3D VISUALIZATION OF SIMULATION DATA IN A NETWORK CONTEXT: A CASE STUDY FROM SYSTEMS BIOLOGY

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ABSTRACT

Methods for 3D visualization are well established in all disciplines where simulation preprocessing data (e.g. FE meshes) or simulation output data is directly coupled to the geometry of the real system. The situation is quite different, when this connection is missing because the system is conceptually modeled by abstract structures. The complex interconnected biochemical reaction networks in living cells which are studied in Systems Biology are a typical example. Here, it is a challenge to design visual representations of these networks showing all wanted structural features combined with quantitative data from simulation runs or experiments. This paper presents and evaluates three case studies that illustrate new visualization approaches in 3D to display structural and quantitative information related to biochemical networks and discusses the potential of interactive 3D network visualization in context of Systems Biology.

INTRODUCTION

Visualizing Simulation Data

Information visualization techniques are well established for systems with a direct spatial relation in 2D or 3D space. This does not only hold for all kinds of partial differential equation applications (continuum mechanics, fluid dynamics, electro magnetism etc.) but also to discrete systems with spatial compartmentalization (multi body dynamics, material flow, traffic etc.) (Hege and Polhier 1997). In each case powerful visualization techniques have been developed to present the simulation results and animate time dependent data. Moreover, simulation preprocessing is supported, for example by visualizing computational grids or domain decompositions. Likewise, derived simulation data like sensitivity results or eigenfunctions can be visualized.

The situation is quite different when models with a conceptual (i.e. non spatial) compartmentation are considered. This holds for example for chemical reaction networks where the chemical species all occupy the same space but are conceptually represented by a reaction network. In this situation the visualization of simulation results by the time courses of all state variables is still predominating. However, this is not a satisfying solution because the network context is lost. Clearly, it would be more appealing if all data is directly represented in association with the network structure. A particular problem of biochemical networks here is their size, heterogeneity, and complexity of networks.
For this reason, the present contribution explores some new methods to visualize simulation related data on networks. Particularly, the potential of 3D visualization is explored. The examples stem from the field of biochemical network modeling in Systems Biology. Three case studies concerned with direct simulation data, sensitivity related information and simulation preprocessing are briefly discussed.

Biochemical Networks

Biochemical networks consist of nodes and edges (cf. Fig. 1) wheras the nodes represent chemical substances and reactions and edges represent interactions between these components (Gottschalk 1986; Michal 1999).

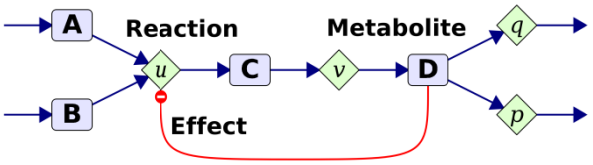

Figure 1: A typical biochemical reaction network with nodes for metabolites/reactions and edges for material flow/effector relationships (activation or inhibition).

In contrast to electrical networks, where edges always represent a flow of electrons, biochemical networks do not only contain flow edges representing chemical reactions, but also regulatory edges defining an influence of a chemical substance on a chemical reaction (Fig. 1) (Noack, Wahl et al. 2007). The direction of an edge either defines the sign of a material flow or the role of two connected nodes (source-target, effector-influenced reaction etc.).

As opposed to electrical networks for which planarity is of great technical importance, biochemical networks are usually not planar even for simple pathways. Moreover, because biochemical networks are frequently the result of systems analysis activities identifying the most im-

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portant interactions in a real system, they are often enriched by a functional decomposition of the network (Kremling, Jahreis et al. 2000; Palsson 2006). This leads to the concepts of metabolic pathways, spatial compartmentation, functional units or motifs, hierarchical network decompositions, genetic operons and regulons, or networks with metabolic/genetic/signal transduction levels.

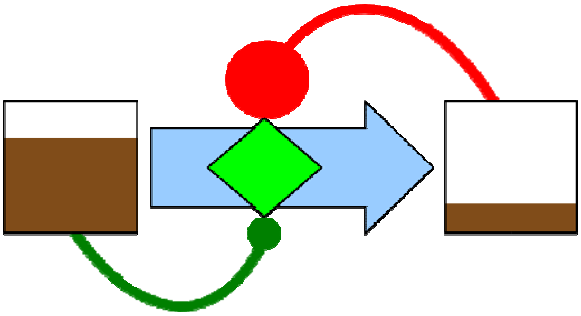


Figure 2: 2D representation of fluxes (arrow), pool sizes (partly filled rectangles) and regulatory interactions (edges with circle arrowhead) used in MetVis (Noack, Wahl et al. 2007). Sequential or time dependent data can be interactively visualized by using a slider.

Networks, which are enriched in that way by semantic structural information, demand for a graphical representation reflecting the underlying structural systems analysis. This results in the problem of designing a biochemical network in such a way that certain structural information is visually preserved in the layout. Three-dimensional (3D) network visualization is one possible way to reach this goal.

Established Visualization Methods

The aforementioned design problem becomes even stronger when biochemical networks are augmented by quantitative data from biochemical systems simulations or network wide data available from experiments. These data are associated to the network nodes and edges. A rather simple but frequently applied kind of representing quantitative data in networks is to annotate nodes and edges with numbers, bars, time courses (Junker, Klukas et al. 2006; Klamt, J. et al. 2003; Klamt, Saez-Rodriguez et al. 2007). A more direct visualization of data can be obtained by mapping numerical values or states to visual parameters of the graphical items like size, color, transparency, orientation, shape, filling etc. All these methods have been established in 2D. The reader is referred to (Qeli, Wahl et al. 2003; Rost and Kummer 2004; Sudermann and Hallett 2007) for more details.
Typically, these data are also time dependent or sequential (i.e. taken from a series of experiments). One way to visualize such serial data is to produce animations with changing graphical items over time. Interactive exploring of single time slots can be offered by using a slider as described in (Qeli, Wahl et al. 2003).

A novel development has been presented in (Noack, Wahl et al. 2007) where not only the fluxes and pool sizes but also the regulatory interaction between substance nodes and reaction nodes has been given by a quantitative measure (Fig. 2). The 2D visualization tool MetVis (Noack, Wahl et al. 2007) simultaneously visualizes metabolic fluxes, metabolite pool sizes and regulatory strength as they change over time.

3D Visualization

Because 3D representations of networks are rather seldom encountered in the literature – particularly with applications to biochemical networks – 3D visualization methods are still under development (Sudermann and Hallett 2007).
Switching to a 3D context, quantitative data associated with networks can be visualized in even more ways. However, the big question is whether this can improve rapid information perception and intuitive understanding. 3D network visualization, particularly in the biochemical network context, has not been in the main focus of the graph visualization community even in recent years (Sudermann and Hallett 2007). Several ways of 3D network representations have been suggested in the literature (Cohen, Eades et al. 1995; Dickerson, Yang et al. 2004; Frati and Battista 2007; Ho and Hong 2006; Koike 1993). Another way is the 2.5D approach (Brandes, Dwyer et al. 2003; Dwyer, Rolletschek et al. 2004) that stacks different planar data visualizations in the third dimension in order to facilitate direct comparison of time series.

Briefly, the general advantages of a 3D network representation are

- the representation of non-planar networks without edge intersections
- the option to represent modular networks and hierarchically organized structures in a more intuitive way (e.g. by top-down arrangements of subnetworks)
- the exploitation of human 3D perception capabilities to enlarge the amount of information that can be simultaneously transferred.

Some of these advantages turn into disadvantages from a technical viewpoint:

- 3D representation require a special graphics hardware (e.g. shutter glasses, caves, animation) to make the third dimension perceptible
- 3D networks loose all their expressiveness when printed on a sheet of paper
- The navigation within a complex 3D network is even more difficult than in 2D networks.

However, these are technical problems and, thus, it is a challenging problem to invent new methods and tools for 3D visualization and to compare them with their 2D counterparts. Aiming at this goal, an ongoing research project explores different concepts for 3D visualization

related to biochemical networks. The following sections present some first results and discuss central problems.

CASE STUDY 1: NETWORK THERMODYNAMICS

Foundations

Like any other process in nature biochemical reaction steps are governed by energetic principles. A reaction can only proceed in its nominal direction if the sum of the energetic reaction potentials of the reaction sources is larger than the sum of these of the reaction products. Here it should be noticed that thermodynamics does only make a statement on possible reaction directions but not on their quantitative magnitude. Even if a reaction step has a large energy gradient there might be some regulatory interaction controlling the amount of flux through this reaction step (cf. Fig. 1 and case study 2).

The free Gibbs energy potential of a chemical substance with concentration (or, more precisely, activity) x is given by

$$\Delta G = \Delta G^0 + RT \ln(x) . \qquad (1)$$

Here the term ΔG^0 is free Gibbs energy potential under standard conditions. R is the Boltzmann constant and T is temperature (Beard, Babson et al. 2004; Kümmel, Panke et al. 2006; Maskow and Stockar 2005; Qian and Beard 2005). If a chemical reaction step has sources A, B,… and targets U, V,… then it must consequently hold

$$\Delta G_A + \Delta G_B + ... > \Delta G_U + \Delta G_V + ... \qquad (2)$$

for the reaction to proceed in forward direction. The set of thermodynamic constraints obtained in this way by collecting the respective inequalities for every reaction step imposes a multidimensional relation between possible substance concentrations, free Gibbs energies under standard conditions and flux directions.

Because Eq. (2) holds both for the steady state and for dynamic transients, the display of thermodynamic potentials is an interesting complement to other simulation data like concentrations or fluxes.

3D Visualization

Using the third dimension is an appealing method to represent energy levels in a metabolic network. Here the analogy between reaction flow and hydrodynamic flow helps to understand the thermodynamic concept more intuitively.

For this purpose we developed ThermoVis, a three dimensional thermodynamic visualization tool that visualizes the energies of metabolites and reactions on a two dimensional network using the third dimension. For fast and intuitive conceiving of the network features ThermoVis uses color. Reactions proceeding in the feasible direction are indicated with green edges whereas reactions proceeding in the non-expected way are indicated with red edges. Furthermore the tool supports interactive navigation in the network moving, rotating and zooming in the scene and also by focusing single reaction nodes. Fig. 3 shows a three-dimensional representation of some part of central metabolism with certain measured substance concentrations.

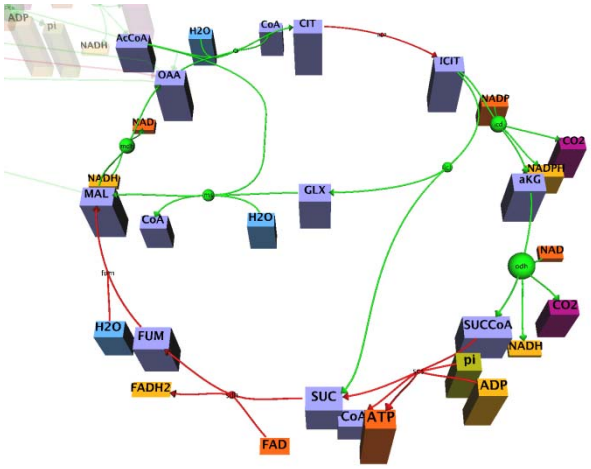
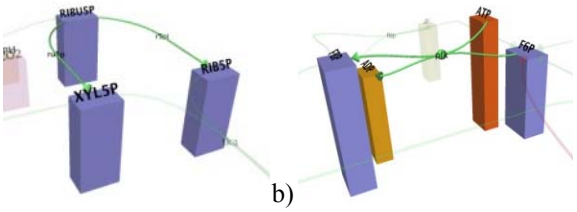


Figure 3: Snapshot of a thermodynamic visualization. Here the citric acid cycle is shown.

Many reacting metabolite pools have almost the same Gibbs energy level and, of course, are not really distinguishable. Because reactions between such pools cannot be classified in their direction ThermoVis visualizes the energy gradient of a reaction as sphere whose diameter indicates the size of this gradient (see Figs. 3 and 4). Fig. 4a shows two reactions which can be easily directed by the help of reactions energy level.



a) b)

Figure 4: ThermoVis snapshots of (interesting) single reactions

Reaction steps can procees in the direction of an upward energy step when they are driven by a second downward reaction that supplies the required energy. This situation is shown in Fig. 4b.

CASE STUDY 2: SENSITIVITY RELATED DATA

Foundations

Generally, thermodynamic driving forces determine the direction of fluxes but not their magnitude. Typically, in biological networks those reaction steps with large

energy gradients are highly regulated on an enzymatic level. In the hydrodynamic analogon this corresponds to controlled valves. Several metabolite pools can have a regulatory influence on one reaction flux (Fig. 1). These influences are quite similar to sensitivities of reaction rates w.r.t. several influencing factors. For this reason regulatory dependencies are a good example for sensitivity visualization in a network context.

2D Visualization

A first approach visualizing the quantities describing the metabolic data (metabolites and fluxes) inside the metabolic network is published in (Qeli, Wahl et al. 2003), called MetVis (Metabolic Visualizer). MetVis is able to animate metabolic networks visualizations based on data generated by simulation.
To indicate the concentration level of metabolites in the network, they are drawn as variable filled rectangles like illustrated in Fig. 2. The size of the filling level is restricted to a certain range and its minimum and maximum value is understandable in every moment because they correspond to the size of the rectangle representing the metabolite. The strength of reaction flows is indicated by the width of the corresponding flux edges. Inhibition is represented with red edges and activation with green ones. The influence of an effector to a reaction is indicated by the radius of the circle-arrows (cf. Fig. 2).

3D Visualization

2D visualizations are very helpful for analyzing both topological and other simulation related properties of metabolic networks. However, 2D views have some restrictions which could possibly be avoided by using 3D visualizations. Thus, some pathways, as for example the pentose phosphate pathway, cannot be drawn in 2D without line intersections. A much more difficult problem occurs when metabolic cofactors like ATP or NADH are involved. They are coupled to almost all central metabolic reaction steps and induce a strong network connection resulting in many line crossings. In the case of metabolic networks, the crossing problem increases additionally when activation/inhibition effects are considered. The crossings issue can be treated by using 3D visualization techniques to displace edges in different planes.

In (Qeli 2007), a three dimensional approach of visualizing time series of data in metabolic network as a 3D extension of the two dimensional MetVis tool is presented. Basically, the 3D visualization is a transformation from 2D into the 3D space following certain rules. Therefore, a generated 3D network is similar to its 2D counterpart, without creating totally different layouts which do not conform to biochemical conventions. The 2D rectangle representation of metabolites in MetVis is mapped to 3D cubes and the two dimensional Bézier curves representing edges now are mapped to tubes that have the shape of a three dimensional Bezier curve and with a certain diameter. The 3D view is intended to be used as a complementary part to the 2D view, allowing the elimination of edge crossings in 2D. To reach this aim, the inner control points of the Bézier curves are displaced in different z-planes. Fig. 5 presents a comparison between a 2D network with several edge crossings and its transformation in 3D, where the intersecting edges are displaced in the z-plane.

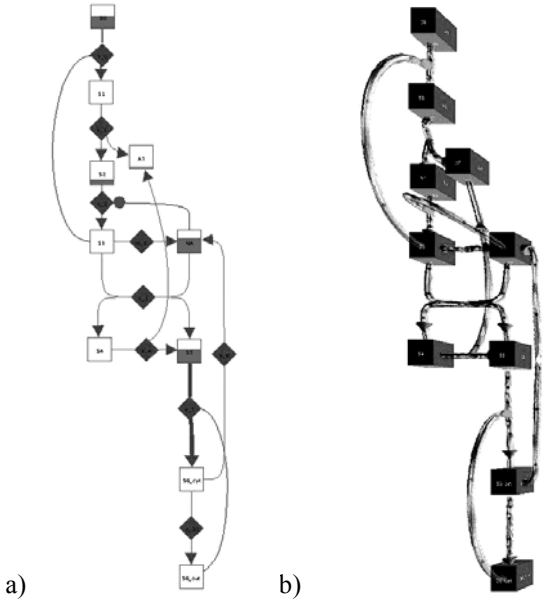


Figure 5: Comparison between 2D and 3D representation of a small metabolic network containing edge intersections.

To animate the 3D views, the raw data taken from a simulation is converted into relative percentages of the respective metabolite or flow. Two types of items are animated:

- The z-dimension of the cubes representing the metabolites varies according to the scaled concentration of the corresponding metabolite.
- Tubes represent flows for both material flux and effector influence. They are drawn semitransparent due to spheres moving within the tubes represent the material flow for the corresponding reaction. For the reaction flows, these spheres are colored with a nuance of blue, for inhibition they are colored in red and for activation they are colored in green. The speed of flow of these spheres depends on the scaled rate of the respective reaction.

Depending on the point of time, the height of cubes will show the measure of metabolite concentrations, and the velocity of spheres in the tubes indicate the reaction flow respectively the effector influence. Thus, whereas in the 2D animation one must be concentrated to view the changes in different flows, in 3D animation the speed of the movement of spheres makes it directly clear which part of the metabolic network is more active.

CASE STUDY 3: SIMULATION PREPROCESSING

Foundations

Isotope labeling experiments are an important tool to determine intracellular fluxes in a living organism. In this context not the metabolite network has to be visualized but a related network that shows the flow of ^{13}C carbon atoms or groups of such carbon atoms.
Isotope labeling networks associated to metabolic networks have an extremely high dimension. Details on these networks can be found in (Weitzel, Nöh et al. 2007). Essentially, they describe the fate of isotope labeled substances metabolized by the cell. To account for the fate of each differently labeled molecule each metabolite pool has to be divided into so-called cumomer pools (different labeled/unlabeled states).
If a metabolite has n atoms which are accessible by isotope labeling then there are 2^n different cumomers associated to this substance. These cumomers are connected by cumomer reactions which are analogous to the underlying edges in the metabolic network. Interestingly, it could be proven (Weitzel, Nöh et al. 2007) that cumomer networks can always be decomposed into smaller subnetworks. The exploitation of this decomposition has a strong impact on the performance of simulation algorithms, measurement evaluation or experimental design (Wiechert 1999).
Consequently, this is a good example for network visualization in the phase of simulation preprocessing analogous to the visualization of finite element nets in other simulation fields.

3D Visualization

Cumomer networks of even small metabolic networks can have quite a large number of nodes which makes it extremely difficult to visually disentangle the complicated structure of the network. However, this structured knowledge is important for required computing time, interpretation of simulation results or experimental design.
This immediately suggests a three dimensional representation of cumomer networks where the metabolic network is represented in a planar way on the "ground" level and the cumomers are stacked on top of the metabolite nodes using the third dimension. Fig. 6 shows the cascaded structure of a cumomer network subdivided in several levels that contain cumomers of common weight. The arrangement of nodes and edges in every level is based on the underlying planar metabolic network layout. Clearly, it is a big challenge to visualize these 3D networks in such a way that the user can recognize important structural features of the network.

The CumoVis tool has been implemented to visualize this structural information. Here, the primary challenge was to facilitate the navigation within the network, the sequential decomposition of networks and the tracing of reaction sequences. CumoVis takes a metabolic network layout and automatically arranges the cumomers on top of each metabolite node. Moreover, CumoVis takes up the structural analysis results of a graph analysis algorithm (Weitzel, Nöh et al. 2007) that decomposes the network into the aforementioned weight levels, connected and strongly connected components.

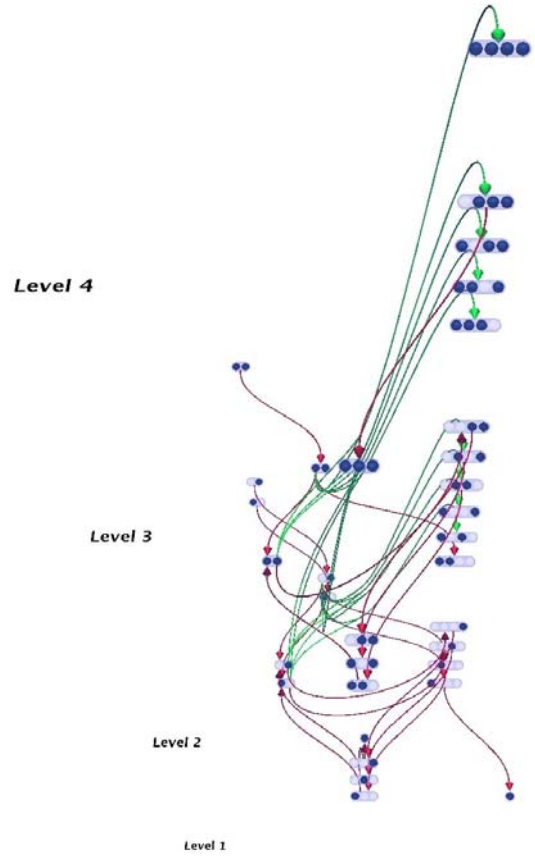


Figure 6: Cumomer visualization of a simple example network with 7 metabolites and 5 reactions.

The following interaction techniques have been implemented in the cumomers tool:

- A rough understanding of the overall complexity and structure of isotope labeling networks can be achieved by visualizing the whole network.
- More detailed impressions can be obtained by interactively rotating the network and zooming into certain parts of it. Here, navigation is made easy by the stacked network organization.
- The user can now hierarchically break up the network into smaller sub networks.
- To understand the labeling dynamics in an experiment the search for cyclic paths is very important because, essentially, these cycles make the quantitative determination of isotope enrichment in a network a non-trivial task. For this reason, cyclic structures are automatically detected and displayed on demand.
- The fate of a labeled particle can be studied by path tracing in forward and backward direction. The respective reaction paths are graphically highlighted.

This is one of the most time consuming operations that are frequently performed by experimentalists (but manually).

DISCUSSION

Experiences

Communication processes between experimentally working biologists and modelers (frequently with a mathematics or engineering background) are central activities in any interdisciplinary research project in Systems Biology. The transfer of results from systems analysis and simulation studies can be greatly facilitated by using visualization techniques. However, the investigated networks are becoming more and more complex and, consequently, are demanding for more advanced and sophisticated visualization tools. 3D representations are an option here, although they are more difficult to handle than their 2D counterparts.

Several of the tools mentioned before have already been successfully used in project meetings and teaching. Here, the built in interaction features turned out to be of great benefit because specific aspects of the networks could be explained by pointing, zooming, and highlighting. Generally, 3D network visualization makes little sense without interactive features, animation or even the use of 3D graphics facilities.

On the other hand, as also becomes clear from the figures shown above, 3D networks loose much of their expressiveness when printed on sheet of paper. This problem can be solved by publishing the visualization tool together with the paper.

Future Developments

Further work will concentrate on the 3D visualization of more complex networks involving metabolic and genetic processes. Here, constraint based 3D graph layout from given network components will also be an issue. Finally, more advanced graphics hardware (shutter glasses or a cave) will be used and evaluated.

Clearly, at the present state, the mentioned visualization tools are rather meant as prototypes to explore the potential of 3D visualization for biochemical network structure and simulation/measurement data. The greatest challenge now is to identify some general concepts which will help to unify the different approaches and still leave the full flexibility.

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