Estimation and modelling of fMRI BOLD response

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Abstract

One of the current topics of research in neuroimaging techniques is related to explaining and modelling the Blood Oxygen Level Dependent (BOLD) responses. BOLD responses are estimated by processing functional Magnetic Resonance Imaging (fMRI) data. BOLD responses are caused by hemodynamic responses to neural activity which alter the levels of blood oxygenation at local brain regions. The main aims of the current thesis were to i) develop and examine methods regarding BOLD response estimation from the visual cortex and the frontal cortex of human brain and to ii) develop a model in order to explain the physiological mechanisms which cause the estimated BOLD responses.

In order to satisfy the main aims, fMRI data were provided by the Center of Medical Imaging and Visualization (CMIV). The provided fMRI data consist of fMRI brain measurements of twelve healthy human subjects who were subjected to visual stimulation. By processing the fMRI data, Regions Of Interest (ROIs) were extracted at the anatomical sites of the visual cortex and the frontal cortex. Afterwards, the fMRI data were manipulated in order to extract BOLD responses from the visual cortex and the frontal cortex. Various methods were developed and compared in terms of which technique provided well representative BOLD responses.

Subsequently, a model was developed by using software Wolfram Mathematica 9 in order to explain the physiological mechanisms of the estimated BOLD responses at the visual and the frontal cortex. The model aimed to solve for oxygen concentration in blood plasma as blood flows from the arterial part to the venous part of the blood circulation system through a capillary. Oxygen outward diffusion through the capillary wall and oxygen concentration at the extravascular environment were modelled as well. Blood plasma oxygen concentration was turned into hemoglobin oxygen saturation \( \text{Sa}\text{O}_2 \) through hemoglobin oxygen dissociation curve and Henry’s law for gases. As a result, the \( \text{Sa}\text{O}_2 \) was estimated through modelling for oxygen concentration in blood plasma. Finally, the developed model ended to a system with input the fractional change of Cerebral Blood Flow (CBF) velocity and Cerebral Metabolic Rate of Oxygen (CMRO\text{O}_2) and as output a proportional signal to the BOLD response. By simulating for different scenarios of fractional changes of CBF velocity and CMRO\text{O}_2 and by comparing the resulted BOLD responses to the estimated ones, it was attempted to explain for the physiological mechanisms which caused the BOLD responses at the anatomical sites of the visual and frontal cortex.
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<tbody>
<tr>
<td>MRI</td>
<td>Magnetic Resonance Imaging</td>
</tr>
<tr>
<td>fMRI</td>
<td>functional MRI</td>
</tr>
<tr>
<td>$O_2$</td>
<td>Oxygen</td>
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<tr>
<td>RF</td>
<td>Radio Frequency</td>
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<tr>
<td>BOLD</td>
<td>Blood Oxygen Level Dependent</td>
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<tr>
<td>CBF</td>
<td>Cerebral Blood Flow</td>
</tr>
<tr>
<td>CBV</td>
<td>Cerebral Blood Volume</td>
</tr>
<tr>
<td>CMRO$_2$</td>
<td>Cerebral Metabolic Rate of $O_2$</td>
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<tr>
<td>HRF</td>
<td>Hemodynamic Response Function</td>
</tr>
<tr>
<td>ROI</td>
<td>Region Of Interest</td>
</tr>
<tr>
<td>SOT</td>
<td>Stimulus Onset Time</td>
</tr>
<tr>
<td>CMIV</td>
<td>Center for Medical Image and Visualization</td>
</tr>
<tr>
<td>TR</td>
<td>Time of Repetition</td>
</tr>
<tr>
<td>PSD</td>
<td>Power Spectral Density</td>
</tr>
<tr>
<td>DFT</td>
<td>Discrete Fourier Transform</td>
</tr>
<tr>
<td>SNR</td>
<td>Signal to Noise Ratio</td>
</tr>
<tr>
<td>Sa$O_2$</td>
<td>Saturation of $O_2$</td>
</tr>
<tr>
<td>Pa$O_2$</td>
<td>Partial pressure of $O_2$</td>
</tr>
<tr>
<td>PDE</td>
<td>Partial Differential Equation</td>
</tr>
<tr>
<td>FDM</td>
<td>Finite Difference Method</td>
</tr>
<tr>
<td>ODE</td>
<td>Ordinary Differential Equation</td>
</tr>
<tr>
<td>OHb</td>
<td>Oxyhemoglobin</td>
</tr>
<tr>
<td>DHb</td>
<td>Deoxyhemoglobin</td>
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1. Introduction
1.1 Physiological principles of fMRI
The vascular system consists of a complex network of large and small vessels which supply oxygen ($O_2$) and glucose to the cells of the brain. In the brain, the arterial circulation system transfers those substances to the capillary bed. $O_2$ is transferred through hemoglobin molecules in the red blood cells. When hemoglobin molecules bind to $O_2$ molecules, they are known as oxyhemoglobin (OHb) and when they do not, they are known as deoxyhemoglobin (DHb). In the capillary bed, $O_2$ is exchanged between blood and cells through small vessels. Then, the venous circulation system transports the less oxygenated blood away from the capillary bed. (1)

As it is explained in Appendix A., fMRI is $T_2^*$ weighted contrast. $T_2^*$ weighted contrast depends on local field inhomogeneities. In the brain, the size of local field inhomogeneities depends on local blood supply. Local neuronal activity is characterized by supply of oxygenated blood, $O_2$ consumption, relatively high levels of OHb at arterial circulation system and relatively low levels of OHb at venous circulation system. Neuronal activity is shown in Fig. 1 where blood inflows into the capillary bed rich in OHb and outflows with relative lower OHb levels due to tissue $O_2$ consumption. (2)

![Figure 1 Blood flow from arterial to venous circulation system through capillary bed. a) The state when there is normal $O_2$ consumption from tissues is known as baseline state. b) When neural tissues are stimulated there is higher $O_2$ consumption. Red dots indicate OHb and blue dots DHb. White arrows are larger in b) than in a), which indicates that cerebral blood flow is increased when neural tissues are stimulated. (2) Figure as originally published in (2). Reprinted with permission. Copyright © 2012 ISCBFM.](image)

OHb has diamagnetic properties and DHb has paramagnetic properties. So, an increase in DHb levels would cause a decrease in $T_2^*$ because paramagnetic properties increase the local field inhomogeneity (Appendix A.). Therefore, the increase in local field inhomogeneity, which is caused by higher DHb levels, suppresses the MR signal. So, due to the fact that local field inhomogeneity depends on the levels of OHb and DHb, $T_2^*$ weighted contrast in MRI indicates the Blood Oxygenation Level Dependent (BOLD) contrast. Functional MRI (fMRI) is a temporally resolved MRI and the contrast is based on $T_2^*$. The whole concept of
fMRI in order to identify blood oxygenation levels temporally is known as BOLD fMRI. (1-3)

1.2 BOLD response modelling
Neural activity is believed to be connected with blood oxygenation levels because the neural system cooperates with the blood circulation system in order to fulfil brain tissues needs in 
\(O_2\), glucose and other substances. (2) The fMRI signal, which is observed when brain tissues are stimulated, is known as a BOLD signal. A typical BOLD signal is shown in Fig. 2. It was obtained from visual cortex and motor cortex when brain tissues were stimulated with a short time duration stimulus. (1)

Several models have been developed in order to explain the physiological mechanisms which result in BOLD signals. According to Buxton et al.(4), the BOLD signal is sensitive to the cerebral blood flow (CBF), the metabolic \(O_2\) rate (CMR\(O_2\)) and the cerebral blood volume (CBV). When neurons of the brain are stimulated, there is demand for \(O_2\) and glucose and as a result CMR\(O_2\) increases. The vascular system of the brain responds by increasing CBF in order to supply \(O_2\) and glucose to the brain tissues. Buxton et al.(4) demonstrated that during the stimulation of tissues in the brain, CBF increases and contributes to lower levels of DHb, than when neural tissues are in resting state. CBF and CMR\(O_2\) have opposite effects on BOLD signal. When CBF increases, the levels of DHb are decreased. On the other hand, when CMR\(O_2\) increases, levels of DHb are increased.

A standard shape was used in literature to explain the Hemodynamic Response Function (HRF) and is shown in Fig. 2a). This response is known as the canonical HRF to one short time stimulus of neural activity. In Fig. 2b), measured responses of the visual and motor
cortex were given. It was observed that in the first 1-2 seconds of BOLD response the BOLD signal was decreased. This phase is known as the initial dip. However, the initial dip is not always observed. The stimulation is believed to increase the CMRO₂. An increased CMRO₂ causes more O₂ to be diffused outwards the vessels in the capillary bed, a fact which increases the levels of DHb and inhomogeneity as well. (1-4)

Afterwards, the blood circulation system responds by increasing CBF, so as the oxygenated blood refreshes the activated areas of the brain. As a result, the BOLD signal is increased and this rise has an onset around two seconds after the stimulus. A peak is expected to be around 5-8 seconds in the visual and motor cortex as it is observed in Fig. 2b). (3) This increase is caused due to the fact that the effect of CBF is higher than the effect of CMRO₂ in BOLD signal. Buxton et. al(4) introduced a coupling ratio which was defined as the fractional change of CBF divided by the fractional change of CMRO₂ in response to a stimulus. This coupling ratio was believed to influence the amplitude of the BOLD signal.

After the peak, the BOLD signal decreases and returns to a level below the baseline. This phase is known as post stimulus undershoot. Buxton et al.(5) referred that the post stimulus undershoot is believed to be caused because CBF decreases more rapidly than CBV. This phase may last 30 seconds or more. During this phase, the signal returns slowly to the baseline.

1.3 Aims
Part A (sections 2-4) of this thesis aimed at extracting BOLD responses to short time stimuli from the Regions Of Interest (ROIs) at the visual cortex and the frontal cortex. The ROIs are defined as the specific parts of the cortices which were activated by the short time stimuli. For that reason, fMRI data was processed in order to implement statistics regarding the behavior of fMRI BOLD responses to neural stimuli. Several methods were developed aiming at extracting well representative BOLD responses in terms of a high Signal to Noise Ratio (SNR) and similar shape compared to the BOLD responses found in literature.

Part B (sections 5-7) of this thesis aimed at developing a model in order to explain for the physiological mechanisms of the extracted BOLD responses of part A. Therefore, through the developed model, it was aimed to explain the physiological mechanisms at the visual cortex and the frontal cortex when these regions respond to short time stimuli. The model aimed at estimating hemoglobin O₂ saturation (SaO₂) when blood flows through a capillary and the parameters CBF and CMRO₂ vary in time. Levels of DHb are believed to affect magnetic properties of flowing blood and as a result the BOLD fMRI signal. Therefore, it was attempted to estimate how the BOLD fMRI signal depends on CMRO₂ and CBF. Through the estimated dependence of BOLD fMRI signal on CMRO₂ and CBF, it was aimed to explain for the physiological mechanisms which are responsible for the estimated BOLD responses of part A.
Part A -- Estimation of fMRI BOLD response

2 fMRI BOLD response estimation -- Methods

This chapter describes the methods which have been developed for estimating BOLD responses at the ROIs of the visual and frontal cortex. Specifically, the following steps were implemented:

1) A description of the experiment according to which the fMRI data have been retrieved.
2) Statistical parametric analysis with software SPM8 (6) in order to i) perform fMRI preprocessing steps ii) extract neural activity contrast images and iii) identify ROIs at the anatomical sites of the visual and frontal cortex.
3) Digital signal processing methods and manipulation of the fMRI data in order to extract BOLD responses from the identified ROIs.

2.1 Description of fMRI experiment

In order to extract BOLD responses from the ROIs of the visual and frontal cortex, fMRI data was supplied as 4 dimensional data by the Center for Medical Imaging and Visualization (CMIV) of Linköping University. The fMRI data consisted of brain fMRI measurements from 12 healthy subjects. The Time of Repetition (TR) was 2 seconds and every measured voxel size was 3x3x3 mm3.

Simultaneously with fMRI brain measurements, every subject was exposed to visual stimulation during two sessions. During the experiment, the subjects were looking at the center of the images which were exposed to them. The visual stimuli consisted of images with a central word. The task of the subjects was to identify the color of the central word. The visual stimuli consisted of four cases: red congruent, green congruent, red incongruent, and green incongruent. During congruent stimulation the color of the stimulus was only green or red respectively. Red incongruent stimulation was applied when the color of the central word was red and the color of the words at the periphery was green. Green incongruent stimulation was applied when the color of the central word was green and the color of the periphery words was red. In Fig. 3a) and in Fig. 3b), examples of red congruent stimulus and red incongruent stimulus are shown respectively.

![Figure 3](image-url)

*Figure 3 Examples of stimulus which were used during the experiment. a) Red congruent stimulus was applied when all the words had red color. b) Red incongruent was applied when the central word had red color and the periphery words had green color.*
Visual stimuli were exposed at specific time intervals during the experiment. The time points which depicted when the stimuli were initiated, were called Stimulus Onset Times (SOTs). Stimuli were initiated on SOTs and were lasting for a short duration time for around 500 ms. The time interval between the SOTs varied during the experiment in the range of \( \{2.6 \text{– } 20.6\} \) s. The purpose of the current work was to observe BOLD responses to only one stimulus. In current thesis, it was presumed that after 19 seconds the BOLD levels would have returned to their baseline conditions. Therefore, the fMRI data were only accounted when the time interval between two stimuli lasted more than 19 seconds.

### 2.2 Statistical parametric analysis

SPM8, was used in order to perform fMRI preprocessing steps and implement fMRI statistics so as to extract contrast images. fMRI statistics were implemented by using the General Linear Model (GLM). When using the GLM, it was attempted to calculate a t-test value for every voxel of the brain. The t-test value indicated the statistical correlation between the brain voxels and the expected fMRI signal at the activated brain regions due to neural stimulation. Contrast images depicted the t-test value of every voxel. Therefore, contrast images reflected neural activity. (6)

The process of producing a contrast image by implementing fMRI statistics on fMRI data of one subject was defined by (6) as 1st level analysis. In this work, the contrast images produced by 1st level analysis were called individual contrast images and this kind of analysis was called individual analysis. By observing the individual contrast images, high t-test values were identified at the anatomical sites of the visual and the frontal cortex. At those high t-test values, two ROIs were extracted for every subject, one ROI at the visual cortex and one ROI at the frontal cortex. In this work, the extracted ROIs at the visual cortex and the frontal cortex of every subject were called individual masks.

Additionally, SPM8 was used in order to perform 2nd level analysis. In this work, this kind of analysis was called group analysis. Group analysis was the process when all the individual contrast images were used in order to extract general contrast images. The general contrast images reflected an average contrast image of a whole group of fMRI data of subjects. In this work, a general contrast image was extracted by SPM8 when using all the individual contrast images. The general contrast image contains average t-test values. By observing high t-test values of the general contrast image at the anatomical sites of visual and frontal cortex, two ROIs were extracted, one ROI at the visual cortex and one ROI at the frontal cortex. In this work, those two ROIs, which were extracted through the general contrast image, were called general masks.

#### 2.2.1 fMRI preprocessing steps

Before the fMRI data were processed so as to extract contrast images of neural activity, fMRI data should be preprocessed and prepared for individual and group analysis. A diagram of all the involved preprocessing steps is depicted in Fig. 4.
The SPM8 option ‘Realign: estimate and reslice’ was used to correct for motion artifacts. One 3D image was used as a reference image and the rest of the 3D images were realigned to the reference image. For every image, 6 parameters of spatial transformation, which denoted spatial rotation and translation, were calculated. This procedure was performed for every session of data. At the output of this step, the images were realigned so as to match anatomically to the reference image. The reference image, which was chosen from the user, was the first image, e.g. the image which was recorded first in the beginning of every session. (6)

The images at the output of ‘Realign: estimate and reslice’ were passed to the step of slice timing correction. Every 3D image was sampled every TR (equal to 2 s in this case). This means that the time difference between the first and the last slice of every volume was sampled with a time difference of 2 seconds. Therefore, slices of the same volume have been sampled with a time difference smaller than 2 seconds. Slice timing correction was used to correct for those time differences by using interpolation techniques in order to estimate the value of a voxel between two successive time-points. (6)

In order to implement group analysis, there was a need to normalize the data of every subject’s session so as they have similar anatomical space. The option of SPM8 ‘Normalise: estimate & reslice’ allowed for normalizing all data according to template images supported by SPM8. In the case of the current work, all images were normalized according to a template image. This resulted to all images having similar anatomical space to the template.
image. More specifically, all data sessions had similar spatial coordinates for the same anatomical positions and therefore they could be included in a group analysis.(6)

Furthermore, after normalization, the data was passed to SPM8 option for smoothing. The data was smoothed with a spatial filter 8 mm in width in every direction, 8 x 8 x 8 mm³. The width 8 mm was chosen since it is at least larger than twice every pixel’s width, which was 3 mm. Smoothing was performed by convolution of the image volumes with a Gaussian kernel to suppress noise and effects due to residual differences in functional and gyral anatomy during inter-subject averaging. Smoothing was the last step of preprocessing. After smoothing, the data was passed to the fMRI statistics section of SPM8.(6)

2.2.2 fMRI statistics

The already preprocessed data was given as input to the fMRI model specification step. In the fMRI model specification, the design matrix of the model was defined. The design matrix had one row for every scan (3D volume) and every column for every stimulus or variable which explained the fMRI signal. Stimuli were loaded as multiple conditions with onset times and durations. The SOTs of the stimulus were specified and were loaded to SPM8. The durations of all stimuli were loaded as zero because stimuli durations were short around 500 ms. Therefore, stimuli were considered as a spike of neural activity because of their short time duration.

Through individual contrast images, individual masks were produced at the ROIs of visual and frontal cortex. Masks were real valued 3D data which had a positive value at the spatial coordinates of the specified ROIs and 0 everywhere else. So, by dividing masks with their positive value, integer valued 3D data was extracted with 1 at the spatial coordinates of interest and 0 everywhere else. By observing all the individual contrast images, the ROIs at visual and frontal cortex were specified for all the individuals. Masks with a radius of 20 mm were produced by SPM8. Individual analysis resulted in 1 individual mask at the visual cortex and 1 individual mask at the frontal cortex for every subject. So, individual analysis for all the subjects resulted in 12 contrast images, 12 individual masks at the visual cortex and 12 individual masks at the frontal cortex.

In SPM8, a model of group analysis was implemented by importing 12 contrast images extracted from the individual analysis. In the group analysis, a contrast image of the average t-contrast for all responses was created. This contrast image was used in order to observe and extract general masks at the visual and the frontal cortex. The extracted general masks were spheres with a radius of 20 mm, namely 2 general masks for all subjects. The anatomical positions of the centers of the extracted spheres were shown in Fig. 5 and Fig. 6 for the visual and frontal cortex respectively.
Figure 5 Contrast through group analysis which is displayed on an anatomical MRI image. At a), b) and c) the center of the ROI at the visual cortex is depicted as the point where the blue lines meet each other. a) Right lateral view of the brain. b) Posterior view of the brain. c) Superior view of the brain. d) Gradient scale of contrast values.

Figure 6 Contrast through group analysis which is displayed on an anatomical MRI image. At a), b) and c) the center of the ROI at the frontal cortex is depicted as the point where the blue lines meet each other. a) Right lateral view of the brain. b) Posterior view of the brain. c) Superior view of the brain. d) Gradient scale of contrast values.
2.3 Filtering approach

2.3.1 Weighted coefficients calculation

In this chapter, a filtering approach was developed in order to calculate weighted averaged BOLD time series from the extracted ROIs. More specifically, the purpose of this method was to create weighted coefficients for all the voxels of the ROIs. Weighted coefficients were weighted in terms of having a higher value at the voxels where t-test value was high and a low value at the voxels where t-test value was low. The MATLAB files derived from SPM8 represented the masks, the contrast images and the preprocessed fMRI data. Those files were turned into Wolfram Mathematica 9 files. The rest of the methods and visualizations were implemented in Wolfram Mathematica 9.

In Fig. 7, the mask which was produced at the visual cortex after group analysis is presented. The black color corresponds to the maximum value of the data volume and the white color corresponds to zero. For simplicity of the method development, the masks were normalized in the range \( \{0,1\} \) by dividing the voxel’s values with the maximum value. Therefore, masks have value 1 at the voxels inside the specified ROIs and value 0 at the voxels outside the ROIs.

![ROI at the visual cortex](image)

*Figure 7 Mask produced from group analysis at the visual cortex. The black color corresponds to 1 and the white color corresponds to 0. X,Y and Z are measured in spatial points and correspond to the discretized points of space in three dimensions.*

In Fig. 8, the highest positive values of the contrast image derived from individual analysis of Subject 1 were depicted. The values of every voxel of the contrast image were divided with the maximum value and therefore the range of positive values of the contrast image is \( \{0,1\} \). In Fig. 9, the result of an element by element multiplication was depicted between the mask in Fig. 7 and the contrast image in Fig. 8. In Fig. 9, it was observed that the voxels inside the mask have values in the range \( \{0,1\} \) and outside the mask values equal to zero. In this way, weighted coefficients were created based on the ROI and the contrast image.
**Figure 8** High positive values of contrast image from Subject 1 in the range \([0,1]\). \(X, Y\) and \(Z\) are measured in spatial points and correspond to the discretized points of space in the three dimensions.

**Figure 9** Result of element by element multiplication between the mask and the contrast image. Weighted coefficients at the space of mask in the range \([0,1]\). \(X, Y\) and \(Z\) are measured in spatial points and correspond to the discretized points of space in the three dimensions.

The same method was able to be implemented for every subject given a mask and the contrast image. In summary, the steps followed for calculating weighted coefficients for every subject and ROI were the following:

1) Division of the mask values with the mask’s maximum value so as voxels have values 0 outside the mask and 1 inside the mask
2) i) Division of the contrast image voxels’ values with their maximum value and ii) zeroing of all the negative contrast values. Therefore, negative contrast was not taken into account for the calculation of the average time series. Negative contrast at a specific voxel indicates a negative statistical correlation between the voxel’s fMRI time series and the expected fMRI time series as a response to stimulation.

3) Multiplication element by element of the images created at 1) and 2).

The above steps resulted in the creation of weighted coefficients in the range \(\{0,1\}\). At the spatial coordinates where the t-contrast was negative, the weighted coefficients were zero. In Fig. 10, the same method as above is depicted for subject 1 at the ROI of frontal cortex.

**Figure 10** a) mask created at the frontal cortex by group analysis b) contrast image of subject 1 c) created weighted coefficients for subject 1 at the frontal cortex as a result of element by element multiplication of figures a and b. d) Gray level scale of the plotted values, 1 corresponds to the black color and 0 corresponds to the white color. X,Y and Z are measured in spatial points and correspond to the discretized points of space in the three dimensions.

### 2.3.2 Regulation of weighting

Herein, it was examined how the weighted coefficients could vary so as to give more or less importance to high contrast voxels. For example, for two weighted coefficients \(w_1 = 0.8\) and \(w_2 = 0.6\), it is true that \(w_1 = 1.333 \cdot w_2\). Therefore, it could be said that \(w_1\) is 1.333 more significant than \(w_2\). If the coefficients were exposed to the power of \(r \exp = 2 > 1\), then...
$w_1' = 0.8^2 = 0.64$ and $w_2' = 0.6^2 = 0.36$ and it would be true that $w_1' = 1.777 \; w_2'$. So, $w_1'$ would be more important than $w_2'$ rather than $w_1$ would be than $w_2$ ($1.777 > 1.333$). Therefore, if the weighted coefficients in the range $\{0,1\}$ were exposed to the power of a value $\text{rexp} > 1$, then, the higher the coefficients; the more important they would be.

On the other hand, if $w_1$ and $w_2$ were exposed to the power of $\text{rexp} = 0.5 < 1$, then $w_1'' = 0.8^{0.5} = 0.894$ and $w_2'' = 0.6^{0.5} = 0.775 \Rightarrow w_1'' = 1.154 \; w_2''$, which shows that $w_1''$ is less important than $w_2''$ rather than $w_1$ is to $w_2$ because $1.154 < 1.333$. This could be explained by the curves in Fig. 11. For $\text{rexp} < 1$ (e.g. $\text{rexp} = 0.5$), the high contrast voxels would become less important than the low contrast voxels while for $\text{rexp} > 1$ (e.g. $\text{rexp} = 2$), the high contrast voxels would become more important than the low contrast voxels. Also, for a very high value of $\text{rexp}$, the mask would be weighted almost completely to the highest contrast voxel because $\lim_{\text{rexp} \to \infty} \; w^{\text{rexp}} \to 0$ for $w < 1$. If $\text{rexp} = 0$, then all the weighted coefficients would become become $w^0 = 1$.

![Figure 11 Correlation among weighted coefficients (w) and their exposed values to rexp.](image)

In Fig. 12a), the weighted coefficients at the visual cortex of subject 1 were depicted when $\text{rexp} = 0.5$, in Fig. 12b) when $\text{rexp} = 1$ and in Fig. 12c) when $\text{rexp} = 2$. Through Fig. 12 it was observed that by regulating rexp value it would be possible to vary the weighting of the mask so as to focus more or less on high contrast voxels.
2.3.3 Calculation of ROIs’ weighted average time series

After the calculation of the weighted coefficients, the next step was to calculate a time series from the identified ROIs. The fMRI data from which the time series were calculated was the data obtained after the smoothing step in the fMRI preprocessing. The fMRI data consisted of \( n \) voxels. In the previous step, the product of the mask and the contrast image resulted in \( n \) weighted coefficients: \( w_1, w_2, \ldots, w_n \). There were also \( n \) time-series for every session of fMRI data: \( t_{s1}, t_{s2}, \ldots, t_{sn} \). Weighted average time series were calculated according to the following formula:

\[
\text{aver}_t = \frac{w_1 \cdot r^{exp} t_{s1} + w_2 \cdot r^{exp} t_{s2} + \cdots + w_n \cdot r^{exp} t_{sn}}{w_1 \cdot r^{exp} + w_2 \cdot r^{exp} + \cdots + w_n \cdot r^{exp}} = \frac{\sum_{i=1}^{n} w_i \cdot r^{exp} t_{si}}{\sum_{i=1}^{n} w_i \cdot r^{exp}} \quad \text{Eq. 1.}
\]

An example of calculated time series at the visual cortex of subject 1 was given in Fig. 13. The time series were calculated by applying the general mask of visual cortex after group analysis and \( r^{exp} = 2 \).
2.3.4 Baseline drift elimination

From Fig. 13, it was observed that the calculated time series contained baseline drifts. This means that they had low frequency components which did not represent the expected fMRI signal but rather they represented noise components. In Fig. 14a), the power spectral density (PSD) of the time-series was shown and in Fig. 14b) the absolute Discrete Fourier Transform (DFT) was shown.

As expected, it was shown that the calculated time-series contained low frequency components. Low frequency noise appears due to physical sources such as scanner drift, e.g.
the ambient temperature of a scanner, due to physiological sources such as respiration or cardiac cycles and due to residual movement effects which interact with the static magnetic field. When the subjects were subjected to visual stimulus, signal components were added which were desirable to be removed from noise.\(^7\) The sampling frequency of the fMRI measurements was \(fs = 1/TR = 1/2 = 0.5\) Hz. Therefore, according to the Nyquist theorem, the maximum frequency which might have been calculated for both PSD and DFT is \(fs/2 = 0.25\) Hz.

The PSD and DFT in Fig. 14 agreed with the results obtained by Henson\(^7\) who showed that noise in fMRI signals had high energy at low frequency components and a form \(1/f\) which means that noise decreased for high frequency components. The low frequencies of the calculated time-series which did not belong to the BOLD responses; needed to be eliminated with a high pass filter. However, identifying a cut-off frequency which eliminated noise and did not distort the BOLD signal was not obvious through Fig. 14. Henson\(^7\) introduced a signal to noise ratio as \(SNR = S/N\), where \(S\) is the energy of BOLD responses and \(N\) is the energy of noise. Also, he referred that a high pass filtering of time-series would be possible to distort the BOLD signal and energy \(S\), but to distort noise \(N\) much more than energy \(S\), so as \(SNR\) would have been increased. Therefore, a cut-off frequency of the high pass filter must have been chosen so as to eliminate noise as much as possible and to distort BOLD responses as little as possible. In the current experiment, the time difference between two successive Stimulus Onset Times (SOTs) was not greater than 21 seconds. BOLD response extraction from the acquired experimental data focused on BOLD responses when two successive SOTs differed in time more than 19 seconds. Therefore, the repetition of BOLD responses were depicted in frequency components around frequency \(f_b\), where:

\[
\frac{1}{21s} < f_b < \frac{1}{19s} \quad \Rightarrow \quad 0.047\, \text{Hz} < f_b < 0.0527\, \text{Hz} \quad \text{Eq. 2.}
\]

Prior to acquiring the experimental data, the optimum cut-off frequency was not estimated in terms of a high SNR. A criteria for choosing the cut-off frequency was that it shouldn’t intervene in the range \([0.047, 0.052]\) Hz. However the post-stimulus undershoot may include slow frequency components lower than 0.047 Hz. For that purpose, a cut-off frequency was chosen as \(f_c = 0.04\) Hz.

### 2.3.5 Digital filter design

A digital filter was designed with Wolfram Mathematica using Mathematica function “LeastSquaresFilterKernel”. A Blackman window was also used to suppress the attenuation in the stop-band and smooth the filters’ response at the cut-off frequency. In Fig. 15, the frequency response of the non-windowed, the windowed high pass filter and the Blackman window are shown for cut-off frequency 0.04 Hz. The Blackman window was multiplied with the non-windowed filter in the time domain which means a convolution in the frequency domain. The windowed filter was used to high pass filter the calculated average time-series.
The designed filters have a non-zero phase which causes a shift in time of the filtered signal. Therefore, the filtering of signals was done according to zero phase digital filtering. Zero phase digital filtering was implemented by filtering the time-series both in a forward and backward direction. Forward filtering causes a shift in time to the forward direction and backward filtering causes a shift in time to the opposite direction. An algorithm for zero phase digital filtering is given in appendix C.

2.3.6 BOLD response statistics

A way to estimate BOLD responses was to observe how fMRI signals behaved statistically after every stimulus. In the experiment used herein, the durations among the stimulus onset times (SOTs) varied between 2.60 to 20.62 seconds. To examine a BOLD response to one stimulus, statistics were implemented after every SOT which differed in time from the previous SOT by more than 19 seconds.

The SOTs were given in seconds. However, the fMRI data was sampled with a rate \( r = 1/TR = 1/2 = 0.5 \, Hz \). For that reason, the calculated time-series were sampled every two seconds. Slice timing correction was used in the post processing steps to correct the timing of all slices so they were synchronized according to the middle slice. The middle slice was approximately located in time in the middle of the first and the last slice. The middle slice of the first image was believed to be located at \( t = 1 \, s \) between the first slice at \( t = 0 \, s \) and the last slice at \( t = 2 \, s \). Therefore, the calculated time-series were sampled every 2 seconds starting from \( t = 1 \, s \). So, the calculated time-series were sampled at \( \{1,3,5,...,2 \times (n_t - 1)\} \), where \( n_t \) was the number of time points. One way to locate SOTs in discrete time was to round them to the nearest time point. For example, if one SOT had been located at 4.5 s, the nearest time point would have been at 5 s. This method revealed a maximum error of 1 second in locating a SOT. In the current work, a method was examined that adds new time points between the sampled time points through linear interpolation. The new sampling period was \( newTR = 0.2 \, s \). In that way, the maximum error of locating a SOT was 0.1 s.

After locating SOTs, the next step was to split the calculated time-series into smaller signals \( s_j, j = 1,2,...,n_j \) where \( n_j \) was the maximum number of signals. Each signal \( s_j \) contained the time-series values among two successive SOTs. New data was created and contained the value \( s_j(t_i) \) at every time \( t_i = 0,1,2...ns \) where \( ns \) was the maximum number of time points of all the signals. Statistics were used to calculate a mean value as:
Estimation of fMRI BOLD response

\[
\mu(i) = \frac{\sum_{j=1}^{n_j} s_j(t_i) - s_j(t_0)}{n_j} \quad \text{Eq. 3.}
\]

The mean standard deviation for every time point, where \( i \) and \( s_j(t_0) \) was the initial value of every signal when every stimulus occurred as:

\[
\sigma(i) = \frac{\sqrt{\sum_{j=1}^{n_j} (s_j(t_i) - s_j(t_0) - \mu(i))^2}}{n_j} \quad \text{Eq. 4.}
\]

For example, for \( i = 1 \) and time \( t_1 \) the mean value \( \mu(1) \) and the standard deviation \( \sigma(1) \) were calculated. Both the mean value and the standard deviation for every time point consisted of an error bar plot. Such an example was presented in Fig. 16.

The mean value \( \mu(i) \) depicted an estimation of the average BOLD response. The mean standard deviation \( \sigma(i) \) depicted the range of values \( s_j(t_i) - s_j(t_0) \). For \( i = 0 \), \( \mu(0) = 0 \) and \( \sigma(0) = 0 \). In Fig. 16, the length of every bar was two times the mean standard deviation \( \sigma(i) \) and in the middle of every bar was the mean value \( \mu(i) \).

![Figure 16 Statistics for both sessions of fMRI data from Subject 4, Visual cortex, applied mask from the group analysis, \( r_{exp} = 2 \), high pass filter with cut-off frequency 0.04 Hz.](image)

A quantitative way was used to evaluate BOLD response statistics by grading them in terms of a signal-to-noise ratio index. Assuming that the mean value estimated the BOLD response and the mean standard deviation estimated the error of the signal then a signal-to-noise ratio index was defined as:

\[
\text{SNR index} = \frac{\text{Max}[\mu(i)]}{\text{Mean}[\sigma(i)]}, \quad \text{Eq. 5.}
\]

\( \text{Max}[\mu(i)] \) was the amplitude of the estimated response and \( \text{Mean}[\sigma(i)] \) was the mean value of the mean standard deviation. The amplitude of the estimated response indicated the energy of the detected signal and the mean of the mean standard deviation was indicative of the noise in the fMRI signal. This index was used in order to compare BOLD signal statistics when using individual masks and general masks and for comparing different values of \( r_{exp} \).
3 Results: Estimation of fMRI BOLD response

3.1 BOLD response error bar plots

Herein, BOLD responses statistics were implemented at the identified ROIs of visual and frontal cortex in order to extract statistically BOLD responses. BOLD responses at the visual and frontal cortex were extracted statistically as a mean value of all the BOLD responses recorded in the weighted averaged time-series of visual and frontal cortex respectively. For example, in order to calculate statistically a BOLD response at the visual cortex, firstly, for all subjects the weighted averaged time-series of the visual cortex were calculated. Afterwards, BOLD response statistics were implemented at all the extracted weighted time-series in order to calculate a mean BOLD response and a mean standard deviation as well. The same process was implemented for the extracted weighted time-series at the frontal cortex as well.

BOLD response error bar plots extracted from the visual and frontal cortex are shown in Fig. 17,18,19 and 20 when: i) using general masks derived from group analysis and ii) using individual masks derived from individual analysis. Alongside with BOLD response statistics, the amplitude of the estimated BOLD signal (maximum mean value) and the predefined SNR index were estimated. BOLD response statistics were also analyzed when the calculated time-series were interpolated with ten times more points in order to locate SOTs.

![Visual cortex, General mask](image1.png) ![Visual cortex, Individual masks](image2.png)

*Figure 17 BOLD response (as mean value and mean standard deviation) of all the subjects at a) Visual cortex when the general mask was used (Amplitude = 6.61, SNR index= 0.58) and b) Visual cortex when the individual masks were used (Amplitude=5.56, SNR index=0.47), rexp=1.*
Figure 18 BOLD response (as mean value and mean standard deviation) of all the subjects at a) Frontal cortex when the general mask was used (Amplitude = 1.32, SNR index= 0.22) and b) Frontal cortex when the individual masks were used (Amplitude=1.66, SNR index=0.22), rexp=1.

Figure 19 BOLD response (as mean value and mean standard deviation) of all subjects at the visual cortex when calculated time-series were interpolated with ten times more points for SOTs location. a) When the general mask was used (Amplitude=6.57, SNR index = 0.61) b) when the individual masks were used (Amplitude=5.19, SNR index = 0.50), rexp=1.
Results: Estimation of fMRI BOLD response

3.2 Individual vs general masks

Firstly, BOLD response statistics were implemented when the general masks at the visual and the frontal cortex were used. Additionally, BOLD response statistics were implemented when the individual masks were used. The purpose was to compare which method of either general analysis or individual analysis was more efficient for estimating statistically BOLD responses. The following figures show the mean values and the calculated SNR index of the estimated BOLD responses when interpolation for SOTs location was used and $r_{exp} = 1$.

Figure 20 BOLD response (as mean value and mean standard deviation) of all the subjects at the frontal cortex when calculated time-series were interpolated with ten times more points for SOTs location. a) When the general mask was used (Amplitude=1.51, SNR index = 0.27) and b) when the individual masks were used (Amplitude=1.72, SNR index = 0.24), $r_{exp}=1$. 
3.3 Interpolation for SOTs location

The method of inserting new points with interpolation 10x was compared to non-interpolation by observing the differences between the estimated BOLD responses. In Fig. 23, the estimated BOLD responses at the visual cortex are shown, when the general mask was used and in Fig. 24 when the individual masks were used. In Fig. 25, the estimated BOLD responses at the frontal cortex are shown when the general mask was used and in Fig. 26 when the individual masks were used.
Results: Estimation of fMRI BOLD response

Figure 23 Comparison between estimated BOLD responses (as mean value) at the visual cortex when interpolation for SOTs location was used and when interpolation for SOTs location was not used, rexp = 1, General mask.

Figure 24 Comparison between estimated BOLD responses (as mean value) at the visual cortex when interpolation for SOTs location was used and when interpolation for SOTs location was not used, rexp = 1, Individual masks.
3.4 Regulation of weighting

BOLD responses were also estimated for variable rexp value. Value rexp was varied in order to regulate weighting at the visual cortex (Fig. 27,28) and at the frontal cortex (Fig. 29,30).
Figure 27 Estimated BOLD responses (as mean value) at the visual cortex for variable rexp value when the general mask was used. Ampl denotes the amplitude (maximum value) of the estimated BOLD responses. Interpolation 10x.

Figure 28 Estimated BOLD responses (as mean value) for variable rexp value at visual cortex when the individual masks were used. Ampl denotes the amplitude (maximum value) of the estimated BOLD responses. Interpolation 10x.
Figure 29 Estimated BOLD responses (as mean value) for variable rexp value at the frontal cortex when the general mask was used. Ampl denotes the amplitude (maximum value) of the estimated BOLD responses. Interpolation 10x.

Figure 30 Estimated BOLD responses (as mean value) for variable rexp value at the frontal cortex when the individual masks were used. Ampl denotes the amplitude (maximum value) of the estimated BOLD responses. Interpolation 10x.
4 Discussion: Estimation of fMRI BOLD response

4.1 BOLD response error bar plots

BOLD response error bar plots showed an estimation of BOLD responses at the visual cortex and the frontal cortex when using individual and general analysis masks. The estimated mean values of every time point showed the estimated values of the BOLD responses at every time point. Together with the mean values, the mean standard deviations for every time point were plotted which indicated the variance of the estimated values.

BOLD response error bar plots, which are depicted in Fig. 17 and Fig. 19 agree that an overshoot and a post-stimulus undershoot were estimated at the visual cortex. The overshoot was denoted by the estimated positive mean values between 0 and 10 seconds which have a peak at around 6 seconds. The post-stimulus undershoot was denoted by the estimated negative mean values which follow after 10 seconds. However, an initial dip was not observed at the visual cortex. (Fig. 17, Fig. 19)

BOLD response error bar plots which are depicted in Fig. 18 and Fig. 20 agree that an initial dip, an overshoot and a post-stimulus dip were estimated at the frontal cortex. The initial dip was denoted by the negative mean values, which were estimated in the first two seconds of the estimated BOLD responses. The Overshoot was denoted by the estimated positive mean values between 2 and 8 seconds, which had a peak at around 6 seconds. Also, the post-stimulus undershoot was denoted by the estimated negative mean values which followed after 8 seconds (Fig. 18, Fig. 20).

As can be observed from Fig. 20 – Fig. 23, BOLD response estimations at the visual cortex resulted in a higher BOLD overshoot than the BOLD overshoot at the frontal cortex for both general and individual analysis masks. Also, in all cases, the calculated SNR index was calculated larger at the visual cortex than at the frontal cortex, which indicated a relatively higher effect of the standard mean deviation at the frontal cortex than at the visual cortex. In other words, a BOLD response was better estimated at the visual cortex than the frontal cortex in terms of higher estimated mean values of the BOLD response overshoot in contrast to their mean standard deviations.

4.2 Individual vs general analysis masks

In Fig. 21, a comparison of the estimated BOLD responses at the visual cortex is shown for the cases when individual masks were used and when the general mask was used. For both cases, interpolation 10x was used. The main difference between those two cases was that a higher overshoot was estimated when the general mask was used. Also, the SNR index was greater when the general mask was used. Therefore, when a general mask was used at the visual cortex, a higher amplitude of BOLD response was estimated and the effect of the mean standard deviation was not increased because the SNR index was higher when a general mask was used. Also, a difference was found among these two cases regarding the estimation of post-stimulus undershoots. The post-stimulus undershoot was estimated to be slightly higher when a general mask was used. However, post-stimulus undershoots were estimated to return to the baseline at the same time for both cases.
In Fig. 22, a comparison of the estimated BOLD responses in the frontal cortex is shown for the cases when individual masks were used and when the general mask was used. For both cases interpolation 10x was used. Here, an initial dip was estimated which looks similar for both cases with the main difference being that it lasts longer when a general mask was used. Also, a higher overshoot and a lower post-stimulus undershoot were estimated when the individual masks were used. However, the SNR index was calculated higher when the general mask was used.

4.3 Interpolation for SOTs location

In Fig. 23, a comparison is shown between the estimated BOLD responses at the visual cortex when a general mask was used for the cases of interpolation 10x and without interpolation. A difference between the two estimated responses was observed in the first two seconds, where the BOLD response was estimated lower when interpolation was not used. The overshoot appeared to be similar in both cases. However, the estimated post-stimulus undershoot, when interpolation 10x was used, returned more slowly to the baseline state than when interpolation was not used.

Similarly, when individual masks were used (Fig. 24), a difference between estimated BOLD responses with interpolation 10x and without interpolation was found in the estimation of the post-stimulus undershoot. Without interpolation, the post-stimulus undershoot was estimated to return quickly to the baseline state. However, when the interpolation was 10x, the post-stimulus undershoot lasted longer and returned more slowly to the baseline state.

Differences were also observed between the estimated BOLD responses at the frontal cortex with interpolation 10x and without interpolation as shown in Fig. 25 and Fig. 26. The main difference was that a deeper initial dip was observed without interpolation. Also, a difference was observed between the estimated BOLD responses regarding the post-stimulus undershoot because a higher post-stimulus undershoot was observed without interpolation.

Additionally, without interpolation, it was not able to locate a peak of overshoot between the time-points on the temporal grid. For example, assuming a temporal grid \{0,2,4,\ldots\}, then without interpolation, a peak would only be located on one of those time points. Therefore, if a peak was to be located on the 5th second, then this would have been impossible without interpolation. This can be clearly seen in Fig. 26, where the peak of the overshoot was estimated earlier when interpolation 10x was used. Without interpolation the estimated peak was located at 6 s, but with interpolation the estimated peak was located at 5.4 s. However, sampling a time-series every $TR = 2$ s, means that there is already a lack of information about the behavior of the time-series between the sampled time-points. Therefore, this lack of information hinders the identification of an exact location of a peak overshoot and for that reason exactly locating a peak of overshoot with interpolation points was an almost impossible task.

The differences between the estimated BOLD responses with and without interpolation were due to the different locations of SOTs. SOTs were given in seconds. Therefore they needed to be located in the discrete time, because fMRI time-series were discrete time signals.
For example, an assumption would be that an fMRI signal was recorded in discrete time every TR = 2 s \( \{0,2,4,\ldots\} \) and a SOT was located on 9.2 s. This SOT is between 8 and 10 s and it should be rounded to the nearest time-point (on 10 s) in order to be located. Therefore, this SOT, in order to be located, was shifted up 0.8 s (from 9.2 s to 10 s) which means a location error +0.8 s. Additionally, if a SOT was located on 38.8 s, it would be rounded to the nearest time-point (on 38 s) which would mean a location error -0.8 s. Errors in locating SOTs mean that there were errors regarding when a BOLD response started to be recorded. In this example, BOLD responses would start to be recorded +0.8 s and -0.8 s respectively, than when they should start. Therefore, those two hypothetical BOLD responses would have a phase difference of 1.6 s.

On the other hand, error of SOTs location was believed to be reduced when interpolation 10x was used. Interpolation 10x means that a temporal grid \( \{0,2,4,\ldots\} \) would become \( \{0,0.2,0.4,0.6,\ldots\} \). For example, a SOT located at 9.2 s would be located without error because the temporal grid would be \( \{\ldots,9.0,9.2,9.4,\ldots\} \). Therefore, the maximum error of locating a SOT was ±0.1 s because the maximum distance of a SOT to the nearest time-point would be 0.1 s. Instead, when interpolation was not used, the maximum error for locating a SOT was ±1 s. As a result, errors on locating SOTs were believed to be reduced when using interpolation.

### 4.4 Regulation of weighting

By regulating the value \( r_{exp} \), which was introduced in subchapter 2.3.2, it was attempted to observe the estimated BOLD responses when the filtering approach was based more or less to high contrast voxels. The results are shown in Fig. 27, Fig. 28, Fig. 29 and Fig. 30. In all cases, when \( r_{exp} \) value was increased, the amplitude of the estimated BOLD responses was estimated to increase as well. However, the SNR index was decreased when the \( r_{exp} \) value was increased. This means that when calculation of average time-series was based more (\( r_{exp} = 2 \)) on high contrast voxels, BOLD response statistics resulted in a higher maximum mean value and even higher mean standard deviations.

At the visual cortex when the general mask was used (Fig. 27), there was a slight difference for \( r_{exp} \) value in the range \( \{0.1-2\} \). This indicated that there were not significant differences when the calculation of average time-series was based more or less at high contrast voxels at the visual cortex and with the usage of the general mask. On the other hand, when individual masks were used at the visual cortex with a ranging of the \( r_{exp} \) value in the range \( \{0.1-2\} \), then this resulted in larger differences than when the general mask was used (Fig. 28). Additionally, for both cases (Fig. 27, Fig. 28) and higher \( r_{exp} \) values, BOLD response statistics resulted in slightly lower amplitude of post-stimulus undershoot.

At the frontal cortex, differences were also observed regarding the estimation of overshoot and post-stimulus undershoot. For both a general mask and the individual masks, BOLD response statistics resulted in a larger post-stimulus undershoot for a higher \( r_{exp} \) (Fig. 29, Fig. 30). This means that higher contrast voxels not only contributed to a larger overshoot, but also, to a larger post-stimulus undershoot.
Regulation of weighting expresses how significant was the contribution of ROI voxels to the calculation of the ROIs average time-series. For $r_{exp} = 0.1$, low contrast voxels participated more to the calculation of average time-series and, as a result, the peak of overshoot was estimated lower because low contrast voxel time-series were expected to be closer to the baseline. Additionally, when $r_{exp}$ was higher, low contrast voxels participated less to the calculation of ROIs average time-series, and this was depicted by the higher estimated peak of overshoot.
5 Conclusions: Estimation of fMRI BOLD response

Finally, it was concluded that, the visual cortex and the frontal cortex had differences regarding BOLD response estimations. Specifically, an initial dip was estimated at the frontal cortex while it was not estimated at the visual cortex. Additionally, the BOLD overshoot was estimated at both regions and it was estimated higher at the visual cortex. Also, the post-stimulus undershoot was estimated at both regions.

Using a general mask was preferable to using individual masks at the visual cortex, because it resulted in BOLD response estimations with a higher maximum mean value and higher SNR index, as well. However, the choice of either a general mask or individual masks at the frontal cortex; was a controversial issue, because individual masks resulted in higher overshoot but a lower SNR index. Also, individual masks at the frontal cortex resulted in lower post-stimulus undershoots estimations, an issue which also indicated that a conclusion regarding whether individual or general masks should be used, needs further investigation.

Interpolation 10x for SOTs location behaved better than non-interpolation because, in all cases, it resulted in estimations of slowly post-stimulus undershoots returning to baseline; which agree with the ones found in literature. Interpolation for SOTs location also contributed to less error for SOTs location as it has been explained in subchapter 4.3. Additionally, in all cases, the SNR index was calculated higher when interpolation 10x was used than when interpolation was not used.

Regulation of weighting did not result in significant differences when a BOLD response was estimated for different values of rexp. In all cases, the shape of the estimated BOLD responses were similar for different values of rexp with the only difference being that overshoot and post-stimulus undershoot were slightly lower or higher.

Afterwards, a model was developed in part B in order to explain how the parameters CBF and CMRO₂ contribute to the estimated BOLD responses and the differences between BOLD response estimations at the visual cortex and at the frontal cortex.
Part B -- Modelling of fMRI BOLD response

6 Modelling of fMRI BOLD response -- methods

6.1 Introduction

In current work, a model was developed in order to aid an understanding of the physiological mechanisms of the estimated BOLD responses of part A. The estimated BOLD responses of part A have a specific shape which consists of an initial dip (at the frontal cortex), an overshoot and a post-stimulus undershoot (at both the visual and frontal cortex). Part B of current thesis aimed at developing a model in order to explain how these phases (initial dip, overshoot and post-stimulus undershoot) depend on CBF and CMRO$_2$. Moreover, through the developed model, it was attempted to explain how CBF and CMRO$_2$ varied during the fMRI experiment in order to result to the estimated BOLD responses of part A. Additionally, through the developed model, it was aimed to explain the differences between the visual cortex and the frontal cortex regarding the behavior of CBF and CMRO$_2$ during the fMRI experiment.

6.2 Theoretical Background

6.2.1 Pathway of O$_2$—From RBCs to tissues

For the purpose of explaining how BOLD responses depend on CMRO$_2$ and CBF, a model was developed to describe how OHb and DHb levels are affected when blood flows through a capillary, $O_2$ is consumed by surrounding tissues with a variable in time CMRO$_2$ and Red Blood Cells (RBCs) are transported in the blood with a variable in time CBF velocity.

Levels of OHb and DHb denote a value for hemoglobin SaO$_2$. In current thesis, SaO$_2$ was measured as the percentage of hemoglobins which are oxygenated. Seong-Gi Kim et al. (2) described an equation according to which the fMRI signal is proportional to the stimulus-induced variation of venous SaO$_2$ $\Delta Y$ when CBV is constant:

$$\%BOLD = \frac{\Delta Y}{A-Y} \text{ Eq. 6.}$$

Where %BOLD is a proportional to BOLD signal, $\Delta Y = Y(t) - Y(0)$, $Y(t) = SaO_2v/100$ where $SaO_2v$ is the SaO$_2$ of venous blood at a time $t > 0$ and $Y(0) = SaO_2a/100$ at resting state before neural stimulation, $A = SaO_2a/100$ where $SaO_2a$ is the SaO$_2$ in the arterial blood. The overall purpose of current methods was to model for SaO$_2$ inside capillaries and after capillaries when CMRO$_2$ increases and blood circulation system responds by increasing CBF velocity. Then, the estimated SaO$_2$ was used to calculate an fMRI signal through Eq. 6.

Jung Hwan Kim et al. (8) described a four compartment model to explain the physiological mechanisms of the BOLD response as can be seen in Fig. 31. This model described the mechanisms of $O_2$ transfer in the RBCs, blood plasma, extravascular environment and the tissues intracellular environment.
$O_2$ molecules are transported in blood through hemoglobin and blood plasma. An $O_2$ dissociation curve highlights the relation between $O_2$ concentration in plasma and hemoglobin $SaO_2$. Therefore, if the $O_2$ concentration in blood plasma is known; then a prediction for hemoglobin $SaO_2$ can be derived through an $O_2$ dissociation curve.

Additionally, $O_2$ diffuses from blood plasma to the extravascular environment, through the capillaries wall, driven by the difference of partial pressures of $O_2$ inside and outside the wall of the capillary. The $O_2$ partial pressure of the extravascular environment depends both on $O_2$ diffusion through capillaries wall and $CMRO_2$ uptake. $CMRO_2$ uptake indicated the rate of $O_2$ flow from the extravascular environment to tissues for consumption.

An attempt to understand $O_2$ consumption and delivery in tissues during evoked neural activity was given by Alberto L. Vazquez et al. (9). In Fig. 32, blood flows through a capillary with flow measured in units of $[m^3/sec]$ which is known as CBF in the case of blood circulation in human brain. Blood inflows from arterial circulation system with a relative high $O_2$ concentration ($c_a$ in Fig. 32). As blood passes the capillary, outwards $O_2$ diffusion through the vessel wall causes a reduction in $O_2$ concentration which is shown by the red line in Fig. 32. $C_v$ is the $O_2$ concentration in venous blood. $C_t$ is the $O_2$ concentration at the extravascular environment. The difference between intravascular $O_2$ concentration (red line) and extravascular $O_2$ concentration $C_t$ was the concentration gradient which led to $O_2$ outward diffusion through the vessel wall which is depicted by vertical arrows in Fig. 32.
Herein, the convection diffusion equation was used in order to model the $O_2$ concentration in blood plasma in a capillary and the $O_2$ outward diffusion. Afterwards, Henry’s Law was applied in order to calculate for $O_2$ partial pressure in blood plasma through $O_2$ concentration in blood plasma. Finally, the $O_2$ dissociation curve, which was acquired from Wolfram Alpha (10), was used to calculate $SaO_2$ through $O_2$ partial pressure.

Alongside with convection diffusion modelling, an Ordinary Differential Equation (ODE) was used to model for extravascular $O_2$ concentration $C_t$. Therefore, in current thesis both modelling for intravascular and extravascular $O_2$ concentration was implemented.

### 6.2.2 Henry’s Law

According to Johansson (11), when $O_2$ is dissolved in blood, the $O_2$ concentration is in direct proportion with its partial pressure. This is known as Henry’s law and it generally states that the concentration of a dissolved gas in a liquid is in direct proportion to its partial pressure in that liquid. Therefore, $O_2$ concentration $c [mol/m^3]$ in blood plasma is connected to its partial pressure $PaO_2 [Pascals]$ according to the relation $c = H PaO_2$, where $H$ was given by Johansson (11) as $H = 10^{-5} mol/(m^3Pa)$. Therefore, when solving for $O_2$ concentration in blood plasma, an estimation of the $O_2$ partial pressure in blood plasma was implemented through Henry’s law.

### 6.2.3 Hemoglobin $O_2$ dissociation curve

The ability of blood to transfer enough $O_2$ to tissues is mediated through the ability of hemoglobin to bind to $O_2$. The hemoglobin $O_2$ dissociation curve which is depicted in Fig. 33 shows the relation between $SaO_2$ in relation to $PaO_2$. In current work, the $O_2$ dissociation curve of Fig. 33 was used in order to estimate $SaO_2$ for a given $PaO_2$. The hemoglobin $O_2$ dissociation curve depends on the partial pressure of carbon dioxide ($CO_2$), the temperature and the pH of blood.

![Hemoglobin $O_2$ dissociation curve](downloaded-hemoglobin-sao2-curve-from-wolframalpha-for-partial-pressure-of-cao2-40-mmhg-temperature-t-37-c-and-ph-7.4-10.png)

Figure 33 Downloaded hemoglobin $SaO_2$ curve from Wolfram Alpha for partial pressure of $CaO_2 = 40 \text{ mmHg}$, temperature $T = 37 ^\circ \text{C}$, and $pH = 7.4$ (10)

The hemoglobin $O_2$ dissociation curve was acquired from Wolfram Alpha. A user of Wolfram Mathematica can interact with Wolfram Alpha, which is a computational
knowledge engine. It is possible for the user to acquire the hemoglobin $O_2$ dissociation curve by choosing the partial pressure of $CaO_2$ in blood, the temperature, and the pH of blood.

6.3 Convection-diffusion equation modelling

6.3.1 Convection-diffusion equation

In order to explain the BOLD fMRI signal, a model was developed for the purpose of estimating the $SaO_2$ in blood as $O_2$ diffuses through a capillary wall. For that purpose, the $O_2$ concentration in blood plasma was modeled in Wolfram Mathematica 9 and the convection diffusion equation was used:

$$\frac{\partial c}{\partial t} = \nabla(D \nabla c) - \nabla (\vec{u} c) \quad \text{Eq. 7.}$$

Where, $c[\text{mol/m}^3]$ is the concentration of $O_2$ in blood plasma, $D[\text{m}^2/\text{sec}]$ is the diffusion coefficient and $\vec{u}[\text{m/sec}]$ is the velocity of blood flow.

In the model development herein, blood was assumed to consist only of blood plasma and $O_2$ was assumed to be dissolved in blood plasma. The convection-diffusion equation (Eq. 7) was solved in cylindrical coordinates $(r, \varphi, z)$ since the assumption was made that vessels have cylindrical shape with radius $r$ and length $z$. Eq. 7 expresses how the concentration of $O_2$ is increased or decreased in time ($\partial c/\partial t$) at cylindrical coordinates $(r, \varphi, z)$. There are two terms of Eq. 7 which affect the time derivative of the concentration, $(\partial c/\partial t)$. The first term, $\nabla(D \nabla c)$, denotes diffusion and the second term $\nabla(\vec{u} c)$ denotes convection. Therefore, $c(r, \varphi, z)$ depends both on diffusion and convection. The diffusion coefficient $D$ was used as isotropic:

$$D = D_r(r, \varphi, z) \hat{r} + D_\varphi(r, \varphi, z) \hat{\varphi} + D_z(r, \varphi, z) \hat{z} = Do \hat{r} + Do \hat{\varphi} + Do \hat{z} \quad \text{Eq. 8.}$$

Where, $\hat{r}$, $\hat{\varphi}$ and $\hat{z}$ are the unit vectors of the cylindrical coordinates. The blood velocity was assumed in the $\hat{z}$ direction across the length of vessel as $\vec{u} = u_z \hat{z}$.

Therefore, Eq. 7 was solved as:

$$\frac{\partial c}{\partial t} = \nabla(D \nabla c) - \nabla (\vec{u} c) = Do \nabla^2 c - u_z \nabla c \quad \text{Eq. 9.}$$

Where, $\nabla c = \frac{\partial c}{\partial r} \hat{r} + \frac{\partial c}{\partial \varphi} \hat{\varphi} + \frac{\partial c}{\partial z} \hat{z} \quad \text{Eq. 10.}$

And

$$\nabla^2 c = \frac{1}{r} \frac{\partial}{\partial r} \left( r \frac{\partial c}{\partial r} \right) + \frac{1}{r^2} \frac{\partial^2 c}{\partial \varphi^2} + \frac{\partial^2 c}{\partial z^2} = \frac{1}{r} \frac{\partial}{\partial r} + \frac{\partial^2 c}{\partial r^2} + \frac{1}{r^2} \frac{\partial^2 c}{\partial \varphi^2} + \frac{\partial^2 c}{\partial z^2} \quad \text{Eq. 11.}$$

So, through Eq. 10 and Eq. 11,

$$\text{Eq. 9 } \Rightarrow \frac{\partial c}{\partial t} = Do \left( \frac{1}{r} \frac{\partial c}{\partial r} + \frac{\partial^2 c}{\partial r^2} + \frac{1}{r^2} \frac{\partial^2 c}{\partial \varphi^2} + \frac{\partial^2 c}{\partial z^2} \right) - u_z \frac{\partial c}{\partial z} \quad \text{Eq. 12.}$$
6.3.2 Geometry of the model
A geometry of the model for the convection diffusion equation in a capillary is shown in Fig. 34 for r and z coordinates. Blood flows from ‘Geometry 1’, which represents the geometry of arterioles, through ‘Geometry 2’, which represents the geometry of capillaries, to ‘Geometry 3’, which represents the geometry of venules. The r coordinate expresses the radius coordinate of vessels and the z coordinate expresses the length of vessels. For simplicity, arterioles, venules and capillaries had the same radius at \( r = r_{\text{max}} \).

![Figure 34 Geometry of convection diffusion modelling problem.](image)

6.3.3 Boundary conditions
Eq. 9 was the governing equation of the current problem in order to simulate for the intravascular \( O_2 \) concentration \( c \). Also, there were boundary conditions which needed to be satisfied so as the problem be solved. In Fig. 35, these boundary conditions are shown.

![Figure 35 Boundary conditions. \( PaO_2 \): partial pressure of \( O_2 \) in arterial blood [Pascals], \( H \): constant of Henry’s law \( [\text{mol} \text{Pa}^{-1} \text{m}^3] \). \( Cin \): concentration at the entrance of ‘Geometry 1’ \( [\text{mol}] \). \( Do \): diffusion coefficient \( [\text{m}^2 \text{sec}^{-2}] \). Pac: permeability coefficient of the tissue membrane \( [\text{mol} \text{sec}^{-1} \text{m}^{-2}] \). \( C_t \): concentration of \( O_2 \) in extravascular tissue \( [\text{mol} \text{m}^{-3}] \).](image)

Arterial blood at the entrance of ‘Geometry 1’ has high values of \( SaO_2 \). In (12), the arterial blood has a partial pressure of \( O_2 PaO_2 = 100 \text{ mmHg} \) and \( SaO_2 = 97.5 \% \). By converting mmHg to Pascal units:

\[
PaO_2[\text{mmHg}] = 100 \text{ mmHg} \Rightarrow PaO_2[\text{Pa}] = 13.332 \times 10^3 \text{ Pascals Eq. 13.}
\]
According to Henry’s law, the concentration of dissolved \( O_2 \) in arterial blood is:

\[
C_{in} = H PaO_2 [Pa] = 0.13332 \text{ mol/m}^3 \quad \text{Eq. 14.}
\]

Therefore, in the boundary condition at \((z = 0, r, t)\), the \( O_2 \) concentration is \( c(z = 0, r, t) = 0.13332 \text{ mol/m}^3 \) and it was considered as boundary condition (bc) 1:

\[
\text{bc1: } c(z = 0, r, t) = 0.13332 \text{ mol/m}^3.
\]

For \((r = r_{max}, 0 < z < z_1, t)\) the boundary condition indicated insulation. Insulation means that the \( O_2 \) concentration doesn’t vary across that bound. So, boundary condition 2 was formed as:

\[
\text{bc2: } \frac{\partial c(r=r_{max}, 0<z<x_1, t)}{\partial r} = 0.
\]

Boundary condition of insulation was satisfied also for \((r = r_{max}, x_2 < z < z_{max}, t)\) where boundary condition 3 was formed as:

\[
\text{bc3: } \frac{\partial c(r=r_{max}, x_2<z<x_{max}, t)}{\partial r} = 0.
\]

At the bound \((r = r_{max}, z_1 < z < z_{2}, t)\), it was assumed that diffusion takes place due to the \( O_2 \) concentration gradient between intravascular and extravascular \( O_2 \) concentration across the capillary wall. According to Johansson (11), the convection diffusion equation in a capillary of the respiratory system was modelled with \( O_2 \) diffusing from the alveoli into the capillary. \( O_2 \) diffusion from the alveolus into the capillary was modelled as:

\[
-N n = Pac (palv \cdot H - c) \quad \text{Eq. 15.}
\]

In this equation, \( n \) denoted the direction of diffusion so \(-N n \) [mol/(m\(^2\)s)] was the flow of \( O_2 \) from the alveolus into the capillary and the \(-\) sign indicated the negative direction of \( O_2 \) flow. \(-N n \) [mol/(m\(^2\)s)] described the amount of \( O_2 \) which diffuses across the capillary wall in units of moles per area and per time. palv [pascals] was the partial pressure of \( O_2 \) in the alveolus, \( H \) [mol/(m\(^3\)Pascals)] was the solubility constant used in Henry’s law, Pac [m/sec] was the permeability coefficient of the tissue membrane between alveolus and capillary and \( c \) was the concentration of \( O_2 \) on the inside of the wall of capillary. Herein, the boundary condition of \( O_2 \) diffusion was modelled in the same way with the difference that in the capillaries of the brain, \( O_2 \) diffuses from blood to tissues. The equation which was used to model the diffusion from the capillary to the tissue was:

\[
N n = Pac (c - c_t) \quad \text{Eq. 16.}
\]

Here \( c_t \) [mol/m\(^3\)] is the concentration of \( O_2 \) at the tissue around the capillary, \( c \) [mol/m\(^3\)] is the concentration of \( O_2 \) on the inside of the wall of the capillary and the other parameters are the same as Eq. 16. The outward flow of \( O_2 \) \( N n \) [mol/m\(^3\)s] was modeled as \( n = Do \ (\partial c/\partial r)[\text{mol/(m}^2\text{s)}] \). The permeability coefficient Pac for current work was chosen as
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\( Pac = 0.0045 \, [m/sec] \) as it was given by Johansson (11). Therefore, the fourth boundary condition which described the \( O_2 \) diffusion for \((r = r_{\text{max}}, z_1 < z < z_2)\) was formed as:

\[
\text{bc4: } D_o \frac{\partial c(r=r_{\text{max}},z_1<z<z_2)}{\partial r} = Pac \, (c - c_t) \quad \text{Eq. 17.}
\]

For the bound at \((0 < r < r_{\text{max}}, z = z_{\text{max}})\) no algebraic conditions were derived. However it was considered that Eq. 12 should be satisfied on that bound so as the convection diffusion equation was satisfied.

### 6.4 Extravascular \( O_2 \) concentration modelling

In the extravascular environment, the concentration of \( O_2 \) was considered to depend on two flows of \( O_2 \). On one hand, outward diffusion through capillary walls increases the extravascular \( O_2 \) concentration. On the other hand, CMRO\(_2\) decreases the extravascular \( O_2 \) concentration because it causes \( O_2 \) to flow from the extravascular environment to the intracellular environment of the surrounding tissues for consumption. Vasquez et. al. (9) described an ODE for extravascular \( O_2 \) concentration \( C_t \). At this equation, \( C_t \) was described as a dependence on both capillary wall outward \( O_2 \) diffusion and CMRO\(_2\).

Similar to the equation written by Vasquez et al. (9), an ODE was developed in current thesis to model \( C_t \).

\[
V_t \frac{\partial C_t}{\partial t} = Pac \, S \, (c - c_t) - \text{CMRO}_2(t) \quad \text{Eq. 18.}
\]

Here, \( V_t \, [m^3] \) was the volume of the extravascular tissue, \( Pac \, [m/sec] \) was the capillary membrane’s permeability of \( O_2 \), \( S \, [m^2] \) was the capillary wall area through which \( O_2 \) diffuses outwards and \( \text{CMRO}_2 \, [mol/sec] \) was the rate of \( O_2 \) transfer from the extravascular environment to tissues for consumption.

Because of bc4, the term \( Pac(c - c_t) = -D_o \frac{\partial c(r=r_{\text{max}},z_1<z<z_2)}{\partial r} \). Therefore,

\[
\text{Eq. 18} \Rightarrow V_t \frac{\partial C_t}{\partial t} = -S \, D_o \frac{\partial c(r=r_{\text{max}},z_1<z<z_2,t)}{\partial r} - \text{CMRO}_2(t) \quad \text{Eq. 19.}
\]

The area \( S \) was calculated as:

\[
S = 2 \pi r_{\text{max}} \, (z_2 - z_1) \quad \text{Eq. 20.}
\]

Additionally, an assumption was that the extravascular environment covers symmetrically around the vessel over a depth the same way as it is shown in Fig. 36. Therefore, the volume of the extravascular environment was calculated as the volume of a cylinder with radius \( r_{\text{max}} + \text{depth} \) minus the volume of a cylinder with radius \( r_{\text{max}} \).

\[
V_t = \pi \, (r_{\text{max}} + \text{depth})^2(z_2 - z_1) - \pi \, r_{\text{max}}^2 \, (z_2 - z_1) \\
= \pi \, (z_2 - z_1)((r_{\text{max}} + \text{depth})^2 - r_{\text{max}}^2) \quad \text{Eq. 21.}
\]
6.5 Formation of PDE problem
The purpose of the current work was to solve Eq. 12 at the described geometry and satisfy the described boundary conditions. Due to the independence of the boundary conditions of the cylindrical \( \phi \) coordinate, the problem was considered to be independent of variable \( \phi \). Therefore, \( \partial c / \partial \phi = 0 \), and \( \partial^2 c / \partial \phi^2 = 0 \) and Eq. 12 was written as:

\[
\text{Eq. 12} \Rightarrow \frac{\partial c}{\partial t} = D_o \left( \frac{1}{r} \frac{\partial c}{\partial r} + \frac{\partial^2 c}{\partial r^2} + \frac{\partial^2 c}{\partial z^2} \right) - u_z(t) \frac{\partial c}{\partial z} \quad \text{Eq. 22}
\]

Additionally, at the extravascular tissue the governing equation was Eq. 19. Therefore, Eq. 22 and Eq. 19 were the governing equations of intravascular and extravascular environment respectively.

The boundary conditions were summarized as:

bc1: \( c(z = 0, r, t) = 0.13332 \ \text{mol/m}^3 \)

bc2: \( \frac{\partial c(r=r_{max}, 0<z<z_1, t)}{\partial r} = 0 \)

bc3: \( \frac{\partial c(r=r_{max}, z_1<z<z_2, t)}{\partial r} = 0 \)

bc4: \( D_o \frac{\partial c(r=r_{max}, z_1<z<z_2, t)}{\partial r} = Pac (c(r=r_{max}, z_1 < z < z_2, t) - c_t) \)

bc5: Eq. 22

6.6 FDM implementation
6.6.1 Spatial discretization
The first step in the implementation of the Finite Difference Method (FDM) was to create a mesh suitable for the geometry of the problem. The problem was solved in three dimensions \((r, z, t)\) where \((r, z)\) described the cylindrical space with independence of angle \( \phi \) and \( t \) described time. The mesh had \( N_r \cdot N_z + \text{Next} \) points where \( N_r \) was the number of points in the \( r \) direction, \( N_z \) was the number of points in the \( z \) direction and \( \text{Next} \) was the number of points which described the extravascular \( O_2 \) concentration across the capillary wall \((r = r_{max}, z_1 < z < z_2)\).
In the intravascular environment, discrete points had a distance $h_r = r_{max}/(N_r - 1)$ in the $r$ direction and distance $h_z = z_{max}/(N_z - 1)$. In Fig. 37 the described mesh is shown. Variables $c_{i_r,i_z}(t)$ denoted the $O_2$ concentration at every point $\{i_r,i_z\}$ at time $t$. The black dots denoted the points inside the intravascular geometry and the white dots denoted the points on the bounds of the intravascular geometry. Outside the intravascular geometry across the capillary wall, where diffusion of $O_2$ takes place, new points were created in order to model for $O_2$ concentration at the extravascular environment: $c_{ext,iz1}(t), c_{ext,iz1+1}(t) \ldots c_{ext,iz2}(t)$.

**Figure 37** Mesh created for solving for $O_2$ concentration $c_{i_r,i_z}(t)$ in the intravascular environment and $O_2$ concentration $c_{ext}(t)$ at the extravascular tissue.

### 6.6.2 Solving a PDE problem in a mesh

The next step was to apply the governing equations (Eq. 22 and Eq. 19) and the boundary conditions $bc1, bc2, bc3, bc4, bc5$ to the defined mesh shown in Fig. 37. Eq. 22 was applied at every point $\{i_r,i_z\}$ of the mesh so as to develop a system of ODEs. Eq. 19 was applied at all the points of the extravascular environment so as to develop one ODE at every point. For all points inside the geometry (black dots in Fig. 37), the partial derivatives in Eq. 22 were replaced by their central finite difference approximation. More specifically, Eq. 22 was transformed in a finite difference expression of $O_2$ concentration at a point $\{i_r,i_z\}$ as:
\[ \frac{\partial c_{ir,iz}}{\partial t} = D_o \left( \frac{1}{r_r h_r} \frac{\partial c_{ir,iz}(t)}{\partial r} + \frac{\partial^2 c_{ir,iz}(t)}{\partial r^2} + \frac{\partial^2 c_{ir,iz}(t)}{\partial z^2} \right) - u_z \cdot \frac{\partial c_{ir,iz}(t)}{\partial z} \text{ Eq. 23.} \]

The following central finite difference approximations of partial derivatives were replaced at Eq. 23:

\[ \frac{\partial c_{ir,iz}(t)}{\partial r} = \frac{c_{ir+1,iz}(t) - c_{ir-1,iz}(t)}{2 h_r} \text{ Eq. 24.} \]

\[ \frac{\partial c_{ir,iz}(t)}{\partial z} = \frac{c_{ir,iz+1}(t) - c_{ir,iz-1}(t)}{2 h_z} \text{ Eq. 25.} \]

\[ \frac{\partial^2 c_{ir,iz}(t)}{\partial r^2} = \frac{c_{ir+1,iz}(t) - 2c_{ir,iz}(t) + c_{ir-1,iz}(t)}{h_r^2} \text{ Eq. 26.} \]

\[ \frac{\partial^2 c_{ir,iz}(t)}{\partial z^2} = \frac{c_{ir,iz+1}(t) - 2c_{ir,iz}(t) + c_{ir,iz-1}(t)}{h_z^2} \text{ Eq. 27.} \]

By replacing Eq. 24,25,26,27 in Eq. 23, Eq. 28 was derived which expressed the time derivative \( \frac{\partial c_{ir,iz}}{\partial t} \) for every point \( \{ir, iz\} \) inside the geometry in relation to \( O_2 \) concentration of adjacent points:

\[ \frac{\partial c_{ir,iz}}{\partial t} = a_1 c_{ir,iz}(t) + a_2 c_{ir+1,iz}(t) + a_3 c_{ir-1,iz}(t) + a_4 c_{ir,iz+1}(t) + a_5 c_{ir,iz-1}(t) \text{ Eq. 28.} \]

Eq. 28 is a finite difference expression of Eq. 23 where, \( a_1 = \frac{-2 \cdot D_o}{h_r^2}, a_2 = \frac{D_o}{2 h_r^2}, a_3 = -\frac{D_o}{2 h_r^2}, a_4 = \frac{D_o}{2 h_z^2}, a_5 = \frac{D_o}{2 h_z^2}. \)

Therefore, inside the geometry there was one ODE for every point which expressed the time derivative of the \( O_2 \) concentration in relation to the \( O_2 \) concentration of adjacent points in a finite difference expression. In the same way as for the intravascular environment, Eq. 19 was developed in the defined mesh as:

\[ V_t \frac{\partial c_{ext,iz}}{\partial t} = -S Do \frac{\partial c_{N_r,iz}}{\partial r} - \text{CMRO}_2(t) \text{ Eq. 29.} \]

\( \frac{\partial c_{N_r,iz}}{\partial r} \) on every boundary point \( \{N_r, iz\} \) was replaced by its finite difference approximation by using the Wolfram Mathematica function 'NDsolve'FiniteDifferenceDerivative'. This function is described in details in Appendix.

### 6.6.3 Treatment of boundary conditions

One ODE for every point at the bounds was furthermore developed. However, the central difference approximations could not be developed at the boundaries because there were no points out of the bounds. On the bounds, partial derivatives were approximated with the finite difference method by the function documented in Wolfram Mathematica as 'NDsolve'FiniteDifferenceDerivative'. Therefore, in order to produce finite difference expressions for boundary conditions, the partial derivatives in bc2, bc3 and bc4 boundary conditions were replaced by their finite difference approximations produced by 'NDsolve'FiniteDifferenceDerivative'.


For example, at boundary point \((i_r, i_z) = (N_r = 30, 2)\) where bc2 should be satisfied, bc2 becomes in the form:

\[
375c_{326,2}[t] - 2000c_{327,2}[t] + 4500c_{328,2}[t] - 6000c_{329,2}[t] + 3125c_{330,2}[t] = 0
\]

Eq. 30.

Where \(c_{30,2}[t]\) is the \(O_2\) concentration at the boundary point \((i_r, i_z) = (N_r = 30, 2)\). Solving Eq. 30 for \(c_{30,2}[t]\) the result is:

\[
c_{30,2}[t] \rightarrow \frac{1}{25}(-3c_{26,2}[t] + 16c_{27,2}[t] - 36c_{28,2}[t] + 48c_{29,2}[t])
\]

Eq. 31.

Therefore, bc2 was satisfied for \((i_r, i_z) = (N_r = 30, 2)\) in the system by replacing \(c_{30,2}[t]\) by \((1/25)(-3c_{26,2}[t] + 16c_{27,2}[t] - 36c_{28,2}[t] + 48c_{29,2}[t])\). In the same way, \(O_2\) concentration at every boundary point was replaced by a term which depended on the boundary condition. Finally, by developing the finite difference approximations of partial derivatives at the boundary points, and by replacing them at Eq. 23, an ODE was created for every boundary point.

6.6.4 Numerical solution of the ODE system

The function of Wolfram Mathematica documentation which is found as 'NDSolve' was used in order to find numerical solutions to the formulated PDE problem. All the created ODEs, one ODE at every point of the MESH, contribute to an ODE system. The ODE system was written in the form:

\[
dV = M \cdot V \text{ Eq. 32.}
\]

\[
\begin{align*}
&c_{1,1}(t) \\
&c_{1,2}(t) \\
&\vdots \\
&c_{nr,nz}(t) \\
&\vdots \\
&c_{ext_{i2}}(t)
\end{align*}
\]

Where, \(V = c_{1,1}(t)\) is the vector of variables which 'NDSolve' must solve for, \(dV = \frac{dc_{1,1}}{dt} \ldots \frac{dc_{nr,nz}}{dt} \ldots \frac{dce_{ext_{i2}}}{dt}\) is the vector of time derivatives of variables, and,
The derived ODE equations at every discrete point were imported to 'NDSolve'. Additionally, the vector of variables V were imported to 'NDSolve' so as 'NDSolve' solved for those variables. The initialization of variables was also imported as \( V(t = 0) = V_0 \) where \( V_0 \) denotes the values of variables \( V \) at time \( t = 0 \). 'NDSolve' uses a step in time \( dt \) and starting from the imported initialization calculates the variables \( V(0 + dt), V(0 + 2dt) \ldots V(t_{\text{end}}) \) with a step \( dt \) in time until the final time of simulation “tend”. “tend” was also imported in 'NDSolve'.

CBF depends on the vessel’s radius and blood’s velocity \( u_z \). Mathematically, CBF was expressed as \( CBF = u_z \cdot \pi r_{\text{max}}^2 [m^3/s] \). During the simulations of current thesis, velocity \( u_z \) and CMRO\(_2\) were variable in time. Therefore, by simulating in a range of time \( t \) \{0, tend\}, it was attempted to find a solution for the hemoglobin SaO\(_2\) variance in time and how it is related to CBF and CMRO\(_2\) variance.
7 Results: Modelling of fMRI BOLD response

7.1 Assignment of values to parameters

The first step of simulating the developed model was to assign values to the model’s parameters. It was derived from literature that the CBF velocity varied between 0.5 mm/s to 1.5 mm/s. (13) Therefore, the velocity was assumed to be \( u_z = 1 \text{ mm/s} = 10^{-3} \text{ m/s} \).

Mishra et al. (14) found that the diameter of cerebral capillaries is around 5 \( \mu \text{m} \) and 10 \( \mu \text{m} \). The radius of the blood vessel of the model was assumed to be \( r_{max} = 5 \times 10^{-6} \text{ m} \). The length of the capillary was assumed to be \( (z_2 - z_1) = 0.6 \text{ mm} \), as it was suggested in a computer exercise assignment by Johansson (11). The length of the arteriole and the venule was assumed to be 1 mm so as there is enough space for convection diffusion equation to be developed in arterioles and venules. So, \( z_{max} = 1 + 0.6 + 1 = 2.6 \text{ mm} \) and \( z_1 = 1 \text{ mm} \), \( z_2 = 1.6 \text{ mm} \). The diffusion coefficient of \( O_2 \) in blood was assumed to be \( D_0 = 2 \times 10^{-9} \text{ m}^2/\text{s} \) as it was suggested by Johansson (11).

7.2 Constant extravascular \( O_2 \) concentration

Here, the model was simulated with a constant \( O_2 \) concentration in the extravascular environment, as it is shown in Fig. 38. In a resting state condition, \( O_2 \) concentration in the extravascular environment was assumed to correspond to partial pressure 40 mmHg = 5332.9 Pascals.

Also, \( O_2 \) concentration was assumed to be dissolved in the extravascular environment and therefore Henry’s law could be applied. Through Henry’s Law the corresponding \( O_2 \) concentration was calculated as \( C_t = H \times 5332.9 \text{ Pa} = 0.0533 \text{ mol/m}^3 \). A simulation of the model is shown in Fig. 38 for up to 4 seconds and all the initial values of \( O_2 \) concentration were equal to zero, \( c_{ir,iz}[0] \to 0 \).

![Figure 38 Modelling of formulated PDE problem assuming a constant concentration at the extravascular environment. SaO2: hemoglobin SaO2, z: cylindrical coordinate for length of vessel, r: cylindrical coordinate for radius of vessel. SaO2 is 97.7% in arterial blood and 75% in venous blood.](image)
The mean hemoglobin SaO₂ in the venous blood is shown in Fig. 39. It seems that venous SaO₂ had a steady state solution SaO₂ = 75% after 1.8 seconds.

Figure 39 SaO₂ in the venous blood during the time of simulation (0.4) seconds.

7.3 Simulation of intravascular and extravascular O₂ concentration

7.3.1 Baseline condition modelling

Additionally, CMRO₂(t) had to be introduced so that the model covers both the intravascular and the extravascular environment. Baseline state was assumed when the O₂ concentration at the extravascular environment was constant in time so as $\frac{\partial c_{\text{ext},i,z}}{\partial t} = 0$. Therefore:

$$\text{Eq. 29} \Rightarrow -S D_o \frac{\partial c_{N_r,i,z}}{\partial r} = \text{CMRO}_2(t) \quad \text{Eq. 33}$$

meaning that diffusion rate from intravascular to extravascular environment and O₂ uptake CMRO₂ should be equal. Through the solution specified in subchapter 6.2 (Fig. 38), an average value was calculated for $\frac{\partial c_{N_r,i,z}}{\partial r}$ at the border ($N_r, i_{z1} < i_z < i_{z2}$). Furthermore, $S$ was calculated through Eq. 20 and $D_o$ was given in subchapter 7.1. Therefore, through Eq. 33, a value for the baseline O₂ uptake was calculated as:

$$\text{CMRO}_2(t) = 5.993 \times 10^{-15} \text{mol sec}^{-1} \quad \text{Eq. 34.}$$

The formulated PDE problem was simulated with the calculated CMRO₂. The O₂ concentration was initialized both in the intravascular and the extravascular environment with the O₂ concentrations equal to zero, $c_{i_r,i,z}[0] \to 0$ and $c_{\text{ext},i,z}[0] \to 0$. The model was simulated for 30 seconds, {0,30}. The calculated SaO₂ in the venous blood is shown in Fig. 40 and it was calculated as the mean SaO₂ value of the venous blood. As it is shown in Fig. 40b, a baseline condition with steady state conditions was achieved at 7 seconds. In Fig. 41, the hemoglobin SaO₂ was shown during baseline state conditions after 7 seconds. In Fig. 42, the extravascular O₂ concentration out of the capillary wall is shown.
Figure 40 Modelling of formulated PDE with baseline conditions. $\text{SaO}_2$ in the venous blood was calculated as the mean $\text{SaO}_2$ value of the venous blood. a) Ranges of values of venous $\text{SaO}_2$ until steady state conditions were reached. Values of $\text{SaO}_2$ are negative because of numerical simulation, e.g. numerically negative values. b) After the 7th second baseline condition was reached with venous $O_2$ saturation $\text{SaO}_2 = 74\%$ which corresponds to partial pressure of $O_2$ 39.3 mmHg through $O_2$ dissociation curve of Figure 33.

Figure 41 Hemoglobin $\text{SaO}_2$ at the space of formulated PDE problem during baseline conditions at a time point after 7 seconds of simulation.
7.3.2 CMRO₂ effect

Hyder et al. (15) calculated CMRO₂ for a short time stimulation lasting 500 ms. The calculated CMRO₂ time series is shown in Fig. 43. This scenario was similar to the experimental data used in this thesis because the subjects were also stimulated for a short period of time. Therefore, it was assumed that CMRO₂ behaved similarly. So, the current PDE problem was modelled when CMRO₂ varied according to Fig. 43. In Fig. 44 the fractional change of CMRO₂ as a function of time is shown. CMRO₂ was assumed to start increasing at 9.5 seconds, reach a peak of 15% increase at 12 seconds and returns to baseline CMRO₂ at 16.2 seconds. The model was simulated for 30 seconds.

Fig. 45a) shows how the hemoglobin SaO₂ of the venous blood varied in time during the simulation. In Fig. 45b), the fMRI signal is shown as a proportional change of BOLD signal (%BOLD) and it was calculated through Eq. 6 by using the calculated mean hemoglobin SaO₂ of the venous blood. Calculation of the proportional BOLD signal started at 9 seconds and it is shown up to 30 seconds. In Fig. 45c), both fractional change of CMRO₂ and proportional BOLD signal are depicted.
Figure 43 Estimated \( \text{CMRO}_2 \) time series as a response to a short time stimulus by Hyder et al. LFP stands for local field potential e.g. stimulation of neural tissues. Figure originally published in (15). Reprinted with permission.

Figure 44 Fractional change of \( \text{CMRO}_2 \).
7.3.3 CMRO₂ and CBF velocity effect

7.3.3.1 BOLD signal overshoot

Several scenarios of fractional changes in CMRO₂(t) and CBF(t) were also simulated in order to attempt to explain the physiological mechanisms of BOLD responses to short time stimulus. Hodge et al. (16) found that during visual stimulation an increase in CMRO₂ was observed between 3 % and 25 %. Additionally, they found that there was a linear relationship between CMRO₂ and CBF increase with a coupling ratio \( n \approx 2 \) which means that the CBF increase is two times larger than the CMRO₂ increase. The higher fractional increase of CBF than CMRO₂ was believed to be the reason why the BOLD signal overshoot was observed (5,15,16). Here, a scenario was simulated for a CBF velocity increase up to 30 % and a CMRO₂ increase up to 15 % assuming a coupling ratio \( n = 2 \). CMRO₂ and CBF fractional change as a function of time and the corresponding %BOLD signal are shown in Fig. 46. Additionally, a scenario was simulated for a CBF velocity increase up to 45 % and a CMRO₂
increase up to 15% assuming a coupling ratio \( n = 3 \). CMRO\(_2\), CBF as a function of time and the corresponding proportional to BOLD signal are shown in Fig. 47.

\[
\frac{\Delta x}{x} = \frac{\text{Estimated %BOLD}}{\text{CMRO}_2 \text{ fractional change}} \quad \text{CBF velocity fractional change}
\]

![Figure 46 Estimated %BOLD signal response for specific fractional changes of CMRO\(_2\) and CBF velocity for a coupling ratio \( n = \frac{30\%}{15\%} = 2 \).](image)

![Figure 47 Estimated %BOLD signal response for specific fractional changes of CMRO\(_2\) and CBF velocity for a coupling ratio \( n = \frac{45\%}{15\%} = 3 \).](image)

7.3.3.2 BOLD initial dip

In Fig. 48, the estimated %BOLD signal is shown when the model was simulated with a mismatch between the CBF velocity and the CMRO\(_2\) increase assuming a coupling ratio \( n = 2 \). In Fig. 49 and Fig. 50, the estimated %BOLD signals are shown when the model was simulated with a mismatch between the CBF velocity and the CMRO\(_2\) increase assuming a coupling ratio \( n = 3 \) and \( n = 4 \) respectively.

The CBF velocity delay was assumed to be 0.5 s. Buxton (17) has stated that a mismatch between CMRO\(_2\) and CBF increase was believed to be the main reason why the BOLD
signal initial dip has been observed. The CMRO$_2$ increase before an increase of CBF was believed to cause an increase in DHb levels and as a result a decrease in BOLD fMRI signal. However, Buxton (17) also stated that the physiological mechanisms responsible for the initial dip are, as yet, unexplained.

![Figure 48](image1.png)

*Figure 48 Mismatch between CBF and CMRO$_2$ resulted in an initial dip. CBF starts increasing 0.5 seconds after CMRO$_2$. Coupling ratio $n = \frac{30\%}{15\%} = 2$."

![Figure 49](image2.png)

*Figure 49 Mismatch between CBF and CMRO$_2$ resulted in an initial dip. CBF starts increasing 0.5 seconds after CMRO$_2$. Coupling ratio $n = \frac{45\%}{15\%} = 3$."

Mismatch between CBF and CMR\(O_2\) resulted in an initial dip. CBF starts increasing 0.5 seconds after CMR\(O_2\). Coupling ratio \(n = \frac{60\%}{15\%} = 4\).

### 7.3.3.3 BOLD signal post-stimulus undershoot

Additionally, in Fig. 51 and Fig. 52 a post-stimulus increase of CMR\(O_2\) and a post-stimulus undershoot of CBF were added respectively, in order to explain for the post-stimulus undershoot. According to Chen et al. (18), possible origins of the BOLD post-stimulus undershoot have been reported because of a post-stimulus increase of CMR\(O_2\) and a post-stimulus undershoot of CBF. Measurements were also implemented and post-stimulus undershoot of CBF was found. It was also reported that CBV changes play an important role for the post-stimulus undershoot. However, simulations were not calculated in current work for changes of CBV.
Figure 52 Additionally to Fig. 51, a post-stimulus undershoot of CBF velocity was added and resulted in a higher post-stimulus undershoot than the post-stimulus undershoot of Fig. 51.
8 Discussion: Modelling of the fMRI BOLD response

8.1 Constant extravascular concentration

Firstly, the model was simulated for a constant $O_2$ concentration of the extravascular environment which corresponds through Henry’s law to partial pressure equal to 40 mmHg. The result of this simulation, which is shown in Fig. 38, was used in order to define a baseline diffusion rate of $O_2$ from the intravascular to the extravascular environment by calculating the term $SDO = \frac{\partial c_{N_2}}{\partial r}$ [mol/s]. At $z = 1 \text{ mm}$ (Fig. 38), blood enters the capillary and diffusion of $O_2$ takes place from the intravascular to the extravascular environment. Blood leaves the capillary at $z = 1.6 \text{ mm}$. Therefore, $SaO_2$ falls sharply from 98% to 75% because $O_2$ diffusion starts to take place at $z = 1 \text{ mm}$.

$SaO_2$ 75 % corresponds to partial pressure 40 mmHg according to the $O_2$ dissociation curve shown in Fig. 33. The higher $SaO_2$ 98 % of the incoming blood corresponds to partial pressure equal to 100 mmHg according to the $O_2$ dissociation curve shown in Fig. 33. The $O_2$ partial pressure difference $100 - 40 = 60 \text{ mmHg}$, between intravascular and extravascular environment, causes $O_2$ diffusion. However, $SaO_2$ falls sharply to 75% at the entrance of capillary wall, $z = 1 \text{ mm}$, which means that the intravascular partial pressure of $O_2$ at the rest of the capillary wall, up to $z = 1.6 \text{ mm}$, has become almost 40 mmHg and the $O_2$ partial pressure difference $40 - 40 = 0 \text{ mmHg}$. Therefore, there is no diffusion of $O_2$ at the rest of the capillary wall and that is the reason why, after the sharp fall of $SaO_2$ at $z = 1 \text{ mm}$, $SaO_2$ remained constant and equal to 75%. If there was outward diffusion only at the beginning of the capillary wall, then, $O_2$ wouldn’t diffuse outwards at the rest of the capillary wall and the need for $O_2$ for the rest of the surrounding tissue would not be satisfied.

In Fig. 39, the $SaO_2$ of venous blood during the time of simulation is shown. $SaO_2$ was equal to zero up to 0.8 seconds because the initial values of intravascular $O_2$ concentration were zero. The solution of the model was numerical and the intravascular $O_2$ concentration started increasing because of the boundary condition bc1. In total: 0.8 seconds were needed until intravascular $O_2$ concentration of venous blood started increasing and 1.8 seconds were needed until it reached a steady state solution $SaO_2 = 75\%$.

8.2 Baseline condition modelling

The larger $O_2$ concentration of intravascular environment than the $O_2$ concentration of the extravascular environment drives $O_2$ diffusion from the intravascular to the extravascular environment. The larger this difference is, the higher the $O_2$ diffusion rate becomes. The diffusion rate was essential to be defined because $SaO_2$ of venous blood depends on the diffusion rate. For example, if the diffusion rate increased then more $O_2$ would diffuse outwards the capillary wall and less $O_2$ would lead to the venous blood and, as a result, $SaO_2$ of venous blood would be expected to decrease. Therefore, the $O_2$ concentration of the extravascular environment was modelled because it affects the diffusion rate from the intravascular to the extravascular environment. The $O_2$ concentration of the extravascular environment was modeled according to Eq. 19. According to Eq. 19, extravascular $O_2$ concentration increased when diffusion rate was higher than CMRO$_2$ and decreased when diffusion rate was lower than CMRO$_2$. 


As can be observed in Fig. 40, the baseline condition was achieved after 7 seconds of simulation when the numerical solution of SaO₂ of venous blood reached steady state conditions 74%. Fig. 40 is essential in order to understand how the developed model works. In the beginning of the simulation, both intravascular and extravascular O₂ concentration were initialized with zero values. Therefore, their difference was zero and the diffusion rate of O₂ was zero as well. So, extravascular O₂ concentration was affected more by CMRO₂ in the beginning and decreased to numerically negative values. The decreasing extravascular O₂ concentration increased the diffusion rate of O₂ by increasing the difference between extravascular and intravascular O₂ concentration. As a result, the increase of the diffusion rate caused less O₂ to stay in the venous blood and venous SaO₂ decreased to numerically negative values.

As the diffusion rate increased and became more important than CMRO₂, the extravascular O₂ concentration increased. The increase in extravascular O₂ concentration decreased the difference between the extravascular and intravascular O₂ concentration. As a result, the diffusion rate decreased and the O₂ concentration at venous blood increased. Therefore, whether venous SaO₂ increased or decreased depends on which effect of either the diffusion rate or CMRO₂ has the greatest effect on the extravascular O₂ concentration. In Fig. 53a), the described effects of CMRO₂ and the diffusion rate on venous SaO₂ have been highlighted. In Fig. 53b), alternations between the significance of CMRO₂ and the diffusion rate effect caused venous SaO₂ to oscillate until a steady-state solution at 74% was reached after 7 seconds of simulation. The achievement of this model was that venous SaO₂ was balanced at a constant value at 74% which is considered a typical SaO₂ of venous blood at baseline conditions. When baseline conditions were achieved, the diffusion rate was equal to CMRO₂ and the extravascular O₂ concentration was constant. As a result, venous SaO₂ remained constant as well.

![Figure 53](image)

*Figure 53 a) Effects of the diffusion rate and CMRO₂ affect venous SaO₂ b) alternations of the most important effects either of the diffusion rate or CMRO₂ effects until a steady state condition was achieved.*
The steady state solution of SaO$_2$, which is shown in Fig. 41, showed that arterial SaO$_2$ (98 %) gradually decreased inside the capillary to venous SaO$_2$ (74 %) at the end of the capillary. In contrast to simulating with constant extravascular concentration, SaO$_2$ decreased gradually and not sharply. This happened because extravascular $O_2$ concentration decreased also gradually in relation to cylindrical coordinate $z$ as it is shown in Fig. 42. As the distance between the extravascular environment and the arterial blood increased, for $z >> 0.001$ mm in Fig. 42, extravascular $O_2$ concentration decreased. In other words, the closer to the arterial blood, the more $O_2$ was concentrated at the extravascular environment. As a result, intravascular $O_2$ concentration at the capillary wall followed the behavior of the extravascular $O_2$ concentration.

8.3 CMRO$_2$ effect

The next step was to vary CMRO$_2$ after the 7th second of simulation, when baseline conditions were achieved, in order to observe the effect on the fMRI BOLD signal. CMRO$_2$ was given as a function of time according to a fractional change described in Fig. 44. In Fig. 45a it was observed that venous SaO$_2$ decreased when CMRO$_2$ increased. Therefore, an estimation of a proportional BOLD signal change, %BOLD according to Eq. 6, resulted in a %BOLD shape with similar behavior to CMRO$_2$ fractional change.

When CMRO$_2$ increased, the extravascular $O_2$ concentration decreased because the effect of CMRO$_2$ was more significant than the effect of the diffusion rate. The decrease in extravascular $O_2$ concentration caused more $O_2$ to flow outwards the capillary wall and less $O_2$ to lead to the venous blood. Therefore, venous SaO$_2$ decreased and the estimated proportional to BOLD signal decreased as well. However, the decreased extravascular $O_2$ concentration created an increased $O_2$ concentration gradient across the capillary wall which increased the diffusion rate. For that reason, when CMRO$_2$ returns to baseline level, the increased diffusion rate has a higher effect than CMRO$_2$ and the extravascular $O_2$ concentration increases. As extravascular $O_2$ concentration increases, the diffusion rate of $O_2$ decreases because the $O_2$ concentration gradient decreases as well. Therefore, more $O_2$ led to the venous blood and increased the venous SaO$_2$ so as to return to the baseline conditions.

8.4 CMRO$_2$ and CBF velocity effect

Additionally to the variance of CMRO$_2$ as a function of time, CBF velocity variance as a function of time was added as well. Therefore, the developed model was simulated for different scenarios of both CMRO$_2$ and CBF velocity fractional change in order to observe their effects on the estimated proportional to BOLD signal.

8.4.1 BOLD overshoot

In Fig. 46, the result of the model’s simulation is shown for specific fractional changes of CMRO$_2$ and CBF velocity in order to explain BOLD signal overshoot. At this simulation, CMRO$_2$ and CBF velocity fractional changes had the same timing, e.g. they started increasing and decreasing at the same time. Herein, CMRO$_2$ fractional change has been considered to have triangular shape because of Fig. 43. Additionally, fractional change of CBF velocity has been considered to have triangular shape because local regions of brain
have been considered to increase CBF similarly to CMRO₂. The neurovascular coupling was considered as $n = (30\%)/(15\%) = 2$, which means that CBF velocity fractional change was two times larger than CMRO₂ fractional change. The result of this simulation was an increasing BOLD signal which is similar to a BOLD signal overshoot.

The increased CBF velocity caused an elevation of intravascular $O_2$ concentration levels at the capillary wall and as a result the $O_2$ concentration gradient increased at the capillary wall which caused the diffusion rate to increase as well. The increased diffusion rate caused the extravascular $O_2$ concentration to increase. On the other hand, CMRO₂ increased as well and that caused the extravascular $O_2$ concentration to decrease. Therefore, extravascular $O_2$ concentration was affected by two opposite powers, CMRO₂ and the diffusion rate, which tend to decrease and increase respectively the extravascular $O_2$ concentration. However, the effect of the diffusion rate was higher than the effect of CMRO₂ and as a result the extravascular $O_2$ concentration increased. The increase of extravascular $O_2$ concentration caused an increase of the venous SaO₂ which resulted in an increase of BOLD signal.

In Fig. 47, the estimated proportional to BOLD signal is shown when there was a coupling ratio $n = 3$. For $n = 3$ in Fig. 47, the overshoot was greater than when the coupling ratio was $n = 2$ in Fig. 46. This shows that the BOLD signal overshoot depends on the coupling ratio. According to those simulations, when the coupling ratio was greater, the BOLD signal overshoot was greater as well.

8.4.2 BOLD initial dip

In Fig. 48, the model was simulated when there was a mismatch between CMRO₂ and CBF velocity fractional change in order to explain the BOLD signal initial dip. The difference from the scenario in Fig. 46 is that CBF velocity fractional change was shifted 0.5 s and started increasing 0.5 s after the CMRO₂ increase. This delay denotes the delayed response of the blood circulation system to the neural activity. The resulted proportional to BOLD signal was denoted in Fig. 48 and it was observed that there was an initial decrease of the proportional to BOLD signal in the beginning (0-1 s) of the simulation.

For the first 0.5 s, CMRO₂ effect was higher than the diffusion rate effect. Therefore, the extravascular $O_2$ concentration decreased and this caused an increase in the diffusion rate at the capillary wall. Due to the increase in the diffusion rate, more $O_2$ diffused outwards to the capillary wall and less $O_2$ led to the venous blood, dropping down SaO₂ of venous blood and proportional to BOLD signal as well. At the same time, CBF velocity started increasing 0.5 s after CMRO₂ and this caused an increase in the diffusion rate. As a result, the diffusion rate effect became higher than CMRO₂ effect and this caused an elevation of extravascular $O_2$ concentration. Following, BOLD overshoot was caused as it is explained in subchapter 7.4.1.

Additionally, in Fig. 49 and Fig. 50 the model was simulated when CBF velocity delayed to start increasing 0.5 s and for coupling ratios $n = 3$ and $n = 4$ respectively. In Fig. 48, Fig. 49 and Fig. 50, it was observed that the initial dip was less observable when there was a higher coupling ratio. This was explained by the fact that a larger increase in CBF velocity caused the diffusion rate effect to become faster more important than CMRO₂. As a result
the proportional to BOLD signal started increasing faster for a higher coupling ratio. Therefore, a faster increase of CBF velocity caused the initial dip to last for less time.

8.4.3 BOLD post-stimulus undershoot
Scenarios of specific fractional changes of CMRO$_2$ and CBF velocity were also simulated in order to explain the BOLD post-stimulus undershoot. The results of simulations are shown in Fig. 51 and Fig. 52. The difference from the previously simulated scenario in Fig. 48 was that; in the scenario in Fig. 51 the model was simulated for an additional post-stimulus overshoot of CMRO$_2$. The resulting proportional to BOLD signal in Fig. 51 showed that the BOLD signal overshoot was followed by a negative BOLD signal which returned slowly to the baseline. A further increased CMRO$_2$ and a zero fractional change of CBF velocity resulted in a post-stimulus decreased BOLD signal due to the higher effect of CMRO$_2$ than the diffusion rate to the extravascular $O_2$ concentration. As a result, the decreased extravascular $O_2$ concentration caused more $O_2$ to diffuse outwards the capillary wall and less $O_2$ led to the venous blood.

In the scenario in Fig. 52, a post-stimulus undershoot of CBF velocity was added to the scenario of Fig. 51. The post-stimulus undershoot of CBF velocity contributed to a higher post-stimulus undershoot than the one of Fig. 51. Here, both the post-stimulus increased CMRO$_2$ and the post-stimulus decreased CBF velocity contributed to a post-stimulus decrease of extravascular $O_2$ concentration. The post-stimulus decreased extravascular $O_2$ concentration caused a decreased post-stimulus undershoot of %BOLD signal because the diffusion rate increased and less $O_2$ led to the venous blood.
9 Conclusions

Attempting to explain the physiological principles of the estimated BOLD responses, a model was created in order to explain how BOLD fMRI depends on CBF velocity of blood flowing in cerebral microcirculation and $O_2$ metabolism CMRO$_2$ of cerebral tissues.

Several scenarios of CBF velocity and CMRO$_2$ as a function of time were simulated in order to observe how the estimated proportional to BOLD responses vary in time as well. Those simulations showed that the amplitude of BOLD signal overshoot depended on the coupling ratio. The higher the coupling ratio, the higher was the amplitude of BOLD signal overshoot. BOLD responses at the visual cortex were estimated to have a higher amplitude of overshoot than BOLD responses at the frontal cortex. Therefore, it is concluded that, according to the developed model of current thesis, the region of the visual cortex responded to stimuli with a higher coupling ratio than the region of the frontal cortex.

The conclusion that coupling ratio of BOLD response was higher at visual cortex than frontal cortex can also be supported by observing the initial dip of BOLD response estimations. Estimations of BOLD responses showed that an initial dip was not observed at the visual cortex and that an initial dip was observed at the frontal cortex. Simulations of the developed model showed that the higher the coupling ratio the less time the initial dip lasted and that is why it was less observable. Therefore, in order for simulations to agree with BOLD response estimations it is concluded that the coupling ratio at the frontal cortex was small enough so as an initial dip could have been observable. Additionally, it is concluded that at the visual cortex, the coupling ratio was not small enough for an initial dip to be observed. Here, it must also be noted that the temporal resolution ($TR = 2\ s$) was quite low and this also worsened the estimations of the initial dip because an initial dip could last up to 2 s. Therefore, both low temporal resolution and high coupling ratio at the visual cortex reduced the probability of estimating an initial dip.

Also, a post-stimulus undershoot was observed at both the visual cortex and the frontal cortex. Post-stimulus undershoot was explained by simulations of the developed model as a post-stimulus increased CMRO$_2$ or a post-stimulus decreased CBF velocity or both a post-stimulus increased CMRO$_2$ and a post-stimulus decreased CBF velocity.
10 Additional approaches -- Future developments
Additionally, the already developed methods could be extended with additional approaches in order to result in improved methods.

Regarding the first part of the current thesis, a shape of a band-pass filter should be examined in terms of maximizing a defined SNR. In current work, the cut-off frequency and the shape of the designed high pass filter have not been examined if they are the optimum ones in terms of an SNR index. Also, a shape of a low-pass filter for distorting noise of high frequency components could result in a higher SNR index.

Regarding the second part of the current thesis, the developed model could be extended so as to incorporate CBV changes. CBV could also vary in time during the simulation, in the same way as CMRO\textsubscript{2} and CBF velocity, by varying in time the radius of the capillary. Also, another formula for estimating the %BOLD signal should be used because Eq. 6 doesn’t incorporate blood volume changes. In that case, only the levels of DHb, which contribute to the fMRI BOLD signal, should be estimated during the time of simulation in order to estimate the fMRI BOLD signals.
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Appendices
A. Physical principles of fMRI

Magnetic Resonance Imaging (MRI) is based on the fact that all nuclei with an odd number of protons are magnetically excitable. Atoms of Hydrogen $^1H$ have only one proton in their nucleus and are abundant in human tissues. Protons have the property to rotate with a spin around their axes and thus this spin induces small directed magnetic fields. Normally, these spins have random direction and cancel each other. However, if an external relatively high magnetic field on a certain direction is applied, the spins are directed parallel either to or against the direction of the external magnetic field. Each proton has a magnetic field parallel towards or against the external magnetic field. The sum of those magnetic fields forms a magnetic field which is shown in Fig. 54. The number of spins aligned in the direction of the external magnetic field is higher than those aligned against it forming a magnetic field $M_0$ in the direction of the external magnetic field. The spin of a proton rotates around the axis of the external magnetic field. This movement is known as precession. (1)

![Image](image.png)

Figure 54 a) Random magnetic fields b) Magnetic fields of protons parallel to the external magnetic field either for or against to it. $M_0$ denotes the formed magnetic field of protons. c) A spin of a proton rotates around the axis of the external magnetic field. This movement is known as precession. Figure as originally published in (1). Reprinted with permission. Copyright © Springer-Verlag Berlin Heidelberg 2007.

The precession frequency of the protons depends on the strength of the external magnetic field and is connected to it through Larmor equation $\omega_0 = \gamma B_0$, where $\omega_0$ is the precession frequency, $\gamma$ is the gyromagnetic ratio and $B_0$ is the strength of the external magnetic field. In a coordinate system of three dimensions $(x,y,z)$, the direction of $B_0$ is along the $z$ direction which is transverse to the $x - y$ plane as it is shown in Fig. 55.

If a Radio Frequency (RF) pulse with the same frequency as the precession frequency is applied, protons become excited and the spins are flipped according to an angle $\alpha$ towards the transverse $x - y$ plane. For example, if an electromagnetic pulse causes the spins to flip 90°, then the spins are flipped from pointing towards the $z$ direction to pointing parallel to the $x - y$ plane in Fig. 55. In Fig. 55a) it is shown that total magnetization is flipped an angle $\beta < 90^\circ$ from the $z$ direction. $M_0$ consists of a sum of magnetization field vector at the transverse plane $x - y M_{xy}$ and magnetization field vector at the $z$ direction $M_z$. In Fig. 55b), it is shown that when magnetization field $M_0$ is flipped 90° from the $z$ direction then $M_{xy}$ is higher than $M_z$ and most of the magnetic field energy is in the $x - y$ plane. (1)
Estimation and Modelling of fMRI BOLD response

Figure 55 a) Magnetization field is flipped an angle $\beta < 90^\circ$ from $z$-direction to $x$-$y$ plane. Magnetic field $M_0$ consists of a sum of a magnetic field vector which shows the magnetization field in the $x$-$y$ plane $M_{xy}$ and a magnetic field vector $M_z$ which shows the magnetic field towards the $z$ direction. b) Magnetization field is flipped an angle $\alpha = 90^\circ$ from the $z$-direction to the $x$-$y$ plane. Most of the energy is in the $x$-$y$ plane. Figure as originally published in (1). Reprinted with permission. Copyright © Springer-Verlag Berlin Heidelberg 2007.

After excitation with the RF pulse, the spins in the $x - y$ plane are in phase and add up so as to form a strong magnetization vector in the $x - y$ plane. However, interactions between magnetic fields of protons in the $x - y$ plane lead to slightly different local magnetic fields. Therefore, due to the Larmor equation, spins rotate with slightly different precession frequencies in the $x$-$y$ plane and get out of phase gradually. This process is known as dephasing. As a result, dephasing causes the total magnetic field in the $x$-$y$ plane $M_{xy}$ to be decreased exponentially according to a time constant $T_2^*$, $M_{xy}(t) = M_{xy}(t = 0) \exp(-t/T_2^*)$.

Dephasing can be observed in Fig. 56. Protons spin with their precession frequency and the magnetization field in the $x - y$ plane $M_{xy}$ (blue line) is received by a coil. The precession frequencies of protons differ and the proton spins get gradually out of phase. The differences of frequency precessions are due to inhomogeneities and difference in the local chemical environment as well. For that reason, the amplitude of received energy (red line) is gradually decreased according to a time constant $T_2^*$. $T_2^*$ is defined as the time when $M_{xy}(T_2^*) = M_{xy}(t = 0) \exp(-1)$. Therefore, a contrast based on $T_2^*$ is used to image local field inhomogeneity.
The result of local field inhomogeneity would be that a higher level of inhomogeneity would cause a faster dephasing of the transverse magnetization field $M_{xy}$. If the magnetic field was ideally homogeneous, then the spins of protons would have the same phase and the measured field $M_{xy}$ would decrease because of loss of energy in time which doesn’t depend on $T_2^*$ but on another time constant which is known as $T_2$. (1) Physiological tissues are characterized by local field inhomogeneity and as it is referred by Lindquist (3) $T_2^*$ contrast is used for contrast in fMRI.
B. Fundamentals of finite difference method (FDM)

B.1 Spatial discretization

Finite difference method (FDM) is used for solving partial differential equations. The partial differential equation’s space is discretized in a grid of points over which a solution is attempted to be found. This grid of points is also known as “mesh”. For example, supposing that \( U(x) \) is one-dimensional continuous function for \( x \in \{p, q\} \), then the discretized grid of \( U(x) \) function is shown in Fig. 57. The continuous space is discretized in \( N \) points \( \{x_1, x_2, ..., x_N\} \) which have an equal distance between them \( h = \Delta x = \frac{q-p}{N-1} \).

![Figure 57 Discretized grid of a function U(x) for x ∈ {p, q}. (19)](image)

B.2 Finite difference approximation of partial derivatives

The partial derivatives of a function \( U(x), x \in \{p, q\} \) can be estimated in discrete coordinates if the values \( U(x_1), U(x_2), ..., U(x_N) \) are known. According to FDM, Taylor’s method is used to calculate partial derivatives in a mesh. Taylor’s method describes that for the defined function \( U(x) \) which has \( n \) continuous derivatives in an interval \([p, q]\), then if \( p < x_0 < x_0 + h < q \), the value \( U(x_0 + h) \) can be estimated as:

\[
U(x_0 + h) = U(x_0) + h U_x(x_0) + h^2 \frac{U_{xx}(x_0)}{2!} + \cdots + h^n \frac{U_{(n-1)}(x_0)}{(n-1)!} + O(h^n) \quad \text{Eq. 35.}
\]

Where \( U_x = \frac{\partial U}{\partial x} \), \( U_{xx} = \frac{\partial^2 U}{\partial x^2} \), ..., \( U_{(n-1)} = \frac{\partial^{n-1} U}{\partial x^{n-1}} \), \( U_x(x_0) \) is the derivative of \( U \) evaluated at \( x = x_0 \) and \( O(h^n) \) is an unknown error term. For example, if the real value of \( U \) evaluated at \( x_0 + h \) is \( U_r(x_0 + h) \), then \( O(h^n) = U_r(x_0 + h) - U(x_0 + h) \).

Taylor’s method is used in FDM in order to calculate partial derivatives and replace them in partial differential equations. Eq. 35 can be used in order to estimate partial derivatives. For example for \( n = 1 \) and solving Eq. 35 for \( U_x(x_0) \) gives an estimation of \( U_x(x_0) \).

\[
U_x(x_0) = \frac{U(x_0 + h) - U(x_0)}{h} + O(h^2) = \frac{U(x_0 + h) - U(x_0)}{h} + O(h) \quad \text{Eq. 36.}
\]

Neglecting \( O(h) \) from Eq. 36, \( U_x(x_0) \) is estimated with an error \( O(h) \) as

\[
U_x(x_0) = \frac{(U(x_0 + h) - U(x_0))}{h} \quad \text{and this estimation is known as the forward finite difference approximation.}
\]

The following equation is derived when replacing in Eq. 35 \( h \) by \(-h\).

\[
U(x_0 - h) = U(x_0) - h U_x(x_0) + h^2 \frac{U_{xx}(x_0)}{2!} + \cdots + h^n \frac{U_{(n-1)}(x_0)}{(n-1)!} - O(h^n) \quad \text{Eq. 37.}
\]

From Eq. 37 and \( n = 1 \) the backward finite difference approximation of \( U_x(x_0) \) gives:

\[
U_x(x_0) = \frac{(U(x_0) - U(x_0 - h))}{h} \quad \text{with error } O(h).
\]
Multiplying Eq. 37 with \((-1)\) and \(n = 2\), the following equation is derived as:

\[-U(x_o - h) = -U(x_o) + h \frac{U_{xx}(x_o)}{2} + O(h^3) \text{ Eq. 38.}\]

Eq. 35 for \(n = 2\) becomes:

\[U(x_o + h) = +U(x_o) + h \frac{U_{xx}(x_o)}{2} + O(h^3) \text{ Eq. 39.}\]

Adding Eq. 38 and Eq. 39, and solving for \(U_x(x_o)\), the following equation is revealed:

\[U_x(x_o) = \frac{U(x_o + h) - U(x_o - h)}{2h} + \frac{O(h^3)}{h} = \frac{U(x_o + h) - U(x_o - h)}{2h} + O(h^2) \text{ Eq. 40.}\]

which gives the central difference approximation with error \(O(h^2)\).

Central difference approximation gives a better approximation in terms of error than the forward and the backward approximation because \(O(h^2) < O(h)\).

In (19), a table with finite difference approximations of partial derivatives based on the Taylor’s method is given. The central finite difference approximation of the second partial derivative can be calculated in a similar way. In Table 1, finite difference approximations of first and second partial derivatives are given. These finite difference approximations are used in current work in order to estimate the first and second order partial derivative.

<table>
<thead>
<tr>
<th>Partial derivative</th>
<th>Finite Difference Approximation</th>
<th>Error</th>
</tr>
</thead>
<tbody>
<tr>
<td>(\frac{\partial U(x_o)}{\partial x}) = (U_x)</td>
<td>(\frac{U(x_o + h) - U(x_o - h)}{2h})</td>
<td>(O(h^2))</td>
</tr>
<tr>
<td>(\frac{\partial^2 U(x_o)}{\partial x^2}) = (U_{xx})</td>
<td>(\frac{U(x_o + h) - 2U(x_o) + U(x_o - h)}{h^2})</td>
<td>(O(h^2))</td>
</tr>
</tbody>
</table>

Table 1 Central finite difference approximations for first and second derivative of a function \(U(x)\) evaluated at point \(x_o\).

B.3 Finite difference approximation of partial derivatives with Wolfram Mathematica

In Wolfram Mathematica documentation there is a function which calculates finite difference approximations of partial derivatives. This function is found as "NDSolve'FiniteDifferenceDerivative" and approximates the partial derivatives of a function on a given spatial grid. In the current work, "NDSolve'FiniteDifferenceDerivative" is used to approximate finite difference approximations at the bounds of a given spatial grid. "NDSolve'FiniteDifferenceDerivative" is given as input the spatial grid, the values of the function of interest on the points of the grid, the order of the partial derivative which is needed to be approximated and the "DifferenceOrder" which denotes how many backward and forward points should be used for approximating the partial derivative.

For example, assuming that a function has values \(\{a_0, a_1, ..., a_{10}\}\) at a grid of points \(\{0, h_1, ..., h_{10}\}\) and finite difference approximation of 1\(^{st}\) order is needed with DifferenceOrder \(-> 2\).

The executable in Mathematica is in the following figure (Fig. 58). As can be observed, finite difference approximations of partial derivatives across the grid dimension are returned for every point of the grid. Therefore, "NDSolve'FiniteDifferenceDerivative" returns finite
difference approximations not only at the points inside the grid but also at the bounds 
\[-\frac{3a_0}{2h} + \frac{2a_1}{h} - \frac{a_2}{2h}\) at point 0 and 
\[\left(\frac{a_7}{2h} - \frac{2a_8}{h} + \frac{3a_9}{2h}\right)\) at point 9h in the current execution.

```
values = {a0, a1, a2, a3, a4, a5, a6, a7, a8, a9};
grid = {0, h, 2 h, 3 h, 4 h, 5 h, 6 h, 7 h, 8 h, 9 h};
NDSolveFiniteDifferenceDerivative[1, grid, values, DifferenceOrder -> 2]
```

```
\{-\frac{3a_0}{2h} - \frac{2a_1}{h} - \frac{a_2}{2h} - \frac{a_3}{2h}, \frac{a_1}{2h} - \frac{a_3}{2h}, \frac{a_2}{2h} - \frac{a_4}{2h}, \frac{a_3}{2h} - \frac{a_5}{2h}, \\
- \frac{a_4}{2h} - \frac{a_6}{2h} - \frac{a_7}{2h} - \frac{a_8}{2h} - \frac{a_9}{2h}, \frac{a_7}{2h} - \frac{a_9}{2h}, \frac{a_7}{2h} - \frac{a_8}{2h}, \frac{a_9}{2h} - \frac{a_8}{2h}\}
```

Figure 58 Execution of "NDSolveFiniteDifferenceDerivative" function in Wolfram Mathematica.
C. Zero phase digital filtering

If the Discrete Fourier Transform of a discrete signal is $x[n] \overset{DTFT}{\leftrightarrow} X(e^{j\omega})$ then $x[-n] \overset{DTFT}{\leftrightarrow} X^*(e^{j\omega})$ where $x[-n]$ is a reversed in time signal of $x[n]$. Supposing that the input signal is $x[n]$ and the high pass filter is described by $h[n] \overset{DTFT}{\leftrightarrow} H(e^{j\omega})$, then:

1) $Z[e^{j\omega}] = H[e^{j\omega}] \cdot X[e^{j\omega}]$. $z[n] \overset{DTFT}{\leftrightarrow} Z(e^{j\omega})$ is the output of the high pass filter
2) $z[n]$ is reversed to $w[n]$. $W[e^{j\omega}] = Z^*(e^{j\omega}) = H^*(e^{j\omega}) \cdot X^*(e^{j\omega})$
3) high pass filtering of $w[n]$ outputs to $v[n] \overset{DTFT}{\leftrightarrow} V(e^{j\omega})$. $V[e^{j\omega}] = H[e^{j\omega}] \cdot W[e^{j\omega}] = H[e^{j\omega}] \cdot H^*(e^{j\omega}) \cdot X^*(e^{j\omega})$
4) $v[n]$ is reversed to $y[n] \overset{DTFT}{\leftrightarrow} Y(e^{j\omega})$. $Y[e^{j\omega}] = H[e^{j\omega}] \cdot H^*(e^{j\omega}) \cdot X(e^{j\omega})$

Therefore, $y[n]$ is calculated through forward and backward high pass filtering of signal $x[n]$ because $y[n] \overset{DTFT}{\leftrightarrow} Y(e^{j\omega})$, $Y[e^{j\omega}] = H[e^{j\omega}] \cdot H^*(e^{j\omega}) \cdot X(e^{j\omega})$. 
