

# Dynamic optical tomography: A new approach for investigating tissue–vascular coupling in large tissue structures

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**Abstract:** Investigation of vascular dynamics is a new direction for optical tomography. In this report we discuss the physiological basis of vascular reactivity and the types of information that may be derived by applying time–series analysis methods to image data. By example, we also present an overview of results from physiological studies reported in more detail in accompanying reports. These include the real–time vascular response of the forearm to local and centrally mediated stimuli examined in a cross–sectional view.

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## Introduction:

The vasculature is uniquely responsible for the delivery of essential nutrients to tissue and for removal of metabolic wastes. It also serves as the central conduit mediating a broad range of action–at–a–distance processes. A hallmark of the vascular system is the speed and magnitude with which abrupt changes in the local perfusion state of tissue can occur. Vascular perfusion is not uniform in space or time, nor is there sufficient blood in the body to simultaneously perfuse the entire vascular bed. Instead, the vasculature is continuously shunting blood through one region of tissue and then another. This process is mainly under control of the autonomic nervous system, and is further modulated by local metabolic needs. Basically, the vasculature is a hyper–reactive organ capable of varying blood volume to local tissue sites by as much as an order of magnitude within a few seconds or less. Even at rest, modulation of tissue perfusion is occurring in the form of vasomotion.

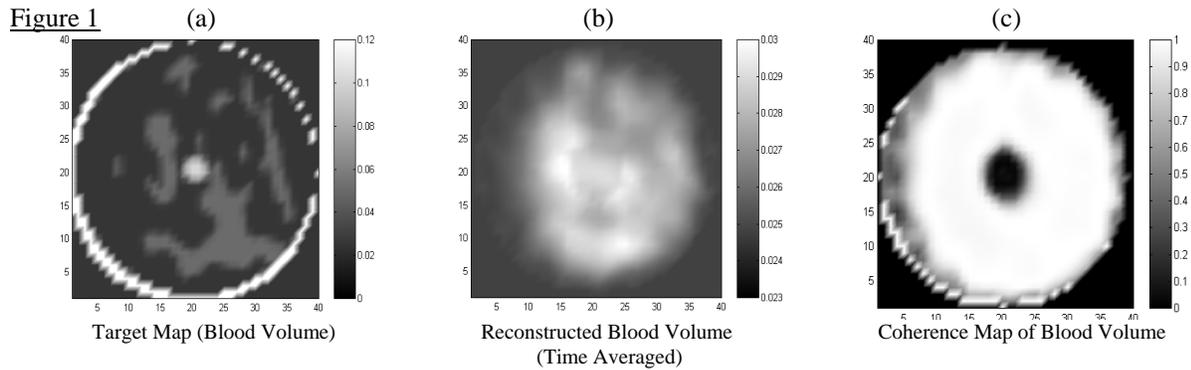
A range of clinically significant states can alter vascular coupling to local and central stimuli [1]. These include conditions leading to hypoperfusion, vasospastic disorders, acute vascular accidents and neovascularization. Quantitative assessment of the perfusion status of small vessels near the surface can be made using laser Doppler techniques. At greater depths, primarily only the large vessels can be evaluated. Most often this is accomplished using one or more imaging methods, in particular duplex ultrasound, MR angiography and contrast–enhanced x–ray imaging [2]. Small–vessel perfusion can also be gauged by radioscintigraphic methods. While these techniques provide useful information concerning the general state of tissue perfusion, they provide little insight regarding the details of *tissue/vascular* coupling. This is a subject matter that has proven stubbornly difficult to evaluate *in vivo* due to the lack of suitable noninvasive methods. An understanding of this coupling should provide new insights into disease processes and form a basis for rational intervention. Central to this is the collective influence that local and central modulators have on vascular reactivity and connectivity. The latter responses are functions of time and space, and they can be characterized in terms of their kinetics, frequency structure, and time–correlation. It is these parameters that can be derived from analysis of time–series image data collected by dynamic optical tomography.

Investigation of tissue/vascular coupling requires new approaches to instrument design. In an accompanying report (Schmitz *et al.* [3]) we describe instrumentation capable of performing fast parallel (up to 150 Hz) measurements from tissues having arbitrary geometries. Discussed are new imaging head designs that are geometrically adaptable, a novel approach to system calibration, and a new TTL addressable adaptive gain scheme that allows for on–the–fly adjustment of signal amplification and a measuring range of 180 dB.

In a series of preliminary studies, we have implemented various feature extraction methods to evaluate image data collected from the human forearm using a 4Hz parallel measuring system. Two types of experiments were performed. The first imposes local stimuli and explores various measures of the vascular response; the second imposes central stimuli and performs a similar analysis. Examples of the type of information derivable from these studies are given subsequently.

### I. Enhanced Image Contrast of Dynamic Features:

Improvement in image contrast and resolution is important for any imaging method. Thus far, optical imaging methods have produced only images having relatively low contrast and resolution from tissue studies. While refinements in data processing and instrument performance may improve this, at this point it would seem that this might represent a basic feature of optical imaging. Recently we have shown [4], that images of much greater quality can be derived by computing various measures from a time-varying image series. These can include amplitude and phase maps of the Fourier spectrum, and maps of temporal correlations and their frequency composition. As an example, in Figure 1 we show an original image of a complex target medium(a), a reconstructed map of its time-averaged blood volume levels (b), and a coherence image (c) computed from the same data shown in (b) and derived from analysis of a time series. The original is a 2D coronal section of a MR mammogram, for which various optical properties ( $0.04 < \mu_a < 0.3$ ,  $5 < \mu_s < 15 \text{ cm}^{-1}$ ) were assigned to the different tissue types [adipose (dark), parenchyma (gray) and tumor (light)]. In addition, the absorption value for each was made to vary with time (amplitude is 10% of mean). Comparison shows the resolution and contrast of the time-averaged map is relatively low and the tumor is not evident. In contrast, the tumor is clearly revealed in the coherence image. Significantly, this result was obtained without any prior knowledge of the tumor's presence, and instead is dependent solely on the tumor having a *temporal* response different from that of the surrounding tissue. Clinically, such behavior may exist naturally [5], or it could be induced in response to a simple manipulation of the vascular perfusion state. An example of this is described next.



### II. Investigations of Differential Reactivity of the Vascular Tree: Blattman *et al.* [6]

Two principal frequencies associated with the vascular tree originate from cardiac contractility and respiratory activity. The cardiac signal is restricted to the arterial tree and represents a volume displacement action occurring in response to the change in pressure due to ventricular contraction. The respiratory signal, also known as Traube-Hering waves, results from the rhythmic contraction of vascular smooth muscle. This is an active process and is associated mainly with the microvessels, particularly the arterioles and metarterioles. A respiratory beat frequency is also observed in the venous return, but this is primarily a passive response caused by the propagation of mechanical forces generated by the action of the small vessels. The different frequencies and origins of the beat frequencies permit identification of the principal components of the vascular tree in a cross-sectional view. For example, we have computed cross-sectional maps of the forearm that identify the ratio of the Fourier amplitudes at the cardiac and respiratory beat frequencies. Comparison of these to MR angiography correctly identifies the position of the radial, ulna and interosseous arteries, as well as several of the major veins.

Evidence of reactivity attributable to the microvessels can also be derived from analysis of a time series. In one example, we have computed the temporal derivative of the image series for a case involving deep breathing exercises. Upon inspiration, enhanced return of blood to the heart occurs, causing net emptying of blood from the tissue. Upon expiration, net filling occurs in the peripheral blood vessels. We have identified the location of the maximum and minimum values of the temporal derivatives of the computed coefficient values in the cross section for the time series. Although the architecture of the vascular tree is fixed, because of vasomotion the location of net inflow and outflow of blood through the *microvessels* can be expected to vary with time. In contrast, similar measures of major vessels should be fixed, and can be revealed by the coincident position of the maximum and minimum values of the temporal derivatives. It follows that separation of microvessel reactivity from that of the major vessels can be accomplished by identifying the frequency of spatially coincident maximum and minimum values of temporal derivatives upon repeated cycles of deep breathing. For large vessels, the frequency will be high because the architecture of the vasculature is fixed. For small vessels, the frequency should be low due to vasomotion.

### III. Dynamic Imaging of Tissue Reperfusion: Blattman *et al.* [7]

Systemic interruption of blood flow can occur in various surgical procedures. For example, during cardiopulmonary bypass, blood flow to the peripheral tissues can be halted for up to five hours before reperfusion injury occurs. Adequacy of restoration of blood flow to the periphery is not infrequently uncertain, owing to the lack of specific noninvasive measures sensitive to flow. In practice, the surgeon simply feels the temperature of the limb for evidence of return of blood flow. In an accompanying report [7], we have compared maps of  $\mu_a$  that reveal the amplitude of the Fourier spectrum at a low frequency to corresponding maps of temporal correlation from the same data following release of a pressure cuff placed proximal to the measuring site. These maps reveal that the same locations in the cross section of the forearm (mainly interior regions) that show a high-amplitude, low-frequency response upon release of the pressure cuff are also strongly time-correlated ( $>0.8$ ) with each other. In addition, those regions having low amplitudes also show coefficient fluctuations that are uncorrelated in time. These findings strongly suggest that analysis of the image series in this manner identifies those regions experiencing reperfusion of blood following release of the cuff.

### IV. Imaging of Muscle Activity: Graber *et al.* [8]

Local perturbations of blood flow also can be produced in response to muscle activity. In an accompanying report [8], we have employed time series image analysis methods to characterize the dynamic changes observed during a finger flexion study for the fourth digit. The flexor and extensor muscles are located on opposite sides of the arm. We have examined maps of statistical measures (CV) of the variation in coefficient value obtained from analysis of the image series upon repeated flexor/extensor movements. Comparison of these maps to MR data reveal that the regions having the highest variability coincide with the expected muscle groups response for finger movement. In addition, we also found that the region of lowest variability included the ulna and radius and the space between. Inspection of maps of the phase of the Fourier transform at the finger-flex frequency also revealed the expected out-of-phase response in regions spatially coincident with flexors digitorum and extensor digitorum muscles. These findings demonstrate the feasibility of characterizing muscle movement by dynamic optical imaging methods.

### V. Neurological Modulation of Vascular Reactivity. Barbour *et al.* [9]

Tissue/vascular coupling is ordinarily under tight control by the autonomic nervous system. Stress in the form of a temperature shock, fear, anxiety, pain, or other stimuli often leads to peripheral vasoconstriction. This response can be exaggerated or attenuated by a variety of disease states. We have explored the influence that a contralateral cold shock has on the vascular dynamics in the *right* forearm [9]. Following a 30 s rest period, the *left* hand was immersed into an ice slush for 60 s, followed by a 60 s exposure to warm water. All during this time, dual wavelength tomographic measurements were performed at a 2 Hz rate, yielding a total of 300 images per wavelength. While we confirmed the immediate vasoconstrictive response, it was observed that this is accompanied by a simultaneous redistribution of blood whose dynamic properties varied spatially. We also observed that accompanying this response was a ~15 sec delay in the onset of changes in hemoglobin oxygenation; areas experiencing vasoconstriction became more deoxygenated and areas with enhanced blood volume became better oxygenated.

**Conclusions:** In this report we explored various features of vascular reactivity that are amenable to study by analysis of time-series image data. The findings indicate that improved image quality and a wealth of new information concerning the differential reactivity of the vascular tree are discernible in response to various simple manipulations of tissue perfusion states.

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