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Discrete distribution models for relapsing-remitting dynamics observed in Multiple Sclerosis

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Introduction

Multiple sclerosis (MS) is a prototypic autoimmune disease which affects the central nervous system (CNS) with a relapsing-remitting symptomatology [1]. A clinical relapse in MS reflects an acute focal inflammatory event in the CNS that disrupts neural conduction by damaging myelinated axons [2]. Such inflammatory events are evident in T1-weighted MRI recordings as contrast enhancing lesions (CELs).

Observed CEL dynamics are highly unpredictable and characterized by intra- and inter-patient variability. Their distributions along time have not been associated with any specific pattern or precipitator [2]. For the appropriate design of future longitudinal studies and clinical trials, it would be relevant to know the distribution of new CELs longitudinally developed by MS patients over the follow up period. In this study, we fit several discrete distribution models to CEL dynamics observed in nine RRMS patients undergoing monthly MRI for 48 months.

Methods

Patients and MRI scans. Nine patients with MS were sequentially enrolled (never treated with immunomodulatory or immunosuppressive drugs, except during a clinical relapse). The MRIs were monthly performed on a 1.5-T magnet and the number of CELs on T1-weighted post-contrast scans was identified by experienced neurologists and radiologists (Fig1).

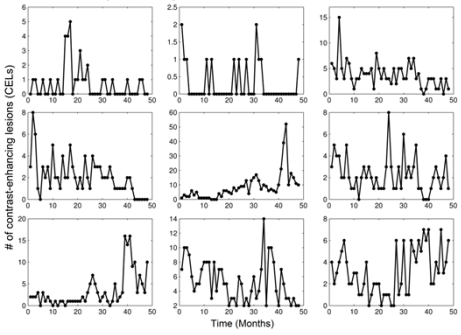


Figure 1. Number of contrast-enhancing lesions (CELs).

Data analysis. Analyses were performed using NONMEM VII. Model evaluation was based on the comparison of several dynamic descriptors calculated for both raw and simulated data. The model selection was based on the objective function provided by NONMEM, which corresponds approximately to -2LL [-2xlog(likelihood)], parameter estimate precision, and the reproducibility of important dynamic descriptors.

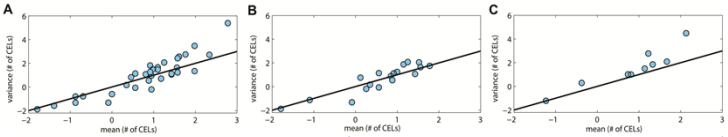


Figure 2. Variance *versus* mean of number of CELs. Observed data (dots); identity line (black). **A.** Variance vs mean of number of CELs observed in each patient with a 12 months time period window. **B.** 24 months time period window. **C.** 48 months time period window.

Models for count data. The number of CELs occurring every month is a discrete response variable. Experience modeling this kind of count data has been previously applied to the analysis of anticonvulsants [4], or epileptic seizures [5] among others. These models are based mainly on a Poisson distribution model. In its simplest version, the Poisson model has only one parameter λ (the mean number of counts in a given time period) and assumes two restrictions: λ is equal to the variance of the data and the number of counts occurring in non-overlapping intervals of time is assumed independent. However, many counting outcomes show (i) bigger or smaller variability than that predicted by the Poisson model, a phenomenon called overdispersion or underdispersion respectively (Fig. 2) and (ii) markovian features. Therefore, other discrete distribution models should be explored.

Fifteen models based on 7different probability distributions were explored: Poisson model [**PS**] (eq. 1, 3), Poisson model with Markov elements [**PMAK1** (eq. 1, 4), **PMAK2**, **nested PMAK2** (eq. 1, 5), **nested nested PMAK2**] , Poisson model with mixture distribution [**PMIX**], Zero-Inflated Poisson model [**ZIP**], Generalized Poisson model [**GP**, **GP PMAK2**, **GP nested PMAK2**], Negative Binomial model [**NB** (eq. 2, 3), **NB PMAK2** (eq. 2, 4), **NB nested PMAK2** (eq. 2, 5), **NB nested nested PMAK2**] and Zero-Inflated Negative Binomial model [**ZINB**].

$$P(Y_i=n)=\frac{e^{-\lambda}\times\lambda^n}{n!} \quad (1) \qquad P(Y_i=n)=\left[\frac{\Gamma\left(n+\frac{1}{OVDP}\right)}{n!\times\Gamma\left(\frac{1}{OVDP}\right)}\right]\times\left(\frac{1}{1+OVDP\times\lambda}\right)^{\frac{1}{OVDP}}\times\left(\frac{\lambda}{\frac{1}{OVPD}+\lambda}\right)^n \quad (2)$$

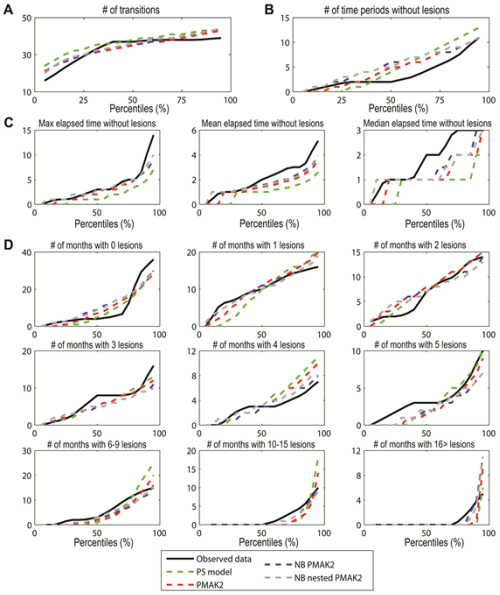
where λ could be,

$$\lambda=\text{const.} \ (3) \qquad \lambda=\lambda_0+\text{PDV}\times\theta_{\text{PDV}} \ (4) \qquad \lambda=\lambda_0+\text{PDV}\times\theta_{\text{PDV}}+\text{PPDV}\times\theta_{\text{PPDV}} \ (5)$$

Results

MODELS	PARAMETERS								-2LL(ΔPS)
PS model	θ_λ 0.744	ω_λ 0.442							2068.725
PMAK1	$\theta_{\lambda1}$ 0.932	$\theta_{\lambda2}$ 2.76	ω_λ 0.542						2001.0 (-67.55)
PMAK2	$\theta_{\lambda0}$ 1.18	θ_{PDV} 0.418	$\omega_{\lambda0}$ 0.562	ω_{PDV} 0.187					1725.51 (-343.212)
nested PMAK2	$\theta_{\lambda0}$ 1.03	θ_{PDV} 0.388	θ_{PPDV} 0.124	$\omega_{\lambda0}$ 0.501	ω_{PDV} 0	ω_{PPDV} 0.164			1713.88 (-354.836)
nested nested PMAK2	$\theta_{\lambda0}$ 0.956	θ_{PDV} 0.396	θ_{PPDV} 0.0974	θ_{PPPDV} 0.0595	$\omega_{\lambda0}$ 0.487	ω_{PDV} 0.143	ω_{PPDV} 0	ω_{PPPDV} 0	1711.49 (-357.231)
PMIX	$\theta_{\lambda1}$ 2.72	$\theta_{\lambda2}$ 1.81	θ_{PM} 0.413	$\omega_{\lambda1}$ 0.529	$\omega_{\lambda2}$ 1.89				1867.23 (-201.493)
ZIP	$\theta_{\lambda1}$ 2.4	θ_{PO} 0.0375	$\omega_{\lambda1}$ 0.91						2036.40 (-32.324)
GP	θ_λ 1.53	θ_{disp} 0.393	ω_λ 0.663						1808.41 (-260.313)
GP_PMAK2	$\theta_{\lambda0}$ 0.902	θ_{disp} 0.371	θ_{PDV} 0.232	$\omega_{\lambda0}$ 0.451	ω_{PDV} 0.0932				1665.50 (-403.219)
GP_nested_PMAK2	$\theta_{\lambda0}$ 0.742	θ_{disp} 0.347	θ_{PDV} 0.121	θ_{PPDV} 0.23	$\omega_{\lambda0}$ 0.365	ω_{PDV} 0.058	ω_{PPDV} 0		1654.96 (413.761)
NB	θ_λ 2.32	θ_{OVDP} 0.254	ω_λ 0.898	ω_{OVDP} 0.829					1758.92 (-309.796)
ZINB	θ_λ 2.32	θ_{OVDP} 0.254	θ_{PO} 0	ω_λ 8.98	ω_{OVDP} 8.29				1758.63 (-310.095)
NB_PMAK2	θ_λ 1.11	θ_{OVDP} 0.161	θ_{PDV} 0.462	ω_λ 0.524	ω_{OVDP} 0	wPDV 0.155			1642.85 (-425.868)
NB_nested PMAK2	θ_λ 0.94	θ_{OVDP} 0.155	θ_{PDV} 0.43	θ_{PPDV} 0.141	ω_λ 0.44	ω_{OVDP} 0	ω_{PDV} 0.121	ω_{PPDV} 0	1634.36 (-434.357)
NB_nested nested PMAK2	θ_λ 0.817	θ_{OVDP} 0.157	θ_{PDV} 0.448	θ_{PPDV} 0.104	θ_{PPPDV} 0.0955	ω_λ 0.401	ω_{OVDP} 0	ω_{PDV} 0.0849	ω_{PPDV} 0	ω_{PPPDV} 0	1630.77 (-437.95)

Table I. Explored models. θ - model parameters; ω - distribution variance



Selected model. Based on the number of model parameters, the -2LL values showed on table I, and the goodness of VNPC (Fig. 3), the selected model was the negative binomial with λ affected each time *t* by the observations of the 2 previous time points, *t-1* & *t-2*: **NB nested PMAK2**.

Figure 3. Visual Numerical Predictive Check (VNPC). Different dynamic descriptors were calculated for the observed data (black solid line) and the simulated data from the different selected models (dashed lines). Those descriptors were evaluated at different percentiles from 5th to 95th with an increasing step of 5.

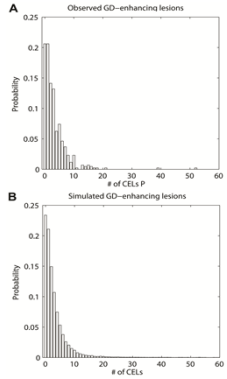


Figure 4. Probability CEL distribution. Observed data **(A)** *versus* the probability distribution of simulated data **(B)** generated by the selected model (NB nested PMAK2).

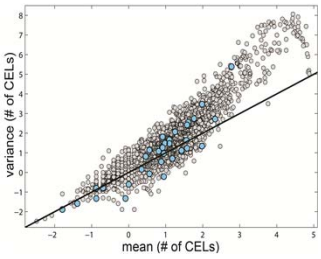


Figure 5. Variance *versus* mean of number of CELs. Observed data (blue dots) and simulated data **(grey points)** generated by the selected NB nested PMAK2 model. Variance and mean of number of CELs in each patient (observed – simulated) were calculated using 12 months time period window.

A very significant drop in the -2LL [-2×Log (Likelihood)] was observed when a first order markov element (*t-1*) was incorporated (eq.4). When a second order markov element (*t-2*) was included (eq. 5), the drop was still significant (table I). Interestenly, θ_{PDV} was always bigger thant θ_{PPDV}. The same pattern was observed, $\theta_{PDV} > \theta_{PPDV} > \theta_{PPPDV}$, when a third order markov element (t-3) was signficant although the improvement was not significant.

Conclusion

The natural history CEL dynamics is highly variable intra- and inter-patients, being its pattern highly unpredictable. In this study we analyzed the best statistical model fitting the distribution of CELs. Significant improvements were observed in the probability distribution models when the information about what happened in the two previous months was incorporated, although the importance of these previous observations seems to be diluted along the disease course. In the future, mechanistic elements, as balance between effector and regulatory T cell, will be incorporated [6] in order to identify latent variables that explain variations in the parameter λ.

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