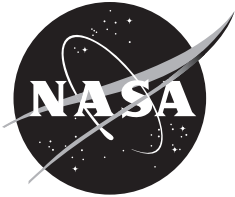


NASA/TP—2001–210775



# **A Log Logistic Survival Model Applied to Hypobaric Decompression Sickness**

*Johnny Conkin, Ph.D.  
One Baylor Plaza, NA-425  
Houston, TX 77030-3498*

## The NASA STI Program Office ... in Profile

Since its founding, NASA has been dedicated to the advancement of aeronautics and space science. The NASA Scientific and Technical Information (STI) Program Office plays a key part in helping NASA maintain this important role.

The NASA STI Program Office is operated by Langley Research Center, the lead center for NASA's scientific and technical information. The NASA STI Program Office provides access to the NASA STI Database, the largest collection of aeronautical and space science STI in the world. The Program Office is also NASA's institutional mechanism for disseminating the results of its research and development activities. These results are published by NASA in the NASA STI Report Series, which includes the following report types:

- **TECHNICAL PUBLICATION.** Reports of completed research or a major significant phase of research that present the results of NASA programs and include extensive data or theoretical analysis. Includes compilations of significant scientific and technical data and information deemed to be of continuing reference value. NASA counterpart of peer-reviewed formal professional papers, but having less stringent limitations on manuscript length and extent of graphic presentations.
- **TECHNICAL MEMORANDUM.** Scientific and technical findings that are preliminary or of specialized interest, e.g., quick release reports, working papers, and bibliographies that contain minimal annotation. Does not contain extensive analysis.
- **CONTRACTOR REPORT.** Scientific and technical findings by NASA-sponsored contractors and grantees.
- **CONFERENCE PUBLICATION.** Collected papers from scientific and technical conferences, symposia, seminars, or other meetings sponsored or co-sponsored by NASA.
- **SPECIAL PUBLICATION.** Scientific, technical, or historical information from NASA programs, projects, and missions, often concerned with subjects having substantial public interest.
- **TECHNICAL TRANSLATION.** English-language translations of foreign scientific and technical material pertinent to NASA's mission.

Specialized services that complement the STI Program Office's diverse offerings include creating custom thesauri, building customized databases, organizing and publishing research results ... even providing videos.

For more information about the NASA STI Program Office, see the following:

- Access the NASA STI Program Home Page at <http://www.sti.nasa.gov>
- E-mail your question via the Internet to [help@sti.nasa.gov](mailto:help@sti.nasa.gov)
- Fax your question to the NASA STI Help Desk at (301) 621-0134
- Telephone the NASA STI Help Desk at (301) 621-0390
- Write to:  
NASA STI Help Desk  
NASA Center for Aerospace Information  
7121 Standard Drive  
Hanover, MD 21076-1320

NASA/TP—2001–210775



# **A Log Logistic Survival Model Applied to Hypobaric Decompression Sickness**

*Johnny Conkin, Ph.D.\**  
*Lyndon B. Johnson Space Center*  
*Houston, Texas*

*\*Assistant Professor*  
*Baylor College of Medicine*

National Aeronautics and  
Space Administration

Lyndon B. Johnson Space Center  
Houston, Texas 77058

---

December 2001

Available from:

NASA Center for AeroSpace Information  
7121 Standard Drive  
Hanover, MD 21076-1320  
301-621-0390

National Technical Information Service  
5285 Port Royal Road  
Springfield, VA 22161  
703-605-6000

This report is also available in electronic form at <http://techreports.larc.nasa.gov/cgi-bin/NTRS>

# Contents

	Page
Acronyms and Nomenclature .....	iv
Acknowledgment .....	iv
Abstract .....	1
Introduction .....	2
Methods .....	2
Selecting the Appropriate Hazard Function .....	2
Data .....	4
Management of O <sub>2</sub> Prebreathe .....	5
Analytical Process .....	6
Parameter Estimation by Maximum Likelihood .....	6
Results .....	7
Conclusions .....	10
References .....	13
Appendix A: Two Forms of the Log Logistic Survival Model .....	15
Appendix B: Variables in the Hypobaric Decompression Sickness Database .....	17

## Tables

I	Various Log Logistic Survival Models for DCS .....	8
---	--	---

## Figures

1	The proportion of 1574 cases of DCS as a function of time at altitude .....	3
2	The empirical cumulative distribution $F_n(t)$ for 1574 cases of DCS out of 3895 exposures .....	3
3	The empirical function $F_n(t)$ for 536 cases of VGE out of 1401 exposures .....	4
4	The $P(\text{DCS})$ at either 3.5, 4.3, or 6.0 psia with (solid line) or without (dashed line) exercise at a particular time after decompression .....	9
5	Predicted vs. observed DCS incidence in 66 groups used to fit Eq. (17) .....	9
6	The $P(\text{DCS})$ vs. time at altitude from Eq. (12) .....	10
7	A bar graph to show the observed incidence of DCS in 10 intervals compared to the predicted $P(\text{DCS})$ from Eq. (12) .....	10
8	A scatter plot that shows the observed incidence of DCS in a group and the calculated decompression dose #1 .....	11
9	A scatter plot that shows the observed incidence of DCS in a group and the calculated decompression dose #2 .....	11
10	The resulting $f(t; z)$ for the average DP of 6.0 psia from the $f(t; z)$ equation on Fig. 9 .....	12
11	The approximate flight envelope of the T-38 and the resulting cabin pressure under nominal flight conditions .....	12
12	The flight and cabin pressure envelope under extreme flight conditions .....	13

## Acronyms and Nomenclature

DCS	decompression sickness
EVA	extravehicular activity (spacewalk)
F(t)	cumulative distribution function (cdf)
$F_n(t)$	empirical representation of F(t)
f(t)	probability density function (pdf)
HDSD	hypobaric decompression sickness databank
h(t)	hazard function
H(t)	cumulative hazard function
ISS	International Space Station
LL	log likelihood
LRT	likelihood ratio test
$N_2$	nitrogen
$O_2$	oxygen
P1	pressure before depressurization (psia)
$P1N_2$	computed nitrogen pressure in a theoretical tissue compartment (psia)
P2	pressure after depressurization (psia)
P(DCS)	probability of decompression sickness
psia	pounds per square inch absolute
S(t)	survival function
TR	tissue ratio ( $P1N_2 / P2$ , unit less)
VGE	venous gas emboli

## Acknowledgment

This body of work, which was published and presented in Seattle, Washington, at the May 19, 1998, Undersea and Hyperbaric Medical Society Workshop on Survival Analysis in Environmental Physiology, could not have been done were it not for the exchange of ideas between my colleagues and me. These colleagues include: Michael R. Powell, Philip P. Foster, Alan H. Feiveson, Michael L. Gernhardt, Vasantha Kumar, James M. Waligora, Karin C. Loftin, Hugh D. Van Liew, Wayne A. Gerth, R. Srinivasan, and Kallappa M. Koti. NASA supported part of this work through the NASA Cooperative Agreement NCC 9-58 with the National Space Biomedical Research Institute.

## **Abstract**

Decompression sickness (DCS) is a complex multivariable problem. A mathematical description or model of the likelihood of DCS requires a large amount of quality research data, ideas on how to define a decompression dose using physical and physiological variables, and an appropriate analytical approach. It also requires a high-performance computer with specialized software since thousands of exposure records with tens of variables are now available. I have used published DCS data (from hypobaric decompressions of humans in altitude chambers) to develop my decompression doses, which are variants of equilibrium expressions for evolved gas plus other explanatory variables. The analytical approach I have chosen is survival analysis, where the time of DCS occurrence is modeled. I chose this approach because a log logistic survival analysis is a powerful method by which to test competing hypotheses as well as to develop probability models about hypobaric DCS. My conclusions can be applied to simple hypobaric decompressions – ascents lasting from 5 to 30 minutes – and, after minutes to hours, to denitrogenation (prebreathing). My conclusions are applicable to long or short exposures, and can be used whether the sufferer of DCS is at rest or exercising at altitude. Ultimately I would like my models to be applied to astronauts to reduce the risk of DCS during spacewalks, as well as to future spaceflight crews on the Moon and Mars.

## Introduction

Scientists have been challenged to understand and prevent hypobaric decompression sickness (DCS) ever since humans were taken high into the atmosphere following development of the jet engine. DCS, in all of its myriad forms and manifestations, is fundamentally linked to evolved gas in the body. A fundamental axiom about DCS is that a transient gas supersaturation, also called overpressure or pressure difference ( $\Delta P$ ), exists in a region of tissue. The sum of all gas partial pressures there is greater than the ambient pressure opposing the release of the gas. The metastable condition may resolve with a phase transition (in the presence of micronuclei), and some of the excess mass (moles) of gas in the form of bubbles may be accommodated by the tissue and cause no symptoms. The likelihood or probability that DCS increases as the evolved gas dose increases is a necessary but not sufficient condition in the mechanical view of DCS. We do not yet know all of the complex biophysical processes responsible for evolved gas in the tissue. We know even less about the linkage between evolved gas and subsequent signs or symptoms of DCS.

What we do know is that because of the complex and dynamic biophysical, biochemical, and physiological processes associated with living tissue, micronuclei and later bubbles may or may not form given the same experimental conditions. Even when bubbles grow, symptoms may or may not develop under the same experimental conditions. It is therefore better (or appropriate) to consider DCS as a probabilistic rather than a deterministic event.<sup>1,2</sup> By this I mean that the presence or absence of symptoms — for the same individual and under identical experimental conditions — may or may not be observed from one day to the next. So, a quantitative description of DCS requires a large number of quality research data,<sup>3</sup> ideas on how to define a multivariable decompression dose, and analytical approaches that maximize the available information. A log logistic survival analysis provided me with a powerful method to test competing hypotheses about DCS as well as to provide DCS probability models.<sup>4-7</sup>

## Methods

### Selecting the Appropriate Hazard Function

Since the survival function  $S(t)$ , cumulative distribution function (cdf)  $F(t)$ , hazard function  $h(t)$ , cumulative hazard function  $H(t)$ , and probability density function (pdf)  $f(t)$  are different expressions of the same survival analysis, it is possible to derive all of them by just knowing one of them.<sup>7,8,9</sup> The survival function is defined as  $S(t) = 1 - F(t)$ . Since the probability density function,  $f(t) = dF(t) / dt$ , is related to the hazard function,  $h(t) = f(t) / S(t)$ , the functional form of  $h(t)$  may be revealed given  $F_n(t)$  from a plot of DCS data, where  $F_n(t)$  is the empirical representation of  $F(t)$ . An equivalent definition of  $h(t)$  is  $dF(t) / dt / (1 - F(t))$ . The mathematical relationship between  $h(t)$  and  $F(t)$  is clearer with this form. I will discuss my approach in terms of  $h(t)$  because an *a priori* rationale exists for determining  $h(t)$  for hypobaric DCS.

The hazard function  $h(t)$  defines the instantaneous failure rate at a specific time, given that the subject survived to at least that specified time point without a response. It is expressed in  $\text{hour}^{-1}$  in my application. Lee<sup>9</sup> states, “ $h(t)$  gives the conditional failure rate; the probability of failure during a small time interval, assuming that the individual has survived to the beginning of the interval, or as the limit of the probability that an individual fails in a very short interval,  $t$  to  $t + \Delta t$  per unit time, given that the individual has survived to time  $t$ .” In my case,  $h(t)$  gives the probability of decompression sickness  $P(\text{DCS})$  per unit time during the altitude exposure given that the individual has survived to time  $T$  while at altitude. The instantaneous failure rate for hypobaric DCS eventually goes to zero; indeed, some subjects never get DCS at a lower pressure, assuming that the lower pressure is greater than about 2.5 psia since hypoxia and ebullism prevent humans from going to a vacuum. If humans remain at the lower pressure long enough — say, for 48 hours — they will come into a new equilibrium with that environment and are not at risk for DCS unless they once again ascend to an even lower ambient pressure. This situation differs from the lifetime of



light bulbs, for example. Eventually all light bulbs in a random sample will fail, so  $h(t)$  will never be zero for light bulbs. A new type of survival analysis, which is called “cure models,” may improve my current methods; these models properly address the reality that some subjects will never have DCS.

The function  $h(t)$  to describe DCS failure time might be selected based on a list of available functions, an understanding of the underlying failure process, a study of the cumulative distribution of the failure time  $F_n(t)$ , or combinations of all three. The function may increase, decrease, remain constant, or have a complex form due to an underlying complex process.<sup>9</sup> Many variables interact to define the failure time (or survival time depending on preference). The distribution of failure time for hypobaric DCS in a large data set from different tests is skewed to the right. Figure 1 shows 1574 cases of DCS in the hypobaric decompression sickness databank (HDSD)<sup>3</sup> partitioned into

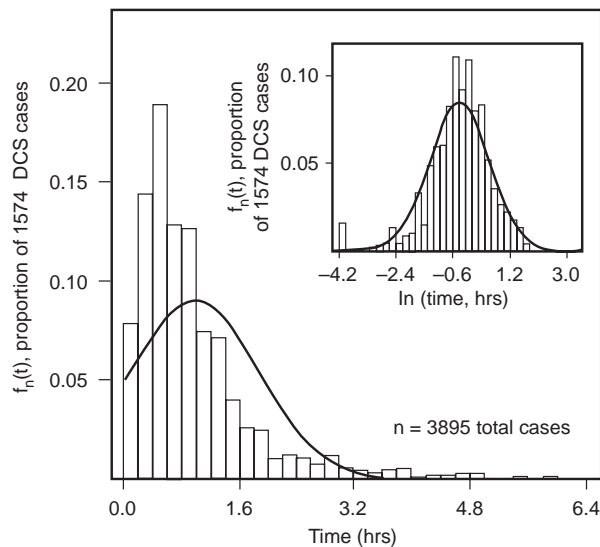


Figure 1. The histogram shows the proportion of 1574 cases of DCS as a function of time at altitude. The histogram is the empirical probability density function  $f_n(t)$ . The inset shows the natural log transformation of the skewed distribution into a normal distribution. These data show that DCS, under a variety of different test conditions, is manifested early; that is, within the first 2 hours of exposure.

0.2-hour intervals. This figure is a histogram representation of  $f(t)$ , in which the symbol  $f_n(t)$  is used to signify the empirical representation of  $f(t)$ . The solid curve is the histogram smoothed with the normal density function. The inset shows the same information replotted after a natural log transformation of failure time. This distribution appears normal. There were some severe tests, and symptoms were reported prior to or immediately on arrival at the test altitude. These symptoms actually developed during ascent to altitude, and the few cases that developed were assigned a 1-minute failure time in the HDSD since the convention was to start exposure time upon arrival at the test altitude. This convention accounts for the few cases seen at the left of the otherwise normal log distribution. Figure 2 shows the cumulative DCS failure distribution of the 1574 cases of DCS described in Figure 1. The inset shows an expanded view of the failure time over the first hour to better visualize the shape of  $F(t)$  near time = 0.

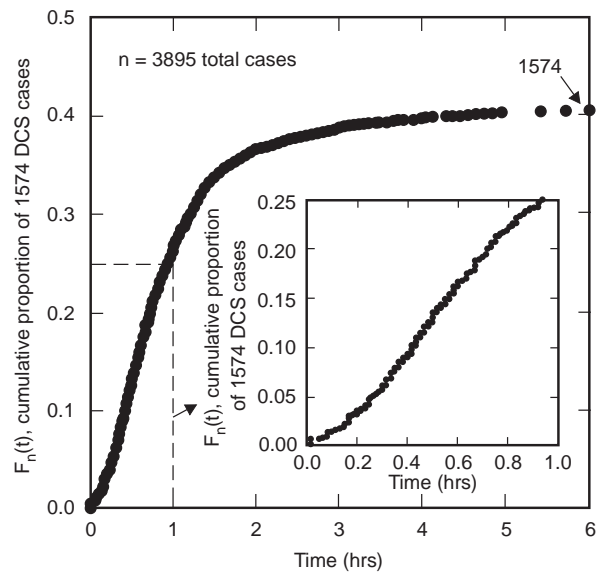


Figure 2. The empirical cumulative distribution  $F_n(t)$  for 1574 cases of DCS out of 3895 exposures.  $F(t)$  is the cumulative distribution of failure time divided by the total number of records in the tests. The inset shows the same data, but the time axis is limited to the first hour after reaching the test altitudes. The changing slope is easier to see on this expanded time scale, and this slope is important to the selection of an appropriate survival model.

There are several observations about DCS that help us to define an appropriate  $h(t)$ . First, the rate at which DCS occurs is a function of time, so the exponential distribution of failure time is not considered here. The exponential distribution defines  $h(t)$  as a constant, so the time at altitude has no relation to the failure rate. If  $h(t)$  was constant, the cumulative distribution of failure time, approximating the  $F(t)$ , would be an increasing exponential defined as:  $1 - \exp(-k * t)$ , where  $k$  is a constant. The function  $S(t)$  would be a decreasing exponential defined as:  $\exp(-k * t)$ . The natural log transformation of  $S(t)$  yields  $\ln S(t) = -k * t$ , which is a linear function of time. It is easy to reject that the failure times come from an exponential distribution since a plot of  $\ln S(t)$  against time in Figure 2 is not a straight line, with the slope  $k$  being the constant hazard rate. Second, observations of failure times and symptom intensity also help to define  $h(t)$ . The onset of a symptom is not instantaneous, and the risk of having a symptom increases with time. But, it is unlikely that a person will develop a symptom if he/she survives past some critical time since breathing 100% oxygen ( $O_2$ ) (as is usually done at altitude) will ultimately reduce the nitrogen ( $N_2$ ) pressure in the tissues. Also, some subjects with Type I (pain-only) symptoms report that the intensity of pain reaches a peak before it subsides; and that, in some cases, the pain is completely gone before the end of a test. Third, observations about venous gas emboli (VGE) are helpful to define  $h(t)$  for DCS since evolved gas is fundamentally linked to a subsequent report of pain or other signs and symptoms.<sup>6,10</sup> The two types of data share a common underlying etiology. Figure 3 shows the cumulative VGE failure distribution for 536 of 1401 records in the HDS. Not all tests produced VGE.

Therefore in hypobaric decompressions, the instantaneous risk of DCS may increase with time, but only up to a certain point. The observed pattern of DCS and VGE failure time and the intensity of symptoms lead me to conclude that the incidence of DCS from hypobaric decompressions

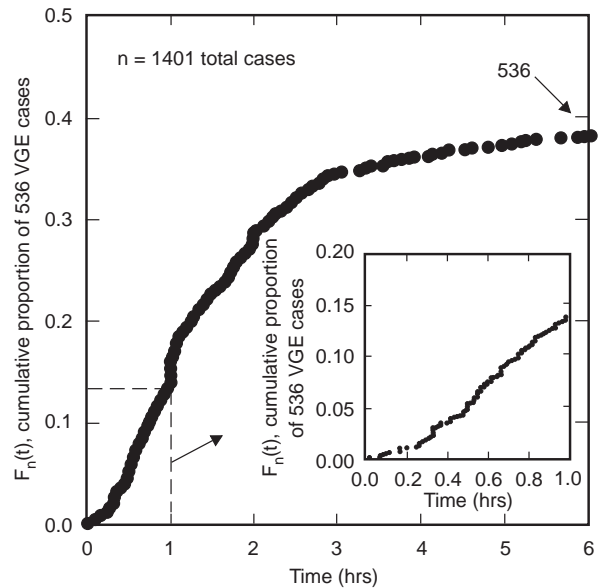


Figure 3. The empirical function  $F_n(t)$  for 536 cases of VGE out of 1401 exposures. The inset shows the data up to 1 hour. VGE are detected noninvasively with Doppler ultrasound technology. The pulmonary artery is insonated with the ultrasound beam, and the presence of moving bubbles on the way to the pulmonary circulation is noted. Figure 2 has a similar shape, which suggests that VGE and DCS share a common etiology.

would be described well with an  $h(t)$  that rises to a peak before it decreases with time. The log normal or log logistic survival models are good candidates for this, since both provide for a non-monotonic  $h(t)$ . Unfortunately, the functions  $F(t)$  and  $S(t)$  for both models may be “S”-shaped. It is at the level of  $h(t)$  and  $f(t)$  that the two distributions are distinguishable. The log logistic model does not provide a slow increase of  $h(t)$  and  $f(t)$ , but the log normal model does provide for this. The log normal is slightly better in most cases, due in part to its ability to describe this “lag” component of  $h(t)$ ; but the log logistic model is easier to implement. Details about the log logistic survival model are shown in Appendix A.

## Data

Analyses presented here are based on results from documented hypobaric chamber tests and approaches<sup>11</sup> that account for failure and

censored times. Investigators in the U.S. Navy have also exploited information about DCS failure time in divers.<sup>12</sup> In my application, failure time is defined as elapsed time from the beginning of a test after the decompression to the first report of a DCS symptom. Censored time is defined as elapsed time from the beginning of a test after the decompression to the scheduled end of the test, also called right censored time. I define  $h(t)$  in terms of several variables —  $P1N_2$ ,  $P_2$ , the presence or absence of exercise at  $P_2$ , time at  $P_2$ , the presence or absence of VGE, etc. — and I use the notation  $h(t; z) = f(\text{time}, P_2, P1N_2, \text{exercise}, \text{VGE}, \text{etc.})$  to denote the hazard function for a decompression dose model, where  $t$  is time and  $z$  represents various combinations of variables and constants. Appendix B lists some of the variables and their definitions in the HDSO that were used to model DCS.

The HDSO is a computerized repository of information that was reported in the literature\* about DCS experienced in hypobaric chambers.<sup>3</sup> The HDSO currently contains information from 456 altitude tests. A test is a collection of altitude exposures where one or more subjects were used to evaluate a particular test condition. The total number of exposures in 456 tests is 131,399. Twenty-seven tests had 117,422 exposures; none of the results reported here contain information from these 27 tests. A subset of the 456 tests provided detailed information for each subject in the test, such as height, weight, age, gender, failure time to first detection of VGE, etc. There were 211 tests with 3895 exposures; the data in these tests were used in this report. The outcome or response variable is the presence (coded as 1) or absence (coded as 0) of any DCS sign or symptom — excluding paresthesia when it was the only symptom — plus the failure time to the report of the first symptom.

\*The literature represents a sample of DCS research done from the year 1940 to the present.

## Management of O<sub>2</sub> Prebreathe

Prebreathing 100% O<sub>2</sub> or O<sub>2</sub>-enriched mixtures prior to a hypobaric decompression is an effective and often-used technique to prevent DCS. It is therefore necessary to account for the use of O<sub>2</sub>-enriched mixtures prior to decompression to use the majority of information in the HDSO.

The N<sub>2</sub> partial pressure in a tissue is an important variable in any mechanistic model about DCS. Equation (1) defines how  $P1N_2$  is calculated by approximating the more complex process of dissolved N<sub>2</sub> kinetics in living tissue by a first-order kinetics. Following a step-change in N<sub>2</sub> partial pressure in the breathing medium, such as during a switch from ambient air to a mask connected to 100% O<sub>2</sub>, the N<sub>2</sub> partial pressure that is reached in a designated tissue compartment after a specific time is:

$$P1N_2 = P_0 + (P_a - P_0) * (1 - \exp^{-k * t}), \quad (1)$$

where  $P1N_2$  = the N<sub>2</sub> partial pressure in the tissue after  $t$  minutes,  $P_0$  = initial N<sub>2</sub> partial pressure in the compartment,  $P_a$  = ambient N<sub>2</sub> partial pressure in breathing medium,  $\exp$  = base of natural logarithm, and  $t$  = time at the new  $P_a$  in minutes. The tissue rate constant  $k$  is related to the tissue N<sub>2</sub> half-time ( $t_{1/2}$ ) for N<sub>2</sub> pressure in a compartment, and is equal to  $0.693 / t_{1/2}$ , where  $t_{1/2}$  is the 360-minute tissue N<sub>2</sub> partial pressure half-time, and 0.693 is the natural log of 2. Half-time is the time taken for N<sub>2</sub> pressure to increase or decrease to one-half of the difference between the initial and final values. About 94% of this difference is achieved within four half-time periods. A half-time of 360 minutes is used because Type I altitude DCS and VGE have been shown to correlate well with long half-times, using 100% O<sub>2</sub> in altitude chamber flights eliminates faster compartments as potential contributors to DCS, and long half-times also govern the return of divers from saturation exposures. The initial, equilibrium N<sub>2</sub> pressure ( $P_0$ ) in the tissue at sea level is taken as 11.6 psia instead of an average alveolar N<sub>2</sub> pressure of 11.0 psia. The use of dry-gas, ambient N<sub>2</sub> pressure as

equilibrium tissue N<sub>2</sub> pressure (P<sub>0</sub>), and as the N<sub>2</sub> pressure in the breathing mixture (P<sub>a</sub>) makes the application of Eq. (1) simple. The ratio of P1N<sub>2</sub> to P2 is the tissue ratio (TR), where P1N<sub>2</sub> is the calculated N<sub>2</sub> pressure just prior to ascent to altitude and P2 is the ambient pressure after ascent. The importance and implication of TR as an expression of evolved gas is developed elsewhere.<sup>6,13</sup>

I have described the logic that led me to select an appropriate h(t), have briefly described my source of response and explanatory variables, and will now provide an example of the analytical steps that gained me a better understanding of hypobaric DCS.

### Analytical Process

The hazard function h(t) for the log logistic survival model<sup>7</sup> is:

$$h(t) = \lambda * (t^{\lambda-1}) * \rho^\lambda / [1 + (t * \rho)^\lambda], \quad (2)$$

where  $\lambda$  and  $\rho$  are index (unitless) and scale (hour<sup>-1</sup>) parameters to be estimated, respectively, and t is time in hours in this application. When  $\lambda > 1$ , h(t) has a maximum and resembles a bell shape.

The cumulative hazard function H(t) is obtained by integrating h(t). Thus:

$$H(t) = \int_0^t h(x) dx, \quad (3)$$

where x is the dummy variable of integration. Note that h(t) may not vary with time, as with the exponential model, but the integral of h(t) will give H(t) in terms of the starting and ending time at P2. A combination of Eq. (2) and Eq. (3) yields:

$$H(t) = \ln [1 + (t * \rho)^\lambda], \quad (4)$$

where ln is the natural logarithm. Since the survival function S(t) is also defined as:

$$S(t) = e^{-H(t)}, \quad (5)$$

I obtained the following expression for S(t) from Eq. (4) and Eq. (5) for the log logistic model:

$$S(t) = 1 / [1 + (t * \rho)^\lambda]. \quad (6)$$

The probability density function f(t) is:

$$f(t) = h(t) * e^{-H(t)}, \quad (7)$$

which may be expanded as follows from Eq. (2) and Eq. (4) for the log logistic model:

$$f(t) = \lambda * (t^{\lambda-1}) * \rho^\lambda / [1 + (t * \rho)^\lambda]^2. \quad (8)$$

Now P(DCS) given failure time T ≤ the exposure time t becomes:

$$P(\text{DCS } T \leq t) = 1 - e^{-H(t)}. \quad (9)$$

In order to account for variables other than time that influence P(DCS), I expand the hazard function h(t) but retain its functional form as given by Eq. (2). The gas phase contribution to h(t) could be as simple as 1 / P2, or as complex as ((P1N<sub>2</sub> + c1) / P2) - 1)<sup>c2</sup>, but the exercise contribution is always in the form (1 + (c3 \* exercise)), where exercise at P2 is one or zero, and c1, c2, and c3 are estimated parameters. The modified h(t; z) for the log logistic model that includes P2 and exercise is:

$$h(t; z) = \lambda * (1 / P2)^{c2} * [1 + (c3 * \text{exercise})] * (t^{\lambda-1}) * \rho^\lambda / [1 + (1 / P2)^{c2} * [1 + (c3 * \text{exercise})] * (t * \rho)^\lambda]. \quad (10)$$

The function H(t; z) from Eq. (3) and Eq. (10) becomes an expression of decompression dose as a function of three variables associated with DCS plus the fitted parameters that maximize the agreement between dose and response:

$$\begin{aligned} \text{Dose} &= H(t; z) \\ &= [\ln (1 + (1 / P2)^{c2} \\ &\quad * [1 + (c3 * \text{exercise})] * (t * \rho)^\lambda)], \quad (11) \end{aligned}$$

and P(DCS) given failure time T based on P2, exercise, and time t at P2 becomes:

$$P(\text{DCS } T \leq t) = 1 - e^{-\text{Dose}}. \quad (12)$$

### Parameter Estimation by Maximum Likelihood

Maximum likelihood is the preferred method to optimize unknown parameters in a probability model where the response variable is

dichotomous and the predicted value is a probability. The maximum likelihood method provides the probability that  $y = 1$  (the response) given a value for  $x$  (the dose). This has been clearly explained by others.<sup>2,8,14</sup> The likelihood function for a set of data containing  $(d + n)$  elements with some right censored times has two components, one for the failure times (subset  $d$ ) and the other for the censored times (subset  $n$ ). Denoting the failure times by  $t_i$ ,  $i = 1, 2, \dots, d$ , and the censored times by  $t_i$ ,  $i = d + 1, d + 2, \dots, n$ , the likelihood function ( $L$ ) is:<sup>8</sup>

$$L = \prod_{i=1}^d f(t_i) * \prod_{i=d+1}^n S(t_i). \quad (13)$$

A subject with DCS contributes a term  $f(t_i)$  to the likelihood, the density of failure at  $t_i$ . The contribution from a subject whose survival time is censored at  $t_i$  is  $S(t_i)$ , the probability of survival beyond  $t_i$ .

The log likelihood (LL) is:

$$L = \sum_{i=1}^d \ln f(t_i) + \sum_{i=d+1}^n \ln S(t_i). \quad (14)$$

The SYSTAT (ver. 5.03) Nonlin module<sup>15</sup> was used to estimate unknown parameters in the models. Estimation by maximum likelihood was accomplished by specifying the negative LL in the LOSS statement:

$$\text{LOSS} = -\ln(\text{ESTIMATE}), \quad (15)$$

where ESTIMATE is a number from one to zero from the LL function, as explained below. The LL function structured in SYSTAT for the log logistic model, as an example, is:

$$\text{LL} = [\text{DCS} * \underbrace{\lambda * (t^{\lambda-1}) * \rho^\lambda / [1 + (t * \rho)^\lambda]^2}_{f(t) \text{ or } f(t; z)} + [(1 - \text{DCS}) * \underbrace{1 / (1 + (t * \rho)^\lambda)}_{S(t) \text{ or } S(t; z)}]. \quad (16)$$

The computer evaluates Eq. (16) for the first row of hundreds of rows of data. The first row contains values for the observed DCS (1 or 0),

$\text{PIN}_2$  (psia), P2 (psia), exercise (1 or 0), and time (hours): failure time when DCS = 1, or censored time when DCS = 0. When DCS is one,  $f(t; z)$  is evaluated, and when DCS is zero,  $S(t; z)$  is evaluated. The numerical result, between zero and one in each case, is called ESTIMATE, which is evaluated with initial values of the unknown parameters in the model and is used in Eq. (15). The LL calculation from Eq. (15) is repeated over all rows, and the LL is summed over all rows. The summed LL is then minimized using the Quasi-Newton algorithm.<sup>15</sup> Iterations continue for parameters in the model until a predetermined convergence criterion is reached.

## Results

Table I is a compilation of a number of log logistic survival models for DCS, expressed as  $h(t; z)$ , included in two of my reports.<sup>4,5</sup> This table shows a progression from simple to more complex models. The complexity comes as I attempt to describe evolved gas with combinations of variables and constants associated with evolved gas, and with my notions of how pain is perceived as tissues are deformed by evolved gas (see Appendix in ref. 6). Also, some information — such as the VGE information, which when added to the model improves the description of DCS failure time — in the complex models is strictly correlative with DCS. Values and other details of the fitted constants are not reproduced here. Equation (17) identified prebreathe ( $\text{PIN}_2$ ), the final altitude pressure (P2), the presence of exercise at altitude, and the length of the exposure as important variables to describe the DCS failure time in 1075 exposures. Figure 4 summarizes my three main conclusions that, for a given calculated  $\text{N}_2$  pressure in the 360-minute half-time compartment, DCS risk increases (1) as P2 decreases (any vertical line through the curves), (2) as time at P2 increases (two filled circles along the 4.3 psia curve), and (3) if exercise is performed at P2 (two filled circles at 4 hours exposure on the 4.3 psia solid and dashed curves).



Table I. Various Log Logistic Survival Models for DCS

Model	Parameters
log logistic survival model (null model)	
$h(t) = \lambda * (t^{\lambda-1}) * \rho^\lambda / (1 + (t * \rho)^\lambda)$	2 ( $\lambda, \rho$ )
log logistic hazard function with additional variables and constants (accelerated model)	
$h(t; z) = [\lambda * z_n * (t^{\lambda-1}) * \rho^\lambda] / [1 + z_n * (t * \rho)^\lambda]$	
$z_1 = 1 / P2$	2
$z_2 = P1N_2 / P2$	2
$z_3 = (P1N_2 / P2) - c$	3
$z_4 = (P1N^2 / (P2 + c1)) - 1.0$	3
$z_5 = ((P1N_2 + c1) / P2) - 1.0$	3
$z_6 = (((P1N_2 + c1) / P2) - 1.0) * (1 + (c3 * exercise))$	4
$z_7 = ((P1N_2 / (P2 + c1)) - 1.0)^{c2} * (1 + (c3 * exercise))$	5
$z_0 = (((P1N^2 + c1) / P2) - 1.0)^{c2} * (1 + (c3 * exercise))$	5 Eq. (17)
$z_8 = z_0 * [1 + (c4 * vge)]$	6
$z_9 = z_0 * [1 + (c4 * vge)] * \{1 + [c5 * (1 / vgetm)]\}$	7
$z_{10} = z_0 * [1 + (c4 * mvge)] * \{1 + [c5 * (1 / vgetm)]\}$	7
$z_{11} = z_0 * [1 + (mvge^{c4})] * \{1 + [c5 * (1 / vgetm)]\}$	7
$z_{12} = z_0 * [1 + (c4 * vgeI,II)] * [1 + (c5 * vgeIII)] * [1 + (c6 * vgeIV)]$	8
$z_{13} = z_0 * [1 + (c4 * vgeI)] * [1 + (c5 * vgeII)] * [1 + (c6 * vgeIII)]$ $* [1 + (c7 * vgeIV)]$	9
$z_{14} = z_0 * [1 + (c4 * vgeI,II)] * [1 + (c5 * vgeIII)] * [1 + (c6 * vgeIV)]$ $* \{1 + [c7 * (1 / vgetm)]\}$	9 Eq. (18)

An important conclusion is that for the same TR, in this case 1.65, the risk of DCS is greater at a lower P2 for a given exposure time and exercise condition (two filled circles on the 4.3 psia and 6.0 psia curves at 4 hours exposure). The fitted constant c1 in the numerator of Eq. (17) is responsible for this result. Other ways of accommodating the constant did not provide as good a fit of the model to the data. I suspect that the importance of the constant is its linkage to metabolic gases in the evolved gas.<sup>13,16</sup>

Once the best model from a family of models is determined, it is still not clear whether there is a

good fit of the best model to the data. The likelihood ratio test<sup>9,17</sup> defines when no further improvement is possible by adding more degrees of freedom (parameters to fit) to the model. However, the test offers no absolute goodness-of-fit summary such as is provided by the coefficient of determination ( $\rho^2$ ) in a least-squares regression. There are few available analytical tools, outside of a Statistics Department, to assess goodness-of-fit of a survival model. I use graphical approaches to “visually” assess goodness-of-fit. Figure 5 shows the predicted vs. the observed group incidence of DCS in 66 tests; i.e., the tests that provided the

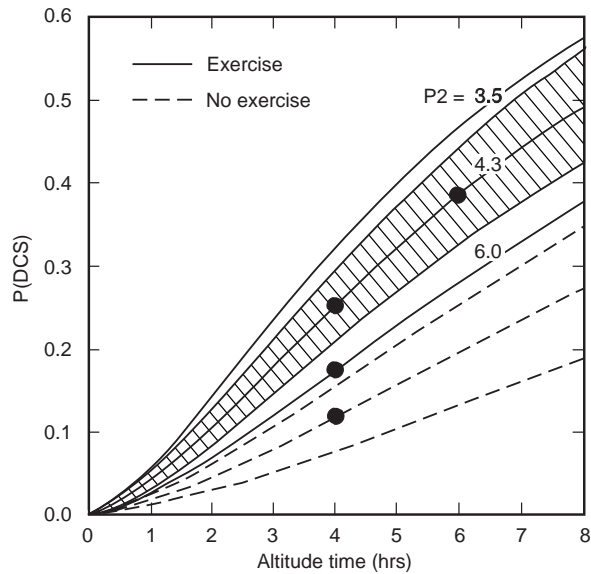


Figure 4. The  $P(\text{DCS})$  at either 3.5, 4.3, or 6.0 psia with (solid line) or without (dashed line) exercise at a particular time after decompression. The ratio of  $P1N_2$  to  $P2$  (TR) in Eq. (17) was 1.65 for each curve, but notice the  $P(\text{DCS})$  increases as  $P2$  decreases at any particular time after decompression. The 95% confidence interval is provided for the curve specific to the 4.3 psia exposure that included exercise.

1075 decompression records. A perfect description of the data by my model would require that all tests fall along the identity line. I have also validated this model in a set of data not used to optimize the model.<sup>4</sup> I conclude that Eq. (17) (expressed through Eq. (12)) describes reasonably well both the DCS and the no DCS cases in 1075 exposures, and could be used prospectively.

Figure 6 is a simulation based on Eq. (18) (expressed through Eq. (12)) where data about VGE were available in 1322 records that would improve the estimate of DCS failure time. The figure shows that the presence of Grade IV VGE increases the risk of DCS compared to all lesser grades. Additional information about the simulation is provided in the description of the figure. Although it can be argued that any information on VGE used to describe DCS is invalid — since both DCS and VGE are responses to decompression — the intensity and

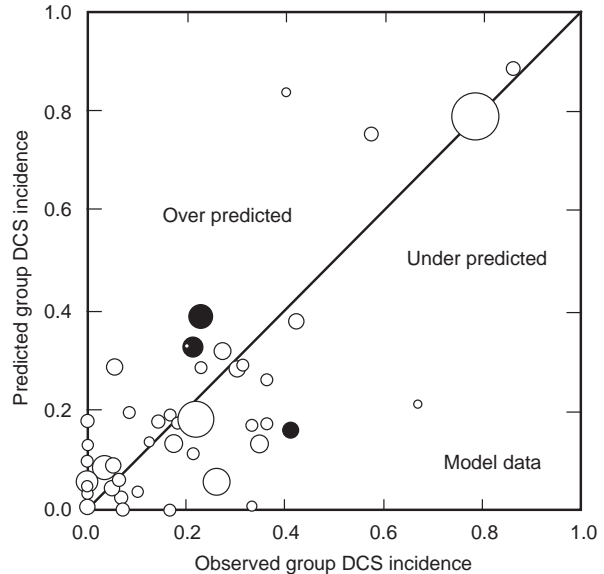


Figure 5. Predicted vs. observed DCS incidence in 66 groups used to fit Eq. (17). The area of a circle is proportional to the number of subjects in a group. The three filled circles are results from NASA tests at 4.3 psia with TRs between 1.60 and 1.65 where exercise is (the two circles above identity line) and is not (the circle below identity line) part of the test. The model neither over- nor underestimates the entire data set, but it did overestimate the incidence of DCS in several small groups that reported no symptoms.

time course of VGE are information that relate (correlate) to a subsequent DCS symptom.<sup>10</sup>

I conclude that the inclusion of VGE information into my basic model (Eq. (17)) was beneficial, and it also improved the goodness-of-fit. Figure 7 is a visual representation of goodness-of-fit for Eq. (18). This presentation differs from Fig. 5 in that each subject in the 1322 exposures had a unique  $P(\text{DCS})$  since no two subjects necessarily had identical VGE information. As before, I conclude that Eq. (18) describes reasonably well the DCS and no DCS cases in 1322 exposures.

Equation (17) and Eq. (18) were attempts to develop useful hypobaric DCS probability models. Like other researchers,<sup>18</sup> I explored using survival analysis to test a specific hypothesis. I was curious about the linkage between evolved gas in a tissue and the report of a DCS symptom. Often elegant and complex models about bubble growth in tissue neglect this aspect of the

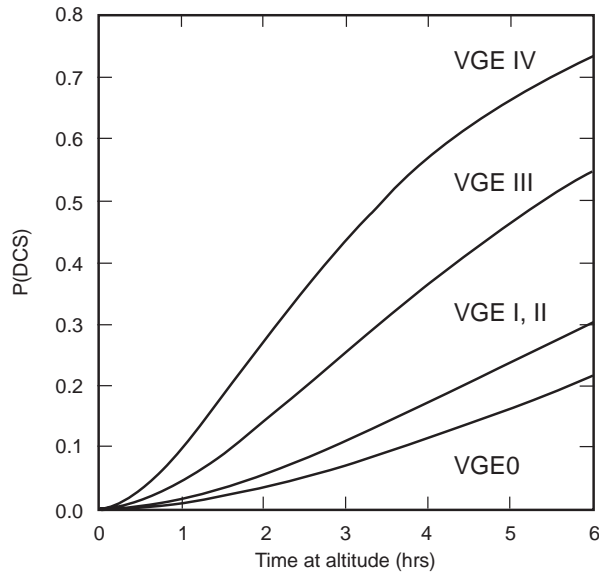


Figure 6. The  $P(\text{DCS})$  vs. time at altitude from Eq. (12), given by Eq. (18) in Table I, for a simulated decompression at a TR of 1.65 (7.1 P1N<sub>2</sub> / 4.3 P2), all with exercise, with a VGETM of 1 hour, and with the presence of VGE at Grades I and II, III or IV, and the absence of VGE (Grade 0). Review Appendix B for the definition of the variables used in this analysis.

problem. The published report<sup>6</sup> develops the rationale about how a power term fitted to my simple equations of evolved gas may link evolved gas to the  $P(\text{DCS})$ . Conceptually, as the intensity of a symptom increases (as a power) the  $P(\text{DCS})$  increases to a certainty. Figures 8 and 9 show the dramatic improvement in describing the DCS failure times in 1085 exposures simply by including a power term in a simple expression ( $\Delta P$ ) of evolved gas.

The solid curve on Fig. 8 from a model without a power term does not pass near the majority of group DCS incidence data as compared to the curve on Fig. 9. I was motivated to evaluate this concept based on an earlier analysis by Nims.<sup>19</sup> Figure 10 shows that my survival model as a probability density function  $f(t; z)$  gave results similar to Nims's results, but my statistical methods differed greatly from the deterministic methods used.

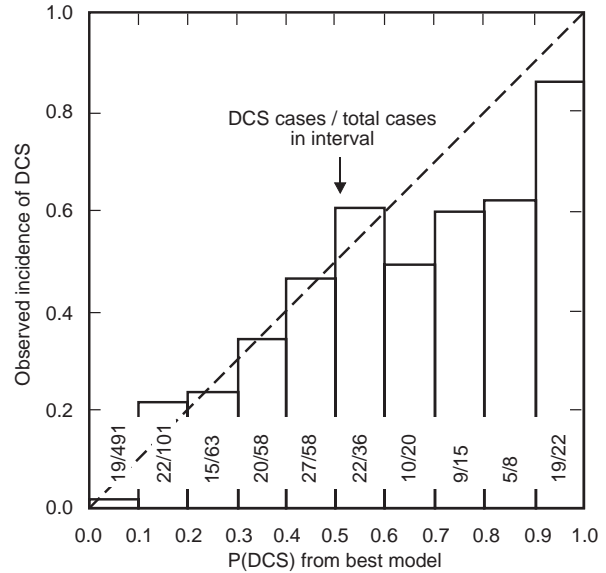


Figure 7. A bar graph to show the observed incidence of DCS in 10 intervals compared to the predicted  $P(\text{DCS})$  from Eq. (12), given by Eq. (18) in Table I. The 1322 records were first divided into 10 probability intervals based on the  $P(\text{DCS})$  from Eq. (12) for each record. The number of DCS cases in the interval were then divided by the total number of cases in the interval to give the incidence of DCS. Equation (12) did not systematically under- or over-predict the observed incidence. It did under-predict the observed incidence in intervals from 0.60 to 0.90, however.

Although the shape, if not the magnitude, of the two curves is similar, Nims did not explicitly use a power term in the expression of DCS dose. My observation that different methods lead to similar results reinforced my belief that conclusions from hypothesis testing with incomplete models should be verified with experimental data.

## Conclusions

I have used survival analysis with maximum likelihood optimization as the basis of my description of the failure time for DCS under a variety of decompression conditions tested in hypobaric chambers. My first goal was to identify an appropriate hazard function. This was based on a survey of DCS and VGE data that were contained in a computerized databank as well as on descriptions and observations on how DCS symptoms progress through time (Figs. 1–3).



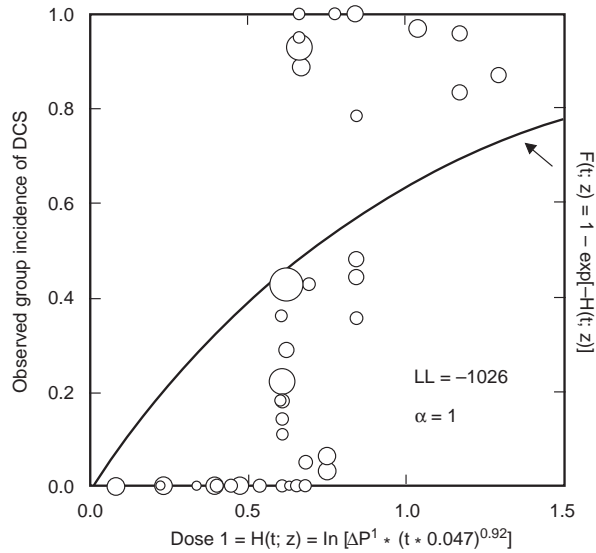


Figure 8. A scatter plot that shows the observed incidence of DCS in a group and the calculated decompression dose with Dose 1 =  $\ln [1 + (P1N_2 - P2)^\alpha * (t * 0.04728)^{0.922}]$ , where  $\alpha = 1$ , and  $P1N_2$  is from the 360-minute half-time, plus a curve from Eq. (12). The position of each circle along the vertical axis depends on the value of Dose 1 for each group. Superimposed on the circles is a solid curve from Eq. (12), given  $f(t; z)$  on the figure, that is the  $P(\text{DCS})$  as a function of Dose 1. The area of a circle is proportional to the number of subjects in a group; the smallest circle represents a test with 2 subjects and the largest circle represents a test with 77 subjects.

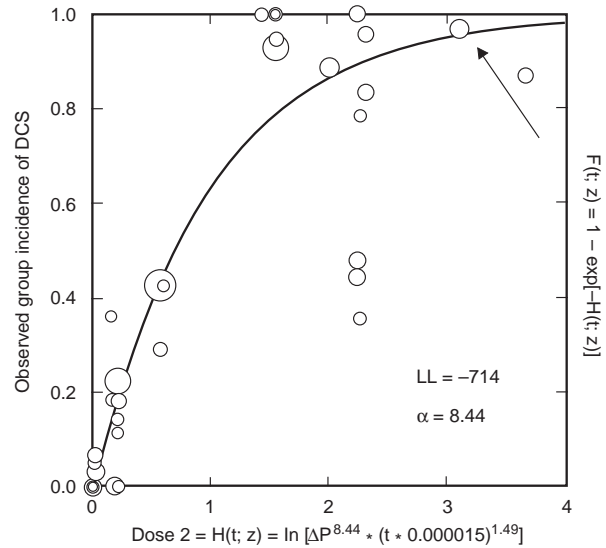


Figure 9. A scatter plot that shows the observed incidence of DCS in a group and the calculated decompression dose with Dose 2 =  $\ln [1 + (P1N_2 - P2)^\alpha * (t * 0.00001517)^{1.491}]$ , where  $\alpha = 8.44$ , and  $P1N_2$  is from the 91-minute half-time, plus a curve from Eq. (12). The horizontal positions of the circles are the same as in Fig. 8, but the vertical positions have changed owing to the recalculation of decompression dose. The goodness-of-fit was improved by estimating the half-time, but the greatest improvement came from estimating  $\alpha$ . The circles are positioned more symmetrically around the curve than in Fig. 8, and the LL improved from  $-1026$  in Fig. 8 to  $-714$  in this figure.

For my purposes, the exponential survival model was clearly inappropriate; and while the log normal model was slightly better than the log logistic, it was more difficult to implement. I also evaluated other models for failure time distribution, but the log logistic model proved to be the best overall for my applications.

My efforts over the past few years have been directed toward developing probability models for DCS that have accounted for major physical and physiological variables (Figs. 4–7). I have not completed analyzing several variables known or suspected to influence the risk of DCS. Age and gender differences continue to be discussed as modifying factors for DCS. While it is difficult to include age and gender in a deterministic (theoretical) model of DCS, it is simple to include

these in a statistical model. I am always surprised to find that one long half-time compartment (about 6 hours) is adequate to describe the results from the variety of hypobaric tests at my disposal. I have brought empirical models into better agreement with bubble models by including a term to account for the presence and consequence of metabolic gases in total evolved gas.

My second use of survival analysis was to test a hypothesis about the inclusion of a power term into simple expressions of evolved gas (Figs. 8–10). My goal was to understand a mechanism about the perception of pain. An exciting area to explore with research and modeling is the biophysical linkage between evolved gas and perception of pain. The future for hypothesis testing and developing better predictive

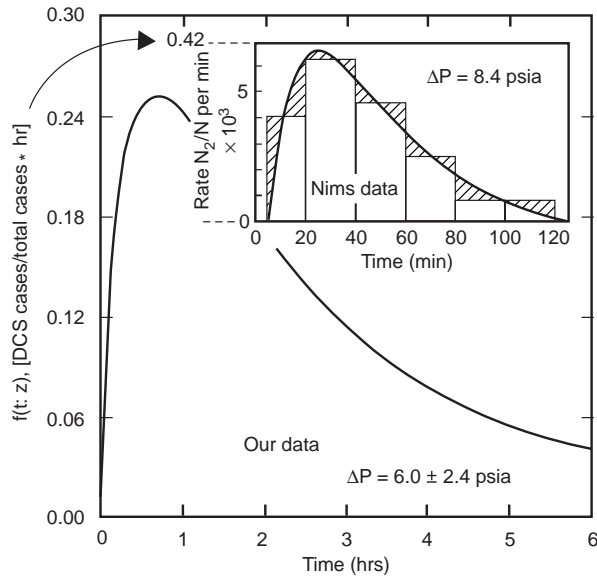


Figure 10. The resulting  $f(t; z)$  for the average  $\Delta P$  of 6.0 psia from the  $f(t; z)$  equation on Fig. 9 where  $\alpha = 8.44$ ,  $\rho = 0.00001517$ ,  $\lambda = 1.491$ , and  $t_{1/2} = 91$  minutes. The  $f(t; z)$  resembles the shape of the curve from Nims<sup>19</sup> (Fig. 40 in ref. 19) in a test with  $\Delta P = 8.4$  psia.

models for DCS is good because new and better data are being collected and shared. New variables such as adynamia<sup>†20,21</sup> and exercise during pre-breathe<sup>22</sup> are now being tested. Future models that include these variables will have application to astronauts during spacewalks, or when spaceflight crews are walking on planets with reduced gravity such as is found on Mars.

Applications for DCS probability models will increase since these are available tools and, if properly applied, can provide useful information. It is possible, for example, to lose cabin pressurization in the T-38 aircraft.<sup>23</sup> What is not known is whether, when pressurization is lost, an emergency landing is needed to avoid DCS. I applied Eq. (17) (expressed through Eq. (12)) under two scenarios for the T-38.<sup>23</sup> The DCS risk for the loss of pressure during a normal flight is seen in Fig. 11; the DCS risk for loss of pressure during a high-altitude flight is seen in Fig. 12.

<sup>†</sup>Adynamia is a concept about how gravity is a variable in DCS, particularly how walking in a gravitational field influence micronuclei that in turn influence the likelihood of DCS.

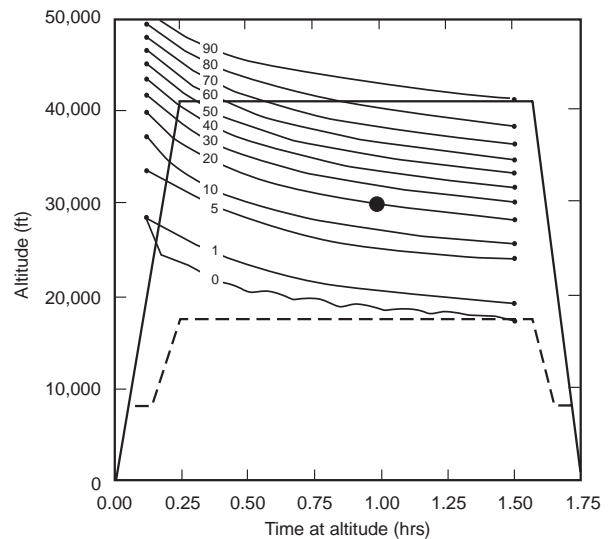


Figure 11. The approximate flight envelope (solid near-vertical lines) of the T-38 and the resulting cabin pressure (dashed line) under nominal flight conditions. Transposed over the flight envelope are 12 DCS isoincidence isopleths for the condition where the crew is not physically active. The proper way to determine the risk is to select a time of exposure and the altitude of the exposure and then to interpolate between the isopleths. For example, the dot at the intersection of 1 hour and 30,000 ft falls directly on the 20% DCS isopleth; this is the best estimate of risk. There is no risk of DCS if cabin pressure is maintained. However, a loss of cabin pressure for even brief periods of time can expose a crew to a high risk of DCS. The likelihood of very serious DCS symptoms is greater as the risk of any DCS symptom increases.

The T-38 can fly high, but only for a short duration. Altitude, duration, prebreathe, and exercise at altitude are variables in Eq. (17). I assumed a limited use of  $O_2$  during the flight (defined in ref. 23) and the aviators were not physically active during flight. Figure 11 shows the  $P(\text{DCS})$  given that the aviator was exposed to a certain decompression for a certain time. Notice that below a normal cabin altitude of 18,000 ft, it is unlikely that DCS will occur. However, a 1-hour exposure to 30,000 ft puts the aviator on the 20% DCS isopleth (solid point). During high-altitude flight, the cabin altitude can increase to 22,000 ft, but the flight time is limited to just over an hour. Figure 12 shows the lowest cabin pressure (22,000 ft) with the T-38 at the highest operating altitude

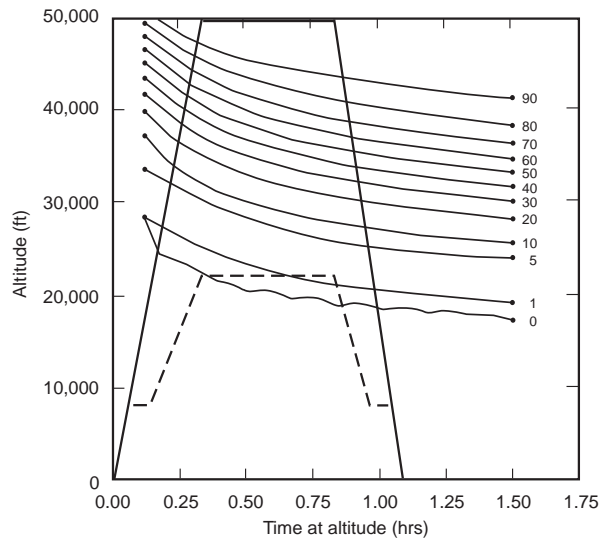


Figure 12. The flight and cabin pressure envelope in the T-38 under extreme flight conditions. Notice that even at the lowest cabin pressurization (22,000 ft) and 45 minutes of exposure, the risk of any symptom of DCS is less than 5%. The majority of the risk is between 0% and 1% under extreme flight conditions.

(50,000 ft); this pressure is associated with a risk of DCS between 1% and 5%. The information in Figs. 11 and 12 can help managers make flight rules that would prevent a loss of cabin pressure in a T-38 leading to the loss of an aircraft and its crew.

## References

- Berghage TE, Woolley JM, Keating LJ. The probabilistic nature of decompression sickness. *Undersea Biomed. Res.* 1974;1:189–96.
- Weathersby PK, Homer LD, Flynn ET. On the likelihood of decompression sickness. *J. Appl. Physiol.* 1984;57:815–25.
- Conkin J, Bedahl SR, Van Liew HD. A computerized databank of decompression sickness incidence in altitude chambers. *Aviat. Space Environ. Med.* 1992;63:819–24.
- Conkin J, Kumar KV, Powell MR, Foster PP, Waligora JM. A probabilistic model of hypobaric decompression sickness based on 66 chamber tests. *Aviat. Space Environ. Med.* 1996;67:176–83.
- Conkin J, Powell MR, Foster PP, Waligora JM. Information about venous gas emboli improves prediction of hypobaric decompression sickness. *Aviat. Space Environ. Med.* 1998;69:8–16.
- Conkin J, Foster PP, Powell MR. Evolved gas, pain, the power law, and probability of hypobaric decompression sickness. *Aviat. Space Environ. Med.* 1998;69:352–359.
- Cox DR, Oakes D. Analysis of survival data. New York: Chapman and Hall, 1984:13–21.
- Brown BW, Jr. Estimation in survival analysis: parametric models, product-limit and life-table methods. In: Mike V, Stanley KE, eds. Statistics in medical research. New York: John Wiley and Sons, 1982:317–39.
- Lee ET. Statistical methods for survival data analysis, 2nd ed. New York: John Wiley and Sons, 1992:8–18.
- Conkin J, PP Foster, MR Powell, JM Waligora. Relationship of the time course of venous gas bubbles to altitude decompression illness. *Undersea Hyperbaric Med.* 1996; 23:141–49.
- Kumar KV, Powell MR. Survivorship models for estimating the risk of decompression sickness. *Aviat. Space Environ. Med.* 1994;65:661–65.
- Weathersby PK, Survanshi SS, Homer LD, Parker E, Thalmann ED. Predicting the time of occurrence of decompression sickness. *J. Appl. Physiol.* 1992;72:1541–48.
- Van Liew HD, Burkard ME. Simulation of gas bubbles in hypobaric decompressions: roles of O<sub>2</sub>, CO<sub>2</sub>, and H<sub>2</sub>O. *Aviat. Space Environ. Med.* 1995;66:50–55.
- Tikuissis P, Nishi RY, Weathersby PK. Use of the maximum likelihood method in the analysis of chamber air dives. *Undersea Biomed. Res.* 1988;15:301–13.
- Wilkinson L. SYSTAT: the system for statistics. Evanston: SYSTAT Inc., 1990:342–87.

16. Foster PP, J Conkin, JM Waligora, MR Powell, RS Chhikara. Role of metabolic gases in separated gas phase formation during hypobaric exposures. *J. Appl. Physiol.* 1998;84:1088–95.
17. Conkin J. Probabilistic modeling of hypobaric decompression sickness [Dissertation]. Buffalo, NY: State Univ. of New York at Buffalo, 1994.
18. Van Liew HD, Burkard ME, Conkin J. Testing of hypotheses about altitude decompression sickness by statistical analyses. *Undersea Hyperbaric Med.* 1996;23:225–33.
19. Nims LF. Environmental factors affecting decompression sickness. Part I: A physical theory of decompression sickness. In: Fulton JF, ed. *Decompression sickness*, Philadelphia: WB Saunders, 1951:192–222.
20. Conkin J, Powell MR. Lower body adynamia as a factor to reduce the risk of hypobaric decompression sickness. *Aviat. Space Environ. Med.* 2001; 72:202–14.
21. Powell MR, Waligora JM, Norfleet WT, Kumar KV. Project ARGO – Gas phase formation in simulated microgravity. NASA Technical Memorandum TM-104762, NASA Johnson Space Center, Houston, TX. 1993.
22. Loftin KC, J Conkin, MR Powell. Modeling the effects of exercise during 100% oxygen prebreathe on the risk of hypobaric decompression sickness. *Aviat. Space Environ. Med.* 1997; 68:199–204.
23. Robinson RR, JP Dervay, J Conkin. An evidenced-based approach for estimating decompression sickness risk in aircraft operations. NASA Technical Memorandum TM-1999-209374, NASA Johnson Space Center, Houston, TX. July 1999.

## Appendix A: Two Forms of the Log Logistic Survival Model

A common form of the log logistic survival function  $S(t)$  is:

$$S(t) = 1 - [ 1 / ( 1 + \exp(-\omega)) ], \quad (\text{A1})$$

where:  $\omega = [\ln(t) - \beta(2)] / \beta(1)$ .

The distribution is specified as a two parameter distribution generalized to include the effects of covariates on survival times. The generalized log logistic is called an accelerated life model where the logarithm of survival time is a linear function of the covariates:

$$\omega = [\ln(t) - \beta(2) - \beta x_1 * x_1 - \dots - \beta x_n * x_n ] / \beta(1). \quad (\text{A2})$$

Other functional expressions of the model are:

$$h(t) = f(t) / S(t) \quad (\text{A3})$$

$$f(t) = \exp[-(\ln(t) - \beta(2)) / \beta(1)] / [(1 + \exp(-(\ln(t) - \beta(2)) / \beta(1)))^2 * \beta(1) * t] \quad (\text{A4})$$

$$h(t) = f(t) / [1 - ( 1 / ( 1 + \exp(-((\ln(t) - \beta(2)) / \beta(1)))))], \quad (\text{A5})$$

and of the accelerated life model are:

$$f(t; z) = \exp[-(\ln(t) - \beta(2) - \beta x_1 * x_1 - \dots - \beta x_n * x_n ) / \beta(1)] /$$

$$[(1 + \exp(-(\ln(t) - \beta(2) - \beta x_1 * x_1 - \dots - \beta x_n * x_n ) / \beta(1)))^2 * \beta(1) * t] \quad (\text{A6})$$

$$h(t; z) = f(t; z) / [1 - ( 1 / ( 1 + \exp(-((\ln(t) - \beta(2) - \beta x_1 * x_1 - \dots - \beta x_n * x_n ) / \beta(1)))))] \quad (\text{A7})$$

where:  $\beta(1)$  = scale parameter

$\beta(2)$  = index or location parameter

$\beta x_n$  = parameter from regression for variable  $n$

$x_n$  = value for the  $n$ th variable

$t$  = time

An alternate form<sup>7</sup> of the log logistic survival model used in my analysis is:

$$S(t) = \exp [-\ln(1 + (t * \rho)^\lambda)]. \quad (\text{A8})$$

It is expanded to include covariates as:

$$S(t; z) = \exp [-\ln(1 + (c_1 * x_1) * \dots * (c_n * x_n) * (t * \rho)^\lambda)]. \quad (\text{A9})$$

The  $h(t)$  expression of the log logistic model is:

$$h(t) = \lambda * (t^{\lambda-1}) * \rho^\lambda / (1 + (t * \rho)^\lambda), \quad (\text{A10})$$

and the accelerated  $h(t)$  is:

$$h(t; z) = \lambda * (c_1 * x_1) * \dots * (c_n * x_n) * (t^{\lambda-1}) * \rho^\lambda / (1 + (c_1 * x_1) * \dots * (c_n * x_n) * (t * \rho)^\lambda) \quad (A11)$$

where:  $\rho$  = scale parameter

$\lambda$  = index or location parameter

$c_n$  = parameter from regression for variable  $n$

$x_n$  = value for the  $n$ th variable

$t$  = time

## **Appendix B: Variables in the Hypobaric Decompression Sickness Database**

### **Dependent Variables**

DCS:	presence (1) or absence (0) of any sign or symptom of decompression sickness (DCS), excluding paresthesia when it was the only symptom.
DCSTM:	failure time to the first sign or symptom of DCS or censored time to the end of the test in those without DCS (hours).

### **Independent Variables**

P1N <sub>2</sub> :	calculated nitrogen pressure (psia) from Eq. (1) to account for all denitrogenation procedures.
P2:	ambient pressure after ascent (psia).
EXERCISE:	presence (1) or absence (0) of repetitive exercise planned for the test.
VGE:	presence (1) or absence (0) of any grade of VGE.
MVGE:	maximum Grade of VGE (0–4) detected during the exposure.
VGEI:	presence (1) or absence (0) of Grade I VGE as the maximum grade of VGE recorded during a test.
VGEII:	presence (1) or absence (0) of Grade II VGE as the maximum grade of VGE recorded during a test.
VGEIII:	presence (1) or absence (0) of Grade III VGE as the maximum grade of VGE recorded during a test.
VGEIV:	presence (1) or absence (0) of Grade IV VGE as the maximum grade of VGE recorded during a test.
VGETM:	failure time to the first VGE detected or censored time to the end of the test in those without VGE (hours).
ALTTM:	scheduled duration of the test or the time t at P2 in a simulation (hours).

REPORT DOCUMENTATION PAGE			Form Approved OMB No. 0704-0188	
Public reporting burden for this collection of information is estimated to average 1 hour per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden, to Washington Headquarters Services, Directorate for Information Operations and Reports, 1215 Jefferson Davis Highway, Suite 1204, Arlington, VA 22202-4302, and to the Office of Management and Budget, Paperwork Reduction Project (0704-0188), Washington, DC 20503.				
1. AGENCY USE ONLY (Leave Blank)	2. REPORT DATE December 2001	3. REPORT TYPE AND DATES COVERED NASA Technical Paper		
4. TITLE AND SUBTITLE A Log Logistic Survival Model Applied to Hypobaric Decompression Sickness			5. FUNDING NUMBERS	
6. AUTHOR(S) Johnny Conkin, Ph.D.				
7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES) Lyndon B. Johnson Space Center Houston, Texas 77058			8. PERFORMING ORGANIZATION REPORT NUMBERS S-885	
9. SPONSORING/MONITORING AGENCY NAME(S) AND ADDRESS(ES) National Aeronautics and Space Administration Washington, DC 20546-0001			10. SPONSORING/MONITORING AGENCY REPORT NUMBER TP-2001-210775	
11. SUPPLEMENTARY NOTES				
12a. DISTRIBUTION/AVAILABILITY STATEMENT Available from the NASA Center for AeroSpace Information (CASI) 7121 Standard Hanover, MD 21076-1320 Category: 54			12b. DISTRIBUTION CODE	
13. ABSTRACT (Maximum 200 words) Decompression sickness (DCS) is a complex, multivariable problem. A mathematical description or model of the likelihood of DCS requires a large amount of quality research data, ideas on how to define a decompression dose using physical and physiological variables, and an appropriate analytical approach. It also requires a high-performance computer with specialized software. I have used published DCS data to develop my decompression doses, which are variants of equilibrium expressions for evolved gas plus other explanatory variables. My analytical approach is survival analysis, where the time of DCS occurrence is modeled. My conclusions can be applied to simple hypobaric decompressions – ascents lasting from 5 to 30 minutes – and, after minutes to hours, to denitrogenation (prebreathing). They are also applicable to long or short exposures, and can be used whether the sufferer of DCS is at rest or exercising at altitude. Ultimately I would like my models to be applied to astronauts to reduce the risk of DCS during spacewalks, as well as to future spaceflight crews on the Moon and Mars.				
14. SUBJECT TERMS decompression sickness; doses, biological effects; altitude sickness; decompression; altitude simulation; exercise physiology; extravehicular activity			15. NUMBER OF PAGES 24	16. PRICE CODE
17. SECURITY CLASSIFICATION OF REPORT Unclassified	18. SECURITY CLASSIFICATION OF THIS PAGE Unclassified	19. SECURITY CLASSIFICATION OF ABSTRACT Unlimited	20. LIMITATION OF ABSTRACT Unlimited	





---