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# STGP: Spatio-temporal Gaussian process models for longitudinal neuroimaging data☆

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ABSTRACT

Longitudinal neuroimaging data plays an important role in mapping the neural developmental profile of major neuropsychiatric and neurodegenerative disorders and normal brain. The development of such developmental maps is critical for the prevention, diagnosis, and treatment of many brain-related diseases. The aim of this paper is to develop a spatio-temporal Gaussian process (STGP) framework to accurately delineate the developmental trajectories of brain structure and function, while achieving better prediction by explicitly incorporating the spatial and temporal features of longitudinal neuroimaging data. Our STGP integrates a functional principal component model (FPCA) and a partition parametric space–time covariance model to capture the medium-to-large and small-to-medium spatio-temporal dependence structures, respectively. We develop a three-stage efficient estimation procedure as well as a predictive method based on a kriging technique. Two key novelties of STGP are that it can efficiently use a small number of parameters to capture complex non-stationary and non-separable spatio-temporal dependence structures and that it can accurately predict spatio-temporal changes. We illustrate STGP using simulated data sets and two real data analyses including longitudinal positron emission tomography data from the Alzheimer's Disease Neuroimaging Initiative (ADNI) and longitudinal lateral ventricle surface data from a longitudinal study of early brain development.



## 1. Introduction

Large-scale longitudinal neuroimaging studies have collected a rich set of ultra-high dimensional imaging data, behavioral data, and clinical data in order to better understand the progress of neuropsychiatric disorders, neurological disorders and stroke, and normal brain development, among many others (Evans and Group., 2006; Almli et al., 2007; Skup et al., 2011; Meltzer et al., 2009; Kim et al., 2010; Weiner et al., 2013). Three primary goals of longitudinal neuroimaging studies are

- (i) to characterize individual change in brain structure and function over time;
- (ii) to characterize the effect of some covariates of interest, such as diagnostic status and gender, on the individual change; and
- (iii) to study the predictive value of early brain developmental trajectories for later brain and cognitive development and disease progression.

Moreover, the objective 2 of the recent National Institute of Mental Health (NIMH) Strategic Plan is to chart mental illness trajectories to determine when, where, and how to intervene by using novel techniques (e.g., imaging). To achieve these goals (i)–(iii), it requires the development of advanced image processing and statistical tools.

A distinctive feature of longitudinal neuroimaging data is that it contains both spatial and temporal dimensions. Specifically, imaging measurements of the same individual usually exhibit positive correlation and the strength of the correlation decreases with the time separation. Moreover, due to the inherent biological structure and function of brain, neuroimaging data are spatially correlated in nature and contain

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spatially contiguous regions. However, since longitudinal neuroimaging data usually has strong heterogeneity in longitudinal trajectories across space, their spatial and temporal dimensions are typically non-separable. Such non-separability has posed unprecedented challenges to most existing statistical methods for achieving goals (i)–(iii). As shown in Derado et al. (2010), appropriately accounting for correlation structure in statistical modeling and estimation can lead to substantial gains in statistical power. Furthermore, accurately modeling the spatial and temporal dependencies is even more critical for prediction (Cressie and Wikle, 2011; Derado et al., 2013; Demel and Du, 2015).

There are two major groups of spatio-temporal models for longitudinal neuroimaging data. The first one is to use temporal evolution models for non-linear image registration to estimate longitudinal spatial transformations that capture time-varying images (Ashburner and Ridgway, 2012; Singh et al., 2015; Hong et al., 2012). Such temporal evolution models are usually characterized by some regularizing term and identified either by fitting parametric progression models on geometric features of the transformation or by choosing an opportune metric in the space of transformations to characterize specific evolution models in the image space. These models usually cannot capture complex spatial–temporal correlation of longitudinal neuroimaging data. The second one, usually identified as voxel-based analysis, is to fit some parametric or semi-parametric regression models (e.g., linear mixed effects and estimating equations) at each voxel of registered images (Bernal-Rusiel et al., 2013; Li et al., 2013; Yuan et al., 2013; Guillaume et al., 2014; Skup et al., 2012). These models usually ignore the moderate-to-long range spatial correlation of imaging data, even though local spatial correlation is usually introduced by the use of Gaussian smoothing with some apriori kernel size.

Recently, there is a growing interest in modeling complex spatial–temporal correlation of longitudinal neuroimaging data (Marco et al., 2015; Lorenzi et al., 2015; Derado et al., 2013; Guo et al., 2008; Woolrich et al., 2004; Gössl et al., 2001; Brezger et al., 2007; Penny et al., 2005). Such models are important for using longitudinal neuroimaging to guide treatment selection for individual patients and predict the progression of disease. For instance, in Guo et al. (2008), a predictive statistical model for PET and fMRI data was proposed to forecast a patient's brain activity following a specified treatment regimen. In Derado et al. (2013), a Bayesian spatial hierarchical model was proposed for predicting follow-up neural activity based on an individual's baseline functional neuroimaging data. In Marco et al. (2015) and Lorenzi et al. (2015), two novel spatio-temporal generative models were proposed by using either the Kronecker product of spatial and temporal covariance matrices or the kernel convolutions of a white noise Gaussian process. In general, borrowing strength from the spatial correlations as well as capturing temporal correlations between brain activity can significantly improve predictive performance.

The aim of this paper is to develop a spatio-temporal Gaussian process (STGP) framework to efficiently and flexibly model the spatial and temporal correlation structure of longitudinal neuroimaging data. Compared with the existing literature (Marco et al., 2015; Lorenzi et al., 2015; Derado et al., 2013; Guo et al., 2008; Woolrich et al., 2004; Gössl et al., 2001; Brezger et al., 2007; Penny et al., 2005), we make several novel contributions. (i) Our STGP uses a functional principal component model (FPCA) to capture a large portion of spatio-temporal dependence structure, while it uses a partition space–time covariance model to capture some local spatio-temporal correlations. In particular, the basis functions for FPCA are directly learnt from data and can capture some key features of longitudinal neuroimaging data, which may not be easily modeled by using specific parametric models (e.g., Markov random field). In contrast, most existing models either assume some specific parametric models (e.g., autoregressive and Markov random field) or use the kernel convolutions of a white noise Gaussian process for a fixed kernel function. (ii) We develop a three-stage efficient estimation procedure to estimate all parameters associated with the spatio-temporal dependence structure. (iii) We propose a prediction method that borrows strength from the spatial and temporal correlations to achieve much better prediction of spatio-temporal changes. (iv) We use two real data sets to illustrate that STGP is a powerful tool for quantifying and/or predicting the spatio-temporal changes of brain structure and function.

## 2. Methods

### 2.1. Model formulation

Consider a longitudinal neuroimaging study with $n$ subjects. We observe neuroimaging measures (e.g., cortical thickness), denoted by $\{y_i(d,t_{ij})\}$, at voxel $d$ of a three-dimensional (3D) volume (or 2D surface), denoted by $\mathcal{D}$, and a $p\times 1$ vector of covariates (e.g., age, gender, and diagnostic status), denoted by $\mathbf{x}_i(t_{ij})=(x_{i,1}(t_{ij}),\ldots,x_{i,p}(t_{ij}))^T$, for the $i$-th subject at time $t_{ij}\in\mathcal{T}$ for $i=1,\ldots,n$ and $j=1,\ldots,m_i$, where $m_i$ denotes the total number of time points for the $i$-th subject. Without loss of generality, $\mathcal{D}$ and $\mathcal{T}$ are assumed to be compact sets in $\mathbb{R}^3$ and $\mathbb{R}$, respectively, and $N_D$ denotes the number of voxels in $\mathcal{D}$.

The measurement model of our spatio-temporal Gaussian process (STGP) is given by.

$$y_i(d,t)=\mu(d,\mathbf{x}_i(t))+\eta_i(d,t)+\epsilon_i(d,t)\ \text{ for }\ i=1,\ldots,n, \tag{1}$$

where $\mu(d,\mathbf{x}_i(t))$ is the mean structure for characterizing the effects of covariates $\mathbf{x}_i(t)=(x_{i,1}(t),\ldots,x_{i,p}(t))^T$ on longitudinal neuroimaging data across $(d,t)$. The $\eta_i(d,t)$ are random functions that characterize both individual image variations from $\mu(d,\mathbf{x}_i(t))$ and the medium-to-long-range dependence of longitudinal imaging data. Moreover, $\epsilon_i(d,t)$ are measurement errors that capture the local spatio-temporal dependence structure of longitudinal imaging data. It is assumed that $\eta_i(d,t)$ and $\epsilon_i(d,t)$ are mutually independent and $\eta_i(d,t)$ and $\epsilon_i(d,t)$ are, respectively, independent and identical copies of $GP(0,\Sigma_\eta)$ and $GP(0,\Sigma_\epsilon)$, where $GP(\mu,\Sigma)$ denotes a Gaussian process with mean function $\mu(d,t)$ and covariance function $\Sigma((d,t),(d',t'))$.

We consider a functional principal component analysis (FPCA) model for the process $\eta_i(d,t)$ or a spectral decomposition of $\Sigma_\eta((d,t),(d',t'))$. Let $\lambda_1\geq\lambda_2\geq\ldots\geq 0$ be the ordered eigenvalues of the linear operator determined by $\Sigma_\eta$ with $\sum_{l=1}^{\infty}\lambda_l<\infty$ and the $\psi_l(d,t)$'s be the corresponding orthonormal eigenfunctions (Yao and Lee, 2006; Hall et al., 2006; Chiou et al., 2004). Then the spectral decomposition of $\Sigma_\eta((d,t),(d',t'))$ is given by

$$\sum\nolimits_\eta((d,t),(d',t'))=\sum_{l=1}^{\infty}\lambda_l\psi_l(d,t)\psi_l(d',t'). \tag{2}$$

Then $\eta_i(d,t)$ admits the Karhunen–Loeve expansion as follows:

$$\eta_i(d,t)=\sum_{l=1}^{\infty}\xi_{i,l}\psi_l(d,t), \tag{3}$$

where $\xi_{i,l}=\int_{\mathcal{T}}\int_{d\in\mathcal{D}}\eta_i(d,t)\psi_l(d,t)d\mathcal{V}(d)dt$ is referred to as the $l$-th functional principal component score of the $i$-th subject, in which $d\mathcal{V}(s)$ denotes the Lebesgue measure. The $\xi_{i,l}$'s are uncorrelated random variables with $E(\xi_{i,l})=0$ and $E(\xi_{i,l}^2)=\lambda_l$. If $\lambda_l\approx 0$ for $l\geq L_0+1$, then Eq. (3) can be approximated by

$$\eta_i(d,t)\approx\sum_{l=1}^{L_0}\xi_{i,l}\psi_l(d,t). \tag{4}$$

Compared with Lorenzi et al. (2015), a key advantage of using FPCA is that $\psi_l(d,t)$ are directly estimated from the data.