### A Model of Sinoatrial Node Cell Regulation by the Autonomic Nervous System:

### Mechanisms of heart rate control

2011 CSGF Conference

Danilo Šćepanović July 22, 2011







### Heart rate control is essential in health and disease

The heart must be able to keep up with daily demands











### Heart rate control is essential in health and disease

Changes in heart rate control precede heart disease





Understanding the system can lead to new diagnostics or therapies







### How is heart rate controlled?







# The brain controls heart rate through the autonomic nervous system







# How is it modeled?







#### Current models of autonomic control are Excellent sinoatrial node cell models exist phenomenological









# We explicitly model the second messenger cascade









# We constructed a detailed, mechanistic model with meaningful parameters

- **57** Nonlinear Coupled ODEs
  - Runs in 3x time using ode15s in Matlab
- **90** parameters from explicit data
  - Example: Cell geometry, Chemical affinities, Binding/ dissociation rates
- 42 parameters from implicit data
  - Fit to 60 data points, 6 equality constraints
  - Example: ion channel conductance with neurotransmitter







### **Does it work?**













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#### The model reproduces dynamic heart rate data



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# What does it teach us?







### Conclusion

- Summarizes a large body of knowledge in an explicit framework
- Explains mechanisms underlying behaviors
- Points out inconsistencies in our understanding
- Identifies important aspects to include in future models
- Our main contribution isn't WHAT the model can do, it's HOW it does it: explicit mechanisms and meaningful parameters
- Future work
  - Model individual nerve varicosities
  - Subcellular compartmentalization





### Acknowledgements

- Richard J. Cohen Lab
- MIT EECS, Harvard Medical School
- Experimental scientists
  - Geoffrey Burnstock (autonomic nerves)
  - Alfred G. Gilman (G-proteins)
  - Terrone L. Rosenberry (acetylcholinesterase)
- DOE CSGF and Krell





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