An optimal design for simple illness–death model

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Abstract

Simple illness–death model arises in many medical and animal experiments. In a typical illness–death model, one is often interested in the event of occurrence of disease or illness (D) which is assumed to be unobservable. This event is followed by the event of failure or death (F) which is observable in addition to the presence of disease. Failure (F) can also be observed before the disease occurs in which case the absence of disease is also recorded. With the development of methodologies for making inference on the distribution of D, the design issue has also attracted some attention although not so greatly. In this work, we consider finding an optimal termination time of the experiment. We also consider the design with one intermediate observation time and address the problem of finding an optimal time for such an intermediate observation. We introduce two new optimality criteria and compare them with traditional $\mathscr{A}$-, $\mathscr{D}$- and c-optimality criteria.

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1. Introduction

Simple illness–death model arises in many medical and animal experiments, examples of which are being considered for the last two decades or more with sustained interest. In a typical illness–death model, one is often interested in the event of occurrence of disease or illness (D) which is assumed to be unobservable. This event is followed by the event of failure or death (F) which is observable in addition to the presence of disease. Failure (F) can also be observed before the disease occurs in which case the absence of disease is also recorded. For notational convenience, let us also mean by D or F the corresponding time of event whenever the context is such. Applications can be found in animal carcinogenicity studies (Kodell and Nelson, 1980; Turnbull and Mitchell, 1984), medical experiments involving human subjects, for example in

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HIV/AIDS research (Kalbfleisch and Lawless, 1989), and in industrial applications with machine faults (Dewanji and Dhar, 1993). Berlin et al. (1979) consider a more complicated illness–death model and discuss the identifiability issue for the related incidence rates. In simple illness–death models, as discussed above, McKnight and Crowley (1984) and Dewanji and Kalbfleisch (1986) prove that the distribution for D is not identifiable without frequent sacrifice plans. However, with parametric assumptions, identifiability can be achieved without such restriction (Portier, 1986).

With the development of methodologies for making inference on the distribution of D, the design issue has also attracted some attention although not so greatly. Bergman and Turnbull (1983) address the problem of finding optimum sacrifice schedule assuming exponential distribution for tumor incidence (D here) for nonlethal tumors (i.e., having no effect on failure F). For a fixed sequence of times $t_1 < \cdots < t_M$, at which one or more sacrifice (i.e., destructive life testing so that the observation cannot be continued) could be made, their procedure suggests how many animals to sacrifice at each time point. Berry (1975) discusses the problem of when to terminate the experiment in terms of maximum Fisher's information per unit cost, assuming a Weibull distribution for disease incidence, and concludes that the optimal strategy is to allow all animals to live out their lives. This is a rather trivial conclusion and, also, applies only to diseases with observable occurrence time or diseases with instantaneous death. In this paper, we consider finding an optimal termination time without such conditions being imposed on disease. Borgan et al. (1984) consider the comparison of several designs with respect to their efficiencies relative to the design of continuous monitoring and conclude that the one with intermediate observation has the highest efficiency. Since continuous monitoring is unrealistic in light of the cost and operational difficulties involved in such a design, we also consider the design with one intermediate observation time and address the problem of finding an optimal time for intermediate observation.

There could be more situations where simple illness–death model will apply and the design issue as described above would be of interest. In cancer-screening studies, it is important to schedule the visits of susceptible patients when they are to be examined for the presence of cancer (Day and Walter, 1984). There are some ad-hoc approaches to schedule the visits usually once in every year or so, although a more objective criterion to choose one or more time points for intermediate observation will be of interest (see Zelen, 1993). The designs that will be introduced in the next section can serve this purpose. In the industrial context, for example, while dealing with a parallel system with two components (Dewanji and Dhar, 1993), one may be interested in the time when the first component failure takes place and, for this purpose, one would like to schedule an inspection of the system before it fails. Similarly, it is important to schedule intermediate inspection(s) for detection of fault in a machine.

In Section 2, we introduce two new optimality criteria, a possible strategy for arriving at a design satisfying such criteria and a model for the joint distribution of D and F. The optimal design clearly depends on the model parameters which need to be estimated based on data from some other sources or from previous stages in a multistage or

sequential framework. In Section 3, we discuss estimation of the parameters based on data with a fixed termination time and then follow it up for data with a fixed intermediate observation time. We consider, in Section 4, the optimal designs by our criteria described in the next section and by the traditional information-matrix-based criteria, and make some comparisons. Section 5 discusses different advantages of our design and its applicability in a more general set-up.

2. Preliminaries

The calculation of expected information matrix for a typical observation from the simple illness–death model seems to be difficult in general (see the discussion in the following sections). Therefore, the task of obtaining an optimal design under the standard likelihood-based criteria, which deal with the expected information matrix, is not straightforward. For this reason, we introduce below two simple optimality criteria which are very easy to deal with and have compelling intuitive appeal. As D is the event of interest, we would like to arrive at a design giving most 'information' on the event D so that t_0 the termination or intermediate observation time whichever is the problem, is not too early to miss most of the disease occurrences. That is, D should occur before t_0, with highest probability. Without any further restriction, this will lead to the trivial optimal design of choosing $t_0 = \infty$. But we do not want t_0 to be too late to observe only the diseases followed by deaths. Therefore, we consider maximizing the probability of the event $\{D < t_0 < F\}$ with respect to t_0. Intuitively, this also has the interpretation of trying to get t_0 as close to D as possible. It has also the natural appeal of incorporating the information on the associated failure process while focusing on the disease process. Let us denote this criterion by $\mathscr{C}_1$.

One alternative to the above criterion $\mathscr{C}_1$ is, in addition to maximizing the probability of the event $\{D < t_0 < F\}$, to minimize the probability of the event $\{D < F < t_0\}$ simultaneously. In order to achieve this, we consider maximizing the difference of the two probabilities, that is $P[D < t_0 < F] - P[D < F < t_0]$. Let us denote this criterion by $\mathscr{C}_2$. This criterion $\mathscr{C}_2$ is particularly useful in the choice of intermediate observation time t_0 as it gives some protection against disease and failure due to disease taking place before the intermediate observation time t_0. For example, in cancer-screening studies, one will be interested in guarding against such happenings. However, in order to do so, the second term in the difference pulls down the optimal value of t_0 from that obtained by maximizing only the first term (i.e., criterion $\mathscr{C}_1$). In cancer-screening studies, one would prefer early intermediate observation (smaller t_0) in order to be able to diagnose or detect the disease early (see Zelen, 1993) so that criterion $\mathscr{C}_2$ may be preferred. However, when the interest is only in the estimation of the distribution of D, one may not need such protection and criterion $\mathscr{C}_1$ may be preferred.

In order to arrive at an optimal choice of t_0, the following strategy may be implemented. We first make a guess of the value of t_0 at $t_0 = t_{01}$ from past experience or prior knowledge, if any. Start the study with n individuals with $t_0 = t_{01}$ fixed. Based

Table 1
Different types of observation with termination time t_0

Types of observation	Indicator (δ)	Likelihood contribution	Frequency
$t = F < D, t_0$	1	$\beta e^{-(\alpha+\beta)t}$	n_1
$t_0 < F, D$	2	$e^{-(\alpha+\beta)t_0}$	n_2
$D < t_0 < F$	3	$\frac{\alpha}{\alpha+\beta-\gamma}[e^{-\gamma t_0} - e^{-(\alpha+\beta)t_0}]$	n_3
$D < F = t < t_0$	4	$\frac{\alpha\gamma}{\alpha+\beta-\gamma}[e^{-\gamma t} - e^{-(\alpha+\beta)t}]$	n_4

on the n observations, estimate the model parameters and obtain the optimal choice of t_0 using these estimates. This idea can be extended to suggest strategies involving multiple stages.

We start with the simple parametric assumption of exponential model for D, with parameter α, having density $f(x) = \alpha e^{-\alpha x}$, $\alpha > 0$, $x > 0$. The assumed conditional distribution of F, given $D = x$, is described in terms of its conditional density as follows:

$$g(y|x) = \begin{cases} \beta e^{-\beta y} & \text{if } y < x, \\ \gamma e^{-\beta x - \gamma(y-x)} & \text{if } y \geqslant x. \end{cases} \tag{1}$$

That is, the conditional hazard β (before disease occurs) changes to γ once the disease occurs (see Freund, 1961). Although, in the following sections, we work with this model, the approach is simple and flexible enough for other general models, as noted in Section 5.

3. Estimation of parameters

We first discuss the case when observation on an individual ceases either at failure or at time t_0, whichever is earlier. Although we do not allow any censoring prior to the terminal censoring at time t_0, it can be easily incorporated if present. As it is, we have four different types of observation as given in Table 1, in which t means a typical time of failure.

In Table 1, the indicator δ denotes the type of observation. The likelihood contributions for different types of observation are also given in Table 1. For $\delta = 1$ and 2, the contributions are easy to see. For $\delta = 3$, the contribution is

$$\begin{aligned} P[D < t_0 < F] &= \int_0^{t_0} \alpha e^{-(\alpha+\beta)x - \gamma(t_0 - x)} \, dx \\ &= \frac{\alpha}{\alpha+\beta-\gamma}[e^{-\gamma t_0} - e^{-(\alpha+\beta)t_0}], \end{aligned} \tag{2}$$

assuming $\alpha + \beta \neq \gamma$. This is the probability we seek to maximize with respect to t_0 for criterion $\mathscr{C}_1$, as described in Section 2. Note that the value of t_0 which maximizes (2) is given by

$$t_0 = \frac{\log[(\alpha+\beta)/\gamma]}{\alpha+\beta-\gamma}. \tag{3}$$

For $\delta = 4$, the contribution is

$$P[D < F = t < t_0] = \int_0^t \alpha e^{-(\alpha+\beta)x} \gamma e^{-\gamma(t-x)}\, dx$$
$$= \frac{\alpha\gamma}{\alpha+\beta-\gamma}[e^{-\gamma t} - e^{-(\alpha+\beta)t}]. \quad (4)$$

For criterion $\mathscr{C}_2$, we need $P[D < F < t_0]$, which can be calculated by integrating (4) over the range $\{0 < t < t_0\}$, and then the difference $P[D < t_0 < F] - P[D < F < t_0]$ can be found as

$$\frac{2\alpha}{\alpha+\beta-\gamma}[e^{-\gamma t_0} - e^{-(\alpha+\beta)t_0}] - \frac{\alpha}{\alpha+\beta}[1 - e^{-(\alpha+\beta)t_0}],$$

assuming $\alpha + \beta \neq \gamma$. Maximizing the above difference with respect to t_0 for criterion $\mathscr{C}_2$, we get the optimal t_0 as

$$t_0 = \frac{1}{\alpha+\beta-\gamma} \log\left[\frac{\alpha+\beta+\gamma}{2\gamma}\right], \quad (5)$$

which can be seen to be less than the t_0 in (3). Note that both the optimal designs in (3) and (5) involve parameters related to both the disease and failure processes, as mentioned in the beginning of Section 2.

Censored individuals at time t' (say) prior to time t_0 (if any) will contribute likelihood terms like those corresponding to $\delta = 2$ or 3, with t_0 replaced by t', depending on whether the disease is absent or present, respectively.

The maximum likelihood method requires taking product over all such contributions from all the individuals to obtain the likelihood function and then maximizing it with respect to the parameters α, β and γ. Looking at the likelihood contributions in Table 1, it is clear that this involves computer-intensive numerical maximization. A simpler alternative, in this case, is the use of EM algorithm (Dempster et al., 1977), since there is a natural choice for the complete version of data. The application of EM algorithm is straightforward and the details are available in Dewanji and Biswas (1998).

Next we consider the case when we carry on the observation on each individual till failure; however, at an intermediate time t_0, the state (absence or presence of disease) of an individual, if not failed, is observed and recorded. As before, the individuals can be allowed to be censored although, for simplicity, we do not consider that in our main results. We now have five different types of observation as given in Table 2. The likelihood contributions for the different types are also given in Table 2.

The indicator δ in Table 2 is different from that in Table 1. Note that the likelihood contributions for $\delta = 1$ and 2 are the same. For $\delta = 3$, the contribution is

$$P[t_0 < D < F = t] = \int_{t_0}^t \alpha e^{-(\alpha+\beta)x} \gamma e^{-\gamma(t-x)}\, dx$$
$$= \frac{\alpha\gamma e^{-\gamma t}}{\alpha+\beta-\gamma}[e^{-(\alpha+\beta-\gamma)t_0} - e^{-(\alpha+\beta-\gamma)t}],$$

assuming $\alpha + \beta \neq \gamma$. Similarly, the contributions for $\delta = 4$ and 5 can be easily obtained as given in Table 2.

Table 2
Different types of observation with intermediate observation time t_0

Types of observation	Indicator (δ)	Likelihood contribution
$t = F < D, t_0$	1	$\beta e^{-(\alpha+\beta)t}$
$t_0 < F = t < D$	2	$\beta e^{-(\alpha+\beta)t}$
$t_0 < D < F = t$	3	$\frac{\alpha\gamma e^{-\gamma t}}{\alpha+\beta-\gamma}[e^{-(\alpha+\beta-\gamma)t_0} - e^{-(\alpha+\beta-\gamma)t}]$
$D < t_0 < F = t$	4	$\frac{\alpha\gamma e^{-\gamma t}}{\alpha+\beta-\gamma}[1 - e^{-(\alpha+\beta-\gamma)t_0}]$
$D < F = t < t_0$	5	$\frac{\alpha\gamma e^{-\gamma t}}{\alpha+\beta-\gamma}[1 - e^{-(\alpha+\beta-\gamma)t}]$

Censored individuals at time t' (say) can be effectively of four different types: namely, (1) $t' < D, F$ (whether $t' < t_0$ or $t' > t_0$), (2) $D < t' < t_0, F$, (3) $D < t_0 < t' < F$ and (4) $t_0 < D < t' < F$. The likelihood contributions corresponding to these four types are

$$e^{-(\alpha+\beta)t'},$$

$$\frac{\alpha e^{-\gamma t'}}{\alpha+\beta-\gamma}[1 - e^{-(\alpha+\beta-\gamma)t'}],$$

$$\frac{\alpha e^{-\gamma t'}}{\alpha+\beta-\gamma}[1 - e^{-(\alpha+\beta-\gamma)t_0}]$$

and

$$\frac{\alpha e^{-\gamma t'}}{\alpha+\beta-\gamma}[e^{-(\alpha+\beta-\gamma)t_0} - e^{-(\alpha+\beta-\gamma)t'}],$$

respectively.

Maximum likelihood estimates of the parameters can be obtained again by using the EM algorithm (see Dewanji and Biswas, 1998). It is to be noted that in this case also, we find the optimal design by maximizing $P[D < t_0 < F]$, or the difference $P[D < t_0 < F] - P[D < F < t_0]$, as argued in Section 2. The corresponding t_0 has the same form as (3) or (5), respectively.

4. Optimal designs

As noted at the end of the last section, regardless of how the parameter estimates are obtained, optimal t_0 under any of the criteria introduced in Section 2 is the same whether one uses it as the terminal time or intermediate observation time and is given by (3) or (5). However, in this section, we intend to carry out some comparative study with traditional $\mathscr{A}$-, $\mathscr{D}$- and c-optimality. As the latter criteria work with the expected information matrix, they will lead to different choices of optimal t_0 as terminal and intermediate observation times. We outline, in the following, the calculation of expected information matrix in both the cases.

First, when t_0 is the termination time, note that the likelihood contribution from a single observation can be written as, using the third column of Table 1,

$$L_1 = [\beta e^{-(\alpha+\beta)t}]^{I_{\{\delta=1\}}} [e^{-(\alpha+\beta)t_0}]^{I_{\{\delta=2\}}} \left[\frac{\alpha e^{-\gamma t_0}}{\alpha+\beta-\gamma}(1-e^{-(\alpha+\beta-\gamma)t_0})\right]^{I_{\{\delta=3\}}}$$
$$\left[\frac{\alpha\gamma e^{-\gamma t}}{\alpha+\beta-\gamma}(1-e^{-(\alpha+\beta-\gamma)t})\right]^{I_{\{\delta=4\}}}, \quad (6)$$

where t denotes failure time for $\delta=1$ and 4. From Table 1, it is clear that observation on a single individual consists of the vector $\{\delta,t\}$ with the range

$$\{\delta=1, 0<t<t_0\} \cup \{\delta=2, t=t_0\} \cup \{\delta=3, t=t_0\} \cup \{\delta=4, 0<t<t_0\}.$$

Therefore, the underlying probability model is given by the joint distribution of $\{\delta,t\}$ which is as given in the third column of Table 1 and also in (6) above. Note that the four disjoint sets in the range of $\{\delta,t\}$, as described above, correspond to the four types of observation in Table 1.

The expected information from a single observation, I, can be obtained from (6) by taking expectation of the negative of second derivative matrix of $\log L_1$, that is $-\partial^2 \log L_1/\partial\theta\partial\theta^{\mathrm{T}}$ with $\theta=(\alpha,\beta,\gamma)$, with respect to the joint distribution of $\{\delta,t\}$. For the calculation of expectations of different elements in the matrix, one needs $P[\delta=i]$, for $i=1,2$ and 3, and integration of some terms involving t over the range $\{\delta=4, 0<t<t_0\}$ multiplied by the corresponding sub-density given by

$$\frac{\alpha\gamma e^{-\gamma t}}{\alpha+\beta-\gamma}(1-e^{-(\alpha+\beta-\gamma)t}),$$

the last term in (6). This integration needs to be done numerically. The probability $P[\delta=1]$ can be easily obtained, by integrating the first term in (6) over the range $\{0<t<t_0\}$, as

$$[1-e^{-(\alpha+\beta)t_0}]\beta/(\alpha+\beta),$$

and for $\delta=2$ and 3, the probabilities are as given in the second and third terms in (6). After calculating the matrix I for a given set of parameters, one needs to take the inverse of it, I^{-1}, to obtain the asymptotic variance–covariance matrix of $\hat{\theta}=(\hat{\alpha},\hat{\beta},\hat{\gamma})$. For our purpose of estimating the distribution of D, we seek to minimize the asymptotic variance of $\hat{\alpha}$, the $(1,1)$th element of I^{-1}, with respect to t_0, which gives the traditional optimal choice for t_0. Let us denote this criterion by $\mathscr{C}_3$. In Table 3 below, we give the optimal choices of t_0 by criteria $\mathscr{C}_1$ and $\mathscr{C}_2$ (given by (3) and (5), respectively) and also by the variance-minimizing criterion $\mathscr{C}_3$ as described above, for different sets of parameters. The asymptotic relative efficiency (ARE) values of the two designs, chosen by $\mathscr{C}_1$ and $\mathscr{C}_2$, with respect to the most efficient one chosen by $\mathscr{C}_3$, are also given in the last two columns of Table 3. These are obtained as the ratio of asymptotic variances (of $\hat{\alpha}$) calculated at t_0 by $\mathscr{C}_3$ and at t_0 by $\mathscr{C}_1$ (and $\mathscr{C}_2$, respectively).

If one is interested in estimating all the parameters (both the distributions of D and F), one would consider the whole matrix I^{-1} and seek to minimize trace of I^{-1}

Table 3
Optimal designs for terminal time t_0

Parameters			Criteria						ARE	
α	β	γ	$\mathscr{C}_1$	$\mathscr{C}_2$	$\mathscr{C}_3$	$\mathscr{A}$	$\mathscr{D}$	c	$\mathscr{C}_1$	$\mathscr{C}_2$
0.2	0.1	0.15	4.62	2.70	7.2	11.0	13.0	12.0	0.92	0.71
	0.2	0.25	3.13	1.75	6.5	10.0	10.5	16.0	0.84	0.60
	0.3	0.35	2.38	1.29	6.5	9.0	9.0	20.0	0.79	0.54
0.1	0.05	0.1	8.11	4.46	14.5	21.0	23.0	34.0	0.88	0.63
	0.1	0.15	5.75	3.08	13.5	18.0	19.0	45.0	0.81	0.55
	0.15	0.2	4.46	2.36	12.5	15.0	16.0	55.0	0.76	0.51
0.05	0.03	0.05	15.67	8.75	28.0	42.0	45.0	65	0.88	0.63
	0.05	0.07	11.89	6.47	27.0	40.0	40.0	120	0.82	0.57
	0.07	0.09	9.59	5.14	25.0	33.0	34.0	100	0.78	0.53
0.02	0.01	0.015	46.21	27.03	70.0	110	130	120	0.92	0.71
	0.02	0.03	28.77	15.42	65.0	90	95	250	0.81	0.55
	0.03	0.045	21.07	10.81	60.0	70	75	130	0.74	0.48
0.001	0.0005	0.001	810.93	446.29	1440	2100	2300	3400	0.88	0.63
	0.001	0.0015	575.36	308.30	1350	1800	1900	2250	0.81	0.55
	0.0015	0.002	446.29	235.57	1250	1500	1600	4750	0.76	0.51

for $\mathscr{A}$-optimality, or determinant of I^{-1} for $\mathscr{D}$-optimality, or sum of all the elements of I^{-1} giving variance of $\hat{\alpha}+\hat{\beta}+\hat{\gamma}$ for c-optimality. The corresponding results are also given in Table 3 in columns under $\mathscr{A}$, $\mathscr{D}$ and c, respectively, for the purpose of comparison. As expected, one needs to carry on the experiment for longer time in order to estimate all the parameters efficiently and that is reflected in the results.

The third criterion $\mathscr{C}_3$ seems to give somewhat larger t_0 than those obtained by $\mathscr{C}_1$ and $\mathscr{C}_2$. Therefore, although the optimal designs by $\mathscr{C}_1$ and $\mathscr{C}_2$ will lead to less efficient estimates (in the sense of having larger variance), they will be more cost efficient. It is to be noted, however, that the calculation of optimal t_0 by $\mathscr{C}_3$ cannot be done analytically and requires extensive computation with numerical integration and numerical minimization, whereas the same by $\mathscr{C}_1$ and $\mathscr{C}_2$ is available in closed form. The optimal t_0 by criterion $\mathscr{C}_2$ is less than the t_0 by $\mathscr{C}_1$, as noted in Sections 2 and 3. Thus, criterion $\mathscr{C}_1$ seems to give a more efficient design for t_0 than does $\mathscr{C}_2$ for estimating α, or the distribution of D, as reflected in the last two columns of Table 3. The asymptotic relative efficiency of $\mathscr{C}_1$ ranges from about 74% to 92% and that of $\mathscr{C}_2$ ranges from about 48% to 71% for the different sets of parameters considered here.

When t_0 is the time of an intermediate observation, likelihood contribution from a single individual, as in (6), can be written, using the third column of Table 2, as

$$L_2 = [\beta e^{-(\alpha+\beta)t}]^{I_{\{\delta=1 \text{ or } 2\}}} \left[\frac{\alpha\gamma e^{-\gamma t}}{\alpha+\beta-\gamma}(e^{-(\alpha+\beta-\gamma)t_0} - e^{-(\alpha+\beta-\gamma)t})\right]^{I_{\{\delta=3\}}} \times \left[\frac{\alpha\gamma e^{-\gamma t}}{\alpha+\beta-\gamma}(1-e^{-(\alpha+\beta-\gamma)t_0})\right]^{I_{\{\delta=4\}}} \left[\frac{\alpha\gamma e^{-\gamma t}}{\alpha+\beta-\gamma}(1-e^{-(\alpha+\beta-\gamma)t})\right]^{I_{\{\delta=5\}}}, \quad (7)$$

Table 4
Optimal designs for intermediate observation time t_0

Parameters			Criteria						ARE	
α	β	γ	$\mathscr{C}_1$	$\mathscr{C}_2$	$\mathscr{C}_3$	$\mathscr{A}$	$\mathscr{D}$	c	$\mathscr{C}_1$	$\mathscr{C}_2$
0.2	0.1	0.15	4.62	2.70	4.8	3.0	2.5	3.0	0.9997	0.93
	0.2	0.25	3.13	1.75	3.3	2.5	2.5	2.0	0.9993	0.93
	0.3	0.35	2.38	1.29	2.5	2.0	2.0	2.0	0.9996	0.94
0.1	0.05	0.1	8.11	4.46	9.0	7.5	5.0	6.0	0.9982	0.91
	0.1	0.15	5.75	3.08	6.1	5.5	4.5	4.5	0.9990	0.93
	0.15	0.2	4.46	2.36	4.7	4.4	4.0	4.0	0.9995	0.94
0.05	0.03	0.05	15.67	8.75	17.0	13.5	10.0	11.0	0.9991	0.92
	0.05	0.07	11.89	6.47	12.5	10.5	8.5	8.0	0.9992	0.93
	0.07	0.09	9.59	5.14	10.0	9.0	8.0	8.5	0.9996	0.94
0.02	0.01	0.015	46.21	27.03	47.0	36.0	26.0	31.0	0.9998	0.94
	0.02	0.03	28.77	15.42	31.0	27.0	22.5	22.0	0.9992	0.93
	0.03	0.045	21.07	10.81	22.5	22.5	19.0	20.0	0.9993	0.93
0.001	0.0005	0.001	810.93	446.29	690	605	410	565	0.9930	0.97
	0.001	0.0015	575.36	308.30	560	460	390	430	0.9994	0.95
	0.0015	0.002	446.29	235.57	460	420	360	370	1.0	0.94

where t denotes the failure time. As before, we find expected information matrix by taking expectation of $-\partial^2 \log L_2/\partial\theta\partial\theta^{\mathrm{T}}$ with respect to the joint distribution of $\{\delta, t\}$. Once the expected information matrix I, and then I^{-1}, is calculated for a given set of parameters, optimal t_0 can be obtained using criterion $\mathscr{C}_3$, that is by minimizing the asymptotic variance of $\hat{\alpha}$ given by the $(1,1)$th element of I^{-1}. As noted before, the optimal designs by using criteria $\mathscr{C}_1$ and $\mathscr{C}_2$ remain the same as those obtained from (3) and (5), respectively. One can also obtain optimal choices of t_0 by satisfying $\mathscr{A}$-, $\mathscr{D}$- and c-optimality criteria, as before.

All the optimal choices of t_0, for different sets of parameters, are given in Table 4 above. The asymptotic relative efficiency (ARE) values of the two designs, chosen by $\mathscr{C}_1$ and $\mathscr{C}_2$, with respect to the most efficient one chosen by $\mathscr{C}_3$, are also given in the last two columns. Since t_0 is an intermediate time of observation, beyond which the study is carried on to accumulate observation on failures, there is no need to have large t_0 (unlike in the earlier case in Table 3 when t_0 is the terminal time) by $\mathscr{A}$-, $\mathscr{D}$- and c-criteria to estimate all the parameters efficiently. In fact, the corresponding t_0 values are somewhat smaller perhaps to facilitate observation on early occurrence of D. However, to estimate α alone, the choices of t_0 by $\mathscr{C}_1$ and $\mathscr{C}_3$ are similar (ARE of $\mathscr{C}_1$ is almost 1), and the one by $\mathscr{C}_2$ is smaller making it little less efficient (ARE of $\mathscr{C}_2$ is above 90%). Note that, for fixed α, the optimal designs in both Tables 3 and 4 are different (and intuitively meaningful) for different values of β and γ. For example, if β is larger, t_0 is smaller to guard against earlier deaths without disease and vice versa.

5. Discussion

As demonstrated in the previous section, the efficiency of our criterion $\mathscr{C}_1$ is quite high. However, whereas the design by $\mathscr{C}_1$ can be obtained in a simple closed form, the one by $\mathscr{C}_3$ is difficult. Criterion $\mathscr{C}_1$, therefore, seems like a useful and appealing alternative to the traditional one, specially when the optimal design is to be obtained by strategies involving multiple stages, as mentioned at the end of Section 2. In cases like cancer-screening studies or inspection of industrial systems, when an intermediate observation is primarily meant for early detection of disease or fault so as to be able to take corrective measures rather than estimating the distribution of D, criterion $\mathscr{C}_2$, given by (5), serves the purpose well.

Since criteria $\mathscr{C}_1$ and $\mathscr{C}_2$ optimize some probability terms only and do not depend on the likelihood, the corresponding designs do not change due to minor changes in the secondary aspects of data. For example, when there is possibility of censoring or some missing mechanism inherent in the data leading to different forms of likelihood, criteria $\mathscr{C}_1$ and $\mathscr{C}_2$ give the same optimal designs given by (3) and (5), respectively; in contrast, for finding an optimal design by the likelihood-based criteria, the calculation of expected information matrix requires knowledge on the censoring distribution or the missing mechanism which is usually unknown. This is the major advantage of our criteria.

Although we demonstrated the results based on the simple model of Section 2, criteria $\mathscr{C}_1$ and $\mathscr{C}_2$ can be easily employed for more general models. The calculation of the probabilities $P[D < t_0 < F]$ and $P[D < F < t_0]$, in general, involves numerical integration, and so, the maximization required for $\mathscr{C}_1$ and $\mathscr{C}_2$ may not have closed form solutions, as in (3) and (5). However, numerically finding the optimal t_0 requires much less computation than having to calculate the expected information matrix for criterion $\mathscr{C}_3$. For example, with model (1) for conditional distribution of F given D, if we assume a Weibull(λ, p) distribution for D, the probability $P[D < t_0 < F]$ takes the form

$$\int_0^{t_0} e^{-\beta x-\gamma(t_0-x)}\lambda^p p x^{p-1} e^{-(\lambda x)^p}\,dx,$$

and the difference $P[D < t_0 < F] - P[D < F < t_0]$ takes the form

$$2\int_0^{t_0} e^{-\beta x-\gamma(t_0-x)}\lambda^p p x^{p-1} e^{-(\lambda x)^p}\,dx - \int_0^{t_0} e^{-\beta x}\lambda^p p x^{p-1} e^{-(\lambda x)^p}\,dx,$$

both of which need numerical integration, which is straightforward. Hence, for different values of $(\lambda, p, \beta, \gamma)$, the optimal choices of t_0 can be found (see Dewanji and Biswas, 1998).

Another advantage of the probability-based criteria $\mathscr{C}_1$ and $\mathscr{C}_2$ is easy incorporation of one or more covariates, denoted by $Z = z$, in the optimal design. For example, if the distribution of D happens to depend on $Z = z$ via the exponential parameter $\alpha = \alpha(z) = \alpha_0 e^{\alpha_1 z}$ (say), the optimal design $t_0 = t_0(z)$ by $\mathscr{C}_1$ or $\mathscr{C}_2$, can be readily obtained simply by replacing α in (3) or (5), respectively, by $\alpha(z)$. Therefore, the

optimal design for individuals with different Z values will be different (making it more realistic) but can be obtained by using one formula. In order to achieve this with variance-minimizing criterion $\mathscr{C}_3$, one has to do the extensive computation again and again for different values of Z.

It is to be emphasized that criterion $\mathscr{C}_1$ is introduced only for the purpose of estimating the distribution of D or any of its characteristics. The corresponding design may be poor if the purpose is anything other than this. As seen in Table 3, the optimal design for estimating all three parameters is very different from that obtained by criterion $\mathscr{C}_1$. Similarly, criterion $\mathscr{C}_2$ is to be employed for finding an optimal choice for an intermediate observation in order to carry out some inspection for early detection of disease or fault as discussed in Section 2. Although $\mathscr{C}_1$ turns out to be a little more efficient than $\mathscr{C}_2$, the latter has protection against failure due to disease or fault before the intermediate observation as discussed in Section 2.

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