Homeostatic conductance regulation in multicompartment model neurons

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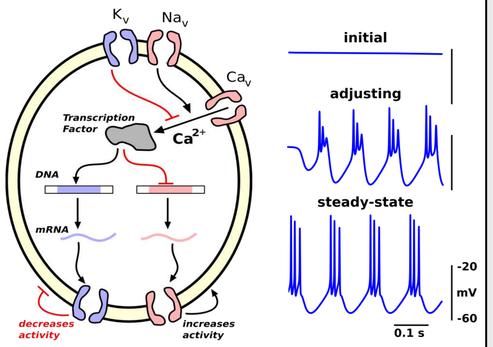
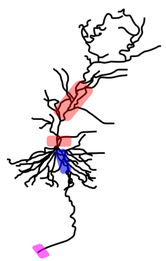
Background

- Feedback control systems keep physiological variables within desired ranges (*e.g. thermoregulation, blood glucose levels*)
- Neurons use similar principles to regulate their activity patterns (e.g. to maintain average firing rates; Hengen et al, 2013)



Models for homeostatic plasticity work well in single-compartments. Above, an activity-dependent conductance regulation rule with negative feedback (*left*) produces a self-organizing bursting cell (*right*), which is robust to perturbations (O'Leary et al., 2014)

But how can homeostatic feedback be incorporated into multicompartment models?



Homeostatic plasticity occurs in sub-cellular domains:

1. **Dendrites**
   Ex: *Npas4* differentially regulates inhibition onto apical dendrites and soma (Bloodgood et al., 2013)
2. **Pre-synaptic terminals**
   Ex: AMPAR blockade increases vesicle pool size (Thiagarajan et al., 2013)
3. **Axon initial segment**
   AIS shifts away from soma following hyperactivity (Grubb & Burrone, 2010)

Problems of interest:

- **Components of feedback system (sensors, actuators, etc.) are spatially separated**
- **Competition between local and global regulation rules (e.g. LTP and synaptic scaling)**
- **Rules for trafficking proteins and mRNA involved in plasticity between sub-cellular compartments**

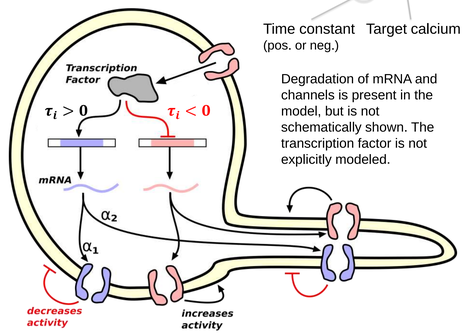
Case #1:

mRNA production/trafficking is much faster than channel translation/insertion

mRNA reaches a steady-state distribution across compartments rapidly. Easy to extend O'Leary et al. (2014):

u_i = mRNA for channel i $\quad \frac{du_i}{dt} = \frac{[Ca] - [Ca]_T}{\tau_i}$

Time constant (pos. or neg.) — Target calcium



Degradation of mRNA and channels is present in the model, but is not schematically shown. The transcription factor is not explicitly modeled.

Equations for changes in maximal conductance:

$$\frac{d\tilde{g}_{i,s}}{dt} = \alpha_{i,s}u_i - \beta_{i,s}\tilde{g}_{i,s} \qquad \bar{g}_{i,s} = \tilde{g}_{i,s}/A_s$$

channel insertion & trafficking bias — degradation rate constant — surface area

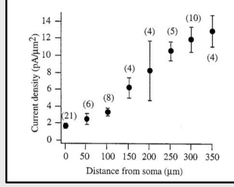
Experimental Prediction: If we assume $\bar{g}_i \approx 0$ for the initial condition of the simulation (e.g. an early stage of neural development), then we observe ***consistent ratios in channel expression between compartments*** across preparations. Similar results were used by O'Leary et al. (2014) to explain correlations *between channel types* across preparations (see, e.g., Schulz et al., 2007)

$$\frac{\bar{g}_{i,s_1}|_{ss}}{\bar{g}_{i,s_2}|_{ss}} \approx \frac{\left(\frac{\alpha_{i,s_1}u_i|_{ss}}{\beta_{i,s_1}}\right)}{\left(\frac{\alpha_{i,s_2}u_i|_{ss}}{\beta_{i,s_2}}\right)} = \frac{\alpha_{i,s_1}\beta_{i,s_2}}{\alpha_{i,s_2}\beta_{i,s_1}} \times \frac{A_{s_2}}{A_{s_1}}$$

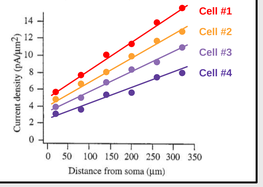
Significance:

- Experimentally measure conductance ratios to determine homeostatic parameters in real neurons
- Develop homeostatic versions of static models by deriving regulation parameters from $\bar{g}_{i,s}$

Average I_H gradient
Magee et al. (1999)



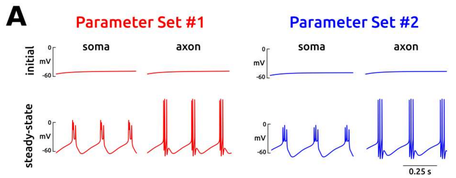
Individual I_H gradients
(schematic, predicted)

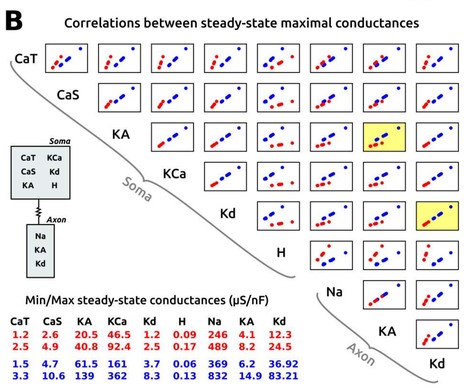


Case #2: Modeling mRNA trafficking explicitly

iPad goes here for animations
http://nbviewer.ipython.org/github/ahwillia/notebooks/tree/master/code_pubs/2014_11_04/trafficking.ipynb

Case #1: Two-compartment example





Min/Max steady-state conductances (μS/nF)

CaT	CaS	KA	KCa	Kd	H	Na	KA	Kd
1.2	2.6	20.5	46.5	1.2	0.09	246	4.1	12.3
2.5	4.9	40.8	92.4	2.5	0.17	489	8.2	24.5
1.5	4.7	61.5	161	3.7	0.06	369	6.2	36.92
3.3	10.6	139	362	8.3	0.13	832	14.9	83.21

Legend and code available at: http://dx.doi.org/10.6084/m9.figshare.1217525

Simple case: a linear cable

Model mRNA movement using mass action kinetics with rate constants a_i and b_i

$$u_1 \underset{b_1}{\overset{a_1}{\rightleftharpoons}} u_2 \underset{b_2}{\overset{a_2}{\rightleftharpoons}} u_3 \underset{b_3}{\overset{a_3}{\rightleftharpoons}} u_4 \underset{b_4}{\overset{a_4}{\rightleftharpoons}} u_5$$

$$\frac{du_i}{dt} = a_{i-1}u_{i-1} + b_i u_{i+1} - (a_i + b_{i-1})u_i$$

$\dot{\boldsymbol{u}} = \mathrm{A}\boldsymbol{u}$ $\quad$ A is a tridiagonal matrix

Goal: Choose a_i and b_i such that mRNA approaches a desired distribution $\boldsymbol{u}_{i,ss} = \tilde{\boldsymbol{u}}_i$

Solution: $\boxed{\frac{\boldsymbol{a_i}}{\boldsymbol{b_i}} = \frac{\tilde{\boldsymbol{u}}_{\boldsymbol{i+1}}}{\tilde{\boldsymbol{u}}_{\boldsymbol{i}}}}$

To see why, solve by substitution:

$$a_{i-1}\tilde{u}_{i-1} + b_i\tilde{u}_{i+1} - (a_i + b_{i-1})\tilde{u}_i = 0$$

$$a_{i-1}\tilde{u}_{i-1} + b_i\tilde{u}_{i+1} = a_i\tilde{u}_i + b_{i-1}\tilde{u}_i$$

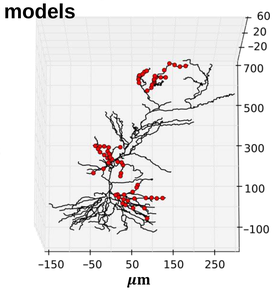
$$\frac{\tilde{u}_i}{\tilde{u}_{i-1}}b_{i-1}\tilde{u}_{i-1} + b_i\tilde{u}_{i+1} = \frac{\tilde{u}_{i+1}}{\tilde{u}_i}b_i\tilde{u}_i + b_{i-1}\tilde{u}_i$$

$$b_{i-1}\tilde{u}_i + b_i\tilde{u}_{i+1} = b_i\tilde{u}_{i+1} + b_{i-1}\tilde{u}_i$$

This works for any branched morphology and any target distribution as long as all $\tilde{\boldsymbol{u}}_i > 0$

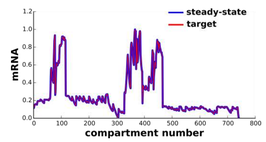
Activity-dependent trafficking in realistic multicompartment models

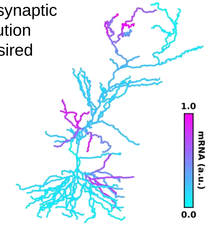
- Model CA1 pyramidal cell (Migliore & Migliore, 2012). Uses NEURON simulator.
- Excitatory synapses at red dots in figure, firing at 50 Hz.
- Plots made using PyNeuron Toolbox (Williams, 2014)



Dynamic and reversible trafficking rules

- A local signal tied to activity (e.g. Ca^{2+}) can be used to define $\tilde{u}_i$.
- mRNA accumulates at active synaptic sites. The steady-state distribution *(right)* exactly matches the desired outcome *(below)*.

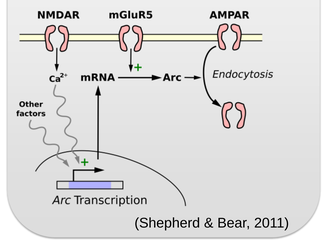




Code and animations available at: http://nbviewer.ipython.org/github/ahwillia/notebooks/tree/master/code_pubs/2014_11_04/trafficking.ipynb

Preliminary work: Interactions between local and global regulation

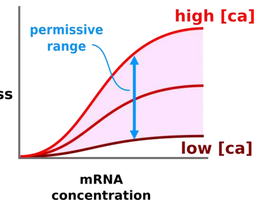
Ex: *Arc*-mediated synaptic plasticity



(Shepherd & Bear, 2011)

$$\frac{d\bar{g}_{i,s}}{dt} = \alpha_{i,s}([Ca]_s, u_i) - \beta_{i,s}\bar{g}_{i,s}$$

$$\bar{g}_{i,s}\Big|_{ss} \approx \frac{\langle \alpha_{i,s}([Ca]_s, u_i) \rangle}{\beta_i}$$



We can model $\alpha_{i,s}$ as a function of local calcium concentration and mRNA expression. Local calcium signals up or down regulate maximal conductance within a permissive range *(blue line in schematic plot)*. This range is regulated by global activity through activity-dependent transcription. *Arc* is an example of a gene whose transcription is controlled by global activity levels and whose trafficking/translation are regulated by local activity *(see box on left)*.

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