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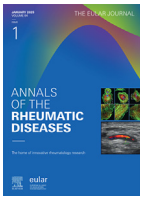

Correspondence

Reevaluating analytical approaches in systemic sclerosis research: challenges of PCA and logistic regression

Rouvière et al [1] conducted a comprehensive study on the stratification of systemic sclerosis patients based on their autoantibody status, revealing distinct molecular signatures. Utilising principal component analysis (PCA) of transcriptomic data, the researchers identified subtle differences between the 2 patient groups, suggesting a continuous spectrum of molecular signatures that encompasses both anticentromere (ACA)- and anti-SCL70 (SCL70)-positive cohorts. To evaluate the clinical outcomes of skin fibrosis, pulmonary fibrosis, and arthritis, they employed 2 logistic regression models. One model incorporated autoantibody status along with the identified features (green curve), providing a multifactorial perspective, while the other relied solely on the identified features (blue curve) to isolate the predictive power of those variables alone. The area under the curve values for these models were calculated to assess their predictive accuracy, and these were subsequently compared with the predictive capacity of autoantibody status alone (orange curve). Additionally, to understand the relative importance of specific predictors in the model, the contributions of individual features were extracted by analysing the absolute values of the feature coefficients [1].

However, this paper raises important methodological questions about the suitability of employing PCA and logistic regression in this context, particularly due to PCA's inherent linearity and the parametric assumptions underlying logistic regression. These choices can lead to misleading interpretations, especially when analysing complex biological data that frequently exhibit nonlinear and nonparametric traits. Numerous peer-reviewed studies highlight the limitations associated with applying linear methods to data that are fundamentally nonlinear and using parametric models on nonparametric data; such misapplications can introduce significant distortions and result in skewed conclusions. This underscores the necessity for caution and methodological rigour when analysing biological data to ensure that the interpretations drawn are both valid and meaningful.

PCA, for instance, operates by emphasising linear relationships among features, potentially overlooking meaningful associations between variables that could provide insights into the underlying biological processes. Furthermore, PCA's reliance on certain assumptions—such as the necessity for linear, meaningful intervariable correlations, the use of continuous and standardised data, a sufficiently large sample size, homoscedasticity, and the presence of minimal outliers—can lead to the exclusion of critical nonlinear features that may be vital for accurately modelling biological systems. Consequently, the violation of these assumptions can significantly distort the results obtained from PCA, rendering it ill-suited for analysing the inherently nonlinear and nonparametric characteristics of biological data [2–6]. This limitation emphasises the need for alternative analytical methods that can more effectively capture the complexities and nuanced relationships present in biological systems.

Similarly, logistic regression is based on parametric assumptions regarding the data, including the independence of predictors and the absence of multicollinearity. When these assumptions are violated, particularly in biological data that often exhibit complex interactions and nonparametric characteristics, logistic regression may yield unreliable results. Just as with PCA, the reliance on these assumptions can lead to significant distortions in the analysis, potentially obscuring critical relationships and insights inherent in the data [7–10]. Therefore, the application of linear and parametric models to such multifaceted biological data warrants careful scrutiny to avoid erroneous interpretations and ensure that the underlying biological truths are accurately represented. This highlights the importance of exploring alternative analytical approaches that are better suited to accommodate the complexities of biological systems.

In this regard, the paper recommends employing nonlinear nonparametric methods such as mutual information analysis and effective transfer entropy to analyse complex interactions among multiple variables, especially when those interactions are characterised by nonmonotonic patterns. These methods can effectively capture the interdependencies and relationships that linear models may overlook, providing a richer and more accurate representation of the underlying biological phenomena.

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