Compositionality Results for Cardiac Cell Dynamics

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Joint work with:

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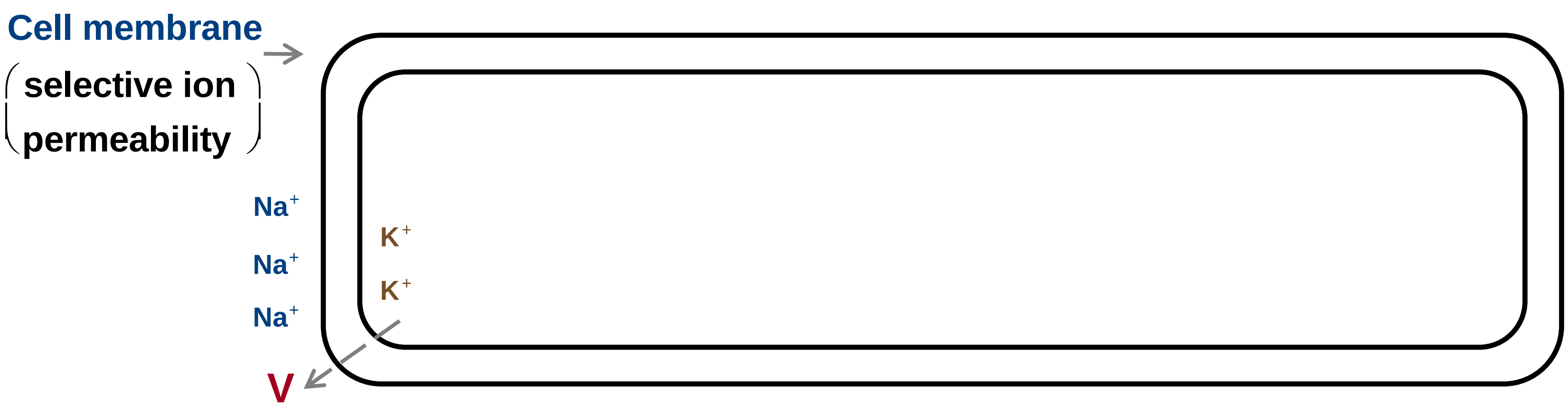
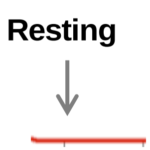
Iyer-Mazhari-Winslow Myocyte Model





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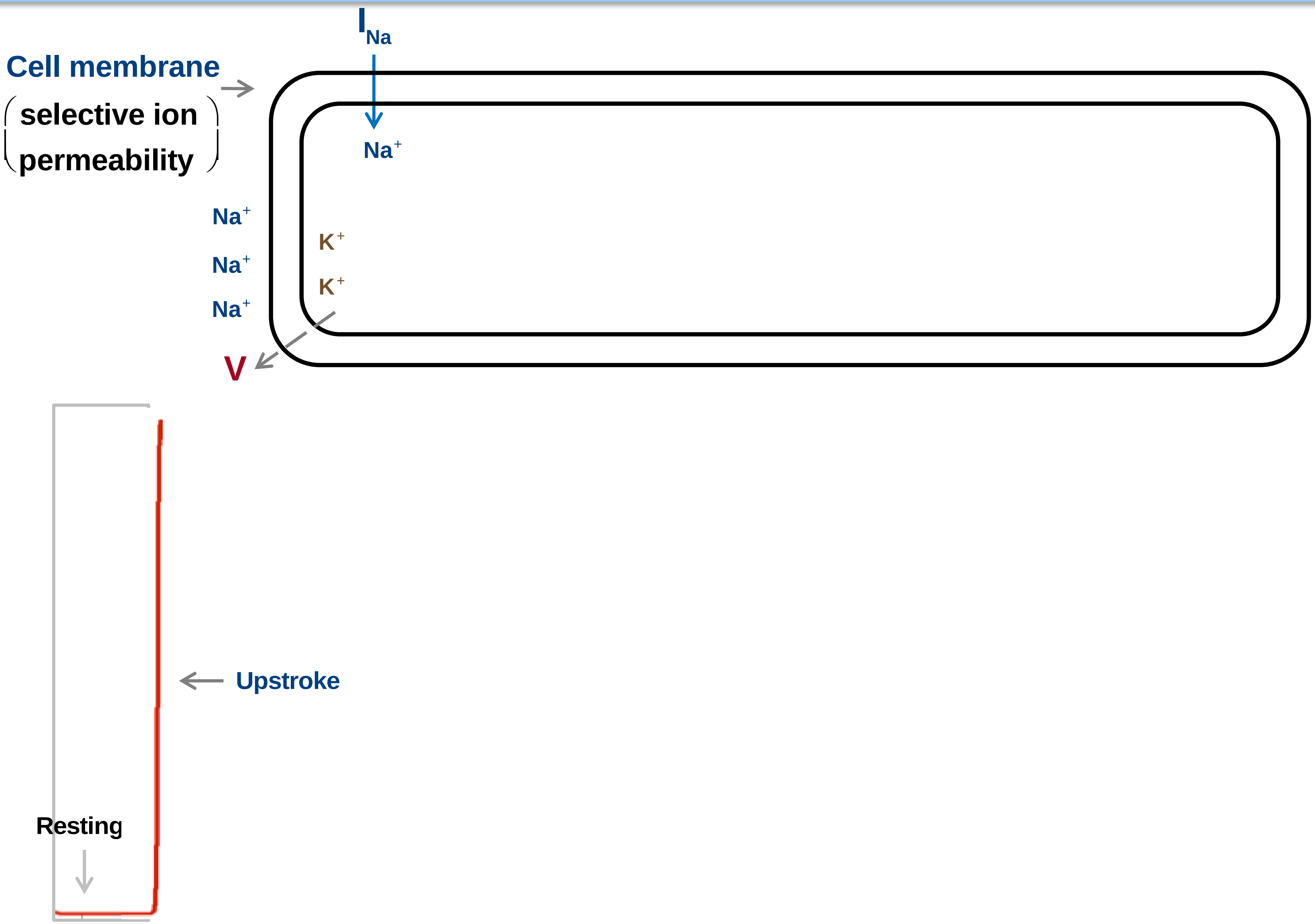

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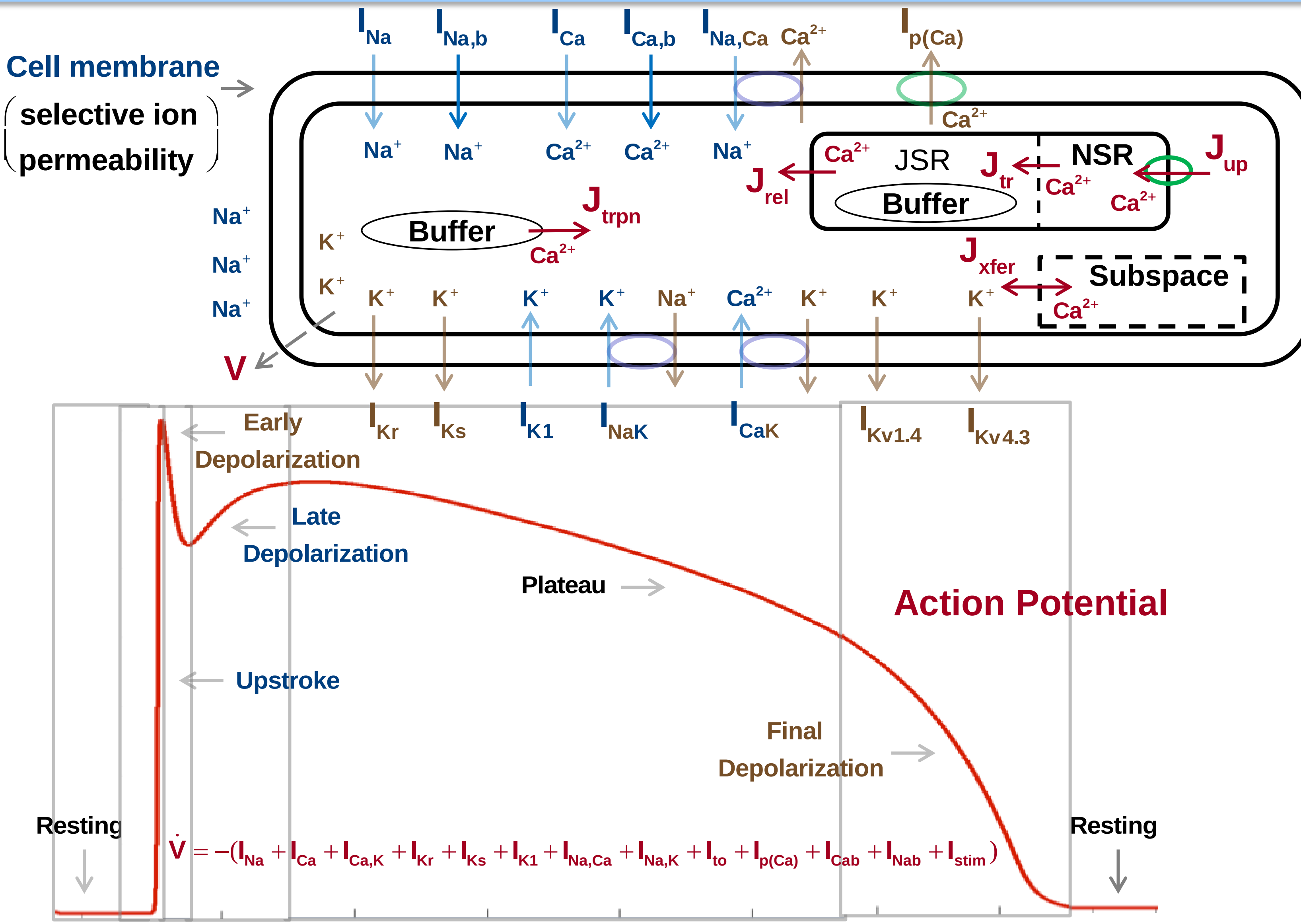
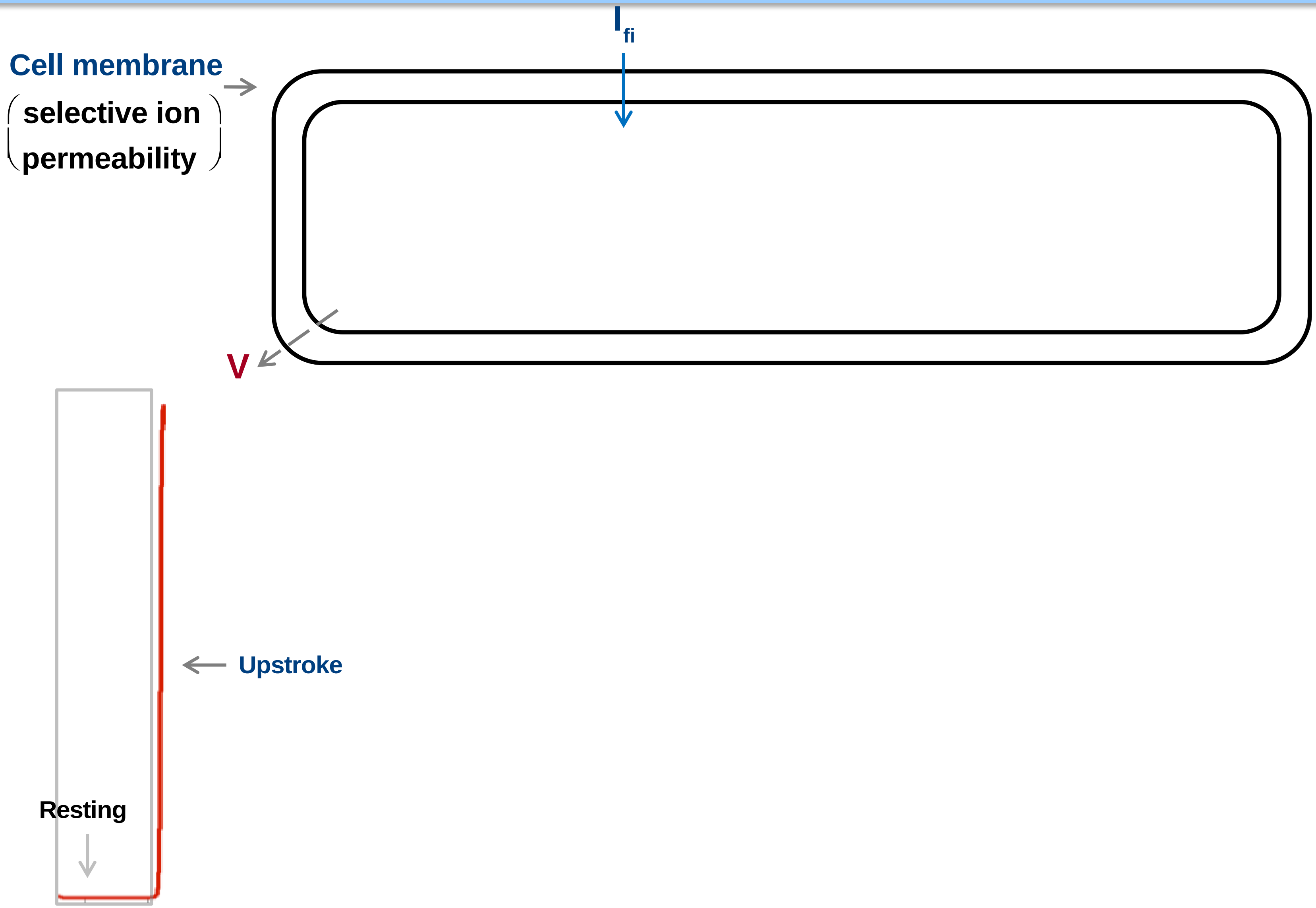


Fenton-Cherry-Orovio Minimal Model



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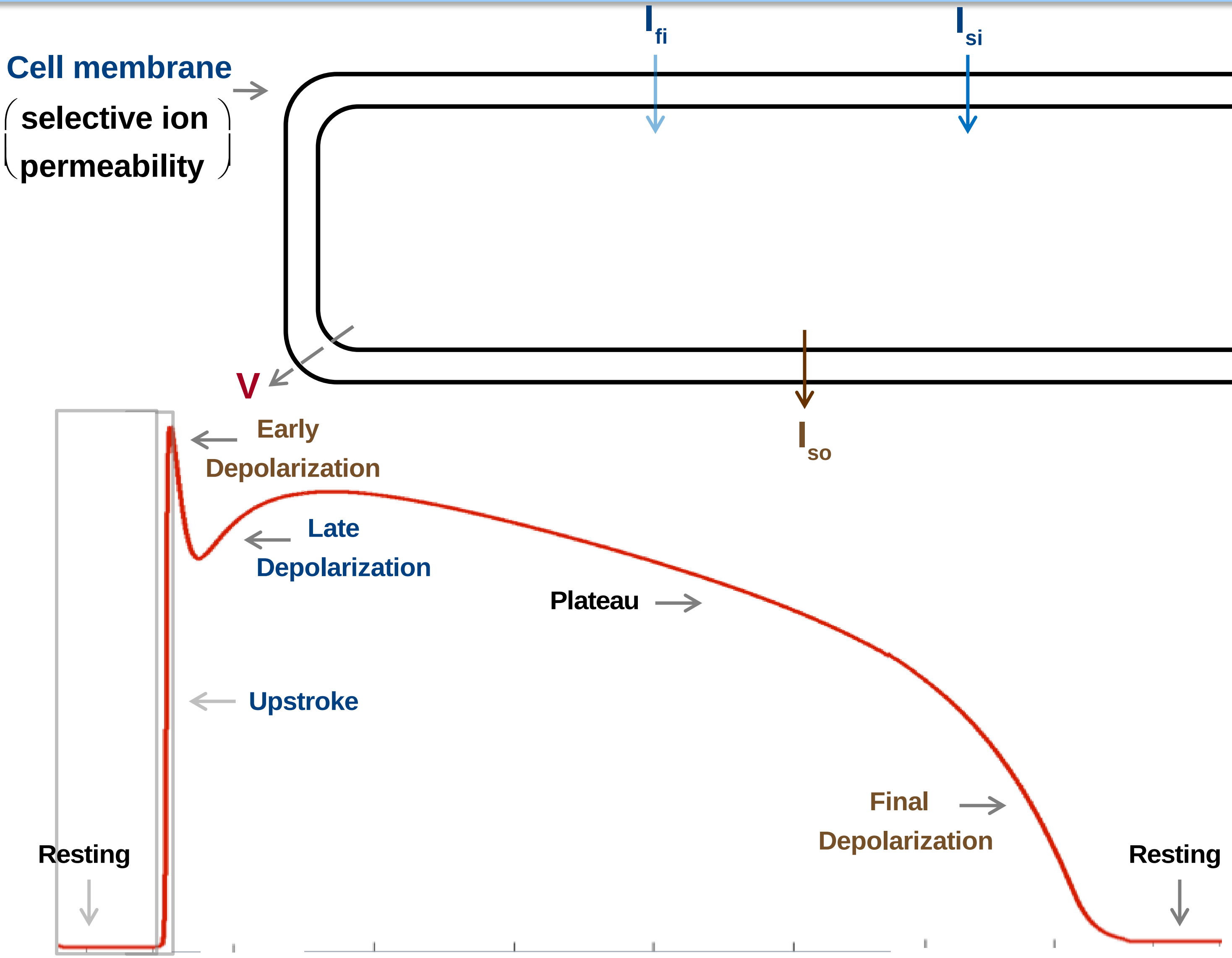

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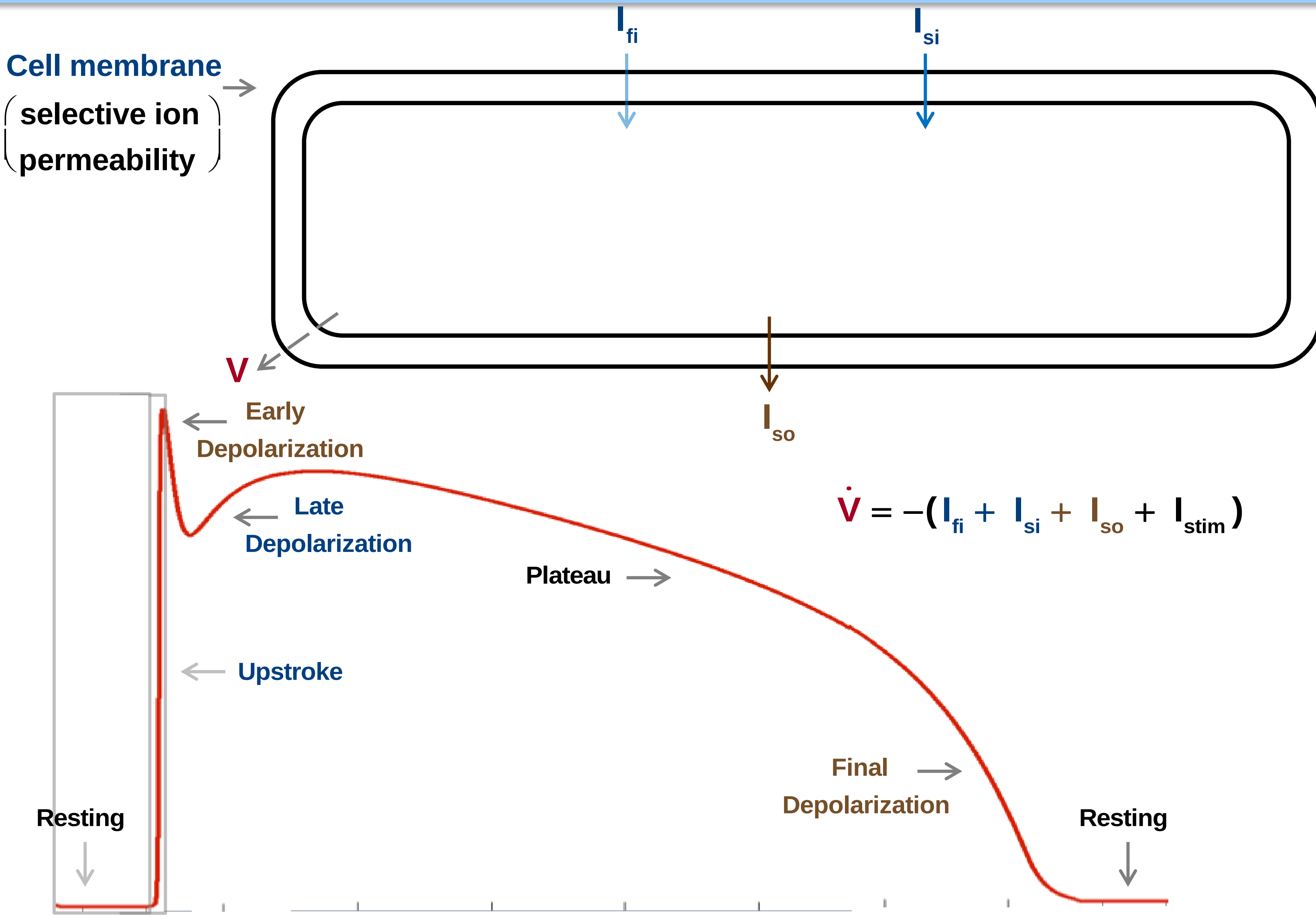
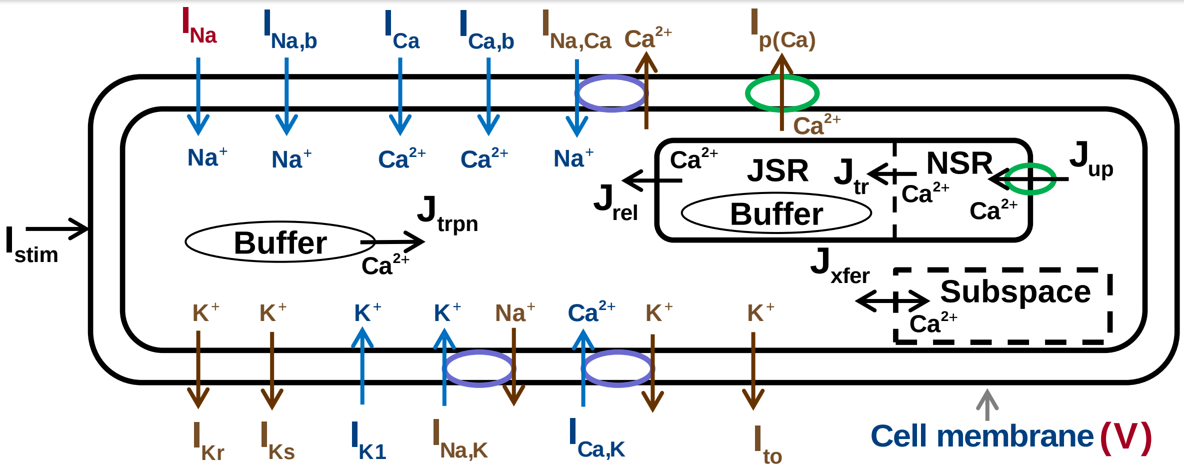
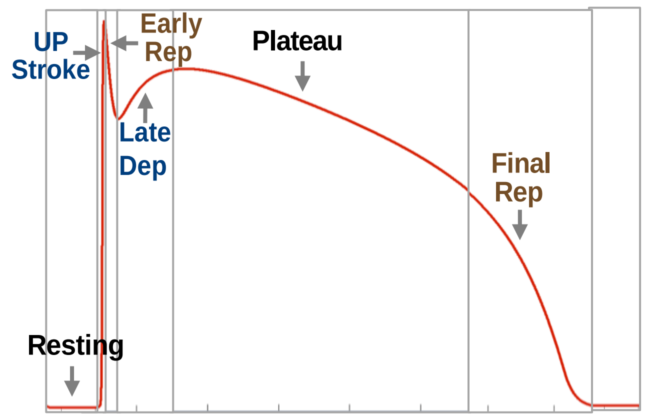


$$\dot{V} = -(I_{fi} + I_{si} + I_{so} + I_{stim})$$

Main Challenge



Schematic diagram of the 67-variable IMW model



IMW model's Action Potential (output)

$$\dot{V} = -(I_{Na} + I_{Ca} + I_{Ca,K} + I_{Kr} + I_{Ks} + I_{K1} + I_{Na,Ca} + I_{Na,K} + I_{to} + I_{p(Ca)} + I_{Cab} + I_{Nab} + I_{stim})$$

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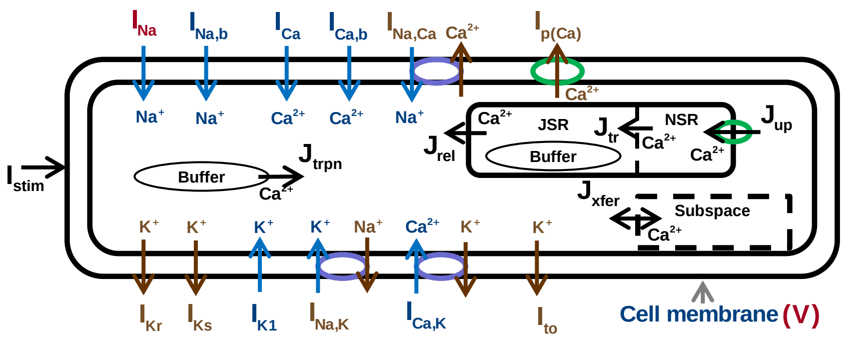

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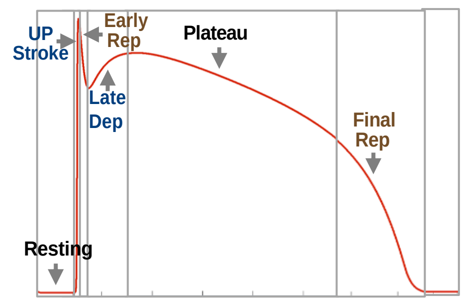

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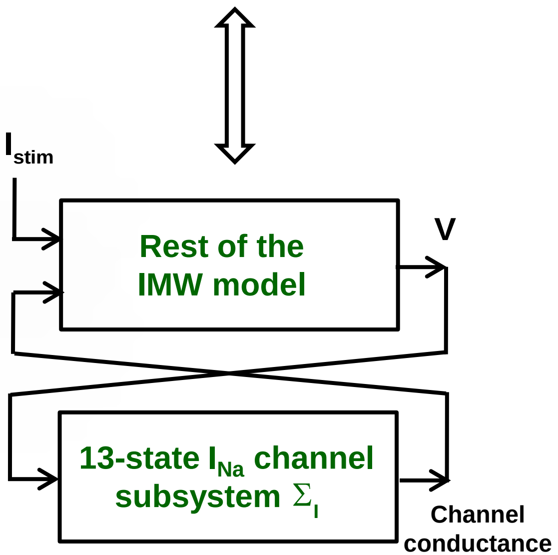

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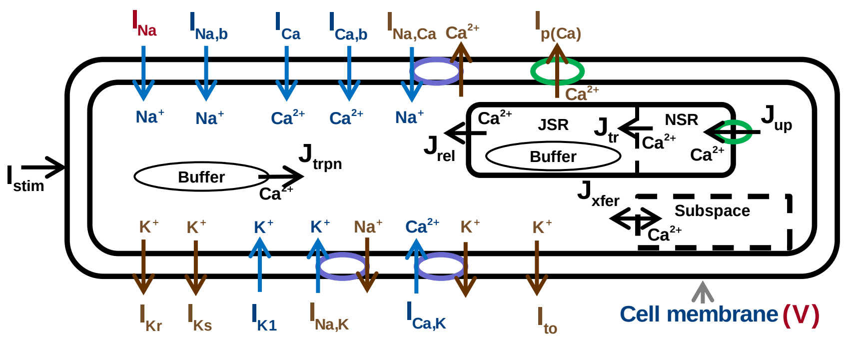

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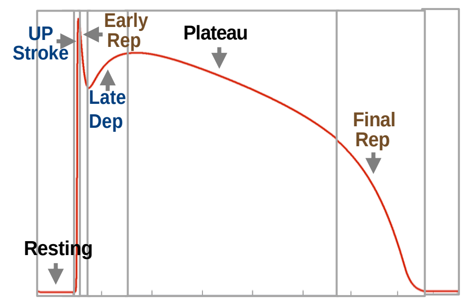

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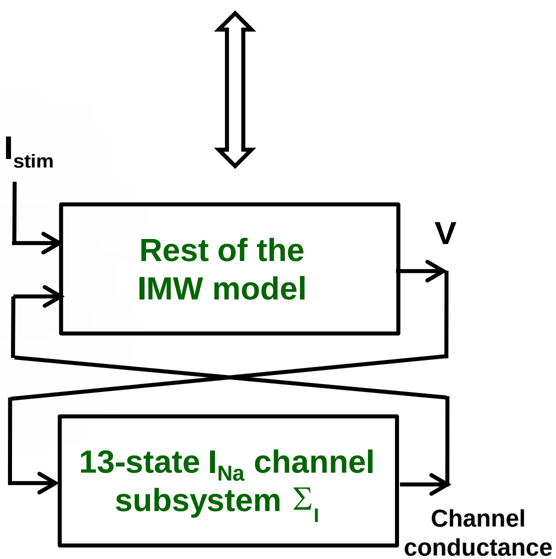

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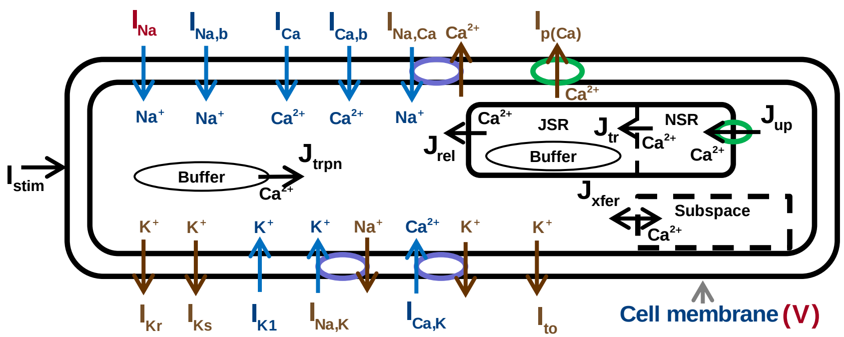

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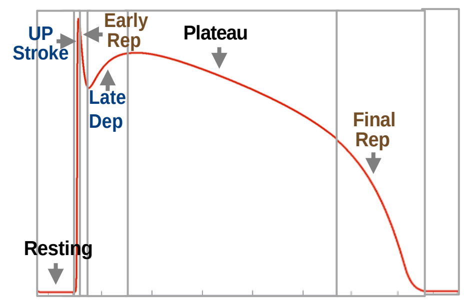

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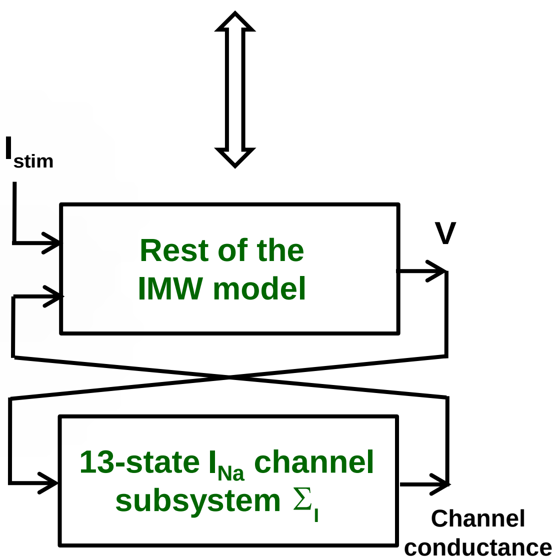

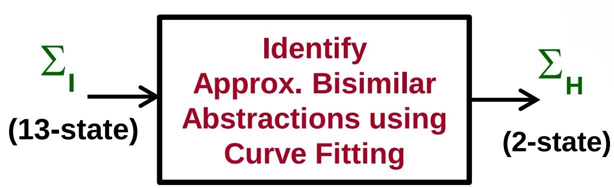

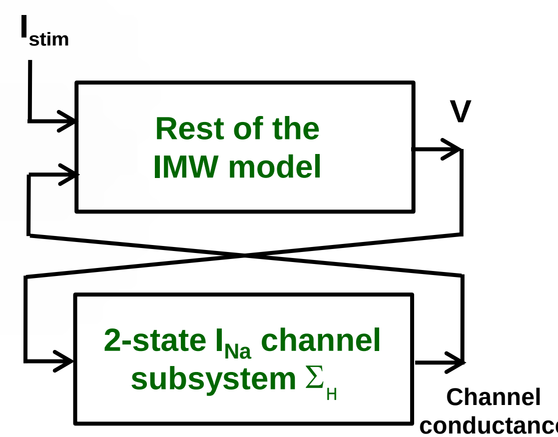

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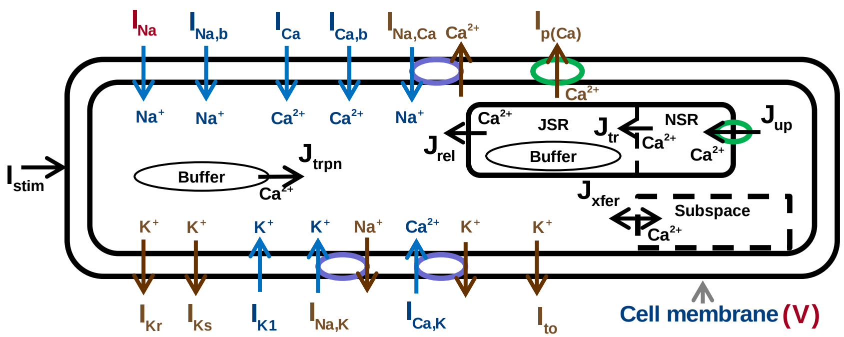

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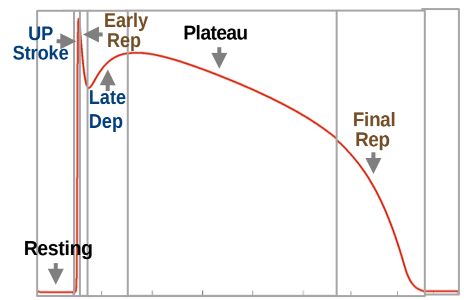

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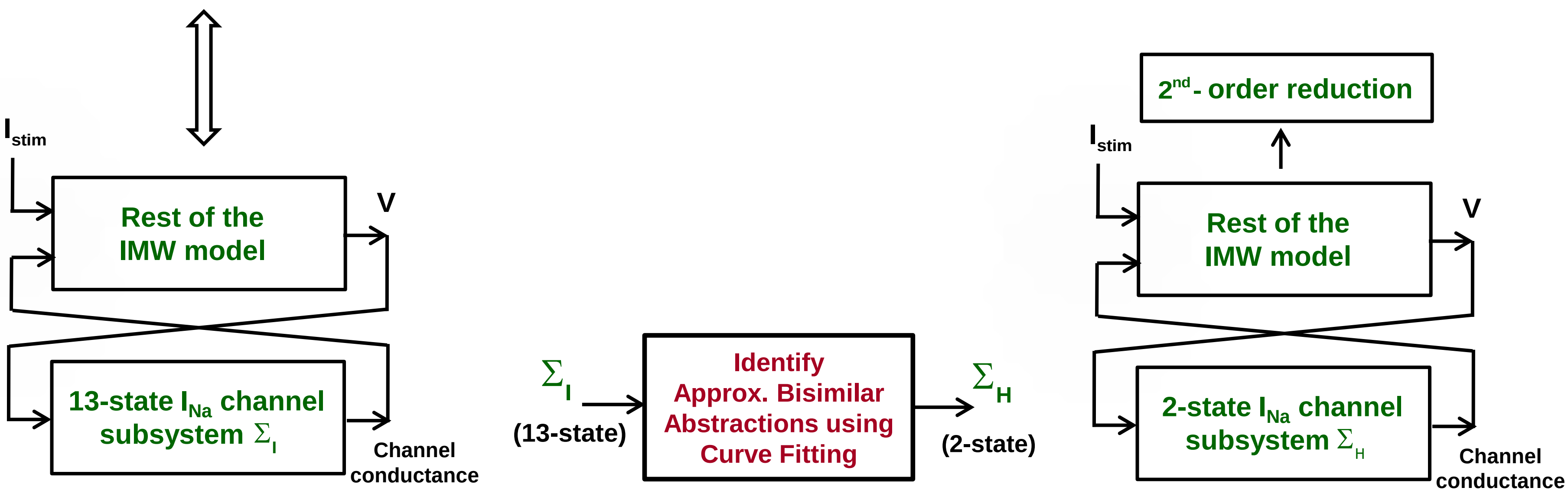

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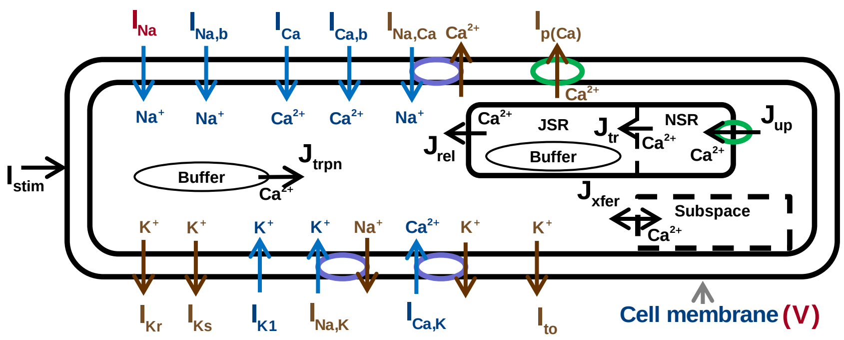

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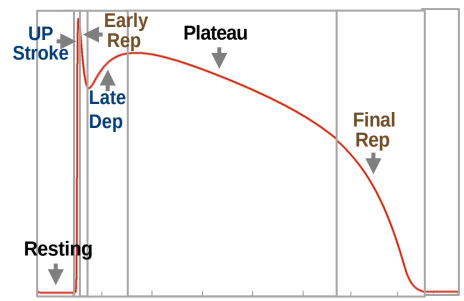

IMW model's Action Potential (output)

Tower of Abstractions
Insightful Analysis
of Cardiac Cell Models

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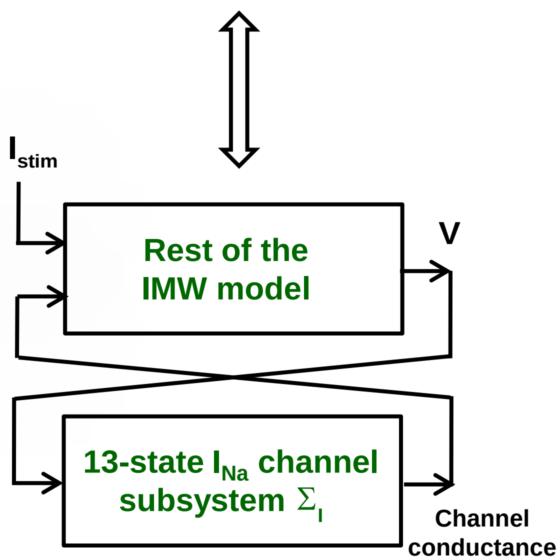

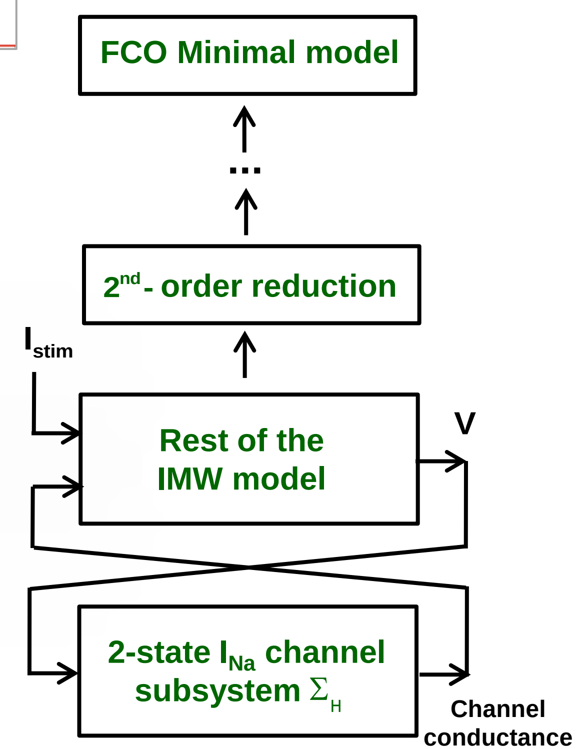

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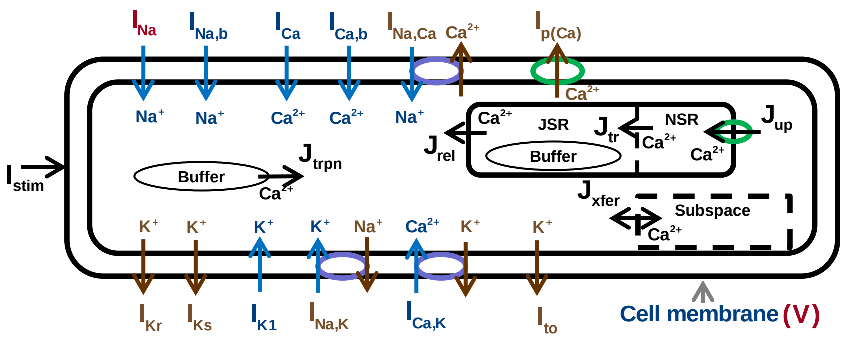

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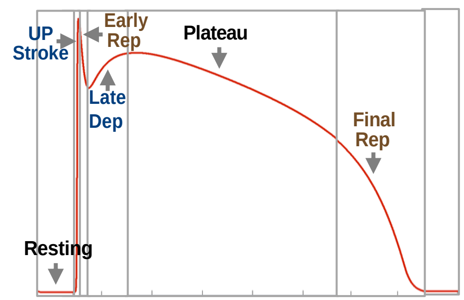

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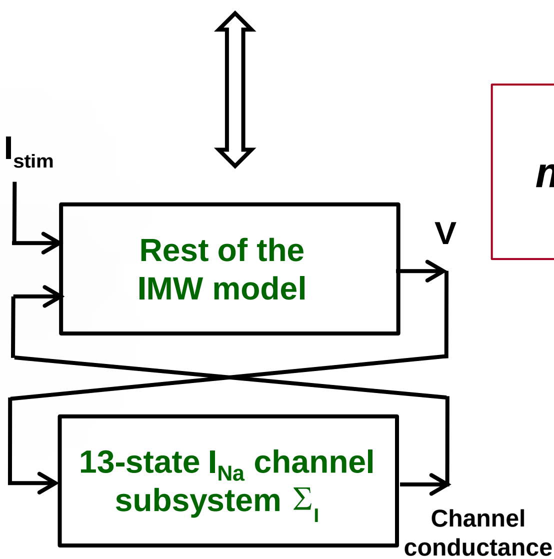
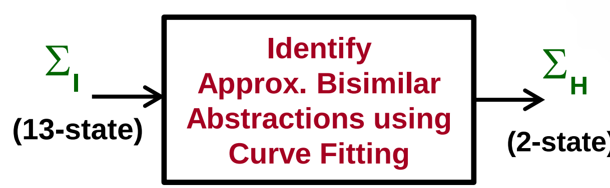
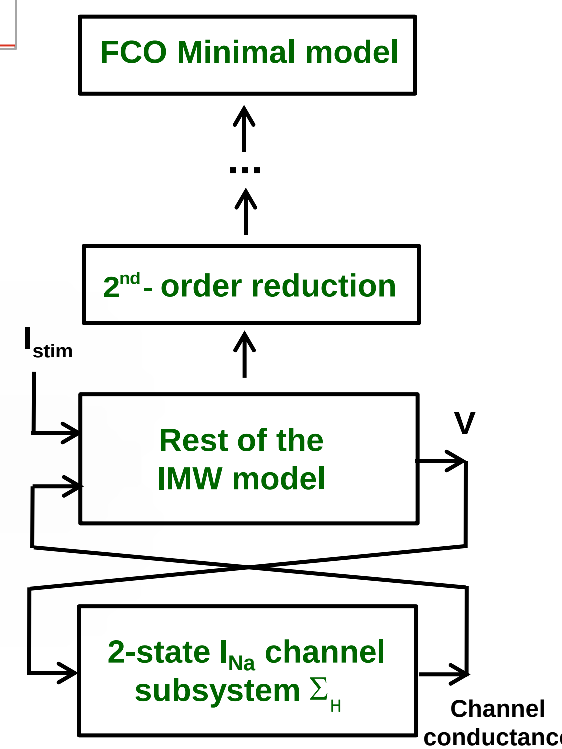


Does component-wise
model reduction & replacement
lead to equivalent models?





Outline

- **Problem Statement**
- **Background**
  - Iyer et al. (IMW) sodium channel component
  - Model-order reduction for identifying Hodgkin-Huxley type abstractions
- **Compositionality**
  - Bisimulation Functions
  - Input-to-Output Stability (IOS)-based equivalence of dynamical systems
  - Small-Gain Theorem for feedback compositionality
- **Computing BFs using Sum-of-Squares Optimization**
- **Results**
- **Conclusions and Ongoing Work**

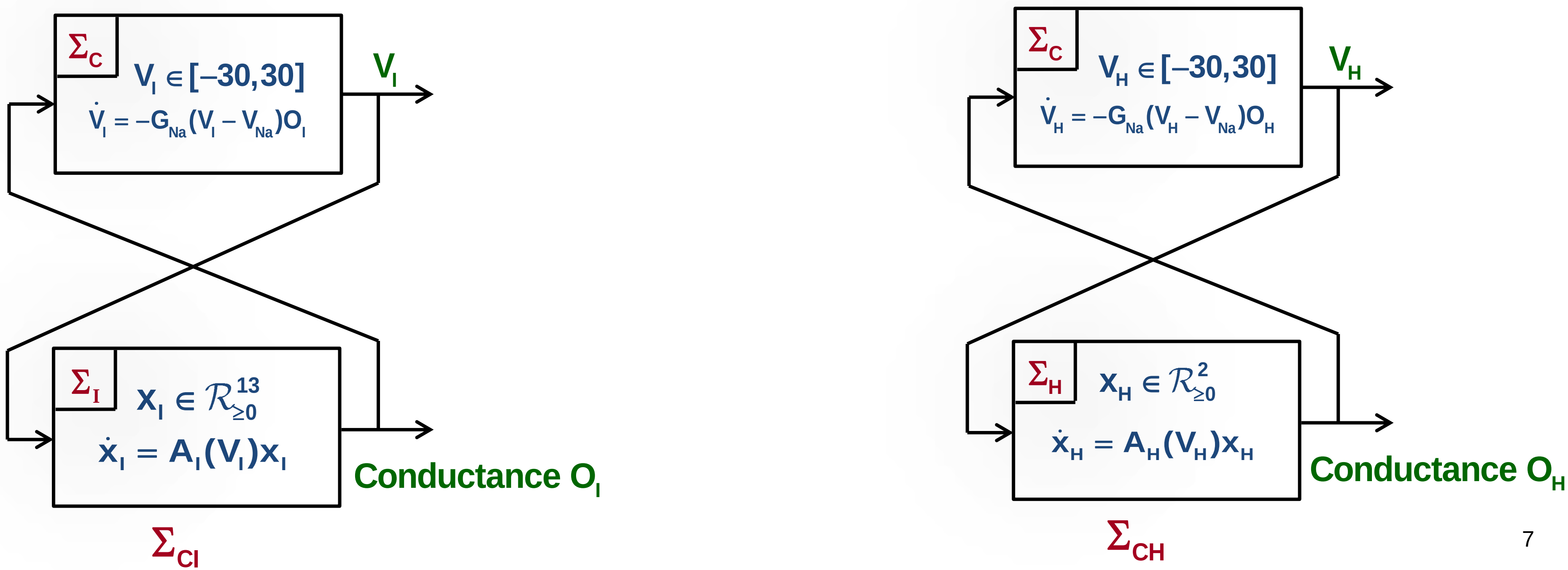
Problem Statement

Σ_I : 13-state voltage-controlled sodium channel Continuous Time Markov Chain (CTMC) subsystem used in the IMW model

Σ_H : 2-state abstraction of Σ_I, identified using curve fitting

Σ_C : Capacitor-like context representing the membrane

Σ_{CI}, Σ_{CH} : Canonical cell models with only the sodium channel subsystem and the membrane composed using feedback



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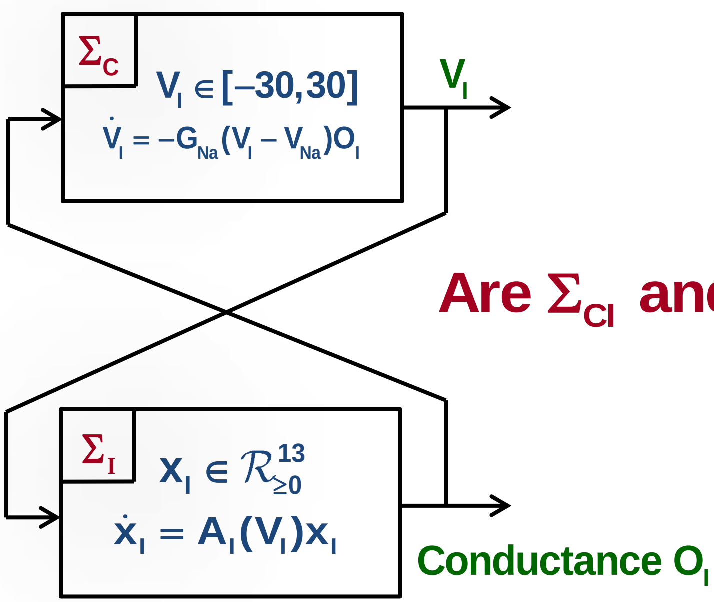
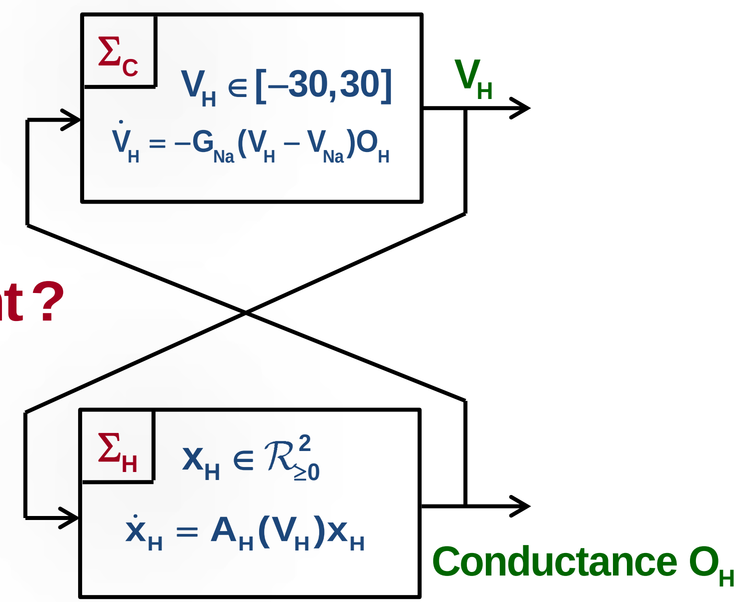


Σ_{CI}

Are Σ_{CI} and Σ_{CH} equivalent?



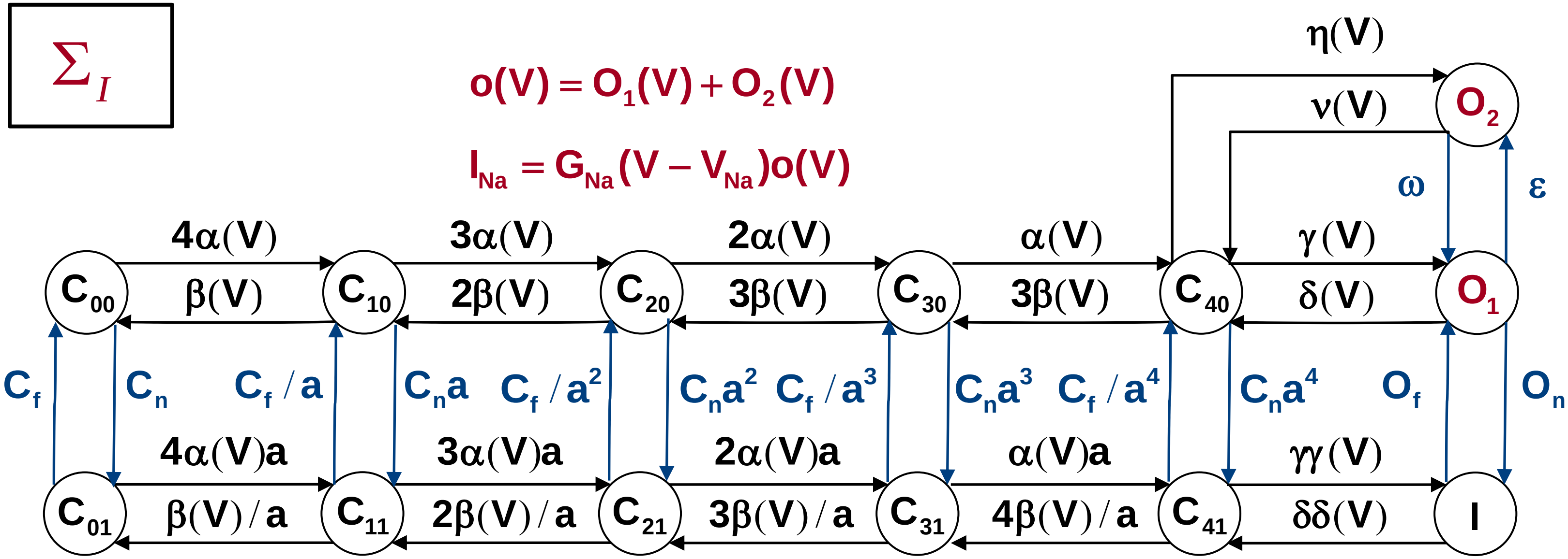
Σ_{CH}

Background: IMW's Sodium Channel Component

Σ_I

$$o(V) = O_1(V) + O_2(V)$$

$$I_{Na} = G_{Na}(V - V_{Na})o(V)$$



- Dynamics: $\dot{x}_I = A_I(V)x_I, \; A_I(V) \in \mathcal{R}^{13} \times \mathcal{R}^{13}$

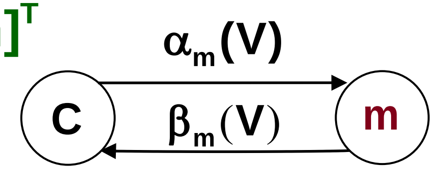
  $x_I = [C_{00}, C_{10}, C_{20}, C_{30}, C_{40}, O_1, O_2, C_{01}, C_{11}, C_{21}, C_{31}, C_{41}, I]^T$

- Input: Trans-membrane voltage V
- Output: Channel conductance o(V), which determines I_{Na}
- Transition rates: Exponential function of V

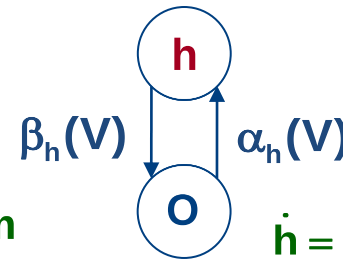
Background: Model-Order Reduction for Identifying Hodgkin-Huxley (HH)-Type Abstractions

Σ_H

$x_H = [m,h]^T$



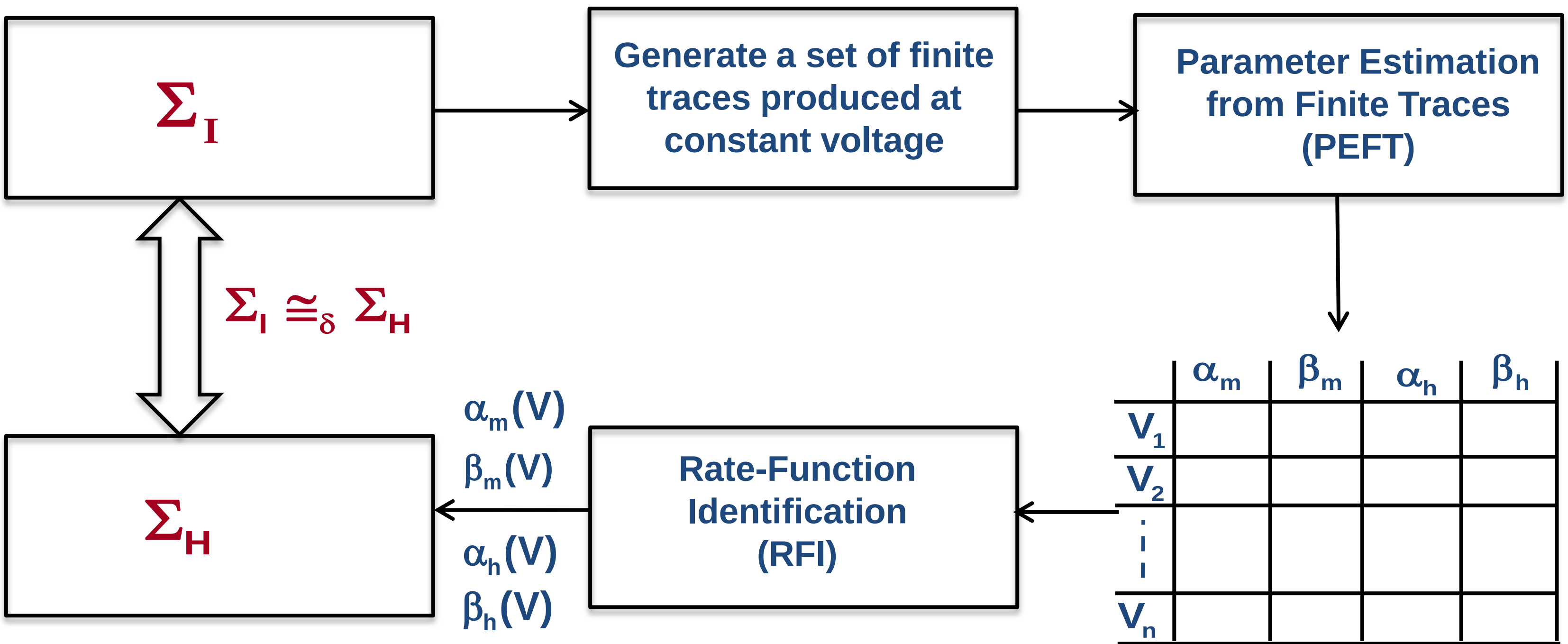
$\dot{m} = \alpha_m(V)(1-m) - \beta_m(V)m$



$o(V) = m^3(V)h(V)$

$I_{Na} = G_{Na}(V - V_{Na})o(V)$

$\dot{h} = \alpha_h(V)(1-h) - \beta_h(V)h$



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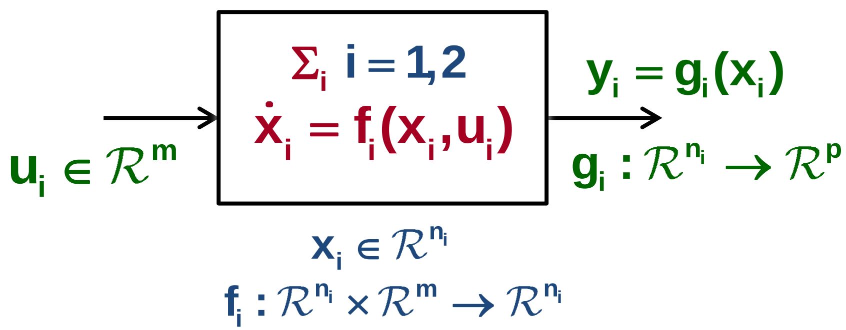
Bisimulation Functions (BFs)

BFs: contractive metrics that characterize IOS-based equivalence of two dynamical systems.



BF $S(x_1, x_2) : \mathcal{R}^{n_1} \times \mathcal{R}^{n_2} \to \mathcal{R}_{\geq 0}$ between Σ_1 and Σ_2 is a smooth function such that,

1. **S** bounds output difference

$$\| g_1(x_1) - g_2(x_2) \| \leq S(x_1, x_2)$$

2. **S** decays along trajectories

$\forall u_1, u_2, x_1, x_2, \exists \lambda > 0, \gamma \geq 0$ such that

$$\frac{\partial S}{\partial x_1} f_1(x_1, u_1) + \frac{\partial S}{\partial x_2} f_2(x_2, u_2) \leq -\lambda S(x_1, x_2) + \gamma \| u_1 - u_2 \|$$

Theorem 1: BFs Imply IOS

IOS : Bounded input difference leads to bounded output difference

For all $\mathbf{t \geq 0}$,

$$\| g_1(x_1(t)) - g_2(x_2(t)) \| \leq S(x_1(t), x_2(t))$$

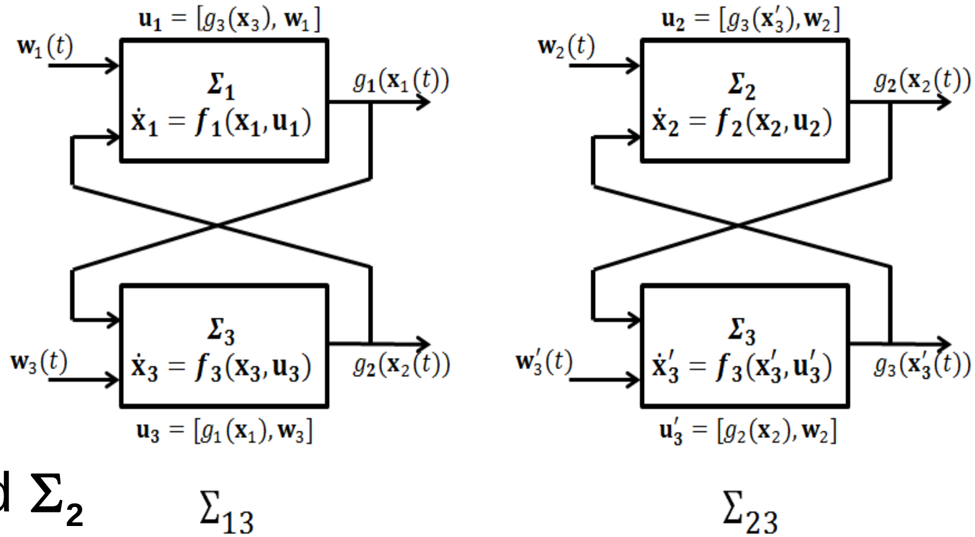
$$\leq e^{-\lambda t} S(x_1(0), x_2(0)) + \frac{\gamma}{\lambda} \| u_1 - u_2 \|_\infty$$

where $\| u_1 - u_2 \|_\infty = \sup_{t \geq 0} \| u_1(t) - u_2(t) \|$

i.e. max difference in input signals

Theorem 2: Small-Gain Theorem for Feedback Composition

BFs can be linearly composed subject to small gain condition (sgc)



$S_{12}(\lambda_{12}, \gamma_{12})$: BF between Σ_1 and Σ_2

$S_3(\lambda_3, \gamma_3)$: BF between Σ_3 and itself

If $\frac{\gamma_{12}\gamma_3}{\lambda_{12}\lambda_3} < 1$ (sgc),

$$S([x_1, x_3], [x_2, x'_3]) = \alpha_1 S_{12}(x_1, x_2) + \alpha_2 S_3(x_3, x'_3)$$

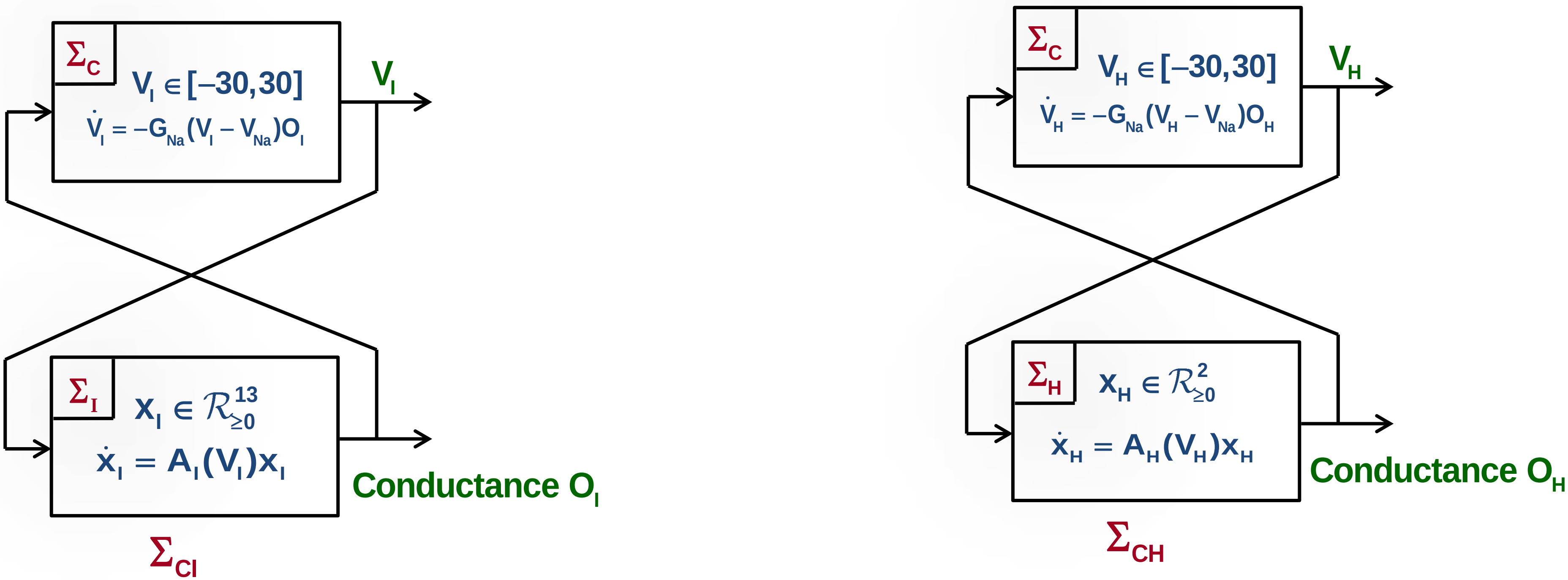
where **S** is a BF between Σ_{13} and Σ_{23}

(α_1, α_2) chosen as:

$$\begin{cases} \frac{\gamma_3}{\lambda_{12}} < \alpha_1 < \frac{\lambda_3}{\gamma_{12}}, \alpha_2 = 1 & \text{If } \lambda_{12} \le \gamma_3 \\ \alpha_1 = 1, \frac{\gamma_{12}}{\lambda_3} < \alpha_2 < \frac{\lambda_{12}}{\gamma_3} & \text{If } \lambda_3 \le \gamma_{12} \\ \alpha_1 = 1 \text{ and } \alpha_2 = 1 & \text{Otherwise} \end{cases}$$

Methodology

Proving **equivalence** of Σ_{CI} and Σ_{CH}



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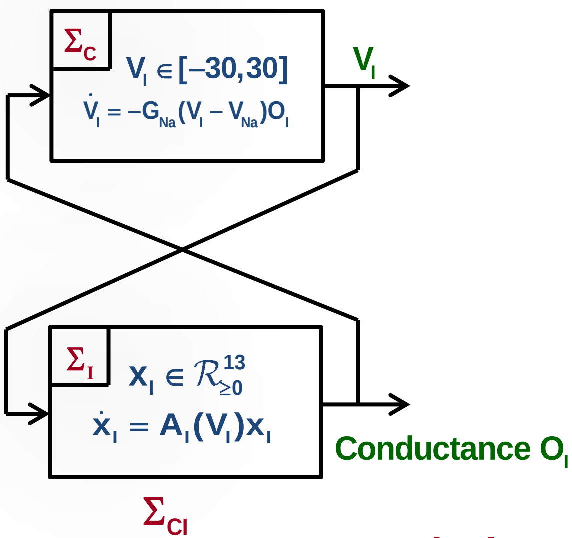
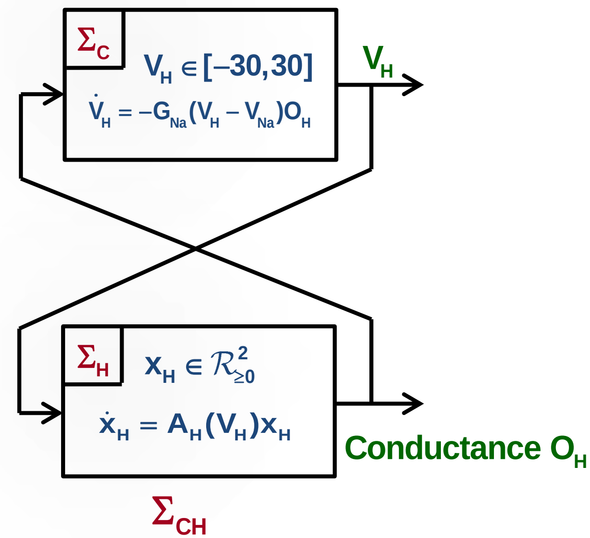
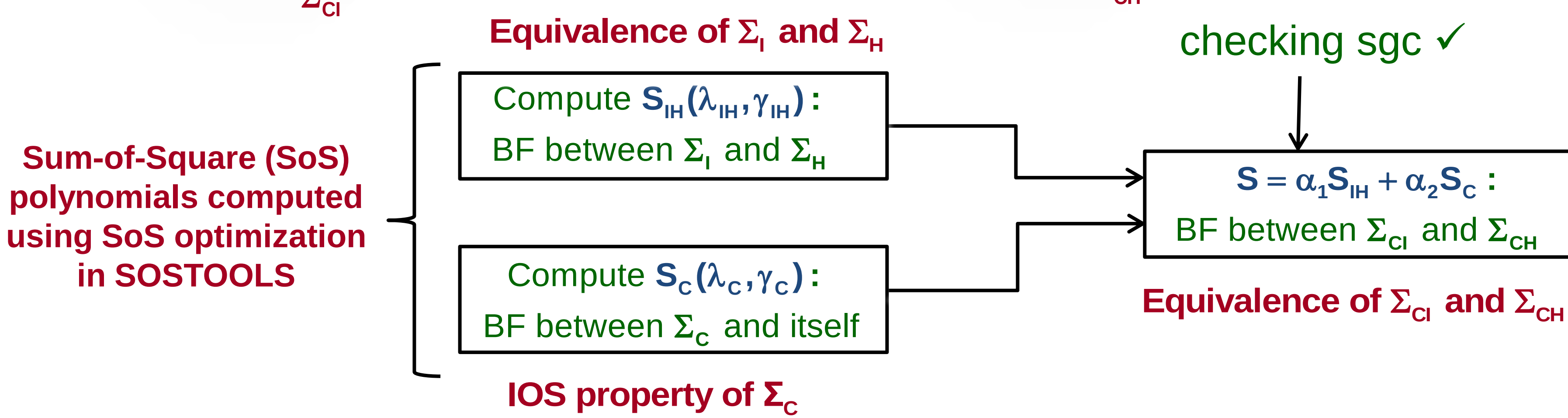
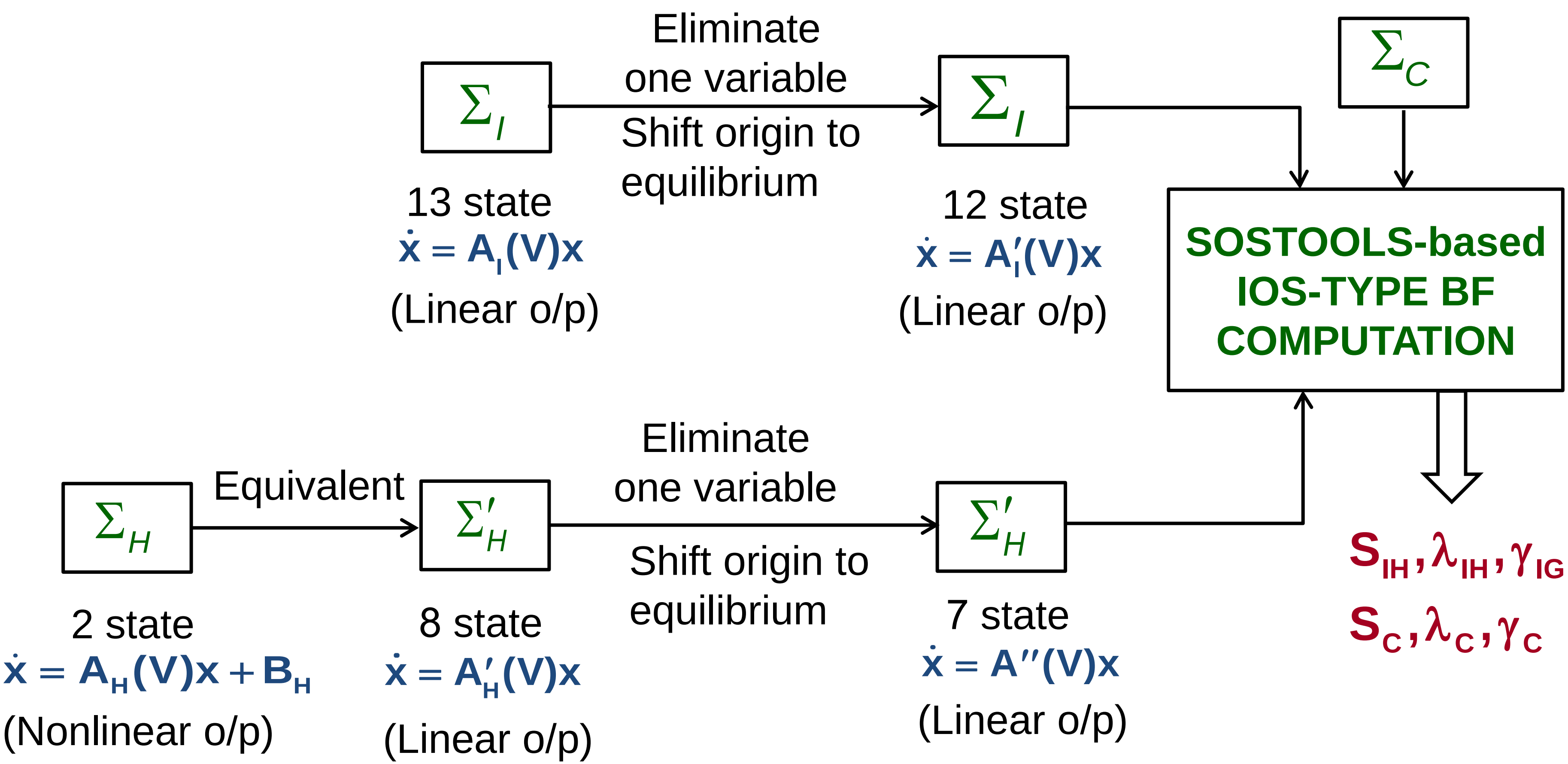






Preprocessing of Σ_I and Σ_H



Equivalent Model of Σ_H

- Output of Σ_H is nonlinear
- Higher degree in output leads to higher degree in BF
- Time complexity increases with degree of BF
- Σ'_H is voltage-controlled counting CTMC with linear output
- Computing BF based on Σ'_H is more time efficient

Σ_H : **Output :** $O = m^3 h$

$$\dot{m} = \alpha_m(V)(1-m) - \beta_m(V)m$$

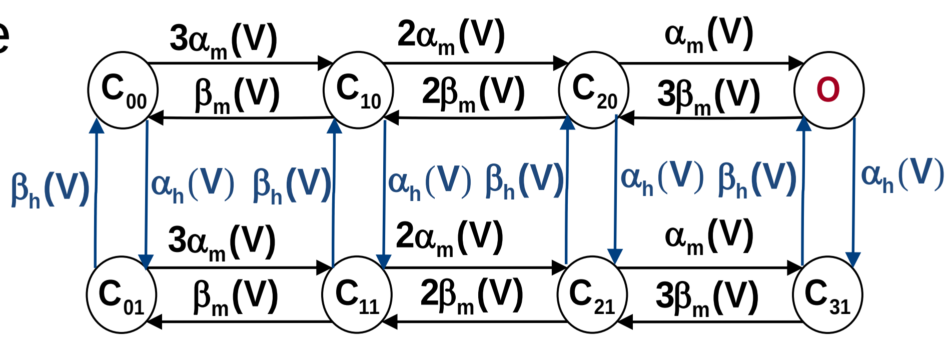
$$\dot{h} = \alpha_h(V)(1-h) - \beta_h(V)h$$

⇕ Equivalent Model (invariant manifold)

Σ'_H : **Output :** O

$$\dot{x}'_H = A'_H(V)x'_H,\ A'_H(V) \in \mathcal{R}^8 \times \mathcal{R}^8$$

$$x'_H = [C_{00}, C_{10}, C_{20}, O, C_{01}, C_{11}, C_{21}, C_{31}]^T$$



SoS Optimization Problem

- SoS Polynomial:

  A multivariate polynomial function $\mathbf{p(x_1, x_2, ..., x_n) = p(x)}$ is an SoS polynomial if there exists $\mathbf{f_1(x), f_2(x), ..., f_m(x)}$ such that

$$\mathbf{p(x) = \sum_{i=1}^{m} f_i^2(x) = c_1 w_1 x_1^n + c_2 w_2 x_1^{n-1} x_2 + \ldots}$$

- SoS Optimization Problem(SOSP):

$$\mathbf{\min_C c^T w}$$

  such that

  $\mathbf{p_i(x)}$ is an SoS for $\mathbf{i = 1, 2, ..., n}$

  where $\mathbf{C = [C_1, C_2, ..., C_n]^T}$, $\mathbf{C_i}$ is co-efficient vector of $\mathbf{p_i(x)}$, for $\mathbf{i = 1, 2, ..., n}$, and $\mathbf{w}$ is some given weight vector.

- SOSTOOLS:

  A Matlab toolbox to solve SoS optimization problem.

Formulation of SOSPs for S_{IH} and S_C

P_{IH} : SOSP to compute S_{IH}

P_{IH} :

$$\min_{C} C^T w$$

such that

$$S_{IH}(x_I, x_H) - (g_I(x_I) - g_H(x_H))^2 \text{ is SoS}$$

$$-(\frac{\partial S}{\partial x_I} A_I'(V_I) + \frac{\partial S}{\partial x_H} A_H''(V_H)) - \lambda_{IH} S(x_I, x_H)$$

$$+\gamma_{IH} \| V_I - V_H \| \text{ is SoS for all } (V_I, V_H)$$

P_C : SOSP to compute S_C

P_C :

$$\min_{C} C^T w$$

such that

$$S_C(x_C, x_C') - (g_C(x_C) - g_C(x_C'))^2 \text{ is SoS}$$

$$-(\frac{\partial S}{\partial x_C}(G_{Na}(x_c - V_{Na})O_I) + \frac{\partial S}{\partial x_C'}(G_{Na}(x_c' - V_{Na})O_H)) -$$

$$\lambda_C S_C(x_C, x_C') + \gamma_C \| O_I - O_H \| \text{ is SoS for all } (O_I, O_H)$$

Issues to compute BFs in SOSTOOLS

- Choosing form of BFs
- Input space quantization
- Choosing optimization function
- Handling λ and γ

Choosing Form of BFs

- First step to compute BFs in SOSTOOLS is to choose form of BFs.
- Ellipsoidal polynomial (sosvar in SOSTOOLS) form is chosen for BFs:

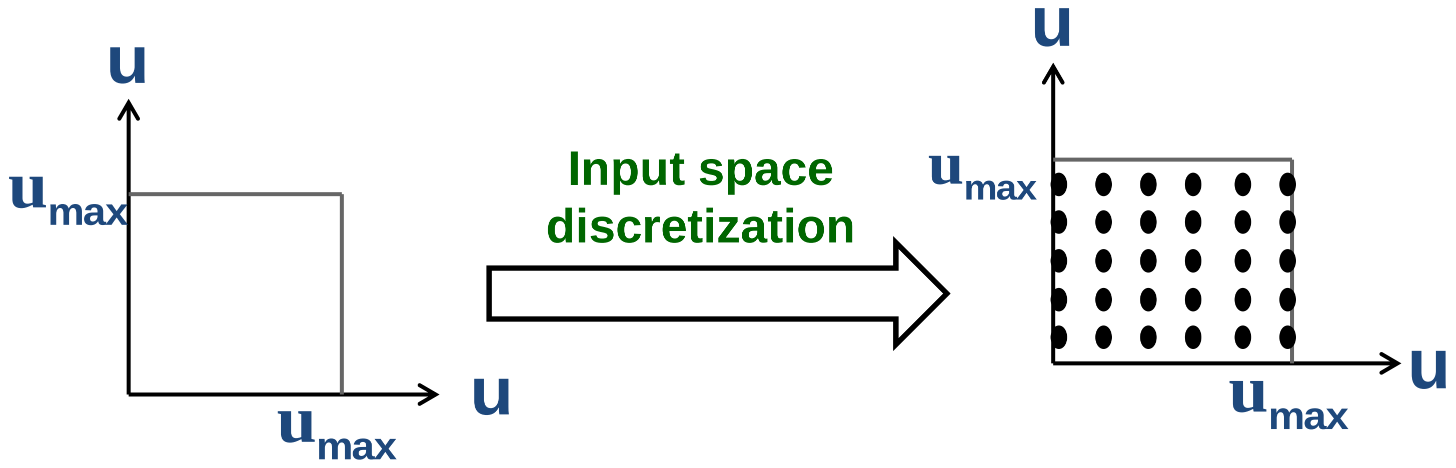
$$\mathbf{S}(\mathbf{x_1},\mathbf{x_2}) = \mathbf{z}^{\mathbf{T}}\mathbf{Q}\mathbf{z}$$

where $\mathbf{z} = [\mathbf{x_1};\mathbf{x_2}]$, $\mathbf{x_i}$, for $\mathbf{i} = \mathbf{1,2}$, is a state vector of Σ_i and $\mathbf{Q}$ is a positive semi-definitve matrix which contains the decision variables of SOSP.

- pvar toolbox is used to define polynomial variable in SOSTOOLS.

Input Space Quantization

- Second condition of BF needs to be held for all pairs of inputs.
- SOSTOOLS can not handle continuous input space.
- BFS are computed using quantized input space in SOSTOOLS.

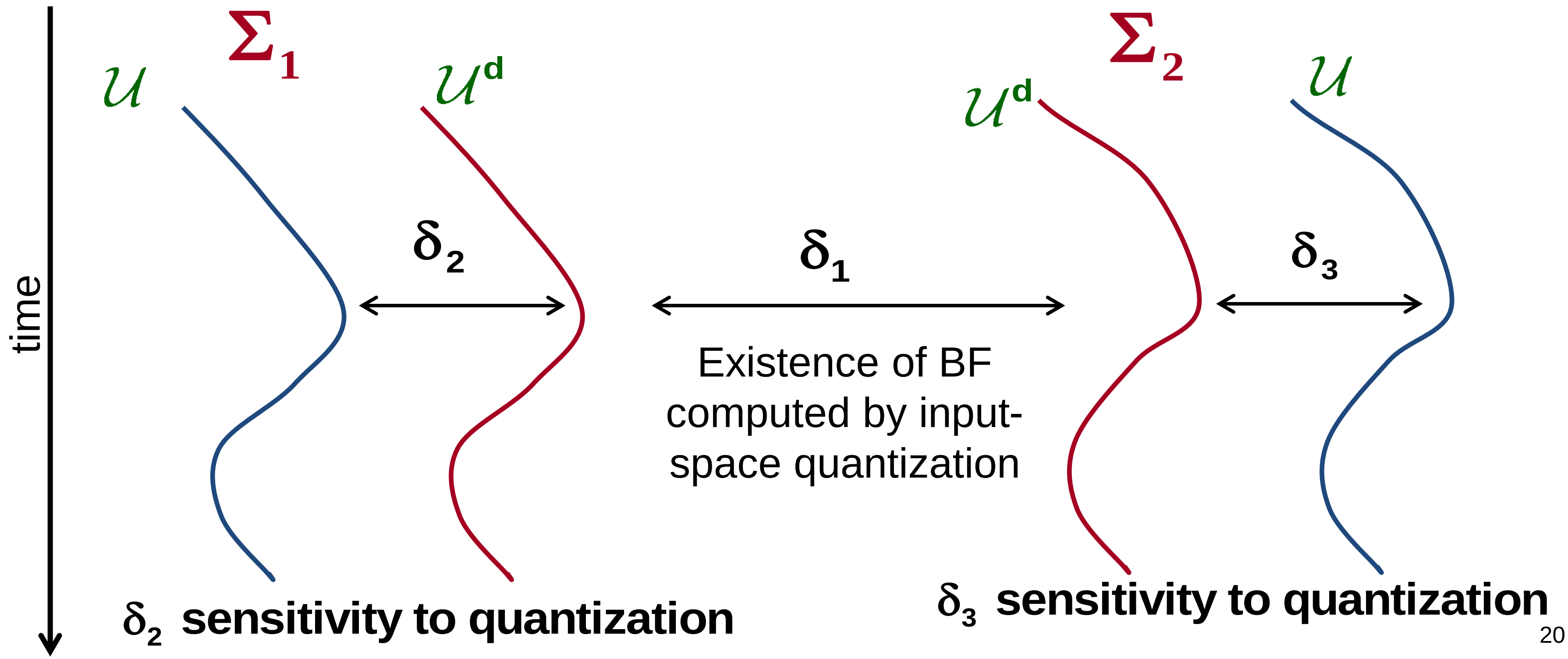


Continuous bounded input space $\mathcal{U}$

Quantized input space $\mathcal{U}^d$

Input Space Quantization Contd.

- Quantization of Input space can be justified by sensitivity analysis.
- Overall bound on output differences computed by BF due to input space quantization: $\delta_1 + \delta_2 + \delta_3$.



Choosing Optimization Functions

- BF bounds outputput differences.
- Choosing a proper objective function is critical to obtain a tight bounds on output differences.
- Theorem 1 implicates BF is maximum at initial states.
- Minimizing BF at initial states provides better bound.

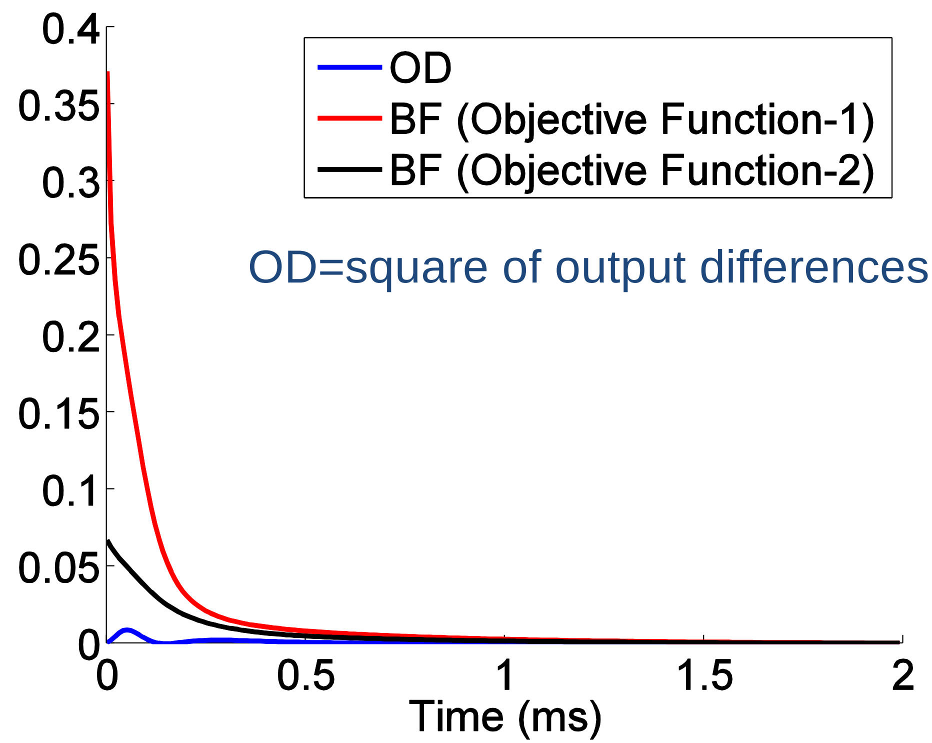


Fig. $\mathbf{S}_{IH}$ plotted along a pair of trajectories of Σ_I and Σ_H. Objective function-1: minimizes BF at all states. Objective function-2: minimizes BF only at initial states.

Handling λ and γ

- Fixed value is used for λ
- Fixed value is used for γ
- Criteria for choosing λ and γ : $\frac{\gamma_{IH}\gamma_C}{\lambda_{IH}\lambda_C} < 1$ (sgc)

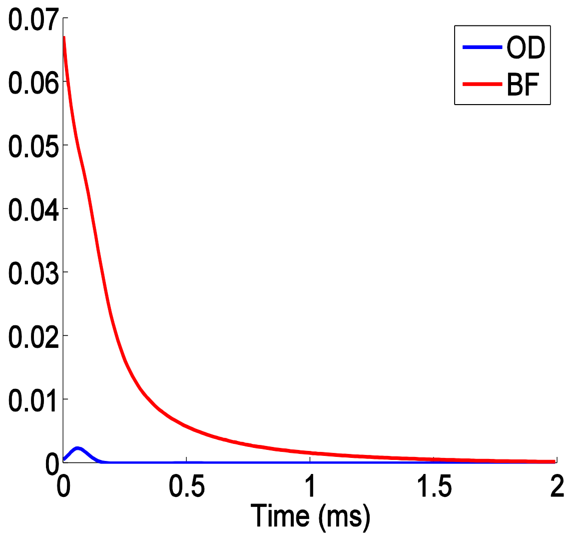
Problem	BF	λ	γ
P_{IH}	S_{IH}	$\lambda_{IH} = 0.1$	$\gamma_{IH} = 0.001$
P_C	S_C	$\lambda_C = 0.01$	$\gamma_C = 0.0001$

Table: Fixed values for λ and γ

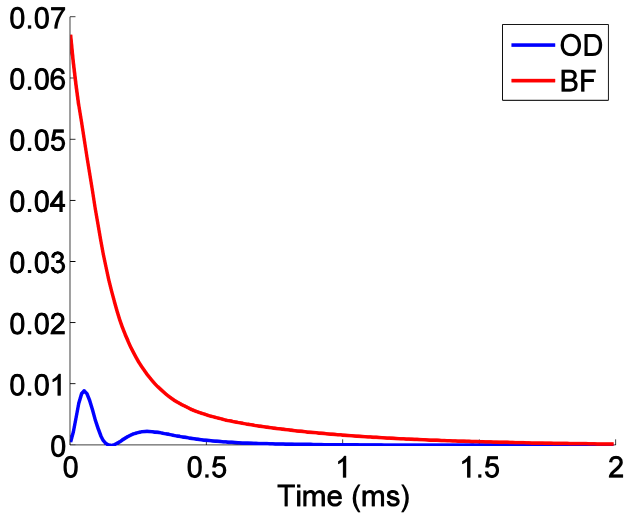
Results: BF between Two Sodium Channels

$$S_{IH} = [x_I; x_H]^T Q [x_I; x_H]$$

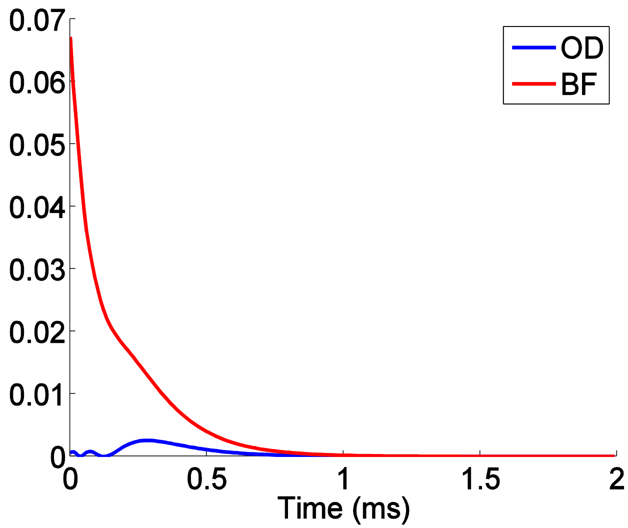
where $x_I \in \mathcal{R}^{12}_{\geq 0}$, $x_H \in \mathcal{R}^{7}_{\geq 0}$ and $Q \in \mathcal{R}^{19} \times \mathcal{R}^{19}$ is a positive semidefinitive matrix



$V_I(t) = -30mV, \; V_H(t) = -30mV$



$V_I(t) = -30mV, \; V_H(t) = 30mV$

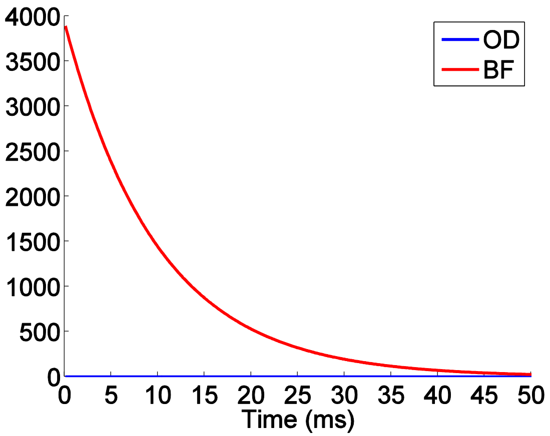


$V_I(t) = 30mV, \; V_H(t) = -30mV$

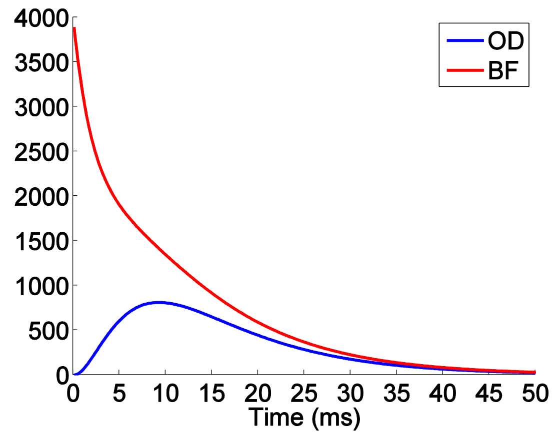
Fig. S_{IH} covers output differences and decays along two trajectories of Σ_I and Σ_H. Three pairs of trajectories are generated using three different pairs of input signals.

Results:
BF for Context

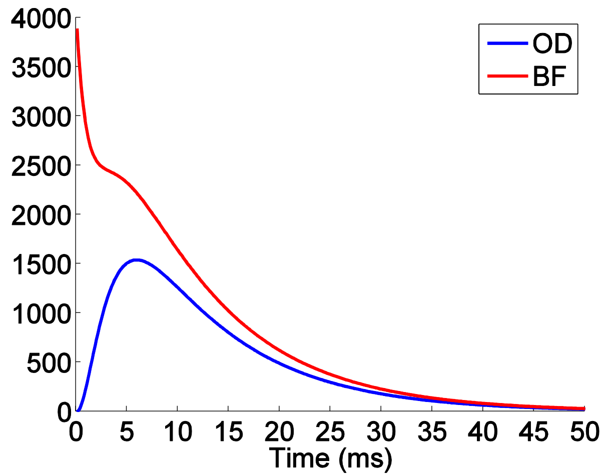
$$S_C = 1.27V_I^2 - 1.4599V_I V_H + 1.27V_H^2$$



$O_1(t) = 0.01,\ O_2(t) = 0.01$



$O_1(t) = 0.04,\ O_2(t) = 0.01$



$O_1(t) = 0.08,\ O_2(t)=0.01$

Fig. $\mathbf{S_C}$ covers output differences and decays along two trajectories of Σ_C. Three pairs of trajectories are generated using three different pairs of input signals.

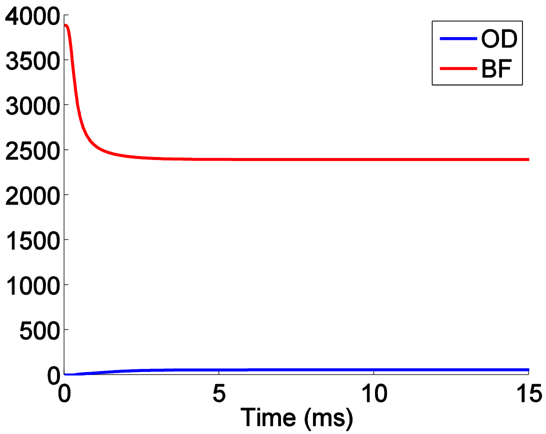
Results: BF between Two Composed Systems

$$S = \alpha_1 S_{IH} + \alpha_2 S_C$$

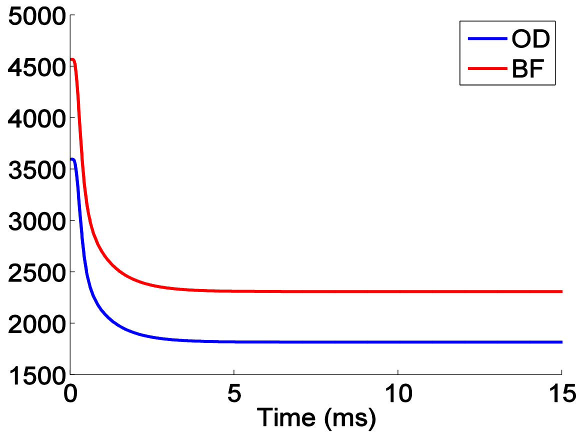
$$(\alpha_1, \alpha_2) = (1, 1)$$

$$\lambda = \min\left(\frac{\alpha_1 \lambda_{IH} - \alpha_2 \gamma_C}{\alpha_1}, \frac{\alpha_2 \gamma_C - \alpha_1 \lambda_{IH}}{\alpha_2}\right)$$

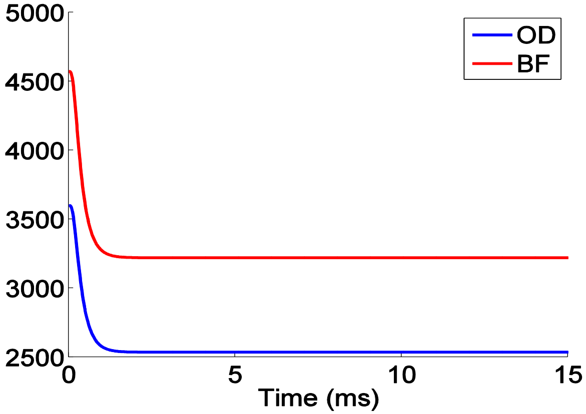
$$= 0.009$$



$V_I(0) = -30\text{mV},\ V_H(0) = -30\text{mV}$



$V_I(0) = -30\text{mV},\ V_H(0) = 30\text{mV}$



$V_I(0) = 30\text{mV},\ V_H(0) = -30\text{mV}$

Fig. **S** covers output differences and decays along two trajectories of Σ_{CI} and Σ_{CH}. Three pairs of trajectories are generated using three different pairs of input signals.

Results:
3D Visualization of BFs

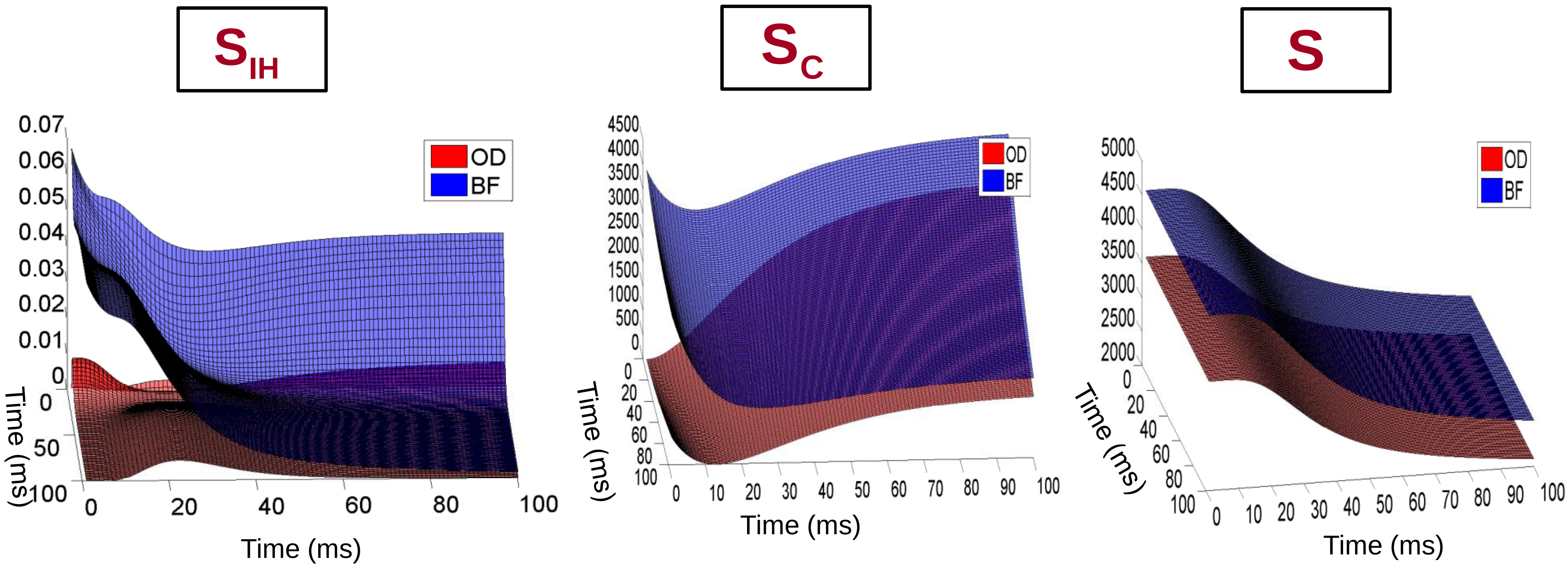
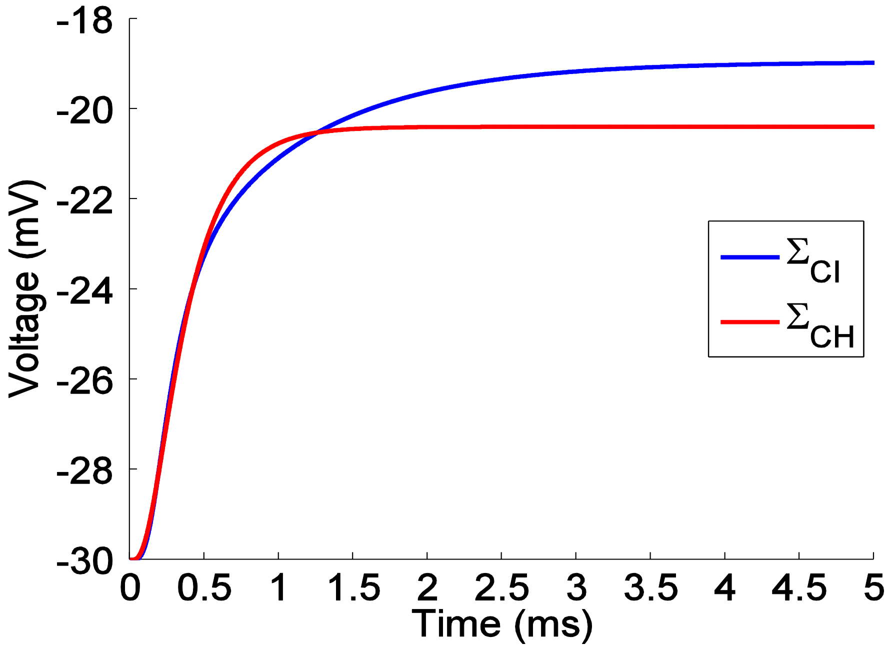


Fig. All three BFs cover the the corresponding output differences and are non-increasing at all time. BFs are plotted along the cross-product of a pair of trajectories of the corresponding systems.

Results:
Empirical Evidence of Compositionality

Voltage Comparison



Conductances Comparison

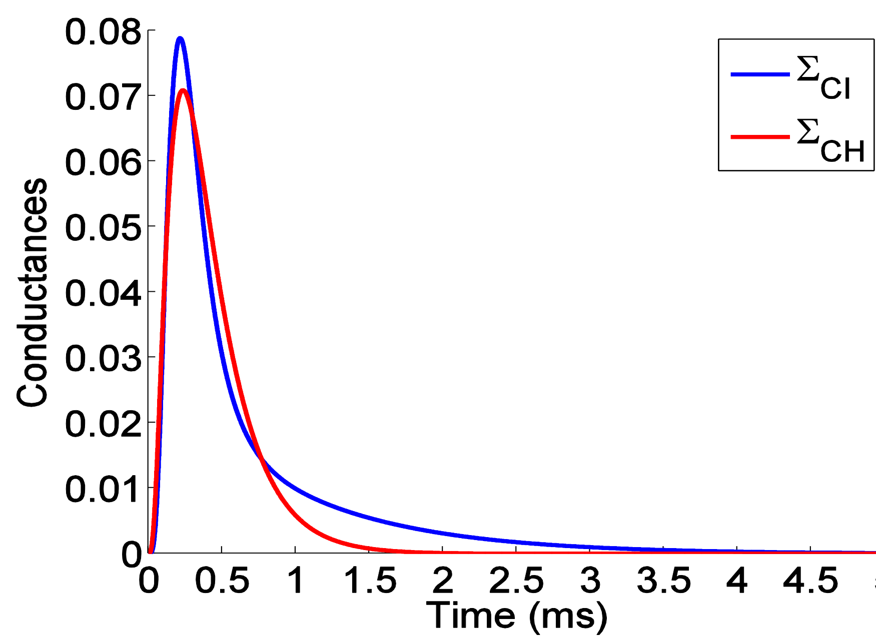


Fig. Simulation of two composed systems Σ_{CI} and Σ_{CH}. Substituition of Σ_I by Σ_H tends to accumultae error, but existence of BF between them ensures that the error is bounded. The mean **L1** error: Conductances: $\mathbf{9 \times 10^{-3}}$, Voltage: **1.42mV**

Ongoing Work

- Applying abstraction and compositional reasoning to other ionic, pump and exchanger currents on IMW model
- More effective ways of covering input spaces
- Finding a better covering of output differences
  - Restricting the domain of BFs
  - Formalization of applying scaling functions on SOSTOOLS-based BFs
- Non-dimensionalization of context for more reasonable composed BF

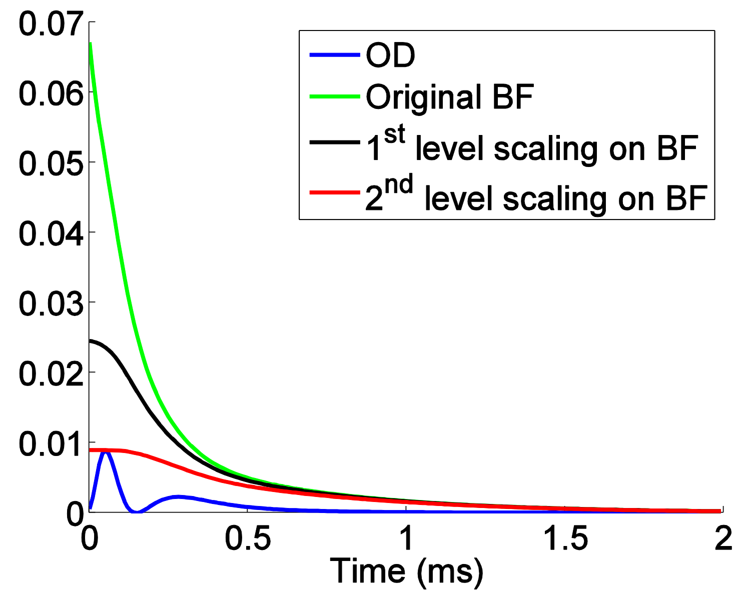


Fig. Application of exponential scaling function on $\mathbf{S}_{IH}$

Conclusions

- Cast IMW cardiac cell model as a feedback composition of sodium channel and rest of the model
- Identified approximately bisimilar 2-state HH-type abstraction for 13-state sodium channel model of IMW using curve fitting-based procedure (PEFT+RFI)
- Identified BFs using Sum-of-Square relaxation in SOSTOOLS
- Verifying small-gain theorem for cardiac cell model
- Compositionality results for cardiac cell dynamics based on BFs