A note on Gutierrez’s kinetics model for oxygen delivery to tissue

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The problems associated with Gutierrez model (1986, Resp. Physiol. 63, 79–96) on O₂ delivery to tissue are discussed. He has used a dimensionally incorrect function for the oxygen dissociation curve (ODC). The dimensionally correct function for the ODC has been used in the analysis and the correct results are given for normoxic, hypoxic and anaemic conditions.

Keywords: Mathematical model; Oxygen dissociation curve; Oxygen delivery to tissue; Kinetics of O₂ with haemoglobin.

1. Introduction

The chemical kinetics of oxygen (O₂) uptake/release by the red blood cells plays an important role in the delivery of O₂ to the tissue. Gutierrez (1986) has proposed a compartmental model to study the effect of O₂ release on capillary O₂ tension. In this model, the oxygen dissociation curve (ODC) is represented by the modified form of Hill’s equation:

\[
\frac{S}{100} = \frac{(\alpha P)^n}{(\alpha P)^n + K}
\]  

in which

\[
K = (\alpha P_{50})^n
\]

where S is the percentage saturation of haemoglobin with O₂, P is the O₂ tension, α is the solubility of O₂ and P₅₀ is the O₂ tension at 50% saturation. Here, the exponent n is expressed as a function of S:

\[
\frac{S}{100} = \frac{(\alpha P)^n}{(\alpha P)^n + (\alpha P)^n_0}
\]

(3)

It appears from his paper that n is considered as the function of S (i.e., variable n) for computing K in Eqn. (2). In fact, a constant value of 2.6 for n corresponding to 50% saturation, has been used by him in Eqn. (2) for computational purposes. This will be clear from the following calculation of absolute error – the difference between the saturation predicted from Eqn. (1) and that based on the standard dissociation curve (Severinghaus 1979). The absolute errors with constant and variable n in Eqn. (2) are depicted in Figs. 1(a–c) for P₅₀ values of 16.8, 26.67 and 36.8, respectively. The curves (□–□) in Figs. 1(a–c) corresponding to constant n are similar to those plotted in Fig. 5 of Gutierrez (1986). The maximum absolute errors are about 2.1 and 0.8% with variable and constant value of n in Eqn. (2). With a constant value of n, for example n = n₀, in Eqn. (2), the function (1) becomes

\[
\frac{S}{100} = \frac{(\alpha P)^n}{(\alpha P)^n + (\alpha P)^n_0}
\]

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Fig. 1. Absolute error of the saturation predicted by Eqn. (1) using different equations for $\alpha$: $\Delta$, variable $\alpha$ defined by Eqn. (8) in relations (1),(2); $\times$, variable $\alpha$ defined by Eqn. (9) in relations (1),(2); $\square$, variable $\alpha$ defined by Eqn. (8) in relation (1) and a constant value of 2.6 in relation (2) (Eqn. (4)).
Although the absolute error with Eqn. (4) is relatively small, it is a dimensionally incorrect function for representing the ODC, i.e. saturation of blood with \( O_2 \) changes with different units of solubility of \( O_2 \) in the blood. Thus, Gutierrez (1986) has used a dimensionally incorrect function for computational purposes. Notice that the dimensionally correct function for ODC proposed by Gutierrez (1986) based on variable \( n \) (Eqn. (3)) in Eqn. (2) introduces a maximum absolute error of 2.1% and it will not accurately describe the lower portion of the ODC which is important in studies related to hypoxia. Henceforth, the constant and variable \( n \) refer to that used in Eqn. (2).

In this note, we mention the correct governing equations of the kinetics model proposed by Gutierrez (1986).

2. Mathematical description

For the sake of completeness, we first briefly describe the model. The capillaries are represented as a series of vascular compartments. The equation governing the concentration of \( O_2 \) (\( C \)) and the fractional saturation of haemoglobin with \( O_2 \) (\( s \)) in the compartments are

\[
\frac{dC_i}{dt} = \frac{Q}{V_i} [C_{art} - C_i] - \frac{\dot{V}_{iO_2}}{V_i} - 4HT_i
\]

\[
\frac{ds_i}{dt} = \frac{Q}{V_i} [s_{art} - s_i] + T_i
\]

\[
\frac{dC_j}{dt} = \frac{Q}{V_i} [C_i - C_j] - \frac{\dot{V}_{jO_2}}{V_i} - 4HT_i
\]

\[
\frac{ds_i}{dt} = \frac{Q}{V_i} [s_i - s_{art}] + T_i, \quad i = 2, 3, \ldots, N
\]

in which

\[
T_i = k' \{C_i(1 - s_i) - Ks_i\}
\]

and

\[
k' = 6325 \exp(1.1537s)^{2.8867}
\]

where \( Q \) is the blood flow rate, \( V_i \) is the volume of the \( i \)th compartment, \( \dot{V}_{iO_2} \) is the rate of \( O_2 \) uptake by the tissue, \( H \) is the total haemoglobin concentration and \( N \) is the total number of compartments. The subscript art indicates the corresponding quantity in the arterial blood. \( K \) appearing in relation (6) is defined by Eqn. (2).

The system of equations (5) is solved with the initial condition, i.e., at \( t = 0 \),

\[
C_i = aP_u
\]

\[
s_i = s_u \quad i = 1, 2, \ldots, N
\]

where \( P_u \) and \( s_u \) are initial \( PO_2 \) and fractional saturation in the \( i \)th compartment.

Notice that the error in saturation function (1) with variable \( n \) at the lower and upper portions of the ODC is large in comparison to constant \( n \) (Figs. 1a–c). The error in the saturation function with variable \( n \) can be made small by expressing \( n \) as a function of \( S \) more accurately. This can be done by calculating \( n \) for different values of \( S \) from Eqn. (1) (considering \( n \) in Eqn. (2) also variable) and standard ODC (Severinghaus 1979). For the paired values of \( n \) and \( S \), we have fitted the function of the form (Eqn. (3)) using the method of least-squares optimization (Marquardt 1963):

\[
n = \frac{2.644S^2 - 288.042S}{S^2 - 107.005S - 126.631}
\]

The system of equations (5) with initial condition (8) has been solved by the predictor corrector method (Gutierrez 1986). Since the differential equations (5) are stiff, the predictor corrector method requires a very small time step for its stability. The solution of the system of equations (5) requires a large number of time steps to attain the steady state and hence it takes a large computation time. On the other hand, under steady state, the system of equations (5) reduces to a system of nonlinear algebraic equations. This can be solved numerically, for example, by the Newton Raphson method (Press et al., 1986). The solution of algebraic equations takes very little time in comparison to the predictor corrector
Table 1. Comparison of end-capillary and venous levels of $P_{O_2}$ and HbO$_2$ for the conditions of normoxia, hypoxia and anaemia.

<table>
<thead>
<tr>
<th></th>
<th>End-capillary ($\text{mmHg}$)</th>
<th>Venous $P_{O_2}$ ($\text{mmHg}$)</th>
<th>$P_{O_2}$ difference ($\text{mmHg}$)</th>
<th>End-capillary</th>
<th>Venous HbO$_2$ %</th>
<th>HbO$_2$ % difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normoxia</td>
<td>40.86</td>
<td>44.18</td>
<td>3.32</td>
<td>79.25</td>
<td>79.20</td>
<td>-0.05</td>
</tr>
<tr>
<td>Hypoxia</td>
<td>9.18</td>
<td>17.93</td>
<td>8.75</td>
<td>26.52</td>
<td>26.39</td>
<td>-0.13</td>
</tr>
<tr>
<td>Anaemia</td>
<td>5.82</td>
<td>27.70</td>
<td>21.88</td>
<td>53.09</td>
<td>52.27</td>
<td>-0.82</td>
</tr>
</tbody>
</table>

Fig. 2. Capillary $P_{O_2}$ profiles for a normal condition of $O_2$ supply computed assuming instant $O_2$ release from RBC (□) and that predicted by the model (+). Input parameters: $P_{aO_2} = 100 \text{ mmHg}$, [haemoglobin] = 15 g/100 ml, cardiac output = 5 l/min, $P_{at} = 26.8 \text{ mmHg}$, transit time = 0.6 s, $V_{O_2} = 200 \text{ ml/min}$.
method. The results obtained from both methods are essentially the same.

3. Results

The errors in the saturation function with the modified \( \alpha \) (Eqn. (9)) are depicted in Figs. 1(a–c). The maximum absolute error is found to be 0.8%. It is clear from the figures that the saturation function with modified variable \( \alpha \) predicts the ODC more accurately than Gutierrez's function. Gutierrez (1986) has wrongly assumed that the steady state solution was reached before 0.01 s. In fact, the changes in the arterial side would not be reflected on the venous side for some time. As a result, the iteration for 0.01 s will not produce the steady state solution (Gutierrez 1988). Also, for the given values of the parameters in the paper, the time evaluation of the model equations beyond 0.01 s leads to negative \( O_2 \) concentration under hypoxic and anaemic conditions, which do not have any physical significance. Gutierrez (1988) has suggested a transit time of 0.6 s instead of 0.5 s and a haemoglobin concentration of 6 g/100 ml instead of 5 g/100 ml in anaemic conditions to

![Graph](image-url)

**Fig. 5.** Capillary \( \text{PO}_2 \) profiles for hypoxemia computed assuming instant \( O_2 \) release from RBC (○) and that predicted by the model (+). The arterial \( \text{PO}_2 = 25 \text{ mmHg} \). The other input parameters are the same as in Fig. 2.
avoid the negative values under hypoxic and anaemic conditions. The correct results corresponding to Table 1, Figs. 12, 13 and 14 of Gutierrez (1986) are given in Table 1, Figs. 2–4, respectively. However, the qualitative conclusions of the model are essentially the same as those published.

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References


Gutierrez, G., 1988, Personal communication.

