Coupled autoencoders for multimodal cell type analysis

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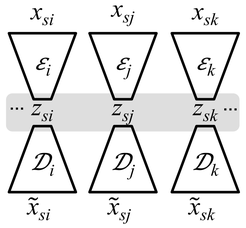
1. Abstract

Recent developments in high throughput profiling of individual neurons have spurred data driven exploration of the idea that there exist natural groupings of neurons referred to as cell types. The promise of this idea is that the immense complexity of brain circuits can be reduced, and effectively studied by means of interactions between cell types. While clustering of neuron populations based on a particular data modality can be used to define cell types, such definitions are often inconsistent across different characterization modalities. We pose this issue of cross-modal alignment as an optimization problem and develop an approach based on coupled training of autoencoders as a framework for such analyses. We apply this framework to a Patch-seq dataset consisting of transcriptomic and electrophysiological profiles for the same set of neurons to study consistency of representations across modalities, and evaluate cross-modal data prediction ability. We explore the problem where only a subset of neurons is characterized with more than one modality, and demonstrate that representations learned by coupled autoencoders can be used to identify types sampled only by a single modality.

2. Coupled autoencoders to learn consistent representations



$$L = \sum_i \alpha_i R_i + \sum_i \lambda_{ij} C_{ij}$$

Reconstruction cost

$$R_i = \left\| X_i - \tilde{X}_i \right\|^2$$

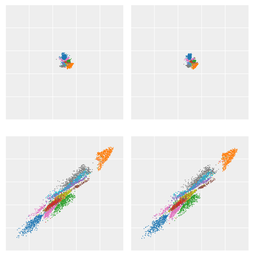
Coupling cost function

$$C_{ij} \sim \left\| z_i - z_j \right\|^2$$

➤ α_i is fixed based on dataset specific noise considerations.

➤ λ_i is controls the tradeoff between reconstruction and coupling costs.

Pathological representations



Batch normalized z

$$z_{id} \longrightarrow \frac{z_{id} - \mu_B}{\sigma_B}$$

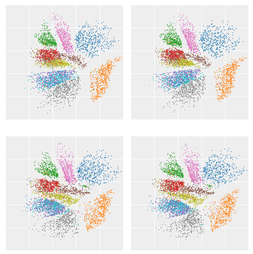
Full covariance normalized z

$$z_i \longrightarrow (B_i^T B_i)^{-1/2} z_i$$

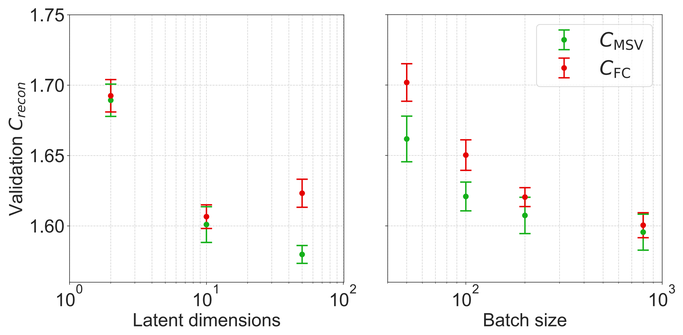
Minimum batch singular value normalized z

$$z_i \longrightarrow \frac{z_i}{\min\{\sigma_i(B_i), \sigma_j(B_j)\}}$$

Desirable representations



➤ Minimum singular value-based normalization outperforms full covariance-based normalization in regimes for which covariance estimates are unreliable.



3. Probabilistic view of the optimization problem

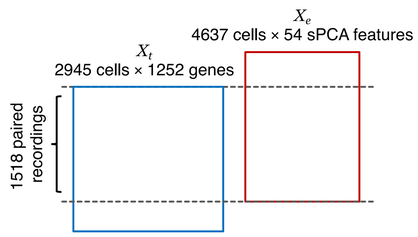
➤ The loss function can be viewed as likelihood maximization with mild assumptions. This provides an interpretation for hyperparameters α_i:

$$\sum_s \log p(x_{st}, x_{se}, z_{st} | z_{se}) = \sum_s \log p(x_{st} | z_{st}) + \log p(x_{se} | z_{se}) + \log p(z_{st} | z_{se})$$

Let $x_{st}|z_{st} \sim N(\tilde{x}_{st}, \sigma_t^2 I)$, $x_{se}|z_{se} \sim N(\tilde{x}_{se}, \sigma_e^2 I)$, and $z_{st}|z_{se} \sim N(z_{se}, \lambda^{-1} I)$

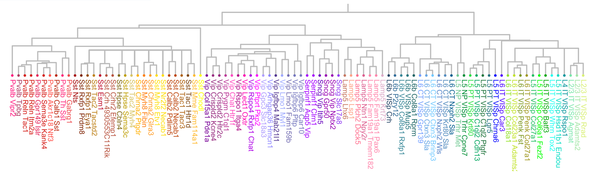
$$L = \sum_s \sigma_t^{-2} \left\| x_{st} - \tilde{x}_{st} \right\|_2^2 + \sigma_e^{-2} \left\| x_{se} - \tilde{x}_{se} \right\|_2^2 + \lambda \left\| z_{st} - z_{se} \right\|_2^2$$

4. Patch-seq dataset



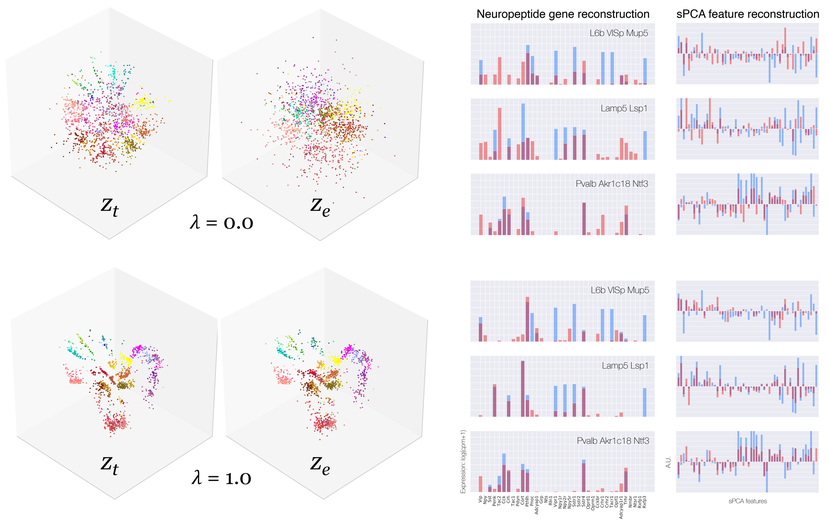
➤ Gene expression values and electrophysiological features are obtained for individual neurons.

➤ A subset of neurons are profiled with both modalities and mapped to an established taxonomy [1] using differential expression of marker genes.



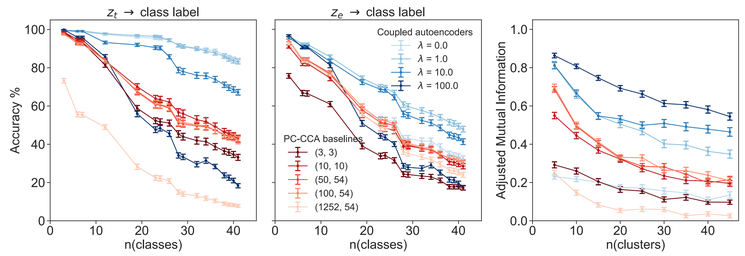
5. Joint representations and reconstructions

➤ Known cell types cluster as distinct islands in 3d representations. Representations preserve salient hierarchical relationships of cell types.



➤ There is a trade-off between how similar the representations are, and accuracy of reconstructions. Coupling constant λ explicitly controls this tradeoff.

6. Cross modal cell type classification



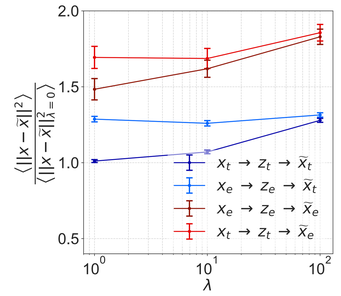
➤ Joint representations agree with established transcriptomic hierarchy. Representations with coupled autoencoders reveal this agreement better than CCA based approaches.

➤ Clusters in the transcriptomic data are consistent with those in the electrophysiology data. Thus, transcriptomic profiles of neurons map better to functionally consequential properties better than previously thought.

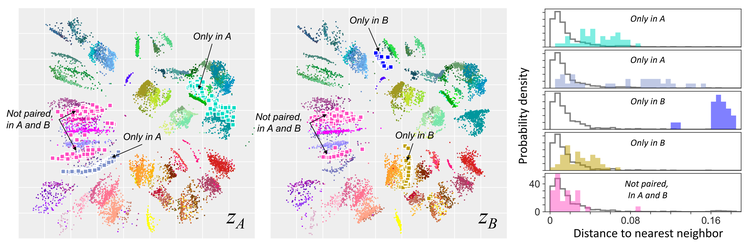
7. Cross modal data prediction

➤ Jointly learned representations enable prediction of transcriptomic gene expression profiles from electrophysiology features and vice versa.

➤ Learning these relationships can minimize measurements required to determine a neurons' distinctive characteristics across modalities.



8. Discovery of shared and distinct cell types



➤ Cell types that are unique to a dataset, or those that are shared across datasets can both be identified using known associations of the remaining types.

References

[1] Tasic B., et al. Shared and distinct transcriptomic cell types across neocortical areas. *Nature* (2018)

[2] Gouwens NW., et al. Classification of electrophysiological and morphological neuron types in the mouse visual cortex. *Nature neuroscience* (2019)

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