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CO-SIMULATION OF COMPOSABLE CELLULAR AUTOMATA DEVS AND DIFFUSION PDE MODELS

Chao Zhang
Hessam S. Sarjoughian

Arizona Center for Integrative Modeling and Simulation
School of Computing, Informatics, and Decision Systems Engineering
Arizona State University
Tempe, AZ 85281, USA

ABSTRACT

It is beneficial to gain insight into cancer biology by modeling and simulating cancerous cells interacting with their environment. The diffusion and agent-based models can define individually continuous and discrete dynamics of different kinds of human cells toward achieving this goal. On the one hand, the continuous diffusion modeling approach is appropriate to define the dynamics gradient formation of CXCL12 chemokines. On the other hand, the Composable Cellular Automata DEVS modeling approach lends itself to defining the CXCR4+ and CXCR7+ cells chemotaxis movement subject to the chemokine gradient. The OpenModelica and DEVS-Suite simulators are well-suited for modeling and simulating diffusion and agent dynamics useful for the study of cancer biology. They are integrated using the FMI standard to develop and co-simulate continuous and event-driven models.

1 BACKGROUND AND MOTIVATION

Human breast cancer involves multiple processes where ligand secretion and diffusion within and across cells interact complexly. A key focus is to model a signaling axis involving CXCL12 ligand and CXCR4 and CXCR7 receptors and their bindings to CXCL12+, CXCR4+, and CXCR7+ cells (Chang et al. 2015). The diffusion of soluble CXCL12 is modeled as a Partial Differential Equation (PDE) system. The cancer cells are modeled as agents and assigned to a discrete two-dimensional grid space. The CXCL12+ cells secret CXCL12 chemokine. The CXCR4+ cells move towards the chemoattractant CXCL12, and the CXCL12+ and CXCR7+ cells move randomly. Interactions between the cells and with its environment take place at discrete time steps.

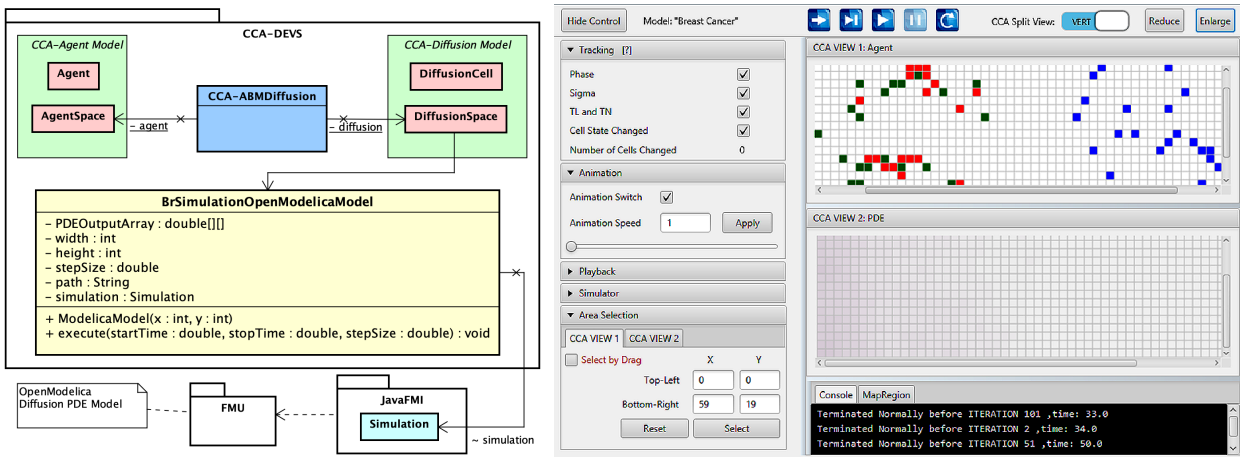
The CCA-DEVS formalism for the agents supports the composition of Cellular Automata with the Parallel DEVS simulation protocol (Zhang et al. 2020). The approach uses the modularity of the agents and the environment. The agents are triggered and may act upon receiving one or more events. The cancer cells, as agents, can move subject to their states and the events they may receive from their immediate neighbors. When an agent needs to move, it first looks for an empty neighbor cell. An empty cell might receive multiple requests from its neighboring agents who also may want to move in the empty cell. Once one of the agents is selected by the empty cell, the selected agent is notified and then it will occupy the empty cell. Agents execute asynchronously and may move at different speeds.

The Java Functional Mockup Interface (JavaFMI) is used for co-simulating Composable Cellular Automata DEVS (CCA-DEVS) and discretized PDE models. The JavaFMI v2.0 (https://bitbucket.org/siani/javafmi) is used to integrate the slave FMU from OpenModelica (https://www.openmodelica.org) v1_14_1 simulator with the master simulator of DEVS-Suite (https://acims.asu.edu/software/devs-suite/).

2 CANCER BIOLOGY CO-SIMULATION WITH DEVS-SUITE & OPENMODELICA VIA FMI

The diffusion process of the CXCL12 phenomenon is defined based on discretizing the space continuum into a grid of square shapes. Each grid cell is defined as an Ordinary Differential Equation (ODE) system. The Method of Line is applied to solve the PDE diffusion process. The ODE model receives inputs from its four neighbors to compute its next value. Meanwhile, in CCA-DEVS, three types of cancer cells (CXCR4+, CXCR7+, and CXCL12+) are modeled as agents with the ability to move in a 2D cellular space. The system environment is filled with CXCL12 chemokine for gradient diffusion, generation, and consumption. The space of diffusion is also discretized to be the same size as the agents. Each grid cell of CXCL12 chemokine is a 4^{th}-order ODE developed in OpenModelica solving by RK4 with step size of 10 ms, which can be easily exported as an Functional Mock-Up Unit (FMU). The spatial x and y dimensions for each grid cell hosting one cancer cell is 10×10 μm. The total spatial dimension of the system is a grid with a size of 60×20. This hybrid model shows the expected chemotaxis of the CXCR4+ (red color) cells, which move toward higher CXCL12 (purple color) concentration area, and CXCR7+ (blue color), CXCL12+ (green color) cells move randomly for a 24 hour period.

The co-simulator design for the DEVS-Suite and OpenModelica simulators is shown in Figure 1a. When the CCA-DEVS master simulation starts, the JavaFMI `Simulation` is instantiated and initialized by loading the generated CXCL12 FMU. During the execution, the FMU data inside the `Simulation` will be overwritten by the CCA-DEVS model; the data is provided by the secretion from each of the CXCL12+ agents). Then, the `doStep()` operation provided in the JavaFMI `Simulation` causes the RK4 solver to execute. Upon completing the FMU simulation steps, the output from CXCL12 FMU is read and used by the CCA-DEVS model via the `ModelicaModel`. This sequential procedure of writing and reading data in the master simulator repeats until the `Simulation` is stopped or terminated. The simulation result of the hybrid ligand and cancer cells are displayed together as shown in Figure 1b.



(a) DEVS-Suite simulator with JavaFMI and FMU

(b) Cancer cells and chemokine states at $t = 50$

Figure 1: Co-simulating CCA-DEVS & PDE models using DEVS-Suite and OpenModelica

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