Theoretical basis of *in vivo* tomographic tracer kinetics

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Abstract. *In vivo* tracer kinetics, as probed by current tomographic techniques, is revisited from the point of view of fluid kinematics. Proofs of the standard intravascular advective perfusion model from first premises reveal underlying assumptions and demonstrate that all single input models apply at best to undefined tube-like systems, not to the ones defined by tomography, *i.e.* the voxels. In particular, they do not and cannot account for the circulation across them. More generally, it is simply not possible to define a single non-zero steady volumetric flow rate per voxel. Restarting from the fact that kinematics requires the definition of six volumetric flow rates per voxel, one for each face, minimalist, 4D spatiotemporal analytic models of the advective transport of intravascular tracers in the whole organ of interest are obtained. Their many parameters, plasmatic volumetric flow rates and volumes, can be readily estimated at least in some specific cases. Estimates should be quasi-absolute in homogeneous tissue regions, regardless of the tomographic technique. Potential applications such as dynamic angio-tractography are presented. By contrast, the transport of mixed intra/extravascular tracers cannot be described by conservation of the mass alone and requires further investigation. Should this theory eventually supersede the current one(s), it shall have a deep impact on our understanding of the circulatory system, hemodynamics, perfusion, permeation and metabolic processes and on the clinical applications of tracer tracking tomography to numerous pathologies.

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1. Introduction

For lack of a better terminology, by perfusion-weighted imaging, we mean any imaging technique allowing to probe quantities such as blood flow or blood volume that are related, directly or not, to hemodynamics, perfusion, permeation or metabolic processes. By definition, they are invaluable tools for pathophysiology and for the clinical diagnosis, prognosis and therapeutic decision-making of numerous pathologies, from vascular diseases to metabolic disorders.

A particularly powerful kind of perfusion-weighted imaging techniques is tracer tracking tomography, *i.e.* any dynamical technique allowing to monitor signals over time that are related to the mass concentrations of an exogenous or endogenous indicator, contrast agent or tracer in voxels of tissue located in some organ of interest. Tracer tracking tomography encompasses a wide range of clinical imaging modalities, including X-ray perfusion computed tomography (CTP) (Konstas et al. 2009) also known as dynamic contrast-enhanced computed tomography (DCE-CT), dynamic susceptibility contrast(-enhanced) magnetic resonance imaging (DSC-MR) (Fieselmann et al. 2011), dynamic contrast-enhanced magnetic resonance imaging (DCE-MR) (Tofts et al. 1999), arterial spin labeling (ASL) (Liu & Brown 2007), ultrasound perfusion or contrast-enhanced imaging (Wiesmann & Seidel 2000), dynamic positron emission tomography (PET) (Watabe et al. 2006) and single photon emission computed tomography (SPECT) (Murase et al. 1992) to name a few.

In this paper, we are interested in tracer kinetics, not in any specific tomographic technique. In particular, we do not deal with the difficult problem of modeling the relationship between measured signals and mass concentrations in each voxel (*e.g.* a linear relationship in CTP, an exponential relationship in DSC-MR, etc.). We simply assume that such a model is available, so that, given a kinetic model of the concentration-time curves, we are provided with a full dynamical model of the tomographic signals for all voxels.

If the contrast agent is confined to the intravascular space (*e.g.* CTP, DSC-MR or DCE-MR imaging of the brain without blood brain barrier disruption), tracer kinetics is usually described by a standard perfusion model (SPM) that goes back to the early works of Stewart, Hamilton and Meier and Zierler (Meier & Zierler 1954, Zierler 1962). The SPM regards each voxel as a single input, single output (SISO) dynamical artery/tissue/vein system and subsequently describes the evolution of the contrast agent mass concentration $c(t)$ in the voxel by the differential equation

$$\frac{\mathrm{d}c}{\mathrm{d}t}(t) = BF\,[c_a(t) - c_v(t)] \tag{1}$$

where BF is the "blood flow", $c_a(t)$ is the arterial input function (AIF) and $c_v(t)$ is the venous output function (VOF). Since the SISO system is linear and time-invariant (LTI), there exists an impulse response $h(t)$ such that $c_v(t) = c_a \otimes h(t)$ and

$$c(t) = BF c_a \otimes R(t) \tag{2}$$

if $c(0) = 0$, where $R(t) \triangleq u(t) - \int_0^t h(\tau)\,\mathrm{d}\tau$ stands for the residue function, $u(t)$ for Heaviside unit step function and $\otimes$ for Volterra convolution product $f \otimes g(t) \triangleq \int_0^t f(\tau)\,g(t-\tau)\,\mathrm{d}\tau$ (Fieselmann et al. 2011, Østergaard et al. 1996).

If the tracer can leave the intravascular space and enter the extravascular space, either because it can cross the intra/extravascular barrier (*e.g.* PET and SPECT radiotracers, ASL arterial tagged blood for brain imaging), because there is no barrier (*e.g.* liver imaging) or because the barrier is disrupted (*e.g.* CTP or DCE-MR imaging of brain tumors), we find a variety of generic parametric permeability models such as the Kety (Tofts et al. 1999), extended Kety-Tofts-Kermode (Tofts et al. 1999) or St Lawrence and Lee (Tofts et al. 1999) models in DCE-CT and DCE-MR and Buxton model in ASL (Buxton et al. 1998). See also Sourbron & Buckley (2012) for a fairly exhaustive survey of perfusion and permeability kinetic models. In addition, we find many organ-specific, single input multi-compartment models accounting for the underlying physiology.

Those models take root in various related fields such as indicator-dilution theory, tracer pharmacokinetics, transport theory, Fick principle, compartmental analysis and LTI system theory. But for our purpose, it is sufficient to notice that most of them assume that the dynamical system has a single input, the AIF in DSC-MR (Fieselmann et al. 2011, Østergaard et al. 1996), CTP (Konstas et al. 2009) and PET (Watabe et al. 2006) or the plasmatic input function in DCE-MR (Tofts et al. 1999) (a notable exception is the liver that has two inputs: the common hepatic artery and the portal vein. But, as we shall see, this just makes our analysis more relevant). Accordingly, each concentration-time curve is modeled as the convolution product of this input with a convolution kernel or more generally as the solution of an inhomogeneous system of ordinary differential equations (Keeling et al. 2007).

While the transport of purely intravascular tracers is a special case of the transport of mixed intra/extravascular tracers, paradoxically the nonparametric convolution SPM formally includes many parametric permeability models as special cases because the residue function $R(t)$ is left unspecified. This issue alone motivates an in-depth investigation of the SPM.

We first undertake to derive the differential SPM for intravascular tracers advected by the plasma from elementary kinetics in order to reveal all underlying assumptions. Then, we discuss the applicability of single input models to tracer tracking tomography and conclude that none of them can account for the underlying geometry and the circulation across the voxels. Fixing this issue yields new standard local and global, 4D spatiotemporal analytic models whose many parameters can be readily estimated at least in some simple cases. The case of mixed intra/extravascular tracers is also examined. Last, some applications of the new theory, such as dynamic angio-tractography, are presented.

2. Notations, definitions and elementary fluid kinematics

Consider a tridimensional flow. Fix an inertial frame of reference $(O, \vec{x}, \vec{y}, \vec{z})$. Let $\vec{v}\,(x, y, z, t)$ be the Eulerian velocity vector field at time t. Let Σ be a given oriented control surface, at rest relative to $(O, \vec{x}, \vec{y}, \vec{z})$ and let $\overrightarrow{\mathrm{d}\Sigma}$ be the locally normal unit vector field on Σ.

The volumetric flow (rate) through surface Σ at time t is defined as the surface integral

$$\Phi_\Sigma(t) \triangleq \iint_\Sigma \vec{v}\,(x, y, z, t) \cdot \overrightarrow{\mathrm{d}\Sigma} \quad [\Phi_\Sigma(t)] = L^3T^{-1} \tag{3}$$

or, equivalently, as

$$\Phi_\Sigma(t) \triangleq \frac{\mathrm{d}V_\Sigma}{\mathrm{d}t}(t) \tag{4}$$

where V_Σ is the volume flowing through Σ during the infinitesimal time interval $[t, t + \mathrm{d}t]$.

Flow rates are additive: if the fluid F is composed of immiscible fluids $F_1, F_2, \ldots$ then $\Phi_\Sigma^F(t) = \Phi_\Sigma^{F_1}(t) + \Phi_\Sigma^{F_2}(t) + \ldots$. For a given outward-oriented closed surface Σ, the Gauss-Green-Ostrogradsky divergence theorem reads as

$$\Phi_\Sigma(t) = \oiint_\Sigma \vec{v}\,(x, y, z, t) \cdot \overrightarrow{\mathrm{d}\Sigma} = \iiint_\mathcal{V} \vec{\nabla} \cdot \vec{v}\,(x, y, z, t)\,\mathrm{d}x\mathrm{d}y\mathrm{d}z \tag{5}$$

where $\mathcal{V}$ is the volume enclosed by Σ. For a homogeneous or heterogeneous incompressible flow, by definition we have $\vec{\nabla} \cdot \vec{v}\,(x, y, z, t) \equiv 0$ so that, by the Gauss-Green-Ostrogradsky divergence theorem, the total volumetric flow rate through a given oriented closed surface is equal to zero. The flow of any incompressible fluid is incompressible.

For a steady flow, velocities and volumetric flow rates do not depend on time. In this case, unless the flow is infinitely compressible, any volumetric flow rate through a closed surface is equal to zero.

A volumetric flux is a volumetric flow rate through a given unit surface.

The principle of locality or separability of classical physics states that a physical system is causally influenced directly only by its immediate surroundings.

3. Proving the standard perfusion model

Let us try to carefully prove the differential SPM for intravascular tracers from those elementary premises. As we shall see, there exist different paths. We start with the most natural one.

Consider the incompressible flow of a fluid mixed with a contrast agent in some organ. Assume the organ to be at rest relative to $(O, \vec{x}, \vec{y}, \vec{z})$ after a possible rigid (*e.g.* motion correction) or non-rigid (*e.g.* for elastic organs such as the liver or the heart) registration phase.

Consider with Zierler (1962), an outward-oriented closed surface Σ, at rest relative to $(O, \vec{x}, \vec{y}, \vec{z})$, comprising a single open input surface Σ_I and a single open output surface

Σ_O. Let Σ_R be the remaining surface: $\Sigma = \Sigma_I \cup \Sigma_O \cup \Sigma_R$. We can regard Σ as the surface of a tube or a pipe, Σ_I being the input cross-section of the tube, Σ_O its output cross-section and Σ_R the surface of the tube itself. Let $m(t)$ be the mass of contrast agent in the volume of measure V enclosed by Σ at time t and let $c(t) \triangleq m(t)/V$ be its mass concentration.

Let $\Phi_{\Sigma_I}(t)$, $\Phi_{\Sigma_O}(t)$ and $\Phi_{\Sigma_R}(t)$ be the volumetric flow rates through surfaces Σ_I, Σ_O and Σ_R respectively at time t. By the Gauss-Green-Ostrogradsky divergence theorem for incompressible flows and additivity, we have

$$\Phi_\Sigma(t) = \Phi_{\Sigma_I}(t) + \Phi_{\Sigma_O}(t) + \Phi_{\Sigma_R}(t) = 0 \tag{6}$$

By definition, $\Phi_{\Sigma_R}(t) \equiv 0$, since the velocity is identically zero on Σ_R, so that $\Phi_{\Sigma_O}(t) = -\Phi_{\Sigma_I}(t) \triangleq \Phi(t)$. Hence we can define a single volumetric flow rate $\Phi(t)$ for such a system, which is not necessarily identically equal to zero.

Consider that the matter flowing through Σ is composed of three immiscible substances due to the intravascular/extravascular barrier:

- The extravascular fluid (EF);
- The blood vessels, *i.e.* the arteries, the veins and/or the capillary bed (BV);
- The intravascular fluid contained in the blood vessels, *i.e.* the blood mixed with the tracer (IF) that we shall call blood in the sequel for the sake of simplicity.

By additivity, we have $\Phi(t) = \Phi^{\mathrm{EF}}(t) + \Phi^{\mathrm{BV}}(t) + \Phi^{\mathrm{IF}}(t)$.

Assume that the tracer mass concentration in the blood remains sufficiently small so that the mechanical properties (*e.g.* the viscosity) of the blood mixed with the tracer and, subsequently, its flow (*e.g.* the volumetric flow rates) do not depend on it.

Because it is assumed, within the SPM, that the artery feeding system Σ through Σ_I and the vein draining it through Σ_O contain only blood, we have *de facto* $\Phi^{\mathrm{EF}}(t) = \Phi^{\mathrm{BV}}(t) \equiv 0$ so that $\Phi(t) = \Phi^{\mathrm{IF}}(t)$.

The intravascular fluid is itself composed of the blood plasma (P) and of the blood cells (C). Therefore, $\Phi(t) = \Phi^{\mathrm{P}}(t) + \Phi^{\mathrm{C}}(t)$.

The mass balance equation for the contrast agent in system Σ over time interval $[t, t + \mathrm{d}t]$ is

$$\mathrm{d}m(t) = \mathrm{d}\left[c(t)V\right] = \mathrm{d}c(t)V = m_I(t) - m_O(t) \tag{7}$$

where $m_I(t)$ is the input mass of contrast agent entering Σ through Σ_I over $[t, t + \mathrm{d}t]$ and $m_O(t)$ the output mass of contrast agent exiting Σ through Σ_O.

Generally speaking, the intravascular tracer can enter and leave system Σ via two different mechanisms: via deterministic advection (*i.e.* advective transport, bulk flow) or stochastic diffusion. Therefore, we have for instance

$$m_I\left(t\right) = m_I^{\mathrm{A}}\left(t\right) + m_I^{\mathrm{D}}\left(t\right) \tag{8}$$

where $m_I^{\mathrm{A}}\left(t\right)$ is the mass of tracer entering system Σ via advection and $m_I^{\mathrm{D}}\left(t\right)$ is the stochastic mass of tracer entering system Σ via diffusion. Whether the input diffusive mass is negligible or not compared to the advective one depends on whether the expected

diffusive mass $\mathrm{E}m_I^{\mathrm{D}}(t)$ and the root mean squared diffusive mass $\sqrt{\mathrm{E}[m_I^{\mathrm{D}}(t) - \mathrm{E}m_I^{\mathrm{D}}(t)]^2}$ are small compared to $m_I^{\mathrm{A}}(t)$ or not. Both diffusive masses depend themselves on several factors but both of them are small if the root mean squared displacement of the tracer by diffusion during its advective residence, mean transit time in system Σ, which itself depends on the diffusion coefficient of the tracer in blood at the body temperature, is small compared to the geometric dimensions of system Σ.

At a first glance, *in vivo* apparent diffusion coefficients of gadolinium-based MR contrast agents are of order $D \simeq 10^{-11}m^2s^{-1}$ (Marty et al. 2013) so that the root mean squared displacement $\sqrt{2Dt}$ during a dynamic tomographic acquisition duration of $t = 100s$ is of order $4\times10^{-5}m$, two orders of magnitude smaller than the characteristic length of millimetric voxels ($10^{-3}m$). *A fortiori*, the root mean squared displacements during typical advective mean transit times are expected to be fairly negligible compared to the voxels characteristic length. For this reason, we shall neglect the input and output diffusive masses in the sequel, as precisely done within the SPM. More precisely, we shall consider that the tracer undergoes advective transport and only advective transport: in particular, no amount of tracer gets stuck in system Σ. As an example, let us consider that the tracer is transported by the blood plasma.

Assume the plasmatic mass concentration of contrast agent to be uniformly equal to $c_I(t)$ respectively $c_O(t)$ in the immediate surroundings of Σ_I respectively Σ_O. Then, by definition, we have

$$m_I(t) = m_I^{\mathrm{A}}(t) = c_I(t)V_I(t) = c_I(t)\frac{\mathrm{d}V_I}{\mathrm{d}t}(t)\mathrm{d}t = c_I(t)\Phi_I^{\mathrm{P}}(t)\mathrm{d}t \tag{9}$$

where $V_I(t)$ is the volume of plasma (mixed with the tracer) flowing through Σ_I over $[t, t+\mathrm{d}t]$ and $\Phi_I^{\mathrm{P}}(t)$ is the plasmatic volumetric flow rate through Σ_I at time t. Similarly, $m_O(t) = c_O(t)V_O(t) = c_O(t)\Phi_O^{\mathrm{P}}(t)\mathrm{d}t$.

Because the mass concentration of contrast agent in a volume of measure V contained in the artery feeding system Σ is assumed to be uniformly equal to $c_a(t)$ within the SPM, the input plasmatic mass concentration is $c_I(t) = c_a(t)V/V_{\mathrm{AIF}}^{\mathrm{P}}(t)$, where $V_{\mathrm{AIF}}^{\mathrm{P}}(t)$ is the measure of the volume of plasma contained in the volume of measure V at time t. Accordingly, the output plasmatic mass concentration is $c_O(t) = c(t)V/V^{\mathrm{P}}(t)$ where $V^{\mathrm{P}}(t)$ is the volume of plasma enclosed by Σ, not $c_O(t) = c_v(t)V/V_{\mathrm{VOF}}^{\mathrm{P}}(t)$ where $V_{\mathrm{VOF}}^{\mathrm{P}}(t)$ is the volume of plasma at time t contained in a volume of measure V contained itself in the vein draining system Σ.

Therefore, we have

$$\mathrm{d}m(t) = \mathrm{d}c(t)V = m_I(t) - m_O(t) = \left[c_a(t)V\Phi_I^{\mathrm{P}}(t)/V_{\mathrm{AIF}}^{\mathrm{P}}(t) - c(t)V\Phi_O^{\mathrm{P}}(t)/V^{\mathrm{P}}(t)\right]\mathrm{d}t \tag{10}$$

Now, as in Meier & Zierler (1954), let us assume that the ratio $\Phi^{\mathrm{C}}(t)/\Phi^{\mathrm{IF}}(t)$ is always and everywhere equal to the flow hematocrit fraction Ht so that $\Phi^{\mathrm{P}}(t) = (1-Ht)\,\Phi^{\mathrm{IF}}(t)$ and

$$\Phi(t) = \Phi^{\mathrm{IF}}(t) = \Phi^{\mathrm{P}}(t) + \Phi^{\mathrm{C}}(t) = \Phi^{\mathrm{P}}(t)/(1-Ht) \tag{11}$$

Therefore, there exists a single plasmatic volumetric flow rate, inward-oriented through Σ_I and outward-oriented through Σ_O

$$\Phi^{\mathrm{P}}(t) = \Phi_I^{\mathrm{P}}(t) = \Phi_O^{\mathrm{P}}(t) = \Phi(t)\,(1 - Ht) \tag{12}$$

It follows that

$$\frac{\mathrm{d}c}{\mathrm{d}t}(t) = \Phi^{\mathrm{P}}(t)\left[c_a(t)/V_{\mathrm{AIF}}^{\mathrm{P}}(t) - c(t)/V^{\mathrm{P}}(t)\right] \tag{13}$$

For a steady flow, we have $\Phi^{\mathrm{P}}(t) \equiv \Phi^{\mathrm{P}}$, $V_{\mathrm{AIF}}^{\mathrm{P}}(t) \equiv V_{\mathrm{AIF}}^{\mathrm{P}}$ and $V^{\mathrm{P}}(t) \equiv V^{\mathrm{P}}$, so that we finally get the differential model

$$\frac{\mathrm{d}c}{\mathrm{d}t}(t) = \Phi^{\mathrm{P}}\left[c_a(t)/V_{\mathrm{AIF}}^{\mathrm{P}} - c(t)/V^{\mathrm{P}}\right] \tag{14}$$

whose formal solution is

$$c(t) = \Phi^{\mathrm{P}}/V_{\mathrm{AIF}}^{\mathrm{P}} c_a \otimes e^{-\Phi^{\mathrm{P}} t/V^{\mathrm{P}}} \tag{15}$$

if $c\,(0) = 0$.

Unless $c(t) = c_v(t)$ and $V_{\mathrm{AIF}}^{\mathrm{P}} = V^{\mathrm{P}}$, which are not necessarily true, this model does not match the differential SPM

$$\frac{\mathrm{d}c}{\mathrm{d}t}(t) = BF\left[c_a(t) - c_v(t)\right] \tag{16}$$

but, on the contrary, Kety differential permeability model (Tofts et al. 1999)

$$\frac{\mathrm{d}c}{\mathrm{d}t}(t) = K^{\mathrm{trans}} c_a(t) - k_{\mathrm{ep}} c(t) \tag{17}$$

if we let $K^{\mathrm{trans}} \triangleq \Phi^{\mathrm{P}}/V_{\mathrm{AIF}}^{\mathrm{P}}$ and $k_{\mathrm{ep}} \triangleq \Phi^{\mathrm{P}}/V^{\mathrm{P}}$.

So, it appears that the differential SPM does not apply to a fluid that is known *a priori* to flow from the feeding artery to the draining vein, so that $\Phi^{\mathrm{P}} \geq 0$, because the output plasmatic mass concentration must be a function of the mass concentration $c(t)$ in system Σ, not a function of the mass concentration $c_v(t)$ in the draining vein that plays no role in the mass balance equation. But, by simply calling "arterial input function" or "venous output function" the concentration-time curves $c_a(t)$ and $c_v(t)$ or by simply assuming positive BF, we are actually assuming the direction of the flow to be known *a priori*, from the feeding artery to the draining vein. It follows that the differential SPM is not applicable and has to be replaced by the Kety-like model previously derived. Hence, the differential SPM can apply at best to a flow whose direction is not known *a priori*.

But in this case, the kinetic model is made of two *a priori* equiprobable models conditional upon the global direction of the flow or, equivalently, upon the sign of the volumetric flow rate Φ^{P}

$$\mathrm{M}: \begin{cases} \mathrm{M}|\Phi^{\mathrm{P}} \geq 0: & \dfrac{\mathrm{d}c}{\mathrm{d}t}(t) = \Phi^{\mathrm{P}}\left[c_a\,(t)\,/V_{\mathrm{AIF}}^{\mathrm{P}} - c\,(t)\,/V^{\mathrm{P}}\right] \\ \mathrm{M}|\Phi^{\mathrm{P}} < 0: & \dfrac{\mathrm{d}c}{\mathrm{d}t}(t) = -\Phi^{\mathrm{P}}\left[c_v\,(t)\,/V_{\mathrm{VOF}}^{\mathrm{P}} - c\,(t)\,/V^{\mathrm{P}}\right] \end{cases} \tag{18}$$

and still does not match the differential SPM that cannot be derived from fluid kinetics only. Indeed, this model is not causal for it gives the state $c(t)$ of the dynamical system

as a "function" of its output $c_v(t)$ instead of giving its output as a "function" of its state. Therefore, it actually does not pertain to dynamical system theory. In particular, its formal solution is not given by equation 2 but simply by

$$c\left(t\right) = BF \int_{t_0}^{t} \left[c_a\left(\tau\right) - c_v\left(\tau\right)\right] d\tau + c\left(t_0\right) \tag{19}$$

However, if the sign of Φ^{P} is not known *a priori*, then by the theorem of total probability, the Bayesian average, marginal, unconditional model is

$$\frac{1}{2}\,\mathrm{M}|\,\Phi^{\mathrm{P}} \geq 0 + \frac{1}{2}\,\mathrm{M}|\,\Phi^{\mathrm{P}} < 0 \tag{20}$$

that is

$$\frac{\mathrm{d}c}{\mathrm{d}t}\left(t\right) = \frac{\Phi^{\mathrm{P}}}{2}\left[c_a\left(t\right)/V_{\mathrm{AIF}}^{\mathrm{P}} - c_v\left(t\right)/V_{\mathrm{VOF}}^{\mathrm{P}}\right] \tag{21}$$

and, if $V_{\mathrm{AIF}}^{\mathrm{P}} = V_{\mathrm{VOF}}^{\mathrm{P}}$,

$$\frac{\mathrm{d}c}{\mathrm{d}t}\left(t\right) = BF\left[c_a\left(t\right) - c_v\left(t\right)\right] \tag{22}$$

if we let

$$BF \triangleq \frac{\Phi^{\mathrm{P}}}{2V_{\mathrm{AIF}}^{\mathrm{P}}} \tag{23}$$

Another line of reasoning yielding the same model is to acknowledge that the tracer plasmatic mass concentration $c_I(t)$ flowing through Σ_I cannot be equal to the tracer mass concentration $c^{\mathrm{P}}(t)$ in the plasma contained in system Σ nor to the tracer mass concentration $c_{\mathrm{AIF}}^{\mathrm{P}}(t)$ in the plasma contained in the feeding artery. Indeed, if the global direction of the flow is not known *a priori*, then the signed mass $m_I(t)$ of the tracer circulating between the artery and system Σ through Σ_I must be invariant, up to sign, by permutation of the artery and system Σ (*i.e.* by inversion of the "tube axis"). Since the flow rate $\Phi_I^{\mathrm{P}}(t)$ is, by definition, invariant up to sign by this permutation (*i.e.* skew symmetric), $c_I(t)$ must also be invariant by this permutation, *i.e.* must be a symmetric function of the mass concentrations $c^{\mathrm{P}}(t)$ and $c_{\mathrm{AIF}}^{\mathrm{P}}(t)$ only. Thus, we are led to set $c_I(t) \triangleq \left[c_{\mathrm{AIF}}^{\mathrm{P}}(t) + c^{\mathrm{P}}(t)\right]/2$ with $c^{\mathrm{P}}(t) = c(t)V/V^{\mathrm{P}}$ and $c_{\mathrm{AIF}}^{\mathrm{P}}(t) = c_a(t)V/V_{\mathrm{AIF}}^{\mathrm{P}}$. Similarly, we set $c_O(t) \triangleq \left[c_{\mathrm{VOF}}^{\mathrm{P}}(t) + c^{\mathrm{P}}(t)\right]/2$ with $c_{\mathrm{VOF}}^{\mathrm{P}}(t) = c_v(t)V/V_{\mathrm{VOF}}^{\mathrm{P}}$. Therefore,

$$\begin{aligned} \mathrm{d}m(t) = \mathrm{d}c(t)V = m_{\Sigma_I}(t) - m_{\Sigma_O}(t) = \\ \left\{ \begin{array}{l} \left[c_a(t)/V_{\mathrm{AIF}}^{\mathrm{P}} + c(t)/V^{\mathrm{P}}\right]\Phi^{\mathrm{P}}(t) - \\ \left[c_v(t)/V_{\mathrm{VOF}}^{\mathrm{P}} + c(t)/V^{\mathrm{P}}\right]\Phi^{\mathrm{P}}(t) \end{array} \right\} V\mathrm{d}t/2 \end{aligned} \tag{24}$$

So, starting from the definition of the volumetric flow rate in fluid kinematics, the Gauss-Green-Ostrogradsky divergence theorem for incompressible flows and the principle of mass conservation, we have derived a Kety-like SISO differential kinetic model for the flow of an intravascular tracer undergoing advective transport by the plasma in a tube-like system when its global direction is known *a priori* and a Bayesian SPM-like differential model when its global direction is not known *a priori*. This latter

model being purely epistemic and not causal, we shall not consider it further in this paper.

Instead of assuming incompressible flow at the beginning and steady flow at the end of the proof, we could have assumed long-term steady flow from the very beginning. In this case, unless the flow is infinitely compressible, the total plasmatic volumetric flow rate $\Phi^{\mathrm{P}}_{\Sigma}$ through Σ is necessarily equal to zero, so that there is no need to assume constant hematocrit fraction $\Phi^{\mathrm{C}}(t)/\Phi^{\mathrm{IF}}(t)$ in order to define Φ^{P}. However, while incompressibility should not be a matter of discussion given the low physiological velocities, by definition long-term steadiness may be well violated especially in acute pathologies.

Those proofs highlight the main limitation of SISO kinetic models: they apply at best to tubes having a single inflow orifice and a single outflow orifice, as stated clearly by Zierler (1962). This geometric condition is logically necessary in order to define a single non-zero volumetric flow rate $\Phi(t)$ through an open surface and subsequently a single non-zero plasmatic volumetric flow rate $\Phi^{\mathrm{P}}(t)$, the total volumetric flow rate $\Phi_{\Sigma}(t)$ through the closed surface Σ being identically zero by incompressibility or steadiness.

However, in tracer tracking tomography, SISO models are used to describe the transport of contrast agents in voxels. Such a voxel is a rectangular parallelepiped whose surface, which is closed, is composed of its six faces. Generally speaking, it is therefore not possible to define *a priori* a single open input surface and a single open output surface, so that it is not possible to define a single non-zero total volumetric flow rate $\Phi(t)$ per voxel, as done within the SPM or the Kety-like model previously derived.

Hence, the genuine volumetric blood flow rate $\Phi^{\mathrm{IF}} = \Phi^{\mathrm{P}}/(1 - Ht)$ of the Kety-like model, which is equal to the total volumetric flow rate under the hypotheses of the SPM, cannot be the volumetric flow rate (through the closed surface) of a voxel because it is not necessarily equal to zero. Conversely, it is useless to estimate the volumetric blood flow rate (through the closed surface) of a voxel because it is equal to zero within the SPM. It follows that, generally speaking, SISO kinetic models are not suitable to describe the transport of contrast agents as probed by tomographic techniques because they define a single non-zero volumetric (blood) flow rate while the volumetric (blood) flow rate (through the closed surface) of a voxel is necessarily equal to zero.

In other words, if Φ^{IF} is ever a volumetric flow rate as defined within fluid kinematics, it is necessarily taken through an open surface. As long as this open surface remains undefined, *i.e.* not localized in space and time, this quantity cannot be a volumetric flow rate because volumetric flow rates are extensive quantities defined through given surfaces. Hence, unless we can define their open surface, we must acknowledge that Φ^{IF} is anything but a volumetric flow (rate). Anyway, the physical dimension of BF is T^{-1} (not $L^3M^{-1}T^{-1}$ as the standard unit $ml/100g/mn$ indicates (Østergaard et al. 1996)). Hence, it is neither a volumetric flow rate (L^3T^{-1}) nor a mass flow rate (MT^{-1}) nor a volumetric flux (LT^{-1}).

4. Can SI(SO) models ever apply to tomographic data?

Can SI(SO) kinetic models nevertheless apply to some special cases of interest?

Assume that the flow through a voxel is of the tube type, with a single open input surface Σ_I and a single open output surface Σ_O. This is the case when the voxel contains a single blood vessel.

We could apply the Kety-like model if those surfaces were known *a priori*. Indeed, again a flow rate is defined through a given surface. It is neither possible to define a volumetric flow rate nor to write a mass balance equation on an undefined control surface or system because they precisely depend on the surface(s). Generally speaking, surfaces Σ_I and Σ_O, *i.e.* the position and direction of the blood vessel, are not known *a priori*, at least not precisely. On the contrary, we may like to determine *a posteriori* whether such surfaces exist or not, *i.e.* whether the flow is rather directional or isotropic, and, in the former case, determine their positions. Thus, the Kety-like model does not apply to a tube-like flow unless surfaces Σ_I, Σ_O and Σ_R are given *a priori*.

Besides, by the principle of locality, $c_a(t)$ has to be taken in the immediate exterior surroundings of the voxel-tube input orifice. This is not common practice, in particular when a global, spatially separated AIF is used for all voxels (Fieselmann et al. 2011, Østergaard et al. 1996), because it is simply impossible.

Now, let us assume that input surface Σ_I is given *a priori*. Then the Kety-like model can apply only if it is located on a single face of the voxel. Indeed, on the one hand, it is assumed that the mass concentration is spatially uniform in the immediate exterior surroundings of Σ_I and identically equal to $c_a(t)$. On the other hand, the mass concentrations in the (at most) six neighbor voxels of the current voxel are not necessarily equal to each other. Hence, if the input surface spans several voxel faces, the Kety-like model assumes equal mass concentrations that are not necessarily equal: contradiction.

Last, we must keep in mind that Meier and Zierler tube, in particular its surface Σ_R, must be contained in the voxel. This is necessary in order for the volumetric flow rate through the voxel surface minus $\Sigma_I \cup \Sigma_O$ to be equal to zero. This implies that the cross-section of the tube-vessel must be small compared to the dimensions of the voxel, a condition that is clearly violated for large arteries and veins, given the current millimetric dimensions of the voxels. If it is not the case, *i.e.* if the cross-section of the tube-vessel spans several adjacent voxels, we have to assume *a priori* the flow trajectories to be parallel to the voxel faces (or even more unlikely hypotheses) in order for the flow rates through them to be again equal to zero. But this geometric condition has probability zero.

This analysis demonstrates, we hope, that SI(SO) kinetic models cannot apply to any conceivable case of interest in tracer tracking tomography. This is the case for all generic permeability models such as the Kety, extended Kety-Tofts-Kermode, St Lawrence and Lee, Buxton as well as dynamic SPECT and PET models since they rely on a single arterial or plasmatic input function and define a single "flow" (*e.g.* K^{trans}

for Kety and extended Kety-Tofts-Kermode models, F for St Lawrence and Lee model, BF for Buxton, PET and SPECT models, etc.).

5. From tubes to voxels: local kinetic models

It is by now straightforward to derive the correct expression of the conservation of the mass of an intravascular tracer undergoing advective transport by the blood plasma and flowing through a parallelepipedic voxel.

Index the six neighbor voxels of the current voxel by $i = 1, 6$. Just like the voxel is the elementary unit of volume in tomography, its faces $F_i,\ i = 1, 6$ are the elementary units of open surface: $\Sigma = \bigcup_{i=1}^{6} F_i$. Let us orient them outward and define the volumetric flow rates

$$\Phi_i(t) \triangleq \iint_{F_i} \vec{v}\,(x, y, z, t) \cdot \overrightarrow{\mathrm{d}\Sigma} \tag{25}$$

As before, we have $\Phi_i(t) = \Phi_i^{\mathrm{EF}}(t) + \Phi_i^{\mathrm{BV}}(t) + \Phi_i^{\mathrm{IF}}(t)$. The mass balance equation for the contrast agent in system Σ over time interval $[t, t + \mathrm{d}t]$ becomes

$$\mathrm{d}m(t) = \mathrm{d}c(t)V = -\sum_{i=1}^{6} m_i(t) \tag{26}$$

where $m_i(t)$ is the tracer signed output mass through F_i, equal to

$$m_i(t) = c_i^O(t)V_i(t) = c_i^O(t)\Phi_i^{\mathrm{P}}(t)\mathrm{d}t \tag{27}$$

where $V_i(t)$ is the signed volume of plasma (mixed with the tracer) flowing through F_i over $[t, t + \mathrm{d}t]$, $\Phi_i^{\mathrm{P}}(t)$ is the plasmatic volumetric flow rate through F_i at time t and $c_i^O(t)$ is the plasmatic mass concentration of the tracer flowing through F_i.

As before, we have $2^6 = 64$ different sub-models conditional upon the signs of the six volumetric flow rates and the plasmatic mass concentrations write accordingly as

$$c_i^O\,(t) = \begin{cases} c\,(t)\,V/V^{\mathrm{P}}(t) & \text{if} \quad \Phi_i^{\mathrm{P}}\,(t) \geq 0 \\ c_i\,(t)\,V/V_i^{\mathrm{P}}(t) & \text{if} \quad \Phi_i^{\mathrm{P}}\,(t) < 0 \end{cases} \tag{28}$$

If we suppose that the flow is steady only at the time scale of the tomographic acquisition duration, then we get the first 7-compartment local model

$$\frac{\mathrm{d}c}{\mathrm{d}t}\,(t) = -\frac{1}{V}\sum_{i=1}^{6} \Phi_i^{\mathrm{P}}\, c_i^O\,(t) \tag{29}$$

with constant plasmatic volumes. Note that this model is weaker than the SPM since it does not require constant flow hematocrit fraction $\Phi^{\mathrm{C}}(t)/\Phi^{\mathrm{IF}}(t)$, which would just imply that $\Phi_\Sigma^{\mathrm{EF}} = -\Phi_\Sigma^{\mathrm{IF}}$ if $\Phi^{\mathrm{BV}} \equiv 0$ for an incompressible flow.

If we further assume that the flow is always steady and not infinitely compressible then $\sum_{i=1}^{6} \Phi_i^{\mathrm{P}} = \Phi_\Sigma^{\mathrm{P}} \equiv 0$. Therefore, there are only five free plasmatic volumetric flow

rates per voxel and, if we discard for instance Φ_6^{P}, the second 7-compartment local model reads as

$$\frac{\mathrm{d}c}{\mathrm{d}t}(t) = -\frac{1}{V}\sum_{i=1}^{5}\Phi_i^{\mathrm{P}}\,c_i^O(t) + \frac{1}{V}c_6^O(t)\sum_{i=1}^{5}\Phi_i^{\mathrm{P}} \tag{30}$$

with constant plasmatic volumes. See Appendix A for a short derivation of those models from the local advection equation.

This second model is to a long-term steady flow in a voxel what the Kety-like model previously derived is to a long-term steady flow in a tube. Indeed, should a voxel have only two neighbors $i = 1, 2$ and should the global direction of the flow be known *a priori*, for instance $\Phi_1^{\mathrm{P}} < 0$, we would have $c_1^O(t) = c_1(t)\,V/V_1^{\mathrm{P}}$ since $\Phi_1^{\mathrm{P}} < 0$ and $c_2^O(t) = c(t)\,V/V^{\mathrm{P}}$ since $\Phi_2^{\mathrm{P}} = -\Phi_1^{\mathrm{P}} > 0$ so that $\frac{\mathrm{d}c}{\mathrm{d}t}(t) = -\Phi_1^{\mathrm{P}}\left[c_1(t)/V_1^{\mathrm{P}} - c(t)/V^{\mathrm{P}}\right]$.

Both models are *a priori* relevant even if the second one may not be suitable for acute pathologies. Thus, within the first one, the absolute value of the total plasmatic volumetric flow rate $\left|\sum_{i=1}^{6}\Phi_i^{\mathrm{P}}\right|$ provides an interesting measure of the long-term unsteadiness of the flow.

6. From local to 4D tomographic kinetic models

Let us index the voxels by their integer coordinates (i, j, k) in $(O, \vec{x}, \vec{y}, \vec{z})$. Let $c_{i,j,k}(t)$ be the tracer mass concentration and $V_{i,j,k}$ be the plasmatic volume in voxel (i, j, k). Let us orient its six faces along the $\vec{x}$, $\vec{y}$ and $\vec{z}$ axes and let us index them as well as the flow rates by their half-integer coordinates $(i \pm 1/2, j, k)$, $(i, j \pm 1/2, k)$ and $(i, j, k \pm 1/2)$.

In this way, the volumetric flow rate in voxel $(i-1, j, k)$ through its face $(i-1+1/2, j, k)$ is actually $\Phi_{(i-1)+1/2,j,k} = \Phi_{i-1/2,j,k}$, in accordance with skew symmetry. Let $\alpha_{i,j,k} \triangleq 1/V_{i,j,k}$ and

$$\begin{aligned}
c^O_{i+\frac{1}{2},j,k}(t) &= V\begin{cases}\alpha_{i,j,k}c_{i,j,k}(t) & \text{if}\quad \Phi_{i+\frac{1}{2},j,k}(t) \geq 0\\ \alpha_{i+1,j,k}c_{i+1,j,k}(t) & \text{if}\quad \Phi_{i+\frac{1}{2},j,k}(t) < 0\end{cases}\\
&\cdots\\
c^O_{i,j,k-\frac{1}{2}}(t) &= V\begin{cases}\alpha_{i,j,k}c_{i,j,k}(t) & \text{if}\quad \Phi_{i,j,k-\frac{1}{2}}(t) < 0\\ \alpha_{i,j,k-1}c_{i,j,k-1}(t) & \text{if}\quad \Phi_{i,j,k-\frac{1}{2}}(t) \geq 0\end{cases}
\end{aligned} \tag{31}$$

With this new orientation convention, the first local model rewrites as

$$\frac{\mathrm{d}c_{i,j,k}}{\mathrm{d}t}(t) = -\frac{1}{V}\left[\begin{array}{l}\Phi_{i+\frac{1}{2},j,k}c^O_{i+\frac{1}{2},j,k}(t) - \Phi_{i-\frac{1}{2},j,k}c^O_{i-\frac{1}{2},j,k}(t) +\\ \Phi_{i,j+\frac{1}{2},k}c^O_{i,j+\frac{1}{2},k}(t) - \Phi_{i,j-\frac{1}{2},k}c^O_{i,j-\frac{1}{2},k}(t) +\\ \Phi_{i,j,k+\frac{1}{2}}c^O_{i,j,k+\frac{1}{2}}(t) - \Phi_{i,j,k-\frac{1}{2}}c^O_{i,j,k-\frac{1}{2}}(t)\end{array}\right] \tag{32}$$

for any voxel (i, j, k) having its six neighbor voxels in the volume of interest, voxels that

we call interior. Similarly, if we discard $\Phi_{i,j,k+\frac{1}{2}}$, the second local model rewrites as

$$\frac{\mathrm{d}c_{i,j,k}}{\mathrm{d}t}(t) = -\frac{1}{V}\left\{\begin{array}{l} \Phi_{i+\frac{1}{2},j,k}\left[c^O_{i+\frac{1}{2},j,k}(t) - c^O_{i,j,k+\frac{1}{2}}(t)\right] - \\ \Phi_{i-\frac{1}{2},j,k}\left[c^O_{i-\frac{1}{2},j,k}(t) - c^O_{i,j,k+\frac{1}{2}}(t)\right] + \\ \Phi_{i,j+\frac{1}{2},k}\left[c^O_{i,j+\frac{1}{2},k}(t) - c^O_{i,j,k+\frac{1}{2}}(t)\right] - \\ \Phi_{i,j-\frac{1}{2},k}\left[c^O_{i,j-\frac{1}{2},k}(t) - c^O_{i,j,k+\frac{1}{2}}(t)\right] - \\ \Phi_{i,j,k-\frac{1}{2}}\left[c^O_{i,j,k-\frac{1}{2}}(t) - c^O_{i,j,k+\frac{1}{2}}(t)\right] \end{array}\right\} \tag{33}$$

For exterior voxels, *i.e.* those having at most five neighbor voxels in the volume of interest, two cases must be considered:

- Either it is known *a priori*, for instance thanks to the anatomy, that all volumetric flow rates through the faces without a neighbor voxel are necessarily equal to zero. Such voxels will be called boundary. In this case, we have reduced equations. For instance, for a boundary voxel (i,j,k) without its $(i-1,j,k)$, $(i,j-1,k)$ and $(i,j,k-1)$ neighbors, we have the reduced equation for the second local model

$$\frac{\mathrm{d}c_{i,j,k}}{\mathrm{d}t}(t) = -\frac{1}{V}\left[\begin{array}{l} \Phi_{i+\frac{1}{2},j,k}c^O_{i+\frac{1}{2},j,k}(t) + \Phi_{i,j+\frac{1}{2},k}c^O_{i,j+\frac{1}{2},k}(t) - \\ \left(\Phi_{i+\frac{1}{2},j,k} + \Phi_{i,j+\frac{1}{2},k}\right)c^O_{i,j,k+\frac{1}{2}}(t) \end{array}\right] \tag{34}$$

- or, at least one volumetric flow rate through a face without a neighbor voxel is not known *a priori* (to be equal to zero). In this case, there is no equation for this voxel, otherwise the resulting system of equations would be underdetermined. Hence, the concentration-time curves in those exterior, non-boundary voxels play the role of global AIFs or VOFs for the tridimensional volume of interest.

Given the volumetric flow rates, the local equations of both models for all interior and boundary voxels form a system of inhomogeneous first-order linear constant coefficient ordinary differential equations that can be written as a matrix differential equation

$$\frac{\mathrm{d}\mathbf{c}}{\mathrm{d}t}(t) = \mathbf{A}\mathbf{c}(t) + \mathbf{B}\mathbf{c}_\mathbf{I}(t) \tag{35}$$

where $\mathbf{c}(t)$ is the vector of all concentrations in the interior and boundary voxels at time t, $\mathbf{c}_\mathbf{I}(t)$ is the corresponding vector for exterior, non-boundary input voxels and $\mathbf{A}$ and $\mathbf{B}$ are large, too large to be written down, but sparse matrices whose coefficients depend on the volumetric flow rates $\mathbf{F} \triangleq \{\Phi_{.,.,.}\}$, the volumes $\mathbf{V} \triangleq \{V_{.,.,.}\}$ or their inverses $\boldsymbol{\alpha}$ and on the geometry of the volume of interest. The formal solution of such system with initial condition $\mathbf{c}(t_0) = \mathbf{c_0}$ is given by

$$\begin{aligned} \mathbf{c}(t) &= e^{\mathbf{A}(t-t_0)}\mathbf{c_0} + e^{\mathbf{A}(t-t_0)}\int_{t_0}^{t} e^{-\mathbf{A}(\tau-t_0)}\mathbf{B}\mathbf{c}_\mathbf{I}(\tau)\,\mathrm{d}\tau \\ &= e^{\mathbf{A}(t-t_0)}\mathbf{c_0} + \int_{t_0}^{t} e^{\mathbf{A}(t-\tau)}\mathbf{B}\mathbf{c}_\mathbf{I}(\tau)\,\mathrm{d}\tau \end{aligned} \tag{36}$$

In particular, if $\mathbf{c_0} = 0$ and $t_0 = 0$, we have

$$\mathbf{c}(t) = \int_0^t e^{\mathbf{A}(t-\tau)}\mathbf{B}\mathbf{c_I}(\tau)\,\mathrm{d}\tau = e^{\mathbf{A}t} \otimes \mathbf{B}\mathbf{c_I} \tag{37}$$

Again, we recognize a Kety-like monoexponential convolution model, but matrix and 4D.

By contrast to current single input models that describe the circulation of contrast agents in voxels completely independently of other voxels, as if there were no inter-voxel exchanges, the new models rely on the fact that, in virtue of the principle of locality, a voxel does not exchange matter with one AIF and one VOF but with its (at most) six immediate neighbor voxels. In other words, each voxel has now six local inputs or outputs, depending on the posterior signs of the flow rates through each face. Geometry and space are completely lost within current local SI(SO) models: for example, shuffling the voxels has no effect on the parameter estimates when a global AIF is used. By contrast, we are now provided with genuine 4D spatiotemporal models of the circulation in the whole organ of interest, whose global AIF is the vector-valued function $\mathbf{c_I}(t)$ comprising the mass concentrations in the exterior, non-boundary input voxels. For instance, in brain imaging, $\mathbf{c_I}(t)$ may comprise the concentration-time curves in the carotid and basilar arteries voxels.

7. General case: mixed intra/extravascular tracers

Let us examine the case where the contrast agent can leave the intravascular space, enter the interstitial, extravascular, extracellular one and possibly go back to the intravascular space.

Once in the extravascular space, we assume that the tracer undergoes only diffusion (*i.e.* no advective transport) as usual. Assuming further, as before, that the root mean squared displacements by diffusion in the blood and in the interstitium during the dynamic tomographic acquisition duration are small compared to the voxels characteristic length, no amount of mass enters or exits the voxel by diffusion during the acquisition so that we shall neglect both the intravascular and extravascular signed diffusive output masses.

Hence, the mass balance equation remains

$$\mathrm{d}m(t) = \mathrm{d}c(t)V = -\sum_{i=1}^{6} m_i(t) \tag{38}$$

if we also neglect the tracer signed output masses that are neither in the intravascular space nor in the extravascular one, *i.e.* that are crossing the intra/extravascular barrier.

We still have $m_i(t) = c_i^{O,\mathrm{P}}(t)\Phi_i^{\mathrm{P}}(t)\mathrm{d}t$ and $c_i^{O,\mathrm{P}}(t) = \begin{cases} c^{\mathrm{P}}(t) & \text{if} \quad \Phi_i^{\mathrm{P}}(t) \geq 0 \\ c_i^{\mathrm{P}}(t) & \text{if} \quad \Phi_i^{\mathrm{P}}(t) < 0 \end{cases}$ under the intravascular uniform dilution assumption.

The total mass of contrast agent at time t in Σ is

$$m(t) = c(t)V = m^{\mathrm{P}}(t) + m^{\mathrm{I}}(t) = c^{\mathrm{P}}(t)V^{\mathrm{P}} + c^{\mathrm{I}}(t)V^{\mathrm{I}} \tag{39}$$

where $m^{\mathrm{P}}(t)$ is the mass of tracer transported by the plasma, V^{P} is the plasmatic volume, $m^{\mathrm{I}}(t)$ is the mass of tracer in the interstitial fluid and V^{I} is the interstitial volume.

Neglecting the vessels volume, we have

$$V = V^{\mathrm{IF}} + V^{\mathrm{EF}} = V^{\mathrm{P}}(t) + V^{\mathrm{IC}}(t) + V^{\mathrm{I}}(t) + V^{\mathrm{EC}}(t) \tag{40}$$

where $V^{\mathrm{EC}}(t)$ and $V^{\mathrm{IC}}(t)$ are the extravascular respectively intravascular cell volumes and $V^{\mathrm{I}}(t)$ is the interstitial, extravascular, extracellular volume. Assuming steady volumetric hematocrit fraction $V^{\mathrm{IC}}(t)/V^{\mathrm{IF}} \equiv \rho^{\mathrm{P}}$ and interstitial cellular fraction $V^{\mathrm{EC}}(t)/V^{\mathrm{EF}} \equiv \rho^{\mathrm{I}}$, we have

$$V = V^{\mathrm{P}}/\left(1-\rho^{\mathrm{P}}\right) + V^{\mathrm{I}}/\left(1-\rho^{\mathrm{I}}\right) \tag{41}$$

and

$$\left\{\begin{array}{l} c^{\mathrm{P}}(t) = \left[c(t)V - c^{\mathrm{I}}(t)V^{\mathrm{I}}\right] / \left[V - V^{\mathrm{I}}/\left(1-\rho^{\mathrm{I}}\right)\right] / \left(1-\rho^{\mathrm{P}}\right) \\ c_i^{\mathrm{P}}(t) = \left[c_i(t)V - c_i^{\mathrm{I}}(t)V_i^{\mathrm{I}}\right] / \left[V - V_i^{\mathrm{I}}/\left(1-\rho^{\mathrm{I}}\right)\right] / \left(1-\rho^{\mathrm{P}}\right) \end{array}\right. \tag{42}$$

so that

$$\begin{array}{rcl} \dfrac{\mathrm{d}c}{\mathrm{d}t}(t) & = & -\dfrac{1}{V}\displaystyle\sum_{i=1}^{6} c_i^{O,\mathrm{P}}(t)\,\Phi_i^{\mathrm{P}}(t) \\ & = & -\dfrac{1}{V}\displaystyle\sum_{i=1}^{6} \Phi_i^{\mathrm{P}}(t) \left\{\begin{array}{ll} \frac{c(t)V - c^{\mathrm{I}}(t)V^{\mathrm{I}}}{(1-\rho^{\mathrm{P}})[V - V^{\mathrm{I}}/(1-\rho^{\mathrm{I}})]} & \text{if} \quad \Phi_i^{\mathrm{P}}(t) \geq 0 \\ \frac{c_i(t)V - c_i^{\mathrm{I}}(t)V_i^{\mathrm{I}}}{(1-\rho^{\mathrm{P}})\left[V - V_i^{\mathrm{I}}/(1-\rho^{\mathrm{I}})\right]} & \text{if} \quad \Phi_i^{\mathrm{P}}(t) < 0 \end{array}\right. \end{array} \tag{43}$$

Assuming long-term steady flow, the total plasmatic flow rate vanishes so that

$$\frac{\mathrm{d}c}{\mathrm{d}t}(t) = -\frac{1}{V}\sum_{i=1}^{5} c_i^{O,\mathrm{P}}(t)\,\Phi_i^{\mathrm{P}}(t) + \frac{1}{V}c_6^{O,\mathrm{P}}(t)\sum_{i=1}^{5}\Phi_i^{\mathrm{P}}(t) \tag{44}$$

In any case, the equations involve unknown interstitial or plasmatic mass concentrations in addition to the mass concentrations in the voxels. It is therefore necessary to introduce additional information or equations in order to separate the plasmatic and interstitial components. Since we stick to fluid kinetics in this paper, *i.e.* to the principle of mass conservation, we have to stop at this point.

8. Applications

We can define and estimate other quantities of interest as well.

The voxel faces being planar, we have for instance for a face F oriented along axis $\vec{x}$

$$\Phi = \iint_F \vec{v}\,(x,y,z)\cdot\vec{x}\mathrm{d}y\mathrm{d}z = \iint_F v_x\,(y,z)\,\mathrm{d}y\mathrm{d}z = S_x\,\langle v_x\rangle \tag{45}$$

where S_x is the measure of F and $\langle v_x\rangle$ is the mean velocity on it along $\vec{x}$ or the flux through it. Hence, we define canonically a mean velocity vector field over the boundary and interior voxels by

$$\begin{array}{rcl} \vec{v}_{i,j,k} & \triangleq & \left(v_x, v_y, v_z\right)_{i,j,k} \\ & \triangleq & \left(\frac{\Phi_{i-\frac{1}{2},j,k}+\Phi_{i+\frac{1}{2},j,k}}{2S_x}, \frac{\Phi_{i,j-\frac{1}{2},k}+\Phi_{i,j+\frac{1}{2},k}}{2S_y}, \frac{\Phi_{i,j,k-\frac{1}{2}}+\Phi_{i,j,k+\frac{1}{2}}}{2S_z}\right) \end{array} \tag{46}$$

and a local mean velocity scalar field by $\langle v_{i,j,k} \rangle \triangleq \sqrt{v_x^2 + v_y^2 + v_z^2}$. Let S_i be the measure of face F_i and $L_i, i = 1,6$ be the dimension of the voxel orthogonal to F_i. We define the local signed mean transit time from the center of the current voxel to the center of neighbor voxel i by

$$MTT_i \triangleq L_i / \langle v_i \rangle = L_i S_i / \Phi_i = V / \Phi_i \tag{47}$$

where Φ_i is the outward-oriented flow rate through F_i. Beyond, from the mean velocity vector field $\vec{v}_{i,j,k}$, we can determine the streamlines, which coincide with the trajectories for a steady flow, by solving the differential equation $\mathrm{d}x/v_x = \mathrm{d}y/v_y = \mathrm{d}z/v_z$ as usual. In this way, we get a dynamic angio-tractography technique via intravascular tomography. In particular, we get the propagation delays along a given trajectory from a given origin, the material acceleration $(\vec{v} \cdot \vec{\nabla})\vec{v}$ and its norm for a steady flow, the material jerk, the material snap, etc.

Last, while the question "how is the tissue perfused?" remains ill-posed as long as the open perfusion surface is not specified, we can nevertheless address the need for a single voxel-wise perfusion measure by introducing the total absolute volumetric flow rate $\sum_{i=1}^{6} |\Phi_i|$, the total quadratic volumetric flow rate $\sum_{i=1}^{6} \Phi_i^2$, the maximum absolute volumetric flow rate $\max_{i=1,6} |\Phi_i|$ or the maximum quadratic volumetric flow rate $\max_{i=1,6} \Phi_i^2$. Let us just keep in mind that we are loosing information and that those quantities are no longer physical quantities defined within fluid mechanics.

9. Parameter estimation

It remains to sketch out how parameters $\{\mathbf{F}, \boldsymbol{\alpha}, t_0\}$ can be efficiently estimated with conventional computational means if we want to render this theory applicable, especially to clinical hyper-emergencies such as acute stroke.

First of all, strictly speaking continuous-time kinetic models have to be converted into discrete-time ones. But, since this conversion may depend on the imaging technique at hand (Clough et al. 2000), we do not deal with this issue here and we simply assume, as usual, that the solutions of the continuous-time models at sampling times are good approximations of the solutions of the corresponding discrete-time models.

Second, observe that the transformation $(\mathbf{F}, \boldsymbol{\alpha}) \mapsto (\lambda \mathbf{F}, \boldsymbol{\alpha}/\lambda)$ leaves the equations invariant for any $\lambda > 0$, so that $\mathbf{F}$ and $\boldsymbol{\alpha}$ are globally underdetermined, nonidentifiable. In order to fix λ in intravascular imaging, we have to set the plasmatic volumes to

$$V_{\max}^{\mathrm{P}} \triangleq 1/\alpha_{\min} \triangleq (1 - Ht')\, V^{\mathrm{IF}} = (1 - Ht')\, V \tag{48}$$

in voxels known to contain only blood (*i.e.* in large arteries and veins), where Ht' is the volumetric hematocrit fraction $V^{\mathrm{C}}/V^{\mathrm{IF}}$, assumed to be always and everywhere constant.

Suppose we are provided with a parametric model $\mathrm{M}: \; s_{i,j,k}(t) = f\left[c_{i,j,k}(t), \Theta_{i,j,k}\right]$ linking the experimental tomographic signals $s_{i,j,k}(t)$ to the theoretical mass concentration-time curves $c_{i,j,k}(t)$ where $\Theta_{i,j,k}$ is the set of the model parameters to be estimated. For instance, we typically have

$$\mathrm{M}: \; s_{i,j,k}(t) = \lambda_{i,j,k} c_{i,j,k}(t) + s_{i,j,k}^0 + \xi_{i,j,k} \tag{49}$$

in CTP/DCE-CT and

$$\mathrm{M}: \; s_{i,j,k}(t) = s^0_{i,j,k} e^{-\lambda_{i,j,k} TE c_{i,j,k}(t)} + \xi_{i,j,k} \tag{50}$$

in DSC-MR, where $s^0_{i,j,k}$ are the baselines, $\xi_{i,j,k}$ the additive noises, TE is the echo time and $\lambda_{i,j,k}$ are conversion constants that have to be fixed *a priori*. For instance, for white, stationary, uncorrelated Gaussian noises $\xi_{i,j,k} \sim \mathcal{N}\left(0, \sigma^2_{i,j,k}\right)$, we have $\Theta_{i,j,k} = \left\{s^0_{i,j,k}, \sigma_{i,j,k}\right\}$.

Bayesian parameter estimation (Jaynes 2003) is the method of choice because it provides, in addition to admissible parameter estimators (*e.g.* minimum variance or maximum *a posteriori* estimators depending on the loss function), credible intervals and their odds, joint and marginal posteriors and the probability of the data given the model. Moreover, the theoretical concentration-time curves in exterior, non-boundary voxels have to be jointly estimated nonparametrically from the experimental ones, a task that can be achieved rigorously only within Bayesian probability theory (Boutelier et al. 2012). Spatial regularization via Markov random fields could also be easily introduced if necessary. But parameter marginal posteriors require the evaluation of multiple definite integrals whose dimension is roughly proportional to the number N of voxels (*e.g.* $O\left(5N\right)$ for the first model with heteroscedastic noises in CTP or DSC-MR), up to $N = 512 \times 512 \times 320 \simeq 84 \times 10^6$ in CTP. Analytic integration seems to be precluded by double exponential integrals in CTP and triple exponential integrals in DSC-MR with Gaussian $\xi_{i,j,k}$ and by the fact that the definite integrals over the volumetric flow rates on $\mathbb{R}$ have to be split into two orthant integrals on $\mathbb{R}^-$ and $\mathbb{R}^+$. Hence, we probably need to design dedicated numerical integration algorithms and this is a non-trivial task to say the least. Variational Bayes may be?

By contrast, joint maximum *a posteriori*, maximum likelihood and nonlinear least squares estimation is operational since efficient generic local optimization methods of large nonlinear functions are available (Yuan 2011). Beyond, we may be able to take benefit of the particular structure of our inference problem and to introduce dedicated algorithms, perhaps similar to those used for inference in Markov random fields such as iterated conditional modes (Besag 1986) for joint maximum *a posteriori* estimation.

Despite the large number of parameters, estimation can be made computationally friendly, if not rigorous, by building for instance on a method that is well known in DCE-MR (Murase 2004). Assume that the experimental concentration-time curves are available (*e.g.* CTP). Integrating the local equations on both sides and replacing the theoretical antiderivatives $C^O_{.,.,.}(t) \triangleq \int_{t_0}^{t} c^O_{.,.,.}(\tau)\,\mathrm{d}\tau$ by their experimental counterparts

$C^{O,\exp}_{.,.,.}(t) \triangleq \int_{t_0}^{t} c^{O,\exp}_{.,.,.}(\tau)\,\mathrm{d}\tau$, yields for instance the pseudo-model from the second model

$$c_{i,j,k}(t) = -\frac{1}{V}\left\{\begin{array}{l} \Phi_{i+\frac{1}{2},j,k}\left[C^{O,\exp}_{i+\frac{1}{2},j,k}(t) - C^{O,\exp}_{i,j,k+\frac{1}{2}}(t)\right] - \\ \Phi_{i-\frac{1}{2},j,k}\left[C^{O,\exp}_{i-\frac{1}{2},j,k}(t) - C^{O,\exp}_{i,j,k+\frac{1}{2}}(t)\right] + \\ \Phi_{i,j+\frac{1}{2},k}\left[C^{O,\exp}_{i,j+\frac{1}{2},k}(t) - C^{O,\exp}_{i,j,k+\frac{1}{2}}(t)\right] - \\ \Phi_{i,j-\frac{1}{2},k}\left[C^{O,\exp}_{i,j-\frac{1}{2},k}(t) - C^{O,\exp}_{i,j,k+\frac{1}{2}}(t)\right] - \\ \Phi_{i,j,k-\frac{1}{2}}\left[C^{O,\exp}_{i,j,k-\frac{1}{2}}(t) - C^{O,\exp}_{i,j,k+\frac{1}{2}}(t)\right] \end{array}\right\} \tag{51}$$

if $c_{i,j,k}(t_0) = 0$.

Compared to the analytic models that are nonlinear in the parameters, pseudo-models are piecewise-bilinear in $\mathbf{F}$ and $\boldsymbol{\alpha}$, *i.e.* they are piecewise-linear in $\mathbf{F}$ given $\boldsymbol{\alpha}$ and linear in $\boldsymbol{\alpha}$ given $\mathbf{F}$. Hence, for white, stationary, uncorrelated and homoscedastic Gaussian $\xi_{i,j,k}$ and for each t_0, we can get a least squares estimator $\mathbf{F}^{\mathrm{LS}}(\boldsymbol{\alpha})$ of $\mathbf{F}$ given $\boldsymbol{\alpha}$ and the linear least squares estimator $\boldsymbol{\alpha}^{\mathrm{LLS}}(\mathbf{F})$ of $\boldsymbol{\alpha}$ given $\mathbf{F}$. Let Ω be the set of all interior and boundary voxels. Therefore, we can minimize

$$\chi^2(\mathbf{F}, \boldsymbol{\alpha}, t_0) = \sum_{(i,j,k)\in\Omega}\sum_{l=1}^{n}\left[c^{\exp}_{i,j,k}(t_l) - c_{i,j,k}(t_l)\right]^2 \tag{52}$$

where $c^{\exp}_{i,j,k}(t_l), l = 1, n$ is the experimental mass concentration at sampling time t_l, by using a fast sparse alternating least squares scheme (Berge 1993) such as

$$\begin{array}{l} \text{For each } t_l, l = 1, n \\ \quad \boldsymbol{\alpha}(t_l) \leftarrow \boldsymbol{\alpha}_0 \\ \quad \text{Repeat} \\ \quad\quad \mathbf{F}(t_l) \leftarrow \mathbf{F}^{\mathrm{LS}}[\boldsymbol{\alpha}(t_l)] \\ \quad\quad \boldsymbol{\alpha}(t_l) \leftarrow \boldsymbol{\alpha}^{\mathrm{LLS}}[\mathbf{F}(t_l)] \\ \quad \text{until } [\mathbf{F}(t_l), \boldsymbol{\alpha}(t_l)] \text{ converges} \\ \quad \text{Compute } \chi^2[\mathbf{F}(t_l), \boldsymbol{\alpha}(t_l), t_l] \\ \text{Estimate } (\mathbf{F}, \boldsymbol{\alpha}, t_0) \text{ as } \arg\min_{l=1,n} \chi^2[\mathbf{F}(t_l), \boldsymbol{\alpha}(t_l), t_l] \end{array} \tag{53}$$

which provably converges to a local minimum.

The constraints $\alpha_{i,j,k} \geq \alpha_{\min} = 1/(1 - Ht')/V$ in intravascular imaging can be enforced by making the substitution $\boldsymbol{\alpha}' = \boldsymbol{\alpha} - \alpha_{\min}$ and by using non-negative linear least squares (Kim et al. 2010) in the $\boldsymbol{\alpha}(t_l) \leftarrow \boldsymbol{\alpha}^{\mathrm{LS}}[\mathbf{F}(t_l)]$ step. If the $\xi_{i,j,k}$ are heteroscedastic, least squares have to be replaced by weighted least squares

$$\chi^2(\mathbf{F}, \boldsymbol{\alpha}, t_0) = \sum_{(i,j,k)\in\Omega}\sum_{l=1}^{n}\left[c^{\exp}_{i,j,k}(t_l) - c_{i,j,k}(t_l)\right]^2/\sigma^2_{i,j,k} \tag{54}$$

and we have to resort to feasible weighted least squares estimators (Rao & Toutenburg 1999) unless the $\sigma_{i,j,k}$ are estimated separately or marginalized, etc.

The main problem occurs in the $\mathbf{F}(t_l) \leftarrow \mathbf{F}^{\mathrm{LS}}[\boldsymbol{\alpha}(t_l)]$ step. Indeed, we have three normal equations for each volumetric flow rate: $\dfrac{\partial \chi^2}{\partial \Phi_{.,.,.}} = 0$ with $\Phi_{.,.,.} > 0$, $\dfrac{\partial \chi^2}{\partial \Phi_{.,.,.}} = 0$ with $\Phi_{.,.,.} < 0$ and $\Phi_{.,.,.} = 0$. Hence, we should solve not less than $3^{|\mathbf{F}|}$ linear systems of normal equations in this step, which is of course absolutely intractable. In order to overcome this combinatorial issue, we have to pre-determine the signs of the volumetric flow rates in order to pre-specify a suitable global kinetic sub-model among the $3^{|\mathbf{F}|}$ *a priori* possible ones.

For this purpose, we first compute the probabilities of the local concentration-time curve $c^{\exp}_{i,j,k}(t)$ given the (at most) $2^6 = 64$ local sub-models (*i.e.* the evidences) in all interior and boundary voxels. For instance, if the six outward-oriented volumetric flow rates are negative, we have the sub-model

$$\frac{\mathrm{d}c_{i,j,k}}{\mathrm{d}t}(t) = -\left[\begin{array}{l} \Phi_{i+\frac{1}{2},j,k}\alpha_{i+1,j,k}c_{i+1,j,k}(t) - \Phi_{i-\frac{1}{2},j,k}\alpha_{i-1,j,k}c_{i-1,j,k}(t) + \\ \Phi_{i,j+\frac{1}{2},k}\alpha_{i,j+1,k}c_{i,j+1,k}(t) - \Phi_{i,j-\frac{1}{2},k}\alpha_{i,j-1,k}c_{i,j-1,k}(t) + \\ \Phi_{i,j,k+\frac{1}{2}}\alpha_{i,j,k+1}c_{i,j,k+1}(t) - \Phi_{i,j,k-\frac{1}{2}}\alpha_{i,j,k-1}c_{i,j,k-1}(t) \end{array}\right] \quad (55)$$

from the first local kinetic model, whose identifiable parameters are the six terms $\Phi_{i+\frac{1}{2},j,k}\alpha_{i+1,j,k}$, $\Phi_{i-\frac{1}{2},j,k}\alpha_{i-1,j,k}$... Similarly, if the six outward-oriented volumetric flow rates are positive, we have the sub-model

$$\frac{\mathrm{d}c_{i,j,k}}{\mathrm{d}t}(t) = -\alpha_{i,j,k}c_{i,j,k}(t)\left(\begin{array}{l} \Phi_{i+\frac{1}{2},j,k} - \Phi_{i-\frac{1}{2},j,k} + \Phi_{i,j+\frac{1}{2},k} - \\ \Phi_{i,j-\frac{1}{2},k} + \Phi_{i,j,k+\frac{1}{2}} - \Phi_{i,j,k-\frac{1}{2}} \end{array}\right) \quad (56)$$

whose identifiable parameter is the $\alpha_{i,j,k}\left(\Phi_{i+\frac{1}{2},j,k} - .... - \Phi_{i,j,k-\frac{1}{2}}\right)$ term.

The sub-model of highest evidence thus allows us to estimate the signs of the six local volumetric flow rates. In this way, we get two estimates of the sign of each volumetric flow rate through a face shared by two interior or boundary voxels. If both estimates are consistent, then we specify the sign in the global kinetic sub-model. If both estimates are inconsistent, we can compute the evidences of the $2^{12-1} = 2048$ sub-models of the tracer kinetics in both voxels in order to estimate the problematic sign one more time. Of course, despite this second estimation step, some inconsistencies will unavoidably remain. However, the corresponding misspecifications in the global kinetic sub-model should have only a local and mild impact for, by definition, they occur for volumetric flow rates that are small in absolute value so that the erroneous terms in the sub-model are also small in absolute value compared to other similar terms.

In fitting the global kinetic sub-model, we may better not constrain the volumetric flow rates to have the pre-specified signs. Indeed, this shall allow us to check the consistency of their signs *a posteriori*. Moreover, unconstrained estimation/optimization is computationally more friendly than constrained estimation/optimization. In particular, we can get the minimum variance Bayes estimator (*i.e.* the posterior expectation) of each unconstrained volumetric flow rate of the global bilinear pseudo-model in closed-form given $\boldsymbol{\alpha}$.

10. Practical considerations

New models apply immediately to tracer tracking tomographic data available so far as soon as they are volumetric, *i.e.* as soon as there is no void between consecutive slices. We should just better pre-segment the organ of interest in order to determine boundary and exterior voxels (*e.g.* carotid and basilar voxels for brain imaging) and register all signals on the same time grid because slices are generally not sampled simultaneously. In fitting analytic models, this is achieved by jointly estimating theoretical concentration-time curves on a fine time grid (Boutelier et al. 2012). In fitting pseudo-models, this is achieved by pre-interpolating all signals on the same fine time grid.

By contrast to current models that allow estimating "blood flows" and "blood volumes" only up to an unknown multiplicative constant (*i.e.* relative blood flows rBF and relative blood volumes rBV) due to the violation of the principle of locality, volumetric flow rates $\mathbf{F}$ and volumes $1/\boldsymbol{\alpha}$ estimates should be quasi-absolute at least in homogeneous tissue regions, regardless of the imaging modality. Indeed, first the models do not suffer partial volumes effects because they are precisely taken into account by design. Second, in homogeneous tissue regions, the relationships between signals and concentration-time curves, in particular the values of the unknown conversion constants $\lambda_{i,j,k}$, are expected to be locally quasi-identical on the average (of course there can exist local MR field inhomogeneities, etc.). Hence, since the parameters are essentially determined by the seven local concentration-time curves, if the seven signal/concentration relationships are quasi-identical, their estimates should also be quasi-absolute.

11. Discussion and conclusion

Current perfusion and permeability models have been revisited from the point of view of fluid kinematics and kinetics. Elementary proofs of local advective intravascular kinetic models reveal that none of them is applicable to tracer tracking tomographic techniques because voxels are not SI(SO) dynamical systems. In particular, they do not and cannot account for the circulation across the voxels and the underlying 3D geometry is lost.

The underlying fundamental geometric issue, one virtual input instead of six real inputs/outputs, has been easily fixed by rewriting the mass balance equation for a tracer undergoing incompressible or steady advective transport through a voxel. This yields simple, global, 4D spatiotemporal analytic models of the tracer transport and the blood circulation in the whole organ of interest. Their many parameters, short-term or long-term steady volumetric flow rates and volumes, can be readily estimated at least in some special cases. At a first glance, the new theory bridges the gap with techniques such as perfusion tensor imaging (Frank et al. 2008), but the exact relationship needs to be worked out.

Working hypotheses, mainly short-term or long-term steadiness and uniform intravascular dilution/concentration, are minimalist and not stronger than before.

Clearly, the uniform dilution/concentration assumption, while logically necessary, never holds. As a consequence it is actually not an assumption but rather an application of the principle of insufficient reason: if we partition the plasmatic space, then we have *a priori* no sufficient reason to consider that a part should have a mass concentration different from the mass concentration in any other part. Therefore, we should regard them as equal. Besides, physiology indicates that we might better replace steady volumetric flow rates and volumes by periodic ones in order to take the cardiac cycle into account.

From a logical standpoint, current single input perfusion and permeability models are thus falsified by fluid kinetics, independently of their practical value, since either they violate the principle of locality or they assert that a voxel has only two neighbors instead of six in general. As a consequence, by the principle/theorem of explosion of classical logic (*i.e. ex falso sequitur quodlibet*), any past, present or future Boolean statement drawn under them is true and false at the same time. In particular, it does not make sense to compare old and new experimental results: we just have to make a choice.

From a mechanical standpoint, the present kinetic theory is nothing but the conservative finite volume method of computational fluid dynamics with first-order upwind numerical flow rates and piecewise-constant solutions (Barth & Ohlberger 2004). The only difference is that the meshed geometry is not tunable but fixed, given *a priori* by the tomographic technique at hand and that the equations are obtained directly for the discrete, discontinuous tomographic medium, not by discretization of the continuity equation. As a consequence, the resulting discrete solutions are not at all expected to approximate the continuous ones because millimetric voxels are orders of magnitude bigger than the maximum elementary volume (Schneider 2009) in the tissue. Interestingly, the situation is quite different with micro-CT perfusion where the characteristic dimensions of the voxels almost match those of the microcapillaries (Nett et al. 2010).

Hence, we are provided with a logically simple, unified, fundamental theory of intravascular imaging that spontaneously solves many current technical and conceptual issues (Fieselmann et al. 2011). For instance, delay and dispersion effects actually arise from the violation of the principle of locality and no longer exist within this theory. By contrast, the mass balance equation for mixed intravascular/extravascular tracers alone is not sufficient to describe the flow and to determine unknown plasmatic or interstitial mass concentrations, volumetric flow rates and volumes. Since fluid kinetics does not seem to permit writing down the mass balance equations for the intravascular and extravascular compartments themselves unless they are given *a priori*, the possibility of inferring intra/extravascular exchanges and permeation from mass concentrations in voxels only may appear doubtful and requires further investigation. Besides, it remains to express the conservation of linear momentum and energy in order to access other useful physical quantities such as local mean pressures.

If something like the theory expounded here eventually supersedes the current one(s), it shall have a deep impact on our understanding of blood circulation, perfusion,

permeation and metabolism and on the clinical applications of perfusion-weighted and tracer tracking imaging to numerous pathologies, from vascular diseases to metabolic disorders. In particular, we would finally estimate real, quasi-absolute volumetric flow rates, volumes, mean velocities, trajectories and propagation delays thanks to those techniques. This is the purpose of a forthcoming paper.

Appendix A: a short derivation of local kinetic models

The local advection equation for an intravascular tracer transported by the plasma is

$$\frac{\partial c^{\mathrm{P}}(x,y,z,t)}{\partial t} + \vec{\nabla} \cdot \left[c^{\mathrm{P}}(x,y,z,t)\, \vec{v}^{\mathrm{P}}(x,y,z,t) \right] = 0 \tag{57}$$

where $c^{\mathrm{P}}(x,y,z,t)$ is the tracer plasmatic mass concentration and $\vec{v}^{\mathrm{P}}(x,y,z,t)$ is the Eulerian velocity vector field of the plasma mixed with the tracer.

Integrating over the voxel volume $\mathcal{V}$, we get on the one hand

$$\begin{aligned} &\iiint_{\mathcal{V}} \frac{\partial c^{\mathrm{P}}(x,y,z,t)}{\partial t} \mathrm{d}x\mathrm{d}y\mathrm{d}z = \\ &\frac{\mathrm{d}}{\mathrm{d}t} \iiint_{\mathcal{V}\setminus\partial\mathcal{V}} c^{\mathrm{P}}(x,y,z,t)\, \mathrm{d}x\mathrm{d}y\mathrm{d}z = \\ &\frac{\mathrm{d}}{\mathrm{d}t} \left[V^{\mathrm{P}}(t)\, c^{\mathrm{P}}(t) \right] = \frac{\mathrm{d}}{\mathrm{d}t} \left[V c(t) \right] = \\ &V \frac{\mathrm{d}c}{\mathrm{d}t}(t) \end{aligned} \tag{58}$$

if $c^{\mathrm{P}}(x,y,z,t) \equiv c^{\mathrm{P}}(t)$ over the plasmatic space. On the other hand, by the Gauss-Green-Ostrogradsky divergence theorem, we have

$$\begin{aligned} &\iiint_{\mathcal{V}} \vec{\nabla} \cdot \left[c^{\mathrm{P}}(x,y,z,t)\, \vec{v}^{\mathrm{P}}(x,y,z,t) \right] \mathrm{d}x\mathrm{d}y\mathrm{d}z = \\ &\oiint_{\partial\mathcal{V}} c^{\mathrm{P}}(x,y,z,t)\, \vec{v}^{\mathrm{P}}(x,y,z,t) \cdot \overrightarrow{\mathrm{d}\Sigma} = \\ &\sum_{i=1}^{6} \iint_{F_i} c^{\mathrm{P}}(x,y,z,t)\, \vec{v}^{\mathrm{P}}(x,y,z,t) \cdot \overrightarrow{\mathrm{d}\Sigma} \end{aligned} \tag{59}$$

Therefore, if $c^{\mathrm{P}}(x,y,z,t) \equiv c_i^O(t)$ on the intersection of the plasmatic space and face F_i, then we have

$$\begin{aligned} &\iiint_{\mathcal{V}} \vec{\nabla} \cdot \left[c^{\mathrm{P}}(x,y,z,t)\, \vec{v}^{\mathrm{P}}(x,y,z,t) \right] \mathrm{d}x\mathrm{d}y\mathrm{d}z = \\ &\sum_{i=1}^{6} c_i^O(t) \iint_{F_i} \vec{v}^{\mathrm{P}}(x,y,z,t) \cdot \overrightarrow{\mathrm{d}\Sigma} = \\ &\sum_{i=1}^{6} c_i^O(t)\, \Phi_i^{\mathrm{P}}(t) \end{aligned} \tag{60}$$

Hence, we recover the general local kinetic model

$$\frac{\mathrm{d}c}{\mathrm{d}t}(t) = -\frac{1}{V} \sum_{i=1}^{6} \Phi_i^{\mathrm{P}}(t)\, c_i^O(t) \tag{61}$$

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