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A cell-based simulation software for multi-cellular systems

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ABSTRACT

CellSys is a modular software tool for efficient off-lattice simulation of growth and organization processes in multi-cellular systems in 2D and 3D. It implements an agent-based model that approximates cells as isotropic, elastic and adhesive objects. Cell migration is modeled by an equation of motion for each cell. The software includes many modules specifically tailored to support the simulation and analysis of virtual tissues including real-time 3D visualization and VRML 2.0 support. All cell and environment parameters can be independently varied which facilitates species specific simulations and allows for detailed analyses of growth dynamics and links between cellular and multi-cellular phenotypes.

Availability: CellSys is freely available for non-commercial use at http://msysbio.com/software/cellsys. The current version of CellSys permits the simulation of growing monolayer cultures and avascular tumor spheroids in liquid environment. Further functionality will be made available ongoing with published papers.

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1 INTRODUCTION

Based on the insight that multi-cellular systems are inherently of multi-scale nature, the focus of research in systems biology is currently shifting towards studies of whole cells or populations of cells to complement sequence analysis (Yu *et al*., 2002), gene expression profiles (Missal *et al*., 2006), research on signal transduction pathways (Swameye *et al*., 2003) and the analysis of biochemical systems (Calzone *et al*., 2006). Realistic multi-cellular approaches should permit both, to include models of sub-cellular processes and to simulate up to biologically or clinically relevant population sizes. For many years, this was hampered by the inherent computational complexity. However, depending on the level of represented detail the steadily increasing computational power of modern processors (CPUs and GPUs) today permits the simulation of up to several millions of cells by agent-based models (Anderson *et al*., 2007; Drasdo *et al*., 2007 and refs. therein) provided an efficient implementation especially in three dimensions.

Here we present an adaptable software tool (named CellSys) that implements a class of lattice-free agent-based models permitting realistic simulations of tissue growth and organization processes of common experimental settings *in vitro*, as the growth dynamics in monolayer cultures and multi-cellular spheroids (Drasdo and Hoehme, 2005). It has further recently been used to model liver regeneration (Hoehme *et al*., 2007, 2010). Therein, the simulation results from CellSys have been directly and quantitatively compared to experimental data, using the same analysis methods for both. CellSys can be used to predict the experiments that are most informative to identify possible mechanisms on the cell and sub-cell scale to explain a certain multi-cellular phenomenon. It also has proved useful to guide the development of continuous models where cells are not resolved individually but are represented by locally averaged quantities: Comparing both model types permits identification of terms and parameters (Byrne and Drasdo, 2009).

2 SIMULATION MODEL

Each individual cell is modeled by an isotropic, elastic and adhesive sphere capable of migration, growth and division. Cell–cell and cell–matrix interaction are mimicked by the experimentally validated (Chu *et al*., 2005) Johnson–Kendall–Roberts (JKR) model that summarizes deformation, compression and adhesion forces, and displays hysteresis if cells move close to or away from one another. Model cells are parameterized by the Young modulus, the Poisson ratio, the density of membrane receptors responsible for cell–cell and cell–substrate adhesion and by its (intrinsic) radius. Proliferating cells double volume and deform into dumb-bells after a given number of time steps before splitting into two daughter cells. By assuming that inertia terms can be neglected, cell migration is modeled by an (Langevin-) equation of motion for each cell center summarizing all JKR-forces on that cell, the friction-forces with substrate or extracellular matrix as well as with other cells (parameterized by friction coefficients), and optionally a random force term. The latter mimics cell micro-motility and is quantified by the cell diffusion constant. We solve the equation for diffusion and consumption of nutrients, growth factors, etc. on a lattice using the Euler forward method while fulfilling the Courant–Friedrichs–Lewy condition (Drasdo and Hoehme, 2005) [for further details, see Supplementary Material (Section 3)]. CellSys also supports the modeling of dynamically varying cell parameters and different cell types as demonstrated for growing cell populations in tissue like environments (submitted for publication). Since the model is completely parameterized in terms of measurable quantities, intracellular control modules can readily be integrated within CellSys by direct coupling the molecular concentrations of intracellular chemicals to the cell-level parameters (Ramis-Conde *et al*., 2008, 2009). Most recently, we used CellSys to predict a so far unknown mechanism in liver regeneration after toxic damage that could be subsequently validated experimentally (Hoehme *et al*., 2007, 2010).

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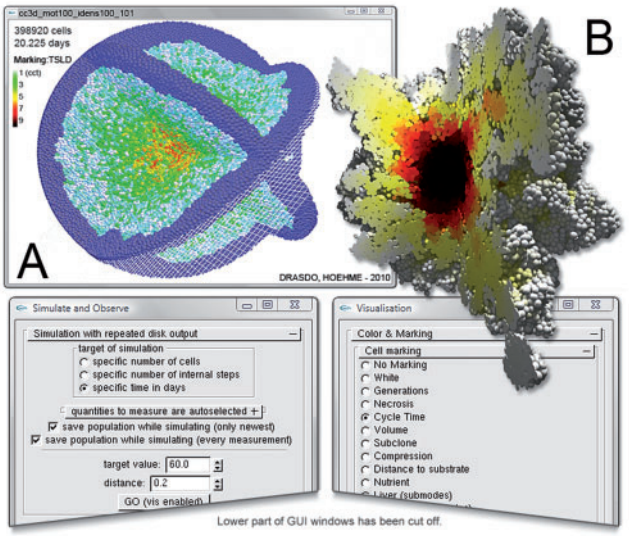

Fig. 1. (**A**) User interface of CellSys integrating real-time 3D visualization (upper window) and facilitating the parameterization, observation and visualization of model simulations (two exemplary windows are shown). (**B**) Simulated multi-cellular tumor grown in an environment of nutrient shortage. The image was created using the ray tracer interface of CellSys.

3 SOFTWARE

CellSys is a software tool that efficiently integrates modeling, simulation, observation and visualization functionality for individual-cell (agent)-based models. It is implemented in portable object-oriented ANSI C++ and thus binaries are available for many operating systems including all recent Windows and Linux variants. A graphical user interface (GUI) that provides real-time visualization of models in 3D based on OpenGL (Fig. 1A) also serves to access the functionality of the software. CellSys is organized in encapsulated modules that lay the foundation for its extensibility and maintainability. Currently, it consists of the following main components: (i) basic classes formulating the major abstractions such as model cells or finite grid elements; (ii) a collection of core algorithms implementing model variants for cellular behavior such as cell-migration or cell-cycle-control; (iii) algorithms for modeling the cellular environment; (iv) modules for observing; and (v) visualizing properties of the cell population and its environment. During the model simulations, CellSys currently automatically permits taking over 60 different observables. Additionally, CellSys is able to output scene descriptions for example in VRML 2.0 or in the script language used in the popular open-source ray tracer PovRay (povray.org) (Fig. 1B). We use the libraries zlib (zlib.net) and libtiff (libtiff.org) to save screenshots, videos and zip-compressed model states in predefined intervals.

The cross-platform GUI is based on the GLUI library (glui.sourceforge.net) and is used to change parameter settings and control the software components (1–5). It allows users to interactively explore model states and, e.g. mark specific properties of cells and their environment. Thereby scalar properties are often mapped to RGB-color vectors as illustrated in Figure 1 and vector-based properties are visualized using 2D or 3D vector fields.

The core algorithms in CellSys are parallelized using OpenMP (openmp.org) to exploit the computational power of modern shared memory multi-core multi-processor machines. The solution of the stochastic equations of motion (Langevin) is supported by the multithreaded version of SuperLU for shared-memory parallel machines (crd.lbl.gov/~xiaoye/SuperLU). We find the solution of the equations of motion and the neighbor detection to be the major performance bottlenecks of lattice-free individual-cell-based models. On an Intel Core Duo E8500 system with 8 GB RAM a typical simulation from 1 to 10^5 cells e.g. takes 44 h (2D, 1 core), 125 h (3D, 1 core) or 41 h (3D, 4 cores). However, runtimes greatly depend on parameter and algorithm choices. For a more detailed introduction refer to the Supplementary Material.

4 SUMMARY/OUTLOOK

CellSys offers a robust and efficient implementation of a lattice-free individual-cell-based model that is parameterized by experimentally measurable quantities. The current version allows the *in silico* simulation and analysis of widespread experimental settings in 2D and 3D such as monolayer cultures and multi-cellular tumor spheroids. Specific cell lines and culturing settings can be mimicked by changing parameters accordingly. The results of model simulations can be visualized by a wide variety of virtual stainings and are quantified by many observables. The modular, object-oriented structure of the software permits extensions like the modeling of the surrounding tissue or vascular networks that will be made available in future versions of CellSys.

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