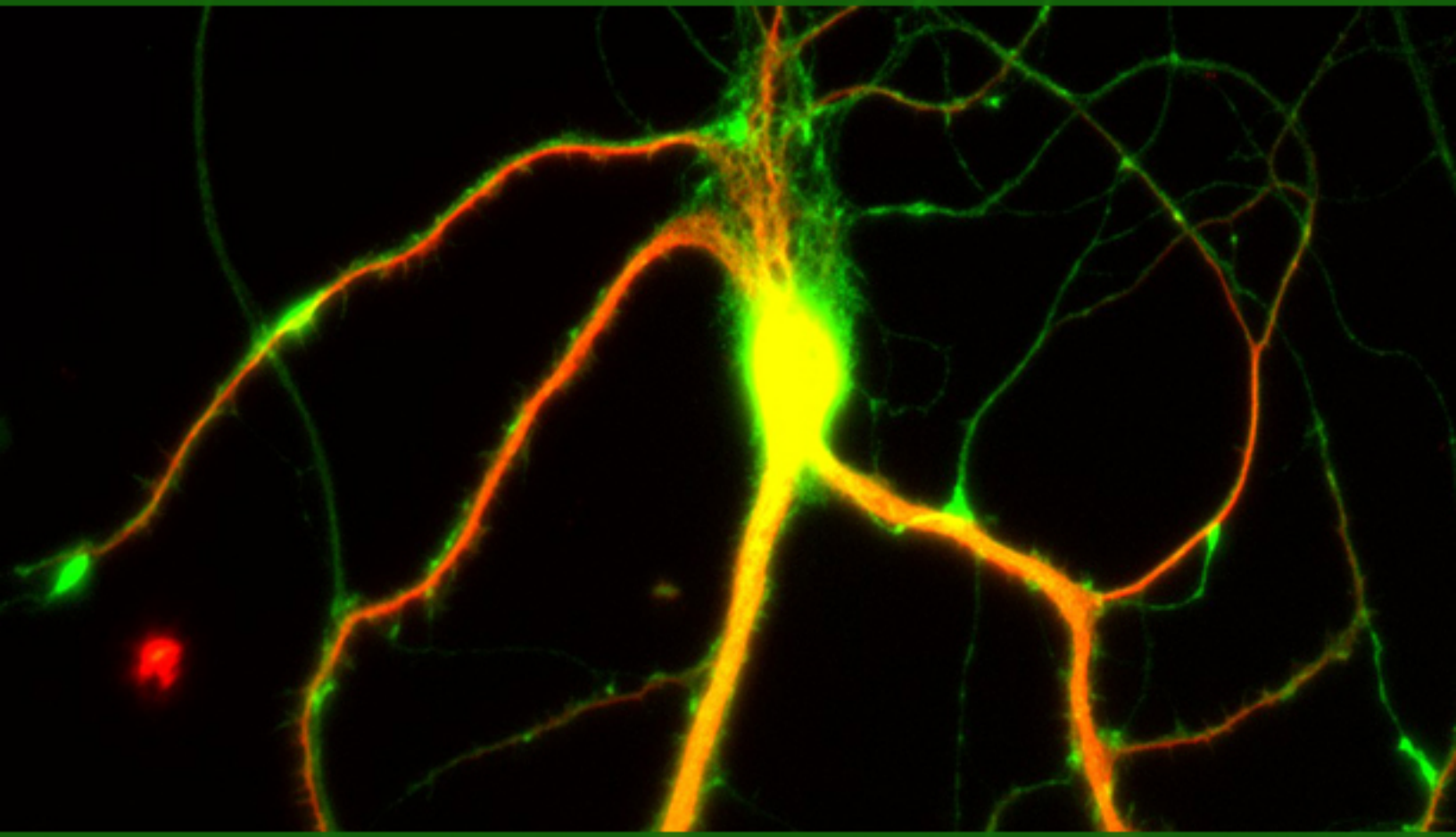
Computational and Cellular Neuroscience



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Chapter 1

Computational Neuroscience

Computational neuroscience is the study of brain function in terms of the information processing properties of the structures that make up the nervous system. It is an interdisciplinary science that links the diverse fields of neuroscience, cognitive science and psychology with electrical engineering, computer science, mathematics and physics.

Computational neuroscience is somewhat distinct from psychological connectionism and theories of learning from disciplines such as machine learning, neural networks and statistical learning theory in that it emphasizes descriptions of functional and biologically realistic neurons (and neural systems) and their physiology and dynamics. These models capture the essential features of the biological system at multiple spatial-temporal scales, from membrane currents, protein and chemical coupling to network oscillations, columnar and topographic architecture and learning and memory. These computational models are used to frame hypotheses that can be directly tested by current or future biological and/or psychological experiments.

History

The term "computational neuroscience" was introduced by Eric L. Schwartz, who organized a conference, held in 1985 in Carmel, California at the request of the Systems Development Foundation, to provide a summary of the current status of a field which until that point was referred to by a variety of names, such as neural modeling, brain theory and neural networks. The proceedings of this definitional meeting were later published as the book "Computational Neuroscience" (1990).

The early historical roots of the field can be traced to the work of people such as Louis Lapicque, Hodgkin & Huxley, Hubel & Wiesel, and David Marr, to name but a few. Lapicque introduced the integrate and fire model of the neuron in a seminal article published in 1907; this model is still one of the most popular models in computational neuroscience for both cellular and neural networks studies, as well as in mathematical neuroscience because of its simplicity. About 40 years later, Hodgkin & Huxley developed the voltage clamp and created the first biophysical model of the action potential. Hubel & Wiesel discovered that neurons in primary visual cortex, the first cortical area to process information coming from the retina, have oriented receptive fields and are organized in columns. David Marr's work focused on the interactions between neurons, suggesting computational approaches to the study of how functional groups of

neurons within the hippocampus and neocortex interact, store, process, and transmit information. Computational modeling of biophysically realistic neurons and dendrites began with the work of Wilfrid Rall, with the first multicompartmental model using cable theory.

Organizations

The Organization for Computational Neuroscience is a non-profit organization one of whose tasks is to organize the annual international Computational Neuroscience meeting.

Major topics

Research in computational neuroscience can be roughly categorized into several lines of inquiries. Most computational neuroscientists collaborate closely with experimentalists in analyzing novel data and synthesizing new models of biological phenomena.

Single-neuron modeling

Even single neurons have complex biophysical characteristics. Hodgkin and Huxley's original model only employed two voltage-sensitive currents, the fast-acting sodium and the inward-rectifying potassium. Though successful in predicting the timing and qualitative features of the action potential, it nevertheless failed to predict a number of important features such as adaptation and shunting. Scientists now believe that there are a wide variety of voltage-sensitive currents, and the implications of the differing dynamics, modulations and sensitivity of these currents is an important topic of computational neuroscience.

The computational functions of complex dendrites are also under intense investigation. There is a large body of literature regarding how different currents interact with geometric properties of neurons.

Some models are also tracking biochemical pathways at very small scales such as spines or synaptic clefts.

There are many software packages, such as GENESIS and NEURON, that allow rapid and systematic *in silico* modeling of realistic neurons. Blue Brain, a project founded by Henry Markram from the École Polytechnique Fédérale de Lausanne, aims to construct a biophysically detailed simulation of a cortical column on the Blue Gene supercomputer.

Development, axonal patterning and guidance

How do axons and dendrites form during development? How do axons know where to target and how to reach these targets? How do neurons migrate to the proper position in the central and peripheral systems? How do synapses form? We know from molecular biology that distinct parts of the nervous system release distinct chemical cues, from

growth factors to hormones that modulate and influence the growth and development of functional connections between neurons.

Theoretical investigations into the formation and patterning of synaptic connection and morphology are still nascent. One hypothesis that has recently garnered some attention is the *minimal wiring hypothesis*, which postulates that the formation of axons and dendrites effectively minimizes resource allocation while maintaining maximal information storage.

Sensory processing

Early models of sensory processing understood within a theoretical framework is credited to Horace Barlow. Somewhat similar to the minimal wiring hypothesis described in the preceding section, Barlow understood the processing of the early sensory systems to be a form of efficient coding, where the neurons encoded information which minimized the number of spikes. Experimental and computational work have since supported this hypothesis in one form or another.

Current research in sensory processing is divided among biophysical modelling of different subsystems and more theoretical modelling function of perception. Current models of perception have suggested that the brain performs some form of Bayesian inference and integration of different sensory information in generating our perception of the physical world.

Memory and synaptic plasticity

Earlier models of memory are primarily based on the postulates of Hebbian learning. Biologically relevant models such as Hopfield net have been developed to address the properties of associative, rather than content-addressable style of memory that occur in biological systems. These attempts are primarily focusing on the formation of medium-term and long-term memory, localizing in the hippocampus. Models of working memory, relying on theories of network oscillations and persistent activity, have been built to capture some features of the prefrontal cortex in context-related memory.

One of the major problems in neurophysiological memory is how it is maintained and changed through multiple time scales. Unstable synapses are easy to train but also prone to stochastic disruption. Stable synapses forget less easily, but they are also harder to consolidate. One recent computational hypothesis involves cascades of plasticity that allow synapses to function at multiple time scales. Stereochemically detailed models of the acetylcholine receptor-based synapse with Monte Carlo method, working at the time scale of microseconds, have been built. It is likely that computational tools will contribute greatly to our understanding of how synapses function and change in relation to external stimulus in the coming decades.

Behaviors of networks

Biological neurons are connected to each other in a complex, recurrent fashion. These connections are, unlike most artificial neural networks, sparse and most likely, specific. It is not known how information is transmitted through such sparsely connected networks. It is also unknown what the computational functions, if any, of these specific connectivity patterns are.

The interactions of neurons in a small network can be often reduced to simple models such as the Ising model. The statistical mechanics of such simple systems are well-characterized theoretically. There has been some recent evidence that suggests that dynamics of arbitrary neuronal networks can be reduced to pairwise interactions.(Schneidman et al., 2006; Shlens et al., 2006.) It's unknown, however, whether such descriptive dynamics impart any important computational function. With the emergence of two-photon microscopy and calcium imaging, we now have powerful experimental methods with which to test the new theories regarding neuronal networks.

In some cases the complex interactions between *inhibitory* and *excitatory* neurons can be simplified using mean field theory that gives rise to population model of neural networks. While many neuro-theorists prefer such models with reduced complexity, others argue that uncovering structure function relations depends on including as much neuronal and network structure as possible. Models of this type are typically built in large simulations platforms like GENESIS or Neuron. There have been some attempts to provide unified methods that bridge, and integrate, these levels of complexity.

Cognition, discrimination and learning

Computational modeling of higher cognitive functions has only begun recently. Experimental data comes primarily from single-unit recording in primates. The frontal lobe and parietal lobe function as integrators of information from multiple sensory modalities. There are some tentative ideas regarding how simple mutually inhibitory functional circuits in these areas may carry out biologically relevant computation.

The brain seems to be able to discriminate and adapt particularly well in certain contexts. For instance, human beings seem to have an enormous capacity for memorizing and recognizing faces. One of the key goals of computational neuroscience is to dissect how biological systems carry out these complex computations efficiently and potentially replicate these processes in building intelligent machines.

The brain's large-scale organizational principles are illuminated by many fields, including biology, psychology, and clinical practice. Integrative neuroscience attempts to consolidate these observations through unified descriptive models, and databases of behavioral measures and recordings. These are the basis for some quantitative modeling of large-scale brain activity.

Consciousness

One of the ultimate goals of psychology/neuroscience is to be able to explain the everyday experience of conscious life. Francis Crick and Christof Koch made some attempts in formulating a consistent framework for future work in neural correlates of consciousness (NCC), though much of the work in this field remains speculative.

Chapter 2

Biological Neuron Model

A **biological neuron model** (also known as a **spiking neuron model**) is a mathematical description of the properties of nerve cells, or neurons, that is designed to accurately describe and predict biological processes. This is in contrast to the artificial neuron, which aims for computational effectiveness, although these goals sometimes overlap.

Artificial neuron abstraction

The most basic model of a neuron consists of an input with some synaptic weight vector and an activation function or transfer function inside the neuron determining output. This is the basic structure used in artificial neurons, which in a neural network often looks like

$$y_j = \phi \left(\sum_i w_{ij} x_i \right)$$

where y_j is the output of the jth neuron, x_i is the ith input neuron signal, w is the synaptic weight, and $\phi$is the activation function. Some of the earliest biological models took this form until kinetic models such as the Hodgkin-Huxley model became dominant.

Biological abstraction

In the case of modelling a biological neuron, physical analogues are used in place of abstractions such as "weight" and "transfer function". The input to a neuron is often described by an ion current through the cell membrane that occurs when neurotransmitters cause an activation of ion channels in the cell. We describe this by a physical time-dependent current $I(t)$. The cell itself is bound by an insulating cell membrane with a concentration of charged ions on either side that determines a capacitance C_m. Finally, a neuron responds to such a signal with a change in voltage, or an electrical potential energy difference between the cell and its surroundings, which is observed to sometimes result in a voltage spike called an action potential. This quantity, then, is the quantity of interest and is given by V_m.

Integrate-and-fire

One of the earliest models of a neuron was first investigated in 1907 by Louis Lapicque. A neuron is represented in time by

$$I(t) = C_m \frac{dV_m}{dt}$$

which is just the time derivative of the law of capacitance, $Q = CV$. When an input current is applied, the membrane voltage increases with time until it reaches a constant threshold V_{th}, at which point a delta function spike occurs and the voltage is reset to its resting potential, after which the model continues to run. The *firing frequency* of the model thus increases linearly without bound as input current increases.

The model can be made more accurate by introducing a refractory period t_{ref} that limits the firing frequency of a neuron by preventing it from firing during that period. Through some calculus involving a Fourier transform, the firing frequency as a function of a constant input current thus looks like

$$f(I) = I/(C_m V_{th} + t_{ref} I)$$

A remaining shortcoming of this model is that it implements no time-dependent memory. If the model receives a below-threshold signal at some time, it will retain that voltage boost forever until it fires again. This characteristic is clearly not in line with observed neuronal behavior.

Leaky integrate-and-fire

In the leaky integrate-and-fire model, the memory problem is solved by adding a "leak" term to the membrane potential, reflecting the diffusion of ions that occurs through the membrane when some equilibrium is not reached in the cell. The model looks like

$$I(t) - \frac{V_m(t)}{R_m} = C_m \frac{dV_m(t)}{dt}$$

where R_m is the membrane resistance, as we find it is not a perfect insulator as assumed previously. This forces the input current to exceed some threshold $I_{th} = V_{th} / R_m$ in order to cause the cell to fire, else it will simply leak out any change in potential. The firing frequency thus looks like

$$f(I) = \begin{cases} 0, & I \leq I_{th} \\ \left(t_{ref} - R_m C_m \log(1 - \frac{V_{th}}{I R_m}) \right)^{-1}, & I > I_{th} \end{cases}$$

which converges for large input currents to the previous leak-free model with refractory period.

Hodgkin-Huxley

The most successful and widely-used models of neurons have been based on the Markov kinetic model developed from Hodgkin and Huxley's 1952 work based on data from the squid giant axon. We note as before our voltage-current relationship, this time generalized to include multiple voltage-dependent currents:

$$C_m \frac{dV(t)}{dt} = -\sum_i I_i(t,V)$$

.

Each current is given by Ohm's Law as

$$I(t,V) = g(t,V) \cdot (V - V_{eq})$$

where $g(t,V)$ is the conductance, or inverse resistance, which can be expanded in terms of its constant average $\bar{g}$ and the activation and inactivation fractions m and h, respectively, that determine how many ions can flow through available membrane channels. This expansion is given by

$$g(t,V) = \bar{g} \cdot m(t,V)^p \cdot h(t,V)^q$$

and our fractions follow the first-order kinetics

$$\frac{dm(t,V)}{dt} = \frac{m_\infty(V) - m(t,V)}{\tau_m(V)} = \alpha_m(V) \cdot (1-m) - \beta_m(V) \cdot m$$

with similar dynamics for h, where we can use either τ and m_∞ or α and β to define our gate fractions.

With such a form, all that remains is to individually investigate each current one wants to include. Typically, these include inward Ca^{2+} and Na^+ input currents and several varieties of K^+ outward currents, including a "leak" current. The end result can be at the small end 20 parameters which one must estimate or measure for an accurate model, and for complex systems of neurons not easily tractable by computer. Careful simplifications of the Hodgkin-Huxley model are therefore needed.

FitzHugh-Nagumo

Sweeping simplifications to Hodgkin-Huxley were introduced by FitzHugh and Nagumo in 1961 and 1962. Seeking to describe "regenerative self-excitation" by a nonlinear positive-feedback membrane voltage and recovery by a linear negative-feedback gate voltage, they developed the model described by

$$\frac{dV}{dt} = V - V^3 - w + I_{\text{ext}}$$
$$\tau \frac{dw}{dt} = V - a - bw$$

where we again have a membrane-like voltage and input current with a slower general gate voltage w and experimentally-determined parameters $a = -0.7, b = 0.8, \tau = 1 / 0.08$. Although not clearly derivable from biology, the model allows for a simplified, immediately available dynamic, without being a trivial simplification.

Morris-Lecar

In 1981 Morris and Lecar combined Hodgkin-Huxley and FitzHugh-Nagumo into a voltage-gated calcium channel model with a delayed-rectifier potassium channel, represented by

$$\begin{aligned} C\frac{dV}{dt} &= -I_{ion}(V,w) + I \\ \frac{dw}{dt} &= \phi\frac{w_\infty(V) - w}{\tau_w(V)} \end{aligned},$$

where $I_{ion}(V,w) = \bar{g}_{Ca} m_\infty(V)(V - V_{Ca}) + \bar{g}_K w(V - V_K) + \bar{g}_L(V - V_L)$.

Hindmarsh-Rose

Building upon the FitzHugh-Nagumo model, in 1984, J. L. Hindmarsh and R. M. Rose proposed a model of neuronal activity described by three coupled first order differential equations:

$$\frac{dx}{dt} = y + 3x^2 - x^3 - z + I,$$
$$\frac{dy}{dt} = 1 - 5x^2 - y,$$
$$\frac{dz}{dt} = r[4(x + 8/5) - z].$$

This extra mathematical complexity allows a great variety of dynamic behaviors for the membrane potential, described by the x variable of the model, which include chaotic dynamics. This makes the Hindmarsh-Rose neuron model very useful, because being still simple, allows a good qualitative description of the many different patterns of the action potential observed in experiments.

Expanded neuron models

While the success of integrating and kinetic models is undisputed, much has to be determined experimentally before accurate predictions can be made. The theory of neuron integration and firing (response to inputs) is therefore expanded by accounting for the nonideal conditions of cell structure.

Cable theory

Cable theory describes the dendritic arbor as a cylindrical structure undergoing a regular pattern of bifurcation, like branches in a tree. For a single cylinder or an entire tree, the input conductance at the base (where the tree meets the cell body, or any such boundary) is defined as

$$G_{in} = \frac{G_\infty \tanh(L) + G_L}{1 + (G_L/G_\infty)\tanh(L)},$$

where L is the electrotonic length of the cylinder which depends on its length, diameter, and resistance. A simple recursive algorithm scales linearly with the number of branches and can be used to calculate the effective conductance of the tree. This is given by

$$G_D = G_m A_D \tanh(L_D)/L_D$$

where $A_D = \pi ld$ is the total surface area of the tree of total length l, and L_D is its total electrotonic length. For an entire neuron in which the cell body conductance is G_S and the membrane conductance per unit area is $G_{md} = G_m / A$, we find the total neuron conductance G_N for n dendrite trees by adding up all tree and soma conductances, given by

$$G_N = G_S + \sum_{j=1}^{n} A_{D_j} F_{dga_j},$$

where we can find the general correction factor F_{dga} experimentally by noting $G_D = G_{md} A_D F_{dga}$.

Compartmental models

The cable model makes a number of simplifications to give closed analytic results, namely that the dendritic arbor must branch in diminishing pairs in a fixed pattern. A compartmental model allows for any desired tree topology with arbitrary branches and lengths, but makes simplifications in the interactions between branches to compensate. Thus, the two models give complementary results, neither of which is necessarily more accurate.

Each individual piece, or compartment, of a dendrite is modeled by a straight cylinder of arbitrary length *l* and diameter *d* which connects with fixed resistance to any number of branching cylinders. We define the conductance ratio of the *i*th cylinder as $B_i = G_i/G_\infty$, where $G_\infty = \frac{\pi d^{3/2}}{2\sqrt{R_i R_m}}$ and R_i is the resistance between the current compartment and the next. We obtain a series of equations for conductance ratios in and out of a compartment by making corrections to the normal dynamic $B_{out,i} = B_{in,i+1}$, as

- $$B_{out,i} = \frac{B_{in,i+1}(d_{i+1}/d_i)^{3/2}}{\sqrt{R_{m,i+1}/R_{m,i}}}$$
- $$B_{in,i} = \frac{B_{out,i} + \tanh X_i}{1 + B_{out,i}\tanh X_i}$$
- $$B_{out,par} = \frac{B_{in,dau1}(d_{dau1}/d_{par})^{3/2}}{\sqrt{R_{m,dau1}/R_{m,par}}} + \frac{B_{in,dau2}(d_{dau2}/d_{par})^{3/2}}{\sqrt{R_{m,dau2}/R_{m,par}}} + \dots$$

where the last equation deals with *parents* and *daughters* at branches, and $X_i = \frac{l_i\sqrt{4R_i}}{\sqrt{d_i R_m}}$. We can iterate these equations through the tree until we get the point where the dendrites connect to the cell body (soma), where the conductance ratio is $B_{in,stem}$. Then our total neuron conductance is given by

$$G_N = \frac{A_{soma}}{R_{m,soma}} + \sum_j B_{in,stem_j} G_{\infty_j}.$$

Synaptic transmission

The response of a neuron to individual neurotransmitters can be modeled as an extension of the classical Hodgkin-Huxley model with both standard and nonstandard kinetic currents. Four neurotransmitters have primarily influence in the CNS. AMPA/kainate receptors are fast excitatory mediators while NMDA receptors mediate considerably slower currents. Fast inhibitory currents go through $GABA_A$ receptors, while $GABA_B$ receptors mediate by secondary *G*-protein-activated potassium channels. This range of mediation produces the following current dynamics:

- $I_{\mathrm{AMPA}}(t,V) = \bar{g}_{\mathrm{AMPA}}[O](V(t) - E_{\mathrm{AMPA}})$
- $I_{\mathrm{NMDA}}(t,V) = \bar{g}_{\mathrm{NMDA}}B(V)[O](V(t) - E_{\mathrm{NMDA}})$
- $I_{\mathrm{GABA_A}}(t,V) = \bar{g}_{\mathrm{GABA_A}}([O_1] + [O_2])(V(t) - E_{Cl})$
- $I_{\mathrm{GABA_B}}(t,V) = \bar{g}_{\mathrm{GABA_B}}\frac{[G]^n}{[G]^n + K_d}(V(t) - E_K)$.

As before, $\bar{g}$ is the average conductance (around 1S) and *E* is the equilibrium potential of the given ion or transmitter (AMDA, NMDA, Cl, or K), while [*O*] describes the fraction of receptors that are open. For NMDA, there is a significant effect of *magnesium block*

that depends sigmoidally on the concentration of intracellular magnesium by $B(V)$. For $GABA_B$, $[G]$ is the concentration of the G-protein, and K_d describes the dissociation of G in binding to the potassium gates.

The dynamics of this more complicated model have been well-studied experimentally and produce important results in terms of very quick synaptic potentiation and depression, that is, fast, short-term learning.

Other conditions

The models above are still idealizations. Corrections must be made for the increased membrane surface area given by numerous dendritic spines, temperatures significantly hotter than room-temperature experimental data, and nonuniformity in the cell's internal structure. Many problems in the temperature and geometry dynamics of the cell during action potential propagation, as well as problems in explaining some pharmacology, are still unsolved, some of which have required unorthodox new models, such as the soliton model, to explain.

Chapter 3

Synaptic Plasticity

In neuroscience, **synaptic plasticity** is the ability of the connection, or synapse, between two neurons to change in strength in response to either use or disuse of transmission over synaptic pathways. Plastic change also results from the alteration of the number of receptors located on a synapse. There are several underlying mechanisms that cooperate to achieve synaptic plasticity, including changes in the quantity of neurotransmitters released into a synapse and changes in how effectively cells respond to those neurotransmitters. Synaptic plasticity in both excitatory and inhibitory synapses has been found to be dependent upon calcium. Since memories are postulated to be represented by vastly interconnected networks of synapses in the brain, synaptic plasticity is one of the important neurochemical foundations of learning and memory.

Historical Discoveries

In the 1960s, long-term potentiation, or LTP, was observed for the first time by Terje Lømo in Oslo, Norway. He was studying the hippocampus of rabbits and happened to notice that a brief burst of electrical stimuli on fibers heading for the hippocampus led to a dramatic and long-lasting increase in transmission at synapses in the hippocampus, an area of the brain believed to be involved in human memory.

Biochemical mechanisms

Two molecular mechanisms for synaptic plasticity (researched by the Eric Kandel laboratories) involve the NMDA and AMPA glutamate receptors. Opening of NMDA channels (which relates to the level of cellular depolarization) leads to a rise in postsynaptic Ca^{2+} concentration and this has been linked to LTP (as well as to protein kinase activation); strong depolarization of the post-synaptic cell completely displaces the magnesium ions that block NMDA ion channels and allows calcium ions to enter a cell - probably causing long-term potentiation (LTP), while weaker depolarization only partially displaces the Mg^{2+} ions, resulting in less Ca^{2+} entering the post-synaptic neuron and lower intracellular Ca^{2+} concentrations (which activate protein phosphatases and induce long-term depression, LTD).

These activated protein kinases serve to phosphorylate post-synaptic excitatory receptors (i.e. AMPA receptors), improving cation conduction, and thereby potentiating the synapse. Also, this signals recruitment of additional receptors into the postsynaptic

membrane, and stimulates the production of a modified receptor type, thereby facilitating an influx of calcium. This in turn increases post-synaptic excitation by a given pre-synaptic stimulus. This process can be reversed via the activity of protein phosphatases, which act to dephosphorylate these cation channels.

The second mechanism depends on a second messenger cascade regulating gene transcription and changes in the levels of key proteins at synapses such as CaMKII and PKAII. Activation of the second messenger pathway leads to increased levels of CaMKII and PKAII within the dendritic spine. These protein kinases have been linked to growth in dendritic spine volume and LTP processes such as the addition of AMPA receptors to the plasma membrane and phosphorylation of ion channels for enhanced permeability. Localization or compartmentalization of activated proteins occurs in the presence of their given stimulus which creates local effects in the dendritic spine. Calcium influx from NMDA receptors is necessary for the activatoin of CaMKII. This activation is localized to spines with focal stimulation and is inactivated before spreading to adjacent spines or the shaft, indicating an important mechanism of LTP in that particular changes in protein activation can be localized or compartmentalized to enhance the responsivity of single dendritic spines. Individual dendritic spines are capable of forming unique responses to presynaptic cells. This second mechanism can be triggered by protein phosphorylation but takes longer and lasts longer, providing the mechanism for long-lasting memory storage. The duration of the LTP can be regulated by breakdown of these second messengers. Phosphodiesterase, for example, is a protein phosphatase that breaks down the secondary messenger cAMP, which has been implicated in increased AMPA receptor synthesis in the post-synaptic neuron.

Long-lasting changes in the efficacy of synaptic connections (long-term potentiation, or LTP) between two neurons can involve the making and breaking of synaptic contacts. Genes such activin ß-A which encodes a subunit of activin A are up-regulated during early stage LTP. The activin molecule modulates the actin dynamics in dentritic spines through the MAP kinase pathway. By changing the F-actin cytoskeletal structure of dendritic spines, spines are lengthened and the chance that they make synaptic contacts with the axonal terminals of the presynaptic cell is increased. The end result is long term maintenance of LTP.

The number of ion channels on the post-synaptic membrane affects the strength of the synapse. Research suggests that the density of receptors on postsynaptic membranes changes, affecting the neuron's excitability in response to stimuli. In a dynamic process that is maintained in equilibrium, N-methyl D-aspartate receptor (NMDA receptor) and alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPA receptor)s are added to the membrane by exocytosis and removed by endocytosis. These processes, and by extension the number of receptors on the membrane, can be altered by synaptic activity. Experiments have shown that AMPA receptors are delivered to the synapse through vesicular membrane fusion with the postsynaptic membrane via the protein kinase CaMKII, which is activated by the influx of calcium through NMDA receptors. CaMKII also improves AMPA ionic conductance through phosphorylation. When there is high-frequency NMDA receptor activation, there is an increase in the expression of a

protein PSD-95 that increases synaptic capacity for AMPA receptors. This is what leads to a long-term increase in AMPA receptors and thus synaptic strength and plasticity.

If the strength of a synapse is only reinforced by stimulation or weakened by its lack, a positive feedback loop will develop, causing some cells never to fire and some to fire too much. But two regulatory forms of plasticity, called scaling and metaplasticity, also exist to provide negative feedback.. Synaptic scaling is a primary mechanism by which a neuron is able to stabilize firing rates up or down.

Synaptic scaling serves to maintain the strengths of synapses relative to each other, lowering amplitudes of small excitatory postsynaptic potentials in response to continual excitation and raising them after prolonged blockage or inhibition. This effect occurs gradually over hours or days, by changing the numbers of NMDA receptors at the synapse (Pérez-Otaño and Ehlers, 2005). Metaplasticity varies the threshold level at which plasticity occurs, allowing integrated responses to synaptic activity spaced over time and preventing saturated states of LTP and LTD. Since LTP and LTD (long-term depression) rely on the influx of Ca^{2+} through NMDA channels, metaplasticity may be due to changes in NMDA receptors, altered calcium buffering, altered states of kinases or phosphatases and a priming of protein synthesis machinery. Synaptic scaling is a primary mechanism by which a neuron to be selective to its varying inputs. The neuronal circuitry affected by LTP/LTD and modified by scaling and metaplasticity leads to reverberatory neural circuit development and regulation in a Hebbian manner which is manifested as memory, whereas the changes in neural circuitry, which begin at the level of the synapse, are an integral part in the ability of an organism to learn.

There is also a specificity element of biochemical interactions to create synaptic plasticity, namely the importance of location. Processes occur at microdomains - such as exocytosis of AMPA receptors is spatially regulated by the t-SNARE Stx4. Specificity is also an important aspect of CAMKII signaling involving nanodomain calcium. The spatial gradient of PKA between dendritic spines and shafts is also important for the strength and regulation of synaptic plasticity. It is important to remember that the biochemical mechanisms altering synaptic plasticity occur at the level of individual synapses of a neuron. Since the biochemical mechanisms are confined to these "microdomains," the resulting synaptic plasticity affects only the specific synapse at which it took place.

Theoretical mechanisms

A bi-directional model, describing both LTP and LTD, of synaptic plasticity has proved necessary for a number of different learning mechanisms in computational neuroscience, neural networks, and biophysics. Three major hypotheses for the molecular nature of this plasticity have been well-studied, and none are required to be the exclusive mechanism:

1. Change in the probability of glutamate release.
2. Insertion or removal of postsynaptic AMPA receptors.

3. Phosphorylation and de-phosphorylation inducing a change in AMPA receptor conductance.

Of these, the first two hypotheses have been recently mathematically examined to have identical calcium-dependent dynamics which provides strong theoretical evidence for a calcium-based model of plasticity, which in a linear model where the total number of receptors are conserved looks like

$$\frac{dW_i(t)}{dt} = \frac{1}{\tau([Ca^{2+}]_i)} \left(\Omega([Ca^{2+}]_i) - W_i\right),$$

where W_i is the synaptic weight of the ith input axon, τ is a time constant dependent on the insertion and removal rates of neurotransmitter receptors, which is dependent on $[Ca^{2+}]$, the concentration of calcium. $\Omega = \beta A_m^{\mathrm{fp}}$ is also a function of the concentration of calcium that depends linearly on the number of receptors on the membrane of the neuron at some fixed point. Both Ω and τ are found experimentally and agree on results from both hypotheses. The model makes important simplifications that make it unsuited for actual experimental predictions, but provides a significant basis for the hypothesis of a calcium-based synaptic plasticity dependence.

Short Term Plasticity

Plasticity can be categorized as short-term, lasting a few seconds or less, or long-term which lasts from minutes to hours. Short-term synaptic enhancement results from an increase in the probability that synaptic terminals will release transmitters in response to presynaptic action potentials. Synapses will strengthen for a short time because of either an increase in size of the readily releasable pool of packaged transmitter or an increase in the amount of packaged transmitter released in response to each action potential. Types of short term plasticity include synaptic augmentation, depression, facilitation, or neural facilitation, and post-tetanic potentiation.

Synaptic Augmentation

Augmentation has been found to be associated with increased efficiency with which action potentials cause release of vesicles containing transmitters.

Synaptic Depression

Depression is usually attributed to the depletion of the readily releasable vesicles. Depression can also arise from postsynaptic processes and from feedback activation of presynaptic receptors. Heterosynaptic depression is thought to be linked to the release of adenosine triphosphate (ATP) from astrocytes.

Long Term Plasticity

Long-term depression and long-term potentiation are two forms of long term plasticity, lasting minutes or more, that occur at excitatory synapses. NMDA-dependent LTD and LTP have been extensively researched, and are found to require the binding of glutamate, and glycine or D-serine for activation of NMDA receptors.

Long-term Depression

Brief activation of an excitatory pathway can produce what is known as long-term depression (LTD) of synaptic transmission in many areas of the brain. LTD is induced by a minimum level of postsynpatic depolarization and simultaneous increase in the intracellular calcium concentration at the postsynaptic neuron. LTD can be inititated at inactive synapses if the calcium concentration is raised to the minimum required level by heterosynaptic activation, or if the extracellular concentration is raised. These alternative conditions capable of causing LTD differ from the Hebb rule, and instead depend on synaptic activity modifications. D-serine release by astrocytes has been found to lead to a significant reduction of LTD in the hippocampus.

Long-term Potentiation

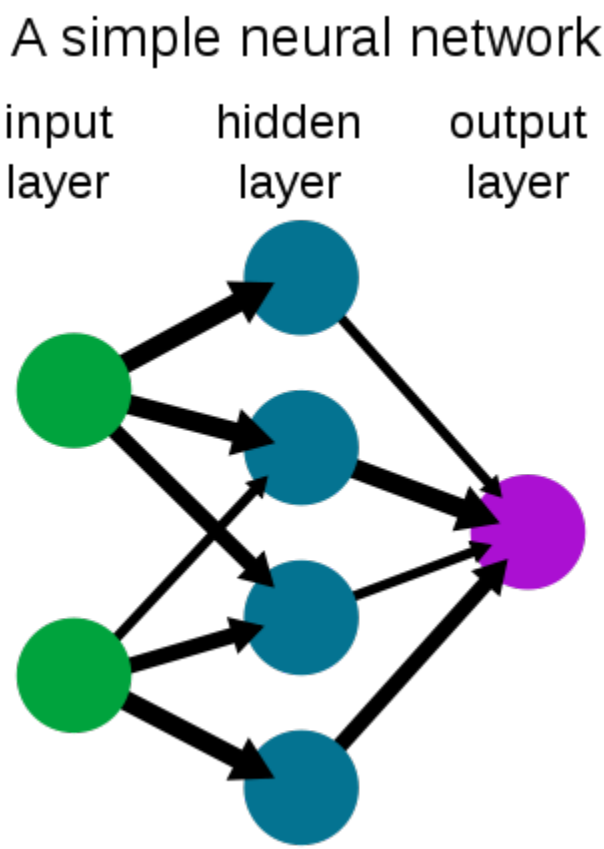
Long-term potentiation, commonly referred to as LTP, is an increase in synaptic response following potentiating pulses of electrical stimuli that sustains at a level above the baseline response for hours or longer. LTP involves interactions between postsynaptic neurons and the specific presynaptic inputs that form a synaptic association, and is specific to the stimulated pathway of synaptic transmission. Modification of astrocyte coverage at the syanpses in the hippocampus has been found to result from the induction of LTP, which has been found to be linked to the release of D-serine, nitric oxide, and the chemokine, s100B by astrocytes. LTP is also a model for studying the synaptic basis of Hebbian plasticity. Induction conditions resemble those described for the initiation of long-term depression (LTD), but a stronger depolarization and a greater increase of calcium are necessary to achieve LTP.

Synaptic Strength

The modification of synaptic strength is referred to as functional plasticity. Changes in synaptic strength involve distinct mechanisms of particular types of glial cells, the most researched type being astrocytes.

Chapter 4

Neural Network



Simplified view of a feedforward artificial neural network

The term **neural network** was traditionally used to refer to a network or circuit of biological neurons. The modern usage of the term often refers to artificial neural networks, which are composed of artificial neurons or nodes. Thus the term has two distinct usages:

1. Biological neural networks are made up of real biological neurons that are connected or functionally related in the peripheral nervous system or the central

nervous system. In the field of neuroscience, they are often identified as groups of neurons that perform a specific physiological function in laboratory analysis.

2. Artificial neural networks are composed of interconnecting artificial neurons (programming constructs that mimic the properties of biological neurons). Artificial neural networks may either be used to gain an understanding of biological neural networks, or for solving artificial intelligence problems without necessarily creating a model of a real biological system. The real, biological nervous system is highly complex and includes some features that may seem superfluous based on an understanding of artificial networks.

Overview

A biological neural network is composed of a group or groups of chemically connected or functionally associated neurons. A single neuron may be connected to many other neurons and the total number of neurons and connections in a network may be extensive. Connections, called synapses, are usually formed from axons to dendrites, though dendrodendritic microcircuits and other connections are possible. Apart from the electrical signaling, there are other forms of signaling that arise from neurotransmitter diffusion, which have an effect on electrical signaling. As such, neural networks are extremely complex.

Artificial intelligence and cognitive modeling try to simulate some properties of biological neural networks. While similar in their techniques, the former has the aim of solving particular tasks, while the latter aims to build mathematical models of biological neural systems.

In the artificial intelligence field, artificial neural networks have been applied successfully to speech recognition, image analysis and adaptive control, in order to construct software agents (in computer and video games) or autonomous robots. Most of the currently employed artificial neural networks for artificial intelligence are based on statistical estimation, optimization and control theory.

The cognitive modelling field involves the physical or mathematical modeling of the behaviour of neural systems; ranging from the individual neural level (e.g. modelling the spike response curves of neurons to a stimulus), through the neural cluster level (e.g. modelling the release and effects of dopamine in the basal ganglia) to the complete organism (e.g. behavioural modelling of the organism's response to stimuli). Artificial intelligence, cognitive modelling, and neural networks are information processing paradigms inspired by the way biological neural systems process data.

History of the neural network analogy

In the brain, spontaneous order arises out of decentralized networks of simple units (neurons). In the late 1940s Donald Hebb made one of the first hypotheses of learning with a mechanism of neural plasticity called Hebbian learning. Hebbian learning is considered to be a 'typical' unsupervised learning rule and its later variants were early

models for long term potentiation. These ideas started being applied to computational models in 1948 with Turing's B-type machines and the perceptron.

The perceptron is essentially a linear classifier for classifying data $x \in \mathbb{R}^n$ specified by parameters $w \in \mathbb{R}^n, b \in \mathbb{R}$ and an output function $f = w'x + b$. Its parameters are adapted with an ad-hoc rule similar to stochastic steepest gradient descent. Because the inner product is a linear operator in the input space, the perceptron can only perfectly classify a set of data for which different classes are linearly separable in the input space, while it often fails completely for non-separable data. While the development of the algorithm initially generated some enthusiasm, partly because of its apparent relation to biological mechanisms, the later discovery of this inadequacy caused such models to be abandoned until the introduction of non-linear models into the field.

The cognitron (1975) designed by Kunihiko Fukushima was an early multilayered neural network with a training algorithm. The actual structure of the network and the methods used to set the interconnection weights change from one neural strategy to another, each with its advantages and disadvantages. Networks can propagate information in one direction only, or they can bounce back and forth until self-activation at a node occurs and the network settles on a final state. The ability for bi-directional flow of inputs between neurons/nodes was produced with the Hopfield's network (1982), and specialization of these node layers for specific purposes was introduced through the first hybrid network.

The parallel distributed processing of the mid-1980s became popular under the name connectionism.

The rediscovery of the backpropagation algorithm was probably the main reason behind the repopularisation of neural networks after the publication of "Learning Internal Representations by Error Propagation" in 1986 (Though backpropagation itself dates from 1969). The original network utilized multiple layers of weight-sum units of the type $f = g(w'x + b)$, where g was a sigmoid function or logistic function such as used in logistic regression. Training was done by a form of stochastic Gradient descent. The employment of the chain rule of differentiation in deriving the appropriate parameter updates results in an algorithm that seems to 'backpropagate errors', hence the nomenclature. However it is essentially a form of gradient descent. Determining the optimal parameters in a model of this type is not trivial, and steepest gradient descent methods cannot be relied upon to give the solution without a good starting point. In recent times, networks with the same architecture as the backpropagation network are referred to as Multi-Layer Perceptrons. This name does not impose any limitations on the type of algorithm used for learning.

The backpropagation network generated much enthusiasm at the time and there was much controversy about whether such learning could be implemented in the brain or not, partly because a mechanism for reverse signaling was not obvious at the time, but most importantly because there was no plausible source for the 'teaching' or 'target' signal.

The brain, neural networks and computers

Neural networks, as used in artificial intelligence, have traditionally been viewed as simplified models of neural processing in the brain, even though the relation between this model and brain biological architecture is debated, as little is known about how the brain actually works.

A subject of current research in theoretical neuroscience is the question surrounding the degree of complexity and the properties that individual neural elements should have to reproduce something resembling animal intelligence.

Historically, computers evolved from the von Neumann architecture, which is based on sequential processing and execution of explicit instructions. On the other hand, the origins of neural networks are based on efforts to model information processing in biological systems, which may rely largely on parallel processing as well as implicit instructions based on recognition of patterns of 'sensory' input from external sources. In other words, at its very heart a neural network is a complex statistical processor (as opposed to being tasked to sequentially process and execute).

Neural coding is concerned with how sensory and other information is represented in the brain by neurons. The main goal of studying neural coding is to characterize the relationship between the stimulus and the individual or ensemble neuronal responses and the relationship among electrical activity of the neurons in the ensemble. It is thought that neurons can encode both digital and analog information.

Neural networks and artificial intelligence

A *neural network* (NN), in the case of artificial neurons called *artificial neural network* (ANN) or *simulated neural network* (SNN), is an interconnected group of natural or artificial neurons that uses a mathematical or computational model for information processing based on a connectionistic approach to computation. In most cases an ANN is an adaptive system that changes its structure based on external or internal information that flows through the network.

In more practical terms neural networks are non-linear statistical data modeling or decision making tools. They can be used to model complex relationships between inputs and outputs or to find patterns in data.

However, the paradigm of neural networks - i.e., *implicit*, not *explicit*, learning is stressed - seems more to correspond to some kind of *natural intelligence* than to the traditional *Artificial Intelligence*, which would stress, instead, rule-based learning.

Background

An artificial neural network involves a network of simple processing elements (artificial neurons) which can exhibit complex global behavior, determined by the connections

between the processing elements and element parameters. Artificial neurons were first proposed in 1943 by Warren McCulloch, a neurophysiologist, and Walter Pitts, an MIT logician. One classical type of artificial neural network is the recurrent Hopfield net.

In a neural network model simple nodes, which can be called variously "neurons", "neurodes", "Processing Elements" (PE) or "units", are connected together to form a network of nodes — hence the term "neural network". While a neural network does not have to be adaptive *per se*, its practical use comes with algorithms designed to alter the strength (weights) of the connections in the network to produce a desired signal flow.

In modern software implementations of artificial neural networks the approach inspired by biology has more or less been abandoned for a more practical approach based on statistics and signal processing. In some of these systems, neural networks, or parts of neural networks (such as artificial neurons), are used as components in larger systems that combine both adaptive and non-adaptive elements.

The concept of a neural network appears to have first been proposed by Alan Turing in his 1948 paper "Intelligent Machinery".

Applications of natural and of artificial neural networks

The utility of artificial neural network models lies in the fact that they can be used to infer a function from observations and also to use it. This is particularly useful in applications where the complexity of the data or task makes the design of such a function by hand impractical.

Real life applications

The tasks to which artificial neural networks are applied tend to fall within the following broad categories:

- Function approximation, or regression analysis, including time series prediction and modeling.
- Classification, including pattern and sequence recognition, novelty detection and sequential decision making.
- Data processing, including filtering, clustering, blind signal separation and compression.

Application areas of ANNs include system identification and control (vehicle control, process control), game-playing and decision making (backgammon, chess, racing), pattern recognition (radar systems, face identification, object recognition, etc.), sequence recognition (gesture, speech, handwritten text recognition), medical diagnosis, financial applications, data mining (or knowledge discovery in databases, "KDD"), visualization and e-mail spam filtering.

Neural networks and neuroscience

Theoretical and computational neuroscience is the field concerned with the theoretical analysis and computational modeling of biological neural systems. Since neural systems are intimately related to cognitive processes and behaviour, the field is closely related to cognitive and behavioural modeling.

The aim of the field is to create models of biological neural systems in order to understand how biological systems work. To gain this understanding, neuroscientists strive to make a link between observed biological processes (data), biologically plausible mechanisms for neural processing and learning (biological neural network models) and theory (statistical learning theory and information theory).

Types of models

Many models are used in the field, each defined at a different level of abstraction and trying to model different aspects of neural systems. They range from models of the short-term behaviour of individual neurons, through models of how the dynamics of neural circuitry arise from interactions between individual neurons, to models of how behaviour can arise from abstract neural modules that represent complete subsystems. These include models of the long-term and short-term plasticity of neural systems and its relation to learning and memory, from the individual neuron to the system level.

Current research

While initially research had been concerned mostly with the electrical characteristics of neurons, a particularly important part of the investigation in recent years has been the exploration of the role of neuromodulators such as dopamine, acetylcholine, and serotonin on behaviour and learning.

Biophysical models, such as BCM theory, have been important in understanding mechanisms for synaptic plasticity, and have had applications in both computer science and neuroscience. Research is ongoing in understanding the computational algorithms used in the brain, with some recent biological evidence for radial basis networks and neural backpropagation as mechanisms for processing data.

Computational devices have been created in CMOS for both biophysical simulation and neuromorphic computing. More recent efforts show promise for creating nanodevices for very large scale principal components analyses and convolution. If successful, these efforts could usher in a new era of neural computing that is a step beyond digital computing, because it depends on learning rather than programming and because it is fundamentally analog rather than digital even though the first instantiations may in fact be with CMOS digital devices.

Criticism

A common criticism of neural networks, particularly in robotics, is that they require a large diversity of training for real-world operation. Dean Pomerleau, in his research presented in the paper "Knowledge-based Training of Artificial Neural Networks for Autonomous Robot Driving," uses a neural network to train a robotic vehicle to drive on multiple types of roads (single lane, multi-lane, dirt, etc.). A large amount of his research is devoted to (1) extrapolating multiple training scenarios from a single training experience, and (2) preserving past training diversity so that the system does not become overtrained (if, for example, it is presented with a series of right turns – it should not learn to always turn right). These issues are common in neural networks that must decide from amongst a wide variety of responses.

A. K. Dewdney, a former *Scientific American* columnist, wrote in 1997, "Although neural nets do solve a few toy problems, their powers of computation are so limited that I am surprised anyone takes them seriously as a general problem-solving tool." (Dewdney, p. 82)

Arguments for Dewdney's position are that to implement large and effective software neural networks, much processing and storage resources need to be committed. While the brain has hardware tailored to the task of processing signals through a graph of neurons, simulating even a most simplified form on Von Neumann technology may compel a NN designer to fill many millions of database rows for its connections - which can lead to abusive RAM and HD necessities. Furthermore, the designer of NN systems will often need to simulate the transmission of signals through many of these connections and their associated neurons - which must often be matched with incredible amounts of CPU processing power and time. While neural networks often yield *effective* programs, they too often do so at the cost of time and money *efficiency*.

Arguments against Dewdney's position are that neural nets have been successfully used to solve many complex and diverse tasks, ranging from autonomously flying aircraft to detecting credit card fraud.

Technology writer Roger Bridgman commented on Dewdney's statements about neural nets:

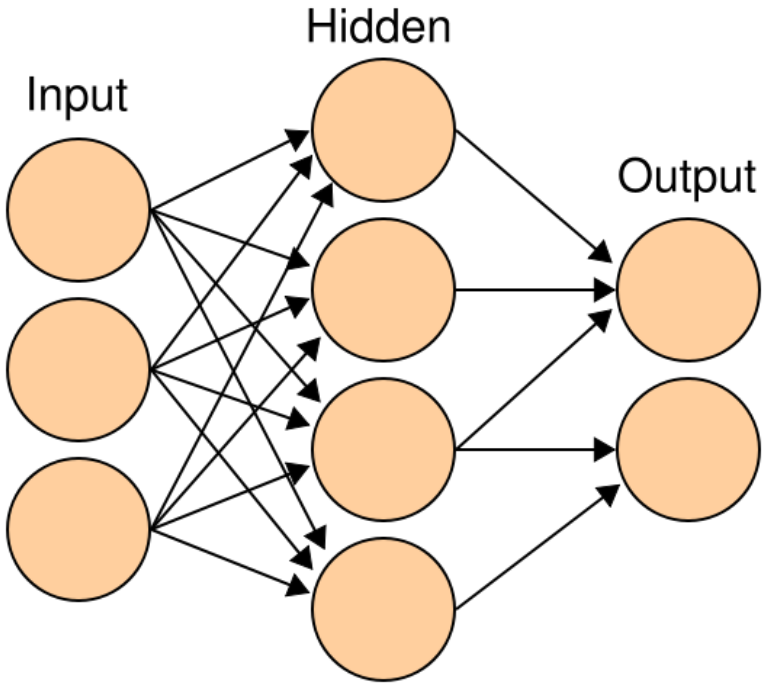
Neural networks, for instance, are in the dock not only because they have been hyped to high heaven, (what hasn't?) but also because you could create a successful net without understanding how it worked: the bunch of numbers that captures its behaviour would in all probability be "an opaque, unreadable table...valueless as a scientific resource". In spite of his emphatic declaration that science is not technology, Dewdney seems here to pillory neural nets as bad science when most of those devising them are just trying to be good engineers. An unreadable table that a useful machine could read would still be well worth having.

Some other criticisms came from believers of hybrid models (combining neural networks and symbolic approaches). They advocate the intermix of these two approaches and believe that hybrid models can better capture the mechanisms of the human mind (Sun and Bookman 1990).

Chapter 5

Artificial Neural Network

An **artificial neural network (ANN)**, usually called **neural network (NN)**, is a mathematical model or computational model that is inspired by the structure and/or functional aspects of biological neural networks. A neural network consists of an interconnected group of artificial neurons, and it processes information using a connectionist approach to computation. In most cases an ANN is an adaptive system that changes its structure based on external or internal information that flows through the network during the learning phase. Modern neural networks are non-linear statistical data modeling tools. They are usually used to model complex relationships between inputs and outputs or to find patterns in data.



An artificial neural network is an interconnected group of nodes, akin to the vast network of neurons in the human brain.

Background

The original inspiration for the term *Artificial Neural Network* came from examination of central nervous systems and their neurons, axons, dendrites, and synapses, which constitute the processing elements of biological neural networks investigated by neuroscience. In an artificial neural network, simple artificial nodes, variously called "neurons", "neurodes", "processing elements" (PEs) or "units", are connected together to form a network of nodes mimicking the biological neural networks — hence the term "artificial neural network".

Because neuroscience is still full of unanswered questions, and since there are many levels of abstraction and therefore, many ways to take inspiration from the brain, there is no single formal definition of what an artificial neural network is. Generally, it involves a network of simple processing elements that exhibit complex global behavior determined by connections between processing elements and element parameters. While an artificial neural network does not have to be adaptive per se, its practical use comes with algorithms designed to alter the strength (weights) of the connections in the network to produce a desired signal flow.

These networks are also similar to the biological neural networks in the sense that functions are performed collectively and in parallel by the units, rather than there being a clear delineation of subtasks to which various units are assigned. Currently, the term Artificial Neural Network (ANN) tends to refer mostly to neural network models employed in statistics, cognitive psychology and artificial intelligence. Neural network models designed with emulation of the central nervous system (CNS) in mind are a subject of theoretical neuroscience and computational neuroscience.

In modern software implementations of artificial neural networks, the approach inspired by biology has been largely abandoned for a more practical approach based on statistics and signal processing. In some of these systems, neural networks or parts of neural networks (such as artificial neurons) are used as components in larger systems that combine both adaptive and non-adaptive elements. While the more general approach of such adaptive systems is more suitable for real-world problem solving, it has far less to do with the traditional artificial intelligence connectionist models. What they do have in common, however, is the principle of non-linear, distributed, parallel and local processing and adaptation.

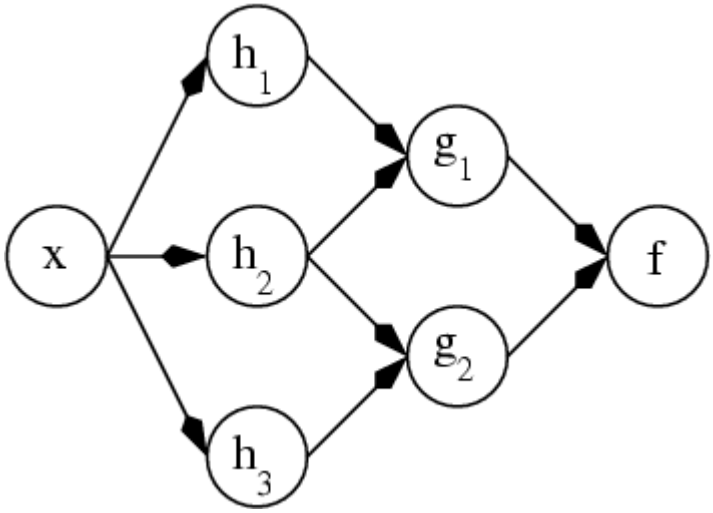
Models

Neural network models in artificial intelligence are usually referred to as artificial neural networks (ANNs); these are essentially simple mathematical models defining a function $f : X \rightarrow Y$ or a distribution over X or both X and Y, but sometimes models are also intimately associated with a particular learning algorithm or learning rule. A common use of the phrase ANN model really means the definition of a *class* of such functions (where members of the class are obtained by varying parameters, connection weights, or specifics of the architecture such as the number of neurons or their connectivity).

Network function

The word *network* in the term 'artificial neural network' refers to the inter–connections between the neurons in the different layers of each system. The most basic system has three layers. The first layer has input neurons, which send data via synapses to the second layer of neurons, and then via more synapses to the third layer of output neurons. More complex systems will have more layers of neurons with some having increased layers of input neurons and output neurons. The synapses store parameters called "weights" that manipulate the data in the calculations.

The layers network through the mathematics of the system algorithms. The network function $f(x)$is defined as a composition of other functions $g_i(x)$, which can further be defined as a composition of other functions. This can be conveniently represented as a network structure, with arrows depicting the dependencies between variables. A widely used type of composition is the *nonlinear weighted sum*, where $f(x)=K\left(\sum_i w_i g_i(x)\right)$, where K(commonly referred to as the activation function) is some predefined function, such as the hyperbolic tangent. It will be convenient for the following to refer to a collection of functions $g_i$as simply a vector $g=(g_1,g_2,\ldots,g_n)$.



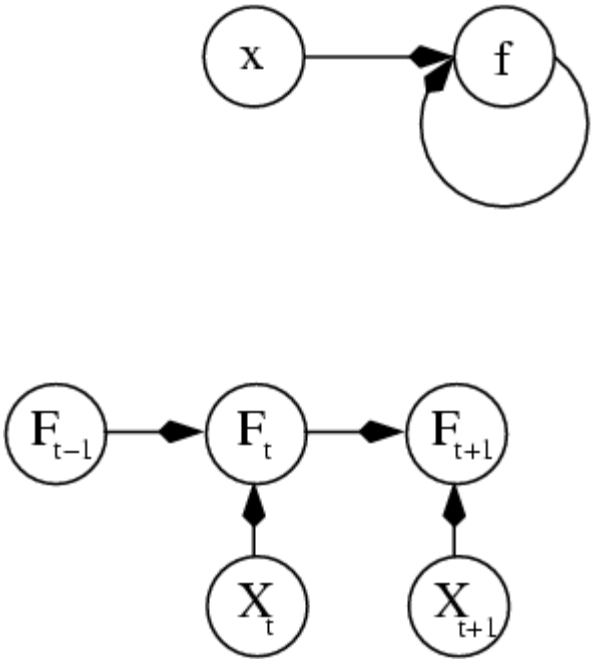
ANN dependency graph

This figure depicts such a decomposition of f, with dependencies between variables indicated by arrows. These can be interpreted in two ways.

The first view is the functional view: the input $x$is transformed into a 3-dimensional vector h, which is then transformed into a 2-dimensional vector g, which is finally transformed into f. This view is most commonly encountered in the context of optimization.

The second view is the probabilistic view: the random variable $F=f(G)$ depends upon the random variable $G=g(H)$, which depends upon $H=h(X)$, which depends upon the random variable X. This view is most commonly encountered in the context of graphical models.

The two views are largely equivalent. In either case, for this particular network architecture, the components of individual layers are independent of each other (e.g., the components of g are independent of each other given their input h). This naturally enables a degree of parallelism in the implementation.



Recurrent ANN dependency graph

Networks such as the previous one are commonly called feedforward, because their graph is a directed acyclic graph. Networks with cycles are commonly called recurrent. Such networks are commonly depicted in the manner shown at the top of the figure, where f is shown as being dependent upon itself. However, an implied temporal dependence is not shown.ANN depends on three basic critareas.... (i)Interconnection between different Layers of Neurons (ii)Learning process of ANN (iii)Activation Function Interconnection shows the relationship between single layer, multiple layers of input output parameters of Neurons it shows the relationship of One to Many it means same input can perform many outputs for different layer of architecture.

Learning

What has attracted the most interest in neural networks is the possibility of *learning*. Given a specific *task* to solve, and a *class* of functions, F, learning means using a set of *observations* to find $f^* \in F$ which solves the task in some *optimal* sense.

This entails defining a cost function $C: F \to \mathbb{R}$ such that, for the optimal solution f^*, $C(f^*) \leq C(f) \forall f \in F$ (i.e., no solution has a cost less than the cost of the optimal solution).

The cost function C is an important concept in learning, as it is a measure of how far away a particular solution is from an optimal solution to the problem to be solved. Learning algorithms search through the solution space to find a function that has the smallest possible cost.

For applications where the solution is dependent on some data, the cost must necessarily be a *function of the observations*, otherwise we would not be modelling anything related to the data. It is frequently defined as a statistic to which only approximations can be made. As a simple example, consider the problem of finding the model f, which minimizes $C = E\left[(f(x) - y)^2\right]$, for data pairs (x, y) drawn from some distribution $\mathcal{D}$. In practical situations we would only have N samples from $\mathcal{D}$ and thus, for the above example, we would only minimize $\hat{C} = \frac{1}{N} \sum_{i=1}^{N} (f(x_i) - y_i)^2$. Thus, the cost is minimized over a sample of the data rather than the entire data set.

When $N \to \infty$ some form of online machine learning must be used, where the cost is partially minimized as each new example is seen. While online machine learning is often used when $\mathcal{D}$ is fixed, it is most useful in the case where the distribution changes slowly over time. In neural network methods, some form of online machine learning is frequently used for finite datasets.

Choosing a cost function

While it is possible to define some arbitrary, ad hoc cost function, frequently a particular cost will be used, either because it has desirable properties (such as convexity) or because it arises naturally from a particular formulation of the problem (e.g., in a probabilistic formulation the posterior probability of the model can be used as an inverse cost). Ultimately, the cost function will depend on the desired task. An overview of the three main categories of learning tasks is provided below.

Learning paradigms

There are three major learning paradigms, each corresponding to a particular abstract learning task. These are supervised learning, unsupervised learning and reinforcement learning.

Supervised learning

In supervised learning, we are given a set of example pairs $(x, y), x \in X, y \in Y$ and the aim is to find a function $f: X \to Y$ in the allowed class of functions that matches the examples. In other words, we wish to *infer* the mapping implied by the data; the cost function is related to the mismatch between our mapping and the data and it implicitly contains prior knowledge about the problem domain.

A commonly used cost is the mean-squared error, which tries to minimize the average squared error between the network's output, f(x), and the target value y over all the example pairs. When one tries to minimize this cost using gradient descent for the class of neural networks called multilayer perceptrons, one obtains the common and well-known backpropagation algorithm for training neural networks.

Tasks that fall within the paradigm of supervised learning are pattern recognition (also known as classification) and regression (also known as function approximation). The supervised learning paradigm is also applicable to sequential data (e.g., for speech and gesture recognition). This can be thought of as learning with a "teacher," in the form of a function that provides continuous feedback on the quality of solutions obtained thus far.

Unsupervised learning

In unsupervised learning, some data $x$is given and the cost function to be minimized, that can be any function of the data $x$and the network's output, f.

The cost function is dependent on the task (what we are trying to model) and our *a priori* assumptions (the implicit properties of our model, its parameters and the observed variables).

As a trivial example, consider the model $f(x)=a$, where $a$is a constant and the cost $C=E[(x-f(x))^2]$. Minimizing this cost will give us a value of $a$that is equal to the mean of the data. The cost function can be much more complicated. Its form depends on the application: for example, in compression it could be related to the mutual information between x and y, whereas in statistical modeling, it could be related to the posterior probability of the model given the data. (Note that in both of those examples those quantities would be maximized rather than minimized).

Tasks that fall within the paradigm of unsupervised learning are in general estimation problems; the applications include clustering, the estimation of statistical distributions, compression and filtering.

Reinforcement learning

In reinforcement learning, data $x$are usually not given, but generated by an agent's interactions with the environment. At each point in time t, the agent performs an action $y_t$and the environment generates an observation $x_t$and an instantaneous cost c_t, according to some (usually unknown) dynamics. The aim is to discover a *policy* for selecting actions that minimizes some measure of a long-term cost; i.e., the expected cumulative cost. The environment's dynamics and the long-term cost for each policy are usually unknown, but can be estimated.

More formally, the environment is modeled as a Markov decision process (MDP) with states $s_1,...,s_n \in S$and actions $a_1,...,a_m \in A$with the following probability distributions: the instantaneous cost distribution $P(c_t|s_t)$, the observation distribution $P(x_t|s_t)$and the

transition $P(s_{t+1}|s_t,a_t)$, while a policy is defined as conditional distribution over actions given the observations. Taken together, the two define a Markov chain (MC). The aim is to discover the policy that minimizes the cost; i.e., the MC for which the cost is minimal.

ANNs are frequently used in reinforcement learning as part of the overall algorithm.

Tasks that fall within the paradigm of reinforcement learning are control problems, games and other sequential decision making tasks.

Learning algorithms

Training a neural network model essentially means selecting one model from the set of allowed models (or, in a Bayesian framework, determining a distribution over the set of allowed models) that minimizes the cost criterion. There are numerous algorithms available for training neural network models; most of them can be viewed as a straightforward application of optimization theory and statistical estimation. Recent developments in this field use particle swarm optimization and other swarm intelligence techniques.

Most of the algorithms used in training artificial neural networks employ some form of gradient descent. This is done by simply taking the derivative of the cost function with respect to the network parameters and then changing those parameters in a gradient-related direction.

Evolutionary methods, simulated annealing, expectation-maximization and non-parametric methods are some commonly used methods for training neural networks.

Temporal perceptual learning relies on finding temporal relationships in sensory signal streams. In an environment, statistically salient temporal correlations can be found by monitoring the arrival times of sensory signals. This is done by the perceptual network.

Employing artificial neural networks

Perhaps the greatest advantage of ANNs is their ability to be used as an arbitrary function approximation mechanism that 'learns' from observed data. However, using them is not so straightforward and a relatively good understanding of the underlying theory is essential.

- Choice of model: This will depend on the data representation and the application. Overly complex models tend to lead to problems with learning.
- Learning algorithm: There are numerous trade-offs between learning algorithms. Almost any algorithm will work well with the *correct hyperparameters* for training on a particular fixed data set. However selecting and tuning an algorithm for training on unseen data requires a significant amount of experimentation.
- Robustness: If the model, cost function and learning algorithm are selected appropriately the resulting ANN can be extremely robust.

With the correct implementation, ANNs can be used naturally in online learning and large data set applications. Their simple implementation and the existence of mostly local dependencies exhibited in the structure allows for fast, parallel implementations in hardware.

Applications

The utility of artificial neural network models lies in the fact that they can be used to infer a function from observations. This is particularly useful in applications where the complexity of the data or task makes the design of such a function by hand impractical.

Real-life applications

The tasks artificial neural networks are applied to tend to fall within the following broad categories:

- Function approximation, or regression analysis, including time series prediction, fitness approximation and modeling.
- Classification, including pattern and sequence recognition, novelty detection and sequential decision making.
- Data processing, including filtering, clustering, blind source separation and compression.
- Robotics, including directing manipulators, Computer numerical control.

Application areas include system identification and control (vehicle control, process control), quantum chemistry, game-playing and decision making (backgammon, chess, racing), pattern recognition (radar systems, face identification, object recognition and more), sequence recognition (gesture, speech, handwritten text recognition), medical diagnosis, financial applications (automated trading systems), data mining (or knowledge discovery in databases, "KDD"), visualization and e-mail spam filtering.

Neural networks and neuroscience

Theoretical and computational neuroscience is the field concerned with the theoretical analysis and computational modeling of biological neural systems. Since neural systems are intimately related to cognitive processes and behavior, the field is closely related to cognitive and behavioral modeling.

The aim of the field is to create models of biological neural systems in order to understand how biological systems work. To gain this understanding, neuroscientists strive to make a link between observed biological processes (data), biologically plausible mechanisms for neural processing and learning (biological neural network models) and theory (statistical learning theory and information theory).

Types of models

Many models are used in the field defined at different levels of abstraction and modeling different aspects of neural systems. They range from models of the short-term behavior of individual neurons, models of how the dynamics of neural circuitry arise from interactions between individual neurons and finally to models of how behavior can arise from abstract neural modules that represent complete subsystems. These include models of the long-term, and short-term plasticity, of neural systems and their relations to learning and memory from the individual neuron to the system level.

Current research

While initial research had been concerned mostly with the electrical characteristics of neurons, a particularly important part of the investigation in recent years has been the exploration of the role of neuromodulators such as dopamine, acetylcholine, and serotonin on behavior and learning.

Biophysical models, such as BCM theory, have been important in understanding mechanisms for synaptic plasticity, and have had applications in both computer science and neuroscience. Research is ongoing in understanding the computational algorithms used in the brain, with some recent biological evidence for radial basis networks and neural backpropagation as mechanisms for processing data.

Computational devices have been created in CMOS for both biophysical simulation and neuromorphic computing. More recent efforts show promise for creating nanodevices for very large scale principal components analyses and convolution. If successful, these effort could usher in a new era of neural computing that is a step beyond digital computing, because it depends on learning rather than programming and because it is fundamentally analog rather than digital even though the first instantiations may in fact be with CMOS digital devices.

Neural network software

Neural network software is used to simulate, research, develop and apply artificial neural networks, biological neural networks and in some cases a wider array of adaptive systems.

Types of artificial neural networks

Artificial neural network types vary from those with only one or two layers of single direction logic, to complicated multi–input many directional feedback loop and layers. On the whole, these systems use algorithms in their programming to determine control and organization of their functions. Some may be as simple, one neuron layer with an input and an output, and others can mimic complex systems such as dANN, which can mimic chromosomal DNA through sizes at cellular level, into artificial organisms and simulate reproduction, mutation and population sizes.

Most systems use "weights" to change the parameters of the throughput and the varying connections to the neurons. Artificial neural networks can be autonomous and learn by input from outside "teachers" or even self-teaching from written in rules.

Theoretical properties

Computational power

The multi-layer perceptron (MLP) is a universal function approximator, as proven by the Cybenko theorem. However, the proof is not constructive regarding the number of neurons required or the settings of the weights.

Work by Hava Siegelmann and Eduardo D. Sontag has provided a proof that a specific recurrent architecture with rational valued weights (as opposed to full precision real number-valued weights) has the full power of a Universal Turing Machine using a finite number of neurons and standard linear connections. They have further shown that the use of irrational values for weights results in a machine with super-Turing power.

Capacity

Artificial neural network models have a property called 'capacity', which roughly corresponds to their ability to model any given function. It is related to the amount of information that can be stored in the network and to the notion of complexity.

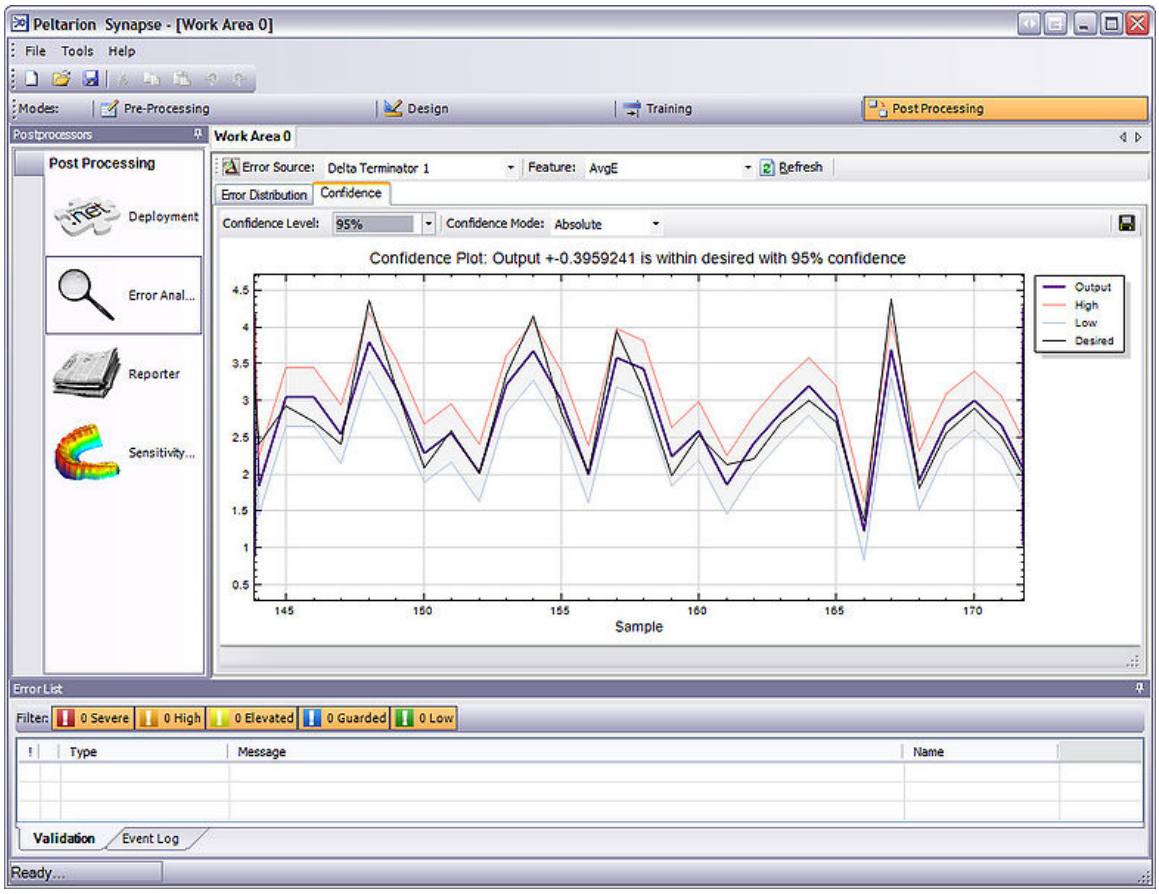
Convergence

Nothing can be said in general about convergence since it depends on a number of factors. Firstly, there may exist many local minima. This depends on the cost function and the model. Secondly, the optimization method used might not be guaranteed to converge when far away from a local minimum. Thirdly, for a very large amount of data or parameters, some methods become impractical. In general, it has been found that theoretical guarantees regarding convergence are an unreliable guide to practical application.

Generalization and statistics

In applications where the goal is to create a system that generalizes well in unseen examples, the problem of over-training has emerged. This arises in convoluted or over-specified systems when the capacity of the network significantly exceeds the needed free parameters. There are two schools of thought for avoiding this problem: The first is to use cross-validation and similar techniques to check for the presence of overtraining and optimally select hyperparameters such as to minimize the generalization error. The second is to use some form of *regularization*. This is a concept that emerges naturally in a probabilistic (Bayesian) framework, where the regularization can be performed by selecting a larger prior probability over simpler models; but also in statistical learning theory, where the goal is to minimize over two quantities: the 'empirical risk' and the

'structural risk', which roughly corresponds to the error over the training set and the predicted error in unseen data due to overfitting.



Confidence analysis of a neural network

Supervised neural networks that use an MSE cost function can use formal statistical methods to determine the confidence of the trained model. The MSE on a validation set can be used as an estimate for variance. This value can then be used to calculate the confidence interval of the output of the network, assuming a normal distribution. A confidence analysis made this way is statistically valid as long as the output probability distribution stays the same and the network is not modified.

By assigning a softmax activation function on the output layer of the neural network (or a softmax component in a component-based neural network) for categorical target variables, the outputs can be interpreted as posterior probabilities. This is very useful in classification as it gives a certainty measure on classifications.

The softmax activation function is:

$$y_i = \frac{e^{x_i}}{\sum_{j=1}^{c} e^{x_j}}$$

Dynamic properties

Various techniques originally developed for studying disordered magnetic systems (i.e., the spin glass) have been successfully applied to simple neural network architectures, such as the Hopfield network. Influential work by E. Gardner and B. Derrida has revealed many interesting properties about perceptrons with real-valued synaptic weights, while later work by W. Krauth and M. Mezard has extended these principles to binary-valued synapses.

Criticism

A common criticism of artificial neural networks, particularly in robotics, is that they require a large diversity of training for real-world operation. Dean Pomerleau, in his research presented in the paper "Knowledge-based Training of Artificial Neural Networks for Autonomous Robot Driving," uses a neural network to train a robotic vehicle to drive on multiple types of roads (single lane, multi-lane, dirt, etc.). A large amount of his research is devoted to (1) extrapolating multiple training scenarios from a single training experience, and (2) preserving past training diversity so that the system does not become overtrained (if, for example, it is presented with a series of right turns – it should not learn to always turn right). These issues are common in neural networks that must decide from amongst a wide variety of responses.

A. K. Dewdney, a former *Scientific American* columnist, wrote in 1997, "Although neural nets do solve a few toy problems, their powers of computation are so limited that I am surprised anyone takes them seriously as a general problem-solving tool." (Dewdney, p. 82)

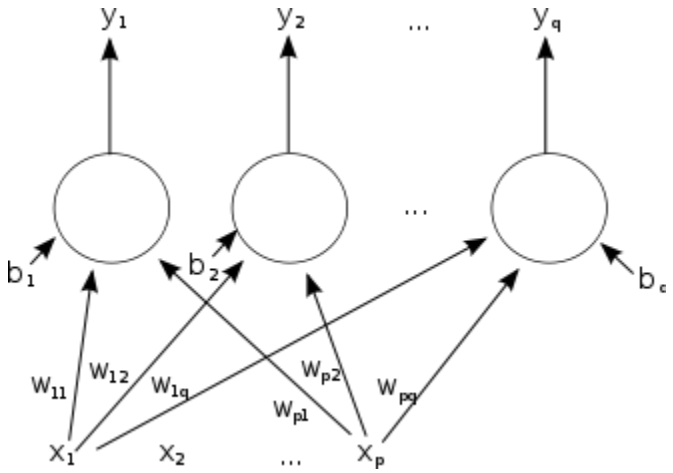
Arguments for Dewdney's position are that to implement large and effective software neural networks, much processing and storage resources need to be committed. While the brain has hardware tailored to the task of processing signals through a graph of neurons, simulating even a most simplified form on Von Neumann technology may compel a NN designer to fill many millions of database rows for its connections - which can lead to abusive RAM and HD necessities. Furthermore, the designer of NN systems will often need to simulate the transmission of signals through many of these connections and their associated neurons - which must often be matched with incredible amounts of CPU processing power and time. While neural networks often yield *effective* programs, they too often do so at the cost of time and money *efficiency*.

Arguments against Dewdney's position are that neural nets have been successfully used to solve many complex and diverse tasks, ranging from autonomously flying aircraft to detecting credit card fraud. Technology writer Roger Bridgman commented on Dewdney's statements about neural nets:

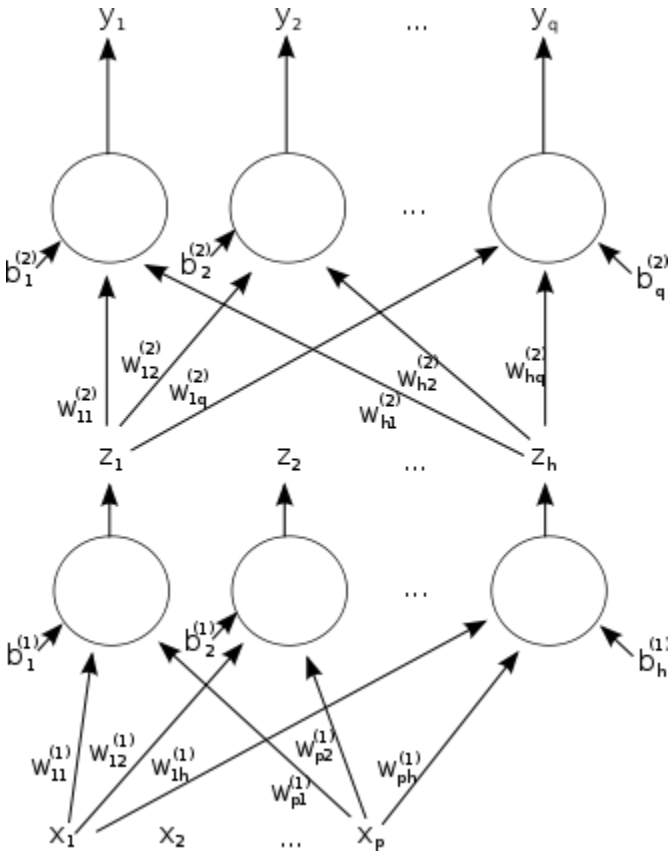
Neural networks, for instance, are in the dock not only because they have been hyped to high heaven, (what hasn't?) but also because you could create a successful net without understanding how it worked: the bunch of numbers that captures its behaviour would in

all probability be "an opaque, unreadable table...valueless as a scientific resource". In spite of his emphatic declaration that science is not technology, Dewdney seems here to pillory neural nets as bad science when most of those devising them are just trying to be good engineers. An unreadable table that a useful machine could read would still be well worth having.

Some other criticisms came from believers of hybrid models (combining neural networks and symbolic approaches). They advocate the intermix of these two approaches and believe that hybrid models can better capture the mechanisms of the human mind (Sun and Bookman 1994).



A single-layer feedforward artificial neural network. Arrows originating from $x_2$are omitted for clarity. There are p inputs to this network and q outputs. There is no activation function (or equivalently, the activation function is $g(x)=x$). In this system, the value of the qth output, $y_q$would be calculated as $y_q=\sum(x_i*w_{iq})$



A two-layer feedforward artificial neural network

Chapter 6

Cable Theory

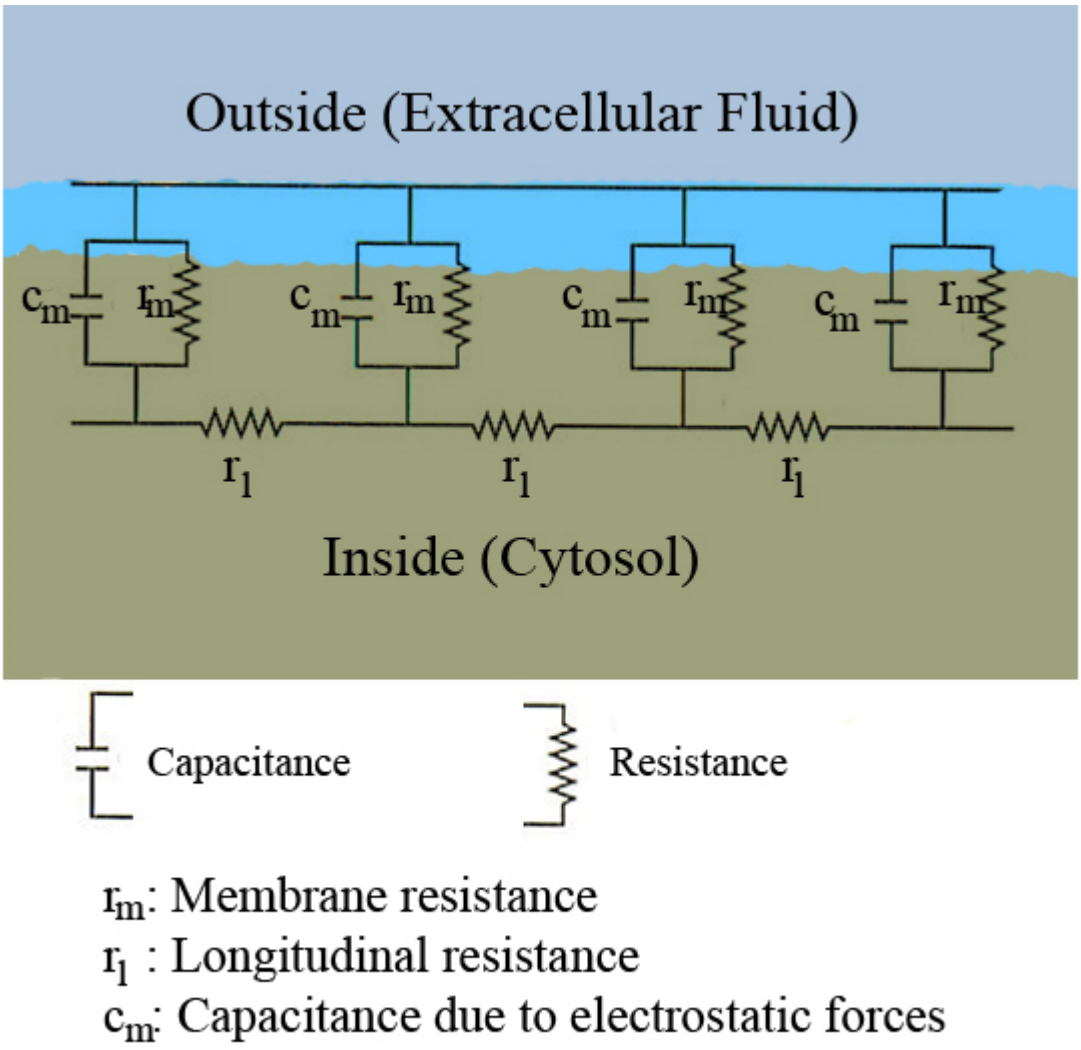


Figure.1: Cable theory's simplified view of a neuronal fiber

Classical **cable theory** uses mathematical models to calculate the flow of electric current (and accompanying voltage) along passive neuronal fibers (neurites) particularly

dendrites that receive synaptic inputs at different sites and times. Estimates are made by modeling dendrites and axons as cylinders composed of segments with capacitances c_m and resistances r_m combined in parallel (See Figure 1). The capacitance of a neuronal fiber comes about because electrostatic forces are acting through the very thin phospholipid bilayer (See Figure 2). The resistances in series along the fiber r_l is due to the cytosol's significant resistance to movement of electric charge.

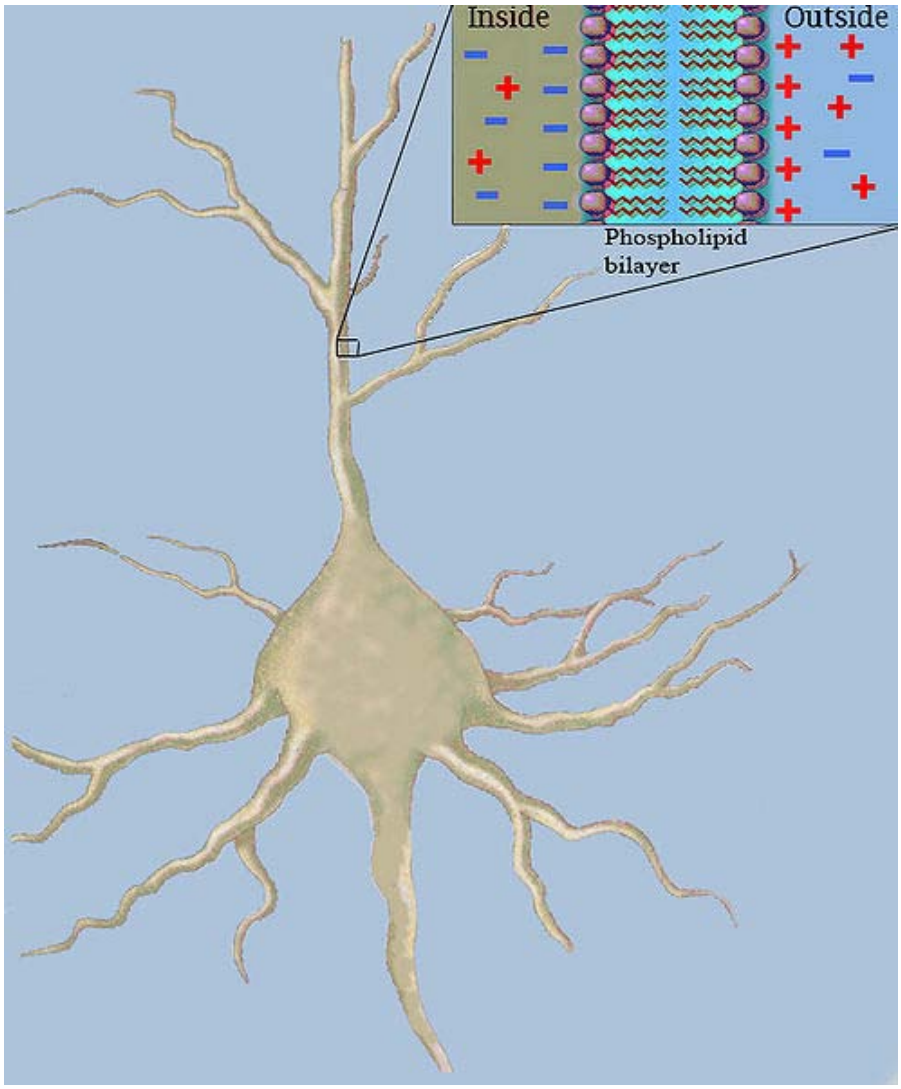


Figure.2: Fiber Capacitance

History

Cable theory in computational neuroscience has roots leading back to the 1850s, when Professor William Thomson (later known as Lord Kelvin) began developing mathematical models of signal decay in submarine (underwater) telegraphic cables. The models resembled the partial differential equations used by Fourier to describe heat conduction in a wire.

The 1870s saw the first attempts by Hermann to model axonal electrotonus also by focusing on analogies with heat conduction. However it was Hoorweg who first discovered the analogies with Kelvin's undersea cables in 1898 and then Hermann and Cremer who independently developed the cable theory for neuronal fibers in the early 20th century. Further mathematical theories of nerve fiber conduction based on cable theory were developed by Cole and Hodgkin (1920s-1930s), Offner et al. (1940), and Rushton (1951).

Experimental evidence for the importance of cable theory in modeling real nerve axons began surfacing in the 1930s from work done by Cole, Curtis, Hodgkin, Sir Bernard Katz, Rushton, Tasaki and others. Two key papers from this era are those of Davis and Lorente de No (1947) and Hodgkin and Rushton (1946).

The 1950s saw improvements in techniques for measuring the electric activity of individual neurons. Thus cable theory became important for analyzing data collected from intracellular microelectrode recordings and for analyzing the electrical properties of neuronal dendrites. Scientists like Coombs, Eccles, Fatt, Frank, Fuortes and others now relied heavily on cable theory to obtain functional insights of neurons and for guiding them in the design of new experiments.

Later, cable theory with its mathematical derivatives allowed ever more sophisticated neuron models to be explored by workers such as Jack, Christof Koch, Noble, Poggio, Rall, Redman, Rinzel, Idan Segev, Shepherd, Torre and Tsien. One important avenue of research became to analyze the effects of different synaptic input distributions over the dendritic surface of a neuron.

Deriving the cable equation

r_m and c_m introduced above are measured per fiber-length unit (usually centimeter (cm)). Thus r_m is measured in ohm-centimeters (Ω·cm) and c_m in microfarads per centimeter (μF/cm). This is in contrast to R_m[Ω·cm²] and C_m[μF/cm²], which represent the specific resistance and capacitance of the membrane measured within one unit area of membrane (cm^2). Thus if the radius a of the cable is known and hence its circumference $2\pi a$, r_m and c_m can be calculated as follows:

$$r_m = \frac{R_m}{2\pi a} \quad (1)$$

$$c_m = C_m 2\pi a \quad (2)$$

This makes sense because the bigger the circumference the larger area for charge to escape through the membrane and the smaller resistance (we divide R_m by $2\pi a$); and the more membrane to store charge (we multiply C_m by $2\pi a$). In a similar vein, the specific resistance R_l of the cytoplasm enables the longitudinal intracellular resistance per unit length r_l[Ω·cm^{-1}] to be calculated as:

$$r_l = \frac{R_l}{\pi a^2} \quad (3)$$

Again a reasonable equation, because the larger the cross sectional area (πa^2) the larger the number of paths for the current to flow through the cytoplasm and the less resistance.

To better understand how the cable equation is derived let's first simplify our fiber from above even further and pretend it has a perfectly sealed membrane (r_m is infinite) with no loss of current to the outside, and no capacitance ($c_m = 0$). A current injected into the fiber at position $x = 0$ would move along the inside of the fiber unchanged. Moving away from the point of injection and by using Ohm's law ($V = IR$) we can calculate the voltage change as:

$$\Delta V = -i_l r_l \Delta x \quad (4)$$

If we let Δx go towards zero and have infinitely small increments of x we can write (4) as:

$$\frac{\partial V}{\partial x} = -i_l r_l \quad (5)$$

or

$$\frac{1}{r_l}\frac{\partial V}{\partial x} = -i_l \quad (6)$$

Bringing r_m back into the picture is like making holes in a garden hose. The more holes the more water will escape to the outside, and the less water will reach a certain point of the hose. Similarly in the neuronal fiber some of the current travelling longitudinally along the inside of the fiber will escape through the membrane.

If i_m is the current escaping through the membrane per length unit (cm), then the total current escaping along y units must be yi_m. Thus the change of current in the cytoplasm Δi_l at distance Δx from position x=0 can be written as:

$$\Delta i_l = -i_m \Delta x \quad (7)$$

or using continuous infinitesimally small increments:

$$\frac{\partial i_l}{\partial x} = -i_m \quad (8)$$

i_m can be expressed with yet another formula, by including the capacitance. The capacitance will cause a flow of charge (current) towards the membrane on the side of the cytoplasm. This current is usually referred to as displacement current (here denoted i_c.) The flow will only take place as long as the membrane's storage capacity has not been reached. i_c can then be expressed as:

$$i_c = c_m \frac{\partial V}{\partial t} \quad (9)$$

where c_m is the membrane's capacitance and $\partial V / \partial t$ is the change in voltage over time. The current that passes the membrane (i_r) can be expressed as:

$$i_r = \frac{V}{r_m} \quad (10)$$

and because $i_m = i_r + i_c$ the following equation for i_m can be derived if no additional current is added from an electrode:

$$\frac{\partial i_l}{\partial x} = -i_m = -\left(\frac{V}{r_m} + c_m \frac{\partial V}{\partial t}\right) \quad (11)$$

where $\partial i_l / \partial x$ represents the change per unit length of the longitudinal current.

By combining equations (6) and (11) we get a first version of a cable equation:

$$\frac{1}{r_l} \frac{\partial^2 V}{\partial x^2} = c_m \frac{\partial V}{\partial t} + \frac{V}{r_m} \quad (12)$$

which is a second-order partial differential equation (PDE.)

By a simple rearrangement of equation (12) it is possible to make two important terms appear, namely the length constant (sometimes referred to as the space constant) denoted λ and the time constant denoted τ. The following sections focus on these terms.

The length constant

The length constant denoted with the symbol λ (lambda) is a parameter that indicates how far a current will spread along the inside of a neurite and thereby influence the voltage

along that distance. The larger λ is, the farther the current will flow. The length constant can be expressed as:

$$\lambda = \sqrt{\frac{r_m}{r_l}} \quad (13)$$

This formula makes sense because the larger the membrane resistance (r_m) (resulting in larger λ) the more current will remain inside the cytosol to travel longitudinally along the neurite. The higher the cytosol resistance (r_l) (resulting in smaller λ) the harder it will be for current to travel through the cytosol and the shorter the current will be able to travel. It is possible to solve equation (12) and arrive at the following equation (which is valid in steady-state conditions, i.e. when time goes to infinity):

$$V_x = V_0 e^{-\frac{x}{\lambda}} \quad (14)$$

Where V_0 is the depolarization at $x = 0$ (point of current injection), e is the exponential constant (approximate value 2.71828) and V_x is the voltage at a given distance x from x=0. When $x = \lambda$ then

$$\frac{x}{\lambda} = 1 \quad (15)$$

and

$$V_x = V_0 e^{-1} \quad (16)$$

which means that when we measure V at distance λ from $x = 0$ we get

$$V_\lambda = \frac{V_0}{e} = 0.368 V_0 \quad (17)$$

Thus V_λ is always 36.8 percent of V_0.

The time constant

Neuroscientists are often interested in knowing how fast the membrane potential V_m of a neurite is changing in response to changes in the current injected into the cytosol. The time constant τ is an index that provides information about exactly that. τ can be calculated as:

$$\tau = r_m c_m \quad (18)$$

which seem reasonable because the larger the membrane capacitance (c_m) the more current it takes to charge and discharge a patch of membrane and the longer this process

will take. Thus membrane potential (voltage across the membrane) lags behind current injections. Response times vary from 1-2 milliseconds in neurons that are processing information that needs high temporal precision to 100 milliseconds or longer. A typical response time is around 20 milliseconds.

The cable equation with length and time constants

If we multiply equation (12) by r_m on both sides of the equal sign we get:

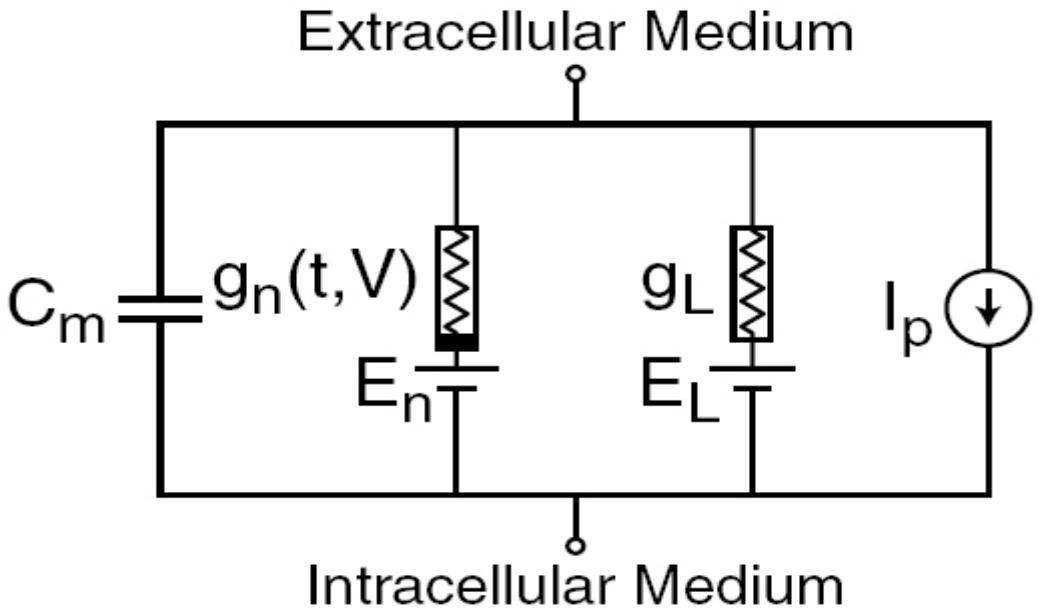
$$\frac{r_m}{r_l}\frac{\partial^2 V}{\partial x^2} = c_m r_m \frac{\partial V}{\partial t} + V \quad (19)$$

and recognize $\lambda^2 = r_m / r_l$ on the left side and $\tau = c_m r_m$ on the right side. The cable equation can now be written in its perhaps best known form:

$$\lambda^2 \frac{\partial^2 V}{\partial x^2} = \tau \frac{\partial V}{\partial t} + V \quad (20)$$

Chapter 7

Hodgkin–Huxley Model



Basic components of Hodgkin–Huxley-type models. Hodgkin–Huxley type models represent the biophysical characteristic of cell membranes. The lipid bilayer is represented as a capacitance (C_m). Voltage-gated and leak ion channels are represented by nonlinear (g_n) and linear (g_L) conductances, respectively. The electrochemical gradients driving the flow of ions are represented by batteries (E), and ion pumps and exchangers are represented by current sources (I_p).

The **Hodgkin–Huxley model** is a mathematical model (a type of scientific model) that describes how action potentials in neurons are initiated and propagated. It is a set of nonlinear ordinary differential equations that approximates the electrical characteristics of excitable cells such as neurons and cardiac myocytes.

Alan Lloyd Hodgkin and Andrew Huxley described the model in 1952 to explain the ionic mechanisms underlying the initiation and propagation of action potentials in the squid giant axon. They received the 1963 Nobel Prize in Physiology or Medicine for this work.

Basic components

The components of a typical Hodgkin–Huxley model are shown in the figure. Each component of an excitable cell has a biophysical analog. The lipid bilayer is represented as a capacitance (C_m). Voltage-gated ion channels are represented by nonlinear electrical conductances (g_n, where n is the specific ion channel), meaning that the conductance is voltage and time-dependent. This was later shown to be mediated by voltage-gated cation channel proteins, each of which has an open probability that is voltage-dependent. Leak channels are represented by linear conductances (g_L). The electrochemical gradients driving the flow of ions are represented by batteries (E_n and E_L), the values of which are determined from the Nernst potential of the ionic species of interest. Finally, ion pumps are represented by current sources (I_p).

The time derivative of the potential across the membrane ($\dot{V}_m$) is proportional to the sum of the currents in the circuit. This is represented as follows:

$$\dot{V}_m = -\frac{1}{C_m}\left(\sum_i I_i\right),$$

where I_i denotes the individual ionic currents of the model.

Ionic current characterization

The current flowing through the ion channels is mathematically represented by the following equation:

$$I_i(V_m, t) = (V_m - E_i)g_i$$

where E_i is the reversal potential of the i-th ion channel.

In voltage-gated ion channels, the channel conductance g_i is a function of both time and voltage ($g_n(t, V)$ in the figure), while in leak channels g_i is a constant (g_L in the figure). The current generated by ion pumps is dependent on the ionic species specific to that pump. The following sections will describe these formulations in more detail.

Voltage-gated ion channels

Under the Hodgkin–Huxley formulation, conductances for voltage-gated channels ($g_n(t, V)$) are expressed as:

$$g_n(V_m) = \bar{g}_n \varphi^\alpha \chi^\beta$$
$$\dot{\varphi}(V_m) = \frac{1}{\tau_\varphi}(\varphi_\infty - \varphi)$$

$$\dot{\chi}(V_m) = \frac{1}{\tau_\chi}(\chi_\infty - \chi),$$

where φ and χ are gating variables for activation and inactivation, respectively, representing the fraction of the maximum conductance available at any given time and voltage. $\bar{g}_n$ is the maximal value of the conductance. α and β are constants and τ_φ and τ_χ are the time constants for activation and inactivation, respectively. φ_∞ and χ_∞ are the steady state values for activation and inactivation, respectively, and are usually represented by Boltzmann equations as functions of V_m.

In order to characterize voltage-gated channels, the equations will be fit to voltage-clamp data. For a derivation of the Hodgkin–Huxley equations under voltage-clamp see. Briefly, when the membrane potential is held at a constant value (i.e., voltage-clamp), for each value of the membrane potential the nonlinear gating equations reduce to linear differential equations of the form:

$$\varphi(t) = \varphi_0 - [(\varphi_0 - \varphi_\infty)(1 - e^{-t/\tau_\varphi})]$$
$$\chi(t) = \chi_0 - [(\chi_0 - \chi_\infty)(1 - e^{-t/\tau_\chi})].$$

Thus, for every value of membrane potential, V_m, the following equation can be fit to the current curve:

$$I_n(t) = \bar{g}_n \varphi^\alpha \chi^\beta (V_m - E_n).$$

The Levenberg–Marquardt algorithm, a modified Gauss–Newton algorithm, is often used to fit these equations to voltage-clamp data.

Leak channels

Leak channels account for the natural permeability of the membrane to ions and take the form of the equation for voltage-gated channels, where the conductance g_i is a constant.

Pumps and exchangers

The membrane potential depends upon the maintenance of ionic concentration gradients across it. The maintenance of these concentration gradients requires active transport of ionic species. The sodium-potassium and sodium-calcium exchangers are the best known of these. Some of the basic properties of the Na/Ca exchanger have already been well-established: the stoichiometry of exchange is 3 Na^+:1 Ca^{2+} and the exchanger is electrogenic and voltage-sensitive. The Na/K exchanger has also been described in detail.

Improvements and alternative models

The Hodgkin–Huxley model is widely regarded as one of the great achievements of 20th-century biophysics. Nevertheless, modern Hodgkin–Huxley-type models have been extended in several important ways:

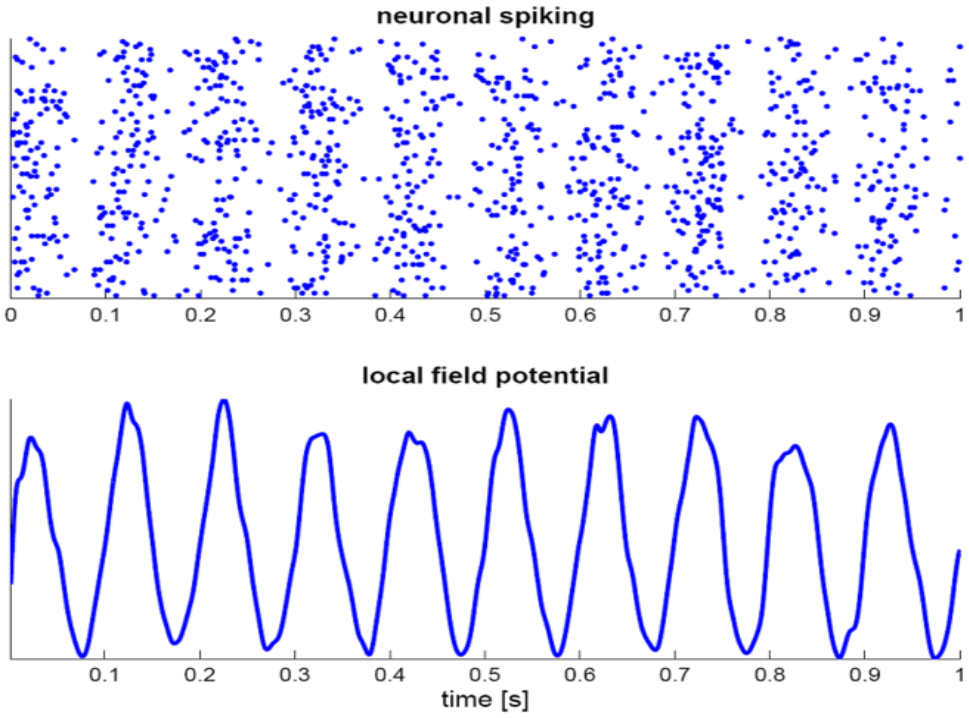
- Additional ion channel populations have been incorporated based on experimental data.
- Models often incorporate highly complex geometries of dendrites and axons, often based on microscopy data.

Several simplified neuronal models have also been developed (such as Fitzhugh-Nagumo model), facilitating efficient large-scale simulation of groups of neurons, as well as mathematical insight into dynamics of action potential generation.

Chapter 8

Neural Oscillation

Neural oscillation is rhythmic or repetitive neural activity in the central nervous system. Neural tissue can generate oscillatory activity in many ways, driven either by mechanisms localized within individual neurons or by feedback interactions among populations of neurons. In individual neurons, oscillations can appear either as subthreshold rhythms of membrane potential rise and fall, or as rhythmic increases and decreases in action potential activity, which then produce rhythmic activation of synapses in target neurons. At the level of neural population, synchronized oscillations of large numbers of neurons can give rise to macroscopic oscillatory electric fields, which can be observed in the electroencephalogram (EEG).



Simulation of neural oscillations at 10 Hz. Upper panel shows spiking of individual neurons (with each dot representing an individual action potential within the population of neurons), and the lower panel the local field potential reflecting their summed activity.

Overview

EEG signals oscillate across a range of frequencies. Scientists have defined a set of frequency bands which group specific ranges of frequencies from this spectrum. The first discovered and best-known frequency band is alpha activity (8–12 Hz). Other frequency bands are: delta (1–4 Hz), theta (4–8 Hz), beta (13–30 Hz) and gamma (30–70 Hz) frequency band. Although neural oscillations in human brain activity are mostly investigated using EEG recordings, they are also observed in animals using more invasive recording techniques such as single-unit recordings. Intracellularly, oscillations are observed in subthreshold membrane potential oscillations, whereas extracellularly they are reflected in changes in local field potentials (LFPs). Large-scale oscillations that are observable outside the scalp with EEG or MEG arise through synchronous activity of large numbers of neurons.

Neural oscillations are characterized by their frequency, amplitude and phase. These signal properties can be extracted from neural recordings using time-frequency analysis. Changes in these characteristics have been linked to various functions. In large-scale oscillations, amplitude changes are considered to result from changes in synchronization within a neural ensemble, also referred to as local synchronization, and have been linked to cognitive functions such as perception and motor control. Apart from local synchronization, changes in the synchronization between oscillatory activity of distant neural ensembles has been observed, which might serve as a neural mechanism for information transfer.

The study of neural oscillations belongs to the field of "neurodynamics", an area of research in the cognitive sciences that places a strong focus upon the dynamic character of neural activity in describing brain function. The term neurodynamics dates back before the 1940s, and is an offshoot of neuro-cybernetics using differential equations to describe neural activity patterns. Research in neurodynamics involves the interdisciplinary areas of contemporary theoretical neurobiology, nonlinear dynamics, complex adaptive systems and statistical physics. Neurodynamics is often contrasted with the popular computational and modular approaches of cognitive neuroscience, and with the implicit or explicit representationalism in cognitive science.

Neural Field Theories is a mathematical framework describing the spatio-temporal evolution of variables such as mean firing rate. In modeling the activity of large numbers of neurons, the central idea is to take the density of neurons to the continuum limit, resulting in spatially continuous neural networks. Models based on these principles provide mathematical descriptions of neural oscillations and EEG rhythms and have been used to investigate visual hallucinations, and mechanisms for short-term memory and motion perception.

Mathematical description

Mathematicians have identified several dynamical mechanisms that generate rhythmicity. Among the most important are harmonic (linear) oscillators, limit-cycle oscillators, and

delayed-feedback oscillators. Harmonic oscillations appear very frequently in nature—examples are sound waves, the motion of a pendulum, and vibrations of every sort. They generally arise when a physical system is perturbed by a small degree from a minimum-energy state, and are well-understood mathematically. Noise-driven harmonic oscillators realistically simulate alpha rhythm in the waking EEG as well as slow waves and spindles in the sleep EEG. Successful EEG analysis algorithms were based on such models. Several other EEG components are better described by limit-cycle or delayed-feedback oscillations. Limit-cycle oscillations arise from physical systems that show large deviations from equilibrium, whereas delayed-feedback oscillations arise when components of a system affect each other after significant time delays. Limit-cycle oscillations can be complex but there are powerful mathematical tools for analyzing them; the mathematics of delayed-feedback oscillations is primitive in comparison.

Linear oscillators and limit-cycle oscillators qualitatively differ in terms of how they respond to fluctuations in input. In a linear oscillator, the frequency is more or less constant but the amplitude can vary greatly. In a limit-cycle oscillator, the amplitude tends to be more or less constant but the frequency can vary greatly. A heartbeat is an example of a limit-cycle oscillation in that the frequency of beats varies widely, while each individual beat continues to pump about the same amount of blood.

Neuronal spiking

Neurons generate action potentials that reflect changes in the electric membrane potential. Neurons can generate multiple action potentials in sequence forming so-called spike trains. These spike trains are the basis for neural coding and information transfer in the brain. Spike trains can form all kind of patterns, such as rhythmic spiking and bursting, and are often considered oscillatory activity.

Mechanisms

Scientists have identified some intrinsic neuronal properties that can result in membrane potential oscillations. In particular, voltage-gated ion channels are critical in the generation of action potentials. The dynamics of these ion channels have been captured in the well-established Hodgkin-Huxley model that describes how action potentials are initiated and propagated by means of a set of differential equations. Using bifurcation analysis, different oscillatory regimes of these neuronal models can be determined, allowing for the classification of types of neuronal responses. The oscillatory dynamics of neuronal spiking as identified using mathematical models closely agree with empirical findings. In addition to periodic spiking, subthreshold membrane potential oscillations, i.e. fluctuations that do not result in action potentials, may also contribute to oscillatory activity by facilitating synchronous activity of neighboring neurons.

Activity pattern

Neuronal spiking can be classified by their activity patterns. The excitability of neurons can be subdivided in Class 1 and 2. Class 1 neurons can generate action potentials with

arbitrarily low frequency depending on the input strength, whereas Class 2 neurons generate action potentials in a certain frequency band, which is relatively insensitive to changes in input strength.

Function

Neuronal spiking is the basis for information transfer in the brain. Different types of coding schemes have been proposed, such as rate coding and temporal coding.

Large-scale oscillations

Apart for single neurons that can generate oscillatory spike trains, groups of neurons often reveal oscillatory behavior. These large-scale oscillations arise to synchronized activity of multiple neurons. Experimentally these oscillations can be measured by fluctuation in the local field potential or by mean of EEG and MEG.

Mechanisms

Network properties

Apart from intrinsic properties of neurons, network properties are also an important source of oscillatory activity. Neurons are locally connected, forming small clusters that are called neural ensembles. Certain network structures promote oscillatory activity at specific frequencies. This is determined by the type of neurons, i.e. *excitatory* or *inhibitory* neurons, time delays and the coupling function. Central pattern generators are a well-known example of neural networks that can endogenously produce rhythmic patterned outputs. Neural synchronization is the process by which the activity of two or more neurons or neural ensembles tend to oscillate with a repeating sequence of relative phase angles. Mathematically, neural ensembles can be considered weakly coupled oscillators, a type of system that readily allows for synchronized oscillatory activity. For example, neuronal activity generated by two populations of interconnected *inhibitory* and *excitatory* cells can show spontaneous oscillations that are described by the Wilson-Cowan model.

Synchronized activity of a large number of neurons results in electromagnetic fields that can be measured outside the scalp with electroencephalography and magnetoencephalography. Using these techniques, synchronized neural activity have been observed throughout the central nervous system and during various tasks. Neural synchronization can be modulated by task constraints, such as attention, and is thought to play a role in feature binding, neuronal communication, and motor coordination.

Large-scale connections

Connections between different brain structures, for instance the thalamus and the cortex, can form loops that support oscillatory activity. Oscillations recorded from multiple cortical areas can become synchronized and form a large-scale network, whose dynamics

and functional connectivity can be studied by means of spectral analysis and Granger causality measures. Coherent activity of large-scale brain activity may form dynamic links between brain areas required for the integration of distributed information.

Neurotransmitters

Certain neurotransmitters are known to regulate the amount of oscillatory activity. GABA concentration has been shown to be positively correlated with frequency of oscillations in induced stimuli. The exact relationship, however, can only be resolved with further pharmacological research on how GABA concentrations affect oscillatory dynamics of single neurons and local field potentials of ensembles of neurons.

Activity patterns

Spontaneous activity

Spontaneous activity is brain activity in the absence of an explicit task, such as sensory input or motor output. It is opposed to induced activity, i.e. brain activity that is induced by sensory stimuli or motor responses. The term *ongoing brain activity* is used in electroencephalography and magnetoencephalography for those signal components that are not associated with the processing of a stimulus or the occurrence of specific other events, such as moving a body part, i.e. that do not form evoked potentials/evoked fields, event-related potentials, or induced activity. Spontaneous activity is usually considered to be noise if one is interested in stimulus processing. However, spontaneous activity is considered to play a crucial role during brain development, such as in network formation and synaptogenesis. Spontaneous activity may be informative regarding the current mental state of the person (e.g. wakefulness, alertness) and is often used in sleep research. Certain types of oscillatory activity, such as alpha waves, are part of spontaneous activity.

Most neuroscience studies have focused on the brain's response to a task or stimulus. However, the brain is very active even in the absence of explicit input or output. Spontaneous activity is investigated using a paradigm that requires subjects to open and close their eyes at fixed intervals while fMRI or EEG activity is recorded. In case of fMRI, spontaneous fluctuations in the blood oxygen level dependent (BOLD) signal reveal correlation patterns that are linked to different resting states. In EEG research, spontaneous fluctuations of oscillatory activity are investigated and power changed in different EEG bands show correlations with the distributed patterns of fMRI activity. Research on spontaneous activity led to the hypothesis that specific brain regions constitute a network supporting a default mode of brain functioning.

Evoked activity

The term evoked activity is used in electroencephalography and magnetoencephalography for certain types of stimulus-related activity. The following explanation is for electroencephalographic activity (EEG), but the concept is the same in magnetoencephalography (MEG).

Evoked potentials and event-related potentials are obtained from the electroencephalogram by stimulus-locked averaging. As a consequence, those signal components that are the same in each single measurement are conserved and all others are averaged out. That is, event-related potentials only reflect oscillations in brain activity that are phase-locked to the stimulus or event. Evoked activity is often considered to be independent from ongoing brain activity although this is an ongoing debate.

Induced activity

Next to evoked activity, neural activity related to stimulus processing may result in induced activity. Induced activity refers to changes in ongoing brain activity induced by processing of stimuli or movement preparation. A well-studied type of induced activity is amplitude change in oscillatory activity. For instance, gamma activity often increases during increased mental activity such as during object representation. Because induced responses may have different phases across measurements and therefore would cancel out during averaging, they can only be obtained using time-frequency analysis. Induced activity generally reflects the activity of numerous neurons and amplitude changes in oscillatory activity are thought to arise from the synchronization of neural activity, e.g. synchronization of spikes or membrane potential fluctuations of individual neurons. Increases and decreases in oscillatory activity are therefore often referred to as event-related synchronization and desynchronization.

Function

Visual system

Neuronal oscillations became a hot topic in neuroscience in the 1990s when the studies of the visual system of the brain by Gray, Singer and others appeared to support the neural binding hypothesis. According to this idea, synchronous oscillations in neuronal ensembles bind neurons representing different features of an object. For example, when a person looks at a tree, visual cortex neurons representing the tree trunk and those representing the branches of the same tree would oscillate in synchrony to form a single representation of the tree. Some scientists have questioned whether these oscillations are prominent, or relevant, in ensembles that consider only action potential activity. These oscillations are, however, prominent in differential LFP recordings taken between upper and lower cortical layers, which suggests a local current, but not action potential, basis for their origin.

EEG studies suggest that visual perception is phase dependent as well as amplitude dependent. In a study in which human subjects were stimulated with flashes of light, it was found that phase dependence accounted for 16% of variability in the measured response to stimuli. The results suggest that ongoing oscillations provide a temporal reference for visual perception via precise spike timing. EEG evidence also suggests that local oscillatory bursts display significant patterns of synchrony. During flickering light simulation of human subjects, quantifiable oscillatory patterns of synchronicity had significantly higher degrees of co-occurrence during stimulation than the background

levels of synchronicity. This suggests that during visual stimulation, oscillatory patterns are reorganized in the visual cortex and propagate throughout the brain.

Evidence suggests that the visual system of children is less entrained by incoming information resulting in less synchronized neural responses. Adults primarily rely on sparse representations formed through experience based temporally synchronized neural interactions. In older age, declines in neuronal density and neurotransmitter chemicals increase the reliance on temporally synchronizing processing.. In the motor system synchronus oscillations between co-operative, co-contracting muscles and between brain and muscle show a developmental profile with the observation that around adolescence there is an increasing prevelance and magnitude of beta and gamma rhythm. These changes occur at at time of signifincant neural pruning.

Other perceptual systems

Neural oscillations may have different functional roles in different brain areas, and their functional role continues to be a matter of debate. Neural oscillations have been hypothesized to be involved in the sense of time and in somatosensory perception among other functions.

Gilles Laurent and colleagues that showed oscillatory synchronization has an important functional role in odor perception and identified some mechanisms by which this function is established. That is, different odors lead to different subsets of neurons firing on different sets of oscillatory cycles and the oscillations can be disrupted by GABA blocker picrotoxin. Disruption of the oscillatory synchronization leads to impairment of behavioral discrimination of chemically similar odorants in bees and to more similar responses across odors in downstream β-lobe neurons.

Motor system

Oscillations have been commonly reported in the motor system. Pfurtscheller and colleagues found a reduction in alpha (8–12 Hz) and beta (13–30 Hz) oscillations in EEG activity when subjects made a movement. Using intra-cortical recordings, similar oscillations were found in motor cortex when the monkeys performed motor acts that required significant attention (retrieval of raisins from unseen locations).. Oscillations at spinal level become synchronised to beta oscillations in motor cortex during constant muscle activation, as determined by MEG/EEG-EMG coherence. Recently it was found that cortical oscillations propagate as waves across the surface of the motor cortex along dominant spatial axes characteristic of the local circuitry of the motor cortex.

Oscillatory rhythms at 10 Hz have been recorded in inferior olive and may be central in motor timing. These oscillations are also observed in motor output of physiological tremor and when performing slow finger movements. These findings may indicate that the human brain controls continuous movements intermittently. In support, it was shown that 6- to 9-Hz pulsatile velocity changes of slow finger movements are directly

correlated to oscillatory activity in a cerebello-thalamo-cortical loop that might represent a neural mechanism for the intermittent motor control.

Memory

Neural oscillations are extensively linked to memory function, in particular theta activity. Theta rhythms are very strong in rodent hippocampi and entorhinal cortex during learning and memory retrieval, and are believed to be vital to the induction of long-term potentiation, a potential cellular mechanism of learning and memory. The coupling between theta and gamma activity is thought to be vital for memory functions. The tight coordination of spike timing of single neurons with the local theta oscillations is linked to successful memory formation in humans, as more stereotyped spiking predicts better memory.

Applications

Brain-computer interfaces

Neural oscillations have been considered for use as a control signal for various brain-computer interfaces.

Pathological oscillations

Specific types of neural oscillations may also appear in pathological situations, such as Parkinson's disease or epilepsy. Interestingly, these pathological oscillations often consist of an aberrant version of a normal oscillation. For example, one of the best known types is the spike and wave oscillation, which is typical of generalized or absence epileptic seizures, and which resembles normal sleep spindle oscillations.

Chapter 9

Neurotechnology

Neurotechnology is any technology that has a fundamental influence on how people understand the brain and various aspects of consciousness, thought, and higher order activities in the brain. It also includes technologies that are designed to improve and repair brain function and allow researchers and clinicians to visualize the brain.

Background

The field of neurotechnology has been around for nearly half a century but has only reached maturity in the last twenty years. Advents of brain imaging revolutionized the field and gave rise to a whole new shift in research that could now directly monitor the brain's activities during experiments. The field of neurotechnology is incredibly relevant to society, though its presence is so commonplace that many do not realize its ubiquity. From pharmaceutical drugs to brain scanning, neurotechnology affects nearly all industrialized people either directly or indirectly, be it from drugs for depression, sleep, ADD, or anti-neurotics to cancer scanning, stroke rehabilitation, and much more. Its potentials reach nearly all aspects of daily life, and as the field's depth increases modern societies will be able to harness and control more of what the brain does and how it influences lifestyles and personalities. It is important to note that there are many technologies that are taken for granted that could apply in the field. Games like BrainAge, and programs like FastForWord are methods for improvement of brain function and therefore apply as well. In addition, numerous pharmaceutical companies develop many new and useful functional drugs that can help improve function and restore normality in a person's life. Currently, modern science can image nearly all aspects of the brain as well as control a degree of the function of the brain. It can help control depression, over-activation, sleep deprivation, and many other conditions. Therapeutically it can help improve stroke victims' motor coordination, improve brain function, reduce epileptic episodes, improve patients with degenerative motor diseases (Parkinson's Disease, Huntington's Disease, ALS), and can even help alleviate phantom pain perception. Advances in the field promise many new enhancements and rehabilitations for patients suffering from neurological problems. The neurotechnology revolution has given rise to the Decade of the Mind initiative, which was started in 2007. It also offers the possibility of revealing the mechanisms by which mind and consciousness emerge from the brain.

Current technologies

Imaging

Magnetic resonance imaging (MRI) is used for scanning the brain for topological and landmark structure in the brain, but can also be used for imaging activation in the brain. While detail about how MRI works is reserved for the actual MRI article, the uses of MRI are far reaching in the study of neuroscience. It is a cornerstone technology in studying the mind, especially with the advent of functional MRI (fMRI). Functional MRI measures the oxygen levels in the brain upon activation (higher oxygen content = neural activation) and allows researchers to understand what loci are responsible for activation under a given stimulus. This technology is a large improvement to single cell or loci activation by means of exposing the brain and contact stimulation. Functional MRI allows researchers to draw associative relationships between different loci and regions of the brain and provides a large amount of knowledge in establishing new landmarks and loci in the brain.

Computed tomography (CT) is another technology used for scanning the brain. It has been used since the 1970s and is another tool used by neuroscientists to track brain structure and activation. While many of the functions of CT scans are now done using MRI, CT can still be used as the mode by which brain activation and brain injury are detected. Using an X-ray, researchers can detect radioactive markers in the brain that indicate brain activation as a tool to establish relationships in the brain as well as detect many injuries/diseases that can cause lasting damage to the brain such as aneurysms, degeneration, and cancer.

Positron emission tomography (PET) is another imaging technology that aids researchers. Instead of using magnetic resonance or X-rays, PET scans rely on positron emitting markers that are bound to a biologically relevant marker such as glucose. The more activation in the brain the more that region requires nutrients, so higher activation appears more brightly on an image of the brain. PET scans are becoming more frequently used by researchers due to the fact that PET scans are activated due to metabolism whereas MRI is activated on a more physiological basis (sugar activation versus oxygen activation).

Transcranial magnetic stimulation

Transcranial magnetic stimulation (TMS) is essentially direct magnetic stimulation to the brain. Because electric currents and magnetic fields are intrinsically related, by stimulating the brain with magnetic pulses it is possible to interfere with specific loci in the brain to produce a predictable effect. This field of study is currently receiving a large amount of attention due to the potential benefits that could come out of better understanding this technology.

Cranial surface measurements

Electroencephalography (EEG) is a method of measuring brainwave activity non-invasively. A number of electrodes are placed around the head and scalp and electrical signals are measured. Typically EEGs are used when dealing with sleep, as there are characteristic wave patterns associated with different stages of sleep. Clinically EEGs are used to study epilepsy as well as stroke and tumor presence in the brain. EEGs are a different method to understand the electrical signaling in the brain during activation.

Magnetoencephalography (MEG) is another method of measuring activity in the brain by measuring the magnetic fields that arise from electrical currents in the brain. The benefit to using MEG instead of EEG is that these fields are highly localized and give rise to better understanding of how specific loci react to stimulation or if these regions over-activate (as in epileptic seizures).

Implant technologies

Neurodevices are any devices used to monitor or regulate brain activity. Currently there are a few available for clinical use as a treatment for Parkinson's disease. The most common neurodevices are deep brain stimulators (DBS) that are used to give electrical stimulation to areas stricken by inactivity. Parkinson's disease is known to be caused by an inactivation of the basal ganglia (nuclei) and recently DBS has become the more preferred form of treatment for Parkinson's disease, although current research questions the efficiency of DBS for movement disorders.

Neuromodulation is a relatively new field that combines the use of neurodevices and neurochemistry. The basis of this field is that the brain can be regulated using a number of different factors (metabolic, electrical stimulation, physiological) and that all these can be modulated by devices implanted in the neural network. While currently this field is still in the researcher phase, it represents a new type of technological integration in the field of neurotechnology.

Gene/cell therapy

Cell therapy is a field devoted to improving cells via genetic enhancement. Currently there are many researchers investigating the ability for programmed regeneration and genetic influencing in the brain. Using viral or nanoparticle vectors (a "carrier" for the gene of interest), scientists are finding new ways to manipulate and improve the brain's capacity, overall health, and resistance to disease. Researchers have begun looking at uses for stem cells in the brain, which recently have been found in a few loci. A large number of studies are being done to determine if this form of therapy could be used in a large scale.

Pharmaceuticals

Pharmaceuticals play a vital role in maintaining stable brain chemistry, and are the most commonly used neurotechnology by the general public and medicine. Drugs like sertraline, methylphenidate, and zolpidem act as chemical modulators in the brain, and they allow for normal activity in many people whose brains cannot act normally under physiological conditions. While pharmaceuticals are usually not mentioned and have their own field, the role of pharmaceuticals is perhaps the most far-reaching and commonplace in modern society.

How these help study the brain

Magnetic resonance imaging is a vital tool in neurological research in showing activation in the brain as well as providing a comprehensive image of the brain being studied. While MRIs are used clinically for showing brain size, it still has relevance in the study of brains because it can be used to determine extent of injuries or deformation. These can have a significant effect on personality, sense perception, memory, higher order thinking, movement, and spatial understanding. However, current research tends to focus more so on fMRI or real-time functional MRI (rtfMRI). These two methods allow the scientist or the participant, respectively, to view activation in the brain. This is incredibly vital in understanding how a person thinks and how their brain reacts to a person's environment, as well as understanding how the brain works under various stressors or dysfunctions. Real-time functional MRI is a revolutionary tool available to neurologists and neuroscientists because patients can see how their brain reacts to stressors and can perceive visual feedback. CT scans are very similar to MRI in their academic use because they can be used to image the brain upon injury, but they are more limited in perceptual feedback. CTs are generally used in clinical studies far more than in academic studies, and are found far more often in a hospital than a research facility. PET scans are also finding more relevance in academia because they can be used to observe metabolic uptake of neurons, giving researchers a wider perspective about neural activity in the brain for a given condition. Combinations of these methods can provide researchers with knowledge of both physiological and metabolic behaviors of loci in the brain and can be used to explain activation and deactivation of parts of the brain under specific conditions.

Transcranial magnetic stimulation is a relatively new method of studying how the brain functions and is used in many research labs focused on behavioral disorders and hallucinations. What makes TMS research so interesting in the neuroscience community is that it can target specific regions of the brain and shut them down or activate temporarily; thereby changing the way the brain behaves. Personality disorders can stem from a variety of external factors, but when the disorder stems from the circuitry of the brain TMS can be used to deactivate the circuitry. This can give rise to a number of responses, ranging from "normality" to something more unexpected, but current research is based on the theory that use of TMS could radically change treatment and perhaps act as a cure for personality disorders and hallucinations. Currently, repetitive transcranial magnetic stimulation (rTMS) is being researched to see if this deactivation effect can be made more permanent in patients suffering from these disorders. Some techniques

combine TMS and another scanning method such as EEG to get additional information about brain activity such as cortical response.

Both EEG and MEG are currently being used to study the brain's activity under different conditions. Each uses similar principles but allows researchers to examine individual regions of the brain, allowing isolation and potentially specific classification of active regions. As mentioned above, EEG is very useful in analysis of immobile patients, typically during the sleep cycle. While there are other types of research that utilize EEG, EEG has been fundamental in understanding the resting brain during sleep. There are other potential uses for EEG and MEG such as charting rehabilitation and improvement after trauma as well as testing neural conductivity in specific regions of epileptics or patients with personality disorders.

Neuromodulation can involve numerous technologies combined or used independently to achieve a desired effect in the brain. Gene and cell therapy are becoming more prevalent in research and clinical trials and these technologies could help stunt or even reverse disease progression in the central nervous system. Deep brain stimulation is currently used in many patients with movement disorders and is used to improve the quality of life in patients. While deep brain stimulation is a method to study how the brain functions per se, it provides both surgeons and neurologists important information about how the brain works when certain small regions of the basal ganglia (nuclei) are stimulated by electrical currents.

Future technologies

The future of neurotechnologies lies in how they are fundamentally applied, and not so much on what new versions will be developed. Current technologies give a large amount of insight into the mind and how the brain functions, but basic research is still needed to demonstrate the more applied functions of these technologies. Currently, rtfMRI is being researched as a method for pain therapy. deCharms et al. have shown that there is a significant improvement in the way people perceive pain if they are made aware of how their brain is functioning while in pain. By providing direct and understandable feedback, researchers can help patients with chronic pain decrease their symptoms. This new type of bio/mechanical-feedback is a new development in pain therapy. Functional MRI is also being considered for a number of more applicable uses outside of the clinic. Research has been done on testing the efficiency of mapping the brain in the case when someone lies as a new way to detect lying. Along the same vein, EEG has been considered for use in lie detection as well. TMS is being used in a variety of potential therapies for patients with personality disorders, epilepsy, PTSD, migraine, and other brain-firing disorders, but has been found to have varying clinical success for each condition. The end result of such research would be to develop a method to alter the brain's perception and firing and train patients' brains to rewire permanently under inhibiting conditions. In addition, PET scans have been found to be 93% accurate in detecting Alzheimer's disease nearly 3 years before conventional diagnosis, indicating that PET scanning is becoming more useful in both the laboratory and the clinic.

Stem cell technologies are always salient both in the minds of the general public and scientists because of their large potential. Recent advances in stem cell research have allowed researchers to ethically pursue studies in nearly every facet of the body, which includes the brain. Research has shown that while most of the brain does not regenerated and is typically a very difficult environment to foster regeneration, there are portions of the brain with regenerative capabilities (specifically the hippocampus and the olfactory bulbs). Much of the research in central nervous system regeneration is how to overcome this poor regenerative quality of the brain. It is important to note that there are therapies that improve cognition and increase the amount of neural pathways, but this does not mean that there is a proliferation of neural cells in the brain. Rather, it is called a plastic rewiring of the brain (*plastic* because it indicates malleability) and is considered a vital part of growth. Nevertheless, many problems in patients stem from death of neurons in the brain, and researchers in the field are striving to produce technologies that enable regeneration in patients with stroke, Parkinson's diseases, severe trauma, and Alzheimer's disease, as well as many others. While still in fledgling stages of development, researchers have recently begun making very interesting progress in attempting to treat these diseases. Researchers have recently successfully produced dopaminergic neurons for transplant in patients with Parkinson's diseases with the hopes that they will be able to move again with a more steady supply of dopamine. Many researchers are building scaffolds that could be transplanted into a patient with spinal cord trauma to present an environment that promotes growth of axons (portions of the cell attributed with transmission of electrical signals) so that patients unable to move or feel might be able to do so again. The potentials are wide-ranging, but it is important to note that many of these therapies are still in the laboratory phase and are slowly being adapted in the clinic. Some scientists remain skeptical with the development of the field, and warn that there is a much larger chance that electrical prosthesis will be developed to solve clinical problems such as hearing loss or paralysis before cell therapy is used in a clinic.

Novel drug delivery systems are being researched in order to improve the lives of those who struggle with brain disorders that might not be treated with stem cells, modulation, or rehabilitation. Pharmaceuticals play a very important role in society, and the brain has a very selective barrier that prevents some drugs from going from the blood to the brain. There are some diseases of the brain such as meningitis that require doctors to directly inject medicine into the spinal cord because the drug cannot cross the blood-brain barrier. Research is being conducted to investigate new methods of targeting the brain using the blood supply, as it is much easier to inject into the blood than the spine. New technologies such as nanotechnology are being researched for selective drug delivery, but these technologies have problems as with any other. One of the major setbacks is that when a particle is too large, the patient's liver will take up the particle and degrade it for excretion, but if the particle is too small there will not be enough drug in the particle to take effect. In addition, the size of the capillary pore is important because too large a particle might not fit or even plug up the hole, preventing adequate supply of the drug to the brain. Other research is involved in integrating a protein device between the layers to create a free-flowing gate that is unimpeded by the limitations of the body. Another direction is receptor-mediated transport, where receptors in the brain used to transport

nutrients are manipulated to transport drugs across the blood-brain barrier. Some have even suggested that focused ultrasound opens the blood-brain barrier momentarily and allows free passage of chemicals into the brain. Ultimately the goal for drug delivery is to develop a method that maximizes the amount of drug in the loci with as little degraded in the blood stream as possible.

Neuromodulation is a technology currently used for patients with movement disorders, although research is currently being done to apply this technology to other disorders. Recently, a study was done on if DBS could improve depression with positive results, indicating that this technology might have potential as a therapy for multiple disorders in the brain. DBS is limited by its high cost however, and in developing countries the availability of DBS is very limited. A new version of DBS is under investigation and has developed into the novel field, optogenetics. Optogenetics is the combination of deep brain stimulation with fiber optics and gene therapy. Essentially, the fiber optic cables are designed to light up under electrical stimulation, and a protein would be added to a neuron via gene therapy to excite it under light stimuli. So by combining these three independent fields, a surgeon could excite a single and specific neuron in order to help treat a patient with some disorder. Neuromodulation offers a wide degree of therapy for many patients, but due to the nature of the disorders it is currently used to treat its effects are often temporary. Future goals in the field hope to alleviate that problem by increasing the years of effect until DBS can be used for the remainder of the patient's life. Another use for neuromodulation would be in building neuro-interface prosthetic devices that would allow quadriplegics the ability to maneuver a cursor on a screen with their thoughts, thereby increasing their ability to interact with others around them. By understanding the motor cortex and understanding how the brain signals motion, it is possible to emulate this response on a computer screen.

Ethics

Stem cells

The ethical debate about use of embryonic stem cells has stirred controversy both in the United States and abroad; although more recently these debates have lessened due to modern advances in creating induced pluripotent stem cells from adult cells. The greatest advantage for use of embryonic stem cells is the fact that they can differentiate (become) nearly any type of cell provided the right conditions and signals. However, recent advances by Shinya Yamanaka et al. have found ways to create pluripotent cells without the use of such controversial cell cultures. Using the patient's own cells and re-differentiating them into the desired cell type bypasses not only the fear of patient rejection of the cells but also gives researchers a more ethical (and larger) supply of available cells. Induced pluripotent cells are by no means perfect though, they still have the potential to form teratomas, or benign (though they can be potentially malignant in effect) tumors, and tend to have poor survivability *in vivo* (in the living body) on damaged tissue. Much of the ethics concerning use of stem cells has subsided from the embryonic/adult stem cell debate due to its rendered moot, but now societies find themselves debating whether or not this technology can be ethically used. Enhancements

of traits, use of animals for tissue scaffolding, and even arguments for moral degeneration have been made with the fears that if this technology reaches its full potential a new paradigm shift will occur in human behavior.

Military application

New neurotechnologies have always garnered the appeal of governments, from lie detection technology and virtual reality to rehabilitation and understanding the psyche. Due to the Iraq War and War on Terror, American soldiers coming back from Iraq and Afghanistan are reported to have percentages up to 12% with PTSD. There are many researchers hoping to improve these peoples' conditions by implementing new strategies for recovery. By combining pharmaceuticals and neurotechnologies, some researchers how found ways to low the fear response and theorize that it may be applicable to PTSD. Virtual reality is also a technology that has found a large amount of attention in the military. If improved upon, it would be possible to train soldiers in complex situations in times of peace in order to better prepare and train a modern army.

Privacy

Finally, when these technologies are being developed society must understand that these neurotechnologies could reveal the one thing that people can always keep secret, what they are thinking. While there are large amounts of benefits associated with these technologies, it is necessary for scientists and policy makers alike to consider implications about "cognitive liberty." This term is important in many ethical circles concerned with the state and goals of progress in the field of neurotechnology. Current improvements such as "brain fingerprinting" or lie detection using EEG or fMRI could give rise to a set fixure of loci/emotional relationships in the brain, although these technologies are still years away from full application. It is important to consider how all these neurotechnologies might affect the future of society, and it is suggested that political, scientific, and civil debates are heard about the implementation of these newer technologies that potentially offer a new wealth of once-private information. Some ethicists are also concerned with the use of TMS and fear that the technique could be used to alter patients in ways that are undesired by the patient.

Chapter 10

Cellular Neuroscience

Cellular neuroscience is the study of neurons at a cellular level. This includes morphology and physiological properties of single neurons. Several techniques such as intracellular recording, patch-clamp, and voltage-clamp technique, pharmacology, confocal imaging, molecular biology, two photon laser scanning microscopy and Ca^{2+} imaging have been used to study activity at the cellular level. Cellular neuroscience examines the various types of neurons, the functions of different neurons, the influence of neurons upon each other, how neurons work together.

Neurons and glial cells

Neurons are cells that are specialized to receive, propagate, and transmit electrochemical impulses. In the human brain alone, there are over a hundred billion neurons. Neurons are diverse with respect to morphology and function. Thus, not all neurons correspond to the stereotypical motor neuron with dendrites and myelinated axons that conduct action potentials. Some neurons such as photoreceptor cells, for example, do not have myelinated axons that conduct action potentials. Other unipolar neurons found in invertebrates do not even have distinguishing processes such as dendrites. Moreover, the distinctions based on function between neurons and other cells such as cardiac and muscle cells are not helpful. Thus, the fundamental difference between a neuron and a nonneuronal cell is a matter of degree.

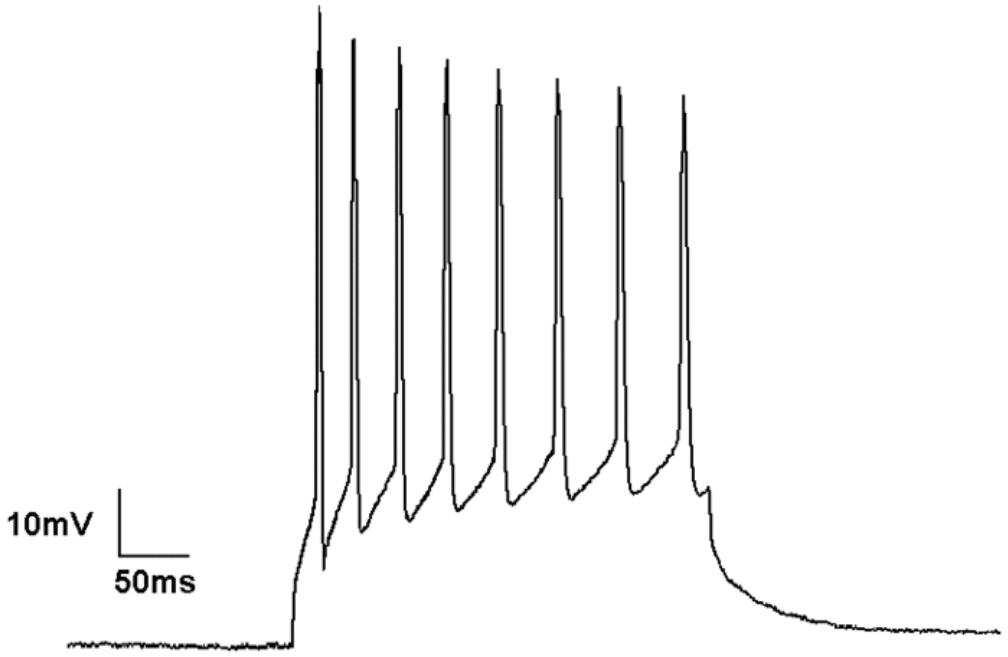
Another major class of cells found in the nervous system are **glial cells**. These cells are only recently beginning to receive attention from neurobiologists for being involved not just in nourishment and support of neurons, but also in modulating synapses. For example, Schwann cells, which are a type of glial cell found in the peripheral nervous system, modulate synaptic connections between presynaptic terminals of motor neuron endplates and muscle fibers at neuromuscular junctions.

Neuronal function

One prominent characteristic of many neurons is excitability. Neurons generate electrical impulses or changes in voltage of two types: graded potentials and action potentials. Graded potentials occur when the membrane potential depolarizes and hyperpolarizes in a graded fashion relative to the amount of stimulus that is applied to the neuron. An action potential on the other hand is an all-or-none electrical impulse. Despite being

slower than graded potentials, action potentials have the advantage of traveling long distances in axons with little or no decrement. Much of the current knowledge of action potentials comes from squid axon experiments by Sir Alan Lloyd Hodgkin and Sir Andrew Huxley.

Action potential



"Current Clamp" is a common technique in electrophysiology. This is a whole cell current clamp recording of a neuron firing a train of action potentials due to it being depolarized by current injection

The Hodgkin-Huxley Model of an action potential in the squid giant axon has been the basis for much of the current understanding of the ionic bases of action potentials. Briefly, the model states that the generation of an action potential is determined by two ions: Na^+ and K^+. An action potential can be divided into several sequential phases: threshold, rising phase, falling phase, undershoot phase, and recovery. Following several local graded depolarizations of the membrane potential, the threshold of excitation is reached, voltage-gated sodium channels are activated, which leads to an influx of Na^+ ions. As Na^+ ions enter the cell, the membrane potential is further depolarized, and more voltage-gated sodium channels are activated. Such a process is also known as a positive-feedback loop. As the rising phase reaches its peak, voltage-gated Na^+ channels are inactivated whereas voltage-gated K^+ channels are activated, resulting in a net outward movement of K^+ ions, which repolarizes the membrane potential towards the resting membrane potential. Repolarization of the membrane potential continues, resulting in an undershoot phase or absolute refractory period. The undershoot phase occurs because unlike voltage-gated sodium channels, voltage-gated potassium channels inactivate much

more slowly. Nevertheless, as more voltage-gated K^+ channels become inactivated, the membrane potential recovers to its normal resting steady state.

Structure and formation of synapses

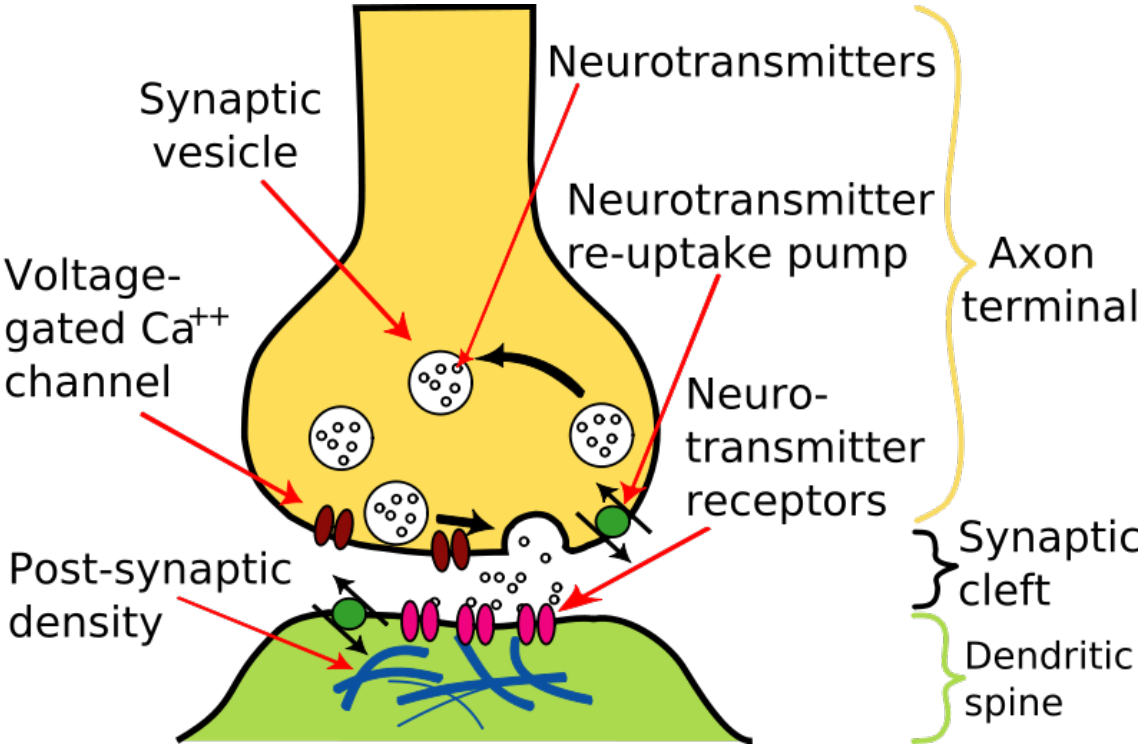


Illustration of the major elements in a prototypical **synapse**. Synapses are gaps between nerve cells. These cells convert their electrical impulses into bursts of neurochemical relayers, called neurotransmitters, which travel across the synapses to receptors on the dendrites of adjacent cells, thereby triggering further electrical impulses to travel down the latter cells.

Neurons communicate with one another via synapses. Synapses are specialized junctions between two cells in close apposition to one another. In a synapse, the neuron that sends the signal is the presynaptic neuron and the target cell receives that signal is the postsynaptic neuron or cell. Synapses can be either electrical or chemical. Electrical synapses are characterized by the formation of gap junctions that allow ions and other organic compound to instantaneously pass from one cell to another. Chemical synapses are characterized by the presynaptic release of neurotransmitters that diffuse across a synaptic cleft to bind with postsynaptic receptors. A neurotransmitter is a chemical messenger that is synthesized within neurons themselves and released by these same neurons to communicate with their postsynaptic target cells. A receptor is a transmembrane protein molecule that a neurotransmitter or drug binds. Chemical synapses are slower than electrical synapses.

Neurotransmitter transporters, receptors, and signaling mechanisms

After neurotransmitters are synthesized, they are packaged and stored in vesicles. These vesicles are pooled together in terminal boutons of the presynaptic neuron. When there is a change in voltage in the terminal bouton, voltage-gated calcium channels embedded in the membranes of these boutons become activated. These allow Ca^{2+} ions to diffuse through these channels and bind with synaptic vesicles within the terminal buttons. Once bounded with Ca^{2+}, the vesicles dock and fuse with the presynaptic membrane, and release neurotransmitters into the synaptic cleft by a process known as exocytosis. The neurotransmitters then diffuse across the synaptic cleft and bind to postsynaptic receptors embedded on the postsynaptic membrane of another neuron. There are two families of receptors: ionotropic and metabotropic receptors. Ionotropic receptors are a combination of a receptor and an ion channel. When ionotropic receptors are activated, certain ion species such as Na^+ to enter the postsynaptic neuron, which depolarizes the postsynaptic membrane. If more of the same type of postsynaptic receptors are activated, then more Na^+ will enter the postsynaptic membrane and depolarize cell. Metabotropic receptors on the other hand activate second messenger cascade systems that result in the opening of ion channel located some place else on the same postsynaptic membrane. Although slower than ionotropic receptors that function as on-and-off switches, metabotropic receptors have the advantage of changing the cell's responsiveness to ions and other metabolites, examples being Gamma Amino-Butyric Acid (inhibitory transmitter), Glutamic Acid (excitatory transmitter), Dopamine, Norepinephrine, Epinephrine, Melanin, Serotonin, Melatonin, and Substance P.

Postsynaptic depolarizations can be either excitatory or inhibitory. Those that are excitatory are referred to as excitatory postsynaptic potential (EPSP). Alternatively, some postsynaptic receptors allow Cl^- ions to enter the cell or K^+ ions to leave the cell, which results in an inhibitory postsynaptic potential (IPSP). If the EPSP is dominant, the threshold of excitation in the postynaptic neuron may be reached, resulting in the generation and propagation of an action potential in the postynaptic neuron.

Synaptic plasticity

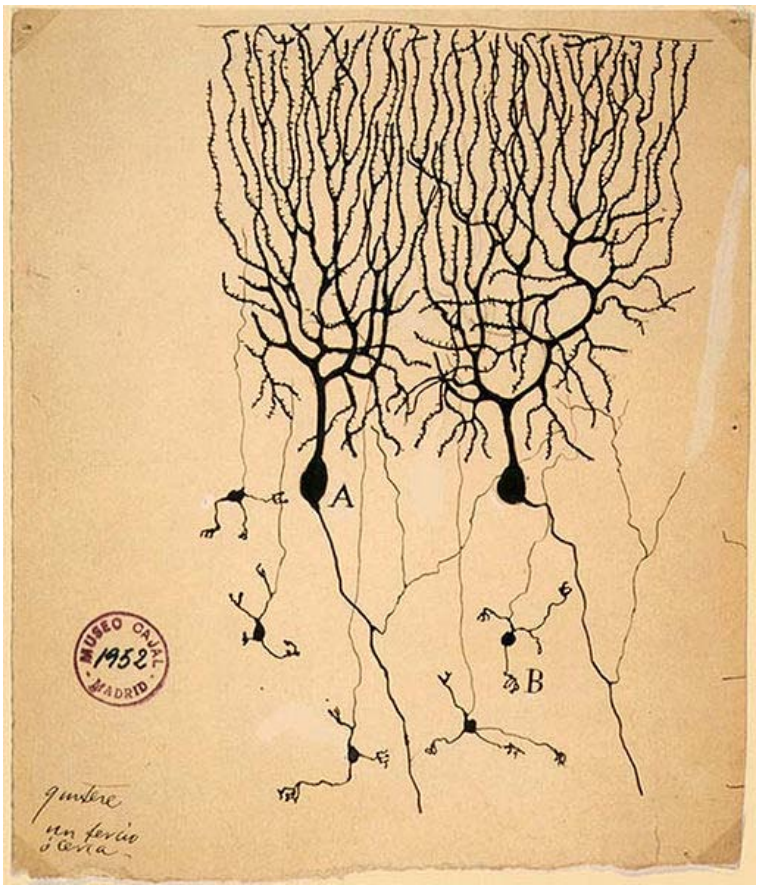
Synaptic plasticity is the process whereby strengths of synaptic connections are altered. For example, long-term changes in synaptic connection may result in more postsynaptic receptors being embedded in the postsynaptic membrane, resulting in the strengthening of the synapse. Synaptic plasticity is also found to be the neural mechanism that underlies learning and memory.

The basic properties, activity and regulation of membrane currents, synaptic transmission and synaptic plasticity, neurotransmisson, neuroregensis, synaptogenesis and ion channels of cells are a few other fields studied by cellular neuroscientists. Tissue, cellular and subcellular anatomy are studied to provide insight into mental retardation at the Mental Retardation Research Center MRRC Cellular Neuroscience Core. Journals such as *Frontiers in Cellular Neuroscience* and *Molecular and Cellular Neuroscience* are published regarding cellular neuroscientific topics.

Chapter 11

Neuron

Neuron: Nerve Cell



Drawing by Santiago Ramón y Cajal of neurons in the pigeon cerebellum. (A) Denotes Purkinje cells, an example of a multipolar neuron. (B) Denotes granule cells which are also multipolar.

NeuroLex ID *sao1417703748*

A **neuron** is an electrically excitable cell that processes and transmits information by electrical and chemical signaling. Chemical signaling occurs via synapses, specialized connections with other cells. Neurons connect to each other to form networks. Neurons are the core components of the nervous system, which includes the brain, spinal cord, and peripheral ganglia. A number of specialized types of neurons exist: sensory neurons respond to touch, sound, light and numerous other stimuli affecting cells of the sensory organs that then send signals to the spinal cord and brain. Motor neurons receive signals from the brain and spinal cord, cause muscle contractions, and affect glands. Interneurons connect neurons to other neurons within the same region of the brain or spinal cord.

A typical neuron possesses a cell body (often called the soma), dendrites, and an axon. Dendrites are filaments that arise from the cell body, often extending for hundreds of micrometres and branching multiple times, giving rise to a complex "dendritic tree". An axon is a special cellular filament that arises from the cell body at a site called the axon hillock and travels for a distance, as far as 1 m in humans or even more in other species. The cell body of a neuron frequently gives rise to multiple dendrites, but never to more than one axon, although the axon may branch hundreds of times before it terminates. At the majority of synapses, signals are sent from the axon of one neuron to a dendrite of another. There are, however, many exceptions to these rules: neurons that lack dendrites, neurons that have no axon, synapses that connect an axon to another axon or a dendrite to another dendrite, etc.

All neurons are electrically excitable, maintaining voltage gradients across their membranes by means of metabolically driven ion pumps, which combine with ion channels embedded in the membrane to generate intracellular-versus-extracellular concentration differences of ions such as sodium, potassium, chloride, and calcium. Changes in the cross-membrane voltage can alter the function of voltage-dependent ion channels. If the voltage changes by a large enough amount, an all-or-none electrochemical pulse called an action potential is generated, which travels rapidly along the cell's axon, and activates synaptic connections with other cells when it arrives.

Neurons of the adult brain do not generally undergo cell division, and usually cannot be replaced after being lost, although there are a few known exceptions. In most cases they are generated by special types of stem cells, although astrocytes (a type of glial cell) have been observed to turn into neurons as they are sometimes pluripotent.

Overview

A neuron is a special type of cell that is found in the bodies of most animals (all members of the group Eumetazoa, to be precise—this excludes only sponges and a few other very simple animals). The features that define a neuron are electrical excitability and the presence of synapses, which are complex membrane junctions used to transmit signals to other cells. The body's neurons, plus the glial cells that give them structural and metabolic support, together constitute the nervous system. In vertebrates, the majority of neurons belong to the central nervous system, but some reside in peripheral ganglia, and many sensory neurons are situated in sensory organs such as the retina and cochlea.

Although neurons are very diverse and there are exceptions to nearly every rule, it is convenient to begin with a schematic description of the structure and function of a "typical" neuron. A typical neuron is divided into three parts: the soma or cell body, dendrites, and axon. The soma is usually compact; the axon and dendrites are filaments that extrude from it. Dendrites typically branch profusely, getting thinner with each branching, and extending their farthest branches a few hundred micrometres from the soma. The axon leaves the soma at a swelling called the axon hillock, and can extend for great distances, giving rise to hundreds of branches. Unlike dendrites, an axon usually maintains the same diameter as it extends. The soma may give rise to numerous dendrites, but never to more than one axon. Synaptic signals from other neurons are received by the soma and dendrites; signals to other neurons are transmitted by the axon. A typical synapse, then, is a contact between the axon of one neuron and a dendrite or soma of another. Synaptic signals may be excitatory or inhibitory. If the net excitation received by a neuron over a short period of time is large enough, the neuron generates a brief pulse called an action potential, which originates at the soma and propagates rapidly along the axon, activating synapses onto other neurons as it goes.

Many neurons fit the foregoing schema in every respect, but there are also exceptions to most parts of it. There are no neurons that lack a soma, but there are neurons that lack dendrites, and others that lack an axon. Furthermore, in addition to the typical axodendritic and axosomatic synapses, there are axoaxonic (axon-to-axon) and dendrodendritic (dendrite-to-dendrite) synapses.

The key to neural function is the synaptic signalling process, which is partly electrical and partly chemical. The electrical aspect depends on properties of the neuron's membrane. Like all animal cells, every neuron is surrounded by a plasma membrane, a bilayer of lipid molecules with many types of protein structures embedded in it. A lipid bilayer is a powerful electrical insulator, but in neurons, many of the protein structures embedded in the membrane are electrically active. These include ion channels that permit electrically charged ions to flow across the membrane, and ion pumps that actively transport ions from one side of the membrane to the other. Most ion channels are permeable only to specific types of ions. Some ion channels are voltage gated, meaning that they can be switched between open and closed states by altering the voltage difference across the membrane. Others are chemically gated, meaning that they can be switched between open and closed states by interactions with chemicals that diffuse through the extracellular fluid. The interactions between ion channels and ion pumps produce a voltage difference across the membrane, typically a bit less than 1/10 of a volt at baseline. This voltage has two functions: first, it provides a power source for an assortment of voltage-dependent protein machinery that is embedded in the membrane; second, it provides a basis for electrical signal transmission between different parts of the membrane.

Neurons communicate by chemical and electrical synapses in a process known as synaptic transmission. The fundamental process that triggers synaptic transmission is the action potential, a propagating electrical signal that is generated by exploiting the

electrically excitable membrane of the neuron. This is also known as a wave of depolarization.

Anatomy and histology

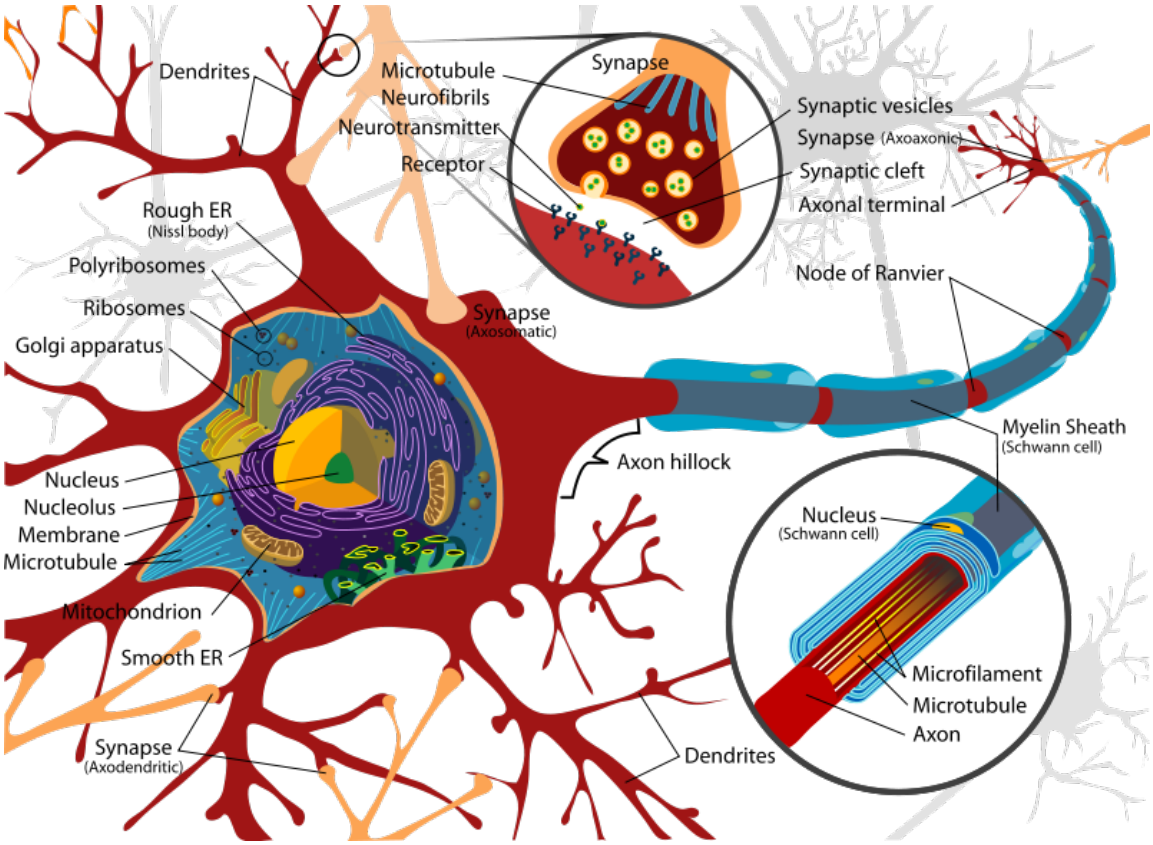


Diagram of a typical myelinated vertebrate motoneuron

Neurons are highly specialized for the processing and transmission of cellular signals. Given the diversity of functions performed by neurons in different parts of the nervous system, there is, as expected, a wide variety in the shape, size, and electrochemical properties of neurons. For instance, the soma of a neuron can vary from 4 to 100 micrometers in diameter.

- The soma is the central part of the neuron. It contains the nucleus of the cell, and therefore is where most protein synthesis occurs. The nucleus ranges from 3 to 18 micrometers in diameter.

- The dendrites of a neuron are cellular extensions with many branches, and metaphorically this overall shape and structure is referred to as a dendritic tree. This is where the majority of input to the neuron occurs.

- The axon is a finer, cable-like projection which can extend tens, hundreds, or even tens of thousands of times the diameter of the soma in length. The axon carries

nerve signals away from the soma (and also carries some types of information back to it). Many neurons have only one axon, but this axon may—and usually will—undergo extensive branching, enabling communication with many target cells. The part of the axon where it emerges from the soma is called the axon hillock. Besides being an anatomical structure, the axon hillock is also the part of the neuron that has the greatest density of voltage-dependent sodium channels. This makes it the most easily-excited part of the neuron and the spike initiation zone for the axon: in electrophysiological terms it has the most negative action potential threshold. While the axon and axon hillock are generally involved in information outflow, this region can also receive input from other neurons.

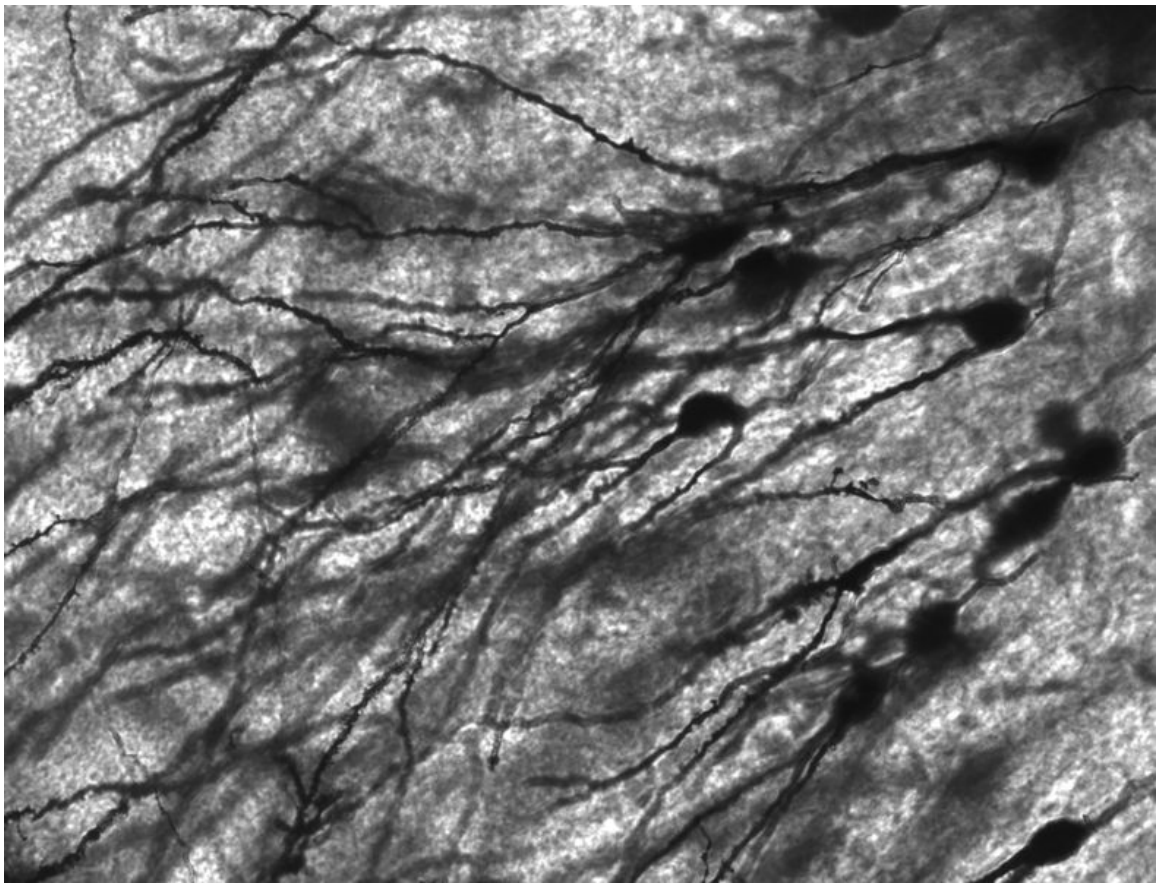
- The axon terminal contains synapses, specialized structures where neurotransmitter chemicals are released in order to communicate with target neurons.

Although the canonical view of the neuron attributes dedicated functions to its various anatomical components, dendrites and axons often act in ways contrary to their so-called main function.

Axons and dendrites in the central nervous system are typically only about one micrometer thick, while some in the peripheral nervous system are much thicker. The soma is usually about 10–25 micrometers in diameter and often is not much larger than the cell nucleus it contains. The longest axon of a human motoneuron can be over a meter long, reaching from the base of the spine to the toes. Sensory neurons have axons that run from the toes to the dorsal columns, over 1.5 meters in adults. Giraffes have single axons several meters in length running along the entire length of their necks. Much of what is known about axonal function comes from studying the squid giant axon, an ideal experimental preparation because of its relatively immense size (0.5–1 millimeters thick, several centimeters long).

Fully differentiated neurons are permanently amitotic; however, recent research shows that additional neurons throughout the brain can originate from neural stem cells found throughout the brain but in particularly high concentrations in the subventricular zone and subgranular zone through the process of neurogenesis.

Histology and internal structure



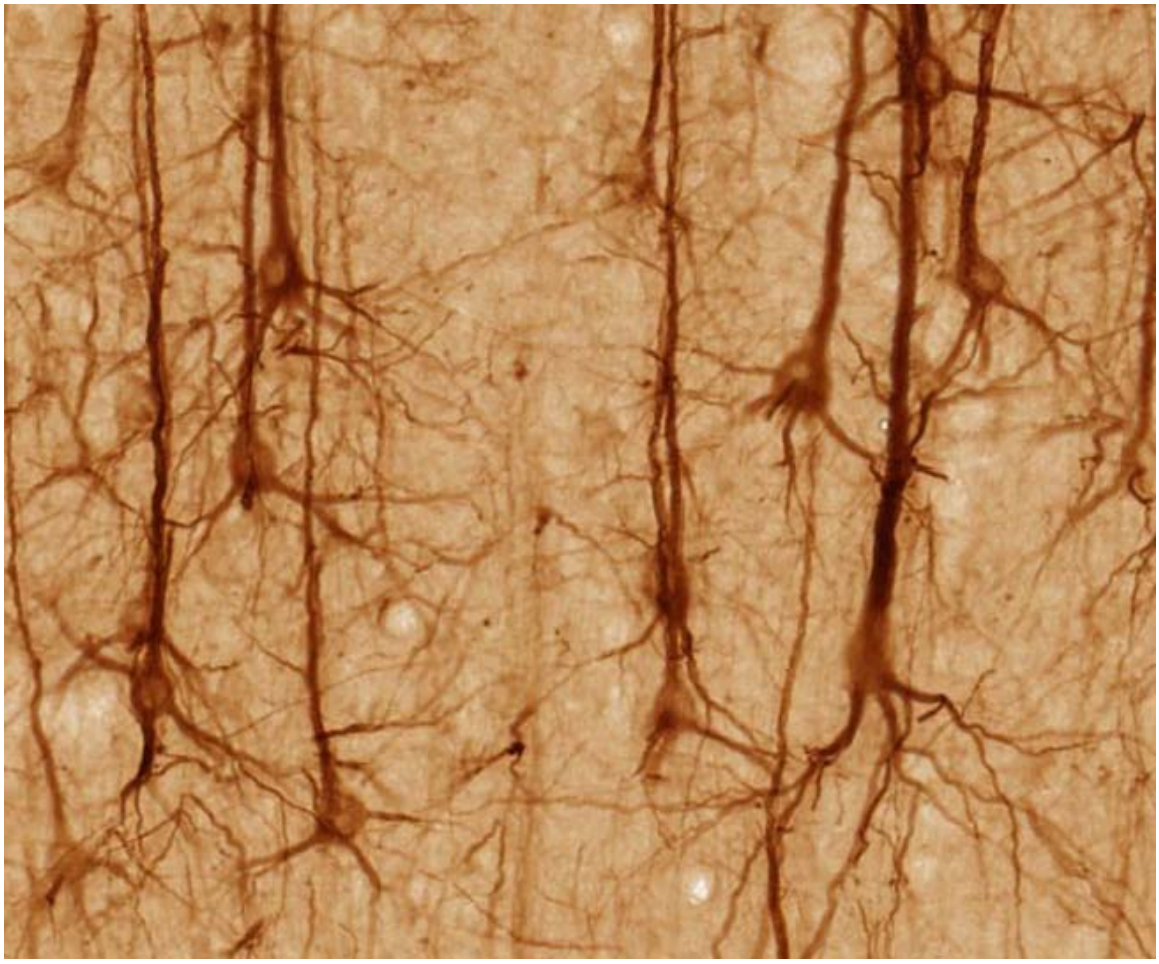
Golgi-stained neurons in human hippocampal tissue

Nerve cell bodies stained with basophilic dyes show numerous microscopic clumps of Nissl substance (named after German psychiatrist and neuropathologist Franz Nissl, 1860–1919), which consists of rough endoplasmic reticulum and associated ribosomal RNA. The prominence of the Nissl substance can be explained by the fact that nerve cells are metabolically very active, and hence are involved in large amounts of protein synthesis.

The cell body of a neuron is supported by a complex meshwork of structural proteins called neurofilaments, which are assembled into larger neurofibrils. Some neurons also contain pigment granules, such as neuromelanin (a brownish-black pigment, byproduct of synthesis of catecholamines) and lipofuscin (yellowish-brown pigment that accumulates with age).

There are different internal structural characteristics between axons and dendrites. Typical axons almost never contain ribosomes, except some in the initial segment. Dendrites contain granular endoplasmic reticulum or ribosomes, with diminishing amounts with distance from the cell body.

Classes



SMI32-stained pyramidal neurons in cerebral cortex

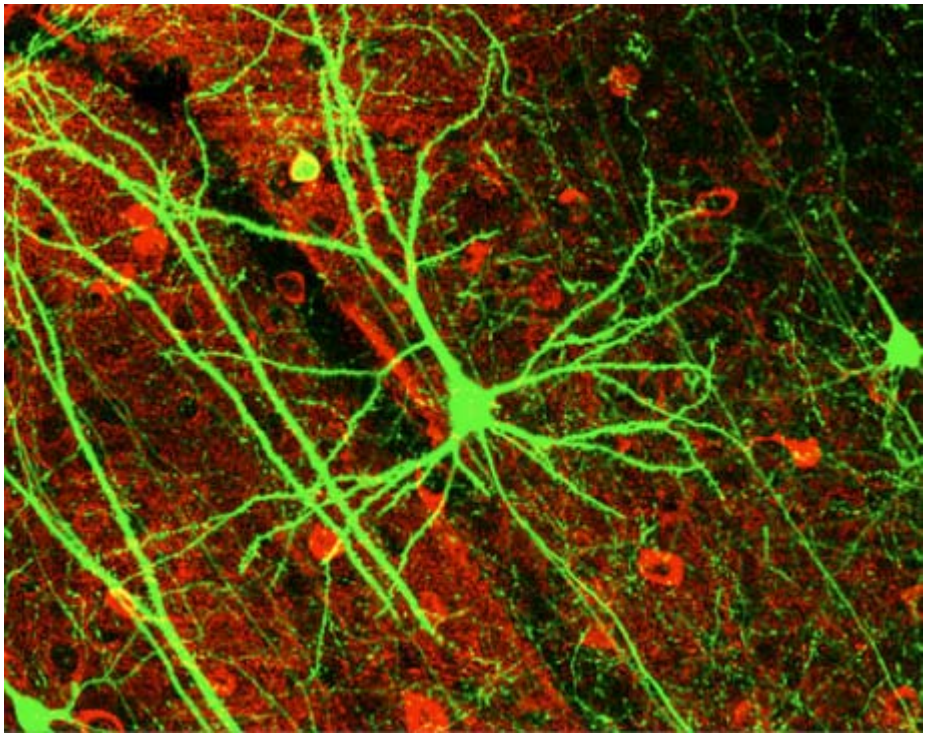


Image of pyramidal neurons in mouse cerebral cortex expressing green fluorescent protein. The red staining indicates GABAergic interneurons.

Neurons exist in a number of different shapes and sizes and can be classified by their morphology and function. The anatomist Camillo Golgi grouped neurons into two types; type I with long axons used to move signals over long distances and type II with short axons, which can often be confused with dendrites. Type I cells can be further divided by where the cell body or soma is located. The basic morphology of type I neurons, represented by spinal motor neurons, consists of a cell body called the soma and a long thin axon which is covered by the myelin sheath. Around the cell body is a branching dendritic tree that receives signals from other neurons. The end of the axon has branching terminals (axon terminal) that release neurotransmitters into a gap called the synaptic cleft between the terminals and the dendrites of the next neuron.

Structural classification

Polarity

Most neurons can be anatomically characterized as:

- Unipolar or pseudounipolar: dendrite and axon emerging from same process.
- Bipolar: axon and single dendrite on opposite ends of the soma.
- Multipolar: more than two dendrites:
    - Golgi I: neurons with long-projecting axonal processes; examples are pyramidal cells, Purkinje cells, and anterior horn cells.

- Golgi II: neurons whose axonal process projects locally; the best example is the granule cell.

Other

Furthermore, some unique neuronal types can be identified according to their location in the nervous system and distinct shape. Some examples are:

- Basket cells, interneurons that form a dense plexus of terminals around the soma of target cells, found in the cortex and cerebellum.
- Betz cells, large motor neurons.
- Medium spiny neurons, most neurons in the corpus striatum.
- Purkinje cells, huge neurons in the cerebellum, a type of Golgi I multipolar neuron.
- Pyramidal cells, neurons with triangular soma, a type of Golgi I.
- Renshaw cells, neurons with both ends linked to alpha motor neurons.
- Granule cells, a type of Golgi II neuron.
- Anterior horn cells, motoneurons located in the spinal cord.

Functional classification

Direction

- Afferent neurons convey information from tissues and organs into the central nervous system and are sometimes also called sensory neurons.
- Efferent neurons transmit signals from the central nervous system to the effector cells and are sometimes called motor neurons.
- Interneurons connect neurons within specific regions of the central nervous system.

Afferent and efferent can also refer generally to neurons which, respectively, bring information to or send information from the brain region.

Action on other neurons

A neuron affects other neurons by releasing a neurotransmitter that binds to chemical receptors. The effect upon the target neuron is determined not by the source neuron or by the neurotransmitter, but by the type of receptor that is activated. A neurotransmitter can be thought of as a key, and a receptor as a lock: the same type of key can here be used to open many different types of locks. Receptors can be classified broadly as *excitatory* (causing an increase in firing rate), *inhibitory* (causing a decrease in firing rate), or *modulatory* (causing long-lasting effects not directly related to firing rate).

In fact, however, the two most common neurotransmitters in the brain, glutamate and GABA, have actions that are largely consistent. Glutamate acts on several different types of receptors, but most of them have effects that are excitatory. Similarly GABA acts on

several different types of receptors, but all of them have effects (in adult animals, at least) that are inhibitory. Because of this consistency, it is common for neuroscientists to simplify the terminology by referring to cells that release glutamate as "excitatory neurons," and cells that release GABA as "inhibitory neurons." Since well over 90% of the neurons in the brain release either glutamate or GABA, these labels encompass the great majority of neurons. There are also other types of neurons that have consistent effects on their targets, for example "excitatory" motor neurons in the spinal cord that release acetylcholine, and "inhibitory" spinal neurons that release glycine.

The distinction between excitatory and inhibitory neurotransmitters is not absolute, however. Rather, it depends on the class of chemical receptors present on the target neuron. In principle, a single neuron, releasing a single neurotransmitter, can have excitatory effects on some targets, inhibitory effects on others, and modulatory effects on others still. For example, photoreceptor cells in the retina constantly release the neurotransmitter glutamate in the absence of light. So-called OFF bipolar cells are, like most neurons, excited by the released glutamate. However, neighboring target neurons called ON bipolar cells are instead *inhibited* by glutamate, because they lack the typical ionotropic glutamate receptors and instead express a class of inhibitory metabotropic glutamate receptors. When light is present, the photoreceptors cease releasing glutamate, which relieves the ON bipolar cells from inhibition, activating them; this simultaneously removes the excitation from the OFF bipolar cells, silencing them.

Discharge patterns

Neurons can be classified according to their electrophysiological characteristics:

- **Tonic or regular spiking**. Some neurons are typically constantly (or tonically) active. Example: interneurons in neurostriatum.
- **Phasic or bursting**. Neurons that fire in bursts are called phasic.
- **Fast spiking**. Some neurons are notable for their high firing rates, for example some types of cortical inhibitory interneurons, cells in globus pallidus, retinal ganglion cells.

Classification by neurotransmitter production

Neurons differ in the type of neurotransmitter they manufacture. Some examples are:

- Cholinergic neurons—acetylcholine. Acetylcholine is released from presynaptic neurons into the synaptic cleft. It acts as a ligand for both ligand-gated ion channels and metabotropic (GPCRs) muscarinic receptors. Nicotinic receptors, are pentameric ligand-gated ion channels composed of alpha and beta subunits that bind nicotine. Ligand binding opens the channel causing influx of Na^+ depolarization and increases the probability of presynaptic neurotransmitter release.

- GABAergic neurons—gamma aminobutyric acid. GABA is one of two neuroinhibitors in the CNS, the other being Glycine. GABA has a homologous function to ACh, gating anion channels that allow Cl- ions to enter the post synaptic neuron. Cl- causes hyperpolarization within the neuron, decreasing the probability of an action potential firing as the voltage becomes more negative (recall that for an action potential to fire, a positive voltage threshold must be reached).

- Glutamatergic neurons—glutamate. Glutamate is one of two primary excitatory amino acids, the other being Aspartate. Glutamate receptors are one of four categories, three of which are ligand-gated ion channels and one of which is a G-protein coupled receptor (often referred to as GPCR).

    1. AMPA and Kainate receptors both function as cation channels permeable to Na^+ cation channels mediating fast excitatory synaptic transmission
    2. NMDA receptors are another cation channel that is more permeable to Ca^{2+}. The function of NMDA receptors is dependant on Glycine receptor binding as a co-agonist within the channel pore. NMDA receptors will not function without both ligands present.
    3. Metabotropic receptors, GPCRs modulate synaptic transmission and postsynaptic excitability.

    Glutamate can cause excitotoxicity when blood flow to the brain is interrupted, resulting in brain damage. When blood flow is suppressed, glutamate is released from presynaptic neurons causing NMDA and AMPA receptor activation moreso than would normally be the case outside of stress conditions, leading to elevated Ca^{2+} and Na^+ entering the post synaptic neuron and cell damage.

- Dopaminergic neurons—dopamine. Dopamine is a neurotransmitter that acts on D1 type (D1 and D5) Gs coupled receptors which increase cAMP and PKA or D2 type (D2,D3 and D4)receptors which activate Gi-coupled receptors that decrease cAMP and PKA. Dopamine is connected to mood and behavior, and modulates both pre and post synaptic neurotransmission. Loss of dopamine neurons in the substantia nigra has been linked to Parkinson's disease.

- Serotonergic neurons—serotonin. Serotonin,(5-Hydroxytryptamine, 5-HT), can act as excitatory or inhibitory. Of the four 5-HT receptor classes, 3 are GPCR and 1 is ligand gated cation channel. Serotonin is synthesized from tryptophan by tryptophan hydroxylase, and then further by aromatic acid decarboxylase. A lack of 5-HT at postsynaptic neurons has been linked to depression. Drugs that block the presynaptic serotonin transporter are used for treatment, such as Prozac and Zoloft.

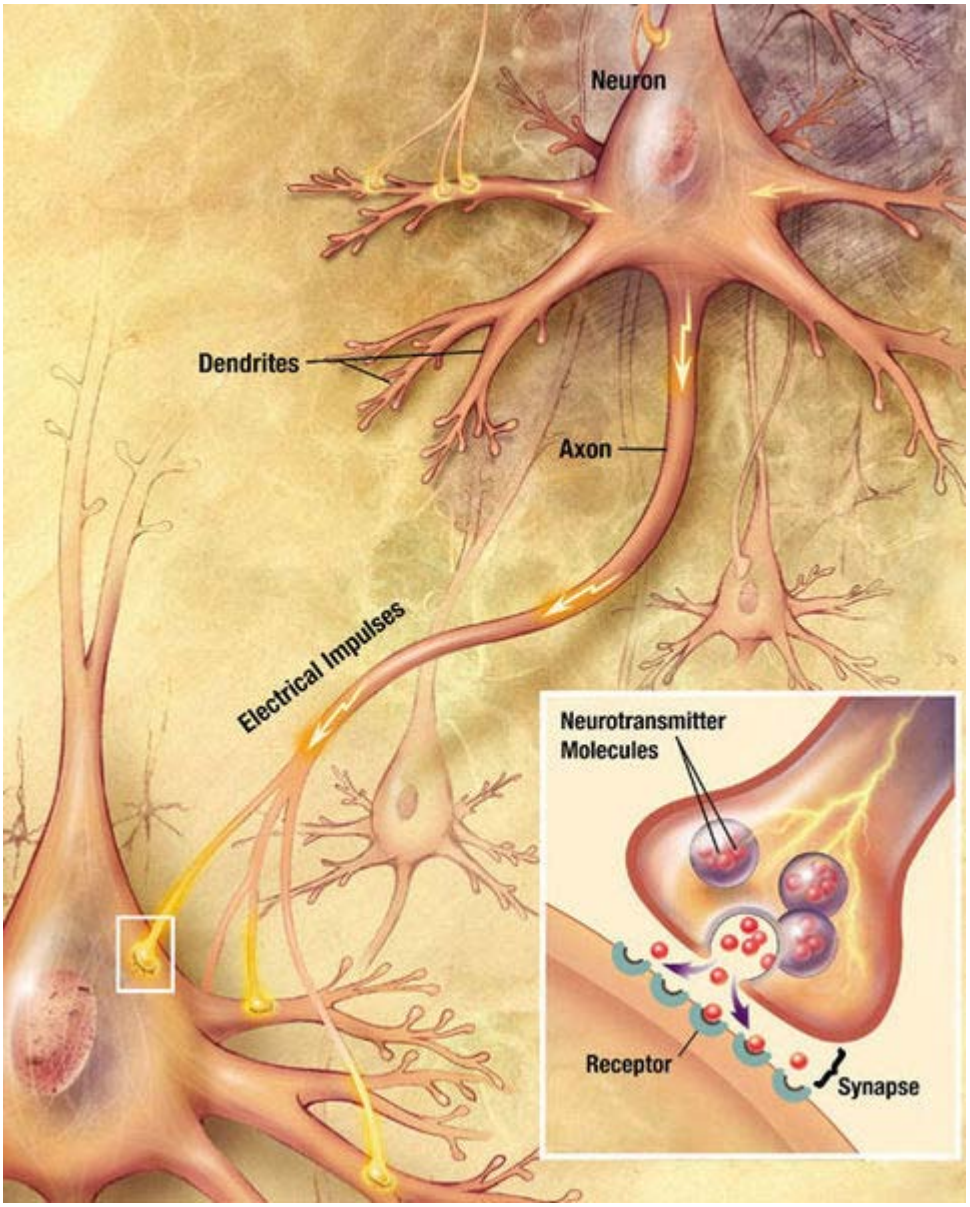
Connectivity

Neurons communicate with one another via synapses, where the axon terminal or *en passant* boutons (terminals located along the length of the axon) of one cell impinges upon another neuron's dendrite, soma or, less commonly, axon. Neurons such as Purkinje cells in the cerebellum can have over 1000 dendritic branches, making connections with tens of thousands of other cells; other neurons, such as the magnocellular neurons of the supraoptic nucleus, have only one or two dendrites, each of which receives thousands of synapses. Synapses can be excitatory or inhibitory and will either increase or decrease activity in the target neuron. Some neurons also communicate via electrical synapses, which are direct, electrically-conductive junctions between cells.

In a chemical synapse, the process of synaptic transmission is as follows: when an action potential reaches the axon terminal, it opens voltage-gated calcium channels, allowing calcium ions to enter the terminal. Calcium causes synaptic vesicles filled with neurotransmitter molecules to fuse with the membrane, releasing their contents into the synaptic cleft. The neurotransmitters diffuse across the synaptic cleft and activate receptors on the postsynaptic neuron.

The human brain has a huge number of synapses. Each of the 10^{11} (one hundred billion) neurons has on average 7,000 synaptic connections to other neurons. It has been estimated that the brain of a three-year-old child has about 10^{15} synapses (1 quadrillion). This number declines with age, stabilizing by adulthood. Estimates vary for an adult, ranging from 10^{14} to 5 x 10^{14} synapses (100 to 500 trillion).

Mechanisms for propagating action potentials



A signal propagating down an axon to the cell body and dendrites of the next cell

In 1937, John Zachary Young suggested that the squid giant axon could be used to study neuronal electrical properties. Being larger than but similar in nature to human neurons, squid cells were easier to study. By inserting electrodes into the giant squid axons, accurate measurements were made of the membrane potential.

The cell membrane of the axon and soma contain voltage-gated ion channels which allow the neuron to generate and propagate an electrical signal (an action potential). These signals are generated and propagated by charge-carrying ions including sodium (Na^+), potassium (K^+), chloride (Cl^-), and calcium (Ca^{2+}).

There are several stimuli that can activate a neuron leading to electrical activity, including pressure, stretch, chemical transmitters, and changes of the electric potential across the cell membrane. Stimuli cause specific ion-channels within the cell membrane to open, leading to a flow of ions through the cell membrane, changing the membrane potential.

Thin neurons and axons require less metabolic expense to produce and carry action potentials, but thicker axons convey impulses more rapidly. To minimize metabolic expense while maintaining rapid conduction, many neurons have insulating sheaths of myelin around their axons. The sheaths are formed by glial cells: oligodendrocytes in the central nervous system and Schwann cells in the peripheral nervous system. The sheath enables action potentials to travel faster than in unmyelinated axons of the same diameter, whilst using less energy. The myelin sheath in peripheral nerves normally runs along the axon in sections about 1 mm long, punctuated by unsheathed nodes of Ranvier which contain a high density of voltage-gated ion channels. Multiple sclerosis is a neurological disorder that results from demyelination of axons in the central nervous system.

Some neurons do not generate action potentials, but instead generate a graded electrical signal, which in turn causes graded neurotransmitter release. Such nonspiking neurons tend to be sensory neurons or interneurons, because they cannot carry signals long distances.

Neural coding

Neural coding is concerned with how sensory and other information is represented in the brain by neurons. The main goal of studying neural coding is to characterize the relationship between the stimulus and the individual or ensemble neuronal responses, and the relationships amongst the electrical activities of the neurons within the ensemble. It is thought that neurons can encode both digital and analog information.

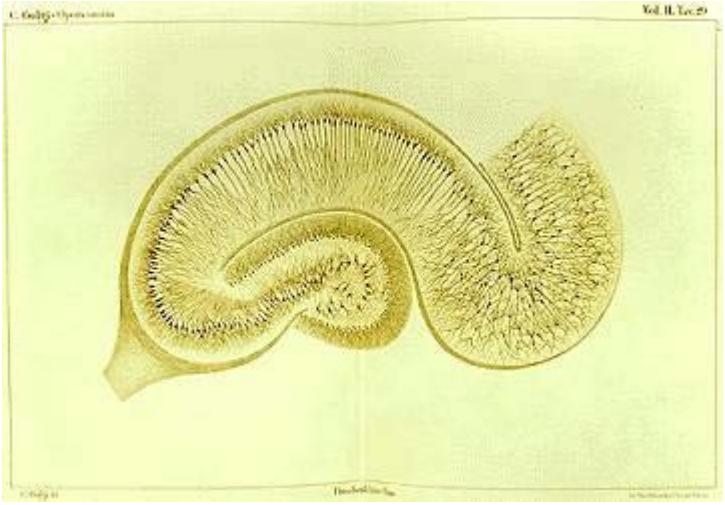
All-or-none principle

The conduction of nerve impulses is an example of an all-or-none response. In other words, if a neuron responds at all, then it must respond completely. Greater intensity of stimulation does not produce a stronger signal but can produce *more* impulses per second. There are different types of receptor response to stimulus, slowly adapting or tonic receptors respond to steady stimulus and produce a steady rate of firing. These tonic receptors most often respond to increased intensity of stimulus by increasing their firing frequency, usually as a power function of stimulus plotted against impulses per second. This can be likened to an intrinsic property of light where to get greater intensity of a specific frequency (color) there have to be more photons, as the photons can't become "stronger" for a specific frequency.

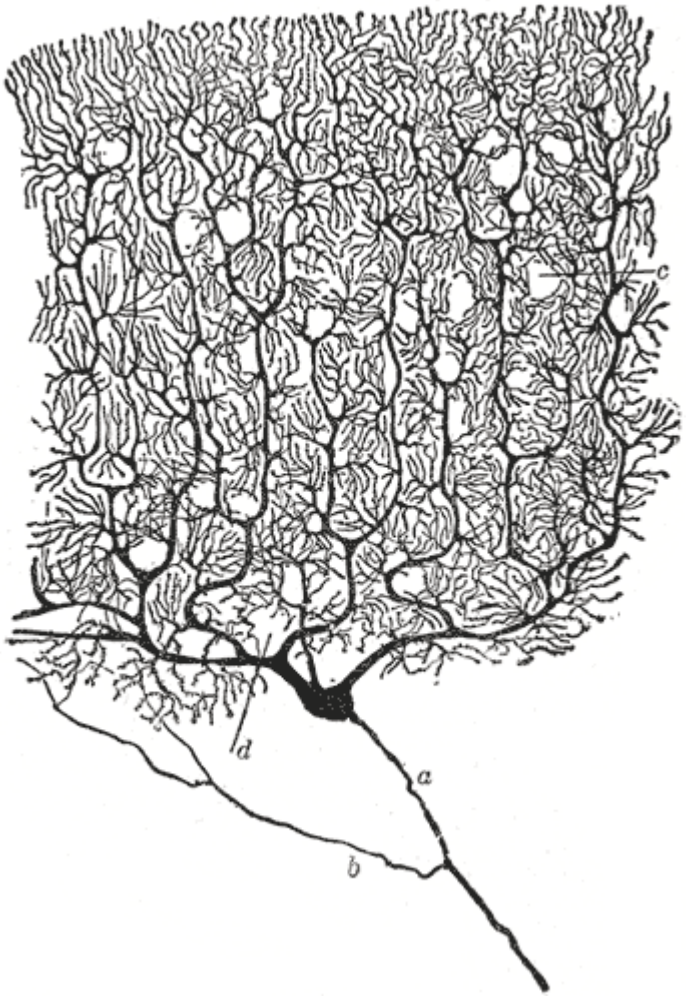
There are a number of other receptor types that are called quickly-adapting or phasic receptors, where firing decreases or stops with steady stimulus; examples include: skin when touched by an object causes the neurons to fire, but if the object maintains even

pressure against the skin, the neurons stop firing. The neurons of the skin and muscles that are responsive to pressure and vibration have filtering accessory structures that aid their function. The pacinian corpuscle is one such structure; it has concentric layers like an onion which form around the axon terminal. When pressure is applied and the corpuscle is deformed, mechanical stimulus is transferred to the axon, which fires. If the pressure is steady, there is no more stimulus; thus, typically these neurons respond with a transient depolarization during the initial deformation and again when the pressure is removed, which causes the corpuscle to change shape again. Other types of adaptation are important in extending the function of a number of other neurons.

History



Drawing by Camillo Golgi of a hippocampus stained with the silver nitrate method



Drawing of a Purkinje cell in the cerebellum cortex done by Santiago Ramón y Cajal, demonstrating the ability of Golgi's staining method to reveal fine detail

The term *neuron* was coined by the German anatomist Heinrich Wilhelm Waldeyer. The neuron's place as the primary functional unit of the nervous system was first recognized in the early 20th century through the work of the Spanish anatomist Santiago Ramón y Cajal. Cajal proposed that neurons were discrete cells that communicated with each other via specialized junctions, or spaces, between cells. This became known as the neuron doctrine, one of the central tenets of modern neuroscience. To observe the structure of individual neurons, Cajal improved a silver staining process known as Golgi's method, which had been developed by his rival, Camillo Golgi. Cajal's improvement, which involved a technique he called "double impregnation", is still in use. The silver impregnation stains are an extremely useful method for neuroanatomical investigations because, for reasons unknown, it stains a very small percentage of cells in a tissue, so one is able to see the complete micro structure of individual neurons without much overlap from other cells in the densely packed brain.

The neuron doctrine

The neuron doctrine is the now fundamental idea that neurons are the basic structural and functional units of the nervous system. The theory was put forward by Santiago Ramón y Cajal in the late 19th century. It held that neurons are discrete cells (not connected in a meshwork), acting as metabolically distinct units.

Later discoveries yielded a few refinements to the simplest form of the doctrine. For example, glial cells, which are not considered neurons, play an essential role in information processing. Also, electrical synapses are more common than previously thought, meaning that there are direct, cytoplasmic connections between neurons. In fact, there are examples of neurons forming even tighter coupling: the squid giant axon arises from the fusion of multiple axons.

Cajal also postulated the Law of Dynamic Polarization, which states that a neuron receives signals at its dendrites and cell body and transmits them, as action potentials, along the axon in one direction: away from the cell body. The Law of Dynamic Polarization has important exceptions; dendrites can serve as synaptic output sites of neurons and axons can receive synaptic inputs.

Neurons in the brain

The number of neurons in the brain varies dramatically from species to species. One estimate puts the human brain at about 100 billion (10^{11}) neurons and 100 trillion (10^{14}) synapses. Another estimate is 86 billion neurons of which 16.3 billion are in the cerebral cortex and 69 billion in the cerebellum. By contrast, the nematode worm *Caenorhabditis elegans* has just 302 neurons making it an ideal experimental subject as scientists have been able to map all of the organism's neurons. The fruit fly *Drosophila melanogaster*, a common subject in biology experiments, has around 100,000 neurons and exhibits many complex behaviors. Many properties of neurons, from the type of neurotransmitters used to ion channel composition, are maintained across species, allowing scientists to study processes occurring in more complex organisms in much simpler experimental systems.

Neurological disorders

Charcot-Marie-Tooth disease (CMT), also known as Hereditary Motor and Sensory Neuropathy (HMSN), Hereditary Sensorimotor Neuropathy (HMSN), or Peroneal Muscular Atrophy, is a heterogeneous inherited disorder of nerves (neuropathy) that is characterized by loss of muscle tissue and touch sensation, predominantly in the feet and legs but also in the hands and arms in the advanced stages of disease. Presently incurable, this disease is one of the most common inherited neurological disorders, with 37 in 100,000 affected.

Alzheimer's disease (AD), also known simply as Alzheimer's, is a neurodegenerative disease characterized by progressive cognitive deterioration together with declining activities of daily living and neuropsychiatric symptoms or behavioral changes. The most

striking early symptom is loss of short-term memory (amnesia), which usually manifests as minor forgetfulness that becomes steadily more pronounced with illness progression, with relative preservation of older memories. As the disorder progresses, cognitive (intellectual) impairment extends to the domains of language (aphasia), skilled movements (apraxia), recognition (agnosia), and functions such as decision-making and planning get impaired.

Parkinson's disease (also known as Parkinson disease or PD) is a degenerative disorder of the central nervous system that often impairs the sufferer's motor skills and speech. Parkinson's disease belongs to a group of conditions called movement disorders. It is characterized by muscle rigidity, tremor, a slowing of physical movement (bradykinesia), and in extreme cases, a loss of physical movement (akinesia). The primary symptoms are the results of decreased stimulation of the motor cortex by the basal ganglia, normally caused by the insufficient formation and action of dopamine, which is produced in the dopaminergic neurons of the brain. Secondary symptoms may include high level cognitive dysfunction and subtle language problems. PD is both chronic and progressive.

Myasthenia Gravis is a neuromuscular disease leading to fluctuating muscle weakness and fatigability. Weakness is typically caused by circulating antibodies that block acetylcholine receptors at the post-synaptic neuromuscular junction, inhibiting the stimulative effect of the neurotransmitter acetylcholine. Myasthenia is treated with immunosuppressants, cholinesterase inhibitors and, in selected cases, thymectomy.

Demyelination

Demyelination is the act of demyelinating, or the loss of the myelin sheath insulating the nerves. When myelin degrades, conduction of signals along the nerve can be impaired or lost, and the nerve eventually withers. This leads to certain neurodegenerative disorders like multiple sclerosis, chronic inflammatory demyelinating polyneuropathy.

Axonal degeneration

Although most injury responses include a calcium influx signaling to promote resealing of severed parts, axonal injuries initially lead to acute axonal degeneration (AAD), which is rapid separation of the proximal and distal ends within 30 minutes of injury. Degeneration follows with swelling of the axolemma, and eventually leads to bead like formation. Granular disintegration of the axonal cytoskeleton and inner organelles occurs after axolemma degradation. Early changes include accumulation of mitochondria in the paranodal regions at the site of injury. Endoplasmic reticulum degrades and mitochondria swell up and eventually disintegrate. The disintegration is dependent on Ubiquitin and Calpain proteases (caused by influx of calcium ion), suggesting that axonal degeneration is an active process. Thus the axon undergoes complete fragmentation. The process takes about roughly 24 hrs in the PNS, and longer in the CNS. The signaling pathways leading to axolemma degeneration are currently unknown.

Nerve regeneration

It has been demonstrated that neurogenesis can sometimes occur in the adult vertebrate brain, and it is often possible for peripheral axons to regrow if they are severed. The latter can take a long time: after a nerve injury to the human arm, for example, it may take months for feeling to return to the hands and fingers.

Chapter 12

Neural Coding

Neural coding is a neuroscience-related field concerned with how sensory and other information is represented in the brain by networks of neurons. The main goal of studying neural coding is to characterize the relationship between the stimulus and the individual or ensemble neuronal responses and the relationship among electrical activity of the neurons in the ensemble. It is thought that neurons can encode both digital and analog information.

Overview

Neurons are remarkable among the cells of the body in their ability to propagate signals rapidly over large distances. They do this by generating characteristic electrical pulses called action potentials or, more simply, spikes that can travel down nerve fibers. Sensory neurons change their activities by firing sequences of action potentials in various temporal patterns, with the presence of external sensory stimuli, such as light, sound, taste, smell and touch. It is known that information about the stimulus is encoded in this pattern of action potentials and transmitted into and around the brain.

Although action potentials can vary somewhat in duration, amplitude and shape, they are typically treated as identical stereotyped events in neural coding studies. If the brief duration of an action potential (about 1ms) is ignored, an action potential sequence, or spike train, can be characterized simply by a series of all-or-none point events in time. The lengths of interspike intervals (ISIs) between two successive spikes in a spike train often vary, apparently randomly. The study of neural coding involves measuring and characterizing how stimulus attributes, such as light or sound intensity, or motor actions, such as the direction of an arm movement, are represented by neuron action potentials or spikes. In order to describe and analyze neuronal firing, statistical methods and methods of probability theory and stochastic point processes have been widely applied.

Encoding and decoding

The link between stimulus and response can be studied from two opposite points of view. Neural encoding refers to the map from stimulus to response. The main focus is to understand how neurons respond to a wide variety of stimuli, and to accurately construct models that attempt to predict responses to other stimuli. Neural decoding refers to the

reverse map, from response to stimulus, and the challenge is to reconstruct a stimulus, or certain aspects of that stimulus, from the spike sequences it evokes.

Coding schemes

A sequence, or 'train', of spikes may contain information based on different coding schemes. In motor neurons, for example, the strength at which an innervated muscle is flexed depends solely on the 'firing rate', the average number of spikes per unit time (a 'rate code'). At the other end, a complex 'temporal code' is based on the precise timing of single spikes. They may be locked to an external stimulus such as in the auditory system or be generated intrinsically by the neural circuitry.

Whether neurons use rate coding or temporal coding is a topic of intense debate within the neuroscience community, even though there is no clear definition of what these terms mean.

Rate coding

Rate coding is a traditional coding scheme, assuming that most, if not all, information about the stimulus is contained in the firing rate of the neuron. Because the sequence of action potentials generated by a given stimulus varies from trial to trial, neuronal responses are typically treated statistically or probabilistically. They may be characterized by firing rates, rather than as specific spike sequences. In most sensory systems, the firing rate increases, generally non-linearly, with increasing stimulus intensity. Any information possibly encoded in the temporal structure of the spike train is ignored. Consequently, rate coding is inefficient but highly robust with respect to the ISI 'noise'.

The concept of firing rates has been successfully applied during the last 80 years. It dates back to the pioneering work of ED Adrian who showed that the firing rate of stretch receptor neurons in the muscles is related to the force applied to the muscle. In the following decades, measurement of firing rates became a standard tool for describing the properties of all types of sensory or cortical neurons, partly due to the relative ease of measuring rates experimentally. However, this approach neglects all the information possibly contained in the exact timing of the spikes. During recent years, more and more experimental evidences have suggested that a straightforward firing rate concept based on temporal averaging may be too simplistic to describe brain activity.

During rate coding, precisely calculating firing rate is very important. In fact, the term “firing rate” has a few different definitions, which refer to different averaging procedures, such as an average over time or an average over several repetitions of experiment.

Spike-count rate

The Spike-count rate, also referred to as temporal average, is obtained by counting the number of spikes that appear during a trial and dividing by the duration of trial. The

length T of the time window is set by experimenter and depends on the type of neuron recorded from and the stimulus. In practice, to get sensible averages, several spikes should occur within the time window. Typical values are T = 100 ms or T = 500 ms, but the duration may also be longer or shorter.

The spike-count rate can be determined from a single trial, but at the expense of losing all temporal resolution about variations in neural response during the course of the trial. Temporal averaging can work well in cases where the stimulus is constant or slowly varying and does not require a fast reaction of the organism - and this is the situation usually encountered in experimental protocols. Real-world input, however, is hardly stationary, but often changing on a fast time scale. For example, even when viewing a static image, humans perform saccades, rapid changes of the direction of gaze. The image projected onto the retinal photoreceptors changes therefore every few hundred milliseconds.

Despite its shortcomings, the concept of a spike-count rate code is widely used not only in experiments, but also in models of neural networks. It has led to the idea that a neuron transforms information about a single input variable (the stimulus strength) into a single continuous output variable (the firing rate).

Time-dependent firing rate

The time-dependent firing rate is defined as the average number of spikes (averaged over trials) appearing during a short interval between times t and t+Δt, divided by the duration of the interval. It works for stationary as well as for time-dependent stimuli. To experimentally measure the time-dependent firing rate, the experimenter records from a neuron while stimulating with some input sequence. The same stimulation sequence is repeated several times and the neuronal response is reported in a Peri-Stimulus-Time Histogram (PSTH). The time t is measured with respect to the start of the stimulation sequence. The Δt must be large enough (typically in the range of one or a few milliseconds) so there are sufficient number of spikes within the interval to obtain a reliable estimate of the average. The number of occurrences of spikes $n_K(t;t+\Delta t)$ summed over all repetitions of the experiment divided by the number K of repetitions is a measure of the typical activity of the neuron between time t and t+Δt. A further division by the interval length Δt yields time-dependent firing rate r(t) of the neuron, which is equivalent to the spike density of PSTH.

For sufficiently small Δt, r(t)Δt is the average number of spikes occurring between times t and t+Δt over multiple trials. If Δt is small, there will never be more than one spike within the interval between t and t+Δt on any given trial. This means that r(t)Δt is also the fraction of trials on which a spike occurred between those times. Equivalently, r(t)Δt is the probability that a spike occurs during this time interval.

As an experimental procedure, the time-dependent firing rate measure is a useful method to evaluate neuronal activity, in particular in the case of time-dependent stimuli. The obvious problem with this approach is that it can not be the coding scheme used by

neurons in the brain. Neurons can not wait for the stimuli to repeatedly present in an exactly same manner before generating response.

Nevertheless, the experimental time-dependent firing rate measure can make sense, if there are large populations of independent neurons that receive the same stimulus. Instead of recording from a population of N neurons in a single run, it is experimentally easier to record from a single neuron and average over N repeated runs. Thus, the time-dependent firing rate coding relies on the implicit assumption that there are always populations of neurons.

Temporal coding

When precise spike timing or high-frequency firing-rate fluctuations are found to carry information, the neural code is often identified as a temporal code. A number of studies have found that the temporal resolution of the neural code is on a millisecond time scale, indicating that precise spike timing is a significant element in neural coding.

Temporal codes employ those features of the spiking activity that cannot be described by the firing rate. For example, time to first spike after the stimulus onset, characteristics based on the second and higher statistical moments of the ISI probability distribution, spike randomness, or precisely timed groups of spikes (temporal patterns) are candidates for temporal codes. As there is no absolute time reference in the nervous system, the information is carried either in terms of the relative timing of spikes in a population of neurons or with respect to an ongoing brain oscillation.

The temporal structure of a spike train or firing rate evoked by a stimulus is determined both by the dynamics of the stimulus and by the nature of the neural encoding process. Stimuli that change rapidly tend to generate precisely timed spikes and rapidly changing firing rates no matter what neural coding strategy is being used. Temporal coding refers to temporal precision in the response that does not arise solely from the dynamics of the stimulus, but that nevertheless relates to properties of the stimulus. The interplay between stimulus and encoding dynamics makes the identification of a temporal code difficult.

The issue of temporal coding is distinct and independent from the issue of independent-spike coding. If each spike is independent of all the other spikes in the train, the temporal character of the neural code is determined by the behavior of time-dependent firing rate r(t). If r(t) varies slowly with time, the code is typically called a rate code, and if it varies rapidly, the code is called temporal.

Phase-of-firing code is a recent type of code which is often categorized as a temporal code. It takes into account a time label for each spike according to a time reference based on phase of local ongoing oscillations at low frequencies.

Population coding

Population coding is a method to represent stimuli by using the joint activities of a number of neurons. In population coding, each neuron has a distribution of responses over some set of inputs, and the responses of many neurons may be combined to determine some value about the inputs.

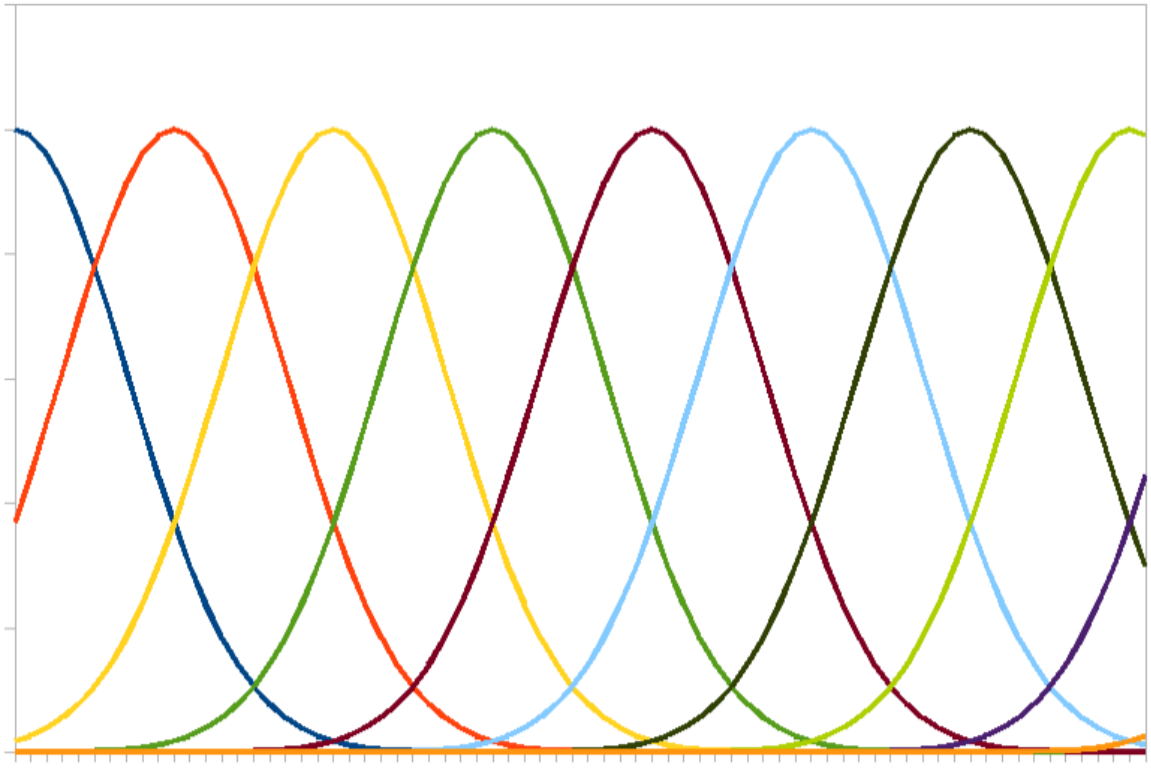
From the theoretical point of view, population coding is one of a few mathematically well-formulated problems in neuroscience. It grasps the essential features of neural coding and yet, is simple enough for theoretic analysis. Experimental studies have revealed that this coding paradigm is widely used in the sensor and motor areas of the brain. For example, in the visual area medial temporal (MT), neurons are tuned to the moving direction. In response to an object moving in a particular direction, many neurons in MT fire, with a noise-corrupted and bell-shaped activity pattern across the population. The moving direction of the object is retrieved from the population activity, to be immune from the fluctuation existing in a single neuron's signal.

Population coding has a number of advantages, including reduction of uncertainty due to neuronal variability and the ability to represent a number of different stimulus attributes simultaneously. Population coding is also much faster than rate coding and can reflect changes in the stimulus conditions nearly instantaneously. Individual neurons in such a population typically have different but overlapping selectivities, so that many neurons, but not necessarily all, respond to a given stimulus.

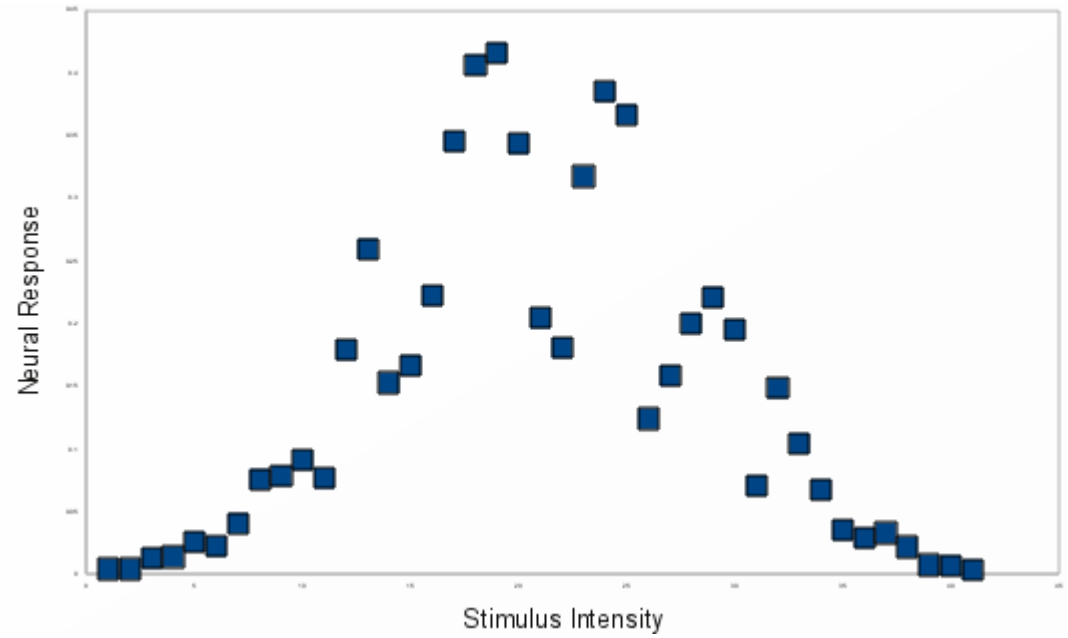
Position coding

A typical population code involves neurons with a Gaussian tuning curve whose means vary linearly with the stimulus intensity, meaning that the neuron responds most strongly (in terms of spikes per second) to a stimulus near the mean. The actual intensity could be recovered as the stimulus level corresponding to the mean of the neuron with the greatest response. However, the noise inherent in neural responses means that a maximum likelihood estimation function is more accurate.

This type of code is used to encode continuous variables such as joint position, eye position, color, or sound frequency. Any individual neuron is too noisy to faithfully encode the variable using rate coding, but an entire population ensures greater fidelity and precision.



Plot of typical position coding



Neural responses are noisy and unreliable

Chapter 13

Neuroregeneration

Neuroregeneration refers to the regrowth or repair of nervous tissues, cells or cell products. Such mechanisms may include remyelination, generation of new neurons, glia, axons, myelin, or synapses. Neuroregeneration differs between the peripheral nervous system (PNS) and the central nervous system (CNS) by the functional mechanisms and especially the extent and speed. When an axon is damaged, the distal segment undergoes Wallerian degeneration, losing its myelin sheath. The proximal segment can either die by apoptosis or undergo the chromatolytic reaction, which is an attempt at repair. In the CNS, synaptic stripping occurs as glia foot processes invade the dead synapse.

Nervous system injuries affect over 90,000 people every year. It is estimated that spinal cord injuries alone affect 10,000 each year. As a result of this high incidence of neurological injuries, nerve regeneration and repair, a subfield of neural tissue engineering, is becoming a rapidly growing field dedicated to the discovery of new ways to recover nerve functionality after injury. The nervous system is divided into two parts: the central nervous system, which consists of the brain and spinal cord, and the peripheral nervous system, which consists of cranial and spinal nerves along with their associated ganglia. While the peripheral nervous system has an intrinsic ability for repair and regeneration, the central nervous system is, for the most part, incapable of self-repair and regeneration. There is currently no treatment for recovering human nerve function after injury to the central nervous system. In addition, multiple attempts at nerve re-growth across the PNS-CNS transition have not been successful. There is simply not enough knowledge about regeneration in the central nervous system. In addition, although the peripheral nervous system has the capability for regeneration, much research still needs to be done to optimize the environment for maximum regrowth potential. Nerve regeneration is important clinically, as it is part of the pathogenesis of many diseases, including multiple sclerosis.

Peripheral nervous system regeneration

Neuroregeneration in the peripheral nervous system (PNS) occurs to a significant degree. Axonal sprouts form at the proximal stump and grow until they enter the distal stump. The growth of the sprouts are governed by chemotactic factors secreted from Schwann cells (neurolemmocytes). Injury to the peripheral nervous system immediately elicits the migration of phagocytes, Schwann cells, and macrophages to the lesion site in order to clear away debris such as damaged tissue. When a nerve axon is severed, the end still

attached to the cell body is labeled the proximal segment, while the other end is called the distal segment. After injury, the proximal end swells and experiences some retrograde degeneration, but once the debris is cleared, it begins to sprout axons and the presence of growth cones can be detected. The proximal axons are able to regrow as long as the cell body is intact, and they have made contact with the Schwann cells in the endoneurial channel. Human axon growth rates can reach 2 mm/day in small nerves and 5 mm/day in large nerves. The distal segment, however, experiences Wallerian degeneration within hours of the injury; the axons and myelin degenerate, but the endoneurium remains. In the later stages of regeneration the remaining endoneurial tube directs axon growth back to the correct targets. During Wallerian degeneration, Schwann cells grow in ordered columns along the endoneurial tube, creating a band of Bungner (boB) that protects and preserves the endoneurial channel. Also, macrophages and Schwann cells release neurotrophic factors that enhance re-growth.

Central nervous system regeneration

Unlike peripheral nervous system injury, injury to the central nervous system is not followed by extensive regeneration. It is limited by the inhibitory influences of the glial and extracellular environment. The hostile, non-permissible growth environment is, in part, created by the migration of myelin-associated inhibitors, astrocytes, oligodendrocytes, oligodendrocyte precursors, and microglia. The environment within the CNS, especially following trauma, counteracts the repair of myelin and neurons. Growth factors are not expressed or re-expressed; for instance, the extracellular matrix is lacking laminins. Glial scars rapidly form, and the glia actually produce factors that inhibit remyelination and axon repair; for instance, NOGO and NI-35. The axons themselves also lose the potential for growth with age, due to a decrease in GAP 43 expression.

Slower degeneration of the distal segment than that which occurs in the peripheral nervous system also contributes to the inhibitory environment because inhibitory myelin and axonal debris are not cleared away as quickly. All these factors contribute to the formation of what is known as a glial scar, which axons cannot grow across. The proximal segment attempts to regenerate after injury, but its growth is hindered by the environment. It is important to note that central nervous system axons have been proven to regrow in permissible environments; therefore, the primary problem to central nervous system axonal regeneration is crossing or eliminating the inhibitory lesion site.

Inhibition of axonal regrowth

Glial scar formation is induced following damage to the nervous system. In the central nervous system, this glial scar formation significantly inhibits nerve regeneration, which leads to a loss of function. Several families of molecules are released that promote and drive glial scar formation. Transforming growth factors B-1 and -2, interleukins, and cytokines all play a role in the initiation of scar formation. The inhibition of nerve regeneration is a result of the accumulation of reactive astrocytes at the site of injury and the up regulation of molecules that are inhibitory to neurite extension outgrowth. The up regulated molecules alter the composition of the extracellular matrix in a way that has

been shown to inhibit neurite outgrowth extension. This scar formation involves contributions from several cell types and families of molecules.

Chondroitin sulfate proteoglycan

In response to scar-inducing factors, like those discussed above, astrocytes up regulate the production of chondroitin sulfate proteoglycans. Astrocytes are a predominant type of glial cell in the central nervous system that provide many functions including damage mitigation, repair, and glial scar formation. The RhoA pathway is involved. Chondroitin sulfate proteoglycans (CSPGs) have been shown to be up regulated in the central nervous system (CNS) following injury. Repeating disaccharides of glucuronic acid and galactosamine, glycosaminoglycans (CS-GAGs), are covalently coupled to the protein core CSPGs. CSPGs have been shown to inhibit regeneration in vitro and in vivo, but the role that the CSPG core protein vs. CS-GAGs had not been studied until recently.

A recent study performed experiments to determine the CS-GAGs present in normal uninjured cortex, as well as those present following injury and the resultant mature glial scar. The difference in CS-GAG types and amounts present between the two was then used to study the inhibitory effects of those CS-GAG types up regulated in glial scar on neurite extension. The resulting analysis showed that the GAG profiles of normal cortex and glial scar tissue were significantly different. Glial scar tissue demonstrated an up regulation of chondroitin-4,6-sulfate, chondroitin-2-sulfate, and chondroitin-6-sulfate. On the other hand, uninjured cortical tissue showed most of the CS-GAG to be chondroitin-4-sulfate but also some chondroitin and chondroitin-6-sulfate present.

Using this information, studies were done to quantify the inhibitory effects of CSPGS on neurite outgrowth. All CSPG samples test were shown to be inhibitory to neurite outgrowth. However, CS-E and aggrecan were shown to be the most inhibitory by a large margin, which contained mostly 4,6-sulfated GAG and 4-sulfated GAG, respectively. An average neurite length for experiments using these samples was 22 ± 40 μm and 24 ± 44 μm, respectively. This is compared to the other averages that were more than ten times these values.

The chondroitin sulfate proteoglycans phosphacan and neurocan have also been shown to play a role in glial scar. Phosphacan has been shown to have decreased levels in glial scar when compared to uninjured cortex. This decrease is beneficial to nerve generation because phosphacan has been shown to inhibit neurite extension similarly to the other CSPGs discussed already. Alternatively, neurocan production is up regulated in astrocytes in glial scar when compared to uninjured cortex and astrocytes in primary cell culture conditions. These elevated neurocan levels have been shown to remain elevated 30 days after the initial injury. This implicates neurocan as having a prolonged role in chronic scar.

The inhibition of Rho-kinase (ROCK) with Y27632 has been shown to activate reactive astrocytes and increase their expression of CSPGs. Studies with Y27632 have shown that central nervous system injury sites treated with Y27632 causes an up regulation of glial

fibrillary acid protein and neurocan. With in vitro cultures of astrocytes, the same treatment showed an increased expression of CSPGs and a resulting decrease in neurite outgrowth extension. This inhibitory effect was reduced by digesting the CSPG components with chondroitinase-ABC.

NG2 is another type of chondroitin sulfate proteoglycan that is expressed by oligodendrocyte precursor cells. Oligodendrocyte precursor cells are another type of glial cell found in the central nervous system that play a role in glial scar formation. These cell types can develop into a normal oligodendrocyte or a glial fibrillary acidic protein positive astrocyte depending on environmental factors. NG2 is found on the surface of these cells and has been shown to inhibit neurite outgrowth extension, as well. These are high molecular weight transmembrane molecules with the largest portion extending into the extracellular space.

Following injury to the central nervous system, NG2 expressing oligodendrocyte precursor cells are seen around the site of injury within 48 hours of the initial injury. The number of NG2 expressing cells continues to increase for the next three to five days and high levels of NG2 are seen within seven–ten days of the injury. In vitro studies have been done to demonstrate the effect that NG2 levels play on neurite growth inhibition. Notably, neurons would not adhere to substrates made solely of NG2, which hints at its inhibitory effects on nerve regeneration. When grown on substrates containing both NG2 and adhesive molecules, neurite extension was shown to be reduced by 40-45% when compared to neurite extension on substrates only containing the adhesive molecules. Furthermore, cultures were created with striped surfaces that alternated NG2 lanes with lanes only containing adhesive molecules. Neurons and axons placed on these striped regions consistently stayed in the lanes without NG2. It is clear, then, that the accumulation of NG2 expressing cells at the site of injury creates an extracellular barrier that inhibits axon regrowth into the glial scar area.

Keratan sulfate proteoglycans

Like the chondroitin sulfate proteoglycans, keratan sulfate proteoglycan (KSPG) production is up regulated in reactive astrocytes as part of glial scar formation. KSPGs have also been shown to inhibit neurite outgrowth extension, limiting nerve regeneration. Keratan sulfate, also called keratosulfate, is formed from repeating disaccharide galactose units and N-acetylglucosamines. It is also 6-sulfated. This sulfation is crucial to the elongation of the keratan sulfate chain. A study was done using N-acetylglucosamine 6-O-sulfotransferase-1 deficient mice. The wild type mouse showed a significant up regulation of mRNA expressing N-acetylglucosamine 6-O-sulfotransferase-1 at the site of cortical injury. However, in the N-acetylglucosamine 6-O-sulfotransferase-1 deficient mice, the expression of keratan sulfate was significantly decreased when compared to the wild type mice. Similarly, glial scar formation was significantly reduced in the N-acetylglucosamine 6-O-sulfotransferase-1 mice, and as a result, nerve regeneration was less inhibited.

Other inhibitory factors

Proteins of oligodendritic or glial debris origin responsible for neuroregeneration:

- **NOGO** –The protein family Nogo, particularly Nogo-A, has been identified as an inhibitor of remyelination in the CNS, especially in autoimmune mediated demyelination, such as found in Experimental Autoimmune Encephalomyelitis (EAE) and Multiple Sclerosis (MS). Nogo A functions via either its amino-Nogo terminus through an unknown receptor, or by its Nogo-66 terminus through NgR1, p75, TROY or LINGO1. Antagonising this inhibitor results in improved remyelination, as it is involved in the RhoA pathway.
- **NI-35** a non-permissive growth factor from myelin.
- **MAG** –Myelin Associated Glycoprotein acts via the receptors NgR2, GT1b, NgR1, p75, TROY and LINGO1.
- **OMgp** –Oligodendrocyte Myelin glycoprotein
- **Ephrin B3** functions through the EphA4 receptor and inhibits remyelination.
- **Sema 4D**(Semaphorin 4D) functions through the PlexinB1 receptor and inhibits remyelination.
- **Sema 3A** (Semaphorin 3A) is present in the scar that forms in both central nervous system and peripheral nerve injuries and contributes to the outgrowth-inhibitory properties of these scars

Clinical treatments

Surgery

Surgery can be done in case a peripheral nerve has become cut or otherwise divided. This is called peripheral nerve reconstruction. The injured nerve is identified and exposed so that normal nerve tissue can be examined above and below the level of injury, usually with magnification, using either loupes or an operating microscope. If a large segment of nerve is harmed, as can happen in a crush or stretch injury, the nerve will need to be exposed over a larger area. Injured portions of the nerve are removed. The cut nerve endings are then carefully reapproximated using very small sutures. The nerve repair must be covered by healthy tissue, which can be as simple as closing the skin or it can require moving skin or muscle to provide healthy padded coverage over the nerve. The type of anesthesia used depends on the complexity of the injury. A surgical tourniquet is almost always used.

Prognosis

The expectations after surgical repair of a divided peripheral nerve depends on several factors:

- **Age**: Recovery of a nerve after surgical repair depends mainly on the age of the patient. Young children can recover close-to-normal nerve function. In contrast, a

patient over 60 years old with a cut nerve in the hand would expect to recover only protective sensation; that is, the ability to distinguish hot/cold or sharp/dull.
- The **mechanism of injury**: Sharp injuries, such as a knife wound, damage only a very short segment of the nerve, availing for direct suture. In contrast, nerves that are divided by stretch or crush may be damaged over long segments. These nerve injuries are more difficult to treat and generally have a poorer outcome. In addition, associated injuries, like injury to bone, muscle and skin, can make nerve recovery more difficult.
- The **level of injury**: After a nerve is repaired, the regenerating nerve endings must grow all the way to their target. For example, a nerve injured at the wrist that normally provides sensation to the thumb must grow to the end of the thumb in order to provide sensation. The return of function decreases with increased distance over which a nerve must grow.

Autologous nerve grafting

Currently, autologous nerve grafting, or a nerve autograft, is known as the gold standard for clinical treatments used to repair large lesion gaps in the peripheral nervous system. It is important that nerves are not repaired under tension, which could otherwise happen if cut ends are reapproximated across a gap. Nerve segments are taken from another part of the body (the donor site) and inserted into the lesion to provide endoneurial tubes for axonal regeneration across the gap. However, this is not a perfect treatment; often the final outcome is only limited function recovery. Also, partial deinnervation is frequently experienced at the donor site, and multiple surgeries are required to harvest the tissue and implant it.

Allografts and xenografts

Variations on the nerve autograft include the allograft and the xenograft. In allografts, the tissue for the graft is taken from another person, the donor, and implanted in the recipient. Xenografts involve taking donor tissue from another species. Allografts and xenografts have the same disadvantages as autografts, but in addition, tissue rejection from immune responses must also be taken into account. Often immunosuppression is required with these grafts. Disease transmission also becomes a factor when introducing tissue from another person or animal. Overall, allografts and xenografts do not match the quality of outcomes seen with autografts, but they are necessary when there is a lack of autologous nerve tissue.

Nerve guidance conduit

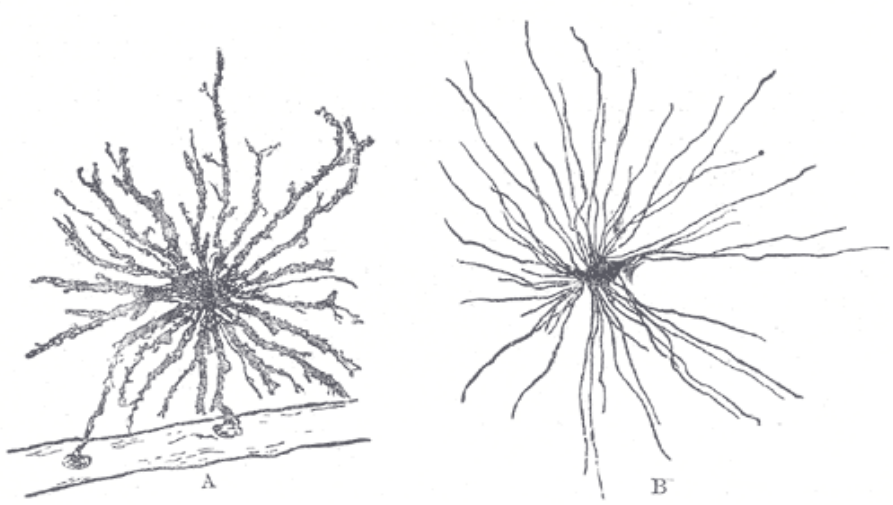
Because of the limited functionality received from autografts, the current gold standard for nerve regeneration and repair, recent neural tissue engineering research has focused on the development of bioartificial nerve guidance conduits in order to guide axonal regrowth. The creation of artificial nerve conduits is also known as entubulation because the nerve ends and intervening gap are enclosed within a tube composed of biological or synthetic materials.

Immunisation

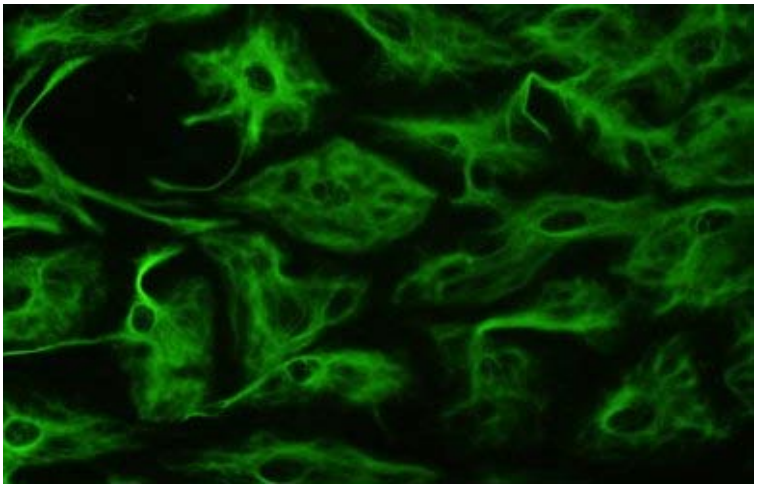
A direction of research is towards the use of drugs that target remyelinating inhibitor proteins, or other inhibitors. Possible strategies include vaccination against these proteins (active immunisation), or treatment with previously created antibodies (passive immunisation). These strategies appear promising on animal models with experimental autoimmune encephalomyelitis (EAE), a model of MS. Monoclonal antibodies have also been used against inhibitory factors such as NI-35 and NOGO.

Chapter 14

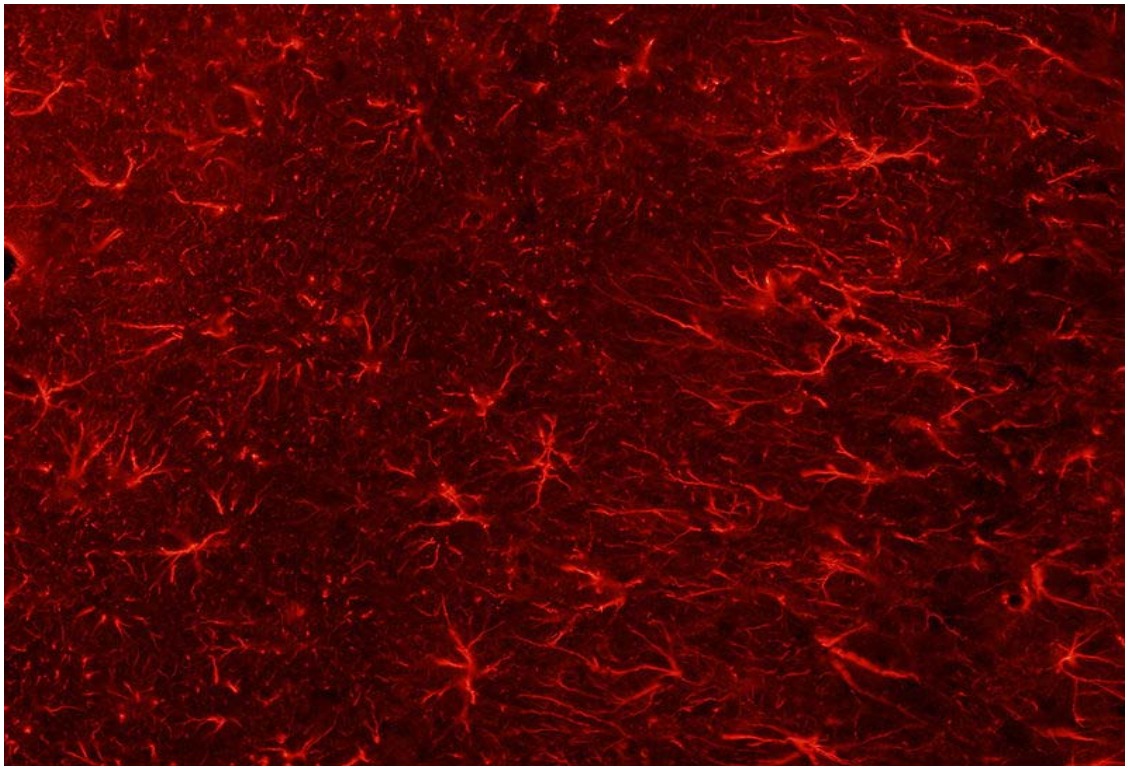
Glial Cell



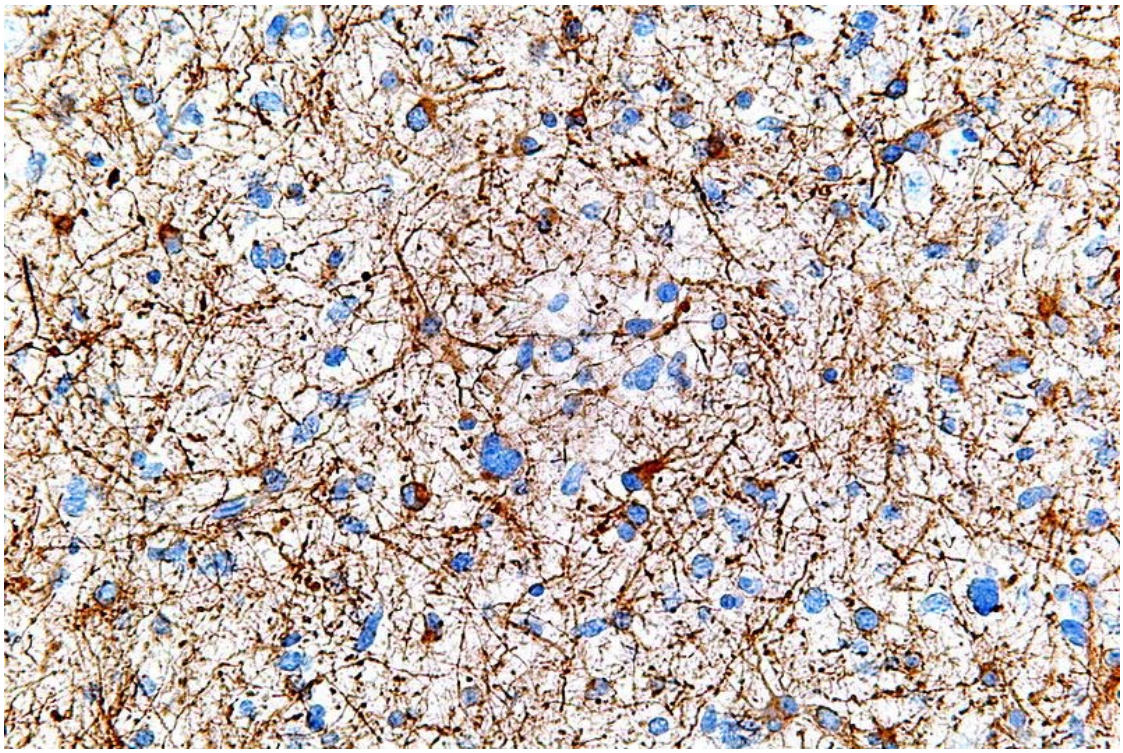
Neuroglia of the brain shown by Golgi's method



Astrocytes can be identified in culture because, unlike other mature glia, they express glial fibrillary acidic protein.



Glial cells in a rat brain stained with an antibody against GFAP



Neoplastic glial cells stained with an antibody against GFAP (brown). Brain biopsy.

Glial cells, sometimes called **neuroglia** or simply **glia** (Greek for "glue"), are non-neuronal cells that maintain homeostasis, form myelin, and provide support and protection for the brain's neurons. In the human brain, there is roughly one glia for every neuron with a ratio of about two neurons for every three glia in the cerebral gray matter.

As the Greek name implies, glia are commonly known as the glue of the nervous system; however, this is not fully accurate. The four main functions of glial cells are to surround neurons and hold them in place, to supply nutrients and oxygen to neurons, to insulate one neuron from another, and to destroy pathogens and remove dead neurons. They also modulate neurotransmission.

Functions

Some glial cells function primarily as the physical support for neurons. Others regulate the internal environment of the brain, especially the fluid surrounding neurons and their synapses, and nutrify neurons. During early embryogenesis, glial cells direct the migration of neurons and produce molecules that modify the growth of axons and dendrites. Recent research indicates that glial cells of the hippocampus and cerebellum participate in synaptic transmission, regulate the clearance of neurotransmitters from the synaptic cleft, release factors such as ATP, which modulate presynaptic function, and even release neurotransmitters themselves.

Glial cells are known to be capable of mitosis. By contrast, scientific understanding of whether neurons are permanently post-mitotic, or capable of mitosis, is still developing. In the past, glia had been considered to lack certain features of neurons. For example, glial cells were not believed to have chemical synapses or to release neurotransmitters. They were considered to be the passive bystanders of neural transmission. However, recent studies have shown this to be untrue.

For example, astrocytes are crucial in clearance of neurotransmitter from within the synaptic cleft, which provides distinction between arrival of action potentials and prevents toxic build-up of certain neurotransmitters such as glutamate (excitotoxicity). It is also thought that glia play a role in Alzheimer's disease. Furthermore, at least in vitro, astrocytes can release neurotransmitter glutamate in response to certain stimulation. Another unique type of glial cell, the oligodendrocyte precursor cells or OPCs, have very well-defined and functional synapses from at least two major groups of neurons. The only notable differences between neurons and glial cells are neurons' possession of axons and dendrites, and capacity to generate action potentials.

Glia ought not to be regarded as 'glue' in the nervous system as the name implies; rather, they are more of a partner to neurons. They are also crucial in the development of the nervous system and in processes such as synaptic plasticity and synaptogenesis. Glia have a role in the regulation of repair of neurons after injury. In the CNS, glia suppresses repair. Glial cells known as astrocytes enlarge and proliferate to form a scar and produce inhibitory molecules that inhibit regrowth of a damaged or severed axon. In the PNS, glial cells known as Schwann cells promote repair. After axonal injury, Schwann cells

regress to an earlier developmental state to encourage regrowth of the axon. This difference between PNS and CNS raises hopes for the regeneration of nervous tissue in the CNS. For example a spinal cord may be able to be repaired following injury or severance.

Types

Microglia

Microglia are like specialized macrophages capable of phagocytosis that protect neurons of the central nervous system. They are derived from hematopoietic precursors rather than ectodermal tissue; they are commonly categorized as such because of their supportive role to neurons.

These cells comprise approximately 15% of the total cells of the central nervous system. They are found in all regions of the brain and spinal cord. Microglial cells are small relative to macroglial cells, with changing shapes and oblong nuclei. They are mobile within the brain and multiply when the brain is damaged. In the healthy central nervous system, microglia processes constantly sample all aspects of their environment (neurons, macroglia and blood vessels).

Macroglia

Location	Name	Description
CNS	Astrocytes	The most abundant type of macroglial cell, *astrocytes* (also called *astroglia*) have numerous projections that anchor neurons to their blood supply. They regulate the external chemical environment of neurons by removing excess ions, notably potassium, and recycling neurotransmitters released during synaptic transmission. The current theory suggests that astrocytes may be the predominant "building blocks" of the blood-brain barrier. Astrocytes may regulate vasoconstriction and vasodilation by producing substances such as arachidonic acid, whose metabolites are vasoactive. Astrocytes signal each other using calcium. The gap junctions (also known as electrical synapses) between astrocytes allow the messenger molecule IP3 to diffuse from one astrocyte to another. IP3 activates calcium channels on cellular organelles, releasing calcium into the cytoplasm. This calcium may stimulate the production of more IP3. The net effect is a calcium wave that propagates from cell to cell. Extracellular release of ATP, and consequent activation of purinergic receptors on other astrocytes, may also mediate calcium waves in some cases.

		In general, there are two types of astrocytes, protoplasmic and fibrous, similar in function but distinct in morphology and distribution. Protoplasmic astrocytes have short, thick, highly branched processes and are typically found in gray matter. Fibrous astrocytes have long, thin, less branched processes and are more commonly found in white matter. It has recently been shown that astrocyte activity is linked to blood flow in the brain, and that this is what is actually being measured in fMRI.
CNS	Oligodendrocytes	*Oligodendrocytes* are cells that coat axons in the central nervous system (CNS) with their cell membrane forming a specialized membrane differentiation called myelin, producing the so-called myelin sheath. The myelin sheath provides insulation to the axon that allows electrical signals to propagate more efficiently.
CNS	Ependymal cells	*Ependymal cells*, also named *ependymocytes*, line the cavities of the CNS and make up the walls of the ventricles. These cells create and secrete cerebrospinal fluid(CSF) and beat their cilia to help circulate that CSF and make up the Blood-CSF barrier. They are also thought to act as neural stem cells.
CNS	Radial glia	*Radial glia cells* arise from neuroepithelial cells after the onset of neurogenesis. Their differentiation abilities are more restricted than those of neuroepithelial cells. In the developing nervous system, radial glia function both as neuronal progenitors and as a scaffold upon which newborn neurons migrate. In the mature brain, the cerebellum and retina retain characteristic radial glial cells. In the cerebellum, these are Bergmann glia, which regulate synaptic plasticity. In the retina, the radial Müller cell is the principal glial cell, and participates in a bidirectional communication with neurons.
PNS	Schwann cells	Similar in function to oligodendrocytes, *Schwann cells* provide myelination to axons in the peripheral nervous system (PNS). They also have phagocytotic activity and clear cellular debris that allows for regrowth of PNS neurons.
PNS	Satellite cells	*Satellite glial cells* are small cells that surround neurons in sensory, sympathetic and parasympathetic ganglia. These cells help regulate the external chemical environment. Like astrocytes, they are interconnected by gap junctions and respond to ATP by elevating intracellular concentration of calcium ions. They are highly sensitive to injury and inflammation, and appear to contribute to pathological states, such as chronic pain.

PNS	Enteric glial cells	Are found in the intrinsic ganglia of the digestive system.They are thought to have many roles in the enteric system, some related to homeostasis and muscular digestive processes.

Capacity to divide

Glia retain the ability to undergo cell division in adulthood, whereas most neurons cannot. The view is based on the general deficiency of the mature nervous system in replacing neurons after an injury, such as a stroke or trauma, while very often there is a profound proliferation of glia, or gliosis near or at the site of damage. However, detailed studies found no evidence that 'mature' glia, such as astrocytes or oligodendrocytes, retain the ability of mitosis. Only the resident oligodendrocyte precursor cells seem to keep this ability after the nervous system matures. On the other hand, there are a few regions in the mature nervous system, such as the dentate gyrus of the hippocampus and the subventricular zone, where generation of new neurons can be observed.

Embryonic development

Most glia are derived from ectodermal tissue of the developing embryo, in particular the neural tube and crest. The exception is microglia, which are derived from hemopoietic stem cells. In the adult, microglia are largely a self-renewing population and are distinct from macrophages and monocytes, which infiltrate the injured and diseased CNS.

In the central nervous system, glia develop from the ventricular zone of the neural tube. These glia include the oligodendrocytes, ependymal cells, and astrocytes. In the peripheral nervous system, glia derive from the neural crest. These PNS glia include Schwann cells in nerves and satellite glial cells in ganglia.

History

Glia were discovered in 1846 by the pathologist Rudolf Virchow in his search for a 'connective tissue' in the brain.

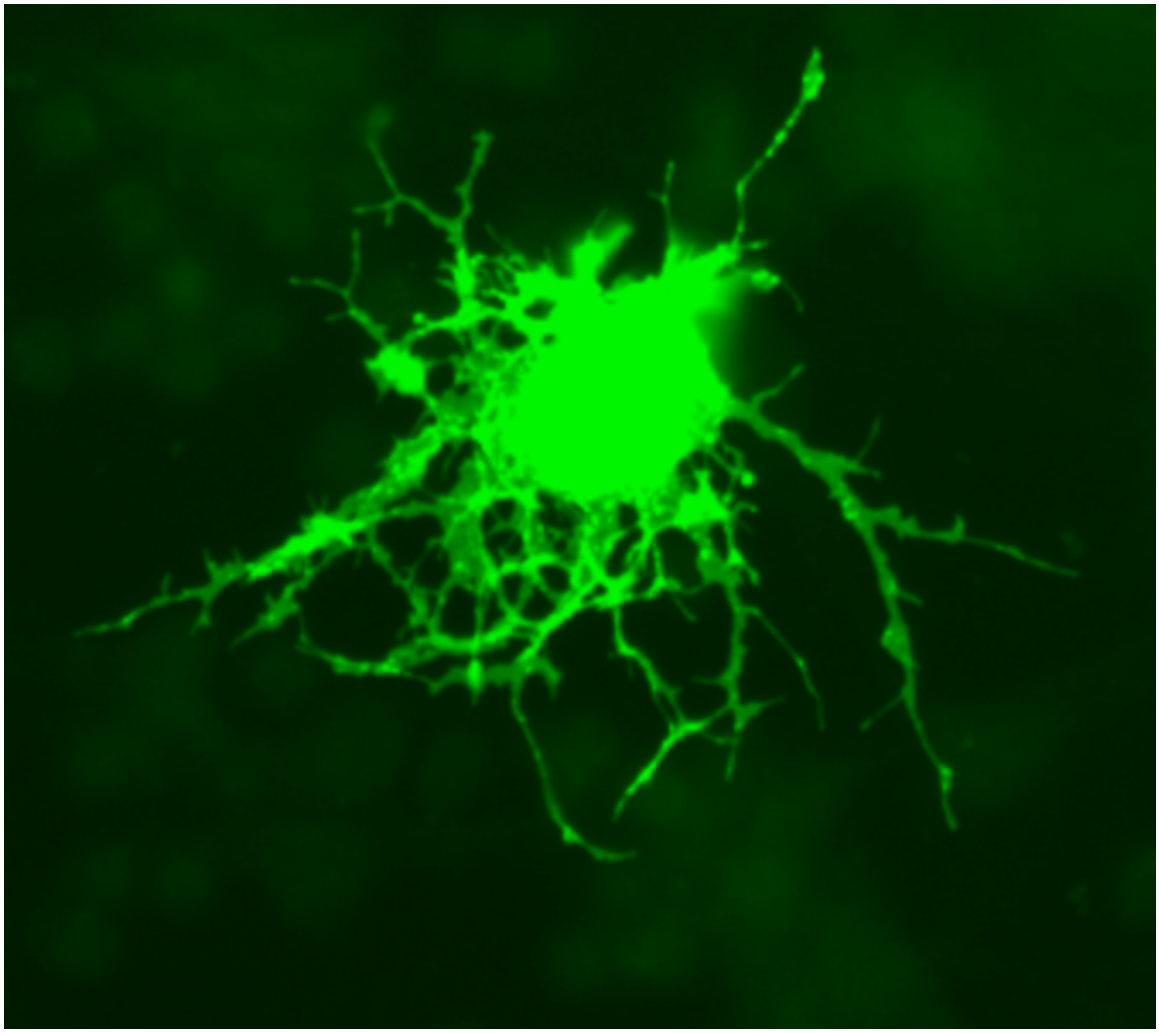
Numbers

The human brain contains roughly equal numbers of glial cells and neurons with 84.6 billion glia and 86.1 billion neurons. The ratio differs between its different parts. The glia/neuron ratio in the cerebral cortex is 3.72(60.84 billion glia; 16.34 billion neurons) while that of the cerebellum is only 0.23 (16.04 billion glia; 69.03 billion neurons). The ratio in the cerebral cortex gray matter is 1.48 (the white matter part has few neurons). The ratio of the basal ganglia, diencephalon and brainstem combined is 11.35.

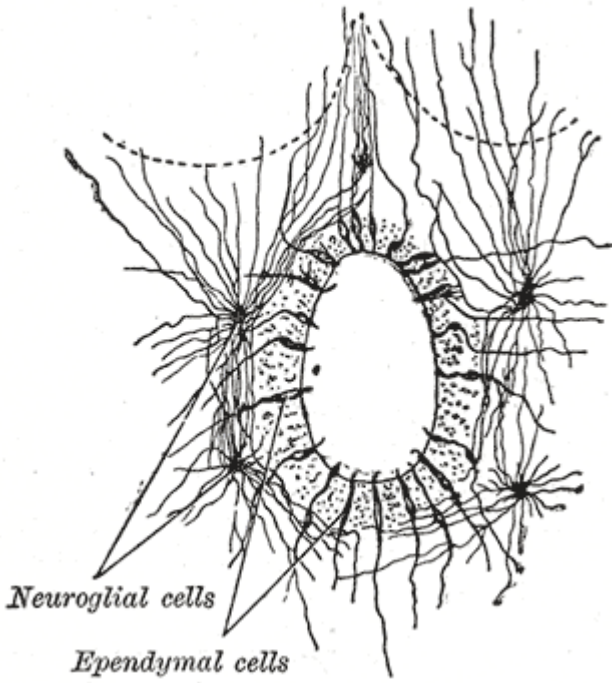
Most cerebral cortex glia are oligodendrocytes (75.6%) then astrocytes (17.3%) and least for microglia (6.5%)

The amount of brain tissue that is made up of glia cells increases with brain size: the nematode brain contains only a few glia, a fruitfly's brain is 25% glia, that of a mouse, 65%, a human, 90%, and an elephant, 97%.

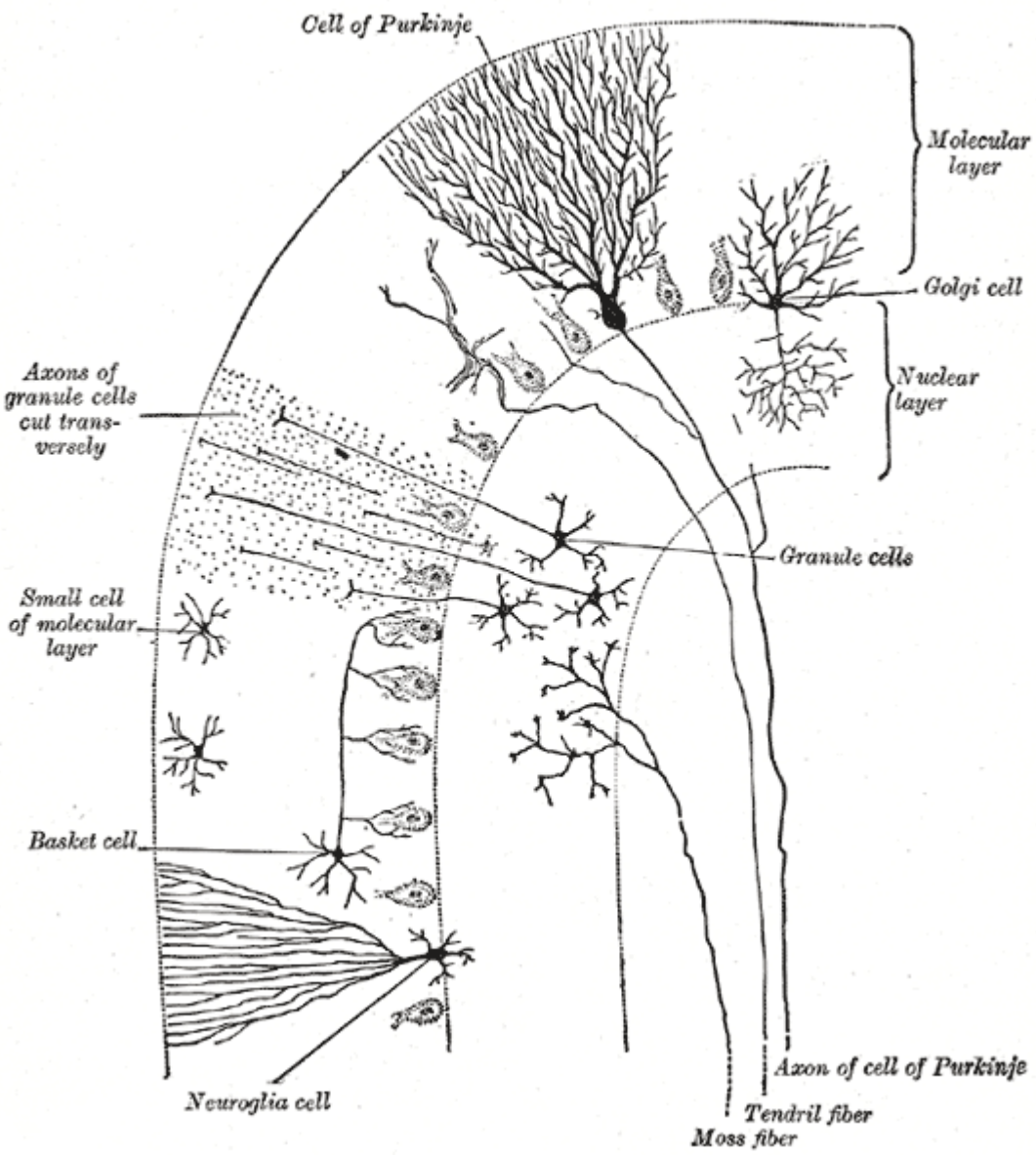
Additional images



Oligodendrocyte



Section of central canal of medulla spinalis, showing ependymal and neuroglial cells



Transverse section of a cerebellar folium

Chapter 15

Synaptic Plasticity

In neuroscience, **synaptic plasticity** is the ability of the connection, or synapse, between two neurons to change in strength in response to either use or disuse of transmission over synaptic pathways. Plastic change also results from the alteration of the number of receptors located on a synapse. There are several underlying mechanisms that cooperate to achieve synaptic plasticity, including changes in the quantity of neurotransmitters released into a synapse and changes in how effectively cells respond to those neurotransmitters. Synaptic plasticity in both excitatory and inhibitory synapses has been found to be dependent upon calcium. Since memories are postulated to be represented by vastly interconnected networks of synapses in the brain, synaptic plasticity is one of the important neurochemical foundations of learning and memory.

Historical Discoveries

In the 1960s, long-term potentiation, or LTP, was observed for the first time by Terje Lømo in Oslo, Norway. He was studying the hippocampus of rabbits and happened to notice that a brief burst of electrical stimuli on fibers heading for the hippocampus led to a dramatic and long-lasting increase in transmission at synapses in the hippocampus, an area of the brain believed to be involved in human memory.

Biochemical mechanisms

Two molecular mechanisms for synaptic plasticity (researched by the Eric Kandel laboratories) involve the NMDA and AMPA glutamate receptors. Opening of NMDA channels (which relates to the level of cellular depolarization) leads to a rise in postsynaptic Ca^{2+} concentration and this has been linked to LTP (as well as to protein kinase activation); strong depolarization of the post-synaptic cell completely displaces the magnesium ions that block NMDA ion channels and allows calcium ions to enter a cell - probably causing long-term potentiation (LTP), while weaker depolarization only partially displaces the Mg^{2+} ions, resulting in less Ca^{2+} entering the post-synaptic neuron and lower intracellular Ca^{2+} concentrations (which activate protein phosphatases and induce long-term depression, LTD).

These activated protein kinases serve to phosphorylate post-synaptic excitatory receptors (i.e. AMPA receptors), improving cation conduction, and thereby potentiating the synapse. Also, this signals recruitment of additional receptors into the postsynaptic

membrane, and stimulates the production of a modified receptor type, thereby facilitating an influx of calcium. This in turn increases post-synaptic excitation by a given pre-synaptic stimulus. This process can be reversed via the activity of protein phosphatases, which act to dephosphorylate these cation channels.

The second mechanism depends on a second messenger cascade regulating gene transcription and changes in the levels of key proteins at synapses such as CaMKII and PKAII. Activation of the second messenger pathway leads to increased levels of CaMKII and PKAII within the dendritic spine. These protein kinases have been linked to growth in dendritic spine volume and LTP processes such as the addition of AMPA receptors to the plasma membrane and phosphorylation of ion channels for enhanced permeability. Localization or compartmentalization of activated proteins occurs in the presence of their given stimulus which creates local effects in the dendritic spine. Calcium influx from NMDA receptors is necessary for the activatoin of CaMKII. This activation is localized to spines with focal stimulation and is inactivated before spreading to adjacent spines or the shaft, indicating an important mechanism of LTP in that particular changes in protein activation can be localized or compartmentalized to enhance the responsivity of single dendritic spines. Individual dendritic spines are capable of forming unique responses to presynaptic cells. This second mechanism can be triggered by protein phosphorylation but takes longer and lasts longer, providing the mechanism for long-lasting memory storage. The duration of the LTP can be regulated by breakdown of these second messengers. Phosphodiesterase, for example, is a protein phosphatase that breaks down the secondary messenger cAMP, which has been implicated in increased AMPA receptor synthesis in the post-synaptic neuron.

Long-lasting changes in the efficacy of synaptic connections (long-term potentiation, or LTP) between two neurons can involve the making and breaking of synaptic contacts. Genes such activin ß-A which encodes a subunit of activin A are up-regulated during early stage LTP. The activin molecule modulates the actin dynamics in dentritic spines through the MAP kinase pathway. By changing the F-actin cytoskeletal structure of dendritic spines, spines are lengthened and the chance that they make synaptic contacts with the axonal terminals of the presynaptic cell is increased. The end result is long term maintenance of LTP.

The number of ion channels on the post-synaptic membrane affects the strength of the synapse. Research suggests that the density of receptors on postsynaptic membranes changes, affecting the neuron's excitability in response to stimuli. In a dynamic process that is maintained in equilibrium, N-methyl D-aspartate receptor (NMDA receptor) and alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPA receptor)s are added to the membrane by exocytosis and removed by endocytosis. These processes, and by extension the number of receptors on the membrane, can be altered by synaptic activity. Experiments have shown that AMPA receptors are delivered to the synapse through vesicular membrane fusion with the postsynaptic membrane via the protein kinase CaMKII, which is activated by the influx of calcium through NMDA receptors. CaMKII also improves AMPA ionic conductance through phosphorylation. When there is high-frequency NMDA receptor activation, there is an increase in the expression of a

protein PSD-95 that increases synaptic capacity for AMPA receptors. This is what leads to a long-term increase in AMPA receptors and thus synaptic strength and plasticity.

If the strength of a synapse is only reinforced by stimulation or weakened by its lack, a positive feedback loop will develop, causing some cells never to fire and some to fire too much. But two regulatory forms of plasticity, called scaling and metaplasticity, also exist to provide negative feedback.. Synaptic scaling is a primary mechanism by which a neuron is able to stabilize firing rates up or down.

Synaptic scaling serves to maintain the strengths of synapses relative to each other, lowering amplitudes of small excitatory postsynaptic potentials in response to continual excitation and raising them after prolonged blockage or inhibition. This effect occurs gradually over hours or days, by changing the numbers of NMDA receptors at the synapse (Pérez-Otaño and Ehlers, 2005). Metaplasticity varies the threshold level at which plasticity occurs, allowing integrated responses to synaptic activity spaced over time and preventing saturated states of LTP and LTD. Since LTP and LTD (long-term depression) rely on the influx of Ca^{2+} through NMDA channels, metaplasticity may be due to changes in NMDA receptors, altered calcium buffering, altered states of kinases or phosphatases and a priming of protein synthesis machinery. Synaptic scaling is a primary mechanism by which a neuron to be selective to its varying inputs. The neuronal circuitry affected by LTP/LTD and modified by scaling and metaplasticity leads to reverberatory neural circuit development and regulation in a Hebbian manner which is manifested as memory, whereas the changes in neural circuitry, which begin at the level of the synapse, are an integral part in the ability of an organism to learn.

There is also a specificity element of biochemical interactions to create synaptic plasticity, namely the importance of location. Processes occur at microdomains - such as exocytosis of AMPA receptors is spatially regulated by the t-SNARE Stx4. Specificity is also an important aspect of CAMKII signaling involving nanodomain calcium. The spatial gradient of PKA between dendritic spines and shafts is also important for the strength and regulation of synaptic plasticity. It is important to remember that the biochemical mechanisms altering synaptic plasticity occur at the level of individual synapses of a neuron. Since the biochemical mechanisms are confined to these "microdomains," the resulting synaptic plasticity affects only the specific synapse at which it took place.

Theoretical mechanisms

A bi-directional model, describing both LTP and LTD, of synaptic plasticity has proved necessary for a number of different learning mechanisms in computational neuroscience, neural networks, and biophysics. Three major hypotheses for the molecular nature of this plasticity have been well-studied, and none are required to be the exclusive mechanism:

1. Change in the probability of glutamate release.
2. Insertion or removal of postsynaptic AMPA receptors.

3. Phosphorylation and de-phosphorylation inducing a change in AMPA receptor conductance.

Of these, the first two hypotheses have been recently mathematically examined to have identical calcium-dependent dynamics which provides strong theoretical evidence for a calcium-based model of plasticity, which in a linear model where the total number of receptors are conserved looks like

$$\frac{dW_i(t)}{dt} = \frac{1}{\tau([Ca^{2+}]_i)} \left(\Omega([Ca^{2+}]_i) - W_i\right),$$

where W_i is the synaptic weight of the ith input axon, τ is a time constant dependent on the insertion and removal rates of neurotransmitter receptors, which is dependent on $[Ca^{2+}]$, the concentration of calcium. $\Omega = \beta A_m^{\mathrm{fp}}$ is also a function of the concentration of calcium that depends linearly on the number of receptors on the membrane of the neuron at some fixed point. Both Ω and τ are found experimentally and agree on results from both hypotheses. The model makes important simplifications that make it unsuited for actual experimental predictions, but provides a significant basis for the hypothesis of a calcium-based synaptic plasticity dependence.

Short Term Plasticity

Plasticity can be categorized as short-term, lasting a few seconds or less, or long-term which lasts from minutes to hours. Short-term synaptic enhancement results from an increase in the probability that synaptic terminals will release transmitters in response to presynaptic action potentials. Synapses will strengthen for a short time because of either an increase in size of the readily releasable pool of packaged transmitter or an increase in the amount of packaged transmitter released in response to each action potential. Types of short term plasticity include synaptic augmentation, depression, facilitation, or neural facilitation, and post-tetanic potentiation.

Synaptic Augmentation

Augmentation has been found to be associated with increased efficiency with which action potentials cause release of vesicles containing transmitters.

Synaptic Depression

Depression is usually attributed to the depletion of the readily releasable vesicles. Depression can also arise from postsynaptic processes and from feedback activation of presynaptic receptors. Heterosynaptic depression is thought to be linked to the release of adenosine triphosphate (ATP) from astrocytes.

Long Term Plasticity

Long-term depression and long-term potentiation are two forms of long term plasticity, lasting minutes or more, that occur at excitatory synapses. NMDA-dependent LTD and LTP have been extensively researched, and are found to require the binding of glutamate, and glycine or D-serine for activation of NMDA receptors.

Long-term Depression

Brief activation of an excitatory pathway can produce what is known as long-term depression (LTD) of synaptic transmission in many areas of the brain. LTD is induced by a minimum level of postsynpatic depolarization and simultaneous increase in the intracellular calcium concentration at the postsynaptic neuron. LTD can be inititated at inactive synapses if the calcium concentration is raised to the minimum required level by heterosynaptic activation, or if the extracellular concentration is raised. These alternative conditions capable of causing LTD differ from the Hebb rule, and instead depend on synaptic activity modifications. D-serine release by astrocytes has been found to lead to a significant reduction of LTD in the hippocampus.

Long-term Potentiation

Long-term potentiation, commonly referred to as LTP, is an increase in synaptic response following potentiating pulses of electrical stimuli that sustains at a level above the baseline response for hours or longer. LTP involves interactions between postsynaptic neurons and the specific presynaptic inputs that form a synaptic association, and is specific to the stimulated pathway of synaptic transmission. Modification of astrocyte coverage at the syanpses in the hippocampus has been found to result from the induction of LTP, which has been found to be linked to the release of D-serine, nitric oxide, and the chemokine, s100B by astrocytes. LTP is also a model for studying the synaptic basis of Hebbian plasticity. Induction conditions resemble those described for the initiation of long-term depression (LTD), but a stronger depolarization and a greater increase of calcium are necessary to achieve LTP.

Synaptic Strength

The modification of synaptic strength is referred to as functional plasticity. Changes in synaptic strength involve distinct mechanisms of particular types of glial cells, the most researched type being astrocytes.

Chapter 16

Chemical Synapse

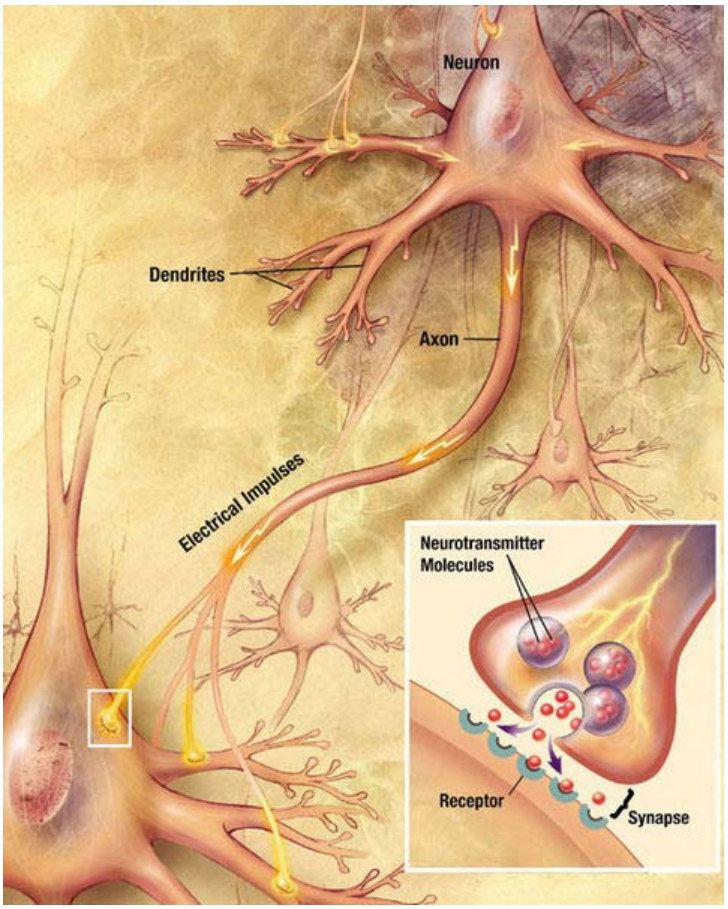


Illustration of the major elements in chemical synaptic transmission. An electrochemical wave called an action potential travels along the axon of a neuron. When the wave reaches a synapse, it provokes release of a puff of neurotransmitter molecules, which bind to chemical receptor molecules located in the membrane of another neuron, on the opposite side of the synapse.

Chemical synapses are specialized junctions through which neurons signal to each other and to non-neuronal cells such as those in muscles or glands. Chemical synapses allow neurons to form circuits within the central nervous system. They are crucial to the

biological computations that underlie perception and thought. They allow the nervous system to connect to and control other systems of the body.

At a chemical synapse, one neuron releases a neurotransmitter into a small space (the synapse) that is adjacent to another neuron. Neurotransmitters must then be cleared out of the synapse efficiently so that the synapse can be ready to function again as soon as possible.

The adult human brain is estimated to contain from 10^{14} to 5×10^{14} (100-500 trillion) synapses. Every cubic millimeter of cerebral cortex contains roughly a billion of them.

The word "synapse" comes from "synaptein", which Sir Charles Scott Sherrington and colleagues coined from the Greek "syn-" ("together") and "haptein" ("to clasp"). Chemical synapses are not the only type of biological synapse: electrical and immunological synapses also exist. Without a qualifier, however, "synapse" commonly means chemical synapse.

Structure

Synapses are functional connections between neurons, or between neurons and other types of cells. A typical neuron gives rise to several thousand synapses, although there are some types that make far fewer. Most synapses connect axons to dendrites, but there are also other types of connections, including axon-to-cell-body, axon-to-axon, and dendrite-to-dendrite. Synapses are generally too small to be recognizable using a light microscope except as points where the membranes of two cells appear to touch, but their cellular elements can be visualized clearly using an electron microscope.

Chemical synapses pass information directionally from a presynaptic cell to a postsynaptic cell and are therefore asymmetric in structure and function. The presynaptic terminal, or synaptic bouton, is a specialized area within the axon of the presynaptic cell that contains neurotransmitters enclosed in small membrane-bound spheres called synaptic vesicles. Synaptic vesicles are docked at the presynaptic plasma membrane at regions called active zones (AZ).

Immediately opposite is a region of the postsynaptic cell containing neurotransmitter receptors; for synapses between two neurons the postsynaptic region may be found on the dendrites or cell body. Immediately behind the postsynaptic membrane is an elaborate complex of interlinked proteins called the postsynaptic density (PSD).

Proteins in the PSD are involved in anchoring and trafficking neurotransmitter receptors and modulating the activity of these receptors. The receptors and PSDs are often found in specialized protrusions from the main dendritic shaft called dendritic spines.

Synapses may be described as symmetric or asymmetric. When examined under an electron microscope, asymmetric synapses are charactrised by rounded vesicles in the presynaptic cell, and a prominent post-synaptic density. Asymmetric synapses are

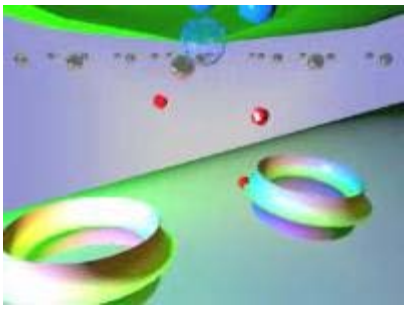
typically excitatory. Symmetric synapses in contrast have flattened or elongated vesicles, and do not contain a prominent post-synaptic density. Symmetric synapses are typically inhibitory.

Between the pre- and postsynaptic cells is a gap about 20 nm wide called the synaptic cleft. The small volume of the cleft allows neurotransmitter concentration to be raised and lowered rapidly.

Signaling in chemical synapses

Overview

Here is a summary of the sequence of events that take place in synaptic transmission from a presynaptic neuron to a postsynaptic cell. Each step is explained in more detail below. Note that with the exception of the final step, the entire process may run only a few tenths of a millisecond, in the fastest synapses.



1. The process begins with a wave of electrochemical excitation called an action potential traveling along the membrane of the presynaptic cell, until it reaches the synapse.
2. The electrical depolarization of the membrane at the synapse causes channels to open that are permeable to calcium ions.
3. Calcium ions flow through the presynaptic membrane, rapidly increasing the calcium concentration in the interior.
4. The high calcium concentration activates a set of calcium-sensitive proteins attached to vesicles that contain a neurotransmitter chemical.
5. These proteins change shape, causing the membranes of some "docked" vesicles to fuse with the membrane of the presynaptic cell, thereby opening the vesicles and dumping their neurotransmitter contents into the synaptic cleft, the narrow space between the membranes of the pre- and post-synaptic cells.
6. The neurotransmitter diffuses within the cleft. Some of it escapes, but some of it binds to chemical receptor molecules located on the membrane of the postsynaptic cell.
7. The binding of neurotransmitter causes the receptor molecule to be *activated* in some way. Several types of activation are possible, as described in more detail

below. In any case, this is the key step by which the synaptic process affects the behavior of the postsynaptic cell.
8. Due to thermal shaking, neurotransmitter molecules eventually break loose from the receptors and drift away.
9. The neurotransmitter is either reabsorbed by the presynaptic cell, and then repackaged for future release, or else it is broken down metabolically.

Neurotransmitter release

The release of a neurotransmitter is triggered by the arrival of a nerve impulse (or action potential) and occurs through an unusually rapid process of cellular secretion, also known as exocytosis: Within the presynaptic nerve terminal, vesicles containing neurotransmitter sit "docked" and ready at the synaptic membrane. The arriving action potential produces an influx of calcium ions through voltage-dependent, calcium-selective ion channels at the down stroke of the action potential (tail current). Calcium ions then bind with the proteins found within the membranes of the synaptic vesicles, allowing the vesicles to "dock" with the presynaptic membrane resulting in the creation of a fusion pore. The vesicles then release their contents to the synaptic cleft through this fusion pore within 180μsec of calcium entry. Vesicle fusion is driven by the action of a set of proteins in the presynaptic terminal known as SNAREs.

The membrane added by this fusion is later retrieved by endocytosis and recycled for the formation of fresh neurotransmitter-filled vesicles.

Receptor binding

Receptors on the opposite side of the synaptic gap bind neurotransmitter molecules. Receptors can respond in either of two general ways. First, the receptors may directly open ligand-gated ion channels in the postsynaptic cell membrane, causing ions to enter or exit the cell and changing the local transmembrane potential. The resulting change in voltage is called a postsynaptic potential. In general, the result is *excitatory*, in the case of depolarizing currents, or *inhibitory* in the case of hyperpolarizing currents. Whether a synapse is excitatory or inhibitory depends on what type(s) of ion channel conduct the postsynaptic current(s), which in turn is a function of the type of receptors and neurotransmitter employed at the synapse. The second way a receptor can affect membrane potential is by modulating the production of chemical messengers inside the postsynaptic neuron. These second messengers can then amplify the inhibitory or excitatory response to neurotransmitters.

Termination

After a neurotransmitter molecule binds to a receptor molecule, it must be removed to allow for the postsynaptic membrane to continue to relay subsequent EPSPs and/or IPSPs. This removal can happen through one or more processes:

- The neurotransitter may diffuse away due to thermally-induced oscillations of both it and the receptor, making it available to be broken down metabolically outside the neuron or to be reabsorbed.
- Enzymes within the subsynaptic membrane may inactivate/metabolize the neurotransmitter.

- Reuptake pumps may actively pump the neurotransmitter back into the presynaptic axon terminal for reprocessing and re-release following a later action potential.

The time frame for these "clearing" processes varies greatly for different types of synapses, ranging from a few tenths of a millisecond for the fastest, to several seconds for the slowest.

Modulation of synaptic transmission

Synaptic transmission can be modulated by e.g. desensitization, homosynaptic plasticity and heterosynaptic plasticity:

Desensitization

Desensitization of the postsynaptic receptors is a decrease in response to the same neurotransmitter stimulus. It means that the strength of a synapse may in effect diminish as a train of action potentials arrive in rapid succession—a phenomenon that gives rise to the so-called frequency dependence of synapses. The nervous system exploits this property for computational purposes, and can tune its synapses through such means as phosphorylation of the proteins involved.

Homosynaptic plasticity

Homosynaptic plasticity (or also homotropic modulation) is a change in the synaptic strength that results from the history of activity at a particular synapse. This can result from changes in presynaptic calcium as well as feedback onto presynaptic receptors, i.e. a form of autocrine signaling. Homosynaptic plasticity can affect the number and replenishment rate of vesicles or it can affect the relationship between calcium and vesicle release. Homosynaptic plasticity can also be post-synaptic in nature. It can result in either an increase or decrease in synaptic strength.

One example is neurons of the sympathetic nervous system (SNS), which release noradrenaline, which, besides affecting postsynaptic receptors, also affects presynaptic α2-adrenergic receptors, inhibiting further release of noradrenaline. This effect is utilized with clonidine to perform inhibitory effects on the SNS.

Heterosynaptic plasticity

Heterosynaptic plasticity (or also heterotropic modulation) is a change in synaptic strength that results from the activity of other neurons. Again, the plasticity can alter the number of vesicles or their replenishment rate or the relationship between calcium and vesicle release. Additionally, it could directly affect calcium influx. Heterosynaptic plasticity can also be post-synaptic in nature, affecting receptor sensitivity.

One example is again neurons of the sympathetic nervous system, which release noradrenaline, which, in addition, generate inhibitory effect on presynaptic terminals of neurons of the parasympathetic nervous system.

Effects of drugs

One of the most important features of chemical synapses is that they are the site of action for the majority of psychoactive drugs. Synapses are affected by drugs such as curare, strychnine, cocaine, morphine, alcohol, LSD, and countless others. These drugs have different effects on synaptic function, and often are restricted to synapses that use a specific neurotransmitter. For example, curare is a poison which stops acetylcholine from depolarising the post-synaptic membrane, causing paralysis. Strychnine blocks the inhibitory effects of the neurotransmitter glycine, which causes the body to pick up and react to weaker and previously ignored stimuli, resulting in uncontrollable muscle spasms. Morphine acts on synapses that use endorphin neurotransmitters, and alcohol increases the inhibitory effects of the neurotransmitter GABA. LSD interferes with synapses that use the neurotransmitter serotonin. Cocaine blocks reuptake of dopamine and therefore increases its effects.

Integration of synaptic inputs

In general, if an excitatory synapse is strong, an action potential in the presynaptic neuron will trigger another in the postsynaptic cell, whereas, at a weak synapse, the excitatory postsynaptic potential ("EPSP") will not reach the threshold for action potential initiation. In the brain, however, each neuron forms synapses with many others, and, likewise, each receives synaptic inputs from many others. When action potentials fire simultaneously in several neurons that weakly synapse on a single cell, they may initiate an impulse in that cell even though the synapses are weak. This process is known as summation. On the other hand, a presynaptic neuron releasing an inhibitory neurotransmitter such as GABA can cause inhibitory postsynaptic potential in the postsynaptic neuron, decreasing its excitability and therefore decreasing the neuron's likelihood of firing an action potential. In this way, the output of a neuron may depend on the input of many others, each of which may have a different degree of influence, depending on the strength of its synapse with that neuron. John Carew Eccles performed some of the important early experiments on synaptic integration, for which he received the Nobel Prize for Physiology or Medicine in 1963. Complex input/output relationships form the basis of transistor-based computations in computers, and are thought to figure similarly in neural circuits.

Synaptic strength

The strength of a synapse is defined by the change in transmembrane potential resulting from activation of the postsynaptic neurotransmitter receptors. This change in voltage is known as a postsynaptic potential, and is a direct result of ionic currents flowing through the postsynaptic ion channels. Changes in synaptic strength can be short–term and without permanent structural changes in the neurons themselves, lasting seconds to minutes — or long-term (long-term potentiation, or LTP), in which repeated or continuous synaptic activation can result in second messenger molecules initiating protein synthesis, resulting in alteration of the structure of the synapse itself. Learning and memory are believed to result from long-term changes in synaptic strength, via a mechanism known as synaptic plasticity.

Volume transmission

When a neurotransmitter is released at a synapse, it reaches its highest concentration inside the narrow space of the synaptic cleft, but some of it is certain to diffuse away before being reabsorbed or broken down. If it diffuses away, it has the potential to activate receptors that are located either at other synapses or on the membrane away from any synapse. The extrasynaptic activity of a neurotransmitter is known as *volume transmission*. It is well established that such effects occur to some degree, but their functional importance has long been a matter of controversy.

Recent work indicates that volume transmission may be the predominant mode of interaction for some special types of neurons. In the mammalian cerebral cortex, a class of neurons called neurogliaform cells can inhibit other nearby cortical neurons by releasing the neurotransmitter GABA into the extracellular space. Approximately 78% of neurogliaforms do not form classical synapses. This may be the first definitive example of neurons communicating chemically where synapses are not present.

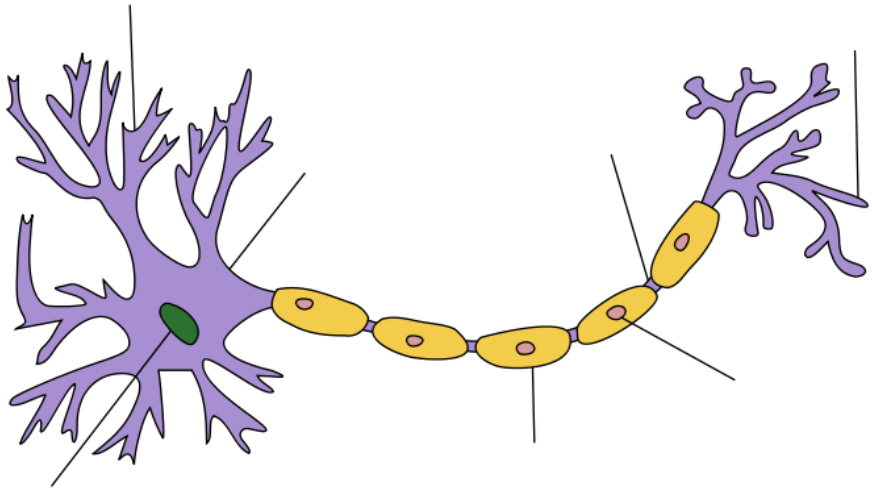
Relationship to electrical synapses

An electrical synapse is a mechanical and electrically conductive link between two abutting neurons that is formed at a narrow gap between the pre- and postsynaptic cells known as a gap junction. At gap junctions, cells approach within about 3.5 nm of each other, rather than the 20 to 40 nm distance that separates cells at chemical synapses. As opposed to chemical synapses, the postsynaptic potential in electrical synapses is not caused by the opening of ion channels by chemical transmitters, but by direct electrical coupling between both neurons. Electrical synapses are therefore faster and more reliable than chemical synapses. Electrical synapses are found throughout the nervous system, yet are less common than chemical synapses.

Chapter 17

Dendrite and Dendritic Spine

Dendrite



Dendrites (from Greek δένδρον *déndron*, "tree") are the branched projections of a neuron that act to conduct the electrochemical stimulation received from other neural cells to the cell body, or soma, of the neuron from which the dendrites project. Electrical stimulation is transmitted onto dendrites by upstream neurons via synapses which are located at various points throughout the dendritic arbor. Dendrites play a critical role in integrating these synaptic inputs and in determining the extent to which action potentials are produced by the neuron. Recent research has also found that dendrites can support action potentials and release neurotransmitters, a property that was originally believed to be specific to axons.

The long outgrowths on dendritic cells are also called dendrites. These dendrites do not process electrical signals.

Electrical properties of dendrites

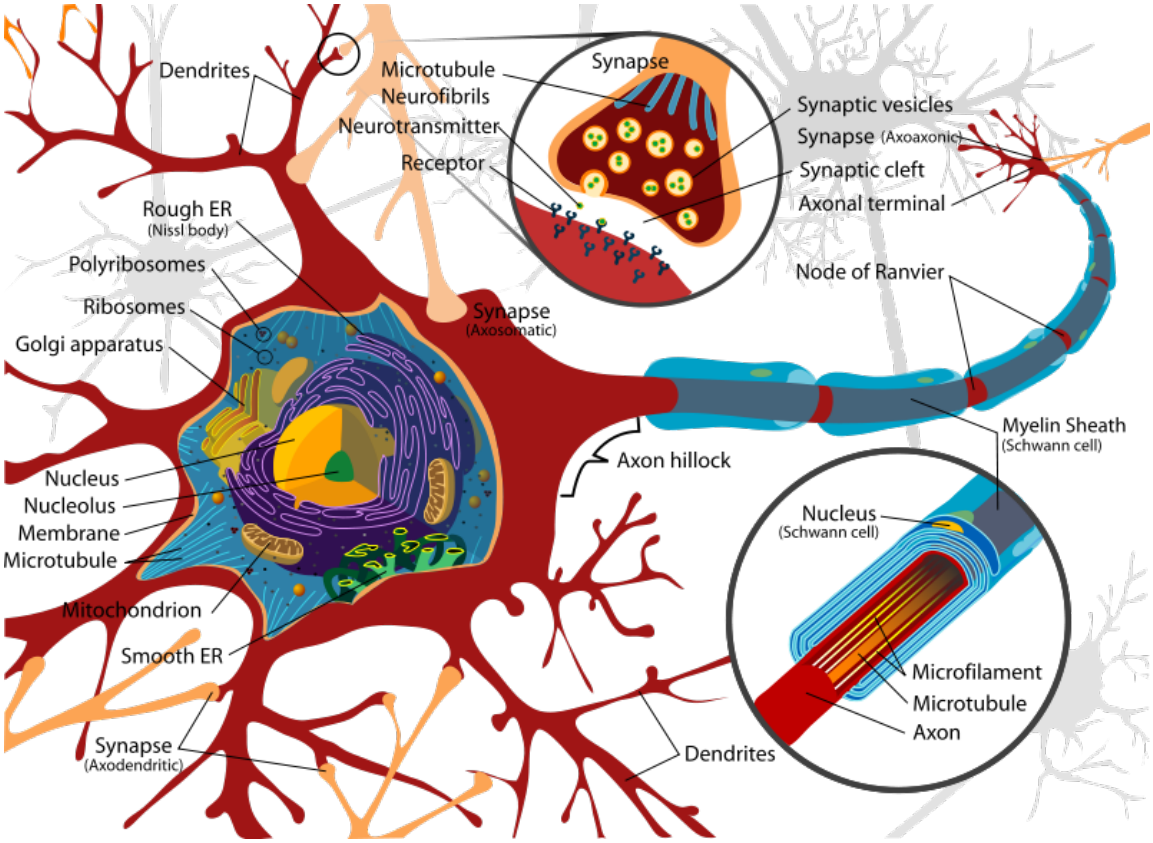
The structure and branching of a neuron's dendrites, as well as the availability and variation in voltage-gated ion conductances, strongly influences how it integrates the input from other neurons, particularly those that input only weakly. This integration is both "temporal" -- involving the summation of stimuli that arrive in rapid succession—as well as "spatial" -- entailing the aggregation of excitatory and inhibitory inputs from separate branches.

Dendrites were once believed to merely convey stimulation passively. In this example, voltage changes measured at the cell body result from activations of distal synapses propagating to the soma without the aid of voltage-gated ion channels. Passive cable theory describes how voltage changes at a particular location on a dendrite transmit this electrical signal through a system of converging dendrite segments of different diameters, lengths, and electrical properties. Based on passive cable theory one can track how changes in a neuron’s dendritic morphology changes the membrane voltage at the soma, and thus how variation in dendrite architectures affects the overall output characteristics of the neuron.

Although passive cable theory offers insights regarding input propagation along dendrite segments, it is important to remember that dendrite membranes are host to a cornucopia of proteins some of which may help amplify or attenuate synaptic input. Sodium, calcium, and potassium channels are all implicated in contributing to input modulation. It is possible that each of these ion species has a family of channel types each with its own biophysical characteristics relevant to synaptic input modulation. Such characteristics include the latency of channel opening, the electrical conductance of the ion pore, the activation voltage, and the activation duration. In this way, a weak input from a distal synapse can be amplified by sodium and calcium currents en route to the soma so that the effects of distal synapse are no less robust than those of a proximal synapse.

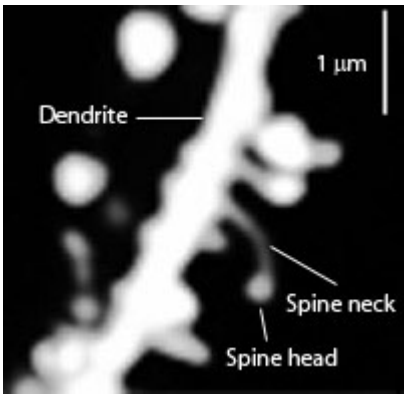
One important feature of dendrites, endowed by their active voltage gated conductances, is their ability to send action potentials back into the dendritic arbor. Known as backpropagating action potentials, these signals depolarize the dendritic arbor and provide a crucial component toward synapse modulation and long-term potentiation.Furthermore, a train of backpropagating action potentials artificially generated at the soma can induce a calcium action potential at the dendritic initiation zone in certain types of neurons. Whether or not this mechanism is of physiological importance remains an open question.

Dendrite development

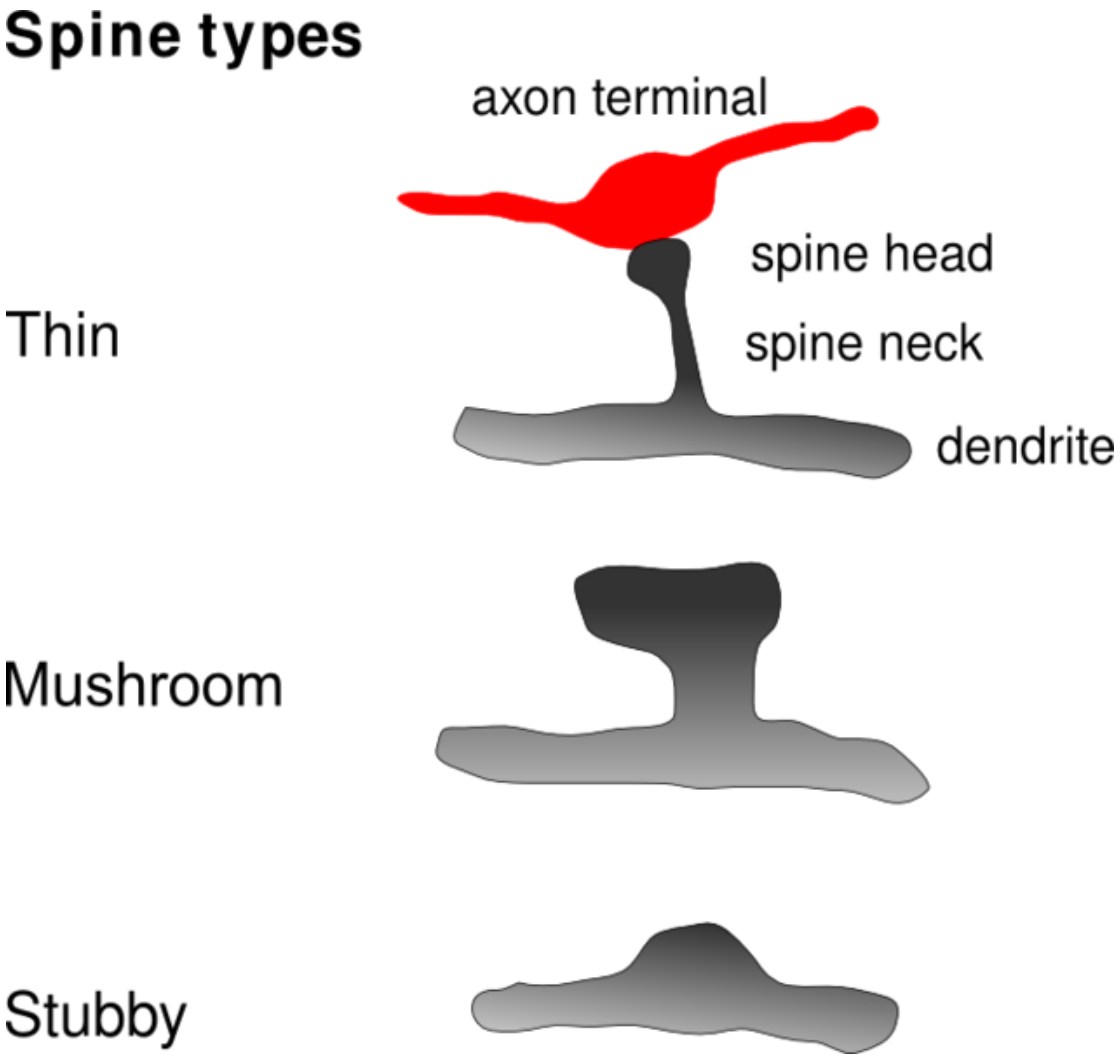


Despite the critical role that dendrites play in the computational tendencies of neurons, very little is known about the process by which dendrites orient themselves in vivo and are compelled to create the intricate branching pattern unique to each specific neuronal class. A balance between metabolic costs of dendritic elaboration and the need to cover receptive field presumably determine the size and shape of dendrites. It is likely that a complex array of extracellular and intracellular cues modulate dendrite development. Transcription factors, receptor-ligand interactions, various signaling pathways, local translational machinery, cytoskeletal elements, Golgi outposts and endosomes have been identified as contributors to the organization of dendrites of individual neurons and the placement of these dendrites in the neuronal circuitry. Important transcription factors involved in the dendritic morphogenesis includes CUT, Abrupt, Collier, Spineless, ACJ6/drifter, CREST, NEUROD1, CREB, neurogenin2 etc. Secreted proteins and cell surface receptors includes neurotrophins and tyrosine kinase receptors, BMP7, Wnt/dishevelled, EPHB 1-3, Semaphorin/plexin-neuropilin, slit-robo, netrin-frazzled, reelin. Rac, CDC42 and RhoA serve as cytoskeletal regulators and the motor protein includes KIF5, dynein, LIS1. Important secretory and endocytic pathways controlling the dendritic development includes DAR3 /SAR1, DAR2/Sec23, DAR6/Rab1 etc. All these molecules interplay with each other in controlling dendritic morphogenesis including the acquisition of type specific dendritic arborization, the regulation of dendrite size and the organization of dendrites emanating from different neurons.

Dendritic spine



Spiny dendrite of a striatal medium spiny neuron



Common types of dendritic spines

A **dendritic spine** (or spine) is a small membranous protrusion from a neuron's dendrite that typically receives input from a single synapse of an axon. Dendritic spines serve as a storage site for synaptic strength and help transmit electrical signals to the neuron's cell body. Most spines have a bulbous head (the spine head), and a thin neck that connects the head of the spine to the shaft of the dendrite. The dendrites of a single neuron can contain hundreds to thousands of spines. In addition to spines providing an anatomical substrate for memory storage and synaptic transmission, they may also serve to increase the number of possible contacts between neurons.

Distribution

Dendritic spines usually receive excitatory input from axons although sometimes both inhibitory and excitatory connections are made onto the same spine head. Spines are found on the dendrites of most principal neurons in the brain, including the pyramidal neurons of the neocortex, the medium spiny neurons of the striatum, and the Purkinje cells of the cerebellum.

Dendritic spines occur at a density of up to 50 spines/10 μm stretch of dendrite. Hippocampal and cortical pyramidal neurons may receive tens of thousands of mostly excitatory inputs from other neurons onto their equally numerous spines, whereas the number of spines on Purkinje neuron dendrites is an order of magnitude larger.

Morphology

Dendritic spines are small with spine head volumes ranging 0.01 μm^3 to 0.8 μm^3. Spines with strong synaptic contacts typically have a large spine head, which connect to the dendrite via a membranous neck. The most notable classes of spine shape are "thin", "stubby", "mushroom", and "branched". Electron microscopy studies have shown that there is a continuum of shapes between these categories. The variable spine shape and volume is thought to be correlated with the strength and maturity of each spine-synapse.

Biochemistry

Receptor activity

Dendritic spines express glutamate receptors (e.g. AMPA receptor and NMDA receptor) on their surface. The TrkB receptor for BDNF is also expressed on the spine surface, and is believed to play a role in spine survival. The tip of the spine contains an electrondense region referred to as the "postsynaptic density" (PSD). The PSD directly apposes the active zone of its synapsing axon and comprises ~10% of the spine's membrane surface area; neurotransmitters released from the active zone bind receptors in the postsynaptic density of the spine. One-half of the synapsing axons and dendritic spines are physically tethered by calcium-dependent cadherin, which forms cell-to-cell adherent junctions between two neurons.

Glutamate receptors (GluRs) are localized to the postsynaptic density, and are anchored by cytoskeletal elements to the membrane. They are positioned directly above their signaling machinery, which is typically tethered to the underside of the plasma membrane, allowing signals transmitted by the GluRs into the cytosol to be further propagated by their nearby signaling elements to activate signal transduction cascades. The localization of signaling elements to their GluRs is particularly important in ensuring signal cascade activation, as GluRs would be unable to affect particular downstream effects without nearby signalers.

Signaling from GluRs is mediated by the presence of an abundance of proteins, especially kinases, that are localized to the postsynaptic density. These include calcium-dependent calmodulin, CaMKII (calmodulin-dependent protein kinase II), PKC (Protein Kinase C), PKA (Protein Kinase A), Protein Phosphatase-1 (PP-1), and Fyn tyrosine kinase. Certain signalers, such as CaMKII, are upregulated in response to activity.

Spines are particularly advantageous to neurons by compartmentalizing biochemical signals. This can help to encode changes in the state of an individual synapse without necessarily affecting the state of other synapses of the same neuron. The length and width of the spine neck has a large effect on the degree of compartmentalization, with thin spines being the most biochemically isolated spines.

Cytoskeleton and Organelles

The cytoskeleton of dendritic spines is particularly important in their synaptic plasticity; without a dynamic cytoskeleton, spines would be unable to rapidly change their volumes or shapes in responses to stimuli. These changes in shape might affect the electrical properties of the spine. The cytoskeleton of dendritic spines is primarily made of filamentous actin (F-actin). While tubulin monomers and microtubule-associated proteins (MAPs) are present, organized microtubules are not present. Because spines have a cytoskeleton of primarily actin, this allows them to be highly dynamic in shape and size. The actin cytoskeleton directly determines the morphology of the spine, and actin regulators, small GTPases such as Rac, RhoA, and CDC42, rapidly modify this cytoskeleton. Overactive Rac1 results in consistently smaller dendritic spines.

In addition to their electrophysiological activity and their receptor-mediated activity, spines appear to be vesicularly active and may even translate proteins. Stacked discs of the smooth endoplasmic reticulum (SERs) have been identified in dendritic spines. Formation of this "spine apparatus" depends on the protein synaptopodin and is believed to play an important role in calcium handling. "Smooth" vesicles have also been identified in spines, supporting the vesicular activity in dendritic spines. The presence of polyribosomes in spines also suggests protein translational activity in the spine itself, not just in the dendrite.

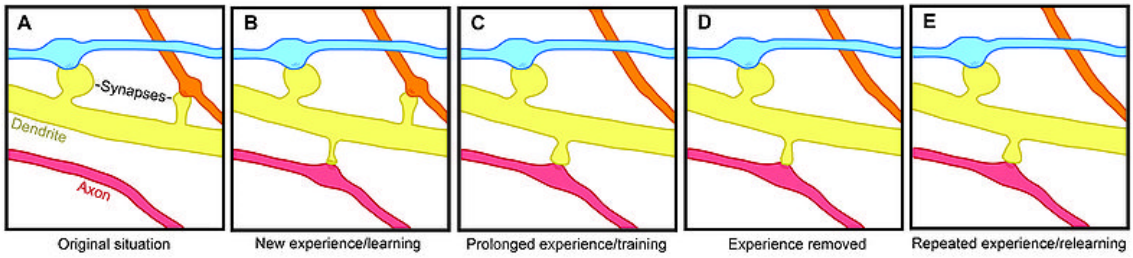
Plasticity

As aforementioned, dendritic spines are very "plastic", that is, spines change significantly in shape, volume, and number in small time courses. Because spines have a primarily actin cytoskeleton, they are dynamic, and the majority of spines change their shape within seconds to minutes because of the dynamicity of actin remodeling. Furthermore, spine number is very variable and spines come and go; in a matter of hours, 10-20% of spines can spontaneously appear or disappear on the pyramidal cells of the cerebral cortex, although the larger "mushroom"-shaped spines are the most stable.

Spine maintenance and plasticity is activity-dependent and activity-independent. BDNF partially determines spine levels, and low levels of AMPA receptor activity is necessary to maintain spine survival, and synaptic activity involving NMDA receptors encourages spine growth. Furthermore, two-photon laser scanning microscopy and confocal microscopy have shown that spine volume changes depending on the types of stimuli that are presented to a synapse.

Importance to Learning and Memory

Evidence of Importance



Experience-dependent spine formation and elimination

Spine plasticity is implicated in motivation, learning, and memory. In particular, long-term memory is mediated in part by the growth of new dendritic spines (or the enlargement of pre-existing spines) to reinforce a particular neural pathway. Because dendritic spines are plastic structures whose lifespan is influenced by input activity, spine dynamics may play an important role in the maintenance of memory over a lifetime.

Age-dependent changes in the rate of spine turnover suggest that spine stability impacts developmental learning. In youth, dendritic spine turnover is relatively high and produces a net loss of spines, with the rate of the elimination of spines surpassing the rate of the formation of spines. This high rate of spine turnover may characterize critical periods of development and reflect learning capacity in adolescence—different cortical areas exhibit differing levels of synaptic turnover during development, possibly reflecting varying critical periods for specific brain regions. In adulthood, however, most spines remain persistent, and the half-life of spines increases. This stabilization occurs due to a

developmentally regulated slow-down of spine elimination, a process which may underlie the stabilization of memories in maturity.

Experience-induced changes in dendritic spine stability also point to spine turnover as a mechanism involved in the maintenance of long-term memories, though it is unclear how sensory experience affects neural circuitry. Two general models might describe the impact of experience on structural plasticity. On the one hand, experience and activity may drive the discrete formation of relevant synaptic connections that store meaningful information in order to allow for learning. On the other hand, synaptic connections may be formed in excess, and experience and activity may lead to the pruning of extraneous synaptic connections.

In lab animals of all ages, environmental enrichment has been related to dendritic branching, spine density, and overall number of synapses. In addition, skill training has been shown to lead to the formation and stabilization of new spines while destabilizing old spines, suggesting that the learning of a new skill involves a rewiring process of neural circuits. Since the extent of spine remodeling correlates with success of learning, this suggesting a crucial role of synaptic structural plasticity in memory formation. In addition, changes in spine stability and strengthening occur rapidly and have been observed within hours after training.

Conversely, while enrichment and training are related to increases in spine formation and stability, long-term sensory deprivation leads to a decrease in the rate of spine elimination and therefore impacts long-term neural circuitry. Upon restoring sensory experience after deprivation in adolescence, spine elimination is accelerated, suggesting that experience plays an important role in the net loss of spines during development. In addition, other sensory deprivation paradigms—such as whisker trimming—have been shown to increase the stability of new spines.

Research in neurological diseases and injuries shed further light on the nature and importance of spine turnover. After stroke, a marked increase in structural plasticity occurs near the trauma site, and a five- to eightfold increase from control rates in spine turnover has been observed. Dendrites disintegrate and reassemble rapidly during ischemia—as with stroke, survivors showed an increase in dendritic spine turnover. While a net loss of spines is observed in Alzheimer's disease and cases of mental retardation, cocaine and amphetamine use have been linked to increases in dendritic branching and spine density in the prefrontal cortex and the nucleus accumbens. Because significant changes in spine density occur in various brain diseases, this suggests a balanced state of spine dynamics in normal circumstances, which may be susceptible to disequilibrium under varying pathological conditions.

Importance Contested

Despite experimental findings that suggest a role for dendritic spine dynamics in mediating learning and memory, the degree of structural plasticity’s importance remains debatable. For instance, studies estimate that only a small portion of spines formed during

training actually contribute to lifelong learning. In addition, the formation of new spines may not significantly contribute to the connectivity of the brain, and spine formation may not bear as much of an influence on memory retention as other properties of structural plasticity, such as the increase in size of spine heads.

Electrotonic properties

Electrotonic conduction refers to the passive conduction of current. Dendritic spines have a number of specific electrotonic properties. A dendritic spine has high input resistance, the resistance increases with smallness of headsize and narrowness of stemsize. The capacitance of the membranes of spines is relatively small with the result that synaptic potentials can be relatively fast. The capacitance of the whole dendrite however becomes higher as the number of spines increases. Because there is an impedance mismatch between the dendritic spine and the dendrite, it is necessary with active signal boosting. The impedance mismatch also causes the spine to follow the potential of the parent dendrite.

Modelling

Theoreticians have for decades hypothesized about the potential electrical function of spines, yet our inability to examine their electrical properties has until recently stopped theoretical work from progressing too far. Recent advances in imaging techniques along with increased use of two-photon glutamate uncaging have led to a wealth of new discoveries; we now suspect that there are voltage-dependent sodium, potassium, and calcium channels in the spine heads.

Cable theory provides the theoretical framework behind the most "simple" method for modelling the flow of electrical currents along passive neural fibres. Each spine can be treated as two compartments, one representing the neck, the other representing the spine head. The compartment representing the spine head alone should carry the active properties.

Baer and Rinzel's Continuum Model

To facilitate the analysis of interactions between many spines, Baer & Rinzel formulated a new cable theory for which the distribution of spines is treated as a continuum. In this representation, spine head voltage is the local spatial average of membrane potential in adjacent spines. The formulation maintains the feature that there is no direct electrical coupling between neighboring spines; voltage spread along dendrites is the only way for spines to interact.

The Spike-Diffuse-Spike Model

The SDS model was intended as a computationally simple version of the full Baer and Rinzel model. It was designed to be analytically tractable and have as few free parameters as possible while retaining those of greatest significance, such as spine neck

resistance. The model drops the continuum approximation and instead uses a passive dendrite coupled to excitable spines at discrete points. Membrane dynamics in the spines are modelled using integrate and fire processes. The spike events are modelled in a discrete fashion with the wave form conventionally represented as a rectangular function.

Modelling spine calcium transients

Calcium transients in spines are a key trigger for synaptic plasticity. NMDA receptors, which have a high permeability for calcium, only conduct ions if the membrane potential is suffiently depolarized. The amount of calcium entering a spine during synaptic activity therefore depends on the depolarization of the spine head. Evidence from calcium imaging experiments (two-photon microscopy) and from compartmental modelling indicates that spines with high resistance necks experience larger calcium transients during synaptic activity.

Development

Dendritic spines are believed to develop from filopodia. During synaptogenesis, dendrites rapidly sprout and retract filopodia, small membrane organelle-lacking membranous protrusions. During the first week of birth, the brain is predominated by filopodia, which eventually develop synapses. However, after this first week, filopodia are replaced by spiny dendrites but also small, stubby spines that protrude from spiny dendrites. In the development of certain filopodia into spines, filopedia recruit presynaptic contact to the dendrite, which encourages the production of spines to handle specialized postsynaptic contact with the presynaptic protrusions.

Spines, however, require maturation after formation. Immature spines have impaired signaling capabilities, and typically lack "heads" (or have very small heads), only necks, while matured spines maintain both heads and necks.

Pathology

Cognitive disorders such as ADHD, autism, mental retardation, and Fragile X Syndrome, may be resultant from abnormalities in dendritic spines, especially the number of spines and their maturity. The ratio of matured to immature spines is important in their signaling, as immature spines have impaired synaptic signaling. Fragile X Syndrome is characterized by an overabundance of immature spines that have multiple filopodia in cortical dendrites.