

Computational neuroanatomy and gene expression: optimal sets of marker genes for brain regions

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Abstract—The three-dimensional data-driven Anatomic Gene Expression Atlas of the adult mouse brain consists of numerized *in situ* hybridization data for thousands of genes, co-registered to the Allen Reference Atlas. We propose quantitative criteria to rank genes as markers of a brain region, based on the localization of the gene expression and on its functional fitting to the shape of the region. These criteria lead to natural generalizations to sets of genes. We find sets of genes weighted with coefficients of both signs with almost perfect localization in all major regions of the left hemisphere of the brain, except the pallidum. Generalization of the fitting criterion with positivity constraint provides a lesser improvement of the markers, but requires sparser sets of genes.

Index Terms—Gene expression, neuroanatomy, optimization, generalized eigenvalue problems.

I. INTRODUCTION: THE ANATOMIC GENE EXPRESSION ATLAS (AGEA) OF THE ADULT MOUSE BRAIN

Neuroanatomy is experiencing a renaissance under the influence of molecular biology and computational methods. The Allen Institute has built a three-dimensional data-driven atlas of the adult mouse C57Bl/6J (see the NeuroBlast User Guide <http://mouse.brain-map.org/>, and [1]–[4]) containing expression data for thousands of genes, co-registered to an atlas of brain regions, the Allen Reference Atlas (ARA) [5]. However, there is no general agreement on the list of brain regions for rodents (see [6], [7]). Given an anatomical atlas such as the ARA, it is therefore natural to ask if brain regions can be recognised in the spatial patterns of gene-expression data. For a molecular approach to the anatomy of the hippocampus, see [8]. In the present note we propose quantitative criteria formalizing the notion of marker genes for brain regions.

For each gene, an eight-week old C57Bl/6J male mouse brain was prepared as fresh-frozen tissue, and expression data were obtained through the following automated sequence of operations:

1. Colorimetric *in situ* hybridization (a coronal section for *Satb2* is shown on Figure 1a);
 2. Automatic processing of the resulting images: cell-shaped objects of size between 10 and 30 microns were looked for in each image in order to minimize artefacts;
 3. Aggregation of the raw pixel data into a unique three-dimensional grid, with voxel side 200 microns (projections of the result is shown on Figure 1b);
- The mouse brain is therefore partitioned into cubic voxels (the whole brain consists of $V = 49,742$ voxels). For every voxel v , the *expression energy* of the gene g is defined as a weighted sum of the greyscale-value intensities I evaluated at the pixels p intersecting the voxel:

$$E(v, g) = \frac{\sum_{p \in v} M(p)I(p)}{\sum_{p \in v} 1}, \quad (1)$$

where $M(p)$ is a Boolean mask worked out at step 2 with value 1 if the gene is expressed at pixel p and 0 if it is not. A maximal-intensity projection of the gene-expression energy of *Satb2* is shown on Figure 1b. The expression energy $E(v, g)$ is therefore expected to be proportional to the quantity of mRNA of gene g in voxel v (there can be saturation of the expression energy at large values, but the expression energy is still a monotonic function of the total number of molecules of mRNA in the voxel).

For numerical applications we focused on a set of genes for which sagittal and coronal sections have been produced at the Allen Institute. For each of these genes, we computed the correlation between sagittal and coronal data. Some of these correlations are negative, and we chose to focus on three quarters of the genes ($G = 3,041$ genes), that make up the top of the distribution of correlation coefficients. The gene-expression data we consider therefore consist of a voxel by gene matrix E defined in Equation 1. Moreover, the Allen Reference Atlas is registered to the same grid as the gene-expression data, so that each voxel in the brain is annotated according to which region it belongs. The ARA comes with several partitions of the brain, of varying coarseness. In particular, the left hemisphere is partitioned into 12 disjoint regions

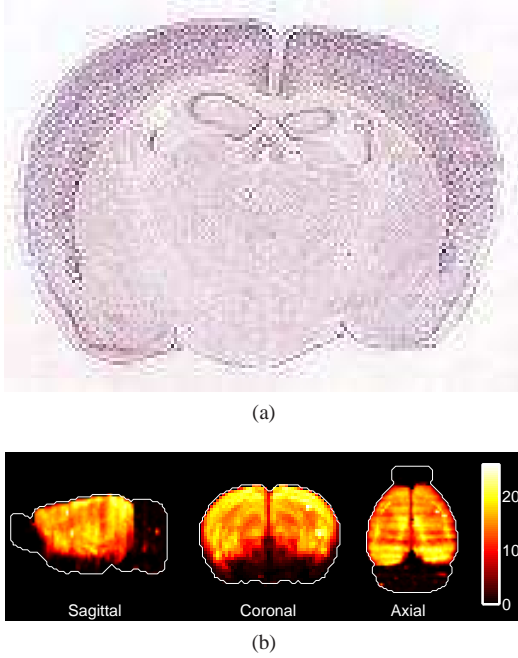


Fig. 1: **ISH-stained coronal slice of brain tissue and numerized data for *Satb2***. (a) A coronal section of brain tissue. Colorimetric ISH gives rise to a blue precipitate where an mRNA for *Satb2* is present. (b) A maximal-intensity projection of the three-dimensional data resulting from the co-registration of all coronal sections for *Satb2* to a regular grid, at a resolution of 200 microns.

in the ARA (each of which has one connected component, see Table I for a list of these regions, and Figures 3b and 4c for an illustration of the cerebral cortex and the midbrain, respectively). This partition is referred to as the Big12 annotation. In the present note we will focus on this annotation for definiteness.

For computational purposes, a brain region ω is therefore equivalent to a set of row indices in the matrix E , and to a (normalized) vector χ_ω in the V -dimensional voxel space, where the row indices are the only non-zero entries:

$$\chi_\omega(v) \Leftrightarrow v \in \omega, \quad \sum_{v=1}^V \chi_\omega(v)^2 = 1. \quad (2)$$

Each gene corresponds to a column of the matrix E , which is also a vector in a V -dimensional space. A marker gene is therefore a gene for which this vector is closely aligned with χ_ω . In the next section we propose two quantitative criteria formalizing this notion.

II. NEUROANATOMY FROM GENE EXPRESSION: RANKING GENES AS MARKERS

A. Ranking genes by localization scores

Given a brain region ω of interest, let us define the localization score of a gene g as the fraction of the (square of the) L^2 norm of its expression energy that is contained in the region:

$$\lambda_\omega(g) = \frac{\sum_{v \in \omega} E(v, g)^2}{\sum_{v \in \Omega} E(v, g)^2}, \quad (3)$$

where Ω denotes the whole brain. We chose the L^2 -norm because it is easy to generalize to a linear combination of genes (see next section).

We computed the localization score of every gene in every region of the Big12 annotation. These scores induce a ranking of genes as markers of each brain region. A perfect marker of the region ω according to this criterion would have a score of 1. Going from a region to another region, one has to be careful when comparing the values of the localization scores: as the volumes of the brain regions vary across the atlas, the localization scores λ_ω are biased by the size of the region ω . We need a reference in order to estimate how good a localization score is compared to what could be expected for a given brain region. For a fixed brain region ω we can use two references.

A gene is a better marker of ω than expected from a uniform expression if its score $\lambda_\omega(g)$ is larger than the uniform reference defined as

$$\lambda_\omega^{\text{uniform}} = \frac{\text{Vol } \omega}{\text{Vol } \Omega}. \quad (4)$$

A data-driven reference is given by the localization score of the average gene-expression profile:

$$\lambda_\omega^{\text{average}} = \frac{\sum_{v \in \omega} E^{\text{average}}(v)^2}{\sum_{v \in \Omega} E^{\text{average}}(v)^2}, \quad (5)$$

$$E^{\text{average}}(v) = \frac{1}{G} \sum_{g=1}^G E(v, g). \quad (6)$$

A gene is a better marker of ω than expected from an average expression if its localization score $\lambda_\omega(g)$ is larger than $\lambda_\omega^{\text{average}}$.

B. Ranking genes by fitting scores

The localization score does not take into account the detailed repartition of the expression energy inside the region of interest. It is therefore interesting to study another ranking of genes, that compares the gene-expression profiles to characteristic functions of brain regions. Such

Region ω (abbreviation in the Allen Reference Atlas)	Percentage of genes above $\lambda_{\omega}^{\text{uniform}}$	Percentage of genes above $\lambda_{\omega}^{\text{average}}$
Cerebral cortex (COR)	59	26
Olfactory areas (OLF)	41	40
Hippocampal region (HIP)	51	35
Retrohippocampal reg. (RHP)	53	33
Striatum (STR)	16	28
Pallidum (PAL)	9	34
Thalamus (THA)	20	38
Hypothalamus (HYP)	15	33
Midbrain (MID)	13	37
Pons (PON)	20	43
Medulla (MED)	30	47
Cerebellum (CER)	22	40

TABLE I: Percentage of a set of 3,041 genes in the Anatomic Gene Expression Atlas above the uniform and average references for the regions in the Big12 annotation of the left hemisphere in the Allen Reference Atlas. There is no particular solidarity between the two columns.

a comparison can be based on the functional distance between the expression profile and the characteristic function of the region. Let us choose the L^2 distance and compute the following fitting score for each gene g in a given region ω :

$$\phi_g(g) = 1 - \frac{1}{2} \sum_{v \in \Omega} (E_g^{\text{norm}}(v) - \chi_{\omega}(v))^2, \quad (7)$$

where E_g^{norm} is the L^2 -normalized g -th column E_g of the matrix of gene-expression energies:

$$E_g^{\text{norm}}(v) = \frac{E(v, g)}{\sqrt{\sum_{v=1}^V E(v, g)^2}}. \quad (8)$$

It is also useful to consider E_g as a vector in the V -dimensional voxel space (it is the gene-expression vector of gene g). Just as in the definition of localization scores, we could have chosen another norm, but the L^2 -norm yields an interesting geometric interpretation of the fitting score. Expanding the expression of the fitting score in powers of the gene-expression data yields the cosine of the angle between the gene-expression vector E_g and the vector χ_{ω} in voxel space. The fitting score is therefore very closely related to the notion of co-expression (which for two genes can be defined as the cosine of the angle between their expression vectors, which is a useful quantity to study in order to estimate collective properties of sets of genes [9]).

A perfect marker of the region ω would be a gene with fitting score equal to 1.

There are conflicts between the two induced rankings of

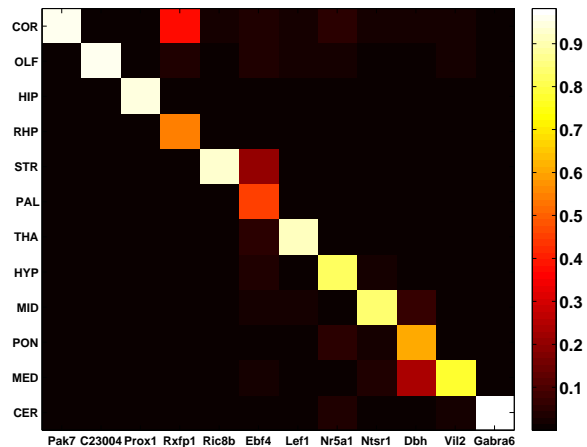


Fig. 2: Localization scores of the best markers of each of the brain regions in the Big12 annotation. The k -th column contains the localization scores of the best marker of the k -th region, hence the diagonal look of the figure. *Gabra6*, the best marker of the cerebellum, is the gene that maximizes the localization scores across all regions, at 98.5 percent.

genes, for instance *Satb2* has the highest fitting score for the cortex (and indeed by the look of Figure 1 it is a good marker of the cortex), whereas it is ranked 8 by the localization scores, with $\lambda_{\text{cortex}} = 0.9345$. On the other hand, *Pak7* is ranked first by localization score, and 7th by fitting score. See Figure 5 for a plot of best fitting and localization scores in the regions of the Big12 annotation. Pallidum is the region for which the best fitting and localization scores are the lowest, and cerebellum is the one for which there are the highest.

III. SETS OF GENES AS MARKERS

A. Generalized localization and generalized eigenvectors

Looking at the scores of the top marker genes for each brain regions, it appears that *Gabra6* maximizes localization scores across all brain regions and all genes, whereas the best marker in pallidum is the hardest to separate from other brain regions. However, comparing the numbers of genes localized above the average and uniform reference values, as in Table I does not show any particular ranking of brain regions.

In order to find better markers, consider a linear superposition of expression energies in our dataset:

$$E_{\alpha}(v) := \sum_{g=1}^G \alpha_g E(v, g), \quad (9)$$

where $G = 3,041$ is the number of genes in our dataset. The localization score in the brain region ω of a weighted

set of genes encoded by Equation 9 is naturally written as

$$\lambda_\omega(\alpha) = \frac{\sum_{v \in \omega} \left(\sum_g \alpha_g E(v, g) \right)^2}{\sum_{v \in \Omega} \left(\sum_g \alpha_g E(v, g) \right)^2} = \frac{\alpha^t J^\omega \alpha}{\alpha^t J^\Omega \alpha}, \quad (10)$$

where the quadratic forms J^ω and J^Ω have coefficients given respectively by scalar products of the projections of gene-expression vectors on ω and the whole brain:

$$J_{g,h}^\omega = \sum_{v \in \omega} E(v, g)E(v, h), \quad J_{g,h}^\Omega = \sum_{v \in \Omega} E(v, g)E(v, h). \quad (11)$$

The (generalized) localization score $\lambda_\omega(\alpha)$ is invariant under multiplication of the vector α . We can fix this dilation invariance by fixing the value of the denominator in Equation 10. Maximization of the localization score boils therefore down to a maximization of the quadratic form J^ω under a quadratic constraint:

$$\max_{\alpha \in \mathbf{R}^G} \lambda_\omega(\alpha) = \max_{\alpha \in \mathbf{R}^G, \alpha^t J^\Omega \alpha = 1} \alpha^t J^\omega \alpha. \quad (12)$$

Introducing the Lagrange multiplier σ associated to the constraint, we are led to the maximization of the quadratic quantity

$$L_{\omega, \sigma}(\alpha) = \alpha^t J^\omega \alpha - \sigma(\alpha^t J^\Omega \alpha - 1). \quad (13)$$

The stationarity condition of $L_{\omega, \sigma}$ wrt the vector α yields a generalized eigenvalue problem,

$$J^\omega \alpha = \sigma J^\Omega \alpha, \quad (14)$$

and the maximum value of the generalized localization score is the largest generalized eigenvalue, while the associated generalized eigenvectors contains the set of weights for genes in the best-localized superposition.

The alternating signs of the coefficients make these sets difficult to interpret in terms of transcriptional activity, and the plot of the sorted coefficients of the generalized eigenvector for the cerebral cortex in Figure 3c shows that the solutions are not sparse. But these algebraic solutions provide absolute bests that one could not beat by taking combinations of genes with positive coefficients. The negative coefficients allow to offset the contribution of some genes outside the region of interest.

B. Generalized fitting scores and sets of genes weighted by positive coefficients

Considering again a linear combination of gene-expression vectors, as in Equation 9, but weighted by positive coefficients: it is natural to propose the following fitting score, which just consists of the (square of) the L^2

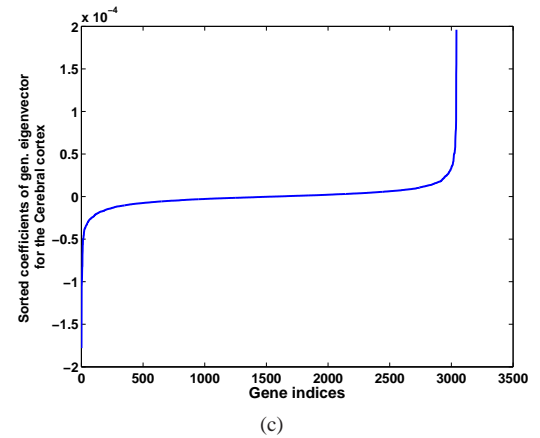
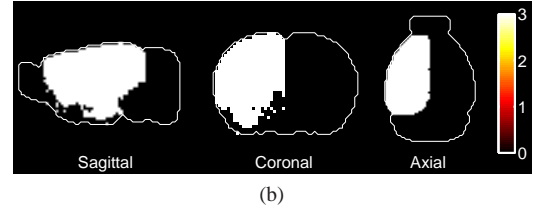
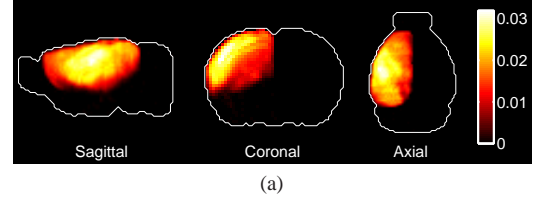


Fig. 3: **The best set of genes as a generalized eigenvector for the cerebral cortex.** (a) A maximal-intensity projection of the linear combination of the genes in the Adult Gene Expression Atlas corresponding to the generalized eigenvector that maximizes the localization in the cerebral cortex. (b) A maximal-intensity projection of the characteristic function of the cerebral cortex. (c) A plot of the sorted coefficients of the genes in the generalized eigenvectors. The localization score in the cortex is 0.9994. *Pak7* is at the second rank by its coefficient in the generalized eigenvector, while *Satb2* is only at the 64th rank.

distance between the normalized sum of the expression energies of all genes in the set, and the characteristic function of the region of interest:

$$\phi_\omega(\alpha) = 1 - \frac{1}{2} \sum_{v \in \Omega} (E_\alpha^{\text{norm}}(v) - \chi_\omega(v))^2, \quad \alpha \in \mathbf{R}_+^G. \quad (15)$$

A generalization of the fitting criterion to sets of genes that both solves the sign problem and the sparsity problem is found quite naturally in terms of an L^2 - L^1 mini-

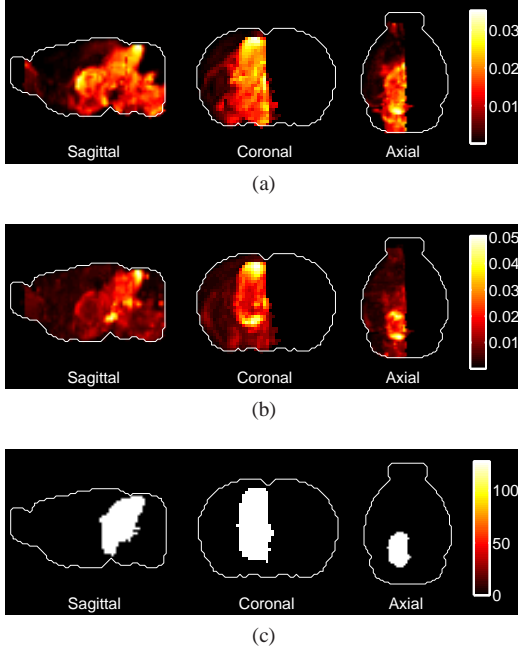


Fig. 4: **Best markers by fitting for the midbrain.** (a) The best single single gene is *Slc7a6*; (b) the best set of genes consists of 8 genes (*Slc17a6*, *Ephb1*, *Sema3f*, *Gla3*, *Nova1*, *Tcf7l2*, *Ddc*, *Chrna6*), at $\Lambda = 0.01 \times \Lambda_{\text{midbrain}}^{\max}$; (c) Projection of the midbrain.

mization. The following function penalizes the L^2 error function of Equation (15) by the L^1 norm of the vector:

$$\text{ErrFit}_{L^1-L^2}^{\omega, \Lambda}(\{\alpha\}) = \|E_{\alpha}^{\text{norm}} - \chi_{\omega}\|_{L^2}^2 + \Lambda \|\alpha\|_{L^1}, \quad (16)$$

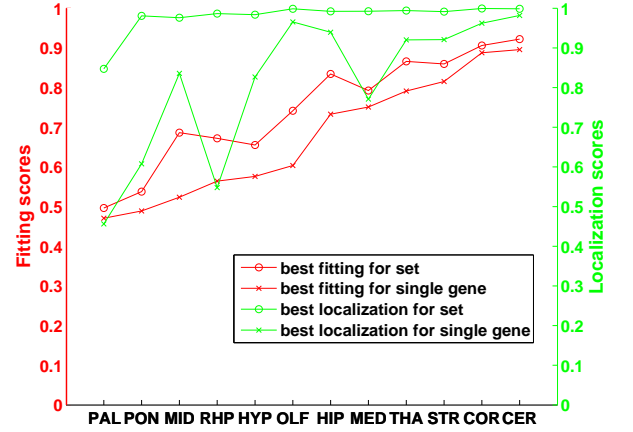
which can be minimized wrt the weights of the genes [10] using Matlab code by K. Koh:

$$\alpha_{\omega}^{\Lambda} = \underset{\alpha \in \mathbb{R}_+^G}{\text{argmin}} \text{ErrFit}_{L^1-L^2}^{\omega, \Lambda}(\{\alpha\}). \quad (17)$$

The range of parameter Λ to be studied can be restricted to $[0, \Lambda_{\omega}^{\max}]$, where

$$\Lambda_{\omega}^{\max} = 2 \max(E^t \cdot \chi_{\omega}), \quad (18)$$

because for larger values of Λ , the quadratic form $\text{ErrFit}_{L^1-L^2}^{\omega, \Lambda}$ is bounded from below by the squared norm of the vector E_{α} , and the solution to the problem of Equation (17) is trivially zero. The best fitting score is generally a decreasing function of Λ , while the sparsity grows with Λ . For each region ω in the Big12 annotation, there is a domain of $[0, \Lambda_{\omega}^{\max}]$ for which the generalized fitting score $\phi_{\omega}(\alpha_{\omega}^{\Lambda})$ is larger than the best fitting score of a single gene (scores are plotted on Figure 5 for $\Lambda = 0.01\Lambda_{\omega}^{\max}$).



(a)

Brain region	PAL	PON	MID	RHP	HYP	OLF
Best-fitting single genes	<i>Ebf4</i>	<i>Klk6</i>	<i>Slc17a6</i>	<i>Rspo2</i>	<i>Gpr165</i>	<i>Ppfibp1</i>
Nb of genes in best-fitted set	7	8	8	9	9	12

(b)

Brain region	HIP	MED	THA	STR	COR	CER
Best-fitting single genes	<i>TC141243t</i>	<i>Gla1</i>	<i>Lef1</i>	<i>Rgs9</i>	<i>Sab2</i>	<i>3110001A13Rik</i>
Nb of genes in best-fitted set	8	8	10	13	8	14

(c)

Fig. 5: (a) Best fitting scores and localization scores of single genes and of best sets of genes for the brain regions of the Big12 annotation. The brain regions are sorted by the best fitting score of single genes (see Table I for the abbreviations of the brain regions in the Allen Reference Atlas). The largest improvement to fitting brought by considering sets of genes rather than single genes in the midbrain. (b,c) Table of genes with highest fitting scores, and numbers of genes contributing to the best-fitted sets of genes.

IV. CONCLUSIONS

Quantitative methods used to rank single genes as markers of brain regions can efficiently spot genes whose expression profile outlines a brain region of interest. In particular, the generalized localization score can yield almost perfectly localized gene expression for all the major brain regions except pallidum, at the price of involving thousands of genes, weighted by coefficients of both signs. The fitting criterion can be generalized

to sparse sets of genes with positive coefficients, even though the improvement of the scores is less spectacular. The complexity of the taxonomy of cell types, and the precise anatomical localization in the brain of some of these cell types, indicates that there must be combinations of large numbers of genes with positive coefficients, corresponding to the superposition of genes given by Equation 9, that mark some brain regions, quite possibly much smaller than the large compartments of the left hemisphere we considered here [11]–[16].

The quantitative criteria used to define marker genes in the present paper are all global in nature, since they all involve comparison of gene-expression vectors to brain regions in terms of the entire voxel space. This does not make use of the fact that the voxels belonging to the same region of the ARA form connected sets of the left hemisphere. One can make these methods more local [17] and look for genes that are aligned to the projection of a brain region to a subspace of voxel space that surrounds the region. Such a set of voxels can be computed using level-sets of the eikonal distance to the boundary of the region [18], [19]. The eikonal distance is also a useful geometric tool for the registration of mouse skulls to a reference skull, which is currently used in a high-throughput neuroanatomy project [20], [21]. Genes separating brain regions from their environment without being particularly well localized or fitted globally are shown in [17]. Moreover, the conservation properties of marker genes (or their lack of conservation properties) when going from the mouse atlas to molecular atlases for other species will be relevant to the study of brain evolution¹.

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¹Co-expression coefficients and localization scores for the human atlas can be found online at <http://addiction.brainarchitecture.org>