VioNeS - Visual Support for the Analysis of the Next Sub-volume Method

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Abstract

Computational simulation is an established method to gain insight into cellular processes. As the resulting data sets are usually large and complex, visualization can play a significant role in data analysis. In this paper, we focus on the visualization of simulation output from the Next Sub-volume Method, a spatial simulation algorithm. In addition to the spatial context of the simulation output, its heterogeneous data types, multiple variables, and the temporal context make high demands on the visualization. To cope with these challenging characteristics, we systematically explore possible visualization concepts with respect to these characteristics. From these findings, we derive our specific solution to visualize the data from the Next Sub-volume Method, using a framework of multiple coordinated views that emphasize the spatial context of the data. Combining these views with a highly interactive user interface, the user is able to adapt the visualization to his current analysis goals and explore the data in its complexity.

1. Introduction

Many cellular processes depend on temporal and spatial interactions between biochemical species. For example, a signal from outside a cell can be transmitted to its nucleus, where it triggers the synthetization of new proteins to alter the behavior of the cell. The signal is transmitted via movements and interactions of molecules. To gain insight into these processes, computational simulation has been established as a supplementary methodology to experiments in the laboratory.

Over the last decades, a variety of simulation methods have been developed. One specific family are spatial stochastic simulation algorithms. As the name suggests, these methods treat all events (movement of particles and reactions between them) as *stochastic*, i.e. random. *Particle algorithms* [15, 3] can trace the position of each single molecule and execute reactions with a given probability whenever two particles collide. In contrast, *lattice-based algorithms*, e.g. the *Next Sub-volume Method* (NSM, [7, 14]), subdivide space into volume elements with an homogeneous distribution of particles.

In this paper, we focus on the visualization of simulation output from the Next Sub-volume Method. As this simulation algorithm produces complex and large data sets, visualization can play a significant role in data analysis. A very important characteristic of the data to be included in the visual representation is the spatial context. Here, many techniques from the field of volume visualization are available, most of them focussing on static and univariate volume data. However, the output of the Next Sub-volume Method is time dependent and multivariate. Although some of the existing approaches deal with multivariate and time dependent volume data, visualizing data with these characteristics remains a challenging task. In addition, the simulation output is composed of two heterogeneous data types. Besides analyzing the simulation data by its states over time, the simulation allows to track the process that leads to changes in the system state. This process is characterized by events, whose characteristics are different from states.

The goal of this work is to develop a visualization that supports the analysis of data derived from the Next Sub-volume Method with its heterogeneous, time-dependent, multivariate, and spatial characteristics. A single view cannot provide a solution for all those aspects. We present in this paper a framework that coordinates multiple views, each covering parts of the data. In particular, visualizations of multivariate state data and of multivariate event data, both including 3D spatial context, are coordinated with each other. Via animation or comparison of discrete time points, the system behavior can be analyzed over time. A highly interactive user interface allows to adapt the visualization according to the user's current questions about the data. As a whole, our visualization allows to explore the data in its complexity and, therefore, support various analysis goals.

This paper is structured as follows. First, we describe the Next Sub-volume Method and the simulation output in Section 2. Based on these characteristics, we classify the given data and discuss visualization approaches for such data in Section 3. Our specific visualization solution for the Next Sub-volume Method is introduced in Section 4, before Section 5 concludes this paper.

2. The Next Sub-volume Method

To simulate the interactions of biochemical species in a spatial and temporal context, the *Next Sub-volume Method* (NSM, [7, 14]) imposes a grid on the volume. In each grid cell (to distinguish from the biological term 'cell', the term 'sub-volume' is used in the remainder of the paper), a homogeneous distribution of particles is assumed. Movements of particles and their interactions are described by events. These events take place with specific rates that depend on the state of the sub-volume, i.e. the current number of particles. The estimated time between two events is an exponentially distributed random number with mean equal to the reciprocal of the sum of reaction and diffusion rates. With high rate or diffusion constants or a large number of particles inside the system, the inter-event times can become very small, i.e. the time scale of the system might drop to the microsecond or nanosecond domain.

Due to the stochastic nature of this algorithm, a single execution is not sufficient to derive valid statistical measures, e.g. means and variances in species populations. Therefore, depending on the model, a number of *replications*, i.e. executions of the same model but with different seeds for the random number generator are necessary, ranging from about 10 to, in some cases, several thousands. From the statistical measures, individual runs can be identified that show a specific behavior, which the analyst wants to evaluate in more detail.

To analyze a single run, the goal of this work is to visualize the data that characterizes its behavior. Two data types can be distinguished: *state data* and *event data*. While state data describes the system state for each time point, event data refers to events that change the system state over time. The state data is given by the number of particles in each sub-volume for each time point. As different species exist in the system, the number of particles has to be differentiated for each species. Thus, the data in each sub-volume is multivariate.

The event data consists of two types: reactions and diffusions. Reactions describe the interaction of multiple particles within one sub-volume. As a consequence, the number of particles is altered within the sub-volume. Reactions are characterized by the particles they involve, the 3D location in the grid, and the time point when they occur. Diffusions describe the movement of a particle from one sub-volume to a neighboring sub-volume. Hence, diffusions are associated with a direction. Diffusions can involve any of the particles in the system whose diffusion constant is non-zero. They are defined by the involved particle, the two neighboring sub-volumes that are affected, and the time point. As both event types are related to a specific subset of the multivariate particles, the events are multivariate as well.

For analysis, both multivariate events and states need to be visualized in their spatial and temporal context.

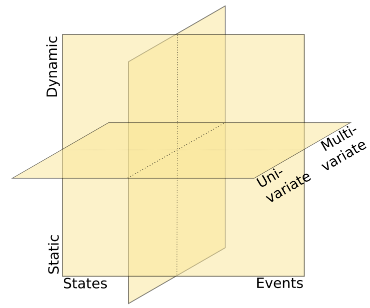


Figure 1. Classification of 3D-spatial data.

3. Classification of data characteristics

Given the simulation output of the Next Sub-volume Method as described in Section 2, it is apparent that the complex data makes high demands on the visualization. The data characteristic that is mandatory to be included in the visualization is the spatial context. Thus, we first review methods to visualize data in a 3D spatial context. In addition, the data can be analyzed with respect to six different characteristics, which can be seen as opposite pairs: events vs. states, static vs. dynamic data, univariate vs. multivariate data (see Figure 1). For each of these pairs, we discuss possible visualization approaches.

3.1. 3D spatial data

The visualization of spatial data, given as one scalar value per point on a 3D grid, has been extensively addressed in volume visualization (see [12] and [8] for an overview). We shortly introduce the two main concepts for rendering: direct volume rendering and surface extraction. In direct volume rendering, the visual representation is directly derived from the volume data, for example by ray casting, splatting, or texture slicing. A transfer function is used, which maps the scalar value of a voxel to graphic attributes. For example, the transfer function can affect the color and transparency of the visual representation of the volume element. Different transfer functions are appropriate depending on the data, the application background, and the rendering method.

To improve the effectiveness of the visualization, illustrative approaches [5] have been explored lately for volume visualization. Alternatively, surface extraction techniques use a threshold to derive an iso-surface, representing a constant value throughout the volume. After that, the iso-surfaces are rendered in the second step.

In general, it can be stated that volume rendering approaches often focus on univariate and static data and usually do not discriminate between event and states.

3.2. States vs. Events

The simulation output consists of two different types: states and events. Although they are semantically related to each other, their distinct characteristics need to be considered when deriving a visualization concept. State data consists of multivariate scalar values for each grid point over time. Events, however, are defined as occurrences at concrete time points and 3D locations.

To visualize state data in the whole 3D domain, volume visualization methods are well suited. They additionally need to include the dynamic and multivariate characteristics, which will be subject of discussion in the next two Sections 3.3 and 3.4.

Visualizing event data requires to highlight discrete points in time and space. A general taxonomy and survey of visualization approaches for events can be found in [6]. Focusing on spatial context of events, the fact that data is only given for parts of the grid is important for the visualization. Basically, approaches in this regard are comparable to 3D scatter plots (see, for example, [9]), where the axes represent spatial dimensions.

3.3. Static vs. Dynamic data

For data analysis, it is important to visualize the data for single time points as well as to evaluate the developments over time. We thus discuss visualization concepts for both static and dynamic data.

At a single time point, the visualization should allow to evaluate the value distribution of state variables in space. In addition, relations among the multivariate state variables as well as between state data and the current event are to be examined. The visualization of a single time point is driven by these goals.

The visualization of data over time, on the other hand, should explicitly reveal the development of the data values over time. To visualize time-dependent data, Aigner et. al. [1] speak of two possible mappings:

- Mapping time on space
- Mapping time on time

When mapping time on space, multiple time points are visualized simultaneously. In contrast, mapping of time on time refers to visualizations changing over time.

Mapping time on space has the advantage that the development over time becomes visible at a glance. Time can be included either explicitly as a spatial dimension or implicitly by using visual comparison techniques. With time mapped on a spatial dimension in the visual representation, as it is done in time value plots, at most two spatial dimensions of the data can be shown. Thus, this approach could be used for 2D slices from the 3D volume, but not for the whole spatial domain.

Visual comparison techniques allow the simultaneous representation of data from multiple discrete time points. They are subdivided into image based comparison and data based comparison [11]. Using image based comparison, multiple visual representations of the same type are arranged on the display, each including a different time point. It therefore uses up more space on the display than the visualization of a single time point.

Data based comparison refers to the combination of data from multiple time points into a single visual representation. One example implementation is a difference image [13] from two time points, where only the values that have changed would be non-zero. With other computational methods, changes in the data can be highlighted while the unchanged data is shown as well.

Overall, only a limited number of time points can be simultaneously shown with visual comparison concepts.

The second approach, *mapping time on time*, is usually referred to as animation. The visualization changes over time according to the consecutive time points given in the data. The speed of animation does not necessarily comply with the time domain of the data, as the scale of the time domain might not be appropriate for the animation. In general, the user is able to sequentially explore the data in an intuitive way. Nevertheless, the data is not directly comparable for multiple time points.

3.4. Univariate vs. Multivariate data

The data analysis for the two data types, event and state data, is required in both a univariate and multivariate context. When regarding univariate event data, the events are discerned by the time point when they occur, the 3D location, and the general event type (diffusion or reaction). Multivariate event data additionally distinguishes events by the state variables they are related to. Looking at state data, the univariate data includes the value distribution over space and time for a single state variable. This data given for all state variables forms the multivariate state data. Thus, for each point in space and time, a scalar value is given for every state variable. The visualization should support the user in evaluating the dependencies among the state variables.

The visualization has to provide methods for a data analysis under all these aspects. As both univariate and multivariate event data refer to the same data entities, similar visualization concepts can be used to locate events in time and space. Multivariate event data, however, requires additional visual cues to discern events by the state variables they are related to.

To visualize the spatial and temporal context of univariate state data, concepts can be applied that have been discussed in Sections 3.1 and 3.3. The visualization of multivariate state data in space and over time is a more challenging task. To handle multivariate data, a number of specific visualization approaches exist. Scatter plots and parallel coordinates are examples, but they are not designed to communicate a 3D context of the data.

For the visualization of multivariate volume data, two general approaches are distinguished in the literature:

- Multivariate direct volume rendering
- Visualization of multivariate data on 2D slices

Using *multivariate direct volume rendering*, the multivariate values per grid point are mapped to graphic attributes of the grid point's visual representation. Then, volume visualization methods (see Section 3.3) can be used for rendering. Akiba et. al. [2] list the following three mapping techniques in this regard: The first technique maps multiple variables to the individual color components of the voxel color. This approach allows to visualize at most 3 variables, as the common color spaces like HSV and RGB compose colors from 3 components. Secondly, one variable value can be selected as the representative value of the grid point. Therefore, a suitable rule needs to be found to select the representative variable. The third approach refers to composing multiple variable values into one value. Here, a proper weighting of values needs to be derived.

An alternative to the multivariate visualization within one volume is to visualize one volume for every variable. Such an image based comparison requires more screen space than a compact visualization. In addition, a direct comparison of values at the same 3D location is not supported by this approach.

To this end, several visualization concepts have been proposed that make use of a *visualization of multivariate data on 2D slices*. Preim et al. [13] propose the use of color icons or a magic lens. Color icons are composed of multiple color values, each derived from the mapping of one scalar value of the voxel. The icon for each voxel is displayed at the corresponding position on the 2D slice. The magic lens, on the other hand, allows to display additional variables in the interactively located lens than in the other parts of the visualization.

All these approaches are designed to visualize at most 3 or 4 variables. This is not only due to technical limitations. More importantly, the limitation arises from the observation that visualizing multiple variables in a spatial context is highly demanding for the user.

4. Visualization Design and Framework

In this section, we introduce our specific visualization framework to handle the data from the Next Subvolume Method. The general design choices of our visualization are subject of Section 4.1. Then, the framework is described in Section 4.2.

4.1. Visualization Design

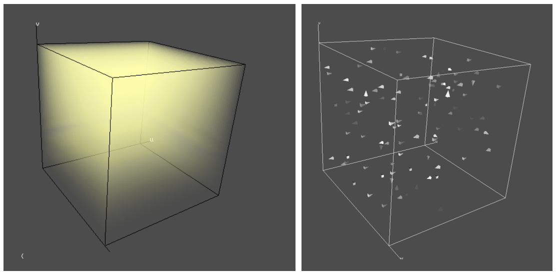
To find an appropriate visualization design, we base our design choices on the characteristics of the data. Mandatory for the visualization is to communicate the spatial context of the data. As discussed in Section 3, three opposite pairs of data characteristics need to be considered in the visualization as well: states vs. events, static vs. dynamic data, and univariate vs. multivariate data. Our goal is to derive a visualization design that allows to evaluate the data by all these characteristics.

4.1.1. States vs. Events

As the first pair of data characteristics, we discuss the visualization for states and events.

In Section 3.2, volume visualization methods have been identified as being suitable for state data. Two general rendering methods, surface extraction and direct volume rendering, are available. As the data at hand is not continuous in space, meaningful iso surfaces cannot be extracted from the volume data. Thus, we make use of the latter variant [8, 10] to analyze the value distribution. To achieve interactive frame rates, we apply texture slicing with object aligned slices [8], as it is one of the fastest approaches for volume rendering (Figure 2a).

To visualize an event in its spatial context, the 3D location has to be communicated by the visualization. To this end, we make use of 3D icons that are placed at the corresponding position (Figure 2b). The two event types, reactions and diffusions, are discerned by the icon shape. As a reaction induces changes within one subvolume, it is encoded by a cube covering the volume element. Diffusion describes the movement of a particle between two neighboring sub-volumes. To convey the direction, the icon is shaped as an arrow pointing from the source sub-volume to the destination.



(a) State view (b) Event view

Figure 2. Basic visualization of states (for a single time point) and events (for multiple time points) in their spatial context

4.1.2. Static vs. Dynamic

The analysis of the simulation includes both the exploration of value distributions at a single time point as well as exploring trends over time. For one time point, the visualization needs to include the multivariate state and event data in spatial context. A visualization of the dynamic data should convey the state changes over time and the sequence of events that leads to these changes.

To include time in the visualization of state data, two concepts have been described in Section 3.3, the mapping of time on time or on space. In our context, both methods are valuable. Animation can reveal the general behavior of the simulation, while the comparison of discrete time points supports a detailed analysis.

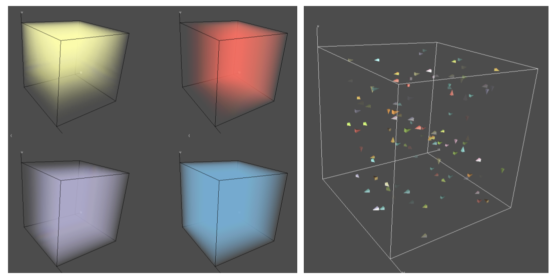
We implement both concepts for event and state data. To show event data over time in an animation, visualizing an event only for the time point where it occurs is visually hard to follow and reveals little information about the temporal context. Instead, the sequence of events from previous time points is visualized by including the respective events within one volume. The temporal order is conveyed by the transparencies of the event icons. After the event icon appears opaque in the visualization of the time point when the event occurs, it slowly fades out. When visualizing state data in an animation, the data shown in the univariate volume is altered over time.

Referring to the comparison of discrete time points, the events at these time points are included within the event visualization. To visualize state data at different time points, we use multiple univariate volume, each for one point in time. As an alternative, two discrete time points can be compared by the difference image from the corresponding univariate volumes.

4.1.3. Univariate vs. Multivariate

Due to distinct characteristics of state and event data, we discuss the visualization concepts to consider univariate and multivariate data separately for two data types.

To visualize univariate state data, standard approaches of direct volume rendering can be applied. To show multivariate state data, the visualization includes one volume for each variable, as shown in Figure 3a. Other approaches like the combination of multiple variables in one volume or the multivariate visualization on 2D slices are not suited for the data at hand, as different scales exist in the data and we want to show the spatial context. Multiple univariate volumes allow the general comparison of value distributions for multiple variables.



(a) State view (b) Event view

Figure 3. Visualization of multivariate data. Left: Combining multiple univariate state volumes. Right: Using colors to encode multivariate event data.

To visualize multivariate events, the visual attributes of event icons are adapted. As the shape is already determined by event type, we make use of the icon color. They are encoded according to the state variables that are related to the event. Diffusions are defined for one state variable. Thus, the color of the variable can be used to encode the event icon. Reactions, however, involve multiple variables. The icon color of a reaction cannot be mapped to those of the corresponding state variables. Instead, one user-defined color is assigned to all reactions that are related to the same state variables. Figure 3b shows multivariate events in the volume.

4.2. Visualization Framework

After designing the visualization of the given data, we now describe the implementation of these concepts within one framework. In general, the data is read from a database and visualized in an interactive post processing step, as the simulation is computationally expensive.

To visualize the data by all the aspects that have been discussed, a single view does not provide a comprehensive solution. We therefore use multiple coordinated views. Accounting for the guidelines to minimize the number of views [4], we try to derive a minimum number of views from the proposed visualization concepts. As it has been shown in the discussion, the two data types event and state data require different visualization concepts. We therefore generally implement separate views for event and state data. The following discussion will show how the characteristics of event data can be included in one view and the characteristics of state data in a second view. We describe the design of these views, their linking, and interaction methods included in the framework to adapt the visualization to the user's needs. Figure 4 gives an overview on our framework.

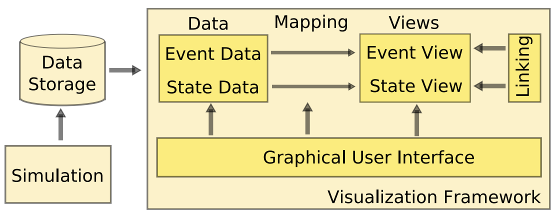


Figure 4. Visualization framework

4.2.1. Event View

The event view integrates the visualization concepts for event data considering all aspects discussed above. We visualize the event for one time point as a 3D icon at the corresponding 3D location. The shape of the icon encodes the event type, while the color discerns events by related state variables. This approach can easily be extended to include multiple events over time. Considering a sequence of events over time, we integrate them all within one volume and convey the temporal order by the transparency of the icon.

However, the color coding of multivariate events has limitations. The user can only discern a limited number of colors, especially as the icons representing the events are pretty small in the visualization. Therefore, the user has the ability to interactively select a subset of events, based on related state variables. The events are then explicitly highlighted in the visualization by the use of color, while all other events are visually de-emphasized by either hiding them or applying a uniform color.

4.2.2. State View

To provide a visualization with all discussed aspects, the state view has to account for developments in the data over time and for the comparison of multiple variables. The univariate volume visualization shows the data for one variable at one point in time. Including multiple univariate volume visualizations for different variables enables the comparison of variables. For comparison of time points, multiple univariate volumes are shown, all for one variable, but different time points.

These methods have in common that they use the visualization of univariate volumes, either in one or multiple representations. To avoid cognitive overload, the number of simultaneously shown univariate volumes is limited to four. The color of a univariate volume is determined by the corresponding state variable, the scalar value of the voxel is mapped to transparency. The limitation to four volumes allows for a very efficient rendering, as the data can be stored within a single 3D texture in $RGBA$ format and loaded into the texture memory. Every element in $RGBA$ contains a transparency value that encodes the data value at that point.

As an alternative to visualizing the values in the volume directly, we allow to build a difference image from the volumes of one variable at two different time points.

4.2.3. Visual Linking of Views

As a general design choice, we decided to separate event and state data visually. However, the two types are related to each other in a temporal and spatial context. These interrelations of the data characteristics can only be communicated by an appropriate linking among the views. To visually link the views by their spatial context, the same volume transformation is applied to all volumes in both views. Providing a linking of the temporal context, state and event view visualize data from the same time points. On the one hand, discrete time points can be visualized in both views. On the other hand, an animation can be run in the state view while the corresponding sequence of events is visualized in the event view, with a transparency encoding to indicate the temporal order of events. In addition, it has to be guaranteed that the same transfer functions are applied to all state variables in all views.

4.2.4. Interaction Methods

Due to the complex data, the user should be able to adapt the visualization to his needs. Therefore, we provide a range of interaction methods. First, the user can adjust the volume transformation that is applied in both the event and state view. In addition, he can select up to four variables that are shown in the state view and the events that should be included in the event visualization. Moreover, the user has control about the visualized time points. He can either do this by selecting time points or by running an animation. Interactions like pausing, adjusting the animation speed, and jumping to time points of interest, give the user full control about the visualization of the temporal domain. As the last aspect, the user can manipulate the colors that are assigned to the state variables and the events.

4.2.5. Discussion

The multiple view framework VioNeS allows to analyze the simulation data from the Next Sub-volume Method in its complexity, while making use of two basic views. This is achieved by subsuming visualization concepts for various analysis aspects in each view. Thus, the user needs to understand few visual representations, which we believe helps the user to get an easier access to the data. The data exploration is further supported by a highly interactive user interface, allowing to intuitively adapt the visualization. The arrangement of views, their current state, and the time points of interest can be adapted with a few mouse clicks on top of the visualization. The variables are chosen in an additional panel, which also allows to manipulate the advanced color coding scheme for variables and combinations of variables. Using a GPU based rendering, the visualization of data sets with a high spatial resolution, i.e. 100x100x100 sub-volumes, is possible at interactive frame rates.

The framework is flexible in the sense that additional views can easily be added. For example, a detail view to analyze multivariate state data on 2D slices is shown in the screen shot of our framework in Figure 5. It is linked with the 3D state view by visualizing the same state variables and reusing their colors, and by the interactive selection of the current 2D slice from the volume.

The VioNeS tool has been used by simulation experts for visual debugging of algorithms. The visualization allows to check the data for unexpected distributions of particles or an accumulation of diffusion events in a specific area, which can hint to errors in the algorithm implementation. The presented methods thus help the user to first get an overview of the state and then zoom in to analyze the specific states of single sub-volumes.

5. Conclusion

In this work, we examined visualization concepts to analyze spatial, heterogeneous, multivariate, and time dependent data that arises from the Next Sub-volume Method, a spatial simulation algorithm of cell biological processes. In a systematic approach, we derived a classification of the data according to its characteristics and explored concepts to visualize such data in a spatial context. From that discussion, we identified appropriate concepts for our data, which were integrated into a framework of multiple coordinated views. Views in the framework have been designed to subsume various visualization concepts appropriately. So, the number of separate views could be reduced to two views, one for each of the heterogeneous data types event and state data.

To our knowledge, our framework brings together such heterogeneous data within a single interface for the first time. It is thus unique in allowing the exploration of the dependencies among the different data types via linked views. This is very valuable in the mentioned application for visual debugging, as our framework not only visualizes the results of the simulation, given by the state data. Moreover, by including event data, it provides information about how these results are generated.

The presented methods are not limited to the visualization of the Next Sub-volume Method, but can be used for other algorithms as well, e.g. single runs of the GMP algorithm [14]. Therefore, the introduced framework can be a valuable tool for users of various simulation systems, as it is not tied to a single simulation algorithm. It rather tries to identify requirements for the visualization of complex time and space dependent data and provide appropriate representation techniques.

To support the user in the analysis of multiple runs of the stochastic simulation, we will explore methods to aggregate data from multiple runs both computationally and visually. This future research aims at simplifying the identification of simulation runs with interesting behavior, which can then be analyzed in detail using the visualization methods we introduced in this paper.

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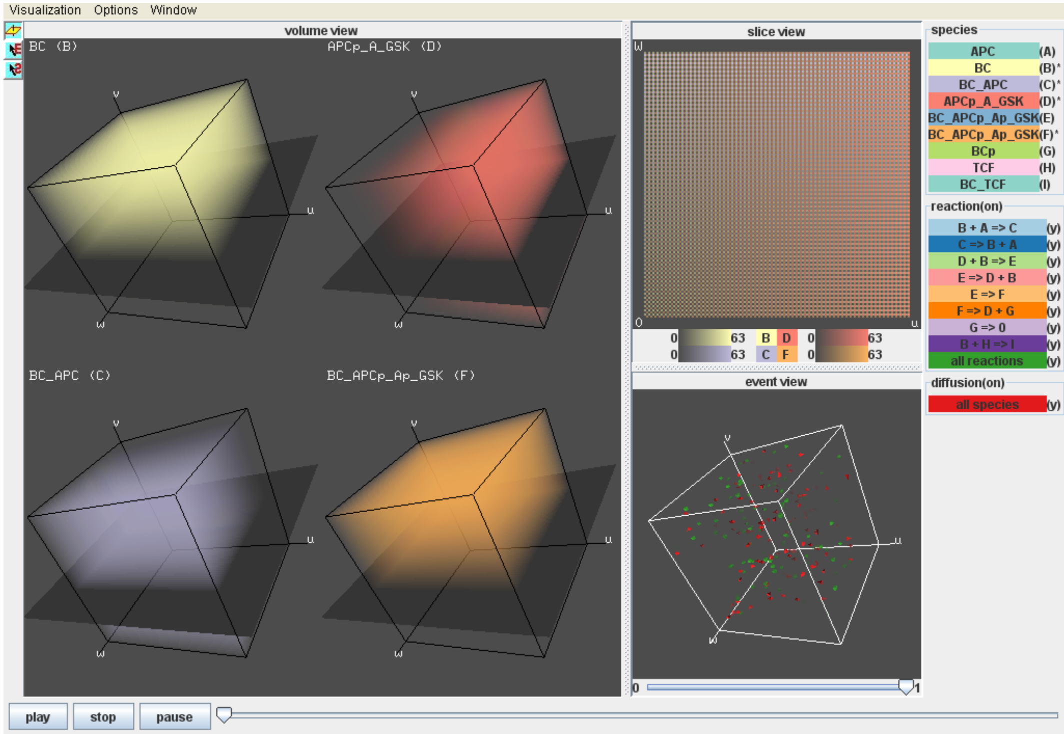

Figure 5. The multiple view framework VioNeS, visualizing data at a single time point. In the state view (left), multiple univariate volumes are shown, each for a different state variable. The event view (bottom right) includes a sequence of previously occurred events in a univariate context, only separating diffusions and reactions. Their age is encoded by transparency. Additionally, a 2D slice view is included at the top right.

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