

Computational analysis of β -adrenergic stimulation and its effects on cardiac ventricular electrophysiology

Citation for published version (APA):

Heijman, J. (2012). Computational analysis of β -adrenergic stimulation and its effects on cardiac ventricular electrophysiology. [Doctoral Thesis, Maastricht University]. Maastricht University. <https://doi.org/10.26481/dis.20120427jh>

Document status and date:

Published: 01/01/2012

DOI:

[10.26481/dis.20120427jh](https://doi.org/10.26481/dis.20120427jh)

Document Version:

Publisher's PDF, also known as Version of record

Please check the document version of this publication:

- A submitted manuscript is the version of the article upon submission and before peer-review. There can be important differences between the submitted version and the official published version of record. People interested in the research are advised to contact the author for the final version of the publication, or visit the DOI to the publisher's website.
- The final author version and the galley proof are versions of the publication after peer review.
- The final published version features the final layout of the paper including the volume, issue and page numbers.

[Link to publication](#)

General rights

Copyright and moral rights for the publications made accessible in the public portal are retained by the authors and/or other copyright owners and it is a condition of accessing publications that users recognise and abide by the legal requirements associated with these rights.

- Users may download and print one copy of any publication from the public portal for the purpose of private study or research.
- You may not further distribute the material or use it for any profit-making activity or commercial gain
- You may freely distribute the URL identifying the publication in the public portal.

If the publication is distributed under the terms of Article 25fa of the Dutch Copyright Act, indicated by the "Taverne" license above, please follow below link for the End User Agreement:

www.umlib.nl/taverne-license

Take down policy

If you believe that this document breaches copyright please contact us at:

repository@maastrichtuniversity.nl

providing details and we will investigate your claim.

Computational analysis of β -adrenergic stimulation and its effects on cardiac ventricular electrophysiology

Jordi Heijman, 2012

1. A novel computer model of the canine ventricular myocyte facilitates the identification of ionic determinants of action-potential duration and its modulation by β -adrenergic stimulation. *This thesis.*
2. The loss of cAMP-dependent I_{Ks} upregulation on top of a dominant-negative reduction in basal I_{Ks} contributes to the clinical severity of long-QT syndrome type 1 due to the mutation KCNQ1-A341V. *This thesis.*
3. β -Adrenergic stimulation is antiarrhythmic in cellular pharmacological models of long-QT syndromes types 2 and 3, but proarrhythmic in a model of long-QT syndrome type 1. *This thesis.*
4. In addition to its contribution to triggered activity, late-diastolic calcium release from the sarcoplasmic reticulum is arrhythmogenic due to its prolonging effects on the following action potential, potentially increasing regional dispersion of repolarization. *This thesis.*
5. Stochastic channel gating is necessary to simulate cellular beat-to-beat variability of repolarization duration. Apart from this, action potential duration, intracellular calcium handling and intercellular coupling modulate repolarization variability. *This thesis.*
6. “Essentially, all models are wrong, but some are useful.”
G.E.P. Box, Empirical Model-Building and Response Surfaces, 1987
“In fact, we can learn as much from the failures of models as from their successes”
D. Noble, Heart Rhythm, 2011
7. “To say that a man is made up of certain chemical elements is a satisfactory description only for those who intend to use him as a fertilizer.”
Hermann Joseph Muller (1890-1967). Nobel Prize in Medicine or Physiology, 1946
8. A systems biology approach combining reductionist and integrative techniques will facilitate a comprehensive understanding of human (patho)physiology.
9. Implementations of computational models should be made as accessible as possible. At the same time, results obtained by those who treat a model as a black box should be viewed with utmost care.
10. Switching-off one’s e-mail client can result in a disproportional speed-up of computational analyses.
11. “Wheresoever you go, go with all your heart.”
Confucius

Computational analysis of β -adrenergic stimulation and its effects on cardiac ventricular electrophysiology

Jordi Heijman, 2012

1. Een nieuw computer model van de ventriculaire hartspiercel vereenvoudigt de identificatie van ion-mechanismen die de basale actiepotentiaal en de veranderingen tijdens β -adrenerge stimulatie beïnvloeden. *Dit proefschrift.*
2. Het verlies van de cAMP-afhankelijke I_{Ks} toename bovenop een dominant-negatieve afname van basale I_{Ks} draagt bij aan de klinische ernst van het lange-QT syndroom type 1 ten gevolge van de mutatie KCNQ1-A341V. *Dit proefschrift.*
3. β -Adrenerge stimulatie werkt antiaritmisch in cellulaire farmacologische modellen van lange-QT syndromen typen 2 en 3, maar aritmogeen in een model van lange-QT syndroom type 1. *Dit proefschrift.*
4. Naast een bijdrage aan abnormale impulsformatie is lokale calcium vrijstelling uit het sarcoplasmatisch reticulum tijdens de late diastole aritmogeen door een verlengend effect op de volgende actiepotentiaal, hetgeen potentieel kan leiden tot toegenomen regionale dispersie van repolarisatie. *Dit proefschrift.*
5. Stochastisch kanaal-gedrag is een noodzakelijke voorwaarde om cellulaire slag-op-slag veranderingen in repolarisatieduur te simuleren. Daarnaast dragen actiepotentiaal-duur, intracellulair calcium en intercellulaire koppeling bij aan repolarisatie-variabiliteit. *Dit proefschrift.*
6. "In principe zijn alle modellen incorrect, maar sommige zijn nuttig"
G.E.P. Box, Empirical Model-Building and Response Surfaces, 1987, vrij vertaald
"We kunnen net zo veel leren van de tekortkomingen van modellen als van hun successen."
D. Noble, Heart Rhythm, 2011, vrij vertaald
7. "De beschrijving dat een mens is opgebouwd uit bepaalde chemische elementen, is enkel relevant als men hem als compost wil gebruiken."
Hermann Joseph Muller (1890-1967). Nobel Prize in Medicine or Physiology, 1946, vrij vertaald
8. Een systeembioologische aanpak waarbij reductionistische en integratieve technieken gecombineerd worden, zal bijdragen aan een allesomvattend begrip van de humane (patho)fysiologie.
9. Computer modellen dienen zo toegankelijk mogelijk gemaakt te worden. Tegelijkertijd dienen resultaten verkregen door mensen die een model als een 'zwarte doos' beschouwen met grote voorzichtigheid benaderd te worden.
10. Het uitschakelen van een e-mail programma kan resulteren in een disproportionele snelheidswinst van wiskundige analyses.
11. "Wheresoever you go, go with all your heart."
Confucius