Count data model for Alzheimer disease progression MMSE score using MonolixSuite

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SimulationsPlus MIDD+22 Model Informed Drug Development

INTRODUCTION

Progression models for Alzheimer's disease (AD) allow to better understand predictors of progression and help to design informative clinical trials. Common scores used to follow AD progression include ADAS-cog, CDR-SB and MMSE. Most published models consider the score as a continuous variable.

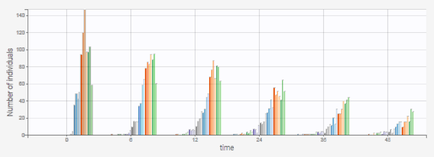
In this poster, we propose a novel model for the MMSE score which captures the score as bounded count data. The model is implemented and estimated in Monolix.

How to implement a model for count data in Monolix?

MMSE scores were extracted from the ADNI study [1] for 895 patients examined every 6 months over 2 years. Available covariates include age, weight, height, sex, BMI, race, baseline MMSE score and number of apolipoprotein E type 4 alleles (APOE).

1/ Which model describes best the disease progression?

2/ Which covariates are predictors of the progression?

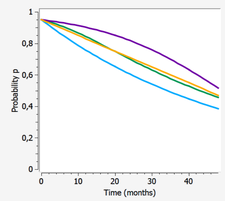


MODEL FORMULATION

The MMSE scores is modeled using a binomial distribution representing the number of correct answers to the n=30 questions of the MMSE test. The probability p of correct answer decreases as the AD progresses.

$$P(\text{MMSE} = k) = \binom{n}{k} p^k (1-p)^{n-k}$$

Several models are tested to describe the evolution of the probability p.



Linear $p = p_0 - \alpha t$

Exponential $p = p_0 \exp(-\alpha t)$

Logistic $p = \frac{p_0}{p_0 + (1-p_0)\exp(-\alpha t)}$

Richard $p = \frac{p_0}{({p_0}^{\beta} + (1^{\beta} - {p_0}^{\beta})\exp(-\alpha\beta t))^{\beta}}$

Model implementation in Mlxtran language for Monolix

```
[LONGITUDINAL]
input={p0, alpha}

EQUATION:
; probability of success => decreases over time
p = p0 /((p0 + (1-p0)*exp(alpha*t)))
n = 30

DEFINITION:
; binomial distribution of n trials and probability of success p
MMSE = {type=count, log(P(MMSE=k))= factln(n)-factln(k)-factln(n-k) +
k*log(p) + (n-k)*log(1-p)}

OUTPUT:
output = MMSE
```

RESULTS

Among the four tested models for the evolution of the probability p, the logistic model which has a concave shape captures the data best.

	-2LL	BIC
Linear	16996	17030
Exp.	16993	17027
Logistic	16913	**16947**
Richard	16911	16973

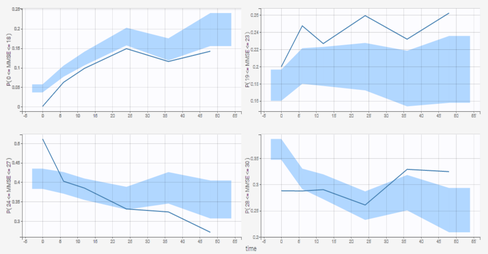
Covariate search was performed using the SCM and COSSAC methods. The following covariates appear as predictive:

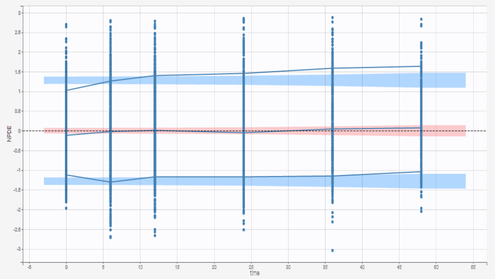
	p0	alpha
AGE	✓	✓
APOE (0,1 or 2)	✓	✓
Cog. Function (CN, MCI or AD)	✓	✓
BMI		✓
WT		
HT		
SEX		
RACE		

The estimated parameter values and RSE are:

	VALUE	RSE (%)
Fixed Effects		
p0_pop	0.924	0.288
beta_p0_APOE_1	-0.173	24.8
beta_p0_APOE_2	-0.211	27.8
beta_p0_logAGE	-0.841	31.6
beta_p0_tARM_G_2	-1.11	4.08
alpha_pop	0.0131	8.68
beta_alpha_APOE_1	0.251	34.5
beta_alpha_APOE_2	0.368	31.3
beta_alpha_logAGE	-1.16	38.2
beta_alpha_logBMI	-0.879	33.4
beta_alpha_tARM_G_2	0.409	21.7
Standard Deviation of the Random Effects		
omega_p0	0.548	3.4
omega_alpha	0.786	5.83
Correlations		
corr_p0_alpha	-0.679	6.8

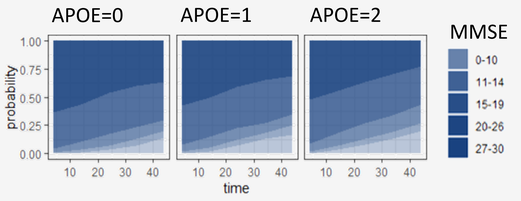
The model captures the main trend of the data:





SIMULATIONS

The disease progression model can be used to simulate the disease progression of new populations with Simulx. Below we compare the progression of a population with 0, 1 or 2 APOE alleles.



REFERENCES

[1] Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu).

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