Simulating the Effects of Anticoagulant Drugs Upon Blood Clotting Dynamics

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Abstract. Linking scales in both modelling and visualisation is a key challenge in computational physiology. We have combined two existing simulations of blood clotting – a large-scale simulation of the physical interactions between platelets in the bloodstream, and a detailed simulation of the chemical signalling inside a platelet based on an accurate mathematical model – and linked them to an interactive 3D visualisation, allowing researchers to immediately see the tissue-scale results of changes to cell-scale models.

1 The Original Simulations

This work is based upon two existing, mature simulations. The first simulation was constructed to explore the effects of combinations of anticoagulant drugs such as aspirin and celecoxib upon blood clotting [1]. These drugs work by inhibiting the production of prostaglandin H synthase, a precursor of signalling molecules such as thromboxane, a key factor in the activation and aggregation of platelets. Its kinetic model of PGHS-1 catalysis within platelets was validated using in-vitro and in-vivo experimental data.

The second simulation was developed as part of the TUNA project to study the low-level platelet behaviours necessary for clotting to emerge [2]. It implements an agent-based model of spatial interaction using concurrent techniques for multicore and distributed simulation, allowing experimentation and cross-validation at realistic scales. The model was later reworked using techniques developed by the CoSMoS project for improved scalability.

Merging these two approaches enables interactive experimentation with the effects of anticoagulant drugs in a realistic spatial environment. The first simulation provides a biologically-accurate model of the key processes within a cell; the second provides the implementation technologies necessary to visualise the emergent effects of those processes at larger scales.

2 The Combined Simulation

Starting with our existing model of platelet chemical signalling, we specified and calibrated a characteristic subset of the model using a hybrid Petri net approach. We designed a declarative embedded domain-specific language (EDSL)

for hybrid Petri nets, and developed a new signalling simulator that could be embedded into the existing spatial simulation enabling fine-grained parallelisation. We extended the spatial simulation to model diffusion of multiple chemical signals with realistic concentrations, and linked it to the new signalling simulation. We also built a new immersive 3D visualisation for the simulation using the Cinder library, which allows easier navigation and exploration of the simulated system, interactive adjustment of parameter values, and more effective visualisation of cell properties (Fig. 1).

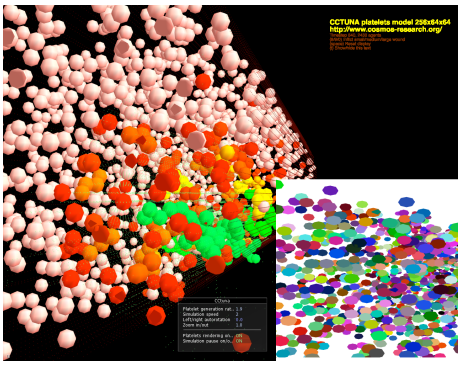

Fig. 1. Clotting in response to a wound in the combined simulator.

The resulting simulation correctly reproduces the intended system behaviours, and provides a number of reusable components for other work within CRISP, integrating equational models of cell signalling with CoSMoS-style models of spatial interaction. We are particularly interested in spatial aspects of cancer growth, and plan to couple the simulation built in this project to our group's biologically-accurate visualisation of cell signalling network dynamics, enabling the user to "zoom in" from a physical view of the world to a conceptual view of the signalling network within a chosen cell.

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References

1. Goltsov, A., Lebedeva, G., Humphery-Smith, I., Goltsov, G., Demin, O., Goryanin, I.: In silico screening of nonsteroidal anti-inflammatory drugs and their combined action on prostaglandin H synthase-1. Pharmaceuticals 3(7), 2059–2081 (2010)
2. Ritson, C.G., Welch, P.H.: A process-oriented architecture for complex system modelling. Concurrency and Computation: Practice and Experience 22, 965–980 (2010)