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Purpose:
Cell cycle synchronization at a specific stage is often an essential requirement to investigate biological events and mechanisms using the large panel of molecular and cellular biology technologies. Optimization of the synchronization parameters is most of the time neglected, which could result in experimental time wasting or even in erroneous conclusions. Here we report the development of a cell cycle checkpoint-oriented simulator, based on agent-based modeling (ABM), that reproduces the dynamic behavior of a proliferating cell population and its response to checkpoint activation.

Experimental Design:
We have developed an online simulation tool to accurately reproduce the cell cycle dynamics of any kind of cell lines. Simulations are performed using an agent-based modeling (ABM) to represent the cells and their microenvironment. The cell cycle is modeled as a sequence of checkpoints (R – restriction point, G1/S, G2M and iM – intra-mitotic) whose transition probabilities are dependent on cell status and local environment (nutriments, growth factors, oxygen, etc.) [1]. Progress of the cells in the cell cycle is organized into Bernouilli processes, thus ensuring the necessary variability to accurately model the cell cycle dynamics [2]. Calibration of the model relies on easily accessible experimental data such as cell cycle phase distribution (bi-parametric flow cytometry analysis) and population doubling time. We have placed a particular attention to generate simulation results in the format the biologists are used to deal with (simulated flow cytometry) in addition to providing new statistical visualization of the growth dynamics for two reasons : (i) easily validate the simulation outputs in order to compare in vitro and in silico data, and (ii) provide an extended understanding of the population dynamics in the virtual culture.
Once calibrated, the model can also be challenged using compounds such as nocodazole or thymidine to impair different cell cycle progression. These drugs are affecting Bernouilli draws probabilities (mitosis process for nocodazole and DNA synthesis process for thymidine) and thus affect the dynamics of the virtual culture.

Results:
We illustrate the use of this simulator to optimize synchronization parameters of HCT116 cells in mitosis using nocodazole treatment and at G1/S using a double-thymidine block and release. Simulations using the optimized conditions are successfully confronted to experimental supporting data.

Conclusion:
Finally, as we believe this simulator will be of tremendous interest for many users, we present a web interface publically available for the scientific community.

References :
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