Optical Ultrastructure of Cardiac Tissue Helps to Reproduce Discordant Alternans by In Silico Data Assimilation

Marcel Hörning [1*], Alessandro Loppini [2], Julia Erhardt [1], Flavio H. Fenton [3], Simonetta Filippi [2,4,5], Alessio Gizzi [2]

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***Abstract*— A relevant issue in cardiology is represented by identifying valuable biomarkers of cardiac dysfunctions and by designing reliable computational models to predict transitions into pathological cardiac dynamics. In this context, alternans regimes have been proven to anticipate tachycardia and fibrillation. Still, an open problem is defining accurate and convenient methods to predict the onset and evolution of alternans patterns and formulate reliable models reproducing alternans features as observed in experiments. In this contribution, we present an FFT-based method on voltage mapping data, named FFI (Fast-Fourier-Imaging), which is able to early identify alternating cardiac dynamics and recover tissue structural information. Our results show that FFI identifies alternans patterns with great accuracy, avoiding excessive data preprocessing required by other methods. The extracted optical ultrastructural details of the tissue are used to inform computational parameters by accurate data assimilation, which enables the in-silico recovery of the experimental ex-vivo observations of a canine heart. *Clinical Relevance*—The application of FFI analysis enables the almost real-time detection of concordant and discordant alternans patterns in cardiac tissue and opens the way to new mathematical approaches with significant impacts on personalized modeling and whole organ simulations.**

I. INTRODUCTION

Understanding and analyzing complex cardiac dynamics is a primary goal for developing reliable therapeutic methods for cardiac diseases. Alternans is arguably one of the most complex and least-understood cardiac rhythms that are potentially life-threatening and a precursor of tachycardia and fibrillation [1]. In this context, alternans is a stable periodic rhythm that occurs at the electric membrane potential, intracellular Calcium concentration, and mechanical contraction patterns in heart tissue [2]. They can be observed in high-frequency wave trains as well as in undesirable stable spiral waves. Two forms of alternans are known, concordant (CA) and discordant alternans (DA), which can produce large regions of dispersion in repolarization [3], by conduction velocity, thermo-mechanical feedbacks [4], and mechanosensitive regulations of the extracellular matrix [5]. While during CA the entire tissue synchronized with to a common rhythm, a spatial separation (domains) of aphasic oscillating rhythms is observed during DA. Those domains are separated by complex formed nodal lines in the tissue that oscillate in non-alternating rhythm [6]. Generally, period-doubling is observed; however, higher-order rhythms in space can be observed too[7].

In this contribution, we show the application of FFI to extract alternans patterns and structural tissue information without the use of spatiotemporal filters. Using the extracted structural tissue information, we can reproduce in numerical simulations the observed alternans patterns, i.e., CA and DA, observed in the experiments. In particular, we assimilate space-dependent parameters based on the dispersion and restitution properties of the observed excitation waves, i.e., conduction velocity (CV) and action potential (AP) shapes.

II. METHODS

A. Fast-Fourier-Imaging. FFI enables the fast and pixel-wise extraction of alternans patterns without the use of spatiotemporal filters. Thus, the spatial resolution of the patterns are restricted by the camera only. This enables the detection of alternans by visualizating the amplitude or phase of half the driving frequency, $f_{1/2} = f_p/2$ [8]. In case of spiral waves $f_{1/2}$ is half of the rotation frequency (see Fig. 1). When no alternans is present the phase is asynchronous at $f_{1/2}$. Higher order alternans can be observed also at $f_{1/4}$, that is when four different action potential shapes periodically repeat at high frequency wave trains, as observed in an ex-vivo canine heart [9]. As the latter is a naturally grown tissue, it is possible to extract optical ultrastructural features that are useful for the understanding of alternans initiation. Only the length of the signal regulates the quality of the resulting visualization, as the signal-to-noise ratio increases with the signal length, i.e. the total number of exposures within a time window. Further details on the experimental setup and data collection can be found in [8] and [9].

B. Mathematical Model. We adopt the four-variable minimal electrophysiological model that reproduces ventricular action potential dynamics [10]. The model can be applied to realistic two-dimensional domains, as extracted from optical imaging data, through the use of the phase-field method [11]. The membrane voltage dynamic is obtained by the three main ion currents, i.e., the fast-inward sodium, slow-outward potassium, and slow-outward calcium channels. Tissue anisotropy and inhomogeneity are defined by a diffusion

* marcel.hoerning@bio.uni-stuttgart.de
[1]Institute of Biomaterials and Biomolecular Systems, University of Stuttgart, 70569 Stuttgart, Germany
[2]Nonlinear Physics and Mathematical Modeling Laboratory, University Campus Bio-Medico of Rome, 00128 Rome, Italy
[3]School of Physics, Georgia Institute of Technology, Atlanta, GA, USA
[4]ICRANet, Piazza delle Repubblica 10, I-65122 Pescara, Italy.
[5]CNR-INO, I-50019 Sesto Fiorentino, Italy.

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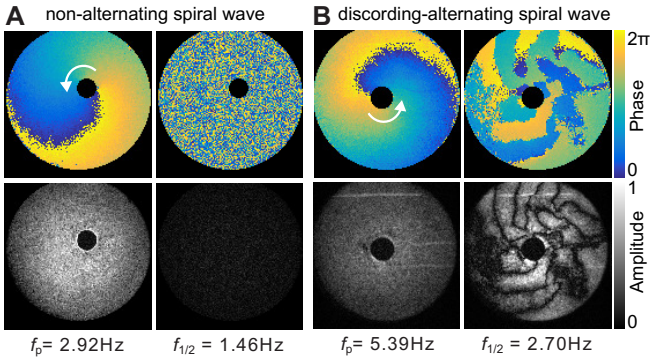

Fig. 1. Experimentally observed spiral waves computed with FFI in Wistar rat cultures [8]. (A) non-alternating spiral wave. (B) DA spiral wave with period-doubling. Nodal lines are seen on the right panels. Phase and amplitude are shown at the upper and lower rows. The spiral waves rotate with the frequency f_p, and occurrence of alternans can be seen at $f_{1/2}$.

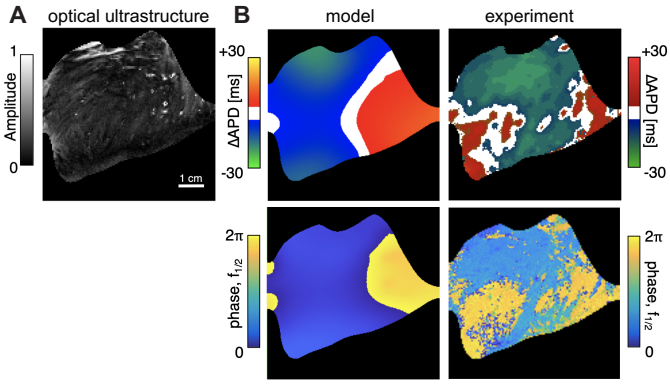

Fig. 2. In-silico recovered DA pattern on canine ventricular endocardium [9]. (A) extracted optical ultrastructure (FFI amplitude at $f = 0.5$ Hz). (B) comparison of in-silico and experimental DA patterns, as activation maps (ΔAPD, top) and FFI phase maps (bottom). Pacing $f_p = 6.2$ Hz.

tensor describing local fiber alignment and variations. Model parameters are fine-tuned to match experimental data. We refer the reader to [9] for a comprehensive list of equations, parameters, and experimental details.

C. In-Silico Data Assimilation. Alternans patterns can be accurately reproduced by in-silico data assimilation from the membrane potential signaling and optical ultrastructure from experimentally studied canine hearts. First, we fit the mathematical parameters to match the dispersion and restitution properties, e.g., CV and AP features of the experimental action potentials in 1D and 2D domains. This alone does not recover the DA patterns (not shown). However, the additional combination with FFI derived heterogeneity maps - that were scaled to the diffusivity and APD-regulating parameters - enabled reproduction of the DA patterns in the high-frequency paced simulations. Fig. 2 shows an example of the extracted optical ultrastructure and the in-silico DA in comparison to the experimental ones (FFI phase and activation maps) [9].

III. DISCUSSION & CONCLUSIONS

By assimilating experimental-based tissue heterogeneity into the model, we were able to 1) recover the expected average CV and AP features and 2) reproduce alternans onset, severity, and complexity of spatial patterns from experiments. Thus, FFI is a fast and reliable analysis method to extract the personalized heterogeneity maps for mathematical modeling, FFI also offers a novel application to real heart monitoring that helps detect undesired arrhythmic dynamics, such as alternans, rotors, and fibrillation. Thus, in this contribution, we present novel methodological approaches for integrative modeling and personalized medicine, which may also be usable in experiments with human iPS-derived heart tissues [12].

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