Massachusetts
Institute of
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Learning Cycle-Linear Hybrid Automata for Excitable Cells

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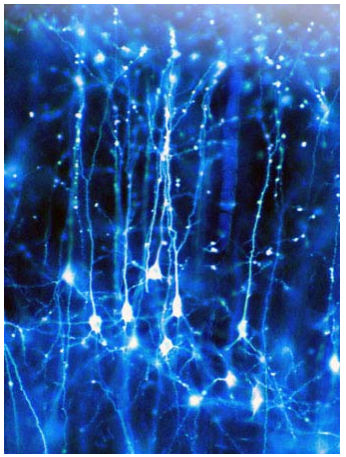
HSCC 2007
Pisa, Italy

Outline

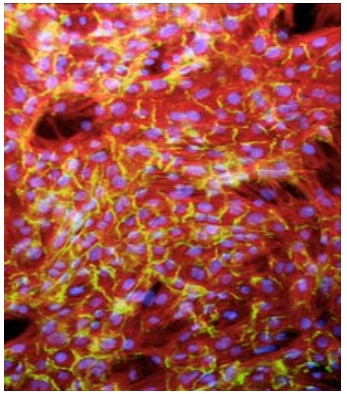
- Excitable cells
- Hybrid model for excitable cells
- Conclusions and future directions

Excitable Cells

- An excitable cell generates electrical pulses or *action potentials* in ***response*** to electrical stimulation
  - Examples: neurons, cardiac cells, smooth muscle cells
- Local regeneration allows electric signal propagation without damping
- Building block for electrical signaling in brain, heart, and muscles



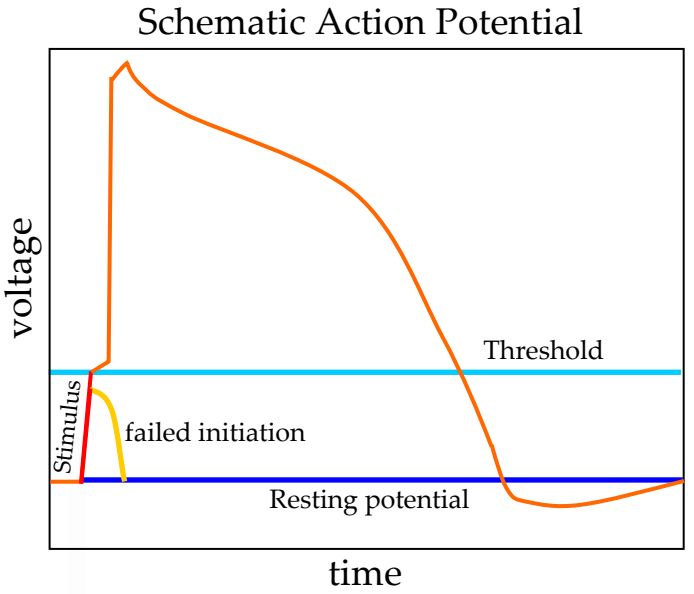
Neurons of a squirrel
University College London

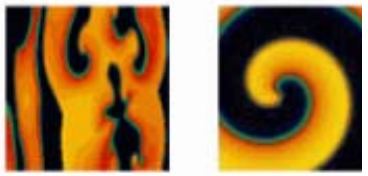


Artificial cardiac tissue
University of Washington

Interaction of Excitable Cells

- Action Potential (AP) depends on stimulus, membrane voltage of neighboring cells, state of cell itself
- Normal: *synchronous pulses*, spiral waves
- Abnormal: *incoherent pulses*, wave breakup
  - Leads to cardiac arrhythmia, epilepsy



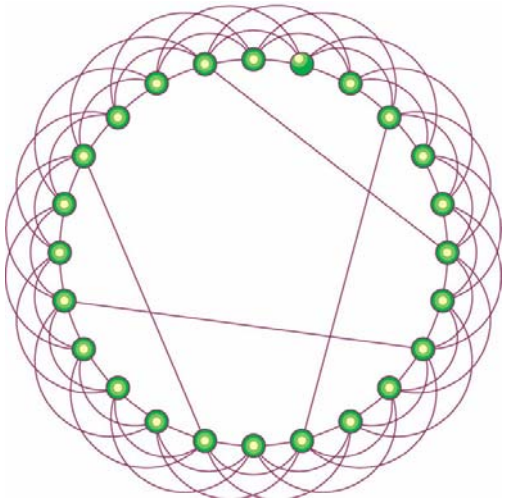


Macro Models of Action Potentials

- Cellular automata
- Oscillators and uniform coupling between cells [Kuramoto`84]
- Small-world network of coupled oscillators [Watts & Strogatz`98]

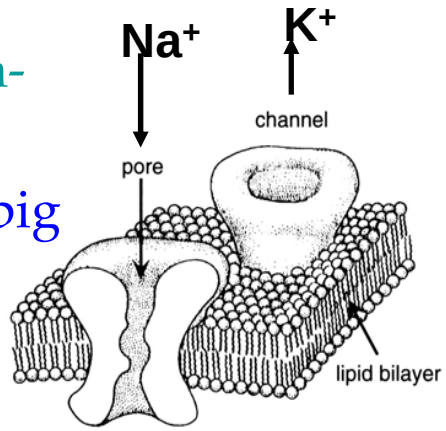
$$\frac{\partial \theta_i}{\partial t} = \omega_i + \frac{K}{N}\sum_{j=1}^{N}\sin(\theta_j - \theta_i)$$

$$i = 1 \ldots N$$



Micro Models for Action Potentials

- Membrane potential for squid giant axon [Hodgkin-Huxley`52]
- Luo-Rudy model (1991) for cardiac cells of guinea pig
- Neo-Natal Rat (NNR) model for cardiac cells of rat



$$C\dot{V} = \bar{g}_{Na}\, m^3 h\, (V_{Na} - V) + \bar{g}_K\, n^4\, (V_K - V) + g_L (V_L - V) + I_{st}$$

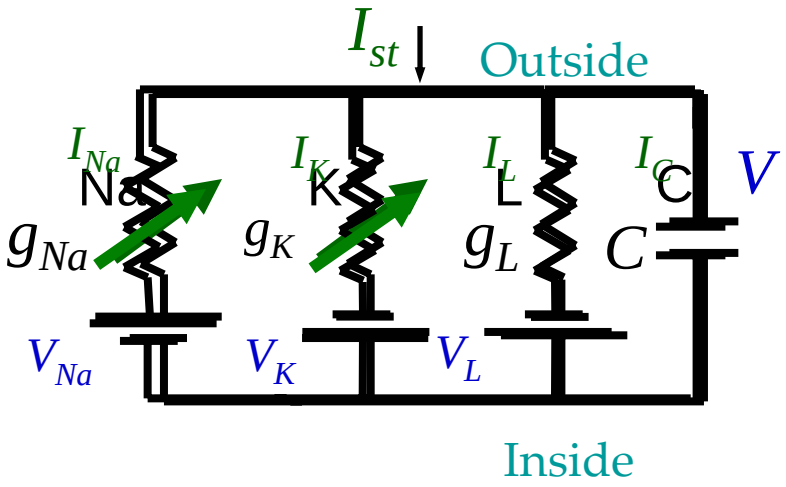
$$\dot{m} = -(\alpha_m + \beta_m)m + \alpha_m \qquad \alpha_m(V) = \frac{(2.5 - 0.1\,V)}{e^{2.5-0.1\,V} - 1}$$

$$\dot{h} = -(\alpha_h + \beta_h)h + \alpha_h \qquad \beta_m(V) = 4e^{-\frac{V}{18}}$$

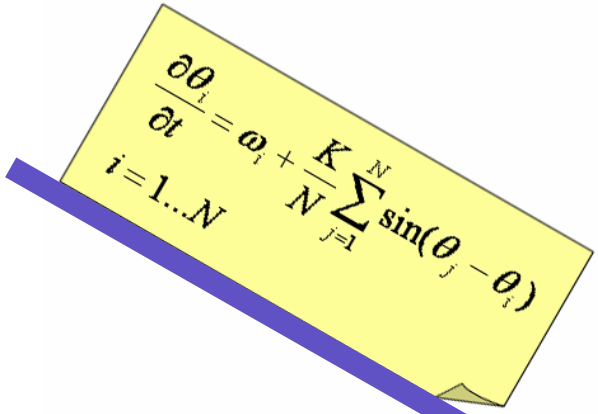
$$\dot{n} = -(\alpha_n + \beta_n)n + \alpha_n \qquad \alpha_n(V) = \frac{(0.1 - 0.01\,V)}{e^{1-0.1\,V} - 1}$$

$$\alpha_h(V) = 0.07\, e^{-\frac{V}{20}} \qquad \beta_n(V) = 0.125 e^{-\frac{V}{80}}$$

$$\beta_h(V) = \frac{1}{e^{3-0.1\,V} + 1}$$



- Large state-space
- Nonlinear differential equations
- Multiple spatial and temporal scales

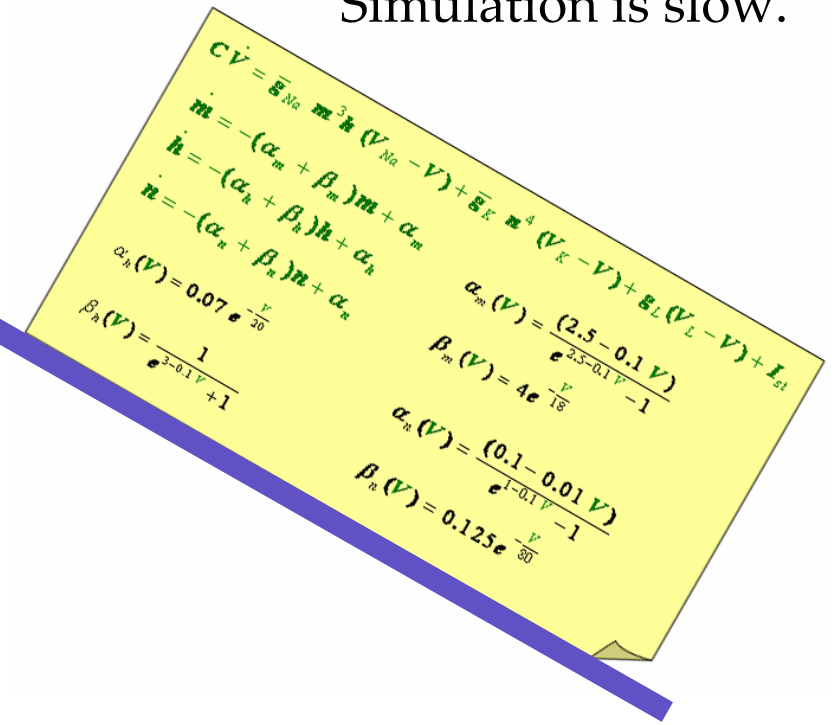


Macro

Analyzable but unrealistic

Micro

Realistic, but not analyzable.
Simulation is slow.



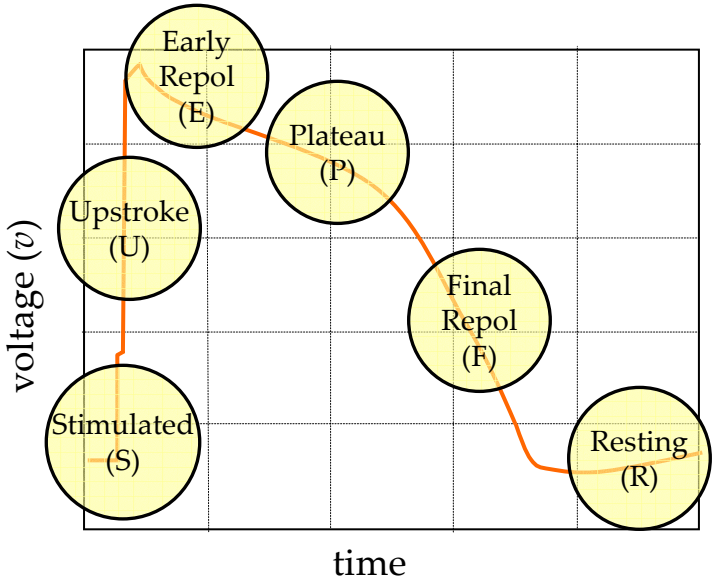
Linear Hybrid Approximations for Action Potentials

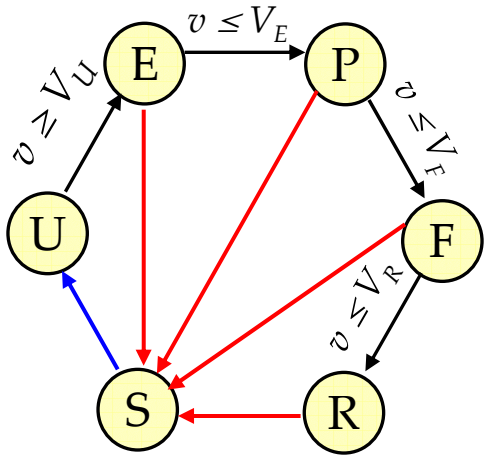
- **Suppose**, AP can be partitioned into modes so that in mode M, v can be approximated by:

$$\dot{x}_i = b_{Mi} x_i$$

$$v = \sum_i x_i, \; M \in \{S,U,E,P,F,R\}$$

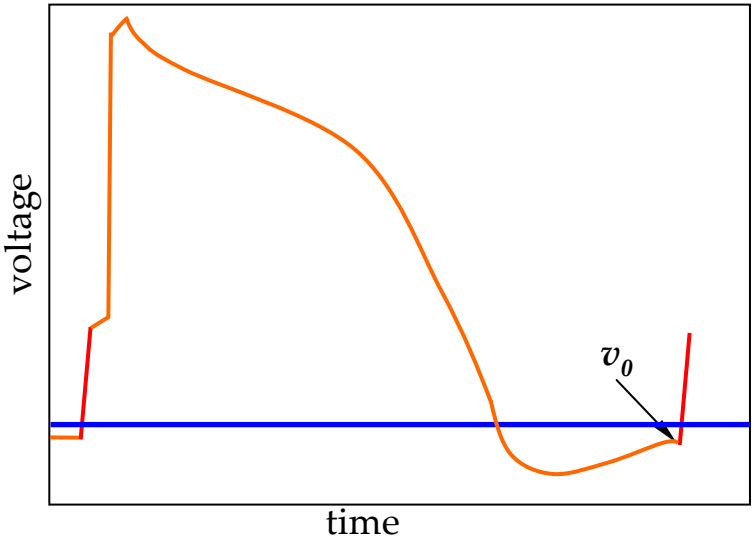
- b_{Mi}'s can be found by Prony's method which fits sum of exponentials to data
- Mode switches
  - at the beginning and end of stimulus
  - when v crosses threshold voltages V_M
- **But**, stimulus can appear at any M
  - State of cell at the time of arrival of stimulus influences behavior of cell for the next AP
  - b_{Mi}'s history dependent

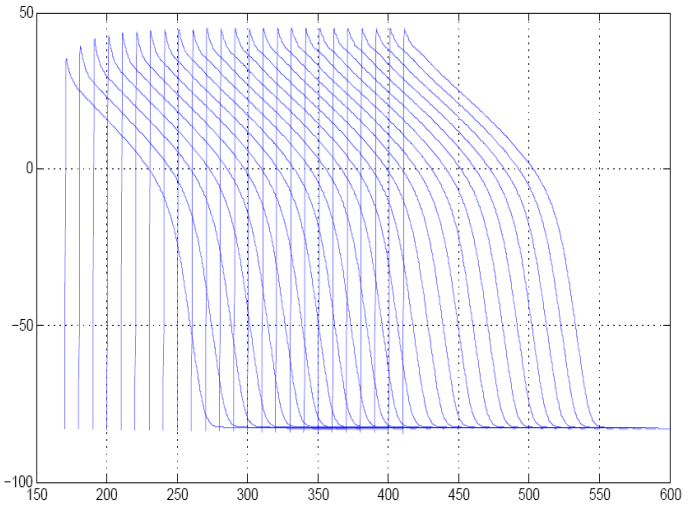




History Dependence of APs

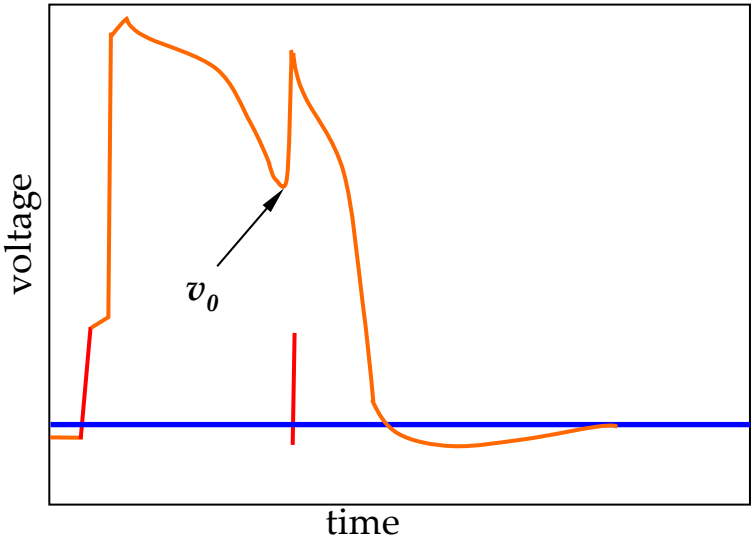
- Frequency of stimulation determines voltage (v_0) at the time of appearance of stimulus, which influences shape of next AP
- Lower frequency: longer *resting time* and v_0 closer to *resting voltage* results in *longer AP*
- Higher frequency: *shorter AP*

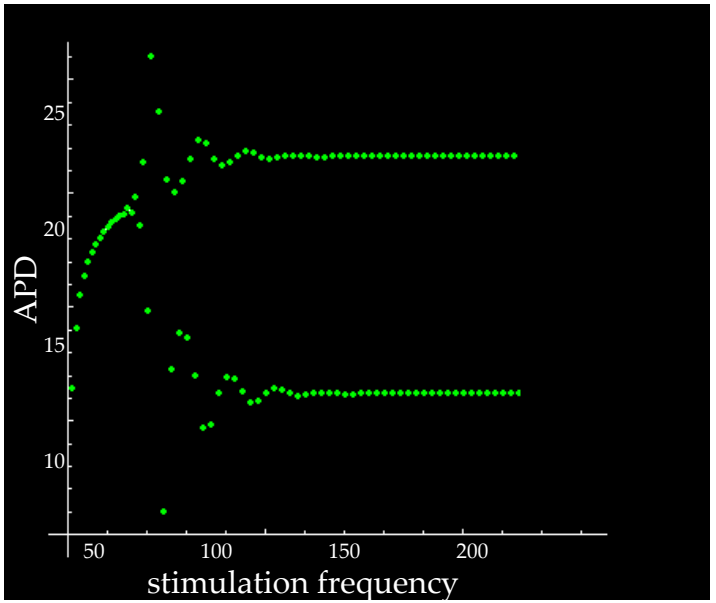




History Dependence of APs

- Frequency of stimulation determines voltage (v_0) at the time of appearance of stimulus, which influences shape of next AP
- Even higher frequency: conjoined AP, bifurcation

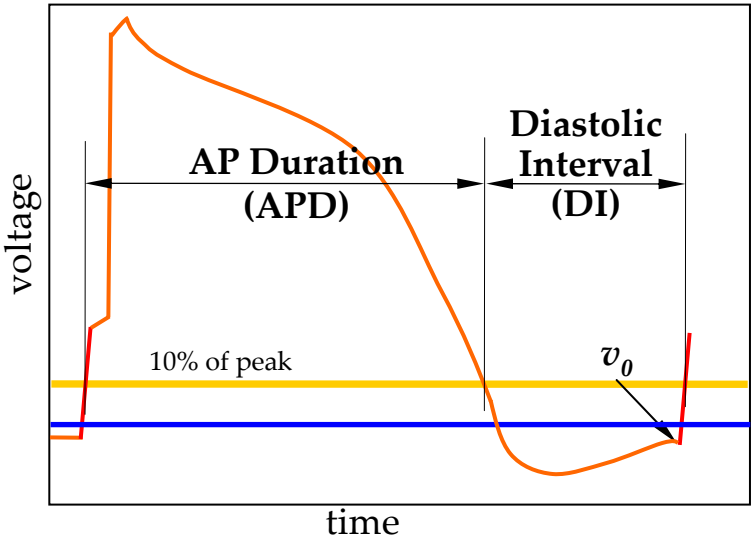


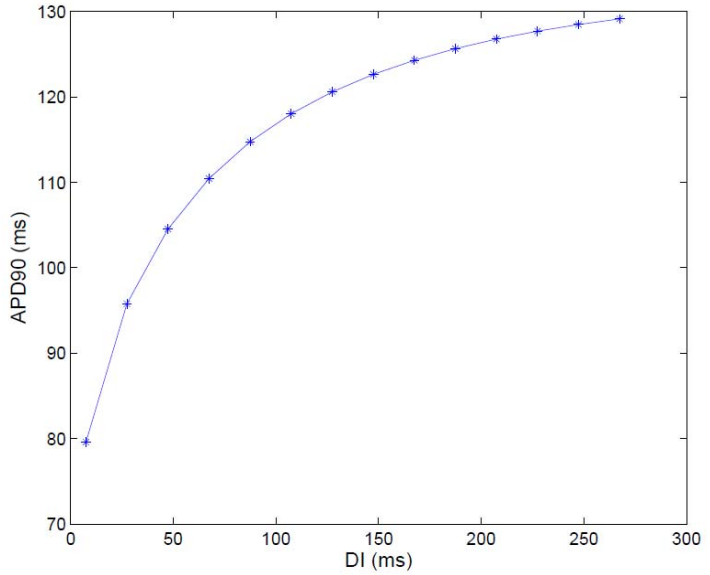


History Dependence and Restitution

- Frequency of stimulation determines voltage (v_0) at the time of appearance of stimulus, which influences shape of next AP

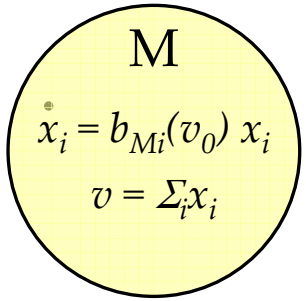
- *Restitution curve:* APD vs. DI
  - Slope > 1 indicates breakup of spiral waves under high frequency stimulation
  - Local to global behavior



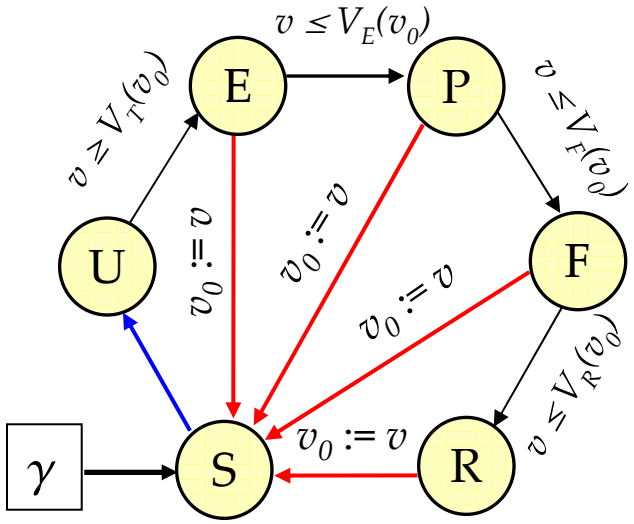


Cycle Linear Hybrid Automata (CLHA)

- Uncountable family of modes
  - $\mathcal{M} = \mathcal{E} \times \mathcal{R}$: *Epoch* and *Regime*
    - $(\mathcal{R}, <)$ is a total order
- Linear dynamics in each mode
- Unique $\gamma \in \mathcal{R}$ that is visited infinitely many times
- There exists a *snapshot function* $\mathcal{S}$: X$\longrightarrow \mathcal{E}$, such that for any switch
  $(x_1, \epsilon_1, r_1) \longrightarrow (x_2, \epsilon_2, r_2)$
  (i) $r_2 = \gamma$ and $\epsilon_2 = \mathcal{S}(x_1)$, or
  (ii) $r_2 \neq \gamma$, $\epsilon_2 = \epsilon_1$ and $r_2 < r_1$
- $\mathcal{R}$ = {S,U,E,P,F,R}
  $\mathcal{E}$ determined by v_0



M ϵ {S,U,E,P,F,R}



Identifying CLHA Parameters for a single AP

For each mode, we seek a solution for LTI:

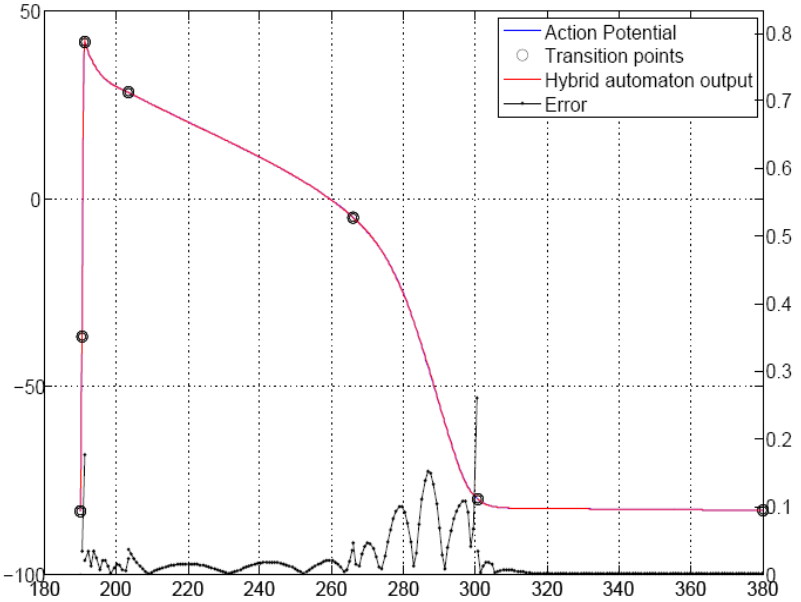
$$\dot{x} = bx, \quad x(0) = a,$$

$$b = diag(b_1, ..., b_n), \quad a = [a_1 ... a_n]^T$$

$$v = \sum_{i=1}^{n} x_i$$

Observable solution is a sum of exponentials:

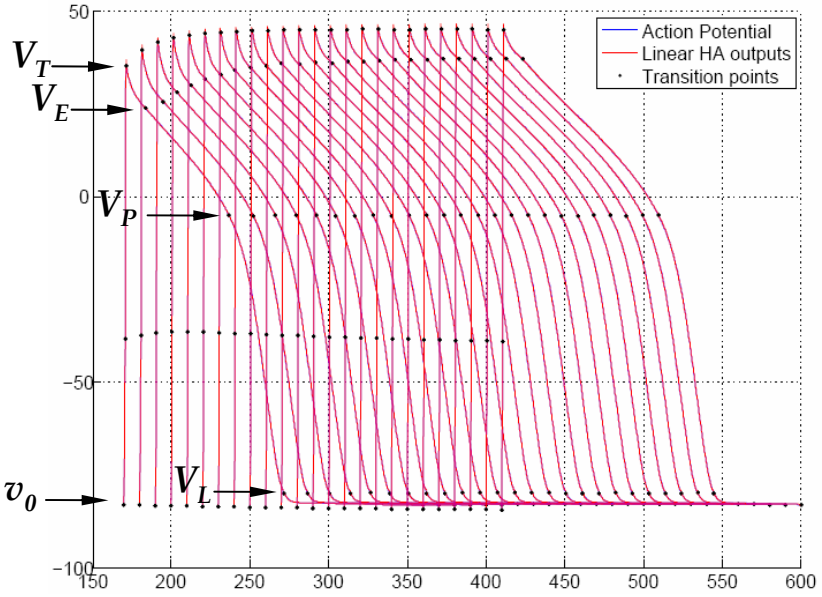
$$v = \sum_{i=1}^{n} a_i e^{b_i t}$$

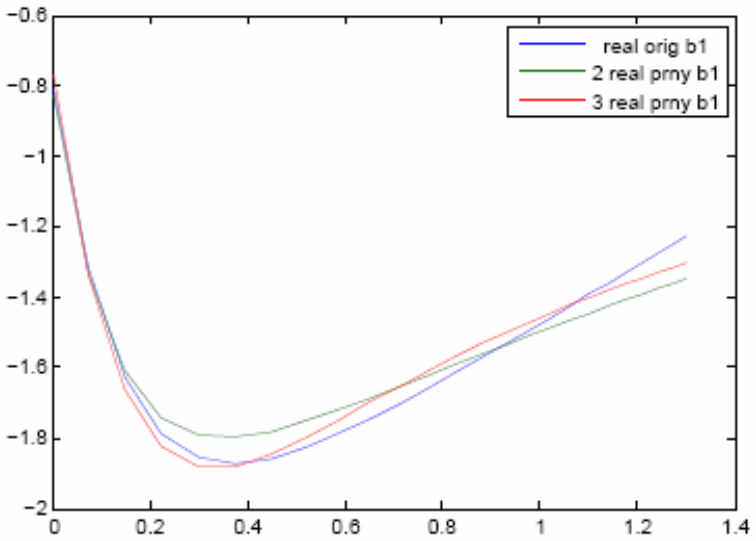


- **Curve segments are Convex, concave or both**
- **Consequences:**
  - **Solutions: might require at least two exponentials**
  - **Coefficients a_i and b_i: positive/negative or real/complex**
- **Exponential fitting: Modified Prony's method [Osborne and Smyth `95]**

Parameters as Functions of History Variable

- Parameters:
  - Threshold voltages V_S, V_E, …
  - Coefficients of differential equations b_{S1}, b_{S2}, b_{E1}, …
  - Coefficients in reset maps
- From each stimulation frequency in the training set, we get a corresponding value for b_{S1}, b_{S2}, …, V_S, V_E, …
- Apply Prony's method (a second time) to obtain b_{S1} as a function of v_0 :
  - $b_{M1}(v_0) = c_{M1}\, exp\,(v_0\, d_{M1}) + c'_{M1}\, exp\,(v_0\, d'_{M1})$, for each M ϵ {S,U,E,P,F,R}
  - $V_T(v_0) = c_T\, exp\,(v_0\, d_T) + c'_T\, exp\,(v_0\, d'_T)$

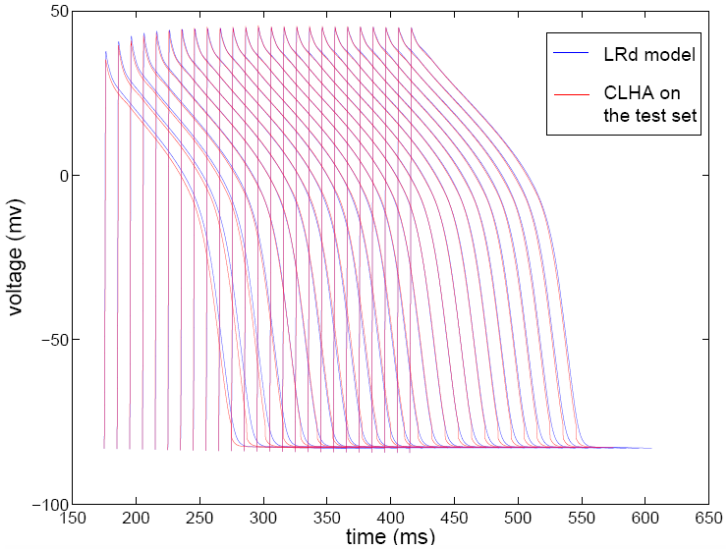


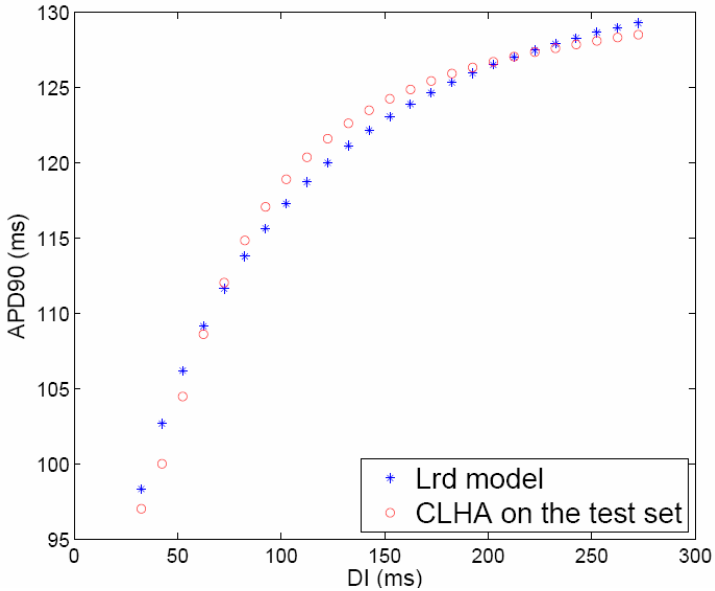


Contributions and Simulation Results

- CLHA as a model for almost periodic systems
- Iterative process to obtain excitable cell model with desired accuracy
- Simulation efficiency (> 8 times faster)

  [True, Entcheva, et al.]
- Biological interpretation of state variables x_1, x_2; restitution curve
- Spiral wave generation and breakup





Spiral waves

Breakup

Future Directions

- CLHA for stimulation with different shapes
- CLHAs coupled through---pulses or diffusion---for analyzing synchronization conditions
- Specification of spatiotemporal voltage patterns
- Distributed control through targeted stimulation