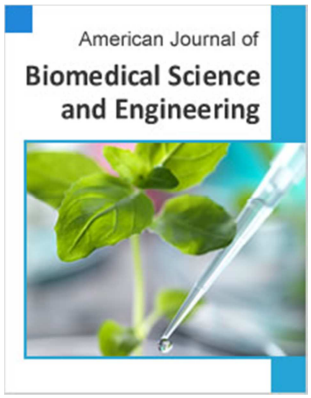
American Journal of Biomedical Science and Engineering
2017; 3(6): 54-63
http://www.aascit.org/journal/ajbse
ISSN: 2381-103X (Print); ISSN: 2381-1048 (Online)

American Association for Science and Technology



Keywords
Optical Imaging,
Near Infrared Spectroscopy,
Phase Space Plot,
Phase Space Analysis,
Movement Decoding,
Brain Hemodynamics

Received: May 1, 2017
Accepted: August 7, 2017
Published: October 17, 2017

Computational Method for Representing the Simultaneous Hemodynamic Relationship between Oxy-Hemoglobin Delivery and Deoxy-Hemoglobin Extraction in Neural Tissues

Nicoladie Tam[1, *], Luca Pollonini[2], George Zouridakis[2, 3, 4]

[1]Department of Biological Sciences, University of North Texas, Denton, USA
[2]Departments of Engineering Technology, University of Houston, Houston, USA
[3]Biomedical Engineering, University of Houston, Houston, USA
[4]Electrical & Computer Engineering, University of Houston, Houston, USA

Email address
nicoladie.tam@unt.edu (N. Tam)
[*]Corresponding author

Citation
Nicoladie Tam, Luca Pollonini, George Zouridakis. Computational Method for Representing the Simultaneous Hemodynamic Relationship between Oxy-Hemoglobin Delivery and Deoxy-Hemoglobin Extraction in Neural Tissues. *American Journal of Biomedical Science and Engineering*. Vol. 3, No. 6, 2017, pp. 54-63.

Abstract
In this study, we propose the use of phase space plot analysis to characterize coupling relationships between two simultaneously recorded hemodynamic variables, i.e., oxy-hemoglobin (oxy-Hb) and deoxy-hemoglobin (deoxy-Hb), using functional near-infrared spectroscopy (fNIRS). To demonstrate the validity of the proposed method, we analyze hemodynamic data recorded from human subjects performing an orthogonal movement task. Our results show that phase space plots can quantify the dynamic time-varying relationships between the two variables based on the trajectory of the loci of data points in the phase space plots. In particular, the location of the phase space plots in different quadrants provides a specific coupling relationship between the two hemodynamic variables. The orientation of the loci of points characterizes further the relationship between these two variables, which can be directly or inversely proportional. The locus of the trajectory along a straight line or an elliptical path can reveal the phase relationship between the two variables. Thus, using phase space analysis on these two simultaneously recorded hemodynamic variables can uniquely identify the movement direction encoded by the motor cortex.

1. Introduction

1.1. Optical Recording of Hemodynamic Signals

Recent advances in neuroimaging have provided many different methodologies for imaging brain activity noninvasively. One of the most recent brain-imaging methodologies is the use of near-infrared spectroscopy (NIRS) [1-9] to detect the changes in hemoglobin concentration in the brain. This serves as a representative measure of metabolic activity of the neural tissues activated by various brain functions. NIRS is an optical imaging technique that can detect changes in both oxy-Hb and deoxy-

Hb concentrations, which represent oxygen delivery to and oxygen extraction from tissues, respectively. The ability to detect the relative changes in concentration between the two types of hemoglobin is due to the unique signature in the absorption spectra of oxy-Hb and deoxy-Hb molecules that show distinct ratios at two different wavelengths (typically at 690 nm and 830 nm) in the near-infrared (NIR) range. The relative changes in hemoglobin concentrations are computed using the modified Beer-Lambert law [6, 8, 10].

This paper focuses on providing a quantitative analysis of simultaneously recorded neural signals using functional NIRS (fNIRS). Since NIR light can penetrate biological tissues, including the skull bones, neurons, and blood vessels, the use of fNIRS can provide a tool to image brain activity optically. The deoxy-Hb signals detected using fNIRS are similar to the deoxy-Hb BOLD (blood-oxygen dependent level) signals detected using fMRI (functional magnetic resonance imaging). Optical fNIRS brain imaging is performed by placing the NIR light emitters and detectors on the skull, such that the light absorption and light scattering are determined using physics laws and ray tracing along the (banana-shaped) bent path between the light emitter and detector. A major limitation of fNIRS is the depth of recording, which is limited to approximately 2 cm in the cortical tissue, beyond which the reduction in signal-to-noise ratio limits the accurate determination of the changes in Hb concentration [6, 11].

1.2. Simultaneous Recording of Changes in Oxy-Hb and Deoxy-Hb Concentrations

The additional advantage of fNIRS recordings is that it can detect changes in both oxy- and deoxy-Hb concentrations simultaneously. This can provide multiple measures of hemodynamic signals to reveal the dynamic interactions of oxygen delivery and oxygen extraction simultaneously. Although relative changes in oxy-Hb and deoxy-Hb concentrations are often computed by the modified Beer-Lambert law, the absolute concentrations of oxy-Hb and deoxy-Hb can also be computed using a bundled-optode technique recently [12]. Given that simultaneous oxy-Hb and deoxy-Hb concentrations are recorded, their dynamical interactions can reveal characteristics of the neural metabolic activities that may not be derived from measuring the single concentration of deoxy-Hb BOLD signal alone.

1.3. Dynamic Interactions Between Oxygen Delivery and Oxygen Extraction

Physiologically, it is well known that the oxy-Hb signal represents oxygen delivery to tissues, whereas the deoxy-Hb signal represents oxygen extraction from the tissue. Given that both oxy- and deoxy-Hb concentrations can be recorded simultaneously, it is often observed that these two hemodynamic signals are temporally coupled in brain tissues [13-19]. That is, most often (but not always) when deoxy-Hb concentration increases, oxy-Hb concentration decreases. This phenomenon is representative of hemodynamic events that when the amount of oxygen extraction (represented by deoxy-Hb level) increases, the measured amount of oxygen delivery (represented by oxy-Hb level) decreases due to extraction, if the blood supply (represented by oxy-Hb + deoxy-Hb) were to remain constant. That is, the amount of oxygen delivery from the capillaries to the tissue is the oxygen loaded in the blood vessels, and the unloaded amount of oxygen is the amount extracted from the tissue. The total blood volume supplied to the tissue can be represented by the sum of oxy-Hb and deoxy-Hb (oxy-Hb + deoxy-Hb). Thus, under most circumstances in aerobic metabolism, these two hemodynamic measures (oxy-Hb and deoxy-Hb) are often inversely coupled (or inversely correlated) because the amount of oxygen loading and unloading is limited by the total available amount of Hb in the blood supply (i.e., a zero-sum game). Most often, when metabolic demand increases, the total blood supply also increases (rather than remaining constant) in response to the changes. However, if the oxygen supply cannot meet the demand during peak metabolic condition, the above relationship between oxy-Hb and deoxy-Hb may be decoupled. This can result in a hypoxic condition.

1.4. Temporal Coupling and Decoupling of Oxy-Hb and Deoxy-Hb Signals

Under the above hypoxic conditions, when oxygen demand in metabolism exceeds the capacity for oxygen delivery, the above two hemodynamic measures of oxy-Hb and deoxy-Hb may not be inversely coupled. For instance, during extreme physical exercise, this anaerobic condition is especially noticeable in muscles, when the oxygen demand is so high that aerobic metabolism reaches the limiting-step. Under these circumstances, aerobic metabolism switches over to anaerobic metabolism in the periphery, but not in the central nervous system (CNS). During this rate-limiting condition at peak metabolism, oxy-Hb (oxygen delivery) and deoxy-Hb (oxygen extraction) may not be coupled.

For instance, this hypoxic condition can often be demonstrated in measurements of the Hb oxygen saturation during physical exercise using an oximeter. During normal resting state, the percentage range of oxygen saturation in Hb is usually recorded between 96% and 99%. However, under strenuous physical exercise conditions, the percentage of oxygen saturation in Hb can be reduced to below 96%, representing a hypoxic condition. At this point, when hypoxia occurs, the metabolism of muscle switches from aerobic to anaerobic metabolism to compensate for the insufficient supply of oxygen by the blood vessels. In contrast, brain metabolism relies solely on aerobic metabolism with limited ability to utilize anaerobic metabolism. Thus, it is important to quantify the dynamical relationship between oxy-Hb and deoxy-Hb levels in the brain under these exceptional conditions.

Thus the rationale for this paper is to address the computational method for quantifying the dynamic coupling relationships between oxy-Hb and deoxy-Hb signals under

different conditions of cognitive demands. It is essential to characterize the co-varying relationships between oxygen delivery (oxy-Hb) and extraction (deoxy-Hb) in order to determine the metabolic demand of the underlying brain tissue that analysis of a single deoxy-Hb variable in BOLD signals may not achieve. Even though the deoxy-Hb level is often used as a measure of oxygen extraction, it will be shown below that the simultaneous relationship between oxy-Hb and deoxy-Hb levels can better describe the intrinsic metabolic demand of the tissue in relation to the oxygen demand and oxygen supply of the blood.

2. Methods

2.1. Phase Space Analysis of Hemodynamic Variables

We propose to use phase space plots [20] to visualize the time evolution of trajectories of the hemodynamic systems in a phase plane. A phase space plot represents the co-varying relationship between two time-dependent dynamic variables, such as changes in oxy-Hb and deoxy-Hb concentrations in this case. A hemodynamic phase space plot is constructed by plotting the relative change of oxy-Hb concentration (ΔHbO) on the x-axis and the relative change of deoxy-Hb concentration (ΔHb) on the y-axis as a phase space diagram for each time step. The relative change (Δ) in concentration is often used in the fNIRS analysis because the traditional modified Beer-Lambert law computes only the relative change in Hb concentration rather than the absolute Hb concentration. Until recently, the absolute Hb concentration could be derived using an alternate computational method based on a bundled-optode method [12], in which case, the absolute Hb concentrations could be used in the phase space analysis.

Traditionally, phase space plots are used to describe the co-varying relationship between the simultaneous dynamics of two interacting variables in real time. The time evolution of the trajectory (locus) traced by the data points in the phase space diagram represents the phase space plot, which can reveal the time sequence of interactions between the two variables, in particular, the effects of *hysteresis*. Hysteresis refers to the history-dependent time lag of one variable in response to changes in another variable. Oftentimes, the effect is that the phase of one variable either lags behind the other or leads the other, depending on the prior history of these variables in relation to each other. This phase-lead or phase-lag relationship may be exhibited in the phase space analysis while the hemodynamic variables enter or exit the rate-limiting condition (when oxygen supply cannot meet the metabolic demand). Thus, phase space analysis of the hemodynamic variables oxy-Hb and deoxy-Hb can describe more than the conventional cross-correlation analysis between these two variables.

2.2. Construction of Phase Space Plots

Let $x(t)$ denotes the change in oxy-Hb concentration, and $y(t)$ denotes the change in deoxy-Hb, as a function of time, t. Then the phase space plot is constructed by plotting the time-series in the coordinate $(x(t), y(t))$. The representation of the correlation relationship between two hemodynamic variables (at any given time) can be described by the specific (quadrant) location of the data points $(x(t), y(t))$ in the x-y plot. Specifically, if the data points lie in the upper-right and lower-left quadrants, then they are positively correlated. Conversely, if the data points lie in the upper-left and lower-right quadrants, they are negatively correlated.

However, the hemodynamic variables are time-varying variables (as a function of time). Therefore, it is essential to determine the locus of the time-evolution of these co-varying relationships between these two variables in order to fully characterize their dynamic interactions. Their trajectory in clockwise direction vs. counter-clockwise direction can be used to determine the phase-lag vs. phase-lead relationship between them.

2.3. Interpretation of Hemodynamic Variables in Phase Space Plots

If the data points lie in a straight diagonal line, then the corresponding variables are directly proportional to each other. They are positively correlated with each other. Conversely, if the data points lie in a straight anti-diagonal line, the variables are inversely proportional to each other. They are anti-correlated to each other. Furthermore, if the data points lie along the diagonal line, the variables neither lag nor lead each other. That is, the two hemodynamic variables change simultaneously in synchrony with each other, without any time lag (delay) or lead with respect to each other.

However, if the hemodynamic variables do not change in synchrony, then the data points would lie beyond the diagonal line, such as along a circular or elliptical path, or along a Lissajous curve (or Bowditch curve). Conversely, non-diagonal loci would mean that one of the hemodynamic variables either leads or lags behind the other, and the two hemodynamic variables do not vary synchronously. These specific curves can also describe some complex harmonic relationship, or other complex dynamics between them (such as chaotic dynamics), which can be revealed by the specific trajectory described by the time evolution of the x-y data points of the changes in oxy-Hb and deoxy-Hb concentrations.

Since phase space analysis plots the data points in a 2-dimensional phase plane, the phase lag or phase lead relationship can be represented by the trajectory of time-evolution of the hemodynamic variables in either clockwise direction or counter-clockwise direction. Thus, the phase relationship between these two hemodynamic variables can be revealed by the locus in the phase space analysis, when the hemodynamic variables enter or exit the peak metabolic demand condition.

2.4. Experimental Methods for Recording Hemodynamic Variables

In order to obtain the simultaneous change of

concentrations in cerebral oxy-Hb and deoxy-Hb, we performed the optical imaging on the motor cortex and the prefrontal cortex (PFC) in human subjects using fNIRS recordings while the subjects performed repetitive arm-movement tasks. We choose to use repetitive arm-movements in order to improve the signal-to-noise (S/N) ratio of the recorded hemodynamic variables by using event-aligned signal averaging techniques for each movement direction. In order to maintain the fidelity of the original data, no smoothing or band-pass filter was applied to the data in the phase space analysis.

We recruited 83 normal volunteers from a population of college-age subjects to perform right-left and front-back arm movements in a horizontal plane of a desk. The subjects were asked to move their dominant arm between two points that are 25 cm apart. They were asked to perform movements in two different orthogonal directions (i.e., front-back and right-left directions) in two separate trials. The movements were either self-paced or initiated by the sound of a bell repeated every 4 seconds for 2 minutes. A resting state of non-movement was recorded prior to the onset, and again at the end of each movement trial. The two resting-state segments provided the baseline control for comparison between the movement and non-movement hemodynamic responses.

The Imagent™ fNIRS instrument (ISS Inc., Champaign, IL, USA) was used to record the optical signals between 2 detectors and 8 emitters in one headpiece placed over the motor cortex, and another 2 detectors and 8 emitters headpiece over the prefrontal cortex simultaneously. The sampling rate of the optical recordings was 10 Hz. The experimental procedure was approved by the Institutional Review Board at both University of Houston and University of North Texas.

Previous studies have demonstrated that there is a close approximation between electrical neural activation and metabolic hemodynamic activation [21]; therefore, a relationship between the electrical firing and the hemodynamic signals can be assumed [22]. These studies confirm our findings that the movement direction encoded in the neural firing signals can be decoded from the corresponding hemodynamic signals.

Previous electrophysiological studies have shown that volitional movement direction can be decoded by computing the population vector of the neural firing rate recorded from individual neurons using multi-electrodes implanted in the motor cortex [23-27]. Subsequent studies have also shown that orthogonal movement directions can be differentiated from each other by the difference in the time-varying profile of the oxy-Hb and deoxy-Hb responses [13-19].

2.5. Analytical Method for Phase Space Plots

To obtain the phase space plots for our analysis, we considered the two simultaneously recorded changes in concentrations of oxy-Hb and deoxy-Hb, which can be used to represent the corresponding neural activation/deactivation of the population of neurons between the optical emitter and detector. Analysis of these phase space plots allowed us to characterize the synchronized and desynchronized changes in oxy-Hb and deoxy-Hb hemodynamic responses during the arm-movement tasks.

In order to obtain better signal-to-noise ratio in the phase space plots, we performed averaging of the signals recorded during the repetitive movement by aligning the beginning of similar movements, i.e., aligning the onset time of the hemodynamic responses for all rightward movements within the same experimental episode, and separately for all leftward movements. This produced a time series of average hemodynamic signals from the beginning to end of a movement. For example, if the front-back arm movement was repeated 30 times, each of the time points in the resulting hemodynamic signal was the average of 30 samples in the phase space plot. In a similar fashion, we averaged all frontward and separately all backward trials before performing the phase space plot analysis.

3. Results

3.1. Hemodynamic Responses for Frontward and Backward Arm Movements

Figure 1 shows the phase space plot for the relative changes of concentration in oxy-Hb and deoxy-Hb recorded from the primary motor cortex in the dominant hemisphere of a representative subject to illustrate the capability of the above analytical technique.

The location of the optical channel emitter-detector pair in Figure 1 corresponds to the topographical representation of the arm area in the primary motor cortex in the left hemisphere of the dominant right-hand subject. Each ($x(t)$, $y(t)$) data point in the phase space plot represents a pair of signal-averaged relative changes in hemodynamic concentrations (ΔHbO, ΔHb) for each movement direction relative to the onset of movement. That is, the trajectory locus in the phase space plot is generated by the time series representing the time sequence of hemodynamic response from onset to end of the arm movement (in the same movement direction).

Furthermore, Figure 1 shows that most of the data points for the backward arm movement lie in the upper-left quadrant while most of the data points in the frontward movement lie in the lower-left quadrant. The location of the loci of data points in the upper-left quadrant for backward movement indicates that a relative decrease in oxy-Hb concentration changes synchronously with a relative increase in deoxy-Hb concentration.

The physiological interpretation is that when oxygen delivery decreases, it is synchronized with an increase in oxygen extraction for backward arm movement without any phase lead or phase lag. They are anti-correlated with each other, i.e., as one increases, the other decreases.

On the contrary, the location of the loci of data points in the lower-left quadrant for frontward movement indicates that a relative decrease in oxy-Hb concentration is also synchronized with a relative decrease in deoxy-Hb

concentration. That is, they both decrease simultaneously. The physiological interpretation is that when oxygen delivery decreases, it is synchronized with a decrease in oxygen extraction for frontward arm movement. This suggests that the hemodynamic responses may have reached the rate-limiting condition when oxygen supply cannot meet the demand, which results in both variables decrease simultaneously.

In relation to the specific movement direction, the hemodynamic response to backward movement is indicated by an increase in deoxy-Hb concentration while for frontward movement the deoxy-Hb concentration decreases relatively, even though oxy-Hb concentration continues to decrease for both opposing movement directions.

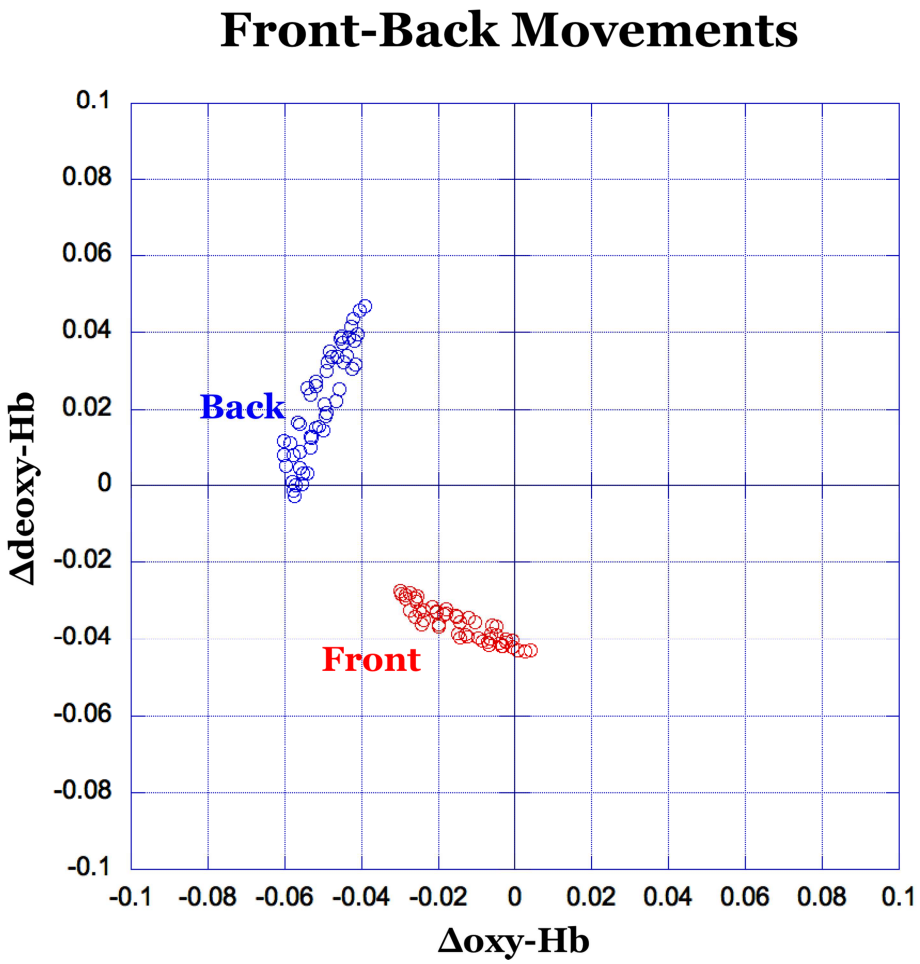


Figure 1. *Phase space plot representing relative changes in concentration for oxy-Hb vs. deoxy-Hb. Frontward arm movement is denoted by red circles and backward arm movement is denoted by blue circles. The loci of the data points for backward and frontward movements are located in different quadrants. The loci of points are also oriented in opposite diagonal-oriented and anti-diagonal oriented directions. The units in the x- and y-axes are in mM (millimoles) concentrations for ΔHbO and ΔHb, respectively.*

Thus, the phase space analysis reveals that the oxygen extraction rate is dependent upon movement directions, i.e., oxygen demand increases for backward-movement direction, but decreases for forward-movement direction. In contrast, the oxygen delivery rate remains to decrease, independent of whether the movement direction is frontward or backward.

This can be revealed by the loci of most data points which lie in the left quadrant for both backward and frontward movement directions, indicating a relative decrease in oxy-Hb concentration independent of the opposing (backward or frontward) movement directions. In other words, oxygen delivery decreases for both movement directions, while oxygen extraction increases for backward movement but decreases for frontward movement.

3.2. Identification of Three Different Hemodynamic Phenomena

In summary, the phase space analysis reveals three important phenomena of the hemodynamic responses to backward vs. frontward movements:

First, oxygen extraction increases for backward movement, which can be interpreted as neural activation by an increase in oxygen demand (as revealed by the loci of points in the upper quadrant in Figure 1). This suggests an increase in oxygen metabolism in the population of neurons recorded between the optical emitter and detector pair for backward movement. On the other hand, oxygen extraction decreases for frontward movement, which can be interpreted as neural deactivation by a decrease in oxygen demand (as revealed by

the loci of points in the lower quadrant in Figure 1). This suggests a decrease in oxygen metabolism in the same population of neurons recorded between the optical emitter and detector pair for frontward movement. Yet, oxygen delivery decreases in both movement directions, independent of oxygen extraction by the neural tissue. In other words, oxygen supply decreases for both movement directions, while oxygen demand increases for backward movement but decreases for frontward movement.

Second, even though oxy-Hb concentration decreases in both movement directions (as indicated by the loci of points located in the left quadrants in the phase space plot in Figure 1), the relative changes in concentration with respect to oxy-Hb and deoxy-Hb are opposite to each other. In other words, changes in oxy-Hb concentration are directly proportional to the relative changes in deoxy-Hb concentration for backward movement (as revealed by the diagonally-oriented loci in Figure 1). On the contrary, changes in oxy-Hb concentration are inversely proportional to the relative changes in deoxy-Hb concentration for frontward movement (as revealed by the anti-diagonally-oriented loci in Figure 1).

Third, the loci of points in Figure 1 lie along the off-axis, diagonally-oriented or anti-diagonally-oriented line without any circular trajectory. This indicates that there is little or no time lag or time lead in hemodynamic responses between the oxy-Hb and deoxy-Hb signals.

3.3. Hemodynamic Responses for Rightward vs. Leftward Movements

Figure 2 shows the phase space plot of oxy-Hb vs. deoxy-Hb (for the same population of neurons recorded by the optode pair in Figure 1) for rightward and leftward arm movements. This analysis is to illustrate the different hemodynamic responses revealed by the phase space plot for orthogonal movement directions.

It can be seen that the loci of the trajectory of data points for rightward movement are located in the upper-left quadrant, while for leftward movement, most of the data points are located in the lower-left quadrant. The phase space plot reveals that the same population of neurons participated in both orthogonal directions (front-back and right-left directions), but the hemodynamic responses show different characteristics in their trajectories in the phase space plot.

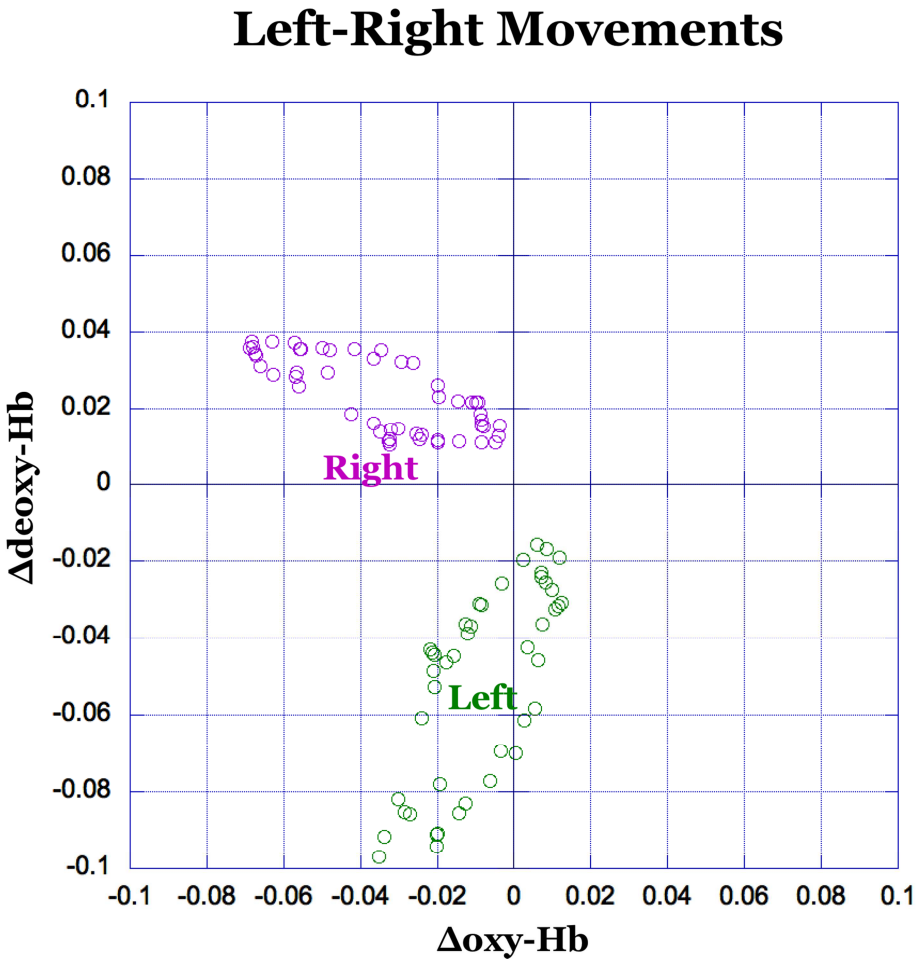


Figure 2. *Phase space plot of oxy-Hb vs. deoxy-Hb for rightward (purple circles) and leftward (green circles) movement recorded from the same optode emitter-detector pair as in Figure 1. This shows that loci and orientation of data points for front-back and right-left movements can be differentiated from each other based on this phase space plot analysis.*

Although the loci of data points are in the upper-left quadrant for rightward movement as for backward movement, the orientation of the loci of the data points is opposite (see Figure 3). That is, for rightward movement, the loci of points lie along an elliptical trajectory oriented in an antidiagonal-oriented direction. They are anti-correlated with each other.

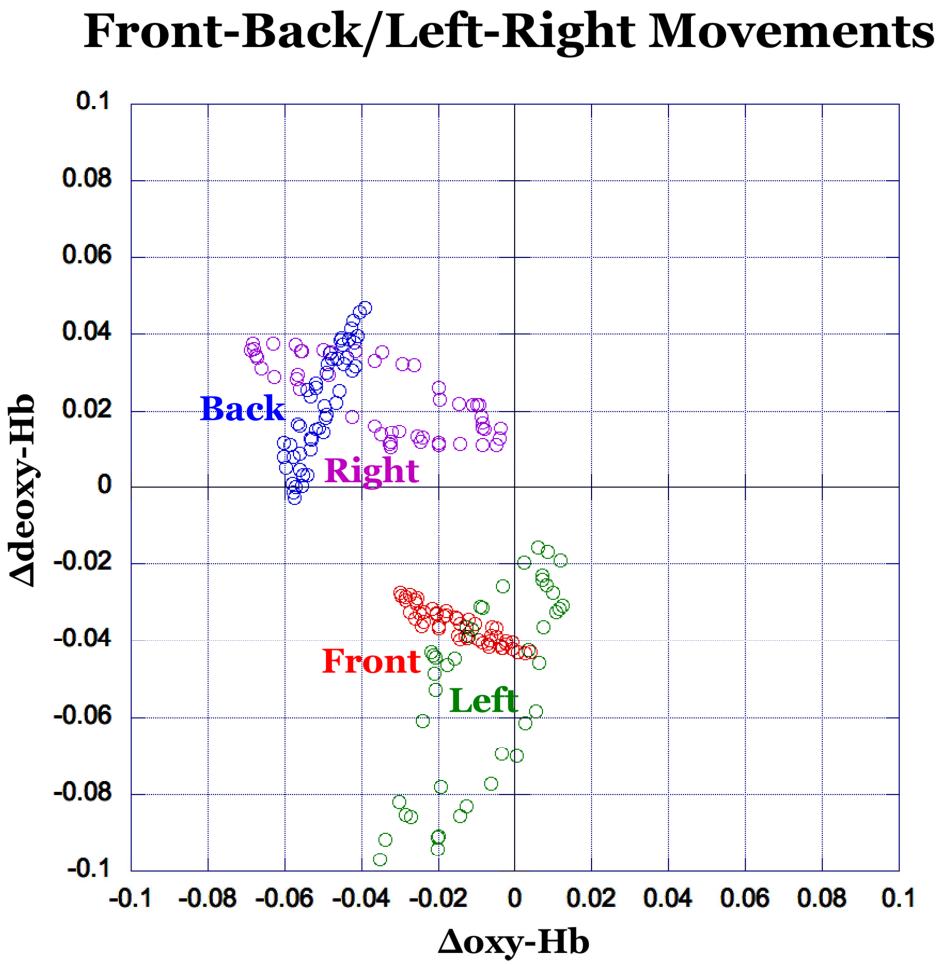


Figure 3. *Combined phase space plot of Figures 1 and 2 showing all 4 orthogonal movement directions in the same plot to illustrate the orientations of the trajectory and quadrant locations of the hemodynamic variables.*

However, for backward movement (see Figures 1 and 3), the loci of data points lie along a straight line in a diagonal-oriented direction. In other words, oxy-Hb and deoxy-Hb are directly correlated for backward movement but anti-correlated for rightward movement. Furthermore, the elliptical trajectory shows that there is a phase difference in the coupling relationship for rightward movement direction, whereas there is little or no phase difference in the coupling relationship when the loci of data points lie in a straight line (instead of along an elliptical path) for rightward movement.

Similarly, for leftward movement, most of the loci of points are found in the lower-left quadrant, even though the orientation of the elliptical trajectory of points is aligned in the diagonal direction. Thus, even though for both frontward and leftward movements the loci of data points are located in the lower-left quadrant, their orientations are different. Furthermore, the trajectory of the loci of points is elliptical for leftward movement, but they lie along a straight line for frontward movement (see Figure 1).

Again, it shows that there are similarities between the loci of data points in the lower-left quadrant for both frontward and leftward movements, their orientations are not only different but also follow a straight line rather than an elliptical trajectory. Thus, the phase space plot reveals that leftward movement differs from the frontward movement by the phase difference for leftward movement but little or no phase-difference for frontward movement.

This suggests oxygen extraction increases while oxygen delivery decreases for rightward movement. On the other hand, for leftward movement, oxygen extraction decreases as oxygen delivery primarily decreases with a phase difference (indicated by the elliptical trajectories). On the contrary, there is little or no phase difference for frontward or backward movements (indicated by the linear trajectories) (see Figures 1 and 3).

Most importantly, we are able to distinguish the difference between different movement directions in the phase space plot, even though there are overlaps of data points in the same quadrant for orthogonal movements (such as frontward

and leftward movements). The ability to differentiate the movement direction is based on the orientation of the loci of the trajectory in the time evolution of the data points. For leftward movement, the trajectory is oriented in the diagonal orientation, whereas frontward movement is oriented in the anti-diagonal orientation. Furthermore, the locus of data points is elliptical for leftward movement, while frontward movement exhibits a linear or near-elliptical locus.

In other words, it is the phase relationship between these two hemodynamic variables that allows us to differentiate the different hemodynamic responses to orthogonal movement directions. Without examining the phase relationship, the hemodynamic responses of orthogonal movement directions cannot be discerned easily (because the data points are overlapped). This demonstrated that if a single hemodynamic variable (such as either oxy-Hb or deoxy-Hb alone) were used in the analysis, the orthogonal movement directions would not be distinguished from each other.

4. Discussions

4.1. Differential Changes of Oxy-Hb and Deoxy-Hb Concentrations

The above phase space plot analysis illustrated some intriguing differential dynamics of synchronized coupling and desynchronized coupling between the changes in oxy-Hb and deoxy-Hb concentrations, depending on whether the movement direction is frontward or backward, rightward or leftward. The differential coupling and decoupling can be synchronized or desynchronized with a phase difference of oxygen delivery and extraction. These captivating hemodynamic responses can be revealed by the loci of points in the different quadrants of the phase space plot as well as the orientation, and the elliptical vs. straight trajectory of the data points. Specifically, opposing and orthogonal movement directions can be decoded from:

(1) the loci of points in different quadrants of the phase space plot;
(2) the diagonal-oriented or anti-diagonal-oriented loci of points irrespective of which quadrant they are located in; and
(3) the linear or elliptical trajectory of the time evolution of the data points.

This phase space analysis shows that the phase space plot can be used as an effective computational tool to identify complex hemodynamic responses between the relative changes in oxy-Hb and deoxy-Hb concentrations. Effectively, the phase space analysis can reveal not only whether the Hb concentrations increase or decrease simultaneously or with a phase difference, but also whether such changes are directly or inversely proportional to each other for opposite and/or orthogonal movement directions.

4.2. Coupling and Decoupling Relationships

The phase space hemodynamic analysis illustrated that the same population of neurons participated in all four orthogonal and opposite movement directions, with various differential coupling and synchronization relationships with respect to oxy-Hb and deoxy-Hb concentrations. The changes in hemodynamic response are not necessarily opposite of each other for opposite movement directions; rather, such changes can be complementary to each other with differential synchrony, coupling relationship, and phase difference.

This analysis is complementary to the population vector representation of movement direction by computing the vectorial sum of individual neuronal firings in an ensemble of neurons in the primary motor cortex [23, 26-29]. It is congruent with the interpretation that the same population of neurons can encode different movement directions depending on the differential firing rates among the neurons in the population ensemble. Yet, this phase space analysis of the optical imaging of the neural activation/deactivation patterns using fNIRS revealed that movement directions can be encoded by the scalar sum of the neural population activation/deactivation patterns (instead of the vectorial sum of the firing rates).

4.3. Dissociated Oxygen Extraction and Delivery

This phase space analysis demonstrated that the oxygen demand of neural tissue during a movement differs depending upon the movement direction: oxygen extraction increases in one movement direction but decreases in the opposite direction. This opposing relationship is true for both front-back and right-left movement directions. On the other hand, oxygen delivery remains to decrease for all movement directions, i.e., for both opposite and orthogonal movement directions. Yet, the physiological relationships between oxygen delivery and extraction are different for the orthogonal movement directions. That is, a front-back movement demands different oxygen from a right-left movement.

4.4. Synchronized and Desynchronized Hemodynamic Relationships

Front-back movements show little or no phase difference (as revealed by a linear trajectory), but right-left movements show phase differences (as revealed by the elliptical trajectory). Thus, the location of the quadrant, the orientation, and the trajectory shape of the linear vs. elliptical path can all be used to identify the subtle but revealing differences in the relationships between the simultaneously recorded hemodynamic variables.

4.5. Correlation of Two Simultaneously Recorded Hemodynamic Variables (oxy-Hb and deoxy-Hb)

If a single hemodynamic variable, such as deoxy-Hb concentration, were recorded (by fMRI BOLD signals) without the other oxy-Hb hemodynamic variable, the proposed phase space analysis would not be possible. Without the intriguing, yet tale-telling characteristics

captured by the phase space plots it would not be possible to separate the different hemodynamic responses, and therefore, we would not be able to differentiate orthogonal from opposite-direction movements.

4.6. Determination of Movement Direction without using a Population Vector

It should also be noted that the same population of neurons in the primary motor cortex is participating in both orthogonal and opposite direction movements, with differing hemodynamic relationships between the changes in oxy-Hb and deoxy-Hb concentrations. More specifically, this phase space analysis is consistent with the population vector hypothesis that the same subpopulation of neurons can participate in issuing the motor command signals to execute different movement directions by generating different firing patterns [23, 26-29].

4.7. Determination of Movement Direction without Using Hundred Simultaneous Recorded Firing Rates

The noticeable difference between these two analyses is that the final movement generated by the population vector hypothesis is the vectorial sum of the preferred movement direction of a large number of neurons (about 100) within a specific subpopulation in the motor cortex. In contrast, in the phase space analysis, the resulting movement direction is represented by the presumably scalar (non-vectorial) sum of the metabolic hemodynamic signals within the neuronal subpopulation sampled by the optode pairs.

In contrast, population vector computation of movement direction requires recording of approximately one hundred individual neurons using (invasive) implanted electrodes. The reduction from one hundred variables (in population vector analysis) describing firing rates to two hemodynamic variables (in phase space plot analysis) is a significant saving in computational power to decode movement directions. Most importantly, the noninvasive recordings based on optical imaging are often preferred by paralyzed patients over the use of invasive electrode implants to decode of movement direction that is required for population vector analysis.

4.8. Hemodynamic Responses for Non-Orthogonal Movement Directions

To illustrate the capability of phase space analysis to identify the intriguing relationships between oxy-Hb and deoxy-Hb concentration, we have chosen to use orthogonal movement directions on a horizontal plane to demonstrate the presence of various couplings, types of synchronization, and phase-difference relationships. In real life, movements are performed in any arbitrary directions in three dimensions. This does not preclude the use of phase space analysis to identify any arbitrary unconstrained movement direction. The choice of using an orthogonal movement direction to demonstrate the capability of phase space analysis is also based on the future plan to implement such computational method to drive a wheelchair to assist paraplegic patients to perform brain-activated control of wheelchair. It is our goal to develop a BCI (brain-computer-interface) as a neuro-prosthetic device to provide hands-free navigation of a wheelchair by physically impaired patients.

Finally, even though we have used the hemodynamic responses for a single human subject to illustrate the capability of the phase space analysis, this same analysis can be applied to the averaged response for a population of human subjects in order to identify the trend of responses. Furthermore, if a different optode-pair is used in the analysis [18] (i.e., recording from a different part of the motor cortex), the orientations and the loci in the quadrant of the data points for orthogonal and opposite movement directions would be different because different subpopulation (sub-network) of neurons encoding different parts of the body in the motor cortex cooperate differently in their neural responses to the same movement direction.

This analysis demonstrated that phase space analysis can provide a reduced dimensional analysis in 2-D phase plane without the need for multidimensional analysis of a population vector to characterize the internal dynamics within a subpopulation of neurons.

5. Conclusion

The proposed computational method of phase space analysis can quantitatively characterize the interactions between two simultaneously recorded hemodynamic response variables, namely oxy-Hb and deoxy-Hb, in a 2-D phase space. The phase space plot of these two hemodynamic variables is characterized by the specific location of the data points in different quadrants, with different orientations, and different phase relations (which are revealed by an elliptical or linear trajectory). The corresponding relationships between the oxygen extraction and delivery can also be revealed physiologically in terms of whether oxygen supply can meet the demand during peak metabolism of the neural tissues, at different phases of physiological function (movement direction in this case example).

Acknowledgements

We thank Ms. Krista Smith for proofreading this manuscript.

References

[1] B. Abibullaev and J. An, "Classification of frontal cortex haemodynamic responses during cognitive tasks using wavelet transforms and machine learning algorithms," *Medical Engineering and Physics,* vol. 34, pp. 1394-1410.

[2] M. Ferrari and V. Quaresima, "A brief review on the history of human functional near-infrared spectroscopy (fNIRS) development and fields of application," *Neuroimage,* vol. 63, pp. 921-35, Nov 1 2012.

[3] C. Hirth, H. Obrig, J. Valdueza, U. Dirnagl, and A. Villringer, "Simultaneous assessment of cerebral oxygenation and hemodynamics during a motor task. A combined near infrared and transcranial Doppler sonography study," *Adv Exp Med Biol,* vol. 411, pp. 461-9, 1997.

[4] Y. Hoshi, "Towards the next generation of near-infrared spectroscopy," *Philos Trans A Math Phys Eng Sci,* vol. 369, pp. 4425-39, Nov 28 2011.

[5] N. Liu, X. Cui, D. M. Bryant, G. H. Glover, and A. L. Reiss, "Inferring deep-brain activity from cortical activity using functional near-infrared spectroscopy," *Biomed Opt Express,* vol. 6, pp. 1074-89, Mar 1 2015.

[6] B. Montcel, R. Chabrier, and P. Poulet, "Time-resolved absorption and hemoglobin concentration difference maps: a method to retrieve depth-related information on cerebral hemodynamics," *Opt Express,* vol. 14, pp. 12271-87, Dec 11 2006.

[7] H. Obrig, C. Hirth, J. G. Junge-Hulsing, C. Doge, T. Wolf, U. Dirnagl*, et al.*, "Cerebral oxygenation changes in response to motor stimulation," *J Appl Physiol,* vol. 81, pp. 1174-83, Sep 1996.

[8] A. Pellicer and C. Bravo Mdel, "Near-infrared spectroscopy: a methodology-focused review," *Semin Fetal Neonatal Med,* vol. 16, pp. 42-9, Feb 2011.

[9] V. Toronov, A. Webb, J. H. Choi, M. Wolf, A. Michalos, E. Gratton*, et al.*, "Investigation of human brain hemodynamics by simultaneous near-infrared spectroscopy and functional magnetic resonance imaging," *Med Phys,* vol. 28, pp. 521-7, Apr 2001.

[10] W. B. Baker, A. B. Parthasarathy, D. R. Busch, R. C. Mesquita, J. H. Greenberg, and A. G. Yodh, "Modified Beer-Lambert law for blood flow," *Biomed Opt Express,* vol. 5, pp. 4053-75, Nov 1 2014.

[11] H. Watanabe, M. A. Sato, T. Suzuki, A. Nambu, Y. Nishimura, M. Kawato*, et al.*, "Reconstruction of movement-related intracortical activity from micro-electrocorticogram array signals in monkey primary motor cortex," *J Neural Eng,* vol. 9, p. 036006, Jun 2012.

[12] H. D. Nguyen, K. S. Hong, and Y. I. Shin, "Bundled-Optode Method in Functional Near-Infrared Spectroscopy," *PLoS One,* vol. 11, p. e0165146, 2016.

[13] N. D. Tam and G. Zouridakis, "Optical imaging of motor cortical hemodynamic response to directional arm movements using near-infrared spectroscopy," *International Journal of Biological Engineering,* vol. 3, pp. 11-17, 2013.

[14] N. D. Tam and G. Zouridakis, "Temporal decoupling of oxy- and deoxy-hemoglobin hemodynamic responses detected by functional near-infrared spectroscopy (fNIRS)," *Journal of Biomedical Engineering and Medical Imaging,* vol. 1, pp. 18-28, Aprill 6, 2014 2014.

[15] N. D. Tam and G. Zouridakis, "Decoding movement direction from motor cortex recordings using near-infrared spectroscopy," in *Infrared Spectroscopy: Theory, Developments and Applications*, ed Hauppauge, NY: Nova Science Publishers, Inc., 2014.

[16] N. D. Tam and G. Zouridakis, "Decoding of movement direction using optical imaging of motor cortex," in *BMC Neuroscience*, 2013, p. P380.

[17] N. D. Tam and G. Zouridakis, "Optical imaging of motor cortical activation using functional near-infrared spectroscopy," *BMC Neuroscience,* vol. 13, p. P27, 16 July 2012 2012.

[18] N. D. Tam, L. Pollonini, and G. Zouridakis, "Decoding movement direction using phase-space analysis of hemodynamic responses to arm movements based on functional near-infrared spectroscopy," in *38th Annual International Conference of the IEEE Engineering in Medicine & Biology Society*, Orlando, FL, 2016, pp. 1580-1583.

[19] N. D. Tam, L. Pollonini, and G. Zouridakis, "Phase space analysis of hemodynamic responses to intentional movement directions using functional near-infrared spectroscopy (fNIRS) optical imaging technique," in *25th Annual Computational Neuroscience Meeting: CNS-2016*, Jeju, South Korea, 2016, p. 54.

[20] J.-P. Eckmann, S. O. Kamphorst, and D. Ruelle, "Recurrence plots of dynamical systems," *EPL (Europhysics Letters),* vol. 4, p. 973, 1987.

[21] N. K. Logothetis, J. Pauls, M. Augath, T. Trinath, and A. Oeltermann, "Neurophysiological investigation of the basis of the fMRI signal," *Nature,* vol. 412, pp. 150-7, Jul 12 2001.

[22] T. Obata, T. T. Liu, K. L. Miller, W. M. Luh, E. C. Wong, L. R. Frank*, et al.*, "Discrepancies between BOLD and flow dynamics in primary and supplementary motor areas: application of the balloon model to the interpretation of BOLD transients," *Neuroimage,* vol. 21, pp. 144-53, Jan 2004.

[23] A. B. Schwartz, R. E. Kettner, and A. P. Georgopoulos, "Primate motor cortex and free arm movements to visual targets in three-dimensional space. I. Relations between single cell discharge and direction of movement," *J Neurosci,* vol. 8, pp. 2913-27, Aug 1988.

[24] A. B. Schwartz, D. M. Taylor, and S. I. Tillery, "Extraction algorithms for cortical control of arm prosthetics," *Curr Opin Neurobiol,* vol. 11, pp. 701-7, Dec 2001.

[25] A. B. Schwartz, "Direct cortical representation of drawing," *Science,* vol. 265, pp. 540-2, Jul 22 1994.

[26] A. P. Georgopoulos, R. E. Kettner, and A. B. Schwartz, "Primate motor cortex and free arm movements to visual targets in three-dimensional space. II. Coding of the direction of movement by a neuronal population," *J Neurosci,* vol. 8, pp. 2928-37, Aug 1988.

[27] A. P. Georgopoulos, A. B. Schwartz, and R. E. Kettner, "Neuronal population coding of movement direction," *Science,* vol. 233, pp. 1416-9, Sep 26 1986.

[28] R. E. Kettner, A. B. Schwartz, and A. P. Georgopoulos, "Primate motor cortex and free arm movements to visual targets in three-dimensional space. III. Positional gradients and population coding of movement direction from various movement origins," *J Neurosci,* vol. 8, pp. 2938-47, Aug 1988.

[29] S. Lin, J. Si, and A. B. Schwartz, "Self-organization of firing activities in monkey's motor cortex: trajectory computation from spike signals," *Neural Comput,* vol. 9, pp. 607-21, Apr 1 1997.