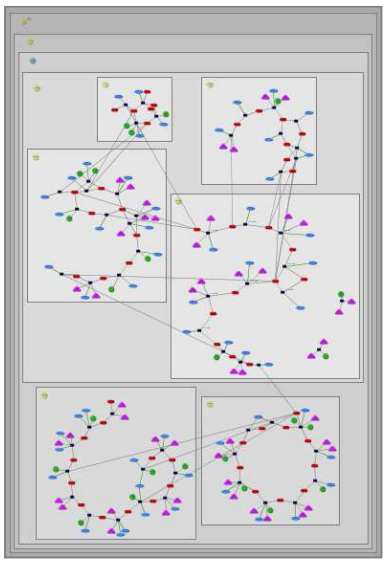
TeraSim Overview



Teranode design tools allow scientists to represent, annotate, and share information about biological systems and experiments through clear visual models. As larger, cross-disciplinary teams are assembled, they require a tool that enables them to model biological pathways, design mathematical-based experiments, and analyze large and diverse data sets.

TeraSim is a solution for *in silico* biological modeling that provides scientists with a visual environment for data and information management combined with dynamic analysis and simulation. Scientists can use TeraSim to visually represent hypotheses in the context of internal and external information sources, and to predict dynamic system behaviors in the context of experimental outcomes, all without in-depth knowledge of computer programming and computational sciences. TeraSim also provides an open plug-in architecture that allows computational biologists and informaticists to add custom visualization techniques, analysis methods, and simulation methodologies without reinventing standard components of software applications.

Whether you want to design a simple pathway or draft a complete mathematical representation of an organism with simulation ability, TeraSim is where to start.

Key Features

- Rich graphical pathway editor enables rapid qualitative modeling of biochemical pathways across any discipline, and across different time and spatial scales.
- Automatic continuous translation of visual pathway designs into mathematical models for interactive computer simulations.
- Extensive predictive capabilities, including deterministic kinetics using differential equations, stochastic simulations based on random processes, and steady-state flux-balance analysis.
- Powerful analysis capabilities, including interactive simulation control and visualization, optimization, Monte Carlo analysis, and sensitivity analysis.
- Seamless integration with Teranode's laboratory process design product for extended capabilities.

Application Areas

- **Cell Signaling:** qualitative modeling of cell signaling pathways to analyze data on specific biochemical reactions.
- **Electrophysiology:** ion channel behavior, where the energy barriers between ionic binding sites in the channel are used to calculate rate constants for state transitions of the channel.
- **Cardiology:** neuronal or cardiac action potentials created by integrating the currents through many different channels and pumps, in the context of a whole cell.
- **Metabolism:** steady-state concentrations of metabolites and fluxes through metabolic enzymes predict the effect of gene knockouts and changes in cell growth.
- **Biotransport and Pharmacokinetics:** whole organ and whole body models of transport of small molecules across capillary walls, and metabolism in body tissues.

Graphical Pathway Modeling

- **Hierarchy:** Hierarchical automatic layout allows users to organize complex biological networks within functional and physical boundaries.
- **Annotation:** Nodes and edges in TeraSim graphs can be annotated with information about the objects they represent, including user-entered text, drawings, file attachments, links to other resources or databases, or parameters for configuration of simulations.
- **Customization:** User groups can define different biological entities (node types) and relationships (edge types) to suit specific needs. Node appearance (color, shape, size) and edge appearance (line color, style, thickness) can also be customized to define precise graphical semantics.
- **Data Integration:** Data (proteomic arrays, microarrays, phosphoarrays, etc.) or simulation results can be mapped to nodes in a graph and control the way the nodes are displayed.

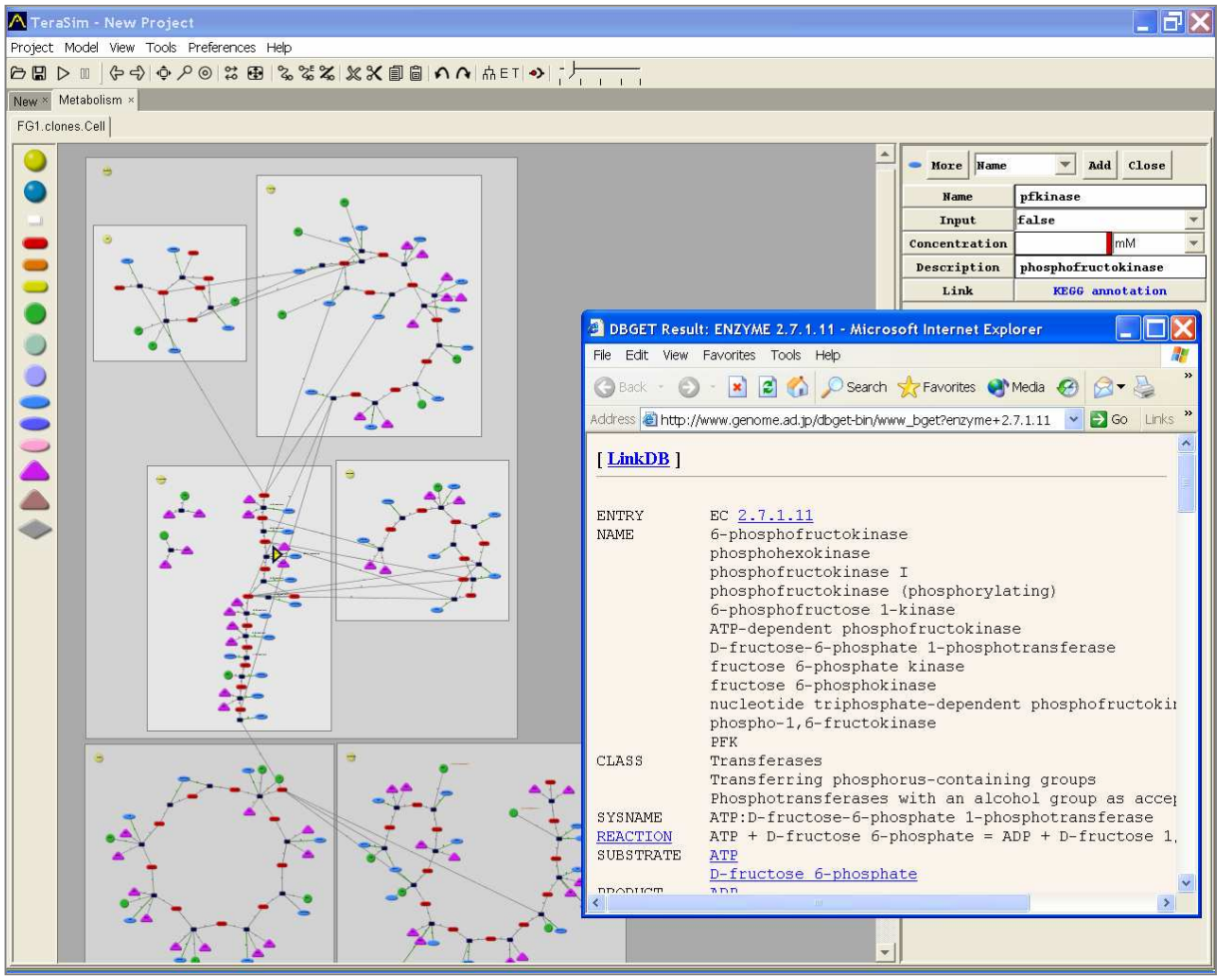


Figure 1: Model of the central metabolic pathways, including carbohydrate metabolism and glycolysis (top of canvas), fatty acid metabolism (lower right) and the Krebs cycle (lower left). Information in the graph was obtained from the KEGG metabolic pathway database. The yellow triangle indicates the location of phosphofructokinase in the graph; the panel to the right of the canvas shows additional information about this enzyme, including a link to more information stored in the KEGG database and displayed in a web browser.

Biological Modeling Language

TeraSim graphical models are also represented by text-based languages, such as SBML. TeraSim includes constructs for various types of biochemical reactions, ion channels and pumps, and receptor binding. These higher-level model constructs are continuously translated into mathematical systems for simulation and analysis.

Hierarchical model configuration maximizes component reuse. For example, a blood-tissue exchange (BTEX) model can be constructed with components of convection and trans-membrane exchange. The BTEX model itself is then readily used as a biological component for higher-level model construction, such as in whole-organ modeling.

TeraSim's biological modeling language is:

- **Extensible:** New biological entities can be defined from the TeraSim base classes.
- **Hierarchical:** TeraSim's hierarchical compartments include physical compartments and functional groupings (pathways).
- **Reusable:** Biological sub-systems can be repackaged and reused in different contexts, speeding model development.
- **Standards compliant:** TeraSim can translate models to and from standard XML-based formats like SBML and CellML.
- **Human readable:** Unlike raw XML, TeraSim text-based Biological Modeling Language (BML) is easily editable by humans.

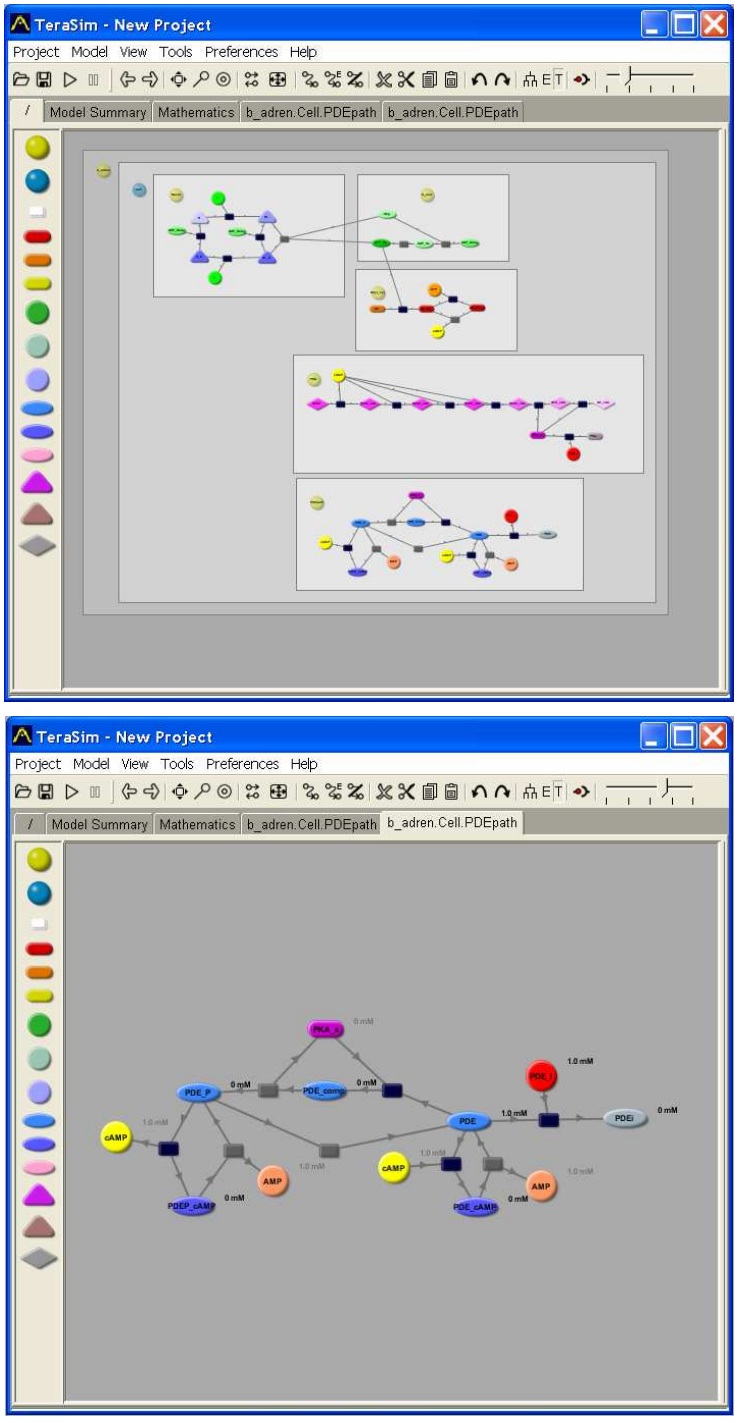


Figure 2: Model of the signaling pathway downstream of the beta-adrenergic receptor. The view on the top shows interactions between the receptor, a G-protein, and several downstream enzymes involved in the regulation of cAMP. The right panel shows a close up view of the conversion of cAMP into AMP by PDE.

Mathematical Modeling

- **Supports Multiple Methodologies:** Ordinary differential equations, partial differential equations, Markov processes, and non-linear algebraic equations can be used to define a TeraSim model. Analysis methods can use either dynamic or steady-state simulation results.
- **General and extensible:** Users can define new math language constructs and numerical methods through TeraSim's API and plug-in mechanisms.
- **Automatic unit conversion:** Units can be assigned to model parameters, and conversion between different units is performed automatically.
- **Standards compliant:** TeraSim can import and export models in MathML, the XML-based standard for exchanging mathematics between different software applications.

Simulation and Analysis

TeraSim simulations are generated automatically from text or graphical models. TeraSim has powerful features that allow scientists to use their model to analyze experimental data. TeraSim supports a number of analysis methodologies including interactive simulation control and visualization, optimization, Monte Carlo analysis, and sensitivity analysis. These capabilities are further extensible via API.

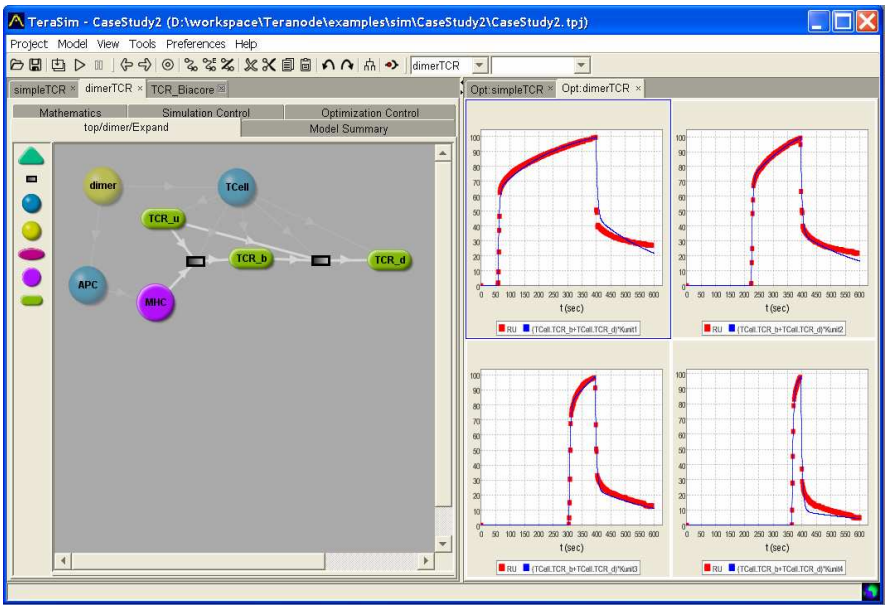


Figure 3: An optimization case study using previously published data from BIACORE-based experiments compared the time course of TCR/MHC association to predictions from a two-step binding model. In this example, experimental time course data is shown in red and simulation curves are shown in blue. Optimized model fits to data validating the two-step binding model, and provided estimates of the rate constants needed to match the model to data. Alam SM, et al., *Immunity*, 1999. 10(2): p. 227-37.

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