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Bridging the Mental Gap between Convolution Approach and Compartmental Modeling in Functional Imaging: Typical Embedding of an Open Two-Compartment Model into the Systems Theory Approach of Indicator Dilution Theory

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***Abstract*—** Functional imaging procedures for the non-invasive assessment of tissue microcirculation are highly requested, but require a mathematical approach describing the trans- and inter-capillary passage of tracer particles. Up to now, two theoretical, for the moment different concepts have been established for tracer kinetic modeling of contrast agent transport in tissues: pharmacokinetic compartment models, which are usually written as coupled differential equations, and the indicator dilution theory, which can be generalized in accordance with the theory of linear-time-invariant (LTI) systems by using a convolution approach. Based on mathematical considerations, it can be shown that also in the case of an open two-compartment model well-known from functional imaging, the concentration-time course in tissue is given by a convolution, which allows a separation of the arterial input function from a system function being the impulse response function, summarizing the available information on tissue microcirculation. Due to this reason, it is possible to integrate the open two-compartment model into the system-theoretic concept of indicator dilution theory (IDT) and thus results known from IDT remain valid for the compartment approach. According to the long number of applications of compartmental analysis, even for a more general context similar solutions of the so-called forward problem can already be found in the extensively available appropriate literature of the seventies and early eighties. Nevertheless, to this day, within the field of biomedical imaging – not from the mathematical point of view – there seems to be a trench between both approaches, which the author would like to get over by exemplary analysis of the well-known model.

***Keywords*—** Functional imaging, Tracer kinetic modeling, LTI system, Indicator dilution theory / convolution approach, Two-Compartment model.

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I. Introduction

FOR a long time, physiological tissue parameters could be obtained only with nuclear medicine imaging techniques. Recent advances in computed tomography (CT) and magnetic resonance (MR) imaging technology, however, have helped to reduce scanning times and image repetition rates. Owing to this development, dynamic imaging with high temporal resolution has become possible by CT and MR techniques as well. Functional imaging procedures as non-invasive methods for the assessment of tissue microcirculation are highly requested, but require a mathematical approach describing the trans- and intercapillary passage of tracer particles. In this context, mainly diffusible extracellular contrast agents (contrast media, CM) are considered, nevertheless intravascular contrast agents may be taken into account as a borderline case of the methods presented in this paper.

The intravenous injection of a diffusible extracellular MR or CT contrast agent is followed by a distribution of the tracer particles in the intravascular (strictly speaking: plasma) volume and, owing to the bidirectional permeability of capillary walls, a reversible diffusion between intravasal (plasma) and interstitial (extracellular, extravasal) space then occurs. The kinetics of these processes, often abbreviated as "wash-in – wash-out", specially depends on physiological tissue parameters such as capillary permeability and surface area, plasma flow, extent of distribution volume in plasma and interstitial space (referring to the whole tissue volume in the region considered). That's why also the concentration-time courses in tissue revealing the differences in the underlying physiologies are considerably shaped by these factors. Certain types of disease are accompanied with significant changes in one or more of the above-mentioned (or further) micro-circulation parameters. State of the art and future trends concerning functional imaging with MR or CT technology are summarized, for instance, in Padhani [1] and Lee [2];

furthermore, both papers emphasize the increasingly important role of microcirculation parameters for diagnosis, patient prognosis, and follow-up. Therefore, to gain an insight into various physiological aspects, it is highly desirable to determine as many as possible of these functional parameters from one and the same dynamic image data set.

In this context, two theoretical concepts have been established for tracer kinetic modeling of contrast agent transport in tissues until now: pharmacokinetic compartment models, which are usually written as coupled differential equations, and the indicator dilution theory (IDT), which can be generalized in accordance with the theory of linear-time-invariant (LTI) systems by using a convolution approach. Consequently, theoretical approaches in differential as well as in integral form are available.

It is the primary goal of this paper to mathematically analyze the for the moment conceptionally different approaches of IDT and compartmental modeling and, in particular, to integrate the open two-compartment model, illustrated in Fig. 1 and well-known from functional imaging with MR or CT technology, into the systems theory approach of IDT.

Using the theory of causal LTI systems as a starting point – independently of IDT or compartment approach –, all models with the following property are being recorded:

The (spatially independent) concentration-time course in tissue can be expressed as a convolution of the arterial input function C_A and a function Q (aside from time) only depending on system properties.

According to the nature of (mathematical) distribution theory, this system function Q is the impulse response function of the tissue and summarizes the whole information on tissue microcirculation. Therefore, this Q is suitable for determining (estimating) the desired tissue specific parameters (using fitting procedures for instance) and thus has a key role within the analysis of functional studies.

As a secondary objective, it can be shown that the system function, now established for the compartment model under discussion as well, has a parameterization facilitating the determination of microcirculation parameters mentioned above and frequently used for compartment approaches.

By the way, it should be noticed that most of the investigations, which have to be pointed out in this paper, come under the heading of "The Forward Problem," known as the analytic theory of linear and nonlinear compartmental systems (Jacquez [4]). Many years ago, this forward problem has been solved – even in a more general context as it is looked upon in this article (compare e.g. [4] – [14]). Nevertheless, to this day, within the field of biomedical imaging, not from the mathematical point of view, there seems to be a mental gap between the system-theoretic concept of IDT and the compartment approach – a trench, which the author would like to get over by exemplary analysis of the above-mentioned well-known model.

II. Theory

In the sequel, the two approaches mentioned in the introduction have to be analyzed in more detail. In this context, the following notations are used regardless of any tracer kinetic model:

As already mentioned at the beginning, C_A denotes the arterial input function (AIF); in the same way let C_V be the venous concentration of the tracer. C_A and C_V are functions of the time t (using the term "function" in its classical meaning); due to requirements of causality, $C_A \mid (-\infty, 0) = 0$, i.e. $\mathrm{supp}(C_A) \subseteq [0, \infty)$ [1] is assumed. Furthermore, let F denote the plasma flow and for the volumes to be considered the notations are as follows: Let V_T be the tissue volume under study as well as V_P and V_I the distribution volumes of the tracer in plasma and interstitial space (inside V_T), respectively. Then $f_P := V_P V_T^{-1}$ and $f_I := V_I V_T^{-1}$ are the corresponding relative distribution volumes inside the tissue region being in focus. Assuming complete distribution of an extracellular CM and disregarding the small proportion of transcellular fluid, the extracellular volume V_E (inside V_T) is obviously received by the sum of V_P and V_I. In any case, the cellular volume (inside V_T) is represented by the difference $V_T - V_E$.

In addition, let σ be the step function at zero defined by

$$\sigma : \mathbb{R} \to \mathbb{R},\ t \mapsto \sigma(t) := \begin{cases} 1, & \text{if } t > 0. \\ 1/2, & \text{if } t = 0. \\ 0, & \text{if } t < 0. \end{cases}$$

According to the context, every function considered in this paper has to be understood as function in the classical sense or as distribution (generalized function). Finally, the convolution of two (generalized) functions is denoted by $*$, as usual.

A. Models based on IDT

About 50 years ago, the fundamental principles of IDT have been developed and presented by Meier / Zierler and co-workers in serveral pioneering publications (compare [15] – [18]). Those aspects which are relevant for our discussion are summarized below.

For the present, only an ideal system with a single inflow and a single outflow (SISO system) is considered. The time required for a given tracer particle to flow from entrance to exit through the system (after an impulsive input), by whatever path, is known as its exit or (overall) transit time. No one transit time applies to all tracer particles; rather, there is a family of transit times depending on travel velocity and path taken. Hence, the (overall) transit time is regarded as a random variable in the sense of probability theory, and it is supposed that this random variable can be described by a locally integrable (probability) density [2] h, which satisfies $h \mid (-\infty, 0) = 0$, i.e. $\mathrm{supp}(h) \subseteq [0, \infty)$, due to causality

[1] $\mathrm{supp}(f)$ denotes the support of a (generalized) function f.

[2] In the older literature the term "frequency function" was applied to what we call density.

requirements. The expectation (first moment) of this random variable is often called system mean transit time and denoted by $\bar{t} = \bar{t}\,(h)$. Furthermore, let H be the distribution function corresponding to h. Obviously, $H = h * \sigma$ holds.

For application of indicator dilution techniques and simplification of mathematical descriptions, some further basic assumptions about the biological system and the tracer being studied apply:

- Plasma flow F and fluid system volumes such as V_P, V_I, V_T are constant.
  Constant volume implies that the system has no stagnant pools, that is, every unit of fluid entering the system must finally leave the system.
- The distribution of transit times for entering particles remains constant during the measurement / experiment.
- The distribution of transit times of tracer particles is identical with the distribution of transit times of the carrier fluid (tracee).

There are no further assumptions about the internal structure of the system. Indicator recirculation may be considered via the AIF. Definitions and results cited in the sequel are valid for intravascular as well as for diffusible extracellular CM. For a pure intravascular tracer simply $V_I = 0$ has to be taken.

In accordance with the theory of LTI systems, let the concentration of tracer at outflow (output), i.e. the venous concentration C_V, be given by a convolution of the arterial input function C_A and the system dependent density h:

$$C_V = C_A * h \ . \qquad \text{[IDT.1]}$$

This equation may be regarded as the basic relation of IDT. Next, consider the convolution algebra with the underlying set consisting of all distributions with support contained in [0, ∞). According to Titchmarsh's theorem, this convolution algebra has no zero divisors ≠ 0 (see [19], [20]). Due to this reason, the locally integrable function h in Eq. [IDT.1] is uniquely determined except for a (Lebesgue) null set: If g, h are two locally integrable, causal functions satisfying $C_A * h = C_V = C_A * g$ then $h = g$ (Lebesgue) almost everywhere, and we may "identify" h and g.

In order to establish an IDT model in dealing with the terminology of this paper, a more precise definition is recommended:

In the set of all locally integrable probability densities with support contained in [0 , ∞) , the following equivalence relation ~ is defined:

$$h \sim g \quad \underset{\text{Def.}}{\Leftrightarrow} \quad h = g \ \text{(Lebesgue) almost everywhere} \ .$$

If the assumptions above hold for a system under consideration and the basic convolution approach is satisfied by a locally integrable, causal density h, then the equivalence class of h is called the IDT model belonging to h and denoted by $\tilde{h}$. Often it is sufficient only to make use of a representative of this equivalence class, for instance h itself. In addition, h is uniquely determined except for the value at $t = 0$, if the supplementary requirement for continuity on (0 , ∞) frequently realized in biological systems is taken into account.

For the IDT model $\tilde{h}$ just described, more precisely for its representative h, we define [3]:

$$R_h^{\mathrm{IDT}} := \sigma - h * \sigma = \sigma - H$$
$$\text{and} \qquad \text{[IDT.2]}$$
$$Q_h^{\mathrm{IDT}} := \frac{F}{V_T} R_h^{\mathrm{IDT}} \ .$$

Because the distribution function H corresponding to h is independent of the choice of representatives, obviously $R_g^{\mathrm{IDT}} = R_h^{\mathrm{IDT}}$ and $Q_g^{\mathrm{IDT}} = Q_h^{\mathrm{IDT}}$ hold for all $g \in \tilde{h}$. Furthermore, R_h^{IDT} and Q_h^{IDT} are time dependent functions, but apart from that they are only depending on system properties; due to this reason, they are of great importance:

Assuming that the tissue concentration C_T is only time (but not position) dependent, then it follows from the principle of mass balance, the causality condition $\mathrm{supp}(C_T) \subseteq [0 , \infty)$, the relation $H = h * \sigma$, and the above Eqs. [IDT.1], [IDT.2]:

$$\begin{aligned} C_T(t) &= \frac{F}{V_T} \int_{-\infty}^{t} (C_A(s) - C_V(s))\, ds \\ &= \frac{F}{V_T} \int_{-\infty}^{\infty} (C_A(s) - C_V(s))\, \sigma(t-s)\, ds \\ &= \frac{F}{V_T} \left[(C_A * \sigma)(t) - (C_A * h * \sigma)(t) \right] \\ &= \frac{F}{V_T} \left[(C_A * (\sigma - H))(t) \right] \\ &= \frac{F}{V_T} (C_A * R_h^{\mathrm{IDT}})(t) \\ &= (C_A * Q_h^{IDT})(t) \ . \end{aligned}$$

In summary:

$$C_T = \frac{F}{V_T} C_A * R_h^{\mathrm{IDT}} = C_A * Q_h^{\mathrm{IDT}} \ . \qquad \text{[IDT.3]}$$

The system function Q_h^{IDT} is the impulse response function, in which the whole information available of tracer *in tissue* is

[3] *Remark.* The definition of the step function σ at its step discontinuity zero as the arithmetic mean of the left-hand and the right-hand limits of σ at zero, i.e. the mean value property

$$\sigma(0) := \frac{1}{2} = \frac{\sigma(0-) + \sigma(0+)}{2} \ ,$$

ensures that (the prevailing) impulse response function (of the (sub)system considered) and (the associated) system function – as functions in the classical sense – match at the discontinuity of the step function as well. This is valid independently of the specially chosen concept for modeling microcirculation.

summarized. R_h^{IDT} is known as residual function and $F V_{\mathrm{T}}^{-1}$ is the tissue perfusion (compare [21], [22], in addition).

An integration of the equation

$$\frac{F}{V_{\mathrm{T}}}\, C_{\mathrm{A}} * (\sigma - H) \;=\; C_{\mathrm{T}} \;=\; C_{\mathrm{A}} * Q_h^{\mathrm{IDT}}$$

using the theorem of Fubini, followed by integration by parts on the left-hand side, leads to the system mean transit time, which is independent of the choice of representatives:

$$\bar{t} \;=\; \bar{t}(h) \;=\; \frac{F}{V_{\mathrm{T}}} \int_{-\infty}^{\infty} Q_h^{\mathrm{IDT}}(t)\, dt\,.$$

In consequence, the next two statements (compare Meier / Zierler [15] – [18]), valid for IDT-models, are equivalent:

- Stewart-Hamilton Principle [4] (for the system as a whole): The system mean transit time can be calculated as quotient of distribution volume (of tracer injected) and plasma flow; i.e., regardless of the choice of representatives, the following equations hold:

$$\bar{t} \;=\; \bar{t}(h) \;=\; \int_{-\infty}^{\infty} t\, h(t)\, dt \;=\; \int_{0}^{\infty} t\, h(t)\, dt \;=\; \frac{V_{\mathrm{P}} + V_{\mathrm{I}}}{F}\,. \qquad \text{[IDT.4]}$$

- The (improper) integral of the impulse response function is the relative distribution volume (i.e., the distribution volume referring to the tissue volume studied) of the tracer being applied:

$$\int_{-\infty}^{\infty} Q_h^{\mathrm{IDT}}(t)\, dt \;=\; \int_{0}^{\infty} Q_h^{\mathrm{IDT}}(t)\, dt \;=\; \frac{V_{\mathrm{P}} + V_{\mathrm{I}}}{V_{\mathrm{T}}} \;=\; f_{\mathrm{P}} + f_{\mathrm{I}}\,. \qquad \text{[IDT.5]}$$

Immediately from $H(0) = 0$, it follows:

- The (right-hand) limit of the impulse response function as $t \to 0+$ represents the tissue perfusion:

$$\lim_{t \to 0+} Q_h^{\mathrm{IDT}}(t) \;=\; \frac{F}{V_{\mathrm{T}}}\,. \qquad \text{[IDT.6]}$$

So far as needed for the paper on hand, Eqs. [IDT.4], [IDT.5], [IDT.6] may be regarded as the central results of Zierler's theory. In particular, this is true for Eq. [IDT.4]. In addition, some remarks about the sum $f_{\mathrm{P}} + f_{\mathrm{I}}$ in Eq. [IDT.5] should be pointed out: Fixing eyes on the present IDT model $\tilde{h}$, writing $Q \coloneqq Q_h^{\mathrm{IDT}}$ for notational brevity, and starting from the convolution product

$$C_{\mathrm{T},C_{\mathrm{A}}} \;=\; C_{\mathrm{A}} * Q$$

including the previous causality requirements and for the moment explicitly expressing the dependence on the AIF C_{A} with respect to the tissue response, properties concerning the system function Q allow different interpretations:

It is known that LTI systems can be characterized not only by their impulse response $C_{\mathrm{T},\delta} = Q$, but also by means of their step response $C_{\mathrm{T},\sigma} = \sigma * Q$, where

$$C_{\mathrm{T},\sigma}(t) \;=\; \int_{-\infty}^{t} Q(s)\, ds\,.$$

If now the (improper) integral of Q represents the relative distribution volume of the injected tracer in the sense of [IDT.5], one obtains:

$$\lim_{t \to \infty} C_{\mathrm{T},\sigma}(t) \;=\; \lim_{t \to \infty} \int_{-\infty}^{t} Q(s)\, ds \;=\; \int_{-\infty}^{\infty} Q(s)\, ds \;=\; f_{\mathrm{P}} + f_{\mathrm{I}}\,.$$

In this way, the sum $f_{\mathrm{P}} + f_{\mathrm{I}}$, on the one hand, can be understood as area below the temporal course of the system function or rather impulse response, but, on the other hand, an interpretation as limit of the step response as $t \to \infty$ is possible just as well – two aspects of one and the same object.

Furthermore, simply from the convolution equation as well as the theorem of Fubini it follows:

$$\begin{aligned} f_{\mathrm{P}} + f_{\mathrm{I}} \;&=\; \int_{-\infty}^{\infty} Q(t)\, dt \\ &=\; \frac{\int_{-\infty}^{\infty} C_{\mathrm{A}}(s)\, ds \;\cdot\; \int_{-\infty}^{\infty} Q(t)\, dt}{\int_{-\infty}^{\infty} C_{\mathrm{A}}(s)\, ds} \\ &=\; \frac{\int_{-\infty}^{\infty} (C_{\mathrm{A}} * Q)(t)\, dt}{\int_{-\infty}^{\infty} C_{\mathrm{A}}(s)\, ds} \\ &=\; \frac{\int_{-\infty}^{\infty} C_{\mathrm{T},C_{\mathrm{A}}}(t)\, dt}{\int_{-\infty}^{\infty} C_{\mathrm{A}}(t)\, dt} \;=\; \frac{\int_{0}^{\infty} C_{\mathrm{T},C_{\mathrm{A}}}(t)\, dt}{\int_{0}^{\infty} C_{\mathrm{A}}(t)\, dt}\,. \end{aligned}$$

This is the frequently used geometric meaning of the sum $f_{\mathrm{P}} + f_{\mathrm{I}}$, showing that the relative distribution volume of the tracer can be calculated as a quotient of two areas, namely the area below the concentration-time curve in tissue and the area below the AIF curve.

B. Open Two-Compartment Model (TCM)

For modeling the transport of a diffusible, extracellular CM after passing the input point via the AIF C_{A}, within the theory of compartment models, for the sake of simplicity, it is assumed that the tissue considered can be described by two compartments: a (central) plasma compartment with volume exactly alike V_{P} and a (peripheral) interstitial compartment with volume exactly alike V_{I}. In addition, the assumptions below apply in the course of this paper:

[4] The "Stewart-Hamilton Principle" has also become known as "Central Volume Theorem" or "Area-to-Height-Relation".

- In accordance with the first section, the blood flow through the capillaries or rather the plasma flow F as well as the volumes V_P , V_I , and V_T are regarded as constant. Furthermore, as usual, the flow of indicator particles is assumed to be representative of the flow of total fluid and the distribution of transit times for entering particles is assumed to be constant during the measurement / experiment.
- The solubility of the employed CM may be regarded as the same in the interstitial fluid and in plasma. The permeability, describing the diffusion of tracer particles through the capillary walls, i.e. between plasma and interstitial space, is assumed to be the same in both directions as well as constant in space and time. Hence, the diffusion of the CM can be described bidirectionally by the constant permeability-surface area (PS) product.

For the moment, CM concentrations in plasma, interstitial space, and overall tissue depend on both position and time. A mathematical modeling of the underlying biophysical situation using Fick's law leads to a pair of partial differential equations as it can be found, for example, in St. Lawrence / Lee [23], Brix [3], and Moran / Prato [24]. From the literature, there are known further more models based on partial differential equations (compare e.g. Perl / Chinard [25], Bassingthwaighte [26], Fletcher [27]), but they shall not really be discussed in this paper.

In contrast to such sophisticated considerations, pharmacokinetic models – for the sake of simplicity – are founded on a further assumption:

- Each compartment is well stirred, so that any contrast agent entering the compartment is instantaneously distributed throughout the entire compartment.
  This implies that for the particular problem at hand we do not have to worry about transport of tracer within the compartment. In this way it is attained that the CM concentrations C_P in the plasma compartment, C_I in the interstitial compartment, and C_T in the tissue considered do not depend on position and are functions of time only. In particular, $C_P = C_V$ holds.
  [*Remark.* In general terms and in metalanguage, the following relations are valid: $C_A(t)$ = $C_P(t, \textit{position} = \text{inlet})$ and $C_V(t)$ = $C_P(t, \textit{position} = \text{outlet})$.]

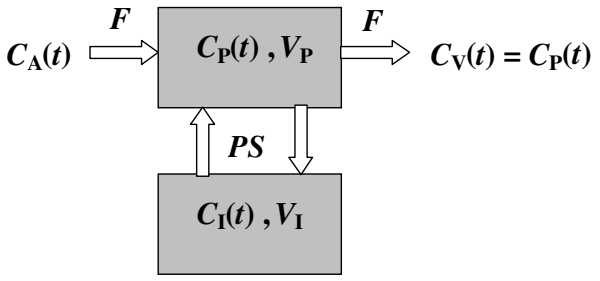

Fig. 1 Open two-compartment model in accordance with [3] in order to describe the trans- and intercapillary transport of a diffusible, extracellular contrast medium

Working on these simplifying assumptions, the box-model from Fig. 1 leads to the following pair of ordinary differential equations (ODEs) by applying the principle of conservation of mass to each compartment:

$$\left.\begin{aligned} V_P \dot{C}_P &= F(C_A - C_V) - PS(C_P - C_I) \\ &= F(C_A - C_P) - PS(C_P - C_I) \quad \text{[ODE.a]} \\ V_I \dot{C}_I &= PS(C_P - C_I) \quad \text{[ODE.b]} \end{aligned}\right\} \text{[ODE]}$$

or in matrix notation:

$$\begin{bmatrix} \dot{C}_P(t) \\ \dot{C}_I(t) \end{bmatrix} = \begin{bmatrix} -FV_P^{-1} - PSV_P^{-1} & PSV_P^{-1} \\ PSV_I^{-1} & -PSV_I^{-1} \end{bmatrix} \begin{bmatrix} C_P(t) \\ C_I(t) \end{bmatrix} + \begin{bmatrix} FV_P^{-1} C_A(t) \\ 0 \end{bmatrix} \qquad \text{[ODE′]}$$

Below it is intended to investigate, to what extent this extremely reduced approach represents the well-known statements of IDT and, furthermore, can be subordinated to IDT; in other words: In what way does the reduced TCM approach supply the IDT-model belonging to the available system characterized by the assumptions referred to. In view of initial conditions, [ODE′] represents a classical initial value problem, as long as for the AIF C_A a continuous concentration-time course is assumed. In this case the classical solution is "straightforward." If it is desired to refer to systems theory and to consider Dirac's delta impulses and other distributions as input functions as well, then the problem has to be solved by using methods of distribution theory.

[ODE′] or rather the affiliated initial value problem can be applied to two different situations:

(I) For $PS > 0$ [ODE′] is a system of coupled differential equations and deals with the case of diffusible, extracellular CM.

(II) For $PS = 0$ the two differential equations in [ODE′] are uncoupled from each other, resulting in the basic equation(s) of a non-extravasating contrast agent.

First and foremost, the following considerations are valid for the more complex

CASE (I): $PS > 0$, i.e. diffusible, extracellular CM.

The Box-Model and its Theory

[ODE′] is a linear nonhomogeneous first-order ODE system with constant coefficients; the associated system matrix, i.e. the matrix of coefficients, is denoted by **K**:

$$\mathbf{K} := \begin{bmatrix} -FV_P^{-1} - PSV_P^{-1} & PSV_P^{-1} \\ PSV_I^{-1} & -PSV_I^{-1} \end{bmatrix}.$$

K has two different, real eigenvalues λ_1, λ_2 :

$$\lambda_1 := -\frac{1}{2}(PSV_I^{-1} + PSV_P^{-1} + FV_P^{-1}) + \frac{1}{2}\sqrt{(PSV_I^{-1} + PSV_P^{-1} + FV_P^{-1})^2 - 4\,FPS\,V_I^{-1}V_P^{-1}},$$

$$\lambda_2 := -\frac{1}{2}(PSV_I^{-1} + PSV_P^{-1} + FV_P^{-1}) - \frac{1}{2}\sqrt{(PSV_I^{-1} + PSV_P^{-1} + FV_P^{-1})^2 - 4\,FPS\,V_I^{-1}V_P^{-1}}.$$

According to the theory of linear ODE systems with constant coefficients, a determination of the eigenvectors of **K** belonging to the eigenvalues λ_1 and λ_2, respectively, results in a fundamental matrix of the homogenous ODE system associated with [ODE′]: For example,

$$\mathbf{Y}(t) := \begin{bmatrix} \exp(\lambda_1 t) & \exp(\lambda_2 t) \\ \beta_1 \exp(\lambda_1 t) & \beta_2 \exp(\lambda_2 t) \end{bmatrix}$$

is a special choice of such a fundamental matrix, where

$$\beta_i := FPS^{-1} + 1 + V_P PS^{-1}\lambda_i \quad \text{for} \quad i \in \{1,2\}$$

is used for notational brevity. Apart from the classical solutions, the homogeneous ODE system has no further distribution solutions. Concerning the notations and abbreviations, the following relations are valid, which are frequently used in the course of this paper:

$$\lambda_1 + \lambda_2 = -(PSV_I^{-1} + PSV_P^{-1} + FV_P^{-1}),$$

$$\lambda_1 - \lambda_2 = \sqrt{(PSV_I^{-1} + PSV_P^{-1} + FV_P^{-1})^2 - 4\,FPS\,V_I^{-1}V_P^{-1}},$$

$$\lambda_1 \lambda_2 = FPS\,V_P^{-1}V_I^{-1},$$

$$\left.\begin{aligned} \lambda_i \beta_i &= -(FV_I^{-1} + V_P V_I^{-1}\lambda_i) \\ V_P + V_I \beta_i &= -F\lambda_i^{-1} \end{aligned}\right\} \quad for\ i \in \{1,2\},$$

$$\beta_1 \beta_2 = -V_P V_I^{-1} = -f_P f_I^{-1}.$$

Using the fundamental matrix $\mathbf{Y}(t)$ mentioned above, an approach applying the "variation-of-constants" procedure in distributional form yields the response of plasma and interstitial space to Dirac's delta impulse (with respect to zero) (compare e.g. [19], [28]):
Considered as regular distributions, the causal bi-exponential functions

$$h_1 : \mathbb{R} \to \mathbb{R},\ t \mapsto h_1(t) :=$$

$$:= \frac{F}{V_P}\,\frac{PS}{V_P(\lambda_2 - \lambda_1)}\,[\beta_2 \exp(\lambda_1 t) - \beta_1 \exp(\lambda_2 t)]\ \sigma(t)$$

$$= \frac{V_I}{V_P}\,\frac{\lambda_1 \lambda_2}{\lambda_2 - \lambda_1}\,[\beta_2 \exp(\lambda_1 t) - \beta_1 \exp(\lambda_2 t)]\ \sigma(t)$$

and

$$h_2 : \mathbb{R} \to \mathbb{R},\ t \mapsto h_2(t) :=$$

$$:= \frac{F}{V_P}\,\frac{PS}{V_P(\lambda_2 - \lambda_1)}\,\beta_1\beta_2\,[\exp(\lambda_1 t) - \exp(\lambda_2 t)]\ \sigma(t)$$

$$= \frac{V_I}{V_P}\,\frac{\lambda_1 \lambda_2}{\lambda_2 - \lambda_1}\,\beta_1\beta_2\,[\exp(\lambda_1 t) - \exp(\lambda_2 t)]\ \sigma(t)$$

$$= -\frac{\lambda_1 \lambda_2}{\lambda_2 - \lambda_1}\,[\exp(\lambda_1 t) - \exp(\lambda_2 t)]\ \sigma(t)$$

$$= \left[\frac{\lambda_2}{\lambda_2 - \lambda_1}(-\lambda_1)\exp(\lambda_1 t) - \frac{\lambda_1}{\lambda_2 - \lambda_1}(-\lambda_2)\exp(\lambda_2 t)\right]\sigma(t)$$

satisfy the nonhomogeneous ODE system

$$\begin{bmatrix} \dot{h}_1 \\ \dot{h}_2 \end{bmatrix} = \begin{bmatrix} -FV_P^{-1} - PSV_P^{-1} & PSV_P^{-1} \\ PSV_I^{-1} & -PSV_I^{-1} \end{bmatrix} \begin{bmatrix} h_1 \\ h_2 \end{bmatrix} + \begin{bmatrix} FV_P^{-1}\delta \\ 0 \end{bmatrix} \qquad [\text{ODE}'']$$

which can also be verified by "calculation with distributions" without any problems. By convolution of each of the impulse response functions h_1 , h_2 and the AIF C_A – considered as distribution – it immediately follows from [ODE″] that

$$C_P = C_A * h_1 \quad \text{and} \quad C_I = C_A * h_2 \qquad [\text{TCM.1a}]$$

are causal distribution solutions of the initial ODE system [ODE′]. The requirement of causality, which reduces the space of solutions to solutions with support contained in [0, ∞), ensures the uniqueness of a solution, because the difference to any further causal solution is an element of the solution space of the associated homogeneous ODE system and hence the null function (zero vector function). Due to this reason, the pair of convolution products mentioned in [TCM.1a] is the unique solution of [ODE′].

In passing, the following properties concerning h_1 and h_2 should be mentioned, recalling that the term "function" is used in its classical meaning here:

- h_1 and h_2 are (probability) densities as they are already considered in the framework of IDT-models, in particular:
  $$\int_{-\infty}^{\infty} h_i(t)\,dt = \int_0^{\infty} h_i(t)\,dt = 1 \quad \text{for} \quad i \in \{1,2\}.$$

- h_2 is continuous on $\mathbb{R}$ (in particular at zero) and $h_2(0) = 0$.
  h_1 has a step discontinuity at zero:
  $h_1(0-) := \lim_{t \to 0-} h_1(t) = 0$ and
  $h_1(0+) := \lim_{t \to 0+} h_1(t) = \frac{F}{V_P}$.

The assumption of instantaneous mixing, specially resulting in $C_V = C_P$ as already observed within the basics, and the first equation in [TCM.1a] imply

$$C_V = C_A * h_1 . \qquad \text{[TCM.1b]}$$

Equation [TCM.1b] is the decisive message, because it states Eq. [IDT.1] for the locally integrable, causal density $h := h_1$. Due to this reason, the accompanying equivalence class $\tilde{h}_1$ is the IDT model belonging to the compartment model under study. Hence, the system or rather impulse response function $Q^{TCM} := Q^{IDT}_{h_1}$ and the residual function $R^{TCM} := R^{IDT}_{h_1}$ are defined according to [IDT.2]. In addition, all further statements within the section about IDT models remain valid word for word with h_1 instead of h. Of course, a direct verification is also possible. Finally, it should be emphasized, that Q^{TCM} is a linear combination of h_1 and h_2 with weighting factors f_P and f_I, respectively:

$$Q^{TCM} = f_P h_1 + f_I h_2 ,$$

in particular revealing the impulse response function in terms of a parameterization, which uses $F V_T^{-1}$, $PS V_T^{-1}$, $V_P V_T^{-1}$, $V_I V_T^{-1}$ as model parameters. According to [IDT.3] and [TCM.1a], the above equation implies

$$\begin{aligned} C_T &= C_A * Q^{TCM} = C_A * (f_P h_1 + f_I h_2) \\ &= f_P C_P + f_I C_I , \end{aligned}$$

i.e. the tissue concentration is the sum of the two compartmental CM concentrations – each summand weighted with the corresponding relative distribution volume inside the region being in focus.

The (Peripheral) Interstitial Compartment

If the interstitial compartment is studied on its own and thus only [ODE.b] with C_P as input function has to be discussed, then a nonhomogeneous ODE is available, which can be treated in a similar way with the methods presented using the previous initial or rather causality conditions. This leads to

$$C_I = C_P * h_I ,$$

where h_I denotes the following causal mono-exponential function:

$$h_I : \mathbb{R} \to \mathbb{R} , \; t \mapsto h_I(t) := \frac{PS}{V_I} \exp(-\frac{PS}{V_I} t) \; \sigma(t) .$$

Again, h_I is a (probability) density in the previous sense. Therefore, the mean transit time for the tracer passing over the interstitial compartment is given by

$$\bar{t} = \bar{t}(h_I) = \int_{-\infty}^{\infty} t \, h_I(t) \, dt = \frac{V_I}{PS} .$$

Furthermore, $h_2 = h_1 * h_I$ by using what has gone before and continuity on $(0, \infty)$.

Mean Residence Times for Compartmental Subsystems

Besides transit times, it is often desired to consider residence times as well, specially in the case of proper subsystems. To make a distinction, the term transit time means first exit time after an impulsive input, i.e. time spent by a particle from its entry into a (sub)system to its next exit, while residence time refers to the time that a material or tracer particle resides in the (sub)system under study, likewise after an impulsive input. Transit and residence times are identical for (sub)systems if all material leaving cannot reenter. For a (sub)system with reentry they differ, because the duration of each visit is taken into account when referring to residence times. Obviously, distributions of residence times and mean residence times can be defined in analogy to transit times (compare e.g. [29], [30]).

If the ODE system [ODE′] would have been formulated for amounts instead of concentrations as it is usual for the most part of papers dealing with mathematical biology, the transpose $\mathbf{K}^T$ of $\mathbf{K}$ has to be considered as associated compartmental matrix. It is well known, that $\mathbf{K}$ or rather $\mathbf{K}^T$ is nonsingular, if and only if the compartment system has no traps. In this case, which is true for the box model under discussion, the entries of the negative inverse of the compartmental matrix $\mathbf{K}^T$ have a well-known important physical interpretation – namely that of mean residence times. Taking a closer look at this situation as it is done at several places in the literature (compare e.g. Eisenfeld [31] – [33], [7], [4], [34]),

$$\left[\bar{T}_{ij} \right]_{i,j \in \{1,2\}} := -\left(\mathbf{K}^T\right)^{-1} = \begin{bmatrix} V_P F^{-1} & V_P F^{-1} \\ V_I F^{-1} & V_I PS^{-1} + V_I F^{-1} \end{bmatrix}$$

has to be considered. Generally speaking, the (i, j)-element $\bar{T}_{ij}$ of the above matrix is the mean residence time that a random particle spends in compartment i having commenced the system in compartment j (by an impulsive input), before being excreted. This notation is based on the assumption that compartment numbering and equation order in the underlying ODE system match. In our special case, the excretory system is loaded in a single compartment, namely the (central) plasma compartment, which is the first compartment in the above notation. Therefore, only the first column of $-\left(\mathbf{K}^T\right)^{-1}$ is of further interest:

$\bar{T}_{11} = V_P F^{-1}$ and $\bar{T}_{21} = V_I F^{-1}$ are the mean residence times for tracer particles dwelling on the central plasma compartment (first compartment) and on the peripheral

interstitial compartment (second compartment), respectively. Notice on the other hand, that the mean transit time for particles passing over the interstitial space could be calculated as $\bar{t}(h_I) = V_I\, PS^{-1}$. The sum $\bar{T}_{11} + \bar{T}_{21}$, i.e. the 1-column sum of $-\left(\mathbf{K}^T\right)^{-1}$, is the system mean residence time. According to [IDT.4], this sum also equals the system mean transit time, due to the observation that both mean transit time and mean residence time refer to an impulsive input and, hence, by definition there is no reentry of material when considering the system as a whole.

The theoretical explanations to the compartment approach should be closed with a brief consideration of

Case (II): *PS* = 0 , i.e. intravascular CM.

Because of the de-coupling of the two equations in [ODE], the second Eq. [ODE.b] can be integrated directly, which results in a constant concentration C_I. In more detail, $C_I = 0$ holds on the previous initial or rather causality conditions, since there are no different complexions even when looking from the distribution theoretic point of view. It remains the basic equation of a non-extravasating contrast agent:

$$\dot{C}_P = -\frac{F}{V_P}(C_P - C_A) = -\frac{F}{V_P} C_P + \frac{F}{V_P} C_A .$$

Looked at from purely mathematical aspects, this is an [ODE.b]-type equation; thus, the considerations of the section above (compare "The (Peripheral) Interstitial Compartment") can be applied. Keeping up the initial or rather causality conditions of standard-issue, the solution is given by

$$C_P = C_A * h_P ,$$

where h_P denotes the following causal mono-exponential function and (probability) density:

$$h_p : \mathbb{R} \to \mathbb{R} , \; t \mapsto h_p(t) := \frac{F}{V_P} \exp(-\frac{F}{V_P} t) \; \sigma(t) ,$$

which is the impulse response function with respect to plasma when looking upon as regular distribution. With $Q^{iv} := Q^{IDT}_{h_P}$ $= f_P\, h_P$ and using what has gone before, it follows

$$C_T = C_A * Q^{iv} = f_P\, C_P \; (= f_P\, C_P + f_I\, C_I) .$$

Q^{iv} is system function as well as impulse response function of the tissue under discussion (in case of a purely intravascular tracer). Finally, the central properties repeatedly discussed up to now are also valid for blood-pool contrast agents, as expected:

$$\bar{t} = \bar{t}(h_P) = \int_{-\infty}^{\infty} t\, h_P(t)\, dt = \frac{V_P}{F} ,$$

$$\int_{-\infty}^{\infty} Q^{iv}(t)\, dt = \int_{-\infty}^{\infty} f_P\, h_P(t)\, dt = f_P ,$$

$$Q^{iv}(0+) := \lim_{t \to 0+} Q^{iv}(t) = \frac{F}{V_T} .$$

III. Discussion and Conclusion

The theory of LTI systems may be regarded as a common general outline of IDT and compartment approach. In particular, by the analysis carried out in this paper not the trench, but the causal relationship between TCM and IDT introduced at the beginning could be confirmed, revealing that the compartment approach leads to the IDT model of the system under discussion, if – aside from standard requirements – specially the assumption of an instantaneous distribution applies to each compartment:

As well-founded in the section about IDT models, in the present investigation an IDT model of a system studied is understood as that equivalence class of locally integrable, causal probability densities describing the (overall) transit times of tracer particles, whose representatives satisfy the central convolution approach [IDT.1]. This system-theoretic approach specially assumes the existence of such a representative.

As one result of the box-model analysis, the solution of [ODE′] is given by

$$\begin{bmatrix} C_V \\ C_I \end{bmatrix} = \begin{bmatrix} C_P \\ C_I \end{bmatrix} = \begin{bmatrix} C_A * h_1 \\ C_A * h_2 \end{bmatrix}$$

with the locally integrable, causal probability densities h_1 and h_2 satisfying [ODE″]. In particular, it follows: The equivalence class of h_1 consisting of all locally integrable, causal probability densities, which are equal to h_1 (Lebesgue) almost everywhere, is the IDT model of the system under consideration. On the conclusive spot, this result makes use of the assumption of well stirred compartments.

In this way, all statements valid for IDT models are also applicable to the compartment approach. We note in passing that it is also possible, of course, to derive these results for the box-model on its own without recourse to IDT models and their theory. To this end, corresponding statements valid for IDT models and compartment approach, respectively, would have been developed parallel to a large extent.

Following [4] (and applied to the box-model), we have concentrated on the forward problem: Given the structure, how does the system behave? The inverse problem reads: Given the experimental measurements of behavior, i.e. an input-output sequence, what is the structure? This inverse problem is the one usually faced by the biomedical experimenter; it includes model specification, definition of the experiments, identifiability [29], [30], parameter estimation [4], [37], and validation. There are many levels of complexity at which the inverse problem represents itself. In its most general form, there may be no information about the system; one may not even know whether the system is representable as a compartmental system [38], never mind the box-model from Fig. 1. In this context, it seems worth to note that the system

functions (tissue response and residual function) of the above open TCM do not "know" any time-related delay as it is possible within the realms of other model classes, e.g. within the class of all IDT models. The important question, for instance, to what extent the assumption of instantaneous distribution may be considered to be realistic and performed in applications, can only be answered in practice, of course. Hence, the handling of the inverse problem is beyond the scope of this paper, even if this problem will be the more interesting one.

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