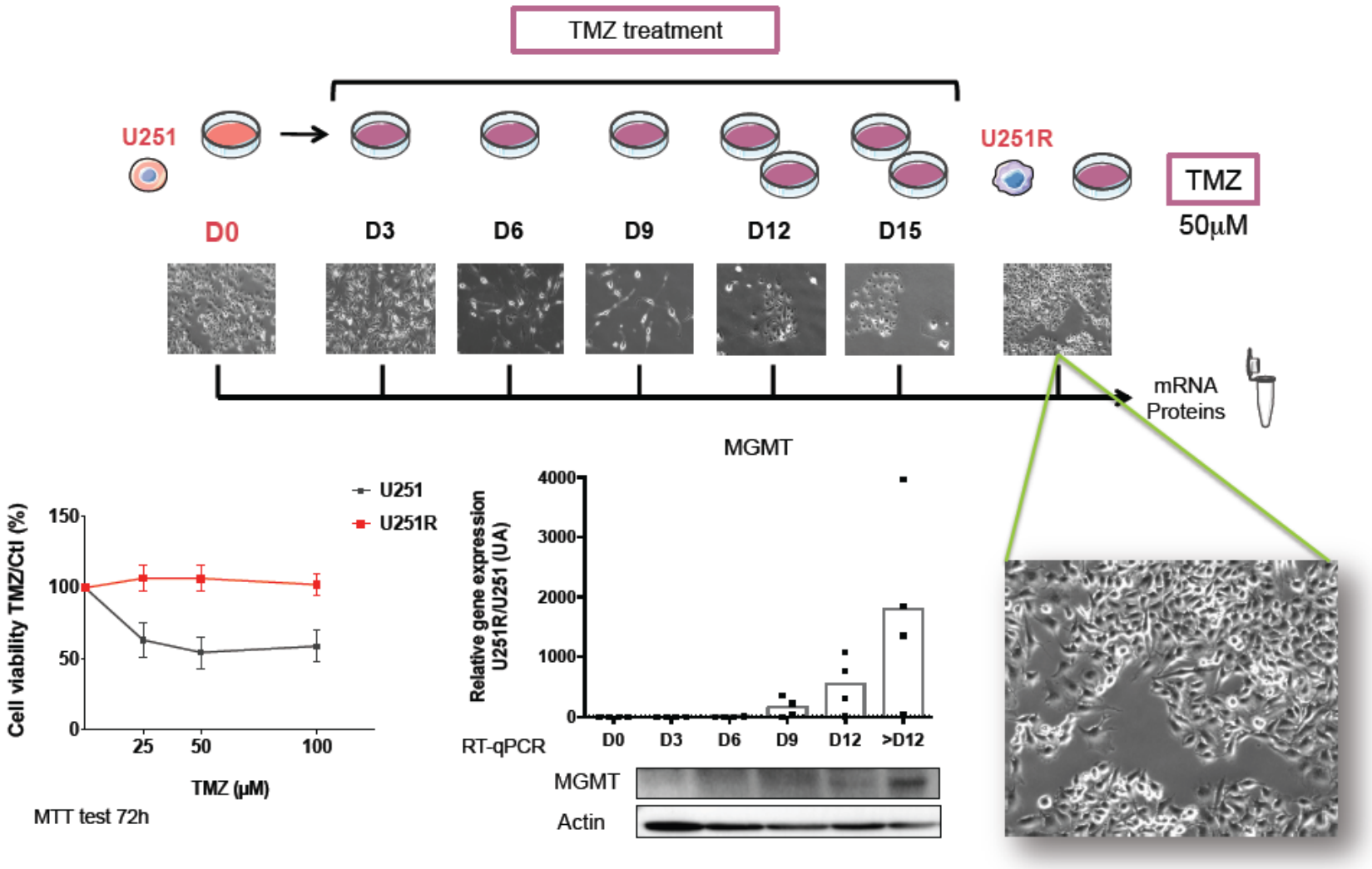
from F. Vallette's INSERM team in Nantes

Glioblastoma and temozolomide: as in *Sharma Cell 2010*



from F. Vallette's INSERM team in Nantes

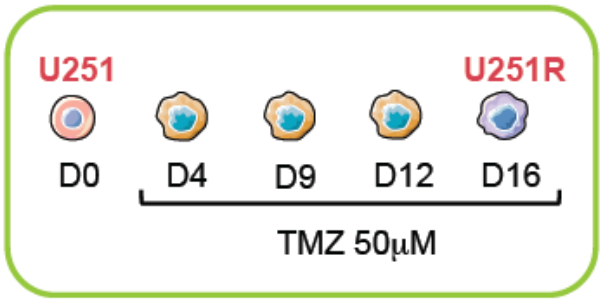
Glioblastoma and temozolomide: as in *Sharma Cell 2010*

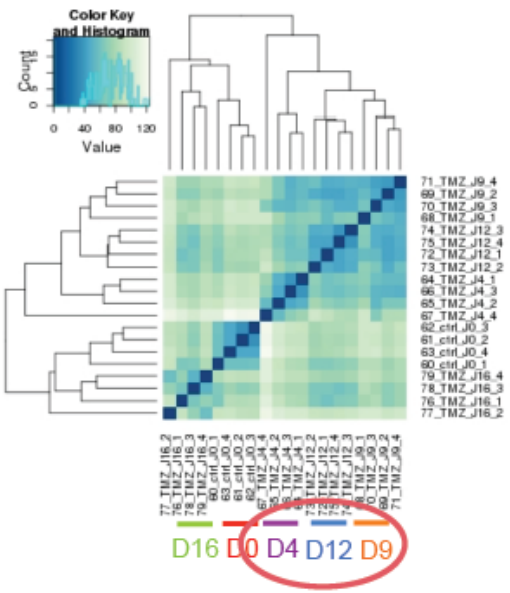


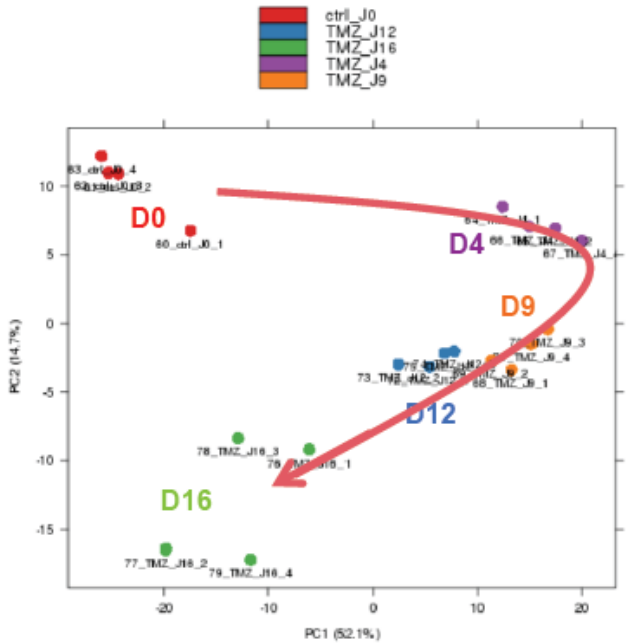
Gene expression followed from D0 to D16 (PCA)

Whole transcriptome sequencing

RNA-Seq







Short time window for combined treatment with an epigenetic drug??

from F. Vallette's INSERM team in Nantes

Modelling *bet hedging* using 3 cell-functional variables?

- What is more relevant for stress response of a cell population (adaptable, as in the case of a tumour): maintain a subpopulation of all-stress resistant cells, or maintain a subpopulation of cells expressing 'cold genes' and able to launch different resistance mechanisms in different cells? (... stochastically chosen?)

- *Bet hedging* as a 'tumour strategy' to diversify its responses to deadly stress (as high doses of cytotoxic drugs) by launching different stress response mechanisms in different cells? (ABC transporters, detoxication enzymes, DNA repair...)

- Stress response through derepression of *cold genes*? Wu et al. PNAS 2015: existence of very ancient genes, constituted in a remote past of our planet, able to put at work survival programs in a state of emergency, with *bet hedging*, in a cancer cell population?

- Does *bet hedging* shuffle phenotypes, setting favorable bases for the emergence of specialisation (Michod et al. JTB 2006) and cooperativity in tumours (Tabassum & Polyak Nature Rev. Cancer 2015, Polyak & Marusyk Nature 2014), making them viable?

- Bet hedging setting for $n(x, y, \theta, t)$, with x=fecundity, y=viability, θ=plasticity:

$$n_t + \nabla \cdot \{V(x, y, \theta, D)\, n\} = \alpha(\theta) n_{xx} + \beta(\theta) n_{yy} + n \left\{ r(x, y, \theta) - \frac{\rho(t)}{C(x, y)} - \mu(x, y, \theta, D) \right\}$$

(underway with C. Carrère, T. Lorenzi, G. Nadin)

References: articles about mathematical modelling

- 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.
- 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.
- 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.
- 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*, 14:1181–1188, 2016.
- 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(11):2627-2645, 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, 2016.
- Pouchol, C., Trélat, E, Lorz, A, *JC*. Asymptotic analysis and optimal control of an integro-differential system modelling healthy and cancer cells exposed to chemotherapy. *JMPA*, 2017.

- See also `https://who.rocq.inria.fr/Jean.Clairambault/JCarticles.html`

Why is evolution important in cancer? Basic questions on *multicellularity and cancer*

- **Cancer is a disease of multicellular organisms**, that has been evidenced, including in fossils, in the whole animal kingdom
- Cancer *is* the failure of maintenance of a coherent (=founded on stable cellular differentiations) multicellularity, or else:
- **Cancer may be defined as a loss of cohesion of tissues and organs of a same organism following failures in differentiation**
- Does there exist in the construction of multicellularity a qualitative succession of emergences of families of genes responsible for 1. proliferation and apoptosis 2. differentiation (transcription factors?); 3. epigenetic control of differentiations ? Phylogenetic scenarios of evolution of mutations in AML go in the opposite direction with increasing malignancy (Hirsch et al. Nature Comm. 2016)
- Some gene mutations predispose subjects to well-identified organ cancers: do these genes play a role in the anatomic constitution of multicellularity?
- Evolution proceeds by *tinkering* (*François Jacob*, 'Evolution and tinkering', *Science* 1977), using every possible avaible material: what in such a succession of tinkerings makes an organism viable but fragile?
- **The genes that are altered in cancers are the same that serve multicellularity design** (*Domazet-Lošo & Tautz 2010, Davies & Lineweaver 2011*): can we methodically collect these genes?

Questions (continued)

- What is more relevant for stress response of a cell population (adaptable, as in the case of a tumour): maintain a subpopulation of all-stress resistant cells, or maintain a subpopulation of cells expressing 'cold genes' and able to launch different resistance mechanisms in different cells? (... stochastically chosen?)

- *Bet hedging* as a 'tumour strategy' to diversify its responses to deadly stress (as high doses of cytotoxic drugs) by launching different stress response mechanisms in different cells? (ABC transporters, detoxication enzymes, blocking influx, DNA repair)

- Stress response through derepression of *cold genes*? Wu et al. PNAS 2015: existence of very ancient genes, constituted in a remote past of our planet, able to put at work des survival programs in a state of emergency, with *bet hedging*, in a cancer cell population?

- Does *bet hedging* shuffle phenotypes, setting favorable bases for the emergence of specialisation (Michod et al.) and cooperativity in tumours (Tabassum & Polyak, Polyak & Marusyk), making them viable?

- Bet hedging setting for $n(x, y, \theta, t)$, with x=fecundity, y=viability, θ=plasticity:

$$n_t + \nabla \cdot \{V(x, y, \theta, D)\, n\} = \alpha(\theta) n_{xx} + \beta(\theta) n_{yy} + n \left\{ r(x, y, \theta) - \frac{\rho(t)}{C(x, y)} - \mu(x, y, \theta, D) \right\}$$

A few articles that open ways and challenges

One may also consult a few personal articles

- Goldman, A., Kohandel, M., Clairambault, J. Integrating Biological and Mathematical Models to Explain and Overcome Drug Resistance in Cancer, Part 1: Biological Facts and Studies in Drug Resistance, Current Stem Cell Reports, 3:253-259 (August 2017)

- Goldman, A., Kohandel, M., Clairambault, J. Integrating Biological and Mathematical Models to Explain and Overcome Drug Resistance in Cancer, Part 2: From Theoretical Biology to Mathematical Models, Current Stem Cell Reports, 3:260-268 (August 2017)

- Chisholm, R.H., Lorenzi, T., Clairambault, J. Cell population heterogeneity and evolution towards drug resistance in cancer: biological and mathematical assessment, theoretical treatment optimisation. BBA General Subjects, special issue on system genetics, 1860:2627-2645 (June 2016)

- Almeida, A., Chisholm, R.H., Clairambault, J., Lorenzi, T., Lorz, A., Pouchol, C., Trélat, E. Why is evolution important in cancer and what mathematics should be used to treat cancer? Focus on drug resistance. pp. 107-120 in *Trends in Biomathematics: Modeling, Optimization and Computational Problems*, Springer 2018 (17th BIOMAT conference, Moscow, October 2017)

- *See also* `https://who.rocq.inria.fr/Jean.Clairambault/JCarticles.html`

Mathematical Biology *on the Mediterranean* Conference, Samos island, Greece, September 1-14, 2019

MBMC-Samos2019 http://actuarweb.aegean.gr/mbmc2019

- International Summer school, 1-6, and workshop, 8-14 September 2019
- Expected 60 participants: PhD students, junior or confirmed mathematicians
- 5 lecturers to the Summer school (4-5 hours of lectures each):
  - José Antonio Carrillo (London): *Attractive-repulsive models in collective motion*
  - Benoît Perthame (Paris): *Modellling and analysis for adaptive dynamics in biology*
  - Nikos Sfakianakis (St. Andrews): *Mathematical problems in evolutionary theory*
  - James Sneyd (Auckland): *Topics in mathematical physiology*
  - Nicolas Vauchelet (Paris): *Control of vector-borne diseases and their epidemics*
- Keynote speakers to the workshop:
  - Mats Gyllenberg, University of Helsinki, Helsinki, Finland
  - Doron Levy, University of Maryland at College Park, Maryland, USA
  - Charalambos Makridakis, IACM, FORTH, Heraklion, Greece
  - Anna Marciniak-Czochra, Heidelberg University, Heidelberg, Germany
  - Luigi Preziosi, Politecnico di Torino, Torino, Italy
  - Christian Schmeiser, University of Vienna, Vienna, Austria

Scientific and Organisation Committees

- Scientific Committee

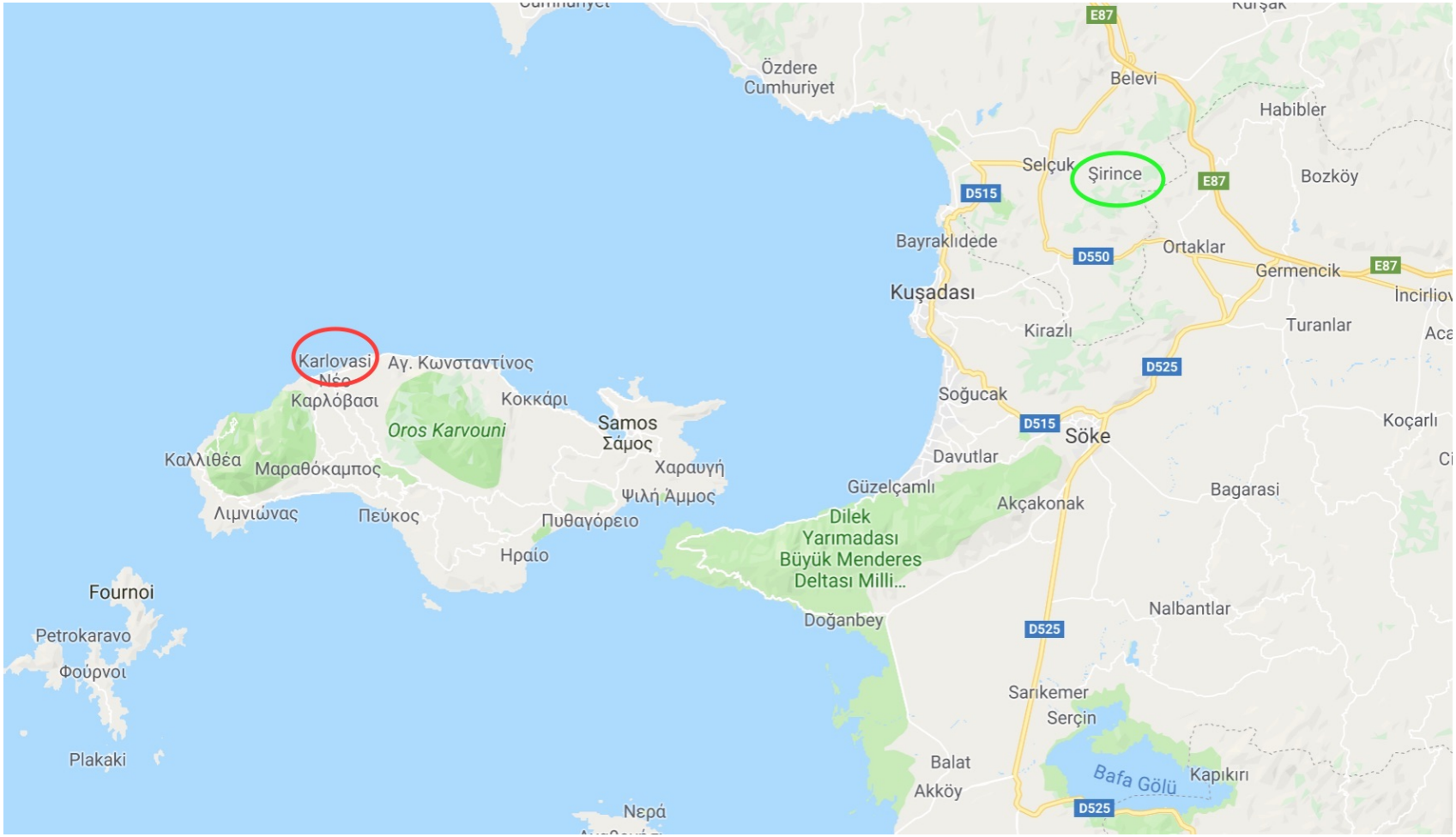
  Tomás Alarcón <tomasalarc@gmail.com>,
  Helen Byrne <helen.byrne@maths.ox.ac.uk>,
  Marcello Delitala <marcello.delitala@polito.it>,
  Odo Diekmann <O.Diekmann@uu.nl>,
  Jack Tuszynski <jack.tuszynski@gmail.com>,

- Organisation Committee

  Stelios Xanthopoulos <xanthos@aegean.gr>, Committe Chair,
  Pierre-Alexandre Bliman <pierre-alexandre.bliman@inria.fr>,
  Jean Clairambault <jean.clairambault@inria.fr>, Scientific Chair,
  Nikolaos Kavallaris <n.kavallaris@chester.ac.uk>,
  Athena Makroglou <athena.makroglou2@gmail.com>,
  Christos Nikolopoulos <cnikolo@aegean.gr>,
  Nikolaos Sfakianakis <n.sfakianakis@st-andrews.ac.uk>

The Aegean sea and Samos island

Samos island and the Aegean coast of Turkey



Two illustrious mathematicians from Samos

Pythagoras

Aristarchos