The University of Manchester
Wolfson Molecular Imaging Centre

Input Functions in PET

Rainer Hinz

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Input function: What is it and why is it needed?

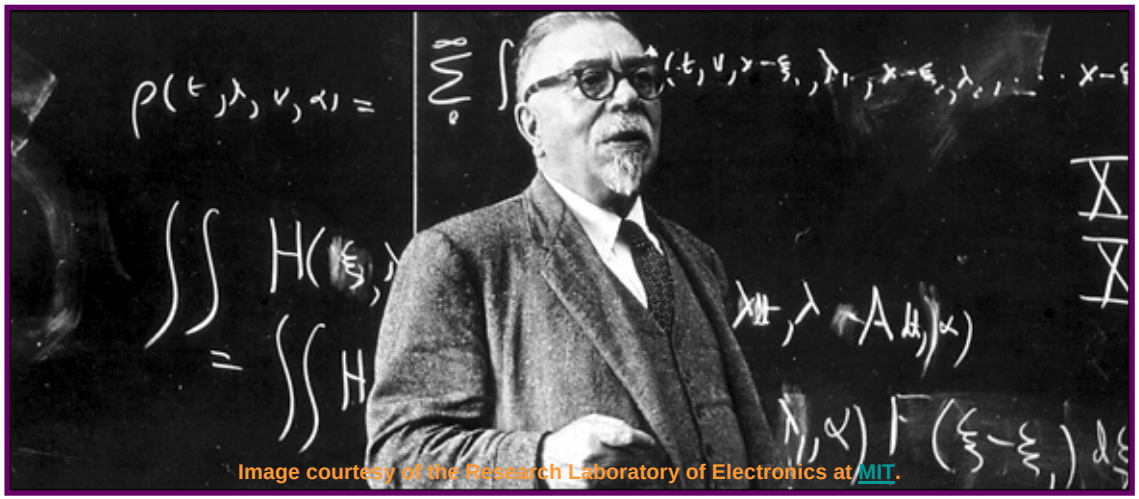
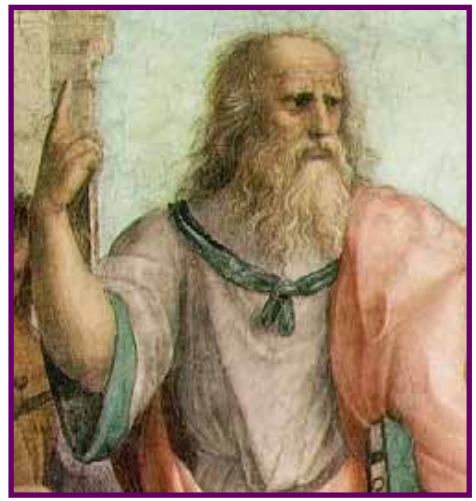


Image courtesy of the Research Laboratory of Electronics at MIT.



1948

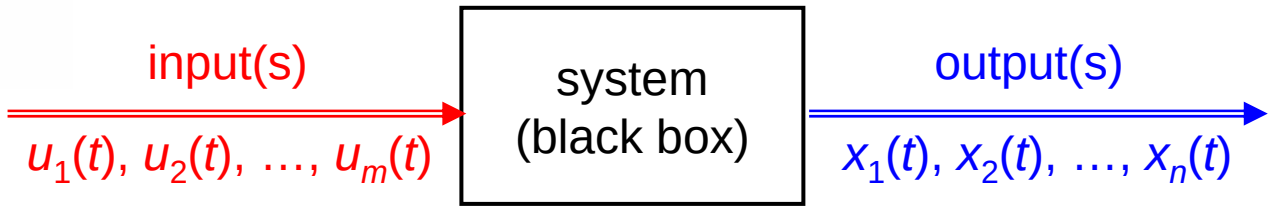
CYBERNETICS

or control and communication in the animal and the machine

NORBERT WIENER

Dynamical model in a nutshell

The concept of a *dynamical model*:

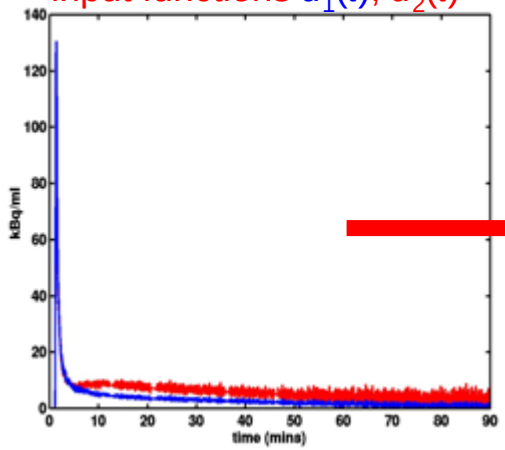


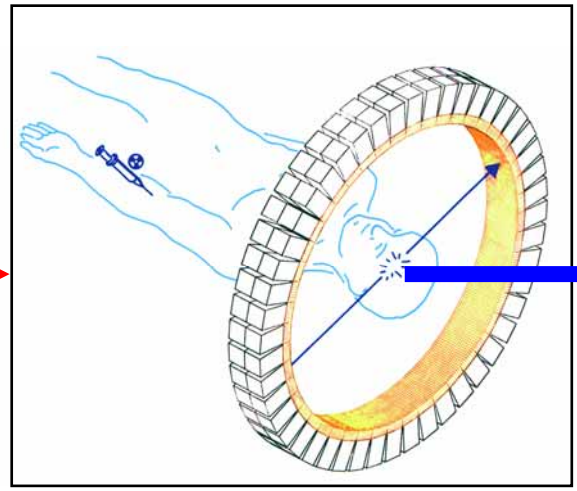
System identification:

perturb the system with an *input function*, observe the *system response* and try to infer the *system parameters* from the time series.

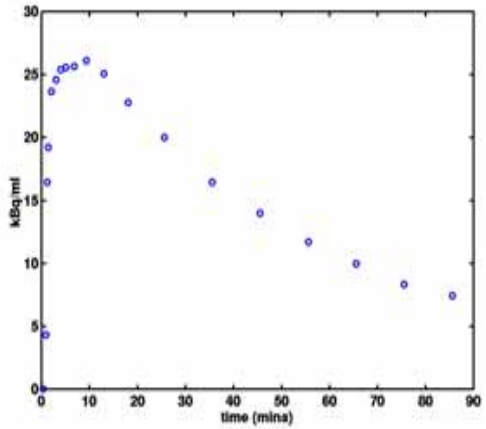
In PET:

input functions $u_1(t)$, $u_2(t)$





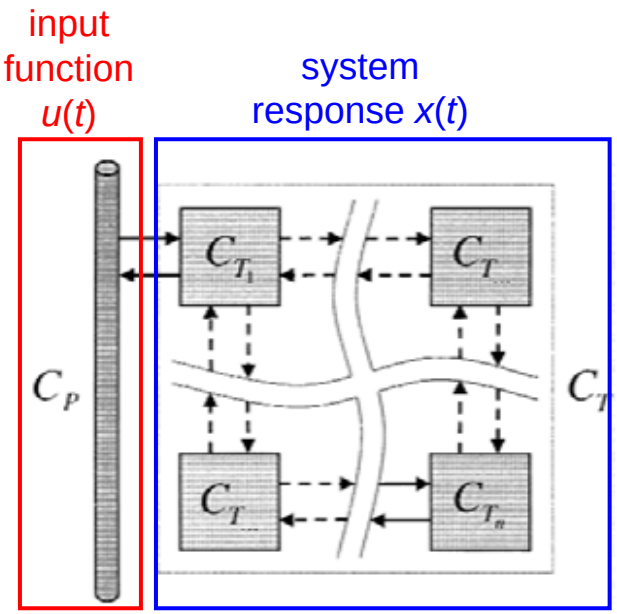
system response $x(t)$

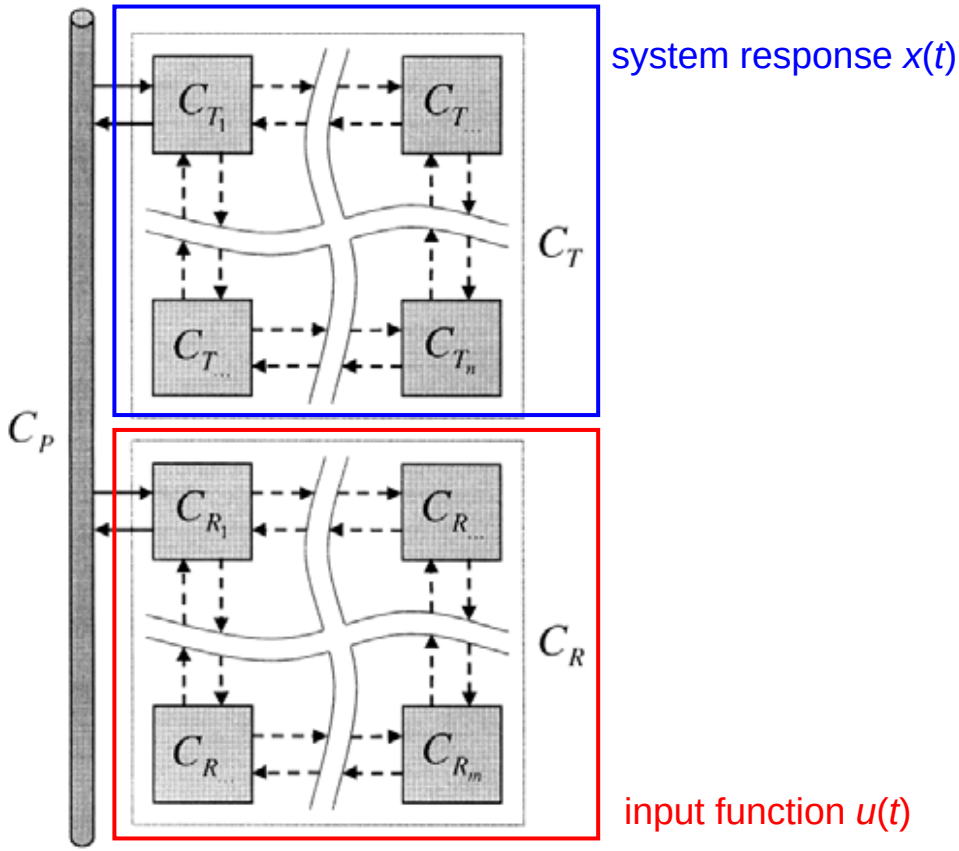


Input function: What is it and why is it needed?

In PET, the mathematical models are classified by their type of input in:

- plasma input models
- reference tissue input models





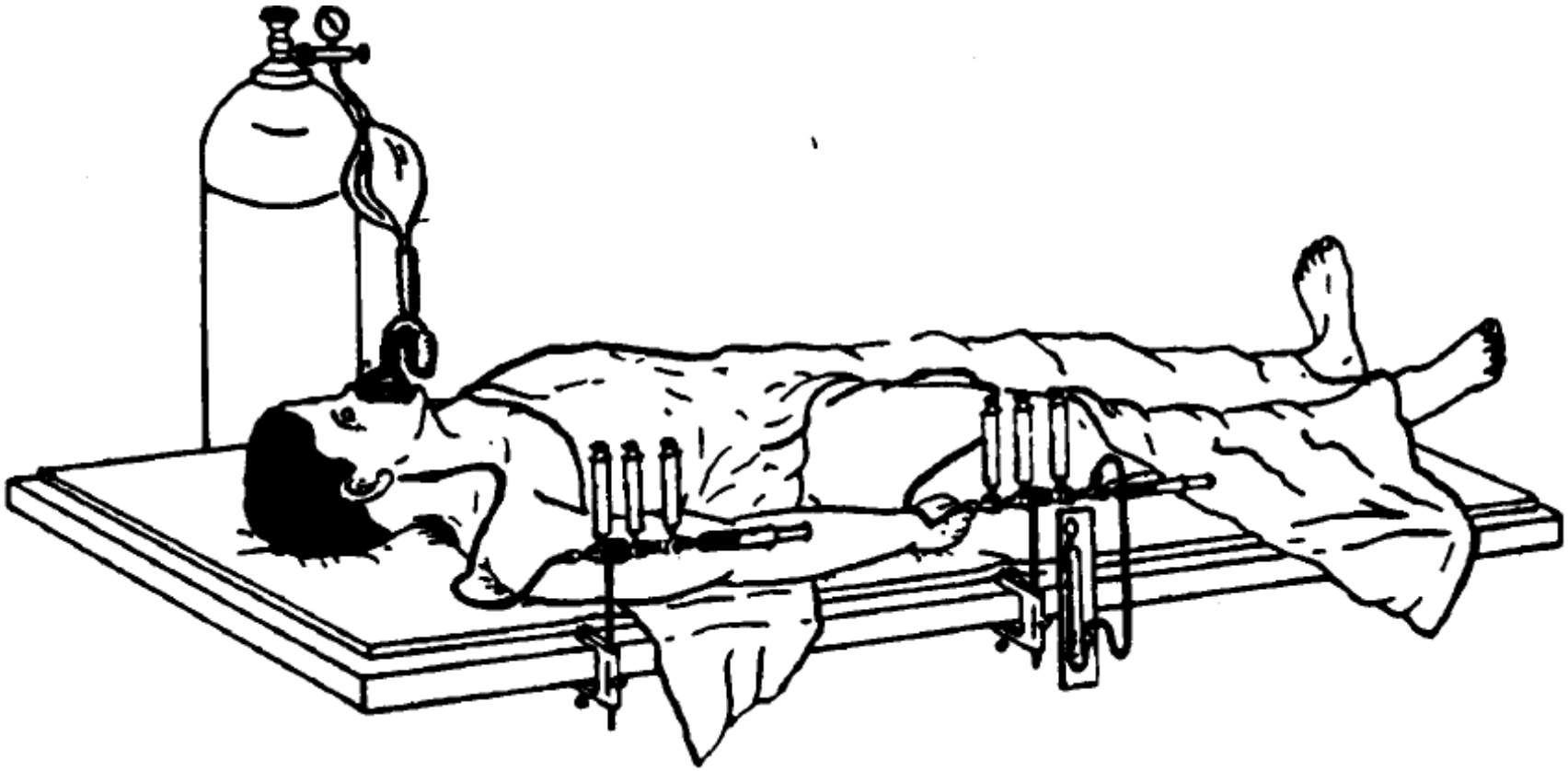
All about modelling: next week's educational seminar

Marie-Claude Asselin - Kinetic Models in PET

Life before PET

THE NITROUS OXIDE METHOD FOR THE QUANTITATIVE DETERMINATION OF CEREBRAL BLOOD FLOW IN MAN: THEORY, PROCEDURE AND NORMAL VALUES[1]

By SEYMOUR S. KETY and CARL F. SCHMIDT



J. Clin. Invest. **27** (1948), 476–483.

The dawn of PET in the 1970s

Quantitative Measurement of Local Cerebral Blood Flow in Humans by Positron Computed Tomography and ^{15}O-Water

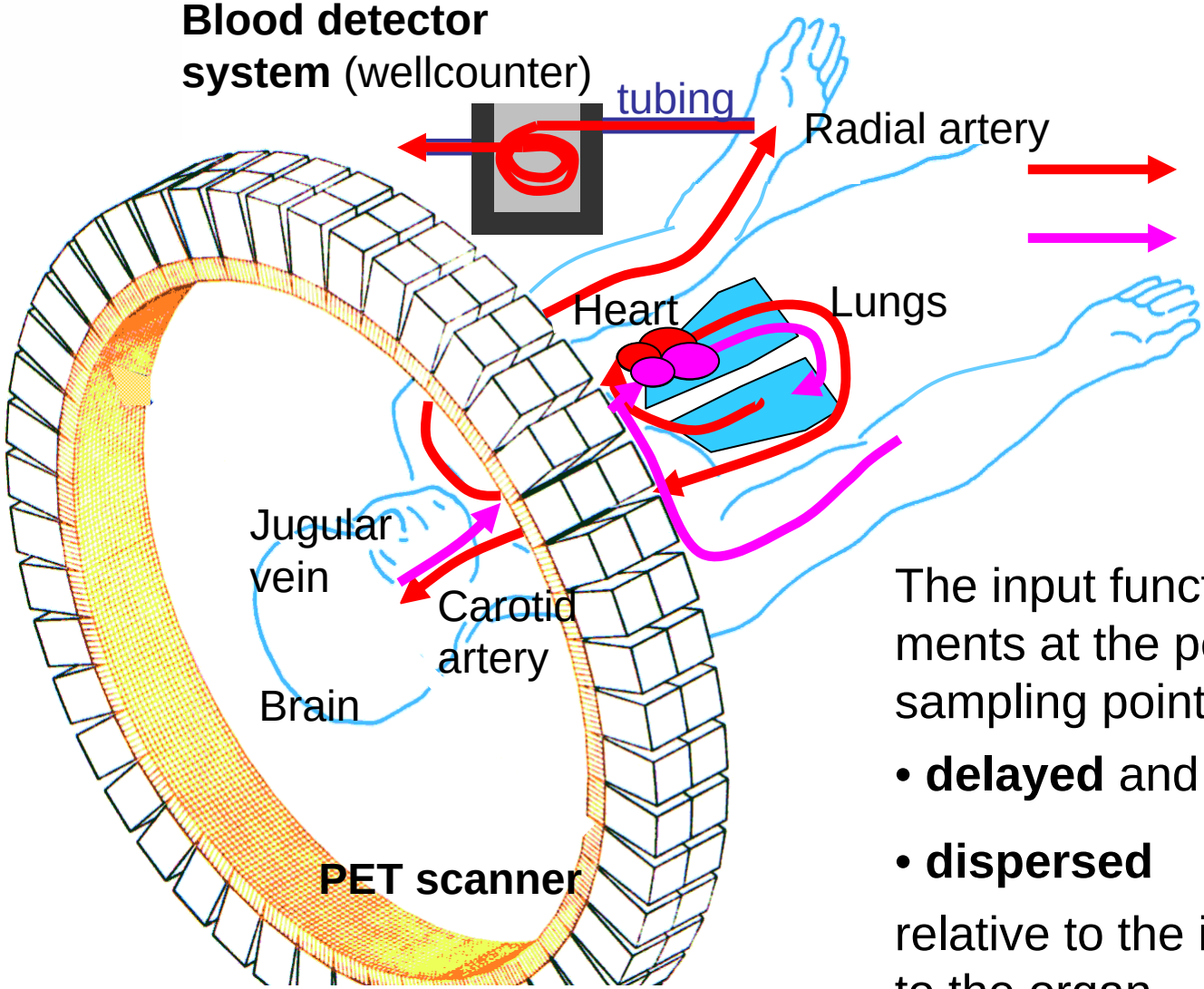
S.-C. Huang, R. E. Carson, E. J. Hoffman, J. Carson, N. MacDonald, J. R. Barrio, and M. E. Phelps

Division of Biophysics, Department of Radiological Sciences, UCLA School of Medicine, and Laboratory of Nuclear Medicine, Laboratory of Biomedical and Environmental Sciences, University of California, Los Angeles, California

Summary: A noninvasive method that employs ^{15}O-water and positron-computed tomography (PCT) was used to measure quantitative local cerebral blood flow (lCBF) in man. ^{15}O-Water (about 30–50 mCi) was introduced through a single-breath inhalation of ^{15}O-carbon dioxide or through an intravenous bolus injection of ^{15}O-water. A sequence of five 2-min PCT scans was initiated at the time of tracer administration. A series of 15–20 blood samples (1 ml each) was withdrawn from the radial artery of the subject over a period of 10 min. Oxygen-15 radioactivities in the blood samples were immediately counted in a well counter to give an input function, which together with the projection data collected by PCT were processed to provide images of lCBF and local water distribution volume. The method was found to be convenient to use and gave good-quality images of lCBF. Quantitative values of lCBF in images were 59 ± 11 and 20 ± 4 ml/min/100 g for gray and white matter, respectively, with a gray-to-white matter ratio of 2.93 and a global flow value of 42 ± 8 ml/min/100 g. Distribution volume of water was 0.85 ± 0.03, 0.76 ± 0.03, and 0.81 ± 0.02 ml/g respectively, for gray matter, white matter, and whole brain. **Key Words:** Cerebral blood flow—Distribution volume of water—^{15}O-water—Positron computed tomography.

Journal of Cerebral Blood Flow and Metabolism
3:141–153 © 1983 Raven Press, New York

PET input function explained



The input function measurements at the peripheral sampling point are

- **delayed** and
- **dispersed**

relative to the input function to the organ.

Overview: plasma input function measurements

withdrawal times → pot weights

Foot Switch

Balance

Well Counter (NaI)

Automatic Gamma Counter

Centrifuge

discrete blood samples

whole blood

plasma

Continuous whole blood

Blood Trolley (BGO)

Metabolite Analysis

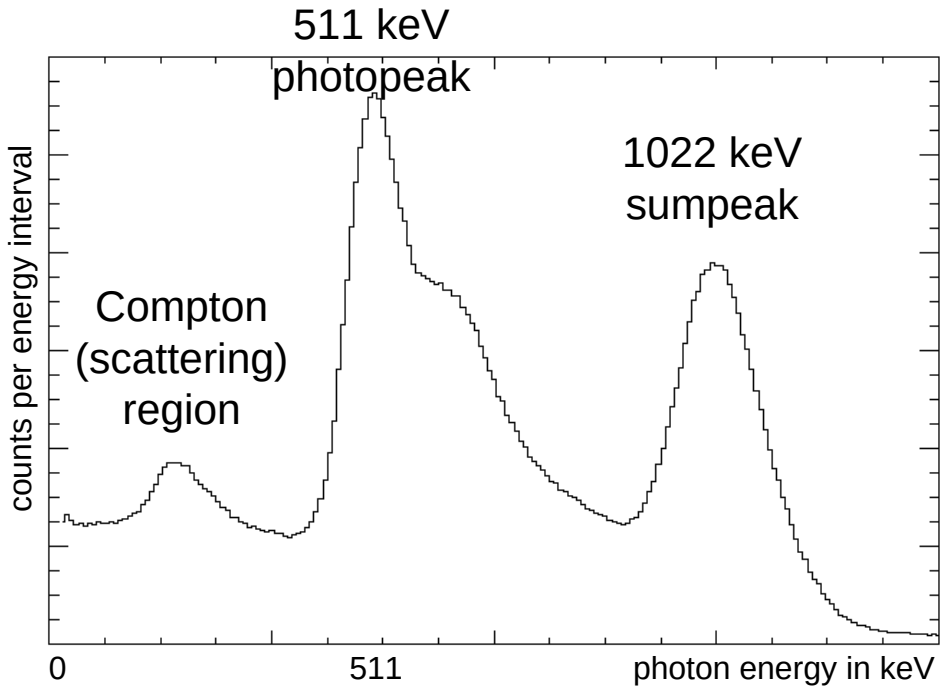
Computer

Physics background: inorganic scintillation detectors

Scintillator properties

	Sodium iodide NaI(Tl)	Bismuth germanate BGO	Lutetiumoxy orthosilicate LSO(Ce)
density	3.7 g·cm^{-3}	7.1 g·cm^{-3}	7.4 g·cm^{-3}
effective atomic number	51	75	66
relative scintillation efficiency	100	15	75
scintillation decay time	230 ns	300 ns	fast: 12 ns slow: 40 ns

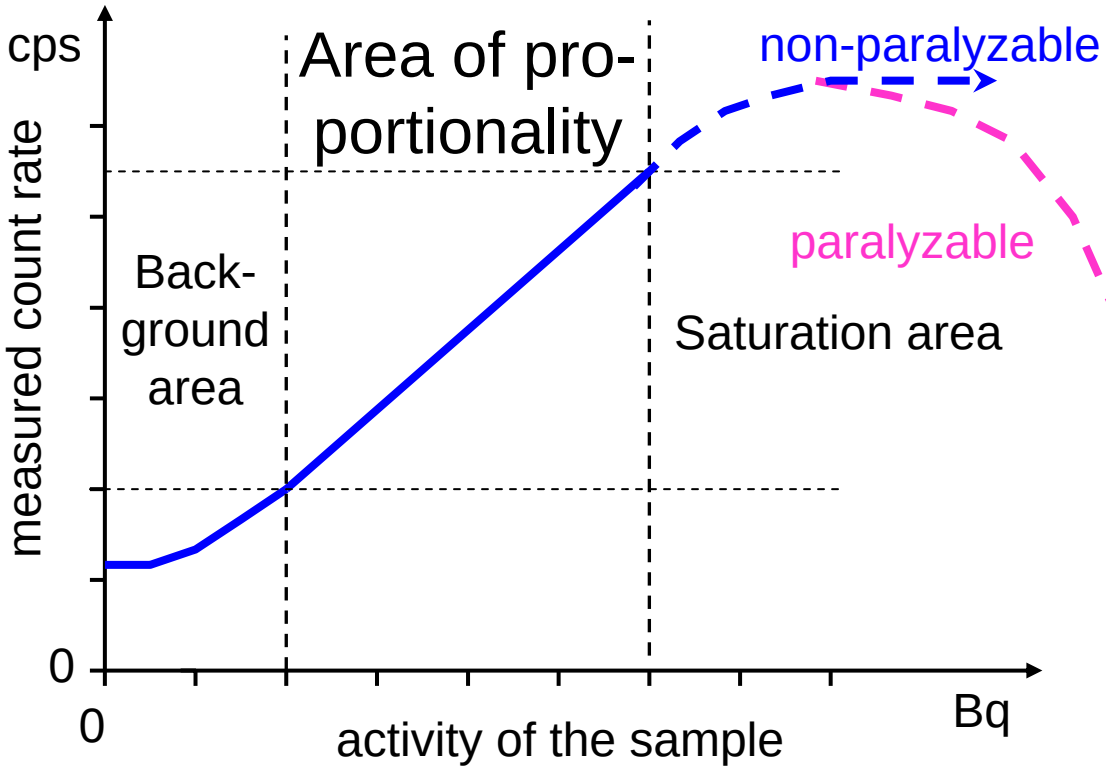
Energy spectrum from a β^+ emitting isotope

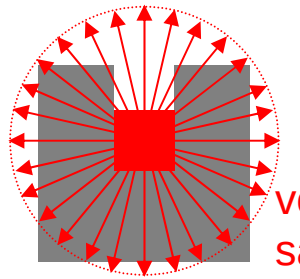


Physics background: radiation detection

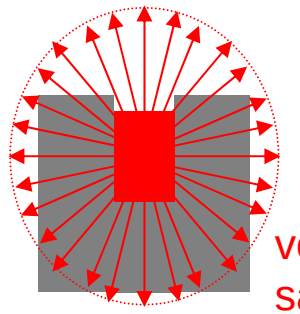
The measured count rate has to be corrected for:

- background (and crosstalk on the Automatic Gamma Counter)
- deadtime losses
- geometrical factors (volume effect)
- radioactive decay





small volume sample



big volume sample

Analysis of the discrete samples

Foot Switch

Radio controlled clock

Scan start time and sample withdrawel times

Whole blood and plasma activity concentration in kBq/ml (decay corrected to scan start time)

Well counter

Background, deadtime, geometry and decay correction

Corrected count rates

Balance

Pot weights (empty & full)

Sample weights

Sample volumes

Blood and plasma density (g/ml)

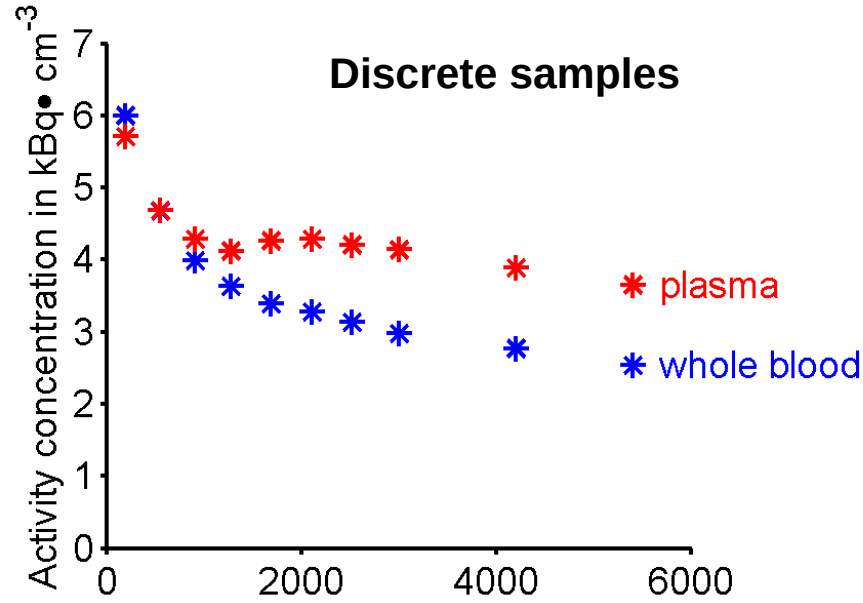
Generation of plasma input functions

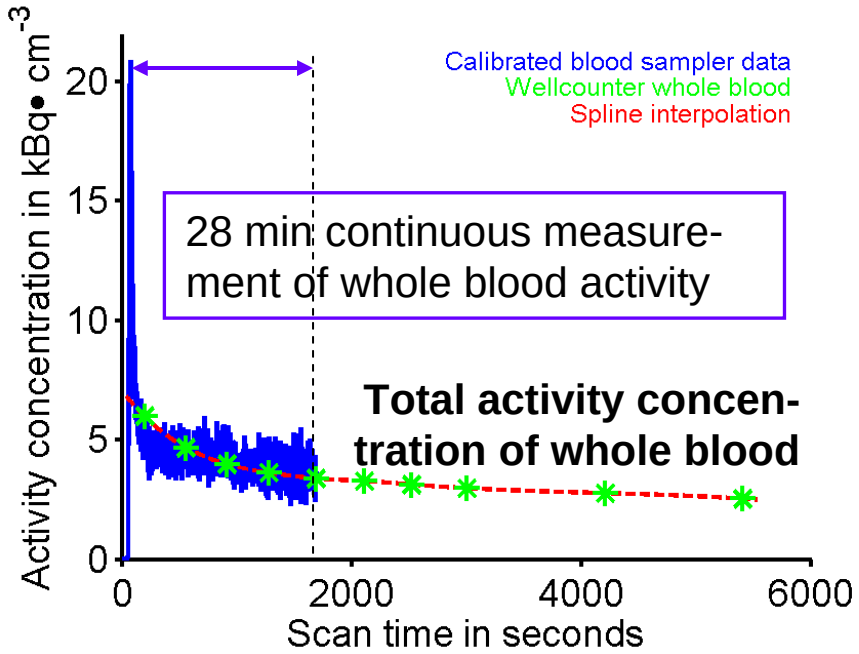
Example: serotonin transporter radioligand [^{11}C]DASB study

Discrete Sampling protocol

no	time
1	3 min
2	9 min
3	15 min
4	21 min
5	28 min
6	35 min
7	42 min
8	50 min
9	70 min
10	92 min

Eight samples selected for the determi-nation of the parent fraction in plasma.





Activity concentrations shown in the plots are corrected for radioactive decay and were obtained in a healthy volunteer after a 529 MBq bolus injection.

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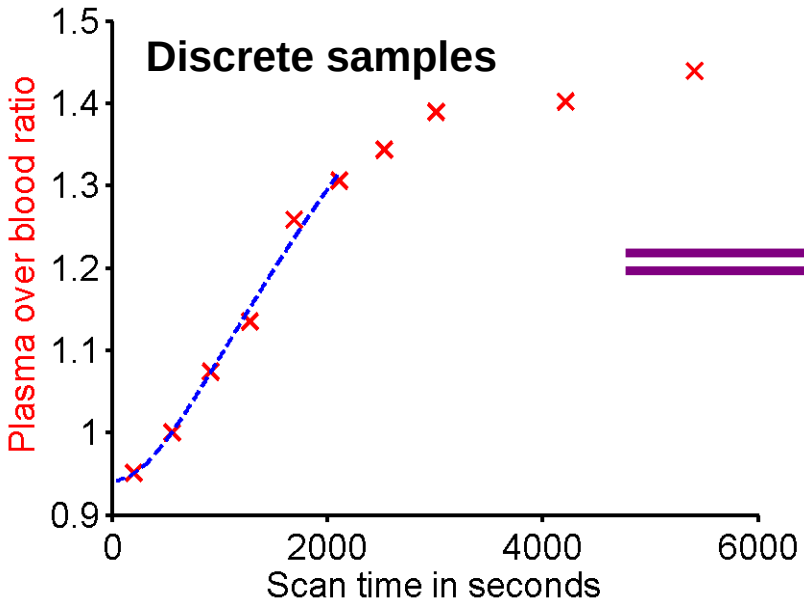
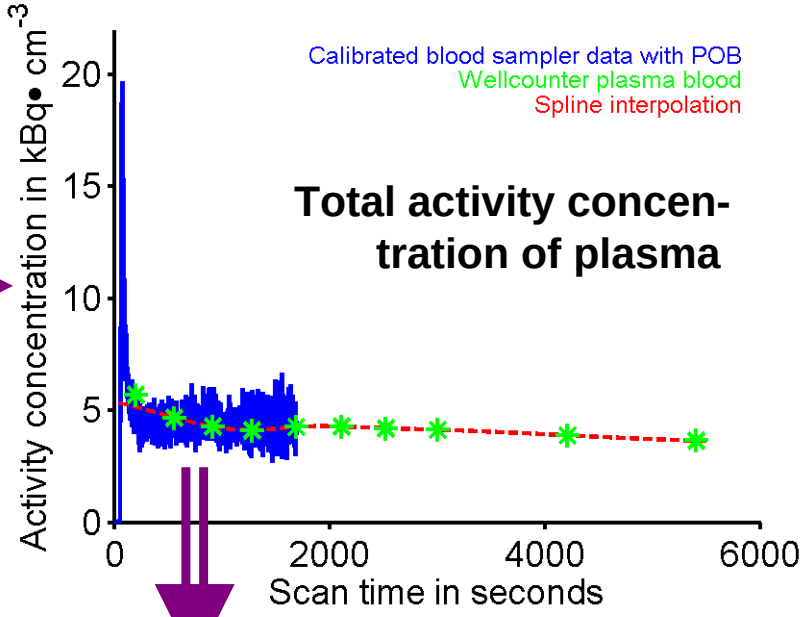
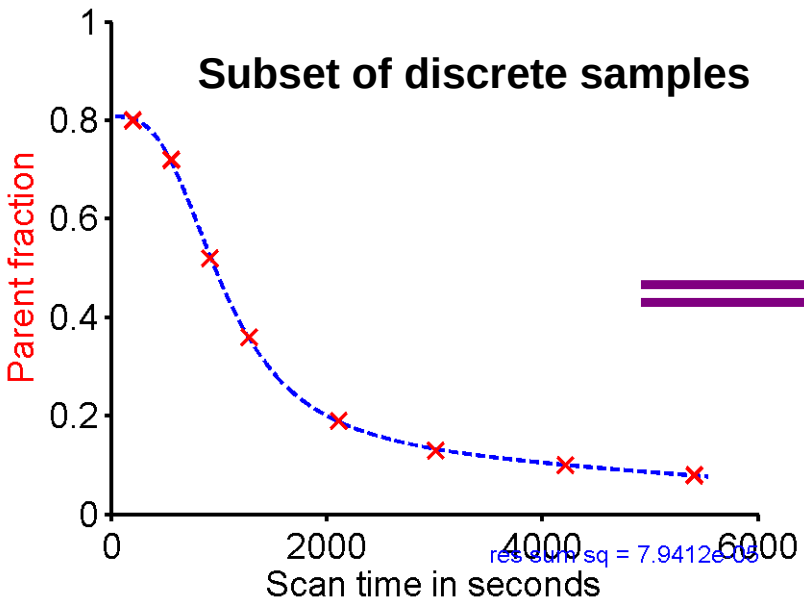
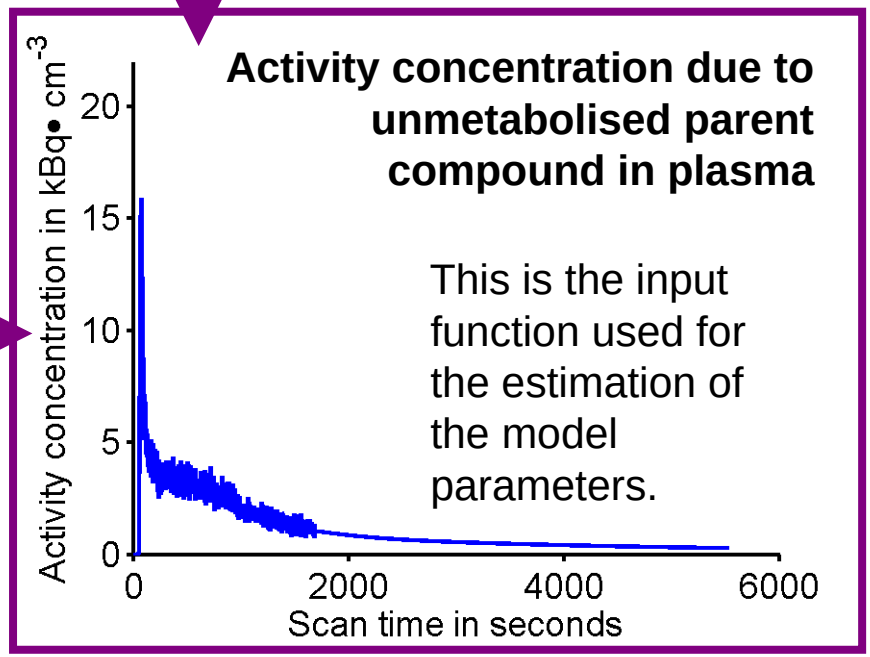
Generation of plasma input functions









Arterial cannulation – a risky procedure?

Follow-up of Radial Arterial Catheterization for Positron Emission Tomography Studies

Peter H. Jons,[1]* Monique Ernst,[1] James Hankerson,[2] Kristina Hardy,[1] and Alan J. Zametkin[1]

[1]*Laboratory of Cerebral Metabolism, National Institute of Mental Health, National Institutes of Health, Bethesda, MD 20892-1384*
[2]*Clinical Center, Department of Anesthesia, National Institutes of Health, Bethesda, MD 20892-1384*

Abstract: Radial arterial catheterization is needed for repeated arterial blood samples to construct tracer input curves of positron emission tomography (PET) scans (Herscovitch [1993]: Rheum Dis Clin North Am 19:765–794). Complications resulting from such short-term catheterizations are rare. Sixteen investigators followed 106 subjects who had arterial lines placed in the context of a PET study. Abnormalities were reported in 8 of 106 (7.5%) cases. Of these eight cases, three (37.5%) were inpatients diagnosed with anorexia nervosa, a condition that may represent a risk factor. All abnormalities were benign, did not affect motor function, and did not require medical intervention. *Hum. Brain Mapping 5:119–123, 1997.*

Arterialised venous blood input function – an alternative?

Physiological Modeling of Dynamic Measurements of Metabolism Using Positron Emission Tomography

Thomas F. Budinger, Ronald H. Huesman, Brian Knittel, Robert P. Friedland, and Stephen E. Derenzo

Donner Laboratory and Lawrence Berkeley Laboratory, University of California, Berkeley, California, 94720

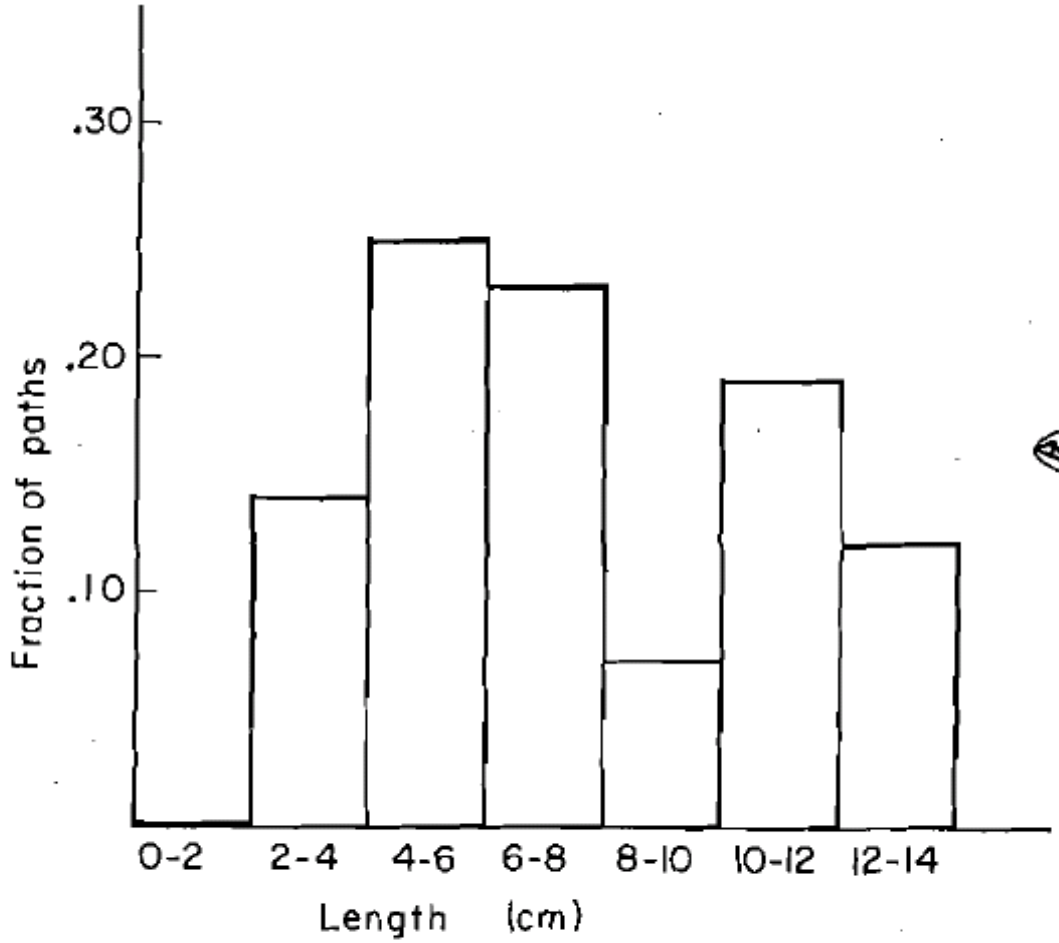
Seventh Nobel Conference

Based on the proceedings of the Seventh Nobel Conference held at Saltsjöbaden, Sweden, May 17–20, 1983.

The Metabolism of the Human Brain Studied with Positron Emission Tomography

Raven Press ■ New York

Arterialised venous blood input function – an alternative?



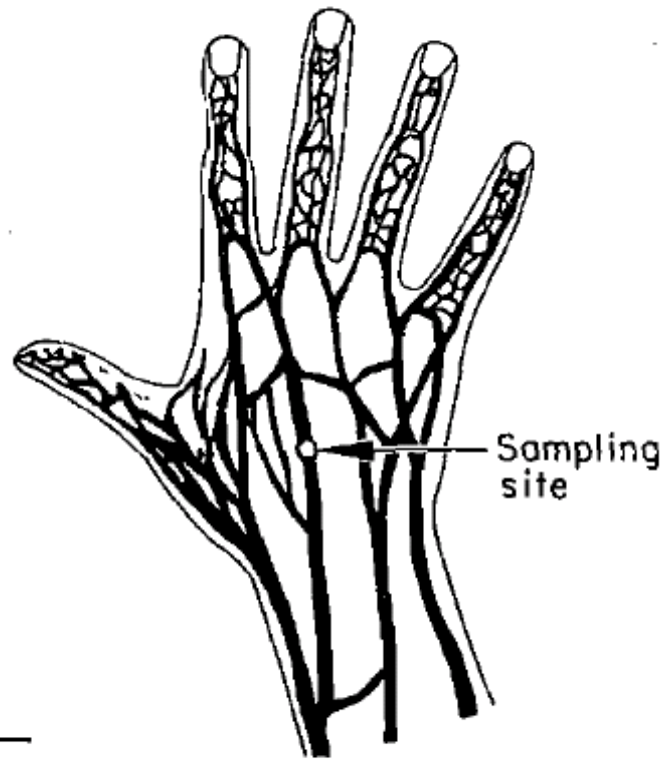


FIG. 4. Expected spread of arterial input. A histogram of path lengths for medium-sized veins in the hand, based on data extracted from an anatomical atlas. Assuming a constant velocity through each path, the time of arrival of the isotope will be distributed according to the distribution of path lengths.

Arterialised venous blood input function – an alternative?

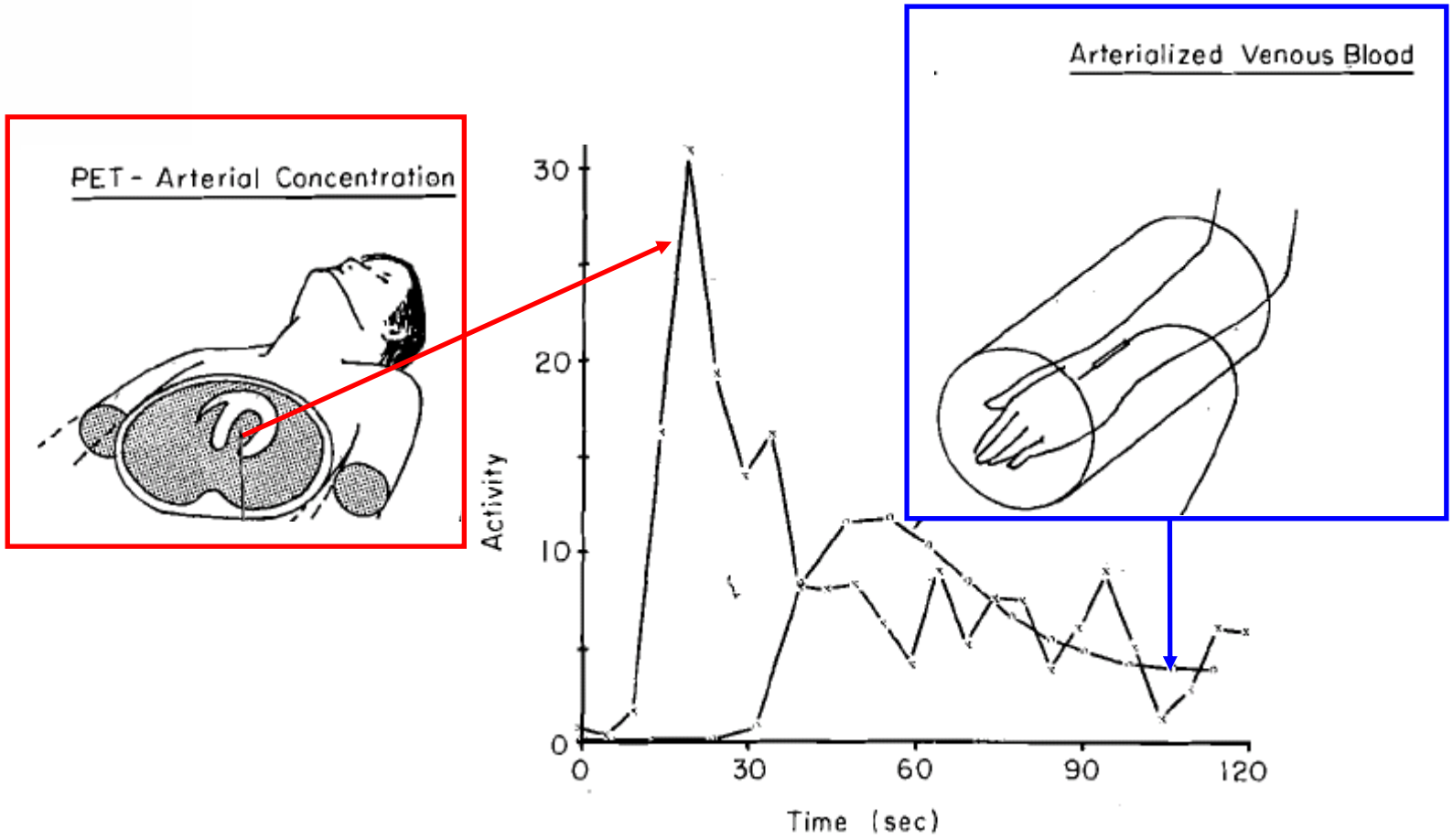


FIG. 6. Comparison between the concentration of ^{18}F-FDG in arterial blood and in "arterialized" venous blood. This illustration represents one of a series of 6 experiments where the arterial concentration was measured in the left ventricular cavity using PET and initial sampling times of 5.0 sec.

Arterialised venous blood input function – an alternative?

SUMMARY

Given an input function that properly represents the concentration of a tracer being delivered to an organ as a function of time, and an accumulation or residue curve, the standard three-compartment rate parameter estimates can be made with a reliability that depends on the statistics of the region of interest from which the residue curve is extracted. We have learned that the arterialized venous blood input function method is not valid for dynamic PET studies unless some modification is made of the measured input data to compensate for the spreading of the time versus activity curve and the 30 to 40 sec delay.

(for FDG)

Some methods (e.g. the Patlak plot) use integral measurements of the activity concentration and are therefore less sensitive to the dispersion of the input function.

Image-derived input functions

Idea: derive the time course of the activity concentration in the arterial blood from a blood pool (e.g. left ventricle, aorta or other big blood vessels) in the reconstructed tomographic image.

Limitation: only the whole blood activity concentration can be derived. It is impossible to obtain plasma concentrations or parent fractions in plasma.

Problem: Subject and organ (e.g. heart) motion during the scan and the partial volume effect require additional efforts (such as a blood volume scan with [^{15}O]CO or MR images of the brain) to recover the blood activity concentration.

Advantages: obviates the need for blood sampling, no cross-calibrated peripheral equipment required, reduced delay and dispersion of the input function.

Widely used in PET cardiology for tracers like [^{15}O]water and [^{18}F]FDG. Difficult to use in other parts of the body and for other tracers.

Image-derived input functions

Measurements of Regional Tissue and Blood-Pool Radiotracer Concentrations from Serial Tomographic Images of the Heart

Eberhard Henze, Sung-Cheng Huang, Osman Ratib*, Edward Hoffman, Michael E. Phelps, and Heinrich R. Schelbert

UCLA School of Medicine, and University of California at Los Angeles, Los Angeles, California

J Nucl Med 24: 987–996, 1983

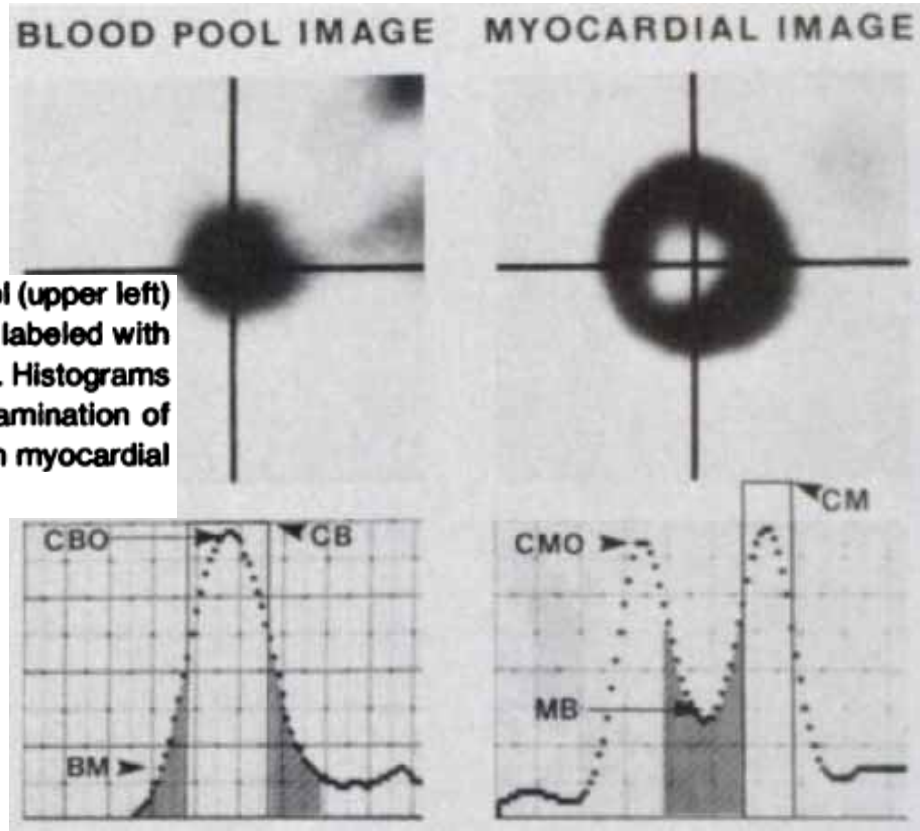


FIG. 2. Histograms (lower panel) from PCT blood-pool (upper left) and myocardial (upper right) images. Blood pool was labeled with ^{11}CO; myocardium with Ga-68 albumin microspheres. Histograms are roughly Gaussian, with measureable cross-contamination of blood-pool counts into myocardial areas (BM) or from myocardial to blood-pool areas (MB).

PCT= positron-emission computerized tomography

Image-derived input functions

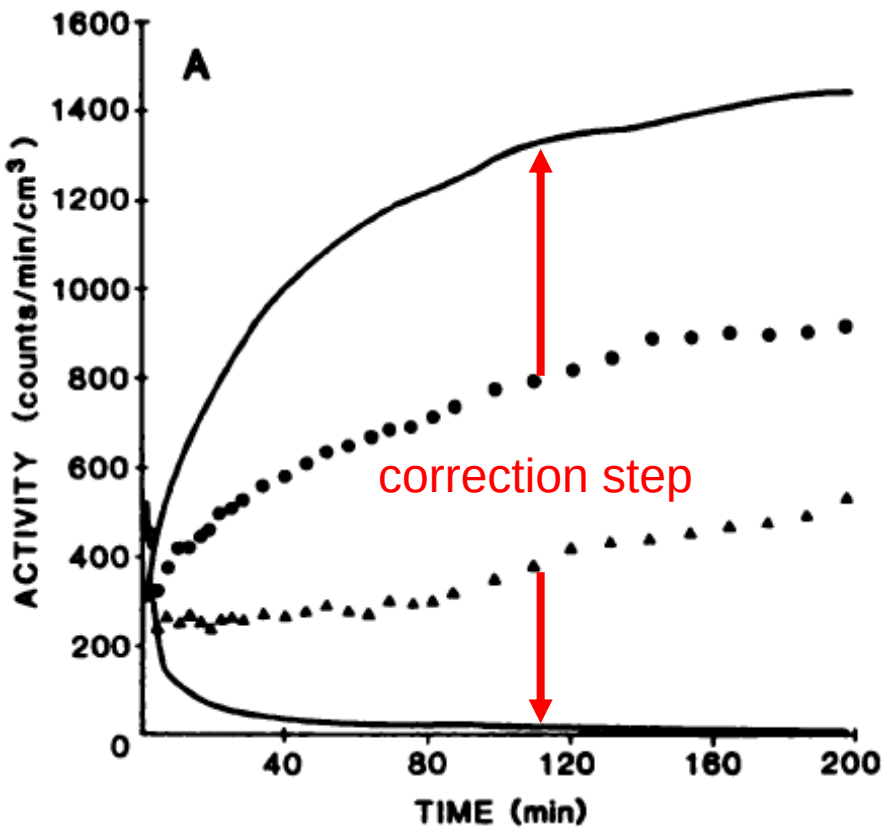


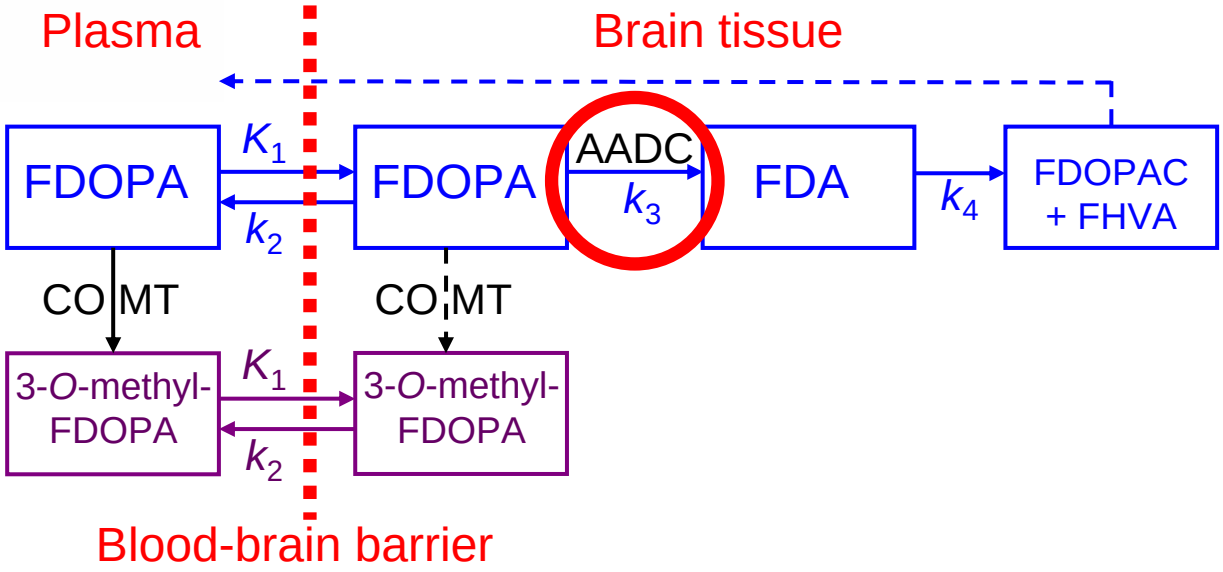
FIG. 3. Myocardial and blood-pool time-activity curves obtained from serial PCT images after intravenous F-18 deoxyglucose. Solid lines indicate true myocardial and true blood-pool activities as measured by Fick principle (myocardium) or by well counting (blood pool). Panel A plots activities observed before correction for cross-contamination and partial-volume effect;

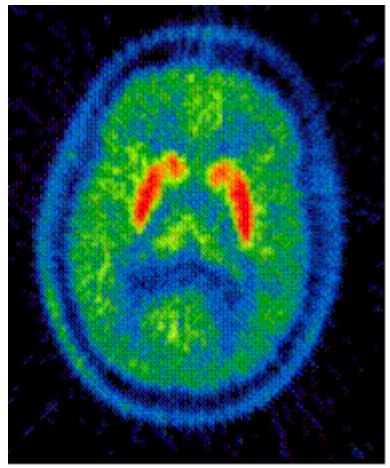
Note underestimation of myocardial activity before correction step, due mainly to partial-volume effect; also overestimation of blood-pool activity caused by cross-contamination from myocardial counts.

PCT= positron-emission computerized tomography

Reference tissue input functions

Example: evaluation of striatal dopaminergic function with 6-[^{18}F]fluoro-L-DOPA (FDOPA)





Specific problems for the quantification of the FDOPA tissue signal relative to the plasma input:

- Brain entering radiolabelled metabolite → administration of COMT inhibitor to reduce peripheral metabolism.
- Compartmental models with dual input functions: high technical effort for analysis of radiolabelled compounds in plasma, too many rate constants to estimate.
- Competition for the large neutral amino acid transporter → large variability due to other amino acids in blood.

Reference tissue input functions

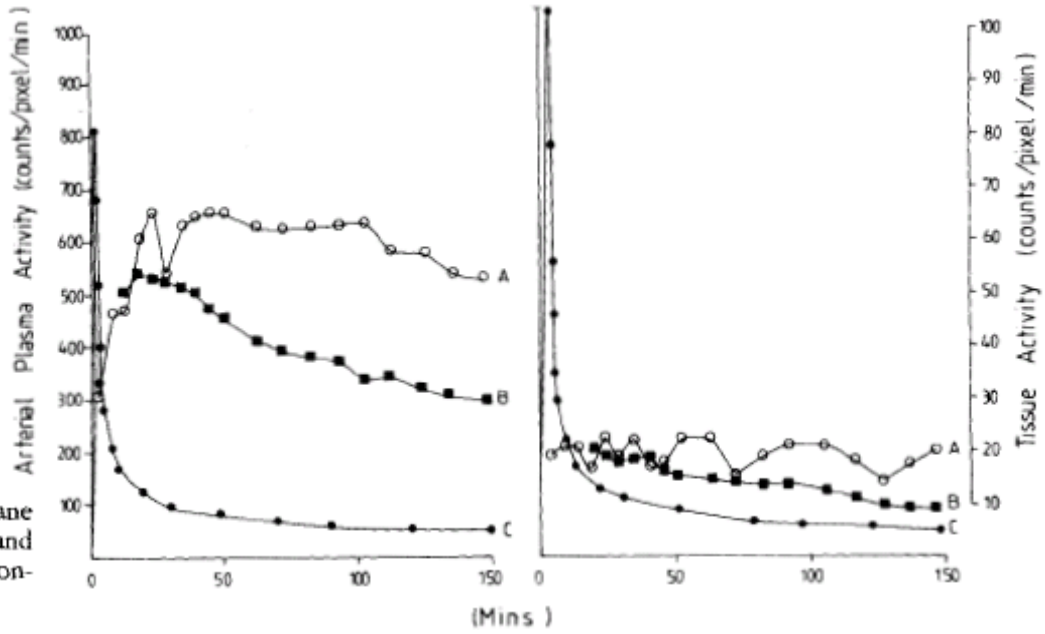
Ann Neurol 20:258–262, 1986

K. L. Leenders,* W. H. Poewe,† A. J. Palmer,* D. P. Brenton,‡ and R. S. J. Frackowiak*

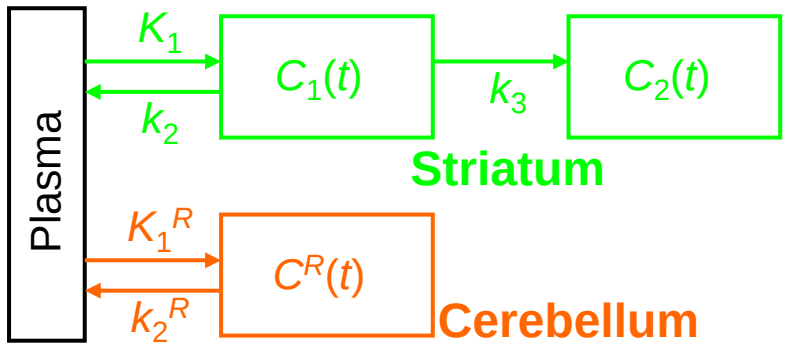
Inhibition of L-[^{18}F]Fluorodopa Uptake into Human Brain by Amino Acids Demonstrated by Positron Emission Tomography

From the MRC Cyclotron Unit, Hammersmith Hospital, Du Cane Rd, London W12 OHS; and the Departments of †Neurology and ‡Metabolic Medicine, University College Hospital, Gower St, London WC 1, England.

Fig 2. Numerical representation of L-{^{18}F}fluorodopa concentration in brain tissue and arterial plasma over time. Baseline measurements are shown on the left. Measurements after amino acid loading are shown on the right. A = striatal tissue; B = surrounding brain; C = arterial plasma concentration.



Solution: express the kinetics in the striatum not relative to the plasma input function – use instead the response in a *reference tissue* (occipital cortex or cerebellum) as “input function”.



Research and future developments at the WMIC

- We have already got one of the best equipped PET blood and analytical chemistry laboratories worldwide → USE IT !!!
- Robert is working on image-derived input functions for oncology applications in the body.
- The HRRT provides superior image resolution – in conjunction with the Vicra motion tracking system: revisit image-derived input functions in brain studies.
- Supervised cluster analysis approach to extract a reference tissue input function in [^{11}C]PK11195 brain scans – collaboration with Imperial College London.

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MANCHESTER 1824

An introduction to PET research and methods

17/01/07 Beyond diagnosis: Quantitative human imaging for better treatment

25/01/07 Isotope production and targetry

01/02/07 PET principles, hardware and data acquisition

08/02/07 PET data reconstruction and corrections

15/02/07 Radiochemistry

22/02/07 Analytical chemistry

01/03/07 Input functions in PET

08/03/07 Kinetic models in PET

22/03/07 PET in psychiatry research

29/03/07 PET in oncology research

19/04/07 PET in drug development

26/04/07 PET in neuroscience research

⌘

Seminars will take place at 4pm at the Wolfson Molecular Imaging Centre
27 Palatine Road, Withington