My notes on VW model (Feb 2010)

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The VW model was finally published in 2009 but it was first submitted in 2007, and rejected (twice!). I wrote it in a tutorial style because I found the literature in this area very confusing and sometimes misleading. I thought I would be doing a service to clarify various concepts and bring material science and biology together. But the reviewers thought it was a waste of space. Obviously there were other aspects that the reviewers objected.

I kept the rejected manuscript and gave it to my graduate student as background reading for modelling biophysical systems. She said it was the most helpful reading she could find in this specific area. (Thanks!)

So this note was based on my first manuscript. I have deleted most material that the reviewers objected, deleted the results section as it is similar to the published paper. I have kept a section in the discussion in which I suggested the model could be used as a unified model for stress-strain modelling. I still think so… but not the reviewer …

I hope the material is helpful for graduate students to understand how venous blood vessels might work and where all the equations in the literature come from.

Modelling delayed compliance using a dynamic parameter of the pressure-volume curve

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Abstract

The delayed response of cerebral blood volume (CBV) to rapid changes in cerebral blood flow (CBF) is often described by the term 'delayed compliance'. This paper examined the viscoelastic properties of blood vessels, and presented a dynamic model relating changes in CBF to changes in CBV. A novel feature of this viscoelastic windkessel (VW) model is that the parameter characterising the pressure-volume relationship of blood vessels was modelled dynamically as a function of the rate of change of CBV, taking on different values during vessel dilation and contraction, and producing different pressure-volume curves during the two transient states. The VW model was demonstrated to have the following characteristics typical of viscoelastic materials: (1) hysteresis, (2) creep, and (3) stress relaxation. The delayed compliance was an emergent property of the model which was able to predict the observed differences between the time series of CBV and that of CBF measurements following changes in neural activity. [delete] In addition, the VW model augments the Maxwell and Voigt models of viscoelastic material by incorporating hysteresis effects. Hence it provides a unified model of the viscoelastic properties of the vasculature with more general applications in the study and modelling of the haemodynamics of circulatory and cardiovascular systems and their dysfunction.

Introduction

It is known that a temporal mismatch exists between the changes in cerebral blood flow (CBF) and cerebral blood volume (CBV) in response to changes in neural activity. Specifically CBV returns to baseline level much slower than the CBF. The coupling between CBF and CBV is a critical component in dynamic models linking the Blood Oxygen Level Dependent (BOLD) signals obtained in functional Magnetic Resonance Imaging (fMRI) studies to the underlying changes in neural activity (Buxton et al., 2004; Friston et al., 2000; Huppert et al., 2007; Zheng et al., 2005; Zheng et al., 2002) . In particular the post-stimulus undershoot observed in the BOLD signal was thought to be partly caused by the mismatch between CBF and CBV (Buxton et al., 1998; Mandeville et al., 1999). Although there are several models that mimic this difference in response, they are not based on the physics of viscoelastic properties of blood vessels. We present here a formal model, which is a development of that proposed by Mandeville et al (1999), in which the phenomenon of delayed compliance is an emergent property.

The viscoelastic properties of blood vessels have been extensively studied by physiologists. Weber (1846) observed that an arterial wall being stretched would expand rapidly to a certain length, and then continue expansion gradually for maybe hours or days before reaching an equilibrium. Roy (1881) used the phrase 'elasticity after-action' to describe this phenomenon which was later termed 'the delayed compliance' by Alexander et al (Alexander et al., 1953). The pressure-volume relationships of blood vessels were measured under static and dynamic conditions by various researchers (Alexander et al., 1953; Bergel, 1961; Linehan et al., 1986; Porciuncula et al., 1964; Remington and Alexander, 1955). The dynamic conditions were characterised by hysteresis during cycles of vessel dilation and contraction.

Many of the models of blood vessels and the circulation system are based on the windkessel theory (Frank, 1930). In the simplest form, the relationship between arterial blood pressure and blood flow was modelled in electrical terms by a resistor and a capacitor connected in parallel. This was known as the two-element windkessel model. The capacitor models the blood vessel compliance and the resistor models the vessel resistance encountered by blood flowing through the vascular system. Extensions of the simple model into three- and four-element windkessel models were developed (Fogliardi et al., 1996; Jones, 1969; Molino et al., 1998; Segers et al., 1999; Stergiopulos et al., 1999; Westerhof et al., 1971) to better characterise the pulmonary arterial system. The resistors and capacitors in these models were linked to blood vessel radius (or volume) and arterial blood pressure. The windkessel model was further extended into multi-compartment models (Linehan et al., 1986; Ursino et al., 2000). All of these models suffered from the same weakness in that they only considered static compliance and not the dynamic compliance.

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In this paper, both the static and dynamic behaviour of blood vessels will be modelled by incorporating their viscoelastic properties. As will be shown below, the dynamic compliance is found to be an emergent property of the model rather than modelled directly (Fogliardi et al., 1996; Linehan et al., 1986; Ursino et al., 2000). The key point is that a parameter characterising the steady state pressure-volume curve becomes time varying during transient states. This is modelled by a simple first order nonlinear dynamic system driven by the rate of change of volume. At steady state the parameter returns to its static value on the steady state pressure-volume curve. During transient states (i.e., following changes in CBF), the parameter takes on different values depending on the rate of change of volume. The model will be referred to as the viscoelastic windkessel (VW) model throughout this paper.

Theory

Viscoelasticity of blood vessels

Blood vessels are known to be viscoelastic, i.e., their behaviour can be thought of as somewhere between that of elastic solids and liquids. A cylinder made of pure elastic material has the property that a step change in transmural pressure (stress) causes instantaneous step change in vessel volume (strain), and vice versa. On the other hand, the mechanical behaviour of fluid is such that stress is directly proportional to rate of change of strain (for Newtonia fluid), independent of the strain itself. For blood vessels, the relationship between transmural pressure (inside pressure - outside pressure) and vessel volume exhibits the characteristics of both elastic solids and liquids in that it is dependent on baseline conditions as well as the rate of change of the driving input (volume or pressure).

Poiciuncula et al (1964) conducted a series of experiments in which the transmural pressure was manipulated and changes in the volume of a typical large vein (the external jugular vein) were measured as a function of time. They observed that a step increase in transmural pressure causes a rapid increase in volume, followed by a slow but continuous increase in volume over a longer time period in the absence of any further changes in transmural pressure. This is known as ‘creep’, a term used in material science to describe the tendency of a material to deform over a long period of time, and is one of the properties of viscoelastic material (Young, 1983). This characteristic is depicted in Figure 1(a). Poiciuncula et al. also demonstrated that as transmural pressure were varied sinusoidally, the volume of the vein was smaller during vessel dilation than it was during vessel contraction at any given pressure. Hence the pressure-volume curve forms a loop during the period of the sinusoid, as shown in Figure 1(b). This is another property of viscoelastic material known as hysteresis. Furthermore it was shown (see Figures 5 and 6 of (Porciuncula et al., 1964)) that the shape of the hysteresis was dependent on the period of the sinusoidal pressure as well as the mean transmural pressure for a given sinusoidal amplitude.

Instead of manipulating transmural pressure, experiments were also conducted by manipulating the radius or length of a blood vessel while the vessel wall tension was measured (Linehan et al., 1986; Remington and Alexander, 1955). It was shown that a rapid increase in vessel diameter (or length) resulted in a sharp increase in the vessel wall tension before it gradually decreases to a new steady state. This is known as ‘stress relaxation’ (Figure 1(c)) and is a term used to describe how a viscoelastic material relieves stress under constant strain.

All of the above characteristics of viscoelastic material can be shown to be dependent on the rate of change of the manipulated variable. For instance if the vessel volume is increased at slow enough rate, increase in vessel wall tension will be gradual without any overshoot, hence stress relaxation will not occur. Also if the transmural pressure changes slowly in a sinusoidal fashion, hysteresis will almost disappear (Porciuncula et al., 1964).

If one increases transmural pressure of a (venous) blood vessel in steps, and at each step the volume of the vessel is measured *once it has reached its steady state*, then the steady state pressure-volume (P-V) curve of the vessel can be obtained. The characteristic of the curve is that for the same transmural pressure drop, the change in volume is higher at a lower baseline pressure than that at a higher baseline value. This is depicted in Figure 2(a). It is crucial to recognise that during dynamic changes of vessel dilation and contraction, the P-V curve will deviate from this steady-state curve, resulting in hysteresis. The dynamic model described in this paper is derived from the P-V curve of a blood vessel and exhibits properties of 'creep', 'stress relaxation' and 'hysteresis', as observed in viscoelastic materials.

Compliance

The term 'compliance' is used to describe the ability of a blood vessel to expand and contract as transmural pressure across the vessel wall changes. It is determined by the amount of volume change per unit change in transmural pressure, and hence is the gradient of the P-V curve, shown in Figure 2(a). As the curve is generally nonlinear, the vessel compliance varies from one steady state to another. During the transient period, the P-V relationship of a blood vessel deviates from the steady state curve. Based on these observations, we classify the compliance of a blood vessel into two categories: one is *static* compliance characterising the relationship between transmural pressure and volume at steady state (or equilibrium), the other *dynamic* compliance reflecting the properties of the blood vessel during dilation and contraction. Whereas the static compliance is calculated from the steady-state P-V curve, the dynamic compliance is dependent on the rate of change of the manipulated variables (volume or pressure).

Several models have been used in the literature to relate static compliance to the transmural pressure. For example, Fogliardi et al (1996) tested two models of static compliance. One modelled compliance as an exponential decay in transmural pressure. The implication of this model is that the steady state volume increases exponentially with pressure, converging to a constant as pressure increases. The other model characterised compliance as a bell shaped curve with respect to transmural pressure, thus implying an S-shaped curve (or a sigmoid) for the steady state P-V relationship. Ursino et al (2000) assumed that static compliance was inversely proportional to the transmural pressure. Hence steady state blood volume was related to pressure via a logarithmic function. The common problem associated with all these models is that they assumed that during dynamic phases, the P-V curve remained unchanged. To our knowledge no other models in the literature have distinguished between static and dynamic compliance in their attempt to model blood vessel compliance. This distinction is a fundamental property of viscoelastic materials and is made explicit in deriving the viscoelastic windkessel (VW) model presented here.

The relationship between CBF and CBV

We start with the widely used balloon model (Buxton et al., 1998) which was designed to capture the transient aspect of the BOLD signal. As the BOLD signal reflects primarily changes in deoxy-hemoglobin, the balloon model assumes that the blood volume changes occur mainly in the venous compartment, and that the entire compartment is modelled by a 'balloon', shown in Figure 3(a). F_{in} is the blood inflow to the venous compartment, and F_{out} is the blood outflow from the compartment. P_1 represents the blood pressure at the capillary end of the venous compartment, P_2 represents the blood pressure at the outlet of the venous compartment, and P_{ic} is the intracranial pressure. V denotes blood volume and dV/dt is the rate of change of blood volume. Conservation of mass requires that

$$\frac{dV}{dt} = F_{in} - F_{out} \tag{1}$$

Assuming blood is an incompressible uniform viscous liquid, the blood vessel is a straight cylindrical tube, and blood flow is laminar stationary, then according to Poiseuille's Law, blood flow is proportional to the longitudinal pressure drop $P_L = P_1 - P_2$ along the compartment and the fourth power of the radius of the tube as

$$F_{out} = \frac{\pi\rho^4 P_L}{8\eta L} \tag{2}$$

where ρ is the internal radius of the vessel, η is the blood viscosity and L is the length of the vessel along the axial direction. By assigning the resistance of the tube as

$$R = \frac{8\eta L}{\pi\rho^4}, \tag{3}$$

blood flow can be written in terms of the resistance and the longitudinal pressure drop as

$$F_{out} = \frac{P_L}{R} \tag{4}$$

This equation resembles the current-voltage-resistor relationship in electrical circuit theory, hence the electrical analogue of the venous compartment is often used in the literature, as shown in Figure 3(b) (i.e., a simple two-element windkessel model). The venous resistance is modelled by the time-varying resistor R and the venous compliance is modelled by the time-varying capacitor C.

Equation (3) implies that for a fixed cylinder length and viscosity, and for laminar flow, the venous resistance R is inversely proportional to the fourth power of the internal radius of the vessel, i.e., $R \propto 1/\rho^4$. As the volume of a cylindrical tube is proportional to the square of the vessel radius, the resistance is related to the volume of the tube by $R \propto \frac{1}{V^2}$. However the assumptions under which Poiseuille's Law holds are not generally satisfied in the venous compartment. For example the blood flow is less likely to be laminar stationary during transient changes in flow. Also blood vessels are branched and curved instead of straight. A modification of the vessel resistance expressed in terms of blood volume is often used (Mandeville et al., 1999) as

$$R \propto \frac{1}{V^{\gamma}} \tag{5}$$

where the exponent γ is equal to 2 under laminar flow in which resistance is lower than that under turbulent flow. Note that no simple equation exists to compute resistance for turbulent flow. Eqn. (5) above is an approximation with the exponent $\gamma < 2$. This model of blood vessel resistance characterises the time varying nature of the resistor, i.e., as blood (vessel) volume increases the vessel resistance decreases. Substituting equations (4) and (5) into (1) yields:

$$\frac{dV}{dt} = F_{in} - \frac{P_L}{R} = F_{in} - k_1 P_L V^{\gamma} \tag{6}$$

where k_1 contains all the coefficients and parameters which will be eliminated by normalisation at a later stage. The above model links CBF, CBV and the longitudinal pressure across the venous compartment. However the longitudinal pressure gradient P_L cannot be easily measured in a physiological experiment. To eliminate it from the above equation, we turn to the P-V curve associated with the static compliance of the vessel.

A viscoelastic vessel

The general shape of the steady state P-V curve of a blood vessel is depicted in Figure 2(a). A mathematical model adopted by Mandeville et al (1999) to describe the shape is

$$V = A P_T^{1/\beta}, \quad \beta > 1 \tag{7}$$

where P_T denotes the transmural pressure and the constraint on the constant $\beta > 1$ ensures diminished volume reserve at high transmural pressure. The parameter A is dependent on the vascular tone of the blood vessel (Klabunde, 2005) and is constant for the steady state P-V curve of any given vessel. If we sweep through a range of values in the parameter A, a family of P-V curves can be obtained, shown in Figure 2(b).

As the blood vessel dilates and contracts, the P-V relationship of the vessel exhibits the characteristic of hysteresis, as plotted in Figure 2(b) superimposed with the family of steady-state P-V curves. This suggests that hysteresis could be modelled by allowing the parameter A to vary during the dynamic period, but returns to its baseline value as a new P-V steady state is reached. More specifically, the parameter A decreases from its baseline value during vessel dilation, but increases during vessel contraction.

The transmural pressure P_T across the blood vessel wall is generally different from the longitudinal pressure gradient P_L along the vessel. However for the venous compartment, these two quantities may be assumed the same (Mandeville et al., 1999) due to the fact that the intracranial pressure and the pressure at the outlet of the venous compartment are similar in magnitude (Mayhan and Heistad, 1986; Orrison et al., 1995; Wei and Kontos, 1982). Hence the model uses the assumption that $P_L = P_T$ and combines equations (6) and (7) to yield

$$\frac{dV}{dt} = F_{in} - \frac{k_1 V^{\beta+\gamma}}{A^{\beta}} \tag{8}$$

We now have a model which relates CBF, CBV and the unknown time-varying parameter A. As most measurement techniques for CBF and CBV measure changes rather than absolute values, the above model can be further written in terms of the following normalised quantities:

$$f_{in} = \frac{F_{in}}{F_0}, \quad f_{out} = \frac{F_{out}}{F_0}, \quad v = \frac{V}{V_0}, \quad a = \frac{A}{A_0}$$

The subscript 0 denotes the baseline condition. The normalised model is in the form

$$\tau_v \frac{dv}{dt} = f_{in} - \frac{v^{\beta+\gamma}}{a^{\beta}} \tag{9}$$

where $\tau_v = \dfrac{V_0}{F_0}$ is the venous transit time. Note that the unknown constant k_1 is cancelled during normalisation. The above model can be further simplified as

$$\tau_v \frac{dv}{dt} = f_{in} - \frac{v^{\alpha}}{w} \tag{10}$$

where $\alpha = \beta + \gamma$ is an unknown time-invariant parameter and the normalised variable $w = a^{\beta}$ is a monotonic function of a. Comparing the above model to the original balloon model (Buxton et al., 1998) we see that the parameter α is equivalent to the inverse of the Grubb's exponent (Grubb et al., 1974), and the original balloon model is a special case of the above model if $w = 1$ at all times.

By recognising that dynamic compliance is not given by the steady state P-V curve and that the response of viscoelastic material to loading is highly dependent on the rate of change of loading, we modelled the normalised variable w as a function of the rate of change of volume by the first order dynamic system:

$$\tau_w \frac{dw}{dt} + w = exp\left(-b\frac{dv}{dt}\right), \quad b > 0 \tag{11}$$

This model captures several characteristics of viscoelastic material:

(1) At any steady state, $dv/dt = 0$, hence $w = 1$. This preserves the steady state P-V relationship of the blood vessel.

(2) During vessel dilation, $dv/dt > 0$, hence $exp(-b\, dv/dt) < 1$ (for $b > 0$). This will result in w decreasing from its baseline value of unity, hence the parameter A will decrease, resulting in a P-V curve 'below' the steady state curve during dilation. By the same reasoning, the P-V curve during vessel contraction is 'above' the steady state curve, as shown in Figure 2(b), thus generating a hysteresis loop in the P-V plane as that observed by Poiciuncula et al (1964).

(3) The use of the exponential function provides desirable constraints on the range of values of w. As dv/dt ranges from $-\infty$ to $+\infty$, the exponential function varies from 0 to $+\infty$. Since w is modelled by the first order dynamic system eqn. (11), this ensures that w will never become negative. Consequently the parameter A as defined by eqn. (7) will be guaranteed to lie within the range of $(0,+\infty)$, and the P-V trajectories predicted by the model will always lie within the first quadrant of the P-V plane.

(4) The finite time constant τ_w ensures a delayed response of w to any change in CBV. The model is therefore able to capture both the 'creep loading' and the 'stress relaxation' phenomena of blood vessels.

To summarise, the proposed viscoelastic windkessel (VW) model can be implemented by solving simultaneously the following two differential equations:

$$\begin{aligned} \tau_v \frac{dv}{dt} &= f_{in} - \frac{v^\alpha}{w} \\ \tau_w \frac{dw}{dt} &= -w + \exp\left(-b\frac{dv}{dt}\right) \end{aligned} \tag{12}$$

Results

[Similar to published paper]

Discussion

We have modelled the venous compartment by a VW model which combines the law of mass conservation, the steady state P-V relationship, as well as the viscoelastic property that the compliance of a blood vessel is dependent on the rate of change of the manipulated variable. The model is guided by the mechanical properties of viscoelastic material, independent of the underlying physiological mechanisms coupling haemodynamic changes to changes in neural activity.

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A unified stress-strain model for viscoelastic material

Two well known models have been used in the field of material science in modelling the mechanical properties of viscoelastic material. They are Maxwell model and Voigt model (Young, 1983). They both attempt to model the relationship between the stress and strain of viscoelastic material in order to reproduce the 'creep' and 'stress relaxation' phenomena observed.

Maxwell model consists of a spring and a dashpot connected in series. The dynamic relationship between stress (σ) and strain (x) can be expressed as

$$\frac{d\sigma}{dt} + a_m \sigma = b_m \frac{dx}{dt} \tag{15}$$

where a_m and b_m are related to the physical properties of the spring and the dashpot. If the driving input is strain x, then the response of stress to a step change in strain resembles the behaviour of stress relaxation. However if the driving input is a step increase in stress σ, the model's prediction of creep is poor.

Voigt's model, on the other hand, can predict well the creep phenomenon. It consists of a spring and a dashpot connected in parallel. The dynamic relationship between stress and strain can be expressed as

$$\frac{dx}{dt} + a_v x = b_v \sigma \tag{16}$$

where a_v and b_v are related to the physical properties of the spring and the dashpot. If the driving input is a step change in stress σ, the response in strain is characterised by a typical response of a first order dynamic system, which resembles creep loading. However if the input and output are interchanged and strain becomes input, the Voigt model provides poor prediction of stress relaxation.

The VW model is able to produce characteristics of both creep and stress relaxation. If we denote pressure as stress σ and volume as strain x, then their relationship may be modelled by the following equations:

$$x = A\sigma^{1/\beta}, \quad \beta > 1 \tag{17a}$$

$$\tau_A \frac{dA}{dt} + A = A_0 \exp\left(-b\frac{du}{dt}\right) \tag{17b}$$

where the variable u is the manipulated input such that

$$u = \begin{cases} x & \text{for stress relaxation} \\ \sigma & \text{for creep loading} \end{cases} \tag{17c}$$

The parameter A_0 is the steady state value of A, and the finite time constant τ_A determines the speed at which the output of the model returns to its new steady state. To model stress relaxation, the input to the model is strain, and the output is stress. To model the phenomenon of creep, the input becomes stress, with strain as the output response of the model. Preliminary simulation results (not shown here) demonstrate the capabilities of this model in reproducing the phenomena of creep and stress relaxation. In addition the model displays the characteristic of hysteresis which is not modelled by Maxwell or Voigt model.

Further investigation is needed to test the above model against experimental data. It is possible, as discussed above, that eqn. (17a) may be different for different viscoelastic materials. The key equation is eqn. (17b) which models the appropriate parameter in the steady state P-V curve by a dynamic system, driven by the rate of change of the manipulated variable. Inherent in this equation is the characteristic of hysteresis of viscoelastic material, as the equation guarantees that the parameter it models is different during stretching and compression.

Conclusions

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References

Alexander, R.S., Edwards, W.S., Ankeney, J.L., 1953. The Distensibility Characteristics of the Portal Vascular Bed. Circulation Research 1, 271-277.

Bergel, D.H., 1961. The Static Elastic Properties of Arterial Wall. Journal of Physiology-London 156, 445-457.

Buxton, R.B., Uludag, K., Dubowitz, D.J., Liu, T.T., 2004. Modeling the hemodynamic response to brain activation. Neuroimage 23, S220-S233.

Buxton, R.B., Wong, E.C., Frank, L.R., 1998. Dynamics of blood flow and oxygenation changes during brain activation: the balloon model. Magnetic Resonance in Medicine 39, 855-864.

Fogliardi, R., Di Donfrancesco, M., Burattini, R., 1996. Comparison of linear and nonlinear formulations of the three-element windkessel model. American Journal of Physiology-Heart and Circulatory Physiology 40, H2661-H2668.

Frank, O., 1930. Evaluation of the shock volume of the human heat on the basis of waves and Windkessel theory. Zeitschrift fur Biologie 90, 405-409.

Friston, K.J., Mechelli, A., Turner, R., Price, C.J., 2000. Nonlinear responses in fMRI: the balloon model, volterra kernels, and other hemodynamics. Neuroimage 12, 466-477.

Grubb, R.L., Raichle, M.E., Eichling, J.O., Terpogos.Mm, 1974. Effects of Changes in Paco2 on Cerebral Blood Volume, Blood Flow, and Vascular Mean Transit Time. Stroke 5, 630-639.

Huppert, T.J., Allen, M.S., Benav, H., Jones, P.B., Boas, D.A., 2007. A multicompartment vascular model for inferring baseline and functional changes in cerebral oxygen metabolism and arterial dilation. Journal of Cerebral Blood Flow and Metabolism 27, 1262-1279.

Jones, R.T., 1969. Blood Flow. Annual Review of Fluid Mechanics 1, 223-244.

Klabunde, R.E., 2005. Cardiovascular Physiology Concepts. Lippincott Williams & Wilkins, US.

Linehan, J.H., Dawson, C.A., Rickaby, D.A., Bronikowski, T.A., 1986. Pulmonary Vascular Compliance and Viscoelasticity. Journal of Applied Physiology 61, 1802-1814.

Mandeville, J.B., Marota, J.J.A., Ayata, C., Zaharchuk, G., Moskowitz, M.A., Rosen, B.R., Weisskoff, R.M., 1999. Evidence of a cerebrovascular postarteriole windkessel with delayed compliance. Journal of Cerebral Blood Flow and Metabolism 19, 679-689.

Mayhan, W.G., Heistad, D.D., 1986. Role of Veins and Cerebral Venous-Pressure in Disruption of the Blood-Brain-Barrier. Circulation Research 59, 216-220.

Molino, P., Cerutti, C., Julien, C., Cuisinaud, G., Gustin, M.P., Paultre, C., 1998. Beat-to-beat estimation of windkessel model parameters in conscious rats. American Journal of Physiology-Heart and Circulatory Physiology 43, H171-H177.

Orrison, W., Lewine, J., Sanders, J., Hartshorne, M., 1995. Functional Brain Imaging. Elseview.
Porciuncula, C.I., Armstrong, G.G., Stone, H.L., Guyton, A.C., 1964. Delayed Compliance in External Jugular Vein Ofdog. American Journal of Physiology 207, 728-732.
Remington, J.W., Alexander, R.S., 1955. Stretch Behavior of the Bladder as an Approach to Vascular Distensibility. American Journal of Physiology 181, 240-248.
Roy, C.S., 1881. The elastic properties of the arterial wall. J. Physiol. 3, 125-159.
Segers, P., Brimioulle, S., Stergiopulos, N., Westerhof, N., Naeije, R., Maggiorini, M., Verdonck, P., 1999. Pulmonary arterial compliance in dogs and pigs: the three-element windkessel model revisited. American Journal of Physiology-Heart and Circulatory Physiology 277, H725-H731.
Stergiopulos, N., Westerhof, B.E., Westerhof, N., 1999. Total arterial inertance as the fourth element of the windkessel model. American Journal of Physiology-Heart and Circulatory Physiology 276, H81-H88.
Ursino, M., Ter Minassian, A., Lodi, C.A., Beydon, L., 2000. Cerebral hemodynamics during arterial and CO2 pressure changes: in vivo prediction by a mathematical model. American Journal of Physiology-Heart and Circulatory Physiology 279, H2439-H2455.
Weber, E., 1846. Wagner's Handwörterbuch der Physiologie. . Braunschweig. Vieweg.
Wei, E.P., Kontos, H.A., 1982. Responses of Cerebral Arterioles to Increased Venous-Pressure. American Journal of Physiology 243, H442-H447.
Westerhof, N., Elzinga, G., Sipkema, P., 1971. An Artificial Arterial System for Pumping Hearts. Journal of Applied Physiology 31, 776-781.
Young, R.J., 1983. Introduction to Polymers. Chapman and Hall.
Zheng, Y., Johnston, D., Berwick, J., Chen, D.M., Billings, S., Mayhew, J., 2005. A three-compartment model of the hemodynamic response and oxygen delivery to brain. Neuroimage 28, 925-939.
Zheng, Y., Martindale, J., Johnston, D., Jones, M., Berwick, J., Mayhew, J., 2002. A model of the hemodynamic response and oxygen delivery to brain. Neuroimage 16, 617-637.