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Bimodal decompression sickness onset times are not related to dive type or event severity

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ABSTRACT

Human decompression sickness (DCS) is a condition associated with depressurization during underwater diving. Human research dive trial data containing dive outcome (DCS, no-DCS) and symptom information are used to calibrate probabilistic DCS models. DCS symptom onset time information is visualized using occurrence density functions (ODF) which plot the DCS onset rate per unit time. For the BIG292 human dive trial data set, a primary U.S. Navy model calibration set, the ODFs are bimodal, however probabilistic models do not produce bimodal ODFs. We investigate the source of bimodality by partitioning the BIG292 data based on dive type, DCS event severity, DCS symptom type, institution, and chronology of dive trial. All but one variant of data partitioning resulted in a bimodal or ambiguously shaped ODF, indicating that ODF bimodality is not related to the dive type or the DCS event severity. Rather, we find that the dive trial medical surveillance protocol used to determine DCS symptom onset time may have biased the reported event window. Thus, attempts to develop probabilistic DCS models that reproduce BIG292 bimodality are unlikely to result in an improvement in model performance for data outside of the calibration set.

1. Introduction

Decompression sickness (DCS) is a condition associated with depressurization of the body from underwater diving. During a dive, exposure to increased ambient pressure allows elevated partial pressures of inert gas in the lung to dissolve into the blood. When this blood circulates, the inert gas can diffuse into the body's tissues. During decompression and after surfacing from a dive, the excess inert gas is normally circulated back to the lungs to be exhaled. However, if the ambient pressure is reduced sufficiently far below the partial pressure of the dissolved gases, then gaseous bubbles may form in the blood and/or tissues. The signs and symptoms of DCS can include, but are not limited to joint pain, paresthesia, fatigue, abdominal pain, and paralysis [1]. DCS cases are typically categorized into either Type I (also called mild) or Type II (also called serious), in which Type I includes pain-only cases and Type II includes neurological and cardiopulmonary cases. In addition, DCS manifestations which subsequently spontaneously resolve without recompression treatment are categorized as marginal DCS cases. Examples of marginal cases are pain in one joint lasting less than 60 min or pain in two joints lasting less than 30 min [2,3].

Decompression modeling originated in the early 20th century when Boycott et al. introduced the theory that DCS was caused by the formation of bubbles in the body during decompression due to the elevated partial pressure of dissolved nitrogen gas in the body's tissues [4]. The model presented by Boycott and coworkers, later known as the Haldane model, was deterministic, as DCS could be avoided if a set of criteria were followed and was inevitable if those criteria were violated. However, deterministic modeling cannot account for the variation in DCS occurrence and symptoms present in divers executing identical dive profiles as recorded in empirical dive data [2,3]. This variability in DCS outcome prompted the development of probabilistic models, introduced by Berghage et al. [5] and Weathersby et al. [6], which compute a non-zero probability of DCS occurrence for a given dive profile. Such probabilistic models used to predict the incidence and onset time of DCS rely on risk calculated from survival analysis [7] and either a gas content or bubble model. These models allow dive profiles to be created with a level of risk tailored to the diver's objective. An advantage of probabilistic modeling is that their

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parameters can be calibrated with empirical dive data via numerical optimization. Model parameters can be estimated to maximize the likelihood, which is a statistic that quantifies the agreement between the model and the corresponding experimental data. In addition, including the time of onset of DCS symptoms from experimental data during optimization has been shown to improve a model's ability to describe the data [8]. To facilitate calibration of probabilistic DCS models with experimental dive data, Temple et al. published a compilation of dive profile and DCS manifestation descriptions corresponding to both air and nitrogen-oxygen human dive trials conducted by the United States, United Kingdom, and Canadian militaries between 1944 and 1997 [2,3]. These research trials were conducted in hyperbaric chambers and include both wet and dry dives during which a medical officer monitored divers and determined the time of onset of DCS symptoms. Temple's report includes the bottom times, depths, and ascent rates which characterize each dive profile, and the corresponding dive conditions (wet or dry), inspired gas mixtures, DCS symptom descriptions and onset times, and references to the originating dive trial reports. The dive types performed during these research trials include single air, single non-air, repetitive and multilevel air, repetitive and multilevel non-air, air and oxygen decompression, saturation, sub-saturation, surface decompression with air, and surface decompression with oxygen. The calibration set known as the BIG292 standard DCS data set is a subset of the data presented by Temple et al. that includes a portion of the single air, single non-air, repetitive and multilevel air, repetitive and multilevel non-air, and saturation dive types. This calibration set has been used in optimizing the parameters for a probabilistic model known as the LE1-USN93 model [9]. The LE1 model consists of three perfusion-limited parallel compartments, two with mono-exponential gas uptake and elimination and one with mono-exponential uptake and linear elimination after a crossover tension is exceeded [10]. The BIG292 calibration data set is analyzed in the present work.

An occurrence density function (ODF) describes the number of occurrences of a particular event per unit of time, and can be used to graphically assess the agreement between a model's estimations and observed DCS occurrences and onset times. These plots map time relative to the final surface interval on the abscissa and the number of DCS occurrences on the ordinate. A probabilistic model that most accurately predicts the onset time of DCS would generate an ODF which closely resembles that of empirical dive data. The ODF constructed with the BIG292 dive data set is bimodal, peaking in DCS occurrences at both the completion of decompression and 2 h following decompression. However, current probabilistic models, including the LE1-USN93 [9] and the BVM(3) [11], used to predict the onset time of DCS do not produce bimodal ODFs. The ODFs of the LE1-USN93 and BVM(3) models each contain only one peak, located after the completion of decompression. Simulating the bimodality of the empirical data would improve the fit of the model to the data, creating a better likelihood match.

Recently, Hada [12] investigated using inert gas input delay in a class of probabilistic pharmacokinetic models with perfusion coupled compartments [13] and perfusion-diffusion coupled compartments in an effort to align model onset time predictions with the bimodal onset times found in the BIG292 data. Of the 11 delay-differential probabilistic pharmacokinetic models Hada optimized and analyzed, many showed an improvement in model fit with the addition of the single-parameter input delay but none showed enough improvement by the Akaike Information Criterion to justify adding input delay. Additionally, none of the models, when optimized on the BIG292 data, predicted bimodal ODFs. This finding motivated our present study to investigate bimodality of the BIG292 dive data. We wish to know if there is a feature, such as dive type, event severity, symptom type, or breathing gas, generates the two peaks in the ODF. If so, this might inform what model changes could lead to improved onset time prediction. If no feature can be identified, or if the bimodality is a result of some type of measurement bias, then attempts to reproduce bimodality in model prediction are unlikely to be successful or useful.

2. Methods

2.1. Data

The BIG292 standard DCS data set from two Naval Medical Research Institute (NMRI) reports was used [2,3] in this study. The BIG292 data set, which is a subset of the dive data detailed in Refs. [2,3], contains dive profiles from 3322 exposures of air and nitrogen-oxygen diving conducted by the United States, United Kingdom, and Canadian militaries between 1944 and 1997. The BIG292 data set includes single air, single non-air, repetitive and multilevel air, repetitive and multilevel non-air, and saturation dive types, resulting in 190 DCS cases and 110 marginal DCS cases. Marginal DCS is defined as a case involving signs or symptoms associated with DCS that were deemed not serious enough to be treated with recompression and subsequently spontaneously resolved [2,3]. In the BIG292 data set, all DCS cases and 68 of the 110 marginal DCS cases are reported with symptom onset times T_1 and T_2, where T_1 is the last known time a diver was symptom free, and T_2 is the earliest time the diver was definitely experiencing symptoms. Following our previous work on the efficacy of using marginal DCS events in fitting probabilistic DCS models, we scored marginal cases as non-events when considering the BIG292 data set in this work so that only full DCS events were analyzed [14,15]. Because these dive trial data are de-identified and are freely available to the public in the form of two U.S. Government reports, IRB approval was not required for this retrospective study.

The 190 DCS cases in the BIG292 data set can be further classified by perceived severity index (PSI) [16,17]. As introduced by Howle et al., the PSI scale is defined with the following six indices, in order of increasing severity: constitutional (fatigue, nausea, dizziness), skin bends (rash, itching, marbling), pain (aches, joint pain, stiffness), mild neurological (numbness, paresthesia), cardiopulmonary (dyspnea, cough, hemoptysis), and serious neurological (dysfunction of vision, hearing, bladder, bowel, coordination) [17]. Based on the DCS symptom descriptions in the two NMRI reports [2,3], the 190 DCS cases were each assigned an index by Howle et al., with 6 indicating constitutional and 1 indicating serious neurological. If a DCS case fell into more than one of these categories, it was assigned an index corresponding to the highest severity present. Traditionally, DCS is categorized into Type I (mild) and Type II (serious), where Type I includes the PSI categories of constitutional, skin, and pain, and Type II includes mild neurological, cardiopulmonary, and serious neurological manifestations. An alternative approach to classifying DCS severity was proposed by Howle et al. [17], called Type A/B splitting. Type A (mild) includes the PSI categories of constitutional, skin, pain, and mild neurological, while Type B (serious) includes the cardiopulmonary and serious neurological PSI categories. In the BIG292 data set, there are 152 cases of Type I DCS and 38 cases of Type II DCS. Applying Type A/B splitting, the BIG292 data set contains 170 Type A and 20 Type B DCS cases. When exploring DCS symptom type as a potential source of the bimodal ODF in this work, both Type I/II and Type A/B splitting were applied to the BIG292 data. DCS cases corresponding to each individual PSI were also examined.

2.2. Computational modeling

Many probabilistic DCS models are derived using the methods of survival analysis [7]. For these models, the probability of DCS is defined as

$$P(E) = 1 - e^{-\sum_i g_i \int r_i dt} \tag{1}$$

where $P(E)$ is the probability of a DCS event occurring, the index i counts over the risk-bearing model compartments, g_i is the i^{th} compartmental gain, r_i is the i^{th} compartmental hazard function, and the definite integral