Life and death of agent-based populations

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Quantifying cellular growth is crucial to understanding the dynamics of cell populations such as microbes and cancer cells. The evolution of a cell community is strongly affected by the heterogeneity at a single cell level. We are interested in how the effect of cell-to-cell variability on drug treatment can be modelled and predicted.

**Stochastic lineage dynamics**

The variability at a single cell level can be traced back to internal traits as size, age or cell cycle stage. Such internal traits increase with time leading to large variability across lineages.

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The sampling of the population on a given time does not provide information on future and previous variability inside forward and ancestor lineages. Here is the question: is it possible to characterize forward and ancestor cell life time in a cell population under treatment?

**Drug treatment**

Cells heterogeneity impacts also on drug efficiency which is crucial to provide more effective medical treatment. During a treatment, cells are targeted by the drug and the evolution of the cell population is driven by two transitions:

- Cell death
- Cell proliferation

**Dormancy in breast cancer**

The building blocks of cancer exhibit a wide variability. Among heterogeneous tumor cell populations within primary breast cancer, tumor cells exist in the form of cellular dormancy. These dormant cells are refractory to cancer therapies and become enriched following cancer treatments. During the cancer therapies, the tumor cells may perform different transitions:

- Cell death
- Cell proliferation
- Cell going into dormancy

Cancer cells can be modeled as individuals who can die, duplicate and convert into a dormant state where they rest until awakening. The dormancy is a useful strategy for the cells to escape the drug treatment.

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**Analytical methods**

We introduce a novel stochastic model where cells are represented by agents who perform transitions in response to an internal continuous state $x$ which increases with time.

To account the continuous heterogeneity, the system abundance are described by stochastic functions. The rate of each transition is then a function of the internal trait of the cell undergoing the transitions. For example, dormancy in breast cancer.

\[
\frac{dP(n_1, n_2, t)}{dt} = \sum_i \frac{\delta}{\tau_i(n_1, n_2, t)} P(n_1, n_2, t) + \sum_j \frac{\gamma_j(x)}{\tau_j(n_1, n_2, t)} P(n_1, n_2, t)
\]

where $\delta$ represents the functional step operator:

\[
e^{\epsilon} P(n_1, n_2, t) = P(n_1 + \delta, n_2, t)
\]

and $x$ represents the functional step operator:

\[
\epsilon x P(n_1, n_2, t) = x \delta(n_1, n_2, t)
\]

The master equation can be reshaped in a Functional Derivative Equation for the generating functional which can be manipulated using a generalized characteristic curves methods to obtain information about the stochastic moments, extinction probability and lineages distributions.

**Results**

The developed analytical method bounded with a set of simulation algorithms allows to obtain a complete characterization of cell populations under treatment. In the following, there are reported the main results regarding cell population dynamics under drug treatment scenario and the breast cancer dormancy scenario.

**Results on drug treatment**

The analytical and numerical results allow to draw a quantitative picture regarding drug treatment efficiency in a cell population.

The efficiency of the drug treatment approaches the asymptotic values faster when the drug dosage is higher.

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**Conclusions**

1. Mathematical modelling quantitatively predicts the efficiency of drug treatments.
2. We predict the existence of a drug dose threshold for complete killing of cancer cell population.
3. Our insights apply not only to cancer but can equally be applied to persistence in antimicrobial resistance.

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