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A model for transit time distributions through organs that accounts for fractal heterogeneity

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ABSTRACT

It has been shown that density functions of organ transit time distributions of vascular markers (washout curves) are characterized by a power-law tail, reflecting the fractal nature of the vascular network. Yet, thus far, no closed-form model is available that can be fitted to such organ outflow data. Here we propose a model that accounts for the existing data. The model is a continuous mixture of inverse Gaussian densities, implying flow heterogeneity in the organ. It has been fitted to outflow data from the rabbit heart and rat liver. The power-law decay with exponent -3 observed in the heart, corresponds to an intra-organ flow distribution with a relative dispersion of about 35%.

1. Introduction

Tracer washout experiments, i.e., the measurement of organ outflow curves of tracers after impulse input, are an important tool for investigating kinetic processes at the organ level (Bassingthwaighte et al., 1998). Because an outflow curve of a vascular marker represents the density of the transit time distribution through the organ, resulting from the pathway length and flow distribution in the vascular network, it was natural to look for a suitable distribution function. There is some rationale for the use of the density of the Brownian passage-time distribution (also called inverse Gaussian distribution) (Sheppard, 1962; Weiss, 1997), and it could be shown that a mixture of two inverse Gaussian densities (2IG) provided an excellent fit to outflow concentration–time data of vascular markers in the perfused liver (Weiss et al., 1997) and hindlimb (Weiss and Roberts, 1996) of the rat.

The fractal character of washout curves was shown by Bassingthwaighte and colleagues for the heart, both experimentally (Bassingthwaighte and Beard, 1995) and theoretically (Beard and Bassingthwaighte, 1998; Beard and Bassingthwaighte, 2000). Here, fractal essentially means 'self-similar', which was indicated by the fact that the downslope of the outflow curves could be fitted by power law function. Although the 2IG model fits the tail of sucrose outflow curves from experiments performed in perfused livers (Weiss et al., 1997), it does not exhibit a power law tail. Thus one could argue that this is in contrast to the fractal properties of the hepatic sinusoidal network (Gaudio et al., 2005; Warren et al., 2008). But the reason why power law tails have not been observed in liver outflow curves may lay in the limited time period of sampling. But there is another point why the 2IG model appears not optimal from a theoretical point of view. Given the flow heterogeneity in the liver, why should the distribution function have only two components, and what is their meaning? Here we propose an extension of the 2IG model, which is based on a continuous mixture of IG distributions. The latter may reflect flow distribution in the organ, similarly to the approach used by Beard and Bassingthwaighte (1998). This new model has several advantages: it exhibits a power law tail and contains less free parameters than the 2IG model. We show that model fits available outflow data from the heart (Bassingthwaighte and Beard, 1995) and the liver (Weiss et al.,1997; 2010). To our knowledge this is the first closed-form model that describes the whole outflow curve, including the power-law tail.

2. Model development

2.1. Inverse Gaussian distributed transit times

A simple model for distribution of organ transit times of vascular markers is the inverse Gaussian (IG) density function

$$f(t)=\sqrt{\frac{MTT}{2\pi RD^2t^3}}\exp\left[-\frac{(t-MTT)^2}{2RD^2MTTt}\right] \quad (1)$$

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which emerges as a solution of the advection–dispersion equation, based on the assumption that the dispersion is purely advective and determined by architecture of the vascular network (Roberts et al., 2000; Weiss, 1997). The density $f(t)$ of the random transit time T through an organ is the normalized outflow concentration ($f(t)=C(t)/\int_0^\infty C(t)dt$), the mean transit time is given by $E(T)=MTT=V/Q$ (V and Q denote the vascular volume and blood flow), and $RD^2=Var(T)/MTT^2$ is the relative dispersion of the transit time distribution (TTD) caused by geometrical dispersion in the microcirculatory network. Because of the significant limitation of not fitting the tail part of the liver outflow curves, Eq. (1) has been extended into a mixture of two IG densities (2IG)

$$f_{2IG}(t)=pf_1(t)+(1-p)f_2(t) \tag{2}$$

which represents a two-point distribution with probability p of outcome IG_1 with parameters MTT_1, RD_1^2 and probability $(1-p)$ of outcome IG_2 with parameters MTT_2, RD_2^2, where the IG with the longer MTT accounts for the tail part (Weiss et al., 1997). Note that both density functions, IG (Eq. (1)) and 2IG (Eq. (2)), exhibit an exponential tail for $t\to\infty$.

2.2. Incorporating flow heterogeneity

Let us assume that flow heterogeneity within an organ can be modeled by a flow distribution across subsystems (pathways) which exhibit an IG transit time density and are characterized by the same volume V_i and dispersion RD_i^2. In deriving the mixture of inverse Gaussians, based on a continuous flow distribution, we follow the approach by Desmond and Yang (2010), who derived this model in a completely different context. Using the IG (Eq. (1)) in a reparameterized form,

$$f(t)=\left(\frac{\lambda}{2\pi t^3}\right)^{1/2}\exp\left(\frac{-\lambda(\kappa t-1)^2}{2t}\right)>0 \tag{3}$$

where

$\kappa=1/MTT_i=Q_i/V_i$ and $\lambda=MTT_i/RD_i^2$, and assuming that κ obeys a normal distribution with mean k and variance ν/λ, i.e., $RD_\kappa^2=\nu/(\lambda k^2)$, the transit time density is obtained as

$$h(t;\nu,d,\lambda)=a\int_{-\infty}^{\infty}f(t;\lambda|\kappa)g(\kappa;k,\nu)d\kappa \tag{4}$$

where the density of the distribution of the variable κ is denoted by $g(\kappa;d,\nu)$. Since this integral, which was first evaluated by Whitmore (1986), is the density of a defective distribution, Desmond and Yang (2010) derived a proper density assuming a truncated normal distribution to avoid that κ can take negative values. The normalization factor then depends on t and the parameters, and the inverse Gaussian-normal mixture density (mixIG) of the transit times was obtained as $h(t)\equiv f_{mixIG}(t)$,

$$h(t)=a\left(\frac{\lambda}{2\pi t^3(\nu t+1)}\right)^{1/2}\exp\left(\frac{-\lambda(kt-1)^2}{2t(\nu t+1)}\right)\quad t>0 \tag{5}$$

where the normalization factor is given by

$$a=\frac{\Phi[(\nu+k)\lambda^{1/2}(\nu^2t+\nu)^{-1/2}]}{\Phi(k\sqrt{\lambda/\nu})}$$

and Φ is the cumulative normal distribution function.

3. Fitting of mixIG to tracer data

The mixIG model (Eq. (5)) was fitted to outflow data from single-pass perfused rabbit heart and rat liver experiments. Washout data of [^{15}O] water measured in isolated, blood-perfused rabbit heart were obtained by digitization from the graph published by Bassingthwaighte and Beard (1995). Hepatic outflow data of the extracellular markers [^{14}C] sucrose and [^{125}I] bovine serum albumin stem from experiments in red blood cell perfused (Weiss et al., 2010) and buffer perfused (Weiss et al., 1997) rat livers, respectively. Curve fitting was done using ADAPT5 (D'Argenio et al., 2009) and maximum likelihood analysis with the variance model $VAR_i=[\sigma_0+\sigma_1C(t_i)]^2$; where VAR_i is the variance of the ith data point and $C(t_i)$ is the model prediction. Precision of parameter estimates is indicated by their asymptotic (approximate) standard deviations. Model simulations were done with MAPLE 8 (Waterloo Maple, Waterloo, ON, Canada).

4. Results

4.1. Fitting experimental data

Fig. 1 shows the fit of the mixIG model (Eq. (5)) to the ouflow data of labeled water measured by Bassingthwaighte and Beard (1995) in rabbit heart. The model fits very well the whole range of experimental data (Fig. 1(A)) and exhibits a power law tail, $h(t)\sim t^{-3.1}$, for $t>100$ s (Fig. 1(B)). Typical results of model fits

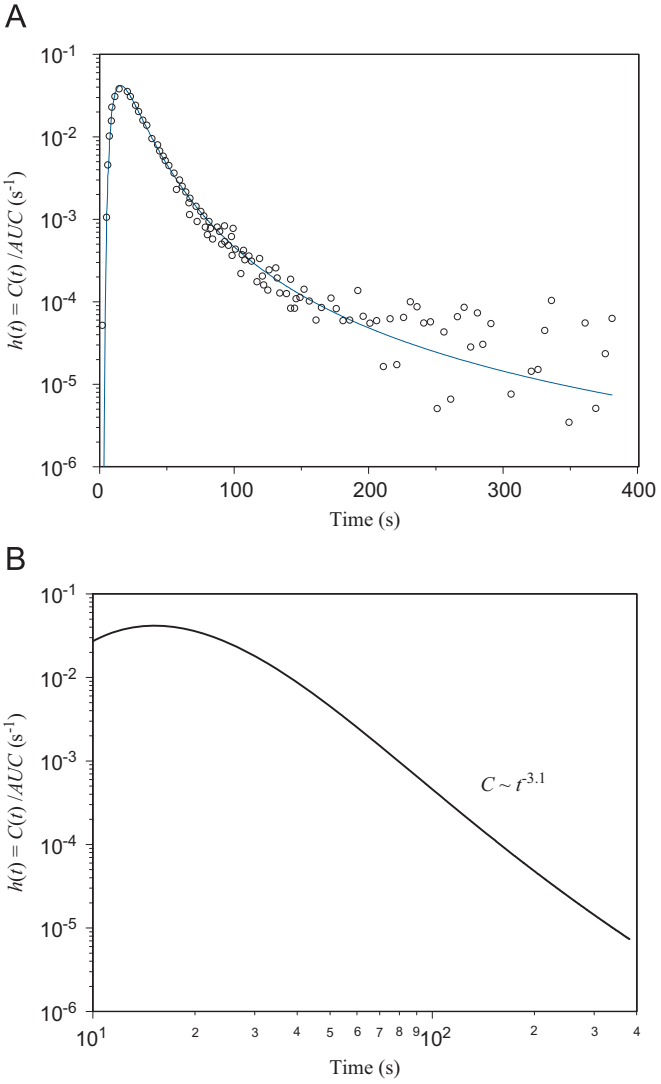

Fig. 1. (A) Plot of washout data of tracer-labeled water from the rabbit heart. (Fig. 3 in Bassingthwaighte and Beard, (1995)) together with the fitted curve (mixIG model, $h(t)$). (B) Log–log plot of the fitted curve showing the power-law decline.