Integrated Modeling of Signal Transduction and Electro-Physiology

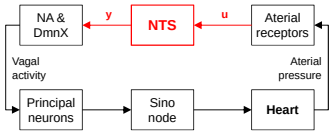
Dirk Fey*, Rajanikanth Vadigepalli†, Eric Bullinger*, Thomas Sauter§, James Schwaber†

* Hamilton Institute, National University Ireland Maynooth, dirk.fey@nuim.ie

† DBI, Thomas Jefferson University, Philadelphia; § ISYS, University Stuttgart, Germany

Introduction

Blood pressure control…



Nucleous Tractus Solitaris (NTS)…

- Input to output: Physiological transfer function?

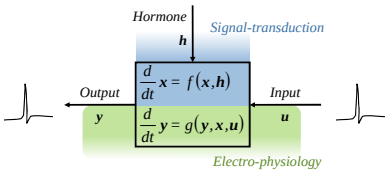
⇒Hodgkin-Huxley model of Electro-physiology.

Adaptive processes of neurons in the NTS…

- ***Electro-physiology*** *(ms)*
- ***Signal-transduction*** *(s to min)*
- Gene-regulation *(h)*

Aim

Integrated NTS model of neuronal adaptation…



How do hormones influence the signal processing of NTS neurons?

Model integration

Link of signal transduction & electro-physiology…

Modulation of maximal K_{DR} conductance upon phosphorylation by PKC and CaMK II

$$Kv + 4PKC \xrightarrow{k_1} Kv^1 + 4PKC \qquad Kv^1 \xrightarrow{k_{-1}} Kv$$
$$Kv + 4CaMKII \xrightarrow{k_2} Kv^2 + 4CaMKII \qquad Kv^2 \xrightarrow{k_{-2}} Kv$$
$$Kv^1 + 4CaMKII \xrightarrow{k_2} Kv^{1,2} + 4CaMKII \qquad Kv^{1,2} \xrightarrow{k_{-2}} Kv^1$$
$$Kv^2 + 4PKC \xrightarrow{k_1} Kv^{1,2} + 4PKC \qquad Kv^{1,2} \xrightarrow{k_{-1}} Kv^2$$

$$g_{KDR} = g^0_{KDR} Kv + g^1_{KDR} Kv^1 + g^2_{KDR} Kv^2 + g^{1,2}_{KDR} Kv^{1,2}$$

Important Issues…

- V-dependency in signaling ✓
- Cell-size: Transport rates & ionic currents ✓
- Ca^{2+} dynamics: Membrane & intracellular?
- Phosphorylation model: Parameters?

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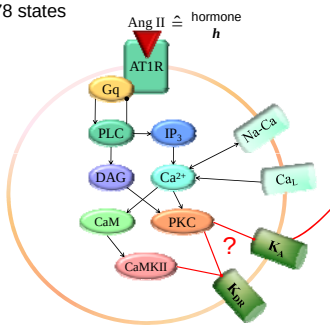
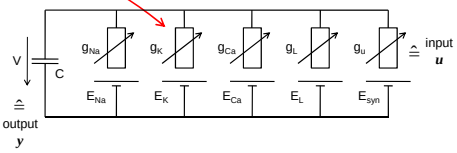
Hormone & **signal-transduction** model
⇒ 178 states



Firing behavior & **electro-physiology** model
⇒ 10 states

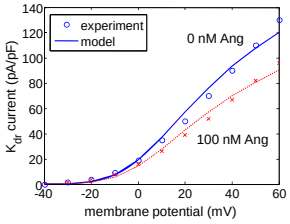
$$C\frac{d}{dt}V = \sum g_i m_i^{M_i} h_i^{H_i} (E_i - V)$$
$$\vdots$$



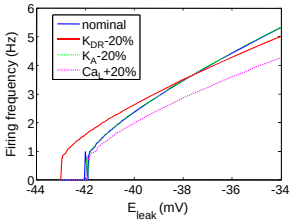
Tuning, Analysis and Simulation

Ang II effect on conductances…

Changing the K_{DR} maximal conductance is sufficient to explain the Ang II response.

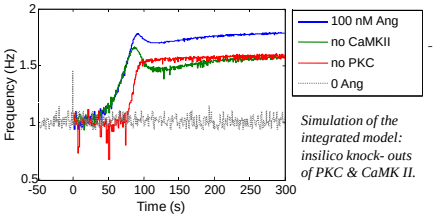


Channel modulation effect on firing frequency…



The effects of the K_{DR} channel modulation is the only one consistent with the experimental observations.

Kinase contribution to frequency modulation…



Simulation of the integrated model: insilico knock- outs of PKC & CaMK II.

Different effects of PKC and CaMK II

Only K_{DR} mimics Ang II Experiment

Results

Biology…

- K_{DR} plays a major role. Ca^{2+} activation not through Ca_L
- Phosphorylation of voltage-gated ion channels can explain neuro-modulation
- PKC & CaMK II distinguish the duration of the Ang II stimulus.

Theory…

Integrative multi-scale modeling is necessary to analyze neuronal plasticity

Conclusion

The current model …

- **highlights important issues**
- **inspires new experiments**

Outlook

Theory…

- Parameter estimation?
- Model reduction & time-scale analysis?
- Stochastic vs. chaos?

Biology…

- Network of neurons?
- Closed loop blood pressure control?

Fully integrated neuron model on all levels…

- Electro-physiology,
- Signal-transduction and
- Gene expression.

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