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A Validated In Silico Model for Predicting Human Pluripotent Stem Cell Proliferation Dynamics in a Vertical Wheel Bioreactor

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ABSTRACT

In silico models, which are computational tools for simulating biological processes, have emerged as essential for understanding complex biological processes in the field of tissue engineering, particularly in human pluripotent stem cells (hPSCs) research. Traditional *in vitro* and *in vivo* methods have been foundational in advancing our understanding of hPSCs, providing essential data that are instrumental in the development of in silico models. While these methods are invaluable, they can be resource-intensive and time-consuming. In silico methods complement these approaches by using computational modeling to offer a cost-effective and efficient alternative for accelerating research processes and enhancing productivity. This study develops a comprehensive in silico model to accurately simulate the proliferation dynamics of hPSCs within a bioreactor system, incorporating both biochemical and biophysical influences. Specifically, we constructed a system of ordinary differential equations (ODEs) that integrates key factors such as shear stress, energy dissipation, and nutrient availability within hPSC aggregates. These factors, along with initial cell density, glucose concentration, and lactate accumulation, are incorporated into the model through ODE source/sink terms and modulation functions that follow constant, linear, and Michaelis-Menten kinetics. To validate the model, we applied it to investigate media exchange strategies, a critical factor influencing nutrient availability, waste removal, and cell expansion efficiency. We compared experimental proliferation outcomes against model predictions under 20% and 50% media exchange conditions, observing a close alignment with less than 5% error. Additionally, we tested the model on a different hPSC cell line, where it also demonstrated strong predictive accuracy, further confirming its robustness. By enabling precise simulation of experimental scenarios, the proposed model provides valuable insights into optimizing cell culture conditions, improving cell yield, and reducing costs. Ultimately, this work has significant implications for advancing regenerative medicine by refining stem cell expansion strategies and enhancing scalability for therapeutic applications.