Discovery and Characterization of Neural Circuitry from Behavior, Connectivity Patterns and Activity Patterns

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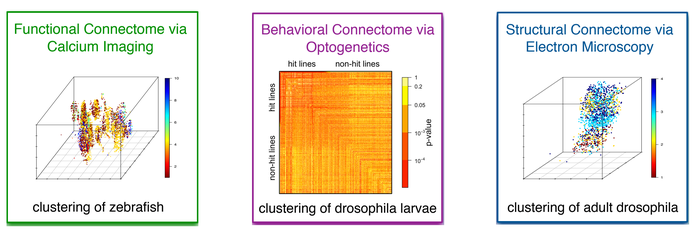
1. Project Summary

A recent study [1] has generated a neuronline behavior atlas of the *Drosophila* larval nervous system. "This atlas is a starting point for connectivity- and activity-mapping studies to further investigate the mechanisms by which neurons mediate diverse behaviors." *Drosophila* larvae, with 10,000 neurons, offer an opportunity to determine how an entire nervous system generates behavior. The current atlas is a fantastic step toward achieving that goal – Timothy O'Leary & Eve Marder [2] write that it will "usher in a new era of integrated methods for deciphering how an entire nervous system generates behavior" and that it has "achieved a technical, multidisciplinary tour de force that will provide a rich source of research questions" – but it needs to be refined to single neuron resolution. Marta Zlatic and Jim Truman at Janelia Farm have refined the library of neuronal lines used in the current publication, driving expression in a single cell pair in the larval nervous system. Optogenetically activation of this new collection will allow the application of multiscale unsupervised structure learning to the behavior data and yield a single neuron behavior map covering all neuron types in the larval nervous system. In parallel, Albert Cardona at Janelia Farm is using electron microscopy (EM) to map a wiring diagram of the larval nervous system. Marta Zlatic is also generating a neuron activity map of the entire *Drosophila* larval nervous system using calcium imaging, as described for zebra fish in Ahrens et al. [3]. *The objective of this project is to develop principled statistical pattern recognition & machine learning methods for clustering neurons based on these three different data sets, both individually and jointly.* The extent to which clusters obtained from the three datasets agree, and the manner in which they disagree, will provide a characterization of neural circuitry from behavior, connectivity patterns and activity patterns.



(a) activity (b) behavior (c) connectome

Figure 1: *Three data sets*

2. Project Description

We propose *fusion and inference from multiple disparate data sources for discovery and characterization of neural circuitry from behavior, connectivity patterns and activity patterns.*

This interdisciplinary project will consist of my team from Johns Hopkins University Department of Applied Mathematics and Statistics working closely with neuroscientists from HHMIs Janelia Farm Research Campus to develop principled statistical pattern recognition and machine learning methods for clustering neurons based on three different data sets extracted from the *Drosophila* larval nervous system: calcium imaging neural activity data (A for Activity), optogenetic behavior data (B for Behavior), and an EM connectome (C for Connectome). *Drosophila* larvae, with $n = 10,000$ neurons, offer an opportunity to determine how an entire nervous system generates behavior. The clustering results will provide the basis for determining how the structure of neural circuits relates to their function.

Let A be an $n \times n$ functional connectivity matrix for the calcium imaging neural activity data; let B be an $n \times n$ similarity matrix for the optogenetic behavior data; let $C = ([n], E)$ be the connectome representing the EM wiring diagram, with neurons-as-vertices $[n] = \{1, 2, \cdots, n\}$. Given A, B, and C, our task is to develop advanced methods, in conjunction with the Janelia Farm neuroscientists, for clustering neurons based on these three different data sets, both individually and jointly. We will know (almost exactly) which neuron v_B in the optogenetic behavior data maps to which neuron v_C in the EM connectome; however, there will be more ambiguity in the map $(v_B, v_C) \mapsto v_A$ for the associated calcium imaging neural activity data. Methodologically, we will first assume that these maps are known; then, based on our assessment of the performance of our algorithms for resolving the ambiguity, we will adapt our cross-modality cluster analysis methodology to account for the extant ambiguity.

Step 1: We must participate in the three experimental data collections, with our colleagues at Janelia Farm. First, the data collection itself is proceeding with our input regarding experimental design. Once the data are collected, data processing must ensure that the three data objects – matrices A, B, and C – are commensurate (in particular, we require full knowledge of the cross-modality neuron identification maps) and appropriate for subsequent cluster analysis.

Step 2: From each of A, B, and C, we will generate a clustering – a partition of $[n]$, which we will denote P_A, P_B, and P_C, respectively. (There is much hidden in the succinct "we will generate a clustering." Each of the three objects are fundamentally different, and thus we require three separate clustering methodologies. Furthermore, as we do not know the "correct" number of clusters, this inherently tricky model selection issue must be addressed ... thrice. Finally, to facilitate our subsequent analysis, it will be preferable to have the three clustering and model selection methodologies be as similar to one another as possible, so that when we compare clusterings we are comparing like clusterings. All of these issues will be formally addressed in conjunction with the Janelia Farm neuroscientists.) A method for comparing partitions, such as the pairwise Adjusted Rand Index – $\mathrm{ARI}(i, j)$ for $i \neq j \in \{P_A, P_B, P_C\}$ – can then be used to assess the similarity of the three clusterings. For example, in the unlikely case that the pairwise ARIs are all equal to one, we conclude that all three data modalities yield identical clusterings. At the other extreme, in the unlikely case that the pairwise ARIs are all equal to zero, we conclude that all three data modalities yield clusterings no more similar to one another than would be expected by chance. The extent to which $\mathrm{ARI}(i, j)$ is larger than zero yet smaller than one will be the starting point for our analysis of the similarities and differences of the three neuronal clusterings.

Step 3: Here we will consider a joint analysis of the three data objects. We begin by constructing a $3n \times 3n$ omnibus matrix M. The three $n \times n$ diagonal blocks of M are given by our three data matrices; that is, $M[1 : n, 1 : n] = A$, $M[n + 1 : 2n, n + 1 : 2n] = B$, and $M[2n + 1 : 3n, 2n + 1 : 3n] = C$. The remaining $n \times n$ off-diagonal blocks of M are all set to equal the $n \times n$ identity matrix I_n, which captures the information that we know the i^{th} neuron in A matches with the i^{th} neuron in B matches with the i^{th} neuron in C. (These off-diagonal blocks of M will have to be altered to account for ambiguity in our cross-modality neuron identification.) From this omnibus matrix, a SMACOF algorithm for multidimensional scaling will be used to generate a Euclidean embedding. That is, we will map $M \mapsto X \in (\mathbb{R}^d)^{3n}$, where the $3n \times d$ matrix X represents each neuron in each modality as a point in $\mathbb{R}^d$ such that the original data similarities and the neuron matching knowledge are simultaneously respected to the extent possible. (The choice of the embedding dimension d is another issue of model selection; principled approaches exist.) The significance of the geometry of this embedding is that when all three embedded points for a single neuron – one each from the calcium imaging neural activity data, the optogenetic behavior data, and the EM wiring diagram – lie close together, then this neurons relationship to the entire collection of neurons is similar *across all three modalities*. Consider clustering these $3n$ points, irrespective of modality, yielding a partition P^M of $[3n]$. Then, using this P^M together with the individual neurons' three modalities we again generate three partitions of $[n]$, denoted P_A^M, P_B^M, and P_C^M. If, for each neuron, the three embedded points lie close together, then these three clusterings will be similar and $\mathrm{ARI}^M(i, j)$ for $i \neq j \in \{P_A^M, P_B^M, P_C^M\}$ will be close to one. If, on the other hand, the optimization is unable to respect the neuron matchings, because the structure of the three similarity matrices are sufficiently different, then these $\mathrm{ARI}^M(i, j)$ values will be closer to zero. Furthermore, the relative geometry of the three modality-specific embeddings will tell us how and why the clusterings differ, providing the basis for a characterization of neural circuitry from behavior, connectivity patterns and activity patterns. For example, we might find that even though a specific collection of neurons cluster together in both P_A^M and P_B^M – that is, based on the embeddings of the calcium imaging neural activity data and the optogenetic behavior data – the geometry of the embedding of the EM wiring diagram does not respect this structure and P_C^M splits the neurons in this collection into multiple clusters. Subsequently, we would be able to investigate, through the geometry of the embedding of the connectome C for this specific collection of neurons, what it is in the structure of the EM wiring diagram that precludes clustering consistency across modalities.

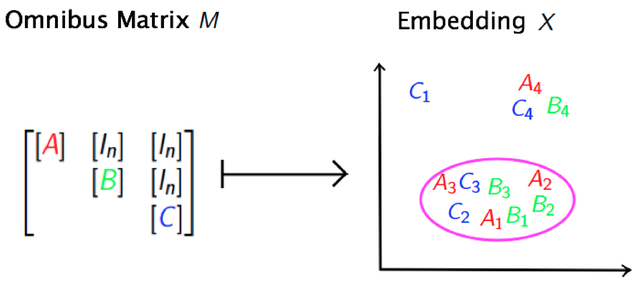


Figure 2: *Artists rendition of the embedding $M \mapsto X$ of the $3n \times 3n$ omnibus matrix M to $X \in (\mathbb{R}^d)^{3n}$. This figure illustrates the example wherein the specific collection of neurons $\{1, 2, 3\}$ cluster together based on the embeddings of the calcium imaging neural activity data A and the optogenetic behavior data B, but the geometry of the embedding of the connectome C does not respect this structure and splits neuron 1 into a separate cluster. Subsequently, we would investigate, through the original omnibus matrix and the geometry of the embedding, what it is in the structure of the connectome that precludes clustering consistency across modalities.*

References

[1] Joshua T Vogelstein, Youngser Park, Tomoko Ohyama, Rex A Kerr, James W Truman, Carey E Priebe, and Marta Zlatic, "Discovery of brainwide neural-behavioral maps via multiscale unsupervised structure learning.," *Science*, vol. 344, no. 6182, pp. 386–392, Apr. 2014.

[2] Timothy O'Leary and Eve Marder, "Neuroscience. Mapping neural activation onto behavior in an entire animal.," *Science*, vol. 344, no. 6182, pp. 372–373, Apr. 2014.

[3] Misha B Ahrens, Michael B Orger, Drew N Robson, Jennifer M Li, and Philipp J Keller, "Whole-brain functional imaging at cellular resolution using light-sheet microscopy," *Nature Methods*, vol. 10, no. 5, pp. 413–420, Mar. 2013.

This work is supported in part by NSF BRAIN EAGER DBI-1451081.