

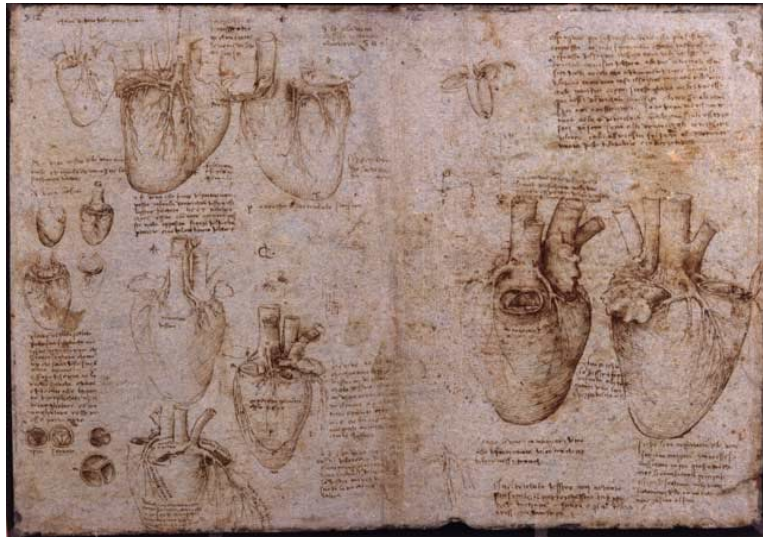


***In-silico* Clinical Trials as a REALITY: The case of the Cardiovascular System**

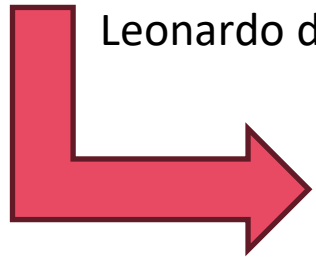
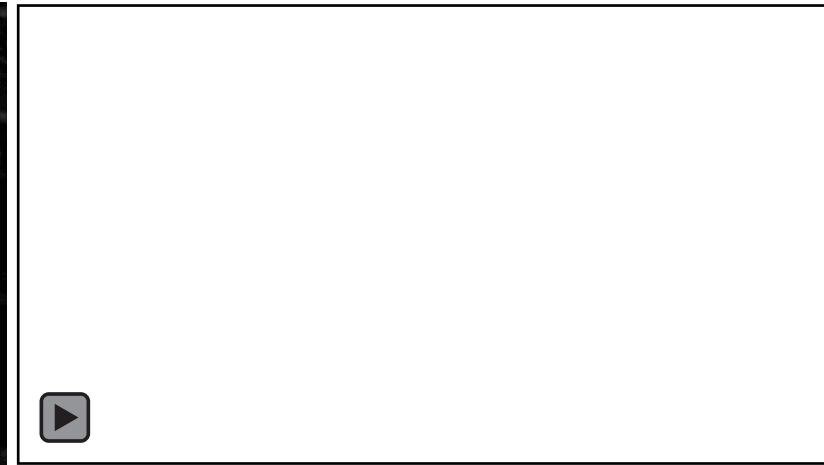
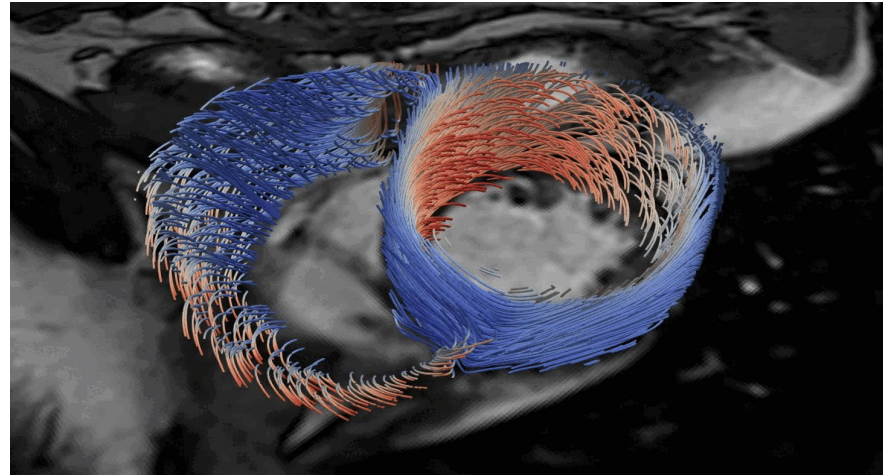
**Jazmin Aguado-Sierra, PhD
Scientific Lead,
ELEM Biotech**

ELEM
THE VIRTUAL
HUMANS FACTORY

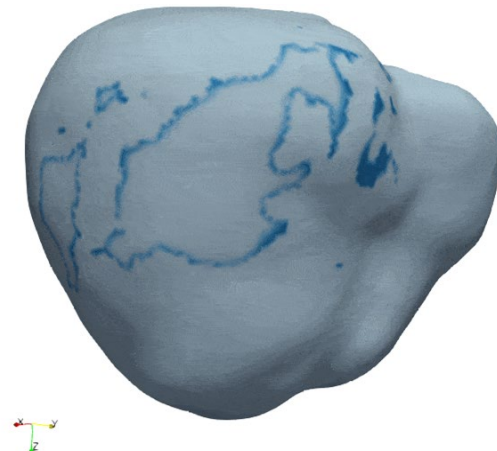
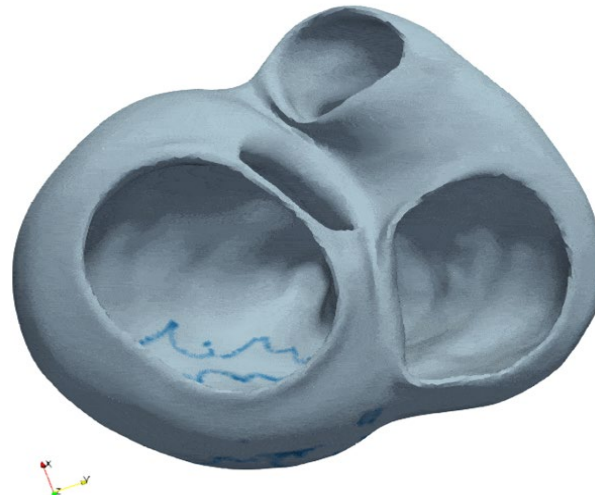
The HEART is one of the most studied body organs



Leonardo da Vinci, 1510

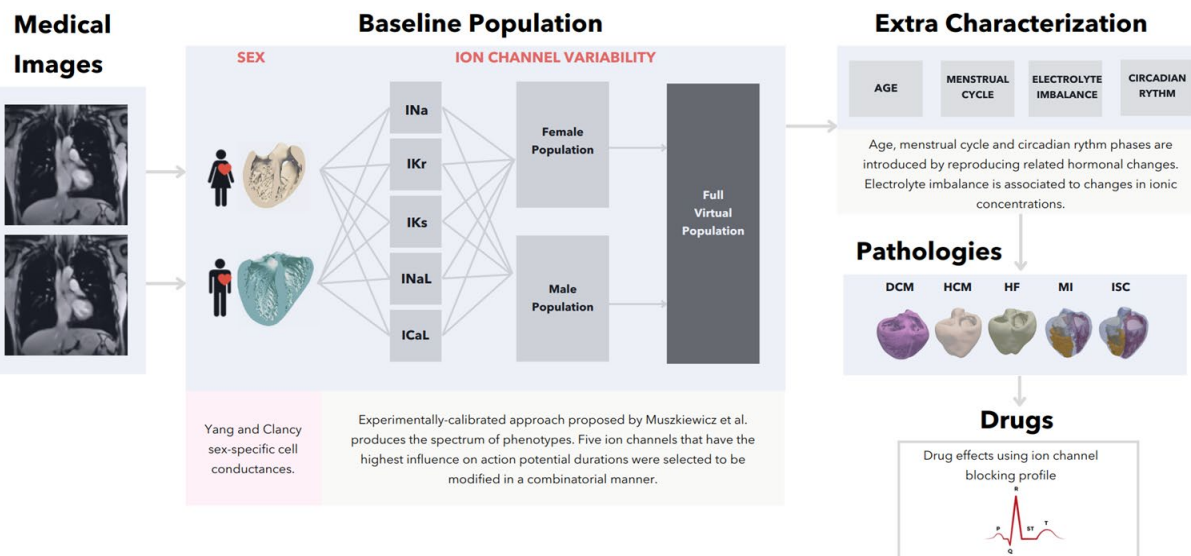


515 YEARS
LATER

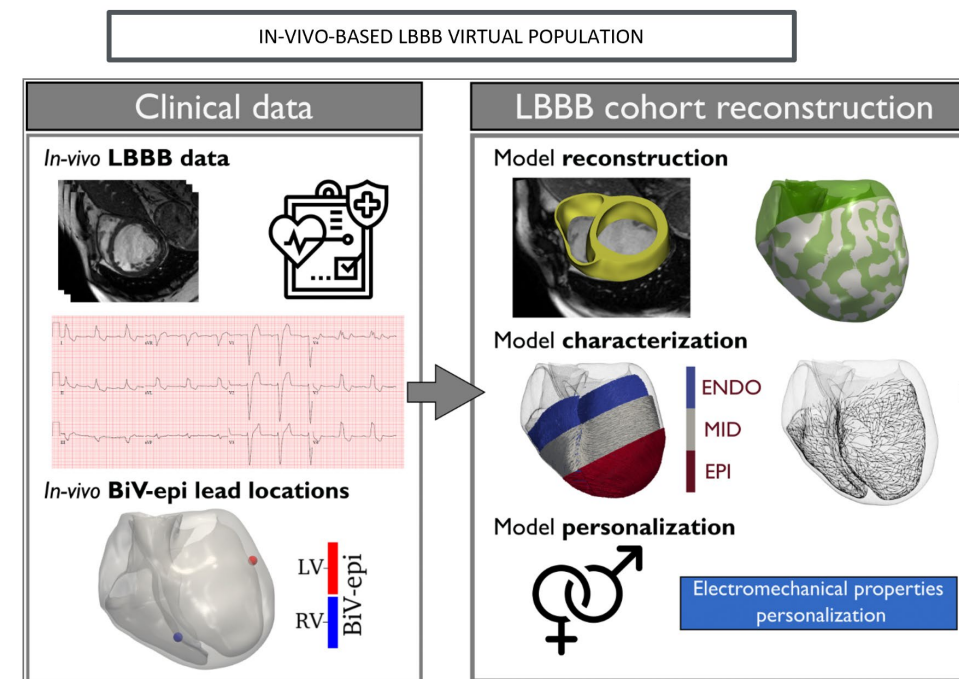


How are we creating Cardiovascular In-Silico Clinical Trials?

Models based on ex-vivo, in vitro, bibliographical and statistical clinical data



A group of models created from personalised patient data



What are the main inputs to create Cardiac In-Silico Clinical Trials?

Virtual Populations

1. Human anatomies (cMRI, cCT)
2. Sex
3. ECG markers **within clinical ranges**
4. Functional information **within clinical ranges**
5. Therapy information
6. Other clinical relevant data (hypertension, etc) **within clinical ranges**

Personalised models

1. Patient anatomy (cMRI, cCT)
2. ECG markers, Electrocardiogram
3. Sex
4. Functional information (echo, perfusion, ECV, etc)
5. Therapy information
6. Other clinical relevant data (hypertension, etc)

Context of Use (CoU)

What are the main outputs for In-Silico Clinical Trials?

Virtual Populations

1. Approximate characterisation of the population variability
2. Computational clinical trial markers that can be compared to clinical trial outcomes
3. Translation of therapeutical inputs to cohort-specific clinical behaviour

Personalised Models

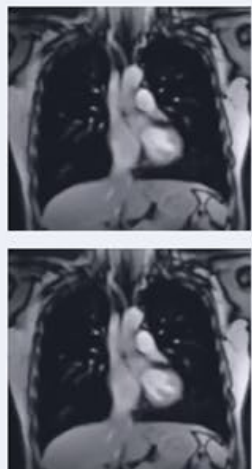
1. Patient-Specific characterization of the human trial subjects
2. Clinical input markers used for personalisation
3. Additional computational markers can be employed for therapy characterisation
4. Selection of validation markers according to CoU

Validation as comparison to clinical data (CoU)

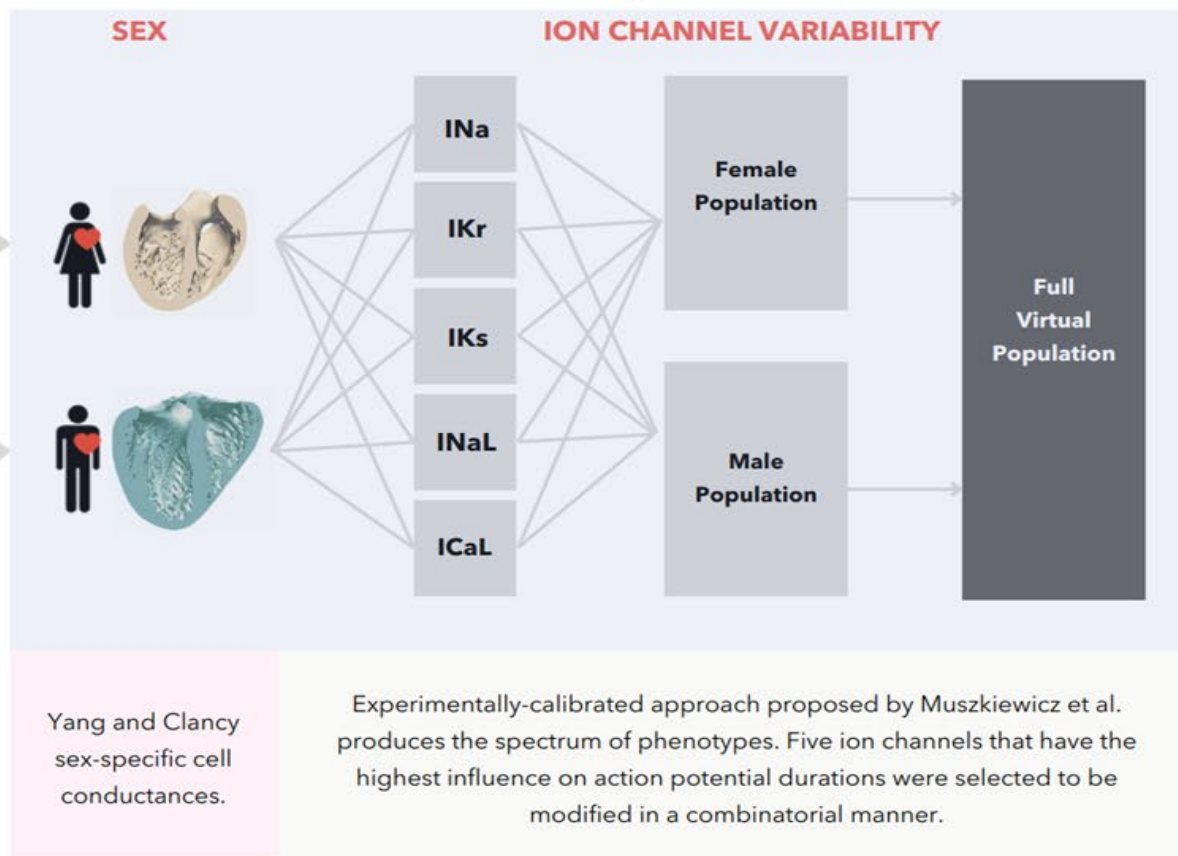


Virtual Human In-Silico Study

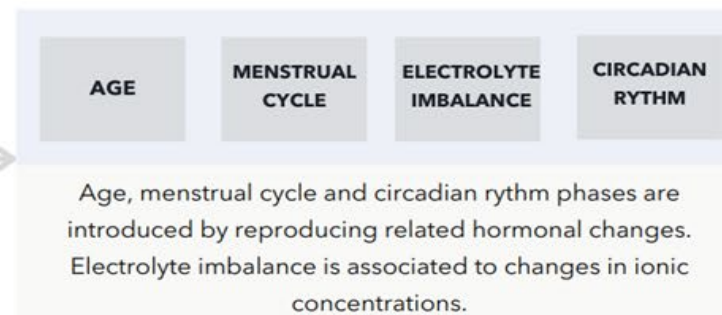
Medical Images



Baseline Population



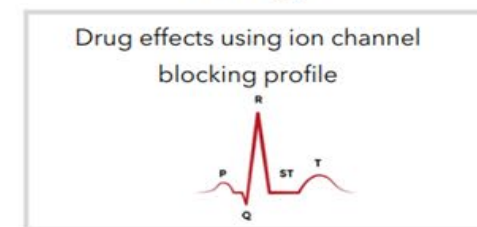
Extra Characterization



Pathologies

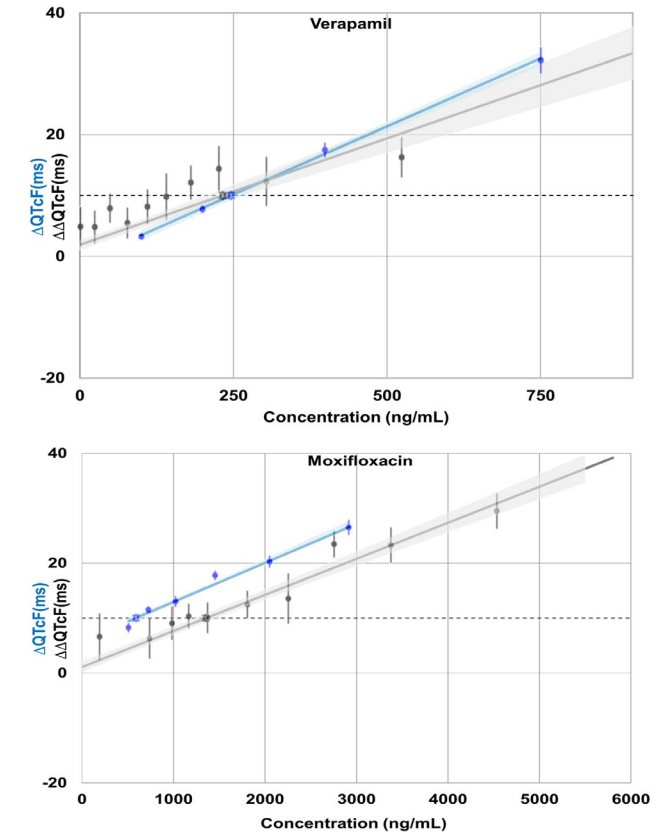
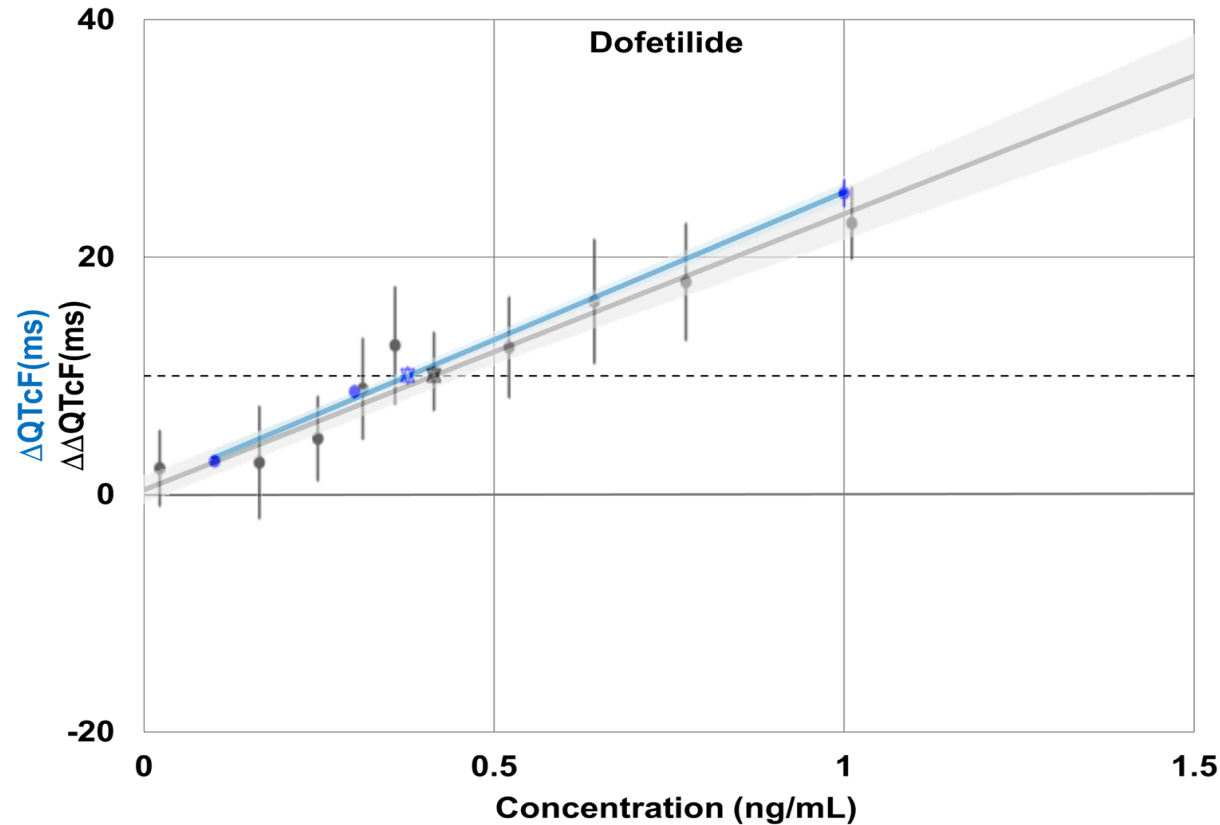


Drugs



Translation from in-vitro data to human clinical marker prediction

Exposure-Response QT-interval prolongation using virtual cardiac populations

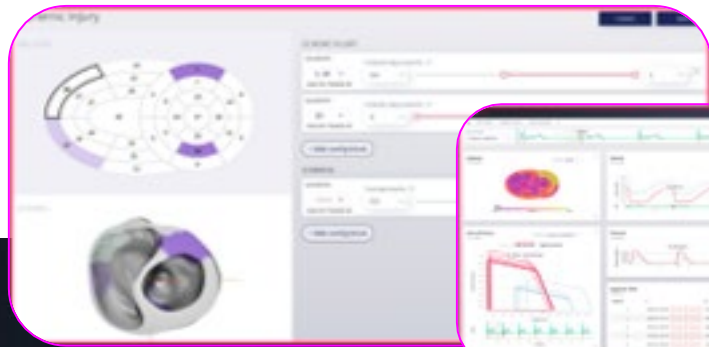


VIRTUAL CLINICAL QT EXPOSURE-RESPONSE STUDIES – A TRANSLATIONAL COMPUTATIONAL APPROACH.
AGUADO SIERRA ET AL..JOURNAL OF PHARMACOLOGICAL AND TOXICOLOGICAL METHODS, 2024

V.HEART-SAFETY

Your own Virtual CRO - Available Now (Cloud-Deployed)

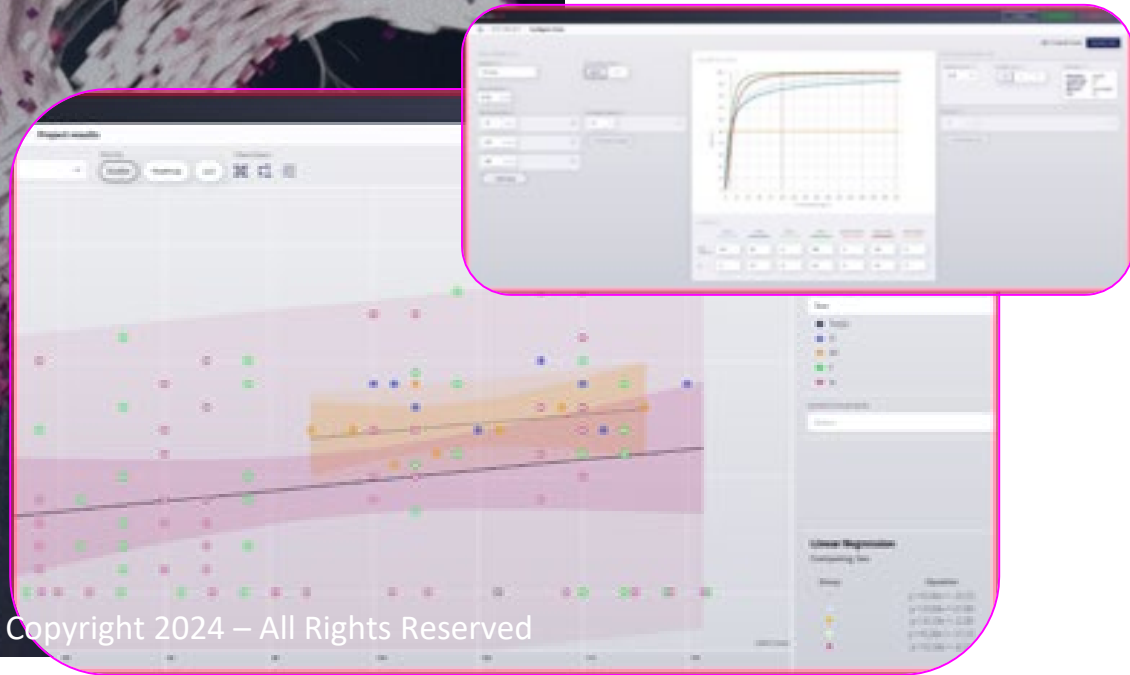
V.HEART-Safety is ELEM's solution for Pharmaceutical companies to compute the pro-arrhythmic effect of drugs on the human heart and to analyse, quantify and characterised drug induced risks in human populations by performing clinical trials virtually, in silico.



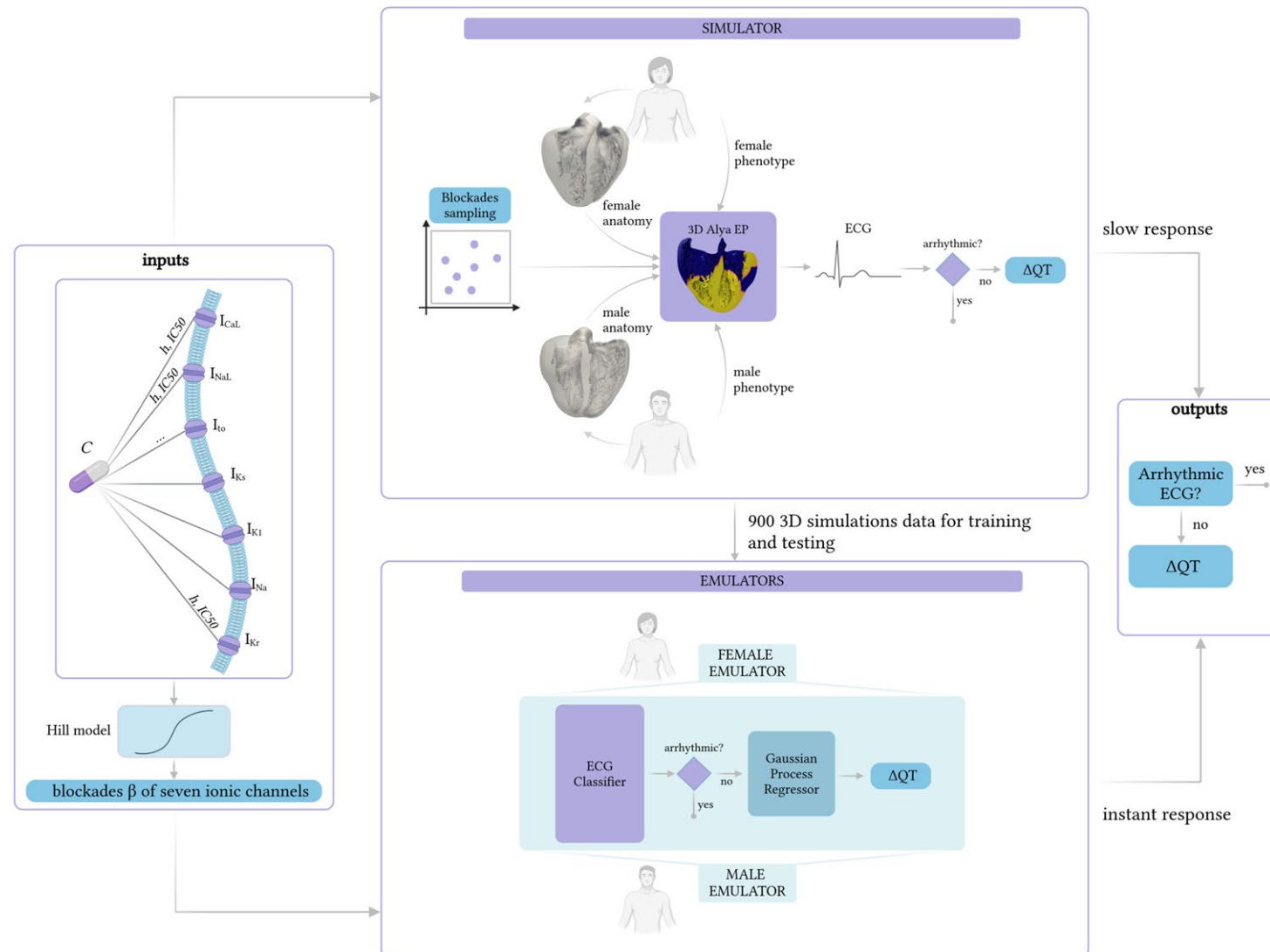
V. HEART

Cardiac Trials, Virtual Population,
High Performance Computing

ELEM's Virtual Human Twin technology
for the human heart



V.HEART-SAFETY DISCOVERY: AI-Based Platform



Recent studies demonstrate that Virtual Populations provide better translation of in-vitro data to predict drug-induced QT-interval prolongation than cell populations

Two electrophysiology models were compared:

- Optimized Ohara-Rudy from Passini 2017 methodology (89% accuracy)
- Tomek-Rodriguez (87% accuracy)

Context of use: Exposure-Response
Concentration-QT prolongation

Miss-classified Drugs by Single Cell methodology (Optimized O'Hara and Tomek cell models)

Drug	Passini 2017	Tomek 2019	TdP level
Mexiletine			
Paroxetine			
Voriconazole			
Metronidazole			
Clozapine			
Dasatinib			
Saquinavir			
Procainamide			
Lidocaine			
Ranolazine			
Sertindole			
Nilotinib			

TdP Risk
None
Conditional
Possible
High

Total drugs
N=62

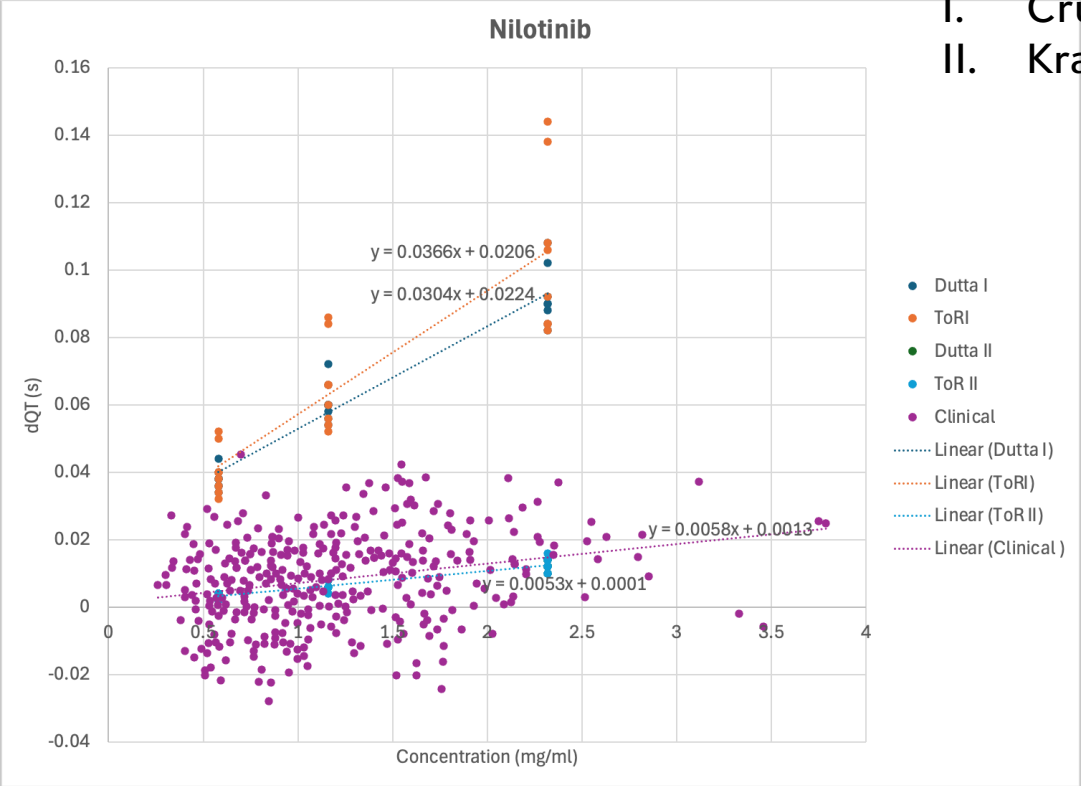
Input drug data has a greater impact on predictions than different cell models employed to solve Virtual Populations

Nilotinib at Clinical Concentrations

Clinical data (at day 8) digitized from:

Larson RA. Et al. Population pharmacokinetic and exposure-response of nilotinib in Ph+ cronic myeloid patients with newly diagnosed chronic myeloid leukemia in chronic pase. Eur J Clinical Pharmacol (2012): 68, 723-733.

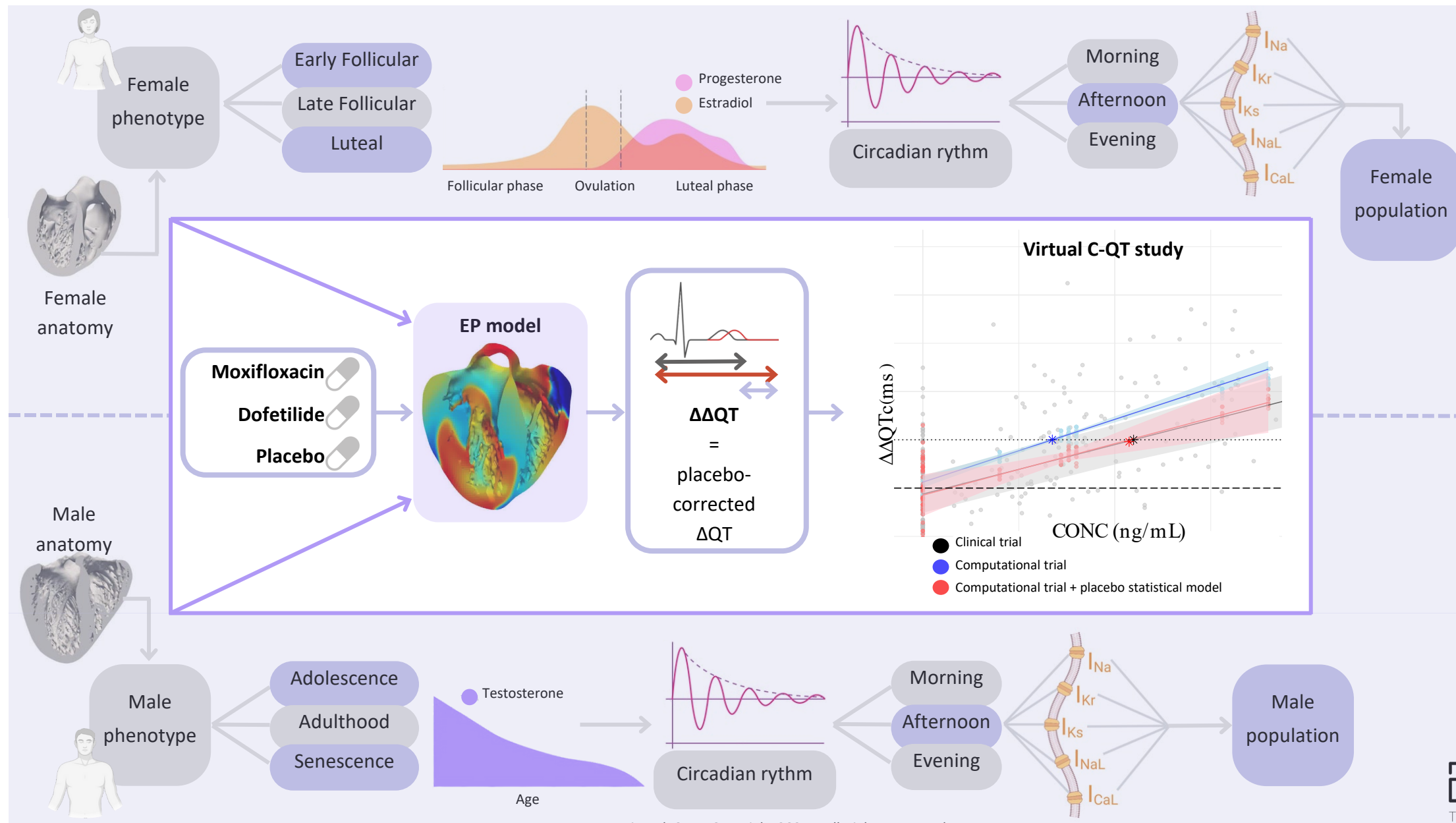
ToR and Dutta model with Kramer IC50s provide exact same predictions in accordance to the clinical trial.



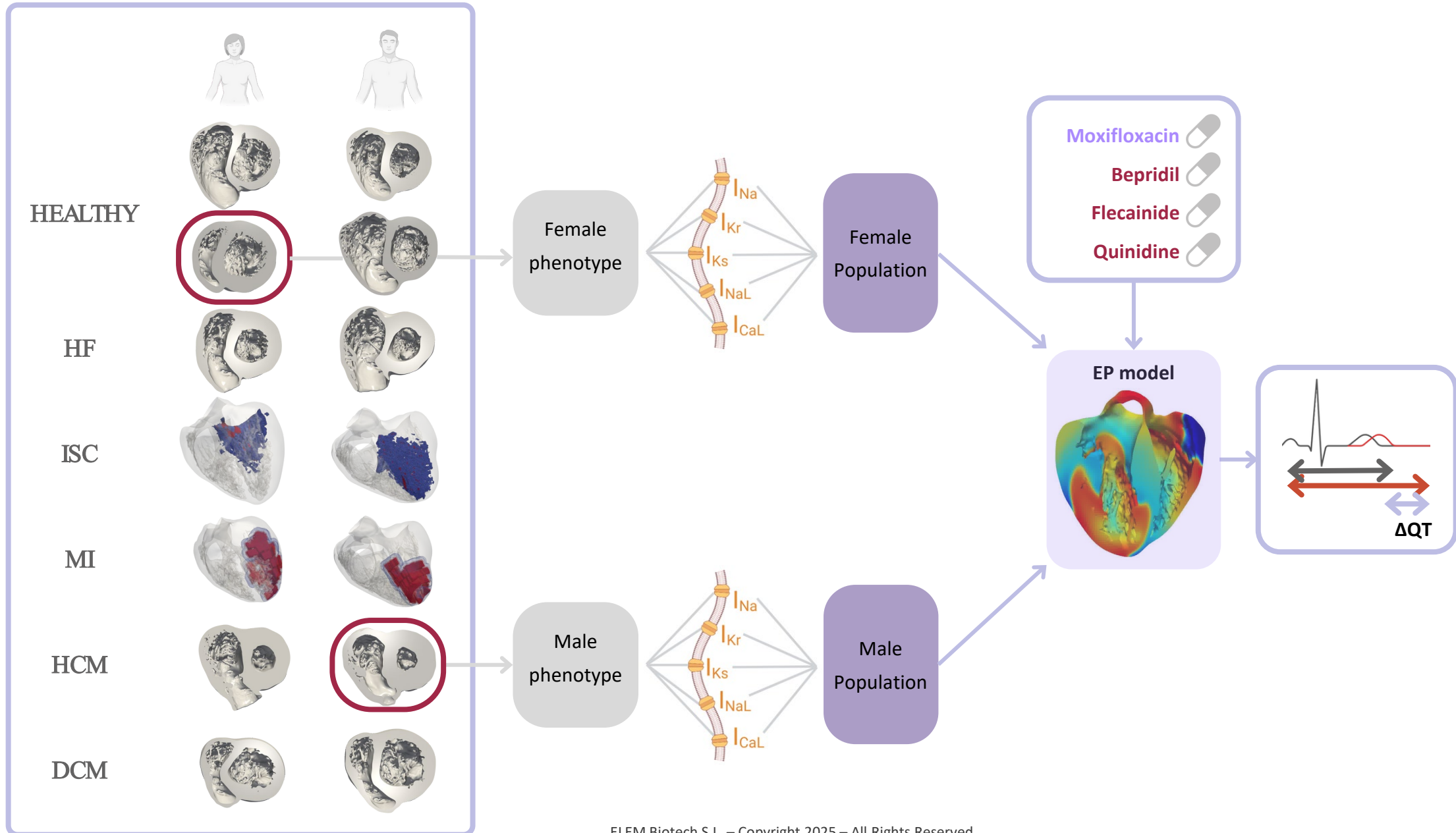
IC50 values:
I. Crumb et al.
II. Kramer et al.

Compound List		IC ₅₀ (h) ^{REF} , with IC ₅₀ in μM						EFTPC max (μM)	PPB%	TdP risk category
		I _{Na}	I _{Kr}	I _{CaL}	I _{NaL}	I _{Ks}	I _{to}			
4	Nilotinib I		0.091(0.8) ⁴		4.706(1.9) ⁴			0.172 ³	98.0%	2
	Nilotinib II	13.3(2.11) ³	1(0.96) ³	17.5(1) ³						

Placebo Effects in Drug Computational Trials



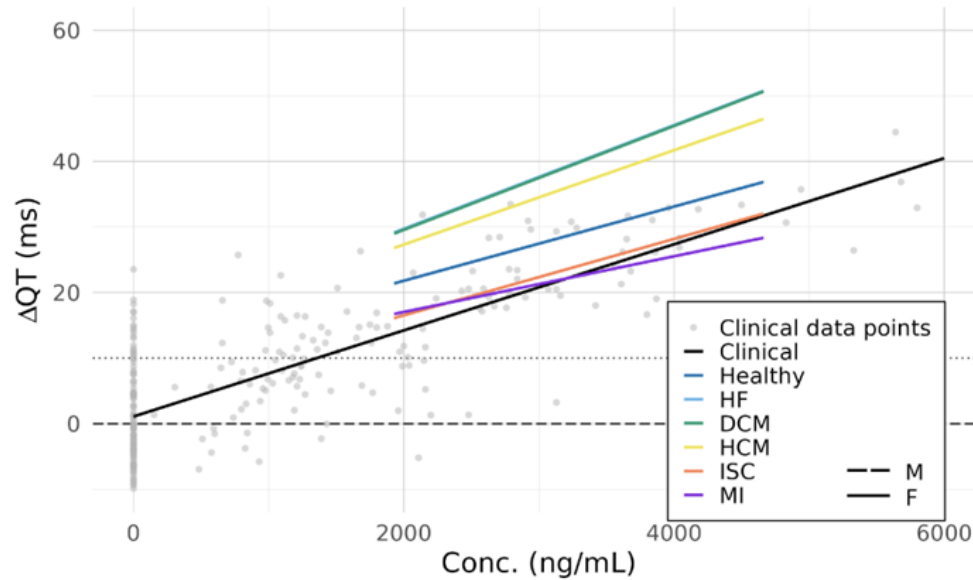
Comorbidities Representation in Drug Computational Trials



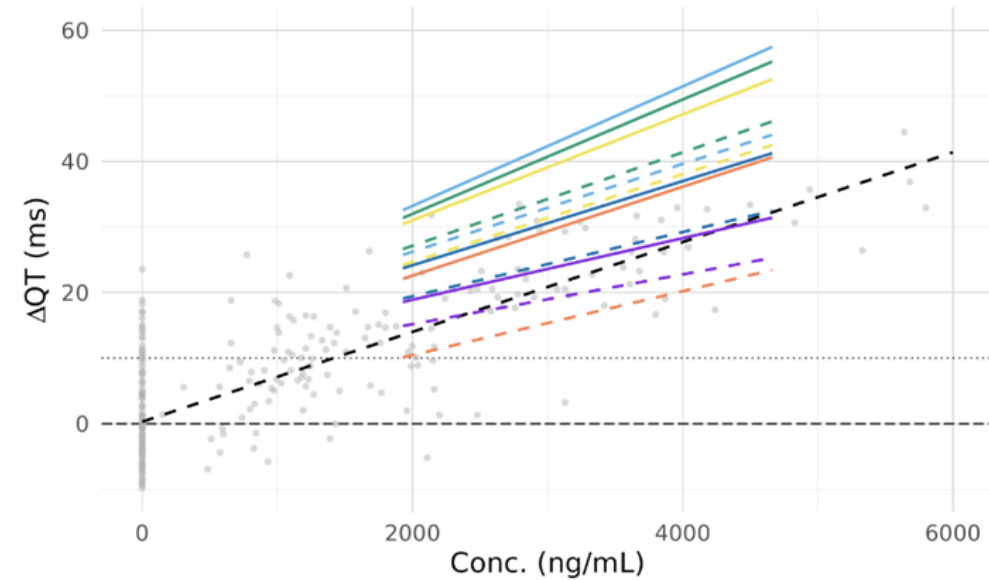


QT-Drug Exposure Effect with Pathophysiology

Moxifloxacin



(A) Average regression models.



(B) Sex-specific regression models.

Figure 7: Concentration-QTc effect relationship models estimated for moxifloxacin from computational (healthy, HF, DCM, HCM, ISC and MI - ΔQT) and clinical data (healthy - placebo-adjusted ΔQT).

How do you validate conditions of high risk for human trials?

What to do when no human clinical data can become available due to Ethical concerns??

These conditions may include:

PREGNANT WOMEN

CHILDREN

ELDERLY SUBJECTS

FRAILITY DUE TO COMORBIDITIES

Personalised models of an Elderly cohort

DATASET



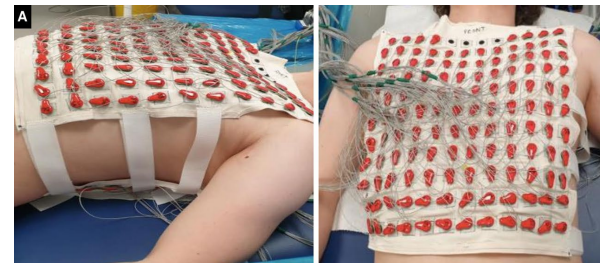
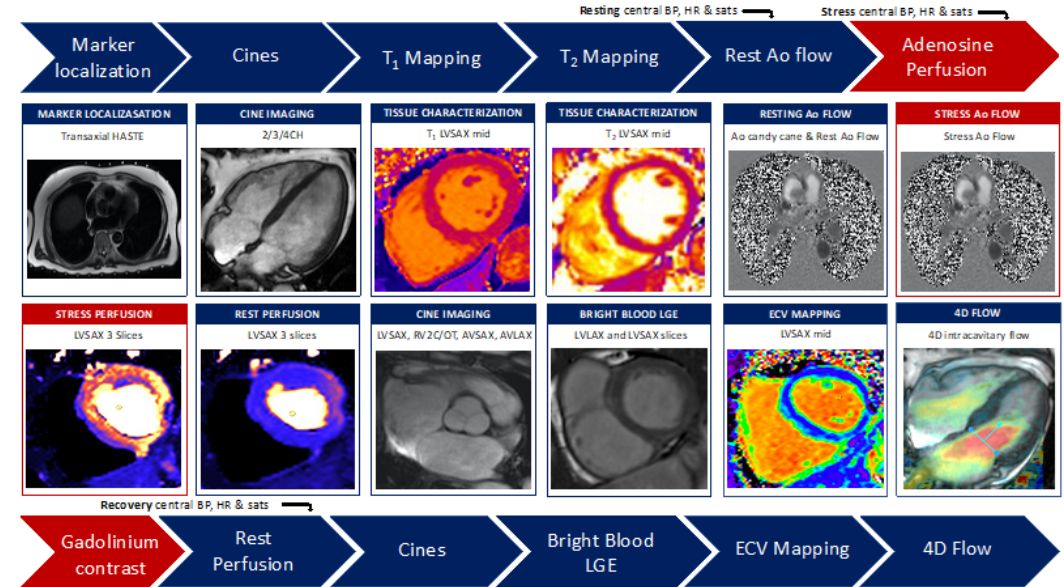
MYOFIT46

- Subset of the longest running population study, National Survey of Health and Development (NSHD)
- More than 450 participants
- All born the same week in March 1946 in the UK
- Detailed cardiac magnetic resonance (CMR) analysis and Electrocardiographic imaging (ECGi) per patient
- Multiple data collections along participant's life
- Socioeconomic status, lifestyle, past medical history

Dr Gaby Captur, Dr Matt Webber, Dr Fiona Chan, Dr Debbie Falconer, PhD Michele Orini, Dr Alun Hughes



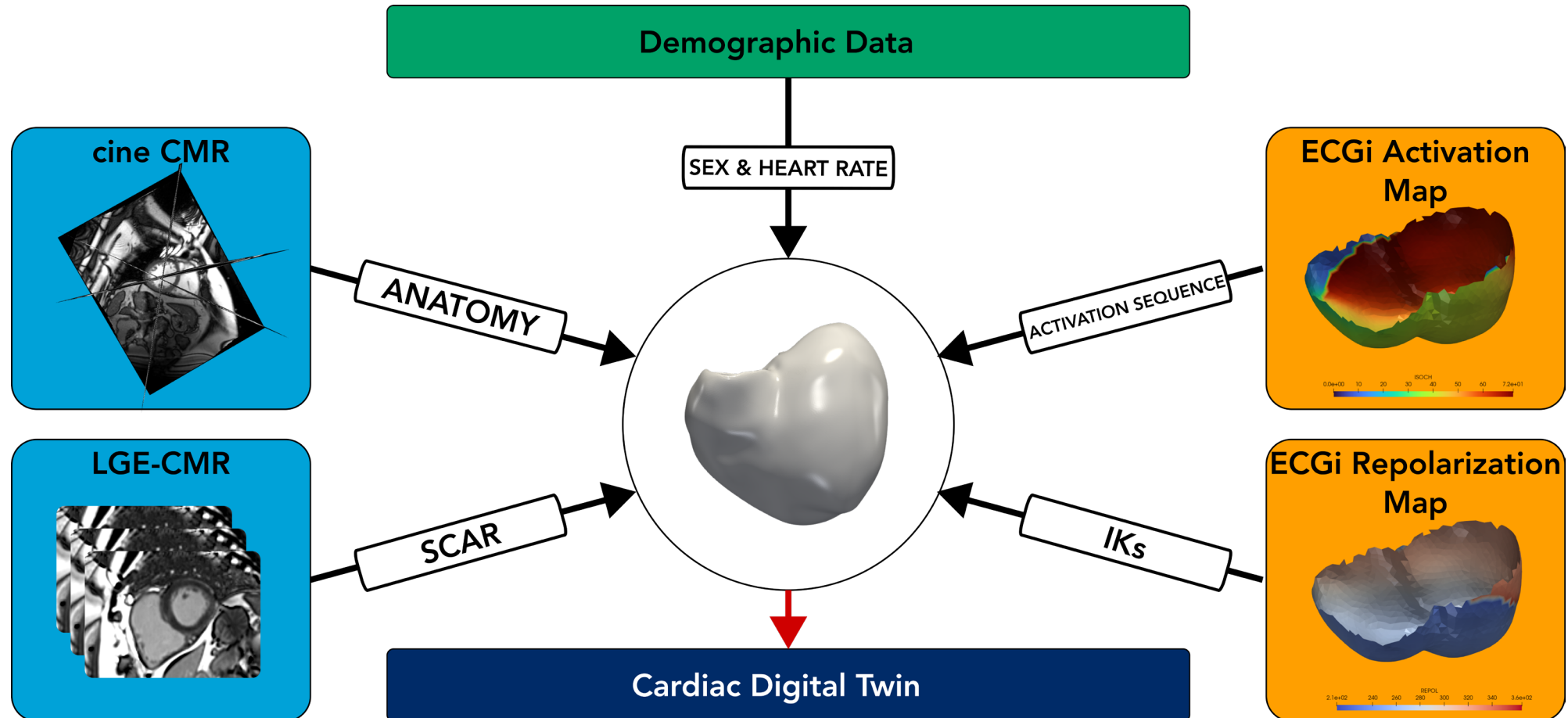
Medical
Research
Council



Digital Twin Generation and Personalization Pipeline



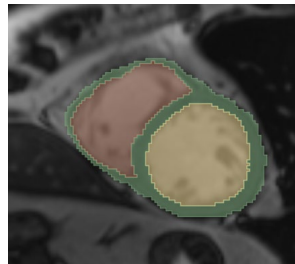
MERIT: Multimodal data based cardiac digital Twin pipeline



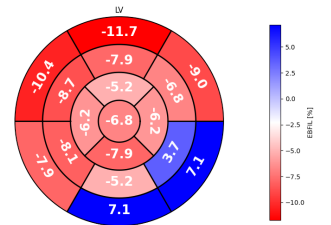
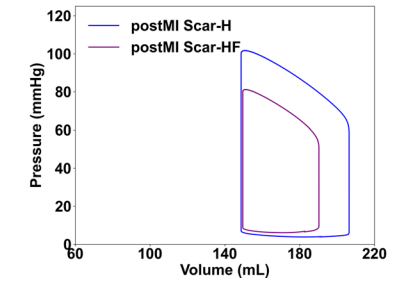
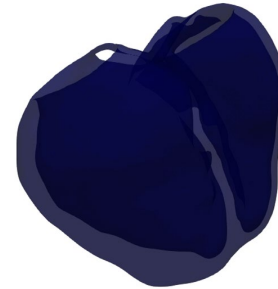
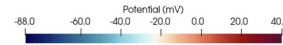
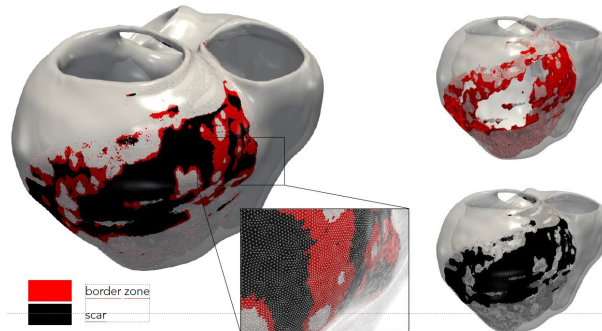
The objective

Patient-specific anatomy

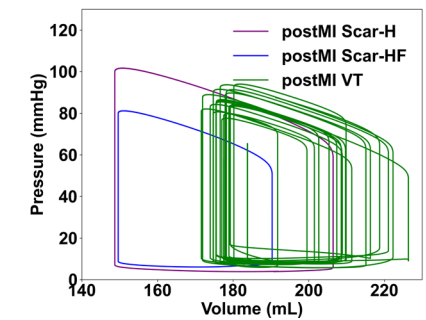
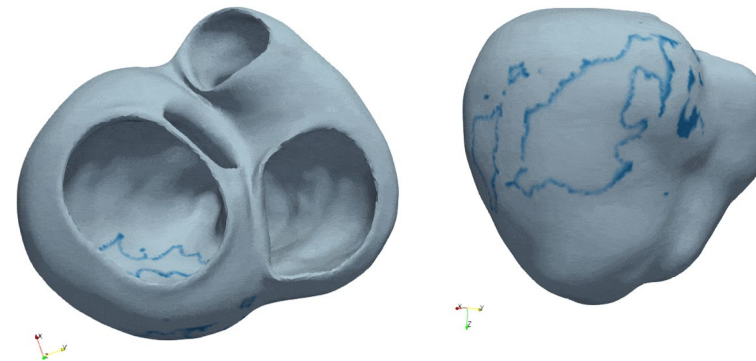
Biventricular geometry from a 58 years old patient with monomorphic VT due to chronic MI



Segmented
CMR



HF with reduced EF modelling: reduced contractility and reduced strains in the whole tissue and lost of elasticity in scar region



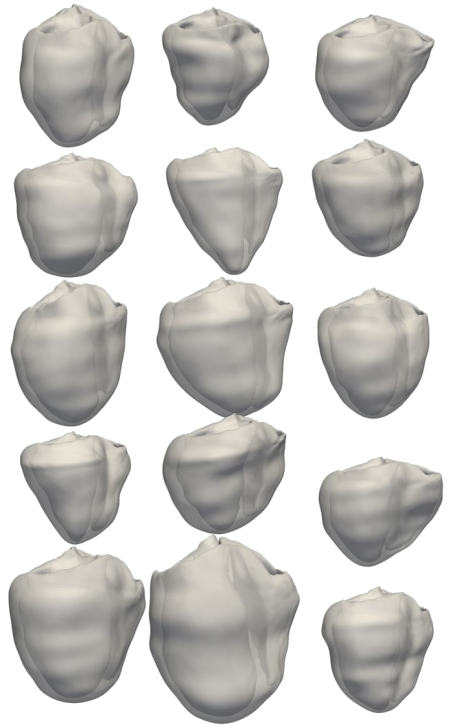
VT induced: chaotic hemodynamical behaviour and increased SV

Personalised trial enhancement with Virtual Humans

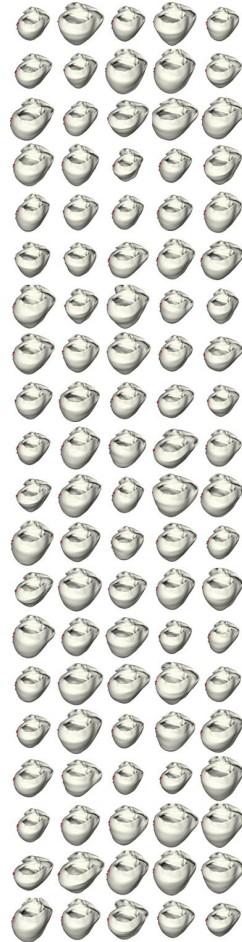


DEVELOPMENT OF SYNTHETIC LBBB VIRTUAL POPULATION

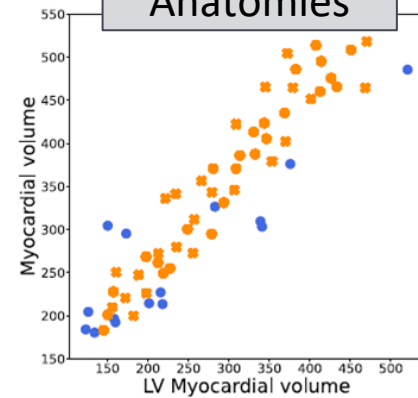
IN-VIVO-BASED LBBB VIRTUAL POPULATION



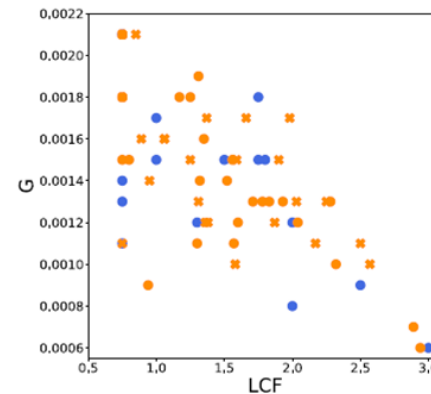
Statistical
Shape
Model



Anatomies

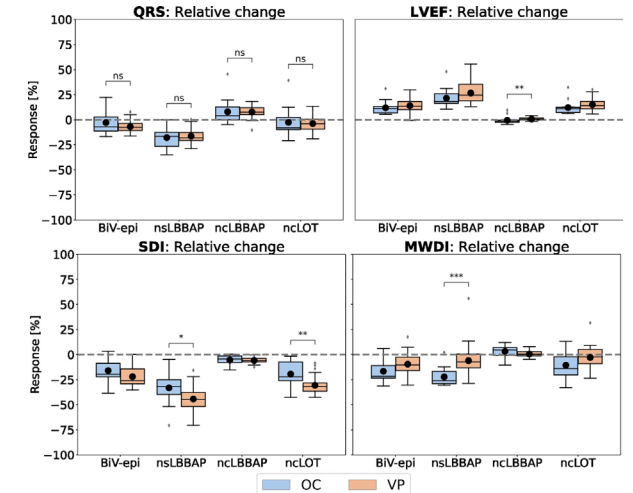
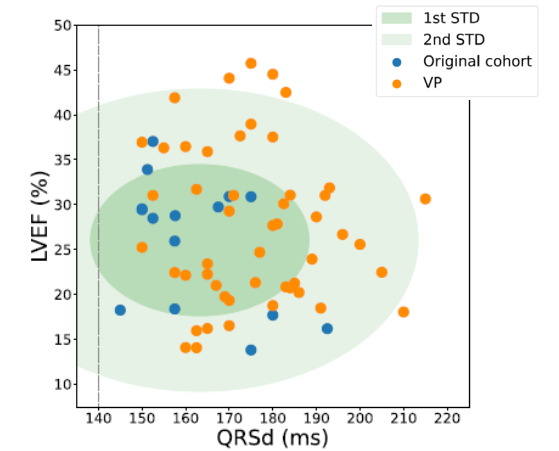


Myocardial properties



● Original cohort ● VP - Female ● VP - Male

SYNTHETIC LBBB VIRTUAL POPULATION



Conclusions

Cardiac in-silico trials are already a REALITY, but we require a stronger push for acceptance to provide quantitative evidence when there is none, or only anecdotal case reports. Those areas are exactly where these methodologies will provide the biggest impacts.

These frameworks are moving us towards precision medicine applications, but the pipelines and platforms require to be robust enough for scaling them to a clinical every day use.

Medical trials working for
EVERYONE
THE FUTURE IS NOW

Thank you



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