

# Scoring Sequences of Hippocampal Activity using Hidden Markov Models

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**Abstract**—We propose a novel sequence score which we expect will enable us to detect and analyze hippocampal replay more effectively than current approaches. In particular, we show how hidden Markov models (HMMs) can be used to model and analyze sequences of neural activity, and how the resulting joint probability of an observation sequence and an underlying sequence of states naturally lead to the development of a two component sequence score in which the sequential and contextual information are decoupled. We also show how this score can discriminate between true and shuffled sequences of hippocampal neural activity.

## I. INTRODUCTION

Numerous experiments connect ensemble spiking with behavior during learning and memory recall, but the mechanistic role(s) of “introspection”—internally generated spiking during behavioral pauses, quiescence or sleep—has been harder to probe. To address the role of internally generated activity we focus on the phenomenon of sequential reactivation (“replay”) in the hippocampus—a region of the brain critical for memory.

The reliable detection and subsequent analysis of such replay events are challenging tasks, and in this paper we develop some of the tools necessary for such an undertaking. In particular, we use hidden Markov models (HMMs) to characterize sequences of neural activity, and we use the HMM framework to derive a two component sequence score that can help us to detect, and quantify the quality of replay events. This score evaluates both contextual as well as sequential (trajectory) information of putative sequences. HMMs are perfectly suited to model replay events—where behavioral correlates are unobservable—but in this paper we deliberately limit our attention to sequences of neural activity for which the behavioral correlates (the animal’s position as a function of time) are known, so that we can demonstrate and evaluate the efficacy of our novel sequence score.

Populations of place cells in the hippocampus are known to encode an animal’s location in its environment, and this population code was studied using a HMM and nonparametric extensions by [1]. In particular they showed that as expected, the latent states of the hippocampus found by the HMM during active exploration correspond to spatial

locations in the environment, and they further showed that nonparametric Bayesian extensions to the HMM were useful to dynamically infer the number of hidden states in the model, and that the predictive performance could be improved by explicitly modeling the durations between state transitions using a hidden semi-Markov model [2].

Even though [1] and [2] did not consider replay events specifically, the HMM framework is ideally suited for it and applies without modification, and we may reasonably expect the same findings to hold true for replay events as was found for hippocampal sequences during active exploration. In particular, we expect that the states underlying (or encoded in) replay events correspond to spatial locations. If indeed the states underlying replay events represent spatial locations, then these states can be thought of as *virtual place fields*, and we should expect to see plausible trajectories through the virtual place field states during replay events.

How then can we determine whether or not sequences of neural activity (especially during replay events) represent spatially consistent trajectories through these virtual place fields? If the environment under consideration is relatively simple, then one commonly used approach is to construct templates of neural activity corresponding to particular trajectories through the environment, and to use some template matching approach to determine how closely the neural activity matches that of the templates (see e.g. [3]). Unfortunately, it is difficult to extend such an approach to more complicated environments, since the number of required templates can quickly become prohibitively large. In addition, [4] showed that replay events can represent trajectories through the environment that were never explicitly experienced (such as shortcuts), for which no templates (which are based on experienced activity) would exist. Furthermore, what if we only have access to the neural activity during quiescent states (i.e., we cannot observe the behavioral correlates of the neural activity), so that constructing templates would be impossible?

Here we describe how we can use the HMM framework to effectively learn the underlying hidden states (virtual place fields), and the approach is agnostic to whether the behavioral correlates are available or not. We also demonstrate how our novel sequence score can be used to determine to what extent the neural activity is consistent with trajectories through the virtual place fields in an associated environment.

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## II. HIDDEN MARKOV MODELS OF SEQUENTIAL NEURAL ACTIVITY

HMMs are statistical models where the systems being modeled are Markov chains (or more generally Markov processes) with unobserved or hidden states, and they have been widely used for sequential pattern recognition and processing in fields ranging from speech recognition to bioinformatics (see [5] for an excellent tutorial introduction).

In this section we loosely follow the approach and notation presented by [1] to demonstrate how HMMs can be used to model sequential neural activity, and we also present our two-component sequence score, which we use to characterize sequences in terms of their sequential consistency, as well as their contextual activity.

### A. Model specification

Let  $\mathbf{y}_t$  denote the *observation* at time  $t$ , where  $\mathbf{y}_t \in \mathbb{Z}^C$  is a vector of spike counts for  $C$  hippocampal place cells. It is assumed that the observations are sampled at discrete, equally-spaced time intervals, so that  $t$  can be an integer-valued index, with some associated  $\Delta t$ .

We further assume that the hidden state space is *discrete*. That is,  $S_t \in \{1, \dots, m\}$  can take on one of  $m$  possible states, with each possible state loosely corresponding to a particular location in the environment (a “virtual place field”).

To define a probability distribution over sequences of observations, we then need to specify a probability distribution over the initial state  $P(S_1)$ , with  $\pi_i \equiv \Pr(S_1 = i)$ , the  $m \times m$  state transition probability matrix,  $\mathbf{P}$ , with  $\mathbf{P}_{ij}$  defining  $P(S_t = j | S_{t-1} = i)$ , and the output or emissions model defining  $P(\mathbf{y}_t | S_t)$ .

We will further assume that our model is time-invariant: the state transition probability matrix and the output model does not change over time. The state sequences are also assumed Markovian, so that  $P(S_t | S_{t-1}, \dots, S_1) = P(S_t | S_{t-1})$ —that is, the state sequence forms a first order Markov chain—and we also assume that observations are conditionally independent given the underlying states.

For the output model we assume Poisson firing statistics for each spike train, so that the emission probability for the  $i$ th state is modeled by a spatially varying (state-dependent) multivariate Poisson process:

$$\begin{aligned} P(\mathbf{y}_t | S_t = i; \theta) &= \prod_{c=1}^C P(y_{c,t} | S_t = i; \theta) \\ &= \prod_{c=1}^C \prod_{j=1}^m P(y_{c,t} | S_t = j; \theta)^{S_{t,i}} \\ &= \prod_{c=1}^C \prod_{j=1}^m \left( \frac{\exp(-\lambda_{jc}) \lambda_{jc}^{y_{c,t}}}{y_{c,t}!} \right)^{S_{t,i}} \end{aligned}$$

where  $\theta = \{\pi, \mathbf{P}, \mathbf{\Lambda}\}$  are the model parameters,  $\mathbf{\Lambda} \in \mathbb{R}^{m \times C}$  are the tuning curve parameters (a spike firing rate  $\lambda$  for every possible state  $j \in \{1 \dots m\}$  for each place cell  $c \in \{1, \dots, C\}$ ), and  $S_{t,i} = 1$  iff  $S_t = i$ , and 0 otherwise.

Given a training set  $\mathcal{D} = \{\mathbf{y}_{1:T_1}^{(1)}, \dots, \mathbf{y}_{1:T_N}^{(N)}\}$ , containing  $N$  sequences of observations, and since the training sequences are assumed to have been drawn independently, the complete data likelihood takes the form

$$P(\mathcal{D}, \mathbf{S} | \theta) = \prod_{n=1}^N P(\mathbf{y}_{1:T_n}^{(n)} | \theta, S_{1:T_n}^{(n)}) P(S_{1:T_n}^{(n)}). \quad (1)$$

The model parameters  $\theta = \{\pi, \mathbf{P}, \mathbf{\Lambda}\}$  can then be estimated using standard methods such as expectation maximization, variational Bayes, or Monte Carlo methods (the solutions presented in [5] use expectation maximization, for example).

Making the dependence on  $\theta$  implicit, the joint distribution of a sequence of states and the resulting observations can then be factored as follows:

$$P(S_{1:T}, \mathbf{y}_{1:T}) = P(S_1) P(\mathbf{y}_1 | S_1) \prod_{t=2}^T P(S_t | S_{t-1}) P(\mathbf{y}_t | S_t), \quad (2)$$

which is equivalent to

$$P(S_{1:T}, \mathbf{y}_{1:T}) = \underbrace{\left[ P(S_1) \prod_{t=2}^T P(S_t | S_{t-1}) \right]}_{\text{sequential (seq)}} \underbrace{\left[ \prod_{t=1}^T P(\mathbf{y}_t | S_t) \right]}_{\text{contextual (ctx)}}. \quad (3)$$

We base our novel sequence score, introduced next, on (3).

### B. Sequence scoring

HMMs are useful in analyzing and modeling sequential neural activity, and allow us to answer questions such as “what is the *most probable underlying sequence of states*?” for a particular sequence of observations—this is analogous to *decoding* position from the neural activity—or “how likely is a particular sequence of observations?”. Furthermore, it is often useful to score these sequences. Indeed, several scores (sometimes referred to as metrics) have previously been proposed for sequences of hippocampal replay activity [4], [6], [7], where a score is critical to help decide whether a sequence is truly replay, or whether it is simply a result of chance neural activity. The ability to quantify the quality of a sequence is another attractive reason to use such a score.

We are interested in evaluating (i) how well a particular sequence of observations fit in an underlying context, and (ii) how well that sequence captures the sequential nature of an associated (experienced or imaginary) trajectory through the environment, and (iii) we want to be able to compare different sequences (possibly of different lengths) to each other using these criteria. Ideally, we also need to study the error statistics of any score that we use, so that we can answer questions such as “What is the chance that random neural activity would achieve a particular score or better?” and “What is the chance that a real sequence would achieve a given score threshold?” (see e.g. [8]). Instead of analyzing error statistics, many authors choose to compare their scores (of putative sequences) to scores obtained when shuffling the sequences in a variety of ways.

1) *Existing sequence and replay scores*: Probably the most widely used scores for replay sequences include the “replay score” by [6], and the weighted correlation, defined as Pearson’s product-moment correlation weighted by the decoded posterior probability [9]. A decoding-free approach was also presented by [4]. More recently, [7] summarized six previously used metrics, namely the (i) weighted correlation, (ii) maximum jump distance, (iii) slope of the best linear fitted trajectory along the entire track, (iv) aforementioned replay score, (v) sharpness of decoded probability, and (vi) position occupancy. They found that the maximum jump distance along with correlation were the strongest differentiating factors. The jump distance captures the continuity of movement, while the correlation captures the population neural activity (including both sequential and contextual information). Other scores exist too (see again e.g. [8]), but the scores presented there assume that all the sequences must be the same length, making the comparison and evaluation of sequences of different lengths challenging.

Indeed, none of the abovementioned scores can directly answer our questions about the decoupled contextual and sequential information in a sequence, and several of them assume linear, constant velocity motion, and have several empirical filtering steps, such that a more elegant, and more general solution is needed. Our novel two component score is an attempt to improve on these existing scores.

2) *Novel sequence score*: We consider the *contextual* and *sequential* factors of the joint distribution of a (known) sequence of states and its associated sequence of observations, as given in (3), and we modify them as follows:

$$q_{\text{ctx}} = \frac{1}{T} \sum_{t=1}^T \max_S \left\{ \log P(\mathbf{y}_t | S) \right\} \quad \text{and} \quad (4)$$

$$q_{\text{seq}} = \log |\mathcal{S}| + \frac{1}{T} \left( \log P(\mathbf{y}_1) + \sum_{t=2}^T \log P(\mathbf{y}_t | \mathbf{y}_{t-1}) \right) \quad (5)$$

where  $|\mathcal{S}|$  denotes the cardinality of the set of states visited:  $\mathcal{S} = \{S_t\}_{t=1}^T$ . That is,  $|\mathcal{S}|$  is simply the number of unique states visited in the sequence, but since the true state sequence might be unknown, we will use the Viterbi sequence instead. Here we also divide the log probabilities by the sequence length,  $T$ , to normalize the scores for sequences of different lengths.

Note that in evaluating the contextual component (which tells us how well the neural activity matches the tuning curves associated with the virtual place fields) of a sequence, we evaluate the probabilities using the symbol-by-symbol memoryless maximum a posteriori (MAP) state estimates at each time point: we do this so that the contextual score is free from any model-imposed trajectory structure, and only depends on the unordered, spatially independent population activity in any given context.

Our two component score (i) is easy to interpret (without the need to first compare them to scores obtained from shuffle distributions), (ii) accommodates sequences of different lengths, (iii) is appropriate for complex environments without modification (including nonlinear movement, both in terms

of speed and trajectory), and (iv) directly penalizes sequences of neural activity for which an animal is close to being stationary (this is in contrast to existing approaches, where a minimum velocity threshold is usually used along with an average velocity for the sequence).

It is encouraging that the factorization of the joint distribution of (3) naturally leads to the sequential and contextual factors, and that [7] found the maximum jump distance (sequential information) and weighted correlation (contextual information) the most useful in discriminating between real sequences and random data. However, the weighted correlation is not completely decoupled from the sequential information as is the case with our score, so that we argue that it is easier to interpret our contextual and sequential components than the weighted correlation. Similarly, the maximum jump distance is a very coarse metric for sequential activity, so that we argue that our sequential score component is more elegant and informative (it summarizes the sequential nature of the entire sequence, and not just one particular time step, as is the case for the maximum jump distance).

### III. RESULTS

To demonstrate the efficacy of our novel sequence score in discriminating true sequences from random data, we used data from the online repository `CRCNS.org`. In particular, we used the hippocampal data set `hc-3`, with animal `gor1` which ran on two linear tracks per day<sup>1</sup> (see [10] for details). Here, results are shown for the second session of day one, but similar results are obtained for every session<sup>2</sup>.

Fig. 1 shows the ( $m = 20$ ) state transition probability matrix learnt from about half of the subsequences that were extracted during active behavior (when the animal was moving at least  $3 \text{ cm}\cdot\text{s}^{-1}$ ). Note the strong diagonal, which reveals that the timescale of the binned data is much faster than that of the inferred state transitions. Nevertheless, we can see that the model captured the linear movement quite well (for which we expect a matrix with a small upper bandwidth).

Using this HMM, we computed the contextual and sequential scores for the remaining subsequences during active behavior. The scores are shown in Fig. 2 where the sequences are clearly separated from the trajectory-shuffled data. The trajectory shuffle only shuffles the binned spike count data so that the time bins are out of sequence. This type of shuffle should make it more difficult to discriminate between real and shuffled sequences than other commonly used shuffling strategies including the unit identity shuffle (see e.g. [6]), since the trajectory shuffle leaves the correlations between place cells unaltered. Indeed, the contextual score is completely invariant to the trajectory shuffle, whereas it will be highly affected by most other shuffling techniques.

Aside from the few samples close to the margin (which are there mostly due to being short sequences), the sequen-

<sup>1</sup>The linear tracks are actually the same track, just in a different position/orientation.

<sup>2</sup>The second session was chosen for this day, since the position data for the first session are incomplete.

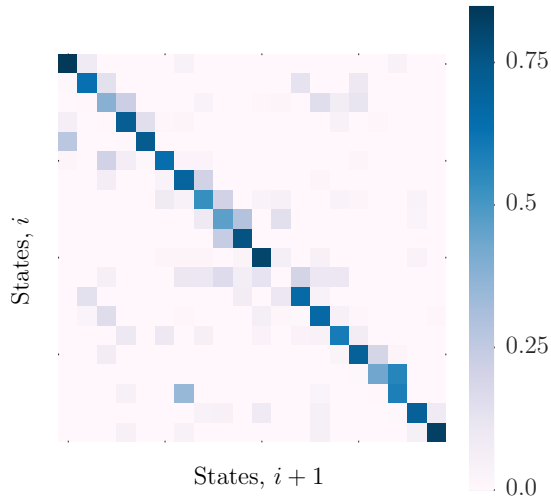


Fig. 1. Ordered state transition matrix ( $m = 20$  states) learnt from a random subset ( $\approx 50\%$ ) of subsequences during active ( $> 3 \text{ cm} \cdot \text{s}^{-1}$ ) locomotion.

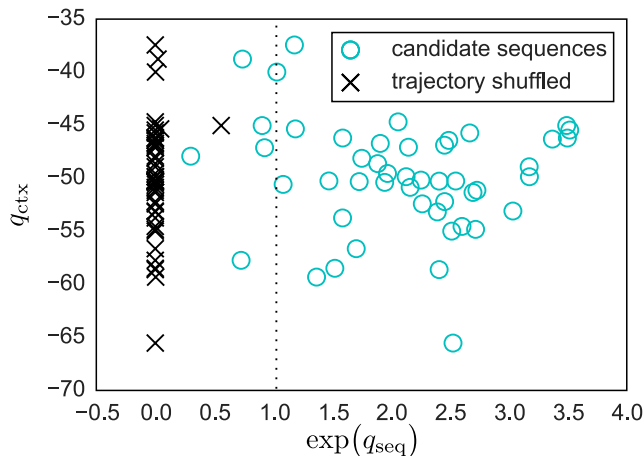


Fig. 2. Sequence scores for previously unseen sequences and trajectory-shuffled versions of those sequences. Note that the contextual score is invariant to trajectory-shuffling, and that the sequential score clearly discriminates between true and shuffled sequences.

tial score alone clearly discriminates true sequences from shuffled data, and the scores are interpretable even without this comparison—exponentiated sequential scores close to or above 1.0 are expected to stem from true sequences, and higher scores usually imply sequences with longer travel distances (more states were visited).

#### IV. DISCUSSION

The results are shown for sequences during active behavior, because we know the true positions of the animal during those times. However, the idea is really to use this sequence score for replay detection and analysis, where the true (or even the imagined) position is unknown and unobservable. Indeed, HMMs are ideally suited to the replay case (where the underlying states are truly unobservable), and work equally well when using *only* data from replay events, unlike the template matching or Bayesian decoding approaches for which behavioral data is a prerequisite.

Using HMMs for the analysis of sequential data allows us to do many other interesting things too. For example, it is very simple (and very effective) to learn different models in different contexts, and then to evaluate a sample sequence and to determine from which (if any) of those contexts the sequence was derived. We have also trained models using *only* sequences corresponding to active behavior, and different models using *only* sequences corresponding to sharp wave ripple (SWR) events (with which replay sequences co-occur, and which is trained on a compressed timescale), and we are then able to (i) discriminate between SWR and active behavior sequences (after normalizing the timescales), but also to (ii) meaningfully evaluate SWR sequences in the active behavior models, and vice versa.

#### V. CONCLUSION

HMMs are ideally suited for sequential analysis, and even more so in the case of replay, where the underlying states are unobservable. We have shown how HMMs can be used to model and analyze neural activity, and we have shown how it leads to our novel two component sequence score, which is interpretable even in the absence of scores of shuffled data, and which can easily discriminate between real sequences and shuffled data. We will use this score to perform replay detection and analysis, and we believe that our score is an improvement on (refinement of) the two metrics used by [7].

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