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Exploring Multi-Cellular Tumor Spheroids in Virtual Reality

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Goal: Exploring cells inner dynamics of 3D biological models 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 developed a 3D *in silico* model of the growth of *in vitro* MCTS. 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. In this model, we used Bernoulli processes, a mathematical tool that allows a discretization of time and the regulation of the cell cycle advancement speed based on sequences of probabilistic draws. Intercellular variability is modelled by randomly choosing the duration of each phase following a log-normal law [Sherer et al., Biotechnol BioEng 2008] every time a new cell is created. The representation of the cell cycle we used is generic enough to integrate additional external events. Under optimal condition, draw probabilities are all equal to one, leading to cell cycling as fast as they can. Taking into consideration environmental modifications requires modifying the draw probabilities accordingly. Cells are interacting in a 3D virtual environment based on a mass-spring-damper system. Oxygen gradients are simulated using finite differences. Using a diffusion and consumption model of oxygen proposed by [Grimes et al., J. Royal Soc. 2014] applied to experimental data based on proliferation marker (i.e. EdU), we were able to correlate cell cycle elongation in depth to oxygen concentration decay. This allows to calculate during the simulation the elongation of the cell cycle of the cells in the MCTS. To improve our understanding of the inner dynamics of the system, we have developed a VR set up in which the simulated growing MCTS can be visualized in real-time. We paid particular attention to the visualization of the virtual cells. We have simulated the effects on cell cycle dynamics, on 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, or FACS analysis. Using VR allows users to naturally interact with the visualized MCTS, for instance by cutting it to explore its inner structures. Users can also easily navigate in the simulation both in time (using a handheld controller) and space (by moving and reorienting in the room).

Results: Here we report on a 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 plan 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.