Journal of Multidisciplinary Engineering Science Studies (JMESS)
ISSN: 2458-925X
Vol. 8 Issue 2, February - 2022

Examination Of Kinetics In Autocatalytic Reaction Of Oxygen And Human Hemoglobin

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***Abstract*—Autocatalysis is fundamental to many biological processes, and kinetic models of autocatalytic reactions can be mathematically represented. Mutations usually occur in these autocatalytic reactions in which reactants combine to form products that can alter the rate of the reaction. This work involves kinetic analysis of oxy-hemoglobin reaction and the development of models that explain these reactions with respect to time. The model was tested with physical data obtained from patients in a hospital. The ratio of reactants concentration against time was plotted and a straight-line graph with a slope of 0.020 and intercept of 0.001 was obtained, with a rate constant of 2.8 x 10^{-5} M^{-1}min^{-1}. The reaction reached a maximum at rate of 1.38 x 10^{-9} M/min. The rate-concentration curve for the reaction was parabolic and the conversion-time graph had a sigmodal curve, thus validating the model developed for the oxy-hemoglobin reaction.**

Keywords—Mutation, Autocatalysis, Oxy-hemoglobin, Kinetics

INTRODUCTION

A chemical reaction is said to be autocatalytic if one of the reaction products is also a catalyst for the same or a related process. Such a reaction is called an autocatalytic reaction. [1]. Autocatalytic reactions are of profound importance in the chemical sciences in the following areas:

- chemical evolution and the origin of life,
- dissipative chemical systems, and
- chemical signaling and information processing systems.

An example is the Permanganate-oxalate reaction in which the reaction involves two stages, that is the primary stage in which trivalent manganese oxalate complex ions are formed and the second stage in which these ions are decomposed. Potassium permanganate is standardized against pure oxalic acid. It involves a redox reaction. Oxalic acid is oxidized to carbon dioxide by $KMnO_4$, which itself is reduced to $MnSO_4$ [2]

$$2KMnO_4 + 5H_2C_2O_4 + 3H_2SO_4 \rightleftharpoons 2MnSO_4 + 10CO_2 + 8H_2O +$$

Another example is the thermal decomposition of Arsine, which is also an autocatalytic reaction. In its standard state, Arsine is a colorless, is denser than air and slightly soluble in water. At a temperature of about 230 °C, it decomposes to arsenic and hydrogen as shown below and the arsenic freed during the reaction acts as a catalyst for the same reaction [3].

$$\underset{\text{(arsine)}}{2AsH_3} \rightarrow \underset{\text{(hydrogen gas)}}{3H_2} + \underset{\text{(arsenic)}}{2AS}$$

Autocatalysis has also been found to be essential in the description of biological systems, including the growth of individual living beings, population evolution, and gene evolution which come about through a self-regeneration mechanism, where the molecules end up producing those molecules that have produced them. In these reactions, the rate equations are nonlinear, that is, the reaction is having slow beginning and increasing steadily as products are formed [1]. The Brusselator model which describes autocatalytic oscillations in the living bodies was presented as follows [4]:

$$A \overset{k_1}{\rightarrow} X$$

$$2X + Y \overset{k_2}{\rightarrow} 3X$$

$$B + X \overset{k_3}{\rightarrow} D + Y$$

$$X \overset{k_4}{\rightarrow} E$$

where A and B are the reactants, X and Y are the intermediate products while D and Y are the final products. The reaction rate constants are given as k_1 to k_4. They used it to describe rhodopsine to metarhodopsine autocatalytic transformations.

In the case under review oxygen is bound by Hemoglobin (Hb), which is a spherical protein molecule that is found in red blood cells comprising two alpha and two beta subunits that surround an iron-containing heme group in the ferrous (Fe^{2+}) state. Oxygen readily binds this heme group which is a metalloporphyrin, responsible for the red color of blood [5]. This is shown schematically in Figure1.

$$H_{b(aq)} \quad + \quad O_{2(g)} \rightleftharpoons H_bO_{2(aq)}$$

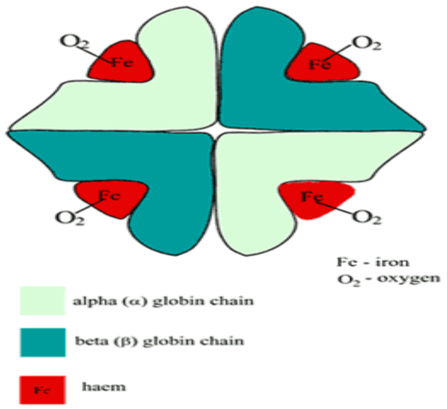

Fig 1: *Schematic of oxygenated hemoglobin* [5].

As more oxygen molecules are bound to the heme group, the ability of oxygen to bind increases. This ability can be affected by disease states or when there is an alteration in the conditions of the body resulting in either an increase or decrease in the ability to dissociate from hemoglobin. Hence anemia can be defined as the reduction in the oxygen-carrying capacity of blood due to a reduction in erythrocyte numbers and/or a reduction in the blood concentration of hemoglobin (*c*tHb [5].

Table 1: The reference ranges for Hemoglobin concentrations in adults [6].

Category	(Hb) Concentration reference ranges
Male	14-18g/dl or 8.7-11.2mmol/l
Female	12-16g/dl or 7.4-9.9mmol/l
Pregnant female	>11g/dl
Elderly	Slight decrease in values

Mutation

With respect to living things, mutation can be described as a change that occurs in DNA sequence, either due to mistakes when the DNA is copied or as the result of environmental factors such as UltraViolet light [7] which can contribute to genetic variation within species. Mutations can also be inherited and can disrupt normal gene activity and cause diseases, like cancer which is one of the most common human genetic disease, caused by mutations which occur in growth-controlling genes [8].

Mutation in autocatalysis

Direct autocatalysis, which is a process whereby a product directly catalyzes its production through the formation of only short-living intermediates, can be differentiated from network autocatalysis, in which multiple stable products cooperatively accelerate their production and which has become a basis for a variety of models propounded by scientists in understanding the origin of life.

In this work, the observations [9] were examined in which they studied the kinetics of tumor development using age-at-tumor diagnosis of familial adenomatous polyposis coli (FAP) patients and sporadic colorectal cancer (CRC) patients. They plotted Age-at-tumor diagnosis data against age and the resulting curve was sigmoidal-shaped which is characteristic of autocatalytic reactions showing that the tissue mechanism that develops in colorectal cancer involves an autocatalytic reaction. They observed also that mutation increases autocatalytic tissue polymerization and induces tumor tissues to autocatalyze their progressive growth, thereby driving the development of tumor in the colon.

Kinetic analysis of autocatalytic reactions

The simplest example of autocatalysis is a reaction in which the product acts as a catalyst for its production. This can be represented as:

$$A + R \rightleftharpoons R + R$$

where R is the product and is also the catalyst.

The rate equation is,

$$-r_A \frac{dC_A}{dt} C_A C_R \qquad (1)$$

The total number of moles of A and R remain unchanged as A is consumed, hence at any time, the following can be written:

$$C_o = C_A + C_R = C_{AO} + C_{RO} = \text{constant}$$

Thus, the rate equation becomes;

$$-r_A = -\frac{dC_A}{dt} = kC_A(C_R - C_O)$$

Rearranging and breaking into partial fractions, we obtain

$$-\frac{dC_A}{C_A(C_O - C_A)} = -\frac{1}{C_O}\left(\frac{dC_A}{C_A} + \frac{dC_A}{C_O - C_A}\right) = kdt \qquad (2)$$

Integrating Equation (2) gives;

$$\ln\frac{C_{AO}(C_O - C_A)}{C_A(C_O - C_{AO}} = \ln\frac{C_R/C_{RO}}{C_A/C_{AO}} = C_O kt = (C_{AO} + C_{RO})kt \qquad (3)$$

The relationships between conversion and time and that between reaction rate and concentration are shown in Figure 2.

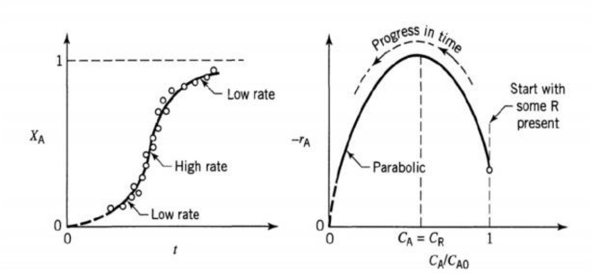

Figure 2: *Conversion-time and rate-concentration curves for an autocatalytic reaction* [10].

Taking into consideration the initial reactant ratio M = C_{RO}/C_{AO} and fractional conversion of A, Equation (4) can be written as;

$$\ln\frac{M + X_A}{M(-X_A)} = C_{AO}(M+1)kt = (C_{AO} + C_{RO})kt \qquad (4)$$

An examination of the above equation reveals that if the reaction starts with a very small concentration of R, the rate will rise as R is formed and as A is used up the rate drops to zero. This is seen in Fig. 2, which indicates that the rate follows a parabolic pattern, with a maximum at the point where the concentrations of A and R are equal [10].

For an autocatalytic reaction, the concentration-time graph of Eq. 3 or 4 is a straight line passing through the origin.

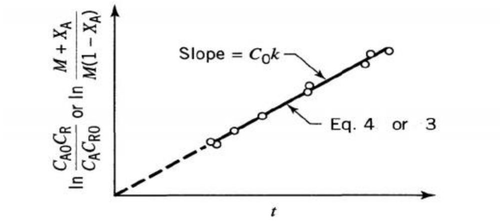

Figure 3: *Test for the autocatalytic reaction* [10].

Oxy-hemoglobin kinetics

In analyzing the kinetics of the oxygen-hemoglobin reaction, it is important to note that the reaction time is very short, hence kinetic coefficients play more role than equilibrium coefficients. On this basis, the kinetic relationships are expressed in terms of molecular segments that contain one heme group, which is one-quarter of the hemoglobin molecule. Hence,

$$Hb_{(aq)} + O_{2(aq)} \rightleftharpoons HbO_{2(aq)} \qquad (5)$$

$$R = k_1[O_2][Hb] - k_2[HbO_2] \qquad (6)$$

with constant reaction rate coefficients, k_1 and k_2 corresponding to the rate of the chemical reaction and the following equations hold:

where [Hb] denotes the molar concentration.

$$\frac{d[O_2}{dt} = -R\frac{dHb}{dt} = -R\frac{dHbO_2}{dt} = R \qquad (7)$$

Since the total number of moles of Hb and O_2 remain unchanged as O_2 is consumed, then at any time;

$$C_0 = [Hb] + [O_2] = [Hb]_0 + [O_2]_0 = Constant \qquad (8)$$

Thus, the rate equation becomes;

$$-r_A = -\frac{d[Hb]}{dt} = k[Hb]([O_2] - [C_O]) \qquad (9)$$

Rearranging,

$$-\frac{d[Hb]}{[Hb](C_O - [Hb])} = -\frac{1}{C_O}\left(\frac{d[Hb]}{[Hb]} + \frac{d[Hb]}{C_O - [Hb]}\right) = kdt \qquad (10)$$

which on integration gives;

$$\ln\frac{[Hb]_0(C_O - [Hb])}{[Hb](C_O - [Hb]_0)} = \ln\frac{[O_2]/[O_2]_0}{[Hb]/[Hb]_0} = C_O kt = ([Hb]_0 + [O_2]_0)kt \qquad (11)$$

In terms of the initial reactant

$M = \frac{[O_2]_O}{[Hb]_O}$

and

$$\ln\frac{M + X_{Hb}}{M(1 - X_{Hb})} = [Hb]_0(M + 1)kt = ([Hb]_0 + [O_2]_0)kt \qquad (12)$$

Experimental Procedures for obtaining the concentrations of hemoglobin and oxygen in oxy-hemoglobin reaction.

This procedure obeyed the beer-lambert's law. Here there is a linear relationship between the concentration and the absorbance of the solution, which enables the concentration of a solution to be calculated by measuring its absorbance [11]. To test for the autocatalytic, experimental data for the reaction of hemoglobin with oxygen at 37°C and a pH value of 7.1 was obtained and analysis done through a time interval of 0-240mins.

25 µl of Blood was diluted in a Drabkin's reagent (solution containing potassium ferricyanide and potassium cyanide). The result of the procedure is that Potassium ferricyanide oxidizes the iron in the heme group to the ferric state forming methemoglobin, which is converted to hemoglobin cyanide (HiCN) by potassium cyanide. Table 2 shows the measured concentration for the reaction of hemoglobin with oxygen at normal body tempe rature (37°C) and pH of 7.1 within the time interval of 0-240 mins.

Table 2: Concentration of Hemoglobin and Oxygen at various time intervals

Time (min)	[Hb] (M)	[O$_2$] (M)	$\ln\frac{[Hb]_0[O_2]}{[Hb][O_2]_0}$
0	0.0115	0.0025	0
30	0.0098	0.0042	0.523
60	0.0085	0.0055	1.091
90	0.0072	0.0072	1.526
120	0.0063	0.0078	1.74
150	0.0054	0.0081	1.932
180	0.0036	0.0095	2.545
210	0.0029	0.0108	2.841
240	0.0019	0.0114	3.318

RESULTS AND DISCUSSION

Model developed

- For oxygen hemoglobin reaction:

$$Hb_{(aq)} + O_{2(aq)} \rightleftharpoons HbO_{2(aq)}$$

$$\frac{d[O_2]}{dt} = -R\frac{dHb}{dt} = -R\frac{dHbO_2}{dt} = R$$

where R is the overall rate for the reaction, which gives our equation for graph test;

Model Evaluation

The above equation can be related to the equation of a straight line;

Y = MX + C

where;

$$y = \ln\frac{[Hb]_0(C_O - [Hb])}{[Hb](C_O - [Hb]_0)} = \ln\frac{[O_2]/[O_2]_0}{[Hb]/[Hb]_0}$$

m = slope $= C_O k$

x = t

C = Intercept

Since $C_0 = [Hb] + [O_2] = [Hb]_0 + [O_2]_0 = Constant$
= 0.0115M+ 0.0025M= 0.0014M

This value remains constant at all times of the reaction. Thus the rate constant k can be calculated from the slope of the graph.

Results of tests on the autocatalytic reaction equations

A straight-line graph of

$$\ln\frac{[Hb]_0(C_O - [Hb])}{[Hb](C_O - [Hb]_0)} \text{which is} = \ln\frac{[O_2]/[O_2]_0}{[Hb]/[Hb]_0}$$

with a slope of 0.020 was obtained from the plot of against time t. From literature, the intercept is zero but from the experimental data, an intercept of 0.001 was obtained which is negligible.

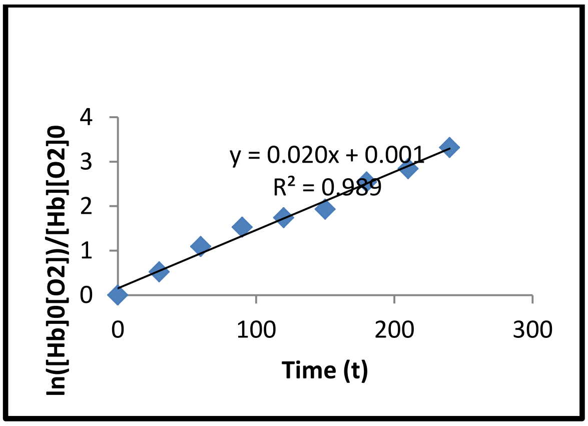

Fig 4: *Test on the kinetic model for the reaction of hemoglobin with oxygen.*

Oxy-hemoglobin rate constant calculation:

The rate constant k was calculated from the slope as follows;

m = slope $= C_O k$

$0.020 = C_O k$

k = 0.020 x 0.0014 = $\underline{2.8 \times 10^{-5} M^{-1} min^{-1}}$.

Rate of reaction calculations at 0-240mins:

$$-r_{HbO_2} = k_1[O_2][Hb]$$

Thus, for the formation of O_2 , the rate of reaction was calculated at all times within the specified interval as shown in Table 3.

Table 3: Concentration of hemoglobin and oxygen versus the rate of reaction

Time (mins)	[Hb] (M)	[O$_2$] (M)	$-r_{HbO_2} = k_1[O_2][Hb]$ (M/min)
0	0.0115	0.0025	8.05×10^{-10}
30	0.0098	0.0042	1.15×10^{-9}
60	0.0085	0.0055	1.31×10^{-9}
90	0.0072	0.0072	1.38×10^{-9}
120	0.0063	0.0078	1.34×10^{-9}
150	0.0054	0.0081	1.22×10^{-9}
180	0.0036	0.0095	9.60×10^{-10}
210	0.0029	0.0108	8.80×10^{-10}
240	0.0019	0.0114	6.05×10^{-10}

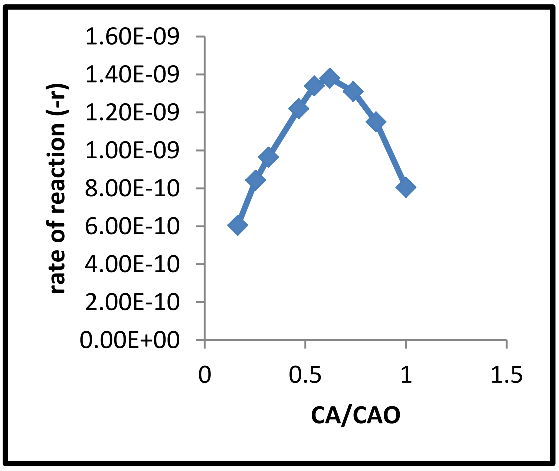

Fig 5: *Rate concentration curve for hemoglobin and oxygen gas reaction.*

For the oxygen hemoglobin reaction that starts with a small concentration of oxygen gas, it was observed that the rate of reaction rises as oxy-hemoglobin is formed as seen in Table 3. It was observed from Figure 5 that the rate forms a parabolic curve as also observed in literature. The reaction reached a maximum (that is the point where the concentration of both reactants was the same) after 90mins with the rate of 1.38 x 10^{-9}M/min. After the maximum point, the concentration of hemoglobin started to decrease gradually. The rate approached zero as the reactant was about to be used up. The results presented in Table 4 show the conversion of Hemoglobin in the reaction at the specified time interval of 0-240mins. The conversion is given by the following formula

$$X_{Hb} = 1 - \frac{[Hb]}{[Hb]_0} \qquad (15)$$

TABLE 4: Conversion of hemoglobin in oxy-hemoglobin reaction versus variation in time.

Time (mins)	$\frac{[Hb]}{[Hb]_0}$	$X_{Hb} = 1 - \frac{[Hb]}{[Hb]_0}$
0	1	0
30	0.85	0.15
60	0.74	0.26
90	0.63	0.37
120	0.55	0.45
150	0.47	0.53
180	0.31	0.69
210	0.25	0.75
240	0.17	0.83

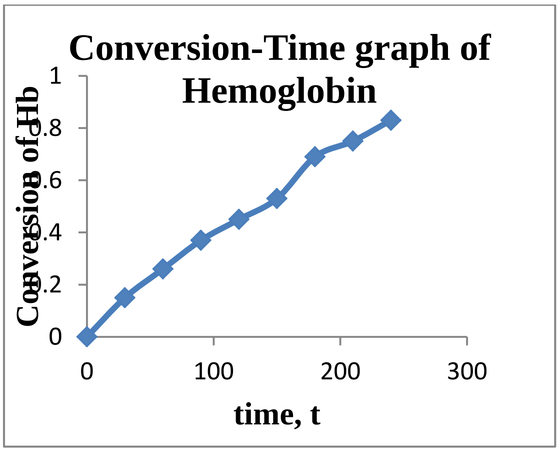

Fig 6: *Conversion-time graph of hemoglobin in oxy-hemoglobin reaction*

The curve in Figure 6 is almost similar to the well-known sigmodal curve for autocatalytic reactions as described in literature.

CONCLUSION

This kinetic analysis of oxy-hemoglobin reaction and the development of models that explain these reactions with respect to time were examined. The model was tested with physical data obtained from patients in a hospital. The ratio of reactants concentration against time was plotted and a straight-line graph with a slope of 0.020 and intercept of 0.001 was obtained, with a rate constant of 2.8 x $10^{-5}M^{-1}$min^{-1}. The reaction reached a maximum at a rate of 1.38 x 10^{-9} M/min. The rate-concentration curve for the reaction was parabolic and the conversion-time graph had a sigmodal curve, thus validating the model developed for the oxy-hemoglobin reaction. Following the physical tests carried out it was observed that the rate-concentration curve for the reaction was parabolic and the conversion-time graph had a sigmodal curve which is similar to that obtained in literature.

Acknowledgment

The author acknowledges the assistance of Chidera Hospital & Maternity Mgbidi, Imo State, Nigeria who provided data for the experiments.

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