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A visual analytics system to support the formation of a hypothesis from calcium wave data

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ABSTRACT

In most species, calcium waves in the oocyte are considered common phenomena in the activation of eggs. However, the mechanism of calcium waves has not yet been clarified. By collaborating with biologists studying *Caenorhabditis elegans* (*C. elegans*), which is widely used as a model organism, we observed that the following requirements must be satisfied to form a useful hypothesis based on calcium waves captured using high-speed in vivo imaging: (1) the ability to obtain an overview of how the calcium waves are propagated and (2) the ability to understand the propagation of waves in a narrow region. However, conventional visualization methods cannot satisfy these requirements simultaneously. Therefore, we propose a visual analytics system that allows users to understand and explore calcium wave images using cross-correlation analysis of the time-series data of the Ca^{2+} fluorescence intensity at each point. The interface of this system comprises an overview visualization, a detail visualization, and user interactions to satisfy these requirements and realize exploratory visualization. Some views present an overview visualization that displays the clustering results of a directed graph calculated using cross-correlation analysis. These views enable the users to understand the overview of wave propagation, thereby helping users find a region of interest. The detail visualization shows the relationship between the region of interest and other areas. Furthermore, users can use the proposed system with overview-detail and brush-link exploration to assign meaning to the region of interest and construct a hypothesis for its role. In this paper, we demonstrate how the proposed visual analytics approach works and how new hypotheses can be formed using the analysis of *C. elegans* calcium waves.

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1. Introduction

It is known that the concentration of intracellular calcium ions increases during fertilization in animal oocytes and eggs (Whitaker, 2006). This phenomenon is termed as calcium waves because the increase in calcium ions propagates as a waveform from the sperm entry point. In addition, depending on the species, calcium oscillation occurs, which involves repeated increase and decrease of calcium ion concentration (Stricker, 1999). An increasing calcium ion concentration is an important signal for activating the oocyte and causing subsequent cell division. Previously, numerous studies on calcium waves have been conducted because the relationship between calcium waves and subsequent evolution can be clarified by elucidating the propagation of calcium waves.

We collaborated with life scientists who are investigating to reveal the mechanism of calcium waves, as well as the differences between measured and simulated calcium waves. Compared to simulated waves, the measured data demonstrate a complicated behavior. These scientists are investigating the mechanisms responsible for such complex behaviors and the physiological meaning of those mechanisms. However, there is lack of hypotheses on which to perform an experiment and

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improve simulations because the complexity of calcium waves observed in imaging data makes it difficult to extract useful information. Furthermore, these scientists hope to reveal the specificity of the phenomenon in a data-driven manner. One approach to satisfy these objectives is to support hypothesis construction using visual analytics.

In several meetings with domain experts, we determined that two design requirements must be satisfied to support hypothesis formation from calcium wave data: (1) the ability to obtain an overview of how calcium waves are propagated and (2) the ability to understand the propagation of waves in a narrow area. To enable experts to observe and interpret a region of interest (ROI), both requirements must be satisfied simultaneously. Some methods that satisfy these requirements individually have been proposed. Methods that satisfy requirement (1) include flow visualization (Afrashteh et al., 2016) using optical flow and flow visualization (Yamashita et al., 2012) using Granger causality (Granger, 1980). Methods that satisfy requirement (2) include calculating the direction of the vector of the flow field (Takagaki et al., 2011) and cross-correlation analysis within a small area of the image. However, to the best of our knowledge, no existing methods can satisfy both requirements simultaneously.

In this study, we introduce a visual analytics system for calcium wave data to realize exploratory visualization in order to find and interpret ROIs. The proposed system enables users to (1) understand an overview of the relationships among various areas in calcium wave images, (2) select an ROI, and (3) visualize the detailed relationships between the selected ROI and other areas. The proposed system comprises an overview visualization that supports finding ROIs and a detail visualization to facilitate interpretation of the ROIs. The overview visualization uses cross-correlation analysis to calculate a directed graph that indicates the relationship of increased calcium concentration at various points in the oocyte. To make this directed graph easier to understand, we cluster it using an Infinite Relational Model (IRM) (Kemp et al., 2006). In addition, we used the Sugiyama framework (Sugiyama et al., 1981) to visualize the other graph to enable users to view the relationships between clusters. The detail visualization uses the cross-correlation analysis results to shows how the area selected by the users relates to the remaining areas. By connecting these visualizations, users can repeatedly find and interpret ROIs to form a valid hypothesis. In this paper, we demonstrate the effectiveness of the proposed visual analytics system by analyzing calcium waves in *Caenorhabditis elegans* (*C. elegans*).

2. Related Work

This section presents the related works on three closely related research topics.

Calcium Wave Analysis. The propagation of calcium waves during fertilization and signal transmission by calcium waves are common phenomena in many animals. Fabrizio et al. (2014) applied Granger causality (Granger, 1980) and cross-correlation to test and visualize the relationships between the measured intercellular calcium concentrations at 11 points in the 30-somite stage embryo of a zebrafish. Buibas et al. (2010) formed networks of neurons and glia by computing the vector field obtained from calcium signaling imaging data using an optical flow technique. Milovic et al. (2013) developed a system that employed image processing to automatically recognize calcium waves generated during signal transmission between cells. In addition, they analyzed the wave-front velocity. The results of these studies indicated that time-series analysis and image analysis algorithms are effective for the analysis of calcium waves. However, these studies did not focus on finding and interpreting ROIs. In this study, we propose a visual analysis system that supports finding and interpreting ROIs based on the method proposed by Fabrizio et al. (2014). However, our study differs in that the number of locations where calcium waves are defined is approximately 200, which is significantly greater than the 11 points examined by Fabrizio et al. To make it possible for experts to understand the cross-correlation analysis results, we have developed a visual analysis system that includes multiple views and user interactions.

Visualization of Geographic Relational Data. Visualization of the origin-destination flow is related to the proposed system in that our approach utilizes a directed graph to depict the relationship at each point in the oocyte. Both approaches require the information to be displayed along with the directional geographic information. Several studies have investigated visualization of relational data using geographic positions. For example, Guo and Zhu (2014) proposed a method used to extract major flow patterns from large geographic mobility data to understand mobility flows. Da Lozzo et al. (2015) proposed a method used to draw a georeferenced graph to explore relationships using 2.5D visualization. Von Landesberger et al. (2012) proposed a visual analytics system for categorical spatiotemporal data that can be used to understand and explore geographic temporal movement of categorical data. However, these approaches do not focus on searching for characteristic areas using geographical relational data by considering the relationship of an ROI to other areas. The proposed system is designed to help experts explore such ROIs interactively.

Visualization and Visual Analytics for Relationship Analysis. Several studies have proposed visualization and visual analytics techniques that enable users to reveal various relationships. Zhang et al. (2015) proposed a visual analytics method used to support correlation analysis between multivariate data, and Wang and Mueller (2016) extended this system to support causality analysis based on regression analysis. In addition, Wang and Mueller (2016) indicated that their method could be extended to time-series data using Granger causality (Granger, 1980). However, the method proposed by Wang et al. cannot handle numerous time-series data easily. Köthur et al. (2015) proposed a visual analytics approach to perform windowed cross-correlation analysis (Boker et al., 2002) to overcome the difficulty associated with windowed cross-correlation in two time-series ensembles when more than two ensembles are present. Frey et al. (2012) proposed a visualization method used to explore similarity using spatiotemporal data. Their visualization illustrates the clustering of similar time-series data based on correlation. These methods help users understand and

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