Stochastic modelling of age-structured populations

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Quantifying cellular growth is crucial to understanding cell populations' dynamics such as microbes and cancer cells. The standard behaviour of batch cultures is well known and it is usually characterised by a delay before the start of exponential growth, an exponential phase, and a steady phase; however, at the single-cell level, growth varies drastically from cell to cell due to the fluctuations in the cell cycle duration, variability caused by changing environments, and cells interactions. At the present time, understanding how cell-to-cell variability affects the evolution of the entire population is still a challenge; de facto, there is still lacking solid theoretical and simulation methods to forecast the effects of cell heterogeneity on population dynamics. We propose a novel stochastic model where the cell is represented by agents who divide, die, convert to other species, and rejuvenate in response to an internal continuous state which increases with time. While such models are usually only amenable to simulations, we show that the population structure can be characterized by a functional master equation which can be manipulated to obtain a novel integral renewal equation. Compared to the classic results of renewal theory, as the Bellman-Harris branching process, the latter equation takes a step further. In fact, it provides a solid and compact stochastic description of the role played by cell heterogeneity on population dynamics. The analytical framework allowed us to fully describe the population size distribution, population growth rate, and ancestor and division times distributions. Moreover, we provide an analytical and numerical characterization of the extinction probability and first extinction times distribution for any cell-to-cell heterogeneity range. We also propose a novel way to simulate the evolution of cell populations affected by the variability of the individuals. Such computational tools allowed us to substantiate the analytical and numerical results obtained during this investigation. Our last results also provide novel methods to address the role of cell-to-cell variability in time-dependent environments. We showed that the stochastic description of agent-based population dynamics could be obtained in scenarios where the reaction network rates depend explicitly on time in addition to the internal traits of the cells. In conclusion, the following research project proposes a novel methodology to describe the stochastic behaviour of cell structured population with numerical, computational and analytical methods. Our results open a new theoretical path to understanding stochastic mechanisms underlying fluctuations in various biological and medical applications as the extinction of cancer cell populations under treatment, cell population growth in adverse environments, dormancy-awakening transition in breast cancer and microbial quiescence.