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Comments of Sickle cell aneamia through variational and oscillatory methods

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ABSTRACT

In the present paper, the theoretical computation of minimum oxygen concentration that a sickle red blood cell (SRBC) can absorbed during vaso-occlusion is made through variation principle and analysis of harmonic and an harmonic oscillators. The concentration of oxygen is found to follow circular functional path which oscillates about a point in comfort zone. Hence there exist some kind of dependence between the crystalline behaviors of the SRBC and oscillatory property of harmonic and an harmonic vibrators. The blood of a sickle blood system is found to be both mechanical and quantum mechanical systems and vaso-occlusion principle is the determining factor for the assertion.

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Introduction

Sickle Cell aneamia (SCA) is a genetic disorder commonly found among the black race especially American Negroes, Africans and the people of the Mediterranean countries.SCA is one of frequent child mortality in the sub-Saharan Africa where children with this ailment hardly survive beyond 5 years and very few survive beyond 18 years. In the West where there is improved medical care, the life expectancy for SCA patients is very high. Platt et.al [13]. Studied the life expectancy and risk factor for early death of SCA patients and found that median age at death was 42 years for men and 48 years for females and SCA patients with heamoglobin C median age at death was 60 years for men and 68 years for females.

Sickle cell anemia (SCA) is caused by a "defective" allele (mutant form) of the gene coding for a sub-unit of the haemoglobin protein. Haemoglobin binds oxygen within red blood cells, which then transport the oxygen to body tissues where it is released from the haemoglobin molecule. The sickle haemoglobin (in a person with a mutant allele) tends to precipitate, or "clump together", within the red blood cell after releasing its oxygen. If the clumping is extensive, the red blood cell assumes an abnormal "sickle" shape. These sickle red blood cells blocks the blood vessels, thus preventing the passage of normal red blood cells through the blood vessels(see[4]) .This consequently deprived the tissues with needed oxygen ([4],[17]&[21]).This often lead to destructions of vital organs such as kidney, liver and lungs of the patient which eventually lead to stroke ([13],[17]&[21]).

SCA is associated with a multitude of medical complications ranging from acute painful crises caused by the damage to the spleen, kidneys, lungs, heart, muscles and brain as mentioned above. The patient undergoes repeated hospitalization for intravenous pain medication, antibiotic therapy and blood transfusions to treat medical problems that arises ([4]).

SCA patients often die of overwhelming infection or acute or chronic damage to the body organs ([13], [17] & [21]).Under certain situations, it was found that SCA patient's the blood forms ($Hb-O_2-NO$) crystals whose behaviors was approximated by harmonic oscillators. The concentration of oxygen in the blood was found to be oscillatory and falls to zero at some points in the blood vessels. The principle of exclusion ([8],[10]&[11]) and crystal geometry were used to analyze the model. It was suggested that a good drug for SCA should be such that the Womersley number must be high([12b]).

Furthermore, it was noted that sickle red blood cells tend to polymerize to form crystals then the concentration of oxygen tends to be negligible as deoxygenated blood tends to obstruct the blood vessel. The vaso-occlusion principle is said that have happen. This is the most dangerous situation in the life circle of SCA patient that must always be avoid. If we regard the coupling of Hb – O_2 – No as harmonic oscillator as crystals are being formed and no nitric oxide yielding drugs applied to the patient, then $N=0$ and because of the difficulty in absorbing oxygen by the blood The Womersley number for the models being $W_N = R\sqrt{\frac{\beta}{\nu}}$ where R is the radius of the blood vessel, β is the angular frequency of the oscillatory crystal formed by the blood and *v* is the kinematic viscosity of the blood. We expect the viscosity of the blood to increase as the blood polymerized to form crystals, therefore, for good drug; it is advisable that W_N should be high for the blood to be less viscose.

Statement of Problem

2.1 Impulsive Sickle Cell aneamia model

$$\frac{\partial C(t,x)}{\partial t} = D\frac{\partial^2 C(t,x)}{\partial x^2} - kC(t,x)H(t,x), x \neq x_k, \mathrm{k} = 0,1,2,... \quad (1)$$

$$\frac{\partial H(t,x)}{\partial t} = kC(t,x)H(t,x), x \neq x_k, \mathrm{k} = 0,1,2,... \quad (2)$$

$$C(t, x = x_k) = I(x_k) \quad (3)$$

For $0 < x < L, t > 0$ satisfying the initial - boundary condition

$C(0,x) = g(x)$ (4)

$H(t,0) = H_0$ (5)

$H(0,L) = H_L$ (6)

For $0 < x_1 < x_2 < x_3 < ... < x_k, \lim_{k\to\infty} x_k = \infty$

Where $C(t,x)$ is the concentration of oxygen at time t and x distance along the blood vessel.

$H(t,x)$ is the concentration of the haemoglobin at time t and x distance along the vessel

D and k is the coefficient of diffusion of oxygen across the cells and the coefficient of association of oxygen and haemoglobin respectively.

We assume that *C(t,x)* and *H(t,x)* satisfy all the usual regular conditions that allow the existence and uniqueness of solution of equations (1-6)(see [11]&[12b]).

In the Lungs of SCA patients, $4O_2 + Hb \xrightarrow{lungs} H_bO_8$ .The oxygen molecules O_2 diffuses through the membrane with diffusion coefficient D and combine with haemoglobin molecules to form the product oxygenated blood $4O_2 + Hb \xrightarrow{k} H_bO_8$ where *k* is the oxygenation rate. We assume have that $\frac{\partial C(t,x)}{\partial t}|_{(L,t)} = -\frac{D}{x}\frac{\partial C(t,x)}{\partial x}|_{(L.t)}$ where $C(t,x)$ is the concentration of oxygen in the haemoglobin at time t and distance x along the blood vessel of length *L* and *D* is diffusion constant. Using the mass-action law, the conservation of mass and impulsive theoretic we have the impulsive Fokker-Planck equation in equations (1-3) with impulsive absorption of oxygen by haemoglobin being described by the equation (3).

Comfort zone

The set $\Omega_c = \{(H,C,N) \in R^3_+ :| C | + | H | + | N |< r, r \in R^+\} \subseteq R^+$ will called comfort zone.

The comfort zone can be interpreted as the scenario in the body of the patient wherein the oxygen is absorbed in the right proportion by the sickle red blood cell in the presence of nitric oxide.

Methods

3.1 Sickle Blood system as a mechanical system

The flow of blood in the SCA patient is continuous except at some impulsive points along the blood vessels. If we assume that the interactions between the molecules of the oxygen and heamoglobin are described by spring like couple oscillators then we can treat the coupling Hb and O_2 molecules as a mechanical system with blood considered as noncompressible fluid, hence we have

$$m_{Hb}\ddot{x}_{Hb} + k_0 \cos x_{Hb} - k_1(x_{Hb} - x_{O_2}) = 0 \quad (7)$$

$$m_{O_2}\ddot{x}_{O_2} + k_1 \cos x_{Hb} - k_1(x_{Hb} - x_{O_2}) = 0 \quad (8)$$

If x_{Hb} and x_{O_2} are very small,the solution becomes

$$x_{Hb}(t) = A_a \cos(w_a t + \varphi_a) + A_s \cos(w_s t + \varphi_s) \quad (9)$$

$$x_{O_2}(t) = A'_a \cos(w'_a t + \varphi'_a) + A'_s \cos(w'_s t + \varphi'_s) \quad (10)$$

3.2 Sickle blood system as a quatum mechanical system

At critical state in the flow of blood under vaso-occlusion regime,the blood vassels are blocked by the deoxygenerated sickle cells([12b]). The blood ceases to be continuous or impulsive but in quata form,hence it will be appropriete to investigate the flow from quatum realisational point of view.If we investigate the system from a quatum mechanical system realisation.Then the Einstain's mean energy of a normal vibrating mode of a crystal with characteristic frequency ν is

$$E_T(\nu) = \frac{h\nu}{2} + \frac{h\nu}{e^{h\nu/kT} - 1} \quad (11)$$

Where h is the plack's constant,k Bostmant's constant and T is the temperature of the vibrating lattice.Then the zero-point energy for the system(T=0) is $E_0(\nu) = \frac{1}{2}h\nu$ then if t is very large we can obtain E_∞ by expanding $E_T(\nu)$ in Taylor's form as

$$E_T(\nu) = kT[1 + \frac{h\nu^2}{12kT} + O((\frac{h\nu}{kT})^2)] \quad (12)$$

Hence,passing the limit we have $\lim_{T\to\infty} E_T(\nu) = kT$.

Remark 1

In Fig.1 SCA blood are contained in the cube;in Fig.2 an oxygen molecules treated like couple oscillator in the SCA blood cells.Fig.3 the red blood cells coagulated together to block the flow of the blood in the vassels.

From our previous work see[12b],we noted that $E_T(D) = E_0(D)\deg(D)^{1-2d} vol(D)^{2/d}$ .From Toshikazu [23] the energy of crystalline solid can be physically be regarded as harmonic oscillator.Hence,we will ssume that the formation of $Hb - O - NO$ chrystals or lattice are made during the vaso-occlusive regime.

Hence

$$E(D) = \sum_{i=1}^{n} E_T(\nu_i)\deg(D)^{2/d}(\frac{4}{3}\pi r^3)^{2/d}$$

$$= (\frac{4}{3}\pi r^3)^{2/d}\deg(D)^{2/d}\sum_{i=1}^{n} E_T(\nu_i) \quad (13)$$

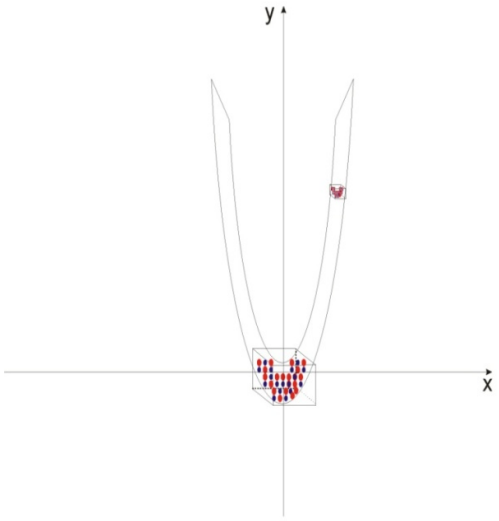

Fig 1: Sickle Cell with cubes Containing Oxygen and homoglobin molecules

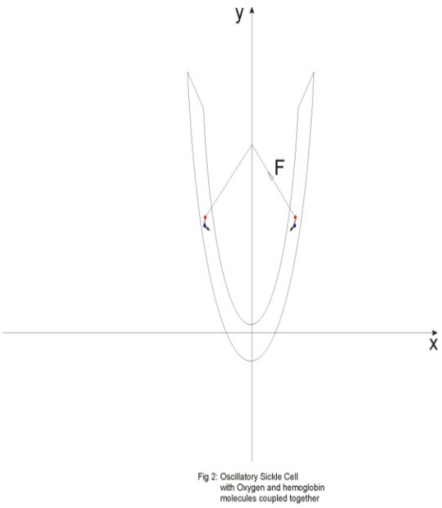

Fig 2: Oscillatory Sickle Cell with Oxygen and hemoglobin molecules coupled together

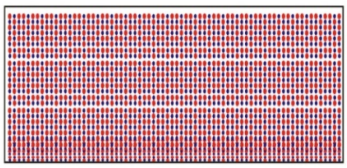

Fig 3: Schematic View of Free Oxygen in Hemoglobin

D is sphere with radius R blood cells is contained in. The position of the oxygen molecules at the time *t* and wave function for oscillation of the Oxygen in SCA blood can be calculated from the independent Schrödinger's equation

$$i\hbar^2 \frac{\partial \varphi(r,t)}{\partial t} = \frac{\hbar^2}{2m}\Delta^2\varphi(r,t) + V(r,t)\varphi(r,t) \qquad (14)$$

Where

φ is wave function of the vibrating Hb-O-No. Crystals treated as quantum system.,i^2=-1, $\hbar$ is the reduced plank constant and Δ^2 is the Laplace operator.

V(r,t) is the potential energy of the potential energy of the molecules at position *r* and time *t*.

The equation(2) can be written in Hamiltonian form as

$$E\varphi = H\varphi \qquad (15)$$

$$E = i\hbar^2 \frac{\partial}{\partial t}, H = -\frac{\hbar^2}{2m}\Delta^2 + V = -\frac{\hbar^2}{2m}\sum_i^n \frac{p_i^{\,2}}{2m} + \frac{1}{2}mw^2\sum_{(i,j)}(x_i - x_j) \qquad (16)$$

We can determine probability of the molecules at position r and time t from

$$P(r,t) = \left\{ |\varphi(r,t)|^2 : E\varphi = H\varphi \right\} \quad (17)$$

Where E and H are defined above.

Since *P(r,t)* is a probability function then

(1) $P(r,t) > 0, (r,t) \in D \times R^+$

(2) $\sum_{i=1}^{n} p(r_i,t) = 1, r_i \in D$

For n-particle non-interacting

$$E\varphi = -\frac{\hbar^2}{2}\frac{1}{m}\sum_{i=1}^{n}\frac{\partial^2}{\partial x^2}\varphi + V\varphi \quad (18)$$

The solution to the equation(16) can be obtained analytically or by numerical means using the forth order Runge-Kutta method or the Crank-Nicholson method to get the wave function for the SCA at various scenario .The probability for the molecules to exist at various positions and times can be determined from the equation (17) once the wave function from equation(16) is known.

Applying Fourier Transform we get

$$\varphi = e^{-iEt/\hbar}\varphi(r_1, r_2, ..., r_n) \quad (19)$$

For non-interacting particles

$$\varphi = e^{-Et/h}\prod_{i=1}^{n}\varphi(r_i)$$

$$V(r_1, r_2, ...r_n) = \sum_{i=1}^{n} V(r_i)$$

$$= \frac{1}{2}mw^2\sum_{(i,j)}(x_i - x_j)^2 \quad (20)$$

$w = R\sqrt{\frac{\beta}{v}}$ Where R is the radius of the blood vessel, B is the angular frequencies of the oscillatory crystal formed by the blood and *v* is the kinematic viscosity of the blood.

Numerical computation of the Schrödinger equation using forth order Runge-Kutta method:

$$\frac{\partial \varphi_j}{\partial t}|_{t=nk} = F(\varphi_j{}^n) = i\left(a(\frac{\varphi_j{}^{n+1} - 2\varphi_j{}^n + \varphi_{j-1}{}^n}{h^2}) + (V(x) + s|\varphi_j{}^n|^2) \right)\varphi_j{}^n$$

$$\varphi_j{}^{n+1} \approx \varphi_j{}^n + \frac{\delta t}{6}(k_1 + 2k_2 + 2k_3 + k_4)$$

$$k_1 = F(\varphi_j{}^n), k_2 = F(\varphi_j{}^n + \frac{\delta t}{2}k_1)$$

$$k_3 = F(\varphi_j{}^n + \frac{\delta t}{2}k_2), k_4 = F(\varphi_j{}^n + \delta t k_3)$$

$$V(x_j) = \frac{1}{2}\omega^2 \sum_{j=1}^{N} \frac{m_j}{|x_j - x_0|^2}$$

$$h = \delta x, k = \delta t,$$

The free propagations of O_2 in the blood using the Gaussian wave package is

$$\varphi(x,t) = \mu \exp\left(-\frac{(x - x_0)t^2}{2\sigma^2} \right) \quad (21)$$

3.3 Anharmonic oscillators

We can the concept of anharmonic oscillator to study the molecular vibration of crystalline sickle red blood cells under the vaso-occlusive regime .We will use the Morse potential

$$V(x) = D_e[(1 - e^{-\beta(x - x_i)^2}] \quad (22)$$

$$\text{where } \beta = \sqrt{\frac{\nu\omega^2}{2D_e}}$$

With exactly solvable using super symmetric quantum mechanics and has eigenenergies

$$E_n = -D_e + \sqrt{\frac{\hbar\beta^2}{\nu} 4D_e}(n + \frac{1}{2}) - \frac{\hbar\beta^2}{2\nu}(n + \frac{1}{2})^2 \quad (23)$$

(Recall $\omega = (k / v)^{½}$). x is the bond length and x_i is the bond length at equilibrium. D_e is the depth of the minimum in the curve

3.4 Variation Problem

Suppose we assume that a film of sickle red blood cells is contained in a spherical container. During vaso-occlusion period we can determine the shortest curve by joining two points on the sphere as follows:

$$J(y) = \int_a^b \sqrt{\cos^2 y(x) + y'^2(x)}dx \quad (24)$$

Where *x* is the longitude and *y(x)* is the latitude of the point on the curve. Our aim is to determine minimum value for J(y) using variation principle.

Results

By variation principle the minimum value of J(y) in the equation(24) can be determined from the solution of the following Jacobi equation

$$y'' + y = 0 \qquad (25)$$

And the solution is found to be $Y(x) = C\cos x + D\sin x$

Where C and D are constants of integration. Therefore ,from equation (25) the concentration of oxygen follows circular functional path which oscillates about a point in comfort zone. Hence there exist some kind of dependence between the crystalline behaviors of the SCA blood and oscillatory property of harmonic vibrator.

Conclusion

A sickle blood system has been found to be both mechanical and quantum mechanical systems vaso-occlusive principle is the determining factor for quantifying the blood system. At vaso-occlusive period the vessels are blocked by the deoxygenated blood cells which formed crystals along the vessels. On the other, for oxygenated blood to flow freely the crystals need to be deformed to allow free flow of oxygen molecules to cells, tissues and organs in body Therefore, further research work need be conducted on crystals deformation theory of sickle red blood cells from quantum mechanical point of view.

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