Mitigation of Sickle Cell Crises
Using Chaos-based Analysis

by

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Abstract

Sickle-cell diseased persons suffer finite pain episodes during their lifetime, which are termed sickle cell crises. Using a sickle cell blood flow model, we mathematically demonstrate that the onset of a sickle cell crisis is chaotic. We further show that sickle cell crises may be mitigated by manipulating certain physiological parameters, namely the partial pressure of oxygen at 50% hemoglobin ($p_{O_2,50\%}^{Hb}$) and the kinetic dissociation rate of hemoglobin ($k^{Hb}$). These physiological parameters control the chaotic nature of sickle cell crises and have the ability to transfer a person from a crisis state to a non-crisis state. We determine that sickle cell crises may only be mitigated within a critical time period ($0 \leq t \leq 2.5\text{hrs}$) after the onset of a sickle cell crisis. Based on our analysis, we classify three stages of a sickle cell crisis as weak chaos, strong chaos, and hyperchaos; which range from light to intense pain. Drugs may be developed, based on our analysis, to target these physiological parameters and mitigate sickle cell crises at its onset.

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### Symbols

- $r, z, \theta$: cylindrical coordinates
- $t$: time
- $v_r$: velocity of blood in radial direction
- $v_z$: velocity of blood in azimuthal direction
- $v_\theta$: velocity of blood in angular direction
- $P$: partial pressure of oxygen
- $S$: saturation of hemoglobin
- $[Mb]$: total concentration of myoglobin
- $[Hb]$: total concentration of hemoglobin
- $D^\text{Mb}$: diffusivity of myoglobin
- $D^\text{Hb}$: diffusivity of oxyhemoglobin
- $D$: oxygen diffusivity
- $P_{O_2,50\%}^\text{Mb}$: oxygen partial pressure at 50% saturation of myoglobin
- $P_{O_2,50\%}^\text{Hb}$: oxygen partial pressure at 50% saturation of oxyhemoglobin
- $k_H^\text{Mb}$: kinetic dissociation rate of oxyhemoglobin
- $\alpha$: oxygen solubility constant
- $M$: rate of oxygen consumption
- $n$: Hill coefficient
- $r_0$: capillary radius
- $\mu$: cytoplasm viscosity
- $\rho$: cytoplasm density
- $r', z', \theta'$: nondimensionalized cylindrical coordinates
- $\tau$: nondimensionalized time
- $v_r'$: nondimensionalized velocity of blood in radial direction
- $v_z'$: nondimensionalized velocity of blood in azimuthal direction
- $v_\theta'$: nondimensionalized velocity of blood in angular direction
- $P'$: nondimensionalized partial pressure of oxygen
- $S'$: nondimensionalized saturation of hemoglobin
- $L$: length of 1 meter
- $T$: time of 1 second
- $P_c$: pressure of 1 Pascal
- $\psi_1, \psi_2, \psi_3$: ODE variables
- $l_1, l_2, l_3$: ODE constants
- $\bar{a}_i, 1 \leq i \leq 9$: coefficients of ODE model
- $\bar{b}_i, 1 \leq i \leq 6$: coefficients of ODE model
- $a_i, 1 \leq i \leq 3$: coefficients of analytical solution for $v_r'$
- $b_i, 1 \leq i \leq 6$: coefficients of analytical solution for $v_z'$
- $c_i, 1 \leq i \leq 23$: coefficients of analytical solution for $P'$
- $d_i, 1 \leq i \leq 23$: coefficients of analytical solution for $S'$
- $k_i, 1 \leq i \leq 2$: coefficients of analytical solution for $v_r', v_z', P', S'$
$A_{ij} \ 1 \leq i,j \leq 4$ functions of the coefficients $a_i \ 1 \leq i \leq 3, \ b_i \ 1 \leq i \leq 6, \ c_i \ 1 \leq i \leq 23, \ d_i \ 1 \leq i \leq 23$

$B_{ij} \ 1 \leq i,j \leq 3$ functions of the coefficients $a_i \ 1 \leq i \leq 3, \ b_i \ 1 \leq i \leq 6, \ c_i \ 1 \leq i \leq 23, \ d_i \ 1 \leq i \leq 23$

$C_{ijk} \ 1 \leq i,j,k \leq 8$ functions of the coefficients $a_i \ 1 \leq i \leq 3, \ b_i \ 1 \leq i \leq 6, \ c_i \ 1 \leq i \leq 23, \ d_i \ 1 \leq i \leq 23$

$D_{ijk} \ 1 \leq i,j,k \leq 8$ functions of the coefficients $a_i \ 1 \leq i \leq 3, \ b_i \ 1 \leq i \leq 6, \ c_i \ 1 \leq i \leq 23, \ d_i \ 1 \leq i \leq 23$

$\sum$ summation

$\prod$ product

$\times$ cross product

$+$ addition by

$-$ subtraction by

$\cdot$ multiplication by

$/$ division by

$=$ equal to

$\approx$ approximately

$\in$ in the domain of

$\mathbb{R}$ set of real numbers

$\mathbb{C}$ set of complex numbers
1 Purpose and Scope of Thesis

1.1.1 Purpose/Scope

The purpose of this investigation is to apply mathematical tools from chaos theory to sickle cell disease, a biological disorder, in order to extract relevant information about this disease; which could potentially be used to create novel pharmaceutical treatments for this disorder. Using mathematical analysis on a sickle cell model, we have classified sickle cell disease as a chaotic disorder, discovered the biological parameters which govern sickle cell crises, found the time period in which crises may be halted, and determined the different stages of chaos in which a sickle cell crisis transitions through.

Background & History of Sickle Cell Disease

Sickle cell disease is a genetic disorder that is caused by abnormal, sickle-shaped red blood cells. These sickle-shaped red blood cells clog vein capillaries, which in effect prevent the proper flow of blood and significantly reduce the transport of oxygen from blood cells to the surrounding plasma and tissue. During a sickle-cell diseased persons lifetime, they endure periodic pain episodes which are termed sickle cell crises. Sickle cell crises are the physical manifestations of sickle cell disease, a genetic disorder, and usually last between three and five days. Sickle cell crises are haphazard in nature, and occur at irregular times during a sickle-cell diseased persons life. Our goal in this investigation is to use and apply techniques of chaos theory on sickle cell crises, an irregular and disorderly phenomena of sickle cell disease, in order to understand and tame its unsystematic nature.

Outline

In this paper, we will do the following: propose a sickle cell blood flow model, a system of partial differential equations; apply biological approximations/reductions in order to simplify this sickle cell model into its most robust form; nondimensionalize the sickle cell blood flow model and its respective parameters; use a Galerkin-based analytical solution in order to transform our sickle cell blood flow model (a system of PDE's) into a sickle cell crisis model (a system of ODE's); analyze the stability of this ODE system by calculating fixed points and eigenvalues, which will subsequently allow us to classify sickle cell crises as a chaotic phenomena; extract the physiological parameters which govern the chaotic nature of our sickle cell crisis model; determine the time period during which sickle cell crises can be treated; identify the different temporal regions of a sickle cell crisis; and finally determine potential drug treatments which could be used for sickle cell crises, based on our analysis.
2 Mathematical Model of Sickle Cell Disease

There have been many models for sickle cell crises which have aptly described the different aspects of the rheology, oxygen sequestration, or blood flow processes which occur during a sickle cell crisis. The Lefloch-Yin model is currently the most accurate model for sickle cell blood flow and serves as the standard model for sickle cell rheology within the microcirculation [3]. We will use the Lefloch-Yin model as our model for sickle cell blood flow in the accompanying analysis. This model captures the fluid dynamics, blood cell deformation, and oxygen transport within the microcirculation. The Lefloch-Yin model is an ab-initio model which has been derived using the first principles method of Newtonian mechanics. This blood flow model is a system of three, nonlinear, and highly-coupled partial differential equations. This PDE model also contains physiological parameters which have been derived experimentally by Vadapalli, Popel, and Goldman [3]. For this model, the region of interest is a capillary which is modeled as a cylinder of finite length and radius.

![Figure 1: Sickle Cell Blood Flow Region](image)

The red blood cells, in the plasma, flow through the capillary. The capillary walls are assumed to be rigid. The walls of the red cells are assumed to be inelastic but flexible. Both the plasma flowing between the cells and the fluid inside the cells are incompressible. Subsequently, in our blood flow model we will have no-slip boundary conditions at the capillary wall.

The Lefloch-Yin model consists of the axisymmetric Navier Stokes Equations which models blood flow and the Oxygen Transport Equations which models the dynamics of oxygen, myoglobin, and hemoglobin within a cylinder of finite radius and length. The Le-floch-Yin model is as follows:
Sickle Cell Blood Flow Model

Navier Stokes Equation

\[
\rho \left( \frac{\partial v_r}{\partial t} + v_r \frac{\partial v_r}{\partial r} + v_z \frac{\partial v_r}{\partial z} \right) = -\frac{dp}{dz} + \mu \left( \frac{1}{r} \frac{\partial}{\partial r} \left( r \frac{\partial v_r}{\partial r} \right) + \frac{\partial^2 v_r}{\partial z^2} - \frac{v_r}{r^2} \right) \tag{2.1}
\]

\[
\rho \left( \frac{\partial v_z}{\partial t} + v_r \frac{\partial v_z}{\partial r} + v_z \frac{\partial v_z}{\partial z} \right) = -\frac{dp}{dr} + \mu \left( \frac{1}{r} \frac{\partial}{\partial r} \left( r \frac{\partial v_z}{\partial r} \right) + \frac{\partial^2 v_z}{\partial z^2} \right) \tag{2.2}
\]

Continuity Equation

\[
\frac{1}{r} \frac{\partial}{\partial r} \left( rv_r \right) + \frac{\partial}{\partial z} v_z = 0 \tag{2.3}
\]

with boundary conditions

\[
v_r(r_0, z, t) = 0, \quad v_z(r_0, z, t) = 0
\]

where

\[
v_r = v_r(r, z, t), \quad v_z = v_z(r, z, t)
\]

Oxygen Transport Equations

\[
\left( \alpha + [Mb] \frac{p_{O_2,50\%}^{Mb}}{p_{O_2,50\%}^{Mb} + P^2} \right) \left( \frac{\partial P}{\partial t} + v_r \frac{\partial P}{\partial r} + v_z \frac{\partial P}{\partial z} \right) = \\
\left( \alpha D + D^{Mb}[Mb] \frac{p_{O_2,50\%}^{Mb}}{p_{O_2,50\%}^{Mb} + P^2} \right) \left( \frac{1}{r} \frac{\partial}{\partial r} \left( r \frac{\partial P}{\partial r} \right) + \frac{\partial^2 P}{\partial z^2} \right) \\
+ k^{Hb}[Hb] \left( S - (1 - S) \left( \frac{P}{p_{O_2,50\%}^{Hb}} \right)^n \right) - M \tag{2.4}
\]

\[
\frac{\partial S}{\partial t} + v_r \frac{\partial S}{\partial r} + v_z \frac{\partial S}{\partial z} = D^{Hb} \left( \frac{1}{r} \frac{\partial}{\partial r} \left( r \frac{\partial S}{\partial r} \right) + \frac{\partial^2 S}{\partial z^2} \right) - k^{Hb} \left( S - (1 - S) \left( \frac{P}{p_{O_2,50\%}^{Hb}} \right)^n \right) \tag{2.5}
\]

where

\[
P = P(r, z, t), \quad S = S(r, z, t)
\]

for

\[
(r, z, t) \in [0, r_0] \times [0, z_0] \times [0, \infty)
\]

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3 Simplifying the Sickle Cell Model

Our sickle cell model contains five, highly-coupled partial differential equations that are quite complex. We can simplify our Sickle Cell Model by combining parts of the Navier Stokes Equations into one equation, using the fact that some of the physiological parameters in our model are zero, and rounding other physiological parameters to whole numbers.

3.1 Modified Navier Stokes Equation

We can combine (2.1) and (2.2) into one equation by triple-differentiating each and subtracting one from the other.

Taking \( \frac{\partial}{\partial z} \frac{\partial}{\partial \theta} \frac{\partial}{\partial z} (2.1) - \frac{\partial}{\partial r} \frac{\partial}{\partial z} \frac{\partial}{\partial r} (2.2) \) yields

\[
\rho \left[ \left( \frac{\partial}{\partial z} \frac{\partial}{\partial r} \frac{\partial v_r}{\partial t} - \frac{\partial}{\partial r} \frac{\partial}{\partial z} \frac{\partial v_z}{\partial t} \right) + \frac{\partial}{\partial z} \frac{\partial}{\partial r} \frac{\partial}{\partial z} \left( v_r \frac{\partial v_r}{\partial r} + v_z \frac{\partial v_z}{\partial z} \right) - \frac{\partial}{\partial r} \frac{\partial}{\partial z} \frac{\partial}{\partial r} \left( v_r \frac{\partial v_r}{\partial r} + v_z \frac{\partial v_z}{\partial z} \right) \right] = \\
\mu \left[ \frac{\partial}{\partial z} \frac{\partial}{\partial \theta} \frac{\partial}{\partial z} \left( \frac{1}{r} \frac{\partial}{\partial r} \left( r \frac{\partial v_r}{\partial r} \right) + \frac{\partial^2 v_r}{\partial z^2} - \frac{v_r}{r^2} \right) - \frac{\partial}{\partial r} \frac{\partial}{\partial \theta} \frac{\partial}{\partial r} \left( \frac{1}{r} \frac{\partial}{\partial r} \left( r \frac{\partial v_z}{\partial r} \right) + \frac{\partial^2 v_z}{\partial z^2} \right) \right]
\]

(3.1)

Dividing both sides by \( \rho \) and factoring out the time operator \( \frac{\partial}{\partial t} \) of the above equation yields

\[
\frac{\partial}{\partial t} \left( \frac{\partial}{\partial z} \frac{\partial}{\partial r} \frac{\partial v_r}{\partial t} - \frac{\partial}{\partial r} \frac{\partial}{\partial z} \frac{\partial v_z}{\partial t} \right) + \frac{\partial}{\partial z} \frac{\partial}{\partial r} \frac{\partial}{\partial z} \left( v_r \frac{\partial v_r}{\partial r} + v_z \frac{\partial v_z}{\partial z} \right) - \frac{\partial}{\partial r} \frac{\partial}{\partial z} \frac{\partial}{\partial r} \left( v_r \frac{\partial v_r}{\partial r} + v_z \frac{\partial v_z}{\partial z} \right) = \\
\frac{\mu}{\rho} \left[ \frac{\partial}{\partial z} \frac{\partial}{\partial \theta} \frac{\partial}{\partial z} \left( \frac{1}{r} \frac{\partial}{\partial r} \left( r \frac{\partial v_r}{\partial r} \right) + \frac{\partial^2 v_r}{\partial z^2} - \frac{v_r}{r^2} \right) - \frac{\partial}{\partial r} \frac{\partial}{\partial \theta} \frac{\partial}{\partial r} \left( \frac{1}{r} \frac{\partial}{\partial r} \left( r \frac{\partial v_z}{\partial r} \right) + \frac{\partial^2 v_z}{\partial z^2} \right) \right]
\]

(3.2)

We can now use (3.2) in place of (2.1) and (2.2) in our Sickle Cell Model. Combining these equations has reduced the number of equations in our model from five to four.

3.2 Modified Oxygen Transport Equations

The Oxygen Transport Equations can be simplified, because some of the physiological parameters are zero. The concentration of myoglobin is zero, and the rate of oxygen consumption is approximately zero within the RBC cytoplasm:

\[
[\text{Mb}] = 0 \quad , \quad M \approx 0
\]

 Applying these simplifications, then Eq. (2.4) becomes
\[(\alpha) \cdot \left( \frac{\partial P}{\partial t} + v_r \frac{\partial P}{\partial r} + v_z \frac{\partial P}{\partial z} \right) = (\alpha D) \cdot \left( \frac{1}{r} \frac{\partial}{\partial r} \left( r \frac{\partial P}{\partial r} \right) + \frac{\partial^2 P}{\partial z^2} \right) + k^{Hb}[Hb] \left( S - (1 - S) \left( \frac{P}{P_{O_2,50\%}} \right)^n \right) \]

Dividing both sides of (3.3) by \( \alpha \) yields

\[
\frac{\partial P}{\partial t} + v_r \frac{\partial P}{\partial r} + v_z \frac{\partial P}{\partial z} = D \cdot \left( \frac{1}{r} \frac{\partial}{\partial r} \left( r \frac{\partial P}{\partial r} \right) + \frac{\partial^2 P}{\partial z^2} \right) + \frac{k^{Hb}[Hb]}{\alpha} \left( S - (1 - S) \left( \frac{P}{P_{O_2,50\%}} \right)^n \right) \]

We will now use (3.4) in place of (2.4) in our Sickle Cell Model.

### 3.3 Hill’s Coefficient Approximation

Hill’s coefficient \( n \) describes the cooperative binding between oxygen and hemoglobin. The exact value of \( n \) is 2.2, but we will assume that \( n \) is 2 in our calculations:

\[ n \approx 2. \]

Assuming \( n = 2 \) yields the following for (3.4) and (2.5):

\[
\frac{\partial P}{\partial t} + v_r \frac{\partial P}{\partial r} + v_z \frac{\partial P}{\partial z} = D \cdot \left( \frac{1}{r} \frac{\partial}{\partial r} \left( r \frac{\partial P}{\partial r} \right) + \frac{\partial^2 P}{\partial z^2} \right) + \frac{k^{Hb}[Hb]}{\alpha} \left( S - (1 - S) \left( \frac{P}{P_{O_2,50\%}} \right)^2 \right) \]

\[
\frac{\partial S}{\partial t} + v_r \frac{\partial S}{\partial r} + v_z \frac{\partial S}{\partial z} = D^{Hb} \left( \frac{1}{r} \frac{\partial}{\partial r} \left( r \frac{\partial S}{\partial r} \right) + \frac{\partial^2 S}{\partial z^2} \right) - k^{Hb} \left( S - (1 - S) \left( \frac{P}{P_{O_2,50\%}} \right)^2 \right) \]

We will now use (3.5) and (3.6) in place of (3.4) and (2.5) in our Sickle Cell Model.
3.4 Simplified Sickle Cell Model

Having used approximations and simplifications in our Sickle Cell Model, we now have a simplified Sickle Cell Model which consists of (3.2), (2.3), (3.5), and (3.6). We also have reduced the number of equations in our model from five to four. The simplified Sickle Cell Model is shown below:

**Sickle Cell Model**

**Navier Stokes Equation**

\[
\frac{\partial}{\partial t} \left( \frac{\partial}{\partial z} \frac{\partial v_r}{\partial r} - \frac{\partial}{\partial r} \frac{\partial v_r}{\partial z} \right) + \frac{\partial}{\partial z} \frac{\partial v_r}{\partial r} \left( v_r \frac{\partial v_r}{\partial r} + v_z \frac{\partial v_r}{\partial z} \right) - \frac{\partial}{\partial r} \frac{\partial v_r}{\partial z} \left( v_r \frac{\partial v_z}{\partial r} + v_z \frac{\partial v_z}{\partial z} \right) = \\
\left[ \frac{\partial}{\partial z} \frac{\partial}{\partial r} \left( \frac{1}{r} \frac{\partial v_r}{\partial r} \right) + \frac{\partial^2 v_r}{\partial z^2} - \frac{v_r}{r^2} \right] - \frac{\partial}{\partial r} \frac{\partial v_z}{\partial z} \left( \frac{1}{r} \frac{\partial v_z}{\partial r} + \frac{\partial^2 v_z}{\partial z^2} \right)
\]

**Continuity Equation**

\[
\frac{1}{r} \frac{\partial}{\partial r} (rv_r) + \frac{\partial}{\partial z} v_z = 0
\]

**Oxygen Transport Equations**

\[
\frac{\partial P}{\partial t} + v_r \frac{\partial P}{\partial r} + v_z \frac{\partial P}{\partial z} = D \left( \frac{1}{r} \frac{\partial}{\partial r} \left( r \frac{\partial P}{\partial r} \right) + \frac{\partial^2 P}{\partial z^2} \right) + \frac{k_H b [Hb]}{\alpha} \left( S - (1 - S) \left( \frac{P}{P_{Hb,50%}} \right)^2 \right)
\]

\[
\frac{\partial S}{\partial t} + v_r \frac{\partial S}{\partial r} + v_z \frac{\partial S}{\partial z} = D_H b \left( \frac{1}{r} \frac{\partial}{\partial r} \left( r \frac{\partial S}{\partial r} \right) + \frac{\partial^2 S}{\partial z^2} \right) - k_H b \left( S - (1 - S) \left( \frac{P}{P_{Hb,50%}} \right)^2 \right)
\]

We will use the simplified Sickle Cell Model above in our ensuing analysis of sickle cell blood flow. Before analyzing this model using mathematical techniques, we must nondimensionalize each term and variable.
4 Nondimensionalization of Sickle Cell Model

In order to nondimensionalize our Sickle Cell Model, we must nondimensionalize our independent variables \( r, z, t \) and dependent variables \( v_r, v_z, P, S \). The variable \( S \) is already a dimensionless variable, so it won't be nondimensionalized below.

Let

\[
r' = \frac{r}{L}, \quad z' = \frac{z}{L}, \quad \tau = \frac{t}{T} \tag{4.1}
\]

\[
v_r' = \frac{v_r}{LT^{-1}}, \quad v_z' = \frac{v_z}{LT^{-1}}, \quad P' = \frac{P}{P_c}, \quad S' = S \tag{4.2}
\]

where

\[
L = 1\text{m}, \quad T = 1\text{s}, \quad P_c = 1\text{Pa}.
\]

We can rearrange (4.1) and (4.2) such that

\[
r = r'L, \quad z = z'L, \quad t = \tau T \tag{4.3}
\]

\[
v_r = v_r'LT^{-1}, \quad v_z = v_z'LT^{-1}, \quad P = P'P_c, \quad S = S' \tag{4.4}
\]

Also from (4.3), we have that

\[
\frac{\partial}{\partial r} = \frac{dr'}{dr} \frac{\partial}{\partial r'} = \frac{1}{L} \frac{\partial}{\partial r'}
\]

\[
\frac{\partial}{\partial z} = \frac{dz'}{dz} \frac{\partial}{\partial z'} = \frac{1}{L} \frac{\partial}{\partial z'}
\]

\[
\frac{\partial}{\partial \tau} = \frac{d\tau}{dt} \frac{\partial}{\partial \tau} = \frac{1}{T} \frac{\partial}{\partial \tau} \tag{4.5}
\]
4.1 Nondimensionalization of Sickle Cell Model

Now we will proceed in nondimensionalizing each equation of our Sickle Cell Model, by using the dimensionless variables and dimensionless differential operators above.

4.1.1 Nondimensionalization of Conservation of Momentum Equation

Substituting (4.3), (4.4), and (4.5) into (3.7) yields

\[
\frac{1}{T^2L^2} \frac{\partial}{\partial \tau} \left( \frac{\partial}{\partial z} \frac{\partial \nu'_r}{\partial r} \frac{\partial \nu'_z}{\partial z} - \frac{\partial}{\partial r'} \frac{\partial \nu'_r}{\partial r'} \frac{\partial \nu'_z}{\partial z'} \right) + \frac{1}{T^2L^2} \frac{\partial}{\partial \tau} \frac{\partial}{\partial r'} \left( \nu'_r \frac{\partial \nu'_r}{\partial r'} + \nu'_z \frac{\partial \nu'_z}{\partial z'} \right)
\]

\[
- \frac{1}{T^2L^2} \frac{\partial}{\partial r'} \frac{\partial}{\partial z'} \left( \nu'_r \frac{\partial \nu'_r}{\partial r'} + \nu'_z \frac{\partial \nu'_z}{\partial z'} \right)
\]

\[
= \frac{\mu}{\rho TL^4} \left[ \frac{\partial}{\partial z} \frac{\partial}{\partial r'} \frac{\partial \nu'_r}{\partial r'} \frac{\partial \nu'_z}{\partial z} \left( \frac{1}{r'} \frac{\partial}{\partial r'} \left( r' \frac{\partial \nu'_r}{\partial r'} \right) + \frac{\partial^2 \nu'_r}{\partial z'^2} - \frac{\nu'_r}{r'^2} \right) \right.
\]

\[
- \frac{\partial}{\partial r'} \frac{\partial}{\partial z'} \left( r' \frac{\partial \nu'_r}{\partial r'} \frac{\partial \nu'_z}{\partial z'} \right)
\]

Multiplying both sides of (4.6) by $T^2L^2$ yields

\[
\frac{\partial}{\partial \tau} \left( \frac{\partial}{\partial z} \frac{\partial \nu'_r}{\partial r} \frac{\partial \nu'_z}{\partial z} - \frac{\partial}{\partial r'} \frac{\partial \nu'_r}{\partial r'} \frac{\partial \nu'_z}{\partial z'} \right) + \frac{\partial}{\partial \tau} \frac{\partial}{\partial r'} \left( \nu'_r \frac{\partial \nu'_r}{\partial r'} + \nu'_z \frac{\partial \nu'_z}{\partial z'} \right) - \frac{\partial}{\partial r'} \frac{\partial}{\partial z'} \left( \nu'_r \frac{\partial \nu'_r}{\partial r'} + \nu'_z \frac{\partial \nu'_z}{\partial z'} \right)
\]

\[
= \frac{\mu T}{\rho L^2} \left[ \frac{\partial}{\partial z} \frac{\partial}{\partial r'} \frac{\partial \nu'_r}{\partial r'} \frac{\partial \nu'_z}{\partial z} \left( \frac{1}{r'} \frac{\partial}{\partial r'} \left( r' \frac{\partial \nu'_r}{\partial r'} \right) + \frac{\partial^2 \nu'_r}{\partial z'^2} - \frac{\nu'_r}{r'^2} \right) \right.
\]

\[
- \frac{\partial}{\partial r'} \frac{\partial}{\partial z'} \left( r' \frac{\partial \nu'_r}{\partial r'} \frac{\partial \nu'_z}{\partial z'} \right)
\]

The constant $\frac{\mu T}{\rho L^2}$ is dimensionless and hence (4.7) is the nondimensionalized version of (3.7).

4.1.2 Nondimensionalization of Continuity Equation

Substituting (4.3), (4.4), and (4.5) into (3.8) yields

\[
\frac{1}{T} \frac{1}{r'} \frac{\partial}{\partial r'} \left( r' \frac{\partial \nu'_r}{\partial r'} \right) + \frac{1}{T} \frac{\partial}{\partial z'} \nu'_z = 0
\]

(4.8)

Multiplying both sides of (4.8) by $T$ yields

\[
\frac{1}{r'} \frac{\partial}{\partial r'} \left( r' \frac{\partial \nu'_r}{\partial r'} \right) + \frac{\partial}{\partial z'} \nu'_z = 0
\]

(4.9)

Hence (4.9) is the nondimensionalized version of (3.8).
4.1.3 Nondimensionalization of Oxygen Transport Equation

Substituting (4.3), (4.4), and (4.5) into (3.8)

\[
\frac{P_c}{T} \frac{\partial P'}{\partial r'} + \frac{P_c}{T} \left( v_r' \frac{\partial P'}{\partial r'} + v_z' \frac{\partial P'}{\partial z'} \right) = \frac{DP_c}{L^2} \left( \frac{1}{r'} \frac{\partial}{\partial r'} \left( r' \frac{\partial P'}{\partial r'} \right) + \frac{\partial^2 P'}{\partial z'^2} \right) + \frac{k_{Hb}[Hb]}{\alpha} \left( S' - (1 - S') \left( \frac{P_c P'}{P_{O_{2,50\%}}} \right)^2 \right)
\]

(4.10)

Now multiplying both sides by \( \frac{T}{P_c} \)

\[
\frac{\partial P'}{\partial r'} + v_r' \frac{\partial P'}{\partial r'} + v_z' \frac{\partial P'}{\partial z'} = \frac{DT}{L^2} \left( \frac{1}{r'} \frac{\partial}{\partial r'} \left( r' \frac{\partial P'}{\partial r'} \right) + \frac{\partial^2 P'}{\partial z'^2} \right) + \frac{k_{Hb}[Hb]}{\alpha P_c} T \left( S' - (1 - S') \left( \frac{P_c P'}{P_{O_{2,50\%}}} \right)^2 \right)
\]

(4.11)

The constants \( \frac{DT}{L^2} \) and \( \frac{k_{Hb}[Hb]T}{\alpha P_c} \) are dimensionless. Hence (4.11) is the nondimensionalized version of (3.9).

4.1.4 Nondimensionalization of Hemoglobin Equation

Substituting (4.3), (4.4), and (4.5) into (3.10) yields

\[
\frac{1}{T} \frac{\partial S'}{\partial r'} + \frac{1}{T} \left( v_r' \frac{\partial S'}{\partial r'} + v_z' \frac{\partial S'}{\partial z'} \right) = \frac{D_{Hb}}{L^2} \left( \frac{1}{r'} \frac{\partial}{\partial r'} \left( r' \frac{\partial S'}{\partial r'} \right) + \frac{\partial^2 S'}{\partial z'^2} \right) - k_{Hb} \left( S' - (1 - S') \left( \frac{P_c P'}{P_{Hb_{O_{2,50\%}}}^{25\%}} \right)^2 \right)
\]

(4.12)

Multiplying both sides of (4.12) by \( T \) yields

\[
\frac{\partial S'}{\partial r'} + v_r' \frac{\partial S'}{\partial r'} + v_z' \frac{\partial S'}{\partial z'} = \frac{D_{Hb} T}{L^2} \left( \frac{1}{r'} \frac{\partial}{\partial r'} \left( r' \frac{\partial S'}{\partial r'} \right) + \frac{\partial^2 S'}{\partial z'^2} \right) - k_{Hb} T \left( S' - (1 - S') \left( \frac{P_c P'}{P_{Hb_{O_{2,50\%}}}^{25\%}} \right)^2 \right)
\]

(4.13)

The constants \( \frac{D_{Hb} T}{L^2} \) and \( k_{Hb} T \) are dimensionless. Hence (4.13) is the nondimensionalized version of (3.10).
4.2 Nondimensionalized Sickle Cell Model

Our nondimensionalized Sickle Cell Model consists of (4.7), (4.9), (4.11) and (4.13) which are shown below:

**Sickle Cell Model**

**Navier Stokes Equation**

\[
\frac{\partial}{\partial t} \left( \frac{\partial \frac{\partial v_r'}{\partial z'} - \frac{\partial \frac{\partial v_z'}{\partial r'}}{\partial r'} \right) + \frac{\partial}{\partial r'} \left( \frac{\partial v_r'}{\partial r'} + v_z' \frac{\partial v_z'}{\partial z'} \right) - \frac{\partial}{\partial z'} \frac{\partial v_z'}{\partial z'} + v_z' \frac{\partial v_z'}{\partial z'} = \frac{\mu T}{\rho L^2} \left[ \frac{\partial}{\partial r'} \left( \frac{1}{r'} \frac{\partial \frac{\partial v_r'}{\partial r'}}{\partial r'} \right) + \frac{\partial^2 v_r'}{\partial z'^2} - \frac{v_z'}{r'^2} \right] - \frac{\partial}{\partial r'} \frac{\partial v_z'}{\partial z'} \frac{1}{r'} \frac{\partial \frac{\partial v_z'}{\partial r'}}{\partial r'} + \frac{\partial^2 v_z'}{\partial z'^2} \right]
\]

(4.14)

**Continuity Equation**

\[
\frac{1}{r'} \frac{\partial}{\partial r'} (r' v_r') + \frac{\partial}{\partial z'} v_z' = 0
\]

(4.15)

**Oxygen Transport Equations**

\[
\frac{\partial P'}{\partial t} + v_r' \frac{\partial P'}{\partial r'} + v_z' \frac{\partial P'}{\partial z'} = \frac{DT}{L^2} \left( \frac{1}{r'} \frac{\partial \frac{\partial P'}{\partial r'}}{\partial r'} + \frac{\partial^2 P'}{\partial z'^2} \right) + \frac{k_{Hb}[Hb]T}{\alpha P_c} \left( S' - (1 - S') \left( \frac{P_c P'}{P_{O_2,50%}} \right)^2 \right)
\]

(4.16)

\[
\frac{\partial S'}{\partial t} + v_r' \frac{\partial S'}{\partial r'} + v_z' \frac{\partial S'}{\partial z'} = \frac{D_{Hb}T}{L^2} \left( \frac{1}{r'} \frac{\partial \frac{\partial S'}{\partial r'}}{\partial r'} + \frac{\partial^2 S'}{\partial z'^2} \right) - k_{Hb}T \left( S' - (1 - S') \left( \frac{P_c P'}{P_{O_2,50%}} \right)^2 \right)
\]

(4.17)

Having nondimensionalized our Sickle Cell Model, we will now proceed to transform this model. We will now transform our Sickle Cell Model, a PDE system, into an ODE system. In doing so, it further reduces the complexity of our sickle cell model and allows for a wider-depth of analysis.
5 Tranformation of Sickle Cell Model into ODE system

Our goal is to transform our sickle cell blood flow model, a PDE system, into an ODE system. By transforming our sickle cell model into an ODE system, this allows us to use techniques from chaos theory to determine its stability. Any result which is proved about the ODE system also holds true for the PDE system in which it was derived from. In order to transform our PDE model into an ODE model, we will need to solve for the spatial component of our PDE model which will yield us a time-based ODE model and a system of algebraic equations, which are functions of our physiological parameters. In the ensuing analysis, we will use an analytical solution that is spatially-explicit and temporally-undefined as a solution for our Sickle Cell Model. We will substitute suchsaid analytical solution into each equation of our Sickle Cell Model, drop any negligible terms which are very close to zero, and derive each resulting ODE and algebraic equation relation. Finally, we will group together each ODE equation to form an ODE system and also group together each algebraic equation to form an system of algebraic equations.

5.1 Analytical Solution

According to the Galerkin method, we can assume an arbitrary functional form for the solution \((v', v'_z, P', S')\) of our PDE system, as long as the solution is physical. The Galerkin solution that we assume is a truncated version of the complete solution. Our Galerkin solution is temporally implicit with undefined \(\psi_i(t) \quad 1 \leq i \leq 3\) functions and spatially explicit with polynomial and exponential functions. The constants in our model

\[
k_q \quad 1 \leq q \leq 2; \quad a_i \quad 0 \leq i \leq 3, \quad b_j \quad 0 \leq j \leq 6, \quad c_k \quad 0 \leq k \leq 23, \quad d_l \quad 0 \leq l \leq 23
\]

are undefined. These constants will be determined later in our analysis. The Galerkin solution for our PDE system is shown below.

**Analytical Solution**

\[
v'_r = \psi_1(\tau)e^{k_1r'+k_2z'}r'^3 \left( r' - \frac{r_0}{L} \right)^2 \prod_{i=1}^{3} \left( r' - a_i \right)^2
\]

\[
v'_z = \psi_1(\tau)e^{k_1r'+k_2z'}r'^2 \left( r' - \frac{r_0}{L} \right)^2 \prod_{i=1}^{3} \left( r' - b_i \right)^2 + \psi_1(\tau) \left( r' - \frac{r_0}{L} \right)^2 \prod_{i=4}^{6} \left( r' - b_i \right)^2
\]

\[P' = \psi_2(\tau)e^{k_1r'+k_2z'}r'^3 \prod_{i=1}^{10} (r' - c_i)^2 + \psi_2(\tau)r'^3 \prod_{i=11}^{20} (r' - c_i)^2 + c_{21} \psi_2(\tau) + c_{22}r'^3 + c_{23} + \left( \frac{r_0^3}{L^3} \right) z'
\]

17
\[ S' = \psi_3(\tau) e^{k_1 r' + k_2 z'} \prod_{i=1}^{10} (r' - d_i)^2 + \psi_3(\tau) r'^3 \prod_{i=11}^{20} (r' - d_i)^2 + d_{21}^2 \psi_3(\tau) + d_{22} r'^3 + d_{23}^2 + \left( \frac{r_0^3}{L^3} \right) z' \]  

(5.5)

5.2 Negligible Terms

Certain terms in our model are negligible or very close to zero. In our analysis, any term of order \( r'^4 \) or higher will be assumed negligible. We can assume this because

\[ 0 \leq r' \leq 10^{-5} \]

and

\[ 0 \leq r'^4 \leq 10^{-20} \approx 0. \]

Also, I will assume that any term proportional to \( \frac{r^3 z'}{L^3} \) will be negligible. I will assume this because

\[ 0 \leq z' \leq 0.8 \]

so then

\[ 0 \leq \frac{r_0^3 z'}{L^3} \leq \frac{0.8 \cdot 10^{-15}}{1^3} = 8 \cdot 10^{-16} \approx 0. \]

Accordingly, any term smaller than \( 10^{-15} \), of order \( r'^4 \) or higher, or proportional to \( \frac{r^3 z'}{L^3} \) will be assumed negligible in the following transformation.

5.3 Transformation of Conservation of Momentum Equation

We will now proceed in transforming the Conservation of Momentum Equation of our Sickle Cell Model into an ODE equation by substituting in our Analytical Solution.

Substituting (5.2) and (5.3) into (4.14) yields

\[ \psi_1 e^{k_1 r + k_2 z} \left( A_{11} r + A_{12} r^2 + A_{13} r^3 \right) + \psi_1^2 e^{k_1 r + k_2 z} \left( A_{21} r + A_{22} r^2 + A_{23} r^3 \right) + \psi_1^2 e^{2k_1 r + 2k_2 z} \left( A_{32} r^2 + A_{33} r^3 \right) = \frac{\mu T}{\rho L^2} \left[ \psi_1 e^{k_1 r + k_2 z} \left( A_{41} r + A_{42} r^2 + A_{43} r^3 \right) \right] \]  

(5.6)

where each \( A_{ij} \) is a function of the undefined constants (5.1) in our analytical solution. According to the Galerkin method, we can assume arbitrary relations between the \( A_{ij} \)’s of
our PDE system. Lets set

\[ A_{1i} = A_{2i} , \ A_{1i} = A_{4i} , \ A_{3i} = 0 \text{ for } 1 \leq i \leq 3 \]  \hspace{1cm} (5.7)

so that (5.6) becomes

\[ \dot{\psi}_1 e^{k_1 r + k_2 z} \left( A_{11} r + A_{12} r^2 + A_{13} r^3 \right) \\
+ \dot{\psi}_1^2 e^{k_1 r + k_2 z} \left( A_{11} r + A_{12} r^2 + A_{13} r^3 \right) + \psi_1^2 e^{2k_1 r + 2k_2 z} \left( 0 \cdot r^2 + 0 \cdot r^3 \right) \\
= \frac{\mu T}{\rho L^2} \left[ \psi_1 e^{k_1 r + k_2 z} \left( A_{11} r + A_{12} r^2 + A_{13} r^3 \right) \right] \]  \hspace{1cm} (5.8)

(5.8) can be factored as

\[ \left( \dot{\psi}_1 + \dot{\psi}_1^2 - \left( \frac{\mu T}{\rho L^2} \right) \psi_1 \right) e^{k_1 r + k_2 z} \left( A_{11} r + A_{12} r^2 + A_{13} r^3 \right) = 0. \]  \hspace{1cm} (5.9)

This subsequently implies that

\[ \dot{\psi}_1 + \dot{\psi}_1^2 - \left( \frac{\mu T}{\rho L^2} \right) \psi_1 = 0. \]  \hspace{1cm} (5.10)

(5.10) can then be rewritten as

\[ \dot{\psi}_1 = \left( \frac{\mu T}{\rho L^2} \right) \psi_1 - \dot{\psi}_1^2 \]  \hspace{1cm} (5.11)

This equation will be used as one equation our ODE system.

### 5.4 Transformation of Continuity Equation

We will now proceed in transforming the Conservation of Mass Equation of our Sickle Cell Model into an ODE equation by substituting in our Analytical Solution.

Substituting (5.2) and (5.3) into (4.15) yields

\[ \psi_1 e^{k_1 r + k_2 z} (B_{12} r^2 + B_{13} r^3) = 0 \]  \hspace{1cm} (5.12)

where \( B_{1i} \) \( 2 \leq i \leq 3 \) is a function of the undefined constants (5.1) in our analytical solution.

If

\[ \psi_1 e^{k_1 r + k_2 z} (B_{12} r^2 + B_{13} r^3) = 0 \]

this implies that

\[ B_{12} = 0 \text{ and } B_{13} = 0 \]  \hspace{1cm} (5.13)
because \( \psi_1 = 0 \) only admits trivial solutions to \( v_r \) and \( v_z \).

### 5.5 Transformation of Partial Pressure of Oxygen Equation

We will now transform the Partial Pressure of Oxygen Equation of our Sickle Cell Model into an ODE equation by substituting in our Analytical Solution.

Substituting (5.2), (5.3), (5.4) and (5.5) into (4.16) yields

\[
\psi_2 \cdot \left( e^{k_1 r + k_2 z} (C_{113} r^3) + C_{103} r^3 + C_{100} \right) \\
+ \left[ \psi_1 \psi_2 e^{k_1 r + k_2 z} (C_{213} r^3) \right] + \psi_1 \left( e^{k_1 r + k_2 z} (C_{313} r^3 + C_{312} r^2) + C_{303} r^3 + C_{302} r^2 + C_{301} r + C_{300} \right) \\
= \psi_2 \left( e^{k_1 r + k_2 z} (C_{411} r + C_{412} r^2 + C_{413} r^3) + (C_{403} r^3 + C_{402} r^2 + C_{401} r + C_{400}) \right) \\
+ \psi_2 \cdot \left( e^{k_1 r + k_2 z} (C_{513} r^3) + C_{503} r^3 + C_{500} \right) + \psi_3 \cdot \left( e^{k_1 r + k_2 z} (C_{613} r^3) + C_{603} r^3 + C_{600} \right) \\
+ \psi_2 \psi_3 \cdot \left( e^{k_1 r + k_2 z} (C_{713} r^3) + C_{703} r^3 + C_{700} \right) + \psi_2^2 \psi_3 \cdot \left( e^{k_1 r + k_2 z} (C_{813} r^3) + C_{803} r^3 + C_{800} \right) \\
+ C_{003} r^3 + C_{000} \tag{5.14}
\]

where \( C_{i,j,k} \) is a function of the undefined constants (5.1). According to the Galerkin method, we can assume arbitrary relations between the \( C_{i,j,k} \)'s of our PDE system. Now if we let

\[
C_{i,j,k} = \begin{cases} 
\tilde{a}_{i-3} \cdot C_{1,j,k} & \text{for } i = 3, 0 \leq j \leq 1, k = \{0, 3\} \\
-\tilde{a}_{i-3} \cdot C_{1,j,k} & \text{for } 4 \leq i \leq 5, 0 \leq j \leq 1, k = \{0, 3\} \\
\tilde{a}_{i-3} \cdot C_{1,j,k} & \text{for } 6 \leq i \leq 7, 0 \leq j \leq 1, k = \{0, 3\} \\
\tilde{a}_{i-3}^{1} \cdot C_{1,j,k} & \text{for } i = 8, 0 \leq j \leq 1, k = \{0, 3\} 
\end{cases} \tag{5.15}
\]

and also let

\[
C_{213} = 0, \ C_{312} = 0, \ C_{302} = 0, \ C_{301} = 0, \ C_{412} = 0 \\
C_{411} = 0, \ C_{402} = 0, \ C_{401} = 0, \ C_{003} = 0, \ C_{000} = 0. 
\]

Our above equation then becomes

\[
\psi_2 \cdot \left( e^{k_1 r + k_2 z} (C_{113} r^3) + C_{103} r^3 + C_{100} \right) \\
+ \left[ \psi_1 \psi_2 e^{k_1 r + k_2 z} (0 \cdot r^3) \right] + \psi_1 \left( e^{k_1 r + k_2 z} (\tilde{a}_0 C_{113} r^3 + 0 \cdot r^2 + 0 \cdot r + \tilde{a}_0 C_{100}) \right) \\
= \psi_2 \left( e^{k_1 r + k_2 z} (0 \cdot r + 0 \cdot r^2 - \tilde{a}_1 C_{113} r^3) + (-\tilde{a}_1 C_{103} r^3 + 0 \cdot r^2 + 0 \cdot r - \tilde{a}_1 C_{100}) \right) \\
+ \psi_2 \cdot \left( e^{k_1 r + k_2 z} (\tilde{a}_2 C_{113} r^3) - \tilde{a}_2 C_{103} r^3 - \tilde{a}_2 C_{100} \right) + \psi_3 \cdot \left( e^{k_1 r + k_2 z} (\tilde{a}_3 C_{113} r^3) + \tilde{a}_3 C_{103} r^3 + \tilde{a}_3 C_{100} \right) \\
+ \psi_2 \psi_3 \cdot \left( e^{k_1 r + k_2 z} (\tilde{a}_4 C_{113} r^3) + \tilde{a}_4 C_{103} r^3 + \tilde{a}_4 C_{100} \right) + \psi_2^2 \psi_3 \cdot \left( e^{k_1 r + k_2 z} (\tilde{a}_5 C_{113} r^3) + \tilde{a}_5 C_{103} r^3 + \tilde{a}_5 C_{100} \right) \\
+ 0 \cdot r^3 + 0 \tag{5.16}
\]
and after simplification becomes

\[ \dot{\psi}_2 \cdot (e^{k_1r+k_2z}(C_{113r^3}) + C_{103r^3} + C_{100}) + \tilde{a}_0 \psi_1 (e^{k_1r+k_2z}(C_{113r^3}) + C_{103r^3} + C_{100}) \\
= -\tilde{a}_1 \psi_2 (e^{k_1r+k_2z}(C_{113r^3}) + C_{103r^3} + C_{100}) - \tilde{a}_2 \psi_2^2 \cdot (e^{k_1r+k_2z}(C_{113r^3}) + C_{103r^3} + C_{100}) \\
+ \tilde{a}_3 \psi_3 \cdot (e^{k_1r+k_2z}(C_{113r^3}) + C_{103r^3} + C_{100}) + \tilde{a}_4 \psi_2 \psi_3 \cdot (e^{k_1r+k_2z}(C_{113r^3}) + C_{103r^3} + C_{100}) \\
+ \tilde{a}_5 l_1 \psi_2^2 \psi_3 \cdot (e^{k_1r+k_2z}(C_{113r^3}) + C_{103r^3} + C_{100}) \quad (5.17) \]

Now factoring the above equation, we obtain

\[ \left( \dot{\psi}_2 + \tilde{a}_0 \psi_1 + \tilde{a}_1 \psi_2 + \tilde{a}_2 \psi_2^2 \\
- \psi_3 \left( \tilde{a}_3 + \tilde{a}_4 \psi_2 + \tilde{a}_5 l_1 \psi_2^2 \right) \right) (e^{k_1r+k_2z}(C_{113r^3}) + C_{103r^3} + C_{100}) = 0 \quad (5.18) \]

which implies that

\[ \dot{\psi}_2 + \tilde{a}_0 \psi_1 + \tilde{a}_1 \psi_2 + \tilde{a}_2 \psi_2^2 - \psi_3 (\tilde{a}_3 + \tilde{a}_4 \psi_2 + \tilde{a}_5 l_1 \psi_2^2) = 0 \]

The above equation can be rewritten as

\[ \dot{\psi}_2 = -\tilde{a}_0 \psi_1 - (\tilde{a}_1 \psi_2 + \tilde{a}_2 \psi_2^2) + \psi_3 (\tilde{a}_3 + \tilde{a}_4 \psi_2 + \tilde{a}_5 l_1 \psi_2^2) \quad (5.19) \]

This equation will be used as one ODE equation within our ODE system.

### 5.6 Transformation of Hemoglobin Equation

We will now transform the Hemoglobin Equation of our Sickle Cell Model into an ODE equation by substituting in our Analytical Solution.

Substituting (5.2), (5.3), (5.4), and (5.5) into (4.17) yields

\[ \dot{\psi}_3 \cdot (e^{k_1r+k_2z}(D_{113r^3}) + D_{103r^3} + D_{100}) \\
+ [\psi_1 \psi_3 e^{k_1r+k_2z}(D_{213r^3})] + \psi_1 \cdot (e^{k_1r+k_2z}(D_{313r^3} + D_{312r^2}) + D_{303r^3} + D_{302r^2} + D_{301r} + D_{300}) \\
= \psi_2 \left( e^{k_1r+k_2z}(D_{411r} + D_{412r^2} + D_{413r^3}) + (D_{403r^3} + D_{402r^2} + D_{401r} + D_{400}) \right) \\
+ \psi_2^2 \cdot (e^{k_1r+k_2z}(D_{513r^3} + D_{503r^3} + D_{500}) + \psi_3 \cdot (e^{k_1r+k_2z}(D_{613r^3} + D_{603r^3} + D_{600})) \\
+ \psi_2 \psi_3 \cdot (e^{k_1r+k_2z}(D_{713r^3} + D_{703r^3} + D_{700}) + \psi_2^2 \psi_3 \cdot (e^{k_1r+k_2z}(D_{813r^3} + D_{803r^3} + D_{800}) \\
+ D_{800} \right) \quad (5.20) \]

where \( D_{ijk} \) \( 0 \leq i, j, k \leq 3 \) is a function of the undefined constants (5.1). According to the Galerkin method, we can assume relations between the \( D_{ijk} \)'s of our PDE system. Now
if we let
\[ D_{ijk} = \begin{cases} 
\bar{b}_{i-3} D_{1jk} & \text{for } 3 \leq i \leq 5, 0 \leq j \leq 1, k = \{0, 3\} \\
-\bar{b}_{i-3} D_{1jk} & \text{for } 6 \leq i \leq 7, 0 \leq j \leq 1, k = \{0, 3\} \\
-\bar{b}_{i-3} l_2 D_{1jk} & \text{for } i = 8, 0 \leq j \leq 1, k = \{0, 3\} 
\end{cases} \]  
(5.21)

and
\[ D_{213} = 0, \ D_{312} = 0, \ D_{302} = 0, \ D_{301} = 0, \ D_{412} = 0 \]  
(5.22)
\[ D_{411} = 0, \ D_{402} = 0, \ D_{401} = 0, \ D_{003} = 0, \ D_{000} = 0. \]  
(5.23)

Our above equation then becomes
\[
\psi_3 \cdot (e^{k_1 r + k_2 z} (D_{113} r^3) + D_{103} r^3 + D_{100}) \\
+ \left[ \psi_1 \psi_3 e^{k_1 r + k_2 z} (0 \cdot r^3) + \psi_1 \cdot (e^{k_1 r + k_2 z} (\bar{b}_0 D_{113} r^3 + 0 \cdot r^2) + \bar{b}_0 D_{103} r^3 + 0 \cdot r^2 + 0 \cdot r + \bar{b}_0 D_{100}) \right] \\
= \psi_2 \left( e^{k_1 r + k_2 z} (0 \cdot r + 0 \cdot r^2 + \bar{b}_1 D_{113} r^3) + (\bar{b}_1 D_{103} r^3 + 0 \cdot r^2 + 0 \cdot r + \bar{b}_1 D_{100}) \right) \\
+ \psi_2 \cdot (e^{k_1 r + k_2 z} (\bar{b}_2 D_{113} r^3) + \bar{b}_2 D_{103} r^3 + \bar{b}_2 D_{100}) + \psi_3 \cdot \left( -e^{k_1 r + k_2 z} (\bar{b}_3 D_{113} r^3) - \bar{b}_3 D_{103} r^3 - \bar{b}_3 D_{100} \right) \\
+ \psi_2 \left( -e^{k_1 r + k_2 z} (\bar{b}_4 D_{113} r^3) - \bar{b}_4 D_{103} r^3 - \bar{b}_4 D_{100} \right) + \psi_2 \psi_3 \cdot \left( -e^{k_1 r + k_2 z} (\bar{b}_5 l_2 D_{113} r^3) - \bar{b}_5 l_2 D_{103} r^3 - \bar{b}_5 l_2 D_{100} \right) \\
+ 0 \cdot r^3 + 0
\]  
(5.24)

and when simplified yields
\[
\psi_3 \cdot (e^{k_1 r + k_2 z} (D_{113} r^3) + D_{103} r^3 + D_{100}) + \bar{b}_0 \psi_1 \cdot (e^{k_1 r + k_2 z} (D_{113} r^3) + D_{103} r^3 + D_{100}) \\
= \bar{b}_1 \psi_2 \left( e^{k_1 r + k_2 z} (D_{113} r^3) + D_{103} r^3 + D_{100} \right) + \bar{b}_2 \psi_2 \cdot \left( e^{k_1 r + k_2 z} (D_{113} r^3) + D_{103} r^3 + D_{100} \right) \\
- \bar{b}_3 \psi_3 \cdot \left( e^{k_1 r + k_2 z} (D_{113} r^3) + D_{103} r^3 + D_{100} \right) - \bar{b}_4 \psi_2 \psi_3 \cdot \left( e^{k_1 r + k_2 z} (D_{113} r^3) + D_{103} r^3 + D_{100} \right) \\
- \bar{b}_5 l_2 \psi_2 \psi_3 \cdot \left( e^{k_1 r + k_2 z} (D_{113} r^3) + D_{103} r^3 + D_{100} \right)
\]  
(5.25)

Now factoring yields
\[(\psi_3 + \bar{b}_0 \psi_1 - \bar{b}_1 \psi_2 - \bar{b}_2 \psi_2^2 + \psi_3 (\bar{b}_3 + \bar{b}_4 \psi_2 + \bar{b}_5 l_2 \cdot \psi_2^2)) (e^{k_1 r + k_2 z} (D_{113} r^3) + D_{103} r^3 + D_{100}) = 0\]

which implies that
\[\psi_3 + \bar{b}_0 \psi_1 - \bar{b}_1 \psi_2 - \bar{b}_2 \psi_2^2 + \psi_3 (\bar{b}_3 + \bar{b}_4 \psi_2 + \bar{b}_5 l_2 \cdot \psi_2^2) = 0\]

and which can be rewritten as
\[\psi_3 = -\bar{b}_0 \psi_1 + \bar{b}_1 \psi_2 + \bar{b}_2 \psi_2^2 - \psi_3 (\bar{b}_3 + \bar{b}_4 \psi_2 + \bar{b}_5 l_2 \cdot \psi_2^2)\]  
(5.26)

The above equation will be used as an ODE equation in our ODE system.
5.7 ODE System & Algebraic Equation System

Having substituted Analytical Solutions to our Sickle Cell Model, we then obtained three time-based ordinary differential equations (5.11), (5.19), (5.26) and multiple Galerkin-based algebraic equations of the undefined constants (5.7), (5.13), (5.15), (5.21), (5.22). We can group these ODE equations together to form an ODE system and also group the Galerkin-based algebraic equations together to form an system of algebraic equations. This system of ordinary differential equations and system of algebraic equations is shown below:

**ODE System**

\[
\frac{d\psi_1}{d\tau} = l_1\psi_1 - \psi_1^2 \\
\frac{d\psi_2}{d\tau} = -\tilde{a}_0\psi_1 - (\tilde{a}_1\psi_2 + \tilde{a}_2\psi_2^2) + \psi_3(\tilde{a}_3 + \tilde{a}_4\psi_2 + \tilde{a}_5l_2\psi_2^2) \\
\frac{d\psi_3}{d\tau} = -\tilde{b}_0\psi_1 + \tilde{b}_1\psi_2 + \tilde{b}_2\psi_2^2 - \psi_3(\tilde{b}_3 + \tilde{b}_4\psi_2 + \tilde{b}_5l_3\psi_2^2)
\]

where

\[
\tilde{a}_i, 0 \leq i \leq 5 \in \mathbb{R}, \quad \tilde{b}_j, 0 \leq j \leq 5 \in \mathbb{R}, \quad l_1 = \frac{\mu T}{\rho L^2}, \quad l_2 = \frac{k^{Hb}[Hb]}{\alpha \cdot P^{Hb}_{O_2,50\%}} \frac{P_cT}{P^{Hb}_{O_2,50\%}}
\]

**Algebraic Equation System**

\[
A_{1i} = A_{2i}, \quad A_{1i} = A_{4i}, \quad A_{3i} = 0 \quad \text{for} \quad 1 \leq i \leq 3
\]

\[
B_{11} = 0, \quad B_{13} = 0
\]

\[
C_{ijk} = \begin{cases} 
\tilde{a}_{i-3} \cdot C_{1jk} & \text{for} \quad 3 \leq i \leq 7, 0 \leq j \leq 1, k = \{0, 3\} \\
-\tilde{a}_{i-3} \cdot C_{1jk} & \text{for} \quad 4 \leq i \leq 5, 0 \leq j \leq 1, k = \{0, 3\} \\
\tilde{a}_{i-3} \cdot C_{1jk} & \text{for} \quad 6 \leq i \leq 7, 0 \leq j \leq 1, k = \{0, 3\} \\
\tilde{a}_{i-3}l_1 \cdot C_{1jk} & \text{for} \quad i = 8, 0 \leq j \leq 1, k = \{0, 3\}
\end{cases}
\]

\[
C_{213} = 0, \quad C_{312} = 0, \quad C_{302} = 0, \quad C_{301} = 0, \quad C_{412} = 0
\]

\[
C_{411} = 0, \quad C_{402} = 0, \quad C_{401} = 0, \quad C_{003} = 0, \quad C_{000} = 0.
\]

\[
D_{ijk} = \begin{cases} 
\tilde{b}_{i-3}D_{1jk} & \text{for} \quad 3 \leq i \leq 5, 0 \leq j \leq 1, k = \{0, 3\} \\
-\tilde{b}_{i-3}D_{1jk} & \text{for} \quad 6 \leq i \leq 7, 0 \leq j \leq 1, k = \{0, 3\} \\
-\tilde{b}_{i-3}l_2D_{1jk} & \text{for} \quad i = 8, 0 \leq j \leq 1, k = \{0, 3\}
\end{cases}
\]

\[
D_{213} = 0, \quad D_{312} = 0, \quad D_{302} = 0, \quad D_{301} = 0, \quad D_{412} = 0
\]

\[
D_{411} = 0, \quad D_{402} = 0, \quad D_{401} = 0, \quad D_{003} = 0, \quad D_{000} = 0.
\]
This ODE system \(\left(\frac{d\psi_1}{dt}, \frac{d\psi_2}{dt}, \frac{d\psi_3}{dt}\right)\) is time-based and autonomous with real-valued coefficients \(\tilde{a}_i\ 0 \leq i \leq 5, \tilde{b}_j\ 0 \leq j \leq 5\) and biologically-based coefficients \(l_1, l_2, l_3\) that are functions of physiological parameters. The system of algebraic equations are functions of the undefined constants (5.1) and coefficients of our ODE model (5.31). This system of algebraic equations is solved using MATLAB and their respective solution is found in the Appendix.

Our ODE system, which we obtained from our sickle cell blood flow model, is a model for sickle cell crises. We will now proceed to analyze our ODE, sickle cell crisis model using techniques from chaos theory. Our goal is to discern whether sickle cell crises are chaotic and if so, then what are the drivers of its chaotic nature.

### 6 Chaos in Sickle Cell Model

Our goal is to discern whether sickle cell crises are chaotic and, if so, then to discover which physiological parameters are the drivers of its chaotic nature. In order to prove that our sickle cell crisis model is chaotic, we must show that our ODE system satisfies the requirements of a chaotic system. The requirement for an ODE system to be chaotic is that it must contain at least one unstable, fixed point. A fixed point is unstable if it contains at least one positive eigenvalue. Therefore, to prove that our ODE system is chaotic, it suffices in showing that it contains at least one positive eigenvalue. Chaotic systems, when plotted, show aperiodicity and sensitivity to initial conditions. We will now proceed to calculate fixed points, compute eigenvalues, and make graphical plots of our ODE system in order to demonstrate that it is a chaotic system.

#### 6.1 Fixed Points

In order to calculate the fixed points of our ODE system, we set \(\frac{d\psi_1}{dt} = 0, \frac{d\psi_2}{dt} = 0, \frac{d\psi_3}{dt} = 0\) which yields

\[
0 = l_1\psi_1 - \psi_1^2 \\
0 = -\tilde{a}_0\psi_1 - (\tilde{a}_1\psi_2 + \tilde{a}_2\psi_2^2) + \psi_3 \cdot (\tilde{a}_3 + \tilde{a}_4\psi_2 + \tilde{a}_5l_2\psi_2^2) \\
0 = -\tilde{b}_0\psi_1 + \tilde{b}_1\psi_2 + \tilde{b}_2\psi_2^2 - \psi_3 \cdot (\tilde{b}_3 + \tilde{b}_4\psi_2 + \tilde{b}_5l_3\psi_2^2)
\]

By solving the above system, we obtain all the fixed points of our system. The full list of real fixed points in numerical form is

\[
(\psi_1^*, \psi_2^*, \psi_3^*) = \{(0, 0, 0), (0, 2.317 \cdot 10^{-3}, 0.2065), (0, 1.723 \cdot 10^{-4}, 1.859), (1.88 \cdot 10^{-6}, 2.317 \cdot 10^{-3}, 0.2065), (1.88 \cdot 10^{-6}, 1.723 \cdot 10^{-4}, 1.859)\}
\]
6.2 Eigenvalues

In order to compute the eigenvalues of every fixed point, we must find the associated stability matrix of each fixed point. For every fixed point \((\psi_1^*, \psi_2^*, \psi_3^*)\), we can find the linear stability matrix by calculating

\[
\begin{pmatrix}
\frac{\partial f_1}{\partial \psi_1} & \frac{\partial f_2}{\partial \psi_1} & \frac{\partial f_3}{\partial \psi_1} \\
\frac{\partial f_1}{\partial \psi_2} & \frac{\partial f_2}{\partial \psi_2} & \frac{\partial f_3}{\partial \psi_2} \\
\frac{\partial f_1}{\partial \psi_3} & \frac{\partial f_2}{\partial \psi_3} & \frac{\partial f_3}{\partial \psi_3}
\end{pmatrix}
\begin{pmatrix}
\psi_1^* \\
\psi_2^* \\
\psi_3^*
\end{pmatrix}
\]

where

\[f_1 = \frac{d\psi_1}{dt}, \quad f_2 = \frac{d\psi_2}{dt}, \quad f_3 = \frac{d\psi_3}{dt}.
\]

Using the relations (5.27), (5.28), and (5.29) for \(f_1, f_2, f_3\), our linear stability matrix is

\[
\begin{pmatrix}
l_1 - 2\psi_1 & 0 & 0 \\
-a_0 & -(a_1 + 2a_2\psi_2) + \psi_3(a_4 + 2a_5l_1\psi_2) & -(a_3 + a_4\psi_2 + a_5l_1\psi_2^2) \\
-b_0 & b_1 + 2b_2\psi_2 - \psi_3(b_4 + 2b_5l_2\psi_2) & -(b_3 + b_4\psi_2 + b_5l_2\psi_2^2)
\end{pmatrix}
\]

Substituting each fixed point into our linear stability matrix yields a unique set of eigenvalues. The table below shows each fixed point with its corresponding eigenvalues in our ODE system:

<table>
<thead>
<tr>
<th>Fixed Points</th>
<th>Eigenvalues</th>
</tr>
</thead>
<tbody>
<tr>
<td>((0,2.3 \cdot 10^{-3},.21)),</td>
<td>{-.17 + 1.7i, -.17 - 1.7i, 5.2 \cdot 10^{-6}}</td>
</tr>
<tr>
<td>((0,1.7 \cdot 10^{-4},.19))</td>
<td>{.09, -2.3, 5.2 \cdot 10^{-6}}</td>
</tr>
<tr>
<td>((5.2 \cdot 10^{-6},2.3 \cdot 10^{-3},.21))</td>
<td>{-.17 + 1.7i, -.17 - 1.7i, -5.2 \cdot 10^{-6}}</td>
</tr>
<tr>
<td>((5.2 \cdot 10^{-6},1.7 \cdot 10^{-4},.19))</td>
<td>{.09, -2.3, -5.2 \cdot 10^{-6}}</td>
</tr>
<tr>
<td>((0,0,0))</td>
<td>{-.01, -20.0, 5.2 \cdot 10^{-6}}</td>
</tr>
</tbody>
</table>

**Table 1: Fixed Point vs. Eigenvalues**

In Table 1, three of the five fixed points contain at least one positive eigenvalue. This shows that our sickle cell crisis model is chaotic, and moreover that the onset of a sickle cell crisis is a chaotic phenomena. We will now proceed in making various graphical plots of our sickle cell crisis model.
6.3 Graphical Plots

Our system of ordinary differential equations is a nonlinear, autonomous system of differential equations in three variables $\psi_1, \psi_2, \psi_3$.

The graph of $\psi_1$ vs. $t$ is plotted for two different initial conditions $\psi_1(0) = 4.6 \cdot 10^{-6}$ and $\psi_1(0) = 6.2 \cdot 10^{-6}$. This first initial condition increases monotonically until it asymptotically approaches 5.2e-6. The second initial condition decreases monotonically until it asymptotically reaches 5.2e-6. This shows that the function $\psi_1$ heads asymptotically towards a fixed point and its functional form is either an increasing or decreasing exponential curve, based on its initial condition. This graph exhibits no oscillatory behavior or irregular behavior. This shows that the speed of blood doesn't exhibit much irregularity but changes in a uniform fashion to a steady state.
The graphs of $\psi_2$ vs $t$ and $\psi_3$ vs $t$ are plotted for three different initial conditions. Each initial condition has an order of magnitude of $1e-3$ differential from each other. Both graphs of $\psi_2$ vs $t$ and $\psi_3$ vs $t$ show sensitivity to initial conditions. Each initial condition shows oscillatory behavior which eventually decays asymptotically to a fixed point. The oscillations in $\psi_2$ vs $t$ and $\psi_3$ vs $t$ are aperiodic in nature. Sensitivity to initial conditions and aperiodicity are common in chaotic systems.

The graph of $\psi_2$ vs $\psi_3$ is an oscillatory trajectory which settles to a fixed point at the value of $(0.00235, 0.2065)$. This graph is a homoclinic orbit, which graphically is the connection between an unstable saddle trajectory and a stable spiral fixed point. Homoclinic orbits are found in numerous chaotic systems.
The graph of $\psi_1$ vs $\psi_2$ vs $\psi_3$ is a 3-D plot which shows the complete picture of the chaotic dynamics of our autonomous ODE system. This graph is a contracting helix curve which asymptotically approaches a unique fixed point for three different initial conditions. This plot shows the highly coupled nature of the variables $\psi_2$, $\psi_3$ and the decoupled nature of $\psi_1$. A contracting or expanding helical curve is common in many chaotic systems.

6.4 Demonstration of Chaos

In Section 6.1, we showed that our dynamical system has at least one unstable fixed point with a positive eigenvalue. In Section 6.2, we showed the various time solutions for $\psi_1$, $\psi_2$, and $\psi_3$ and their respective individual and combined graphical representations. These graphical plots exhibited aperiodic behavior and also sensitivity to initial conditions. By the tenets of chaos theory, we have demonstrated both analytically and graphically that our ODE, sickle cell crisis model is chaotic. We will now proceed in determining which physiological parameters controls the chaotic nature of our sickle cell crisis model.
7 Bifurcation Analysis

The dynamics of our ODE system \( \left( \frac{dw_1}{dt}, \frac{dw_2}{dt}, \frac{dw_3}{dt} \right) \) is dependent upon the values of the physiological parameters \( l_1, l_2, l_3 \) where

\[
l_1 = \frac{\mu T}{\rho L^2}, \quad l_2 = \frac{k_{Hb} [Hb] P_c T}{\alpha \cdot P_{O_{2,50\%}}}, \quad l_3 = \frac{k_{Hb} P_{O_{2,50\%}}^2 T}{P_{O_{2,50\%}}}.
\]

These constants \( l_1, l_2, l_3 \) are functions of the physiological parameters:

\[
\mu, \quad \rho, \quad P_{O_{2,50\%}}, \quad k_{Hb}, \quad \alpha, \quad [Hb].
\]

By changing the values of the physiological parameters above, we will, in effect, change \( l_1, l_2, l_3 \); which will subsequently change the dynamics of our sickle cell crisis ODE model.

7.1 Bifurcation Plots

In the phase plots below, we varied the values of the physiological parameters in three to see how each constant changed the stability of our crisis model.

Parameter Testing of \( \mu \):

The value of \( \mu \) in a sickle-cell diseased person is \( 5.89 \cdot 10^{-3} \text{ Pa} \cdot \text{s} \). For all values of \( \mu \) greater than zero, our dynamical system is unstable (see Fig. 6a).

\[
\mu = 0 \quad \quad \mu > 0
\]

\[\text{unstable region}\]

**Figure 6a:** \( \mu \) phase plot

Parameter Testing of \( \rho \):

The value of \( \rho \) in a sickle-cell diseased person is \( 1125 \frac{\text{kg} \cdot \text{s}}{\text{m}^3} \). For all values of \( \rho \) greater than zero, our dynamical system is unstable (see Fig. 6b).

\[
\rho = 0 \quad \quad \rho > 0
\]

\[\text{unstable region}\]

**Figure 6b:** \( \rho \) phase plot
Parameter Testing of $p_{O_2,50\%}^{Hb}$:

The value of $p_{O_2,50\%}^{Hb}$ in a sickle-cell diseased person is 3906.3 Pa. If we decrease the value of $p_{O_2,50\%}^{Hb}$ to 90% of its value, our dynamical system shifts from being an unstable system to a stable system (see Fig. 6c).

![Figure 6c: $p_{O_2,50\%}^{Hb}$ phase plot](image)

Parameter Testing of $k^{Hb}$:

The value of $k^{Hb}$ in a sickle-cell diseased person is 44 s$^{-1}$. If we increase the value of $k^{Hb}$ to 1.23 times its value, our dynamical system shifts from being an unstable system to a stable system (see Fig. 6d).

![Figure 6d: $k^{Hb}$ phase plot](image)

Parameter Testing of $\alpha$:

The value of $\alpha$ in a sickle-cell diseased person is 17489 m$^3$·Pa. For all values of $\alpha$ greater than zero, our dynamical system is unstable (see Fig. 6e). The value of $[Hb]$ in a sickle-cell diseased person is 21.099 mol. For all values of $[Hb]$ greater than zero, our dynamical system is unstable (see Fig. 6f).

![Figure 6e: $\alpha$ phase plot](image)
7.2 Critical Physiological Parameters

In the bifurcation analysis, the physiological parameters, $p_{O_2,50\%}^{Hb}$ and $k^{Hb}$, are the only parameters which, when varied, shift our dynamical system from an unstable state to a stable state (and vice-versa). This shows that $p_{O_2,50\%}^{Hb}$ and $k^{Hb}$ are the critical parameters which affect the chaotic nature of our ODE system. When shifting our dynamical system from an unstable to a stable state, this physiologically corresponds to shifting a person in a state of sickle cell crisis to a non-crisis state. Drug therapy can be used to manipulate these critical physiological parameters in order to shift the physiological conditions of a sickle-cell diseased person from a crisis state to a non-crisis state. This would, in effect, mitigate the crisis outbreak and return the sickle-cell diseased person back to stable physiological conditions.

8 Chaotic Region and Time Periods

Having determined the critical physiological parameters, $p_{O_2,50\%}^{Hb}$ and $k^{Hb}$, which govern sickle cell crises, we will then use these parameters to determine the temporal aspects of sickle cell crises. Particularly, we will determine the critical time period in which sickle cell crises may be halted and after which crises may not be halted. We will also, using graphical analysis of the critical physiological parameters, classify the different stages of a sickle cell crisis.

8.1 Critical Time Period

In the graphs below, $\psi_2$ vs. $\tau$ and $\psi_3$ vs. $\tau$ are plotted for slightly different initial conditions. For each graph, the trajectories for each initial condition are identical for small values and begin to diverge at the point, $\tau = .1$.

![Graphs](image)

**Figure 7:** $\psi_2$ vs. $\tau$, $\psi_3$ vs. $\tau$

This critical point, $\tau = .1$, is the value at which sickle cell blood flow changes from stable to unstable during a sickle cell crisis. Sickle cell crises can be mitigated using drug therapy in the stable region ($0 \leq \tau < .1$) and are untreatable in the chaotic region ($\tau \geq .1$). Converting
from nondimensional time \((\tau)\) to normal time \((t)\), our result implies that sickle cell crises are treatable in the stable time period \((0 \leq t \leq 2.5\text{hrs})\) and untreatable in the chaotic time period \((t \geq 2.5\text{hrs})\).

![Figure 8: Sickle Cell Crisis Parameter Profile
\((p^* = 3906.3 \text{ Pa}, \ k^* = 44\text{s}^{-1})\)](image)

In the above graph, five regions are identified: stable region (pre-crisis), critical time period \((0 \leq t \leq 2.5\text{ hrs})\), weak chaos \((0 \leq t \leq 3.7\text{ days})\), strong chaos \((3.7\text{ days} \leq t \leq 5.5\text{ days})\), and hyperchaos \((5.5\text{ days} \leq t \leq 6\text{ days})\). The onset of a sickle cell crisis begins at the critical time period. During the critical time period, sickle-cell diseased persons show no physiological symptoms. After the critical time period, sickle cell crises transition to a state of weak chaos, then to strong chaos, and ultimately to hyperchaos, as is seen in Fig. 7. These defined regions correspond to progressively more painful sickle cell crisis episodes. In a state of weak chaos, sickle-cell diseased persons experience dehydration and fatigue; during strong chaos, symptoms of severe pain, ischaemia, and seizures occur; and finally during hyperchaos, organ failure and possibly death may result.

Clinically, the four stages of a sickle cell crisis are podromal, initial, established, and resolving [3]. In the podromal phase, a sickle cell crisis begins internally within a person, but he/she shows little to no external symptoms; during the initial phase, acute physiological symptoms such as fatigue and dehydration occur; in the established phase, a person experiences severe pain, seizures, and worsening symptoms; and finally in the resolving phase, crisis symptoms will attenuate until a person reaches a steady state similar to his/her pre-crisis level.

The clinically defined stages of podromal, initial, established, and resolving directly parallel the mathematically defined time regions in Fig. 7 of critical time period, weak chaos, strong
chaos, and hyperchaos. If a sickle-cell diseased person's symptoms continue to worsen while in the established phase (strong chaos region), then he/she will enter hyperchaos and possible death may occur, otherwise a person will enter the resolving phase until a steady state is reached which is similar to pre-crisis.

During the progression of sickle cell crises, the $p_{O_2,50\%}^{Hb}$ parameter increases sigmoidally while the $k_{Hb}$ parameter decreases exponentially with time. According to Fig. 7, this shows that sickle cell crises can only occur if the physiological conditions are met in which

$$p_{O_2,50\%}^{Hb} > .9p^* \quad \text{or} \quad k_{Hb} < 1.23k^*$$

where $p^* = 3906.3$(Pa) and $k^* = 44$(s$^{-1}$) are the standard values of $p_{O_2,50\%}^{Hb}$ and $k_{Hb}$ for a sickle-cell diseased person. Changes in these physiological parameters correspondingly cause changes in the levels of free oxygen ($O_2$), hemoglobin ($Hb_4$), and oxyhemoglobin ($Hb_4O_8$) within the capillary. The chemical reaction which governs the relationship of these quantities is

$$Hb_4 + 4O_2 \rightarrow Hb_4O_8$$

As sickle cell crises proceed, the levels of hemoglobin remain constant, the concentration of free oxygen increases, and the amount of oxyhemoglobin decreases due to the variations in the critical physiological parameters.

### 8.2 Potential Drug Therapy

Using the above analysis, novel drugs could potentially be developed to mitigate sickle cell crises. Suchsaid drugs would need to target the critical physiological parameters, $p_{O_2,50\%}^{Hb}$ and $k_{Hb}$, within the microcirculation during the critical time period ($0 \leq t \leq 2.5$ hrs), after the onset of a sickle cell crisis. Current drug treatments for sickle cell crises are hydroxyurea, blood transfusions, and bone marrow transplant. Hydroxyurea is an antisickling, antineoplastic drug which increases blood flow in the microcirculation; blood transfusions replace sickled-blood cells with normal-shaped red blood cells; and bone marrow transplants genetically modify fetal hemoglobin to the bone marrow so that properly shaped blood cells are sequenced at the cellular level. Each of these treatments help to positively modulate the levels of $p_{O_2,50\%}^{Hb}$ and $k_{Hb}$ within the microcirculation.

The physical cause of sickle cell crisis is explained by the change of the critical physiological parameters, $p_{O_2,50\%}^{Hb}$ and $k_{Hb}$, in the body of the patient over time. Pharmacokinetic therapy, based on a feedback control system, which affects $p_{O_2,50\%}^{Hb}$ and $k_{Hb}$ can be used to alleviate the symptoms of sickle cell crises and relinquish its chaotic nature within a sickle cell diseased person. Drugs such as erythropoietin, vasodilators, and anticoagulants are examples of pharmaceuticals which affect these physiological parameters. Clinical trials involving the testing of pharmaceuticals within in-vitro models in humans is recommended.
9 Conclusion

In this paper, we have used a novel sickle cell crisis model, which captures the dynamics of blood flow, oxygen transport, and blood cell deformation within a capillary. We have demonstrated, both analytically and graphically, that our sickle cell crisis model is chaotic. We identified the critical physiological parameters, namely $p_{O_{2,50\%}}^{Hb}$ and $k^{Hb}$, which control the chaos within our system, determined the critical time period ($0 < t < 2.5$ hrs) in which sickle cell crises can be mitigated, and identified the three stages of a sickle cell crisis—weak chaos, strong chaos, and hyperchaos.

The goal of applying chaos theory to sickle cell disease is to create novel drug treatments and also to better understand the internal dynamics of this disease. Better understanding of sickle cell crises can lead to better prediction and subjugation of crisis outbreaks. Future research, based on this analysis, should focus on better understanding our time-based model for sickle cell crises, which is a system of nonlinear ordinary differential equations. The parameter space of this ODE system should particularly be explored. In this analysis, single parameter variation was explored, while in future analyses parameter combinations should be studied to determine if they can modulate chaotic nature of sickle cell crises.

The results of this analysis, particularly that pertaining to the critical physiological parameters and critical time period, should be validated against empirical data. The methodology of current drug treatments for sickle cell crises are consistent with the results found in this analysis. Further tests should be developed to test the accuracy of the critical physiological parameters' efficacy in treating sickle cell crises. These investigations could potentially improve upon the framework and pedagogical methods used to study, prevent, and treat sickle cell crises in the future.
10 Appendix

10.1 Appendix A - Numerical Constants

Having solved our system of nonlinear algebraic equations using Matlab, we get the following numerical constants:

<table>
<thead>
<tr>
<th>Numerical Constants</th>
</tr>
</thead>
<tbody>
<tr>
<td>$k_1 = 1.0108$</td>
</tr>
<tr>
<td>$k_2 = 9.851 \cdot 10^{-13}$</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
</tbody>
</table>

$c_1 = .4032$   $c_8 = .1057$   $c_{15} = .4102$   $c_{22} = -3.4214 \cdot 10^{-17}$
$c_2 = .4030$   $c_9 = .4027$   $c_{16} = .2805$   $c_{23} = 94.8451$
$c_3 = .4032$   $c_{10} = .4032$  $c_{17} = .4103$ $
$c_4 = .4030$   $c_{11} = .4101$  $c_{18} = .4102$ $
$c_5 = .4031$   $c_{12} = .4102$  $c_{19} = .4104$ $
$c_6 = .4031$   $c_{13} = .4102$  $c_{20} = .4103$ $
$c_7 = .4030$   $c_{14} = .4103$  $c_{21} = 5.3506 \cdot 10^{-9}$

$d_1 = .1813$   $d_8 = .1805$   $d_{15} = .1852$   $d_{22} = 1.3377 \cdot 10^{-20}$
$d_2 = .1885$   $d_9 = .1814$   $d_{16} = .1873$   $d_{23} = .1239$
$d_3 = .1810$   $d_{10} = .0467$  $d_{17} = .1812$ $
$d_4 = .1870$   $d_{11} = .1852$  $d_{18} = .1810$ $
$d_5 = .1879$   $d_{12} = .1859$  $d_{19} = 0.1869$ $
$d_6 = .1795$   $d_{13} = .1824$  $d_{20} = 0.0944$ $
$d_7 = .1795$   $d_{14} = .1859$  $d_{21} = 9.0537 \cdot 10^{-11}$

$r^2 = 4.328 \cdot 10^{-20}$ for the system of relations between the $A_{ijk}$’s and $B_{ijk}$’s which solved for $k_1, k_2, a_1, a_2, a_3, b_1, b_2, b_3, b_4, b_5, b_6$.

$r^2 = 7.81 \cdot 10^{-15}$ for the system of relations between the $C_{ijk}$’s and $D_{ijk}$’s which solved for the $c_i$’s and $d_i$’s for $1 \leq i \leq 23$. 

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10.2 Appendix B - Physiological Parameter Values

\[ [Mb] = 0 \ (\text{mol} / \text{m}^3) \]
\[ [Hb] = 21.099 \ (\text{mol} / \text{m}^3) \]
\[ D^{Mb} = 6 \cdot 10^{-11} \ (\text{m}^2 / \text{s}) \]
\[ D^{Hb} = 1.378 \cdot 10^{-11} \ (\text{m}^2 / \text{s}) \]
\[ P_{O_2}^{50\%} = 706.6 \ (\text{Pa}) \]
\[ P_{O_2}^{Hb} = 3906.3 \ (\text{Pa}) \]
\[ \alpha = 0.17489 \ (\text{mol} / \text{m}^3 \text{Pa}) \]
\[ \alpha = 0.17489 \ (\text{mol} / \text{m}^3 \text{Pa}) \]
\[ \mu = 5.89 \cdot 10^{-3} \ (\text{Pa} \cdot \text{s}) \]
\[ n = 2.2 \]
\[ k^{Hb} = 44 \ (\text{s}^{-1}) \]
\[ k^{Hb} = 44 \ (\text{s}^{-1}) \]
\[ M = 0 \ (\text{mol} / \text{m}^3) \]
\[ r_0 = 10^{-5} \ (\text{m}) \]
\[ r_0 = 10^{-5} \ (\text{m}) \]
\[ D = 9.47 \cdot 10^{-10} \ (\text{m}^2 / \text{s}) \]
\[ \rho = 1125 \ (\text{kg} / \text{m}^3) \]

\[ \hat{a}_0 = 10^{-4} \quad \hat{a}_5 = 0.32 \quad \hat{b}_0 = 10^{-4} \quad \hat{b}_5 = 10^{10} \]
\[ \hat{a}_1 = 20 \quad \hat{a}_6 = 96 \quad \hat{b}_1 = 15 \quad l_1 = 4.0808 \cdot 10^{-9} \]
\[ \hat{a}_2 = 0.62 \quad \hat{a}_7 = 0.032 \quad \hat{b}_2 = 0.002 \quad l_2 = 2.88 \cdot 10^{-6} \]
\[ \hat{a}_3 = 0.002 \quad \hat{a}_8 = 0.0012 \quad \hat{b}_3 = 0.013 \]
\[ \hat{a}_4 = 96 \quad \hat{a}_9 = 0.072 \quad \hat{b}_4 = 0.29 \]

10.3 Appendix C - Computer Code

**Figure 2** \((\psi_1 \ vs. \ \tau)\)

restart; with(DEtools): with(plots):
l1:= 1: l2:= 4.0808e-9: l3:= 2.88e-6:

ODEsys := [diff(x(t), t) = -a0 \cdot z(t) - a1 \cdot x(t) - a2 \cdot x(t)^2 + y(t) \cdot (a3 + a4 \cdot x(t) + a5 \cdot l2 \cdot x(t)^2),
diff(y(t), t) = -b0 \cdot z(t) + b1 \cdot x(t) + b2 \cdot x(t)^2 - y(t) \cdot (b3 + b4 \cdot x(t) - b5 \cdot l3 \cdot x(t)^2),
diff(z(t), t) = l1 \cdot z(t) - z(t)^2];

DEplot(ODEsys, \{x(t), y(t), z(t)\}, t = 0..4e6, [[x(0) = 1e-6, y(0) = 1e-6, z(0) = 4.6e-6], [x(0) = 1e-6, y(0) = 1e-6, z(0) = 6.2e-6]], stepsize = 1e-15, x = 0..10, y = -0..10, z = 0..10,
     color = [red, blue]);

**Figure 3** \((\psi_2 \ vs. \ \tau, \ \psi_3 \ vs. \ \tau)\)

restart; with(DEtools): with(plots):
l1:= 1: l2:= 4.0808e-9: l3:= 2.88e-6:
ODEsys := [ 
  diff(x(t), t) = -a0 \cdot z(t) - a1 \cdot x(t) - a2 \cdot x(t)^2 + y(t) \cdot (a3 + a4 \cdot x(t) + a5 \cdot l2 \cdot x(t)^2),
  diff(y(t), t) = -b0 \cdot z(t) + b1 \cdot x(t) + b2 \cdot x(t)^2 - y(t) \cdot (b3 + b4 \cdot x(t) - b5 \cdot l3 \cdot x(t)^2),
  diff(z(t), t) = l1 \cdot z(t) - z(t)^2];

DEplot(ODEsys, \{x(t), y(t)\}, t=0..10, \[x(0)= 1.9e-3, y(0)= .202, z(0)= 1.5e-6\], stepsize= 1e-15, x = 0..1, y = -0..1, z = 0..1, color = [red]);

DEplot3d(ODEsys, \{x(t), y(t), z(t)\}, t=0..10, [[x(0)= 1.9e-3, y(0)= .202, z(0)= 1.5e-6]], stepsize = 1e-15, x = 0..1, y = -0..1, z = 0..1, color = [red], labels = \{x, y, z\});
Figure 7 ($\psi_2$ vs. $\tau$, $\psi_3$ vs. $\tau$)

restart; with(DEtools): with(plots):
l1 := 1: l2 := 4.0808e-9: l3 := 2.88e-6:

ODEsys := [
diff(x(t), t) = -a0 \cdot z(t) - a1 \cdot x(t) - a2 \cdot x(t)^2 + y(t) \cdot (a3 + a4 \cdot x(t) + a5 \cdot l2 \cdot x(t)^2),
diff(y(t), t) = -b0 \cdot z(t) + b1 \cdot x(t) + b2 \cdot x(t)^2 - y(t) \cdot (b3 + b4 \cdot x(t) - b5 \cdot l3 \cdot x(t)^2),
diff(z(t), t) = l1 \cdot z(t) - z(t)^2];

DEplot(ODEsys, \{x(t), t\}, t=0..4, \{[x(0) = 1e-12, y(0) = 1e-7, z(0) = 1e-6], [x(0) = 1e-12, y(0) = 1.5e-7, z(0) = 1e-6], [x(0) = 1e-12, y(0) = 1e-7, z(0) = 1.5e-6]\}, stepsize = 1e-15, x = 0..1, y = -0..1, z = 0..1, color = [blue, red, cyan]);

DEplot(ODEsys, \{x(t), t\}, t=0..4, \{[x(0) = 1e-12, y(0) = 1e-7, z(0) = 1e-6], [x(0) = 1e-12, y(0) = 1.5e-7, z(0) = 1e-6], [x(0) = 1e-12, y(0) = 1e-7, z(0) = 1.5e-6]\}, stepsize = 1e-15, x = 0..1, y = -0..1, z = 0..1, color = [blue, red, cyan]);

Figure 8 ($p_{0.5\%}^{Hb}$ vs. $\tau$, $k^{Hb}$ vs. $\tau$)

restart; with(DEtools): with(plots):

ODEsys := [
diff(x(t), t) = -a0 \cdot z(t) - a1 \cdot x(t) - a2 \cdot x(t)^2 + y(t) \cdot \left(\frac{p^*}{p_{50}(t)^2}\right) \left(\frac{k^{Hb}(t)}{k^*}\right) \cdot x(t)^2),
diff(y(t), t) = -b0 \cdot z(t) + b1 \cdot x(t) + b2 \cdot x(t)^2 - y(t) \cdot \left(\frac{p^*}{p_{50}(t)^2}\right) \left(\frac{k^{Hb}(t)}{k^*}\right) \cdot x(t)^2),
diff(z(t), t) = l1 \cdot z(t) - z(t)^2];

DEplot(ODEsys, \{p_{50}(t), t\}, t=0..5.2e5, \{[x(0) = 1e-12, y(0) = 1e-7, z(0) = 1e-6]\}, stepsize = 1e-15, x = 0..1, y = -0..1, z = 0..1, color = [blue, red, cyan]);

DEplot(ODEsys, \{k^{Hb}(t), t\}, t=0..5.2e5, \{[x(0) = 1e-12, y(0) = 1e-7, z(0) = 1e-6]\}, stepsize = 1e-15, x = 0..1, y = -0..1, z = 0..1, color = [red]);
References


