Overview of Part II: Mathematics of the Biodistribution of Radiopharmaceuticals

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In general, nuclear medicine physicians are fully aware of the essential role that the biodistribution of radiopharmaceuticals plays in determining the success of diagnostic and therapeutic nuclear medicine procedures. In addition, they appreciate the importance of the biologic mechanisms that determine the biodistribution of the various radiopharmaceuticals. However, often they are unfamiliar with the mathematics that describe these physiologic or molecular biologic processes or they are unaware of the degree to which a conceptual understanding of the relevant mathematics can inform the interpretation of clinical studies.

Stated differently, the simplest approach to image interpretation is pattern recognition (Aunt Minnie), a more sophisticated approach adds an understanding of the biologic processes that determine the biodistribution of the radiopharmaceutical, and the most complete approach includes a conceptual knowledge of the mathematical equations that describe the quantitative relationships among the various biologic parameters. In this book the mathematics is presented before the biology of the biodistribution of radiopharmaceuticals because each one of a relatively small number of equations applies to many nuclear medicine studies.

The next six chapters cover the mathematics that pertain to (1) the movement of radiopharmaceuticals through the vascular system during the first circulation; (2) the clearance of radiopharmaceuticals from the vascular space into organs, tissue, and lesions; (3) the passage of radiopharmaceuticals through parenchymal excretory systems; (4) the movement of radiopharmaceuticals through compartments; and (5) the calculation of relative and absolute functional measurements. The last chapter in Part II discusses a few miscellaneous mathematical techniques.

It is important to note that the more complex equations are never solved for any of the applicable nuclear medicine studies but that a conceptual knowledge of the structure of the equations can provide insights that may assist in the interpretation of images. Some of the simpler equations are utilized by the technologist in a formulaic fashion, but it is important for nuclear medicine physicians to have an understanding of these equations for purposes of quality control and interpretation.

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Noticeable by its absence is compartmental analysis. Unfortunately, the use of compartmental analysis to model the biodistribution of radiopharmaceuticals as a function of time requires creation of an accurate model of the system under study, use of rate constants to describe the movement of the radiopharmaceutical between compartments (often bidirectional), measurement of an input function (ideally arterial), measurement of the amount of radiopharmaceutical in tissues and compartments as a function of time, and calculus for obtaining the solution in terms of rate constants [1–3]. Because these requirements are, in general, never met in nuclear medicine studies, compartmental analysis is not used in the clinical setting.

For an equation to be included in the chapters of Part II, Mathematics of the Biodistribution of Radiopharmaceuticals, it must (1) relate to the biodistribution of radiopharmaceuticals and (2) be clinically useful, either conceptually or by quantifying a biological parameter, e.g., renal clearance. At the same time, equations that relate to nuclear medicine but are not directly related to the biodistribution of radiopharmaceuticals, such as radioactive decay, modulation transfer function, image reconstruction (SPECT and CT), correction for cross talk, etc., are not included. These equations and algorithms are adequately discussed in textbooks of medical physics.

The first mathematical chapter, Chap. 4, Evaluation of Clearance, discusses the equation for clearance of a radiopharmaceutical out of a flowing system, usually from blood. Most, but not all, nuclear medicine studies involve clearance. Of the 39 nuclear medicine studies discussed in this book, 30 involve clearance. Twenty-seven of the 30 involve clearance of the radiopharmaceutical from blood, one involves clearance from lymph flow, and two involve clearance from flowing air, i.e., ventilation. The clearance equation consists of four factors, which are simply multiplied together. How this equation can be used conceptually to assist in image interpretation is discussed and demonstrated. The chapter on the evaluation of clearance is presented first in Part II because of the importance of the clearance process in a large proportion of nuclear medicine studies.

Chapter 5, Mean Transit Time: Central Volume Principle, discusses the relatively simple relationship between the volume of a compartment or region, the flow of blood or other fluids through the compartment or region, and the mean transit time through the compartment or region. This relationship is known as the "central volume principle." The mean transit time and the related leading edge transit time are used as relatively independent indicators of disease in a number of nuclear medicine studies. In all but one of them, clearance is also measured.

Chapter 6, Blood Flow: First Circulation Time-Activity Curves, discusses the information content of rapid serial images acquired during the first circulation of a radiopharmaceutical following intravenous injection. There are five nuclear medicine studies that routinely include first circulation images. In four of these studies, there are paired structures of interest, and in two of these four studies, paired time-activity curves are generated from the symmetrical structures. An understanding of the information content of paired time-activity curves from a mathematical point of view informs the visual interpretation of both the first circulation images and any time-activity curves that might be generated. The paired time-activity curves are not routinely quantitated.

Chapter 7, Regional Transit Times: Convolution Analysis, discusses the situation in which one is interested in the passage of a bolus of radiopharmaceutical through a region, often the parenchyma of an excretory organ such as the kidney. Evaluating the resulting serial images and any time-activity curve(s) generated from the images is relatively easy if the tracer enters the region in question as a discrete instantaneous bolus.

However, usually the incoming bolus is spread out over a considerable distance and enters the region of interest (ROI) over time. The resulting time-activity curve from a ROI is the result of the frequency distribution of transit times through the ROI convolved by the shape of the incoming time-activity curve. This happens routinely in studies of excretory organs like the kidneys and hepatobiliary system. This chapter looks at the underlying mathematics of the convolution process.

Chapter 8, Quantitation of Function: Relative Measurements, discusses the common situation in which activity in two paired organs is compared at one point in time or the activity in one organ is compared at different points in time. The Renal Tubular Secretion Study with Tc-99m-MAG3 includes examples of both: measurement of the percent of total renal function in each kidney is an example of relative comparison at one point in time, and measurement of the change in activity in the renal parenchyma over time is an example of relative comparison at multiple points in time. A defining characteristic of relative quantitative measurements is that the amount of administered dose is not part of the equation.

Relative measurements, particularly in planar images, are relatively simple compared to absolute measurements because attenuation correction is unnecessary. Attenuation will be essentially the same when measurements at two or more different time points are compared from the same ROI and will be nearly the same when measurements from symmetrical structures like the two kidneys are compared at the same time point.

Chapter 9, Quantitation of Function: Absolute Measurements, discusses measurements of function that are made in absolute terms, i.e., relative to the amount of radiopharmaceutical that was administered. Examples include renal clearance in the Renal Tubular Secretion Study with Tc-99m-MAG3, thyroid uptake in the Thyroid Uptake Measurement with I-123, and the SUV (standard uptake value) in the Tumor Glucose Metabolism Study with F-18-fluorodeoxyglucose. In all measurements of absolute function, there has to be an unbroken series of quantitative links from the counts in the ROI in the image back to the amount of administered activity in units of millicuries. In addition, when function is quantified in absolute terms, photon attenuation must be corrected for.

Chapter 10, Other Quantitative Techniques, discusses three nuclear medicine studies with quantitative measurements that do not fit in the preceding chapters. These are the Cystogram – Direct Study with Tc-99m-DTPA, which includes the measurement of post-void residual bladder volume; the Cisternogram with In-111-DTPA, which may include quantification of cerebrospinal fluid leaks into the nasal cavity; and the GLOFIL® Study with I-125-iothalamate that measures renal clearance with blood samples rather than images. In addition, the Body Surface Area Normalization assessment algorithm, which is a general method to determine whether an equation that measures a biologic function needs to be normalized for

body surface area (BSA), is discussed [4]. (The GLOFIL® Study, a non-imaging study, is not widely performed and is not in the Nuclear Medicine Procedure Manual but is included in this book because it fits well in Chap. 10.)

These chapters in Part II, Mathematics of the Biodistribution of Radiopharmaceuticals, cover all of the mathematics that relates to extracting functional measurements from and applying quantitative concepts to nuclear medicine images. In turn, these mathematical methods will be integrated with the physiology and molecular biology that determine the biodistribution of radiopharmaceuticals in Part III, Quantitative Evaluation in Nuclear Medicine Studies.

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