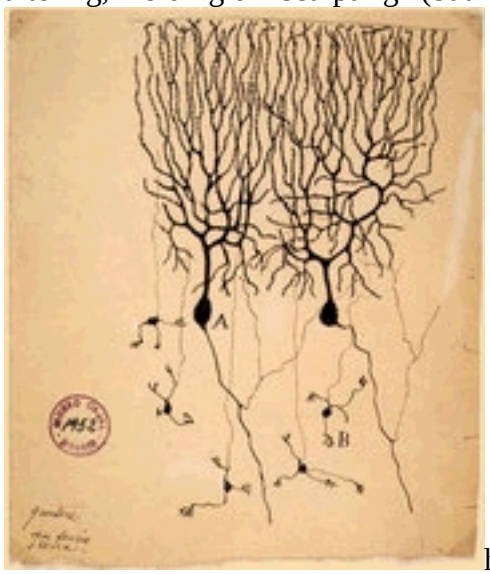
Central Synaptic Transmission

The main excitatory transmitter in the brain is the amino acid glutamate. The main inhibitory transmitters in the brain are the amino acids glycine (in the spinal cord) and gamma-amino butyric acid (GABA, in the rest of the CNS). Although both ionotropic and metabotropic glutamate receptors are found at many synapses, rapid excitation occurs when the cation-selective pore of the ionotropic glutamate receptor allows sodium ions to enter and depolarize the postsynaptic cell, like at the neuromuscular junction. Although central synapses operate in a manner similar to the neurpomuscular junction, they are very diverse. In particular, while the nmj is an extremely powerful, reliable connection formed by many synapses acting in parallel, many central excitatory connections are rather weak, and cannot by themselves reliably fire the postsynaptic cell. Instead, the cooperative action of several, or many, inputs is often required. This means that a neuron "computes" and communicates some, hopefully useful, function of its inputs. Neuroscientists believe that learning occurs when synapses gradually alter so that the computation performed by individual neurons becomes more useful.

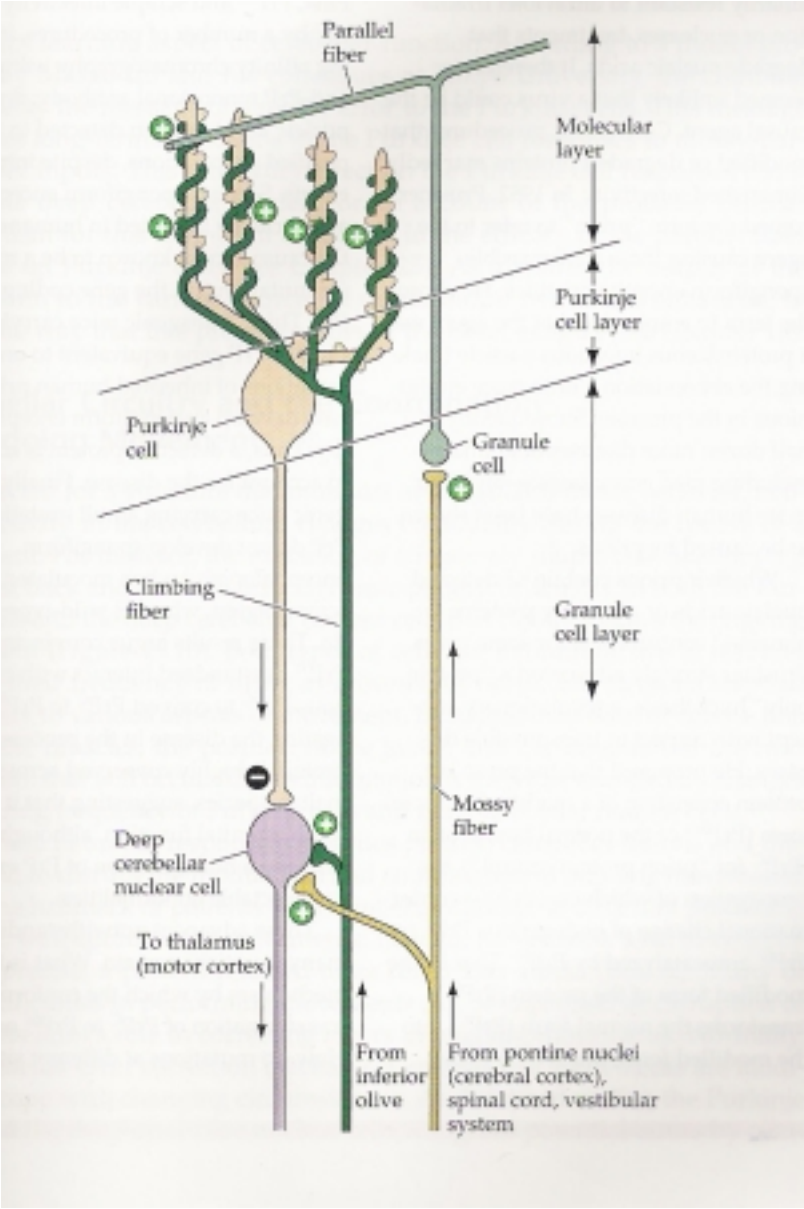
<u>An illustration – the cerebellum</u>.

The cerebellum is a cauliflower-shaped and sized structure at the back of the brain that appears to be involved in aspects of motor learning. It is composed of a folded sheet of neurons (the cerebellar cortex) linked by white matter (the incoming and exiting axons) to deep clusters of neurons, the cerebellar nuclei. The most striking neurons of the cerebellar cortex are the large Purkinje cells (PCs), whose cell bodies lie in a tight plane, and whose dendrites spread out in the "molecular layer" lying above (see Fig 1). However, although the PC dendrites are very elaborate, and highly branched, they lie in a single plane, and all the PC dendrites are parallel to each other. The PC cell is inhibitory and releases GABA, and its axon travels to the deep cerebellar nuclei (DCN). These axons are the sole output of the cerebellar cortex, and work by inhibiting, and thus altering, molding or "sculpting" (but not initiating) the ongoing activity of the DCN cells.



historic drawing by Ramon y Cajal of 2 Purkinje cells with 5 granule cells.

The PCs are excited in 2 very different ways. Each PC cell receives a very strong connection from a single “climbing fiber” (CF) , the axon of cells in the inferior olive of the brain stem. A single action potential in a CF triggers a massive epsp in the PC, which is strong enough to cause a burst of spikes in the PC, the so-called “complex” spike. As we will see, the CFs carry “error signals”, which measure how close an actual movement was to the intended movement. Thus as one learns to play better a piece of piano music or to improve a golf swing, fewer and fewer CFs will fire. We will not discuss how the inferior olive actually computes these error signals.



The other excitatory input arrives via “mossy fibers”, which mostly arise from nuclei in the pons (which are themselves targets for axons coming from the neocortex, and from sensory neurons). The mossy fibers synapse on the short dendrites of granule cells (GCs), which lie in a layer just beneath the PC layer. There are huge numbers of these tiny GCs, probably more than all the other neurons in the brain, and far more than there are mossy fibers, so there is a large “divergence” from mossy fibers to GCs. Each GC sends an axon up into the molecular layer, which splits into 2, like a “T”, and then runs perpendicular to the plane which defines the PC dendrites, strung through these dendritic trees like telephone wires through a telephone pole. Each PC cell receives a single synapse from 200,000 of these Parallel fiber” (PF) axons. Thus the PC receives information about the neocortical movement commands and their sensory context arriving on the mossy fibers, but because of the massive divergence, each PC samples a unique and limited subset of these mossy fiber inputs. Furthermore, because each PF makes only a single, rather weak, synapse, which can only depolarize a PC by less than a millivolt, a number of PFs must fire at roughly the same time to drive the PC to threshold, when it fires a single “simple” spike. We say that a number of PF epsps must “summate” to fire the cell. However, not all PF synapses have the same strength, so the exact number (and timing) of the PF spikes required to fire the PC will vary.

While the CF synapses are made on the dendritic shafts, the PF synapses are made on dendritic protrusions called “spines”, which are made up of a thin stalk about 1 um long, and a “head” on which the synaptic knob (or “bouton”) sits. In almost all neurons the spike is initiated at the beginning of the axon, where it leaves the cell body, the “axon hillock” or “initial segment” (IS). The spike threshold is lower there than elsewhere because of the high density of sodium channels. It was once thought that the spine neck could act as a barrier to the passage of synaptic current to the dendrite (and ultimately, after considerable leakage across the dendritic and somatic membrane, to the axon hillock) it is now clear that the spine neck conductance is always much higher than the synaptic conductance itself, and therefore does not form an electrical impediment. We now think that spines exist because they aid synaptic plasticity, either by compartmentalizing calcium signals, or by allowing new synapses to form even at locations where axons and dendrites do not actually touch.

Both the CFs and the MFs send side branches (known as collaterals) to the DCN neurons. The PC input to the DCN therefore “sculpts” or modifies ongoing activity caused by the arrival of MF and CF spikes.

The key point here is that the CF connection is very strong and always fires the PC, while the PF connections are individually very weak, and must cooperate to fire the PC, even though in both cases glutamate is responsible.
How does this arrangement lead to motor learning? The key event seems to be “long term depression” (LTD) of the PF connections – a persistent weakening of certain PF synapses caused by the nearly coincident firing of those PFs and a CF. AS we will see in a later lecture, this LTD seems to be caused by the combination of PC complex spiking (caused by its CF) and the activation of a particular set of PFs, such that in the future different patterns of PF activity will be required to initiate simple spikes in that PC, producing

changes in the PC-induced sculpting of the pattern of motor activity in DCN neurons. In particular, any patterns of PC sculpting which result in movement errors will tend to be suppressed by LTD, so the number of errors will gradually fall.

Excitatory Conductances, Currents and Potentials

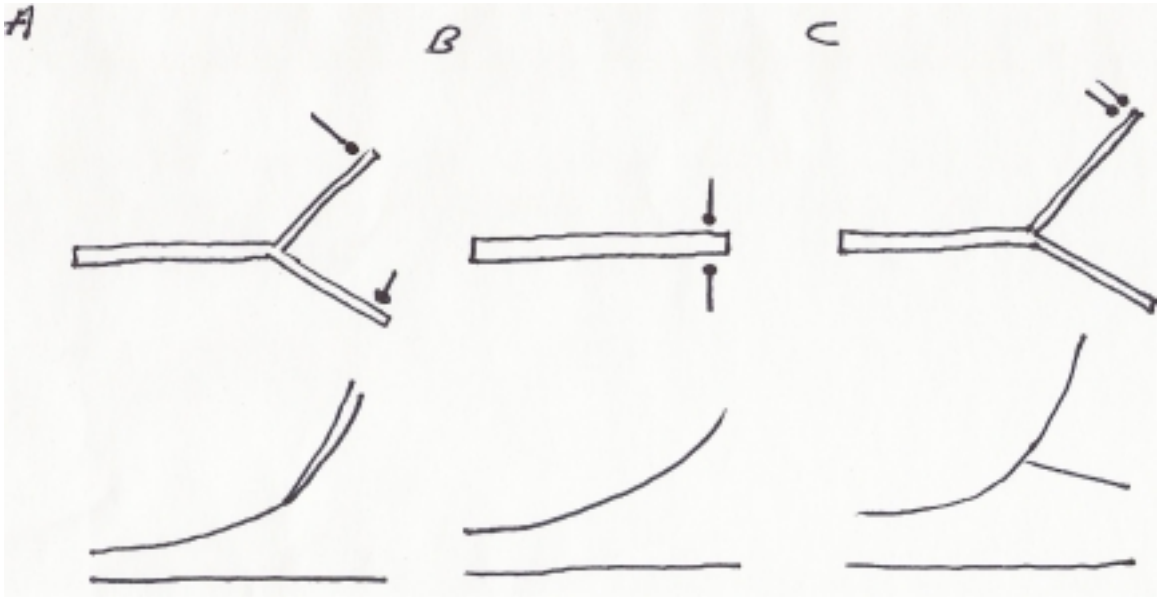
Open glutamate receptors do not discriminate between Na+ and K+, and since the external concentration of Na and the internal concentration of K are approximately equal, the Goldman equation predicts (1) that the reversal potential will be zero (2) the current through a single open glutamate receptor will vary linearly with voltage, according to $i = g_{ex}(V-0)$ (exactly like the nAChR at the neuromuscular junction). Thus we can think of the firing of excitatory synapses as briefly inserting a parallel conductance $G_{ex} = ng_{ex}$ (where n is the total number of glutamate receptors that open as a result of synaptic action) across the resting membrane (or "leak") conductance G_L (which is in series with the leak battery E_L). The synaptic depolarisation ΔV will therefore be given by $\Delta V = -E_L Gex/(Gex+G_L)$. This is a hyperbola which saturates at $-E_L$ for large values of Gex (i.e. a very large synaptic input will drive the neuron close to the synaptic reversal potential, 0mV). The synaptic conductance change which produces a half maximum potential change will be equal to the resting conductance. Most important, small synaptic conductance changes ($Gex << G_L$) will produce a depolarization which is proportional to the conductance change, the proportionality constant being given by the resting membrane conductance (or the reciprocal of the input resistance). For example, the same synaptic action will produce a larger depolarization in small cells than in large cells. Thus weak synapses essentially act as pure current sources (and in fact since threshold is closer to rest than to zero, excitatory synapses can generally be regarded as pure current sources).

This discussion implicitly assumed that the cell was isopotential (e.g. that the synapses are formed on the cell body). However, most excitatory synapses are formed on dendrites (spines or shafts). Since these synapses are individually weak ($Gex<< G_L$), they act as pure current sources (they do not drive the local membrane potential close to zero). Therefore to a first approximation we can use passive cable theory to understand how these currents will combine at the IS. (Please bear in mind that dendrites are not actually passive, and that saturation effects may play important roles in high input resitance structures like spines and narrow dendrites.)

Let us first neglect the role of the membrane capacity. If the dendrites were very long, then only a small fraction of the injected excitatory current would reach the IS. However, dendrites are typically quite short compared to the membrane space constant and so less attenuation will occur.
In principle we could calculate the degree of attenuation in the short cable if we could replace the dendritic tree by a single equivalent cable, using the Rall law requirement that the sum of the 3/2 power of the daughter diameters equals the 3/2 power diameter of the parent branch. We would also need to take account of the fact that the soma is itself an appreciable electrical load on one end of the cable (i.e. that the cable is not sealed at both ends), and we would have to assume that all dendrites terminate at the same electrical

length (i.e. physical length divided by space constant). For example, in a sealed cable 1 length constant long, the greatest attenuation (i.e. with the synapses placed at the tips of the denhdrites) would be about 65% (cosh 0/cosh1), but for a cable terminating in a large leaky soma) the attenuation will be much greater (indeed, complete if the soma acts as a true short-circuit).

Fig 1. Distribution of steady state voltage in a branched dendrite. The top row shows 3 different versions of a branched dendrite. Passive membrane properties are uniform. The bottom row shows the corresponding ways the steady depolarisations produced by synapses at the dendritic tips will decay along the dendrites. The bottom lines show the resting potential, which is the same everywhere.
A.This shows a branched dendrite with active synapses at each tip. The voltage initially decays quite rapidly because the space constant of these thin branches is short (the voltage decays identically in each branch, but a slight difference has been drawn for illustration only). From the branch point on, the cable thickens, so the space constant is longer, and the decay is slower. Because these branches have identical lengths, the synapses are equally strong, if Rall's Law holds we can represent A by B. Note that the same total amount of current is injected into the single equivalent cylinder. The decay follows the short sealed cable equation. In C, the same amount of current is again injected, but this time only into one of the tips. In this case we cannot use the equivalent cylinder, because the 2 dendrites are nonidentical. Because the input resistance of the branch is larger than that of the equivalrnt cylinder, the initial voltage under the synapses will be larger than in B. When the synaptic current reaches the branch point, the majority flows into the parent dendrite, and a small amount into the nonexcited daughter branch (more flows into the parent than into the daughter because the former has a lower input resistance). However, the voltage decays rather weakly in the unexcited daughter, because it is much shorter than the whole dendrite.



It should be noted that if the synaptic actions are strong enough so that the local potential approaches the reversal potential, the resulting nonlinearity will depend strongly on the relative locations of the participating synapses. For example, in fig 1 A the synapses are far apart, so the depolarization produced by one will not be much affected by the other. In Fig 1C, the synapses are colocalised, so the depolarization produced by one will greatly reduce the driving force for the other, decreasing the total synaptic current. This effect is probably particularly important for synapses on the same spine, and probably explains why typically there is only one excitatory synapse per spine.

Ball and Stick Model

If the dendrites can be represented as an equivalent cylinder, we can represent the soma-dendrite combination as a "ball and stick" model. Clearly, if current is injected into the soma, then the steady state distribution of voltage along the cable will be given by the standard short cable equation, allowing for the fact that only some fraction of the injected current will flow into the cable (the remainder flows across the somatc membrane). This fraction is called rho, it is difined by the ratio of the somatic and dendritic input resistances. It is typically around 1, or slightly less. However, the outcome will be more complex if the current is injected into the dendrite, for example via an excitatory synapses (see Fig). Under these conditions solutions are usually found by computer simulation.

Although real cables have capacity, these calculations will still us what the *charge* attenuation will be (since the effect of capacity is merely to smear the voltage changes over longer times, but not to affect the charge flow. This reflects the fact that capacitors store charge, rather than allowing it to cross the membrane.). This leads to the prediction that there will be relatively little *charge* attenuation even if the synaptic currents are brief compared to the membrane time constant. But as we will now discuss there will be significant *voltage* attenuation.

Time-dependent cable equations become quite complicated even for somatic current injection into ball-and-stick models, though careful analysis of experimental responses to step currents sometimes allows determination of cable parameters such as tau, lambda, rho and L.

Fig 2 shows an example of numerical simulations for injections of synapse-like currents. The "synaptic" current (middle row of figure) has a rise time equal to the decay time constant (alpha function). It can be seen that the voltage reponse is much larger when the "synapse" is close to the soma, than when it is far away. The attenuation of the distal input is much greater than in the steady state case because most of the injected current flows across the dendrite before reaching the soma. Also, the risetime of the response is greatly increases when the synapse is located distally, in just the same way we saw already for the delay in the voltage response to current steps in cable theory. The decay times are the same everywhere, because they basically reflect the membrane time constant. Patch clamp experiments, using whole cell recording from different points in the dendritic tree, have confirmed these predictions experimentally.

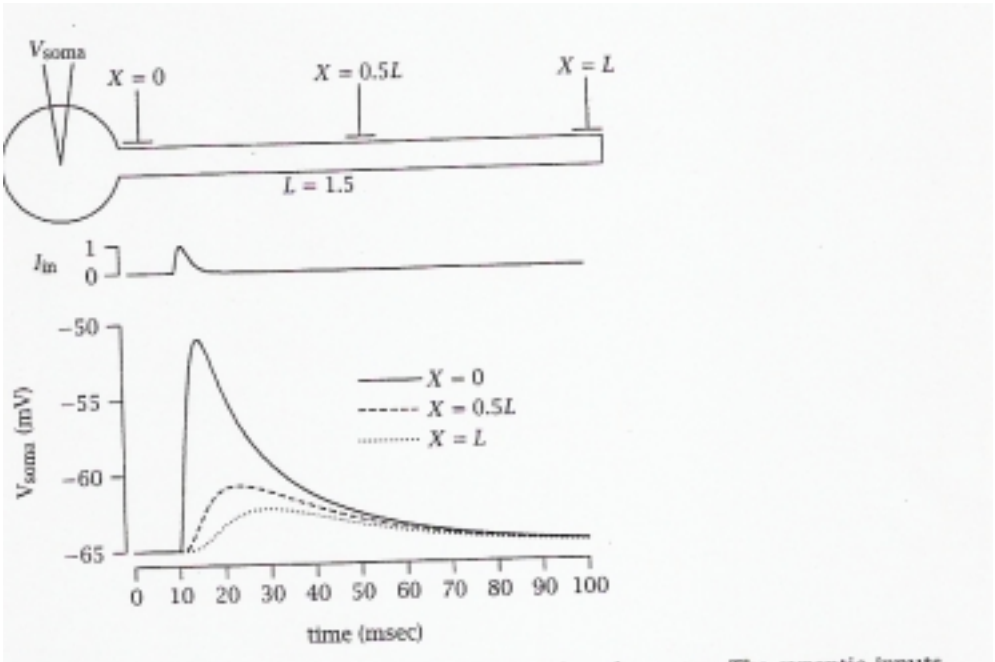


Figure 4.27 Shapes of simulated EPSPs measured in the soma. The synaptic inputs were represented by a conductance change in the form of an alpha function ($I_s = G_s(t/\alpha)e^{-\alpha t}(V_m - E_s)$). I_{in} illustrates the shape of the current injected by the synapse at each of the indicated locations in the dendrites. Same compartmental model as in figure 4.25.

Interestingly there is some evidence that neurons may compensate for this strong attenuation of brief distal synaptic inputs in at least 2 different ways: the quantal size may be larger for more distal synapses, and active membrane properties may boost more remote inputs.

Another way that neurons may respond to this problem is by zoning synapses from inputs that have different roles or origins on different parts of the dendritic tree. For example, in the relay neurons of visual thalamus (LGN), retinal inputs are targeted to proximal dendrites and layer 6 neocortical feedback excitation to more distal dendrites. It is likely that the timing of individual spikes might be important in relaying retinal information to cortex, whereas the cortical feedback may exert a slower, more modulatory role. In order to minimize saturation, synapses impinging on the same zone should be scattered as widely as possible over that zone (for example at similar electrotonic distances but on different dendrites). Indeed it is often found that the synapses made by a single axon on a single postsynaptic cell are widely scattered (this suggests that new synapses are formed independently of each other).

Spatial and Temporal Summation.

With this background, let us consider the vital question of how excitatory input is translated to spike output. If the synapses act as pure current generators, then whether and when a spike is emitted will depend on the net current reaching the IS, where the voltage threshold is lowest (because of the high Na channel density). In general this could only be

predicted by solving the HH equations for the particular current waveform. But to a first approximation, we could consider the voltage threshold to be fixed, so the critical question becomes whether the combined synaptic input exceeds that threshold. This leads to the notions of spatial and temporal summation.

In the simplest case we could consider the various synaptic currents (possibly distorted by cable properties) to arrive at the same time in the cell body, where they will add together, and may drive the IS to threshold. Since the synaptic currents add together, this is described as "spatial summation". If one synaptic current arrives shortly after another, with a delay much less than the membrane time constant, spatial summation will still occur (and as noted above will be more accurate if the contributing synapses are dispersed over the dendritic tree). If the delay t between the arrival of the synaptic currents is comparable to the membrane time constant (tau), then some decay of the first somatic epsp will have occurred before the later ones arrive, so now the currents themselves will not add, but the currents weighted by a factor exp-t/tau. This is called temporal summation: currents add, but after weighted by their arrival times. If the arrival times differ several times the time constant, they will not summate at all.

This leads to 2 different views of the neuron: as "integrator" (i.e. faithful summation) or as "coincidence detector" (subthreshold epsps only trigger spikes when they are close together in time). These 2 views are closely related to the debate about the nature of the neural code.
We know that spikes carry information between neurons, but what aspect of the spikes convey that information? Since the spikes themselves are all or none events, the information must be coded in the intervals between the spikes. There are 2 extreme possibilities: all the information could be coded in the mean rate (average of reciprocal spike interval) , and no information in the actual spike intervals, or the information could be coded by the actual lengths of each individual interval. The former case is called a "rate code" and the latter a "timing code". Note that the information per spike (bits/spike) will be much greater in the latter case. There are several situations in which careful information theoretic analysis has shown that a timing code is employed (several bits/spike), but there are also good reasons to suppose that many neurons use a rate code. For example, if a neuron is typically fired only by the combined effect of many axons (eg the PC cells in response to PFs), then it is difficult to see how the neuron can "keep track" of the arrival times of the incoming spikes. In these situations the individual synapses are small and quite "noisy" (for example, because quantal responses involve only small numbers of open channels), but the synaptic noise is averaged over many inputs (at the cost of smearing the potentially available timing information). In other situations, for example in early parts of the auditory system, connections are very strong, so inputs can precisely control the timing, and not just the rate, of the output spikes. On balance it seems likely that a variety of codes are used in different situations. It is quite possible that even in a single neural circuit the nervous system can rapidly adjust the nature of the code to match the statistical properties of incoming signals.

If a timing code is used, it has to be "decoded" at some point. It turns out that the temporally-weighted summation process described above is exactly what is needed to

decode a timing code (it is obviously highly responsive to the delay between incoming spikes). So the apparent drawback of temporal summation (i.e. that the summation is not faithful) is actually an advantage.

If the membrane time constant is much shorter than the mean interval between spikes, then temporal decoding becomes very inefficient and much of the information in a timing code becomes unavailable. Under these conditions the neuron act as a coincidence detector: subthreshold synaptic inputs only fire the output cell if they arrive at nearly the same time. One interesting use of coincidence detection is in detecting the arrival time differences for sounds at the 2 ears, in order to estimate spatial position of sound sources.

As we will see in discussing Hebb synapses, coincidence detection can also be implemented exploiting the biophysical properties of the NMDA receptor, and although this is usually considered in relation to synaptic plasticity, it could also play a role in neuronal coincidence detection.