

TSim, a Platform for Simulation of Multi-cellular Systems

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The simulation of intra-cellular processes such as metabolic networks or gene expression control mechanisms has been widely covered in many tools available today^{1,2} however the simulation of multiple cells interacting in a common environment such as tissues is not yet fully available.

TSim (Tissue Simulator) was initially developed for the study of early growth of tumours inspired on works previously done in the area³ but unlike these studies, the simulation process in TSim happens both inside and outside the cells.

TSim works with a grid of slots that can represent empty spaces, blood vessels, cells of different kinds and other representations yet to be imagined. Each of these slots contains a state vector that defines both the type of the entity represented by the slot and the properties of these entities. For instance, for the simulation of tumour growth the state vector variables used were pH, pO₂ and Glucose concentration in the extra-cellular environment as in literature. However in order to test the response of the cells to hypoxia and compare the efficiency of anaerobic versus aerobic glycolysis, this model was extended to include part of glycolytic kinetic equations available from other

studies⁴.

Future developments of TSim should include support to SBML as well as multi-processing for quicker simulation of bigger systems. Beta versions of Tsim can be downloaded at no charges at <http://www.i-genics.com>.

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Major Features

TSim can be used for both design and simulation of biological systems. The design process begins by choosing the dimensions of the simulated system (height, width and depth).

The model can be seen either in 3 dimensions or in 2 dimensions through slice views.

Both the 2D and 3D views can be configured to display either the simulated entities (cells of different types, blood vessels, empty space, etc.) or the concentration of the species in the system, such as pH, pO₂, Glucose, etc.

The model is divided into spaces named “slots”. Each slot can be edited in order to comply with the desired model properties, meaning that not only the user can choose if a specific slot will represent a cell but also it can specify the concentrations of the metabolites within this cell as well as the kinetic properties of its enzymes.

Once the model is complete, it is saved in a file for future use.

There are two types of files: the first is has the extension “.sfr” and contains the information of a model; the second has the extension “.sfl” and contains the result of the simulation of one model.

One model can be simulated in the simulation screen of TSim and stored in a file.

This file can then be read by TSim and displayed in real-time the progress of the

simulation.

As an alternative, the user might use the Chart View that will draw a graph of the concentration of metabolites and other species during the simulation.

The Chart View allows customized zooming in the charts as well as allows exporting the graphs and saving them as JPEG pictures.

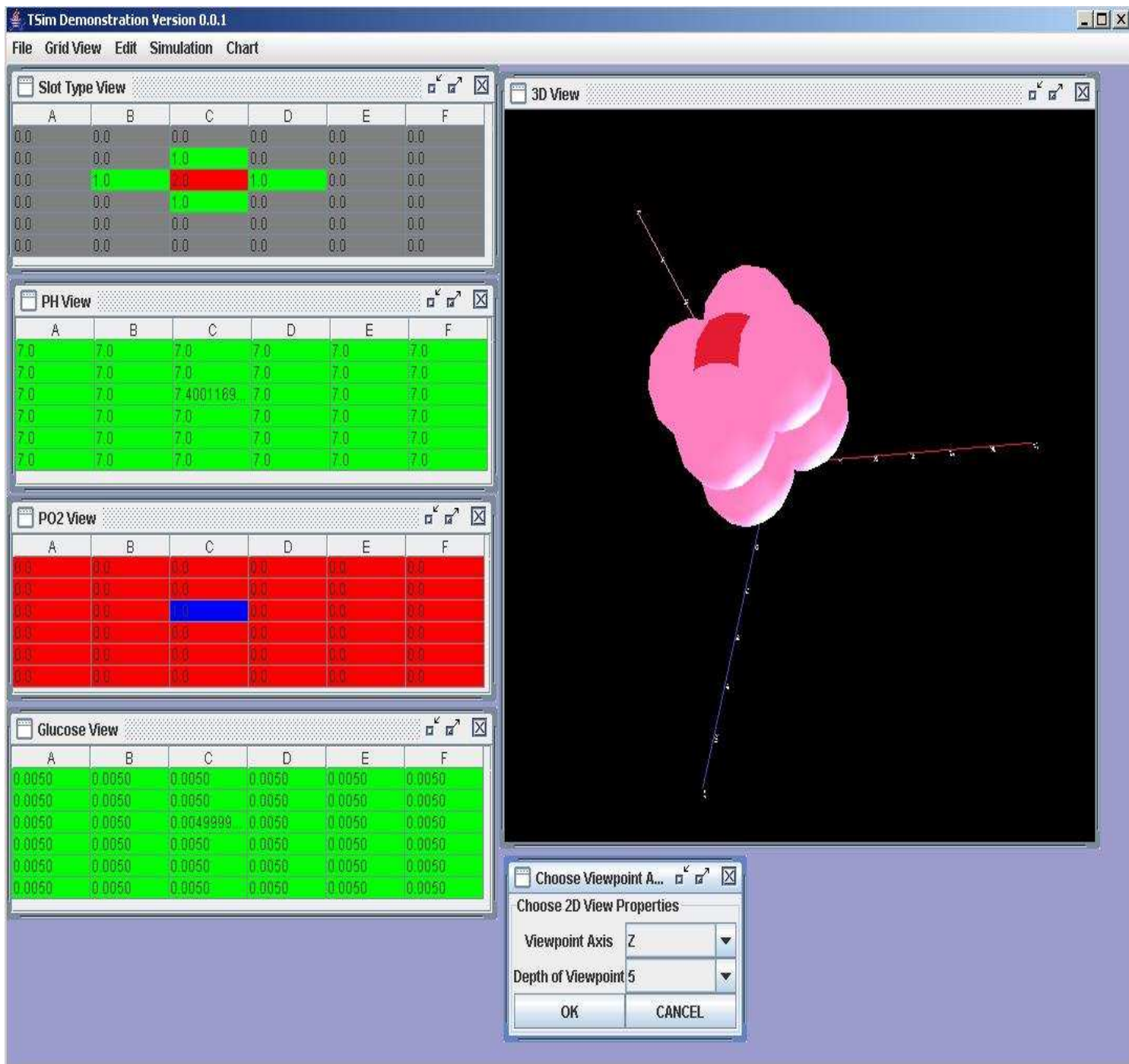


Figure 1: Main screen of TSim displaying on the left the 2D views showing the concentration of glucose as well as pH and pO₂ while on the right a 3D view of the model can be seen

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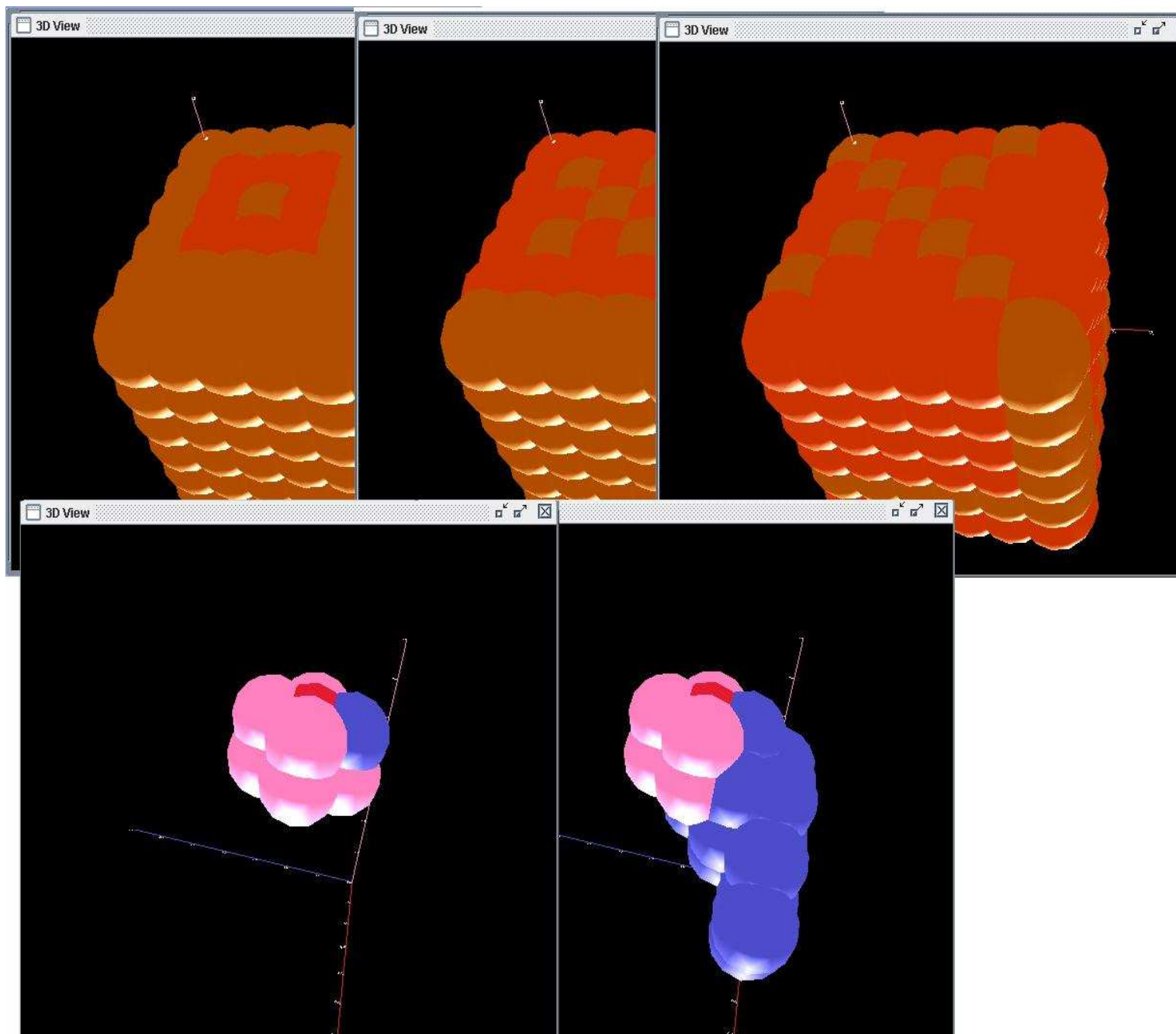


Figure 2: The 3D view of TSim allows real-time follow-up of the simulations. The user can either choose to observe the variations of species concentrations or watch the progress of cell duplication and death.

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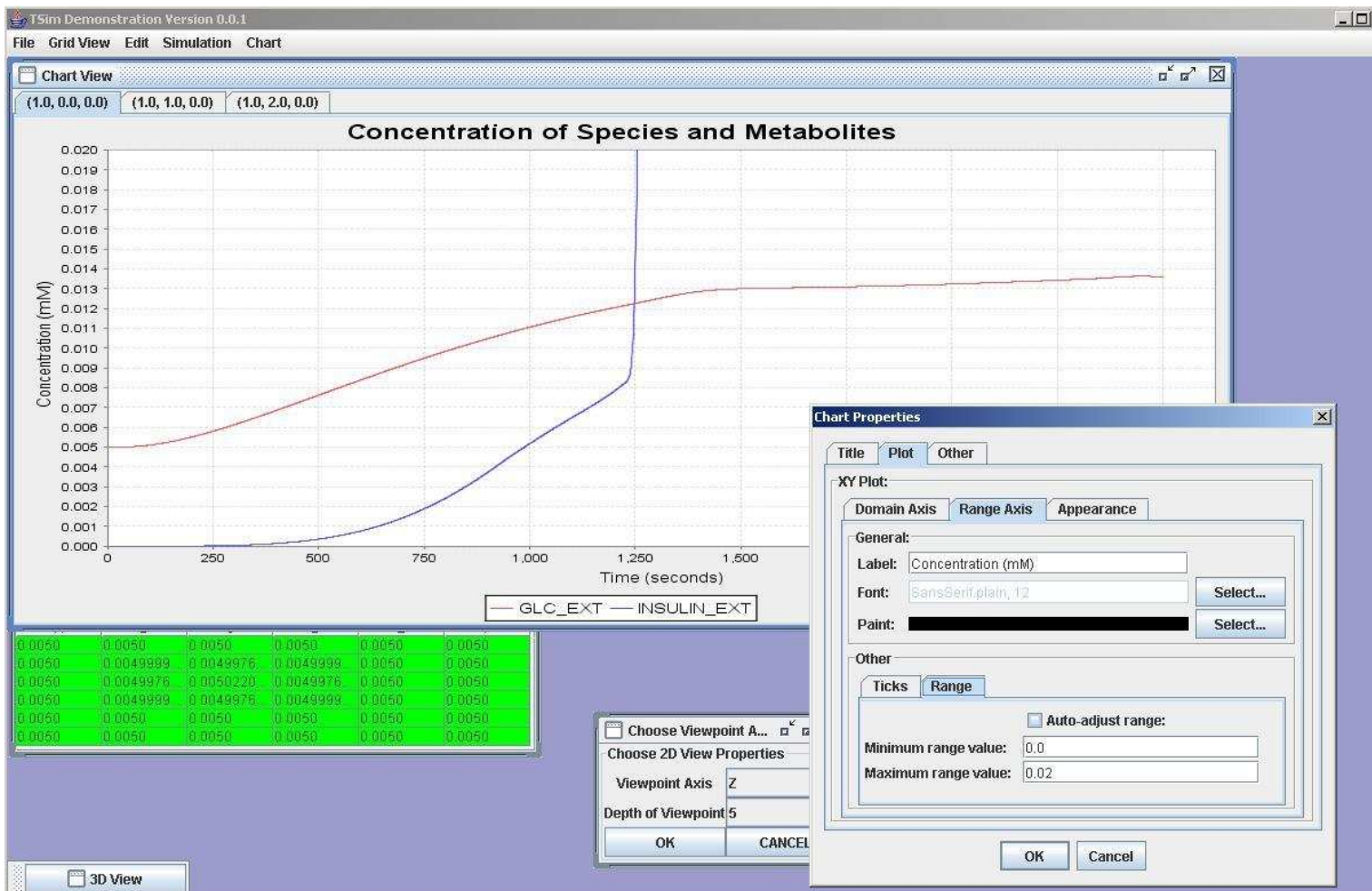


Figure 3: The Chart View of TSim displays the concentrations of the species in a time-dependent graph. The user might choose to zoom-in or zoom-out in part of the graph, modify its default fonts and colors as well as exporting it to a JPEG picture.

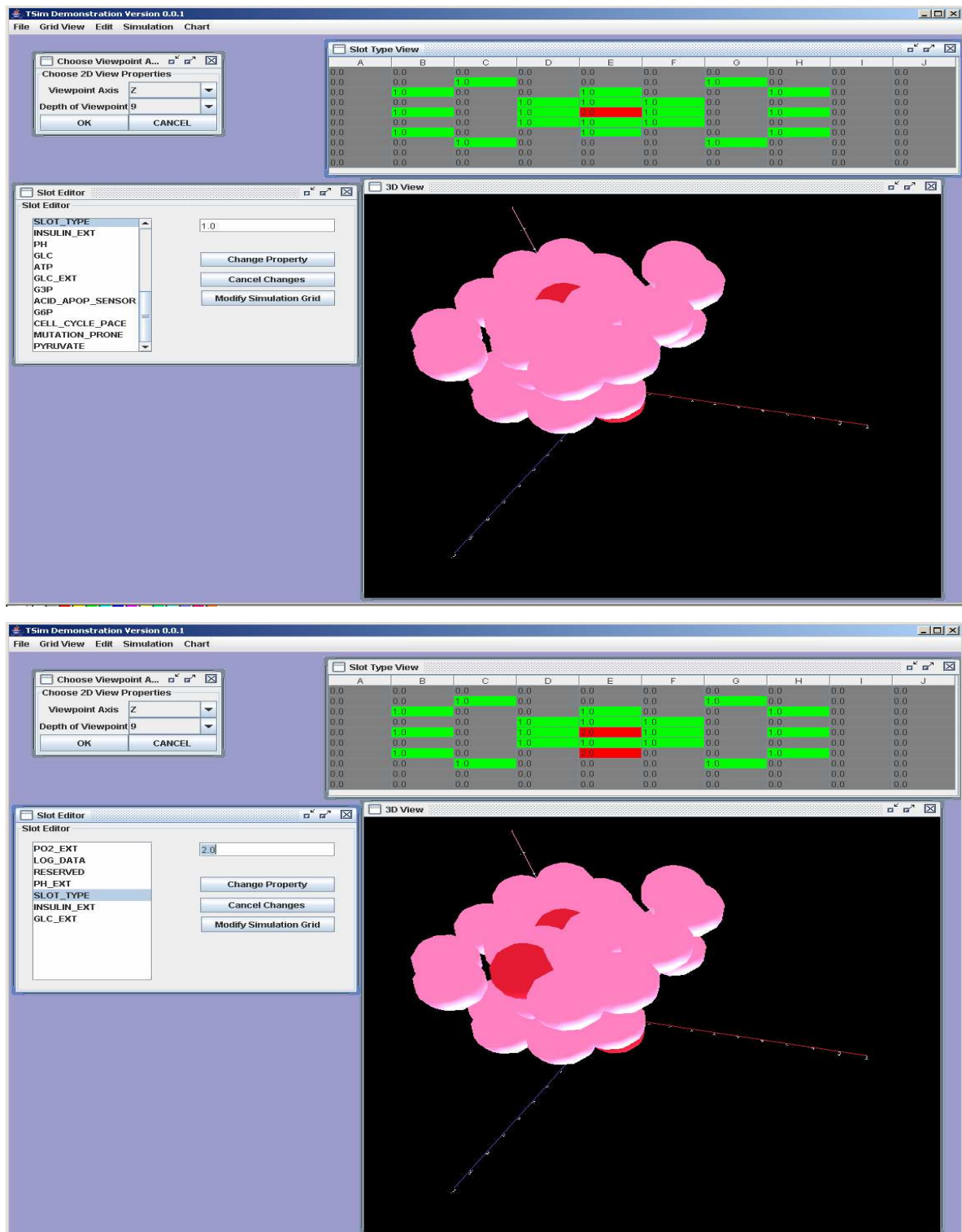


Figure 4: The user can modify its model and watch the result as he works. One can add new cells, remove the existing ones and change their properties.

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Current status and next steps:

TSim is in its first demonstration version that was used to simulate a tumour growth model and the insulin-secretory behaviour of pancreatic Beta-cells in Langerhans islets.

These two models will be presented as posters in ICSB 2006 under the titles of “Study of Early Tumour Development and its Glycolytic Properties” and “Study of Dependency of Synchronization of Beta-cells Insulin Secretion on Size of Langerhans Islets” respectively and will be available for download at www.i-genics.com briefly.

The next steps towards a release version of TSim are:

- Support of SBML in order to allow exchange of models with other tools;
- Increase in performance in order to allow bigger models as well as faster simulation and calculation time;
- Major improvements in user interface in order to make the software more user-friendly;

Implementation:

TSim is coded in Java and is fully compliant with Java1.5 release.

It uses one library that is not provided with the package but can be freely downloaded at JfreeChart website

<http://www.jfree.org/jfreechart/>.

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TSim runs in Windows, Linux and Solaris Operating Systems.

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2. Kitano, H et al. Next generation simulation tools: the Systems Biology Workbench and BioSPICE integration. *OMICS* **7** (4), 355-72 (2003)
3. Robert A. Gatenby et al. A Cellular Automaton Model of Early Tumor Growth and invasion: The Effects of Native Tissue Vascularity and Increased Anaerobic Tumor Metabolism. *Journal of Theoretical Biology* **213** (3), 315-331 (2001).
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