Bias in Least Squares Estimation of Hemodynamic Response Function in Resting State due to Uncertainty in Neural Input

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INTRODUCTION

- The coupling between neural activity and the accompanying hemodynamic response is typically modeled using a linear time invariant (LTI) system with impulse response known as Hemodynamic Response Function (HRF)
- Estimation of the HRF under resting state conditions involves fitting a linear system between a noisy input (i.e. strength of spontaneous neural activity, as estimated from electrical recordings), and a noisy output (i.e. hemodynamic response)
- We investigate the effect of the "input noise" on the HRF estimated using the least squares (LS) approach
- Theoretical and simulation results demonstrate that the input noise makes estimated HRF biased, and may result in a non-causal estimated HRF even when the true HRF is causal
- We also use simultaneously acquired local field potentials (LFPs) and optically measured hemodynamic response from the rat brain [1] to demonstrate that the estimated HRF can indeed be non-causal

THEORY

Conventions:

- $f[n]$: Noise free neural input function
- $h_{true}[n]$: True HRF
- $h_{est}[n]$: Estimated HRF
- $y[n]$: Noise free hemodynamic response
- $w_f[n]$: Noise in measured / estimated neural input function
- $w_y[n]$: Noise in measured hemodynamic response

LTI Model for neurovascular coupling:

$$y[n] = f[n] * h_{true}[n]$$

Least squares HRF estimation:

$$h_{LS}[n] = \underset{h_{est}[n]}{argmin} \sum_n \left|(y[n] + w_y[n]) - ((f[n] + w_f[n]) * h_{est}[n])\right|^2$$

Non-causal IIR Wiener filter estimate for HRF:

$$h_w[n] = \underset{h_{est}[n]}{argmin}\, E\left\{\left|(y[n] + w_y[n]) - ((f[n] + w_f[n]) * h_{est}[n])\right|^2\right\}$$

- Assuming jointly wide-sense stationary processes, it is sraightforward to show that [2]

$$H_w(z) = H_{true}(z)\frac{P_{ff}(z)}{P_{ff}(z) + \sigma^2_{w_f}} = H_{true}(z)H_b(z) \quad (1)$$

- $h_b[n]$ is non-causal, since $H_b(z) = H_b^*\left(\frac{1}{z^*}\right)$
- Therefore, $h_w[n]$ can be non-causal even if $h_{true}[n]$ is causal, due to imperfections in our knowledge of the neural input
- Since least squares filter is an unbiased and consistent estimate of Wiener filter under the assumptions of wide-sense stationarity and ergodicity, this result is directly applicable to the least-squares HRF estimation, as long as the HRF model can span the Wiener filter

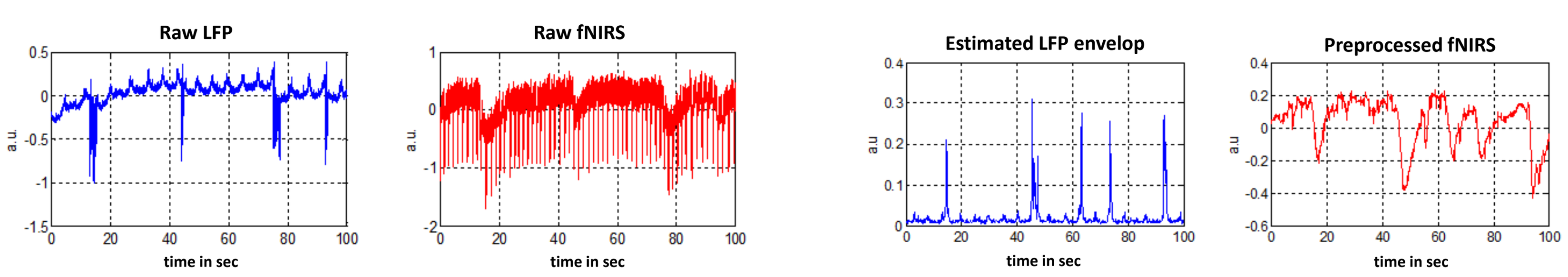
METHODS

Data Acquisition:

- Simultaneous hemodynamic (fNIRS) and neuronal recordings (LFP) were made from the primary somatosensory cortex of rats under anesthesia at 1200 samples per second [1]
- Fine optical fibers (~ 100 micro diameters) were used for light delivery to the site and photon collection at the same site
- Parallel fibers were set closely adjacent and connected to an LED light source (of near infrared wavelength such as 810nm) and photodiode detector
- Micro-glass electrodes (Ag/Ag-Cl) were used for LFP recording

Data Pre-processing:

- Respiratory and cardiac peaks were visually identified, and removed using notch filtering
- Amplitude of filtered LFP (1-30 Hz) was extracted using Hilbert transform
- LFP and optical signals were downsampled to 10 Hz
- Raw and preprocessed signals from one of the recordings are shown below

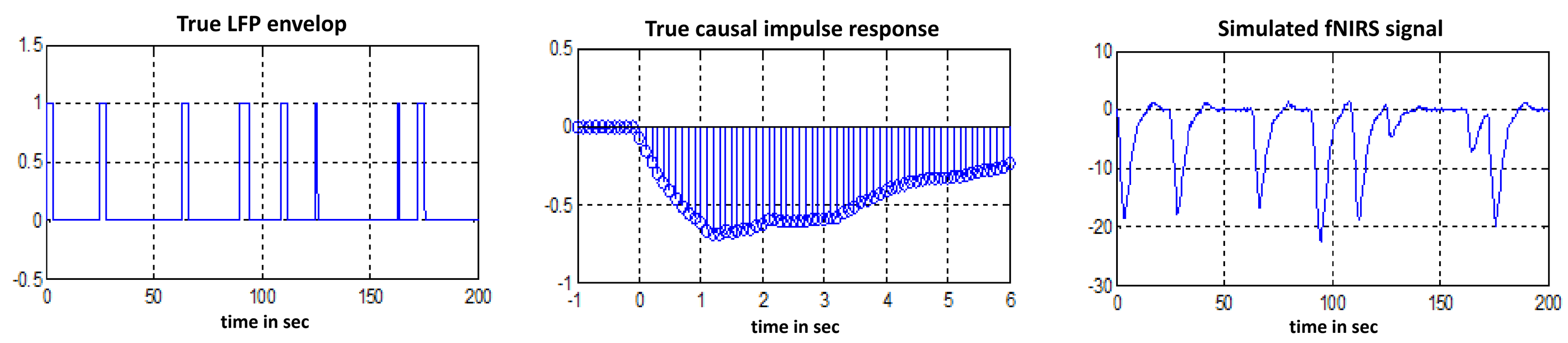


HRF estimation:

- An FIR filter was fitted between the LFPs and optical recordings using the LS approach
- Non-causality of 1s was allowed in the model to investigate potential non-causality of the estimated HRF

Simulations:

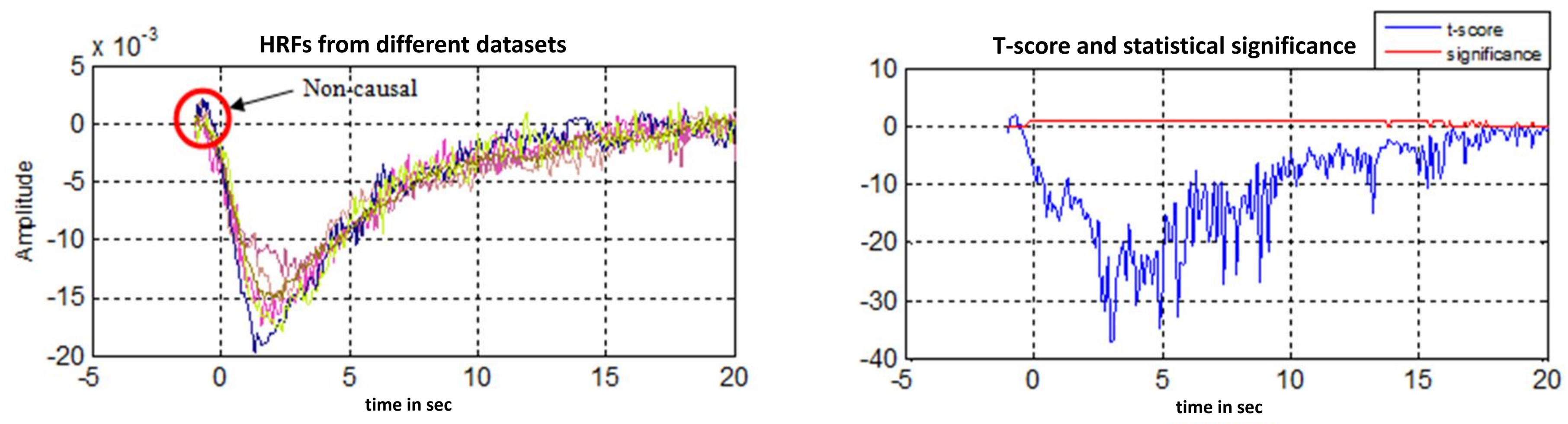
- "True" LFP envelope, consisting of randomly spaced pulses with random widths, was generated. Pulse widths as well as inter-pulse durations were based on neural activity burst widths and inter-bust intervals observed in the real data
- Simulated optical signal was generated by convolving the true LFP envelope with a causal "true" HRF This process is summarized in the figure shown below:



- LFP signal was generated by multiplying the LFP envelope with bandpass filtered white noise
- Preprocessing and HRF fitting steps were performed as described earlier

RESULTS

Real data:

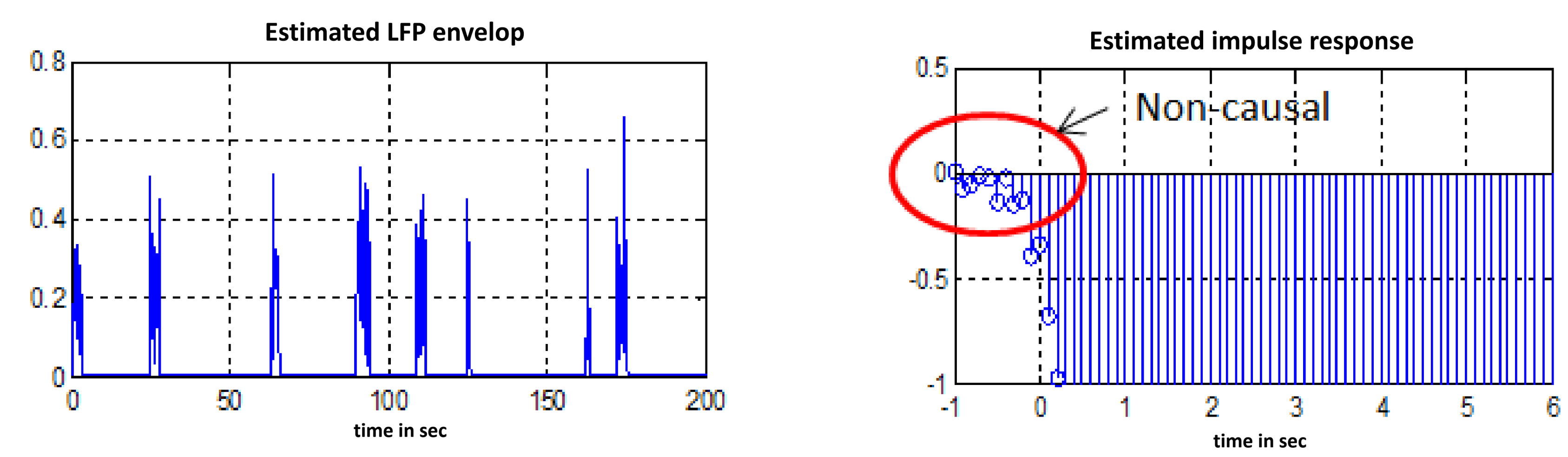


The estimated HRFs were found to be consistently non-causal across datasets, as evident from consistently positive values for t < 0

The results of one sample t-test suggest that the estimated HRF is significantly different from zero even for t < 0. (p < 0.05)

- The non causality of the estimated HRF may not have a physiological origin, since it may also be attributed to the input noise, as shown in the Theory section

Simulations:



LFP envelope estimated from the simulated LFP data is different from the true envelope. This imperfection in our knowledge of the neural input function can be modeled as noise

The estimated HRF is non-causal, even though the true HRF used to generate the simulated data is causal. This can be attributed to the uncertainty in our knowledge of the "true" neural input driving the hemodynamic response

DISCUSSION

- With an exponential growth in the number of studies utilizing spontaneous hemodynamic fluctuations to study brain activity at rest, it is becoming increasingly important to study the neurovascular coupling, and hence the HRF, in resting state
- In contrast with the task-based studies, the input function for HRF estimation is not readily available in resting state studies, has to be estimated from the neural recordings, and is not noise free
- Equation (1) shows that the presence of noise in our estimate of neural input introduces a bias in HRF estimates obtained using least-square and Weiner filtering approaches
- Therefore, based on the findings of this study, the HRF estimated using LS is always biased in resting state, and may turn out to be non-causal even when the true HRF is causal
- Thus, our study highlights a fundamental limitation on the study of neurovascular coupling at rest using the prevalent experimental and analysis paradigms

REFERENCES

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[2] Hayes, M.H., Statistical digital signal processing and modeling. 2009: John Wiley & Sons

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