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Analytic gain in probabilistic decompression sickness models

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ABSTRACT

Decompression sickness (DCS) is a disease known to be related to inert gas bubble formation originating from gases dissolved in body tissues. Probabilistic DCS models, which employ survival and hazard functions, are optimized by fitting model parameters to experimental dive data. In the work reported here, I develop methods to find the survival function gain parameter analytically, thus removing it from the fitting process. I show that the number of iterations required for model optimization is significantly reduced. The analytic gain method substantially improves the condition number of the Hessian matrix which reduces the model confidence intervals by more than an order of magnitude.

1. Introduction

Decompression sickness (DCS) is a man-made disease that is caused by a rapid reduction in the ambient pressure after an exposure to a greater pressure of sufficient magnitude and duration. The disease affects divers, astronauts, high altitude aviators, and commercial compressed air workers. While DCS can include various barotraumas, for the models considered in this paper, I focus on the pathological effects caused by bubbles that can form when inert gas dissolved in tissues comes out of solution during or after exposure to decompression. As discussed by Francis and Gorman [1], the pathological effects of bubbles include the primary effects of mechanical compression (nervous tissue, cochlear, middle ear, blood vessel, and endothelium), tissue compression (non-compliant tissue, nervous tissue, blood vessels, lymphatics), and obstruction of blood vessels. Secondary pathological effects of bubbles include activation of leukocytes, endothelial cells, and platelets as well as activation of biochemical pathways (coagulation, fibrosis, complement) [1]. The symptoms of DCS can present as Type I (mild – musculoskeletal, skin rash, lymphatic, fatigue) or Type II (serious – neurological, cardiorespiratory, vestibular/auditory, shock) as well as paralysis and death [2].

Recompression therapy is an effective treatment for DCS [3]. The currently recommended recompression treatments (known as treatment Tables), may be found in the U.S. Navy Diving Manual [4]. Type I DCS is treated with Table 5 and, if symptoms are not completely relieved within the first 10 min at a pressure of 60 feet of seawater, Table 6 is indicated. For treatment of arterial gas embolism or Type II DCS, Table 6 is indicated with Table 6A indicated for unchanged or worsening severe symptoms. For cases where treatment with Tables 6 or 6A is ineffective, treatment of DCS for saturation dives, omitted decompression procedures, or for air-only treatment, other Tables are indicated. Evaluation of recompression therapy efficacy by the U.S. Navy found that DCS symptoms were relieved in over 90% of cases when the treatment followed the recommended procedures [4].

The foundations of decompression models and decompression procedures were built by the physiologist J. S. Haldane when he was engaged by the Royal Navy in 1906 to study the disease. Together with co-workers, Haldane developed a staged decompression procedure to bring workers safely to surface pressure after prolonged exposure to greater pressures [5]. According to Hempleman [6], "The Royal Navy adopted the Haldane tables in 1908, and the first tables for the USN, devised by French and Stillson in 1915, were based on the Haldanian concepts…". Many modifications of the dive tables, such as the addition of tissue compartments with different half-times or changes in allowable compartmental pressure ratios (M-values) have been made since Haldanian tables were first put into practice [6]. Early staged decompression tables and, in fact, many of the modern decompression tables were/are deterministic. That is, the tables establish a sharp boundary between safe and unsafe dives and do not predict the risk associated with a given decompression exposure [7].

The probabilistic nature of DCS was noted by Berghage et al. [8] in a study involving the explosive decompression of 288 mice. Noting the variability of DCS outcomes of divers undergoing the same exposure to decompression, Weathersby et al. [8] used the method of maximum likelihood [9] to study several simple

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probabilistic decompression models. These probabilistic models assign a probability that a diver subjected to a given decompression exposure will experience DCS. This is in contrast to a deterministic model that assumes that DCS is a binomial event. The vast majority of recent research and development of DCS models use the probabilistic approach.

Once a probabilistic model is developed, optimized, and validated, there is a clear and immediate question: What DCS risk is acceptable? The issue of acceptable risk was addressed in detail by Vann and Thalmann [10]. For hypobaric exposures, ground-based studies indicated that neurological DCS cases were rare. Therefore, an acceptable DCS risk of 6% was proposed for operations on the Space Shuttle. For the more remote Space Station, 1% was proposed [11]. For hyperbaric exposures, the acceptable risk varies with discipline and with the governing body. In recreational diving, guidance is for vanishing risk [10]. For commercial, offshore air-diving in the North Sea, a risk of 0.5% might warrant the curtailing of diving operations [12]. For compressed-air caisson workers, a 2% risk was generally tolerated [13]. Current guidance for U. S. Navy diving operations permits dives with DCS risk below 3% while dives with DCS risk 3–5% require prior approval and dives with DCS risk greater than 5% are prohibited [14].

Although there have been several variants of survival functions used to develop probabilistic DCS models, most currently used probabilistic DCS models include a gain vector to scale and render a hazard function vector dimensionless [15–17]. In our previous work [18], we presented an analytic gain expression for a simple subclass of DCS models – incidence only without fractional weighting of marginal DCS events – but we did not investigate the benefit of using the analytic gain method nor did we derive analytic gain expressions for more complicated classes of DCS models; for example, time of occurrence models with fractional weighting of marginal DCS events. In this paper, I derive analytic gain vector expressions for four classes of probabilistic DCS models. Additionally, I prove optimality and document improvements in optimization speed and fitting quality as measured by the model's 95% confidence interval.

2. Analytic gain derivation

In this Section, I derive analytic gain solutions, prove optimality, and derive Hessian matrix components for four categories of survival models typically used for probabilistic decompression models. In order of increasing complexity, these four model categories include (a) incidence-only survival models, (b) incidence-only survival models using fractional weighting for marginal DCS events, (c) survival time models, and (d) survival time models with fractional weighting of marginal DCS events.

2.1. Incidence-only survival models

Throughout this paper, I consider a non-homogeneous Poisson survival process [19] of the form

$$P_{DCS} = 1 - e^{-\vec{g}\cdot\vec{R}}, \tag{1}$$

applied to a probabilistic DCS model, where $\vec{g}$ is a vector of tissue compartment gains and $\vec{R}$ is a hazard (or intensity) vector which relates the severity of a decompression exposure to the probability that a diver experiences DCS. The hazard vector $\vec{R}$ generally contains parameters, sometimes physiologic, designed to model the uptake and elimination of gas(es) from a number of hypothetical tissue compartments in the human body. Given the form of Eq. (1), the probability of a non-event, of not experiencing DCS in this case, is

$$P_o = e^{-\vec{g}\cdot\vec{R}} \tag{2}$$

which follows from the law of total probability. For the derivations to follow, it will be convenient to express Eqs. (1) and (2) in a shorthand notation. For this purpose, I use the notation

$$P_{DCS} = 1 - e^{-\vec{g}\cdot\vec{R}} = 1 - e^{-\sum_{c=1}^{C} g_c R_c} = 1 - \prod_{c=1}^{C} e^{-g_c R_c} = 1 - \xi$$
$$P_0 = e^{-\vec{g}\cdot\vec{R}} = e^{-\sum_{c=1} g_c R_c} = \prod_{c=1}^{C} e^{-g_c R_c} = \xi \tag{3}$$

where the index c counts over the C tissue compartments. In Eq. (3), R_c is the hazard function for the cth tissue compartment and g_c is the unknown gain for that same tissue compartment. This paper considers analytic methods for finding the gain vector, $\vec{g}$; thus eliminating this vector from the parameter fitting procedure.

For an incidence-only survival model, the hazard function typically has the form

$$R_c = \int_{t=0}^{t=T_3} r_c dt \tag{4}$$

where T_3 is the right censoring time beyond which any follow up as to the outcome of the exposure is lost [17,20,21]. The instantaneous risk kernel, r_c, typically contains one or more parameters that are found, most often, by the method of maximum likelihood [9]. As is pointed out elsewhere [22], using the likelihood directly suffers from numerical problems so the log likelihood

$$LL = \sum_{i=1}^{D} \ln\left((P_{DCS,i})^{\delta}(P_{0,i})^{1-\delta}\right) \tag{5}$$

is often used. In Eq. (5), $\delta = 1$ if the i^{th} decompression exposure results in DCS and $\delta = 0$ otherwise. Also in Eq. (5), D is the total number of exposures in the data set. The model is considered optimized when the parameter set resulting in the maximum LL is found.

2.1.1. Analytic gain solution

In order to find an expression for the stationary gain set for a given risk function parameter set, I require that the partial gradient of the log likelihood function (Eq. (5)) with respect to (w.r.t.) the gain vector must vanish. This is equivalent to optimizing the problem on a manifold defined by gain stationarity but not stationarity of the other model parameters. Note that the candidate risk function set, $\vec{R}$, need not be optimal for the purpose of finding the optimal gain set for that $\vec{R}$. For the cth tissue compartment, where $1 \le c \le C$, the partial derivative of LL w.r.t. the gain is

$$\frac{\partial}{\partial g_c}(LL) = \frac{\partial}{\partial g_c}\left[\sum_{i=1}^{D} \ln\left((P_{DCS,i})^{\delta}(P_0)^{1-\delta}\right)\right]. \tag{6}$$

Now, suppose that the dive data set contains D total exposures resulting in S cases of DCS and Z cases of no-DCS such that $S + Z = D$. Then, using Eq. (3), the laws of exponents, and the laws of logarithms, Eq. (6) becomes

$$\frac{\partial}{\partial g_c}(LL) = \frac{\partial}{\partial g_c}\left[\sum_{s=1}^{S} \ln(1-\xi_s) + \sum_{z=1}^{Z} \ln(\xi_z)\right] = \sum_{s=1}^{S} \frac{R_{c,s}\xi_s}{1-\xi_s} - \sum_{z=1}^{Z} R_{c,z}. \tag{7}$$

In Eq. (7), and for the following derivations, the notation $R_{x,y}$ signifies the integrated risk function for the xth tissue compartment and the yth decompression exposure in the corresponding subset of all decompression exposures. Note that the final expression in Eq. (7) can be simplified further in order to reduce the computational operation count by multiplying each term inside the left summation by ξ_s^{-1}/ξ_s^{-1}. After making this simplification, and after equating to zero the final expression in Eq. (7), the