I.1

Early Nerve Studies

Over the millennia, philosophers and scientists have pondered life and its connection to the soul. Aristotle believed that the source of sensations such as pain was the heart. The brain did not play a major role. Such considerations were not based on experimental evidence. Dissections of dead bodies were not performed. This changed during the Roman period, when in the third century AD, Galenos of Pergamon performed anatomical studies. There are several lines of thought, starting from Galenos and René Descartes to Luigi Galvani, Alessandro Volta, and Julius Bernstein, which eventually led to the current electrophysiological view of nerve action. Today, nerve action is mostly understood as an electrical phenomenon related to the flow of charged ions and the charging of cell membranes, which act as capacitors. Over the centuries, however, there have been other views and arguments that attribute nerve action also to mechanical or thermodynamic phenomena. These views are not always easy to distinguish, since electrostatics is part of thermodynamics, and the Nernst potentials in electrophysiological theories resemble a Boltzmann distribution of ions in an electrostatic potential. Furthermore, several experiments on nerves are not included in the current understanding of nerve action. In this introduction, we briefly review some of the history of the understanding of the brain and nerve function.

I.1.1 Galenos of Pergamon and the Animal Spirits

While the early Greek understanding of nerves and the brain was not based on anatomical studies, this changed during the Roman Empire. Unlike his predecessors, the Greek anatomist Galenos of Pergamon (129–216 AD) (Figure I.1.1) dissected the bodies and brains of animals (probably never humans). His findings are summarized in a 14-volume book called *Methodus medendi*.

It served as the basis for medical education until the seventeenth century. For Galenos, the human being was a synthesis of soul and body subject to both spiritual and material influences. According to Galenos, there are various spirits that control the interaction of the different parts of the body: the *spiritus animals* (animal spirit), which connects the brain to the nerves, the *spiritus vitalis* (vital spirit), which connects the heart to the arteries, and the *spiritus naturalis* (natural spirit), which connects the liver to the veins. One must imagine these spirits as a kind of light matter flowing in nerves, arteries, or veins.

Physics of Nerves and Excitatory Membranes, First Edition. Thomas Heimburg.

Figure I.1.1 Galenos of Pergamon (129–216 AD). *Source*: National Library of Medicine/Wikimedia Commons/Public Domain.

As for the brain, Galenos concluded that it controls the function of the muscles through nerves. He noted that special nerves control well-defined muscles through the animal spirits. Galenos’ work was considered so complete that many of these studies were not repeated until the Renaissance, and deviations from Galenos’ writings found in later experiments were attributed to errors or degeneracies.

I.1.2 Descartes and the Hydraulic Nerve

René Descartes was born on 31 March 1596 in La Haye en Touraine, France, and died on 11 February 1650 in Stockholm. For many reasons, Descartes is one of the most important figures in the history of science. In his famous monograph *Discours de la méthode* (Discourse on the Method), published anonymously in Leiden in 1637, he described the analytical method of scientific investigation. This method outlined an approach to understanding the world based on one’s own common sense rather than reference to authority and belief. His advice is never to use anything in a line of argument that you have not checked beyond doubt to be true. His method is analytical, working from the simple picture to the more complex.

Descartes was very interested in anatomy and apparently carried out many anatomical studies himself. In his book *Traité de l’homme*, he supported the idea of Galenos that a human being has two parts, the soul and the body, which communicate with each other through animal spirits. While the concept of an animal spirit is somewhat mysterious in the ancient writings, in Descartes’ view it is akin to a liquid. For Descartes, the human body was a hydraulic machine similar to those existing in the royal gardens in Saint-Germain-en-Lay. In these gardens, various figures and statues were moved by the hydraulic pressure of a system of water pipes.[1] He argued that the blood is pumped by the heart, filled with oxygen in the lungs, and that it flows subsequently to the different body parts. The blood then flows back to the heart in veins. The most animated parts of the blood (with the highest pressure) flow into the brain, where the pressure fills the nerves with the animal spirit. The nerves control the muscles via a hydraulic mechanism in the same way as the water pressure controls the motion of the statues in the Royal Gardens. Small aliquots of the animal spirits in the nerves are transferred into the muscles. Via this mechanism, the muscle expands in diameter and shortens in length. A drawing by Descartes of the muscles and nerves surrounding the eyeball is shown in Figure I.1.2 (center). The soul plays the role of the engineer that opens and closes the valves of the pipe system. An obvious consequence of this view is that a muscle must change its volume when the *animal spirits* are injected.

Descartes was a friend and correspondent of Galileo Galilei. When Galileo was condemned by the Catholic Church in 1633, Descartes did not dare to publish "*Traité de l'homme*," which was written in the same year. It only appeared after Descartes' death in

Figure I.1.2 Left: René Descartes (1596–1650). Jan Baptist Weenix/Wikimedia Commons/Public Domain. Center: Drawing of the eye ball surrounded by muscles and nerves from "*Traité de l'homme*." Right: Jan Swammerdam (1637–1680). DALIBRI/Wikimedia Commons/Public Domain.

1 "… visitors described an automaton Neptune with a streaming blue beard, brandishing his trident, naked astride a chariot pulled by seahorses, accompanied by three round-bellied, horn-playing tritons. Farriers, "their faces black with filth and sweat," hammered iron on an anvil and - "that which is most pleasant and seems made to provoke laughter" - drenched their eager audiences with surprise sprays of water. Mercury posed by a window with one foot carelessly propped, "loudly intoning a trumpet." Elsewhere, Orpheus played his lyre for an audience of animals and trees who, including the trees, stretched and craned toward him. A towering Perseus descended upon a mighty dragon arising from beneath the waves. Perseus swung his sword to behead the fearsome beast, sending it, slain, back down into the watery depths; whereupon farther back in the grotto, Andromeda promptly lost her chains. Meanwhile busy figures of artisans - blacksmiths, weavers, millers, carpenters, knife-grinders, fishermen - went about their sundry tasks." Quote from [1].

Latin translation (“*De homine*”). Parts of it were summarized in “*Discours de la méthode.*” Descartes was nevertheless subject to prosecution. The University of Utrecht condemned him in 1643, and he fled to Den Haag in order to avoid the public burning of his books. In the later 1640s, he was also condemned by the University of Leiden. This might be the reason he moved to Stockholm in the last year of his life.

The hydraulic theory of Descartes was disproven by the Dutch microscopist Jan Swammerdam (1637–1680), who showed that the muscle does not change its volume during contraction. Thus, it does not act as a hydraulic piston [2]. He also showed that a frog muscle disconnected from the frog’s brain still contracts when the nerve is irritated. Thus, the contraction of the muscles did not require the brain as the source of an *animal spirit*.

> *“From these experiments, therefore, it may, I think, be fairly concluded, that a simple and natural motion or irritation of the nerve alone is necessary to produce muscular motion, whether it has its origin in the brain, or in the marrow, or elsewhere [3].”*

Swammerdam rather argued that the action of nerves can be likened to a vibration.

> *“I would have it seriously considered, that it cannot be demonstrated by any experiments, that any matter of sensible or comprehensible bulk flows through the nerves into the muscles. Nor does any thing else pass through the nerves to the muscles: all is a very quick kind of motion, which is indeed so rapid, that it may be properly called instantaneous. ... Therefore the spirit, as it is called, or that subtile [sic] matter, which flies in an instant through the nerves into the muscles, may with the greatest propriety be compared to that most swift motion, which, when one extremity of a long beam or board is struck with the finger, runs with such velocity along the wood, that it is perceived almost at the same instant at the other end [3].”*

I.1.3 Gassendi, Willis, and Newton

The hydraulic theory of Descartes was very popular in his days. However, it left open the question of how the soul interacts with the nerves and muscles, i.e., how the hydraulic machine can be subject to willful decisions. It is fair to say that this question has remained unanswered until today.[2]

The French philosopher Pierre Gassendi (1592–1655) (Figure I.1.3) (left) is another important figure who critically discussed both Aristotelian philosophy and the teachings of Descartes. He was seen as the main adversary of Descartes in his days. His view on nerves and muscles was mechanical, without an explicit notion of a soul. In his opinion, the hydraulic theory of Descartes could not work because it required solid hollow pipes. However, Gassendi noted that the nerves are made of a soft and tender material, which would not be suitable to transmit a force sufficient to make a muscle contract. He remarked:

2 For the following paragraphs, we follow a historical review of Wallace [4] and use quotes cited therein.

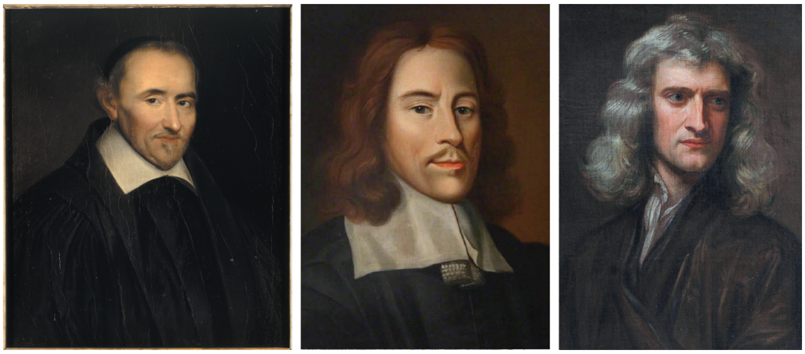

Figure I.1.3 Left: Pierre Gassendi (1592–1655). Œuvres complètes de Voltaire/Wikimedia Commons/Public Domain. Center: Thomas Willis (1621–1675). Bodleian Libraries/Public domain. Right: Isaac Newton (1643–1727). James Thronill/Wikimedia Commons/Public Domain.

> *"For if the nerves, as is sometimes said, issued from a firm and solid origin, the attraction which occurs between the part that is moved and the origin of movement could truly be attributed to the nerves; but since the nerves issue from the marrow, which is a soft, tender and slack material, and since the nerves themselves at their origin are both very soft and very tender, consequently they cannot be fit for attracting the [moving] parts, nor for being the true and physical organs of movement." ... "What then can we say comes to the muscle from the brain, by the intermediary of the nerve, without which the muscle is not capable of moving? Certainly this seems to be nothing other than the commandment to move, which is somehow signified to the muscle by the arrival of the spirits transmitted by the nerve, such that without this front of spirits , the muscle remains sleeping, but if it has been excited thereby, as if awoken, it acts."*

Gassendi also noticed that the muscle can contract by itself when stimulated from the exterior. As a consequence, Gassendi believed that the nerve does not transmit a force but rather a signal that makes the muscle contract. The muscle possesses its own machinery that allows it to contract, and the nerves just transmit the order.

> *"Nothing is transmitted from the brain to the muscle by the intermediary of the nerve, except this order, and this commandment, which is like the Will or the Appetite. And the Understanding, or Phantasy as mistress and directress, signifies to the tendon or to the muscle as to a slave, so that it should make such and such a movement, and that it should move such and such a body part."*

In summary, Gassendi's view was that the nerve mediates muscular contraction. However, it transmits a signal and not a force. Further, the signal resembles light or fire because it is too fast to be transmitted by the motion of particles or fluids.

William Croone (1633–1684) was another philosopher who noted that the spirits in the nerve are not sufficient to inflate a muscle. He rather proposed that the nerves inject tiny amounts of a spirit into the blood of a muscle. The consequent contraction of the muscle is caused by a chemical reaction induced by those spirits. In the tradition of Gassendi, the English doctor Thomas Willis (1621–1675), (Figure I.1.3) (center) who made the first detailed anatomic descriptions of the nervous system and the brain, published his book *Cerebri Anatome* in 1664, and two more books called *De motu musculari* (1670) and *De anima brutorum* (1670). In contrast to Descartes, he made use of microscopes, just like Antonie Philips van Leeuwenhoek (1632–1723), who is often called the father of microbiology. Just like van Leeuwenhoek, he could not find any hollow structures in nerves. Therefore, he proposed the so-called solid nerve, i.e., a fiber that is not a hollow hydraulic pipe but rather a solid tissue that transports stimuli of a much more subtle nature than liquids:

> *"The passages of the nerves are not hollowed out like those of the arteries and veins, because their substance is not only impervious to any stylus, but the use of a lens or microscope confirms that there is no cavity present in them. ... The nerves are clearly formed of a compact and firm substance so that the subtle humor, which is the vehicle of the spirits, may pass through their structures not otherwise than spirits of wine through the tensed cords of a lute, only by slowly creeping through. Hence it may be argued that the animal spirits require no manifest cavity within the nerves for their expansion."*

He believed that the spirits in the neuron are rather a kind of waves:

> "*For just as in a river, various kinds of waves are thrown up by the winds or by things cast into it, so the animal spirits, when awoken by objects, go forth to carry out the functions of sense and motion, stretching hither and thither within the nervous kind, and being agitated there in other ways." ... "But since it is not trivial to distinguish spirits and waters by their motions and consistency, perhaps it will better illustrate the matter if the spirits ... are compared to the beaming forth of different rays of light. ... The animal spirits irradiate and swiftly cross all parts of the nervous system, both primary and secondary, so that light is scarcely carried faster through a diaphanous medium, than the communication of spirits is made from one end of the nervous system to the other."*

Willis also referred to the nervous impulse as a vibration as in a stringed instrument. This is clearly a view that is different from that of Descartes.

The aforementioned views became most popular through the writings of Issac Newton (Figure I.1.3 (right)). He added short but important sections on nerves to the second edition of his *Principia Mathematica* from 1713. Newton also used the term "solid nerve" and explained the signal of the nerve in the following manner:

> *"And now we might add something concerning a certain most subtle spirit which pervades and lies hid in all gross bodies; by the force and action of which spirit the particles of bodies attract one another at near distances, and cohere, if contiguous; and electric bodies operate to greater distances, as well repelling as attracting the neighboring corpuscles; and light is emitted, reflected, refracted, inflected, and heats bodies; and all sensation is excited, and the members of animal bodies move at the command of the will, namely, by the vibrations of this spirit, mutually propagated along the solid filaments of the nerves, from the outward organs of sense to the brain, and from the brain into the muscles."*

Thus, Newton adopted views from Gassendi and Willis and favored an electrical or light-like mechanism for the transmission of a signal (the spirits). Like Gassendi, Croone, and Willis, he proposed that muscle contraction is the consequence of chemical reactions induced by the influx of spirits from the nerves.

For more details, we refer to the very detailed review of Wallace [4].

I.1.4 Galvani, Volta, and the Electrical Nerve

The controversy between Luigi Galvani (1737–1798) (Figure I.1.4) (left) and Alessandro Volta (1745–1827) (Figure I.1.4 (right)) is famous. It led to the present understanding that the nerve pulse is predominantly an electrical phenomenon.

Luigi Galvani was an Italian scientist from Bologna. He made three important experiments that established that the nerve pulse is an electrical phenomenon. He showed that the legs of a frog contracted when electrically excited by either a Leyden jar (a capacitor), a machine producing a charge, or by touching the sciatic nerve with a charged scalpel. He noted:[3]

> *"I dissected and prepared a frog and placed it on a table, on which was an electrical machine... widely removed from its conductor and separated by no brief interval [distance]. When by chance one of those who were assisting me gently touched the point of a scalpel to the medial crural nerve of this frog, immediately all the muscles of the limbs seemed to be so contracted that they appeared to have fallen into violent tonic convulsions. But another of the assistants, who was on hand when I did electrical experiments, seemed to observe that the same thing occurred whenever a spark was discharged from the conductor of the machine..."*

After finding that the muscles of frogs contracted when electrical sparks occurred in the proximity of the preparation, or the nerve was touched in the presence of such electrical

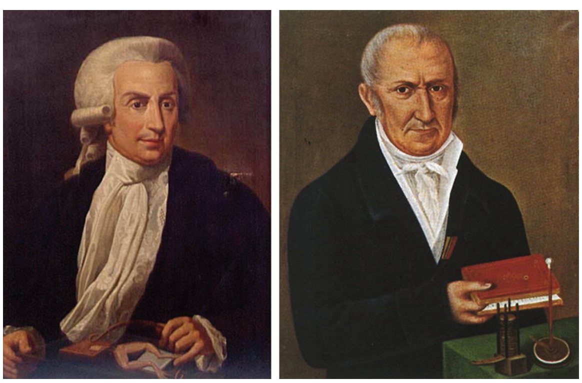

Figure I.1.4 Left: Luigi Galvani (1737–1798). Unknown author/Wikimedia Commons/CC BY-SA 3.0. Right: Alessandro Volta (1745–1827). Wolfgang Peter/Wikimedia Commons/Public Domain.

3 This section follows a review by Geddes and Hoff [5] and the English translations of Galvani's writings by Green [6].

machines, Galvani also wondered whether muscle action could be induced by atmospheric electricity, i.e., during thunderstorms:

"Having discovered the effects of artificial electricity on muscular contractions ..., there was nothing we would sooner do than to investigate whether atmospheric electricity, ..., would afford the same phenomena, ... Therefore we erected, in the fresh air, in a lofty part of the house, a long and suitable conductor, namely an iron wire, and insulated it and to it, when a storm arose in the sky, attached by their nerves either prepared frogs, or prepared legs of warm animals .... Also we attached another conductor, namely another iron wire, to the feet of the same, and this as long as possible, that it might extend as far as the waters of the well indicated in the figure. Moreover, the thing went according to our desire, just as in artificial electricity; for as often as the lightning broke out, at the same moment of time all the muscles fell into violent and multiple contractions, so that, just as the splendor and flash of the lightning are wont, so the muscular motions and contractions of those animals preceded the thunders, and, as it were, warned of them; ..." [5]

Since the effect of lightning could be observed prior to thunder, but at the same time as the lightning, it was shown that the lightning was the cause of the muscle contraction. Thus, he demonstrated that nerve contraction is an electrical phenomenon.

Galvani made a second experiment of a different nature, which is related to the contact of nerves with metals. He describes this experiment as follows:

"Wherefore, since I had sometimes seen prepared frogs placed on iron gratings which surrounded a certain hanging garden of my house, equipped also with bronze [some accounts refer to copper or brass] hooks in their spinal cord, fall into the customary contractions, not only when the sky was lightning but also sometimes when it was quiet and serene, I thought these contractions derived their origin from the changes which sometimes occur in atmospheric electricity. Hence, not without hope, I began diligently to investigate the effects of these changes in these muscular motions in various ways. Wherefore at different hours, and for many days, I inspected animals, appropriately adjusted therefor; but there was scarcely any motion in their muscles. Finally, weary with vain expectation I began to press the bronze hooks, whereby their spinal cords were fixed, against the iron gratings, to see whether by this kind of device they excited muscular contractions, and in various states of the atmosphere, and of electricity whatever variety and mutation they presented; not infrequently, indeed, I observed contractions, but bearing no relation to varied state of atmosphere or of electricity. " ... "Nevertheless, since I had not inspected these contractions except in the fresh air, for I had not yet experimented in other places, I was on the point of seeking such contractions from electricity of the atmosphere, which had crept into the animal and accumulated in him and gone out rapidly from him in contact of the hook with the iron grating; for it is easy in experimentation to be deceived, and to think one has seen and discovered what we desire to see and discover." [5]

Galvani found that the frog muscles connected to the metal hooks contracted even in the absence of lightning.

The important requirement for Galvani's second experiment was that the hook to which the nerve was connected consisted of two different metals. Galvani believed that the nerve served as a kind of capacitor (Leyden jar) that was charged with *animal electricity*, and that the hook represented a conductor that discharged the capacitor. According to Galvani, the muscle contracts upon discharging the nerve.

Galvani's experiments quickly became very popular. They were demonstrated in public, and many scientists and laymen reproduced them.

Alessandro Volta (1745–1827) was born and lived in Como (Italy). He is known as the inventor of the battery (Voltaic cells). Basically, the Voltaic cell consists of two different metals separated by an electrolyte. Volta arranged such elementary batteries in series and noted that the effect of the battery is similar to that of a Leyden jar. He writes:

> *"Thirty, forty or more pieces of copper, or rather silver, applied each to a piece of tin, or zinc, which is much better, and as many strata of water or any other liquid which may be a better conductor, such as salt water, ley [lye], etc., or pieces of pasteboard skin etc. well soaked in the liquids; such strata are interposed between every pair or combination of two different metals in an alternate series, and always in the same order of these three kinds of conductors are all that is necessary for constituting my new instrument, which as I have said, imitates the effect of the Leyden flask, or of electric batteries by communicating the same shock as these do."* [5]

Thus, according to Volta, in Galvani's second experiment, the metal hook actually formed a battery, and the nerve liquids acted as electrolytes. Therefore, it was actually Volta who paved the way for the emergence of a bioelectric potential from chemical sources built up in electrolytic solutions. The reinterpretation of Galvani's experiments and the rejection of the concept of *animal electricity* is known as the Galvani–Volta controversy and holds an important place in the history of science.

As a reaction to Volta's experiments, Galvani performed a third experiment, in which he bent the leg of the frog such that it touched the injured nerve and showed that the muscles contracted. This shows that the biological tissue itself can act as a battery. The voltage created in this arrangement is called the injury potential, due to its origin from the injured sciatic nerve.

Galvani's late experiments were confirmed and refined by Carlo Matteucci (1811–1868) by employing a galvanometer. He showed that the injured nerve in contact with a muscle creates an electrical current, and that the contraction of the muscle is correlated with a transient current and the disappearance of the bioelectric potential, which later came to be known as the *action potential*.