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Temporal trajectory and progression score estimation from voxelwise longitudinal imaging measures: Application to amyloid imaging

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Abstract

Cortical β -amyloid deposition begins in Alzheimer's disease (AD) years before the onset of any clinical symptoms. It is therefore important to determine the temporal trajectories of amyloid deposition in these earliest stages in order to better understand their associations with progression to AD. A method for estimating the temporal trajectories of voxelwise amyloid as measured using longitudinal positron emission tomography (PET) imaging is presented. The method involves the estimation of a score for each subject visit based on the PET data that reflects their amyloid progression. This amyloid progression score allows subjects with similar progressions to be aligned and analyzed together. The estimation of the progression scores and the amyloid trajectory parameters are performed using an expectation-maximization algorithm. The correlations among the voxel measures of amyloid are modeled to reflect the spatial nature of PET images. Simulation results show that model parameters are captured well at a variety of noise and spatial correlation levels. The method is applied to longitudinal amyloid imaging data considering each cerebral hemisphere separately. The results are consistent across the hemispheres and agree with a global index of brain amyloid known as mean cortical DVR. Unlike mean cortical DVR, which depends on *a priori* defined regions, the progression score extracted by the method is data-driven and does not make assumptions about regional longitudinal changes. Compared to regressing on age at each voxel, the longitudinal trajectory slopes estimated using the proposed method show better localized longitudinal changes.

Keywords

Progression score; amyloid; Pittsburgh compound B; PiB; longitudinal image analysis

1 Introduction

Cortical β -amyloid deposition is a neuropathological hallmark associated with Alzheimer's disease (AD), and begins years before any cognitive symptoms of AD are evident [8]. Studying within-subject longitudinal changes is limited by the number of follow-up visits. The relatively short span of longitudinal positron emission tomography (PET) studies of amyloid deposition compared to its hypothesized timeline makes it difficult to extensively study the longitudinal brain amyloid changes that occur in the preclinical stages of AD.

It is possible to “stitch” data across subjects in order to obtain temporal biomarker trajectories that fit an underlying model. This is the premise of the Disease Progression Score method, which has been applied to studying changes in cognitive and biological markers related to Alzheimer's disease [3, 9]. It is assumed that there is an underlying progression score (PS) for each subject visit that is a linear transform of the subject's age, and given this PS, it is possible to place biomarker measurements across a group of subjects onto a common timeline. The linear transformation of age removes across-subject variability in baseline biomarker measures as well as in their rates of longitudinal progression. Each biomarker is associated with a parametric trajectory as a function of PS, whose parameters are estimated along with the PS for each subject.

Other methods for analyzing trajectories of biomarkers have been proposed. One approach involves fitting a piecewise linear model to longitudinal data assuming that each biomarker becomes abnormal a certain number of years before clinical diagnosis, and this duration is estimated for each biomarker to yield the longitudinal trajectories as a function of time to diagnosis [13]. In another approach, an event-based probabilistic framework is used to determine the ordering of changes in longitudinal biomarker measures as well as the appropriate thresholds for separating normal from abnormal measures [14]. The second method is agnostic to clinical diagnosis, but does not allow for the characterization of longitudinal biomarker trajectories except for determining the ordering of the change points. The first method does delineate the longitudinal trajectories for each biomarker, but requires knowledge of clinical diagnosis and therefore is not suitable for studying the earliest changes in healthy individuals.

Here, we adopt the disease progression score principle, but make two substantial innovations. First, the voxelwise PET measures constitute the biomarkers in the model. Since voxelwise PET measures have an underlying spatial correlation, we incorporate the modeling of the spatial correlations among the biomarker error terms and estimate the spatial correlations along with the subject and trajectory parameters. Modeling spatial correlations makes the inference of the subject-specific progression scores less susceptible to the inherent correlations among the voxels. Second, instead of using an alternating least-squares approach for parameter estimation, we formulate the model fitting as an expectation-maximization (EM) algorithm, which guarantees optimality and convergence. In experiments using this approach, we first show using simulated data that the model parameters are estimated accurately, then apply the method to each cerebral hemisphere separately using distribution volume ratio (DVR) images derived from Pittsburgh compound B (PiB) PET imaging, which show the distribution of amyloid. Models fitted using data for

75 participants with a total of 271 visits reveal that the precuneus and frontal lobes show the greatest longitudinal increases in amyloid, with smaller increases in lateral temporal and temporoparietal regions, and minimal increases in the occipital lobe and the sensorimotor strip. Results are consistent across the two hemispheres, and the estimated PS agrees with a widely used global index of brain amyloid known as mean cortical DVR.

2 Method

2.1 Model

The progression score s_{ij} for subject i at visit j is assumed to be a linear transformation of age t_{ij} :

$$s_{ij} = \alpha_i t_{ij} + \beta_i, \quad (1)$$

where (α_i, β_i) are assumed to be uniformly distributed random variables on a fixed and large domain $\Omega \subset \mathbb{R}^2$. The collection of K biomarker measurements (the intensities at each PiB-PET DVR voxel reflecting amyloid levels) make up the $K \times 1$ vector $\mathbf{y}_{ij}$. The longitudinal trajectories associated with these biomarkers are assumed have a linear form parameterized by $K \times 1$ vectors $\mathbf{a} = [a_1, a_2, \dots, a_K]^T$ and $\mathbf{b} = [b_1, \dots, b_K]^T$:

$$\mathbf{y}_{ij} = \mathbf{a} s_{ij} + \mathbf{b} + \boldsymbol{\varepsilon}_{ij}. \quad (2)$$

Here, $\boldsymbol{\varepsilon}_{ij} \sim \mathcal{N}_K(\mathbf{0}, R)$ is the observation noise. The covariance matrix R is assumed to be of the form $R = \lambda^2 C(\rho)$, where λ is a positive scalar and C is a correlation matrix parameterized by ρ . The parameters $(\mathbf{a}, \mathbf{b}, \lambda, \rho)$ make up $\boldsymbol{\theta}$.

2.2 Log-likelihood function

Let $\mathbf{y}_i$ be the vector consisting of all biomarker measurements stacked across all visits of subject i and let $\mathbf{u}_i = [\alpha_i, \beta_i]^T$. We then define $\mathbf{y} = [\mathbf{y}_1^T, \mathbf{y}_2^T, \dots, \mathbf{y}_n^T]^T$ and $\mathbf{u} = [\mathbf{u}_1^T, \mathbf{u}_2^T, \dots, \mathbf{u}_n^T]^T$, where n is the number of subjects. The pair $(\mathbf{y}, \mathbf{u})$ is the complete data. The complete log-likelihood for the model, ignoring the constants, is given by

$$\ell(\mathbf{y}, \mathbf{u} | \boldsymbol{\theta}) = - \sum_{i,j} \left[\log(\det R) + (\mathbf{y}_{ij} - Z_{ij} \mathbf{u}_i - \mathbf{b})^T R^{-1} (\mathbf{y}_{ij} - Z_{ij} \mathbf{u}_i - \mathbf{b}) \right], \quad (3)$$

where $Z_{ij} = \mathbf{a} [t_{ij} \ 1]$ and $R = \lambda^2 C(\rho)$.

2.3 EM algorithm derivation

The observations $\mathbf{y}$ include biomarker measurements $\{\mathbf{y}_{ij}\}$ at each visit. The hidden variables $\mathbf{u}$ are the subject-specific parameters $\{\alpha_i\}$ and $\{\beta_i\}$. The unknown parameters are $\boldsymbol{\theta} = (\mathbf{a}, \mathbf{b}, \lambda, \rho)$.

E-step—Let $\boldsymbol{\theta}$ be the previous estimate of the parameters. The expectation step involves evaluating an expression for

$$E \left[\ell(\mathbf{y}, \mathbf{u} | \boldsymbol{\theta}) | \mathbf{y}, \boldsymbol{\theta}' \right] = \sum_i \int f(\tilde{\mathbf{u}}_i | \mathbf{y}_i, \boldsymbol{\theta}') \ell(\mathbf{y}_i, \tilde{\mathbf{u}}_i | \boldsymbol{\theta}) d\tilde{\mathbf{u}}_i. \quad (4)$$

Note that

$$f(\mathbf{y}_i | \tilde{\mathbf{u}}_i, \boldsymbol{\theta}') = \phi(\mathbf{y}_i; Z'_i \tilde{\mathbf{u}}_i + \mathbf{b}'_i, R'_i) \quad (5)$$

$$= \phi(\hat{\mathbf{u}}'_i; \tilde{\mathbf{u}}_i, S'_i), \quad (6)$$

where

$$\hat{\mathbf{u}}'_i = \left(\sum_j Z'^T_{ij} R'^{-1}_{ij} Z'_{ij} \right)^{-1} \sum_j Z'^T_{ij} R'^{-1}_{ij} (\mathbf{y}_{ij} - \mathbf{b}'), \quad (7)$$

$S'_i = \left(\sum_j Z'^T_{ij} R'^{-1}_{ij} Z'_{ij} \right)^{-1}$, and $\phi(\cdot; \boldsymbol{\mu}, \boldsymbol{\Sigma})$ is a multivariate Gaussian density with mean $\boldsymbol{\mu}$ and covariance $\boldsymbol{\Sigma}$. For ease of notation, we have used $\mathbf{b}'_i$ to denote $\mathbf{b}'$ stacked across the visits of subject i and R'_i to denote diagonally stacked R' matrices across the visits of subject i . Z'_i is obtained by diagonally stacking $Z'_{ij} = \mathbf{a}' [t_{ij} \ 1]$ across the visits of subject i .

The uniform prior assumption on $\mathbf{u}_i$ allows us to write $f(\tilde{\mathbf{u}}_i, \boldsymbol{\theta}) = 1/c$, where c is a constant. Rewriting the expectation using Bayes' rule and plugging in the result from (6) yields

$$E \left[\ell(\mathbf{y}, \mathbf{u} | \boldsymbol{\theta}) | \mathbf{y}, \boldsymbol{\theta}' \right] \propto \sum_i \int_{\Omega} \frac{\phi(\hat{\mathbf{u}}'_i; \tilde{\mathbf{u}}_i, S'_i)}{f(\mathbf{y}_i, \tilde{\mathbf{u}}_i | \boldsymbol{\theta})} \ell(\mathbf{y}_i, \tilde{\mathbf{u}}_i | \boldsymbol{\theta}) d\tilde{\mathbf{u}}_i. \quad (8)$$

If Ω is large enough, we can approximate the expectation as an infinite domain integration over $\mathbf{u}_i$ to obtain

$$E \left[\ell(\mathbf{y}, \mathbf{u} | \boldsymbol{\theta}) | \mathbf{y}, \boldsymbol{\theta}' \right] \propto \sum_i \int \phi(\hat{\mathbf{u}}'_i; \tilde{\mathbf{u}}_i, S'_i) \ell(\mathbf{y}_i, \tilde{\mathbf{u}}_i | \boldsymbol{\theta}) d\tilde{\mathbf{u}}_i \quad (9)$$

$$\propto - \sum_{i,j} \log[\det R] - \sum_{i,j} (\mathbf{y}_{ij} - \mathbf{b})^T R^{-1} (\mathbf{y}_{ij} - \mathbf{b}) + 2 \left(\sum_{i,j} s'_{ij} \mathbf{y}_{ij} - \mathbf{b} \sum_{i,j} s'_{ij} \right)^T R^{-1} \mathbf{a} - \mathbf{a}^T R^{-1} \mathbf{a} \left(\frac{n}{\mathbf{a}'^T R'^{-1} \mathbf{a}'} + \sum_{i,j} s'^2_{ij} \right), \quad (10)$$

where $s'_{ij} = [t_{ij} \ 1] \hat{\mathbf{u}}'_i$.

M-step—Let $g(\boldsymbol{\theta}, \boldsymbol{\theta})$ be the function obtained at the end of the E-step. We set the derivatives $\frac{\partial g}{\partial \mathbf{a}}$ and $\frac{\partial g}{\partial \mathbf{b}}$ equal to 0 and solve for the parameters to obtain

$$\mathbf{a} = \frac{\sum_{i,j} s'_{ij} (\mathbf{y}_{ij} - \bar{\mathbf{y}})}{\frac{1}{\mathbf{a}'^T \mathbf{R}^{-1} \mathbf{a}} + \sum_{i,j} s'^2_{ij} - \frac{1}{\sum_i v_i} \left(\sum_{i,j} s'_{ij} \right)^2}, \quad (11)$$

$$\mathbf{b} = \frac{\left(\frac{1}{\mathbf{a}'^T \mathbf{R}^{-1} \mathbf{a}} + \sum_{i,j} s'^2_{ij} \right) \left(\sum_{i,j} \mathbf{y}_{ij} \right) - \left(\sum_{i,j} s'_{ij} \right) \left(\sum_{i,j} s'_{ij} \mathbf{y}_{ij} \right)}{\left(\sum_i v_i \right) \left(\frac{1}{\mathbf{a}'^T \mathbf{R}^{-1} \mathbf{a}} + \sum_{i,j} s'^2_{ij} \right) - \left(\sum_{i,j} s'_{ij} \right)^2}, \quad (12)$$

where v_i is the number of visits for subject i , and $\bar{\mathbf{y}} = \frac{1}{\sum_i v_i} \sum_{i,j} \mathbf{y}_{ij}$.

We must use numerical optimization to solve for the covariance parameters λ and ρ as a closed form solution does not exist. Instead of performing this optimization over the two parameters simultaneously, we perform coordinate descent: we first fix ρ at its previous estimate and optimize over λ , and then we fix λ and optimize over ρ . This process increases the value of the expectation instead of maximizing it, but the convergence property of the EM algorithm is not violated. This simplification allows us to write down a closed form solution for λ . When ρ is fixed, meaning that the covariance matrix C is fixed, we have that

$$\lambda = \sqrt{\frac{1}{K \sum_i v_i} \left[\frac{2n \mathbf{a}^T C^{-1} \mathbf{a}}{\mathbf{a}'^T \mathbf{R}^{-1} \mathbf{a}} + \sum_{i,j} \left(\mathbf{y}_{ij} - \mathbf{a} s'_{ij} - \mathbf{b} \right)^T C^{-1} \left(\mathbf{y}_{ij} - \mathbf{a} s'_{ij} - \mathbf{b} \right) \right]}, \quad (13)$$

where $\mathbf{a}$ and $\mathbf{b}$ are as given in (11) and (12). We then optimize over ρ using a numerical method, fixing $\mathbf{a}$, $\mathbf{b}$ and λ at their current estimates as given in (11), (12) and (13):

$$\rho = \arg \max_{\rho} g(\boldsymbol{\theta}, \boldsymbol{\theta}'). \quad (14)$$

The EM steps are iterated until the relative change in the function $g(\boldsymbol{\theta}, \boldsymbol{\theta}')$ is less than a small tolerance. Upon convergence, the subject-specific parameters $\mathbf{u}_i = [\alpha_i, \beta_i]^T$ are estimated using (7).

2.4 Selection and initialization of the spatial correlation function

We obtain an initial fit assuming that $C = I_{K \times K}$ and calculate the empirical semivariogram using the robust estimator [5]

$$\hat{\gamma}(s) = \left(\frac{1}{2N(s)} \sum_{i,j} \sum_{d(k,k')=s} |r_{ijk} - r_{ijk'}|^{0.5} \right)^4 / (0.457 + 0.494/N(s)), \quad (15)$$

where $\mathbf{r}_{ij} = \frac{1}{\lambda^2} (\mathbf{y}_{ij} - \mathbf{a} s_{ij} - \mathbf{b})$ is the standardized residual, $d(k, k')$ is the Euclidean distance between voxels k and k' , and $N(s)$ is the number of voxel pairs that are separated by a distance s .

We consider the spatial correlation functions described in Table 1. Note that all of these spatial correlation functions yield valid correlation matrices C for $\rho > 0$, ensuring the positive semi-definiteness of the covariance matrix R . These functions are selected based on their similarity with the correlation pattern observed in our data, and we limit our consideration to functions described by a single parameter to simplify calculations. Using the identity that $\gamma(s) = 1 - h(s)$, where $\gamma(s)$ is the semivariogram calculated using observations with zero mean and unit variance and $h(s)$ is a correlation function, we convert the spatial correlation functions in Table 1 into semivariogram functions, and fit them to the empirical semivariogram. The function with the smallest sum of squared error is selected as the spatial correlation function for the data. We initialize ρ at the value obtained from the semivariogram fitting. The entries of the correlation matrix $C(\rho)$ are given by $C_{kk'} = h(d(k, k'); \rho)$. We perform the EM algorithm again, this time also estimating ρ along with the rest of the model parameters.

2.5 Implementation details

The units of the estimated PS are arbitrarily defined. After fitting, we scale the PS values so that at baseline their mean is 0 and variance is 1. We also ensure that the median value of the subject-specific parameter α is positive so that increasing PS corresponds to increasing age. Given these scalings, the PS model is identifiable, as shown in [9].

The correlation parameter ρ must be positive, meaning that constrained optimization must be used to perform the maximization given in (14). Instead of using constraints, we reparametrize such that $\rho = e^{\log \rho} = e^{\rho_0}$. This enables unconstrained optimization over ρ_0 , and ρ is set to e^{ρ_0} after this optimization.

C and R are sparse matrices. Limiting the optimization range to $[\rho_{\min}, \rho_{\max}]$ allows us to avoid computing the elements $C_{kk'}$ where the distance between voxels k and k' is larger than a threshold δ ; we simply assign the value 0 to these elements of the correlation matrix. This distance threshold δ is picked such that the correlation matrix is numerically positive semi-definite when $\rho = \rho_{\max}$.

2.6 Image acquisition and preprocessing

We used longitudinal positron emission tomography (PET) data for participants with at least two visits from the Baltimore Longitudinal Study of Aging (BLSA) [12] neuroimaging substudy [11]. PET scans were acquired on a GE Advance scanner immediately following an intravenous bolus injection of Pittsburgh compound B (PiB), which binds to fibrillar β -amyloid. Dynamic PET data were acquired over 70 minutes, yielding 33 time frames each with $128 \times 128 \times 35$ voxels. Voxel size is $2 \times 2 \times 4.25$ mm³. Data for 75 participants, ages 55.7–92.4 at baseline, with a total of 271 visits were used.

The frames of each dynamic PET scan were aligned to the average of the first two minutes to remove motion [10]. For registration purposes, we obtained static images by averaging the first 20 minutes of the dynamic PET scan. Follow-up PET scans were rigidly registered onto the baseline PET within each participant using the 20-minute average images. Baseline magnetic resonance images (MRIs) were rigidly registered onto their corresponding 20-

minute averages, and their FreeSurfer segmentations [6, 7] were transformed accordingly. Distribution volume ratio (DVR) images were calculated in the native space of each PET image using the simplified reference tissue model with the cerebellar gray matter as reference tissue [15]. The MRIs coregistered with the PET were deformably registered [1] onto a study-specific template [2, 4] and transformed to MNI space using a pre-calculated affine transformation. The resulting mappings were applied to the DVR images to bring them into the MNI space. The spatially normalized DVR images in MNI space were downsampled to have 4 mm isotropic voxels. The PS model was fitted separately to the left and right cerebral hemispheres. This served two purposes: first, to reduce the computational burden by using a smaller number of voxels in the fitting, and second, to enable the comparison of the estimated parameters and progression scores across the hemispheres for assessing model stability. We refer to the progression score calculated using the DVR images as PiB-PS.

3 Results

3.1 Simulation Experiments

We generated α_i , β_i , and a_k from independent uniform distributions in the range $[-1, 1]$, and b_k in the range $[-10, 10]$ for 100 subjects and 125 biomarkers that were arranged in a $5 \times 5 \times 5$ image with 4 mm isotropic voxels. Each subject was randomly assigned to have 2 to 5 visits, with 2 being more probable than 5. Age at baseline was generated independently for each subject from a uniform distribution in the range $[20, 80]$. The intervals between consecutive visits were randomly assigned to be 1, 2, or 3. PS was calculated as

$s_{ij}^{(\text{truth})} = \alpha_i t_{ij} + \beta_i$ and standardized such that at baseline it had zero mean and unit variance. The subject-specific parameters α_i and β_i were normalized accordingly. Biomarker values (voxel values in the images) were calculated using the current values of the model

parameters as $y_{ijk}^{(\text{truth})} = a_k s_{ij}^{(\text{truth})} + b_k$ and standardized to have zero mean and unit variance across all visits and subjects. The trajectory parameters a_k and b_k were normalized accordingly. Noise was generated from a multivariate normal distribution with covariance matrix $R = \lambda^2 C(\rho)$ for given λ and ρ , and added to the biomarker values to yield the observations y_{ijk} . The model fitting was then performed to recapture the model parameters a_k , b_k , α_i , β_i , λ , and ρ .

We performed 100 simulation experiments for each combination of the following values of λ^2 and ρ : $\lambda^2 = 0.01, 0.05, 0.10, 0.15, 0.20$ and $\rho = 0, 2, 4, 6, 8$. For each experiment, we calculated the mean squared error for y and PS as

$$\text{MSE}_y = \frac{1}{K \sum_i v_i} \sum_{i,j,k} \left(\hat{y}_{ijk} - y_{ijk}^{(\text{truth})} \right)^2 \text{ and } \text{MSE}_{\text{PS}} = \frac{1}{\sum_i v_i} \sum_{i,j} \left(\hat{s}_{ij} - s_{ij}^{(\text{truth})} \right)^2, \quad (16)$$

where $\hat{y}_{ijk}$ and $\hat{s}_{ij}$ are the values obtained using the estimated parameters. These mean squared error values, averaged across the 100 simulations for each combination of λ^2 and ρ , are presented in Fig. 1. Since the biomarker values and baseline PS were scaled to have zero mean and unit variance, the mean squared error values are directly interpretable. The mean

squared error is much lower than the unit variance associated with the biomarker values and baseline PS at all noise variances λ^2 and correlation parameters ρ , indicating that model fitting is accurate.

3.2 DVR images

Based on the sum of squared error of the fitted semivariograms over a 100 mm distance calculated using 20 equidistant points, the algorithm selected the exponential correlation function for both hemispheres. The correlation parameter ρ was using the value were obtained from the semivariogram fitting, as described in §2.4. At convergence, ρ was 14.2 for the left hemisphere and 14.8 for the right.

The estimates for the subject-specific variables α and β , as well as the PiB-PS across the cerebral hemispheres are presented in Figure 2. The Pearson correlation coefficients across the hemispheres for α , β , and PiB-PS at baseline are 0.90, 0.89, and 0.98, respectively.

PiB-PS, which reflects the progression of fibrillar amyloid- β deposition as measured by PiB-PET, reveals a pattern similar to that of mean cortical DVR, which is an average of DVR values across cortical regions that are early accumulators of amyloid (Pearson correlation coefficient at baseline = 0.93) (Fig. 3). The progression as measured using DVR images is not linearly associated with age, and the PiB-PS is able to capture this.

The trajectory slope parameters $\mathbf{a}$ estimated for the left and right cerebral hemispheres reveal largely symmetric patterns (Fig. 4), with the precuneus and frontal lobe showing the greatest increases in DVR with PiB-PS, smaller increases in lateral temporal and temporoparietal regions, and minimal increases in the occipital lobe and the sensorimotor strip.

The linear mixed effects model is commonly used to analyze the longitudinal trajectories of voxelwise imaging values. We compared the image of the trajectory slope parameter $\mathbf{a}$ to the image of the slope associated with the age term in a linear mixed effects model (Fig. 5). For visualization, the histogram of the slope image associated with the age term in the linear mixed effects model was matched to the histogram of the image of trajectory slope parameter $\mathbf{a}$ from the PS model. Overall, there are strong similarities in the two results. However, in the result from the PS model, longitudinal changes in the anterior frontal lobe are better contained within the cortical gray matter, and also lateral frontal lobe changes are more pronounced.

4 Discussion and Conclusion

PiB-PS is highly correlated with mean cortical DVR, the widely used measure for quantifying PiB-PET scans and assessing longitudinal change. This indicates that PiB-PS is a meaningful score extracted from voxelwise imaging data. However, there are important differences between the PiB-PS and mean cortical DVR. Since there is no longitudinal consistency requirement in the calculation of mean cortical DVR, its estimates exhibit fluctuations from visit to visit, whereas PiB-PS, due to the linear relationship assumed between age and PS in the model, exhibits longitudinally smoother trajectories. Furthermore, mean cortical DVR calculations require anatomical labels, and slight

misalignment of the labels could result in the inclusion of non-cortical voxels in the calculation, yielding an incorrect mean cortical DVR value. On the other hand, PiB-PS is calculated on the whole hemisphere and does not use anatomical labels. Slight misregistration of boundary voxels has much less influence on the PiB-PS estimates since voxels with high registration errors are likely to have trajectory slope estimates close to 0 due to the lack of a clear relationship between voxel intensity and time.

There are several methodological differences between the PiB-PS and mean cortical DVR calculations. PiB-PS is constructed using all voxels in a given cerebral hemisphere, and assumes a single way of progressing through the voxelwise changes. The mean cortical DVR on the other hand, uses only a subset of the cortical gray matter voxels and there is no assumption of a single progression pattern. Furthermore, PiB-PS models correlations among the voxels, while this is not done for mean cortical DVR. This spatial correlation modeling has elements similar to voxelwise partial volume correction: instead of estimating the point spread function of the underlying imaging data, the purpose of modeling spatial correlations is to estimate a function that acts analogously to blur the ground truth biomarker values. The estimate of this function is then used to decorrelate the measures in order to recover the underlying biomarker values. Decorrelation is performed by multiplying by the inverse of the covariance matrix R , and has a direct effect on the estimates of the subject-specific variables, as in (7). We see that mean cortical DVR shows a slight downward trend with age in the low DVR group, most likely due to atrophy and the lack of partial volume correction. In contrast, this effect has flattened out for PiB-PS, possibly due to the modeling of the spatial correlation being similar to partial volume correction.

Deposition of cerebral amyloid is thought to affect both hemispheres in a symmetric fashion. The similarity of the subject-specific variables and the trajectory slopes estimated for the cerebral hemispheres indicates that the spatial PS model is not sensitive to slight changes in the data.

The PS model relies on the estimated progression scores rather than age for staging the subjects and assessing longitudinal change. This allows for alignment of subjects according to their amyloid burden and progression, yielding slope images that show better localized longitudinal changes compared to regressing on age using a linear mixed effects model. Certain longitudinal changes that could not be detected when regressing on age can be detected with the PS model due to this alignment of subjects. For example, the longitudinal amyloid increases in the frontal lobe did not extend to the lateral frontal regions in our linear mixed effects model analysis, whereas the PS model showed that these regions do exhibit longitudinal increases (Fig. 5).

The presented method is applicable to other types of medical imaging and biomarker data, and can be used to extract progression scores that reveal how each individual compares to the rest of the sample. For different types of medical images where a summary score such as the mean cortical DVR is not available, the progression score estimates provided by our method can be greatly informative for disease staging and potentially an early diagnosis. Calculation of PS using voxelwise imaging data not only yields a staging variable for the individuals, but also enables the comparison of voxelwise trajectories to determine the

temporal ordering of changes. The model is amenable to a hypothesis testing framework to evaluate whether certain regions of the brain show the earliest or fastest changes.

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Fig. 1. The mean squared error for (a) the progression scores (PS) and (b) the biomarker values y , averaged across 100 simulations for each combination of the noise variance λ^2 and correlation parameter ρ . The error bars correspond to ± 1 standard deviation of the mean squared error across the 100 simulations.

Fig. 2.

Comparison of the subject-specific parameters (a) α , (b) β and (c) progression scores (PS) at baseline across the cerebral hemispheres. PiB = Pittsburgh compound B.

Fig. 3. (a) Mean cortical DVR and (b) PiB-PS averaged across left and right cerebral hemispheres plotted against age. The longitudinal data points are connected by lines within each subject. Different colors are used across subjects for visualization. DVR = Distribution volume ratio, PS = progression score, PiB = Pittsburgh compound B.

Fig. 4.

Trajectory slope parameter $\mathbf{a}$ projected onto the inner cortical surface associated with the template space. Left hemisphere (*top*) and right hemisphere (*bottom*) lateral and medial cerebral surfaces. For each unit increase in PiB-PS, the DVR value increases by a_k at voxel k . DVR = Distribution volume ratio, PS = progression score, PiB = Pittsburgh compound B.

Fig. 5.

Comparison of the image of the trajectory parameter $\mathbf{a}$ in (a) the progression score (PS) model to the image of the slope associated with the age term in (b) the linear mixed effects model. Longitudinal changes in the anterior frontal lobe are better contained within the cortical gray matter and lateral frontal lobe changes are more pronounced in the PS result.

Table 1

Spatial correlation functions.

Exponential	$h(s; \rho) = e^{-s/\rho}$
Gaussian	$h(s; \rho) = e^{-(s/\rho)^2}$
Rational quadratic	$h(s; \rho) = \frac{1}{1+(s/\rho)^2}$
Spherical	$h(s; \rho) = \left(1 - \frac{3}{2} \frac{s}{\rho} + \frac{1}{2} \left(\frac{s}{\rho}\right)^3\right) \mathbb{1}(s < \rho)$

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