Title:

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 whose impulse response is known as the 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 noisy output (i.e. hemodynamic response). In this study, we investigate the effect of the “input noise” on the HRF estimated using the least squares (LS) approach.

Methods:

Mathematical derivation:

Let $f[n]$ and $d[n]$ be the true (noise-free) input function and hemodynamic response respectively. Assuming an LTI underlying system, $d[n] = f[n] * h_{true}[n]$, where $h_{true}[n]$ is the true HRF. Let $x[n] = f[n] + w_f[n]$ and $y[n] = d[n] + w_d[n]$be the measured input and output, where w_f and w_d represent zero-mean white noise, uncorrelated with $f[n]$ as well as $d[n]$. Assuming joint wide-sense stationarity, it can be shown that the impulse response $h_{est}[n]$ that minimizes $E((y[n] - x[n] * h_{est}[n])^2)$ is given by [1] $H_{est}(z) = \frac{P_{yx}(z)}{P_{xx}(z)}$ where $P_{yx}(z)$ and $P_{xx}(z)$ represent z-transforms of auto and cross correlation functions $r_{yx}[k]$ and $r_{xx}[k]$ respectively. $h_{est}[n]$ is also known as the Wiener filter. Now it can easily be shown that $r_{yx}[k] = h_{true}[n] * f[n] \Rightarrow P_{yx}(z) = H_{true}(z)P_{ff}(z)$.
Also $r_{xx}[k] = r_{ff}[k] + \sigma_{w_f}^2 \delta[k]$, $\therefore P_{xx}(z) = P_{ff}(z) + \sigma_{w_f}^2$. Thus

$$H_{est}(z) = H_{true}(z)\frac{P_{ff}(z)}{P_{ff}(z) + \sigma_{w_f}^2} = H_{true}(z)H_b(z) \qquad (1)$$

As can be seen from eq. (1) the Weiner filter will be equal to the true HRF convolved with $h_b[n]$. Please note that $h_b[n]$ is non-causal, since $H_b(z) = H_b^*\left(\frac{1}{z^*}\right)$. Therefore, $h_{est}[n]$ can be non-causal even if $h_{true}[n]$ is causal. Assuming ergodicity, it can be shown that the LS estimate is an unbiased and consistent estimate of the Weiner filter. If the Weiner HRF is biased so is the least square estimate.

Simulation:

The real data consists of simultaneous hemodynamic and neuronal recordings (local field potential LFP) from the primary somatosensory cortex (S1) of four Sprague-Dawley rats, male, 250-300g taken at 1200 samples/sec obtained by the method of fNIRS [2]. Simulated data was generated according to following:

- A square wave was assumed to represent the true LFP envelope (Fig 1a). The width of the square wave pulses, as well as the inter-pulse duration were based on neural activity burst width and inter-bust intervals in the real data.
- Simulated hemodynamic signal (referred to as optical signal) was generated by convolving the true LFP envelope with the “true” HRF chosen based upon causal HRF estimation performed on the real data (Fig 1b).
- Simulated LFP recording was generated by multiplying the true LFP envelope with band-pass filtered (1-30 Hz) white noise signal (Fig 1c).

Simulated LFP signal was band pass filtered between 1 to 30Hz to retain the frequencies from delta to beta range, the envelop of the filtered LFP signal was extracted using Hilbert transform to estimate the input function. Finally, LFP and optical signals were down sampled to 10Hz sampling frequency. The simulated optical signal $y[n]$was modeled as the convolution of LFP envelop $x[n]$ with a non-causal impulse response plus zero mean noise i.e.$y[n] = \sum_{l=-M1}^{M2} h'[l]x[n-l] + e[n]$. $M_2$was determined using the Minimum Description Length criterion. $M_1 = 10$ was arbitrarily chosen to allow non-causality in HRF estimation. Least squares approach for this model has a closed form matrix formulation, and was used to estimate the HRF [3] $\boldsymbol{h}' = (A^H A)^{-1} A^H \boldsymbol{y}$.

Results:

Eq. (1) shows that the LS estimate will be biased due to the presence of noise in neural input. The effect is demonstrated in the simulation as well where the estimated HRF (Fig 2c) turns out to be non-causal although the true HRF (Fig 2b) is causal. This is because the input LFP envelop (Fig 2a) is a noisy estimate of the true LFP envelop (Fig 1a).

Conclusion:

Our theoretical derivations and simulation results indicate that the presence of noise in our estimate of neural input introduces a bias in HRF estimates obtained using least-square and Weiner filtering. This effect renders our interpretation of the estimated HRF prone to error, under resting state conditions. Future work will focus on exploring ways to minimize this effect.

The presence of noise in neural input biases LS and Wiener estimates of HRF in resting state which renders our interpretation of estimated HRF prone to error.

References:

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