**Compositionality Results for Cardiac Cell Dynamics**

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**Cardiac Cell Dynamics**

**Observables (output):** Transmembrane voltage $V$. Transmembrane ion fluxes $I_{Na}$ and $I_{K}$. Electrical signal $S(t)$.

**Input:** Transmembrane electrical stimulation. Ion concentrations $Na^{+}$ and $K^{+}$.

**Model:**

- **Immunnochemical Model (IMW Model):** 13-state sodium and 10-state potassium channel models.
- **Hybrid Automata:** Kripke structures, etc.
- **JSR NSR:** Intermediate Model(s).

**Mathematical Modeling:**

- **Formal Analysis:** Automated exhaustive exploration of state/parameter space.
- **Model Checking:** (MC) Abstract Interpretation (AI), Parameter Estimation.

**Simulation:**

- **Intermediate Model(s):** Evaluated via Refinement (RA).

**Summary:**

- **Sodium Channel:** $I_{Na}$ current, responsible for the AP.
- **Potassium Channel:** $I_{K}$ current, responsible for repolarization.
- **AP:** Endowed by $I_{Na}$, followed by $I_{K}$.

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**Compositionality with Feedback**

Ion-channel component-models are composed with the rest of the cardiac cell model using feedback.

**Small-Gain Theorem for Composing Bifurcation Functions (BFs)**

BFs computed in SOSTOOLS [5] using sum-of-squares relaxations and input space sampling:

1. $S(x_1, x_2) = \|g_1(x_1) - g_2(x_2)\|$ is an SOS polynomial.
2. $\sum_{i=1}^{n} f_i(x_1, x_2) = -\sum_{i=1}^{n} f_i(x_1, x_2) + \|u_1(t) - u_2(t)\|$ is an SOS polynomial. Satisfy constraint at finite $(u_1, u_2)$ pairs that cover the input space.

**Conclusions and Ongoing Work**

- Voltage clamp simulation-based procedure used for model-order reduction of ion-channel models $M_{Na}$ and $M_{K}$ to obtain approximate bisimilar HH-type abstractions $M_{Na'}$ and $M_{K'}$.
- Ion-channel component composed with rest of IMW model using feedback.
- BFs capture input-output stability. Small-gain theorem used to prove compositionality.
- Computed BFs in SOSTOOLS toolbox using sum-of-squares relaxation for simplified neuron-like models.
- Bounded error due to input space sampling.
- Implement model-order reduction and prove compositionality for whole-cell models.

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**References**


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**Simulation Results showing the stability of model-order-reduced ion-channel components within the IMW model.**

**Mean L1 errors $V$: 2.29 mV, conductance: 9.15 pA/pF.**

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**Cardiac Cell Dynamics (a): Transmembrane ion-channel mechanisms and currents in the IMW model. (b): Typical AP (output) produced by the IMW model.**

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**Biological experiments**

- Formal Analysis → Automated exhaustive exploration of state/parameter space
- Model Checking (MC) Abstract Interpretation (AI), Parameter Estimation.

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**Towers of Abstraction** for insightful analysis of cardiac models. Compositionality of model-order reduced components with the rest of the model makes the layers sound.