Identifying neurons in *C. elegans* with continuous relaxations for Bayesian permutation inference

Anonymous Author(s)
Affiliation
Address
email

Abstract

The nematode C. elegans is a unique model organism for neuroscientists as its connectome, or neural wiring diagram, has been known for at least three decades. Despite this knowledge, an understanding of the functional significance of these synaptic connections has remained elusive. Now several groups can routinely image the activity of a large fraction of neurons in the head of the worm, providing a unique opportunity to probe this organism. We propose a hierarchical Bayesian framework that combines strong prior information with data from many experiments to estimate posteriors over the functional connectivity weights. However, these attempts are stifled by a major obstacle: in many cases it is not clear exactly which neurons are being imaged, so to combine information across experiments one must solve a matching, or permutation inference, problem.

In this work we introduce new variational methods that enable the joint inference of connectivity weights and neural identity. Working with actual permutations would involve evaluating and differentiating an intractable partition function. As an alternative, we build upon recent continuous relaxation techniques [Jang et al., 2016, Maddison et al., 2016], extending them from the original case of the probability simplex, to the Birkhoff polytope, the convex hull of permutation matrices. We test our method with simulated data from the true connectome and known covariates (neural position) and show that our approach outperforms many alternatives in identifying neurons.

1 Introduction

The nematode *C. elegans* plays a special role as a model organism in neuroscience, since its neural network is stereotyped from animal to animal and its complete neural wiring diagram is known [Varshney et al., 2011]. Modern calcium imaging technology enables simultaneous measurements of hundreds of these neurons simultaneously [Kato et al., 2015, Nguyen et al., 2016]. Thus, the time seems right to employ modern statistical methods to summarize what can be learned about the functional connectome in this system, and to suggest new experiments to constrain our uncertainty further.

To this end, Bayesian inference stands out as the most suited methodological framework, as it allow us to represent hierarchical probabilistic structures, and to integrate our strong priors on the system components (e.g. sparsity patterns in the connectome, and a priori knowledge of approximate neural positions). In the most general setup, we would be interested on posterior inference of a generic dynamical system that dictates the distribution of next neural state, given history, system's input and behavior. Learning and inference in dynamical systems with MCMC methods is rather standard, even in cases with complicated latent structures De Freitas et al. [2001], Paninski et al. [2010]. Further, methods to account for the hierarchical aspect, i.e., incorporating information from many worms are also widely available [Gelman et al., 2014]. However, we note a fundamental technical hurdle

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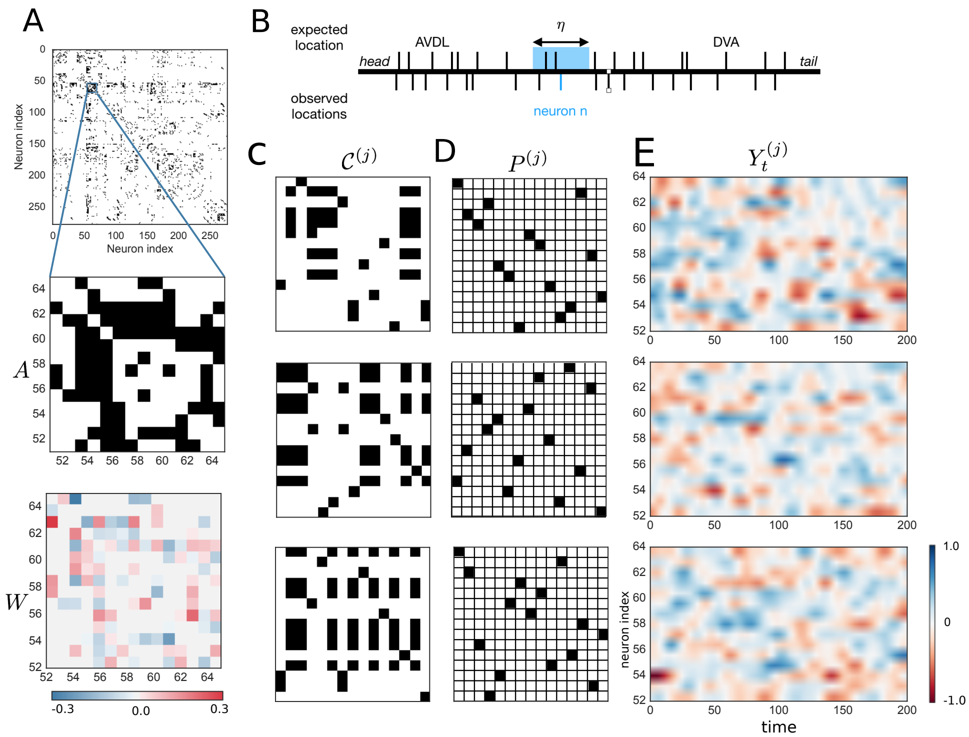

Figure 1: Hierarchical Bayesian framework. **A** We are given the actual adjacency matrix A from [Varshney et al., 2011]. The full matrix is shown (top) along with a zoom-in to 14 neurons (center). We wish to infer the corresponding weight matrix W, an example of which is shown below. **B** We also know the typial locations of the neurons [White et al., 1986, Lints et al., 2005]. Given observed locations, we constrain possible assignments to neuron identities within η of the observed location. **C** These constraints are represented as a matrix $\mathcal{C}^{(j)}$ for worm j which specifies possible assignments of observed neurons to known identities. **D** To infer the weights, we must first infer the permutation $P^{(j)}$ that matches the observed neurons in worm j to the set of known identities. **E** The observed data is a matrix $Y^{(j)}$ whose rows are ordered according to the order in which neurons were observed in that worm. The permutation matrix maps this to the canonical ordering of the adjacency and weight matrices. Given $\{Y^{(j)}\}_{j=1}^{J}$ and A, we infer $\{P^{(j)}\}_{j=1}^{J}$ and W.

complicates our efforts of integrating across-specimens information: in practice, associating recorded traces to neuron names is a painstaking process; experimenters consider the location of the neuron along with its pattern of activity to perform this matching, but the process is laborious and the results prone to error. In the lack of this association, it is impossible to represent recordings canonically, where indexes point to actual neuron names, common to all worms. This technical problem, then, prevent us from automatically applying hierarchical methods.

In this work we present a method for overcoming this hurdle, by incorporating inference over *canonicalizing* permutations. For the sake of simplicity, we focus on the most elementary non-trivial dynamical system. Specifically, given the connectome [Varshney et al., 2011] encoded as a $N = 282$ dimensional (number of somatic neurons) adjacency matrix $A \in \{0,1\}^{N,N}$ (Figure 1A) and J worms, we consider the following hierarchical model with shared linear dynamics (represented by a weight matrix W) to represent the recorded traces $Y_t^{(j)} \in \mathcal{R}^N$ during T timesteps:

$$Y_t^{(j)} = P^{(j)} \left(W \odot A\right) Y_{t-1}^{(j)} {P^{(j)}}^\top + \varepsilon_t^{(j)}, \tag{1}$$
$$\varepsilon_t^{(j)} \sim \mathcal{N}(0, I_N), \quad W \sim \mathcal{N}(0, \sigma_w^2 I_N), \quad P^{(j)} \sim \mathrm{Uniform}(\mathcal{P}_N^{(j)}).$$

The operation $W \odot A$ represents the component-wise product with the adjacency matrix, inducing sparseness in the linear system, and reducing dimensionality. For each worm, we represent by the permutation matrix $P^{(j)}$ the matching between recorded indexes and a canonical arbitrary order. These permutations are confined to the a subset $P_N^{(j)}$, that contains the admissible permutations, based on covariate information. Specifically, we use neural position along the worm's body to constrain the possible neural identities for a given recorded neuron. We use the known positions of each neuron [Lints et al., 2005], approximating the worm as a one-dimensional object with neurons locations distributed as in Fig. 1B. Then, given reported positions of the neurons (Figure 1B) we can conceive a binary confusion matrix $\mathcal{C}^{(j)}$ so that $\mathcal{C}^{(j)}_{mn} = 1$ (observed) neuron m is close enough to (canonical) neuron n; i.e., if their distance is smaller than a tolerance η (Figure 1C) . Also, absolute certainty of neural identity can be encoded in this matrix, by imposing $\mathcal{C}^{(j)}_{mn} = 1$ in for only true index n.

In this setup, then, we are concerned with joint posterior inference of $p(\{W, P^{(j)}\})$. Although this problem may be also addressed with MCMC, and in practice poor mixing is observed, motivating the use or alternative tools. Here, we cast this problem as an instance of the *variational inference* (VI) framework [Blei et al., 2017] and develop new tools the applicability of this framework to the case where the latent variables are permutation, a case that substantially deviates from the standard practice. In section 2 we detail our VI formulation and summarize our developed methods. Finally, in section 3 we show our findings; notably, the supremacy of our method over the naive MCMC sampler.

2 New methods for variational inference of latent permutations

Consider a latent variable model determined by a prior over the latent $z \sim p(z)$ and a likelihood $p(y|z)$ for the observed data y. In the VI framework, instead of accessing the perhaps intractable posterior $p(z|y)$ one aims to find the distribution $q(z;\nu)$ among a certain variational family, parameterized by $\nu \in \mathcal{V}$, such that it minimizes its discrepancy with $p(z|y)$. Typically, one considers the KL divergence:

$$\nu^* = \arg\min_{\nu \in \mathcal{V}} KL\left(p(z|y) \| q(z;\nu)\right). \tag{2}$$

In turn, one can show that the above problem is equivalent to the maximization of the *evidence lower bound* (ELBO):

$$\nu^* = \arg\max_{\nu \in \mathcal{V}} ELBO(q(z;\nu)) \equiv E_{q(z;\nu)}(\log p(y|z)) - KL(q(z;\nu) \| p(z)). \tag{3}$$

To maximize equation (3) one usually appeals to stochastic optimization methods [Kushner and Yin, 1987]: specifically, all the expectations involved in (3) are approximated by Monte Carlo samples, and gradient descent iterations are then performed to this approximation. One critical component is the choice of the Monte Carlo approximation. Perhaps the most common choice is through the so called *score function estimator*, which bases upon the identity $h(\nu)\nabla_\nu \log h(\nu) = \nabla_\nu h(\nu)$. Unfortunately, this estimator, also referred to as REINFORCE [Williams, 1992], cannot be applied to permutations, since it involves the evaluation and differentiation of a likelihood which is intractable for any non-trivial distribution over permutations (computing the partition function involves a summation over N! terms).

An appealing alternative comes from the re-parameterization trick Kingma and Welling [2013], which leads to a new gradient estimator if one can re-parameterize z as a differentiable function of a noise distribution and the parameters; i.e., if for certain f and $\xi \sim p(\xi)$ one has $z = f(\xi, \nu)$. In the case of discrete random variables a re-parameterization always exists and it is given by the *Gumbel trick* [Papandreou and Yuille, 2011, Balog et al., 2017], which states that one can sample from any discrete distribution by perturbing each potential with Gumbel i.i.d noise, and then finding the configuration with the maximum value. Unfortunately, the underlying f to this re-parameterization is the non-differentiable $\arg\max$ operator, precluding the use of gradient descent methods.

Recent work by [Jang et al., 2016, Maddison et al., 2016] proposed a solution to this problem, by replacing the $\arg\max$ by a temperature (τ) dependent $\mathrm{softmax}$ approximation, which in the limit converges to the original $\arg\max$. By combining the Gumbel trick with the softmax approximation, they conceived the *Concrete* or *Gumbel-Softmax* distribution, and obtain explicit distribution formulae. Then, they showed one can learn on a discrete latent variable model using the re-parameterization trick and gradient descent, by replacing the original ELBO with the surrogate arising by this continuous relaxation, as long as τ is chosen in a reasonable range: not too high as it would lead to a degenerate distribution in the simplex; but also not too low, to avoid too high variances of the gradients.

We developed three methods for extending the above to permutations. We name then *stick-breaking*, *rounding* and *Gumbel-Sinkhorn* methods. We refer the reader to sections 3.1 and 3.2 of Linderman et al. [2017] and section 4 of Anonymous [2018] for details, respectively. Here we briefly summarize them: in all of them the primary geometric object is the Birkhoff polytope, the convex hull of permutation matrices, and analog to the probability simplex in this case. For the stick-breaking construction, we generalize to this polytope the one that exists in the simplex [Linderman et al., 2015], surmounting a new complication; of being able to consistently "break the stick" while satisfying both the row and column constrains that characterize a doubly stochastic matrix. For the rounding construction, we start by a noise distribution and force it to be close to permutation matrices by pulling them towards the extreme-points of the Birkhoff polytope. Finally, for the Gumbel-Sinkhorn method we notice that the so-called *Sinkhorn operator*, or infinite and successive row and column normalization of a matrix, is a a natural extension of the softmax operator. With this, we are able to conceive the Gumbel-Sinkhorn distribution, which approximates the sampling of a relevant discrete distribution. Importantly, while stick-breaking and rounding yield explicit densities, Gumbel-Sinkhorn does not. However, there are ways to circumvent this difficulty, and overall we observe the latter performs the best.

3 Results

We compared against three methods: (i) naive variational inference, where we do not enforce the constraint that $X^{(j)}$ be a permutation and instead treat each row of $X^{(j)}$ as a Dirichlet distributed vector; (ii) MCMC, where we alternate between sampling from the conditionals of W (Gaussian) and $X^{(j)}$, from which one can sample by proposing local swaps, as described in Diaconis [2009], and (iii) maximum a posteriori estimation (MAP). Our MAP algorithm alternates between the optimizing estimate of W given $\{X^{(m)}, Y^{(m)}\}$ using linear regression and finding the optimal $X^{(j)}$. The second step requires solving a quadratic assignment problem (QAP) in $X^{(j)}$; that is, it can be expressed as $\mathrm{Tr}(AXBX^{\mathsf{T}})$ for matrices A, B. We used the QAP solver proposed by Vogelstein et al. [2015].

We found that our method outperforms each baseline, Specifically, we show that our method outperforms alternatives when there are many possible candidates (Table 1) and when only a small proportion of neurons are known with certitude (Table 2). Altogether, these results indicate our method enables a more efficient use of information than its alternatives. This is consistent with other results showing faster convergence of variational inference over MCMC [Blei et al., 2017], especially with simple Metropolis-Hastings proposals. We conjecture that MCMC could eventually obtain similar if not better results, if current local proposals—swapping pairs of labels— were replaced by more involved ones.

	10		30		45		60	
	1 worm	4 worms	1 Worm	4 worms	1 worm	4 worms	1 worms	4 worms
NAIVE VI	.34	.32	.16	.16	.13	.12	.11	.12
MAP	.34	.32	.17	.17	.14	.13	.13	.12
MCMC	.34	.65	.18	.28	.14	.17	.13	.15
VI	**.79**	**.94**	**.4**	**.69**	**.25**	**.51**	**.21**	**.44**

Table 1: Accuracy in the C.elegans neural identification problem, for varying mean number of candidate neurons (10, 30, 45, 60) and number of worms.

	40.%		30.%		20.%		10.%	
	$\eta = 0.1$	$\eta = 0.2$	$\eta = 0.1$	$\eta = 0.2$	$\eta = 0.1$	$\eta = 0.2$	$\eta = 0.1$	$\eta = 0.2$
Naive VI .43	.41	.33	.31	.23	.22	.12	.1	
MAP	.42	.41	.33	.32	.23	.22	.12	.11
MCMC	.85	.80	.52	.46	.3	.26	.15	.12
VI	**.97**	**.96**	**.92**	**.84**	**.74**	**.58**	**.44**	**.23**

Table 2: Accuracy in inferring true neural identity for different of proportion of known neurons, and two values of η.

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