# LINEAR CONVOLUTION MODEL OF FETAL CIRCULATION FOR HEMODYNAMIC RESPONSES TO MATERNAL HYPEROXIA USING IN UTERO FUNCTIONAL MRI

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## Abstract

Functional MRI studies have started the hemodynamic responses of the placenta and fetal brain using maternal hyperoxia. While most studies have focused on analyzing the changes in magnitude of fMRI signals, few studies have analyzed the latency and duration of responses to hyperoxia. This paper proposes a linear convolution model of fetal circulation where a chain of responses to maternal hyperoxia are produced in the placenta and fetal brain. Specifically, an impulse response to hyperoxia was modeled as the hemodynamic response function (HRF) which consists of multiple gamma functions. Both time-to-peak and full width at half maximum of HRF were estimated using simulated annealing (SA). A Monte Carlo simulation was carried out to evaluate the performance of the SA-based method for estimating both parameters. Finally, we provided an example of estimating HRFs from fMRI time series of the placenta and fetal brain acquired during maternal hyperoxia in vivo.

## Index Terms

linear convolution model; hemodynamic response function; placenta; fetal brain; hyperoxia; fMRI

## 1. INTRODUCTION

The hemodynamic response of the placenta and fetal brain to maternal hyperoxia has been recently examined using functional magnetic resonance imaging (fMRI). Sörensen et al. reported a significant increase of blood oxygen level dependent (BOLD) signals in the placenta and fetal organs (such as fetal liver, spleen, and kidney) while there were no changes in the fetal brain [1].

While this study focused on analyzing the temporal changes of blood oxygenation during maternal hyperoxia, Luo et al. analyzed the spatiotemporal pattern of BOLD responses of the placenta to maternal hyperoxia, and found that the oxygen time-to-plateau of BOLD time course is significantly correlated with fetal brain volume and placental pathology [2]. The hemodynamic response was modeled as the convolution of a gamma function with the given oxygen paradigm. The gamma model was designed with the baseline assumption that the BOLD signals progressively increase during hyperoxia. However, the placental response to hyperoxia is unpredictable such that it either exhibits a gradual decrease and/or dynamic fluctuations.

In this paper, we propose a linear convolution model (LCM) of fetal circulation in order to study hemodynamic responses related to oxygen timing properties of the placenta and fetal brain to maternal hyperoxia. The fetal circulation model was described as a series of cascaded hemodynamic filters that correspond to the placenta and fetal brain and whose impulse response is given as the hemodynamic response function (HRF) [3]. The HRFs of the placenta and the fetal brain were estimated using the simulated annealing algorithm, and the time-to-peak and duration of the BOLD time course responding to hyperoxia were estimated from HRFs.

## 2. METHODS

### 2.1. Linear convolution model of fetal circulation

The oxygen supplied to the mother is absorbed by the maternal blood vessels through alveoli of the lungs, which results in an increase in arterial oxygen pressure and blood oxygen concentration. The pulmonary blood with increased oxygen concentration finally reaches the placenta via the maternal cardiovascular system, which leads to the increase in placental oxygen concentration. The oxygen dissolved in the placental plasma is transferred to the fetus through oxygen diffusion between the placental terminal villi and fetal vessels. Finally, the oxygenated fetal blood is delivered to the fetal brain via umbilical cord, fetal liver and heart. Although this process is intrinsically nonlinear, simplifying fetal circulation as a linear time-invariant (LTI) system, as depicted in Fig. 1, facilitates the analysis of the global fetal circulation. Comparatively, Birn et al. suggested a similar linear model to quantify the respiration response of the brain [3].

In the linear convolution model, a BOLD response of the placenta to maternal hyperoxia is represented as the convolution of hyperoxia paradigm and *hemodynamic response function* (HRF) with additive noise as shown in (1).

$$y_p(t) = (u * h_p)(t) + e_p(t) \qquad (1)$$
$$= \sum_{m=0}^{N-1} u(t)h_p(t-m) + e_p(t)$$

where $y_p$ is a fMRI time series of the placenta, u denotes a stimulus function, $h_p$ is the placenta HRF, and $e_p$ is a Gaussian noise with zero mean and variance $\sigma_p^2$. In a similar manner, the placental BOLD response can be viewed as a knock-on stimulation to the fetal brain as shown in (2).

$$y_b = (u_b * h_b)(t) + e_b(t) \quad (2)$$

$$= (u_p * h_p * h_b)(t) + e_b(t)$$

$$= \sum_{k=0}^{N-1} \sum_{m=0}^{N-1} u_p(t) h_p(t-m) h_b(t-k) + e_b(t)$$

The HRF $H_I$ of both the placenta and fetal brain ($i \in \{p, b\}$) is represented as the sum of gamma-variate functions as shown in (3) [3].

$$h_i(t) = \sum_{k=1}^{K} c_k g_k(t; p_k, f_k) \quad (3)$$

where $K$ is the number of basis functions, and $g_k(t, p_k, f_k)$ denotes the $k$-th gamma-variate basis function with *time-to-peak* (TTP) $p_k$ and *full width at half maximum* (FWHM) $f_k$ given in (4)

$$g_k(t; p_k, f_k) = \left(\frac{t}{p_k}\right)^{\alpha_k} \exp\left(\frac{-(t-p_k)}{\beta_k}\right) \quad (4)$$

with $\alpha_k = 8\log2 \times p_k^2/f_k^2$ and $\beta_k = f_k^2/(8\log2 \times p_k)$.

## 2.2. Estimation of hemodynamic response functions

The simulated annealing algorithm, which is a probabilistic optimization method to find the global minimum of a given cost function, was used to estimate the HRFs of the placenta and fetal brain [4]. The optimal set of HRF parameters, including TTP($p_k$) and FWHM($f_k$), was chosen to minimize the difference between original BOLD time series and the convoluted time series between stimulation and the estimated HRF; in other words, the parameters ($p_k$, $f_k$, $c_k$) for $k = 1, \ldots, K$ are selected to satisfy the following equation using the simulated annealing method.

$$\min_{p_1, f_1, c_1, \ldots} \sum_{t=0}^{N-1} ((y_p - u * h_p)(t))^2 \quad (5)$$

## 2.3. Experimental setup

In order to evaluate the performance of the proposed HRF estimator, we simulated BOLD time series of the placenta and fetal brain using the equations (1) and (2). The discrete time series of length 8160 with time interval of 0.1 second were generated with the hyperoxia

paradigm which consists of a 2 min baseline, 6 min onset, and 5 min 36 second return to baseline. The stimulus time series was then convoluted with the HRF of two basis functions (K=2) and length 30 whose parameters are given as $c_1, p_1, f_1, c_2, p_2, f_2 = (1, -0.2, 10, 17, 10, 14)$. To evaluate the robustness of the estimator when the time series is perturbed by additive noises, we performed the Monte Carlo simulation of 1000 replications with three signal-to-noise ratios (SNR) 0, 1 and 10 in the logarithmic decibel scale.

To test the HRF estimator for in utero fMRI data, we acquired echo planar imaging (EPI) sequences on a 1.5T GE MR scanner from 10 healthy fetuses in coronal views. The hyperoxia task paradigm was identical to the above simulation, but the MR parameters were set with the repetition time (TR) of 2 seconds, 288 volumes, matrix size of $128 \times 128$, and 18 slices with slice thickness 8 mm. The spatial inhomogeneity of magnetic field (B1) in MR images was corrected using the 4D nonparametric bias estimator (N4ITK). The regions of the placenta and fetal brain were manually delineated on a reference volume by an expert in fetal imaging using ITK-SNAP as illustrated in Fig. 2. Using the region-of-interest (ROI) masks, all volumes were registered to the reference volume through rigid/non-rigid image registration of the Image Registration ToolKit (IRTK). Significantly misaligned volumes were automatically removed and the missing volumes were reconstructed through data imputation [5]. The voxel-wise BOLD signals were finally averaged over each ROI.

## 3. RESULTS

### 3.1. Simulation

Fig. 3 shows an example of a simulated placental signal and placenta HRF which was estimated using the simulated annealing algorithm. The figure also shows how the HRF is characterized by TTP and FWHM. The (red-colored) convolution signal $u * h_p$ between the given stimulus and HRF is a noise-free placental signal, and is regarded as the stimulation to the fetal brain as depicted in Fig. 1.

In Fig. 4, the estimator of TTP for placenta HRF was slightly biased but less than 0.5 second in all three cases of SNR; the median of estimation bias=−0.29, −0.31, −0.33 seconds when SNR=10,1,0. The estimator of FWHM was also biased in all the cases of SNR, and the lower SNR resulted in the increase in estimation bias; the median of estimation bias= −0.33,−0.55,−0.8 seconds when SNR=10,1,0. The estimators of TTP and FWHM in the fetal brain were more biased and less efficient compared to those of the placenta; the median of estimation bias=−0.56, −0.65, −0.7 seconds for TTP, −1.43, −2.61,−2.58 seconds for FWHM when SNR=10,1,0. −

### 3.2. In utero fMRI data

Fig. 5 illustrates the HRFs of the placenta and fetal brain estimated from in utero BOLD signals. The TTP and FWHM were 4 and 48 seconds for the placenta, and 10 and 20 seconds for the fetal brain. The estimated HRF of the placenta does not appear like the typical shape of hemodynamic response function (HRF) of the brain, but exhibits the slowly decaying pattern. The estimated noise-free signal effectively captures the global trend of BOLD signals. The average TTPs were $13.2 \pm 7.2$ and $22.9 \pm 10.9$ seconds (mean $\pm$ SE) for

the placenta and fetal brain while the average FWHMs were $61.6 \pm 14.7$ and $67.5 \pm 40.6$ seconds respectively.

## 4. DISCUSSION

To the best our knowledge, we are the first to propose a linear convolution model of fetal circulation to model the hemodynamic response of the placenta and fetal brain to maternal hyperoxia. The HRF was used to characterize the impulse response to hyperoxia, and it allowed us to quantify not only how rapidly the placenta and fetal brain responded to maternal hyperoxia but also how these responses are sustained. While the current method measures the time-to-plateau without considering the changes in oxygenation for the return to baseline, the temporal patterns of the whole experimental paradigm are also considered to estimate both TTP and FWHM. Moreover, the HRF can be composed of more than two gamma functions while the traditional gamma model only consists of a single gamma function. Despite the added benefits of the proposed model, the response model needs to be further improved to reflect the physiological nonlinearity of the fetal circulation; for example, the nonlinear compartments of the cardiovascular systems can be added to the model to realistically assess the hemodynamic response to hyperoxia.

We also proposed a probabilistic method for estimating both TTP and FWHM of the hemodynamic response function. The estimator, which finds the optimal parameters using simulated annealing, did not fully demonstrate its reliable performance as it was biased for the estimation of TTP and FWHM. The performance of the estimator was less efficient in the fetal brain, which might be attributed to noise amplification due to the cascading effect where the fetal brain HRF is estimated based on the placenta fMRI signal. Nevertheless, the simulation results show that the method is still applicable when the TR is longer than 1 second and the log SNR is greater than 1. The estimation method needs to be improved using more advanced techniques such as Baysian optimization in future work, which is currently underway.

We assessed the HRF estimation method for in vivo fMRI data of the placenta and fetal brain. The estimated HRFs did not have the typical shape of canonical HRF which includes a peak followed by an undershoot. The slowly decaying pattern of HRF may be attributed to the downstream effects of oxygenation for a certain period of time after hyperoxia terminates. It may be beneficial to validate the physiological implications of the hemodynamic parameters using Doppler ultrasound data.

In summary, our preliminary study demonstrates the feasibility of quantifying the hemodynamic mechanisms of the placenta and fetal brain that underlie the responses to maternal hyperoxia. Ongoing work is needed to demonstrate the feasibility of this technique for the fetal brain. The long-term goal of this work will be to build a robust framework for non-invasive quantitative functional assessment of the fetal brain-placental unit, which may in turn enable clinicians to monitor treatment response to emerging fetal therapies including the use of maternal oxygen therapy in high-risk fetuses.

## Acknowledgments

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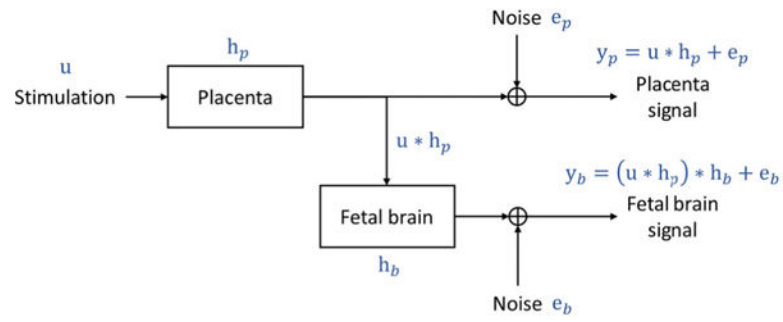
**Fig. 1.**
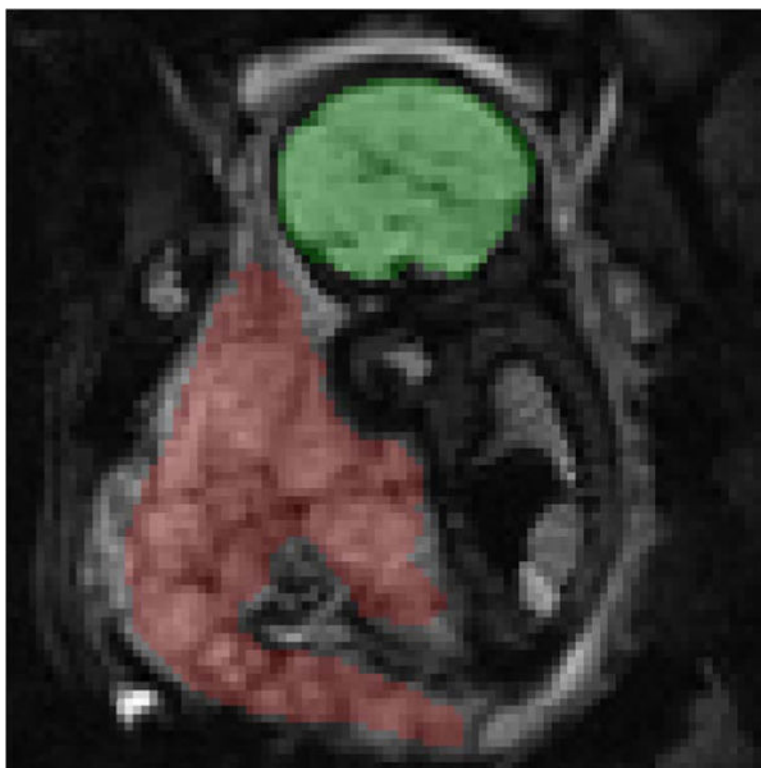The linear convolution model of fetal circulation.

**Fig. 2.**
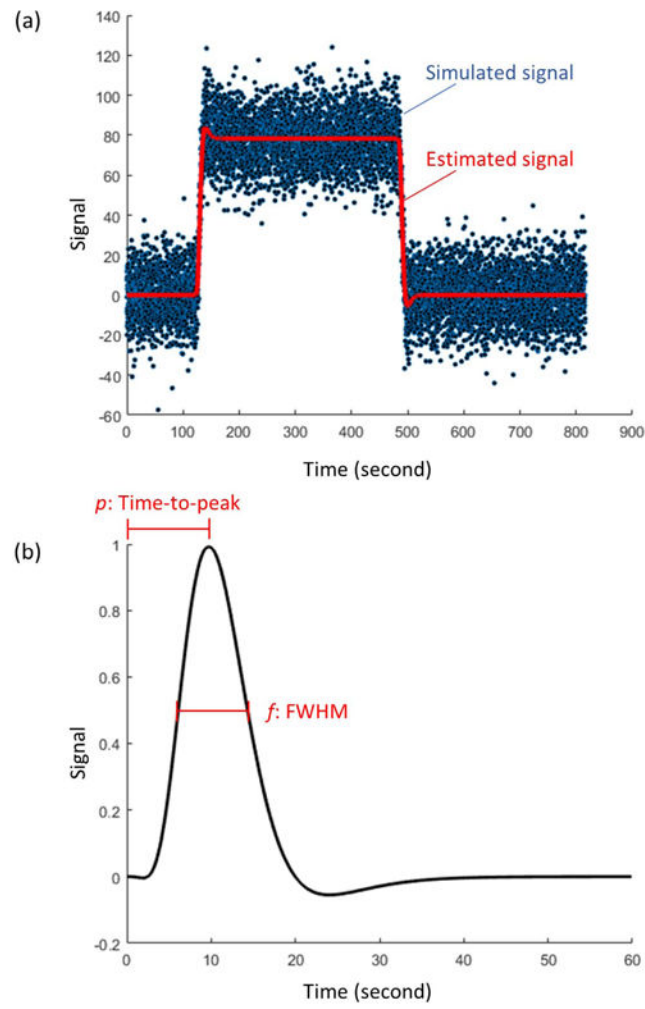An example of in utero fMRI BOLD images including the placenta and fetal brain.

**Fig. 3.**
Estimation of HRF from simulated hyperoxia signal; (a) simulated and fitted signal, and (b) estimated HRF.
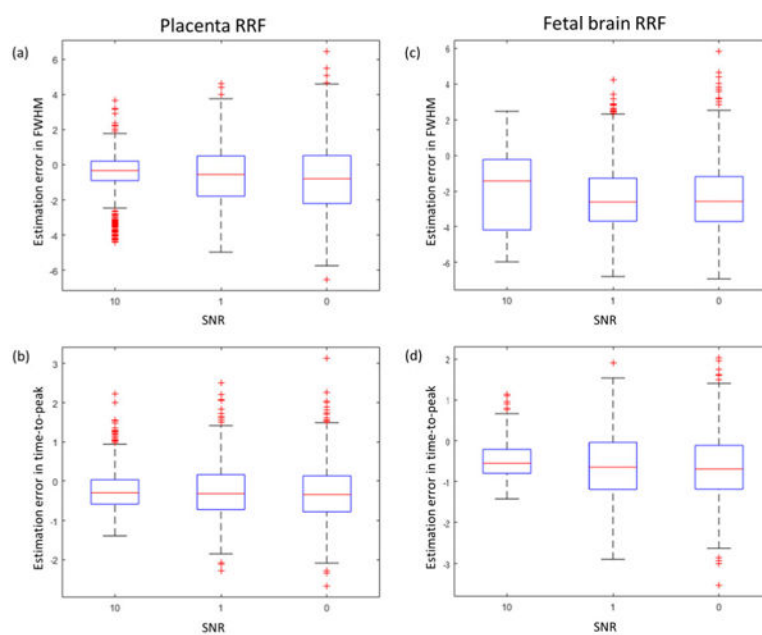
**Fig. 4.**
The estimation bias of TTP and FWHM of estimated HRFs (a–b) in the placenta, and (c–d) in the fetal brain.
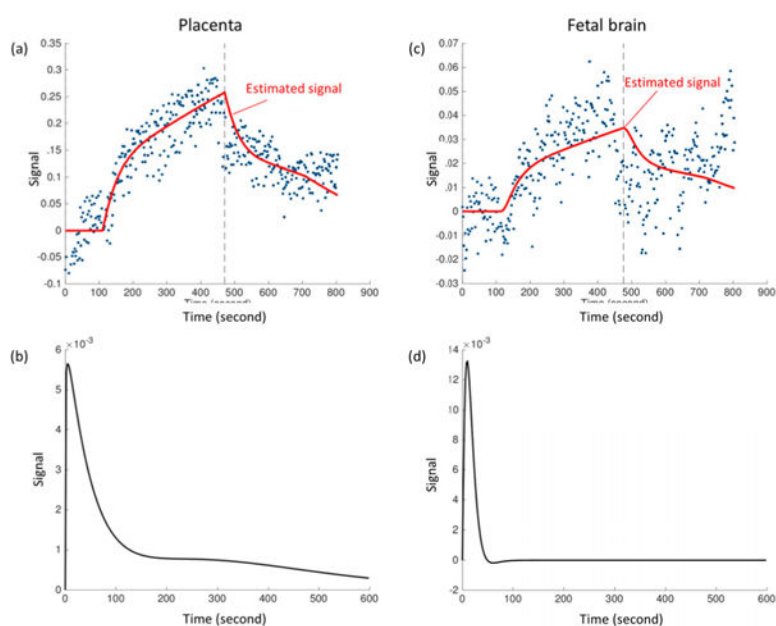
**Fig. 5.**
An example of estimating the HRFs (*bottom*) of the placenta and fetal brain from in utero BOLD fMRI signals (*top*).