Adding cerebral autoregulation to a lumped parameter model of blood flow

Russell Gentile
University of Central Florida

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ADDING CEREBRAL AUTOREGULATION TO A LUMPED PARAMETER MODEL OF BLOOD FLOW

by

RUSTY GENTILE

A thesis submitted in partial fulfillment of the requirements for the Honors in the Major Program in Mechanical Engineering in the College of Computer Science and Engineering and in The Burnett Honors College at the University of Central Florida Orlando, Florida

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Thesis Chair: Dr. Alain Kassab
ABSTRACT

A mathematical model of blood flow in infants with hypoplastic left heart syndrome (HLHS) was improved by adding cerebral autoregulation. This is the process by which blood vessels constrict or dilate to keep blood flow steady in certain organs during pressure changes. The original lumped parameter model transformed the fluid flow into an electrical circuit. Its behavior is described using a system of thirty-three coupled differential equations that are solved numerically using a fourth-order Runge-Kutta method implemented in MATLAB. A literature review that includes a discussion of autoregulation mechanisms and approaches to modeling them is followed by a description of the model created for this paper. The model is based on the baroreceptor or neurogenic theory of autoregulation. According to this theory, nerves in certain places within the cardiovascular system detect changes in blood pressure. The brain then compensates by sending a signal to blood vessels to constrict or dilate. The model of the control system responded fairly well to a pressure drop with a steady state error of about two percent. Running the model with or without the control system activated had little effect on other parameters, notably cardiac output. A more complete model of blood flow control would include autonomic regulation. This would vary more parameters than local autoregulation, including heart rate and contractility. This is suggested as a topic of further research.
Dedicated to my mother and father.
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CHAPTER 1: INTRODUCTION

Building a mathematical model of the human circulatory system is not an easy task. Although software now makes computational fluid dynamics much easier than it was in the past, it is still not practical to build a detailed model of the entire system. The level of detail in a model can vary greatly depending on the need and available computational power. The goal of this research is to improve a model currently being developed by adding to it, a specific detail, cerebral autoregulation. Autoregulation is the process by which the rate of blood flow is kept fairly constant in certain organs. The brain, for example, needs a constant, steady supply of blood and oxygen to function. This would be difficult to achieve since systemic pressure changes are inevitable. For example, if a person who was lying down were to suddenly stand up, the heart would have to overcome the additional pressure head loss due to gravity in order for blood to reach the brain. Blood vessels in the brain help to compensate for this by constricting or dilating to appropriately change the resistance to flow.

The Hybrid-Norwood Procedure

The model being developed here is one of infants with hypoplastic left heart syndrome (HLHS) who have undergone the hybrid-Norwood procedure. Children with this rare congenital heart defect have an underdeveloped left ventricle. The hybrid procedure involves placing bands on the pulmonary artery and adding a stent to the ductus arteriosus (Galantowicz et al. 2008). A Blalock–Taussig shunt connecting the pulmonary artery to a branch of either the subclavian or carotid artery may also be used. This allows the right ventricle, instead of the
underdeveloped left ventricle, to pump blood to both the lungs and the rest of the system. This procedure is the first in a series of operations used to treat HLHS. The model of this system can be used to study, for example, the effect of the shunt’s location.

The Hydraulic-Electrical Analogy and the Multiscale Model

A common method of simplifying blood flow models is to reduce the system to just one dimension. Incompressible fluid flow behaves similarly to electric current in many situations. Current flowing through a resistor is like fluid flowing through a pipe. The voltage drop across a resistor is analogous to the pressure drop or head loss in pipe flow. Similar to Ohm’s law, the Hagen-Poiseuille law gives:

\[ \Delta P = QR \]

where \( \Delta P \) is the pressure drop, \( Q \) is the flow rate and \( R \) is a function of the pipe’s dimensions and fluid viscosity. Using this, a network of pipes can be modeled as a network of electrical resistors provided the flow is steady and the walls are rigid.

These assumptions, however, do not hold in blood vessels. To better model blood flow in arteries, dynamic circuit elements are used. To model the compliance of a vessel, a capacitor is used. Compliance here refers to the phenomenon of a vessel deforming and holding more fluid under pressure. The charge in a capacitor is proportional to the voltage across it. In this analogy then, charge in a capacitor is equivalent to the amount of extra fluid in a vessel due to the increase in volume brought about by pressure. To simulate fluid inertia effects, the inductor is used. Inductors resist fast changes in current. This is similar to the effect of convective
acceleration in incompressible flow. These three elements are combined to form windkessel elements. There are several common variations of the windkessel circuit (Li 1987; Olufsen et al. 2004). The final circuit element in this analogy is the diode. Diodes allow electric current to pass in only one direction. This can be used to model valves in the heart that allow blood to pass in only one direction.

Using this analogy, a model of the entire circulatory system can be made. Arteries and artery beds are represented by windkessel elements. The heart is modeled as a series of windkessel elements with a capacitance that varies with time. Time variant capacitance is like a pumping heart. The walls of the heart flex and, in essence, change their compliance to either drive blood out or allow it to flow in. This electric circuit model is used in conjunction with a more detailed three-dimensional model. The three-dimensional model is made from CT scan images of the aortic arch and pulmonary artery. This is used to provide a more detailed analysis of flow using CFD software. The circuit model is used to generate boundary conditions for the CFD model. In this way, they are coupled to form a multiscale model.
CHAPTER 2: LITERATURE REVIEW

Autoregulation Mechanisms

The exact mechanism and feedback channels of autoregulation are presently unknown (Mitagvaria et al. 2009). There are three main theories that explain it. The myogenic theory proposes that artery walls respond to changes in pressure without any input from the brain or nerves. A rise in pressure would increase myogenic activity and cause the artery walls to constrict. The opposite occurs for a drop in pressure. This is believed to be the fastest acting mechanism. Next, the neurogenic theory states that changes in pressure are perceived by nerves or baroreceptors. The brain then responds to these changes by sending commands to the vessel walls to appropriately constrict or dilate. Finally, the metabolic theory asserts that concentrations of certain chemicals alter the tone of the vessel walls causing a contraction or dilation. This also allows the brain to alter blood flow based on changes in its metabolic need. It is the slowest acting of the three mechanisms. There is evidence supporting the existence of all of these mechanisms and it is reasonable to assume that autoregulation involves a combination of them.

Regardless of which combination of these feedback mechanisms is at play, the physical manifestation of autoregulation is an increase or decrease in muscle tension in artery walls (Ursino 1991). Tension, in this case, refers to wall tension or force per unit length. Using Laplace’s Law for a thin walled vessel:

\[ Pr = T_a + T_e \]
where $P$ is the difference between pressure inside the artery and cerebral perfusion pressure, $r$ is the inner radius of the artery, $T_e$ is the elastic tension developed in the wall and $T_a$ is the active tension coming from the muscles. This is a somewhat simplified model of wall behavior. The assumption that the artery walls are thin enough will not hold for most of the arteries in the brain. Also, a third, time derivative-dependent component of tension must be added to model viscoelastic behavior.

Since the artery walls cannot be stretched or constricted infinitely, there is a limited pressure range over which autoregulation is effective. If cerebral perfusion pressure were to move outside of this range, there would be no response in vascular resistance. This is an important feature of autoregulation that is accounted for by all of the models being presented here.

**Approaches to Modeling Cerebral Blood Flow**

There are many ways to model cerebral blood flow. A common approach is to focus on the circle of Willis (Cieslicki et al. 2005; Devault et al. 2008; Ferrandez et al. 2002). The circle of Willis is the main distribution center for blood in the brain. It consists of a ring-like structure of large arteries. This ring-like shape provides protection from occlusions by giving the blood alternate pathways to follow. Blood enters this network from three locations (Cieslicki et al. 2005). The vertebral-basilar arteries supply the posterior section while the left and right interior carotid arteries supply the anterior section. These are connected by the posterior and anterior communicating arteries to form the circle. In several locations, smaller arteries branch into the
rest of the brain from the circle of Willis. Finally, it is also worth noting that the geometry and dimensions vary significantly from person to person (Ursino 1991). In fact, it is quite common for the circle to be incomplete. It has been found in more than half of healthy brains that at least one artery is absent or underdeveloped (Devault et al. 2008).

A straightforward way to add autoregulation to this model is to utilize control theory. One such study modeled autoregulation as a PI controller that varied only the resistances in the peripheral arteries of the circle of Willis (Ferrandez et al. 2002). Peripheral arteries were modeled as porous blocks attached to the ends of pipes. The permeability constant, $k$, was varied by the PI controller. Darcy’s Law was then used to generate a fluid resistance value for each time step.

The controller mechanism was based on the difference in flow rate from its nominal value. Several features of autoregulation had to be considered. First, the pulsatile nature of blood flow necessitates that its periodic changes must be filtered out. Otherwise, resistance would vary within each beat of the heart. Next, the time taken by the system to respond must be considered. This was done by introducing a time constant, $\tau$, that was utilized in the following equation:

$$\tau \frac{d}{dt} y(t) + y(t) = u(t)$$

where $y(t)$ is the actual change in vascular resistance and $u(t)$ is the change in vascular resistance given by the PI controller. Finally, the limits of autoregulation were imposed by
applying a sigmoidal function to the resistance value. An example of a sigmoidal function is the logistics curve. A plot of this function has horizontal asymptotes equal to the lower and upper limits. At values within those limits, it is similar to the function $y = x$. This kept the resistances within the appropriate limits of autoregulation without imposing sharp, sudden changes to them.

These final calculated resistances were used to define boundary conditions for the outlets in a two-dimensional model of the circle of Willis. The simulation was run several times to study the effects of missing various sections of the circle. This two-dimensional model captured the basic geometry of the circle and assumed that the walls are rigid. The effects of compliance in the circle walls were assumed to be negligible. It is also worth noting that using this technique ignores the effect of the myogenic, metabolic and neurogenic mechanisms. Another possible shortcoming of this model is that the resistances in the circle itself play a role in autoregulation. The diameters of the arteries in the circle can also change to compensate for flow changes (Ursino 1991).

Another simulation of blood flow that included cerebral autoregulation also modeled the effects of gravity and autonomic regulation (Olufsen et al. 2005). This study focused on blood flow during posture changes from sitting to standing. A discussion of the technique used to model gravity is not relevant to this research. Autonomic regulation, however, is another control mechanism that regulates heart rate, heart contractility, vascular resistances, and
vascular compliances throughout the body. The autonomic control system is governed by the nervous system and includes both baroreceptors and chemoreceptors (Purves et al. 2001).

The body was modeled using the electric circuit analogy (Olufsen et al. 2005). A total of eleven “compartments” were simulated using capacitors separated by resistors. These included the two ventricles of the heart, five systemic arteries and four systemic veins. The circuit did not include inductors or a model of the pulmonary system. Similar to the hybrid-Norwood model described previously, the left and right ventricles of the heart were modeled as time-variant capacitors. Resistances in this model were non-linear. That is, they were a function of pressure. This simulates the change in radius of the arteries as pressure increases or decreases. A sigmoid function was used to keep radii within realistic limits.

To model autonomic regulation, compliances and resistances were modified by the following equations:

\[
\frac{dx(t)}{dt} = -x(t) + x_{ctr}(\bar{p}_a) \frac{1}{\tau}
\]

where \(x(t)\) is the controlled parameter (either a resistance or compliance), \(x_{ctr}(\bar{p}_a)\) is a control equation, and \(\tau\) is the time taken for the system to respond. Note that, when algebraically rearranged, the form of this equation is identical to the one used by Ferrandez et al. Average pressure, \(\bar{p}_a\), was calculated by using a weighted average integral where the present is weighted higher than the past. This eliminated the problem of pulsatility affecting the control system. The control equations were:
\[ x_{ctr}(\bar{p}_a) = (x_M - x_m) \frac{\alpha_2^k}{\bar{p}_a^k + \alpha_2^k} + x_m \]

for resistances and:

\[ x_{ctr}(\bar{p}_a) = (x_M - x_m) \frac{\bar{p}_a^k}{\bar{p}_a^{-k} + \alpha_2^k} + x_m \]

for compliances. These equations are also of sigmoidal form, with compliances decreasing with a pressure decrease and resistances increasing with a pressure decrease. Values for \( \alpha_2 \) were chosen such that controlled parameters returned to their calculated steady state. Values for \( k \) were first taken as initial guesses and later optimized, along with several other parameters, using the Nelder-Mead algorithm. This minimized the difference between values calculated by the model and experimental data. Changes in heart rate were also taken from experimental data.

Since the relationship between autoregulation and autonomic regulation is not understood, autoregulation was also estimated using experimental data. Autoregulation was expressed in this model by changes only in the resistance of the cerebral arteries. This resistance was modeled using a piecewise linear function with points taken from estimates given by experimental data. Although this study does not provide a model of a specific autoregulation mechanism or feedback channel, it is still relevant to this research. The technique used to model autonomic regulation is applicable to cerebral autoregulation.
Another model, indeed, used a very similar approach to simulate cerebral autoregulation (Lu et al. 2004). Similarly, cerebral blood flow was simulated as a lumped-parameter model with windkessel circuits. This study, however, differed in that the control equation was based on blood flow rate and CO₂ concentrations. Compliances were altered sigmoidally and a functional relationship was established between resistance and compliance.

Finally, a model that utilizes a more bottom-up approach will be considered (Carlson et al. 2008). The myogenic and metabolic mechanisms were simulated along with a third, shear-dependent mechanism. First, the vessels were divided into seven types, upstream arteries, large arterioles, small arterioles, capillaries, small venules, large venules, and downstream veins. Blood flow was assumed to follow the Hagen-Poiseuille law with the vessels acting not unlike a branching network of resistors. Autoregulation was assumed to act only on the large and small arterioles with each section being treated separately. The diameters of these vessels were made a function of pressure and muscle tension. Muscle tension was the sum of a passive and an active component with the active component representing the autoregulation mechanisms:

\[ T_{tot} = T_{pass} + AT_{act}^{max} \]

The active component was represented as the maximum active tension times the degree of activation, \( A \), given by:

\[ A = \frac{1}{1 + e^{-Stone}} \]
The term $S_{tone}$ was the part of the system varied by the autoregulation mechanisms using a linear relationship:

$$S_{tone} = C_{myo}T - C_{shear}\tau_{wall} - C_{meta}S_{CR} + C''$$

with $T$, $\tau_{wall}$, and $S_{CR}$ representing wall tension, shear stress and the concentration of ATP respectively. All $C$ terms were calculated by fitting the model to experimental data. The concentration of ATP was assumed to be controlling the metabolic mechanism. Red blood cells release at a rate dependent on their oxyhemoglobin saturation level and, in this way, act as sensors for metabolic demand.
CHAPTER 3: A DESCRIPTION OF THE AUTOREGULATION MODEL

The model developed for this paper does not include every feature of autoregulation. There are a number of assumptions and simplifications that have been made. First, the brain is represented in the circuit as only a single windkessel element (Figure 1). This element is only one part of the complete lumped parameter model. The entire model is a much more complicated circuit describable by thirty-three coupled differential equations. This system of equations was solved numerically using a fourth order Runge-Kutta solver implemented in MATLAB. Since the three-dimensional CFD model does not include arteries in the brain, a detailed look at cerebral blood flow is not necessary. What is of interest is how the system as a whole responds. Capturing the geometry of the circle of Willis, for example, is not necessary.

![Windkessel Circuit Element Representing Cerebral Blood Flow](image)

Figure 1 - Windkessel Circuit Element Representing Cerebral Blood Flow

The next simplification that was made is of the control mechanism. Since the model does not need to be detailed, only the baroreceptor or neurogenic mechanism of autoregulation was used. Using a technique borrowed from yet another model, the response
was assumed to be a function of only the average pressure in the carotid sinus (Danielsen et al. 2004). A value, $n_s$, representing the nervous system’s sympathetic response was established using the following sigmoidal equation illustrated in Figure 2:

$$n_s = \frac{1}{1 + (\bar{p}_{cs}/\mu)^\nu}$$

where $\bar{p}_{cs}$ is the average carotid sinus pressure over one heart period, $\mu$ is the optimal carotid sinus pressure, and $\nu$ is a parameter representing the steepness of the sigmoid curve. This value, $n_s$, varies between zero and one, with one representing a large pressure drop and zero representing a large pressure increase. It takes a value of one half under normal conditions when carotid sinus pressure is at its optimal level. Carotid sinus pressure is taken as the voltage across the capacitor, $C_{icb}$. By using the average pressure over one heart period, changes due to pulsatility are filtered out.

Figure 2 - Sympathetic Response
To complete the control mechanism, the resistor, $R_{lcb}$, is varied as a function of $n_s$:

$$\frac{dR_{lcb}}{dt} = \frac{1}{\tau_R} \left( -R_{lcb} + \alpha_R n_s + \gamma_R \right)$$

where $\tau_R$ is a time constant and $\alpha_R$ and $\gamma_R$ are parameters that would typically be obtained by curve fitting to experimental data. Combining these equations, the steady state value of vascular resistance as a function of carotid sinus pressure is illustrated in Figure 3.

![Figure 3 - Vascular Resistance as a Function of Carotid Sinus Pressure at Steady State](image)

Since experimental data characterizing autoregulation in infants with congenital heart defects was not available, several parameters in this model were estimated. To begin, the upper and lower limits of autoregulation were established. These are the highest and lowest values that vascular resistance can take. A maximum change of $\pm 40\%$ was taken as a typical
value by which to vary resistance. This number was taken from literature and may or may not be an accurate representation of an infant’s limits of autoregulation (Danielsen et al. 2004). Using this along with an optimal value from the original lumped parameter model as a starting point, the parameters $\alpha_R$ and $\gamma_R$ can easily be determined. The time constant, $\tau_R$, was also taken from literature as a typical value (Ferrandez et al. 2002). Nominal carotid sinus pressure, $\mu$, was established by running the model without the control system activated. The final parameter, $\nu$, was estimated by trial and error.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\alpha_R$</td>
<td>-58.33 mmHg s/mL</td>
</tr>
<tr>
<td>$\gamma_R$</td>
<td>99.17 mmHg s/mL</td>
</tr>
<tr>
<td>$\tau_R$</td>
<td>10 s</td>
</tr>
<tr>
<td>$\mu$</td>
<td>63.029 mmHg</td>
</tr>
<tr>
<td>$\nu$</td>
<td>5</td>
</tr>
</tbody>
</table>

*Table 1 - Summary of Baroreceptor Parameters*
CHAPTER 4: RESULTS

To test the autoregulation mechanism, a pressure drop was simulated by increasing a resistance separate from the brain at $t = 5\ s$. This could represent a blood clot or possibly a sudden change in posture. An arbitrary value by which to increase the resistance was selected to create a noticeable change in cerebral blood flow rate. The system’s response can be seen in Figure 4. Blood flow rate drops initially during a pressure drop and returns close to its nominal value after the control mechanism is activated with a steady state error of about 2%. Compare to Figure 5 where the control system was disabled.

![Figure 4 - Cerebral Blood Flow Rate with Control System Active](image)

*Figure 4 - Cerebral Blood Flow Rate with Control System Active*
Cardiac output is illustrated in Figure 6. This is an important parameter that is used as a boundary condition in the CFD model. Unfortunately, enabling or disabling the control system did not produce a significant change in cardiac output. This result is not surprising, however, given the small change that the control system makes. Modeling autonomic regulation as opposed to local autoregulation would have likely had a much more noticeable effect on this result. Autonomic regulation varies many more parameters throughout the body, including heart rate and contractility.
Figure 6 - Cardiac Output during Transition
CHAPTER 5: CONCLUSIONS

This research is only a first step in building a comprehensive model of regulated blood flow. The biggest shortfall of this model is that the control parameters had to be estimated. An obvious improvement would be to curve fit the model with experimental data. To accomplish this, however, autonomic regulation would likely need to be included. This would be difficult using the current lumped parameter model. Its circuit is much more complicated than those used in the previous examples from literature. It contains many more parameters which would need to be varied by the control system. A redesign of the circuit may be necessary to simplify matters. Another challenge is the lack of experimental data needed for curve fitting. This would make an excellent topic for further research. Another improvement to this model would be to more accurately model a blood clot or posture change. Again, a more simplified circuit may be needed for this. In spite the model’s shortcomings, this paper illustrates a simplified example of how to approach modeling blood flow controls.
APPENDIX: MATLAB CODE
clear all

h=2*10^-5; %timestep
max_time=60;
max_i=ceil(max_time/h);

%Elastance Function
E_ra = 7.35;
c_ra = 1/E_ra;
E_min = 0.06;
HR = 130;
T_max = 60/HR;
E_max = 2.35;
E_n = @(time)(1/(1+((time/T_max)/0.508)^21.9))... *(((time/T_max)/0.303)^1.32)/(1+((time/T_max)/0.303)^1.32);
E_healthy = @(time)E_max*E_n(time)+E_min;
delta = 1;
E_rv = @(time)delta*E_healthy(time);

c_rv = @(time)1/E_rv(time);
R_rv = 0.03;
delta_t = 10^-6;
dc_rv = @(time)(c_rv(time+delta_t)-c_rv(time))/delta_t;
R_tric = 0.0001;

%factors used to tune the model
R_fact = 1.5;
R_fact_bed = 2.5;
R_fact_bed_par = 1.5*R_fact_bed;
c_fact = 0.7;
c_fact_par = 0.5*c_fact;
c_pa = 0.27410*0.09;
R_pa = 0.02835*3;
L_pa = 0.00165;

%Pulmonary Bed
R_rpa = 12.5;
R_lpa = 12.5;
Tot_Rpa = (1/R_rpa+1/R_lpa)^-1;
R_rlung = 0.83376*R_fact_bed_par;
c_rlung = 0.02039*c_fact;
c_rpvb = 0.44375*c_fact;
c_lpvb = c_rpvb;
L_rlung = 0.001;
R_llung = R_rlung;
c_llung = c_rlung;
L_llung = L_rlung;
R_rpvb = 0.02194*R_fact_bed_par;
R_lpvb = R_rpvb;
%Aortic Arch
R_ia = 0.164;
c_ao = 0.0415548*c_fact;
R_ao = 0.15;
L_ao = 0.003;
R_da = 0.19883;

%Distributed Arch Inertances
L_ductus = L_ao/5;
L_da_lsa = L_ao/5;
L_lsa_lca = L_ao/5;
L_lca_ia = L_ao/5;
L_ia_cora = L_ao/5;
L_shunt = L_ao/5;

%Distributed Arch Resistances
R_ductus = 0.0187;
R_da_lsa = 0.327;
R_lsa_lca = 0.072;
R_lca_ia = 0.041;
R_ia_cora = 1.552;
R_shunt = 50;

%Arterial Beds
L_lvb = 0.01069;
c_lvb = 0.077575*c_fact;
c_ivb = (0.077575+2.03945)*c_fact;
R_lvb = 7.02239*R_fact_bed*0.6;
R_ivb = (0.64510+0.16529)*R_fact_bed;
R_lsa = 0.533;
R_rsa = 0.106;
R_rca = 0.4272;
R_lca = 0.715;
R_lsb = 2*14.004478*R_fact_bed;
R_lcb = R_lsb;
R_rcb = R_lsb;
R_rsb = R_lsb;
R_dsb = 2*(0.6451+0.16529)*R_fact_bed;
R_dcb = R_dsb;
c_lsb = (0.088592/2)*c_fact;
c_rsb = c_lsb;
c_lcb = c_lsb;
c_rcb = c_lsb;
c_dsb = (0.15515/2+2.03945/2)*c_fact;
c_dcb = c_dsb;
L_{lsb} = 2*0.02138;
L_{rsb} = L_{lsb};
L_{lcb} = L_{lsb};
L_{rcb} = L_{lsb};

%Coronary Circulation
R_{cor_{max}} = 400;
R_{rcora} = @(y)8.043;
R_{lcora} = @(y)7.5;
R_{rcorab} = @(y)2*10.6739;
R_{lcorab} = @(y)R_{rcorab}(y);
%R_{corvb} = @(y)2*(10.6739+21.6477+10.6739);
R_{corvb} = @(y)(1+y(1)*R_{cor_{max}}/12.5)*R_{fact};
c_{rcorab} = (1.94351/2)*10^-3*c_{fact};
c_{lcorab} = c_{rcorab};
c_{corvb} = (5.18269*10^-3+7.77404*10^-3+0.5*10^-4)*c_{fact};

%Baroreceptor Parameters
nu = 5;
alpha_R = -58.33;
gamma_R = 99.17;
T_{res} = 10;
oc_{cs}=63.029;

%Set of ODE's
I_{in} = @(y,leak_rate)(y(27)-y(1))/R_{ivb}+(y(28)-y(1))/R_{dsb}+...
    (y(29)-y(1))/R_{dcb}+(y(30)-y(1))/R_{corvb}(y)+(y(31)-y(1))/R_{lpvb}+...
    (y(32)-y(1))/R_{rpvb}-leak_rate;
i_1 = @(y)((y(1)-y(2))/R_{tric})*(y(1)>y(2));
i_2 = @(y)((y(2)-y(3))/R_{rv})*(y(2)>y(3));
v1 = @(y)(y(4)+y(7)/R_{rpa}+y(5)/R_{lpa}-y(9)-y(10))/(1/R_{rpa}+1/R_{lpa});
v2 = @(y)R_{da}*(y(9)-y(13))+y(11);
v3 = @(y)R_{lsa}*(y(13)-y(16))+y(14);
v4 = @(y)R_{lca}*(y(16)-y(19))+y(17);
v5 = @(y)v6(y)+R_{ia}*(y(10)+y(19)+y(24));
v6 = @(y)(1/R_{rsa}+1/R_{rca})^-1*(y(10)+y(19)-y(24)+y(20)/R_{rsa}+y(22)/R_{rca});
v7 = @(y)(1/R_{rcora}(y)+1/R_{lcora}(y))^-1*(y(24)+y(25)/R_{rcora}(y)+y(26)/...
    R_{lcora}(y));

numeq=33;
ki=1:numeq;
dy1 = @(t, y, leak_rate)(1/c_{ra})*(I_{in}(y, leak_rate)-i_1(y));
dy2 = @(t, y)(1/c_{rv}(t))*i_1(y)-i_2(y)-y(2)*dc_{rv}(t));
dy3 = @(t, y)(1/c_{pa})*(i_2(y)-y(4));
dy4 = @(t, y, clot)(1/L_{pa})*(y(3)-y(4)*(R_{pa}+clot)-v1(y));
dy5 = @(t, y)(1/c_{Llung})*((v1(y)-y(5))/R_{lpa}-y(6));
dy6 = @(t, y)(1/L_{Llung})*(y(5)-y(6)*R_{Llung}-y(1));
dy7 = @(t, y)((v1(y)-y(7))/R_rpa-y(8));
dy8 = @(t, y)((v1(y)-y(8))*R_Llung-y(1));
dy9 = @(t, y)((v1(y)-y(9)*R_ductus-v2(y));
dy10 = @(t, y)((v1(y)-y(10)*R_shunt-v5(y));
dy11 = @(t, y)((v2(y)-y(11))/R_da-y(12));
dy12 = @(t, y)((v2(y)-y(12))*R_lvb-y(27));
dy13 = @(t, y)((v2(y)-y(13))*R_da_lsa-v3(y));
dy14 = @(t, y)((v3(y)-y(14))/R_lsa-y(15));
dy15 = @(t, y)((v3(y)-y(15)*R_lsb-y(29));
dy16 = @(t, y)((v4(y)-y(16)*R_lca-v4(y));
dy17 = @(t, y)((v4(y)-y(17))/R_lca-y(18));
dy18 = @(t, y)((v4(y)-y(18)*R_lsa_lca-v4(y));
dy19 = @(t, y)((v4(y)-y(19)*R_lsa_lca-v5(y));
dy20 = @(t, y)((v6(y)-y(20)/R_rsa-y(21));
dy21 = @(t, y)((v6(y)-y(21)*R_rsb-y(28));
dy22 = @(t, y)((v6(y)-y(22))/R_rca-y(23));
dy23 = @(t, y)((v6(y)-y(23)*R_rcb-y(29));
dy24 = @(t, y)((v5(y)-y(24)*R_ra_cora-v7(y));
dy25 = @(t, y)((v7(y)-y(25))/R_rcorab(y)-...  
    (y(25)-y(30))/R_rcorab(y));
dy26 = @(t, y)((v7(y)-y(26))/R_lcorab(y)-...  
    (y(26)-y(30))/R_lcorab(y));
dy27 = @(t, y)((v12(y)-y(27)-y(1))/R_pv);  
    t_per = 0;  
    t = zeros(1, max_i+1);  
    y = zeros(numeq, max_i+1);  
    y(1,1) = 4.0114;  
    y(2,1) = 4.0114;  
    y(3,1) = 55.6427;  
    y(4,1) = 1.5179;  
    y(5,1) = 14.7764;  
    y(6,1) = 3.4445;  
    y(7,1) = 14.7764;  
    y(8,1) = 3.4445;  
    y(9,1) = -4.9618;  
    y(10,1) = -0.0388;  
    y(11,1) = 55.5038;  
    y(12,1) = 3.844;  
    y(13,1) = -5.4776;

% Cerebral Vascular Resistance
%
dy33 = @(t, y, n_s)(1/T_res)*(-y(33)+alpha_R*n_s+gamma_R);
\[
y(14,1) = 58.1061;
y(15,1) = 0.6638;
y(16,1) = -4.1413;
y(17,1) = 58.3037;
y(18,1) = 0.6663;
y(19,1) = -2.7982;
y(20,1) = 58.0929;
y(21,1) = 0.6632;
y(22,1) = 58.5211;
y(23,1) = 0.6697;
y(24,1) = -0.1902;
y(25,1) = 58.4729;
y(26,1) = 58.4729;
y(27,1) = 15.0744;
y(28,1) = 11.6903;
y(29,1) = 11.6733;
y(30,1) = 59.6994;
y(31,1) = 4.2853;
y(32,1) = 4.2853;
y(33,1) = R_{lcb};
\]

\[
n_s = \text{zeros}(1, \text{max}_i+1);
n_p = \text{zeros}(1, \text{max}_i+1);
\]

%Time Loop
for i=1:max_time/h
    t(i+1)=(i+1)*h;
    t_per=(t_per+h)*(t_per<=T_max);

%Hemorrage and Blood Clot
leak_rate=0; %2*((t(i)>1)&(t(i)<21));
clot=1*(t(i)>5);

%Average Carotid Sinus Pressure
if t(i)>0.5
    p_cs(i+1)=mean(y(17,ceil(i-T_max/h):i));
else
    p_cs(i+1)=63.029;
end

%Runge-Kutta solver
k1(1) = h*dy1(t_per,y(:,i),leak_rate);
k1(2) = h*dy2(t_per,y(:,i));
k1(3) = h*dy3(t_per,y(:,i));
k1(4) = h*dy4(t_per,y(:,i),clot);
k1(5) = h*dy5(t_per,y(:,i));
k1(6) = h*dy6(t_per,y(:,i));
k1(7) = h*dy7(t_per,y(:,i));
k1(8) = h*dy8(t_per,y(:,i));
k1(9) = h*dy9(t_per,y(:,i));
k1(10) = h*dy10(t_per,y(:,i));
k1(11) = h*dy11(t_per,y(:,i));
k1(12) = h*dy12(t_per,y(:,i));
k1(13) = h*dy13(t_per,y(:,i));
k1(14) = h*dy14(t_per,y(:,i));
k1(15) = h*dy15(t_per,y(:,i));
k1(16) = h*dy16(t_per,y(:,i));
k1(17) = h*dy17(t_per,y(:,i));
k1(18) = h*dy18(t_per,y(:,i));
k1(19) = h*dy19(t_per,y(:,i));
k1(20) = h*dy20(t_per,y(:,i));
k1(21) = h*dy21(t_per,y(:,i));
k1(22) = h*dy22(t_per,y(:,i));
k1(23) = h*dy23(t_per,y(:,i));
k1(24) = h*dy24(t_per,y(:,i));
k1(25) = h*dy25(t_per,y(:,i));
k1(26) = h*dy26(t_per,y(:,i));
k1(27) = h*dy27(t_per,y(:,i));
k1(28) = h*dy28(t_per,y(:,i));
k1(29) = h*dy29(t_per,y(:,i));
k1(30) = h*dy30(t_per,y(:,i));
k1(31) = h*dy31(t_per,y(:,i));
k1(32) = h*dy32(t_per,y(:,i));
k1(33) = h*dy33(t_per,y(:,i),n_s(i));

k2(1) = h*dy1(t_per+h/2,y(:,i)+k1(1)/2,leak_rate);
k2(2) = h*dy2(t_per+h/2,y(:,i)+k1(2)/2);
k2(3) = h*dy3(t_per+h/2,y(:,i)+k1(3)/2);
k2(4) = h*dy4(t_per+h/2,y(:,i)+k1(4)/2,clot);
k2(5) = h*dy5(t_per+h/2,y(:,i)+k1(5)/2);
k2(6) = h*dy6(t_per+h/2,y(:,i)+k1(6)/2);
k2(7) = h*dy7(t_per+h/2,y(:,i)+k1(7)/2);
k2(8) = h*dy8(t_per+h/2,y(:,i)+k1(8)/2);
k2(9) = h*dy9(t_per+h/2,y(:,i)+k1(9)/2);
k2(10) = h*dy10(t_per+h/2,y(:,i)+k1(10)/2);
k2(11) = h*dy11(t_per+h/2,y(:,i)+k1(11)/2);
k2(12) = h*dy12(t_per+h/2,y(:,i)+k1(12)/2);
k2(13) = h*dy13(t_per+h/2,y(:,i)+k1(13)/2);
k2(14) = h*dy14(t_per+h/2,y(:,i)+k1(14)/2);
k2(15) = h*dy15(t_per+h/2,y(:,i)+k1(15)/2);
k2(16) = h*dy16(t_per+h/2,y(:,i)+k1(16)/2);
k2(17) = h*dy17(t_per+h/2,y(:,i)+k1(17)/2);
k2(18) = h*dy18(t_per+h/2,y(:,i)+k1(18)/2);
k2(19) = h*dy19(t_per+h/2,y(:,i)+k1(19)/2);
k2(20) = h*dy20(t_per+h/2,y(:,i)+k1(20)/2);
k2(21) = h*dy21(t_per+h/2,y(:,i)+k1(21)/2);
k2(22) = h*dy22(t_per+h/2,y(:,i)+k1(22)/2);
k2(23) = h*dy23(t_per+h/2,y(:,i)+k1(23)/2);
k2(24) = h*dy24(t_per+h/2,y(:,i)+k1(24)/2);
k2(25) = h*dy25(t_per+h/2,y(:,i)+k1(25)/2);
k2(26) = h*dy26(t_per+h/2,y(:,i)+k1(26)/2);
k2(27) = h*dy27(t_per+h/2,y(:,i)+k1(27)/2);
k2(28) = h*dy28(t_per+h/2,y(:,i)+k1(28)/2);
k2(29) = h*dy29(t_per+h/2,y(:,i)+k1(29)/2);
k2(30) = h*dy30(t_per+h/2,y(:,i)+k1(30)/2);
k2(31) = h*dy31(t_per+h/2,y(:,i)+k1(31)/2);
k2(32) = h*dy32(t_per+h/2,y(:,i)+k1(32)/2);
k2(33) = h*dy33(t_per+h/2,y(:,i)+k1(33)/2,n_s(i));

k3(1) = h*dy1(t_per+h/2,y(:,i)+k2(1)/2,leak_rate);
k3(2) = h*dy2(t_per+h/2,y(:,i)+k2(2)/2);
k3(3) = h*dy3(t_per+h/2,y(:,i)+k2(3)/2);
k3(4) = h*dy4(t_per+h/2,y(:,i)+k2(4)/2, clot);
k3(5) = h*dy5(t_per+h/2,y(:,i)+k2(5)/2);
k3(6) = h*dy6(t_per+h/2,y(:,i)+k2(6)/2);
k3(7) = h*dy7(t_per+h/2,y(:,i)+k2(7)/2);
k3(8) = h*dy8(t_per+h/2,y(:,i)+k2(8)/2);
k3(9) = h*dy9(t_per+h/2,y(:,i)+k2(9)/2);
k3(10) = h*dy10(t_per+h/2,y(:,i)+k2(10)/2);
k3(11) = h*dy11(t_per+h/2,y(:,i)+k2(11)/2);
k3(12) = h*dy12(t_per+h/2,y(:,i)+k2(12)/2);
k3(13) = h*dy13(t_per+h/2,y(:,i)+k2(13)/2);
k3(14) = h*dy14(t_per+h/2,y(:,i)+k2(14)/2);
k3(15) = h*dy15(t_per+h/2,y(:,i)+k2(15)/2);
k3(16) = h*dy16(t_per+h/2,y(:,i)+k2(16)/2);
k3(17) = h*dy17(t_per+h/2,y(:,i)+k2(17)/2);
k3(18) = h*dy18(t_per+h/2,y(:,i)+k2(18)/2);
k3(19) = h*dy19(t_per+h/2,y(:,i)+k2(19)/2);
k3(20) = h*dy20(t_per+h/2,y(:,i)+k2(20)/2);
k3(21) = h*dy21(t_per+h/2,y(:,i)+k2(21)/2);
k3(22) = h*dy22(t_per+h/2,y(:,i)+k2(22)/2);
k3(23) = h*dy23(t_per+h/2,y(:,i)+k2(23)/2);
k3(24) = h*dy24(t_per+h/2,y(:,i)+k2(24)/2);
k3(25) = h*dy25(t_per+h/2,y(:,i)+k2(25)/2);
k3(26) = h*dy26(t_per+h/2,y(:,i)+k2(26)/2);
k3(27) = h*dy27(t_per+h/2,y(:,i)+k2(27)/2);
k3(28) = h*dy28(t_per+h/2,y(:,i)+k2(28)/2);
k3(29) = h*dy29(t_per+h/2,y(:,i)+k2(29)/2);
k3(30) = h*dy30(t_per+h/2,y(:,i)+k2(30)/2);
k3(31) = h*dy31(t_per+h/2,y(:,i)+k2(31)/2);
k3(32) = h*dy32(t_per+h/2,y(:,i)+k2(32)/2);
k3(33) = h*dy33(t_per+h/2,y(:,i)+k2(33)/2,n_s(i));

k4(1) = h*dy1(t_per+h,y(:,i)+k3(1),leak_rate);
k4(2) = h*dy2(t_per+h,y(:,i)+k3(2));
k4(3) = h*dy3(t_per+h,y(:,i)+k3(3));
k4(4) = h*dy4(t_per+h,y(:,i)+k3(4), clot);
k4(5) = h*dy5(t_per+h,y(:,i)+k3(5));
k4(6) = h*dy6(t_per+h,y(:,i)+k3(6));
k4(7) = h*dy7(t_per+h,y(:,i)+k3(7));
k4(8) = h*dy8(t_per+h,y(:,i)+k3(8));
k4(9) = h*dy9(t_per+h,y(:,i)+k3(9));
k4(10) = h*dy10(t_per+h,y(:,i)+k3(10));
k4(11) = h*dy11(t_per+h,y(:,i)+k3(11));
k4(12) = h*dy12(t_per+h,y(:,i)+k3(12));
k4(13) = h*dy13(t_per+h,y(:,i)+k3(13));
k4(14) = h*dy14(t_per+h,y(:,i)+k3(14));
k4(15) = h*dy15(t_per+h,y(:,i)+k3(15));
k4(16) = h*dy16(t_per+h,y(:,i)+k3(16));
k4(17) = h*dy17(t_per+h,y(:,i)+k3(17));
k4(18) = h*dy18(t_per+h,y(:,i)+k3(18));
k4(19) = h*dy19(t_per+h,y(:,i)+k3(19));
k4(20) = h*dy20(t_per+h,y(:,i)+k3(20));
k4(21) = h*dy21(t_per+h,y(:,i)+k3(21));
k4(22) = h*dy22(t_per+h,y(:,i)+k3(22));
k4(23) = h*dy23(t_per+h,y(:,i)+k3(23));
k4(24) = h*dy24(t_per+h,y(:,i)+k3(24));
k4(25) = h*dy25(t_per+h,y(:,i)+k3(25));
k4(26) = h*dy26(t_per+h,y(:,i)+k3(26));
k4(27) = h*dy27(t_per+h,y(:,i)+k3(27));
k4(28) = h*dy28(t_per+h,y(:,i)+k3(28));
k4(29) = h*dy29(t_per+h,y(:,i)+k3(29));
k4(30) = h*dy30(t_per+h,y(:,i)+k3(30));
k4(31) = h*dy31(t_per+h,y(:,i)+k3(31));
k4(32) = h*dy32(t_per+h,y(:,i)+k3(32));
k4(33) = h*dy33(t_per+h,y(:,i)+k3(33),n_s(i));

y(ki,i+1)=y(ki,i)+(k1(ki)'+2*k2(ki)'+2*k3(ki)'+k4(ki)')/6;

%Sympathetic and Parasympathetic Responses
n_s(i+1)=1/(1+(p_cs(i+1)/op_cs)^5);
n_p(i+1)=1-n_s(i+1);

%Used to monitor solver progress
if mod(i, 5000)==0
    a=t(i+1)
    b=y(1,i+1)
    j
end
end
LIST OF REFERENCES


