Gene expression

TissUUmaps: interactive visualization of large-scale spatial gene expression and tissue morphology data

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Abstract

Motivation: Visual assessment of scanned tissue samples and associated molecular markers, such as gene expression, requires easy interactive inspection at multiple resolutions. This requires smart handling of image pyramids and efficient distribution of different types of data across several levels of detail.

Results: We present TissUUmaps, enabling fast visualization and exploration of millions of data points overlaying a tissue sample. TissUUmaps can be used both as a web service or locally in any computer, and regions of interest as well as local statistics can be extracted and shared among users.

Availability and implementation: TissUUmaps is available on github at github.com/wahlby-lab/TissUUmaps. Several demos and video tutorials are available at http://tissuumaps.research.it.uu.se/howto.html.

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Supplementary information: Supplementary data are available at Bioinformatics online.

1 Introduction

Histopathology refers to the examination of tissue samples through a microscope to study the manifestations of disease. Typically, tissue morphology is visualized by common stains such as hematoxylin and eosin (H&E). Today, novel techniques make it possible to also detect and visualize the molecular composition of the tissue with subcellular resolution, while preserving spatial information. Techniques like in-situ sequencing (ISS), MERFISH, osmFISH, seqFISH and STARmap explained in Strell et al. (2019), produce millions of spatially resolved data points describing transcript locations of hundreds to thousands of targeted genes. Technological advances allow for fast scanning with high resolution, resulting in gigapixel whole slide images (WSI) on one hand, and millions of data points on the other. Furthermore, tissue morphology, such as size, shape and neighborhood relations of cells, or more complex features defined by deep learning, can be quantified and presented as color-coded markers.

All these sources of information combined provide cues on manifestation of disease, and are pivotal for the discovery of new biomarkers relevant for clinical decision making and personalized medicine. As an analogy, one can combine geographic data (satellite and terrain images) with Global Positioning Data (spatial coordinates), where emerging patterns can be observed and new associations between information modalities can be studied.

To build open source software, certain considerations have to be taken into account. As explained in Mareé (2019), a software can be made for running in the desktop (locally) or in the web. An example of a local WSI viewer is QuPath (Bankhead et al., 2017) and examples of web viewers are OMERO.viewer (Allan et al., 2012) and Cytomine (Mareé et al., 2016). They all require an extensive set of libraries to function, because they aim to cover a very broad range of digital pathology practices basically turning the computer into a full server with intricate interconnections between many different libraries.

TissUUmaps focuses on the information visualization aspect of data analysis where visual representations of data lead to better human cognition and interpretation. Apart from interaction, such as zooming, panning, changing of marker size and shape and switching between data from different imaging modalities, the user can also draw regions of interest and extract localized information to explore tissue heterogeneity. TissUUmaps is designed for three types of users; the user only wanting to view and explore data made available by someone else, the user that has own data and wants to use the standard functionality locally, and the advanced user that wants to provide it as a service and/or add new functionality. For the first category of users, no external installations are required because it only needs a web browser (e.g. Chrome, Firefox, Safari) which comes preinstalled in modern computers. To run locally, you only need to copy the TissUUmaps repository and transform the images to tiled format. To provide TissUUmaps as service, the flexibility of the open source framework makes it easy to deploy new, specialized tools, e.g. for viewing pairs of tissue slices simultaneously by instantiating synchronized viewers and selecting control points for aligning images of consecutive tissue slices. We have created a collection of video tutorials (tissuumaps.research.it.uu.se/howto.html) for a...
standard user and up to an advanced level on how to extend TissUMaps.

Point data visualized by TissUMaps are not limited to gene profiling. Working with the tiled WSI, individual cells can be segmented using tools such as CellProfiler (Kamentsky et al., 2011) or Ilastik (Berg et al., 2019), followed by automated extraction of a large number of different per-cell measurements, such as cell shape, area, perimeter, etc. After transformation to global coordinates, this type of information can be visualized as color-coded point data using TissUMaps, quickly providing an overview of heterogeneity in tissue morphology.

2 Implementation, deployment and use

TissUMaps is open source and created using standard web development tools, pure html, CSS and vanilla JavaScript. It uses a small number of libraries, as described below, making it easy to setup and maintain without containers.

In its base configuration, TissUMaps organizes the data into image data and marker data. Image data are the WSI in a tiled format, and marker data are everything that can be overlaid on it, such as points representing gene expression, per-cell measurements, regions and annotations or any other spatially resolved data. This is reflected in the user interface where the corresponding tabs allow the user to navigate the data.

To display image data, we use OpenSeadragon (openseadragon.github.io) which can manage Deep Zoom pyramidial images (DZI) and additionally offers a scalable vector graphics (SVG) canvas on which point data can be drawn. Just like the map analogy where only the large cities are displayed at low resolution, TissUMaps does not have any prerequisites apart from a modern web browser.

TissUMaps can simultaneously display image data and point data, e.g. DAPI stained cell nuclei imaged using fluorescence microscopy combined with (i) gene expression, (ii) cell morphology (measured by CellProfiler), (iii) manually or automatically drawn regions and (iv) cell outlines (segmented by CellProfiler). Multiple viewers can be instantiated and synchronized.

To set up TissUMaps as a service, we used an Apache web server, such as NGINX or a python http.server, to serve a prediction map, displayed using WebGL shaders (tissuumaps.research.it.uu.se). To use TissUMaps when offered as a service already setup, other web servers, such as NGINX or a python http.server, would also work as TissUMaps is a basic html file and does not need a special web framework.

3 Conclusion

A case study for TissUMaps is presented in Partel et al. (2019) where more than two million gene transcripts were decoded from a 97 gene panel ISS assay of a coronal section of mouse brain (Fig. 1i). The results can be interactively visualized and explored with TissUMaps at the demo (tissuumaps.research.it.uu.se/demo/isseq.html and isseq2.html). Spatial anatomical compartments automatically defined in the same study can also be imported and visualized in TissUMaps (Fig. 1ii), along with 16 different morphological features extracted with CellProfiler (Fig. 1iii), or overlapping and comparing with cellular morphology from the underlying nuclei stain (Fig. 1iv).

TissUMaps also offers the possibility to visualize more complex features as spatial gene constellation learned by spage2vec (tissuumaps.research.it.uu.se/spage2vec) from Partel and Wahlby (2020), representing different subcellular spatial domains involved in cellular differentiation. Another example is presented in Strom et al. (2020) where H&E slides of prostate biopsies are synchronized with a prediction map, displayed using WebGL shaders (tissuumaps.research.it.uu.se/STHLM3).

There are several visualization options for WSI but to our knowledge, none offer an easy and convenient way for visualizing millions of data points along with image data. Additionally, TissUMaps can be used both as a web service or locally in any computer and does not have any prerequisites apart from a modern web browser.

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Fig. 1. TissUMaps can simultaneously display image data and point data, e.g. DAPI stained cell nuclei imaged using fluorescence microscopy combined with (i) gene expression, (ii) cell morphology (measured by CellProfiler), (iii) manually or automatically drawn regions and (iv) cell outlines (segmented by CellProfiler). Multiple viewers can be instantiated and synchronized. TissUMaps allows for operations in the image data through plugins, such as shaders, brightness and contrast modification.
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