Chapter 6: a complex organism – the neuron

background reading

Bray, D. (2009), *Wetware*, Yale University Press, New Haven, CT.

Dawkins, R. (2005), *The Ancestor's Tale: a pilgrimage to the dawn of life*, Phoenix, London.

Fortey, R. (1997), *Life: an unauthorised biography*, HarperCollins, London.

Gee, H. (2021*), A (very) Short History of Life on Earth: 4.6 billion years in 12 chapters*, Picador, London.

Morowitz, H. (2002), *The Emergence of Everything: how the world became complex*, Oxford University Press, New York.

Thompson, R. (2000), *The Brain: a neuroscience primer*, Worth Publishers, New York, 3rd edition.

notes

Constructive comments are welcome.

"***make weapons, catch food***", Cudmore 1977:13.

"***a whole range of ways of life***", Tudge 2006:68.

"**In level 6, individual generalist cells**", it took less time for single cells to evolve than for them to come together to make multicellular organisms. Bacterial life was well established on earth by 3.5 billion years ago, within about 1 billion years of the earth's formation (Baggott 2015:247). But it took more than 2 billion years of further evolution for these independent cells to be able to work together to make multicellular organisms (Baggott 2015:figure 75, p. 266).

Less than 1 billion years ago, some organisms started to consume other living organisms, and the biological world acquired predators and prey (Baggott 2015:figure 75, p. 266). The earliest fossils of soft-bodied, multicellular animals date from around 600 million years ago, though molecule DNA analysis indicates an earlier origin (Campbell 2015:732). These fossils provide the earliest evidence of the existence of predators and prey. Some species had protective shells, which in themselves are evidence of predation, and some shells have holes in them, suggesting a predator drilled through to gain access to the soft-bodied organism inside.

For modern accounts of the evolution of life see, for example, Fortey 1997, Margulis 1997, Dawkins 2005, Jastrow 2008, Kaplan 2010, Baggott 2015.

6.1 the emergence of multicellularity

6.1.1 choanoflagellates

"**Choanoflagellates are small aquatic organisms**", Morris 2013:27-10 and 28-7, Dayel 2011.

Choanoflagellates appear to be the closest living relatives of animals (Campbell 2015:732). Many genes once thought to be unique features of animals have been found in choanoflagellates (Morris 2013:27-11).

"**However, when they detect prey bacteria**", choanoflagellates only form colonies when they encounter a select range of species of bacteria (Yong 2016:58, Morris 2013:28-7). These bacteria secrete specific molecules, and when the choanoflagellates detect these molecules they come together in predatory colonies.

6.1.2 green algae

"**Aquatic green algae**", Boraas 1998, Morris 2013:28-2. Algae are a large and diverse group of eukaryotic organisms that contain chlorophyll and photosynthesise, producing oxygen (Madigan 2003:492). Most algae are tiny micro-organisms, but some are large, such as seaweeds that can grow to 30 metres long. Algae are quite distinct from cyanobacteria, which also photosynthesise, but are prokaryotes.

"**For example, within 20 generations**", Boraas 1998.

"**The alga *Chlamydomonas***", Herron 2019.

"***One way to avoid such mortality***", Boraas 1998:160.

"**Similar behaviour has been observed**", Herron 2019.

Figure 6.1(a) is from https://vcresearch.berkeley.edu/news/did-bacteria-spark-evolution-multicellular-life, courtesy of Dr. Mark Dayel, and with kind permission from Professor Nicole King, University of California, Berkeley.

Figure 6.1(b) is Herron 2019: figure 1, with approximate scale bars added.

Figure 6.1(c)-left: the microscope image is from http://cfb.unh.edu/phycokey/Choices/Cyanobacteria/cyano_filaments/cyano_unbranched_fil/untapered_filaments/heterocysts/no_visible_sheath/ANABAENA/Anabaena_Image_page.html .

This image is from Baker, A.L. et al. 2012. Phycokey -- an image based key to Algae (PS Protista), Cyanobacteria, and other aquatic objects. University of New Hampshire Center for Freshwater Biology, at http://cfb.unh.edu/phycokey/phycokey.htm.

Figure 6.1(c)-right is based on Madigan 2003:figure 12.80, Alberts 2008:figure 1-19, and Claessen 2014:figures 1 and 3.

Figure 6.1(d)-left: the SEM composite view of the slime mould life cycle is from http://dictybase.org/Multimedia/LarryBlanton/index.html and is also used in Phillips 2013:figure 2.37.

The image is copyright M. J. Grimson and R. L. Blanton, Biological Sciences Electron Microscopy Library, Texas Tech University. The labels, timings, scale bar, and the dashed line showing the sequence of stages have been added to the original image. The description of the way the cell ensembles were positioned is from Professor Blanton.

Timings in the slime mould cycle are from https://file.biolab.si/biolab/supp/bi-visprog/dicty/dictyExample-2.html. Different sources give different scales, and the scale bar is based on http://www.uni-koeln.de/med-fak/biochemie/cellular_homeostasis/02_organism.shtml, which makes the fruiting body about 1.5 mm high, in agreement with Madigan 2003:figure 14.25.

Figure 6.1(d)-right: the optical microscope view is courtesy of Dr. Fernando Rossine, Harvard Medical School, and Professor Corina Tarnita, Princeton University. The image has been cropped, and a scale bar has been added to give some idea of the height of the slime mould growths.

6.1.3 cyanobacteria – anabaena

"**Cyanobacteria are photosynthetic organisms**", this section is based on Bonner 1998:34, Madigan 2003:section12.25, Claessen 2014.

It's likely that these were the first photosynthesising organisms on earth, evolving about 2.5 billion years ago, and produced the first atmospheric oxygen (Madigan 2003:421, Claessen 2014:120). Atmospheric oxygen has built up in two stages, first, from about 2-15% around 2.3 billion years ago, and second, from about 15% to the present value around 600 million years ago (Morris 2013:figure 28.14). The maximum sizes of organisms increased over this time, largely in line with the atmospheric oxygen level (Phillips 2013:figure 18.29).

See Alberts 2008:69 and 843 on photosynthesis, and Madigan 2003:sections 12.25 and 17.28 on nitrogen fixation.

"**However, the bacteria**", Bonner 1998:34.

"**The heterocysts export their glutamine**", Madigan 2003:figure 12.80, Claessen 2014:Box 1.

"**To do this**", Bonner 1998:35.

"**Specialisation can also terminate**", Claessen 2014:120.

"***differentiated cell types***", Claessen 2014.

6.1.4 slime moulds

This section is based on Bonner 1998, Purves 1998:565, Morris 2013:27-12, Madigan 2003:491, Campbell 2008:595, Phillips 2013:75, Fuller-Wright 2020, and Rossine 2020.

"***Dictyostelium discoideum***", these are different to the acellular slime moulds, which form a plasmodium – a large number of nuclei in a "pool" of cytoplasm, all enclosed within a single membrane (Campbell 2008:594, Madigan 2003:490, Purves 1998:565).

The cellular slime mould life cycle is shown in Campbell 2008:figure 28.25 and in Madigan 2003:figure 14.25.

"***appear to be poised***", Phillips 2013:75.

"**In the absence of food**", Madigan 2003:491, Purves 1998:566.

Cyclic AMP is also known as acrasin (Purves 1998:835), and its structure is shown in Alberts 2008:117. Cyclic AMP acts as an intra-cellular signal molecule in all prokaryotic and animal cells that have been studied, and plays a part in altering the transcription of a cell's DNA (Alberts 2008:905−909). It's classed as a second messenger because it is the intra-cellular response to the arrival of of an extra-cellular first messenger, such as a hormone (Garrett 2005:1053, Purves 1998:835). The normal concentration of cyclic AMP in the cell's cytoplasm is ~10^{-7} M, but this can increase by a factor of more than 20 in a few seconds, when the cell detects an extra-cellular signal molecule (Alberts 2008:905).

"**Individual cells migrate**", Phillips 2013:figure 2.38.

"**Each of these spores**", Phillips 2013:75.

"***remain poised to respond***", Phillips 2013:76.

"**However, a small fraction**", in wild slime mould populations, as many as 30% of cells can behave as loners (Fuller-Wright 2020).

"***a bet-hedging strategy***", Fuller-Wright 2020.

"***seemingly asocial loners***", Rossine 2020:12.

"***the decision not to become part***", Rossine in Fuller-Wright 2020.

"***soil-dwelling amoeba***", Phillips 2013:75.

6.1.5 three requirements for complex multicellularity

"**The key to multicellularity**", Morowitz 2002:98. Alberts outlines the universal mechanisms of animal development (Alberts 2008:chapter 22).

"**The organism's genome**", Purves 1998:628.

"***the butterfly genome***", Morowitz 2002:92.

"**The simple examples**", Morris 2013:28-6, Phillips 2013:76.

"***simply cannot survive on their own***", Baggott 2015:261.

6.2 the principles of cell signalling

bacterial cells are elective collaborators

"***sniff out nutrients***", Alberts 1998a:481.

"**Each cell can also signal**", Bassler 2010, Diggle 2008, Madigan 2003:224 and 381, Waters 2005, Williams 2007.

"**Through quorum sensing**", Crespi 2001, Diggle 2008, Kolter 2006, Williams 2007.

"**For example, pathogenesis**", Bassler 2010.

"**This enables bacteria**", Waters 2005:332.

the cells of a multicellular organism are obligate cooperators

6.2.1 cells communicate by transferring signal molecules

This section is based on Campbell 2008:chapter 11 and section 45.1, Morris 2013:chapter 9 and section 38.4, Purves 1998:chapter 38, Purves 2019:chapter 7, Alberts 1998a:chapter15, and Alberts 2008:chapters 15 and 18.

"***any busy community***", Alberts 1998a:481.

"**We communicate**", when we're at an early stage of learning to use language, around 1-2 years old, we communicate quite effectively with one-word sentences, known as holophrases (Crystal 2010:chapter 41).

"***communicate by means of***", Alberts 2008:880.

"**A signalling cell**", Alberts 1998a:482, Morris 2013:9-2 and 28-7.

In a cellular "conversation", cell 1 releases signal molecule A for which cell 2 has receptors, which signifies that molecule A has "meaning" for cell 2. Similarly, if cell 2 "replies" with molecule B, then this must have meaning for cell 1. Each cell must release a signal molecule that the other can relate to, so each cell must "know" what's going on inside the other cell. The two cells only have their molecular conversation if they both benefit from the exchange, hence "*relevant signals are those that are adaptive for the signaller to perform and for the receiver to respond to*" (Scott-Phillips 2008:392). This seems to be a molecular precursor of a human conversation, described in section 8.2.6, which can only be meaningful when each person says things that the other can relate to.

"**This molecular means of communication**", this is stated as being "*universal among both prokaryotes and eukaryotes*", Morris 2013:9-2.

6.2.2 a target cell responds to a molecular signal

Figure 6.2 is based on Alberts 2008:figures 15-1 and 15-4B, Purves 1998:figures 38.1a and 38.16, Campbell 2015:figures 9.5, 9.6 and 9.15.

"**When the vesicles merge**", this is known as exocytosis, and is commonly used to release molecules from cells (Alberts 2008:799). Synaptic vesicles play an important part in nerve function (Alberts 2008:808).

"**The target cell has the genetic information**", this is a highly condensed summary of gene expression. For a full account, see Alberts 2008:chapter 6, with a summary in figure 6-97, and Campbell 2015:chapter 17, with a summary in figure 17.24.

"**It's sufficient to think of the RNA molecule**", Alberts 2008:4. This is, in fact, messenger RNA, or mRNA.

"**The binding of molecule A**", Campbell 2015:219. Molecule A is known as a first messenger, while molecules D and E are known as second messengers (Alberts 2008:893).

"**The faster the turnover**", Alberts 2008:886 and figure 15-11.

6.2.3 different cells respond differently to the same signal molecule

Figure 6.3 is based on Alberts 2008:figure 15-9. The acetylcholine receptors are different on heart and skeletal muscle cells, but this is not the full explanation for these cells' different responses, and so they have been shown with the same receptors (Alberts 2008:885). These eukaryotic cells are shown with nuclei, but no other internal components.

"**A heart muscle cell**", Kandel 2021:250.

"**In another example**", Campbell 2008:221, Purves 1998:834. This is a striking example of the power and sophistication of the signalling process. The binding of a single epinephrine molecule leads to a signal pathway with six intermediate molecules, which amplify the signal step by step, resulting in the breakdown of 100 million glycogen molecules (Campbell 2008:figure 11.15).

"***has little information content***", Alberts 2008:886.

6.2.4 cells integrate multiple signals

Figure 6.4 is based on Alberts 2008:figure 15-8.

"**Each cell in a complex organism**", Alberts 2008:884.

"**The cell receives**", Alberts 2008:884.

6.2.5 apoptosis – cells need constant signals to stay alive

"***specialized members***", Alberts 1998a:582.

"**In each of these normal, routine cell deaths**", this raises the question as to whether a cell that is a component of an organism, with the same DNA as all the other cells, can "die" (Campbell 2008:223). The cell can't survive as a free individual, and only continues to exist within the organism by receiving constant survival signals. Nevertheless, the cell has a physical and metabolic presence in the organism, and these can be terminated by other cells in the organism.

In many multicellular organisms, cell division and replacement continues throughout the organism's lifetime, but varies very much with cell type (Alberts 1998a:547). In adult humans nerve and muscle cells do not divide, liver cells divide around once a year, and some cells in the intestine divide more than once each day. Each individual must make many millions of new cells every second just to survive.

"***activates a suicide program***", Alberts 2008:884.

"**The term "apoptosis""**", Alberts 2008:1115, Campbell 2008:223, Lodish 2000:1045.

"**Most, possibly all, animal cells**", Lodish 2000:1044.

"**This might seem surprising**", Alberts 2008:1126, Lodish 2000:1044.

"**Typically, the dying cell shrinks**", Lodish 2000:figure 23-45.

"***the cell dies neatly***", Alberts 2008:1115.

"***programmed cell death***", Alberts 1998a:587.

"**Programmed cell death shapes the hands**", Alberts 2008:1116, Campbell 2008:figure 11.21.

"**Similarly, more than half**", Alberts 2008:1126, and figure 18-13,. During the development of the human embryo half of the neurons are eliminated, and by the end of gestation, these neurons have lost half of their initial synapses (Campbell 2008:1078). After birth, the brain gets larger because of the growth of dendrites, axons and synapses on the existing neurons, and not because of an increase in the number of neurons (Purves 2019:542).

"**Generally, in a developing organism**", Alberts 2008:1116.

"**Programmed cell death continues to work**", Baggott 2015:264. Alberts (2008:1115) states that billions of cells in the intestines and bone marrow "die" every hour.

"***are part of the normal "social" controls***", Alberts 2008:1126.

6.2.6 local – paracrine signalling

"**This is known as paracrine signalling**", Campbell 2008:976.

paracrine signalling is fast but local

"**Paracrine signalling**", Morris 2013:9-4.

"**For example**", Morris 2013:9-4.

"**Another example**" Purves 1998:833, Morris 2013:38-17.

6.2.7 long distance signalling – the endocrine system and the neuron

Figure 6.5(a) is based on Alberts 2008:figures 15-4D and 15-5A, Morris 2013:figure 38.13a, and Campbell 2008:figures 11.5c and 40.6; **part (b)** is based on Alberts 2008:figures 15-4C and 15-5B, Morris 2013:figures 35.13 (synapse) and 38.13b, and Campbell 2008:figures 11.5b and 40.6.

"**Large organisms**", Alberts 2008:881.

"**This is endocrine signalling**", (Morris 2013:9-3 and chapter 38,). The origin of the word "hormone" is from Campbell 2008:975.

"**Endocrine signalling**", Campbell 2008:859.

"**Endocrine signalling with hormones**", Campbell 2008:976.

"**Another example is the hormone**", Morris 2013:9-4.

"***long-distance electrical signals***", Campbell 2008:1047.

"**Thus neural, or synaptic signalling**", Morris describes neural communication as a specialised form of paracrine signalling (Morris 2013:9-4).

Kandel likens synaptic transmission to endocrine hormone release, but with the difference that it is fast and precisely directed (Kandel 2021:249).

"**Neurons are specialised**", Morris 2013:38-17.

"**Paracrine signalling**", quotes are from Alberts 1998a:481.

6.3 the neuron

sponges – multicellular animals with no neurons

"**Sponges are about the simplest**", Kaplan 2010:93, Purves 1998:631, Dawkins 2005:Rendezvous 31, Lentz 1968:chapter 2, Renard 2009, Margulis 1998:A-2.

"**These cells spontaneously organise themselves**", Purves 1998:632, Dawkins 2005:500.

"**Sponges have no nervous system**", Renard 2009, Purves 2019:chapter 6.

"**Using simple molecular signalling**", the molecule glutamate (the active part of the well-known food additive monosodium glutamate) will induce contractions in a sponge, and these can be so violent, by sponge standards, that they can tear the sponge apart (Wilkinson 2016:178).

"**So, sponges can feed**", Lentz 1968:18, Purves 1998:632.

"**If a sponge is cut**", Lentz 1968:7.

"**So, the different cells in a sponge**", it appears that "*sponges have many of the basic components of a functioning neuromuscular system: contractile cells that respond to applied chemicals as muscles respond to neurotransmitters, and sensory cells that presumably release such chemicals when stimulated. The only bits that sponges are missing are the nerves themselves and the attendant electrical signalling*" (Wilkinson 2016:178). In short, a sponge shows us what a "*pre-nervous animal*" looks like (Wilkinson 2016:176).

mobile animals need neurons

"**The marine sea squirt**", Margulis 1998:A-35, Greenfield 1997:34.

And in an elongated, worm-like body that moves in one direction – forwards – the important sensory information comes to the front end, and so the neural circuitry concentrates there, and later evolves into the brain (Wilkinson 2016:188).

"**We can organise**", Morowitz 2002:93.

"***plants and fungi get their food***", Morowitz 2002:108.

"**The lifestyles of animals**", Morowitz 2002:chapter 16, Purves 1998:628.

"**This requires detailed information**", Margulis 1998:207.

the evolution of the neuron

"***large and responsive animal***", Morowitz 2002:99.

"***among the most ancient***", Alberts 2008:1383.

"**appeared around 700 million years ago**", Morowitz 2002:101.

"***from jellyfish to humans***", Thompson 2000:8, and also see Purves 1998:905.

"***no fundamental functional or biochemical differences***", Kandel 2001:567.

"***more neurons put together***", Thompson 2000:8.

"***a cell type***", Morowitz 2002:106.

"***a switching station***", Morowitz 2002:100.

6.3.1 the basic neuron

"***it is born***", Thompson 2000:29.

"***probably the most fastidious cells***" and "***rely almost entirely***", Alberts 2008:102.

"**Unlike other cells**", Thompson 2000:122.

"**The neuron is a "go-between""**, Alberts 2008:675. Glial cells are an important component of the nervous system, and support neuron function (Kandel 2021:63 and 151, Purves 1998:906). We can understand the basic features of neuron function without glial cells, and so they are omitted here.

"**The average neuron**", Kandel 2021:241.

"**The human brain**", Purves (1998:907) gives a range of 1−100 billion, but a more modern estimate seems to be 80−90 billion (Herculano-Houzel 2012).

"**But each neuron**", Bray 2009:211, Purves 1998:907. Kandel (2021:241) states that "*the average neuron forms several thousand synaptic connections and receives a similar number of inputs*".

"**Neurons range in length**", Alberts 2008:1049 and 1383.

"**A neuron relays a signal**", Kandel 2021:64.

"**In general, the signal is transmitted**", Phillips 2013:682.

"**Figure 6.6(b) shows the two major features**", Kandel 2021:131 and 133.

"***a high degree of morphological***", Kandel 2021:133.

"***electrically and chemically excitable***", Kandel 2021:133.

"**There are three basic types of neuron**", Kandel 2021:59, Morris 2013:35-2, Campell 2008:1048. There are hundreds of distinct types of neurons, but almost all carry out the four major functions, as represented by the model neuron in part (b) (Kandel 2021:133).

"**The vast majority of neurons**", Campbell 2008:1048, Kandel 2021:61.

The average human body has a complement of about 100 billion (10^{11}) neurons, but out of this vast number, only about 5 million (or 1 in 20,000) carry information from the various sense organs to the central nervous system, and only a few hundred thousand (or 1 in 200,000) carry information from the central nervous system to the various muscles (Wills 1994:262). These are known as peripheral neurons, because they lie outside the brain and spinal cord. The vast majority of neurons are inter-neurons, and they "*form the connecting links between the world we perceive and the world we act on*" (Wills 1994:262). The ratio of inter-neurons to peripheral neurons reveals the remarkable evolution of the human brain. The average rat has only about 20 inter-neurons for every peripheral neuron, but for the average human, the ratio is about 20,000.

From this, one might infer that neurons are more densely packed in a human brain, compered to other animals, but the reverse is true (Wills 1994:262). The cortex of a rat's brain has about 100,000 neurons in each cubic millimetre, while a human cortex has only about 10,000. Human neurons are less densely packed because each neuron has more dendrites and a more branched axon. The result is that human neurons can make contact with 10−100 times as many neurons as rat neurons. So, a human brain has a huge number of highly inter-connected neurons and a very large ratio of inter-neurons to peripheral neurons, and these factors give humans their ability to manipulate and compare complex information.

See also the reference to inter-neurons in the note to section 7.1.1.

"**A sensory neuron**", Campbell 2008:1048.

"**Motor neurons bring about**", Morris 2013:35-2.

"***rapid electrical transmission***", Phillips 2013:681.

"***provide the brain with data***", Kandel 2021:61.

"***sensory information***", Campbell 2008:1047.

Figure 6.6(b) is based on Kandel 2021:figures 3-1 and 3-8, Campbell 2008:figure 48.5, Phillips 2013:figure 17.1, Morris 2013:figure 35.4, Purves 1998:figure 41.3, and Purves 2013:figure A.1.

The model neuron in **part (b)** is drawn from Campbell 2008:figure 48.6. The sensory neuron in **part (d)** is drawn from Kandel 2021:figures 3-8 and 18-8, and Purves 2019:figure 9.5. The motor neuron in **part (e)** is drawn from Kandel 2021:figure 3-8.

"***never function in isolation***", Purves 2019:10.

"***synapses are constantly being created***", Alberts 2008:1050.

6.3.2 neurons have high investment and running costs

"**A nervous system**", Purves 2019:1, Kandel 2021:29.

"**A person's brain**", Attwell 2001, Thompson 2000:122, Roth 2005, Herculano-Houzel 2012.

A vertebrate animal typically uses 2−8 % of its resting energy intake to power its central nervous system, but for adult humans the figure is about 20%, and is over 50% for children less than 4 years old (Laughlin 2003: 1872, Hofman 1983:499 −500).

"**As much as two thirds**", Attwell 2001:1139, Purves 2019:74.

"**In fact, actively signalling neurons**", Attwell 2001:1143.

the energy costs of firing an action potential

"**A neuron has a vastly greater demand**", Lennie 2003:493 and figure 1.

6.3.3 the resting potential

"**A neuron is always in a state**", there are concentration imbalances in all of the physiologically important ions: sodium, Na^+, potassium, K^+, chloride, Cl^-, calcium, Ca^{2+} and hydrogen, H^+ (Purves 2019:72).

"**The Na+/K+ pump**", the Na^+/K^+ pump moves 3 Na^+ ions out of the cell for every 2 K^+ ions moved in, and this leaves the cell with an internal deficit of positive electric charge, so the inside of the membrane is slightly negatively charged with respect to the outside (Phillips 2013:692, Kandel 2021:195). However, it is the movements of ions across the membrane that produce the large, transient polarisations that enable the neuron to function.

"**The cell's membrane**", organisms make use of a large "toolkit" of ion channels, and more than 200 specific genes for different ion channels have been identified, and humans alone have 10 Na^+ channel genes (Purves 2019:68-69).

Figure 6.7 is based on Campbell 2008:figures 48.6 and 48.7, Morris 2013:figure 35.8, Phillips 2013:figure 17.9, and Purves 1998:figures 41.6-8. The figure shows a simple, schematic view of the Na^+/K^+ pump, and a more detailed view is shown in Purves 2019:figures 4.10 and 4.12.

The Na^+/K^+ pump maintains a low internal Na^+ ion concentration, about $1/10^{th}$ of the external concentration, and a high internal K^+ ion concentration, about 20 times the external concentration (Kandel 2021:65). The bare Na^+ ion is smaller than a bare K^+ ion, but its smaller size gives it a stronger electric field, which attracts a bigger "cloud" of polar water molecules (Kandel 2021:169 and 222, and figure 8-1). The K^+ channel is wide enough to let K^+ ions through, but too narrow for Na^+ ions.

"**The movement of K+ ions**", Campbell 2008:1051, Purves 2019:39.

"**When the inside of the cell**", an ion's equilibrium potential is given by the Nernst equation (Campbell 2008:1051, Phillips 2013:684, Purves 2019:39, Kandel 2021:194).

"***electrochemical equilibrium***", Purves 2019:39.

"**This is the equilibrium potential**", a neuron's membrane potential is the difference between the inside and outside potentials, and since the outside potential is defined as zero, the membrane potential is simply the inside potential (Kandel 2021:191).

"**The number of K^+ ions**", Purves 2019:39.

"**With only the Na^+ ion channels open**", the values for the K^+ and Na^+ potentials are from Campbell 2008:1051.

"***tune its membrane electrical potential***", Phillips 2013:683.

"**When the neuron is in its inactive, resting state**", Morris 2013:35-7. Neuron resting potentials range from −40 to −85 mV, and are commonly between −60 and −70 mV, and so this value is used here (Morris 2013:35-7, Kandel 2021:191).

"***steady state***", Kandel 2021:195.

"**The ions of these two metals**", Phillips 2013:686.

"***cautious interplay***" and "***Thought is the most***", both from Atkins 1995:14.

6.3.4 the action potential

"**All animal cells carry membrane potentials**", Morris 2013:35-7.

"**This might seem to be a very small potential difference**", Alberts 2008:681.

"**The K^+ and Na^+ ion channels**", Purves 2019:figures 4.3 and 4.5.

"**If we apply a weak electrical pulse**", Phillips 2013, figure 17.23.

"**These channels let in a flood of Na^+ ions**", a single Na^+ ion channel allows more than 1,000 ions to pass through in 1 millisecond (Alberts

2008:681).

"**Once the membrane potential returns**", Kandel 2021:220).

"**It also takes some time**", Kandel 2021:220.

"**This "dead time" is known**", Morris 2013:35-8.

Figure 6.8(a) is based on Alberts 2008:figure 11-29, Campbell 2008:figure 48.10, Kandel 2021:219, Morris 2013:figure 35.9, Phillips 2013:figure 17.23, Purves 1998:figure 41.9, and Purves 2019:figure 4.3. In **part (b)**, the time sequence of the operation of the Na^+ and K^+ channels is based on Kandel 2021:figure 10-7.

This figure shows the action potential as it is commonly represented, but different cells in different animals show a range of action potentials (Phillips 2013:figure 17.3).

"***gradually store energy***", Purves 2019:73.

"**In 1 second, a single ion channel**", single channel flow rates are 10^7-10^8 ions/second, while pumps "*operate at speeds more than 10,000 times slower*" (Kandel 2021:195).

"**They open more slowly**", Kandel 2021:figure 10-7, Phillips 2013:711.

"**This is an action potential**", Alberts 2008:676, Campbell 2008:103, Morris 2013:35-8, Purves 1998:912.

"**But this is not the case**", Morris 2013:35-8, Purves 1998:912.

"**It is the neuron's refractory period**", Morris 2013:35-8.

6.3.5 transmitting the action potential

Figure 6.9 is based on Campbell 2008:figure 48.11, Morris 2013:figures 35.10 and 35.11, Purves 1998:figure 41.10, and Purves 2019:figure 3.10. The length of the sections of myelin sheath is from Kandel 2021:207.

"**The result is**", Purves 2019:57.

"**For example, each of our eyes**", Purves 1998:914.

"**Neurons have evolved**", Purves 1998:910, Purves 2019:57 and figures 3.11-12.

"**A myelinated axon**", the sections of myelin sheath are 1–2 mm long, separated by gaps ~1 µm (0.001 mm) wide (Kandel 2021:207).

"**Instead of action potentials travelling**", Campbell 2008:figures 48.12-13, Morris 2013:figure 35.11.

"**Myelination greatly speeds up signal transmission**", Purves 2019:table 3.1.

"**There are situations**", Purves 1998:915.

6.3.6 the synapse

"**So we come to the synapse**", there are two types of synapse, chemical and electrical synapses, with chemical synapses being much more common (Campbell 2008:1057, Morris 2013:35-12, Purves 2019:80, Kandel 2021:241). In this section I'll look only at chemical synapses.

Electrical synapses allow electric current to flow directly from one neuron to another, and are used mainly to send "*rapid and stereotyped depolarizing signals*" (Kandel 2021:241). So, these synapses synchronise the activities of neurons responsible for rapid, unvarying behaviours, such as escape responses in squid, lobsters and crayfish.

In contrast, chemical synapses function by the transfer of neurotransmitter molecules, and so they are slower, but they are capable of variable signalling, and so can enable more complex interactions, and this is the basis for an organism to remember and learn, and respond to change.

"**The figure shows the cycle**", Alberts 2008:684.

"**Only one axon terminal**", Purves 1998:916.

"**The neurotransmitter for all**", Purves 1998:916.

Figure 6.10 is based on Alberts 2008:687 and figures 11-39 and 13-73, Campbell 2008:figure 48.15, Morris 2013:figure 35.13, Phillips 2013:695 and figure 17.10, Purves 1998:figures 41.14-15, Purves 2013:figure A.3, Purves 2019:figures 5.4, 5.8 and 6.2, and Kandel 2021:260 and figure 12-1.

The mean opening time for a Na^+ ion channel is ~1 ms, and in this time it lets ~17,000 ions into the muscle cell (Kandel 2021:260).

"**The neuron synthesises**", acetylcholine is synthesised from acetyl coenzyme A (acetyl CoA) and choline. The neuron makes its own acetyl CoA, from glucose, but can't make choline, so this is obtained from foods, such as egg yolks and vegetables, and is imported into the neuron by specific ACh channels (Thompson 2000:121, Purves 2019:107).

"**The synaptic cleft**", Phillips 2013:129 estimates about 4 µs for ACh. In comparison, glucose, which is a smaller molecule, will diffuse 10 nm in about 0.2 µs, so it will diffuse 20 nm in about 1 µs – see figure 5.5.

"**In step 4 the acetylcholine molecules**", the ACh channel needs 2 ACh molecules to bind to it for it to open (Alberts 2008:685, Kandel 2021:figure 12-10). To keep the diagram simple, I'm showing it opening with only 1 ACh molecule.

The ion channels allow both Na^+ and K^+ ions to pass through. This might seem a self-cancelling action, but we must remember that the rate of flow of ions is a balance between their concentration gradient and their voltage gradient. Both types of ions are moving with their concentration gradients, but the Na^+ ions are moving with their electric charge gradient, while the K^+ ions are moving against it. So, when the ion channels open, a large number of Na^+ ions flow in, while few K^+ ions flow out. The figure shows only the Na^+ ions (Alberts 2008:685).

"**These Na+ ions depolarise**", Alberts 2008:686, Phillips 2013:695.

"**Finally, in step 9**", because the neuron can't make its own choline, this is recycled, while the neuron makes the acetyl CoA part afresh. For simplicity, the diagram shows each ACh molecule split into 2 similar parts, which both diffuse back into the neuron, where they spontaneously come together, and enter a new vesicle.

"**Within this time**", each vesicle is about 50 nm across, and contains about 10,000 acetylcholine molecules, and a single action potential releases about 100 vesicles, and this is enough to stimulate a muscle fibre to twitch (Purves 1998:917, Purves 2019:83 and 87).

The acetylcholine is normally hydrolysed by the acetylcholinesterase (AchE) and removed from the ion channels within about 1 millisecond (Alberts 2008:685). The complete synaptic vesicle cycle, from fusion with the membrane to being re-formed and stocked with acetylcholine molecules, takes about a minute (Purves 2019:89). In the case of the frog, an axon terminal has about 300,000 vesicles, and there are about 2,000 acetylcholine receptors in the muscle endplate (https://en.wikipedia.org/wiki/Neuromuscular_junction). This provides a reservoir for very many action potentials, maybe as many as 300,000/100 = 3,000 action potentials. There are about 20,000 acetylcholine receptors in each 1 μm^2

of the muscle cell membrane at the synapse (Alberts 2008:685).

Alberts gives a peak rate of 30,000 Na^+ ions in 1 millisecond (Alberts 2008:686), and Kandel gives a figure of 17,000 (Kandel 2021:260). I've given a value of 20,000 in the figure.

Acetylcholinesterase is a fast-acting enzyme, and each molecule can break up about 5,000 acetylcholine molecules per second, back to actetate and choline (Purves 2019:107).

"**But this is not the case**", Kandel 2021:333 and 355. Kandel describes events at a synapse in terms of quantal units of neurotransmitter, with a quantum corresponding to the contents of a single synaptic vesicle.

6.3.7 summing inputs

"**Neurons use a wide range**", Campbell 2008:1058, Morris 2013:35-13, Purves 1998:918, and Purves 2019:100. The action of acetylcholine is always to depolarise the post-synaptic neuron (Purves 1998:918).

"**Depolarising the post-synaptic neuron**", in the technical literature a depolarisation is called an excitatory post-synaptic potential, EPSP, and a hyper-polarisation is called an inhibitory post-synaptic potential, IPSP. I'll avoid these long terms and tricky acronyms, and just refer to excitatory and inhibitory synapses.

Figure 6.11 is based on Campbell 2008:figure 48.16, Morris 2013:figure 35.15, Purves 1998:figure 41.16, and Purves 2019:figure 5.20.

"**Hence neurons have both**", Morris 2013:35-13.

"**Whether a synapse is excitatory or inhibitory**", Kandel 2021:274.

"***the same neurotransmitter***", Purves 1998:919. For example, acetylcholine excites skeletal muscle cells, but inhibits cardiac muscle cells in the heart (Thompson 2000: 123).

"***transmit relevant information***", Morris 2013:35-13.

"***interplay between multiple excitatory***", Campbell 2008:1058.

"**A neuron may have more than 1,000 inputs**", Purves 1998:919, Alberts 2008:688.

6.3.8 graded signals

"***digital bit***", Phillips 2013:711.

"***in a succession of jerks***", Adrian 1932.

"**However, within this constraint**", Morris 2013:35-8.

"**This enables neurons**", encoding is the process by which "*features of a stimulus are represented by neural activity*" (Kandel 2021:98).

"**The neuron has a stretch receptor**", Kandel 2012:figure 18-9. Most receptor potentials are depolarising, and so they are excitatory. Hyper-polarising (inhibitory) receptor potentials are found in the retina (Kandel 2021:65).

"***louder sounds are reflected***", Campbell 2008:1053.

"**Most neurons**", Morris 2013:35-8, Campbell 2008:1053, Alberts 2008:689 and figure 11-41, and Phillips 2013:711 and figure 17.22.

"***code information***", Morris 2013:35-8.

"**Typically, a faster firing rate**", Campbell 2008:1053, Morris 2013:35-8.

"***all the information contained***", Purves 1998:919.

"**Some neurons are spontaneously active**", Kandel 2021:68.

"**The two types of input**", Kandel 2021:68, Phillips 2013:figure 17.22.

Figure 6.12 is based on Kandel 2021:65 and figures 3-9 and 18-9.

a diminishing response to prolonged stimulation

"***a neuron that is stimulated***", Alberts 2008:690.

"***to react sensitively to change***", Alberts 2008:690.

6.4 neural circuits

"***are very much alike***", Edgar Adrian, quoted in Kandel 2021:67.

"***essentially indistinguishable***", Phillips 2013:711.

"***carried into the nervous system***", Kandel 2021:67.

"***carry the rich variety***", Kandel 2021:68.

"***The answer is simple***", Kandel 2021:68.

"***the message of an action potential***", Kandel 2000:31.

"***the neurons divided***", Thompson 2000:31.

6.4.1 the knee-jerk reflex circuit

This section is based on Campbell 2008:1066, Purves 1998:923, Purves 2019:10, Morris 2013:35-18, and Kandel 2021:62.

"***Neurons never function in isolation***", and "***integrate and relay information***", Purves 2019:10 and 5.

"**We walk on two legs**", Morris 2013:35-19, Kandel 2021:62.

"**This is handled**", the knee-jerk reflex is formally known as the myotatic reflex (Purves 2019:10). The wrist, elbow and ankle also show similar reflexes (Purves 1998:923).

"**The inter-neuron**", Purves 1998:922.

"**However, the inter-neuron has an inhibitory synapse**", whether a synapse is excitatory or inhibitory doesn't depend on the type of neurotransmitter molecule, but on the type of ion channels in the post-synaptic cell (Kandel 2021:274).

Figure 6.13(a) is based on Campbell 2008:figure 49.3, Kandel 2021:figures 3-5 and 13-1, Morris 2013:figure 35.20, Purves 1998:figure 41.19, and Purves 2019:figures 1.7-9; **part (b)** is based on Purves 2019:figures 1.8 and 1.9. The depiction of the leg is drawn from Purves 2019:figure 1.7.

"**The reflex circuit shown in figure 6.13**", Kandel 2021:63.

"***protects the body***", Campbell 2008:1066.

6.5 Neural plasticity – learning and memory

"**So, we could expect**", in this section I focus on a two specific forms of learning, which are based on synaptic plasticity. These are (1) habituation, which is an example of non-associative learning, and (2) classical conditioning, which is an example of associative learning. These specific cognitive functions are found within the system of learning and memory, which is summarised below.

learning and memory

There are several forms of learning and memory, and they use different neural mechanisms, in different parts of the brain (Thompson 2000:figure 11.8 and chapter 11, Purves 2013:figure 8.1 and chapter 8, Purves 2019:figure 30.1 and chapter 30, Kandel 2021:1292 and 1312, figures 52-5 and 53-1, and chapter 53, and Lieberman 2000:section 1.6).

Memory is first divided into two major types, according to how long the information is retained (Purves 2013:248 and Purves 2019:647). The first type is **short-term**, or working memory, which retains information for a few minutes at most, for example, a string of random numbers. The second type is **long-term memory**, which can last a lifetime, and this is divided into two types, according to how it is expressed.

The first type is explicit, or **declarative** memory, which holds "*memories we can be aware of and describe*" (Thompson 2000:366, and quote from p. 392). We use this to consciously recall and describe either events (**episodic** memory), such as what we had for breakfast, and our most recent conversation with a friend, or facts (**semantic** memory), such as the meanings of words, and the names of celebrities.

The second type of long-term memory is implicit, or **procedural** memory. This operates "*unconsciously and automatically*", and is "*expressed through behavior without conscious awareness*", for example, playing the piano or tying your shoe laces (quotes from Kandel 2021:1312 and 1297, and see also Purves 2013:251 and Purves 2019:645). Procedural memory can be thought of as knowing "how", as opposed to declarative memory, which can be thought of as knowing "what" (Thompson 2000:365). In the simplest cases, procedural memory is stored in the reflex pathways (Kandel 2021:caption to figure 53-1).

Procedural memory can be **non-associative**, and deal with a single stimulus, or it can be **associative**, and deal with the relationship between two things, which may be two stimuli, or an action and its consequence (Kandel 2021:1304 and 1317, Lieberman 2000:42, Purves 2013:266, and Thompson 2000:370).

Non-associative memory includes **habituation**, whereby an organism learns to ignore a repeated harmless stimulus, and **sensitisation**, which enhances an organism's defensive reflex responses (Kandel 2021:1316).

Associative memory includes **classical conditioning**, which involves an organism "*learning a relationship between two stimuli*", and **operant conditioning**, which involves "l*earning a relationship between the organism's behavior and the consequences of that behavior*" (both quotes from Kandel 2021:1306).

While they involve different types of association, both types of conditioning follow similar laws (Kandel 2021:1307). Classical, or Pavlovian conditioning, is so called because it was the first type of conditioning to be discovered, and also as a tribute to Pavlov's eminence (Gleitman 2004:127).

The analysis of human memory reveals a comprehensive and intricate system of information storage and recall, which would seem to be based on processes that are well beyond the capabilities of single neurons and their synapses. But this is based on the analysis of an organism that has already become highly evolved over billions of years of evolution. From the start of biological evolution, the simplest organisms lived in environments in which it was important to make the right response to varying conditions. For example, we've seen in section 5.1.7 how a bacterial cell navigates towards a source of food using signal molecules sent from the nutrient detector proteins in its membrane to its flagellar motor.

While learning and memory are complex processes, involving different parts of the brain (Kandel 2021:figure 53-1, Thompson 2000:figure 11.8), they are rooted in synaptic processes (Kandel 2021:350, and chapters 53 and 54). Thus, we find the foundations of learning and memory in the simplest organisms, operating at the level of single cells.

I want to describe how an organism may have only a simple nervous system with no brain, but still can learn about the workings of its external world. I've selected two examples, which are fairly well understood at the cellular level: habituation and classical conditioning. In these examples, I'll focus on the process of learning, rather than on the retention of the memory, because remembering only becomes relevant once something useful has been learned.

learning and memory

"***the biological process***" and "***the process of retaining***", both from Kandel 2014:163.

"***the modification of behavior by experience***", Purves 1998:966.

"***are essential to the full functioning***", Kandel 2021:1291.

6.5.1 habituation – learning to ignore one stimulus

This section is based on Thompson 2000:367, Purves 1998:922, Purves 2013:272, Purves 2019:162, Kandel 2021:1314.

"**The process whereby an organism**", Kandel 2021:1314.

"**The sea anemone**", Thompson 2000:367.

Aplysia californica

"**Many invertebrate species**", Purves 1998:922.

"**One example is the marine mollusc**", Purves 1998:922, Purves 2013:272, Purves 2019:162, Kandel 2021:1314.

Aplysia's 20,000 nerve cells are clustered in 10 anatomical units called ganglia, 5 on each side of the body, with each ganglion containing about 2,000 neurons (Kandel 2001:568).

Figure 6.14 is re-drawn by Hilary McNeil from Lodish 2000:figure 21-51. The animal shown is actually *Aplysia punctata*, which is very like *Aplysia californica*. Both species are members of the genus *Aplysia*, with *californica* found on the Californian coastline, and *punctata* found in the north-eastern Atlantic.

See https://en.wikipedia.org/wiki/California_sea_hare and https://en.wikipedia.org/wiki/Aplysia_punctata.

"**With successive stimulations**", the sensory neuron releases fewer vesicles containing glutamate molecules. The sensitivity of the glutamate receptors in the motor neuron does not change (Kandel 2021:1314). Habituation is not due to the neurotransmitter molecules being "used up", but to a decrease in the number of Ca^{2+} ions entering the axon terminal (Thompson 2000:figure 11.9).

"***pruning of synaptic connections***", Kandel 2021:1324. This is a simplification of events within the axon terminal of the sensory neuron. In

addition to the reduction in the number of synaptic contacts, there is a reduction in the number of vesicles releasing glutamate molecules from the axon terminals (Bailey 1983 and 1988), and this in turn, is linked to a reduction in the number of calcium, Ca^{2+} ions entering the sensory neuron's axon terminal (Thompson 2000:369). A typical sequence of events at a neuro-muscular synapse is shown in figure 6.10.

Figure 6.15(a) and (b) are based on Kandel 2021:figure 53-2B and C; **part (c)** is based on Kandel 2021:figure 53-3B; and **part (d)** is based on Kandel 2021:figure 53-9A. The circuit shown in Kandel 2021:figure 53-2B includes an interneuron, which plays no part in the habituation response, and so, for simplicity, I've omitted it here.

The sensory neurons release the neurotransmitter glutamate on to the motor neurons (Kandel 2021:1314), and the neurotransmitter released by the motor neurons on to the gill muscle is acetylcholine, which is commonly found at neuromuscular junctions (Weiss 1984).

habituation is adaptive

"**Habituation generally occurs**", Thompson 2000:369. Not all synapses habituate, and generally sensory systems show little habituation.

"***It makes good adaptive sense***", Thompson 2000:369.

6.5.2 associative learning – one event predicts another

This section is based on Thompson 2000:370, Lieberman 2000:section 2.2, Gleitman 2004:125, Purves 2013:266, Purves 2019:650, Kandel 2021:1306.

classical conditioning

"***an innate reflex***", Purves 2013:266.

"**The essence of classical conditioning**", Kandel 2021:1306.

"**The classic example**", Thompson 2000:370, Purves 2013:266, Lieberman 2000:section 2.2, and Gleitman 2004:125.

"**This can be summarised**", Thompson 2000:figure 11.10, Lieberman 2000:figure 2.7, Gleitman 2004:figure 4.2.

"***innate reflex is modified***", Purves 2013:266.

"***as diverse as ants***" and "***crabs have been conditioned***", Gleitman 2004:127.

An animal needs very few neurons to be capable of associative learning. For example, the nematode worm *Caenorhabditis elegans* has only 302 neurons, but appears to be capable of associative learning (Zhang 2005:179). *C. elegans* feeds on a variety of bacteria, some of which are harmful. When a worm has been exposed to harmful bacteria, it subsequently avoids the odours of these bacteria, and preferentially feeds on a non-harmful strain.

contingency

"**For classical conditioning to succeed**", Rescorla 1988a, Gleitman 2004:143, Kandel 2021:1306.

"**However, this alone is not enough**", Rescorla 1988b, Thompson 2000:figure 11.11, Gleitman 2004:145, Kandel 2021:figure 52-12.

classical conditioning of Aplysia

This section is based on Carew 1983, Hawkins 1983 and 1984, Kandel 1992, 2000:chapter 63, and 2021:chapter 53.

Figure 6.16 is based on Hawkins 1983:figure 1, Kandel 1992:figure on p. 81, Kandel 2000:figure 63-4, and Kandel 2021:figure 53-5, which are both adapted from Hawkins 1983.

SN1 and SN2 are separate neurons and come from the siphon, which is not shown, and are widely separated in the figure to make the circuit clearer.

Hawkins applied stimuli to the tail and two individual siphon neurons (Hawkins 1983:401), and Kandel 2000:figure 63-4 shows the tail, siphon and mantle shelf, while Kandel 2021:figure 53-5 is simplified and shows only the tail and one siphon neuron.

The sensory neurons release the neurotransmitter glutamate on to the motor neurons (Kandel 2021:1314); the inter-neurons release serotonin on to the axon terminals of the sensory neurons (Kandel 2021:figure 53-6, Purves 2019:figure 8.4); and the motor neurons release acetylcholine on to the gill muscle (Kandel 2021:figure 12-1, Weiss 1984).

This sources of figure 6.16 bring together the results of many experiments on *Aplysia*. Some experiments used 2 separate neurons from the siphon, and some used neurons from the siphon and the mantle – another part of *Aplysia*. In some experiments the sensory neurons were stimulated just by touching, while in others, such as Hawkins 1983, they were given a series of carefully calibrated electric shocks, each one just enough to generate an action potential. In drawing figure 6.16 I've followed Kandel 2021, and used 2 siphon neurons, which are just touched, not shocked. This does not detract from the pattern of behaviour, and makes a clearer distinction between the unconditioned and conditioned stimuli.

"**In fact, the signal in the motor neuron was sometimes slightly smaller**", Hawkins 1983:402, Kandel 2021:figure 53-5.

"**The result is that sensory neuron SN2 became sensitised**", I've taken this term from Kandel, who wrote that the cellular mechanism of classical conditioning "*is largely an elaboration of the mechanism of sensitization*" (Kandel 2021:1317). The processes taking place inside the SN2 axon terminal are highly complex, and we don't need to consider them.

"**It was found that to produce this enhancement**", Kandel 1992:83, Kandel 2021:1317.

a convergence of signals

"**There was nothing special**", Kandel 1992:82.

"**We see this convergence**", this is a simplistic view of classical conditioning. Figure 6.16 shows classical conditioning occurring just by a pre-synaptic facilitation mechanism, but there are also post-synaptic processes, where signals pass from the motor neuron back to the sensory neuron (Roberts 2003, Kandel 2000:1253). Furthermore, there are many more neurons involved than just the ones shown in figure 6.16 (Croll 2003).

associative learning

"***allowed animals to adjust***", Lieberman 2000:64.

"***the way that organisms***", Rescorla 1988b, and quote from Thompson 2000:374. Thompson also writes, on p. 405, "*the way that organisms, including humans, learn about the causal structure of the world*".

"***the learning that results***", Rescorla 1988b:152.

"***learns a representation***", Thompson 2000:374.

"***the organism is better seen***", Rescorla 1988b:156.

"***a hierarchical organisation***", Rescorla 1988b:157.

"**Thus, *Aplysia* can learn**", see Rescorla 1988a, Kandel 2021:figure 52-12 on the rat.

"**Associative learning**", Kandel 2021:chapter 53.

"***seem to depend on changes***", Purves 2013:270.

"***learning depends on neural plasticity***", Gleitman 2004:154.

"***built into the neural architecture***", Kandel 2009:12749.

biological individuality

"***Modern cognitive psychology***", Kandel 2000:1277.

"***the architecture of each of our brains***", Kandel 1992:86.

"***This distinctive modification***", Kandel 2021:1336.

6.6 review of level 6

levels 4 and 6 are analogous

one thing represents another

"**Thus, an object, an event, or an action**", Calvin 1997:107.

Nick Lane sums it up as, "*there's no reality but nerves*" (Lane 2010:238).

remembering experiences

a neural representation of causality

"***stores an internal representation***", Kandel 2000a:1277.

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