Mathematical Modelling

7

Novak S.J. Elliott

Contents

With Paul Harris

N.S.J. Elliott
Department of Mechanical Engineering,
Curtin University, Perth, WA, Australia
e-mail: n.s.j.elliott@curtin.edu.au

7.1   Introduction

A model is a representation of objects and processes that, when analysed, may reveal their properties and behaviour (Dym and Ivey 1980). A familiar example in medical research is the animal model. For an animal of sufficient likeness to human anatomy (objects), physiology and pathological response (processes), the outcomes of experiment may be extrapolated to human medicine. The model may refer to the animal itself, especially if purpose bred, or its combination with the treatment protocol to reproduce the desired pathology. For example, animal models of human posttraumatic syringomyelia have been developed using injections of kaolin and quisqualic acid in rats (Stoodley et al. 1999; Brodbelt et al. 2003a). Likewise, physiological or pathophysiological processes acting on normal or abnormal anatomy may be expressed in terms of force and mass balances, according to the laws of mechanics, which are most naturally formulated as mathematical equations. By careful manipulation of these equations, using well-established rules, one may construct a mathematical model—a theoretical representation of a physical system.

Neurosurgeons regularly make judgments involving the mechanical properties of the spinal cord and brain, as part of routine diagnosis and treatment. For example, when examining computed tomography (CT) and static magnetic resonance (MR) images of a Chiari malformation, clinicians will make some estimate of the pressure acting upon and the deformation of the

hindbrain. The opening pressure of the cerebrospinal fluid (CSF) is taken during lumbar puncture using a column manometer. The protein concentration of the CSF subsequently collected gives an indication of viscosity. During a spinal procedure, the surgeon may gently palpate the exposed spinal cord, in order to determine the degree of scar tissue build-up or the size and location of syrinxes or tumours and may thereby be making an estimate of compliance. Dynamic MR imaging is used to identify CSF flow obstructions, which are areas of high resistance, and the pulse-wave speed of the cerebrospinal fluid can also be appreciated from this imaging modality.

The uncertain surgical prognosis for syringomyelia and the difficulties of carrying out experimental work make mathematical modelling of the mechanics of this condition very attractive for research. Such models do, however, rely upon accurate measurement of mechanical properties of the cerebrospinal system, but these are difficult to obtain due to both the delicate nature of neurological tissues and their inaccessibility in situ. The risks to the patient of making such measurements may also outweigh any benefit gained. Further, the more realistically one attempts to represent the cerebrospinal fluid system, the more complex the mathematics become. For all these reasons, mathematical models of syringomyelia have been slow to evolve. Nonetheless, useful insights are now being made, with models that are consistent with the pathology and adhere to the laws of mechanics (Elliott et al. 2013).

7.2 Background

7.2.1 The Laws of Mechanics

In our everyday lives, we observe and experience certain physical phenomena that occur in a *predictable* way. For example, if a car breaks down and needs to be pushed, it requires a lot of effort to get going, but this becomes easier once the car is moving. While driving, applying the brakes in an emergency will cause the passengers to be thrown forwards against their seatbelts. The harder a golf ball is struck, the more rapidly it will gain speed. When standing on solid ground, we feel our own weight through the soles of our feet. These events all involve force, motion and strength of materials—'mechanics' as termed by Galileo (Fung 1993)—and may be described by the *laws of mechanics*, a subset of the so-called physical laws of nature. In 1687, Sir Isaac Newton, the English mathematician, physicist and astronomer,[1] published his monograph *Philosophiæ Naturalis Principia Mathematica*, in which he stated three laws of motion:

1. In the absence of any external forces, an object that is still will remain still, and an object that is in motion will continue with constant speed in a fixed direction. An object is thus said to possess *inertia* (Latin 'iners': idle), a tendency to resist any change in its state of rest or motion. A measure of an object's inertia is its mass, i.e. how much 'stuff' the object is made of, which is equal to its density times its volume. The above example of a car braking can be explained by the inertia of the car and its occupants, respectively.

2. Force is equal to mass multiplied by acceleration, where the resulting acceleration is in the same direction as the applied force. So, a golf ball correctly driven down the fairway will reach great speed, whereas it will move much slower when gently putted on the green, even ignoring the friction of the air and grass.

3. For every action, there is an equal and opposite reaction. A person's weight is the force produced by their mass being subjected to the acceleration of gravity towards the centre of earth. Opposing this is a force exerted by the earth of equal size but directed back into the person's feet.

When objects change shape as a result of applied forces—a good example being flowing liquids—we also need to consider the *law of conservation of mass*. This states that the total amount of matter in an isolated system will remain constant over time. Similarly, when temperature changes become appreciable, the *law of conservation of energy*[2] is called into play; e.g.

---

[1] Also natural philosopher, alchemist and theologian.

[2] A generalisation of the laws of thermodynamics.

freshly poured coffee warms the cup (and cools the coffee) due to the transfer of thermal energy.

Conservation appears to be a principle that all laws of nature follow. Newton's laws of motion may be reformulated in terms of *momentum*, i.e. mass multiplied by velocity, which, it turns out, is also conserved. When working with conservation laws, one is essentially keeping a running tally of the various quantities to make sure the budgets balance.

When considering the everyday functioning of the human body, the above laws generally suffice. When working on the very large scales of the cosmos or the very small scales of atoms, additional phenomena become important. These are described by laws of gravitation (Newton, Einstein) and quantum electrodynamics (Feynman), respectively. Laws, however, are simply generalisations of physical behaviour, based on empirical observations. What is so special about them, to earn the title 'law', is their simplicity, universal nature and lasting truth, despite being falsifiable[3] through the possibility of contradictory observations. Newton once said "I have told you how it moves, not why" (Feynman 1965). Laws describe what happens, but theories seek an explanation.

7.2.2 Fundamentals of Biomechanics

Living creatures populate the physical world and are thus subject to the same mechanical laws as inanimate objects. Biomechanics is a relatively modern term applied to a long-established practice, the application of mechanics to biology.[4] In fact, medicine and mechanics evolved symbiotically out of the joint efforts of physical and biological scientists, and it was once not uncommon to be educated and active in both disciplines (Fung 1993; Ethier and Simmons 2007). We consider two notable examples:

1. Thomas Young (1773–1829) was a London physician with a doctorate in physics (Fung 1993). Amongst his numerous contributions was his characterisation of the elastic nature of solid materials, which followed his studies of the human voice. When a force pushes on an object, it will exert a pressure on its surface (pressure equals force divided by area) that will be transmitted as *stress* (σ) and cause the object to become compressed. Likewise, if the force pulls on the surface, the stress causes the object to stretch, producing a state of tension. The ratio of the stress to the fractional change in length, or strain (ε), is termed Young's modulus of elasticity (E) and is a fundamental property of the material, i.e.

$$E = \sigma / \varepsilon. \tag{7.1}$$

Hard vertebrae have a much larger Young's modulus than the soft dura mater, as a greater stress (about 100 times) is required to produce the same strain. The concept of elasticity is at the foundation of solid mechanics.

2. The Frenchman Jean Louis Marie Poiseuille (1797–1869) was an experimental physiologist with formal training in mathematics and physics (Sutera and Skalak 1993). He was first interested in 'the force of the aortic heart' and so invented the U-tube mercury manometer to measure arterial blood pressure in horses and dogs. Continuing his study of haemodynamics, Poiseuille next turned his attention to the microcirculation. On observing frog mesenteric blood vessels, he noted that red cells would stream in the centre of the vessels, whereas white blood cells tended to stick to the vessel walls. To understand the nature of these flow patterns, he subsequently conducted an extensive series of experiments in small-diameter glass tubes. Fluid flows from high to low pressure, and Poiseuille established the relationship between the fall in driving pressure along the tube (Δp), the length (L) and diameter (D) of the tube and the

---

[3] For its relevance as a demarcation criterion between science and pseudoscience, a hotly debated topic, see, for example, Popper (1998).

[4] At the cellular level is the emerging subdiscipline of mechanobiology, which is attempting to uncover the molecular mechanism by which cells sense and respond to mechanical signals. For a recent overview of this topic, specific to the nervous system, see Bilston and Stucky (2011).

subsequent volumetric flow rate (Q). The fluid property connecting these four quantities is the viscosity (μ), and their relation is known as Poiseuille's law:

$$Q = \left(\pi D^4 / 128 \mu L \right) \Delta p. \qquad (7.2)$$

Thus, for a given pressure drop, there will be a greater volumetric flow rate through vessels having a larger diameter or a lower viscosity. Such differences come into play when we compare the calibres of subarachnoid and perivascular spaces and the viscosities of CSF and blood. Mathematics also gives us the converse relation, in that a greater drop in pressure will result from a larger flow rate.

7.2.3 Constructing a Mathematical Model

What mathematics is and its utility are widely misunderstood (Stewart 2011). Mathematics (Greek 'máthēma', to learn) is a branch of science that deals with concepts of quantity, space, structure and change. It is often referred to as the 'language of nature' for its ability to communicate the ideas of physical phenomena. Mathematics has symbols and a grammar for arranging them, but over and above a traditional language, it also includes a system of *reasoning*. We can explain equations in words but seldom the connection between them; herein lies the power of mathematics (Feynman 1965).

The first step in constructing a mathematical model is to decide upon the level of detail. It is not feasible to include every physical feature that influences the phenomenon being studied. Nor, in fact, is this desirable as doing so would only reproduce the complexity inside the 'black box' that we did not understand in the first place. The aim, therefore, is to retain the features with the greatest influence and omit the rest. Every mathematical model is thus a deliberate idealisation of the phenomenon being studied. Choosing what to include is a process of trial and error, guided by the intuition of experience and the comparison of predictions with empirical data (Barenblatt

2003). There is no one 'correct' model of a given system and what to include depends on the question being asked. A useful starting point is to eliminate quantities that are relatively 'small'. For example, the vertebrae are very hard and stiff compared to the meninges and spinal cord, so their shape is much less affected by typical subarachnoid fluid pressures; in mathematical notation, $\varepsilon_{\text{bone}}$ will have a much smaller value than $\varepsilon_{\text{soft tissue}}$. Thus, it may be reasonable to omit the elasticity of the vertebrae when, say, studying the effects of cough-based pressure pulses in the spinal canal. In contrast, if one were interested in spinal trauma, then the much higher forces involved would demand the bone be treated as an elastic material. By convention, mathematicians and engineers would tend to say "we assume the vertebrae are rigid", rather than "we omit the elasticity of the vertebrae"; these statements mean the same thing, and what is being assumed is that omitting these features from the model so will not significantly change the outcome of subsequent calculations and predictions.

Once all of the simplifying assumptions have been made, one can write down a set of equations that govern the system. This is the essence of the mathematical model. The next task is to solve the equations, for which there are two choices: (1) solve them by hand using pen and paper or (2) solve them on a computer. The former is called an *analytical solution* and yields great insight into the underlying phenomenon by obtaining a relation describing it explicitly, e.g. Eq. (7.2). While this approach is preferable, it is usually only possible for the very simplest equations, so instead one often employs computer programs to obtain a *numerical solution*. Computers are digital so they can only store information as a set of discrete samples. As a result, solving an equation on a computer may introduce error due to the continuums of time and space being approximated as a finite number of values. The finer the partitioning, the smaller the error will be but also the more demanding it becomes to compute. Thus, compromise must be made.

To demonstrate that a mathematical model makes reliable predictions, it should be *validated* against empirical data. For example, Eq. (7.2) was

derived mathematically from the laws of mechanics by Eduard Hagenbach (1860), and it matched the relationship that Poiseuille obtained from his glass-tube experiments (Sutera and Skalak 1993). Unfortunately, it is often the case with problems in biomechanics that a controlled experiment, equivalent to that of Poiseuille, is not possible. Instead, in these situations, one deconstructs the model into sufficiently general components, such as water flow through a pipe that can be validated separately. Solutions that are obtained via computer also need to be *verified* to ensure that no mistakes were made in the software; simpler versions of the equations can be computed and compared to well-known analytical solutions, such as the speed of pressure waves in a fluid-filled elastic tube (e.g. Cirovic and Kim 2012). Thus, *validation* ensures that the correct equations are being solved, while *verification* ensures that the equations are being solved correctly.

7.2.4 Modelling Predictions

The real usefulness of a mathematical model lies in its predictive capabilities. Once validated, a mathematical model can be used to determine what happens in hypothetical situations and, most prominently, situations that are not amenable to physical observation and measurement. For example, in a model of posttraumatic syringomyelia, the efficacy of various shunt treatments have been evaluated (Elliott et al. 2011). Crucially though, one must ensure that predictions are consistent with the assumptions upon which the model is based (Dym and Ivey 1980). For biological materials, the elasticity as defined in Eq. (7.1) is only applicable for small strains. This means that in a spinal canal model, one would likely have to choose small enough input pressures to ensure that this condition were not violated.

In clinical and animal studies, a sufficiently large cohort is required to make representative predictions. The empirical findings are analysed in terms of their statistical distribution (mean, standard deviation, confidence intervals, etc.) but may not be predicted precisely. In contrast, mathematical models based on Newton's laws of

mechanics are *isolated* from external influences, so there is no random variation, making them *deterministic*, rather than stochastic (Murthy et al. 1990). It is this ability to remove confounding factors that permits analysis with absolute certainty. However, it is a certainty limited to the model itself. The relevance of mathematical predictions to the biological system depends on the degree to which the model is representative of the biological system.

7.3 Mechanics of the Healthy Cerebrospinal System

7.3.1 Solid and Fluid Components

The spinal cord and brain constitute a soft, elastic solid that is housed within the rigid confines of the vertebral canal and cranial cavity. The intervening subarachnoid spaces, which also extend as cavities (ventricles) into the brain, are filled with cerebrospinal fluid (CSF), not unlike sea water. As the cord and brain themselves are also largely water by mass, they float within their bony container but are hitched in place, loosely by the arachnoid trabeculae and, in the case of the cord, more substantially by the denticulate ligaments and filum terminale (see Chap. 3). These elastic connections span the subarachnoid space which is lined by the pia mater along the cord and brain surface and by the arachnoid layer that is adherent to the dura mater that lines the vertebrae and skull (England and Wakeley 2006).

7.3.2 Elastic Properties of the Soft Tissues

The elasticity of any material is determined by its microstructure, and in the case of soft biological tissues, this largely means the quantity and arrangement of collagen and elastin fibres. The collagen protein molecule has a triple-helix structure, and when grouped into fibrils, and subsequently into fibres, it becomes a much stiffer structure than elastin fibres, which are rubbery, convoluted, thin strands (Fung 1993). The spinal dura mostly

consists of collagen fibres, densely arranged in longitudinal bundles but with a network of fine elastin fibres threading in all directions (Tunturi 1977; Maikos et al. 2008). In contrast, the spinal pia consists of small bundles of collagenous fibres together with individual collagen and elastin fibres that are all loosely woven into a reticular pattern (Tunturi 1978). The spinal cord parenchyma itself has a negligible amount of collagen and elastin so its elasticity instead depends on the axonal fibres and their myelin sheaths.

Estimates of the Young's moduli for dura, pia and the spinal cord vary widely in the literature, but broadly speaking, the dura is about 100 times stiffer than the pia (i.e. greater E), which in turn is about 100 times stiffer than the soft cord tissue (Elliott et al. 2013). These tissues, like all materials, can only withstand a certain amount of strain before they become permanently damaged; i.e. they no longer recover their original shape when the forces are removed and may, in fact, rupture. The stress corresponding to this 'mechanical failure' is referred to as the *yield strength*. Collagen, for example, has a Young's modulus of 1–1.5 GPa,[5] but as it can only withstand a strain of 10–20 %, its yield strength is much lower, 70–150 MPa (Meyers et al. 2008).[6] The pia's greater stiffness than the spinal cord to which it is attached limits the strain that the cord endures, thereby performing a mechanically protective role (Bertram 2010; Ozawa et al. 2004).

7.3.3 Fluid Pathways

CSF is secreted from the choroid plexus and commences a slow bulk flow from the ventricles, continuing through the subarachnoid space before the fluid is reabsorbed back into the superior sagittal sinus and venous system via the arachnoid villi. The total volume of CSF (about 150 ml) is

replaced about three times daily (Bradbury 1993). Ill-defined amounts of CSF are also filtered from blood plasma and absorbed into the lymphatic system (Brodbelt and Stoodley 2007). In the human cranial subarachnoid space, the arteries and veins reside within pia-like tubular sheaths. The arterial sheaths continue into the brain parenchyma, while the veins lose their sheaths at the pia mater interface (Zhang et al. 1990). Although not proven, it seems likely that the situation is the same in the spinal canal. As the interstitial and cerebrospinal fluids may pass through pores and leaky gap junctions in the pia, the extracellular, perivascular and subarachnoid spaces thus form a single continuous fluid compartment (Rennels et al. 1985; Stoodley et al. 1996; Johanson 2008; Saadoun and Papadopoulos 2010). Superimposed on the bulk CSF flow is a reciprocating flow of more substantial magnitude—measurable with MRI—that is due to the periodic *volume changes* of the blood vessels with the cardiac and respiratory cycles.

7.3.4 Volume Compliance

The volume change of a distensible vessel is related to pressure change through compliance. However, there are two measures of compliance: *static* and *dynamic* (Bertram 2010).

Static compliance is defined as the change in vessel volume resulting from a given change in the pressure acting across the vessel walls:

$$C = \Delta V / \Delta P. \qquad (7.3)$$

i.e. the slope of the volume versus pressure curve, with which most clinicians are familiar. In the main fluid compartment of the cerebrospinal system, the CSF reservoir, it is well established that static compliance is not constant but decreases as the compartment becomes distended. The cranial pressure-volume index (PVI)[7] attempts to describe this filling-volume-dependent quantity with a single value (Marmarou et al. 1975).

---

[5] Pascals (Pa) is the S.I. unit of measure with the prefixes k, M and G denoting quantities of 10^3, 10^6 and 10^9, respectively; pounds per square inch (psi) is the less-commonly used imperial unit of measure.

[6] For $E = 1.5$ GPa and a maximum strain of $\varepsilon = 0.1$ (10 %) Eq. (7.2) can be expressed as $\sigma = E\,\varepsilon$, predicting a yield stress of 150 MPa.

[7] PVI is the notional volume (ml) which, when added to the craniospinal volume, causes a tenfold rise in intracranial pressure (mmH_2O).

Heiss et al. (1999) measured the static compliance of the human craniospinal system as ranging between 3 and 15 ml/mmHg. Marmarou et al.'s (1975) measurements on cats suggest that the spinal canal contributes about a third of the total. Conceptualising the cerebrospinal system as collection of compartments (CSF, blood, brain, spinal cord) allows it to be expressed mathematically as a hydraulic *lumped-parameter* model. The compliance and flow resistance between adjacent compartments are 'lumped at' (assigned to) their interface; i.e. these properties are spatially averaged over each compartment and so do not vary within compartments. The solution consists of the discrete compartment pressures as they vary in time. This modelling technique has long been popular in studying disorders of the intracranial CSF system, such as hydrocephalus (e.g. Agarwal et al. 1969; Ambarki et al. 2007), but including intraspinal compartments to investigate syringomyelia has only been attempted in three studies (Chang and Nakagawa 2003, 2004; Elliott et al. 2011). The reason for this disparity is that it is easier to measure the inter-compartmental compliances and resistances of the head than the spinal canal. The cranial volume may be considered constant due to the rigidity of the skull, the so-called Monro-Kellie doctrine, which makes any internal volume (hence pressure) changes well defined. In the spinal canal, the dura mater is surrounded by fluid (distensible veins) and fatty tissue that are necessary for the mobility of the spine so the total compartment volume is variable.

Dynamic compliance is a measure of how *time-varying* changes in pressure and volume are related, as in pulsation. It governs the speed of pressure waves which feature prominently in the spinal canal. A cough elevates the pressure in the thorax that squeezes blood from the thoracic veins into the adjacent epidural veins. Distension of these veins transmits pressure to the spinal subarachnoid space, leading to a travelling pressure wave (Lockey et al. 1975). Williams (1976) was the first to measure the speed of these waves using pressure transducers connected to lumbar puncture needles. A non-invasive technique, using MRI, has recently been developed (Kalata et al. 2009). Wave speeds are typically around 4 m/s.

The propagation of pressure waves in elastic, fluid-filled tubes is a well-studied problem of classical mechanics (Lamb 1898; Womersley 1955). The spinal cord may be thought of as an annular, elastic, solid cylinder, containing an inner cylindrical central canal and sheathed in a tube of pia mater, which in turn is surrounded by an annular cylinder of fluid, the spinal subarachnoid space that is contained by the outer tube of dura mater. A number of mathematical models of the spinal canal have been developed from variants of this system of coaxial tubes (Lockey et al. 1975; Loth et al. 2001; Berkouk et al. 2003; Carpenter et al. 2003; Bertram et al. 2005, 2008; Cirovic 2009; Elliott et al. 2009; Bertram 2009, 2010; Martin et al. 2012; Cirovic and Kim 2012; Elliott 2012; Cheng et al. 2012), elucidating the mechanics of a number of wave modalities.

The wave recorded by Williams (1976), normally described as the 'CSF pulse wave' or the 'subarachnoid pressure wave', is made up of a moving section of cord constriction and an adjacent segment of dura distension. Of the known wave types, this one involves the largest cord motion and so is most easily observed with MRI. Another wave exists in which the cord distends, rather than constricts, but this vanishes as the central canal is obliterated by adulthood (Milhorat et al. 1994). The healthy spinal canal supports at least two further waves, one similar to the previous but also involving lengthwise cord compression and a final wave, almost exclusively involving stretching of the dura (Cirovic 2009; Bertram 2009; Cirovic and Kim 2012). A cough will initiate a pressure pulse in the thoracolumbar region which will set up each of the above wave types in pairs, one wave travelling in the rostral direction and the other in the caudal direction (analogous to the way surface waves radiate from a stone dropped into a pond). These waves will successively reflect at the craniocervical junction and the lumbar cistern, respectively, and vice versa. This may amplify the fluid pressure, and tissue stresses in regions where opposite-moving wave components superimpose. Individual waves will not persist indefinitely though. The motion of fluid and solid spinal components involves kinetic energy (Greek kinētikos, 'to move') that will be

lost to internal friction. This friction is termed *viscosity*[8] in fluids and *viscoelasticity* in solids and is responsible for attenuating waves as they travel. Getting the speed of the CSF pulse wave in a mathematical model to match that measured in the human body has become a useful way of validating the model as it ensures that the dynamic compliance is anatomically realistic.

Although pressure waves are induced by abrupt percussive events, they do not induce a significant amount of CSF motion in the spinal subarachnoid space. The alterations in the shape of the cord and dura occur too quickly for the fluid to keep up so the tissue only has a 'massaging' effect, gently stirring the fluid into motion (Bertram 2009). The reciprocating motion of CSF, well known to the clinician, is due to the lower-frequency pulsations of the cardiac cycle (Bertram 2010). The interdependence of pressure drop and flow rate means that the pressure drop along the spinal subarachnoid space changes from positive to negative, and vice versa, twice per cardiac cycle.

7.4 Mechanics of Syringomyelia

7.4.1 Syrinxes

Mechanically, syrinxes provide the cord with additional localised compliance through displacement of the contained fluid when the syrinx is squeezed into a different shape. Williams (1980) hypothesised that a CSF pulse wave would compress the syrinx at one end, causing the fluid to 'slosh' to the other end, akin to squeezing a water balloon, with the syrinx subsequently extending by tissue dissection. In a computer-based mathematical model, Bertram (2009) demonstrated that a CSF pulse wave travelling rostrocaudally induces axial motion of the syrinx fluid relative to the syrinx walls, leading to fluid pressure at the caudal end of the syrinx exceeding spinal subarachnoid space pressure at the same level, and a

distending (tensile) stress at the caudal tip of the syrinx wall. The pulse wave slowed down as it passed the syrinx, agreeing with Cirovic's (2009) analytical prediction, but not enough to induce the substantial sloshing motions of syrinx fluid proposed by Williams. Consequently, the incurred stress had relatively little potential for tearing the cord tissue and concomitant lengthening of the syrinx. It was acknowledged, though, that a higher-resolution model of the spinal cord is needed to better capture the large stress gradients at the ends of the syrinx.

An additional complication arises with the presence of a syrinx—partial wave reflection and refraction. When a pressure wave reaches a syrinx border, some of the wave continues ahead, and the remainder doubles back due to the change in cross-sectional constitution. Given that there are many types of wave, all moving at different speeds, and that overlapping waves sum together (either reinforcing or cancelling each other), the resulting state of fluid pressure/velocity and tissue stress/displacement easily becomes complicated (e.g. see figure 10 in Bertram 2009). This, unfortunately, does not lend the wave mechanics to intuitive theorising, and some wave-based theories, while being admirable attempts to explain the pathophysiology of syrinx filling, are conceptually unphysical (e.g. Greitz 2006).

7.4.2 Syrinxes with Associated CSF Obstruction

Stenosis occurs at the craniocervical junction in the presence of a herniated hindbrain. It also occurs elsewhere along the spinal subarachnoid space due to, most commonly, scar tissue build-up following spinal trauma. These pathologies obstruct the CSF circulation and act as amplification sites for pressure and stress through the wave reflections that they produce. Their frequent juxtaposition with syrinxes has motivated several groups to pursue a mathematical line of enquiry (Berkouk et al. 2003; Carpenter et al. 2003; Bertram et al. 2005; Elliott et al. 2009; Bertram 2010; Cirovic and Kim 2012; Elliott 2012).

---

[8] For example, honey has more viscosity, or is said to be more viscous ('thicker'), than water, and so loses kinetic energy more rapidly as it flows.

Carpenter and colleagues developed a pathogenesis hypothesis based on the theory of shockwaves (Berkouk et al. 2003; Carpenter et al. 2003). They demonstrated in a mathematical model of coaxial tubes that a pulse wave will become steeper as it propagates, much like a beach wave does on reaching shallow water. If the concomitant elevation in pressure difference between the spinal subarachnoid space and the cord/syrinx reaches the maximal value, then a so-called shock-like elastic jump occurs, which is mathematically similar to the beach wave breaking. When this pressure wave reaches a complete stenosis, the incident and reflected components superimpose, creating an abnormally large tissue stress/syrinx pressure that could potentially damage the cord/expand a syrinx. Although the predictions make a fundamental contribution to the mathematical modelling community, subsequent analysis reveals that the proposed mechanism is unlikely to play a role in the human body; the gross dimensions of the spinal canal and its contents only confer marginal shock-like stress/pressure changes (Elliott et al. 2009). When additional features are included in the coaxial tube representation of the spinal system, such as fluid viscosity and the ability to capture a spectrum of frequencies, shock-like phenomena become even less likely. The pressure waves tend to spread out and attenuate rather than steepen and amplify (Bertram et al. 2005).

Numerous medical (Williams 1980, 1986; Oldfield et al. 1994; Fischbein et al. 1999; Brodbelt et al. 2003b) and engineering (Carpenter et al. 2003; Martin et al. 2005; Bertram 2010) investigators have hypothesised various scenarios in which wave-induced fluid exchange across the pia mater could play a role in syrinx formation. In an analytical model with a permeable pia mater, Elliott (2012) showed that pressure waves will attenuate as they travel due to fluid crossing the pia mater, thereby alleviating the tissue stress therein. Furthermore, dilated perivascular spaces, spinal subarachnoid obstructions, and a stiffer and thicker pia mater—all associated with syringomyelia—will increase transpial flux and retard wave travel. An associated mechanism for syrinx formation remains to be investigated.

A rather different situation arises during the cardiac cycle, unaided by pressure waves, when a partial CSF obstruction occurs at the same level as a syrinx. The obstruction itself acts as a flow resistor causing a localised drop in pressure. This was demonstrated in both simplified (Bilston et al. 2006) and anatomically accurate (Cheng et al. 2012) computer models of a rigid-walled spinal subarachnoid space with simulated subarachnoid scar tissue. When one adds in tissue compliance, the partial obstruction is able to move in response to the reciprocating flow through the spinal subarachnoid space, driven by the cardiac cycle. The net effect is a resonant oscillation[9] in pressure gradient about the obstruction, which lowers in frequency and attenuates more rapidly as the obstruction increases in severity. This has been demonstrated in both mathematical modelling (Bertram 2010) and engineering experiments (Martin and Loth 2009; Martin et al. 2010). The mechanical features of the trans-stenosis pressure gradient (including its time-varying nature and non-negligible viscous forces) meant that a Venturi effect,[10] postulated elsewhere as being important (Greitz 2006), was in fact small (Bertram 2010) if not nonexistent (Martin and Loth 2009; Martin et al. 2010). More dramatically, the addition of a syrinx at the same level as the stenosis created a one-way valve. The pressure drop across the stenosis caused the syrinx to be compressed at one end and distended at the other, thereby narrowing the already obstructed spinal subarachnoid pathway. As the flow resistance past the obstruction was higher during (simulated) diastole than systole the result was a one-way valve, *dissociating* the CSF

---

[9] A natural frequency of the cerebrospinal system, coinciding with the cardiac excitation frequency. One familiar example is a playground swing. Pushing a person in a swing at its resonant frequency will make the swing go higher, while pushing the swing at a faster or slower tempo will result in smaller arcs.

[10] The reduction in pressure and increase in velocity that occurs, due to mass conservation alone, when a fluid flows through a narrowed section of pipe (and vice versa). Named after Giovanni Battista Venturi (1746–1822), an Italian physicist, this is an application of Bernoulli's equation; for details see (Tritton 1988; Houghton and Carpenter 2003).

pressure caudal to the stenosis from that rostral to it (Bertram 2010). This longitudinal pressure dissociation had two important ramifications. Firstly, the pressure in the spinal subarachnoid space caudal to the stenosis was higher than that in the underlying syrinx when averaged over the cardiac cycle (also predicted by Chang and Nakagawa 2004). This presents a pressure gradient favouring CSF flow into the syrinx, potentially through the perivascular spaces of penetrating arteries; i.e. a filling mechanism. Secondly, the distending stress at the caudal end of the syrinx was much higher with the one-way valve in operation, in fact high enough (relative to the input pressure amplitude) to raise the possibility of cord tissue rupture and syrinx expansion (Bertram 2010).

While the existing models can predict stresses and strains near a fissure, it is the spinal cord's microstructure that determines the critical conditions for rupture and this has not yet been modelled. The study of *fracture mechanics* provides the relevant mathematical techniques, a discipline born out of the demand for reliable ships and aeroplanes in World War II (Anderson 2005). The empirical data needed to complete such a model (e.g. the material property 'fracture toughness') have not, however, been obtained. A rat model of posttraumatic syringomyelia showed that there is a proliferation of cells following syrinx formation that are involved in glial scar formation (Tu et al. 2010, 2011; Fehlings and Austin 2011). This suggested a mechanism to limit syrinx enlargement, which is consistent with the principles of fracture mechanics.

7.4.3   Cord Tethering

In addition to obstructing CSF flow, subarachnoid scar tissue may tether the cord, constraining its movement. Bertram et al. (2008) mathematically predicted that CSF pulse wave transmission past a tethered section of cord could lead to a distending stress in the underlying tissue. The computed stress values were not large enough to conclude a damaging effect but the simulated tethering did not include flow obstruction and their simultaneous effect remains to be investigated.

7.4.4   Perivascular Pumping

It is a commonly held view that syrinx fluid originates from CSF. This is based on their having a similar chemical composition (Table 17.1) and physical properties (Kiernan 1998; Bloomfield et al. 1998) and is reinforced by the histological studies that establish the perivascular spaces around penetrating arteries as forming a hydraulic connection between the syrinx cavity and the spinal subarachnoid space (Brodbelt and Stoodley 2007). On this premise, a computer model of fluid flow through a perivascular space has been developed (Bilston et al. 2010). The inner surface was cyclically distended to simulate the cardiac pulsation of the enclosed artery and the superficial end of the perivascular space was given a pressure signal, computed from flow-rate measurements in the human spinal subarachnoid space (Bilston et al. 2006). The relative timing of these two cardiac-based pulsations was varied. Provided the two pulses were not in synchrony, a net amount of fluid would be pumped into or out of the cord, with maximal inflow occurring when the pulses were out of phase. It was postulated that interruptions to the local blood supply, such as might be created by scar tissue, could lead to these phase differences (Bilston et al. 2010). Martin et al. (2012) demonstrated that, in fact, there may be a *natural* variation between the timing of the vascular and CSF pulses in the spinal canal. In a computer model that included the entire cardiovascular tree represented as a collection of elastic tubes interacting with a like representation of the spinal subarachnoid space, the vascular-to-CSF pulse delay was found to vary a great deal along the length of the spinal canal depending on craniospinal compliance and vascular anatomy.

Elliott et al. (2011) examined how effective the phasic-pumping mechanism would be when perivascular spaces are incorporated into a lumped-parameter model of the whole cerebrospinal system. The model had compartments representing (1) the spinal cord, (2) the spinal subarachnoid space, (3) the venous bed of the spinal cord, (4) the venous bed of the spinal

subarachnoid space and epidural space and (5) a vascular pressure source. Fluid was permitted to exchange between the spinal subarachnoid space and the spinal cord (interstitium). Their pia mater interface was compliant, and similar compliances allowed for collapse of the cord's venous bed and displacement of fluid in the epidural space. The phasic pumping of CSF into the cord was predicted. However, the pressure gradient driving fluid into the cord also constricts the cord, so the two effects are in competition. Thus, for the phasic-pumping mechanism to operate, the spinal cord must have volume compliance due to displacement of blood from the cord venous bed, which is unlikely to be substantial.

7.5   Pathophysiology Yet to Be Modelled

Some aspects of spinal pathophysiology are less amenable to mathematical modelling than others, leaving their mechanics relatively uncharted. We highlight two notable examples.

Greitz proposed a syringogenesis mechanism in which the syrinx fluid is derived from blood plasma, rather than CSF, and that it involves a disruption to the blood-spinal cord barrier (e.g. Greitz 2006). While some mechanical features of the proposed event cascade may require further thought, the spinal arteries certainly provide a favourable pressure gradient for flow into a syrinx. In a recent paper on normal pressure hydrocephalus, Tully and Ventikos (2011) adapted a method from geomechanics for modelling the effects of porosity: the brain parenchyma was treated as an elastic solid matrix, permeated by low-porosity pores (interstitial spaces) and high-porosity fissures (blood vessels) with fluid transport permitted between them (the blood–brain barrier). Such an approach may also prove useful for the spinal cord and would permit investigation of the proposal of oedema as a 'pre-syrinx state' (Fischbein et al. 2000). Before attempting this, however, a better understanding is required of the mechanical interaction between the elastic cord tissue and fluid-filled interstitial pores. Harris and Hardwidge's (2010) computer model

of a porous spinal cord and Elliott's (2012) analytical model of wave-induced fluid transport across the pia mater provide a mathematical starting point.

The herniated hindbrain features prominently in Chiari-based syringomyelia. Williams (1974) built a physical model of the cerebrospinal system that simulated the hindbrain-plugging of the craniocervical junction following a cough. This has not yet been attempted mathematically but others have modelled the simpler problem, when the hindbrain is 'frozen' in position (Roldan et al. 2009). The dynamic range of CSF velocities at the craniocervical junction makes obtaining accurate validation data an additional challenge (Santini et al. 2009; Odéen et al. 2011; Battal et al. 2011).

Conclusions

In our everyday lives, we observe and experience certain physical phenomena that occur in a predictable way. These events may be described by the laws of mechanics which can be used to construct a mathematical model—a theoretical representation of a physical system.

The cerebrospinal system consists of solid and fluid components that interact through their volume compliance. From this single concept, we can gain an appreciation of how:

1. Abrupt pressure impulses, such as from a cough, lead to wave propagation in the spinal canal.
2. Slower pulsation, due to the cardiac cycle, accelerates the fluid in the spinal subarachnoid space back and forth.

An isolated syrinx increases the cord's compliance but does not appear to lead to adverse pressures or stresses. When coupled with an overlying stenosis, however, a one-way valve may be set up in the spinal subarachnoid space that presents favourable circumstances for CSF flow into the syrinx and syrinx elongation by stress-induced tissue rupture. Another one-way valve, in the perivascular spaces, also promotes CSF influx but is limited by the collapsibility of the cord's venous reservoir.

It is hoped that this chapter gives the clinician greater accessibility to mathematical modelling concepts which will facilitate closer collaborations with mathematicians and engineers.

References

Agarwal GC, Berman BM, Stark L (1969) A lumped parameter model of the cerebrospinal fluid system. IEEE Trans Biomed Eng BME-16:45–53

Ambarki K, Baledent O, Kongolo G et al (2007) A new lumped-parameter model of cerebrospinal hydrodynamics during the cardiac cycle in healthy volunteers. IEEE Trans Biomed Eng 54(3):483–491

Anderson TL (2005) Fracture mechanics: fundamentals and applications. CRC Press/Taylor & Francis, Boca Raton

Barenblatt GI (2003) Scaling. Cambridge texts in applied mathematics. Cambridge University Press, Cambridge

Battal B, Kocaoglu M, Bulakbasi N et al (2011) Cerebrospinal fluid flow imaging by using phase-contrast MR technique. Br J Radiol 84:758–765

Berkouk K, Carpenter PW, Lucey AD (2003) Pressure wave propagation in fluid-filled co-axial elastic tubes, part 1: basic theory. ASME J Biomech Eng 125(6): 852–856

Bertram CD (2009) A numerical investigation of waves propagating in the spinal cord and subarachnoid space in the presence of a syrinx. J Fluids Struct 25(7): 1189–1205

Bertram CD (2010) Evaluation by fluid/structure-interaction spinal-cord simulation of the effects of subarachnoid-space stenosis on an adjacent syrinx. ASME J Biomech Eng 132(6):061009

Bertram CD, Brodbelt AR, Stoodley MA (2005) The origins of syringomyelia: numerical models of fluid/structure interactions in the spinal cord. ASME J Biomech Eng 127(7):1099–1109

Bertram CD, Bilston LE, Stoodley MA (2008) Tensile radial stress in the spinal cord related to arachnoiditis or tethering: a numerical model. Med Biol Eng Comput 46(7):701–707. doi:10.1007/s11517-008-0332-0

Bilston LE, Stucky CL (2011) Mechanotransduction in the nervous system. In: Bilston LE (ed) Neural tissue biomechanics. Studies in mechanobiology, tissue engineering and biomaterials. Springer, Berlin, pp 231–245

Bilston LE, Fletcher DF, Stoodley MA (2006) Focal spinal arachnoiditis increases subarachnoid space pressure: a computational study. Clin Biomech 21(6):579–584

Bilston LE, Stoodley MA, Fletcher DF (2010) The influence of the relative timing of arterial and subarachnoid space pulse waves on spinal perivascular cerebrospinal fluid flow as a possible factor in syrinx developments. J Neurosurg 112(4):808–813

Bloomfield IG, Johnson IH, Bilston LE (1998) Effects of proteins, blood cells and glucose on the viscosity of cerebrospinal fluid. Pediatr Neurosurg 28(5):246–251

Bradbury M (1993) Anatomy and physiology of CSF. In: Schurr PH, Polkey CE (eds) Hydrocephalus. Oxford University Press, Oxford, New York, pp 19–47

Brodbelt A, Stoodley M (2007) CSF pathways: a review. Br J Neurosurg 21(5):510–520

Brodbelt A, Stoodley M, Watling A et al (2003a) Fluid flow in an animal model of post-traumatic syringomyelia. Eur Spine J 12:300–306

Brodbelt AR, Stoodley MA, Watling AM et al (2003b) Altered subarachnoid space compliance and fluid flow in an animal model of posttraumatic syringomyelia. Spine 28(20):E413–E419

Carpenter PW, Berkouk K, Lucey AD (2003) Pressure wave propagation in fluid-filled co-axial elastic tubes, part 2: mechanisms for the pathogenesis of syringomyelia. ASME J Biomech Eng 125(6):857–863

Chang HS, Nakagawa H (2003) Hypothesis on the pathophysiology of syringomyelia based on simulation of cerebrospinal fluid dynamics. J Neurol Neurosurg Psychiatry 74(3):344–347

Chang HS, Nakagawa H (2004) Theoretical analysis of the pathophysiology of syringomyelia associated with adhesive arachnoiditis. J Neurol Neurosurg Psychiatry 75(5):754–757. doi:10.1136/jnnp.2003.018671

Cheng S, Stoodley MA, Wong J et al (2012) The presence of arachnoiditis affects the characteristics of CSF flow in the spinal subarachnoid space: a modelling study. J Biomech 45(7):1186–1191

Cirovic S (2009) A coaxial tube model of the cerebrospinal fluid pulse propagation in the spinal column. ASME J Biomech Eng 131(2):021008

Cirovic S, Kim M (2012) A one-dimensional model of the spinal cerebrospinal-fluid compartment. ASME J Biomech Eng 134(2):021005

Dym CL, Ivey ES (1980) Principles of mathematical modelling. Academic Press Inc, New York

Elliott NSJ (2012) Syrinx fluid transport: modeling pressure-wave-induced flux across the spinal pial membrane. ASME J Biomech Eng 134(3):031006. doi:10.1115/1.4005849

Elliott NSJ, Lockerby DA, Brodbelt AR (2009) The pathogenesis of syringomyelia: a re-evaluation of the

elastic-jump hypothesis. ASME J Biomech Eng 131(4):044503

Elliott NSJ, Lockerby DA, Brodbelt AR (2011) A lumped-parameter model of the cerebrospinal system for investigating arterial-driven flow in posttraumatic syringomyelia. Med Eng Phys 33:874–882

Elliott NSJ, Bertram CD, Martin BA et al (2013) Syringomyelia: a review of the biomechanics. J Fluids Struct 40:1–24. doi:10.1016/j.jfluidstructs.2013.01.010

England MA, Wakeley JW (2006) Color atlas of the brain and spinal cord: an introduction to normal neuroanatomy. Mosby, Philadelphia

Ethier CR, Simmons CA (2007) Introductory biomechanics: from cells to organisms. Cambridge University Press, Cambridge

Fehlings MG, Austin JW (2011) Editorial: posttraumatic syringomyelia. J Neurosurg Spine 14(5):570–572

Feynman RP (1965) The character of physical law. M.I.T Press, Cambridge

Fischbein NJ, Dillon WP, Cobbs C et al (1999) The "pre-syrinx" state: a reversible myelopathic condition that may precede syringomyelia. AJNR Am J Neuroradiol 20(1):7–20

Fischbein NJ, Dillon WP, Cobbs C et al (2000) The "pre-syrinx" state: is there a reversible myelopathic condition that may precede syringomyelia? Neurosurg Focus 8(3):1–13

Fung YC (1993) Biomechanics: mechanical properties of living tissues, 2nd edn. Springer, New York

Greitz D (2006) Unravelling the riddle of syringomyelia. Neurosurg Rev 29(4):251–264

Hagenbach E (1860) Ueber die Bestimmung der Zähigkeit einer Flüssigkeit durch den Ausfluss aus Röhren [On the determination of the viscosity of a fluid by flow experiments through tubes]. Annalen der Physik 185(3):385–426. doi:10.1002/andp.18601850302

Harris PJ, Hardwidge C (2010) A porous finite element model of the motion of the spinal cord. In: Constanda C, Pérez ME (eds) Integral methods in science and engineering, vol 2, Computational methods. Birkhäuser, Boston, pp 193–201

Heiss JD, Patronas N, DeVroom HL et al (1999) Elucidating the pathophysiology of syringomyelia. J Neurosurg 91:553–562

Houghton EL, Carpenter PW (2003) Aerodynamics for engineering students, 5th edn. Butterworth-Heinemann, Amsterdam

Johanson CE (2008) Choroid plexus—cerebrospinal fluid circulatory dynamics: impact on brain, growth, metabolism, and repair. In: Conn PE (ed) Neuroscience in medicine, 3rd edn. Human Press, Totown

Kalata W, Martin BA, Oshinski JN et al (2009) MR measurement of cerebrospinal fluid velocity wave speed in the spinal canal. IEEE Trans Biomed Eng 56(6):1765–1768

Kiernan JA (1998) Barr's the human nervous system, an anatomical viewpoint, 7th edn. Lippincott-Raven, Philadelphia

Lamb H (1898) On the velocity of sound in a tube, as affected by the elasticity of the walls. Manch Literary Philos Soc Memoirs Proc 42:1–16

Lockey P, Poots G, Williams B (1975) Theoretical aspects of the attenuation of pressure pulses within cerebrospinal-fluid pathways. Med Biol Eng 13(6):861–869

Loth F, Yardimci MA, Alperin N (2001) Hydrodynamic modelling of cerebrospinal fluid motion within the spinal cavity. ASME J Biomech Eng 123:71–79

Maikos JT, Elias RAI, Shreiber DI (2008) Mechanical properties of dura mater from the rat brain and spinal cord. J Neurotrauma 25(1):38–51

Marmarou A, Shulman K, LaMorgese J (1975) Compartment analysis of compliance and outflow resistance of the cerebrospinal fluid system. J Neurosurg 43:523–534

Martin BA, Loth F (2009) The influence of coughing on cerebrospinal fluid pressure in an in vitro syringomyelia model with spinal subarachnoid space stenosis. Cerebrospinal Fluid Res 6(17):18. doi:10.1186/1743-8454-6-17

Martin BA, Kalata W, Loth F et al (2005) Syringomyelia hydrodynamics: an in vitro study based on in vivo measurements. ASME J Biomech Eng 127(7):1110–1120

Martin BA, Labuda R, Royston TJ et al (2010) Spinal subarachnoid space pressure measurements in an in vitro spinal stenosis model: implications on syringomyelia theories. ASME J Biomech Eng 132(11):111007

Martin BA, Reymond P, Novy P et al (2012) A coupled hydrodynamic model of the cardiovascular and cerebrospinal fluid system. Am J Physiol Heart Circ Physiol 302(7):H1492–H1509

Meyers MA, Chen P-Y, Lin AY-M et al (2008) Biological materials: structure and mechanical properties. Prog Mater Sci 53:1–206

Milhorat TH, Kotzen RM, Anzil AP (1994) Stenosis of central canal of spinal cord in man: incidence and pathological findings in 232 autopsy cases. J Neurosurg 80:716–722

Murthy DNP, Page NW, Rodin EY (1990) Mathematical modelling: a tool for problem solving in engineering, physical biological and social sciences. Permagon Press, Oxford

Odéen H, Uppman M, Markl M et al (2011) Assessing cerebrospinal fluid flow connectivity using 3D gradient echo phase contrast velocity encoded MRI. Physiol Meas 32(4):407–421

Oldfield EH, Muraszko K, Shawker TH et al (1994) Pathophysiology of syringomyelia associated with Chiari I malformation of the cerebellar tonsils. Implications for diagnosis and treatment. J Neurosurg 80:3–15

Ozawa H, Matsumoto T, Ohashi T et al (2004) Mechanical properties and function of the spinal pia mater. J Neurosurg Spine 1:122–127

Popper K (1998) Science: conjectures and refutations. In: Cover JA, Curd M (eds) Philosophy of science: the central issues. WW Norton & Co, New York, pp 3–10

Rennels ML, Gregory TF, Blaumanis OR et al (1985) Evidence for a 'paravascular' fluid circulation in

the mammalian central nervous system, provided by the rapid distribution of tracer protein throughout the brain from the subarachnoid space. Brain Res 326(1):47–63

Roldan A, Weiben O, Haughton V et al (2009) Characterization of CSF hydrodynamics in the presence and absence of tonsillar ectopia by means of computational flow analysis. AJNR Am J Neuroradiol 30:941–946

Saadoun S, Papadopoulos MC (2010) Aquaporin-4 in brain and spinal cord oedema. Neuroscience 168: 1036–1046

Santini F, Wetzel SG, Bock J et al (2009) Time-resolved three-dimensional (3D) phase-contrast (PC) balanced steady-state free precession (bSSFP). Magn Reson Med 62:966–974

Stewart I (2011) Mathematics of life. Basic Books, New York

Stoodley MA, Jones NR, Brown CJ (1996) Evidence for rapid fluid flow from the subarachnoid space into the spinal cord central canal in the rat. Brain Res 707(2): 155–164

Stoodley MA, Gutschmidt B, Jones NR (1999) Cerebrospinal fluid flow in an animal model of non-communicating syringomyelia. Neurosurgery 44(5): 1065–1077

Sutera SP, Skalak R (1993) The history of Poiseuille's law. Annu Rev Fluid Mech 25:1–19

Tritton DJ (1988) Physical fluid dynamics, 2nd edn. Clarendon, Oxford

Tu J, Liao J, Stoodley MA, Cunningham AM (2010) Differentiation of endogenous progenitors in an animal model of post-traumatic syringomyelia. Spine 35(11):1116–1121

Tu J, Liao J, Stoodley MA et al (2011) Reaction of endogenous progenitor cells in a rat model of post-traumatic syringomyelia. J Neurosurg Spine 14(5): 573–582

Tully B, Ventikos Y (2011) Cerebral water transport using multiple-network poroelastic theory: application to normal pressure hydrocephalus. J Fluid Mech 667: 188–215

Tunturi AR (1977) Elasticity of the spinal cord dura in the dog. J Neurosurg 47(3):391–396

Tunturi AR (1978) Elasticity of the spinal cord, pia, and denticulate ligament in the dog. J Neurosurg 48(6): 975–979

Williams B (1974) A demonstration analogue for ventricular and intraspinal dynamics (DAVID). J Neurol Sci 23:445–461

Williams B (1976) Cerebrospinal fluid pressure changes in response to coughing. Brain 99:331–346

Williams B (1980) On the pathogenesis of syringomyelia: a review. J R Soc Med 73(11):798–806

Williams B (1986) Progress in syringomyelia. Neurol Res 8:130–145

Womersley JR (1955) Method for the calculation of velocity, rate of flow and viscous drag in arteries when the pressure gradient is known. J Physiol 127: 553–563

Zhang ET, Inman CBE, Weller RO (1990) Interrelationships of the pia mater and the perivascular (Virchow-Robin) spaces in the human cerebrum. J Anat 170:111–123