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Interactive Compartmental Modeling

TO THE EDITOR: Burger and Buck (*1*) emphasize that their interactive compartmental modeling software package is a highly versatile tool for the analysis of time-activity curves from clinical PET and SPECT studies. They conclude that its main features are easy model configuration, evaluation and use after a short training session (*1*).

Mathematical models in nuclear medicine literature appear to be rather plain and straightforward (*1–4*), though they are not necessarily so simple (*5–8*). Relevant description of organ function in complex biological structures is difficult, particularly because the complexity is both geometrical and temporofunctional and data are based on external measurement of radioactivity distribution in space and time (*5,8*). Also, classical medical training often has not prepared physicians to use mathematical models properly, although image resolution (spatial and temporal), reconstruction errors, signal-to-noise ratio and other quantitation inaccuracies are well understood. Nuclear medicine physicians who begin to use quantitative models and software packages for describing and interpreting their data on tracer kinetics in situ, however, often find it difficult to get started. Here, I would like to emphasize that the suitable approach is often not to start with the direct formulation of the equations as suggested by Burger and Buck (*1*), but with (a) thorough consideration of the in vivo reactions during the study and (b) deep analysis of the basic and fundamental assumptions of the model.

Often the principal questions are the following:

- What is the reaction of interest (perfusion or metabolism or both) under study?
- How is this reaction related to local structure? (In most instances, structure and function are intimately inter-related because tracers distribute according to their substrate nature and to the anatomic distribution of the system features.)
- Do local functions affect global input?
- To what degree does fundamental nonlinearity of the systems exist?
- Are measured features common to all individuals and under all pathophysiological conditions?

It is most essential to make "correct" assumptions that are based wherever possible on previous physiological and anatomical observations. The biochemical fate of tracers has to be known completely. In addition, no fundamental chemical and physical laws can be broken. Only by thoroughly combining data from a particular nuclear medicine procedure with actual structure and function of the system under the study can a logical model be composed.

Next, there are several basic and fundamental assumptions underlying the compartmental model:

- The system is mathematically linear.
- Each compartment is wholly and instantaneously mixed so that the concentration within it is uniform at all times.
- The system is in a steady state with respect to mother substance (tracee) so that tracer exchange rates are first order.
- The volumes and exchange rates between compartments are constant.

The main problem with the compartmental, stirred tank model is its failure to meet the second condition. For example, it is obvious that the plasma is not an instantaneously mixed compartment although this is commonly assumed. A further condition is therefore appropriate: Time required for complete mixing in a volume (compartment) is very short compared to the time constant of the fastest exchange process. These are very restrictive assumptions. For example, the arteriovenous (A-V) difference of glucose across most organs is small (only a few percent). However, a steady-state A-V difference for the nontracer mother substance is not critical here, but it is the first-pass, instantaneous extraction of the tracer that counts (*8*). The first-pass extraction of fluorodeoxyglucose (FDG) is about 50%, a huge gradient, and so the estimates of the transfer rate constants (k_{ij}) by compartmental models tend to be too high, sometimes by a factor of 2 to 4 (*8*). Even in the brain, where the capillary network is a well-ordered, highly tortuous stereoscopic arrangement of capillaries (a well-mixed compartment), there is a relevant concentration gradient for the slowly diffusible tracers (such as FDG) that destroys the validity of the compartmental model, which assumes that each compartment is wholly and instantaneously mixed so that the concentration within it is uniform at all times.

Applied software packages are an essential part of the imaging system to analyze the data to provide clinically and scientifically relevant information. In particular, in-house programming, which certainly represents the developing edge of nuclear medicine, usually lacks proper quality assurance and testing (*9*). In short, with thorough consideration of the in vivo reactions during the study (under normal or pathophysiological conditions) and with the valid assumptions and testing of the model, the proposed software package (*1*) can be used to add diagnostic or scientific value to the nuclear medicine procedure.

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Is It Time for a Change?

TO THE EDITOR: I read with interest Dr. Henry N. Wagner's recent letter to the editor concerning merging the Society of Nuclear Medicine (SNM) and the American College of Nuclear Physicians (ACNP) (*1*). Dr. Wagner is a respected member of our community, and any time he voices an opinion we should give it due consideration. However, in terms of the material presented to support Dr. Wagner's point of view, there are a few confounding issues.

The American Society of Internal Medicine and the American College of Physicians are two organizations that permit only physicians to be members. To the best of my knowledge, they do not represent technologists, basic scientists or other medical professionals.