

Discussion of LESA: Longitudinal Elastic Shape Analysis of Brain Subcortical Structures

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We congratulate the authors on an interesting paper which combines the ideas of shape analysis with longitudinal data analysis. With the increasing complexity of experiments involving imaging data, including a number of important longitudinal imaging studies, not least those presented, it is important to develop methodology that allows for a considered analysis of such data, and this paper goes a long way to helping address these issues.

There are a number of important choices made in the paper. The registration of the shapes themselves is done through an approach which first received prominence in a statistical functional data context in Srivastava et al. (2011), where the square-root velocity function plays an analogous role to the square-root normal field (SRNF) (Jermyn et al., 2012). This approach has highly beneficial properties that allow for the definition of reparameterization invariant metrics as described for the SNRF approach in this paper. It is very interesting to see the approach using mixed-effect models which again has connections to the literature in functional data and registration (Marron et al., 2015; Tucker et al., 2013; Hadjipantelis et al., 2015). However, as with many instances of longitudinal data analysis, particularly with sparse observations, it is very natural to consider the temporal components of the data to be a form of functional data, and hence the PACE approach (Yao et al., 2005) is a more suitable framework to model these in. There are many possible extensions to the

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original PACE idea, and all these could be implemented if relevant to the application. Of course, this would also set up a number of challenging theoretical questions, particularly given the non-Euclidean nature of shape spaces.

One aspect that stands out in the paper is the computational tradeoffs that need to be made in these types of approaches. The authors have chosen to use a Euclidean framework for PCA in contrast to the SRNF approach used for the image registration. It is rightly pointed out that it would be possible to adapt methods of Kurtek et al. (2010) to do this more formally in the original metric, but a Euclidean approximation is chosen for computational reasons. It would be very interesting to determine how quickly this approximation breaks down under certain specific modelling choices. For example, is it possible to determine how far the results can be extrapolated based on the approximation if projections of subsequent shapes outside the original set are of interest? It should, however, be noted that such approximations have ultimately allowed the authors to conduct a comprehensive analysis of thousands of images from multiple studies, which further substantiates their findings.

A different approach would be to use a methodology which aims to model shapes through diffeomorphic deformations, or more specifically, through vector fields that characterise these diffeomorphic functions in the framework of Younes (2010). This approach was considered by Lila and Aston (2022) in the context of a joint analysis of brain shape and connectivity, where a joint model was used to account for the non-Euclidean nature of both brain shape and functional connectivity (non-negative definite covariance matrices). The geometry of the space was preserved through linear tangent space mapping of the data which then allows the statistical estimates to be projected onto the original space. This, of course, loses some of the elegance of the SRNF framework, but at a considerable ease of preserving the topology of the data and avoiding Euclidean approximations. Indeed, an interesting direction would be to integrate these approaches and leverage the effectiveness of the SRNF framework to define a metric between shapes that leads to accurate registration while adopting diffeomorphic functions to represent shapes in the original space, avoiding complex inversions of SRNFs, which may have motivated the adoption of a Euclidean framework post registration in the first place. Comparisons of these different approaches, and their integration, might well be an obvious next step.

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