THE CASE FOR MIXED PHARMACOKINETIC MODELS AS A DESCRIPTOR OF DECOMPRESSION SICKNESS

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Introduction

We have previously shown that probabilistic models of decompression sickness (DCS), which typically rely upon a series of parallel perfusion-limited compartments, describing gas content within theoretical tissues do not always accurately predict the probability of DCS in divers [1]. Our conclusions were consistent with Doolette, Upton, and Grant's experimental pharmacokinetics work showing that a diffusion component was needed to accurately describe the gas uptake and washout in sheep [2,3]. We further found that a diffusion component did not unilaterally improve model agreement for human data, but did so for certain types of dive data (for example, air dives versus non-air dives).

Methods

Numerous pharmacokinetic gas content models, some previously proposed by Doolette et al. and some new, were programmed in C# and fitted to the NMRI98 dive data set [4] by the method of maximum likelihood survival analysis. Fitting was carried using the Nelder-Mead Algorithm. In fitting the models, marginal DCS events were considered to be non-events [5].

These models were assumed to only have well-stirred compartments, bidirectional diffusion, and mass balance was enforced. A single perfusion limited compartment (PLB shown in Figure 2) was used as the null model for all statistics. A complete discussion of all of the models being investigated was provided in 2014 [1].

Results and Discussion

Using Akaike Information Criterion, we compared all of the models fit to determine which additional parameters were statistically justified and which were not.

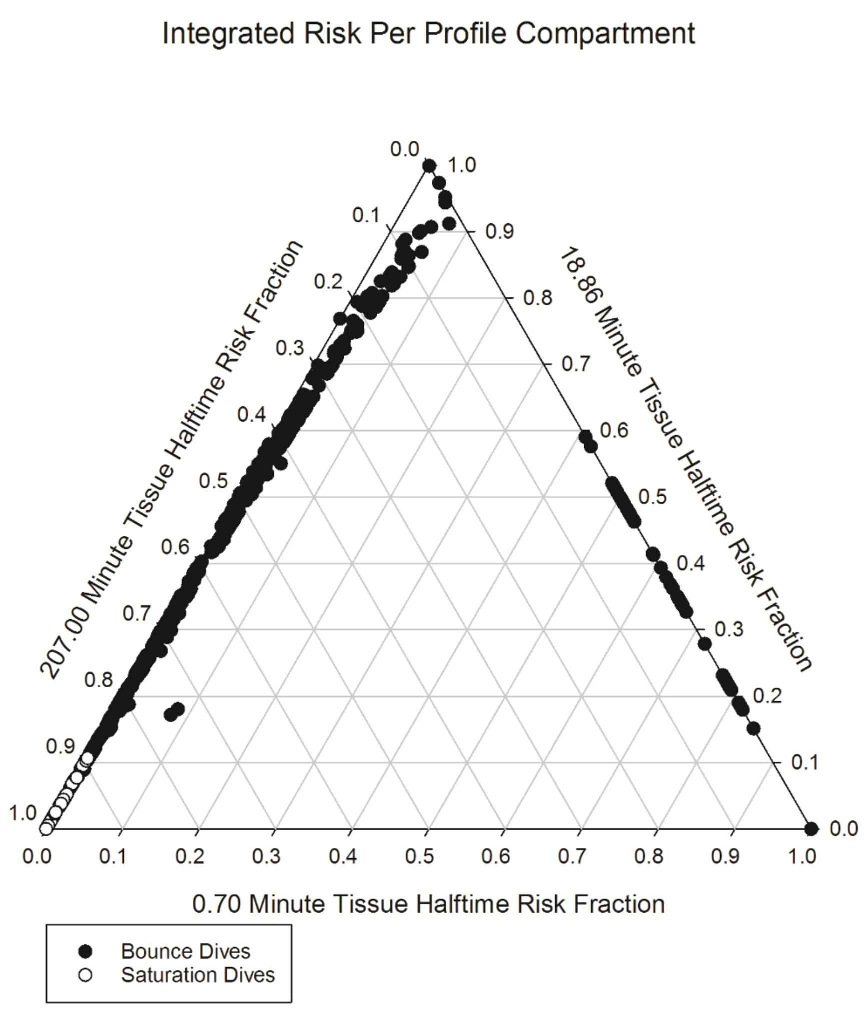

Figure 1: Graph of Integrated Risks

Table 1 summarizes our results when we fit the entire data set for each model being considered. CS2T_3 (shown in Figure 3) best described the data, but the perfusion diffusion base model (PDB) performed nearly as well. However, if we split the dives into two groups; bounce and saturation then saturation dives were best fit by a single PLB model and the bounce dive data were best described by CS2T (which differs from the CS2T_3 in that it does not include the first compartment in the risk calculation). Saturation dives are best described by a single slow perfusion limited compartment and do not show a need for more complex model structures.

Figure 1 provides clear computational evidence that a diffusion and/or delay component is needed to best describe the bounce dive data. Risk for almost all dives comes entirely from either the second or third compartment in CS2T_3.

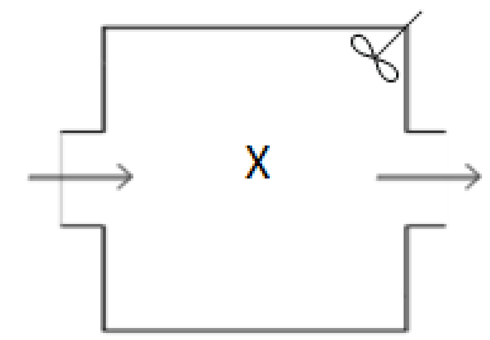

Figure 2: PLB Model

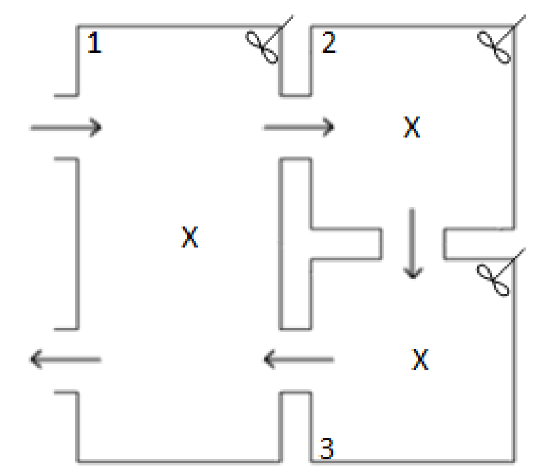

Figure 3: CS2T_3 Model

With only a few outliers using multiple compartments. The second and third compartments in CS2T_3 also benefits from the delay added by the first compartment showing that delay is essential to properly describing the data. Using a collection of PLB functional units allows the saturation dive data to have an excessive influence over the rest of the data. This can be seen by noting that most data falls in the same compartment as them in the CS2T_3 fit, but that data is not well described by a single PLB unit.

Conclusion

These findings provide evidence that the commonly used collection of three PLB compartments do not best describe the data. A delay mechanism such as diffusion or serial compartments are needed to best describe the bounce dive data. Future work will investigate these mechanisms.

Model	Negative Log Likelihood	AIC Weight
CS2T	-1169.27	1.61E-01
CS2T_3	-1167.67	2.92E-01
PDB	-1169.86	2.44E-01
PDCCD	-1169.7	3.83E-02
PLB	-1272.28	1.63E-44
PLCCD	-1271.84	3.41E-45
S2LP	-1170.65	1.10E-01
S2LPD	-1169.33	5.56E-02
S2T	-1271.86	9.12E-45
S3T	-1170.75	9.96E-02

Table 1: Model Best Fit Results

References

[1] Murphy, Hada, Doolette, Howle LE, UHM-ASM 2014; 2
[2] Doolette, Upton, Grant, Journal of Applied Physiology 2005; 563.2:529-539
[3] Doolette, Upton, Grant, Acta Physiologica Scandinavica 2005; 185:109-121
[4] Parker, Survanshi, Massell, Weathersby, Journal of Applied Physiology 1998; 84.3:1096-1102
[5] Howle, Weber, Vann, Campbell, Journal of Applied Physiology 2009; 107.3:1539-2547

Acknowledgements

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