

## Parametric imaging in nuclear medicine

Niels A. LASSEN,\* Hidehiro IIDA\*\* and Iwao KANNO\*\*

\*Department of Clinical Physiology and Nuclear Medicine, Bispebjerg Hospital,  
DK-2400 Copenhagen NV, Denmark

\*\*Department of Radiology and Nuclear Medicine, Akita Research Institute of Brain  
and Blood Vessels, Japan

EMISSION TOMOGRAPHY by PET or SPECT allows after certain corrections, to calculate the isotope concentration in the tissue. However, if one wants to image the underlying physiological parameter that the tracer is designed to trace, then these concentration images must be transformed pixel-by-pixel, using appropriate tracer kinetic models. These transformed images are called *Parametric Images*. They are scaled in the relative units or absolute units pertaining to the parameter imaged, conventionally ml/100 g/min for blood flow, ml/100 g for distribution volume and nM/litre for receptor density to give some specific examples.

The text gives a brief review of parametric imaging. The basic tool is the *convolution integral*. It was introduced for tracer kinetic analysis by Seymour S. Kety in 1951,<sup>1</sup> and soon after applied by his group for processing autoradiographic images of brain slices to calculate cerebral blood flow in ml/100 g/min<sup>2</sup>. The first sections explain the convolution integral and the basic equation of Kety for readers having elementary knowledge of calculus.

### The Convolution Integral

Consider that we were able to inject one unit of tracer as an infinitely brief bolus at the arterial inlet to one gram of brain tissue. The inflow rate of tracer, the brief bolus, is called the *unit impulse input* and it is denoted by  $\delta(t)$ . It enters the tissue when  $t = 0$  as a brief spike of one unit of tracer and this causes the tissue concentration to rise abruptly from 0 to 1 at time zero. The corresponding tissue concentration as a function of time is called the unit

impulse residue function  $g(t)$ . It is the function describing what remaining (or "resides") in the tissue at time  $t$  after the bolus injection.

We will change the time variable to  $\tau$  for reasons that will become clear later and calculate the tissue concentration resulting from an arbitrary input  $i(\tau) = f \cdot Ca(\tau)$ , blood flow ( $f$ ) times arterial concentration ( $Ca(\tau)$ ). This calculation is accomplished by considering the tracer inflow as a sequence of a large number of brief rectangular impulses. Each impulse has the height  $i(\tau)$ , the duration  $d\tau$ , and it lasts from  $\tau$  to  $\tau + d\tau$  (Fig. 1).

The system is assumed to be stationary and linear. *Stationarity* means that if a unit amount is injected as an impulse at time  $\tau$  instead of at time zero, then its response function is  $g(t - \tau)$ , i.e. it is the same as before, but delayed by  $\tau$  minutes. *Linearity* means that if two or more impulses are injected, then the response will be the sum of the individual responses. It also means, that if an impulse is multiplied by a constant  $A$ , the response will also be multiplied by  $A$ . Linearity is a general property of tracers as the chemical amount of substance used is negligibly small.

As stated above, we divide the arbitrary inflow into a sequence of infinitely many impulses. Consider the injected amount  $i(\tau) d\tau$  entering from time  $\tau$  to  $\tau + d\tau$ . Due to linearity the magnitude of the response will be  $i(\tau)d\tau$  times the unit impulse response  $g(t)$ , and in accordance with stationarity this response is shifted by the time  $\tau$ . Thus, with  $d$  denoting that the response is only the response to a very small impulse of indicator, the residue at time  $t$  stemming from  $i(\tau)d\tau$  is (see also Fig. 1):

$$dC(t) = i(\tau) \cdot g(t - \tau) d\tau \quad (1)$$

Adding all the responses from 0 to  $t$  gives the tissue concentration at time  $t$

$$C(t) = \int_0^t i(\tau) \cdot g(t - \tau) d\tau \quad (2)$$

Based on an invited lecture at the 34th Annual Scientific Meeting of the Japanese Society of Nuclear Medicine, Sapporo, September 1994.

For reprint contact: Iwao Kanno, M.D., Department of Radiology and Nuclear Medicine, Akita Research Institute of Brain and Blood Vessels, 6-10, Senshu-kubota-machi, Akita 010, JAPAN.

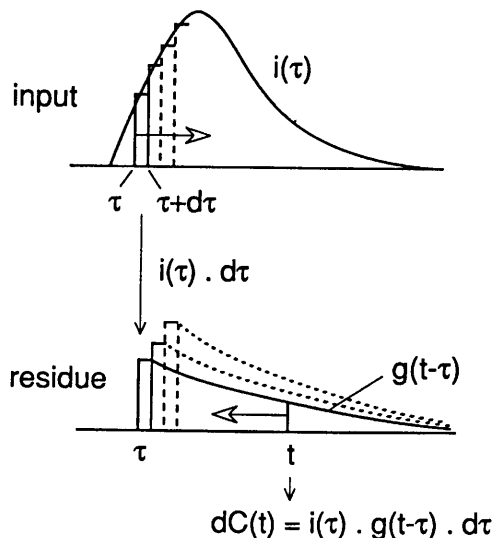


Fig. 1 Principle of convolution integral.

This is the *Convolution Integral* which may also be written  $C(t) = i(t) * g(t)$  with the asterix, \*, denoting the convolution operation. It is the area under the product of two functions, having the time variables,  $(t - \tau)$  and  $\tau$ , respectively. In this complex form of multiplication the time variables of the two functions move in opposite directions during the integration:  $i(\tau)$  moves forward in time as we integrate from 0 to  $t$ , while  $g(t - \tau)$  moves backward in time, from  $t$  to 0. This can be considered as a twisting together of the two functions, the first end of one is multiplied by the last end (before  $t$ ) of the other and vice versa. The two functions are therefore said to be convolved: from latin, con = with or together with; volvere = to twist or turn; convolvere = to twist together.

#### The Basic Equations

In his original paper Kety analyzed the exchange of freely diffusible tracers, i.e. tracers that freely permeate the capillary wall. For a single homogeneous tissue, a so-called single compartment, the wash-out function of one unit of tracer takes the well known monoexponential form

$$g(t) = \exp(-f/\lambda \cdot t) \quad (3)$$

Here  $g(t)$  is the residue (tissue concentration) of a unit impulse input,  $f$  is the blood flow per gram of tissue, and  $\lambda$  is the volume of distribution of the tracer per gram of tissue. Combining eq. (4) with eq. (3) gives the basic kinetic equation for a single compartment when the input rate varies,  $i(t) = f \cdot Ca(t)$

$$C(t) = f \cdot Ca(t) * \exp(-f/\lambda \cdot t) \quad (4)$$

This equation is often called the "autoradiographic" equation, as an autoradiographic technique was employed to measure the concentration  $C(t)$  in the first studies Kety's group performed based on eq. (4).<sup>2</sup>

The volume of distribution, that Kety used the greek letter  $\lambda$  to symbolize, is an important parameter. It is

defined as the equilibrium ratio  $C(\text{tissue})/C(\text{blood})$ . This means, that it denotes the number of millilitres of blood that at equilibrium contains the same amount of tracer as one gram of tissue. In the more recent literature, the symbol  $Vd$  is often used instead of  $\lambda$ , because  $Vd$  directly conveys the meaning of the parameter:

$$\lambda = Vd = \left[ \frac{C(\text{tissue})}{C(\text{blood})} \right]_{\text{eq.}} \text{ ml/g} \quad (5)$$

As pointed out by Meier and Zierler (1954), the mean transit time of the tracer through the tissue  $\bar{t}$  equals  $Vd/f$ , the distribution volume/flow ratio.<sup>3</sup> This relation holds both for a single compartment and for a multicompartmental system.

In some situations one may instead of considering the total tissue mass, i.e. the tissue and its contained blood, prefer only to consider the tissue proper. In this case the inflow  $K_1$  is the so-called "clearance," i.e. the millilitres of blood cleared of tracer as the blood passes through the brain vessels, i.e.  $K_1 = f \cdot E$  where  $E$  is the extraction, that is the fractional loss of tracer from an element of blood passes through the tissue. Changing also the symbol for the distribution volume from  $\lambda$  to  $Vd$  we can write the basic equation (eq. 5) as

$$C(t) = K_1 Ca(t) * \exp(-K_1/Vd \cdot t) \quad (6)$$

When using the convolution integral to analyze SPECT or PET images, we must take into account that a pixel value does not represent  $C(t)$ , but that it is the cumulative counting rate over the period of scanning, from  $t_1$  to  $t_2$ . Hence the convolution integral must be integrated from  $t_1$  to  $t_2$ . The result is a double integral of rather impressive form:

$$C_i = \left[ \text{Pixel value} \right]_{t_1}^{t_2} \\ = \int_{t_1}^{t_2} \int_0^t K_1 Ca(t - \lambda) \cdot \exp(-k_2 \cdot \tau) d\tau dt \quad (7)$$

where  $K_1$  and  $k_2$  are the values of these parameters in pixel  $i$ , a volume of tissue so small that it is be considered homogeneous (a "single compartment"), and where  $C_i$  and  $Ca(t)$  are both decay corrected.

Homogeneity of the tissue comprised by a pixel is the crucial assumption needed to derive equations (3) to (7). With autoradiographic techniques a spatial resolution in order of less than 1 mm in all three dimensions can easily be achieved. But with  $\gamma$  emission tomography the best resolution obtained by PET under favourable conditions is in the order of 3 to 4 mm. As the cortex in man is only about 2 mm thick it is clear that the homogeneity requirement cannot be fulfilled. For this reason it is important to design the experiments in such a way as to minimize the error due to inhomogeneity, the so-called partial volume effect. An adequate discussion of this important point lies,

however, outside the scope of the review as it would demand detailed presentation and analysis of the precise experimental study to be imaged parametrically.

#### Deconvolution

The convolution integral must be solved in order to calculate the parameters that we want to image,  $K_1$ ,  $k_2$ , and  $V_d = K_1/k_2$ . This process is called deconvolution. It requires that  $C_i$  and  $C_a(t)$  have both been recorded and that they are expressed in the same units by proper cross-calibration.

Conventionally, the deconvolution is performed by *iterative convolution*. This means that initial values of the correct order of magnitude for  $K_1$  and  $k_2$  are first assumed. Then the double integration is performed on a computer for all data points ( $C_i$ ). Using the variance (sum of the square of the difference between calculated and observed  $C_i$ ), the convolution is repeated, i.e. iterated, until the variance reaches a minimal value. This approach necessitates several data sets and is time consuming as iterative fitting must be performed for every single pixel. The procedure is so widely used and used for so many different purposes that it is not easy to give a specific reference to where it was first used in nuclear medicine.

An alternative approach to the least-square iterative deconvolution is the table look-up deconvolution method. It was first used for parametric imaging of cerebral blood flow by Kanno and Lassen in 1979 using inhaled  $^{133}\text{Xenon}$  gas and a fast rotating SPECT instrument.<sup>4</sup> The method is based on taking the *ratio of pixel values* and comparing them to the *ratio of the double integral* in eq. (8). This eliminates  $K_1$ , so that the ratio is solely a function of  $k_2$ . Thus the ratio of only two observations,  $C_i [t_1 \rightarrow t_2]$  and  $C_i [t_3 \rightarrow t_4]$ , allows uniquely to determine  $k_2$  from the table. In the paper by Kanno and Lassen a sequence of four data observations (images) was, however, used. This was implemented by introducing a weighting function so as to de-emphasize time points for which the ratio changed little as a function of  $k_2$ . With  $^{133}\text{Xenon}$   $k_2$  can be taken as a measure of tissue blood flow as  $V_d$  is close to unity. The approach was subsequently modified by Celsis et al. in order to counteract effects of Compton scatter.<sup>5</sup>

Iida and co-workers have recently applied the table look-up approach for  $^{123}\text{Iodide}$  labelled isopropylidoamphetamine, IMP.<sup>6</sup> The aim is to calculate  $K_1$ , and as extraction of IMP is almost unity, thus tissue blood flow. Two sets of data points are collected, an early and a late image. This allows to calculate  $k_2$  and also  $K_1$  as just described pixel by pixel. The procedure essentially consists in correcting the early picture for wash-out of tracer. In other terms, IMP is considered as a chemical micro-embolus for measuring blood flow correcting for the imperfect retention by determining  $k_2$ . Iida et al. also analyzed the situation when the  $K_1/k_2$  ratio was assumed to have a fixed value, i.e. a fixed value for the distribution volume was assumed. In this situation only one scan, the

early one soon after IMP injection is needed.<sup>7</sup> The method of Iida et al.<sup>4</sup> is, due to the high extraction of the tracer, so far the best of the CBF techniques based on brain retained tracers. The  $^{99\text{m}}\text{Technetium}$  labelled tracers HMPAO and ECD are only about 50% extracted in a single passage through the brain, and as this extraction is not constant, reliable quantitation of CBF is not possible with these compounds.

The table look-up approach has by Onishi et al. (1995) now also been applied to parametric imaging of  $V_d$  for  $^{123}\text{Iodine}$  labelled iomazenil, IMZ a benzodiazepine (Bz) receptor ligand.<sup>8</sup> This  $V_d$  is proportional to the Bz-receptor concentration,  $B_{\text{max}}$ , because there is no endogenous ligand occupying receptor sites and because unspecific binding of the tracer in brain is negligibly small relative to the specific binding to the receptor.

#### Comment

In this brief account of parametric imaging by deconvolution, we only presented the single tissue model of Kety. It should be noted, however, that also two-compartment models can be handled by the same basic principles, i.e. by iterative fitting or table look-up deconvolution. It is clear from the current literature that the methods here described are gaining wide use. Perhaps this all will change in the near future as co-registration of PET or SPECT with magnetic resonance imaging (MRI) opens up new possibilities: iterative reconstruction of isotope scans and of parametric derivatives of such scans can then be based on "prior" anatomical knowledge from MRI. This may reduce statistical noise but will not alter the basic principle of the parametric imaging by deconvolution.

#### REFERENCES

1. Kety SS. The theory and applications of the exchange of inert gas at the lungs and tissues. *Pharmacological Reviews* 3 (1), 1951.
2. Landau WH, Freygang WH, Rowland LP, Sokoloff L, Kety SS. The local circulation of the living brain; values in the unanesthetized and anesthetized cat. *Trans Amer Neurol Ass* 80: 125-129, 1955.
3. Meier P, Zierler KL. On the theory of the indicator-dilution method for measurement of blood flow and volume. *J Appl Physiol* 6 (12): 731-744, 1954.
4. Kanno I, Lassen NA. Two methods for calculating regional cerebral blood flow from emission computed tomography of inert gas concentrations. *J Comput Assist Tomogr* 3 (1): 71-79, 1979.
5. Celsis P, Goldman T, Henriksen L, Lassen NA. A method for calculating regional cerebral blood flow from emission computed tomography of inert gas concentrations. *J Comput Assist Tomogr* 5: 641-645, 1981.
6. Iida H, Itoh H, Bloomfield P, et al. A method to quantitate CBF using a rotating gamma camera and I-123-amphetamine (IMP) with one blood sampling. *Eur J Nucl Med* 21: 1072-1084, 1994.

7. Iida H, Itoh H, Nakazawa M, Hatazawa J, Nishimura H, Onishi Y, et al. Quantitative mapping of regional cerebral blood flow using Iodine-123-IMP and SPECT. *J Nucl Med* 35: 2019–3030, 1994.
8. Onishi Y, Yonekura Y, Mukai T, Nishizawa S, Tanaka F,

Okazawa H, et al. Simple quantification of Benzodiazepine receptor binding and ligand transport using Iodine-123-lomazenil and two SPECT scans. *J Nucl Med* 36 (7): 1201–1210, 1995.