Robust Computational Modeling of Human Ventricular Activation

2017 CASIS Workshop

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Postdoctoral Research Staff Member

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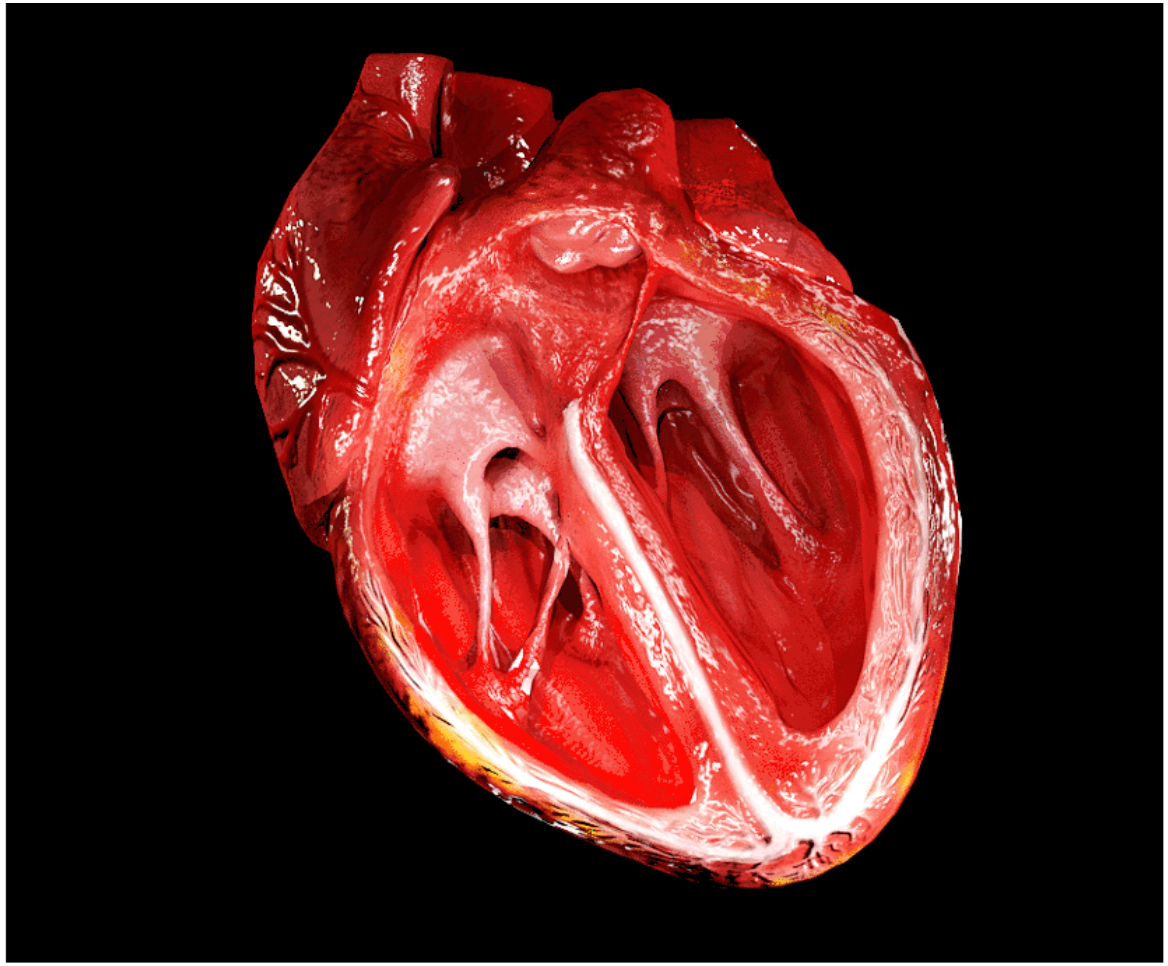
The Heart

A Mechanical *and Electrical System*

Every life-sustaining heartbeat must have coordinated contraction of the ventricles



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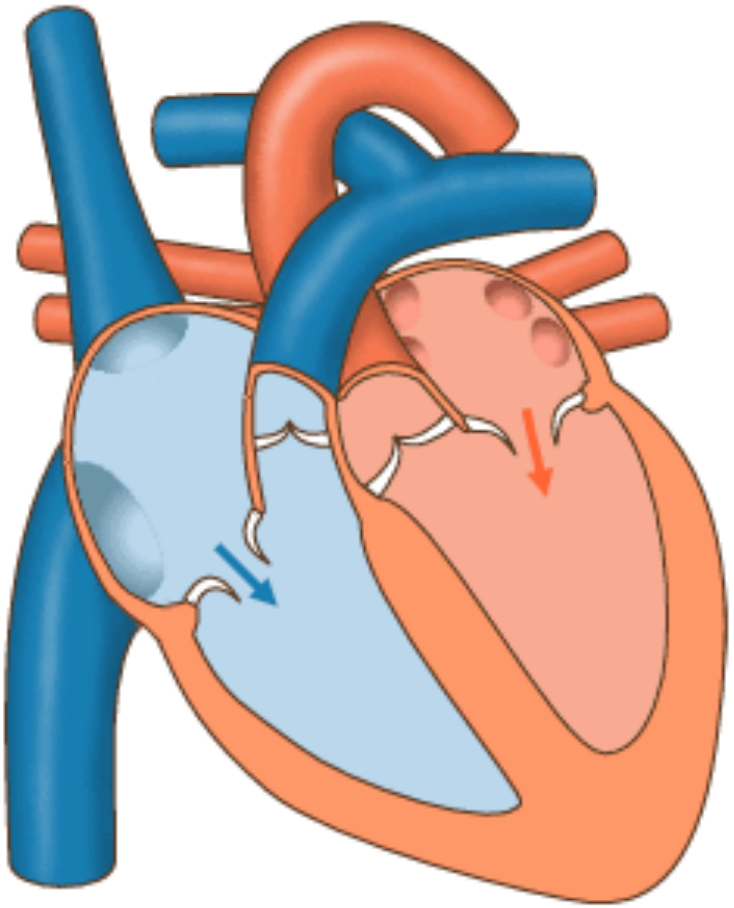

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RV = right ventricle
LV = left ventricle
S = Septum
W = Wall
RA = right atrium
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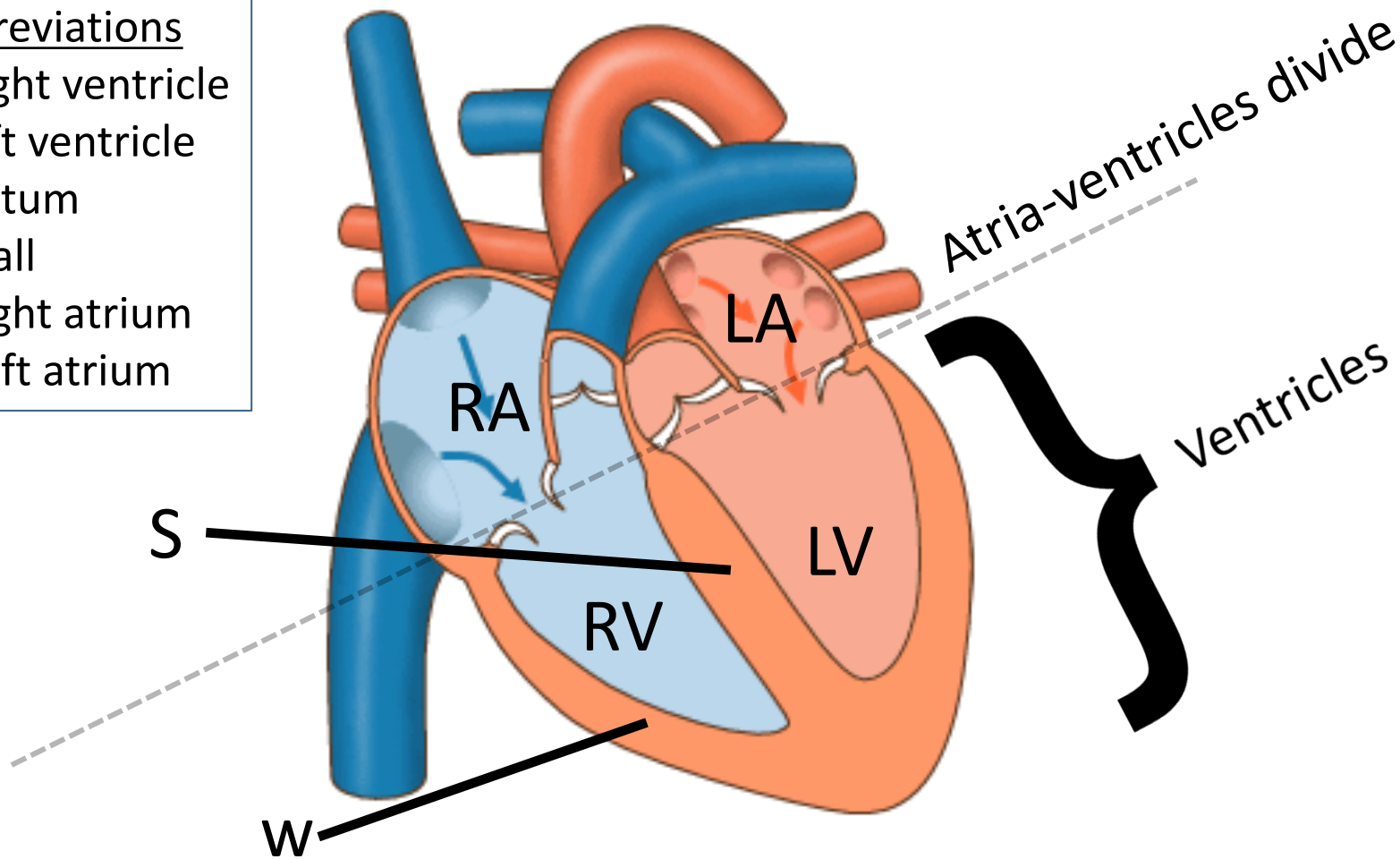

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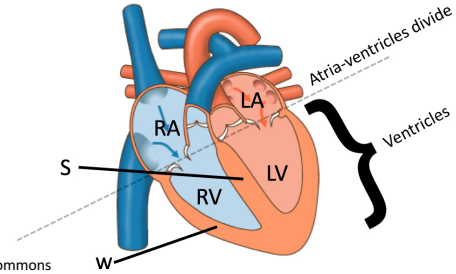

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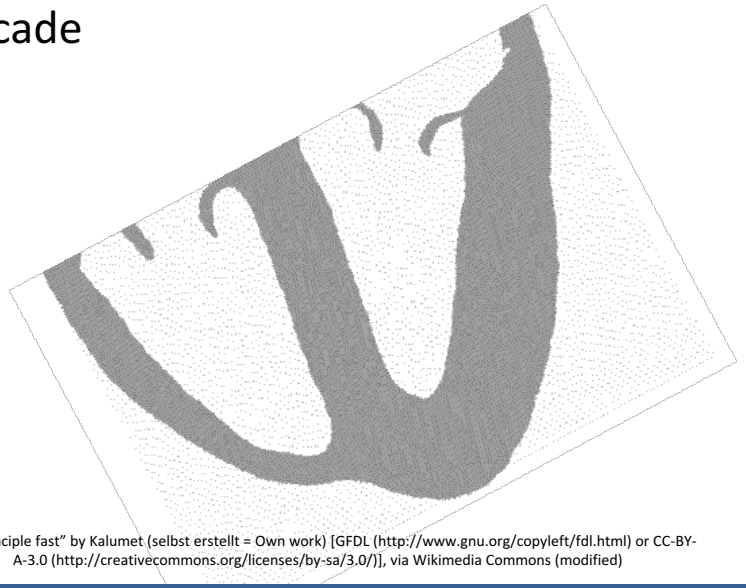
Coordinated ventricular contraction is regulated by electrical depolarization cascade



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The heart's electrical system drives the mechanical system

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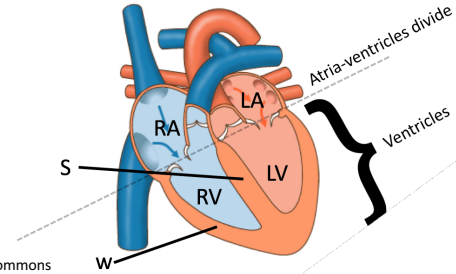

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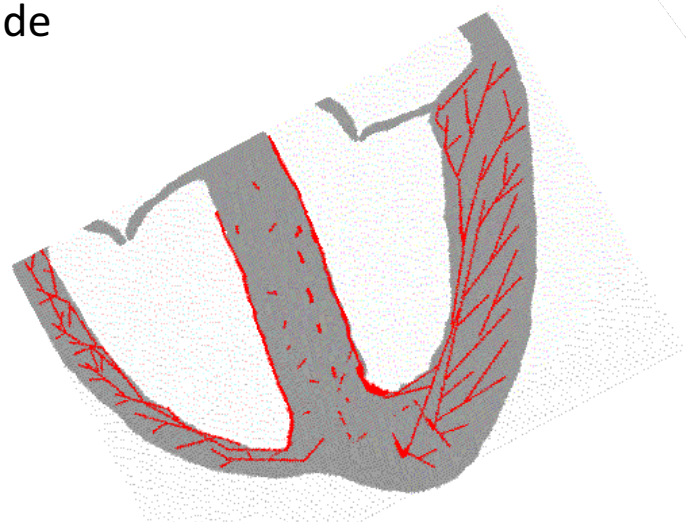

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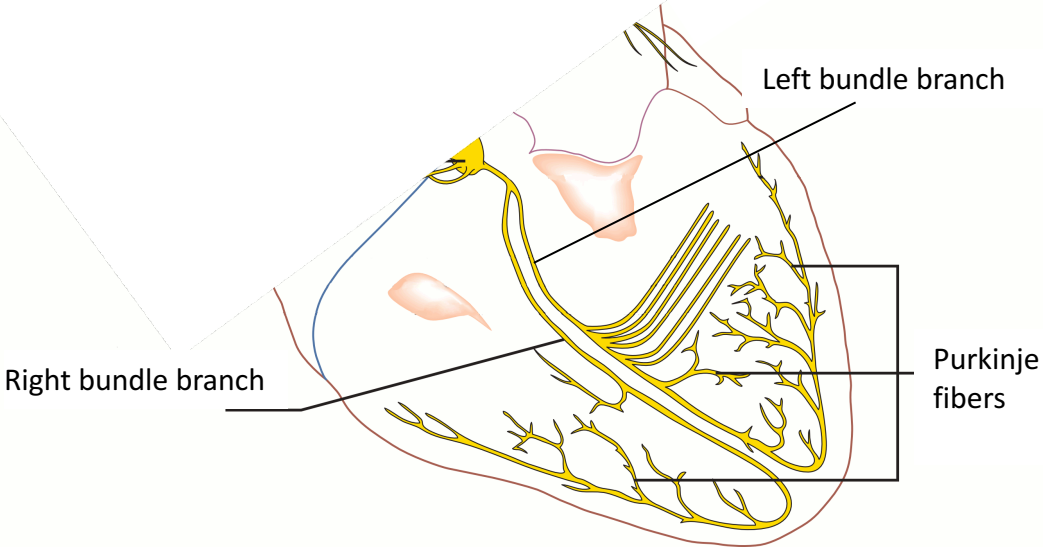
Ventricular depolarization cascade is initiated by the Purkinje network



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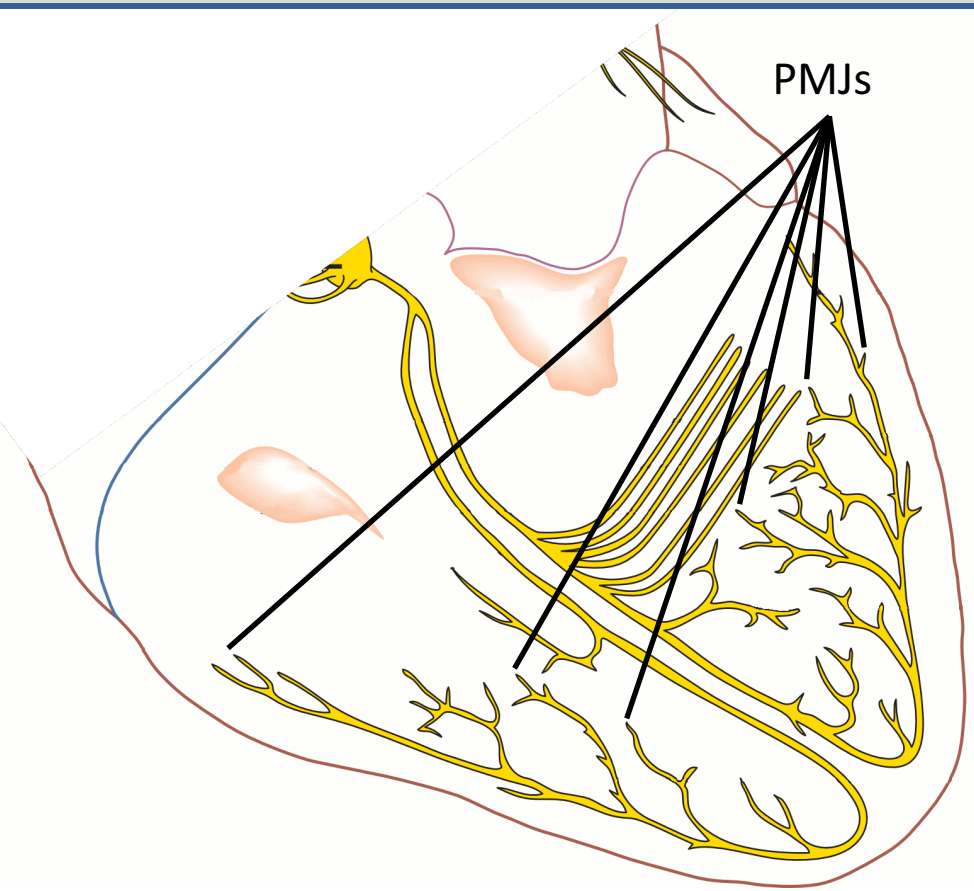
The heart's electrical system drives the mechanical system

The Purkinje Network



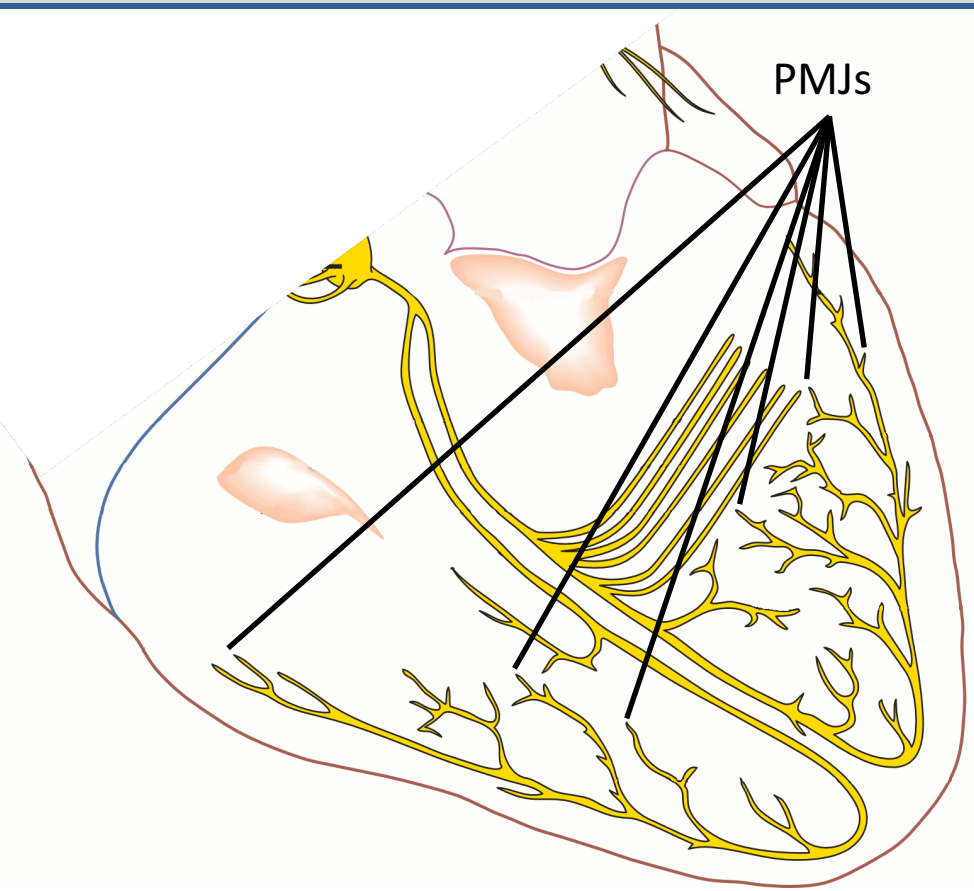
Is an "insulating superhighway" until the very ends

At the ends are the Purkinje-myocyte junctions (PMJs)

PMJs deliver charge to a large amount of tissue nearly synchronously

PMJs provide critical initial conditions for electrical wave propagation

The Purkinje Network



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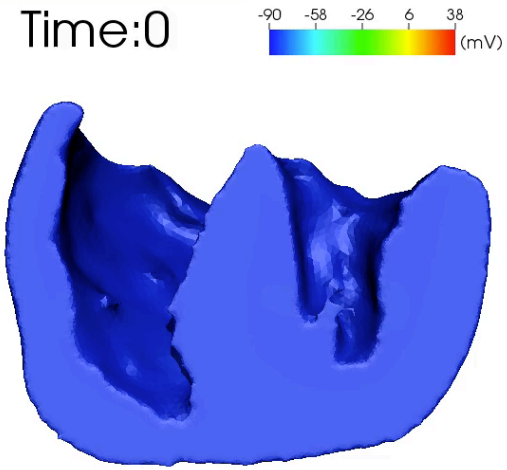
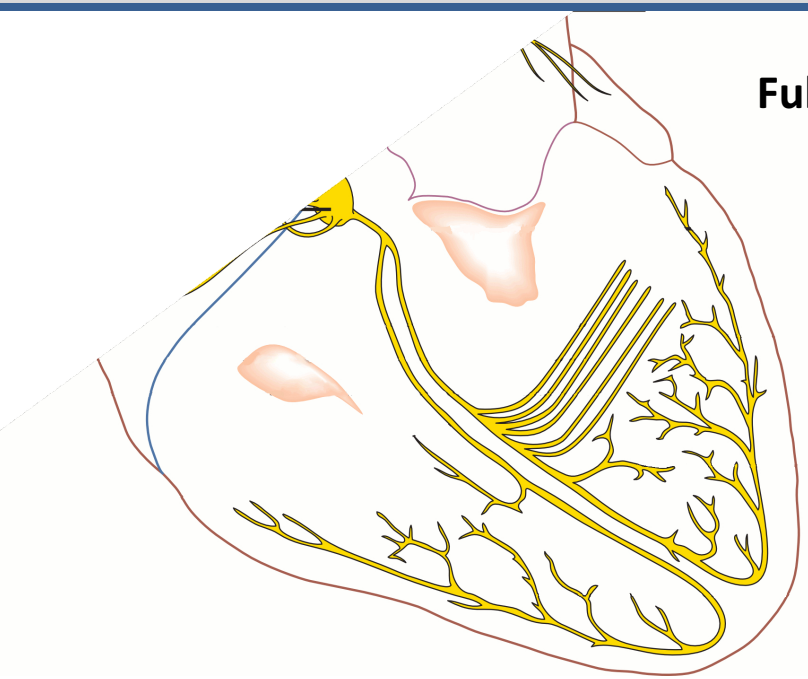


PMJs provide proper initial conditions critical for physiological electrical wave propagation, and thus, regulate proper contraction

Modeling the Purkinje Network



Full Purkinje network modeling

<u>Fractal trees</u>

Pros: automate/parameterize/optimize network

Cons: irregular geometry breakdown, portability

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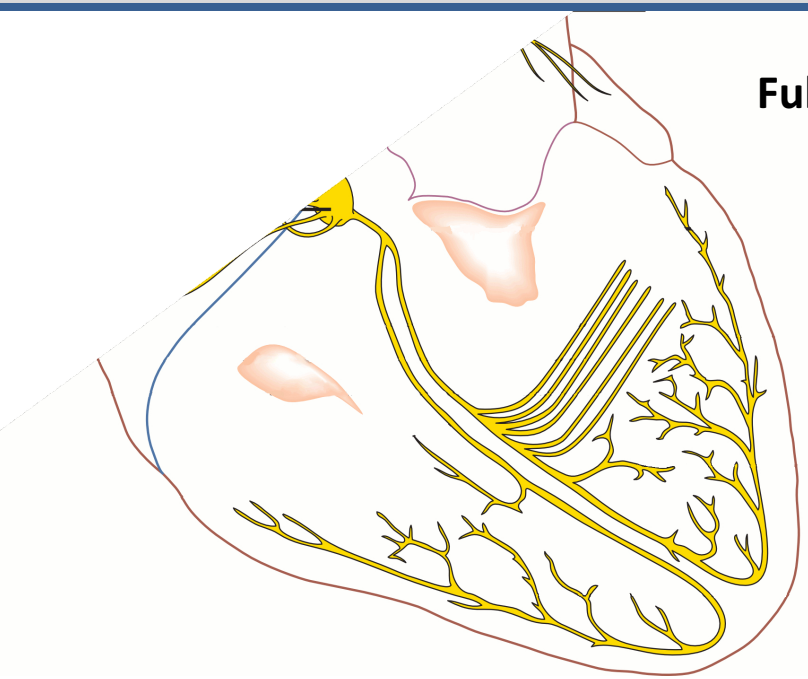

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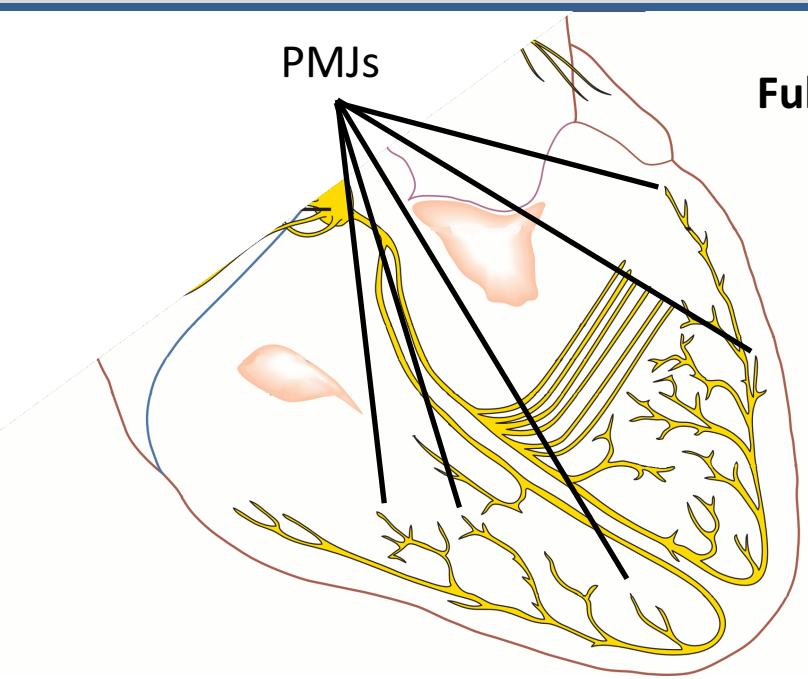
<u>Superimpose Purkinje dissection images</u>

Pros: anatomical basis

Cons: anatomically nonspecific (Purkinje images from other ventricles/animals), time intensive

Modeling the Purkinje Network



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Why not just model the "business end" of the Purkinje network: the PMJs?

Model PMJs as a collection of current injection "stimuli" with location and timing properties

Pros: easily implementable, portable, anatomical basis (ventricular activation timing experiments)

Cons: limited use in investigating Purkinje network/cell defects

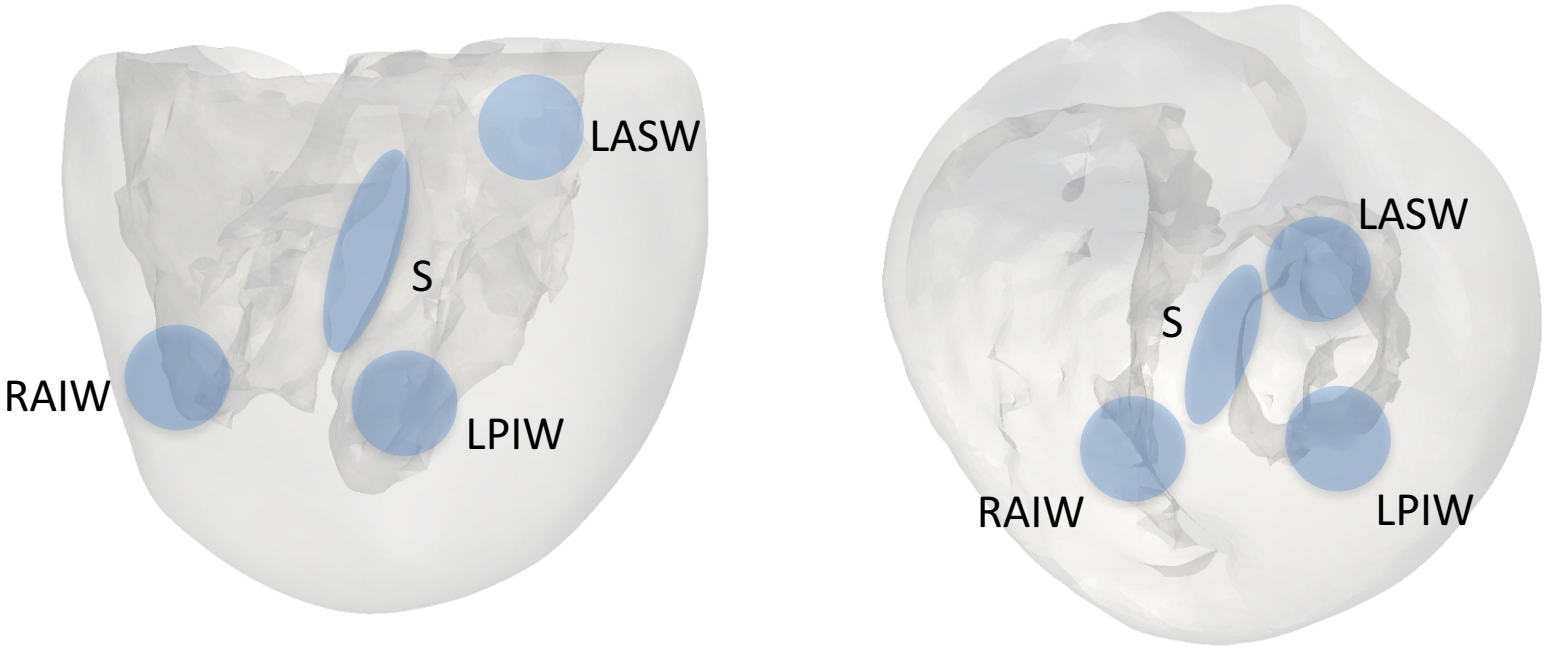
Missing piece: robust stimulus protocol to simulate healthy human heart

Our Model of PMJs

Our location/timing of stimuli based on Durrer et al. experiments[1]

- used 870 in-tissue electrodes on 7 isolated human hearts
- measured activation timing throughout ventricles

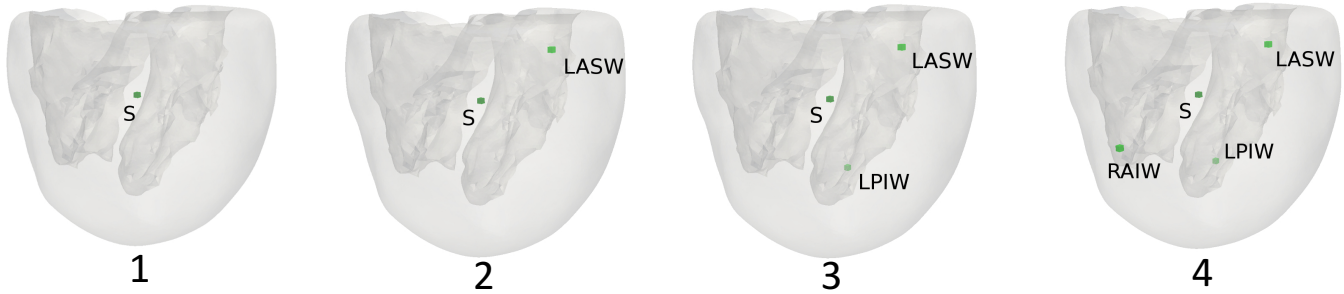
Identified 4 early activation regions



Region	S	LASW	LPIW	RAIW
Timing (ms)	0	0	0	5

[1]D. Durrer, R.Th.V. Dam, G.E. Freud, M.J. Janse, F.L. Meijler, R.C. Arzbaecher. (1970) Circulation, 41, 899-912

Our Model of PMJs: Sensitivity Analysis



<u>Sensitivity analysis</u>

How many stimuli need to accurately approximate early activation regions?

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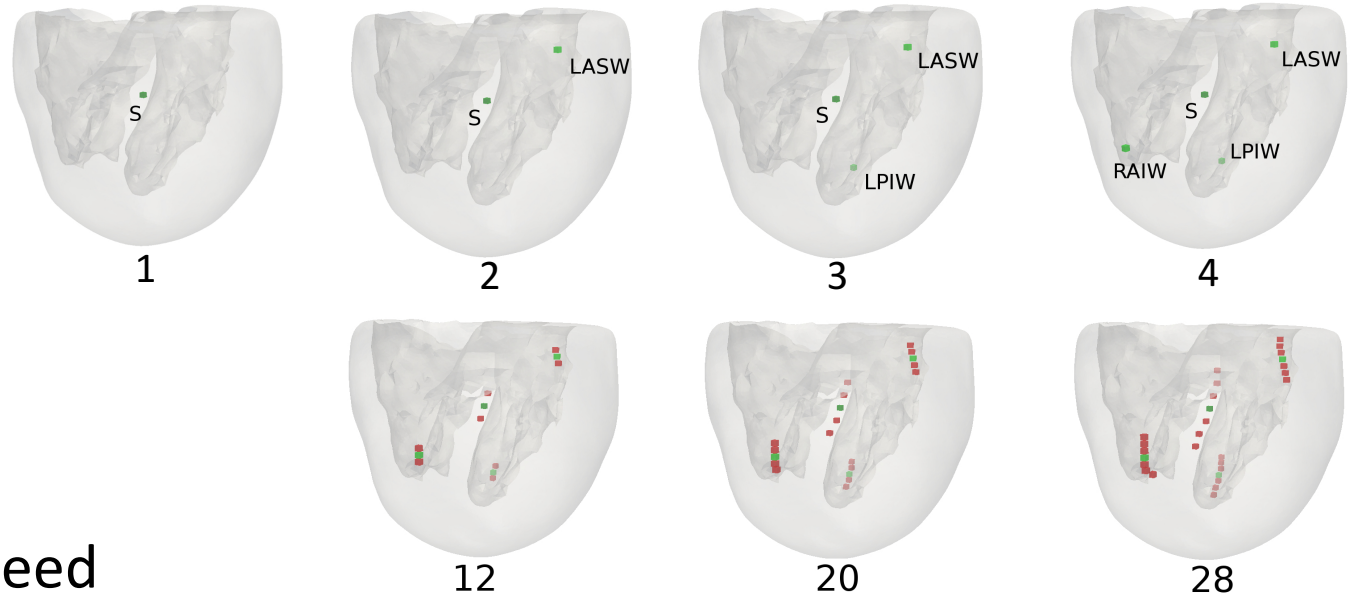

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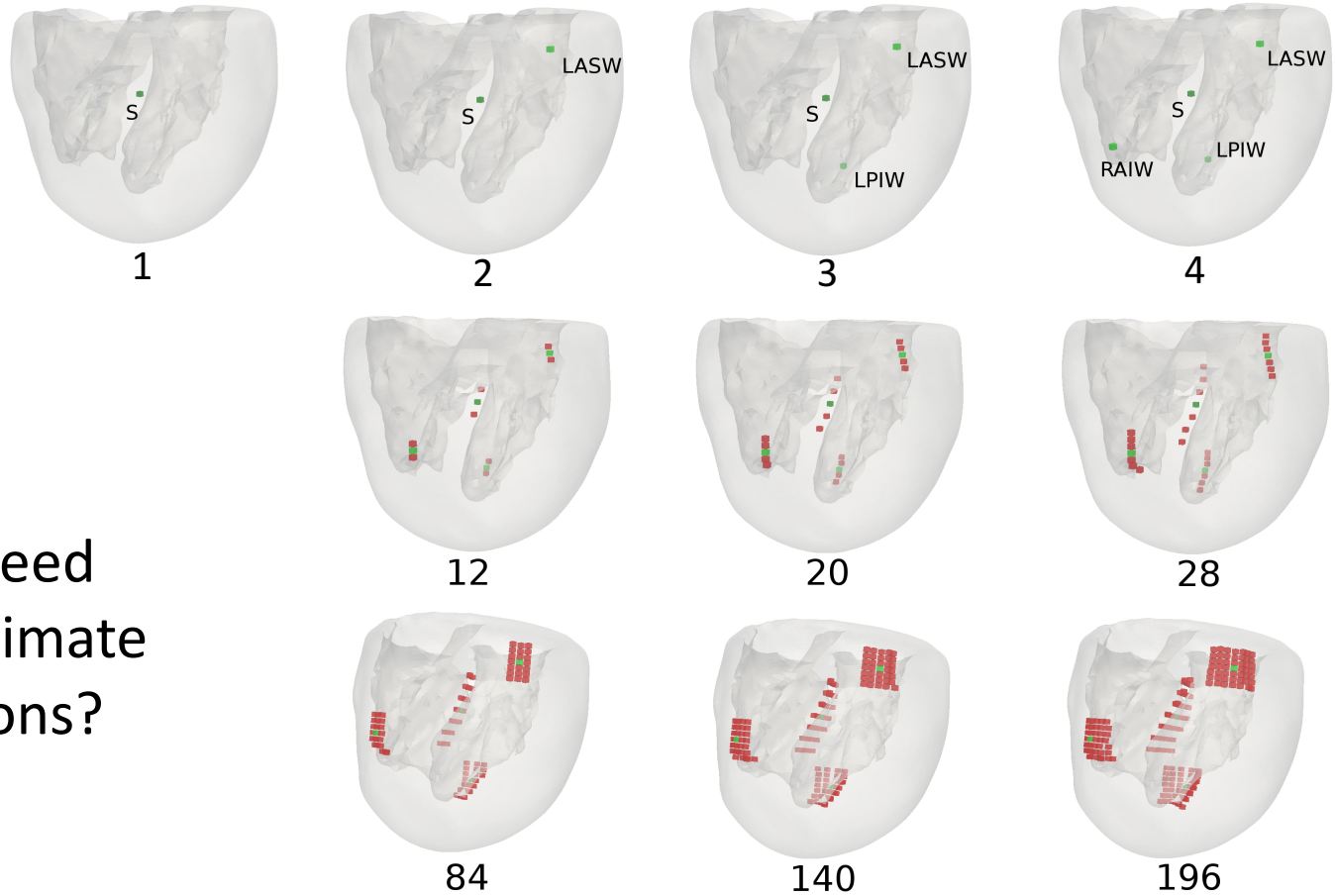

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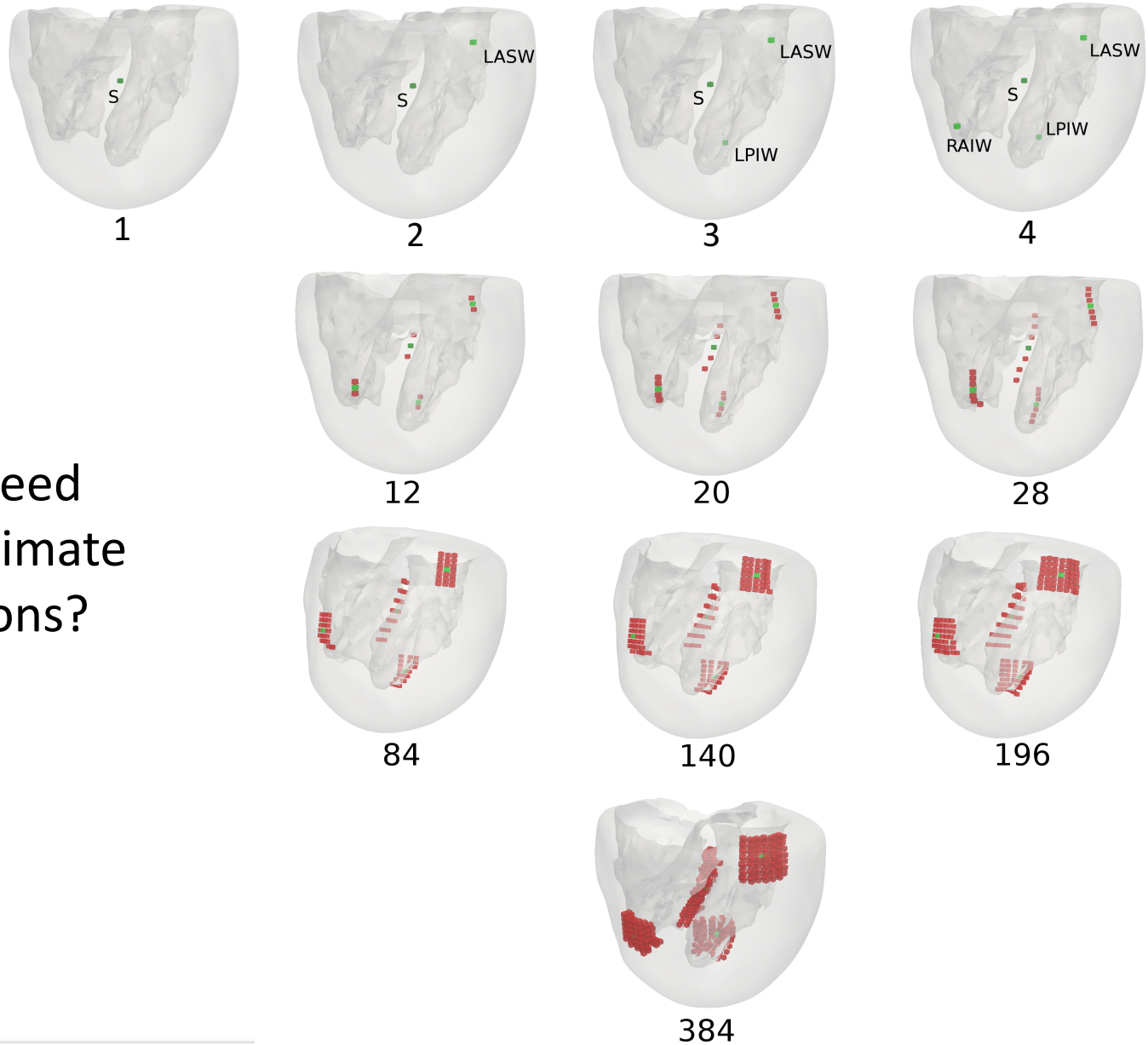

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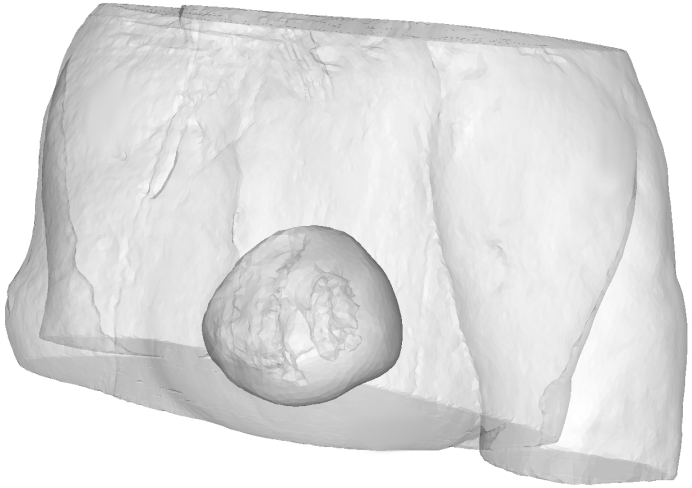
Sensitivity analysis

How many stimuli need to **accurately approximate** early activation regions?

What are the metrics/criteria?

Metrics/criteria derived from ECG (connection to clinic)

Yes, we can simulate an ECG!



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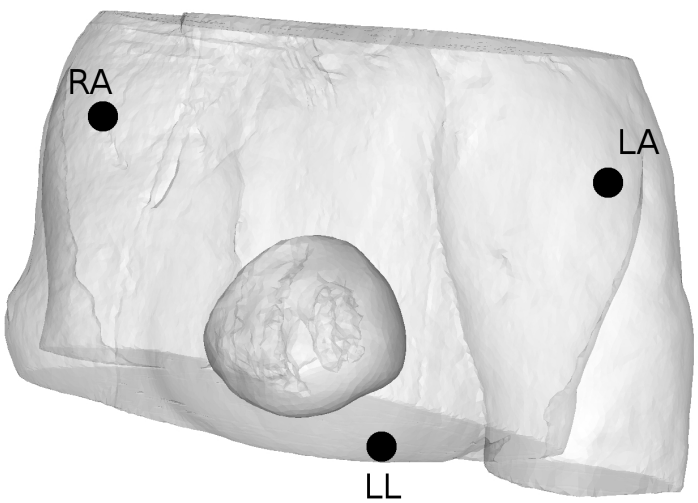

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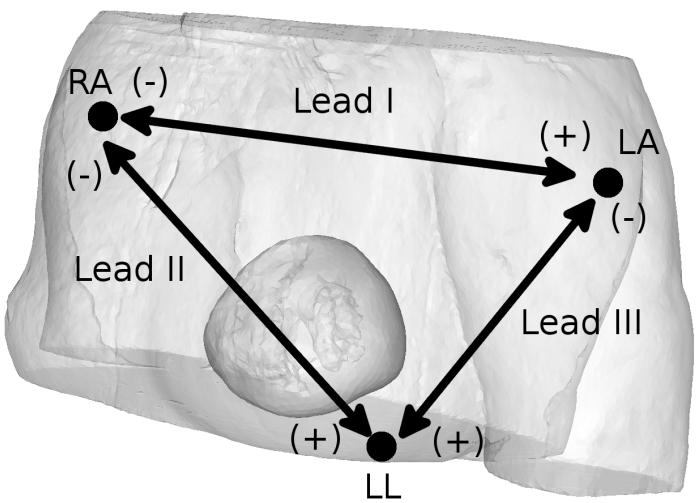

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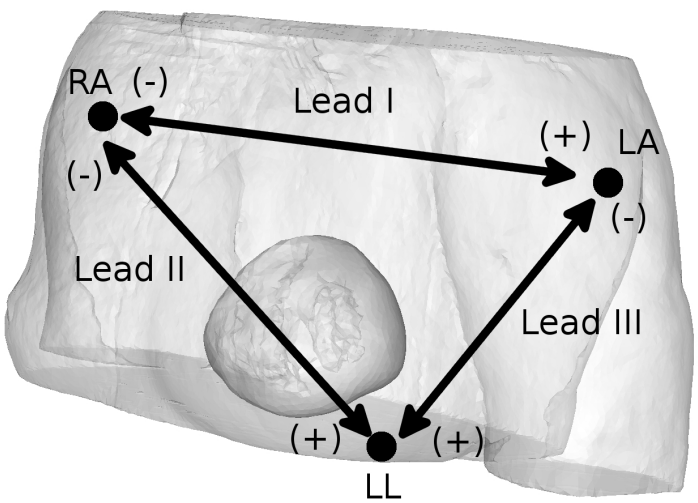
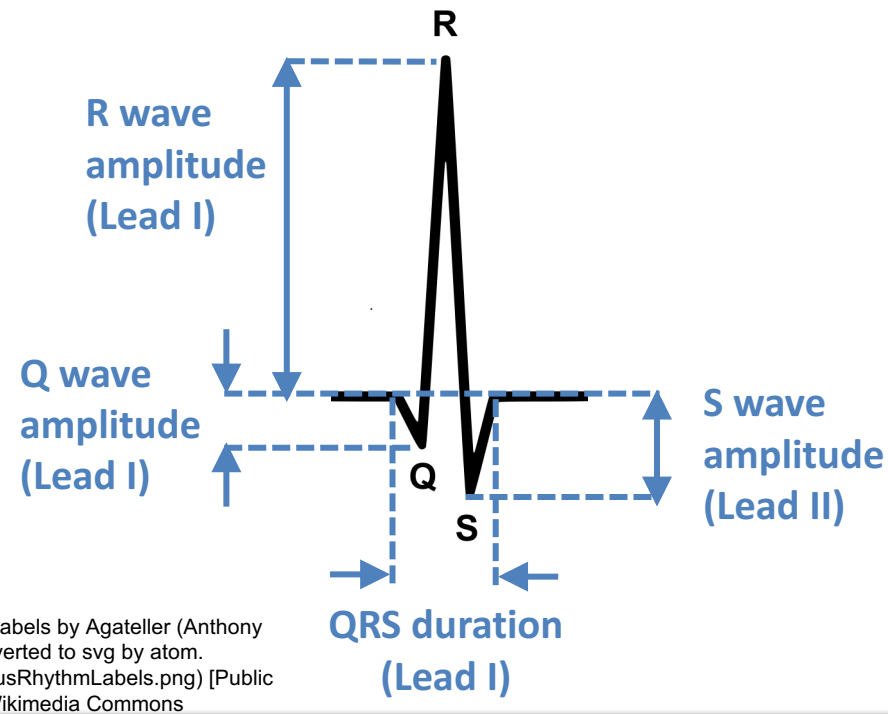
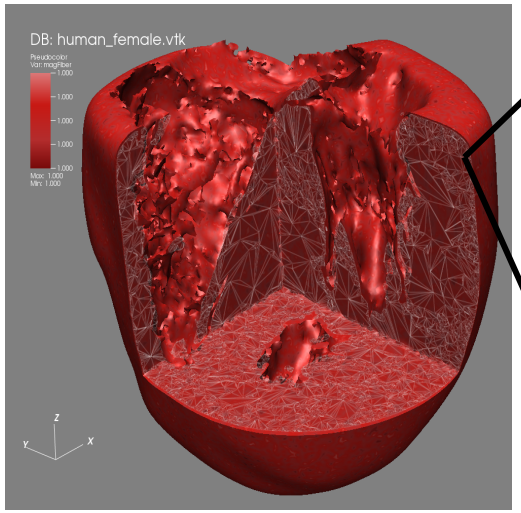




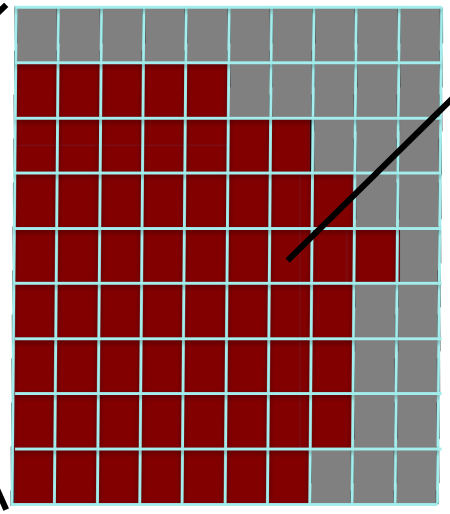
SinusRhythmLabels by Agateller (Anthony Atkielski), converted to svg by atom. (en:Image:SinusRhythmLabels.png) [Public domain], via Wikimedia Commons

Modeling Electrophysiology

LLNL's Cardioid code: near perfect scaling to over 1M cores



Geometry from Visible Human Project®



Discretized on grid

Rxn-diffusion equation

$$C_m \frac{\partial V_m}{\partial t} = \frac{1}{\beta} \nabla \cdot (\mathrm{D} \nabla V_m) - I_{ion} + I_{stim}$$

Capacitive charging — Diffusion — Rxn — Early activation stimuli

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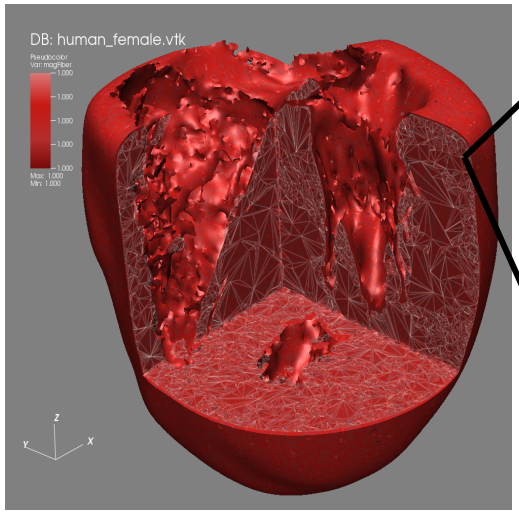

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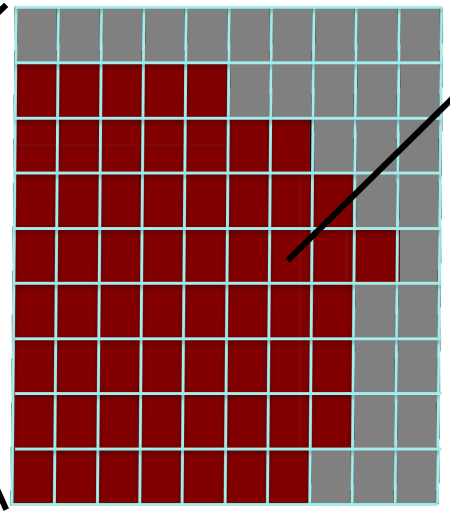

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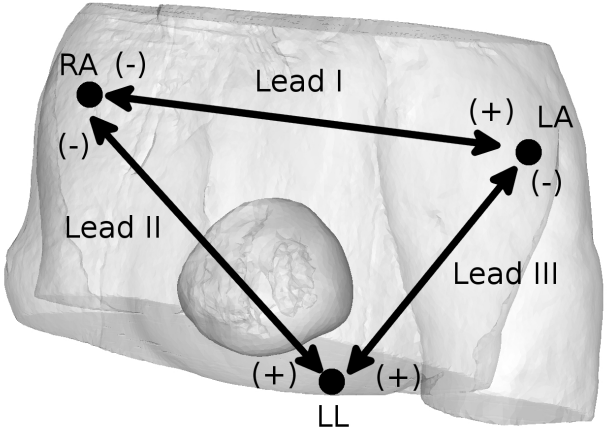
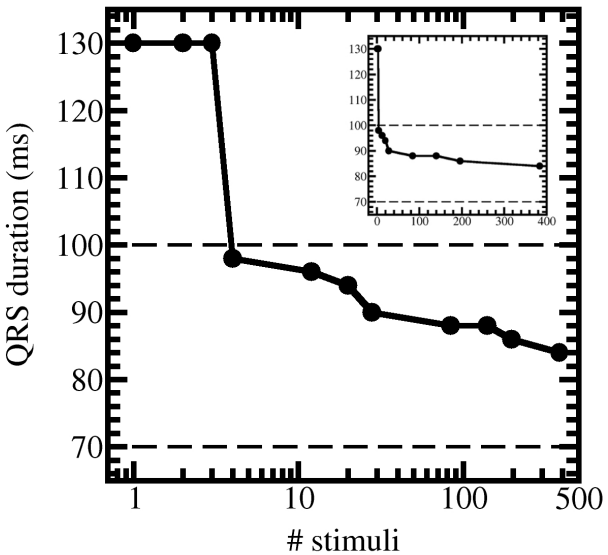
ECG code

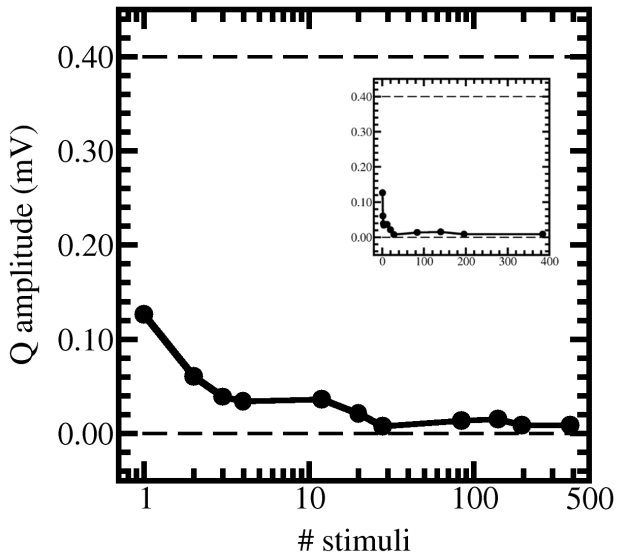
"Wraps" torso volume conductor around ventricles

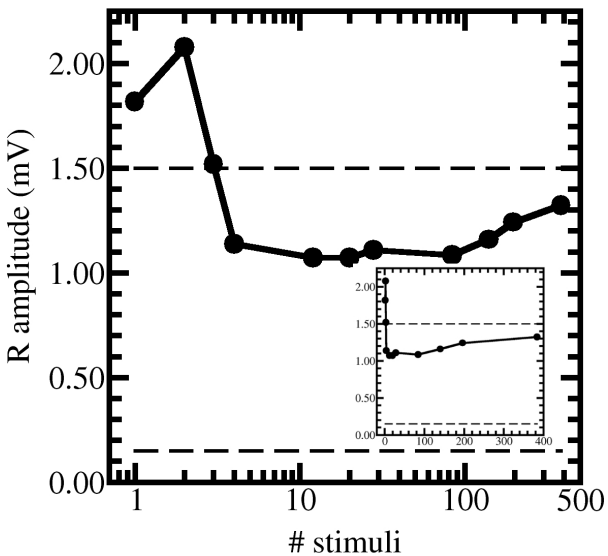
Solves Poisson's equation in torso domain using V_m in ventricles as source

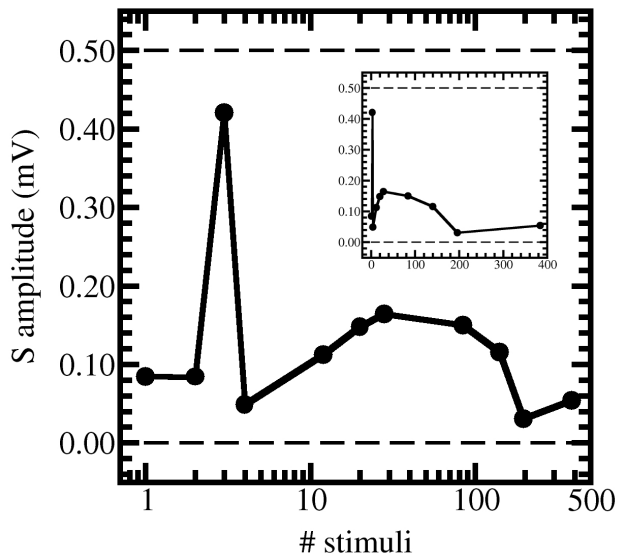


Sensitivity Analysis Results









Observations

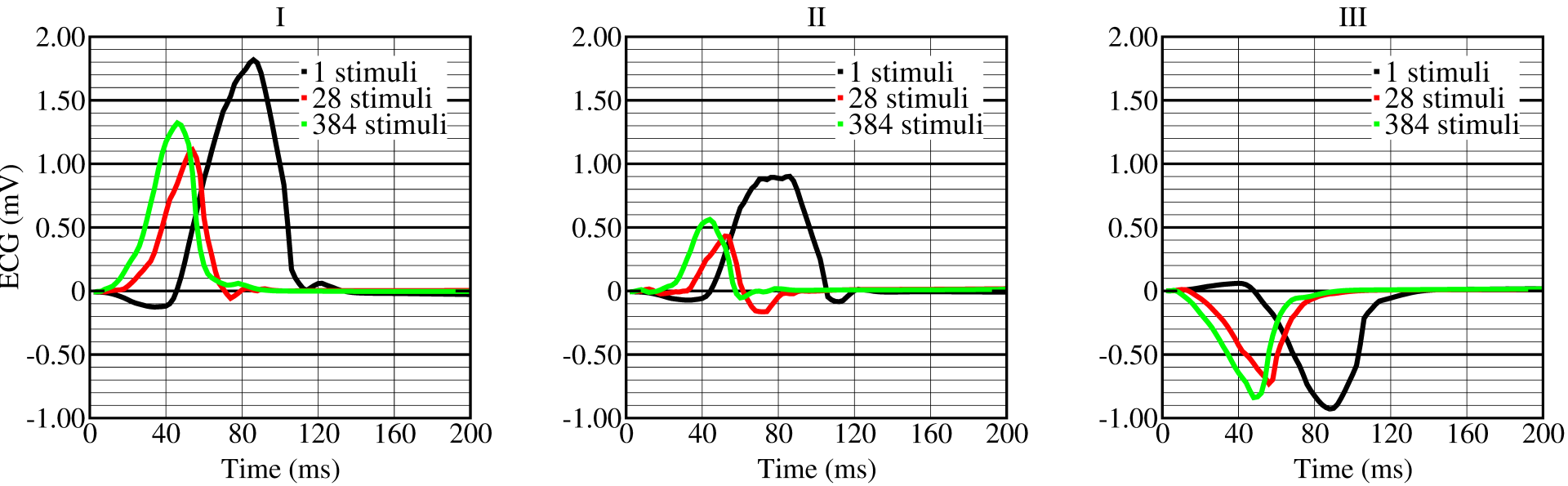
Use all 4 seed stimuli
→ metrics in physiological range

Desensitization to using more and more stimuli

28 or more stimuli
→ Metrics *comfortably* in physiological range

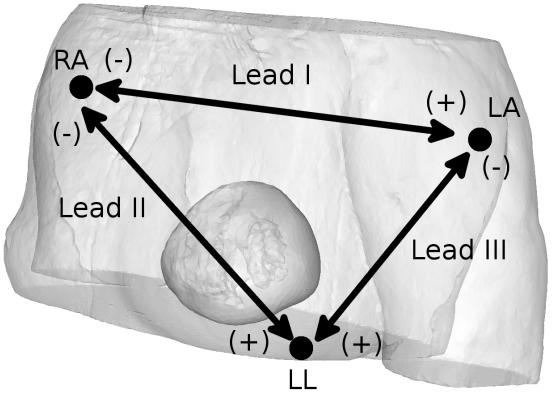
28 stimuli protocol is reasonable middle ground to reproduce physiological metrics

Sensitivity Analysis Results



Adding 27 stimuli to 1 stimulus → big change in ECG

Adding 356 stimuli to 28 stimuli → relatively smaller change ECG



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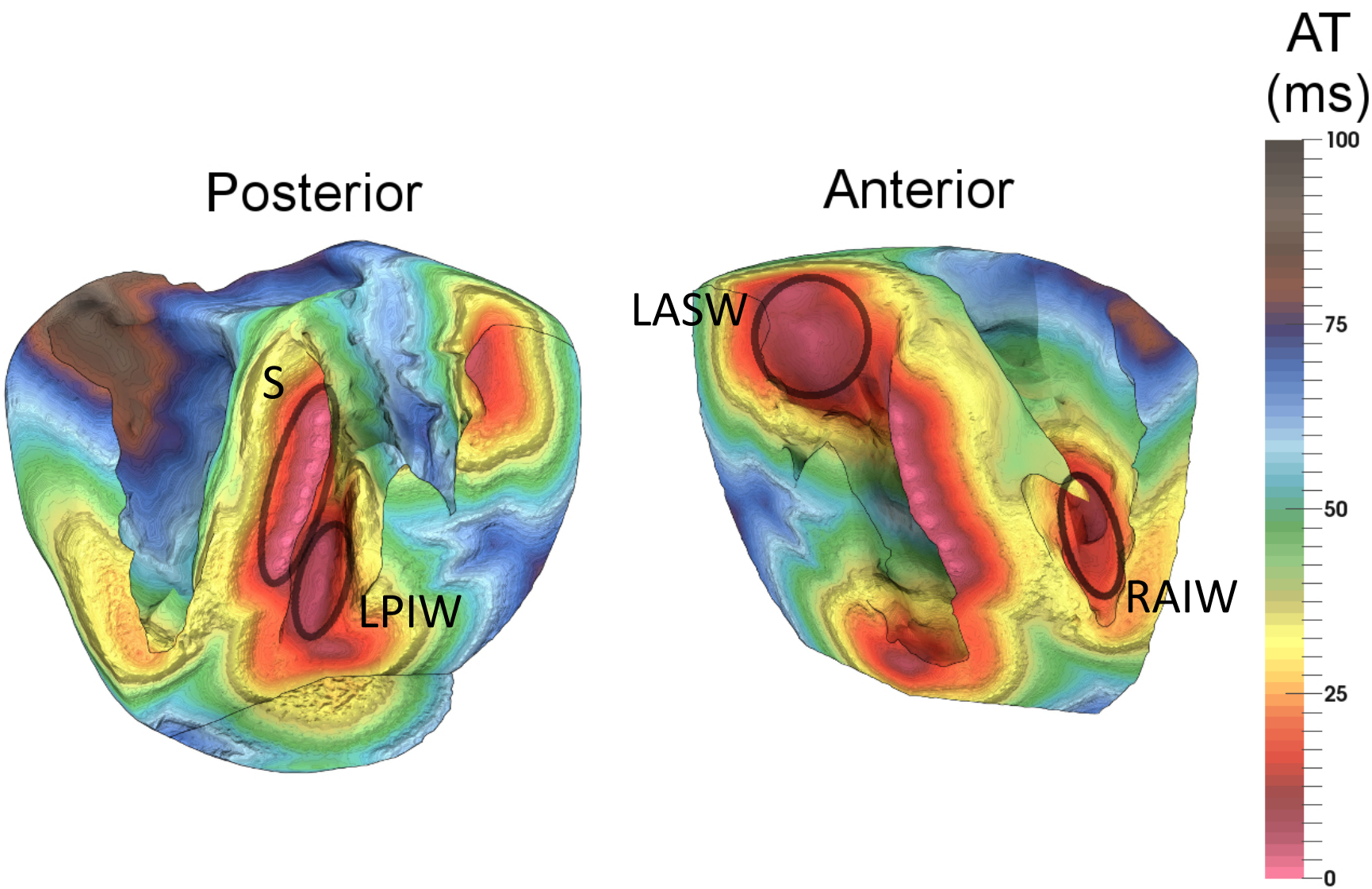
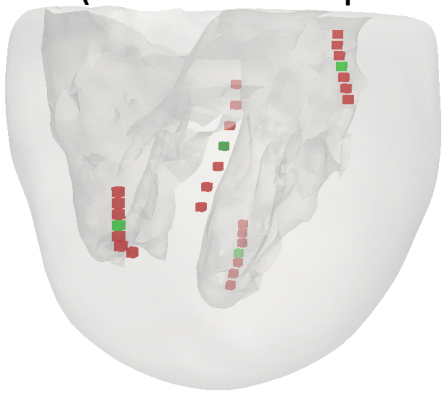
Ventricular Activation Timings



28 stimuli protocol qualitatively reproduces early activation regions seen in experiments

Number Versus Coverage of Stimuli

Inter-stimuli distance of 0.3 cm (0.5 cm for septum)



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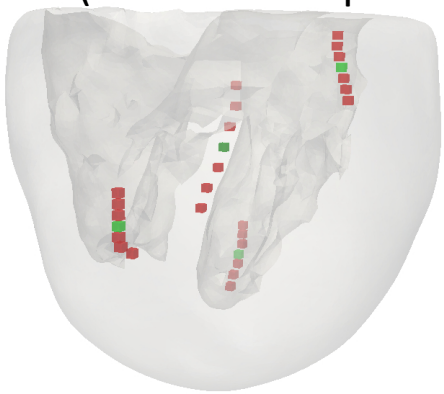

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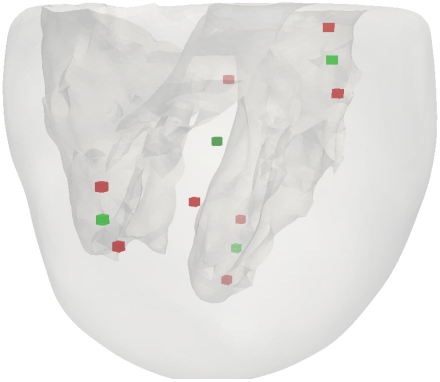
Inter-stimuli distance of 0.7 cm (1.6 cm for septum)



12
"sparse approximation"

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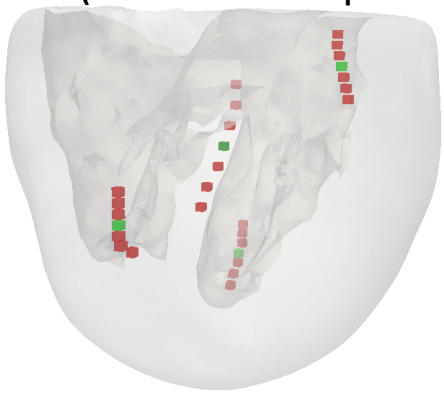

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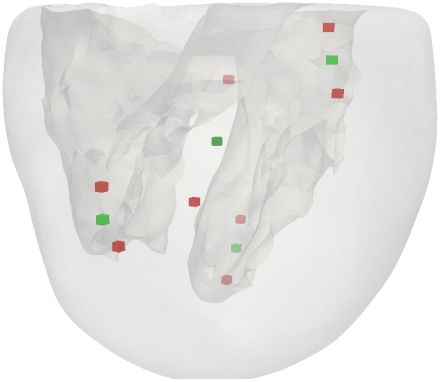

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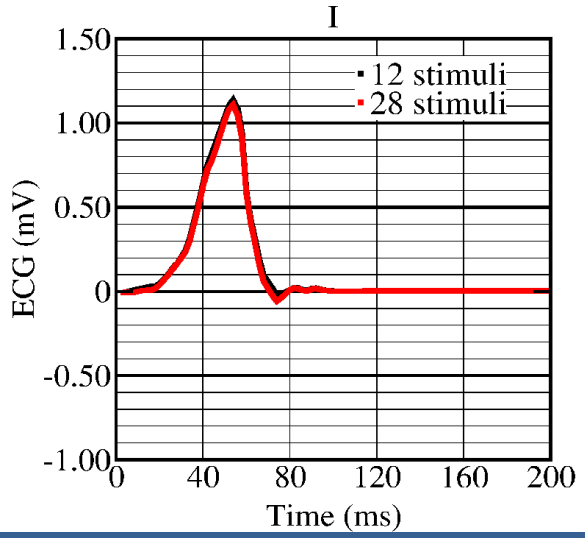

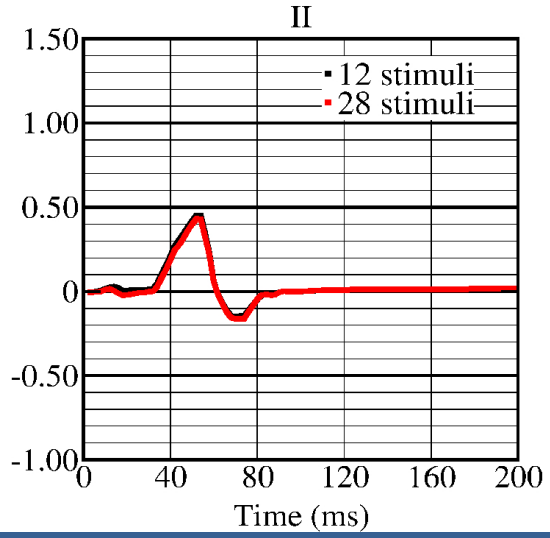

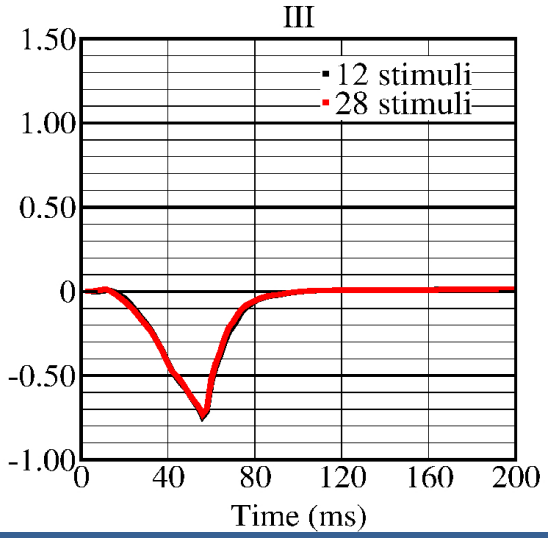

Coverage of stimuli dominates over shear number of stimuli

Conclusions

12-stimulus protocol reproduces salient features of ECG seen in clinic and regions of ventricular early activation seen in experiments

Based on sensitivity, we submit that *any* protocol with 3 stimuli located in each of the 4 key regions of early activation, and inter-stimuli distance of 0.7 cm (1.6 cm for septum) is a reasonable activation protocol and model of PMJs

Do we need to keep modeling denser and denser Purkinje networks?

Maybe not

Do we need Purkinje network models at all?

Yes, for studying defects in the network and defects of the Purkinje cells themselves

No, use 12-stimulus protocol for studying defects downstream of early activation

Future: test robustness on different heart/torso geometries, and on different diseases

We hope the these simple guidelines for modeling activation allow other researchers to quickly and accurately model ventricular activation, enabling more time to develop patient-specific models of downstream disorders, ultimately to create tailored electrophysiological therapies

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