Synaptic Coupling

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Modeling Electrical Coupling

Coupling through gap junctions, also called **electrical synapses** is achieved by the flow of small molecules, including ions, through connexons. The main effect is that the two cells connected by gap junctions become electrically coupled. This is a bidirectional coupling, where both cells are effected. This type of coupling is very easy to model; the coupling term is simply $I_{gap} = g_{gap}\Delta V$, where g_{gap} is the gap junctional cunductance and is proportional to the number of gap junctions connecting the cells, and ΔV is the voltage difference between the cells. For cell one,

$$C_m \frac{dV_1}{dt} = -[I_{ion}(\text{cell } 1) + g_{gap}(V_1 - V_2)/p] \tag{1}$$

where $p \in [0, 1]$ is the cell 1 surface area divided by the surface area of the sum of the two cells, so if the cells are of equal size then $p = 0.5$. For cell two,

$$C_m \frac{dV_2}{dt} = -[I_{ion}(\text{cell } 2) + g_{gap}(V_2 - V_1)/(1 - p)] \ . \tag{2}$$

Although a cell can be electrically coupled to many cells, it is always restricted to neighboring cells. For each connection, terms like those above must be added to each of the coupled cells.

Modeling Coupling Through Chemical Synapses

Chemical synapses are not bidirectional as are gap junctions, but instead have an orientation. There is a presynaptic region in one cell and a post-

synaptic region in the receiving cell. So information flow is from the presynaptic neuron to the postsynaptic neuron. The size of the signal depends on the amount of neurotransmitter released and the number and binding properties of the postsynaptic receptors. The amount of transmitter that is released is proportional to the number of presynaptic vesicles that fuse to the synaptic terminal when an impulse arrives. The postsynaptic receptors are proteins embedded in the postsynaptic membrane across from the presynaptic terminal that bind to a particular neurotransmitter with some affinity.

Let $\mathrm{V_{pre}}$ denote the voltage of the presynaptic neuron and $\mathrm{V_{post}}$ denote that of the postsynaptic neuron. Transmitter is released only when the presynaptic cell is depolarized by an impulse, and can be modeled as a sharp increasing sigmoidal function:

$$Tr = \frac{Tr_{max}}{1 + e^{\left(\frac{V_p - V_{pre}}{k_p}\right)}} \tag{3}$$

where Tr_{max} is the maximum amount of transmitter that can be released by the presynaptic neuron and is a parameter, V_p is the value of $\mathrm{V_{pre}}$ at which Tr is half maximal, and k_p sets the slope of the sigmoidal curve (a smaller k_p makes the curve sharper).

Binding of transmitter molecules to the postsynaptic receptors can be described as a Markov process with the reaction scheme below, where "activated" means that a transmitter molecule has bound to the receptor.

$$\text{Not activated} \underset{\beta}{\overset{\alpha}{\rightleftharpoons}} \text{Activated}$$

The forward, binding, rate α, is proportional to the amount of neurotransmitter released. The law of mass action can be applied to this reaction scheme, producing a differential equation for the fraction of postsynaptic receptors bound by neurotransmitter (x):

$$\frac{dx}{dt} = \alpha_x(1-x)Tr - \beta_x x \tag{4}$$

and where $1-x$ is the fraction of receptors that are unbound.

For ionotropic receptors, the receptor is also a channel. (There are also metabotropic receptors which are not channels, but which activate G proteins that in turn can activate channels. We won't focus on these.) The conductance of the population of these channels, which we'll call the *synaptic conductance*, is the product of the number of receptors that are expressed, the single-channel conductance of each receptor, and the fraction of receptors bound. The product of the first two factors can be expressed by a parameter, $\bar{g}_s$, so the conductance is then $\bar{g}_s x$. The *synaptic current* is the product of the conductance and the driving force. This driving force is the difference between the postsynaptic voltage and the reversal potential for the ion type(s) that moves through the receptor . Thus,

$$I_s = \bar{g}_s x(V_{post} - V_{rev}) \quad . \tag{5}$$

The neurotransmitters glutamate and acetylcholine are both excitatory because their (ionotropic) receptors are primarily permeable to both Na^+ and K^+, but mostly Na^+. The reversal potential is $V_{rev} \approx 0$ mV for both. This would be considered an excitatory synapse. In contrast, the neurotransmitter GABA is typically inhibitory because its (ionotropic) receptors are primarily permeable to choloride, which usually has a Nernst potential near -65 mV. So for ionotropic GABA receptors, $V_{rev} = -65$ mV, and this is an inhibitory synapse.

Finally, to incorporate the effects of synaptic coupling onto the postsynaptic neuron, we add the synaptic current from **all** presynaptic neurons to the voltage equation of the postsynaptic neuron. Thus,

$$C_m \frac{dV_{post}}{dt} = -[I_{ion} + \sum (I_{exc} + I_{inh})] \tag{6}$$

where I_{exc} means excitatory synaptic input (this current will be negative) and I_{inh} means inhibitory synaptic input (this current will be positive).

Metabotropic Receptors

When a neurotraansmitter binds to a receptor it activates a G-protein signaling pathway, which can initiate a variety of things, like Ca^{2+} release from the ER, which in turn activate enzymes. These enzyme can then have short-term consequences (like activation/inactivation of ion channels) and long-term consequences (like gene expression). Each of these steps

can be modeled mathematically using ordinary differential equations. For example, if x is an deactivated G-protein and y is an activated G-protein, and k^+ the activation transition rate (which increases when the receptor is bound) and k^- the deactivation transition rate, then by the law of mass action,

$$\frac{dx}{dt} = k^- y - k^+ x \tag{7}$$

$$\frac{dy}{dt} = k^+ x - k^- y \ . \tag{8}$$

However, there is a conservation principle that can be used, since each G-protein is either deactived or activated. Thus, $x + y = 1$, so $x = 1 - y$. We therefore only need the y ODE.

Every other step in the signaling cascade can be dealt with in a similar fashion: first identify the players, then write down a kinetic diagram, then apply the law of mass action, and finally use conservation principles to reduce the dimensionality of the system.