

Automated discovery of precise spike timing by simple time warping models

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Summary. Neural spike times are typically aligned to stimulus triggers or behavioral events on repeated trials. However, on each trial, neural activity is often shifted and/or skewed in time due to variable delays in sensation, decision-making, reaction times, and other unobserved processes. We developed a class of statistical models that capture these effects on a trial-by-trial basis with linear and piecewise-linear time warping functions. These models yield more interpretable results than classical time warping methods, are less prone to overfitting, and are computationally scalable to large datasets. On multielectrode recordings from different animal models (Rhesus monkey, mouse, and rat) and different tasks (discrete reaching, timed motor production, and olfaction), linear warping reveals precise firing patterns that are invisible in raw data. Despite being fit to neural activity, the learned time warps can be tightly correlated with measurable behaviors on each trial—e.g., explaining ~80% of the variability in reaction times in cued reaching in primates, and ~90% of the variability in inhalation onset in mouse olfaction. Intriguingly, the optimal time alignment is partly decoupled from behavior in other cases, suggesting that unmeasured, internal variables can strongly influence the timing of neural dynamics. In rat motor cortex during timed motor production, we identify precisely timed theta-band oscillations that are imperceptible in raw spike trains. In some neurons, these oscillations are precisely initiated at (but not phase-locked to) the first motor action, suggesting a potential mechanistic importance for the task. In primate motor cortex during movement preparation, we identify similar oscillations at the level of multiunit spikes, which are not phase-locked to behavior. Thus, even in systems close to the sensory/motor periphery which are thought to be tightly locked to experimental cues, simple time warping models can reveal striking spike patterns that are likely to be otherwise overlooked.

Additional Detail. Neural activity exhibits high levels of noise, and thus a dominant experimental design paradigm is to record activity over repeated trials. This paradigm works best when the firing patterns are faithfully reproduced on each trial, so that trial-averaging produces an accurate estimate of neural firing rates. Our understanding of a neural system can be extremely misled when this assumption is violated. For example, the temporal precision of olfactory neurons was vastly underestimated by early work that aligned each trial to stimulus onset. Measuring inhalation on each trial and re-aligning spike times relative to this cue revealed a precise temporal code [1].

Finding good alignments for spike trains is a difficult problem. Even in olfaction, the complexities of intranasal airflow suggest several potential models of alignment [2]. More complex tasks involve sequential stimuli, internal decisions, motor actions, and rewards in each trial; this results in multiple alignment choices, including several heuristic procedures (see e.g. [3]). Time warping models (Fig. 1) can identify good alignments in a data-driven fashion. Let $y_n^k(t)$ denote the binned spike times of neuron n on trial k . The model estimates a *template* firing pattern $\mathbf{z}_n(t)$ for each neuron, and a *warping function* $\omega_k : t \mapsto \tau_k$ on each trial. The template can be thought of as the trial-averaged activity for neuron n after timing variations—as parameterized by the warping functions—have been accounted for. The model is fit to find the best approximation $y_n^k(t) \approx \mathbf{z}_n(\tau_k)$ averaged over all neurons and trials. Our code (<https://github.com/ahwillia/affinewarp>) allows users to optimize the model with respect to a Gaussian (least-squares) or Poisson likelihood criterion.

Until very recently, time warping models have been scarcely applied to neural data [4-6]. The primary difficulty is that classic methods, such as Dynamic Time Warping (DTW), are prone to overfit to noisy data. This is

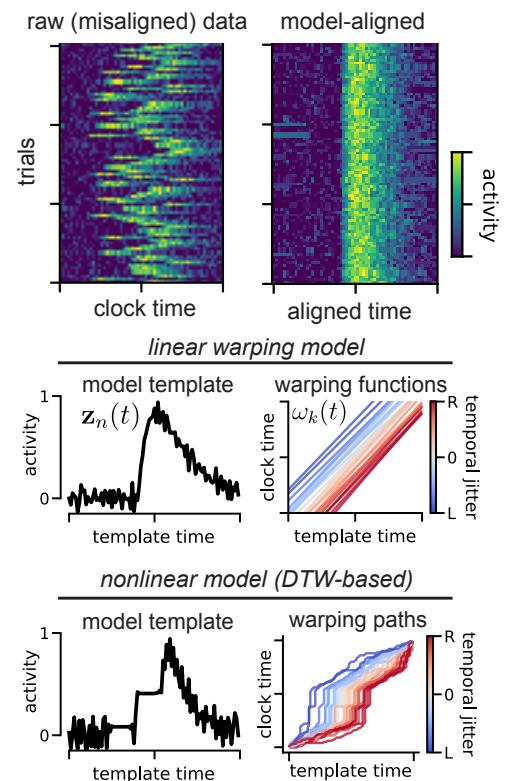


Figure 1: Simple warping functions are less prone to overfitting.

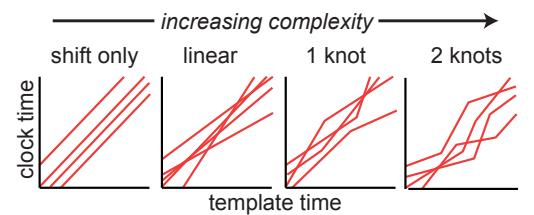


Figure 2: Piecewise linear warps enable us to tune model complexity.

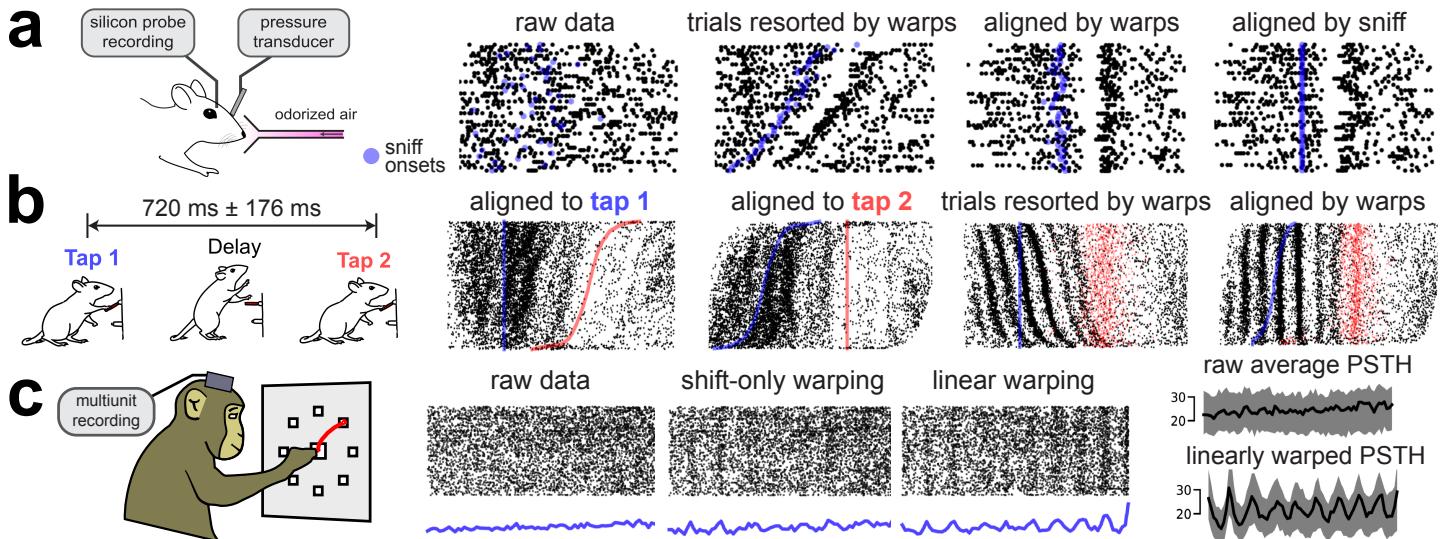


Figure 3: (a) Example olfactory neuron with raw spikes aligned to odor onset (left); a shift-only warping model (middle) reveals temporal precision that even exceeds alignment to sniff onset (right). (b) Example rat motor cortical neuron with raw spikes aligned to lever press events (left); shift-only time warping (right) reveals precise theta-band oscillations not previously observed or characterized in rodent motor cortex. Oscillation onset is behaviorally gated by the first lever press in some neurons. (c) Example multiunit spike raster in primate motor cortex during reach preparation. Simple warping models reveal subtle beta-band oscillations at the level of spikes. Oscillations are in-phase across electrodes; averaging across electrodes yields a robust oscillation (right).

demonstrated in Fig. 1, in which a simulated neuron is time-shifted on a trial-by-trial basis (top left). DTW identifies *nonlinear* warping functions, that non-uniformly stretch and compress the template on each trial, leading to an overfit template estimate. In contrast, *linear* warping produces a more reliable and interpretable fit. In particular, the linear model temporally stretches or compresses the template by a constant factor (the slope of the warping function) and time-shifts the template by a constant amount (controlled by the y-intercept of the warping function). Since the synthetic data in Fig. 1 contains only temporal translations, the slope of the optimized linear warping functions is close to one in all cases, and the intercept is correlated with the ground truth time shift (color scale).

Linear and piecewise linear warping models have not been well-studied in the machine learning community. We developed novel optimization methods that exploit (a) closed-form updates for the model template with fast banded matrix operations, and (b) parallel optimization of low-dimensional warping functions across trials. On a modern laptop, the model can be fit to data from 1000 neurons, 100 timepoints, and 1000 trials in under 1 minute. DTW-based methods (<https://github.com/rtavenar/tslearn>) iterate ~10-100x slower and converge to spurious local minima on the same dataset. Recent applications of time warping on neural data have either used DTW as a subroutine [4] or a different nonlinear model with similar computational and interpretational complexity [5, 6].

Another key methodological advance is our ability to fit models with gradually increasing warping complexity—warping functions are piecewise linear; the number of segments is a user-specified parameter (Fig. 2). Since these models can be rapidly optimized, we were able to apply them across a variety of experimental datasets and find that, surprisingly, *extremely simple warping functions are sufficient to uncover spike patterns that are otherwise imperceptible*. Representative results are summarized in Fig 3. Most strikingly, we uncovered theta-band oscillations in individual neurons in rat motor cortex, which were modulated by motor behavior in some neurons (not shown). Such oscillations have not yet been characterized in rodent motor cortex to our knowledge.

In all datasets, we found that warping functions fit on a subset of neurons generalized well to held out cells. In addition to providing a useful cross-validation procedure, this yields two scientifically interesting observations. For the systems we examined, variability in neural timing is (a) low-dimensional (i.e., described by linear warps), and (b) shared across neurons. The relative simplicity of these results suggests that the latent biological causes of timing variability might be identified by experimental studies in the near future. We expect linear and piecewise linear time warping will be a broadly useful analytic tool to characterize similar phenomena in other neural systems.

References. [1] Shusterman et al. (2011) *Nat Neurosci* 14.8: 1039. [2] Shusterman et al. (2018) *bioRxiv* 174417. [3] Kobak et al. (2016) *eLife* 5: e10989. [4] Lawlor et al. (2018) *J Comput Neurosci* 10.1007/s10827-018-0696-6. [5] Duncker & Sahani (2018) *bioRxiv* 331751. [6] Poole et al. (2016) *Cosyne Abstracts* III-14.