Towers of Abstraction for Insightful Analysis of Cardiac Models

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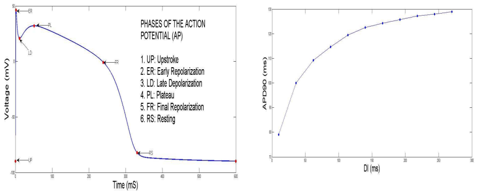
NSF Expeditions in Computing



a. b.

a. Action Potential (AP) – Response of an excitable cell. b. Restitution Curve (RC)showing refractory properties, APD: Action Potential Duration, DI: Diastolic Interval

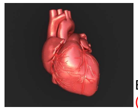
Computational Model
Linear Hybrid Automata (LHA) [6], Kripke structure, etc.

Formal Analysis

Model Checking (MC), Abstract Interpretation (AI), Parameter Estimation.

Qualitative/ Quantitative Insights (Abstract parameter and state-space)

Abstraction, Linearization, handling under-determination, Pre-processing, etc.



Modeling

Biological Phenomenon
(Cardiac excitation: AP and RC)

$$\frac{dx_i}{dt} = f_i(t, x_1(t), x_2(t) .. x_i(t) .... x_n(t))$$

Mathematical Model
(Possibly Non-linear)

Minimal Model
Variables: 4
Parameters: 27

Tuscher-Noble-Panfilov-03
Variables: 17
Parameters: 44

Iyer Model
Variables: 67
Parameters: 94

Systematic Refinement

Abstraction

Tower of Abstraction for Cardiac Models

Intermediate Models

Physiological Insights
- Root-cause detection
- Personalized treatment
- Pharmacology

Towers of Abstraction [1]

Starting from large intricate models, series of principled approximations/abstractions leading to reduced models at different scales.

Cardiac Models

The Minimal Model [3]

- Scaled membrane potential – u
- Abstract currents: fast inward (J_{fi}), slow outward (J_{so}), slow inward (J_{si})
- Scalable formal analysis – post linearization [6]

$$\dot{u} = \nabla(\tilde{D}\nabla u) - (J_{fi} + J_{so} + J_{si}), \quad \dot{v} = \frac{(1-H(u-\theta_v))(v_\infty - v)}{\tau_v^-} - \frac{H(u-\theta_v)v}{\tau_v^+}$$

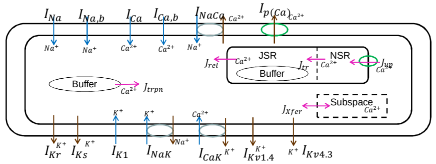
$$J_{fi} = -vH(u-\theta_v)(u-\theta_v)(u_u - u)/\tau_{fi}$$

$$\tau_v^- = (1 - H(u-\theta_v^-)\tau_{v1}^- + H(u-\theta_v^-)\tau_{v2}^-, \quad v_\infty = \begin{cases} 1 & u < \theta_v^- \\ 0 & u \geq \theta_v^- \end{cases}$$

The Iyer Model [2]

- Change in membrane potential V: sum of physiological currents due to ion-flows across membrane

$$\frac{dV}{dt} = -(I_{Na} + I_{Ca} + I_{CaK} + I_{Kr} + I_{Ks} + I_{K1} + I_{NaCa} + I_{NaK} + I_{Kv1.4} + I_{Kv4.3} + I_{p(Ca)} + I_{Cab} + I_{Nab} + I_{stim})$$



Trans-membrane currents modeled by the Iyer model. Green circles: Ionic pumps, Blue circles: exchangers, single arrows: ionic channels.

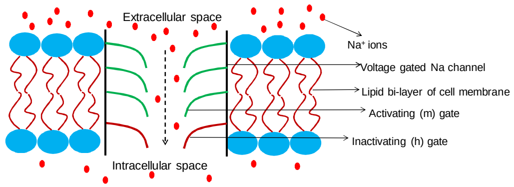
Abstraction for Upstroke Phase of the AP

Dominant current: Minimal model. J_{fi} Abstract model: Sigmoidal switching

↑

Dominant current: Iyer model. I_{Na} Physiological model: Parametric CTMC

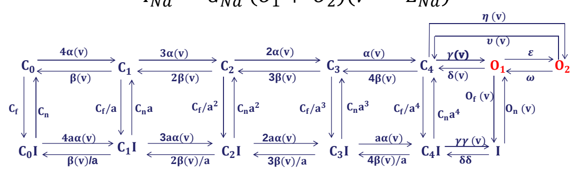
Fast Inward Sodium (Na+) Current



Upstroke Phase of the AP: Influx of Na+ ions through a voltage gated channel - I_{Na} current.

Abstracting I_{Na} Current of the Iyer Model

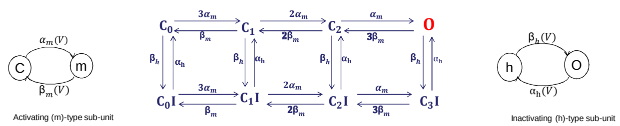
$$I_{Na} = \overline{G_{Na}}(O_1 + O_2)(V - E_{Na})$$



Channel gating modeled as a 13-state parametric CTMC. Scaling factor – a: dependence between m and h-type gates.

Abstraction: Conditional Independence.

Hodgkin-Huxley (HH) Type Sodium Channel [4]
- independence between activation and inactivation gates.
- Least-Squares (Neldar-Mead) fitting with randomized seeding.



8-state parametric CTMC abstraction, based on Hodgkin-Huxley model [4]. State O: open state, all three m gates are open and the h gate is closed.

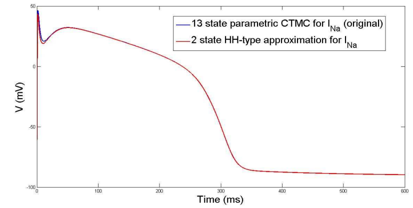
Abstraction: Stable Invariant Manifolds (Exact).

Invariant Manifold Reductions [5]
Multinomial distribution is an exact solution for the 8-state parametric CTMC.

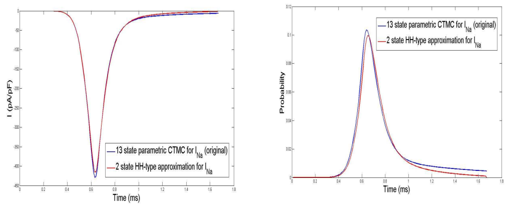
$$\frac{dm}{dt} = \alpha_m(1-m) - \beta_m m, \quad \frac{dh}{dt} = \alpha_h(1-h) - \beta_h h$$

$$O(t) = \{m(t)\}^3 h(t)$$

Results



APs generated by the original Iyer model and the reduced version, where the 2-state abstraction has replaced the 13-state I_{Na} parametric CTMC.



Internals of the upstroke phase of the two APs: (a.) Dominant current I_{Na} (b.) gating probability $(O_1 + O_2)$ for the 13-state CTMC and m^3h for the 2-state abstraction.

Conclusions and Future Work

- Reduction achieved for I_{Na} current: 13-states to 2 states
- Abstraction techniques: conditional independence + invariant manifolds
- Approximate-bisimulation-based reduction
- Extending work to other phases of the AP

REFERENCES

1. J. Fisher, David Harel and Thomas Henzinger, Biology as Reactivity, Communications of the ACM, October 2011.
2. V. Iyer, Reza Mazhari and Raimond Winslow. A Computational Model of the Human Left-Ventricular Epicardial Myocyte. Biophys. Journal 2004.
3. A. Bueno-Orovio, M.E. Cherry and F.H. Fenton. Minimal Model for Human Ventricular Potentials in Tissue. Journal of Theoretical Biology 2008.
4. A.L. Hodgkin and A.F. Huxley. A Quantitative Description of Membrane Current and its Application to Conduction and Excitation in nerve. Journal of Physiology 1952.
5. J. Keener. Invariant manifold reductions for Markovian Ion Channel Dynamics. Journal of Math. Biology 2009.
6. R. Grosu et. al. From Cardiac Cells to Genetic Regulatory Networks. CAV 2011.

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