Sex-Specific Cardiac Digital Twins of Human Ventricular Electrophysiology Using 12-Lead ECG and MRI

Julia Camps[1,2]*, Maxx Holmes[2]*, Ruben Doste[2], Lucas Arantes Berg[2], Zhinuo Jenny Wang[2], Blanca Rodriguez[2]

[1]Universitat Pompeu Fabra, Barcelona, Spain
[2]University of Oxford, Oxford, United Kingdom

Abstract

A cardiac digital twin is a virtual tool representing a patient's heart that can simulate new events, such as evaluating therapies to inform clinical decision-making.

We present a sex-specific digital twinning framework for personalising electrophysiological function based on routinely acquired magnetic resonance imaging data and the standard 12-lead electrocardiogram (ECG), while preserving known sex-related differences at the ionic level in the resulting digital twins.

We demonstrate our digital twinning framework in three subjects, two female and one male, where our inferred reaction-Eikonal models reproduced the patient's ECG with a Pearson's correlation coefficient of 0.9 on average. The framework can be downloaded from GitHub.

1. Introduction

Cardiac electrophysiology exhibits sex-dependent differences in the balance and distribution of ionic currents. Myocardial action potentials in adult females tend to be longer [1], partly due to a reduced repolarisation reserve compared to males, and comparatively enhanced calcium cycling. Female excitation-contraction coupling also differs from males, with a lower amplitude and longer calcium transient duration. These differences manifest in the clinical ECG, and are important when considering therapeutic strategies

A cardiac digital twin is a tool that coherently integrates patient data to produce virtual hearts to help realise the vision of precision medicine in cardiology [2]. Cardiac digital twins should be consistent with the patient's sex to guarantee their relevance in diagnostic and therapeutic decision-making.

We present a sex-specific extension to our digital twinning framework for personalising electrophysiological function based on routinely acquired magnetic resonance imaging (MRI) data and the standard 12-lead electrocardiogram (ECG), while preserving known sex-related differences at the ionic level in the resulting digital twins.

2. Methods

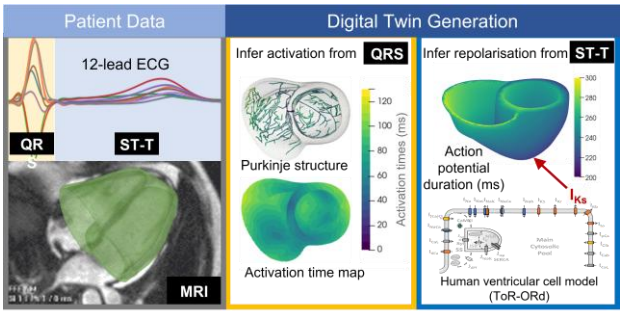

Figure 1. Cardiac digital twinning framework [2] showcasing example visualisations of the activation (e.g., Purkinje properties inferred from the QRS signals) and repolarisation (e.g., action potential duration gradients from the T waves) parameter spaces.

We generate the MRI-based biventricular geometry. Then, we use a sequential Monte Carlo approximate Bayesian computation algorithm to infer the heart's electrical activation and repolarisation properties from the QRS, and from the T wave, respectively. We estimate the tissue conduction speeds [3], Purkinje structure [4], and repolarisation gradients [2] simultaneously and carry uncertainties to the final inferred population.

2.1. Clinical data

This study used clinical MRI and 12-lead ECG data from three healthy subjects (Table 1) as in [2]. The subject cohort included participants of different ages, sexes, body shapes, heart sizes, and resting heart rates to showcase the robustness of our pipeline. Ventricular meshes were generated from the MRI data at ~1.5 mm edge length.

Table 1. Subject cohort [2]. Age (years); Sex: Female (F), Male (M); Body mass index (BMI); Heart rate (HR) (bpm).

Subject ID	Age	Sex	BMI	HR
Subject 1	56	F	20.96	66
Subject 2	76	F	33.56	48
Subject 3	23	M	23.84	74

2.2. Sex differences

Table 2. Female ionic scaling of parameters in an endocardial electrophysiological myocyte model compared to the parameters in the male model.

Ionic parameter	Female Scaling
G_{pCa}	1.6
G_{Kr}	0.79
G_{Ks}	0.83
G_{K1}	0.86
G_{NaCa}	1.15
$CMDN_{max}$	1.21

We use a dictionary of action potential models generated using sex-specific electrophysiology characteristics implemented on the ToR-ORd cellular model [5] by calibrating the ionic conductances using relative mRNA expression ratios of ion channel markers from non-diseased adult human male and female ventricular myocytes [5]. We propose the scaling factors to produce a female version of the ToR-ORd model, based on differences to a calibrated male endocardial baseline (Table 2) (further details on the male baseline calibration can be found in [5]). These sex-specific models paced at the recorded heart rates (Table 1) were used to generate the action potential duration-based dictionaries by varying the models' slow delayed rectifier potassium current (I_{Ks}) [2].

These new sex-specific models, combined with the MRI-derived geometries for the heart and torso, enabled personalising to the sex of the subjects.

2.3. Parameter inference

The inference framework implements the sequential Monte Carlo approximate Bayesian computation algorithm in combination with a graph-based Eikonal model and the pseudo-ECG formulation to calculate the 12-lead ECG [3].

The inferred parameter space includes discrete root nodes derived from rule-based Purkinje trees [4], as well as continuous conduction speeds (sheet-fibre, dense-endocardial, and sparse-endocardial), and action potential duration (APD) gradients and ranges [2].

We demonstrate the inference of all these parameters simultaneously using subject-specific electrophysiology.

2.4. Reproducibility

All digital twinning tools are available at github.com/juliacamps/Cardiac-Digital-Twin alongside examples and tutorials to run the pipeline. The adult male and female electrophysiology models can be found at github.com/MaxxHolmes/Sex_Specific_Human_Electro mechanics. Moreover, we will add the action potential dictionaries used for this work to the digital twins GitHub repository (github.com/juliacamps/Cardiac-Digital-Twin).

The inference iterative process took ~ 36 hours for each subject on a desktop computer.

3. Results

We applied our framework to data from three subjects. The inferred population of parameter-sets that matched the clinical ECGs with a Pearson's correlation coefficient (PCC) of 0.9 on average (Table 3).

Table 3. Pearson correlation coefficient (PCC) between the simulated and clinical ECGs after the inference.

Subject ID	PCC
Subject 1	0.88 ± 0.008
Subject 2	0.92 ± 0.004
Subject 3	0.89 ± 0.008

The framework was able to estimate the values of all continuous (i.e., tissue conduction speeds and action potential duration gradients) and discrete (root nodes) parameters simultaneously for all three subjects, reaching the desired error value for them after 11, 35, and 25 iterations for Subjects 1, 2, and 3, respectively (Table 3).

The inference process extensively explored the parameter space (Figures 2 and 3) to find the parameter sets that reproduced the clinical data (Figure 2). The root nodes converged to the free-wall mid and basal regions for both ventricles for Subject 2 (Figure 3.A); thus, moving away from apical and septal regions. On the other hand, the root nodes remained scattered throughout the LV at the end of the inference process for the male subject (Subject 3 – Figure 3.B).

The inference for the eldest female subject (i.e., Subject 2) yielded the best (PCC) match to the clinical data (Table 3); however, the inferred parameter-set population presented considerable variability for various parameters (Figure 2.C) as well as for the characteristics of their simulated ECGs (Figure 2A and B). This variability in the simulations suggests that there would still be margin for improving the match to the clinical data, given additional computational power and/or time.

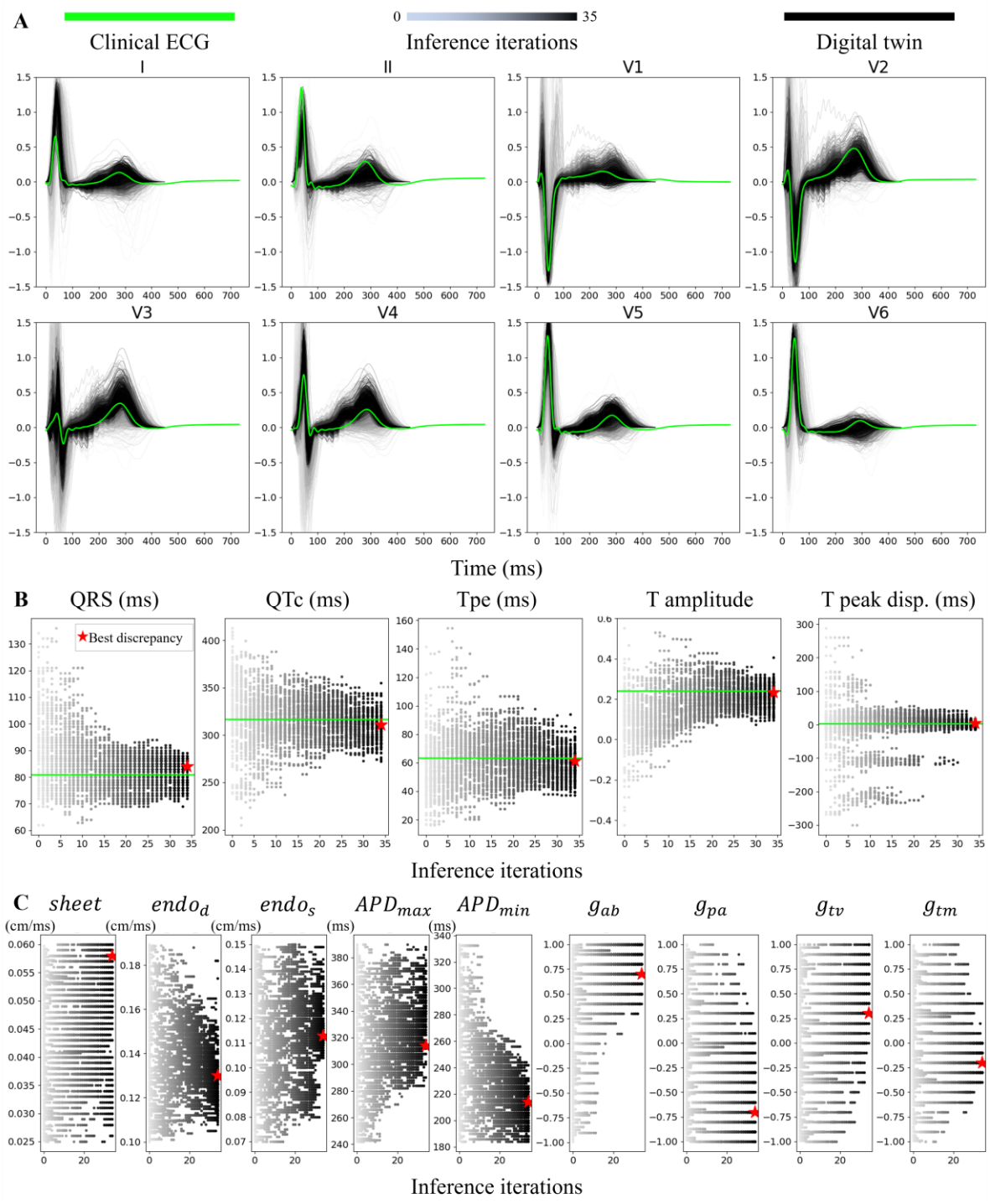

Figure 2. Inference (Subject 2) iterations effectively explore the biomarker space when considering an action potential model calibrated for female electrophysiology. A) ECG simulation evolution throughout the inference process. B) Simulated QRS width, QTc interval, T-peak to T-end interval (Tpe), average T wave amplitude, dispersion of T peak timing between V3 and V5 evolution (greyscale), clinical values (lime horizontal line), value for the parameter-set with the lowest discrepancy (red star). C) Evolution of the parameter space, where $sheet$, $endo_d$ and $endo_s$ are the conduction speeds in the sheet-fibre direction, dense endocardial and sparse endocardial regions. $APD_{\max}$ (maximum action potential duration), APD_{min} (minimum action potential duration), g_{ab} (APD gradient in the apex-to-base direction), g_{pa} (APD gradient in the posterior-to-anterior direction), g_{tv} (APD gradient in the transventricular direction) and g_{tm} (APD gradient in the transmural direction).

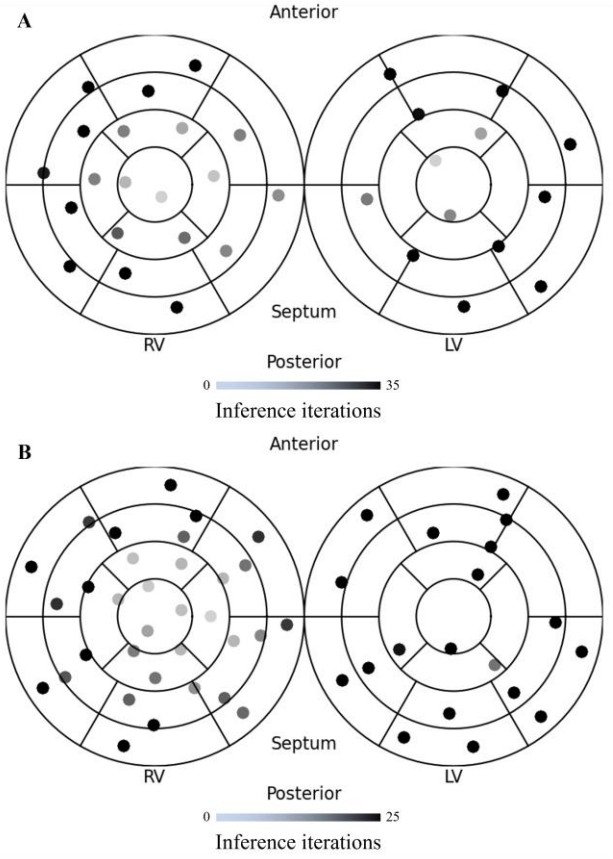

Figure 3. Inference iterations explore the root node parameter space (shown over AHA segments as in [4]) for female (A – Subject 2) and male (B – Subject 3) subjects.

4. Discussion

We extend our previous open-source cardiac digital twin generation framework [2] to incorporate sex-specific calibration of the electrophysiology modelling.

We had previously shown the capacity of the inference to match clinical QRS [4] and T wave [2] signals using electrophysiology models based on male data. The inclusion of the female-specific electrophysiology models in the inference increases the relevance of this technology towards in silico trials.

All inference runs were terminated by reaching the desired discrepancy thresholds, suggesting that they could have been run for longer to reduce further the mismatch between clinical and simulated data (Table 3).

Our inference framework produces a population of parameter-sets representing each digital twin (Figures 2 and 3) to propagate the uncertainty into the applications where the digital twins get deployed. This aspect is crucial for their adoption in either in silico trials or clinical environments, as it allows extracting confidence in the predicted parameter values, as well as considering the full range of alternative possibilities that yield a similar match to the clinical data.

Given our results, we anticipate that our framework will successfully generalise to new male and female cases in the human population.

Recent works show the potential of novel cross-sex translators, enabling estimation of therapeutic response on the ECG using a calibrated sex-specific model [6].

Acknowledgments

The project that gave rise to these results received the support of a fellowship from “la Caixa” Foundation (ID 100010434) to JC (LCF/BQ/PI25/12100029), and a Wellcome Trust Fellowship in Basic Biomedical Sciences to BR (214290/Z/18/Z).

(*) JC and MH have contributed equally to this study.

References

[1] C. Prajapati, J. Koivumäki, M. Pekkanen-Mattila, and K. Aalto-Setälä, ‘Sex differences in heart: from basics to clinics’, *Eur. J. Med. Res.*, vol. 27, no. 1, p. 241, Nov. 2022, doi: 10.1186/s40001-022-00880-z.

[2] J. Camps *et al.*, ‘Harnessing 12-lead ECG and MRI data to personalise repolarisation profiles in cardiac digital twin models for enhanced virtual drug testing’, *Med. Image Anal.*, vol. 100, p. 103361, Feb. 2025, doi: 10.1016/j.media.2024.103361.

[3] J. Camps *et al.*, ‘Inference of ventricular activation properties from non-invasive electrocardiography’, *Med. Image Anal.*, vol. 73, p. 102143, Oct. 2021, doi: 10.1016/j.media.2021.102143.

[4] J. Camps *et al.*, ‘Digital twinning of the human ventricular activation sequence to clinical 12-lead ECGs and magnetic resonance imaging using realistic Purkinje networks for in silico clinical trials’, *Med. Image Anal.*, vol. 94, p. 103108, May 2024, doi: 10.1016/j.media.2024.103108.

[5] M. Holmes *et al.*, ‘Sex-specific human electromechanical multiscale in-silico models for virtual therapy evaluation’, *J. Mol. Cell. Cardiol. Plus*, p. 100479, Aug. 2025, doi: 10.1016/j.jmccpl.2025.100479.

[6] R. Shetty, S. Morotti, V. Sobota, J. D. Bayer, H. Ni, and E. Grandi, ‘Development and clinical validation of a cross-sex translator of ECG drug responses’, *JACC Clin. Electrophysiol.*, vol. 0, no. 0, doi: 10.1016/j.jacep.2025.05.015.

Address for correspondence:

Julia Camps.
Tanger building, Tanger, 122-140, Barcelona, Spain.
julcamps@gmail.com