European Journal of Clinical Investigation (1989) **19,** 154–158

Statistical analysis of fever interval data

C. J. STOK, J. W. M. VAN DER MEER* & A. C. NIEUWENHUIJZEN KRUSEMAN†, Department of Medical Informatics, Leiden University and Departments of *Infectious Diseases and †Internal Medicine, University Hospital, Leiden, The Netherlands

Received 2 May 1988 and in revised form 18 November 1988

Abstract. Periodic fever syndromes usually do not show a clear fixed periodicity, and hence cannot be described by the mean and the standard deviation of the interval length. In those cases statistical tools must be used. Fever interval data can be described as a random point process; the renewal density function and its Fourier transform can be used to uncover hidden periodicities. In this report the estimation and evaluation of the renewal density function are described. The data of three patients with periodic fever were investigated. In one of these patients, suffering from periodic fever originating at the level of the hypothalamus, a 30-day periodicity was observed. In a female patient with hyperimmunoglobulinaemia D and periodic fever, menstruation often coincided with or was preceded by a fever episode. In the third patient with a Familial Hibernian Fever-like syndrome, an irregular fever pattern and no periodicity were found. The computerized analysis of the fever intervals may be useful in assessing various periodic fever syndromes.

Keywords. Biorhythm, biostatistics, fever, periodic disease.

Introduction

Patients suffering from recurrent fever are an intriguing problem for the clinician. In some patients, a hidden infection, inflammatory process or malignancy may be responsible for the symptomatology, whereas in others the idiopathic periodic fever syndromes may be the explanation. These latter syndromes include Familial Mediterranean Fever (FMF) [1], Familial Hibernian Fever (FHF) [2] or the hyperimmunoglobulinaemia D and periodic fever syndrome [3]. Rarely, hypothalamic disorders are responsible for the clinical picture of recurrent elevated temperature [4, 5].

Although the adjective 'periodic' suggests some regularity, most often there is no fixed periodicity of the fever attacks. For the present study, we questioned whether there might be some hidden rhythms in some of these syndromes. We therefore performed a computerized analysis of fever interval data in three patients with well-documented periodic fever.

Patients and methods

Patients

Three of our patients with periodic fever syndromes produced ample fever interval data to allow computer analysis.

Patient A is a 72-year-old Dutch male suffering from recurrent episodes of fever (up to 40°C), which last 1 day and are associated with nausea, headache, excessive sweating, and logorrhoea. The attacks have been present since 1971, and recur irregularly about every 2 or 3 weeks. Apart from obesity, physical examination is normal. There is no Cushingoid appearance. Repeated clinical and laboratory investigations have not provided a diagnosis. The patient has a negative noradrenalin provocation test and manifests a high frequency of attacks during medication with colchicine; these results seem to exclude Familial Mediterranean Fever. Serum immunoglobulin D concentrations were low. Unexpectedly, computer tomography of the abdomen disclosed a tumor (size 3 cm) in the right adrenal. This finding initiated endocrine evaluation, which revealed ACTH-dependent rather than primary hyperadrenocorticism. X-rays and computer tomography of the pituitary fossa and hypothalamic region were normal. There was no evidence for hyperthyroidism or presence of a phaeochromocytoma. The clinical findings resemble those of a case reported by Wolff *et al.* [5] and suggest that our patient could well

Part of this paper has been presented at the fever workshop of the 20th Annual Meeting of the European Society for Clinical Investigation at Scheveningen, The Netherlands on 19–22 March 1986.

*Present address: University Hospital St Radboud, PO Box 9101, 6500 HB Nijmegen, The Netherlands.

†Present address: Department of Internal Medicine, University Hospital, Maastricht, The Netherlands.

Correspondence: Prof. J.W.M. van der Meer, Department of Internal Medicine, University Hospital St Radboud, PO Box 9101, 6500 HB Nymegan, The Netherlands.

be suffering from a hypothalamic abberation, explaining both fever and hormonal abnormalities. The data for the present analysis were provided by the patient who kept a diary of all his attacks.

Patient B is a 25-year-old female of Dutch ancestry suffering from hyperimmunoglobulinaemia D and periodic fever; her case report has been published in detail elsewhere [3]. This patient suffers from febrile attacks since early childhood. The attacks, lasting for approximately 5 days, are preceded by chills and may be accompanied by diarrhoea, swollen lymphnodes and occasionally a painful erythema on the distal part of the extremities. During the attack there is granulocytosis and a rise of acute phase proteins. Serum IgD is always between 3000 and 6000 l^{-1} (normal range 0–150 l^{-1}). This patient has registrated most of her attacks and menstrual data over a period of 8 years, when she was not on oral contraceptives and not using any drug to suppress fever.

Patient C is a 38-year-old male of Dutch ancestry with a lifelong history of recurrent fever episodes, which are accompanied by erythema of the groin and genital region and oedema of the external genital organs. These attacks last 4–5 days. During the attack there is granulocytosis and a rise of acute phase proteins. Extensive investigations did not reveal a primary cause for these episodes, e.g. complementary studies were performed and excluded angioneurotic oedema. The father of this patient may have suffered from a similar condition. The clinical picture of this patient resembles that of Familial Hibernian Fever [2]. The response to glucocorticosteroids has not been fully assessed yet. This patient did not register his attacks himself. The data over a period of $4\frac{1}{2}$ years were reconstructed from the illness records kept by his employer.

Mathematics

In the analysis of fever interval data presented here, an attack of fever is considered to be an event and a series of fever attacks is considered to be a realization of a stochastic (random) univariate point process, in which an event is completely characterized by its time of occurrence [6]. For example, the duration of the attack, the presence of symptoms or the course of the body temperature during the attack are not included in the analysis. Let $\{x_1, x_2, \ldots, x_N\}$ indicate a set of N time intervals between episodes of fever. In the sequel it is assumed that these intervals are presented in units of days and as positive integers (e.g., $x_1 = 5$ days, $x_2 = 24$ days), thus introducing discrete intervals and a minimum time difference of 1 day. This was found to be accurate in dealing with fever interval data. If an attack lasts for more than 1 day, the first day is regarded as the time of occurrence.

A registration of times of occurrence of episodes of fever might, at first sight, not show any periodicity at all even though it is periodic to some extent. The raw data of patient A (Fig. 1a) can serve as an example. An artificial example of such a case is constructed from a

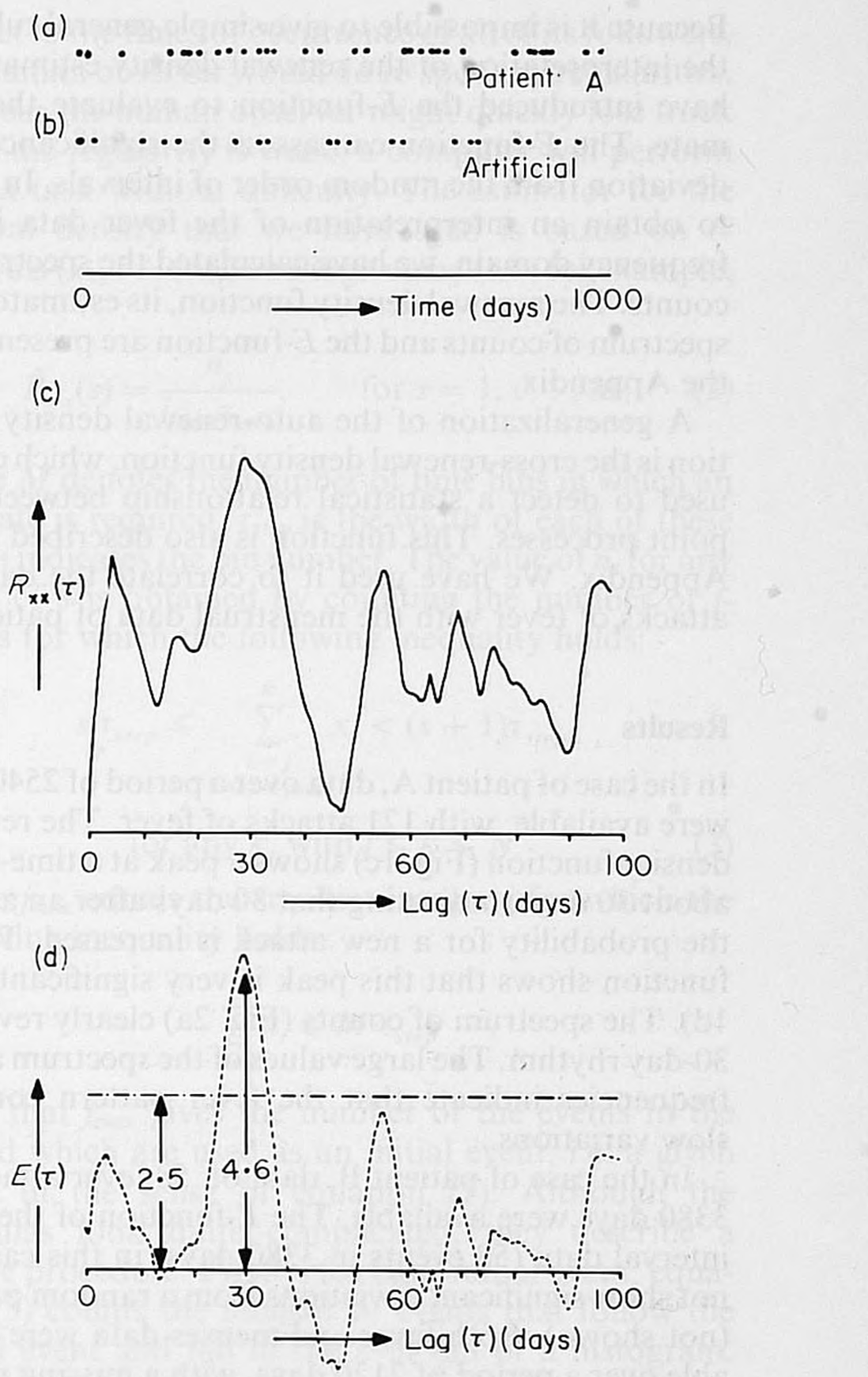

Figure 1. (a and b) Examples of point processes showing that time triggering of event occurrences is not easily detected by visual inspection. Each dot indicates an event. Upper trace (a) shows when patient A had fever attacks in a 1000 days period. The weak 30 days rhythm that was found by computation can not be easily seen. The lower trace (b) shows a series of events that was created by adding some random events to a regular (1 per 115–120 days) series of events. Although the rhythm can be found immediately by using a ruler, the naked eye fails to see it. By increasing the regular rhythm and leaving events out, in addition to adding them, one can create an example that resembles the upper trace. (c) Estimate of the renewal density function of the fever intervals of patient A. The large peak at a time lag of 30 days suggests a regularity in the series of intervals but statistical evaluation of the peaks height is required. (Smoothed histogram estimator.) (d) Statistical evaluation of the renewal density estimate shown in (c) by means of the so-called *E*-function. It shows that the peak at a time lag of 30 days could not be explained by random order of the series of intervals since it deviates by 4·6 times the standard deviation at that time lag.

regular rhythm to which random episodes of fever are added (Fig. 1b). the underlying regularity of the pattern cannot be readily discerned. In order to detect such regularities, we have used the (*auto-*)*renewal density function* (or conditional intensity function), which is employed for instance in electrophysiology for the analysis of series of action potentials [7, 8].

Because it is impossible to give simple general rules for the interpretation of the renewal density estimate, we have introduced the *E*-function to evaluate the estimate. The *E*-function can assess the significance of a deviation from the random order of intervals. In order to obtain an interpretation of the fever data in the frequency domain, we have calculated the spectrum of counts. The renewal density function, its estimator, the spectrum of counts and the *E*-function are presented in the Appendix.

A generalization of the auto-renewal density function is the cross-renewal density function, which can be used to detect a statistical relationship between two point processes. This function is also described in the Appendix. We have used it to correlate the dates of attacks of fever with the menstrual data of patient B.

Results

In the case of patient A, data over a period of 2540 days were available, with 121 attacks of fever. The renewal density function (Fig. 1c) shows a peak at a time-lag of about 30 days, indicating that 30 days after an attack, the probability for a new attack is increased. The *E*-function shows that this peak is very significant (Fig. 1d). The spectrum of counts (Fig. 2a) clearly reveals a 30-day rhythm. The large values of the spectrum at low frequencies indicate that the fever pattern contains slow variations.

In the case of patient B, data on 58 fever attacks in 3380 days were available. The *E*-function of the fever interval data (58 events in 3380 days) in this case did not show significant deviations from a random pattern (not shown). Both fever and menses data were available over a period of 2120 days, with a missing period of 474 days of menses data. The cross-renewal density based on these fever and menses data (Fig. 2b) showed that 0–6 days before menstruation, the probability for an attack of fever was significantly increased. A smaller increase was apparent approximately 28–34 days before menstruation and at 21-27 days after menstruation there is only a small peak in the cross-renewal density.

In the case of patient C, data for only 28 fever attacks over a period of 1760 days were available. Although this number is large enough to allow analysis and to yield results when the regularity is strong, the *E*-function showed no significant deviations from a random pattern.

Discussion

The computer analysis used in this study, i.e. the renewal density estimation, appears to be applicable to patients with well-documented periodic fevers, and is able to reveal periodicities that cannot be detected by visual inspection. It estimates the probability of encountering a new attack of fever on any day after the occurrence of an attack. Fourier analysis of the renewal density can be helpful to uncover periodicity.

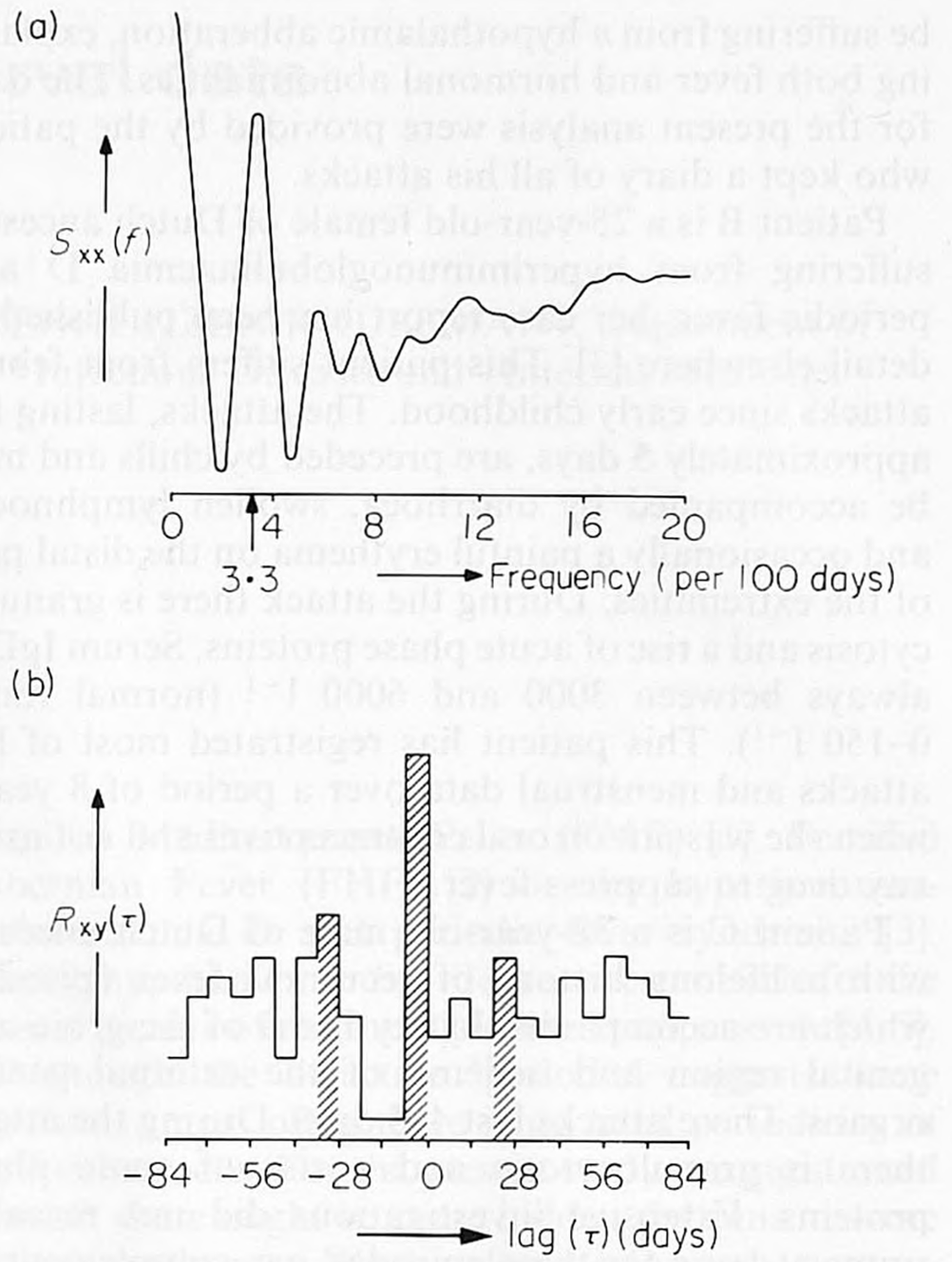

Figure 2. (a) Fourier transformation of the renewal density of patient A, shown in Fig. 1c, results in the spectrum of counts shown here. The high value of S_{xx} (f) at low frequencies represents the slow variations in the fever pattern over 7 years. The large peak at 3·3 per 100 days gives evidence for a 30 days rhythm. (b) Cross-renewal density of menses data (trigger channel) and fever data of patient B. The middle shaded bar indicates the probability of encountering an attack of fever in the period 0 to 6 days before menstruation. This probability is significantly elevated. Note that there is no significant elevation in the period before the next or previous most likely (28 days cycle) menstruation date. (Unsmoothed histogram estimator.)

The computer analysis, the results of which are summarized in Fig.2, enabled us to recognize a 30-day rhythm in patient A, a rhythm linked to menstruation in patient B and no pattern in patient C.

The rhythms found in patients A and B could be related to biorhythms, which probably originate at the level of the hypothalamus. In patient A the observed abnormality of the regulation of the hypothalamus-pituitary-adrenal axis is consistent with this suggestion, although it fails to explain fever attacks *per se*. In patient B, with the hyper IgD syndrome, the analysis suggests that the menstrual cycle significantly increases the chance of an attack. Thus, changes in sex hormones could act as a cofactor in the pathogenesis of a febrile attack. A clustering of attacks around the menstrual period has been observed in a number of patients with Familial Mediterranean Fever (reviewed in [1]).

In patient C, who may be suffering from Familial Hibernian Fever, a relation to a biorhythm is unlikely because the available data give evidence for a random pattern. However, it should be noted that the number of intervals is small. In these kinds of study it is in

general a problem to obtain sufficient trustworthy data. Very few patients with paroxysmal diseases appear to keep diaries of their attacks, and medical charts usually do not contain enough data.

However, from our study it should not be concluded that the attacks in some patients with periodic fever syndromes occur on the basis of biorhythms. We suggest that a number of exogenous factors play a role as triggers for attacks, but endogenous factors cannot be denied. The methods given in this paper can be used to investigate whether attacks of fever relate to other events. They can be used by bio-statisticians to investigate periodic fevers and other episodic diseases and may be helpful in the detection of hypothalamic disorders.

References

1 Eliakim M, Levy M, Ehrenfeld M. Recurrent Polyserositis (Familial Mediterranean Fever, periodic disease). Amsterdam: Elsevier, 1981.

2 Williamson LM, Hull D, Mehta R, Reeves WG, Robinson BHB, Toghill PJ. Familial hibernian fever. Quart J Med 1982; New Series LI, 204: 469–80.

3 Van der Meer JWM, Vossen JM, Radl J *et al.* Hyperimmunoglobulinaemia D and periodic fever: a new syndrome. Lancet 1984; i:1087–90.

4 Lipton JM, Rosenstein J, Sklar FH. Thermoregulatory disorders after removal of a craniopharyngioma from the third cerebral ventrical. Brain Res Bulletin 1981;7:369–73.

5 Wolff SM, Adler RC, Buskirk ER, Thompson RH. A syndrom of periodic hypothalamic discharge. Am J Med 1964;36:956–67.

6 Cox DR, Isham V. Point processes. London: Chapman and Hall, 1980.

7 Perkel DH, Gerstein GL, Moore GP. Neuronal spike trains and stochastic point processes. I. The single spike train. Biophys Journ 1967;7:391–418.

8 Glaser EM, Ruchkin DS. Principles of neurobiological signal analysis. New York: Academic Press, 1976.

9 Stok CJ, Weperen JH, Mars NJI. The VENUS project was supported by STW Grant ADG44.0708 and carried out at Medical Informatics, PO Box 9604, 2300 RC Leiden, The Netherlands.

10 Cox DR, Lewis PAW. The statistical analysis of series of events. London: Methuen & Co, 1966.

11 Harris FJ. On the use of windows for harmonic analysis with the discrete Fourier transform. Proc IEEE 1978;66:51–83

Appendix

The (auto-)renewal density function $R_{xx}(\tau)$ of a point process $\{x_i\}$ is defined as the probability to encounter an event in the time interval $(t+\tau,t+\tau+\delta)$ given an event at time t divided by δ and in the limit $\delta \to 0$. In formula:

$$R_{xx}(\tau) = \lim_{\delta \to 0+} \frac{\text{Prob}\{\text{event in } (t+\tau, t+\tau+\delta) | \text{ event at } t\}}{\delta} \quad (1)$$

In order to estimate this function of τ, a computer program for point process analysis, VENUS [9], was used for all calculations presented here. In order to estimate the renewal density function, the program took into account the times of occurrence of each event with respect to the times of occurrence of all of its followers, as a human observer would do to spot any regularities. Whereas the human observer might quickly lose track when the regularity is weak, a computer will perform such a task without difficulty. The estimator for the renewal density that we have used is based on N intervals $\{x_1, \ldots, x_N\}$ and is given by (*see*, for example, [8]):

$$\hat{R}_{xx}(s) = \frac{n_s}{j_{max}\tau_{step}}, \qquad \text{for } s = 1, \ldots, M, \quad (2)$$

where M denotes the number of time bins in which an estimate is required, τ_{step} is the width of each of these bins, s indicates the bin number. The value of n_s for any value of s is obtained by counting the number of j-values for which the following inequality holds:

$$s\,\tau_{step} \leqslant \sum_{\substack{i=j \\ 1 \leqslant j \leqslant j_{max}}}^{k} x_i < (s+1)\tau_{step},$$

$$\text{for any } k, \text{ with } j \leqslant k \leqslant N, \quad (3)$$

where j_{max} equals the smallest integer j for which the following inequality holds:

$$\sum_{i=j}^{N} x_i \leqslant M\,\tau_{step}$$

Note that j_{max} gives the number of the events in the record which are used as an initial event, i.e. a given event in the sense of equation (1). Although the formulas look quite complicated, they describe a simple procedure. Firstly, for each initial event, equation (3) counts the number of events that follow the initial event and fall in the k-th bin of a histogram. Secondly, equation (2) provides proper scaling. A small value of τ_{step} yields a high resolution but also a large variance, which, however, can be reduced by smoothing. We choose $\tau_{step} = 1$ day (the smallest value possible in our case) and a Parzen weighting function to reduce variance.

Likewise the cross-renewal density $R_{xy}(\tau)$ of two point processes $\{x_i\}$ and $\{y_i\}$ (for instance fever and menses data), is defined by [6]:

$$R_{xy}(\tau) = \lim_{\delta \to 0+} \frac{\text{Prob}\{\text{event of } x \text{ in } (t+\tau, t+\tau+\delta) | \text{ event of } y \text{ at } t\}}{\delta} \quad (4)$$

The cross-renewal density function may exhibit peaks and throws when the two processes are linked, for instance if an event in x is often followed by an event in y, some time τ_{delay} later, $R_{xy}(\tau)$ will exhibit a peak at $\tau = -\tau_{delay}$. The cross-renewal density function was estimated as similar to the auto-renewal density function. However, it is not by definition a symmetric function and hence must be estimated for positive as well as for negative values of τ.

The Fourier transform of the auto-renewal density was computed in order to obtain the spectrum of

counts $S_{xx}(f)$ of the interval series [10], which may reveal hidden periodicities. Variance reduction in the spectrum was obtained by applying a Parzen window to the estimated renewal density before transformation [11].

We used shuffling to assess the significance of the renewal density estimates. Suppose that a renewal density $\hat{R}_{xx}(s)$ has been estimated from the set of intervals $\{x_i\}$. Shuffling places these intervals in random order. By computing the renewal densities of L different shuffled series of the same collection of intervals one may compute the average $\hat{R}_{xx}^{(av)}(s)$ and standard deviation $\hat{R}_{xx}^{(sd)}(s)$ of L renewal densities. (In all actual calculations $L = 100$ was used.) Finally, the E-function is computed, which is defined as:

$$E(s) = \frac{\hat{R}_{xx}(s) - \hat{R}_{xx}^{(av)}(s)}{\hat{R}_{xx}^{(sd)}(s)} \tag{5}$$

The E-function is used to give an indication of the randomness of the original series of intervals. For instance, assuming a reasonable amount of data and suitable parameter settings, if $E(s) < -2$ or $E(s) > 2$ occurs for more than 10% of the values of s, or if $E(s) > 4$ for some values of s, then the original series of fever intervals exhibits a very unlikely ordering. The detailed probability properties of the E-function are not yet understood and therefore its trace must be interpreted with care.