Mathematical modelling of population dynamics in biomedical problems

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Outline

Population dynamics in biomedicine

Mathematical modelling of breast cancer dormancy

Modelling the effect of a quiescent sub-population: a mechanism for evolutionary escape

Multi-scale modelling of angiogenesis and tumour growth
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Many biomedical problems fit within this framework:

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- The interaction between the cells of the immune system and infected cells in viral infections
- Evolution of drug resistance
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The aim of this talk is to illustrate how concepts and techniques from mathematical population dynamics can be used to address and shed some light on a number of issues relevant in different biomedical contexts.
Mathematical modelling using population dynamics

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- The remaining of this talk is devoted to show examples of how these three frameworks are applied to three different problems of biomedical significance
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  - Vascularised metastases that are held at an equilibrium size by the immune system
- By investigating a mathematical model and applying it to empirical data, we have identified that a small number of non-angiogenic micro-metastases as a possible mechanism which can explain relapse data

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Summary of the model

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Parameter values are determined from estimates in the relevant literature and by fitting to relapse data (Early Breast Cancer Trialists Collaborative Group database) using Approximate Bayesian Computation subject to a number of statistics.
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  - A growth ($n(t) \rightarrow G$) event causing escape from growth restriction such as eg genetic or epigenetic mutations inducing switch to the angiogenic phenotype which occurs at probability rate $\kappa$.
- Relapse occurs after a growth event in time $\tau$.

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Number of metastasis tend to one
Long-term dormancy is maintained is maintained by 1-5 micrometastases

This figure shows for all viable values of $\kappa$ the frequency with which dormancy patients have less than or equal to 3, 5 or 10 metastases at 10 and 20 years post-resection. Dormancy patients surviving beyond 10 years have less than or equal to 5 metastases with a probability of at least 60% provided that the growth event has a half-life time of 69 years or less. If the growth event half-life time is of 23 years or less 80% of the patients have between 1 and 3 micrometastases.
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  - Genetic mutations drive a process of random search in genome space.
  - Drug acts as a selective pressure driving this random search towards genomes that furnish the surviving population with resistance to the drug.
- We put forward an alternative mechanism based on a structured, heterogeneous population and the emergence of small sub-population of quiescent cells which do not proliferate but are insensitive to the drug\(^3\).

Although our model was originally formulated to study the effects of hypoxia on tumours under treatment, there are other areas in which our model may be relevant:

**Bacterial persistence**


**Latent reservoir persistence in HIV**

The model

- We consider three different types of individuals which differ in the way they respond to the treatment.
- Types 1 and 2 have similar proliferation and death rates when no drug is present.
- The drug is lethal to 2 and neutral to 1.
- The question we pose is under which circumstances the presence of a third type (type 3) of individual which stays in a dormant state (does not produce offspring) but it is insensitive to the drug can rescue the population from extinction.

Structure of the population

\[ (a) \quad \quad \quad \quad (b) \quad \quad \quad \quad (c) \]
Quiescence rescues Model B from extinction

Simulation results for \( r_{12} = 0.5 \)
Competition dynamics

Fixation probability of a population that can undergo quiescence against a continuously-proliferating population

Squares: drug, circles: no drug.
Therefore ...

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- Quiescence rescues a population under stress from extinction
- Quiescence gives an evolutionary advantage in the presence of drug
- The interesting aspect of this mechanism is that it does not involve an increase in the net reproduction rate of the population, as opposed to the mechanisms proposed by Iwasa et al.
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Multi-scale Modelling of Vascular Tumour Growth in 3D

Schematic organisation of the model

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T. Alarcón (CRM, Barcelona, Spain)
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The complexity of this model poses a barrier to its analysis but opens very interesting avenues for its application.
Image reconstruction

![Real vasculature](A)

![Virtual vasculature](B)

- **A**: Real vasculature
  - Inflow (pressures 35...45 mmHg)

- **B**: Virtual vasculature
  - Outflow (pressures 15...25 mmHg)
Evolution from vascular networks obtained from image reconstruction II

Tumour growth under reconstructed vasculature
The simulations shown in the previous slide constitute a proof-of-concept exercise.
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Such information constitutes a valuable tool to evaluate model predictions specially concerning new therapeutic protocols and interventions.
Conclusions

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By means of three particular examples we have illustrated different modelling approaches.

The decision as to which one we must use in each case essentially depends on the amount of information available: constant parameters is a parsimonious assumption in the absence of further information but other choices are possible if more information becomes available.
Acknowledgements

- Modelling breast cancer dormancy
  - Lisa Willis (CoMPLEX, University College London)
  - Dr. Karen M. Page (Dep. Mathematics, University College London)
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- Modelling latent sub-populations
  - Prof. Henrik Jeldtoft Jensen (IMS & Dep. Mathematics, Imperial College London)

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http://sites.google.com/site/tomasalarc

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