

A NONLINEAR VERSION OF THE COBURN, FORSTER AND KANE MODEL OF BLOOD CARBOXYHEMOGLOBIN*

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Abstract—We provide an integrated form of the preferred nonlinear form of the Coburn, Forster and Kane (1965, *J. clin. Invest.* **41**, 1899-1910) model. The new technique guarantees numerical accuracy, yet substantially reduces the computational burden.

Key word index: Carbon monoxide (CO), human, dose response function.

INTRODUCTION

In 1965 Coburn, Forster and Kane (CFK) suggested a differential equation model of the rate of change of blood carboxyhemoglobin (COHb) in man as a function of time and a number of physiological parameters. Since then it has been widely used. See Stewart (1975) for a review. It is important to recognize that the model was suggested to describe low level exposures for steady state conditions.

Using the differential equation model requires some method to integrate it, either numerical or analytical. Treating all physiological parameters as constants leads to a linear differential equation in time, which can be integrated analytically. Unfortunately, at high exposure levels the linearized model yields impossible values corresponding to COHb saturations of greater than 100%.

Peterson and Stewart (1975) noted that the problem arose from treating O₂Hb (the amount of oxygenated hemoglobin) as a constant across time. They suggested a simple numerical method to approximate the solution to the resulting nonlinear differential equation (using the integrated linear form in an iterative technique). Their heuristic method is of unknown analytical accuracy. Naturally, general numerical integration techniques could also be applied for greater accuracy at the cost of much greater programming complexity. In discussing these and other approaches, Marcus (1981a, b) concluded that O₂Hb must be allowed to vary for accurate predictions.

We present here an analytically integrated nonlinear form of the CFK equation. The resulting equation expresses time to achieve a new COHb level as a function of COHb. The equation must be inverted numerically, but this is an extremely simple and

accurate process. One need compute solutions at points of interest only, and the accuracy of the solution is independent of which points are of interest. Compared to Peterson and Stewart's method, the new method is essentially as convenient to program, and is more accurate. Compared to numerical integration of the nonlinear form, the new method is much more convenient to program, and is at least as accurate. The solution method also applies to a commonly used form of the Michealis-Menton kinetics model.

INTEGRATION OF EQUATION

Earlier results

Table 1 describes typical values for the various species of hemoglobin found in the normal human. See Henry (1979) for a brief discussion of the information in Table 1. Note that reduced hemoglobin is available to bond reversibly with either CO or O₂, while methemoglobin must be reduced by enzyme systems before it can bond.

Table 2 summarizes other variables of interest in modeling COHb. Typical values and units are given to help interpretation of models discussed below. In modeling normal subjects the most interest usually lies

Table 1. Hemoglobin species in normal human blood

Species	Symbol	Typical* value	
		ml/ml blood	%
Oxygenated	O ₂ Hb	0.1984	96.2
Carboxylized	COHb	0.0016	0.8
Reduced	RHb	0.0052	2.5
Met-	MHb	0.0010	0.5
Other	(various)		0.0
Total			100.0

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* Values are typical for a healthy, young non-smoking male.

in the CO level. Alveolar ventilation rate is the other variable typically of most importance to COHb levels.

Coburn, Forster and Kane (1965) suggested a differential equation model for the rate of change in [COHb] as a function of time. The model may be written as

$$\frac{\partial[\text{COHb}]}{\partial t} = \left[\frac{V_{\text{CO}}}{V_b} + \frac{P_{\text{Ico}}}{BV_b} \right] - \frac{[\text{COHb}]}{[\text{O}_2\text{Hb}]} \left[\frac{\bar{P}_{\text{CO}_2}}{MBV_b} \right]. \quad (1)$$

Here

$$B = \frac{1}{D_{\text{LCO}}} + \frac{P_L}{V_A}, \quad (2)$$

and all other variables are defined in Tables 1 and 2. Treating all variables as constants except [COHb] leads to a linear first order differential equation. This can be easily integrated to give

$$\frac{A[\text{COHb}]_t - BV_{\text{CO}} - P_{\text{Ico}}}{A[\text{COHb}]_0 - BV_{\text{CO}} - P_{\text{Ico}}} = \exp[-tA/V_b B]. \quad (3)$$

In the above, [COHb]_t is the carboxyhemoglobin level at time *t* and [COHb]₀ is the initial level,

$$A = \bar{P}_{\text{CO}_2} / M[\text{O}_2\text{Hb}], \quad (4)$$

and all other variables are as defined earlier.

Peterson and Stewart (1975) noted that (3), the solution to the linearized CFK model, assumes that only [COHb] changes with time. Since CO and O₂ compete for the same sites, [O₂Hb] must get smaller at higher concentrations of [COHb]. To allow [O₂Hb] to vary across time, Peterson and Stewart suggested a heuristic numerical method to modify (3) to give an approximate solution.

Marcus (1981a, b) reviewed a number of models for [COHb], including those above. He concluded that [O₂Hb] must be allowed to vary across time, hence rejecting (3), the integrated linear form of CFK. He recommended using

$$\%[\text{O}_2\text{Hb}] = 100 - \%[\text{RHb}] - \%[\text{COHb}]. \quad (5)$$

He also recommended using numerical integration techniques as applied to the differential Equation (1), with [%O₂Hb] defined from (5) as varying over time, and [%RHb] taken as a constant 3.6%. He noted that the role of RHb was ill-defined and deserved study.

New results

Since Table 1 indicates that

$$[\text{THb}] = [\text{O}_2\text{Hb}] + [\text{RHb}] + [\text{COHb}] + [\text{MHb}], \quad (6)$$

an alternative to (5) is

$$\begin{aligned} \%[\text{O}_2\text{Hb}] &= 100 - \%[\text{RHb}] - \%[\text{COHb}] \\ &\quad - \%[\text{MHb}] \end{aligned} \quad (7)$$

which is in percent total hemoglobin. Below we shall assume that [RHb] and [MHb] are constant across time. Hence (7) and (5) will not differ in practice (with appropriate choice of constant values). We suggest the change for conceptual accuracy and possible study in other applications. It is interesting to speculate as to what role the pool of available hemoglobin, [RHb], plays in very short exposure periods (< 5 min).

This leads us to write the nonlinear differential equation

$$\begin{aligned} \frac{\partial[\text{COHb}]}{\partial t} &= \left[\frac{V_{\text{CO}}}{V_b} + \frac{P_{\text{Ico}}}{BV_b} \right] \\ &\quad - \frac{[\text{COHb}]}{([\text{THb}] - [\text{RHb}] - [\text{MHb}] - [\text{COHb}])} \left[\frac{\bar{P}_{\text{CO}_2}}{MBV_b} \right]. \end{aligned} \quad (8)$$

Table 2. Variables of interest for COHb modeling

Symbol	Typical* value	Units	Variable
V_b	5500	ml	blood volume
D_{LCO}	30	ml min ⁻¹ mmHg ⁻¹	pulmonary CO diffusion rate
M	218	(unitless)	Haldane constant; relative blood affinity of CO to O ₂
P_b	760	mmHg	barometric pressure
$P_{\text{H}_2\text{O}}$	47	mmHg	vapor pressure of water at body temperature
P_L	760-47	mmHg	
\bar{P}_{CO_2}	100	mmHg	partial pressure of O ₂ in pulmonary capillaries
P_{Ico}		mmHg	inspired air partial pressure CO (P_{Ico} = 0.00076 ppm CO)
V_{CO}	0.007	ml min ⁻¹	endogenous CO production rate
V_A	6000	ml min ⁻¹	alveolar ventilation rate

* Values are typical for a healthy, young, non-smoking male at rest.

Assuming only [COHb] is time varying, this may be written more conveniently as

$$\frac{\partial[\text{COHb}]}{\partial t} = c_0 - \frac{c_1[\text{COHb}]}{K - [\text{COHb}]}, \quad (9)$$

with K , c_0 and c_1 all nonzero, positive constants defined by context in (8). In this form, it is readily apparent that the model is equivalent to a Michaelis-Menton kinetics model. See Tong and Metzler (1980) for a general discussion of its properties.

Although many nonlinear differential equations are not analytically integrable, the one given by (9) is. Equation (A4) from Appendix 1 provides the solution since it expresses time as a function of [COHb]_t and constants. The conditions for applying the theorem insure that the function is uniquely invertible, for the interval of interest. Despite that, the function does not appear to be analytically invertible. This is not an obstacle since inverting a bounded strictly monotone function numerically is very simple.

Equation (A4) can also be written as

$$f(y) = -(c_0 + c_1)t + y - [\text{COHb}]_0 - \{K - [\text{COHb}]_\infty\} \ln \left\{ \frac{[\text{COHb}]_\infty - y}{[\text{COHb}]_\infty - [\text{COHb}]_0} \right\} \quad (17)$$

$$\frac{(c_0 + c_1)[\text{COHb}]_t - Kc_0}{(c_0 + c_1)[\text{COHb}]_0 - Kc_0} = \exp \left\{ \frac{-t(c_0 + c_1)^2}{Kc_1} \right\} \times \exp \left\{ \frac{(c_0 + c_1)[\text{COHb}]_t - (c_0 + c_1)[\text{COHb}]_0}{Kc_1} \right\}. \quad (10)$$

Equation (10) allows easy calculation of the asymptotic COHb level. As t goes to infinity, the right hand side of (10) goes to zero. Hence

$$\frac{(c_0 + c_1)[\text{COHb}]_\infty - Kc_0}{(c_0 + c_1)[\text{COHb}]_0 - Kc_0} = 0, \quad (11)$$

which yields

$$[\text{COHb}]_\infty = \frac{Kc_0}{c_0 + c_1} \quad (12)$$

$$= \frac{(BV_{\text{CO}} + P_{1\text{CO}})K}{BV_{\text{CO}} + \bar{P}_{\text{CO}_2}/(MB)}. \quad (13)$$

The expression (12) for the asymptote may be used to show that the solution Equation (A4) may be written as

$$(c_0 + c_1)t = [\text{COHb}]_t - [\text{COHb}]_0 - \{K - [\text{COHb}]_\infty\} \ln \left\{ \frac{[\text{COHb}]_\infty - [\text{COHb}]_t}{[\text{COHb}]_\infty - [\text{COHb}]_0} \right\}. \quad (14)$$

Marcus (1981b) stated that the CFK differential Equation (1) is "nonlinear in COHb even for constant CO except in a form that expresses time t as a function of COHb; explicitly, when $O_2Hb = 1$

– COHb . . .". Marcus then presented an equation which can be shown to be equivalent to (A4), allowing for differences in notation and scaling. Next Marcus reviewed and criticized approximations to the solution of the differential equation. He concluded by recommending approximations based on linear differential equations, or numerical integration. He did not mention the integral equation again.

An interval halving (binary search) algorithm can be used to compute [COHb]_t. See Southworth and Deleeuw (1965) or any other introductory numerical analysis text for a detailed description of root finding algorithms.

Step 1: Compute the asymptotic level, [COHb]_∞. Note that

$$[\text{COHb}]_0 \leq [\text{COHb}]_t \leq [\text{COHb}]_\infty \quad (15)$$

or

$$[\text{COHb}]_\infty \leq [\text{COHb}]_t \leq [\text{COHb}]_0. \quad (16)$$

Step 2: In the first case initialize the solution interval, $[L, U]$, as $[[\text{COHb}]_0, [\text{COHb}]_\infty]$, and in the second case as $[[\text{COHb}]_\infty, [\text{COHb}]_0]$.

Step 3: Evaluate

at the end-points and the midpoint of the interval, $M = (L + U)/2$, giving $f(L)$, $f(M)$ and $f(U)$. This function is based on (14).

Step 4: If any of the function values computed in Step 3 is zero the solution has been found. Otherwise the pattern of signs must be either $-++$, $--+$, $+--$, or $+-$. These imply the new solution interval $[L, M]$, $[M, U]$, $[L, M]$ or $[M, U]$, respectively.

Step 5: If the length of the solution interval is acceptably small, stop and compute [COHb]_t as the midpoint of the interval. Otherwise repeat Steps 3–5 until convergence is reached.

APPLICATIONS

Many values are needed to create plots of the CFK equation. In all calculations for the following plots, $K = 0.20$ was used. All %COHbs are in terms of percent

saturation (Peterson and Stewart, 1975) rather than percent total hemoglobin (Instrumentation Laboratories, 1980). Finally, all other values were taken from Table 2.

Figure 1 plots asymptotic %COHb as a function of ppm CO. Obviously a portion of the plot involves lethal %COHb levels. The model does not account for the known disintegration of function at very high levels. Note that any linear approximation of the model (such as that presented in the original CFK paper) would produce a straight line shooting off to 100% COHb at about 500–1000 ppm CO.

Figure 2 plots %COHb predicted by the solution of Equation (10) as a function of time, for 25–500 ppm CO. Data from Table 1 of Peterson and Stewart (1975) are also included. For the range of conditions studied, the model obviously fits the data extremely well. Peterson and Stewart presented a similar figure, based on their heuristic approximation to solving the non-linear model. Peterson and Stewart's approximation also fits the data well.

Figure 3 summarizes the difference in predicted %COHb between the Peterson–Stewart approximation and the integrated equation. Only when predicted COHb reaches life-threatening levels does the difference become more than a small part of 1% COHb.

CONCLUSIONS

The method suggested here provides the most convenient method yet for using the preferred non-linear form of the CFK equation. The equation fits continuous low level exposure data extremely well. It also applies to Michealis–Menton kinetics, in some cases. It avoids the computational complexity needed to implement and insure accuracy of numerical integration methods. The solution can be inexpensively computed to any desired numerical accuracy, with no need to compute solution points not of interest (as

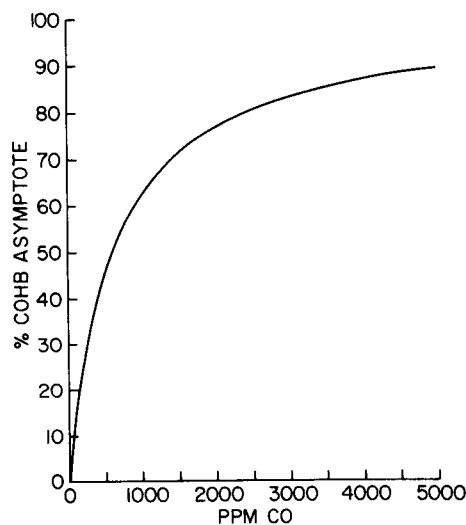


Fig. 1. Asymptotic %COHb level predicted by integrated nonlinear CFK equation.

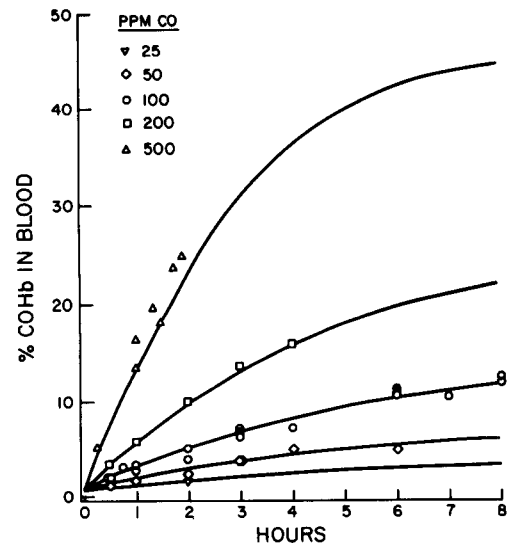


Fig. 2. %COHb predicted by integrated nonlinear CFK equation, with data from Peterson and Stewart (1975).

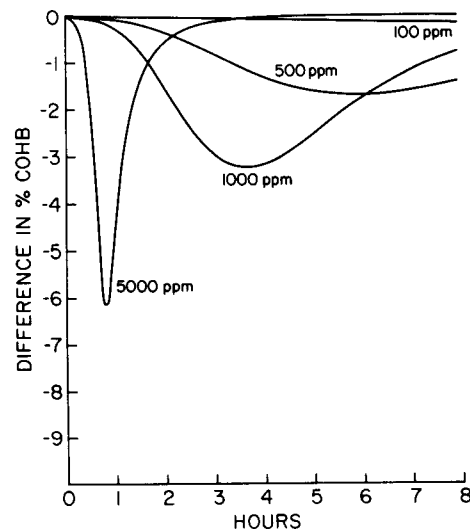


Fig. 3. Peterson–Stewart %COHb prediction minus integrated nonlinear CFK prediction for a range of times and exposures.

with numerical integration). The additional work needed compared to linear approximations is so small as to eliminate the use of the latter.

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APPENDIX 1

A theorem from Chapter 1 of Dickinson [1972] may be applied to give the form of the integral. First note that (9) is of the form

$$\frac{\partial y}{\partial t} = q(y), \quad (\text{A1})$$

for $q(\)$ a continuous function on an interval J . The end-points of the interval are the initial $[\text{COHb}]_0$, for $t = 0$, and asymptotic $[\text{COHb}]_\infty$, the latter for $t = \infty$. Assuming CO level is constant over the time interval of interest guarantees that $q(\)$ is either positive or negative everywhere on the interval. The function q is positive everywhere if asymptotic $[\text{COHb}]_\infty$ is higher than initial $[\text{COHb}]_0$ and negative everywhere if asymptotic $[\text{COHb}]_\infty$ is lower than initial $[\text{COHb}]_0$. With these conditions, theorem 1.8.1 from Dickinson [1972, p. 25] immediately guarantees that a unique function exists on the interval of interest which satisfies the differential equation. The solution for $[\text{COHb}]_t$ is defined as the inverse of the function

$$t = \int_{[\text{COHb}]_0}^{[\text{COHb}]_t} \frac{1}{c_0 - \frac{c_1 u}{K - u}} du. \quad (\text{A2})$$

(Without loss of generality, the initial time is taken to be zero.) The integral simplifies to

$$t = \int_{[\text{COHb}]_0}^{[\text{COHb}]_t} \frac{K - u}{c_0 K - u(c_0 + c_1)} du, \quad (\text{A3})$$

which in turn is the sum of two easily integrable forms. Straightforward calculus yields

$$\begin{aligned} (c_0 + c_1)t = & ([\text{COHb}]_t - [\text{COHb}]_0)(c_0 + c_1) \\ & - c_1 K \ln \{Kc_0 - (c_0 + c_1)[\text{COHb}]_t\} \\ & + c_1 K \ln \{Kc_0 - (c_0 + c_1)[\text{COHb}]_0\}. \end{aligned} \quad (\text{A4})$$

