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A Queueing Model for Chronic Recurrent Conditions under Panel Observation

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SUMMARY. In many chronic conditions, subjects alternate between an active and an inactive state, and sojourns into the active state may involve multiple lesions, infections, or other recurrences with different times of onset and resolution. We present a biologically interpretable model of such chronic recurrent conditions based on a queueing process. The model has a birth–death process describing recurrences and a semi-Markov process describing the alternation between active and inactive states, and can be fit to panel data that provide only a binary assessment of the active or inactive state at a series of discrete time points using a hidden Markov approach. We accommodate individual heterogeneity and covariates using a random effects model, and simulate the posterior distribution of unknowns using a Markov chain Monte Carlo algorithm. Application to a clinical trial of genital herpes shows how the method can characterize the biology of the disease and estimate treatment efficacy.

KEY WORDS: Birth–death process; Chronic disease; Herpes simplex virus; Hidden Markov model; Markov chain Monte Carlo algorithm; Panel data; Queueing process.

1. Introduction

In many medical conditions, subjects make repeated transitions between two states, such as the presence or absence of symptoms or the presence or absence of infection. Furthermore, each sojourn into the active state may involve more than one recurrence of a lesion, infection, or other phenomenon. For example, individuals with an active malaria infection may become superinfected with a different strain of the pathogen, resulting in a sojourn into the active state that is composed of multiple infections (Bailey, 1982), and individuals with latent herpes-virus infections may experience multiple reactivations and reinfections with the virus (Whitley, 1996). The frequency and duration of sojourns into the active state and the frequency and duration of the distinct recurrences may both be of interest.

Such disease processes operate in continuous time, but for practical and economic reasons, subjects may only be observed at discrete time points. The data from such studies consist of a series of states each individual was observed to be in at various points in time and is termed as panel data. Furthermore, the data at each time point may indicate only the active or inactive state, and not the number of recurrences present at that time. For example, a laboratory test may indicate the presence or absence of infection on a given day, but

not the number of concurrent infections, or a clinician may record the presence or absence of lesions, but not the number. Hence, the exact times of transition between active and inactive states and the times of onset and resolution of distinct recurrences are all unknown.

Continuous-time Markov models have been widely used to analyze panel data (Kalbfleisch and Lawless, 1985). However, when additional recurrences may arrive and prolong the time in the active state, the hazard of moving to the inactive state depends on the length of time in the active state, and the Markov assumption may not be appropriate. Semi-Markov models, in which time-in-state can follow an arbitrary distribution, may better describe the biological process, but analysis of semi-Markov models under panel observation is difficult except in very special cases (Lawless and Yan, 1993). We develop a model of such chronic, recurrent conditions that has a clear biological interpretation and can be fit to panel data. The model is based on the Markov/Markov/ ∞ (M/M/ ∞) queueing process (Kleinrock, 1975). The M/M/ ∞ queue has an underlying birth–death process describing recurrences, and a two-state semi-Markov process describing the alternation between active and inactive states. The birth–death process is a continuous-time Markov process, and the analysis of panel data can be achieved using hidden Markov methods. Using

our methods, we estimate characteristics of both the underlying recurrence process and the semi-Markov process.

We apply the model to genital herpes, a chronic, recurrent infection caused by herpes simplex virus type 2 (HSV-2). We analyze panel data collected during a clinical trial of anti-HSV-2 therapy and demonstrate how our methods can be used to characterize the biology of the disease and estimate the effects of treatment. In this application, the M/M/ ∞ queue also serves as a within-host model describing the pathology of the virus in an infected person, and our procedures allow us to infer virologic activity that cannot be observed in human subjects.

In Section 2, we present the model. Section 3 presents estimation procedures, which include a hidden Markov approach for expressing the likelihood, a random effects model to accommodate subject-to-subject variation in the disease process and covariates, and a Markov chain Monte Carlo (MCMC) algorithm for posterior estimation. Application of our method to the HSV-2 clinical trial is presented in Section 4. We conclude with a discussion in Section 5.

2. Model

The M/M/ ∞ queue model, illustrated in Figure 1, has an underlying birth-death process of recurrences and a two-state process alternating between an active and an inactive state. In the birth-death process, recurrences arrive according to a homogeneous Poisson process with intensity $\lambda > 0$. The death rate per recurrence is $\mu > 0$; equivalently, the lifetime of each recurrence is exponentially distributed with mean μ^{-1} . New recurrences may arrive while the system is occupied. Let $Z(t)$ denote the number of recurrences in the system at time t .

Figure 1. The M/M/ ∞ queueing model and panel observation.

Define a two-state process $Y(t)$ that is in the active state (denoted by 1) if any recurrences are present and in the inactive state (denoted by 0) otherwise. Information on the number and timing of recurrences arriving or ending within an active period is lost in the two-state process.

This model describes the biology of the disease using two parameters, λ and μ , which may be interpreted as the arrival rate and resolution rate of recurrences, respectively. Many useful properties of $Z(t)$ and $Y(t)$ have been developed (Kleinrock, 1975) or are readily derived. When the model is applied to chronic recurrent disease, these properties have biological or clinically relevant interpretations. $Z(t)$ is a continuous-time Markov process whose stationary distribution is Poisson with mean λ/μ . Hence one can calculate the probability of having any given number of recurrences concurrently. $Y(t)$ is a semi-Markov process in which sojourns in the inactive state are exponentially distributed with mean λ^{-1} , and sojourns in the active state have mean duration $\lambda^{-1}(e^{\lambda/\mu} - 1)$ and a distribution function described recursively by Daley (2001). The stationary distribution of $Y(t)$ is Bernoulli with probability $e^{-\lambda/\mu}$ for state 0. It is straightforward to derive the probability of visiting the active state during an interval of length s as $s\lambda e^{-\lambda/\mu}$ and the expected number of sojourns in the active state during the interval as $1 - \exp\{-\lambda(\mu^{-1} + s)\}$. These quantities express the risk of relapsing into the disease state over a given period of time.

3. Estimation Procedures

We develop methods of analysis of panel data collected from the two-state semi-Markov process $Y(t)$. For notational convenience, we initially consider data from a single subject with recurrence parameters λ and μ . Let $\mathbf{y} = \{y(t_1), y(t_2), \dots, y(t_m)\}$ denote the observations at time points $\mathbf{t} = (t_1, t_2, \dots, t_m)$. We propose a hidden Markov approach (MacDonald and Zucchini, 1997) to express the likelihood. In a hidden Markov model, a sequence of hidden finite state random variables evolves according to a Markov process. At each observation point, an observation occurs that is conditional on the hidden state. In our formulation, the hidden Markov process is $Z(t)$ and the observations are taken from $Y(t)$. The likelihood of the observed data

$$L(\lambda, \mu; \mathbf{y}, \mathbf{t}) \propto \Pr\{Y(t_1) = y(t_1), \\ Y(t_2) = y(t_2), \dots, Y(t_m) = y(t_m)\} \quad (1)$$

may be computed using the forward recursion procedure for hidden Markov models developed by Baum et al. (1970); see also Lange (1999). Denote the hidden states at the observation points as $Z(t_1), \dots, Z(t_m)$. The procedure constructs the likelihood by recursively evaluating the joint probabilities

$$\alpha_k(u) = \Pr\{Y(t_1) = y(t_1), \dots, Y(t_{k-1}) = y(t_{k-1}), Z(t_k) = u\}. \quad (2)$$

At the first observation point, $\alpha_1(u) = \Pr\{Z(t_1) = u\}$. The update is

$$\alpha_{k+1}(u) = \sum_l \alpha_k(l) p_{lu}(t_{k+1} - t_k) \phi\{y(t_k) | l\}, \quad (3)$$

where $p_{lu}(t_{k+1} - t_k) = \Pr\{Z(t_{k+1}) = u | Z(t_k) = l\}$ are the finite-time transition probabilities for the hidden Markov process and $\phi\{y(t_k) | l\} = \Pr\{Y(t_k) = y(t_k) | Z(t_k) = l\}$ is the conditional distribution of the observation given the hidden state. Construction of the likelihood is completed by computing

$$\sum_l \alpha_m(l) \phi\{y(t_m) | l\} \quad (4)$$

at the final observation point.

Assuming a stable disease process over the period of observation, the initial distribution of hidden states may be taken as the stationary distribution of $Z(t)$. To derive the finite-time transition probabilities $p_{lu}(t)$, define the generating function

$$Q(s, t, l) = \sum_{u=0}^{\infty} p_{lu}(t) s^u \quad (5)$$

for $s \in [0, 1]$, from which one may derive the probabilities

$$p_{lu}(t) = \frac{1}{u!} \frac{\partial^u}{\partial s^u} Q(s, t, l) |_{s=0}. \quad (6)$$

Using the treatment of Kendall's birth-death-immigration process in Lange (2003), we obtained the generating function for the recurrence process as

$$Q(s, t, l) = \{1 + (s - 1)e^{-\mu t}\}^l \exp\left\{\frac{\lambda}{\mu}(s - 1)(1 - e^{-\mu t})\right\}. \quad (7)$$

By the definition of $Y(t)$, the conditional distribution $\phi\{y(t_k) | l\}$ is an indicator function equaling 1 if $\{Z(t) = 0, Y(t) = 0\}$ or $\{Z(t) \geq 1, Y(t) = 1\}$, and 0 otherwise.

We now consider a group of n subjects, indexed by i . Individual heterogeneity in disease patterns may be accommodated using a random effects model that ascribes to each subject their own recurrence parameters λ_i and μ_i . In our application, each subject has two sequences of data, $\mathbf{y}_i^P$ under placebo and $\mathbf{y}_i^T$ under treatment, taken at times recorded in the vectors $\mathbf{t}_i^P$ and $\mathbf{t}_i^T$, respectively. Different number of observations per individual are allowed and observation times may be unequally spaced and different for different subjects. The two sequences of data may be considered to arise from two sets of parameters, (λ_i^P, μ_i^P) and (λ_i^T, μ_i^T) , and are conditionally independent given these parameters. Thus, the likelihood of each sequence may be computed independently.

A random effects distribution that accommodates wide variation in disease patterns and the positivity of the parameters is the multivariate log-normal distribution. To model the effects of covariates, we express the mean of the random effects distribution as a function of covariates. Let $\psi_i = \{\ln \lambda_i^P, \ln \mu_i^P, \ln \lambda_i^T, \ln \mu_i^T\}$, and let $\mathbf{X}_i$ denote the design matrix for individual i . The random effects model is $\psi_i \sim N(\mathbf{X}_i \boldsymbol{\beta}, \boldsymbol{\Sigma})$.

EM-type algorithms and empirical Bayes procedures could be considered for computing maximum likelihood estimates in this model, but would be computationally difficult with uncertain performance. In contrast, estimation of this model is readily achieved using a full Bayesian approach with Gibbs sampling. Gibbs sampling also facilitates inference for the

nonlinear functions of λ and μ that characterize the two-state semi-Markov process. Thus, we propose a Bayesian framework and MCMC methods to perform inference. To complete the Bayesian specification, one may use independent prior distributions

$$\boldsymbol{\beta} \sim N(\mathbf{b}, \mathbf{C}) \quad (8)$$

$$\boldsymbol{\Sigma}^{-1} \sim W\{\nu, (\nu \boldsymbol{\Lambda})^{-1}\}, \quad (9)$$

where $W(\eta, \boldsymbol{\Gamma})$ denotes the Wishart distribution with η degrees of freedom and scale matrix $\boldsymbol{\Gamma}$.

A Gibbs sampling algorithm can be derived from the model specification. Let $(\boldsymbol{\theta} | \cdot)$ denote the full conditional distribution of $\boldsymbol{\theta}$ given all other parameters. The full conditional distributions used in the Gibbs sampler are

$$(\psi_i | \cdot) \sim L(\lambda_i^P, \mu_i^P; \mathbf{y}_i^P, \mathbf{t}_i^P) L(\lambda_i^T, \mu_i^T; \mathbf{y}_i^T, \mathbf{t}_i^T) N(\mathbf{X}_i \boldsymbol{\beta}, \boldsymbol{\Sigma}) \quad (10)$$

$$(\boldsymbol{\beta} | \cdot) \sim N(\hat{\boldsymbol{\beta}}, \mathbf{V}_\beta) \quad (11)$$

$$(\boldsymbol{\Sigma}^{-1} | \cdot) \sim W\left[\nu + n, \left\{\nu \boldsymbol{\Lambda} + \sum_{i=1}^n (\psi_i - \mathbf{X}_i \boldsymbol{\beta})(\psi_i - \mathbf{X}_i \boldsymbol{\beta})^T\right\}^{-1}\right], \quad (12)$$

where $\mathbf{V}_\beta = (\sum_{i=1}^n \mathbf{X}_i^T \boldsymbol{\Sigma}^{-1} \mathbf{X}_i + \mathbf{C}^{-1})^{-1}$ and $\hat{\boldsymbol{\beta}} = \mathbf{V}_\beta \{\sum_{i=1}^n \mathbf{X}_i^T \boldsymbol{\Sigma}^{-1} \psi_i + \mathbf{C}^{-1} \mathbf{b}\}$.

The full conditional distribution of ψ_i is a nonstandard distribution involving computation of the likelihood using the forward recursion procedure. To simulate these parameters, we propose a Metropolis step with a random walk proposal. The full conditional distributions for $\boldsymbol{\beta}$ and $\boldsymbol{\Sigma}^{-1}$ are standard distributions that can be readily simulated.

From the posterior distribution of $\boldsymbol{\beta}$, one may obtain the posterior distributions of $E(\ln \lambda)$ and $E(\ln \mu)$ for given covariate values. Transformation from the log-normal yields the posterior distributions of $E(\lambda)$ and $E(\mu)$, which characterize the recurrence process. Features of the semi-Markov process may be obtained as functions of $E(\lambda)$ and $E(\mu)$, as described in Section 2. The posterior distributions of these quantities may be simulated by computing each quantity at each sweep of the Gibbs sampler.

4. Application: HSV-2 Antiviral Clinical Trial

Genital herpes, a condition affecting about 20% of the U.S. adult population (Fleming et al., 1997), is a chronic recurrent disease caused by infection with HSV-2 (Corey and Wald, 1999). HSV-2 causes disease by establishing latency in nerve cells in the sacral ganglia and intermittently reactivating to infect the genital tract. During genital infection, the virus enters secretions, where its presence is termed viral shedding. During a shedding episode, individuals are infectious and may develop lesions. Viral shedding often occurs asymptotically. A shedding episode may involve multiple genital infections beginning and ending at different times. The immune system responds to and resolves the genital infections. However, the

virus remains latent in the nerve cells and continues to reactivate intermittently.

Many features of the disease are poorly understood. The causes of viral reactivation have not been identified, and reactivation occurs at an anatomical site that cannot be monitored in human subjects. Data from HSV-2-infected subjects can be collected by periodically sampling genital secretions and testing for the presence of HSV-2. However, such panel data indicate only the shedding state at a series of discrete time points, and not the times of viral reactivation, the times of transition between shedding and nonshedding states, or the number of genital infections present at the time the sample was taken. Hence there is a need for methods of inferring viral activity based on the available data. Furthermore, available treatments reduce but do not fully control viral activity (Corey, 2002). Hence there is also a need for methods of characterizing treatment efficacy.

The model may be applied to this disease as follows. Consider each genital infection a recurrence. Genital infections are initiated by reactivations of latent virus, which occur at largely random times. Let λ be the intensity of the Poisson process of reactivation, and let μ be the genital infection-clearance rate. The model now fully parameterizes the biological activities of reactivation of virus in the ganglia and genital infection, and explains how these activities give rise to viral shedding patterns. Such models of viral activity in an infected individual are termed within-host models. Deterministic within-host models have been widely used to study human immunodeficiency virus and other viruses (Perelson, 2002). We note that in the herpes literature, the term “recurrence” is typically used to describe a symptomatic genital infection, whereas we use the term more generally to refer to a genital infection regardless of whether or not it is accompanied by symptoms.

We applied the model to data from a randomized, double-blind, placebo-controlled, clinical trial of anti-HSV therapy. The trial, described in Wald et al. (1996, 1997), had a crossover design in which the subjects, all women, were randomly assigned to receive acyclovir for 70 days, followed by a 14-day washout period under placebo, then placebo for 70 days, or the study medications in the reverse order. Viral shedding was ascertained by collecting swabs of genital secretions once daily and testing for HSV-2 using highly sensitive DNA polymerase chain reaction (PCR) assays, with detection limits of 200–500 genome copies per milliliter. We analyzed the viral shedding data from the 14 subjects who participated in both arms of the trial. For subjects to whom placebo was administered first, the washout period was included in the placebo period. The subjects had PCR results for a mean of 71 days while on placebo (range 57–83 days) and a mean of 59 days on treatment (range 8–74 days).

We used the multivariate log-normal random effects model with covariates for treatment effects on the natural logarithm of the reactivation rate and genital infection clearance rate. For prior distributions, we used noninformative specification of the hyperparameters $\mathbf{b}$ and $\mathbf{C}$ in (8). Because the small sample contained little information on the covariance matrix, we used prior information from 13 similar subjects to specify the hyperparameter Λ in the prior for Σ in (9) and set ν equal to 13. Gibbs sampling procedures were performed using C programming language code developed for this model. We

Figure 2. Kernel density plots of prior and posterior densities.

ran the Gibbs sampler for 20,000 iterations, and discarded the first 5000 as burn-in. Based on the examination of trace and autocorrelation plots, convergence appeared to occur within the first 1000 iterations, and mixing was good.

Posterior results for the effect of treatment on $E(\ln \lambda)$ and $E(\ln \mu)$ and comparison with the prior distribution are presented in Figure 2. The figure shows that the data were highly informative and that the treatment affected both virologic processes, shifting the reactivation rate down and the genital infection clearance rate up. The posterior probability that the difference in $E(\lambda)$ between the treatment and the placebo periods exceeded zero was 0.005, and the posterior probability that the difference in $E(\mu)$ exceeded zero was 0.012, indicating strong evidence of a significant treatment effect.

Table 1 provides estimates of specific viral activities under placebo and treatment. The placebo results provide the first estimates of the natural rate of reactivation of the virus in the sacral ganglia in human subjects. The results portray a highly active, rapidly changing infection, in which subjects reactivated the virus frequently and experienced multiple short genital infections. Virus was shed from the genital tract in short, frequent bursts lasting for about 2 days on average.

The estimates for viral activity under treatment locate and quantify the drug’s effect. Acyclovir reduced the frequency of reactivation by about half. This finding suggests that the drug was effective in the nerve cells where reactivation occurs, or acted immediately after reactivation to suppress viral replication in the genital tract before it reached detectable levels. The drug was quite effective in the genital tract; treatment doubled the genital infection clearance rate, thereby halving the mean length of genital infections. These two effects are reflected in the viral shedding pattern. Under treatment, subjects had a much sparser pattern of shedding, with episodes that were both less frequent and shorter.

As a measure of infectiousness, we estimated the proportion of time in a shedding state. This proportion was about one-quarter under placebo, and was significantly reduced under treatment. We also estimated the probability of experiencing any shedding on a given day. This measure may be useful in communicating with patients about the highly active nature of the infection and the risk of infecting sexual

Table 1
Posterior summary of herpes simplex virus activity under placebo and acyclovir treatment

Viral activity measure	Placebo		Treatment		Percent change	
	Posterior median	95% credible interval	Posterior median	95% credible interval	Posterior median (%)	95% credible interval
Annual number of reactivations in sacral ganglia ^a	58	(28, 102)	26	(13, 44)	-56	(22%, -80%)
Duration of a genital tract infection (days)	1.8	(1.1, 2.7)	0.9	(0.5, 1.6)	-49	(-13%, -74%)
Annual number of shedding episodes	43	(28, 66)	24	(13, 40)	-44	(-5%, -70%)
Duration of a shedding episode (days)	2.2	(1.2, 3.3)	1.0	(0.5, 1.6)	-55	(-21%, -78%)
Duration of a nonshedding period (days)	6.3	(3.0, 10)	14	(6.8, 23)	56	(22%, 80%)
Proportion of time in a shedding state	0.25	(0.12, 0.44)	0.065	(0.027, 0.12)	-75	(-56%, -88%)
Probability of shedding on any given day	0.36	(0.20, 0.58)	0.13	(0.07, 0.21)	-64	(-44%, -81%)

^aReactivations resulting in a detectable level of viral shedding in the genital tract.

partners. This probability was also significantly reduced under treatment.

5. Discussion

In many chronic recurring medical conditions, sojourns into the active state involve multiple recurrences of lesions, infections, or other pathological phenomena with overlapping times of onset and resolution. However, panel data collected from the subjects may indicate only the active or inactive state at a series of discrete time points and not the transition times or number of recurrences. We have proposed a model for such chronic recurrent conditions that has a lucid biological interpretation and can be applied to panel data. Using our methods, one can estimate features of both the two-state active-inactive disease process and the underlying recurrence process. The procedures accommodate subject-to-subject variation in disease patterns.

Under the model, chronic recurrent conditions are decomposed into two biological processes, recurrence arrival and resolution, which may have different etiologies. Using the methods proposed in this article, one can model the effect of covariates on these processes separately and thereby obtain a better understanding of the biology of the disease. The decomposition may also be useful in guiding clinical management of the condition. For example, some subjects may have frequent recurrences that resolve quickly, while others have infrequent recurrences that resolve slowly. In the former case, treatments targeting the frequency of recurrences may be most effective while in the latter case, speeding the resolution of recurrences may be indicated.

By parameterizing the biological process, the model enables the use of available data to infer biological activity that is difficult to observe. By applying the model to viral shedding data from genital swabs collected during a clinical trial for genital herpes, we were able to infer viral activity at an anatomical

site (the sacral ganglia) that is not readily accessible in human subjects. We were also able to estimate the effectiveness of a drug treatment in different physiological compartments. Such estimates may be a useful adjunct to pharmacokinetic studies.

The model proposed in this article is appropriate when recurrences may be assumed to arrive at random times and run their course independently of each other. Under these assumptions, the recurrence process has Markov properties, which permit the analysis of panel data using a hidden Markov approach. Some physiological conditions not meeting these assumptions might be accommodated using different assumptions in the underlying birth-death process. We have also restricted attention in this article to time-homogeneous processes. Inhomogeneous processes could be addressed by incorporating time dependence into the birth-death parameters.

In summary, we have proposed a model for chronic conditions when the active state of the condition involves multiple recurrences of lesions, infections, or other phenomena. The model has a biological interpretation that is useful in characterizing and managing chronic conditions and can be applied when monitoring is intermittent and provides only a binary assessment of the condition.

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RÉSUMÉ

Dans beaucoup de maladies chroniques, les sujets alternent entre un état dit «actif» et un état dit «inactif», le maintien durable dans un état actif impliquant souvent des lésions multiples, des infections ou d'autres événements récurrents, pouvant intervenir avec divers timings de débuts et de fins de crises. Nous présentons un modèle biologiquement interprétable de telles conditions récurrentes chroniques, basé sur un processus de type «files d'attente». Le modèle se compose d'un processus décrivant les récurrences des événements et d'un processus semi-markovien décrivant l'alternance entre les états actifs et inactifs; on peut de surcroît l'adapter, en utilisant une approche markovienne «masquée», à des données où l'on ne connaît qu'une évaluation binaire de l'état actif ou inactif des patients pour une série de temps discrets. Grâce à un modèle à effets aléatoires, nous pouvons aussi prendre en compte la présence de covariables et modéliser l'hétérogénéité entre les patients. Enfin, nous pouvons simuler la distribution a posteriori de paramètres inconnus, en utilisant un algorithme de Monte Carlo de chaîne de Markov. Une application de cette méthode à un essai clinique sur l'herpès génital illustre sa capacité à caractériser la biologie de la maladie et à estimer l'efficacité d'un traitement à l'étude.

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