PRACTICAL APPLICATIONS OF THE NONPARAMETRIC STATISTICAL THEORY FOR COUNTING PROCESSES

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Contents:

(The paper is a collection of material from lectures that have been given on several occasions, including the following:

1) Invited talk at The European conference of Statisticians at Grenoble, September 1976.

2) Talk at The Conference of Medical Statistics in Brussels, May 1979.

3) Invited talks at The Summer School of Probability Theory in Kuusamo, Finland in June 1981.)

1. INTRODUCTION

We will present some examples illustrating the use of nonparametric methods for counting processes. The discussion will be quite informal. The material is related to theoretical work by the author, in the sense that this work has contributed somewhat to extending and making a theoretical basis for the methods. As far as survival analysis is concerned the basic ideas have been in the litterature for quite a few years. Important early references are Kaplan and Meier (1958), Mantel and Haenzel (1959), Gehan (1965) and Nelson (1969). Although a good deal of the present paper is also concerned with survival analysis, we give in addition some examples of a different nature and show that similar methods may be applied to them.

Applications of the theory of counting processes which are very different from those given here may be found in Becker (1977, 1979, 1981). Those papers are concerned with estimation of infectiousness of epidemic diseases.

Our use of the term counting process refers to a general point of view which serves to unify several different models. This point of view may be described in the following way:

One observes the occurrence over time of several events, which may be of different types. We assume that the types are numbered from 1 up to k.

Consider a given time t and let $N_i(t)$ be the number of events of type i which has occurred up to (and including) time t. Obviously the stochastic process $N_i(t)$ will have a jump of size 1 each time an event of type i occurs. $N_i(t)$ can be said to count the events of type i, and hence we call it a counting process. Such a process is illustrated in Figure 1.

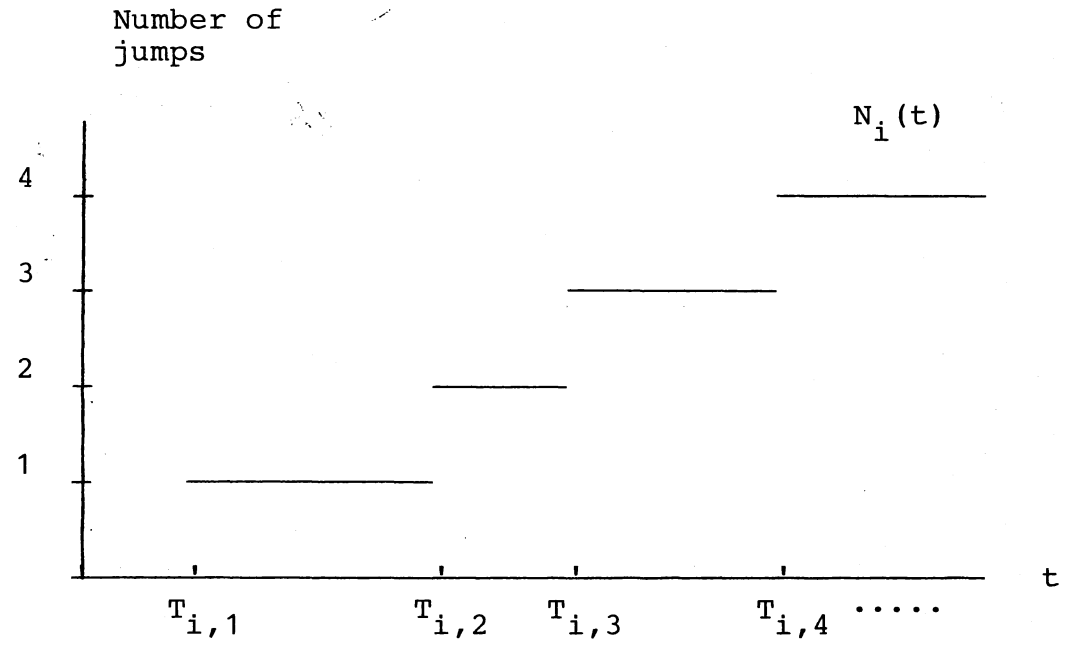


Figure 1. A counting process.

For each counting process it is useful to consider the concept of an intensity process, denoted $\Lambda_i(t)$. It is defined in the following way: $\Lambda_i(t)dt$ is the conditional probability of an event of type i happening in the time interval (t, t + dt) given all that has happened before time t.

In all examples below the processes $\Lambda_i(t)$, $i = 1,\ldots,k$, can be written as follows:

$$\Lambda_i(t) = \alpha_i(t)\ Y_i(t)$$

where $\alpha_i(t)$ is an unknown function while $Y_i(t)$ is an observed process which may depend arbitrarily on the past. This model is called the multiplicative intensity model. One is interested in making non-parametric statistical inference about the α-functions. It is shown in Aalen (1978 b) that the socalled martingale approach makes it possible to develop such a theory without imposing almost any structure on the counting processes (which means that the form of the Y-processes, their interdependence and dependence on the past do not need to be specified).

We will briefly go through the examples treated below and indicate what is the interpretation of the α's and the Y's in each example.

(i) Competing risks

We will use the terminology of survival studies. The process $N_i(t)$ counts the occurrence of deaths due to cause no. i. The process $Y_i(t)$ represents the number of individuals at risk at time t (and hence is the same for each i). The function $\alpha_i(t)$ is the same as the hazard (or mortality) rate at time t. It should be intuitively reasonable that the intensity of a death due to cause no. i is equal to $\alpha_i(t)\ Y_i(t)$.

(ii) Birth and death process

There are two counting processes, $N_1(t)$ and $N_2(t)$, which count the births and deaths respectively. $Y_1(t)$ and $Y_2(t)$ are both equal to the number of individuals alive at time t. The functions

$$\alpha_1(t) \text{ and } \alpha_2(t)$$

correspond to the birth and death rates respectively.

(iii) Epidemic example

Let $N(t)$ count the number of infections in a population and let $I(t)$ and $S(t)$ be the number of infectives and susceptibles, respectively, at time t. Then a simple model says that the intensity of another individual being infected is given by

$$\alpha(t)\ I(t)\ S(t)$$

where the function $\alpha(t)$ is a measure of infectiousness. We once more have the multiplicative intensity model with $Y(f) = I(t)\ S(t)$.

(iv) Mating of Drosophila

Let $M(t)$ and $F(t)$ represent the numbers of male and female Drosophila in a chamber that have not started mating at time t. A simple model assumes that the intensity of

another mating starting is of the form

$$\alpha(t)\ M(t)\ F(t).$$

Practical examples where the counting process framework has been used may also be found in other papers. For instance, Andersen et al. (1981) give an example concerning admission to psychiatric hospitals among women giving birth. In that case the counting processes register admissions to, and discharges from psychiatric hospitals among women in various parity groups. Statistical tests based on counting process theory is used for comparing the intensities of admission among women in the different groups.

2. COMPETING RISKS

2A. General remarks

The notion of competing risks, or multiple decrement models, is fundamental in the statistical analysis of survival data. In actuarial science, demography and epidemiology there is an age old tradition for the study of competing risks models. Hence, one should think that this field would be more or less completely developed, and that not much new could be said on the subject. This, however, is not true. The clinical trials and animal experiments which have become very common during the last 20 or 30 years, have posed new problems which require new methods. One feature, for instance, of a clinical trial which makes it different from, say, an actuarial mortality study, is the much smaller number of individuals which are involved in the former one. A clinical trial may involve maybe a hundred people (which means a large trial) while an actuarial study may involve tens of thousands of people (and perhaps much more).

It has turned out that the small scale survival studies may sometimes be usefully analysed by means of nonparametric methods, which may be entirely irrelevant for the large scale studies. ("Nonparametric" means that no assumption at all is made about the functional form of the mortality rates). The prototype of these nonparametric procedures is the Kaplan-Meier survival curve.

Even though these procedures may occasionally look like rather simple modifications of traditional methods, their nonparametric character still requires a new theoretical underpinning. The mathematical apparatus needed to do this is quite a bit more formidable than that required by traditional methods. This mathematics can not be dispensed with since it is essential for the construction of confidence intervals, computation of p-values and so on. Hence a blossoming of new activity has taken place as regards the statistical analysis of competing risks model. This may be witnessed by the overflow of such papers in various journals.

Below we will illustrate the use of some nonparametric methods, in particular the Nelson plot and a generalized Kaplan-Meier estimate. We will consider two sets of data, one from an animal survival experiment and the other from a study of the intrauterine contraceptive device (IUD). The second example illustrates the use of competing risks methods to other data than those arising in survival studies.

2B. The Nelson plot with application to animal survival data. Two sample testing. Test for increasing intensity.

The well known Kaplan-Meier survival curve is very useful in situations where one wants to estimate the total mortality in the presence of censoring. In a competing risks setting, however, one often wishes to estimate the separate effects of several causes of death. The Kaplan-Meier plot is sometimes used for this purpose, too. For instance, Hoel and Walburg (1972) studies the mortality of irradiated mice due to three different causes of death (or risks). For each cause of death they compute a Kaplan-Meier survival curve, regarding death from the other causes as censoring. Each Kaplan-Meier curve is then supposed to estimate the hypothetical mortality from the given cause of death in the case that none of the other risks were operating. This is only true and meaningful if one makes the assumption of independent risks. Hoel and Walburg argue that this will probably hold in their case.

We will argue that another plot, closely related to the Kaplan-Meier plot, has a more general validity in a competing general setting. This is the socalled Nelson plot, which estimates the cumulative intensity. This latter concept is defined in the following way. Let $\lambda_i(t)$ be the death intensity (hazard rate, mortality rate) due to cause no. i, and assume there are k causes in all. The cumulative intensity is defined by the formula

$$\beta_i(t) = \int_0^t \lambda_i(s)ds \ .$$

Nelson (1969) suggested to estimate $\beta_i(t)$ in the following way. Let $Y(t)$ be the number of individuals at risk just before time t.

We allow the possibility of censoring which means that $Y(t)$ may decrease without a death taking place. Let $T_{i1} < T_{i2} < \cdots$ be the observed times of death from cause no. i. Nelson's estimate is given by

$$(2.1) \qquad \hat{\beta}_i(t) = \sum_{T_{ij} \leq t} \frac{1}{Y(T_{ij})} .$$

Intuitive justification for this estimate may be found in Nelson (1969) or Altshuler (1970), while a mathematical justification and theory, partly based on counting processes, may be found in Aalen (1976, 1978b). The variance of $\hat{\beta}_i(t)$ may be estimated by

$$\hat{\tau}_i(t) = \sum_{T_{ij} \leq t} \frac{1}{[Y(T_{ij})]^2} .$$

The estimated cumulative intensity is intended for plotting purposes. The result is called a Nelson plot. This was first developed by Nelson for applications in reliability life testing. It does not seem to have been used so much in a biostatistical context, and one object of this paper is to argue for its usefulness.

It may be easily shown that the Nelson plot is very closely related to the Kaplan-Meier plot.

However, since the intensities $\lambda_i(t)$, $i = 1,\ldots,k$, are always well defined, also when the risks are dependent, the Nelson plot will always convey a clear information in a competing risks setting as opposed to the Kaplan-Meier plot.

The plots of $\hat{\beta}_i(t)$ give information of the following kind:

(i) The <u>slopes</u> of $\hat{\beta}_i(t)$, $i = 1,\ldots,k$, are estimates of the values of the intensities, and hence give information about the influence of the various causes of death at any time t.

(ii) The value of $\hat{\beta}_i(t)$ at any time t is an estimate of the expected number of deaths from cause no. i that would have taken place if there were constantly a single individual at risk (see Altshuler, 1970). Of course, this is not a common quantity to consider, but it may still convey some information.

(iii) The plots may be used to check various parametric models for the intensities. A constant intensity would yield approximately a straight-lined plot. If the intensity follows the Weibull law, then $\beta_i(t)$ will be a straight line if both axes are put in a logarithmic scale. Nelson (1969, 1972) has developed several kinds of "probability paper" that can be used for checking the validity of various models.

(iv) It follows from Aalen (1976, Thm. 3.2) that the $\hat{\beta}_i(t)$, $i = 1,\ldots,k$, can be considered approximately <u>independent</u> processes, implying that the Nelson plots for the various risks

may be judged independently of each other.

By the way, one should note that Day (1976) suggests that the cumulative intensity is a very natural measure for age standardized incidence. To be more precise, if one considers the time interval (t_1,t_2) then Day suggests to use $\beta_i(t_2) - \beta_i(t_1)$ as a measure of incidence due to cause no. i. This can, of course, be estimated by $\hat{\beta}_i(t_2) - \hat{\beta}_i(t_1)$. Day argues that such a measure has great practical advantages.

As a first illustration of the Nelson plot we will reanalyze the data of Hoel and Walburg (1972). The data, which are given in Table 1, come from observation of two groups of RFM strain male mice which have received a radiation dose of 300 r at an age of 5-6 weeks. Group I consisted of 95 mice living in a conventional laboratory environment, while group II consisted of 82 mice in a germfree environment. Three causes of death are considered for each group: thymic lymphoma (cause no. 1), reticulum cell sarcoma (cause no. 2) and all other causes combined (cause no. 3).

The Nelson plots for the conventional mice and the germfree mice are given in Figures 2 an 3 respectively. The figures give a clear impression of the importance of the various causes of death at each age. Consider for instance Figure 2. From the age of about 180 days, thymic lymphoma and "other causes" start to "operate" among the conventional mice, the two causes of death being of equal importance.

Until the age of about 450 days, the intensities of these two causes seem to be quite constant (the plots being more or less straight). After this time thymic lymphoma ceases to be of importance, while the mortality due to "other causes" starts to increase (the slope of the plot becoming steeper). Reticulum cell sarcoma is of very little importance as a cause of death until about 550 days when the mortality due to this cause starts to rise sharply. Soon it becomes the dominant cause of death.

Figure 3 shows that the picture for germfree mice is quite different. In order to make a more detailed comparison, the Nelson plots of the germfree and conventional mice are compared pairwise for each cause of death in Figures 4,5 and 6. Figure 4 indicates what the germfree environment has little effect as regards thymic lymphoma, at least up to the age of 450 days. In contrast, Figure 5 shows that the effect is very great for reticulum cell sarcoma, the death rate being greatly reduced in the germfree environment. A similar but much weaker effect can be seen for "other causes" from Figure 6. In this case it seems that the only difference between the two curves, is that one is "delayed" somewhat in comparison to the other. Hence, as far as "other causes" is concerned the effect of the germfree environment seems to be to prolong life a certain amount (about a 100 days).

In Figure 7, finally, the obseved difference for reticulum cell sarcoma is analyzed more closely.

The figure presents a "probit plot", i.e the cumulative intensity values (taken from Figure 5) for the conventional mice are plotted against the corresponding values for the germfree mice. The values are, of course, taken from the age interval where they can be compared. Over this interval, the probit plot fits well with a straight line. This indicates a proportional relationship between the two mortalities. Hence, it seems that the presence of germs has the effect of roughly, multiplying the mortality due to reticulum cell sarcoma by a constant amount.

The idea of the probit plot was suggested by Keiding and Weis Bentzon (1976).

As mentioned earlier, one of the important uses of the Nelson plot is for checking the validity of various parametric models. As a rough illustration of this, we have in Figure 8 taken some values from the Nelson plot for "other causes" and put them into a logarithmic coordinate system. "Time" in the logarithmic diagram starts at the moment the first death from "other causes" takes place. It is shown in Figure 8 that a straight line roughly approximates the plot. This is an indication that the intensity of dying from "other causes" may be considered approximately Weibull.

All these conclusions should of course not be taken too literally. The point, so far, is that these simple plots give quite a lot of information about the structure in the given data. Such information may be used for suggesting various hypotheses.

We will now consider how to test some of the hypotheses that are suggested from the plots. We will start by showing how the pairwise comparisons of the Nelson plots may be made precise. It is shown in Aalen (1978b) that reasonable non-parametric tests for comparison of two Nelson plots, say $\hat{\beta}^1(t)$ and $\hat{\beta}^2(t)$ may be written in the following way. Let $S_1 < S_2 < \ldots$ be the successive times at which jumps occur in either $\hat{\beta}^1(t)$ or $\hat{\beta}^2(t)$, and let $\Delta\hat{\beta}^i(S_j)$ be the sizes of the jumps. Then a test statistic may be written as

$$(2.2) \qquad T = \sum_j W_j \left(\Delta\hat{\beta}^1(S_j) - \Delta\hat{\beta}^2(S_j)\right).$$

Where each W_j is a weight which may be chosen as a function of what has been observed before the time S_j. Clearly, T is a rather direct and reasonable measure of comparison of the two plots. By choosing the weights in various ways one gets a whole family of possible measures. A general expression of the variance of T is given in Aalen (1978b) where it is also shown that T can under certain circumstances be regarded as approximately normally distributed.

It turns out that most nonparametric tests that have been suggested for censored data can be represented in the above way by choosing the W's appropriately. (In the context of competing risks one can think of the causes of death which are not of interest for the analysis at the moment as corresponding to censoring). Let $Y^1(t)$ an $Y^2(t)$ be the numbers at risk at time t corresponding to the $\beta^1(t)$ and $\beta^2(t)$ respectively.

Then the well known Gehan (or Breslow) test arises by choosing

$$(2.3) \qquad W_j = Y^1(S_j)\ Y^2(S_j).$$

The Savage (or logrank, Mantel-Haenzel, Cox) test arises by choosing

$$(2.4) \qquad W_j = \frac{Y^1(S_j)\ Y^2(S_j)}{Y^1(S_j) + Y^2(S_j)}.$$

As an illustration we will compute the Gehan statistic for the difference between the two plots in Figure 6. By inserting (2.3) into (2.2) and considering the definition (2.1) we get

$$T = \sum_j [Y^2(S_j) I_j - Y^1(S_j) J_j]$$

where $I_j = 1$ if the jump at time S_j occurs in $\hat{\beta}^1(t)$ and $I_j = 0$ otherwise. J_j is defined similarly with respect to $\hat{\beta}^2$.

Hence, T is computed by the following simple algorithm. Whenever a jump occurs in process 1, one counts the number at risk for process 2, and then add these numbers up. Whenever a jump occurs in process 2, one substracts the number at risk for process 1.

From the general theory it follows that the variance of T is given by

$$V = \sum_j Y^1(S_j)\ Y^2(S_j) \ .$$

Performing the computations for the plots in figure 5 we get

$$T = 1326$$

$$V = 145632$$

Hence, the standardized test statistic $T/\sqrt{V} = 3.47$. Comparing this with the standard normal distribution one finds a p-value of less than 0.001. Hence, the difference observed in Figure 6 is strongly significant.

Most of the Nelson plots in Figure 2 and 3 seem to be convex upwards, implying an increasing death intensity (mortality rate). This feature of the plots can be tested by means of a test suggested in Section 3.4 of Aalen and Hoem (1978). (In fact, Richard Gill has pointed out certain difficulties with the theory of that part of our paper. However, those difficulties can probably be resolved). I will not describe the test here, just indicate its application to our data. As an example, we will test whether the apparent upwards convexity of the Nelson plot for "other causes" in Figure 2 is significant. We will look at the period from 200 to 700 days. The cumulative total time on test statistic in Aalen and Hoem (1978, Section 3.4) assumes the value 18.45.

The value of the normalized version mentioned on p. 99 of the same paper is equal to 2.18. This is to be compared with a standard normal distribution, giving a p-value of 1.5 %.

Finally, it should be mentioned that one can apply Kolmogorov-Smirnov type procedures. One way of doing this is outlined in Section 8 of Aalen (1976). Other possibilities are studied in Fleming and Harrington (1981) and Fleming et. al. (1980) where extensive discussions are given together with a practical example. This work is partly based on that of the present author, and hence constitutes an example of the usefulness of the martingale approach.

Table 1

From: D.G. Hoel and H.E. Walburg, Jr.: Statistical analysis of survival experiments. J.Natl. Cancer Inst. 49: 361-372, 1972.

Necropsy data for RFM male mice exposed to 300 R X radiation at 5-6 weeks of age

Cause of death	Individual ages at death (days)
	A. Conventional mice (95)
Thymic lymphoma (23%)	159, 189, 191, 198, 200, 207, 220, 235, 245, 250, 256, 261, 265, 266, 280, 343, 356, 383, 403, 414, 428, 432
Reticulum cell sarcoma (40%)	317, 318, 399, 495, 525, 536, 549, 552, 554, 557, 558, 571, 586, 594, 596, 605, 12, 621, 628, 631, 636, 643, 647, 648, 649, 661, 663, 666, 670, 695, 697, 700, 705, 712, 713, 738, 748, 753
Other causes (37%)	163, 179, 206, 222, 228, 249, 252, 282, 324, 333, 341, 366, 385, 407, 420, 431, 441, 461, 462, 482, 517, 517, 524, 564, 567, 586, 619, 620, 621, 622, 647, 651, 686, 761, 763
	B. Germfree mice (82)
Thymic lymphoma (35%)	158, 192, 193, 194, 195, 202, 212, 215, 229, 230, 237, 240, 244, 247, 259, 300, 301, 321, 337, 415, 434, 444, 485, 496, 529, 537, 624, 707, 800
Reticulum cell sarcoma (18%)	430, 590, 606, 638, 655, 679, 691, 693, 696, 747, 752, 760, 778, 821, 986
Other causes (47%)	136, 246, 255, 376, 421, 565, 616, 617, 652, 655, 658, 660, 662, 675, 681, 734, 736, 737, 757, 769, 777, 800, 807, 825, 855, 857, 864, 868, 870, 870, 873, 882, 895, 910, 934, 942, 1015, 1019

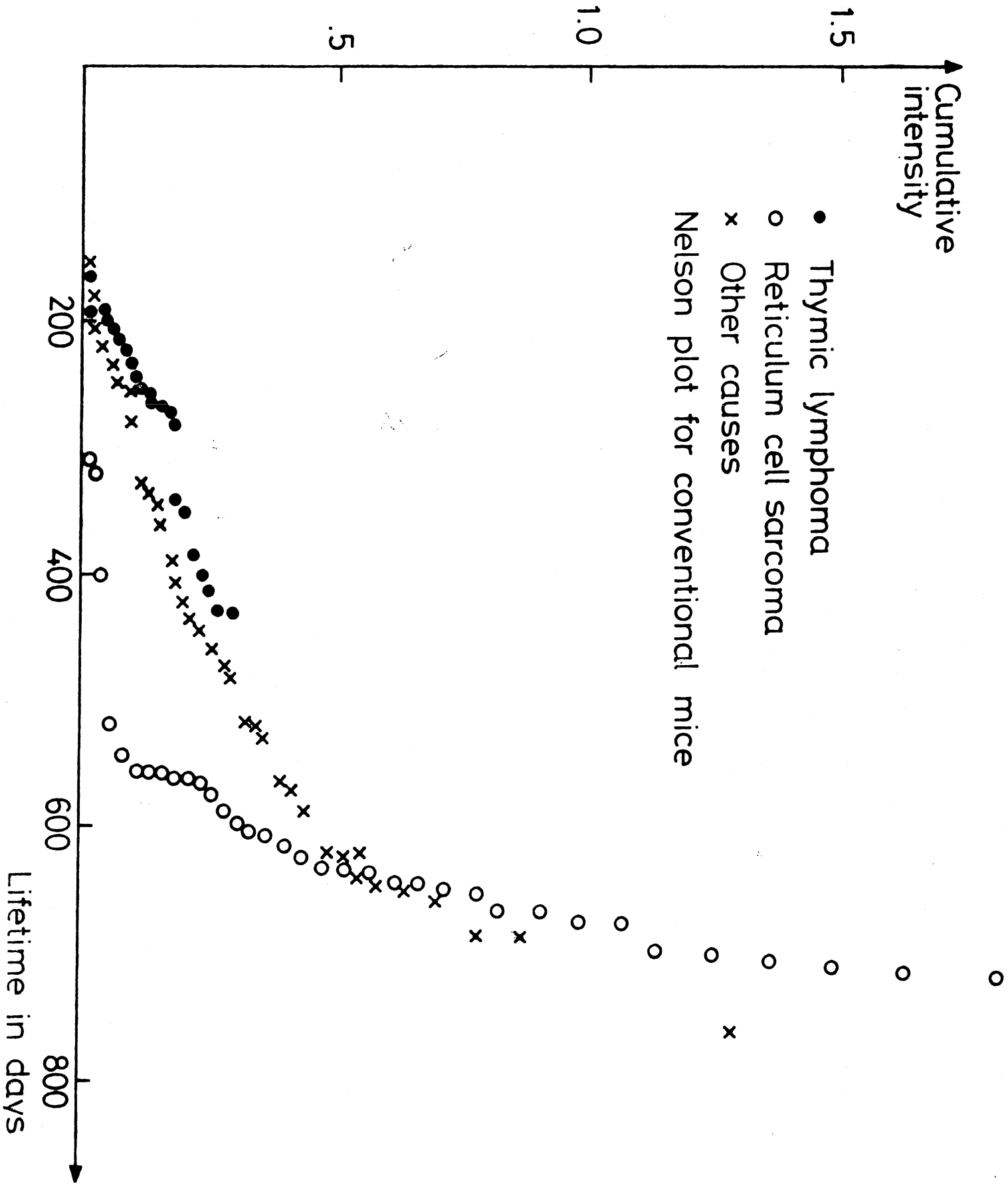


Figure 2. Estimated cumulative death intensities for conventional mice.

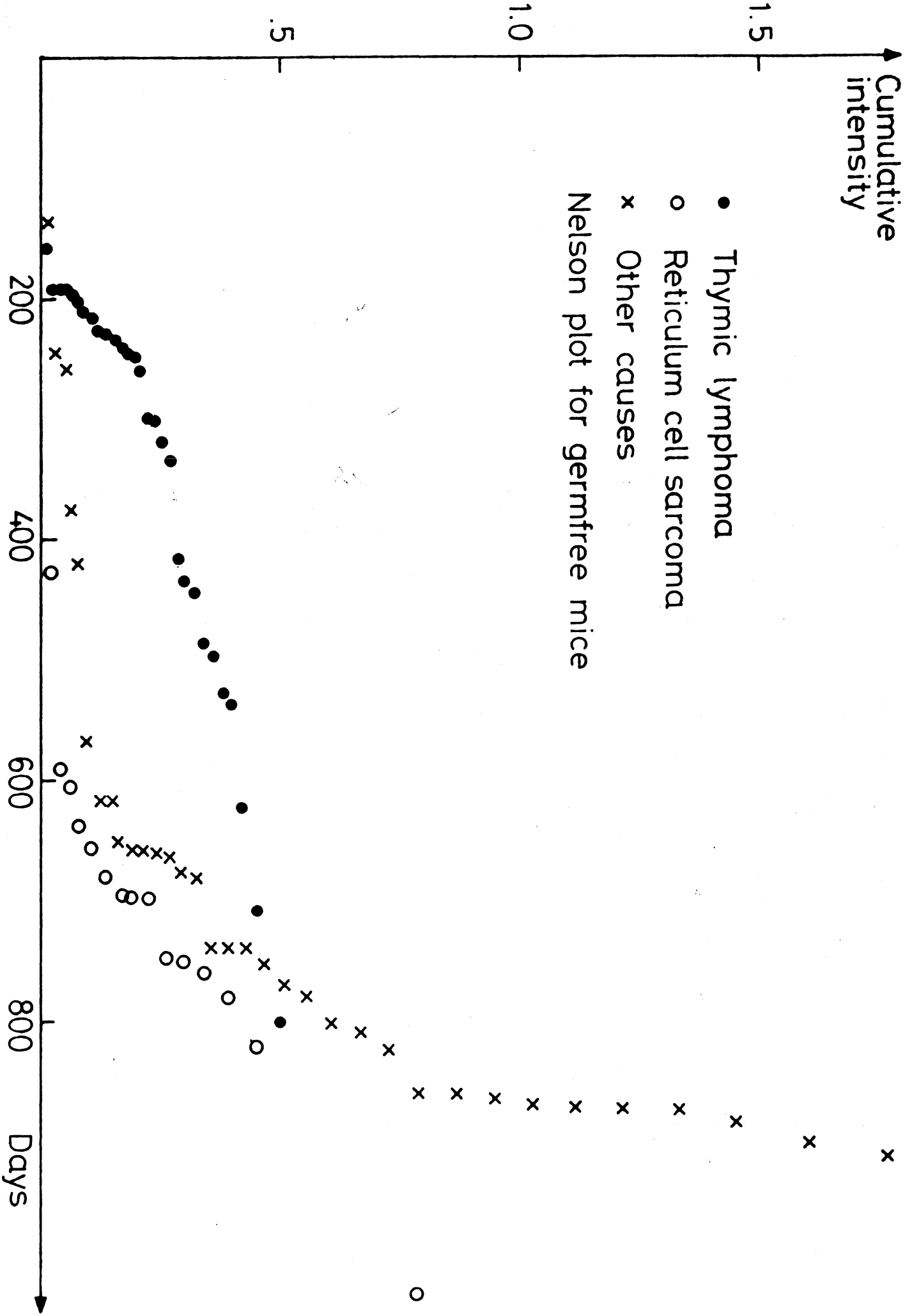


Figure 3. Estimated cumulative death intensities for germfree mice.

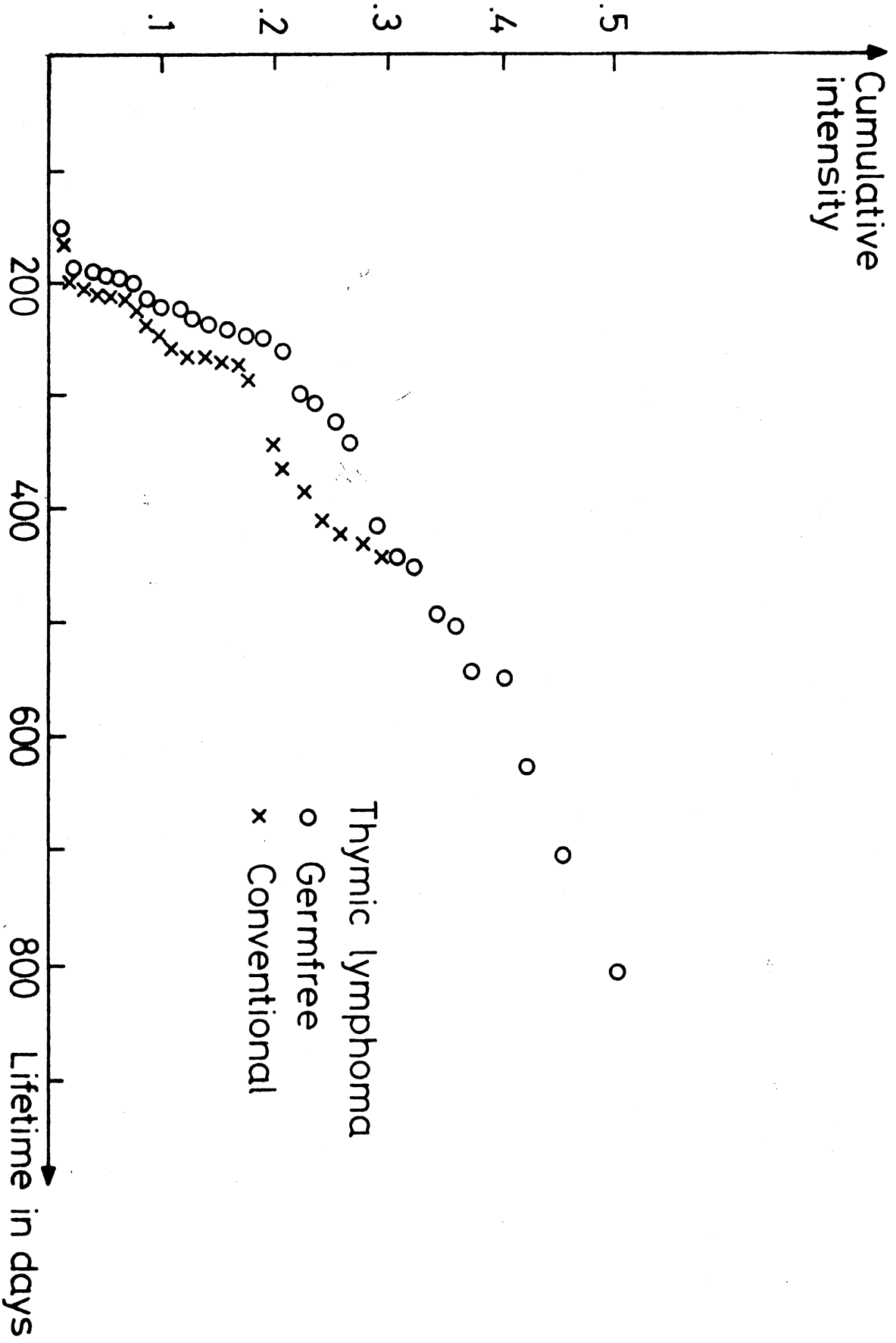


Figure 4. Estimated cumulative death intensities for thymic lymphoma among germfree and conventional mice respectively.

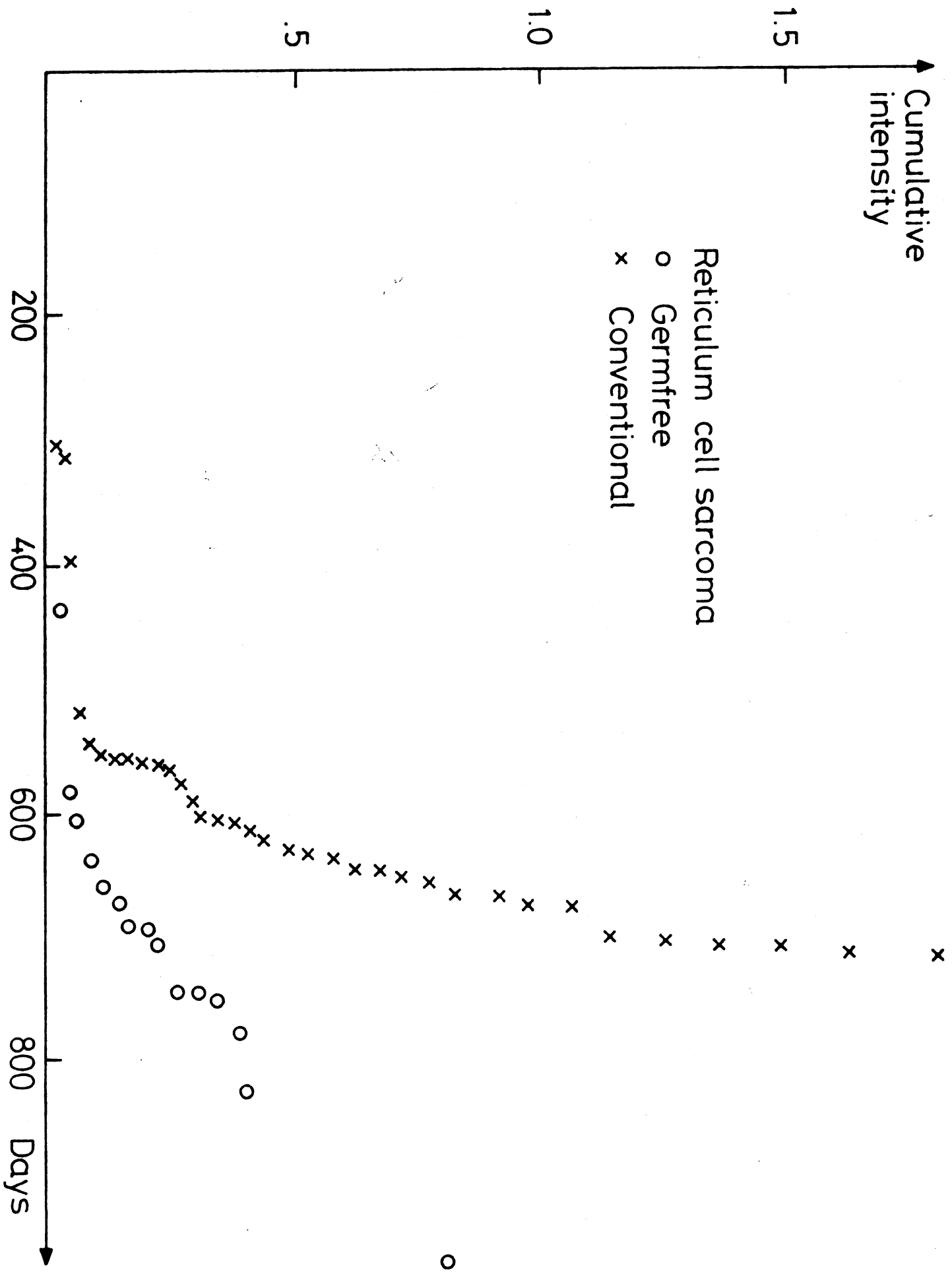


Figure 5. Estimated cumulative death intensities for reticulum cell sarcoma among germfree and conventional mice respectively.

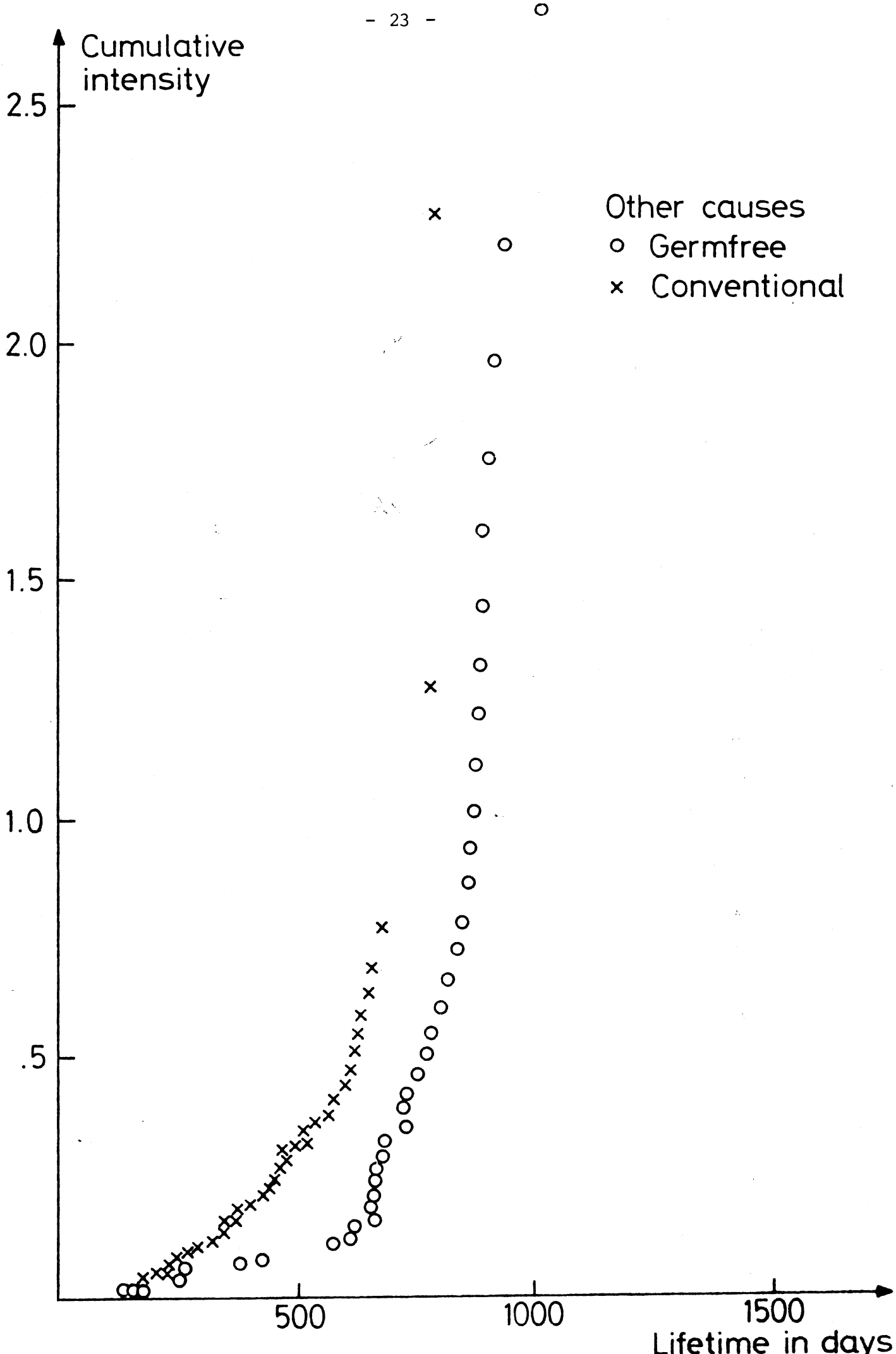


Figure 6. Estimated cumulative death intensities for "other causes".

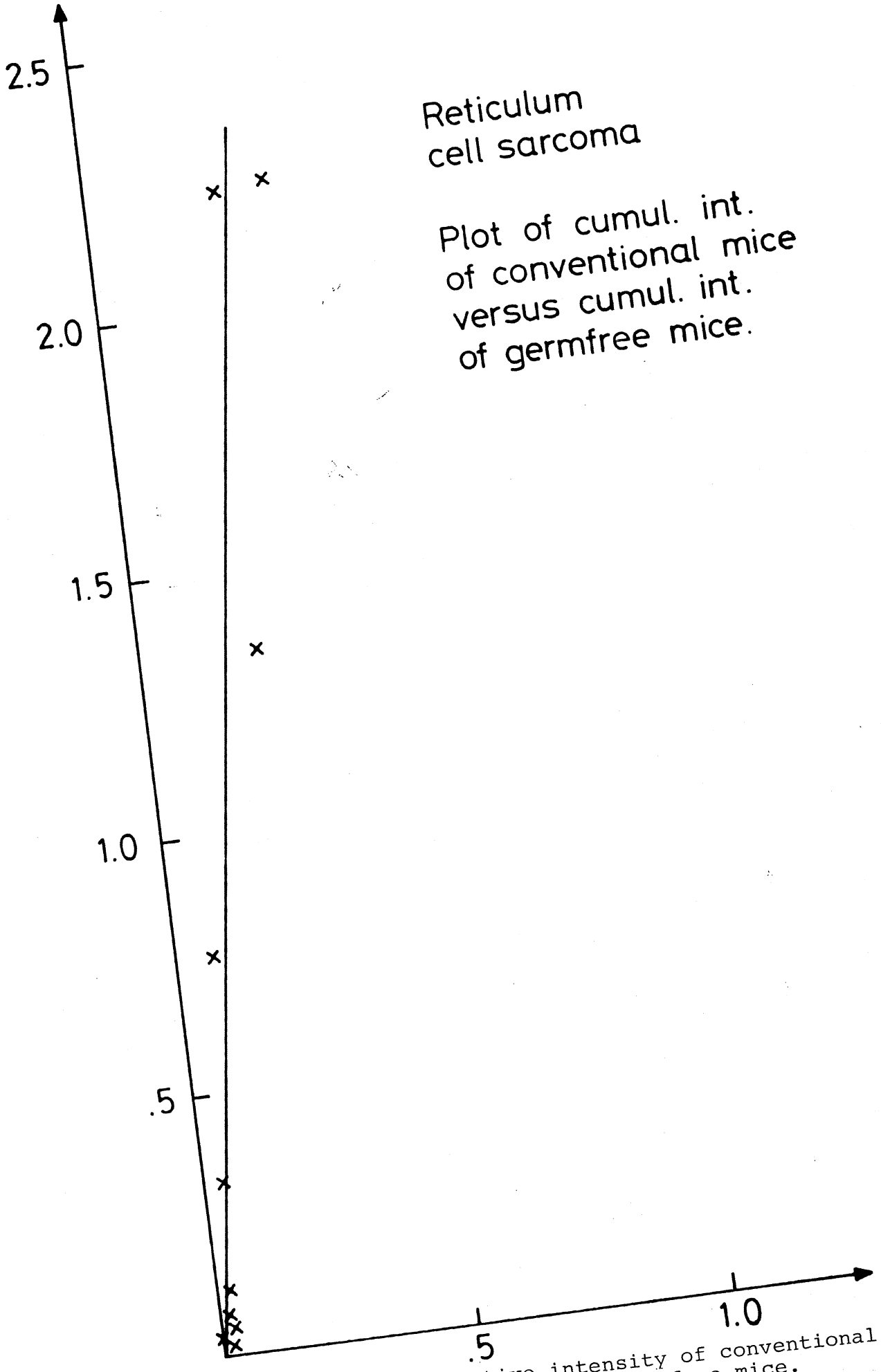


Figure 7. Probit plot of cumulative intensity of conventional mice versus cumulative intensity of germfree mice.

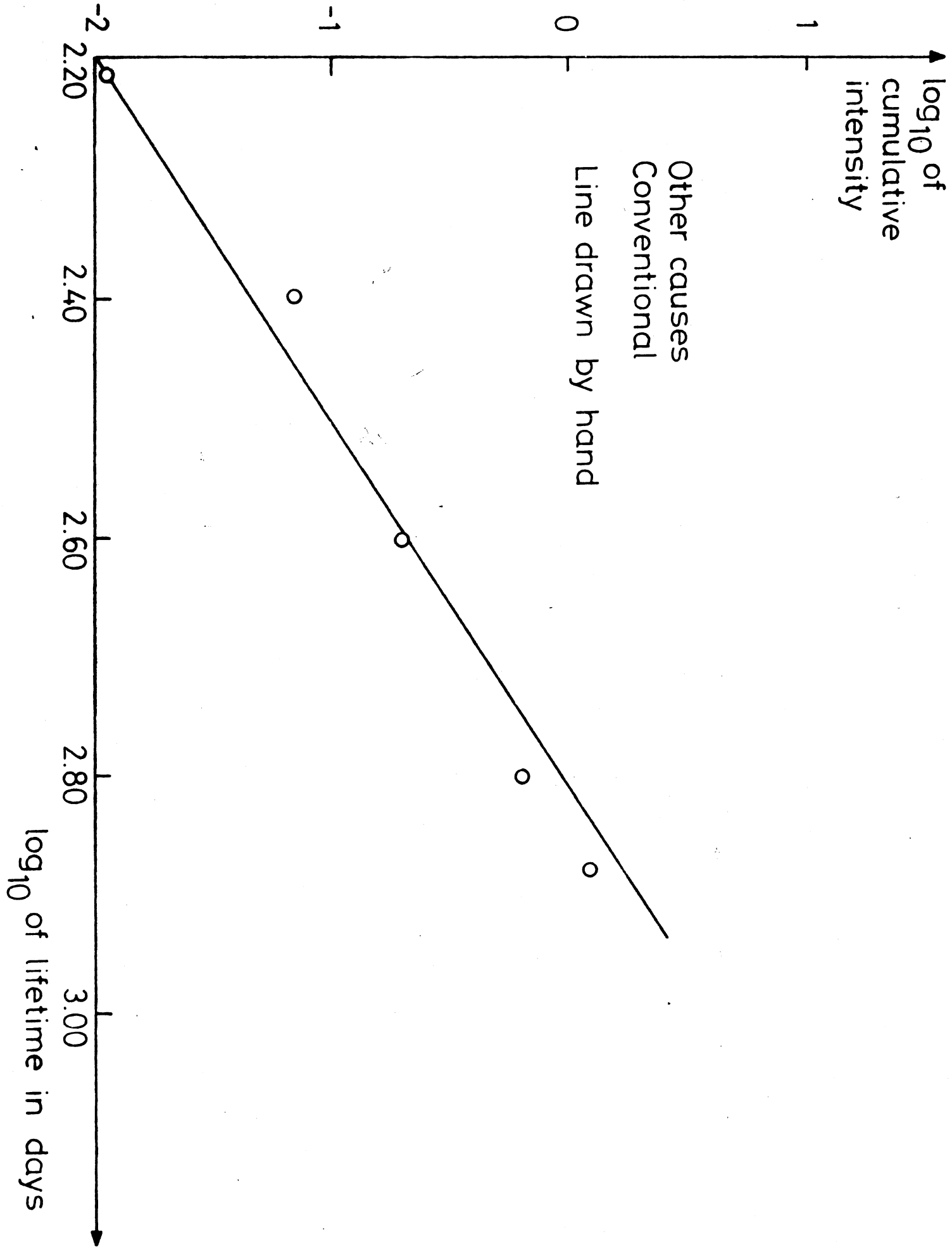


Figure 8. Estimated cum. death intensity for "other causes" among conv. mice. Both axes are in logarithmic scale. The line is drawn by hand.

2C . Generalized Kaplan-Meier estimates when the risks are independent.

When the risks can be assumed independent, then Kaplan-Meier plots, as used by Hoel and Walburg (1972), may give interesting information. In this section we will show the use of a generalized Kaplan-Meier estimate suggested in Aalen (1978a). The idea is the following: We assume that one of the causes of death could be eliminated, and we then ask what pattern would be observed as regards deaths from the remaining causes. This sort of question has an old history. Posed as a mathematical question it originated with Daniel Bernoulli who in 1760 asked what mortality pattern would be observed if smallpox were eradicated.

A Kaplan-Meier plot answers this question as regards the total mortality. We will consider the more general question of the probability of dying from each specific of the remaining causes. If one shall be able to answer such a question from mortality data only, then the assumption is essential that the risk being eliminated is independent of the others. This fact has been discussed a lot in the literature, see for instance David and Moeschberger (1978).

We still assume that there are k causes of death (risks). We consider cause no. k as being eliminated (i.e. the mortality is put equal to 0) and we want to estimate the new probability, $P_i(t,k)$, of dying from cause no. i during the time interval $(0,t)$. We use the notation in (2.1). The generalized Kaplan-Meier estimate is given by the following formula:

$$(2.5)\quad \hat{P}_i(t,k) = \sum_{T_{ij} \le t} \Big[\prod_{\substack{T_{mn} < T_{ij} \\ m<k}} \Big(1 - \frac{1}{Y(T_{mn})}\Big) \Big] \frac{1}{Y(T_{ij})}$$

An estimate of the variance is given in section 5 of Aalen (1978 a). In section 4 of that paper it is shown that the $\hat{P}_i(t,k)$ may be considered approximately normally distributed under certain assumptions.

As an example we consider the data of Hoel and Walburg, asking what would be the probabilities of dying from reticulum cell sarcoma and "other causes", respectively, among the conventional mice, if thymic lymphoma was eliminated. The estimated probabilities computed by means of (2.5) are given in Table 2.

We will take the opportunity in this section to illustrate also the use of the results in Aalen and Johansen (1978). That paper is concerned with estimating the transition probabilities of a Markov chain when one has censored observations. A competing risks model is a particular case of a Markov chain. Eliminating one risk in the fashion done before is equivalent to regarding this risk as censoring. Hence the results of Aalen and Johansen (1978) may be applied.

We will consider the same example as before. Eliminating thymic lymphoma, the remaining model can be described as a Markov chain on the state space shown in Figure 9.

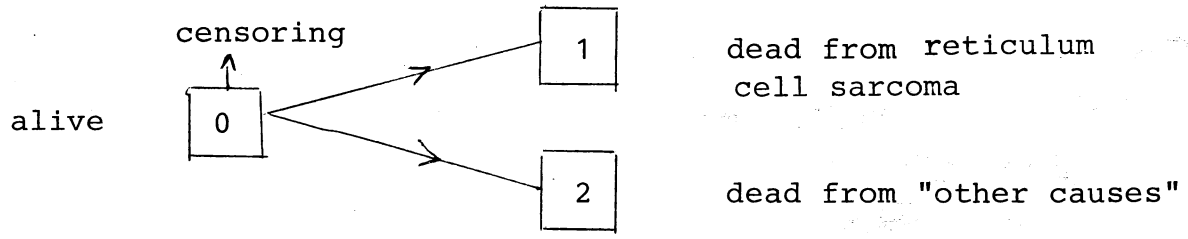


Fig. 9. The state space of a competing risks model with thymic lymphoma being eliminated.

The transition probability matrix $P(t)$ is given by

$$\begin{array}{c} \\ 0 \\ 1 \\ 2 \end{array} \begin{array}{c} \begin{array}{ccc} 0 & 1 & 2 \end{array} \\ \begin{pmatrix} 1-P_1(t,3) - P_2(t,3) & P_1(t,3) & P_2(t,3) \\ 0 & 1 & 0 \\ 0 & 0 & 1 \end{pmatrix} \end{array}$$

The matrix is estimated in the following way. Whenever a transition takes place from state 0 to state 1 (at time T_{1j}, say) one computes the following matrix:

$$(2.6) \qquad \begin{pmatrix} 1 - \frac{1}{Y(T_{1j})} & \frac{1}{Y(T_{1j})} & 0 \\ 0 & 1 & 0 \\ 0 & 0 & 1 \end{pmatrix}$$

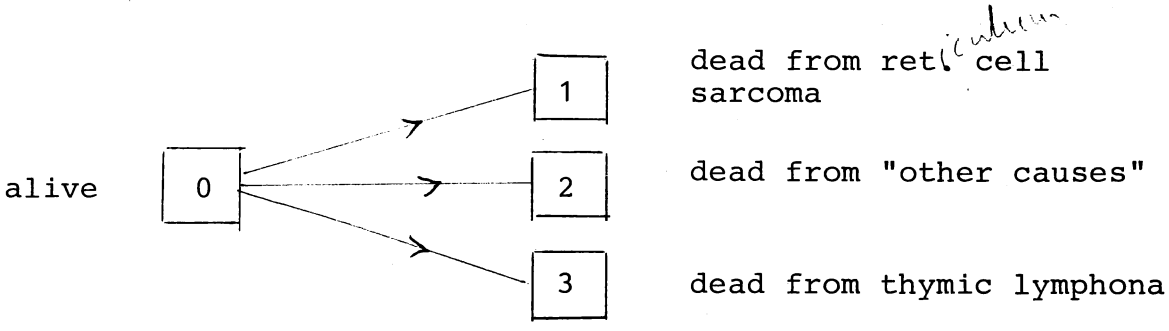
If the transition takes place from state 0 to state 2 one computes the following matrix:

$$(2.7) \qquad \begin{pmatrix} 1 - \frac{1}{Y(T_{2j})} & 0 & \frac{1}{Y(T_{2j})} \\ 0 & 1 & 0 \\ 0 & 0 & 1 \end{pmatrix}$$

One then multiplies together all matrices of the form (2.6) and (2.7) for $T_{1j} \leq t$ and $T_{2j} \leq t$. The order of the matrices in the multiplication shall follow the chronological order of the T's. The result is the estimate $\hat{P}(t)$ of $P(t)$.

This procedure produces the same result as (2.5). It does however have a more general scope since it is applicable to much more general Markov chains than competing risks models. Also, the procedure should have a simple intuitive appeal.

The above procedures can be easily modified to cover the following situation. Instead of eliminating entirely one of the risks, one might assume that the death intensity of this risk was reduced (or increased) by a certain amount. If for instance the intensity of dying from cause no. i was reduced by 50 %, what would be the observed mortality pattern ? This situation can be described by the following Markov model, with the intensity of transition to state no. 3 being halved. The state space is shown in Figure 10.



(This figure heading belongs to the figure on the bottom of page 29).

Fig. 10. The state space of the competing risks model (with the death intensity of thymic lymphoma being halved).

The task, now is to estimate the transition probability matrix $P^*(t)$ given by

$$\begin{array}{c} \\ 0 \\ 1 \\ 2 \\ 3 \end{array} \begin{array}{c} \begin{array}{cccc} 0 & 1 & 2 & 3 \end{array} \\ \begin{pmatrix} 1-P_1^*(t)-P_2^*(t)-P_3(t) & P_1^*(t) & P_1^*(t) & P_3^*(t) \\ 0 & 1 & 0 & 0 \\ 0 & 0 & 1 & 0 \\ 0 & 0 & 0 & 1 \end{pmatrix} \end{array}$$

where $P_i^*(t)$ denotes the probability of dying from cause no. i during the age interval (0,t) when the death intensity for thymic lymphoma is halved.

A modification of the derivations in Aalen and Johansen (1978) gives the following procedure for estimating $P^*(t)$. One should multiply in chronological order all matrices of the following kind (for $T_{ij} \leq t$):

(i) When a transition takes place from state 0 to state 1 (at time T_{1j}), use the following matrix:

$$\begin{pmatrix} 1 - \frac{1}{Y(T_{1j})} & \frac{1}{Y(T_{1j})} & 0 & 0 \\ 0 & 1 & 0 & 0 \\ 0 & 0 & 1 & 0 \\ 0 & 0 & 0 & 1 \end{pmatrix}$$

(ii) When a transition takes place from state 0 to state 2 (at time T_{2j}) use the following matrix:

$$\begin{pmatrix} 1 - \frac{1}{Y(T_{2j})} & 0 & \frac{1}{Y(T_{2j})} & 0 \\ 0 & 1 & 0 & 0 \\ 0 & 0 & 1 & 0 \\ 0 & 0 & 0 & 1 \end{pmatrix}$$

(iii) When a transition takes place from state 0 to state 3 (at time T_{3j}) use the following matrix:

$$\begin{pmatrix} 1 - \frac{1}{2Y(T_{3j})} & 0 & 0 & \frac{1}{2Y(T_{3j})} \\ 0 & 1 & 0 & 0 \\ 0 & 0 & 1 & 0 \\ 0 & 0 & 0 & 1 \end{pmatrix}$$

The resulting estimates of $P_1^*(t)$, $P_2^*(t)$ and $P_3^*(t)$ are given in Table 2.

Table 2

Estimated partial probabilities of dying from the respective causes. Data from Hoel and Walburg (1972).

Age in days	Thymic lymphoma is eliminated		The death intensity of thymic lymphoma is halved		
	Ret.cell. sarc. $P_1(t,3)$	Other causes $P_2(t,3)$	Ret.cell. sarc. $P_1^*(t)$	Other causes $P_2^*(t)$	Thymic lymph. $P_3^*(t)$
50	0.00	0.00	0.00	0.00	0.00
100	0.00	0.00	0.00	0.00	0.00
150	0.00	0.00	0.00	0.00	0.00
200	0.00	0.02	0.00	0.02	0.03
250	0.00	0.07	0.00	0.06	0.05
300	0.00	0.09	0.00	0.09	0.08
350	0.03	0.13	0.02	0.12	0.09
400	0.04	0.16	0.03	0.15	0.10
450	0.04	0.21	0.03	0.19	0.12
500	0.05	0.25	0.05	0.23	0.12
550	0.10	0.30	0.08	0.27	0.12
600	0.21	0.34	0.18	0.30	0.12
650	0.35	0.41	0.30	0.36	0.12
700	0.45	0.44	0.39	0.39	0.12
750	0.52	0.44	0.45	0.39	0.12
800	0.53	0.47	0.46	0.41	0.12

2D. Data from a study of the IUD. Cox residuals. Mixing of the intensities.

We will conclude this presentation of methods for competing risks by giving an example where the Nelson plots suggest a simple parametric model. The example also illustrates the usefulness of considering mixing distributions on the intensities.

Peterson (1975) presents data on the experiences of a sample of 100 women with an experimental intrauterine contraceptive device (IUD). The women were followed until one of three events occurred: Expulsion of IUD, removal of IUD due to medical or personal reasons, planned removal of IUD. We are going to consider the two former events which both have a considerable amount of randomness in them. The relevant data, together with estimated cumulative intensities and their standard deviations are given in Table 3. We will analyze the data in a way which is different from that of Peterson, but in our opinion more illuminating.

Figure 11 shows the Nelson plot for expulsions and unplanned removals respectively. Clearly the intensity of unplanned removals remains more or less constant throughout the time period, while the intensity of expulsions, after being initially above that of removals, drops sharply after a short time. (This seems to be a common phenomenon, see Aalen (1972)).

We will now take a closer look at the functional form with which the intensities may be approximated.

Assuming first a constant intensity of unplanned removal, this may be estimated by the usual occurrence/exposure rate, i.e. the total number of unplanned removals is divided by the sum of observed individual times with IUD in situ. This gives a value of 8.98×10^{-4} pr day. The corresponding straight-lined cumulative intensity is drawn in Figure 11, and is seen to approximate well to the Nelson plot. This indicates that unplanned removals follow, more or less, a Poisson process. In other words, an unplanned removal is, considered on a group basis, more or less a haphazard event, becoming neither more nor less likely as time goes on. (Of course, it should be remembered that we only have data for about a year).

In order to check whether the deviation of the Nelson plot from the straight line can be explained by random variation, we will compute a set of residuals as suggested by Cox (1979). Let S_1 be the total time at risk up to the fourth removal (i.e. S_1 is the sum of the times during this period that each individual has had the IUD in situ). Let S_2 be the total time at risk between the fourth and the eight removal, S_3 between the eight and the twelfth, and so on up to S_6.

Define

$$Z_j = -\log(\tfrac{1}{4} S_j) - \frac{3}{23} \qquad j = 1, \ldots, 6$$

where log denotes natural logarithm. If the intensity, say ρ, of removal is constant, then $Z_1, \ldots, Z_6$ is approximately

independent random variables with expectation log ρ and standard deviation 0.53. Inserting our estimate of ρ we get log ρ = -7.02. Some computation gives us the following values for the Z's:

$$Z_1 = -6.93, \qquad Z_2 = -7.16, \qquad Z_3 = -7.44$$

$$Z_4 = -6.71, \qquad Z_5 = -7.47, \qquad Z_6 = -6.35$$

We see that the maximal difference between any pair of Z's is 1.12. This is a little more than two standard deviations, and therefore no more than one should expect to get because of random variation. Hence, there is for unplanned removals no significant deviation from constant intensity.

We will note at this point a connection between the above approach and the results of Aalen and Hoem (1978). In that paper one considers a transformation of the time axis, the new time being measured in units of total time at risk (this concept being defined as above). This means that "time" runs fast when a large number of people are at risk, and more slowly when fewer people are at risk. It is shown that when this time transformation is performed, then the process of events can be considered a Poisson process. In our example, for instance, the occurrence of unplanned removals and of expulsions would both constitute Poisson-processes.

The above method of Cox simply consists in applying standard methods for Poisson-processes to this time transformed process.

The contribution of Aalen and Hoem (1978) in this context, is to give a thorough justification for the validity of this time transformation in a general setting. In addition it follows from results in that paper that, for instance, the Poisson-process of unplanned removals, and that of expulsions in our example, will be independent of each other. It follows that if Cox residuals were computed also for expulsions, it would be independent of the Cox residuals for unplanned removals. This may be important for application of the residuals.

Considering now expulsions, we will apply a method which gave good results in a similar problem studied in Aalen (1972, Section 5A). We will assume that for each individual there is a constant intensity of expulsion throughout the period considered. The size of this intensity, however, varies in the population, some women being at high risk with respect to expulsion, and others being at low risk. To be more specific, we will assume that the intensity varies according to a gamma distribution, with density:

$$f(\lambda) = \frac{\beta^{\alpha}}{\Gamma(\alpha)} \lambda^{\alpha-1} e^{-\beta\lambda}, \quad \lambda > 0$$

Here λ is the intensity, and α and β are the parameters of the distribution. Even if the individual intensity is constant, the observed intensity of expulsion in a group of individuals will not be constant. This is because the high risk individuals will tend to leave the risk group (due to expulsion) pretty soon, while those in the low risk group will tend to remain. Hence the group intensity will necessarily decrease with time. Under the above assumption it is a standard result that the

group intensity will be

$$\mu(t) = \frac{\alpha}{\beta+t}$$

where t is time from insertion of IUD. The corresponding cumulative intensity is given by

$$\int_0^t \mu(s)ds = \alpha \log(1+\frac{t}{\beta})$$

(log meaning natural logarithm).

The question, now, is whether α and β may be chosen so that this function fits well to the Nelson plot for expulsions in Figure 11. Such a fitting can of course be done in a proper mathematical fashion, but we have contented ourselves with a trial and error approach. This produces the values $\alpha = 0.035$, $\beta = 7$, that is

$$\int_0^t \mu(s)ts = 0.035 \log(1 + \frac{t}{7})$$

This curve is drawn in Figure 11and seen to approximate well to the Nelson plot.

The fact that we get a reasonable result, does, of course, not prove that our detailed mathematical model is a true description of what is going on. Many other models would have produced the same $\mu(t)$. On the other hand, the model we have presented is a simple and standard one, and hence it is interesting that it produces a good result. A similarly good fit to another set of data was presented in Aalen (1972, p. 53).

Table 3

IUD-data from A.V. Peterson (1975).

Expulsions

Time in days since insertion of IUD	No. at risk	Estimated cumulative intensity	Stand.dev. of est. cum. int.
2	100	0.010	0.010
8	99	0.020	0.014
10	98	0.030	0.017
25	95	0.041	0.020
28	93	0.052	0.023
28	92	0.063	0.026
32	91	0.074	0.028
63	88	0.085	0.030
86	86	0.097	0.032
159	80	0.109	0.035
354	48	0.130	0.040

(The table continues on the next page).

Removals (unplanned)

Time in days since insertion of IUD	No. at risk	Estimated cumulative intensity	Stand. dev. of est. cum. int.
14	97	0.010	0.010
21	96	0.021	0.015
27	94	0.031	0.018
40	90	0.042	0.021
42	89	0.054	0.024
83	87	0.065	0.027
86	85	0.077	0.029
92	84	0.089	0.031
110	83	0.101	0.034
147	82	0.113	0.036
148	81	0.125	0.038
165	79	0.138	0.040
166	78	0.151	0.042
178	77	0.164	0.044
183	76	0.177	0.046
203	75	0.190	0.048
207	74	0.204	0.050
272	73	0.218	0.051
272	72	0.232	0.053
288	71	0.246	0.055
288	70	0.260	0.057
288	69	0.274	0.059
297	68	0.289	0.061
318	67	0.304	0.062
331	64	0.320	0.064
376	21	0.367	0.080

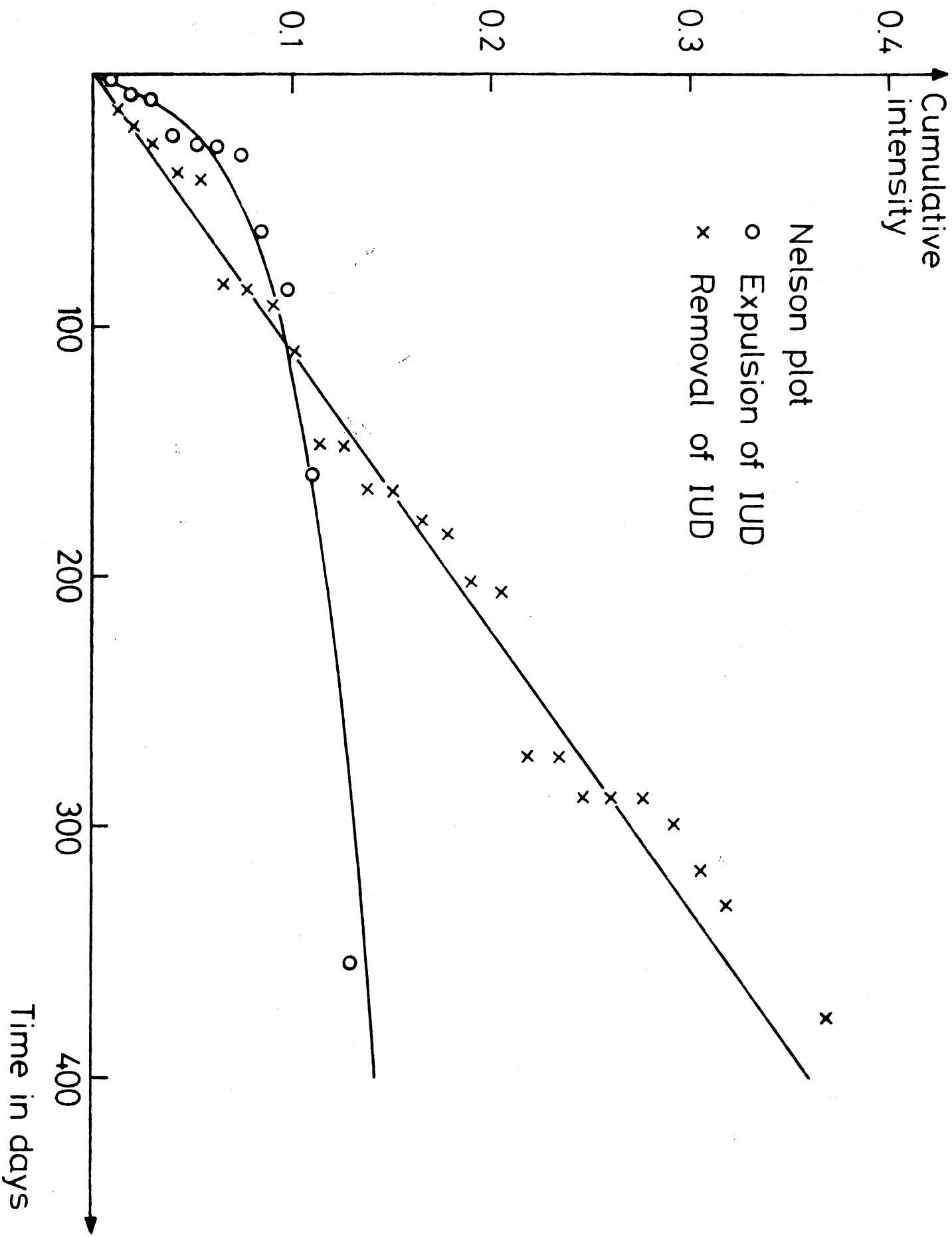


Figure 11. Estimated cum. intensities for expulsion and unplanned removal of IUD. The curves are fitted as explained in the text.

3. A BIRTH AND DEATH PROCESS

We will consider a population undergoing a simple birth and and death process (see for instance Karlin (1966)). Let X(t) be the population size at time t, and let $\lambda(t)$ and $\mu(t)$ denote the time-dependent intensities of an individual giving birth to a new individual or dying. The process B(t) counts the number of births that occur in the population (i.e. B(t) increases by 1 each time a birth happens), while D(t) counts the deaths occurring. The intensity processes of B(t) and D(t) are $\lambda(t)\ X(t)$ and $\mu(t)\ X(t)$, and hence the situation falls within the general framwork of Aalen (1978b). This means that the methods discussed for competing risks may be extended to cover analysis of our birth and death process.

Keiding (1977) analyzes a set of observations of births and deaths in a baboon troop over a year. The object of the study is to find out whether the observations fit well with a simple birth and death process with constant $\lambda(t)$ and $\mu(t)$. Among other methods he applies the extended Nelson plot suggested in Aalen (1978b). We will review briefly part of Keidings results.

Let $T_1 < T_2 < \ldots < T_n$ be the successive times at which the first n births occur. We wish to estimate the cumulative birth intensity

$$\beta(t) = \int_0^t \lambda(s)\, ds.$$

In analogy with the approach used for the competing risks model, we use the following estimate:

$$\hat{\beta}(t) = \sum_{T_i \leq t} \frac{1}{X(T_i-)}$$

where the minus sign means that one shall take the value of $X(t)$ just prior to time T_i.

The estimated cumulative intensity for deaths is, of course, defined analogously. The resulting Nelson plots for Keiding's data are given in Figure 12. (Three emigrations are included among the deaths). It is clear from the figure that births and deaths happen mainly in the latter part of the year, and it does not seem that constant intensities are warranted.

The generalized cumulative total time on test statistic suggested by Aalen and Hoem (1978), section 3.4, may be applied here. For deaths & emigrations this yields the value of 10.23 (n = 15) giving a p-value less than 0.5 %. For births we get the non-significant value of 5.26 (n = 10). Hence the deviation from a constant intensity is statistically significant only for deaths & emigrations. This shows that a stationary birth and death process does not explain the observations well.

One will observe that in Figure 12 the Nelson plot is drawn as a continuous pathwise constant curve. This is a change from earlier when we have presented it as discrete points indicating where the jumps take place. The presentation in Figure 12 is the most correct one, following literally the definition of the Nelson plot. However, when there is a lot of jumps and several Nelson plots in a diagram, it may give a better picture when one uses the pointwise representation.

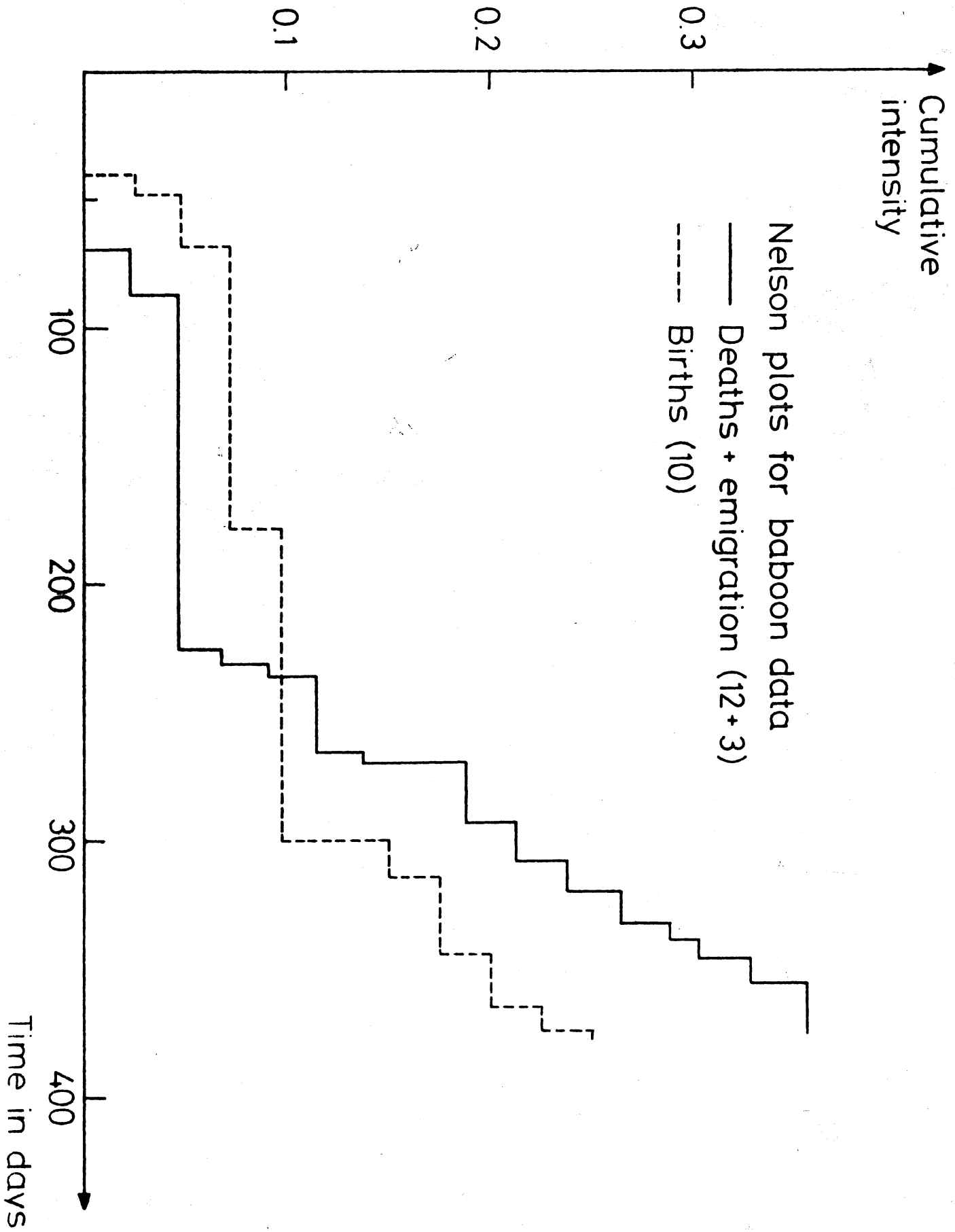


Figure 12. Estimated cumulative birth and death intensities in the baboon troop.

4. AN EXAMPLE FROM THE THEORY OF EPIDEMICS

D.M. Thompson and W.H. Foege have studied an outbreak of smallpox in a closed community of 120 people in southeastern Nigeria. 30 people became ill. The time of first symptoms for each individual was registered. When a person became ill, he was immediately removed from the population. The data are given in Bailey and Thomas (1971), and are quoted in the table below. Becker (1977) analyzes the data from a different point of view.

Times in days of individual outbreaks of smallpox:

0, 13, 20, 22, 25, 25, 25, 26, 30, 35, 38, 40, 40, 42, 42,
47, 50, 51, 55, 55, 56, 57, 58, 60, 60, 61, 66, 66, 71, 76.

We will be interested not in the time of outbreak of disease, but in the time that infection took place. Of course, this can not be observed directly. We know, however, that the incubation period for smallpox is about 12 days. If we therefore subtract 12 days from each of the numbers in the table above, we shall get approximately the times of infection. In fact, if we define time 0 as being the time of the first infection, then the numbers in the table can, on this new scale, be considered as just the times of infection. Each infected person is then, effectively, being left to remain in the population for 12 days after this time, and is then removed. During these 12 days he may infect other people in the community, he is an infective. (This rough procedure was suggested by Steffen Lauritzen).

Define the following quantities:

N(t) - number of persons that have been infected during the time interval (0,t).

I(t) - number of infectives just prior to time t (i.e. number of people that have been infected not more than 12 days prior to time t).

S(t) - number of susceptibles just before time t.

A common epidemic model can be formulated in the following way: The intensity process $\Lambda(t)$ corresponding to the counting process N(t) is decomposed as follows:

$$\Lambda(t) = \alpha(t)\ I(t)\ S(t)$$

This means that the intensity of infection is proportional with the number of infectives and with the number of susceptibles.

This is, of course, quite reasonable. The function $\alpha(t)$ can be considered a measure of the infectiousness of a single infected individual. One sees that this model fits the general framework of the introduction.

Let $T_1<T_2<\ldots$ be the successive times of infection. The cumulative intensity

$$\beta(t) = \int_0^t \alpha(s)\ ds$$

is then estimated by

$$\hat{\beta}(t) = \sum_{T_i \leq t} \frac{1}{I(T_i)S(T_i)}$$

with variance estimated by

$$\sum_{T_i \leq t} \frac{1}{[I(T_i)S(T_i)]^2}$$

The results of the computations are given in Table 4 while the Nelson plot is shown in Figure 13. The plot shows a slight convexity downwards, which would seem to indicate a decreasing $\alpha(t)$. This might be reasonable since one would expect the most susceptible individuals to become ill first, so that the remaining ones would be less susceptible. The question, however, is whether this is a statistically significant tendency.

By the results in Aalen and Hoem (1978) one may perform a time transformation to obtain a Poisson process in a similar manner as was discussed in section 2D. What corresponds to "total time at risk" in this case, will be the process

$$\int_0^t I(s)S(s)\, ds.$$

From the discussion of Section 2D it follows that we can compute Cox type residuals in the following manner. Define

$$S_1 = \int_0^{T_4} I(s)S(s)\, ds,$$

$$S_2 = \int_{T_4}^{T_8} I(s)S(s)\, ds,$$

.

.

.

$$S_7 = \int_{T_{24}}^{T_{28}} I(s)S(s)\, ds.$$

Then the following quantities will be analogous of the Cox residuals:

$$Z_j = -\log\left(\frac{1}{4} S_j\right) - \frac{3}{23} \qquad j = 1, \ldots, 6$$

From our data we get

$$Z_1 = -7.01, \quad Z_2 = -6.87,$$

$$Z_3 = -7.44, \quad Z_4 = -7.46,$$

$$Z_5 = -6.83, \quad Z_6 = -6.69,$$

$$Z_7 = -7.65$$

As in section 2D, the standard deviation under the assumption of constant $\alpha(t)$ should be 0.53. The maximal deviation among the Z's is less than two standard deviations, and hence can very well be explained as random variation.

The cumulative total time on test statistic can also be computed in this case, giving the non-significant value of 13.14.

Hence, the tendency of decreasing α can not be considered significant. Assuming a constant intensity, we may estimate it by the generalized occurrence/exposure rate given in Aalen and Hoem (1978, p. 97). The estimate is given by

$$\hat{\alpha} = \frac{\text{number of outbreaks (minus the first)}}{\int_0^\infty I(s)S(s)\,ds}$$

$$= \frac{29}{36210} = \underline{8.0 \times 10^{-4}}$$

Table 4.

Data and estimated cumulative intensity for the epidemic example.

Time of infection	No. infectives I(t)	No.susceptibles S(t)	Estimated cum.int. $\hat{\beta}(t)$	Stand.dev. $\hat{SD}(\hat{\beta}(t))$
13	1	119	0.008	0.008
20	1	118	0.017	0.012
22	2	117	0.021	0.013
25	3	116	0.024	0.013
25	3	115	0.027	0.013
25	3	114	0.030	0.014
26	6	113	0.031	0.014
30	6	112	0.033	0.014
35	6	111	0.034	0.014
38	6	110	0.036	0.014
40	3	109	0.039	0.014
40	4	108	0.041	0.014
42	5	107	0.043	0.015
42	6	106	0.045	0.015
47	6	105	0.046	0.015
50	6	104	0.048	0.015
51	7	103	0.049	0.015
55	5	102	0.051	0.015
55	6	101	0.053	0.015
56	5	100	0.055	0.015
57	6	99	0.057	0.015
58	7	98	0.058	0.015
60	8	97	0.059	0.015
60	9	96	0.060	0.016
61	9	95	0.062	0.016
66	8	94	0.063	0.016
66	9	93	0.064	0.016
71	6	92	0.066	0.016
76	3	91	0.070	0.016

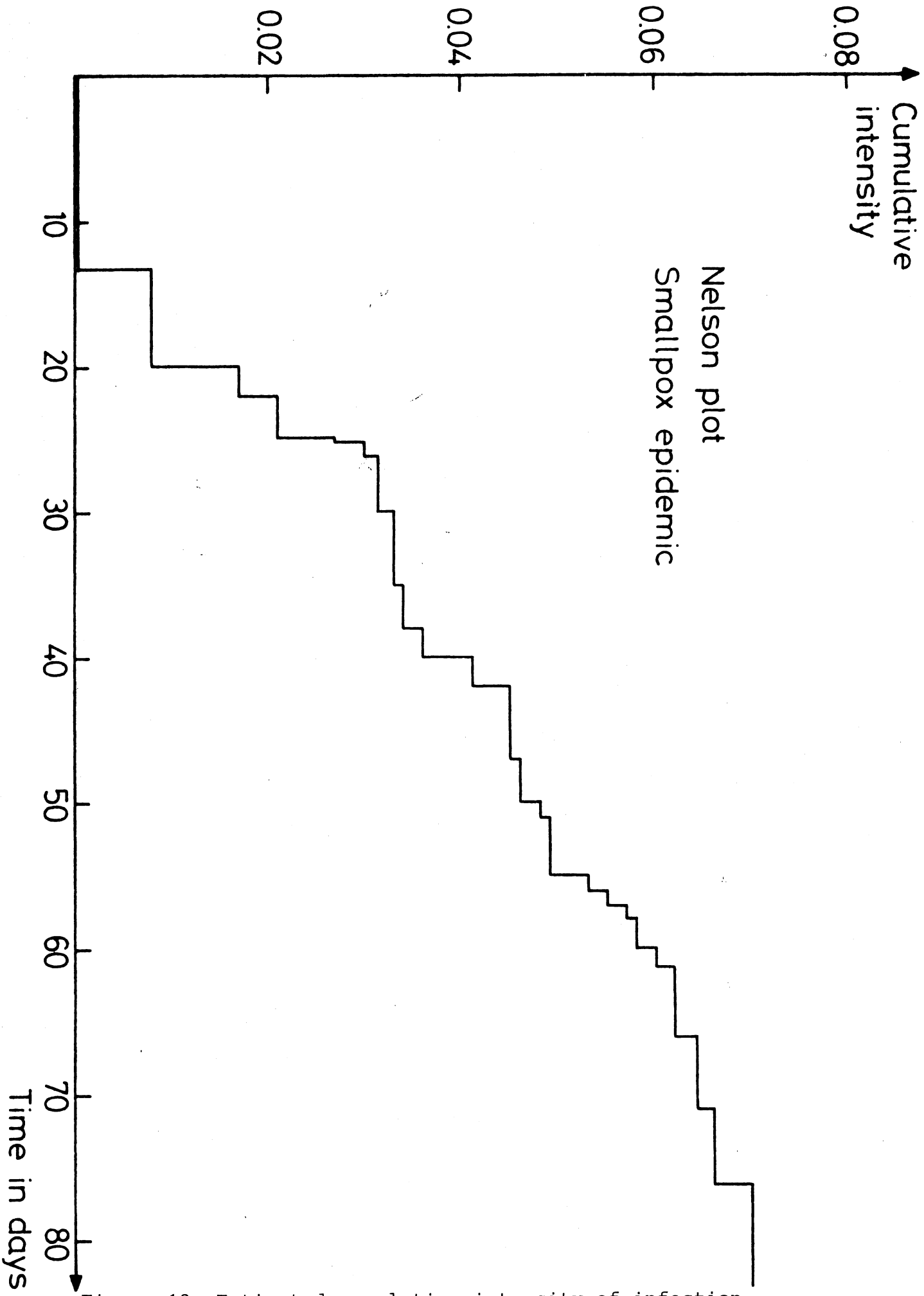


Figure 13. Estimated cumulative intensity of infection for smallpox data.

5. MATING INTENSITIES FOR DROSOPHILA

Christiansen (1971) has carried out experiments concerning the mating intensities of Drosophila. Statistical analysis of these data is discussed in Barndorff-Nielsen (1968), Andersen (1975) and Aalen (1978 b). In this section we will consider a problem which these papers have not taken up. Our presentation will illustrate the use of the k-sample tests for comparison of counting processes developed by Andersen, Borgan, Gill and Keiding (1981). Their theory is also based on the martingale approach to counting processes.

The experiment consists in putting a number of male and female Drosophila together in a chamber. One then observes the times at which matings start. It is assumed that each fly only mates once (at most) during the period of observation. The following is a simple model for the experiment: Assume that just before time t there are M(t) males and F(t) females who have not yet started to mate. Then the intensity for a mating to take place is assumed to equal $\alpha(t)\, M(t)\, F(t)$, where $\alpha(t)$ is the intensity one would have if only a single couple were present.

Since we have another case of the multiplicative intensity model we can compute once more Nelson plots. Let $T_1 < T_2 < \ldots$ be the successive times at which matings start. Then the cumulative intensity

$$\beta(t) = \int_0^t \alpha(s)\, ds$$

is estimated by

$$\hat{\beta}(t) = \sum_{T_i \leq t} \frac{1}{M(T_i)F(T_i)} \quad .$$

We will use data from three of Christiansen's experiments. They were all performed on Drosophila of the "oregon" type. The data are given in Table 5. The Nelson plots (up to the time of 2500 seconds) are shown in Figure 14. One sees that the curves deviate somewhat from each other, that of experiment no. 2 increasing faster than the others. Since all experiments are performed in exactly the same way, and with the same type of flies, one should hope that the deviation can be accounted for by random variation. (It may be mentioned that we have here only picked a part of the data for illustration, so that our actual conclusion should not be taken too seriously).

To study the statistical significance of the deviation observed in the plots, we will apply two of the tests of Andersen et al. (1981). The null hypothesis is that the function $\alpha(t)$ is identical in each experiment.

The first test is a generalization of the Kruskal-Wallis non-parametric test. We will describe briefly the simple computations.

Let $T_{i1} < T_{i2} < \ldots$ be the successive times at which mating start in experiment no. i. Let $M_i(t)$ and $F_i(t)$ be defined as earlier for experiment no. i. Put $Y_i(t) = M_i(t)F_i(t)$ and $\bar{Y}(t) = Y_1(t)+Y_2(t)+Y_3(t)$. The test statistic is based on the quantities

$$Z_i = \sum_{j:T_{ij} \leq T} \bar{Y}(T_{ij}) - \sum_{k,j:T_{kj} \leq T} Y_i(T_{ij}) \qquad i = 1,2,3,$$

where (O,T) is the time interval over which the comparison is made. The variances of these quantities under the null hypothesis, are estimated by

$$V_{ii} = \sum_{k,j:T_{kj} \leq T} [\bar{Y}(T_{kj}) Y_i(T_{kj}) - Y_i(T_{kj})^2]$$

while the covariances are estimated by

$$V_{i\ell} = - \sum_{k,j:T_{kj} \leq T} Y_i(T_{kj}) Y_\ell(T_{kj})$$

Let $\underset{\sim}{Z}$ be the vector of Z's and $\underset{\sim}{V}$ the matrix of V's. Then the test statistic is given by

$$D = \underset{\sim}{Z}^T \underset{\sim}{V} \underset{\sim}{Z}$$

(where the superscript T means "transpose"). The distribution of D under the null hypothesis is chi-squared with two degrees of freedom.

In our example the statistic D assumes the value 4.65 which gives a p-value of about 10 %. (We use T = 3000 seconds).

The generalized Kruskal-Wallis statistic used above is most sensitive when the values of the Y's are greatest. In our

example, this means that differences between the β's over the earlier parts of the time interval will have much greater effect than those over the latter parts of the interval. Another statistic suggested by Andersen et al. (1981) does not have such an effect. This is their generalized logrank test. The computations can be described in simple terms, like the ones above, but we will not give the details here. The value of the generalized logrank test for our example is 5.81 which should again be compared with a chi-squared distribution with 2 degrees of freedom. This gives a p-value between 5 and 6 %. This statistic seems to give somewhat stronger evidence of deviation than the previous one. That this is resonable can be seen from Figure 14 where it is clear that the curves deviate most in the latter part of the time interval.

In conclusion, one can not say definitely that there is any real difference between the α's, although a difference may be indicated. One main reason for being cautious about the conclusion is that the simple model employed may not be quite realistic.

Table 5

Mating of Drosophila. Christiansen's data.

Experiment no. 1 (Performed Oct.19, 1970)			Experiment no. 2 (Performed Nov.13, 1970)			Experiment no. 3 (Performed Nov.17, 1970)		
I	II	III	I	II	III	I	II	III
555	29	39	403	30	37	635	30	40
742	28	38	625	29	36	710	29	39
746	27	37	718	28	35	750	28	38
795	26	36	754	27	34	793	27	37
934	25	35	782	26	33	906	26	36
967	24	34	826	25	32	906	25	35
982	23	33	853	24	31	938	24	34
1043	22	32	881	23	30	979	23	33
1055	21	31	890	22	29	998	22	32
1067	20	30	935	21	28	1048	21	31
1081	19	29	935	20	27	1083	20	30
1296	18	28	972	19	26	1210	19	29
1353	17	27	994	18	25	1299	18	28
1361	16	26	1103	17	24	1299	17	27
1462	15	25	1119	16	23	1336	16	26
1731	14	24	1217	15	22	1367	15	25
1985	13	23	1327	14	21	1469	14	24
2051	12	22	1427	13	20	1646	13	23
2292	11	21	1445	12	19	1702	12	22
2335	10	20	1461	11	18			
2514	9	19	1477	10	17			
2570	8	18	1532	9	16			
2970	7	17	1646	8	15			
			1969	7	14			

I: Times at which matings start.

II: Number of males which have not started mating up to the time given.

III: Number of females which have not started mating up to the time given.

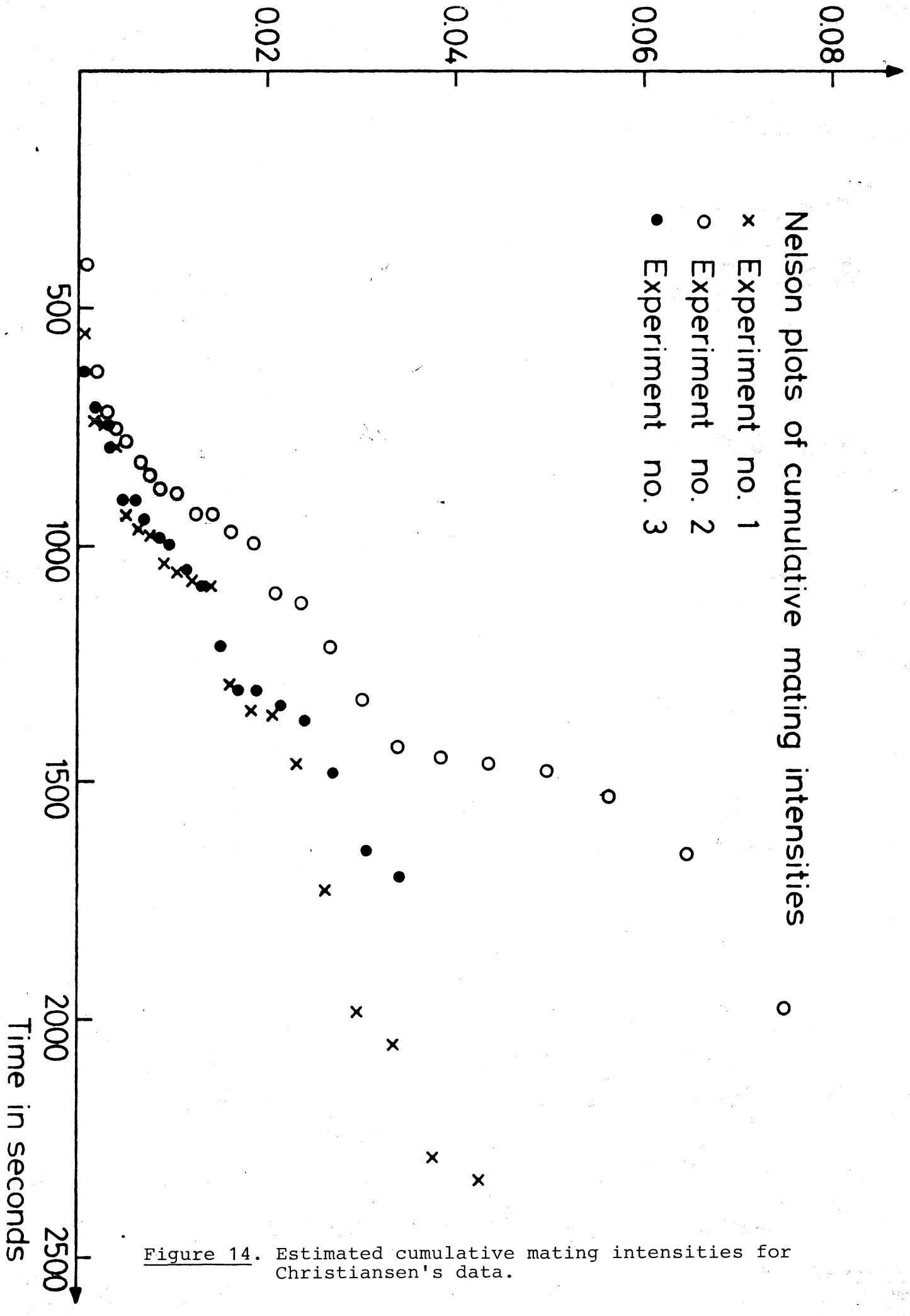


Figure 14. Estimated cumulative mating intensities for Christiansen's data.

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