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Mathematical model for the dynamics and control of sickle cell disease and its complications in a population

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Abstract: In this paper we developed a mathematical model to study the dynamics of sickle cell disease in a population. We assumed that an incidence of the disease occurs if a person inherits the disease from his parents, at first without complications, and then with time the person may develop complications. The study partitioned the population of sicklers into; Population of sicklers without complications and population of sicklers with complications. The major result of this study suggested that; a study of the genetics of the transmission mechanism of the sickle cell gene should be carried out with a view to adopt artificial selection (*that is; to counsel carriers of the sickle cell gene and full blown sicklers on marital couple selection*) to control the incidence of the disease, this will in turn control sickle cell disease in a population.

Key Words: Artificial, haplotype, selection, gene, population, sickle cell, mutation, selection coefficient (selective disadvantage)

Introduction

Sickle cell disease is an inherited genetic blood disorder that affects red blood cells. The disease is due to the mutation of the sixth position of the beta globin chain of Haemoglobin, Nikki *et al* (2008). In fact Sickle-cell disease (SCD) was the first genetic disease to be linked to the mutation of a specific protein. The disease is caused by a point mutation in the molecule haemoglobin, the active constituent of red blood cells (RBCs) that transports oxygen from the lungs to the rest of the body. Unlike the normal protein, haemoglobin A (HbA), the mutant protein, haemoglobin S (HbS), polymerizes to form filaments under deoxygenated conditions typical of the venous system, a process that is reversible upon oxygenation in the lungs. The resulting HbS polymers alter the rigidity of RBCs and can lead to the characteristic sickled cell shape associated with the disease. The stiffer RBCs slow down in the venous system where further oxygen starvation exacerbates the effect, eventually leading to vaso-occlusion, clogging, and haemostasis resulting in a crisis Cohen and Mahadevan (2013). The fundamental unit of living tissue, in fact of life itself, is the biological cell. Currently there is enormous interest in silico modeling of the cell in its many aspects. The cell is, of course, an enormously complex machine which can be understood at many levels, functional, signalling, metabolic, and regulatory levels and so on. However, there is a growing recognition that understanding its structure and the physical nature of intracellular

objects, as well as their three dimensional spatialrelationships, can yield significant insights into physiology and functionality, Venugopal (2007).

Systems biology of red blood cell is complex and researchers worldwide. An effort was successful in defining the human red cell Proteome (2004). Venugopal (2007) reported in his work that; the research done by other group indicates that current red blood cell in-silico model includes 36 dynamic, independent variables. There is still some phenomenon left, in order to extend the existing model; the most important one is deformation of shape of membrane. In every red blood cell there are 280 million molecules of haemoglobin protein, which is a long twisted strand of amino acids, having heme disk whose iron in the center attracts, carries and releases oxygen. The structure has been crystallized and its double strand has been described by Royer *et al*. (1997), Royer *et al*. (1998). Sickled cell haemoglobin (Hbs) is mutated and polymerized into long, stiff, rod-like fibre Hofrichter (1990). The genetic mutation in haemoglobin A (HbA) give rise to HbS. The consequence of this mutation is the resultant in loss of oxygen by HbS and formation of rigid14-stranded polymers. This changes the shape of the protein: a small protrusion (or dent) appears on the surface of the proteins.

Nikki *et al* (2008) in their paper 'A mathematical model for sickle cell depolymerisation: dynamical properties and numerical experiments' the mathematical model was to assess the effects of carbon monoxide (CO) on sickle cell haemoglobin (HbS) during HbS polymer melting. Assuming a buffer solution in which a mixture of HbS solution and fibres is rapidly mixed with CO, the model describes the subsequent dynamic interaction of four phases
of the HbS components. They presented stability analysis of the model in the CO-free case, the CO-saturated case and the general case. The model supports the proposition that CO binds directly to solution phase as well as polymerized HbS, and it predicts that while all the HbS becomes CO-bound at equilibrium, not all the HbS fibres are necessarily melted, indicating the presence of CO-bound fibre molecules.

Masatoshi (1975) developed a mathematical model for recessive gene frequency dynamics under the influence of selection, assuming no mutation, the model was used to study recessive gene frequency change with time, the result of his work showed that the gene frequency of recessive genes increases very slowly when it is small but very rapidly when it is large
Jeam (2007) formulated a realistic demographic model that captures the pattern of inheritance of the sickle cell gene using general pair formations. The model equation was implicitly solved via Laplace transform technique, while the existence of unique solution was proved by applying the contraction mapping principle. One of the main results is the boundedness of the solution. He concluded that; the fundamental reason for the persistence of sickle cell anaemia is probably due to the role played by the selective advantage of the abnormal sickle cell gene over the normal haemoglobin A in tropical regions, and the fact that carriers are more fertile and survive longer, because they are essentially asymptomatic.

Cohen and Mahadevan (2013) develop a multiphase model that couples the kinetics and hydrodynamics of a flowing suspension of normal and sickled cells in a fluid. They used the model to derive expressions for the cell velocities and concentrations that quantify the hydrodynamics of haemostasis, and provide simple criteria as well as a phase diagram for occlusion, consistent with their simulations and earlier observations.

Materials and Methods

Assumptions:

- ✓ The population of sicklers is finite
- ✓ Birth rate is a function of time
- ✓ Rate of developing complications is constant
- ✓ Rate of recovery from complications is constant
- ✓ Natural death rate is constant
- ✓ Artificial selection allowed
- ✓ Death due to complications is constant
- ✓ A control measure to inhibit developing complications is introduced and is constant
- ✓ Incidence of the disease occurs without complication

- ✓ Complications are developed with time after the incidence

Notations:

- ✓ $x(t)$ − − Number of sicklers without complications
- ✓ $y(t)$ − − Number of sicklers with complications
- ✓ μ − − − Natural death rate
- ✓ σ − − − Rate of developing complications
- ✓ β − − − Death due to complications
- ✓ γ − − − Rate of recovery from complication
- ✓ k − − − Control effectiveness for inhibiting complication(s) development
- ✓ $\rho(t)$ − − − Incidence (birth) rate for sicklers
- ✓ t − − − Is time

Description of the dynamics of sickle cell disease

In a population, an incidence of sickle cell disease occurs at a rate $\rho(t)$, at first without complications into $x(t)$, and then with time a person develops complications at a rate σ and moved into $y(t)$, a person may recover from complications $(y(t))$ at a rate γ back to sicklers without complication $(x(t))$. The population of sicklers without complications is affected negatively by natural death at a rate μ, and control measures through the control effectiveness parameter$k$, also the population of sicklers with complications is affected negatively by natural death at a rate μ, death as a result of complications β. The dynamics can be schematically represented as follow

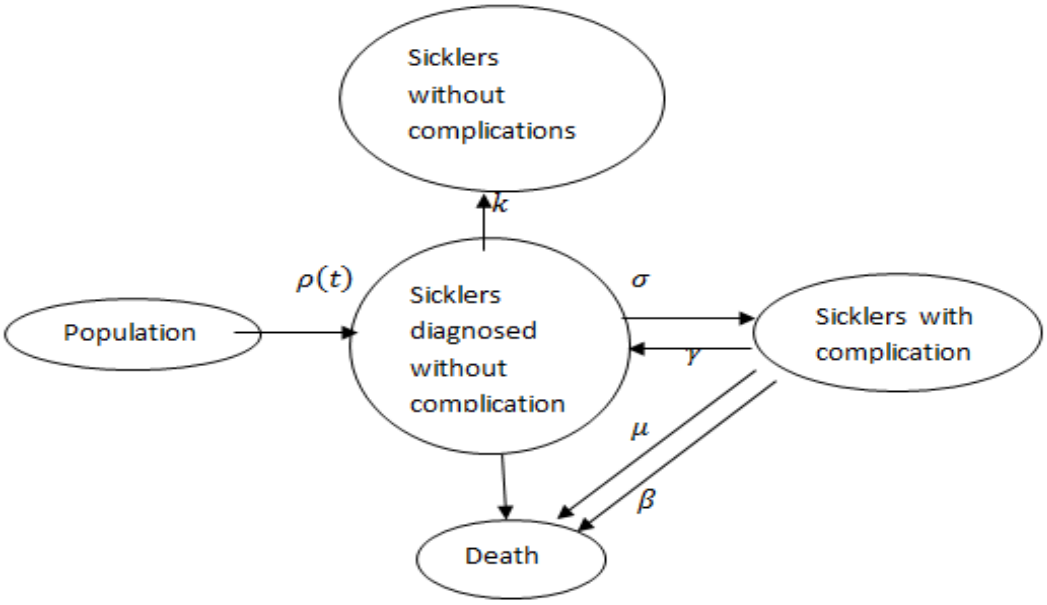


Fig. 1: Schematic diagram of the dynamics of sicklers in a population

Model development

Looking at schematic representation of the dynamics of sicklers and the description of the dynamics, we mathematically compose the dynamics as follows.

$$\frac{dx(t)}{dt} = -\sigma x(t) + \gamma y(t) - \mu x(t) - kx(t) + \rho(t) = \rho(t) - (\sigma + \mu + k)x(t) + \gamma y(t),\ x(0) = d_o$$

$$\frac{dy(t)}{dt} = \rho x(t) - \gamma y(t) - \mu y(t) - \beta y(t) \quad = \quad \rho x(t) - (\gamma + \mu + \beta)y(t) \quad y(0) = 0$$

This simplifies to the following initial value problem (IVP):

$$\frac{dx(t)}{dt} = \rho(t) - (\gamma + \mu + k)x(t) + \gamma y(t), \quad x(0) = d_o \quad - - - (1)$$

$$\frac{dy(t)}{dt} = \rho x(t) - (\gamma + \mu + \mathrm{k})x(t) + \gamma y(t), \quad y(0) = 0 - - - (2)$$

Results and Discussion

We have developed a mathematical model that describes the dynamics of sicklers in a population the model is given as;

$$\frac{dx(t)}{dt} = \rho(t) - (\gamma + \mu + \mathrm{k})x(t) + \gamma y(t), \quad x(0) = d_o - - - (1)$$

$$\frac{dy(t)}{dt} = \rho x(t) - (\gamma + \mu + \mathrm{k})x(t) + \gamma y(t), \quad y(0) = 0 - - - (2)$$

With notations as defined above

Solution for IVP

We solve the IVP analytically so as to be able to gain more insight into the dynamics of the disease and carry out sensitivity analysis. To this effect, we assume a steady state of incidence, i.e.$\rho(t) = \rho(constant)$. Differentiating the first equation with respect to t we have;

$$\frac{d^2x(t)}{dt^2} = -(\mathrm{k} + \rho + \mu)x'(t) + \gamma y'(t)$$

Substituting equation (1) & (2) and letting $\phi = \mathrm{k} + \sigma + \mu$, $\theta = \gamma + \mu + \beta$ we have

$$\frac{d^2x(t)}{dt^2} = -(\mathrm{k} + \sigma + \mu)\big(\rho - \phi x(t) + \gamma y(t)\big) + \gamma\big(\sigma x(t) - \theta y(t)\big); \quad x(0) = d_o, y(0) = 0$$

$$\Rightarrow \frac{d^2x(t)}{dt^2} = (\phi^2 + \gamma\sigma)x(t) - (\phi\gamma + \gamma\theta)y(t) - \phi\rho \quad x(0) = d_o, y(0) = 0 - - - -(3)$$

From equation (1), we have

$$y(t) = \frac{1}{\gamma}\big(x'(t) - \rho + \phi x(t)\big) - (4)$$

and

$$x(t) = x_c(t) + x_p(t) = c_1 exp(-\eta_1)t + c_2 exp(-\eta_2)t - \frac{\delta\rho}{n}$$

Next we determine the constants using the initial conditions as follows;

$$x(0) = c_1 + c_2 - \frac{\delta\rho}{n} \Rightarrow c_1 = d_0 - c_2 + \frac{\delta\rho}{n} - - - - - - - - - - - - - - - - - - (7)$$

Using (4) in (3), we have

$$\frac{d^2x(t)}{dt^2} = (\phi^2 + \gamma\sigma)x(t) - \frac{(\phi\gamma + \gamma\theta)}{\gamma}\big(x'(t) - \rho + \phi x(t)\big)$$

Let $\delta = \phi + \theta$ & $n = \phi^2 + \gamma\sigma - \theta$, we have;

$$\frac{d^2x(t)}{dt^2} + \delta x'(t) - nx(t) = \delta\rho - - - - - - - - - - - - - - - (5)$$

The complementary solution is given as

$$x_c(t) = c_1 \exp\frac{1}{2}(-\delta + \sqrt{\delta^2 - 4n})t + c_2 \exp\frac{1}{2}(-\delta - \sqrt{\delta^2 - 4n})t - - - - - - - (6)$$

Where c_1 and c_2 are arbitrary constants

The particular solution is $x_p(t) = -\frac{\delta\rho}{n}$, therefore the complete solution is:

$$x(t) = x_c(t) + x_p(t) = c_1 \exp\frac{1}{2}(-\delta + \sqrt{\delta^2 - 4n})t + c_2 \exp\frac{1}{2}(-\delta - \sqrt{\delta^2 - 4n})t - \frac{\delta\rho}{n}$$

Substituting $x(t)$ into equation (4), simplifying and letting

$\eta_1 = \frac{1}{2}\big(\delta + \sqrt{\delta^2 - 4n}\big)$, and $\eta_2 = \frac{1}{2}\big(\delta - \sqrt{\delta^2 - 4n}\big)$, we have;

$$y(t) = \frac{1}{\gamma}\Big[(-\eta_1 c_1 \exp(-\eta_1)t + (-\eta_2)c_2\exp(-\eta_2)t - \rho + \phi\Big(c_1\exp(-\eta_2)t + c_2\exp(-\eta_2)t - \frac{\delta\rho}{n}\Big)\Big]$$

$$y(0) = \frac{1}{\gamma}\left(-\eta_1 c_1 - \eta_2 c_2 - \rho + \phi\left(c_1 + c_2 - \frac{\delta\rho}{n}\right)\right) \Rightarrow c_2 = \frac{(\phi - \eta_1)nd_0 + \delta\rho\eta_1 - n\rho}{n(\eta_2 - \eta_1)} - - (8)$$

Therefore the solutions $x(t)$ & $y(t)$, which gives the number of sicklers without and with complications respectively in a population is given as:

$$x(t) = x_c(t) + x_p(t) = c_1 exp(-\eta_1)t + c_2 exp\,(-\eta_2)t - \frac{\delta\rho}{n}$$

$$y(t) = \frac{1}{\gamma}\left[(-\eta_1 c_1 \exp(-\eta_1)t + (-\eta_2)c_2\exp(-\eta_2)t) - \rho + \phi\left(c_1\exp(-\eta_2)t + c_2\exp(-\eta_2)t - \frac{\delta\rho}{n}\right)\right]$$

Where;

$$\phi = k + \sigma + \mu, \theta = \gamma + \mu + \beta, \ \delta = \phi + \theta,$$
$$n = \phi^2 + \gamma\sigma - \theta,$$

$$\eta_1 = \frac{1}{2}\left(\delta + \sqrt{\delta^2 - 4n}\right), \eta_2 = \frac{1}{2}\left(\delta - \sqrt{\delta^2 - 4n}\right), \ c_1 = \frac{(\eta_2 - \eta_1)nd_0 - (\phi - \eta_2)nd_0 + \delta\rho\eta_1 - n\rho + \delta\rho(\eta_2 - \eta_1)}{n(\eta_2 - \eta_1)},$$
$$c_2 = \frac{(\phi - \eta_1)nd_0 + \delta\rho\eta_1 - n\rho}{n(\eta_2 - \eta_1)}$$

Discussion of results

In order to discuss our results, we digitalize the parameters $k, \sigma, and\ \gamma$, (*since μ and β are rates of natural death and death due to sickle cell disease, we may not have any control over these deaths, so we exclude them in our analysis*) to have binary values for 0 (low) and 1 (high) with the following possible values;

Case I: $\sigma = 0\ and\ \sigma = 1$; Case II: $\gamma = 0\ and\ \gamma = 1$; Case III: $k = 0\ and\ k = 1$

In this respect, we have the following tree diagram

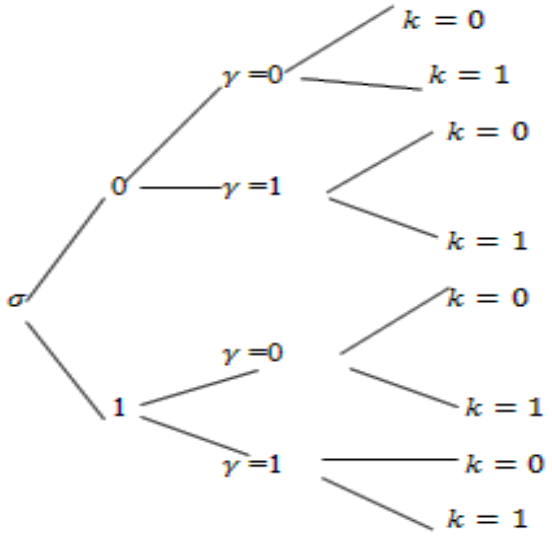


Fig: Diagram for possible values for σ, γ and k

The above tree gives eight branches with values as follows;

Branch 1: $\sigma = 0, \gamma = 0, k = 0 \Rightarrow$ Population of sicklers remain static

Branch 2: $\sigma = 0, \gamma = 0, k = 1 \Rightarrow$ Population of sicklers under artificial control

Branch 3: $\sigma = 0, \gamma = 1, k = 0 \Rightarrow$ Not possible because if $\sigma = 0$, then $\gamma \neq 1$

Branch 4: $\sigma = 0, \gamma = 1, k = 1 \Rightarrow$Artificial control, because if $\sigma = 0$, then $\gamma \neq 1$

Branch 5: $\sigma = 1, \gamma = 0, k = 0 \Rightarrow$ Population of sicklers with complications will explode

Branch 6: $\sigma = 1, \gamma = 0, k = 1 \Rightarrow$ Only artificial control and no recovery from complications

Branch 7: $\sigma = 1, \gamma = 1, k = 0 \Rightarrow$ Population of sicklers will remain without complicationswithout artificial control

Branch 8: $\sigma = 1, \gamma = 1, k = 1 \Rightarrow$ High recovery and high artificial control

Equilibrium point

At equilibrium point, we have that;

$$\frac{dx}{dt} = \rho(t) - (k+\sigma+\mu)x(t) + \gamma y(t) = 0 \text{---(9)}$$

$$\frac{dy}{dt} = \sigma x(t) - (\gamma+\mu+\beta)y(t) = 0 \text{ ---------(10)}$$

From which we obtained;

$$x(t) = \frac{(\gamma+\mu+\beta)\rho(t)}{(k+\sigma+\mu)(\gamma+\mu+\beta)-\gamma\sigma} \text{ ----------(11)}$$

$$y(t) = \frac{\sigma\rho(t)}{(k+\sigma+\mu)(\gamma+\mu+\beta)-\gamma\sigma} \text{ --------(12)}$$

Therefore the equilibrium point solutions are given by (11) and (12)

Qualitative analysis

Consider the dynamics equations;

$$\frac{dx}{dt} = \rho(t) - (k+\sigma+\mu)x(t) + \gamma y(t) = f(x,y)$$

$$\frac{dy}{dt} = \sigma x(t) - (\gamma+\mu+\beta)y(t) = g(x,y)$$

Now the Jacobian is given by

$$\begin{bmatrix} \frac{\partial f}{\partial x} & \frac{\partial f}{\partial y} \\ \frac{\partial g}{\partial x} & \frac{\partial g}{\partial y} \end{bmatrix} = \begin{bmatrix} -(k+\sigma+\mu) & \gamma \\ \sigma & -(\gamma+\mu+\beta) \end{bmatrix}$$

For the Eigen values, we evaluate the determinant of (A-λI) as follows;

Det(A- λI) =

$$\begin{vmatrix} -(k+\sigma+\mu)-\lambda & \gamma \\ \sigma & -(\gamma+\mu+\beta)-\lambda \end{vmatrix}$$

We do the computation along each branch of figure 1 as follows;

CASE 1: $\sigma = 0, \gamma = 0, k = 0$ gives

Det(A- λI) =

$$\begin{vmatrix} -\mu-\lambda & 0 \\ 0 & -(\mu+\beta)-\lambda \end{vmatrix} = (\mu+\lambda)\big((\mu+\beta)+\lambda\big)$$

Now Det(A- λI)=0, gives,

$$\lambda_1 = -\mu \text{ and } \lambda_2 = -(\mu+\beta)$$

In this case both Eigen values are both real with same sign

CASE 2: $\sigma = 0, \gamma = 0, k = 1$ gives

Det(A- λI) =

$$\begin{vmatrix} -(1+\mu)-\lambda & 0 \\ 0 & -(\mu+\beta)-\lambda \end{vmatrix} = \big((1+\mu)-\lambda\big)\big((\mu+\beta)+\lambda\big)$$

Now Det(A- λI)=0, gives,

$$\lambda_1 = \frac{-(1+2\mu+\beta)+\sqrt{\beta^2-2\beta+1}}{2} \text{ and, } \quad \lambda_2 = -\frac{-(1+2\mu+\beta)-\sqrt{\beta^2-2\beta+1}}{2}$$

λ_1, λ_2 will be real if $\beta^2 - 2\beta + 1 \geq 0 \equiv \beta^2 \geq 2\beta - 1$, this valid $\forall\, \beta \in [0,1]$, similarly λ_1, λ_2 will be complex if $\beta^2 \leq 2\beta - 1$, this is not possible since $\beta \geq 0$. Therefore λ_1, λ_2 cannot be complex.

CASE 3: $\sigma = 0, \gamma = 1, k = 0$ gives

Det(A-λI) =

$$\begin{vmatrix} -(\mu+\lambda) & 1 \\ 0 & -(1+\mu+\beta)-\lambda \end{vmatrix} = (\mu+\lambda)\big((1+\mu+\beta)+\lambda\big)$$

Now Det(A- λI)=0, gives,

$$\lambda_1 = \frac{-(2\mu+\beta+1)+\sqrt{(2\mu+\beta+1)^2-4\mu(\mu+\beta+1)}}{2} \text{ and,}$$

$$\lambda_2 = \frac{-(2\mu+\beta+1)-\sqrt{(2\mu+\beta+1)^2-4\mu(\mu+\beta+1)}}{2}$$

Now, λ_1, λ_2 will be real if $(2\mu+\beta+1)^2-4\mu\,(\mu+\beta+1)\geq 0 \equiv \beta^2+2\beta+1\geq 0$, since by definition $\beta \geq 0$, $this \Rightarrow$ $\beta^2+2\beta+1\geq 0$ is valid. similarly λ_1, λ_2 will be complex if $\beta^2+2\beta+1\leq 0$, this is not possible since $\beta \geq 0$. Therefore λ_1, λ_2 cannot be complex.

CASE 4: $\sigma = 0, \gamma = 1, k = 1$ gives

$$\lambda_1 = \frac{-(2+2\mu+\beta)+\sqrt{(2+2\mu+\beta)^2-4(1+2\mu+\mu^2+\beta+\mu\beta)}}{2} \; and,$$

$$\lambda_2 = \frac{-(2+2\mu+\beta)-\sqrt{(2+2\mu+\beta)^2-4(1+2\mu+\mu^2+\beta+\mu\beta)}}{2}$$

Now, λ_1, λ_2 will be real if $(2+2\mu+\beta)^2-4(1+2\mu+\mu^2+\beta+\mu\beta)\geq 0 \equiv \beta^2 \geq 0$

Since by definition $\beta \geq 0 \Longrightarrow \beta^2 \geq 0$ is valid $\forall\, \beta \in [0,1]$ similarly λ will be complex if $\beta^2 < 0$. Also by definition, $\beta \geq 0 \Longrightarrow \beta^2 < 0$ is not possible $\forall\, \beta$. Therefore λ_1, λ_2 must be real, with same sign or not

CASE 5: $\sigma = 1, \gamma = 0, k = 0$ gives

$$\text{Det(A-}\lambda\text{I)} = \begin{vmatrix} -(1+\mu)-\lambda & 0 \\ 1 & -(\mu+\beta)-\lambda \end{vmatrix} = \big((1+\mu)+\lambda\big)\big((\mu+\beta)+\lambda\big)$$

Det(A- λI) = 0, gives,

$$\lambda_1 = \frac{-(1+2\mu+\beta)+\sqrt{(1+2\mu+\beta)^2-4(1+\mu)(\mu+\beta)}}{2} \; and,$$

$$\lambda_2 = \frac{-(1+2\mu+\beta)-\sqrt{(1+2\mu+\beta)^2-4(1+\mu)(\mu+\beta)}}{2}$$

Now, λ_1, λ_2 will be real if $(1+2\mu+\beta)^2-4(1+\mu)(\mu+\beta)\geq 0 \Longrightarrow \beta^2 \geq 2\beta-1$, this is valid for $\beta \in [0,1]$, similarly λ_1, λ_2 will be complex if $(1+2\mu+\beta)^2-4(1+\mu)(\mu+\beta)<0$ $\Longrightarrow \beta^2 < 2\beta-1$, this is not possible $\forall$ value of β. Therefore λ_1, λ_2 must be real, with same sign or not

$$\text{Det(A-}\lambda\text{I)} = \begin{vmatrix} -(1+\mu)-\lambda & 1 \\ 0 & -(1+\mu+\beta)-\lambda \end{vmatrix} = \big((1+\mu+\beta)+\lambda\big)\big((1+\mu)+\lambda\big)$$

Now Det(A- λI)=0, gives,

CASE 6: $\sigma = 1, \gamma = 0, k = 1$ gives

$$\text{Det(A-}\lambda\text{I)} = \begin{vmatrix} -(2+\mu)-\lambda & 0 \\ 1 & -(\mu+\beta)-\lambda \end{vmatrix} = \big((2+\mu)+\lambda\big)\big((\mu+\beta)+\lambda\big)$$

Det(A- λI) = 0, gives,

$$\lambda_1 = \frac{-(2+2\mu+\beta)+\sqrt{(2+2\mu+\beta)^2-4(2+\mu)(\mu+\beta)}}{2} \; and,$$

$$\lambda_2 = \frac{-(2+2\mu+\beta)-\sqrt{(2+2\mu+\beta)^2-4(2+\mu)(\mu+\beta)}}{2}$$

Now, λ_1, λ_2 will be real if $(2+2\mu+\beta)^2-4(2+\mu)(\mu+\beta)\geq 0 \Longrightarrow$ $\beta^2 \geq 4\beta-4$. This is valid for $\beta \in [0,1]$. Similarly λ_1, λ_2 will be complex if $(2+2\mu+\beta)^2-4(2+\mu)(\mu+\beta)<0 \Longrightarrow$ $\beta^2 < 4\beta-4$, this is not possible $\forall$ value of β. Therefore λ_1, λ_2 must be real, with same sign or not

CASE 7: $\sigma = 1, \gamma = 1, k = 0$ gives

$$\text{Det(A-}\lambda\text{I)} = \begin{vmatrix} -(1+\mu)-\lambda & 1 \\ 1 & -(1+\mu+\beta)-\lambda \end{vmatrix} = \big((1+\mu)+\lambda\big)\big((1+\mu+\beta)+\lambda\big)$$

Det(A- λI) = 0, gives,

$$\lambda_1 = \frac{-(2+2\mu+\beta)+\sqrt{(2+2\mu+\beta)^2-4\big((2+\mu)(\mu+\beta)+1+\mu\big)}}{2} \text{ and,}$$

$$\lambda_2 = \frac{-(2+2\mu+\beta)-\sqrt{(2+2\mu+\beta)^2-4\big((2+\mu)(\mu+\beta)+1+\mu\big)}}{2}$$

Now, λ_1, λ_2 will be real if $(2+2\mu+\beta)^2-4\big((2+\mu)(\mu+\beta)+1+\mu\big) \geq 0 \Rightarrow$ $\beta^2 \geq 0,$ this is valid for $\beta \in [0,1]$ since by definition $\beta > 0$. Similarly λ_1, λ_2 will be complex if $(2+2\mu+\beta)^2-4\big((2+\mu)(\mu+\beta)+1+\mu\big) < 0 \Rightarrow$ $\beta^2 < 0$, this is not possible $\forall$ value of β. Therefore λ_1, λ_2 must be real, with same sign or not

CASE 8: $\sigma = 1, \gamma = 1, k = 1$ gives

Det(A- λI) =

$$\begin{vmatrix} -(2+\mu)-\lambda & 1 \\ 1 & -(1+\mu+\beta)-\lambda \end{vmatrix} = \big((2+\mu)+\lambda\big)\big((1+\mu+\beta)+\lambda\big)-1$$

Det(A- λI) = 0, gives,

$$\lambda_1 = \frac{-(3+2\mu+\beta)+\sqrt{(3+2\mu+\beta)^2-4(2+\mu)(1+\mu+\beta)}}{2} \text{ and,}$$

$$\lambda_2 = \frac{-(3+2\mu+\beta)+\sqrt{(3+2\mu+\beta)^2-4(2+\mu)(1+\mu+\beta)}}{2}$$

Now, λ_1, λ_2 will be real if $(3+2\mu+\beta)^2-4(2+\mu)(1+\mu+\beta) \geq 0 \Rightarrow$ $1-2\beta+2\beta^2 \geq 0, \quad \equiv \beta^2 \geq 2\beta-1,$ this is valid for $\beta \in [0,1]$ since by definition $\beta > 0$. Similarly λ_1, λ_2 will be complex if $(3+2\mu+\beta)^2-4(2+\mu)(1+\mu+\beta) < 0 \Rightarrow$ $1-2\beta+2\beta^2 < 0, \equiv \beta^2 < 2\beta-1$, this is not possible $\forall$ value of β. Therefore λ_1, λ_2 must be real, with same sign or not

Interpretation of results

We first present a summary of the case discussions above as follows;

CASE 1: $\sigma = 0, \gamma = 0$, k = 0: In this case, both Eigen values as obtained are real negative $\forall \mu \in [0,1]$ *and* β $[0,1]$

CASE 2: $\sigma = 0, \gamma = 0$, k = 1: In this case, both Eigen values are real negative $\forall \mu \in [0,1]$ *and* β $[0,1]$

CASE 3: $\sigma = 0, \gamma = 1$, k = 0: In this case, both Eigen values are real negative $\forall \mu \in [0,1]$ *and* β $[0,1]$

CASE 4: $\sigma = 0, \gamma = 1$, k = 1: In this case, both Eigen values are real negative $\forall \mu \in [0,1]$ *and* β $[0,1]$

CASE 5: $\sigma = 1, \gamma = 0$, k = 0: In this case, both Eigen values are real negative $\forall \mu \in [0,1]$ *and* β $[0,1]$

CASE 6: $\sigma = 1, \gamma = 0$, k = 1: In this case, both Eigen values are real negative $\forall \mu \in [0,1]$ *and* β $[0,1]$

CASE 7: $\sigma = 1, \gamma = 1$, k = 0: In this case, both Eigen values are real negative $\forall \mu \in [0,1]$ *and* β $[0,1]$

CASE 8: $\sigma = 1, \gamma = 1$, k = 1: In this case, both Eigen values are real negative $\forall \mu \in [0,1]$ *and* β $[0,1]$

Furthermore, the equilibrium point solution for the system of equations describing the dynamics of sicklers without complications (x(t)) and sicklers with complications (y(t)) in a population are given by;

$$x(t) = \frac{(\gamma+\mu+\beta)\rho(t)}{(k+\sigma+\mu)(\gamma+\mu+\beta)-\gamma\sigma} \text{ ----------(13)}$$

$$y(t) = \frac{\sigma\rho(t)}{(k+\sigma+\mu)(\gamma+\mu+\beta)-\gamma\sigma} \text{ ----------(14)}$$

Now from the summary of cases 1-8, we see that all the Eigen values are negative real numbers, this suggest that the equilibrium point solution is a sink, i.e. all solutions $x(t)$ & $y(t)$ for all values of t > 0 will die at the equilibrium point (*see graphical picture in appendix A1*), by implication, the population of sicklers without complications and the population of sicklers with complications will stabilize around the equilibrium point.

Looking at the equilibrium point solutions (13) and (14), we see that $x(t)$ & $y(t)$ depends on the incidence rate $\rho(t)$ for particular values of $\sigma, k, \mu, \gamma \text{ and } \beta$.

Combining the results of the last two paragraphs above, we see that; to control sickle cell disease in a population we need to put the following measures in place:

1) Control the incidence of the disease in a population.

Manage sicklers so as to avoid developing complications.

Controling the incidence

We look at each measure analyze it and proffer solution As stated in our introduction, sickle cell disease is caused by a mutant recessive gene in a population, thus the sickle cell gene has to exist in a homologous form before an individual manifests the sickle cell phenotype. The individual remain a carrier if the sickle cell gene exists in a haplotype form. Thus to control the incidence of sickle disease, we model the dynamics of the sickle cell gene as follows.

Assumptions:

1. A single sickle cell associated susceptibility factor (allele(s) or haplotype(s) is assumed to express transmission distortion.
2. Let 'A_1' denote the allele(s)/haplotype(s) expressing transmission distortion and conferring increase susceptibility of sickle cell disease, while 'A_2' denote all other allele(s)/haplotype(s) in a diploid population
3. Inheritance can be mendelian or otherwise, such that for mendelian population , the probability of inheriting 'A_1' from a heterozygous (A_1,A_2) parent is 0.5.
4. Mating is random
5. Mutation is allowed to occur
6. Selection is allowed to occur
7. Generations are discrete.

Notations

X_1,X_2 - Relative frequencies of gene A_1& A_2 respectively such that X_2=1-X_1 in a generation.

W_{ij} - Fitness of the possible genotypes A_iA_j i=1,2 ; j=1,2

$\overline{W}$- Mean fitness of the population

μ_{ij} - Forward mutation for gene X_i (j→i)

μ_{ji} - Reverse mutation for gene X_i (i→j)

t - Time(in generation)

s - Selection coefficient (selective disadvantage)

t_0 - Initial time

X_0 - Initial frequency at time t_0

Modelling

From the contributions by Red'ko (1998) and Masatoshi (1975), and adopting the notations by Masatoshi (1975), we can deduce that; the evolutionary dynamics of the population in terms of the gene frequencies denoted here by $\tilde{X_i}$ *(i.e. gene frequency change from generation to generation)* is:

i) Proportional to genotype selection proportion of organisms in accordance with their fitness relative to gene X_i, i=1,2.

ii) Proportional to mutation contribution,

iii) And inversely proportional to mean fitness of the population

Mathematically, we put it as (*denoting gene frequency in the next generation by* $X_1^{\sim}$)

$$X_i^{\sim} = p[\text{Genotype selection proportion of organism in accordance with their fitness} + \text{proportion for mutation contribution}] * \frac{1}{\text{Mean fitness of the population}}$$

$$X_i^{\sim} = \left(\sum_{j=1}^{2}\frac{1}{j} * JX_iX_jW_{ij} + \sum_{j=1}^{2} X_j\mu_{ij} - \sum_{j=1}^{2} X_i\mu_{ji}\right)\Big/\overline{W};\ \text{where } p \text{ is the proportionality constant}$$

$$= \frac{1}{\overline{W}}\left((X_1^2W_{11} + \tfrac{1}{2}*2X_1X_2W_{12}) + X_2\mu_{12} - X_1\mu_{21}\right);\ \because \mu_{11} = 0$$

Now the amount of change in gene frequency from one generation to the immediate next generation is given by;

$$\Delta X_1 = X_1^{\sim} - X_1$$
$$= \frac{1}{\overline{W}}\{X_1(1-X_1)[X_1(W_{11}-W_{12}) + (1-X_1)(W_{12}-W_{22})] - \mu_{21}X_1 + \mu_{12}(1-X_1)\}$$

--(15)

Since $\overline{W} = X_1^2W_{11} + 2X_1(1-X_1)W_{12} + (1-X_1)^2W_{22}$, we have;

$$\Delta X_1 = \frac{X_1(1-X_1)}{2\overline{W}}\frac{d\overline{W}}{dX_1} - \frac{\mu_{21}X_1 + \mu_{12}(1-X_1)}{\overline{W}} \text{----------(16)}$$

Now If selection coefficients are small; $\overline{W} \cong 1$ & ΔX_1 is small, then we have;

$$\lim_{\Delta t\to 0}\frac{\Delta X_1}{\Delta t} = \frac{dX}{dt} = X(1-X)[X(W_{11}-W_{12}) + (1-X)(W_{12}-W_{22}) - \mu_{21}X + \mu_{12}(1-X)$$

ΔX_1 depends on the relative values of W_{11}, W_{12}, W_{22} and not their absolute values.

Since sickle cell gene is recessive, In line with Masatoshi (1975), we have for recessive gene, W_{11}*= 1,* W_{12}*=* W_{22}*=1-s,* where s is the selection coefficient for the sickle cell gene. In this case, we have;

$$\lim_{\Delta t\to 0}\frac{\Delta X_1}{\Delta t} = \frac{dX}{dt} = X^2(1-X)s - \mu_{21}X + \mu_{12}(1-X)$$
$$= sX^2 - sX^3 - kX + \mu_{12};\ \text{where } k = \mu_{12} + \mu_{21}$$

Since μ_{12}(forward mutation) is of order 10^{-5}/generation, and because of the reccessivity of the sickle cell gene, the term μ_{12} can be eliminated to simplify algebraic treatment without lost of generality. Thus we have

$$\frac{dX}{dt} = sX^2 - sX^3 - kX = sX^2(1-X) - kX \text{----------(17)}$$

Equation (17) is the required equation (Differential Equation) that describes the recessive sickle cell gene frequency dynamics over time t.

Solution of the Resultant Differential Equation

Consider the differential equation (17)

Separating variables and integrating, we have;

$$\int \frac{dX}{sX^2(1-X) - kX} = \int dt \text{----------(18)}$$

Now;

$$\frac{1}{1-X} = \sum_{k=1}^{\infty} x^k \Rightarrow 1 - X = \frac{1}{\sum_{k=1}^{\infty} x^k} \cong 1, \because \sum_{k=1}^{\infty} x^k \to 1\ \forall\ |x| < 1.$$

$$We\ have\ \int \frac{dX}{sX^2(1-X) - kX} = \int \frac{dX}{sX^2 - kX} = \int dt$$

$$\equiv -\frac{1}{k}(\ln X + C_1) + \frac{1}{k}(\ln(sX-k) + C_2) = (t + C_3) \text{------(19)}$$

Let $-C_1 + C_2 - kC_3 = \ln X_0 - \ln(sX_0 - k)$, (6) becomes

$$-\ln X + \ln(sX-k) + \ln X_0 - \ln(sX_0 - k) = kt$$

$$\equiv \ln\frac{X_0(sX-k)}{X(sX_0-k)} = kt \equiv \frac{X_0(sX-k)}{X(sX_0-k)} = e^{kt}$$

thus

$$X(t) = \frac{k}{\left(s - \left(s - \frac{k}{X_0}\right)e^{kt}\right)} \text{----------(20)}$$

$\frac{K}{X_0}$ is a fraction of the sum total mutations determined by the initial sickle cell gene frequency X_0. $\frac{K}{X_0}$ can be considered as a

measure of recessivity of the sickle cell gene in a population.

Solving for t, we have;

$$t = \frac{1}{k}\ln\left(\frac{sX-k}{X\left(s-\frac{k}{X_0}\right)}\right) \text{----------(21)}$$

Equation 21 gives the time it will take to achieve certain sickle cell frequency, given the values of k, s & X_0.

Sensitivity analysis

In this section of the work, we give a graphical sensitivity analysis with respect to the selection coefficient, s, i.e. to investigate how the gene frequency X_0 changes with changing hypothetical values of the selection coefficient, s.

Now

$$\mu_{12} \cong 0.5 * 10^{-5}(in\ the\ order\ of\ 10^{-5})\ \&\ \mu_{21} = \frac{1}{10}\mu_{12}$$

; Masatoshi (1975), thus k = $\mu_{12} + \mu_{21} = 0.55 * 10^{-5}$. Applying different values of s to equation 20 with X_0=0.01, k=0.0000055 for t=1000 (generations), we generated the gene frequency table in appendix A2 and plotted the following graph. We also study the behavior of the solution X(t) of the D.E. by looking at the effect of the values of the selection coefficient S with respect to the

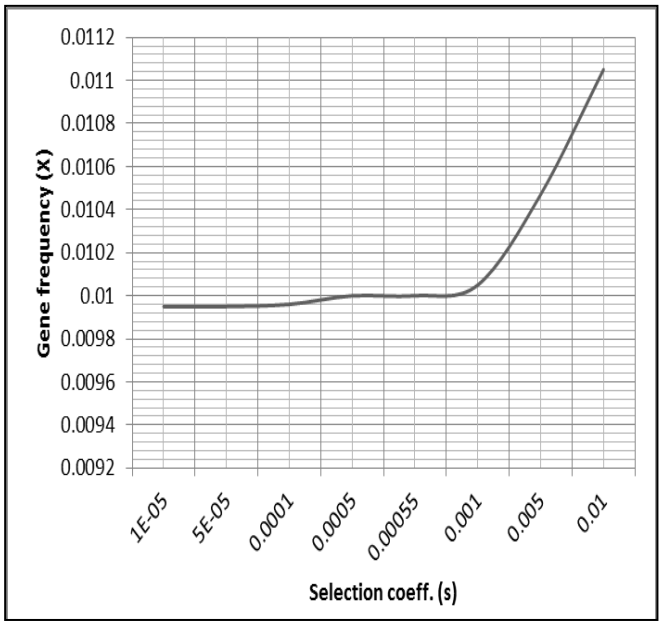


Fig 2: Graph of gene frequency (X) change with change in selection coefficient (S)

measure of recessivity $\frac{k}{X_0}$ of the sickle cell under the following cases;

CASE I: S<$\frac{k}{X_0}$, CASE II: S=$\frac{k}{X_0}$, CASE III: S>$\frac{k}{X_0}$, CASE IV: S=0 , CASE V: S=1

CASE I: S < $\frac{k}{X_0}$, *(Meaning, selection coefficient is less than the measure of recessivity of the sickle cell),* then,

$$S - \left(S - \frac{k}{X_0}\right)e^{kt} \to \infty\ as\ t \to \infty$$

$$\Rightarrow X(t) \to 0, i.e.\ if\ the\ selection\ coefficient\ S\ is\ less\ than\ \frac{k}{X_0},\ then\ the\ diabetic\ gene\ frequency\ X(t)\ decreases\ with\ time\ t$$

CASE II: S = $\frac{k}{X_0}$, *(Meaning, selection coefficient is equal to the measure of recessivity of the sickle cell),* then

$$\left(s - \frac{k}{X_0}\right)e^{kt} = 0 \Rightarrow X(t) = \frac{k}{s} = \frac{k}{k}X_0 = X_0$$

This means if the selection coefficient s=$\frac{k}{X_0}$, then the sickle cell gene frequency X(t) will be constant over time.

CASE III: S > $\frac{k}{X_0}$, *(Meaning, selection coefficient is greater than the measure of recessivity of the sickle cell),*clearly S > S - $\frac{k}{X_0}$

since S > 0, $\Rightarrow$ S – (S - $\frac{k}{X_0}$) > 0

Also $e^{kt} > 0 \Rightarrow$ (S - $\frac{k}{X_0}$) e^{kt} > 0

Since t varies from 0 to ∞ i.e. $t \in [0, \infty) \Rightarrow$ (S - $\frac{k}{X_0}$) e^{kt} < (S - $\frac{k}{X_0}$) e^{kt_1} $\forall$ $t_1 > t > 0$; Thus:

i) $S - \left(S - \frac{k}{X_0}\right)e^{kt} > 0, \forall t \in \{t | t < t^* \ \& S > (S - \frac{k}{X_0})\, e^{kt}\}$

This means that the effect of the measure of recessivity is suppressed by total mutation rate k, with time via the exponential term e^{kt}. In this case

$$X(t) \to 1 \ as \ t \to t^*$$

ii) $S - \left(S - \frac{k}{X_0}\right)e^{kt} = 0, \ for \ a \ value \ of \ t = t^* \ such \ that \ S = (S - \frac{k}{X_0})\, e^{kt}$

This means that the effect of the measure of recessivity is balanced up by total mutation rate k, with time via the exponential term e^{kt}.

iii) $S - \left(S - \frac{k}{X_0}\right)e^{kt} < 0, \forall t \in \{t | t > t^* \ \& S < (S - \frac{k}{X_0})\, e^{kt}\}$

This means that the effect of the measure of recessivity cannot be suppressed by total mutation rate k, with time via the exponential term e^{kt}.

Therefore

$$S - \left(S - \frac{k}{X_0}\right)e^{kt} = \begin{cases} = 0, & for \ t = t^* \ such \ that \ S = \left(S - \frac{k}{X_0}\right)e^{kt} \\ > 0 \ \& \lim_{t \to \infty} \left(S - \left(S - \frac{k}{X_0}\right)e^{kt}\right) \to 0 \ \forall t < t^* \ such \ that \ S > \left(S - \frac{k}{X_0}\right)e^{kt} \\ < 0 \ \& \lim_{t \to \infty} \left(S - \left(S - \frac{k}{X_0}\right)e^{kt}\right) \to -\infty \forall t > t^* \ such \ that \ S < \left(S - \frac{k}{X_0}\right)e^{kt} \end{cases}$$

By implication;

$$X(t) = \begin{cases} Underfined, & for \ t = t^* \\ \to 1, on \ the + ve \ X(t) \ axis & as \ t \to t^* \\ \to 0 \ on \ the - ve \ X(t) \ axis, & as \ t(> t^*) \to \infty \end{cases}$$

i) **CASE IV:** s=0, $X(t) = \frac{k}{\left(\frac{k}{X_0}\right)e^{kt}} \Rightarrow \frac{X_0}{e^{kt}}$

In this case;

$\lim_{t \to \infty} X(t) = 0$

ii) **CASE V:** s=1, $then, X(t) = \frac{k}{1 - \left(1 - \frac{k}{X_0}\right)e^{kt}}$

> 0 if $e^{kt}\left(1 - \frac{k}{X_0}\right) < 1.$

$$i.e. \ t < \frac{1}{k} \ln \left(\frac{1}{1 - \frac{k}{X_0}}\right)$$

Discussion

1. Figure 2 summarizes the effect of the dynamics of selection coefficient S, on the gene frequency X(t). It shows that the gene frequency increases with increase in the value of selection coefficient S.
2. From the behavior of the solution X(t) of the differential equation, CASES I-V, we deduce that to reduce the incidence of sickle cell, we need to reduce the sickle cell gene frequency to a value below the measure of recessivity $\frac{k}{X_0}$, i.e. S must be less than $\frac{k}{X_0}$ (i.e. S < $\frac{k}{X_0}$) for the sickle cell gene frequency X(t) to drop progressively over time t, thus reducing the incidence of sickle cell.

Summary

From the above results and discussions, we deduce the follows;

1. The optimal method of controlling sickle cell disease is to:
   Manage the dynamics of the sickle cell gene frequency by reducing the selection coefficient, S, which will in turn reduce the sickle cell gene frequency in the population over generations, thus making individuals of the population more fit.
1. Manage and retard the rate of developing complications of the disease (sickle cell)

In summary, a mathematical model for the dynamics of sicklers (without and with complications) in a population under the influence of artificial selection and mutation was developed. The result of the work suggested that;

1) We need to control the incidence of sickle cell disease by way of introducing artificial selection based, in addition to natural selection, on sickle cell gene screening to control sickle cell disease.
2) We need to manage sufferers of the disease (sickle cell) with a view to reduce the rate of developing complications, and to reverse and recondition sicklers with complications until natural death.

Conclusion

From the above preliminary results & discussions, we conclude that;

i) We need to control the incidences of sickle cell through reducing the selection coefficient S. This can be done by adopting the following strategies;
ii) Avoid inbreeding by way of introducing artificial selection based (in addition to natural selection) on sickle cell sufferers.
1) Genetic screening to detect carriers so that couples that carriers of the sickle cell will be counseled not to marry.
2) Avoid exposing individuals dangerous radiations that can cause genetic mutation

Also any population with selection coefficient S=0.0005 and below & initial gene frequency of X_0=0.01, will experience a steady sickle cell gene frequency decrease with time.

References

Cohen S. I. A. and Mahadevan L. (2013) Hydrodynamics of Haemostasis in Sickle-Cell Disease, *Physical Review Letters* (PRL) 110 (138104) Pp 138104-1 to 138104-5

Goodman, S. R., Kakhniashvili, D. G., Bulla, L. A. (2004). The human erythrocyte proteome: analyses by iron trap mass spectrometry. *Mol. Cell Proteomics*, 3(5):501-509.

Hofrichter, J., Eaton, E.A (1990). Sickle cell haemoglobin polymerisation. *Adv. Protein Chemistry*, 273:40-63.

Jeam T. (2007) Theoretical population dynamics model of genetically transmitted disease: Sickle cell anaemia, *Bulletin of Mathematical Biology*, 69:699-730

Masatoshi N. (1975) Molecular Population genetics and evolution; north Holland research monographs, *Frontiers of Biology* vol. 40

Nikki D. J., Mingxiang C., Dominic P. C., Gregory G. (2008). A mathematical model for sickle cell depolymerisation: dynamical properties and numerical experiments. *International Journal of Qualitative Theory of Differential Equations and Applications*. 2(2): 183–200

Red'ko V.G. (1998); Mathematical methods of population genetics; Principia cybernetic Web.

Royer, W.E, Harrington, D.J., Adachi, K (1997). The high resolution crystal structure of deoxyhemoglobin. *S. J Mol Biol*., 272(3): 398-407.

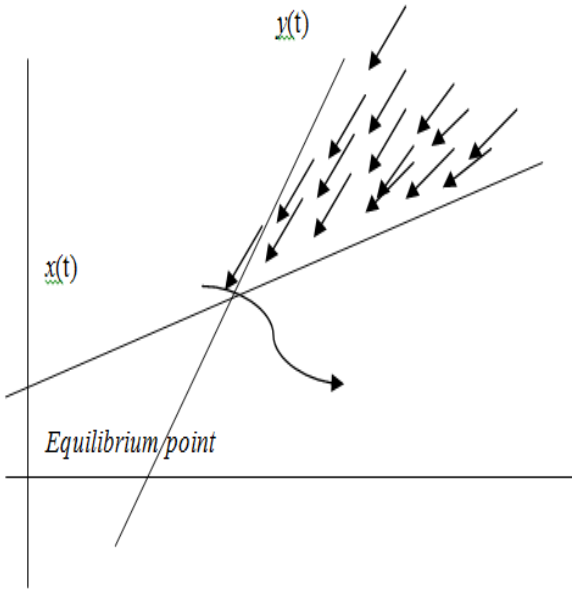
Royer WE Jr. Harrington DJ, Adachi K (1998) Crystal structure of deoxy-human haemoglobin beta6. implications for the structure and formation of the sickle cell. *J Biol Chem*., 273(49): 32690-32696.

Venugopal V. (2007). Supercomputer Education Research Centre Indian Institute of Science Bangalore – 560012, Master's thesis in Computational Science.

Appendix A1: (A sketch of the direction of motion for $x(t)$ & $y(t)$

Sketching the graph of the null clines and using the Eigen values of the system of equations that describe the dynamics of $x(t)$ & $y(t)$, we have;

Fig. 1: A sketch of the direction of motion for $x(t)$ & $y(t)$



Appendix A2 (Showing generated gene frequency as a function of selection coefficient S)

Table 1: Showing generated gene frequency as a function of selection coefficient S

Selection coefficient S	Gene freq. X(t)
0.00001	0.00995
0.00005	0.00995
0.0001	0.00996
0.0005	0.01
0.00055	0.01
0.001	0.01005
0.005	0.01047
0.01	0.01105