Exploring Multi-Cellular Tumor Spheroids in Virtual Reality

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Goal

Exploring the inner dynamics of 3D biological structures is of central interest. It is particularly the case for multi cellular tumor spheroids (MCTS) to design new efficient therapeutic protocols. However, exploring them *in vitro* is technically challenging. Nowadays, computer science can help by providing increasingly realistic digital models and accessible means of visualization and interaction, especially also relying on virtual reality (VR) approaches.

Experimental Design

To this end, we have a developed a 3D *in silico* model of *in vitro* MCTS. In our model, cells are controlled by a cell cycle based on Bernoulli processes (BP). The model of the cell cycle considers and offers the possibility to manipulate four checkpoints: "R", the restriction point in the G1 phase, the G1/S and G2/M checkpoints, and the intra-mitotic (iM) checkpoint in the M phase. They divide the cell cycle model into a sequence of 7 BP: $G1_{preR}$, *R*, $G1_{postR}$, *S*, *G2*, M_{preiM} and M_{postiM}. A BP is composed of a given number of draws t_x^{min} which represent the minimum amount of time a cell will spend in one phase under optimal conditions. Draws have a success probability P_x that regulates the speed of cells to advance in their cycle. Intercellular variability is modelled by randomly choosing the minimum success amount of each BP following a log-normal law [Sherer et al., Biotechnol BioEng 2008] every time a new cell is created.
Such representation of the cell cycle is generic enough to integrate additional external events. Under optimal condition, draw probabilities are all equal to one. Taking into consideration environmental modifications requires modifying the draw probabilities accordingly.

Cells are physically modelled in a 3D virtual environment based on a mass-spring-damper system. Oxygen gradients are simulated using a model proposed by [Grimes et al., J. Royal Soc. 2014]. It is based on hypoxia measurements and the size of the MCTS. Using proliferation marker data (EdU marking in central slices of fixed HCT116 MCTS), we were able to correlate the cell cycle elongation to the oxygen concentration.

To improve the understanding of the inner dynamics of the system, we have developed a VR set up in which the simulated MCTS can be visualized at real-time speeds. We paid particular attention to the visualization of the virtual cells. We have simulated the effects of existing markers such as proliferation markers (*i.e* EdU) or hypoxia markers (*i.e.* pimonidazole) to evaluate the realism of the virtual MCTS based on data biologists are used to analyze. Our markers are calculated for each time step, therefore reflecting model changes ad-hoc, during the simulation. As the simulation provides access to additional data, users can also color cells with regards to their cell cycle duration, the oxygen concentration, etc. Finally, the VR room (it is a room-scale simulation relying on HTC's Vive device) also contains a virtual board for plotting data such as the population size, phase repartition, FACS analysis.

Using VR allows users to naturally interact with the visualized MCTS, for instance by cutting it to explore its internal structures. Users can also easily navigate in the simulation both in time (using a remote controller) and space (by moving and reorienting in the room).

Results

Here we report on new application that allows the exploration of simulated MCTS in VR. The agent-based model used is reproducing the inner proliferation dynamics of the MCTS. We have developed a set of VR tools aimed at improving the comprehension of the complex spatiotemporal dynamics exhibited. In the future, we want the tool to be usable to explore and evaluate new therapeutic strategies by allowing biologists to visualize and pre-analyze possible outcomes of treatment protocols before actually running them in the wet lab.