Physiological and evolutionary modelling in cancer

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Outline

Introduction

Physiological modelling: Multiscale modelling of tumour growth

Summary and discussion
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Cancer 101

The set of diseases we globally call cancer consists of disturbances of normal cellular functions which lead to phenotypes able to avoid normal homeostatic controls. Such disturbances are assumed to be genetic in origin and lead to the uncontrolled growth of a cellular population which does not carry out any of the functions of the normal tissue while obliterating resources.
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- The formulation of efficient therapeutic strategies has proven, in general, to be a difficult task, as many of the transformations suffered by the normal tissue when becoming cancerous involve resistance mechanisms.
Cancer therapy

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- Therapies that seek to target physiological process
  - Anti-angiogenic therapy
- Therapies that seek to correct particular genetic defects
  - Gene therapy

None of the above are exempt of difficulties, with the latter two presenting problems of their own which will occupy much of this talk.
Cancer as a multiscale process. An example: Angiogenesis

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5. In addition, hypoxia drives evolutionary processes whereby more aggressive varieties (eg metastatic phenotypes) are selected

Take-home message

Processes involving widely different time and length scales are coupled and (dis)regulate each other.
Cancer is an evolutionary process\textsuperscript{1}

Hallmarks of cancer

Cancer is an evolutionary process that occurs in multicellular organisms in which somatic mutations (that is, mutations acquired by the cells upon duplication, not inherited from the parents through the germ line) lead to the breakdown of cell cooperation within the organism.

\textsuperscript{1}Martin Nowak. \textit{Evolutionary dynamics: Exploring the equations of life.}
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2 While analysing each of these levels separately provides useful information, we need to formulate frameworks which account for the coupling between the different levels to properly understand the dynamics of tumour growth and formulate proper therapeutic strategies.

3 The only way forward is to formulate mathematical models that allow to integrate the experimental results coming from different sources within a coherent framework.
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What is multiscale modelling about?

Our BlueMotion range combines lighter materials, enhanced aerodynamics, economical engines and tyres that create less friction, which saves you fuel and can reduce your tax, which means you will have more money.
Multiscale modelling: Scales

- The **intracellular scale** involves pathways and processes occurring within one cell (e.g., cell-cycle)
  - Modelled in terms of ordinary differential equations of the corresponding biochemical pathways
- The **cellular scale** involves interactions between cells (e.g., competition for resources and space)
  - Modelled in terms of cellular-automaton-like rules
- The **tissue scale** is related to processes involving a large number of cells (e.g., vascular remodelling, blood flow)
  - Modelled in terms of continuous hydrodynamic equations

**Caveats:**

- Note that, whilst this subdivision may not be completely accurate from the biological point of view, it constitutes a (first) attempt to rationalisation of the biological complexity allowing for a mathematical approach
Multiscale model for solid tumours

T. Alarcón (IMS, Imperial College, London)  Physiology and evolution in cancer

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- Oxygen and signalling cues produced by the tissue are modelled as continuous fields governed by reaction-diffusion equations

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The corresponding pathways are modelled in terms of systems of ODEs and modulated by the extracellular concentration of oxygen.
Model for the cell-cycle

Simple model for the $G_1/S$ transition. $z(r)$ p27 concentration

\[
\frac{dx(r)}{dt} = \frac{(k_3' + k_3'' u(r))(1 - x(r))}{J_3 + 1 - x(r)} - \frac{k_4 m(r) y(r) x(r)}{J_4 + x(r)},
\]
\[
\frac{dy(r)}{dt} = k_1 - (k_2' + k_2'' x(r) + k_2''' z(r)) y(r),
\]
\[
\frac{dm(r)}{dt} = \mu m(r) \left(1 - \frac{m(r)}{m_*}\right),
\]
\[
\frac{dz(r)}{dt} = \chi(m, r) - k_5' \frac{P(r)}{B + P(r)} z(r),
\]
\[
\frac{du(r)}{dt} = k_6' - (k_6' + k_6 y(r)) u(r),
\]
\[v = 1 - u,
\]

- Each cell in our lattice has an internal cell dynamics that determines when it is ready to divide as a function of the local concentration of oxygen, $P(r)$, where $r$ is the position of the corresponding in the lattice.
Modelling scales: The cellular layer

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![Cellular Automaton Diagram](image-url)
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- It deals with competition between normal and cancer cells for space and resources (oxygen).
- The dynamics of the cells is described in terms of cellular-automaton like rules in terms of:
  - The state of neighbouring lattice sites
  - The internal state of each cell as per its intracellular dynamics
Cell division: coupling to the intracellular layer

1. When a cell completes its cell division cycle, as per the intracellular layer, it checks its surroundings.

2. If at least one of its first-neighbours is unoccupied, it divides and the newly born cell goes to the space most abundant in oxygen. Otherwise, if there is no empty sites, the cell attempting division gets killed.

Cell quiescence

1. Normal cells do not undergo quiescence.

2. Cancer cells are dubbed as quiescence when they are unable to complete the G₁/S transition. Such cells become point sources of VEGF.
Cell death

1. When the levels of intracellular process controlling cell death reaches a given threshold the cell is killed and the space made available.

2. Cancer quiescent cells are killed after a given time span has lapsed.

Fixing the threshold

- The threshold for cell death is fixed according to the occupancy status of the neighbours.
Modelling scales: The vascular layer

- The outcome of this layer is the spatial distribution of red blood cells over the vascular network. This provides a spatially extended, heterogeneously distributed source of oxygen, which then enters the tissue and diffuse over it.
Linking modules: Diffusible species

- Diffusible substances (oxygen and angiogenic factor (VEGF)) are treated as continuous fields and modelled using reaction-diffusion equations.

**Diffusible species: Oxygen**

- **Source.** The oxygen source is provided by the vascular layer and is proportional to both the amount of red blood cells contained in a given vessel and the perimeter of the vessel.

\[
0 = D_c \nabla^2 C + 2\pi R(r) \mathcal{P}(C_{blood} - C) - k_c(r)C
\]

where \( \mathcal{P} \) is the permeability of the vessel wall and \( R(r) \) is the radius of the vessel if there is one at \( r \) and zero otherwise.
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0 = D_c \nabla^2 C + 2\pi R(r)P(C_{\text{blood}} - C) - k_c(r)C
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- Since oxygen diffusion has a much smaller characteristic time scale than the time scales of the tissue, we consider a quasi-stationary regime in which the dynamics of the oxygen is slaved to the dynamics of the tissue.

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Linking the scales II

Oxygen: Top to bottom
1. Oxygen is provided by the vasculature
2. It regulates cell division (intracellular layer)...
3. ...which in turn regulates cell numbers (cellular layer)
4. When cell numbers become too big, VEGF secretion ensues

VEGF: Bottom to top
1. VEGF is produced by quiescent cells (intra- and cellular layer)
2. It regulates vascular adaptation and angiogenesis (vascular layer)
3. When the vasculature adapts to the corresponding stimulus, oxygen increases and VEGF secretion stops
Results for fixed vascular topology with variable microvascular density\(^4\)

Low MVD

Medium MVD

High MVD

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Summary

- We have formulated a framework that allows to model in detail the physiological conditions under which tumour growth takes place and their influence on the latter process.
- Our model allows to integrate experimental data coming from wide range of different sources under a single model, thus providing extra insight of how different processes described in the experimental literature related to different aspects of tumour growth influence and/or drive each other to produce global behaviour.
- Consequently, emergent properties, such as the results shown relating tumour size to vascular density, may be obtained.
- Although our work so far has focused on hypoxia and angiogenesis, other environmental conditions and the corresponding response can be incorporated in our model.
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- Philip K. Maini (Centre for Mathematical Biology, Oxford, UK)
- Markus R. Owen (Centre for Mathematical Medicine, Nottingham, UK)

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- Henrik J. Jensen (Institute for Mathematical Sciences, Imperial College, London, UK)

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