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# Theories, Data Analysis, and Simulation Models in Neuroimaging—An Overview

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Functional neuroimaging techniques provide novel and exciting means for the investigation of working brains. Successful implementation of these tools requires an understanding of how to incorporate and adapt existing empirical results and theoretical frameworks for the design and analysis of imaging studies. Development of new techniques for analyzing data from neuroimaging is also important. No single technique can optimize the amount of information that can be extracted from neuroimaging studies; a broad spectrum of theoretical approaches is required. This chapter gives a brief overview of theoretical methods that are central to the field of experimental neuroimaging. The topics discussed include inferential, exploratory and causal methods of data analysis, theories of cerebral function and both biophysical and computational models of neural nets. As well this section helps to guide the reader by referring to later chapters.

## 1.1 Functional Neuroimaging: Answers without Questions?

The total effort devoted to functional neuroimaging is so great that it has led to the formation a new scientific field, Human Brain Mapping or Brain Imaging, with large numbers of associated conferences and journals. This intense interest is rooted in the distinctive power of techniques such as functional magnetic resonance imaging (fMRI) and positron emission tomography (PET), which provide noninvasive means of viewing global patterns of neuronal processing in the human brain with spatial resolution at the millimeter scale. After its recent introduction by Ogawa et al. (1990a,b), fMRI in particular, has had an enormous impact. In the fields of cognitive neuroscience and systems neuroscience, fMRI became “the” registration technique of choice for examining macroscopic activation correlates in the working brain (Cabeza and Kingstone, 2000).

While there is tremendous interest in functional brain imaging, there is lively debate about its ultimate value and use. A recent article states succinctly: “It is unclear that we will come to a better understanding of mental processes simply by observing which neural loci are active while subjects perform a task,” (Kosslyn, 1999). The author holds the view that the context given by prior studies and theories of cerebral function is required to pose questions that can be investigated by imaging studies. Kosslyn (1999) discerns two classes of questions that can be easily addressed by neuroimaging: first, how is information processing implemented in the brain and second, what are the time courses of activation of particular structures and processes. The work and theories that Kosslyn draws on have come from electrophysiological experiments, studies of the effect of brain damage on human behavior and cognition, and neuroanatomical descriptions of connections between different regions. Thus, there is a demand to translate prior empirical results and associated theories to the new medium of brain imaging. That is, to ask how can these be represented in mathematically defined ways. In the following, we will characterize approaches to data analysis and modeling in the context of functional brain imaging.

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## 1.2 Techniques of Functional Neuroimaging: Strengths and Limitations

First, we will briefly describe the substance of different neuroimaging methods. Specifically, it is important to recall that all current techniques measure local neuronal activity by indirect means. PET and fMRI measure local properties of the cerebral blood flow: the fMRI signal is based on blood oxygen level dependence (BOLD), and the PET signal on regional cerebral blood flow (RCBF); for an introductory review, see (Horwitz et al., 2000). The mechanisms that link metabolic measures to neural activation are not yet well understood. The general impression is that the BOLD signal reflects the magnitude of synaptic events more closely than that of firing rates (Jueptner and Weiller, 1995; Magistretti and Pelerin, 1999).

Recently, this view has received further experimental support by a study that combined fMRI with electrophysiological recordings in animal models (Logothetis et al., 2001). Despite the indirect linkage between the BOLD signal and spike rate, fMRI has sufficient spatial resolution to resolve elements of functional architecture that were originally defined by the spatial distribution of stimulus evoked single-cell activity, such as orientation columns in the visual cortex (Kim et al., 1999). At present fMRI achieves the best spatial resolution that is possible for whole brain imaging but it is still 4–5 orders of magnitude away from discriminating single cells. New experimental methods are being developed, however, for characterizing the spatial distribution of neuronal populations beyond the technical spatial resolution of fMRI, see the adaptation paradigm proposed in the chapter by Tolias and colleagues.

Imaging methods that depend on hemodynamic coupling are not only severely limited in spatial but also in temporal resolution. Technically, fMRI can be sampled at intervals less than 100ms, however, the hemodynamic response is unlikely to convey changes in neuronal response on such brief time scales. For example, the BOLD response begins with a weak dip in the blood oxygen level (depletion dip) that lags the neuronal response by 1sec. The most pronounced BOLD response, the overshoot in oxygen level does not peak until about 5–7s after the neuronal event (Frahm et al., 1994). Therefore, fMRI and PET provide only a version of the neuronal response that is low-pass filtered by 6 orders of magnitude.

Other measures of brain function permit superb temporal resolution. For example, EEG (electroencephalogram) electrodes and MEG (magnetoencephalogram) sensors record the electric or magnetic field arising from neuronal activity and achieve temporal resolution on the millisecond scale. In the past, these fast techniques provided very poor spatial resolution since they rely on integrating signals from large areas, 1–2cm around a detector. To some extent, spatial resolution can be increased by using a larger number of sensors. In the past few years, the number of detectors that can be fitted on a 2D surface near the skull has increased steadily; the present limit is about 256 detectors. From the field distribution recorded by many detectors on the surface of the skull, it is under certain circumstances possible to perform “source reconstruction,” that is, to localize the spots of high density of dendritic currents in the brain underlying the measured field distribution. Thus, current encephalogram methods can also be thought of as a form of neuroimaging. Recent approaches have made progress in improving the spatial resolution of EEG/MEG and in resolving principal problems with source reconstruction. To date, EEG/MEG recordings can achieve accuracy on a scale of about 1cm, but not the millimeter scale of fMRI. Subsequent chapters will describe new analytical methods to improve sensitivity and spatial resolution (see section 1.5) and approaches that combine the advantages of EEG/MEG recordings with those of fMRI (see section 1.7.2).

### 1.3 Theories of Brain Function

A theory of brain function is a teleological interpretation of experimentally defined brain states. The traditional experimental bases of functional brain theories fall into two broad categories: a) Lesion studies that assess how cerebral injuries or other manipulations effect function; b) Recordings with electrodes or microelectrodes that measure neuronal activity in response to peripheral stimulation or during the performance of tasks. Lesion studies, for instance, provided the initial basis for hypotheses about the localization of brain function – a particular class of functional theories that specify which brain regions are involved in producing particular functions. Lesions in the occipital cortex, for example, produce blindness (Munk, 1880). Recordings of neuronal activity with microelectrodes placed in the brain provided the basis for functional theories at the neuronal level. For instance, neurons in the occipital cortex were found to code particular low-level properties of the external visual world such as stimulus orientation (Hubel and Wiesel, 1962). A hypothetical function of the primary visual cortex is therefore the decomposition of visual scenes into stereotyped features.

Two general principles of cerebral function derive largely from studies of brain lesions and recordings from single or small groups of neurons: One is the concept of functional specialization of brain regions (Zeki, 1990). The second is the hypothesis of functional integration (Gerstein and Perkel, 1969; Gerstein et al., 1989), which states that cerebral functions are carried out by networks of interacting regions and that different functions correspond to different networks.

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### 1.4 Data Analysis of fMRI and PET

Functional neuroimaging complements traditional avenues of brain research by opening a macroscopic window on processing in the working brain. Changes of activity associated with various stimulus conditions and behaviors are referred to as functional correlates in brain activity. The extraction of functional correlates from spatio-temporal fMRI or PET data sets requires the application of sophisticated data analysis. One main difficulty in resolving functional correlates is to separate these from various types of distortion present in the measured signal, e.g. low pass filtering, physiological and scanner noise. Another problem in interpretation stems from the possibility that functional correlates of brain activity may relate to given behavioral paradigms in complicated ways. This latter difficulty would remain even if all issues of signal distortion and filtering were solved. Delineating functional correlates in the spatio-temporal structure of the data cannot be done without making assumptions about general working principles in the brain. Currently, there are two main types of assumption underlying the interpretation of functional neuroimages, as represented by the subtraction paradigm and the covariance paradigm (Horwitz et al., 2000).

### 1.4.1 Data Analysis Paradigms

The subtraction paradigm assumes that different brain regions are engaged in different brain functions (Horwitz and Sporns, 1994); that is, it relies on the existence of functional specialization. The subtraction paradigm has become the standard in most fMRI and PET studies. These studies commonly employ an experimental protocol known as block design, which involves switching between two steady states, or blocks, one a rest interval and the other a functional condition. This simple alternation between control state and behavioral task constrains the temporal structure of functional components of the signal. Thus, the data can be subjected to a regression analysis to reveal functional activation at any given location, see section 1.4.3. Many issues, however, cannot be addressed directly with experiments that use block design protocols, including studies about continuous voluntary movements, self-paced tasks and various forms of cognitive tasks.

The second paradigm is called the covariance paradigm (Horwitz and Sporns, 1994). It is motivated by the hypothesis of functional integration. Covariance paradigms assess the temporal covariance between different brain regions during a particular task. Significant covariance between regions associated with a particular brain function is termed functional connectivity. Originally, functional connectivity was determined by seed methods, by establishing signal covariance in different brain regions with respect to a chosen seed region. Currently, exploratory analysis techniques allow assessment of functional connectivity without reliance on seed regions (exploratory data analysis is explained in section 1.4.4 of the chapter).

In order to resolve all the functional components of a given cerebral process available from an fMRI data set, it is often necessary to take advantage of the complementary views that the subtraction and the covariance paradigms provide. For example, areas that are activated during a particular task, but not exclusively activated, would be missed in studies that rely on the subtraction paradigm alone. On the other hand, if only one small region, rather than multiple sites, is activated during a given task, its functional role would be undetected by the covariance approach. Therefore, analyzing the data with both approaches is often necessary. So far, we have given only broad definitions of the two main types of data analysis. In the following four paragraphs we will characterize new strategies of signal preprocessing and analysis and explain how these approaches relate to the subtraction and covariance paradigms.

### 1.4.2 Data Preprocessing

The detection of functional correlates from fMRI data sets can be improved by using the subtraction or covariance paradigms for preprocessing. For example, the covariance paradigm (combined with the anatomical finding that local networks are interconnected), led to the suggestion that functional activation extends over more than a single unit of measurement, or voxel (typically  $1\text{mm} \times 1\text{mm} \times 3\text{mm}$ ). This realization, in turn, gave rise to various means of reducing noise in measurements

of spatially extensive functional correlates spatial averaging such as smoothing by convolution with a Gauss-kernel. Further approaches to averaging came to include selection of voxel sets by similarity in signal time-course rather than by spatial proximity. Partitions for such selective averaging approaches can be found by explorative data analysis methods, see section 1.4.4 and the chapter of McKeown.

### 1.4.3 Inferential Data Analysis

Inferential analysis tests hypotheses about functional correlates in data sets from neuroimaging. A general approach to inferential analysis is to use spatially extended processes, statistical parametric maps (SPM). The most established sort of SPM is the general linear model, including familiar methods like ANCOVA (regression analysis), correlation coefficients and t-test as special cases (Friston et al., 1995). Inferential analysis involves the use of hypotheses drawn independently from the data set under study. Some experimental paradigms make a straightforward suggestion for the independent hypothesis to use. For block designs with block durations several times longer than the time constant of the hemodynamic response (6s), the hypothetical time course of the functional correlate is given by a box-car function, high levels during task periods and low levels during rest periods. The hypothesis can be tested in the SPM framework for each voxel. The resulting map of t-values is a picture of the spatial distribution of functional activity induced by the task. Other experimental paradigms, however, might suggest several competing hypotheses, or none at all. Previously, Burock and Dale (2000) developed a voxel-based method to estimate activation functions from data sets in cases for which no hypothesis is available. They also proposed a statistical framework capable of testing the activation functions estimated from those data sets. For testing competing hypotheses a novel Bayesian approach is presented in the chapter by Hansen and colleagues.

### 1.4.4 Exploratory Data Analysis

Strategies of multivariate data analysis that rely on the covariance paradigm represent other types of approaches that are free of preassumptions about activation functions. For example, methods of unsupervised learning, like cluster analysis or principal/independent component analysis, are able to reveal voxel sets with co-varying time courses. Such algorithms, combined with only few preassumptions, have the ability to detect regularities in data from neuroimaging. Many studies have demonstrated that functional activity can be detected without reference to the experimental protocol at all. Exploratory data analysis has the capacity to reveal other components in the data as well, including scanner and motion artifacts. Exploratory data analysis is a main focus of this book; the methods and their application for different imaging techniques are described by a number of chapters: fMRI: Samorjai and colleagues, McKeown; event-related fMRI: Wichert and colleagues; MEG/EEG: Tang and Barak, Vigario and colleagues; autoradiography: Nair and Gonzalez-Lima.

### 1.4.5 Causal Data Analysis

The types of analysis we described above were developed to reveal statistical regularities in the data that can be associated with brain function. The next step is to explore the processes that produce functional correlates in the brain, for instance, how different coactivated or sequentially activated areas influence one another. These issues cannot be resolved by determining functional connectivity alone. If, during task execution, activation of one region is associated with that of the next, the two are described as functionally connected; the causes or nature of the association, however, is unspecified. To explore potential mechanisms of interaction among regions, the data must be analyzed anew. Instead of statistical inference, a different type of analysis, causal inference, becomes important. Standard inference assumes that parameters that describe a given distribution can be inferred from samples taken from that distribution. These parameters can be employed to infer associations among variables, like the BOLD signal or behavioral features, with methods such as regression analysis. Causal analysis (originally developed for effect analysis in economics) goes one step further, by providing the means to make inferences about the processes involved in generating the data. It cannot be applied in all cases, however, since it requires supplementary information about the mutual interactions among variables like knowledge of anatomical connections. For a comprehensive introduction to the general concept of causal inference, see (Pearl, 2002). McIntosh and Gonzalez-Lima (1991) were the first to apply causal analysis to functional neuroimaging. In particular, they used structural equation modeling (SEM), a linear version of causal analysis. Their analyses provided a way to quantify the influence that a given cortico-cortical pathway (already known to exist from anatomical studies) has on its target area by generating path coefficients<sup>1</sup>. High coefficients indicated strong “effective connectivity” and negative coefficients indicated inhibitory effects.

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## 1.5 Data Analysis of EEG and MEG

Since electro- and magneto-encephalogram registration is a longer established technique than fMRI or PET, the various problems of associated data analysis have received much previous attention. Here we limit the discussion of this longer used technique to two recent methods of exploratory data analysis and the combination with data from blood-flow based neuroimaging techniques.

The main goal of EEG/MEG data analysis is source reconstruction, as already has been described in section 1.2. The result of source reconstruction is a configuration of sources in the brain (time-dependent electric or magnetic dipoles or multipoles)

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1. For technical reasons a SEM analysis has to be restricted to networks including only a handful of areas of interest.

that reproduce the field measured on the cranial surface. The reconstructed sources correspond to local cerebral regions with high dendritic current densities. In general, however, source reconstruction has no unique solution and so falls into the category of ill-posed problems<sup>2</sup>.

One approach to reduce ambiguity in source reconstruction is to decompose the data set in a sensible way and to try to explain the components separately. Some approaches decompose the data by means of the same exploratory data analysis techniques described in section 1.4.4. Recent approaches using independent component analysis of single trial EEG and MEG will be described in the chapters of Tang and Pearlmutter, and Vigario and colleagues. Even after successful source reconstruction the spatial resolution of EEG/MEG is 1cm or coarser, far worse than the spatial resolution of fMRI—it depends on the number and localization of sources.

Another approach to reduce ambiguity in source reconstruction is to combine EEG/MEG with other imaging methods. Since advantages and disadvantages of EEG/MEG on the one hand and blood-flow based methods on the other are complementary, the combination of MEG/EEG with blood-flow based imaging methods is particularly appealing. The hope is to achieve high temporal and spatial resolution at the same time. The problems with combining different neuroimaging methods and ways to overcome them will be addressed in two of the following chapters, see section 1.7.2 below.

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## 1.6 Neural Network Models

Applying causal data analysis in neuroimaging bears a close relationship to approaches of brain modeling in the field of computational neuroscience (Sejnowski et al., 1988); for a recent review see the supplement to *Nature Neuroscience* (volume 3, 2000). A central class of models are neural networks, which, at various levels of detail or abstraction, describe the interactions among groups of neurons. Two different types of neural networks are of particular value in the context of neuroimaging, biophysical models and computational models.

### 1.6.1 Biophysical Models

Biophysical models are descriptions of biological domains in the usual sense of physics. In physics, a model provides a sketch; a simplified view of a domain, with the degree and quality of the simplification determined by the modelers. They

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2. Mathematical problems are ill-posed if they do not satisfy each of three criteria: a solution exists, is unique, and depends continuously on the initial data. To solve ill-posed problems, well-posedness must be restored by restricting the class of admissible solutions (Hadamard, 1923).



select experimental phenomena, mechanisms, and interactions that are regarded as essential to describe and formulate the descriptions in mathematical language. The resulting mathematical model can be treated analytically, numerically, or implemented in computer simulations. The biophysical model can be used to predict how experimental parameters influence other ones. To assess the validity of the model, the predictions it makes can be tested experimentally. Faithful or valid models usually result from a recursive trial and modification process. A biophysical model should not only be predictive, it should be explanatory too. Explanation largely results from the simplification process, which helps to identify the most important mechanisms involved in biological processes, such as how local interactions effect macroscopic behavior. Fidelity and simplification/reductionism are equally essential to biophysical modeling. A model that does not faithfully represent the system it seeks to describe becomes invalid; as does one that fails to provide reductionistic explanations for the actions of that system. Of course, model simplification is dictated by pragmatic reasons as well; mathematical models have to be tractable and should not include parameters that cannot be measured empirically. Naturally, these pragmatic limitations change as mathematical tools and technology develop. For example, recent advances in computing power and new experimental techniques have expanded the scope of biophysical models. A classic example of a biophysical neural network model is one that draws on the properties of single neurons and their synaptic interactions to explain the behavior of the network as a whole (Pinsky and Rinzel, 1994; Traub et al., 1996). Other biophysical models describe how extracellular field potentials, measured by EEG/MEG, are produced by postsynaptic potentials of large groups of neurons (Nunez, 1990).

### 1.6.2 Computational Models

The cybernetics movement introduced the computational paradigm of brain function, that is, the idea that the role of the brain is computation. This movement initiated the search for algorithmic formalizations of cerebral functions ( Craik, 1943; Rosenblueth et al., 1943; Wiener, 1948). Just as biophysical models describe neuronal domains, algorithms provide mathematical descriptions of cerebral functions. Cybernetics eventually gave rise to the field of Artificial Intelligence (AI), whose goal is to describe cognitive brain functions with mathematical algorithms. The rationale of this synthetic approach was that biological functions might be easier to mimic than to analyze in situ. Thus, algorithms implemented in a technical system (a computer) yield predictions that can be compared with the performance of biological systems. The hope was that if artificial and natural behaviors were similar, algorithmic elements would help to define the biological working principles. While the AI approach is interesting, its use in specifying the mechanisms of biological behavior is limited by the fact that different algorithms can produce identical outcomes. Computational brain models share with AI the goal of reproducing brain functions in an artificial system. But in addition, the structures and processes in the models are constrained by biophysics. Thus, neural networks used as computa-

tional models link interfaces to two different aspects of the brain, its biophysics and the algorithms it implements. Algorithms performed by neural networks that are important for neuroimaging include, for instance, associative memory, the storage and recall of activity patterns.

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## **1.7 Neural Network Models for PET and fMRI**

### **1.7.1 Links to Multielectrode Recordings**

Biophysical models developed to describe functional activity as measured by PET and fMRI have been designed (Arbib et al., 1995; Tagamets and Horwitz, 1999; Horwitz and Tagamets, 1999) to bridge the gap between results from microelectrode recordings of single cells and imaging of the whole brain. At present, these models are selective in scope because the path between single cell recording and functional imaging is long and only loosely charted. These models have been constructed to include information about various connectivity schemes between different local neuronal populations and between the areas of interest. Initially the models were used for simulations that explored the role of inhibitory and excitatory neuronal populations and the biophysical relationship between blood flow and neural activity. An important future role for the simulations will be to plan novel neuroimaging experiments. (see chapters Arbib and colleagues, Tagamets and Horwitz.).

### **1.7.2 Links between Different Neuroimaging Techniques**

Blood flow based and electrophysiological measurements have complementary strengths and weaknesses in space and time; thus experiments that combine both approaches are potentially powerful. Before these approaches can be brought together, however, two main obstacles must be overcome. First, technical solutions must be found for solving interference problems caused by the conjoint application of both techniques (see chapter Kruggel and Hermann). Second, a means to combine the signals measured with the two techniques must be developed. The approach to this second problem is not clear cut. Indeed, it is not even known whether both signals arise from the same or different groups of cells (Nunez and Silberstein, 2000). As well, there is considerable debate about which properties of the EEG signals (e.g., ERP peak height, different bands of spectral power) correlate best with the fMRI BOLD signal (see chapter Makeig and colleagues).

### **1.7.3 Refined Causal Data Analysis**

The strength of causal data analysis of fMRI/PET has recently been improved by the inclusion of biophysical models. Early methods of causal data analysis reflected only rudimentary descriptions of the biophysical substrate for interactions between regions. More recent methods of causal data analysis use fuller descriptions of

biophysical properties, including populations of inhibitory as well as excitatory neurons and the relationship between blood flow and neuronal activity (Taylor et al., 2000). Moreover, principles from computation modeling, like pattern storage or hierarchical processing have also been implemented. These revised analyses determine the influences brain regions exert on each other more realistically than previous causal analyses had done.

#### 1.7.4 Neuroimaging Studies on Learning

Learning is one of the most exciting subjects of studies that can be addressed by causal data analysis. One common computational model predicts that learning initiates changes in synaptic connectivity. Hence, learning might induce changes in effective connectivity as well. In fact, associative learning of visual objects and their location was shown to influence effective connectivity between regions specialized for spatial and object recognition (Büchel et al., 1999). Developmental influences on such learning effects is the subject of an autoradiographic study of neural tissue in the chapter of Nair and Gonzalez-Lima.

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## 1.8 Final Remarks

This overview gave brief accounts of different approaches to neuroimaging, including methods of analysis, modeling and the development of experimental techniques. In addition, we tried to convey a sense of how the different approaches relate to one another. For instance, there are close relationships between causal data analysis and biophysical modeling, and between functional theories and computational models. Last, by discussing biophysical and computational models separately, we hoped to clarify the different roles that neural network models play in understanding and integrating different types of information about the working brain.

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