

Application of a new method for multivariate analysis of longitudinal ordinal data testing robenacoxib in canine osteoarthritis

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Background & Objective

Robenacoxib is a coxib non-steroidal anti-inflammatory drug approved for the treatment of osteoarthritis in dogs. In clinical trials, its efficacy is assessed through multiple scores and the classical way to analyse the data is to sum the scores and analyse this sum as a continuous variable (e.g., [1]). Although straightforward, this approach ignores the ordinal nature of the data and loses important information on the way scores are correlated and are improved within a subject.

Objective: to analyse all scores simultaneously to capture all aspects of drug efficacy and identify possible redundancies between scores

Methods and Material

Data were obtained from 3 clinical studies in osteoarthritic dogs where robenacoxib was given once or twice a day over 28 to 84 days at one or 3 different daily doses. The time courses of 4 scores (Table 1) were analyzed simultaneously using a multivariate probit mixed effects model. The analysis was performed on 1191 time points documented in 232 subjects.

Posture at a stand	Pain at palpation	Lameness at walk	Lameness at trot
0 - normal	0 - none	0 - none	0 - none
1 - slightly abnormal	1 - mild	1 - mild	1 - mild
2 - markedly/severely abnormal *	2 - moderate	2 - obvious/marked *	2 - obvious/marked *
	3 - severe		

Table 1. Clinical scores used for the analysis. * two categories were merged

The k^{th} score ($k = 1 \dots K$) was viewed as the categorization of a continuous, latent variable denoted Y_k^* with, in subject i at time t_{ij} :

$$Y_{kij}^* = -E_k \times (1 - \exp(-k_{e0} \times t_{ij})) + \eta_{ki} + \varepsilon_{kij}$$

where E_k is the maximal effect of robenacoxib at steady state for score k , k_{e0} the equilibration rate constant, η_{ki} and ε_{kij} random effects for inter- and intra-individual variability.

$$\begin{pmatrix} \eta_{1i} \\ \dots \\ \eta_{Ki} \end{pmatrix} \stackrel{\text{iid}}{\sim} N \left(\begin{pmatrix} 0 \\ \dots \\ 0 \end{pmatrix}, \Omega \right) \quad \begin{pmatrix} \varepsilon_{1ij} \\ \dots \\ \varepsilon_{Kij} \end{pmatrix} \stackrel{\text{iid}}{\sim} N \left(\begin{pmatrix} 0 \\ \dots \\ 0 \end{pmatrix}, \Sigma \right) \quad \eta_{ki} \perp \varepsilon_{kij}$$

Ω is a variance-covariance matrix and Σ a correlation matrix.

Model parameters were estimated using a stochastic EM algorithm developed in a previous work [2]. Some modifications to the algorithm were made: especially, a pairwise approach [3] was implemented to circumvent the computational difficulties related to the high number of scores.

Model evaluation was performed with visual predictive checks (VPC) and a principal component analysis (PCA) was carried out on Ω and Σ to summarize the correlations between scores, independently of drug effect.

Conclusion

Overall, the multivariate analysis appears more complex than conventional analyses (sum of scores or separate univariate analyses) but provides additional insights that are worthwhile:

- **A better evaluation of drug effect on meaningful clinical endpoints** e.g. % of subjects with all scores back to normal
- **Information about the scoring system itself.** Here, what we actually measure looks more like 2 sub-scores with very different weighting 3:1 and a sum of scores would count 3 times the same information.

- References**
- [1] Raymond N et al. J Vet Pharmacol Ther 35 (2011): 175-183
 - [2] Laffont CM and Concordet D. PAGE 20 (2011) Abstr 2157.
 - [3] Fieuws S and Verbeke G. Biometrics 62 (2006): 424-431.

Results

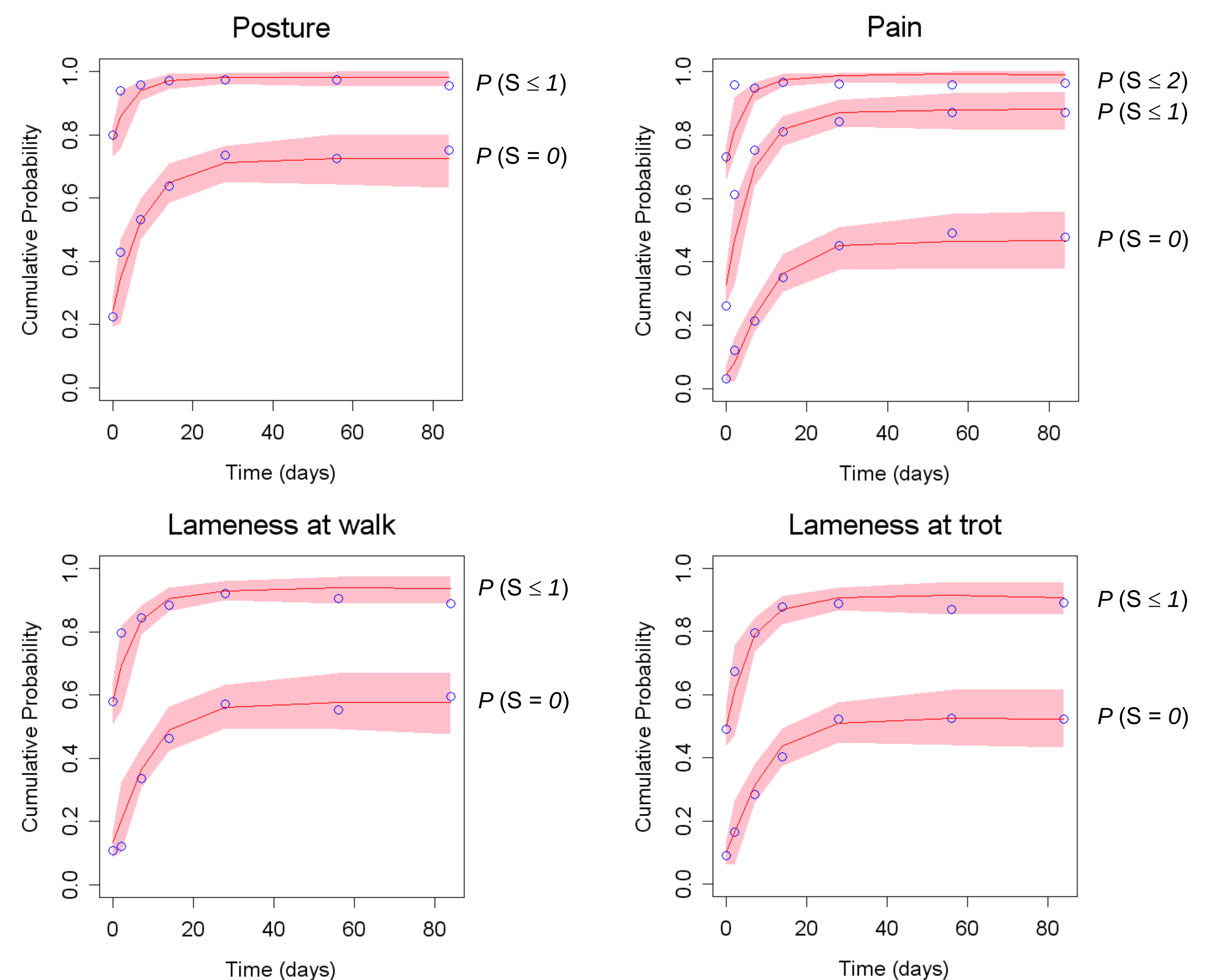


Figure 1. VPC for marginal distributions of scores (S). Dots = observations. Pink area = 95% confidence interval for model predictions. Red curve = median model predictions.

- **Good prediction of marginal and joint distributions** (Figs. 1 and 2).
- **Prediction of the percentages of subjects reaching the target**
 - $\approx 25\%$ of dogs with all scores = 0 (no symptoms) at steady-state. This percentage is severely underestimated by 60% if scores are wrongly assumed independent (Fig. 2).
 - $\approx 80\%$ of dogs with all scores ≤ 1 (no/mild symptoms) at steady-state.

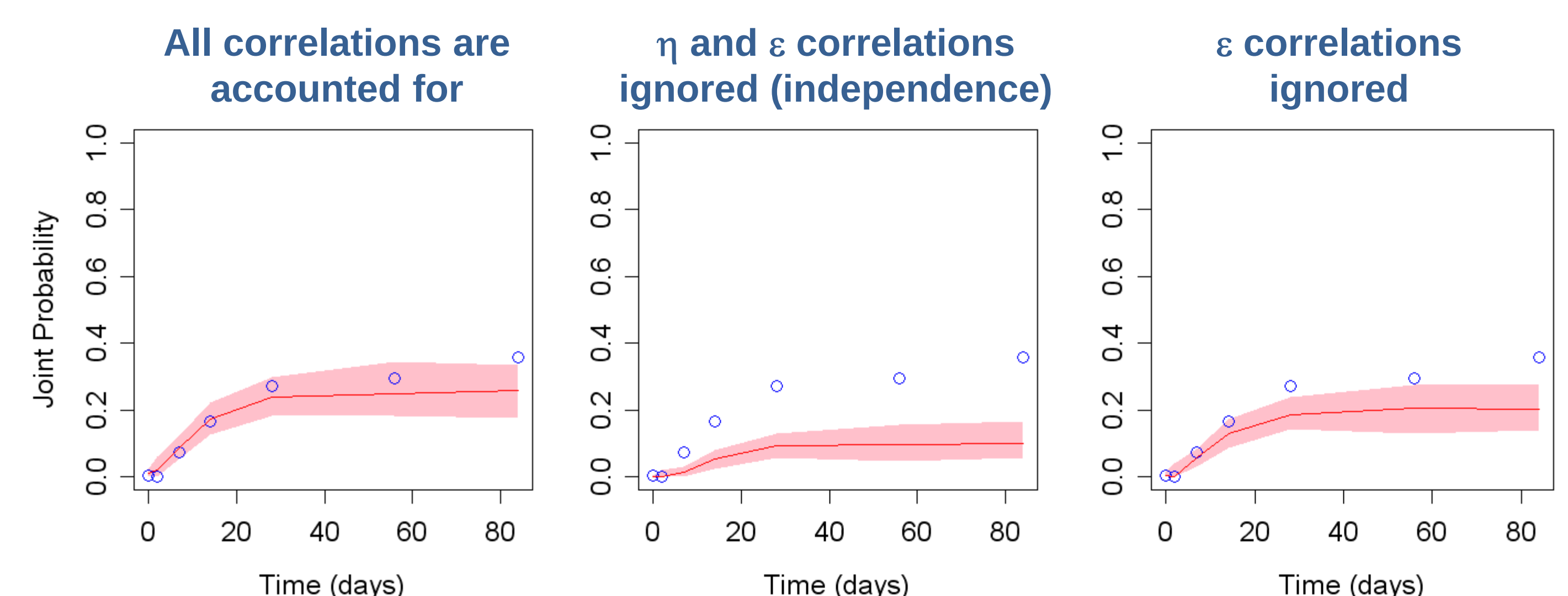


Figure 2. VPC for the joint probability that all scores = 0 (normal). Dots = observations. Pink area = 95% confidence interval for model predictions. Red curve = median model predictions.

- **Identification of redundancies between scores.** PCA results are displayed on Fig. 3 for the first two components which explained 86 - 89% of the variability. Three scores appeared to be highly correlated ('posture', 'lameness at walk', 'lameness at trot') while 'pain' appears to document a different aspect of the disease. Treatment effect was about the same for the 4 scores.

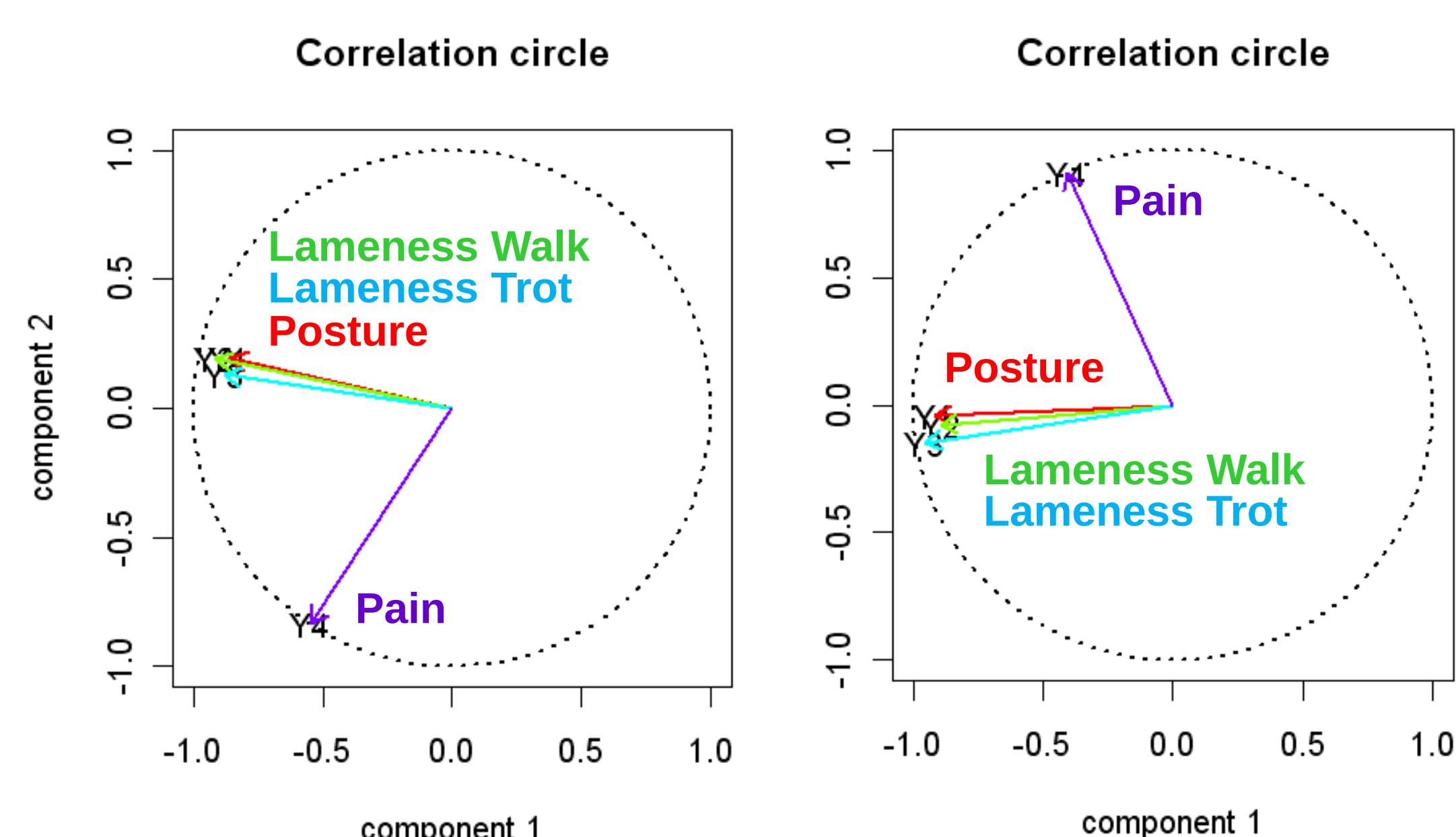


Figure 3. Results of PCA on Σ (left) and Ω (right)