On the role of biomechanics in the growth of multicellular spheroids

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Many diseases and dysfunctions occur on a multi-cellular level and are reflected by the multi-cellular phenotype. An example is cancer. A common experimental technique to study growing tumor cell populations is multicellular spheroids.
We demonstrate by direct comparison with experimental observations that surprisingly many aspects of multi-cellular spheroids growing in liquid suspensions can be explained by a single-cell-based model that approximates complex biological cells by homogeneous elastic adhesive objects capable to migrate, grow and divide in a lattice-free space (e.g. Drasdo and Hoehme, Phys. Biol. 2005; Galle, Loeffler, Drasdo, Biophys. J. 2005).
A model cell is parameterized by effective quantities that can all be experimentally measured, for example, its material constants, the surface density of cell-cell and cell-surface adhesion molecules, its diffusion constant, and its cycle time.
The expansion kinetics of multi-cellular spheroids can largely be explained by a biomechanical form of contact inhibition that leads to an inherent link between the entrance into the cell cycle at the local degree of deformation or compression.
This complies with recent findings on the important role of biomechanics in tissue growth (e.g. Helmlinger et.al., Nat. Biotech. 1997; Nelson et. al.; Shraiman; Ingber, all PNAS 2005).
We find that besides the temporal development of the cell population size and the tumor diameter, the cell size, the spatial distribution of cell sizes within the multicellular spheroid and the spatial structure are correctly reproduced.
For spheroids growing in an environment of other cells (co-cultures) our model predicts a saturation kinetics and an instability if the motility of the embedding cells is small or cell-cell aggregation clusters form as a consequence of strong cell-cell adhesion. In this case the cell population grows into the direction of least mechanical resistance.
We suggest using our model as an interface between the molecular and multi-cellular scale in the systems biology of multi-cellular systems where an understanding requires analyzing the interplay of many time and lengths scales from the molecular to the multi-cellular scale. On one hand the effective model parameters subsume the effect of molecular regulation on the cellular phenotype; on the other hand, the assumptions on the level of an individual cell necessary to reproduce a certain multi-cellular phenotype give hints on the potential function of intracellular regulatory networks and signal pathways.
Along this line of argument we illustrate that an active down-or up-regulation of the cell stiffness can significantly affect the multi-cellular growth pattern.