# Personalized Computational Framework to Study Arrhythmia Mechanisms on Top of ECGI-Detected Substrate

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## Abstract

*Electrocardiographic Imaging (ECGI) can unmask electrical abnormalities that were difficult to detect using the standard 12-lead ECG. However, it is still challenging to interpret the potential arrhythmogenic consequence of electrical patterns found with ECGI. Here, we introduce a computational framework that allows personalized simulations of cardiac electrophysiology (EP) to mimic electrical substrate as detected in an individual, to study the interaction between that substrate and premature ventricular complexes (PVCs).*

*In patient data, electrical substrate identified using ECGI shows regions of pronounced dispersion of local recovery (i.e., recovery gradients). A computational model of ventricular EP was developed and then used to mimic the recovery gradients and PVCs found in patients. We studied a variety of gradients (6-98 ms/cm) and coupling intervals of the extra stimulus (-70 to +260 ms relative to the end of local recovery), which showed that re-entry can only occur when dispersion of recovery is large (≥76 ms/cm), and the extra stimulus occurs just after local recovery ended (~ +40 ms).*

*In conclusion, this computational framework allows to identify the specific conditions under which ECGI-detected substrates and PVCs can lead to re-entry in a personalized approach.*

## 1. Introduction

The electrocardiogram (ECG) is a well-established, validated, patient-friendly, quick, reproducible and cheap tool to assess the electrical activation and recovery of the heart as projected on the body surface. However, it is a superimposed and 'smeared' representation of the actual cardiac electrical activity. Thus, it lacks the capacity to assess electrical activity at high resolution at the level of the heart muscle. Conversely, electrocardiographic imaging (ECGI) is a modality that noninvasively images electrical activation and recovery directly at the heart surface. ECGI computes direct representations of electrical activity at the heart surface by combining extensive recordings from ~200 body-surface electrodes with a precise, patient-specific torso-heart geometry. [1] ECGI provides significantly more detailed and localized information than the clinical ECG and has the potential to bring new insights in arrhythmogenesis and improved risk stratification for sudden, life-threatening cardiac arrhythmias such as ventricular fibrillation (VF). We have quantitatively validated ECGI activation and recovery isochrones previously [2] and showed then that it can detect clinically concealed recovery abnormalities in patients, which might play a role in arrhythmogenesis. [3]

However, it is challenging to interpret the potential arrhythmogenic consequence of electrical patterns found with ECGI. Here, we introduce a computational framework that allows personalized simulations of electrophysiology (EP) to mimic recovery substrate as detected in an individual, to study the interaction between that substrate and premature ventricular complexes (PVCs).

## 2. Arrhythmia substrate

Application of ECGI in patients has previously unmasked recovery gradients that could not be detected from the 12-lead ECG. In recent studies ECGI has revealed the presence of recovery abnormalities in ARVC patients [4], and in sudden cardiac death survivors [5]. In another study, the steepness of ECGI-detected recovery gradients was higher in patients with Long QT syndrome, and especially in symptomatic patients [6]. These studies have not investigated the relationship between such substrate

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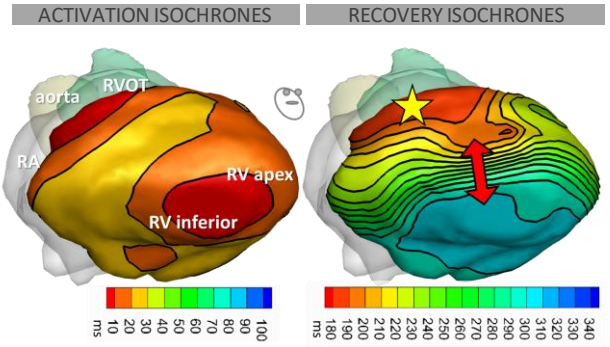


Figure 1. Example of ECGI findings in a patient who had idiopathic VF. Left: Normal activation pattern during sinus rhythm. Right: Abnormally early recovery at the right ventricular outflow tract (RVOT) and steep recovery gradients (arrow). Short-coupled PVCs originated from the RVOT (star).

and triggers. Amongst other causes, PVCs are recognized as potential triggers of arrhythmias. In Figure 1, we illustrate the case of a 47-year old female patient who had VF for which no explanation could be found during clinical follow up. Application of ECGI showed normal activation patterns during native rhythm, but unmasked the presence of steep recovery gradients (Δ = 55 ms/cm). Additionally, this patient showed frequent PVCs from a region that recovered early during native rhythm.

Based on these previous studies and clinical data, we hypothesize that regions of large recovery dispersion form a region of conduction block during new beats, and that PVCs can trigger re-entrant arrhythmias on top of such primary electrical substrate. This arrhythmia hypothesis is illustrated in Figure 2.

It is not known when recovery gradients are steep enough to be arrhythmogenic. It is also not known at which coupling intervals PVCs can indeed trigger re-entry on top of such substrate. In the remainder of this paper, we will develop a computational EP model that can be personalized with ECGI findings from individual patients, to study the substrate-trigger characteristics that may lead to re-entry. The perfect control provided by computational models can help to bridge the insights from patient studies to arrhythmia mechanisms and personalized risk assessment.

## 3. Computational model

We developed a computational model of cardiac electrophysiology based on the Mitchell-Schaeffer equations. Our implementation of this model has been described previously. [7] In short, this model is governed by six parameters, of which four are related to time constants. These time parameters $\tau_{in}$, $\tau_{out}$, $\tau_{open}$ and $\tau_{close}$

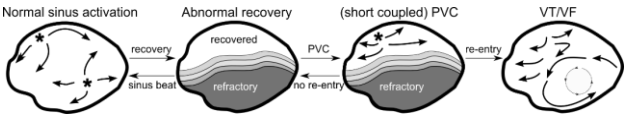


Figure 2. Arrhythmia hypothesis studied in this paper: On top of (concealed) recovery gradients, PVCs may initiate VF.

control the duration of the four stages of the action potential (Figure 3). This allows to easily incorporate individual findings from ECGI by locally adapting the corresponding parameter in the digited patient's heart. For example, if ECGI unmasks regions of early recovery, these can be mimicked in the computational model by adapting the $\tau_{close}$ at the corresponding region.

Artificial stimuli were applied in this model to simulate activation and recovery isochrones, which were qualitatively validated with invasive canine data (Figure 4). The acquisition of these experimental canine data is described previously. [2]

## 4. Personalized simulations

The computer model was used to mimic the recovery gradients and trigger origins found in the patient of Figure 1, to study wave-front propagation under different conditions. The cardiac tissue was divided in two zones: one with normal recovery characteristics ($\tau_{close}$ = 150 ms), and one with delayed recovery ($\tau_{close}$ = 250 ms). This resulted in a zone of steep recovery gradients between the two zones, with local dispersion of recovery times of Δ = 98 ms/cm. An extra stimulus S2 was then given on the early side of this gradient, mimicking the observed patient's PVCs from the region of early recovery.

The results are displayed in Figure 5. In normal conditions, the extra stimulus S2 (star) at t = 400 ms is propagated homogeneously and then extinguishes (top row). In the presence of a local gradient in recovery times (arrow, middle row), the extra stimulus does not extinguish

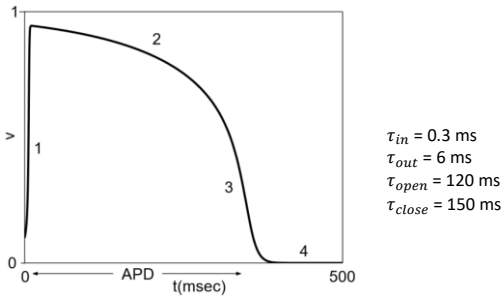


Figure 3. The four phases of the action potential (left) related directly to the four temporal parameters of the Mitchell-Schaeffer model (right). These parameters can be adapted locally to match ECGI findings from an individual patient.

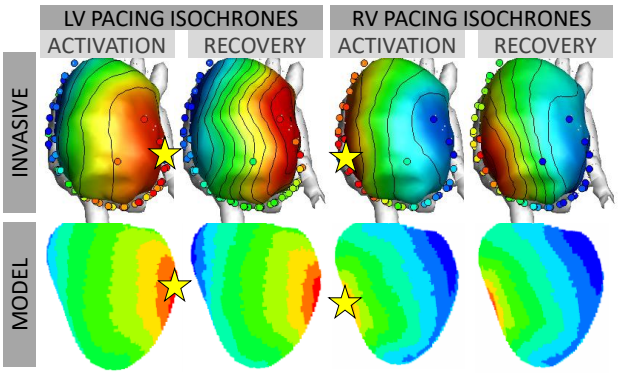


Figure 4. Top: Invasive animal recordings were obtained during pacing on the heart (at the location of the yellow star). Bottom: the computational model was used for virtual pacing at the same location, yielding qualitatively similar patterns of activation and recovery.

but results in re-entry. When the extra stimulus is given at a later time instant (t = 500 ms), all tissue is already recovered and the premature beat extinguishes without resulting re-entry. In other words, only the combined presence of 1) recovery gradients, and 2) an *early* (short-coupled) triggered beat results in re-entry in this personalized simulation.

We then varied the steepness of the recovery gradient, and the timing (coupling interval) of the extra stimulus. The region of delayed recovery was varied from a normal value ($\tau_{close}$ = 150 ms) to several abnormal values ($\tau_{close}$ = 200, 230 and 250 ms). This resulted in local gradients of $\Delta$ = 6, 44, 76 and 98 ms/cm respectively. The coupling intervals of the extra stimulus were varied from 270-600 ms relative to the initial stimulus, which corresponded with -70 to +260 ms relative to the end of local recovery. The resulting simulations are displayed in Figure 6. The extra stimulus S2 does not capture (i.e., does not generate an activation wave front from the stimulus location) when the tissue is not recovered yet, i.e., when the local recovery time is longer than the moment of extra stimulus. The extra stimulus results re-entry when the coupling interval is a bit longer (~ +40 ms) than the local recovery time, *and* there is a significantly large gradient (≥76 ms/cm). Longer coupling intervals result in normal propagation without re-entry. Similarly, small recovery gradients also do not result in re-entry.

## 5. Discussion

In this study, we have introduced an EP modelling framework that can be personalized by incorporating ECGI-detected electrical substrate to study its arrhythmogenic consequence. This personalized framework allows to study the interaction between triggers and observed electrical substrate in a controlled environment, and may allow us to obtain a much more thorough, patient-specific understanding of arrhythmia mechanisms leading to sudden life-threatening arrhythmias such as VF than has been possible until now.

The Mitchel-Schaeffer model employed in this study is relatively simple compared to the complex and detailed models used to study the consequence of structural abnormalities. [8] The benefit of a simple model is that it allows to easily incorporate local abnormalities in activation and recovery that are captured by ECGI, since both activation and recovery characteristics relate directly to the few temporal parameters of the model. In more complex ionic models, it might be difficult to determine which parameters should be changed to reflect local changes in activation and recovery. Another advantage of our approach is that its computational efficiency allows to test a large variety of substrate characteristics and coupling intervals. However, it remains to be determined whether this model is detailed enough to capture the full complexity

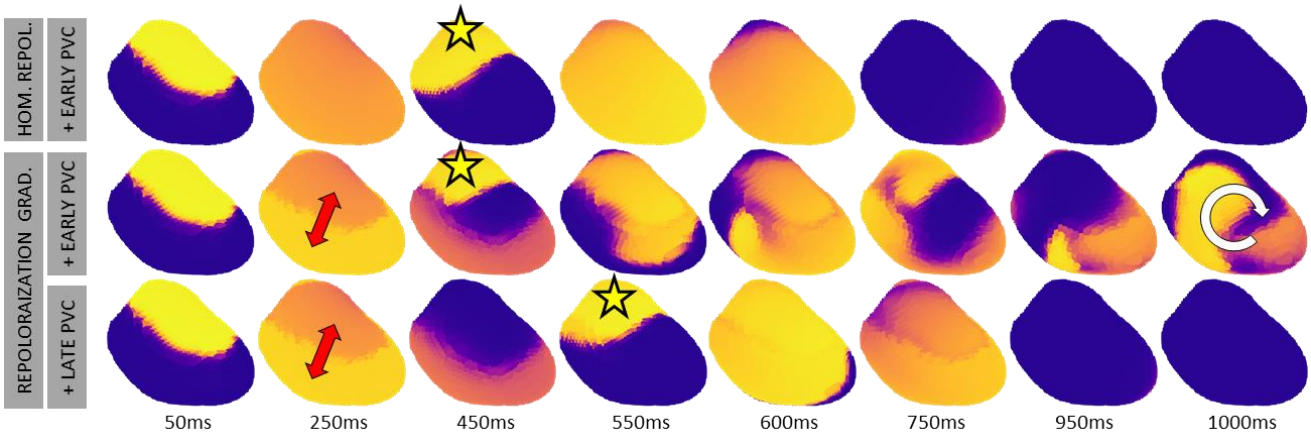


Figure 5. Transmembrane potential maps (blue = resting potential, yellow = peak action potential). Mimicking the observed patient abnormalities, the personalized model shows that re-entry mechanisms (white arrow) only develop in the presence of both the observed recovery gradient (red arrows), and an early premature ventricular complex (PVC, star) as trigger.

of arrhythmogenesis. Due to the fact that ECGI's spatial resolution is limited to a ~1 cm level [2], the relatively simple Mitchel-Schaeffer model might proof sufficient to test the interaction between PVCs and relatively coarse ECGI-detected recovery gradients. A more detailed model, on the other hand, would allow to incorporate a patient's known genetic mutations to further personalize the EP simulations.

We have qualitatively validated our implementation of the EP model in a previous study [7] and in Figure 4. However, a thorough validation of actual arrhythmogenicity of the detected ranges of recovery gradients and coupling intervals is essential to expand this tool for personalized risk stratification. This requires a stable *in vivo* or *ex vivo* experimental setup in which recovery gradients and S2 intervals can be controlled in great detail.

In conclusion, we have demonstrated a computational framework that integrates ECGI and EP simulations. This framework allows to identify the specific conditions under which ECGI-detected substrates and PVCs could lead to re-entry in a personalized approach. In the future, this approach potentially helps to better understand patient-specific arrhythmia mechanisms and could allow to study different personalized treatment options.

## Conflicts of interest

None.

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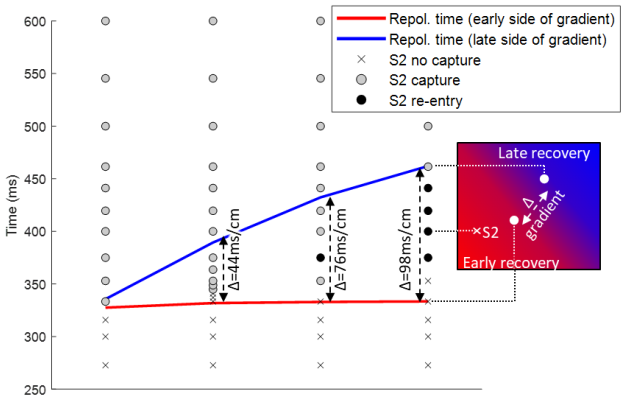


Figure 6. Relationship between the dispersion of recovery times between regions of early (red) and late (blue) recovery, the resulting recovery gradient Δ, and the inducibility of re-entry when virtually pacing is performed from the S2 location in the early-recovery region. The extra stimulus S2 only results in re-entry when the gradient is large enough (76 or 98 ms/cm) and the timing of S2 is within a small vulnerable window.


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