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Appendix E1

Modeling of Contrast Material Propagation through PBPK Model

The technique was based on sets of equations that model the time courses of chemicals transported to and from various tissues via the blood throughout the body (45). As a first-order approximation, contrast-enhanced blood was assumed to be a uniform mixture of blood and contrast material propagating through a web of blood vessels and organ compartments. As this mixture reaches the compartment, it is evenly distributed through the compartment and subsequently washed out. During this process, the concentration of the contrast material in the blood is changing.

To evaluate the change in concentrations of contrast material in blood, each compartment, organ, or vessel was assigned to a corresponding mass balance differential equation. The generic mass balance equation used for a vessel compartment was:

$$\frac{dA}{dt} = (Q_i \cdot C_i) - (Q_o \cdot C_o), \quad (1)$$

where A is the mass of contrast material in the tissue, t is the time, C_i and C_o are the input and output concentrations, and Q_i and Q_o are the input and output flow rates (45). In this model, a blood vessel is considered as a well-stirred compartment with a constant volume ($\frac{dV}{dt} = 0$) and single inlet and outlet flow rates, and hence $Q_i = Q_o = Q$. Therefore, Equation 1 can be reformulated into a first-degree differential equation as:

$$\frac{dC_o}{dt} = \frac{Q}{V}(C_i - C_o), \quad (2)$$

which simply states that the rate of change in the amount of contrast material with respect to time is proportional to the difference between the rates by which the material enters and leaves the compartment.

As noted earlier, each organ compartment was assumed as three interacting subcompartments: intravascular, extracellular, and intracellular (46). Each subcompartment was modeled as a single well-mixed compartment. As a result, contrast material mass transfer occurs due to not only the transport of blood, but also the diffusion through the membrane of extra-and intracellular spaces. For a membrane, the mass transfer rate was formulated by

$$\frac{dM}{dt} = \mathrm{PS} \cdot (C_i - C_o), \quad (3)$$

where M is iodine mass and PS is the product of permeability degree and surface area of the membrane. In this work, since iodinated contrast material usually does not diffuse through the cells, diffusion was only considered for intravascular and extracellular spaces. Therefore, for an organ compartment, a set of two mass balance equations were used:

$$\frac{dC_{IV}}{dt} = \frac{1}{V_{IV}}\left[Q(C_i - C_{IV})\right] - \frac{1}{V_{IV}}\left[PS(C_{IV} - C_{EC})\right] \quad (4a)$$

and

$$\frac{dC_{EC}}{dt} = \frac{1}{V_{EC}}\left[PS(C_{IV} - C_{EC})\right], \quad (4b)$$

where Q, C_i, t, and P are described above, C_{IV} and C_{EC} are intravascular and extracellular concentrations, and V_{IV} and V_{EC} are intravascular and extracellular volumes (37,45). The first equation was assigned to the intravascular subcompartment and the second equation to the extracellular subcompartment. Note that the first term on the right side of the Equation 4a describes the blood-flow mass balance, as it is proportional to difference of the input concentration and intravascular concentration, while the second term describes the diffusion of contrast material through the membrane of the capillaries. Finally, for the extracellular space, there is only one term describing the contrast diffusion within the extracellular space.

With specific parameters and equations assigned to the compartments, the compartments were integrated into a single computational system. Contrast material is typically injected through the antecubital vein; it then mixes with the blood and flows into the right side of the heart and finally distributes throughout the body. In our model, this distribution was described by a series of differential equations, the solutions to which can provide the iodine mass delivery rate to each tissue. The iodine mass in each compartment represents the accumulation of injected contrast material in addition to the recirculated contrast medium in the cardiovascular system. Two rounds of circulation were modeled in this study. The coding was done through a scientific computing platform (Matlab R2014a; Mathworks). The equations were solved using Runge-Kutta method built-in Matlab function ode45 (47).

As the next step in this method, the concentration of iodine in each organ was calculated from the ratio of the total mass of contrast material within the organ to the organ volume. The total mass of contrast medium in an organ was determined from the summation of the solutions of the Equations 4a and 4b, C_{IV} and C_{EC}, multiplied by V_{IV} and V_{EC}, respectively. Finally, intravascular, extracellular, and intracellular volumes were added to calculate organ volume, and hence the iodine concentration.