Quantitative hybrid modeling to predict realistic mechanical stresses in growing tumor spheroids and tissues using agent-based models.

Paul Van Liedekerke*, Tim Johann†, Johannes Neitsch† and Dirk Drasdo*,†

* Institut national de Recherche en Informatique et Automatique (INRIA)
2 Rue Simone iff, 75012 Paris, France
e-mail: Paul.Van_Liedekerke@inria.fr
† Interdisciplinary Center for Bioinformatics (IZBI)
Univerisity of Leipzig
Haertelstrasse 16-18, Leipzig, Germany

ABSTRACT

Agent based models with cells represented as spheres permit to estimate the physical forces on cells during growth. They are amenable to about 1 Mio cells in a few weeks computation time on a standard desktop computer. However, these center based models (CBM) models generally lack a self-consistent definition cell volume, shape and mechanical stresses [1]. Modeling of tissue micro architecture is often incompatible with the assumption of rigid cell shape. The geometry and topology of the micro-vessel network requires cells of variable shape that geometrically and mechanically adapt to its micro-environment. Another major issue in center based models, often ignored in simulations, is that common pair-wise contact forces (type Hertz, JKR, ..) become largely inaccurate when cells are densely packed. The origin of this problem is that Hertz forces are defined pairwise and exclude the contributions from other interactions.

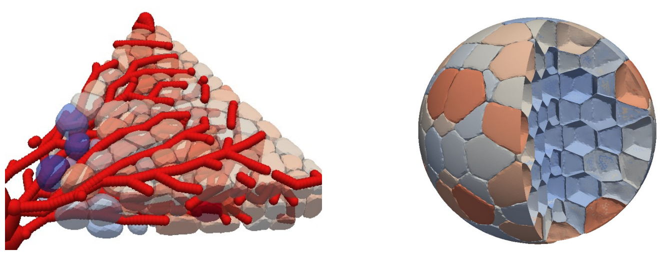

Fig. : (left) Simulations of tissue including bood vessels (CBM) with and cells (DCM). (right) Simulation of compressed spheroid with DCM to estimated correct contact forces. Coloring is according to mechanical stress.

These issues can be circumvented by using deformable cell models (DCM) instead [2]. In this model type, each cell is constructed by nodes interacting with each other through viscoelastic elements. Here, deformations and stresses can be tracked more precisely. Deformable Cell Models are able to capture the complex shapes of cells and quantify forces in great detail. However, a DCM simulation is computationally very expensive

A solution to this is proposed using a hybrid computational modeling strategy, in which the interaction forces of the CBM are calibrated from numerical experiments using the DCM. We show this calibration leads to realistic pressures inside spheroids. We also show that CBM and DCM can be used in the same simulation, where the active high-interest regions are represented with DCM and passive structures are respresented by CBM.

REFERENCES

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