



Towards a principled decoding of hippocampal replay

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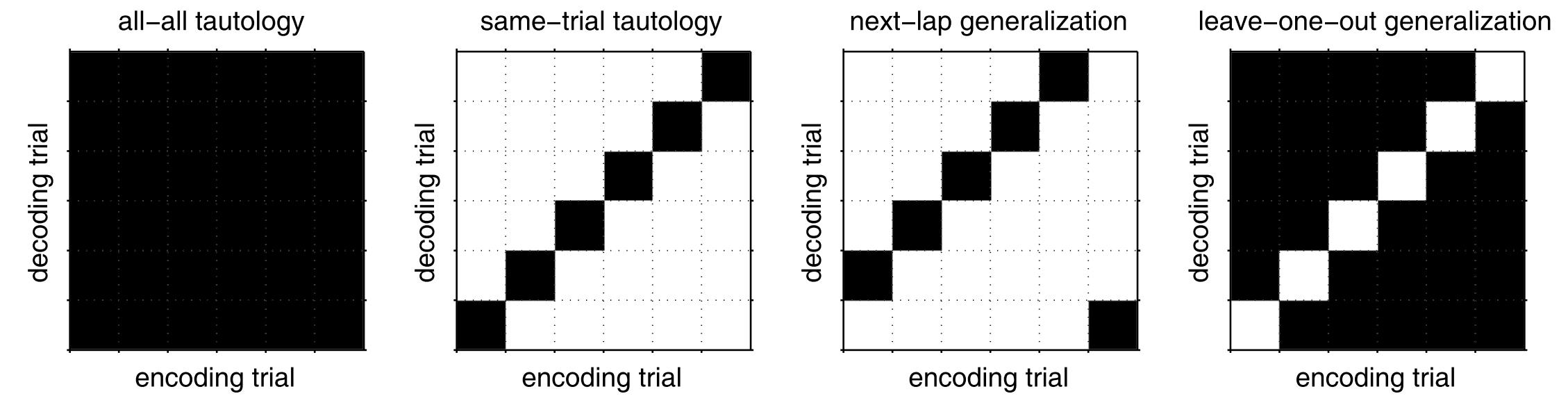
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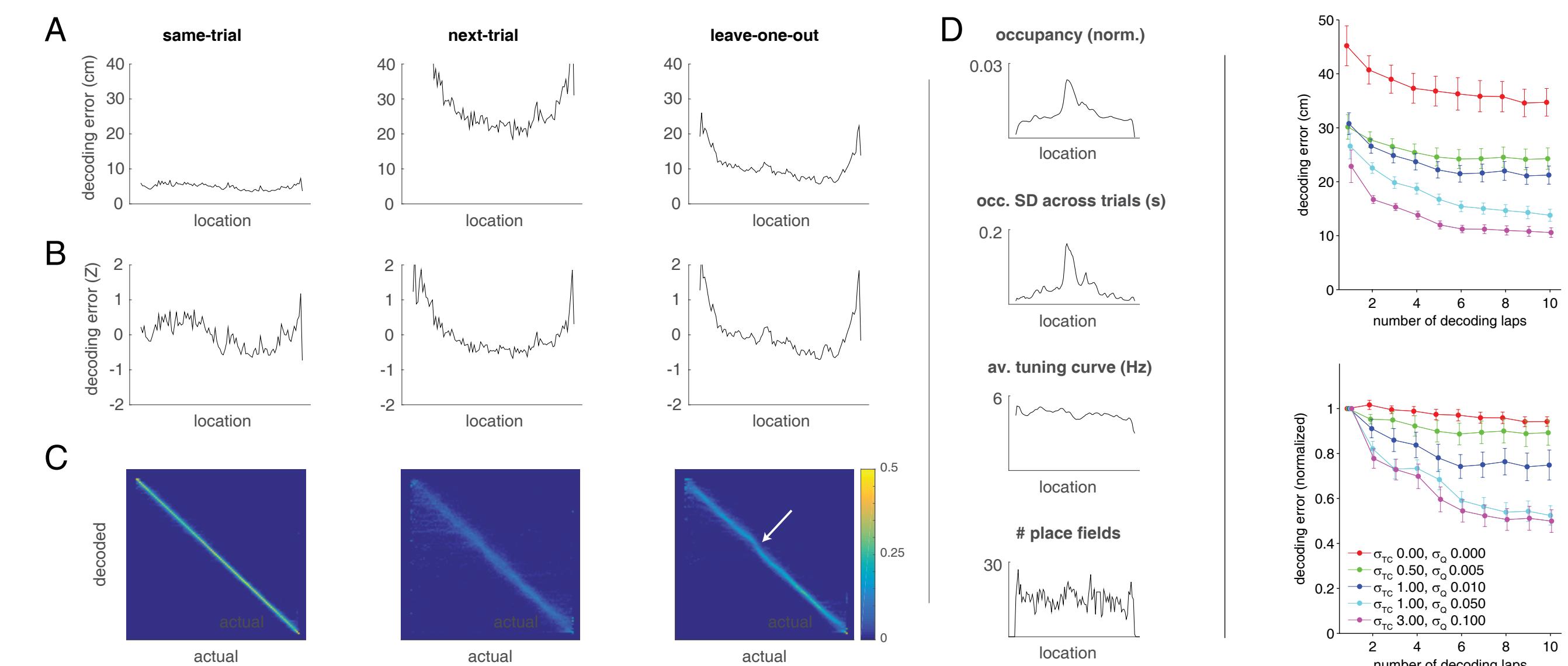
Decoding replay requires optimizing for generalization



Decoding requires a mapping from position (x) to firing rates (n), which can be estimated from data when position is known. Splitting the data into a training set for estimating this encoding model and a testing set for evaluating decoding accuracy -- common practice in statistics and machine learning, but not consistently applied in place cell decoding studies -- is important for two reasons:

- 1) to prevent overfitting (fitting the model to "noise"; idiosyncratic features of individual trials that may be present even when the underlying encoding model does not change)
- 2) to model scenarios in which the true encoding model is changing (as likely happens for replay)

Cross-validation unmasks biases in decoding accuracy



Raw (A) and normalized (B) decoding errors as a function of location differ for different data splits. For instance, increases in decoding error at the start and of the track are only apparent for cross-validated decoding. This is crucial when interpreting the results of decoding replay: for instance, an "effect" of replay content emphasizing the choice point is in fact simply expected from lower generalization performance in these areas. Using 5 or more trials is sufficient for stable decoding accuracy (right column).

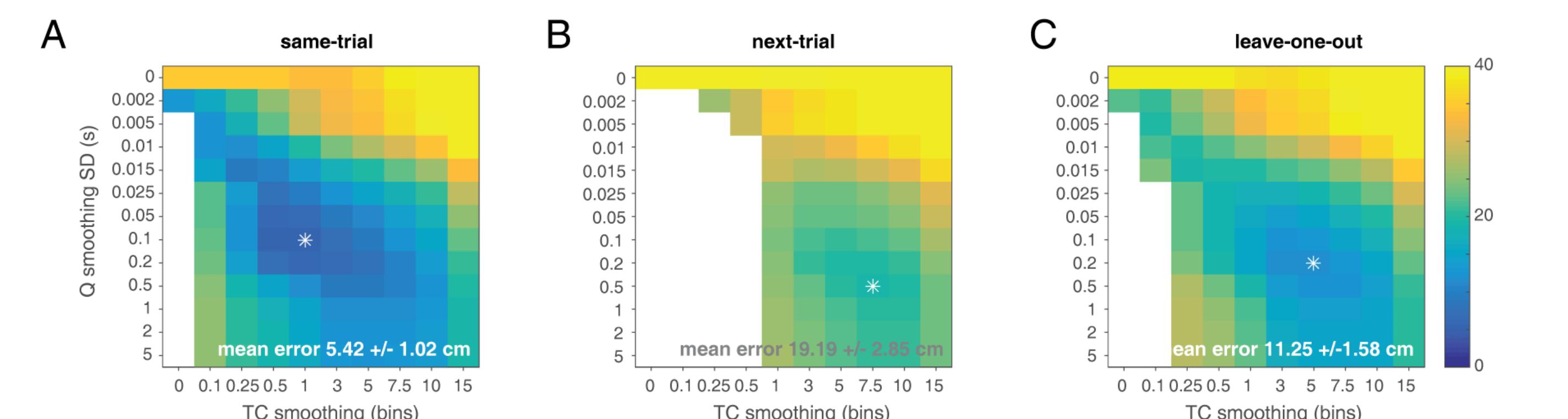
Overfitting or changes in neural code?

Why is there a difference between tautological and cross-validated decoding? Comparing decoding errors across trials reveals the relative contributions of overfitting (A, compare same-trial and next-trial) and drift in the hippocampal code for place.

The increase in decoding error with increasing trial distance could not be explained by overt behavioral differences, such as the difference in trial time and distance run (linear mixed model fits including all nuisance variables were significantly improved by adding trial distance or elapsed time between trials).

This is consistent with observations of encoding of trial-unique features in the hippocampal place code (e.g. Allen et al. 2012), a gradually changing temporal context (Howard & Kahana, 2002) and changes in the place code (Ziv et al. 2013), and suggests replay may similarly carry trial-unique signatures (Takahashi, 2015).

Decoding with spike density functions improves accuracy



Pseudocolor (above) shows the mean decoding error (in cm). Results here shown were obtained with a decoding time bin size (τ) of 25ms; only sessions with at least 20 cells were included. The white star indicates the parameter combination resulting in the lowest mean decoding error along with the standard error over subjects ($n=4$; 19 sessions total).

References

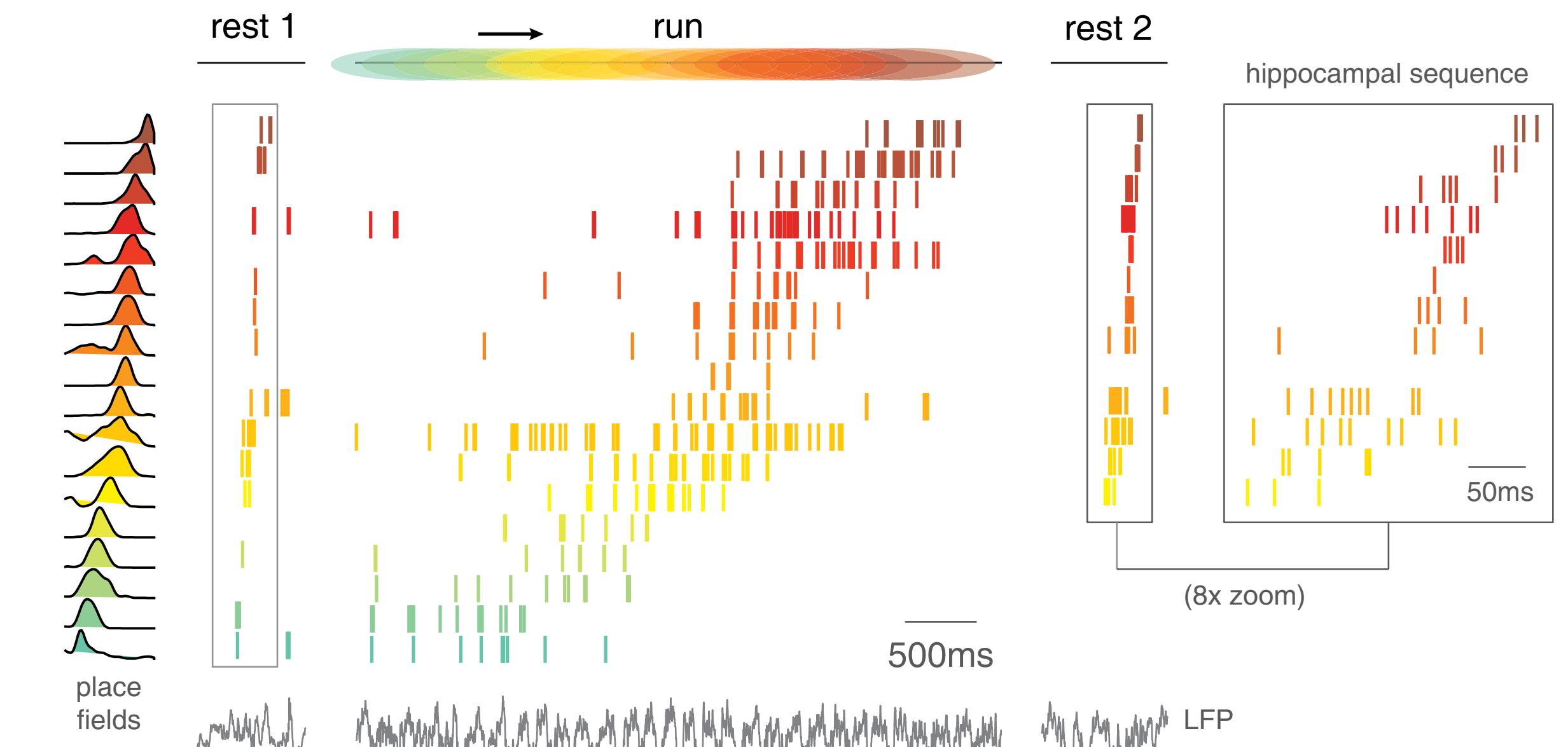
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Introduction

Hippocampal place cell activity forms internally generated sequences called "replays" that represent spatiotemporal trajectories during periods of rest or quiescence. There is much current interest in decoding the content of these sequences, in order to access the contents of memory retrieval, consolidation and planning. However, because these sequences are covert phenomena (i.e., without observable behavior) it is unclear how a principled approach to decoding these sequences can be made in the absence of ground truth. Here, we present a dual approach framework to systematically quantify

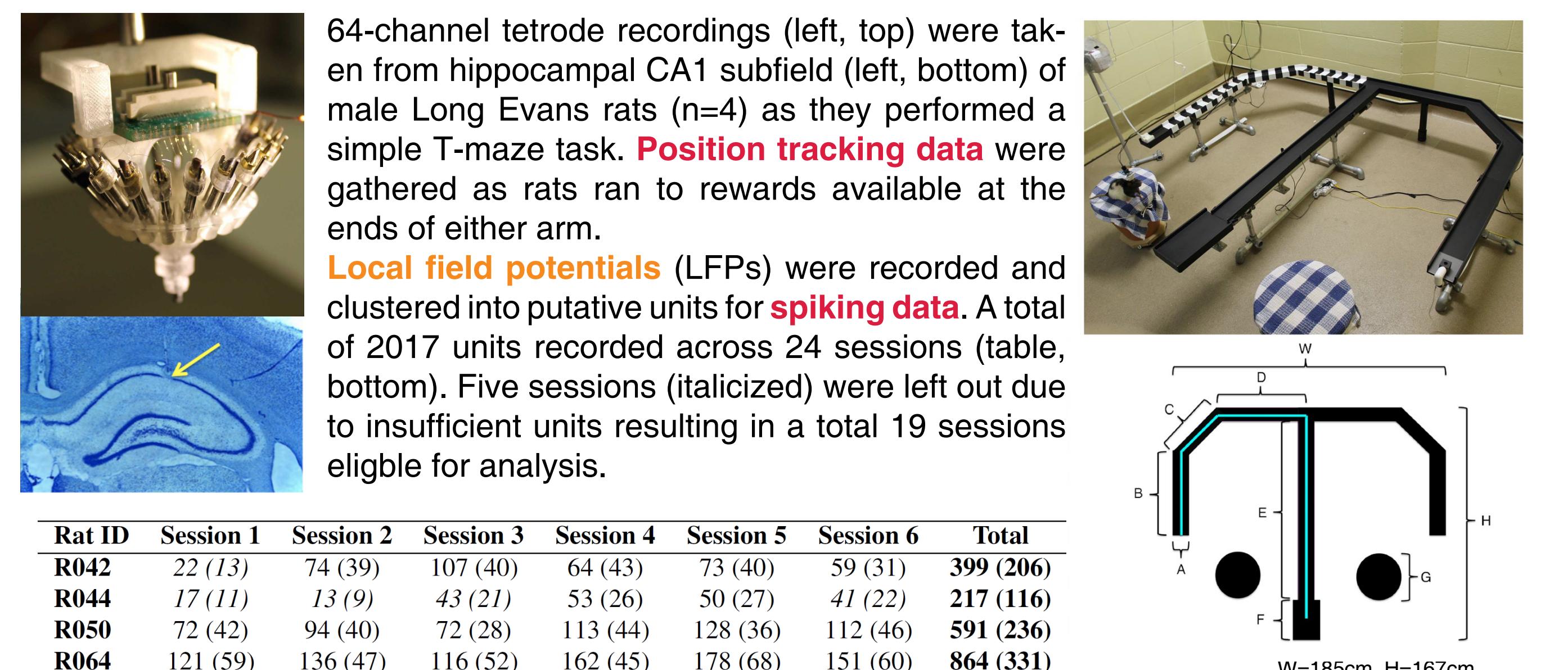
and improve decoding of these covert phenomena. The first is to optimize decoding for generalization performance and quantify the effect or parameter choice and biases in the input data on decoding accuracy. The second is to develop a generative model of hippocampal replay and establish a suite of population level statistical measures. To the extent that the model generated data is a good description of experimental data at the population level, the simulated data can then be used to determine how to best approach decoding the (now known) ground truth [1].

What are hippocampal replays?



Sequential activation of place cells occurs as an animal moves through an environment. These sequences can be reactivated during different behaviours (e.g., sleep, grooming, rest) and are separable by timescales (run vs rest1/rest2). The local field potential (LFP) has two major oscillations of interest. Theta (~6–10Hz) is observed during locomotion and active sensing (middle-bottom) while sharp-wave ripples (~150–250Hz) are observed during rest (left/right bottom).

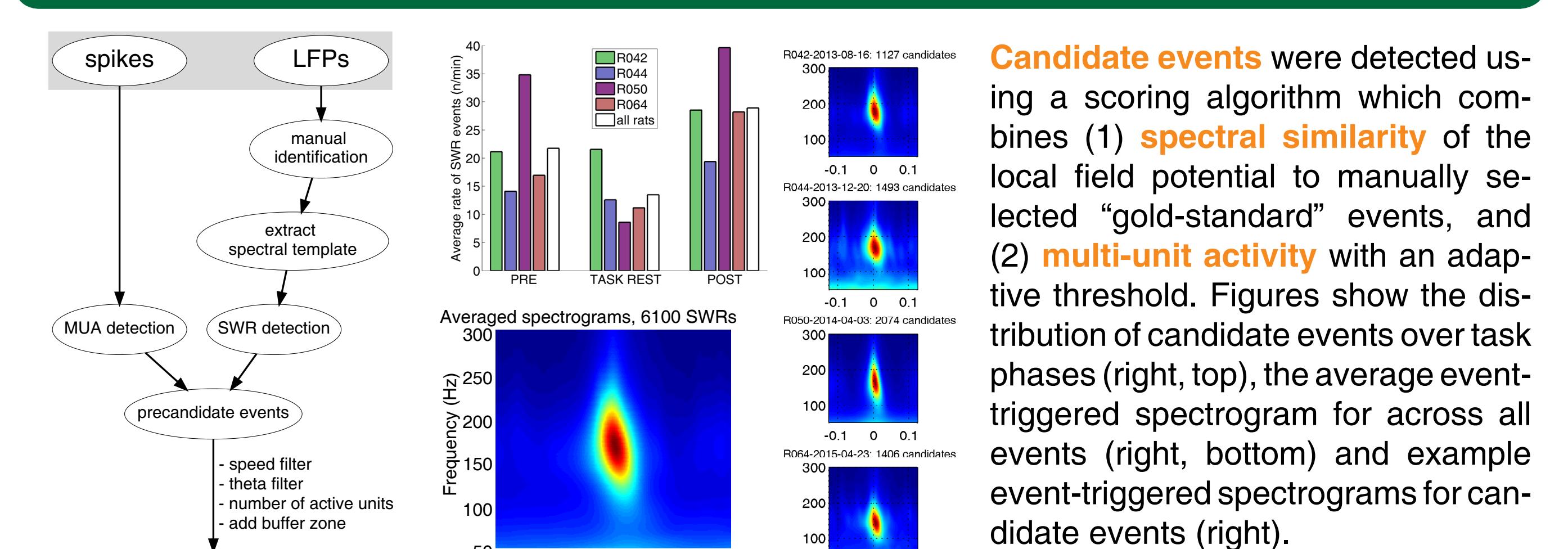
Recording data



64-channel tetrode recordings (left, top) were taken from hippocampal CA1 subfield (left, bottom) of male Long Evans rats ($n=4$) as they performed a simple T-maze task. Position tracking data were gathered as rats walk to rewards available at the ends of either arm.

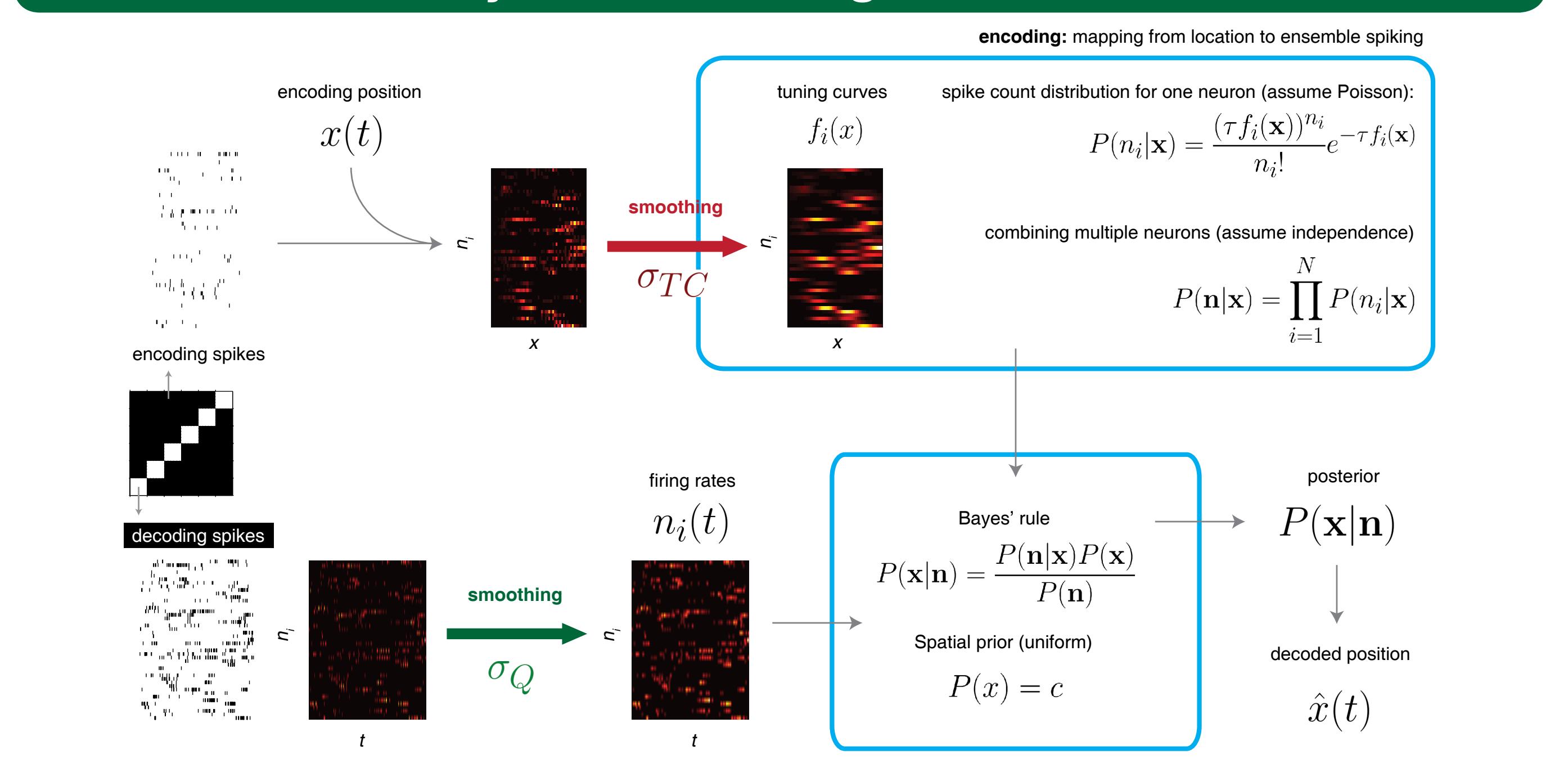
Local field potentials (LFPs) were recorded and clustered into putative units for spiking data. A total of 2017 units recorded across 24 sessions (table, bottom). Five sessions (italicized) were left out due to insufficient units resulting in a total 19 sessions eligible for analysis.

Sharp-wave ripple candidates



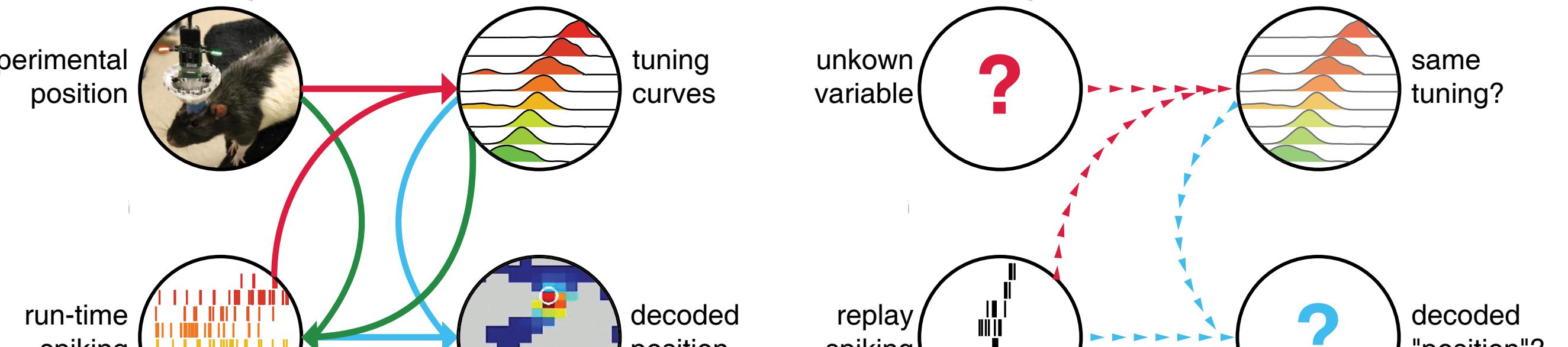
Candidate events were detected using a scoring algorithm which combines (1) spectral similarity of the local field potential to manually selected "gold-standard" events, and (2) multi-unit activity with an adaptive threshold. Figures show the distribution of candidate events over task phases (right, top), the average event-triggered spectrogram for across all events (right, bottom) and example event-triggered spectrograms for candidate events (right).

Bayesian decoding schematic



Schematic of bayesian decoding (Brown et al. 1998, Zhang et al. 1998). The overall workflow follows the canonical procedure based on the common assumptions of Poisson-distributed spike counts around mean firing rates given by stable tuning curves, and independence between neurons. Variables of interest include (1) spikes in the data between trials used for estimating tuning curves ("encoding spikes") and decoding ("decoding spikes"), (2) the width of the Gaussian kernel σ_{TC} used to smooth the tuning curves, and (3) the width of the Gaussian kernel σ_Q used to obtain the spike density functions used as the input to the decoder.

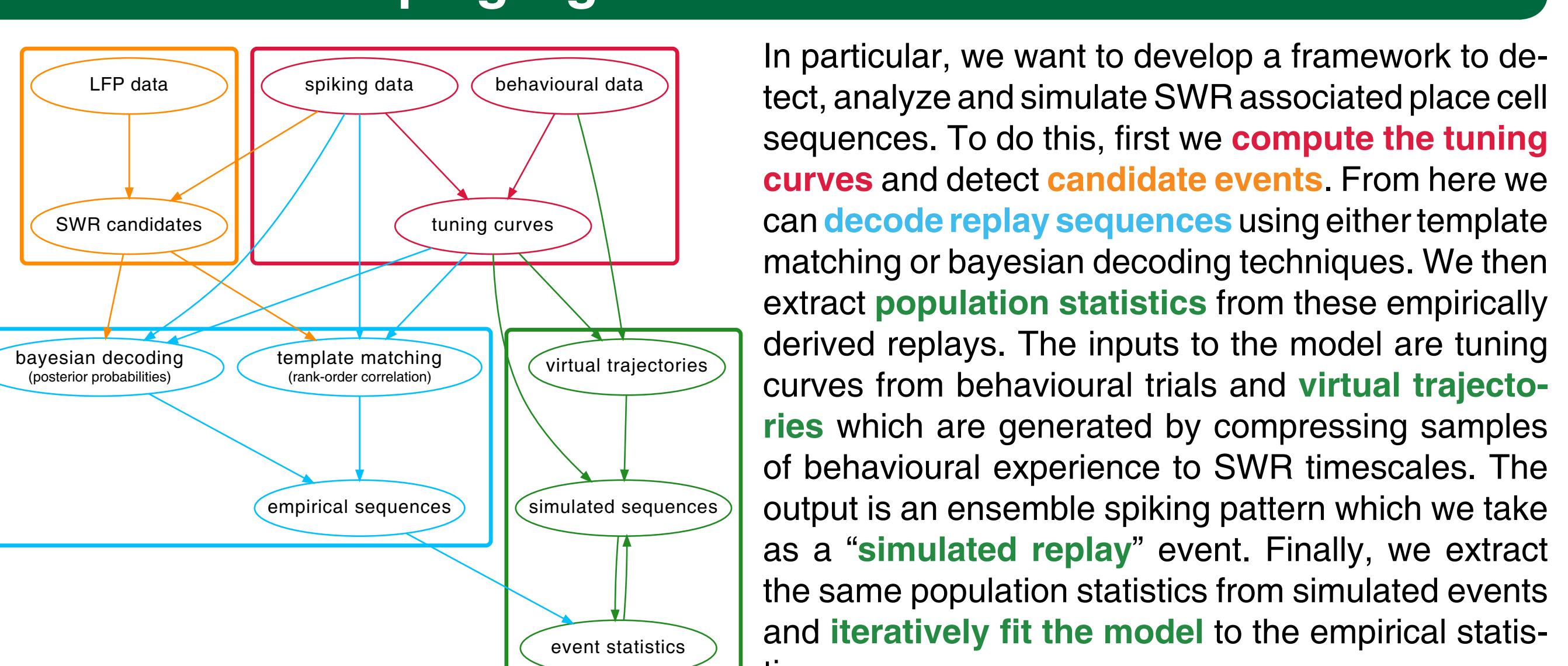
How do we analyze replays?



ENCODING tuning curves = behavioral variable + spike trains
DECODING reconstruction = tuning curves + spike trains
GENERATIVE spike trains = tuning curves + behavioral variable

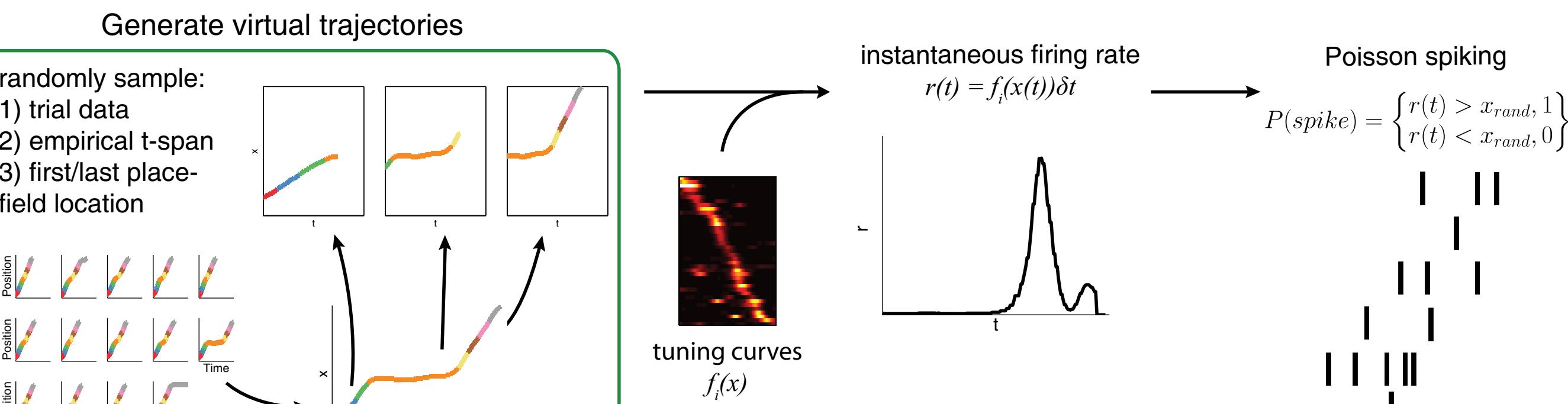
During running behaviour (left), the relationship between place cell firing and the rat's position can be understood in terms of an **encoding model** (i.e., tuning curves). This position can also be reconstructed at a given time through a **decoding model**. Alternatively, the spikes can be reconstructed using a **generative model**. These interrelated techniques (Johnson et al., 2008, Johnson et al., 2009) require both a measurable variable and a neural signature. In the case of replay (right), we only have SWR associated spiking and no access to the cognitive variable. In the **absence of ground truth**, how do we assure that our decoding is reasonable? The generative approach is one way of checking the consistency of both encoding and decoding models. To do so we need to make a generative model of replay.

Developing a generative model framework



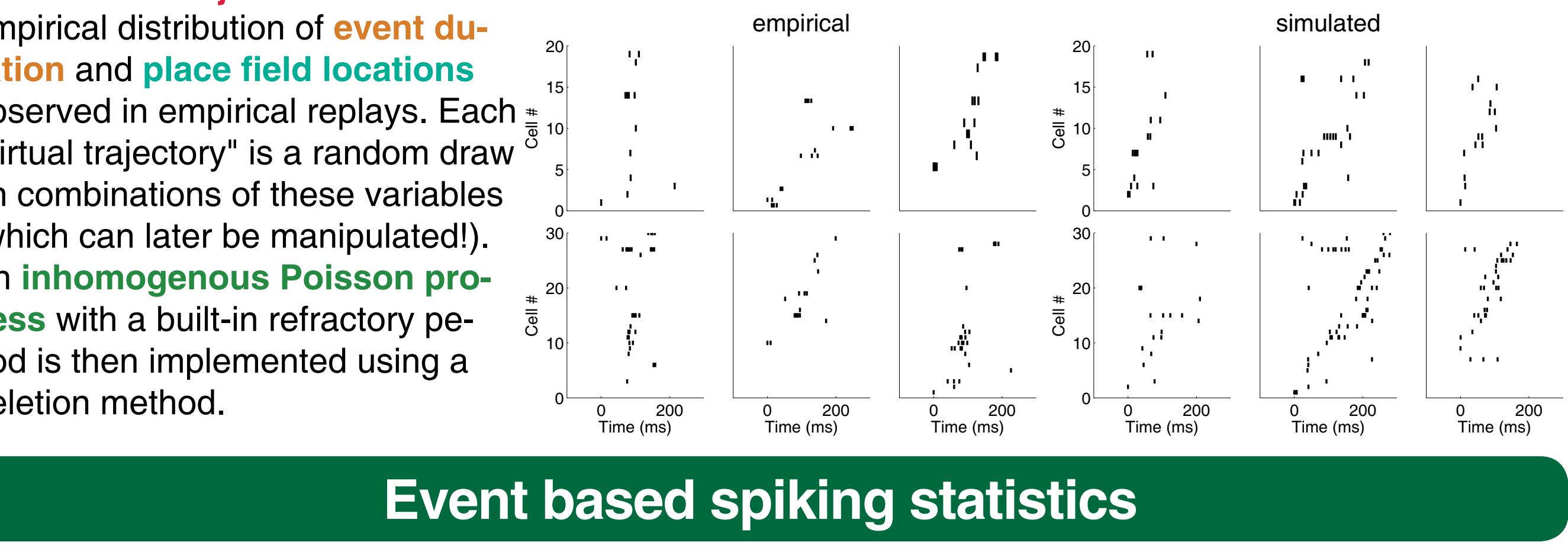
In particular, we want to develop a framework to detect, analyze and simulate SWR associated place cell sequences. To do this, first we **compute the tuning curves** and detect **candidate events**. From here we can **decode replay sequences** using either template matching or bayesian decoding techniques. We then extract **population statistics** from these empirically derived replays. The inputs to the model are tuning curves from behavioural trials and **virtual trajectories** which are generated by compressing samples of behavioural experience to SWR timescales. The output is an ensemble spiking pattern which we take as a "simulated replay" event. Finally, we extract the same population statistics from simulated events and **iteratively fit the model** to the empirical statistics.

Simulating replay spiking



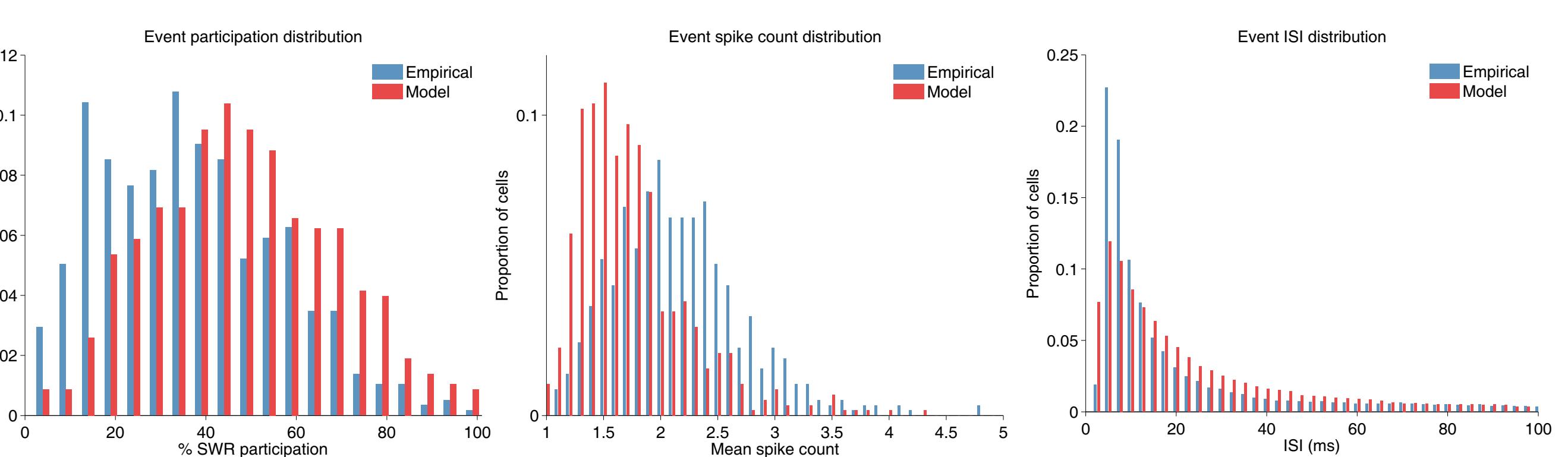
Schematic of Poisson spike generation. Point process models, and extensions thereof (e.g., linear-nonlinear Poisson, generalized linear models) have been successful in modelling early sensory systems (Pillow et al., 2008, Snoek et al., 2013). Recent models of ensemble place cell activity during running have also shed light on the organization of population activity (Chadwick et al., 2015). Here, we take a similar approach (above) by implementing a simple hypothesis (i.e., **replay is sped-up experience**). To generate virtual trajectories we draw samples from **actual behavioural trajectories** and the empirical distribution of **event duration** and **place field locations** observed in empirical replays. Each "virtual trajectory" is a random draw on combinations of these variables (which can later be manipulated). An **inhomogenous Poisson process** with a built-in refractory period is then implemented using a deletion method.

Example sequences

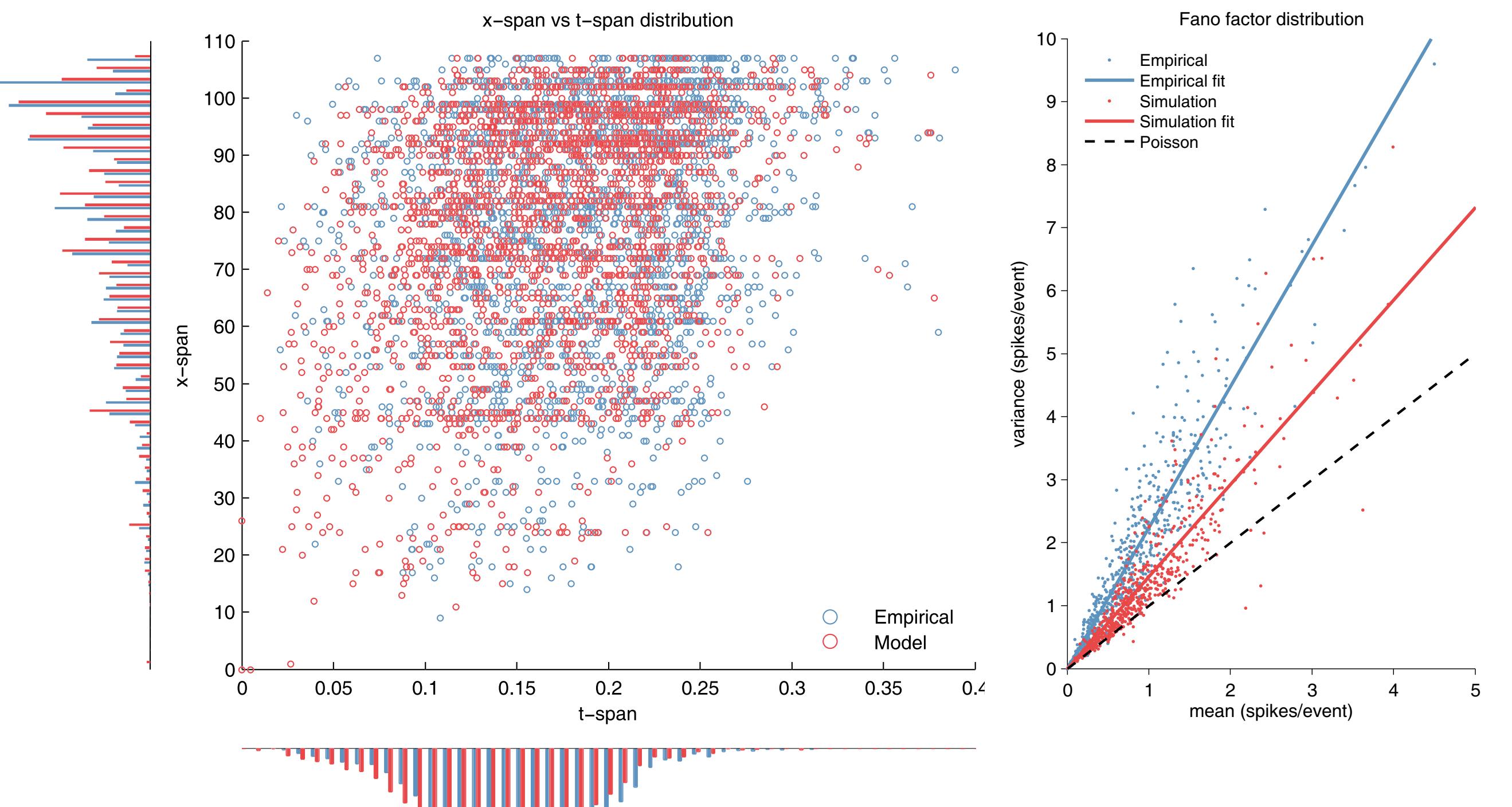


Statistical models of sequences that rely on learning the relationship of the spike train to stimuli do so by optimizing model likelihood over the parameters (e.g., Pillow et al., 2008). However, when this relationship is unknown, secondary measures such as spike train synchrony (Victor & Purpura, 1997; van Rossum 2001) and representational similarity analysis (Kriegeskorte et al. 2008) can also be used. We propose a simpler approach. Characterize putative replays using several simple metrics and fit population level statistics. For a given replay event, we can calculate the **spike count**, **inter-spike interval**, and the distance ("x-span") and duration ("t-span") of a sequence (Zheng et al., 2016). Using the spike count distribution, we can also calculate the event participation (Nadasdy et al., 1999), and fano factor distributions.

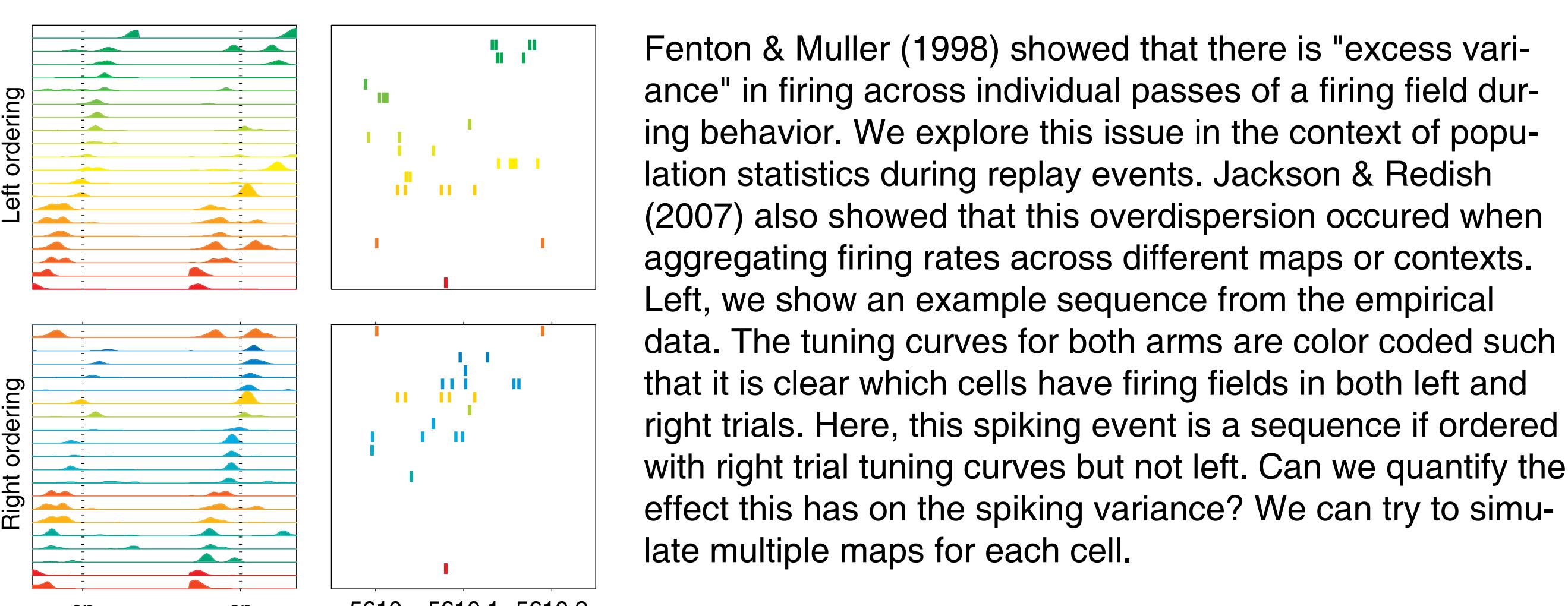
"Sped-up experience" does not fit population statistics



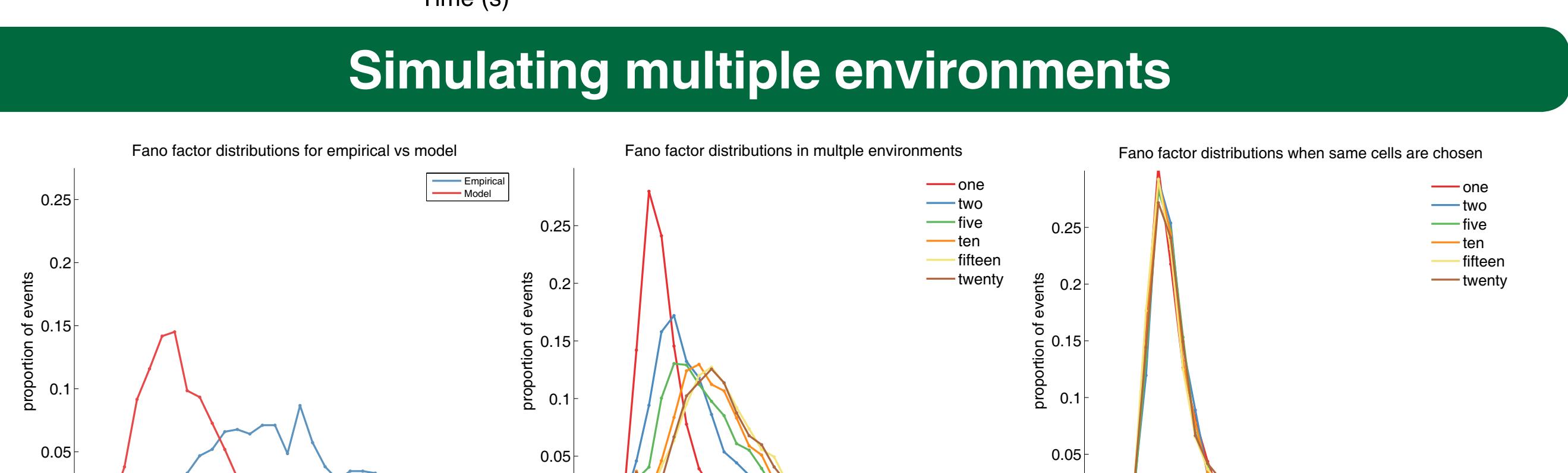
The figures above show the distributions of several measures across all place cells. Each measure was calculated for each cell across all events and total proportions are shown on the ordinates. The model average number of events cells participate in (left) and the average spike count per events participated in (middle) are both proportionally related to the firing rate set by the tuning curves. However, in the data (not shown) the probability of spiking is greater if that cell already participates making this relationship non-linear. The inter-spike interval (right) is qualitatively different between the empirical and model data; the latter being a function of the inhomogeneous Poisson process.



The x-span (3cm bins) and t-span (seconds) distributions (above, left) were directly fit in the model. Slight left shift in the distribution is due to random noise (from the Poisson generator) and a ceiling effect of the empirical distributions. Under the hypothesis of sped-up experience, we expect that the model should approximate the event based spiking characteristics if the distribution of "experiences" (i.e., spatial locations) are matched. That is, the distribution of mean and variance should be similar. We use fano factor, the ratio of the variance to the mean because the fano factor of Poisson processes being 1 makes it a good reference point. Here (above, right) we observe the empirical data to have higher variance than our model and importantly, a larger spread.



Fenton & Muller (1998) showed that there is "excess variance" in firing across individual passes of a firing field during behavior. We explore this issue in the context of population statistics during replay events. Jackson & Redish (2007) also showed that this overdispersion occurred when aggregating firing rates across different maps or contexts. Left, we show an example sequence from the empirical data. The tuning curves for both arms are color coded such that it is clear which cells have firing fields in both left and right trials. Here, this spiking event is a sequence if ordered with right trial tuning curves but not left. Can we quantify the effect this has on the spiking variance? We can try to simulate multiple maps for each cell.



As an experimenter, we only ever have access of the mapping to behaviour **only for those environments we record in**. Given a place cell has ~35% chance of being tuned to a given environment (Vazdarjanova & Guzowski, 2004). Alme et al., (2014) showed that cells are exponentially distributed in the number of environments they are tuned to, of which only 13% were active for two rooms. We expect that the more number of environments a cell is tuned to, the higher the variance should be. We generate synthetic replays for multiple maps by simulating multiple environments. As the number of environments increases, the variance increases as does the spread of the fano factor distribution.

IMPORTANT "NEXT-STEP" QUESTIONS TO TEST USING THE GENERATIVE MODEL APPROACH

- 1) how do sampling biases affect decoder results?
 - i) vary spiking statistics (e.g., non-poisson, normalized, burst firing)
 - ii) vary coverage of place fields (e.g., uniform, clustered)
 - iii) vary behavioural sampling (e.g., bias at starts/ends)
- 2) what determines decoding power / effect size?
 - i) number of replays?
 - ii) number of cells?
 - iii) number of maps vs rate remapping?
- 3) what factors control the content of replay?

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