Implementation of cellular transport models within a multiscale simulation software

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I. Extended Abstract

Agent-based models (ABM) have been increasingly employed to study dynamics of biological systems. However, these mostly lack transport mechanisms that interface between the agents and their microenvironment. We considered a set of 5 general transport mechanisms (see Fig. 1), written as ODE models and built on top of Fick's Second Law of Diffusion and R-MM kinetics, and their implementation within an ABM software. Unit testing of said models was performed on static, liposome-like agents. We also studied the effect of varying agent and microenvironment-related parameters on the dynamic. We then connected a few of these mechanisms to the agent phenotype, developing a toy example that emulates the experimental decreased tumorigenic growth dynamics of Cytochalasin β.

II. Introduction

Cell transport mechanisms are remarkably relevant for many biological system dynamics. At the same time, agent-based modeling (ABM) software employed for studying tissue and cell-level dynamics usually lacks said mechanisms. In light of this, we set to develop and implement a compendium of general transport systems within an open-source, physics and agent-based multiscale simulation software: PhysiCell [1].

III. Materials & Methods

All simulations have been carried with PhysiCell v1.9.1 (https://github.com/MathCancer/PhysiCell.git) [1]. Note that, as a multiscale simulation software, it works with three different timescales: The phenotype (6 *min*), the mechanics (0.1 *min*) and the diffusion timescale (0.01 *min*). For the development and implementation of the transport models, we will mostly work at the diffusion timescale. To obtain quantitative results of these dynamics, a small extension of *tools4physicell* (https://github.com/migp11/tools4physicell) was developed.

IV. Preliminary results & discussion

Model building. In order to generalize the different transport systems, we two common mechanisms: Diffusion and two-step enzymatic reactions. For this reason, all models will be built through tweaks and combinations of the simple diffusion and facilitated diffusion carriers.

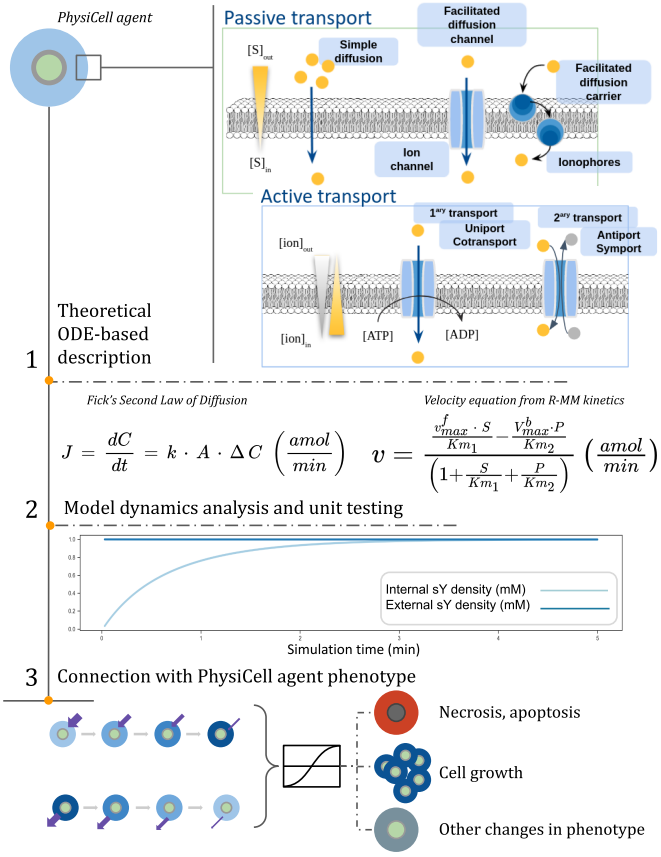

Fig. 1. Graphical abstract describing the employed workflow for the development and implementation of different transport mechanisms within PhysiCell. In point 1, R-MM refers to Reversible Michaelis-Menten kinetics.

Simple diffusion (SD) across the cell membrane is the simplest mechanism. Implementation is based on a small variation of Fick's Second Law of Diffusion, in order to align it with the space (μm) and time (*min*) of PhysiCell (see Point 2 of Fig. 1) by accounting for the permeability coefficient (k ($\frac{\mu}{min}$), the agent surface (A (μm^2)) and the concentration gradient (ΔC (mM)). Implementation within PhysiCell consisted in integrating the flux at each diffusion timestep (0.01 *min*) with additional biophysical constraints.

The second common mechanism is a facilitated diffusion carrier (FDC). Following a Reversible Michaelis-Menten (R-MM) kinetic, its rate laws can be employed to represent it as a system of four coupled ODEs. From these, and assuming

standard Quasi-Steady State and total substrate and receptor mass balance, we can obtain a relatively simpler velocity equation (See Point 2 of Fig. 1). Implementation consisted in assuming the substrate flux to be equal to the this equation, which was obtained through integration of the ODE system at each diffusion timestep.

Facilitated diffusion channel (FDCh) mechanisms can be understood as the flow of a substrate through a ”pore” in the cell membrane that opens or closes under certain conditions. For this reason, we implemented it as a step-function SD model. The channel has two states, Open (O) and Closed (C), and the cause of transitioning between these states is what differentiates the channel types. For Aquaporin-like channels, the condition that determines the state of the channel is just stochastic, obtaining a value from a N(1,1) distribution to compute the amount of Open channels. For Ligand-gated channels, they are considered to be open if there is some Ligand (L) attached to the receptor (R). This amount of RL complex is computed following a Receptor-Ligand kinetic model, implemented as a three coupled-ODE system.

Primary active transport model (PA) was implemented as system of two coupled mechanisms: An independent ATP-ADP exchange system and a carrier enzyme with an FCD-like mechanism, transporting a substrate against gradient each time an ATP is hydrolyzed. Simialrly, the Secondary active (SA) transport model, was built like two coupled FCD-like mechanisms, where one of them moves a substrate along gradient, and the other one moves another substrate against gradient. Here, the coupling is through the equivalence of the pumping rate of a substrate to the passive entry rate of the along-gradient substrate.

***In silico* experiments** Assessment of transport dynamics was carried through two experiments: Experiment A, in which the simulation consisted of agents devoid of substrate, and a microenvironment with certain substrate density (see Point 3 of Fig. 1); And experiment B, where we have the opposite scenario. These experiments were carried with sets of static, liposome-like agents in a closed system, without changes in phenotype, cell cycle nor cell death. This was done in order to avoid seeing dynamics not directly obtained from the transport model.

For the SD model, in both Experiments A and B, both densities inside and outside the agent reached equilibrium following a logarithmic curve while maintaining net balance of the total amount of substrate. This was observed for a wide range of k values (10^{-4} to 1000 $\frac{\mu m}{min}$), indicating that this model allows for simulation of a wide variety of different types of substrate types (see Table 1 from [3]). Identically, for the FDC model, for both Experiments A and B, the same equilibrium-reaching dynamic was seen, and mass balance of both substrate and receptor were maintained.

We explored variations of different parameters of the simulation to assess the effect on the dynamic. For both SD and FDC models, and in both experiments, increasing cell number resulted in a faster equilibrium at a lower concentration, and increasing cell volume resulted om a slower equilibrium, lower concentration. This is explained given that the SD model accounts for the surface, which increases quadratically with the volume.

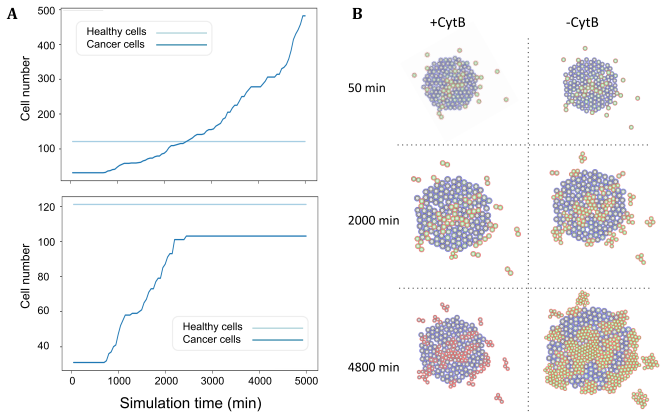

Fig. 2. Blocking of Glucose transport by addition of *Cyt*β at 2500 min. Glucose enters the cells through a FCD mechanism, as a GLUT transporter. *Cyt*β enters agents through an SD model. Both cell types show heterogeneity in the initial amount of receptors per agent, although the cancerous cells contain twice as many receptors [2]. (A) Healthy cell count is constant, as these were set to not divide. (B) PhysiCell output screenshots for both experiments. Red-outlined cells are cancerous cells. Blue-colored cells are healthy cells. Green-coloured cytoplasm indicates levels of Glucose inside the agent.

Next, we set to emulate the dynamics of adding Cytochalasin β (*Cyt*β) (Fig. 2). a mycotoxic compound commonly employed to treat cancer by inhibition of GLUT transporters [2], which have an FDC-like mechanism. As expected, cancerous cells divide faster due to the increased amount of GLUT transporters, but addition of *Cyt*β shows a decrease in growth due to the ”blocking” of the channels (Fig. 2.A, lower panel), as observed experimentally [4].

Note that the efforts of this work are directed towards fitting said models with specific cell-line pharmacokinetic data in order to represent more realistic behaviours, which is notably valuable in the context of personalized medicine treatment research.

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Othmane Hayoun received his BSc degree in Biotechnology from Universitat de València, Spain in 2020. Now he is carrying his MSc degree in Bioinformatics for Health Sciences (Universitat Pompeu Fabra, Spain), and is doing his MSc Thesis at the Computational Biology group of the Barcelona Supercomputing Center (BSC).