BIOMETRICS 46, 337–349
June 1990

Is Multiple Sclerosis an Infectious Disease? Inference About an Input Process Based on the Output

Lawrence Joseph*
Department of Mathematics and Statistics,
McGill University, 805 Sherbrooke Street West,
Montréal, Québec H3A 2K6, Canada
Christina Wolfson
Department of Epidemiology and Biostatistics and Montreal Neurological Institute,
McGill University, 1020 Pine Avenue West, Montréal, Québec H3A 1A2, Canada
and
David B. Wolfson
Department of Mathematics and Statistics,
McGill University, 805 Sherbrooke Street West,
Montréal, Québec H3A 2K6, Canada

SUMMARY

The output process of an infinite-server queue with a Poisson process input is observed starting at time 0 with an empty queue. It is assumed that the service time distribution is known. This article discusses statistical inference about the *input* intensity. A controversial issue in the study of multiple sclerosis is addressed as a motivation for the model and methods developed.

1. Introduction: Is Multiple Sclerosis an Infectious Disease?

In the study of epidemics the time between the receipt of infection and the appearance of symptoms is called the incubation period. As is mentioned in Bailey (1975), it is important, on the basis of observation of when infected individuals become symptomatic, to be able to make inference about the infection rate. It is, of course, often not possible to observe when individuals in a population become infected. Such is the situation in the following application.

A controversial issue in the study of *multiple sclerosis* (MS) (a demyelinating disease of the central nervous system) is whether the disease is infectious. Recently Kurtzke and Hyllested (1986) put forward a detailed argument to support the claim that MS is spread from one individual to another probably by means of a virus. Their belief is based on the apparently sudden occurrence of MS in the Faroe Islands shortly after the arrival of British troops who had been stationed there in 1941. Assuming the British troops did introduce MS into the Faroe Islands (this is still not certain!), the model and methods of the following sections are used to examine Kurtzke and Hyllested's claim.

If their theory is correct, then assuming that the infection occurred according to a Poisson process, the intensity, $\lambda(t)$, of the input process should have increased as the disease spread from one individual to another. On the other hand, if the British troops merely introduced

* Current address: Division of Clinical Epidemiology, Montréal General Hospital, 1650 Cedar Avenue, Montréal, Québec H39 1A4, Canada.

Key words: Inference about input; Multiple sclerosis; Poisson process.

some unknown but noninfectious agent that precipitated MS among the Faroese, then the intensity of infection may have been constant. Under both of these hypotheses the onset rate would have increased. An attempt is made to address the issue of whether $\lambda(t)$ was constant or increasing, the difficulty being that only the times of onset and not the times of infection can be observed.

The Data The time origin was taken to be 1941. The data consist of the times (from this origin) at which onset occurred in the 32 individuals in Group A and Group B of Table 8 of Kurtzke and Hyllested (1986). These individuals had either not been off the Faroe Islands before onset (Group A) or had been off the islands for less than 2 years before onset (Group B). Ties were broken by distributing those observations tied at year j, independently and uniformly over the interval $[j - \frac{1}{2}, j + \frac{1}{2}]$. See Table 1.

It is important to note that in the following analysis it is assumed that no one had MS (latent or symptomatic) prior to the arrival of the British troops in 1941. This assumption

Table 1
Total patient series

Patient #	Sex	Age at onset (in years)	Ordered times of onset* (in years)	Ordered untied times of onset	Group**
1	M	30	2	2.00	A
2	M	15	3	2.53	A
3	M	24	3	2.93	A
4	M	48	3	3.48	A
5	F	19	4	3.66	A
6	F	44	4	3.98	B
7	F	39	4	4.14	B
8	M	24	5	5.17	A
9	M	38	5	5.42	A
10	F	26	5	5.48	A
11	M	32	6	5.54	A
12	F	19	6	5.95	A
13	F	16	7	6.53	A
14	M	25	7	6.95	B
15	F	32	8	7.53	A
16	M	20	8	7.54	A
17	F	42	11	11.00	A
18	F	18	12	12.00	A
19	F	14	13	13.00	A
20	M	17	14	14.00	A
21	F	19	15	15.00	B
22	M	19	16	16.00	A
23	M	37	17	17.00	A
24	F	19	18	17.65	A
25	M	29	18	18.14	A
26	M	21	19	19.00	A
27	M	40	20	20.00	A
28	F	27	24	24.00	B
29	F	21	27	27.00	B
30	F	17	28	28.00	A
31	F	20	29	29.00	A
32	F	33	32	32.00	B

* Time origin 1941.
** A: Individuals not off islands before onset.
B: Individuals off islands less than 2 years before onset.

coincides with that of Kurtzke and Hyllested and is based on their careful investigation of medical records dating back to 1900. According to these records, there had been no cases of MS among the Faroese since 1900.

The approach taken to this problem is to regard the times of infection as occurring according to a Poisson process, the incubation times as the service times of an infinite-server queue, and the times of onset as the departure times from this queue. In this context, quite general methods are developed.

In Section 2 the details of the model are presented and some tests based on this model are given in Section 3. Section 4 considers other hypotheses for testing about input processes. The data are analysed in Section 5, and the question of power is investigated in Section 6. For clarity, some technical details are deferred to an Appendix.

2. The Model

Let $\{N(t),\ t \geqslant 0\}$ be a nonhomogeneous Poisson process with intensity function $\gamma(t) = \int_0^t \lambda(t-u)\, dF(u)$, where $\lambda(t) \geqslant 0$ and $F(t)$ is a distribution function with support on $[0, \infty)$. That is, suppose that

$$\Pr\{N(t) = k\} = \frac{1}{k!}\left\{\int_0^t \gamma(x)\, dx\right\}^k \exp\left\{-\int_0^t \gamma(x)\, dx\right\} \quad \text{for } k = 0, 1, 2, \ldots.$$

It is well known [see, e.g., Mirasol (1962)] that $\{N(t),\ t \geqslant 0\}$ can be viewed as the output process of an infinite-server queue with a Poisson process input with intensity $\lambda(t)$ and service time distribution F. Assuming only the exit times from such a queue in equilibrium are observed, when $\lambda(t) \equiv \lambda$, a constant, Kendall (1964) has shown that $F(u)$ is not identifiable. Nevertheless, it is possible to make inference about $F(t)$ (Clarkson and Wolfson, 1983, 1985; Léger and Wolfson, 1987) if observation of the output begins at time $t = 0$. On the other hand, Brown (1970) has dealt with the estimation of $F(t)$, with information on the arrival times of customers as well as their departure times, although not necessarily matched, for an M/G/∞ queue in equilibrium.

It is the aim here to deal with the problem of testing hypotheses about the input intensity $\lambda(t)$, based solely on the observation of the times of exit from the queue and knowledge of F. For instance, one may wish to test for a constant input intensity versus an increasing input intensity. Also discussed is the comparison between the input intensities of two independent Poisson processes, again where only the output processes are observed.

Henceforth it will be supposed that: (i) Observation of the output starts at time $t = 0$, and (ii) there are no customers in the system at time $t = 0$.

Let $T_1, T_2, \ldots$ be the observable departure times of an infinite-server queue with Poisson input, and service time distribution $F(x)$. Let the input intensity be $\lambda(t)$. Let $\gamma(t)$ and $\Gamma(t)$ denote the output intensity and mean value function, respectively, of the Poisson output process. When $\lambda(t) \equiv 1$, a constant, $\gamma(t)$ will be denoted by $\gamma_c(t)$ and $\Gamma(t)$ by $\Gamma_c(t)$.

It is desired to make inference about $\lambda(t)$ based on the observable sequence $\{T_i\}_{i=1,2,\ldots}$; to this end the sequence of transformed times $\{S_i\}_{i=1,2,\ldots}$ where $S_i = \Gamma_c(T_i)$, plays a crucial role. It is well known [see, e.g., Karr (1986, p. 22) for a general discussion] that the sequence $\{S_i\}$ forms the occurrence times of a Poisson process. A superscript "T" ("Transformed") will be used to denote the intensity and mean value function, respectively, of the Poisson process generating the sequence $\{S_i\}$. The above notation is summarized, for convenience, in Table 2.

Proposition 2.1 below is important because it allows for inference about the input process to be transferred to inference about the process generating the sequence $\{S_i\}$.

Table 2
Intensities and mean value functions (MVFs)

	Input process (intensity)	
	$\lambda(t)$	$\lambda(t) \equiv 1$
Output process (intensity)	$\gamma(t) = \int_0^t \lambda(t-u)\, dF(u)$	$\gamma_c(t) = F(t)$
MVF	$\Gamma(t) = \int_0^t \int_0^s \lambda(s-u)\, dF(u)\, ds$	$\Gamma_c(t) = \int_0^t F(x)\, dx$
Transformed output process (intensity)	$\gamma^T(t)$	$\gamma_c^T(t)$
MVF	$\Gamma^T(t)$	$\Gamma_c^T(t)$

It is easily shown that

$$\gamma^T(t) = \frac{\gamma(\Gamma_c^{-1}(t))}{\gamma_c(\Gamma_c^{-1}(t))}. \tag{2.1}$$

Equation (2.1) follows from

$$\gamma^T(t) = \frac{d}{dt}\, \Gamma(\Gamma_c^{-1}(t)).$$

Definition 2.1 Given two intensities $\lambda_1(t)$ and $\lambda_2(t)$, we say that $\lambda_1(t)$ is locally ordered with respect to $\lambda_2(t)$ and write $\lambda_1(t) >_{\ell} \lambda_2(t)$ if $\lambda_1(t)/\lambda_2(t)$ is nondecreasing in t (Keilson and Sumita, University of Rochester, Graduate School of Management Working Paper Series, No. 8006, 1980; 1982).

Let C_{ℓ} be the class of unbounded intensities such that every pair of intensities within C_{ℓ} is locally ordered, i.e., $\lambda_1(t)$ and $\lambda_2(t)$ belong to C_{ℓ} if and only if either $\lambda_1(t)/\lambda_2(t)$ is nondecreasing or $\lambda_2(t)/\lambda_1(t)$ is nondecreasing and $\lambda_1(t)$ and $\lambda_2(t)$ are unbounded.

Proposition 2.1 Let

$$H_0: \quad \lambda(t) \equiv \lambda, \text{ a possibly unknown constant} \tag{2.2}$$

and

$$H_0^*: \quad \gamma^T(t) \equiv \lambda. \tag{2.3}$$

Let

$$H_a: \lambda(t) \text{ is increasing} \tag{2.4}$$

and

$$H_a^*: \quad \gamma^T(t) \text{ is increasing.} \tag{2.5}$$

Then,

$$(H_0, H_a) \quad \text{is equivalent to} \quad (H_0^*, H_a^*).$$

Proof Let H_0 hold with $\lambda(t) \equiv \lambda$, say. Then it follows immediately from equation (2.1) that $\gamma^T(t) \equiv \lambda$.

Conversely, let H_0^* hold and suppose $\lambda(t)$ is continuous and increasing. Then $\gamma(t) \equiv c$ implies

$$\gamma(\Gamma_c^{-1}(t)) \equiv c\gamma_c(\Gamma_c^{-1}(t)) \quad \text{for some constant } c.$$

Letting $\Gamma_c^{-1}(t) = s$, this implies that

$$\int_0^\infty g_s(u)\, dF(u) \equiv cF(s), \tag{2.6}$$

where $g_s(u) = \lambda(s - u)I(u)_{[0,s)}$ is nonnegative and increasing to infinity, and $I(u)_{[0,s)}$ is the indicator function on $[0, s)$. Since $\lim_{s\to\infty} cF(s) = c$, the limit on the left-hand side of (2.6) must exist and be c. But by the monotone convergence theorem,

$$\lim_{s\to\infty} \int_0^\infty g_s(u)\, dF(u) = \int_0^\infty \lim_{s\to\infty} g_s(u)\, dF(u) = +\infty,$$

which is impossible. Hence, $\lambda(t) \equiv c$ and it follows that $\lambda(t) \equiv \lambda$. Therefore H_0 is equivalent to H_0^*. Showing that H_a implies H_a^* reduces to showing that

$$R(t) = \frac{\int_0^t \lambda_1(t - u)\, dF(u)}{\int_0^t \lambda_2(t - u)\, dF(u)}$$

is increasing if $\lambda_1(t)/\lambda_2(t)$ is increasing. The proof is given in the Appendix. Conversely, if H_a does not hold, that is, if $\lambda(t)$ is constant, it follows from the first part of this proposition that $\gamma^T(t)$ is constant. Hence H_a^* implies H_a.

Note: We close this section with the observation that the most often used monotonic input intensities,

$$\lambda_\alpha(t) = ae^{\alpha t}, \quad a, \alpha > 0,$$

$$\lambda_\alpha(t) = \frac{\alpha}{\theta}\left(\frac{t}{\theta}\right)^{\alpha-1}, \quad \text{for } \alpha > 1, \quad \theta \text{ constant},$$

and

$$\lambda_\alpha(t) = \gamma \log(\alpha t + \delta), \quad \text{for } \alpha, \gamma, \delta > 0,$$

all have the property $\lambda_\alpha(t)/\lambda_\beta(t)$ is increasing for $\alpha > \beta \Leftrightarrow \lambda_\alpha(t) < \lambda_\beta(t)$ for all t, and $\lambda_\alpha(t)$ is unbounded on $[0, \infty)$. Therefore, each of these classes of intensities consists of locally ordered intensities.

3. Some Tests

In Section 2 it was shown how the hypotheses of a constant versus an increasing input intensity for the process $\{T_i\}$ could be transferred to the hypotheses of a constant versus an increasing output intensity for the process $\{S_i\}$. Three of the most important test statistics for testing for a constant versus an increasing intensity for an observed Poisson process are discussed in Barlow et al. (1972). In that context, the Poisson process about which inference is to be made, is actually observed. Define

$$L_n = \sum_{i=1}^{n-1} \frac{S_i}{S_n},$$

known as the cumulative total-time-on-test statistic,

$$X_n = -2 \sum_{i=1}^{n-1} \ln\left(\frac{S_i}{S_n}\right),$$

and for $1 \leqslant k \leqslant n$ fixed,

$$Y_k = \frac{k(S_n - S_k)}{(n - k)S_k}.$$

Under the null hypothesis of a constant intensity, X_n has a chi-square distribution with $2n - 2$ degrees of freedom, Y_k has an F distribution with $2k$ and $2(n - k)$ degrees of freedom, while for $n \leqslant 13$ the null distribution of L_n is given in Barlow et al. (1972). As $n \to \infty$, L_n is asymptotically normal. One rejects the null hypothesis in favour of an increasing intensity for large values of L_n, and for small values of X_n and Y_k. Of course, the statistic Y_k depends on k and it is not clear a priori which k to use.

Let Π_α denote the power of the test based on the test statistic X_n, when the alternative hypothesis is H_α: $\lambda(t) = \lambda_\alpha(t)$. It can be shown (see Corollary 1.3 in the Appendix) that $\Pi_\alpha \leqslant \Pi_\beta$ whenever $\lambda_\alpha(t) \leqslant \lambda_\beta(t)$ for all t and whenever $(\lambda_\beta, \lambda_\alpha) \in C_{\ell}$. While similar results probably hold for the test statistics L_n and Y_k, the proofs seem difficult.

4. Other Hypotheses

Using the same principles as in Section 3, one may test

$$H_0\colon \lambda(t) = \lambda_\alpha(t) \tag{4.1}$$

vs

$$H_a\colon \quad \lambda(t) = \lambda_\beta(t) \quad \text{for some } \beta > 0 \text{ and all } t \geqslant 0, \tag{4.2}$$

where $\lambda_\alpha(0) = \lambda_\beta(0)$, $\lambda_\beta(t)/\lambda_\alpha(t)$ is increasing, and $\lambda_\beta(t) > \lambda_\alpha(t)$, for $t > 0$. As before, one finds

$$\gamma^{\mathrm{T}}(t) = \frac{\int_0^t \lambda_\beta(t - u)\, dF(u)}{\int_0^t \lambda_\alpha(t - u)\, dF(u)},$$

after making the transformation

$$S_i = \Gamma_\alpha(T_i),$$

where

$$\Gamma_\alpha(t) = \int_0^t \lambda_\alpha(t - a)\, dF(a).$$

It then follows from the proof of Proposition 2.1 that $(H_0, H_a) \Leftrightarrow (H_0^*, H_a^*)$, where

$$H_0^*\colon \quad \gamma^{\mathrm{T}}(t) \equiv \text{constant},$$

and

$$H_a^*\colon \quad \gamma^{\mathrm{T}}(t) \text{ is increasing.}$$

The two-sample case Here the data are generated by two independent displaced Poisson processes with "input" intensities $\lambda_1(t)$ and $\lambda_2(t)$, respectively. It is desired to test

$$H_0\colon \quad \frac{\lambda_1(t)}{\lambda_2(t)} = c \quad \text{for all } t \in [0, \infty)$$

vs

$$H_a\colon \quad \frac{\lambda_1(t)}{\lambda_2(t)} \text{ is increasing in } t.$$

The service time distribution, F, is assumed to be the same for both processes and *unknown.* Keeping the same notation as we used in the previous sections,

$$\gamma_i(t) = \int_0^t \lambda_i(t - u)\, dF(u), \quad \text{for } i = 1, 2.$$

Let H_0^* and H_a^* be given by

$$H_0^*: \ \frac{\gamma_1(t)}{\gamma_2(t)} = k, \quad \text{constant for all } t \in [0, \infty)$$

vs

$$H_a^*: \ \frac{\gamma_1(t)}{\gamma_2(t)} \text{ is increasing for all } t \in [0, \infty).$$

It follows as before that $(H_0, H_a) \Leftrightarrow (H_0^*, H_a^*)$. Consequently, without knowing F, one can test H_0 vs H_a by observing only the displaced processes and by using, for example, the results of Lee and Pirie (1981). See also Bovett and Saw (1980). Again, it is not difficult to show that the tests are unbiased and have monotone power in the two-sample case.

5. Analysis: Is Multiple Sclerosis an Infectious Disease?

In this section we return to the question posed in the introduction, of whether the British troops introduced an infectious agent onto the Faroe Islands, that caused the apparent outbreak of multiple sclerosis. The infinite-server queueing model introduced in Section 2 is applied as follows:

(i) The times of arrivals of customers are represented by the times of infection (unobserved).
(ii) The service times are represented by the incubation periods of multiple sclerosis in different individuals.
(iii) The departure times are represented by the times of onset of MS in different individuals (observed).

Therefore, the question about "infection rate" based on observed data about "onset rate" and knowledge of the incubation distribution translates into a question about the arrival intensity of customers in an infinite-server queue based on the observed departure times and knowledge of the service time distribution.

Results Two distributions were considered for the service time (incubation period) of the disease. These were the chi-square and the standard Weibull. In the absence of any data to suggest an appropriate incubation period distribution, these two distributions were selected because of their contrasting shapes. The former, though, would probably be the more reasonable as an incubation period distribution. It was decided to select the chi-square distributions with 6, 10, and 20 degrees of freedom, and the standard Weibull distributions with parameters $c = .333$, $c = .295$, and $c = .257$, corresponding to means of 6, 10, and 20 years, respectively. A mean of 6 years for the incubation period was used in accordance with the estimate made by Kurtzke and Hyllested (1986), and is somewhat less than other literature in the area has indicated. For this reason, means of 10 years and 20 years were also selected for comparison.

The three statistics of Section 3 were used to test for a constant versus an increasing intensity for the infection process. The numbers of data points (individuals with multiple sclerosis) used were chosen as follows:

1. For both the chi-square and Weibull distributions, all three tests were performed using all 32 individuals.
2. For the χ_6^2 and Weibull ($c = .333$) distributions, the first 17 ordered observations were used. Their inclusion covers the period when the onset rate appears to increase. This corresponds to a time period of 5 years from the time the British troops first arrived on the Faroe Islands until they left, plus a mean of 6 years from infection to onset (a total of 11 years from 1941). One can see from Table 1 that the ordered time of onset equal to 11 years corresponds to the 17th observation (i.e., $T(17) = 11$).
3. For the χ_6^2 distribution the first 23 observations were also considered. This corresponds to the time period from 1941 until roughly 95% of individuals "infected" during the occupation, will have experienced disease onset. This procedure was also done for the Weibull distribution ($c = .333$) and it was found that all 32 individuals should be included.

In deciding how many data points to include corresponding to incubation period distributions with larger means (i.e., 10 years and 20 years), the same criteria were imposed.

The details of the analysis are summarized in Table 3 (for the chi-square distributions) and Table 4 (for the standard Weibull distributions), where only the results obtained using the test statistic X_n are presented. This choice for presentation was made because the results obtained using the statistics L_n and Y_k led to exactly the same conclusions.

Table 3
Results: Incubation period with a chi-square distribution

	χ_6^2	χ_6^2	χ_6^2	χ_{10}^2	χ_{10}^2	χ_{10}^2	χ_{20}^2
Number of observations	32	23	17	32	30	21	32
Incubation distribution mean (years)	6	6	6	10	10	10	20
X_n	144.13	97.17	68.63	212.58	200.26	139.67	457.11

Table 4
Results: Incubation period with a standard Weibull distribution

	Weibull parameter (c)				
	.333	.333	.295	.295	.257
Number of observations	32	17	32	21	32
Incubation distribution mean (years)	6	6	10	10	20
X_n	88.92	32.05	88.48	44.45	87.88

None of the test statistics shown in Tables 3 and 4 is statistically significant ($P \gg .10$). This shows that the increase in the observed onset rate of MS on the Faroe Islands following the arrival of the British troops in 1941 is not necessarily indicative of an infectious agent. The data are compatible with the introduction of some noninfectious cause (as yet unknown) which might have led to a *transient* increase in the observed onset rate of MS.

6. Simulations

Because the service time distribution is presumed known in the application of this model, the effect of its misspecification on power was studied by computer simulations.

Also examined was the change in input intensity. The following are features of the simulation:

1. Owing to the considerable cost involved in carrying out these simulations, no attempt was made to be exhaustive in the choice of service time distributions, input intensities, or sample size. Rather, the aim was to obtain a rough idea of the behaviour of the power function under some selected but different conditions. Specifically, the chi-square and Weibull distributions were used as service time distributions because they were used in the analysis of the data in Section 1. Degrees of freedom and parameters for the two distribution types were chosen in the range of those most likely to have arisen in the application of Section 1. The negative exponential distribution was also considered because of its frequent use as a service time distribution. A reasonable range of input intensities, of the types introduced in Section 2, was used.

2. Various "service time–transformation" combinations were considered. In the case where the service time distribution was chi-square, the only transformations considered were chi-square; the Weibull and negative exponential are of such different shapes from the chi-square that misspecification by using the latter two distributions is unlikely. On the other hand, different exponential–Weibull combinations were considered, their general distributional shapes being similar. Unfortunately, the costs involved in studying Weibull (true)–exponential (transformed) combinations (numerical integration with singularities arise) were prohibitive and for this reason no simulations were carried out. It is unlikely, though, that results in these cases would have differed very much from those already obtained.

3. Each simulation was carried out 400 times. This gives a 95% confidence interval for the power, of width .08. Several simulations were carried out using a constant input intensity and a correctly specified transformation. This was done as a check on the validity of the simulations; in all instances values close to the nominal level of significance of 5% were obtained.

4. In each of Tables 5 and 6 "F(true)" denotes the true service time distribution while "F(trans)" denotes the assumed distribution, i.e., the distribution used in the transformation.

6.1 *Discussion of the Results*

1. As is to be expected, in all cases the power increases as the input intensity increases.

2. When the distribution used for the transformation coincides with the true service time distribution, the power is high in most cases. The exceptional cases occur invariably when the input intensity is of the form $\log(\alpha t + \delta)$, which increases very slowly.

3. When the true service time distribution is χ^2_m and the transformation distribution is χ^2_n with $n > m$, the power is seen to decrease (compared with the case $m = n$). Similarly, when $m > n$ the power increases. That this should happen is a consequence of the local ordering of the family of chi-square distributions indexed by their parameters. See Appendix, Corollary 1.3. Of course, the quite dramatic increase in power in the case $m > n$ is accompanied by an increase in significance level which, in selected simulations, rose to as much as .300. When $m < n$ the significance level decreases with the power. Considering the comparative lack of information in carrying out the tests, the powers obtained compare favourably with those obtained from direct observation of the input process (see Bain, Englehardt, and Wright, 1985).

In summary, the tests are "valid," in the sense that significance levels are less than or equal to α when $m < n$, and the tests are "powerful," in the sense of rejecting the null hypothesis when $m > n$.

Table 5
Simulation results

Input intensity	α	$F(\text{true}) = \chi^2_m$ m	$F(\text{trans}) = \chi^2_n$ n	Power
$e^{\alpha t}$	.5	4	4	.975
			6	.783
			8	.358
		6	4	1.000
			6	.983
			8	.760
		8	4	1.000
			6	1.000
			8	.953
	1.0	4	4	.995
			6	.933
			8	.603
		6	4	1.000
			6	.995
			8	.930
		8	4	1.000
			6	1.000
			8	.993
$\alpha t^{\alpha-1}$	1.5	4	4	.605
			6	.103
			8	.025
		6	4	.938
			6	.583
			8	.155
		8	4	.993
			6	.893
			8	.530
	2	4	4	.890
			6	.396
			8	.080
		6	4	.995
			6	.820
			8	.396
		8	4	1.000
			6	.983
			8	.775
	3	4	4	.995
			6	.823
			8	.280
		6	4	1.000
			6	.970
			8	.733
		8	4	1.000
			6	.995
			8	.958
$\log(\alpha t + e)$	2	4	4	.408
			6	.128
			8	.058
		6	4	.763
			6	.255
			8	.038
		8	4	.960
			6	.760
			8	.373

Table 6
Simulation results

Input intensity	α	F(trans)*	Power
$e^{\alpha t}$	.5	$\frac{1}{6}e^{-x/6}$	.973
$e^{\alpha t}$	1	$\frac{1}{6}e^{-x/6}$	1.000
$e^{\alpha t}$	.5	$e^{-x^{.333}}$	1.000
$e^{\alpha t}$	1	$e^{-x^{.333}}$	1.000
$\alpha t^{\alpha-1}$	1.5	$\frac{1}{6}e^{-x/6}$	.523
$\alpha t^{\alpha-1}$	2	$\frac{1}{6}e^{-x/6}$	.850
$\alpha t^{\alpha-1}$	3	$\frac{1}{6}e^{-x/6}$	.998
$\alpha t^{\alpha-1}$	1.5	$e^{-x^{.333}}$	.980
$\alpha t^{\alpha-1}$	2	$e^{-x^{.333}}$	1.000
$\alpha t^{\alpha-1}$	3	$e^{-x^{.333}}$	1.000
$\log(\alpha t + e)$	2	$\frac{1}{6}e^{-x/6}$	.298
$\log(\alpha t + e)$	2	$e^{-x^{.333}}$	.903

* F(true) for all simulations = $e^{-x/6}/6$.

4. Several simulations were done with 20 output observations to investigate the effect on power of reduced sample size. There was roughly a 10% reduction in power.

6.2 *Conclusion*

The simulations carried out, although limited, indicate that particularly when the input intensity increases rapidly, it is possible to obtain tests with reasonably high power, even when the transformation distribution is misspecified. When one considers that the tests are based solely on the observed output and inference is to be made on the input, this is rather surprising. While it is impossible to assess the true power of the tests carried out on the MS data from the Faroe Islands, nevertheless the failure to reject a constant input intensity seems to warrant the consideration of alternative causes for the apparent sudden outbreak of MS after the arrival of the British troops.

Acknowledgements

This research was supported in part by a grant from the Natural Sciences and Engineering Council of Canada (Grant No. A9261), by the Fonds pour la Formation de Chercheurs et l'Aide à la Recherche du Gouvernment du Québec, and by La Fondation Pierre Saint Onge pour la Récherche en Sclérose en Plaque.

Résumé

Dans un phénomène de file d'attente, où l'entrée du système est régi selon un processus de Poisson, et le processus en sortie génère une file d'attente avec un nombre d'évènements illimité, on commence l'observation au temps 0, avec une queue vide. On suppose que la distribution des temps, décrivant la file d'attente en sortie, est connue. Cet article discute de la statistique d'inférence relative à l'intensité du processus à l'entrée. Un résultat controversé de l'étude de la sclérose multiple montre l'intérêt du modèle et des méthodes traitées.

References

Bailey, N. T. J. (1975). *The Mathematical Theory of Infectious Diseases.* New York: Hafner Press.

Bain, L. J., Englehardt, M., and Wright, F. T. (1985). Tests for an increasing trend in the intensity of a Poisson process: A power study. *Journal of the American Statistical Association* **80,** 419–422.

Barlow, R. E., Bartholomew, D. J., Bremner, J. M., and Brunk, H. D. (1972). *Statistical Inference Under Order Restrictions.* New York: Wiley.

Bovett, J. M. and Saw, J. G. (1980). On comparing two Poisson intensity functions. *Communications in Statistics—Theory and Methods* **A9,** 943–948.
Brown, M. (1970). An M/G/∞ estimation problem. *Annals of Mathematical Statistics* **1,** 651–654.
Clarkson, D. B. and Wolfson, D. B. (1983). An application of a displaced Poisson process. *Statistica Neerlandica* **37,** 21–28.
Clarkson, D. B. and Wolfson, D. B. (1985). A displaced Poisson process applied to screening for breast cancer in stratified samples with false negatives. *Statistica Neerlandica* **39,** 361–373.
Karlin, S. (1968). *Total Positivity, Vol.* 1. Stanford, California: Stanford University Press.
Karr, A. F. (1986). *Point Processes and Their Statistical Inference.* New York: Marcel Dekker.
Keilson, J. and Sumita, U. (1982). Uniform stochastic ordering and related inequalities. *Canadian Journal of Statistics* **10,** 181–198.
Kendall, D. G. (1964). Some recent work and further problems in the theory of queues. *Teor. Verojat Primen* **9,** 3–15.
Kurtzke, J. K. and Hyllested, K. (1986). Multiple sclerosis in the Faroe Islands II. Clinical update, transmission and the nature of MS. *Neurology* **36,** 307–328.
Lee, L. and Pirie, W. R. (1981). A graphical method for comparing trends in series of events. *Communications in Statistics—Theory and Methods* **A19,** 827–848.
Léger, C. and Wolfson, D. B. (1987). Hypothesis testing for a nonhomogeneous Poisson process. *Communications in Statistics—Stochastic Models* **3,** 439–455.
Mirasol, N. M. (1962). The output of an M/G/∞ queueing system is Poisson. *Journal of Operations Research* **11,** 282–284.
Saw, J. G. (1975). Tests on the intensity of a Poisson process. *Communications in Statistics—Theory and Methods* **A4,** 778–782.

Received February 1987; *revised April* 1988 *and April* 1989; *accepted July* 1989.

APPENDIX

Proof of Proposition 2.1 ($H_a \Leftrightarrow H_a^*$)

The proof follows as a corollary to the next lemma.

Lemma A.1 Let $\lambda_1(t) > 0$, $\lambda_2(t) > 0$, and suppose $(\lambda_1, \lambda_2) \in C_\ell$, so that $\lambda_1(t)/\lambda_2(t)$ is increasing as t increases. Let $F' = f$ (the density of F) be a member of PF_2 the class of Polya frequency functions of order 2; see, e.g., Karlin (1968). Then

$$R(t) = \frac{\int_0^t \lambda_1(t-u)\, dF(u)}{\int_0^t \lambda_2(t-u)\, dF(u)} \quad \text{is increasing as } t \text{ increases.}$$

Note: It is easy to show that $f \in PF_2$ if and only if $f(x) \geq 0$ for all x and $f(x-\Delta)/f(x)$ is increasing in x for $\{x: f(x) > 0\}$ and $\Delta > 0$.

Proof. Let $t_0 > 0$ be arbitrary. We show that $R(t)$ is increasing for all $0 < t \leq t_0$. Define

$$\lambda_1^*(t) = \begin{cases} c_1\lambda_1(t) & \text{for } 0 < t \leq t_0 \\ 0 & \text{for } t > t_0 \end{cases}$$

$$\lambda_2^* = \begin{cases} c_2\lambda_2(t) & \text{for } 0 < t \leq t_0 \\ 0 & \text{for } t > t_0 \end{cases}$$

where c_1, c_2 are chosen such that $\int_0^\infty \lambda_i^*(t)\, dt = 1$, $i = 1, 2$.

Then λ_1^* and λ_2^* are probability density functions. Identify with them random variables X_1 and X_2, respectively. On $[0, t_0]$, $\lambda_1^*(t)/\lambda_2^*(t)$ is increasing for all $\{t: \lambda_2^*(t) > 0\}$, which is equivalent to the statement that $X_2 <_\ell X_1$ (X_2 is locally uniformly smaller than X_1) (Keilson and Sumita, University of Rochester, Graduate School of Management Working Paper Series, No. 8006, 1980; 1982).

Let Y be a random variable associated with the distribution function F, and independent of X_1 and X_2. Then $X_2 + Y <_\ell X_1 + Y$ on $[0, t_0]$ (Keilson and Sumita, 1980, 1982). The density of $X_i + Y$ is $\int_0^t \lambda_i(t-u)\, dF(u)$. Hence $R(t)$ is increasing for all $t < t_0$.

Corollary A.2

$$H_a \Leftrightarrow H_a^*$$

Proof. In Lemma A.1 take $\lambda_1(t) = \lambda(t)$, increasing and $\lambda_2(t) \equiv \lambda_0$, constant.

Note: The class of PF_2 density functions contains many of the common densities.

Corollary A.3 Consider the set of hypotheses H_0^* vs H_a^*. Let the true service time distribution F_0 have density f_0, and suppose that f_1 and f_2 are two different densities used for the transformation. Suppose further that

$$\frac{f_1(t)}{f_0(t)} \text{ is increasing for all } \{t: f_0(t) > 0\} \tag{A.1}$$

and

$$\frac{f_2(t)}{f_0(t)} \text{ is decreasing for all } \{t: f_0(t) > 0\}. \tag{A.2}$$

Then

(i) the power of the test based on the statistic X_n and transformation density f_1 is greater than or equal to the power of the test based on the transformation density f_0.
(ii) The power of the test based on the statistic X_n and transformation density f_2 is less than or equal to the power of the test based on the transformation density f_0.

Proof An argument similar to that used in the proof of Lemma A.1 suffices, since, according to Saw (1975), it is enough to show that

$$\frac{\int_0^t \lambda(t-u) f_i(u)\,du}{\lambda_0 F_0(t)} \Bigg/ \frac{\int_0^t \lambda(t-u) f_0(u)\,du}{\lambda_0 F_0(t)} = \frac{\int_0^t \lambda(t-u) f_i(u)\,du}{\int_0^t \lambda(t-u) f_0(u)\,du}, \quad \begin{array}{l}\text{is increasing in } t \text{ for } i=1\\ \text{and decreasing in } t \text{ for } i=2.\end{array}$$

The details are omitted. The class of densities that possess the properties (A.1) or (A.2) includes, for example, the gamma, the normal, Weibull, and log-normal (indexed by the appropriate parameters) (Keilson and Sumita, 1980; 1982).

Of course, since it will often happen that f_0 will belong to the same class as the transformation density, it follows easily from Corollary A.3 that the test based on X_n will have isotonic power with respect to the local uniform ordering of the random variables X_i associated with the densities f_i in the class. The simulations in Section 6 illustrate this feature.