NOTOX

Predicting long-term toxic effects using computer models based on systems characterization of organotypic cultures

Modeling spheroid formation for later organotypic toxicity prediction

Geraldine Celliere, Paul van Liedekerke, Dirk Drasdo, Elmar Heinzle

Aim

Development of an agent-based force-driven mathematical model to:

- Understand the mechanisms behind cell aggregation and spheroid formation
- Investigate the diffusion process and concentrations of toxic compounds inside the spheroid. Prediction of cell death
- Calibrate the physical parameters for this model, for future toxicity prediction in the liver

Modeling tools

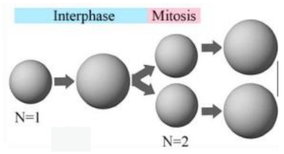
Each cell is modeled by an elastic and adhesive sphere, which is capable of:

- Interacting with other cells and the substrate (adhesion, repulsion and friction)
- Active migration
- Responding to local concentration of chemicals
- Growth, division and death

(I)The cells move according to friction dominated eq. of motion:

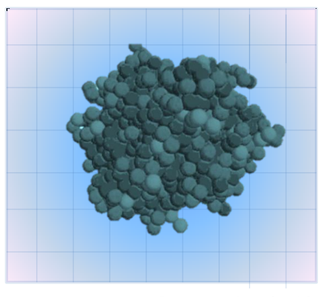
$$\underbrace{\sum_j (\vec{v_i} - \vec{v_j})\,\gamma^{cc}}_{\text{cell-cell friction}} + \underbrace{\gamma \vec{v_i}}_{\text{cell-ECM friction}} = \underbrace{\sqrt{2d\gamma^2 D}\,\vec{n}}_{\text{micro-motility}} + \underbrace{\sum_j [\frac{4}{3}(R_i + R_j - d_{ij})^{3/2} \widetilde{E_{ij}} \sqrt{\frac{R_i R_j}{R_i + R_j}}}_{\text{cell-cell repulsion}} - \underbrace{\xi W \pi \frac{R_i R_j}{R_i + R_j}]\vec{u_i}}_{\text{cell-cell adhesion}}$$

(II)Cell growth and division: Stepwise increase of cell volume. Two daughter cells replace mother cell when cell volume has doubled



(III)The diffusion of chemicals in the spheroid is computed according to the reaction-diffusion equations, and couples with the cell density

$$\underbrace{\frac{\partial C(\mathbf{r},t)}{\partial t}}_{\text{diffusion}} = D\nabla^2 C(\mathbf{r},t) + \underbrace{\alpha n(\mathbf{r},t)}_{\text{Absorption by cells}} - \underbrace{DC(\mathbf{r},t)}_{\text{degradation}}$$

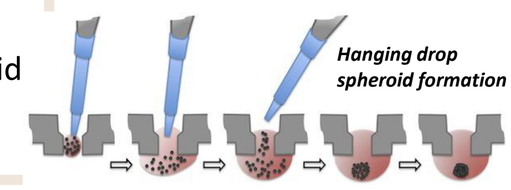


Computational grid

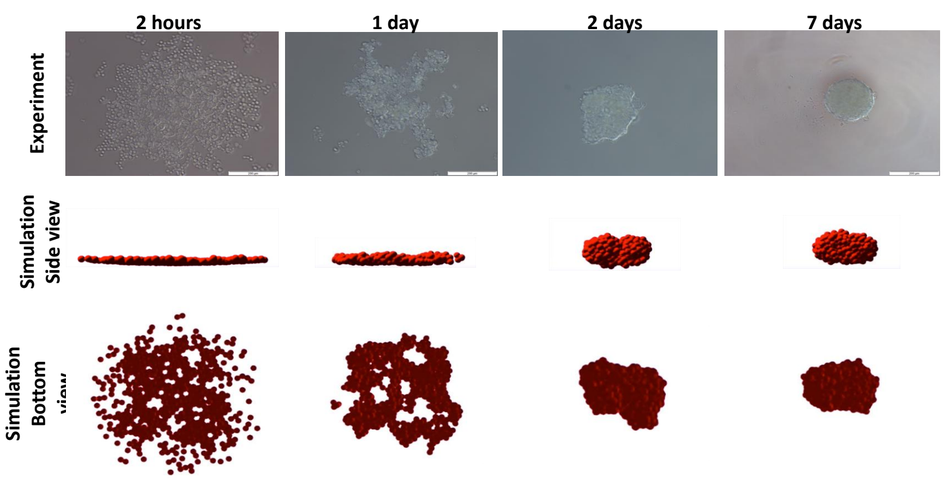
Results: hanging drop spheroids

Aim: Model aggregation process to gain insight on several aspects:

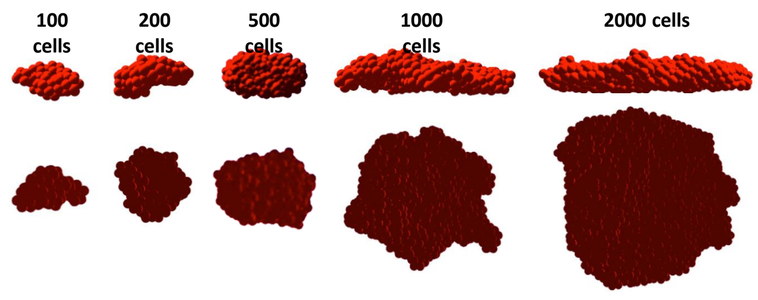
- Which forces drive the formation?
- Multicellular architecture inside spheroid
- Influence of drop curvature
- Influence of ECM



(I) The spheroid formation with 500 cells can be qualitatively reproduced. The process requires high cell adhesion and high cell motility



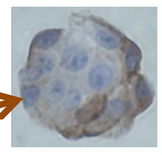
(II) As observed experimentally, an elongated instead of a spherical shape is obtained for large cell numbers



Outlook

The model will be extended and improved to:

- Better model the localization of the extracellular matrix (currently homogeneous and implicit)
- Model the two types of cells observed in *in vitro* spheroids: hepatocytes and biliary epithelial cells



- Identify parameter values promoting aggregation. Can a lack of cell-cell adhesion be compensated by cell-matrix adhesion ?
- Model the impact of drugs on spheroids, and cast it into a full *in silico* liver lobule model (including blood vessels) with calibrated parameters

Contact:
Paul van Liedekerke, Paul.Van_Liedekerke@inria.fr
Geraldine Celliere, geraldine.celliere@inria.fr

SEURAT-1
Cosmetics Europe the personal care association
SEVENTH FRAMEWORK PROGRAMME