APPENDIX A

The Rate Equations and their Solutions for the 2CM, 2CG, 3CM and 3CG Models

The rate equations and their solutions are here given explicitly for the 3CG model (Fig.1C). This model reduces to the 2CM, 2CG and 3CM models by selectively simplifying the 3CG model. The solutions for the 2CM, 2CG and 3CM models are briefly outlined as well.

The rate equations and their solutions, written in terms of Henry's law-based partial pressures (11, 21), "p_i", in the three compartments are needed. The "p"-based rate equations are derived from the "q"-based rate equations shown in Equations (A1).

$$\begin{aligned}
\dot{q}_1(t) &= -(f_{10} + f_{12} + f_{13})\, q_1(t) + f_{21} q_2(t) + f_{31} q_3(t) + i_1^{(q)}(t) \\
\dot{q}_2(t) &= f_{12} q_1(t) - (f_{20} + f_{21}) q_2(t) + i_2^{(q)}(t) \\
\dot{q}_3(t) &= f_{13} q_1(t) - (f_{30} + f_{31}) q_3(t) + i_3^{(q)}(t)
\end{aligned} \qquad \text{(A1)}$$

Here, "q_j" is the quantity of dissolved N_2 in compartment "j",

$\dot{q}_j(t) \equiv dq_j(t)/dt$, "$i_j^{(q)}(t)$" is the quantity-based input function for compartment "j", and "f_{ij}" is the "fractional transfer coefficient" for transfer of dissolved N_2 from compartment "i" to "j". "$i_j^{(q)}(t)$" is the contribution to $\dot{q}_j(t)$ due only to input of N_2 to compartment "j" from the circulatory system. "f_{ij}" is a quantity-based rate constant. It is simply the fraction of dissolved nitrogen in compartment "i", transferred from compartment "i" to "j" per unit time. "j" can be either another compartment or the circulatory system (in the latter case it is "0"). Fractional transfer coefficients can always

be made "fractional" (i.e. < 1) by a suitable choice of the time unit. The relative merits of using these quantity-based rate constants, as opposed to the better-known concentration-based rate constants are discussed in Ref. (16, Chapter 1). In this work, because the volumes of the compartments are taken to be constant with respect to nitrogen transfer, these two types of rate constants are equivalent. Fractional transfer coefficients were chosen in order to be consistent with Jacquez (16, Chapters 1, 2). Also, here, the subscript "ij" means $i \rightarrow j$, which is the convention used in chemical kinetics and pharmacokinetics, but is the opposite of the convention used in Ref. (16).

By applying Henry's law and steady-state conditions, and assuming the temperature and compartment volumes are constant, Equations (A1) are transformed to the p-based form of the rate equations shown in Equations (A2).

$$\begin{aligned}
\dot{p}_1(t) &= -(f_{10} + f_{12} + f_{13})p_1(t) + f_{12}p_2(t) + f_{13}p_3(t) + f_{10}p_{a,n}(t) \\
\dot{p}_2(t) &= f_{21}p_1(t) - (f_{20} + f_{21})p_2(t) + f_{20}p_{a,n}(t) \\
\dot{p}_3(t) &= f_{31}p_1(t) - (f_{30} + f_{31})p_3(t) + f_{30}p_{a,n}(t)
\end{aligned} \tag{A2}$$

Here, $p_{a,n}(t)$ is the arterial partial pressure of inert gas (here nitrogen, "n"). It is further described in Appendix B, section (1c).

Equations (A2) are coupled, linear, inhomogeneous differential equations. The inhomogeneity stems from the input terms, i.e., the last terms on the right-hand sides of these equations. The form of the exact solution for such equations has been known for many years (9, 14). It involves the sum of two terms: the first provides the solution of the homogeneous component of the equations, and the second provides an exact correction

for the inhomogeneity. Provided the eigenvalues are distinct (see below and Table 2), the exact solution (or integrated form) of Eqs. (A2) is given by Eq. (A3).

$$\bar{p}(t) = \sum_{j=1}^{3} \bar{u}_j \left\{ c_j e^{\lambda_j t} + \int_0^t k_j(\tau) e^{\lambda_j (t-\tau)} d\tau \right\} \qquad \text{(A3)}$$

The first term in the curly brackets provides the solution of the homogeneous part of the equations; the second term corrects exactly for the inputs.

The λ_j's and $\bar{u}_j$'s (j = 1 - 3) are the system eigenvalues and eigenvectors, respectively. The eigenvalues have physical significance. Their magnitudes are the decay constants for the compartments, there being three distinct decay constants per compartment in this model. As seen from Equations (A3) or (A10), the eigenvectors provide the weight functions for the system. Their elements give the proper relative weight, in each compartment to each of the three terms in the sum whose total gives the compartmental dissolved gas partial pressure. The eigenvalues and eigenvectors depend only on the f_{ij}'s, the values of which are determined from the calibration. The eigenvalues are obtained from the three roots of the characteristic polynomial

$$\begin{vmatrix} -(f_{10} + f_{12} + f_{13} + \lambda) & f_{12} & f_{13} \\ f_{21} & -(f_{20} + f_{21} + \lambda) & 0 \\ f_{31} & 0 & -(f_{30} + f_{31} + \lambda) \end{vmatrix} = 0$$

which, written out, is:

$$\lambda^3 + a_1\lambda^2 + a_2\lambda + a_3 = 0 \qquad \text{(A4)}$$

where

$$a_1 = f_{10} + f_{12} + f_{13} + f_{20} + f_{30} + f_{21} + f_{31}$$

$$a_2 = f_{20}\left(f_{12} + f_{31} + f_{13} + f_{30} + f_{10}\right) + f_{30}\left(f_{21} + f_{12} + f_{13} + f_{10}\right) + f_{31}\left(f_{12} + f_{21} + f_{10}\right) + f_{21}\left(f_{10} + f_{13}\right)$$

$$a_3 = \left(f_{31} + f_{30}\right)\left(f_{10}f_{20} + f_{10}f_{21} + f_{12}f_{20}\right) + f_{13}f_{30}\left(f_{20} + f_{21}\right).$$

These expressions, which are for the most general form of the 3CG model contain more unknowns (seven) than are resolvable (three). The approximations used here to simplify the general 3CG model in order to render it tractable are described at the end of this Appendix.

Equation (A3) is valid when the solution of Eq.(A4) produces three distinct eigenvalues – a condition that was always met here. The eigenvalues found were real, distinct and negative (Table 2).

In Eq.(A3), $\bar{p}(t)$ and $\bar{u}_j$ are the column vectors.

$$\bar{p}(t) = \begin{pmatrix} p_1(t) \\ p_2(t) \\ p_3(t) \end{pmatrix} \quad ; \quad \bar{u}_j = \begin{pmatrix} u_{1j} \\ u_{2j} \\ u_{3j} \end{pmatrix}$$

The elements of $\bar{u}_j$ are:

$$u_{ij} = \begin{cases} 1 & i=1; j=1-3 \\ \dfrac{f_{i1}}{f_{i0}+f_{i1}+\lambda_j} & i=2,3; j=1-3 \end{cases}$$

The c_j's are constants with respect to time that are worked out anew for each segment in the profile (see below). They depend on the f_{ij}'s, the initial conditions, and the measurement scale used (e.g. *atm, fsw*, etc.)

Eq.(A3) is valid for any arbitrary input function and, in principle, can be applied to profiles with variable rates of ascent and descent. However, to simplify the explicit form of the working equations, and to conform to usual practice, we will assume that all ascent and descent rates are constant (but not necessarily equal), so that the entire depth vs time dive profile can be decomposed into a series of linear segments joined at nodes. From Eq.(A2), for linear input, the p-based input function is given by Eq.(A5)

$$i_j^{(p)}(\tau) = f_{j0}\, p_{a,n}(\tau) = f_{j0}(a + b\tau), \quad j = 1-3 \tag{A5}$$

Here, "a" $\left(= p_{a,n}(0)\right)$ is the arterial inert gas partial pressure at the start of the segment as determined by the arterial gas equation, and "b" is the rate of change of inert gas partial pressure along the segment (with air as the breathing mixture, $b \cong .79R$ where R is the rate of ascent or descent along the "ramp"). At the surface or along an underwater plateau, $b = R = 0$.

$k_j(\tau)$ in Eq.(A3) is the j^{th} component of the time-dependent column vector $\left(\bar{\bar{u}}\right)^{-1}\bar{i}^{(p)}(\tau)$; i.e.,

$$\bar{k}(\tau) \equiv \begin{pmatrix} k_1(\tau) \\ k_2(\tau) \\ k_3(\tau) \end{pmatrix} = \left(\bar{\bar{u}}\right)^{-1} \begin{pmatrix} i_1^{(p)}(\tau) \\ i_2^{(p)}(\tau) \\ i_3^{(p)}(\tau) \end{pmatrix} \tag{A6}$$

The matrix elements $\left(u_{ij}\right)^{-1}$ are obtained by inverting the matrix $\bar{\bar{u}}$, where

$\overline{\overline{u}} = \begin{pmatrix} 1 & 1 & 1 \\ u_{21} & u_{22} & u_{23} \\ u_{31} & u_{32} & u_{33} \end{pmatrix}$. The elements u_{ij} were given above. The result of inverting the matrix is:

$$\left(u_{11}\right)^{-1} = \left(u_{22}u_{33} - u_{23}u_{32}\right)/D; \left(u_{12}\right)^{-1} = \left(-u_{33} + u_{32}\right)/D; \left(u_{13}\right)^{-1} = -\left(-u_{23} + u_{22}\right)/D$$

$$\left(u_{21}\right)^{-1} = -\left(u_{21}u_{33} - u_{31}u_{23}\right)/D; \left(u_{22}\right)^{-1} = -\left(u_{31} - u_{33}\right)/D; \left(u_{23}\right)^{-1} = \left(u_{21} - u_{23}\right)/D$$

$$\left(u_{31}\right)^{-1} = \left(u_{21}u_{32} - u_{31}u_{22}\right)/D; \left(u_{32}\right)^{-1} = \left(u_{31} - u_{32}\right)/D; \left(u_{33}\right)^{-1} = -\left(u_{21} - u_{22}\right)/D \qquad \text{(A7)}$$

with $D = u_{31}\left(u_{23} - u_{22}\right) + u_{21}\left(u_{32} - u_{33}\right) + u_{22}u_{33} - u_{23}u_{32}$.

Substituting Eqs.(A5) into Eq.(A6) gives Eq. (A8) for the components of $\overline{k}\left(\tau\right)$.

$$k_j\left(\tau\right) = \sum_{\alpha=1}^{3}\left(u_{j\alpha}\right)^{-1} i_{\alpha}^{(p)}\left(\tau\right), \qquad j = 1-3 \qquad \text{(A8)}$$

The $\left(u_{j\alpha}\right)^{-1}$ are written out in Eq.(A7).

Next, substitute Eq.(A5) for $i_{\alpha}^{(p)}\left(\tau\right)$ into Eq.(A8) to get:

$$k_j\left(\tau\right) = k_j\left(0\right) + k_j^{'}\tau \qquad j = 1-3 \qquad \text{(A9)}$$

where $k_j\left(0\right) = a\sum_{\alpha=1}^{3}\left(u_{j\alpha}\right)^{-1} f_{\alpha 0} \qquad j = 1-3$

$$k_j^{'} = \left(\frac{b}{a}\right)k_j\left(0\right) \qquad j = 1-3$$

Finally, using Eq.(A9) for $k_j\left(\tau\right)$ in Eq.(A3) and doing the integration in Eq.(A3) analytically gives Eq.(A10).

$$\bar{p}(t) = \sum_{j=1}^{3} \bar{u}_j \left\{ c_j e^{\lambda_j t} + \left[\left(e^{\lambda_j t} - 1 \right) / \lambda j \right] \left[k_j(0) + k_j'' \right] - k_j'' t \right\} \qquad \text{(A10)}$$

Here $k_j'' \equiv k_j' / \lambda j$. Eq.(A10) is used to obtain $\{p_1(t), p_2(t), p_3(t)\}$ analytically at any point in any segment of the profile. Everything on the right-hand side of Eq.(A10) is calculable from the f_{ij}'s and the initial conditions of each profile segment. Since Eq.(A4) is a cubic equation that can be solved analytically for $\{\lambda_1 \lambda_2 \lambda_3\}$, the values of $\{p_1(t) p_2(t) p_3(t)\}$ are obtained very rapidly and accurately. As a check on Eq.(A10), note that for profile segments at a fixed depth (or at the surface), $k_j'' = 0$, $j = 1-3$, for which Eq.(A10) reduces to the form given in Ref. (16, Chapter 2) for "fixed input". Furthermore, for systems with output but no input, all the terms except the first in curly brackets in Eq.(A10) vanish, again resulting in a reduction of Eq.(A10) to the correct form for this case (16, Chapter 2).

For any segment at $t = 0$, Eq.(A10) becomes

$$\bar{p}(0) = \sum_{j=1}^{3} c_j \bar{u}_j \qquad \text{(A11)}$$

Eq.(A11) provides the linear equations that are solved analytically for the three unknowns $\{c_1, c_2, c_3\}$, using the matrix elements of $\bar{u}_j$ given above. The elements of $\bar{p}(0)$ for segment "$m+1$" are obtained from the values of the corresponding elements at the end of segment "m".

An outline of how the rate equations and their solutions are obtained for the 2CM, 2CG and 3CM models from the corresponding expressions for the 3CG model follows.

The 3CG model reduces to the 3CM model by setting $i_2^{(q)}(t)=i_3^{(q)}(t)=0$ in Eq.(A1), and by setting $f_{20}=f_{30}=0$ in all the expressions containing these rate constants.

The 3CG model reduces to the 2CG model by removing compartment "3". Operationally, this is done by setting $f_{13}=f_{31}=f_{30}=i_3^{(p)}(t)=0$. The cubic polynomial in Eq.(A4) is, for the 2CG model, reduced to the quadratic shown in Eq.(A12):

$$\lambda^2+a_1\lambda+a_2=0 \qquad \text{(A12)}$$

Here, $a_1=\left(f_{10}+f_{20}+f_{21}+f_{12}\right)$

$$a_2=f_{10}\left(f_{20}+f_{21}\right)+f_{12}f_{20}$$

The two roots of Eq.(A12) give the model's two eigenvalues. The elements of the eigenvectors for the 2CG model are given by

$$u_{ij}=\begin{cases}1 & i=1;\ j=1-2\\ \dfrac{f_{i1}}{f_{i0}+f_{i1}+\lambda_j} & i=2;\ j=1-2\end{cases}$$

The 2CG model reduces to the 2CM model on setting $i_2^{(p)}(t)=f_{20}=0$. The sums in Eqs.(A3), (A8), (A10) and (A11) are reduced from three to two on going from the 3CG and 3CM to the 2CG and 2CM models, respectively.

Finally, an important distinction between traditional compartmental analysis and the way it is implemented here is described. The distinction is relevant to the number of distinct eigenvalues and f_{ij}'s that can be resolved for any given compartmental model.

Historically, compartmental analysis was applied to washout experiments in which the actual quantity or concentration of material in one of the model's tissues/compartments (e.g. $q_1(t)$, where "1" is the central compartment) was determined explicitly as a function of time. It has been shown for the 3CM model, for example, that all five of its f_{ij} 's are theoretically resolvable, provided that error-free data in the form $q_1(t)$ *vs* t is available (16, Chapter 14). However, data in the form of $q_1(t)$ *vs* t (or, equivalently, $p_1(t)$ *vs* t) provides more information than is available in diving applications where the fit is to observed $P(DCS)$ data. Fitting to $P(DCS)$ data entails fitting to a function that involves a time integral of $p_1(t)$, and not $p_1(t)$ itself (see Appendix B). The former has less information than the latter. Consequently, the number of compartmental f_{ij}'s that can be resolved is reduced in diving applications. It becomes equal to the number of resolvable eigenvalues, as can be seen from Eqs (A4) and (A12). The latter depends on the model and the dataset used for calibration, as described below.

The model (not the dataset) limits the maximum number of resolvable eigenvalues for a given interconnected model. For an n-compartment interconnected model, the characteristic polynomial is n^{th} order, so that the maximum number of resolvable eigenvalues is "n". Increasing the size or altering the composition of a dataset influences the accuracy of the parameters being determined but not (for a given model) the maximum number of resolvable parameters. However, a sufficiently sparse or noisy dataset can reduce the actual number of resolved eigenvalues from the theoretical maximum. For example, if the 3CM or 3CG model were fitted to a dataset for which the underlying washout function could be adequately represented by a sum of two exponentials, the solution of Eq (A4) would

produce only two distinct eigenvalues. Two of the three eigenvalues would be statistically indistinguishable from each other. For the dataset used here (Table 1) the number of resolved eigenvalues was found to be two for the 2CM and 2CG models and three for the 3CM and 3CG models, at the 95% level-of-confidence (Table 2). Thus the dataset used was sufficient for the purpose of resolving all the distinct eigenvalues that exist for each of these four models at this level-of-confidence.

The method used to reduce the number of unknowns is to impose "equality constraints" (connecting equations) between two or more f_{ij}'s (16, Chapter 14). Two equality constraints are required in the 3CM model to reduce its number of f_{ij}'s from five to three. While there is no unique or generally accepted way of doing this, basic kinetics suggests the following strategy. Since the slow rate constants will be rate-limiting, try to identify the fast rate constants in the model and approximate them by a single average rate constant.

From the observation that perfusion of well-perfused tissues and diffusion within them of low molecular weight solutes (such as N_2) occur on relatively fast and (very roughly) similar time scales (16, Chapter 10), two approximations suggest themselves, namely: $f_{10} \approx f_{12}; f_{10} \approx f_{13}$. Making the approximation: $f_{1x} = f_{10} = f_{12} = f_{13}$, where $f_{1x} = \frac{1}{3}\left(f_{10} + f_{12} + f_{13}\right)$ results in a simplified 3CM model with three independent and resolvable rate constants f_{1x}, f_{21}, f_{31}.

As indicated previously, the 3CG model in its most general form has seven f_{ij}'s. This model required four equality constraints to reduce the number of independent f_{ij}'s to three. The relations: $f_{20} = PR_2 f_{21}$ and $f_{30} = PR_3 f_{31}$, in addition to

$f_{1x} = f_{10} = f_{12} = f_{13} = \frac{1}{3}\left(f_{10} + f_{12} + f_{13}\right)$ were used. "PR_i" is the "perfusion ratio" in peripheral compartment "i". It is the ratio of the perfusion : diffusion rate constants out of compartment "i". PR_2 and PR_3 were each arbitrarily set to 0.2, simply in order to illustrate the properties of the 3CG model. Also, by definition $PR_2 = PR_3 = 0$, for the 3CM model.

The 2CM model required one equality constraint which, following the above, was taken to be $f_{10} = f_{12} = f_{1x}$. Again, using the notation $f_{1x} = \frac{1}{2}\left(f_{10} + f_{12}\right)$, this equality constraint reduces the number of independent f_{ij}'s in this model from three $\left(f_{10}, f_{12}, f_{21}\right)$ to two $\left(f_{1x}, f_{21}\right)$, which were adequately resolved (Table 2).

The 2CG model required an additional constraint (relative to the 2CM model) which, by analogy with the 3CG model, was taken to be $f_{20} = PR_2 f_{21}$, with PR_2 again, for illustrative purposes, arbitrarily set equal to 0.2. With these two constraints, the number of independent rate constants in the 2CG model was reduced from four $\left(f_{10}, f_{20}, f_{12}, f_{21}\right)$ to two $\left(f_{1x}, f_{21}\right)$, which, again, were adequately resolved (Table 2).

It is important to note that it was confirmed in the calibrations that, for each of the four simplified interconnected compartmental models (2CM, 2CG, 3CM and 3CG), f_{1x} was indeed, as assumed, the fastest rate constant in the model (Table 2). This provides partial support for the choices that were made for the equality constraints, and for the simplified models that resulted from them.

APPENDIX B

Computational and Statistical Methods

(1) Calculation of $P(DCS)$

1 a) Interconnected models (2CM, 2CG, 3CM, 3CG)

The calculation of the integrated risk "R_j" along any profile segment "j" that involves decompression was obtained by numerical integration of the integral in Eq.(B1).

$$R_j = \int_{t_1}^{t_2} r(t)dt \tag{B1}$$

Here $r(t)$ is obtained from Eq.(1) and (t_1, t_2) are the initial and final times that define segment "j". "$p_1(t)$" in Eq.(1) is the Henry's law-based partial pressure of Nitrogen in compartment "1" at any time point "t" on the profile segment. It is obtained analytically from Eq.(A10).

$P(DCS)$ is obtained from

$$P(DCS) = 1 - \exp(-R)$$

where "R", the total integrated risk over all "j" segments that involve decompression is given by

$$R = \sum_j R_j$$

Negative values of $r(t)$, when they arise, are re-set to zero. Thus, if $r(t)$ falls to zero at $t_2' < t_2$, R_j is evaluated using

$$R_j = \int_{t_1}^{t_2'} r(t)dt$$

The numerical integrations were done using Gauss Quadrature (30). Forty Gauss points were found to give at least four-figure accuracy for any integral being evaluated, and were used for all the quadratures.

The integrated risk after surfacing ($R_{surface}$, below) comprised at least 90% of the total risk for most of the profiles considered here, and requires special care. Direct application of Gauss Quadrature to the integral

$$R_{surface} = \int_0^{\infty} r(t)dt \qquad \text{(B2)}$$

often produces an inaccurate result. (In Eq.(B2) the time of surfacing is set to zero for purposes of doing the integration.) The remedy is to replace the infinite upper limit, by the time "t_u" at which $r(t)$ falls to zero, so that

$$R_{surface} = \int_0^{t_u} r(t)dt \qquad \text{(B3)}$$

"t_u" must be evaluated numerically, and the following method was used.

"t_u" is the solution of $r(t_u) = 0$. This is equivalent (see Eq.(1)) to solving for "t_u" as the root of:

$$p_1(t_u) - [P_0 + B] = 0 \qquad \text{(B4)}$$

with $P_0 = 1atm$ and $B = .0211atm$. "Bisection" was the numerical method used to find "t_u". While some other root-finding routines converge more rapidly, bisection, unlike many faster methods, is 100% reliable. The bisection algorithm given in Ref. 30 was used, and "t_u" was obtained to at least four-figure accuracy.

For the profiles dealt with here, the calculation of $P(DCS)$ required $0\left(10^{-3} - 10^{-2}\right)$ sec per profile on a desk-top PC with a 2.8 GHz processor.

1 b) Independent Parallel Compartment Model (2CP)

Here, the compartments are perfusion-limited and follow the first-order rate law:

$$\frac{dp_i(t)}{dt} = k_i\left(p_{a,n} - p_i\right) \qquad i = 1,2 \qquad \text{(B5)}$$

In the above, "k_i" is a first-order rate constant, "$p_{a,n}$" is the nitrogen partial pressure determined from the arterial gas equation, and "p_i" is the (Henry's law-based) partial pressure of nitrogen in compartment "i". The latter is known analytically, for both ramps and plateaus, from the integrated form of Eq.(B5).

The calculations for this model were straightforward and were similar to descriptions of them given elsewhere (34, 36). The risk integrals were done analytically for underwater plateaus and surface decompressions, and numerically (using 40-point Gauss Quadrature) for the ramp decompressions.

1 c) Arterial Nitrogen Partial Pressure

As in other work (34), the arterial nitrogen partial pressure is assumed equal to the alveolar nitrogen partial pressure, and was taken to be given by:

$$p_{a,n} = .79\left(P_0(t) - P_{H_2O}(v)\right) \qquad \text{(B6)}$$

where (as elsewhere) $P_0(t)$ is the total hydrostatic ambient pressure and $P_{H_2O}(v)$ is the vapour pressure of water at body temperature. Using $P_0(t)=(1+d(t)/33)atm$, with $d(t)$ as the depth in *fsw*, and $P_{H_2O}(v)=.06053atm$ in Eq.(B6) gives Eq.(B7) as the working equation for the arterial nitrogen partial pressure.

$$p_{a,n}(t)=.79\left(.9395+\left(d(t)/33\right)\right)atm \qquad \text{(B7)}$$

This expression was used in both Eq.(B5), for the independent parallel compartment model, and in Eq.(A2), for all four interconnected models.

(2) Calibration

All the calibrations were based on maximizing the Likelihood Function "L" with respect to the model parameters. The method has been described elsewhere (3, 36 and 40). A brief outline is given below for purposes of completeness.

"L" is given by Eq.(B8)

$$L\equiv\prod_{i=1}^{ND}P_i^{Y_i}\left(1-P_i\right)^{(1-Y_i)}=\prod_{j=1}^{NPR}P_j^{SY_j}\left(1-P_j\right)^{\left(NTR_j-SY_j\right)} \qquad \text{(B8)}$$

The form on the left is a product over the total number of dives (ND) in the dataset. The form on the right, which is a compact version of the form on the left, is a product over the number of profiles in the dataset (NPR). For numerical convenience (36), one instead minimizes the negative logarithm of L shown in Eq.(B9).

$$-\ln L=\sum_{j=1}^{NPR}\left\{SY_j\ln\left(\left(1-P_j\right)/P_j\right)-NTR_j\ln\left(1-P_j\right)\right\} \qquad \text{(B9)}$$

In Eqs.(B8) and (B9), P_j is the model-computed $P(DCS)$ value for profile "j", NTR_j is the number of trials for profile "j", and SY_j is the total number of "hits", including "marginals", for profile "j".

$$SY_j = NH_j + WM(NM)_j \qquad \text{(B10)}$$

In Eq.(B10), "NH_j", "NM_j" and "WM" are respectively the number of hits (*bona-fide* DCS cases), the number of marginals (mild DCS -like cases that resolve themselves without recompression treatment) and the weight given to marginals. For reasons given in the text, WM was taken to be 0.1.

The minimization technique used was "simulated annealing" (19, 20) which is a Monte Carlo-based method that is useful for avoiding and, when necessary, escaping from local minima – a frequent problem encountered when minimizing multi-dimensional functions. It has the powerful theoretical advantage that it can be *guaranteed* to locate a global minimum, provided the simulated cooling schedule used is suitable (8) The latter, however, entails extremely slow simulated cooling schedules that are computationally impractical. The technique was, therefore, implemented in the usual way. Initial guesses for the parameters are made, the algorithm for the method (19, 20 and 30) is implemented, and the values of the parameters that minimize $-\ln L$ are obtained. The main details follow.

The maximum trial displacements for each parameter were re-set, at each simulated temperature, to 10% of the respective value of the parameter obtained from the previous simulated temperature in the run. This helped ensure efficient (non-zero and non-unit) acceptance rates for each parameter throughout

the run. The simulated temperatures were reduced, after 100 – 1000 "passes" over the parameters at each simulated temperature, in steps of 10% increments. A "pass" is a set of trial changes, with one attempted change for each of the model parameters. The calculation is repeated using different numbers of passes, different numbers of simulated temperatures, and different initial guesses of the parameter values to ensure that the same final result for the parameters and for $-\ln L$ is obtained. When repeated runs produce essentially the same result, one assumes one is at the global minimum, and the resultant parameter values are taken as the solution.

(3) Confidence Intervals ("CI's")

3 a) Model Parameters

As with the minimization technique that was used to determine the parameter values, the method used to determine their CI's was also Monte Carlo-based. The method, developed initially for use in astrophysics (1, 23), has been generalized (30). It involves the creation of "synthetic" datasets by means of a Monte Carlo realization. These synthetic datasets lead to synthetic parameter sets which, in turn, provide the CI's. The method is well-suited to diving applications. Its only requirement (apart from sufficient computer time) is knowledge of how the observations are distributed. Incidence rate data used in diving are known to be distributed binomially.

The method consists of the following steps. (i) Use the actual dataset to minimize " χ^2 " by maximizing the likelihood function " L " with respect to the model parameters. In other words, calibrate the model as described above

in (2). (ii) Create "M" synthetic datasets as follows. For each profile "j" in the actual dataset, generate "M" integer values of "NH_j" – the expected number of hits for profile "j" (e.g. 0, 1, 2,…, NTR_j). Do this by sampling "M" times from a binomial distribution characterized by NTR_j trials and a hit rate of P_j. P_j is obtained by applying the parameter set determined in step (i) to profile "j" for the model under consideration. Distribute these "M" values of NH_j among "M" bins, one to each bin, and repeat the process for all the profiles in the dataset. The "M" bins now each contain one synthetic dataset. (iii) Do a "χ^2" minimization (by maximizing "L") on each of the synthetic datasets, exactly as was done in step (i) for the actual dataset. This provides "M" synthetic parameter sets (one from each bin). (iv) Use the distribution of the "M" synthetic values of each of the model parameters, to create the desired confidence interval for each parameter.

The method has the very desirable feature of providing stochastically exact CI's. This means, that as the run lengths and "M" are increased, the parameter distributions and the resultant CI's become increasingly exact (given the model and the observed dataset), with no systematic bias. In practice, "M" was taken to be 100. This value produced CI's that were within about 10% of those found with $M = 30$.

There are two additional technical points. (1) The effect of marginals is included implicitly through their influence on the calculated values of P_j and NH_j. It is not possible to determine separate values of NH_j and NM_j for the synthetic datasets since, from a value of NTR_j and P_j, only the sum

$NH_j + WM(NM)_j$ is known uniquely. Therefore, NM_j is taken as zero in all the synthetic datasets, and their influence is carried by (the raised values of) NH_j. This has no effect on the size of the CI's. (2) Techniques for sampling from various types of distribution functions are available from the numerical methods literature (22). The "Rejection Method" described in Refs. (22) and (30) was used to properly sample from a binomial distribution. The algorithm given for it in (30) was used.

3 b) $P(DCS)$ Values

Once the "M" synthetic parameter sets for a given model have been generated, it is straightforward to work out the CI's for the model-predicted $P(DCS)$'s for any profile. One simply uses the "M" synthetic parameter sets generated above in step (iii) to generate "M" sets of $P(DCS)$ values, from which a CI of any desired size is extracted.

APPENDIX C

Estimation of the Threshold Pressure, Threshold Depth, and "*B*"

The value of "B" needed for use in Eq.(1) was obtained as follows. The threshold pressure, "P_{th}", is first determined from Eq.(C1) applied at saturation (i.e., $t \geq 1440$ min) and at threshold depth, "d_{th}".

$$r_i(t) = 0 \tag{C1}$$

Using Eq.(1) for $r_i(t)$ in Eq.(C1), $p_i(t) = p_{a,n}(d_{th})$, (which holds for all the models at saturation), Eq.(B7) for $p_{a,n}(d_{th})$, and $P_0 = 1atm$, gives Eq.(C2) with "d_{th}" in units "fsw".

$$P_{th}(atm) = {}^{.79}\!/_{33} d_{th} - .06672 \tag{C2}$$

Combining this with the definition of "B" (Eq.(1)) and the value $P_{fvg} = .19212atm$ (34) gives

$$B(atm) = {}^{.79}\!/_{33} d_{th} - .25884 \tag{C3}$$

The value of "d_{th}" was estimated by fitting $P(DCS)$ as given by Eq.(C4), to the direct ascent, air, human, saturation incidence rate datasets listed in Table 1 (see entries for "Saturation, Air").

$$P(DCS) = 1 - \exp(-R) \tag{C4}$$

$$R = \left(\frac{d - d_{th}}{A}\right)^m, \qquad d \geq d_{th}$$

Eq.(C4) represents $P(DCS)$ as a three-parameter hazard function (12,13) and $\exp(-R)$, the "survivor fraction", is in the form of a three-parameter Weibull

function (12). The profiles used, which span eight depths in the range (20 – 33) fsw, and involved 180 individual trials, represent all the relevant data, using air, for dives of this kind that exists. As with all the other calibrations, marginals were weighted as 0.1, Maximum Likelihood and Simulated Annealing were used to obtain the parameter estimates, and the confidence intervals were determined as described in Appendix B. The results are given in Table C1, together with earlier estimates for these parameters determined by Hills (12, 13). The entries are consistent with, and not markedly different from Hills' values, despite major differences in how they were obtained. Unlike here, Hills did not use raw data for his calibration. Rather, he used a quasi-dataset that he created (13) using assumptions now considered questionable.

The large uncertainties of the parameter estimates reflect the very limited dataset available for this purpose, and the requirement that three parameters be extracted from it. Using $d_{th} = 11.7\, fsw$ gives $P_{th} = .21 atm$, and $B = .021 atm$. This value of B was used in the $r_i(t)$ expressions for all the models.

Table C1. Parameter estimates for the hazard function (Eq.C4)

Source	$d_{th}(fsw)$	$A(fsw)$	m
This work	11.7 (0 – 20)	26 (16 – 43)	3.8 (.7 – 9.6)
Refs. (12,13)	14.3	25.1	4.73

Entries in parentheses are 95% confidence intervals.

The method described above for determining the value of "d_{th}" was used for two reasons: (1) it takes into account the definition of "d_{th}" (see text and Eq

(C4) ; (2) it obviates the need to introduce "d_{th}" as a fifth adjustable parameter in the calibrations of the 2CP, 3CM and 3CG models.

However, it is important to know whether these models' characteristic properties, i.e. those illustrated in Figs. 2, 3 and 5, hinge on a specific value of "d_{th}". To address this, the 2CP, 3CM and 3CG models were each recalibrated with "d_{th}" taken as an adjustable parameter, without consideration of its definition. The same dataset (Table 1) used in the main calibrations was used. To prevent unphysical solutions (negative or very large "d_{th}"values), the values of "d_{th}" were constrained to the range 0-20 *f*sw. These limits were suggested by the 95% confidence interval shown in Table C1. As with the main calibrations, the rate and proportionality constants were unconstrained, except for the requirement that they be positive. For this recalibration, "d_{th}" was given one of a series of values in the range 0-20 *fsw*. For each of these values, the four remaining constants (k_1,k_2,c_1,c_2) or (f_{1x},f_{21},f_{31},*c)* were re-evaluated (as before using Maximum Likelihood and Simulated Annealing).

For each of these three models, "-ln *L*" displayed a broad flat minimum for "d_{th}" in the range 15-19 *fsw*. The flatness of this curve in the vicinity of the minimum made it difficult to determine of the precise location of the minimum. Since getting precise solutions for "d_{th}" was irrelevant to the purpose of this exercise, "d_{th}" was simply approximated by 18 *fsw* for all three models. In other words, for each of the recalibrated models, "d_{th}" was set equal to18 *fsw*. Then, "-ln *L"* was minimized for each model with respect to the remaining four

parameters. The resulting four parameters values, together with d_{th} = 18 *fsw,* defined each recalibrated model. The qualitative features of the main results are summarized below.

The goodness-of-fit, relative to fits based on d_{th} = 11.7 *fsw,* was improved for all three models. This is not surprising, in view of the small number of adjustable parameters (four) in the original models.

For each of the 2CP, 3CM and 3CG models, the level of agreement with the USN93D results described in the text and shown in Table 4 was greatly reduced. Specifically, using the calibration based on d_{th} = 18 *fsw,* the number of "overlaps" between the 2CP, 3CM and 3CG models' predictions, and those of the USN93D model, dropped from 12,15 and 15, to 3, 0 and 0 , respectively.

It is highly significant, however, that the distinctive qualitative features of both the 3CM and 3CG models remained unchanged on recalibration. Specifically, the recalibrated 3CM and 3CG models provided extrapolated *P(DCS)* values that were very close to those of the original 3CM model shown in Fig 2. Also, the recalibrated 3CM and 3CG models predicted the relatively large stop-induced *P(DCS)* abatements found for the earlier 3CM and 3CG models. Specifically, the *P(DCS)* abatements for the recalibrated models were similar to those shown in Figs 3 and 5 for the original 3CM and 3CG models.

The recalibrated 2CP model behaved similarly to the original 2CP model with respect to the results shown in Figs 2 and 3. It did, however, show a more rapid *P(DCS)* abatement with stop time, relative to the result shown for it in Fig. 5.

To summarize, the main qualitative features of the 3CM and 3CG models do not hinge on a specific value of "d_{th}". Also, the choice of 11.7 *fsw* for "d_{th}" is, for the 2CP, 3CM and 3CG models, significantly better than the choice of 18 *fsw*, with respect to the level of agreement with the USN93D results shown in Table 4.This is not surprising, since the former value arose from a calibration that took into account the definition of "d_{th}", while the latter value was based on a calibration that did not.