Neurokinetics

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The Dynamics of Neurobiology In Vivo

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Preface

Attempts to understand physiological processes by quantification and interpretation of observations made in vivo have challenged the biological and physical sciences for centuries. From the earliest physiological experiments in living organisms, the joint approaches of biology and physics to the discovery of these processes, from cells to humans, have yielded profound insights and have had a major impact on our understanding of all organ systems and on the modern practice of medicine as a whole. The work of Helmholz (1821–1894) is an example of the early merger of physics and biology that ultimately led to the most recent formulation of a systems biology approach that is no less than the quest for complete quantification of the dynamic processes of entire organisms and organs in health and disease, for example in the shape of the Physiome Project of Bassingthwaighte (2000) and the Blue Brain Project of Markram (2006).

In this compendium, we focus on the dynamics of brain physiology in vivo from the perspective of the methods of tracer kinetics (neurokinetics). Applications of neurokinetics seek to measure the processes that take place in the tissue without disturbing these processes, and subsequently to map these measurements onto images of brain tissue.

Applications of physiological kinetics (including neurokinetics) use "indicators" or markers, ranging from the dyes introduced at the dawn of experimental physiology, via stable (nonradioactive) or unstable (radioactive) isotopes introduced in the 1960s, to the most recent methods of in vivo imaging of optical, magnetic resonance (MR), and magnetic field (MEG) signals for visualization and detection.

The authors dedicate this book to the consolidation of many neurokinetic concepts with roots in the neurophysiology of the mid-20th century with the state-of-the-art imaging and parametric mapping methods of the first decade of the 21st century.

In one of the earliest attempts to quantify the pharmacokinetics of a substance in blood, Widmark (1919) followed the concentration of a single dose of acetone injected into the bloodstream. Widmark and others subsequently examined a number of so-called "model" configurations, including the first account of a one-compartment open model (Widmark and Tandberg 1924) and the later extension to two compartments (Gehlen 1933).

Models of Living Systems

Apostel (1960) described a model of a living system as an artificial system that "simulates a biological system. The kinetic analysis of the model (which usually describes a dynamic process) tests the validity of the model of the combined kinetic behavior of the elements of each compartment. The model provides the basis for prediction of subsequent behavior. Thus, the model is the mathematical expression of the biological system, and the mathematical analysis is the test of predictions generated by the hypothesis."

Statistical hypothesis testing often is used to judge whether a model is appropriate or not. The model is defined by operational equations that yield a dependent variable for each set of independent variables. The statistical evaluation of the kinetic analysis cannot of itself establish the truth of the model, which is why it is more accurate to describe the validated model as "not yet rejected" and therefore still potentially useful to the solution of a given problem. Likewise, the answers provided by the operational equation are only "consistent" with the experimental or clinical observations. For this reason, it is important to identify those situations in which the model is rejected by the chosen compartmental analysis, e.g., by application of a criterion of information content (Akaike 1974) in which statistical goodness of fit is balanced against the number of parameters fitted.

Kinetics and Molecular Biology

The purpose of kinetic analysis of living matter is to obtain quantitative measures of the rate of molecular reactions. Quantitative approaches were uncommon in biology and medicine prior to the second half of the nineteenth century and only slowly gained ground against traditionally qualitative considerations. The competition between quantitative and qualitative perspectives is felt even today.

The struggle reflects the changing views of disease in the medical sciences in which a disorder originally was thought to represent a major imbalance among qualitatively different matters of nature and life, including the four elements (water, air, fire, and earth) and the four cardinal fluids (blood, phlegm, yellow bile, and black bile).

This imbalance no longer is a valid consideration. The imbalance underlying disease appears to follow minute but specific errors which are now known to create the effects of disease by turning open thermodynamic systems implemented in biochemical and physiological compartments into closed systems that must ultimately fail because entropy rises in closed systems as order is replaced by disorder. Thus, it is a fundamental observation that truly closed systems eventually become incompatible with life.

The concept of imbalance is quantitative, as is the injunction of living matter to respond to exigencies with moderation. Thus, measurement is the modern practice, although it is tied to an increasing understanding of the limits of certainty.

Competing with this understanding is the rise of information technology, according to which the quantitative properties of the components of living systems could be less important, implying that only their structural relations are informative. Thus, there is a current sense that the tide of scientific philosophy is returning in the direction of the holistic and qualitative. Only the practice of meticulous kinetic analysis can correct this misunderstanding.

Kinetics and Genomics

Living matter is distinguished from nonliving matter primarily by its ability to maintain steady-states of incredibly complex molecular compartments far from thermodynamic equilibrium. The information enabling the realization of this enormous potential resides in a remarkably inert and robust molecule called deoxy-ribonucleic acid (DNA). However, the DNA molecule itself does nothing; its entire and completely passive role is to be decoded by a machine or mechanism. Its power to elicit action derives from the ability of other molecules in living tissue to read its instructions at the right time and place.

As the decoder must understand the message of at least the opening sections of the manual (the rest can be learned in due course), in advance of the decoding, the fundamental goal of metabolite and tracer kinetic analysis in biology and medicine is to describe and quantify the processes in their entirety from the conception to the termination of the organism. For example, it is estimated that at the peak of neuronal proliferation during human gestation, as many as 250,000 new brain cells of identical composition are created every minute. Yet, metabolite concentrations everywhere remain inside carefully regulated limits. A snapshot of any one cell would produce an unremarkable image; only the proper tracer kinetic analysis could reveal the astounding dynamics of the metabolite fluxes contributing to this development.

Kinetics and Proteomics

The rate of molecular reactions typically is constrained by proteins. An important measure of health is steady-state, in which proteins maintain the concentrations of metabolites while the molecular fluxes adjust to local and global requirements. Most importantly, the composition of living matter remains constant in steady-state (hence the name) and a momentary glimpse reveals none of the dynamics of the underlying molecular fluxes. The further the steady-state is from a state of equilibrium, the greater is the work required to maintain it, and the greater are the fluxes controlled by the proteins. Only a few processes are near equilibrium and they typically do not interfere with the regulation of the important molecular fluxes of living matter.

When concentrations normally do not change outside tightly controlled limits, past attempts to understand the underlying dynamics by perturbing a system often removed the system from its normal state and sometimes failed to specifically reveal the normal dynamic properties of its kinetics. The introduction of suitably flagged ("labeled") and hence identifiable representatives of the native molecules, called "tracers," accomplishes a minimal perturbation without disturbing the steady-state of the system, provided the quantity of tracer is kept too low to change the system's properties. Methods of doing just that form the core of the tracer kinetic analysis of biological processes.

Role of Tracers in the Study of Models

A physiological/biological process to be studied is often exposed by means of a tracer (not always radioactive), that is a marker of a native molecule relevant to the process that can be detected by an instrument, e.g., radioactive counting or light or magnetic measurement. The tracer must be present in such low mass/quantity that the characteristics of the processes in which the tracer participates do not change (e.g., does not compete with the endogenous processes, in the case of neuroreceptor imaging the tracer does not occupy significant receptor sites to notably compete with endogenous neurotransmitters).

The purpose of this requirement is to rule out the departure from steady-state that would otherwise cause the concentrations of native molecules to change as functions of time. The departure of the native system from steady-state would in turn interfere with the first-order relaxation of tracer compartments, discussed in the text.

Organisms and organs are collections of cells that internalize the tracer in different ways according to the physical and chemical properties of the tracer, and the biochemical and physiological properties of the cells. A physiological model can be formulated as a collection of compartments that represent the different states of the tracer and its metabolites. Strictly speaking, the compartments have no formal relation to the structure of the target organ, except to the extent that the anatomy delineates the processes in which the tracer or its metabolites participate (e.g., a tracer may bind to an active site as a receptor or transport mechanism when its structure fits the receptor or transporter site in the right chemical fashion). For this reason the model may be much simpler than that of the actual native system and still be a valid portrayal of the kinetic behavior of the tracer. In other words, the model is of the tracer, not of the native system. Often, compartments reflect the biochemistry of an organ and refer to quantities of tracer or its metabolites that need not be confined to separate subdivisions of the organ.

Sheppard (1948) defined compartments as quantities of a tracer or its metabolites, the concentrations of which remain the same everywhere, each quantity having a single state that may vary in time but not in space. A quantity is the number of

molecules in units of moles (mol), 1 mol holding $6.0225 \cdot 10^{23}$ atoms or particles. Thus, initially, a tracer is neither in a steady-state, nor in equilibrium. However, there are other noncompartmental approaches to physiological quantification that can also be employed (see text).

Role of Models as Interpreters of Biological Dynamics

When researchers interpret processes of physiology and pathophysiology by means of tracers or other marker tools, they examine the results with specific methods that include biochemical measures (e.g., mass spectrometry and radioactivity counting) or external recording in vivo (e.g., positron or single photon emission tomography [PET or SPECT]). There is rather a tendency (often naive) to search for a tracer acting as a "magic bullet" that provides a picture of the entire process by biochemical measures or external imaging of a subject. In the example of external imaging, waiting a specified time after intravenous injection typically occurs in the clinical setting of recording of static images for evaluation of, say, heart or bone in conditions in need of a diagnosis.

However, when attempts are made to understand and quantify a physiological approach with the greatest scientific rigor, evaluation of the full dynamic process prior to a steady-state is necessary, even when mathematical simplifications are later found to be acceptable. This necessity usually includes not only the brain kinetics of the tracer but also the input record which reflects the dynamic history of the tracer itself, circulating from the injection site to the planned target (e.g., the blood volume spaces at the blood–brain barrier interface).

This book is also dedicated to the understanding of the underlying principles of kinetic properties of dynamic biological processes of brain physiology, the so-called "neurokinetics."

Approaches to Physiological Modeling

Physiological processes are best determined by mathematical descriptions which then are subject to the well established rules of computation of the physical and chemical sciences rather than any qualitative approach that is limited and can lead to erroneous extrapolations beyond the actual empirical data.

Compartmental Modeling

The most common approach to the in vivo quantification of dynamic brain processes (as networks of complex chemical systems) is that of compartmental modeling. This

approach divides the physiological processes into definable units. In the case of brain images, it depends at a minimum on records of the tracer input function (usually from plasma or whole-blood samples) and one or more brain compartments . The assumptions and principles are outlined in Chaps. 1 and 2.

Non-Compartmental Modeling

A presentation of noncompartmental models is beyond the scope of this book. However, there are early examples of attempts to quantify physiological properties such as blood flow or blood volume, as in the case of the indicator dilution method reviewed by Zierler (2000).

Distributed models attempt to account for spatial gradients in concentrations (e.g., in blood-tissue exchange) in contrast to compartmental models that depend on concentration averages within each compartment (Kuikka et al. 1991).

In the compartmental models to be discussed in the following chapters, the usual assumption is the existence of homogeneous and fully stirred compartments. There are attempts at modeling that directly address this inhomogeneity with so-called "distributed" models, such as in the case of myocardial blood flow estimation, including fractal analysis, a branch of mathematical analysis (Qian and Bassingthwaighte 2000). Unfortunately, little progress has been made in the field of quantification of dynamic brain processes with noncompartmental models (one attempt was made by Wong and Gjedde in 1996), limited in part by the poorly resolved temporal and spatial sampling of brain images, compared to data obtained from cardiovascular and other systems, perhaps in part due to the more invasive tools used in the study of the latter.

Some distributed models have been proposed for use with PET and external imaging as in the measurement of oxygen consumption (Deussen and Bassingthwaighte 1996), with special attention to small tissue regions (Li et al. 1997). However, the majority of these applications used invasive approaches to imaging, with direct measurement of the tracer concentrations.

Nomenclature

The nomenclature adopted in this books originated in publications spanning more than 35 years. Other nomenclatures have been presented in more recent attempts to reach consensus that we intend to evaluate in future editions, as discussed in the Glossary section of this book where all terms are explained. In this edition, we chose to retain the nomenclature as originally published while we wait for further refinement of the current consensus reports.

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Contents

Chapter 1
Introduction to Compartmental Analysis*

1.1 Concept of Compartments

1.1.1 Living Systems

In the context of compartmental analysis, a living organism can be described as an open biological system existing in a *steady-state* far from *thermodynamic equilibrium.* Thermodynamic equilibrium is a state in which no biological processes can occur because there are no potential gradients to drive them; no differences in mechanical potential to drive blood flow, in concentrations to drive diffusion, in chemical potentials to drive metabolism, in electrical potentials to drive ions, and in temperature to drive heat flow. Steady-state and thermodynamic equilibrium share the characteristic that they are invariant in time. Thermodynamic equilibrium is also invariant in space. The steady-state variance of constituent chemicals in space is the focus of compartmental analysis. Spatial variance is assigned to the interfaces between abstract compartments rather than to the living system as a whole. As the compartments by this definition are in thermodynamic equilibrium internally, they are incompatible with life but we choose to ignore this fundamental characteristic.

Compartmental analysis uses the principles of biophysics and mathematics to determine the velocity of exchanges among the compartments (biochemical processes) and the relative size of the individual compartments (biochemical pools) in vivo, using tracer molecules, defined as markers that do not perturb the system.

During a medical study or biological experiment, the tracer and its metabolites assume different states, each of which may be well defined but all of which change and interact as functions of time. Eventually, one or more of these states may reach the steady-state characteristic of the native system, though far from thermodynamic equilibrium. This steady-state can be maintained only in thermodynamically open systems. If energy is no longer provided or expended, potential

* Adapted from Gjedde (1995a) Compartmental analysis. In: *Principles of Nuclear Medicine*, 2nd edition, eds Wagner HNJr, Szabo Z, Buchanan JW. Saunders, Philadelphia, pp. 451–461, with permission from Saunders, Philadelphia.

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