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Modeling the of volume tumor evolution in rats using SAEM algorithm

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Abstract : *The purpose of this study is to modeling the growth of the tumor volume in the rats. Using the SAEM algorithm in R and non-linear mixed model for a longitudinal data to predict future tumor volume in the rats.*

Keywords: *Nonlinear mixed effects model; Breast cancer; SAEM algorithm; Longitudinal Data.*

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I. Introduction

The breast cancer is one of widespread and dangerous diseases in the world, for this reason, this issue must be seriously studied. Modeling breast tumor growth is usually a complex issue for several reasons. Rat mammary cancers generally resemble many features of human breast cancer. The purpose of this article is to analyze the growth of induced mammary tumors in rats. The advantage of using mathematical models is that they facilitate the analysis and interpretation of the observed data because they describe the evolution l aw as a function of only a few parameters that can be statistically compared. To this end, we introduce the nonlinear mixed-effects model to predict future tumor volume in the rat.

For repeated measurements data, mixed-effects models offer a flexible and powerful tool in which Population characteristics are modeled as a fixed effects and unit-specific variation is modeled as random effects. Linear mixed-effects (LME) models (Laird and Ware 1982 [10]; Ware 1985 [12] ; Diggle et al. 1994

[14]) and nonlinear mixed-effects (NLME) models (Lindstrom and Bates (1990); Davidian and Giltinan 1995 [11]; Vonesh and Chinchilli 1997[9]; (Comets, Lavenu, and Lavielle 2017) [1]) are widely used in longitudinal data analysis. The stochastic approximation expectation maximization (SAEM) (Comets, Lavenu, and Lavielle 2017)[1] algorithm, combining a stochastic approximation to the likelihood with an EM algorithm, has proven very efficient for nonlinear mixed effect models, quickly converging to the maximum likelihood estimators (Delyon, Lavielle, and Moulines 1999).We will show in this article that the SAEM algorithm can be extended to quickly and efficientlyperform joint modeling and parameter estimation in the general nonlinear framework and in the presence of censored data.

In the present paper, the analysis was performed with the SAEM algorithm in the R software through the saemix package (Comets, Lavenu, and Lavielle 2017) [2].

II. Data

The data analyzed in this paper come from a study on the influence of lipids on the development of cancer. These results are integrated in a series of studies performed by Escrich and al. [5] during the past two decades, in order to determine the dynamics of breast tumor growth under a variety of conditions Escrich, Solanas and Segura [6] and Escrich and al. [5].

The data object is created through the function saemixData. Our aim is to specify the name of the

dataframe, while the columns containing the grouping factor (indicating the subject), the predictor(s) and the response. In our case, the grouping factor is Rat, and the number of the rat is given in the first column, while that the second contains the time (the predictor) and the third its volume of tumor (the response). The plot of the data show in Figure 1.

III. Modeling

Different mathematical functions can be used to describe growth tumor. We propose the model bellow to predict y_{ij}, the volume tumor at time t_{ij}:

$$y_{ij} = \frac{2\beta_1 \exp(t_{ij}-\beta_2)}{1+2\exp(\frac{t_{ij}-\beta_2}{\beta_3})} + \varepsilon_{ij}, \qquad (1)$$

where:

y_{ij} : The total tumor volume in rat i at time t_{ij},

β_1: Hypothetical maximum tumor volume,

β_2: The time of tumor appearance,

β_3 : The rate of tumor growth,

ε_{ij} : The residual error.

The parameter β_3 makes the model sufficiently flexible in shape. When $\beta_3 > 1$ it describes an exponential growth. When $\beta_3 < 1$ it is adequate to describe regressing tumors and $\beta_3 = 1$ values define a logistic-like dynamics.

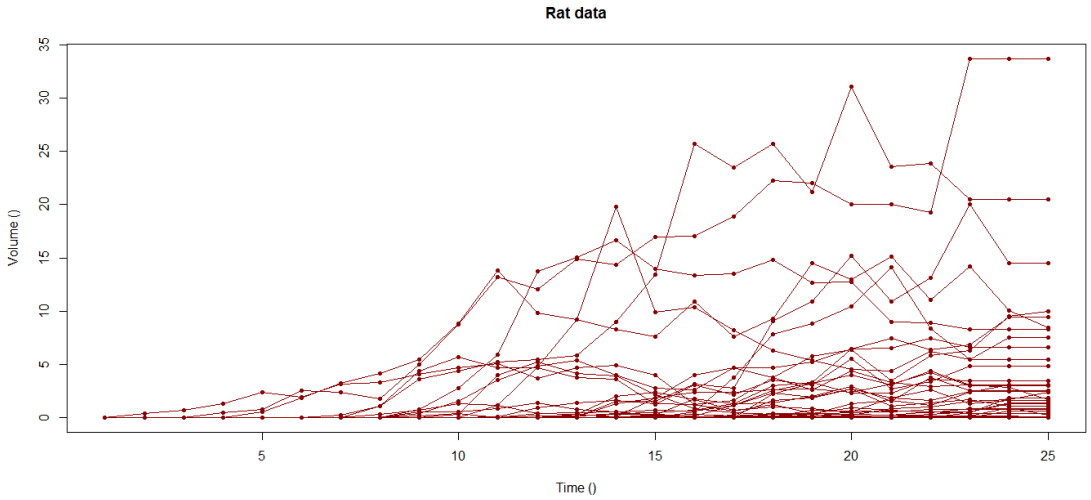

Figure 1: The volume tumor as a function of time

The model in terms of fixed and random effects, can be written as:

$$y_{ij} = \frac{\exp\left(t_{ij} - (\beta_2 + R_2)\right) + (\ln \beta_1 + R_1)}{1 + \exp\left(\frac{t_{ij} - (\beta_2 + R_2)}{\beta_3 + R_3}\right)} + \varepsilon_{ij}, \quad (2)$$

$$\Phi_i = C_i\beta + v_i, \quad (3)$$

where $\beta = (\beta_1, \beta_2, \beta_3)$ is an unknown vector of fixed effects, $v_i = (R_1, R_2, R_3)$ is an unknown vector of random effects and C_i is a design matrix specific covariates (in our case C_i is the identity). In saemix, we make some additional assumptions. We further assume that the vector of random effects v_i follows a multinormal distribution $v_i \backsim \mathcal{N}(0, \Omega_i)$ and $\varepsilon_i \backsim \mathcal{N}(0, \sigma_i)$ with ε_i is the variance of the residual error. Finally, we need to estimate the unknown set of $\theta = (\beta, \Omega, \sigma)$ where Ω is the vector of the parameters of the variance-covariance matrix Ω_i and σ is the parameters of the residual error model.

IV. Results

For each parameter estimated in the model, estimates of the standard error are reported, as an absolute value (SE) and relative to the estimate, as a coefficient of variation (% CV). In the present case, all the fixed parameters are well estimated, with coefficients of variation less than 25%,

Fixed effect			
Parameter	**Estimate**	**SE**	**CV %**

β_1	3.80	0.814	21.4
β_2	18.95	1.922	10.1
β_3	0.96	0.021	2.2

Table 1: Estimation of the fixed effect

Variance of random effects			
Parameter	**Estimate**	**SE**	**CV %**
Ω_1	1.0827	0.3240	30
Ω_2	0.2816	0.0769	27
Ω_3	0.0086	0.0032	37

Table 2 : Estimations of the variance of random effects.

In general, Akaike's information criterion (AIC) (Akaike 1974) [3] and Bayesian information criterion (BIC) (Schwarz 1976) [4] were used to compare several alternative models.
The smallest value for both criteria indicates the best fit.

Statistical criteria		
Method	**AIC**	**BIC**
Linearization	2865.934	2877.397
importance sampling	2918.074	2929.537
Gaussian quadrature	2917.643	2929.106

Table 3: Akaike and Schwarz statistical criteria computed by different approximations.

The residues showed in figure 2 seem well centered on zero, Henry's lines (Figs 5 and 6) show points that are globally aligned. The assumptions of normality therefore seem reasonable. The hypotheses we have made seem realistic.The progression of convergence is assessed through plots, shown in Figure 2. The vertical line in the plots delineates two phases in the algorithm. During the first iterations, the algorithm explores freely the parameter space, while during the second phase , the step size decreases slowly to ensure parameter convergence. The individual parameters of each subject are estimated during the second phase. Finally, we can check that the model is able to describe the observed data by producing plots of the individual fits : The result is shown in Figure 3 and illustrates a very good fit of the model.

Figure 3.4 shows the predicted values compared to the observed concentrations, for the population Predictions (left) and the individual predictions (right). Figure 3.5 shows the individual data for the 12 subjects, with the individual predictions overlayed (smoothed predictions were obtained). Both plots indicate good model adequacy.

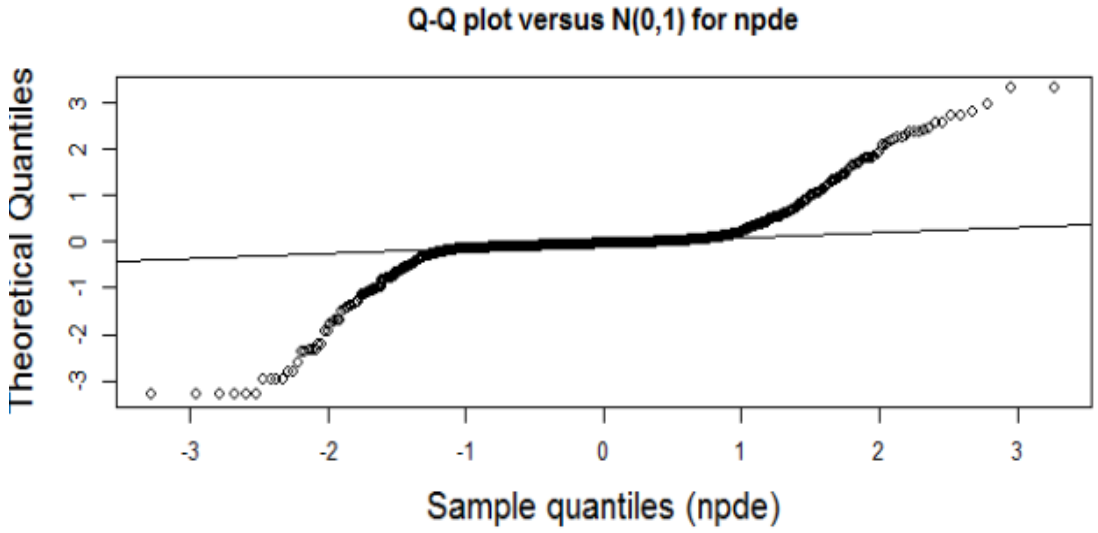

Figure 2: Convergence plots for the breast cancer data.

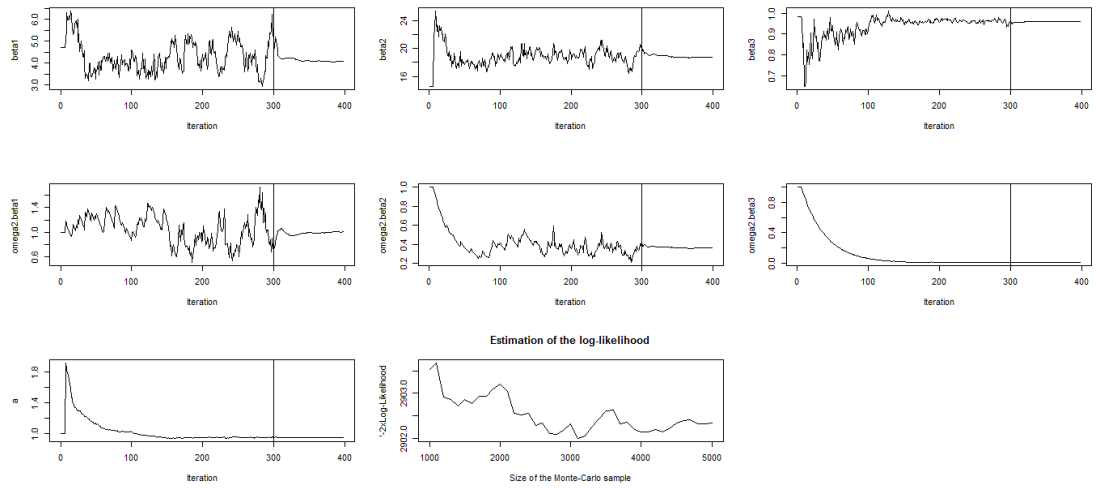

Figure 3: Convergence plots for the breast cancer data.

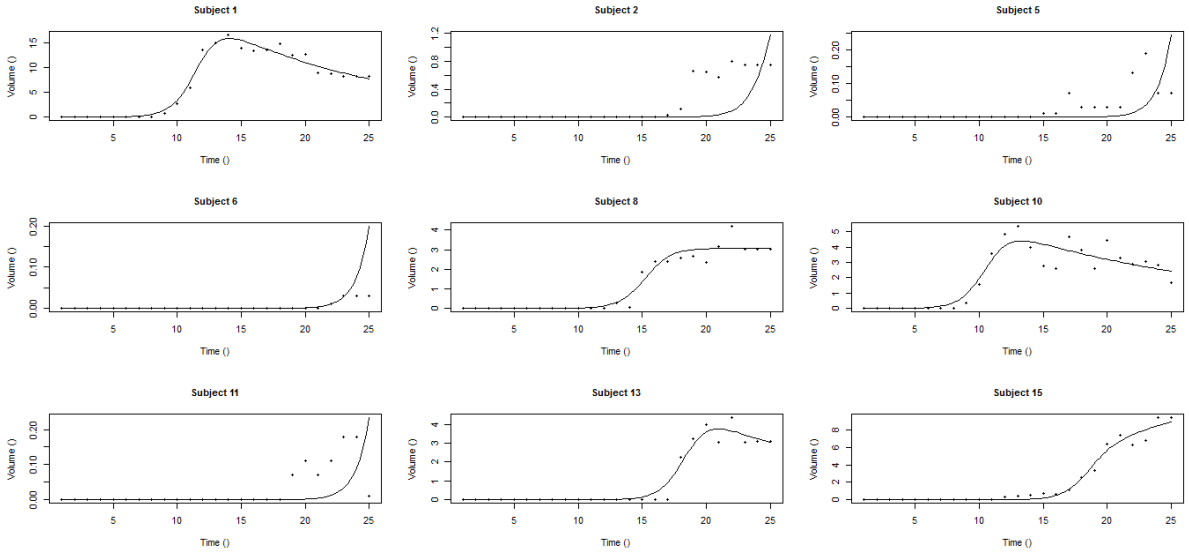

Figure 4: Plots showing the individual predictions (solid line) overlaid on the observations (black dots) for some random rat in the dataset.

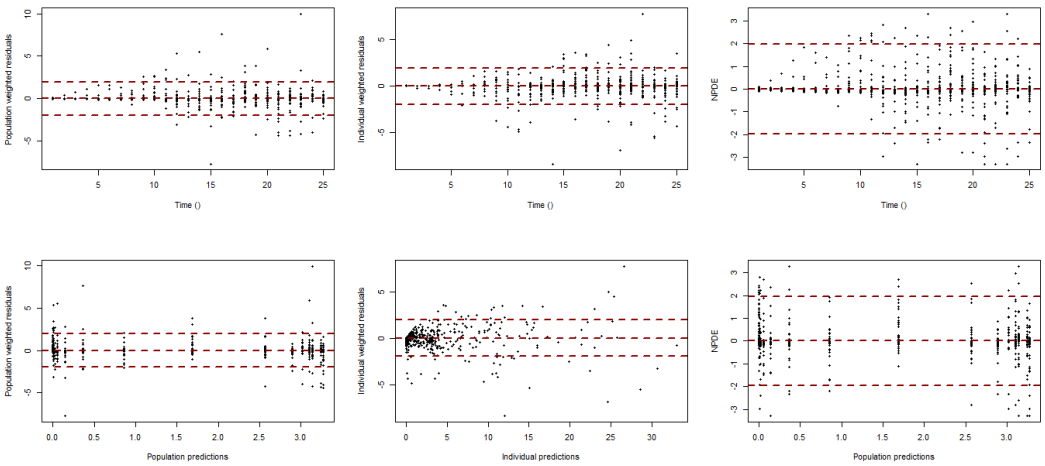

Figure 5: Scatterplots of the residuals versus time and predictions.

V. Conclusion

The modeling and simulation of the breast cancer data using Nonlinear Mixed-Effects Models showed a good results. We can say that the Nonlinear Mixed Effects Models and specially the SAEM algorithm can help to characterize and to understand many complex nonlinear biological processes, this study showed the effectiveness of the non-linear mixed effects models, As a new approach to explain the breast cancer data.
Finally, the proposed model fitted with SAEM algorithm showed good estimations for all three parameters in the model. In addition, he ensured the convergence towards the parameters. Our model fitted with the SAEM algorithm.

In this paper, the use of modeling and simulation nonlinear mixed effect models can help to characterize and to understand many complexes nonlinear biological processes, As a new approach to explain the breast cancer data

References

[1]. E. Comets, A. Lavenu , M. Lavielle *(2017).* Parameter Estimation in Nonlinear Mixed Effect Models Using saemix, an R Implementation of the SAEM Algorithm. Journal of Statistical Software. doi:10.18637/jss.v080.i03.
[2]. E. Comets, A. Lavenu , M. Lavielle (2017). saemix: Stochastic Approximation Expectation Maximization (SAEM) Algorithm. R package version 2.1, URL https://CRAN.R-project. org/package=saemix.
[3]. H.Akaike, (1974). A new look at the statistical model identification. IEEE Trans. Autom. Control, *19(6), 716--723.*
[4]. G. Schwarz, *(1978).* Estimating the dimension of a model. Ann. Statist., *6(2), 461--464*.
[5]. E.Escrich , M. Solanas , M. C. Ruiz de Villa, R. Ribalta Muntané Segura (1994) Experimental diets for the study of lipid influence on the induced mammary carcinoma in rats: I-diet definition. International Journal In Vivo Research, *8: 1007-1012.*
[6]. E. Escrich ,M .Solanas and R. Segura *(1994)* Experimental diets for the study of lipid influence on the induced mammary carcinoma in rats: I-diet definition. International Journal In Vivo Research, 8: 1099--1106.
[7]. KP. Burnham , DR. Anderson (2002). Model Selection and Multimodel Inference: A Practical Information-Theoretic Approach. 2nd edition. Springer-Verlag, New York.
[8]. AP Dempster, NM Laird and DB Rubin, Maximum Likelihood From Incomplete Data via the EMAlgorithm, Journal of the Royal Statistical Society B. 39(1),(1977).
[9]. E. F. Vonesh, and V. M Chinchilli,. (1997). Linear and nonlinear models for the analysis of repeatedmeasures. Marcel Dekker, New York.
[10]. Laird, N. M., and Ware, J. H. (1982). Random-effects models for longitudinal data. Biometrics, 38(4), 963--974.
[11]. M. Davidian and D.M Giltinan (1995). Nonlinear models for repeated measurement data, Chap-man and Hall, London.
[12]. J.H. Ware. (1985). Linear models for the analysis of longitudinal studies. Ann. Statist., 39(2), 95--101.
[13]. J. C. Pinheiro and D. M. Bates. (2000). Mixed-effects models in S and S-PLUS, Springer, New York.
[14]. P. J. Diggle. (1994). Analysis of longitudinal data, Oxford University Press, New York.

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