Biphasic Blood Flow in Mesentery Microcirculatory Networks
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Abstract
The purpose of this paper is to investigate how changes in the plasma skimming coefficient affect the hemoconcentration within blood vessel networks. Due to the differences in plasma and red blood cells (RBCs) phases, the RBCs tend to flow at a different rate causing a difference in hematocrit concentration at a bifurcation in a network. This can be quite important when looking into how efficiently tissues are being oxygenated, especially in important regions such as mesentery tissue. This paper will analyze a plasma skimming coefficient model and attempt to utilize a polynomial fit to form a new model to see if improvements can be made by decreasing the number of variables.

1. Introduction
Understanding blood flow and hematocrit levels in the microcirculation of the brain is crucial to diagnosing and treating problems within the brain tissue. When the blood vessels are at such a small size, as in capillaries, blood follows a biphasic model. One phase is the oxygenated erythrocytes and the other phase is the blood plasma. As most oxygen is carried by the erythrocytes, the distribution of these cells and plasma in the microcirculation is important to the oxygenation of tissues, especially in complex neurological tissues of the brain. Because of this, a concise mathematical model of the spatial distribution within the blood is needed to predict how tissues are oxygenated.

At a bifurcation in the vessel the plasma close to the vessel wall will “skim” off into the branch with a smaller diameter, which dilutes the blood, leading to a lower hematocrit level. In the larger branch the opposite is true and hemoconcentration occurs. The higher hematocrit level in the larger branch is beneficial because it leads to the pathway effect, where the high RBC concentration in the large daughter branches through the systemic circulation takes the longest path throughout the body [2].

Parameters that are useful in modeling plasma skimming are viscosity, bulk flow rate, and the geometry of the vessel [1]. Even with one bifurcation the computations for plasma skimming can be quite tedious due to the parameters involved.

2. Methods
Even with the biphasic properties of blood, the flow must follow conservation balances at each node (or bifurcation). In other words, the flow in and flow out must be equal for the mass balance to be satisfied. Figure 2 demonstrates this basic property as seen in a single bifurcation. The value being conserved are volumetric flow to satisfy mass balance, while the hematocrit is not conserved since it is a ratio of RBCs in the respective vessels.

The vessels considered for microcirculation tend to have a diameter that is less than 100 microns [1]. It is in these micro vessels where the red blood cells (RBC) tend to collect in the center, while the plasma migrates to the vessel wall. This separation is what causes the two different phases that come with different velocity and flow profiles. Hematocrit is defined as the volume ratio of RBCs in the blood vessel. This value will change dramatically the more bifurcations there are in the larger blood vessel. The cause of this hematocrit change is plasma skimming.

Figure 1. Example of microcirculatory network in mesentery [1]

Figure 2. Example of simple bifurcation in blood vessel. It is assumed that $A_1 > A_2 > A_3$ and $Q_1H_1 = Q_2H_2 + Q_3H_3$. 

The node in Figure 2 represents a bifurcation in the blood vessels and at each vessel an H value is assigned. The H values represent the volumetric fraction of RBCs [2]. The flow and hematocrit at the parent branch and flow out at the final branches are known values and using those values the unknown hematocrits can be determined for daughter vessels. Unlike mass conservation, the hematocrit levels do not equal each other on each side off a node. This is due to the fact that hematocrit is based on the volumetric ratio of RBCs to the total volume of blood in a vessel.

In order to show the balance of hematocrit the plasma skimming coefficient can be implemented. This can be done using a straightforward calculation shown below:

\[ \theta_i = \frac{A_i}{A_1} \frac{1}{M} \]  

The plasma skimming coefficient is represented by \( \theta \), and this value is calculated for each daughter branch. \( A_i \) is the cross-sectional area of the daughter branch and \( A_1 \) is the cross-sectional area of the parent vessel. The plasma skimming coefficient is therefore highly dependent on the ratio between the areas of the daughter and parent vessels. This makes sense because the amount of plasma found in daughter vessels has been found to be dependent on how large or small the vessels are. Typically larger amounts of plasma are found in smaller vessels. The M parameter is also quite important in the calculation because it represents forces between the vessel wall and the RBCs that tend to collide with it. M values greater than 1 tend to be in larger vessels where the separation of plasma and RBCs is less noticeable and better mixed [1]. When below 1, the M value causes the cross-sectional area ratio to be lower than it physically is, which cannot be accurate [1].

Due to the fact that oxygen consumption in the mesentery (as well as other tissues) is a function of adjusted discharge hematocrit, H*, this value will need to be determined [3]. Discharge hematocrit is the total hematocrit flux leaving the bifurcation. The plasma skimming coefficient above helps to account for the difference in size of the two branches coming off the parent vessel. Each vessel will have its own hematocrit value which is the vessel’s plasma skimming coefficient multiplied by H*. Applying a hematocrit balance results in the equation below:

\[ Q_1H_1 = Q_2H_2 + Q_3H_3 \]  

Then by applying what is known about each hematocrit value for each daughter vessel:

\[ Q_1H_1 = Q_2\theta_2H^* + Q_3\theta_3H^* \]  

Assuming the volumetric flow rates of each vessel are determined and the plasma skimming coefficients have been calculated, the only unknown value in the equation is the discharge hematocrit. Solving for discharge hematocrit the following equation is determined:

\[ H^* = \frac{Q_1H_1}{Q_2\theta_2+Q_3\theta_3} \]

Therefore, the respective hematocrit values for the daughter branches are:

\[ H_i = H^* \theta_i \]

With each hematocrit value, the oxygenation of the tissue along each route can be determined. The timeline of this method is as follows. First, the volumetric flows need to be determined by experimental means along with the cross-sectional areas. The cross-sectional areas can be found using the radii of each vessel, obtained from experimental means as well. After finding the previous values, the hematocrit of the parent branch should also be determined. From there, the equations can then be implemented to find the hematocrit of daughter branches. In order to verify these equations, a simulation was run using arbitrary values for the areas of the vessels and hematocrit of the parent vessel. The M parameter was set to 1 to simplify the equations.

For the single bifurcation simulation, it is assumed that the volumetric flow in each daughter vessel is different from one another, but add up to that of the parent branch’s volumetric flow. The daughter branch volumetric flows also change as the diameter (or cross-sectional area) changes to be more realistic. It is also assumed that the plasma skimming coefficients, or cross-sectional area ratios, of the daughter vessels add up to 1. The areas of the daughter vessels were set as vectors to show a change in the plasma skimming coefficients so it could be determined how the changes affect the system or specifically the discharge hematocrit. An example of how the cross-sectional area is changing for this single bifurcation model is shown in figure 3.
Figure 3. Display of how the simulation changes the diameters (cross-sectional areas). One daughter vessel starts out large and the other small. The larger vessel is reduced in size while the smaller vessel increases. Using this model for the single bifurcation, the discharge hematocrit and subsequently the hematocrits of each respective daughter vessel can be determined at each step in the transition from large to small vessel and small to large vessel. After obtaining the results from the simulation, a polynomial fit dependent on the plasma skimming coefficients will be determined to see if a newer hematocrit model can be made. This new model will only be dependent on the plasma skimming coefficient, \( \theta \), unlike the other dependent variables in equations (4) and (5).

For a larger network, the role of hemoconcentration becomes important. As discussed previously, the pathway effect ensures that a high concentration of RBCs will take the longest path throughout the body. This is due to the fact that RBCs tend to flow more into larger daughter vessels than smaller daughter vessels. With a large enough network having many branches, the hemoconcentration becomes much more noticeable.

In figure 4, a network consisting of ten bifurcations is simplified by having all small daughter vessels at each bifurcation equal to each other and having all large daughter vessels smaller than the vessel before them. To verify the role of hemoconcentration in a network, simulation was performed using this ten bifurcation system. The simulation has \( A_1 \) equal to 1 with each small daughter vessel equal to 0.05 and large daughter vessels equal to the parent vessel minus 0.05. The simulation also assumes that all volumetric flows have been measured and that they balance at each bifurcation and that the hematocrit in the first parent vessel is known as \( H_1 = 0.5 \). With these assumptions made, equation (4) can be implemented to find discharge hematocrit at each bifurcation and in turn equation (5) can be used to find the hematocrit of the large daughter vessel. For the plasma skimming coefficient calculations, an M value of 1 was used for more realistic values. The values of \( A_1 \) through \( A_{21} \) can be found in Table 1 and values of \( Q_1 \) through \( Q_{21} \) can be found in Table 2. After finding the hematocrit in the large daughter vessels in the ten bifurcation simulation, the polynomial fitting method from the single bifurcation will be applied to the system to see if the equations can match with the known values from the current models. The code for the single bifurcation simulation and ten bifurcation microcirculatory network simulation can be found in the Appendix.

3. Results

In this section the results obtained from the single bifurcation simulation and the ten bifurcation network simulation will be shown and analyzed to understand the meaning of the data.

Figure 5. Discharge hematocrit, \( H' \), as function of the plasma skimming coefficient (\( \theta_2 \)) for daughter vessel 2 in the single bifurcation simulation. The plasma skimming coefficient is the ratio of the daughter vessel cross-sectional area (\( A_2 \)) and parent vessel (\( A_1 \)) due to the M parameter being constant at 1. Therefore, the plasma skimming coefficient is changing due to change in area ratio.

In figure 5 it is evident that the discharge hematocrit leaving the bifurcation follows a parabolic curve with respect to the increasing values of the plasma skimming coefficient, which in this case is due to the M parameter being equal to 1. This makes the plasma...
skimming coefficient the cross-sectional area ratio of vessel 2 to the parent vessel. Due to the parabolic nature of the discharge hematocrit there is a maximum of 1 at a cross-sectional area ratio of 0.5.

Table 1. Cross-sectional areas of each vessel, $A_i$ through $A_{21}$. Each column represents a bifurcation, with the first column being the starting point, therefore only one value is present.

<table>
<thead>
<tr>
<th>$A_1$</th>
<th>$A_2$</th>
<th>$A_4$</th>
<th>$A_6$</th>
<th>$A_8$</th>
<th>$A_{10}$</th>
<th>$A_{12}$</th>
<th>$A_{14}$</th>
<th>$A_{16}$</th>
<th>$A_{18}$</th>
<th>$A_{20}$</th>
</tr>
</thead>
<tbody>
<tr>
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<td>0.99</td>
<td>0.98</td>
<td>0.97</td>
<td>0.96</td>
<td>0.95</td>
<td>0.94</td>
<td>0.93</td>
<td>0.92</td>
<td>0.91</td>
<td>0.9</td>
</tr>
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<td>$A_3$</td>
<td>$A_5$</td>
<td>$A_7$</td>
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<td>$A_{11}$</td>
<td>$A_{13}$</td>
<td>$A_{15}$</td>
<td>$A_{17}$</td>
<td>$A_{19}$</td>
<td>$A_{21}$</td>
<td></td>
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<tr>
<td>0.05</td>
<td>0.05</td>
<td>0.05</td>
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</tr>
</tbody>
</table>

Table 2. Volumetric flow rate of each vessel, $Q_i$ through $Q_{21}$. Each column represents a bifurcation, with the first column being the starting point, therefore only one value is present.

<table>
<thead>
<tr>
<th>$Q_1$</th>
<th>$Q_2$</th>
<th>$Q_4$</th>
<th>$Q_6$</th>
<th>$Q_8$</th>
<th>$Q_{10}$</th>
<th>$Q_{12}$</th>
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<th>$Q_{16}$</th>
<th>$Q_{18}$</th>
<th>$Q_{20}$</th>
</tr>
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<tbody>
<tr>
<td>0.5</td>
<td>0.49</td>
<td>0.48</td>
<td>0.47</td>
<td>0.46</td>
<td>0.45</td>
<td>0.44</td>
<td>0.43</td>
<td>0.42</td>
<td>0.41</td>
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<td>$Q_3$</td>
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<td>$Q_{17}$</td>
<td>$Q_{19}$</td>
<td>$Q_{21}$</td>
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<tr>
<td>0.01</td>
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<td>0.01</td>
<td>0.01</td>
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<td>0.01</td>
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</tr>
</tbody>
</table>

Figure 6. Discharge hematocrit, $H^*$, as function of the plasma skimming coefficient ($\theta_3$) for daughter vessel 3 in the single bifurcation simulation. The plasma skimming coefficient is the ratio of the daughter vessel cross-sectional area ($A_3$) and parent vessel ($A_1$) due to the M parameter being constant at 1. Therefore, the plasma skimming coefficient is changing due to change in area ratio.

Figure 6 shows a similar parabolic distribution of discharge hematocrit as figure 5, except that the plasma skimming coefficient (or cross-sectional area ratio due to M parameter being constant at 1) for daughter vessel 3 is decreasing. As the curve is similar to figure 5, this shows that if one daughter vessel is decreasing in cross-sectional area and the other daughter vessel increasing, at some point they will reach the same ratio to that of the parent vessel and will have about the same discharge hematocrit values. According to figures 5 and 6, both vessels reach the same discharge hematocrit of 1 at 0.5 ratio as expected which means their hematocrits, according the values are not exactly 0.5 is most likely due to the volumetric flow rates not being completely identical for each vessel at the respective cross-sectional areas. While the discharge hematocrit is about the same for both vessels even though one vessel may be larger and the other smaller, this does not mean their respective hematocrits will be the same like they were for a 0.5 ratio. As equation (5) shows, the hematocrit of each vessel is the discharge hematocrit multiplied by the plasma skimming coefficient. This means that if the discharge hematocrit is the same at 0.2 ratio for figure 5 and at 0.8 ratio for figure 6, the hematocrit will be larger for the vessel in figure 6 because 0.8 is a larger plasma skimming coefficient value than in figure 5. This follows what we know in regards to RBC distribution, as RBCs tend to concentrate more in larger vessels.
Figure 7. Hematocrit \( H_2 \) for daughter vessel 2 as a function of the plasma skimming coefficient \( (\theta_2) \) of that vessel. Due to the M parameter being constant at 1, the plasma skimming coefficient values are equivalent to the cross-sectional area of daughter vessel with respect to the parent vessel. Therefore, the plasma skimming coefficient is changing due to area changes.

In figure 7 and 8 the hematocrit values of both daughter vessel 2 and 3 are shown respectively. As expected, the hematocrit increases with increasing plasma skimming coefficient, or in this case cross-sectional area ratio. The results shown in figure 7 and 8 verify that RBCs tend to flow more into larger vessels due to their higher flow rate in the center of the vessel, so much so that the hematocrit may even rise to 0.8 when one daughter vessel is almost the same size of the parent vessel and the other daughter vessel is quite small. This is because plasma “skims” off into the small daughter vessel while the majority of the RBCs concentrate in the larger daughter vessel.

Figure 8. Hematocrit \( H_3 \) for daughter vessel 3 as a function of the plasma skimming coefficient \( (\theta_3) \) of that vessel. Due to the M parameter being constant at 1, the plasma skimming coefficient values are equivalent to the cross-sectional area of daughter vessel with respect to the parent vessel. Therefore, the plasma skimming coefficient is changing due to area changes.

The purpose of figures 9 and 10 is to illustrate that in a single bifurcation it is possible to form a polynomial equation that describes the hematocrit of a daughter vessel as a direct function of the plasma skimming coefficient of that vessel. To do this, the x-coordinate values (plasma skimming coefficient) and y-coordinate values (hematocrit) were input into the polyfit function in MATLAB and this function returned the coefficients for the polynomial equation. Because the graph did not appear to be parabolic in nature, the degree polynomial set in the MATLAB function was 3. When plotted, a 3rd degree polynomial seemed to fit with the data. The equation implied by the coefficients returned by polyfit in figure 9 and 10 are as follows:

\[
Hematocrit_2 = -0.3455\theta_2^3 + 1.2512\theta_2^2 - 0.0404\theta_2 
\]

\[
Hematocrit_3 = -0.6742\theta_3^3 + 0.6412\theta_3^2 + 0.8494\theta_3 - 0.0021
\]

Even though the equations appear quite different, both result in similar 3rd degree polynomial curves. Through these equations the hematocrit of each daughter vessels can now be calculated at a single bifurcation simply by knowing the plasma skimming coefficient. This could be beneficial as it saves time.
in computing discharge hematocrit over and over again and then multiplying that by the plasma skimming coefficient to solve for individual hematocrits of daughter vessels.

Figure 11. Hematocrit ($H_i$) as a function of the decreasing larger daughter vessels ($A_i$) in a ten bifurcation microcirculatory network. Every 0.05 change in cross-sectional area represents a new larger daughter vessel at each bifurcation in the network. The hematocrit at each bifurcation becomes more concentrated in the larger daughter vessels. The $M$ parameter is constant at 1.

Figure 11 shows the results of the ten bifurcation microcirculatory network simulation. The main goal of the simulation was to verify the pathway effect along the route of a network. As stated previously, the pathway effect ensures that the higher concentration of oxygenated RBCs goes through the longest path in the circulation. This allows for all areas of tissue in the body to receive oxygen. Due to plasma skimming, the larger daughter branch at one bifurcation will receive a higher concentration of RBCs than the smaller daughter branch. At subsequent bifurcation, the larger daughter branch should attain a higher hematocrit. Figure 11 verifies this trend. In order to calculate realistic values, an $M$ value of 1 was assumed when coding for the plasma skimming coefficients at each daughter vessel at each bifurcation. According to figure 11, if a network were to go on for infinite bifurcations, eventually the hematocrit would also approach infinity as the graph resembles an exponential. However, in the body, only so many bifurcations occur until reaching the capillaries and returning deoxygenated RBCs back to the heart through the veins. Still, this graph shows how dramatic of an increase the hematocrit can go assuming all branches have the same cross-sectional area for the smaller daughter branches.

4. Discussion

The polynomial model proposed to predict the hematocrit values of each large daughter vessel at each bifurcation in a large network does not match up to the discharge hematocrit model described earlier. While the hematocrit values follow the same trend, the values are highly exaggerated to the point of unrealistic values greater than 1. This could mean that the 3$^{rd}$ order equation template is correct for the model, but the coefficients involved are not correct. This could be due to the fact that the method used to find equations (6) and (7) were done under the assumption that the parent hematocrit was 0.5. When applying the polynomial method to the ten bifurcation network the parent hematocrit had to be adjusted each time to form new equations and it is possible the loop devised to calculate these equations was incorrect.
5. Verification
In this paper the data that needs verification pertains to the increase in hematocrit, or increase in RBC concentration as a vessels diameter, and subsequently, volumetric flow increases. In another study, it was found that with an increasing fractional blood flow, the RBC flux also increases [1]. Similarly, in the models shown in this paper, when volumetric flow increased, due to an increase in the cross-sectional area, the RBC concentration increased. Due to these similarities, the models shown in this paper are at least correct with regards to the overall trend seen in plasma skimming.

6. Conclusion
The need for a model to cover the RBC distribution in bifurcating microvessels is crucial to understanding oxygenation of tissue in important neurological organs such as the mesentery. Following a biphasic distribution of RBCs and blood plasma for smaller vessels is important because the RBC concentration changes at bifurcations, with more hematocrit in the larger daughter vessel than the smaller daughter vessel, ensuring tissue can be oxygenated over a large area [1]. By using a plasma skimming coefficient, this phenomenon can be modeled to see how much discharge hematocrit there is at a bifurcation and this can be used to determine if enough hematocrit is in the daughter vessels not just for one bifurcation, but for many bifurcations throughout a microcirculatory network. While models have already been put in place to show the effects of the change in plasma skimming coefficients, a new model was attempted. However, this new model failed to compare as it had higher than expected values.

References
Intellectual Property
Biological and physiological data and some modeling procedures provided to you from Dr. Linninger’s lab are subject to IRB review procedures and Intellectual property procedures. Therefore, the use of these data and procedures are limited to the coursework only. Publications need to be approved and require joint authorship with staff of Dr. Linninger’s lab.


Appendix

clear all
close all
c1c

% Cross-sectional area of parent vessel measured
A1=5;
%Possible cross-sectional areas of daughter vessels measured
A2=0.2:0.2:4.8;
A3=fliplr(A2);

[x,y]=size(A2);
%M parameter set to 1 for simplicity
M=1;
%Measured hematocrit of parent vessel and measured volumetric flow of
%parent vessel
H1=0.5;
Q1=5;
%Possible measured volumetric flows for daughter vessels
step=1/y;
Q2=2:step:3-step;
Q3=5-Q2;

%Calculations for plasma-skimming coefficients for each daughter vessel
for i=1:y
    theta21(i)=(A2(i)/A1)^(1/M);
end
for i=1:y
    theta31(i)=(A3(i)/A1)^(1/M);
end
thetathree=fliplr(theta31);

t=[1 0.9 0.8 0.7 0.6 0.5 0.4 0.3 0.2 0.1 0];
%discharge hematocrit calculation
Hstar=(Q1*H1)./(Q2.*theta21+Q3.*theta31);
figure(1)
plot(theta21,Hstar)
xlabel('Plasma Skimming Coefficient (Theta2)')
ylabel('Discharge Hematocrit (H*)')

figure(2)
plot(thethree,Hstar)
set(gca,'XTickLabel',t)
xlabel('Plasma Skimming Coefficient (Theta3)')
ylabel('Discharge Hematocrit (H*)')

%Hematocrit calculations for each daughter vessel
H2=theta21.*Hstar;
H3=theta31.*Hstar;

figure(3)
plot(theta21,H2,'o');
hold on
xlabel('Plasma Skimming Coefficient (Theta2)')
ylabel('Hematocrit')
p1=polyfit(theta21,H2,3);
tt=fliplr(t);
y2=polyval(p1,tt);
plot(tt,y2)
hold off
legend('Simulated Data','Fitted Polynomial')

figure(4)
plot(theta31,H3,'o');
hold on
xlabel('Plasma Skimming Coefficient (Theta3)')
ylabel('Hematocrit')
p2=polyfit(theta31,H3,3);
y3=polyval(p2,tt);
plot(tt,y3)
hold off
legend('Simulated Data','Fitted Polynomial')

%%10 bifurcation network
% A=[1 0.95 0.9 0.85 0.8 0.75 0.7 0.65 0.6 0.55 0.5;0 0.05 0.05 0.05 0.05 0.05 0.05 0.05 0.05 0.05 0.05];
A=[1 0.99 0.98 0.97 0.96 0.95 0.94 0.93 0.92 0.91 0.9;0 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01];
Q=[0.5 0.49 0.48 0.47 0.46 0.45 0.44 0.43 0.42 0.41 0.4;0 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01];
H=[0.5 0 0 0 0 0 0 0 0 0 0];
M=1;
theta22=zeros(1,11);
theta22(1)=1;
for i=2:11
    theta2=(A(1,i)/A(1,i-1))^((1/M));
    theta3=(A(2,i)/A(1,i-1))^((1/M));
    H(i)=(Q(1,i-1)*H(i-1))/(Q(1,i)*theta2+Q(2,i)*theta3);
    H22(i)=H(i)*theta2;
\[
\theta_{22}(i) = \theta_2;
\]

\begin{verbatim}
end
H22(1)=H(1);
figure(5)
a=fliplr(A);
plot(a(1,:),H22)
t2=A(1,:);
set(gca,'XTickLabel',t2)
xlabel('Decreasing diameter for large daughter vessels')
ylabel('Hematocrit')

y4=polyval(p1,theta22);
y4(1)=0.5;
figure(6)
plot(a(1,:),y4)
figure(7)
[xx,yy]=size(H);
c1=a(1,:);
for i=2:yy
    \%
    Hstar1=(Q1*H(i))./(Q2.*theta21+Q3.*theta31);
    H222=theta31.*Hstar1;
    pp=polyfit(theta31,H222,3);
    p(i,:)=pp;
    yy5(i)=polyval(pp,theta22(i));
\end
end
c1(:,1)=[ ];
yy5(:,1)=[ ];
t2(:,1)=[ ];
plot(c1,yy5)
set(gca,'XTickLabel',t2)
xlabel('Decreasing diameter for large daughter vessels')
ylabel('Hematocrit')
\end{verbatim}