# 19

Filtering, Smoothing, and Extrapolations in Dose-Response Experiments: With Application to Data on Respiratory Tumor in Rats

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Abstract

A method for inference and extrapolations in certain dose-response, damage-assessments and accelerated life-testing studies as been proposed by Meinhold and Singpurwalla in 1986. The method is based on a use of the Kalman-filter algorithm and involves the double lognormal as the distributional assumption. In this paper, we discuss issues pertaining to a practical implementation of this methodology. This involves some insights based on a simulation study about the specification of prior parameters and an application of the proposed methodology to some published data on doses of bischloromethyl ether administered to rats.

Key Words and Phrases: Accelerated Testing, Bioassay, Kalman Filtering, Bayesian Methodology, Damage Assessment.
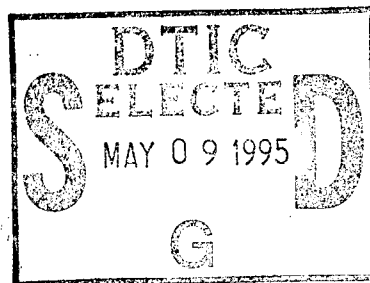
1. INTRODUCTION AND OVERVIEW

Let x denote a dose or a stress that is applied to a biological or an engineering system, and suppose that x takes values in $[0, \infty)$. Let $Y(x)$ be the response to x, and suppose that $0 \leq Y(x) \leq 1$; $Y(x)$ could be viewed as the propensity of each item to respond to x, or the extent of damage incurred by each item when subjected to stress x. Thus, for example, $Y(x) = 1(0)$ could imply total resistance (demolition) to (under) x. Often, it is true that we are able to test more than one item at any x, but that it may not be possible to repeat the test at any x, because doses and stresses cannot be exactly controlled. In what follows, we shall assume that the values of x are known to an experimenter, but that the $Y(x)$ are unknown "states of nature" about which it is desired to make inferences. Such inferences are

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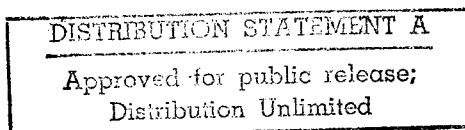
based on background knowledge about a particular scenario under consideration, an assumed relationship between $Y(x)$ and x, and tests conducted at several values of x. The tests conducted at the several values of x give us information about $Y(x)$, but that $Y(x)$ cannot be directly observed.

It is often the case that $Y(x)$ responds to x in a nonlinear fashion, and in view of this, plus considerations of the type cited in Section 1.1, we propose, as a model for relating $Y(x)$ and x, the relationship

$$Y(x) = \exp[-\alpha(x)x^{\beta(x)}], \alpha(x), \beta(x) > 0; \qquad (1.1)$$

$\alpha(x)$ and $\beta(x)$ are unknown parameters which depend on x. In what follows, $E(Y(x))$ will denote expectation of the unknown quantity $Y(x)$.

1.1 Arguments Supporting Choice of the Relationship

As a special case of (1.1), suppose that

$$\alpha(x) = \alpha \text{ and } \beta(x) = \beta, \text{ for all } x \geq 0.$$

Then

$$Y(x) = \exp(-\alpha x^{\beta}), \alpha, \beta > 0; \qquad (1.2)$$

the right hand side of the above is the survival function of a Weibull distribution. A virtue of (1.2) is flexibility in expressing a wide class of subjective opinions about the dose-response and stress-damage relationships. For example, it has been recommended for use in food safety assessment studies and clinical trials in the biological scenarios [cf. Final Report of the SCF-SC (1980)], and in studying the effects of underwater nuclear explosions on submarine miniatures in the engineering scenario [cf. McDonald (1989), Shaked and Singpurwalla (1990)]. The relationship (1.2) [and also (1.1)] can be linearized enabling one to employ standard filtering techniques, and when used in connection with data sets on human risk assessment studies, it gives an estimated risk at low doses which lies between the estimates for the "gamma multi-hit" and the "Armitage-Doll" models. Also, the relationship (1.2) has been reported to give good empirical fits to the data. In any particular application, it is suggested that the statistical analyst and the subject matter specialist examine plots of the Weibull dose-response curves for several combinations of values of α and β, and choose that curve or curves that best describe their judgments of the dose-response relationship. The above can be most effectively done on personal computers.

1.2 Statement of the Problem

Suppose that at T distinct dose levels $x_1 > x_2 > \ldots > x_T$ an item or several items are tested and the corresponding observed responses $y(x_1), y(x_2), \ldots, y(x_T)$, recorded; note that $y(x_i)$ provides information about the unobservable $Y(x_i), i = 1, \ldots, T$. We are required to:

i) Make statements of uncertainty about the true responses $Y(x)$, at any x, including the x_i's, $i = 1, \ldots, T$, at which the tests are conducted.

ii) Assess $Y(x_{T+1})$, the response at a very low dose x_{T+1}, where $x_{T+1} \ll x_T$

1.3 The Proposed Approach

Our approach for addressing the above issues is Bayesian, and involves a use of the technology of Kalman filtering and Kalman filter smoothing. The underpinnings of our approach are outlined in Meinhold and Singpurwalla (1987), where due to limitations of space and the need for an expository focus, applications of the methodology to practical scenarios was not undertaken. An aim of this paper is to fill the above gap and to attempt to demonstrate the potential usefulness of the Kalman filter approach to problems of the kind considered here. It is helpful to point out that Blackwell and Singpurwalla (1988) undertake an endeavor similar to the one discussed here, but focus attention on the case of exponentially distributed lifetimes; furthermore, they do not address the issue of smoothing that is relevant to problems of this type.

1.4 Overview of Paper

In Section 2 we motivate the Kalman filter model, state the distributional assumptions, and present the necessary smoothing and extrapolation formulae. In Section 3 we describe approaches for obtaining the starting values of the Kalman filter algorithm (i.e. specifying the prior parameters), and in Section 4 we describe an application of our approach to some data on respiratory tumor of rats subjected to doses of bischloromethyl ether. In Section 5 we offer some conclusions and suggest some direction for future research along the lines outlined here.

2. THE FILTERING AND SMOOTHING MODEL

Our review of the literature suggests that there is a dearth of dose-response relationships based on pharmacokinetic, oncological or engineering considerations. Thus one's choice of (1.2), the Weibull survival function, is at best a reasonable approximation, and hence one should incorporate into one's analyses some measure of uncertainty about such approximations. Furthermore, there is no reason to sacrifice flexibility by making the Weibull scale parameter α, and the shape parameter β, invariant with the dose x. On the contrary, there is evidence in the engineering sciences, that high stresses cause a change in the basic failure mechanisms, making it reasonable to assume that α and β depend on x - thus our choice of the relationship (1.1). The dynamic nature of α and β introduces the novelty of our approach over the currently used ones. Once the above is undertaken,

our set-up fits into the general form of a Kalman-filter model - provided that some details which facilitate an iterative computational scheme are attended to.

2.1 The Kalman-Filter Model and Distributional Considerations

Assume that $E(y(x)) = \exp(-\alpha(x)x^{\beta(x)})$, and suppose that we require $y^*(x) \overset{\text{def}}{=} \log\{-\log y(x)\}$, to be such that

$$y^*(x) \sim \mathcal{N}(\mu(x), \sigma^2(x)),$$

where "$\sim \mathcal{N}(\mu, \sigma^2)$" denotes "normally distributed with mean (variance) $\mu(x)(\sigma^2(x))$". Then, it can be seen that $y(x)$ must have a "double lognormal distribution" [cf. Meinhold and Singpurwalla (1987)] with parameters $\mu(x)$ and $\sigma^2(x)$, where $\mu(x)$ is the median of the distribution of $y(x)$. The distribution cited above, has a density which is flexible enough to express a wide variety of subjective opinions about $y(x)$, and is an attractive alternative to the beta density for modelling data on proportions - see Ahsanullah and Holland (1989). Motivated by the fact that when $\sigma^2(x)$ is small, $E(y(x)) \approx \exp\{-\exp(\mu(x))\}$, we propose, as the *observation equation* of the Kalman filter

$$y^*(x) = (1, \log x) \begin{bmatrix} \gamma \\ \beta \end{bmatrix}_x + \nu(x), \tag{2.1}$$

where $\nu(x) \sim \mathcal{N}(0, V(x))$, $V(x)$ is the conditional variance of $y^*(x)$, $(\gamma, \beta)'_x = (\gamma(x), \beta(x))'$, and $\gamma(x) = \log \alpha(x)$.

The set-up (2.1) also implies that $y(x) = (Y(x))^{\lambda(x)}$, where $\log \lambda(x) = \nu(x)$, and $y^*(x) = \log\{-\log y(x)\}$; the innovation $\lambda(x)$ has a lognormal distribution with parameters 0 and $\sigma^2(x)$. For the *system equation* of the Kalman filter, we propose the "steady model" [cf. Meinhold and Singpurwalla (1983)]

$$\begin{bmatrix} \gamma \\ \beta \end{bmatrix}_{(x)} = \begin{bmatrix} \gamma \\ \beta \end{bmatrix}_{(x-1)} + w(x), \tag{2.2}$$

where $w(x) \sim \mathcal{N}(0, W(x))$, and $W(x)$ is the variance-covariance matrix of $\gamma(x)$ and $\beta(x)$ conditional on $\gamma(x-1)$ and $\beta(x-1)$; $\nu(x)$ is assumed independent of $w(x)$; $(x-1)$ is the dose previous to dose x. The values $V(x)$ and the four entries of $W(x)$ must be specified by a user. Also to be specified by the user are the "starting values" of the Kalman filter algorithm; these are $\hat{\gamma}(0)$, $\hat{\beta}(0)$, $V(x_0)$ and $W(x_0)$. A strategy for specifying these is outlined in Section 3.

2.2 Results from Filtering and Smoothing

For compactness of notation, we let $y^*(x_j) = y_j^*$, $[\gamma, \beta]'_{x_j} = \theta_j$, $[1 \log x_j] = F_j$, $V(x_j) = V_j$, $W(x_j) = W_j$, $\nu(x_j) = \nu_j$ and $w(x_j) = w_j$. Then (2.1) and (2.2) can be written as

$$y_j^* = F_j \theta_j + \nu_j, \text{ and}$$

$$\theta_j = G_j \theta_{j-1} + w_j,$$

where G_j is a 2×2 identity matrix. If we assume that $\theta_{j-1} \sim \mathcal{N}(\hat{\theta}_{j-1}, \Sigma_{j-1})$, then, upon observing y_j^*, $\theta_j \sim \mathcal{N}(\hat{\theta}_j, \Sigma_j)$, and

$$\hat{\theta}_j = G_j \hat{\theta}_{j-1} + K_j(y_j^* - F_j G_j \hat{\theta}_{j-1}), \Sigma_j = (I - K_j F_j) R_j, \qquad (2.3)$$

where

$$R_j = G_j \Sigma_{j-1} G'_j + W_j, K_j = R_j F'_j (F_j R_j F'_j + V_j)^{-1},$$

and I is an identity matrix. The relationships in (2.3) are referred to as the *forward-recurrence equations* of the Kalman filter. Note that, in the above scheme, inference for θ_j is based upon the previous data, $y_j^*, y_{j-1}^*, \ldots, y_1^*$, $j = 1, 2, \ldots, T$, only. Thus, with the exception of θ_T, inference for the other θ_j's is not based on all the data. Should we desire inference for θ_j based on all the data $y_1^*, \ldots, y_T^*$, then we need to smooth using the *backward-recurrence equations* [see Appendix A of Meinhold and Singpurwalla (1987)], whereby

$$\begin{cases} \hat{\theta}_j(T) = \hat{\theta}_j(j) + J_{j+1}[\hat{\theta}_{j+1}(T) - G_{j+1}\hat{\theta}_j(j)], \\ \Sigma_j(T) = \Sigma_j(j) - J_{j+1}[\Sigma_{j+1}(T) - R_{j+1}]J'_{j+1}, \end{cases} \qquad (2.4)$$

where $J_j = \Sigma_{j-1}(j-1) G'_j R_j^{-1}$ and $\hat{\theta}_j(k)[\Sigma_j(k)]$ is the mean [covariance] of the normal distribution of θ_j based on $y_1^*, \ldots, y_k^*$. The standard Kalman-filter algorithm enables us to produce $\hat{\theta}_1(1), \hat{\theta}_2(2), \ldots, \hat{\theta}_T(T)$ in an efficient manner; see (2.3).

Once $\hat{\theta}_T(T)$ is obtained, inference about $Y(x_{T+1})$ follows from the fact that $\log(-\log(Y(x_{T+1}))) \sim \mathcal{N}(F_{T+1} \hat{\theta}_T(T), F_{T+1} \Sigma_T(T) F'_{T+1})$, and so

$$E(Y(x_{T+1})) \approx \exp(-\exp(F_{T+1}\hat{\theta}_T(T))). \qquad (2.5)$$

3. SPECIFICATION OF INPUTS FOR THE KALMAN FILTER

Let x_0 and x_{-1}, $x_{-1} > x_0 > x_1$, be two dose levels at which the subject matter specialist has the most knowledge about the responses, $Y(x_0)$ and $Y(x_{-1})$ respectively. Typically, these would be very large dose levels; also,

we require that x_0 and x_{-1} be close to each other. Suppose that, in the opinion of the specialist, the *most likely* values of $Y(x_0)$ and $Y(x_{-1})$ are $\tilde{Y}(x_0) = 1 - \delta_0$ and $\tilde{Y}(x_{-1}) = 1 - \delta_1$, where δ_0 and δ_1 are large with $\delta_0 < \delta_1$; what we have in mind is $\delta_0 = .995$ and $\delta_1 = .999$. Then, for x_0 close to x_{-1}, we may write

$$\log\{-\log(1 - \delta_0)\} \approx \hat{\gamma}(x_0) + \hat{\beta}(x_0) \log x_0,$$

$$(3.1)$$

$$\log\{-\log(1 - \delta_1)\} \approx \hat{\gamma}(x_0) + \hat{\beta}(x_0) \log x_{-1},$$

from which it follows that

$$\hat{\beta}(x_0) = \frac{\{\log(-\log(1 - \delta_0)) - \log(-\log(1 - \delta_1))\}}{\{\log x_0 - \log x_{-1}\}},$$

and

$$\hat{\gamma}(x_0) = \log(-\log(1 - \delta_0)) - \hat{\beta}(x_0) \log x_0.$$

The values $\hat{\beta}(x_0)$ and $\hat{\gamma}(x_0)$ thus computed will become the starting values for the Kalman-filter algorithm.

Our next task is to pin down $V(x_0), \ldots, V(x_T)$, the variances of the innovations $\nu(x_i)$, $i = 0, \ldots, T$. In specifying the above, two considerations must be borne in mind. The first, is that since $y(x)$ is between 0 and 1, the variance of $\lambda(x)$ must be the smallest when $Y(x)$ is either 0 or 1, and the largest when $Y(x) = .5$. Second, under binomial testing, the variance of $y(x)$ is approximately of the form $m(x)(1 - m(x))/n(x)$, where $m(x)$ is the median of the distribution of $y(x)$ and $n(x)$ is the number of units tested at dose x. Following a line of reasoning given in Appendix A, a first order approximation to $V(x) = \sigma^2(x)$ is of the form

$$\sigma^2(x) \approx \log\left\{\frac{1}{2}(1 + [1 + 4(1 - m(x))/n(x)m(x)(\log(m(x)))^2]^{\frac{1}{2}})\right\}. \quad (3.2)$$

Note that in the above expression, $\sigma^2(x) \to 0$ as $m(x) \to 0[1]$ provided that $n(x) > (m(x))^{-1}[(1 - m(x))^{-1}]$, and so as is commonly done by engineers, we may set $V(x_0) = 0$. In (3.2) above, $m(x) = \exp\{-\exp(\mu(x))\}$, with $\mu(x)$ replaced by its predicted value $\hat{\mu}(x)$ obtained from the Kalman-filter algorithm. Specifically,

$$\hat{\mu}(x_1) = \hat{\gamma}(x_0) + \hat{\beta}(x_0) \log x_1, \text{ and}$$
$$\hat{\mu}(x_i) = F_i \hat{\theta}_i, \quad i = 1, \ldots, T,$$

where $\hat{\theta}_i$ is given by (2.3), the forward mechanism of the Kalman filter.

Our next step is to pin down $W(x_0)$, the variance covariance matrix of the starting values $\hat{\gamma}(x_0)$ and $\hat{\beta}(x_0)$. For this, we require that the subject matter specialist specify, in addition to $\tilde{Y}(x_0)$ and $\tilde{Y}(x_{-1})$, ν_1, ν_2 and ρ, the

variances of $Y(x_0), Y(x_{-1})$ and the correlation between $Y^*_{(x_0)}$ and $Y^*_{(x_{-1})}$, as perceived by the specialist. The variances ν_1 and ν_2 will typically be very small, something like $(.001)^2$ and $(.0003)^2$, respectively, and ρ should be nonnegative, say something of the order of .7 or .8. Once the above are done, the relationship (3.1) can be used to show that if $b = [\nu_1, \nu_2, \rho]'$, and if $Z = [\text{Var}(\hat{\gamma}(x_0)), \text{Var}(\hat{\beta}(x_0)), \text{Cov}(\hat{\gamma}(x_0), \hat{\beta}(x_0))]'$, then $Z = A^{-1}b$, where the matrix A is of the form

$$A = \begin{bmatrix} 1 & (\log x_0)^2 & 2\log x_0 \\ 1 & (\log x_{-1})^2 & 2\log x_{-1} \\ \frac{4\rho}{\nu_1+\nu_2+2\rho\sqrt{\nu_1\nu_2}} & \frac{\rho(\log x_0+\log x_{-1})^2}{\nu_1+\nu_2+2\rho\sqrt{\nu_1\nu_2}} & \frac{4\rho(\log x_0+\log x_{-1})}{\nu_1+\nu_2+2\rho\sqrt{\nu_1\nu_2}} \end{bmatrix}.$$

Once Z is known, the matrix $\Sigma(x_0)$ can be constructed, and this enables us to undertake the first iteration of the Kalman-filter algorithm. Subsequent iterations of the algorithm require that we specify $W(x_j)$, $j = 1, \ldots, T$. For this, we propose, based on some simulation studies, that

$$W(x_j) = .5(1.5)^j(x_{j-1} - x_j)\Sigma(x_0). \tag{3.3}$$

The multipliers of $\Sigma(x_0)$ given above, reflect the following considerations:

i) The factor .5 (or any other number less than 1) reflects the fact that our uncertainty about the parameters, subsequent to observing data, should be less than our uncertainty about them prior to the data.

ii) The factor $(1.5)^j$ (or for that matter any other number greater than 1) reflects the fact that our uncertainty about the parameters should increase as we get closer to the low dose levels.

iii) The factor $(x_{j-1} - x_j)$ reflects the fact that if the separation between two consecutive doses is large then our uncertainty about the model parameters should increase.

It should be clear from the above, that the scheme proposed here could be automated once $\tilde{Y}(x_0)$, ν_1, $\tilde{Y}(x_{-1})$, ν_2 and ρ are specified.

4. APPLICATION-Data on Respiratory Tumor in Rats

For purposes of illustration, we consider some data on doses (the number of six hour exposures by inhalation of 100 parts per billion) of bis-chloromethyl ether administered to rats. This data has been abstracted from the Final Report of the SCFSC (1980), wherein its analysis using the Weibull survival model has been advocated and undertaken. In Table 4.1 below, we present our data; the response is 0 if a rat develops respiratory tumor and 1 otherwise - thus 43/46 denotes the fact that 43 out of 46 rats have not developed tumors. Our aim is to predict the responses at low doses, say 7, 5, 2 and 1.

Table 4.1. Dose-Response Data on Respiratory Tumors in Rats

Dose: x_i	10	20	40	60	80	100
Observed Response	40/41	43/46	14/18	14/18	19/34	8/20

We let $x_1 = 100, x_2 = 80, \ldots, x_6 = 10$, and $y(x_1) = 40/41, y(x_2) = 43/46, \ldots, y(x_6) = 8/20$. For x_0 and x_{-1} we choose the doses 250 and 280 respectively, and for δ_0 and δ_1 we choose .995 and .999, respectively. Our other choices follow the recommendations of Section 3; specifically, $\nu_1 = (.001)^2, \nu_2 = (.0003)^2$ and $\rho = .7$. Substituting the above in the formulae for $\hat\beta(x_0), \hat\gamma(x_0)$ and A, we obtain, as starting values for the Kalman filter, the following:

$$\hat\gamma(x_0) = -11.256, \hat\beta(x_0) = 2.3405, \mathrm{Var}(\hat\gamma(x_0)) = 1.668 \times 10^{-3},$$

$$\mathrm{Var}(\hat\beta(x_0)) = 5.217 \times 10^{-5} \text{ and Cov } (\hat\gamma(x_0), \hat\beta(x_0)) = -2.95 \times 10^{-4}.$$

In Table 4.2 below, we give filtered and smoothed estimates of the parameters $\gamma(x_i)$ and $\beta(x_i), i = 1, \ldots, 6$. The filtered estimates are obtained via the forward recurrence equations (2.3) whereas the smoothed estimates are obtained via the backward recurrence equations (2.4). The entries in Table 4.2 indicate that smoothing does have an effect on the filtered estimates and that the estimates of $\gamma(x_i)$ and $\beta(x_i)$ do change with x_i. Note that when $i = 6$, that is, for $x_6 = 10$, the smoothed estimate is indeed the filtered estimate.

Table 4.2. Filtered and Smoothed Estimates of $\gamma(x_1)$ and $\beta(x_i)$

Dose: x_i	100	80	60	40	20	10
Filtered Est. of $\gamma(x_i)$	-10.652	-9.563	-10.079	-7.702	-7.965	-7.604
Smoothed Est. of $\gamma(x_i)$	-9.801	-9.780	-9.651	-7.704	-7.965	-7.604
Filtered Est. of $\beta(x_i)$	2.234	2.041	2.132	1.712	1.759	1.695
Smoothed Est. of $\beta(x_i)$	2.083	2.080	2.057	1.713	1.759	1.695

In Table 4.3 we give the observed values $y(x_i)$ and the predicted, filtered and smoothed values of $Y(x_i), i = 1, \ldots, 6$. Note that

i) $E(Y(x_i)|y(x_{i-1}), \ldots, y(x_1))$, is the predicted value of $Y(x_i)$, where $y(x_0) = Y(x_0)$,

ii) $E(Y(x_i)|y(x_i), \ldots, y(x_0))$ is the filtered value of $Y(x_i)$, and

iii) $E(Y(x_i)|y(x_6), \ldots, y(x_0))$ is the smoothed value of $Y(x_i)$.

The above conditional expectations can be obtained via formulae analogous to (2.5).

Table 4.3. Predicted, Filtered, Smoothed and Observed Values of $Y(x_i)$

Dose: x_i	100	80	60	40	20	10
Observed Val. of $y(x_i)$	.4	.5588	.7778	.7778	.9348	.9756
Predicted Val. of $Y(x_i)$	.5377	.6559	.7411	.8963	.9265	.9756
Filtered Val. of $Y(x_i)$	.4995	.5834	.7712	.7788	.9348	.9756
Smoothed Val. of $Y(x_i)$	.4439	.5986	.7465	.7789	.9348	.9756

We note from Table 4.3, that smoothing has a tendency to lower the filtered values of $Y(x_i)$ and that the predicted values have a tendency to be larger than the observed values. Finally, in Table 4.4, we give predicted values of $Y(x_i)$, for $x_i = 7, 5, 2$ and 1, low doses, at which no testing was done and at which inference is most crucial. Note that here the predicted values $\hat{y}(x_i)$ are given by $E(Y(x_i)|y(x_6), \ldots, y(x_0))$, and that this quantity is obtained via (2.5). Also given in Table 4.4 are the 90% Probability of Coverage Intervals (L_i, U_i) for the above $Y(x_i)$'s.

Table 4.4. Predicted Values of $Y(x_i)$ at Low Doses

Dose: x_i		7	5	2	1
$\hat{y}(x_i)$		.9866	.9924	.9984	.9995
90% PCI	L	.98658	.99239	.9984	.9995
for $Y(x_i)$	U	.98662	.99242	.9984	.9995

4.1. Comparison with Maximum Likelihood Approach

It is of interest to compare the results produced by our approach with those produced via the conventional approach, in which the relationship (1.2) is assumed, and α and β estimated by the method of maximum likelihood. It can be easily verified that $\hat{\alpha}$ and $\hat{\beta}$, the maximum likelihood estimates of α and β, respectively, are $\hat{\alpha} = 7.496 \times 10^{-4}$, and $\hat{\beta} = 1.513$. Replacing α and β by $\hat{\alpha}$ and $\hat{\beta}$ respectively, in (1.1), we obtain the maximum likelihood estimates of $Y(x_i)$. These are shown in Table 4.5; also shown there, for purposes of comparison, are the smoothed values of $Y(x_i)$ and the observed values $y(x_i)$. We note from Table 4.5, that whereas the

differences between the maximum likelihood estimates of $Y(x_i)$ and the s-
moothed values of $Y(x_i)$ are significant at the higher doses, the differences
at the lower doses, particularly the doses at which predictions are sought,
are negligible if not nonexistent. Thus it appears that a use of our approach
does not lead one to conclusions that would be significantly different from
those obtained via a more conventional approach, except that should the
situation so demand, our approach would provide a greater flexibility than
the conventional one. Finally, we also note that the smoothed values of
$Y(x_i)$ tend to be larger than those of the maximum likelihood estimates.

Table 4.5. A Comparison of the Observed and Smoothed Values and
Maximum Likelihood Estimates of $Y(x_i)$

Dose: x_i	Observed Value of $y(x_i)$	Smoothed Value of $Y(x_i)$	Max. Likelihood Est. of $Y(x_i)$
100	.4000	.4439	.4515
80	.5588	.5986	.5667
60	.7778	.7465	.6926
40	.7778	.7789	.8197
20	.9348	.9348	.9327
10	.9756	.9756	.9759
7		.9866	.9859
5		.9924	.9915
2		.9984	.9979
1		.9995	.9993

5. SUMMARY AND CONCLUSIONS

It appears to us that using the dynamic linear model set-up of Kalman
filtering is a potentially useful approach for making inference under dose-
response experiments. Its chief virtues are flexibility in modelling - specifi-
cally, making the parameters dose dependent - and the ease of undertaking
inference. Its chief disadvantage, especially to a non-Bayesian, is the need to
specify the starting values. However, as indicated in Section 3, some general
guidelines can be followed, and once this is done the procedure is almost
automatic. A computer code which facilitates the required computations
are given by Chen and Campodonico (1989). An issue that remains to be
addressed, and one that we have not been able to satisfactorily undertake,
is that pertaining to the determination of a "safe dose". Specifically, what
is needed is inference about x_s when $Y(x_s)$ is specified; $Y(x_s)$ is typically,
a number close to 1, say .999 or .9999. Finally, regarding further research
along the above lines, it would be desirable to develop an inference mech-
anism which does not rely, as heavily as we have, on a use of the Gaussian
distribution.

APPENDIX A

THE SPECIFICATION OF $\sigma^2(x)$

Let $Z(x) = -\log y(x) = (-\log Y(x))\lambda(x)$, then $Z(x)$ has a lognormal distribution with parameters $\log(-\log Y(x))$ and $\sigma^2(x)$.

Since $y(x) = m(x) \cdot \exp\{-(Z(x) + \log m(x))\}$, we have by a Taylor's series expansion

$$
\begin{aligned}
y(x) &= m(x) \sum_{k=0}^{\infty} (-1)^k (Z(x) + \log m(x))^k / k! \\
&\approx m(x)(1 - (Z(x) + \log m(x))),
\end{aligned}
$$

from which it follows that

$$
\begin{aligned}
\text{Var}\,(y(x)) &\approx m^2(x) \cdot \text{Var}\,(Z(x)) \\
&= m^2(x)(\log Y(x))^2 e^{\sigma^2(x)}(e^{\sigma^2(x)} - 1).
\end{aligned}
$$

However, $Y(x) = m(x)$, since

$$
\begin{aligned}
.5 &= P(y(x) \leq m(x)) \\
&= P(Y(x)^{\lambda(x)} \leq m(x)) \\
&= P(\lambda(x) \geq \log m(x) / \log Y(x)).
\end{aligned}
$$

Therefore, $\log m(x) / \log Y(x)$ equals to the median of $\lambda(x)$, which is equal to 1. Now (3.2) follows from simple algebra and the fact that $\text{Var}(y(x)) = m(x)(1 - m(x))/n(x)$.

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