Unimapper: An Online Interactive Analyzer/Visualizer of Optical Mapping Experimental Data

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Abstract

Time series of spatially-extended two-dimensional recordings are the cornerstone of basic and clinical cardiac electrophysiology. The data source may be either multipolar catheters, multi-electrode arrays, optical mapping with the help of voltage and calcium-sensitive fluorescent dyes, or the output of simulation studies. The resulting data cubes (usually two spatial and one temporal dimension) are shared either as movie files or, after additional processing, various graphs and tables. However, such data products can only convey a limited view of the data. It will be beneficial if the data consumers can interactively process the data, explore different processing options and change its visualization.

This paper presents the Unified Electrophysiology Mapping Framework (Unimapper) to facilitate the exchange of electrophysiology data. Its pedigree includes a Java-based optical mapping application. The core of Unimapper is a website and a collection of JavaScript utility functions for data import and visualization (including multi-channel visualization for simultaneous voltage/calcium mapping), basic image processing (e.g., smoothing), basic signal processing (e.g., signal detrending), and advanced processing (e.g., phase calculation using the Hilbert transform). Additionally, Unimapper can optionally use graphics processing units (GPUs) for computationally intensive operations. The Unimapper ecosystem also includes utility libraries for commonly used scientific programming languages (MATLAB, Python, and Julia) that allow the data producers to convert images and recorded signals into a standard format readable by Unimapper.

Unimapper can act as a nexus to share electrophysiology data – whether recorded experimentally, clinically or generated by simulation – and enhance communication and collaboration among researchers.

1. Introduction

Recording the propagation of electrical activity is the cornerstone of basic and clinical cardiac electrophysiology. Cardiac arrhythmias, responsible for significant morbidity and mortality, are the manifestation of abnormalities in the orderly propagation of cardiac electrical activity.

In both experimental and clinical settings, one common way to assess cardiac electrical activity is to record extracellular potential with the help of multi-electrode grids and arrays. However, by just recording extracellularly, this method loses valuable repolarization phase information. Another method that allows for accurate and spatially dense mapping of the transmembrane potential and intracellular calcium concentration is optical mapping with the help of fluorescent voltage- and calcium-sensitive dyes. Optical mapping (applicable only experimentally, not clinically) has been instrumental in deciphering the mechanisms of various cardiac arrhythmias.

In a typical optical mapping setup, the heart tissue under study is fixed in a chamber and is perfused continuously (e.g., using the Langendorff's apparatus). The excitation light source shines a nearly monochromatic light on the tissue. The optical sub-system is made of filters and lenses that guide the emission (fluorescent) light into one or two fast high-sensitivity CCD or CMOS cameras. Considering the high sampling rate (500-1000 Hz) and despite low to medium spatial resolution (from 128 x 128 to 1024 x 1024), an optical mapping system is capable of generating 10-1000 MB of data per second. Thus, each recording (a few seconds to minutes in duration) can easily be as large as a few GB.

The raw output of optical mapping systems is usually not usable in its native form and needs to be heavily processed and reduced to be interpretable. This fact is a hindrance in sharing the data, especially among collaborators working remotely. Traditionally, collaboration happens

by offline processing and sharing finished data products. However, these products can only capture some limited aspects of the data. A better option is to give each collaborator the ability to process the data interactively and in real time.

2. Previous Imaging Software

RHYTHM is an open-source imaging toolkit for cardiac panoramic optical mapping [1]. This software, which runs in MATLAB, can combine optical mapping recordings from several cameras around a Langendorff-perfused heart to create a 3D surface of the visualized heart with a superimposed color map of the voltage (or calcium) signal across the surface of the heart over time. The software can draw the heart surface and perform 3D geometric reconstruction as well as some manipulation of the experimental optical mapping, such as averaging in time and space. The software has been used to generate activation maps during ventricular fibrillation in rabbit, rat, and mouse hearts.

ElectroMap is a high-throughput open-source program for analysis and mapping of cardiac electrophysiology [2]. It allows data analysis from diverse acquisition modalities, including in silico, animal models with optical mapping, and data sets from in vivo multi-electrode arrays in patients. The software can run in MATLAB or as an executable alone.

COSMAS is a lightweight toolbox for cardiac optical mapping analysis [3] written in both MATLAB and Python. This software can be used to analyze static and dynamical dispersion in voltage or calcium as well as calculate restitution curves and alternans in space.

The predecessor of **Unimapper** is an interactive code, first written in Fortran and then ported to Java, that allows drift removal, filtering and analysis of optical mapping signals from voltage and calcium, as shown in Figure 1. The advantage of the Java code was that it was independent of the operating system. This code has been used to analyze voltage and calcium signals in hearts of a large variety of species including guinea pigs [4], rabbits [5, 6], dogs [7], pigs [8], alligators and horses [9].

Some of the possible operations in the Java code include normalization; removal of baseline drift; smoothing in time and space with various filters; defining, reading, and writing masks; calculating the action potential duration (APD) and diastolic interval (DI); spatial alternans plots; animations; and saving of data and movies.

3. Methods

The core of **Unimapper** is a web-based application and a collection of JavaScript utility functions for data import and visualization. We invite the interested readers to try **Unimapper** at `svtsim.com/VF/optical\_mapper\_tres.HTML`.

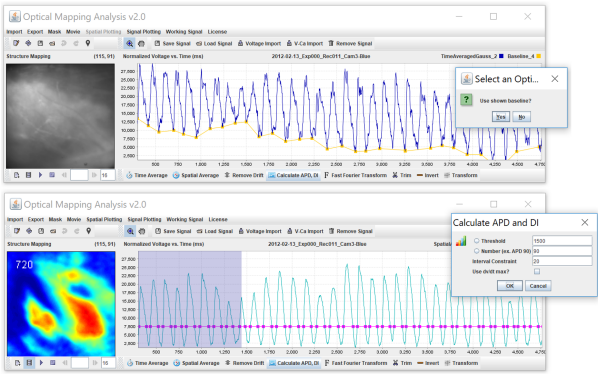

Figure 1. Two examples of optical mapping data analyzed using the Java code. Left image shows the spatial signal and right plot the signal in time for a selected pixel in the left window. Changing the pixel in the left image automatically updates the trace shown at the right. Top: example of drift removal using minima. Bottom: Signal during fibrillation and automatic calculation of the APD and DI.

The images recorded by the camera(s) need to be preprocessed in a form accessible to **Unimapper**. Currently, this pre-processing is done using a Julia program that converts voltage and calcium data into a three-dimensional data cube (two spatial dimensions and one time) and combines it with the geometry (coordinates of the pixels) to generate a JSON/BSON file. We plan to implement the importer code in other programming languages (MATLAB, Python, and JavaScript) to facilitate data sharing among different groups. **Unimapper** reads this file and applies three levels of image and signal processing before plotting the data. The following processing routines are currently supported or planned for the near future.

3.1. Level I

Level I is the general image processing algorithms that are not specific to electrophysiology data. It includes image smoothing (convolution with a Gaussian kernel) and contrast adjustment (γ-adjustment).

3.2. Level II

Level II encompasses algorithms that work on the level of a single-pixel. A typical algorithm in this category is linear detrending. We also need to normalize signals to account for different dye loading and variations in illumination (see Figure 2).

The key to many electrophysiology data processing routines is detecting the upstroke of action potentials, which is usually done using a (dynamic) threshold-crossing algorithm applied to a high-pass filtered version of the in-

put signal. Then, armed with the timing of the upstrokes, we can calculate action potential duration (APD) and find the *phase* by linear interpolation between the spikes. Another method to calculate phase is by the Hilbert transform (analytic continuation) of the signal using the Fast Fourier Transform of the signal.

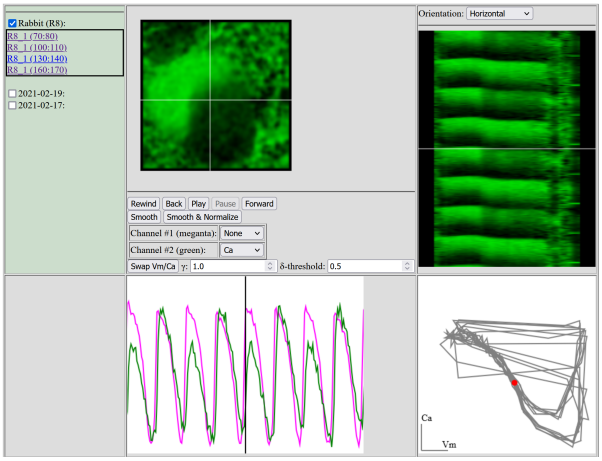

Figure 2. Example of the **Unimapper** showing data from a rabbit heart during a period-doubling bifurcation. Voltage time trace (pink) shows small alternans in APD; however, alternans in calcium is very pronounced (green). The V-Ca phase space shows two periodic orbits corresponding to the period-doubling. The 1D spatial *scan line* or *stack diagram* shows the spatiotemporal distribution of the calcium signal.

3.3. Level III

Level III algorithms combine the data from neighboring pixels. Common level III processes are the calculation of the Laplacian and edge detection using Sobel's kernel. In addition, conduction velocity and curvature measurements are also level III. Combining the APD data from multiple pixels (calculated in Level II), we can also calculate concordant and discordant maps [7, 10, 11], as shown in Figure 3. Similar plots for concordant and discordant in APD amplitude [5] and intracellular calcium can also be generated [6].

4. Advantages of the Unimapper

As **Unimapper** is written in JavaScript, it can run in any web browser and is independent of operating system and device (see Figure 4). This allows for easy visualization and sharing of data across research groups. Loaded data can be visualized in various ways. For example, simultaneous voltage and calcium recordings [6, 12] can be visualized independently (Figure 2) or at the same time

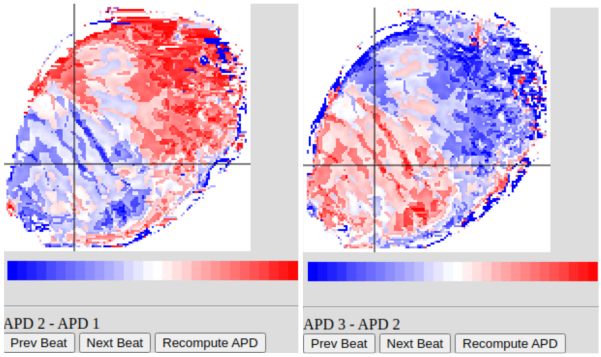

Figure 3. Example of ΔAPD alternans maps between two beats for a rabbit heart dataset. In steady state, regions with large ΔAPD (red) will have a small ΔAPD (blue) on the next beat and vice versa.

(Figure 4). While the movie of the surface recording plays, the user can choose to visualize just voltage, just calcium, or both. Similarly, a 1D *"scan view"* along a user-selected spatial line showing changes of voltage, calcium, or both in time (vertical axis) can be displayed in a second window; the menu gives options for diagonal, parallel, or perpendicular 1D cuts across the 2D domain. The voltage and calcium signal for any selected point in the domain as a function of time is displayed in the lower window, and the location can be chosen interactively by clicking anywhere in the 2D domain window. In a fourth window, the V-Ca phase space signal is displayed for the selected pixel, which can be used to characterize when calcium lags voltage and to identify any period doubling or presence of higher-order periods.

5. Future work

Unimapper is under active development and we are planning multiple enhancements.

We plan to expand the pre-processor to import images from a variety of scientific cameras used for optical mapping.

We also would like to expand the signal processing repertoire. One useful feature is the ability to mark the nodal lines (the set of pixels with zero APD alternans that separate alternating regions of different polarities). Moreover, we are porting computationally expensive operations to the graphics processing unit (GPU) using libraries such as GPU.jl and WebGL.

Unimapper is primarily developed as an online collaboration tool. As such, an annotation functionality will be very useful. Similarly, we would like to add the capability to save and share processing workflows.

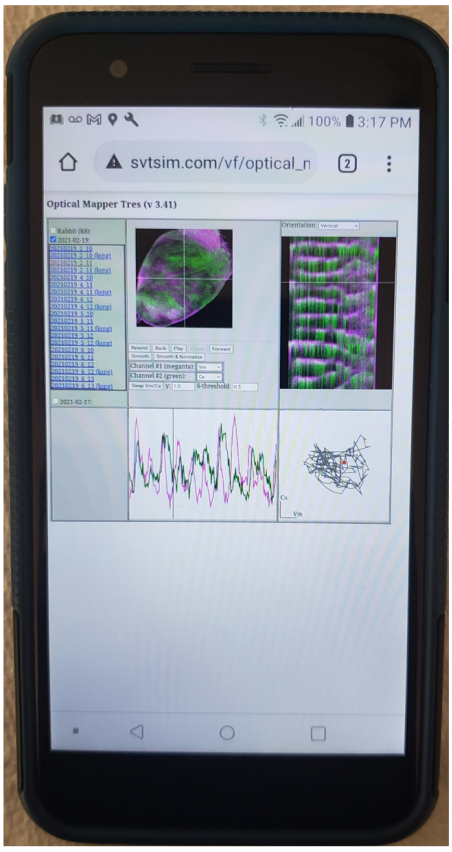

Figure 4. Analysis and visualization of optical mapping with **Unimapper** is independent of operating system and platform and can be run even on smart phones. Data shown is simultaneous voltage and calcium signals from a rabbit heart during fibrillation.

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