Computing with Neural Spikes

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What is the neural code?

- Of all the objects in the universe, the human brain is the most complex - the brain, the final frontier. “How is information coded in neural activity?” is listed on top of the “10 Unsolved Mysteries of the Brain” (Eagleman, 2007).

- Is it possible to decipher the syntax or set of rules that transform electrical pulses coursing through the brain into perceptions, decisions, memories, emotions
What is the neural code – One step at a time

• Neural coding for the understanding of the frontal cortical areas associated with decision and control
Individual neurons – representation of relevant features of the environment

Population codes - unambiguous representation of the environment

External stimulus -> time locking, reverse correlation (spike triggered averages)

Intrinsically -> from neural circuits
Examples of rate code

The rate code - the average number of action potentials/spikes per unit time

In motor neurons, the strength of an innervated muscle flexion depends solely on the firing rate
Cosine tuning curve: orderly variation in the frequency of discharge of a motor cortical cell with the direction of movement (Georgopoulos, et al. 1982)
Tuning curve of a V4 neuron

Population-tuning curves for V1 neurons

(McAdams & Maunsell, 1999)
Examples of temporal code  (Gray & Singer, 1989)

• Neurons of the cat visual cortex oscillate in range 40-60 Hz in synchrony in response to visual stimulus
• Such oscillation is tightly correlated with the phase and amplitude of an oscillatory local field potential
• The oscillatory responses may provide a general mechanism by which activity patterns in spatially separate regions of the cortex are temporally coordinated.
It is commonly accepted that …

In most sensory systems, the firing rate increases, generally non-linearly, with increasing stimulus intensity.

Rapid changing stimuli tend to generate precisely timed spikes and rapidly changing firing rates no matter what neural coding strategy is being used.
How neurons encode information

• What is the neural code for intrinsic brain states involved in complex behavioral process beyond laboratory designed sensory stimulus, e.g., perception, cognition, decision.
• Difficult problem, especially in the frontal cortex - many kind of cells, inter-mixed/ intertwined
Cortical areas under study

- The frontal cortex plays a crucial role in working memory, it is thus of particular interest when studying trial and error learning.
- The PM and M1 areas receive information from striate, parietal, and prefrontal and thalamic structures (Markowitsch et al., 1987). Also, they send information to subcortical structures and spinal cord.
- The PFC (Roesch & Olson, 2003), anterior cingulate cortex ACC (Carter et al., 1998), basal ganglia (Falkenstein et al., 2001), all are related with performance monitoring, are in connection with PM and M1.
- The PMv is involved in sensory transformations for visually guided actions and in perceptual decisions, connected with sensory, motor, and high-level cognitive areas related to performance monitoring. The site for representing sensory perception for action and for evaluating the decision consequences. (Vazquez et al, 2008).
Means of investigation

Integrated experimental and computational approach - computation solely based on recorded neural data, to minimize human imposed experimental conditions & modeling assumptions

Cognition task:
Decision & control

Natural behavior (non-stereotypical)

Experiments using a rat model

Electrophysiology:
Single unit recording

Computation w/ neural spikes & Modeling
Experimental Set-up

TDT 16-channel pre-Amp

TDT RX5

Synchronized
Neural signal

Synchronized
Behavioral

Neural Recording
Data Tank

Video stream

Light cue
Sound cue
Paddle extension
Paddle retraction
Food reward

Behavioral

Control Center

Video computer

monitor

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Rats learn to perform a directional control task for a reward

Behaviors - working for a reward, learning by trial & error, non-stereotypical movement

Neural activities – dynamics at cellular and molecular level
dynamics at individual neural spike level
population of neurons

Measurable parameters - neural waveforms (≈24kHZ) and thus spikes, rat movement trajectory, task outcome of success or failure

Challenges - variations in neural activities (intrinsic & environmental noise), variations in behaviors (freely moving, non-stereotypical), simultaneous multi-channel single unit, chronic/long term
Behavioral learning curves

Accuracy (percentage)

Session (day)

- 4 fast rats
- 4 slow rats
Spike raster plot and peri-event time histograms (PETHs)

Rat: T10, channel6, 12/6/2010

Rat: T10, channel15, 12/15/2010
Analysis based on hypothesis driven studies of

- Spike firing rates
- Spike timing
- Statistical properties
- Neural network properties – predictive, dynamic model
Question – what can be found from the spike rate profiles in relation to rat behavior?
1. Spike rate reveals impact of trial outcomes and the rate modulation occurs differently over the course of a trial, over different phases of learning
X-axis: the overall accuracy in percentage for a single session
Y-axis: accuracies for trials post-success (read) and post-error (black), respectively
Bottom row, The distribution of behavioral index (BI).
Naïve stage - no significant difference between post-success and post-error accuracies, and BI centered at 1.
Learning stage - post-error accuracy is larger than post-success accuracy (Student’s t-test, p<0.05); BI centered at 1.06.
Learned stage, no significant difference; BI centered at 1.

Behavioral Index \( I_{\text{beh}} = \frac{p_E - p_S}{p_E + p_S} \)
Blue: error trials
Green: success trials

Significant # of M1 & PM neurons are rate modulated during the task

Current trial outcome

Previous trial outcome

Reward in the current trial

Reward in the previous trial

a PM neuron example
The reward-related activity of all the neurons (N = 1058) recorded. The reward index 
(I_{rew}(k) = \frac{f_{E(k)}-f_{S(k)}}{\max(f_{E(k)},f_{S(k)})}) shown by color intensity for each neuron with trial lag = 0 (left) and trial lag = 1 (right).
Distribution of \( (I_{\text{rew}}(k) = \frac{f_{E(k)} - f_{S(k)}}{\max(f_{E(k)}, f_{S(k)})}) \) over neurons.

White bars: the number of neurons whose discharge rates are significantly different in correct and incorrect trials in cue-on period (one-way ANOVA, \( p<0.01 \)). Black bars: neurons whose discharge rates are not significantly different.
What do we learn from a rate code during a cognitive control task?

• Insight on trial and error learning at single unit level, which was not available before, despite large body of literature on behavior studies, fMRI and EEG studies based on single session recordings

• Within a single session: rat cognitive dynamics may be used to simulate a human learning dynamics based on similar working memory load, attention levels

• Rats provided opportunity to provide long term neural data which gives us a slow motion picture of brain activities during trial and error learning.
2. Spike timing reveals strong correlation of neural activity with a trial start, over different phases of learning
The Temporal Code

• Theoretical development
  Von der Malsburg (1981): combining features by synchronous activation, the correlation theory of brain function.

• Experimental evidence: from electrophysiological recordings using single unit multiple electrode arrays, Gray and Singer (1989).

• Further investigation
  a ubiquitous phenomenon in cortical networks; hypothesized to serve a variety of functions (Singer 1999; Uhlhaas et al., 2009).
• Synchrony strength modulation
  o Stimulus/task-evoked (Raichle 2010)
  o intrinsic activity-related, cognitive activities for the interpretation of stimulus
  o the latter case less attended to but needed for studying goal-directed natural behavior.
• In this study, synchrony strength is evaluated by statistical measures such as modified cross-correlation.
Computing the Joint Peristimulus Time Histogram (JPSTH)

- Neuron pairs (x and y) are considered
- Bin size is 1 ms. Bin value is 1 if there is a spike, 0 otherwise

Peristimulus Time Histogram (PSTH)

\[ \sum_{k} x^{i} k \]

\[ \sum_{k} y^{j} k \]

Where \( i \) is the bin index, \( k \) is the trial index

JPSTH between neuron \( x \) at bin \( i \) and neuron \( y \) at bin \( j \):

\[ J(i, j) = E[N_x^{(k)}(i) * N_y^{(k)}(j)] = \frac{1}{M} \sum_{k=1}^{M} N_x^{(k)}(i) * N_y^{(k)}(j) \]

where \( M \) is the total trial number.

Normalization:

\[ \hat{J}(i, j) = \frac{J(i, j) - Px(i) * Py(j)}{S(i, j)} \]

Where:

\[ Px(i) = E[N_x^{(k)}(i)] = \frac{1}{M} \sum_{k=1}^{M} N_x^{(k)}(i) \]

\[ S(i, j) = \sqrt{\{E[N_x^{(k)}(i) - Px(i)]^2\} * \{E[N_y^{(k)}(j) - Py(j)]^2\}} \]
Synchrony strength: is computed by normalized cross-correlation $\bar{J}(i,j)$ between two neurons within a small time lag (i-j). It is obtained by averaging all elements along the +/-5ms paradiagonal band of the JPSTH matrix. Equivalently, it can be obtained by averaging over the coincidence histogram bin values or averaging bin values from -5ms to +5ms of Crosscorrelogram.
Result – One of the 3 neuron pairs of Rat L10

(a) Learning stage

(b) Learned stage

Result – One of the 6 neuron pairs of Rat A09
Synchrony strength and rat behavior – results based on 4 rats

• Computed the synchrony strength from the window after cue-on (AC) and the window between trials (BT).
• Computed the synchrony strength during learning stage (LG) and learned stage (LD).
Synchrony Strength of Rat W09

AC/BT direction: stronger synchrony after cue-on than resting during learning stage
LG/LD direction: Stronger synchrony during learning stage than learned stage
T-test for Synchrony Strength comparison

- $p = 0.0242$; comparing learned stage (LD) and learning stage (LG) between trials (BT);
- $p = 2.2060 \times 10^{-06}$; comparing learned stage (LD) and learning stage (LG) after cue on (AC);
- $p = 7.4419 \times 10^{-04}$; comparing after cue on (AC) and between trials (BT) at learning stage (LG);
- $p = 0.0164$; comparing after cue on (AC) and between trials (BT) at learned stage (LD);
Synchrony strength and rat behavior – results based on 2 more rats who did not finish learning.

What do we learn from spiking timing?

• Synchrony strength is higher during learning stage than that during the learned stage.
• While learning the task, the synchrony strength is stronger when the rat attended to the task at the beginning of a trial than when the rat was at rest.
3. Network connectivity reveals functional synaptic plasticity between neurons over the course of learning
Synaptic efficacy

- Any significant and consistent synaptic connections among neurons are expected to result in significant neural spiking dependency among neurons.

- **Spike-timing-dependent plasticity** (STDP) - a biological process that adjusts the connection strengths based on the relative spike timing of an input neuron and a target neuron. If an input spike to a neuron tends, on average, to occur immediately before that neuron's output spike, then that particular input is made somewhat stronger. If an input spike tends, on average, to occur immediately after an output spike, then that particular input is made somewhat weaker.
Objective

• To study neuronal interaction taking into account a neural ensemble using a functional approach supported by *in vivo* data.
Existing methods for estimating neuronal interaction

• Pair-wise measurement:
  o correlation coefficients;
  o inter-spike intervals;
  o phase lag index;
  o Granger causality;
• Statistical inference model:
  o maximum likelihood (ML);
  o maximum a posteriori probability (MAP).
• A limitation: Pair-wise measurement may not reveal true topology of neural interaction.
• Statistical inference model reveal true topology but parameter estimation procedure very complex, requires assumption. (Okatan et al., 2005)

Fig. Direct and Indirect neural interaction. Granger causality (for example) is unable to differentiate (Ding et al., 2006).
Neural physiological model regarding synapse interaction

• Spike response model (SRM) (Gerstner et al., 2002)
  o a good approximation to the Hudgkin-Huxley model;
  o postsynaptic neural membrane potentials depends on pre-synaptic neurons’ activities.
• Spike rate model (Gerstner et al., 1995)
  o neuron firing rate depends on the history of neural ensemble activities.
• Neural spiking probability depends on neural firing history of a population.
\[ \lambda_i(t + \Delta t | \alpha_i, H_t) = \exp\left(\alpha_{i,0} + \sum_{c=1}^{C} \sum_{m=1}^{M} \alpha_{i,c,m} I_{c,m}(t)\right) \]

Given history, \( H_{t1}, H_{t2}, \ldots, H_{tT} \)
Identical patterns are classified into \( S \) clusters.

\[ H_t = \{I_{1,1}(t), \ldots, I_{1,M}(t), I_{2,1}(t), \ldots, I_{2,M}(t), \ldots, I_{C,1}(t), \ldots, I_{C,M}(t)\} \]
A network likelihood model

\[ \lambda_i(t \mid \alpha_i, H_t) \] Spike firing probability given \( \alpha_i, H_t \)

\( \alpha_i = \{ \alpha_{i,0}, \alpha_{i,c,m} \mid c \in C, m \in M \} \) neuronal correlation strength between neurons \( i \) and \( c \) at time bin \( m \).

\( \alpha_{i,0} \) Reflective of average firing rate

\( H_t \) neural ensemble firing history.

\[ \lambda_i(t \mid \alpha_i, H_t) = \exp \left( \alpha_{i,0} + \sum_{c=1}^{C} \sum_{m=1}^{M} \alpha_{i,c,m} I_{c,m}(t) \right) \]
Estimating $\alpha_{i,c,m}$ by a least squares method

- Neural firing probability

$$P_t = \lambda_i(t + \Delta t | \alpha_i, H_t)\Delta t = \Delta t \exp \left( \alpha_{i,0} + \sum_{c=1}^{C} \sum_{m=1}^{M} \alpha_{i,c,m}I_{c,m}(t) \right)$$

- Estimating Bernoulli trial probability $P^s$ by firing frequency

$$P^s = \frac{n(s)}{N(s)} \quad n(s): \# \text{ of fired spikes given } H_t$$

$$N(s): \text{cardinality of } H_t$$

$$g^{-1}\left( \frac{P^s}{\Delta t} \right) = \left[ \alpha_{i,0} + \sum_{c=1}^{C} \sum_{m=1}^{M} \alpha_{i,c,m}I_{c,m}^s(t) \right]$$
Estimating $\alpha_{i,c,m}$ by a least squares method

- Estimating $\alpha_{i,c,m}$ by solving the equation below

$$\alpha_i I_H = P$$

where

$$P = \left[ g^{-1}\left(\frac{P^1}{\Delta t}\right), \ldots, g^{-1}\left(\frac{P^s}{\Delta t}\right), \ldots, g^{-1}\left(\frac{P^S}{\Delta t}\right) \right]^T$$

$$I_H = \begin{bmatrix}
1 & \cdots & 1 & \cdots & 1 \\
\vdots & \ddots & \vdots & \ddots & \vdots \\
I_{1,c,m} & \cdots & I_{1,c,m} & \cdots & I_{1,c,m} \\
\vdots & \ddots & \vdots & \ddots & \vdots \\
I_{1,c,M} & \cdots & I_{1,c,M} & \cdots & I_{1,c,M}
\end{bmatrix}$$

$P_s$ is the probability of firing history cluster $s$
How to interpret statistically significant neural interaction $\alpha_{i,c,m}$

- Data shuffle removes any correlations in a time series;
- Significant neural interaction: when it is significantly different from that of the shuffled spike trains;
- In a shuffled spike train, the firing probability given neural firing history only depends on mean firing rate.
Functional plasticity characterization

- Positive plasticity: inhibitory → null/excitatory
- Negative plasticity: inhibitory ← null/excitatory
Example, Rat L: left cue-left press

After learning, selective excitation, some specific excitatory patterns become more useful in information coding
Plasticity of significant neuronal interactions underlying cognitive learning

For rat B, O, W and A’s left trial, negative plasticity was the majority. Rat A never learned right trial, positive plasticity was majority for A’s right trials.
What do we learn from ensemble network model via functional synaptic efficacy?

- Alterations in behavior must ultimately be caused by changes in neuronal firing - how synaptic plasticity modifies the output of neurons?
- To understand the relationship between synaptic plasticity and learning it is important to elucidate how synaptic plasticity alters the input-output characteristics of neurons.
- In temporal coding, learning is explained by activity-dependent synaptic delay modifications.
- Functional spike-timing-dependent plasticity (STDP) using in vivo data
  - functionally excitatory synaptic connections become more inhibitory after learning
Conclusions

1) Neural activities become organized as subjects perform voluntary and goal-directed tasks. This cortical re-organization seems to involve both spatial and temporal features, and additional properties such as plasticity.

2) More organized neural firing activities may lead to more clear and accurate predictions of his control decisions (a hypothesis).
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