Data and text mining

Vizardous: interactive analysis of microbial populations with single cell resolution

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Abstract

Motivation: Single cell time-lapse microscopy is a powerful method for investigating heterogeneous cell behavior. Advances in microfluidic lab-on-a-chip technologies and live-cell imaging render the parallel observation of the development of individual cells in hundreds of populations possible. While image analysis tools are available for cell detection and tracking, biologists are still confronted with the challenge of exploring and evaluating this data.

Results: We present the software tool Vizardous that assists scientists with explorative analysis and interpretation tasks of single cell data in an interactive, configurable and visual way. With Vizardous, lineage tree drawings can be augmented with various, time-resolved cellular characteristics. Associated statistical moments bridge the gap between single cell and the population-average level.

Availability and implementation: The software, including documentation and examples, is available as executable Java archive as well as in source form at https://github.com/modsim/vizardous.

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Supplementary information: Supplementary data are available at Bioinformatics online.

1 Introduction

Single cell analysis with time-lapse (fluorescence) microscopy has been widely established in the life sciences in recent years. Whereas microarray analysis and flow cytometry yield population level data at a particular point in time, time-lapse live-cell imaging targets the assessment of individual cell parameters with their spatial and temporal (lineage) context. Microfluidic lab-on-chip technologies have enabled the parallel cultivation of hundreds of cells over several generations (Nobs and Maerkl, 2014; Wang et al., 2010). Combined with time-lapse imaging, it has been used, e.g. to study the dynamics of cellular regulation mechanisms and stochasticity of metabolism (Kiviet et al., 2014; Levine et al., 2013; Locke and Elowitz, 2009; Young et al., 2012), to investigate cellular size homeostasis (Campos et al., 2014; Taheri-Araghi et al., 2014) and phenotypic heterogeneity in dependence of stressors as well as the detection of rare events (Balaban et al., 2004; Rosenthal and Elowitz, 2012).

The easy availability of time-resolved data poses new challenges on data analysis by the mere amounts and complexity of acquired information. While several, typically organism-specific, image analysis tools are available for cell detection, feature extraction and tracking tools for the generic task of analyzing and understanding this information are lacking. We developed the software tool Vizardous to assist researchers with the following single cell data related tasks: (i) visualize data with single cell resolution in the lineage context, (ii) visually detect emerging structural patterns such as (a)symmetries in subtrees and (iii) assessing joint cellular properties and structural motifs.

2 Description

The single cell community has adopted phylogenies (lineage trees, Fig. 1) to visualize mother–daughter relationships in context of
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3 Vizardous exploration workflow

The most important analysis steps are explained with a representa-
tive evaluation workflow using pre-processed time-lapse videos of a
growing Corynebacterium glutamicum population under transient
carbon limitation (for details see Supplement 1):

Step 1: Importing experimental data. Single cell data are read from
phyloXML and MetaXML file pairs containing lineage information
and figures about individual cells, respectively. One or more of such
file pairs can be imported from a local file system or an external
storage location, e.g. OMERO (Allan et al., 2012).

Step 2: Visualization of lineage trees. Lineage trees are generated
and visualized alongside population distributions for a complete
experiment or a specific time point (temporal slice). As an indica-
tor of population heterogeneity statistical moments (mean, SD) are
calculated for the selection.

Step 3: Highlighting individual cells. When screening for rare events
or outliers in populations, the highlighting of single cells in a lin-
eage tree according to cellular properties is especially useful. Two
different approaches are implemented:

1. Change the property of a lineage tree element (node or branch)
   according to a specified cellular property, e.g. nodes are sized according to the cell area.
2. Set a threshold for a cellular property and highlight all cells
   that exceed the defined value.

Step 4: Selecting cells for inspection. The user has the possibility to
interactively select (and deselect) individual cells of interest from
the lineage tree. The associated information is visualized in trace
charts (Fig. 1). These charts unlock the contextual interpretation
of feature dynamics along the temporal axis therewith bridging the
gap between the ancestral relationships of cells and their meta-
information.

Step 5: Exporting lineage trees and charts. The lineage trees and sin-
gle cell traces are fully customizable and exportable to publication
ready vector graphics (SVG) or bitmap formats (JPEG, PNG).
Additionally, the data underlying single cell traces can be saved to
tabular data formats (XLS, CSV) for further processing.

4 Results and conclusions

Vizardous has been used in several studies, e.g. (Binder et al., 2014;
Mustafi et al., 2014; Nanda et al., 2014; Probst et al., 2015), by sci-
ents with different backgrounds to answer a variety of scientific
questions. These and further case studies (cf. Supplementary Data)
show that Vizardous is a versatile tool that supports researchers in
various aspects with the discovery-driven, explorative analysis of
single cell experiments. By supporting additional input formats and
seamless integration with available bioimage analysis software we
anticipate that a range of fields including biological and medical sci-
ences will benefit in the future.

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Fig. 1. Lineage tree extracted from an experiment with fluorescence reporters
to elucidate the regulation dynamics of key genes. Time-resolved fluores-
cence traces are shown in the bottom chart for two lineages. Cellular charac-
teristics, i.e. cell area, fluorescence, are shown for selected cells in the table
on the left.