Visual Analytics for Stochastic Simulation in Cell Biology

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ABSTRACT

Visual Analytics is successfully employed for an integrated data analysis by means of combining visual and analytical methods. The starting point for current Visual Analytics tools and workflows is usually the readily available data set. Rarely though, Visual Analytics goes beyond the data set and also incorporates the data generating processes that have led to the data in the first place into the analysis. And indeed, in many use case scenarios, this is hardly possible, as these processes cannot be captured as data to be analyzed themselves. Yet for the applications, in which this is feasible, new opportunities and challenges open up.

In this paper, we illustrate these opportunities and challenges by our efforts to bring together Visual Analytics and stochastic simulation for cell biological applications. The integration of both is possible, as the data generating process runs *in silico* and can thus be captured and analyzed alongside the mere simulation result. For this, we present solutions and tools, which permit Visual Analytics on all stages of this particular data generating process – on the stages of the model, the experiment, the simulation runs, and a combination of all three.

Categories and Subject Descriptors

H.5.m [**Information Interfaces and Presentation**]: Miscellaneous; I.6.6 [**Simulation and Modeling**]: Simulation Output Analysis

General Terms

Design

Keywords

Visual analytics, stochastic event-based simulation, cell biological models

1. INTRODUCTION

Visual Analytics is a novel multidisciplinary field. In the last few years different solutions and success stories have been developed, which aim at supporting the user in obtaining deeper insights of models and data by means of Visual Analytics [19]. For this, Visual Analytics relies on a broad set of methods from Statistics, KDD/Data Mining, and Information Visualization. Yet, what is often neglected is the fact that data does not appear by itself, but is the result of a data generation, data collection, or measurement process. These processes determine which data is gathered how often and at which level of accuracy – provenance aspects, which should be included in the analysis but current analysis methods generally do not support this.

Simulation studies offer the opportunity to consider the data generation process when presenting and analyzing the simulation results. This is highly desirable as simulation studies contain many interdependent steps and methods that might influence the outcome. The modeling and simulation life cycle comprises many different steps [33] and alone for executing in silico simulation experiments, six steps have been identified [23]: **requirement specification**, which might stretch from comparing a single simulation trajectory with given data to sweeping the parameter space of a model, **configuration**, which identifies points in the model parameter space that needs to be investigated, **execution of the model**, which refers to the algorithm used for calculating the model, **observation of the model**, which includes identifying the crucial part of information to be collected, **analysis of the simulation traces**, which might refer to single or multiple runs, **evaluation**, which might lead to new configurations or results to be presented, e.g., for face validation. Many of those steps are supported by a plethora of methods which have an impact on subsequent steps and the overall quality and reliability of the simulation study and the achieved results [32]. Not without reason, Perrone et. al. [28] state that "the level of complexity of rigorous simulation methodology requires more from net-working researchers than they are capable of handling with-out additional support from software tools." This observation applies also to other fields, especially those in which more complex systems are under study, as it is the case in cell biology.

Cell biological systems are characterized by dynamics that happen at different temporal and spatial scales. Recent findings emphasize the central role that stochasticity [27] and space [21] play in inter- and intracellular dynamics. Thus,

an urgent need exists to take the relay of information within and between cells into consideration. In fact, space has been termed the final frontier in the simulation of cell biological systems [22], a frontier which has been approached from the direction of both modeling languages (e.g., [5, 17]) and simulation algorithms (e.g., [9, 16]) over the last years.

Therefore, spatio-temporal visual exploration of models and simulation processes requires the visualization of huge volumes of multivariate data and their structural dependencies in space and time. An overview of the aspects of spatio-temporal Visual Analytics is given in the Visual Analytics roadmap [19], as well as in [3]. While on one side the visualization of time-dependent data remains a challenging aspect [1], on the other side the plotting of simulation data is an integral part of simulation systems and described in number of publications, such as [6, 12]. In addition, the visualization of simulation parameter spaces has recently gained considerable attention in the visualization community, with a whole session dedicated to it at VisWeek'10 [2, 4, 24, 39].

Visualization techniques exploited by state of the art simulation tools are typically constrained to presenting results visually and towards focusing on one particular step of the Modeling&Simulation life cycle, i.e. the trace analysis. However, for complex temporal and spatial dynamics, as found, e.g., in cell biological systems, the usual batch method – run multiple simulation experiments and then mine the output for clues [26] and animate the results [7, 29] – though being valuable is not adequate to address the modeling and simulation life cycle as a whole.

Consequently, simulation studies in cell biology with their specific challenges are an excellent application area for Visual Analytics as they offer opportunities to take the data generation process into account, and are also heavily in need for advanced analytical and visual support, due to the dynamics operating at different temporal and spatial scales. Current simulation tools in this area include 2D and 3D graphical interfaces, e.g., for animating processes and visualizing data, but they primarily focus on representing results rather than integrating visual methods with the Modeling&Simulation process. In this paper, we aim to take a first step in this direction by combining stochastic discrete event-based Modeling&Simulation and visualization in the spirit of Visual Analytics.

Given the diverse steps involved in simulation studies, plenty of possibilities for support through Visual Analytics exist. In the following, we will focus on **models**, representing the underlying "blueprint" for the in silico experiment, and two central steps of in silico experiment – the **configuration** of the experiment, referring to the parametrization of the model, and the **trace analysis** referring to single or multi-run simulation data. This is in tune with earlier approaches, such as [38], which also highlight these three stages as being crucial to support with visual methods. So, we step through each of them by presenting a Visual Analytics solution for a concrete cell biological scenario. This is sensible, as different scenarios ask for different modeling formalisms, which in turn require different means of visual analysis:

- **models** – in this case for biochemical reaction networks, which form large complex hypergraph model structures which are nearly impossible to overview and investigate without the aid of visualization. In Sec. 2, we use a table-based visual analysis approach for bipartite graphs, to which we transform the hypergraphs.
- **configuration** – here we will focus on parallel optimization of large hierarchical models, which can have 100.000's of components spread across multiple hierarchy levels – each of which individually parametrized to a given initial state. In Sec. 3, we use a space-efficient point-based layout of the hierarchy to make as much of the initial parametrization visible as possible.
- **trace analysis** – in particular with a focus on spatial distributions, as they are produced by spatial stochastic simulations, e.g., by lattice-based approaches. In Sec. 4, we make use of an animated volume visualization that allows to trace the simulation trajectory across time and space in coordinated multiple views.

These "partial" solutions focusing on the individual stages of in silico experiments illuminate the opportunities and challenges each of these steps provide for Visual Analytics and are a basis towards a comprehensive and integrated support of simulation studies by Visual Analytics. While the tools realizing these solutions have been individually presented before, this paper brings them together to illustrate the importance of visual support for the entire Modeling&Simulation process – either for individual steps of this process or for the process as a whole. For the latter, a first approach to integrate all three steps is shown in Sec. 5 for stochastic, non-spatial simulation studies of cell biological systems. It basically considers simulation as the "Analysis First" step of the Visual Analytics mantra (*analyse first, show the important, zoom, filter and analyse further, details on demand*) [20] and thus provides a first example of Visual Analytics for stochastic event-based simulation as a whole. All presented visual analysis solutions tie in with the JAva-based Multi-purpose Environment for Simulation JAMES II [10], available at `http://www.jamesii.org`.

The paper is concluded by a short summary and ideas for future work in Sec. 6.

2. VISUAL ANALYTICS FOR MODELS

As the underlying model plays an important role for the suitability and performance of simulation algorithms, their visual analysis is worthwhile before even a single simulation run is conducted. The challenge lies here in the size and complexity of cell biological models. The reason for this is the abundance of factors possibly influencing cell biological processes – from the estimated 25,000 genes of the human genome to the 100,000 different forms of the human proteome all the way to the 4,000 biochemical reactions of the human reactome, which are distributed across 800 different functional pathways. Methods for their visual representation and analysis play a key role in current research, as visual tools are effective means of curating models of cell biological processes and exploring their interrelations [25].

Especially these interrelations, the reactome, which conceptually forms a large hypergraph with the chemical compounds (called *species*) as nodes and the reactions as directed hyperedges connecting a number of reactants and products, poses a challenge to its interactive exploration.

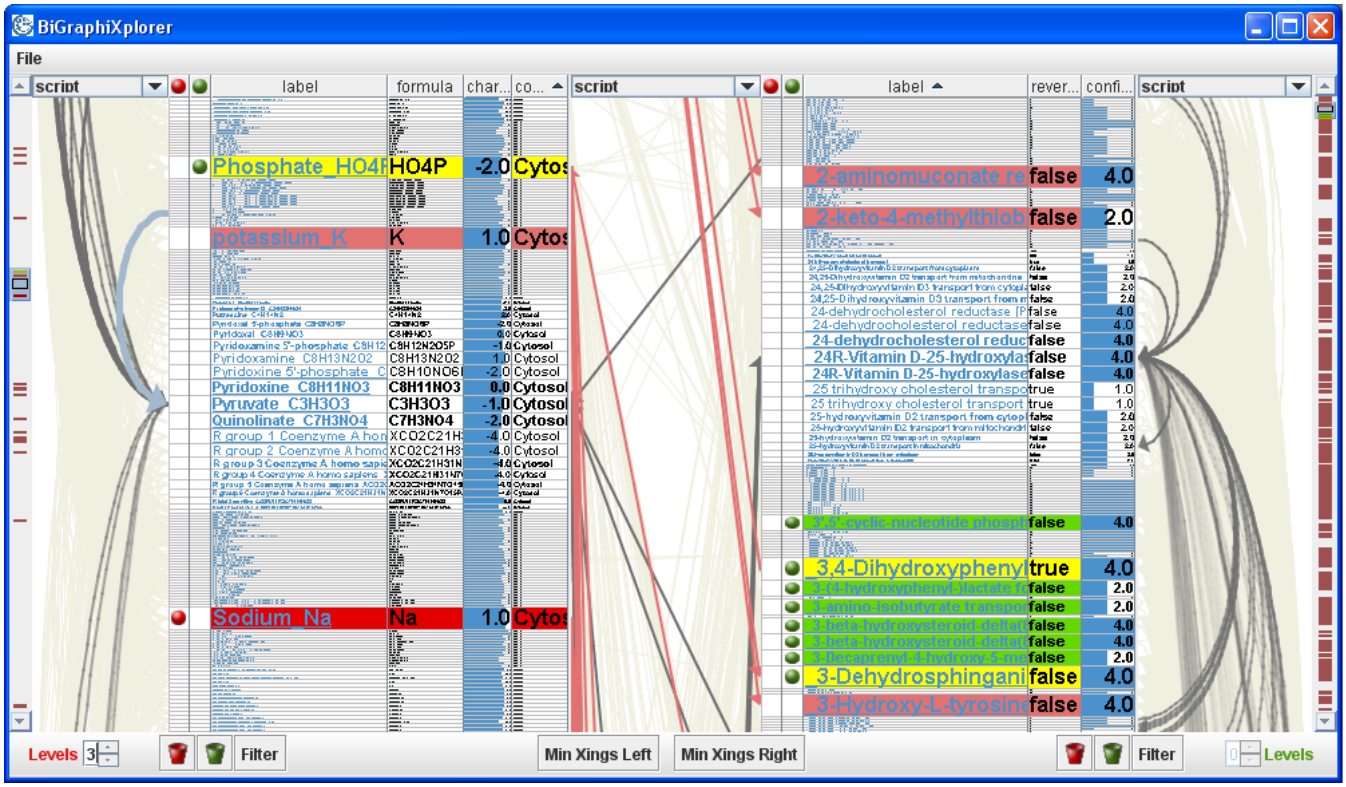

Figure 1: The table-based visualization approach [35] showing a part of the human reactome model. The species are listed in the left table with the cell compartments they reside in shown in the far right column, the reaction are listed in the right table. The links in between both tables indicate which species participate in which reaction. The arcs at both sides are shortcuts for a faster traversal of the network without the need to go back and forth between both tables to follow up on dependencies. Different automated selections have been made in this example, using a script-based selection mechanism.

These collections of biochemical reactions are often modeled in a rule-based manner [11], capturing not only the structure of the reactome, but also the reaction kinetics. The resulting models can be stored in specific exchange formats, such as the Systems Biology Markup Language (SBML).

In order to provide a visualization with a lot of possibilities for interactive analysis, we developed a table-based representation for such models of reaction networks [35]. In this table-based representation attributes are used for representing discrete space, by assigning species to reside in discrete compartments, e.g., outside of the cell, within the cytosol, within the nucleus, etc. (see also [30]).

It starts out with computing a graph-theoretical transformation, the so-called *König's Transformation* [36], which converts the hypergraph structure into a bipartite graph structure. This bipartite graph contains the species as one node set, with their compartment encoded as a node attribute, the reactions as another node set, and the edges between both node sets indicate which species partake in which reactions. An overview of the table-based visualization showing both node sets and the edges in between is given in Fig. 1.

The benefits of this approach are apparent: tables scale up to 100,000 entries [8], they do not clutter, they are interactively re-orderable, and they can be used with all the enhancements that have been developed for tables, e.g., the table lens and its extensions [18]. The integrated exploration of both tables is supported by edge-based traveling techniques, which allow to investigate biochemical dependencies in detail even if they are scattered across larger tables. Additional analytical support is given by a script-based selection mechanism, which is able to automatically generate follow-up selections by carrying out a script that traverses the network according to the given script logic. Process knowledge about analytical procedures on reaction networks, such as dependency analysis, can thus be encoded in such a script, carried out whenever needed with a single mouse click, and even passed on for use by other researchers as well. This way, all aspects of Visual Analytics are naturally supported: the visualization with the table-based representation, the interactive analysis through a multitude of interaction facilities, and the computational analysis via script-based analytical methods focusing mainly on the model topology [35].

3. VISUAL ANALYTICS FOR CONFIGURATIONS

The last section dealt with a flat model structure. Modeling of spatial dynamics is realized via attributes, e.g., to describe $\beta - catenin$ shuttling from the cytosol to the nucleus, the value of the attribute denoting its location would change

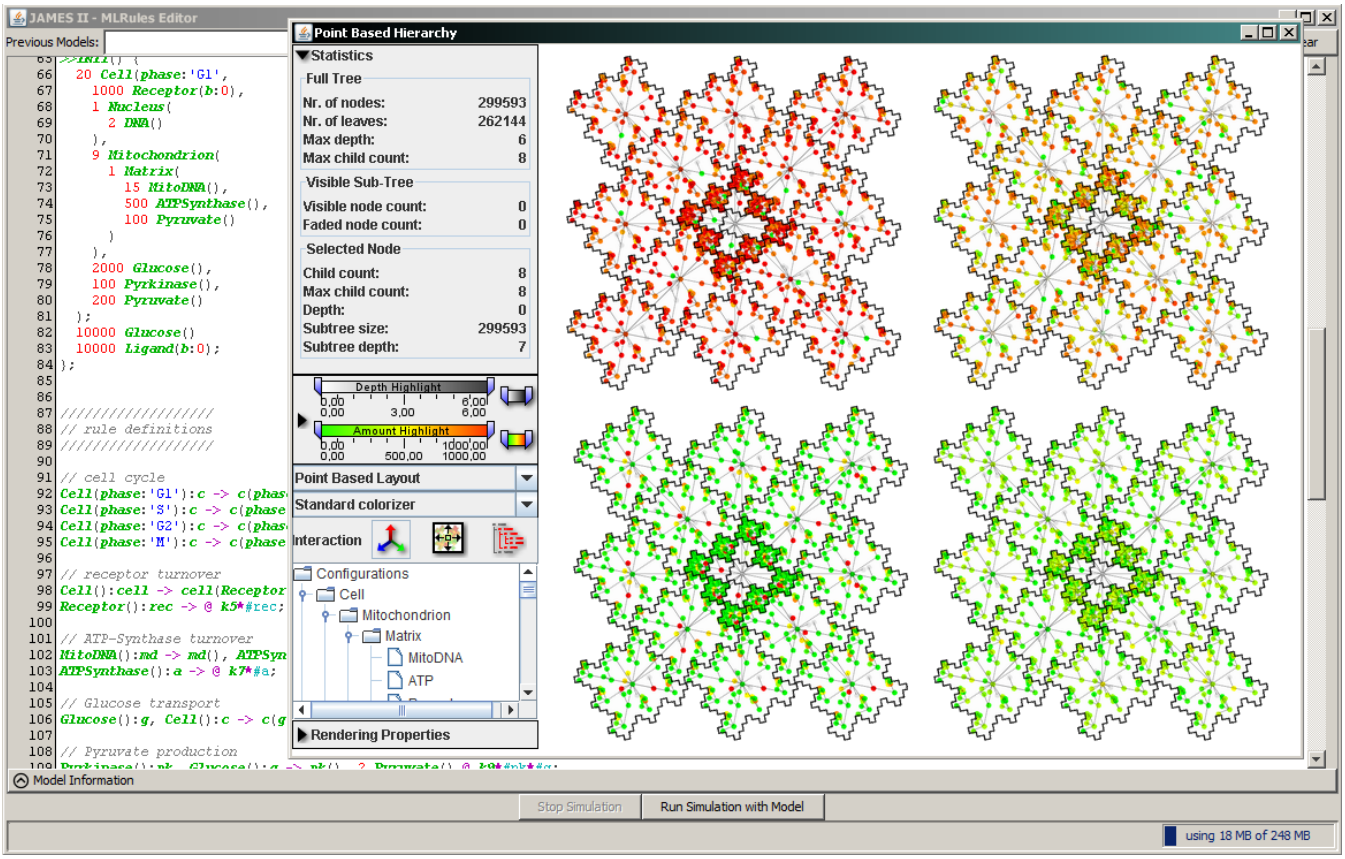

Figure 2: The point-based tree layout, as it is integrated in the James II simulation framework for comparative analysis of different configurations of hierarchical models. The initial states are color-coded on the model structure, showing different cells and within the cells multiple compartments and finally species. As low initial concentrations are colored in green and high concentrations are colored in red (see color scale at the left), differences between the configurations become instantly visible.

from cytosol to nucleus. Discrete localization of a species can also be modeled via an explicit hierarchical model structure which breaks the cell down in its compartments on the first level and then subsequently into subcompartments to which the species are finally assigned as leaves. In this case, a table cannot represent the more complex model structure.

To represent such tree-structured models and the configurations based on them, we propose to use a point-based fractal layout [34], which distributes the hierarchically ordered species nicely in the available drawing area. At the same time, it maintains their compartmentalization by assigning each branch of the model a different region of the layout. Initial concentrations, i.e. the configurations, defined on top of such a model are then color-coded at each point, with red standing for high initial values and green for low values.

Because the layout is space-filling it scales up to even large models with hundreds of thousands of objects at the leaf-level. This allows for an overview of a configuration in which a maximum number of individual species (leaves) and their assigned initial concentrations is visible in minimal required space. A high degree of space-efficiency is required, as often a number of configurations are generated to cover the parameter space of a model as best as possible.

Fig. 2 shows the point-based layout for configurations, as it is integrated in the JAMES II framework. A number of different configurations for parallel optimization that have been generated for being executed concurrently [13] are shown side by side to allow for their comparative visual analysis.

The depicted model is used to describe the processes of endocytosis and exocytosis, which engulf molecules into the cell or expel them from it, respectively, in case these molecules are too big to pass the cell membrane. The configurations thus differ in the initial concentrations of such molecules (species) in the different outside and inside of each cell.

This rather attribute-centric view of a configuration is complemented with a set of interactive features that are specifically designed to illuminate the structural aspects as well – e.g., interactions to investigate a leaf's path to the root node, thus enumerating the (sub-)compartments it is part of. Along such a leaf-to-root path, it is possible to show for example how much the concentration of a single species contributes to the solution of the compartments it is contained in. Analytical methods, such as statistical tests, are available through JAMES II, so that the proper distribution of initial values in a single configuration and across a set of configurations can be tested. Together, the point-based vi-

sualization of model structure and configuration, the visual analysis by means of interactive exploration of the model topology, and the computational analysis of the configurations' distribution across the parameter space yield a versatile Visual Analytics approach for this step of the Modeling&Simulation process.

4. VISUAL ANALYTICS OF SIMULATION TRACES

Simulating cell biological models and the subsequent visual analysis of the resulting simulation data poses a number of challenges. One of the main challenges stems again from the spatial aspect, which results in species not being equally distributed within the cell, but concentrated differently not only between compartments, but even within compartments.

The simulation of cell biological processes hence accounts for this by using either particle-based simulation methods with a distinct position for each particle, or lattice-based methods with different square regions being inhabited by a different number of species. Thus, the spatial aspect of an inhomogeneous molecule distribution is represented not by discretizing the volume into explicit compartments as before, but by an implicit grid-like mesh. This mesh, or lattice, forms the basis for a series of stochastic approaches that account not only for reactions within a voxel but also for diffusion events between neighbored ones [9, 15, 16, 31]

As a cell is not a flat object, but stretches out in all three dimensions, volumetric visualization is needed to represent the three-dimensional space in which the simulation runs. Also, this level adds the temporal dimension to the data, as not simply individual states of the simulation are given, but entire simulation traces across a high-dimensional parameter space. Hence the visualization has to account for time, space, and high-dimensional data at once.

In the following, we are targeting the visualization of lattice-based simulation traces, which indicate for each modeled species at each time point of the simulation how many particles are contained in each voxel of a three-dimensional lattice. This is a huge amount of data, which can only be visually analyzed at interactive frame rates for selected subvolumes of about $100 \times 100 \times 100$ voxels in size. Moreover, the simulation data does not only contain information about the states (the number of particles) at each time point, but also about the events which lead to this state. In our cell biological case, these events can be either biochemical reactions, which transform some species into other species, thus changing their particle count, or they can be diffusions of particles from one voxel into a neighboring voxel, which also changes their count for the participating voxels.

The VioNeS toolkit [37] used for the visual analysis of this large volume of data utilizes multiple coordinated views to cope with the many individual aspects of the data, such as the spatial distribution of selected species and the events occurring at each time point. The different views are shown and described in Fig. 3. For visualizing the three-dimensional lattice and the distribution of the species within it, it relies on direct volume rendering, which is GPU-accelerated to guarantee interactive frame rates when animating the simulation trace or adjusting the time-slider manually. To represent the temporal aspect, a mapping from time onto time is used, meaning that only one time point is shown, but it can be manually selected from a time line or an animation can automatically move through the series of time points. It is coupled with the James II simulation framework, which thus could be used for analytical operations for time series analysis, e.g., to perform a steady state analysis. Apart from that, especially the analysis of cause and effect are supported by the multiple views showing the events (cause) and the subsequent state (effect) side by side. Hence, this Visual Analytics approach is able to yield not only information about how the states change from one time point to the next, but also more importantly knowledge about why they do so.

5. VISUAL ANALYTICS FOR SIMULATION: AN INTEGRATED APPROACH

The ideal case from a Visual Analytics point of view is when data on different steps is available, e.g., about the model, the configuration, and traces from single or multiple runs. As this is not always possible, it is important that the individual approaches and tools mentioned in the previous sections exist and can be used in their own right. Yet, if indeed all of these different information from the different steps of the Modeling&Simulation workflow come together, it is not only challenging to manage the large volumes of heterogeneous data (a graph structure describing the model, a set of node attributes assigned with initial states/values, single- or multi-run data for each such configuration containing data with spatio-temporal dependencies), but also to organize it visually to still allow for an intuitive analysis.

In this integrated case, the novel idea is that the visual analysis does not start with the simulation data, but that the process of simulation itself is a means of analysis. This is also in line with recent developments in modeling and simulation which exploit methods from workflow systems to guide users and document the different steps in modeling and simulation [32].

It generates as much additional data through repeated stochastic simulation as is needed to get a meaningful analysis result of statistical significance. This can include further configurations to cover so far unexplored spots of the parameter space, as well as further replications to gain a better understanding of observed trends in the data.

The Mosan framework [38, 14], which we employed for our analysis, integrates the averaged outcome of the multi-run simulation in an overview, thus "Showing the important", which is depicted in a node-link graph view in Fig. 4. It communicates the underlying model and its structure through the graph layout, which again encodes a chemical reaction network with the nodes being the reactants and products and the hyperedges (the dark blue shapes with arrowheads indicating the directionality of the hyperedge) represent the reactions. The major trends of the evolution of the species' concentrations as they were revealed by the simulation are embedded as iconographic representations within each node, so that upward and downward trends are clearly visible already from this overview. The issue of multi-scale data is countered by different icon backgrounds which indicate the order of magnitude for each of the shown concentrations.

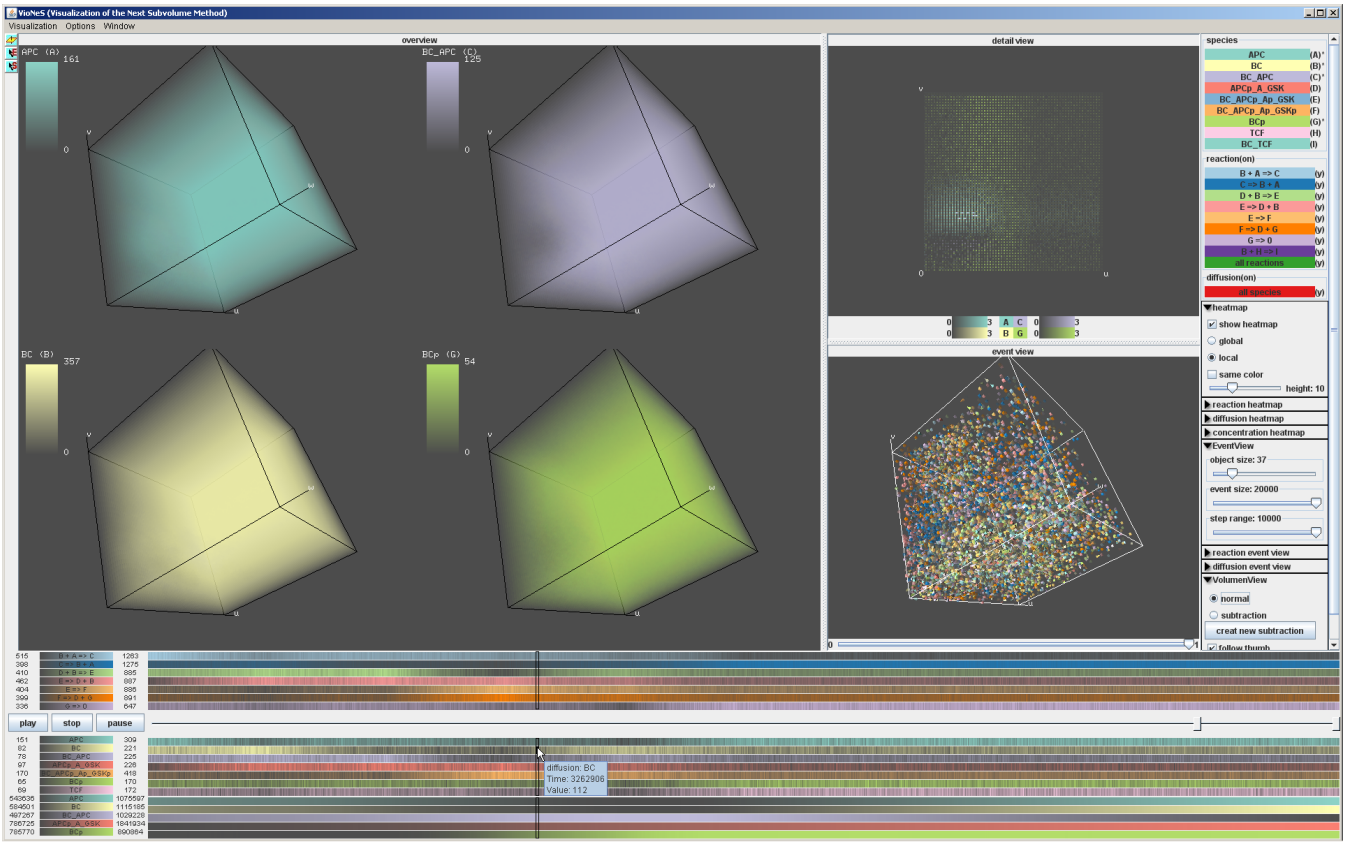

Figure 3: The VioNeS toolkit [37] showing a snapshot of a simulation run where the particles are already well-stirred and rather homogeneously distributed within the three-dimensional lattice, as it can be seen in the overview on the left. The recent reactions and diffusion events that have lead to this state are shown in the "event view" at the lower right. Details can be investigated on demand in the detail view at the top right, where a cut through the lattice is shown in the form of a two-dimensional grid. The time slider at the bottom can be used to move back and forth through the simulation trace, in which case the different views are adapted to reflect states and events of the currently chosen time point.

From this compact yet comprehensive overview "Details on demand" can then be brought up in linked, adjoint views which allow the user to investigate individual species and individual simulation runs thereof. Alternatively, the experiment view can also be subdivided to show simulation runs for multiple experiments side by side for a comparative visual analysis. Time points in focus as well as value ranges of interest for a species' concentration can be adjusted, which in turn filters the large amounts of data to the instances meeting these criteria – e.g., only those simulation runs, in which the concentration of a certain species exceeds a given threshold. This is aided by integrated analytical tools, e.g., for clustering time series in an "Analyse further" step.

The integration of different steps within one visual framework permits the user to move back and forth between the data from the different stages of the in-silico experimentation process, thereby allowing a better understanding of them and adding to the quality of simulation studies. Especially more complex analysis questions can be answered with such a combined visual access to all data, e.g., finding experiments that contain simulation runs that share a rarely observed trend. To realize such a fluent interactive back and forth between visualizations of data and analysis results from all stages of the experimentation is hardly possible with a collection of individual toolkits.

6. CONCLUSION

In this paper we identified the importance and challenge of taking the data generating process into account for Visual Analytics. Especially in the case where the data generation is done by simulation, the opportunity to gather additional data about the generation of the resulting data is given. Yet, how to incorporate this data derived from all stages of the in-silico experiment process with the Visual Analytics mantra is not straightforward, as it depends heavily on the requirements and available tools of the application scenario at hand. Hence, we have highlighted four different exemplary solutions for such an integration in the Modeling&Simulation life cycle for cell biological applications. These have added visual analysis support to help exploring the model, the configuration of the simulation experiment, and the simulation traces produced, as well as to combine all three of them, while at the same time tapping into the power of the analytical methods provided by the simulation and the statistical tools.

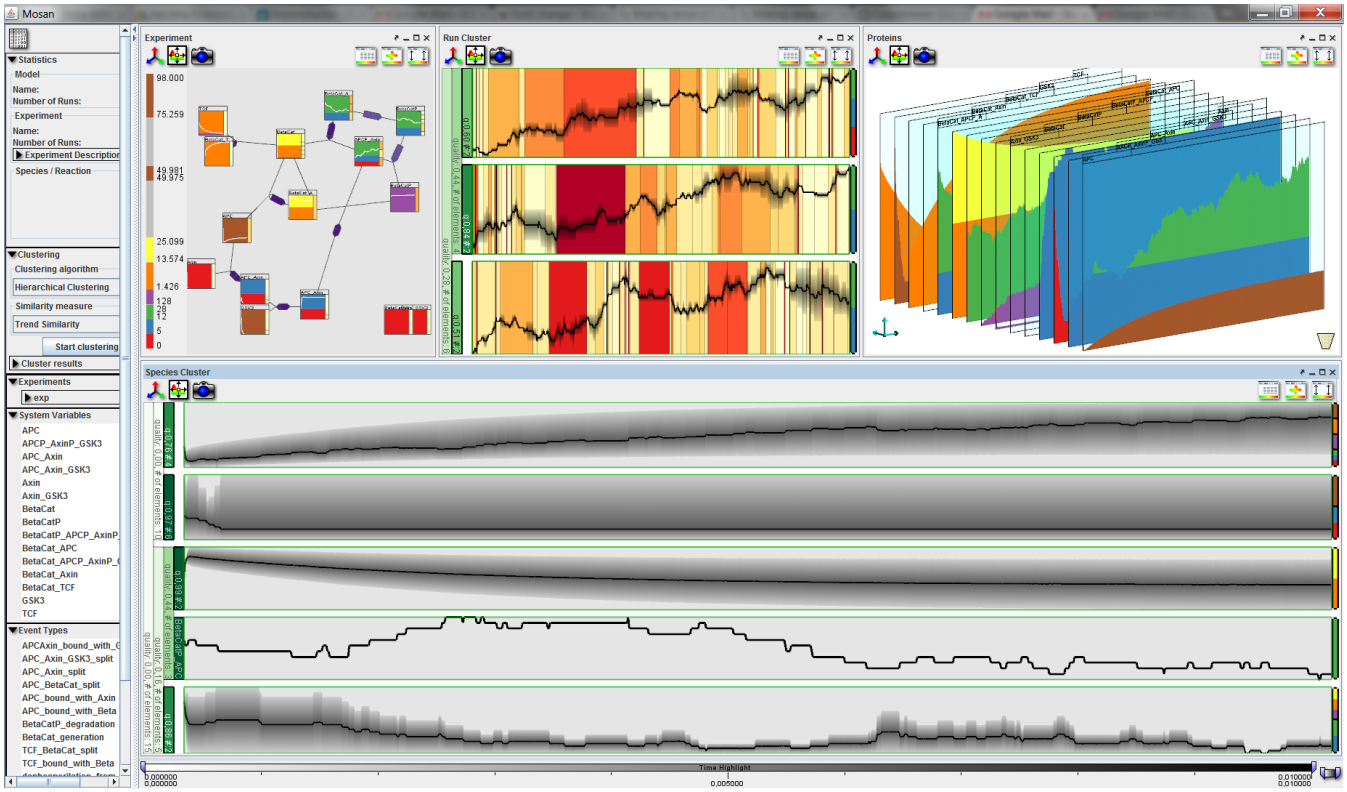

Figure 4: The integrated visual analysis of model, experiment setup, and multi-run simulation data in the Mosan framework [38, 14]. It combines three steps in its overview shown at the top left, where the averaged simulation data from multiple runs are embedded as icons in the model structure, which is in this case not as complex, because it only models a single pathway. The remaining views are used for in-depth investigation into individual species, single-run, and multi-run data.

The presented approaches cover only one direction of analysis – the visual analysis of data generated by the simulation process. The feedback towards the simulation, which would allow its interactive steering from within the visualization based on the already produced data, remains an open research question. However, it is this reverse direction, which would finally tightly intertwine Visual Analytics and the Modeling&Simulation life cycle, as it permits to use simulation not only for the "Analysis First" step, but also for repeated "Analyse Further" steps. This could mean, e.g., to exchange simulators to generate more precise outcomes for a region of interest, that has been identified in an overview originally produced from data generated by a first, faster running, approximative simulation algorithm. Hence, this is an important aim, which we will pursue in future work.

A first step in this direction is to also take into account those stages of the Modeling&Simulation workflow which were so far skipped, such as, the requirement specification or the observation of the model. These stages govern which aspects of a real system are actually modeled and then observed during simulation. They are important to investigate and support visually especially when the systems under study get even larger and more complex. Hence they are integral for extending the presented concepts and tools into a seamless support for an interactive and dynamic Modeling&Simulation process by means of Visual Analytics.

7. ACKNOWLEDGMENTS

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