3rd Cuneo City ImmunoTherapy Conference (CCITC)

Immunotherapy in Hematological Malignancies 2023

CUNEO
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Spazio incontri Fondazione CRC

Organized by Prof. Massimo Massaia, SC Ematologia AO S.Croce e Carle, Cuneo, Italy
and Centro Interdipartimentale di Ricerca in Biologia Molecolare (CIRBM), Torino, Italy

DICHIARAZIONE

Relatore: TOMMASO LORENZI

Come da nuova regolamentazione della Commissione Nazionale per la Formazione Continua del Ministero della Salute, è richiesta la trasparenza delle fonti di finanziamento e dei rapporti con soggetti portatori di interessi commerciali in campo sanitario.

- Posizione di dipendente in aziende con interessi commerciali in campo sanitario **(NIENTE DA DICHIARARE)**
- Consulenza ad aziende con interessi commerciali in campo sanitario **(NIENTE DA DICHIARARE)**
- Fondi per la ricerca da aziende con interessi commerciali in campo sanitario **(NIENTE DA DICHIARARE)**
- Partecipazione ad Advisory Board **(NIENTE DA DICHIARARE)**
- Titolarità di brevetti in compartecipazione ad aziende con interessi commerciali in campo sanitario **(NIENTE DA DICHIARARE)**
- Partecipazioni azionarie in aziende con interessi commerciali in campo sanitario **(NIENTE DA DICHIARARE)**

Dissecting Cancer Development and Response to Therapy Through Mathematics

A (very) short introduction through a few case studies

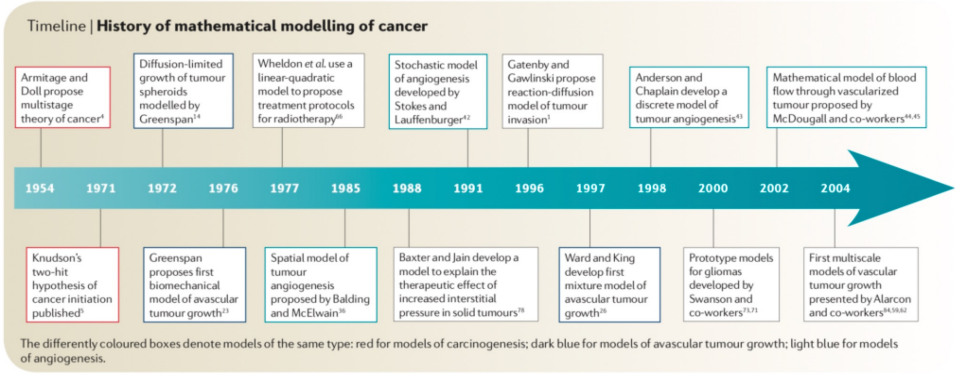
Tommaso Lorenzi

Department of Mathematical Sciences
Politecnico di Torino

Premises

Mathematical modelling of cancer

- The mathematical modelling of the processes that underpin cancer dynamics has been a very active research area in the last 70 years.



Adapted from Byrne, Nat. Rev. Cancer. 10:221–230, 2010.

- Cancer modelling has been a fruitful source of knowledge transfer and mutual enrichment between mathematics and cancer research.

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Knowledge transfer between mathematics and cancer research

- Mathematics gives theoretical support to cancer research by:
  - offering a formal framework in which to consolidate the profusion of experimental and clinical data being generated;
  - providing models to virtually dissect cancer dynamics and carry out *in silico* investigations to identify targets of therapeutic intervention.
- Cancer research acts as a catalyst for mathematical progress by:
  - providing a fertile ground for mathematical challenges, which entail developing new mathematical methods and techniques;
  - stimulating interdisciplinary research that has promoted cross-fertilisation of multiple branches of the mathematical sciences.

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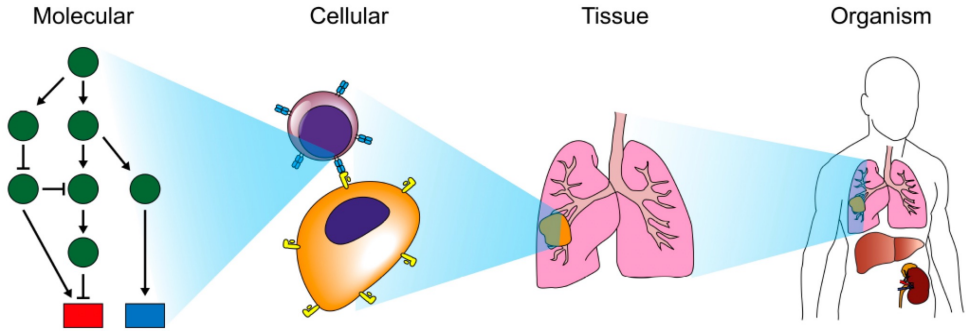
Representation scales in cancer modelling

- A wide range of mathematical models for the mechanisms that underlie cancer dynamics at different biological scales has been developed.



Adapted from Reticker-Flynn and Engleman, eLife 2020;9:e53839, 2020.

- The focus of this talk is on mathematical models for the dynamics of phenomena that are observed at the cellular and tissue scales.

Types of mathematical models for complex phenomena

- When studying complex phenomena, such as those implicated in cancer, two main types of mathematical models can be employed:

  1. more comprehensive models that capture as many aspects and facts as possible ⇒ more detailed description but more parameters to estimate and little mathematical tractability ⇒ less robust conclusions;

  2. less comprehensive models that capture only salient aspects and facts ⇒ less detailed description but fewer parameters to estimate and greater mathematical tractability ⇒ more robust conclusions.

- In this talk, mathematical models of the second type that are formulated as partial differential equations (PDEs) will be considered.

PDE models in physics and biology

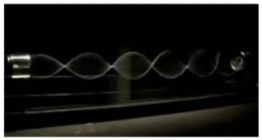
- Such PDE models have been used to describe physical phenomena.

heat diffusion

$\partial_t u - \Delta u = 0$

(Fourier)

wave propagation



$\partial^2_{tt} u - \Delta u = 0$

(D'Alembert)

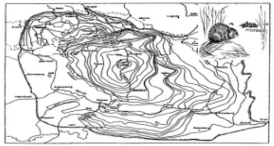
gas dynamics

$\partial_t f + \xi \cdot \nabla f = Q(f, f)$

(Boltzmann)

- More recently, they have been used to describe biological phenomena.

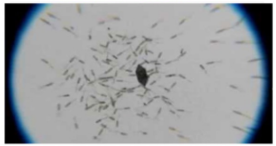
species invasion



$\partial_t n - \Delta n = f(n)$

(Fisher-Kolmogorov-
-Petrovskii-Piskunov)

bacterial chemotaxis



$$\begin{cases} \partial_t n - \nabla \cdot (\nabla n - n\chi \nabla c) = 0 \\ \partial_t c - \Delta c = n - c \end{cases}$$

(Keller-Segel)

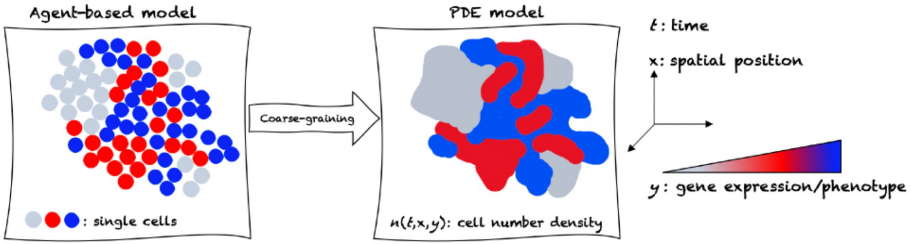
formation of animal patterns

$$\begin{cases} \partial_t u - D_u \Delta u = f(u, v) \\ \partial_t v - D_v \Delta v = g(u, v) \end{cases}$$

(Turing)

PDE models in cancer research

- My research interests center around PDE models for cellular processes that are implicated in the emergence and evolution of:
  - clonal heterogeneity in acute leukemias and intra-tumour heterogeneity;
  - resistance to anti-cancer drugs and adaptive immune resistance;
  - cancer invasion and metastasis.
- These models describe the evolutionary & spatial dynamics of cell populations and can be derived through the coarse-graining of agent-based models (i.e. models that track dynamics of single cells).



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Case Study I

Mathematical models for studying immune infiltration into solid tumours and the response to immunotherapy

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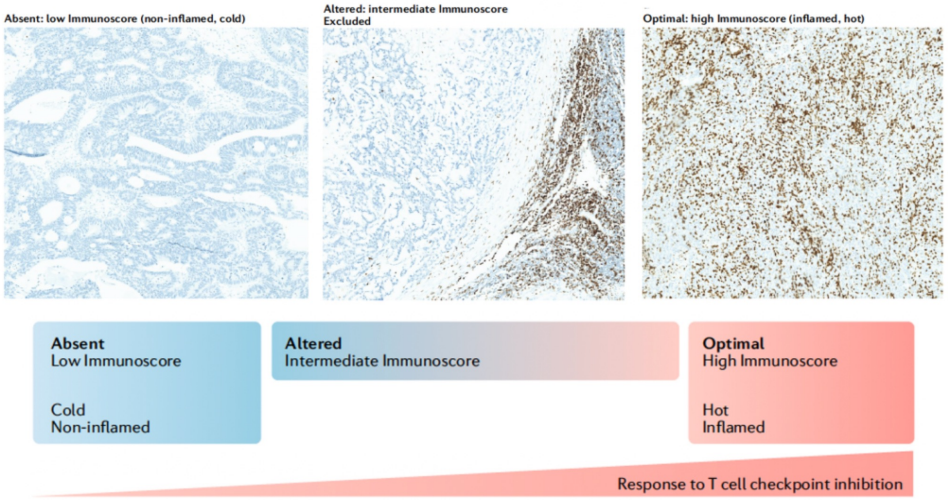
Background

Immune cell infiltration into solid tumours

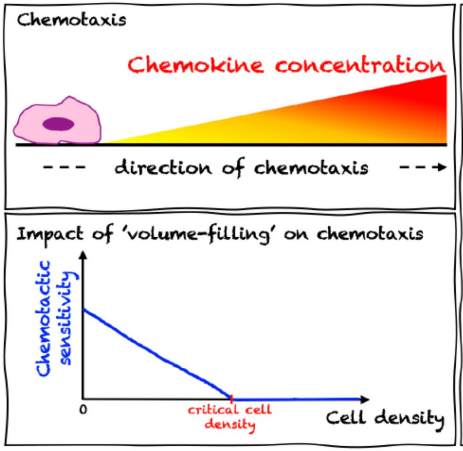


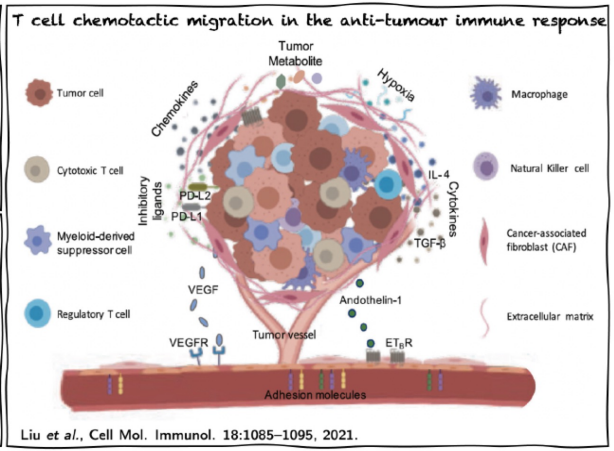
Adapted from Galon and Bruni, Nat. Rev. Drug Discov. 18:197–218, 2019.

T. Lorenzi (Politecnico di Torino)

Background

T cell chemotactic migration in the anti-tumour immune response





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Research question

How do the governing parameters of T cell chemotactic migration impact on immune infiltration and on the response to anti-cancer immunotherapy?

Mathematical model

$n(t,x)$: tumour cell density $\quad c(t,x)$: density of activated $CD8^+$ T cells

$\phi(t,x)$: concentration of chemokines

$$
\begin{cases}
\partial_t n = \underbrace{(\alpha_n - \mu_n N)\, n}_{\text{proliferation and death}} - \underbrace{\zeta_n K(c) n}_{\text{death caused by T cells}} \\
\partial_t c - \underbrace{\nabla \cdot (\beta_c \psi(\rho) \nabla c - c \gamma_c \psi(\rho) \nabla \phi - c \beta_c \psi'(\rho) \nabla \rho)}_{\text{migration}} = \underbrace{\Sigma(t,x) - M(C) c}_{\text{immune regulation}} \\
\partial_t \phi - \underbrace{\beta_\phi \Delta \phi}_{\text{diffusion}} = \underbrace{\alpha_\phi n - \kappa_\phi \phi}_{\text{secretion and decay}} \\
\rho(t,x) := n(t,x) + c(t,x), \quad N(t) := \int_\Omega n(t,x)\,dx, \quad C(t) := \int_\Omega c(t,x)\,dx
\end{cases}
\qquad x \in \Omega
$$

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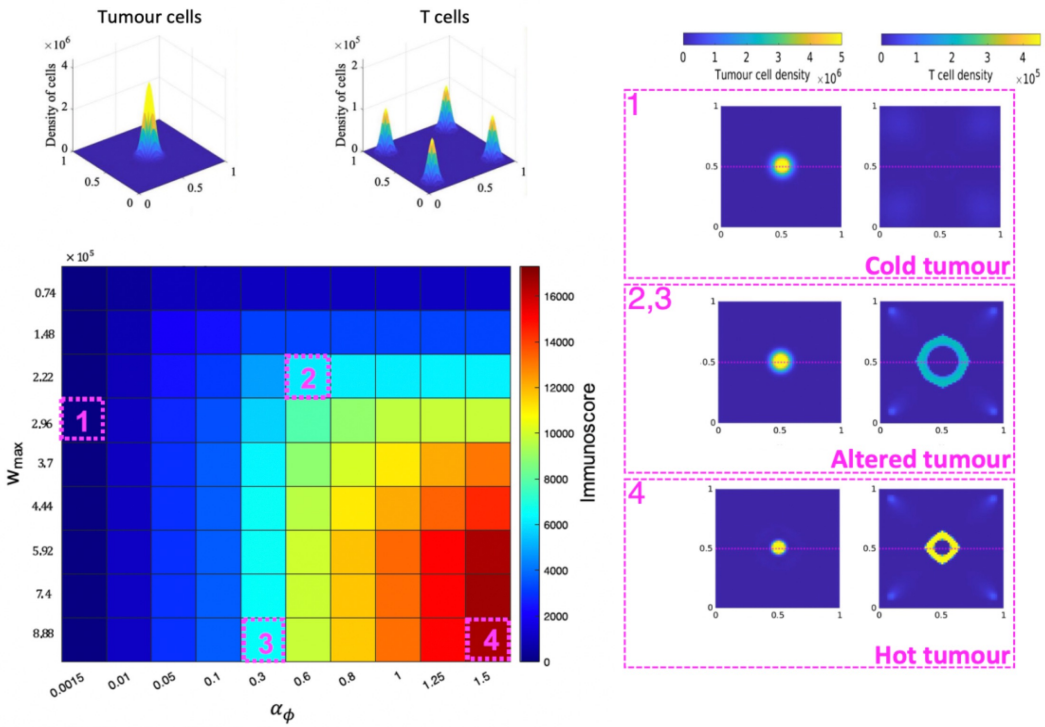
Main results



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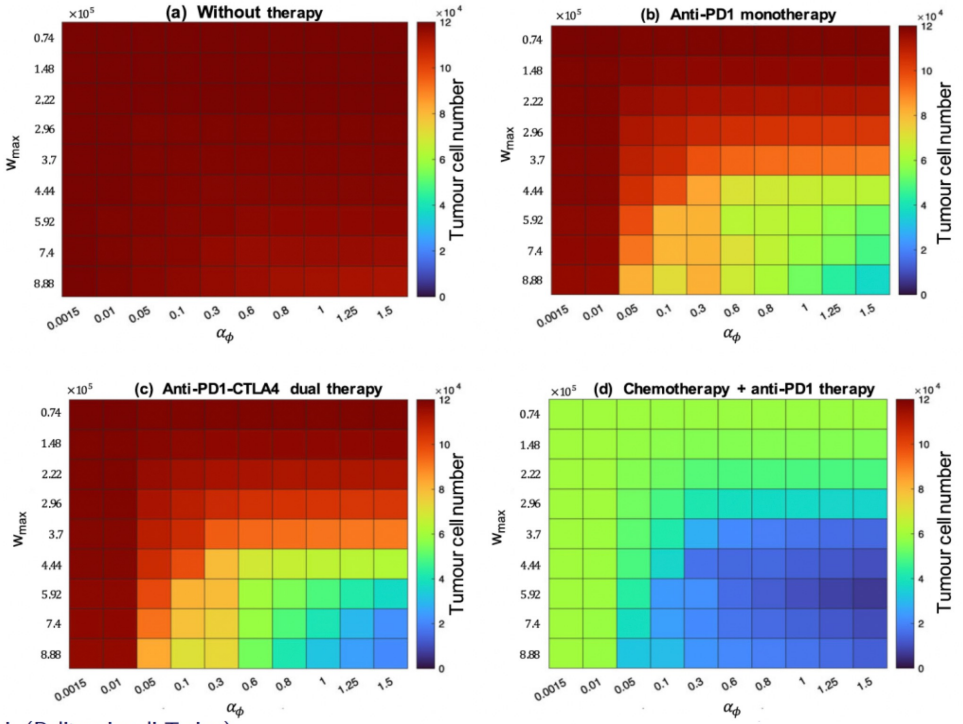
Main results



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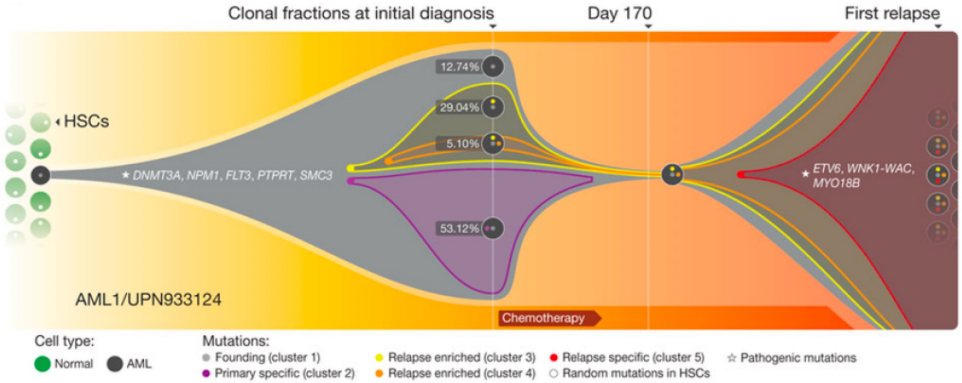
Case Study II

Mathematical models for studying clonal heterogeneity in acute leukemias

T. Lorenzi (Politecnico di Torino)

Background

Clonal heterogeneity in acute leukemias



Ding *et al.*, Nature 481:506–510, 2012.

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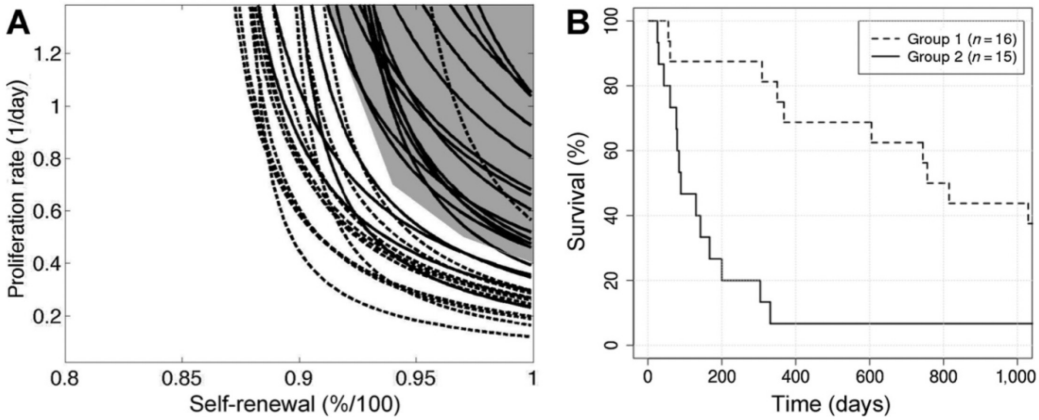
Background

Proliferation rate and self-renewal fraction of leukemic cells affect course of disease



Stiehl *et al.*, Cancer Res. 75:940–949, 2015.

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Research question

How do the proliferation rate and the self-renewal fraction of leukemic cells shape the development of clonal heterogeneity in acute leukemias?

Mathematical model

$n_i(t,y)$: number density of leukemic cells of clone $y \in (0,1]$ at maturation stage i

$i=1$: stem cells $\quad$ $i=2,\dots,M-1$: progenitor cells $\quad$ $i=M$: leukemic blasts

$$
\begin{cases}
\partial_t n_1 = \underbrace{\left(\dfrac{2\,a_1(y)}{1+K\rho_M}-1\right)p_1(y)\,n_1}_{\text{self-renewal}} \\
\partial_t n_i = \underbrace{2\left(1-\dfrac{a_{i-1}(x)}{1+K\rho_M(t)}\right)p_{i-1}(y)\,n_{i-1}}_{\substack{\text{differentiation of cells}\\ \text{at maturation stage } i-1}} \\
\qquad\quad + \underbrace{\left(\dfrac{2\,a_i(y)}{1+K\rho_M}-1\right)p_i(x)\,n_i}_{\text{self-renewal}}, \qquad i=2,\dots,M-1 \qquad y\in(0,1] \\
\partial_t n_M = \underbrace{2\left(1-\dfrac{a_{M-1}(y)}{1+K\rho_M}\right)p_{M-1}(y)\,n_{M-1}}_{\substack{\text{differentiation of cells}\\ \text{at maturation stage } M-1}} - \underbrace{d\,n_M}_{\text{death}} \\
\rho_M(t) := \displaystyle\int_0^1 n_M(t,y)\,\mathrm{d}y
\end{cases}
$$

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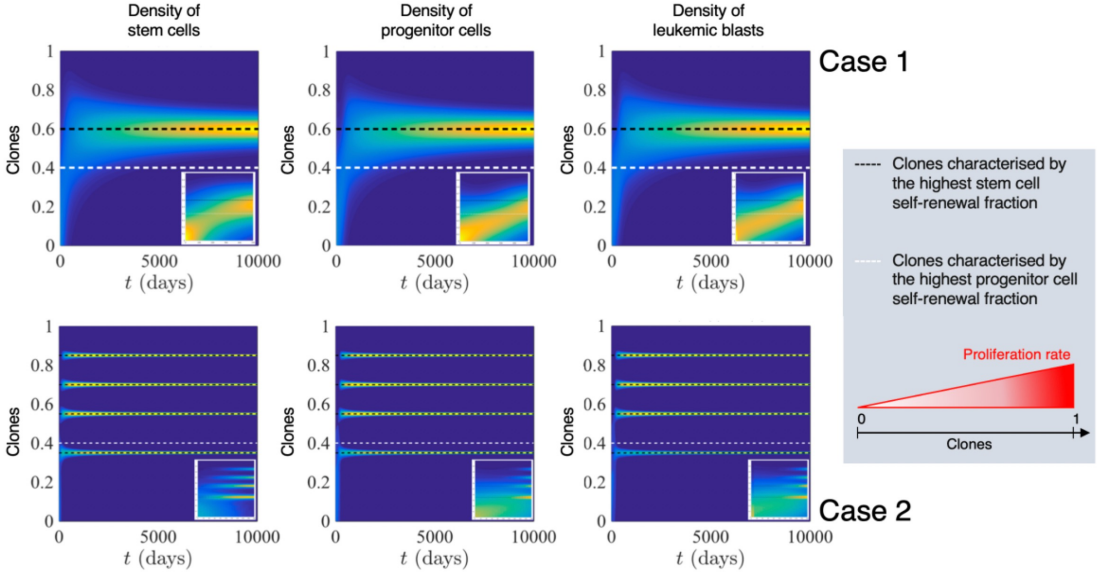
Main results



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Case Study III

Mathematical models for studying intra-tumour heterogeneity in vascularised tumours

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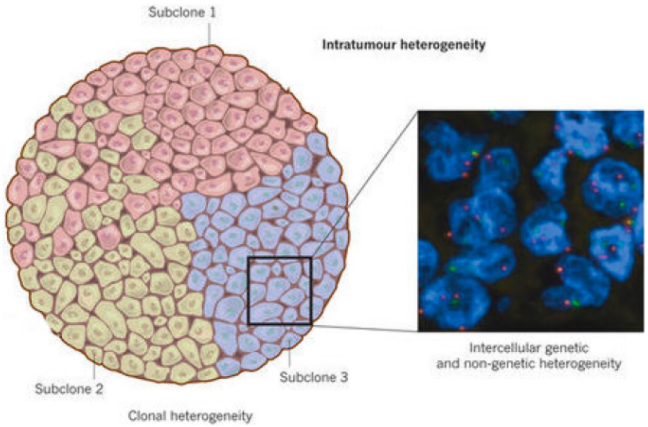
Background

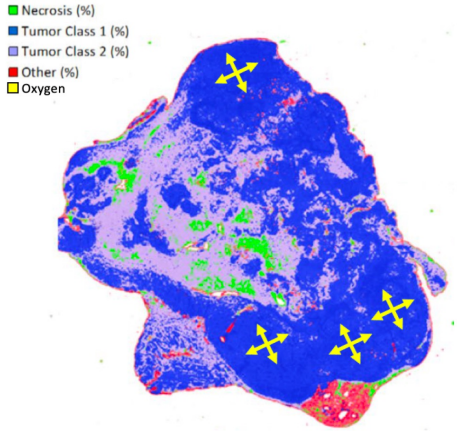
Intra-tumour heterogeneity



Adapted from Burrell *et al.*, Nature 501:338–345, 2013.

Background

Links between cell characteristics and oxygen distribution in vascularised tumours



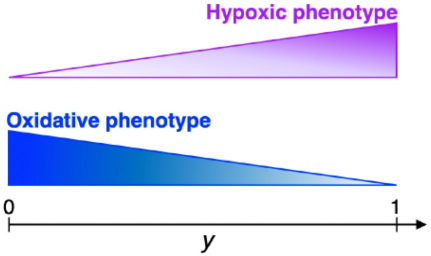
Adapted from Gallaher *et al.*, Sci. Rep. 9:2425, 2019.

- oxygenated regions → oxidative phenotype
- hypoxic regions → hypoxic phenotype

Research question

Can we explain such experimental observations
as the outcome of adaptation of tumour cells
to the spatial distribution of oxygen?

Mathematical model



$n(t,x,y)$: density of tumour cells in metabolic state y

$s(t,x)$: oxygen concentration

$$\begin{cases} \partial_t n - \underbrace{\alpha \Delta_x n}_{\text{movement}} = \underbrace{(r(s,y) - \zeta\rho)\, n}_{\text{proliferation and death}} + \underbrace{\beta\, \partial^2_{yy} n}_{\text{phenotype changes}} & y \in \times(0,1) \\ \rho(t,x) := \displaystyle\int_0^1 n(t,x,y)\,\mathrm{d}y & x \in \Omega \\ \partial_t s - \underbrace{\alpha_S\, \Delta s}_{\text{diffusion}} = \underbrace{\Sigma(t,x) - \lambda_s\, s}_{\text{influx and decay}} - \underbrace{\displaystyle\int_0^1 q(s,y) n(t,x,y)\,\mathrm{d}y}_{\text{consumption}} \end{cases}$$

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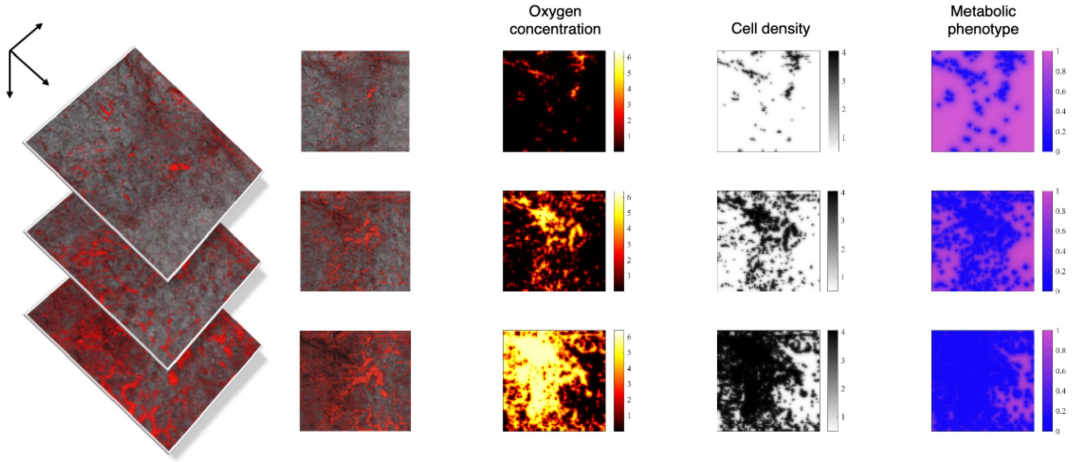
Main results



Data in the left column from Schuh *et al.*, Dermatol Ther 7:187–202, 2017.

Concluding Remarks

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- Object of study: mathematical models for the evolutionary and spatial cellular dynamics implicated in cancer, which are formulated as PDEs.

- Research method: develop, study, and use mathematically tractable models that make it possible to achieve more robust conclusions.

- Outcomes:
  1. theoretical results that shed light on the mechanisms that underpin cancer development and response to therapy;
  2. new testable biological hypotheses;
  3. novel mathematical problems, methods, and results.

Many thanks to my collaborators:

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