Time-dependent myogenic behavior of arterioles

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1 Introduction

The circulatory system has the ability to maintain relatively constant blood flow over a wide range of pressures – a phenomenon known as autoregulation. Small arteries and arterioles are responsible for this, and they regulate blood flow by changing their diameters. These changes in diameter occur due to contraction or relaxation of the surrounding vascular smooth muscle (VSM).

This study focuses on the myogenic response; that is, how the arteriolar diameter changes in response to changes in intraluminal pressure. We examine how diameter of the arteriole changes with time, and try to improve upon time constants given in [2] to better coincide with available experimental data.

2 Model for myogenic response

The Law of Laplace relates diameter and pressure to circumferential wall tension as follows:

$$T = \frac{PD}{2}.$$

Thus, to examine arteriolar diameter is to examine arteriolar wall tension.

2.1 Tension in the vessel wall

Tension in the vessel wall can be modeled as the sum of a passive component and an active component induced by the vascular smooth muscle (VSM) [2]. We can thus write the total

tension in the vessel wall as follows:

$$T_{total} = T_{pass} + AT_{act}^{max}, \tag{1}$$

where T_{pass} is the passive tension, T_{act}^{max} is the maximal active tension that is generated at a given vessel circumference, and A is the degree of activation which represents the level of VSM tone.

The passive tension has been observed to be a nonlinear function of diameter, and is approximated by the following exponential relationship:

$$T_{pass} = C_{pass} \exp[C'_{pass}(D/D_0 - 1)], \tag{2}$$

where D is the vessel diameter, C_{pass} is the passive tension at a diameter of D_0, and C'_{pass} determines the steepness of the exponential curve. The reference diameter D_0 is the passive diameter of the blood vessel at an intraluminal pressure of 100 mmHg [3].

The plot of this exponential relationship is given:

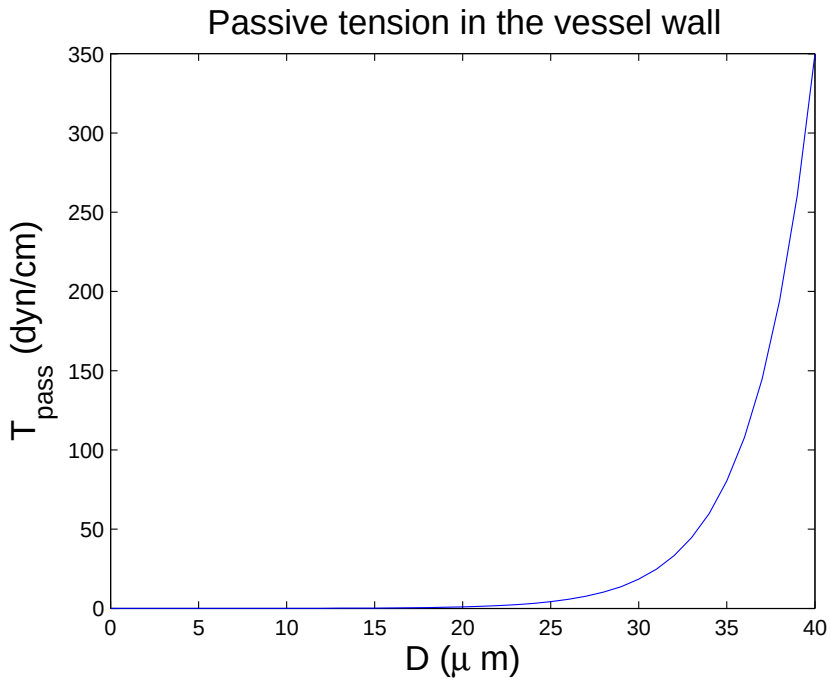

Figure 1: The curve shows the exponential relationship between the passive tension in the vessel wall and the diameter of the vessel.

Note that for larger diameters, the passive tension grows quickly, since the vessel is getting close to being maximally stretched.

The maximal active tension generated by the VSM cells in the vessel wall has been observed to peak at a specific diameter, then decrease symmetrically above and below this diameter. T_{act}^{max} is thus modeled by a Gaussian curve [3]:

$$T_{act}^{max} = C_{act} \exp\left[-\left(\frac{D/D_0 - C'_{act}}{C''_{act}}\right)^2\right], \tag{3}$$

where C_{act} represents peak magnitude, C'_{act} represents relative peak location, and C''_{act} represents relative curve width.

The plot of this Gaussian relationship is given:

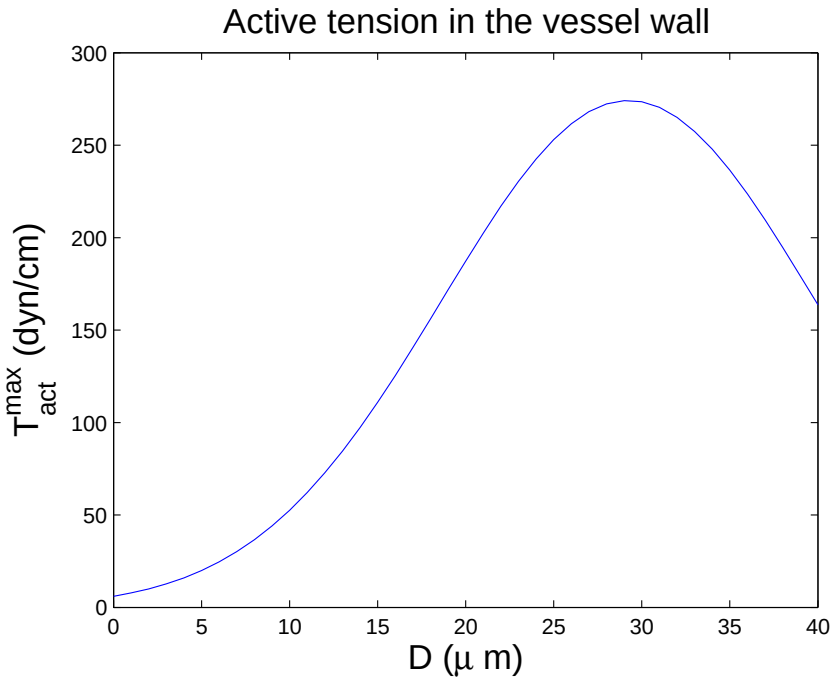

Figure 2: The curve shows the Gaussian relationship between the active tension in the vessel wall and the diameter of the vessel.

Combining the passive and active tension, and assuming full constriction of the vessel ($A = 1$), we get the following plot of the total tension (plotted alongside the passive tension, to see the effect of the active component):

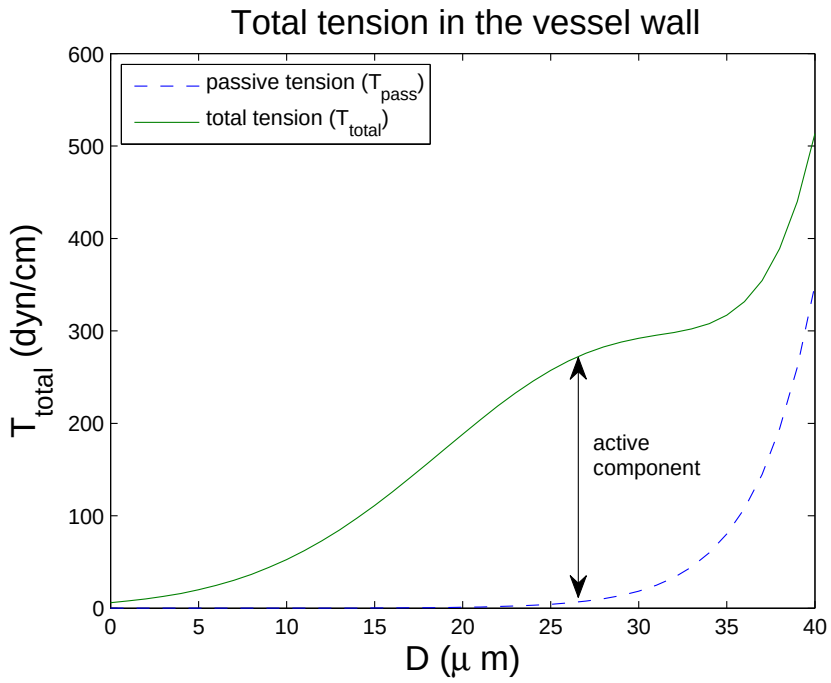

Figure 3: The curve shows the difference between the total tension with and without the active contribution.

2.2 VSM Tone

The level of activation can potentially depend on a number of factors; here it is assumed that the VSM tone is a function of the vessel wall tension. It has been suggested that this is a sigmoidal dependence, so as in [2],

$$A_{total} = \frac{1}{1 + \exp(-C_{myo}T + C'_{tone})}, \tag{4}$$

where C_{myo} determines the steepness of the sigmoidal curve and C'_{tone} determines the tension at half-maximal activation ($A = 0.5$).

This dependence of activation on wall tension implies that wall tension is controlled by a negative feedback mechanism. That is, an increase in tension leads to an increase in activation (tone) and thus contraction, which reduces wall tension for a fixed intraluminal pressure according to the law of Laplace.

The parameters C_{pass}, C'_{pass}, C_{act}, C'_{act}, C''_{act}, C_{myo}, and C'_{tone} were estimated to best fit the available data, and are given in Table 1.

Parameter	Value
C_{myo}, cm/dyn	0.0547
C'_{tone}	8.031
C_{pass}, dyn/cm	316
C'_{pass}	16.702
C_{act}, dyn/cm	900.050
C'_{act}	0.910
C''_{act}	0.374
D_0, μm	65
D_c, μm	14.8
τ_d, s	1
τ_a, s	20

Table 1: Parameter values for arteriolar diameter and activation

2.3 Diameter and activation level change with time

When pressure is changed, blood vessels show a passive transient change in diameter followed by an active VSM contraction or dilation to a different equilibrium diameter [1]. This behavior can be modeled by the following system of differential equations:

$$\frac{dD}{dt} = \frac{1}{\tau_d}\frac{D_c}{T_c}(T - T_{total}) \tag{5}$$

$$\frac{dA}{dt} = \frac{1}{\tau_a}(A - A_{total}), \tag{6}$$

where D_c and T_c are the diameter and tension at a control state, T_{total} and A_{total} are steady-state values of wall tension and VSM activation given by equations (1) and (4), and τ_d and τ_a are time constants governing the rates of passive diameter and activation change, respectively [1].

3 Response to changes in pressure

Consider an arteriolar diameter at equilibrium. We first examine what happens to the diameter when the intraluminal pressure is increased as a pulse; that is, the pressure is held constant so that the diameter reaches a steady state, then the pressure is increased to a new constant for a period of time, and the response of the diameter is observed.

The plot of the pressure step is as follows:

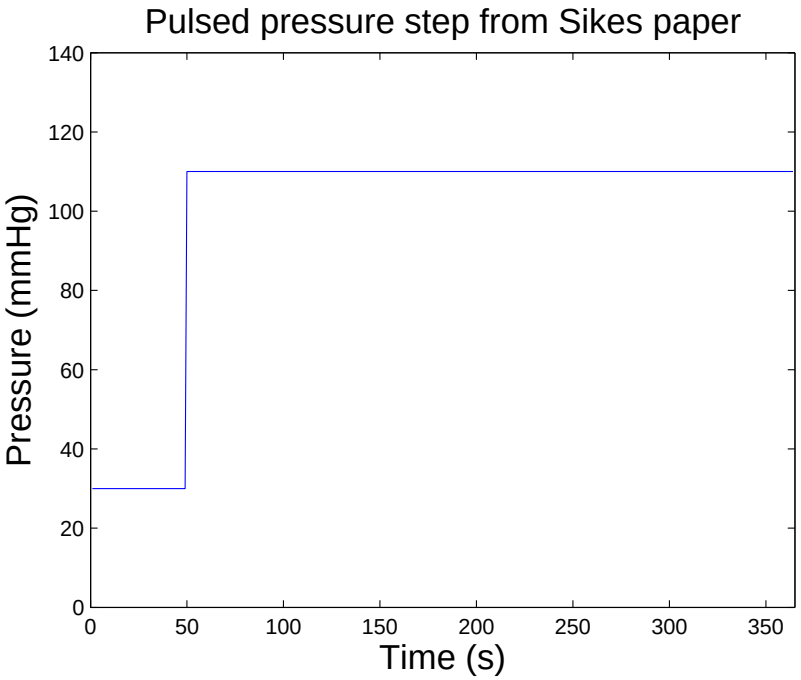

Figure 4: Pressure-time curve from Sikes paper, which is given as a constant pulse.

And the corresponding diameter plotted versus time:

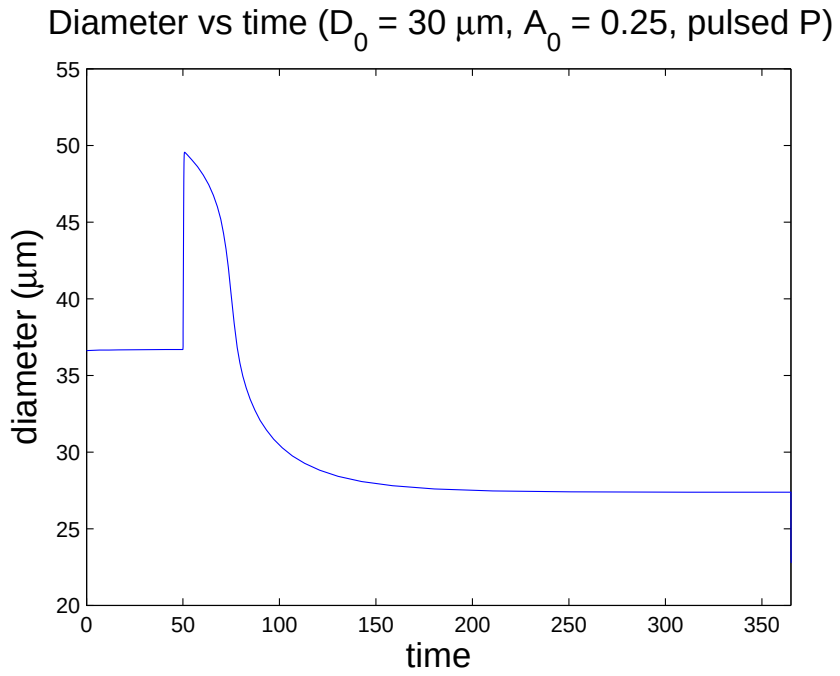

Figure 5: Diameter-time curve from model for pulsed pressure.

Notice the initial passive spike in diameter followed by the active regulation bringing the arteriolar diameter back down to a steady state. The presence of VSM tone is seen in the plot of activation versus time:

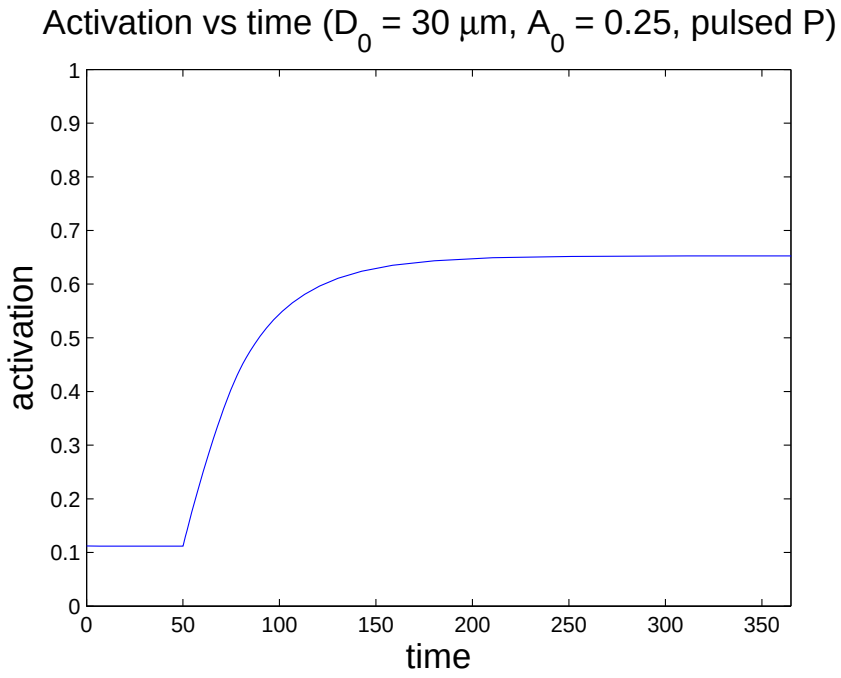

Figure 6: Activation-time curve from model for pulsed pressure.

The VSM activation is initially at 0.5, but increases in response to the increased pressure. When the pressure and activation balance out, the activation curve and the diameter curve level out to equilibrium.

3.1 Ramped pressure

Above, the responses of diameter and activation have been measured when pressure is changed to a constant higher or lower than the equilibrium pressure. This corresponds to a pulse, where the pressure change is given graphically by a step function. However, we can also see the response to changes in pressure which are not given by a pulse. In the Davis and Sikes paper, an example is given where pressure is increased linearly over time, and the corresponding diameter response is observed. We attempt to do this here, finding the least-squares line that best approximates the data from the paper, and using this as our pressure that varies with time. That is, when the pressure curve looks as follows:

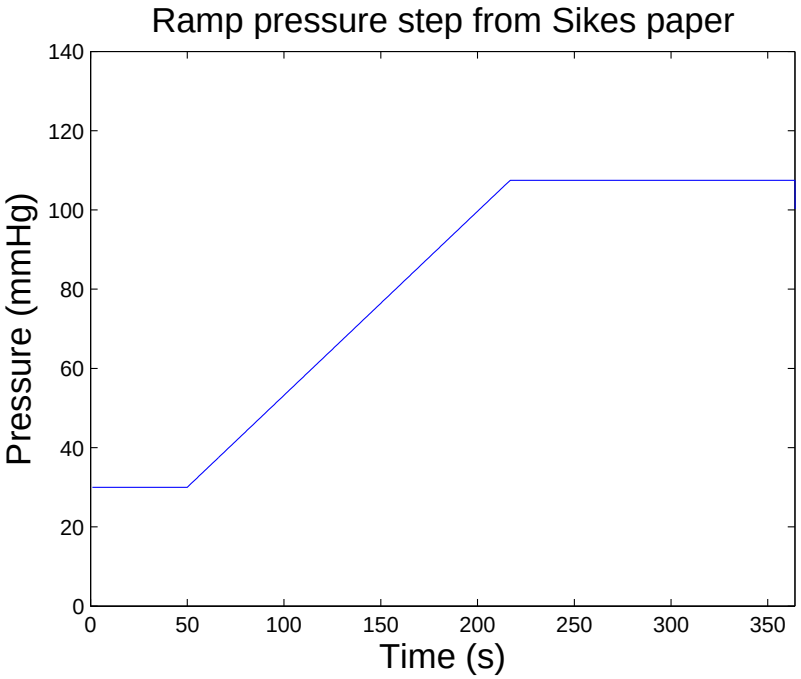

Figure 7: Pressure-time curve from Sikes paper, which ramps up linearly over time, rather than being a constant pulse.

With this comes the corresponding plot of diameter versus time:

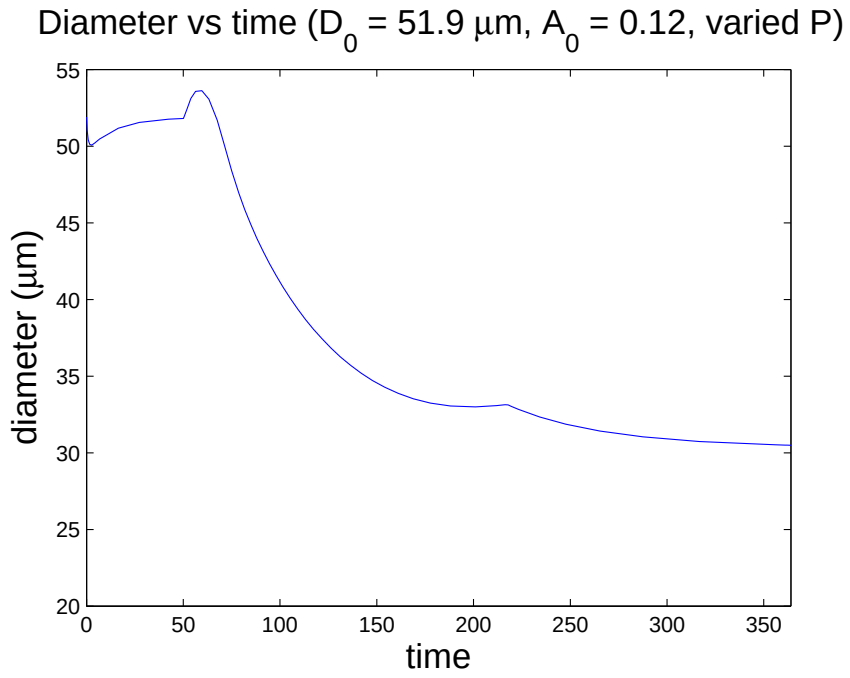

Figure 8: Diameter-time curve from model for ramped pressure.

As well as the plot of activation versus time:

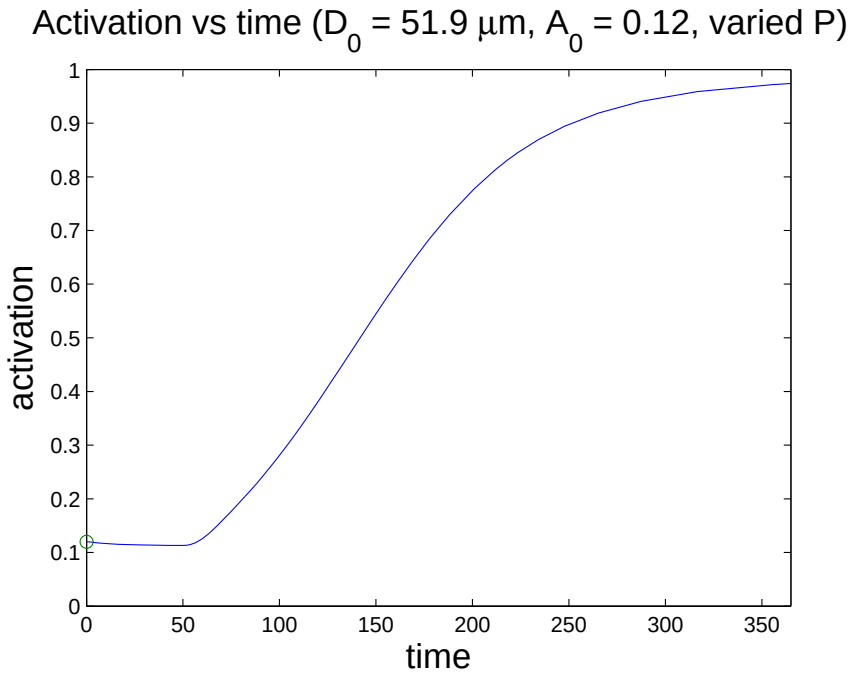

Figure 9: Activation-time curve from model for ramped pressure.

In this case, the passive response is less pronounced. This is what we would expect, as the pressure is being gradually increased, so the passive dilation isn't as extreme. As the level of VSM tone catches up to the pressure, the diameter of the arteriole is again brought back down to a steady state.

3.2 Determining a better time constant

In our time-dependent model, the time constant τ_d affects the length of the passive transient (spike) response of the diameter-time graph. The time constant τ_a affects how long the diameter takes to get to equilibrium.

Since the passive transient response seems to occur on a very short time scale, and because we don't have any data with high enough resolution, it is unlikely we will be able to improve on the approximation of 1 second for how long the response lasts. So $\tau_d = 1$ seems fairly accurate as it is. However, since the active response occurs on a larger time scale, it is easier to observe what the constant τ_a should be. τ_a is now set to 60 because the authors were aware that the passive and active responses occurred on different time scales, but weren't sure exactly what τ_a should be; so since the passive response was assumed to be 1 second, they assumed the active response to be 1 minute.

Based on the data given in [4] and [3], it seems likely that we can improve upon this time constant.

To do this, we want to find a D_0 (the passive diameter of the vessel at an intraluminal pressure of 100 mmHg) such that all other other parameters are determined by the equations in the Carlson paper, and (as given in the Sikes paper) at 30 mmHg the diameter is $\sim 45 - 48\mu m$, and at 110 mmHg the diameter is $\sim 27\mu m$. This will give us a model which matches the experimental data at the plateaus; that is, when the diameter is at equilibrium.

With the pressure ramped up linearly (and with $\tau_a = 60$), the plateaus are fairly accurate, but it is clear that the time scales for the VSM contraction and relaxation are off:

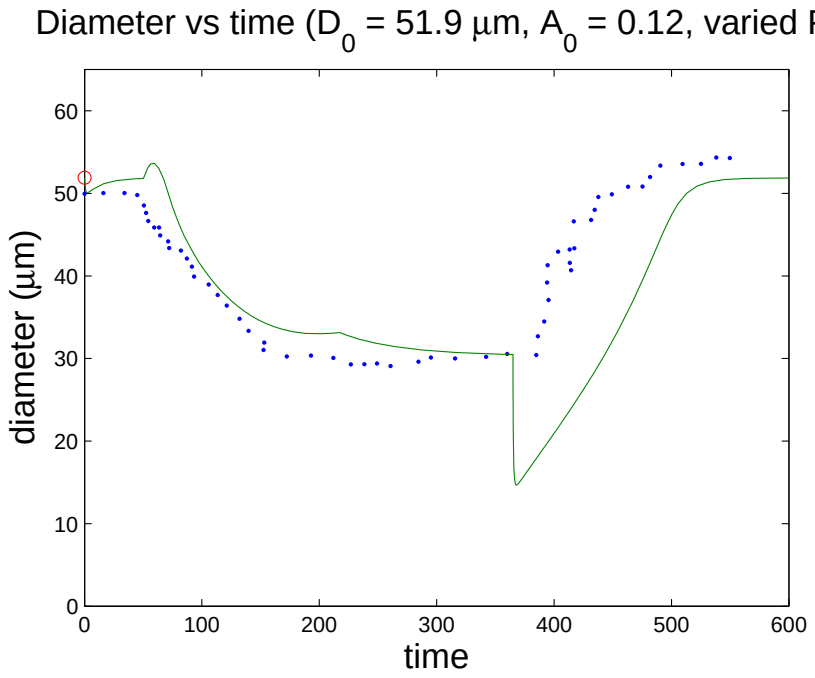

Figure 10: Diameter-time curve from model compared to Sikes data for linearly ramped pressure. Here $\tau_a = 60$.

The results are similar with pulsed pressure:

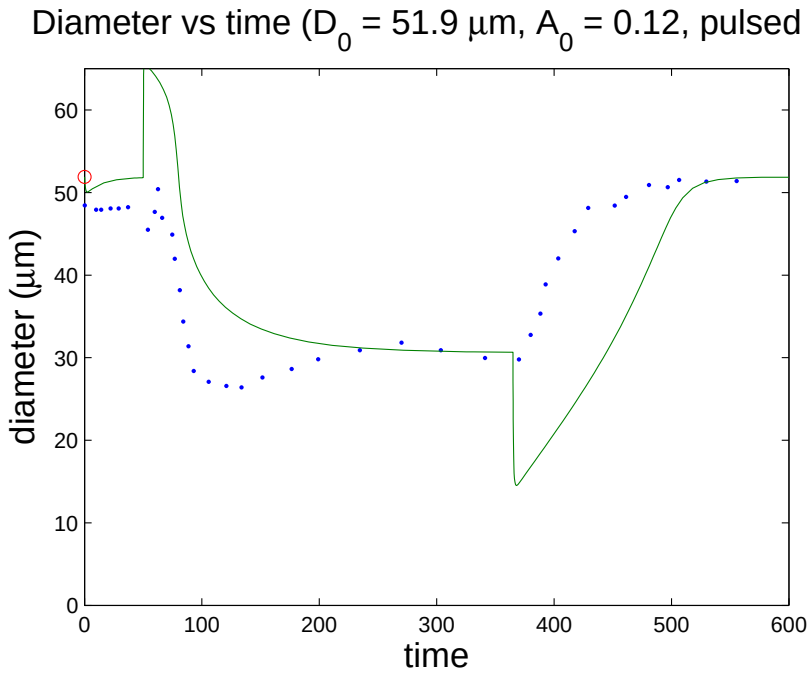

Figure 11: Diameter-time curve from model compared to Sikes data for pulsed pressure. Here $\tau_a = 60$.

So we have found parameters to fit the steady state data, which give us the plateaus. To try to match the transient behavior, we look at τ_a.

To determine the best value for τ_a, we took the one which minimized RMS deviation between the model and the experimental data:

Value of τ_a	RMS pulse	RMS ramp	RMS average
10	6.5777	6.3675	6.4726
20	5.4533	4.0515	4.7524
30	7.0504	5.1926	6.1215
40	8.7983	7.4761	8.1372
50	10.6716	9.2668	9.9692
60	12.5499	10.7358	11.6429

This gave $\tau_a = 20$. For the pulsed pressure case, this gave the following diameter curve:

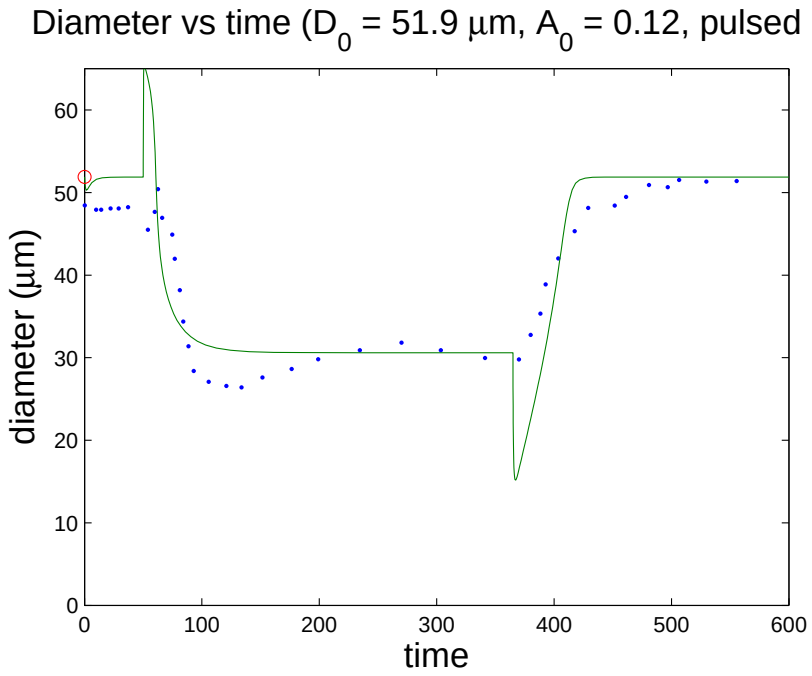

Figure 12: Diameter-time curve from model compared to Sikes data for pulsed pressure. Here $\tau_a = 20$.

And for the ramped pressure case, $\tau_a = 20$ gave the following diameter curve:

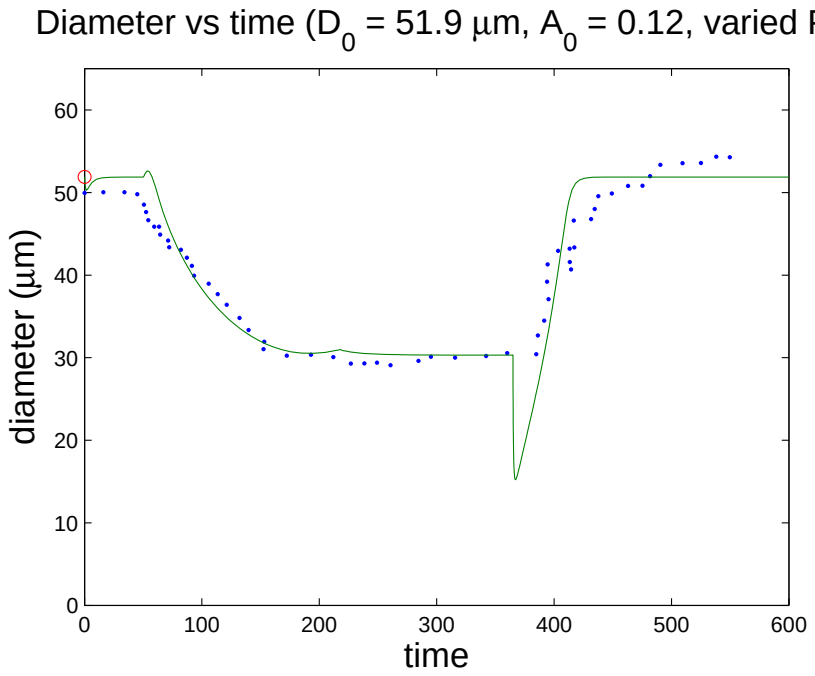

Figure 13: Diameter-time curve from model compared to Sikes data for ramped pressure. Here $\tau_a = 20$.

Using $\tau_a = 20$ appears to better capture the time-dependent behavior of the arterioles.

4 Discussion

The objective of this study was to examine the time-dependent responses of arteriolar diameters to changes in intraluminal pressure.

Adapting the model from [1] and [3], we were able to fit the parameters to capture the steady state behavior of the arteriolar diameter experimental data from [4]. After an increase in pressure, the steady state diameters of the arterioles were noticeably smaller. This is due to the myogenic response (where the VSM contracts in the presence of increased pressure), and was captured by the model.

The more interesting part of the data occurs after the pressure change, but between steady states. We want to know not only the equilibrium diameter, but how long the arteriolar diameter takes to equilibrate, and what shape the curve of diameter versus time looks like. After determining which activation time constant best fit the data ($\tau_a = 20$), the model ended up fitting the data well, with an RMS deviation of 4.75.

This was not a bad fit, considering the shape of the experimental data for the pulsed pressure case. After the initial passive response, the diameter decreases due to the active myogenic response, but then increases again then decreases again – a result our model had no hope of capturing. This phenomenon may just be noise incorporated into the data, or perhaps there is some currently unknown explanation as to why the diameter would behave in such a way.

For both the cases where the pressure was increased as a pulse and where the pressure was increased linearly, there were two different time scales for the diameter to come to equilibrium observed in the experimental data. When the VSM contracts in response to the increase in pressure, the diameter levels out to steady state much faster than when the VSM relaxes in response to the decrease in pressure. This suggests that perhaps the time constant τ_a is different for the contraction and relaxation of the smooth muscle.

References

[1] Julia C. Arciero, Brian E. Carlson, and Timothy W. Secomb. Theoretical model of metabolic blood flow regulation: roles of atp release by red blood cells and conducted responses. *American Journal of Physiology - Heart and Circulatory Physiology*, 295:H1562–H1571, October 2008.

[2] Brian E. Carlson, Julia C. Arciero, and Timothy W. Secomb. Theoretical model of blood flow autoregulation: roles of myogenic, shear-dependent, and metabolic responses. *American Journal of Physiology - Heart and Circulatory Physiology*, 295:H1572–H1579, October 2008.

[3] Brian E. Carlson and Timothy W. Secomb. A theoretical model for the myogenic response based on the length-tension characteristics of vascular smooth muscle. *Microcirculation*, (12):327–338, 2005.

[4] Michael J. Davis and Patricia J. Sikes. Myogenic responses of isolated arterioles: test for a rate-sensitive mechanism. *American Journal of Physiology - Heart and Circulatory Physiology*, 259(6):H1890–H1900, 1990.