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# Agent-based and continuum approaches to growing cell aggregates

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## ABSTRACT

Predicting growth and therapy of tumors is still an open challenge. It requires to understand how information is transformed from the molecular scale of nanometers up to multi-cellular scale of centimeters. Studying the link between genetic, metabolic and signal transduction networks on individual cells level favors agent-based models in which each cell is represented individually. Studying tumors on the scale of centimeters favors continuum models. On intermediate scales cellular automaton (CA) models have advantages: they coarse grain the individual-cell information but still permit to represent inherent inhomogeneities and stochasticity on the cell scale.

We show by a quantitative analysis of a biophysical agent-based, a CA model, and a continuum mechanical model that for densely packed aggregates the expansion of the cell population is dominated by cell proliferation controlled by mechanical stress. The biophysical agent-based model approximates each cell as an isotropic, homogeneous, elastic, spherical object parameterized by measurable biophysical and cell-biological quantities [1]. The interaction between cells is simulated by the Johnson-Kendall-Roberts force model which has recently been experimentally shown to provide a good approximation to cell-cell-and cell-substrate forces [2]. Cell migration is modelled both by a Metropolis-algorithm and by Langevin equations. The CA model parameterizes dense growing aggregates by a minimum number of parameters and rules [3]. The same model can be used to simulate growth of cells on spherical micro-carriers in bioreactors for vaccine production. Cells in the CA model are defined as Voronoi cells with a proper distribution of construction points to avoid artifacts from lattice symmetries and to insure a proper cell-size distribution. The continuum model uses mass conservation with a stress-controlled growth term and D'Arcy's law.

We show that all three models exhibit the same growth kinetics, with initial exponential growth of the population size and aggregate diameter followed by linear growth of the diameter and power-law growth of the cell population size hence yield the same result in

the studied biological situation. This growth kinetics agrees quantitatively with experimental findings in monolayer and multi-cellular spheroids. The model comparison of the stress and density profiles further facilitates to link macroscopic to some of the microscopic parameters and to the rules of the cellular automaton model. In this way it can be insured that all model types describe the same growth dynamics. A rigorous coarse graining turned out to be not feasible.

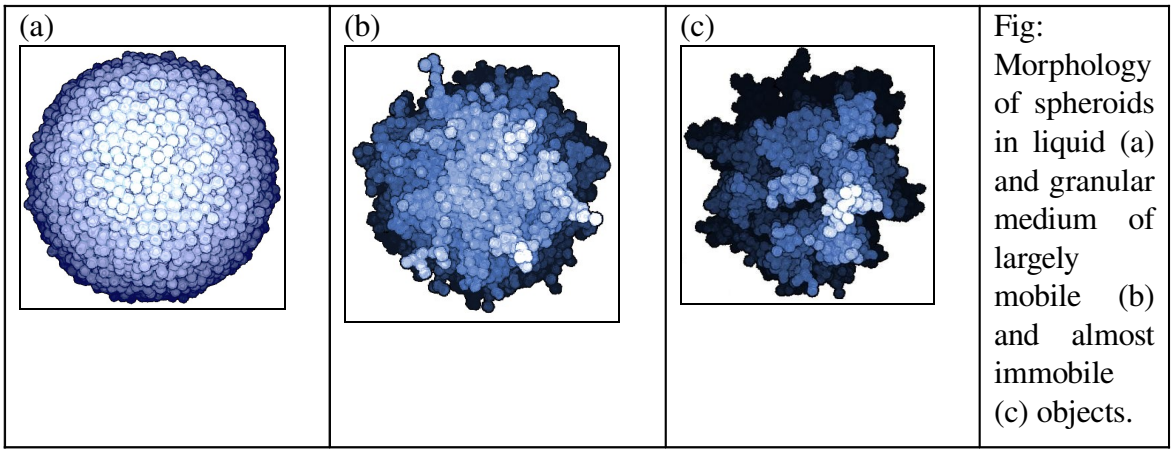


Fig: Morphology of spheroids in liquid (a) and granular medium of largely mobile (b) and almost immobile (c) objects.

Finally we use the biophysical agent-based model to compare the growth pattern of cell aggregates in agarose-like media and show that, while the growth kinetics can be well explained by a purely physical model, the explanation of the measured cell death pattern needs the assumption of active cell death control. We use the model to predict the growth pattern in granular tissue-like media [4]. For certain conditions such as a small mobility, small density or small elastic modulus of external granular objects a Saffman-Taylor-like instability is predicted as the consequence of the mechanical stress-based growth control (Fig.; only cell aggregate cells are shown, granular objects are missed out). The agent-based model permits to easily include the effect of mutations. We illustrate that if mutations are permitted that affect the cell-kinetic and cell-biomechanical parameters, the model exhibits those scenarios that are found during the transformation of tumours in-situ to invasive cancer.

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