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Erroneous and inappropriate use of gamma fits to tracer-dilution curves in magnetic resonance imaging and nuclear medicine[1]

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Recently, Benner et al. [1] used the gamma distribution as a fitting function in order to smooth and extrapolate dilution curves distorted by recirculated indicator during magnetic resonance imaging procedures. Similar applications of this versatile fitting function occur in nuclear medicine [2,3], with the same misunderstanding of the appropriate non-linear regression methods for unbiased parameter estimation, and a surprising unawareness of the underlying physics and statistics of dilution processes. It is straightforward to rectify these oversights and so make significant progress in interpreting tracer-dilution indications for medical diagnoses.

Benner et al. [1] work with the gamma variate definition

$$C_\Gamma(t) = A \cdot (t - D)^B \cdot e^{-(t-D)/C} \tag{1}$$

where $C_\Gamma(t)$ is measured concentration, t is the time, and, we are led to believe, A, B, C and D are four unknown parameters. The fitting, which also estimates A, B, C and D and their precisions, is performed via non-linear regression using the Levenberg-Marquardt method. However, as Thompson et al. stressed in their 1964 paper [4], A is non-linear in the parameters as follows:

$$A = \frac{F}{C^{B+1}\Gamma(B+1)} \tag{2}$$

where F is the area under the concentration-time curve and $C^{B+1}\,\Gamma(B+1)$ normalizes the gamma variate in Eq. (1) so that it can be a probability distribution that integrates to unity. F then scales the distribution to fit the observed curve of area other than unity. The full non-linear-in-the-parameters dependency of A in Eq. (2) needs to be taken into account in the non-linear regression to obtain unbiased estimates of F, B, C, and D from Eq. (1), as Thompson et al. [4] state. We have noticed [5,6] that at the coarse sampling rates of, say, 0.5 Hz seen in magnetic resonance imaging, the bias induced by adopting the Benner et al. [1] approach often leads to a value of F that is 50% out. Of course, including a formula for $\Gamma(B+1)$ makes for a complicated non- linear regression equation, with the possibility of computational overflow. However, if one uses Stirling's or the Lanczos formula [7] much better accuracy is obtained, even with as few as 7 data points for estimating 4 parameters, on curves with signal-to-noise ratio of about 10. So one can use either:

$$\Gamma(B+1) = \sqrt{2\pi B} \cdot B^B \cdot e^{-B+1/(12B)} \tag{3}$$

or

$$\Gamma(B+1) = \sqrt{2\pi} \cdot (B+5.5)^{B+0.5} \cdot e^{-(B+5.5)} \cdot \left[1 + \sum_{i=1}^{6} \frac{k_i}{B+i}\right] \tag{4}$$

where in Eq. (4) the coefficients k_i are known to 15 decimal places [7].

This implies that the gamma distribution is not very simple to work with empirically, and one might as well use the appropriate local density random walk (LDRW) distribution for Brownian motion with positive drift [8]. Use of LDRW enables proper estimation of the median first passage time and mean transit (residence) time of particles, taking account of back-dispersion in diffusion processes. An up-to-date introduction to such applications in hydrology and hydrodynamics that is very relevant to considerations of dispersion across capillaries, including use of tensors and fractals, was given by Bredehoeft [9]. Other

[1] Re: Benner, et al., 1997. Accuracy of γ-variate fits to concentration-time curves from dynamic susceptibility-contrast enhanced MRI: influence of time resolution, maximal signal drop and signal-to-noise. Magn Reson Imag 1997;15:307-317.

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important properties of dispersion processes [7,8] were uncovered by Wise [10] and Bogaard et al. [11,12].

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