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Full Length Research Paper

The development of the atoms of deoxy-hemoglobin in sickle cell Anaemia: A numerical prospective

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In this paper, the Langevin equation is used to solve hemoglobin aggregation in patients of sickle cell anaemia. The resulting second order nonlinear differential equation is solved to obtain a sigmoid deformation behavior. The deformation and the absorbance satisfy the Verhulst Model of the first order which is well- known in population dynamics. A time-dependent general expression is obtained for the coefficient of viscosity and the elastic modulus that characterize the aggregation of the sickle hemoglobins. Finally, the use of a Taylor second order approximation showed the viscoelastic and the elasto-thixotropic properties of the sickle hemoglobins polymer.

Key words: Deoxy- hemoglobin S, red blood cells polymerization, shear rate, viscoelastics, thixotropy, population dynamics, absorbance.

INTRODUCTION

Sickle cell disease is characterized by a molecular hemoglobin defect which causes the polymerization of deoxygenated hemoglobins and results in reduced ery-throcyte flexibility, deformation and numerous rheologic effects. Sickle cell anaemia produces an abnormal type of hemoglobin called hemoglobin S (HbS), which has less oxygen-carrying capacity. It results when the amino acid valine is substituted for normal glutamic acid in the sixth amino acid position of the beta-globin chain of hemoglo-bin from both parents giving the molecule the abnormal structure ($_{2}{}_{2}^{S}$). When hemoglobin S is exposed to low-oxygen states, it crystallizes, distorting the red blood cells into a deformation. The abnormal cells are fragile and easily destroyed. They cannot pass easily through tiny blood vessels and block flow to various organs and tissues, causing a vaso-occlusive sickle cell crisis that can be life-threatening.

The mechanism of the polymerization of the molecules, which is the main cause of the pathology, is not clearly known. Several authors have been working on this problem. In 1974, Hofrichter, Eaton and Ross studied the polymerization mechanism associated with the kinetics of sickle cell gelation. Dejardin et al. (1985) proposed a mathematical model for the polymerization of Deoxy-hemoglobin S molecules. However, in their model they have not considered the elastic properties of the sickle hemoglobin polymers. In order to improve the previous model, Olatunji (1989) proposed to include the elasticity properties of the blood. The result was interesting but, in his model, the coefficient of viscosity and the coefficient of elasticity were constant. Several other authors (Morris et al., 2009) pointed out in their article the use of several different equations to describe the physical properties of the sickle cell hemoglobin during the gelation process. In this paper we make use of the well-known Langevin equation to solve the sickle cell aggregation dynamic. We established the expression of a time-dependent coeffi-cient of viscosity and a time-dependent coefficient of elasticity. These coefficients are then more general than the one expressed by Dejardin et al. (1985) and by Olatunji (1989). The Langevin equation has been used in the past (Park H., 2001) for tracking each particle making up an aggregate in a Brownian dynamic motion of particles. In their paper, Park et al. (2001) consider the motion caused by thermal forces and the electrostatic forces. In this paper, we consider hemoglobin molecules as particles undergoing motion due to the kinetics force proportional to the square of the speed of the particles, the spring force proportional to the deformation and the friction force proportional to the speed of the particles of

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hemoglobins S.

In other research (Kovalchuk et al., 2008) computer simulations of colloidal suspensions based on the Langevin equation helped obtain quantitative information on clustering in colloidal suspensions. In their paper, Monti et al. (2009) has proposed a model based on Langevin equation, to measure the rate of motion for cells that aggregate. There's no doubt that the Langevin equation can be applied to sickle cell hemoglobin molecules flowing in the blood and tending to aggregate.

MATERIALS AND METHODS

The experimental plots of the absorbance measured in turbidity on deoxy-hemoglobin S solutions at various concentrations in buffer phosphate and at a given pH give a sigmoid (Poyart et al., 1981; Morris et al., 2009)

Studying the kinetic aggregation of the deoxy-hemoglobin S, Dejardin et al. (1985) established the expression of the absorbance that characterizes the time evolution of the average number of molecules of deoxy-hemoglobin S that aggregate. The expression

of the absorbance then was given by $A(t) = A_\infty \left[1 + l\exp(-\alpha t)\right]^{-1/\nu}$

from which it is easy to obtain the following differential equation:

$\ddot{A} + \eta\dot{A} - (\nu+1)\frac{\dot{A}^2}{A} = 0$ where $\eta\dot{A}$ expresses the viscous properties of the blood. The insufficiencies of the model represented by the previous equation were studied by Olatunji (1989) who used the dynamical equation $\ddot{A} + \eta\dot{A} - (\nu+1)\frac{\dot{A}^2}{A} + GA = 0$, where the last term of the left side is the spring force. This equation indicates that each molecule of deoxy-hemoglobin S undergoes a set of constraints such as the viscosity of a viscous fluid in a non turbulent regime, the constraint of inertia during the polymerization and the elastic constraint of modulus G.

As we can see, in the previous model used by Olatunji (1989), the coefficient of viscosity and the elastic modulus are considered constant. However, as we know, the deformation Q(t) is a rheological variable proportional to the Absorbance. In this work, knowing that Brownian motion occurs during the polymerization process, we make use of the Langevin equation in order to better explain the motion of the molecules of deoxy-Hemoglobin S. We therefore consider the molecule of Hemoglobin S as a particle of mass m. This allows us to obtain a second order differential equation similar to the one used by Olatunji and Dejardin with the exception that this equation based on the Langevin equation has a different physical meaning and uses the fact that a Brownian motion occurs during the polymerization process. Also, the evolution equation obtained has been solved through an appropriate change of variables and the use of physical boundary conditions. The expression of the time-dependent deformation Q(t) and absorption A(t) can then be obtained.

It is interesting to introduce in the model a delay term representing the shear rate used successfully by Cushing et al. (1977). In one hand the integro-differential equation obtained

$\frac{\dot{A}}{A} = a_1 - a_2 A^\nu - a_3 \int_0^t A^\nu(s) k(t-s) ds$ can be changed into a Volterra integro-differential equation. In this paper, we solved the previous differential equation by using some kernel $k(t\ \ s)$ used successfully in mathematical biology. We found also a general expression for the coefficient of the viscosity and the elastic modulus. The case $a_3\ \ 0$ represents a special case studied by Olatunji (1989). After performing the Taylor approximation of the second order, we found an explicit form of the population of deoxy-hemoglobin S molecules as a function of time. We can therefore retrieve the viscoelastics and the elasto-thixotropic properties of the blood.

RESULTS AND DISCUSSION

In order to find the equations for the dynamics of the polymerization of deoxy-hemoglobin S molecules, let us assume m and $Q(t)$ are repectively the mass and the deformation of a molecule of hemoglobin in random motion, the Brownian motion occurs and we can apply the Langevin equation:

$$m\ddot{Q}(t) = F(t) - \gamma\dot{Q}(t)\ . \qquad (1)$$

The force exerted on the particles of hemoglobin is given by:

$$F(t) = \frac{m}{2}\frac{\dot{Q}^2(t)}{Q(t)} - kQ(t)\ . \qquad (2)$$

and the friction force exerted on the hemoglobin S in motion, $\frac{dQ}{dt}$ withthe coefficient of friction. $kQ(t)$ is the spring force and k the spring constant.

The deformation $Q(t)$ is the extra stretch of the polymer with respect to the initial position x_0 where the velocity, v_0 , is zero.

We then have the following evolution equation:

$$\ddot{Q}(t) + \eta\dot{Q}(t) - \frac{1}{2}\frac{\dot{Q}^2(t)}{Q(t)} + \omega^2 Q(t) = 0\ , \qquad (3)$$

where is the frequency of vibration of the polymer and , the coefficient of friction per unit of mass.

We can now find the solution of the evolution equation in a steady regime using the change of variable:

$$f = \frac{\dot{Q}}{Q}\ . \qquad (4)$$

We then transform the evolution equation (3) in the form of a differential equation of Riccati, that is:

$$\dot{f} = -\frac{1}{2}f^2 - \eta f - \omega_0^{\ 2} = -\frac{1}{2}(f - f_1)(f - f_2)\ . \qquad (5)$$

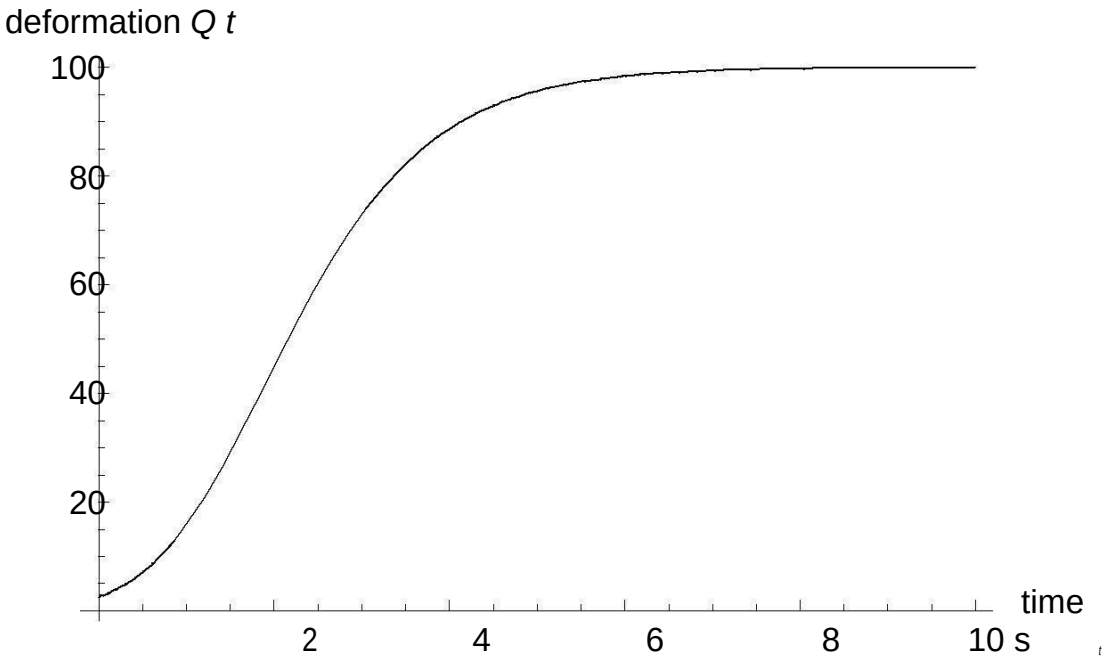


Figure 1. Evolution of the Deformation as a function of time: the deformation increases until a maximum asymptotical value Q . The plot of the deformation gives a sigmoid (Lesecq et al., 1997).

f_1 and f_2 are the roots of the quadratic equation (5).

The boundary conditions that satisfy the dynamics of the system are $\lim_{t\ 0} f(t)\ f_0$ and $\lim_{t} f(t)\ 0$.

Indeed, when the polymer is formed over a long period of time, the system of the hemoglobin molecules velocity is zero; the growth has reached its maximum and the aggregation frequency can be written:

$$f(t) = \frac{f_1 l \exp(-\alpha t)}{1 + l \exp(-\alpha t)} \ , \qquad (6)$$

where (, *l,*) are the coupling parameters of the rheological constants with the following definitions:

$$\alpha = \eta\delta \ ; \qquad \delta = [1 - \frac{2\omega_0^{\ 2}}{\eta^2}]^{1/2} \ ; \qquad (7)$$

$$l = \frac{f_0}{f_1 - f_0} \ ; \qquad f_1 = -\eta - \eta\delta \ ; \qquad \nu = \frac{\alpha}{f_1} . \qquad (8)$$

Finally, using equations (6), (7) and (8) we obtain the variation of Q as a function of time:

$$Q(t) = Q_\infty \left[1 + l \exp(-\alpha t)\right]^{-1/\nu}, \qquad (9)$$

with the condition $\lim_{t} Q(t) \quad Q$.

RESULT 1

The Graph of the time-dependent deformation $Q(t)$ gives a sigmoid (see Figure 1).

Moreover, using the Beer-Lambert Law it can be proved that the absorbance is proportional to the deformation. Therefore we can definitively write the absorbance, $A(t)$ measured in turbidity in the following form:

$$A(t) = A_\infty \left[1 + l \exp(-\alpha t)\right]^{-1/\nu} \ , \qquad (10)$$

which gives the new expression of the parameter l as

$$l \ \frac{A}{\overline{A}_0} \quad 1 \ ,$$

where $A_0\ 0$ and $A\ 0$ are respectively the values of the absorbance, $A(t)$, at t = 0 and at t = . Using equation (10), it is possible to get the following differential equations for the variable $Q(t)$ and the aggregation frequency, $f(t)$:

$$\frac{\dot{Q}}{Q} = \frac{\alpha}{\nu}\left[1 - \left(\frac{Q}{Q_\infty}\right)^{\nu} \right] \ , \qquad (11)$$

this is a first order deterministic differential equation;

$$\ddot{Q} = -\alpha\dot{Q} + (\nu+1)\frac{\dot{Q}^2}{Q} \quad , \tag{12}$$

which is a nonlinear differential equation of second order;

$$ff^2 f \, , \tag{13}$$

which is a differential equation (Riccati type) for the aggregation frequency, $f(t)$.

Finally we get for the absorbance, $A(t)$ a similar equation to (11) which is the following deterministic differential equation:

$$\frac{\dot{A}}{A} = \frac{\alpha}{\nu}\left[1 - \left(\frac{A}{A_\infty}\right)^\nu\right] = a_1 - a_2 \, \mathrm{A}^\nu \tag{14}$$

where a_1 and a_2 A with 0 .

RESULT 2

The deformation in equation (11) and the absorbance in equation (14) satisfy the Verhulst Model of the first order (Hallam et al., 1986).

To better describe the characteristics of the model in terms of molecular dynamics we will now introduce the dynamical equation with a delay term $\frac{d}{dt}$ homogeneous to a shear rate (Cushing, 1977):

$$\frac{\dot{A}}{A} = a_1 - a_2 A^\nu - \dot{\gamma}(t) \, , \tag{15}$$

Where $$\dot{\gamma}(t) = a_3 \int_0^t A^\nu(s) k(t-s) ds \, . \tag{16}$$

Finally the following equation represents the mathematical model for the kinetics aggregation of the deoxyhemoglobin S molecules:

$$\frac{\dot{A}}{A} = a_1 - a_2 A^\nu - a_3 \int_0^t A^\nu(s) k(t-s) ds \, . \tag{17}$$

The kernel $k(t \quad s)$ is a memory function (Cushing, 1977) called the heredity kernel. An integro-differential equation of Volterra type can be obtained by setting $p(t) \quad A \quad (t)$. Therefore,

$$\frac{\dot{p}}{p} = \nu \frac{\dot{A}}{A} \, . \tag{18}$$

The integro-differential equation (17) becomes:

$$\frac{\dot{p}}{p} = a - bp - c\int_0^t p(s) k(t-s) ds \, , \tag{19}$$

with $a \quad a_1 \quad b \quad a_2 \quad c \quad a_3$.

In equation (19) a represents the intrinsic growth rate r from the Malthusian model and b represents K/r where K is the carrying capacity or the population size that the available resources can continue to support in the Verhulst model. The condition $c \; 0$ in equation (19) represents the Verhulst model (Zwanzig, 1973). We will now use some examples of kernels k(t) used successfully in mathematical biology:

First example: k(t) = 1 = constant

In this case, the general dynamical model (19) reduces to the Volterra model:

$$\frac{\dot{p}}{p} = a - bp - c\int_0^t p(s) ds \, . \tag{20}$$

We observe that the shear rate takes its simplest expression, that is:

$$\dot{\gamma}(t) = c\int_0^t p(s) ds \, . \tag{21}$$

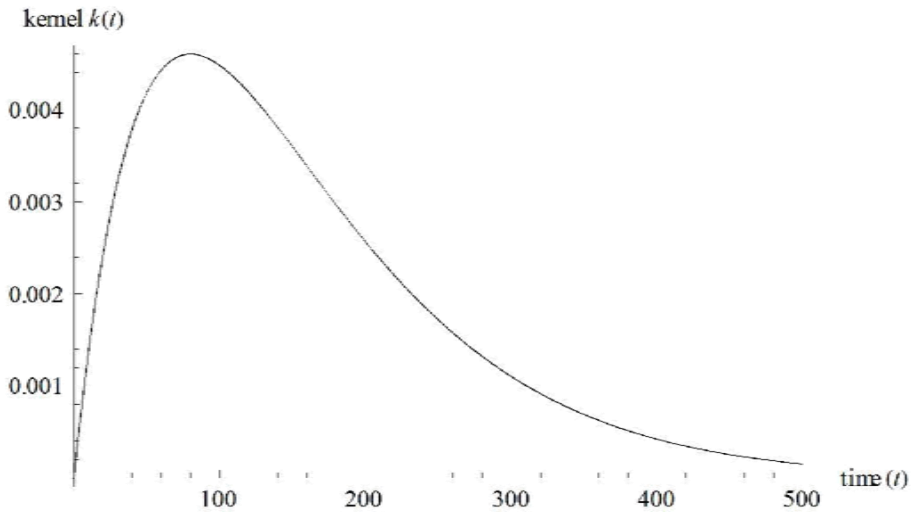
Second example: $k(t) \quad \frac{1}{T} e^{\quad t / T}$

In this example, T > 0 and has the dimension of time and

$$\int_0^\infty |k(t)| dt = 1 \, . \tag{22}$$

k(t) is the first generic kernel (Cushing, 1977) also called moderate kernel. Qualitatively, the model represents a moderate delay. The kernel decreases exponentially. This kind of kernel corresponds to the viscoelastics rheological behavior of Voigt-Kelvin materials and Maxwell simple fluids. Another example of a moderate kernel is shown in Figure 2.

We now find the mathematical model for the viscosity coefficient $^*(t)$ and the elastic modulus $G^*(t)$, we use



$$\frac{t}{640}\exp\left(-\frac{t}{80}\right).$$

Figure 2. Variation of a moderate kernel k(t) =

the general dynamical model represented by equation (17) with the shear rate $\dot{\gamma}(t) = a_3 \int_0^t A^{\nu}(s)\,ds$, we can study in detail the Volterra integro-differential equation given by:

$$\frac{\dot{A}}{A} = a_1 - a_2 A^{\nu} - a_3 \int_0^t A^{\nu}(s)ds\,. \tag{23}$$

It is possible to get from (23) an equation of evolution of second order which involves the molecular interaction forces of the form:

$$\ddot{A} + \alpha^*(t)\dot{A} - (\nu+1)\frac{\dot{A}^2}{A} + G^*(t)A = 0\,. \tag{24}$$

where *(t) is a new time- dependent friction coefficient and G*(t) is a new induced elastic modulus of the elastic force with the following definitions:

$$\alpha^*(t) = \alpha\left(1 - \frac{a_3}{a_1}\int_0^t A^{\nu}(s)ds\right) - \frac{a_3}{a_2}, \tag{25}$$

$$G^*(t) = \frac{a_3 a_1}{a_2}\left(1 - \frac{a_3}{a_1}\int_0^t A^{\nu}(s)ds\right). \tag{26}$$

It can be observed that if $a_3 \quad 0$, equations (25) and (26) lead to previous models (Dejardin et al., 1985) where the elastic modulus, G^*, was zero. As a result, equations (25) and (26) represent a more general form of the

RESULT 3

$$\alpha^*(t) = \alpha\left(1 - \frac{a_3}{a_1}\int_0^t A^{\nu}(s)ds\right) - \frac{a_3}{a_2}$$

The expressions and coefficients of viscosity and the elasticity.

$$G^*(t) = \frac{a_3 a_1}{a_2}\left(1 - \frac{a_3}{a_1}\int_0^t A^{\nu}(s)ds\right)$$

give respectively the general form of the viscosity coefficient and the elastic modulus.

We will now try to obtain the solution of the Volterra model in molecular dynamics by making the appropriate change of variable $q \int_0^t p(s)ds$ in equation (20). Using the initial conditions $q(0)\ 0$ and $p(0)\ p_0$ for the initial population, the solution of equation (20) can then be put in implicit form as follows:

$$p = \omega(q) = \frac{a}{b} + \frac{c}{b^2} - \frac{c}{b}q - \left(\frac{a}{b} + \frac{c}{b^2} - p_0\right)e^{-bq}, \tag{27}$$

with

$$t = \int_0^q \frac{ds}{\omega(s)} \tag{28}$$

For $p_0\ a/b$, (q) presents a maximum and tends to zero (extinction); but for $p_0\ a/b$ there is no maximum for (q); however, there's an extinction of the population. This paper considers all values such that

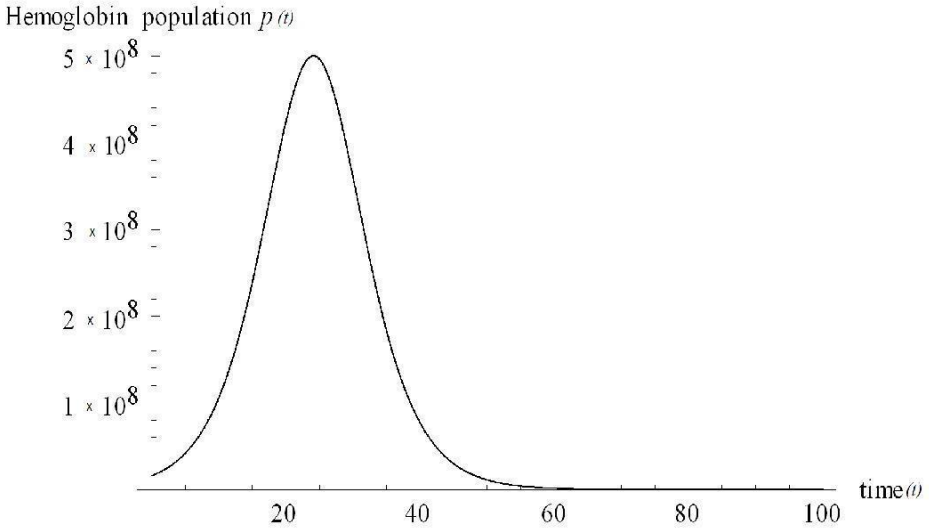


Figure 3. Evolution of the population of Hemoglobins as a function of time for q_1 0 and q_2 0

p_0 a / b where there is both maximum and extinction.

In such conditions, the coordinates of the maximum are given by:

$$p_m = \frac{a}{b} - \frac{c}{b^2}\ln\left(\frac{ab + c - p_0 b^2}{c}\right), \tag{29}$$

$$q_m = \frac{1}{b}\ln\left(\frac{ab + c - p_0 b^2}{c}\right). \tag{30}$$

We can also find the explicit solution to the integro-differential equation by Taylor's approximations. The first order approximation consist of setting

$$e^{-bq} = 1 - bq. \tag{31}$$

Therefore we have directly p as a function of time t:

$$p(t) = p_0 e^{\lambda t}, \tag{32}$$

with $\lambda = a - p_0 b > 0.$ (33)

Equation (32) represents the Malthusian model in population dynamics which, as we know, is not quite realistic. In the second order approximation we use,

$$e^{-bq} = 1 - bq - \frac{1}{2}b^2 q^2. \tag{34}$$

Equation (27) becomes:

$$p = \omega(q) = p_0 + (a - p_0 b)q - \frac{1}{2}(ab + c - p_0 b^2)q^2 \tag{35}$$

Equation (35) can be put in the equivalent following form:

$$p = \omega(q) = p_0 + \lambda q - Bq^2, \tag{36}$$

where $B = \frac{1}{2}(ab + c - p_0 b^2)$.

The discriminant of equation (36) is given by $4Bp_0$ and p can be written:

$$p = \omega(q) = -B(q - q_1)(q - q_2), \tag{37}$$

where q_1 and q_2 are the roots of the quadratic equation (36).

It is then possible to find $q(t)$ and $p(t)$ explicitly as follows:

$$q(t) = \frac{q_1 q_2[1 - e^{B(q_2 - q_1)t}]}{[q_2 - q_1 e^{B(q_2 - q_1)t}]} \tag{38}$$

$$p(t) = \frac{p_0(q_2 - q_1)^2 e^{B(q_2 - q_1)t}}{[q_2 - q_1 e^{B(q_2 - q_1)t}]^2} \tag{39}$$

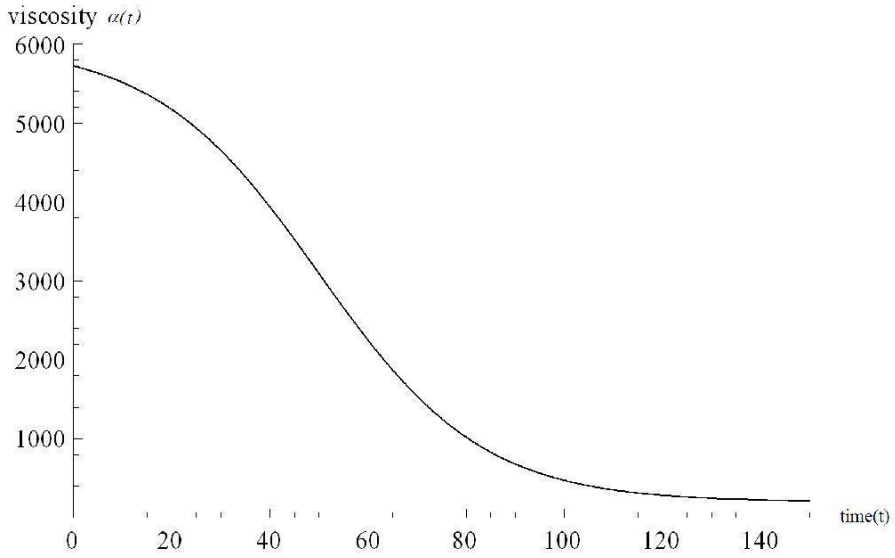


Figure 4. Variation of the viscoelastics coefficient with respect to time. Here the viscosity decreases over time and shows the elasto-thixotropic behavior.

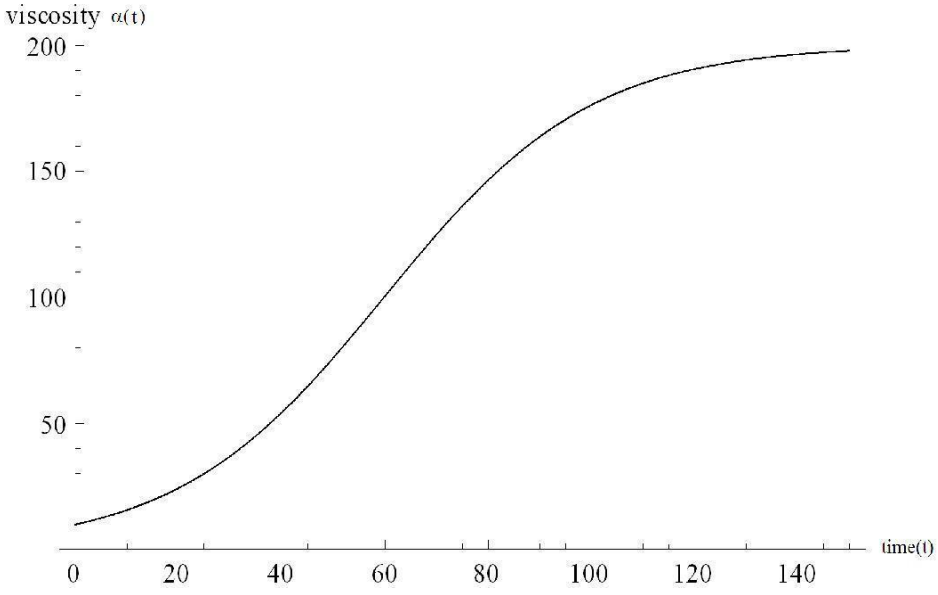


Figure 5. Variation of the viscoelastics coefficient with respect to time. In this graph, the viscosity increases over time showing the visco-elastic behavior.

The study of the variations of p(t) proves that the second order approximation is more interesting (see Figure 3). The components of the maximum of p(t) in the previous expression are given by:

$$t_m = \frac{1}{B(q_2 - q_1)} \ln\left(\frac{-q_2}{q_1}\right) \quad \text{and} \quad p_m = p_o + \frac{(a - p_o b)^2}{2(ab + c - p_o b^2)}. \tag{40}$$

The analytical expression of the rheological functions *(t) and G*(t) can now be written as follows:

$$\underline{a}^{**3}(t)(0)\ a_1 q(t). \tag{41}$$

$$G^*(t) = G^*(0)[\,1 - \frac{a_3}{a_1} q(t)], \tag{42}$$

with the following definitions:

$$\alpha^*(0) = \alpha - \frac{a_3}{a_2} \text{ and } G^*(0) = \frac{a_1 a_3}{a_2}$$

RESULT 4

The Taylor second order approximation shows the viscoelastic (increasing part of the graph) and the elasto-thixotropic (decreasing part of the graph) properties of the blood.

In this model it is interesting to look for the viscoelastics and the elasto-thixotropy behavior (Quemada, 1984) of the blood. These properties can be found by considering the hypothesis of a closed system with the shear rate,

$$\dot{\gamma}(t) = -a_3 \int_0^t A^v(s) ds \,. \tag{43}$$

Therefore the dynamical equation becomes:

$$\ddot{A} = -\alpha^*(t)\dot{A} + (v+1)\frac{\dot{A}^2}{A} + G^*(t)A \,, \tag{44}$$

with the following modifications:

$$\alpha^*(t) = \alpha^*(0) + \frac{\alpha a_3}{a_1} q(t) \text{ and } G^*(t) = G^*(0)\left[1 + \frac{a_3}{a_1} q(t)\right], \tag{45}$$

where $\frac{a_3}{a_2}(0)$ and $G^*(0) \; a_2$.

The coefficient of viscosity can then be written:

$$\alpha^*(t) = \frac{\alpha^*_\infty (1 + sle^{-\gamma t})}{(1 + le^{-\gamma t})} \,, \tag{46}$$

with the following definitions:

$$s = \frac{1}{\alpha^*_\infty}\left[\alpha^*_0 - \frac{\alpha a_3 q_1}{a_1 l}\right]; \qquad \alpha_\infty^* = \alpha^*(0) + \frac{\alpha a_3}{a_1} q_1;$$

and

$$G^*_\infty = G^*(0)\left[1 + \frac{a_3}{a_1} q_1\right].$$

Figure 4 and 5 show the variation of the elasto-thixotropic and the viscoelastic behaviors of the sickle cells polymer.

Conclusion

This study shows that the use of Langevin equation to describe the polymerization of the deoxy-hemoglobin S molecules in sickle cell anaemia is relevant. The graph of the time-dependent deformation of the molecules of deoxy-hemoglobins S gives a sigmoid. It is also shown that the verhulst model is satisfied by the deformation and the absorbance. Moreover the use of the Langevin equation helps to describe the mechanical properties, (visco-elasticity and elasto-thixotropy), of the aggregation of sickle hemoglobins S molecules.

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