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Exploring neuro-vascular and neuro-metabolic coupling in rat somatosensory cortex

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Abstract

The existence of a coupling between changes in neuronal activity, cerebral blood flow and blood oxygenation is well known. The explicit relationship between these systems, however, is complex and remains a subject of intense research. Here, we use direct electrophysiological recordings to predict blood flow and oxygenation changes measured with optical methods during parametric stimulation applied to the somatosensory cortex in rat brain. Using a multimodal model of the cerebral functional unit, we estimate a neurovascular and a neuro-metabolic transfer function relating the experimentally measured neural responses with the inputs to a vascular model predicting hemodynamic and blood oxygenation changes. We show that our model can accurately predict experimentally measured parametric hemodynamic evoked responses by using a single linear transfer function relationship with a reduced number of state parameters to relate the level of neural activity to evoked cerebral blood flow and oxygen metabolism changes. At the same time, we characterize the metabolic and vascular neural response functions and interpret their physiological significance.

1. Introduction

The ability to observe functional activation of the human brain has been progressing rapidly in recent years through the advancement of several hemodynamic-dependent techniques, such as optical methods (Villringer and Chance 1997, Strangman *et al* 2002), functional magnetic resonance imaging (Moonen and Bandettini 1999, Ogawa *et al* 1990) and positron emission tomography (Carson *et al* 1998). These techniques are primarily used to study changes in brain activity at the metabolic and vascular levels, thus providing a picture of what happens in the brain following neuronal activation. Electro-encephalography (EEG) and magneto-encephalography (MEG) provide more direct measures of the underlying neuronal activation, but these imaging technologies have limitations to their spatial resolution and identification of unique brain activation patterns. Regardless of whether neural or vascular-based imaging methods are used, the picture provided is incomplete. The ability to provide a comparison between these two types of experiments is crucial to furthering understanding of the brain and providing an interpretation of results from across the growing number of studies utilizing differing and in some cases concurrent multi-modal neuroimaging techniques. Currently, the intrinsic relationships between neuronal activation and the resulting metabolic and vascular responses are poorly understood (Buxton *et al* 2004, Riera *et al* 2008).

At the biochemical level, neural–vascular and neural–metabolic relationships have intensely been studied (see Aubert *et al* (2001), Aubert and Costalat (2002) for an overview); however, the relationship of these microscopic results to human-scale neuroimaging studies is difficult. The introduction of vascular descriptions, such as the Balloon model proposed by Buxton *et al* (1998), and the Windkessel model by Mandeville *et al* (1999), and their later advancements to consider oxygen transport into the tissue from the different vascular compartments (Zheng *et al* 2002, 2005, Vazquez *et al* 2006, Huppert *et al* 2007), has offered tools to study the interplay between blood flow, volume and oxygenation and observable hemodynamic measurements made by fMRI or optical methods. Connecting these vascular and oxygen transport models to the underlying neuronal activity, however, is more complex. Friston *et al* (2000) included the dynamics of perfusion changes that are contingent on underlying synaptic activation to describe hemodynamics as predicted by the Balloon model in an input-state-output model. This model used a fixed canonical linear transfer function to model these neuro-vascular and neuro-metabolic relationships, which provided predictive information about the fMRI signal, but did not provide a means to directly estimate the parameters of this transfer function. Conversely, Riera *et al* (2005) proposed a bottom-up approach to estimate parameters from electroencephalogram (EEG) and fMRI fused data on humans and link neural-source and vascular-source signals. In the Rierra model, both EEG and fMRI data were treated as observable outputs of the system and the model was inverted in order to estimate the internal parameters and states within the model that jointly predicted these dual outputs. This model provided a framework to empirically estimate the neuro-vascular relationship, but made assumptions about the linearity of this relationship by relying on a biologically-plausible, but untested, model.

The purpose of this study was to investigate the plausibility of a linear transfer function relating underlying neural, metabolic and vascular changes, which formed the basis of both the Rierra and Friston models. We hypothesized that given the neural information as an input one can predict the corresponding vascular and metabolic changes through a canonical transfer function that characterizes the system. In this work, we develop a model to estimate both these neuro-metabolic and neuro-vascular transfer functions by simultaneously considering concurrent electrophysiological and hemodynamic measurements. Our model, which is an extension of our multi-compartment Windkessel model as described by Huppert *et al* (2007), uses a bounded nonlinear parameter estimation routine to predict the values of the underlying system. By considering the electrophysiological measurements as inputs rather than the naive stimulus onset and stimulus condition information provided solely by the experimental design, we provide a neural basis for the estimated metabolic and vascular responses to the stimulus, while at the same time significantly reducing the number of model parameters when analyzing experimental data of parametric stimuli. Below we describe our model, analysis of experimental data from parametric rat whisker stimulation, and discuss the physiological significance of the estimated neuron-metabolic and neuron-vascular transfer functions.

2. Methods

2.1. Experimental procedures

The experimental data used in this study have been published in Huppert *et al* (2007). In brief, we performed the following procedure.

2.1.1. Animal protocol—We used seven male Sprague–Dawley rats (250–350 g), which were anesthetized with 2% halothane and prepared as previously described by Dunn *et al* (2005). The skull over the somatosensory cortex was thinned until transparent. After surgery, the anesthetic was switched to 50 mg kg⁻¹ bolus of α -chloralose followed by continuous

infusion at $40 \text{ mg kg}^{-1} \text{ h}^{-1}$. The MGH Subcommittee on the Research Animal Care approved all the experimental procedures.

The stimulation protocol consisted of a single whisker deflection with varying amplitude, 2 s of duration and at 8 Hz, similar to Devor *et al* (2003). The deflection varied from $240 \mu\text{m}$ to $1200 \mu\text{m}$, divided into nine different conditions with equal amplitude increments. Stimuli were presented using a rapid, randomized event-related paradigm.

2.1.2. Electrophysiology—Single metal microelectrodes (FHC, Bowdoinham, ME, 5–17 M Ω) were used for electrophysiological recordings. The recorded potential was amplified and filtered into two different signals (Ulbert *et al* 2001): one referred to as the local field potential (LFP) (low-pass filtered, 0.1–500 Hz) and the other high-pass filtered (150–5000 Hz) to provide multiple unit activity (MUA). Then the MUA data were smoothed along the time axis using a Gaussian kernel of 1 ms full width at e^{-1} of peak amplitude. Both LFP and MUA responses were normalized to the peak amplitude of the ninth condition before group averaging.

We analyzed both the peak magnitude and the integrated amplitude of the LFP and MUA responses. The peak magnitudes were defined as the magnitude of the first evoked response in the stimulus train; the integrated electrical response was defined as the sum of the amplitudes for the entire two s train of responses.

2.1.3. Optical imaging—Multi-wavelength spectroscopic imaging of total hemoglobin concentration and oxygenation were performed. The cortex was illuminated by a filtered mercury xenon arc lamp (10 nm band-pass filters centered at six different wavelengths: 560, 570, 580, 590, 600 and 610 nm). Images were acquired onto a cooled 12 bit CCD camera at a frame rate of 18 Hz. Oxy- and deoxy-hemoglobin concentration changes were calculated from the modified Beer–Lambert law. Differential path-length factors were used to account for the individual optical path lengths at each wavelength (Kohl *et al* 2000).

Blood flow was also measured using laser speckle contrast (Dunn *et al* 2001). Images of relative cerebral blood flow (CBF) changes were determined by calculating the changes in the speckle contrast in a series of laser speckle images, and then were averaged across trials and the averaged set was converted to relative blood flow by converting each speckle contrast value to an intensity autocorrelation decay time (Briers 2001) and dividing by baseline (Dunn *et al* 2005). Both laser speckle and spectroscopic results were deconvolved using the stimulus presentation timing to determine the blood flow and hemoglobin responses, respectively. Regions of interest were defined by manually selecting a region enclosing the barrel cortex corresponding to the stimulated whisker. A group average of the seven animals was calculated after normalizing to the amplitude of the ninth condition (the largest whisker deflection amplitude).

2.2. Estimating the neuro-metabolic and neuro-vascular transfer functions

The relationship between the underlying level of neural activity and the corresponding hemodynamic responses is hypothesized to be represented by linear and time-invariant (LTI) transformations from electrophysiological activity to both the vascular and metabolic responses (Nangini *et al* 2006). This hypothesis is implied in both the Friston *et al* (2000) and Riera *et al* (2005) models and that neuronal activity can be used to predict both the vascular and/or metabolic responses. The convolution of the neuronal signal with the corresponding transfer function to give a model of blood flow and oxygen metabolism changes forms the inputs to the vascular and oxygen transport models, which predict changes in deoxy- and oxy-hemoglobin, blood volume and flow changes.

By measuring neuronal activity and the vascular response simultaneously, we were able to use neuronal information to guide temporal dynamic changes of the active dilation of the arteries (arterial dilation, D_A) and the cerebral metabolic rate of oxygen ($CMRO_2$) by a convolution of the electrophysiology recordings ($N(t)$) with the transfer functions $f(t)$ to be estimated (see section 2.4):

$$\Delta D_A(t) = \int_{-\infty}^{\infty} N(\tau) \cdot f_{D_A}(t - \tau) d\tau \quad (1)$$

$$\Delta CMRO_2(t) = \int_{-\infty}^{\infty} N(\tau) \cdot f_{O_2}(t - \tau) d\tau. \quad (2)$$

The results of these convolutions form the input for the vascular model, specifically equations (8) and (14) by Huppert *et al* (2007). (The conversion of arterial dilation to arterial resistance is given by Poiseuille's law, equation (7) in the cited paper.) The changes in the dynamic states that describe the transfer functions were assumed to have a gamma-variant functional form,

$$f(t) = \Theta(t - \tau_0) \frac{(t - \tau_0)^2 \cdot \Delta f}{N} \exp\left(\frac{-(t - \tau_0)^2}{\sigma^2}\right), \quad (3)$$

where the function $\Theta(t)$ represents the Heaviside-step function, and τ_0 and σ are the onset (delay) time and temporal width of the response, respectively. Δf represents the amplitude change and N is a normalizing factor. These transfer functions are determined by three free parameters (amplitude, onset time and width).

2.3. Description of the vascular model

Huppert *et al* (2007) described a multi-compartment Windkessel model using an inductive approach where both vascular and metabolic parameters are estimated by inverting a nonlinear state-space model which describes the dynamic responses of blood flow, blood volume and oxygenation. The forward model is divided into both vascular and oxygen transport equations which separate contributions from the arteries, capillaries and veins for the cerebral hemodynamic changes, as well as the oxygen content changes in the surrounding bulk extra-vascular tissue.

The vascular component of this model is derived from an analogy of electrical circuits to fluid mechanics based on a dilating arteriole, two compliant vascular Windkessel compartments (Cope 1965) and a constant volume compartment that models the pial veins. The model relies on the original description of the single compartment Balloon/Windkessel model described by Buxton *et al* (1998) and by Mandeville *et al* (1999). In summary, changes in arterial diameter are used as input driving states to the calculation of the blood flow between each compartment, which is derived from the gradient of the hydrostatic pressure between the compartments and the vascular resistance of the blood vessels. The latter is inversely related to the diameter of the blood vessels according to Poiseuille's law and thereby related to vascular volumes.

For the metabolic component, the oxygen transport forward model is based on the calculation of the oxygen content in the vascular segments and the bulk extra-vascular parenchyma tissue, using the oxygen transport model described by Herman *et al* (2006). The rate of transport across each vascular segment depends on the relative permeability of the segment, which can be described by first-order differential equations and determined from steady-state flow and baseline oxygen saturation.

2.4. Fitting procedures

The temporal characteristics of the full cerebral-vascular system are determined by a set of lumped model parameters that define the static and baseline properties of the vascular network such as the vascular compliance, vascular transit time and baseline oxygen saturations of each compartment. In general, these unknown parameters may vary between subjects and vascular regions and thus must be estimated as part of the model. A total of 14 independent states, described below, are fit to each dataset, and the transfer functions that determine the neurovascular and neuro-metabolic coupling are estimated within the physiological range given by the constraint bounds.

The state vector consists of both structural and functional properties of the system. The former relies on unknown physiological constants and proposed Windkessel parameters that are expected to remain constant for different stimulus conditions. The functional properties represent the transfer functions from the neuronal to metabolic and hemodynamic responses, which should also be the same between different stimulus conditions. This implies a reduction in the number of unknowns when fitting parametric data simultaneously, and is a unique feature of this proposed model. In this work, specifically, we fit all the nine hemodynamic responses due to different stimulus amplitudes using only 14 parameters, significantly less than the 59 used by Huppert *et al* (2007).

The steps of our proposed forward model are schematically illustrated in figure 1. A vector of unknowns (i.e. the state vector) describes the arterial dilation and oxygen consumption transfer functions which are convolved with the electrophysiological measurements to obtain the inputs into the multicompartment Windkessel model. The multicompartment Windkessel model then produces a prediction of the blood flow and hemoglobin responses to the neuronal activity. These predictions are compared with the observations using a weighted least-squares cost-function. We used a nonlinear Levenberg–Marquardt method implemented in Matlab (Mathworks, Inc. Natick MA, Version 7.4) for estimating the state vector that produces a prediction that optimally agrees with the observations. This fitting routine was iterated until a defined convergence criterion (10^{-6} times the variance of the measurement error) was met. The differential time step for the update of the vascular and oxygen transport models was fixed at 1 ms.

In order to test the confidence bounds and to estimate the variance in fitting parameters, we also performed a Markov Chain Monte Carlo (MCMC) sampling of the parameter state space and estimated the 95% confidence intervals for each parameter (Carter and Kohn 1996). Model fits were repeated for 30 iterations of uniformly sampled initial positions of the state vector for the Levenberg–Marquardt algorithm.

3. Results and discussion

Recorded LFP and MUA for each of the nine stimulus amplitudes, obtained from the region-of-interest averaged response of the seven rats is shown in figure 2(a) for conditions 3, 6 and 9, as examples. For this work, we considered either the magnitude of each peak or the area under the peak for each electrophysiology measurement summed over the 16 pulses in the stimulus train, which provided four different possible combinations of input data as constraint to guide the parameter estimation (MUA_{peak} , MUA_{area} , LFP_{peak} and LFP_{area}).

The model was used to fit the experimental averaged response curves of cerebral blood flow and hemoglobin concentrations for all the nine conditions simultaneously. Figure 2(b) shows the model fits to the experimental data for conditions 3, 6 and 9, when the integrated MUA peaks (MUA_{area}) were taken as the neuronal input information to the convolution with the

transfer function to be estimated. Similar matches between experimental and model prediction were found when using the other three combinations of input data.

The model parameters estimated for all four MUA and LFP cases analyzed were within the physiological ranges reported previously (Mandeville *et al* 1999, Boas *et al* 2003, Zheng *et al* 2005, Herman *et al* 2006), and close to those obtained by Huppert *et al* (2007). The structural parameters did not differ among the trials, independent of the input data we used, as expected. The Windkessel vascular reserve, for example, was estimated between 2.4 and 2.8, while the vascular transit time remained in a range of 0.72 and 0.74 s. Both parameters are in agreement with evoked responses found in previous studies (Mandeville *et al* 1999, Zheng *et al* 2005). In addition, we examined the 95% confidence intervals with Monte Carlo simulations, as described in section 2.3. We also analyzed the influence of the initial guess of the model parameters, and verified that the final estimates did not change significantly among trials and they always fell within the model uncertainty, independent of the starting position. Table 1 summarizes all these findings for MUA_{area}.

The goodness-of-fit was examined by the correlation between the measured and predicted responses. The averaged R^2 values from the nine conditions were calculated for our four sets of input data, and are provided in table 2, as well as their comparison to those obtained by Huppert *et al* (2007). Although slightly smaller when compared to those obtained in the previous cited paper, our optimization model yielded highly statistically significant fits for all combinations of input data. Furthermore, these new model fits were obtained using the electrophysiological measurements as constraints, significantly decreasing the degrees of freedom in the system, i.e. the total number of parameters to be estimated. This is clearly seen in the F-statistics for each of these models, which penalizes for the additional degrees-of-freedom of the Huppert *et al* model. According to the F-statistics, our neural transfer model is significantly better, being able to provide similar modeling of the data with 70% fewer degrees-of-freedom.

The transfer functions estimated from either MUA or LFP to the arterial dilation and CMRO₂ changes are presented in figure 3(a). Irregardless of the type of the input data (integrated sum or peak magnitude), the transfer function obtained for each electrophysiology observation was similar, although the amplitude of the LFP transfer functions was smaller. The transfer function for the vascular response was more delayed in its onset and had a wider temporal response, while the transfer function for the metabolic response was more instantaneous and narrower in time. The temporal width of the transfer functions suggests that the vascular response (arterial dilation) is slower than the metabolic response, which is reasonable given the biomechanical nature of the vascular response.

The physiological response of each system, represented by the change in CMRO₂ and arterial dilation, can be calculated from the direct convolution of the input data with the corresponding transfer function estimated. Figure 3(b) shows the changes in these states for conditions 3, 6 and 9 when using LFP_{area} to guide the optimization process. The maximum flow—oxygen consumption ratio, a common rate calculated from functional responses, was found at 3.27, which is consistent with reported values (Kastrup *et al* 2002, Hoge *et al* 2005).

Electrophysiological recordings evidence different processes of the neuronal system. MUA is directly related to spiking activity, while LFP measures a weighted sum of transmembrane currents due to synaptic and dendritic activities (Devor *et al* 2003). Because these measurements clarify different neuronal-related mechanisms, one might analyze the influence of one or another when used as neuronal information for studying the neuro-metabolic-vascular coupling of the cerebral evoked response. Indeed MUA statistics are slightly higher than LFPs in our results, as shown in table 2, but this difference was not statistically significant ($P < 0.05$;

T-test). Perhaps these differences would become more apparent with different stimulation paradigms that evoked characteristically different behavior in MUA and LFP. Of particular interest is the surround vaso-constriction behavior observed during fore-paw stimulation (Devor *et al* 2007) that appears to arise from relatively greater hyper-polarization and supports the intriguing hypothesis that depolarization drives dilation and hyperpolarization drives constriction. Our analysis framework enables a model test of this hypothesis by separating the MUA and LFP responses into depolarization and hyperpolarization components that individually drive dilation and/or constriction. We tested this idea with the present whisker barrel data and found no significant support for or against this hypothesis.

4. Summary

Evoked changes in blood oxygenation, volume and flow are nonlinearly related to changes in the vascular tone and oxygen metabolism in underlying cerebral tissue and can be approximated by models of the vascular dynamics. In this work, we have shown that measured neuronal activity can be used to predict such measured hemodynamic changes through a linear model of the neuro-vascular and neuro-metabolic coupling relationship to the underlying arterial dilation and oxygen consumption changes and the nonlinear response of the vasculature to these physiological inputs. We used the Windkessel vascular model to fit experimental parametric hemodynamic and electrophysiological data in order to characterize these coupling functions. The empirical neuro-vascular and neuro-metabolic relationships both appear to be linear, however, our results show clear differences between the magnitude and timing of these two transfer functions. This model offers considerable improvement over previous descriptions and shows that multiple levels of neural and vascular activity can be modeled using a single transfer function relationship. Thus, compared to our previous Windkessel model, this current description uses a considerably lower number of the model parameters while providing equal quality predictions of the multimodal data. Our estimates of arterial dilation and CMRO₂ changes, as well as other structural properties of the neuro-metabolic-vascular system are in agreement with previous findings. Furthermore, our model offers an electrophysiological basis for previous available vascular and metabolic models, and tested its dependence on amplitude of the evoked response. This feature can open more opportunities to study the behavior of the metabolic and hemodynamic responses under different conditions, such as parametric studies on stimulus frequency and/or duration, where the temporal time course of the blood flow and oxygenation changes varies considerably.

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Figure 1.

Schematic representation of the model framework proposed. Electrophysiological data are convolved with metabolic and vascular response functions to predict oxygen consumption and arterial dilation changes, respectively. These functions, together with structural and physiological parameters, are state parameters for the multicompartment Windkessel model, as presented by Huppert *et al* (2007), whose outputs predict the changes in CBF and oxygenation. The predictions are minimized to the experimental data using a pseudo-Bayesian approach, in the form of a weighted least-squares cost function, through a state vector of unknowns with 14 parameters.

Figure 2.

(a) Average LFP (black) and MUA (blue) responses (not normalized) for the entire 2 s stimulus train of whisker stimulation for three different stimulus amplitudes. (b) Evoked hemodynamic responses for these amplitudes; average CBF, HbO, HbR and HbT measurements are shown as black, red, blue and green dots. The error bars show standard error estimated from the seven rats used in the experiment. Solid curves represent the model fits to the data (MUA_{area}). Columns 1, 2 and 3 are responses to conditions 3, 6, and 9 respectively. In both cases, $t = 0$ corresponds to the beginning of stimulation.

Figure 3.

Estimated transfer function for the (a) neuro-metabolic and (b) neuro-vascular systems, which represents their respective response to a single stimulus pulse. Solid (dotted) lines correspond to estimation when using integrated area over MUA (LFP) recordings. In the bottom panel, we show the convolved response of the transfer function (LFP_{area}) with a train of pulses from electrophysiological recordings, resulting in parametric estimates in (c) CMRO₂ and (d) arterial dilation changes for evoked responses to whisker barrel stimulation (only conditions 3, 6 and 9 are plotted for a better visualization).

All 14 model parameters used to fit the experimental data: three for each of the transfer functions; four to describe the structural variables of the system; and four parameters to describe the baseline oxygenation. Physiological ranges were used to bound the estimates of each of the parameters. In the last two columns we present, respectively, the model estimates for the state vector, when using LFP_{area} to guide CMRO₂ and arterial dilation changes, and their confidence bounds, calculated from the MCMC simulations.

Table 1

Description	Symbol	Physiological constraint	Estimate	Confidence interval
<i>Arterial dilation transfer function</i>				
Amplitude change	Δf_A	(0–10)%	1.04%	[1.03–1.26]
Delay time of the amplitude change	$\tau_{0,A}$	(0–5) s	0.45 s	[0.43–0.55]
Width of the amplitude change	σ_A	(0.7–3) s	1.83 s	[1.82–1.86]
<i>Oxygen consumption transfer function</i>				
Amplitude change	Δf_{O_2}	(0–10)%	0.70%	[0.57–0.71]
Delay time of the amplitude change	τ_{0,O_2}	(0–2) s	0.001 s	[0.00–0.15]
Width of the amplitude change	σ_{O_2}	(0.7–3) s	0.84 s	[0.79–0.86]
<i>Structural variables</i>				
Initial arterial resistance	$R_A(0)$	(0.2–0.9) au	0.59 au	[0.58–0.60]
Windkessel vascular reserve	β	(1–5) au	2.43 au	[2.35–2.46]
Vascular transit time	τ	(0.5–4) s	0.73 s	[0.70–0.76]
Pial venous transit time	τ_{pial}	(0–4) s	0.33 s	[0.21–0.58]
<i>Hemodynamic variables</i>				
Total baseline hemoglobin concentration	[HbT](0)	(40–140) μmol^{-1}	86.5 μmol^{-1}	[84.3–86.8]
Baseline arterial oxygen saturation	$S_aO_2(0)$	(90–100)%	92.4%	[90.0–92.8]
Baseline capillary oxygen saturation	$S_cO_2(0)$	(60–90)%	71.3%	[71.1–71.4]
Baseline venous oxygen saturation	$S_vO_2(0)$	(55–89)%	65.9%	[65.8–66.2]

Goodness-of-fit for the model fits of the four combinations of electrophysiological parameters. Uncertainty of the values was calculated from standard deviation of the fits to the nine stimulus conditions. The total R^2 values indicate the fraction of the total variance accounted for by all measurements. The F -values consider the degrees-of-freedom from each model, and were calculated from the R^2 values. The last column shows R^2 values obtained for the fits of the nine conditions with the multicompartment Windkessel model, without any neuronal information as a prior, described by Huppert *et al* (2007).

Table 2

	Model fitting				Model fit from Huppert <i>et al</i> (2007)
	MUA area	MUA peak	LFP area	LFP peak	
HbO					
R^2 value	0.94 ± 0.03	0.94 ± 0.04	0.93 ± 0.04	0.93 ± 0.04	0.97 ± 0.03
F value	1063 ± 38	1063 ± 44	902 ± 38	902 ± 37	523 ± 16
HbR					
R^2 value	0.93 ± 0.04	0.92 ± 0.04	0.92 ± 0.04	0.92 ± 0.05	0.96 ± 0.06
F value	902 ± 34	781 ± 34	781 ± 36	781 ± 38	389 ± 23
HbT					
R^2 value	0.92 ± 0.05	0.92 ± 0.06	0.91 ± 0.06	0.91 ± 0.06	0.96 ± 0.04
F value	781 ± 44	7813 ± 51	687 ± 46	687 ± 45	389 ± 16
CBF					
R^2 value	0.83 ± 0.10	0.82 ± 0.11	0.82 ± 0.11	0.82 ± 0.11	0.92 ± 0.08
F value	332 ± 41	310 ± 40	310 ± 42	310 ± 40	187 ± 17
Total					
R^2 value	0.90 ± 0.05	0.90 ± 0.06	0.89 ± 0.06	0.90 ± 0.06	0.95 ± 0.05
F value	611 ± 38	611 ± 42	550 ± 39	611 ± 43	308 ± 17