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Longitudinal Modeling of Appearance and Shape and its Potential for Clinical Use★

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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.

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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 base-line 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 imagig 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 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. Figure 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:

$$y_i = X_i\beta + Z_i b_i + e_i \quad i=1,\ldots,M, \quad (1)$$

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:

$$y_i = f(\phi_i, t_i) + e_i, \quad (2)$$

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. Figure 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 subject-specific growth trajectory and predictive intervals Sadeghi et al. (2014).

In pediatric examination, comparison of body length or head circumference to a normative model of growth is ubiquitous. Such a comparison places a child's measurement against the population average to monitor normal (or abnormal) development. Here we present an analogous example from a normative neuroimaging study of early brain development outlined in more detail in Sadeghi et al. (2013), but methods and analysis procedure are generic and applicable to a broad range of applications where longitudinal images are available.

Change over time is modeled as a Gompertz function, a sigmoid curve with three intuitive parameters: asymptote, delay and speed. Individual and group level Gompertz trajectories are jointly estimated in a NLME scheme. Once average trajectories are obtained for different groups, we can make inferences about parameters of the regression. In the examples illustrated here, inferences are made in regard to regional differences and growth is described quantitatively in terms of the estimated Gompertz parameters asymptote, delay and speed. Figure 3 illustrates the concept. Population modeling results in the overall prediction interval, shown as gray shaded area. Given measurements of a new individual, here one or two timepoints shown as blue dots, NLME calculates the individual subject trajectories and its prediction intervals (blue solid line and light blue area). The red dots show the additional measurements from each subject not used for modeling but available for testing of prediction. The figure clearly demonstrates the narrowing of the subject prediction interval with availability of more data. This clearly illustrates the power of mixed-effects modeling for subject-specific analysis and prediction based on growth trajectories, which could include comparison of an individual's measurements to a normative model, a procedure commonly used in clinical practice.

4 Longitudinal Analysis of Shape

Most longitudinal studies involve extracting clinically relevant measurements from imaging data and fitting a regression model to the discrete values. Typical choices for regression include non-parametric methods such as kernel regression, or polynomials of fixed degree. These choices come with limitations; there is no clear anatomical or biological interpretation to help choose the regression model. It is particularly challenging to account for multiple clinical variables, as independent models for each variable do not account for correlation between measures, effectively removing clinical measurements from their anatomical context. This motivates the study of shape, as we believe that shape models can capture more realistic anatomical trajectories than would be estimated from discrete scalar measurements. Further, shape models have the benefit to include multiple sources of geometry, properly accounting for the spatial relationship between objects.

One natural way to characterize geometry is to consider the distribution of particles on the surface of a shape. Variability is then measured by the displacement of particles between shapes Datar et al. (2012, 2009). The major downside is this requires explicit correspondence between shapes, to be able to trace the displacement of a given particle on one shape to its corresponding location on another. In that sense, shape differences are dependent on the specific parameterization of the shapes, rather than capturing intrinsic geometric properties.

As an alternative, shape variability can be measured by the deformation of space needed to align one shape to another. It is highy recommended to read the excellent visionary work by D'Arcy Thompson on *Growth and Form* Thompson (1992). By using the mathematical representation of transformations to study anatomical variability, the reliance on a given parameterization of shape is eliminated. Deformations of the ambient space itself are therefore independent of the specific representation of any shapes embedded into the space. This is particularly important in the study of anatomy, as structures extracted from medical images have numerous shape representations, such as points, curves, surfaces, as well as the volumetric image data itself. We assume that several anatomical structures (with potentially different representations) sharing the same ambient space do not undergo independent transformations, rather the entire ambient space deforms with various structures embedded into it. It is therefore important for a spatiotemporal model to leverage various shape representations, and particularly advantageous to handle multiple shapes in any combination. This is precisely the vision of D'Arcy Thompson Thompson (1992), to compare objects without the need for a specific definition or form of shape. This motivates spatiotemporal models which estimate a single deformation of the ambient space taking into account a variety of sources of structural/geometric information Durrleman et al. (2014).

Beyond studying the difference between static shape, problems in medicine are often characterized by dynamic changes over time. Serial MRI acquired from the same patient over time represent snapshots of anatomical structures, which can be considered a sparse probing of the underlying dynamic process of change. From observations distributed sparsely in time, we must infer the continuous evolution in an attempt to capture the dynamics of anatomical change. In recent years, our lab has focused on spatiotemporal models based on the assumption that the mechanism which drives anatomical change is a continuous process, and is therefore temporally smooth; the path traced by a particle on an anatomical surface is continuously differentiable, without discontinuities.

To summarize, the necessary tool for modeling shape change is a deformation model which acts on the ambient space, to elegantly handle multiple shape representations and images in various combinations. For medical applications, such deformations should also preserve topology, so as not to tear or generate holes in anatomical structures. For modeling change over time, we require a model which guarantees temporally smooth evolution, to match our understanding of the smooth process which drives anatomical change. With this criteria in mind, we base our spatiotemporal models on the Large Deformation Diffeomorphic Metric Mapping (LDDMM) framework. Diffeomorphic transformations are well suited for the study of anatomy as they are one-to-one and invertible mappings. Further, the action of a diffeomorphism on medical images and extracted geometric structures is well studied, allowing for the embedding of multiple shapes in a variety of representations. Spatiotemporal models can be defined in the LDDMM framework by specifying a family of curves on the infinite dimensional manifold of diffeomorphisms, curves that minimizes length for example. Such shortest path curves represent geodesic flows of diffeomorphisms, and the resulting geodesic regression model can be thought of as an extension of linear regression to the manifold of diffeomorphisms.

4.1 Deformation Model

The LDDMM framework supplies the mathematical tools we need to work with the infinite dimensional manifold of diffeomorphisms, by providing a finite dimensional parameterization for flows of diffeomorphisms. Such flows are parameterized by initial momenta, a finite dimensional vector field defined in the tangent space. The momenta vectors act as initial conditions to compute a flow of diffeomorphisms starting from the identity transformation. In the case of images, this is either a scalar or vector momenta field defined at every voxel. In the case of shape data, the momenta are defined at the vertices of the shape.

The key ingredient needed to define a spatiotemporal model which handles multiple shapes and images in different combinations is a parameterization of diffeomorphisms which is independent of the specific representation of the data, i.e. not tied to the voxels or vertices. Let $\mathbf{c}(t) = \{c_1(t), \ldots, c_N(t)\}$ be the coordinates of a set of N control points for each time t, which carry momenta vectors $\boldsymbol{\alpha}(t) = \{\alpha_1(t), \ldots \alpha_N(t)\}$. The finite set of control point/momenta pairs define the time-varying velocity field everywhere in space as

$$\dot{x}(t) = v_t(x) = \sum_{p=1}^{N} K(x, c_p(t))\,\alpha_p(t), \tag{3}$$

where K is a Gaussian kernel $K(x,y)=\exp\left(-\|x-y\|^2/\sigma_V^2\right)$ defining the metric properties of the reproducing kernel Hilbert space (RKHS) through parameter σ_V. Eq. (3) is referred to as the *flow* equation.

The time-varying velocity field v_t then builds a flow of diffeomorphisms as in the LDDMM framework by integration:

$$\dot{\phi}_t(x(t)) = v_t(\phi_t(x(t))) = \sum_{p=1}^{N} K(x(t), c_p(t))\,\alpha_p(t) \tag{4}$$

given initial value $x(0)$. Additionally, the location of control points evolve in time according to the equation of motion in the same manner, written as

$$\dot{c}_t(t) = \sum_{p=1}^{N} K(c_i(t), c_p(t))\,\alpha_p(t) \tag{5}$$

given initial values $c_i(0)$. The trajectory $x(t)$ is computed by solving (4), which is defined fully by the control point/momenta pairs.

The geodesic path connecting ϕ_0 to ϕ_1 is the path which minimizes the total kinetic energy of the the velocity field v_t

$$\frac{1}{2}\int_0^1 \|v_t\|_V^2 \, dt \int_0^1 \sum_{p=1}^{N}\sum_{q=1}^{N} \alpha_p(t)^t K\left(c_p\left(t\right), c_q\left(t\right)\right) \alpha_q\left(t\right) \; dt, \tag{6}$$

which is defined entirely by $\mathbf{c}(t)$ and $\boldsymbol{\alpha}(t)$. The $\mathbf{c}(t)$ and $\boldsymbol{\alpha}(t)$ that minimize (6) satisfy the following set of differential equations:

$$\begin{cases} \dot{c}_i\left(t\right) = \sum_{p=1}^{N} K\left(c_i\left(t\right), c_p\left(t\right)\right) \alpha_p\left(t\right), \\ \dot{\alpha}_i\left(t\right) = -\sum_{p=1}^{N} \alpha_i(t)^t \alpha_p\left(t\right) \nabla_1 K\left(c_i\left(t\right), c_p\left(t\right)\right) \end{cases} \tag{7}$$

with initial conditions $\mathbf{c}_0$ and $\boldsymbol{\alpha}_0$, which are referred to as the *shooting* equations, or geodesic shooting. This shows that a geodesic flow of diffeomorphisms is parameterized completely by the initial control points and initial momenta.

In Fishbaugh et al. (2014) we combine this parameterization of diffeomorphic flows within a variational framework to estimate a geodesic flow of diffeomorphisms which minimizes the sum-of-squared distance to observations, which can take the form of images or shapes in any combination in 2D or 3D. All available shape information from images and extracted objects is therefore leveraged to estimate a single time-varying deformation. Compared to image regression alone, shape data provides anatomical information that constrains estimation, particularly in regions of low image contrast. Compared to shape regression alone, image information provides data in regions where segmentations are not available, as well as providing context for the embedded anatomical objects.

We illustrate the concept of geodesic regression with two examples. First, the estimation of a population average genu fiber tract from a cross-sectional dataset of infants and young children. Snapshots of the estimated growth model are shown in figure 4. Such an experiment is made possible by the ambient space deformation model, as it is not feasible to establish point correspondence between fiber bundles from different subjects. The second example is a subject-specific model of a patient with Huntington's disease with observations acquired at baseline, 1 year, and 2 years. The resulting personalized growth model is summarized in figure 5, where we explore an additional 4 years by extrapolation. The model was estimated using volumetric imaging data as well as extracted geometry of the white matter surface and left/right caudate. The inclusion of shape information helps drive the deformation over time in areas where image contrast alone is not sufficient, capturing the elongation and thinning of the caudate as well as ventricle expansion.

4.2 From Regression to Mixed-Effects Models

In the previous section, we outlined a generic and flexible deformation model designed to include combinations of shapes with various representations. Around this concept, we designed a spatiotemporal model which can be thought of as the straightforward extension

of linear regression to the space of diffeomorphisms. Early work in our lab focused on using regression to estimate subject-specific trajectories, in order to age match against a normative model of evolution Fishbaugh et al. (2012). However, what remains is to incorporate such regression models into a mixed-effects framework, to jointly estimate individual and group trends, as in section 3.1.

However, such an extension is non-trivial, as mixed-effects models given manifold valued data require careful consideration. For the general Riemannian manifold, we must deal explicitly with the curvature of the space. To solve for the parameters of a geodesic, one has to solve a second order ODE which relates the second derivative of Jacobi fields with the Riemannian curvature tensor Thomas Fletcher (2013). For a given manifold, the difficulty is in defining the exponential/log maps as well as computing sectional curvature. Furthermore, an implicit Riemannian mixed-effects model requires a notion of distances between geodesics, which again requires cumbersome manifold specific calculations of covariant derivatives and explicit computation of curvature. The challenge in extending the statistical models of section 3.1 to general manifold valued data can be attributed to the nonlinearity of the space, where simple and fundamental operations are not defined.

Promising early work is presented in Muralidharan et al. (2014, 2016) where LME is applied to longitudinal anatomical shape complexes after establishing point-to-point correspondence via LDDMM regression of subject-specific trajectories. Modeling follows the principle outlined in equation 1 for LME followed by hypothesis permutation test based on the Hotelling's T^2 statistics. Figure 6 illustrates a preliminary result of fixed effects for control and Huntington's subjects. LME modeling of scalar data (left figure) was extended to shape complexes of subcortical structures (right) for studying locality and type of changes. This scheme eases the estimation of an LME model for shapes by assuming that each particle on the surface follows a linear trajectory, even though overall shape change is nonlinear. A linear approximation is well suited to studying the subtle changes associated with HD, but may not be appropriate for periods of rapid change, such as early childhood development. Due to the difficulty of the problem and the fact that high quality and well controlled longitudinal imaging data is just now becoming available, very few true longitudinal mixed-effects models for shape currently exist. This is an area that is of great interest, to show that there is indeed rich information encoded by shape beyond scalar measures such as volume. Beyond the development of additional methods/theory, what is needed are compelling applications to demonstrate the power of longitudinal shape models to the scientific community, to leverage strengths as outlined in section 3.

5 Challenges for consistency of longitudinal image data

Longitudinal image analysis primarily makes the assumption that data acquisition, i.e. the "camera" and its parameters, remains the same over the observation period and variations would due to noise attributed to different sources. Would the imaging process change due to systematic technology upgrade, we would no longer be able to decouple changes due to time from changes due to imaging conditions. This is a critical and challenging problem in medical imaging as the community does not only see rapid progress in novel and improved processing methodologies but also in imagining technology. Manufacturers of scanners

regularly provide updates of software in order to improve imaging capabilities but which often require updates of imaging protocols, thus affecting consistency of image quality. Even more, so called upgrades of scanners are available in regular intervals of 5 to 10 years, where the word upgrade stands for a full replacement with new hardware.

Large-scale analysis of patient populations acquired across multiple sites is chosen as an option to include a larger number of subjects to increase statistical power. Examples are the Alzheimer's Disease Neuroimaging Initiative (ADNI), the Autism Brain Imaging Data Exchange (ABIDE), or the Autism Centers of Excellence (ACE) network projects, just to name a few, where consortia spend strong efforts to freely distribute large imaging databases in order to invite the scientific community to accelerate progress of analysis methodologies and to compete in so called challenges. In addition to questions of site-specific consistency of longitudinal data, multi-site studies generate additional variability by pooling scans from multiple sites.

Longitudinal and multi-site imaging studies therefore require advanced concepts for multi-site imaging calibration by developing standardization, calibration via geometric and/or human phantom scanning, and evaluation and modeling of cross-site differences and stability. This seems an excellent opportunity for the medical image analysis community as questions of quantification of image quality, comparison of images, and correction and calibration are core research topics. Besides improving consistency of the imaging process, increased efforts are necessary to evaluate and improve robustness of processing pipelines in view of intra-, inter-site and longitudinal variability of imaging data.

The following illustrates an example of scanner comparison and quality control Gouttard et al. (2008). As part of a longitudinal infant high-risk autism study (ACE-IBIS), inter-site and intra-site variability was assessed with human phantoms annually scanned at all participating sites with repeated imaging in intervals of several hours. In order to answer the question if different scanner types than 3T Tim Trio could be included, the human phantoms also got scanned on a 3T Allegra. Images were processed with a well-established automatic atlas-moderated tissue segmentation pipeline based on expectation maximization (EM) after rigid co-registration of data from the individual phantoms. Figure 7 illustrates a subset of MRI and segmentation images with a graph which shows percentage tissue volumes for Trio and Allegra results. Note that here we do not include modeling of intra-, inter-site and longitudinal variability which is published elsewhere but just illustrate a simplified overview analysis. Results clearly show large differences of tissue segmentations of the same subject between Trio and Allegra image data although MRI data and segmentation images visually look very similar. We conclude that using the same scanner type and controlled protocols over multiple sites results in relatively small variabilities whereas the use of a different scanner appears like an outlier. The observed differences may be attributed to subtle spatial deformations due to head coil differences or to sensitivity of tissue segmentation methods to different contrast-to-noise ratio. Significantly more research effort by our scientific community is needed to develop methodologies for calibration and robust segmentation and analysis, as this is a precondition for optimal use of longitudinal imaging. Since large-scale clinical longitudinal studies represent enormous efforts and costly investments in recruiting,

scanning, data preprocessing and analysis, questions on re-using data in combination with newly planned studies on new scanner technologies are of utmost importance.

6 Conclusion

Longitudinal imaging is becoming a method of choice for measuring subject-specific temporal profiles of change of anatomy and function due to disease progression or therapeutic intervention. Experience with clinical collaborations demonstrate that subject-specific modeling of changes due to disease progression or response to therapeutic treatment are highly sought for improved diagnosis or prediction, but that image analysis procedures to extract such information from imaging data lag far behind progress in acquisition methodologies. Spatiotemporal profiles may include volume changes, shape deformations, alterations of tissue contrast or changes of functional measures. We discuss that using time-sampled repeated image data, the inherent correlation of such data needs to be considered for statistical modeling to set it apart from cross-sectional analysis, favoring mixed-effects modeling over regression. Such models provide improved statistical power of longitudinal versus cross-sectional analysis and not only result in average trajectories of change but in individual, subject-specific change profiles. Whereas mixed-effects modeling is a standard concept in statistical analysis of scalar and low-dimensional data, its extension to high-dimensional data such as shapes or images and/or inclusion of nonlinear functions to accommodate application-specific trajectories is still to be seen at an early stage of research.

With imaging often collected over years, in particular in studies of mental illness, early brain growth or aging, rapidly evolving scanner technology creates significant obstacles as it prohibits a standardization of imaging. The improved contrast, spatial resolution and novel capabilities after scanner upgrades may not be appreciated in longitudinal studies since associated changes in image appearance, anatomical details or diffusion and functional imaging, for example, cannot just be seen as noise in these measurements but represent systematic differences that represent significant challenges for longitudinal modeling and analysis. Although most of the rapidly emerging longitudinal studies face these problems, there are, to our knowledge, no convincing solutions yet that would allow a flexible change or mixing of scanner types in such studies. Geometric phantoms are used for calibration of scanner-related spatial deformations, but subject-induced deformations and differences due to different contrast and spatial resolution still await novel solutions.

Future research also needs to include solutions for multi-modal integration, either via joint use of multiple imaging modalities or multiple geometric structures such as images, surfaces, lines and points as discussed above. Scenarios where both, shape and appearance, will change over time (such as early development, aging or pathology progression, e.g.) will require joint modeling of appearance and anatomical boundaries, thus combining techniques as discussed above. Moreover, longitudinal changes of brain connectivity characterized as graphs altered through disease, pathology or growth, seem superb open challenges for medical imaging research as such data have become available to scientists. We are convinced that longitudinal imaging and analysis for improved diagnosis, prediction of disease and monitoring of efficacy of treatment will translate to the clinic and will have a major impact

on health care, given that medical image analysis researchers will overcome current limitations by providing novel solutions.

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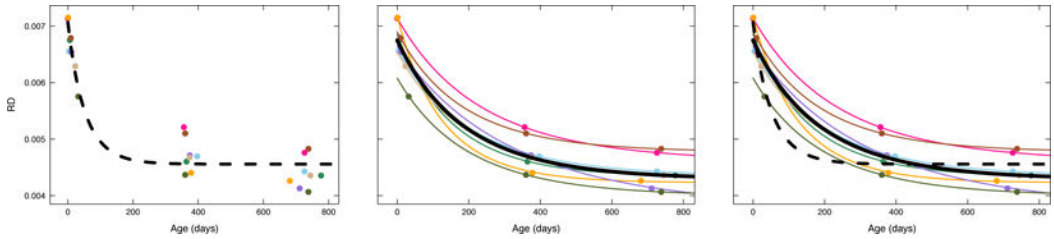

Fig. 1.

Modeling of longitudinal data. Left: Nonlinear least squares (NLS) regression without considering repeated time points. Middle: Nonlinear mixed-effects modeling (NLME) with fixed effect (black) and subject-specific random effects (colored curves). Right: Regression result overlaid on NLME result. The figures indicate that regression provides a plausible model would one not know about repeated time points, but that mixed-effects modeling provides a significantly different result that reflects the average of the individual trajectories. The data, used here as an example, represents radial diffusivity changes of a brain subregion in longitudinal infant DTI datasets taken at neonate, 1 year and 2 years of age.

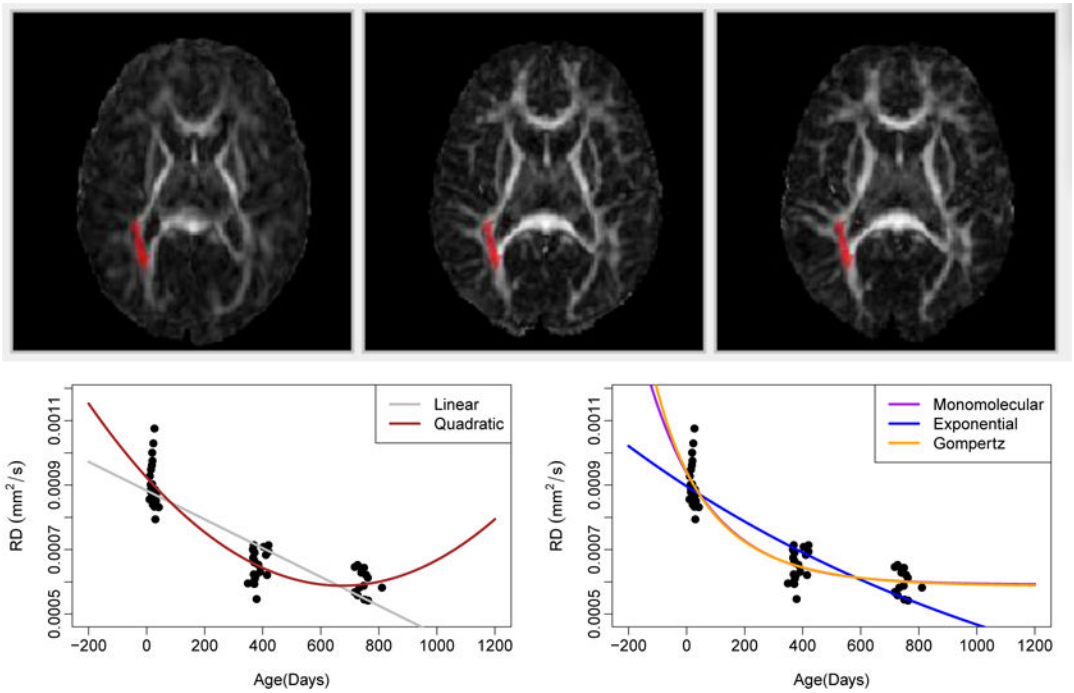

Fig. 2.

Comparison of different growth models for longitudinal RD data of posterior thalamic radiation. Top: Posterior thalamic radiation is shown as red label on the longitudinal FA images of one subject. Images taken at 2 weeks, 1 year and 2 years. Bottom left: Linear mixed-effects models of RD. Bottom right: nonlinear mixed-effects models.

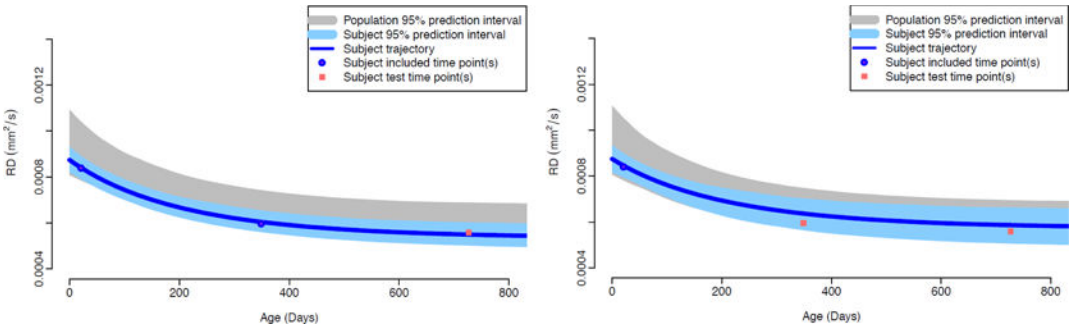

Fig. 3.

Subject-specific interval compared to the overall prediction for RD of posterior thalamic radiation. Left: Subject-specific interval calculated based on only one time point (neonate). Right: Subject-specific interval calculated based on scans at neonate and 1 year. Subject-specific 95% prediction intervals (light blue) are compared to the overall prediction interval (gray shaded) for RD of posterior thalamic radiation. Solid blue curves illustrate the predicted subject trajectories based on NLME analysis. Red dots indicate subject's test data left out for analysis but available for testing.

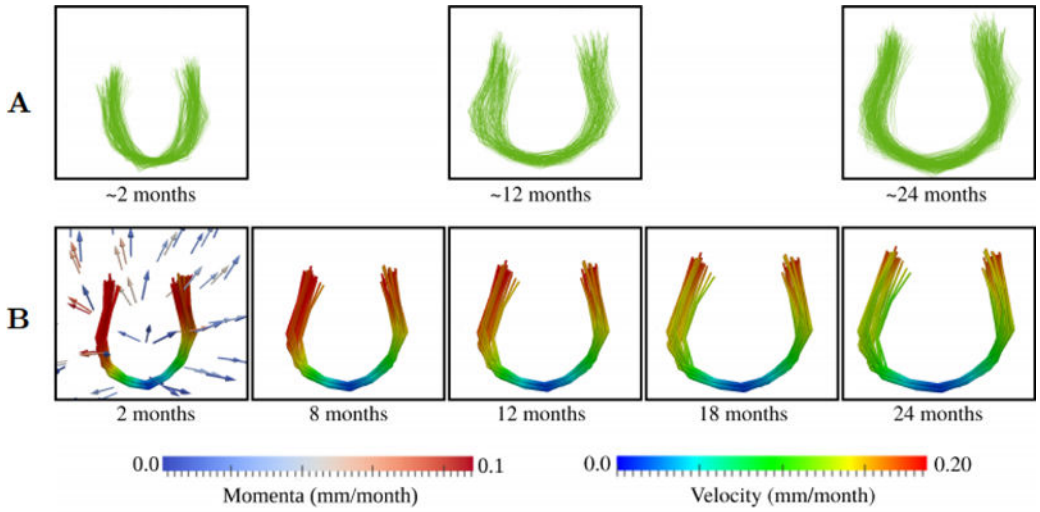

Fig. 4.

Average development of genu fiber tract from 2 to 24 months. A) Observed data for all subjects, which is clustered around 2, 12, and 24 months. B) Genu fiber tracts estimated at several time points with velocity of fiber development displayed on the surface of the estimated fibers.

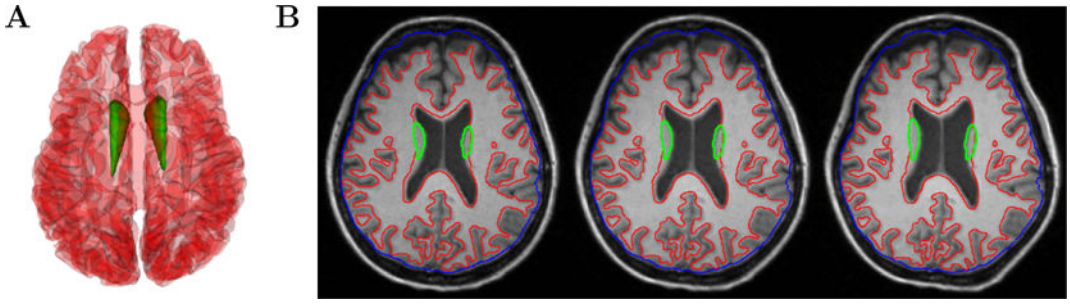

Fig. 5.

A) Shape data used for model estimation in addition to image data. B) Evolution estimated for an HD subject at baseline, 3 years, and 6 years.

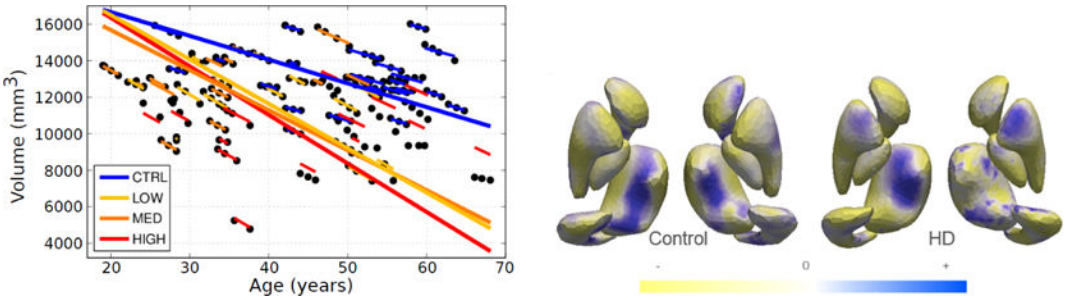

Fig. 6.

Left: LME modeling of control versus risk Hungtinton's groups. Right: Fixed effects trends from linear mixed-effects shape modeling. Example illustrates LME modeling of longitudinal segmentations of subcortical structures with three time points over two years from 7 controls and 6 Huntington's subjects. Colormaps of fixed effects slopes for controls and HD indicate local expansion (blue) or contraction (yellow). Data and analysis courtesy of PREDICT-HD study and PhD thesis of Manasi Datar, Utah 2013.

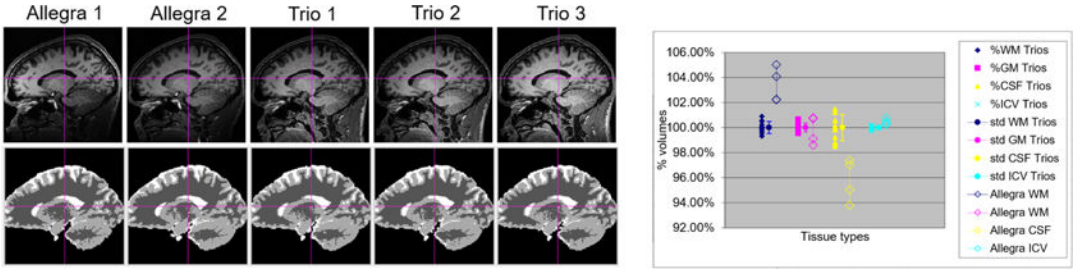

Fig. 7.

Scanner comparison via traveling phantom. Left: Subset of sagittal MRI of 3T Allegra and 3T Trio brain scans (top) and tissue segmentations (bottom). Right: Graph of normalized percentage tissue volumes for Tim Trio and Allegra data. White matter, gray matter, cerebrospinal fluid and intracranial volume are indicated as GM, WM, CSF and ICV. The Allegra results are plotted as open squares. Statistical analysis shows that the Allegra data differs significantly from the Trio data for WM, CSF and ICV. Results from 3 sites with 2 repetitions and 2 phantoms with Trio and 1 site with 2 repetitions and 2 phantoms with Allegra scanners are shown.