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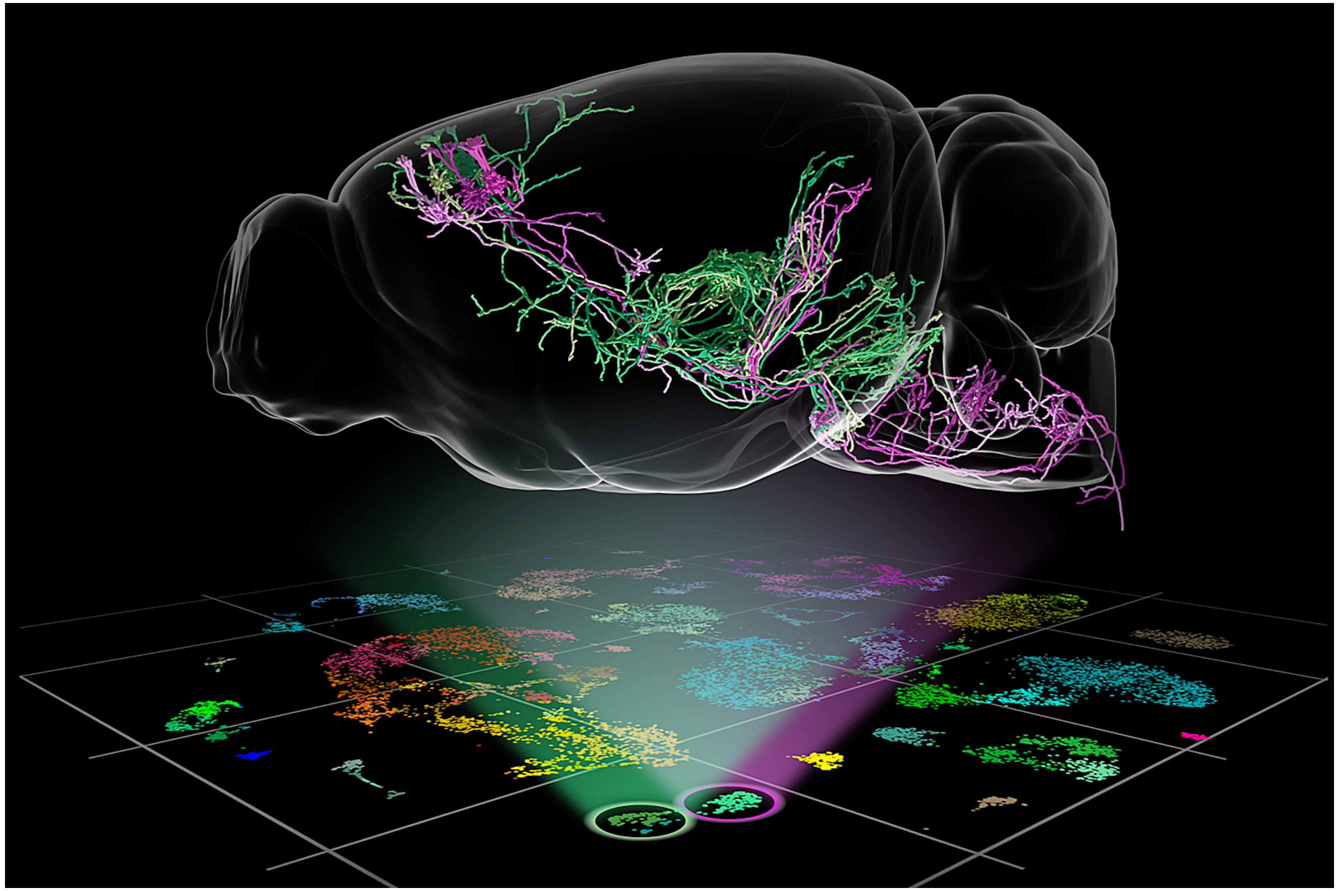
Joint identification of neuron types and type-specific activity-regulated genes with coupled autoencoders

04/12/2021

Yeganeh Marghi

Motivation

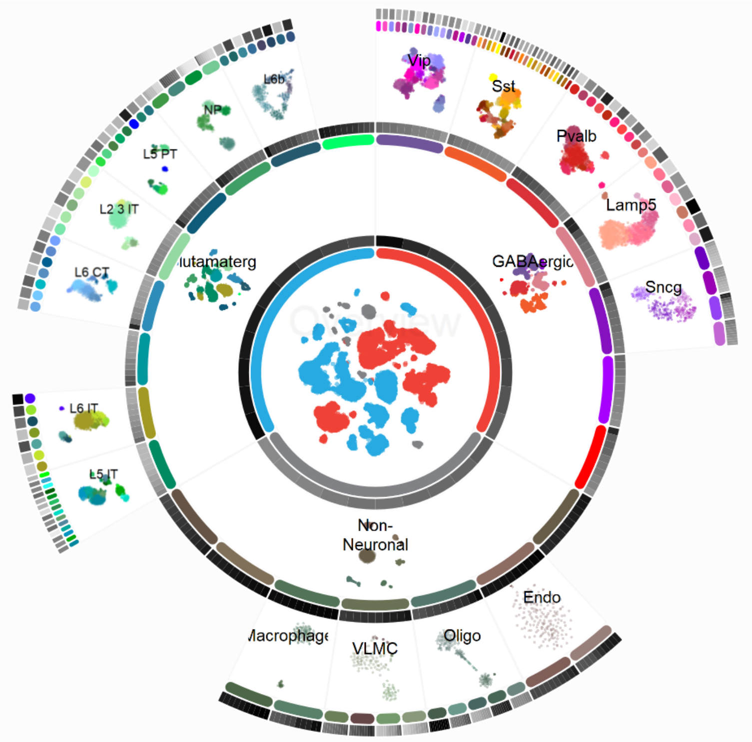
- From in-depth analysis of cells to understanding the brain
- Studying the whole brain at single-cell resolution by single-cell omics
- The potential to unravel the molecular programs underlying the cellular diversity



Allen Institute for Brain Science, Press releases, 2018.

Motivation

- From in-depth analysis of cells to understanding the brain
- Studying the whole brain at single-cell resolution by single-cell omics
- The potential to unravel the molecular programs underlying the cellular diversity
- Measurement noise and biological variation cause significant challenges

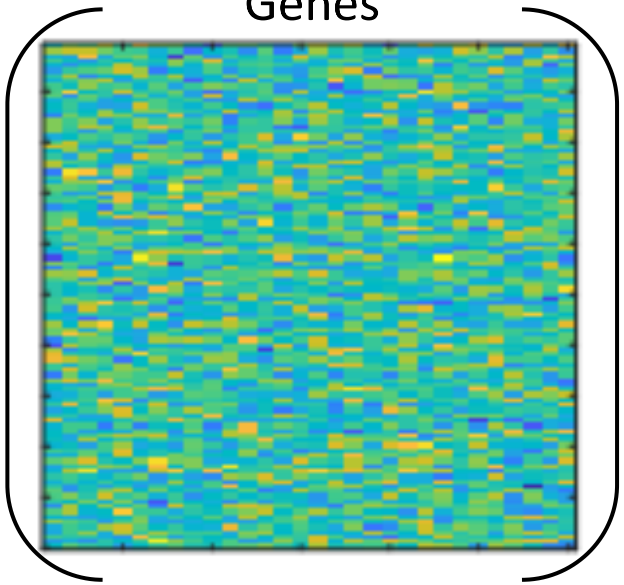


Allen Institute for Brain Science, Press releases, 2018.

X

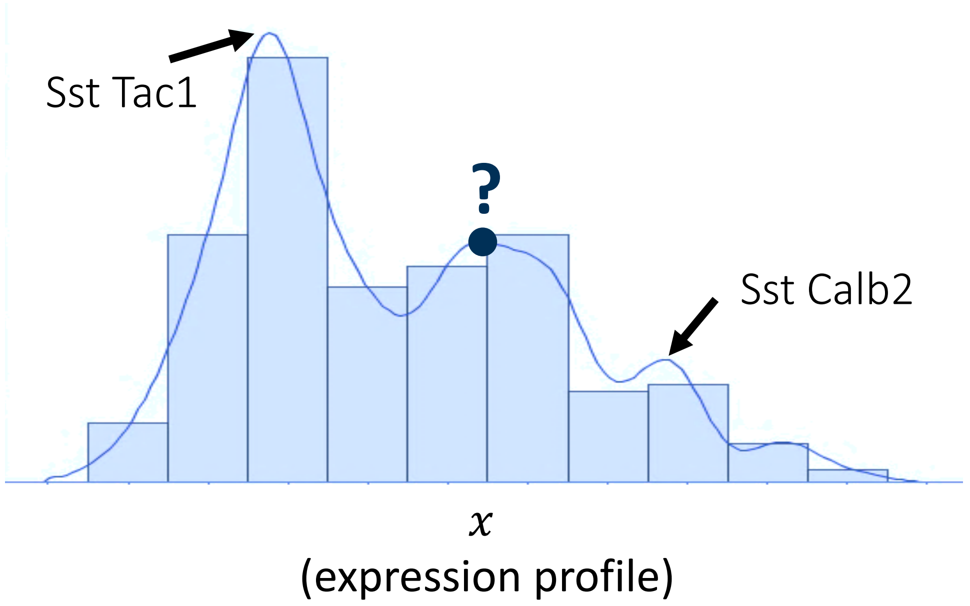
Genes

Cells



Single-cell data: a mixture landscape

Mixture models: measurement is a function of two (random) variables.

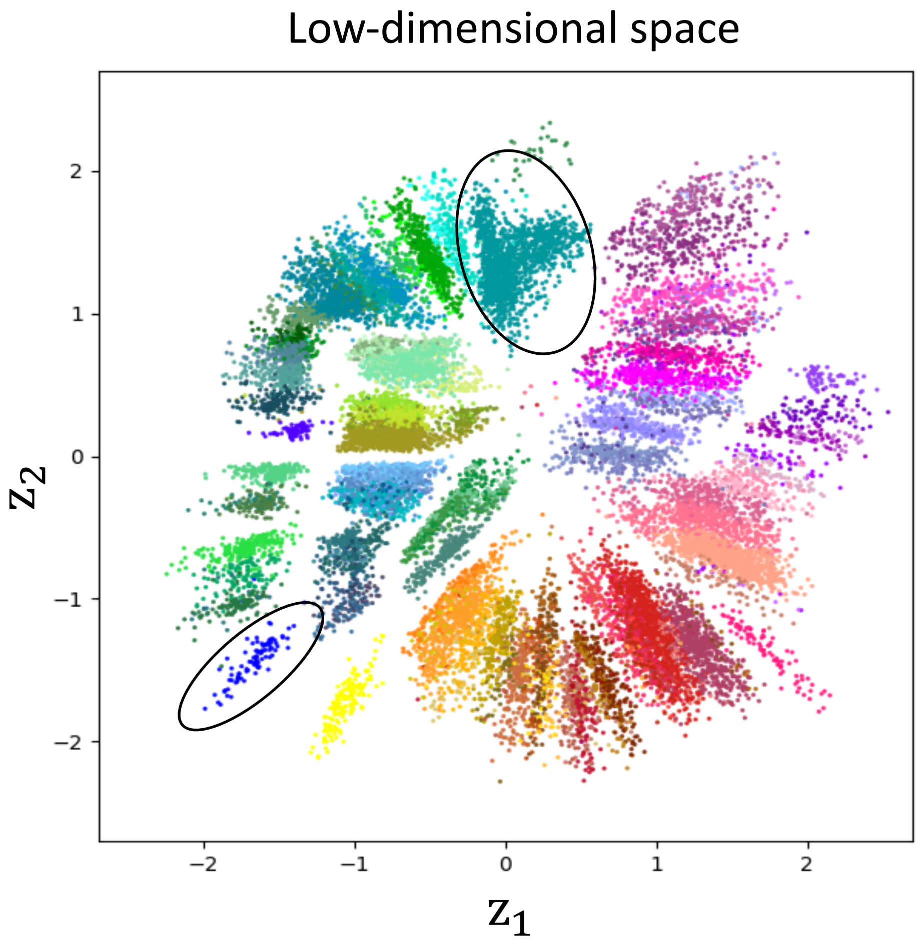


x: scRNA-seq data
c: cell type (discrete factor)
s: cell type-dependent variations (continuous factor)

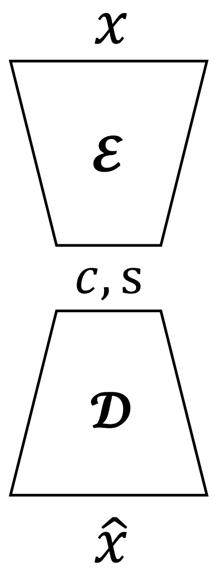
$$x = f(c, s)$$

Single-cell data: a mixture landscape

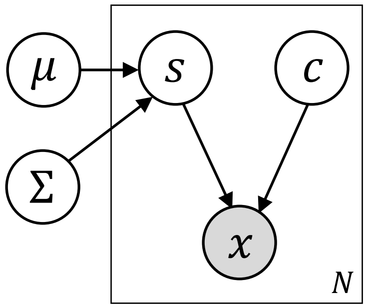
Mixture models: measurement is a function of two (random) variables.

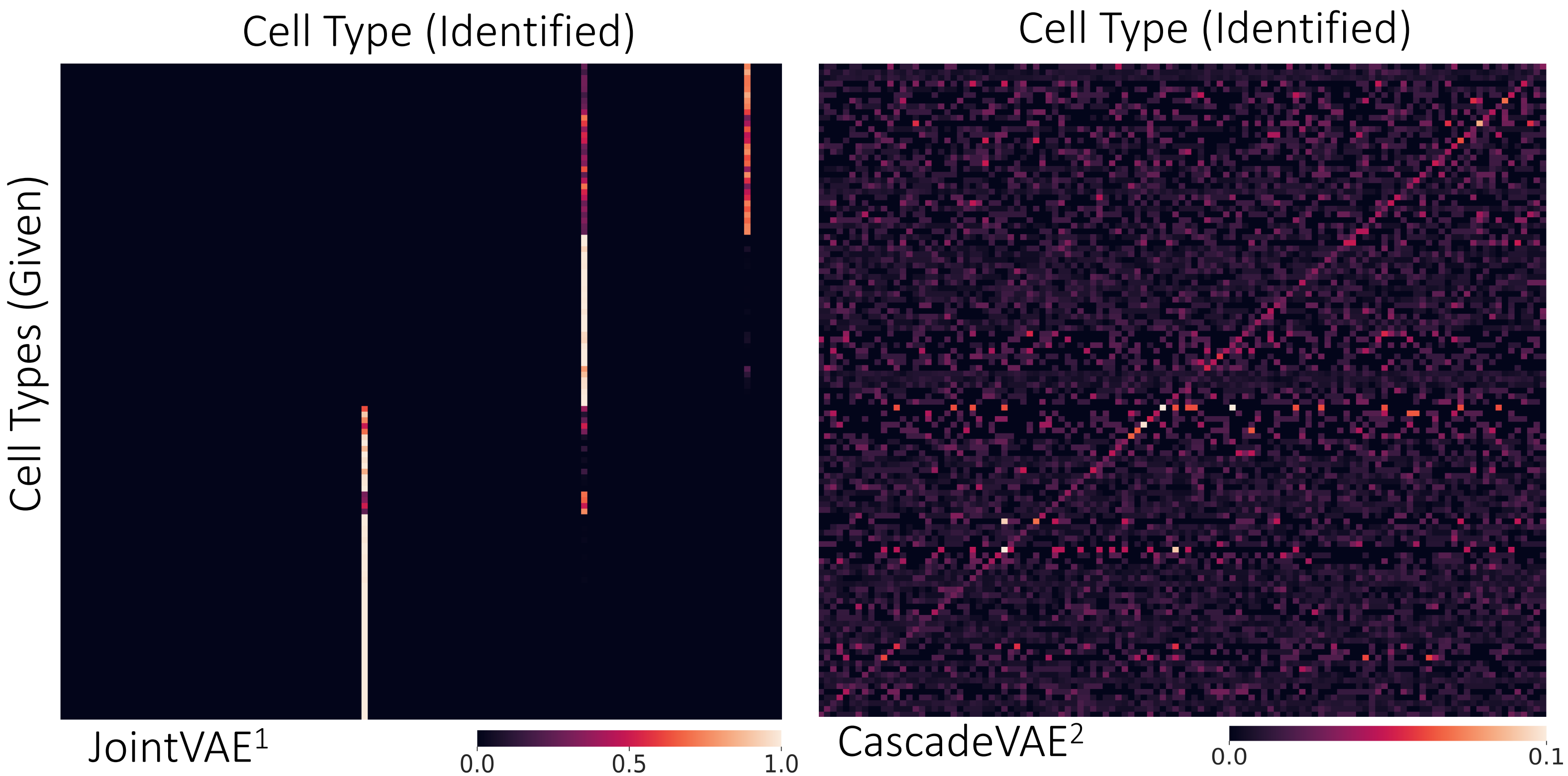


Mixture representation learning: variational approach



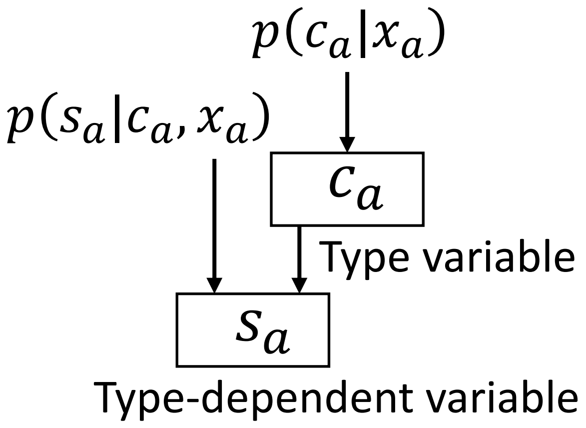
$$\mathcal{L}(\boldsymbol{\phi}, \boldsymbol{\theta}) = \mathbb{E}_{q_{\boldsymbol{\phi}}(\mathbf{s},\mathbf{c}|\mathbf{x})}\left[\log p_{\boldsymbol{\theta}}(\mathbf{x}|\mathbf{s},\mathbf{c})\right] - D_{KL}\left(q_{\boldsymbol{\phi}}(\mathbf{s}|\mathbf{x})\|p(\mathbf{s})\right) - D_{KL}\left(q_{\boldsymbol{\phi}}(\mathbf{c}|\mathbf{x})\|p(\mathbf{c})\right)$$

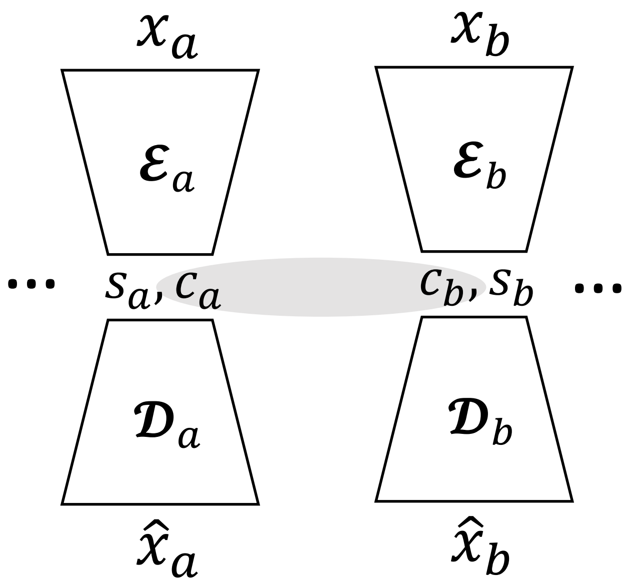


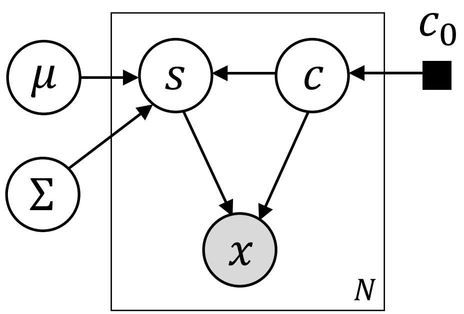


1. Dupont, Emilien. "Learning disentangled joint continuous and discrete representations." *NeurIPS*, 2018.
2. Jeong, Yeonwoo, and Hyun Oh Song. "Learning discrete and continuous factors of data via alternating disentanglement." ICML, 2019.

Mixture representation learning: variational approach





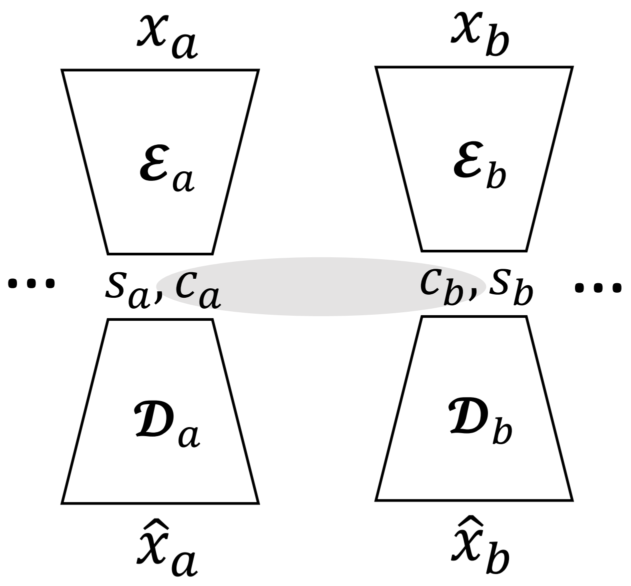


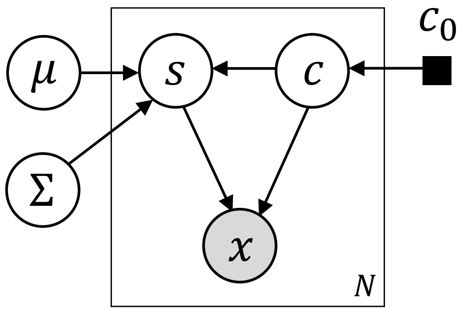
$$x_a = f(c_a, s_a)$$

$$f(c_a, s_a) = p(c_a)p(s_a|c_a)$$

c_a: cell type (discrete)
s_a: cell type-dependent variations (continuous)

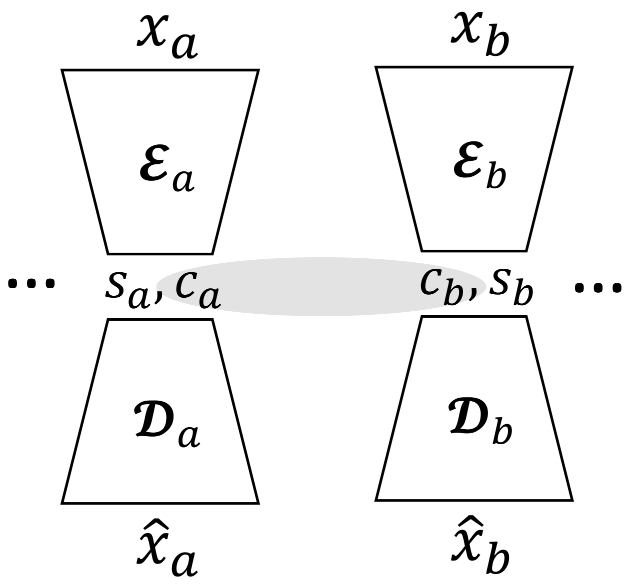
Coupled mixture VAE framework (cpl-mixVAE)

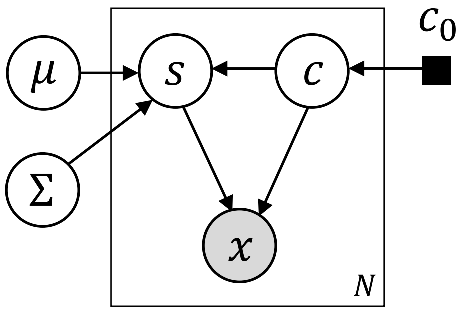




Objective function: $$\max \sum_{a=1}^{A} (A-1)\left(\mathbb{E}_{q(\mathbf{s}_a,\mathbf{c}_a|\mathbf{x}_a)}[\log p(\mathbf{x}_a|\mathbf{s}_a,\mathbf{c}_a)] - \mathbb{E}_{q(\mathbf{c}_a|\mathbf{x}_a)}[D_{KL}(q(\mathbf{s}_a|\mathbf{c}_a,\mathbf{x}_a)\|p(\mathbf{s}_a|\mathbf{c}_a))]\right)$$
$$-\sum_{a<b} \mathbb{E}_{q(\mathbf{s}_a|\mathbf{c}_a,\mathbf{x}_a)}\mathbb{E}_{q(\mathbf{s}_b|\mathbf{c}_b,\mathbf{x}_b)}[D_{KL}(q(\mathbf{c}_a|\mathbf{x}_a)q(\mathbf{c}_b|\mathbf{x}_b)\|p(\mathbf{c}_a,\mathbf{c}_b))]$$
$$\text{s.t. } \mathbf{c}_a = \mathbf{c}_b \quad \forall a,b \in [1,A],\ a<b$$

Coupled mixture VAE framework (cpl-mixVAE)





Objective function: $\max \sum_{a=1}^{A} \mathbb{E}_{q(\mathbf{s}_a, \mathbf{c}_a | \mathbf{x}_a)} \left[\log p(\mathbf{x}_a | \mathbf{s}_a, \mathbf{c}_a)\right] - \mathbb{E}_{q(\mathbf{c}_a | \mathbf{x}_a)} \left[D_{KL}\left(q(\mathbf{s}_a | \mathbf{c}_a, \mathbf{x}_a) \| p(\mathbf{s}_a | \mathbf{c}_a)\right)\right] + H(\mathbf{c}_a | \mathbf{x}_a)$

$$s.t.\ \mathbb{E}_{q(\mathbf{c}_a | \mathbf{x}_a)} \left[d^2(\mathbf{c}_a, \mathbf{c}_0)\right] < \epsilon$$

Coupled mixture VAE framework (cpl-mixVAE)

Proposition 1. *Consider the problem of mixture representation learning in a multi-arm VAE framework. For* $A > B \geq 1$ *and* $\forall m$,

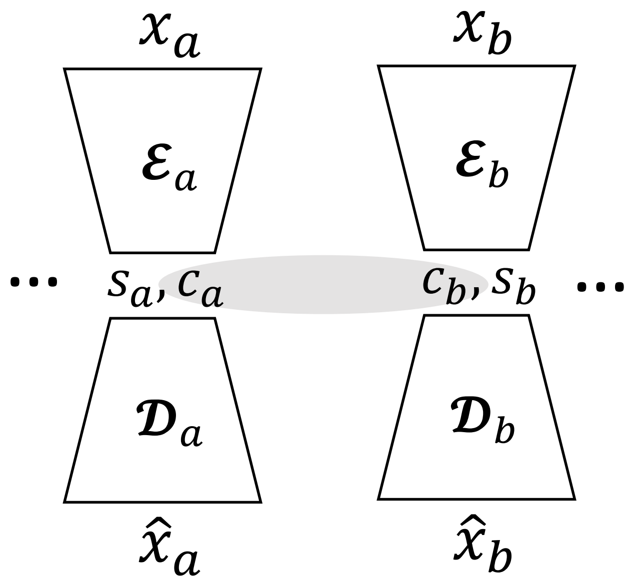
$$\mathcal{C}_m^A(m) > \mathcal{C}_m^B(m).$$

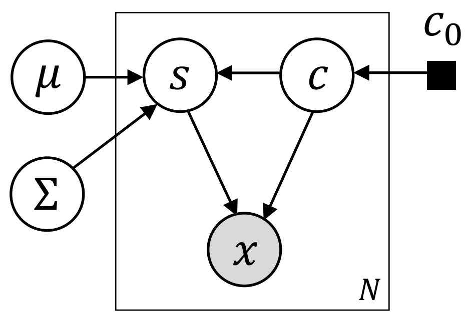
Proposition 2. *In the A-arm VAE framework, there exists an* A *such that* $\forall m, n,\ m \neq n$,

$$\mathcal{C}_m^A(m) > \mathcal{C}_m^A(n),$$

independent of the relative abundances of categories.

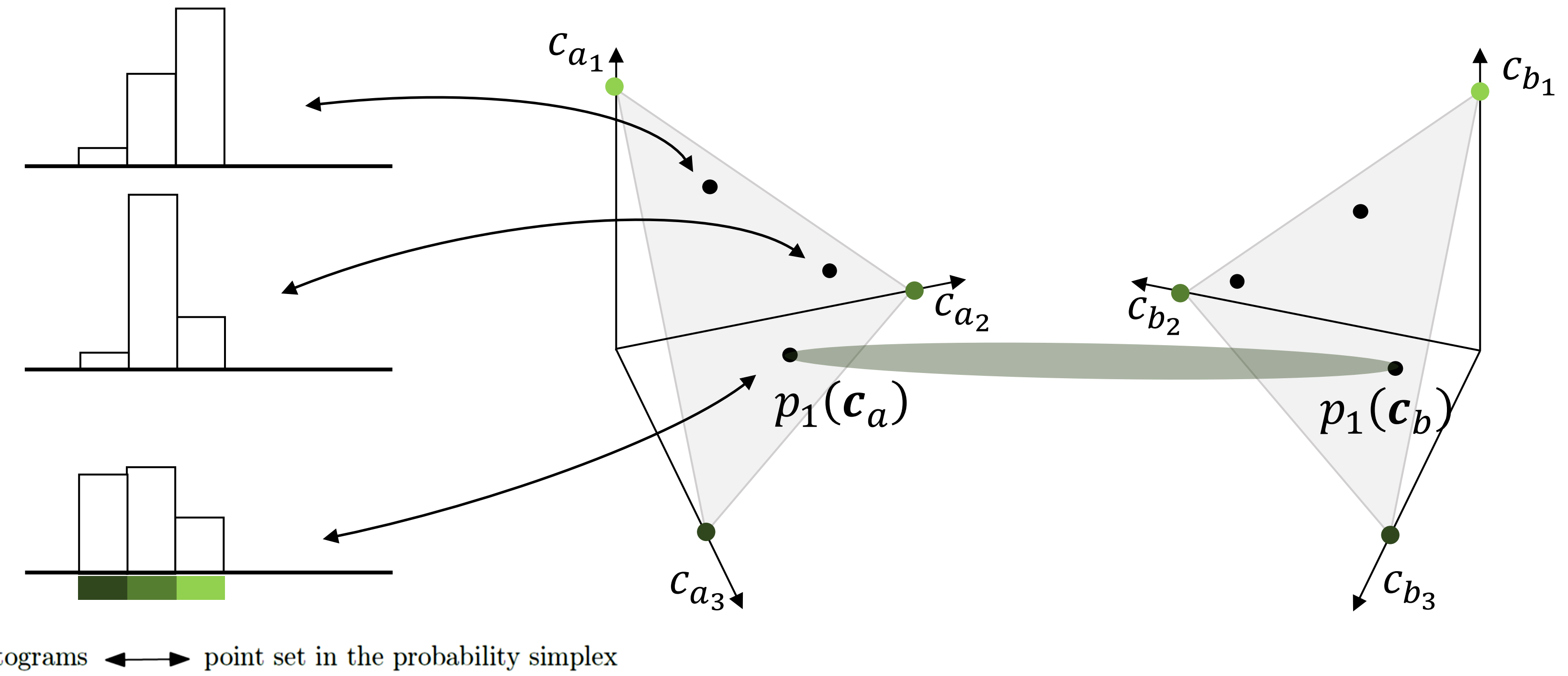
$$\mathcal{C}_m(k) = \mathbb{E}_{\mathbf{x}|m}\left[\log p(c = k|\mathbf{x})\right]$$





Marghi, Yeganeh M., Rohan Gala, and Uygar Sümbül. "Joint Learning of Discrete and Continuous Variability with Coupled Autoencoding Agents." *arXiv preprint arXiv:2007.09880* (2020).

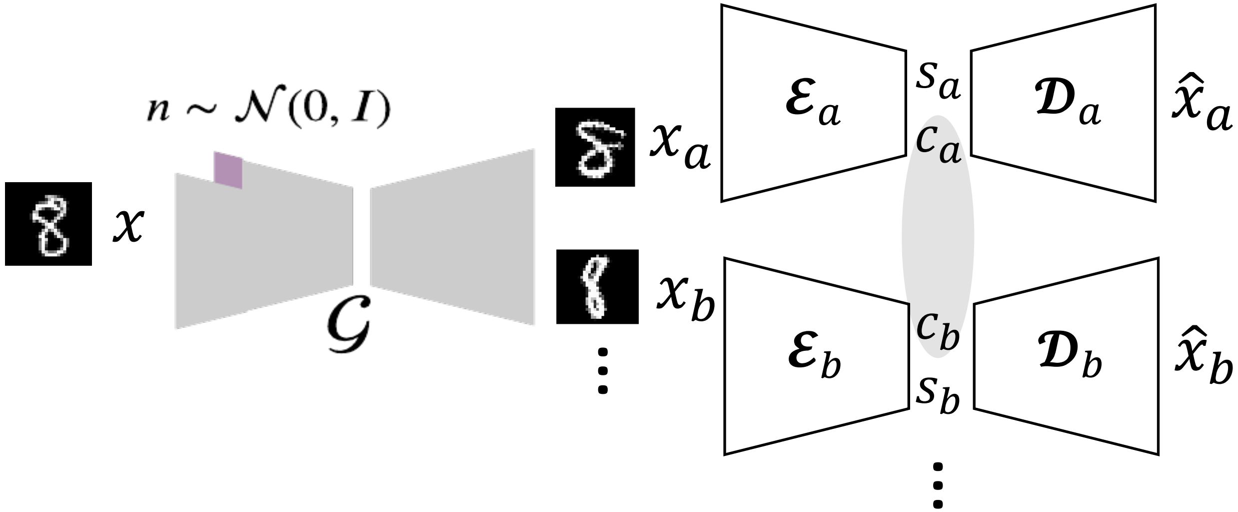
Consensus assignment



Using Aitchison geometry: $d(\boldsymbol{c}_a, \boldsymbol{c}_b) = D_A(\boldsymbol{c}_a, \boldsymbol{c}_b), \quad \boldsymbol{c}_a, \boldsymbol{c}_b \in \boldsymbol{S}^K$

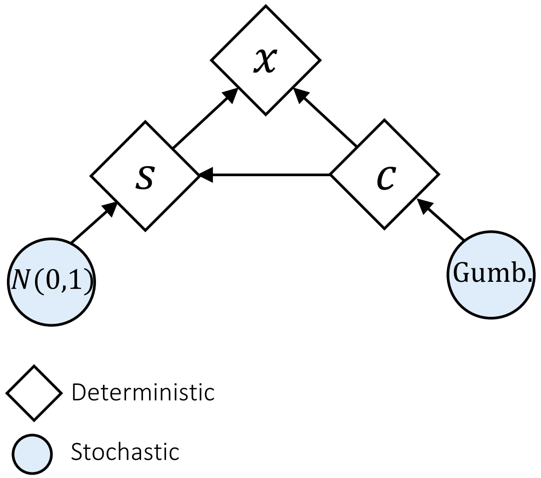
Analogy in machine learning

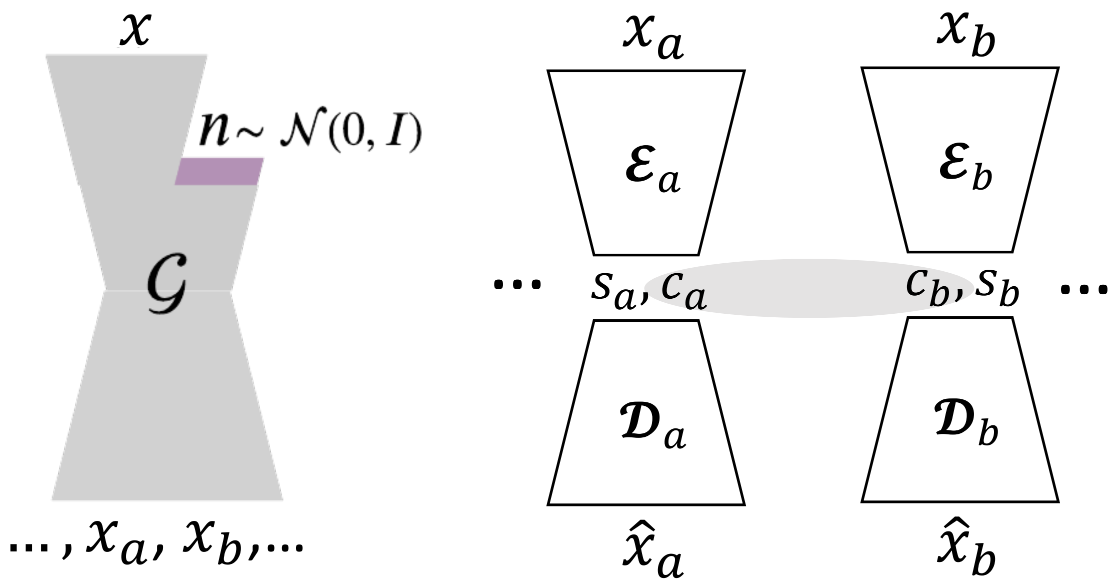
The MNIST dataset



A-arm VAE framework

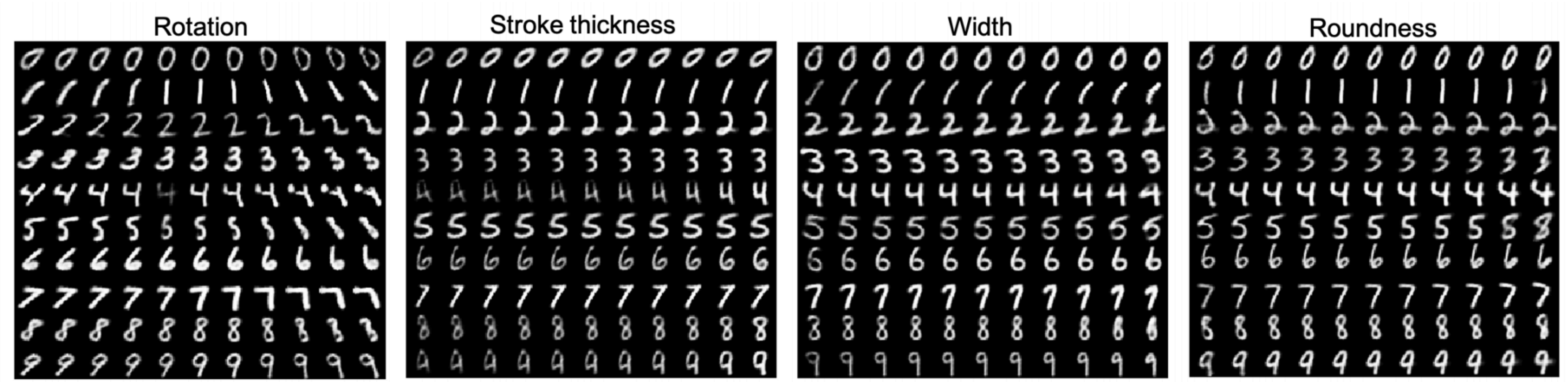
Network implementation



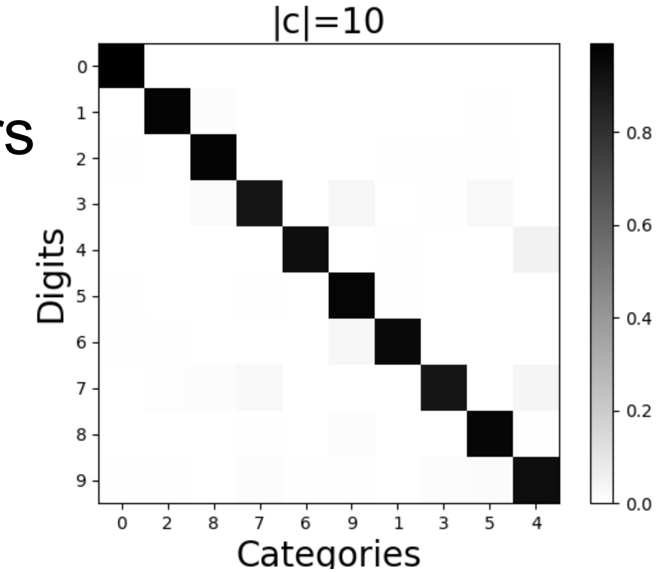


Benchmark dataset: interpretation of c & s

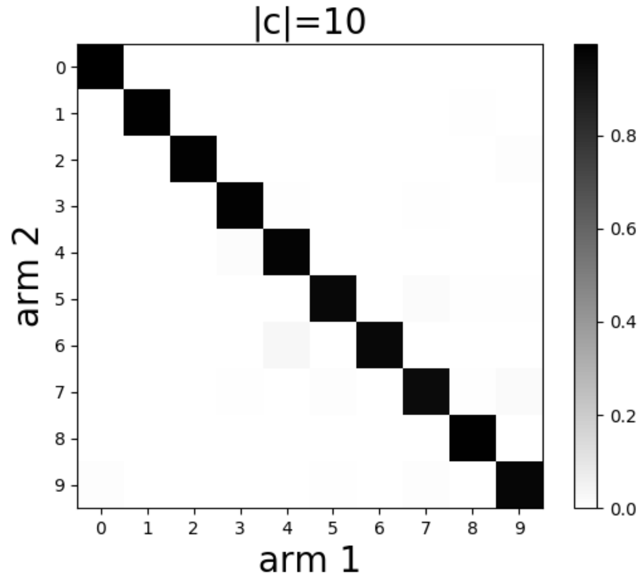
Continuous factors



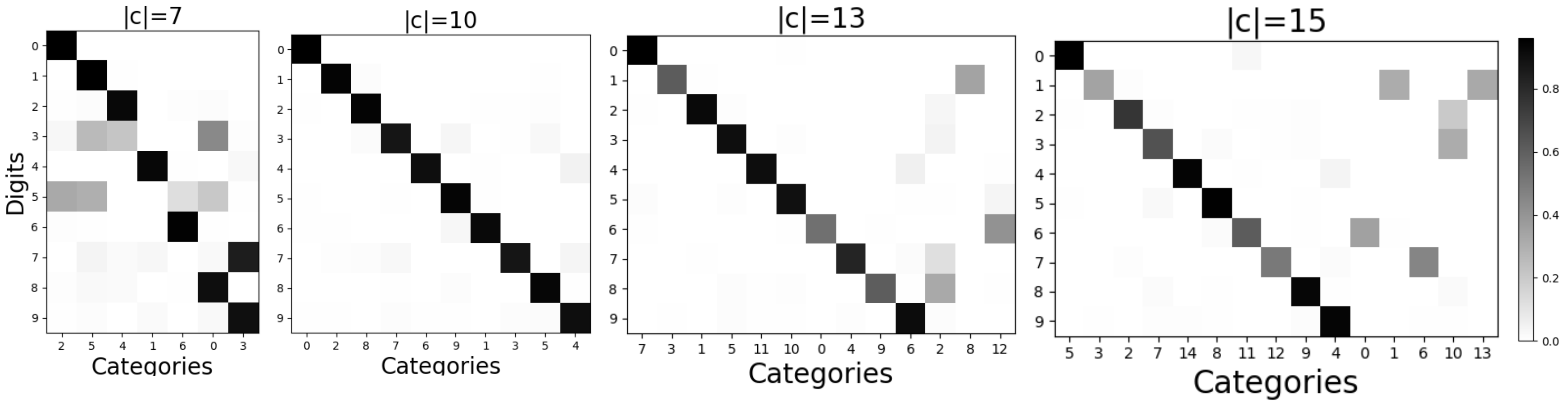
Discrete factors

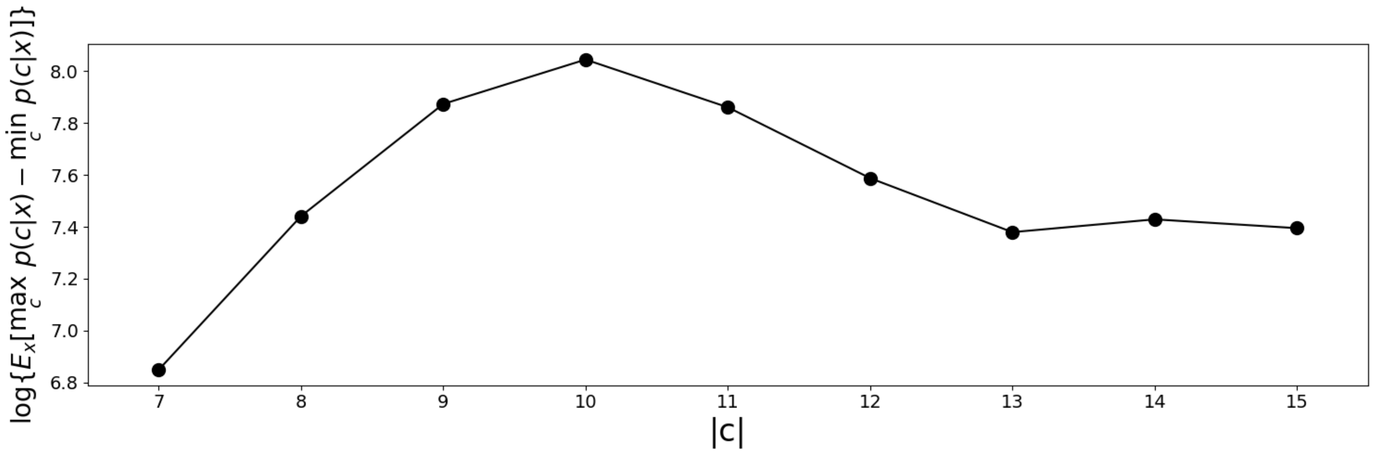


Consensus among arms

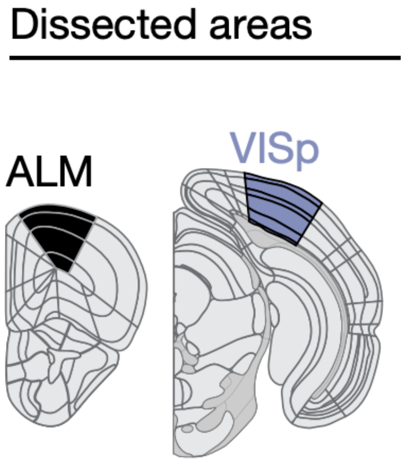


Benchmark dataset: unknown $|c|$

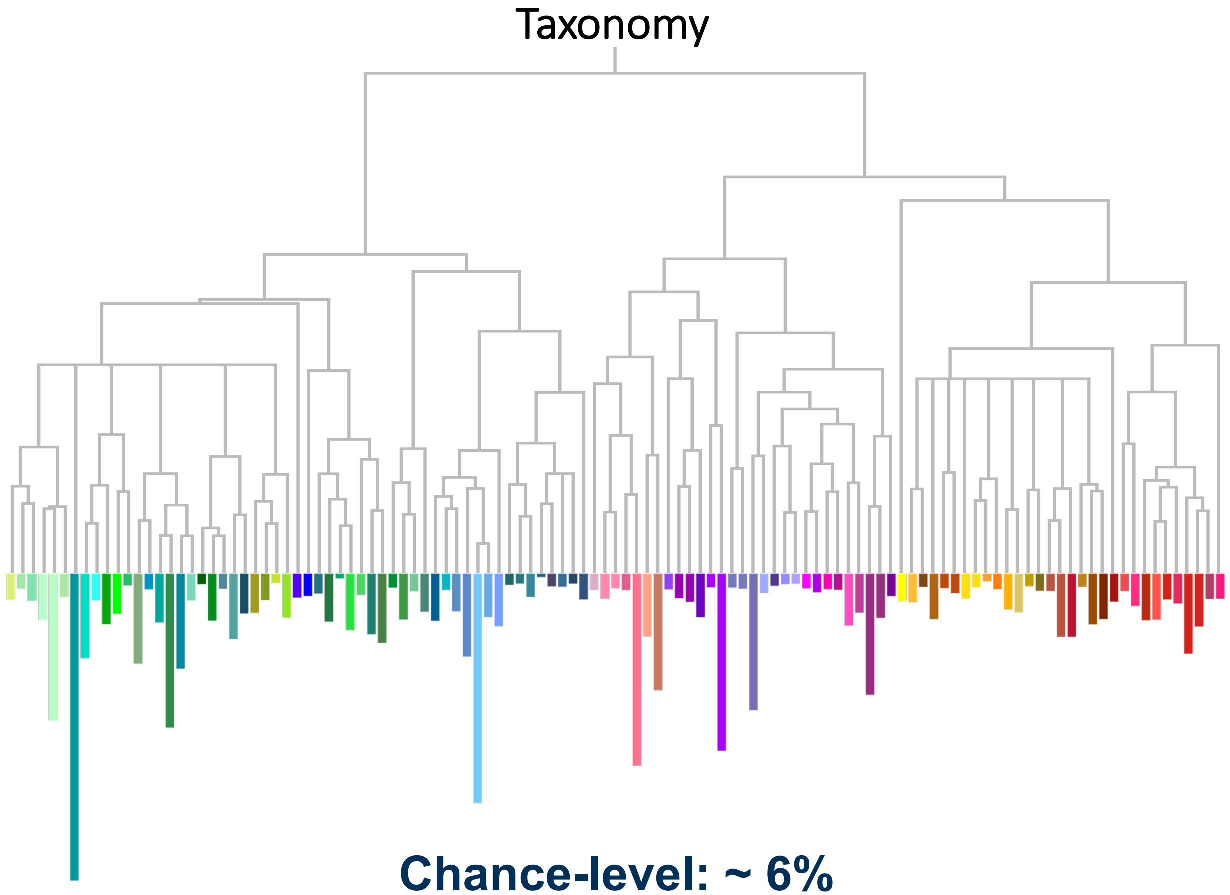




scRNA-seq dataset (Tasic et al., 2018)

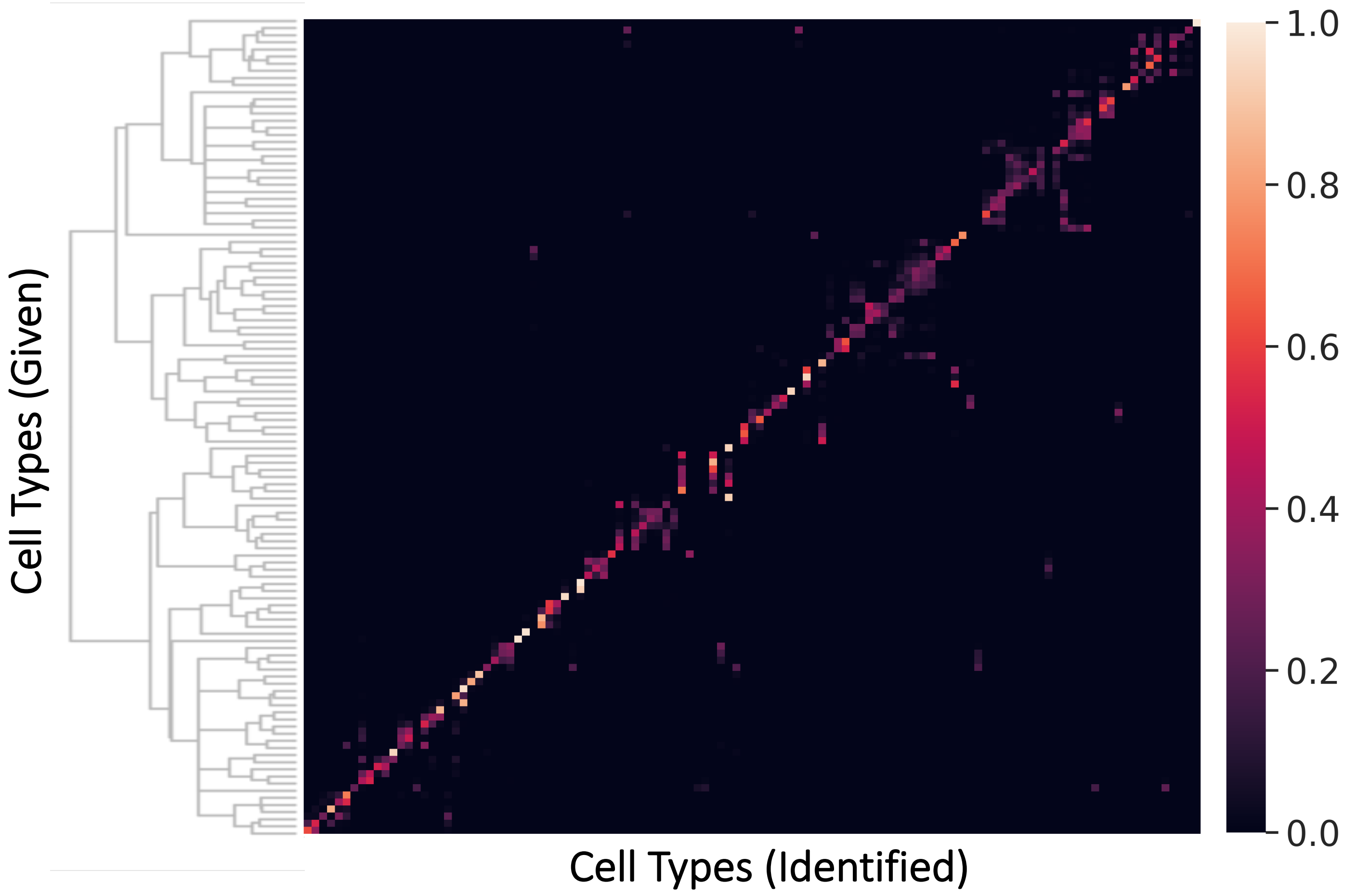


- transcriptomic profiles for **22,365** cells
- **115** excitatory and inhibitory neuron types
- 5000 DE genes

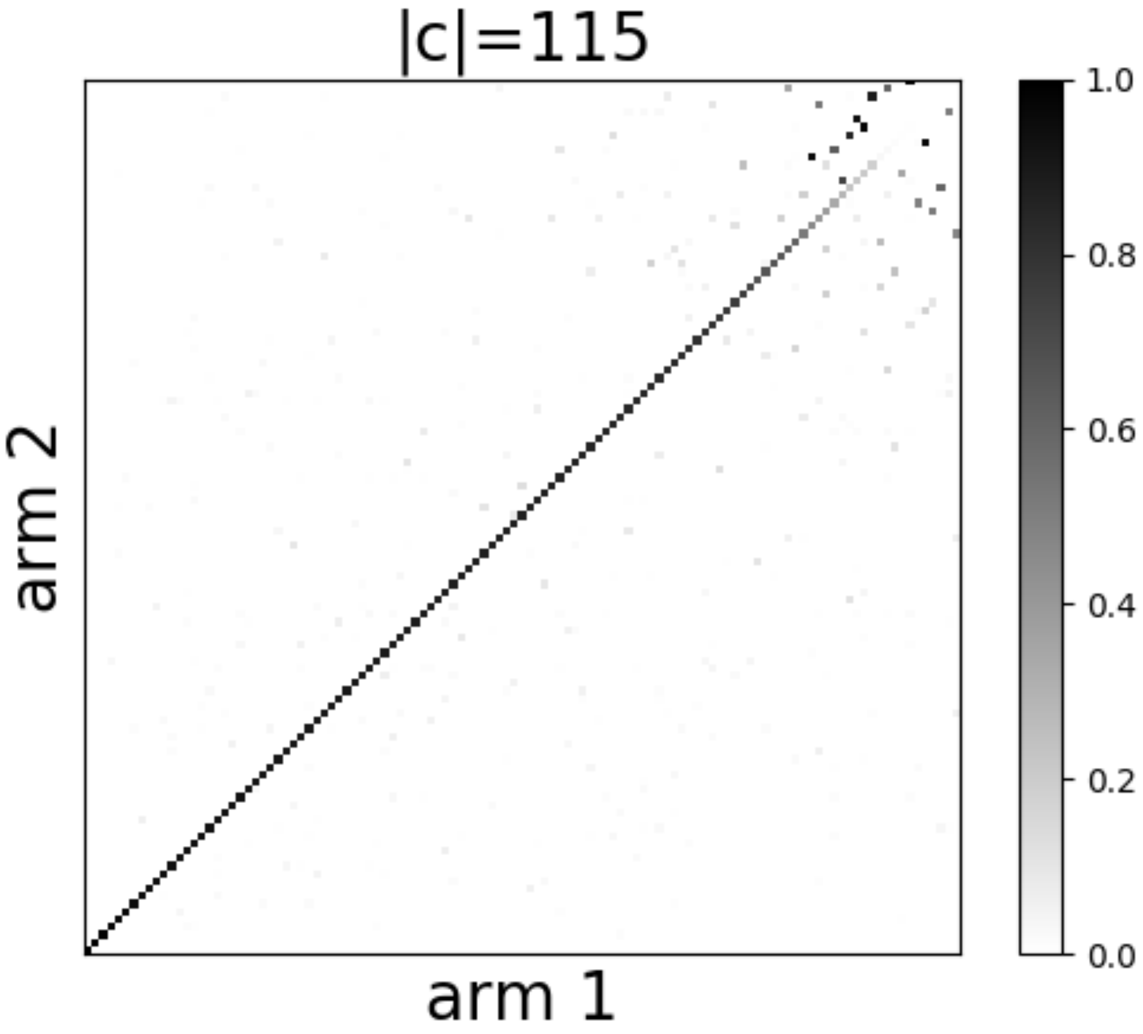


Chance-level: ~ 6%

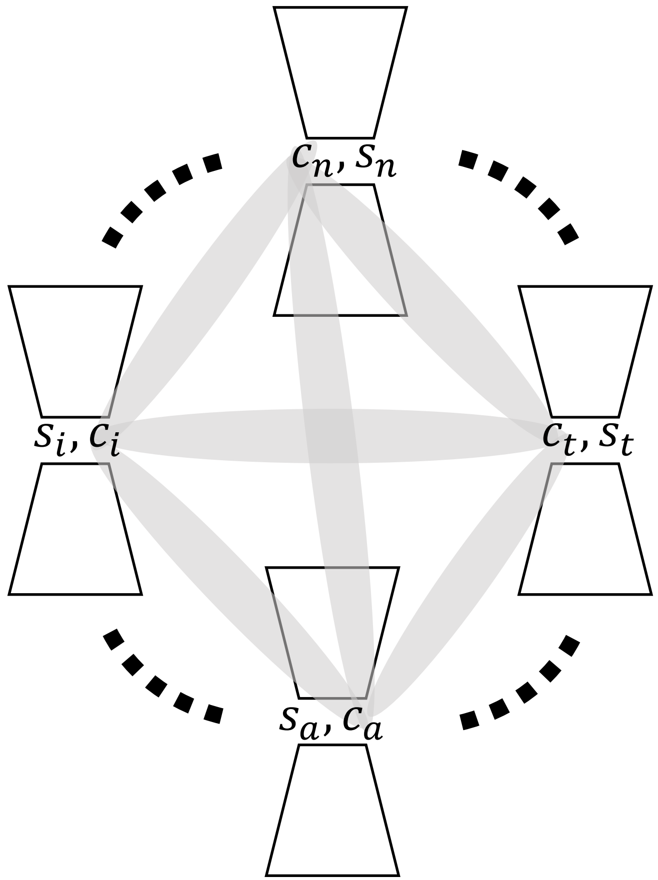
scRNA-seq dataset: transcriptomic identities

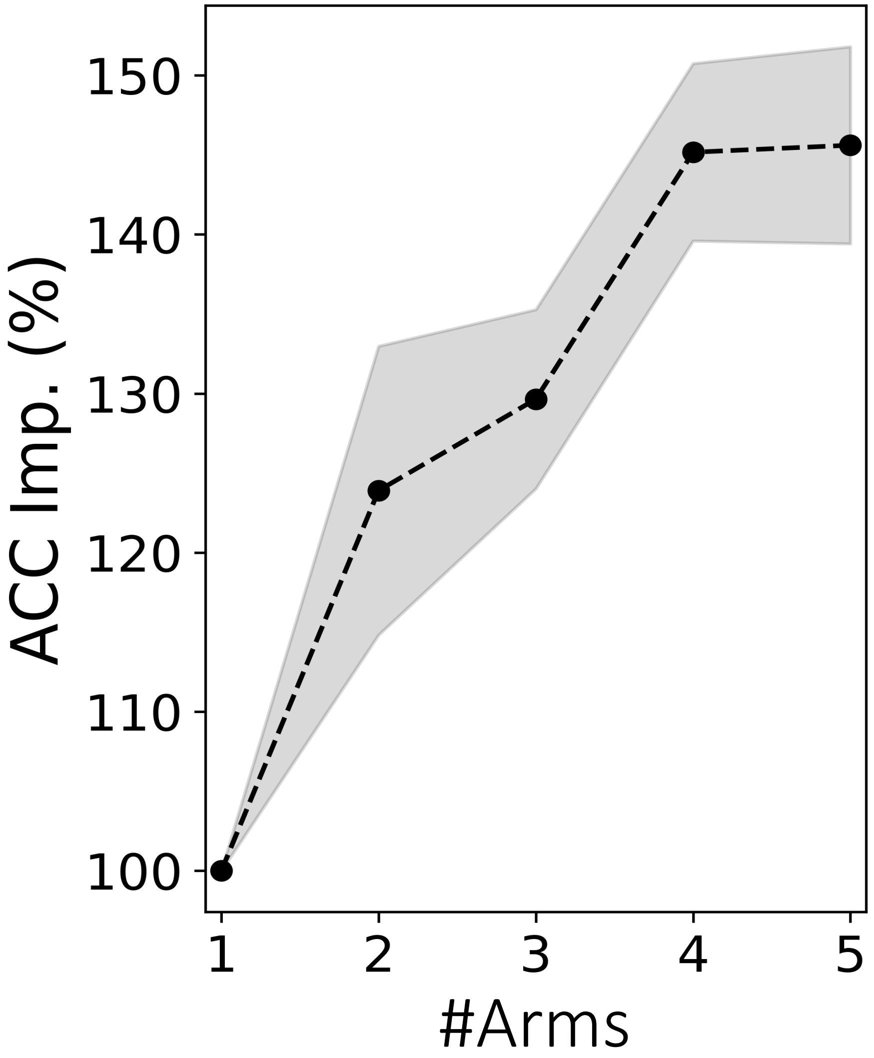


scRNA-seq dataset: transcriptomic identities

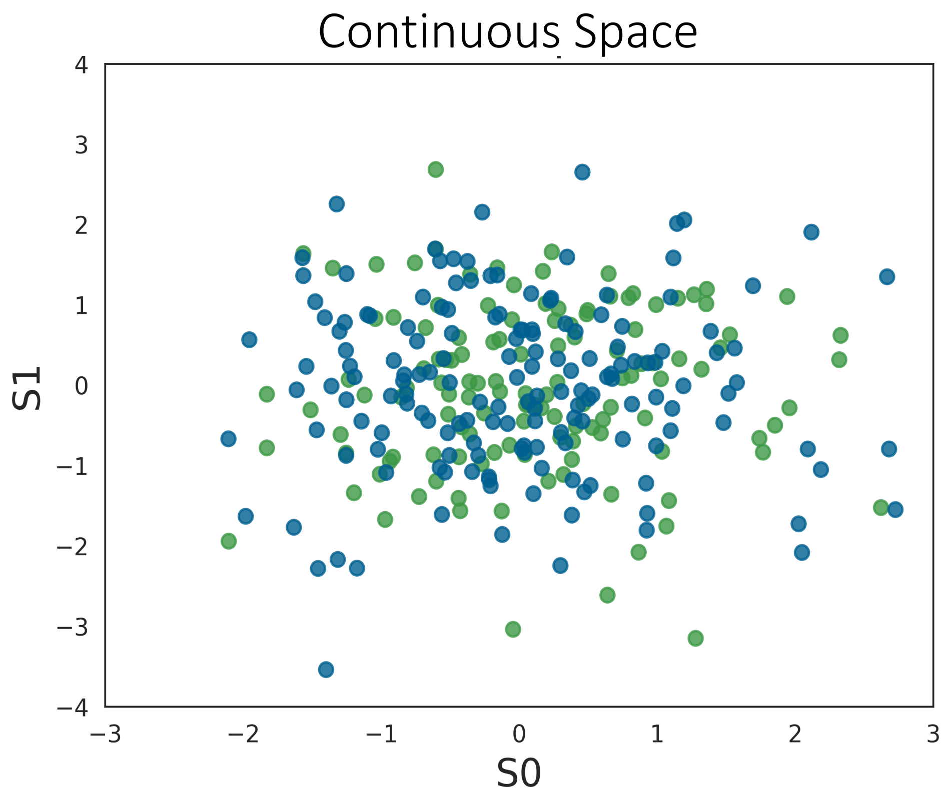


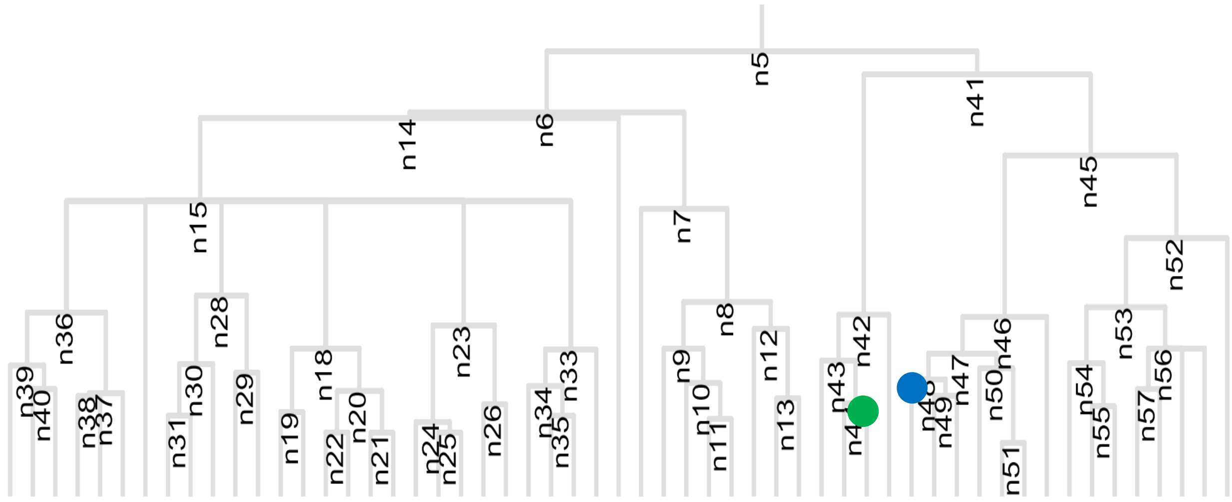
scRNA-seq dataset: more than 2 arms



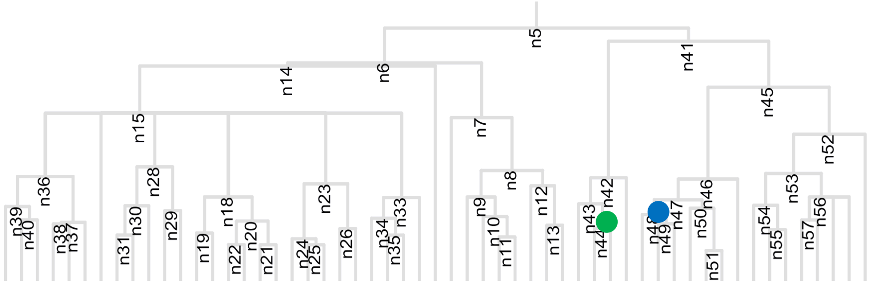


Identifying genes regulating continuous variability

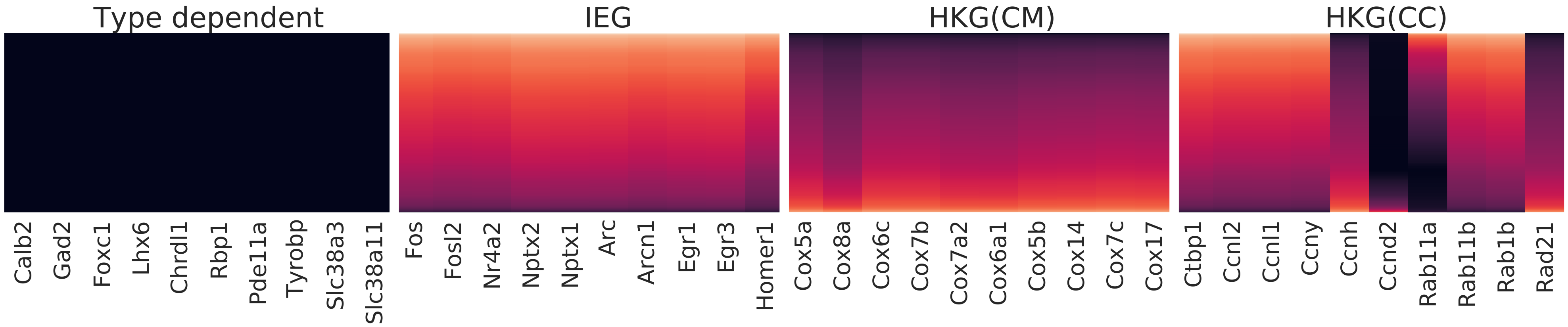




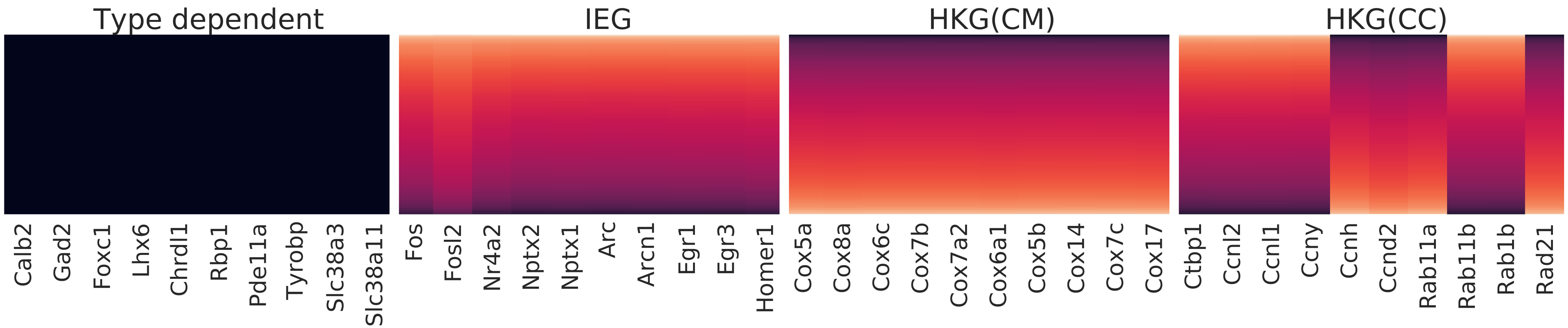
Identifying genes …



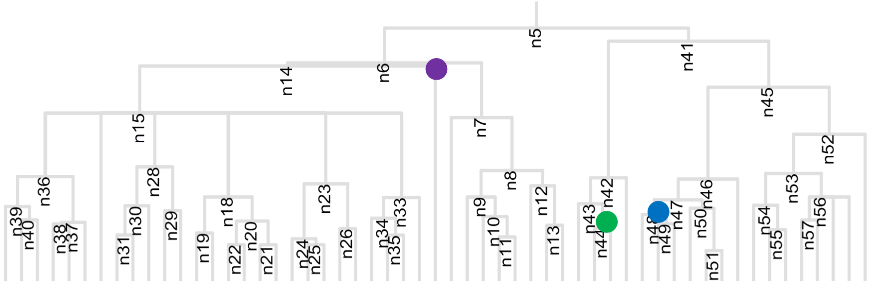
L5 NP ALM Trhr Nefl (n44)

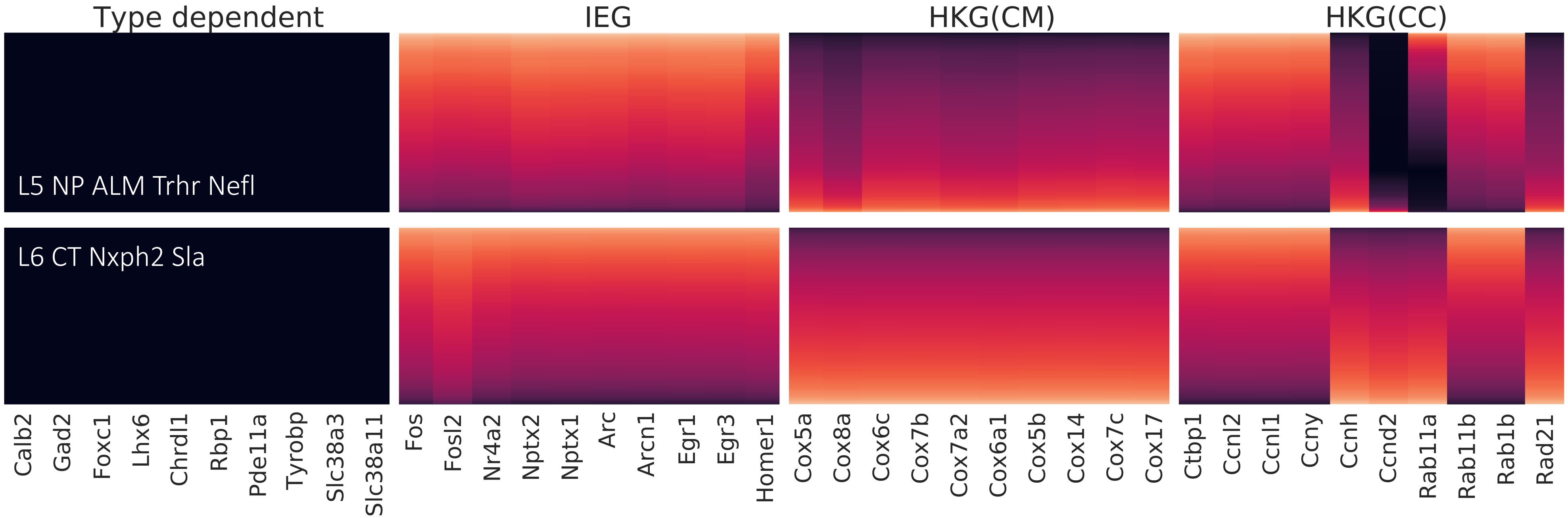


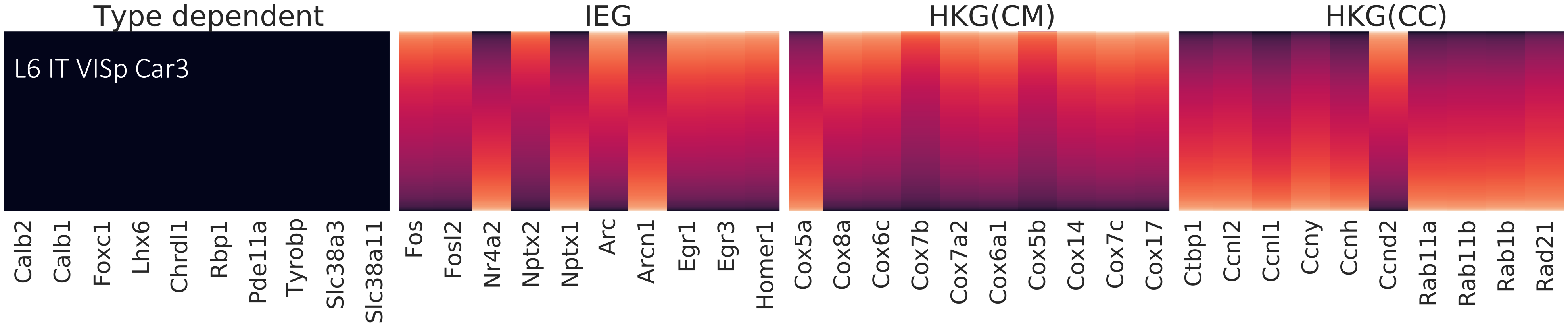
L6 CT Nxph2 Sla (n48)



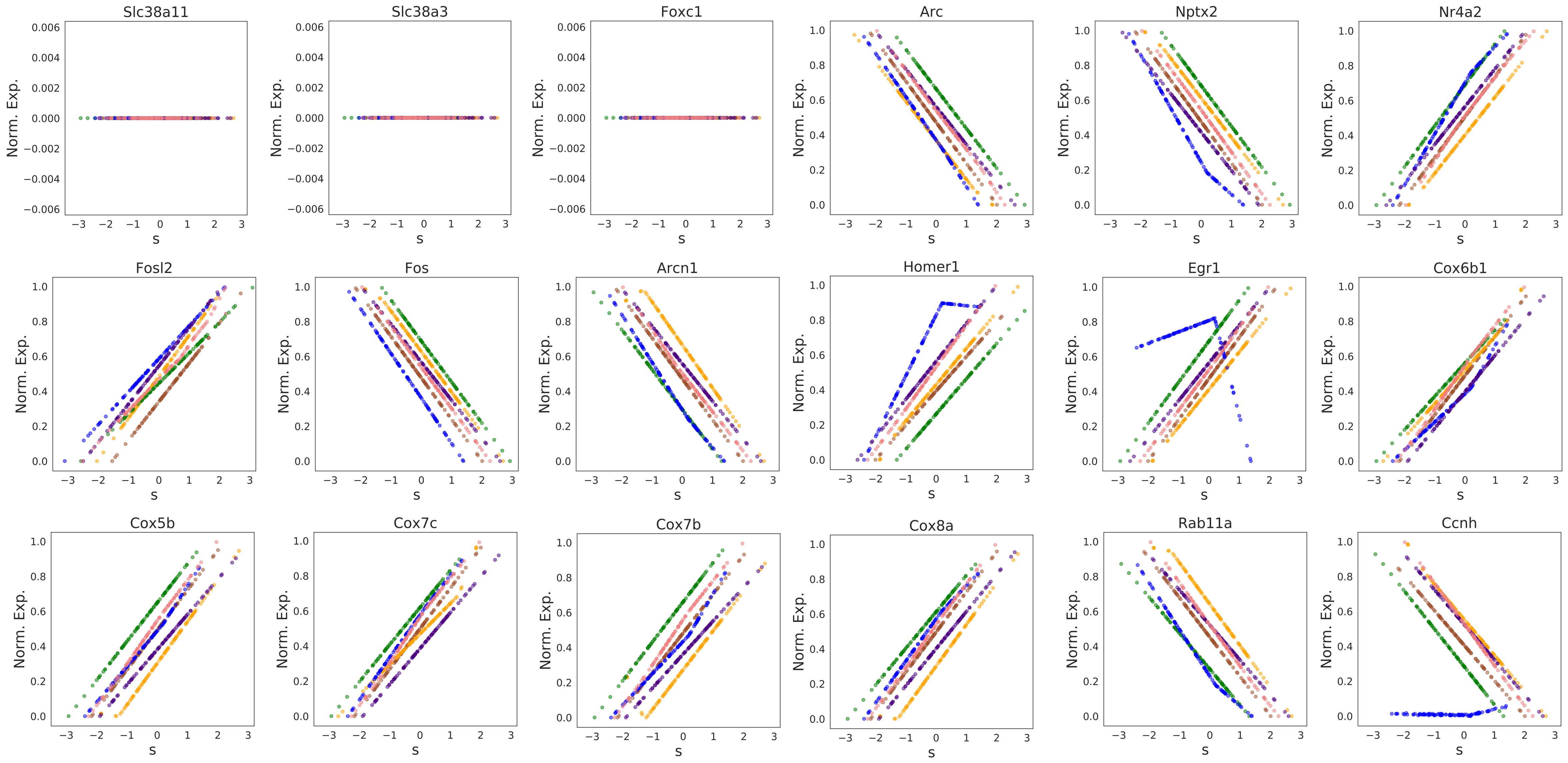
Identifying genes …





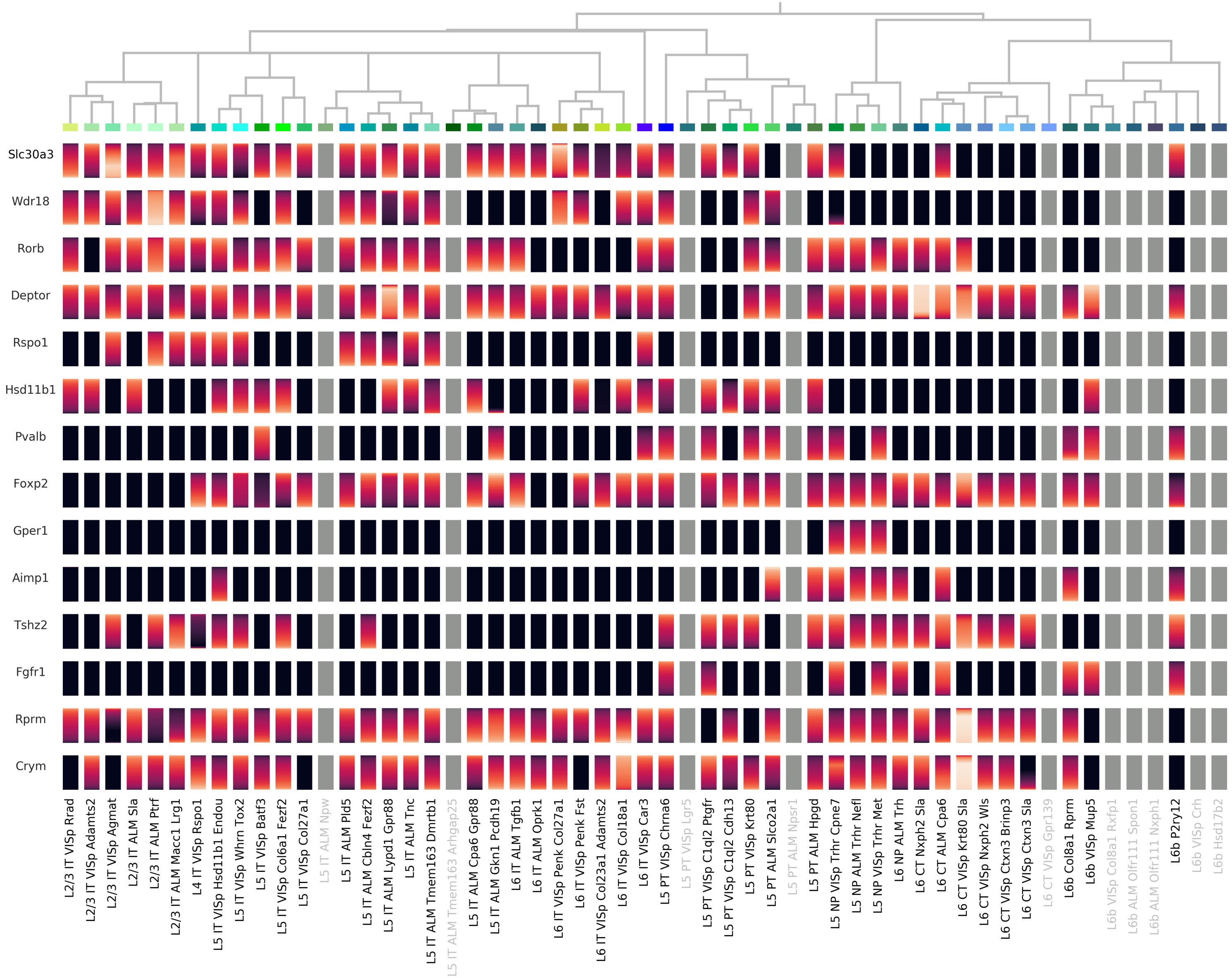


Robustness of type-dependent variabilities



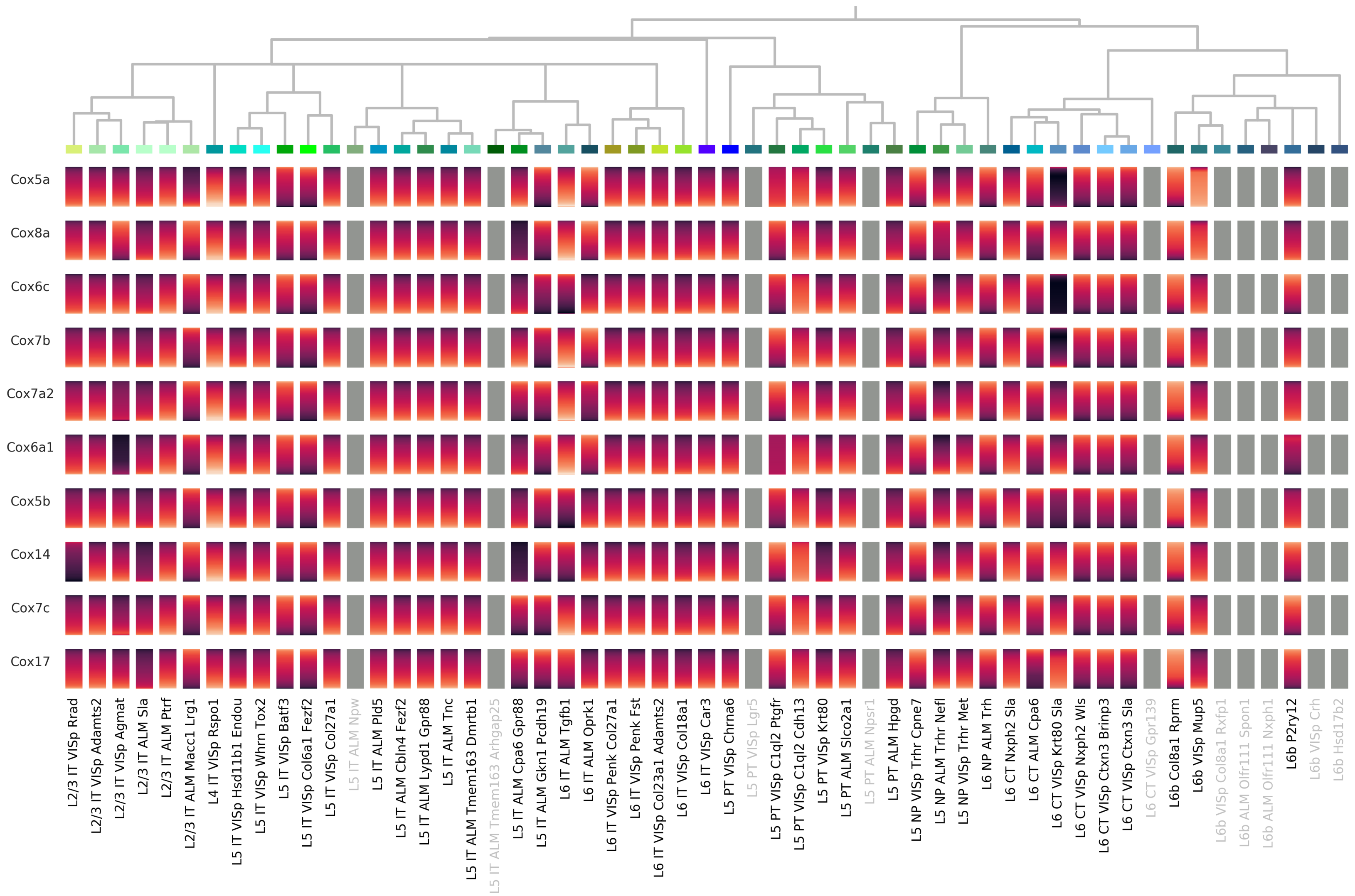
Glutamatergic cells

Marker genes



Glutamatergic cells

House-keeping genes



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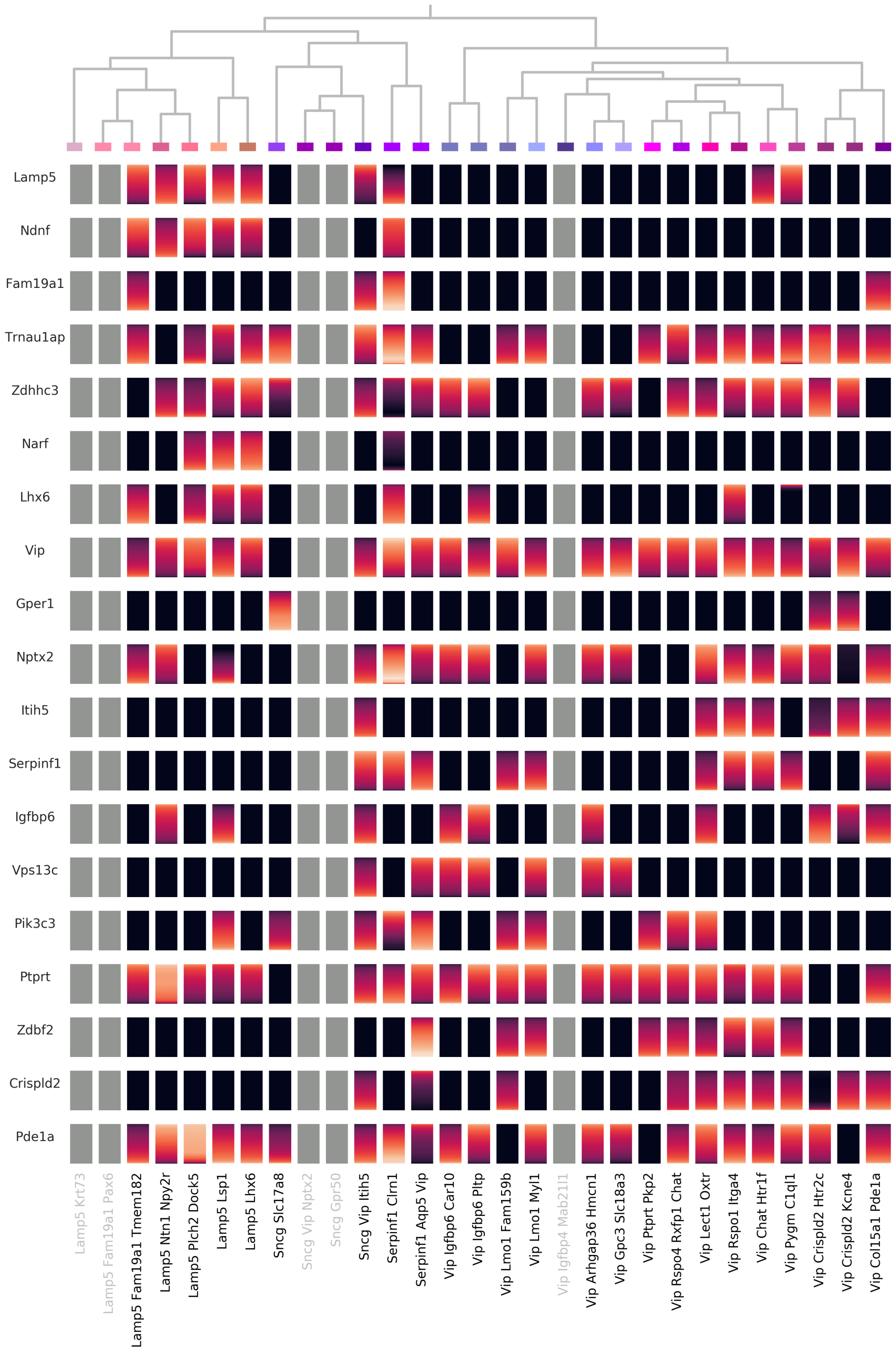
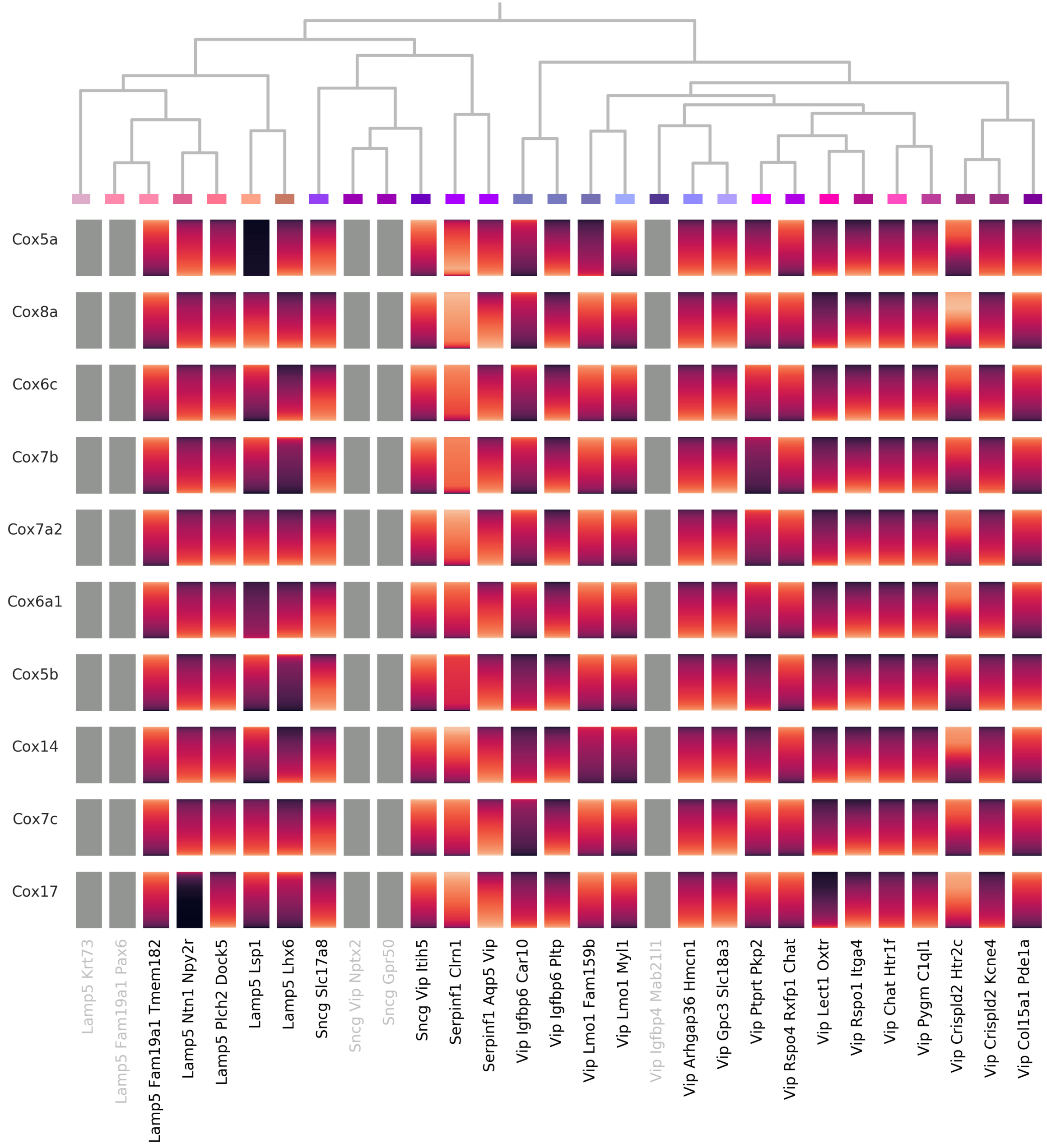
GABAergic cells

Marker genes



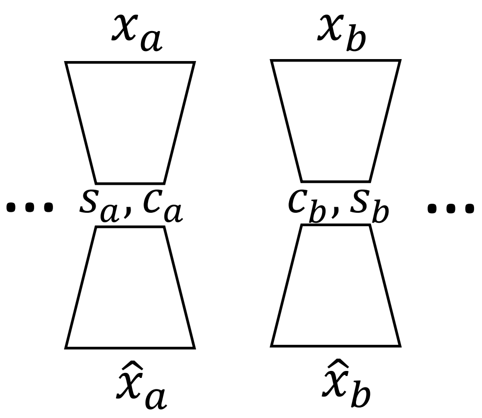
GABAergic cells

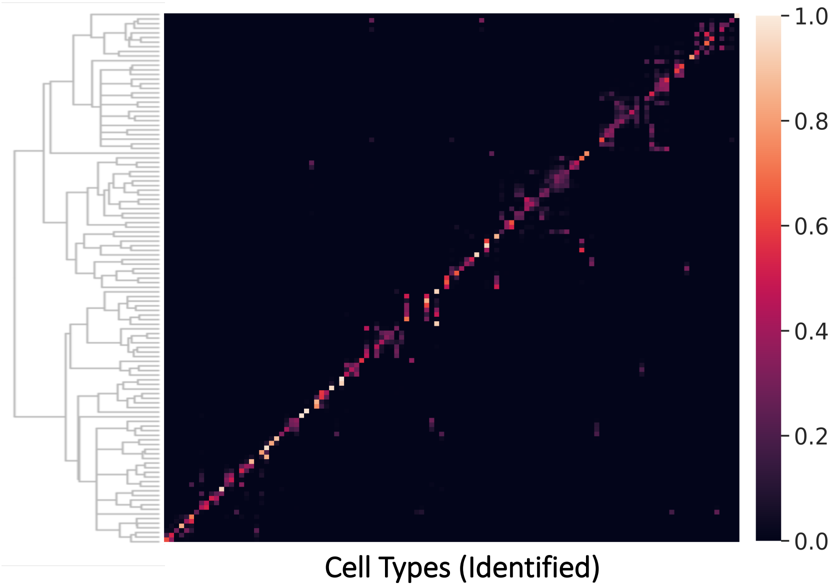
House-keeping genes

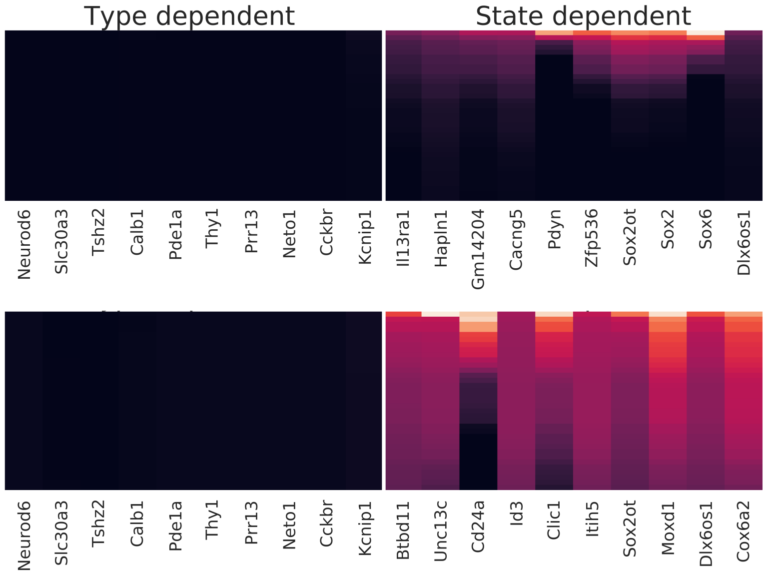


Summary

- Introducing cpl-mixVAE as a general framework to apply the power of collective decision making in unsupervised joint learning of discrete and continuous generative factors.
- Determining the neuronal cell types in an unsupervised setting, while identifying the genes implicated in regulating biologically relevant neuronal states.
- Studying (differential) gene expression variabilities using the type-dependent continuous factor.



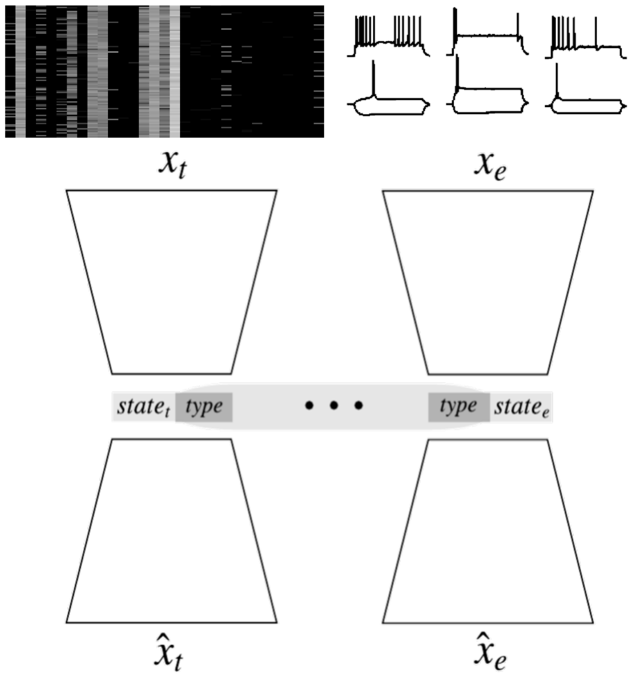




Future studies

- Multi-modal datasets (Joint identification of cell types and states in different modalities)

- Trajectory-based differential expression analysis for single-cell sequencing data



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THANK YOU

Team:

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Olga Gliko

Fahimeh Baftizadeh

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THANK YOU

We wish to thank the Allen Institute founder, Paul G. Allen, for his vision, encouragement, and support.

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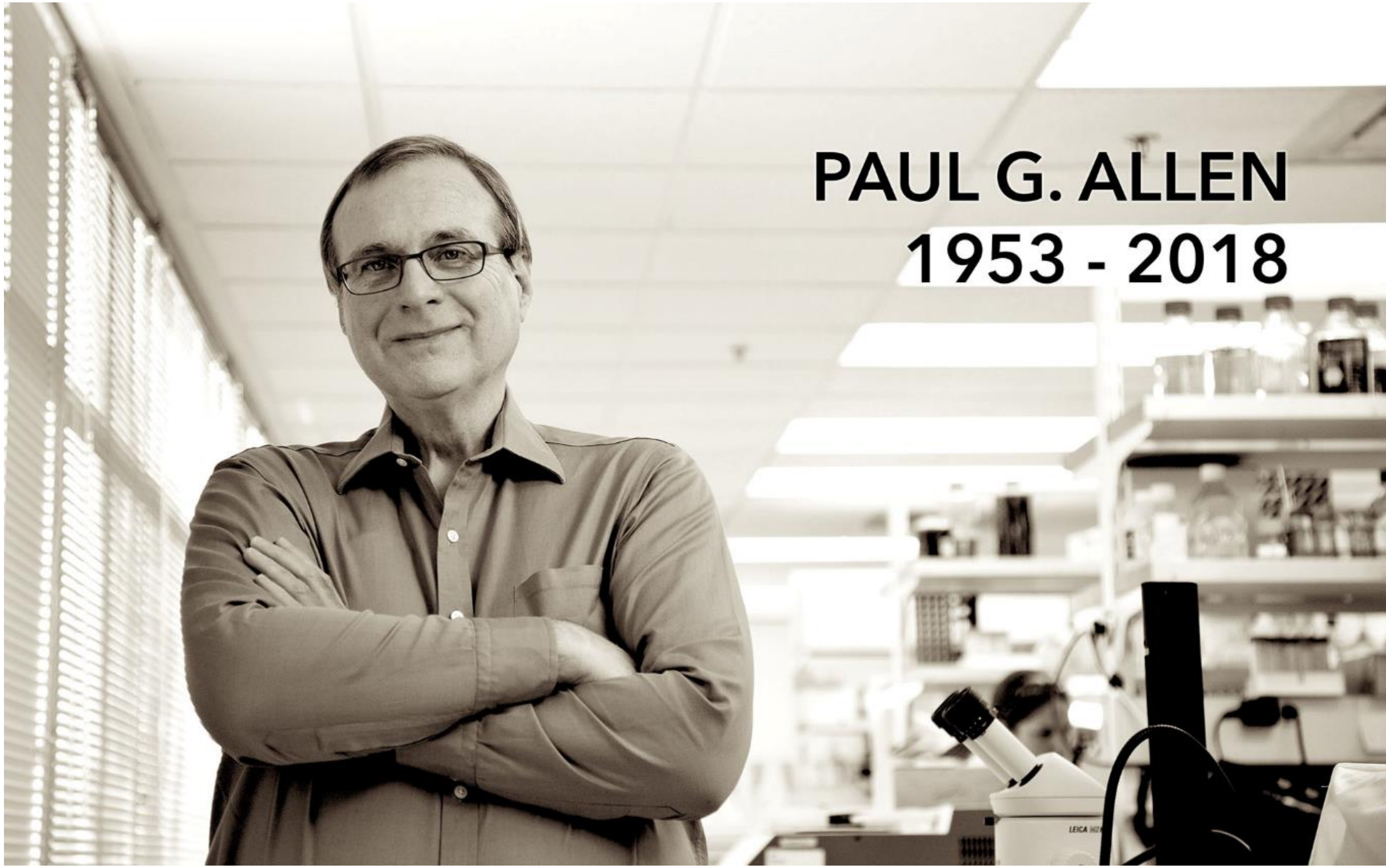

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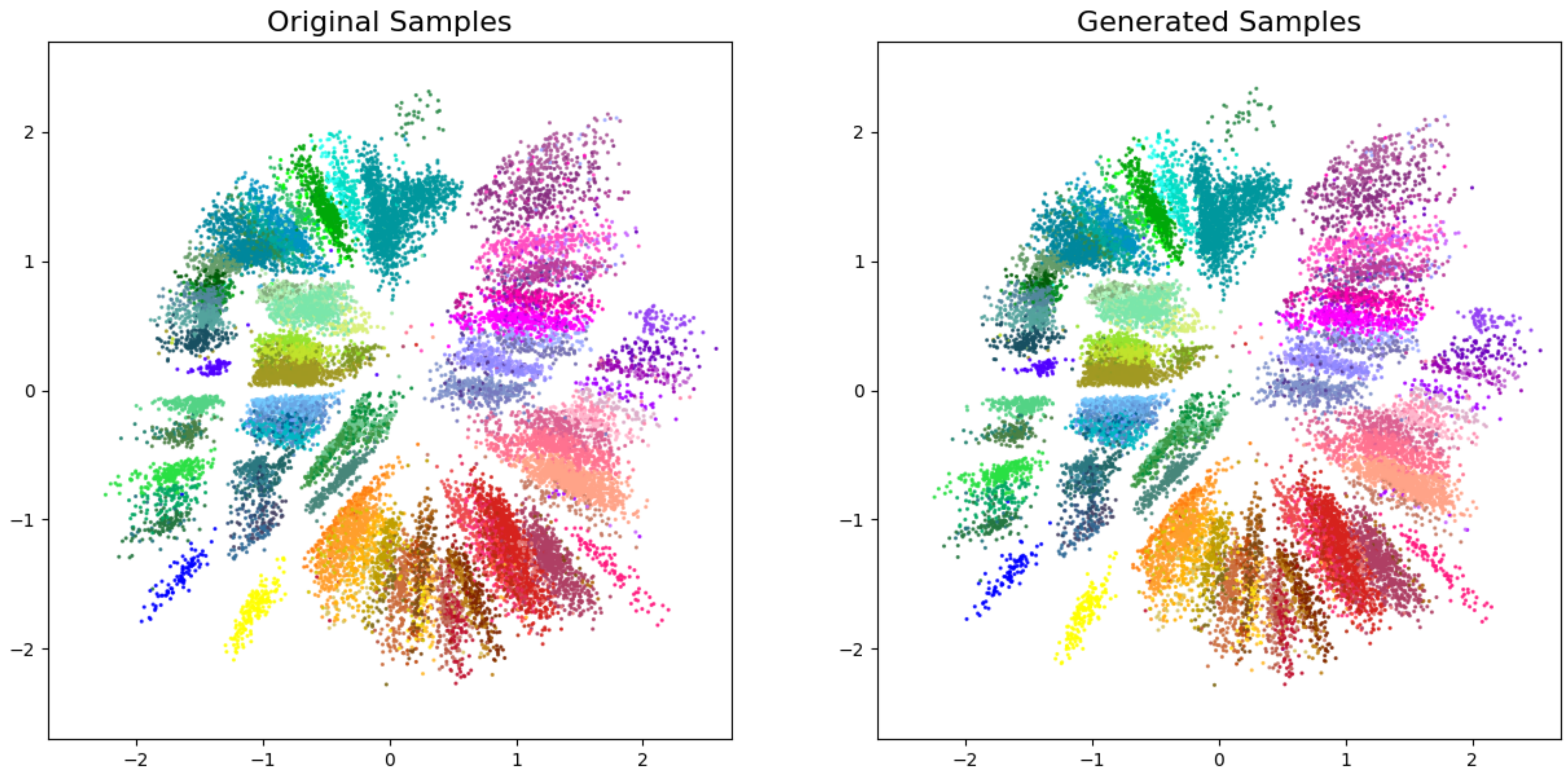
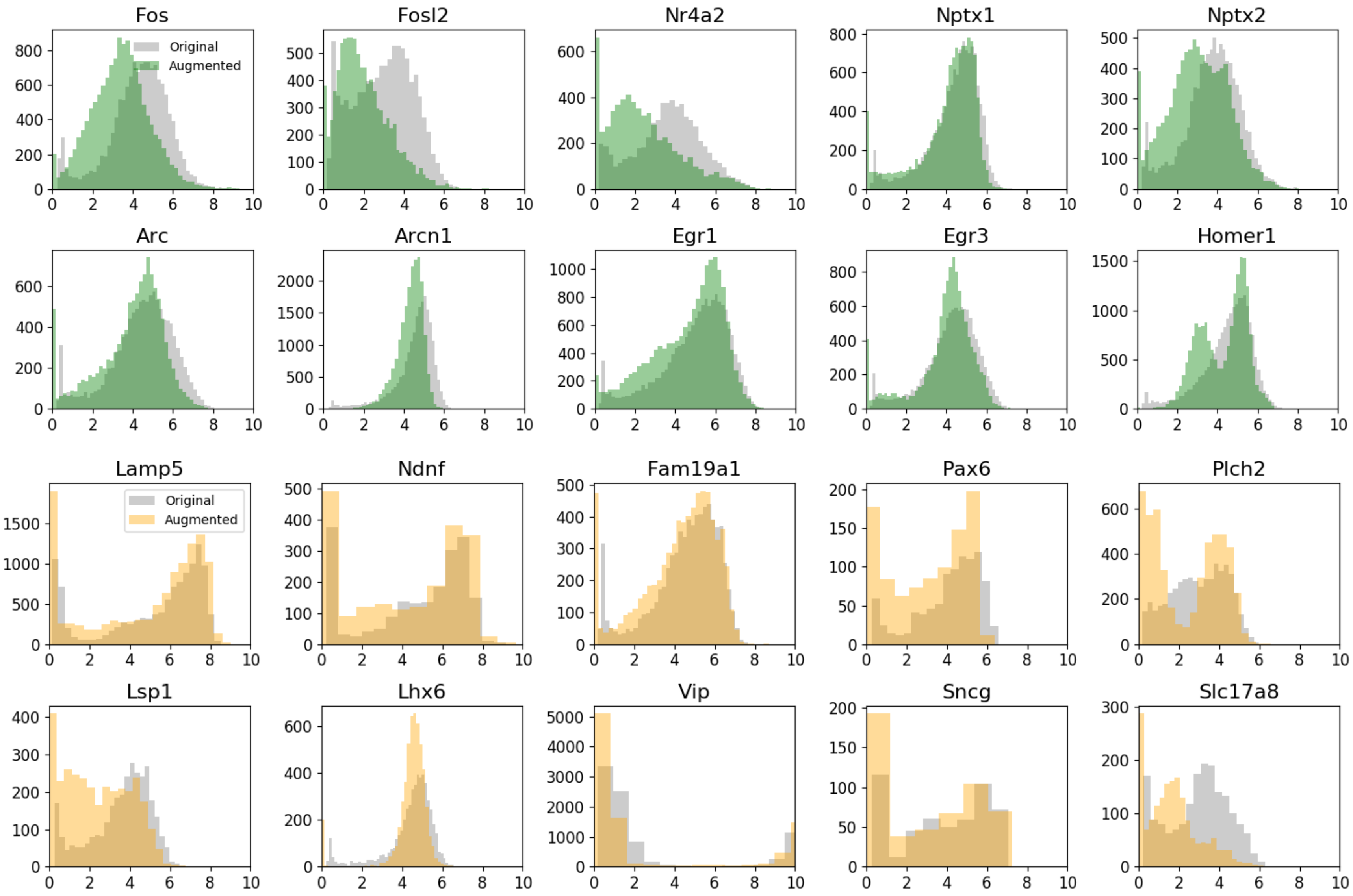
Supplement

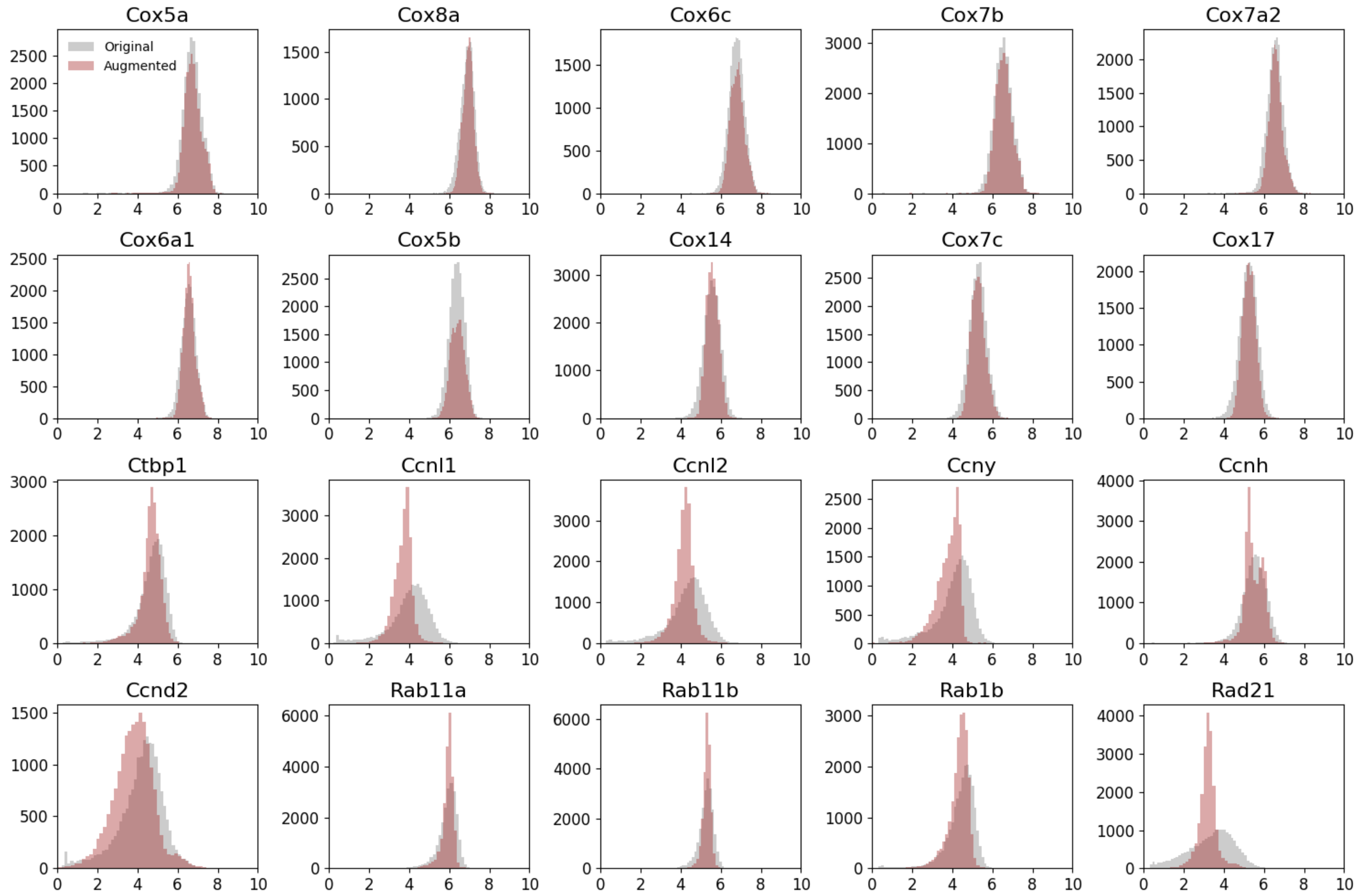
Single-cell generator



Single-cell generator



Single-cell generator



All datasets: overall performance

Dataset	Chance-level	$\|c\|$	$\|s\|$	Method	ACC (%) ↑ (mean ± s.d.)	Computation ↑ (iteration/sec)	Disentanglement score
MNIST	10.0%	10	2	InfoGAN	77.87 ± 21.68	12.2	–
			10	JointVAE	68.99 ± 11.76	74.1	
				CascadeVAE	81.41 ± 09.54	23.8	
				cpl-mixVAE	**84.56 ± 06.47**	17.5	
dSprite	33.3%	3	6	JointVAE	44.79 ± 03.88	52.6	74.51 ± 05.17
				CascadeVAE	78.84 ± 15.65	15.4	90.49 ± 05.28
				cpl-mixVAE	**96.30 ± 09.15**	20.6	89.98 ± 04.09
scRNA-seq	06.3%	115	2	JointVAE	12.53 ± 01.83	28.6	–
				CascadeVAE	02.69 ± 00.05	03.4	
				cpl-mixVAE	**38.78 ± 01.26**	10.1	

Consensus assignment