OXYGEN AND HAEMOGLOBIN PAIR MODEL FOR SICKLE CELL ANEAMIA PATIENTS†

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Abstract

In this paper, we studied the concentration of oxygen in the haemoglobin of the sickle cell patient using the Oxygen-heamoglobin pair (OHP) model which is an impulsive Hill-Fokker-Planck equation. Using the B-transform of Oyelami and Ake we determine the best concentration for oxygen or haemoglobin to support the patient using life-supporting drug like nitric oxide providing drugs. Since the sickle nature of the erythrocyte of the patient has the contributory factor to sickling problem and there is the need to correct this defect and to enhance the haemoglobin affinity for oxygen absorption, thereby, reducing the patient’s physiological problem. Using Lagrangian optimization method coupled with the application of simple calculus and B-transform we found that $0.5000 < c_a < (1 - 1/k)^{1/2} \ m^{-3}$ gives range of the concentration of oxygen that is required to be absorbed by Haemoglobin of the sickle cell anemia patient for effectively performance of the body. Using entropy objective function, the Lagrange function is unbounded above and could not offer much information on the optimal concentration of haemoglobin to support the patient.

Keywords: Model, Sickle cell anemia, B-transform, Oxygen and Haemoglobin.

44A20, 68W30, 35C20 & 34A37.

1. INTRODUCTION

Sickle cell anemia 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 plug the blood vessels, thus preventing normal red blood cell passage and, consequently, depriving the tissue of needed oxygen and leading to a short lived red cell survival ([5],[17]&[21]). This situation often lead to stroke as result of sequestration of blood into the lung, liver or spleen and cerebral vessels([13],[17]&[21]).

Sickle cell anemia is a genetic disorder commonly found among the black race especially American Negroes, Africans and the people of the Mediterranean countries. It is a genetic mutation problem wherein the normal haemoglobin N in the blood is replaced with a defective haemoglobin S (defective allele). Haemoglobin S is found to be extremely inefficient in carrying oxygen ([4], [5] & [17]) as a result of heterozygote advantage against malaria, the inherited haemoglobin disorders are the commonest monogenic disease ([13]). Acute pain crises may be caused by infection, dehydration, environmental temperature change, or change PH level of the blood especially if it is too acidic. Supportive therapy includes fluid hydration, analgesic, and antibiotic therapies when infection is suspected ([17]).

Sickle cell anemia is one of frequent child mortality in the sub-Saharan Africa where children with this disease hardly survive beyond 5 years and very few survive beyond 18 years. Sickle cell anemia 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. Repeated hospitalization for intravenous pain medication, antibiotic therapy and blood transfusions is undertaken to treat medical problems as they arise. These patients often die early of overwhelming infection or as a consequence of acute or chronic damage to the body organs ([13], [17] & [21]).

Recent researches from experimental point of view have it that sickle cell disease is the polymerization of deoxygenated sickle haemoglobin S, reducing red blood cell sickling is to increase red blood cell in the Hbs affinity for oxygen([2]). Moreover, research finding also indicated that low concentration of
nitric oxide with increased oxygen affinity and could serve as an alternative therapeutic model for studying sickle cell anemia ([2],[6],[13] & [21]).

There are several mathematical models on sickle cell anemia. There are models built upon the Hardy-Weinberg laws ([8],[13]) with fundamental assumption that gene frequency does not change with time that is, fixed from generation to generation. There are those models that are of stochastic origin like the HW family but fundamental developed using the idea of the birth and death processes. More recently, mathematical models using impulsive differential equations are being applied to biophysics with special applications to sickle cell anemia modeling ([8],[13]).

Impulsive differential equations are systems that are characterized by short time perturbations in form of jumps, shocks, rapid structural changes that act momentarily. This branch of knowledge was developed not quite long if we compared it to other branches of dynamical systems. The (IDEs) has found many applications in medicine, biotechnology, and pharmaceutics and so on ([1],[3]). We hope it will find useful applications in genetic engineering and computer based simulation of biomedical systems ([8-13],[18],[19]).

In ([8],[13]) using geometric and impulsive theoretic we are able to compute the blood pressure generated in the body of the sickle cell anemia patient and even established to some extent that some physiological problems of the patients are directly or indirectly connected to the blood pressure infringed on the blood vessels of the patients.

Furthermore, the sickle nature of the erythrocyte of the patient has a contributory factor to the sickle’s problem and there is the need to correct this defect and enhance the haemoglobin affinity to absorb oxygen to reduce the patient’s physiological problems ([5],[8],[13],[15] & [22]). However, bone marrow transplantation, an expensive, high-risk medical procedure, remains the only known cure for this disease ([21]).

In the modern times, several optical methods are developed to measure haemoglobin concentration of oxygen saturation and principal dyshaemoglobins in vitro and in vivo. Amongst these methods are pulse oximeters, fiber optic oximeter, multiwavelengths haemoglobin photometers (co-oximeters) and infrared spectroscopy kind of equipment ([2],[23]).

The oxygen dissociation curve (ODC) of haemoglobin (Hb) and the Bohr effect associated with the ODC because of the shift of the curve to the right as PH decreases has profound clinical importance, as it is being applied in numerous
health and disease situations. Areas of applications ODC are in the neonatal period, haemoglobinopathies such as sickle cell disease and so on ([15-17]). The ODC is sigmoid in shape with unique properties, that oxygen saturation (SaO2) approaches a horizontal asymptote as the oxygen tension exceeds 70 mmHg, while it declines precipitously down the steep slope toward a point of inflexion when the oxygen tension falls off the “shoulder” of the ODC below 60 mmHg(see[7]).

In this paper, we intend to study the blood pressure of the sickler using oxygen-haemoglobin pair; determine the absorption potential (range of absorption) of oxygen by the haemoglobin or the best concentration of oxygen in the haemoglobin if the patient is to be on life supporting drugs like nitric oxide providing drugs ([22]).

2. STATEMENT OF THE PROBLEM AND METHODS

2.1 The Model

We propose that the partial pressure exerted by the oxygen on the haemoglobin of the patient is of the form

$$P(H,C) = KH^\lambda C^\mu$$  \hspace{1cm} (1)

where H is the concentration of the haemoglobin in the blood plasma; C is the concentration of oxygen in the blood plasma; K is non-dimensional constant which can be obtained experimentally; \( \lambda \) and \( \mu \) are some dimensional constants and by simple dimensional analysis we can show that \( \lambda = 1/3 \) and \( \mu = 1 \).

We consider the oxygenation of a haemoglobin( Hb) molecule as four sequential steps, given that each of the four heme groups within the two \( \alpha \)-globin and two \( \beta \)-globin chains binds to a molecule of oxygen(O2) (see[7]) for detail formulation. The reaction process is formulated in the figure 1 below:

![Figure 1 oxygeneration of Hb by O2. Source [5]](image-url)
where $k_i, i=1,2\ldots4$ in Figure 1 are association constants, by Hill’s mass action law (see [5]&[13])

$$S_{Hbo_2} = \frac{[Hbo_2]}{[Hb]} = \frac{k_{Hbo_2}[O_2]^n}{1 + k_{Hbo_2}[O_2]^n}$$

$S_{Hbo_2}$ the saturation $Hbo_2$; $k_{Hbo_2}$ the net association constant of $Hbo_2$

$n$, is the Hill coefficient and

$$+ S_{Hbo_2} (%) = \frac{\text{Total oxyhaemoglobin}(Hbo_2)}{\text{Total haemoglobin(Hb)}}$$

, [.] is the concentration of (.)

The actual data on human Hb is $S_{a_o} = 2.0 \pm 1.1 \times 10^{-6}$ and $2.9 \pm 1.4 \times 10^{-6} m^{-1}$ for $\alpha$ – chain($k_\alpha$) and $\beta$ - chain($k_\beta$) of haemoglobin respectively ([7]).

### 2.2 B-Transform

The B-transform of the function $x(t)$ with impulses at fixed moments $\{t_k\}, k=1,2,\ldots$ during the evolutionary process is [1, 8, 10 &11]

$$B^r x(t) = x_c(q) + x_l(q)$$  \hspace{1cm} (2)

where $x_c(q)$ and $x_l(q)$ are the $L_c$ and $L_l$ components of the $B$-transform and are defined as

$$x_c(q) = L_c x(t) = \int_0^q e^{-q't} x(t)dt, t \neq t_k, k = 0,1,2,\ldots$$ \hspace{1cm} (3)

$$x_l(q) = L_l x(t) = \sum_{t_k<t<e} e^{n'/q'} I(x(t=t_k))$$ \hspace{1cm} (4)

where

$n' = 0, 1, 2,\ldots$; $n'$ is the order of the transform. For sake of simplicity, we will choose $n' = 1$. The advantage of taking $n' = 1$ lies in the derivation of the inverse transform.
The inverse transform for components of $x_c(q)$ and $x_I(q)$ can be obtained (see [8,10 & 11]) as follows:

$$x_c(t) = \frac{1}{2\pi} \int_{-\infty}^{+\infty} x_c(q) e^{iq} dq$$ \hspace{1cm} (5)

$$x_I(t) = \sum_{t_o < t_k < t} \psi(t_k, q) I(x(t_k))$$

In ([8][13]), using B-transform method we obtained the pressure the sickle red blood cell exerted on the blood vessels of the sickle cell patient as

$$P(r, x) = e^{2\pi r} P_o(r) - \delta \pi^3 x^3 e^{-2\pi p} P(r_o, P_o, \rho, u_m)$$
$$+ 4 \pi^2 x^2 e^{-2\pi r} g(A_0, x, r) + \sum_{x_o < x_k < x} e^{-2\pi x_k} f_o(\alpha, x_k)$$ \hspace{1cm} (6)

where

$$P(P_o, x, \rho, u_m) = 2 C_f \frac{x}{D} \rho u_m^2$$ \hspace{1cm} (7)
C_f = Coefficient of friction;  D = Diameter of the vessel

$u_m^2 = \text{Mean square velocity of the blood plasma}$

$A_0 = A_0(1 - e^{-rx})$ is the area cut-off as a result of sickle shape of the blood cell.

$g(A_0, x, r) = \frac{x dA_0}{dr} = x^2 e^{-rx} A_0(r)$ is the Arihall potential of the sickle red blood cell.

r is the radius of the sickle red blood cell; $\rho$ is the density of the blood

$x$ is the movement of the blood along the $x$-axis

It will be recalled (see [8]), that we stated that $x_k - x_{k+1} = f_0(\alpha, x_k)$, $k = 0, 1, 2, \ldots$ and $x_k$ depends on the surface density $\alpha$ and $f_0(\alpha, x_k)$ is a piecewise continuous function. It was also noted that $x_k$ is, in fact, impulsive because of vibration and variation effect of the texture of the composition of the surface of the sickle blood cell.

In figure 3 we try to replicate a typical sickle cell anemia blood cells as simulated by some functions

Figure 3: Typical sickle cell anemia blood cells as simulated by some functions

In figure 3 we try to replicate a typical sickle cell erythrocyte by a means of simulation. The simulation is carried out by finding the equation that describes
the area cut-off from the normal red blood cell as a result of sickle shape of the blood cell. We observed that as the thickness of the each parabola in figure 1 increases we have something that is similar to typical sickle red blood cells.

1.2 Oxygen-haemoglobin model (OHM)

Consider the Oxygen-haemoglobin model which is an impulsive Hill-Fokker-Planck equation

\[
\frac{\partial H}{\partial t} = -v_o \frac{\partial H}{\partial x} - kHC + D \frac{\partial^2 H}{\partial x^2}
\]

\[
\frac{\partial C}{\partial t} = k_1HC - \frac{k_2C^n}{1 + k_2C^n}
\]

\[
\Delta C(t = t_k, x) = \gamma_k C(t_k) + g_k
\]

Subject to initial conditions

\[
H(0, t) = H_0(t) \text{ and } \frac{\partial H(0, t)}{\partial x} = H_1(t)
\]

\[
0 < t_0 < t_1 < t_2 < ... < t_k, \lim_{k \to \infty} t_k = +\infty
\]

where

\(D\) is the diffusion coefficient; \(v_o\) is the velocity of conviction; \(x\) is the distance of the sickle erythrocyte in the blood vessel; \(k\) and \(k_1\) are rate constants due to mass action; \(k_2\) is the net association of \(HbO_2\) and \(n\) is Hill’s constant \(C = C(t, x)\) and \(H = H(t, x)\) are the concentration of \(O_2\) and \(Hb\) at time \(t\) at distance \(x\) along blood vessel.\

\(\gamma_k\) and \(g_k\) account the impulsive effect of movement of sickle blood cell as a result absorption of \(O_2\) by \(Hb\).

**Remark 1**

\(k, k_1 = 0\) The equation is the Fokker-Planck equation and \(HC\) accounts for the mass-action for the oxygen and haemoglobin respectively. The equilibrium state
for the model can be found by setting \( \frac{\partial H}{\partial t} = 0, \frac{\partial C}{\partial t} = 0 \) and \( \Delta C(t_{k+1}, x) = \text{constant} \) for fixed \( x \) in the equation (8).

Therefore

\[
H = \frac{k_2 C^{n-1}(x, t)}{1 + k_2 C^n(x, t)}
\]

And

\[
-\nu_0 \left( \frac{\partial}{\partial x} \left( \frac{k_2 C^{n-1}(x, t)}{1 + k_2 C^n(x, t)} \right) \right) - \frac{k_2 C^n(x, t)}{1 + k_2 C^n(x, t)} + D \left( \frac{\partial^2}{\partial x^2} \left( \frac{k_2 C^{n-1}(x, t)}{1 + k_2 C^n(x, t)} \right) \right) = 0
\]

Set \( n = 4, \nu_0 = -0.25, k_2 = 0.5, k_1 = 0.08, D = 0.008 \) and

\[ F(z) := \frac{(z - 1)^{0.75}}{z} \]

in the above equation we have

\[
-1.5625 \frac{d}{dz} \left( \frac{(z - 1)^{0.75}}{z} \right) + 0.004 \frac{d^2}{dz^2} \left( \frac{(z - 1)^{0.75}}{z} \right) = 0
\]

Thus

\[
-1.5625 \frac{d}{dz} F(z) + 0.004 \frac{d^2}{dz^2} F(z) = 0
\]

and the solution is

\[ F(z) = C_1 + C_2 e^{\frac{3125z}{8}} \]

where \( C_1 \) and \( C_2 \) are arbitrary constants.

But

\[
\frac{dF(z)}{dz} = \frac{0.75}{(z - 1)^{0.25}} z - \frac{(z - 1)^{0.75}}{z^2}
\]

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Therefore \( F(1) = 0, \lim_{z \to \infty} \frac{dF(z)}{dz} = 0 \) which implies that \( C_2 = 0 \) and \( C_1 = 0 \). And therefore \( F(z) = 0 \) which implies that \( z = 1 \) or infinity. It follows that the equilibrium point is such that \( H = 0, C = 0 \) and \( \Delta C(t_{k+1}, x) = \text{constants} \) and for \( C \) to be at infinity is not realistic.

2.3 Formulation of Optimization problem for the Oxygen Haemoglobin model

We intend to find the optimal concentration for the oxygen to be absorbed by the haemoglobin for the sickle cell patient for effective physiological processes. In other to achieve this we use the Lagrange multiplier method as follows:

\[
\min_x C(t, x) = kp(t, x)H^\frac{1}{2} (t, x), \text{ subject to } C(t, x) \leq \frac{kC^n(t, x)}{1 + kC^n(t, x)}
\]

(13)

We define the Lagrange equation as

\[
L(C, \lambda) = C(t, x) - \lambda(C(t, x) - \frac{kC^n(t, x)}{1 + kC^n(t, x)})
\]

(14)

We will find \( x \) and \( \lambda \) such that \( \frac{\partial L}{\partial C} = 0, \frac{\partial L}{\partial \lambda} = 0 \) that minimises \( L(C, \lambda) \).

2.4 Maximum Entropy Weights

We define \( L_e \) as a negative entropy function

\[
L_e(w_1, w_2, \ldots, w_n) = \sum_{i=1}^{n} w_i \log w_i . \text{Let } \Omega_i \text{ be convex hull of points } h_1, h_2, \ldots, h_n \text{ which contains } \mu = \frac{\sum w_i h_i}{n} \text{ and this occurs almost surely for large } n. \text{ We are now in the position to find the weight to minimize } L_e \text{ as follows:}
\]

\[
\min L_e(w_1, w_2, \ldots, w_n), \text{ subject to } \sum_{i=1}^{n} w_i h_i = \mu, \sum_{i=1}^{n} w_i = 1
\]

Let \( h_i, i = 1, \ldots, n \) are the concentration of haemoglobin at moment \( i \) and
Define the Lagrange function for the above problem as

\[ L = \sum_{i=1}^{n} w_i \ln(h_i) - \nu \sum_{i=1}^{n} w_i - \lambda \sum_{i} w_i h_i = 0. \]

We need to determine \( \nu \) and \( \lambda \) for which

\[ \frac{\partial L}{\partial h_i} = 0, \quad \frac{\partial L}{\partial \nu} = 0 \quad \text{and} \quad \frac{\partial L}{\partial \lambda} = 0. \]

### 3. RESULTS AND DISCUSSIONS

Using Maple 11 for Lagrange equation we obtained sufficient condition for extremum as

\[ \frac{\partial L}{\partial C} = 1 - \lambda \left(1 - \frac{kC^{n-1}}{(1+kC^n)} + \frac{k^2 C^{2n-1} n}{(1+kC^n)^2}\right) = 0, \quad \frac{\partial L}{\partial \lambda} = C - \frac{kC^n}{(1+kC^n)} = 0 \quad (15) \]

It implies that

\[ kC^n - kC^{n-1} - 1 = 0, \quad \lambda = \frac{1}{1 - \frac{kC^{n-1}}{1+kC^{n-1}} + \frac{k^2 nC^{2n-1}}{(1+kC^n)^2}} \quad (16) \]

The first equation in equation (16) has \( n \)-roots by fundamental theorem of algebra and some of the roots are real and others occur in complex conjugate. To find the solution in general, it is intractable but using Galois theory the solution can be found using radical expression or we find the numerical approximation to the roots. We simulated the model for \( n = 4 \) and \( k = 2.4 \times 10^{-6} m^{-1} \) found that

\[ \lambda_1 = 0.9807000, \lambda_2 = 1.02007, \lambda_3 = 0.9996 + 0.01967i \quad \text{and} \quad \lambda_4 = 0.996 - 0.01967i. \]

Where \( i^2 = -1 \).

Therefore \( \min L(C, \lambda) = 0.5000 m^{-3} \) this is the minimum concentration of oxygen required to be absorbed by Hb for effectively performance of the body.
We found that

\[ \nu = \left\{ 2 \left( \sum_{i=1}^{n} \ln(h_i) + 1 \right) + \left( \sum_{i=1}^{n} w_i \right) \right\} \times \frac{1}{n(n+1)}, \quad \lambda = -\frac{\sum_{i=1}^{n} w_i}{\sum_{i=1}^{n} h_i} \]

and therefore,

\[
L = \left( \sum_{i=1}^{n} w_i \ln(h_i) \right) - \left\{ 2 \left( \sum_{i=1}^{n} \ln(h_i) \right) + \left( \sum_{i=1}^{n} w_i \right) \left( \sum_{i=1}^{n} w_i \right) \right\} \times \frac{1}{n(n+1)}
\]

\[ + \left( \sum_{i=1}^{n} w_i \right) \left( \sum_{i=1}^{n} w_i \right) h_i \times \frac{1}{\sum_{i=1}^{n} h_i} \]

i.e.,

\[
\therefore L = \left( \sum_{i=1}^{n} w_i \ln(h_i) \right) - \frac{2 \left( \sum_{i=1}^{n} \ln(h_i) \right) + \left( \sum_{i=1}^{n} w_i \right)}{n(n+1)} + \frac{\sum_{i=1}^{n} w_i h_i}{\sum_{i=1}^{n} h_i},
\]

since \( \sum_{i=1}^{n} w_i = 1 \).

**Proposition 1**

Give that \( h_i, i = 1, \ldots, n \) are non-negative concentrations of haemoglobin at the period \( i \) such that the weight \( w_i \) are such that \( |w_i| \leq 1 \). Then

\[ |L| \leq 2 \sum_{i=1}^{n}|\ln(h_i)| + n(n+1) \]

and it is unbounded above as \( n \to \infty \).

**Proof**

Straight forward by estimating (majorizing) \( L \) and taking note that \( \sum_{i=1}^{n} |w_i| \leq \frac{n}{2} (1 + n) \).

**Remark 1**
The clinical implication of proposition 1 is that we cannot say much about the concentrations of haemoglobin as the coupling size \( n \) becomes large whether the maximum or minimum concentration exist using entropy objective function. Therefore, it is advisable to rely on the concentration of oxygen in the blood plasma as obtained from the analysis of the equations (15&16).

### 3.2 Application of B-Transform

We assume that the solution of the equation (6) exists and continuously depend on the initial data (see [12],[18-19]) then the B-transform can be applied to Oxygen-haemoglobin pair model as follows:

Equation (8) becomes

\[
\begin{align*}
k_i \frac{\partial H}{\partial t} + k \frac{\partial C}{\partial t} &= -v_0 k_i \frac{\partial H}{\partial x} + kD \frac{\partial^2 H}{\partial x^2} - \frac{kKC^n}{1 + kC^n} \\
\end{align*}
\]

Applying B-Transform we have

\[
\begin{align*}
L_c \left( \frac{\partial H}{\partial x} \right) &= \int_0^\infty \frac{\partial H}{\partial x} e^{-x/q} dq = -\overline{H_0} + \frac{1}{q} \overline{H} \\
L_c \left( \frac{\partial^2 H}{\partial x^2} \right) &= \int_0^\infty \frac{\partial^2 H}{\partial x^2} e^{-x/q} dq = -\frac{1}{q} \overline{H_0} + \overline{H_1} + \frac{1}{q} \overline{H} \\
L_c \left( \Delta C(t, x = x_k) \right) &= \sum_{x_0 < x_k < x} e^{-x_k/q} (\gamma_k C(x_k)) + g_k \\
\end{align*}
\]

Now let \( z(x) = 1 + kC^n \) for fixed \( t \) then \( L_c \left( \frac{C^n}{1 + C^n} \right) = \int_0^\infty \left( 1 - \frac{1}{z(s)} \right) e^{-x/q} dq \).

Therefore application of B-Transform to the equation (17) gives

\[
\begin{align*}
k_i \frac{\Delta H}{\Delta t} + k \frac{\Delta C}{\Delta t} &= (qv_0 k_i - kD) \overline{H_0} + qkD \overline{H_1} + (kD - v_0 k_i) \overline{H} \\
&+ \int_{\Delta t}^{\Delta t} \frac{1}{K} \left( 1 - \frac{1}{z(s)} \right) e^{-x/q} dq + \sum_{x_0 < x_k < x} e^{-x_k/q} (\gamma_k C(x_k)) + g_k \\
\end{align*}
\]

But
\[
\int_0^t \frac{\partial \overline{H}}{\partial s} \, ds = \overline{H}(t, q) - \overline{H}(0, q), \quad \int_0^t \frac{\partial \overline{C}}{\partial s} \, ds = \overline{C}(t, q) - \overline{C}(0, q)
\]

Therefore, taking the inverse B-Transform of equation (18) and after simplifying the equation we get

\[
H(t, x) = H(0, x) - \frac{k}{k_1} (C(t, x) - C(0, x)) + \frac{v_0 k t}{2 \pi i} \int \overline{q H_0}(0, q) e^{uq} \, dq
\]

\[
- k D t \overline{H_0}(0, x) + k D t \int \overline{q H_0}(0, x) e^{uq} \, dq + (k D - v_0 k_1) \int_0^t H(s, x) \, ds
\]

\[
+ \frac{1}{2 \pi i} \int_{\Omega}^{1} K(1 - \frac{1}{z(s)}) e^{-x/s + uq} \, dq + \sum_{x_0 < x_k < x} \varphi(x_k) (\gamma_k C(x_k) + g_k),
\]

where

\[
\varphi(x_k) = \frac{1}{2 \pi i} \int_C e^{q q - x_k / q} \, dq.
\]

We can use equation (1) to find the relation between \( H(t, x) \) and \( p(t, x) \) as

\[
H(t, x) = H_0(0, x) - \frac{k}{k_1} (p(t, x) H^{-\gamma}_0(t, x) - p_0(x) H^{-\gamma}_0(0, x))
\]

\[
+ \frac{v_0 k t}{2 \pi i} \int_{\Omega}^{1} q H_0(0, q) e^{uq} \, dq - k D t H_0(0, x) + \frac{k D t H_0(0, x)}{2 \pi i} u(t)
\]

\[
+ (k D - v_0 k_1) \int_0^t H(s, x) \, ds + \frac{1}{2 \pi i} \int_{\Omega}^{1} K(1 - \frac{1}{z(s)}) e^{-x/s + uq} \, dq ds
\]

\[
+ \sum_{x_0 < x_k < x} \varphi(x_k) (\gamma_k C(x_k) + g_k)
\]

where \( u(x) = \int_{\Omega} q e^{uq} \, dq = \begin{cases} 1 & \text{if } x > 0 \\ 0 & \text{otherwise} \end{cases} \).

In order to determine \( H(t, x) \) completely we need to solve the integral equation in the equation (20) completely.
The following theorem shows how the concentration of Oxygen changes with that of haemoglobin:

**Theorem 1**

The haemoglobin of sickle cell anemia patient will have maximum potential absorption if there exists a \( c^* > 0 \) such that

\[
\frac{1}{2\pi} \int_{\Omega} \frac{c^{n-1}(s, q)}{1 + k c^n(s, q)} e^{-\gamma t s + \eta q} dq ds = \frac{1}{nk} \text{ and } c^* < (1 - \frac{1}{k})^{\frac{1}{\gamma}} \tag{21}
\]

**Proof**

By differentiating the equation (20) twice with respect to C we get

\[
\frac{\partial H}{\partial C} = -\frac{k}{k_1} + \frac{kn}{2\pi} \int_{\Omega} \frac{C^{n-1}(s, q)}{1 + k C^n(s, q)} e^{-\gamma t s + \eta q} dq ds
\]

\[
\frac{\partial^2 H}{\partial C^2} = \frac{kn}{2\pi} \int_{\Omega} \frac{(n + nk C^n(s, q) - kn) C^{n-1}(s, q)}{(1 + k C^n(s, q))^2} e^{-\gamma t s + \eta q} dq ds
\]

By simple rule in calculus the proof follows immediately but we must note that if \( c^* = (1 - \frac{1}{k})^{\frac{1}{\gamma}} \) we have point of inflexion for which we cannot infer whether the absorption is maximum or minimum.

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