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MODEL FOR ANALYSIS OF TIME TO ONSET OF CONVULSIONS IN 100% O_2 AT DEPTH

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In an atmosphere of 100% O_2 the time to onset of convulsions decreases with increased depth. The observations on 23 dogs at 45 feet, 15 dogs at 60 feet and 10 dogs at 86 feet are used to develop a probability model for the risk in time of onset of convulsion as a function of depth. The best description was given by a 2-reaction model in which the rate constant was a logistic function of the depth. The resulting two parameter model was used to predict the expected time to onset of convulsions.

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1. Introduction

In diving research there has been an interest in the pulmonary effects of 100% O_2 at depth. In addition to pulmonary effects convulsions also occur. The time to onset of convulsions is reduced as depth is increased. In this report we develop a mathematical description of the time to onset of convulsions based on the data of Bradley shown in Table 1. Note that the time to onset of convulisons is given for each of 23 dogs at a depth of 45 feet, 15 dogs at a depth of 60 feet and 10 dogs at a depth of 86 feet. At lower depths the pulmonary changes develop before the onset of convulsions and may actually prevent the onset of convulsions. This feature has not yet been incorporated into the model except that we do introduce a form for the depth relationship which extrapolates to no convulsions at a zero depth. Several generalizations of the mathematical model which are introduced provide a basis for evaluations of the model.

2. Descriptions of Time to Onset of Convulsions

For each depth we assume that the time t to onset is a random variable which has a density function f(t). The density function f(t) is a mathematical function such that the area given by

$$\int_{t_1}^{t_2} f(x)dx$$

is the probability of convulsions in the interval t_1 to t_2. We may designate this probability by $Pr(t_1 \leq t \leq t_2)$. If we introduce the cumulative distribution function

$$F(t) = \int_o^t f(x)dx$$

then

$$Pr\{t_1 \leq t \leq t_2\} = F(t_2) - F(t_1)$$

and F(t) is the probability of onset of convulsions before t. If one groups the data for time to onset of convulsions into intervals the relative frequency, i.e. the number of animals convulsed between t_1 and t_2 divided by the number of animals studied, corresponds to the observed probability of convulsions in the interval. Likewise the proportion of the total number of animals that convulse before t corresponds to F(t).

An equivalent alternative description is provided by the risk or hazard function for convulsion

$$h(t) = f(t)/(1-F(t))$$

which is the likelihood of the onset of convulsions at t given that convulsions have not yet occurred.

Our preliminary perception of the problem was that the risk of convulsions initially would be at or near zero and increase with time. Also it was felt that onset of convulsions could be thought of as occurring as the result of a chain one or more reactions or processes. From this idea we formulate a mathematical form which describes the random time to onset of convulsions.

3. The N-Reaction Model

Following the development of Bailey et al. [1974] we equate the time to onset of convulsions with the transit time through a chain of first order consecutive reactions in which the reaction constants are taken to be equal. The resulting cumulative distribution function is

$$F_n(t) = 1 - \exp(-kt) \sum_{i=0}^{n-1} \frac{(kt)^i}{i!}$$

where k is the reaction constant and n is the number of reactions. From this we find the density function

$$f_n(t) = \frac{d\ F_n(t)}{dt}$$

$$= \frac{k\ (kt)^{n-1}}{(n-1)!} \exp(-kt)$$

consequently

$$h_n(t) = \frac{k\ (kt)^{n-1}}{(n-1)!} \quad \left(\sum_{i=o}^{n-1} \frac{(kt)^i}{i!} \right)^{-1}.$$

For $n = 1$, $h_1(t) = k$. That is the hazard function is a constant. For $n = 2$ or greater this hazard function is zero at $t = 0$ and increases to the asymptote k as $t \to \infty$. In particular for $n = 2$

$$h_2(t) = \frac{k^2 t}{1 + kt}$$

and for $n = 3$

$$h_3(t) = \frac{k\ (kt)^2}{1 + kt + (kt)^2/2}.$$

The distribution of t is further characterized by either the moments about the origin

$$\mu'_\nu = \frac{(\nu + n-1)!}{(n-1)!\ k^\nu} \qquad \nu = 1, 2, 3, \ldots$$

or the cumulants

$$\kappa_\nu = \frac{n(\nu-1)!}{k^\nu}$$

which are readily obtained from the moment generating function

$$M(s) = \frac{k^n}{(k-s)^n}.$$

We use these expressions to obtain the mean time to onset of convulsions

$$\mu'_1 = \frac{n}{k}$$

and the variance for the time to onset of convulsions

$$\text{Var}(t) = \frac{n}{k^2}.$$

4. Evaluation of the N-Reaction Model for the Analysis of Time to Onset of Convulsions

Several generalizations of the n-reaction model were needed to evaluate the model. First we added a hazard component α to the risk function for n = 2 and 3. So that for t = 0 the risk would be α. The estimate of α was computationally indistinguishable from zero and we concluded that the constraint that the model have an initial risk of zero in these cases was justified. Furthermore as is shown in Table 2 the best fit for the n-reaction model is for n = 2.

The form

$$h_2(t) = \frac{k^2 t}{1 + kt}$$

was generalized to the form

$$h_2(t) = \frac{k (t/\alpha)}{1 + (t/\alpha)} .$$

Furthermore, the integral of $h_2(t)$ designated by

$$H_2(t) = \int_o^t h_2(t)dt$$

$$= k [t - \alpha \ln(1 + (t/\alpha))]$$

was generalized by replacing (t/α) by $(t/\alpha)^\beta$ so

$$H_2(t) = k[t^\beta - \alpha^\beta \ln (1 + (t/\alpha)^\beta)].$$

This model was fitted assuming a common β for each of the three depths. The log likelihood for this model was -285.98 which is only a slight improvement over the likelihoods for the corresponding (n=2) 2 and 3 parameter models as displayed in Table 2.

5. The Depth Relationship

In our n-reaction model we make k a logistic function of depth.

That is

$$k = \frac{(d/\theta_1)^{\theta_2}}{1 + (d/\theta_1)^{\theta_2}}.$$

This introduces one additional parameter. θ_1 is a scale parameter for the depth and θ_2 is a shape parameter. With n = 2 the resulting two parameter model as shown in Table 2 is practically indistinguishable from the three parameter model in which depths are treated separately.

We conclude that a 2-reaction model with the two parameter logistic form is a very appealing and suitable model for the description of the data in Table 1.

6. Estimates and Projections based on the Model.

In Table 3 we use the maximum likelihood estimates for the 2-reaction model with the depth relationship of the previous section to predict the upper asymptote k for the risk function, the expected time to convulsions μ, and the variance of the distribution of time to convulsions. The parameters were entered into the model as $\theta_1 = e^{\theta_1'}$ and $\theta_2 = e^{\theta_2'}$ so that θ_1' and θ_2' are estimated. That is $\theta_i' = \log \theta_i$. We have $\theta_1' = 5.86$ and $\theta_2' = 0.873$ with the approximate estimated covariance matrix

θ_1'	θ_2'
0.166	-0.0887
	0.0479.

The risk/min is plotted as a function of the time in hours for depths of 45, 60 and 86 feet in Figure 1. The log of the expect time to convulsions in hours is shown as a function of the depth in Figure 2.

7. Additional Observations

Following the analysis of the observations in Table 1, an additional seven dogs were observed at a depth of 30 feet. There were two dogs observed for 10 hours, four for 15 hours and one for 18 hours. In each case there was no onset of convulsions. Although these data are not out of line with the predictions given in Table 3, estimates of the parameters for our 2-reaction model were reevaluated using the additional data. The revised parameter estimates are $\theta_1' = 5.47$ and $\theta_2' = 1.129$ with the approximate covariance matrix

θ_1'	θ_2'
0.0384	-0.0254
	0.0175.

Revised predictions are shown in Table 4. The data for the 30 foot depth is in a range of experimentation which is more difficult because of the longer time to onset and the predicted increase in variability. Futhermore, the very range of difficult experimentation is one in which there is the greatest practical interest.

Table 1. Observed Time to Convulsions for each dog at each of three depths

	Time to convulsion (hours, minutes)		
	45 feet	60 feet	86 feet
	0:28	0:51	0:48
	1:05	5:31	0:27
	6:38	5:02	0:25
	0:26	0:49	1:52
	5:15	2:40	0:24
	8:05	2:15	1:06
	8:39	2:01	1:28
	1:17	4:42	0:17
	1:00	5:20	1:22
	6:30	3:04	0:46
	1:00	4:25	
	4:38	1:32	
	1:00	0:49	
	7:46	0:54	
	7:19	0:26	
	5:38		
	4:51		
	7:26		
	7:02		
	3:28		
	1:10		
	4:13		
	5:21		
n	23	15	10
Average	4:22	2:41	0:54

Table 2. Log likelihood for the n-reaction model in which it shown that n = 2 gives the best fit and that depths are significantly different.

n	depths pooled 1 parameter	depth fitted to the logistic form 2 parameters	Log likelihood depths treated separtely 3 parameters
1	-294.77	>-292.09*	-292.09
2	-293.12	-288.24	-287.71
3	-299.67	-292.30	-291.49

*The form of the 2 parameter model was not run since it can not give a lower value than obtained for the 3 parameter model and the maximized likelihood is clearly at n = 2.

Table 3. Predictions at selected depths for the upper asymptote k of the risk function, the average time to convulsions and the variance of the time to convulsions based on our maximum likelihood estimates for the 2-reaction model.

Depth, in feet	$k(min^{-1})$	$\mu(min)$	$Var(min^2)$
5	3.79×10^{-5}	5.28×10^{4}	1.39×10^{9}
10	1.99×10^{-4}	1.00×10^{4}	5.05×10^{7}
15	5.25×10^{-4}	3.81×10^{3}	7.25×10^{6}
20	1.05×10^{-3}	1.91×10^{3}	1.83×10^{6}
30	2.76×10^{-3}	7.26×10^{2}	2.63×10^{5}
45*	7.24×10^{-3}	2.76×10^{2}	3.81×10^{4}
60*	1.43×10^{-2}	1.40×10^{2}	9.75×10^{2}
86*	3.33×10^{-2}	6.00×10	1.81×10^{3}
100	4.70×10^{-2}	4.30×10	9.04×10^{2}
200	2.06×10^{-1}	9.70	4.71×10
500	7.00×10^{-1}	2.86	4.00
1000	9.24×10^{-1}	2.16	2.34

*Indicates observed depths as shown in Table 1.

Table 4. Revised predictions based on the additional seven observations at 30 feet. For selected depths the estimate of the upper asymptote k of the risk function, the average time to convulsions and the variance of the time to convulsions based on our revised maximum likelihood estimates for the 2-reaction model.

Depth, in feet	$k(min^{-1})$	$\mu(min)$	$Var(min^2)$
5	6.47×10^{-6}	3.09×10^{5}	4.78×10^{10}
10	5.52×10^{-5}	3.62×10^{4}	6.56×10^{8}
15	1.94×10^{-4}	1.03×10^{4}	5.34×10^{7}
20	4.71×10^{-4}	4.24×10^{3}	9.01×10^{6}
30	1.65×10^{-3}	1.21×10^{3}	7.35×10^{5}
45	5.76×10^{-3}	3.47×10^{2}	6.03×10^{5}
60	1.39×10^{-2}	1.44×10^{2}	1.03×10^{4}
86	4.12×10^{-2}	4.85×10	1.18×10^{3}
100	6.41×10^{-2}	3.12×10	4.86×10^{2}
200	3.69×10^{-1}	5.42	1.47×10
500	9.09×10^{-1}	2.20	2.42
1000	9.88×10^{-1}	2.02	2.05

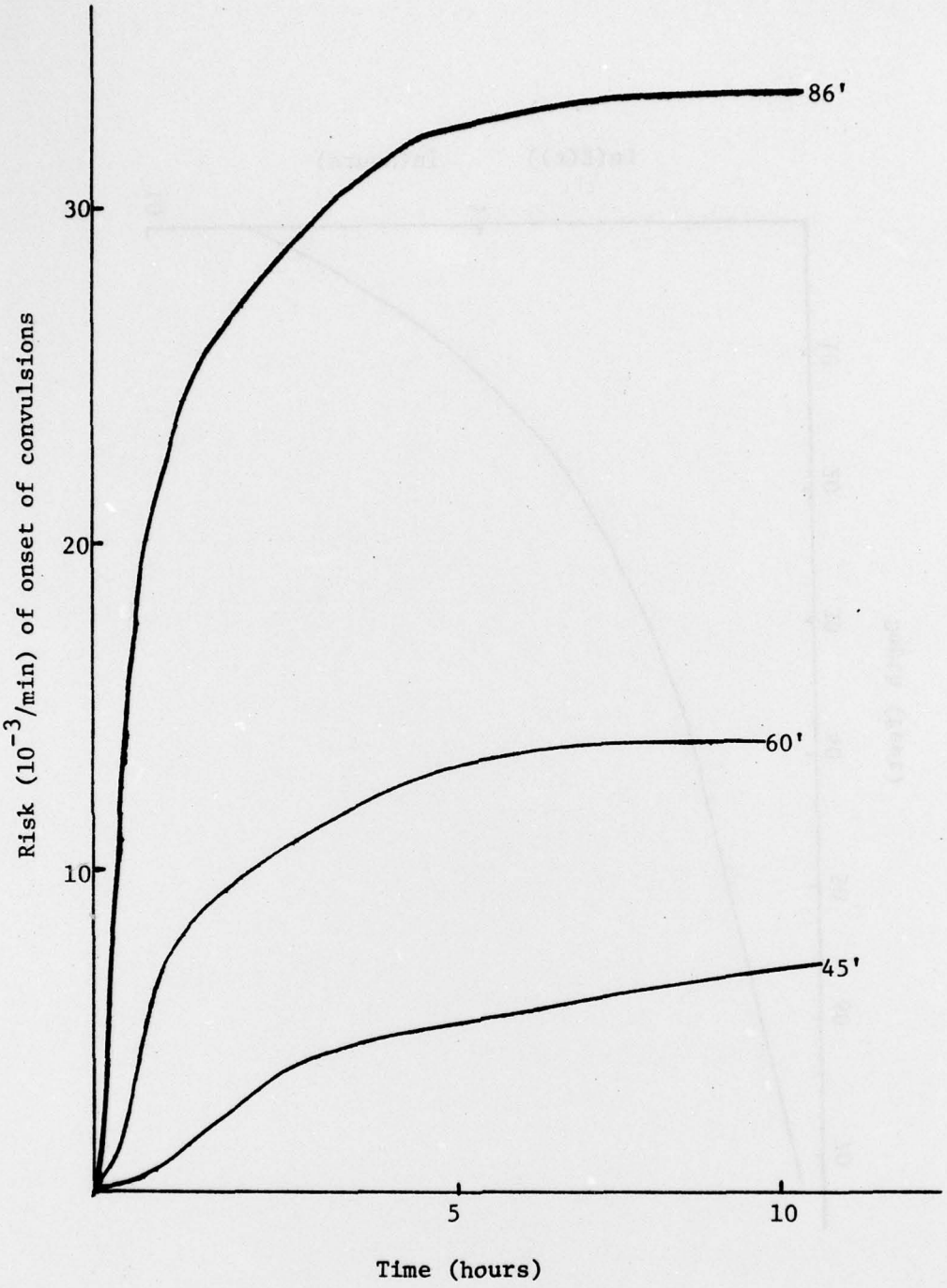

Figure 1. Risk of onset of convulsions in 100% O_2 with time for depths of 45', 60' and 86'.

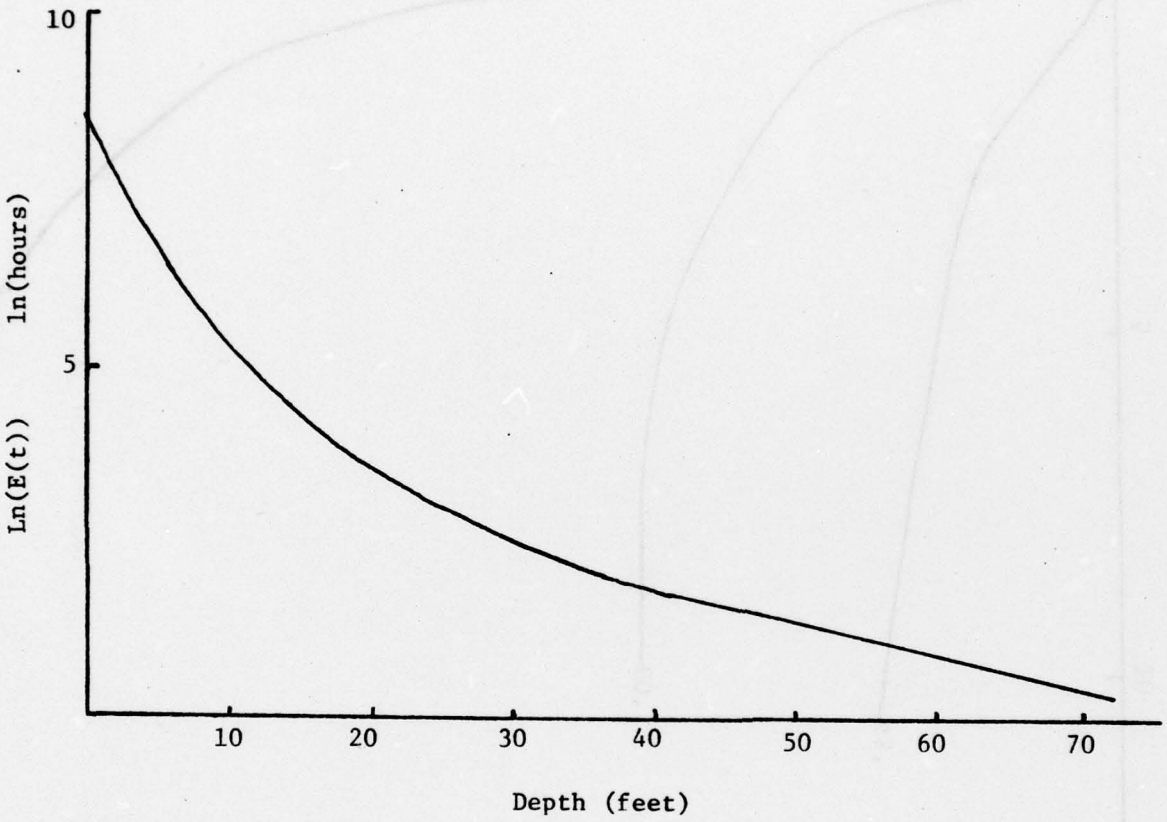

Figure 2. The estimated relationship between the natural logarithm of the expected time to onset of convulsions in 100% O_2 and depth.

Reference

Bailey, R.C., Eadie, G.S., and Schmidt, F.H. [1974]. Estimation procedures for consecutive first order irreversible reactions. *Biometrics 30*, 67-75.