Single-trial *DI* estimation: Pre-processing, quantification and significance testing.

Adrià Tauste Campo

The directionality analysis presented here is a refinement of our previous method to analyze spike-train directional correlations (1). We estimated directional information between every neuron pair within a population using a Bayesian estimator of the directed information-theoretic measure (2) between a pair of discrete time series that were assumed to be generated according to a Markovian process. In more specific terms, for a pair time series (x^T, y^T) of length T, where $x^T = (x_1, \dots, x_T)$ and $y^T = (y_1, \dots, y_T)$, a time delay $D \geq 0$, and Markovian orders equal to $M_1 > 0$ and $M_2 > 0$, respectively, the directed information-theoretic measure between the underlying stationary processes of x^T and y^T, i.e., (X, Y), is estimated through the formula:

$$\hat{I}_D(X \to Y) \triangleq \frac{1}{T}\sum_{t=1}^{T}\sum_{y_t}\hat{P}\left(Y_t = y_t \middle| X_{t-D-M_2}^{t-D} = x_{t-D-M_2}^{t-D}, Y_{t-M_1}^{t-1} = y_{t-M_1}^{t-1}\right) * \\ log\frac{\hat{P}\left(Y_t=y_t \middle| X_{t-D-M_2}^{t-D}=x_{t-D-M_2}^{t-D}, Y_{t-M_1}^{t-1}=y_{t-M_1}^{t-1}\right)}{\hat{P}\left(Y_t=y_t \middle| Y_{t-M_1}^{t-1}=y_{t-M_1}^{t-1}\right)},$$

[Eq. S1]

where, the joint and marginal probability distributions of (X, Y) are estimated using the context-tree weighting algorithm (CTW, [3, 4]). Matlab code for the CTW-based estimation of the directed information-theoretic measure can be downloaded from https://web.stanford.edu/~tsachy/DIcode/. Equation 1 quantifies the information that the past of X^T at delay D, i.e., $X_{t-D-M_2}^{t-D}$, has about the present of Y^T, i.e., Y_t, given the most recent part of Y^T, i.e., $Y_{t-M_1}^{t-1}$. This estimator is consistent as long as the two neuronal time series (X^T, Y^T) form a jointly stationary irreducible aperiodic finite-alphabet Markov process whose order does not exceed the prescribed maximum depth in the CTW algorithm (4). Prior to estimating the directed information-theoretic measure, we preprocessed our data as follows. For a single trial, we first binarized spike-train trials using bins of 1ms (mapping 1 to each bin with at least one spike and 0, otherwise). Second, in stimulus-present trials, we removed the variable-time pre-stimulus period in every trial and aligned all trials to the stimulus onset time. In contrast, in stimulus-absent trials, we aligned the trials to the probe down event (PD). We then divided each trial time series into twenty non-overlapping task intervals of 0.25s (250 bins). At each task interval, the spike train was assumed to be generated by a random process that satisfied the estimator requirements with a maximum memory of 2ms ($M_1 = M_2 = 2$ bins) both for the joint and the marginal spike-train processes. Under the estimator requirements, it can be easily checked that the directed information-theoretic measure is asymptotically equivalent to the transfer entropy measure (5) in the limit of the time-series length. To assess that neurons were able to express minimal information through their spike-train responses, we assessed the significance of the entropy value (a particular case of the directed information-theoretic measure when X^T and Y^T coincide) of each spike train at every task interval with maximum memory, $M = 2$. This step removed segments of spike trains with zero or small number of spikes. Finally, among those pairs of spike-train segments with significant entropy, we ran the delayed directed information-theoretic measure estimator (Eq. S1) at time delays *D*=0, 2, 4, 6, 8, 10, 12, 14, 16, 18, 20 ms.

We dealt with the multiple test problem over delays by using the maximum directed information-theoretic measure over all preselected delays as a test statistic:

$$I_{\mathrm{STAT}}(X \to Y) \triangleq \max_{D \epsilon [0,2,\cdots,20]} \hat{I}_D\,(X \to Y) \qquad \text{[Eq. S2]}$$

To assess the significance of the above statistic (Eq. S2), we used a Monte-Carlo permutation test (6). In this test, the original (i.e., non-permuted) estimation was compared with the tail of a distribution obtained by performing 20 equally-spaced (to maximize independent sampling) circular shifts of the target spike train Y^T within the range [50,200]ms and computed the corresponding P-value (7). Hence, the significance test provides three outputs: the significance assessment $(0/1)$, the statistic value and the maximizing delay $\widehat{D}$. In particular, any spike-train pair during a trial is considered to convey directional information (*DI*) at a given task interval if the corresponding test yields significance.

References

1. Tauste Campo A, Martinez-Garcia M, Nácher V, Luna R, Romo R, Deco G (2015) Task-driven intra- and interarea communications in primate cerebral cortex. *Proc Natl Acad Sci USA* 112:4761–4766.
2. Massey J. (1990). Causality, feedback and directed information. *In Proc Int Symp Inf Theory Applic* 27–30.
3. Jiao J, Permuter HH, Zhao L, Kim YH, Weissman T (2013) Universal estimation of directed information. *IEEE Trans Inf Theory* 59(10):6220–6242.
4. Willems FM, Shtarkov YM, Tjalkens TJ (1995) The context-tree weighting method: basic properties. *IEEE Trans. Inf. Theory* 41(3):653-664.
5. Schreiber T (2000) Measuring Information Transfer. *Phys Rev Lett* 85:461-464.
6. Ernst MD (2004) Permutation Methods: A Basis for Exact Inference. *Stat Sci* 19:676–685.
7. Phipson B, Smyth GK (2010) Permutation P-values should never be zero: calculating exact P-values when permutations are randomly drawn. *Stat Appl Genet Mol Biol*, 9(1).