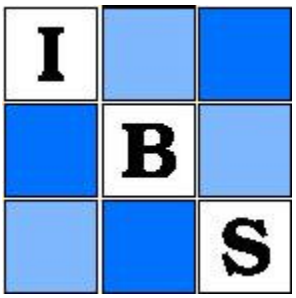

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A Markov Model for Sequences of Ordinal Data from a Relapsing–Remitting Disease

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SUMMARY

Many chronic diseases follow a course with multiple relapses into periods with severe symptoms alternating with periods of remission; experimental allergic encephalomyelitis, the animal model for multiple sclerosis, is an example of such a disease. A finite Markov chain is proposed as a model for analyzing sequences of ordinal data from a relapsing–remitting disease. The proposed model is one in which the state space is expanded to include information about the relapsing–remitting status as well as the ordinal severity score, and a reparameterization is suggested that reduces the number of parameters needed to be estimated. The Markov model allows for a wide range of relapsing–remitting behavior, provides an understanding of the stochastic nature of the disease process, and allows for efficient estimation of important characteristics of the disease course (such as mean first passage times, occupation times, and steady-state probabilities). These methods are applied to data from a study of the effect of a treatment (transforming growth factor-β_1) on experimental allergic encephalomyelitis.

1. Introduction

Many chronic diseases follow a course with multiple relapses of severe symptoms separated by periods with mild or no symptoms. This paper proposes a class of Markov models for analyzing sequences of ordinal data from a relapsing–remitting disease. The model is one in which the state space is expanded to include information about the ordinal severity score as well as the relapsing–remitting status, and a parameterization is suggested that reduces the number of parameters to be estimated. The model is illustrated using data from a study of experimental allergic encephalomyelitis (EAE).

EAE is a relapsing–remitting disease, characterized pathologically by inflammation and demyelination in the central nervous system, which can be induced in mice and closely mimics relapsing–remitting multiple sclerosis (MS) in humans. The disease course manifests itself clinically by nondeterministic fluctuations between periods of worsening symptoms and periods when symptoms improve. A frequently used design for the study of the effect of a new therapeutic agent on EAE is to induce EAE in a group of mice, and then randomize each mouse to either a placebo or a therapeutic agent. In our example, individual mice were subsequently examined (follow-up period of 40 days) for daily signs of disease and graded on a 0–4 scale of increasing severity: 0, no abnormality; 1, a floppy tail with mild hind limb weakness; 2, a floppy tail with moderate hind limb weakness; 3, hind leg paresis but not complete paralysis; and 4, total paralysis of hind legs, which may be associated with moderate forelimb weakness (Pettinelli and McFarlin, 1981). The scientific interest of these studies is to understand the stochastic nature of the disease process as well as the effect of a treatment on that process.

Ware, Lipsitz, and Speizer (1988) classify models for repeated categorical data as being either marginal, where changes in the marginal distribution of the outcome are of interest, or transitional, where an individual's changing response is of interest. The proposed model is transitional, where the interest is in describing and making inferences about an individual's relapsing–remitting disease course. A number of discrete-time Markov models have been proposed for analyzing repeated

Key words: Finite Markov chains; Relapsing–remitting diseases; Repeated measures; Stochastic processes.

categorical data. Muenz and Rubinstein (1985) propose discrete-time Markov chains for modeling binary sequences; others have proposed Markov chains for analyzing repeated categorical and ordinal data [Bishop, Fienberg, and Holland (1975), Chuang and Francom (1986), and Hopper and Young (1988), among others]. These models are all Markov chains with a state space containing the levels of the observed outcome. The model proposed in this paper is a Markov chain that allows for a flexible representation of relapsing–remitting behavior by expanding the state space to include, in addition to the levels of the observed outcome, an indicator function for whether the process is relapsing or remitting.

Section 2 develops the Markov chain model with an expanded state space; a parameterization for the transition probabilities is proposed. In Section 3, measures for summarizing disease severity are proposed and model-based estimates are derived. The model is applied to the analysis of EAE data in Section 4, and a discussion with suggestions for extensions is provided in Section 5.

2. Statistical Model

Denote X_t as a Markov chain with states $((Y_t, S_t), Y_t = 0, 1, 2, 3, \ldots, k, S_t = 1 \text{ and } -1)$, where Y_t is the category of disease severity at time t, and S_t indicates whether the process is relapsing (worsening) ($S_t = 1$) or remitting (improving) ($S_t = -1$) at time t. We have five levels of disease severity in the EAE example; therefore, we take $k = 4$. The process is remitting ($S_t = -1$) if the last nonzero change in disease severity ($Y_t - Y_{t-1}$) is negative. Likewise, the process is relapsing ($S_t = 1$) if the last nonzero change in disease severity ($Y_t - Y_{t-1}$) is positive. The unrestricted one-step transition probability matrix, containing 50 nonzero elements (parameters), is given in the Appendix. The decomposition of the transition probabilities as the product of two conditional probabilities,

$$P[(Y_t, S_t)|(Y_{t-1}, S_{t-1})] = P(S_t|S_{t-1}, Y_{t-1})P(Y_t|Y_{t-1}, S_t, S_{t-1}),$$

suggests parameterizations that have biological interpretation, allow for a wide range of relapsing–remitting behavior, and reduce the number of parameters needed to estimate.

The two conditional probabilities on the right side of the above equation have different biological interpretations. The probabilities $P(S_t|S_{t-1}, Y_t)$ describe the transitioning between relapsing and remitting, and the probabilities $P(Y_t|Y_{t-1}, S_t, S_{t-1})$ characterize the rate of symptom worsening while relapsing and symptom improvement while remitting. Inspection of EAE data indicated that these probabilities were relatively constant for intermediate values of Y_{t-1}, hence motivating the following parameterization.

The basic model proposed is an eight-parameter formulation in which $P(S_t|S_{t-1}, Y_t)$ and $P(Y_t|Y_{t-1}, S_t, S_{t-1})$ are modeled with four parameters each. First $P(S_t|S_{t-1}, Y_{t-1})$ can be parameterized by

$$P(S_t = 1|S_{t-1} = -1, Y_{t-1}) = \begin{cases} 0 & Y_{t-1} = 4, \\ \theta & 0 < Y_{t-1} < 4, \\ \theta_0 & Y_{t-1} = 0, \end{cases}$$

and (2.1)

$$P(S_t = -1|S_{t-1} = 1, Y_{t-1}) = \begin{cases} 0 & Y_{t-1} = 0, \\ \Delta & 0 < Y_{t-1} < 4, \\ \Delta_4 & Y_{t-1} = 4, \end{cases}$$

where θ and θ_0 are the probabilities of transitioning from remitting to relapsing (over unit time) given prior disease ($0 < Y_{t-1} < 4$) or no disease ($Y_{t-1} = 0$), respectively. Likewise, Δ and Δ_4 are the probabilities of transitioning from relapsing to remitting over unit time. This parameterization allows for different probabilities of relapsing and remitting at the boundaries of Y_{t-1} (θ_0 and Δ_4) as compared with values of Y_{t-1} between those boundaries (θ and Δ).

Second, the probability of a change in disease severity from Y_{t-1} to Y_t given continued relapsing or remitting status ($P(Y_t|Y_{t-1}, S_t = 1, S_{t-1} = 1)$ or $P(Y_t|Y_{t-1}, S_t = -1, S_{t-1} = -1)$) can be parameterized by

$$P(Y_t \le y|Y_{t-1}, S_t = 1, S_{t-1} = 1) = \begin{cases} 0 & y < Y_{t-1}, \\ \dfrac{\exp(\delta + \beta_1(y - Y_{t-1}))}{1 + \exp(\delta + \beta_1(y - Y_{t-1}))} & Y_{t-1} \le y < 4, \\ 1 & y = 4, \end{cases} \quad (2.2)$$

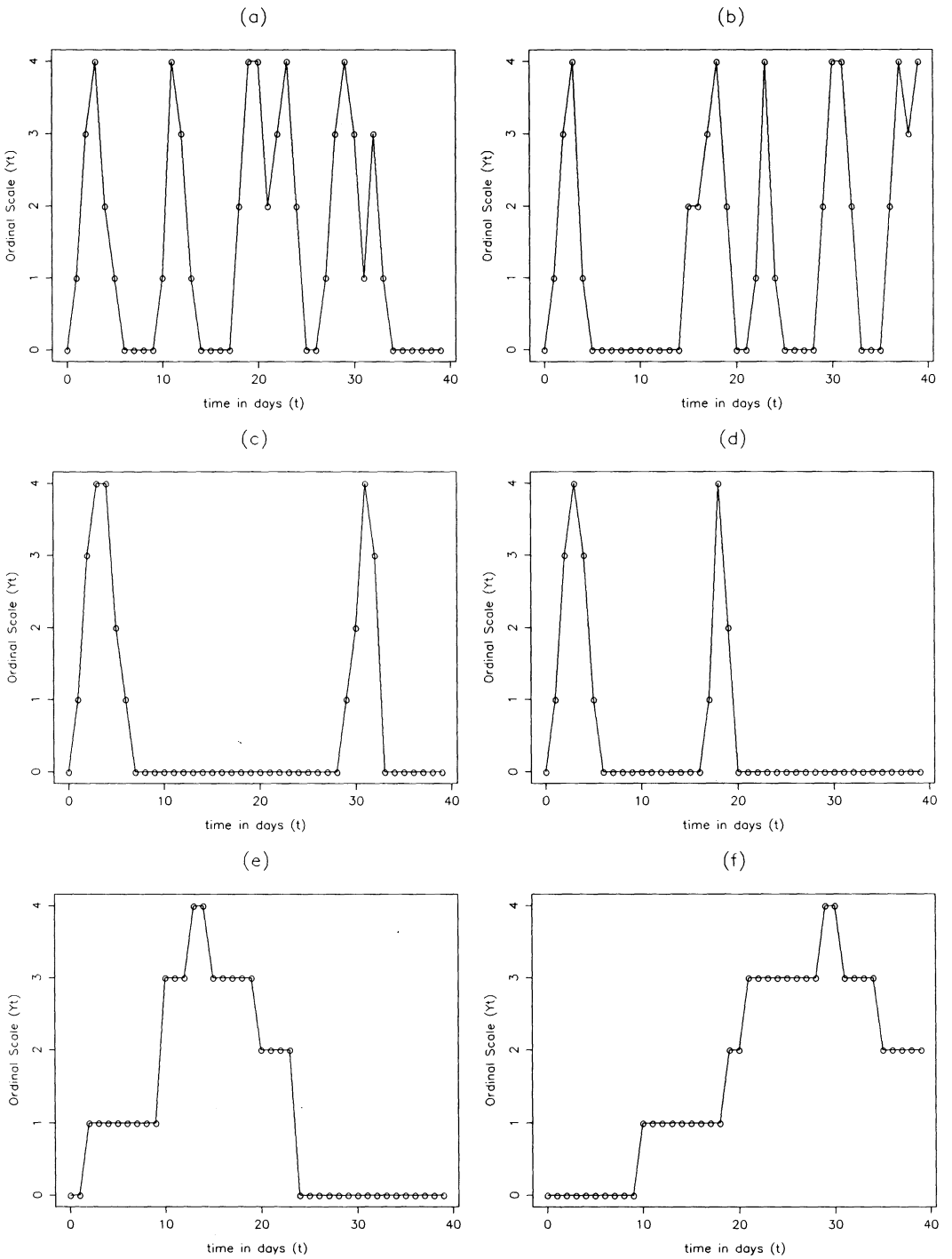

Figure 1. Two simulated realizations from the Markov relapsing–remitting model from each of three sets of parameter values: (a) and (b) are generated from a process with parameters $\phi = (\theta_0\ \theta\ \Delta\ \Delta_4\ \gamma\ \delta\ \beta_D\ \beta_I) = (.1\ .1\ .1\ .5\ -2\ -2\ 2\ 2)$, (c) and (d) from $\phi = (.02\ .02\ .02\ .5\ -2\ -2\ 2\ 2)$, and (e) and (f) from $\phi = (.02\ .02\ .02\ .5\ 2\ 2\ 2\ 2)$.

and

$$P(Y_t \geq y | Y_{t-1},\ S_t = -1,\ S_{t-1} = -1) = \begin{cases} 0 & Y_{t-1} < y, \\ \dfrac{\exp(\gamma + \beta_D(Y_{t-1} - y))}{1 + \exp(\gamma + \beta_D(Y_{t-1} - y))} & 0 < y \leq Y_{t-1}, \\ 1 & y = 0, \end{cases}$$

where δ and γ are the logit-transformed probabilities of having a constant disease severity given a continued relapsing and remitting status, respectively. Large values of β_I and β_D translate to small probabilities of increases or decreases of more than one level in disease severity over a unit time. In parameterizing the probabilities of a change in disease severity from Y_{t-1} to Y_t given a changing relapsing–remitting status, we assume that these probabilities depend on S_{t-1} only in that $Y_t - Y_{t-1}$ must be nonzero. The probabilities are normalized to permit the probabilities of allowable events to sum to 1:

$$P(Y_t = w|Y_{t-1} = v, S_t = 1, S_{t-1} = -1) = \begin{cases} \dfrac{P(Y_t = w|Y_{t-1} = v, S_t = 1, S_{t-1} = 1)}{1 - P(Y_t = v|Y_{t-1} = v, S_t = 1, S_{t-1} = 1)} & v < w, \\ 0 & \text{otherwise,} \end{cases}$$

and (2.3)

$$P(Y_t = w|Y_{t-1} = v, S_t = -1, S_{t-1} = 1) = \begin{cases} \dfrac{P(Y_t = w|Y_{t-1} = v, S_t = -1, S_{t-1} = -1)}{1 - P(Y_t = v|Y_{t-1} = v, S_t = -1, S_{t-1} = -1)} & w < v, \\ 0 & \text{otherwise.} \end{cases}$$

Maximum likelihood estimates of the model parameters $\phi = (\theta_0\ \theta\ \Delta\ \Delta_4\ \gamma\ \delta\ \beta_D\ \beta_I)$, denoted by the vector ϕ, can be obtained by maximizing the log-likelihood (see Appendix) by a Newton–Rapshon procedure.

This Markov model provides a representation for a wide range of relapsing–remitting behavior. Two simulated realizations from each of three sets of parameter values are shown in Figure 1. Two typical realizations (Figures 1a and 1b) from a process with parameters $\phi = (\theta_0\ \theta\ \Delta\ \Delta_4\ \gamma\ \delta\ \beta_D\ \beta_I) =$ (.1 .1 .1 .5 −2 −2 2 2) show rapid cycling between relapses and remissions with rapid progression into and out of periods with severe symptoms. Two realizations from a second set of parameters [$\phi = (\theta_0\ \theta\ \Delta\ \Delta_4\ \gamma\ \delta\ \beta_D\ \beta_I) =$ (.02 .02 .02 .5 −2 −2 2 2)] show less frequent exacerbations but a rapid deterioration followed by a rapid improvement when the exacerbations occur (Figures 1c and 1d). Two realizations from the last set of parameters [$(\theta_0\ \theta\ \Delta\ \Delta_4\ \gamma\ \delta\ \beta_D\ \beta_I) =$ (.02 .02 .02 .5 2 2 2 2)] show much more gradual improvement and worsening of symptoms (Figures 1e and 1f).

3. Measures of Disease Severity

The Markov relapsing–remitting model allows for the efficient estimation of various measures of disease severity, including occupation times, first passage times, and steady-state probabilities. Denote $N_{(i)j}(T)$ as a number of visits to state j over T transitions given that the process is in the ith state at time 0; these are called occupation times (Parzen, 1962). The mean occupation times can be written as sums of expectations of indicator functions ($I_j^l = 1$ if the process is in the jth state at time l, $I_j^l = 0$ otherwise). Noting that $E(I_j^l; \phi) = P^l[i, j; \phi]$, where $P[i, j, \phi]$ is the one-step transition matrix parameterized by ϕ, we have

$$E(N_{(i)j}(T; \phi)) = \sum_{l=1}^{T} P^l[i, j; \phi]. \tag{3.1}$$

A model-based comparison of the mean occupation times in a relapse (the number of visits to a state with disease severity $\geq A$, denoted by $N_{(i)A}$) between treatment and placebo groups can be made by substituting the Markov model parameters estimated from both groups into expression (3.1). An estimate of the variance of $E(N_{(i)A}(T; \hat{\phi}))$ can be obtained by using the multivariate generalization of the delta method (Serfling, 1980) as

$$\operatorname{var}(E(N_{(i)A}(T; \hat{\phi}))) = \frac{\partial E(N_{(i)A}(T, \phi))}{\partial \phi} \operatorname{var}(\hat{\phi}) \frac{\partial E(N_{(i)A}(T, \phi))'}{\partial \phi},$$

where the gradient of the expected occupation times with respect to ϕ can be computed numerically by using a forward difference method (Kennedy and Gentle, 1980). Similarly, the Markov relapsing–remitting model can be applied to estimate the mean first passage time from a relapse to a remission or from a remission to a relapse (see Appendix Section A.3 for details) and steady-state probabilities [e.g., $\lim_{t\to\infty} P(Y_t \geq A|(Y_0, S_0))$, the steady-state probability of being in a relapse].

4. Illustration

A recent experiment (Racke et al., 1991) evaluated the effect of a treatment (transforming growth factor-β) on the disease course for a group of EAE-induced mice. Ten mice that were genetically identical, born on the same day, and subjected to the same environmental conditions, were immunized to produce EAE and separated into two groups, one group receiving the treatment and the other a placebo (Figure 2). The five mice in each group were subsequently examined for daily signs of disease and graded on the ordinal (0–4) scale discussed in the introduction; mice were followed for 40 days following either treatment or placebo. Since genetic and environmental

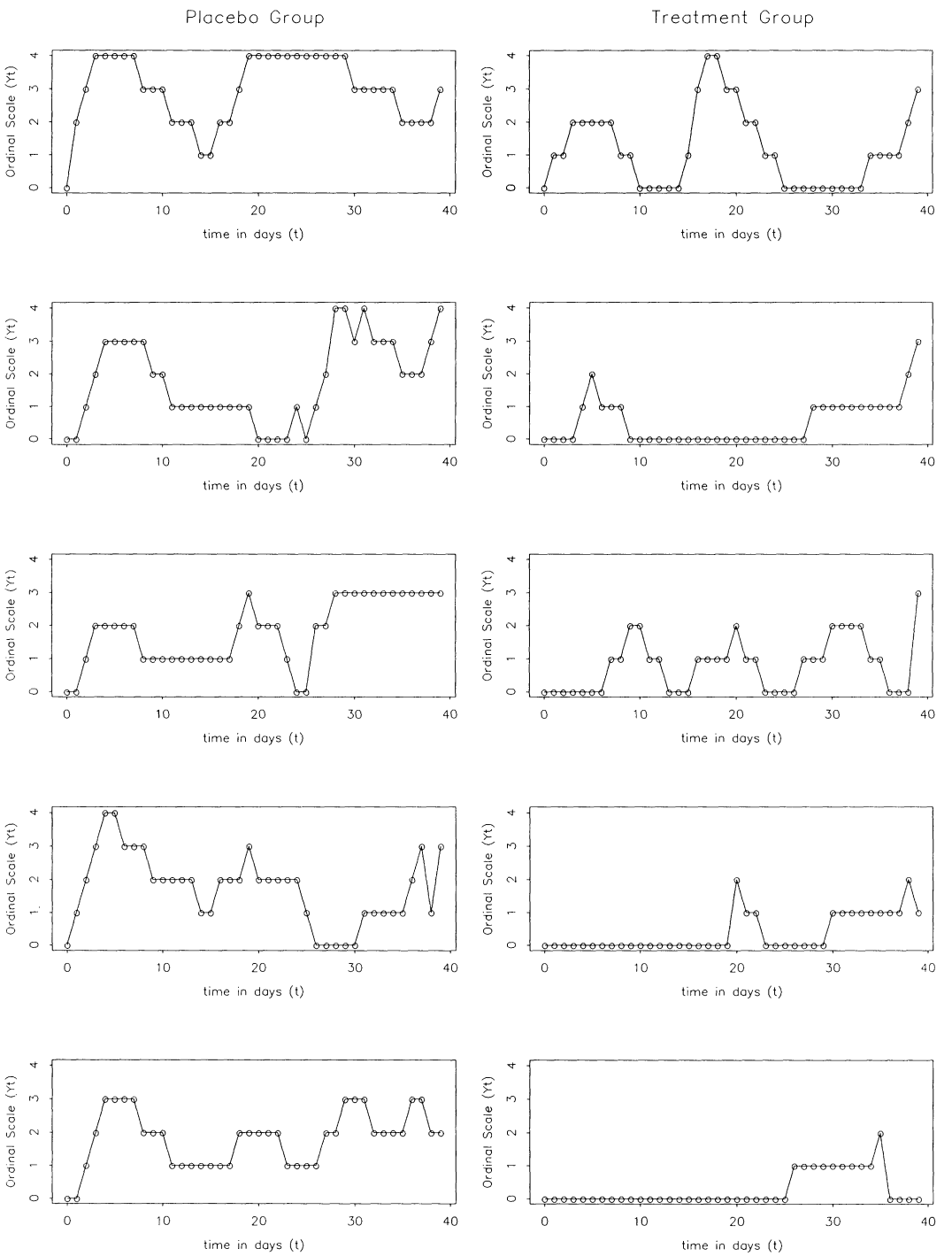

Figure 2. Observed realizations from two groups (placebo and treatment groups down columns 1 and 2, respectively) of five mice.

Table 1
Parameter estimates from Markov relapsing models fit to five placebo and five TGF-β mice

Parameters	Placebo group	TGF-β group	Parameters	Placebo group	TGF-β group
θ_0	.333[a]	.130	γ	1.56	.000
	(.136)[b]	(.046)		(.305)	(.471)
θ	.128	0	δ	.467	1.67
	(.036)	(0)		(.255)	(.257)
Δ	.157	.127	β_D	3.44	3.04
	(.044)	(.042)		(1.48)	(1.55)
Δ_4	.238	.500	β_I	2.95	2.07
	(.093)	(.354)		(.876)	(.717)

[a] Maximum likelihood parameter estimates.
[b] Standard errors based on a delta method approximation.

conditions for the ten mice were held constant, mice from the same group were treated as independent realizations from the same process. Also, EAE induction causes mice to immediately enter a relapse, hence $S_0 = 1$ for all mice. The model parameters were estimated by maximum likelihood for both the placebo and treatment groups (Table 1). A comparison between the two sets of estimated parameters suggests that the treatment group has a more gradual worsening of symptoms while relapsing ($\gamma = 0$ vs 1.56) and a more rapid improvement in symptoms while remitting ($\delta = 1.67$ vs .467).

Goodness-of-fit statistics were computed (as described in the Appendix) as $X = 23.0$ and $X = 36.9$ for the placebo and treatment groups, respectively; these statistics provide a global test of departure from the Markov relapsing–remitting model. Asymptotically (large numbers of mice for fixed follow-up) these test statistics are chi-square with 28 (45 possible transitions minus 9 possible states minus 8 model parameters) degrees of freedom. Since the expected cell counts were very small (the majority less than 1), a parametric bootstrap (Efron, 1982) was employed to estimate the distribution for both statistics under the null hypothesis. Ninety percent confidence intervals computed by using the parametric bootstrap with 100 realizations for both the placebo and treatment groups were (9.1, 30.9) and (7.0, 37.3), respectively. The goodness-of-fit tests suggest that the placebo group showed little departure from the model. However, there was more substantial, yet still nonsignificant, departure for the treatment group.

Model-based mean occupation times, mean first passage times, and steady-state probabilities were estimated for both treatment and placebo groups. Standard errors for these quantities were estimated using a delta method approximation. Table 2 presents the averaged observed and expected number of days in each severity level, as well as in a relapse (defined as $Y_t \geq 3$) and in a remission (defined as $Y_t \leq 1$), for both the placebo and treatment groups. Note that the expected number of days in a relapse was significantly higher for the placebo group as compared with the treatment group (Z-score of 3.37 based on the model). Similarly, the mean time to first relapse ($Y_t \geq 3$) was significantly larger for the treatment group [the estimated means (standard errors) on the log scale were 2.52 (.24) and 3.60 (.37) for the placebo and treatment groups, respectively], whereas

Table 2
Mean occupation times for placebo and treatment groups

	Placebo		Treatment	
Y_t	Avg. observed #[a]	Expected #	Avg. observed #[a]	Expected #
0	4.0	5.5	22.4	19.3
1	9.6	8.6	12.0	10.6
2	12.0	8.6	4.0	5.9
3	10.0	9.2	1.2	3.3
4	4.4	7.9	.4	.9
≥3	14.4	17.2	1.6	4.2
		(3.5)[b]		(1.6)
≤1	13.6	14.1	34.4	29.9
		(3.2)		(2.6)

[a] Average observed number computed by averaging occupation times over the five mice in each group.
[b] Standard errors based on the Markov relapsing model using a delta method approximation.

Table 3
Simulation results for model-based estimation of disease severity

Measure	True value	Avg. estimated value	Avg. delta method SE	Monte Carlo SE
		Parameter Set I		
Mean time in relapse	17.20	17.27	3.48	3.28
Log mean time to first relapse	2.52	2.53	.26	.24
Steady-state prob. of being in a relapse	.51	.51	.11	.11
		Parameter Set II		
Mean time in relapse	4.20	4.34	1.42	1.77
Log mean time to first relapse	3.60	3.56	.42	.41
Steady-state prob. of being in a relapse	.12	.12	.04	.04

Note: Parameter sets I and II correspond to ϕ estimated from the placebo and treatment groups, respectively. A relapse is defined as being in a state with disease severity (Y_t) greater than or equal to 3. The mean time to first relapse is defined as the mean number of days from the origin [state $X_0 = (0, 1)$] to the first state in a relapse (state (3, 1) or (4, 1)].

the estimated steady-state probabilities of being in a relapse were significantly lower [.51 (.11) and .12 (.05) for the placebo and treatment groups, respectively].

A small (Monte Carlo) simulation study was conducted to examine the statistical properties of the model-based estimates of disease severity. For sets of parameter values corresponding to those estimated for the placebo and treatment groups, 100 samples (five sequences of length 40) were generated according to the model. The results (Table 3) suggest that asymptotic inferences on these estimates are reasonable, since, for both sets of parameters, there was little bias (true value minus average estimated value), and the delta method approximations were close to the Monte Carlo sample variance.

Of the three measures of disease severity, average occupation times can be estimated directly for each group of mice (and compared across groups by using a t-test). The model-based estimates, however, are more efficient since they use the Markov chain to borrow strength over the entire sequence. As an illustration, a simulation study was conducted (similar to the one discussed above) to examine the relative gain in efficiency for model-based estimation of the occupation times as compared with simple group averages. For parameter values corresponding to those estimated for the treatment group, the simulation showed a 25% and 45% gain in efficiency for estimating the number of days in a remission ($Y_t \leq 1$) and a relapse ($Y_t \geq 3$), respectively. Large efficiency gains were also present for parameter values corresponding to the placebo group.

5. Discussion

This paper proposes an eight-parameter Markov chain model for ordinal sequences from a relapsing–remitting disease in which the state space (Y_t, S_t) is defined by the disease severity (Y_t) as well as by whether the disease is relapsing ($S_t = 1$) or remitting ($S_t = -1$) at time t. This formulation allows for a wide range of relapsing–remitting behavior and provided a good fit to our EAE data. The Markov chain structure provides a way of understanding the stochastic nature of the disease process and allows for the efficient estimation of important characteristics of the disease process. The model may be useful in predicting the future course of a relapsing–remitting disease (along with the variability associated with that prediction) and for designing future studies.

The model can be extended in different directions, allowing for more flexible parameterizations, covariate dependence (heterogeneity), or time inhomogeneity. The eight-parameter model formulation specifies that the probabilities of transitioning between relapsing and remitting statuses [equations (2.1)] are constant for intermediate states, but can differ at the boundaries. Such a parameterization nicely described the EAE data; in other applications, however, extensions can be formulated that allow these probabilities to depend on the intermediate state (perhaps through a linear function of Y_t on the logit scale). The model also specifies that the probabilities governing changes in Y_t for a given relapsing–remitting status [equations (2.2) and (2.3)] are functions of increments in $(y - Y_{t-1})$. Treating the levels of Y_t as quantitative here was reasonable for the EAE data; however, an extension can be made in which increments in $(y - Y_{t-1})$ are replaced by

$(\nu(y) - \nu(Y_{t-1}))$, where ν is a function assigning quantitative values to the ordinal scores. A model allowing for covariate dependence can be formulated by introducing covariates into expressions (2.1), (2.2), and (2.3). Model-based summaries of the disease course could then be estimated for any set of independent variables. Such extensions will be useful for applications to human studies where heterogeneity would be expected.

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Résumé

Dans beaucoup de maladies chroniques, on voit se succéder des périodes de rechutes avec des symptômes sévères alternant avec des périodes de rémission; l'encephalomyélie allergique expérimentale, le modèle animal de la sclérose en plaque est un exemple de maladies de ce type. On propose, pour analyser les séquences de données ordinales venant de la maladie avec rechute et rémission, un modèle de chaîne de Markov fini. Dans le modèle proposé, l'espace des états est étendu pour inclure l'information relative à l'état rechute ou rémission, ainsi que celle relative au degré de gravité, et on suggère une reparamétrisation permettant de réduire le nombre de paramètres à estimer. Le modèle markovien convient à un large spectre de paramètres à estimer. Le modèle markovien convient à un large spectre de comportement de rechute–rémission, permet de comprendre la nature stochastique de la maladie et fournit une estimation efficace de caractéristiques importantes du déroulement de la maladie (comme le temps moyen de premier passage, les temps d'occupation et les probabilités d'états stables). On applique ces méthodes aux données provenant d'une étude de l'effet d'un traitement (le facteur β_1 de transformation de la croissance) sur l'encéphalie allergique expérimentale.

References

Billingsley, P. (1961). Statistical methods in Markov chains. *Annals of Mathematical Statistics* **32,** 12–40.

Bishop, Y. M., Fienberg, S. E., and Holland, P. W. (1975). *Discrete Multivariate Analysis.* Cambridge, Massachusetts: MIT Press.

Chuang, C. and Francom, S. F. (1986). A structural model for the Markov chain of change in vote intention. *Communications in Statistics—Theory and Methods* **15,** 3475–3487.

Chung, K. L. (1960). *Markov Chains with Stationary Transition Probabilities.* Berlin: Springer-Verlag.

Efron, B. (1982). *The Jackknife, the Bootstrap and Other Resampling Plans.* Philadelphia: Society for Industrial and Applied Mathematics.

Hopper, J. L. and Young, G. P. (1988). A random walk model for evaluating clinical trials involving serial observations. *Statistics in Medicine* **7,** 581–590.

Kennedy, W. J. and Gentle, J. E. (1980). *Statistical Computing.* New York: Marcel Decker.

Muenz, L. R. and Rubinstein, L. V. (1985). Markov models for covariate dependence of binary sequences. *Biometrics* **41,** 91–101.

Parzen, E. (1962). *Stochastic Processes.* San Francisco: Holden-Day.

Pettinelli, C. B. and McFarlin, D. E. (1981). Adoptive transfer of experimental allergic encephalomyelitis in SJL/J mice after *in vitro* activation of lymph node cells by myelin basic protein: Requirement for Lyt 1+2- lymphocytes. *Journal of Immunology* **127,** 1420–1423.

Racke, M. K., Dhib-Jalbut, S., Cannella, B., Albert, P. S., Raine, C. S., and McFarlin, D. E. (1991). Prevention and treatment of chronic relapsing experimental allergic encephalomyelitis by transforming growth factor-β_1. *Journal of Immunology* **146,** 3012–3017.

Serfling, R. J. (1980). *Approximation Theorems of Mathematical Statistics.* New York: Wiley.

Ware, J. H., Lipsitz, S., and Speizer, F. E. (1988). Issues in the analysis of repeated categorical outcomes. *Statistics in Medicine* **7,** 139–148.

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Appendix

A.1. *Transition Probability Matrices and Log-Likelihood*

The 10×10 one-step transition matrix for the model with state space ((0, 1), (1, 1), (2, 1), (3, 1), (4, 1), (0, −1), (1, −1), (2, −1), (3, −1), (4, −1)) can be written as

$$\begin{bmatrix}
P_{00}^{++} & P_{01}^{++} & P_{02}^{++} & P_{03}^{++} & P_{04}^{++} & 0 & 0 & 0 & 0 & 0 \\
0 & P_{11}^{++} & P_{12}^{++} & P_{13}^{++} & P_{14}^{++} & P_{10}^{+-} & 0 & 0 & 0 & 0 \\
0 & 0 & P_{22}^{++} & P_{23}^{++} & P_{24}^{++} & P_{20}^{+-} & P_{21}^{+-} & 0 & 0 & 0 \\
0 & 0 & 0 & P_{33}^{++} & P_{34}^{++} & P_{30}^{+-} & P_{31}^{+-} & P_{32}^{+-} & 0 & 0 \\
0 & 0 & 0 & 0 & P_{44}^{++} & P_{40}^{+-} & P_{41}^{+-} & P_{42}^{+-} & P_{43}^{+-} & 0 \\
0 & P_{01}^{-+} & P_{02}^{-+} & P_{03}^{-+} & P_{04}^{-+} & P_{00}^{--} & 0 & 0 & 0 & 0 \\
0 & 0 & P_{12}^{-+} & P_{13}^{-+} & P_{14}^{-+} & P_{10}^{--} & P_{11}^{--} & 0 & 0 & 0 \\
0 & 0 & 0 & P_{23}^{-+} & P_{24}^{-+} & P_{20}^{--} & P_{21}^{--} & P_{22}^{--} & 0 & 0 \\
0 & 0 & 0 & 0 & P_{34}^{-+} & P_{30}^{--} & P_{31}^{--} & P_{32}^{--} & P_{33}^{--} & 0 \\
0 & 0 & 0 & 0 & 0 & P_{40}^{--} & P_{41}^{--} & P_{42}^{--} & P_{43}^{--} & P_{44}^{--}
\end{bmatrix},$$

where $P_{vw}^{++} = P[(w, 1)|(v, 1)]$, $P_{vw}^{--} = P[(w, -1)|(v, -1)]$, $P_{vw}^{+-} = P[(w, -1)|(v, 1)]$, and $P_{vw}^{-+} = P[(w, 1)|(v, -1)]$.

For our experiments, the EAE induction procedure places the animal into a relapsing status at t_0; hence we take $S_0 = 1$ for each mouse. The contribution of each mouse to the likelihood for estimating the model parameters (ϕ) is

$$L = P(Y_1, S_1|Y_0, 1; \phi) \prod_{t=2}^{n} P(Y_t, S_t|Y_{t-1}, S_{t-1}; \phi).$$

For cases in which S_0 is unknown, the likelihood is more complicated and its maximization requires the use of missing data techniques.

A.2 *Estimating the Mean First Passage Times*

In order to estimate the mean first passage time from a remission to a relapse (defined by reaching a state with disease severity greater than some value), we need an expression for the mean first passage time to any one of a group of states. Results are derived for the mean first passage time to any of two states; extensions to more than two states are straightforward. Let $f_{ij}^{[k]}(n; \phi)$ be the probability that starting in state i, the first occurrence of state j without first passing through state k occurs on day n. These first passage time probabilities can be computed by using the recursive relationship

$$f_{ij}^{[k]}(l; \phi) = P_{ij}^{[k]}(l; \phi) - \sum_{m=1}^{l-1} f_{ij}^{[k]}(m; \phi) P_{jj}^{[k]}(l - m; \phi), \quad f_{ij}^{[k]}(1; \phi) = P_{ij}^{[k]}(1; \phi),$$

where $P_{ij}^{[k]}(n; \phi)$ are called taboo probabilities (Chung, 1960) and denote the probability that starting in state i, the process is in state j at time n having never passed through state k; these probabilities can be computed by the recursion formula

$$P_{ij}^{[k]}(n + 1; \phi) = \sum_{s \in S_{(-k)}} P_{is}^{[k]}(n; \phi) P_{sj}(1; \phi),$$

where $S_{(-k)}$ includes all states except k. The probability of the first visit to either state j or k occurring at time n given an initial state i can be written as

$$f_{i(j,k)}(n; \phi) = f_{ij}^{[k]}(n; \phi) + f_{ik}^{[j]}(n; \phi),$$

and these can be used to compute the mean first passage time to any of two states,

$$\mu_{i(j,k)}(\hat{\phi}) = \sum_{n=1}^{\infty} n f_{i(j,k)}(n; \hat{\phi}),$$

where $\hat{\phi}$ is the maximum likelihood estimator of ϕ. Variance estimates of $\mu_{i(j,k)}(\hat{\phi})$ can be computed by a delta method approximation.

A.3 *A Chi-Square Goodness-of-Fit Statistic for the Relapsing Markov Model*

Let N_{vw}^{kl} be the number of transitions from state (v, k) to (w, l), where k and l take on values -1 and 1; and v, w are the five levels of disease severity in our group of five mice. For both groups, a chi-square-type measure of fit can be computed by using the statistic

$$X = \sum_{\substack{v,w=0,1,\ldots,4 \\ v \le w}} \frac{(N_{vw}^{11} - E(N_{vw}^{11};\ \hat{\phi}))^2}{E(N_{vw}^{11};\ \hat{\phi})} + \sum_{\substack{v,w=0,1,\ldots,3 \\ v < w}} \frac{(N_{vw}^{-11} - E(N_{vw}^{-11};\ \hat{\phi}))^2}{E(N_{vw}^{-11};\ \hat{\phi})}$$

$$+ \sum_{\substack{v,w=0,1,\ldots,3 \\ v \ge w}} \frac{(N_{vw}^{-1\,-1} - E(N_{vw}^{-1\,-1};\ \hat{\phi}))^2}{E(N_{vw}^{-1\,-1};\ \hat{\phi})} + \sum_{\substack{v,w=0,1,\ldots,4 \\ v > w}} \frac{(N_{vw}^{1\,-1} - E(N_{vw}^{1\,-1};\ \hat{\phi}))^2}{E(N_{vw}^{1\,-1};\ \hat{\phi})},$$

where $E(N_{vw}^{kl};\ \phi) = N_{v\cdot}^{k\cdot} P((w, l)|(v, k);\ \phi)$ and $N_{v\cdot}^{k\cdot} = \Sigma_{w=0}^{4}(N_{vw}^{k\,-1} + N_{vw}^{k\,1})$. Asymptotically (all N_{vw}^{kl} in the above expression going off to infinity, which is obtained as the number of mice increases to infinity for a fixed number of follow-up days) this statistic has a chi-square distribution with degrees of freedom equal to the number of possible transitions minus the number of possible states minus the number of model parameters (Billingsley, 1961); however, since for a group of five mice followed over 40 days most of the expected values of N_{vw}^{kl} are very small, a parametric bootstrap was employed to estimate the distribution under the null.