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Estimation in follow-up studies.

by

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Contents.

1. Introduction.

"Follow-up studies" are frequently used when the effect of a certain treatment (B) for a spesific illness (A) is examined. L patients, suffering from A, are treated with B and are thereafter observed until a certain fixed date or for a fixed period of time. At the end of the observation period the experiment is considered completed. Each patient can then be classified as being in one of the following states: i) still suffering from A, ii) recovered from A, iii) dead from A, iv) lost for other reasons.

Statistical conclusions in "follow-up studies" of this kind, usually have been based only on the relative number of patients in the different states at the end of the period. The length of time each patient has spent in the different states during the observation period has not been taken into account. Important information are thereby not utilized.

In this paper we shall discuss how different information concerning transfers of states during the observation period are going to influence on estimation in a "follow-up study". The work is based on papers by E. Fix and J. Neyman, 1961 [2] and E. Sverdrup, 1966 [3]. In his paper Sverdrup considers a model utilizing the length of time each patient stays in the different states during the observation period. This model will be denoted "complete design".

It is, however, sometimes difficult to observe exactly when a patient changes states, particularly to notice exactly when a patient changes from sick to healthy, or vice versa Hence the complete design is frequently not applicable. In the following we shall try to construct stochastic models for "follow-up studies", models that in different situations utilize as much as possible of the information at hand. These models are then compared to see what can be gained by introducing specified additional information in the analysis.

2. Notation.

The following notation will be used throughout the paper.

Every patient, taking part in the study, belongs at any time to one of the four states:

(2.1)
T_1: suffering from A (sick),
T_2: recovered from A (healthy),
T_3: dead from A (dead),
T_4: lost for other reasons (lost).

In principle it is possible to split the patients in more states, but we shall only consider these four. We shall also postulate that the only possible transfers are the following:

$T_1 \to T_2$, from sick to healthy,
$T_2 \to T_1$, from healthy to sick,
$T_1 \to T_3$, from sick to dead,
$T_2 \to T_4$, from healthy to lost.

For a sick person x years of age we define the parameters

μ_x = force of mortality (concerns transfer from $T_1 \to T_3$)

σ_x = force of recovering (concerns transfer from $T_1 \to T_2$)

$\alpha_x = \mu_x + \sigma_x$ = force of decrement from illness.

Thus $\mu_x dx$ is the probability that a sick person, x years old, shall die (from A) before age $x+dx$, and $\sigma_x dx$ is the probability that he shall recover (from A) before age $x+dx$.

For a healthy person x years old, we similarly introduce:

ν_x = force of loss (concerns transfer from $T_2 \rightarrow T_4$)

ρ_x = force of sickness (concerns transfer from $T_2 \rightarrow T_1$)

$\gamma_x = \nu_x + \rho_x$ = force of decrement from T_2.

Clearly, the forces of transfers usually depend on the age of the patients and of the duration of the illness. In the cases where a patient has several transfers from one state to another, it may also depend on his number of transfers. In this paper we are going to study the particular case where all forces of transfers are constants, independent of age x as well as of duration of stay in the different states. This assumption is commonly made in mortality statistics. The model may still be quite realistic if the group of patients is relatively homogenous with regard to age and state of illness. Furthermore the usual assumptions made in connection with birth and death processes ([1] ch.17) about independence etc., are postulated.

The probability that a person who at a certain time is in T_i, t years later will be in state T_j, is denoted

$$p_t^{ij}, \quad i = 1,2; \quad j = 1,2,3,4.$$

These probabilities are determined as functions of μ, σ, ρ and ν are given in the Appendix (A.1).

A patient will be allowed to have more than one transfer from one state to another during the observation period. Hence we need the probabilities that a person who at a certain time is in T_i, t years later will be in T_j, having had n_j transfers from T_1 to T_2. These probabilities are denoted

$$(2.5) \qquad p_t^{ij \cdot n_j}; \quad i = 1,2, \quad j = 1,2,3,4; \quad n_j = 1,2,\ldots .$$

These probabilities are also determined as functions of μ, σ, ρ and ν and are given in the Appendix (A.2).

Attention is restricted to the case where all the patients (L) are suffering from A (are in T_1) when entering the study. For person no. k, $k = 1,2,\ldots,L$ the following notation is used (all quantities referring to the total observation-period):

$$(2.6) \qquad \begin{aligned} M_k &= \text{the number of transfers from } T_1 \rightarrow T_3 \\ &\qquad\qquad\qquad\qquad\qquad\qquad \text{(dying from A)}, \\ S_k &= \text{the number of transfers from } T_1 \rightarrow T_2 \\ &\qquad\qquad\qquad\qquad\qquad\qquad \text{(sick to healthy)}, \\ R_k &= \text{the number of transfers from } T_2 \rightarrow T_1 \\ &\qquad\qquad\qquad\qquad\qquad\qquad \text{(healthy to sick)}, \end{aligned}$$

N_k = the number of transfers from $T_2 \rightarrow T_4$ (healthy to lost),

V_k = the total time the patient stays in T_1 (sick),

W_k = the total time the patient stays in T_2 (healthy),

U_k = the time from entrance to death if the patient dies from A without being recovered.

M_k and N_k can of course only take on the values 0 or 1. Furthermore we introduce the following notation:

(2.7) $y_k^{j \cdot n_j}$ = 1 if patient no. k at the end of the observation period is in T_j, having had n_j transfers from T_1 to T_2.

= 0 otherwise.

Hence $L_{j \cdot n_j} = \sum_{k=1}^{L} y_k^{j \cdot n_j}$ is the number of patients, being in T_j at the end of the observation period, having had n_j transfers from T_1 to T_2.

3. Designs with constant observation period.

In this section we shall study the case where each patient is observed a fixed time τ. With the assumptions made in Chapter 2, we may handle the material as if all patients enter at time $t = 0$ and were observed a fixed time τ, which without loss of generality is taken to be 1.

Different designs are conceivable. We shall consider four of them. In Chapter 4 the corresponding estimates for μ, σ, ρ and ν will be discussed.

3.1. Design I. Reduced design based on the total number of transfers between the different states.

If a person during the observation-time τ is allowed to have more than one transfer from one state to another, the relative frequencies of patients in the different states at the end of the experiment will not yield sufficient information for estimation of the forces μ, σ, ρ and ν. We shall assume that the total number of transfers from one state to another is determined and base the estimates on:

$$
\begin{aligned}
\sum M_k &= \text{total number of transfers from } T_1 \to T_3 \\
&\qquad\qquad \text{(dead from A)}, \\
\sum S_k &= \text{total number of transfers from } T_1 \to T_2 \\
&\qquad\qquad \text{(sick to healthy)}, \\
\sum R_k &= \text{total number of transfers from } T_2 \to T_1 \\
&\qquad\qquad \text{(healthy to sick)},
\end{aligned}
\tag{3.1}
$$

(3.1) $\sum N_k$ = total number of transfers from $T_2 \rightarrow T_4$ (healthy to lost).

In the Appendix (A.3) the expectations of M,S,R,N are expressed as functions of μ,σ,ρ and ν.

$$\begin{aligned} E(M) &= \varphi_1(\mu,\sigma,\rho,\nu), \quad E(S) = \varphi_2(\mu,\sigma,\rho,\nu), \\ E(R) &= \psi_1(\mu,\sigma,\rho,\nu), \quad E(N) = \psi_2(\mu,\sigma,\rho,\nu). \end{aligned} \tag{3.2}$$

If we replace the left hand sides of (3.2) with the corresponding estimates $\frac{\sum M_k}{L}$, $\frac{\sum S_k}{L}$, $\frac{\sum R_k}{L}$ and $\frac{\sum N_k}{L}$ the solutions of (3.3) w.r.t. $\tilde{\mu},\tilde{\sigma},\tilde{\rho}$ and $\tilde{\nu}$ can be used as estimates of μ,σ,ρ and ν.

$$\begin{aligned} \varphi_1(\tilde{\mu},\tilde{\sigma},\tilde{\rho},\tilde{\nu}) &= \frac{\sum M_k}{L}, \quad \varphi_2(\tilde{\mu},\tilde{\sigma},\tilde{\rho},\tilde{\nu}) = \frac{\sum S_k}{L}, \\ \psi_1(\tilde{\mu},\tilde{\sigma},\tilde{\rho},\tilde{\nu}) &= \frac{\sum R_k}{L}, \quad \psi_2(\tilde{\mu},\tilde{\sigma},\tilde{\rho},\tilde{\nu}) = \frac{\sum N_k}{L}. \end{aligned} \tag{3.3}$$

This method is proposed by Sverdrup [3]. The estimates are asymptotically unbiased. To be able to discuss their relative goodness we need their asymptotic variances. These can be derived from the covarians matrix for M,S,R,N (A.4). We shall return to this question in Chapter 4.

3.2. Design II. Reduced design based on number of patients with specific number of transfers.

If we observe the number of patients in the different

states at the end of the observationperiod and in addition how many transfers each of them has had from T_1 to T_2, estimates for μ, σ, ρ and ν can be constructed based on the statistics:

(3.4) $L_{j \cdot n_j} = \sum Y_k^{j \cdot n_j}$ = number of patients that at the end of the observation period are in state T_j, having had n_j transfers from T_1 to T_2.

($Y_k^{j \cdot n_j}$ is defined in (2.7) and is either 0 or 1.)

$$Y_k = (Y_k^{1.0}, Y_k^{1.1}, \ldots, Y_k^{1.n_1}, Y_k^{2.1}, \ldots, Y_k^{4.n_4}), \quad k=1,2,\ldots,L,$$

are now considered as L realizations of the stochastic vector $(Y^{1.0}, Y^{1.1}, \ldots, Y^{1.n_1}, Y^{2.1}, \ldots, Y^{4.n_4})$ with one and only one component 1 and the others 0. The "likelihood-function" for these L observations is given by

$$(3.5)\quad f(y_1,y_2,\ldots,y_L) = (p^{11.0})^{L_{1.0}} (p^{11.1})^{L_{1.1}} \ldots (p^{11.n_1})^{L_{1.n_1}} (p^{12.1})^{L_{2.1}} \ldots (p^{14.n_4})^{L_{4.n_4}},$$

$p^{ij \cdot n_j}$ (2.5) being the probability that $Y_k^{j \cdot n_j} = 1$. In the Appendix (A.2) $p^{ij \cdot n_j}$ are given as functions of μ, σ, ρ and ν. If these expressions are introduced in (3.5) the maximum-likelihood estimates M.L.E. for μ, σ, ρ and ν can be determined in the usual way.

The length of the observation time τ will usually put a natural upper bound to the number of transfers from T_1. The number of factors on the right hand side of (3.5) hence will be small. If, however, some of the patients have a large number of transfers from T_1, it will be a rather cumbersome work to determine the M.L.E. A shortcut approach might be to count just the patients with few transfers (at most one or two), establish the corresponding likelihood-function and proceed from there. These estimates will, of course, be less accurate than the preceding ones. We shall discuss the different estimates and their accuracy in Chapter 4.

3.3. Design III. Reduced design with time of death included.

As already mentioned, it is often impossible to determine the exact point of time a patient transfers from sick to healthy ($T_1 \rightarrow T_2$), or equivalently from healthy to sick ($T_2 \rightarrow T_1$). However, the times of death are usually easier to determine. If this information is introduced into the model, it should be possible to establish more accurate estimates of μ, σ, ρ and ν than the ones obtained in the preceding designs. To simplify the notation we assume that the patients who die from A have had no transfers from T_1 to T_2 and back to T_1. (This will usually be the case.)

We shall base our estimates on the following statistics:

$L_1.n_1 = \sum Y_k^{1.n_1}$: the number of patients in T_1 at the end of the observationtime, having had n_1 transfers from T_1, $n_1 = 1,2,\ldots$.

$L_2.n_2 = \sum Y_k^{2.n_2}$: the number of patients in T_2 at the end of the observationtime, having had n_2 transfers from T_1, $n_2 = 1,2,\ldots$.

$\sum M_k$ = number of transfers from $T_1 \rightarrow T_3$, it is equivalent to the number of patients who die from A during the observation period.

$\sum U_k$ = the total time from start until death for all the patients who die during the observation-period.

As in Design II $Y_k = (Y_k^{1.0}, Y_k^{1.1}, \ldots Y_k^{1.n_1}, Y_k^{2.1}, \ldots Y_k^{4.n_4}, U_k)$, $k = 1,2,\ldots,L$, are considered as L realizations of the stochastic vector $(Y^{1.0}, Y^{1.1}, \ldots, Y^{4.n_4}, U)$ where one of the Y's is one, the others are zero, and U denotes the time from entrance to death when $Y^{3.1}$ is one, and otherwise is zero. The "likelihood-function" will now be

$$(3.6)\quad f(y_1,y_2,\ldots,y_L)=(p^{11.0})^{L_{1.0}+\sum U_k}\cdot(p^{11.1})^{L_{1.1}},\ldots$$
$$(p^{12.n_2})^{L_{2.n_2}}(p^{14.1})^{L_{4.1}}\ldots(p^{14.n_4})^{L_{4.n_4}}\cdot\mu^{\sum M_k}$$

where the factor with $p^{13.0}$ is left out since the probability of dying between u and $u+du$ is $\mu(p^{11.0})^u du$. The expressions for $p^{ij\cdot n_j}$ given in (A.2) are now introduced into (3.6) and M.L.E. of μ,σ,ρ and ν are determined.

As in Design II it is possible, as a short-cut approach, to ignore patients with more than one (or possibly 2) transfers from T_1 to T_2 and thereby reduce the number of factors on the right hand side of (3.6).

The corresponding M.L.E will be asymptotically unbiased. We shall in Chapter 4 discuss their accuracy compared with the corresponding estimates obtained in the other designs.

3.4. Design IV. The complete design.

In the situation where for each patient the number of transfers between states as well as time of occurence for such transfers are observable, the estimates can be based on the following statistics:

$\sum M_K$ = the total number of transfers from $T_1 \rightarrow T_3$ (patients who die),

$\sum S_K$: the total number of transfers from $T_1 \rightarrow T_2$ (sick to healthy),

$\sum R_k$: the total number of transfers from $T_2 \rightarrow T_1$ (healthy to sick),

(3.7)

$\sum N_k$: the total number of transfers from $T_2 \rightarrow T_4$ (patients lost),

$\sum V_K$: the total time the patients spend in T_1 (are sick)

$\sum W_K$: the total time the patients spend in T_2 (are healthy).

In this case the "likelihood function" for the L sets of observations is given in [3] and will be:

$$(3.8)\quad f(y_1, y_2, \ldots, y_L) = e^{-(\mu+\sigma)\sum V_K} e^{-(\rho+\nu)\sum W_K} \mu^{\sum M_K} \sigma^{\sum S_K} \rho^{\sum R_K} \nu^{\sum N_K}$$

The M.L.E. of μ, σ, ρ and ν are now determined in the usual way.

4. A comparison of the estimates obtained in the different designs.

The estimates mentioned in Chapter 3 are all asymptotically unbiased estimates of μ, σ, ρ and ν, as the number (L) of patients tends to infinity. The asymptotic variances shall be used as a criterion for accuracy of these estimates. Evaluation of the asymptotic variances will, however, in most cases be tedious and lead to lengthy expressions, even if there are no principle difficulties in carrying through these computations. We will therefore restrict ourselves to simplified cases.

In Section 4.1 we shall discuss how information about the times of death will influence the estimates, when the forces of relapse and loss after being recovered, are set equal to zero ($\rho = \nu = 0$). This assumption will be realistic if we ignore what happens to a patient after having been cured.

In Section 4.2 we shall discuss the difference between Design I and Design II and in particular see how the accuracy of the estimates of Design II changes when patients with several transfers from T_1 are left out. Here we assume that the forces of death and loss are zero ($\mu = \nu = 0$). This assumption will be realistic when the illness considered is mild, and it is common to recover and relapse several times during the observationperiod, while the risk of dying from the illness and the possibility of loss can be ignored.

Even if the use of such specialized models will be

limited, they may give a first indication of the goodness of the estimates suggested for the different designs. In particular, one will be able to study how the estimates improve when more information is introduced into the models.

4.1. Influence of information about the times of death. when $\rho = \nu = 0$.

In this particular case, the probability that a patient who has recovered, again will relapse during the observationperiod is set equal to zero. This implies that his number of transfers from T_1 to T_2 can be at most 1. The expressions are thereby considerably simplified. For this case we introduce:

$$
\begin{aligned}
& L_1 = L_{1.0} : \text{number of patients who stay sick,} \\
(4.1) \quad & L_2 = L_{2.1} : \text{number of patients who recover (from A),} \\
& L_3 = L_{3.0} : \text{number of patients who die (from A).}
\end{aligned}
$$

We shall now discuss the M.L.E. of μ and σ for the following designs:

Design II (based on L_1, L_2 and L_3),

Design III (based on L_1, L_2 and L_3 and the times of death),

Design IV (based on L_1, L_2 and L_3 and the times of transfers between states).

4.1.1. Design II ($\rho = \nu = 0$).

In this particular case the estimates proposed for Design I and Design II will coincide. The "likelihood-function" (3.5) will be

$$(4.2)\quad f_1(y_1, y_2, \ldots, y_L) = e^{-(\sigma+\mu)} \left[\frac{\sigma(1-e^{-(\sigma+\mu)})}{\sigma+\mu}\right]^{L_2} \left[\frac{\mu(1-e^{-(\sigma+\mu)})}{\sigma+\mu}\right]^{L_3},$$

where we have replaced $p^{ij\cdot n}$ with the expressions from (A.2) with $\rho = \nu = 0$. The M.L.E. (μ^*, σ^*) are now given as the solutions of the following equations:

$$\frac{\sigma^*(1-e^{-(\mu^*+\sigma^*)})}{\mu^*+\sigma^*} = \frac{L_2}{L}, \quad \frac{\mu^*(1-e^{-(\sigma^*+\mu^*)})}{\sigma^*+\mu^*} = \frac{L_3}{L}.$$

σ^* and μ^* coincide with the estimates from the classical actuarial statistics, $\frac{\sigma(1-e^{-(\sigma+\mu)})}{\sigma+\mu}$ is the probability that a patient shall recover during the observationperiod, while $\frac{\mu(1-e^{-(\sigma+\mu)})}{\sigma+\mu}$ is the probability that he is going to die during this period. The solutions to the equations are:

$$(4.3)\quad \sigma^* = -\frac{\ln \frac{L_1}{L}}{1+\frac{L_3}{L_2}}, \quad \mu^* = -\frac{\ln \frac{L_1}{L}}{1+\frac{L_2}{L_3}},$$

and the matrix of the asymptotic covariances is

$$- \begin{Bmatrix} E\frac{\delta^2 \ln f_1}{\delta \mu^2}, & E\frac{\delta^2 \ln f_1}{\delta \mu \delta \sigma} \\ E\frac{\delta^2 \ln f_1}{\delta \mu \delta \sigma}, & E\frac{\delta^2 \ln f_1}{\delta \sigma^2} \end{Bmatrix}^{-1}$$

where f_1 is given by (4.2). This covariance matrix is determined and the results given in (A.5). Numerical evaluation of the asymptotic variances has been carried out for selected values of μ (= 0, 0.1, 0.5, 1 and 2) and of σ (= 0, 0.1, 0.5, 1 and 2), and the results are given in Table 1, p. 20, column V and VIII.

4.1.2. Design III ($\rho = \nu = 0$).

In addition to L_1, L_2 and L_3 (4.1) we now, for each k, observe u_k (the time from entrance to death if patient nr. k dies during the observationperiod). The "likelihood-function" (3.6) then becomes

$$(4.4) \quad f_2(y_1, y_2, \ldots, y_L) = \left[e^{-(\mu+\sigma)}\right]^{L_1 + \Sigma U_K} \mu^{L_3} \left[\frac{\sigma(1-e^{-(\sigma+\mu)})}{\sigma+\mu}\right]^{L_2}$$

where we have replaced $p^{ij \cdot n}$ with the expressions from (A.2) with $\rho = \nu = 0$. ΣU_K is the total time from entrance to death for the patients who die during the observation-period. The M.L.E. $(\hat{\hat{\mu}}, \hat{\hat{\sigma}})$ hence are found as the solutions

of the equations:

$$(4.5)\qquad \frac{1}{\hat{\hat{\sigma}}} - \frac{1}{\hat{\hat{\sigma}}+\hat{\hat{\mu}}} + \frac{e^{-(\hat{\hat{\sigma}}+\hat{\hat{\mu}})}}{1-e^{-(\hat{\hat{\sigma}}+\hat{\hat{\mu}})}} = \frac{L_1}{L_2} + \frac{\sum U_K}{L_2},$$

$$\frac{\hat{\hat{\mu}}}{\hat{\hat{\sigma}}} = \frac{L_3}{L_2}$$

Explisit expressions for $\hat{\hat{\mu}}$ and $\hat{\hat{\sigma}}$ can not be found but for given values of L_1, L_2 and L_3 there are clearly no difficulties in finding numerical values for the estimates. The matrix for the asymptotic covariances of $\hat{\hat{\mu}}$ and $\hat{\hat{\sigma}}$ is

$$-\begin{Bmatrix} E\frac{\partial^2 \ln f_2}{\partial \mu^2}, & E\frac{\partial^2 \ln f_2}{\partial \mu \partial \sigma} \\ E\frac{\partial^2 \ln f_2}{\partial \mu \partial \sigma}, & E\frac{\partial^2 \ln f_2}{\partial \sigma^2} \end{Bmatrix}^{-1}$$

where f_2 is given by (4.4). This matrix is determined, and the result given in (A.6). Numerical evaluation of the asymptotic variances has been carried out for selected values of μ (= 0, 0.1, 0.5, 1, 2) and σ (= 0, 0.1, 0.5, 1, 2), and the results given in Table 1 p.20, column IV and VII.

4.1.3. Design IV ($\rho = \nu = 0$).

In addition to L_1, L_2 and L_3 (4.1) we know the dates of transfers for each of the patients and are able to observe V_k, the time he spends in T_1 (sick). In this

particular case the "likelihood-function" (3.8) may be written:

$$f_3(y_1, y_2, \ldots, y_L) = e^{-(\mu+\sigma)\Sigma V_K} \mu^{L_3} \sigma^{L_2}, \tag{4.6}$$

and the M.L.E. of μ and σ $(\hat{\mu}, \hat{\sigma})$ are

$$\hat{\mu} = \frac{L_3}{\Sigma V_k}, \quad \hat{\sigma} = \frac{L_2}{\Sigma V_k}. \tag{4.7}$$

Furthermore the matrix for the asymptotic covariances for $\hat{\mu}$ and $\hat{\sigma}$ is

$$-\begin{Bmatrix} E\dfrac{\partial^2 \ln f_3}{\partial \mu^2}, & E\dfrac{\partial^2 \ln f_3}{\partial \mu \partial \sigma} \\ E\dfrac{\partial^2 \ln f_3}{\partial \mu \partial \sigma}, & E\dfrac{\partial^2 \ln f_3}{\partial \sigma^2} \end{Bmatrix}^{-1}$$

f_3 being given by (4.6). This matrix is determined, and the result is given in (A.7). Numerical calculations for selected values of μ (= 0, 0.1, 0.5, 1 and 2) and σ (= 0, 0.1, 0.5, 1 and 2) has been carried out. The results are given in Table 1, p.20, column III and VI.

Table 1

The maximal observationtime τ set equal to 1, $\rho = \nu = 0$.

$\hat{\mu}, \hat{\sigma}$ are the MLE corresponding to Design IV,
$\hat{\hat{\mu}}, \hat{\hat{\sigma}}$ are the MLE corresponding to Design III,
μ^*, σ^* are the MLE corresponding to Design II.

I	II	III	IV	V	VI	VII	VIII
		L var $\hat{\mu}$	L var $\hat{\hat{\mu}}$	L var μ^*	L var $\hat{\sigma}$	L var $\hat{\hat{\sigma}}$	L var σ^*
0.1	0	0.105	0.105	0.105	-	-	-
0.5	0	0.635	0.635	0.649	-	-	-
1	0	1.582	1.582	1.718	-	-	-
2	0	2.956	2.956	6.389	-	-	-
0	0.1	-	-	-	0.105	0.105	0.105
0.1	0.1	0.110	0.110	0.110	0.110	0.110	0.110
0.5	0.1	0.665	0.668	0.682	0.133	0.133	0.134
1	0.1	1.649	1.662	1.806	0.165	0.165	0.166
2	0.1	4.786	4.852	6.728	0.239	0.239	0.244
0	0.5	-	-	-	0.635	0.649	0.649
0.1	0.5	0.133	0.134	0.134	0.665	0.679	0.682
0.5	0.5	0.791	0.807	0.825	0.791	0.807	0.825
1	0.5	1.931	2.007	2.191	0.965	0.984	1.030
2	0.5	5.447	5.817	8.246	1.362	1.363	1.536
0	1	-	-	-	1.582	1.718	1.718
0.1	1	0.165	0.166	0.166	1.649	1.791	1.806
0.5	1	0.965	0.994	1.030	1.931	2.093	2.191
1	1	2.313	2.498	2.754	2.313	2.498	2.754
2	1	6.314	7.163	10.586	3.157	3.369	4.226
0	2	-	-	-	2.906	6.389	6.389
0.1	2	0.239	0.244	0.244	4.786	6.598	6.728
0.5	2	1.362	1.486	1.536	5.447	7.431	8.246
1	2	3.157	3.689	4.226	6.314	8.444	10.586
2	2	8.149	10.324	17.473	8.149	10.324	17.473

4.1.4. Conclusive remarks.

We shall follow the usual practice, expressing the relative goodness of two asymptotically unbiased estimates by their asymptotic relative efficiency (a.r.e.), defined as the reciprocal ratio of their asymptotic variances.

The results in Table 1 indicate that the estimates obtained in the different situations are almost equally accurate as long as the forces of transfers are small. If, however, these forces are large, the accuracies of corresponding estimates increases when one goes from Design II to Design III and further on to Design IV. When, for instance, $\mu = \sigma = 2$, the asymptotic efficiency of the estimates obtained in Design IV (all dates included) relative to the corresponding estimates of Design II (no times included) is easily found to be

$$\text{a.r.e.}(\hat{\mu} : \mu^*) = \text{a.r.e.}(\hat{\sigma} : \sigma^*) = \frac{\lim_{L\to\infty} \text{var}\,\mu^*}{\lim_{L\to\infty} \text{var}\,\hat{\mu}} = \underline{2.14}.$$

Similarly the asymptotic efficiency of estimates obtained in Design IV relative to the corresponding estimates of Design III (times of death included) is considerably less:

$$\text{a.r.e.}(\hat{\mu} : \hat{\hat{\mu}}) = \text{a.r.e.}(\hat{\sigma} : \hat{\hat{\sigma}}) = \frac{\lim_{L\to\infty} \text{var}\,\hat{\hat{\mu}}}{\lim_{L\to\infty} \text{var}\,\hat{\mu}} = \underline{1.27}.$$

These results indicate that it is of particular importance that follow-up studies are conducted according to the design, utilizing the maximum possible information, when the forces

of transfer are large.

4.2. Comparison of the estimates obtained in Design I, II and IV, when $\mu = \nu = 0$.

We shall now discuss the situation where the forces of death and loss can be ignored, and each patient may repeatedly recover and relapse within the observation-period. In this case Design II and Design III coincide while Design I and Design II will yield different estimates. We shall discuss the estimates under the following conditions:

In Design I one restricts oneself to observe the total number of transfers from $T_1 \rightarrow T_2$ (sick to healthy) and from $(T_2 \rightarrow T_1)$ (healthy to sick).

In Design IIa the estimates are based on the number of patients $(L_{1.0})$ who stay in T_1 (sick) all the time and the number of patients $(L_{2.1})$ who change from T_1 to T_2 only once.

In Design IIb the estimates are in addition to $L_{1.0}$ and $L_{2.1}$ based on the number of patients $(L_{1.1})$ who recover and again relapse during the observation period.

In Design IIc the estimates are in addition to $L_{1.0}, L_{2.1}$, and $L_{1.1}$ based on the number of patients

($L_{2.2}$) who recover, relapse and again recover during the observationperiod.

In Design IV the number of transfers from $T_1 \rightarrow T_2$ and from $T_2 \rightarrow T_1$ as well as the total time the patients stay in T_1 (sick) and in T_2 (healthy) are recorded.

4.2.1. Design I ($\mu = \nu = 0$).

Our task is now to construct estimates for σ and ρ, ($\tilde{\sigma}$ and $\tilde{\rho}$) that are based on

$$\begin{aligned} \textstyle\sum S_K &= \text{the total number of transfers from } T_1 \rightarrow T_2 \\ &\qquad\qquad \text{(sick to healthy)}, \\ \textstyle\sum R_K &= \text{the total number of transfers from } T_2 \rightarrow T_1, \\ &\qquad\qquad \text{(healthy to sick)}. \end{aligned} \tag{4.8}$$

Using the formulaes for ES and ER given in (A.3), $\tilde{\sigma}$ and $\tilde{\rho}$ are determined as the solutions of the equations:

$$\begin{aligned} \frac{\sum S_K}{L} &= \frac{\tilde{\sigma}}{\tilde{\sigma}+\tilde{\rho}}\left(\tilde{\rho} + \tilde{\sigma}\,\frac{1-e^{-(\tilde{\sigma}+\tilde{\rho})}}{\tilde{\sigma}+\tilde{\rho}}\right), \\ \frac{\sum R_K}{L} &= \frac{\tilde{\rho}}{\tilde{\sigma}+\tilde{\rho}}\left(\tilde{\sigma} - \tilde{\sigma}\,\frac{1-e^{-(\tilde{\sigma}+\tilde{\rho})}}{\tilde{\sigma}+\tilde{\rho}}\right). \end{aligned} \tag{4.9}$$

Explicit expressions for $\tilde{\sigma}$ and $\tilde{\rho}$ are not obtainable. To find the asymptotic variances of the estimates we proceed

as follows:

We denote the solutions by

$$\tilde{\sigma} = s(S.,R.), \tilde{\rho} = r(S.,R.),$$

s and r being unknown functions, $S. = \frac{\Sigma S_k}{L}$ and $R. = \frac{\Sigma R_k}{L}$. Since, as $L \to \infty$,

$$S. \xrightarrow{p} ES \quad \text{and} \quad R. \xrightarrow{p} ER,$$

S.(R.) will with large probability be close to ES(ER) when L is large. We now expand the functions s(S.,R.) and r(S.,R.) in a Taylor series about (ES, ER), leaving out terms of second and higher order. Then

$$s(S.,R.) \approx s(ES,ER) + \frac{\delta^* s}{\delta S.}{}^{1)} (S.-ES) + \frac{\delta^* s}{\partial R.}(R.-ER),$$

$$r(S.,R.) \approx r(ES,ER) + \frac{\delta^* r}{\partial S.}(S.-ES) + \frac{\delta^* r}{\partial R.}(R.-ER). \tag{4.10}$$

Then

$$\text{as.var}(\tilde{\sigma}) = (\frac{\delta^* s}{\delta S.})^2 \cdot \text{var } S. + (\frac{\delta^* s}{\partial R.})^2 \cdot \text{var } R. + 2 \frac{\delta^* s}{\delta S.} \cdot \frac{\delta^* s}{\partial R.} \cdot \text{cov.}(R.,S.),$$

$$\text{as.var}(\tilde{\rho}) = (\frac{\delta^* r}{\delta S.})^2 \cdot \text{var } S. + (\frac{\delta^* r}{\partial R.})^2 \cdot \text{var } R. + 2 \frac{\delta^* r}{\delta S.} \cdot \frac{\delta^* r}{\partial R.} \cdot \text{cov}(R.,S.). \tag{4.11}$$

1) The $*$ index means that after the differentiation of r (S.,R.) and s(S.,R.) w.r.t. S. and R., these are replaced by ES and ER respectively.

From the covariance matrix of R,S,M,N in (A.4) we get

$$\text{var}(R) = -ER-(ER)^2+2\varrho\left(\frac{\delta}{\delta\sigma}ER - \frac{\delta}{\delta\nu}ER\right),$$

$$\text{(4.12)}\quad \text{var}(S) = -ES-(ES)^2+2\sigma\left(\frac{\delta}{\delta\sigma}ES - \frac{\delta}{\delta\mu}ES\right),$$

$$\text{cov}(R,S) = -ER\cdot ES + \varrho\left(\frac{\delta}{\delta\varrho}ES - \frac{\delta}{\delta\nu}ES\right) + \sigma\left(\frac{\delta}{\delta\sigma}ER - \frac{\delta}{\delta\mu}ER\right).$$

By differentiating ES and ER (A.3) with respect to μ, σ, ϱ and ν whereafter μ and ν are set equal to zero (A.19), we are able to express (4.12) by σ and ϱ. Furthermore

$$\begin{Bmatrix} \frac{\delta^* s}{\delta S.} , \frac{\delta^* r}{\delta S.} \\ \frac{\delta^* s}{\delta R.} , \frac{\delta^* r}{\delta R.} \end{Bmatrix} = \begin{Bmatrix} \frac{\delta}{\delta\sigma}ES , \frac{\delta}{\delta\varrho}ES \\ \frac{\delta}{\delta\sigma}ER , \frac{\delta}{\delta\varrho}ER \end{Bmatrix}^{-1}$$

By inverting the last matrix we then have all the terms of (4.11) expressed by σ and ϱ.

Numerical evaluations of the asymptotic variances of $\tilde{\sigma}$ and $\tilde{\varrho}$ have been carried out for selected values of σ (= 0, 0.1, 0.5, 1,2) and ϱ (= 0, 0.1, 0.5, 1, 2). The results are given in table 2 and 3 column IV.

4.2.2. Design IIa ($\mu = \nu = 0$).

In this case the estimates are based on

$L_{1.0}$ = number of patients in T_1 (sick) all the time,

and

(4.13) $L_{2.1}$ = number of patients who has one transfer from T_1 to T_2 (sick to healthy).

By introducing $\mu = \nu = 0$ into the expressions of $p^{11.0}$ and $p^{12.1}$ (A.2) the "likelihood-function" will be

$$(4.14)\quad f_4(y_1,\ldots,y_L) = e^{-\sigma L_{1.0}}\left(\sigma\frac{e^{-\varrho}-e^{-\sigma}}{\sigma-\varrho}\right)^{L_{2.1}} \left(1-\frac{\sigma e^{-\varrho}-\varrho e^{-\sigma}}{\sigma-\varrho}\right)^{L-L_{1.0}-L_{2.1}}$$

from which the M.L.E. of σ and ϱ, here denoted σ^*, ϱ^*, can be determined.

The necessary expressions for $\frac{\delta \ln f_4}{\delta\sigma}$ and $\frac{\delta \ln f_4}{\delta\varrho}$ are given in (A.8). Explisit expressions for σ^* and ϱ^* are not obtainable. The matrix for the asymptotic covariances of σ^* and ϱ^* is

$$-\begin{Bmatrix} E\frac{\delta^2 \ln f_4}{\delta\sigma^2} & , & E\frac{\delta^2 \ln f_4}{\delta\sigma\,\delta\varrho} \\ E\frac{\delta^2 \ln f_4}{\delta\sigma\,\delta\varrho} & , & E\frac{\delta^2 \ln f_4}{\delta\varrho^2} \end{Bmatrix}^{-1}$$

where the second order derivatives are given in (A.9).

Numerical evaluations of the asymptotic variances of σ^* and ϱ^* for selected values of σ (=0, 0.1, 0.5, 1, 2) and ϱ (= 0, 0.1, 0.5, 1, 2) are carried out, and the results are given in Table 2, p.31 and Table 3, p.32 column V.

4.2.3. Design IIb ($\mu = \nu = 0$).

In addition to $L_{1.0}$ and $L_{1.1}$ defined in (4.13) the estimates are based on

(4.15) $L_{1.1}$: the number of patients, who recover and again relapse within the observationperiod.

The "likelihood-function" connected with this design is

$$(4.16)\quad f_5(y_1,\ldots,y_L) = e^{-\sigma L_{1.0}}\left(\sigma\frac{e^{-\varrho}-e^{-\sigma}}{\sigma-\varrho}\right)^{L_{2.1}} \left(\frac{\sigma\varrho}{\sigma-\varrho}\left(\frac{e^{-\varrho}-e^{-\sigma}}{\sigma-\varrho}-e^{-\sigma}\right)\right)^{L_{1.1}} \cdot \left(\frac{(\sigma-\varrho)^2-(\varrho^2-2\sigma\varrho-\sigma^2\varrho+\sigma\varrho^2)e^{-\sigma}-\sigma^2 e^{-\varrho}}{(\sigma-\varrho)^2}\right)^{L-L_{1.0}-L_{2.1}-L_{1.1}},$$

with $p^{11.0}, p^{12.1}, p^{11.1}$ replaced by the corresponding expressions given in (A.2) for $\mu = \nu = 0$. The M.L.E. of σ and ϱ, here denoted σ^{**} and ϱ^{**}, are determined the usual way. ($\frac{\delta \ln f_5}{\delta \sigma}$ and $\frac{\delta \ln f_5}{\delta \varrho}$ are given in (A.10)). Explicit expressions for σ^{**} and ϱ^{**} are not obtainable. The matrix for the asymptotic covariances of σ^{**} and ϱ^{**} is given by

$$-\begin{Bmatrix} E\frac{\delta^2 \ln f_5}{\delta \sigma^2} & E\frac{\delta^2 \ln f_5}{\delta\sigma\delta\varrho} \\ E\frac{\delta^2 \ln f_5}{\delta\sigma\delta\varrho} & E\frac{\delta^2 \ln f_5}{\delta\varrho^2} \end{Bmatrix}^{-1}$$

The second order derivatives of this matrix are given in (A.11).

Numerical evaluations of the asymptotic variances of σ^{**} and ϱ^{**} for selected values of σ (=0, 0.1, 0.5, 1, 2) and ϱ (= 0, 0.1, 0.5, 1, 2) have been carried out. The results are given in Table 2, p. 31 and Table 3, p. 32 column VI.

4.2.4. Design IIc ($\mu = \nu = 0$).

The estimates of σ and ϱ are now in addition to $L_{1.0}, L_{2.1}, L_{1.1}$, defined in (4.13) and (4.15), based on:

(4.17) $L_{2.2}$: the number of patients that during the observationperiod recover, relapse and recover again.

The "likelihood-function" for this case is obtained from (3.6) with $p^{11.0}, p^{12.1}, p^{11.1}$ and $p^{12.2}$ replaced by the corresponding expressions given in (A.2) for $\mu = \nu = 0$.

$$f_6(y_1,\ldots,y_L) = e^{-\sigma L_{1.0}} \left(\sigma \frac{e^{-\varrho} - e^{-\sigma}}{\sigma - \varrho}\right)^{L_{2.1}}$$

$$(4.18)\left(\sigma\varrho \frac{e^{-\varrho} - (1+\sigma-\varrho)e^{-\sigma}}{(\sigma-\varrho)^2}\right)^{L_{1.1}} \left(\sigma^2\varrho \frac{(\sigma-\varrho+2)e^{-\sigma} + (\sigma-\varrho-2)e^{-\varrho}}{(\sigma-\varrho)^3}\right)^{L_{2.2}}$$

$$\left(\frac{(\sigma-\varrho)^3 + (\varrho^3 - 3\sigma\varrho^2 - \sigma^2\varrho^2 + \sigma\varrho^3)e^{-\sigma} + (3\sigma^2\varrho + \sigma^2\varrho^2 - \sigma^3\varrho - \sigma^3)e^{-\varrho}}{(\sigma-\varrho)^3}\right)^{L-L_{1.0}-L_{2.1}-L_{1.1}-L_{2.2}}$$

The M.L.E. of σ and ϱ, here denoted σ^{***} and ϱ^{***}, are then obtained the usual way. ($\frac{\delta \ln f_6}{\delta \sigma}$ and $\frac{\delta \ln f_6}{\delta \varrho}$ are given in (A.12)).

The equations to be solved are here more complicated than in the preceding cases, but as in the preceding sections numerically values for the estimates can be determined for given values of $L_{1.0}, L_{2.}, L_{2.2}$ and $L_{1.1}$.

The asymptotic covariancematrix of $\sigma^{***}, \varrho^{***}$ is

$$-\begin{pmatrix} E\frac{\delta^2 \ln f_6}{\delta \sigma^2} & E\frac{\delta^2 \ln f_6}{\delta \sigma \delta \varrho} \\ E\frac{\delta^2 \ln f_6}{\delta \sigma \delta \varrho} & E\frac{\delta^2 \ln f_6}{\delta \varrho^2} \end{pmatrix}^{-1}$$

with the second order derivatives of the matrix given in (A.13). Numerical calculations of σ^{***} and ϱ^{***} have been carried out for selected values of σ (= 0, 0.1, 0.5, 1, 2 and ϱ (= 0, 0.1, 0.5, 1, 2). The results are given in Table 2, p. 31 and Table 3, p. 32 column nr. VII.

4.2.5. Design IV ($\mu = \nu = 0$).

In this case the estimates are based on

$\sum S_K$: total number of transfers from T_1 to T_2 (sick to healthy),

(4.19)

$\sum R_K$: total number of transfers from T_2 to T_1 (healthy to sick),

$\sum V_K$: the total time the patients are in T_1 (sick),

$\sum W_K$: the total time the patients are in T_2 (healthy).

The "likelihood-function" for this case is given by

$$(4.20) \quad f_7(y_1, y_2, \ldots, y_L) = e^{-\sigma \sum V_K} e^{-\varrho \sum W_K} \sigma^{\sum S_K} \varrho^{\sum R_K},$$

and the M.L.E. for σ and ϱ, ($\hat{\sigma}$ and $\hat{\varrho}$) are found to be $\hat{\sigma} = \frac{\sum S_K}{\sum V_K}$ $\hat{\varrho} = \frac{\sum R_K}{\sum W_K}$.

The asymptotic covariancematrix of $\hat{\sigma}$, $\hat{\varrho}$ is

$$- \begin{Bmatrix} E \frac{\delta^2 \ln f_7}{\delta \sigma^2}, & E \frac{\delta^2 \ln f_7}{\delta \sigma \delta \varrho} \\ E \frac{\delta^2 \ln f_7}{\delta \sigma \delta \varrho}, & E \frac{\delta^2 \ln f_7}{\delta \varrho^2} \end{Bmatrix}^{-1}$$

with elements given in (A.14).

Numerical calculations of $\hat{\sigma}$ and $\hat{\varrho}$ have been carried out for selected values of σ (= 0, 0.1, 0.5, 1, 2) and ϱ (= 0, 0.1, 0.5, 1, 2). The results are given in Table 2, p. 31 and Table 3, p.32, column III.

Table 2.

The maximal observationtime τ put equal to $1, \mu = \nu = 0$.

$\hat{\sigma}, \hat{\varrho}$ are MLE corresponding to Design IV.
$\tilde{\sigma}, \tilde{\varrho}$ are estimates corresponding to Design I.
σ^{*}, ϱ^{*} are MLE corresponding to Design IIa.
$\sigma^{**}, \varrho^{**}$ are MLE corresponding to Design IIb.
$\sigma^{***}, \varrho^{***}$ are MLE corresponding to Design IIc.

I	II	III	IV	V	VI	VII
σ	ϱ	$\mathrm{var}\sqrt{L}\hat{\sigma}$	$\mathrm{var}\sqrt{L}\tilde{\sigma}$	$\mathrm{var}\sqrt{L}\sigma^{*}$	$\mathrm{var}\sqrt{L}\sigma^{**}$	$\mathrm{var}\sqrt{L}\sigma^{***}$
0.1	0.1	0.105	0.105	0.105	0.105	0.105
0.5	0.1	0.630	0.644	0.648	0.643	0.643
1	0.1	1.557	1.693	1.714	1.690	1.690
2	0.1	4.488	6.388	6.400	6.379	6.379
0.1	0.5	0.104	0.104	0.105	0.104	0.104
0.5	0.5	0.613	0.626	0.649	0.625	0.625
1	0.5	1.473	1.607	1.718	1.598	1.593
2	0.5	4.050	5.771	6.390	5.504	5.452
0.1	1	0.104	0.104	0.105	0.104	0.104
0.5	1	0.596	0.612	0.649	0.609	0.608
1	1	1.396	1.524	1.718	1.517	1.516
2	1	3.673	5.186	6.388	4.988	4.983
0.1	2	0.103	0.103	0.105	0.103	0.103
0.5	2	0.572	0.583	0.649	0.586	0.586
1	2	1.295	1.411	1.718	1.415	1.415
2	2	3.212	4.446	6.389	4.439	4.416

Table 3.

I	II	III	IV	V	VI	VII
σ	ϱ	$L^1 \mathrm{var}\,\hat{\varsigma}$	$L^1 \mathrm{var}\,\tilde{\varsigma}$	$L^1 \mathrm{var}\,\varsigma^{*}$	$L^1 \mathrm{var}\,\varsigma^{**}$	$L^1 \mathrm{var}\,\varsigma^{***}$
0.1	0.1	2.135	2.174	2.174	2.174	2.158
0.5	0.1	0.484	0.493	0.493	0.493	0.493
1	0.1	0.280	0.284	0.285	0.284	0.284
2	0.1	0.180	0.183	0.186	0.186	0.183
0.1	0.5	12.095	13.335	13.250	13.250	13.001
0.5	0.5	2.718	2.977	3.032	3.029	2.966
1	0.5	1.556	1.705	1.760	1.760	1.691
2	0.5	0.988	1.090	1.152	1.151	1.064
0.1	1	27.956	34.208	34.495	34.352	34.200
0.5	1	6.223	7.858	7.873	7.847	7.466
1	1	3.523	4.335	4.591	4.591	4.245
2	1	2.195	2.727	3.038	3.037	2.649
0.1	2	72.15	113.62	115.34	115.34	113.25
0.5	2	15.801	24.875	26.695	26.652	24.516
1	2	8.781	14.096	15.823	15.807	13.457
2	2	5.301	8.660	10.778	10.773	8.185

4.2.6. Conclusive remarks.

The results of the tables illustrate how the accuracies of the estimates differ from one design to another. When the forces of transfers are small, the accuracies of the estimates are asymptotically only slightly different. When, however, these forces get as large as $\sigma = \varsigma = 2$, the following asymptotic relative efficiencis, defined as reciprocal rates of asymptotic variances, are found:

$$\text{a.r.e.}(\hat{\sigma}:\tilde{\sigma}) = 1.38,$$
$$\text{a.r.e.}(\hat{\sigma}:\sigma^{x}) = 1.99,$$
$$\text{a.r.e.}(\hat{\sigma}:\sigma^{xx}) = 1.38,$$
$$\text{a.r.e.}(\hat{\sigma}:\sigma^{xxx}) = 1.37.$$

Hence the numerical results indicate that when the forces of transfers are small, the estimates obtained using Design IIa is almost as accurate as the others. If, however, the forces of transfers are large, one ought to use Design IIb or IIc for estimating the forces. The accuracies of the estimates in Design I do not differ very much from the estimates in Design IIb, but in all cases they are more accurate than the estimates in Design IIa.

5. Designs with varying observationtime.

In the preceding sections we assumed that the maximal observationtime was constant. In this Chapter we will discuss the case where we have no patients when the experiment starts, and the L patients enter the experiment successively during the period, which we without loss of generality set equal to 1. The observationtime for patient nr. k, Z_k, are then uniformly distributed $(0,1)$. (It means $G(z) = z$ or $dG(z) = 1$) As in Chapter 4.1 we will look at the special case, $\rho = \nu = 0$. During the observationtime the patients will then either stay sick, recover or die. In this Chapter we shall discuss 4 designs:

Design A: based only on the number of transfers.

Design B: based on the number of transfers and the time from entrance to death for the patients who die.

Design C: based on number of transfers, time from entrance to death for those who die, and time from entrance until the experiment ends for those who stay sick all the time.

Design D: based on number of transfers and the time of occurence for these transfers.

As in the earlier sections we shall find the corresponding M.L.E. and discuss the accuracies of the estimates for different values of μ and σ.

5.1. Design A. Reduced design based on the number of transfers ($\rho = \nu = 0$).

The assumption $\rho = \nu = 0$ implies that the maximal number of transfers a person can have is 1. To base the estimation on the number of transfers will then be the same as basing it on the number of patients in the different states at the end of the experiment. As in Chapter 4.1 we can simplify the notation. Let

y_k^j = 1 if patient no. k at the end of the observationtime is in T_j.
= 0 otherwise.

(5.1)
$L_1 = \sum y_k^1$: number of patients who stay sick all the time.
$L_2 = \sum y_k^2$: number of patients who recover from A.
$L_3 = \sum y_k^3$: number of patients who die from A.

We consider $y_k = (y_k^1, y_k^2, y_k^3)$; k = 1,2,...,L, as L realizations of the stochastic vector (y^1, y^2, y^3). The "likelihood-function" now will be:

$$(5.2)\quad f_8(y_1, y_2, \ldots, y_L) = \left(\frac{1-e^{-(\sigma+\mu)}}{\sigma+\mu}\right)^{L_1} \left(\frac{\sigma\left(1-\frac{1-e^{-(\sigma+\mu)}}{\sigma+\mu}\right)}{\sigma+\mu}\right)^{L_2} \left(\frac{\mu\left(1-\frac{1-e^{-(\sigma+\mu)}}{\sigma+\mu}\right)}{\sigma+\mu}\right)^{L_3}$$

since for all k

$$P(y_k^2 = 1) = \int_0^1 \int_0^z \sigma\, p_t''\, dt\, dz = \frac{\sigma}{\mu+\sigma}\left(1 - \frac{1-e^{-(\mu+\sigma)}}{\mu+\sigma}\right),$$

$$P(\gamma_k^3 = 1) = \int_0^1 \int_0^z \mu\, p_t^{11}\, d\,t\,d\,z = \frac{\mu}{\mu+\sigma}\left(1 - \frac{1-e^{-(\mu+\sigma)}}{\mu+\sigma}\right),$$

$$P(\gamma_k^1 = 1) = 1 - P(\gamma_k^2 = 1) - P(\gamma_k^3 = 1) = \frac{1-e^{-(\sigma+\mu)}}{\sigma+\mu},$$

where p_t^{11} are replaced by the corresponding expressions from (A.1) with $\rho = \nu = 0$. The M.L.E. (μ^*, σ^*) are now found as the solutions of the following equations :

$$(5.3) \qquad \frac{\sigma^*\left(1 - \frac{1-e^{-(\sigma^*+\mu^*)}}{\sigma^*+\mu^*}\right)}{\sigma^*+\mu^*} = \frac{L_2}{L}, \qquad \frac{\mu^*\left(1 - \frac{1-e^{-(\sigma^*+\mu^*)}}{\sigma^*+\mu^*}\right)}{\sigma^*+\mu^*} = \frac{L_3}{L}.$$

Explicit expressions for σ^* and μ^* are not obtainable, but for given values of L_1, L_2 and L_3 numerical values of the estimates are easily found.

The matrix of the asymptotic covariances of μ^* and σ^* is

$$-\begin{Bmatrix} E\,\dfrac{\delta^2 \ln f_8}{\delta \mu^2}, & E\,\dfrac{\delta^2 \ln f_8}{\delta \mu\, \delta \sigma} \\ E\,\dfrac{\delta^2 \ln f_8}{\delta \mu\, \delta \sigma}, & E\,\dfrac{\delta^2 \ln f_8}{\delta \sigma^2} \end{Bmatrix}^{-1},$$

f_8 being given by (5.2). This matrix is determined, and the results given in (A.15). Numerical evaluation of the asymptotic variances has been carried out for selected values of μ (= 0, 0.1, 0.5, 1, 2) and of σ (= 0, 0.1, 0.5, 1, 2). The results are given in Table 4 p. 42 column VI and X.

5.2 Design B. Reduced design based on the number of transfers and the time from entrance to death for the patients who die. ($\varrho = \nu = 0$).

For patient no. k, k=1,2,..., L, we introduce a random variable U_k being 0 if he survives the observationperiod, and being equal to the time from entrance to death if patient nr.k dies.

(5.4) $\sum U_k$ is the total time from entrance to death for those who die.

The estimates are now based on L_1, L_2, L_3(5.1) and $\sum U_k$. We consider $(y^1_k, y^2_k, y^3_k, U_k)$, k = 1,2,..., L, as L realizations of the stochastic vector (y^1, y^2, y^3, U). The "likelihood-function" is:

$$(5.5)\quad f_9(y_1,y_2,\ldots,y_L) = \left(\frac{1 - e^{-(\sigma+\mu)}}{\sigma+\mu}\right)^{L_1} \cdot e^{-(\sigma+\mu)\sum U_k} \cdot \mu^{L_3} \left(\sigma \cdot \frac{1 - \frac{1 - e^{-(\sigma+\mu)}}{\sigma+\mu}}{\sigma+\mu}\right)^{L_2}$$

since for all k the probability of dying between u and u+du is $\mu \cdot e^{-(\sigma+\mu)u} du$. The M.L.E. (μ^{**}, σ^{**}) are found as solutions of the equations :

$$L_1\left(\frac{e^{-(\sigma^{**}+\mu^{**})}}{1-e^{-(\sigma^{**}+\mu^{**})}} - \frac{1}{\sigma^{**}+\mu^{**}}\right) - \sum U_k + \frac{L_3}{\mu^{**}} + L_2\left(-\frac{2}{\sigma^{**}+\mu^{**}} + \right.$$

$$\left. + \frac{1-e^{-(\sigma^{**}+\mu^{**})}}{\sigma^{**}+\mu^{**}-1+e^{-(\sigma^{**}+\mu^{**})}}\right) = 0 \; ; \quad \frac{\sigma^{**}}{\mu^{**}} = \frac{L_2}{L_1}$$

Again explicit expressions for μ^{**} and σ^{**} are not obtainable.

The asymptotic covariance matrix for μ^{**}, σ^{**} is

$$-\begin{Bmatrix} E\frac{\delta^2 \ln f_9}{\delta \mu^2} & E\frac{\delta^2 \ln f_9}{\delta \mu \delta \sigma} \\ E\frac{\delta^2 \ln f_9}{\delta \mu \delta \sigma} & E\frac{\delta^2 \ln f_9}{\delta \sigma^2} \end{Bmatrix}^{-1}$$

f_9 being given by (5.5). This matrix is determined and the result given in (A.16). Numerical evaluation of the asymptotic variance has been carried out for selected values of $\mu(= 0, 0.1, 0.5, 1, 2$ and $\sigma(= 0, 0.1, 0.5, 1, 2)$. The results are given in Table 4 p 42 column V and IX.

5.3 Design C. Reduced design based on the number of transfers, the time from entrance to death for those who die and, the time from entrance to the experiment ends for those who stay sick. ($\varrho = \nu = 0$).

This design is applicable when one knows the date each patient enter the experiment and the dates for those who die. For patient no. k, k= 1,2,...,L, we introduce a random variable X_k being equal to the time from entrance to death if patient no. k dies, equal to the time from entrance to the experiment ends if the patient stays sick all the time, and zero if patient no. k goes from T_1 to T_2 during the observation time.

Hence

(5.6) $\sum X_k$ = total time from entrance to death for those who die and from entrance to experiment ends for those who stay sick all the time.

The "likelihood - function" for the L observations now becomes

$$(5.7)\quad f_{1o}(y_1, y_2, \ldots, y_L) = e^{-(\sigma+\mu)\sum X_k}\, \mu^{L_3} \left(\sigma \frac{1 - e^{-(\sigma+\mu)}}{\sigma+\mu}\right)^{L_2},$$

and the M.L.E. $(\hat{\hat{\mu}}, \hat{\hat{\sigma}})$ are found as solutions of the equations :

$$(5.8)\quad -\sum X_k + \frac{L_3}{\hat{\hat{\mu}}} + L_2\left(-\frac{2}{\hat{\hat{\sigma}}+\hat{\hat{\mu}}} + \frac{1 - e^{-(\hat{\hat{\sigma}}+\hat{\hat{\mu}})}}{\hat{\hat{\sigma}}+\hat{\hat{\mu}} - 1 + e^{-(\hat{\hat{\sigma}}+\hat{\hat{\mu}})}}\right) = 0,$$

$$\frac{\hat{\hat{\sigma}}}{\hat{\hat{\mu}}} = \frac{L_2}{L_3}.$$

Again explicit expressions for $\hat{\hat{\sigma}}$ and $\hat{\hat{\mu}}$ are not obtainable, but as in the preceding sections for given values of L_1, L_2, L_3 and $\Sigma \chi_k$ numerical values of the estimates are easily found.

The asymptotic covariancematrix for $\hat{\hat{\mu}}$ and $\hat{\hat{\sigma}}$ is

$$-\begin{Bmatrix} E\frac{\delta^2 \ln f_{10}}{\delta \mu^2}, & E\frac{\delta^2 \ln f_{10}}{\delta \mu \delta \sigma} \\ E\frac{\delta^2 \ln f_{10}}{\delta \mu \delta \sigma}, & E\frac{\delta^2 \ln f_{10}}{\delta \sigma^2} \end{Bmatrix}^{-1}$$

f_{10} being given by (5.7). This matrix is determined, and the result given in (A.17). Numerical evaluation of the asymptotic variances has been carried out for selected values of μ (= 0, 0.1, 0.5, 1, 2) and of σ (= 0, 0.1, 0.5, 1, 2). The results are given in Table 4, p. 42 column IV and VIII.

5.4. Design D. Complete design. ($\rho = \nu = 0$).

The estimates in this design are based on L_1, L_2, L_3 (5.1) and

(5.9) ΣV_K : the total time the L patients stay in T_1 (are sick).

As in (4.6) the "likelihood-function" is

$$(5.10)\quad f_{11}(y_1, y_2, \ldots, y_L) = e^{-(\mu+\sigma)\Sigma V_k} \mu^{L_3} \sigma^{L_2} ,$$

and the M.L.E. $(\hat{\mu}, \hat{\sigma})$ are

$$\hat{\mu} = \frac{L_3}{\Sigma V_k} , \quad \hat{\sigma} = \frac{L_2}{\Sigma V_k} .$$

The matrix of the asymptotic covariances for $(\hat{\mu}, \hat{\sigma})$ is

$$-\begin{pmatrix} E\,\frac{\delta^2 \ln f_{11}}{\delta \mu^2} , & E\,\frac{\delta^2 \ln f_{11}}{\delta \sigma \delta \mu} \\ E\,\frac{\delta^2 \ln f_{11}}{\delta \sigma \delta \mu} , & E\,\frac{\delta^2 \ln f_{11}}{\delta \sigma^2} \end{pmatrix}^{-1}$$

f_{11} being given by (5.10). This matrix is determined, and the result given in (A.18). Numerical evaluations of the asymptotic variances has been carried out for selected values of μ (= 0, 0.1, 0.5, 1, 2) and of σ (= 0, 0.1, 0.5, 1, 2). The results are given in Table 4, p. 42 column III and VII.

Table 4.

The maximum observationtime is uniformly distributed $\varsigma = \nu = 0$.

$\hat{\mu}, \hat{\sigma}$ are the MLE corresponding to Design D,
$\hat{\hat{\mu}}, \hat{\hat{\sigma}}$ are the MLE corresponding to Design C,
μ^{xx}, σ^{xx} are the MLE correspnding to Design B,
μ^{x}, σ^{x} are the MLE corresponding to Design A.

I	II	III	IV	V	VI	VII	VIII	IX	X
μ	σ	Lvar	$\hat{\mu}$ Lvar	$\vec{\mu}$ Lvar	μ^{xx} Lvar	μ^{x} Lvar	$\hat{\sigma}$ Lvar	$\hat{\hat{\sigma}}$ Lvar	σ^{xx} Lvar	σ^{x} Lvar
0.1	0	0.207	0.207	0.211	0.211	-	-	-	-
0.5	0	1.173	1.173	1.270	1.288	-	-	-	-
1	0	2.718	2.718	3.147	3.330	-	-	-	-
2	0	7.046	7.046	8.921	11.130	-	-	-	-
0	0.1	-	-	-	-	0.207	0.207	0.211	0.211
0.1	0.1	0.214	0.214	0.217	0.217	0.214	0.214	0.217	0.217
0.5	0.1	1.210	1.213	1.331	1.331	0.242	0.242	0.246	0.247
1	0.1	2.795	2.818	3.200	3.624	0.280	0.280	0.284	0.288
2	0.1	7.215	7.268	9.220	11.493	0.361	0.361	0.366	0.371
0	0.5	-	-	-	-	1.173	1.189	1.288	1.288
0.1	0.5	0.242	0.243	0.247	0.247	1.210	1.225	1.327	1.331
0.5	0.5	1.359	1.376	1.488	1.512	1.359	1.376	1.488	1.512
1	0.5	3.111	3.181	3.673	3.910	1.556	1.573	1.696	1.755
2	0.5	7.901	9.069	10.252	13.014	1.975	2.001	2.122	2.295
0	1	-	-	-	-	2.718	2.853	3.330	3.330
0.1	1	0.280	0.281	0.286	0.286	2.795	2.933	3.422	3.442
0.5	1	1.556	1.592	1.725	1.755	3.111	3.256	3.787	3.910
1	1	3.523	3.673	3.955	4.544	3.523	3.673	3.955	4.544
2	1	8.781	9.264	11.408	14.732	4.391	4.511	4.951	5.878
0	2	-	-	-	-	7.046	8.356	11.127	11.127
0.1	2	0.361	0.364	0.371	0.371	7.215	8.535	11.349	11.492
0.5	2	1.975	2.060	2.242	2.295	7.901	9.254	11.743	13.017
1	2	4.391	4.733	5.464	5.964	8.781	10.151	12.312	15.074
2	2	10.602	11.944	14.577	19.661	10.602	11.944	14.577	19.661

5.5. Conclusive remarks.

As we see from Table 4 the accuracy of the estimates increases when more information is introduced into the design. If the forces of transfers are small, the differences in accuracy are negligible. When σ and μ are as large as 2, however, the asymptotic relative efficiencies are as follows:

$$\text{a.r.e } (\hat{\mu} : \tilde{\mu}) = 1.13,$$
$$\text{a.r.e } (\tilde{\mu} : \mu^{xx}) = 1.37,$$
$$\text{a.r.e } (\hat{\mu} : \mu^{x}) = 1.85.$$

Hence it seems to be of particular importance to make use of the maximal obtainable information in follow-up studies when the forces of transfers are not small.

6. Summary.

In this paper we have studied different designs for medical follow-up studies and suggested estimates for the forces of transfers in each of these. By numerical evaluation of their asymptotic variances for selected values of the parameters, we have obtained information about the relative accuracy of the estimates. Even if these

computations concern only special situations, the results indicate how accuracy can be gained by making use of the dates of transfers in the estimation procedure. The gain in accuracy is considerable when the forces of transfers are large.

We have already pointed out that the exact time of transfers are frequently difficult or impossible to observe. Our results show that this fact should not have the effect that a design to be used ignores all dates of transfers. Instead one should use a design that utilizes information about the observable times of transfers, for instance the time of death.

Appendix.

In the appendix the formulaes used in this work are given.

The probability that a person who at a certain time is in T_i, t years later will be in T_j is denoted p_t^{ij}. These probabilities are determined when t, μ, σ, ϱ and ν are known.

$$p_t^{11} = \frac{1}{r_2-r_1}\left[(r_2+\alpha)e^{r_1 t} - (r_1+\alpha)e^{r_2 t}\right],$$

$$p_t^{12} = \frac{\sigma}{r_2-r_1}(e^{r_2 t} - e^{r_1 t}),$$

$$p_t^{13} = \int_0^t p_\tau^{11}\mu\, d\tau = \frac{\mu}{r_2-r_1}\left[\frac{(r_2+\alpha)(e^{r_1 t}-1)}{r_1} - \frac{(r_1+\alpha)(e^{r_2 t}-1)}{r_2}\right],$$

$$p_t^{14} = \int_0^t p_\tau^{12}\nu\, d\tau = \frac{\sigma\nu}{r_2-r_1}\left[\frac{e^{r_2 t}-1}{r_2} - \frac{e^{r_1 t}-1}{r_1}\right],$$

(A.1)

$$p_t^{21} = \frac{\varrho}{r_2-r_1}(e^{r_2 t} - e^{r_1 t}),$$

$$p_t^{22} = \frac{1}{r_2-r_1}\left[(r_2+\beta)e^{r_1 t} - (r_1+\beta)e^{r_2 t}\right],$$

$$p_t^{23} = \frac{\mu\varrho}{r_2-r_1}\left[\frac{e^{r_2 t}-1}{r_2} - \frac{e^{r_1 t}-1}{r_1}\right],$$

$$p_t^{24} = \frac{\nu}{r_2-r_1}\left(\frac{(r_2+\beta)(e^{r_1 t}-1)}{r_1} - \frac{(r_1+\beta)(e^{r_2 t}-1)}{r_2}\right),$$

where

$$\left.\begin{matrix} r_1 \\ r_2 \end{matrix}\right\} = \frac{1}{2}\left(-\alpha-\beta \pm \sqrt{(\alpha-\beta)^2+4\sigma\rho}\right),$$

$$\alpha = \mu+\sigma,\ \beta = \rho+\nu.$$

The probability that a person who is in T_i t years later will be in T_j, after n transfers from T_1 to T_2 is called $p_t^{ij.n}$. This probabilities for the values of n used in this work, are given in the following:

$$p_t^{11.0} = e^{-\alpha t},$$

$$p_t^{11.1} = \frac{\alpha\beta}{\beta-\alpha}\left(e^{-\alpha t}+\frac{e^{-\alpha t}-e^{-\beta t}}{\alpha-\beta}\right),$$

$$p_t^{12.1} = \frac{\sigma}{\beta-\alpha}\left(e^{-\alpha t}-e^{-\beta t}\right),$$

$$p_t^{12.2} = \frac{\beta\alpha}{(\beta-\alpha)^2}\sigma\left(e^{-\alpha t}+e^{-\beta t}+2\,\frac{e^{-\alpha t}-e^{-\beta t}}{\alpha-\beta}\right),$$

(A.2)

$$p_t^{13.0} = \frac{\mu}{\alpha}\left(1-e^{-\alpha t}\right),$$

$$p_t^{14.1} = \frac{\nu\sigma}{\beta-\alpha}\left(\frac{1-e^{-\alpha t}}{\alpha}-\frac{1-e^{-\beta t}}{\beta}\right),$$

$$p_t^{22.0} = e^{-\beta t},$$

$$p_t^{21.1} = \frac{\rho}{\alpha-\beta}\left(e^{-\alpha t}-e^{-\beta t}\right),$$

$$p_t^{23.1} = \frac{\mu\rho}{\beta-\alpha}\left(\frac{1-e^{-\alpha t}}{\alpha}-\frac{1-e^{-\beta t}}{\beta}\right),$$

$$p_t^{24.1} = \frac{\nu}{\mathcal{H}}(1 - e^{-\mathcal{H}t}).$$

R.S.N,M,V,W are defined in (2.6). The expectations and the variances can be expressed by the forces of transfers.

$$EM = \int_0^\tau \mu p_t^{11} dt = \frac{\mu}{r_2 - r_1}\left[\frac{(r_2+\alpha)(e^{r_1\tau}-1)}{r_1} - \frac{(r_1+\alpha)(e^{r_2\tau}-1)}{r_2}\right],$$

$$ES = \int_0^\tau \sigma p_t^{11} dt = \frac{\sigma}{r_2 - r_1}\left[\frac{(r_2+\alpha)(e^{r_1\tau}-1)}{r_1} - \frac{(r_1+\alpha)(e^{r_2\tau}-1)}{r_2}\right],$$

(A.3)

$$EN = \int_0^\tau \nu p_t^{12} dt = \frac{\nu\sigma}{r_2 - r_1}\left[\frac{e^{r_2\tau}-1}{r_2} - \frac{e^{r_1\tau}-1}{r_1}\right],$$

$$ER = \int_0^\tau \varsigma p_t^{12} dt = \frac{\sigma\varsigma}{r_2 - r_1}\left[\frac{e^{r_2\tau}-1}{r_2} - \frac{e^{r_1\tau}-1}{r_1}\right],$$

$$EV = \int_0^\tau p_t^{11} dt = \frac{1}{r_2 - r_1}\left[\frac{(r_2+\alpha)(e^{r_1\tau}-1)}{r_1} - \frac{(r_1+\alpha)(e^{r_2\tau}-1)}{r_2}\right],$$

$$EW = \int_0^\tau p_t^{12} dt = \frac{\sigma}{r_2 - r_1}\left[\frac{e^{r_2\tau}-1}{r_2} - \frac{e^{r_1\tau}-1}{r_1}\right],$$

where as before $r_2^{r_1} = \frac{1}{2}\left[-\alpha-\mathcal{H} \pm \sqrt{(\alpha-\mathcal{H})^2+4\sigma\varsigma}\right]$.

The covariance matrix is found in [3, Appendix A].

$$
\begin{aligned}
\text{var } M &= \mu EV(1-\mu EV),\\
\text{cov } (M,S) &= -\mu\sigma\left[(EV)^2 + \frac{\delta}{\delta\mu}EV - \frac{\delta}{\delta\sigma}EV\right],\\
\text{cov } (M,N) &= -\mu\nu EV\cdot EW,\\
\text{cov } (M,R) &= \mu\varrho\left(-EV\cdot EW + \frac{\delta}{\delta\varrho}EV - \frac{\delta}{\delta\nu}EV\right),\\
\text{cov } (M,V) &= -\mu\left[(EV)^2 + \frac{\delta}{\delta\mu}EV\right],\\
\text{cov } (M,W) &= -\mu\left[EV\cdot EW + \frac{\delta}{\delta\nu}EV\right],\\
\text{var } S &= \sigma EV + \sigma^2\left[-(EV)^2 + 2\frac{\delta}{\delta\sigma}EV - 2\frac{\delta}{\delta\mu}EV\right],\\
\text{cov } (S,N) &= \nu\sigma\left[-EV\cdot EW + \frac{\delta}{\delta\sigma}EW - \frac{\delta}{\delta\mu}EW\right],\\
\text{cov } (S,R) &= \sigma\varrho\left[-EV\cdot EW + \frac{\delta}{\delta\varrho}EV - \frac{\delta}{\delta\nu}EV + \frac{\delta}{\delta\sigma}EW - \frac{\delta}{\delta\mu}EW\right]\\
\text{cov } (S,V) &= \sigma\left[-(EV)^2 + \frac{\delta}{\delta\sigma}EV - 2\frac{\delta}{\delta\mu}EV\right],\\
\text{cov } (S,W) &= \sigma\left[-EV\cdot EW + \frac{\delta}{\delta\sigma}EW - \frac{\delta}{\delta\nu}EV - \frac{\delta}{\delta\mu}EW\right],\\
\text{var } N &= \nu\, EW(1-\nu EW),\\
\text{cov } (N,R) &= -\nu\varrho\left[(EW)^2 + \frac{\delta}{\delta\nu}EW - \frac{\delta}{\delta\varrho}EW\right],\\
\text{cov } (N,V) &= -\nu\left[EV\cdot EW + \frac{\delta}{\delta\mu}EW\right],\\
\text{var } R &= \varrho\, EW + \varrho^2\left[-(EW)^2 + 2\frac{\delta}{\delta\varrho}EW - 2\frac{\delta}{\delta\nu}EW\right],\\
\text{cov } (R,V) &= \varrho\left[-EV\cdot EW + \frac{\delta}{\delta\varrho}EV - \frac{\delta}{\delta\mu}EW - \frac{\delta}{\delta\nu}EV\right],\\
\text{cov } (R,W) &= \varrho\left[-(EW)^2 + \frac{\delta}{\delta\varrho}EW - 2\frac{\delta}{\delta\nu}EW\right],\\
\text{var } V &= -(EV)^2 - 2\frac{\delta}{\delta\mu}EV,\\
\text{cov } (V,W) &= -\left(EV\cdot EW + \frac{\delta}{\delta\nu}EV + \frac{\delta}{\delta\mu}EW\right),\\
\text{var } W &= -(EW)^2 - 2\frac{\delta}{\delta\nu}EW,\\
\text{cov } (W,N) &= -\nu\left[(EW)^2 + \frac{\delta}{\delta\nu}EW\right].
\end{aligned}
\tag{A.4}
$$

To be able to calculate the asymptotic variances for the estimates we need the following expressions:

$$E\frac{\delta^2 \ln f_1}{\delta\mu^2} = L\cdot\left[-\frac{e^{-(\sigma+\mu)}}{1-e^{-(\sigma+\mu)}} - \frac{\sigma(1-e^{-(\sigma+\mu)})}{\mu(\sigma+\mu)^2}\right],$$

$$E\frac{\delta^2 \ln f_1}{\delta\mu\,\delta\sigma} = L\cdot\left[-\frac{e^{-(\sigma+\mu)}}{1-e^{-(\sigma+\mu)}} + \frac{1-e^{-(\sigma+\mu)}}{(\sigma+\mu)^2}\right], \quad (A.5)$$

$$E\frac{\delta^2 \ln f_1}{\delta\sigma^2} = L\cdot\left[-\frac{e^{-(\sigma+\mu)}}{1-e^{-(\sigma+\mu)}} - \frac{\mu(1-e^{-(\sigma+\mu)})}{\sigma(\sigma+\mu)^2}\right],$$

(A.5)

where f_1 is the "likelihood-function" (4.2).

$$E\frac{\delta^2 \ln f_2}{\delta\mu^2} = L\cdot\left[-\frac{1-e^{-(\sigma+\mu)}}{\mu(\sigma+\mu)} + \frac{(1-e^{-(\sigma+\mu)})}{(\sigma+\mu)^3} + \frac{\sigma\, e^{-(\sigma+\mu)}}{(\sigma+\mu)(1-e^{-(\sigma+\mu)})}\right],$$

$$E\frac{\delta^2 \ln f_2}{\delta\mu\,\delta\sigma} = L\cdot\left[\frac{\sigma(1-e^{-(\sigma+\mu)})}{(\sigma+\mu)^3} - \frac{\sigma\cdot e^{-(\sigma+\mu)}}{(\sigma+\mu)(1-e^{-(\sigma+\mu)})}\right], \quad (A.6)$$

$$E\frac{\delta^2 \ln f_2}{\delta\sigma^2} = L\cdot\left[-\frac{1-e^{-(\sigma+\mu)}}{\sigma(\sigma+\mu)} + \frac{\sigma(1-e^{-(\sigma+\mu)})}{(\sigma+\mu)^3} - \frac{e^{-(\sigma+\mu)}\cdot\sigma}{(\sigma+\mu)(1-e^{-(\sigma+\mu)})}\right],$$

(A.6)

where f_2 is the "likelihood-function" (4.4).

$$E\frac{\delta^2 \ln f_3}{\delta\mu^2} = -L\cdot\frac{1-e^{-(\sigma+\mu)}}{\mu(\sigma+\mu)}, \quad E\frac{\delta^2 \ln f_3}{\delta\mu\,\delta\sigma} = 0,$$

$$E\frac{\delta^2 \ln f_3}{\delta\sigma^2} = -L\,\frac{1-e^{-(\sigma+\mu)}}{\sigma(\sigma+\mu)}, \quad (A.7)$$

where f_3 is the "likelihood-function" (4.6).

$$\frac{\delta \ln f_4}{\delta \sigma} = -L_{1.0}+L_{2.1}\left(\frac{1}{\sigma}+\frac{e^{-\sigma}}{e^{-\rho}-e^{-\sigma}}-\frac{1}{\sigma-\rho}\right) + (L-L_{1.0}-L_{2.1})$$

$$\left(-\frac{1}{\sigma-\rho}+\frac{1-e^{-\rho}-\rho e^{-\sigma}}{\sigma-\rho-\sigma e^{-\rho}+\rho e^{-\sigma}}\right)$$

(A.8)

$$\frac{\delta \ln f_4}{\delta \rho} = L_{2.1}\left(\frac{1}{\sigma-\rho}-\frac{e^{-\rho}}{(e^{-\rho}-e^{-\sigma})}\right) + (L-L_{1.0}-L_{2.1})$$

$$\left(\frac{1}{\sigma-\rho}+\frac{-1+\sigma e^{-\rho}+e^{-\sigma}}{\sigma-\rho-\sigma e^{-\rho}+\rho e^{-\sigma}}\right),$$

where f_4 is the "likelihood-function"(4.14).

$$\frac{\delta^2 \ln f_4}{\delta \sigma^2} = L_{2.1}\left(-\frac{1}{\sigma^2}-\frac{e^{-(\sigma+\rho)}}{(e^{-\sigma}-e^{-\rho})^2}+\frac{1}{(\sigma-\rho)^2}\right) +$$

$$(L-L_{1.0}-L_{2.1})\left(\frac{\rho e^{-\sigma}}{\sigma-\rho+\rho e^{-\sigma}-\sigma e^{-\rho}}-\frac{(1-\rho e^{-\sigma}-e^{-\rho})^2}{(\sigma-\rho+\rho e^{-\sigma}-\sigma e^{-\rho})^2}+\frac{1}{(\sigma-\rho)^2}\right),$$

$$\frac{\delta^2 \ln f_4}{\delta \sigma \delta \rho} = L_{2.1}\left(\frac{e^{-(\sigma+\rho)}}{(e^{-\sigma}-e^{-\rho})^2}-\frac{1}{(\sigma-\rho)^2}+\right.$$

$$(L-L_{1.0}-L_{2.1})\left(\frac{-e^{-\sigma}+e^{-\rho}}{\sigma-\rho+\rho e^{-\sigma}-\sigma e^{-\rho}}-\frac{(-1+e^{-\sigma}+\sigma e^{-\rho})(1-\rho e^{-\sigma}-e^{-\rho})}{(\sigma-\rho+\rho e^{-\sigma}-\sigma e^{-\rho})^2}-\right.$$

(A 9)

$$\left.\left.\frac{1}{(\sigma-\rho)^2}\right),\right.$$

$$\frac{\delta^2 \ln f_4}{\delta \rho^2} = L_{2.1}\left(-\frac{e^{-(\sigma+\rho)}}{(e^{-\sigma}-e^{-\rho})^2}+\frac{1}{(\sigma-\rho)^2}\right) +$$

$$(L-L_{1.0}-L_{2.1}) \cdot \left(\frac{-\sigma e^{-\rho}}{\sigma-\rho+\rho e^{-\sigma}-\sigma e^{-\rho}}-\frac{(-1+e^{-\sigma}+\sigma e^{-\rho})^2}{(\sigma-\rho+\rho e^{-\sigma}-\sigma e^{-\rho})^2}+\frac{1}{(\sigma-\rho)^2}\right).$$

$$\frac{\delta \ln f_5}{\delta \sigma} = -L_{1.0}+L_{2.1}\left(-\frac{1}{\sigma-\rho}+\frac{e^{-\rho}-e^{-\sigma}}{e^{-\rho}-e^{-\sigma}}-\frac{1}{\sigma-\rho}\right)+L_{1.1}\left(\frac{1}{\sigma}-\frac{2}{\sigma-\rho}+\frac{(\sigma-\rho)e^{-\sigma}}{e^{-\rho}-(1+\sigma-\rho)e^{-\sigma}}\right)+$$

$$(L-L_{1.0}-L_{2.1}-L_{1.1})\cdot\left(\frac{2(\sigma-\rho)+(2\rho-\sigma^2\rho+\sigma\rho^2)e^{-\sigma}-2\sigma e^{-\rho}}{(\sigma-\rho)^2-(\rho^2-2\sigma\rho-(\sigma-\rho)\sigma\rho)e^{-\sigma}-\sigma^2e^{-\rho}}-\frac{2}{\sigma-\rho}\right),$$

(A.10)

$$\frac{\delta \ln f_5}{\delta \rho} = L_{2.1}\left(\frac{1}{\sigma-\rho}-\frac{e^{-\rho}}{e^{-\rho}-e^{-\sigma}}\right)+L_{1.1}\left(\frac{1}{\rho}+\frac{2}{\sigma-\rho}+\frac{e^{-\sigma}-e^{-\rho}}{e^{-\rho}-(1+\sigma-\rho)e^{-\sigma}}\right)+$$

$$(L-L_{1.0}-L_{2.1}-L_{1.1})\left(\frac{-2(\sigma-\rho)-(2\rho-2\sigma-(\sigma-\rho)\sigma+\sigma\rho)e^{-\sigma}+\sigma^2e^{-\rho}}{(\sigma-\rho)^2-(\rho^2-2\sigma\rho-(\sigma-\rho)\sigma\rho)e^{-\sigma}-\sigma^2e^{-\rho}}+\frac{2}{\sigma-\rho}\right),$$

where f_5 is the "likelihood-function" (4.16).

$$\frac{\delta^2 \ln f_5}{\delta \sigma^2} = L_{2.1}\cdot\left[-\frac{1}{\sigma^2}-\frac{e^{-(\sigma+\rho)}}{(e^{-\sigma}-e^{-\rho})^2}+\frac{1}{(\sigma-\rho)^2}\right]+$$

$$L_{1.1}\cdot\left[-\frac{1}{\sigma^2}+\frac{2}{(\sigma-\rho)^2}+\frac{(1-\sigma+\rho)e^{-\sigma}}{e^{-\rho}-e^{-\sigma}(1+\sigma-\rho)}-\left(\frac{(\sigma-\rho)e^{-\sigma}}{e^{-\rho}-e^{-\sigma}(1+\sigma-\rho)}\right)^2\right]+$$

(A.11)

$$(L-L_{1.0}-L_{2.1}-L_{1.1})\cdot\left[\frac{2}{(\sigma-\rho)^2}+\frac{2+(\rho^2-2\sigma\rho-2\rho+\sigma^2\rho-\sigma\rho^2)e^{-\sigma}-2e^{-\rho}}{(\sigma-\rho)^2-(\rho^2-2\sigma\rho-(\sigma-\rho)\sigma\rho)e^{-\sigma}-\sigma^2e^{-\rho}}-\left(\frac{2(\sigma-\rho)+(2\rho-\sigma^2\rho+\sigma\rho^2)e^{-\sigma}-2\sigma e^{-\rho}}{(\sigma-\rho)^2-(\rho^2-2\sigma\rho-(\sigma-\rho)\sigma\rho)e^{-\sigma}-\sigma^2e^{-\rho}}\right)^2\right],$$

(A.11)

$$\frac{\delta^2 \ln f_5}{\delta\sigma\delta\rho} = L_{2.1}\left[-\frac{1}{(\sigma-\rho)^2}+\frac{e^{-(\sigma+\rho)}}{(e^{-\rho}-e^{-\sigma})^2}\right]+L_{1.1}\left[-\frac{2}{(\sigma-\rho)^2}-\right.$$

$$\frac{e^{-\sigma}}{e^{-\rho}-(1+\sigma-\rho)e^{-\sigma}}$$

$$\left.-\frac{(e^{-\sigma}-e^{-\rho})(\sigma-\rho)e^{-\sigma}}{(e^{-\rho}-(1+\sigma-\rho)e^{-\sigma})^2}\right]+(L-L_{1.0}-L_{2.1}-L_{1.1})$$

$$\text{(A.11)}\left[-\frac{2}{(\sigma-\rho)^2}+\frac{-2+(2\sigma\rho-\sigma^2+2)e^{-\sigma}+2\sigma e^{-\rho}}{(\sigma-\rho)^2(\sigma-\rho)^2-(\rho^2-2\sigma\rho-(\sigma-\rho)\sigma\rho)e^{-\sigma}-\sigma^2}-\right.$$

$$(-2(\sigma-\rho)-(2\rho-2\sigma-(\sigma-\rho)\sigma+\sigma\rho)e^{-\sigma}+\sigma^2e^{-\rho})\cdot$$

$$\left.\frac{2(\sigma-\rho)+(2\rho-\sigma^2\rho+\sigma\rho^2)e^{-\sigma}-2\sigma e^{-\rho}}{((\sigma-\rho)^2-(\rho^2-2\sigma\rho-(\sigma-\rho)\sigma\rho)e^{-\sigma}-\sigma^2e^{-\rho})^2}\right],$$

$$\frac{\delta^2 \ln f_5}{\delta\rho^2} = L_{2.1}\left[\frac{1}{(\sigma-\rho)^2}-\frac{e^{-(\sigma+\rho)}}{(e^{-\rho}-e^{-\sigma})^2}\right]+L_{1.1}\left[-\frac{1}{\rho^2}+\frac{2}{(\sigma-\rho)^2}+\right.$$

$$\frac{e^{-\rho}}{e^{-\rho}-(1+\sigma-\rho)e^{-\sigma}}$$

$$\left.-\left(\frac{e^{-\sigma}-e^{-\rho}}{e^{-\rho}-e^{-\sigma}(1+\sigma-\rho)}\right)^2\right]+(L-L_{1.0}-L_{2.1}-L_{1.1})$$

$$\left[\frac{2-(2+2\sigma)e^{-\sigma}\sigma^2e^{-\rho}}{(\sigma-\rho)^2-(\rho^2-2\sigma\rho-(\sigma-\rho)\sigma\rho)e^{-\sigma}-\sigma^2e^{-\rho}}-\right.$$

$$\left.\left(\frac{-2(\sigma-\rho)-(2\rho-2\sigma-\sigma^2+2\sigma\rho)e^{-\sigma}+\sigma^2e^{-\rho}}{(\sigma-\rho)^2-(\rho^2-2\sigma\rho-\sigma^2\rho+\sigma\rho^2)e^{-\sigma}-\sigma^2e^{-\rho}}\right)^2+\frac{2}{(\sigma-\rho)^2}\right].$$

$$\frac{\delta \ln f_6}{\delta \sigma} = -L_{1.0}+L_{2.1}\left(\frac{1}{\sigma}+\frac{e^{-\sigma}}{e^{-\rho}-e^{-\sigma}}-\frac{1}{\sigma-\rho}\right)+L_{1.1}\left(\frac{1}{\sigma}-\frac{2}{\sigma-\rho}+\right.$$

$$\left.\frac{(\sigma-\rho)e^{-\sigma}}{e^{-\rho}-(1+\sigma-\rho)e^{-\sigma}}\right)+$$

(A.12)

$$L_{2.2}\left(\frac{2}{\sigma}-\frac{3}{\sigma-\rho}+\frac{(\rho-\sigma-1)e^{-\sigma}+e^{-\rho}}{(\sigma-\rho+2)e^{-\sigma}+(\sigma-\rho-2)e^{-\rho}}\right)+(L-L_{1.0}-L_{1.1}-L_{2.1}-L_{2.2})$$

$$\left(\frac{3(\sigma-\rho)^2+(\sigma^2\rho^2+\sigma\rho^2-3\rho^2-\sigma\rho^3)e^{-\sigma}+(6\sigma\rho+2\sigma\rho^2-3\sigma^2-3\sigma^2\rho)e^{-\rho}}{(\sigma-\rho)^3+(\rho^3-3\sigma\rho^2-\sigma^2\rho^2+\sigma\rho^3)e^{-\sigma}+(-\sigma^3\rho+\sigma^2\rho^2+3\sigma^2\rho-\sigma^3)e^{-\rho}}-\right.$$

(A.12)

$$\left.\frac{3}{\sigma-\rho}\right)$$

$$\frac{\delta \ln f_6}{\delta \rho} = L_{2.1}\left(\frac{1}{\sigma-\rho}-\frac{e^{-\rho}}{e^{-\rho}-e^{-\sigma}}\right)+L_{1.1}\left(\frac{1}{\rho}+\frac{2}{\sigma-\rho}+\frac{e^{-\sigma}-e^{-\rho}}{e^{-\rho}-(1+\sigma-\rho)e^{-\sigma}}\right)+$$

$$+L_{2.2}\left(\frac{1}{\rho}+\frac{3}{\sigma-\rho}\right.$$

$$\left.+\frac{-e^{-\sigma}+(\rho+1-\sigma)e^{-\rho}}{(\sigma-\rho+2)e^{-\sigma}+(\sigma-\rho-2)e^{-\rho}}\right)+(L-L_{1.0}-L_{1.1}-L_{2.1}-L_{2.2})\cdot$$

$$\left(\frac{-3(\sigma-\rho)^2+(3\rho^2-6\sigma\rho-2\sigma^2\rho+3\sigma\rho^2)e^{-\sigma}+(3\sigma^2-\sigma^2\rho+\sigma^3\rho-\sigma^2\rho^2)e^{-\rho}}{(\sigma-\rho)^3+(\rho^3-3\sigma\rho^2-\sigma^2\rho^2+\sigma\rho^3)e^{-\sigma}+(-\sigma^3\rho+\sigma^2\rho^2+3\sigma^2\rho-\sigma^3)e^{-\rho}}+\right.$$

$$\left.\frac{3}{\sigma-\rho}\right)$$

where f_6 is the "likelihood-function" (4.18).

$$\frac{\delta^2 \ln f_6}{\delta\sigma\delta\rho} = L_{2.1}\left[-\frac{1}{(\sigma-\rho)^2}+\frac{e^{-(\sigma+\rho)}}{(e^{-\rho}-e^{-\sigma})^2}\right]+L_{1.1}\left[-\frac{2}{(\sigma-\rho)^2}-\right.$$

$$\frac{e^{-\sigma}}{e^{-\rho}-(1+\sigma-\rho)e^{-\sigma}}-$$

$$\left.\frac{(e^{-\sigma}-e^{-\rho})(\sigma-\rho)e^{-\sigma}}{(e^{-\rho}-(1+\sigma-\rho)e^{-\sigma})^2}\right]+L_{2.2}\left[-\frac{3}{(\sigma-\rho)^2}+\frac{e^{-\sigma}-e^{-\rho}}{(\sigma-\rho+2)e^{-\sigma}+(\sigma-\rho-2)e^{-\rho}}\right.$$

$$\left.-\frac{(-e^{-\sigma}+(\rho+1-\sigma)e^{-\rho})((\rho-\sigma-1)e^{-\sigma}+e^{-\rho})}{((\sigma-\rho+2)e^{-\sigma}+(\sigma-\rho-2)e^{-\rho})^2}\right]+(L-L_{1.0}-L_{1.1}-L_{2.1}-L_{2.2})$$

$$\left[-\frac{3}{(\sigma-\rho)^2}+\frac{-6(\sigma-\rho)+(2\sigma\rho+2\sigma^2\rho-3\sigma\rho^2-6\rho)e^{-\sigma}+(6\sigma-2\sigma\rho+3\sigma^2\rho-2\sigma\rho^2)e^{-\rho}}{(\sigma-\rho)^3+(\rho^3-3\sigma\rho^2-\sigma^2\rho^2+\sigma\rho^3)e^{-\sigma}+(-\sigma\rho^3+\sigma^2\rho^2+3\sigma\rho^2-\sigma^3)e^{-\rho}}\right.$$

$$\left.-(-3(\sigma-\rho)^2+(3\rho^2-6\sigma\rho-2\sigma^2\rho+3\sigma\rho^2)e^{-\sigma}+(3\sigma^2-\sigma^2\rho+\rho\sigma^3-\sigma^2\rho^2)e^{-\rho})\cdot\right.$$

$$\left.\cdot\frac{3(\sigma-\rho)^2+(\sigma^2\rho^2-3\rho^2+\sigma\rho^2-\sigma\rho^3)e^{-\sigma}+(-3\sigma^2\rho+2\sigma^2\rho+6\sigma\rho-3\sigma^2)e^{-\rho}}{((\sigma-\rho)^3+(\rho^3-3\sigma\rho^2-\sigma^2\rho^2+\sigma\rho^3)e^{-\sigma}+(-\sigma\rho^3+\sigma^2\rho^2+3\sigma\rho^2-\sigma^3)e^{-\rho})^2}\right] .$$

(A.13)

$$\frac{\delta^2 \ln f_6}{\delta\rho^2} = L_{2.1}\left[\frac{1}{(\sigma-\rho)^2}-\frac{e^{-(\sigma+\rho)}}{(e^{-\rho}-e^{-\sigma})^2}\right]+L_{1.1}\left[-\frac{1}{\rho^2}+\frac{2}{(\sigma-\rho)^2}+\right.$$

$$\left.\frac{e^{-\rho}}{e^{-\rho}-(1+\sigma-\rho)e^{-\sigma}}-\right.$$

$$\left.\left(\frac{e^{-\sigma}-e^{-\rho}}{e^{-\rho}-(1+\sigma-\rho)e^{-\sigma}}\right)^2\right]+L_{2.2}\left[-\frac{1}{\rho^2}+\frac{3}{(\sigma-\rho)^2}+\frac{(\sigma-\rho)e^{-\rho}}{(\sigma-\rho+2)e^{-\sigma}+(\sigma-\rho-2)e^{-\rho}}-\right.$$

$$\left.-\left(\frac{-e^{-\sigma}+(\rho+1-\sigma)e^{-\rho}}{(\sigma-\rho+2)e^{-\sigma}+(\sigma-\rho-2)e^{-\rho}}\right)^2\right]+(L-L_{1.0}-L_{1.1}-L_{2.1}-L_{2.2})\cdot\left[\frac{3}{(\sigma-\rho)^2}\right.$$

$$+\frac{6(\sigma-\rho)+(6\rho-6\sigma-2\sigma^2+6\sigma\rho)e^{-\sigma}+(\sigma^3-4\sigma^2-\sigma^2\rho-\sigma^3\rho+\sigma^2\rho^2)e^{-\rho}}{(\sigma-\rho)^3+(\rho^3-3\sigma\rho^2-\sigma^2\rho^2+\sigma\rho^3)e^{-\sigma}+(-\sigma\rho^3+\sigma^2\rho^2+3\sigma^2\rho-\sigma^3)e^{-\rho}}-$$

$$\left(\frac{-3(\sigma-\rho)^2+(3\rho^2-6\sigma\rho-2\sigma^2\rho+3\sigma\rho^2)e^{-\sigma}+(3\sigma^2-\sigma^2\rho+\sigma^3\rho-\sigma^2\rho^2)e^{-\rho}}{(\sigma-\rho)^3+(\rho^3-3\sigma\rho^2-\sigma^2\rho^2+\sigma\rho^3)e^{-\sigma}+(-\sigma^3\rho+\sigma^2\rho^2+3\sigma^2\rho-\sigma^3)e^{-\rho}}\right)^2\Bigg],$$

(A.13)

$$\frac{\delta^2 \ln f_6}{\delta\sigma^2} = L_{2.1}\left[-\frac{1}{\sigma^2}-\frac{e^{-(\sigma+\rho)}}{(e^{-\sigma}-e^{-\rho})^2}+\frac{1}{(\sigma-\rho)^2}\right]+L_{1.1}\left[-\frac{1}{\sigma^2}+\frac{2}{(\sigma-\rho)^2}\right.$$

$$+\frac{(1-\sigma+\rho)e^{-\sigma}}{(e^{-\rho}-(1+\sigma-\rho)e^{-\sigma}}-\left(\frac{(\sigma-\rho)e^{-\sigma}}{e^{-\rho}-(1+\sigma-\rho)e^{-\sigma}}\right)^2\Bigg]+L_{2.2}\cdot\left[\frac{-2}{\sigma^2}+\frac{3}{(\sigma-\rho)^2}+\right.$$

$$\left.+\frac{(\sigma-\rho)e^{-\sigma}}{(\sigma-\rho+2)e^{-\sigma}+(\sigma-\rho-2)e^{-\rho}}-\left(\frac{(\rho-\sigma-1)e^{-\sigma}+e^{-\rho}}{(\sigma-\rho+2)e^{-\sigma}+(\sigma-\rho-2)e^{-\rho}}\right)^2\right]+$$

$$(L-L_{1.0}-L_{1.1}-L_{2.1}-L_{2.2})\left[\frac{3}{(\sigma-\rho)^2}+\right.$$

$$\frac{6(\sigma-\rho)+(6\rho^2-\rho^3+4\rho^2-\sigma^2\rho^2+6\rho^3)e^{-\sigma}+(6\rho+2\rho^2-6\sigma-6\sigma\rho)e^{-\rho}}{(\sigma-\rho)^3+(\rho^3-3\sigma\rho^2-\sigma^2\rho^2+\sigma\rho^3)e^{-\sigma}+(-\sigma\rho^3+\sigma^2\rho^2+3\sigma^2\rho-\sigma^3)e^{-\rho}}$$

$$\left.-\left(\frac{3(\sigma-\rho)^2+(\sigma^2\rho^2+\sigma\rho^2-3\rho^2-\sigma\rho^3)e^{-\sigma}+(6\sigma\rho+2\sigma\rho^2-3\sigma^2-3\sigma\rho^2)e^{-\rho}}{(\sigma-\rho)^3+(\rho^3-3\sigma\rho^2-\sigma^2\rho^2+\sigma\rho^3)e^{-\sigma}+(-\sigma\rho^3+\sigma^2\rho^2+3\sigma^2\rho-\sigma^3)e^{-\rho}}\right)^2\right].$$

$$E\frac{\delta^2 \ln f_7}{\delta\sigma^2} = -\frac{L}{\sigma(\sigma+\rho)}\left(\rho+\sigma\frac{1-e^{-(\sigma+\rho)}}{\sigma+\rho}\right),$$

(A.14)

$$E\frac{\delta^2 \ln f_7}{\delta\sigma\delta\rho} = 0,$$

(A.14)

$$E\frac{\delta^2 \ln f_7}{\delta\rho^2} = -\frac{L\sigma}{\rho(\sigma+\rho)}\left(1-\frac{1-e^{-(\sigma+\rho)}}{\sigma+\rho}\right),$$

where f_7 is given in (4.20).

$$E\frac{\delta^2 \ln f_8}{\delta\mu^2} = L\left[-\frac{1-\frac{1-e^{-(\sigma+\mu)}}{\sigma+\mu}}{\mu(\sigma+\mu)} - \frac{e^{-(\sigma+\mu)}}{(\sigma+\mu)(1-e^{-(\sigma+\mu)})} + \frac{e^{-(\sigma+\mu)}}{\sigma+\mu} + \frac{e^{-(\sigma+\mu)+1}}{(\sigma+\mu)^2} \right.$$

$$\left. - \frac{1-e^{-(\sigma+\mu)}}{(\sigma+\mu)^3} + \frac{(e^{-(\sigma+\mu)} - \frac{1-e^{-(\sigma+\mu)}}{\sigma+\mu})(1-e^{-(\sigma+\mu)})}{(\sigma+\mu)^2(1-\frac{1-e^{-(\sigma+\mu)}}{\sigma+\mu})} \right],$$

$$E\frac{\delta^2 \ln f_8}{\delta\mu\,\delta\sigma} = L\left[-\frac{e^{-(\sigma+\mu)}}{(\sigma+\mu)(1-e^{-(\sigma+\mu)})} + \frac{e^{-(\sigma+\mu)+1}}{(\sigma+\mu)^2} + \frac{e^{-(\sigma+\mu)}}{\sigma+\mu} + \right.$$

(A.15)

$$\left. \frac{e^{-(\sigma+\mu)}}{(\sigma+\mu)^2} - \frac{1-e^{-(\sigma+\mu)}}{(\sigma+\mu)^3} + \frac{(e^{-(\sigma+\mu)} - \frac{1-e^{-(\sigma+\mu)}}{\sigma+\mu})(1-e^{-(\sigma+\mu)})}{(\sigma+\mu)^2(1-\frac{1-e^{-(\sigma+\mu)}}{\sigma+\mu})} \right],$$

$$E\frac{\delta^2 \ln f_8}{\delta\sigma^2} = L\left[-\frac{1-\frac{1-e^{-(\sigma+\mu)}}{\sigma+\mu}}{\sigma(\sigma+\mu)} - \frac{e^{-(\sigma+\mu)}}{(\sigma+\mu)(1-e^{-(\sigma+\mu)})} + \frac{e^{-(\sigma+\mu)}}{\sigma+\mu} + \right.$$

$$\left. \frac{e^{-(\sigma+\mu)}}{(\sigma+\mu)^2} - \frac{1-e^{-(\sigma+\mu)}}{(\sigma+\mu)^3} + \frac{(e^{-(\sigma+\mu)} - \frac{1-e^{-(\sigma+\mu)}}{\sigma+\mu})(1-e^{-(\sigma+\mu)})}{(\sigma+\mu)^2(1-\frac{1-e^{-(\sigma+\mu)}}{\sigma+\mu})} \right],$$

f_8 is given in (5.2).

$$E\frac{\delta^2 \ln f_9}{\delta\mu^2} = L\Big(-\frac{1-\frac{1-e^{-(\sigma+\mu)}}{\sigma+\mu}}{\mu(\sigma+\mu)} - \frac{e^{-(\sigma+\mu)}}{(1-e^{-(\sigma+\mu)})(\sigma+\mu)} + \frac{1-e^{-(\sigma+\mu)}}{(\sigma+\mu)^3} +$$

$$+\frac{\sigma\left(1-\frac{1-e^{-(\sigma+\mu)}}{(\sigma+\mu)^3}\right)}{(\sigma+\mu)^3} + \frac{\sigma}{\sigma+\mu}\left(\frac{e^{-(\sigma+\mu)}}{\sigma+\mu} + \frac{e^{-(\sigma+\mu)}}{(\sigma+\mu)^2} - \frac{1-e^{-(\sigma+\mu)}}{(\sigma+\mu)^3}\right.$$

$$\left.+\frac{\left(e^{-(\sigma+\mu)} - \frac{1-e^{-(\sigma+\mu)}}{\sigma+\mu}\right)(1-e^{-(\sigma+\mu)})}{(\sigma+\mu)^2\left(1-\frac{1-e^{-(\sigma+\mu)}}{\sigma+\mu}\right)}\right),$$

(A.16)

$$E\frac{\delta^2 \ln f_9}{\delta\sigma\delta\mu} = L\Big(-\frac{e^{-(\sigma+\mu)}}{\sigma+\mu} + \frac{1-e^{-(\sigma+\mu)}}{(\sigma+\mu)^3} + \frac{\sigma\left(1-\frac{1-e^{-(\sigma+\mu)}}{\sigma+\mu}\right)}{(\sigma+\mu)^3}$$

$$+\frac{\sigma}{\sigma+\mu}\left(\frac{e^{-(\sigma+\mu)}}{\sigma+\mu} + \frac{e^{-(\sigma+\mu)}}{(\sigma+\mu)^2} - \frac{1-e^{-(\sigma+\mu)}}{(\sigma+\mu)^3} +\right.$$

$$\left.+\frac{\left(e^{-(\sigma+\mu)} - \frac{1-e^{-(\sigma+\mu)}}{\sigma+\mu}\right)(1-e^{-(\sigma+\mu)})}{(\sigma+\mu)^2\left(1-\frac{1-e^{-(\sigma+\mu)}}{\sigma+\mu}\right)}\right),$$

$$E\frac{\delta^2 \ln f_9}{\delta\sigma^2} = L\Big(-\frac{e^{-(\sigma+\mu)}}{(1-e^{-(\sigma+\mu)})(\sigma+\mu)} + \frac{1-e^{-(\sigma+\mu)}}{(\sigma+\mu)^3} + \sigma\frac{1-\frac{1-e^{-(\sigma+\mu)}}{\sigma+\mu}}{(\sigma+\mu)^3}$$

$$-\frac{1-\frac{1-e^{-(\sigma+\mu)}}{\sigma+\mu}}{\sigma(\sigma+\mu)} + \frac{\sigma}{\sigma+\mu}\left(\frac{e^{-(\sigma+\mu)}}{\sigma+\mu} + \frac{e^{-(\sigma+\mu)}}{(\sigma+\mu)^2} - \frac{1-e^{-(\sigma+\mu)}}{(\sigma+\mu)^3}\right.$$

$$\left.+\frac{e^{-(\sigma+\mu)} - \frac{1-e^{-(\sigma+\mu)}}{\sigma+\mu}(1-e^{-(\sigma+\mu)})}{(\sigma+\mu)^2\left(1-\frac{1-e^{-(\sigma+\mu)}}{\sigma+\mu}\right)}\right),$$

f_9 is given in (5.5).

$$E\frac{\delta^2 \ln f_{10}}{\delta\mu^2} = L\Big(-\frac{1-\frac{1-e^{-(\sigma+\mu)}}{\sigma+\mu}}{\mu(\sigma+\mu)} + \frac{\sigma\left(1-\frac{1-e^{-(\sigma+\mu)}}{(\sigma+\mu)^3}\right)}{(\sigma+\mu)^3} + \frac{\sigma}{\sigma+\mu}\Big(\frac{e^{-(\sigma+\mu)}}{\sigma+\mu} +$$

$$+ \frac{e^{-(\sigma+\mu)}}{(\sigma+\mu)^2} - \frac{1-e^{-(\sigma+\mu)}}{(\sigma+\mu)^3} +$$

$$+ \frac{\left(e^{-(\sigma+\mu)} - \frac{1-e^{-(\sigma+\mu)}}{\sigma+\mu}\right)\left(1-e^{-(\sigma+\mu)}\right)}{(\sigma+\mu)^2\left(1-\frac{1-e^{-(\sigma+\mu)}}{\sigma+\mu}\right)}\Big),$$

(A.17)

$$E\frac{\delta^2 \ln f_{10}}{\delta\sigma\delta\mu} = L\Big(\frac{\sigma\left(1-\frac{1-e^{-(\sigma+\mu)}}{\sigma+\mu}\right)}{(\sigma+\mu)^3} + \frac{\sigma}{\sigma+\mu}\Big(\frac{e^{-(\sigma+\mu)}}{\sigma+\mu} + \frac{e^{-(\sigma+\mu)}}{(\sigma+\mu)^2} - \frac{1-e^{-(\sigma+\mu)}}{(\sigma+\mu)^3}$$

$$+ \frac{\left(e^{-(\sigma+\mu)} - \frac{1-e^{-(\sigma+\mu)}}{\sigma+\mu}\right)\left(1-e^{-(\sigma+\mu)}\right)}{(\sigma+\mu)^2\left(1-\frac{1-e^{-(\sigma+\mu)}}{\sigma+\mu}\right)}\Big),$$

$$E\frac{\delta^2 \ln f_{10}}{\delta\sigma^2} = L\Big(-\frac{1-\frac{1-e^{-(\sigma+\mu)}}{\sigma+\mu}}{\sigma(\sigma+\mu)} + \frac{\sigma\left(1-\frac{1-e^{-(\sigma+\mu)}}{\sigma+\mu}\right)}{(\sigma+\mu)^3} + \frac{\sigma}{\sigma+\mu}\Big(\frac{e^{-(\sigma+\mu)}}{\sigma+\mu}$$

$$+ \frac{e^{-(\sigma+\mu)}}{(\sigma+\mu)^2} - \frac{1-e^{-(\sigma+\mu)}}{(\sigma+\mu)^3} + \frac{\left(e^{-(\sigma+\mu)} - \frac{1-e^{-(\sigma+\mu)}}{\sigma+\mu}\right)\left(1-e^{-(\sigma+\mu)}\right)}{(\sigma+\mu)^2\left(1-\frac{1-e^{-(\sigma+\mu)}}{\sigma+\mu}\right)}\Big),$$

f_{10} is given in (5.7).

$$E\frac{\delta^2 \ln f_{11}}{\delta\mu^2} = -L\cdot\frac{1-\frac{1-e^{-(\sigma+\mu)}}{\sigma+\mu}}{\mu(\sigma+\mu)} \quad ,$$

(A.18)

$$E\frac{\delta^2 \ln f_{11}}{\delta\sigma\delta\mu} = 0 \quad ,$$

$$E\frac{\delta^2 \ln f_{11}}{\delta\sigma^2} = -L\cdot\frac{1-\frac{1-e^{-(\sigma+\mu)}}{\sigma+\mu}}{\sigma(\sigma+\mu)} \quad ,$$

f_{11} is given in (5.10).

$$\frac{\delta ES}{\delta\mu} = -\frac{\sigma\rho^2}{2(\sigma+\rho)^2} - \frac{2\sigma^2\rho - \sigma^3}{(\sigma+\rho)^3} + \left(\frac{2\sigma^2\rho - \sigma^3}{(\sigma+\rho)^4} - \frac{\sigma^3}{(\sigma+\rho)^3}\right)(1-e^{-(\sigma+\rho)}),$$

$$\frac{\delta ES}{\delta\sigma} = \frac{\sigma^2+\rho^2}{(\sigma+\rho)^2} + \left(\frac{2\sigma\rho}{(\sigma+\rho)^3} - \frac{\sigma^2}{(\sigma+\rho)^2}\right)(1-e^{-(\sigma+\rho)}),$$

$$\frac{\delta ES}{\delta\rho} = \frac{2\sigma^2}{(\sigma+\rho)^2} - \left(\frac{\sigma^2}{(\sigma+\rho)^2} + \frac{2\sigma^2}{(\sigma+\rho)^3}\right)(1-e^{-(\sigma+\rho)}),$$

(A.19)

$$\frac{\delta ES}{\delta\nu} = \frac{3\sigma^2\rho}{(\sigma+\rho)^3} - \frac{\sigma^2\rho}{2(\sigma+\rho)^2} - \left(\frac{\sigma^2\rho}{(\sigma+\rho)^3} + \frac{3\sigma^2\rho}{(\sigma+\rho)^4}\right)(1-e^{-(\sigma+\rho)}),$$

$$\frac{\delta ER}{\delta\mu} = -\frac{\sigma\rho^2}{2(\sigma+\rho)^2} + \frac{\rho^2\sigma - 2\rho\sigma^2}{(\sigma+\rho)^3} + \left(\frac{2\sigma^2\rho - \rho^2\sigma}{(\sigma+\rho)^4} + \frac{\sigma^2\rho}{(\sigma+\rho)^3}\right)(1-e^{-(\sigma+\rho)}),$$

$$\frac{\delta ER}{\delta\sigma} = \frac{\rho^2-\sigma\rho}{(\sigma+\rho)^2} + \left(\frac{\sigma\rho}{(\sigma+\rho)^2} + \frac{\sigma\rho - \rho^2}{(\sigma+\rho)^3}\right)(1-e^{-(\sigma+\rho)}),$$

$$\frac{\delta_{ER}}{\delta\rho} = \frac{\sigma^2 - 6\rho}{(\sigma+\rho)^2} + \left(\frac{\sigma\rho}{(\sigma+\rho)^2} + \frac{\sigma\rho - \sigma^2}{(\sigma+\rho)^3}\right)(1-e^{-(\sigma+\rho)}),$$

$$\frac{\delta_{ER}}{\delta V} = -\frac{\sigma^2\rho}{2(\sigma+\rho)^2} + \frac{\sigma^2\rho - 2\sigma\rho^2}{(\sigma+\rho)^3} + \left(\frac{\sigma\rho^2}{(\sigma+\rho)^3} + \frac{2\sigma\rho^2 - \sigma^2\rho}{(\sigma+\rho)^4}\right)(1-e^{-(\sigma+\rho)}).$$

References.

[1] Feller, W. 1950. Probability theory and its applications.

[2] Fix, E. and Neyman, J. 1951. A simple stochastic model of recovery, relapse, death and loss of patients. Human Biology, 23, p.205-241.

[3] Sverdrup, E. 1964. Estimates and Test Procedures in connection with Stochastic Models for Deaths, Recoveries and Transfers between different States of Health.