A Spatiotemporal Statistical Shape Model of the Brain Surface during Human Embryonic Development

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Abstract In this paper, we propose an algorithm to construct a spatiotemporal statistical shape model (SSM) of the brain surface of a human embryo. Our model is based on level sets and the model is constructed independently for each Carnegie stage (CS), in which feature space is constructed by spatially-weighted principal component analysis (PCA). The statistics of the shape variation were calculated under the assumption of \( q \)-Gaussian distribution to reduce the risk of over/fitting for datasets of small sizes. To define the statistics of the shape distribution of the intermediate CS, we consider 18 interpolation methods, which are the combinations of three average interpolations (linear, B-spline and information geometry) and six covariance interpolation (rotation, affine-invariant, log-Euclidean, information geometry, Wasserstein geometry and tensor B-spline) techniques, which are exhaustively compared in the experiments. We also propose a method to allow interpolation between distributions with a mixed number of dimensions, i.e., the rank of the covariance matrix. The SSM was constructed and evaluated using 60 sets of brain labels acquired from human embryos from the Kyoto collection. We found that the best interpolation method was a combination of the linear average interpolation method with an information geometry–based covariance interpolation method. We also found that use of the \( q \)-Gaussian distribution and selection of the number of dimensions are effective methods for improving the performance of the spatiotemporal SSM of the human embryo.

Keywords: computational anatomy, spatiotemporal model, embryo, Carnegie stage, growth.

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1. Introduction

In human development, the embryonic stage (3rd to 9th week of pregnancy) is crucial for organ formation. This is a critical period associated with the highest risk of various developmental defects, and is thus important in the study of congenital abnormalities. Moreover, it has been suggested that birth defects account for 25% of all causes of death in newborns [1]. Thus, the analysis of the embryonic stage is an important research topic.

Using modern imaging techniques, a detailed examination of the human embryo has been performed in recent years. Ozeki-Satoh et al. [2] performed a three-dimensional (3D) analysis of the morphogenesis of the middle ear ossicles according to the Carnegie stage (CS) standard, which is the worldwide standard for developmental staging of human embryos [1]. Shiraishi et al. [3] constructed a 3D brain atlas database to analyze brain and cerebral ventricle development. More recently, an interactive 3D digital atlas of the entire body has been developed for quantitative analysis of human development [4]. However, all these studies focus on typical temporal changes during development but not on the statistical variation in anatomical landmarks and shapes, which are important for diagnosis of developmental disorders at the embryonic stage.

Statistical models of anatomical structures (including shapes and landmarks) have played important roles in disease diagnosis. Although various statistical models of adult organs have been reported [5, 6], few studies have focused on human embryos [7]. An embryonic brain spatiotemporal statistical shape model (SSM) [8] would be useful in diagnosing diseases in embryos and predicting future growth. The construction of an SSM for developing subjects such as human embryos is a challenging task for two main reasons: (i) the existence of a relatively large developmental shape deformation including topological change during embryogenesis, and
(ii) a longitudinal 3D dataset, which is beneficial for developing a spatiotemporal model, cannot be acquired from a human embryo. In the early study of spatiotemporal SSM, principal component analysis (PCA) was used to model the temporal changes of the surface of the heart [9]. However, large deformation of the human embryo makes the shape distribution complex, which is difficult to model with a conventional PCA-based method that assumes a unimodal Gaussian distribution.

Wright et al. [10] constructed a temporal surface atlas of the infant brain, in which temporal correspondences were established using spectral matching, after which kernel regression was performed to calculate the average temporal atlases. Dittrich et al. [11] proposed a semi-supervised method for learning a spatiotemporal latent atlas of fetal brain development. However, these models provide only limited information on the shape variability between cases of the same age, i.e., the average surface distance between distinct models generated from disjoint subsets of training data [10] and the magnitude of the gradient of the surface variation [11]. Thus, they cannot be used to generate shapes based on inter-subject shape variability for a given age. Durrleman et al. [12], proposed a diffeomorphic framework to construct a spatiotemporal shape model. However, this method requires a longitudinal dataset. In addition, diffeomorphic deformation cannot deal with topological changes. Alam et al. [13] employed sample-weighted PCA on the shapes represented by level sets to construct a time-dependent SSM of an infant organ surface, which is different from an embryo.

Kishimoto et al. [7] addressed the spatiotemporal statistical modeling of an embryo and developed a spatiotemporal statistical model of anatomical landmarks of a human embryo by interpolating the probability distributions of the datasets of neighboring developmental stages. The authors proposed various interpolation methods and suggested that information geometry was the best interpolation method. The authors also showed that a \( q \)-Gaussian distribution is more suitable than a conventional Gaussian distribution.

This paper focuses on the spatiotemporal statistical shape model (SSM) of the brain surface of a human embryo. Although previous research [7, 8] explored the best interpolation method for obtaining the neighboring probability distribution of anatomical landmarks, this choice does not necessarily apply to the brain surface. Given that the temporal change of the distribution differs depending on the target organ to be modeled, the best interpolation method should be re-examined. As the existing interpolation method might not be sufficient for our purpose, new options should be considered. In addition, the amount of shape variation changes depending on the developmental stage, and a different number of eigenshape modes may be required for different stages.

This paper presents a spatiotemporal SSM of the brain surface of a human embryo. The method combines a level set distribution model (LSDM) [6] and \( q \)-Gaussian-based statistical analysis [14]. The contribution of this paper is summarized as follows:

1. In addition to the interpolation methods reported previously [7, 8], we introduce a higher-order tensor B-spline interpolation method to ensure greater smoothness of the temporal change of the SSM [15]. We explore the best among 18 methods for the construction of a spatiotemporal SSM of the brain surface of a human embryo.
2. This paper shows the results of applying the proposed modeling approach to the brain surface of a human embryo from the Kyoto collection. We focused on the CSs 15 to 20, which is an embryologically important period for brain formation, as relatively large morphological changes occur during these stages. This study is an extended version of the conventional study [8] with respect to the interpolation techniques and the dimensionality selection.

2. Methods

We propose an algorithm to construct a spatiotemporal SSM of the brain surface using a level set–based shape representation. The goal is to find the mean and covariance matrices of the shape distribution for a continuously varying time parameter. The algorithm is shown in Fig. 1 and consists of three steps:

(1) Feature extraction: Spatial standardization followed by PCA is performed to map all the training data in the low-dimensional common feature space.

(2) Estimation of statistics of each CS: Maximum likelihood estimation (MLE) is then performed to calculate the statistics of the shape distribution (mean and covariance) for each stage independently.

(3) Interpolation of the statistics: Mean and covariance at an intermediate point in time are defined by the interpolation between those of neighboring CSs. The

![Flow of the spatiotemporal SSM construction.](image)
2.1 Feature extraction

**Figure 2** illustrates the flow of feature extraction from the training shapes. First, training shapes are registered with a similarity transformation to remove variations in size and pose using a generalized Procrustes analysis [7] to automatically extract the landmarks on the brain surface. This induces $n$ registered shape labels $\{S_i\}_{i=1}^n \in \{0, 1\}^D$, where $D = D_x \times D_y \times D_z$ denotes the number of voxels of a volume, and the corresponding scale factors $\{c_i\}_{i=1}^n \subset \mathbb{R}$. The scaling factor is calculated considering the difference in spatial resolution between volumes. The image resolution after standardization is decided such that the distribution of the scaling factor is centered around 1.

Then, we apply a signed Euclidean distance transformation to the shape $S_i \mapsto \phi_i \in \mathbb{R}^D$ ($i \in \{1, \ldots, N\}$) and perform spatially weighted PCA to reduce the number of dimensions from $D$ to $(n - 1)$:

$$\phi_i \approx \mu + U\alpha_i$$

where $U \in \mathbb{R}^{D \times (n-1)}$ is a matrix of the eigenvectors, $\mu \in \mathbb{R}^D$ represent an average vector, and $\alpha_i \in \mathbb{R}^{n-1}$ is a principal component score vector associated with the data $\phi_i$. Given that the size information is important for the characterization of the developing shape, we combine the shape information $\alpha_i$ with a scale factor $c_i$ to obtain an $n$-dimensional vector $[\alpha_i^T, c_i^T]^T$. Finally, by applying PCA again to the $n$-dimensional vector $[\alpha_i^T, c_i^T]^T$ a $d$-dimensional $(d < n)$ feature vector $x_i \in \mathbb{R}^d$ is obtained that satisfies

$$\begin{bmatrix} \alpha_i \\ c_i \end{bmatrix} \approx \mu' + U'x_i$$

where $\mu' \in \mathbb{R}^n$ and $U' \in \mathbb{R}^{n \times d}$ are the average vector and the matrix of eigenmodes.

2.2 Estimation of statistics of each CS

Let $I = \{15, 16, \ldots, 20\}$ be the CS numbers we focus on in this study, and let $J_k \in \{1, \ldots, N\} (k \in I)$ be the set of indices of the training shapes that belongs to the $k$-th CS in this study. For an arbitrary density function, the mean vector and the covariance matrix of the $k$-th CS is formulated as the maximum likelihood estimation (MLE):

$$\left(\mu_k, \Sigma_k\right) = \arg \max_{(\mu, \Sigma)} \sum_{x \in J_k} \log f(x | \mu, \Sigma)$$

where $f(x | \mu, \Sigma)$ is the $d$-dimensional probability distribution function with a mean $\mu$ and a covariance $\Sigma$. In this study, we consider two options for $f(x | \mu, \Sigma)$, the Gaussian distribution and the $q$-Gaussian distribution functions.

The Gaussian distribution $N(x | \mu, \Sigma)$ is widely used because the MLE of $\mu$ and $\Sigma$ are the sample mean and the covariance, which can be calculated in a straightforward manner. However, the Gaussian assumption may cause overfitting for small-sized datasets. The $q$-Gaussian function is often used as an alternative to the Gaussian distribution [14], which is defined as:

$$f_q(x | \mu, \Sigma) \equiv Z \left[ 1 + \frac{1}{\nu} \left( x - \mu \right)^T \Sigma^{-1} \left( x - \mu \right) \right]^{\frac{1}{2q}}$$

where $Z = \Gamma\left(\frac{d+q}{2}\right)\left(\pi\nu\right)^{d/2}\Gamma\left(\frac{d}{2}\right)\left[\Sigma^{1/2}\right]_{d+q}$ is the normalization factor, in which $\Gamma(x) = \int_0^\infty t^{x-1} e^{-t} dt$ is the gamma function, and $\nu = \frac{2}{q-1} - d$ is the degree of freedom adjusted by the parameter $q$ ($1 < q < 1 + \frac{d}{2}$). This has heavier tails when compared to the Gaussian function, which allows for a robust estimation in small samples. To select the optimal parameter $q$, the Akaike information criterion (AIC) [16] is adopted.

2.3 Interpolation of statistics of neighboring CSs

As the subspace of each CS is constructed using the averages and the eigenvectors of the covariance matrices, the subspace interpolation involves both the interpolation of the average vectors and the covariance matrices. We consider three interpolation methods for the average vectors: linear, information geometry [17] and B-spline;
Table 1 Interpolation methods of mean and covariance proposed in this paper. Asterisks indicate the novel methods proposed in this paper.

| Mean          | Covariance          |
|---------------|---------------------|
| Linear        | Rotation [18]       |
| *B-spline     | Affine-invariant [19] |
| Information geometry [17] | Log-Euclidean [19] |
|               | Information geometry [17] |
|               | Wasserstein geometry [20] |
|               | *Tensor B-spline [15] |

and six interpolation methods for the covariance matrices: rotation [18], tensor B-spline [15], affine-invariant [19], log-Euclidean [19], Wasserstein geometry [20] and information geometry [17]. These methods are summarized in Table 1. By combining them, 3 × 6 = 18 interpolation methods can be considered and are exhaustively compared in this study.

The goal is to define the average vector $\mu_c$ and the covariance matrix $\Sigma_c$ for a continuous value $c$ by interpolating known average vectors and covariance matrices. In the following sections, without loss of generality, we present the equation for interpolation for the case $i \leq c \leq i + 1$, and we denote $p = c - i$.

### 2.3.1 Interpolation of average vectors

The linear interpolation of the average is denoted by $\mu^l_c$, the primitive interpolation method examined in our previous study [7, 8], which is the point that divides the line segment between $\mu_i$ and $\mu_{i+1}$ with the ratio $p : (1 - p)$, i.e.,

$$
\mu^l_c = (1 - p)\mu_i + p\mu_{i+1}.
$$

However, because this is a piecewise linear interpolation method, it only ensures $C^0$ continuity. To impose a higher degree of continuity, we propose using B-spline interpolation with an order $k \geq 2$. Given $(m + k - 2)$ control points $\{c_{i}^{m+k-3} \in \mathbb{R}^d, \}$ where $m$ is the total number of CSs, and the $(k - 1)$-degree B-spline basis function $N_{i,k}(\cdot)$, the interpolated average $\mu^S_c$ is represented as

$$
\mu^S_c = \sum_{i=0}^{m+k-3} N_{i,k}(c)c_i.
$$

Information geometry [17] was another interpolation method employed in our previous study [7, 8], which is derived from the maximization of the amounts of information between two probability distributions. This provides a nonlinear interpolation function:

$$
\mu^I_c = \Sigma^I_c((1-p)\Sigma^I_i \mu_i + p\Sigma^I_{i+1}\mu_{i+1}),
$$

where $\Sigma^I_c$ is the interpolated covariance matrix according to an information geometry–based method (see section 2.3.2).

### 2.3.2 Interpolation of covariance matrices

Interpolation of the covariance matrices is rather complex because they are on the manifold of positive semidefinite matrices and a standard linear operation is thus not applicable. Several methods to interpolate covariance matrices have been proposed based on different coordinate spaces [15, 17–20].

Lina et al. [18] introduced a method to interpolate covariance matrices by interpolating their eigenvectors and eigenvalues. Let $\Sigma_i = E_iS_i^2E_i^T$ be the eigen-decomposition of the covariance matrix of the $i$-th CS. Then, the intermediate covariance matrix at CS-$c$ is defined as:

$$
\Sigma_c = U_p((1-p)S_i + pS_{i+1})U_p^T,
$$

where $U_p$ is the rotation matrix that satisfies $U_pS_i = \Sigma_i$ and $U_pS_{i+1} = \Sigma_{i+1}$, derived from high-dimensional rotation theory [18].

The other interpolation methods [15,17,19,20] consider non-Euclidean space. Information geometry–based [17] interpolation for the covariance matrix is given by the linear interpolation between the precision matrices as:

$$
\Sigma_c^I = \frac{((1-p)\Sigma_i^{-1} + p\Sigma_{i+1}^{-1})^{-1}}{2}.
$$

The Wasserstein geometry–based interpolation method is derived from the optimal transport theorem [20]. Optimal transportation between two Gaussian distributions is given by:

$$
\Sigma_c^W = \frac{|(1-p)I + pW|\Sigma_i[(1-p)I + pW]}{2}.
$$

The affine-invariant and log-Euclidean interpolation methods are derived from the geometry of the Riemannian manifold and are successfully applied to interpolate diffusion tensor field [19]:

$$
\Sigma^A_c = \Sigma^I_c \exp \left( p \log \left( \Sigma_i^I + \Sigma_{i+1}^I \right) \right) \Sigma_i^I,
$$

where $\log(\cdot)$ and $\exp(\cdot)$ are the matrix logarithmic and exponential operations, respectively. Log-Euclidean [19] is a new family of Riemannian metrics, which provides simpler and faster computations of the covariance matrix interpolation:

$$
\Sigma^E_c = \exp((1-p)\log \Sigma_i + p\log \Sigma_{i+1}).
$$

All of the above methods are first-order interpolation methods and only ensure $C^0$ continuity in the temporal change of the covariance matrix. However, due to the nonlinearity of the temporal change of the distribution of the embryonic shape, first-order interpolation may not be suitable. To address this limitation, similar to $\mu^S_c$, we introduce the $k$-th order tensor B-spline [15], which was not described in our previous papers [7, 8], and will be explained below in detail. Given a set of control tensors $\{C_{i}^{m+k-3} \in \mathcal{P}, \}$ which are $d \times d$ positive semidefinite ma-
traces, the covariance matrix at time point \( c \) is implicitly expressed as
\[
\Sigma^S = \arg \min_{S \in \mathcal{P}} \sum_{j=0}^{m+k-3} N_{j,k}(c) \text{dist}^2(S, C_j)
\] (13)
which is a generalized version of Eq. (6) to an arbitrary manifold equipped with a metric \( \text{dist}(\cdot, \cdot) \). Specifically, we use the Riemannian metric: \( \text{dist}(T_1, T_2) = \text{tr} \left\{ \log \left( T_1^{-1/2} T_2 T_1^{-1/2} \right) \right\} \). The control tensor \( C \) is obtained by minimizing the distance between the given covariance matrix \( \Sigma \) and the interpolated one \( \Sigma^T \), i.e.,
\[
E = \sum_{i \in I} \text{dist}(\Sigma^T_i, \Sigma_i)^2,
\] (14)
based on the gradient descent method. The gradient of Eq. (13) with respect to \( C_j \) is given by
\[
\nabla C_j = -\frac{1}{m} \sum_{i \in I} \Lambda_C(\Sigma_i, \Sigma^T_i) N_{j,k}(i)
\] (15)
where \( \Lambda_C(\Sigma_i, \Sigma^T_i) = \log_C(\Sigma_i) - \log_C(\Sigma^T_i) \).

### 2.4 Varying the number of dimensions of the subspace for each CS

In principle, the interpolation method we introduced requires the same number of dimensions of the subspace, or the same rank of the covariance matrices, between different CSs. However, the optimal number of dimensions may be different for each CS because the amount of shape variation changes temporally. To overcome this limitation, we propose a method to select the optimal number of dimensions for each CS and to interpolate between covariance matrices of a different rank.

Let \( r_i \leq d \) be the optimal number of dimensions at the \( i \)-th CS. We can consider several criteria to optimize \( r_i \), e.g., specificity ability and the CS-estimation error (see Section 3.3.3 for details). After reducing the number of dimensions, we obtain a covariance matrix \( \Sigma_i \) with rank \( r_i \). We then retrieve the rank of the covariance matrix \( \Sigma_i \) by adding \( (d - r_i) \) orthogonal bases and by setting the variance along those new bases to \( \epsilon \) (\( > 0 \)). The value \( \epsilon \) should be small enough as not to change the structure of the distribution. In this study, we use \( \epsilon = \frac{\lambda_{\min}}{\beta} \) where \( \lambda_{\min} \) is the smallest eigenvalue across all the CSs and \( \beta > 0 \) is a parameter determined empirically and fixed throughout the experiment.

### 3. Experiments

#### 3.1 Materials and parameters

We used brain data from human embryos from the Kyoto Collection, a large collection of human embryos and fetuses stored at the Congenital Anomaly Research Center in Kyoto University [21]. We focused on CSs 15–20 because these stages represent an embryologically important period for brain formation, and a sufficient number of manual segmentations is available [3]. Magnetic resonance (MR) images were obtained using an MR microscope with a 2.35 T bore (40 cm) superconducting magnet [22]. The pulse sequences used for image acquisition were T1-weighted spin echo sequences with a 100 ms repetition time and an echo time of 10–16 ms [23]. This study was approved by the Ethics Committee of the Graduate School and Faculty of Medicine of Kyoto University (R0316, R0989).

Brain labels were manually delineated on the MR images via the FSL View of the FMRIB Software Library™ (ver. 4.1.9, Analysis Group, FMRIB, Oxford, UK) and Amira™ software (ver. 5.4.0, Visage Imaging, Berlin, Germany) [3]. Figure 3 shows examples of the training brain label volume from CS 15 to CS 20. The image size of the brain label was \( 512 \times 256 \times 256 \) voxels and the spatial resolution ranged from 45 to 100 \( \mu \)m. The difference in spatial resolution was considered when calculating the scale factors. The volume corresponding to the average spatial resolution was used as the initial target of the generalized Procrustes analysis. In this study, we set the number of dimensions of the feature space as \( d = 4 \), at which the cumulative contribution ratio is over 90%.

#### 3.2 Evaluation

The 60 sets of brain data were divided into two groups for twofold cross-validation. The performance of the spatiotemporal SSM was evaluated in terms of generalization and specificity [24], which measure the ability of the model to reconstruct unknown shapes and to generate acceptable instances, respectively. We employed the Jaccard index to calculate generalization and specificity; a higher value indicates better performance (see Appendix A for detailed explanation). The SSM construction and evaluation were carried out using MATLAB (MathWorks, Natick, MA, USA).

#### 3.3 Results and discussion

##### 3.3.1 Comparison between interpolation methods

First, we search for the best choice among the combinations of the interpolation methods of the mean (\( \mu^R \), \( \mu^L \) and \( \mu^E \)) and of the covariance (\( \Sigma^R \), \( \Sigma^L \), \( \Sigma^A \), \( \Sigma^E \), \( \Sigma^W \) and \( \Sigma^S \)).

**Fig. 3** Typical example of the brain label volumes of human embryos. From left to right, CS 15–20.
Although a previous study has suggested that the $q$-Gaussian is better than the Gaussian model [7], comparison was carried out for both models in this study because the best choice of model varies depending on the number of factors such as target organ, CS, features to be modeled, number of cases and dimensions of the feature vector. We first used a fixed number of dimensions; $r_i = d = 4$, for all CS $i \in I$. We exhaustively searched for the optimal method over all $3 \times 6 = 18$ combinations based on specificity. Note that we did not use generalization to search for the optimal interpolation method because the dimensionality of the subspace of each CS is identical to that of the feature space (i.e., $r_i = d \forall i \in I$), and the interpolation method does not affect the generalization ability.

Table 2 (a) and (b) show the specificity scores obtained for all the interpolation methods when assuming the Gaussian and $q$-Gaussian distributions, respectively. In both tables, we applied Mann-Whitney $U$-test to compare the method with the best specificity score and each of the other 17 methods. The highest specificity scores and the scores with no statistically significant difference from the best score ($p > 0.05$) are displayed in bold in the table. When using both the Gaussian and $q$-Gaussian assumption, we arrived at the same conclusion: the method ($\mu^L$, $\Sigma^L$) achieved the best specificity score among the 18 interpolation methods, and the second-best method ($\mu^S$, $\Sigma^L$) demonstrated no statistically significant difference compared to the best one. Our result was different from a previous report [7], in which ($\mu^L$, $\Sigma^R$) and the scores with no statistically significant difference of the other 17 methods. The highest specificity scores ($\mu^L$, $\Sigma^R$) and covariance ($\Sigma^R$, $\Sigma^I$, $\Sigma^L$, $\Sigma^W$, $\Sigma^S$) of the other 17 methods. The highest specificity scores may be accounted for by the improvement was also observed for all other 17 interpolation methods. We performed a two-sided Wilcoxon

| Table 2 | Comparison of the specificity score between different interpolation methods of the mean ($\mu^L$, $\mu^S$) and covariance ($\Sigma^R$, $\Sigma^I$, $\Sigma^L$, $\Sigma^W$, $\Sigma^S$). The numbers in bold represent the best method and the method that is as statistically significant as the best method. |
| --- | --- |
| (a) Gaussian distribution |  |
| Covariance | $\Sigma^R$ | $\Sigma^I$ | $\Sigma^L$ | $\Sigma^W$ | $\Sigma^S$ |
| Mean | $\mu^L$ | 0.7775 | **0.7815** | 0.7786 | 0.7789 | 0.7774 | 0.7769 |
| | $\mu^S$ | 0.7692 | 0.7777 | 0.7722 | 0.7720 | 0.7695 | 0.7724 |
| | $\mu^S$ | **0.7780** | **0.7789** | 0.7765 | 0.7761 |
| (b) $q$-Gaussian distribution |  |
| Covariance | $\Sigma^R$ | $\Sigma^I$ | $\Sigma^L$ | $\Sigma^W$ | $\Sigma^S$ |
| Mean | $\mu^L$ | 0.7796 | **0.7824** | 0.7806 | 0.7801 | 0.7795 | 0.7783 |
| | $\mu^S$ | 0.7720 | 0.7783 | 0.7748 | 0.7746 | 0.7726 | 0.7750 |
| | $\mu^S$ | 0.7788 | **0.7815** | 0.7799 | 0.7794 | 0.7788 | 0.7776 |

Fig. 4 Covariance matrices before and after interpolation displayed with an equi-Mahalanobis distance (1σ) surface. The color on the surface represents the CS value. In (a), the training data is also displayed.
signed rank test for 18 pairs (Gaussian vs. \(q\)-Gaussian) of specificity scores obtained from 18 interpolation methods, and obtained a value of \(p = 1.9 \times 10^{-4} < 0.01\). These findings suggest that the \(q\)-Gaussian assumption provides a steady improvement in the specificity performance regardless of which interpolation method is selected, and is thus a better choice for the statistical shape analysis of a human embryo.

### 3.3.3 Effect of the interpolation on the CS-estimation error

One important application of the spatiotemporal SSM of the human embryo is the estimation of the CS. The CS estimation error is defined as \(E_i(\hat{c}_i \sim \hat{c}_l)\), which is the averaged value of the difference between the true CS \(c_i\) and the estimated one \(\hat{c}_l \in \mathbb{R}\), where \(i\) denotes the index of the test case. According to previous study, \(\hat{c}_l\) is calculated by minimizing the Mahalanobis distance [7]:

\[
\hat{c}_l = \arg \min_{c_l \in [15,20]} \sqrt{(x_i - \mu_i)^T \Sigma_i^{-1} (x_i - \mu_i)} \tag{16}
\]

where \(x_i\) denotes the feature vector of the \(i\)-th test case. For the baseline performance, we also provided the CS estimation error when using the nearest neighbor interpolation, which is calculated as \(E_i(\hat{c}_i \sim \hat{c}_NN)\), where \(\hat{c}_NN \in \mathbb{N}\) is the integer value of the estimated CS:

\[
\hat{c}_NN = \arg \min_{c_l \in [15,16,...,20]} \sqrt{(x_i - \mu_i)^T \Sigma_i^{-1} (x_i - \mu_i)} \tag{17}
\]

First, we compared CS estimation error \(E_i(\hat{c}_i \sim \hat{c}_l)\) of one of the best models (\(q\)-Gaussian with the interpolation method \(\mu^L\) and \(\Sigma^L\)) and that of the nearest neighbor interpolation \(E_i(\hat{c}_i \sim \hat{c}_NN)\) using twofold cross-validation. The results were \(E_i(\hat{c}_i \sim \hat{c}_l) = 0.5668\) and \(E_i(\hat{c}_i \sim \hat{c}_NN) = 0.7500\), which suggests the effectiveness of the proposed interpolation method (\(\mu^L, \Sigma^L\)) over the nearest neighbor interpolation in terms of the accuracy of the CS estimation.

We also compared CS-estimation error between the two best methods; \((\mu^L, \Sigma^L)\) and \((\mu^S, \Sigma^L)\), with the \(q\)-Gaussian assumption. Here, we employed leave-one-CS-out cross-validation\(^1\), which better reflects the effect of interpolation on the CS estimation error. The average CS-estimation error using this validation method was 0.6655 for \((\mu^L, \Sigma^L)\) and 0.7553 for \((\mu^S, \Sigma^L)\). This suggests that spline interpolation \(\mu^S\) is less effective than linear interpolation \(\mu^L\) with regard to estimating CS. One possible reason for the lower CS estimation accuracy of spline interpolation is overfitting. Although such a nonlinear interpolation method is potentially effective in capturing a complex distribution, in general, learning a nonlinear model in a high-dimensional space from relatively few samples poses some risk of overfitting. These results suggest that the distribution of the training data is less complex in this study and that the disadvantage of potential overfitting outweighs the advantages of a nonlinear model.

### 3.3.4 Effect of optimization of the number of dimensions of subspace for each CS

We now discuss the effect of the optimization of the number of subspace dimensions for each CS. Among the various criteria for optimizing the number of dimensions, we focused on CS estimation error. This is because the CS estimation error shown in the previous section (0.5668) does not represent a satisfactory performance for practical use, since a CS estimation error greater than 0.5 indicates that a sample will be misclassified as belonging to another CS. Hence, in this study, we optimized the number of dimensions by minimizing the CS estimation error from Eq. (15).

Table 3 compares the performance of the spatiotemporal SSM for the best method (\(q\)-Gaussian assumption with the interpolation method \(\mu^L\) and \(\Sigma^L\)) with and without dimension selection. For all the performance indices comprising generalization, specificity and CS estimation error, the method with dimension selection achieved better performance. We applied Wilcoxon signed rank test to the CS estimation error and generalization, and Mann-Whitney \(U\)-test to the specificity with a significance level of \(p < 0.01\). Except for the CS estimation error, we observed a statistically significant difference between the spatiotemporal SSM with and that without dimension selection.

Table 4 shows the relationship of the selected number of dimensions \(r_i\) with the determinant of the covariance matrix \(|\Sigma_i|\) for each CS \(i\), which is one of the indicators of the total amount of shape variation. We found that a smaller number of \(r_i\) was selected for the

\[^1\text{In the leave-one-CS-out cross-validation, the first and the last CSs (CS 15 and CS 20) were not used for testing because some of our interpolation methods do not yield extrapolation of mean and covariance. Specificity cannot be defined in leave-one-CS-out strategy in principle, because it requires test samples from all CSs to calculate Eq. (A.3) in Appendix A.}\]
This finding suggests that the proposed dimension estimation reduces the negative influence of the CS estimation accuracy induced by such a large difference in shape variation between CSs.

4. Conclusion

We proposed an algorithm for constructing a spatiotemporal SSM of the human embryonic brain. To reduce the influence of a small sample size, a $q$-Gaussian assumption was introduced to calculate covariance matrices. In order to calculate the statistics of the shape distribution of the intermediate CS, 18 interpolation methods were examined, including novel B-spline–based methods. In addition, an exhaustive comparison among them was conducted to determine the best interpolation method. We also proposed a method to allow interpolation between distributions with a mixed number of dimensions, i.e., the rank of the covariance matrix. An SSM was constructed from 60 sets of brain surface data acquired from the Kyoto collection. We found that the best interpolation method was the combination of the linear ($\mu^L$) average interpolation method and an information geometry ($\Sigma^L$)–based covariance interpolation method. We also found that use of a $q$-Gaussian distribution and selection of the number of dimensions are effective methods for improving the performance of the spatiotemporal SSM of a human embryo. In the future, we will utilize our model in automated brain image segmentation. We also plan to develop a quantification algorithm of the degree of morphological abnormality in the embryonic development. Another important avenue of future research is to investigate the relationship between the training data and the best interpolation method to provide guidelines for selecting the interpolation method for a new dataset.

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References

1. O’Rahilly R, Müller F: Developmental stages in human embryos: revised and new measurements. Cells Tissues Organs. 192(2), pp. 73–84, 2010.
2. Ozeki–Satoh M, Ishikawa A, Yamada S, Uwabe C, Takakuwa T: Morphogenesis of the middle ear ossicles and spatial relationships with the external and inner ears during the embryonic period. The Anat Rec (Hoboken). 299(10), pp. 1325–1337, 2016.
3. Shiraiishi N, Katayama A, Nakashima T, Yamada S, Uwabe C, Kose K, Takakuwa T: Morphology and morphometry of the human embryonic brain: A three-dimensional analysis. Neuroimage. 115, pp. 96–103, 2015.
4. de Bakker BS, de Jong KH, Hagoort J, de Bree K, Besselink CT, de Kanter FEC, Veldhuis T, Bais B, Schildmeijer R, Ruijter JM, Oostra R-J, Christoffels VM, Moorman AFM: An interactive three-dimensional digital atlas and quantitative database of human development. Science. 354(6315), 2016.
5. Heimann T, Meinzer H-P: Statistical shape models for 3D medical image segmentation: A review. Med Image Anal. 13(4), pp. 543–563, 2009.
6. Leventon ME, Grimson WEL, Faugeras O: Statistical shape influence in geodesic active contours, in IEEE Conference on Computer Vision and Pattern Recognition vol. 1, pp. 316–320, 2000.
7. Kishimoto M, Saito A, Takakuwa T, Yamada S, Matsuzoe H, Hontani H, Shimizu A: A spatiotemporal statistical model for eyeballs of human embryos. IEICE Trans Inf Syst E100.D(7), pp. 1505–1515, 2017.
8. Kasahara K, Saito A, Takakuwa T, Yamada S, Shimizu A: A spatiotemporal statistical shape model of brain surface during human embryonic development. In International Forum on Medical Imaging in Asia (IFMIA) 2017, ed, 2017.
9. Mansi T, Durrleman S, Bernhardt B, Sermesant M, Delingette H, Voigt I, Lurz P, Taylor AM, Blanc J, Boudjemline Y, Pennec X, Ayache N: A statistical model of right ventricle in tetralogy of Fallot for prediction of remodelling and therapy planning. In: Yang GZ, Hawkes D, Rueckert D, Noble A, Taylor C (eds) Medical Image Computing and Computer-Assisted Intervention–MICCAI 2009. MICCAI 2009. Lecture Notes in Computer Science, vol 5761. Springer, Berlin, Heidelberg, pp. 214–221, 2009.
10. Wright R, Makropoulos A, Kyriakopoulou V, Patkee PA, Koch LM, Rutherford MA, Hajnal JV, Rueckert D, Aljabar P: Construction of a fetal spatio-temporal cortical surface atlas from in utero MRI: Application of spectral surface matching. Neuroimage. 120, pp. 467–480, 2015.
11. Dittrich E, Riklin Raviv T, Kasprian G, Donner R, Brugger PC, Prayer D, Langs G: A spatio-temporal latent atlas for semi-supervised learning of fetal brain segmentations and morphological age estimation. Med Image Anal. 18(1), pp. 9–21, 2014.
12. Durrleman S, Pennec X, Trouvé A, Braga J, Gerg G, Ayache N: Toward a comprehensive framework for the spatiotemporal statistical analysis of longitudinal shape data. Int J Comput Vis. 103(1), pp. 22–59, 2013.
13. Alam S, Kobashi S, Nakano R, Morimoto M, Aikawa S, Shimizu A: Spatiotemporal statistical shape model construction for longitudinal brain deformation analysis using weighted PCA. Int J CARS. 11(1 Suppl) p. S204, 2016.
14. Yamada M, Hontani H, Matsuzoe H: A Study on model selection from the q-exponential distribution for constructing an organ point distribution model. In: Huang F, Sugimoto A (eds) Image and Video Technology – PSIVT 2015 Workshops. PSIVT 2015.

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**Table 4** Determinant of covariance matrix in each CS.

| CS | 15 | 16 | 17 | 18 | 19 | 20 |
|----|----|----|----|----|----|----|
| Num. of dims. $r_i$ | 3  | 4  | 4  | 3  | 3  | 3  |
| Determinant of covariance $|\Sigma_i|$ | $5.64 \times 10^{11}$ | $3.96 \times 10^{11}$ | $7.96 \times 10^{10}$ | $2.35 \times 10^{9}$ | $1.46 \times 10^{8}$ | $6.83 \times 10^{6}$ |
Appendix A

This section explains the generalization and specificity criteria [24] used to evaluate the SSM. Let \( \{S_1, \ldots, S_n\} \) denote \( n \) test shapes and \( \hat{S}_i \) represent the reconstructed shape of \( S_i \) obtained from the model. Generalization is the ability of the model to describe an unknown shape:

\[
\text{(Generalization)} = \frac{1}{n} \sum_{i=1}^{n} \text{JI}(S_i, \hat{S}_i) \quad (A.1)
\]

where

\[
\text{JI}(S_i, \hat{S}_i) = \frac{|S_i \cap \hat{S}_i|}{|S_i \cup \hat{S}_i|} \quad (A.2)
\]

is the Jaccard index (JI) between two shapes. Specificity evaluates the consistency between the trained shape distribution and the test shape distribution.

\[
\text{(Specificity)} = \frac{1}{m} \sum_{j=1}^{m} \min_{i \in [1, \ldots, n]} \text{JI}(S_i, R(c_j, \alpha_j)) \quad (A.3)
\]

where \( R(c_j, \alpha_j) \) is the shape generated from the SSM with a randomly sampled CS \( c_j \) and shape parameters \( \alpha_j \). The minimum JI is calculated over the test data from all CSs. We assume a uniform distribution for the CS number, i.e., \( c_j \sim [15, 20] \), and a normal distribution for the shape parameter, i.e., \( \alpha_j \sim N(\mu_{c_j}, \Sigma_{c_j}) \). We used \( m = 2000 \), which is double the number of random shapes used in a previous report [7]. Since we confirmed that increasing this number to 10000 does not change the result, with respect to computation time, \( m = 2000 \) was considered sufficient for this study.

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