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Optimal designs for radiation retention with Poisson correlated response

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SUMMARY

In this paper we describe a non-linear model with correlated observations which accounts for the elimination rate of radiation in the lung of individuals who have been exposed to an accidental intake at some time. The response is then modelled as a conditional Poisson distribution. When the leak is moderate or the size of the particles is large a theoretical justification of this assumption is given and D-optimal designs are computed. Copyright © 2006 John Wiley & Sons, Ltd.

KEY WORDS: D-optimality; Markov chains; radioactivity retention

1. INTRODUCTION

In this paper we discuss a mathematical model which describes the dose of radiation retained at any time by a given worker who has suffered an acute intake of aerosol particles after a leak of a hazardous radioactive substance occurs in a factory. Under natural assumptions we determine the probability distribution of the retention under such a situation and show that, in an appropriate parameter range, the conditional distribution is Poissonian. We suppose that a first bioassay is performed in the individual as soon as the accident is detected who is then taken to the proper place for analysis. We next use this framework to describe two-point optimal designs for which the first point is fixed that provide an optimal time t^* to perform a second bioassay in the worker. The aim of such an experiment is to estimate the parameters I and p that measure number and size of

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the absorbed particles corresponding to a fixed subject. The importance from a Mathematical point of view to perform a prompt first observation of the optimal design is discussed in Reference [1].

Following deterministic approaches as well as the International Commission on Radiological Protection norms [2] we assume that the mean value of the retention in the respiratory tract can be modelled by a multi-compartmental toxicokinetic model.

We construct a D-optimal design where the two observations are, obviously, correlated. Based on the overall Mathematical simplicity of the resulting model and actual observations we find it natural to assume that the response follows a conditional Poisson distribution. A theoretical justification of this assumption is presented in Section 2 wherein we develop a stochastic model of lung retention and we find that the response follows, in principle, a Binomial distribution. From a computational point of view it must be noted that calculations with binomial distributions entail important complications that may be overcome approximating the latter by a Poisson distribution. The Fisher information matrix follows naturally from these results. We next discuss the validity of the approximation when either the amount of substance leaked is moderate or the size of the composing particles is large or the time span between observations is long. D-optimal designs, maximizing the determinant of the Fisher information matrix, are computed in Section 3.1. For recent general references on this kind of problem see References [3–7]. Minimax designs have also been computed for the correlated observations case [8].

The Fisher information matrix has been widely used in the literature of optimal experimental design theory, either for uncorrelated or correlated observations, to deal with non-linear models. The use of the Fisher-information matrix is well justified whenever the relevant parameters are fixed, since then the inverse of the information matrix corresponds to the asymptotic covariance matrix of the estimators of the response function parameters. Moreover, Reference [9] shows that if a distribution of the exponential family is considered, the inverse of the (normalized) Fisher information matrix approximates well the mean squared error of the maximum likelihood estimates, even for small samples, as long as the variances of the observations remain small.

2. MODEL BUILDING

2.1. Model requirements

As we have pointed out, we shall suppose that at a given initial time t_0 a certain radioactive leak occurs and some active aerosol substance is inhaled by surrounding individuals. With no loss of generality we take $t_0 = 0$ and measure time in days. Over time, the substance is progressively eliminated and hence the concentration in a given individual will typically diminish away. We shall now introduce a stochastic model that is computationally simple and models appropriately the retention of the substance in individuals after time t. Let y_t denote the amount, in adequate units, of the given substance retained in the lung at time t. Obviously, y_t is a random quantity and hence it is natural to suppose that the current radioactive burden in lungs defines a random process $\{y_t\}_{t\geqslant 0}$ on a probability space $(\Omega, \mathscr{G}, \mathbb{P})$. Let $I \in \mathbb{N}$ be a measure of the initial intake of the worker exposed to the radioactive substance and let p be the activity median aerodynamic diameter (AMAD). This parameter is defined as the median of the distribution of particles that compose the leak, which have in turn different radioactivities and sizes; in short, I counts the number of the particles involved while p measures its size. Typical values of p vary between 1 and 20 standard anatomical units, while values of I corresponding to significant leaks are much larger lying between

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500 and 1500 Bq. The fraction of the leak inhaled that is absorbed in the lung will depend on several factors like conditions of exposure, retention parameters of the worker's body and the AMAD parameter p. Natural *a priori* requirements on the model are: (i) $y_t \in \mathbb{N}$ with $0 \leqslant y_t \leqslant I$, (ii) the 'trajectory' function $t \to y_t$ is decreasing with probability 1, and (iii) the present must contain all statistical information necessary to determine the future; thus $\{y_t\}$ must be a Markov process taking integer values, i.e. a continuous-time Markov chain. Another natural requirement on the model, condition (iv), is that the average amount of radioactive substance present on the given individual at time t must be proportional to the initial intake, i.e. that $\mathbb{E}(y_t) \equiv m(t, p, I) = If(t, p)$ for some $f : \mathbb{R}^2 \to \mathbb{R}$, the 'retention function'. The basic assumption that lung burden is proportional to the exposure is discussed within a simple deterministic model in Reference [10]. The function $f(t, p)$ measures the ratio of radioactive substance remaining in the given individual at time t. This function must satisfy that $0 \leqslant f(t_0, p) \leqslant 1$ and that f is decreasing in both variables t and p. These properties reflect the fact that clearance of inhaled particles augments with time and hence the dose of remaining substance in lungs decreases with time. Finally, bigger particles are eliminated faster than smaller ones. An obvious choice for the elimination rate $1 - f(t, p)$ is to use the one arising from compartmental deterministic models where an overall composite rate is present reflecting several elimination mechanisms between the different compartments and the exterior. See Reference [11] for a general account of multi-compartment kinetic models. To describe inhalation of radioactive aerosols the International Commission on Radiological Protection uses the so-called [2] model. Based on ICRP 66 we require

$$\mathbb{E}(y_t) = If(t, p) \quad \text{where } f(t, p) = \frac{\sum_{i=1}^{k_1} \gamma_i \mathrm{e}^{-\beta_i t - \alpha_i p}}{\sum_{i=1}^{k_2} \gamma'_i \mathrm{e}^{-\alpha'_i p}} \equiv \sum_{i=1}^{k_1} \tilde{\gamma}_i(p) \mathrm{e}^{-\beta_i t - \alpha_i p} \tag{1}$$

Here the indices k_1 and k_2 are related to the number of compartments into which lungs are divided in mathematical multi-compartmental models. Further, γ_j, $\gamma'_{j'}$, α_j, $\alpha'_{j'}$ and β_j, $j = 1, \ldots, k_1$, $j' = 1, \ldots, k_2$ are certain lung inter-compartmental clearance parameters and $\tilde{\gamma}_i(p) \equiv \gamma_i / (\sum_{j=1}^{k_2} \gamma'_j \mathrm{e}^{-\alpha'_j p})$. These *initial deposition parameters* (IDP) must satisfy $\sum_{i=1}^{k_1} \tilde{\gamma}_i(p) \mathrm{e}^{-\alpha_i p} < 1$. See References [1, 12, 13] for an elaboration of these ideas and actual least square estimation of parameters.

In Appendix C we give a useful form of function $f(t, p)$ corresponding to actual data (G. Sánchez, private communication. For an on-line version and more general pharmacokinetic software see Reference [14]). Note that the large number of terms that appear in that sum make it difficult to distinguish between different significant contributions; still we prefer to retain such a complicated expression since it follows the regulations of Reference [2] with parameters drawn by fitting compartmental models to real world data while it does not entail an unacceptable computational burden. A simplified version containing only a few exponentials terms is given in Reference [1].

Remark

In our context the problem of estimating the parameters I and p from observations taken from a given exposed worker arises naturally. Note that $\mathbb{E}(y_t)$ depends linearly on I, unlike what happens with respect to p, a fact that has important implications in the D-optimal design: it is well known that such a non-linear dependence upon p poses a hindrance to an estimation of parameters. This difficulty is usually overcome by giving initial nominal values to this parameter.

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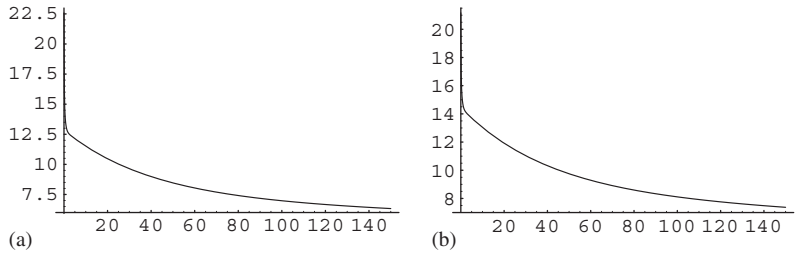

Figure 1. Plot of: (a) $m(t,\, p=15,\, I=1000)$; and (b) $m(t,\, p=10,\, I=500)$.

Figure 1 shows plots of $m(t,\, p,\, I) \equiv If(t,\, p)$ as a function of time for different choices of the parameters.

2.2. The Markov chain

We next elaborate in the construction of the stochastic model. We find it reasonable to assume that elimination of a certain inhaled aerosol particle is not affected by whether or not other particles are being cleared from the lung; thus, in terms of elimination, different absorbed particles are supposed to be statistically independent. We further assume that the probability to eliminate a given particle from the exposed worker's lung during the time interval $[t, t+h)$, $h>0$, can be written as $\mu(t,\, p)h + o(h)$ for some appropriate function μ depending on t and p; μ can be interpreted as being the *infinitesimal lung elimination* rate. Recalling that y_t counts the number of radioactive particles still retained in the lung at time t, it follows after a simple calculation that the infinitesimal generator of the process is given by

$$\begin{aligned} \mathbb{P}(y_{t+h} = j-1 | y_t = j) &= j\mu(t,\, p)h + o(h) \\ \mathbb{P}(y_{t+h} = j | y_t = j) &= 1 - j\mu(t,\, p)h + o(h) \\ \mathbb{P}(y_{t+h} = m | y_t = j) &= o(h), \quad m \neq j,\ \ j-1 \end{aligned} \tag{2}$$

By the general theory of continuous time Markov chains (see, for example Reference [15]) we have that $P_{ij}(t_1, t_2) \equiv \mathbb{P}(y_{t_2} = j | y_{t_1} = i)$, $t_1 < t_2$, $0 \leqslant j \leqslant i$, solves Kolmogorov forward equation

$$\frac{\partial P_{ij}(t_1, t_2)}{\partial t_2} = (j+1)\mu(t,\, p)P_{i,j+1}(t_1, t_2) - j\mu(t,\, p)P_{ij}(t_1, t_2) \tag{3}$$

with initial condition $P_{ij}(t_1, t_1) = \delta_{ij}$, where $\delta_{ij} = 1$ if $i = j$ and $\delta_{ij} = 0$ if $i \neq j$.

Although this infinite system of differential equations with *non-constant coefficients* looks formidable, it can be solved by consideration of the so-called z-transform (see Appendix A). The transition function of the process y_t is found to be given by

$$P_{ij}(t_1, t_2) \equiv \mathbb{P}(y_{t_2} = j | y_{t_1} = i) = \begin{cases} \dbinom{i}{j} \left(\dfrac{\tilde{f}(t_2,\, p)}{\tilde{f}(t_1,\, p)} \right)^j \left(1 - \dfrac{\tilde{f}(t_2,\, p)}{\tilde{f}(t_1,\, p)} \right)^{i-j}, & 0 \leqslant j \leqslant i \\ 0, \quad j > i \end{cases} \tag{4}$$

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i.e. the distribution of y_{t_2} conditional on the value of y_{t_1} is binomial $\mathscr{B}(y_{t_1}, \tilde{f}(t_2, p)/\tilde{f}(t_1, p))$ where we define the function $\tilde{f}(t, p)$ via

$$\tilde{f}(t, p) \equiv \exp\left\{-\int_0^t \mu(s', p)\, \mathrm{d}s'\right\} \tag{5}$$

In view of the physical interpretation of $\mu(t, p)$ it follows that $1 - \tilde{f}(t, p)$ can be interpreted as the *accumulated elimination function* in the time interval $(0, t]$.

Note also that (4) implies that trajectories of the process $\{y_t\}_{t \geqslant t_0}$ are positive and decreasing, having an absorbing boundary at 0. Further, it just requires a simple calculation to show that Chapman–Kolmogorov equations

$$P_{ik}(t_1, t_3) = \sum_{j=0}^{\infty} P_{ij}(t_1, t_2) P_{jk}(t_2, t_3) \tag{6}$$

are satisfied for any times $t_1 \leqslant t_2 \leqslant t_3$ and hence that the process is Markovian.

2.3. Marginal distribution

It is well known that a complete determination of the process requires to specify, in addition to the transition function, the initial distribution. We suppose that every inhaled particle has a common probability, say r, to be retained in the lung and that this initial retention *happens independently* from the fate of the rest of inhaled particles. It follows from this assumption that if the initial intake consisted of I particles then the amount of retained substance at $t = 0$ must be distributed as $y_0 \sim \mathscr{B}(I, r)$. From this observation and formula (4) the distribution of $\{y_t\}$ is evaluated in Appendix B via the theorem of total probability as

$$\mathbb{P}(y_t = j) = \begin{cases} \binom{I}{j} (r\tilde{f}(t, p))^j (1 - r\tilde{f}(t, p))^{I-j}, & 0 \leqslant j \leqslant I \\ 0, & j > I \end{cases} \tag{7}$$

i.e. $y_t \sim \mathscr{B}(I, r\tilde{f}(t, p))$. It follows, in particular, that $\mathbb{E}(y_t) \equiv Ir\tilde{f}(t, p)$ is *linear in the parameter* I as wished. Thus the above-constructed Markov chain satisfies all *a priori* imposed requirements (i)–(iv). Connection with deterministic models is made imposing that $r\tilde{f}(t, p) = f(t, p)$ as given by (1). This corresponds to the following election of the infinitesimal elimination rate function:

$$\mu(t, p) = -\frac{\partial}{\partial t} \log \sum_{i=1}^{k_1} \tilde{\gamma}_i(p) \mathrm{e}^{-\alpha_i t - \beta_i p} \tag{8}$$

In this case y_t is distributed as $y_t \sim \mathscr{B}(I, f(t, p))$.

For ease of notation in the sequel we simply write $f(t, p) \equiv f_t$. It follows from (4) and (7) that the bivariate distribution of the vector (y_{t_1}, y_{t_2}) with $t_1 < t_2$ is given by

$$\begin{aligned} &\mathbb{P}(y_{t_2} = j, y_{t_1} = i) \\ &= \begin{cases} \binom{I}{i} \binom{i}{j} f_{t_1}^i (1 - f_{t_1})^{I-i} \left(\dfrac{f_{t_2}}{f_{t_1}}\right)^j \left(1 - \dfrac{f_{t_2}}{f_{t_1}}\right)^{i-j}, & 0 \leqslant j \leqslant i \leqslant I \\ 0 \quad \text{otherwise} \end{cases} \end{aligned} \tag{9}$$

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Other statistically interesting features follow easily. Thus, we have whenever $t_0 \leqslant t_1 \leqslant t_2$

$$\begin{aligned} \mathbb{E}(y_{t_2} y_{t_1}) &= \mathbb{E}[\mathbb{E}(y_{t_2} y_{t_1} | y_{t_1})] = \mathbb{E}[y_{t_1} \mathbb{E}(y_{t_2} | y_{t_1})] = \mathbb{E}(y_{t_1}^2) \frac{f_{t_2}}{f_{t_1}} = f_{t_2} I (1 - f_{t_1} + I f_{t_1}) \\ \mathbb{E}[(y_{t_2} - \mathbb{E}(y_{t_2}))(y_{t_1} - \mathbb{E}(y_{t_1}))] &= f_{t_2} I (1 - f_{t_1}) \end{aligned} \tag{10}$$

In particular

$$\begin{aligned} &\mathbb{E}[(y_{t_2} - y_{t_1})(y_{t_1} - y_{t_0})] - \mathbb{E}(y_{t_2} - y_{t_1}) \mathbb{E}(y_{t_1} - y_{t_0}) \\ &\quad = - I (f_{t_2} - f_{t_1})(f_{t_1} - f_{t_0}) \end{aligned} \tag{11}$$

and so increments of the process are not independent.

Likewise, the correlation function $\rho(t_1, t_2)$, $t_1 \leqslant t_2$ is obtained as

$$\rho(t_1, t_2) = \frac{\mathbb{E}[(y_{t_2} - \mathbb{E}(y_{t_2}))(y_{t_1} - \mathbb{E}(y_{t_1}))]}{\sqrt{\mathbb{E}(y_{t_2} - \mathbb{E}(y_{t_2}))^2 \mathbb{E}(y_{t_1} - \mathbb{E}(y_{t_1}))^2}} = \left(\frac{f_{t_2}(1 - f_{t_1})}{f_{t_1}(1 - f_{t_2})} \right)^{\frac{1}{2}} \tag{12}$$

2.4. Poisson distribution approximation

Formulae (7) and (9) give us the marginal and joint distributions $\mathbb{P}_{y_{t_1}}$, $\mathbb{P}_{y_{t_1}, y_{t_2}}$ for any times $t_1 \leqslant t_2$. Unfortunately, it is well known that whenever N is large the evaluation of probabilities of the binomial distribution $\mathscr{B}(N, q)$ is cumbersome and one usually must resort to using appropriate approximations. A similar problem is found here when trying to evaluate the Fisher information matrix on which D-optimal designs are based upon. Although the former results allow one to evaluate the log-likelihood function the resulting formulas for the information determinant are, unfortunately, quite involved and not amenable to analytic calculations. Indeed, this process requires finding, say, $\mathbb{E} \frac{\partial}{\partial I} \log \mathbb{P}_{y_{t_1}, y_{t_2}}$; this, in turn, involves the determination of

$$\mathbb{E}\left(\frac{\partial}{\partial I} \log(I - y_{t_1})! \right) = \mathbb{E}\left(\sum_{k=y_{t_1}}^{I-1} \frac{1}{I - k} \right)$$

and it is unclear how this can be computed, even in a purely numerical way. Furthermore, even if some approximations were used, numerical calculations become computationally unwieldy due to the fact that the parameter I may take quite large values, even for moderate leaks. (Typical values of I range between 1500 Bq in large leaks to 100 Bq for small ones; for example, for ^{235}U, the lower detection limit (LDL) below which detectors are unable to detect the leak is 95 Bq).

For all these reasons the binomial distributions (7,9) are not adequate in the D-optimal design methodology. To overcome this difficulty a Gaussian distribution for the retention is frequently assumed in the literature. This can be well understood with our model since whenever both I and $I f(t, p) \equiv I f_t$ are large (typically when $I f_t \geqslant 30$), the individual retention distribution (7) is well approximated by a Gaussian distribution

$$y_t \sim \mathcal{N}(I f_t, I f_t (1 - f_t)) \tag{13}$$

Depending on the actual values of the parameters the approximation may be well justified whenever t is small, the initial leak is important and the AMAD size of the aerosol small.

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For longer times or if these conditions on the leak do not hold (i.e. the initial leak is moderate or the AMAD size of the particles is large) one finds that the latter condition $If_t \geqslant 30$ is quickly saturated and a Gaussian approximation no longer applies. Instead, it is well known that whenever $N \gg 1$ and $Nq = O(1)$ the binomial distribution $\mathscr{B}(N, q)$ can be well approximated by a Poisson distribution $\mathscr{P}(Nq)$ (in practice, the approximation works quite well provided $Nq \leqslant 20$). Hence, if $I \gg 1$ and $If_t \leqslant 20$ we can use the approximation $y_t \sim \mathscr{P}(If_t)$ where $\mathscr{P}$ stands for the Poisson distribution, i.e. one has, approximately

$$\mathbb{P}(y_t = j) = \frac{(If_t)^j}{j!} \mathrm{e}^{-If_t} \tag{14}$$

Likewise we shall approximate the conditional distribution of (4): $\mathbb{P}_{y_{t_2}|y_{t_1}} \sim \mathscr{B}(y_{t_1}, f_{t_2}/f_{t_1})$, by a Poisson distribution $\mathbb{P}_{y_{t_2}|y_{t_1}} \sim \mathscr{P}(y_{t_1} f_{t_2}/f_{t_1})$

$$\mathbb{P}(y_{t_2} = j \,|\, y_{t_1} = i) = \frac{(if_{t_2}/f_{t_1})^j}{j!} \mathrm{e}^{-\mathrm{i} f_{t_2}/f_{t_1}}, \quad t_1 \leqslant t_2, \quad j \leqslant i \tag{15}$$

A rough justification is based on the following. Suppose $I \gg 1$ and let t_1 be a time at which $If_{t_1} \leqslant 20$; then, since f is decreasing, one has also that $\mathbb{E}(y_{t_1} f_{t_2}/f_{t_1}) = If_{t_2} \leqslant If_{t_1} < 20$ for all $t_2 \geqslant t_1$, showing that the (mean of the) 'parameters' in the distribution of $\mathbb{P}_{y_{t_2}|y_{t_1}}$ satisfy also the requirement of applicability of Poisson distribution.

For a deeper argument we note that if $C > 20$ then the probability that $y_{t_1} f_{t_2}/f_{t_1} \geqslant C$ is small; to this end, note that if t_1 satisfies $If_{t_1} \leqslant 20$ then y_{t_1} has Poisson distribution $\mathscr{P}(If_{t_1})$. Using the classical Chebyshev's inequality we can bound $\mathbb{P}(y_{t_1} f_{t_2}/f_{t_1} \geqslant C)$ as

$$\begin{aligned} \mathbb{P}\left(\frac{y_{t_1} f_{t_2}}{f_{t_1}} \geqslant C\right) &= \mathbb{P}\left(y_{t_1} \geqslant \frac{f_{t_1} C}{f_{t_2}}\right) \leqslant \left(\frac{f_{t_2}}{f_{t_1} C}\right)^2 \mathbb{E} y_{t_1}^2 \\ &= \left(\frac{f_{t_2}}{f_{t_1} C}\right)^2 (If_{t_1} + I^2 f_{t_1}^2) \equiv \left(\frac{f_{t_2}}{f_{t_1} C}\right)^2 (m^2 + m(t_1, I, p)) \end{aligned} \tag{16}$$

Note that unless If_{t_1} is quite close to the control value 20 and t_1 to t_2, the right-hand side in Equation (16) will be small and the probability that $y_{t_1} f_{t_2}/f_{t_1}$ be greater than $C > 20$ would also be small. By way of example, suppose that $I = 1000$, $p = 15$ and that t_1 and t_2 are given by $t_1 = \frac{1}{2}$, $t_2 = 100$ (these are typical values for the parameters and optimal observation times t_1, t_2, see Tables I and II). Then, roughly, $f_{t_2}/f_{t_1} \approx \frac{1}{2}$ and we are guaranteed that $\mathbb{P}(y_{t_1} f_{t_2}/f_{t_1} \geqslant C)$ is bounded by 0.10, 0.084 and 0.058 for, respectively, $C = 22$, $C = 25$ and $C = 30$. Alternatively, a sharper bound is obtained using the estimate

$$\mathbb{P}\left(y_{t_1} \geqslant \frac{f_{t_1} C}{f_{t_2}}\right) \leqslant \exp\left(-\frac{f_{t_1} C}{f_{t_2}}\right) \mathbb{E} \mathrm{e}^{y_{t_1}} = \exp\left((e-1) If_{t_1} - \frac{f_{t_1} C}{f_{t_2}}\right) \tag{17}$$

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which shows that, with choice of parameters, the relevant probabilities *vanish exponentially fast* if $C \geqslant 14$. For example, if $C = 20$,

$$\mathbb{P}\left(\frac{y_{t_1} f_{t_2}}{f_{t_1}} \geqslant 20\right) \leqslant 10^{-7}$$

The bivariate two-time distribution and correlation function $\rho(t_1, t_2)$ follow easily and are given, under this approximation, by

$$\mathbb{P}(y_{t_2} = j, y_{t_1} = i) = (I f_{t_1})^i \frac{(i f_{t_2}/f_{t_1})^j}{i!\,j!} \mathrm{e}^{-\mathrm{i} f_{t_2}/f_{t_1} - I f_{t_1}}, \quad \rho(t_1, t_2) = \sqrt{\frac{f_{t_2}}{f_{t_1}}} \tag{18}$$

Finally, we remark that the reader should not be misled into thinking that the Markov chain constructed by this procedure is the same as the classical Poisson process in continuous time, well known in both the applied and theoretical literature (see, for example References [15, 16]). Denote the latter by $\{\hat{y}_t\}$; then, unlike our process, $\{\hat{y}_t\}$ has *increasing* trajectories and a transition function given in terms of a certain parameter λ by

$$\mathbb{P}(\hat{y}_{t_2} = j \,|\, \hat{y}_{t_1} = i) = \frac{\mathrm{e}^{-\lambda(t_2 - t_1)}}{(j - i)!}, \quad t_2 \geqslant t_1, \quad j \geqslant i \tag{19}$$

Differences between (15) and (19) are significant.

3. *D*-OPTIMAL DESIGNS

3.1. Fixed first observation

In this section we shall compute optimal designs that maximize the determinant of the Fisher information matrix. We note that we do not expect a proportional improvement in the design by allowing for another observation (a discussion of this fact in the uncorrelated case is given in Reference [17]. According to the last section (see Equations (14) and (15)) the radiation retention in the lungs may be modelled as follows: (i) at the initial observation time $t_1 \geqslant t_0$ the observation y_{t_1} has distribution $\mathscr{P}(I f_{t_1})$, and (ii) the conditional distribution of the second observation y_{t_2}, given y_{t_1}, is $\mathscr{P}(y_{t_1} f_{t_2}/f_{t_1})$. In our scheme it is convenient that the first observation be taken as soon as possible, i.e. t_1 must be as small as possible (see Reference [1]). The design region for the optimal time variable t_2 is naturally taken as (t_1, ∞). The log-likelihood function follows from (18) and is given by

$$\begin{aligned} L(I, p, t_1, t_2) \equiv \log \mathbb{P}_{y_{t_1}, y_{t_2}} = y_{t_1} \log(I f_{t_1}) - I f_{t_1} + y_{t_2} \log(y_{t_1} f_{t_2}/f_{t_1}) \\ - y_{t_1} f_{t_2}/f_{t_1} - \log(y_{t_1}! y_{t_2}!) \end{aligned} \tag{20}$$

After some algebra we find that the derivatives are simply given by

$$\begin{aligned} \frac{\partial L}{\partial I} &= \frac{y_{t_1}}{I} - f_{t_1} \\ \frac{\partial L}{\partial p} &= \left(\frac{f_{t_1;p}}{f_{t_1}} - \frac{f_{t_2;p} f_{t_1} - f_{t_2} f_{t_1;p}}{f_{t_1}^2}\right) y_{t_1} + \frac{f_{t_2;p} f_{t_1} - f_{t_2} f_{t_1;p}}{f_{t_1} f_{t_2}} y_{t_2} - I f_{t_1;p} \end{aligned} \tag{21}$$

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Note that

$$\mathbb{E}(y_{t_1}) = If_{t_1}, \quad \mathbb{E}(y_{t_2}) = If_{t_2}, \quad \mathbb{E}(y_{t_1}^2) = If_{t_1}(1 + If_{t_1})$$

$$\mathbb{E}(y_{t_2}^2) = \mathbb{E}[\mathbb{E}(y_{t_2}^2|y_{t_1})] = If_{t_2} + If_{t_2}^2(1 + If_{t_1})/f_{t_1} \quad \text{and} \tag{22}$$

$$\mathbb{E}(y_{t_2}y_{t_1}) = \mathbb{E}[y_{t_1}\mathbb{E}(y_{t_2}|y_{t_1})] = \mathbb{E}(y_{t_1}^2)\frac{f_{t_2}}{f_{t_1}} = f_{t_2}I(1 + If_{t_1})$$

Let $p_1 \equiv I$, $p_2 \equiv p$. Then, from (21), (22) the entries of Fisher information matrix

$$M_{ij}(I, p, t_1, t_2) \equiv \mathbb{E}\left[\frac{\partial L}{\partial p_i}\frac{\partial L}{\partial p_j}\right]$$

are found to be given by

$$\begin{aligned}
\mathbb{E}\left[\left(\frac{\partial L}{\partial I}\right)^2\right] &= \frac{1}{I^2}\text{var}(y_{t_1}) = f_{t_1}/I \\
\mathbb{E}\left[\left(\frac{\partial L}{\partial p}\right)^2\right] &= I\frac{f_{t_1;p}^2 f_{t_2}^2 + f_{t_1}^2 f_{t_2;p}^2 + f_{t_1}f_{t_1;p}f_{t_2}(f_{t_1;p} - 2f_{t_2;p})}{f_{t_1}^2 f_{t_2}} \\
\mathbb{E}\left[\left(\frac{\partial L}{\partial I}\right)\left(\frac{\partial L}{\partial p}\right)\right] &= f_{t_1;p}
\end{aligned} \tag{23}$$

where $f_{t;p}$ denotes here the derivative of f_t with respect to p.

Hence, the determinant of the information matrix takes the simple form

$$\begin{aligned}
\det M(I, p, t_1, t_2) &= \begin{vmatrix} f_{t_1}/I & f_{t_1;p} \\ f_{t_1;p} & \dfrac{I}{f_{t_1}^2 f_{t_2}}(f_{t_1;p}^2 f_{t_2}^2 + f_{t_1}^2 f_{t_2;p}^2 + f_{t_1}f_{t_1;p}f_{t_2}(f_{t_1;p} - 2f_{t_2;p})) \end{vmatrix} \\
&= \frac{(f_{t_1;p}f_{t_2} - f_{t_1}f_{t_2;p})^2}{f_{t_1}f_{t_2}}
\end{aligned} \tag{24}$$

It is interesting to point out that the determinant $|M|$ depends *only* on p but not on I, and hence that two-point optimal designs are I *independent*.

Maximizing by standard numerical methods $\det M(I, p, t_1, t_2)$ with respect to t_2 we can obtain a D-optimal second observation time $t_2 = t^*$ for *given* values of the first observation time. In Table I we have shown the corresponding values for the optimal second observation time t_2 for

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Table I. Second observations t^* time and determinant of the information matrix for different first observation times t_1 for a nominal value $p = 10$.

t_1	t^*	$\mid M \mid \times 10^8$
0	3.1	121.9
0.1	35.4	37.35
0.2	72.1	17.12
0.3	89.6	10.39
0.4	99.8	7.443
0.5	106.6	5.839
0.6	111.7	4.816
0.7	115.7	4.099
0.8	119.1	3.569
0.9	122.0	3.164
1	124.4	2.851

Table II. Second observations t_2^* time for different first observation times t_1 and different nominal values of p.

$t_1 \backslash p$	1	3	5	7	9	11	13	15	17	19
0	74.2	28.6	3.4	3.2	3.1	3.0	3.0	2.8	2.8	2.7
0.1	105.9	79.5	56.2	47.8	40.2	29.8	14.4	4.2	3.7	3.4
0.2	120.9	102.1	85.2	79.1	74.6	69.5	63.5	56.4	48.0	37.4
0.3	127.9	113.4	99.7	94.7	91.4	87.8	83.9	79.5	74.6	69.0
0.4	131.3	119.6	108.1	103.9	101.1	98.4	95.3	92.0	88.4	84.4
0.5	133.0	123.4	113.7	110.0	107.7	106.4	102.9	100.1	96.7	94.3
0.6	135.7	126.0	117.7	114.6	112.6	110.6	108.5	106.5	103.5	101.7
0.7	134.9	128.1	121.0	118.3	116.6	114.9	112.9	111.5	108.5	106.6
0.8	135.5	129.7	123.6	121.4	119.9	118.3	116.5	114.8	111.6	111.6
0.9	136.0	131.1	125.9	123.9	122.6	121.3	119.8	118.5	116.6	114.1
1	136.5	131.3	127.8	126.1	125.0	123.8	121.5	121.5	119.1	116.7

different first observation times t_1 with $0 \leqslant t_1 \leqslant 1$. Recall also that the non-linear dependence upon p of the optimal observation entails difficulties in the optimal experiment design process, whose solution involves taking a given initial value for the parameter. Here we consider a nominal value of the AMAD parameter $p = 10$. A remarkable feature that follows is the fast increase in the second optimal time t^* as t_1 grows from zero.

In Table II optimal second times are shown for different values of p and t_1. We take t_1 ranging between 0 and 1 since, as discussed below, we do not expect that in real life situations t_1 could become greater than 1 (see remark 3 below). Note how the optimal measurement time is quite sensitive to variations of t_1 from $t_1 = 0$ whenever the particle size satisfies $p \geqslant 4$. This dependence is however much more moderate if $p \leqslant 3$. This behaviour may be associated to the fact that elimination of particles occurs faster the bigger p is. Furthermore, if $p \geqslant 4$ and $t_1 \geqslant 0.5$ it appears that the optimal time is roughly independent of the particle size.

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Remarks

1. The simple representation (24) for the determinant of the information matrix is mainly due to the fact that the derivatives of the log-likelihood function $\partial L/\partial p_i$ happen to be *affine functions* of y_{t_1}, y_{t_2} (see (21)). No such simple formula is obtained when the original binomial distribution is conserved.
2. The related problem of estimating the intake parameter I *alone*, *for given* p, is interesting from both a statistical and a biophysical perspective. The solution involves optimizing the matrix element $(M^{-1})_{11}$, where M^{-1} is the inverse matrix. A simple calculation shows that, for given p, the optimal time $\tilde{t}^*$ for such an experiment is the time that maximizes the determinant (24) too, i.e. $\tilde{t}^* = t^*$.
3. We follow the discussion of López-Fidalgo *et al*. [1] who stress the fact that an important gain in the optimal design is obtained taking the first time as small as possible. However, in our case, it is somehow unrealistic to simply set $t_1 = 0$. This is due to the following: Typically a radioactive leak can only be detected when filters are analysed which happens every 8 hours (i.e. $\frac{1}{3}$ of a day). After the detection of the leak the worker must be taken to the nearest place where a bioassay can be performed. In the example considered here relative to a specific uranium factory, this time is estimated in 4 hours ($\frac{1}{6}$ of a day). That is, if we assume that the accidental leak occurs at $t_0 = 0$, then the first observation time after the intake can be as great as $\frac{1}{2}$ of a day.

3.2. Random first observation

We already discussed that we do not expect that the first observation time t_1 equals 0 but rather that it takes any value in the interval $[\frac{1}{6}, \frac{1}{2}]$. Thus an interesting generalization of the model is obtained by allowing the time at which the leak is detected to be uniformly distributed on the interval $[0, \frac{1}{3}]$, and hence allowing the initial measurement time t_1 to be uniformly distributed on the interval $[\frac{1}{6}, \frac{1}{2}]$. More generally, we shall consider here the case when t_1 is uniformly distributed on the interval $[a, b]$. In such a case the actual value of t_1 is not known and the mean value of the distribution can be used for parameter estimation. Note that now two conditional distributions define the model: (i) The conditional distribution of the first observation y_{t_1} given a first time t_1, $\mathscr{P}(If_{t_1})$ and (ii) the conditional distribution of the second observation y_{t_2} at time t_2 given y_{t_1} and t_1, $\mathscr{P}(y_{t_1} f_{t_2}/f_{t_1})$.

In this case the formulae given in Section 3.1 are still valid provided that expectations are now understood as conditional expectations given t_1. Thus, in order to compute the Information matrix we need to calculate the expectation of the matrix elements given in Section 3.1. In this case we have that the entries of the information matrix are obtained from (22) upon taking the relevant expectation with respect to t_1. Indeed, one has

$$M_{ij} \equiv \mathbb{E}\left[\frac{\partial L}{\partial p_i}\,\frac{\partial L}{\partial p_j}\right] = \mathbb{E}\left\{\mathbb{E}\left[\left(\frac{\partial L}{\partial p_i}\,\frac{\partial L}{\partial p_j}\right)^2 \middle| t_1\right]\right\}$$

Thus

$$\mathbb{E}\left[\left(\frac{\partial L}{\partial I}\right)^2\right] = \mathbb{E}\left\{\mathbb{E}\left[\left(\frac{\partial L}{\partial I}\right)^2 \middle| t_1\right]\right\} = \frac{1}{I^2}\mathbb{E}[\mathrm{var}(y_{t_1})] = \frac{1}{I}\mathbb{E}(f_{t_1}) \tag{25}$$

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Table III. Second observations times, t_2^* for a fixed first time $t_1 = \frac{1}{3}$ and t_2^{DE}, t_2^{ED} for a random first observation time t_1 and different nominal values of p.

p	1	3	5	7	9	11	13	15	17	19
t_2^*	129.3	115.9	103.0	98.3	95.1	91.9	88.3	84.4	80.0	74.6
t_2^{DE}	127.6	111.8	99.5	93.35	90.33	86.9	82.4	78.9	71.6	66.9
t_2^{ED}	121.9	113.6	98.9	96.4	90.8	86.4	82.5	76.5	71.9	65.7

and so forth. Noting that the only entry of the information matrix depending on t_2 is $\mathbb{E}[(\frac{\partial L}{\partial p})^2|t_1]$ it follows that maximization of Fisher information determinant amounts to finding

$$t_2^{DE} = \arg\max \int_a^b \frac{f_{t_1;p}^2 f_{t_2}^2 + f_{t_1}^2 f_{t_2;p}^2 + f_{t_1} f_{t_1;p} f_{t_2}(f_{t_1;p} - 2f_{t_2;p})}{f_{t_1}^2 f_{t_2}} \, \mathrm{d}t_1$$

$$= \arg\max \int_a^b \frac{(f_{t_1;p} f_{t_2} - f_{t_1} f_{t_2;p})^2 + f_{t_1} f_{t_2}(f_{t_1;p})^2}{f_{t_1}^2 f_{t_2}} \, \mathrm{d}t_1 \tag{26}$$

which, again, depends on p but not on I. Thus our optimization problem to compute the D-optimal second time involves the following steps: for fixed p we maximize the latter expression with respect to t_2 and then we solve to obtain $t_2 = t_2^{DE}$.

Note also that (26) can be written as

$$t_2^{DE} = \arg\max \int_a^b \frac{(f_{t_1;p} f_{t_2} - f_{t_1} f_{t_2;p})^2}{f_{t_1}^2 f_{t_2}} \, \mathrm{d}t_1 \tag{27}$$

As an alternative approach one can consider optimizing with respect to t_2 the expected value of $\det M(t_1, t_2)$ conditional in the value of t_1. This involves

$$t_2^{ED} = \arg\max \mathbb{E}[\det M(t_1, t_2)|t_1] = \arg\max \int_a^b \frac{(f_{t_1;p} f_{t_2} - f_{t_1} f_{t_2;p})^2}{f_{t_1} f_{t_2}} \, \mathrm{d}t_1 \tag{28}$$

Here t_2^{DE} (t_2^{ED}) stands for the optimal time computed by taking the determinant of the expectations of $(\partial L/\partial p_i)(\partial L/\partial p_j)$ (respectively, the expectation of the determinant).

Table III shows D-optimal second times found from (27) and (28), respectively. Due to the analytical complexity involved, optimal times must be obtained by resorting to some numerical approximation. We have found that the Mathematica software works quite well to handle this problem. It is interesting that, in all cases, the results are rather similar.

When the first observation time is randomly distributed it is unclear which of these two approaches must be preferred. Pronzato [18] has argued in favour of maximizing the expected value of the determinant with respect to the possible fluctuations of the experimental variables (and hence using t_2^{ED} as an optimal time) based upon the fact that it is the conditional matrix which carries information on the precision of parameter's estimation; in our context such a situation is obtained if the accident time were known, and hence t_1 given, before the parameter estimation takes place.

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However, the situation that one has in the present paper seems to be different: the accident time is unknown before the parameter estimation is carried out and hence so it is the value of t_1. Thus, for parameter estimation one could naturally use the mean value of the distribution but not t_1 which remains unknown. This suggests that the first approach is more consistent with the problem that has been considered in this paper.

We could also compare with the optimal time obtained in Section 3.1 for a fixed first time at the middle point of the interval, $t_1 = \frac{1}{3}$. The second times are also shown in Table III. To be specific, let us take $p = 10$; then the optimal times obtained by assuming an uniform distribution for t_1 are, respectively, $t_2^{DE} = 88.5$ and $t_2^{ED} = 88.6$. If, however, we fix t_1 to correspond to the middle point of the interval, i.e. if we set $t_1 = \frac{1}{3}$ then the optimal second observation time is obtained as $t^* = 93.6$. More generally, it appears that the optimization procedure corresponding to fixed initial time $t_1 = \frac{1}{3}$ seems *to overestimate the proper optimal time*, as compared to that obtained with an uniformly distributed t_1.

Table III shows D-optimal second times found from (26) when the first observation is assumed to be uniformly distributed on $[\frac{1}{6}, \frac{1}{2}]$ corresponding to different values of p.

4. DISCUSSION

In this paper we have developed a mathematical model which describes the random lung radiation amount retained at any time by a given worker exposed to a leak of aerosol particles. We have given the relevant probability distribution under such a situation and show that, in a certain parameter range, it corresponds to a Poissonian distribution. This theoretical model is used to describe optimal designs that provide an optimal time t^* for second bioassay with the first time given and taken as small as possible. Such an experiment aims to estimate the parameters I and p corresponding to a fixed subject.

The model has been fitted so that the average amount of retention corresponds to the retention function advised by ICRP [2] regulations. The latter is a complex expression having multiple exponential terms (see Appendix C). It is well known that such a model may be reasonably approximated in terms of just a few exponential terms. However, we prefer using the original complex model since we have found that it does not entail an important burden from a computational point of view, corresponds to the real biophysical situation and preserves the physical meaning of the coefficients. A simplified version containing only a few exponentials terms is given in Reference [1].

A glance at Table II shows that t^* is quite sensitive to the first observation. Note that only the bioassay time and the parameters I and p are unknown here, and hence the sooner the second observation is made the sooner the model may be estimated. In view of this fact our results strongly advice for filters to be checked as often as possible as this would result in an important time saving for the optimal observation which, in turn, entails an important gain in both the affected worker's health and the factory's security. Otherwise, statistical models must be modified as to take this deficiency into account.

There are several ramifications of interest. A natural, closely related problem is the estimation of the intake parameter I alone. As commented, the optimal time follows easily from our results. A second interesting avenue stems by considering the more general case when several workers are exposed to the aerosol leak; in this case one may wish to design experiments that aim to estimate the population parameters I and p.

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Another direction in which the model may be improved corresponds to the case when the particle size p is also a random explanatory variable with a given distribution, known only after the bioassay has been performed. This might happen in a situation where the leak affects differently the different sections, and hence workers, of the factory. Again, to account for this more general case a new framework must be considered. See Reference [19] for a description of such an approach.

APPENDIX A

In this Appendix we show how equation (4) is obtained by solving equation (3) for $P_{ij}(s,t) \equiv \mathbb{P}(y_t = j \,|\, y_s = i)$ where $s \leqslant t$ are two times and $i \geqslant j$ are integers. Note that none of the 'backward' variables s and $i \in \mathbb{N}$ appear explicitly in (4) and hence that $P_{ij}(s,t)$ depends upon them only in a parametric way via the initial condition. Thus, for ease of notation, we drop this dependence and set $q(j,t) \equiv P_{ij}(s,t)$ whereupon we find that q solves

$$\frac{\partial q(j,t)}{\partial t} = (j+1)\mu(t,p)q(j+1,t) - j\mu(t,p)q(j,t)$$

with initial condition $q(j, s=t) = \delta_{ij}$.

This equation is solved via the introduction of the 'z-transform' $\phi(z,s)$ defined as

$$\phi(z,t) = \sum_{j=-\infty}^{\infty} z^j q(j,t)$$

and

$$q(j,t) = \frac{1}{2\pi\sqrt{-1}} \int_{S^1} \frac{\phi(z,t)}{z^{j+1}}\,\mathrm{d}z$$

Here z is a complex variable defined on the unit complex circle: $z \in S^1 \equiv \{z \in \mathbb{C} : |z| = 1\}$. See Reference [20, pp. 307–385], for a good account of properties of such an object. We find, upon substitution that $\phi(z,t)$ must solve

$$\frac{\partial \phi(z,t)}{\partial t} + \mu(t,p)(z-1)\frac{\partial \phi(z,t)}{\partial z} = 0$$

with initial condition at $t = s$

$$\phi(z, t=s) = \sum_{j=-\infty}^{\infty} z^j q(j, s=t) = z^i$$

This is a first-order linear partial differential equation that can be solved by the characteristics method. The characteristic variables for this equation can be taken as (t,ω) where $\omega = (z-1)\exp\{-\int_s^t \mu(s')\,\mathrm{d}s'\}$. In these coordinates the above equation reads $\partial\phi(t,\omega)/\partial t = 0$, yielding $\phi = h(\omega)$ for some function h. The initial condition fixes h and gives the solution as

$$\phi = (1+\omega)^i \equiv \left(\frac{\tilde{f}_t}{\tilde{f}_s}(z-1)+1\right)^i$$

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where we recall (see (5)) $\tilde{f}_t \equiv \mathrm{e}^{-\int_0^t \mu(t')\,\mathrm{d}t'}$. Then, we have, by series expansion and use of Cauchy residues theorem

$$\phi(z,t) = \left(\frac{\tilde{f}_t}{\tilde{f}_s}(z-1)+1\right)^i = \sum_{n=0}^{i}\binom{i}{n}\left(1-\frac{\tilde{f}_t}{\tilde{f}_s}\right)^{i-n}\left(\frac{z\tilde{f}_t}{\tilde{f}_s}\right)^n$$

$$P_{ij}(s,t) \equiv q(j,t) = \sum_{n=0}^{i}\binom{i}{n}\left(1-\frac{\tilde{f}_t}{\tilde{f}_s}\right)^{i-n}\left(\frac{\tilde{f}_t}{\tilde{f}_s}\right)^n \frac{1}{2\pi\sqrt{-1}}\int_{S^1}\frac{\mathrm{d}z}{z^{j+1-n}}$$

$$= \begin{cases} \binom{i}{j}\left(1-\dfrac{\tilde{f}_t}{\tilde{f}_s}\right)^{i-j}\left(\dfrac{\tilde{f}_t}{\tilde{f}_s}\right)^j, & 0 \leqslant j \leqslant i \\ 0 \quad \text{otherwise} \end{cases}$$

This is equation (4).

APPENDIX B

Here we recover the distribution of $\{y_t\}$ (7). Again we simply write $\tilde{f}(t,p) \equiv \tilde{f}_t$. Recalling that we define $\tilde{f}_0 = 1$ the theorem of total probability yields that

$$\mathbb{P}(y_t = j) = \sum_i \mathbb{P}(y_t = j | y_{t_0} = i)\mathbb{P}(y_{t_0} = i)$$

$$= \sum_{i:j\leqslant i\leqslant I}\binom{i}{j}\tilde{f}_t^j(1-\tilde{f}_t)^{i-j}\binom{I}{i}r^i(1-r)^{I-i}$$

If $I < j$ the sum is zero. Suppose then that $j \leqslant I$ and let $l \equiv i - j$. One has

$$\mathbb{P}(y_t = j) = \left(\frac{\tilde{f}_t r}{1-r}\right)^j (1-r)^I \sum_{l=0}^{I-j}\binom{l+j}{j}\binom{I}{l+j}\left(\frac{r(1-\tilde{f}_t)}{1-r}\right)^l$$

$$= \left(\frac{\tilde{f}_t r}{1-r}\right)^j (1-r)^I \sum_{l=0}^{I-j}\binom{l+j}{j}\binom{I}{l+j}\left(\frac{\kappa}{1-\kappa}\right)^l$$

where we introduce $\kappa \equiv r(1-\tilde{f}_t)/1-\tilde{f}_t r$. Thus,

$$\mathbb{P}(y_t = j) = \left(\frac{\tilde{f}_t r}{1-r}\right)^j \frac{(1-r)^I}{(1-\kappa)^{I-j}}\sum_{l=0}^{I-j}\binom{l+j}{j}\binom{I}{l+j}\kappa^l(1-\kappa)^{I-j-l}$$

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To proceed further note that

$$\binom{l+j}{j}\binom{I}{l+j} = \binom{I-j}{l}\binom{I}{j}$$

$$\sum_{l=0}^{I-j}\binom{I-j}{l}\kappa^{I}(1-\kappa)^{I-j-l} = 1$$

and that

$$1-\kappa = \frac{1-r}{1-\tilde{f}_t r}$$

Thus, upon simplification, we finally get

$$\mathbb{P}(y_t = j) = \binom{I}{j}(\tilde{f}_t r)^j (1-\tilde{f}_t r)^{I-j}$$

APPENDIX C

Here we give the explicit form of the function $f(t, p)$ of (1)

$$\begin{aligned}
f(t,p) &= \mathrm{e}^{-0.170111p}(0.0128067 + 0.0388835\mathrm{e}^{-0.0201t} + 0.0768815\mathrm{e}^{-0.0011t}) \\
&\quad -\mathrm{e}^{-0.0878945p}(0.0024983\mathrm{e}^{-10.0001t} - 0.0124915\mathrm{e}^{-2.0001t}) \\
&\quad +\left(\frac{0.0212844}{\mathrm{e}^{4.35327p}} + \frac{0.00920991}{\mathrm{e}^{0.147244p}}\right)(0.00699301 \\
&\quad +0.00123877\mathrm{e}^{-102.1t} + 0.00100101\mathrm{e}^{-100.13t} \\
&\quad -0.251008\mathrm{e}^{-10.0001t} + 1.24001\mathrm{e}^{-2.0001t} + 1.00201\mathrm{e}^{-0.0301t}) \\
&\quad +\left(\frac{-0.0110839}{\mathrm{e}^{1.11147p}} + \frac{0.0110839}{\mathrm{e}^{0.123578p}}\right)(0.00699301 \\
&\quad +0.992009\mathrm{e}^{-10.0001t} + 0.999002\mathrm{e}^{-0.0301t}) \\
&\quad -\mathrm{e}^{-102.1t}\frac{0.0012475\left(\dfrac{0.0212844}{\mathrm{e}^{4.35327p}} + \dfrac{0.00920991}{\mathrm{e}^{0.147244p}}\right)^2}{\dfrac{0.0212844}{\mathrm{e}^{4.35327p}} + \dfrac{0.00920991}{\mathrm{e}^{0.147244p}} + \dfrac{0.0100737}{\mathrm{e}^{0.0878945p}}}
\end{aligned}$$

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$$+\left(\frac{-0.0171738}{e^{0.566783p}}+\frac{0.0171738}{e^{0.0577835p}}\right)(0.00699301+0.992009e^{-10.0001t})$$

$$+\frac{0.0110729e^{0.871722p}-0.0221457e^{1.85961p}+0.0110729e^{2.84751p}}{e^{1.98319p}+1.54943e^{2.52788p}-1.e^{2.97109p}-1.54943e^{3.03688p}}$$

$$+e^{-2.0001t}\frac{-0.0125796e^{0.147244p}-0.00544327\,e^{4.35327p}}{e^{0.235138p}+0.432707e^{4.44117p}+0.473291e^{4.50051p}}+e^{-10.0001t}$$

$$\times\left(\frac{0.0171567e^{0.181361p}-0.0171567e^{0.690361p}-0.0171567e^{1.16925p}+0.0171567e^{1.67825p}}{1.e^{0.748144p}+1.54943e^{1.29283p}-1.e^{1.73604p}-1.54943e^{1.80183p}}\right.$$

$$+\frac{0.00251591e^{0.147244p}+0.00108865e^{4.35327p}}{e^{0.235138p}+0.432707e^{4.44117p}+0.473291e^{4.50051p}}$$

$$\left.+\frac{0.00531579e^{0.382382p}+0.00460036e^{4.58841p}}{e^{4.73565p}+0.432707e^{8.94168p}+0.473291e^{9.00103p}}\right)$$

$$+\frac{-0.0265789e^{0.382382p}-0.0230018e^{4.58841p}-0.00497652e^{8.79444p}}{e^{2.0001t}(1.e^{4.73565p}+0.432707e^{8.94168p}+0.473291e^{9.00103p})}$$

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