Application of the method of population modeling in the model of atrial cardiomyocytes of neonatal rats

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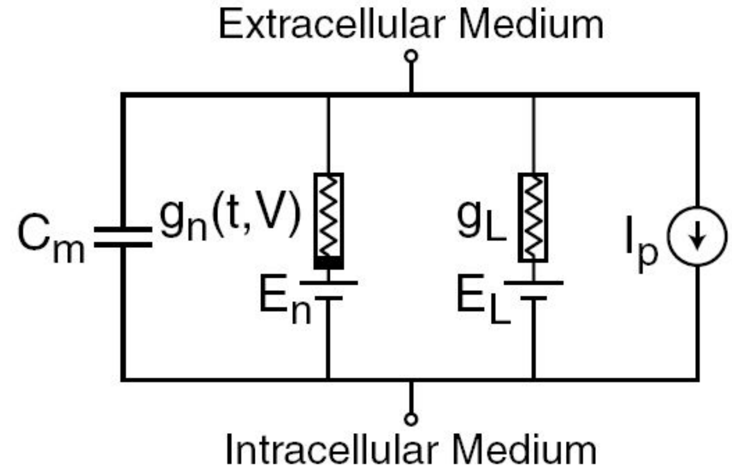
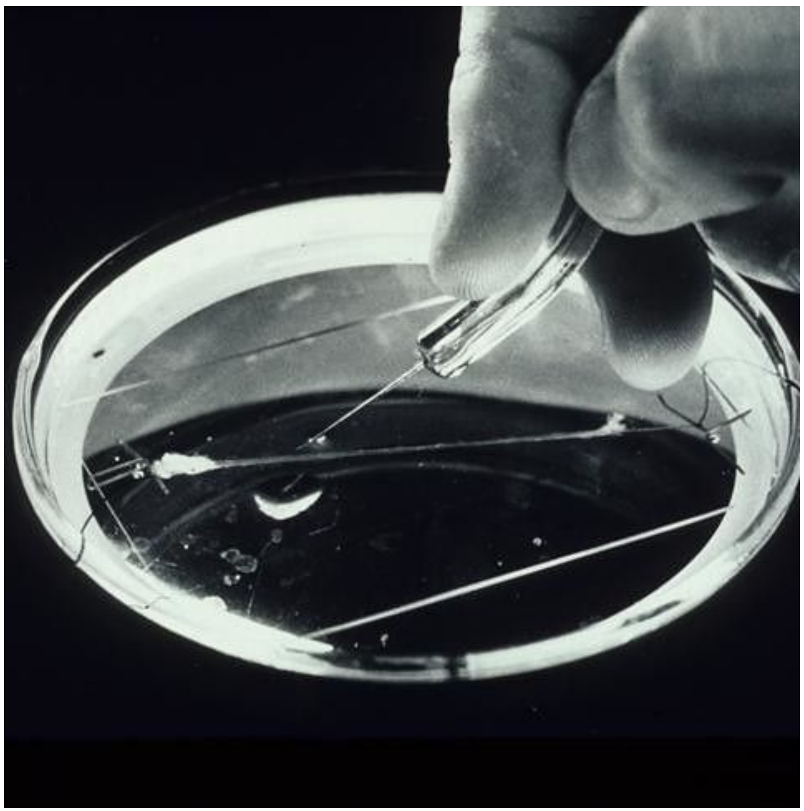
BACKGROUND:
Cellular electrophysiology may be described by a system of ordinary differential equations





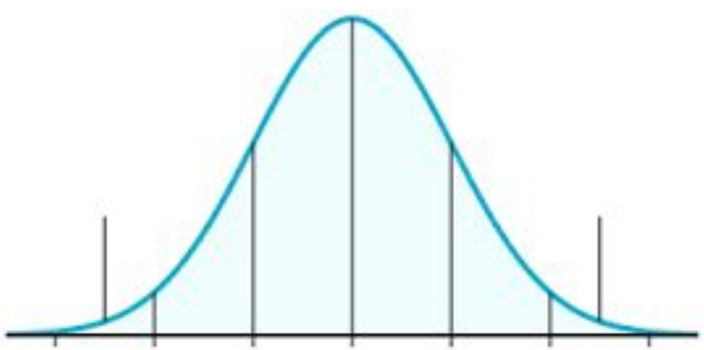
$$C\frac{dV}{dt} = g_K(V - V_K) + g_{Na}(V - V_{Na}) + I(t),$$
$$g_K = g_{K\,max}\cdot n^4,$$
$$g_{Na} = g_{Na\,max}\cdot m^3h,$$
$$\frac{dn}{dt} = \alpha_n(1-n) - \beta_n\cdot n,$$
$$\frac{dm}{dt} = \alpha_m(1-m) - \beta_m\cdot m,$$
$$\frac{dh}{dt} = \alpha_h(1-h) - \beta_h\cdot h,$$
$$\alpha_n = \frac{0{,}01\,(V-10)}{1-e^{(10-V)/10}}, \qquad \beta_n = 0{,}125e^{-V/80},$$
$$\alpha_m = \frac{0{,}1\,(V-25)}{1-e^{(25-V)/10}}, \qquad \beta_m = 4e^{-V/18},$$
$$\alpha_h = 0{,}7e^{-V/20}, \qquad \beta_h = \frac{1}{1+e^{(30-V)/10}}.$$

Hodgkin–Huxley model
(1952, Noble prize 1963)

BACKGROUND: How we can choose model parameters?

1. **Least square methods**
   a. Measurements contains error with normal distribution
   A. Mean is a real value

Truth is here, LSM is not lying!

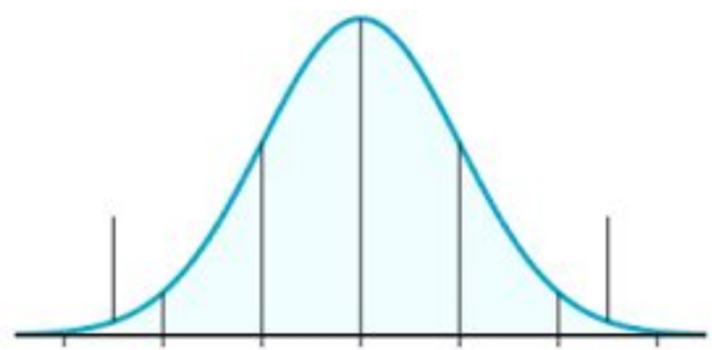


This is wrong assumption. Intracellular variability is significant and increased with age!

Zaniboni et al., 2000; Pathmanathan et al., 2015; Krogh-Madsen et al., 2015; Groenendaal et al., 2015; Coveney & Clayton, 2018

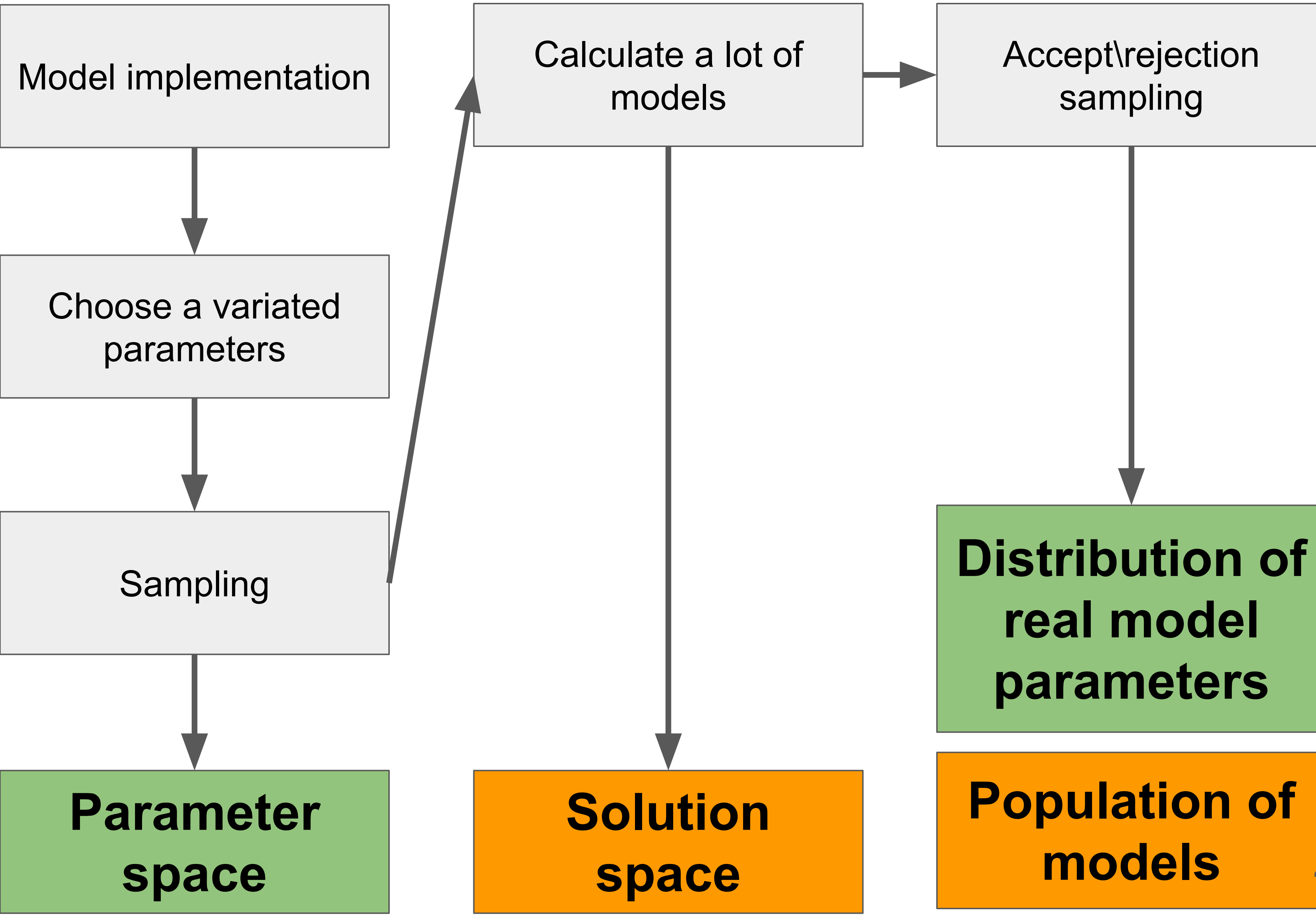
2. **Population based methods**

   A. Almost all measurements are correct
   B. Any analysis should be applied to all models in population
   C. Any conclusion have probability measurements



We all are the truth!

General framework



How to use this for fitting model population to real data?

$$\pi(\theta|x) = \frac{p(x|\theta)p(\theta)}{\int p(x|\theta)p(\theta)d(\theta)}$$

Model parameters

Distribution of model parameters

???

Real observations!

Distribution of parameters in the parameter space

Choice of p(x|θ) are crucially important!

???

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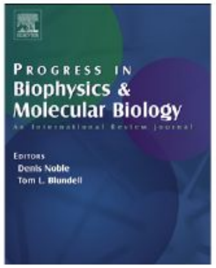

Fitting two human atrial cell models to experimental data using Bayesian history matching

Check for updates

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$$I_n^2(\mathbf{x}) = \frac{\left(E^*[f_n(\mathbf{x})] - z_n\right)^2}{Var^*[f_n(\mathbf{x})] + Var(e_n) + Var(md)}.$$

$$max[I_n(\mathbf{x})] < = I_{threshold}$$

- Iterative process of rejections over sequentially registered data.
- <-- Implausible measure

Choice of $p(x|\theta)$ are crucially important!

???

Goal:

- Analyse an effect of $p(data|\theta)$ to $\pi(\theta|data)$
  - Analyse an effect of chosen method to results

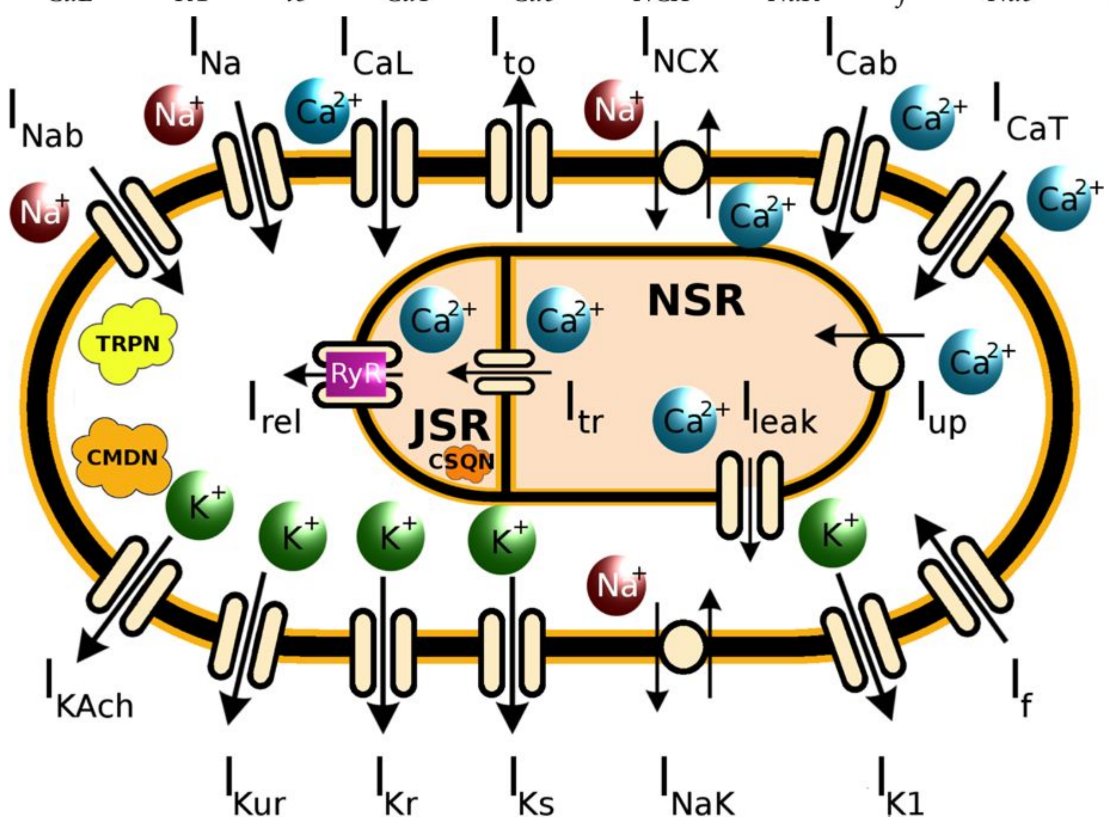
Tasks:

- Prepare case for analysis: Model + Parameter variation
- Comparison of the function $\pi(\theta|data)$ under different definitions of $p(data|\theta)$.
- Analyze the stability results by increasing the dimensionality of the parameter space.
- Verification against the literature data

Majumder 2016: Rat atrial cardiomyocyte

$$\frac{dV}{dt} = \frac{-I_{ion} + I_{stim}}{C_m},$$

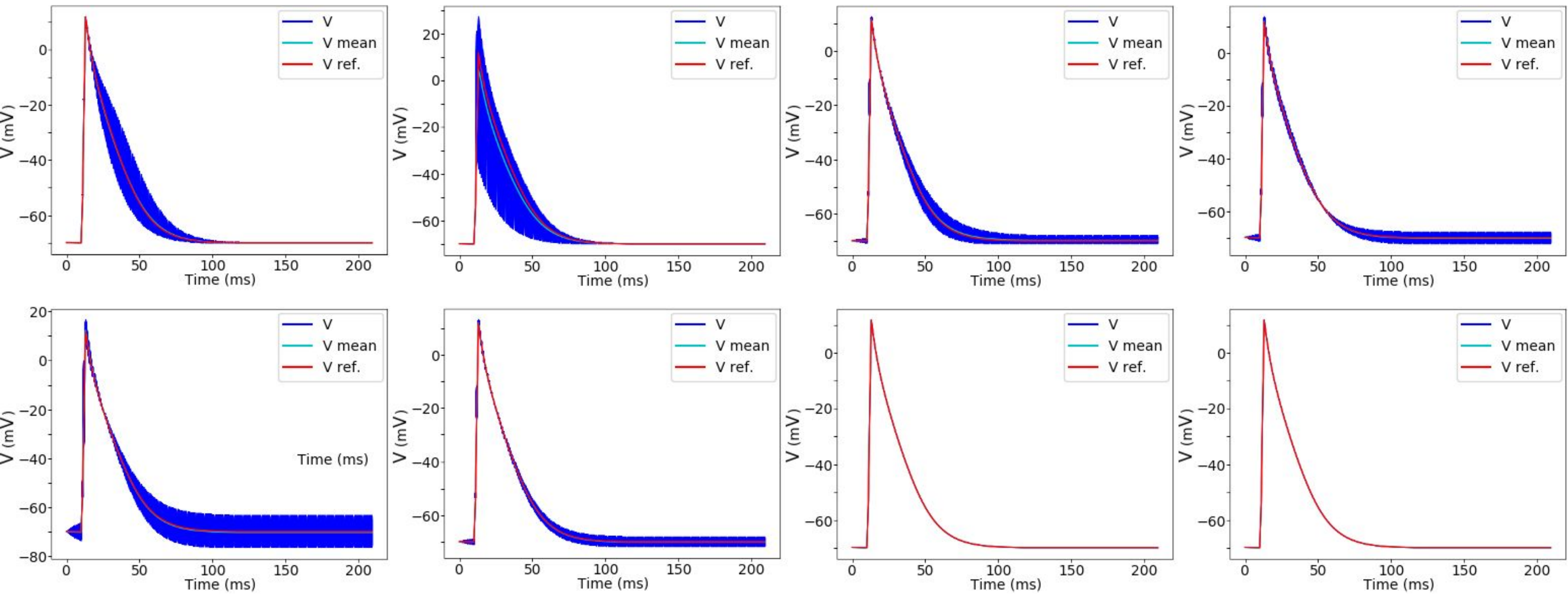
$$I_{ion} = I_{Na} + I_{CaL} + \bar{I}_{K1} + I_{to} + I_{CaT} + I_{Cab} + I_{NCX} + I_{NaK} + I_f + I_{Nab} + I_{Ksus} + I_{KACh}$$



Majumder, R., Jangsangthong, W., Feola, I., Ypey, D. L., Pijnappels, D. A., & Panfilov, A. V. (2016). PLoS computational biology, 12(6).

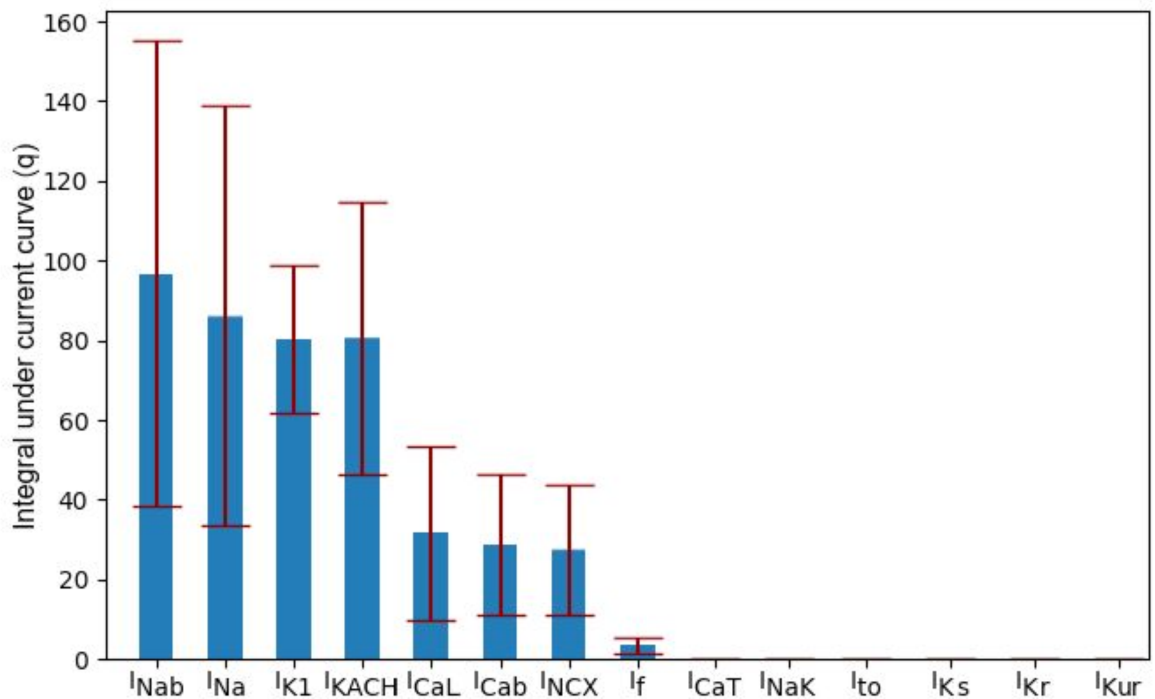
Sensitivity

Analysis of model sensitivity to variations the conductivity for each ionic current. AP shapes for variation of each current separately. **Top row: g_{CaL}, g_{Na}, g_{K1}, g_{NCX}; bottom row: g_{Kur}, g_{CaT}, g_{to}, g_f.** The red curve corresponds to the reference action potential obtained with the reference vector of the model parameters from the original article.



Sensitivity

Analysis of model sensitivity to variations the conductivity for each ionic current. Integral values under the current curves during one cardiac cycle. The “whiskers” indicate the variability of the integrals within the model population.



Intermediate conclusion: g_{CaL}, g_{Na}, g_{K1} are chosen for variation because of:

- Availability of literature data (g_{CaL})
- Strongest effect on action potential (g_{Na}, g_{K1})
- Currents are not background (I_{*b}) or
  raise discussion in model correctness (g_{KACH})

Methods

$$I_n^2(\mathbf{x}) = \frac{(E^*[f_n(\mathbf{x})] - z_n)^2}{Var^*[f_n(\mathbf{x})] + Var(e_n) + Var(md)}.$$

$$max[I_n(\mathbf{x})] <= I_{threshold}$$

Coveney et. al., 2018

OUR IDEA: Inverse distance with diverge metrics instead of rejection. Series of approaches.

$$\pi(\theta_i) = \frac{1}{d(V(\theta_i), \hat{V})} / \sum_{j=0}^{N} \frac{1}{d(V(\theta_j), \hat{V})}$$

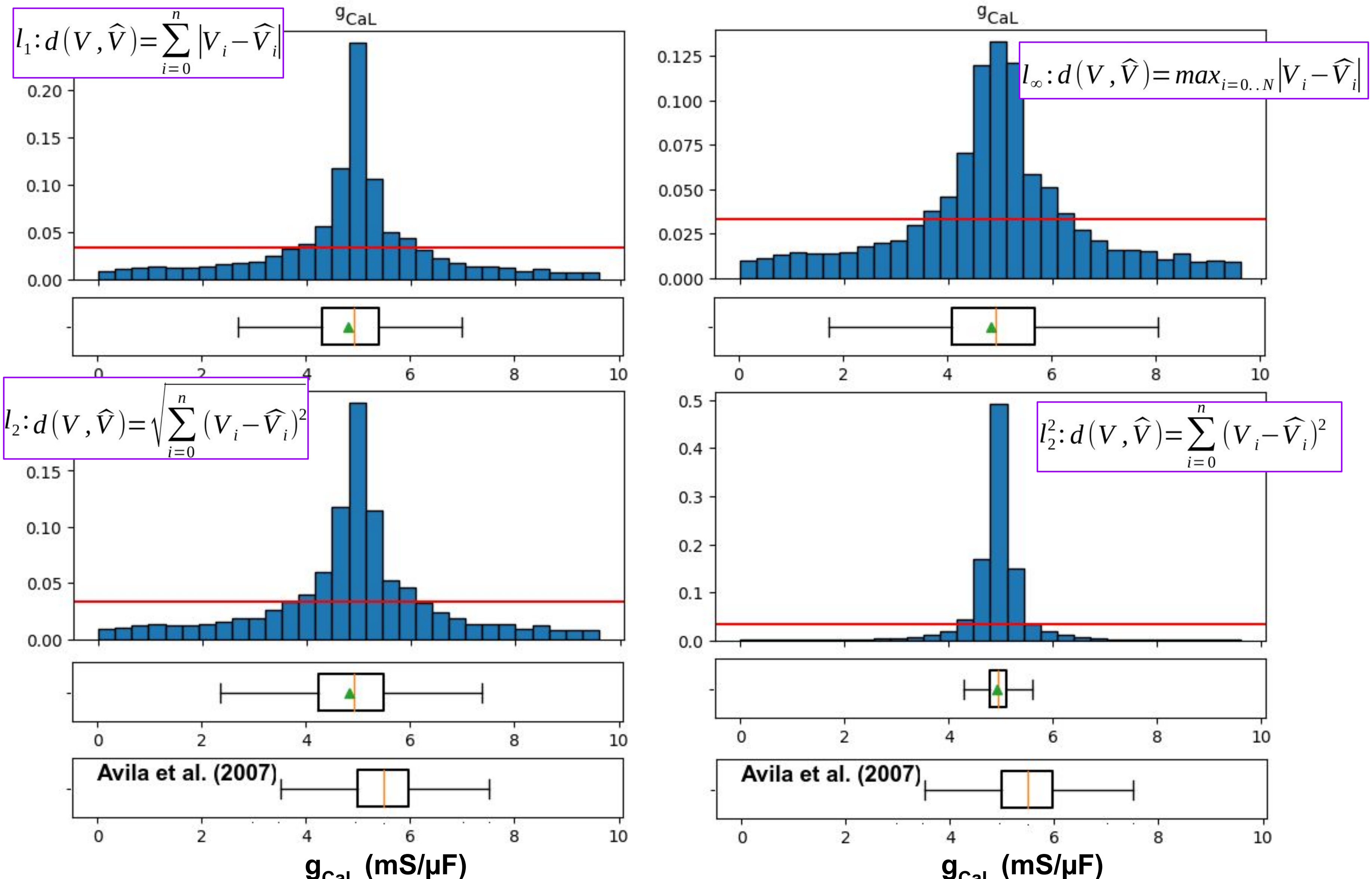
In this study, four different metrics were tried:

$$l_1 : d(V, \widehat{V}) = \sum_{i=0}^{n} |V_i - \widehat{V}_i| \qquad l_\infty : d(V, \widehat{V}) = max_{i=0..N} |V_i - \widehat{V}_i|$$

$$l_2 : d(V, \widehat{V}) = \sqrt{\sum_{i=0}^{n} (V_i - \widehat{V}_i)^2} \qquad l_2^2 : d(V, \widehat{V}) = \sum_{i=0}^{n} (V_i - \widehat{V}_i)^2$$

where *π(θ)* — is the probability function for parameter vector *θ*, *V(θ)* — is the experimentally observed action potential, a ***V*** — is the action potential for the parameter vector *θ*, and *d* is the metric between the observed and simulated action potentials.

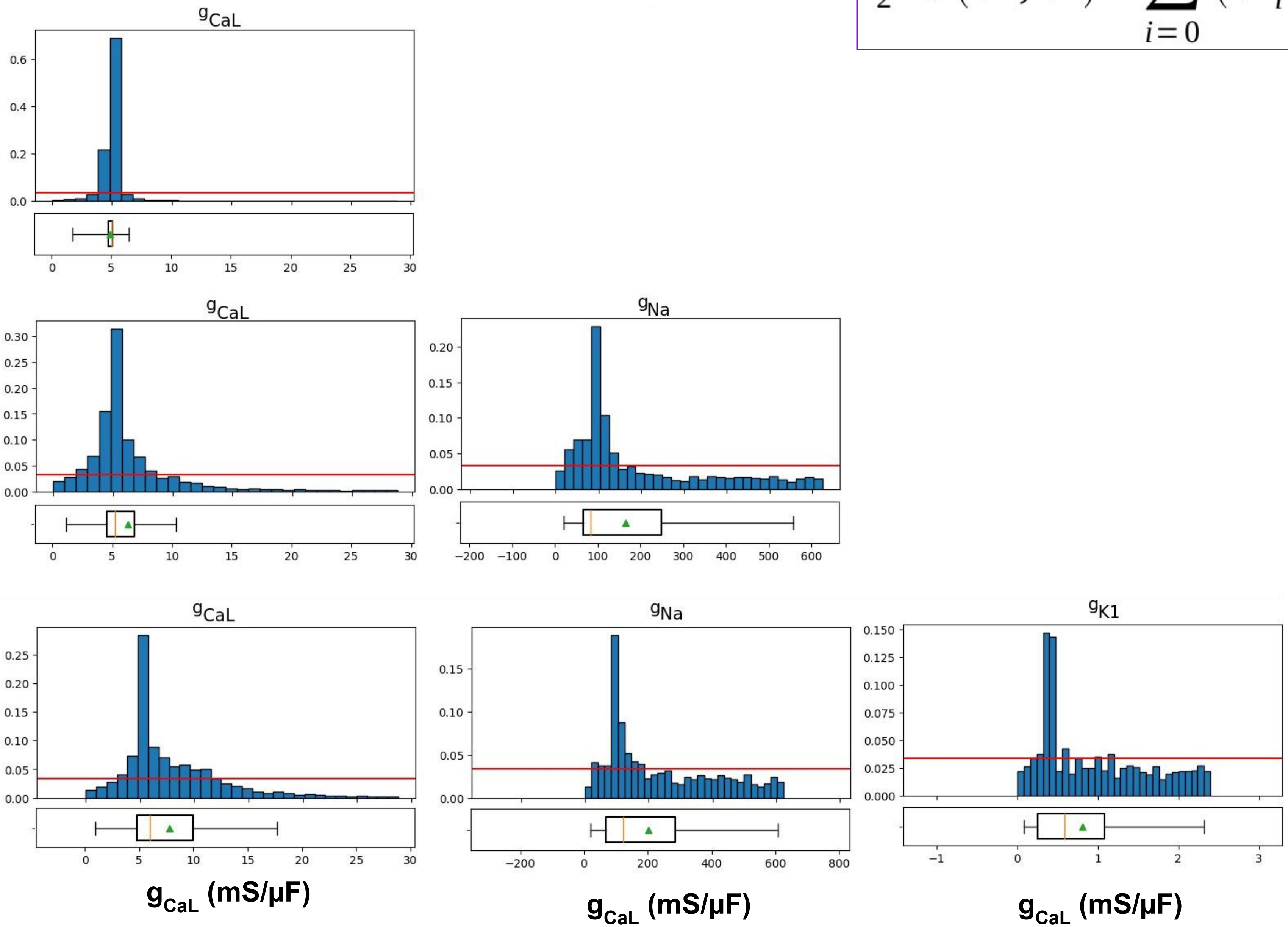
Metrics



G. Avila, I. M. Medina, E. Jiménez, G. Elizondo, & C. I. Aguilar, American Journal of Physiology-Heart and Circulatory Physiology **292**(1), H622-H631 (2007).

Probability density function

$$l_2^2 : d(V, \widehat{V}) = \sum_{i=0}^{n} (V_i - \widehat{V}_i)^2$$



Conclusion

1. Four ion currents (I_{CaL}, I_{Na}, I_{K1}, I_{NCX}) produced the strongest effects on the shape of AP. Also, background currents strongly affect the action and resting potentials.
2. The l_2^2 metric is best suited for the Monte Carlo method in applications for the selection of parameters in models.
3. Increasing the dimension of the parameter space had no significant impact on the final allocation of distribution mean and median in terms of values in physical units.

Acknowledgements

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