Drug resistance in cancer cell populations: Genetic or epigenetic phenomenon? Mathematical and biological assessment

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Micro and macro systems in life sciences, Będlewo 2015

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

Definitions: evolution or adaptation in cell populations

[Naive and utilitary definitions]

- **Evolution**: constitution of a new species (cell population of a new type) by genetic mutations (including single nucleotide substitutions, deletions, translocations...), i.e. irreversible modifications of the genome 'written in the marble of the genetic code', resulting in a new phenotype

- **Adaptation**: modification of a cell type also resulting in a new phenotype in a cell population, but reversible, i.e., amenable to complete restitution of the initial phenotype, with preservation of the intact genome (= of the initial sequence of base pairs)

Mutations and epimutations in cell populations

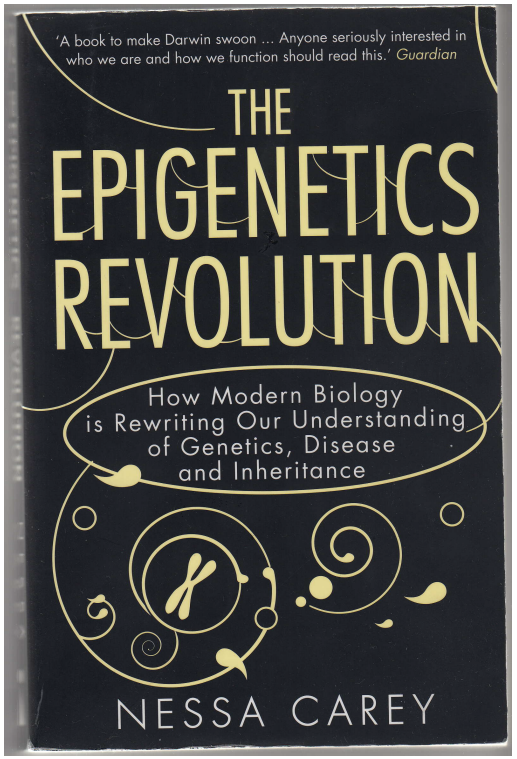
[Again, naive and utilitary definitions]

- **[Genetic] mutation**: irreversible modification of the genome (cf. Evolution)
- **Epigenetic modification** = 'epimutation': modification of the phenotype due to mechanisms that do not affect the genetic code, but are due to silencing of genes (that may be activators or inhibitors of the expression of other genes) by DNA methylation and histone methylation or acetylation

Drug resistance: a genetic or epigenetic phenomenon?

In the same way as one can ask to what extent evolution towards malignancy in premalignant cell populations is genetic (irreversible, due to mutations) or epigenetic (reversible, due to *epimutations*), we can ask whether, in cancer cell populations, drug-induced evolution towards drug resistance is genetic or epigenetic

- hence, is it irreversible or reversible?
- and if it is reversible:
- can we design combined drug strategies to overcome it?



Drug resistance: a phenomenon common to various therapeutic situations

- In therapeutic situations where an external pathogenic agent is proliferating at the expense of the resources of an organism: antibiotherapy, virology, parasitology, target populations are able to develop drug resistance mechanisms (e.g., expression of β-lactamase in bacteria submitted to amoxicillin).

- In cancer, there is no external pathogenic agent (even though one may have favoured the disease) and the target cell populations share much of their genome with the host healthy cell population, making overexpression of natural defence phenomena easy (e.g., ABC transporters in cancer cells).

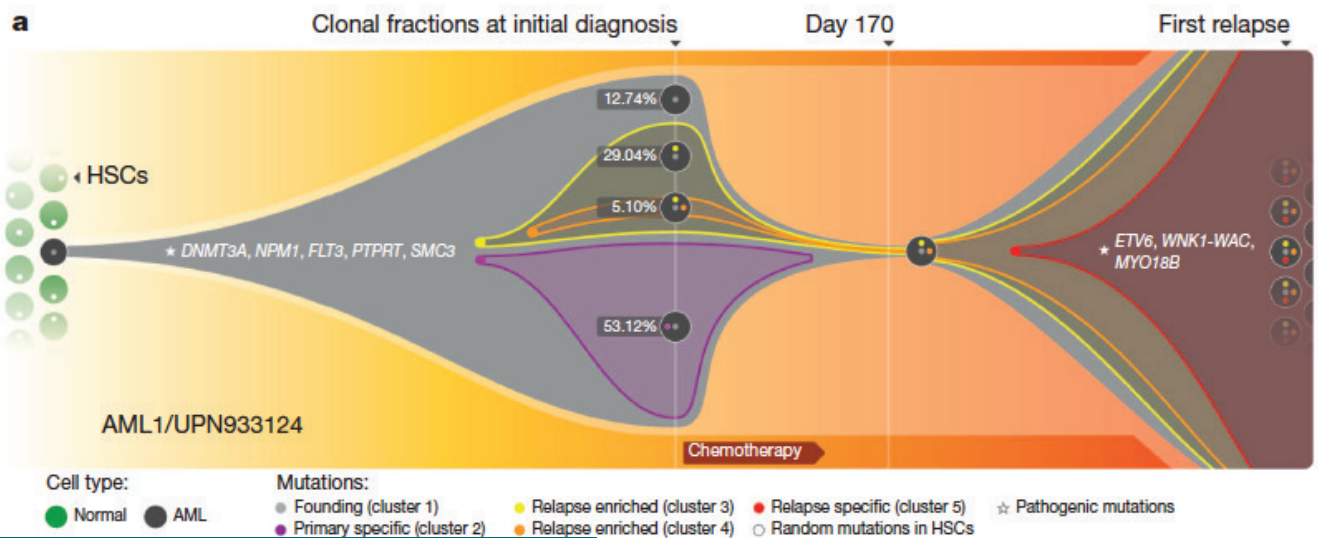
- Drug resistance may account for unexpected failures in targeted therapies.

Mutations toward drug resistance: evolutionary bottlenecks

- Animal genome (of the host to cancer) is rich and amenable to *locally coherent but not globally viable* evolution scenarios that may recapitulate developmental scenarios ('backwards evolution'), resulting in insufficient cohesion of the ensemble (*Davies & Lineweaver 2011; Lineweaver, Davies & Vincent 2014*)

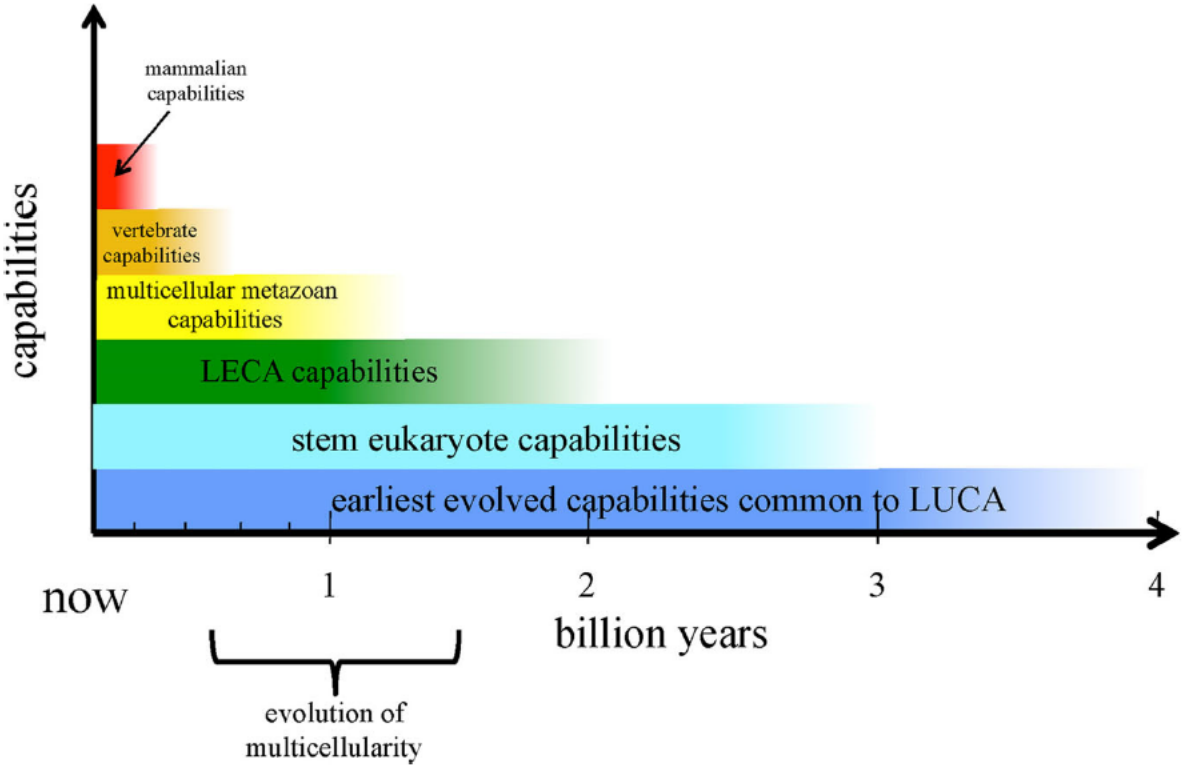
- Such scenarios have been abandoned in the process of evolution from protozoa to metazoa, e.g., by epigenetic downregulating of oncogenes, but may be revived

- In cancer, enhanced heterogeneity (lack of cohesion at the cell population level) with enhanced proliferation may result in a high genetic diversity of proliferating subpopulations, so that drug therapy may be followed, after initial success, by relapse due to the selection of resistant clones (*Ding et al. 2012*).



Why mainly cancer, and not healthy, cell populations? (1)

A possible evolutionary framework: the atavistic hypothesis of cancer



References: *Israel JTB 1996, Davies & Lineweaver Phys Biol 2011, Vincent Bioessays 2011, Lineweaver, Davies & Vincent Bioessays 2014, Chen et al. Nature Comm 2015*

Why mainly cancer, and not healthy, cell populations? (2)

- The atavistic hypothesis asserts that we bear in our genome many attempts of species evolution since billions of years; dead-end ways ('unused attractors' in S. Huang and S. Kauffman's version of the Waddington landscape) have been silenced (e.g., by epigenetic enzymes), but are still there, ready to be revived

- Cancer would thus be 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, i.e., proliferation

- In cancer, global regulations are lost, differentiation is out of control, so that local proliferations without regulation are dominant; *adaptive epigenetic mechanisms are still there, however 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

- 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*

Drug resistance: how does it work? (at the molecular and cell population levels)

- What was formerly assumed: 0-1 expression of genes (e.g., functional or inefficient p53 due to a mutation)
- Varying expressivity of genes in a cell population, or else degree of effectiveness of mutations (e.g., mutated EGFR)
- Varying activity of ABC transporters (e.g., P-gp), main effectors of drug efflux out of cells
- Darwinian effects of drug pressure selecting subpopulations in a heterogeneously constituted (by stochastic variations: bet hedging) cell population?
- *Transient adaptation to hostile environments of subpopulations in the cell population? (Lamarck, not Darwin: we deal with drug-induced drug-resistance)*

Molecular mechanisms at the single cell level vs. phenotypes at the cell population level

- Overexpression of ABC transporters, of drug processing enzymes, decrease of drug cellular influx, etc. are relevant to describe resistance mechanisms at the single cell level.

- At the cell population level, representing drug resistance by a continuous variable x standing for a resistance phenotype (in evolutionary game theory: a strategy) is adapted to describe adaptation from sensitivity ($x = 0$) towards resistance ($x = 1$).

- We question drug resistance as possibly due to sheer Darwinian selection of the fittest or, at least partially, to Lamarckian adaptation in individual cells

Can it be assessed by biological experiments? (1)

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

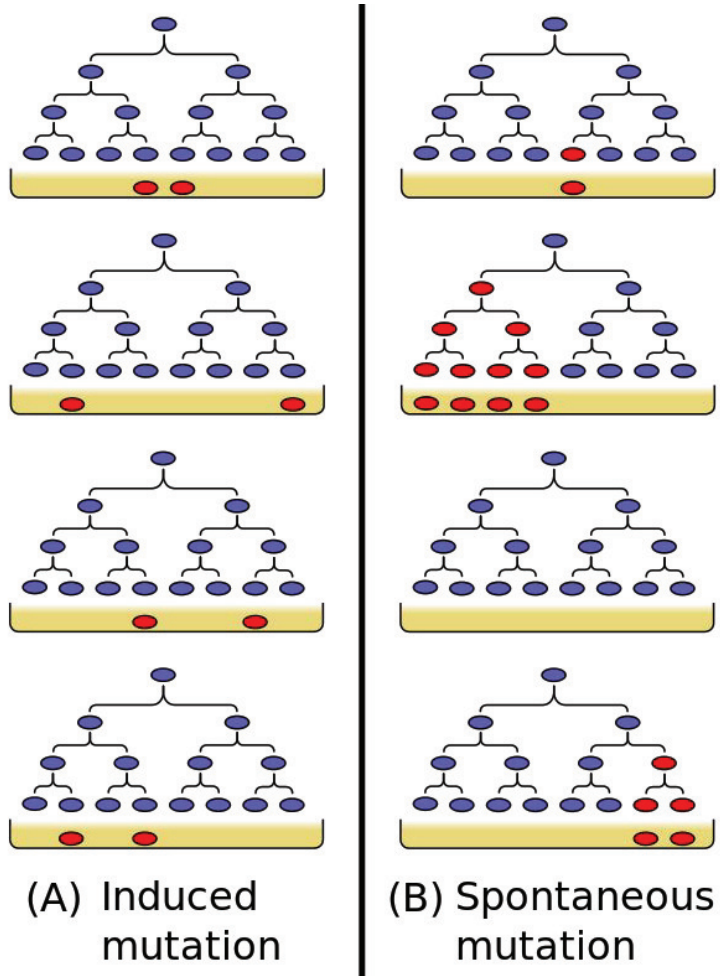
Different Petri dishes, same experimental settings

Bacterial populations firstly proliferating freely, then submitted 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)?

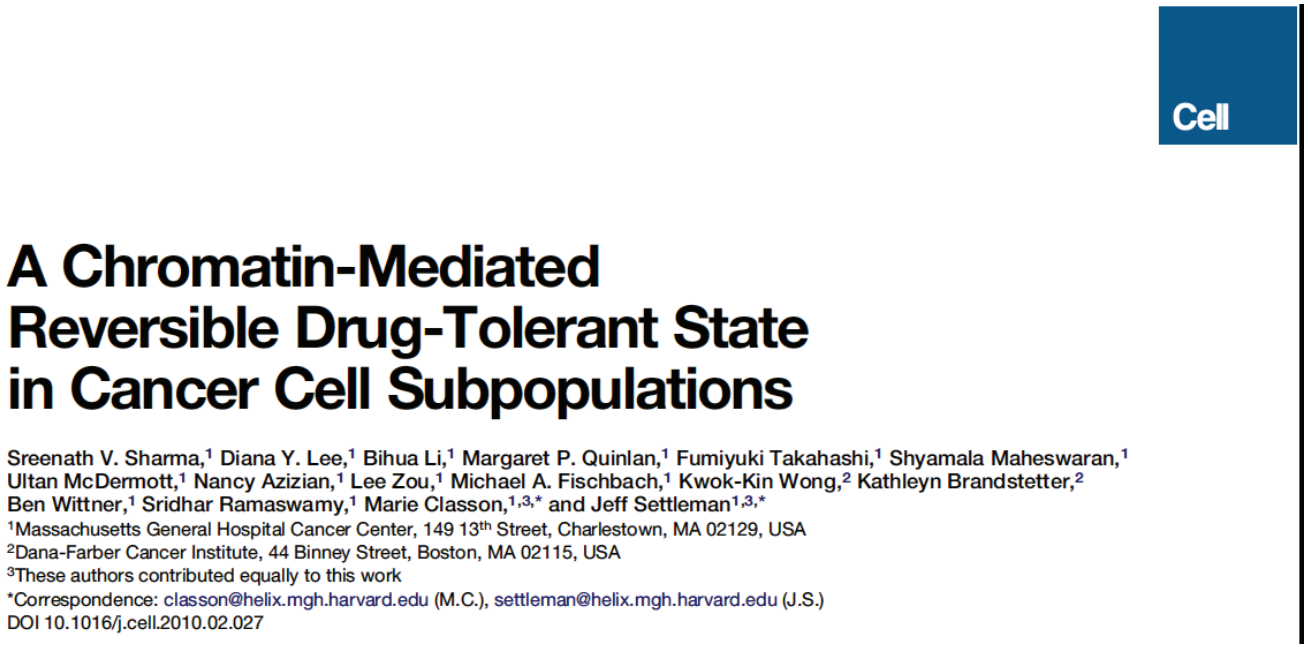
Experiment: the answer is always (B): preexistent mutations before selection

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

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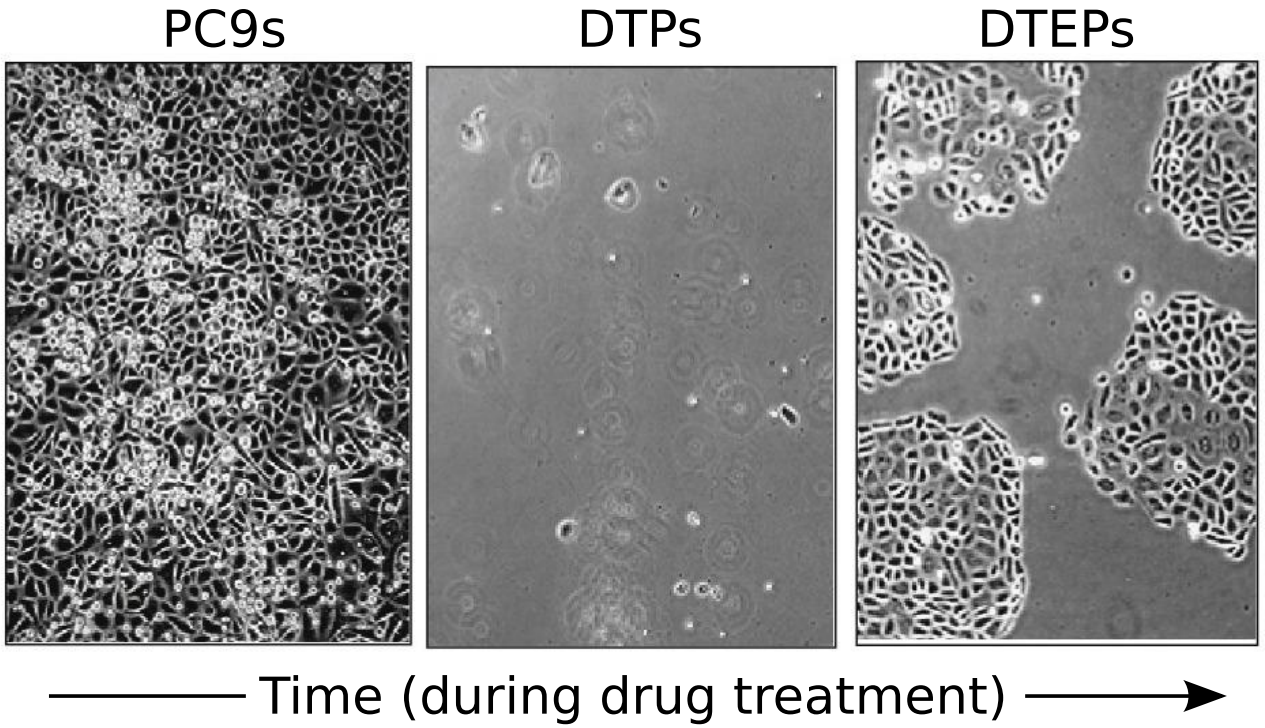
- Motivation: to account for biological observations on a reversible drug-resistant phenotype in cancer cell populations: *Sharma et al. 141:69–80, Cell 2010*
- Underlying hypothesis: epigenetic modifications affect differently survival and proliferation potentials in cancer cell populations submitted to high drug doses
- 2 proposed traits: x, stress survival potential ($\sim$ apoptosis inhibition) and y, proliferation potential ($\sim$ cell division cycle enhancement), both reversible

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:

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

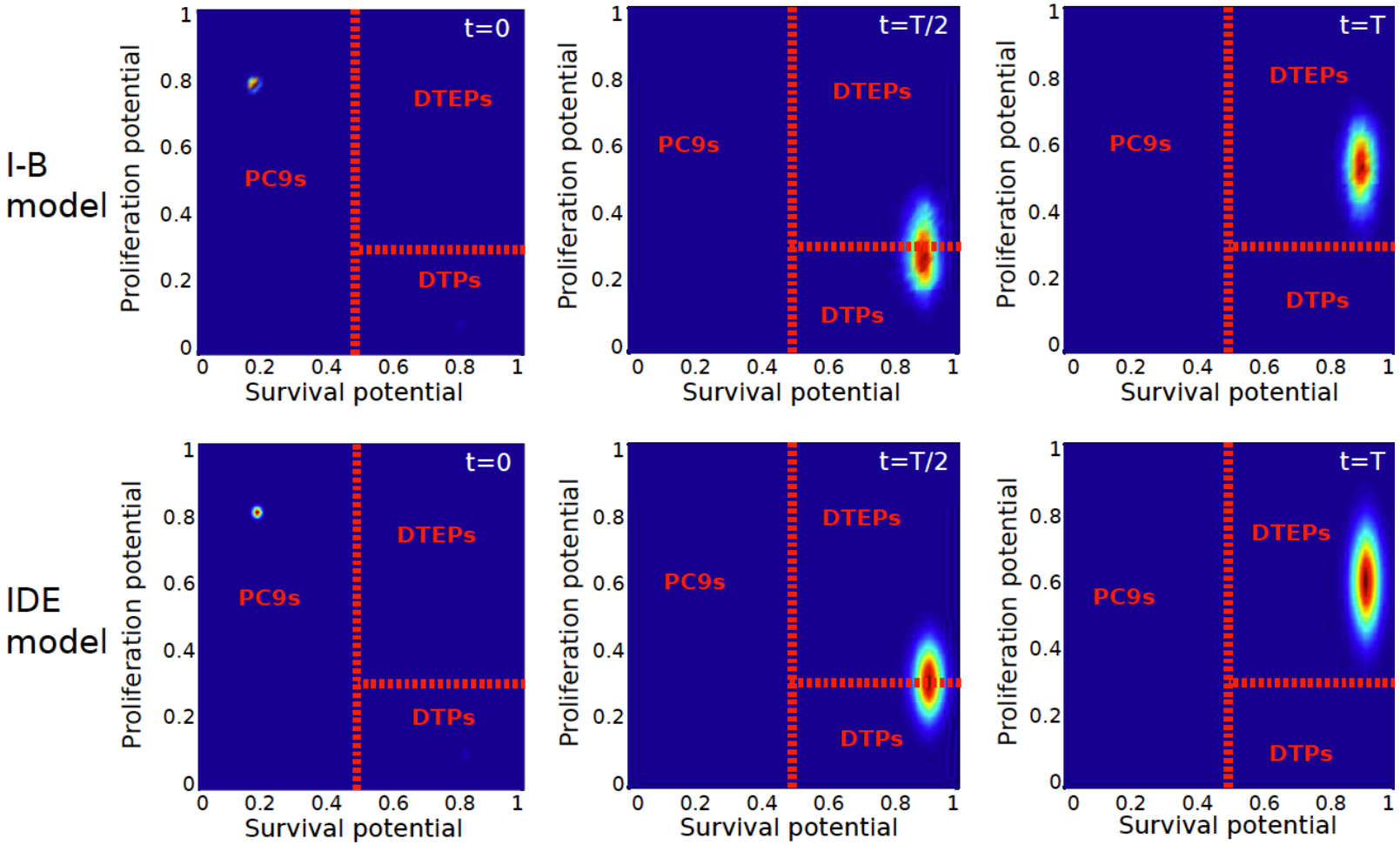
$$\underbrace{\Big[p(x, y, \varrho(t)) - d(x, c(t))\Big] n(x, y, t)}_{\text{selection}} + \underbrace{\beta \Delta n(x, y, t).}_{\substack{\text{non-genetic} \\ \text{phenotype instability}}}$$

- The global population term $\varrho(t) = \int_0^1 \int_0^1 n(x, y, t)\, \mathrm{d}x\mathrm{d}y$ occurs in the proliferation term p as a logistic limiting term (availability of space, nutrients)
- The drift term w.r.t. proliferation potential y represents possible (if drift velocity $v \neq 0$) 'Lamarckian-like', reversible, adaptation from PC9s to DTPs
- $t \mapsto c(t)$ represents drug infusion in the medium
- No-flux BCs
- An agent-based (AB), aka individual-based (IB) model shows the same dynamics

(*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)

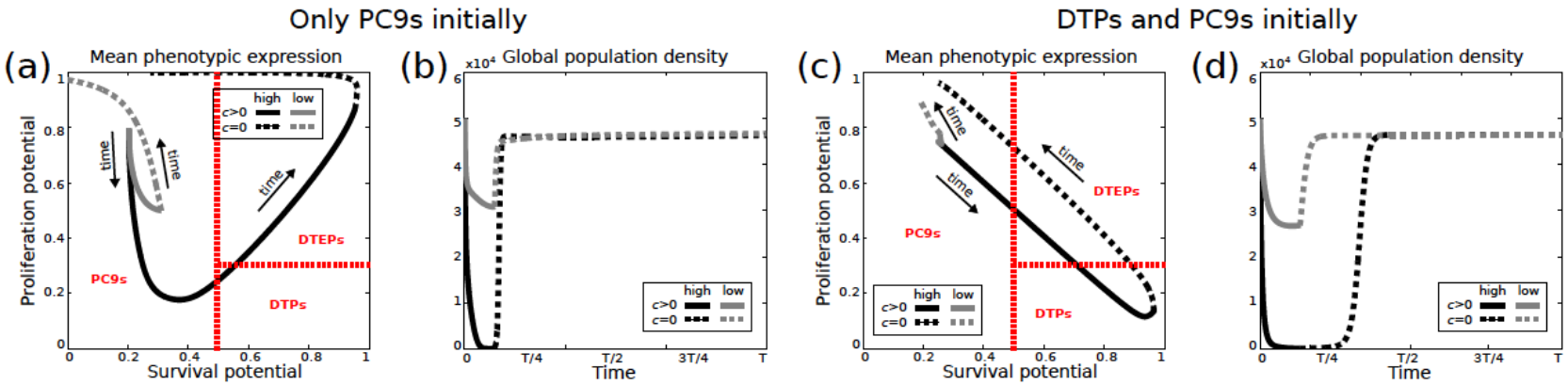


T is the simulation end-time: $0 \leq t \leq T$

(*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)

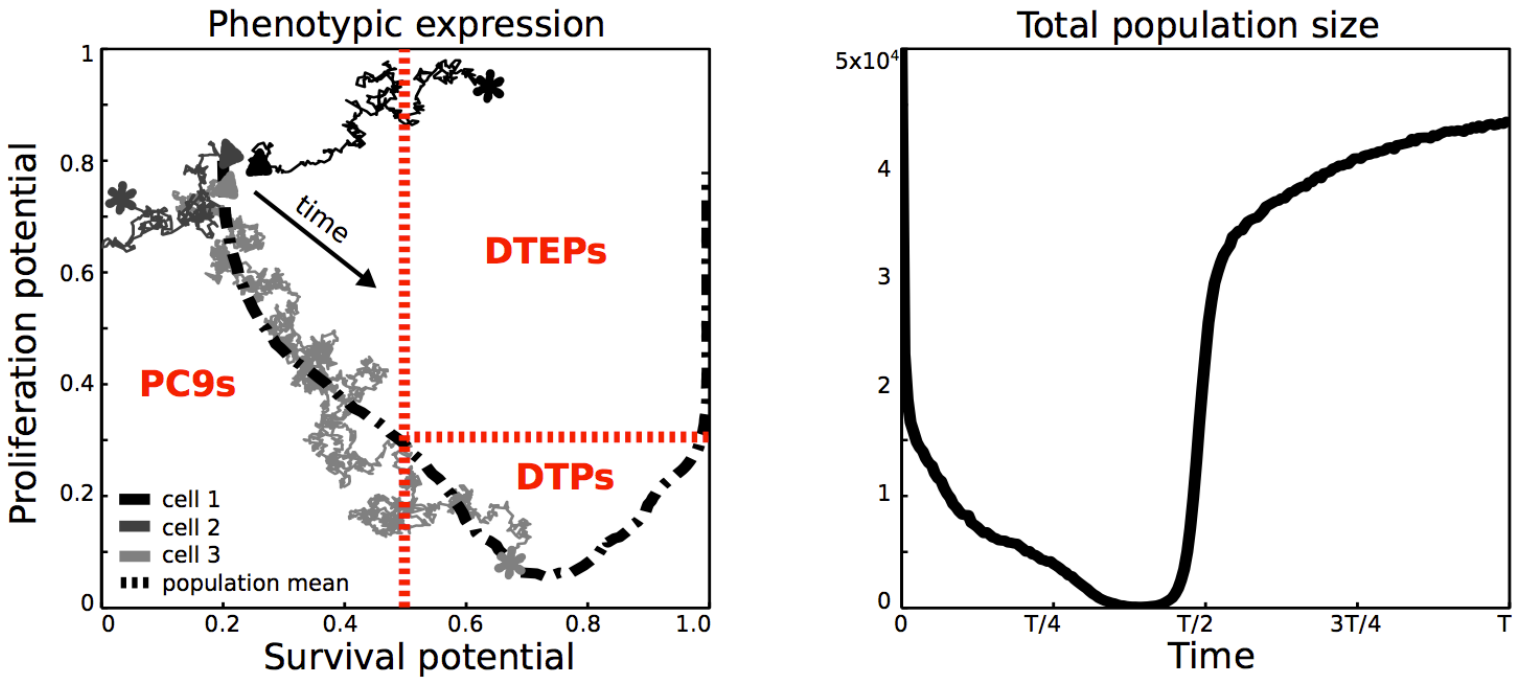


(a), (b) PC9s and DTPs initially, no adaptation $v = 0$: *'Darwinian' scenario*, or Luria-Delbrück scenario (B)

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

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

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



- Evolution in the AB 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 (integral term to be added) generate similar dynamics?

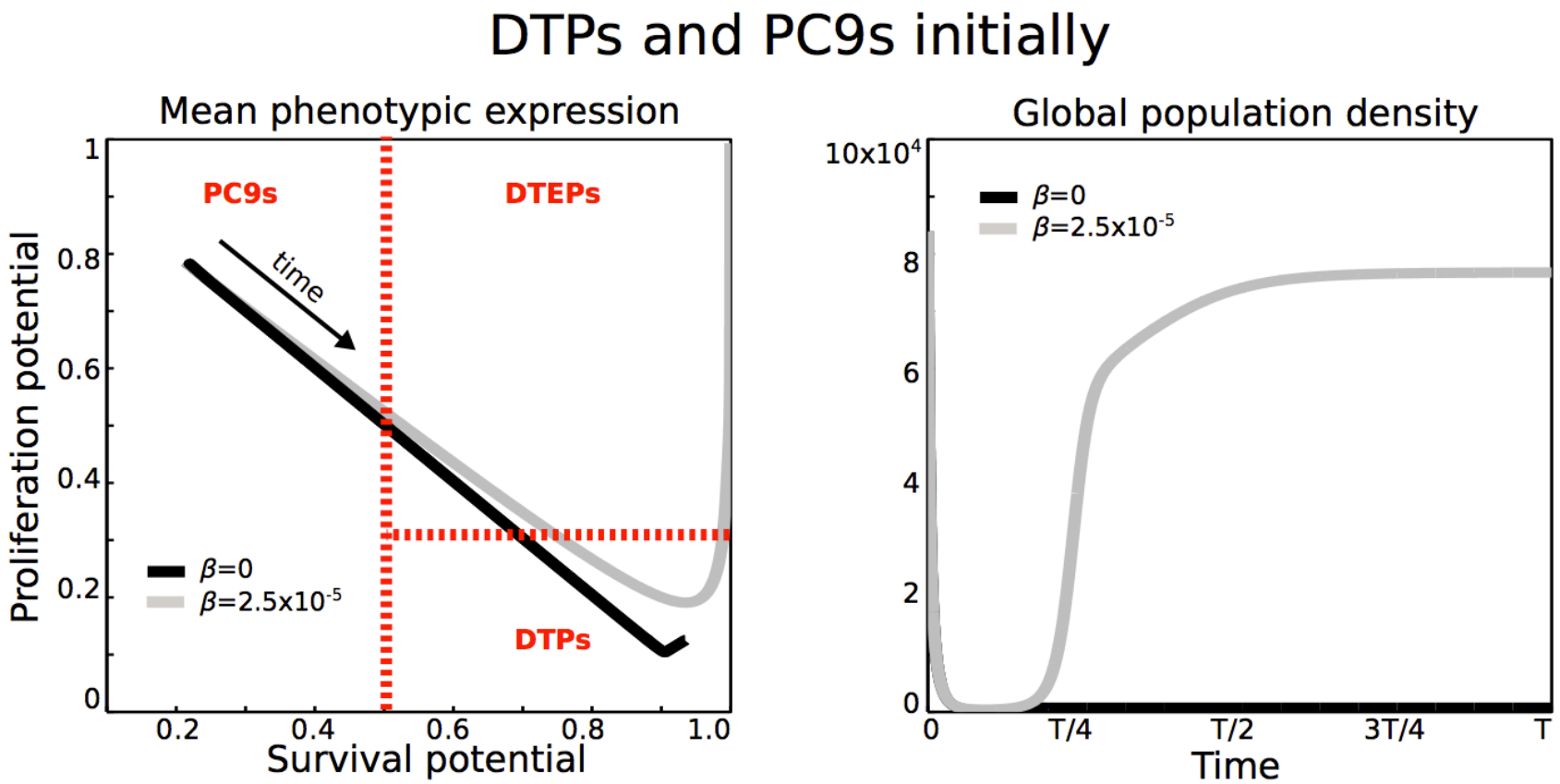
Consider $c(\cdot) = constant$ and two scenarios:

(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 ($v \neq 0$)

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

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

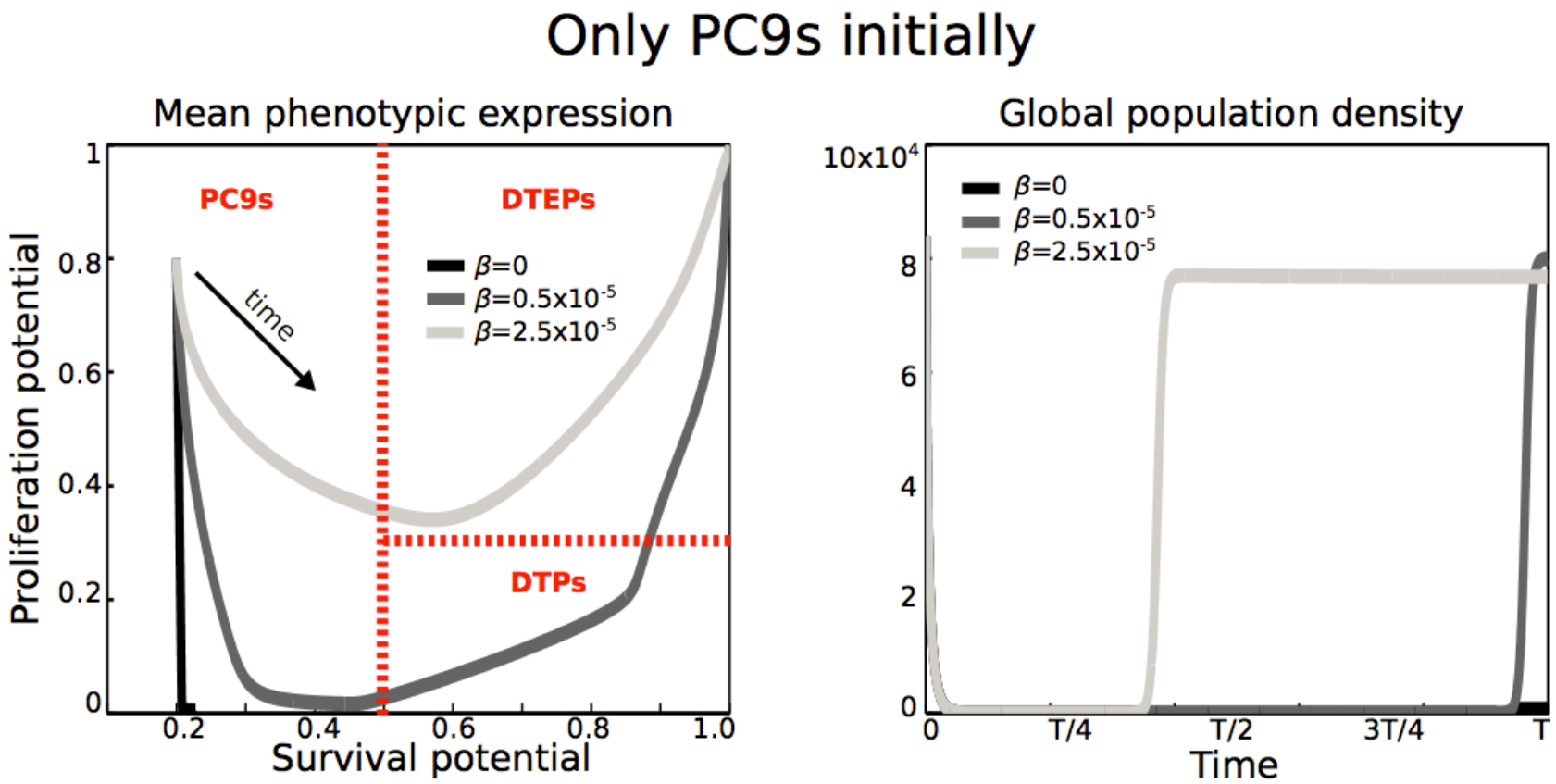


(Adaptation is absent $v = 0$)

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

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

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



(Adaptation is present $v \neq 0$)

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

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

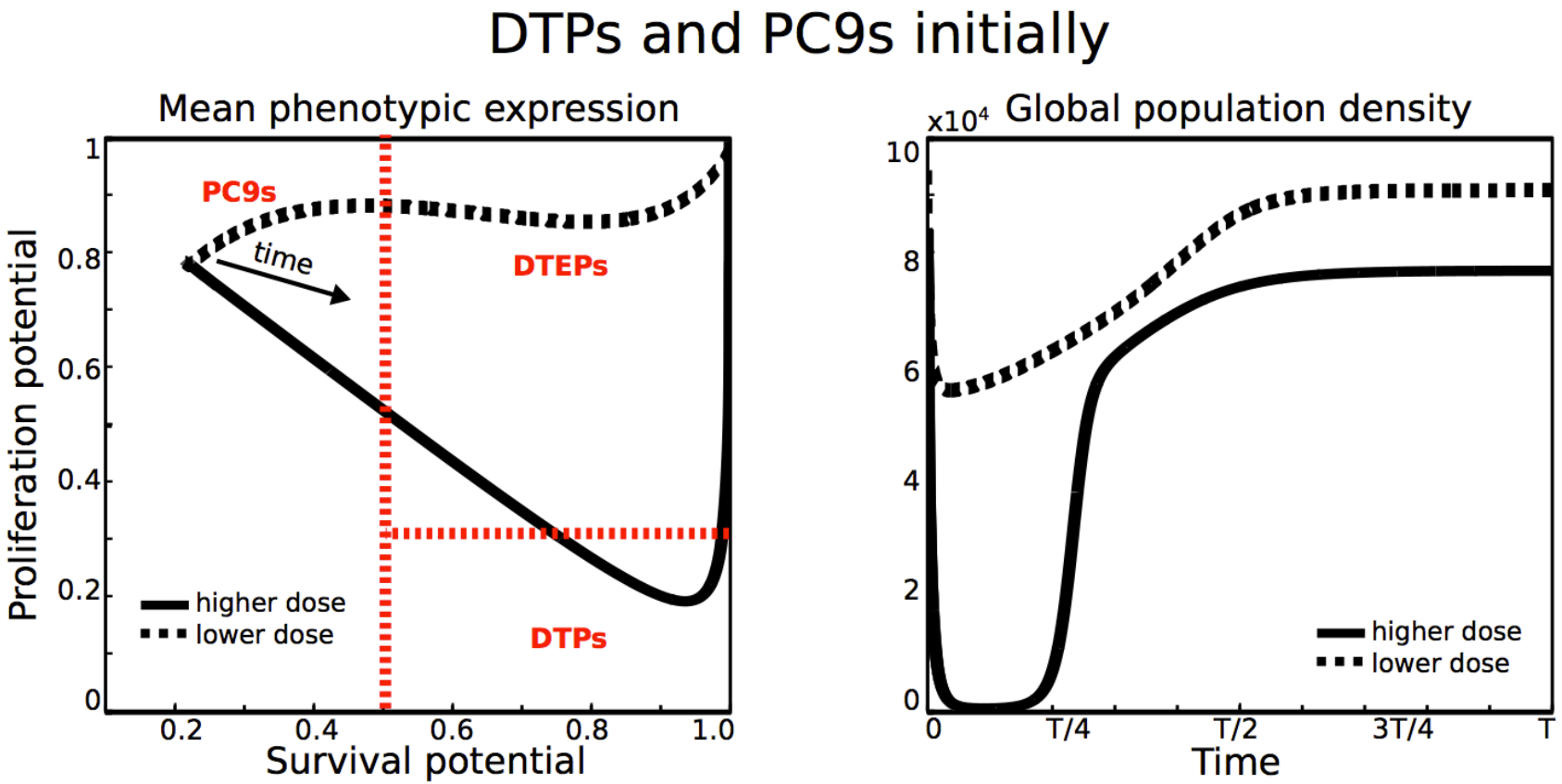
Definition (LC_γ dose)

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]

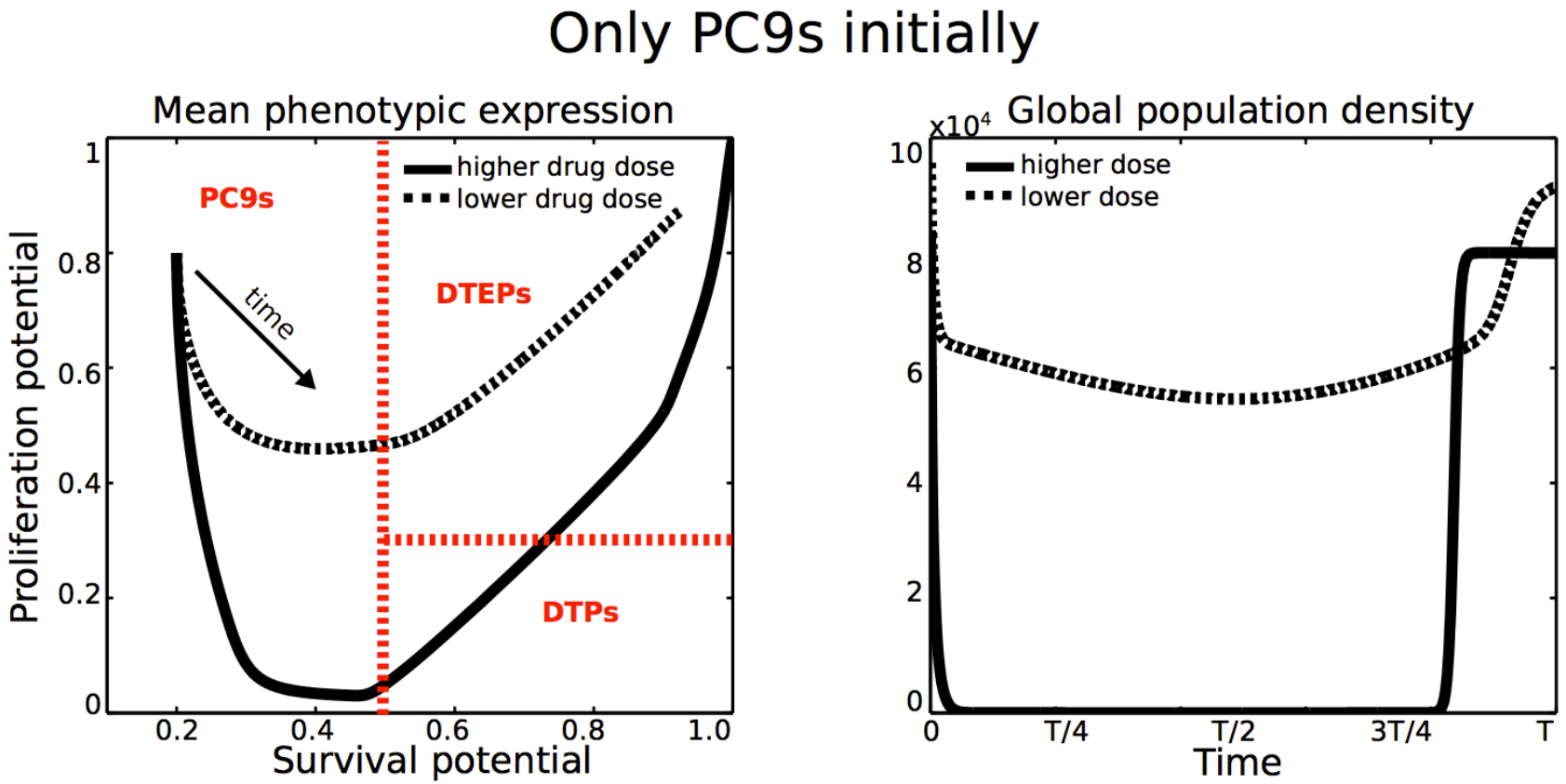


(Adaptation is absent $v = 0$)

(*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]



(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,

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

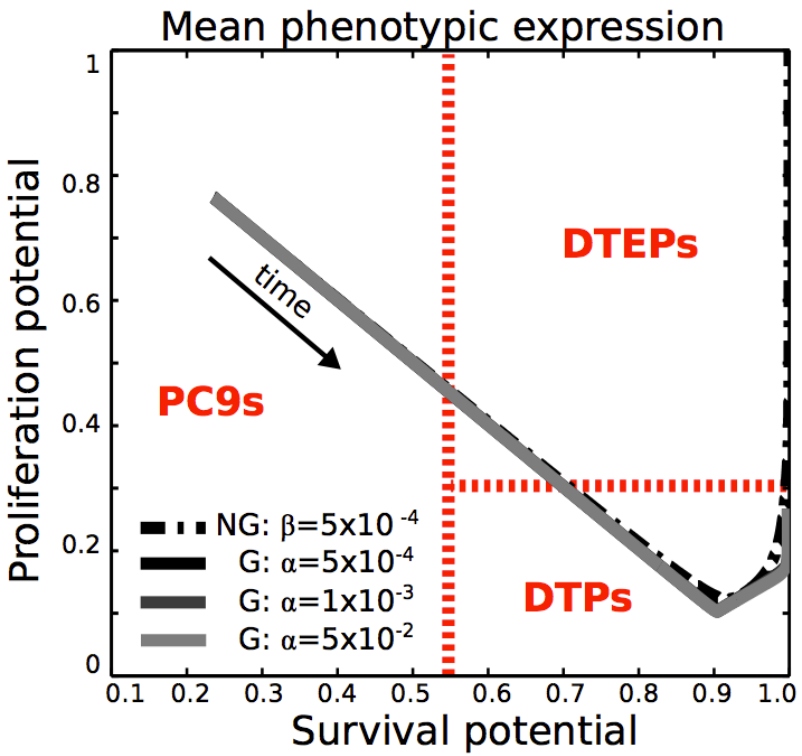
and C_M is a normalisation constant such that

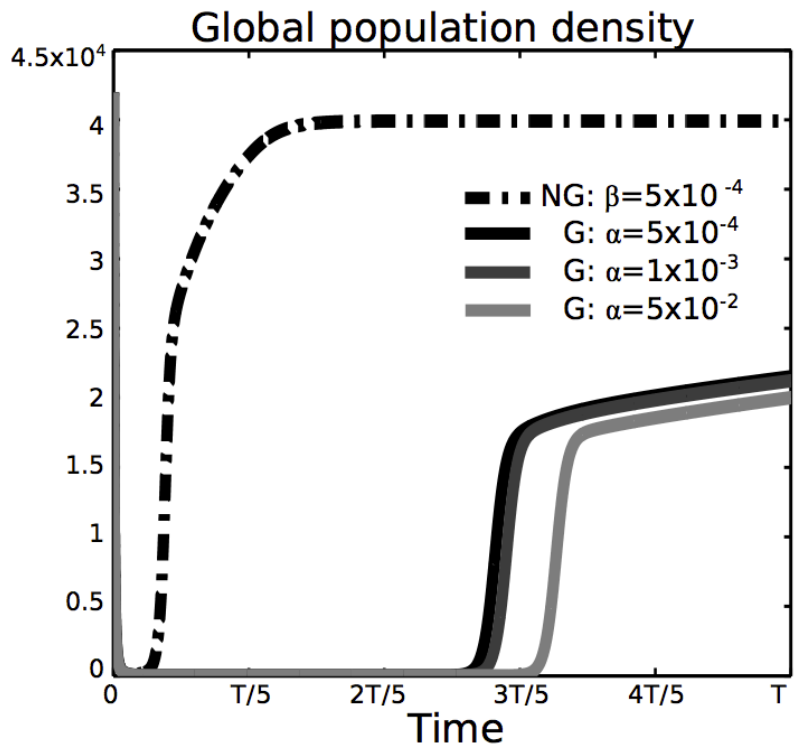
$$\int_0^1 \int_0^1 M(x,y|\cdot,\cdot;\cdot)\mathrm{d}x\mathrm{d}y = 1.$$

A3. Genetic mutations cannot generate similar dynamics

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

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





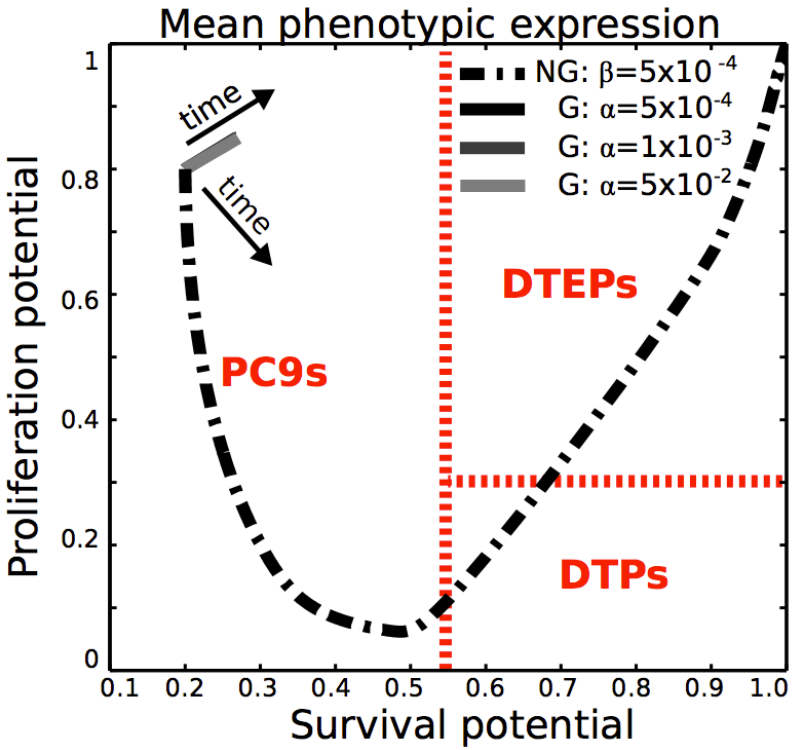
(NG: Adaptation is absent $v = 0$)

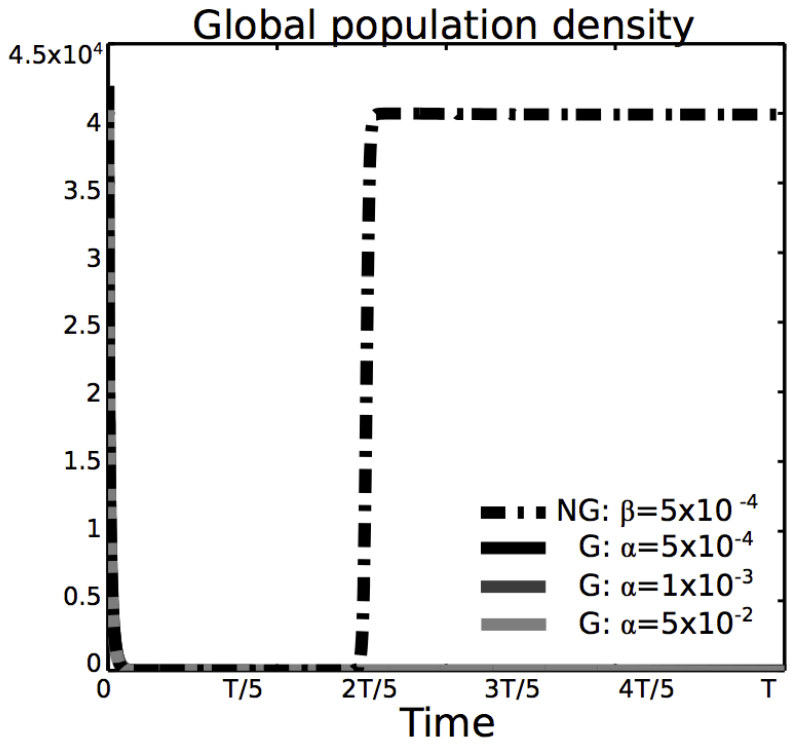
(*Chisholm et al., Cancer Research 2015*)

A3. Genetic mutations cannot generate similar dynamics

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

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





(NG: Adaptation is present $v \neq 0$)

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

Summary of results on the *Sharma et al.* experiment

- Both mathematical models 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 consquences? 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 in the model, not done yet.

Back to evolution towards resistance: pending questions, possible tracks to enrich the model

- Is there a succession of events from a population dynamics point of view between an epigenetic, reversible, state of drug resistance, followed by a possibly acquired, genetic, unbeatable state of resistance to a given drug?

- Is there a way to measure in a molecular way the cost of resistance, so as to design realistic cost functions at the cell population level?

- Can we connect stochastic events such as transcription at the single cell level - ruled by genetic regulatory networks and possibly influenced by the cellular environment - with the determination of cell fate (e.g., drug resistance or EMT phenotype) at the cell population level?

- These are qualitative rather than quantitative models. Identification of a continuous trait x with a resistance phenotype will be linked to a given drug and a given cancer cell population studied in Petri dishes; identifying parameters in model functions of phenotype x is another challenge that might be addressed by inverse problems methods if necessary.

Possible extensions: develop models of cancer and its therapeutic control according to further considerations

- Structuring the population according to a [3,4]-dimensional phenotype: survival potential, proliferation potential, possibly also stem-cell plasticity and 'cohesion'
- Adding space (e.g., radial variable in a tumour spheroid) and available resources, accounting for drug diffusion in the tumour (*Lorz et al. BMB 2015*)
- Adding local metabolism modifications: oxygen, nutrients, TCA cycle, pyruvate, lactate, pH... that may influence survival and proliferation (*ongoing PhD work*)
- Energy reallocation: cell population self-assessment in terms of costs (ATP): even with a non-molecular, but rather symbolical identification of energy costs, choice between dormancy, proliferation or death?
- Mechanics: mechanical stress constraint: impact on evolution? (*pression-structured cell population models: Hele-Shaw*)
- Represent cooperation effects between different subpopulations of cells inside the same tumour, and between tumour cells and stromal cells, e.g., CAAs
- Represent the effects of HDAC inhibitors or other epigenetic drug therapies

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- ...More available at `https://www.rocq.inria.fr/bang/JC/JCarticles.html`

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Mathematical models and methods to investigate heterogeneity in cell and cell population biology

Mathbio session during ICNAAM 2015 (Rhodes, Greece, Sep. 23-29)
(#70) proposed by Jean Clairambault, INRIA & LJLL, UPMC, Paris

This session will investigate hot topics related to mathematical representations of cell and cell population dynamics in biology and medicine, in particular with applications to cancer. Methods in mathematical modelling and analysis, and in statistical inference using single-cell and cell population data, should contribute to focus this session on heterogeneity in cell populations.

- - Intracellular protein dynamics and gene regulatory networks: ODEs, PDEs, DDEs
- - Representation of cell population dynamics using agent-based models (ABMs) and/or PDEs
- - Hybrid models and multiscale models to integrate single-cell dynamics into cell population behaviour
- - Structured cell population dynamics and asymptotic evolution w.r.t. relevant traits
- - Heterogeneity in cancer cell populations: origin, evolution, phylogeny and methods of reconstruction
- - Drug resistance as an evolutionary phenotype: predicting and overcoming it in therapeutics
- - Theoretical therapeutic optimisation of combined drug treatments in cancer

Constraints

- No funding available: you have to find it by yourself
- Upload of a 4-page paper is mandatory (deadline…)
- Conference fees exist (regular / student): see the website, but accommodation in the conference hotel is absolutely not mandatory

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ICNAAM 2015

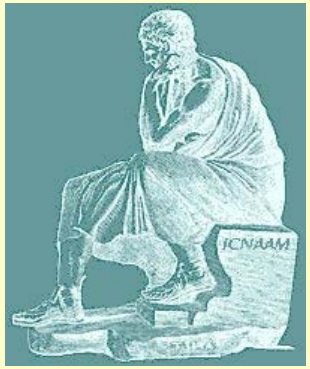
INVITED SPEAKERS

Prof. Dr.	**Raffaele D'Ambrosio,**
Prof. Dr.	**Peter Deuflhard,**
Prof. Dr.	**Wayne Enright,**
Prof. Dr.	**Ludwig Gauckler,**
Prof. Dr.	**C. W. Gear (Bill),**
Prof. Dr.	**Klaus Guerlebeck,**
Prof. Dr.	**Nicola Guglielmi,**
Prof. Dr.	**Ernst Hairer,**
Prof. Dr.	**Felice Iavernaro,**
Prof. Dr.	**Zdzislaw Jackiewicz,**
Prof. Dr.	**David I. Ketcheson,**
Prof. Dr.	**Maria Lopez Fernandez,**
Prof. Dr.	**William F. Mitchell,**
Prof. Dr.	**Yaroslav D. Sergeyev,**
Prof. Dr.	**You-He Zhou**

Honoring Bob Skeel on the occasion of his career on Numerical Analysis and Applied Mathematics

13th INTERNATIONAL CONFERENCE OF NUMERICAL ANALYSIS AND APPLIED MATHEMATICS 2015 (ICNAAM 2015)

23-29 September 2015, Rhodes, Greece



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Dates of Importance

Proceedings paper (3-4 pages) submission deadline	20 July 2015
Notification of acceptance / referees' amendments	29 July 2015
Submission of the source files of the camera ready short papers to AIP Conference Proceedings	1 August 2015
Conference	23-29 September 2015
Submission of the full papers for publication in conference syndicated journals	September 30, 2015 - January 31, 2016

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Aims and Scope

The aim of the International Conference of Numerical Analysis and Applied Mathematics (ICNAAM 2015) is to bring together leading scientists of the international Numerical & Applied Mathematics community and to attract original research papers of very high quality. The topics to be covered include (but are not limited to): All the research areas of Numerical Analysis and Computational Mathematics and all the research areas of Applied Mathematics

Topics

All the research areas of Numerical Analysis and Computational Mathematics:
(Numerical ODEs, Numerical PDEs (inc. BVPs), Scientific Computing and Algorithms, Stochastic Differential Equations, Approximation, Numerical Linear Algebra, Numerical Integral Equations, Error Analysis and Interval Analysis, Difference Equations and Recurrence Relations, Numerical problems in Dynamical Systems, Applications to the Sciences (Computational Physics, Computational Statistics, Computational Chemistry, Computational Engineering etc.), Differential Algebraic Equations, Numerical methods in Fourier analysis etc)

All the research areas of Applied and Industrial Mathematics:
(Mathematical Physics, Mathematical Chemistry, Mathematical Biology and Mathematical Medicine, Optimization and Operational Research, Theoretical Mechanics, Discrete Applied Mathematics, Statistics, Probability, Dynamical Systems, Algorithms, Experimental Mathematics, Theoretical Computer Science, Applied Analysis, Mathematical Modeling (including but not limited to mathematical modeling of engineering and environmental processes, manufacturing, and industrial systems, heat transfer, fluid mechanics, CFD, and transport phenomena; solid mechanics and mechanics of metals; electromagnets and MHD; reliability modeling and system optimization; decision sciences in an industrial and manufacturing context; civil engineering systems and structures; mineral and energy resources; relevant software engineering issues associated with CAD and CAE; and materials and metallurgical engineering, mathematical modeling of social, behavioral and other sciences), Decomposition and Reconstruction Algorithms, Subdivision Algorithms, Continuous and Discrete Wavelet Transform, Time-frequency Localization, Phase-Space Analysis, Subband Coding, Image Compression, Real-Time Filtering, Radar and Sonar Applications, Transient Analysis, Medical Imaging, Multigrid Methods, Frames, Bifurcation and Singularity Theory, Deterministic Chaos and Fractals, Soliton and Coherent Phenomena, Formation of Pattern, Evolution, Complexity Theory and Neural Networks, Analytical Approaches and Simulations for more Accurate Descriptions, Predictions, Experimental Observations and Applications of Nonlinear Phenomena in Science and Engineering, Theoretical and Applied aspects of Computational Geometry, Control Theory and Automation, Fuzzy Sets and Systems and Fuzzy Logic, Applied Algebra, Quality Theory of Differential Equations, Neural Networks , etc.)

Scientific Committee