Synaptic Weight Modulation and Adaptation
Part II: Postsynaptic Mechanisms

A Technical Strategy Brief for the
Neurofuzzy Soft Computing Program

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21 May 2003

Postsynaptic vs. Presynaptic Plasticity

In Part I we looked at a variety of synaptic weight mechanisms involving presynaptic plasticity. Postsynaptic mechanisms differ not only in their biological mechanisms but also in a number of ways that have a direct effect on network functionality. In presynaptic plasticity the most common case is one in which the synaptic changes are generic and non-associative. Generic means the weight change tends to take place at every synapse made by the presynaptic neuron. Non-associative means that the changes are independent of whatever may be going on at synapses made to the same postsynaptic cell by other presynaptic neurons. In contrast, most (but not all) postsynaptic mechanisms are both specific and associative. Specific means the weight change can be confined to the particular synapse. Associative means the weight change mechanism can involve the interaction with signaling going on at other synapses connecting to the postsynaptic neuron or with the output state of the postsynaptic neuron (i.e. the change can depend on whether or not the postsynaptic cell fires an action potential).

Like presynaptic weight changes, postsynaptic plasticity involves three main categories of change: elastic modulation, slow modulation, and plastic changes. However, there are important differences. So far as we know, all postsynaptic elastic modulations involve the action of modulatory voltage gated ion channels. Unlike the presynaptic case, the majority of these channels are potassium (K^+) channels, whereas N-type voltage gated calcium channels were the main players in presynaptic elastic modulation. When calcium channels are involved in postsynaptic changes, they are usually of a different type, e.g. the low-voltage T-type Ca^{2+} channel, and their effects are quite different from the previous cases. Whereas presynaptic elastic modulation is a true modulation of synaptic weight (because it affects the quantity, Q_N, of neurotransmitter release), postsynaptic elastic modulation is almost always a modulation of the integration and AP generation properties of the postsynaptic cell rather than a direct change in synaptic weight. The main exception to this rule occurs out in the dendritic arbor, where activity in one dendritic compartment can affect the response (hence the weight) of other dendritic compartments. We discussed this in our previous tech brief on dendritic integration. The other mechanisms of postsynaptic elastic modulation we will leave for another time since these mechanisms do not involve changes to the synaptic weights.

Postsynaptic mechanisms for slow modulation are primarily based on metabotropic signaling. Many of these effects are similar to the ones we discussed in Part I. However, there are a number of metabotropic signals that do directly affect synaptic weights and not merely the action potential output of the postsynaptic cell. Among them are signals that can enable or disable entire synapses, thereby providing a mechanism for **dynamic reconfiguration** of the neural network of which the postsynaptic neuron is a part. Metabotropic signals are the most important class of postsynaptic modulations that are global (generic within the neuron) rather than specific and localized to a particular synapse.

There are two interrelated forms of postsynaptic plastic weight change. These are: long term potentiation (LTP) and long term depression (LTD). Unlike the presynaptic case where the existence of LTD (from a purely presynaptic mechanism) is in doubt, there is no doubt whatever that purely postsynaptic and localized mechanisms for LTD exist. As for LTP, this form of plastic change in the postsynaptic cell can be both localized and associative (unlike presynaptic LTP). Also unlike presynaptic LTP, postsynaptic LTP is known to involve cooperation between the cell's incoming synaptic signals and its output activity (i.e. the firing or not firing of an AP). Experimental evidence indicates that the clearly documented cases of LTP seem to require that the cell generate action potentials in order to induce LTP. However, at this time the possibility cannot be entirely ruled out that some forms of postsynaptic LTP can be induced in the absence of AP generation by the postsynaptic cell.

The most common and well-documented forms of LTP and LTD, i.e. those that involve induction of the plastic change by postsynaptic action potentials, provide a biological basis for Hebbian adaptation. In Hebb's model, the change in the weight of a synapse, Δw, is some function of the present weight, *w*, the input signal at the synapse, s_i, and the cell's output signal, s_o,

$$\Delta w = f(s_i, s_o, w) \qquad (1).$$

A number of functions for Hebbian weight change have been proposed. Because the precise physics governing this weight change is presently not well understood, these functions are phenomenological. Often they also involve some presupposition of how "information" is represented and transmitted in a neural network. Such a presupposition is known as a "neural coding model". At the present time, no one can claim to know "how" neurons in a neural network "encode information", and, indeed, the assumption that there are many different schemes for neural coding is the most widely accepted hypothesis. So far as we know, Hebbian weight adaptation is an entirely postsynaptic phenomenon; plastic presynaptic weight changes are non-Hebbian mechanisms.

As we will see in this Brief, there is one very important difference between how biological neurons implement Hebbian adaptation and how Hebbian learning rules are commonly applied in conventional artificial neural network theory. In the conventional mathematics of neural network theory, Hebbian learning can take place for both excitatory (positive) synaptic weights and for inhibitory (negative) synaptic weights. We will see here that, again so far as anyone knows, only excitatory, glutaminergic synapses[1] exhibit Hebbian plasticity. **Inhibitory synapses do not exhibit Hebbian plasticity** (again, so far as we know).

Glutaminergic Synapses

Synapses where Glu is the neurotransmitter comprise the most important special case insofar as plastic weight adaptation is concerned. We examined the basic structure of a general synapse in Part I; we repeat our illustration in Figure 1 below. In this Brief our attention is going to focus on the postsynaptic cell side of this structure. For glutaminergic synapses, the postsynaptic receptors are glutamate receptors. There are two general classes of ionotropic Glu

[1] Glutamate is the principal excitatory neurotransmitter in the central nervous system. A glutaminergic synapse is a synapse for which glutamate is the neurotransmitter.

receptors: NMDA receptors and non-NMDA receptors[2]. There are two types of non-NMDA glutamate receptors, the most important of which is called the AMPA receptor.

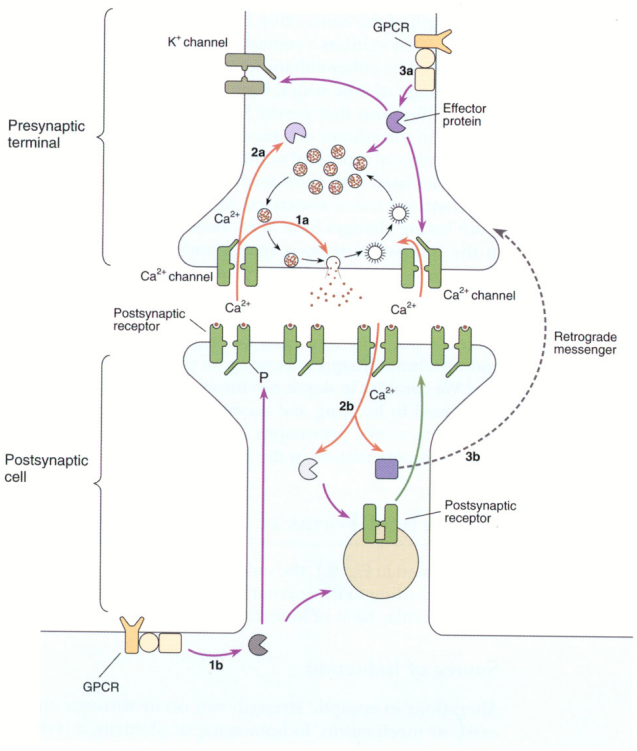

Figure 9.1. A variety of mechanisms and sites for synaptic plasticity. Calcium entry into the presynaptic terminal through voltage-gated Ca^{2+} channels directly triggers release (1a) and acts as a second messenger for short-term homosynaptic plasticity (2a). Activation of G protein–coupled receptors (GPCRs) also alters release (3a) by modulating Ca^{2+} and K^+ channels, altering Ca^{2+} influx, and acting directly on the release machinery and vesicle recycling. Postsynaptic plasticity can be produced in response to stimulation of postsynaptic GPCRs (1b) or by postsynaptic Ca^{2+} influx (2b). These postsynaptic signaling cascades modify fast postsynaptic responses mediated by ionotropic receptors through phosphorylation of receptors in the plasma membrane or by altering the cycling of receptors to and from a cytoplasmic pool. Postsynaptic cells can also generate retrograde messengers that alter release from the presynaptic cell (3b).

Figure 1: Illustration of the basic structure of a synapse.

Binding of Glu to an AMPA receptor opens the ion channel. AMPA receptors conduct both sodium (Na^+) and potassium (K^+) ions. AMPA currents are depolarizing, i.e. they produce an excitatory postsynaptic potential (EPSP) in the cell membrane. They also conduct a small amount of Ca^{2+} current, but this current flow is generally negligible. In specializing Figure 1 to glutaminergic synapses, the non-NMDA receptors are those not shown as conducting Ca^{2+} current in the figure.

NMDA channels conduct Ca^{2+} currents when open. However, unlike non-NMDA receptors, the NMDA channel is voltage dependent. Under normal resting potential conditions, the NMDA channel is blocked by a Mg^{2+} ion. Thus, transmission of Glu from the presynaptic cell enables the NMDA channel, but does not open it. In order to conduct, the dendritic spine (where almost all glutaminergic synapses are localized) must depolarize to about –50 mV in order to flush out the Mg^{2+} ion and open the channel for Ca^{2+} conduction. In Part I we saw that the influx of Ca^{2+} was

[2] NMDA stands for N-methyl-D-aspartate.

the vital mechanism for inducing presynaptic plasticity; the same is true for LTP and LTD in the postsynaptic cell. NMDA channels are represented in Figure 1 as the "2b" channel. Ca^{2+} currents through the NMDA channel appear to have little contribution to EPSPs, but they have a profound effect on synaptic weight.

Detailed experimental evidence gathered in the past few years now indicate that NMDA channels are a basic constituent of all glutaminergic synaptic compartments. The hypothesis is that all glutaminergic synapses contain NMDA receptors. In contrast, the evidence further indicates that AMPA receptors are **not** always expressed at the cell membrane. Because a receptor channel must penetrate the cell membrane in order to be able to receive NTX, this means that not all glutaminergic synapses express active ionotropic AMPA channels. A synapse that lacks expression of AMPA channels at the cell membrane therefore cannot respond to Glu transmission with an EPSP. Such a synapse is called a "silent synapse" because NTX signals do not produce an EPSP. On the other hand, there is experimental evidence that glutaminergic spines **do** maintain a "ready pool" of AMPA channel proteins either within the postsynaptic compartment itself (in a region called the "postsynaptic density") or else in the dendritic shaft near the spine. This ready pool of AMPA proteins is illustrated above in Figure 1 by the brown circle to which a green receptor symbol is attached.

Although there is strong experimental evidence pointing to the existence of "silent synapses", it is also known for a fact that many glutaminergic synapses do contain membrane-spanning AMPA receptors (and therefore are not "silent"). However, it now seems likely that the number of AMPA receptors expressed at the membrane, N_{AMPA}, is not a constant for a glutaminergic synapse. Variation in the number of AMPA receptors that actually span the membrane is thought to be one of the principal mechanism for postsynaptic plasticity at glutaminergic synapses.

Just as there exists a vesicle cycle in the presynaptic terminal, it is now thought that there is an "AMPA cycle" at work in the postsynaptic compartment. As is the case for the vesicle cycle, the AMPA cycle seems to be regulated and controlled by intracellular levels of Ca^{2+}. Furthermore, experimental evidence exists that supports the hypothesis that intracellular calcium concentrations (denoted by the standard symbol $\left[Ca^{2+}\right]_i$) under normal conditions are confined to the dendritic spine to which they were admitted by open NMDA channels. Therefore, Ca^{2+} influx is localized to the dendritic spine and does not affect other nearby synapses. Such a containment of Ca^{2+} within a spine leads to the ability of postsynaptic weight change to be localized to a specific synapse.

The Biomechanics of Ionotropic Signaling

In Part I we expressed synaptic weight as a function of NTX quantity and the numbers of available receptors of various types,

$$w = f\left(Q_N, \{N_R\}\right) \qquad (2).$$

Presynaptic weight changes involve changes in the quantity of NTX; postsynaptic weight change involves a change in the $\{N_R\}$ term. However, the idea of synaptic weight as a measure of the amount of affect registered in the postsynaptic cell by an incoming AP signal is capable of being looked at in several ways from the postsynaptic side. We must decide on "what part of the cell's response" is to be regarded as straight signal processing and what part we are going to lump into

the synaptic weight parameter. In order to make this decision, we need to take a closer look at the biomechanics of ionotropic signaling.

The postsynaptic membrane voltage responds to ionic currents conducted by open ionotropic channels. For most such channels this current can be described using an equation of the form

$$I(t) = G(t) \cdot (V - E_r) \tag{3}$$

where $G(t)$ is a time-varying channel conductance, V is the membrane potential at the synapse, and E_r is an electrochemical potential, called the reversal potential, that depends on the type of ions involved in the current flow. Positive ions flowing into the cell are excitatory, and by convention a current flow in this direction carries a negative sign. Positive ions flowing out of the cell are inhibitory, and these currents carry a positive sign. Negative ions flowing into the cell are also inhibitory, and biological values of V and E_r are such that these currents also carry a positive sign.[3]

The V term in (3) is a cell response term, and it is coupled to equations describing the net membrane current flow established by all the ionotropic and voltage gated channel activity going on at any particular moment. Hence, in (3) we are justified in regarding the conductance term $G(t)$ as the sole correlate between synaptic weight and the biophysics described by the Hodgkin-Huxley equations that describe the cell's electrical activity. For most ionotropic channels this conductance responding to a single AP input at the synapse is adequately described by an equation of the form

$$G(t) = G_{pk} \cdot ((t - t_i)/\tau) \cdot \exp[1 - (t - t_i)/\tau] \tag{4}$$

for $t \geq t_i$, where G_{pk} is the peak conductance, t_i is the arrival time of the incoming AP, and τ is the time required for G to reach its peak value. It is to be understood by (4) that for $t < t_i$ the conductance G is equal to zero.

We have two quantities in (4), G_{pk} and τ, that characterize synaptic strength. It is perhaps obvious that the G_{pk} term is directly proportional to synaptic weight w (with the sign of w being dependent upon whether the current is excitatory or inhibitory). G_{pk} is directly proportional to the number of activated channels, thus is a function of the number of active receptors, N_r, and the probability p that the neurotransmitters will bind to the receptor protein. Since p most directly depends on the amount of NTX available, Q_N, we can regard p as being determined by the presynaptic mechanisms for synaptic weight, leaving only N_r as a postsynaptic term.

But in addition to G_{pk} we also have the time constant τ to consider. The Hodgkin-Huxley equations that describe cell response are a set of coupled nonlinear differential equations, and so the net cell response is a nonlinear function of τ. Equation (4) represents the collective actions of a great many separate membrane-spanning proteins that make up the ionotropic channel. Although (4) is a phenomenological expression, we can justifiably regard it as representing the

[3] The principal excitatory currents are Na^+ and Ca^{2+} currents. The principal inhibitory currents are K^+ and Cl^- currents. For ionotropic channels, the principal inhibitory currents are Cl^- currents, and the principal excitatory ionotropic channels carry a mix of Na^+ and K^+ ions in a proportion such that the Na^+ component dominates the total current flow. NMDA channels conduct Na^+, K^+, and Ca^{2+}, and their proportion is such that there is little net effect on membrane voltage. However, the effect of the calcium influx is metabotropically quite significant.

time dynamics of a statistical representation of a stochastic process made up of individual protein channel openings and closings.[4] τ therefore represents the statistical time course of the cellular processes that regulate the opening and closing of the members of the ensemble of channel proteins.

In addition to their NTX binding sites outside the cell membrane, channel proteins also contain a number of other binding sites located inside the cell ("cytoplasmic sites"). At these sites the binding of other molecules (typically a phosphate group, P) exercises control of whether the membrane channel pore is open or closed, whether the NTX binding site is presented in the cleft, and even whether the channel protein maintains its binding affinity for NTX (i.e. whether the protein "holds on" to the NTX or "releases" it back into the cleft). The cytoplasmic process that regulates these factors is called the "phosphorylation – dephosphorylation cycle." Phosphorylation refers to the binding of a phosphate group at the control site of the protein. Dephosphorylation refers to the removal of such a phosphate group.

For the main inhibitory ionotropic receptor (the GABA receptor protein $GABA_A$), and for the ionotropic receptor for ACh (called nAChR, the nicotinic acetylcholine receptor), phosphorylation usually decreases current flow. We can think of phosphorylation of the main inhibitory channel as causing the $GABA_A$ receptor to release its bound NTX, thereby closing the channel. This action is known as **desensitization** of the channel.[5] Dephosphorylation increases the current flow. The main excitatory receptor, AMPA, usually behaves in just the opposite manner; phosphorylation usually increases current flow, keeping the ionic channel in the open state and increasing the affinity of AMPA receptors to bind with glutamate. This process is known as **sensitization** of the channel. Dephosphorylation acts to decrease excitatory current flow.

We can generalize our discussion of these channel dynamics by abstracting from the biochemistry taking place and simply talking about a **sensitization – desensitization cycle** (which we will abbreviate as the "s-d cycle") in the channel response. $G(t)$ in equation (4) rises during the sensitization part of the cycle, achieving its peak value when $t - t_i = \tau$. For $t > \tau + t_i$ we enter the desensitization phase of the cycle and $G(t)$ decreases back to zero once more. τ is determined by the time course of the s-d cycle.

How does τ affect the magnitude of the cell's response to an action potential? We can get a "feel" for this by considering how τ should relate to membrane voltage V. The membrane voltage is the voltage across a membrane capacitance, and we recall that capacitor voltage is related to capacitor current as

$$I_C(t) = C\frac{dV}{dt}.$$

[4] The statistical nature of channel opening and closing dynamics is made explicit in what are known as kinetic models of ion channels. In essence, these models are Markov process models of channel dynamics.

[5] As I said, this is the *usual* effect of phosphorylation on these channels. However, in some cases the protein kinases that are responsible for the phosphorylation – dephosphorylation cycle exert just the opposite effect. I mention this only in case you should come across some of the literature that talks about the details of these processes. The internal chemistry of the cell is not particularly important so far as our neural network research is concerned; what is important for our purposes is simply to know that a process that regulates channel sensitization and desensitization exists, and that this process controls the temporal dynamics of the channel response.

The capacitor current I_C is made up in part of some fraction of the channel current given by (3). For small EPSPs or IPSPs near the cell's resting potential, we can say (approximately) that I_C is made up entirely of the current in (3). For larger values of τ this current changes more slowly, and thus the second derivative of membrane voltage varies approximately as

$$\frac{d^2V}{dt^2} \propto \left[G_{pk}\left(\frac{1}{\tau} - \frac{t-t_i}{\tau^2}\right)\exp\left[1-(t-t_i)/\tau\right]\right](V-E_r) + G(t)\frac{dV}{dt} \qquad (5).$$

Although (5) has no known closed-form solution, it can be studied numerically. Qualitatively, it is probably not difficult to see that larger values of τ tend to produce smaller rates of change, dV/dt, and therefore smaller EPSPs or IPSPs.

In the absence of slow modulation by metabotropic signals, the channel will have a "base rate" for the s-d cycle that contributes to setting the unmodulated synaptic weight. Metabotropic signals can act to either increase or decrease this weight indirectly through changes in τ or directly through activation or inactivation of the protein channels themselves (that is, through changes in N_r). The first mechanism acts through the time course of $G(t)$, the second through G_{pk}. Thus we can view our synaptic weight function as having the general form

$$w = f\left[Q_N, N_r(G_{pk}, \tau)\right] \qquad (6).$$

Postsynaptic LTP and LTD

The postsynaptic mechanism for long term potentiation and long term depression is made possible by NMDA receptors in glutaminergic synapses. It is possible that there may be other as of yet undiscovered LTP/ LTD postsynaptic mechanisms, but as of yet NMDA is the only one that has been confirmed and no other postsynaptic mechanisms have been suggested. It is now believed that NMDA receptors are present in <u>every</u> glutaminergic synapse. Malenka and Siegelbaum, two very eminent neuroscientists, have gone so far as to make the statement that "LTP has been observed at virtually every excitatory synapse in the mammalian brain that has been studied," but I think this statement is far too broad. First, there is no compelling evidence that demonstrates LTP at any excitatory synapses other than glutaminergic synapses. For example, it has not been shown that LTP can be induced at ACh-nAChR synapses (and these are excitatory synapses). There are excitatory glutaminergic synapses present in the neural network of the retina, but I have heard no one claim that LTP is evidenced in the retina (and it seems to me that LTP in the retina would not be a good thing to have from the point of view of what the retina is supposed to do).

What makes NMDA receptors important for LTP/ LTD is that they are the principal channels for calcium entry into the postsynaptic cell. We have already seen the importance of calcium influx for the presynaptic case in Part I. Ca^{2+} is equally important postsynaptically, although the specific processes of LTP and LTD are different for the postsynaptic cell than they are in the presynaptic terminal.

Let us recall the peculiar properties of the NMDA receptor. Binding of Glu "enables" the NMDA channel to open, but by itself this is not enough to actually open the channel. In addition to the Glu binding, the cell's membrane potential must depolarize to about –50 mV (from a typical resting potential of around –65 mV or so) in order to dislodge the Mg^{2+} ion that blocks the channel pore. The general form of $G(t)$ for an NMDA channel is

$$G(t) = g\frac{\exp(-(t-t_i)/\tau_1) - \exp(-(t-t_i)/\tau_2)}{1+\eta\cdot\left[Mg^{2+}\right]_o \exp(-\gamma\cdot V)} \qquad (7)$$

where g is a parameter called the "single channel conductance", τ_1 and τ_2 are time constants (approximately 80 msec and 0.67 msec, respectively), and $\left[Mg^{2+}\right]_o$ is the concentration of magnesium ions in the cleft (about 1 millimole under biological conditions). η is a proportionality constant (about 0.33 per millimole under biological conditions), and γ is about 0.06 per mV. Membrane potential V is expressed in mV in (7).

Figure 2 illustrates the normalized NMDA conductance for membrane voltages of –65, -40, and –35 mV. G peaks within a few msec of activation and decays very slowly afterwards. The reversal potential for the NMDA channel is approximately 0 volts and so the calcium current is

$$I_{Ca}(t) = G(t)\cdot V(t) \qquad (8).$$

Since most glutaminergic channels are located on dendritic spines, and since spines occupy a very small volume, the opening of NMDA channels produces a large increase in cytoplasmic calcium concentration, $\left[Ca^{2+}\right]_i$, within the spine. Furthermore, it is known that dendritic spines appear to "compartmentalize" the calcium concentration, i.e. the Ca^{2+} somehow remains trapped within the spine and does not significantly "leak out" to the dendritic shaft. This compartmentalization of calcium acts to localize LTP and LTD to the specific spine where the Glu-activated NMDA channels are located.

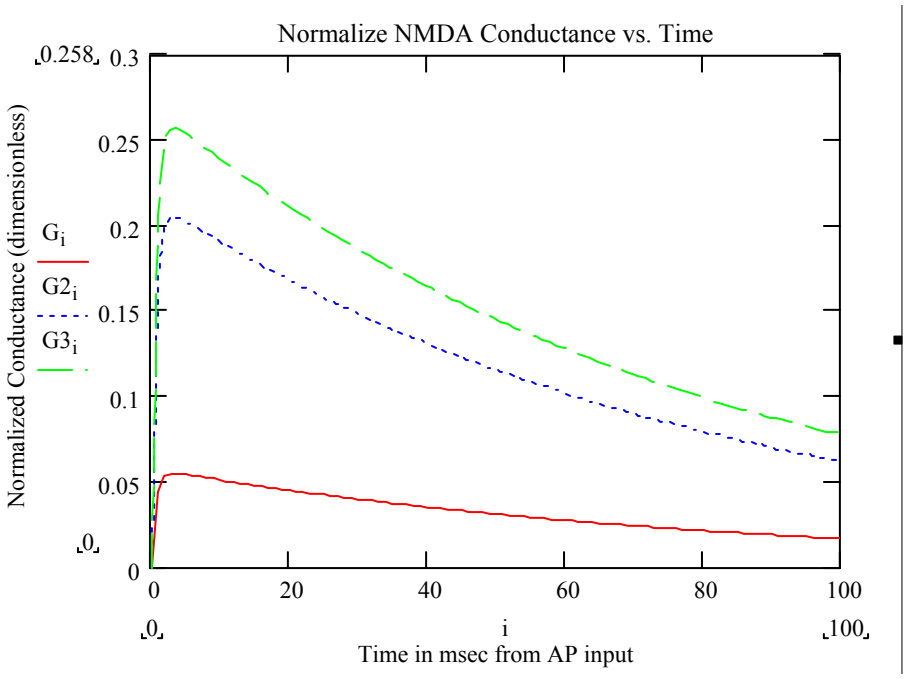

Figure 2: Mathcad calculations of normalized NMDA conductance for membrane voltages of –65 mV (red line), -40 mV (blue dotted line), and –35 mV (green dashed line).

Basal calcium concentration in a cell is always very low due to the action of calcium pumps that remove Ca^{2+} from the cell and because of organelles, such as the endoplasmic reticulum, that absorb and store free Ca^{2+}. Owing to this low basal concentration, the buildup of $\left[Ca^{2+}\right]_i$ is often approximated using simple first-order kinetics of the form

$$\frac{d\left[Ca^{2+}\right]_i}{dt} = \beta \cdot I_{Ca}(t) - \frac{\left[Ca^{2+}\right]_i}{\tau_{Ca}} \tag{9}$$

where β is a scaling factor that accounts for the volume of the dendritic spine[6] and τ_{Ca} is a time constant (approximate value empirically determined as about 125 msec).

Ca^{2+} is a potent secondary effector in metabotropic reactions and gives rise to a number of different biochemical cascades. It is not known for certain what cascade reaction or reactions give rise to NMDA-mediated LTP and LTD in the postsynaptic cell (represented schematically in Figure 1 by line 2b), nor is it known for certain exactly what the mechanism of LTP or LTD is. The leading hypothesis, however, is that the calcium-induced reactions

1. sensitize or desensitize AMPA receptors already located in the membrane; and
2. mobilize AMPA receptors to move from or to the "AMPA receptor pool" (Figure 1).

Sensitization of AMPA receptors enhances their current flow, and if this sensitization is long-lasting this would constitute one form of LTP. Moving AMPA receptors from the ready pool to the membrane increases the number of available receptors, thereby increasing synaptic strength (LTP). There is evidence that both effects do in fact happen in glutaminergic synapses during LTP. The opposite mechanisms (desensitization of AMPA and removal of AMPA receptors from the membrane) gives rise to LTD. All four of these effects can be regarded as changes to AMPA N_R.

That there must be at least two biochemical cascade reactions induced by calcium influx is indicated by the fact that every glutaminergic synapse that expresses LTP when $\left[Ca^{2+}\right]_i$ rises to a high level of concentration also expresses LTD when the $\left[Ca^{2+}\right]_i$ level is lower. There is a **calcium threshold**, below which neither LTD nor LTP is expressed at the synapse (weight stays constant). Above this threshold we observe the onset of LTD. Above a second and higher **threshold of LTP induction**, the synapse exhibits LTP. At present no one knows what the threshold-producing mechanism might be, nor why there should be any threshold at all. But we do know these thresholds exist. The phenomenon is modeled phenomenologically by use of some continuous, differentiable function, $\Omega[Ca]$ having the characteristics

$$\begin{aligned} &\Omega[Ca] = 0, \left[Ca^{2+}\right]_i < \theta_L \\ &\Omega[Ca] < 0, \theta_L \le \left[Ca^{2+}\right]_i < \theta_H \\ &\Omega[Ca] > 0, \theta_H < \left[Ca^{2+}\right]_i \end{aligned} \tag{10}$$

[6] The units of β depend on the units employed in (7) and (8) in calculating the calcium current. Typically g in (7) is reported in the literature in nS per cm^2 and Ca^{2+} ions carry a charge of +2e ($e = 1.602 \cdot 10^{-19}$ coul). Therefore we have two units of current for each Ca^{2+} ion. Calcium concentration is usually expressed in $nmol/mm^3$ = μmol/liter. One mole of Ca^{2+} equals $6.0228 \cdot 10^{23}$ ions.

where θ_L is the low threshold and θ_H is the high threshold.

One computational model for calcium-dependent synaptic weight change that has been proposed by Shouval et al.[7] is based upon the scheme suggested by (10). Shouval et al. normalized the synaptic weight such that

$$0 \le w \le 1$$

and proposed the dynamical model

$$\frac{dw}{dt} = \frac{\Omega[Ca] + w_0 - w}{\tau[Ca]} \tag{11}$$

where w_0 is the basal (unmodified) synaptic weight, $\tau[Ca]$ is a calcium-dependent time constant, and $\Omega[Ca]$ is constrained such that $-w_0 \le \Omega[Ca] \le 1 - w_0$. They modeled the time constant as

$$\tau[Ca] = \frac{\tau_0}{\left(\left[Ca^{2+}\right]_i\right)^3 + 10^{-4}} \tag{12}$$

where τ_0 = 500 msec, $\left[Ca^{2+}\right]_i$ is in nmol/mm^3, and the time constant is in msec. Equation (12) has the property that at low calcium concentration the time constant is over an hour while at high concentrations (1 nmole/mm^3) the time constant is half a second. Equation (11) has the property that w asymptotically approaches $\Omega + w_0$ with time constant $\tau[Ca]$ when $\left[Ca^{2+}\right]_i$ is constant. The model therefore incorporates both LTP and LTD. Shouval et al. call their model the "calcium control hypothesis model."

Note that model equations (11)-(12) are not independent of the calcium concentration dynamics given by (7)-(9). Equations (9) and (11), along with the Hodgkin-Huxley model for membrane voltage, constitute a set of coupled nonlinear differential equations, and their solutions must be evaluated numerically.

Models such as this one determine their various parametric values according to physiological data. One thing we must keep in mind for our project is that the AP duration and firing rates of our artificial neurons are several orders of magnitude faster than biological neurons. For example, the BAN circuit's AP width is about 1 μsec, compared to about 1 msec for biological neurons. The Frenzel neuron is more than two orders of magnitude faster than this. In our work we must account for these differences if we use the biological models in evolving our networks.

Slow Modulation of Postsynaptic Weights

The LTP/ LTD dynamics just discussed are one instance of the effect of metabotropic reactions on the behavior of the neuron. As was the case for the presynaptic terminal, other postsynaptic second messenger metabotropic reactions (initiated by NTX binding to metabotropic receptors) can modulate synaptic weights (including those of non-glutaminergic

[7] cf. W. Gerstner and W. Kistler, *Spiking Neuron Models*, Cambridge, UK: Cambridge University Press, 2002, pp. 377-381.

synapses). Most synapses express metabotropic receptors around the periphery of the synaptic density. This is illustrated in Figure 1. In Part I we talked about the regulatory role these receptors play for the presynaptic terminal. The postsynaptic metabotropic receptors play a similar regulatory role on the postsynaptic side of the cleft.

One of the important regulator enzymes found within neurons is protein kinase A (PKA). Basal levels of PKA are thought to play a key role in maintaining normal levels of receptor function. PKA levels are increased by the metabotropic production of cAMP (cyclic adenosine monophosphate), a chemical whose production is stimulated by both NE (norepinephrine) binding to particular GPCRs and by 5-HT (serotonin) binding to some types of receptors within its family of GPCRs. (5-HT can also cause decreased Ca^{2+} currents in some types of calcium VGCs).

Increasing levels of PKA lead to sensitization of both AMPA and NMDA receptors. At most inhibitory synapses, PKA leads to desensitization of the receptors. One notable exception to this rule is found in retinal cells and in Purkinje cells (the output cells of the cerebellum), where PKA is found to increase GABA-activated currents. The neurotransmitter DA (dopamine), whose receptors are all metabotropic, enhances Na^+ currents in some retinal cells by stimulating PKA-dependent phosphorylation of glutamate receptors, but its usual effect outside of the retina is to desensitize Na^+ channels.

Other types of metabotropic signaling spur the activation of protein kinase C (PKC), a secondary effector that typically desensitizes inhibitory $GABA_A$ and nAChR receptors but sensitizes NMDA and AMPA receptors. Other types of secondary effectors, such as the Ca^{2+}/calmoduline-dependent kinase, desensitize AMPA and NMDA receptors. Other types of metabotropic reactions can tend to inhibit cell firing by increasing K^+ current flow out of the cell. In still other cases, reactions exist that decrease K^+ current flow.

The bottom line of all this is that metabotropic synapses can have inhibitory or excitatory effects, depending on the particular synapse to which the NTX is applied. These effects are widespread throughout the postsynaptic cell and constitute a form of global modulation of cell activity. There are also numerous **interaction effects** from metabotropic signaling, i.e. two different metabotropic signals arriving at two different synapses can cancel each other or, in other cases, can reinforce each other.

We can regard these various metabotropic signaling mechanisms as **control signals** for modulating the response of the postsynaptic neuron. **The implication for our work** is that it is permissible for our evolved neural networks to employ specialized synapses that produce slow modulation of other (ionotropic) synapses. One role such signaling is known to be able to produce in biological neural networks is to effectively **reconfigure the neural network** by deactivating some synapses and activating others. Examples of this are frequently found in neural networks that act as **central pattern generators** producing synchronized "clock" signals for other neurons. If the neural code (whatever it may be) contains anything analogous to conditional and control statements in a computer language (IF-THEN-ELSE; SELECT-CASE; etc.) then the biological foundation is most likely modulation of network connections via metabotropic signaling. The bottom line of all this is that we need not restrict our network designs to be "hard-wired"; slow modulation by metabotropic synapses permits a sort of functional "soft-wiring" of neural networks. In EC terms, Terry describes this as different network weight templates.

Metabotropic signaling effects can be and usually are widespread throughout the postsynaptic cell. (LTP and LTD in NMDA synapses are the main exception to this). These

modulations are slow in onset and relatively long-lasting (but still primarily elastic) in their effects. The mechanisms by which chemical second messengers (e.g. cAMP) and/ or secondary effectors (e.g. PKA) spread throughout the cell are unknown, although it is known that cells possess an active transport mechanism for relocating proteins, NTX, and who knows what else from the cell body to the most distant dendritic spines. It may well be the case, although I know of no experimental data that speaks for or against this guess, that metabotropic slow modulation may spread through the cell like a "wavefront", effecting different locations as it travels from its source to its various destinations. The extent of its effect is a measure of the metabotropic synaptic weight.

Oftentimes a single AP at a metabotropic synapse is sufficient to kick start widespread metabotropic effects. The biochemical cascade reactions responsible for second messenger signaling act as tremendous amplifiers, capable of converting a single bound NTX molecule into a signal that produces many orders of magnitude more second messengers. Figure 3 illustrates the basic signaling scheme employed in second messenger signaling.

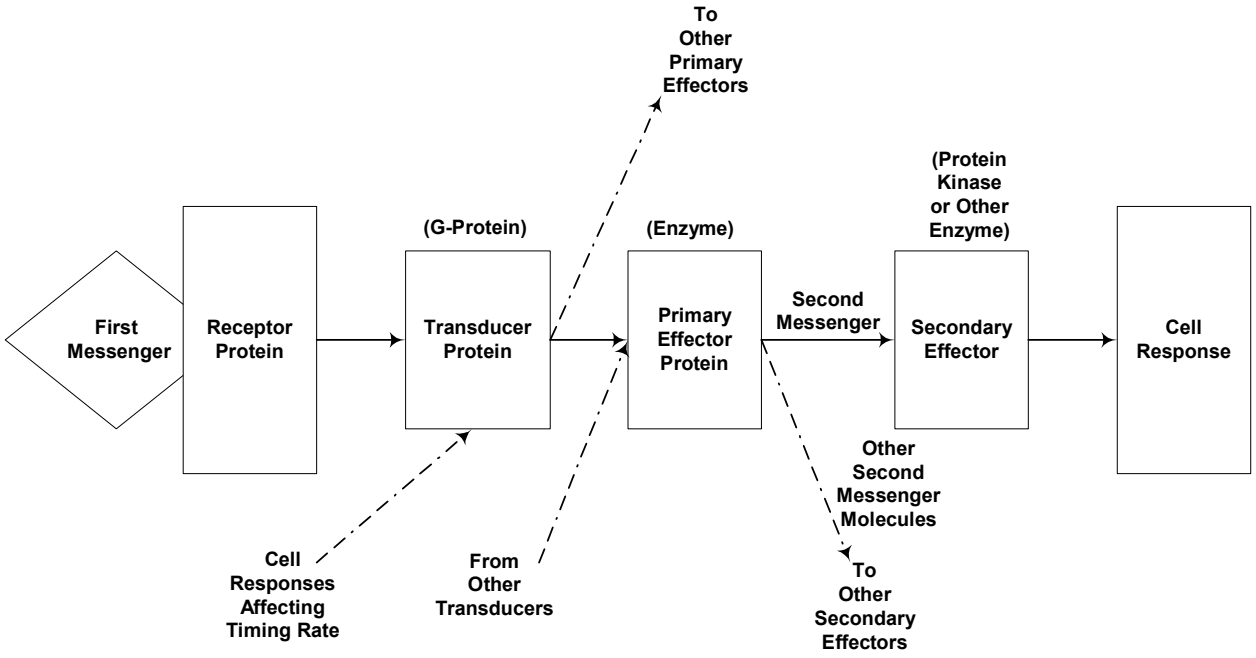

Figure 3: Signal transduction pathway for common metabotropic second-messenger processes. The first messenger is a synaptic neurotransmitter (NTX). Examples include norepinephrine, dopamine, serotonin, and many others. The NTX binds to a receptor protein which then activates one or more transducer G-proteins. A G-protein functions as a molecular timer/ switch that activates the signaling cascade. It is generally self-timing but there are some types of cell responses that can accelerate the G-protein's turn-off rate. A G-protein activates one or more primary effectors. A primary effector is an enzyme that produces second-messenger molecules. It can be regarded as a signal generator and the second messenger molecules can be regarded as its output signal. Some primary effectors output more than one type of second-messenger signals. The primary effector can be excited or inhibited by multiple inputs from different transducers. The second messenger signal typically activates a secondary effector enzyme, although in some cases (such as the second messenger IP_3 = 1,4,5-triphosphate) the second messenger signal itself acts directly to alter the cell response. The second effector is often a protein kinase such as the cAMP-dependent protein kinase (PKA) or the enzyme protein kinase C (PLC). The secondary effector usually binds a phosphate group to a target protein (this is called phosphorylation), and this phosphorylation induces the cellular response. A single protein kinase can phosphorylate many different target proteins and in this way it acts as a signal amplifier. The signal pathway gain through the process shown here is usually many orders of magnitude.

Although the time course for metabotropic modulation can be very long relative to neuron signaling rates, slow modulation effects do eventually terminate and, therefore, unless one of them induces LTP or LTD, they are slow elastic modulations. Schematically they are describable as a signaling cycle, such as is illustrated in Figure 4. The figure caption explains the meaning of the various markers depicting events within the cycle. It is to be noted that different metabotropic signaling sequences can interfere with other sequences already in process, or they can act as triggers to initiate other sequences. Figure 5 illustrates the principal known interactions among metabotropic sequences.

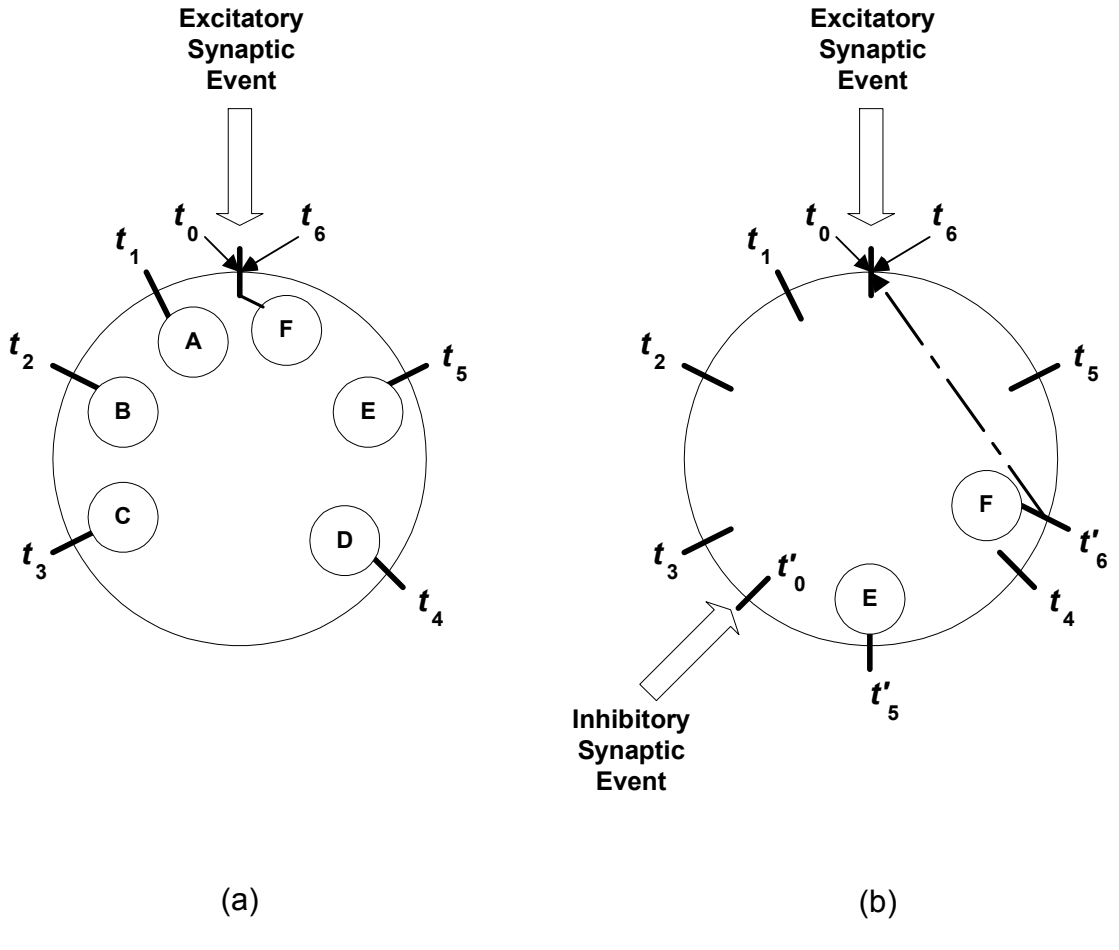

Figure 4: General schema of metabotropic time sequence. 2(a) depicts the metabotropic cycle for a single synaptic event with no cross-talk from other signal cascades. 2(b) depicts the alteration of the sequence when a second inhibitory synaptic event deactivates the cAMP cycle at time t'_0. The small circles mark specific events during the cascade. A = activation of the transducer protein to begin the cAMP cycle; B = activation of the secondary effector protein (PKA); C = beginning of phosphorylation (activation) of L-type calcium VGCs; the number of active VGCs increases from t_3 until t_5; D = deactivation of the primary effector by the transducer; E = beginning of dephosphorylation of the L-type VGCs; the number of available L-type channels now decreases until F, when all are deactivated and the cycle ends. In 2(b) the inhibitory synaptic event advances E to time t'_5 and dephosphorylation F completes early at time t'_6 (indicated by the dashed line back to the top of the circle). It should be noted that other possible synaptic events exist by which the duration of the cAMP cycle can be extended. It should also be noted that the inhibitory synaptic event has its own sequence and so the *totality* of the process may extend beyond t_6 in 2 (b).

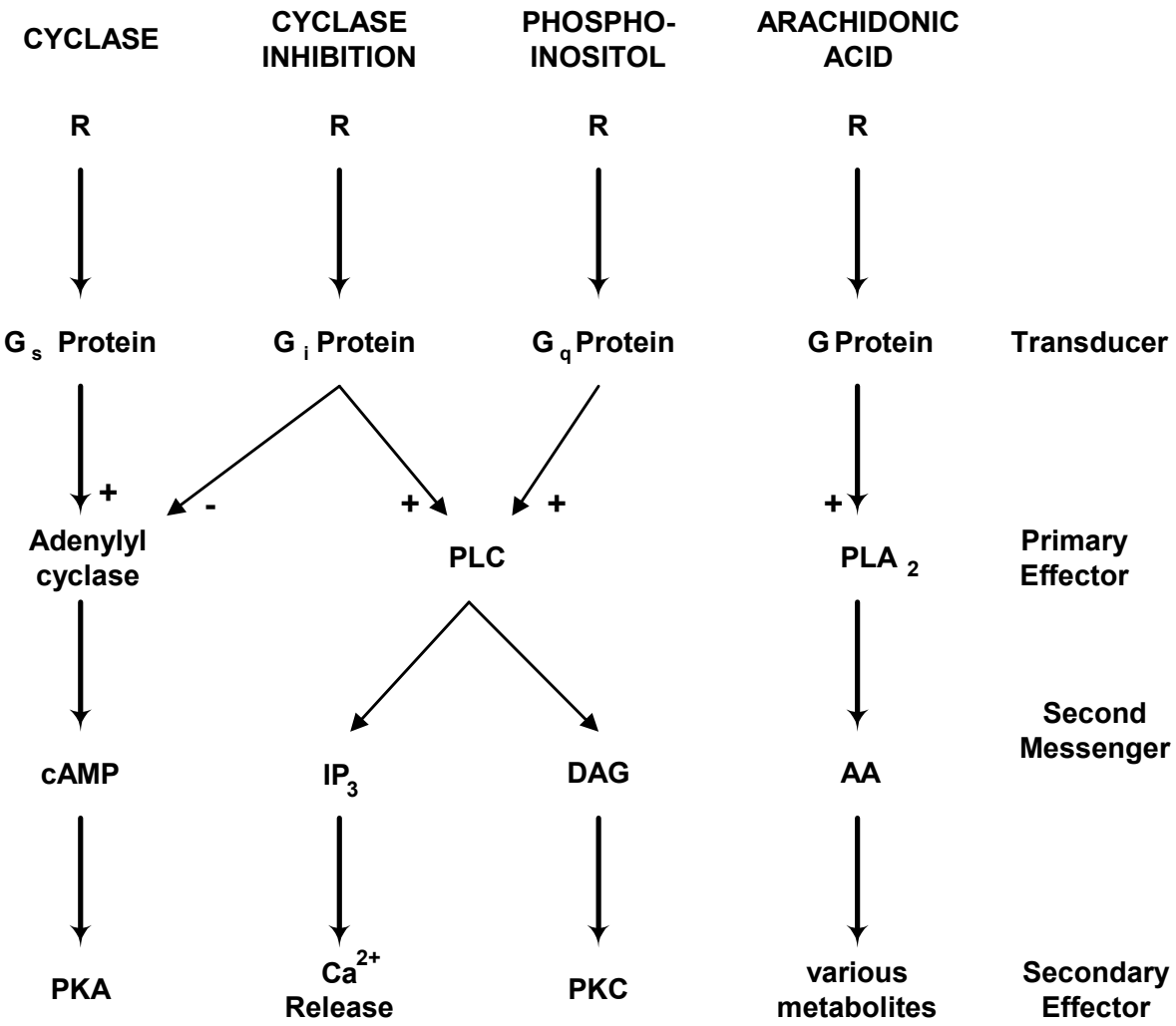

Figure 5: Networking pathways of the principal metabotropic second messenger systems. R = receptor. G_s and G_i denote stimulating and inhibitory G proteins, respectively. G_q is another type of G protein. PLC is the enzyme phospholipase C. PLA_2 is the enzyme phospholipase A_2. IP_3 is inositol 1,4,5-triphosphate. DAG is diacylglycerol. AA is arachidonic acid. PKA is the cAMP-dependent protein kinase. PKC is protein kinase C. A "+" sign indicates activation of a primary effector. A "-" sign indicates deactivation. At present not enough is known about the arachidonic acid process to permit a meaningful network description here. However, some of its metabolites are membrane-permeable and are thought to be capable of modulating nearby neurons.

Different types of neurotransmitter – GPCR pairs have different time scales for their onset (activation) and turn-off (inactivation). Table 1 below illustrates the relative timescales of various signaling and modulation mechanisms, referenced to the basic AP width of a neuron. It is probably not vital to our efforts that everyone know what the different chemical names listed in this table mean; what is pertinent to our work is that metabotropic time scales span the ranges indicated in the table.

TABLE I

RELATIVE TIME SCALES OF VARIOUS SIGNALING AND MODULATION MECHANISMS IN NEURONS. TIMES ARE NORMALIZED WITH ONE UNIT CORRESPONDING TO FAST GLUTAMATE ACTIVATION TIME (APPROX. 1 msec)

Primary First Transmitters	Activation Time Scale	Inactivation Time Scale
Nicotinic acetylcholine, amino acids	1 to 2 or 3 units	10 to 50 units
Muscarinic acetylcholine, catecholamines	10 units or more	as much as 50 kilo-units
Many facilitating or depressing small molecule neurotransmitters	about 100 units	as much as 100 Mega-units
Peptides and hormones	about 10 kilo-units	greater than 1 Giga-unit
Growth factors	about 1 Mega-unit	never; changes are permanent

Backpropagation

One of the putative effects of slow modulation by metabotropic inputs is to enhance the onset of LTP through backpropagation of the neuron's output action potential into the dendritic arbor. (Note that this backpropagation is not the same as, and has nothing whatever to do with, the famous "backpropagation algorithm"). The mechanism involves desensitization of K^+ channels in the dendrite shaft.

Most neurons are not capable of backpropagating their action potential output. The firing of their output AP profoundly affects the membrane potential in the trigger zone and the surrounding cell body, but their dendrites lack the voltage gated Na^+ or Ca^{2+} channels required to conduct action potential propagation along the dendrites. (We discussed this previously in the Brief on dendritic integration). Basically, most dendrites cannot behave like axons. There are only a relative few types of neurons, e.g. neurons in the hippocampus, that possess the ability to backpropagate the output AP into the arbor, thereby triggering the opening of NMDA channels out in the dendritic spines.

However, certain types of metabotropic signals are capable of enhancing, to some degree, backpropagation into the arbor. The mechanism for this is the metabotropically-induced closing of K^+ channels in the dendrite. Closing these K^+ channels reduces the attenuation of the backpropagating AP by decreasing the cross-membrane leakage conductance of the dendrite. If a sufficiently large backpropagated AP reaches dendritic spines where NMDA receptors are currently enabled by the binding of Glu NTX molecules, the increase in membrane potential can flush out the Mg^{2+} blocking particle and trigger Ca^{2+} current inrush, thus satisfying the most basic necessary condition for induction of LTP at a glutaminergic synapse. This mechanism would constitute a biological basis for Hebbian weight adaptation. Such a neuron would be capable of "synaptic learning" for the duration of time the slow modulation effect lasted. The metabotropic modulation could be thought of as being analogous to an "attention getting mechanism" for neurons.

Postsynaptic Fast Elastic Modulation

Finally, biological neurons come equipped with a host of voltage gated channels whose main role is modulation of the signal processing carried out by that neuron. These VGC modulations are capable of producing a variety of neuronal responses including "on responders" (where the neuron fires a single pulse in the presence of a persistent excitation), "off responders" (where the neuron does not fire until the input stimulus stops), "delay responders" (where the neuron delays the firing of its first AP response), burst firing (where the neuron responds to a brief input with a burst of AP outputs), and firing rate modulation (where the neuron changes the frequency of its output AP train). Figure 6 illustrates some of the VGC – mediated responses a neuron might be capable of performing.

By far the largest class of modulating VGCs is the class of different K^+ voltage gated channels. Different K^+ channels vary in terms of membrane potential required for activation, in whether or not the channel is inactivating or non-inactivating, and in their time constants. There exist several non-K^+ modulation channels, including a family of persistent Na^+ channels and a family of low-voltage Ca^{2+} channels. More detail on this terminology and on the major classes of

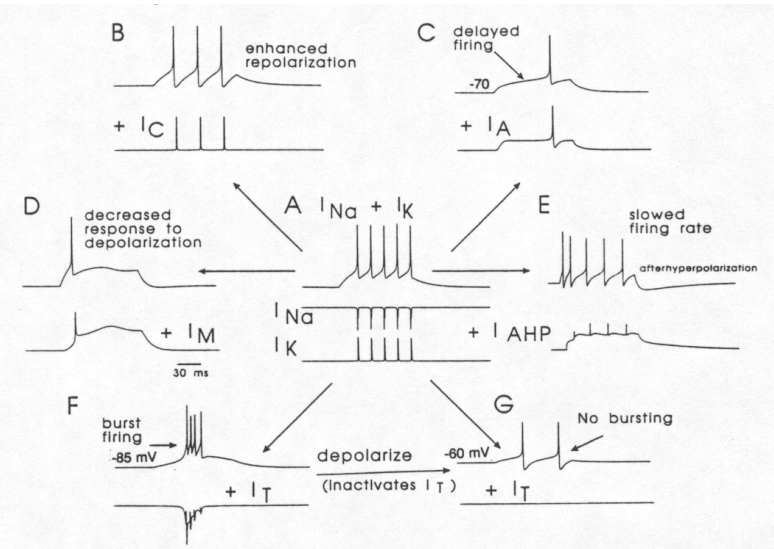

Fig. 2.4. A summary of different types of voltage-gated currents and the impulse firing patterns they produce in a neuron in response to steady injection of depolarizing current. At the center (A) is shown the repetitive impulse response of the classical Hodgkin-Huxley model (voltage recording above, current recordings below). Radiating out from this are changes in this pattern associated with the different types of ionic channels. **B:** Addition of the Ca^{2+}-activated K^+ current I_C (and the high-threshold Ca^{2+} current I_L) facilitates the repolarization of each action potential. **C:** Addition of the depolarization-activated but transient K^+ current I_A results in a delay to onset of action potential generation. **D:** Addition of the depolarization-activated but persistent K^+ current I_M results in a marked decrease in neuronal excitability. **E:** Addition of the slow Ca^{2+}-activated K^+ current I_{AHP} results in spike frequency adaptation and the generation of a slow hyperpolarization after the action potential train (afterhyperpolarization). **F:** Addition of the low-threshold and transient Ca^{2+} current I_T results in the generation of a burst of action potentials at -85 mV. **G:** Depolarization of the cell in F to -60 mV results in inactivation of I_T and now the cell generates a train of two action potentials. [Modified from Shepherd, 1994.] These traces are the result of computer simulations (Huguenard and McCormick, 1994).

Figure 6: Illustration of some types of elastic modulation by VGCs. The center figure (A) illustrates the basal (unmodulated) response of a neuron to a persistent excitation. The surrounding figures (B – G) illustrate different signaling patterns that can be invoked by various VGC modulation channels.

modulating VGCs and their effects can be found in my "Modulation Channels" paper from IECON'02.

Not every neuron expresses every one of these various types of VGCs. Rather, the mix of different VGCs present in a neuron "customizes" the neuron to perform different signal processing functions. Some of these channels, particularly Ca^{2+} VGCs, can also produce indirect elastic modulation effects by, for example, activating calcium-dependent K^{+} channels. The particular "mix" of modulatory VGCs a neuron possesses can produce highly complex signal processing capabilities, one example of which is the ability to act as a frequency – selective "filter" (responding strongly to AP trains coming in at a particular range of firing rates, and responding weakly or not at all to AP excitation coming in at different rates). In evolving our network designs, one thing we should keep in mind is that complex responses of various types are "on the table" should we find them useful.

These elastic modulations are not really synaptic weight modifications, and so the discussion of them in this Brief is in a way somewhat inappropriate. I include them here only for purposes of completeness. VGC – mediated modulations are "true modulations" of the basic signal processing behavior and information processing capabilities of a neuron.