Nifedipine’s Effect on Hypertensive Patients Using the 3-Element Windkessel Model

Thomas M. Ackermann, Cyril J. Bernardo,

Zhenxiang Chen, Johnny Peguero,

and Artur Zych

Introduction

Hypertension, according to Mayo Clinic, is the presence of high blood pressure for an individual. The ideal pressure range for a human being is a systolic pressure less than 120 mmHg and a diastolic pressure less than 80 mmHg. There are certain stages of hypertension, each increasing in severity. The beginning of high blood pressure is called prehypertension with a systolic pressure between 120 and 139 mmHg and a diastolic pressure between 80 and 89 mmHg.

Pressure in the aorta is a function of the flow and the resistance encountered by the flow. Resistance is a function of the radius of the vessel through which the fluid flows. If the radius is increased then the resistance against fluid flow drops. An interesting aspect of fluid flow within a blood vessel is that the wall stress upon the blood vessel will stay constant. The Law of Laplace tells us that the wall stress in a vessel is a function of the radius of the vessel and the thickness (if the thickness is much smaller than the radius and the vessel can be represented as a simple cylinder):

$$\sigma = \frac{P * r}{t}$$

If the pressure within the blood vessel increases (a person could be suffering from hypertension) the thickness of the vessel wall will increase to stabilize the wall stress.

Blood flow is described using Poiseuille's Law. The law relates blood flow rate, pressure, and vessel resistance analogous to an electrical circuit with voltage as the pressure, flow rate as the current and resistance as the parameters that impedes the flow or current. The equation is as follows:

$$Q = \frac{\Delta P}{R}$$

The resistance is the equation:

$$R = \frac{8\eta l}{\pi r_i^4}$$

The equation tells us that the resistance of a blood vessel per unit length is related to the radius of the vessel. Therefore, if there is a stenosis in the aorta, or a narrowing of the vessel, the resistance will be increased and the so will the pressure. Depending on how extensive the stenosis is, this increase in resistance can increase the pressure of the whole arterial tree and cause hypertension.

Compliance relates the volume - pressure relationship in a blood vessel. The compliance equation is:

$$C = \frac{\Delta V}{\Delta P}$$

According to our Snapshots of Hemodynamics textbook, hypertension has been known to be linked with a decrease in arterial compliance.

The medication used in this project to simulate the relief of the high blood pressure is called Nifedipine. This drug is classified as a calcium channel blocker and it affects the blood vessels and heart specifically. Calcium ions are used by the smooth muscles that line the heart and vessels to cause a contraction propelling blood throughout the cardiac system. By lessening the amount of available calcium, the vessels and heart cannot contract as much as they were before the administration of the drug and they relax. This relaxation comes in the form of a widening of the vessel, or an increase in the radius. The increase in arterial radius causes a decrease in resistance, which is directly related to the pressure. A study done by Cholley et al [1] on Nifedipine and other antihypertensive treatments show that arterial compliance tends to increase when taken. A decrease in overall arterial tree resistance as well an increase in arterial pressure allows the pressure of the patient to decrease to healthy levels and avoid the negative effects of hypertension.

Windkessel models are frequently used to describe the load faced by the heart in pumping blood through the systemic arterial system, and the relation between blood pressure and blood flow in the aorta artery. The basic model is a closed hydraulic circuit comprised of a water pump connected to a chamber. The circuit is filled with water except for a pocket of air in the chamber; as the water is pumped into the chamber, the water both compresses the air in the pocket and forces the water out of the chamber, back to the pump. The compressibility of the air in the pocket simulates the elasticity and extensibility of the major artery, just as blood is pumped into artery by the heart's left ventricle. This effect is commonly referred to as arterial compliance, which equals the sum of the compliances of all arteries. The resistance water encounters while leaving the Windkessel and flowing back to the pump, simulates the resistance to flow encountered by the blood as it flows through the arterial tree from the major arteries, to minor arteries, to arterioles, and eventually to capillaries, due to decreasing vessel diameter, this resistance to flow is generally called the peripheral resistance.

The 3-element lumped parameter Windkessel model was utilized to represent healthy cardiovascular conditions of a human, how hypertension alters peripheral resistance, arterial compliance and therefore the pressure load, and finally how Nifedipine, a vasodilator, medication is used to treat hypertension, due to the altered resistances and compliance and therefore the change in the pressure load. The three parameters used in the model are characteristic impedance (R_C), arterial/peripheral resistance (R_A), and arterial compliance (C_A).

The added characteristic impedance is the resistive element between the pump and the air chamber to simulate resistance to blood flow due to the aortic valve; it can be modeled by a fixed resistor.

Assuming the ratio of air pressure to air volume in the chamber is constant and the flow of fluid through the pipes connecting the air chamber to the pump follows Poiseuille's law, as stated previously, and is proportional to the fluid pressure, the following differential equation is found to relate water flow and pressure:

$$I(t) = \frac{P(t)}{R} + C\frac{dP(t)}{dt}$$

Here I(t) is the water flow out of the pump as a function of time measured in volume per time units, P(t) is the water pressure as a function of time measured in force per area units, C is the constant ratio of air pressure to air volume, and R is the flow-pressure proportionality constant. The same equation is analogous to an electrical circuit, which the current, I(t), and the time-varying electrical potential, P(t). Below is a schematic of the electrical circuit corresponding to the 3-element Windkessel model:

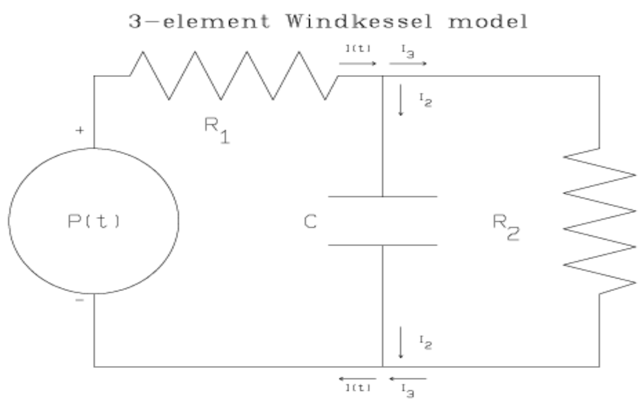

Figure 1: 3-element Windkessel Model

In terms of the physiological system, I(t) is the flow of blood from the heart to the aorta measured in cubic centimeters per second (cm^3/sec), P(t) is the blood pressure in the aorta in millimeters of mercury (mmHg), C is the arterial compliance in the aorta in units of cubic centimeters per millimeter of mercury (cm^3/mmHg), and R is the peripheral resistance in the systemic (or pulmonary) arterial system in units of millimeters of mercury seconds per cubic centimeter (mmHg*s/cm^3). The differential equation previously encounter becomes the following:

$$\left(1+\frac{R_C}{R_A}\right)I(t)+CR_C\frac{dI(t)}{dt}=\frac{P(t)}{R_A}+C\frac{dP(t)}{dt}$$

For a dynamical system, there must be a way to represent all possible values of the system—that is the state space. It is a mathematical model which represents a physical system following this set of equations:

$$y = Ax + Bu$$

$$\dot{x} = Cx + Du$$

Where y is the output vector; x is the state vector; and A, B, C, and D are characteristics of the system in matrix form. From the state space model, many characteristics of the modeled physical system can be extracted and used for analyzing the system mathematically.

Methods

To model the proximal Aorta, a 3-element Windkessel Model is used. In the 3-element Windkessel model, the variable R is used to represent the peripheral resistance, the variable C is used to represent the compliance, and another parameter Z is used to represent impedance. Starting with the differential equation of the 3-element Windkessel model, the Laplace transform was applied in order to obtain the transfer function.

$$\left(1+\frac{Z}{R}\right)Q(s)+sCZQ(s)=\frac{P(s)}{R}+sCP(s)$$

Simplifying the equation, we get

$$\frac{P(s)}{Q(s)}=\frac{RCZs+R+Z}{RCs+1}$$

The flow function was modeled as a sinusoidal function, with the assumption that there is no flow during diastole.

$$Q(t)=\begin{Bmatrix} q_0 sin^2\left(\frac{\pi t}{T_s}\right) & \bigg| & 0\ \le t \le T_s \\ 0 & \bigg| & t_s \le t \le T_c \end{Bmatrix}$$

T_s is the time systole ends and T_c denotes the time the cardiac cycle ends. The values are determined from the heart rate and the assumption that the duration of systole is 40% of the whole cardiac cycle.

```
%Pressure Waveform for a Healthy Patient

%Since there were a range of values for R,C and Z, this script
%attempts to find the proper set of values that will result in a maximum
%pressure of 120mmHg and a minimum pressure of 80mmHg

clear

Tc = 60/75;                                % Total time for one cardiac cycle
Ts = (2*Tc)/5;                             % Total Time for Systolic Phase

i = 1;
t = 0:0.01:Tc;                             % Discretization of times in one cardiac cycle
q(size(t,2)) = 0;                          % Initializing of the vector

q0 = 70/(Ts/2);                            % Peak Flow

for x = 0:0.01:Ts                          % Setting the dependent variable
    q(i) = q0*(sin(pi*x/Ts))^2;            % Dependent Variable q
    i = i + 1;
end

Q = [q,q(2:end)];                          % New Q Matrix of two cycles
Q = Q(1:size(Q,2));
T = 0:0.01:2*Tc;                           % Matrix of 2 cardiac cycles
flag = 0;
```

Figure 2: Defining the first parameters of the code

MATLAB is the program used to create the model. First, the initial parameters will be set. T_c or Tc is the variable used for the time in one cardiac cycle. The code makes the assumption that heartbeat is 75 beats per minute. T_s or Ts is the amount of time for the systolic phase of each heartbeat.

The next set of lines is the creation of matrices. The variable t is a matrix which discretizes the time from 0 to T_c. The matrix q is the initialization of the vector. The variable q_o or q0 is the peak flow from the heart.

The next loop is to set the stage for the rest of the code by discretizing the flow rates and inserting these values into a matrix: the q matrix.

Afterwards, we seek the results of two cycles; this is done with the capital equivalents, Q and T.

```
for R = 0.89:0.01:1.99                          % Various R Values
    for Z = 0.03:0.01:0.06                      % Various Z Values
        for C = 0.47:0.01:1.86                  % Various C Values

            A = -1/(R*C);
            B = 1;
            C_c = (R+Z)/(R*C);
            D = Z;

            sys = ss(A,B,C_c,D);                % State-Space Model

            Y = lsim(sys,Q,T,((80-D)/C_c));     % Time Response given initial condition
            peak = max(Y);                      % Peak Value
            i = i + 1;
            if((peak > 119) && (peak < 121))
                peak2 = max(Y(60:end));
                if((peak2 > 119) && (peak2 < 121))
                    flag = 1;
                    break;
                end
            end
        end
       if (flag == 1)
           break;
       end
    end
    if (flag == 1)
        plot(T,Y)
        title('Pressure Waveform for Healthy Patient')
        xlabel('Time (s)')
        ylabel('Pressure (mmHg)')
        break;
    end
end


fprintf('\nR value calculated: %-3.2f' ,R)
fprintf('\nC value calculated: %-3.2f' ,C)
fprintf('\nZ value calculated: %-3.2f \n' ,Z)
```

Figure 3: Series of loops to test for various R, Z, and C values

Now, we see a series of for and if loops; these will serve as deciders for the program. We see that there are three variables, R, Z, and C, which represent resistance, impedance, and compliance, respectively. The range of values for R and C came of the results of Liu et al [2] and the range for Z came from the results of both Stergiopulos et al [2] and Westerhof et al [2]. After, we create the state space model using the sys and ss functions. The inputs for the ss model—A, B, C_c, and D—represent the matrices in this equation:

$$\dot{x} = Ax + Bu$$

$$y = Cx + Du$$

Then, we log the time response from the given conditions as shown in line 39. The format of the lsim function is lsim(α,β,γ,δ) where α = sys-function output, β = Q, γ = time samples for simulation, and δ = initial condition. In line 40, we seek to find the maximum value of the Y-Matrix for the given R, Z, and C, conditions.

For each peak, we seek to find if the peak value of the two cardiac cycles is between 119 and 121—this is to ensure that the correct R, C, and Z values are logged which are displayed at the end of the code.

Once the set of values that gives an appropriate output is found, the loop ends and the values are plotted. Then, the discovered R, C, and Z values are displayed.

Once a working plot was benchmarked with the 3-element results of Hauser et al [2], we felt safe to proceed and alter the program.

```
%%

%Pressure Waveform for Patient with Hypertension

clear

R = 1.311;
C = 1.234;
Z = 0.069;

Tc = 60/73;
Ts = (2*Tc)/5;

i = 1;
t = 0:0.01:Tc;
q(size(t,2)) = 0;

q0 = 93/(Ts/2);

for x = 0:0.01:Ts
    q(i) = q0*(sin(pi*x/Ts))^2;
    i = i + 1;
end

Q = [q,q(2:end)];
Q = Q(1:size(Q,2));
T = 0:0.01:2*Tc;


A = -1/(R*C);
B = 1;
C_c = (R+Z)/(R*C);
D = Z;

sys = ss(A,B,C_c,D);

P = lsim(sys,Q,T,((134-D)/C_c));

figure

plot(T,P)
title('Pressure Waveform for Patient with Hypertension')
xlabel('Time (s)')
ylabel('Pressure (mmHg)')
axis([0,1.64,130,210])
```

Figure 4: 3-element Windkessel Model for Patient with Hypertension

From the beginning of the code, one can see the difference being the R, C, and Z values. These came from the results of Cholley et al [1] who conducted research on antihypertensive therapies. Along with these values, the beats per minute and maximum flow rate changed in accordance with the results of Cholley et al [1].

```
%Pressure Waveform for Patient Using Nifedipine to Treat Hypertension

clear

R = 0.97;
C = 1.776;
Z = 0.069;

Tc = 60/73;
Ts = (2*Tc)/5;

i = 1;
t = 0:0.01:Tc;
q(size(t,2)) = 0;

q0 = 93/(Ts/2);

for x = 0:0.01:Ts
    q(i) = q0*(sin(pi*x/Ts))^2;
    i = i + 1;
end

Q = [q,q(2:end)];
Q = Q(1:size(Q,2));
T = 0:0.01:2*Tc;


A = -1/(R*C);
B = 1;
C_c = (R+Z)/(R*C);
D = Z;

sys = ss(A,B,C_c,D);

figure

P = lsim(sys,Q,T,((104-D)/C_c));
plot(T,P)
title('Pressure Waveform for Patient using Nifedipine to treat Hypertension')
xlabel('Time (s)')
ylabel('Pressure (mmHg)')
axis([0,1.64,100,170])
```

Figure 5: 3-element Windkessel Model for Patient treated with Nifedipine

Here, we again observe different R, C, and Z values. These are values extracted from the Cholley et al paper who conducted research on patient who were treated with Nifedipine.

Results

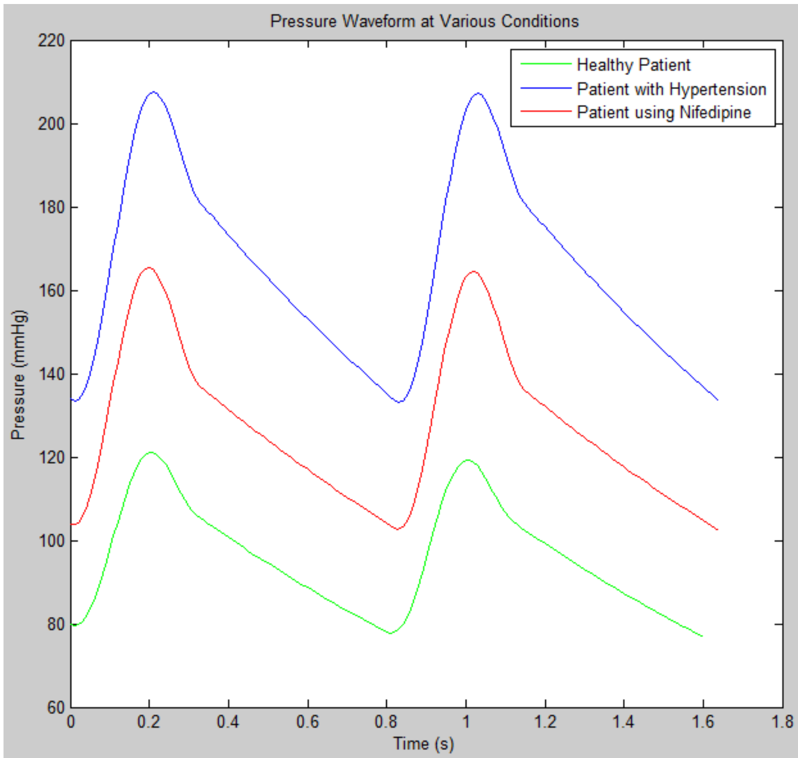

Figure 6: Pressure vs. Time graph of the three scenarios

This graph puts together the results of all the scenarios side-by-side. We can see that there is a noticeable gap between all cases: healthy, hypertension, and treated with Nifedipine. The healthy patient, shown by the green graph, shows the least amount of pressure; the person diagnosed with hypertension, the blue line, shows the highest amount of pressure; the person treated with Nifedipine has their pressure shown by the red line.

It is evident that the person with hypertension will experience a much high blood pressure than a healthy patient. According to the graph, the peak pressure during a cardiac cycle for a patient with hypertension is 210mmHg—a value that is almost 2 times that of a healthy patient.

Nifedipine, a drug meant to treat those with hypertension shows a decrease in blood pressure. Although not to the point of a healthy patient, it does alleviate the high pressure. The peak pressure, which is ~165mmHg makes a noticeable drop from that of the patient who only has hypertension; there is a 21.4% drop between peak values.

Conclusion

The system analysis of the Windkessel model for three conditions was done. The results of our 3-element Windkessel model are consistent with the theoretical results. For healthy patient, the blood pressure ranges from 80mmHg to 120 mmHg. For patient with hypertension, the blood pressure ranges from 130mmHg to 210 mmHg, which (according to Mayo Clinic) bears a diagnosis of stage 2 hypertension and is a serious matter with numerous health defects. After treatment using Nifedipine, the blood pressure of the patient with hypertension decreases, which ranges from 105mmHg to 165mmHg. This is still categorized as stage 2 hypertension but the lower pressure will not have as dramatic of an effect on the patient's healthy tissue.

According to Dr. Richard Klabunde (a PhD in physiology) a pressure vs. time graph of the aorta for a healthy patient looks as follows [3]:

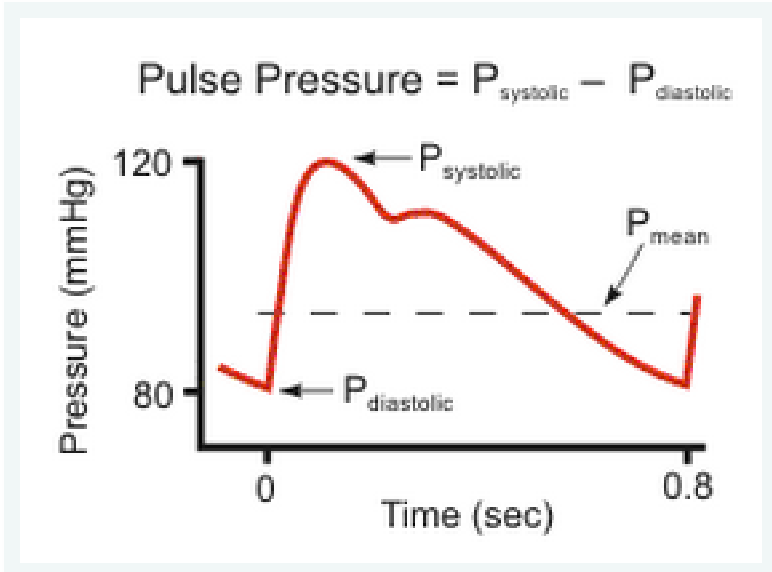

Figure 7: Pressure vs. Time graph of a healthy patient

The peak and minimum pressures, Systolic and Diastolic, respectively, match up with the produced values from the Matlab code. However, the little bump or slight rise in pressure that takes place at about .4 seconds in the graph above is not present in the theoretical graphs obtained from the Matlab code. Had the code been completed with a 4-element Windkessel model the graphs would have definitely been more similar. However, the 3-element model was sufficient enough to simulate the systolic and Diastolic pressures as a function of time and for a patient with hypertension and medicinal treatment.

References

1. Cholley, Bernard P., Sanjeev Shroff, Joanne Sandelski, Claudia Korcarz, Beth A. Balasia, Shelly Jain, David S. Berger, Michael B. Murphy, Richard H. Marcus, and Roberto M. Lang. Differential Effects of Chronic Oral Antihypertensive Therapies on Systemic Arterial Circulation and Ventricular Energetics in African-American Patients." September 12, 1994. Accessed May 2, 2015. http://circ.ahajournals.org/content/91/4/1052.full.

2. Hauser, Jan, Jakub Parak, Miroslav Lozek, and Jan Havlik. "System Analyze Of The Windkessel Models." Faculty of Electrical Engineering Czech Technical University in Prague. Web. 15 May 2015. <http://bmeg.fel.cvut.cz/wp-content/uploads/2013/06/Hauser-SYSTEM_ANALYZE_OF_THE_WINDKESSEL_MODELS.pdf>.

3. Klabunde, Richard. "Arterial and Aortic Pulse Pressure." CV Physiology: Arterial Pulse Pressure. N.p., n.d. Web. 17 May 2015.