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*Short Paper*

# Spatiotemporal Visualization of Gene Expression in the Developing Mouse Brain

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**Abstract**

*Exploring and visualizing the spatiotemporal fold change of gene expression is an increasingly important challenge especially in structures as the developing brain. Focusing on the Allen Developing Mouse Brain data, we propose a visual analytic method to facilitate such exploration. We first use 3D brain atlases and developmental ontology to capture the spatial orientations of entire structures, and next use the fold changes of gene expression to weight them to denote the spatial fold changes between any given stages. We then determine the overall aggregate spatial fold change for a given gene across the entire set of stages and visualize them using 3D renderings and PCA to glean the likely directionality and gradients of gene expression. We examine the performance of the proposed method by investigating several patterns and find that they reflect the expression data. This short paper describes a portion of the larger visual analytic framework we are constructing to visualize spatiotemporal changes of gene expression in a developing brain.*

**Keywords:** Spatiotemporal, fold change, gene expression, developing mouse brain

## 1. Introduction

In computational biology and bioinformatics, fold change is widely used for describing the ratio that how much a gene expression changes between two conditions. Since the expression process underlyingly controls which information should and will be used in order to construct functional gene products, it likely gives rise to phenotypes such as cells and organs of different shapes, types, and functionalities [LG10, gen]. Thus, the fold change of expression over different developmental stages indicates changes of gene activities during brain development. Hence, fold changes of gene expression can be best used for the exploration of the remarkable development of mammalian brains.

However, the development of brain structures follows complex spatiotemporal regulation programs [TJR*15, CWS*16]. Although numerous studies have developed several approaches to reveal the characteristics of gene expression during brain development, few of them have described the exploration of the spatiotemporal fold changes and no reported study used such pattern of fold changes to reflect the brain development [LAC*09, LC13, LGD*]. Thus, exploring and visualizing the spatiotemporal fold changes of gene expression requires innovative approaches and multiple challenges exist such as how to capture the expression changes in various structures and across time; how to integrate them into a spatiotemporal data structure; and how to visualize these spatiotemporal fold changes.

In this paper, targeting the Allen Developing Mouse Brain (ADMBA) data, we propose a visualization method to facilitate the exploration of the spatiotemporal fold changes of gene expression. We will first generate the 3D spatial developmental orientations of brain structures using 3D brain atlases at various stages and developmental ontology of structures. Next, for each available gene, we will use the fold changes of the expression values to weight the magnitudes of these spatial orientations to capture the spatiotemporal fold changes of expression at any given stage as well across entire stages. We will also use 3D rendering to present the visualization of the spatiotemporal fold changes — in the form of collection of vectors — and apply PCA (principal component analysis) method to explore the likely directionality of the gene expression. Finally, we investigate the performance of the proposed method by examining several explored spatiotemporal fold changes and compare them against known cases.

It should be noted, although the proposed method provides a novel visualization for the spatiotemporal fold change, the accuracy of observations and results can not be evaluated since no reported work have been published on this topic that can verify them. Thus, in this case, the evaluation of precision and user studies are not provided in this paper. However, this proposed visualization method can be considered for exploring the spatiotemporal patterns for similar dataset in different areas. The remainder of this paper is organized as follows: in Section 2, we will describe the data col-





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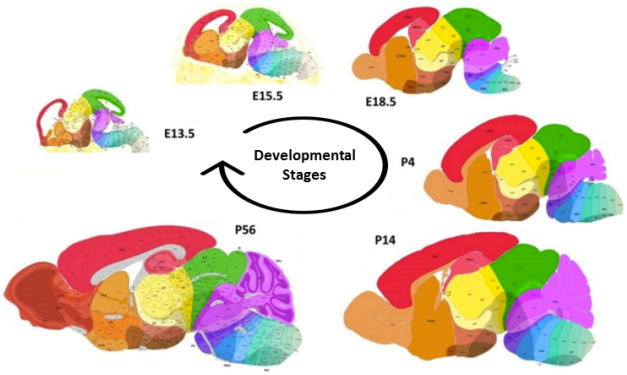


**Figure 1:** ***Reference atlases of mouse brain at six stages.*** *Example atlas slides in the sagittal plane chosen from ADMBA: 13.5 days after embryo (E13.5), 15.5 days after embryo (E15.5), 18.5 days after embryo (E18.5), 4 days after born (P4), 14 days after born (P14), and 56 days after born (P56, adult).*

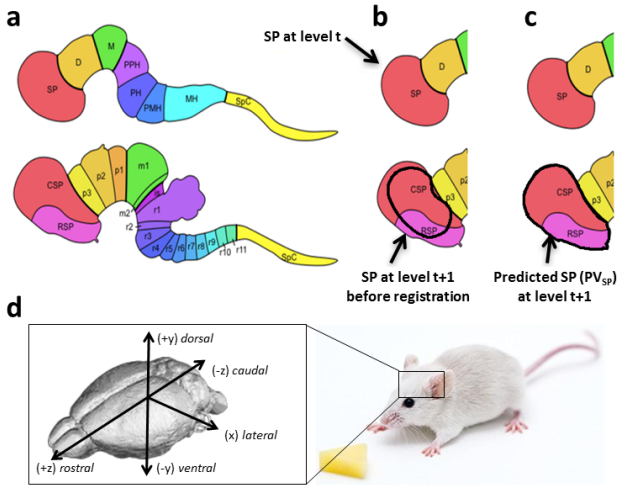


**Figure 2:** ***Example of the ontology-based structure registration.*** *(a) Structure CSP and RSP were developed from SP; (b) Imprecise location of SP, as the black outline shows, without the structure-based registration; (c) Our structure-based registration approach provides the new location of SP, as the black outline shows; (d) 3D system used in the proposed method.*

lected from the ADMBA project; in Section 3, we will introduce the approaches used for the proposed method; in Section 4, we will investigate explored patterns and discuss the result; finally, we will summarize our work in Section 5.

## 2. Data Collection

As one of the discovery projects of the Allen Institute for Brain Science (AIBS), the Allen Developing Mouse Brain Atlas (ADMBA) focuses on describing the transcriptional mechanisms involved in the developing mouse brain [adm]. ADMBA has published an online resources data portal that provides extensive gene expression data containing 1753 well-examined genes in 2489 anatomical structures across six developmental stages including three embryonic (E) and three early postnatal (P): E13.5, *E*15.5, E18.5, P4, P14, and P56 (adult). At each stage, 3D reference brain atlases and the 3D structure-annotated volume are also provided. Figure 1 shows an example of the mouse reference atlases at various developmental stages. Additionally, a hierarchical annotation of various evolving brain structures is available.

## 3. Method

In order to explore and visualize the spatiotemporal fold changes of gene expression as described, our proposed method includes three steps: 1) generate the spatial developmental orientations of brain structures; 2) for each gene at the corresponding structures and stages, use the fold-change of gene expression values to modulate these spatial orientations; and 3) convert the modulate fold-change into the spatiotemporal form and visualize them. In this section, we will describe these steps in greater detail.

### 3.1. Spatial Developmental Orientation

In the first step, we define spatial developmental orientation (DO) for indicating the developmental direction of brain structures. Since the spatial locations of all available brain structures at each stage are available in the 3D annotation atlases and the hierarchical ontology also provides their entire developmental order, the developmental orientation of each structure could be obtained through a 3D vector — from the centroid of the spatial locations of its predecessor to itself. However, simply calculating the 3D vector from the centroids of structure volumes in atlases at different stages could lead to biased results. Even worse, normal 3D imaging registration could not be used in our case either, due to the significant variances of sizes and shapes among the large number of structures. To solve this problem, we designed an ontology-based structure registration approach which assumes a structure's new location at a higher hierarchical level or a later stage. In this approach, we used the union of entire successor structures at the next level to predict the location of the predecessor structure. Equation 1 shows how we calculated DO using the predicted volume (PV) of structure:

$$\begin{aligned} PV_{S_i} &= < V_{S_i} \bigcup ( \bigcup_{j}^{S_j \succ S_i'} V_{S_j} ) >, and \\ \vec{DO}_{S_i} &= < V_{S_i} > - < PV_{S_i} >, where \\ < \vec{V}_{S_i} > &= (C_x, C_y, C_z) | S_i, \end{aligned} \tag{1}$$

where $S_i$ denotes the $i^{th}$ brain structure, $V_{S_i}$ denotes the 3D volume of structure $S_i$ and $< V_{S_i} >$ is its spatial centroid, $S_i'$ denotes the predecessor of $S_i$, and $S_j \succ S_i$ denotes that $S_j$ is a successor structure of $S_i$. Figure 2(a-c) shows an example of the ontology-based structure registration approach, which we believe provides more precision during DO calculation. In Figure 2(a) structure CSP (caudal secondary prosencephalon) and RSP (rostral secondary prosencephalon) were developed from SP (secondary pros-

encephalon) at the previous level. Thus, using the location of SP in the previous 3D atlas (Figure 2(b)) would lead to biased results. However, in the ontology-based structure registration approach, as shown in Figure 2(c), we used the union of the progeny of CSP and RSP to predict the new location of SP at the current level. Moreover, after learning the precise developmental orientations of all structures, we generated them in the form of 3D vectors.

### 3.2. Spatiotemporal Fold Changes of Gene Expression

After capturing the spatial developmental orientation of entire brain structures, we next integrated them with the gene expression values to generate the spatiotemporal fold changes. In this step, for each given gene, we use the fold changes of gene expression values between stages to weight the magnitudes of DOs to capture the spatial fold changes and name them gradient orientations (GOs). Thus, for any given stage $t$, $E_{p,i,t}$ is the expression value of the $p^{th}$ gene at the $i^{th}$ structure at the $t^{th}$ stage, and spatial fold change $GO(\vec{G_p}, S_i, t)$ indicates the directional expression of gene $G_p$ at structure $S_i$. The fold change was calculated using the ratio of the expression values at neighbor stages (e.g., from stage $t-1$ to $t$), and hence GOs are computed as:

$$GO(\vec{G_p}, S_i, t) = \begin{cases} |log_2(\frac{E_{p,i,t}}{E_{p,i,t-1}})| \cdot \vec{DO}_{S_i}, & \text{if } S_i \text{ exist at both} \\ & \text{stages } t \text{ and } t-1 \\ < 0, \vec{0}, 0 > & \text{otherwise} \end{cases} \quad (2)$$

In addition, in order to estimate the overall spatiotemporal fold changes across all stages, we introduced the temporal gradient orientation (TGO) — which can be best described as the sum of the GOs for all stages, and weighted gradient orientation (WGO) — which is the collection of TGOs:

$$TGO(\vec{G}_p, S_i) = \sum_{t=2}^{6} GO(\vec{G_p}, S_i, t) \text{ , and}$$
$$\vec{WGO}_p = < TGO(\vec{G}_p, S_1), TGO(\vec{G}_p, S_2), \ \dots \ , TGO(\vec{G_p}, S_{2489}) > \quad (3)$$

Therefore, both GOs and WGO of any given gene indicate the spatiotemporal fold changes across developmental stages, and hence provide the inherent pattern of the expression behavior of genes during the development of the mouse brain.

### 3.3. Visualization of the Spatiotemporal Fold Changes

In order to provide an intuitive understanding, we next perform the visualization of the GOs and WGO for each gene. For such a 3D vector collection-layout data structure, we believe 3D rendering in the Cartesian space is the best way for presentation. As shown in Fig 2(d), we use $x$, $y$, and $z$ to denote the sagittal, dorsal, and coronal axes and thus for a mouse: origin represents the centroid of the brain, $< +x >$ stands for the left or *lateral*, $< +y >$ stands for up or *dorsal*, $< -y >$ stands for down or *ventral*, $< +z >$ stands for front or *rostral*, and $< -z >$ stands for rear or *caudal*. Thus, the GOs in the WGO of every given gene were used for the visualization. Moreover, we will calculate the first two principal components (PC) for presenting the global directionality of the gene expression. Fig 3 and 4 show the 3D visualization of GOs and WGO of example genes. We will discuss the results in detail in the next section.

## 4. Result

In this section, we investigate the proposed method by demonstrating explored GOs and WGO of two example genes: *Cdh*24 (cadherin 24) and *Mpped*1 (metallophosphoesterase domain containing 1). Fig 3 show the 3D visualization of GOs of *Cdh*24 in the top row. Fig 3(a) shows the normalized 3D expression values in the mouse brain at all available developmental stages; Fig 3(b) shows the GOs of *Cdh*24 across entire structures from stage E15.5 to E18.5; and Fig 3(c) shows the GOs of *Cdh*24 across entire structures from stage P14 to P56. Since the fold change could be positive (the expression value increased) and negative (the expression value decreased), we used the red and green colors to indicate the positive and negative fold changes, respectively.

From the expression data in Fig 3(a), it is clear that in the forebrain area ($< +z >$ direction), the expression of *Cdh*24 significantly increases from E15.5 to E18.5. At the same time, the expression slightly decreases in the direction of the cerebellum ($< +y, -z >$ direction). According to the visualization in Fig 3(b), several positive GOs are shown toward the $< +z >$ direction while some negative GOs are plotted in the $< +x, +y, -z >$ area. On the other hand, as shown in Fig 3(c), from stage P14 to P56, the GO visualization shows negative fold changes in entire brain structures, but the directionality of these GOs are not well determined. This discovered information can also be observed in Fig 3(a), where the expression in P56 is much lower than in P14 and the decrease of the expression occurs throughout the entire brain structures. On the other hand, contrasting with *Cdh*24, the patterns of *Mpped*1 are shown differently (in the bottom row of Fig 3). First, *Mpped*1 shows global positive fold changes in a diffusional way in the brain from E15.5 to E18.5 (Fig 3(e)), and the density of the GOs in $< -z >$ direction is slightly larger. This can be confirmed in Fig 3(d) where the E18.5 shows much higher expression than the E15.5 across all brain structures. Second, although *Mpped*1 also shows negative fold changes in most of the structures from P14 to P56 (Fig 3(f)), the cluster density of the GOs is much higher than those of *Cdh*24 in the visualization. This implies that the expression of *Mpped*1 starts to decrease from the stage P14 in most of the brain structures. However, the amount of the decrease is much lower, and this is also can be observed in Fig 3(d).

Next, we focus on the spatiotemporal fold changes for the entire developmental period, i.e., the summed WGO from E15.5 to P56. Fig 4 shows the WGO of *Cdh*24 and *Mpped*1 across entire stages in three view points. We also generated the vector of the $1^{th}$ PC in blue and $2^{nd}$ PC in cyan to indicate the main directions of the WGO. As shown, the pattern of the entire WGO can be clearly seen: *Cdh*24 has very strong diffusional expression behavior while showing even stronger density in the diagonal $< +x, +y, +z >$ direction; *Mpped*1 has less diffusional expression behavior, and also shows stronger density in the $< +x, +y, +z >$ and $< +x, -y, +z >$ directions. More importantly, although all these observations can be explored through the expression data in Fig 3(a) and 3(d), our

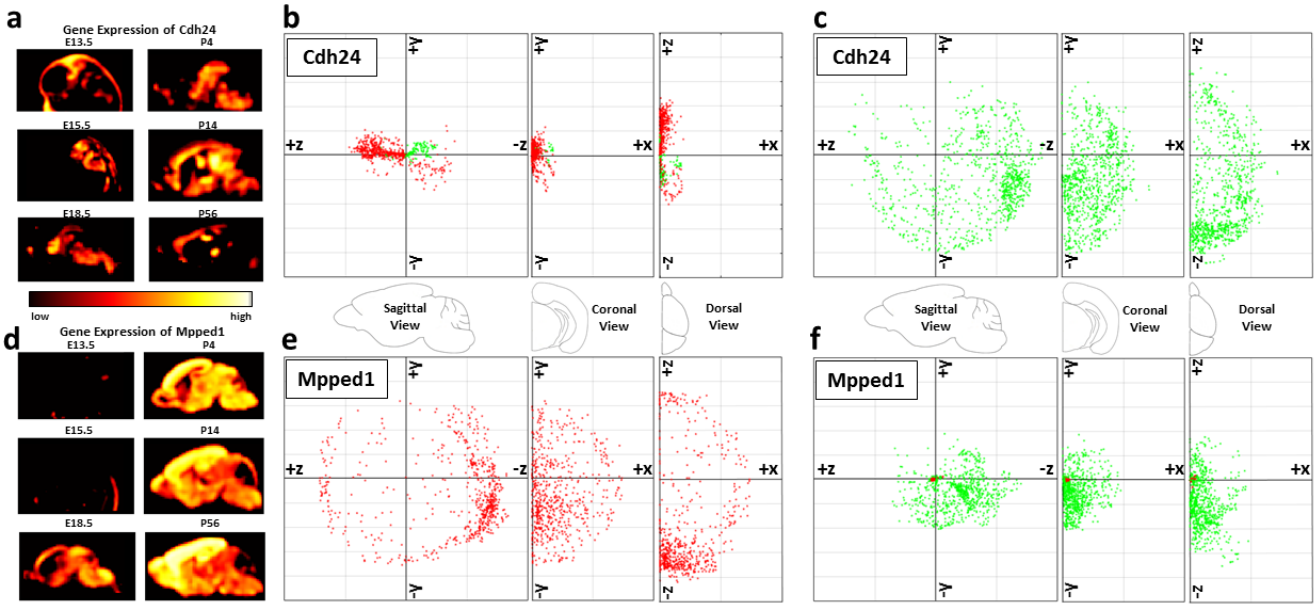


**Figure 3:** ***Visualization of spatiotemporal fold changes of*** *Cdh*24 ***and*** *Mpped*1 ***at various stages.*** *(a) The normalized 3D expression values of Cdh*24*; (b) the GOs of Cdh*24 *across entire structures from stage E15.5 to E18.5; (c) the GOs of Cdh*24 *across entire structures from stage P14 to P56; (d) The normalized 3D expression values of Mpped*1*; (e) the GOs of Mpped*1 *across entire structures from stage E15.5 to E18.5; (f) the GOs of Mpped*1 *across entire structures from stage P14 to P56.*

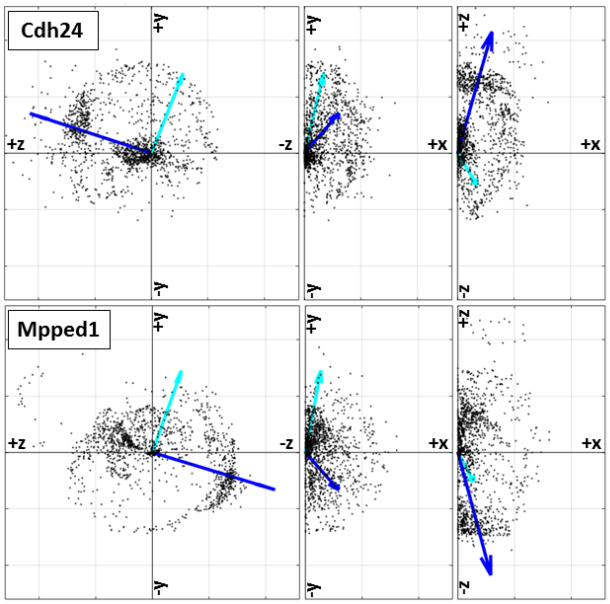


**Figure 4:** ***Visualization of WGO of*** *Cdh*24 ***and*** *Mpped*1*. The WGO of Cdh*24 *(top row) and Mpped*1 *(bottom row) across all six stages. We also generated the vectors of the* $1^{th}$ *PC in blue and* $2^{nd}$ *PC in cyan to indicate the main directions of these WGO.*

visualization method reflects the inherent gene expression data and provides an intuitive pattern exploration.

## 5. Conclusion and Future Works

In this paper, we have proposed a visualization method to facilitate the exploration of the spatiotemporal fold changes of gene expression in the developing mouse brain. Focusing on the Allen Developing Mouse Brain (ADMBA) data, we first generated the 3D spatial developmental orientations of brain structures, and next we used fold changes of the expression values to weight them into the spatiotemporal fold changes of gene expression. Finally, we investigated the precision of the visualization method by examining the explored patterns of targeted genes. The visualization result reflects the expression data and we thereby firmly believe that the proposed method enables the exploration of the spatiotemporal fold changes of gene expression in the developing mouse brain. It should be noted that this is a preliminary work where we visualized the spatiotemporal trend of gene expression in a developing brain. Ongoing work includes providing the integrative measurements of the spatiotemporal patterns of gene expression in different brain regions as well as the visualizations. In addition, we are also verifying the discovered gene patterns with actual experiments as reported in related studies [AAMN, TBB*07].

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## References

[AAMN] AT T., AJ W., MW S., N S.: The developmental transcriptome of the human brain: implications for neurodevelopmental disorders. *Curr Opin Neurol 27*, 2, 149–56. 4

[adm] Allen brain atlas data portal. http://www.brain-map.org/. 2

[CWS*16] CHOU S.-J., WANG C., SINTUPISUT N., NIOU Z.-X., LIN C.-H., LI K.-C., YEANG C.-H.: Analysis of spatial-temporal gene expression patterns reveals dynamics and regionalization in developing mouse brain. *Scientific Reports 6*, 19274 (Jan 2016). 1

[gen] Gene expression. https://en.wikipedia.org/wiki/Gene_expression/. 1

[LAC*09] LYDIA N., AMY B., CHRIS L., CAROLINE C. O., HONG-WEI D., CHIHCHAU K.: An anatomic gene expression atlas of the adult mouse brain. *Nature Neuroscience 12* (2009), 356–62. 1

[LC13] LISCOVITCH N., CHECHIK G.: Specialization of gene expression during mouse brain development. *PLoS Comput Biol 9*, 9 (Sept 2013). 1

[LG10] LENROOT R. K., GIEDD J. N.: The changing impact of genes and environment on brain development during childhood and adolescence: Initial findings from a neuroimaging study of pediatric twins. *Dev Psychopathol* (2010). 1

[LGD*] LI Q., GABRIEL Z., DAVID F., KUN H., RAGHU M.: Observing genomics and phenotypical patterns in the developing mouse brain. *IEEE Computer Graphics and Application*. 1

[TBB*07] TOMANCAK P., BERMAN B. P., BEATON A., WEISZMANN R., KWAN E., HARTENSTEIN V., CELNIKER S. E., RUBIN G. M.: Global analysis of patterns of gene expression during drosophilaembryogenesis. *Genome Biology 8*, 7 (2007). 4

[TJR*15] TE B., JA M., R L., A B., JL B., CK L., D B., NN P., KA S., SM S., DG A., DH G., ES L.: Spatiotemporal dynamics of the postnatal developing primate brain transcriptome. *Hum Mol Genet 24*, 15 (Aug 2015), 4327–39. 1