Virtual Cell Quick Start Guide

Requirements:

Java (version 1.5.x or later: 1.5 recommended)
For Mac, G5 or Intel processor is required for full support.
An Internet connection (broadband, no firewall recommended).

Go to http://www.vcell.org/

Click the link to VCell Software

Click on one of the 2 links to Run VCell as an application:

Java Webstart Application

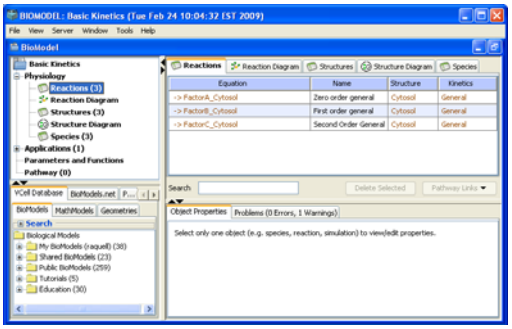
The software will download, give the option to install a local shortcut and start automatically

Tip: Whenever you launch VCell from the local shortcut and are connected to the Internet, it will automatically check for and download any updated version.

Tip: You can run the local VCell application without an Internet connection and without logging in to the model database; in this case, however, you will only be able to save your work by using File > Export, and you will not be able to run simulations and view results until logged in.

Navigation through VCell Modeling Framework

The Virtual Cell opens with four panels. The upper left panel of VCell provides navigation links to different steps of the VCell modeling process which become active in the top right panel. The multiple views for browsing, creating and editing elements of the model Physiology (Structures, Species and Reactions), Applications (Geometry, Specifications, Protocols, Fitting) Parameters, and any imported Pathways.



Tip: For example, species can be specified and edited in both Structure and Reaction Diagram views. Clicking on Species leads to the list of all species in the model.

Tip: Select any element in the top right panel and you can view/edit its Object Properties in the bottom right panel. The "Search" field provides an easy way to find any specific item in what might be a long list, e.g. 10's to 100's parameters or reactions.

The bottom left panel provides an easy way to open models stored in VCell databases, BioModels.net database, as well as to search Pathway Commons for pathways that can be brought into the VCell.

Start from an existing model:

Existing VCell Model

Go to the bottom left navigation bar, or Choose File > Open > BioModel, to access model databases. Click on and open a public or shared BioModel from "Shared Models" (organized in folders by user names), "Education" (associated with classes and teaching resources) or Tutorials (created to introduce users to VCell). Save your private copy of it: use File > SaveAs and pick a new name for your copy of the BioModel.

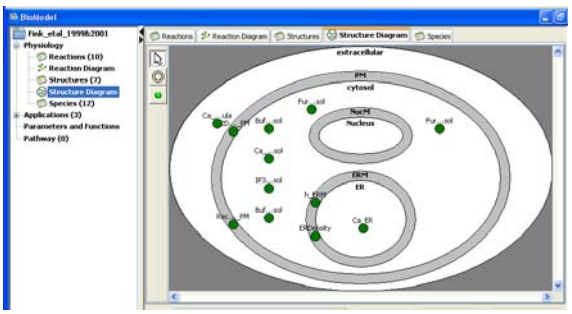
Importing an existing model from other modeling software

First export and save the model from that software into SBML.
In VCell, choose File > Import to import the corresponding file; the import will create a new BioModel from the imported data.

Creating a New VCell Model:

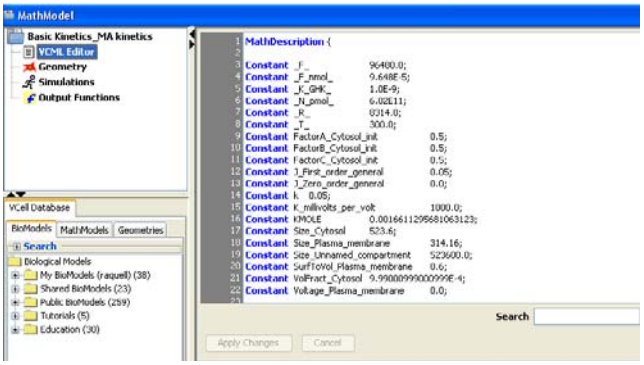
VCell primary documents are the BioModel, MathModel, which each contains Applications and Geometry.

BioModel



Consists of the "Physiology" (conceptual representation of the model: structures, molecules, connectivity map, kinetics) and one or more "Applications" (virtual experiments that can be simulated: initial conditions, actual morphologies, electrical protocols, etc.). An Application can be compartmental or it can use a Geometry (see below). It has a mathematical representation that is automatically generated and can be viewed under the Simulation tab in Applications. For each

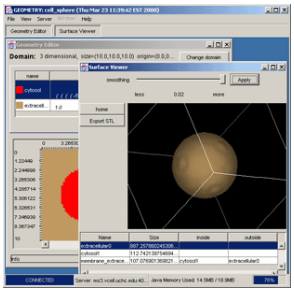
"Application" you can specify one or more "Simulations" (time length, resolution, solvers to use, parameter overrides, etc.) that will run and produce Results. Results can be viewed in VCell or exported to a variety of formats.



MathModel

Is a direct specification of the equations to be solved, using the VCell modeling language. It can be compartmental or it can use a spatial Geometry. One or more Simulations must be defined for each MathModel to run and produce Results.

Tip: Familiarize yourself with VCell by working with BioModels; you can always use the math from a BioModel Application as a valid starting point for a MathModel, but you cannot use math from MathModels in BioModels. Use MathModels only if you are familiar with the VCell math language and if you encounter a specific limitation of BioModels that can be overcome by the use of MathModels.



Geometry

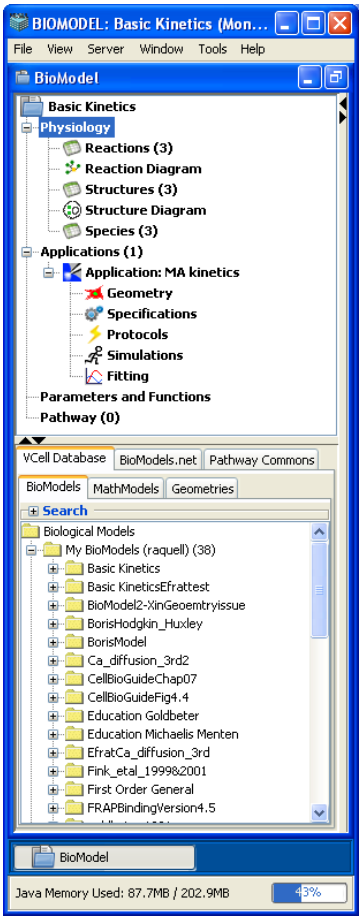
Is a representation of a spatial structure which a BioModel Application (or a MathModel) can use for spatially resolved simulations. It can be 1-D, 2-D, or 3-D, and either analytically defined or based on a digital image.

Create/edit a BioModel:

An "empty" BioModel is created when VCell starts; at any time you can create a new BioModel by selecting File >New > BioModel.

The general workflow when using a BioModel is:

- create the Physiology
  - Species, reactions, structures
- create one or more Applications
  - Geometry, Specifications, Protocols, Simulations
- create one or more Simulations for each Application
  - Methods (solvers), time, output variables
- run Simulations
- view Results
  - ⇒ (optionally) export Results
- keep expanding and modifying your BioModel



BioModels are saved in a database.

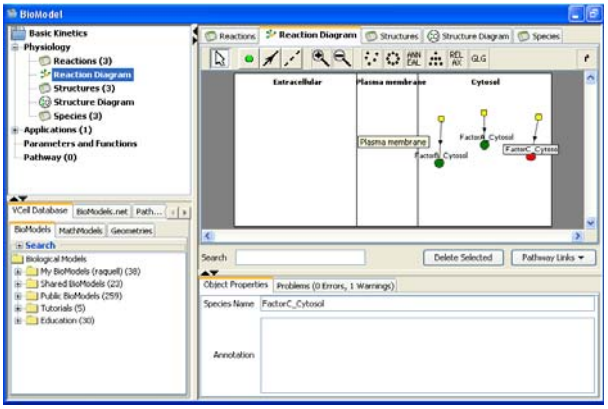
By default, all newly created BioModels are private. Right click BioModels via the set of database resources in the main window or use the Database Manager (File > Manage database) to make any of your models public (accessible to all users) or shared (accessible to one or more specific users). Public or shared access is read-only; only the owner can modify or delete items and other users must save their private copy to make changes.

Tip: A BioModel must be internally consistent and saved to the database whenever you want to run Simulations. This is done automatically, but you will be prompted to take action in one of three cases: (i) the BioModel was never saved before – you will be prompted to provide a name, (ii) when there are inconsistencies that prevent successful math generation – you will be presented a (hopefully) understandable error message, or (iii) when saving will overwrite existing Simulation Results due to upstream changes to the BioModel (and not due just to direct changes to a Simulation) – you will be given the choice to overwrite, save a new edition of the BioModel, or save the BioModel under a new name.

Tip: When making changes upstream they automatically propagate downstream. For example, creating a new compartment in the Physiology will propagate to all Applications and spatial Applications will need to have the extra compartment mapped to the Geometry. For another example, setting a molecular concentration as fixed in an Application will remove it from the list of variables from all Simulations of that Application. A consequence is that if you already have simulation results, often some (or all) become invalidated by changes and must be re-run. It is important to keep in mind the tree-like hierarchy of the BioModel (Physiology > Applications > Simulations) to understand VCell behavior during saves and the effects of editing at various levels.

Working with the Physiology:

Select Physiology or its subdirectories in the Navigation tree to access the Reaction, Structure and Species tabs. Use Structure views to add compartments and membranes; Species to populate compartments and membranes with molecular species (molecules, complexes, or states thereof); Reactions to create reactions or fluxes. Two views are provided for Reactions and Structures. One view allows entry and edit reactions or structures via text based tables, while the Diagram view provides icons for schematic generation of model features and components.



Tip: All items in the Physiology window and reaction editor have context menus that pop up on right mouse button click.

Tip: You can open more than one BioModel at a time

Tip: You can search the database for molecules and reactions already defined in all of your models and models of other users accessible to you (public or shared with you). You can also search public databases via the Pathway Commons for reactions that can be automatically inserted into the Physiology

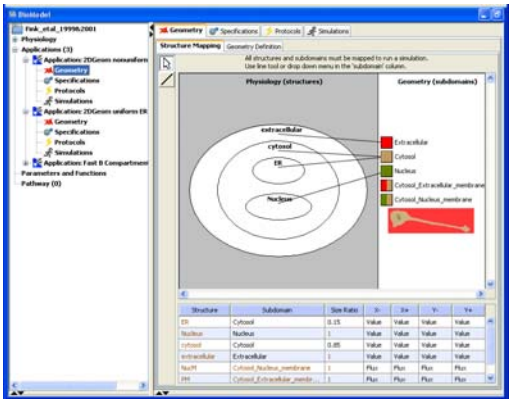
Working with Applications:

Select Application in the Navigation tree to create new Applications. Right click the Application folder or use the local pull-down menu to select Deterministic or Stochastic Application. By default, every new Deterministic and Stochastic Application is compartmental (i.e., every compartment is treated as homogenous and without spatial information, and are all mapped to a standard "0-D Geometry")

Tip: Compartmental Applications require proper specifications under Structure Mapping of the surface and volumes of compartments (e.g. a spherical cell with a 10 micron diameter is 523.33 micrometers cubed).

Tip: Even if your primary goal is to create spatial Applications, compartmental Applications are often a useful starting point to find or verify parameters for a stable initial state of the system.

To make an Application spatial, select Geometry Folder in the directory, click "Create New Geometry" button and create Analytical Geometries, Import New or Open Existing geometries.

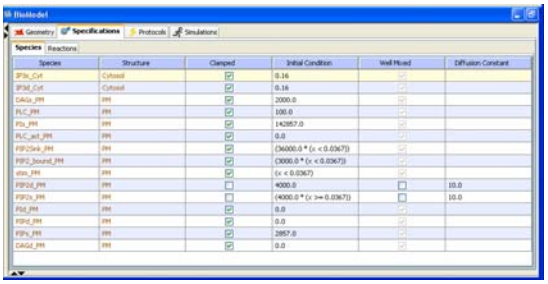


Tip: Spatial Geometries must be created, edited, and saved in the context of a Bio or MathModel.

Tip: Structure Mapping in spatial Applications is always done manually. Map every compartment in your Physiology to a domain (region) in the Geometry and every region must have at least one compartment mapped to it. A child compartment can be mapped to the same region as its parent (unresolved, "distributed").

Tip: Always use the surface viewer to inspect 3-D Geometries, especially ones derived from image stacks; there might be more regions then you think there are, and regions might have illegal common boundaries in places you weren't aware of.

Complete the specifications of the model by working on each directory folder in the Application window before moving to the Simulation tab. You can specify boundary conditions, initial concentrations, enable/disable reactions, set up protocols for events and electrophysiology. Many defaults are OK, but many may not be.



Tip: Do not forget diffusion constants for spatial applications. They default to zero for each molecular species, which may be appropriate for some, but is always illegal when a molecule is involved in a membrane flux.

Tip: You can specify uneven initial concentrations in spatial Applications by using an expression involving x, y, and z coordinates.

Tip: You can specify use of an equilibrium approximation for a reaction by checking the "Fast" checkbox.

Invoke the Math View for each Application by pressing the "Generated Math" tab under the Simulation view. Math is regenerated automatically for each Application whenever the BioModel is being saved (manually, or automatically when running Simulations).

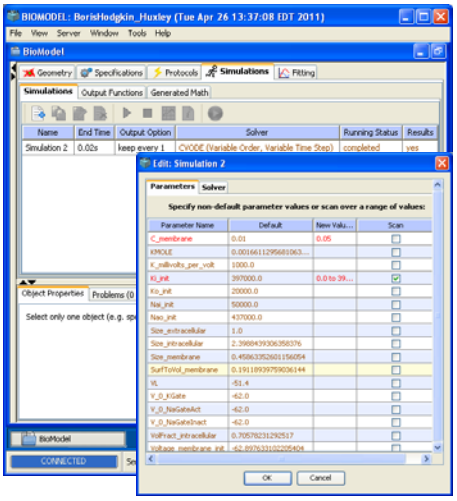
Tip: Before using the Simulations tab, if you have made changes to the Application (or to the Physiology), you should manually regenerate the math of that Application by pressing the "Update Math button". This way, all (existing or new) Simulation specifications will be consistent with the current state of your Application.

Use the Simulations tab to create, edit, and run Simulations and view Results.

Working with Simulations:

Create and manipulate Simulations using the icons to Add, Copy, Edit, Run, get Info, access Results or Quick Run (without saving). When creating new Simulations, always check whether the defaults are appropriate for time, solver, and mesh (applicable in spatial models).

Tip: Use the Ctrl and Shift keys to select multiple Simulations in the list for copying, deleting, running, and viewing Results.
Tip: Timestep is very important for spatial Simulations – if it is too big, the solver will fail, if it is too small, it may take too long to run.
Tip: It is rarely practical or useful to save more then 100 timepoints for spatial Simulations or more then 1000 for compartmental ones.
Tip: When spatial simulations run slowly, first experiment with coarse meshes.
Tip: For compartmental applications, try the CVODE solver when stiffness and numerical instability are an issue.
Tip: For large compartmental models, try the Quick Run option to get quick results without saving the model to the database. Remember to save your model to the database afterwards.

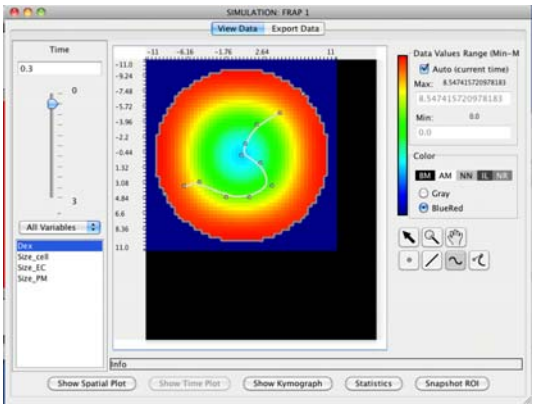


Use the "Parameter" tab in the edit simulation window to create Simulations with specific parameter values being overridden.

Tip: Parameter Scan allows you to run simulations in which one or more parameters vary according to a specified list or range of values.

Simulation Results can be viewed in a separate window invoked by clicking on the "Results" icon.

Tip: Results can be viewed while a Simulation is still running; the data displayed will update automatically at the same time with the Simulation status.
Tip: Line plot windows can display more then one variable at a time – use the Ctrl or Shift keys to select multiple variables for the Y axis.
Tip: When viewing spatial data, use the point and line tools to mark the display area and fetch spatial or time data for the selections; time plots and kymographs are often very useful but can take some time to be displayed on very large datasets.
Tip: You can download data from Simulation Results in a variety of formats from the "Export" tab of Results windows.
Tip: When exporting spatial data into movie formats, you can display more than one variable in the same movie by selecting the "overlay" checkbox option.
Tip: The NRRD format supports export of full spatial datasets including for 3-D simulations (values for all variables at all time points and at all points in space).
Tip: Line plot windows have a button to display tabular values that can be copied and pasted directly into other applications such as a spreadsheet.



Export and Import:

Use File > Export or File > Import to export and import BioModels to and from local files.

Tip: We support several XML formats. VCML is our native format. SBML is used for interoperability with other modeling and simulation software and may not support all features of your BioModel.
Tip: MatLab format supports math export from compartmental Applications.
Tip: Select PDF format to generate a printable description of the BioModel

You can export simulation results from the Results window as described above including as Quick Time movies..
You can export surface information for Geometries in STL and AVS formats from the Geometry editor.
You can export Physiology cartoons in GIF format from local pop-up menus.

Model Storage

The database supports multiple editions of documents. When a document is being saved without changing its name, there are two possibilities: the new document can replace the existing saved version of the document, or, alternatively, a new edition can be saved under the same name (all editions and can be later opened separately and/or compared). By default all saved entries are private, but the owner can use 'Permissions..." functions under the File menu to make them public or accessible to one or more other VCell users. Public and shared access is read-only, users can only change their own copies of VCell documents.

University of Connecticut Health Center, National Resource for Cell Analysis and Modeling, 263 Farmington Avenue, Farmington, CT 06030 Tele: 860-679-1452; Fax 860-679-1039; Email: VCell@uchc.edu; URL: www.vcell.org
April, 2010.