Medical Image Analysis 33 (2016) 114–121

Contents lists available at ScienceDirect

Medical Image Analysis

journal homepage: www.elsevier.com/locate/media

Editorial

Longitudinal modeling of appearance and shape and its potential for clinical use☆

Guido Gerig[a,*], James Fishbaugh[a], Neda Sadeghi[b]

[a] Tandon School of Engineering, Department of Computer Science and Engineering, NYU, 2 MetroTech Center, 10.094, Brooklyn, NY 11201, USA
[b] Section on Quantitative Imaging and Tissue Sciences, Eunice Kennedy Shriver National Institute of Child Health and Human Development, United States

ARTICLE INFO

Article history:
Received 11 April 2016
Revised 6 June 2016
Accepted 13 June 2016
Available online 15 June 2016

Keywords:
Longitudinal imaging
Shape analysis
Shape regression
Mixed-effects modeling

ABSTRACT

Clinical assessment routinely uses terms such as development, growth trajectory, degeneration, disease progression, recovery or prediction. This terminology inherently carries the aspect of dynamic processes, suggesting that single measurements in time and cross-sectional comparison may not sufficiently describe spatiotemporal changes. In view of medical imaging, such tasks encourage subject-specific longitudinal imaging. Whereas follow-up, monitoring and prediction are natural tasks in clinical diagnosis of disease progression and of assessment of therapeutic intervention, translation of methodologies for calculation of temporal profiles from longitudinal data to clinical routine still requires significant research and development efforts. Rapid advances in image acquisition technology with significantly reduced acquisition times and with increase of patient comfort favor repeated imaging over the observation period. In view of serial imaging ranging over multiple years, image acquisition faces the challenging issue of scanner standardization and calibration which is crucial for successful spatiotemporal analysis. Longitudinal 3D data, represented as 4D images, capture time-varying anatomy and function. Such data benefits from dedicated analysis methods and tools that make use of the inherent correlation and causality of repeated acquisitions of the same subject. Availability of such data spawned progress in the development of advanced 4D image analysis methodologies that carry the notion of linear and nonlinear regression, now applied to complex, high-dimensional data such as images, image-derived shapes and structures, or a combination thereof. This paper provides examples of recently developed analysis methodologies for 4D image data, primarily focusing on progress in areas of core expertise of the authors. These include spatiotemporal shape modeling and growth trajectories of white matter fiber tracts demonstrated with examples from ongoing longitudinal clinical neuroimaging studies such as analysis of early brain growth in subjects at risk for mental illness and neurodegeneration in Huntington's disease (HD). We will discuss broader aspects of current limitations and need for future research in view of data consistency and analysis methodologies.

1. Introduction

Clinical researchers increasingly make use of longitudinal image studies to examine subject-specific changes due to pathology, intervention, therapy, neurodevelopment, or neurodegeneration. Moreover, dynamic organ changes as seen in cardiac imaging (Peyrat et al., 2010) or functional changes as measured in perfusion imaging, just to name a few, by definition result in time-series volumetric image data. Expressions such as development, degeneration, disease progression, recovery, monitoring, or prediction inherently carry the aspect of a dynamic process – suggesting that imaging at multiple time points will be necessary. The detection and characterization of changes from baseline due to disease, trauma, or treatment require appropriate image processing and visualization tools for qualitative and quantitative assessment of change trajectories. Whereas longitudinal analysis of scalar data is well known in the statistics (Fitzmaurice et al., 2012) and medical imaging communities, see for example Giedd et al. (1999), Thompson et al. (2000), Shaw et al. (2008), Lebel and Beaulieu (2011), Bernal-Rusiel et al. (2013), its extension to high-dimensional image data, shapes, or functional changes represent significant challenges. Cross-sectional analysis of longitudinal data does not provide a model of growth or change that considers the inherent correlation of repeated images of individuals, nor does it inform how an individual patient changes relative to a comparable

☆ Supported by NIH grants: R01 MH070890, Conte Center MH064065, NA-MIC U54 EB005149, ACE RO1 HD 055741, U01 NS082086, PREDICT HD NS050568.
* Corresponding author. Tel.: +1 646 997 3975.
E-mail address: gerig@nyu.edu (G. Gerig).

http://dx.doi.org/10.1016/j.media.2016.06.014
1361-8415/

healthy or disease-specific population, an aspect which is highly relevant to decision making and therapy planning.

Although successful early results were presented for image regression in infant (Aljabar et al., 2008) and aging studies (Davis et al., 2010) of cross-sectional data across the age range, standard regression is not optimal for longitudinal data because such methods do not account for the correlation between repeated measurements and thus violate the Gauss–Markov assumption of independence. Moreover, individual change trajectories often need to be interpreted in relationship to a population growth model, which in turn is the hidden group model given a representative set of individual trajectories, and require a common framework based on the use of hierarchical linear (or nonlinear) models (HLM). Other typical driving applications are concerned with registration of serial data of the cardiac cycle, sampled at different time points, or measuring object shape changes via shape regression, both requiring new image registration and modeling approaches.

The special nature of longitudinal or repeated, time-series data of individual subjects, with the inherent correlation of structure and function across the sequence of images, spawns the development of new image processing and analysis approaches for 4-D image data. Such advances aim to tackle the challenging issues of registration, segmentation, and analysis in the presence of geometric and contrast changes over time. New methodologies are rapidly evolving, often focusing on the specific application at hand. The following is not a comprehensive survey of state-of-the-art methodologies for spatiotemporal processing of longitudinal image data but discusses a few important key aspects of longitudinal modeling and analysis guided by current projects of the authors.

2. Longitudinal study design

The main characteristics of longitudinal data are the following:

Correlation: Measurements obtained on the same individual are correlated, with measurements obtained closer in time being more correlated than the ones further apart. This correlation across repeated measurements breaks down the fundamental independence assumption of most statistical regression techniques.

Unbalanced data: Most longitudinal studies plan to obtain the same number of measurements for each individual over a time period; however, in practice this is rarely the case. With studies that span over several years, it is inevitable that some individuals will drop out of the studies and some might miss their appointments and reschedule for a later time. Some imaging data also will have to be excluded due to motion of the subject or other imaging artifacts. This leads to uneven spacing of data in the time domain and in missing time points.

3. Longitudinal analysis of appearance: application to DTI

Neurodevelopment or neurodegeneration can be characterized by changes of image contrast or appearance in longitudinal imaging, reflecting specific structural properties, e.g. scalar diffusion invariants from diffusion imaging. In view of unbalanced data and missing time points, a common repeated analysis of variance (repeated ANOVA) is questionable as it assumes that individuals have random effects that are constant over time. Second, experience in different applications demonstrate that temporal change is often not linear but requires a more complex nonlinear modeling (Geng et al., 2012). Both favor the use of parametric growth models that reflect the underlying nature of change, and mixed effects models, a class of statistical methods that model the correlation of measurements of an individual along with modeling the mean response of a population over time. Fig. 1 represents an example where measurements decrease nonlinearly over time (here we measure radial diffusivity from DTI tensor data). Applying nonlinear regression to the sample points as if these were cross-sectional data, we obtain a result which seems to well reflect the time course.

However, considering repeated data from subjects and calculating fixed and random effects via nonlinear mixed-effects modeling (NLME), the result is significantly different since it represents the average trajectory. This example well demonstrates that longitudinal data includes important additional information not available from cross-sectional data, but also highlights that in the presence of true longitudinal data, regression may not be the method of choice. We seek a method such as mixed-effects modeling that enables within-individual changes in the response variable, and thereby has the capacity to separate between cohort and age effects. This is of particular importance in health sciences where heterogeneity of individuals due to genetic and environmental factors plays an important role in the progression of the disease or the response of individuals to treatment.

3.1. Linear and nonlinear mixed-effects models

Linear mixed-effects models are models where both the fixed and random effects enter the model linearly. In these models, the individual trend is a linear model built upon the overall population trend, which is also linear. Linear mixed-effects models can be formulated as:

$$y_i = X_i\beta + Z_i b_i + e_i \qquad i = 1, \ldots, M, \tag{1}$$

where y_i is the $n_i \times 1$ vector of measurements for subject i. β is a $p \times 1$ vector of fixed effects and b_i is the $q \times 1$ vector of random effects. X_i and Z_i are design matrices that relate fixed effects and random effects to y_i. X_i is the $n_i \times p$ matrix, which can include variables such as clinical group, age and gender. Z_i is the $n_i \times q$ matrix for the random effects and includes variables such as age. b_i is a multivariate Gaussian with mean zero, $b_i \sim \mathcal{N}(0, \Psi)$, and e_i is the $n_i \times 1$ measurement error and is normally distributed $\mathcal{N}(0, \sigma^2)$. Random effects and measurement errors are assumed to be independent.

The nonlinear mixed effect model (NLME) is a generalization of linear mixed effect and nonlinear regression (Pinheiro and Bates, 2006). In NLME, some or all of the fixed or random effects enter the model nonlinearly. In the NLME model, each individual's response is modeled as:

$$y_i = f(\phi_i, t_i) + e_i, \tag{2}$$

where $\phi = A_i\beta + B_i b_i$. Similar to the linear mixed effect model, β are the fixed effect and b_i are random effects with distribution $\mathcal{N} \sim (0, \Psi)$. A_i and B_i are design matrices that indicate whether specific fixed or random effect should be included in the model. The function f can be any nonlinear function, to be evaluated based on model selection. Fig. 2 illustrates a comparisons of longitudinal modeling options for nonlinear mixed-effects modeling.

3.2. Analogy to traditional clinical practice

One of the important aspects of longitudinal analysis is the direct measurement of intra-individual changes over time. Even if all the observations for all the time points are not available for a subject, pooling the data from other subjects in the study along with the available observations for the individual enables prediction of individual trajectories (Sadeghi et al., 2014; Rekik et al., 2016). The estimation of personalized growth profiles is of great clinical interest as individuals respond differently to treatment and show different growth trajectories. Also, in cases where only one scan is available, the intensity or diffusion parameters of the subject can be compared to the normative model. This way, one can predict