Sinoatrial Node Cell Response to Isoprenaline Stimulation and Hypocalcemia

Cardiac Modelling group, Institute of Biomedical Engineering (IBT)

Tomas Stary, Moritz Linder, Axel Loewe | October 2, 2023

Introduction

- Chronic Kidney Disease linked with up to 14 higher likelihood of sudden cardiac death

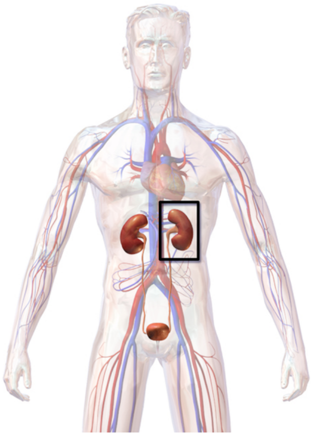
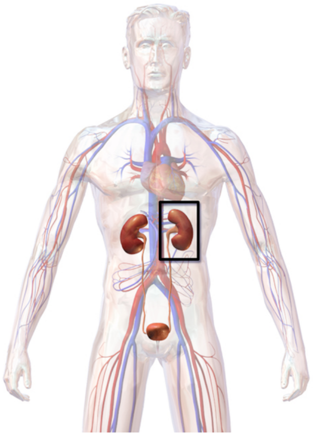


Image by: Bruce Blaus, wikimedia.org, cc-by (2014)

Introduction

- Chronic Kidney Disease linked with up to 14 higher likelihood of sudden cardiac death
- Systematic investigation of possible underlying mechanisms developed in this study



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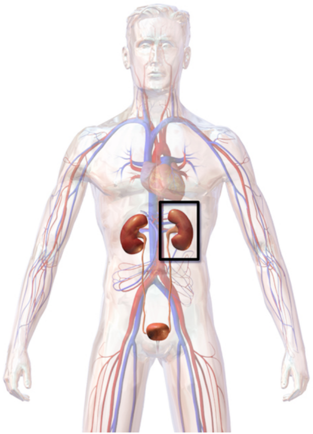
Introduction

- Chronic Kidney Disease linked with up to 14 higher likelihood of sudden cardiac death
- Systematic investigation of possible underlying mechanisms developed in this study
- Single-cell simulation of calcium and autonomic modulation on cardiac sinoatrial node cells



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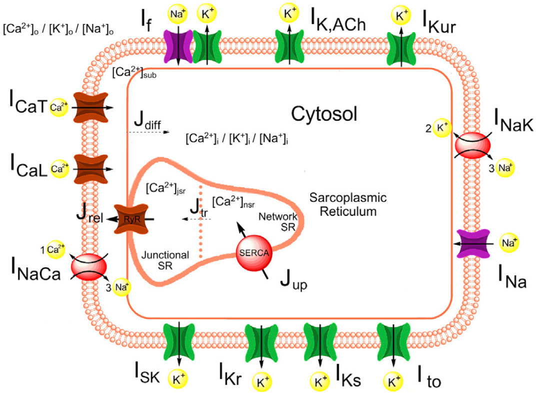
Sinoatrial Node Cell – Schematic

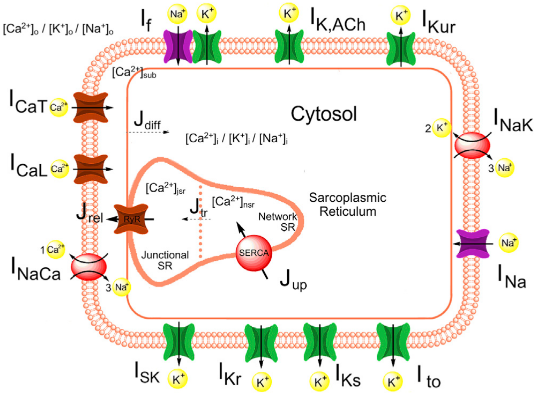


Fabbri *et al.*, J Physiol 595.7 pp 2365–2396, 2017,

Loewe *et al.*, Biophysical J. 117 2244-2254, 2019

Sinoatrial Node Cell – Schematic

- Membrane



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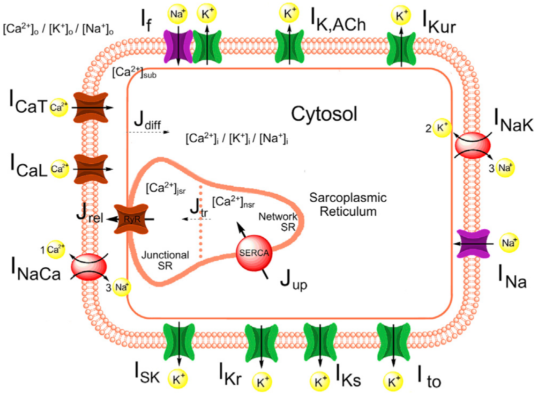
Sinoatrial Node Cell – Schematic

- Membrane
- Extracellular space



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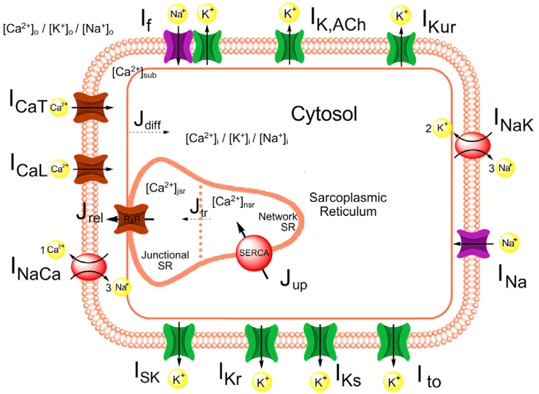
Sinoatrial Node Cell – Schematic

- Membrane
- Extracellular space
- Intracellular space



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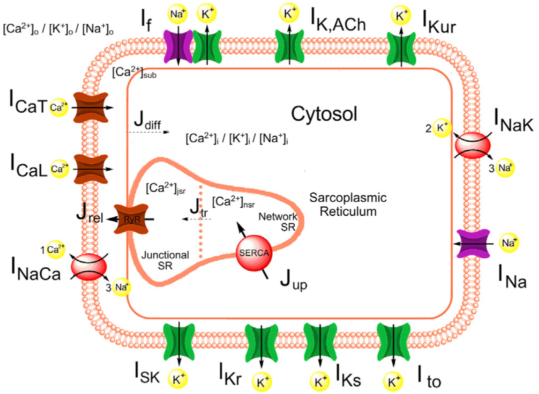
Sinoatrial Node Cell – Schematic

- Membrane
- Extracellular space
- Intracellular space with compartments



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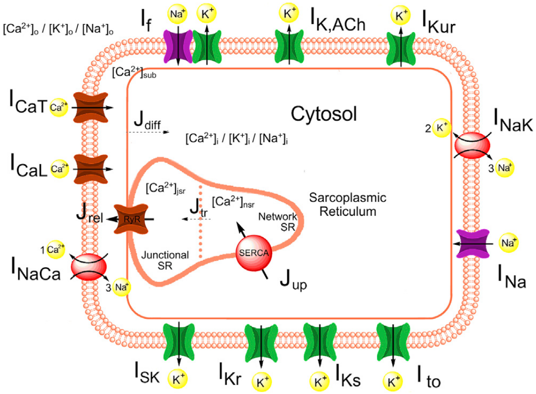
Sinoatrial Node Cell – Schematic

- Membrane
- Extracellular space
- Intracellular space with compartments:
  - Sub-sarcolemal space



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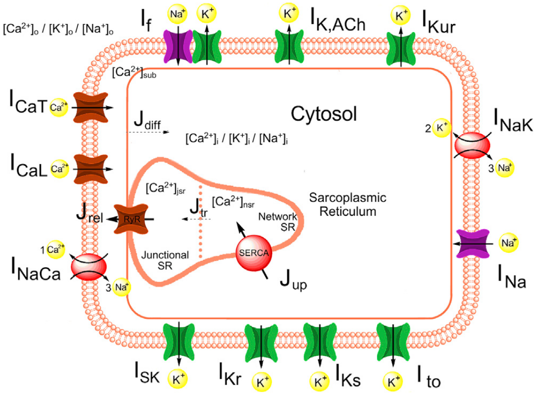
Sinoatrial Node Cell – Schematic

- Membrane
- Extracellular space
- Intracellular space with compartments:
  - Sub-sarcolemal space
  - Cytosol



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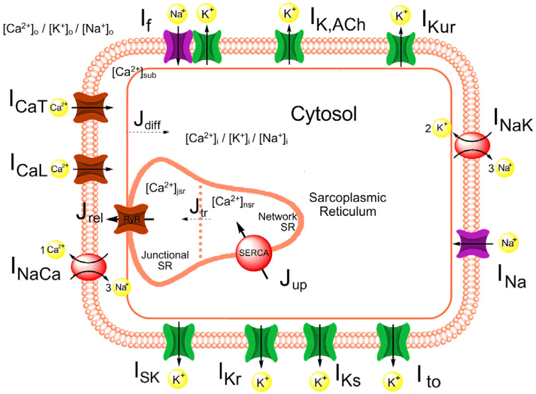
Sinoatrial Node Cell – Schematic

- Membrane
- Extracellular space
- Intracellular space with compartments:
  - Sub-sarcolemal space
  - Cytosol
  - Sarcoplasmic reticulum (SR)



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Sinoatrial Node Cell – Schematic

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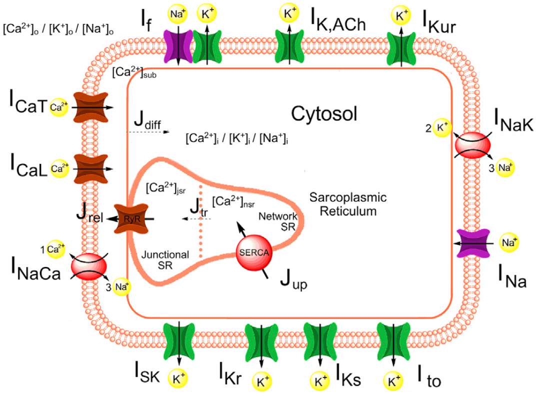
- Membrane
- Extracellular space
- Intracellular space with compartments:
  - Sub-sarcolemal space
  - Cytosol
  - Sarcoplasmic reticulum (SR):
    - Network SR



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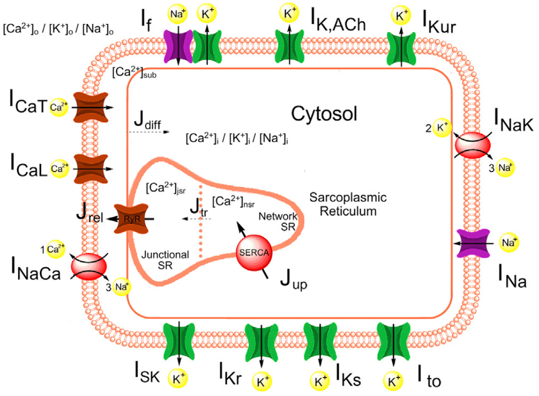
IBT

Sinoatrial Node Cell – Schematic

- Membrane
- Extracellular space
- Intracellular space with compartments:
  - Sub-sarcolemal space
  - Cytosol
  - Sarcoplasmic reticulum (SR):
    - Network SR
    - Junctional SR



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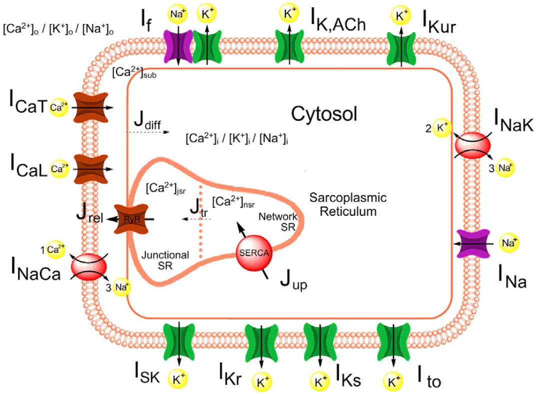
- Ion channels



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  - Sarcoplasmic reticulum (SR):
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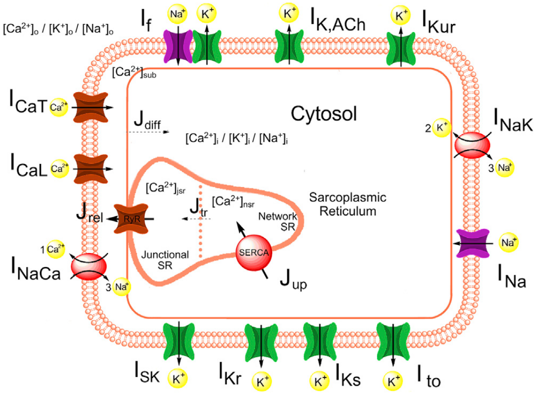
    - Junctional SR
- Ion channels for:
  - Calcium Ca^{+2} (brown)



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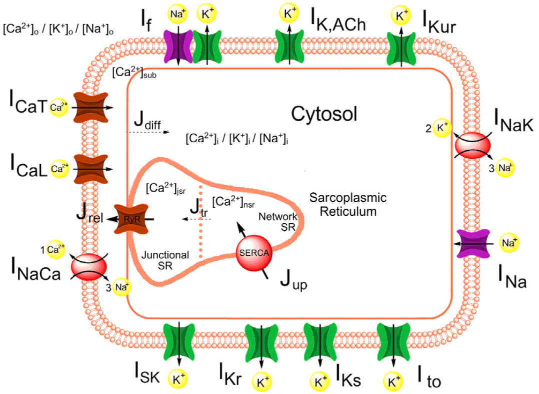

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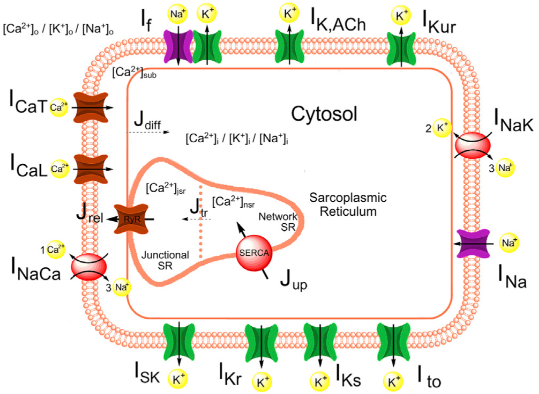

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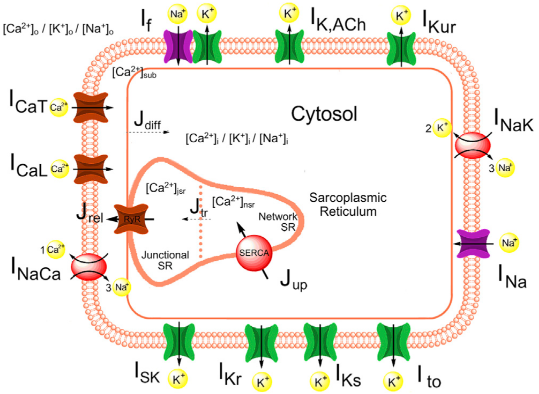
  - Pumps and exchangers (red)



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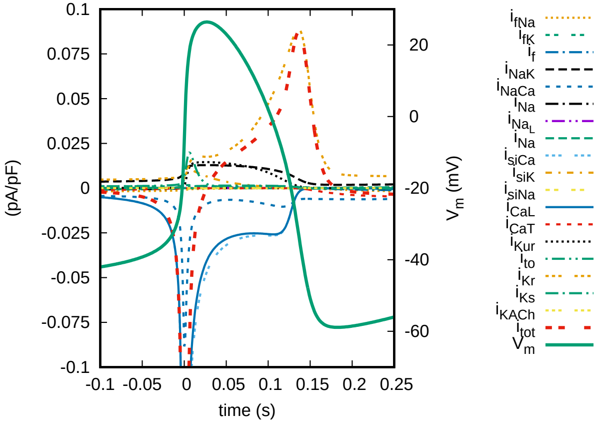
Sinoatrial Node Cell – Simulations

Fabbri *et al.* (2017) model



Sinoatrial Node Cell – Simulations

Fabbri *et al.* (2017) model

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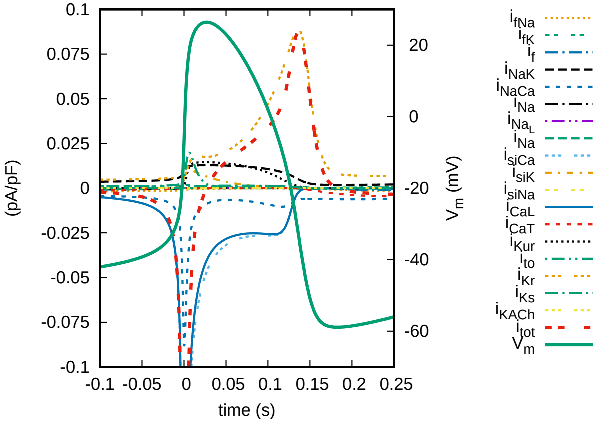

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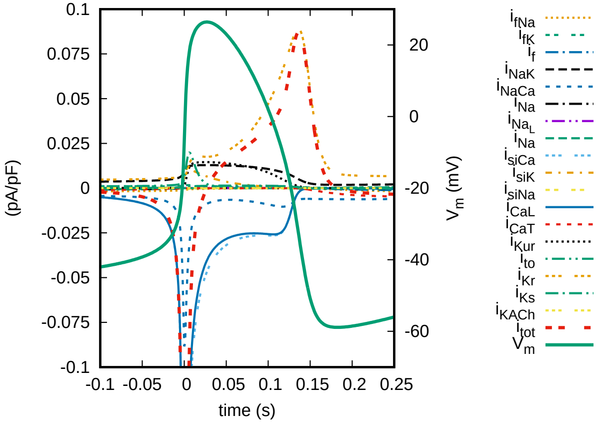

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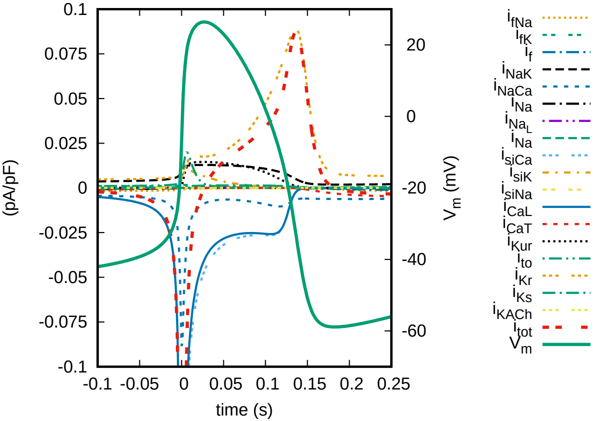

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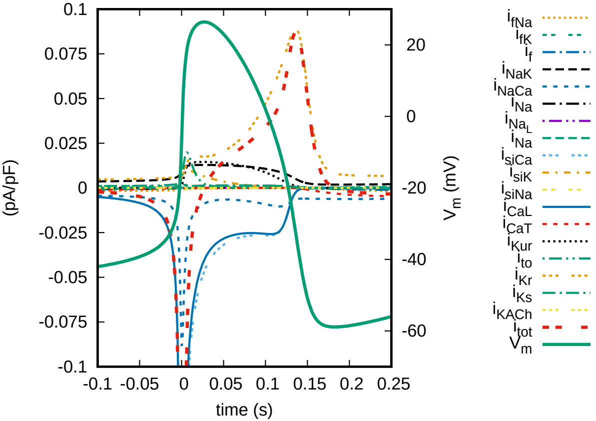

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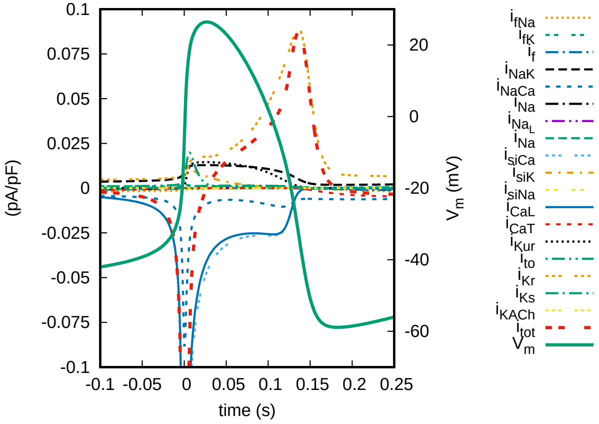
Systolic phase

- Outward: $\mathrm{i_{CaL}}$, $\mathrm{i_{NaCa}}$, $\mathrm{i_{siCa}}$
- Inward: $\mathrm{i_{to}}$, $\mathrm{i_{siK}}$ (upstroke)
- Inward: $\mathrm{i_{Kr}}$, $\mathrm{i_{NaK}}$, $\mathrm{i_{Kur}}$



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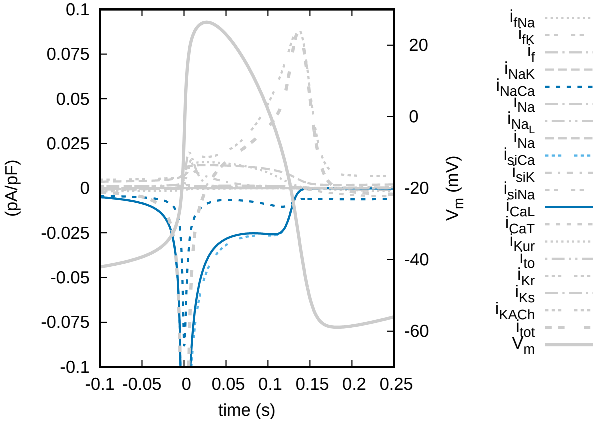

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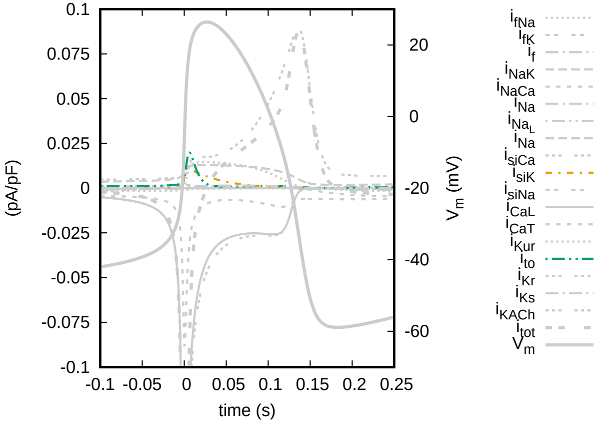

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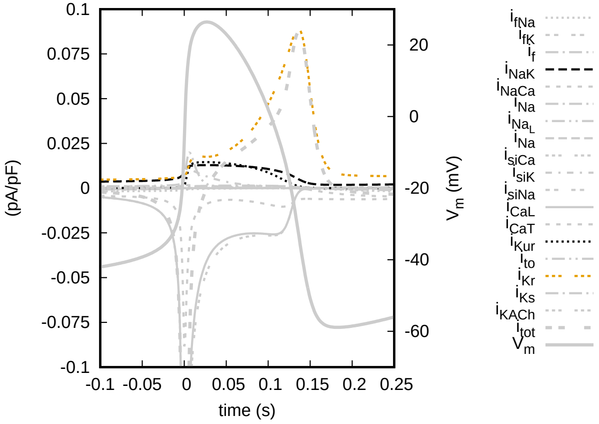

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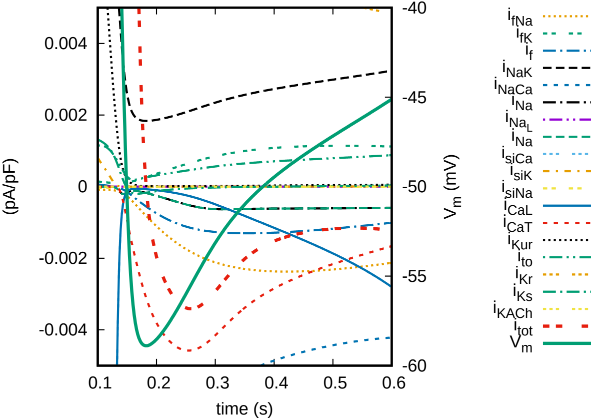
Diastolic phase

- Outward: $\mathrm{i_{NaCa}}$, $\mathrm{i_{CaT}}$, $\mathrm{i_{fNa}}$, $\mathrm{i_f}$
- Inward: $\mathrm{i_{NaK}}$, $\mathrm{i_{fK}}$, $\mathrm{i_{to}}$



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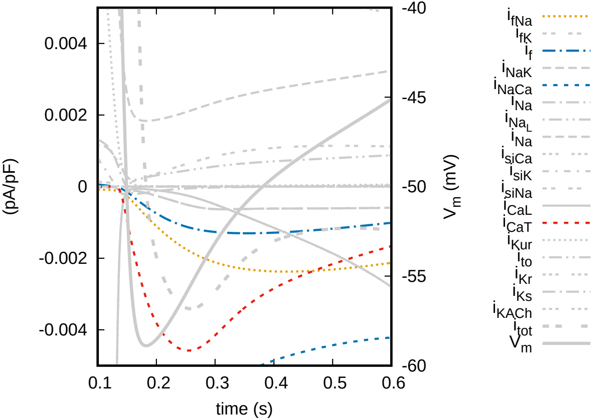

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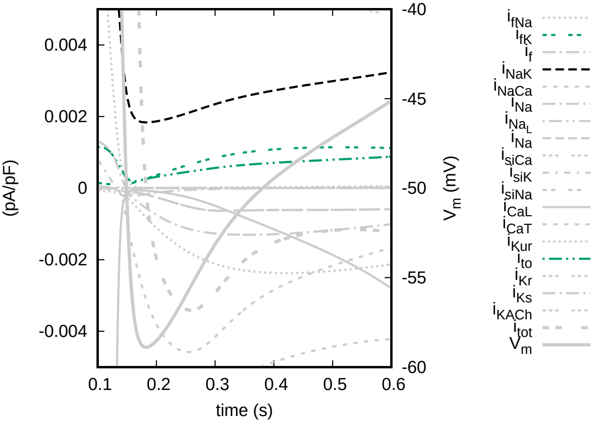
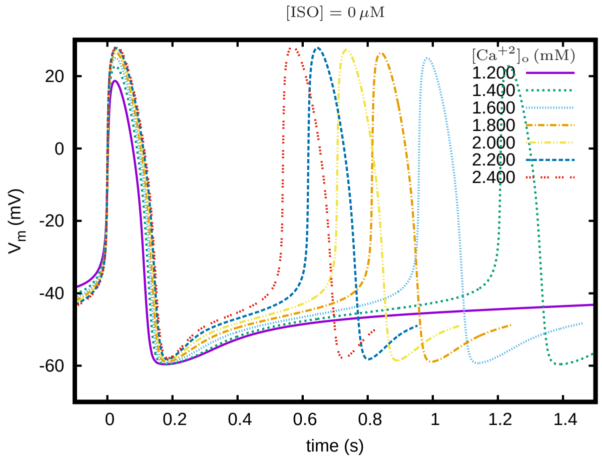


Calcium Alteration

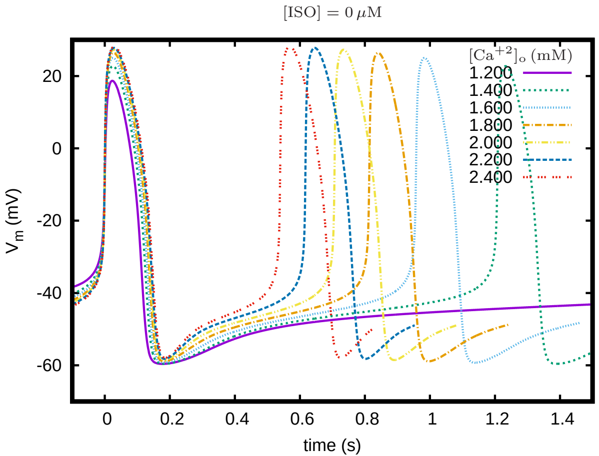
Reduced $[\mathrm{Ca}^{+2}]_o$ increases T_{CL}



Calcium Alteration

Reduced $[\mathrm{Ca}^{+2}]_\mathrm{o}$ increases T_CL

- $[\mathrm{Ca}^{+2}]_\mathrm{o} = 1.8\,\mathrm{mM} \rightarrow T_\mathrm{CL} \approx 0.9\,\mathrm{s}$



Calcium Alteration

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- $[\mathrm{Ca}^{+2}]_\mathrm{o} = 1.2\,\mathrm{mM} \rightarrow T_\mathrm{CL} \approx 2.3\,\mathrm{s}$
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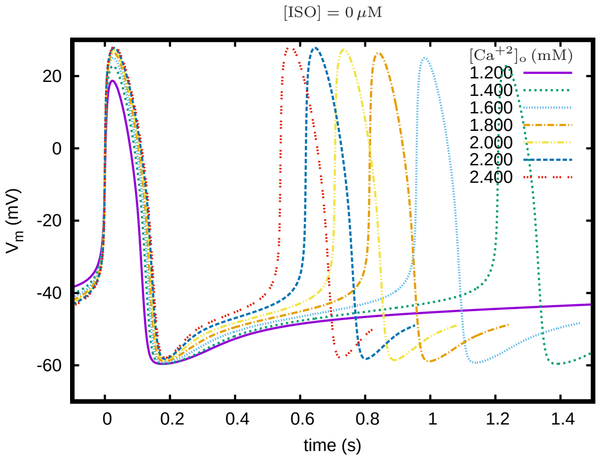

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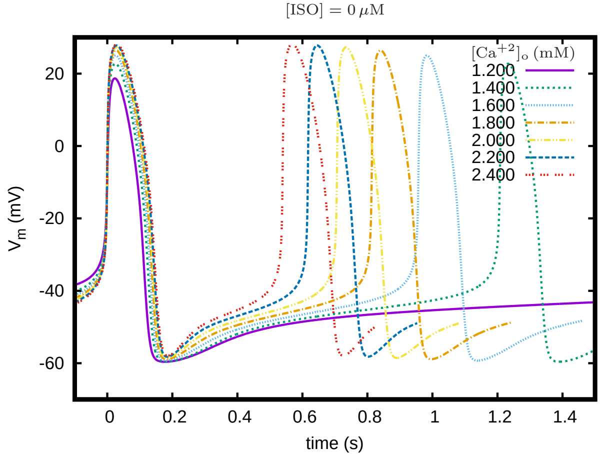
- $[\mathrm{Ca}^{+2}]_\mathrm{o} = 2.4\,\mathrm{mM} \rightarrow T_\mathrm{CL} \approx 0.6\,\mathrm{s}$



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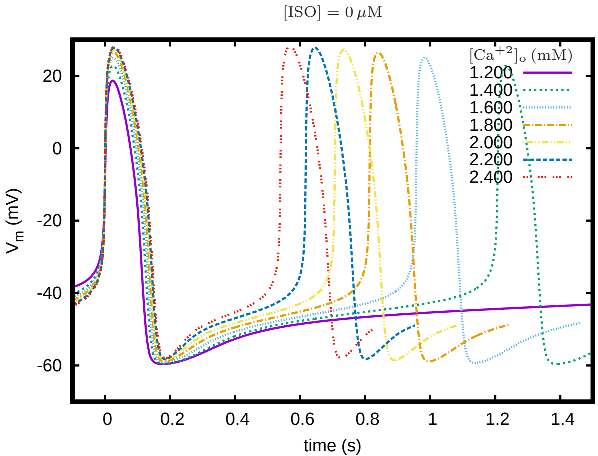
Low $[\mathrm{Ca}^{+2}]_\mathrm{o}$ leads to bradycardia.



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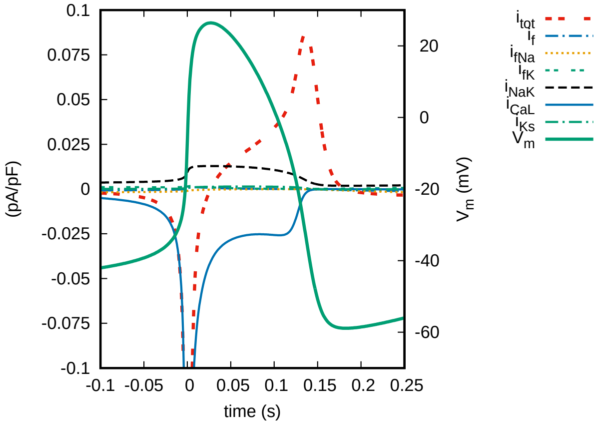
Isoprenaline Stimulation

[ISO] increase cause T_{CL} shortening



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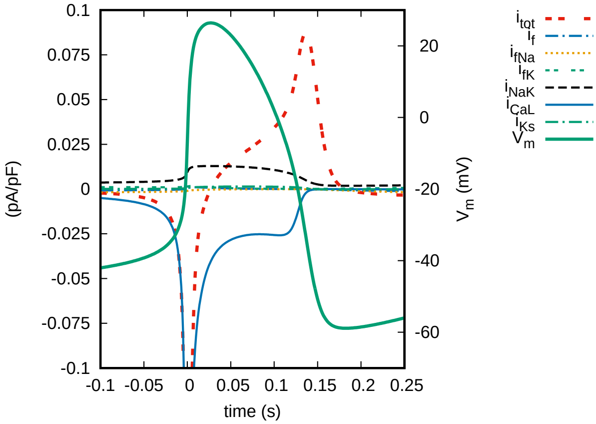

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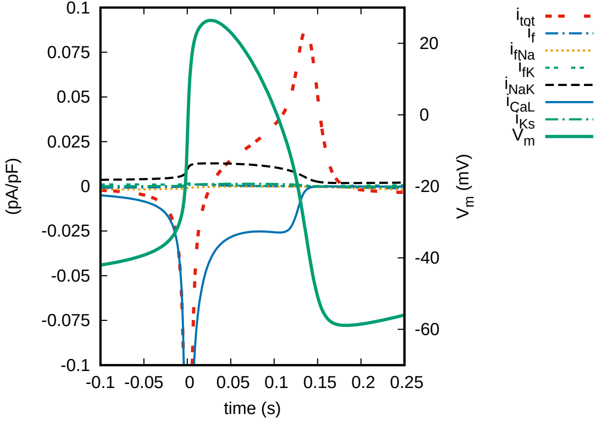

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Isoprenaline Stimulation

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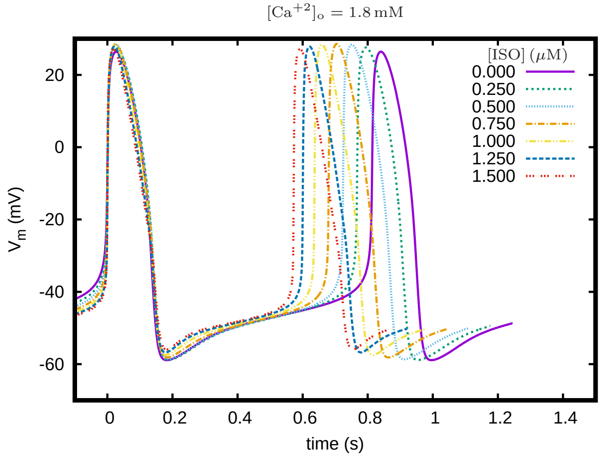

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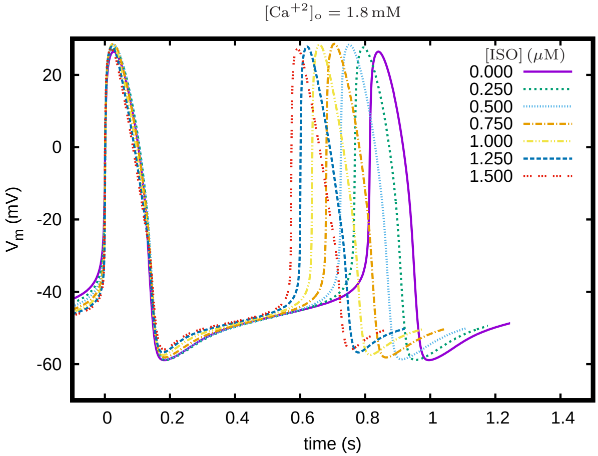
- $[\mathrm{ISO}] = 0.0\,\mu\mathrm{M} \rightarrow T_{\mathrm{CL}} \approx 0.85\,\mathrm{s}$



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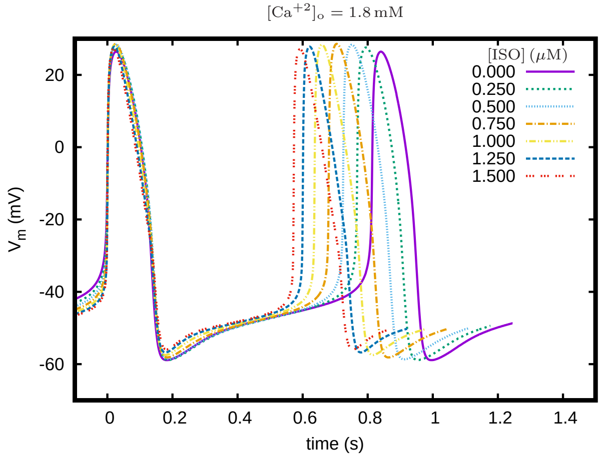

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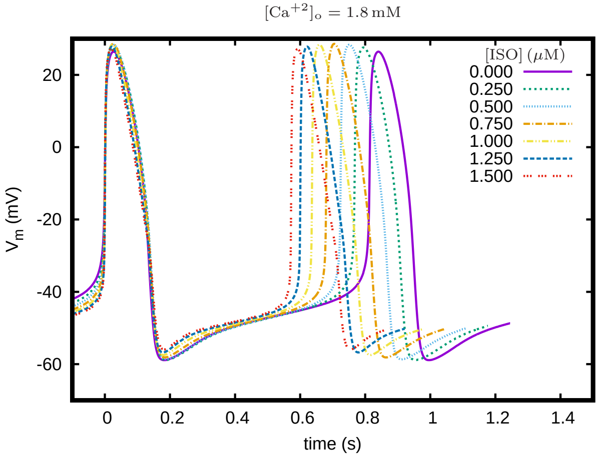

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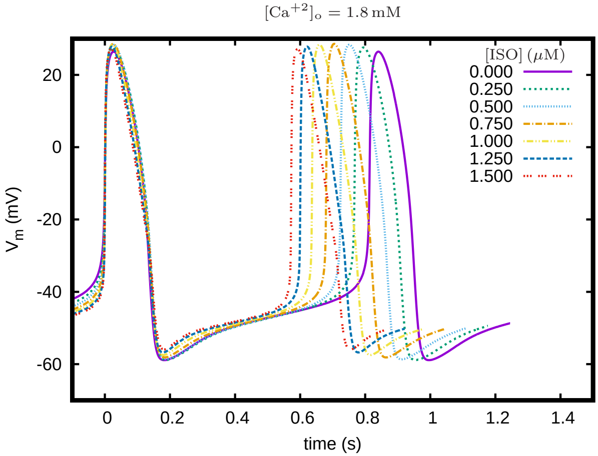
- $[\mathrm{ISO}] = 1.5\,\mu\mathrm{M} \rightarrow T_{\mathrm{CL}} \approx 0.58\,\mathrm{s}$



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Isoprenaline Stimulation

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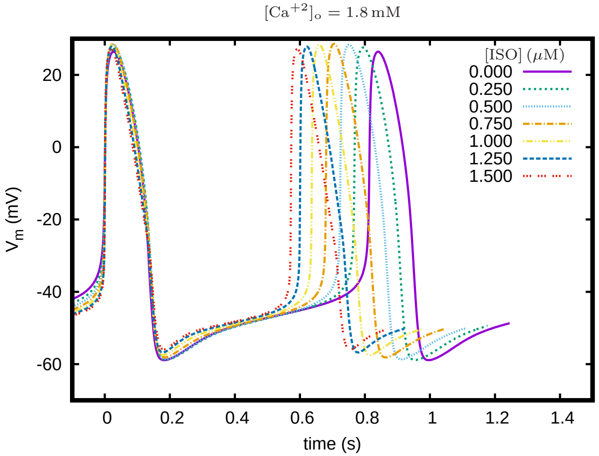
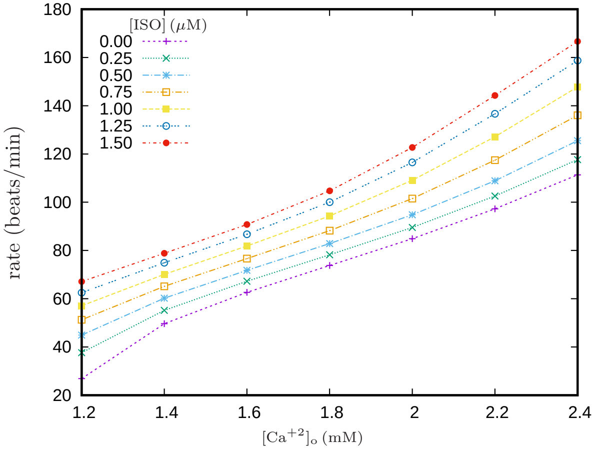
Increased [ISO] counteracts low $[\mathrm{Ca}^{+2}]_\mathrm{o}$ effects.



Heart Rate Alteration by $[\mathrm{Ca}^{+2}]_\mathrm{o}$ and $[\mathrm{ISO}]$

Heart rate $r = 60\,s / T_{\mathrm{CL}}$ beats/min



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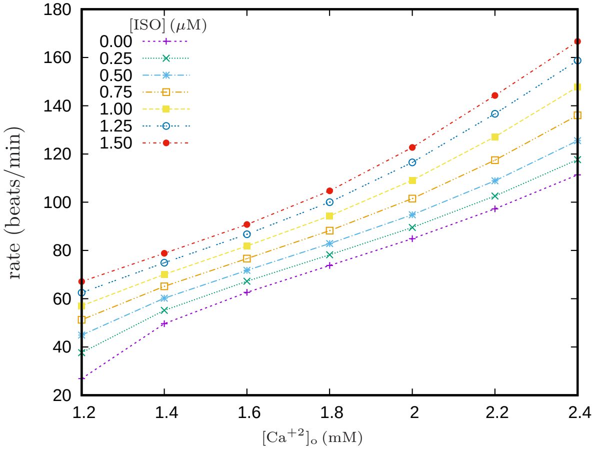

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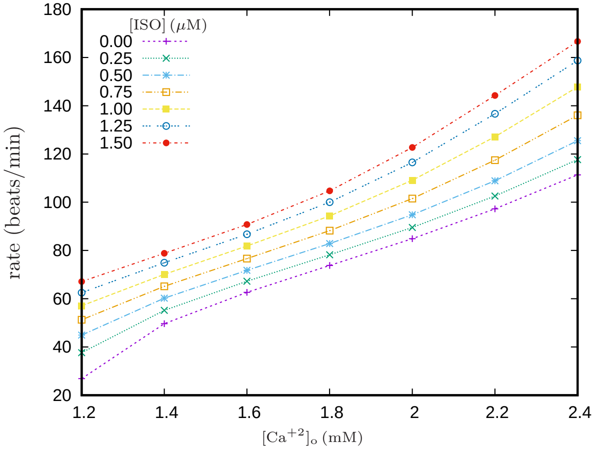
$r \approx 70$ beats/min



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Heart rate $r = 60\,s/T_{\mathrm{CL}}$ beats/min

Visualized as $r([\mathrm{Ca}^{+2}]_\mathrm{o})$

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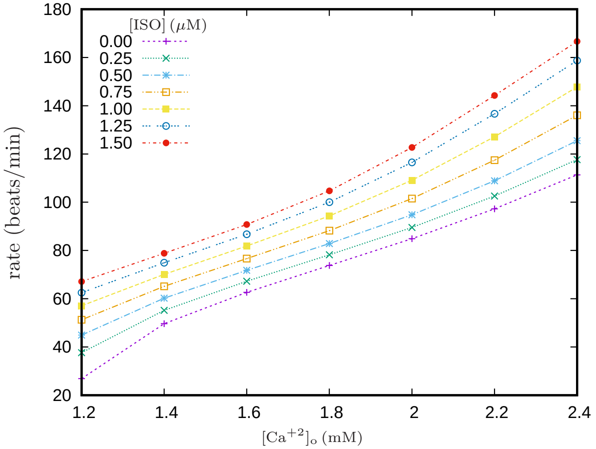
- $[\mathrm{ISO}] = 0.0\,\mu\mathrm{M}$, $[\mathrm{Ca}^{+2}]_\mathrm{o} = 1.8\,\mathrm{mM}$



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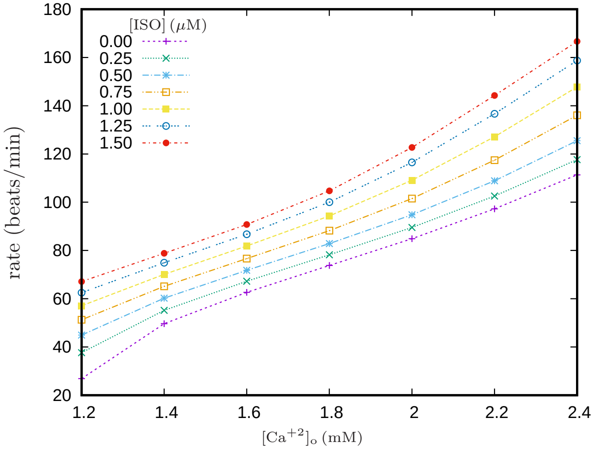

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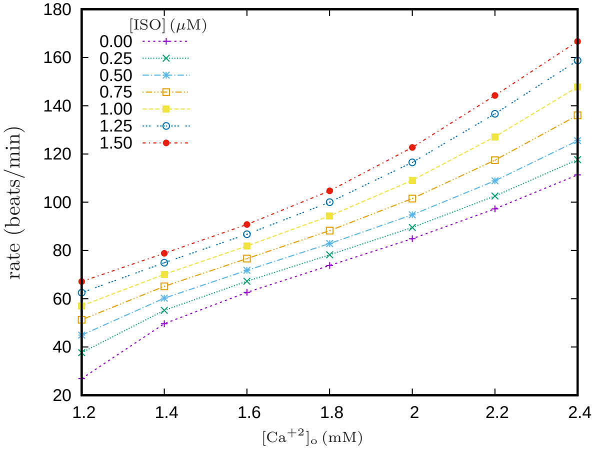
$r \approx 110$ beats/min



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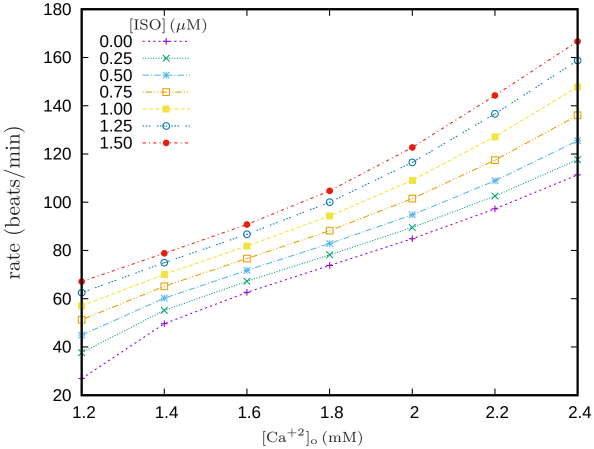

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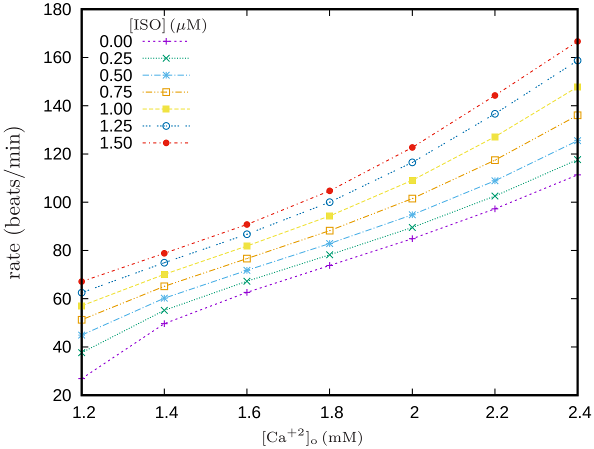

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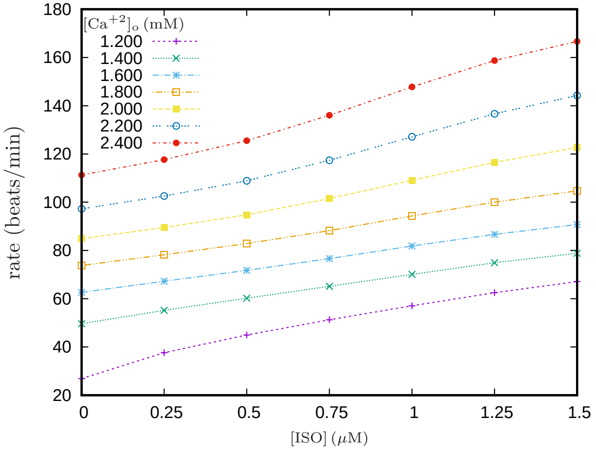

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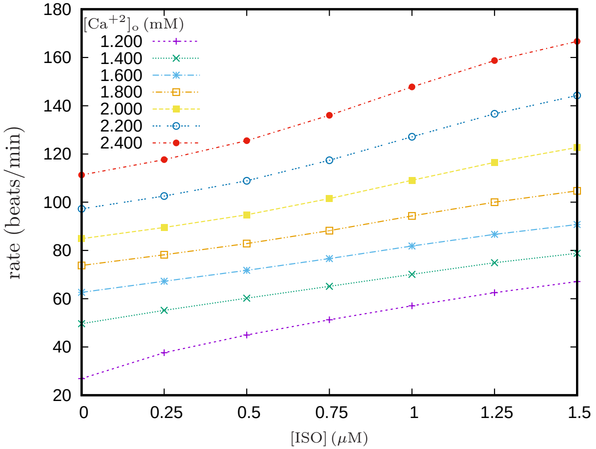
Visualized as $r([\mathrm{ISO}])$

- Almost linearly dependent in both dimensions.



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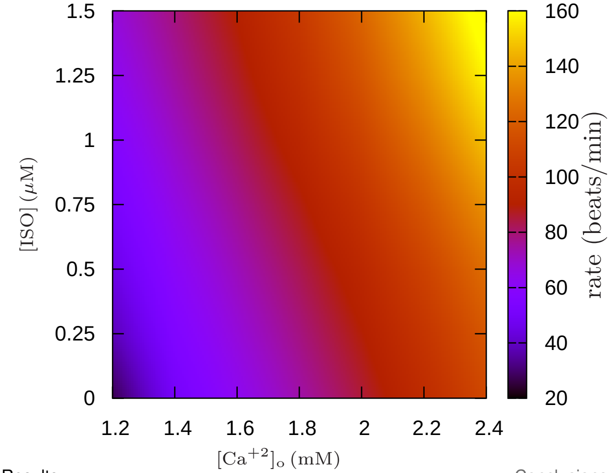
Color-map with the previous results.



Conclusions

- The simulations show interrelation between $[\mathrm{Ca}^{+2}]_{\mathrm{o}}$ and $[\mathrm{ISO}]$

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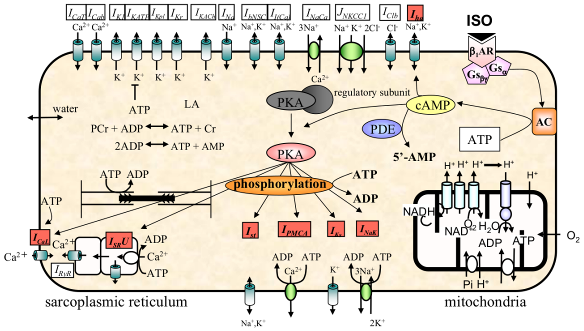

Himeno *et al.*, J. Physiol. Sci. Vol. 58, No. 1; Feb. 2008; pp. 53–65

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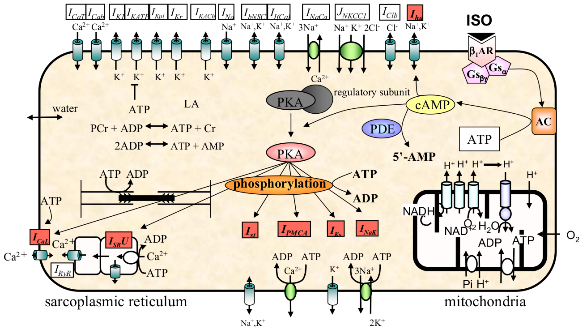
- Cell-by-cell model might help to understand mechanisms of pace and drive capacity (Amsaleg *et al.* 2022)



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Thank you!


CinC 24
Karlsruhe
Thank you!

CinC 24
Karlsruhe
Thank you!
Hope to see you next year!

Follow-up Project Proposal

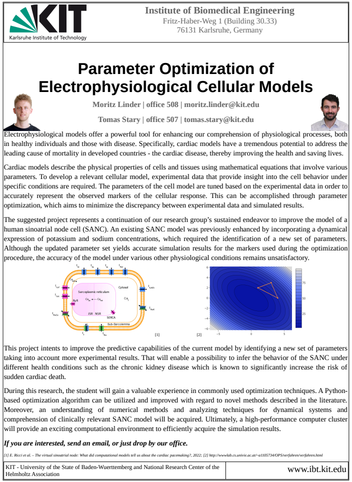
Reproduce iso-stimulation in Loewe *et al.*

- **Perform** sensitivity analysis
- **Suggest** plausible parameter constrains
- **Assess** different optimization algorithms
- **Evaluate** optimal stopping criteria

Help wanted! Please contact us via email:

- moritz.linder@kit.edu
- tomas.stary@kit.edu

Feedback and suggestions are welcome!



Institute of Biomedical Engineering
Fritz-Haber-Weg 1 (Building 30.33)
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Parameter Optimization of Electrophysiological Cellular Models

Moritz Linder | office 508 | moritz.linder@kit.edu

Tomas Stary | office 507 | tomas.stary@kit.edu

Electrophysiological models offer a powerful tool for enhancing our comprehension of physiological processes, both in healthy individuals and those with disease. Specifically, cardiac models have a tremendous potential to address the leading cause of mortality in developed countries - the cardiac disease, thereby improving the health and saving lives.

Cardiac models describe the physical properties of cells and tissues using mathematical equations that involve various parameters. To develop a relevant cellular model, experimental data that provide insight into the cell behavior under specific conditions are required. The parameters of the cell model are tuned based on the experimental data in order to accurately represent the observed markers of the cellular response. This can be accomplished through parameter optimization, which aims to minimize the discrepancy between experimental data and simulated results.

The suggested project represents a continuation of our research group's sustained endeavor to improve the model of a human sinoatrial node cell (SANC). An existing SANC model was previously enhanced by incorporating a dynamical expression of potassium and sodium concentrations, which required the identification of a new set of parameters. Although the updated parameter set yields accurate simulation results for the markers used during the optimization procedure, the accuracy of the model under various other physiological conditions remains unsatisfactory.

[1] [2]

This project intents to improve the predictive capabilities of the current model by identifying a new set of parameters taking into account more experimental results. That will enable a possibility to infer the behavior of the SANC under different health conditions such as the chronic kidney disease which is known to significantly increase the risk of sudden cardiac death.

During this research, the student will gain a valuable experience in commonly used optimization techniques. A Python-based optimization algorithm can be utilized and improved with regard to novel methods described in the literature. Moreover, an understanding of numerical methods and analyzing techniques for dynamical systems and comprehension of clinically relevant SANC model will be acquired. Ultimately, a high-performance computer cluster will provide an exciting computational environment to efficiently acquire the simulation results.

If you are interested, send an email, or just drop by our office.

[1] E. Ricci et al. – The virtual sinoatrial node: What did computational models tell us about the cardiac pacemaking?, 2022; [2] http://wwwlab.cs.univie.ac.at/~a1105734/OPS/verfahren/verfahren.html

KIT - University of the State of Baden-Wuerttemberg and National Research Center of the Helmholtz Association	www.ibt.kit.edu

Acknowledgements

Karlsruhe Institute of Technology

MICROCARD

EuroHPC Joint Undertaking

This work was supported by the European High-Performance Computing Joint Undertaking EuroHPC under grant agreement No 955495 (MICROCARD) co-funded by the Horizon 2020 programme of the European Union (EU), the French National Research Agency ANR, the German Federal Ministry of Education and Research, the Italian ministry of economic development, the Swiss State Secretariat for Education, Research and Innovation, the Austrian Research Promotion Agency FFG, and the Research Council of Norway.

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