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).

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 [-2×Log(likelihood)], parameter estimate precision, and the reproducibility of important dynamic descriptors.

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 anticancerous agents [4] or epileptic seizures [5]. Among others, models are based mainly on a Poisson distribution model. In its simplest version, the Poisson model has only one parameter \( \lambda \) (the mean number of counts in a given time period) and assumes two restrictions: \( \lambda \) is equal to the variance 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 different probability distributions were explored: Poisson model [PS] (eq. 1, 3), Poisson model with Markov elements [PMAK1, PMAK2, nested PMAK2] (eq. 2, 5), Negative Binomial model [NB] (eq. 2, 3), Negative Inflated Poisson model [ZIP] (eq. 5), Generalized Poisson model [GP] (eq. 2, 5), Negative Binomial model [NB] (eq. 2, 3), Negative Inflated Poisson model [ZIP] (eq. 5), Zero-Inflated Negative Binomial model [ZINB] (eq. 2, 5), Negative Inflated Poisson model [ZIP] (eq. 5), Generalized Poisson model [GP] (eq. 2, 5), Negative Inflated Poisson model [ZIP] (eq. 5), Negative Inflated Poisson model [ZIP] (eq. 5), Negative Inflated Poisson model [ZIP] (eq. 5), Zero-Inflated Negative Binomial model [ZINB] (eq. 2, 5).

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\begin{align*}
\lambda & = \text{const.} \\
\lambda & = \lambda + \lambda \cdot PDV \cdot \theta_{PDV} \\
\lambda & = \lambda + \lambda \cdot PDV \cdot \theta_{PDV} + PP \cdot PDV \cdot \theta_{PDV} \cdot \theta_{PP} \\
\end{align*}
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Models were fit using NONMEM VII and selected on the basis of their ability to explain the mean and variance of the observed data (A). Analyses were performed using NONMEM VII and selected models are 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 [-2×Log(likelihood)] and goodness of fit.

Results

The selected model was the negative binomial with \( \lambda \) affected each time \( t \) by the observations of the \( 2 \) previous time points, t-1 & t-2: NB nested PMAK2.

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). Interestingly, \( \theta_{PDV} \) was always bigger than \( \theta_{PP} \). The same pattern was observed, \( \theta_{PDV} > \theta_{PP} \), \( \theta_{PDV} > \theta_{PP} \), \( \theta_{PDV} > \theta_{PP} \). When a third order markov element (t-3) was significant 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 \( \lambda \).

References: