Chaos in the onset of sickle cell crises

A. Apori, R. Coral-Pinto & W. Harris
Department of Aeronautics and Astronautics, Massachusetts Institute of Technology, Cambridge, MA 02139, USA

Abstract

A novel unsteady Eulerian-based model [Apori-Harris model] that includes the oxygen concentration, red blood cell average velocity, cell stiffness, and plasma viscosity as dependent state variables has been developed and is used to investigate the chaotic onset of sickle cell blood flow crises in capillaries. In canonical form, the Apori-Harris model is a set of coupled, non-linear equations in which the velocity-viscosity and viscosity-cell stiffness relationships dominate the physics of the model. The equation set is investigated to determine its chaotic properties with respect to control parameters representing the specific rheology of the sickle cell erythrocytes. Determining the sensitivity of the Apori-Harris model to changes in each parameter defines the process for identifying the dominant control parameters. A mathematically rigorous definition and a clinically acceptable definition of sickle cell crises onset in capillaries have been derived and are based on the eigenvalues of the equation set in 4-dimensional phase space. Results of chaos tests proved positive for a range of the selected control parameters. The results include (a) continuous patterns found in the Poincare section, (b) spectral broadening of the Fourier power spectrum, and (c) positive Lyapunov exponent values. The mathematical prediction of chaotic onset of sickle cell blood flow crises in capillaries based on the Apori-Harris model coincides with the change from a clinically healthy person to a clinically defined crisis state for sickle cell disease. The Apori-Harris model predicts that for a patient in the onset of sickle cell crisis the stiffness of the blood cells will increase monotonically with time leading to permanent damage in the circulatory system.

Keywords: sickle cell crises, chaos, Apori-Harris model.
1 Introduction

By determining the nature of outbreaks or crises in sickle cell disease, one could more accurately predict and subdue these life threatening crises before they ever occur. Determining the possible chaotic mechanism governing sickle crises could enable control theory to be applied in a preventative way to treat sickle cell disease. The scope of this research to use chaos theory to analyze the occurrence of sickle cell crises based on a model of the dynamics in the microcirculation.

The criteria used for classifying a disease as chaotic is the same for that of any other system. The state variables of the system must be determined initially. The disease must be modeled mathematically to derive the governing equations describing the disease. Then the system must be proven to be deterministic, aperiodic, and sensitive to initial conditions. Prior to this investigation there was virtually no way to predict and prevent a crises before it occurs.

Sickle cell disease is a painful disease caused by a hemoglobin disorder. Sickle cell disease is a disease in which patients suffer painful attacks, termed crisis, caused by a lack of adequate oxygen reaching the body tissue. Sufferers have an abnormal type of hemoglobin (hemoglobin S) which is predisposed to taking a sickle shape at low oxygen tension. This sickle shaped blood cell clogs small blood vessels preventing an adequate supply of blood from reaching that part of the body. During crises symptoms include skeletal pain persisting for several days or weeks and fever. No drugs exist that are effective in preventing crises. Therapy consists of hydration, keeping the patient warm and possibly using oxygen. Chronic transfusion therapy has also been used to decrease the frequency of crises.

The objective of this investigation is to develop a model for sickle cell blood flow in the microcirculation that captures the complex interaction of physiological parameters that lead to chaotic manifestation of crises in the microcirculation. The term chaos is synonymous with disorder. Not all systems that appear to be disordered or irregular are necessarily chaotic. Chaos only occurs in nonlinear, dynamical systems. In the mathematical sense, a chaotic system is generally defined as having the following characteristics: sensitivity to initial conditions, aperiodicity, and deterministic origin.

2 Previous models

Several models have been formulated over the years that have formed the basis from which to initiate this research. The Lighthill-Fitzgerald [1] lubrication theory is the model used to describe the flow of red blood cells through the microcirculation. The description of the dynamics of the flow of red blood cells in the microcirculation was an important conclusion for this model.

The theory for oxygen transport in the microcirculation was developed by August Krogh [2] in the early 1920’s. Krogh’s model described how oxygen carried in red blood cells coming from the lungs was dispersed to the body. The Krogh cylinder model provides a solution for the oxygen concentration in both
the capillary and the surrounding tissue as a function of the axial and radial position along the capillary.

Berger and King [3] developed a mathematical model incorporating capillary flow theory and oxygen transport theory to describe the flow of sickle cell blood in the capillaries. The B-K model found that depending on initial conditions and parameter values it was possible for cells to be depleted of oxygen before exiting the capillary. The B-K model established a possible mathematical representation of conditions that led to red blood cell sickling in the capillary.

Cima, Discher, Tong, and Williams [4] followed up the B-K model with an improved sickle cell model of erythrocyte dynamics in the capillaries. These improvements led to the discovery of a previously unknown region of multi-valued solutions for capillary blood cell velocity as a function of blood plasma viscosity.

The Cima model showed that the abrupt onset of a sickle cell crises could be caused by a catastrophic change in the blood velocity in the multi-valued regime as described by state bifurcations in catastrophe theory. The Cima model also showed the extreme dependence of the onset of the multi-valued regime (and thus possible catastrophe induced crises) upon small changes in physiological parameters that vary between individuals.

Past sickle cell models have not been constructed to allow the analysis of long-term behavior of the entire system. However, these models are limited by a lack of autonomy and the Lagrangian formulation of the governing equations.

The previous models stop short of modeling the entire system autonomously. The state variables of the system represent physiological systems in the body which are all interdependent. Previous models have always kept one variable (i.e. blood viscosity) independent to see how the other variables vary with respect to the independent variable and then solved for the profile along the capillary over a finite period of time. In reality there should be no independent variable for the blood flow model other than time. To generate realistic behavior of the system over time it is necessary to make all of the state variables dependent.

Also, the Lagrangian perspective employed for solving the oxygen profile over the length of the capillary prevents the analysis of the systems long term behavior. The Cima model essentially looses validity after the amount of time it takes for one particle to traverse the length of the capillary. An Eulerian model which continuously shows the state of the flow in the capillary is necessary to analyze demonstrate the long term behavior.

3 State equations of the Apori-Harris sickle cell model

The simplified Apori-Harris (A-H) model [5] for sickle cell blood flow in the capillaries is based upon capillary oxygen consumption as described in the previous section. This includes consideration of the equations for capillary flow theory, oxygen transport, and sickle cell rheology developed by Cima and others. The A-H model will be formulated in the Eulerian frame in order to observe the state of the system over time. The physics of sickle cell flow will be simplified and converted from the Lagrangian formulation of previous models.
The state variables of the A-H model are oxygen concentration \((c)\), blood velocity \((u)\), blood cell stiffness \((s)\), and plasma viscosity \((\mu)\). These four equations are necessary to describe the complete state of the sickle cell flow on the microvascular level.

Equation (1) below describes the rate of change of the oxygen concentration \((c)\) in the blood.

\[
\frac{dc}{dt} = a_1c + a_2\mu u + a_3u
\]

where \(a_1\), \(a_2\), and \(a_3\) are parameters, \(u\) is blood velocity and \(\mu\) is plasma viscosity.

The first term on the right of eqn. (1) is \(a_1c\). This term is a diffusion term. The second term on the right is \(a_2\mu u\). This term represents an important nonlinear coupling between velocity and viscosity. This coupling is important to the sickle cell case as described in Cima et al [4] which showed that both \(u\) and \(\mu\) are coupled in determining the oxygen concentration at any given time. The third term \(a_3u\) is a convective term. Oxygen is transferred from the blood to the tissue by axial convection. The rate of oxygen convection to the tissue is directly proportional to the velocity of the blood flow.

The rate of change of the blood velocity \((u)\) is described by the following equations:

\[
\frac{du}{dt} = b_1u + b_2\mu s + b_3s
\]

where \(b_1\), \(b_2\), and \(b_3\) are parameters, \(\mu\) is viscosity and \(s\) is cell stiffness.

The first term on the right of the velocity equation is \(b_1u\). This term is a diffusive term for velocity. The \(b_2\mu s\) term represents the affect of nonlinear coupling between the rheology of the cell and the viscosity of the plasma. The Lighthill-Fitzgerald results when combined with the Cima results for the pressure drop across the cell and the plasma, the coupling of \(\mu s\) is apparent when solving the equations for fixed pressure drop \(\Delta P\). The last term is \(b_3s\). This represents the resistive affect of the stiffness on velocity. This resistive force can cause a change to the overall velocity of the blood flowing through the capillary. This is obvious from their inverse relationship obtained by Cima et al [4].

Equation (3) below describes the rate of change of the stiffness \((s)\):

\[
\frac{ds}{dt} = c_1s + c_2c
\]

where \(c_1\) and \(c_2\) are parameters and \(c\) is oxygen concentration.

The first term on the right of eqn. (3) is \(c_1s\). This is a diffusive term showing that the current stiffness influences the rate of change of the stiffness. The second term in eqn. (3) is \(c_2c\). This term represents the rheological changes that the cell undergoes in the sickle cell case. From experimental data, Cima et al [4] established the following equation for stiffness versus oxygen concentration:

\[
S = S_{ref}(\alpha + (1-\alpha)(c/cref)^2)-1
\]

where \(cref\) is the oxygen concentration upon entering the capillary, \(S_{ref}\) is the stiffness at \(cref\) and \(\alpha\) is a parameter. From the above equation it is apparent
that the cell stiffness is inversely proportional to the oxygen concentration. This relationship is captured in the second term of eqn.(3).

The equation for the rate of change of viscosity ($\mu$) is the following:

$$\frac{d\mu}{dt} = d_1\mu + d_2c$$  (4)

where $d_1$ and $d_2$ are parameters and $c$ is oxygen concentration. The $d_1\mu$ term is a diffusive term. The rate of change of viscosity is dependent upon the current viscosity. The second term in eqn. (4) is $d_2c$. This term describes the physiology of the plasma viscosity. Plasma viscosity can increase for a variety of reasons all of which result in an associated change in oxygen concentration as it will vary the amount of total time cells spend in the capillary.

In assuming an Eulerian perspective, the oxygen concentration is averaged over length of the capillary. The actual dynamics of oxygen transport in the capillary would lead to a profile of decreasing oxygen with capillary distance $x$ as shown by Cima et al [4]. All other assumptions of the Krogh model for oxygen transport also hold.

The velocity of the blood is averaged over the entire capillary. The blood is assumed to be incompressible and flowing strictly in the axial direction. The blood cell stiffness is averaged over the length of the capillary. The cells are assumed to flow down the capillary in single file motion with uniform spacing between them.

The plasma viscosity is averaged over the length of the capillary. The difference in viscosity between the blood cells and the plasma is also neglected as the viscosity is assumed constant over the cells and plasma.

4 Parameter determination

4.1 Characteristic physiological parameters

The physiological parameter ranges are key in determining the dynamics of the non-linear Apori-Harris model. In an experimental setup, parameter value ranges could be measured from known physical quantities in the body. For the A-H system, parameters have been derived in order to normalize each term of eqns. (1)-(4). This allows consistency in units within each equation. These parameters are assumed to correspond to physiological parameters that can be measured in the body.

Ranges of all parameters must be defined consistently. The first step taken in defining the parameters for the A-H equations was to define a set of characteristic values for length, time, stiffness, viscosity, and oxygen concentration. These values represent reference values likely to be found in the body. They are presented in Table 1 below.

Table 1: Characteristic body constants.

<table>
<thead>
<tr>
<th>Length</th>
<th>Time</th>
<th>Cell Stiffness</th>
<th>Viscosity</th>
<th>Oxygen Concentration</th>
</tr>
</thead>
<tbody>
<tr>
<td>556 x 10^-6 m</td>
<td>1.112 sec</td>
<td>185 x 10^6 dynes/m</td>
<td>1.4 x 10^-5 Pa-s</td>
<td>8.3 x 10^-6 mol/L</td>
</tr>
</tbody>
</table>
The characteristic length was taken as the average length of the capillary as defined by Cima et al [4]. This is the capillary length over which oxygen is contributed to the surrounding body tissue as described by the Krogh model[2]. The characteristic time was defined as the time it took for a cell to traverse the capillary with a healthy, non-crisis viscosity of $\mu = 1.4 \text{ Pa-s}$. This time is an average for a healthy individual found in the results of the Cima model. The characteristic stiffness was taken as Sref which is the stiffness for healthy blood cells as defined by Cima et al. This stiffness was interpolated from data measured in experiments where red blood cells were passed through filters[4]. The characteristic viscosity is the value for normal blood and sickle blood in a non-crisis state. The value of the viscosity comes from patient data[4]. The characteristic value for oxygen concentration is the average starting capillary inlet concentration for people with sickle cell blood[4]. This is the average concentration of fully oxygenated red cells that have left the lungs and travelled through the microvascular system to the capillaries.

The characteristic physiological constants are useful to obtain the correct units and order of magnitude for each term. Table 2 displays the units for each parameter and the initial parameter values found by substituting the characteristic values for the required units.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Units</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>A1</td>
<td>1/s</td>
<td>0.88928</td>
</tr>
<tr>
<td>A2</td>
<td>(s/m)(1/Pa-s)(mol/L)(1/s)</td>
<td>10.66</td>
</tr>
<tr>
<td>A3</td>
<td>(s/m)(mol/L)(1/s)</td>
<td>0.014928</td>
</tr>
<tr>
<td>B1</td>
<td>1/s</td>
<td>0.88928</td>
</tr>
<tr>
<td>B2</td>
<td>(1/Pa-s)(m/dynes)(m/s^2)</td>
<td>1736</td>
</tr>
<tr>
<td>B3</td>
<td>(m/dynes)(m/s^2)</td>
<td>2.43</td>
</tr>
<tr>
<td>C1</td>
<td>1/s</td>
<td>0.88928</td>
</tr>
<tr>
<td>C2</td>
<td>(L/mol)(dynes/m)(1/s)</td>
<td>20.044</td>
</tr>
<tr>
<td>D1</td>
<td>1/s</td>
<td>0.88928</td>
</tr>
<tr>
<td>D2</td>
<td>(L/mol)(Pa-s)/s</td>
<td>151.7</td>
</tr>
</tbody>
</table>

4.2 Determination of control parameters

The process for choosing a control parameter required testing the sensitivity of the system to changes in each parameter. To better understand the behavior of the A-H equations it is convenient to analyze the eigenvalues of the non-linear system. For certain parameter values, the solutions of the system will be either stable or unstable. Chaotic behavior can be found only in unstable systems, therefore the control parameters must be able to drive the system of equations from a stable to an unstable state.

To evaluate the eigenvalues of the system, expressions for the fixed points of the system are found by equating the A-H equations to zero. The system has three fixed points. After determining the Jacobian matrix, the eigenvalues are
readily found. For the system to be stable all the eigenvalues are required to have negative real parts, while positive real parts indicate instability.

The parameters were varied over a range of values to assess their ability to drive the solutions from a stable to an unstable state. Each parameter was varied individually while all others were held at their original characteristic values shown in Table 2. Each parameter was varied from a value 1/100th to 100 times the original value. Solutions were plotted in the phase space and temporal domain in order to view the dynamics of the A-H system.

Upon exploring different combinations in the parameter space, the key parameters were found to be $a_1$, $b_1$, $b_2$, $c_1$, $c_2$, and $d_1$. As seen in the A-H equations above, $a_1$, $b_1$, $c_1$, $d_1$ are the diffusion terms for the variables of the A-H system. The diffusion terms determine the contraction or expansion of the volumes of the phase space of the A-H system.

Parameter $b_2$ is the coefficient for the nonlinear coupling between viscosity and stiffness. This parameter was shown to drive the system from a stable state to an unstable state over the A-H equations fixed points, thus controlling the dynamics of the system. The $c_2$ term is the dependence of cell stiffness on oxygen concentration. This parameter determines the transitions from quasiperiodic solutions of the system to chaotic solutions. $C_2$ is the coefficient of the oxygen concentration term in the cell stiffness eqn. (3). In terms of physiology, this parameter represents the complex relationship between the stiffness of the cell and oxygen concentration. The dependence of cell stiffness on oxygen concentration is a phenomenon known to be the key difference between sickle cell blood and normal blood.

**4.3 A-H parameter values for chaos**

The final parameter values to analyze the chaotic properties of the sickle cell model are listed in Table 3.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>$a_1$</td>
<td>.88928</td>
</tr>
<tr>
<td>$a_2$</td>
<td>-10.66</td>
</tr>
<tr>
<td>$a_3$</td>
<td>-.014928</td>
</tr>
<tr>
<td>$b_1$</td>
<td>-.89929</td>
</tr>
<tr>
<td>$b_2$</td>
<td>1736 x .35</td>
</tr>
<tr>
<td>$b_3$</td>
<td>2.43</td>
</tr>
<tr>
<td>$c_1$</td>
<td>-.89930</td>
</tr>
<tr>
<td>$c_2$</td>
<td>Varied (characteristic value is 20.044)</td>
</tr>
<tr>
<td>$d_1$</td>
<td>-.89931 x 3</td>
</tr>
<tr>
<td>$d_2$</td>
<td>151.7</td>
</tr>
</tbody>
</table>

Assigning signs to each term is critical to the stability dynamics of the solutions. Blood flow in general is dominated by viscosity that results in dissipation of energy. In the capillaries, the physiological variables that are affected by the dissipative nature of viscosity are the average velocity and the
stiffness. Therefore, their variation with time will be bounded and the proper sign of the parameters $b_1$, $c_1$, and $d_1$ is negative. To model the oxygen concentration it was assumed that concentration is not a dissipative variable, meaning that it is not completely dominated by the fluid dynamics of the blood but by the blood cell internal structures. Thus, the sign assigned to parameters $a_1$, $c_2$, and $d_2$ was positive. To provide a sign to parameters $a_3$ and $b_3$, the effect of velocity on the rate of oxygen concentration and the effect of viscosity on the rate of change of velocity were considered. Intuitively, tissues will be able to absorb less oxygen per unit time if the velocity of the blood cells passing by the capillaries increases. Therefore, the proper sign for the parameter $a_3$ is negative. In the case of parameter $b_3$, an increase of the rate of change of velocity was assumed to result in an increase of the cell stiffness. Thus, the sign assigned to the $b_3$ parameter was positive. The sign of the nonlinear terms of eqn. (1) and eqn. (2) were chosen based on their impact on the stability dynamics of the system. The nonlinear terms of both eqn. (1) and eqn. (2) led to chaotic behavior when their signs were opposite. The final physiological parameter values of Table 3 reflect the optimal conditions for developing a chaotic attractor in the phase space.

5 Chaotic properties

5.1 Determinism in A-H equations

For chaos to exist, the data observed must be generated by a deterministic process. The apparent disorder must be caused by the complexity of the governing equations. Differentiating between random and chaotic data may be difficult for a system occurring in nature. It requires attractor reconstruction among other mathematical tools to prove that the data is correlated. Equations (1) - (4) are all ordinary differential equations. When solved without any random inputs from parameters or initial conditions, by definition their solutions are deterministic. Throughout the analysis of the A-H model parameters $a_1$, $a_2$, $a_3$, $b_1$, $b_2$, $b_3$, $c_1$, $d_1$, and $d_2$ were kept constant. Different solutions were found by varying $c_2$ and the initial conditions.

The chaos found in the solution of the A-H model was strictly a function of the complex nonlinearity of the governing equations. However, the actual physiological parameters of the body may change over time. The physiological parameters are unlikely to change randomly or chaotically themselves. What is more likely to happen is that the control parameter of the A-H system changes values over some range until reaching a critical limit that leads to an inherently chaotic solution for the blood flow.

5.2 Poincare section

The Poincare section for a chaotic attractor’s trajectories will resemble a curve or pattern. No trajectory will ever intersect the plane at the exact same point but since a strange attractor does have surfaces neighboring trajectories will intersect the cross section plane as if on the surface of the strange attractor. This curve differs from the Poincare section of random data.
Poincare sections for the A-H attractor at $c_2 \times 0.001$ and $c_2 \times 50$ are plotted in Figures 1 and 2. The plots were generated after all initial transients died down by a method that approximated the intersection between trajectories and the cross section.

![Figure 1: Poincare sections of A-H attractor.](image1)

![Figure 2: Poincare sections of A-H attractor.](image2)

For the $c_2 \times 50$ plot, the concentration of the points on the attractor surface provides confirmation of the deterministic and chaotic nature of the solutions. The $\mu$-$u$ Poincare section shows that the attractor intersects the plane in a pattern of lines spread out in a fan-like shape. In contrast, there are only two points on the Poincare section for $c_2 \times 0.001$ when the attractor generates a limit cycle. This is because all trajectories converge on the limit cycle and trace out an identical path in the phase space. This causes them to intersect the plane in the exact same location as they oscillate around the limit cycle.

Determinism supports the fact that crises can occur without drastic and erratic changes to physiological parameters. A patient suffering from sickle cell would not have to go through extreme changes or stressors to the body for the chaotic state of sickle cell blood flow to occur. Chaos could be induced when physiological body parameters vary slightly for normal everyday reasons without a shock to the system or a chaotic perturbation to the body.
5.3 Aperiodicity

5.4.1 Aperiodic times series
The A-H model at \( c_2 \times 50 \) exhibits aperiodic behavior. The state variables vary erratically over time in a pattern that doesn’t repeat itself. As seen in Figure 3, the oxygen concentration oscillates in a pattern of increasing and decreasing amplitudes. The periods of oscillation also vary over time. The oxygen concentration in the blood for an individual with parameter values within the chaotic range would vary between high and low values never becoming stable. This instability would be indicative of a crisis in a sickle cell patient.

![Figure 3: Aperiodic time series of oxygen concentration for A-H attractor.](image)

5.4.1 Fourier analysis
Performing a Fourier analysis on the A-H equations displays the solutions in the frequency domain. Plotting the Fourier power spectrum shows the relative strength of frequencies present in the solution. Abrupt spikes in the power spectrum indicates dominant frequencies. Dominant frequencies induce periodic motion about those frequencies. When there are no dominant frequencies the power spectrum is spread out over a range of frequencies. This is the case for a chaotic power spectrum which shows broadening over the range of frequencies present in the attractor.

The plots of Figure 4 show the time series for the \( \mu \). They were plotted on the left with the control parameter producing a limit cycle (\( c_2 \times .01 \)) and on the right with a chaotic attractor (\( c_2 \times 50 \)). For \( c_2 \times .01 \) all of the state variables oscillate in a single period limit cycle except for \( u \) which oscillates in a period two limit cycle. When the control parameter is increased to \( c_2 \times 50 \) any observable regularity in the time series disappears and the solutions for all state variables become chaotic.

![Figure 4: Time series of limit cycle and A-H attractor.](image)
In Figure 5 are the corresponding Fourier power spectrums for the plots in Figure 4. Along the left are plotted solutions for $c_2 x .01$ and on the right are the solutions for $c_2 x 50$. The power spectrum shows large frequency spikes along with their harmonics for the limit cycle solution ($c_2 x .01$). The power spectrum plots on the right for the A-H attractor show results characteristic of chaotic systems. The frequency ranges that show up in the chaotic domain correspond to the motion of the chaotic time series plotted in Figure 5.

![Figure 5: Fourier power spectrum of limit cycle and A-H attractor.](image)

The Fourier power spectrum for the A-H attractor shows that at $c_2 x 50$ solutions generated are not periodic in nature. All state variables oscillate in an erratic and unpredictable way. Since there are no dominant frequencies, solutions don’t repeat themselves even if iterated for a long period of time. Physiologically, this may indicate that once a sickle cell patient enters the crisis state, levels of oxygen, viscosity, cell stiffness, and blood velocity are impossible to predict.

### 5.4 Initial condition sensitivity

#### 5.4.1 Sensitivity of the strange attractor and time series

All chaotic systems exhibit extreme sensitivity to initial conditions. This is another cause of their unpredictable nature. An infinitesimally small change to an initial condition can cause a drastic difference in the final state of the solution over time. This is because trajectories starting at nearby points separate exponentially fast as they spread out over the attractor.

Five different solutions are plotted in Figure 6. The solutions are for $c_2 x 50$ which lies in the chaotic regime. The first solution plotted contains the baseline values of the initial condition from Table 2. In each of the additional plots one initial condition has been increased on the order of $10^{-6}$ with respect to the initial condition. The exact values of the initial conditions that were changed are presented in Figure 6.

Figure 6 shows to what degree the trajectories diverge on the A-H attractor for the state variable $c$. Initially, the solutions are and the difference in starting conditions is unnoticeable. However, by the end of the plot at $t = 70$ it is impossible to tell the value of each individual because they are all drastically different. The small initial difference has been magnified and the trajectories in the phase space are spread out over various ranges. The lower graph in Figure 6
shows a close-up of the region \( t = 13 \) to \( 25 \) where the solutions separate. The solutions are virtually identical until approximately \( t = 17 \) at which point they begin to diverge. This is the time horizon for which accurate predictions can be made about the A-H system for \( c_2 \times 50 \). Beyond this time, all predictability breaks down and solutions that were once similar become entirely different.

![Figure 6: Sensitivity to initial conditions of A-H time series.](image)

### 6 Mathematical criteria to predict sickle cell crises

The A-H equations are able to predict sickle cell crisis state using an eigenvalue stability criteria. The mathematical analysis of the equation parameters shows that the system of equations can have two different states, stable and unstable depending on the values of the eigenvalues of the system. In terms of patient physiology a mathematical stable state corresponds to a normal functioning of the blood cells while an unstable mathematical state corresponds to sickle cell crises. These physiological conditions of patients are described by the eigenvalues of the A-H equations that depend on the equations parameters.

Thus, determining the eigenvalues at a time where updated values of the parameters are known can predict the onset of a sickle cell crisis. The eigenvalue criteria of the system equations predicts crisis and anticipates the chaotic behavior of the sickle cell disease.

The analysis of the equations parameters showed that by controlling the parameters \( b_2 \) and \( c_2 \) the dynamics of the A-H system can be driven from an stable, unstable and chaotic state. These parameters are defined as the stability parameters. Parameter \( b_2 \) is computed from the velocity of the blood flow, viscosity and stiffness of the cell. The parameter \( c_2 \) is obtained from stiffness of
the blood cell and the viscosity of the blood. The mathematical result indicates that by properly manipulating the physiological variables that define the stability parameters a sickle cell crisis in a patient could be prevented or reversed.

To predict the existence and gravity of a sickle cell crisis, the A-H model predicts a mathematical onset of a crisis or a chaotic state in a crisis according to the eigenvalue criteria and phase space of the system. A mathematical chaotic state of the system indicates uncertainty in the future behavior of the physiological parameters in a patient. It can be interpreted as a physically irreversible sickle cell crisis. A system in the onset of instability can be interpreted as a physiological state where a sickle cell crisis is starting and could possibly be prevented by means of medical treatment that targets the model variables that define the stability parameters. The model once defined unstable, provides an assessment of the degree of controllability of a crisis occurring at given time.

7 A-H model capability to assist physicians

The A-H model equations can provide important information to assist physicians in the diagnosis of sickle cell crisis. To provide an accurate assessment of the actual conditions of a patient, measurements of the four variables that define the A-H model are necessary. The computation of the system parameters and eigenvalue criteria to predict the stability are steps that can be automated by computer programs. The time to provide a result regarding to the predicted condition of an individual is of the order of minutes. As indicated in Figure 7 three possible diagnostics are provided to assist a physician.

![Figure 7: Sickle cell diagnosis diagram.](image)

The outcome of the mathematical analysis depends of the parameters b2 and c2. The parameter b2 determines if the physiological state is stable or unstable. The A-H shows that for every patient there are characteristic values of this parameter that define the stable and unstable states of the disease. For the patient...
diagnosed to be in an unstable state, the parameter $c_2$ determines if the crisis is in its onset or has already become chaotic and irreversible. Similarly as the $b_2$ parameter, characteristic values can be obtained for the $c_2$ parameter that quantify how advanced is the crisis. An onset of crisis is considered as a state where the crisis can be prevented while a chaotic state is defined as irreversible. The values of the stability parameters can be determined directly from the A-H model once the system is calibrated according to the physiology of the patient.

8 Conclusions

A mathematically rigorous definition and a clinically acceptable definition of sickle cell crises onset in capillaries have been derived and are based on the eigenvalues of the equation set in 4-dimensional phase space. Results of chaos tests proved positive for a range of the selected control parameters. The results include (a) continuous patterns found in the Poincare section, (b) spectral broadening of the Fourier power spectrum, and (c) positive Lyapunov exponent values. The mathematical prediction of chaotic onset of sickle cell blood flow crises in capillaries based on the Apori-Harris model coincides with the change from a clinically healthy person to a clinically defined crisis state for sickle cell disease. The Apori-Harris model predicts that for a patient in the onset of sickle cell crisis the stiffness of the blood cells will increase monotonically with time leading to permanent damage in the circulatory system. Our findings identify new ways to prevent and to treat crises and point to specific clinical trials.

References