Intensity Estimation for Non-Homogeneous Poisson Processes Used to Model Real-Time Medication Event Monitor

Yan Wang* Marc I. Rosen† Jie Shen‡ Brent A. Moore§ Eric S. Daar¶
Honghu Liu‖

Abstract

It is challenge to model medication taking behavior and eventually to predict the change of behavior, especially for those vulnerable patients (e.g. substance abusers). With the help of modern technology (e.g. Wisepill device), we are able to monitor the medication taking behavior in real time. In the meanwhile, after a few minutes delay of detecting the events and analyzing the events, a real time intervention can be generated to communicate with patients directly by the packages of Python, such as text messages to the mobile phone of the patients. The statistical methods that can be used to model the complexity of the medication taking events and to predict the future missed dosage are important for designing the personalized module of the device and therefore personalized intervention. This intervention not only will improve the medication adherence, but the personalized intervention will help to build up the correct medication behavior in the future. In this talk, we use Non-Homogeneous Poisson Process (NHPP) to model the sequence of medication taking during the day. The six hour window (3 hours before and after the dose schedule time) is considered as valid medication taking event. The daily real time medication events were monitored for more than 16 week by Wisepill device. We will model the extreme event of medication taking (outside the designed medication event window). Eventually, we use the model to predict the non-adherence events (missing medication event of the day). Therefore a customized intervention for adherence of medication could be performed on patients in the real-time.

Key Words: Non-Homogeneous Poisson Process, Wisepill, Intensity, adherence

1. Introduction

It is very challenge to model medication taking behavior and eventually to predict the change of behavior, especially for those vulnerable patients with HIV positive. Adherence to medication is used to describe taking your medication exactly as prescribed - at the right times, in the right doses and following any special dietary restrictions.Those drug-positive patients have significant worse medication adherence than those drug-negative patients (Hinkin et al., 2007) and substance use is significantly associated with the treatment failure. Non-adherence can lead to poor patient outcomes and increased healthcare costs.

Wisepill devices (Haberer et al., 2010) is a real-time adherence monitor using Smart Pill Box and and Internet technologies. It use GSM (Global System for Mobile) communication chip to send an electronic medication event record to a central management system (Wisepill Web Server) whenever medication is taken. The Wisepill system records patient

*Department of Biostatistics, Fielding School of Public Health, University of Califonia, Los Angles (UCLA), CA 90095

†Yale University School of Medicine, Department of Psychiatry, New Haven, CT, 06517, and VA Connecticut Healthcare System, West Haven, CT, 06516

‡Division of Public Health and Community Dentistry, UCLA School of Dentistry, Los Angeles, CA 90095

§Yale University School of Medicine, Department of Psychiatry, New Haven, CT, 06517, and VA Connecticut Healthcare System, West Haven, CT, 06516

¶Department of Medicine, HarborUCLA Medical Center, Torrance, CA 90509

‖Division of Public Health and Community Dentistry, UCLA School of Dentistry, David Geffen School of Medicine, Fielding School of Public Health, Los Angeles, CA 90095

adherence by recording real-time date and time of device opening events directly to a web database.

Non-Homogeneous Poisson Process (NHPP) is a general extension of Homogeneous Poisson Process. The intensity function is not a constant but changes over time. In this paper, the maximum likelihood estimation (MLE) is used to estimate the intensity function of the behavior in the exponential Fourier series developed in 2013 (Drazek, 2013).

In section 2, we discuss the theory of MLE method for estimate the intensity function and inter-arrival time. The probability for kth event to be coming in certain small time period is derived. In section 3, the methodology in section 2 is applied to a real study which monitors the medication event behavior of HIV patients who are substance abusers. The intensity function in exponential Fourier format is derived for the medication behavior. In section 4, we discuss the conclusion and some limitation of the methodology. Some future directions about NHPP are also discussed.

2. Methods

In order to derive the final format of the maximum likehood extimation of intensity function of Non-Homogeneous Poisson Process (NHPP), we need the detail notation for all the formulas. In the next subsection, a set of notations for NHPP is illustrated.

2.1 Notation

In below, we will use t to denote the time. We assume the counting process $N(t)$ is a Non-Homogeneous Poisson Process (NHPP) with intensity function $\lambda(t)$ (Karlin et al. 1975). $N(T)$ is the number of events from $(0,T)$ and we assume $N(0)=0$. We use $\lambda(t)$ to describe how the Poisson process changes in time, which is usually called the intensity function. We use capital $\Lambda(t)$ to denote the expected number of events of NHPP on the time interval $(0,t)$, where

$$\Lambda(t)=\int_0^t \lambda(s)ds, t>0$$

Here for each $0<t_1<t_2<\cdots<t_n$, $N(t_1), N(t_2)-N(t_1),\cdots,N(t_n)-N(t_{n-1})$ are independent random variables. The inter-arrival times (arriving time) are $s_1=t_1, s_2=t_2-t_1,\cdots$, $s_n=t_n-t_{n-1}$. Therefore, the probability of having k arrivals or k events during the time $(t,t+x)$ is,

$$P\left(N(t+x)-N(t)=k\right)=\frac{(\Lambda(t+x)-\Lambda(t))^k}{k!}e^{-(\Lambda(t+x)-\Lambda(t))} \tag{1}$$

The probability of $s_1>x$ and total events $N(T)>n$ is denoted by $A(x,n)$, which describes the probability that the first event happens after time x, and there are total of n events by time T. It can be derived from (Yakovlev et al., 2005),

$$\begin{aligned} A(x,n) &= P\left(s_1>x\bigcap N(T)=n\right) \\ &= \frac{1}{\Lambda(T)}\times e^{-\Lambda(x)}\times\frac{(\Lambda(T)-\Lambda(x))^n}{n!}e^{-(\Lambda(T)-\Lambda(x))} \qquad (2) \\ &= \frac{e^{-(\Lambda(T)}}{\Lambda(T)}\times\frac{(\Lambda(T)-\Lambda(x))^n}{n!} \qquad (3) \end{aligned}$$

Here $\frac{1}{\Lambda(T)}$ is a normalization constant (the inverse of the expected number of events from $(0,T)$), $e^{-\Lambda(x)}$ is the probability to have no arrivals on the interval $(0,x)$, and the rest of the

formula is the probability of having exactly n events from (x,T). These probability can be multiplied together is because of the independence of number of events between $(0,x)$ and (x,T).

The next useful quantity is the probability of k^{th} event during $(y,y+dy)$. We use $B(x,y,k,n)$ to denote it (Yakovlev et al., 2005).

$$\begin{aligned} dB(x,y,k,n) &= P\left(t_k \in (y,y+dy) \bigcap s_{k+1} > (y+x) \bigcap N(T) = n\right) \\ &= \frac{1}{\Lambda(T)} \times \frac{(\Lambda(y))^{k-1}}{(k-1)!} e^{-\Lambda(y)} \\ &\times \lambda(y)dy \times e^{-(\Lambda(y+x)-\Lambda(y))} \\ &\times \frac{(\Lambda(T)-\Lambda(y+x))^{n-k}}{(n-k)!} e^{-(\Lambda(T)-\Lambda(y+x))} \qquad (4) \\ &= \lambda(y)dy \frac{e^{-(\Lambda(T)}}{\Lambda(T)} \frac{(\Lambda(y))^{k-1}}{(k-1)!} \frac{(\Lambda(T)-\Lambda(y+x))^{n-k}}{(n-k)!} \qquad (5) \end{aligned}$$

The probability is calculated by multiply the following items. First $\frac{1}{\Lambda(T)}$ is the normalization constant similar as in $A(x,n)$. The next term in (4) describes the probability of having exactly $(k-1)$ events during time $(0,y)$. $\lambda(y)dy$ is the number of events at time y. $e^{-(\Lambda(y+x)-\Lambda(y))}$ denotes the probability for no arrivals from $(y,y+x)$. The last item in (4) is the probability of having exactly $(n-k)$ events from $(y+x,T)$. The idea of calculating $B(x,y,k,n)$ is to divided the time interval $(0,T)$ into sub-intervals $(0,y)$, $(y,y+dy)$, $(y,y+x)$, and $(y+x,T)$. Then the events that happened in these sub-intervals are independent. Therefore, the probability can be multiplied to calculate the quantity. With the two important probability at hand, we are ready to derive the inter-arrival time s and therefore the MLE of intensity function $\lambda(t)$.

2.2 Inter-Arrival Time

The inter-arrival time describes the arrival time for the next events in NHPP. There is close form for the density function of this quantity (Yakovlev et al., 2005). The survival function for this random variable s is the probability of having the next events after time x. The survival function for an inter-arrival time $S > x$ is derived from both $A(x,n)$ and the quantity $B(x,y,k,n)$,

$$\begin{aligned} G(x) &= P(S > x) \\ &= \sum_{n=1}^{\infty} A(x,n) + \sum_{n=2}^{\infty} \sum_{k=1}^{n-1} \int_0^{T-x} dB(x,y,k,n) \\ &= \sum_{n=1}^{\infty} A(x,n) + \sum_{n=2}^{\infty} \sum_{k=1}^{n-1} \int_0^{T-x} dB(x,y,k,n) \\ &= \frac{1}{\Lambda(T)} \int_0^{T-x} \lambda(y+x) e^{-(\Lambda(y+x)-\Lambda(y))} dy \qquad (6) \end{aligned}$$

The survival function satisfied $G(0) = 1$ and $G(T) = 0$. Based on $G(x)$, we can derive the probability density function (pdf) of the inter-arrival time x is given by $(1-G(x))'$ - the derivative of negative survival function,

$$-G'(x) = \frac{1}{\Lambda(T)} \left(\int_0^{T-x} \lambda(y+x) e^{-(\Lambda(y+x)-\Lambda(y))} \lambda(y) dy \right) + \frac{1}{\Lambda(T)} \lambda(x) e^{-\Lambda(x)} \qquad (7)$$

There are some special notes for this density function. The first arrival density is missing in the integral part, but the summation second term will compensate. Also, the pdf to have the inter-arrival time x_{i+1}, given $\sum_{m=1}^{i} s_i = y$ is,

$$\lambda(y+x)e^{-(\Lambda(y+x)-\Lambda(y))} \tag{8}$$

The density function of the inter-arrival time can be used to predict the time that next possible event may come. After model the past events with NHPP, the intensity function $\lambda(t)$, which is estimated by MLE method in the next sub-section, can be calculated. Based on the density for next arrival time can be derived. However, the numerical estimation is not trivial. We will not discuss how this can be estimated in the numeric form.

2.3 Maximum Likelihood Estimate for the Intensity function

The estimation method for intensity function is based on the exponential Fourier transformation, which guarantees the intensity function is positive (Drazek, 2013). Suppose we have the data from the sample $\pi = \{x_1, x_2, \cdots, x_n\}$. Recall, some notations in section 2.1, we denote $\Lambda = \Lambda(T) = \int_0^T \lambda(x)dx$ for the total number of events happened until time T. Therefore, the probability of observe n events is $e^{-\Lambda}\frac{\Lambda^n}{n!}$. The probability of observing x_i is $\frac{\lambda(x_i)}{\Lambda}$. Therefore the probability of observing the sample π is calcuated as $\prod \frac{\lambda(x_i)}{\Lambda}$. The likelihood of observing the sample π is

$$L(\lambda, \pi = \{x_1, x_2, \cdots, x_n\}) = e^{-\Lambda}\frac{\Lambda^n}{n!} \times \prod \frac{\lambda(x_i)}{\Lambda} \tag{9}$$

If the sample is ordered as $x_1 < x_2 < \cdots < x_n$, the likelihood of getting the ordered sample is

$$\begin{aligned} L(\lambda) &= e^{-\Lambda}\frac{\Lambda^n}{n!} \times \prod \frac{\lambda(x_i)}{\Lambda} \times n! \\ &= e^{-\Lambda}\prod \lambda(x_i) \\ &= e^{-\int_0^T \lambda(x)dx}\prod \lambda(x_i) \end{aligned} \tag{10}$$

Therefore, the Log-likelihood is (Drazek, 2013),

$$l(\lambda) = \log(L(\lambda)) = -\int_0^T \lambda(x)dx + \sum_{i=1}^{n} \log \lambda(x_i) \tag{11}$$

To find the best $\lambda(t)$ based on log-likelihood is not easy, we will restrict to a certain family of functions - Exponential Fourier series, where

$$\lambda(x) = \exp\left(a_0 + \sum_{j=1}^{n} b_j \sin(2\pi\frac{x}{T}f_j) + c_j \cos(2\pi\frac{x}{T}f_j)\right) \tag{12}$$

- The fitted model is controlled by changing n and $f_j = jf_1$, assume $f_1 = 1$.
- The function is always non-negative. The model is periodic.

Fourier series are well established in the literature. The R code for estimating the intensity function is developed by Drazek in 2013. The data in this paper was analyzed by R studio (2012).

3. Results

CARE study is short for Centralized off-site adherence enhancement intervention. CARE study is a collaboration between Univeristy of California, Los Angeles (UCLA), Yale University, and Los Angeles Biomedical Research Institute. Part of the study collect the medication behavior data using real-time event monitor - Wisepill device (Harberer et al., 2010). The procedure for the data collection and for how the device works to collect real-time data is shown in Figure 1. The Wisepill device is a pill box containing the medication and the SIM card connecting to the central server in South Africa (SA). When the patient open the device to take medication, the signal of device openning is sent to the server in SA. Meanwhile, UCLA team will detect the event with a 24 hour running computer program. The real-time event from the second patient taking medication to UCLA detecting the event is less within 10 minutes. There is further interaction function, such as sending text messages to the patient's cell phone, which is beyond the scope of this paper.

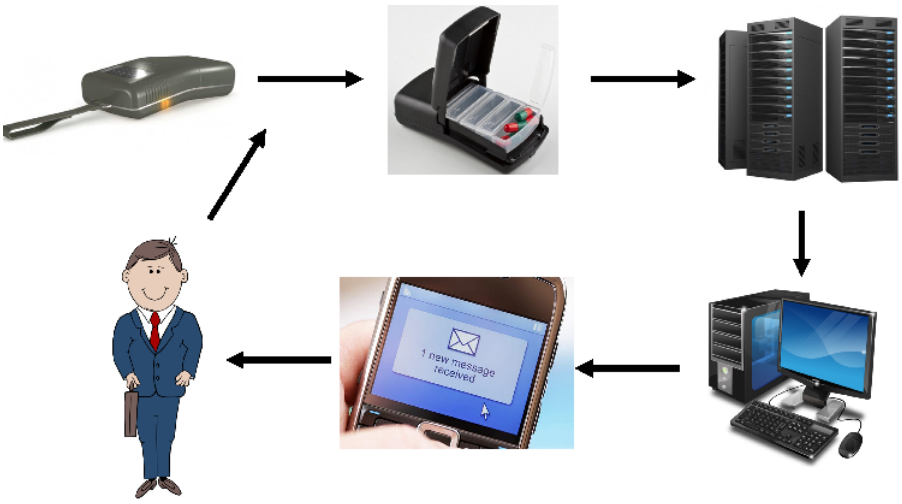

Figure 1: How does the Wisepill work

One example of the data collected from one patient from November 5, 2012 to February 12, 2013 is shown in Figure 2. To examine when these patients take their medications, we illustrate the dose timing intervals using one patient as an example. At the beginning, the dose timing intervals were irregular and this patient was missing some doses. The pattern at the later part of the study indicated that this patient was able to maintain perfect adherence with a regular schedule of taking medication. He was scheduled to take the medication at 10 in the morning and 7 in the afternoon, after the intervention in the study. In this paper, we model the data at the beginning stage, where no intervention is performed. The medication taking behavior can be treated as random events.

We took the data from one patient in a month, with our intervention for his or her medication behavior. The data is the time measured in seconds of medication behavior over a 30-day period. The total number of openning events in the 30 days period (from April 1, 2013 to April 30, 2013) is 63376. We assume in the sub-partition (every 6 hours) there is homogeneous Poisson process. A NHPP is used to model the combination of different homogeneous Poisson process.

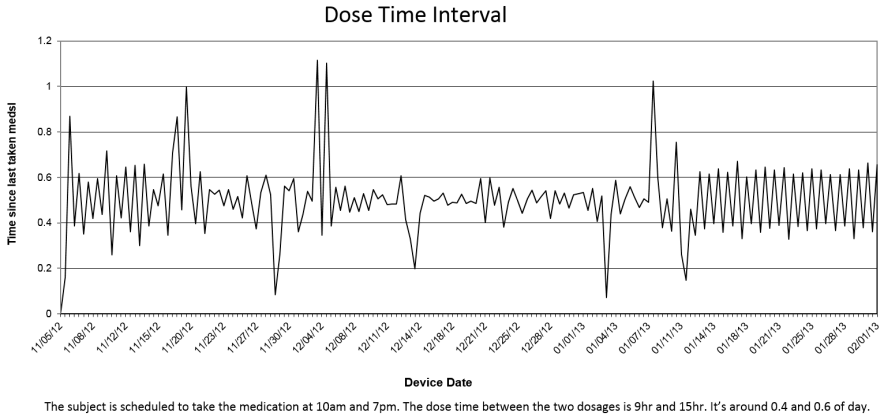

Figure 2: One example of medication taking events

Table 1: Medication events for 30-day period

time	secondtime	second
01APR13:00:00:00	1680393600	0
01APR13:00:02:00	1680393720	120
01APR13:00:08:00	1680394080	480
01APR13:00:08:00	1680394080	480
01APR13:00:09:00	1680394140	540
	... ...	
30APR13:23:56:00	1682985360	2591760
30APR13:23:57:00	1682985420	2591820
30APR13:23:58:00	1682985480	2591880
30APR13:23:59:00	1682985540	2591940

The exponential Fourier format intensity function is as,

$$\lambda(x) = \exp\left(a_0 + \sum_{j=1}^{n} b_j \sin(2\pi \frac{x}{T} f_j) + c_j \cos(2\pi \frac{x}{T} f_j)\right)$$

Use $n = 0$ to $n = 5$ to find the optimal fits to the graph, the estimate coefficients for $a_0, b_1, c_1, b_2, c_2, b_3, c_3, \cdots, b_5, c_5$. We estimate the frequencies used were $f_1 = 1, f_2 = 2f_1, f_3 = 3f_1, \cdots$ etc. for simpler estimation as in (Drazek, 2013). The parameters which are supplied by the user are $\{T, x, n, f_j\}$, where T is the total observing time, x is the current time and n is the nubmer of events. As shown from the R code below, the value of a_0 is almost constant for all n values. However is decreases slowly as n increases, until $n = 5$. For $n = 0$, we have $\exp^{a_0} = -9.05$. This is the value of the intensity of the homogeneous Poisson process for the whole process in 30 days.

We compare the pattern of the intensity function for different number of combinations of homogeneous Poisson process. The output intensity functions are plotted at the below figures for $n = 2$, $n = 3$, $n = 4$, and $n = 5$ (Figure 3). This estimation is unbiased for λ (Drazek, 2013). The nature of intensity function is periodic. We assume the medication behavior is also periodic. Therefore, we can use the periodic Fourier series to estimate the intensity function.

Table 2: Parameters for intensity function λ

n	a_0	b_1	c_1	b_2	c_2	b_3	c_3	b_4	c_4	b_5	c_5
0	-9.050										
1	-9.042	0.033	-0.072								
2	-9.330	0.000	-0.034	-0.712	0.827						
3	-10.982	2.706	1.294	-1.438	1.294	0.888	0.978				
4	-9.923	1.100	-0.609	1.572	0.179	1.212	1.905	-0.007	0.928		
5	-11.561	-1.793	-0.824	-2.654	4.009	-0.333	1.857	1.923	-0.321	0.923	-0.586

The plots of the opening events using the intensity functions are shown in Figure 4 for $n = 1,2,3,4$. The main peak and troughs match the data well when $n = 3$, which indicates a good fit of λ when $n = 3$. When $n = 1,2$, the model does not fit the data. When $n \geq 4$, there is over fit.

4. Discussion

In this paper, we use Non-Homogeneous Poisson Process (NHPP) to model the real-time events of medication behavior. The medication behavior itself is complicated and difficult to model statistically. We hope to find the periodic pattern of the missing dosage and therefore we can predict the missing events. Ideally, we can based on the individualized intensity function of medication events predict the skipped event. An customized, effective, and costless intervention could be developed for each patient.

Medication adherence among the HIV patients who are also substance users is very challenge. The study use the real-time medication event monitor to observe the pattern that a patient taking the medication. The medication events are modeled by NHPP and eventually estimate the personalized intensity function. The function can therefore be used to estimate the inter-arrival time. If the inter-arrival time is greater than expected, some action may be necessary, such as text message reminder for the patients to take his or her medication.

Although we have close form of the density function of inter-arrival time, the numeric solution is not available in this paper. In the future, we can work on derive the explicit solution for estimating the next arrival time of the event, e.g. NewtonRaphson method. There is another limitation in this paper. We do not define the best fit for the density estimation. The density estimation is estimated by the pattern of the judgment of investigator, which is subjective and may not be accurate for modeling the pattern of the medication behavior. A goodness of fit test for the final estimation of intensity function is needed to verify the model.

5. Acknowledgments

We thank the following collaborators for their contributions to the data collection, payment delivery and CBT therapy, in CARE study Karen Ablondi, Anna Sullivan, Mario Guerrero, and Lisa Siqueiros. Also, we thank the patients who participated the CARE study. This work was supported by grant R34DA031643 from the National Institute on Drug Abuse (NIDA)/National Institute of Health (NIH).

REFERENCES

Cebrian, A. C. (2014). Modeling and validation of non homogeneous Poisson processes (R package NHPoisson), last updated July 2, 2014

Drazek, L. C. (2013). Intensity estimation for Poisson Process. *Dissertation in Statistics for Master Degree of The University of Leeds, School of Mathematics*

Haberer, J. E., Kahane, J., Kigozi, I., Emenyonu, N., Hunt, P., Martin, J., Bangsberg, D. R. (2010). Real-Time Adherence Monitoring for HIV Antiretroviral Therapy. *AIDS and Behavior*, 14(6), 13401346. doi:10.1007/s10461-010-9799-4

Hinkin, C. H., Barclay, T. R., Castellon, S. A., Levine, A. J., Durvasula, R. S., Marion, S. D., Longshore, D. (2007). Drug Use and Medication Adherence among HIV-1 Infected Individuals. *AIDS and Behavior*, 11(2), 185194. doi:10.1007/s10461-006-9152-0

Karlin, S., Taylor, H. M. (1975). A First Course in Stochastic Processes, Second Edition. *New York: Academic Press*.

Karlin, S., Taylor, H. M. (1981). A Second Course in Stochastic Processes. *New York: Academic Press*.

RStudio (2012). RStudio: Integrated development environment for R (Version 0.96.122) [Computer software]. Boston, MA. Retrieved May 20, 2012.

Yakovlev, G., Rundle, J. B., Shcherbakov, R., Turcotte, D. L. (2005). Inter-arrival time distribution for the non-homogeneous Poisson process. arXiv:cond-mat/0507657. Retrieved from http://arxiv.org/abs/cond-mat/0507657

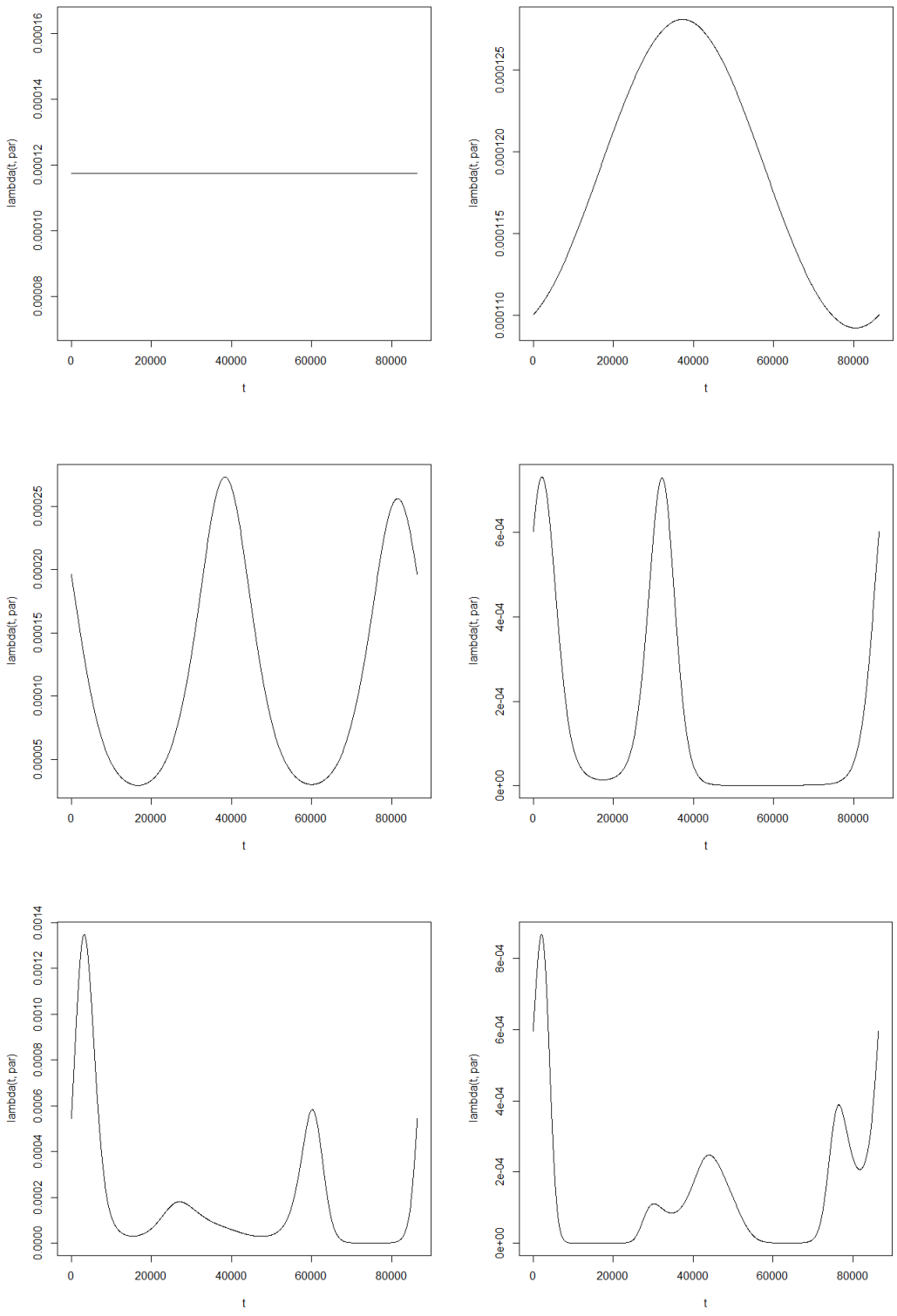

Figure 3: Exponential Fourier Estimation of Intensity function

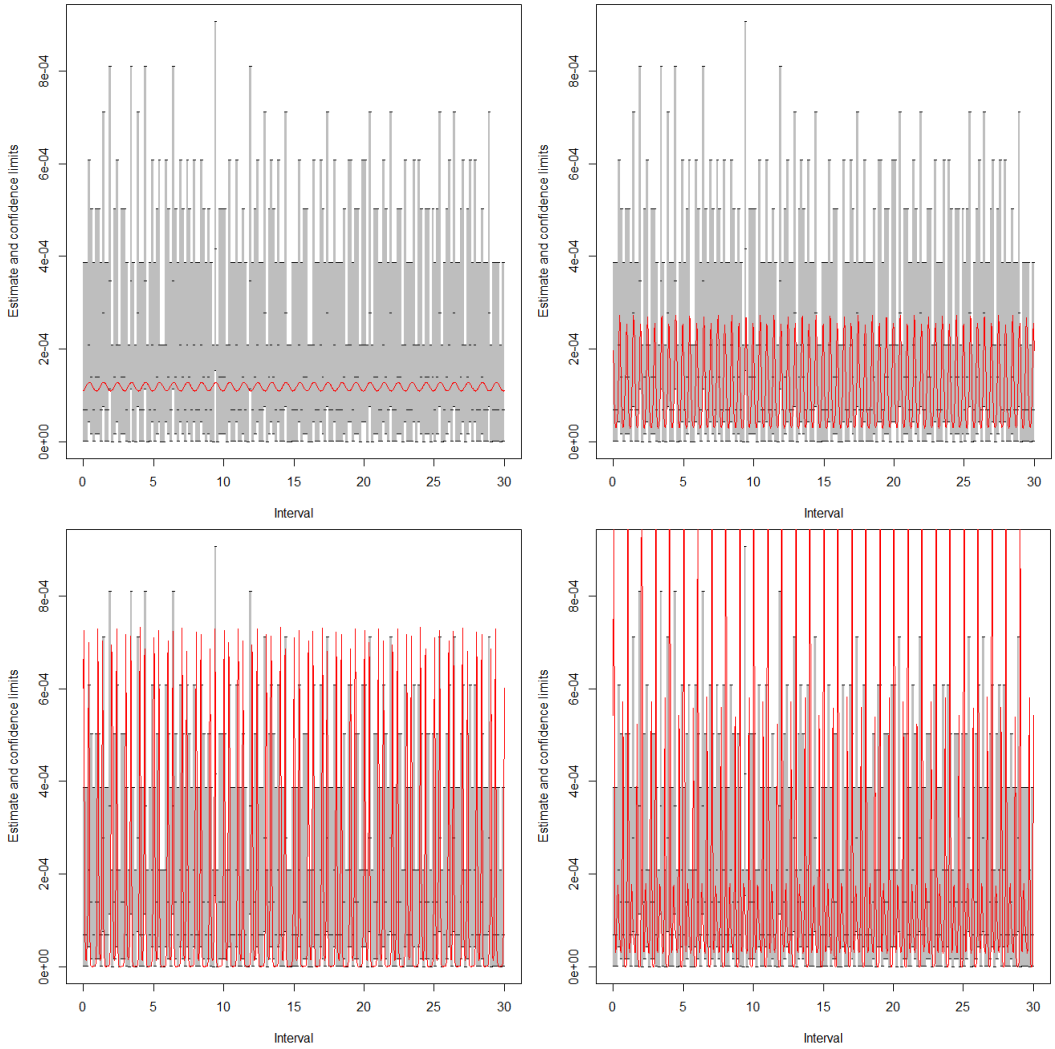

Figure 4: Medication events with intensity function n=1,2,3,4