Synaptic Weight Modulation and Adaptation
Part I: Introduction and Presynaptic Mechanisms

A Technical Strategy Brief for the
Neurofuzzy Soft Computing Program

R. Wells
May 15, 2003

The Biological Basis of Synaptic Weight

A "weight" in an artificial neuron model is meant to be a representation of the amount of effect that a synaptic input has on the overall response of the neuron. The neuron that generates the synaptic input (the "action potential" or AP) is called the "presynaptic neuron"; the neuron receiving the effect of the action potential is called the "postsynaptic neuron". The synapse is the biological structure that connects these two neurons. As such, "the" synapse belongs to neither the presynaptic nor the postsynaptic neuron. The part of the synaptic structure contained within the cell of the presynaptic neuron is called the "presynaptic terminal". The part of the synaptic structure contained within the cell of the postsynaptic neuron is called the "postsynaptic compartment". Between these two is a small, liquid-filled gap called the "synaptic cleft." Transmission from the presynaptic terminal to the postsynaptic compartment takes place by chemical signaling. The presynaptic terminal secretes particular molecules, called neurotransmitters (NTXs), into the cleft. These NTXs bind to receptor proteins on the surface of the postsynaptic compartment, and this chemical binding causes electro-chemical reactions to take place in the postsynaptic cell. Figure 1 illustrates the generic form of a synapse.

The "weight" of a synapse can therefore be regarded as a measure of the amount of postsynaptic response that occurs when an action potential invades the presynaptic terminal. The usual way this is measured[1] is in terms of the change in membrane voltage at the postsynaptic compartment (the "postsynaptic potential") per action potential event in the presynaptic terminal. A postsynaptic potential that depolarizes the postsynaptic cell (makes its membrane voltage less negative) excites the postsynaptic cell (tends to make it more likely the postsynaptic cell will respond by firing an action potential); such a response is called an "excitatory postsynaptic potential" (EPSP) and is associated with a positive synaptic weight. A postsynaptic potential that hyperpolarizes the postsynaptic cell (makes the membrane voltage more negative) inhibits the postsynaptic cell (makes it less likely to fire an action potential); such a response is called an "inhibitory postsynaptic potential" (IPSP) and is associated with a negative synaptic weight.

Boiled down to the lowest basics, synaptic weight is a function of the quantity of neuro-transmitters released, Q_N, and the number of active NTX receptors available at the membrane surface of the postsynaptic compartment, N_R. Complicating the matter a little is the fact that many postsynaptic compartments express more than one kind of NTX receptor, and so it is more accurate to talk about the *set* of active receptors. We can designate the number of active receptors of each type using the notation $\{N_R\}$ (where this notation denotes a set of different numbers of active receptors).

[1] In some kinds of synapses the signals do not produce electrical changes in the postsynaptic cell. Instead they set off biochemical reactions within the postsynaptic cell that change the way the cell behaves (modulation). These kinds of synapses are called "metabotropic". The measure of synaptic weight for them is some measure of the degree and extent of the metabotropic reactions they produce.

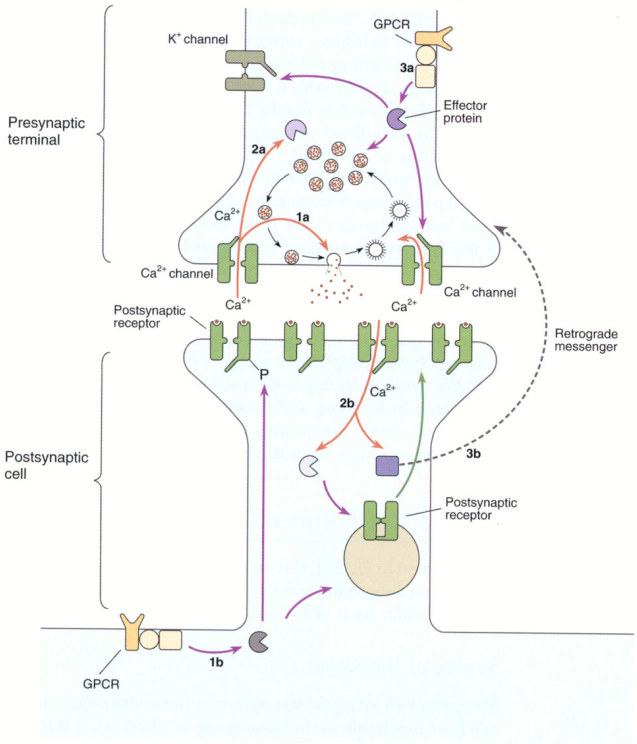

Figure 9.1. A variety of mechanisms and sites for synaptic plasticity. Calcium entry into the presynaptic terminal through voltage-gated Ca^{2+} channels directly triggers release (1a) and acts as a second messenger for short-term homosynaptic plasticity (2a). Activation of G protein–coupled receptors (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.

Two things are important to note in this synaptic organization. The first is that a specific presynaptic neuron is believed to be capable of expressing only one kind of NTX release. This principle is based upon evidence that suggests it is metabolically unfavorable for a neuron to manufacture more than one kind of neurotransmitter. Slightly complicating this simple situation is the additional fact that some (but not all) neurons are capable of secreting both small molecule NTXs (such as GABA or glutamate) and certain neuropeptides (hormones). In the latter case, though, the neuropeptides are generally co-released with the small molecule NTX, and so we still have only one "kind" of chemical signal emitted by the presynaptic neuron.

The second thing that is important to note is that the response of the postsynaptic cell depends on the suite of NTX receptors it expresses in its postsynaptic compartments. The type of NTX receptor, combined with the kind of NTX signaled by the presynaptic cell, determines whether a synapse is going to be excitatory, inhibitory, or strictly modulatory (metabotropic). The different synaptic compartments of a postsynaptic neuron can and do express different kinds of receptors, allowing some synapses to be excitatory, some to be inhibitory, some to be modulatory, and some to be both modulatory and either excitatory or inhibitory (but never both of the latter).

Neuropeptides are always modulatory. Small molecule NTXs that couple to **ionotropic** receptors are either excitatory or inhibitory. The same NTX molecule can be modulatory if it binds to a **metabotropic** receptor. The principal inhibitory NTXs are GABA (gamma aminobutyric acid) and glycine. The principal excitatory NTXs are glutamate ("Glu") and acetyl-choline (ACh). GABA, Glu, and ACh can also be modulatory when they bind with metabotropic receptors. There are also four other major small-molecule NTXs, whose roles are believed to always be modulatory. They are: norepinephrine (NE), serotonin (5-HT), dopamine (DA), and histamine. A summary of this "zoo" of NTX-receptor systems is provided in my "Modulation Channels" paper that I presented at IECON02 during the second meeting of the special session on neurofuzzy soft computing (NFSC-II).

Synaptic weight is some typically nonlinear function of neurotransmitter quantity and active receptor quantity

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

In general, this function is also going to be a function of the past history of synaptic activity because both Q_N and $\{N_R\}$ are activity dependent. This history-dependent variability is called "synaptic plasticity" by the biologists, although their use of the term "plasticity" is a little bit misleading to engineers; in engineering a "plastic" change usually denotes a change that does not or cannot return to the original pre-change condition. Most instances of synaptic weight change are in fact "elastic" (i.e. the change goes away over time and the synapse reverts to a "normal" state corresponding to some "typical state of activity"). To put it another way, synaptic weights when viewed on a small enough timescale are continually time-varying, but in the absence of signals that induce "real" plastic changes they tend to vary in a more or less bounded range about a mean weight value. Most synapses contain mechanisms for regulating the activity of postsynaptic receptors and neurotransmitter outputs, and this tends to reduce the "activity-induced noise" in the synaptic weight. Synaptic "plasticity" therefore can be taken as referring to some reasonable well-definable signaling conditions under which more or less well-defined and functionally significant weight changes occur.

Classification of synaptic plasticity can be defined along three "dimensions": 1) source of the induction of the change (what caused the change); 2) site where the change is expressed (either presynaptic or postsynaptic); and 3) the molecular basis of the induction (biophysical and biochemical mechanisms for the change). For our work, dimensions (1) and (2) are important. As for dimension (3), we can get by well enough with a merely cursory understanding – just enough to let us "see the picture" when asking ourselves if a particular neural network scheme is consistent with neurobiology.

The source of induction divides naturally into two cases: homosynaptic induction and heterosynaptic induction. In homosynaptic induction the only things involved in synaptic weight change are the presynaptic and postsynaptic neurons and the change is due to the intrinsic activity of the synapse. The functional changes in synaptic weight are triggered by processes that are localized in the presynaptic terminal, the postsynaptic compartment, or both. Heterosynaptic induction involves the activity of some "third player" in that the modification of the synaptic weight is due to the activity of a third neuron. This can take place either through direct synaptic action at an axo-axonal synapse (a synapse between the third neuron and the presynaptic terminal), or through indirect action (e.g. diffuse release of a neurotransmitter or hormone

elsewhere, or a metabotropic signal at a synapse located elsewhere on either the presynaptic or the postsynaptic neuron).

The site of expression of the change, as noted above, is either the presynaptic terminal or the postsynaptic compartment. Plasticity in the first case is called presynaptic plasticity; plasticity in the second case is called postsynaptic plasticity.

As for the molecular basis of induction, there are a wide variety of mechanisms that induce synaptic weight changes, but all have their basis in some form of metabotropic second messenger chemical. The "plasticity" can exist for a brief period of time (in which case I prefer to call it "elastic modulation"), or it can exist for a longer (but not permanent) stretch of time (in which case I like to call it "slow modulation"), or the change can be more or less irreversible (in which case I prefer to call it a "plastic weight change"). On a relative timescale, elastic modulation typically takes place over a time course on the order of tens to hundreds of milliseconds, slow modulation lasts from hundreds of milliseconds to several minutes, and plastic weight changes tend to last for days, weeks, or perhaps even a lifetime, and never revert back to the original conditions existing prior to the change. Plastic weight changes depend on the recruitment of gene transcription mechanisms in the cell's nucleus[2] and on the synthesis of new proteins by the cell.

Neurotransmitter Exocytosis

The process of releasing neurotransmitter into the cleft is called "exocytosis". This process basically involves three things: 1) the vesicle cycle; 2) influx of Ca^{2+} ions into the presynaptic terminal in response to an action potential; and 3) rapid induction of neurotransmitter release in response to Ca^{2+} entering the terminal.

Neurotransmitter molecules are stored inside small organelles called "synaptic vesicles". These are represented in Figure 1 by the small circles with the little dots inside them. The stages of the vesicle cycle are: 1) loading the vesicle with NTX molecules; 2) anchoring the vesicle in an actin "web", forming what is usually called the "available pool" of vesicles; 3) mobilization of part of the available pool by budding off the vesicles from the web and moving them toward the presynaptic membrane (these mobilized vesicles form what is usually called the "available for release pool"); 4) fusing the vesicle to vesicle docking sites at the presynaptic membrane (these are called the "ready for release pool"); 5) breaking open the vesicle, spilling its contents into the cleft (this is called "release"); 6) recycling the empty vesicles to begin the cycle all over again. The vesicle cycle is represented by the closed pathway marked by arrows in Figure 1.

Intracellular Ca^{2+} is required for both the mobilization of vesicles (step 3 above) and for the rapid release of neurotransmitter (step 5 above). The arrival of an action potential at the presynaptic cleft opens voltage-gated Ca^{2+} channels in the region of the vesicle docking sites. The resulting influx of Ca^{2+} triggers release of the NTX within a fraction of a millisecond. The synaptic cleft is very narrow (typically about 20 to 30 nm in length), and so NTX diffusion from the release site to the postsynaptic receptors takes place also within a fraction of a millisecond.

The opening of a vesicle is an all-or-nothing event. NTX release is therefore **quantized**. Under normal (unmodulated) conditions, typically either zero or one vesicle opens in response to an action potential. In fact, sometimes a vesicle may open spontaneously (in the absence of an action potential stimulus). This is believed to be due to random binding of residual Ca^{2+} to some structure in the vesicle or the docking site. Thus, NTX release is basically a stochastic process.

[2] The main job of the cell nucleus is the production of new proteins for the cell.

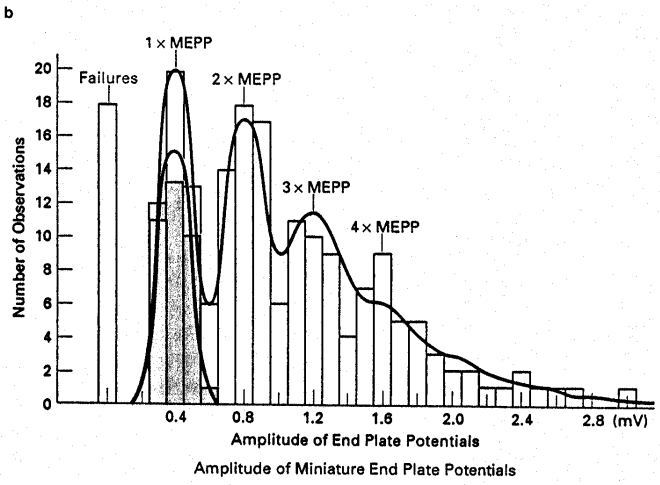

Figure 9–3. End plate potentials (EPPs) are made of multiple miniature EPPs (MEPPs). *a*: Under conditions of low transmitter release, nerve-evoked EPPs have amplitudes that correspond to a unit number of MEPPs. *b*: Histogram showing the relation between the size of EPPs and MEPPs in an experiment by Boyd and Martin (1956) on the cat neuromuscular junction.

Figure 2: Histogram demonstrating the quantized release of NTX during exocytosis

The evidence demonstrating quantized release of NTX is based on the measurement of small postsynaptic potentials (commonly called "miniature end plate potentials" or MEPPs; the name comes from the fact that the first studies of this were carried out in neuromuscular junctions at what are known as muscle "endplates"). Figure 2 illustrates a typical histogram obtained by this method. The case shown in Figure 2 illustrates **enhanced release** of NTX (a modulated condition). These distributions turn out to be multi-modal and can often be modeled with binomial, trinomial, etc. probability distributions. A "failure" occurs when an AP fails to stimulate any NTX exocytosis that produces a postsynaptic response.

The peak value of the postsynaptic MEPP response in the case of a single AP input (separated in time from the previous and the next AP occurrence) tends to scale in discrete steps. These discrete steps are, naturally, correlated to the number of vesicle that open in response to an AP input. Figure 3 illustrates typical MEPP responses.

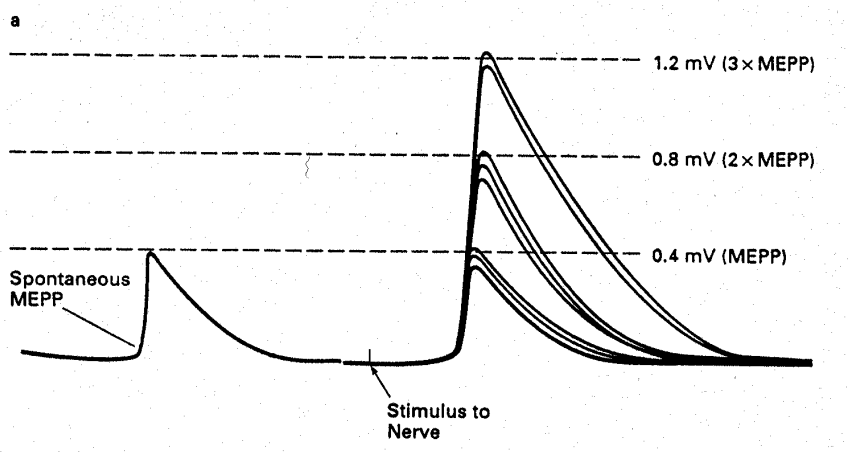

Figure 3: MEPP responses to different numbers of releasing vesicles.

Short-term Enhancement and Depression of NTX Release

The most common form of elastic modulation is presynaptic short-term enhancement or depression of NTX release due to presynaptic signaling activity. The time scale for this modulation is in the range from tens of milliseconds up to several minutes. As you should suspect, the reason for such a large range of time over which the elastic modulation persists is due to the fact that several different presynaptic modulation mechanisms exist. What these mechanisms all have in common is that they are induced by the influx of Ca^{2+} into the presynaptic terminal in response to an action potential.

Paired Pulse Facilitation and Depression

The briefest and most elastic forms of presynaptic weight changes are those associated with pairs of action potentials. Paired pulse facilitation is an increase in NTX output due to the time interval between the pulses; paired pulse depression is a decrease in NTX output due to the time interval between the pulses.

Paired pulse depression (PPD) is invariably observed when the second AP arrives within about 20 msec of the first pulse[3]. It is believed that this is due to the response time of the N-type voltage-gated Ca^{2+} channels that directly affect NTX release. The N-type channel is a slowly inactivating channel[4]. When the paired pulses arrive within 20 msec of each other, it is thought that the N-type channels have not had sufficient time to de-inactivate from the first AP. Therefore, the second AP is unable to produce the additional Ca^{2+} influx needed to trigger another vesicle into releasing its cargo of NTX. Indeed, based on Hodgkin-Huxley modeling of the N-type channel, the arrival of a second AP before the channel has had a chance to de-inactive should cause the channel to remain inactivated. Therefore, when the incoming AP pulse rate is too fast the release mechanism is in effect inactivated and the subsequent pulses produce no additional NTX release. This is basically the equivalent of taking the synaptic weight *w* to zero in response to brief AP spacing. It operates in effect like a "low pass filter" to AP signals. Another way to look at modeling PPD is to say that the NTX release probability drops to zero after the first AP until the N-type channels de-inactivate.

Paired pulse facilitation (PPF) is the opposite of paired pulse depression. It can be observed when the spacing between APs is from 20 msec to as much as 500 msec (in some cases). PPF is most likely due to the residual effects of the Ca^{2+} influx from the first pulse. The greater pulse spacing permits adequate time for the Ca^{2+} channels to de-inactivate. However, the process of "clearing out" residual intracellular Ca^{2+} is somewhat slow and the Ca^{2+} from the first AP has greater time to diffuse deeper into the presynaptic terminal. It is thought that this deeper penetration allows the Ca^{2+} to act upon some higher affinity modulation site for NTX release. PPF enhancement is often two-fold, i.e. it doubles the number of releasing vesicles. This would be the equivalent of doubling the synaptic weight. However, if the second pulse arrives "too late", no facilitation takes place. This would be due to the internal "Ca^{2+} cleanup processes" that clear out excess Ca^{2+} from the presynaptic terminal.

Short Term Enhancement and Depression from Tetanic Stimulation

A "tetanus" is a rapid train of action potentials. Tetanic stimulation is stimulation by such a

[3] To put things in perspective, a typical action potential has a duration of about 1 to 2 msec.
[4] Refer to the "Modulation Channels" paper mentioned earlier for a discussion of "inactivating" and "non-inactivating" voltage-gated channels.

train. The firing rate within a tetanus causing tetanic stimulation must generally fall into the same range as that associated with paired pulse facilitation. This is because of the need for the N-type calcium channels to be able to de-inactivate between successive pulses in the train. Tetanic stimulation produces a longer-lasting synaptic weight change than that produced by PPF.

Four distinct kinetic components of short-term weight enhancement have been observed in response to a tetanus. Two of these, named F1 and F2, are actually quite similar to one another and we probably lose nothing important for our purposes if we group them together and call them "facilitation". The third process is called "augmentation"; the fourth is called "posttetanic potentiation" (PTP). The onset and the decay of these different processes becomes longer as we move from facilitation to augmentation to PTP. In addition to these weight enhancements, there is also, superimposed on them, yet a fourth kinetic process termed posttetanic depression (PTD). Figure 4 illustrates the processes of facilitation, PTP, and PTD.

Facilitation. Facilitation is the most rapid of these processes. As shown in Figure 4, facilitation is characterized by a ramp-up in synaptic weight during the tetanus. This is followed by a leveling-off of synaptic weight, and then rapid decay in synaptic weight at the end of the tetanus. The rise- and fall- time constants for facilitation range from tens of milliseconds (F1) to hundreds of milliseconds (F2). One hypothesis of the cause of facilitation, at least for F1, is that this synaptic enhancement is merely the same mechanism at work as in PPF.

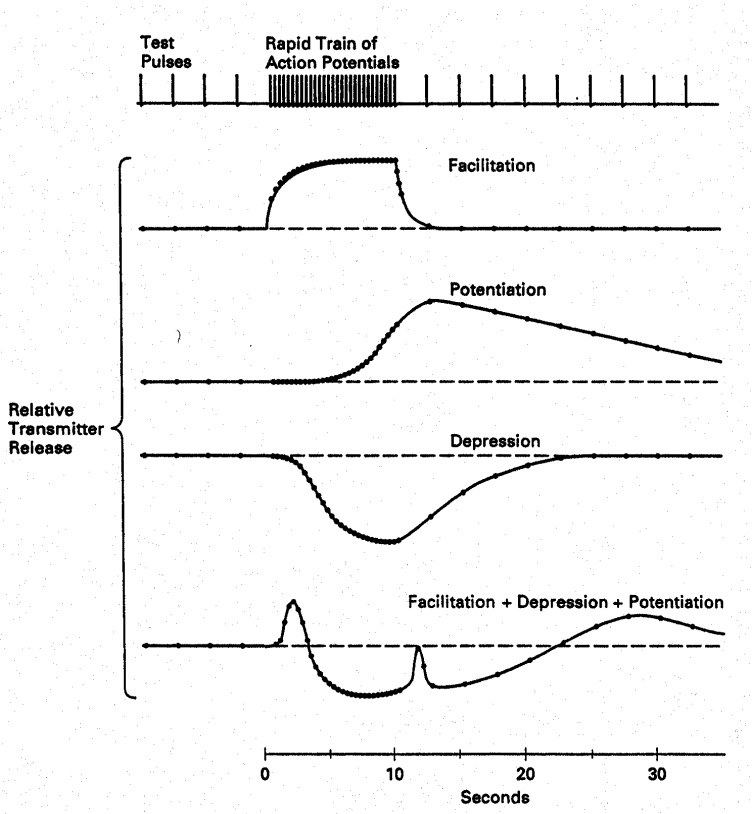

Figure 9–9. Homosynaptic plasticity. Typical time courses of facilitation, potentiation, and depression.

Figure 4: Time courses for short term facilitation, potentiation, and depression.

Augmentation. Augmentation might be thought of as very slow facilitation that never reaches a saturation point in weight enhancement. Augmentation requires several seconds of tetanic stimulation before it sets in. Synaptic weight then rises more or less linearly until the stimulation is stopped. After the end of stimulation, the synaptic weight immediately begins to decay, and this decay follows more or less the same rate as its rise during the tetanus.

The precise underlying mechanism of augmentation does not appear to be very well understood other than the fact that there is agreement that it involves the Ca^{2+} influx due to the APs. The long timescale it follows seems to point to some sort of metabotropic mechanism, and the continual increase in synaptic weight would seem to point to some effect taking place in the basic process of vesicle mobilization, presumably leading to either more docked and "ready to release" vesicles and/ or an increasing probability of Ca^{2+} - induced binding to the vesicle release mechanism. (The affinity for calcium binding with the release site is known to be low; but if the presynaptic terminal is drowning in excess Ca^{2+} then the number of successful binding events should increase simply because there is more opportunity to bind when more calcium is present).

Posttetanic Potentiation. PTP is the longest-lasting slow modulation mechanism and is also the slowest in onset. It requires tens of seconds of stimulation in order to be recruited, and its effects persist over several minutes. Assuming that synaptic plasticity and the phenomenon of memory are indeed related, it is clear that PTP constitutes a biological basis for short term memory. There is some evidence that the PTP mechanism might sometimes depend on a postsynaptic buildup of calcium with a subsequent retrograde signaling via membrane permeable gas molecules (e.g. nitric oxide) or small-molecule metabolites, although this hypothesis is by no means firmly established. It is firmly established that PTP depends on the influx of high concentrations of Ca^{2+} and strong evidence exists that PTP involves a calcium-dependent metabotropic process.

One of the things that high levels of calcium produce in a cell is a chemical reaction that produces a class of enzymes known as Ca^{2+}/calmodulin-dependent protein kinases. There are at least two types of these, known as CaMKI and CaMKII. There is evidence that CaMKII enhances vesicle mobility by attaching a phosphorus ion (a process known as phosphorylation) to the proteins that associate with synaptic vesicles and are involved in anchoring them to the cytoskeleton. There is also evidence that CaMKI may do something similar to this. In either case, the end effect is to dissociate more vesicles from the available pool and mobilize them for delivery to the presynaptic membrane (where they become ready to release NTX).

There is also another mechanism by which presynaptic plasticity could be induced, although this mechanism is likely to be more involved with heterosynaptic plasticity than with homosynaptic plasticity. The mechanism involves an enzyme known as protein kinase A (PKA), and we will talk more about this one below when we discuss heterosynaptic plasticity.

Posttetanic Depression. PTD is the opposite of PTP. It is a relatively long-lasting slow modulation that decreases the amount of NTX release in response to AP inputs. It appears to be the case that any presynaptic terminal capable of expressing PTP is also capable of expressing PTD. The precise mechanism of PTD is unknown, but one hypothesis favored by some is that PTD is caused by a depletion of the readily releasable pool of vesicles. This idea makes a lot of sense because PTD can only be induced by long tetanic bursts, which would deplete the population of ready vesicles, and the process of recycling vesicles is comparatively slow.

On the other hand, another possible mechanism is persistent inactivation of the Ca^{2+} voltage gated channels that bring calcium into the presynaptic terminal. Without an influx of calcium with each AP, the vesicles cannot open and release their NTX into the cleft.

Yet another hypothesis is that some mechanism is present that may inactivate the release process itself. However, what this mechanism may be is presently unknown.

Figure 4 carries the implication that all four mechanisms plus posttetanic depression occur together. In fact this is not the case. Instead it seems to be the case that the mechanisms are functions of the probability of NTX release at the synapse. When the release probability is low (small weights), then the synapse tends to show facilitation, augmentation, or PTP. When the release probability is high, the synapse tends to show posttetanic depression (PTD).

Autoregulation and Heterosynaptic Plasticity

In addition to the voltage gated calcium channels essential for NTX release, most presynaptic terminals also contain metabotropic receptors. A metabotropic receptor when activated does not directly produce the flow of any ionic currents into the cell. Instead it touches off a complex cascading biochemical reaction that alters the way the cell works. Often, but not always, these metabotropic receptors belong to the class of receptors known as "G protein coupled receptors" (GPCRs)[5]. Figure 1 illustrates a GPCR present in the presynaptic terminal. As indicated by the figure, these metabotropic receptors tend to be located away from the region of the synaptic cleft. They provide the presynaptic terminal with two important capabilities. In the first place, they provide the presynaptic terminal with the ability to autoregulate its own NTX release. In the second place, they provide receptors for synaptic connection with facilitating interneurons involved in *heterosynaptic* plasticity (plasticity induced by the actions of a third neuron).

When a neuron releases NTX into the synaptic cleft, not all of the NTX molecules bind with postsynaptic receptors. This potentially has two serious and undesirable possible side effects. First, the NTX chemicals might diffuse out of the cleft and affect other nearby synapses. This would injure the specificity of synaptic connections. Second, excessive buildup of neurotransmitters in the intercellular spaces often is toxic. Some forms of mental illness are believed to be due to toxicity of this sort. For that reason, neurons (and often the glial cells that surround them) come equipped with mechanisms for re-absorbing excess neurotransmitter chemicals. These mechanisms, as a class, are known as "reuptake transporters". It may be interesting to note that many kinds of addictive drugs, such as cocaine, work by disabling the reuptake transporter mechanism, leading to toxic buildup of NTX.

When high-rate tetanic stimulation is applied to the presynaptic cleft (with an accompanying increase in the magnitude of the synaptic weight), the cleft may become flooded with excess NTX. One way to think about this is to regard the situation as one where NTX release overpowers the short-term ability of the reuptake mechanism to clear out the excess chemicals. NTX diffusing out of the cleft can then bind with the GPCRs located out on the periphery of the presynaptic terminal. (Obviously, referring to Figure 1, they may also diffuse out and bind with GPCRs located on the postsynaptic cell as well).

[5] The other main class of metabotropic receptors are those that bind with neuropeptides. These receptors are also often coupled with G proteins, and in this sense they are also GPCRs, but usually a distinction is made between metabotropic receptors for small molecule neurotransmitters and those for neuropeptides.

When the NTX binds with GPCRs on the presynaptic terminal, the effect is usually inhibitory. The metabotropic reaction touched off by this binding has at least two possible inhibitory mechanisms. In the first case, the reaction can inhibit the voltage gated Ca^{2+} channels from opening. This, of course, shuts down further NTX release. The other possible mechanism is that the metabotropic reaction can inhibit something else in the release machinery. The end effect in either case is the same: a temporary resetting of the synaptic weight to zero. However, the second mechanism is in a sense the stronger one because it can inhibit NTX release that might take place owing to the calcium already built up inside the presynaptic terminal. Thus, this constitutes a mechanism by which the presynaptic terminal can autoregulate its own release of NTX. As might perhaps be self-evident, this inhibitory effect is only produced by relatively high frequency tetanic stimulation.

The presence of GPCRs on the presynaptic terminal also makes possible modulation of the synaptic weight through the signaling action of a third (facilitating) neuron. The facilitating neuron makes connection to the presynaptic terminal via a second synapse (called an axo-axonal synapse). This is illustrated in Figure 5. We can regard heterosynaptic plasticity due to this type of connection as a form of "gain control" of the main synaptic weight by the facilitating neuron.

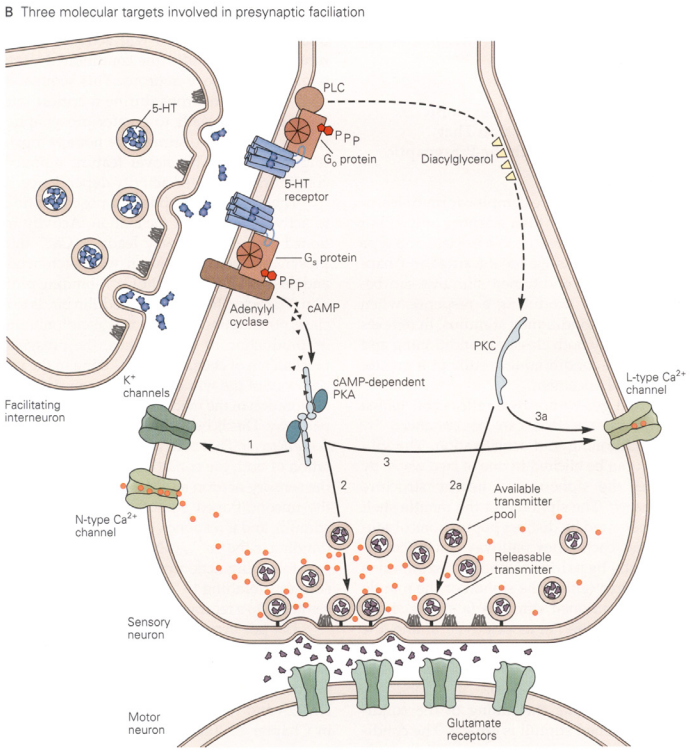

Figure 5: Presynaptic facilitation. In the example presented here we have an axo-axonal connection made to the presynaptic terminal. The NTX is serotonin. This type of connection can facilitate presynaptic transmission to the postsynaptic cell (bottom) through multiple mechanisms. The cAMP signal cascade activates PKA, which can close the K^+ channel by phosphorylation (1) and mobilize synaptic vesicles (2). It can also open L-type Ca^{2+} channels (3). There is also depicted a phosphoinositol system that produces DAG, which activates PKC to open the L-type channel (3a) and mobilize vesicles (2a). Note that 2-2a and 3-3a involve joint action of PKA and PKC. This is called "convergence" of the metabotropic signals.

This type of gain control can be either an enhancement (increase in the target synaptic weight) or a depression (decrease in the target synaptic weight). 5-HT (serotonin) as a modulating signal often leads to weight enhancement. There are two primary mechanisms for this. The first is that 5-HT can cause a widening in the duration of the action potential in the presynaptic terminal. A wider AP holds the presynaptic terminal's voltage gated calcium channels open for a longer interval of time (ultimately limited by inactivation of the calcium channel). This leads to a greater influx of Ca^{2+} and an correspondingly greater NTX release probability. A 10% to 20% increase in the width of the AP typically leads to a 1.5× to 2× increase in the amount of NTX released.

The second mechanism for modulating the synaptic weight is through direct action on the release mechanism and/ or the vesicle cycle. The cAMP signaling path (see Figure 5) is thought to be responsible for this type of modulating action. The metabotropic signaling cascade increases vesicle mobilization, increasing the probability of vesicle fusing to the membrane, and there is evidence that it can also increase the number of vesicle docking sites. It should be noted that 5-HT modulation of the synaptic weight is a mechanism that does not depend on calcium levels in the presynaptic terminal. Thus, modulation by the facilitating interneuron is more or less independent of whether the presynaptic terminal is undergoing plasticity of the types we covered earlier.

5-HT often, but not always, enhances the synaptic weight; in contrast, other types of NTX emitted by a facilitating neuron can depress the synaptic weight. For example, NTX-GPCR pairs that inhibit the cAMP cycle in Figure 5, or which inhibit the opening of voltage gated calcium channels can decrease NTX release from the presynaptic terminal, thereby decreasing the synaptic weight. Metabotropic signaling via histamine is often depressing, as is GABA binding with the metabotropic receptor $GABA_B$. Norepinephrine (NE) can reduce calcium currents and shorten action potential duration. A number of neuropeptides, such as FMRFamide or the mu-opoid peptides, inhibit AP-invoked NTX release as well as release evoked by elevated Ca^{2+} levels. The important point for our neural networks research is this: That heterosynaptic control of synaptic weights is possible, and that this control can be either enhancing or depressing (but never both for the same facilitating synapse).

Metabotropic processes are slow in onset, owing to the complex nature of the biochemical cascade reaction that makes them up. They are also relatively long-lasting, which means the weight modifications we are discussing fall into the slow modulation category. Onset of the modulation effect may take tens of seconds to a few minutes; the modulatory effect can last for many tens of minutes. Modulation by heterosynaptic metabotropic messengers can also be extremely potent. Even a single pulse of 5-HT applied as in Figure 5 is sufficient to produce a modulation effect.

The second messenger chemicals responsible for metabotropic effects can diffuse widely throughout the entire cell. As a consequence, the effects of these modulatory inputs are not necessarily restricted to the presynaptic terminal to which they are applied but can spread to and affect *all* of the presynaptic neuron's synaptic connections.

Presynaptic Long Term Potentiation

It is now known that, in addition to the elastic and slow modulation effects discussed above, long term potentiation (LTP) takes place in at least some presynaptic neurons. LTP is a truly plastic weight change; the synaptic weight does not relax back to the original condition, although some degradation can occur. The effects can last for days, weeks, months, or even years.

In conventional artificial neural network theory, "training" a network and the adaptation algorithms employed in training the network are supposed to reflect LTP (and LTD) in their biological counterparts. An understanding of LTP mechanics in biological systems is arguably a key step in our ability to develop adaptation algorithms for our pulse-coded neural networks.

Presynaptic LTP, as it is presently understood, always involves elevated levels of Ca^{2+} in the presynaptic terminal. Furthermore, there is some fairly strong evidence that indicates that no postsynaptic activity is needed to induce presynaptic LTP, although many argue that in at least some cases postsynaptic activity is involved in presynaptic LTP induction, via some retrograde messenger such as nitric oxide (NO) or possibly metabolites arising from metabotropic signaling cascades. In the case of presynaptic LTP, it seems to be the case that elevated calcium levels act on an enzyme known as adenylyl cyclase, which in turn produces increased levels of cAMP (cyclic adenosine monophosphate), which in turn activate another molecule known as protein kinase A (PKA). PKA is the same molecule associated with the PTP mechanism discussed earlier (see Figure 5). It is thought that PKA acts to modify some aspect of the synaptic vesicle cycle or perhaps acts on the vesicle release machinery itself. Repeated heterosynaptic applications of 5-HT (as in the enhancement modulation discussed above) is known to induce presynaptic LTP. One model of this effect is illustrated in Figure 6.

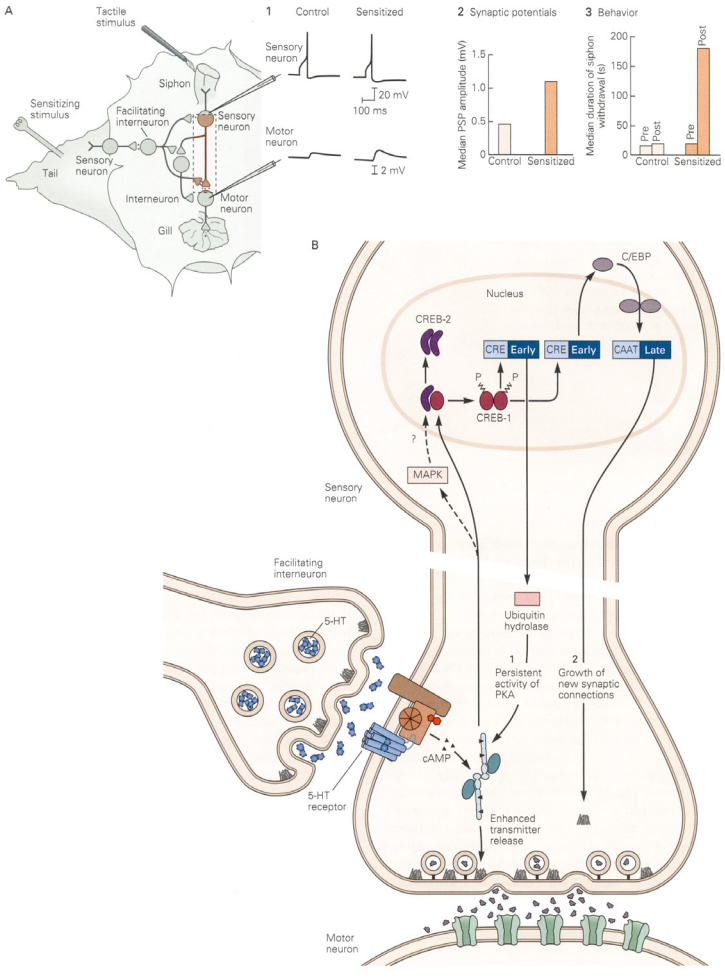

Figure 6: Presynaptic LTP model for induction by serotonin (5-HT)

As indicated in Figure 6, presynaptic LTP involves a biochemical cascade process in which certain molecules are translocated to the cell's nucleus. This produces two responses. In the first, an enzyme is produced (ubiquitin hydrolase) that moves back to the presynaptic terminal and reacts with PKA in such a manner as to disable the ability of this kinase to deactivate. Since PKA is the effector responsible for the enhancement of synaptic weight discussed earlier, its persistent activity acts to continue its effect on the vesicle cycle and/ or vesicle release machinery, thus maintaining the enhanced synaptic weight. This response is called "early phase LTP".

But there is a second effect at the nucleus as well. The nucleus is stimulated to the production of new growth hormones and proteins that lead to the growth of new synaptic connections. After whatever growth period is required, the single original synapse becomes reinforced by additional parallel synaptic connections. This is called "late phase LTP", and it is obviously productive of a permanent increase in synaptic strength.

While it now appears to be fairly certain that presynaptic LTP occurs in at least some neurons, the question is a bit more open when it comes to asking whether or not a purely presynaptic form of long term depression (LTD) also exists. It is known that under certain conditions, those where synaptic activity is persistently very low, synapses can and do "die off." This would certainly qualify as a "depression" since taking away a synapse "kills its weight". But whether this phenomenon is due to an entirely presynaptic mechanism or involves some sort of postsynaptic trigger, is not really known at this time.

Implications for the Neurofuzzy Project

We have discussed the variety of different presynaptic mechanisms for changing synaptic weights. What implications do these mechanisms have for our project? I think there are several.

First, we need to note that **presynaptic** weight change mechanisms are **non-associative**. This means that the weight change is restricted only to those synapses where the presynaptic neuron makes contact and is active. No nearby synapses, connected to other neurons, are affected by the presynaptic mechanisms of weight modulation and adaptation. A great deal of conventional artificial neural network theory concerns itself with building "associators" that pair off different "signal patterns" with each other such that the occurrence of one of these patterns implies the occurrence of the other. Presynaptic weight changes cannot form associations. But it can reinforce signaling sent on to the postsynaptic cells to which the presynaptic neuron is connected.

The next thing to note is that the mechanisms discussed above are **global** in the sense that every one of a neuron's presynaptic terminals normally receives the action potential, and therefore any weight changes brought about through AP activity at one presynaptic terminal is most likely to also occur at all the other presynaptic terminals. The possible exception to this rule is if one of the terminals has an axo-axonal input from a facilitating neuron such that AP transmission to that terminal is blocked by the action of the facilitating neuron. This global character of presynaptic weight change is in contrast to the postsynaptic mechanisms we will discuss in part II, which are **specific** to the particular synapse. We could say that presynaptic weight changes are **generic** to the network, while postsynaptic changes are **discriminating**.

Finally, I think it is of some use to us to simply know that adaptations and modulations as described here are biologically possible and mathematically permissible. Standard neural network theory does not deal with this generic type of adaptation, but biological neural networks use it.