Web-based Supplementary Materials

Estimating Time to Disease Progression Comparing Transition Models and Survival Methods - an Analysis of Multiple Sclerosis Data

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A SAS code for fitting the random effects partial proportional odds model

The data set should contain one row for each transition with variable lagdscat and dscat for the previous and current EDSS categories. In addition, each row contains the covariates values (which can be time dependent) and the id of the subject. To solve convergence problems, a fixed effects model can first be fit and its estimates be used as initial values in the 'parms' command.

```
proc nlmixed data=band5 tech=NRRIDG cov;
parms
            \* constants for the 5-band matrix model*\
        a11=2.01  a12=2.15
        a21=-1.60 a22=0.95  a23=2.29
        a31=-3.30 a32=-1.55 a33=0.69 a34=2.06
        a42=-3.40 a43=-1.61 a44=0.92 a45=2.65
        a53=-3.33 a54=-2.02 a55=0.96
        \* covariates: treatment, baseline EDSS, lesion volume and duration*\
        bFTY05=0.1 bFTY125=0.2 bavnx=0.1
        bbase2=0 bbase3=0 bbase4=0 bbase5=0
        blv=0 bmsdur=0
            \* variance of random effects *\
        sigma2=2;

xb = bFTY05*FTY05 + bFTY125*FTY125 + bavnx*Avnx + bbase2*base2 + bbase3*base3
    + bbase4*base4 + bbase5*base5 + blv*lowlv + bmsdur*diag5yr + u;

logit11=xb+a11; logit12=xb+a12;
logit21=xb+a21; logit22=xb+a22; logit23=xb+a23;
logit31=xb+a31; logit32=xb+a32; logit33=xb+a33; logit34=xb+a34;
logit42=xb+a42; logit43=xb+a43; logit44=xb+a44; logit45=xb+a45;
```

```
logit53=xb+a53; logit54=xb+a54; logit55=xb+a55;


F11=exp(logit11)/(1+exp(logit11)); F12=exp(logit12)/(1+exp(logit12));
F21=exp(logit21)/(1+exp(logit21)); F22=exp(logit22)/(1+exp(logit22));
F23=exp(logit23)/(1+exp(logit23)); F31=exp(logit31)/(1+exp(logit31));
F32=exp(logit32)/(1+exp(logit32)); F33=exp(logit33)/(1+exp(logit33));
F34=exp(logit34)/(1+exp(logit34)); F42=exp(logit42)/(1+exp(logit42));
F43=exp(logit43)/(1+exp(logit43)); F44=exp(logit44)/(1+exp(logit44));
F45=exp(logit45)/(1+exp(logit45)); F53=exp(logit53)/(1+exp(logit53));
F54=exp(logit54)/(1+exp(logit54)); F55=exp(logit55)/(1+exp(logit55));


p11=F11; p12=F12-F11;  p13=1-F12;   p14=0;      p15=0;      p16=0;
p21=F21; p22=F22-F21;  p23=F23-F22; p24=1-F23;  p25=0;      p26=0;
p31=F31; p32=F32-F31;  p33=F33-F32; p34=F34-F33; p35=1-F34;  p36=0;
p41=0;   p42=F42;      p43=F43-F42; p44=F44-F43; p45=F45-F44; p46=1-F45;
p51=0;   p52=0;        p53=F53;     p54=F54-F53; p55=F55-F54; p56=1-F55;


if (lagdscat=1 and dscat=1) then z=p11;
if (lagdscat=1 and dscat=2) then z=p12;
if (lagdscat=1 and dscat=3) then z=p13;


if (lagdscat=2 and dscat=1) then z=p21;
if (lagdscat=2 and dscat=2) then z=p22;
if (lagdscat=2 and dscat=3) then z=p23;
if (lagdscat=2 and dscat=4) then z=p24;


if (lagdscat=3 and dscat=1) then z=p31;
if (lagdscat=3 and dscat=2) then z=p32;
if (lagdscat=3 and dscat=3) then z=p33;
if (lagdscat=3 and dscat=4) then z=p34;
if (lagdscat=3 and dscat=5) then z=p35;
```

```
if (lagdscat=4 and dscat=2) then z=p42;
if (lagdscat=4 and dscat=3) then z=p43;
if (lagdscat=4 and dscat=4) then z=p44;
if (lagdscat=4 and dscat=5) then z=p45;
if (lagdscat=4 and dscat=6) then z=p46;


if (lagdscat=5 and dscat=3) then z=p53;
if (lagdscat=5 and dscat=4) then z=p54;
if (lagdscat=5 and dscat=5) then z=p55;
if (lagdscat=5 and dscat=6) then z=p56;


if (z>1e-8) then ll=log(z);
else ll=-1e100;
model dscat~general(ll);
random u ~ normal(0,sigma2) subject=id;
run;
```

B   Distribution of Baseline EDSS by arm

| | Baseline EDSS | | | | | |
Arm	0-1.5	2-2.5	3-3.5	4-4.5	5-5.5	N
Placebo	29.2%	32.6%	21.2%	11.6%	5.4%	387
Fingolimod 0.5mg / day	40.5%	26.8%	17.6%	10.9%	4.2%	806
Fingolimod 1.25mg / day	39.2%	28.4%	17.2%	9.0%	6.2%	763
Avonex 30μg / week	42.6%	26.8%	17.9%	10.7%	2.0%	392

C   Fixed effects model applied to all data

To check the effect of using the 5-band transition matrix (8), we apply Model (2) without restriction on the transition matrix and compare the estimates. The table below summarizes the results and shows the similarity of the two analyses.

Covariate	5-band		unrestricted	
	estimate	std err	estimate	std err
Gp1-FTY720 0.50 mg q.d.	0.162	0.061	0.176	0.061
Gp2-FTY720 1.25 mg q.d.	0.224	0.062	0.238	0.062
Gp0-Avonex 30 mg q.w.	0.077	0.082	0.083	0.082
EDSS.base=[2, 2.5]	-1.072	0.071	-1.090	0.070
EDSS.base=[3, 3.5]	-1.786	0.089	-1.809	0.088
EDSS.base=[4, 4.5]	-2.560	0.120	-2.607	0.119
EDSS.base=[5, 5.5]	-3.126	0.189	-3.193	0.187
Low T2vol.base	0.144	0.046	0.145	0.046
MS duration<5y	0.225	0.048	0.236	0.048

D   Examples of estimated transition matrices

The estimated transition models are used to generate subject-specific transition matrices. These matrices provide estimates for the probability of moving from one EDSS value to another in 3-month intervals, and reflect the 5-band assumption. Transitions from state 6 (EDSS$\geq$6) were not estimated. Transition matrices for subjects having the same vector of covariates are similar under the fixed-effects model, but are different under the mixed-effects model because different individuals have different values of the latent variable u. We present here the transition matrices for several sets of covariates and for different values of u: $u = 0$ representing the 'median' transition matrix, and $u = \pm 1$, representing matrices of 'one standard deviation' from the median. The matrices illustrate the effect of covariates on transition probabilities, either to higher or lower states. Here we illustrate the effect of treatment arm (placebo and fongolimod 0.5mg) and the baseline EDSS (category [0,1.5] and category [3,3.5]); results for all possible covariate vectors can be similarly obtained. The probability curves shown in Figures 1 and 3 of the main paper use these matrices and provide a convenient summary of the results that is similar to curves generated by survival analysis. The superscripts 'fix' and 'mix' denote the model under which the estimates were calculated (fixed-effects and random-effects, respectively).

The following matrices are the estimates for x corresponding to: **placebo arm, baseline EDSS=1**, lesion volume $<$ median, and disease duration $<$ 5 years.

$$
P_{\text{fix}}(x) =
\begin{pmatrix}
0.915 & 0.077 & 0.008 & 0.000 & 0.000 & 0.000 \\
0.358 & 0.608 & 0.030 & 0.004 & 0.000 & 0.000 \\
0.164 & 0.439 & 0.377 & 0.019 & 0.001 & 0.000 \\
0.000 & 0.266 & 0.482 & 0.246 & 0.005 & 0.001 \\
0.000 & 0.000 & 0.397 & 0.382 & 0.215 & 0.006 \\
NA & NA & NA & NA & NA & NA
\end{pmatrix}
$$

$$
P_{\text{mix}}(x, u = 0) =
\begin{pmatrix}
0.952 & 0.046 & 0.003 & 0.000 & 0.000 & 0.000 \\
0.741 & 0.257 & 0.002 & 0.000 & 0.000 & 0.000 \\
0.756 & 0.222 & 0.023 & 0.000 & 0.000 & 0.000 \\
0.000 & 0.966 & 0.032 & 0.003 & 0.000 & 0.000 \\
0.000 & 0.000 & 0.994 & 0.006 & 0.001 & 0.000 \\
NA & NA & NA & NA & NA & NA
\end{pmatrix}
$$

$$
P_{\text{mix}}(x, u = 1) =
\begin{pmatrix}
0.991 & 0.008 & 0.000 & 0.000 & 0.000 & 0.000 \\
0.943 & 0.057 & 0.000 & 0.000 & 0.000 & 0.000 \\
0.947 & 0.049 & 0.004 & 0.000 & 0.000 & 0.000 \\
0.000 & 0.994 & 0.006 & 0.000 & 0.000 & 0.000 \\
0.000 & 0.000 & 0.999 & 0.001 & 0.000 & 0.000 \\
NA & NA & NA & NA & NA & NA
\end{pmatrix}
$$

$$
P_{\text{mix}}(x, u = -1) =
\begin{pmatrix}
0.773 & 0.212 & 0.015 & 0.000 & 0.000 & 0.000 \\
0.331 & 0.656 & 0.012 & 0.001 & 0.000 & 0.000 \\
0.349 & 0.532 & 0.118 & 0.002 & 0.000 & 0.000 \\
0.000 & 0.829 & 0.156 & 0.014 & 0.000 & 0.000 \\
0.000 & 0.000 & 0.965 & 0.031 & 0.004 & 0.000 \\
NA & NA & NA & NA & NA & NA
\end{pmatrix}
$$

The following matrices are the estimates for x corresponding to: **fingolimod 0.5mg arm, baseline EDSS=1**, lesion volume < median, and disease duration < 5 years.

$$P_{\text{fix}}(x) = \begin{pmatrix} 0.927 & 0.066 & 0.006 & 0.000 & 0.000 & 0.000 \\ 0.396 & 0.575 & 0.026 & 0.003 & 0.000 & 0.000 \\ 0.187 & 0.454 & 0.342 & 0.016 & 0.001 & 0.000 \\ 0.000 & 0.299 & 0.478 & 0.218 & 0.005 & 0.001 \\ 0.000 & 0.000 & 0.436 & 0.369 & 0.190 & 0.005 \\ NA & NA & NA & NA & NA & NA \end{pmatrix}$$

$$P_{\text{mix}}(x, u = 0) = \begin{pmatrix} 0.965 & 0.033 & 0.002 & 0.000 & 0.000 & 0.000 \\ 0.802 & 0.196 & 0.002 & 0.000 & 0.000 & 0.000 \\ 0.815 & 0.169 & 0.016 & 0.000 & 0.000 & 0.000 \\ 0.000 & 0.976 & 0.023 & 0.002 & 0.000 & 0.000 \\ 0.000 & 0.000 & 0.996 & 0.004 & 0.000 & 0.000 \\ NA & NA & NA & NA & NA & NA \end{pmatrix}$$

$$P_{\text{mix}}(x, u = 1) = \begin{pmatrix} 0.994 & 0.006 & 0.000 & 0.000 & 0.000 & 0.000 \\ 0.959 & 0.041 & 0.000 & 0.000 & 0.000 & 0.000 \\ 0.962 & 0.035 & 0.003 & 0.000 & 0.000 & 0.000 \\ 0.000 & 0.996 & 0.004 & 0.000 & 0.000 & 0.000 \\ 0.000 & 0.000 & 0.999 & 0.001 & 0.000 & 0.000 \\ NA & NA & NA & NA & NA & NA \end{pmatrix}$$

$$P_{\text{mix}}(x, u = -1) = \begin{pmatrix} 0.829 & 0.161 & 0.011 & 0.000 & 0.000 & 0.000 \\ 0.413 & 0.578 & 0.009 & 0.001 & 0.000 & 0.000 \\ 0.432 & 0.481 & 0.086 & 0.001 & 0.000 & 0.000 \\ 0.000 & 0.873 & 0.116 & 0.010 & 0.000 & 0.000 \\ 0.000 & 0.000 & 0.975 & 0.022 & 0.003 & 0.000 \\ NA & NA & NA & NA & NA & NA \end{pmatrix}$$

The following matrices are the estimates for x corresponding to: **placebo arm, baseline EDSS=3**, lesion volume < median, and disease duration < 5 years.

$$P_{\text{fix}}(x) = \begin{pmatrix} 0.644 & 0.312 & 0.044 & 0.000 & 0.000 & 0.000 \\ 0.085 & 0.740 & 0.151 & 0.024 & 0.000 & 0.000 \\ 0.032 & 0.171 & 0.689 & 0.101 & 0.006 & 0.000 \\ 0.000 & 0.057 & 0.274 & 0.633 & 0.031 & 0.005 \\ 0.000 & 0.000 & 0.099 & 0.272 & 0.595 & 0.034 \\ NA & NA & NA & NA & NA & NA \end{pmatrix}$$

$$P_{\text{mix}}(x, u = 0) = \begin{pmatrix} 0.104 & 0.582 & 0.314 & 0.000 & 0.000 & 0.000 \\ 0.017 & 0.695 & 0.255 & 0.034 & 0.000 & 0.000 \\ 0.018 & 0.183 & 0.754 & 0.043 & 0.002 & 0.000 \\ 0.000 & 0.142 & 0.557 & 0.299 & 0.002 & 0.000 \\ 0.000 & 0.000 & 0.484 & 0.418 & 0.098 & 0.001 \\ NA & NA & NA & NA & NA & NA \end{pmatrix}$$

$$P_{\text{mix}}(x, u = 1) = \begin{pmatrix} 0.401 & 0.526 & 0.073 & 0.000 & 0.000 & 0.000 \\ 0.089 & 0.846 & 0.060 & 0.006 & 0.000 & 0.000 \\ 0.095 & 0.497 & 0.399 & 0.008 & 0.000 & 0.000 \\ 0.000 & 0.488 & 0.442 & 0.069 & 0.000 & 0.000 \\ 0.000 & 0.000 & 0.844 & 0.137 & 0.018 & 0.000 \\ NA & NA & NA & NA & NA & NA \end{pmatrix}$$

$$P_{\text{mix}}(x, u = -1) = \begin{pmatrix} 0.020 & 0.255 & 0.726 & 0.000 & 0.000 & 0.000 \\ 0.003 & 0.296 & 0.533 & 0.168 & 0.000 & 0.000 \\ 0.003 & 0.039 & 0.743 & 0.205 & 0.011 & 0.000 \\ 0.000 & 0.028 & 0.258 & 0.698 & 0.014 & 0.002 \\ 0.000 & 0.000 & 0.140 & 0.474 & 0.382 & 0.005 \\ NA & NA & NA & NA & NA & NA \end{pmatrix}$$

The following matrices are the estimates for x corresponding to: **fingolimod 0.5mg arm, baseline EDSS=3**, lesion volume $<$ median, and disease duration $<$ 5 years.

$$
P_{\text{fix}}(x) = \begin{pmatrix}
0.680 & 0.282 & 0.037 & 0.000 & 0.000 & 0.000 \\
0.099 & 0.749 & 0.132 & 0.020 & 0.000 & 0.000 \\
0.037 & 0.193 & 0.676 & 0.088 & 0.006 & 0.000 \\
0.000 & 0.067 & 0.302 & 0.601 & 0.026 & 0.004 \\
0.000 & 0.000 & 0.115 & 0.295 & 0.561 & 0.029 \\
NA & NA & NA & NA & NA & NA
\end{pmatrix}
$$

$$
P_{\text{mix}}(x, u = 0) = \begin{pmatrix}
0.141 & 0.615 & 0.244 & 0.000 & 0.000 & 0.000 \\
0.023 & 0.755 & 0.198 & 0.024 & 0.000 & 0.000 \\
0.025 & 0.238 & 0.704 & 0.031 & 0.001 & 0.000 \\
0.000 & 0.190 & 0.577 & 0.231 & 0.002 & 0.000 \\
0.000 & 0.000 & 0.571 & 0.357 & 0.071 & 0.001 \\
NA & NA & NA & NA & NA & NA
\end{pmatrix}
$$

$$
P_{\text{mix}}(x, u = 1) = \begin{pmatrix}
0.488 & 0.460 & 0.053 & 0.000 & 0.000 & 0.000 \\
0.122 & 0.831 & 0.043 & 0.004 & 0.000 & 0.000 \\
0.130 & 0.544 & 0.320 & 0.006 & 0.000 & 0.000 \\
0.000 & 0.576 & 0.374 & 0.050 & 0.000 & 0.000 \\
0.000 & 0.000 & 0.885 & 0.102 & 0.013 & 0.000 \\
NA & NA & NA & NA & NA & NA
\end{pmatrix}
$$

$$
P_{\text{mix}}(x, u = -1) = \begin{pmatrix}
0.028 & 0.322 & 0.650 & 0.000 & 0.000 & 0.000 \\
0.004 & 0.374 & 0.498 & 0.124 & 0.000 & 0.000 \\
0.004 & 0.054 & 0.780 & 0.154 & 0.008 & 0.000 \\
0.000 & 0.039 & 0.324 & 0.626 & 0.010 & 0.001 \\
0.000 & 0.000 & 0.187 & 0.505 & 0.304 & 0.003 \\
NA & NA & NA & NA & NA & NA
\end{pmatrix}
$$

E Goodness of fit

Goodness of fit of models (1) and (6) is examined as described at the end of Section 2.4. Figure 1 displays the expected proportions of one- and two-year transitions between pairs of states and compares them to the observed proportions. The overall performance is satisfactory, though the figure shows some disagreement, especially for transitions from state 5 to other states. This may be due to differential effects of covariates in different phases of the disease. As the number of transitions from state 5 is relatively small, we did not try to fit a model with covariates-lag EDSS interactions, though this may be an important extension of our model when more data are available.
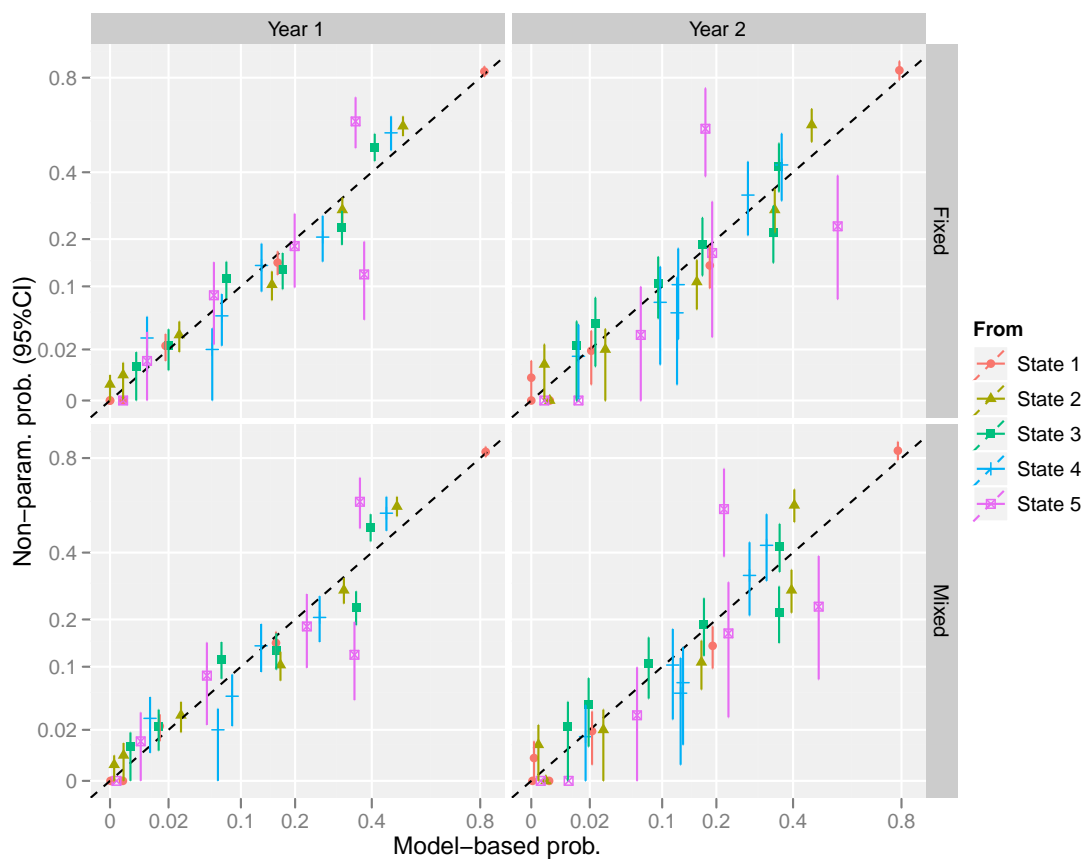

Figure 1: Goodness-of-fit analysis. The crude 95% interval estimates for one- and two-year transition probabilities are compared to the model based estimates.