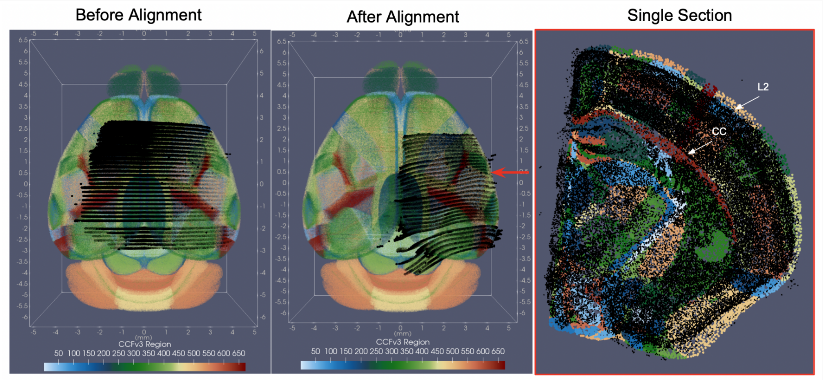
Representing and Mapping 3D Imaging and Spatial-omics Data Simultaneously Across Scales with Image-Varifold

Benjamin Charlier (MIAT, INRAE)

IMT, Toulouse — 13 juin 2025.

- **Context:** Analysis of spatial transcriptomics data, characterized by multiple modalities and scales, high dimensionality, incomplete observations, and limited sample sizes.
- **Collaborators:** (1) *CIS, JHU (Baltimore):* M. Anant, J. Fan, M. Miller, **K. Stouffer**, L. Younès; (2) *ENS (Paris-Saclay), INRAE (Toulouse)):* B. C., A. Trouvé; (3) *Allen institute (Seattle):* X.Chen, M. Kunst, L. Ng, M. Rue, H. Zeng;
- **Topic:** Presentation of *cross-modality Mapping* implemented in the *cross-modality image-varifold LDDMM* (xIV-LDDMM) toolbox. `https://github.com/kstouff4/xIV-LDDMM-Particle`

Global Alignment of Spatial Transcriptomics and Brain Atlas



- **Black dots:** BARseq spatial transcriptomics data (104 genes)
- **Colored regions:** Allen CCFv3 brain atlas (around 700 anatomical regions)

Stouffer KM, Trouvé A, Younès L, et al. Cross-modality mapping using image varifolds to align tissue-scale atlases to molecular-scale measures with application to 2D brain sections. Nat Commun. (2024)

Stouffer KM, Chen X, Zeng H, et al. xIV-LDDMM Toolkit: A Suite of Image-Varifold Based Technologies for Representing and Mapping 3D Imaging and Spatial-omics Data Simultaneously Across Scales. Prepint. (2025)

Keys ingredients

1. **Non-rigid deformations:** Large Deformation Diffeomorphic Metric Mapping (LDDMM) for flexible geometric alignment.
2. **Data representation and distances:** Use of the (image) varifold framework to define geometry-aware similarity measures.
3. **Computational solutions:** Multiresolution strategies and a versatile, parallelized implementation for scalable performance.
4. **Cross-modality data integration:** A registration formulation that accommodates differences in modality and spatial scale.

Non-Rigid Deformation with LDDMM

Varifold norms

Cross modalities Mapping Using Varifolds

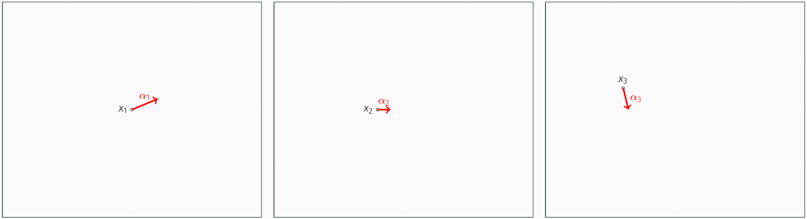
Geometrical deformations: RKHS of vectors fields

- **Space of vectors fields** V **:** an RKHS of vectors fields (smooth, vanishing at infinity). There exists a kernel $K_V : \mathbb{R}^D \times \mathbb{R}^D \to \mathbb{R}^{D \times D}$ such that

$$\text{Span}\{\delta_x^\alpha = K_V(x, \cdot)\alpha, x \in \mathbb{R}^D, \alpha \in \mathbb{R}^D\}$$

is dense in V. In practice, $D = 2, 3$ and

$$K_V(x, y) = e^{-\frac{\|x-y\|^2}{\sigma^2}} Id_D.$$



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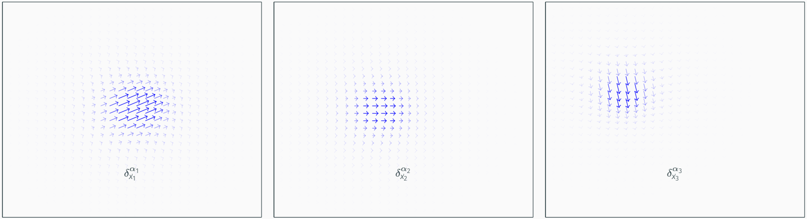

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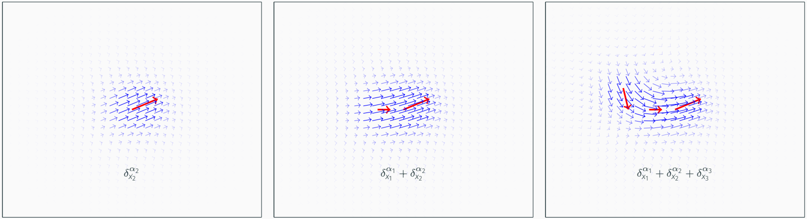
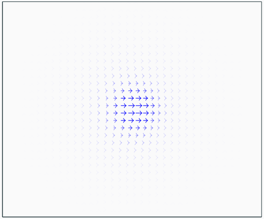
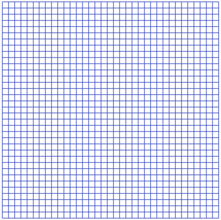


- **Flow:** let $v = (v_t)_{t\in[0,1]} \in V$ be a time dependant vectors field of $\mathbb{R}^D$. Let $\varphi : [0,1] \times \mathbb{R}^D \to \mathbb{R}^D$:

$$\begin{cases} \dot{\varphi}_t(x) = v_t(\varphi_t(x)) \\ \varphi_0(x) = x. \end{cases} \qquad t \in [0,1] \text{ and } x \in \mathbb{R}^D$$





$t = 0$

Geometrical deformations: flow of time varying smooth vector field

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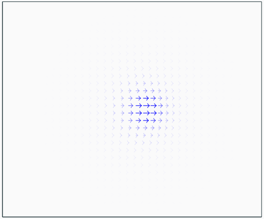

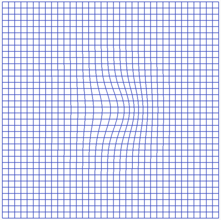

$t = 1/5$

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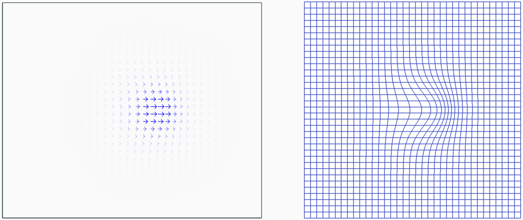

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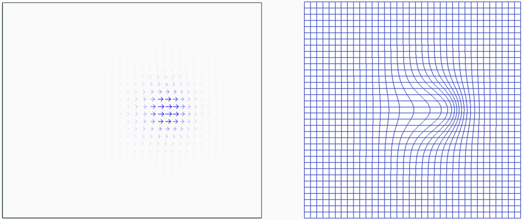

$t = 3/5$

Geometrical deformations: flow of time varying smooth vector field

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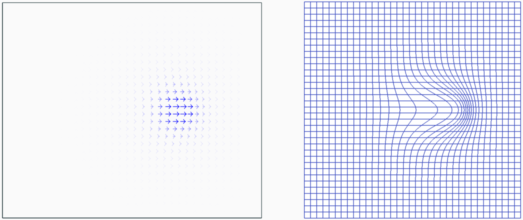

$t = 4/5$

Geometrical deformations: flow of time varying smooth vector field

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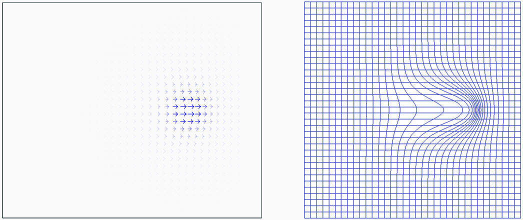

$t = 1$

Geometrical deformations: a group acting on objects

The space V contains smooth vectors fields vanishing at infinity.

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- **Group action :** Let $L^2_V \doteq L^2([0,1],V)$. For all $v \in L^2_V$, $\varphi^v_1(\cdot)$ is a $\mathcal{C}^1$-difféomorphism of $\mathbb{R}^D$. The set
$$G_V = \{\varphi^v_1 : \mathbb{R}^D \to \mathbb{R}^D, v \in L^2_V\}$$
is a group endowed with the (right invariant) distance
$$d^2(\mathrm{Id},\varphi) = \inf\{\|v\|^2_{L^2_V} \doteq \int_0^1 \|v_t\|^2_V dt, \dot{\varphi} = v \circ \varphi, \varphi_1 = \varphi\}$$
- **Initial momentum :** vectors field $p_0 : \mathbb{R}^D \to \mathbb{R}^D$ generating minimum energy deformations by integrating an Hamiltonian system.

Hamiltonian framework

- Momentums $(\boldsymbol{x}, \boldsymbol{p}) = (x_k, p_k)_{1 \leq k \leq N}$ and Hamiltonian :

$$H(\boldsymbol{x}_t, \boldsymbol{p}_t, v_t) = (\boldsymbol{p}_t | v_t \cdot \boldsymbol{x}_t)_{V*,V} - \frac{1}{2}|v_t|_V^2$$

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$$v(\cdot) = \sum_{k=1}^{N} K_V(\cdot, x_k) p_k$$

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- Reduced Hamiltonian:

$$H_r(\mathbf{x}, \mathbf{p}) = \frac{1}{2}\mathbf{p}^T K_V(\mathbf{x}, \mathbf{x})\mathbf{p}$$

- Shooting equations:

$$\begin{cases} \dot{\mathbf{x}}_t = \quad \partial_p H_r(\mathbf{x}_t, \mathbf{p}_t) \\ \dot{\mathbf{p}}_t = -\partial_x H_r(\mathbf{x}_t, \mathbf{p}_t) \end{cases}$$

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Varifold norms

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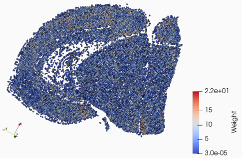
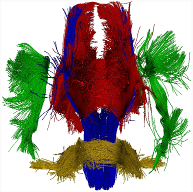
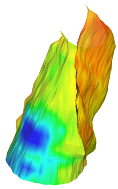
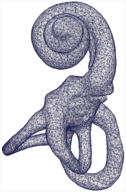
Geometric measure theory to compare shapes









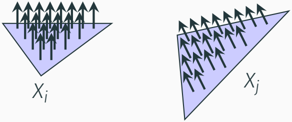
Data with **geometrical** information with (possibly) a feature attached (`signal`, label, etc.)

- Glaunès, Vaillant. Surface Matching via currents. (2006)
- Charon, Trouvé. The Varifold representation of non-oriented shapes for diffeomorphic registration. (2013)
- Kaltenmark et al. A general framework for curve and surface comparison and registration with oriented varifolds. (2017)

Geometric objects as measures

X is curve or surface in $\mathbb{R}^3$.

- A *varifold* μ_X is a **distribution** on $\mathbb{R}^3 \times \mathbb{S}^2$, *i.e.* (position $\times$ tangent space orientation).



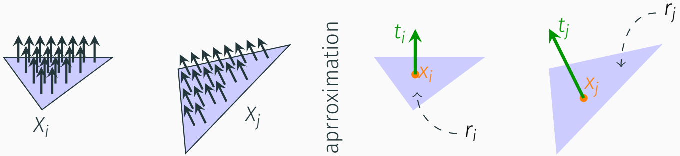
- A Dirac $\delta_{(x,t)}$ is a singular mass located at position $x \in \mathbb{R}^3$ in the direction of $t \in \mathbb{S}^2$.

Remark: invariance to parametrization.

Simplicial meshes as discrete measures

Discrete shapes are polyhedral objects $X = \bigcup_i X_i$.

- Each cell X_i (1D: segments, 2d: triangles) has a corresponding varifold μ_{X_i} approximated by $r_i \delta_{(x_i, t_i)}$:



- Extend to X by linearity: $\tilde{\mu}_X = \sum_i r_i \delta_{(x_i, t_i)} \approx \mu_X$.

Varifolds

Definition

A *varifold* on $\mathbb{R}^d$ is a distribution (or measure) on the space

$$\mathbb{R}^d \times G_k(\mathbb{R}^d),$$

where $G_k(\mathbb{R}^d)$ is the set of k-dimensional subspaces of $\mathbb{R}^d$ (Grassmannian).

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- A Dirac $\delta_{(x,\vec{n})}$ corresponds to a singular mass located at position $x \in \mathbb{R}^d$ in the direction of the subspace $\mathbf{Vect}(\vec{n})$.
- To any non-oriented shape X corresponds the fvarifold μ_X defined for all $\omega \in C_0^1(\mathbb{R}^d \times G_k(\mathbb{R}^d))$:

$$\mu_X(\omega) = \int_X \omega(x, T_x X) d\mathcal{H}^2(x) \approx \left(\sum_i r_i \delta_{(x_i, \vec{n}_i)} \right)(\omega)$$

Choose a RKHS of test functions embedded in $C_0^1(\mathbb{R}^d \times G_k(\mathbb{R}^d))$...

Kernel based metrics for surfaces

Surfaces ($k = 2$) in space ($d = 3$) and $G_2(\mathbb{R}^3) = S^2$

RKHS: Let W be the RKHS dense in $C^1_0(\mathbb{R}^3 \times S^2)$ generated by a product kernel $k_{pos} \otimes k_{or} : (\mathbb{R}^3 \times S^2)^2 \to \mathbb{R}$ induces a Hilbert space structure on the set of shapes that writes:

$$\langle \mu_{(X,f)}, \mu_{(Y,g)} \rangle_{W'}$$

Remark: if the chosen kernels are smooth…varifold norms are differentiable.

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&\approx \sum_i \sum_j k_{pos}(x_i, y_j) k_{or}(\overrightarrow{n}_i, \overrightarrow{m}_j)
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Distance:

$$\|\mu_{(X,f)} - \mu_{(Y,g)}\|_{W'}^2 = \left\langle \mu_{(X,f)}, \mu_{(X,f)} \right\rangle_{W'} + \left\langle \mu_{(Y,g)}, \mu_{(Y,g)} \right\rangle_{W'} - 2 \left\langle \mu_{(X,f)}, \mu_{(Y,g)} \right\rangle_{W'} .$$

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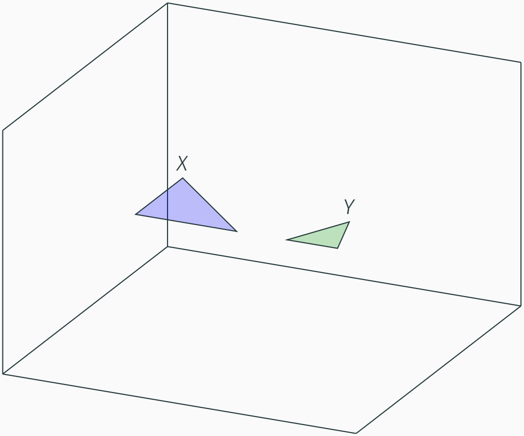
Discrete approximation



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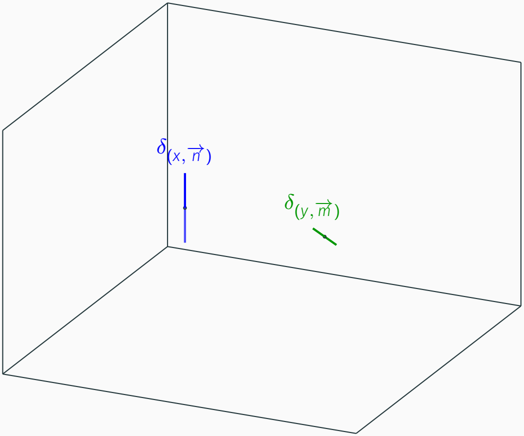

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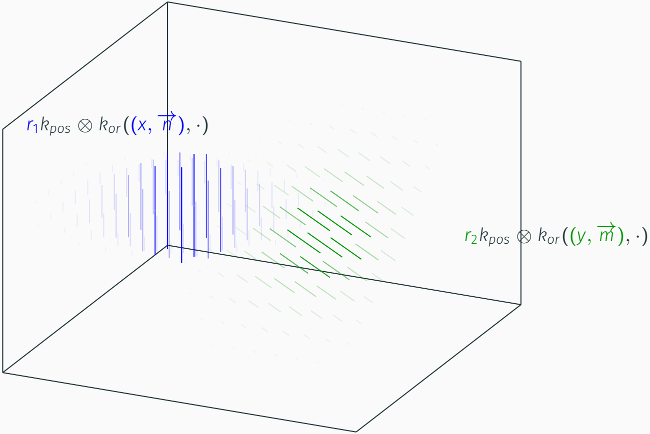

$$
\begin{aligned}
& r_1 r_2 \left\langle k_{pos} \otimes k_{or}((x, \overrightarrow{n}), \cdot), k_{pos} \otimes k_{or}((y, \overrightarrow{m}), \cdot) \right\rangle \\
&= r_1 r_2 k_{pos} \otimes k_{or}((x, \overrightarrow{n}), (y, \overrightarrow{m}))
\end{aligned}
$$

Examples of kernels

The various choices of kernels for k_{pos}, k_{or}, k_{sig} offer a wide range of different metrics:

- Gaussian kernels for k_{pos} and k_{sig} :

$$k_{pos}(x, y) = e^{-\frac{\|x-y\|^2}{\sigma_0^2}}$$

σ_0 measures the typical scale on spatial positions.

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- For curves or surfaces in $\mathbb{R}^3$, Grassmann manifold by non-oriented tangent or normal unit vectors.

$$k_{or}(\overrightarrow{n}, \overrightarrow{n}') = \langle \overrightarrow{n}, \overrightarrow{n}' \rangle^2 \text{ Binet-Cauchy kernel}$$

$$k_{or}(\overrightarrow{n}, \overrightarrow{n}') = e^{-\frac{2}{\sigma_t^2}(1-\langle \overrightarrow{n}, \overrightarrow{n}' \rangle^2)} \text{ Gaussian kernel}$$

Remark: Trivial to implement with KeOps.

Implementation with KeOps (1/2)

Gaussian-CauchyBinet kernel $(K(x, y, u, v)b)_i = \sum_j \exp(-\sigma\|x_i - y_j\|^2)\langle u_i, v_j\rangle^2 b_j$

```
from pykeops.torch import Vi, Vj

def GaussLinKernel(sigma):
    x, y, u, v, b = Vi(0, 3), Vj(1, 3), Vi(2, 3), Vj(3, 3), Vj(4, 1)
    gamma = 1 / (sigma * sigma)
    D2 = x.sqdist(y)
    K = (-D2 * gamma).exp() * (u * v).sum() ** 2
    return (K * b).sum_reduction(axis=1)
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Convert discrete mesh to Varifold dirac

```
def get_center_length_normal(F, V):
    """V: vertices coordinates
       F: Face connectivity of surfaces"""
    V0, V1, V2 = ( V.index_select(0, F[:, 0]),
                   V.index_select(0, F[:, 1]),
                   V.index_select(0, F[:, 2]) )

    centers = (V0 + V1 + V2) / 3
    normals = 0.5 * torch.cross(V1 - V0, V2 - V0)
    length = (normals**2).sum(dim=1)[:, None].sqrt()
    return centers, length, normals / length
```

Implementation with KeOps (2/2)

Varifold data attachment loss for surfaces

```
def lossVarifoldSurf(VS, FS, VT, FT, K):
    """VS, VT: vertices coordinates of target surface,
       FS, FT: face connectivity of source and target surfaces
       K: kernel"""
    CT, LT, NTn = get_center_length_normal(FT, VT)
    CS, LS, NSn = get_center_length_normal(FS, VS)
    return ( (LT * K(CT, CT, NTn, NTn, LT)).sum()
             + (LS * K(CS, CS, NSn, NSn, LS)).sum()
             - 2 * (LS * K(CS, CT, NSn, NTn, LT)).sum() )
```

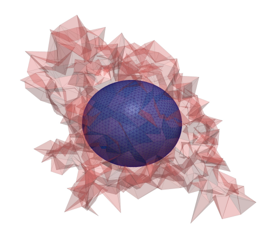
Compatible with torch autodiff:

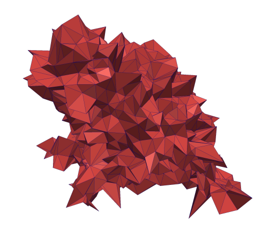
```
VS, FS, VT, FT = torch.load(datafile)
q0 = VS.clone().detach().to("cuda").requires_grad_(True)

L = lossVarifoldSurf(q0, FS, VT, FT, GaussLinKernel(sigma))
L.backward()
```

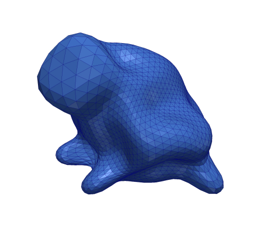
Returns the gradient of the varifold norm with respect to the vertex coordiantes of the source shape.

Varifold norm are robust to noise

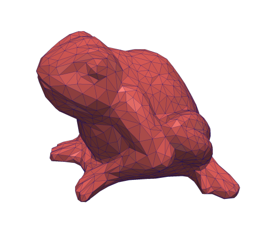




Observation

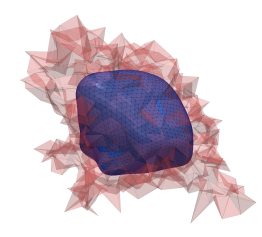


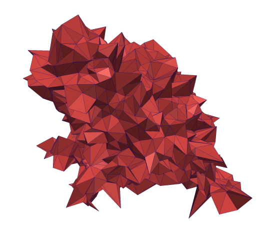
Reconstruction



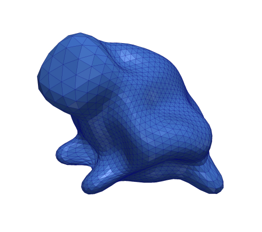
True shape

Varifold norm are robust to noise

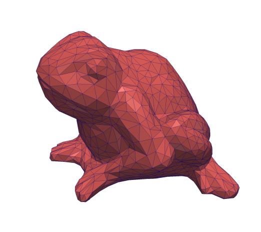




Observation

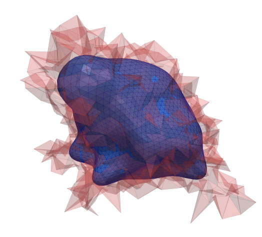


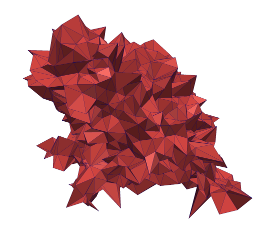
Reconstruction



True shape

Varifold norm are robust to noise





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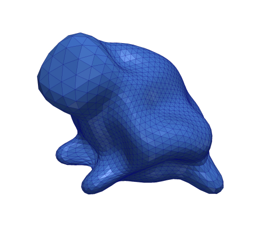

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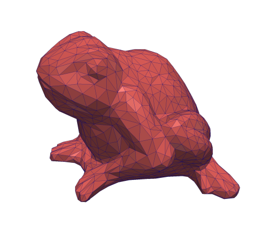

True shape

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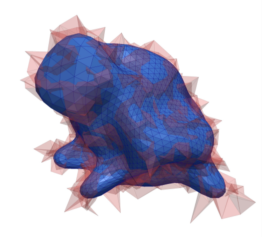
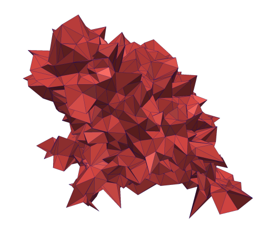
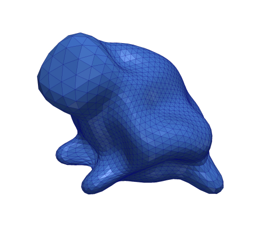
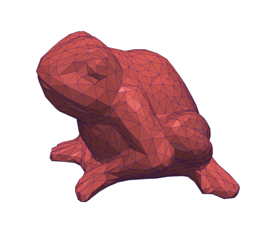




Observation

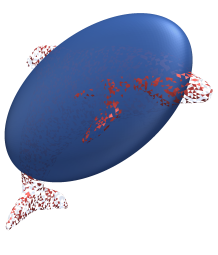


Reconstruction



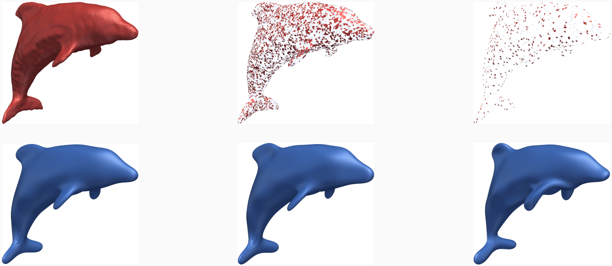
True shape

Varifold norm are robust to missing data

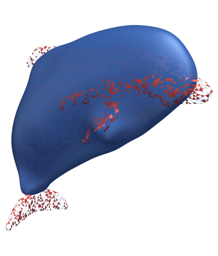


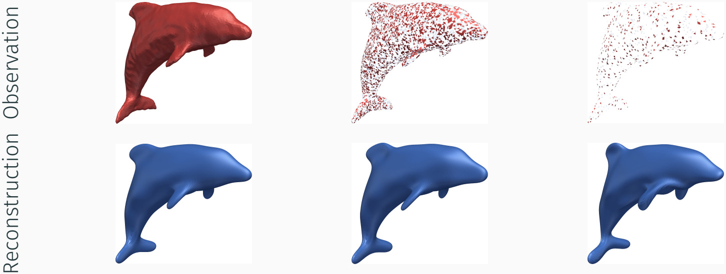
Observation

Reconstruction

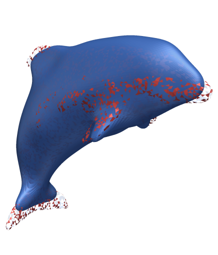


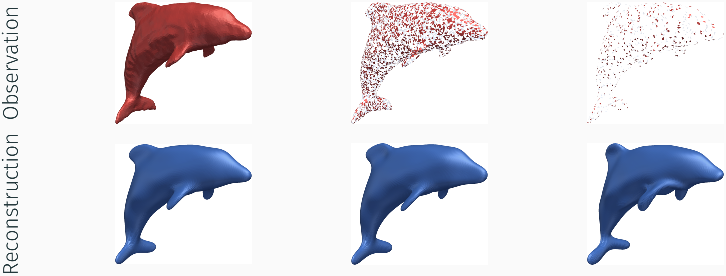
Varifold norm are robust to missing data



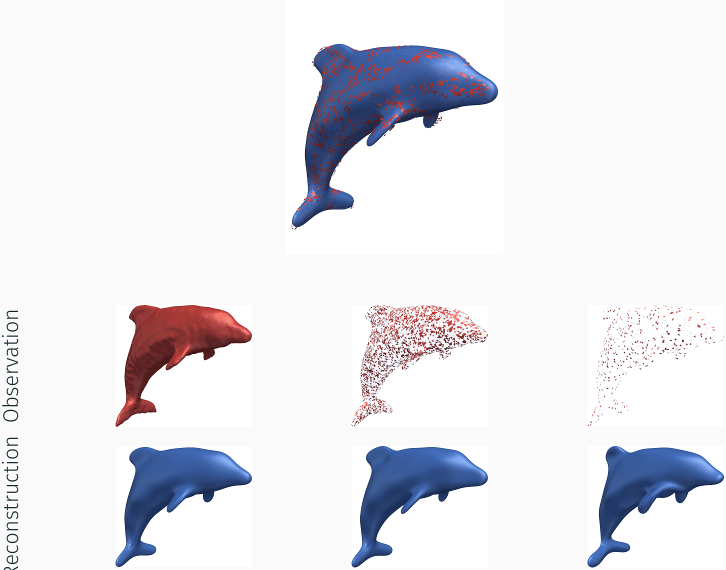


Varifold norm are robust to missing data





Varifold norm are robust to missing data

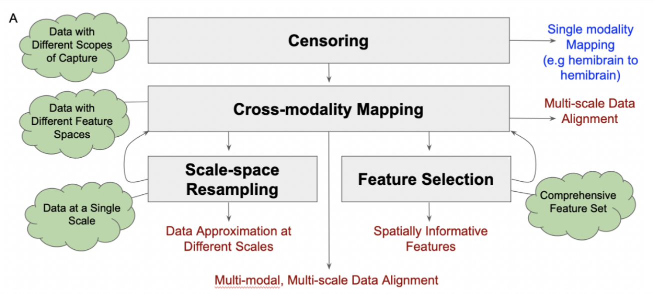


Non-Rigid Deformation with LDDMM

Varifold norms

Cross modalities Mapping Using Varifolds

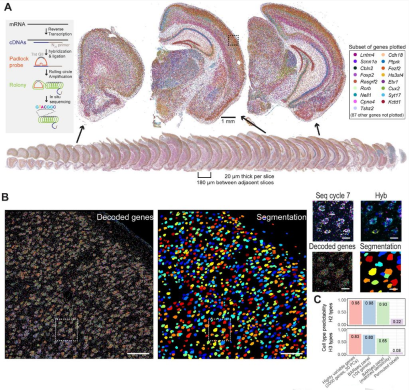
Overview of the xIV-LDDMM toolkit



- Green: input. Red: output. Gray: technologies

Data at molecular scale :

- **BARseq:** 32–40 coronal brain sections, identifying 39 or 52 cell types, based on raw expression of 104 genes. Hemibrain and full brain.



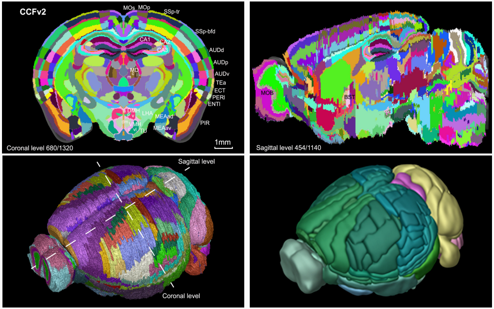
X. Chen et al. *Whole-cortex in situ sequencing reveals input-dependent area identity*. Nature, 2024.

- **MERFISH:** 56 coronal brain sections, profiling 500 genes.

Partial acquisitions (censored data). Feature space is denoted $\mathcal{F}$.

Dataset : Brain Atlases

- Data at tissue scale : Allen Common Coordinate Framework (CCFv3), Franklin and Paxinos Atlas, etc...



Wang, Q., et al. *The allen mouse brain common coordinate framework: a 3d reference atlas.* Cell 181(4), 936–953 (2020)

- Feature space are atlas regions (ontology) denoted $\mathcal{L}$. Assume a spatial homogeneity inside each region: for each $\ell \in \mathcal{L}$, gene distributions (on set $\mathcal{F}$) are similar at every sites belonging to ℓ.

Dataset : Brain Atlases

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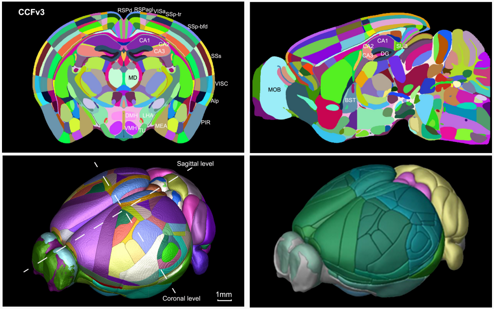

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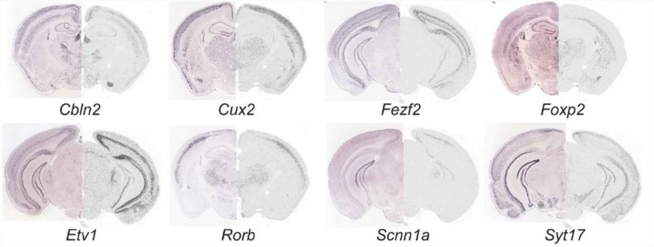
Cross-Modality Data Comparison

- **Task:** Compare different spatial scales (tissue-level vs. molecular-level) and feature types (anatomical ontology vs. gene expression) ...



"The expression patterns of representative genes in Allen Brain Atlas (left half) compared to the current dataset (right half)."

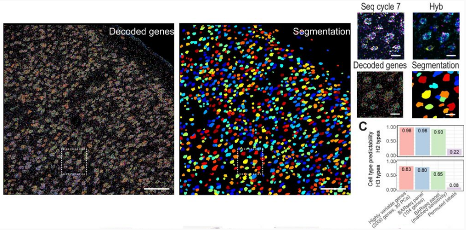
X. Chen et al. *Whole-cortex in situ sequencing reveals input-dependent area identity*. Nature, 2014.

- **Goal:** Automate the comparison and quantify similarity across data modalities.
- **Idea:** Embed all data types (transcriptomics and atlases) into a shared (kernel) varifold space for unified analysis.

A **single read** is a Dirac mass in a product space (location, feature) at:

- location: $x \in \mathbb{R}^d$. Typically $d = 2, 3$
- feature distribution: $wp \in \mathcal{M}(F)$, where $w \geq 0$ is a weight and p is a probability distribution over feature space F. Typically $F = \mathcal{F}, \mathcal{L}$.

- **BARseq**: $\mathcal{F}$ is the set of cell type ($|\mathcal{F}| \sim 30$)
  - w is total cells at location x
  - $p \in \mathcal{M}(\mathcal{F})$ is the probability distribution on cell type.



Generic varifold framework

A **single read** is a Dirac mass in a product space (location, feature) at:

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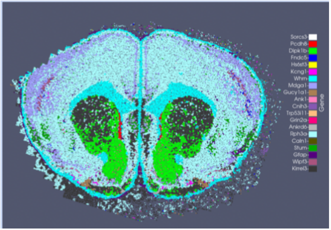
- MERFISH: $\mathcal{F}$ is the set of gene type ($|\mathcal{F}| \sim 700$)
  - w is total mRNA at location x,
  - $p \in \mathcal{M}(\mathcal{F})$ is the probability distribution on gene.



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- **CCFv3 atlas**: $\mathcal{L}$ ontology labels
  - $w = 1$ for location x in foreground tissue
  - $p = \delta_{\ell_x} \in \mathcal{M}(\mathcal{L})$ is the dirac probability distribution on ontology label at the label ℓ_x of x (with $|\mathcal{L}| \sim 500$).

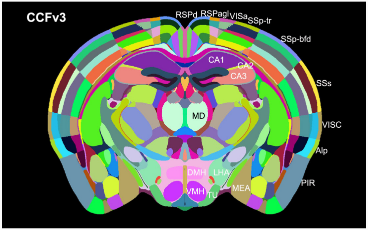


Image varifold framework

- **Image Varifold:**Full acquisition is a linear combination of Dirac indexed by $i \in I$:

$$\mu = \sum_{i \in I} \delta_{x_i} \otimes w_i p_i.$$

  with varifold norm

$$\langle \mu, \mu \rangle_M = \sum_{i,j \in I} w_i w_j K_\sigma(x_i, x_j) \sum_{f,g \in \mathcal{F}} K_F(f,g) p_i(f) p_j(g).$$

  where K_σ is spatial kernel (Gaussian), K_F is a def pos matrix (identity)
- **Computational intensity:** Depending on application we have:
  - $|I| \sim 10^4, 10^5, 10^6, 10^7$ (resolution)
  - $|\mathcal{F}|, |\mathcal{L}| \sim 10, 100, 1000$ (feature size)

  Resampling adjust data resolution to kernel bandwidth
- **Cross modality:** allow us to define distance between objects in the same varifold space. But what's happened when the feature spaces are different ?

Offline Scale-Space Resampling

The full resolution acquisition is $\mu = \sum_{i \in I} \delta_{x_i} \otimes w_i p_i$.

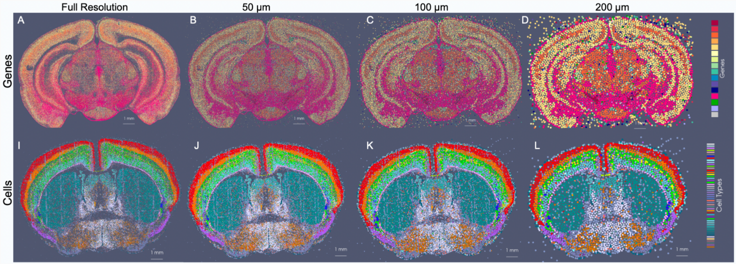
- **Series of scales:** Let $\sigma_1 = 200\,\mu m > \sigma_2 = 100\,\mu m > \sigma_3 = 50\,\mu m > \dots$ and

$$\mu_\sigma = \sum_{i \in I_\sigma} \delta_{x_i} \otimes w_i p_i, \ \{x_i, i \in I_\sigma\}, \text{ for } \sigma = \sigma_1, \sigma_2, \dots$$

- **Closest approximation** in varifold norm. Each μ_σ is defined by

$$\min_{x_i, w_i, p_i, i \in I_\sigma} \|\mu_\sigma - \mu\|_M$$

- **Practical problem:** μ do not fit in GPU memory (tiled optimization procedure).



Single modality Registration

Source and target: MERFISH with location and gene type $\mathcal{F}$ at molecular scale (feature)

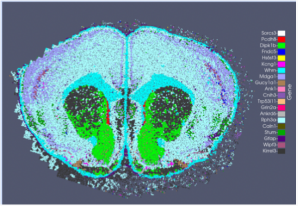
Single modality Registration

Source and target: MERFISH with location and gene type $\mathcal{F}$ at molecular scale (feature)

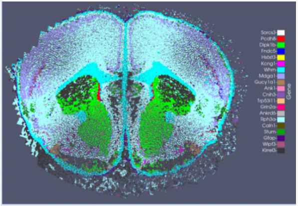
The single modality spatial deformation $\varphi : \mathbb{R}^d \to \mathbb{R}^d$ acts as

$$\varphi \cdot \mu = \sum_{i \in I} \delta_{\varphi(x_i)} \otimes \left(|D\varphi|_{x_i} w_i \right) p_i,$$

where determinant of the Jacobian capture expansion/contraction.



μ



$\varphi \cdot \mu$

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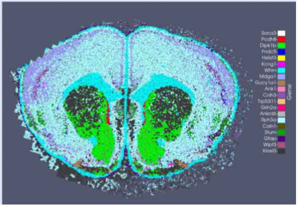
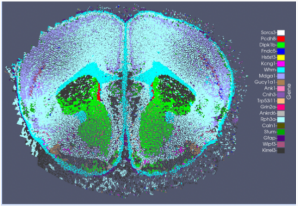


μ



$\varphi \cdot \mu$

Minimize $pen(\varphi) + \|\varphi \cdot \mu_{Source} - \mu_{Target}\|_M^2$ with respect to

- Spatial correspondence: $\varphi : \mathbb{R}^d \to \mathbb{R}^d$, an affine motion and diffeomorphism of $\mathbb{R}^d$
- Hamiltonian formulation (Geodesic shooting) is adapted to update the weight

Cross modality Registration

Source: Atlas with location and atlas ontology $\mathcal{L}$ at tissue scale (feature)

Target: MERFISH with location and gene type $\mathcal{F}$ at molecular scale (feature)

Spatial homogeneity assumption: there exists a (latent) dictionary $(\pi_\ell)_{\ell \in \mathcal{L}}$ where each $\pi_\ell \in \mathcal{M}(\mathcal{F})$.

Cross modality Registration

Source: Atlas with location and atlas ontology $\mathcal{L}$ at tissue scale (feature)

Target: MERFISH with location and gene type $\mathcal{F}$ at molecular scale (feature)

Spatial homogeneity assumption: there exists a (latent) dictionary $(\pi_\ell)_{\ell\in\mathcal{L}}$ where each $\pi_\ell \in \mathcal{M}(\mathcal{F})$.

The *cross modality spatial deformation* (φ, π) acts as

$$(\varphi, \pi) \cdot \mu^A = (\varphi, \pi) \cdot \sum_{i\in I^A} \delta_{x_i} \otimes \underbrace{w_i^A p_i^A}_{\in\mathcal{M}(\mathcal{L})}$$

Remember that since μ^A is an atlas, $w_i^A = 1$ and p_i is a Dirac at ℓ_{x_i} ("one hot").

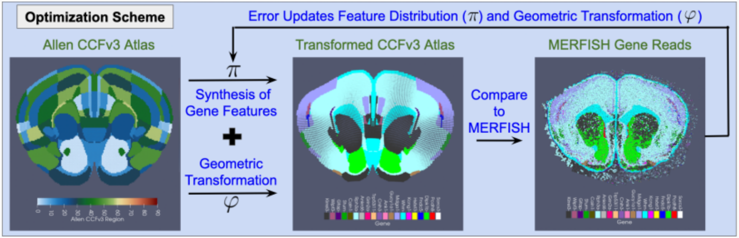
$$\begin{aligned}(\varphi, \pi) \cdot \mu^A &\doteq \varphi \cdot \sum_{i\in I^A} \delta_{x_i} \otimes \underbrace{\pi_{\ell_{x_i}}}_{\in\mathcal{M}(\mathcal{F})} \\ &= \sum_{i\in I} \delta_{\varphi(x_i)} \otimes \underbrace{|D\varphi|_{x_i} \pi_{\ell_{x_i}}}_{\in\mathcal{M}(\mathcal{F})} .\end{aligned}$$

where determinant of the Jacobian capture expansion/contraction.

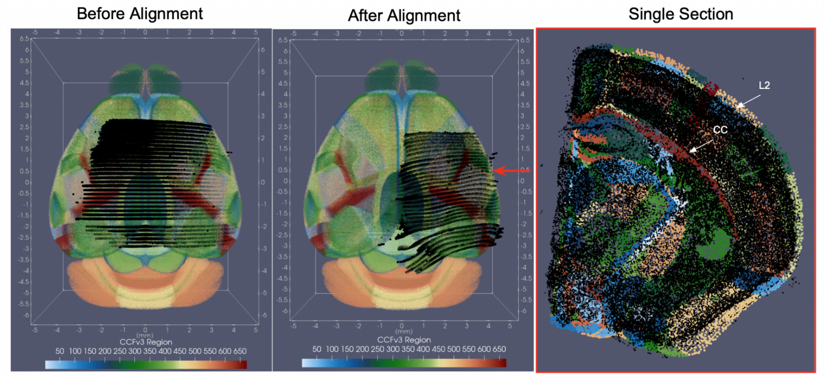
Warning: notation switch between the 2 papers...

Minimize $pen(\varphi) + pen(\pi) + \|(\varphi, \pi) \cdot \mu^A - \mu^{Target}\|_M^2$ with respect to

- Spatial correspondence: $\varphi : \mathbb{R}^d \to \mathbb{R}^d$, an affine motion and diffeomorphism of $\mathbb{R}^d$
- Feature correspondence: $(\pi_\ell)_{\ell \in \mathcal{L}}$ where each $\pi_\ell \in \mathcal{M}(\mathcal{F})$ is a (latent) distribution over $\mathcal{F}$ which should be similar to the $w_i p_i$'s (of the target) in region ℓ.
- KL penalty: $pen(\pi_\ell) = \frac{M_\ell^A}{\sum_{f \in \mathcal{F}} M_f^{Target}} \sum_{f \in \mathcal{F}} \pi_\ell(f) \log\left(\frac{\bar{\pi}_\ell(f)}{1/|\mathcal{F}|}\right)$ where M_ℓ^A (resp. M_f^{Target}) is total mass in region ℓ (resp. feature f), $\bar{\pi}_\ell(f) \doteq \frac{\pi_\ell(f)}{\sum_{f \in \mathcal{F}} \pi_\ell(f)}$.

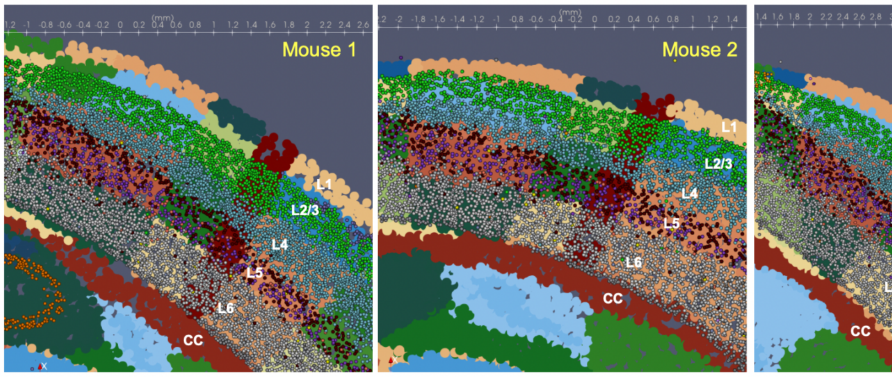


CCFv3 and BARseq: Global Geometric Alignment



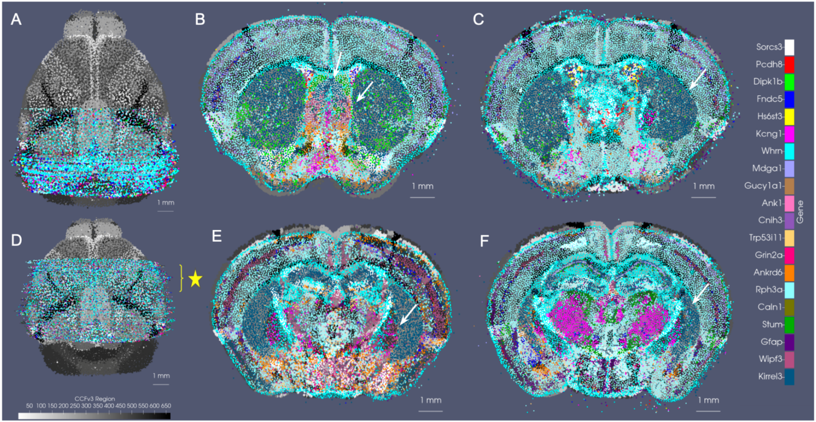
- Black dots: $\sim$ 30 coronal hemi-sections of BARseq spatial transcriptomics data
- Regions denoted by color CCFv3
- Good overlap of low cell density area (BARseq) with CCFv3 corpus callosum (CC), and layer 2/3 cells (BARseq) with CCFv3 layer 2/3.

CCFv3 and BARseq: : Local Geometric Alignment



- Small spheres: BARseq cell center colored according to layer-specific cell type (L2/3 (green), L4/5 (blue), L5 (purple), L6 (grey))
- Plain circles color: CCFv3 Region
- Boundaries between cell types align to cortical layer delineations in the CCFv3, and both corpus callosum (CC) and layer 1 (L1) accurately align with low cell density areas.

CCFv3 and MERFISH



20 selected variable genes. Resolution is 200μm