A Graph Coupling View of Dimension Reduction

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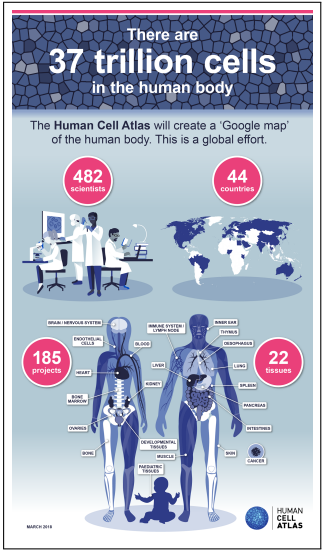
Institut de Mathématiques de Toulouse, October 2022

Outline

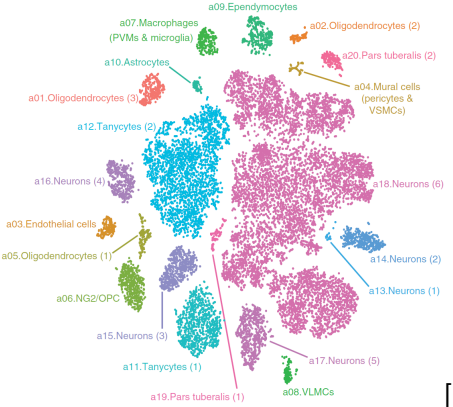
The Single-Cell Revolution

- Cells are the basic unit of living organisms
- Recent technological breakthroughs allow the molecular characterization of cells
- Describe cell population with high dimensional molecular features



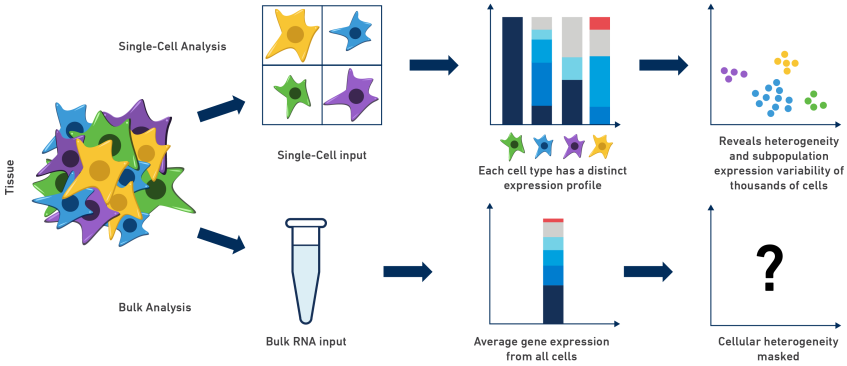
Cell biology goes genome-wide

- Investigate shapes, locations, interactions, functions of cell types
- Classify cells into distinct cell types
- Account for the between-cell variability and heterogeneities



[1]

Single-Cell from a statistician's perspective



From 10X Genomics

An unprecedented challenge

- Genomics was precursor for data representation and visualization

Publication	cells	tissue	Seq. protocol	clusters
Cadwell et al. (2016)	46	visual cortex	Smart-seq2	2
Tasic et al. (2016)	1,679	visual cortex	SMARTer	49
Macosko et al. (2015)	44,808	retina	Drop-seq	39
10x Genomics	1,306,127	brain cells	10x Gen.Chrom.	39

- Dimension reduction is mandatory for any analysis (clustering, visualization, Regulatory networks inference, etc)

High-dimensional count data

$$x_{ij} = \text{expression of gene } j \text{ in cell } i$$

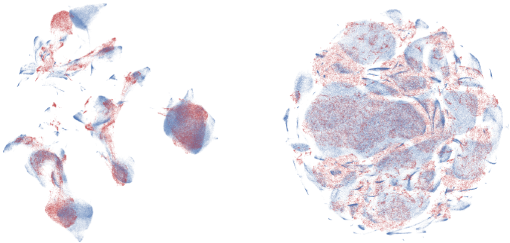
$$\mathbf{X}_{n\times p} = \begin{array}{c} \left[\begin{array}{ccccccc} & & & & & & \\ \hline & & & x_{ij} & & & \\ \hline & & & & & & \end{array}\right] \begin{array}{c} 1 \\ \vdots \\ n \end{array} \Bigg\} \text{cells} \\ \underbrace{\begin{array}{cccccc} 1 & \dots & \dots & \dots & \dots & p \end{array}}_{\text{genes}} \end{array}$$

- **High dimension:** n grows but $\ll p$ & **Big Data:** n and p grow
- **Count data** with ove-rdispersion and excess of zeros

Outline

Beyond Linear methods

- Linear methods like PCA are robust but badly shaped for complex geometries
- High-dim. datas are characterized by multiscale properties (local / global structures)
- Non-Linear projection methods aim at preserving local characteristics of distances
- Many proposed methods such as LargeVis, tSNE, UMAP



(a) UMAP (b) t-SNE

from [3]

Stochastic Neighbor Embedding (SNE) [4]

- $(X_1, \ldots, X_n)$ are the points in the high-dimensional space $\mathbb{R}^p$,
- Consider a similarity between points:

$$p_{i|j} = \frac{\exp(-\|X_i - X_j\|^2/2\sigma_i^2)}{\sum_{\ell \neq i} \exp(-\|X_\ell - X_j\|^2/2\sigma_\ell^2)}$$

- Further symmetrized

$$p_{ij} = (p_{i|j} + p_{j|i})/2N$$

- Hyper-parameter σ_i locally smooths the data, to be tuned
- Linked to the regularity of the target manifold

tSNE and Student / Cauchy kernels

- Consider $(Z_1, \ldots, Z_n)$ are points in the low-dimensional space $\mathbb{R}^2$
- Consider a similarity between points in the new representation:

$$q_{i|j} = \frac{\exp(-\|Z_i - Z_j\|^2)}{\sum_{\ell \neq i} \exp(-\|Z_\ell - Z_j\|^2)}$$

- Robustify this kernel by using Student(1) kernels (ie Cauchy)

$$q_{i|j} = \frac{(1 + \|Z_i - Z_j\|^2)^{-1}}{\sum_{\ell \neq i} (1 + \|Z_i - Z_\ell\|^2)^{-1}}$$

Optimizing tSNE by Gradient descent

- Minimize the KL between p and q to find $Z \in \mathbb{R}^2$ such that:

$$C(Z) = \sum_{ij} KL(p_{ij}, q_{ij})$$

$$\left[\frac{\partial C(Z)}{\partial Z}\right]_i = \sum_j (p_{ij} - q_{ij})(Z_i - Z_j)$$

- Gradient update (adaptive learning rate η)

$$Z^{(t)} = Z^{(t-1)} + \eta \frac{\partial C(Z)}{\partial Z} + \alpha(t)(Z^{(t-1)} - Z^{(t-2)})$$

- $\alpha(t)$ momentum to speed up and improve convergence
- Initialization $Z_i^{(0)} \sim \mathcal{N}(0, \delta I)$, δ small.

Uniform Manifold Approximation and Projection [3]

$$\forall (i,j) \in [n]^2, \quad p_{j|i} = \exp\left(-\frac{\|X_i - X_j\|_2^2 - \rho_i}{\sigma_i}\right)$$

with $\rho_i = \min_{j \neq i} \|X_i - X_j\|^2$. Let us define

$$p_{ij} = p_{j|i} + p_{i|j} - p_{j|i} p_{i|j}$$

and:

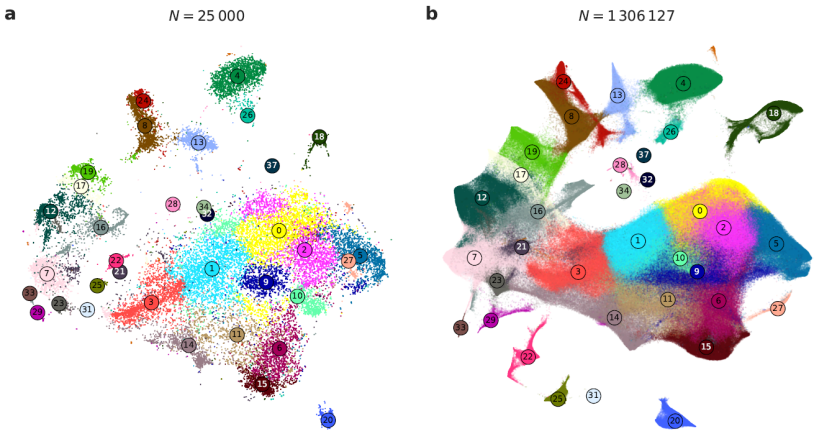
$$\forall (i,j) \in [n]^2, \quad q_{ij} = \left(1 + a\|X_i - X_j\|_2^{2b}\right)^{-1}$$

UMAP solves the following problem:

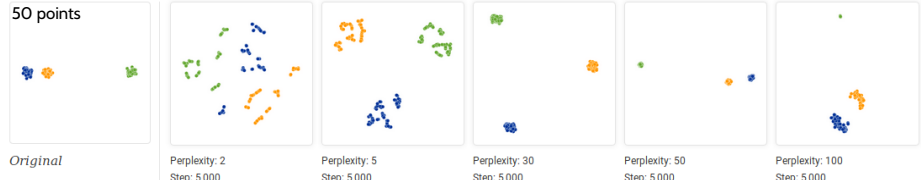
$$\min_{Z \in \mathbb{R}^{n \times d}} \quad -\sum_{i<j} p_{ij} \log q_{ij} + (1 - p_{ij}) \log(1 - q_{ij})$$

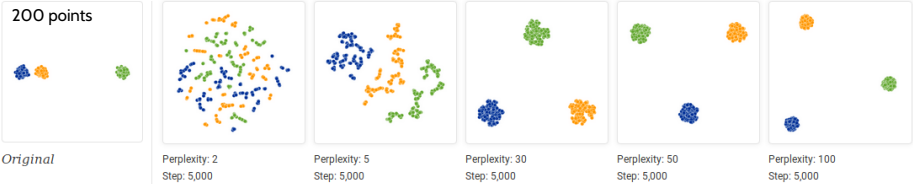
Outline

tSNE on single cell Gene Expression data [2]

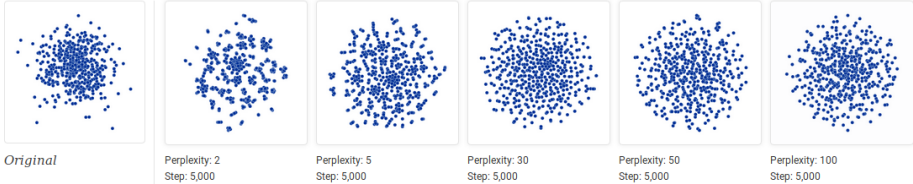


tSNE does not account for between-cluster distance

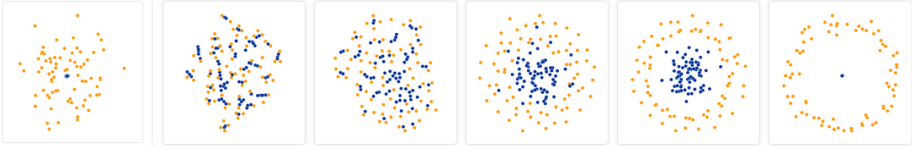




What about random noise ?



Catching Complex Geometries



Original

Perplexity: 2
Step: 5,000

Perplexity: 5
Step: 5,000

Perplexity: 30
Step: 5,000

Perplexity: 50
Step: 5,000

Perplexity: 100
Step: 5,000

Original

Perplexity: 2
Step: 5,000

Perplexity: 5
Step: 5,000

Perplexity: 30
Step: 5,000

Perplexity: 50
Step: 5,000

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Original

Perplexity: 2
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Perplexity: 5
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Perplexity: 30
Step: 5,000

Perplexity: 50
Step: 5,000

Perplexity: 100
Step: 5,000

Properties of t-SNE

- Good at preserving local distances (intra-cluster variance)
- Not so good for global representation (inter-cluster variance)
- Good at creating clusters of points that are close, but bad at positioning clusters wrt each other
- Does not handle well high dimensional data (preliminary PCA and feature selection)
- Sensistive to the calibration of the hyperparameter (smoothing)
- Reproducibility of results due to stochastic optimization

$\rightarrow$ What are the statistical / probabilistic foundations of Stochastic Neighbor Embedding ?

Outline

Hidden Graph to structure observations

- Consider W the adjacency matrix of a hidden random graph
- The graph Laplacian operator is the map L such that for $(i,j) \in [n]^2$:

$$L(W)_{ij} = \begin{cases} -W_{ij} & \text{if } i \neq j \\ \sum_{k\in[n]} W_{ik} & \text{otherwise .} \end{cases}$$

- $L = L(W)$ has the following property:

$$\forall X \in \mathbb{R}^{n\times p}, \quad \sum_{i,j} W_{ij}\|X_i - X_j\|^2 = \mathrm{tr}(X^T L X).$$

- In a first step, consider a graph with one connected component

Conditional distribution of X on a graph W_X

- Consider a Matrix Normal model with row and column dependencies

$$X \mid W_X \sim \mathcal{MN}\left(0, L_X^{-1}, \Sigma^{-1}\right),$$

- L_X^{-1} between-cell correlation, Σ^{-1} between-genes correlation.
- The conditional density relates to the Gaussian kernel

$$k(X_i - X_j) = \exp\left(-\frac{1}{2}\|X_i - X_j\|_\Sigma^2\right),$$

- Which can be generalized to translation invariant kernels:

$$\mathbb{P}(X \mid W_X) \quad \propto \quad \prod_{(i,j)\in[n]^2} k(X_i - X_j)^{W_{X,ij}} .$$

Conditional distribution of Z on a graph W_Z

- Consider that the low-dimensional representation is also structured according to a graph

$$Z \mid W_Z \sim \mathcal{MN}\left(0, L_Z^{-1}, I_q\right),$$

- Consider the Gaussian kernel for Z

$$k(Z_i - Z_j) = \exp\left(-\frac{1}{2}\|Z_i - Z_j\|_{I_q}^2\right),$$

- Conditional distribution of $Z \mid W_Z$:

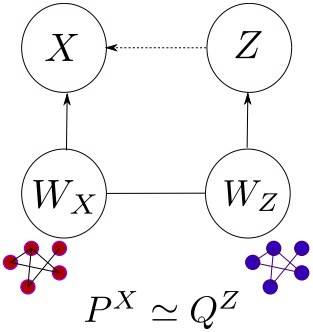
$$\mathbb{P}(Z \mid W_Z) \quad \propto \quad \prod_{(i,j)\in[n]^2} k(Z_i - Z_j)^{W_{Z,ij}}$$

Embedding with Graph Coupling

- Consider two hidden graphs W_X and W_Z
- Couple W_X with W_Z in a probabilistic way
- Match their posterior distributions

$$
\begin{aligned}
P^X &= \mathbb{P}(W_X \mid X) \\
Q^Z &= \mathbb{P}(W_Z \mid X; Z)
\end{aligned}
$$

- Z becomes a parameter to be estimated



Probabilistic Coupling

Graph Coupling with Z as a parameter

- Consider the cross entropy between posteriors

$$\mathcal{H}\big(P^X, Q^Z\big) = -\mathbb{E}_{W_X \sim P^X}\Big(\log \mathbb{P}(W_Z = W_X \mid X; Z)\Big)$$

- Find the best low-dimensional representation such that the two graphs match

$$Z(X) \quad = \quad \arg\min_Z \Big\{\mathcal{H}\big(P^X, Q^Z\big)\Big\}$$

- Connection with the KL between posteriors

$$\mathrm{KL}\big(P^X, Q^Z\big) = \mathcal{H}\big(P^X, Q^Z\big) - \mathcal{H}\big(P^X, P^X\big)$$

First Outline

Done...

- Consider two hidden random graphs W_X, W_Z
- Define a conditional model $X \mid W_X, Z \mid W_Z$
- Consider pairwise similarity distributions (Pairwise Markov Random Field)
- Find Z by matching the posteriors using a cross entropy criterion

...to be done :

- Define/Construct the priors for W_X, W_Z
- Deduce/Induce the posteriors for W_X, W_Z
- Carefully inspect the case with more than one connected component

Outline

Construction of conjugate priors for hidden graphs

- Consider a prior distribution for the hidden graph in the general form ($\alpha = 0$ later on)

$$\mathbb{P}_{\mathcal{P}}(W;\pi) \propto \mathcal{C}_k(W)^{\alpha}\, \Omega_{\mathcal{P}}(W) \prod_{(i,j)\in[n]^2} \pi_{ij}^{W_{ij}}$$

- $\mathcal{P}$ stands for a family of priors s.t:

$\mathcal{P}$		$\Omega_{\mathcal{P}}(W)$	Prior for W
$\mathcal{B}$	Bernoulli	$\prod_{ij} 1_{W_{ij}\leq 1}$	$\mathcal{B}\left(\frac{\pi_{ij}}{1+\pi_{ij}}\right)$
$\mathcal{D}$	Unitary Fixed degree	$\prod_{i} 1_{W_{i+}=1}$	$\mathcal{M}\left(1, \frac{\pi_i}{\pi_{i+}}\right)$
$\mathcal{E}$	Fixed Number of edges	$\prod_{ij}(W_{ij}!)^{-1}$	$\mathcal{M}\left(n, \frac{\pi}{\pi_{++}}\right)$

Deducing the limit posterior for hidden graphs

- We show that the posterior distribution $\mathbb{P}_{\mathcal{P}}(W \mid X; \pi, k)$ converge to (details later)

$\mathcal{P}$		Approximate Posterior for W
$\mathcal{B}$	Bernoulli	$\mathcal{B}\left(\frac{\pi_{ij}k_{ij}}{1+\pi_{ij}k_{ij}}\right)$
$\mathcal{D}$	Unitary Fixed degree	$\mathcal{M}\left(1, \frac{[\pi k]_i}{[\pi k]_{i+}}\right)$
$\mathcal{E}$	Fixed Number of edges	$\mathcal{M}\left(n, \frac{\pi k}{[\pi k]_{++}}\right)$

- $\pi_{ij}k_{ij} = \pi_{ij}k(X_i - X_j)$ is the posterior strength of edges (normalized or not)

Mixing Prior distributions for coupling

- Priors for W_X and W_Z induce the approximate posteriors

$$\mathbb{P}_{\mathcal{P}_X}(W_X \mid X; \pi_X, k_X) = P^{\mathcal{P}_X}$$

$$\mathbb{P}_{\mathcal{P}_Z}(W_Z \mid X; \pi_Z, k_Z) = Q^{\mathcal{P}_Z}$$

- Match the approximate posteriors

$$\mathcal{H}\big(P^{\mathcal{P}_X}, Q^{\mathcal{P}_Z}\big) = -\mathbb{E}_{W_X \sim P^{\mathcal{P}_X}}\left\{ \log \mathbb{P}_{\mathcal{P}_Z}(W_Z = W_X; \pi_Z, k_Z) \right\}$$

Model based Stochastic Neighbor Embedding

- Choosing $\mathcal{P}_X = \mathcal{P}_Z = \mathcal{D}$:

$$\mathcal{H}_{D,D} = -\sum_{i \neq j} P_{ij}^D \log Q_{ij}^D \ .$$

$$P_{ij}^D = \frac{\pi_{ij} k(X_i - X_j)}{\sum_{\ell=1}^n \pi_{i\ell} k(X_i - X_\ell)}, \quad Q_{ij}^D = \frac{\pi_{ij} k(Z_i - Z_j)}{\sum_{\ell=1}^n \pi_{i\ell} k(Z_i - Z_\ell)}.$$

- We defined the generative model for SNE !
- Can be generalized to symmetric graphs

Model based UMAP [3]

- Choose $\mathcal{P}_X = \mathcal{P}_Z = \mathcal{B}$ and define the symmetrized graph

$$\widetilde{W}_X = 1_{W_X + W_X^T \geq 1}$$

- By independence of the symmetrized edges,

$$\widetilde{W}_{X,ij} \sim \mathcal{B}\left(\widetilde{P}_{ij}^B\right) \quad \text{with} \quad \widetilde{P}_{ij}^B = P_{ij}^B + P_{ji}^B - P_{ij}^B P_{ji}^B$$

- Coupling $\widetilde{W}_X$ and W_Z gives:

$$\mathcal{H}_{\widetilde{B},B} = -2 \sum_{i<j} \widetilde{P}_{ij}^B \log Q_{ij}^B + \left(1 - \widetilde{P}_{ij}^B\right) \log\left(1 - Q_{ij}^B\right)$$

General Approach for Graph Coupling

Algorithm	Input Similarity	Latent Similarity	Loss Function
SNE	$P^D_{ij} = \frac{k_x(X_i - X_j)}{\sum_\ell k_x(X_i - X_\ell)}$	$Q^D_{ij} = \frac{k_z(Z_i - Z_j)}{\sum_\ell k_z(Z_i - Z_\ell)}$	$-\sum_{i \neq j} P^D_{ij} \log Q^D_{ij}$
Sym-SNE	$\overline{P}^D_{ij} = P^D_{ij} + P^D_{ji}$	$Q^E_{ij} = \frac{k_z(Z_i - Z_j)}{\sum_{\ell,t} k_z(Z_\ell - Z_t)}$	$-\sum_{i<j} \overline{P}^D_{ij} \log Q^E_{ij}$
LargeVis	$\overline{P}^D_{ij} = P^D_{ij} + P^D_{ji}$	$Q^B_{ij} = \frac{k_z(Z_i - Z_j)}{1 + k_z(Z_i - Z_j)}$	$-\sum_{i<j} \overline{P}^D_{ij} \log Q^B_{ij} + \left(2 - \overline{P}^D_{ij}\right) \log(1 - Q^B_{ij})$
UMAP	$\widetilde{P}^B_{ij} = P^B_{ij} + P^B_{ji} - P^B_{ij} P^B_{ji}$	$Q^B_{ij} = \frac{k_z(Z_i - Z_j)}{1 + k_z(Z_i - Z_j)}$	$-\sum_{i<j} \widetilde{P}^B_{ij} \log Q^B_{ij} + \left(1 - \widetilde{P}^B_{ij}\right) \log(1 - Q^B_{ij})$

Second Outline

Done...

- Consider two hidden random graphs W_X, W_Z
- Define a conditional model $X \mid W_X, Z \mid W_Z$
- Consider pairwise similarity distributions (Pairwise Markov Random Field)
- Find Z by matching the posteriors using a cross entropy criterion
- Define/Construct the priors for W_X, W_Z
- Deduce/Induce the posteriors for W_X, W_Z

...to be done :

- Carefully inspect the case with more than one connected component

The model is not fully integrable

- Suppose the graph has R connected components of size $n_r = \mathrm{Card}(C_r)$.
- By the spectral theorem $L = U \Lambda U^T$ where $U = (U_1, ..., U_n)$ is orthogonal

$$\forall r \in \{1, \ldots, R\}, \quad \lambda_r = 0 \quad \text{and} \quad U_r = \left(n_r^{-1/2} 1_{i \in C_r} \right)_{i \in [n]}$$

- $(U_1, ..., U_R)$ is an orthogonal basis of $\ker(L)$
- The projection of X on $\ker(L)$ is the empirical mean by connected components

$$X_{M,i} = \frac{1}{n_r} \sum_{r \in [R]} \left\{ 1_{i \in C_r} \left(\sum_{\ell \in C_r} X_\ell \right) \right\}$$

- $\mathbb{P}(X \mid W_X)$ is not fully integrable on $\mathbb{R}^{n \times p}$ but only on $\ker(L)^\perp$

$$X - X_M : \text{relative position of points within CC}$$

Diffuse Conditional and Integrability

- To overcome the integrability issue, we introduce a distribution on CC means

$$\mathbb{P}(X \mid W_X) = \mathbb{P}(X_M \mid W_X) \times \mathbb{P}(X - X_M \mid W_X)$$

- We choose a distribution on CC means such that:

$$X_M|\Theta \sim \mathcal{MN}\left(0, \left[\varepsilon U_{1:R} \Theta U_{1:R}^T\right]^{-1}, \Sigma\right)$$

- When $\varepsilon \to 0$, the position of CCs is not informative anymore

Completed model and posterior computations

- Posterior computations are complex wrt to CC membership
- $\mathbb{P}_{\mathcal{P}}(W_X \mid X; \pi, k)$ can not be computed easily
- Taking $\varepsilon \to 0$ compensates for the uninformative diffuse conditional on X_M
- This full model at the limit allows to retrieve an approximate tractable posterior

Outline

Kernel calibration and Perplexity

- tSNE strongly depends on the calibration of the kernel

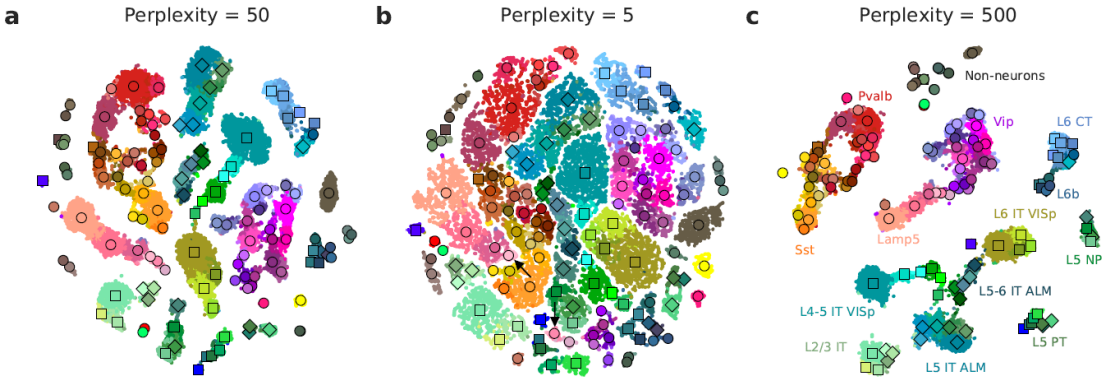
$$k(X_i - X_j; \sigma_i) = \exp\left(-\frac{1}{2\sigma_i}\|X_i - X_j\|_\Sigma^2\right),$$

- σ_i should adjust to local densities (neighborhood of point i)
- In practice, the method is tuned by fixing a given amount of entropy

$$H(p_i) = -\sum_{j=1}^{n} p_{ij} \log_2 p_{ij}$$

- Find σ_i such that $2^{H(p_i)} = \text{perp}$ (user defined)
- Interpreted as the smoothed effective number of neighbors.

Visual inspection of the influence of σ[2]



Back to the coupling strategy

- Maximizing the probability of coupling by minimizing the KL

$$\mathrm{KL}\big(P^X, Q^Z\big) = \mathcal{H}\big(P^X, Q^Z\big) - \mathcal{H}\big(P^X, P^X\big)$$

- $\mathcal{H}\big(P^X, P^X\big)$ is exactly the perplexity parameter
- Constrained coupling with a given degree of entropy

$$\begin{aligned} Z(X) &= \underset{Z, \mathcal{H}\left(P^X, P^X\right) = \mathrm{Perp}}{\arg\min} \left\{ \mathrm{KL}\big(P^X, Q^Z\big) \right\} \\ &= \arg \underset{Z, \mathcal{H}\left(P^X, P^X\right) = \mathrm{Perp}}{\min} \left\{ \mathcal{H}\big(P^X, Q^Z\big) - \mathrm{Perp} \right\} \end{aligned}$$

Perspectives

- The method is based on a preliminary smoothing of the data to retrieve a graph with controlled complexity
- This is related (how ?) to manifold learning and density estimation on manifolds
- The output $\widehat{Z}(X)$ strongly depends on this preliminary step

- Can we generalize the approach by matching arbitrary priors (power-law)
- Introduce clustering and spatial information in the framework

- How graph coupling could be restated in the RKHS ?

A Probabilistic Graph Coupling View of Dimension Reduction, van Assel, H. and Espinasse, T. and Chiquet, J. and Picard, F., NEURIPS 2022
`https://arxiv.org/pdf/2201.13053.pdf`

References

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