Compartmental analysis of dynamic nuclear medicine data: models and identifiability

Fabrice Delbary[1]**, Sara Garbarino**[2] **and Valentina Vivaldi**[2]

[1] Institut für Mathematik, Johannes Gutenberg-Universität Mainz
[2] Dipartimento di Matematica and CNR-SPIN, Genova

Abstract. Compartmental models based on tracer mass balance are extensively used in clinical and pre-clinical nuclear medicine in order to obtain quantitative information on tracer metabolism in the biological tissue. This paper is the first of a series of two that deal with the problem of tracer coefficient estimation via compartmental modelling in an inverse problem framework. Specifically, here we discuss the identifiability problem for a general n-dimension compartmental system and provide uniqueness results in the case of two-compartment and three-compartment compartmental models. The second paper will utilize this framework in order to show how non-linear regularization schemes can be applied to obtain numerical estimates of the tracer coefficients in the case of nuclear medicine data corresponding to brain, liver and kidney physiology.

1. Introduction

Nuclear medicine imaging is a class of functional imaging modality that utilizes radioactive tracers to investigate specific physiological processes. Such tracers are in general short-lived isotopes that are injected in the subject's blood and linked to chemical compounds whose metabolism is highly significant to understand the function or malfunction of an organ. Positron Emission Tomography (PET) [24] is the most modern nuclear medicine technique, utilizing isotopes produced in a cyclotron and providing dynamical images of its metabolism-based accumulation in the tissues. While decaying, the isotope emits positrons that annihilate with the electrons of the tissue thus emitting two collimated gamma rays. These rays are detected by the PET collimators to provide a rather precise indication of their temporal and spatial origin. Applications of PET in the clinical workflow depend on the kind of tracer employed and on the kind of metabolism that such tracer is able to involve. For example, in oncological applications, $[^{18}F]$FDG [1, 7, 19] and $FMISO$ [38] are the most commonly used tracers; neuroimaging studies of Alzheimer disease utilizes ^{11}C and ^{15}O [41], while for myocardium perfusion analysis, ^{82}Rb, $[^{18}F]$FDG and $H_2{}^{15}O$ are the most extensively used tracers [2, 5, 34, 35].

From a computational viewpoint, PET experiments involve two kinds of inverse problems. In the first one, image reconstruction techniques are applied to reconstruct the spatiotemporal location of tracer concentration from the radioactivity measured by

the detectors [23, 16, 37]. The second problem utilizes these reconstructed dynamic PET data to estimate physiological parameters that describe the functional behaviour of the inspected tissues and therefore the flow of tracer between their different constituents. It is also possible to solve the full inverse problem of retrieving the compartment modelling coefficients straight from dynamic PET data. This problem has become increasingly interesting in recent years, and it is typically referred to as a *direct* reconstruction problem [3, 4, 29, 30, 40]; the one of splitting into two different separate problems is, by symmetry, referred to as *indirect*. The present paper is the first one of a series of two that focus on the indirect reconstruction problem and aim to describe it in an ill-posed inverse problems framework.

Models in pharmacokinetics [32, 33] typically assume that in the organ under investigation there co-exist functionally separated pools of tracer, named *compartments*, that can exchange tracer between each other. With the help of the global observation of the organ along time provided by reconstructed PET images, *compartmental analysis* [8, 9, 10, 11, 12, 13] aims at retrieving information on the radioactive tracer exchange rates between compartments. From a mathematical viewpoint, the time dependent concentrations of tracer in each compartment constitutes the state variables that can be determined from PET data and the time evolution of the state variables can be modelled by a system of differential equations for the concentrations, expressing the principle of tracer balance during exchange processes. Assuming that the exchange rates are time independent, and neglecting the spatial exchanges between compartment, the mathematical model for the compartmental problem becomes a linear system of Ordinary Differential Equations (ODEs) with constant coefficients. Although it is certainly possible to take into account macroscopic flow conditions (as particularly useful for modelling cardiac perfusion, for instance) and introduce a PDE-based framework, as in [31], in this paper we will focus on discussing results for compartmental modelling under the standard and simplifying conditions of time independence of parameters and no spatial exchanges between compartment [39].

This paper describes the analytical properties of this forward problem in the case of the general n-compartment system and in the more specific (but highly realistic) cases of the two-compartment and three-compartment catenary systems (where a catenary system refers to system made of chain of compartments, each one connected only to its immediate predecessor and successor in the chain). For all these compartmental problems, the constant coefficients describe the input/output rate of tracer for each compartment and represent the physiological parameters assessing the system's metabolism. Therefore such coefficients are the unknowns to be estimated in compartmental analysis inverse problem. Some results [21] on the identifiability of these coefficients have been obtained recently, for a very specific class of compartment models, by means of graph analysis techniques and a reparametrizations procedure. In this paper, we will focus on an inverse problem approach for the identifiability, and provide the first general discussion of uniqueness for this inverse problem by proving some identifiability results in the case of the two-compartment and three-

compartment catenary models. In a future paper we will provide a general scheme for the numerical solution of these inverse problems and apply it against both synthetic data and experimental measurements acquired by means of a PET system for small animals.

The plan of the present paper is as follows. Section 2 will introduce the formalism for the most general n-th compartment model and for its specialization to the catenary case. Section 3 and Section 4 will provide the identifiability results for the two-compartment and three-compartment catenary models. Our conclusions will be offered in Section 5.
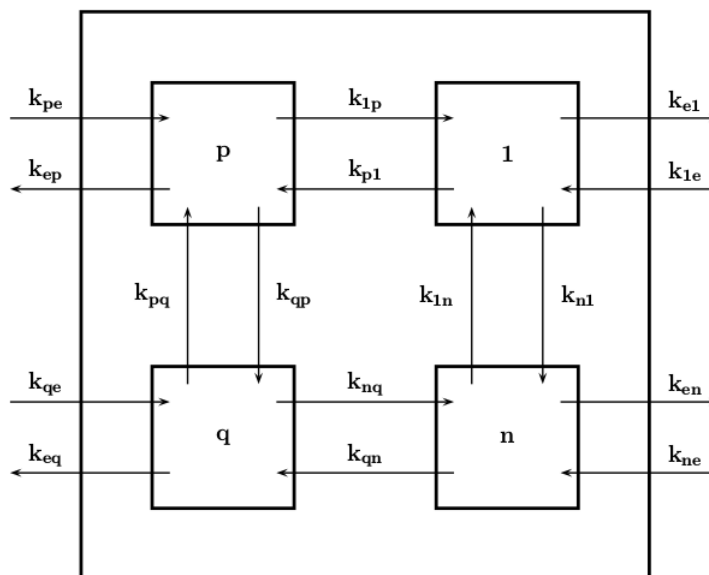
2. The n-compartment systems

Figure 1. Generic n-compartment system; compartments are labelled $p \in \{1, \ldots, n\}$ and for each $p, q \in \{1, \ldots, n\}$, k_{pq} is the constant, non-negative rate of tracer exchange between compartment p and q. The values k_{ep} and k_{pe} denotes the rates at which the tracer is received in the system at compartment p and excreted by the system at compartment p, respectively.

We start our analysis by considering the very general n-compartment model depicted in Figure 1. In all nuclear medicine modalities, the tracer injected into the body may assume different metabolic status. Since the spatial resolution provided by these imaging modalities is not sufficient to anatomically distinguish these different status, they are modelled as compartments, each one just playing a functional role that describes a specific tracer metabolic condition. We denote with C_p the non-negative concentration function of the tracer in the compartment $p \in \{1, \ldots, n\}$. We also assume that the compartment p receives the radioactive tracer from outside the compartmental system with a concentration function C_{pe} and at a constant non-negative rate k_{pe} and excretes the tracer from inside at a constant non-negative rate k_{ep}. Further, the constant non-

negative rate at which the compartment p receives the tracer from a compartment $q \neq p$ is denoted with k_{pq} and, finally, all input concentration functions $(C_{pe})_{p \in \{1,\ldots,n\}}$ are supposed to be non-negative and continuous. Then the evolution of the tracer concentrations in each compartment is governed by the following linear system of Ordinary Differential Equations (ODE) with constant coefficients

$$\dot{C}_p = \sum_{q=1}^{n} k_{pq} C_q + k_{pe} C_{pe}, \qquad p \in \{1,\ldots,n\},$$

with the initial conditions

$$C_p(0) = 0, \qquad p \in \{1,\ldots,n\}, \tag{1}$$

where, for $p \in \{1,\ldots,n\}$, $k_{pp} = -\left(\sum_{q \neq p} k_{qp} + k_{ep}\right)$. Dependence on t is omitted but implied. That is

$$\dot{C} = MC + W, \qquad C(0) = 0, \tag{2}$$

where

$$C = \begin{pmatrix} C_1 \\ \vdots \\ C_n \end{pmatrix}, \qquad W = \begin{pmatrix} k_{1e} C_{1e} \\ \vdots \\ k_{ne} C_{ne} \end{pmatrix}, \tag{3}$$

and the matrix M is given by

$$M_{pq} = k_{pq}, \qquad p, q \in \{1,\ldots,n\}. \tag{4}$$

PET-scan images allow to measure the total amount of radioactive tracer in the tissue or organ of interest, which is, in turn, modelled by the compartmental system. We assume that each compartment contributes to the intensity of the PET image linearly with respect to the amount of tracer in the compartment. Hence PET-scan data give access to the data $\tilde{C}$ such that the measurements and the model are related by the functional equation

$$\tilde{C}(t) = \alpha^T C(t), \qquad t \in \mathbb{R}_+, \tag{5}$$

where $\alpha \in \mathbb{R}_+^{*\,n}$ is assumed to be a known constant vector, representing the blood fraction in the tissue or organ of interest. Of course, the capability to reliably measure the blood fraction is a key point in compartmental analysis. We are aware that there are methods to measure it (as, for instance, in [17]) or to estimate it, as another model parameter in the compartmental model fitting (for instance using Levenberg-Marquardt as in [38], or Maximum-Likelihood as in [10]). For sake of simplicity in this paper, we assume it to be known *a priori*, measured in advance by some experimental procedure, or fixed as the standard value retrieved in literature.

The general n-compartmental inverse problem is the one of recovering the exchange rates $\underline{K} \in \mathbb{R}^{n^2+n}$, where

$$\underline{K} = \begin{cases} k_{ep}, & p \in \{1,\ldots,n^2\}, \ p \equiv 1 \ (\text{mod } n+1), \\ k_{p-n\left\lfloor \frac{p-1}{n} \right\rfloor, 1+\left\lfloor \frac{p-1}{n} \right\rfloor}, & p \in \{1,\ldots,n^2\}, \ p \not\equiv 1 \ (\text{mod } n+1), \\ k_{(p-n^2)e} & p \in \{n^2+1,\ldots,n^2+n\}, \end{cases}$$

using measurements of $\tilde{C}$.

2.1. Properties of n-compartment systems

In this subsection, we propose to recall some noteworthy properties of n-compartment systems. In the following of the document, for a positive integer n and $K \in \mathbb{R}^{n^2+n}$, we denote by $\hat{K} \in \mathbb{R}^{n^2}$ the first n^2 components of K and $\check{K} \in \mathbb{R}^n$ the last n components of K. For a positive integer n, we denote by $\mathscr{M}$ the following linear operator

$$\begin{aligned} \mathscr{M} : \mathbb{R}^{n^2} &\to M_n(\mathbb{R}) \\ H &\mapsto \mathscr{M}(H), \end{aligned} \tag{6}$$

where for all $H \in \mathbb{R}^{n^2}$

$$\mathscr{M}(H)_{pq} = \begin{cases} -H_{1+(n+1)(p-1)} - \displaystyle\sum_{\substack{p'=1 \\ p' \neq p}}^{n} H_{p+n(p'-1)}, & p, q \in \{1, \ldots, n\}, \ p = q, \\ \\ H_{p+n(q-1)}, & p, q \in \{1, \ldots, n\}, \ p \neq q, \end{cases}$$

so that for all $H \in \mathbb{R}_+^{n^2}$, $\mathscr{M}(H)$ is the matrix defined in (4) for the parameters H. First of all, for general n-compartment systems, we have the following theorem [15]

Theorem 2.1. *Consider $H \in \mathbb{R}_+^{n^2}$. Then the eigenvalues of the matrix $M = \mathscr{M}(H)$ as defined in (6) have a non-positive real part and if an eigenvalue has a zero real part, then the eigenvalue is 0, moreover, $\dim(\ker(M)) = m_0$ where m_0 is the multiplicity of 0. In addition, the solution C to*

$$\dot{C} = MC + W, \qquad C(0) = C_0, \tag{7}$$

where $C_0 \in \mathbb{R}_+^n$ and $W : \mathbb{R}_+ \to \mathbb{R}_+^n$, verifies $C_p(t) \geq 0$ for all $p \in \{1, \ldots, n\}$ and $t \in \mathbb{R}_+$.

Remark 2.2. *As remarked in [15], it is the principle of the conservation of mass applied to the system (7) where $W = 0$, which insures that: the eigenvalues of M have a non-positive real part; the multiplicity of the eigenvalue 0 is the dimension of the null–space of M (the solutions are bounded); and the only possible eigenvalue with a zero real part is 0 (if oscillations occur, then they are damped). The positiveness of C is simply the fact that the concentrations are positive quantities.*

Some additional properties on the system matrix M lead to more restrictions on its eigenvalues. In particular, we have [15]

Theorem 2.3. *Consider $H \in \mathbb{R}_+^{n^2}$ and denote by $M = \mathscr{M}(H)$. If M is irreducible, then 0 is an eigenvalue of M if and only if $k_{ep} = 0$ for $p \in \{1, \ldots, n\}$, where for $p \in \{1, \ldots, n\}$, $k_{ep} = H_{1+(n+1)(p-1)}$ (no excretion). In other terms, 0 is an eigenvalue of M if and only if the n-compartment system of exchange rates $H \in \mathbb{R}_+^{n^2}$ and without input is closed. Moreover, in that case, 0 is a simple eigenvalue.*

Remark 2.4. *As remarked in [15], a compartment system without input refers to a system in which all the external inputs are excluded (set to 0).*

Theorem 2.5. *Consider $H \in \mathbb{R}_+^{n^2}$, denote by $M = \mathscr{M}(H)$ and suppose that there exist $(a_p)_{p \in \{1,\ldots,n\}}$ in $\mathbb{R}_+^{*^n}$ such that for all $p, q \in \{1,\ldots,n\}, p \neq q$*

$$k_{pq}a_q = k_{qp}a_p, \tag{8}$$

where for all $p, q \in \{1,\ldots,n\}, p \neq q$, $k_{pq} = H_{p+n(q-1)}$. Then M is diagonalizable and its eigenvalues are real and non-positive.

Remark 2.6. *Note that the condition (8) does not depend on the excretion rates $k_{ep} = H_{1+(n+1)(p-1)}$ for $p \in \{1,\ldots,n\}$. Further, as remarked in [15], the equation (8) is the principle of detailed balance [14, 15, 25] for the closed n-compartment system of exchange rates $(k_{pq})_{p,q \in \{1,\ldots,n\},p\neq q}$: at the equilibrium state, every process is balanced by its inverse.*

As defined in [15, 26, 36], we recall that a connected compartmental system is a system for which it is possible for the tracer to reach every compartment from every other compartment, that a compartmental system with no cycle is a system for which it is not possible for the tracer to pass from a given compartment through two or more other compartments back to the starting compartment and that a compartmental system is sign-symmetric if the associated matrix M is sign-symmetric: $k_{pq}k_{qp} \geq 0$ for $p \neq q$ and $k_{pq} = 0$ if and only if $k_{qp} = 0$. The theorem 2.5 applies in particular to sign-symmetric systems with no cycle. In case of connected sign-symmetric systems with no cycle, like the catenary compartmental system we will use in the following, we also have the following result [26].

Theorem 2.7. *Consider a sign-symmetric cycle-free connected n-compartment system. Then an eigenvalue λ of the system matrix M is multiple if and only if there exists a compartment p, directly connected to at least three other compartments p_1, p_2, p_3, such that λ is an eigenvalue of the matrices N_1, N_2, N_3 of the respective connected subsystems containing p_1, p_2, p_3 and not p.*
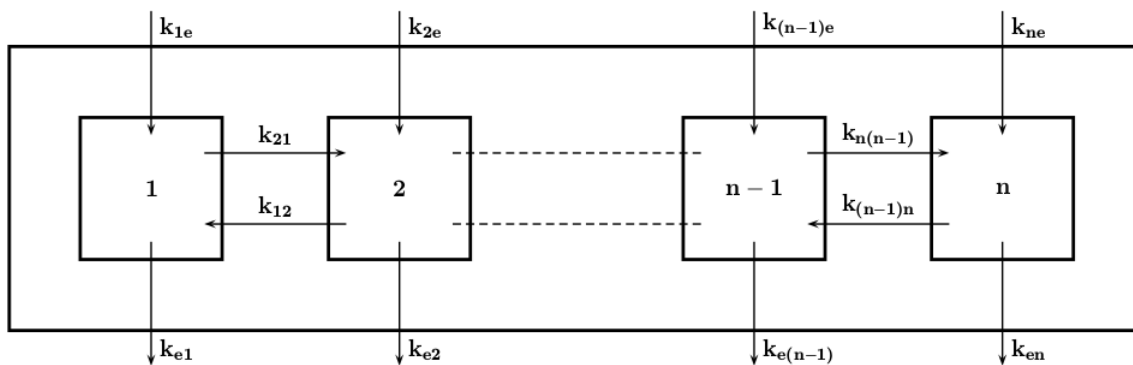
2.2. The n-compartment catenary case

Figure 2. Generic n-compartment catenary system; compartments are labelled $p \in \{1,\ldots,n\}$, and the exchange rates accordingly, following the usual terminology.

A n-compartment catenary system is a n-compartment system such that

$$
\begin{aligned}
k_{ep} &\geq 0, & p &\in \{1, \ldots, n\}, \\
k_{pq} &> 0, & p, q &\in \{1, \ldots, n\}, |p - q| = 1, \\
k_{pq} &= 0, & p, q &\in \{1, \ldots, n\}, |p - q| > 1, \\
k_{pe} &\geq 0, & p &\in \{1, \ldots, n\}.
\end{aligned}
$$

According to the theorems 2.1, 2.3, 2.5, 2.7 of the previous subsection, we have the following theorem

Theorem 2.8. *The matrix M of a n-compartment catenary system is diagonalizable and its eigenvalues are real, non-positive and simple. Moreover, 0 is an eigenvalue of M if and only if the system with no input is closed, that is $k_{ep} = 0$ for all $p \in \{1, \ldots, n\}$.*

2.3. Identifiability definition

We now recall the definition of identifiability [8, 22]. In order to introduce it, we need to denote by $\mathscr{W}$ the following linear operator

$$
\begin{aligned}
\mathscr{W} : C^0(\mathbb{R}_+, \mathbb{R})^n &\rightarrow L(\mathbb{R}^n, C^0(\mathbb{R}_+, \mathbb{R})^n) \\
\check{C} &\mapsto \mathscr{W}(\check{C}),
\end{aligned}
$$

where for all $\check{C} \in C^0(\mathbb{R}_+, \mathbb{R})^n$, $H \in \mathbb{R}^n$ and $p \in \{1, \ldots, n\}$, we have $[\mathscr{W}(\check{C})(H)]_p = H_p \check{C}_p$, so that for all vector of input concentrations functions $\check{C} = (C_{pe})_{p \in \{1, \ldots, n\}} \in C^0(\mathbb{R}_+, \mathbb{R}_+)^n$ and $H \in \mathbb{R}_+^n$, $\mathscr{W}(\check{C})(H)$ is the vector defined in (3) for the input concentrations functions $\check{C}$ and the parameters H. We denote by $\mathscr{C}$ the following function

$$
\begin{aligned}
\mathscr{C} : C^0(\mathbb{R}_+, \mathbb{R})^n &\rightarrow L(\mathbb{R}^{n^2+n}, C^1(\mathbb{R}_+, \mathbb{R})^n) \\
\check{C} &\mapsto \mathscr{C}(\check{C}),
\end{aligned}
$$

where for all $\check{C} \in C^0(\mathbb{R}_+, \mathbb{R})^n$ and $K \in \mathbb{R}^{n^2+n}$, $C = \mathscr{C}(\check{C})(K) \in C^1(\mathbb{R}_+, \mathbb{R})^n$ is the unique solution to

$$
\dot{C} = MC + W, \qquad C(0) = 0,
$$

where $M = \mathscr{M}(\hat{K})$ and $W = \mathscr{W}(\check{C})(\check{K})$. For $\alpha \in \mathbb{R}_+^{*\,n}$, $\mathscr{C}^\alpha$ is the function defined by

$$
\begin{aligned}
\mathscr{C}^\alpha : C^0(\mathbb{R}_+, \mathbb{R})^n &\rightarrow L(\mathbb{R}^{n^2+n}, C^1(\mathbb{R}_+, \mathbb{R})) \\
\check{C} &\mapsto \left[K \mapsto \alpha^T(\mathscr{C}(\check{C})(K)) \right].
\end{aligned}
$$

Consider a positive integer n, input concentration functions $\check{C} \in C^0(\mathbb{R}_+, \mathbb{R}_+)^n$, $\alpha \in \mathbb{R}_+^{*\,n}$ and a subset Ω of $\mathbb{R}_+^{n^2+n}$ of admissible exchange rates K. Define $\tilde{C} = \mathscr{C}^\alpha(\check{C})$ and denote by $\tilde{C}_\Omega$ the restriction of $\tilde{C}$ to Ω.

Definition 2.9.

(i) *The model of equations (2)-(5) is said globally identifiable at $K \in \Omega$, if $\tilde{C}_\Omega^{-1}(\{\tilde{C}(K)\}) = \{K\}$.*

(ii) *The model of equation (2)-(5) is said locally identifiable at $K \in \Omega$ if there exists $\epsilon > 0$ such that $\tilde{C}_{\Omega, K, \epsilon}^{-1}(\{\tilde{C}(K)\}) = \{K\}$ where $\tilde{C}_{\Omega, K, \epsilon}$ denotes the restriction of $\tilde{C}_\Omega$ to the open ball $B_{K, \epsilon}$ of Ω, with centre K and radius ϵ.*

(iii) *The model of equation (2)-(5) is said structurally globally identifiable if it is globally identifiable at all $K \in \Omega$.*

(iv) *The model of equation (2)-(5) is said structurally locally identifiable if it is locally identifiable at all $K \in \Omega$.*

When we have a general n-compartment compartmental system, it is hard to find a precise characterization of identifiability; it is although possible to prove some weak results, as the following lemma, leading, in particular cases, to more precise identifiability results.

We consider (from now on) n-compartment systems where for $p \in \{1, \ldots, n\}$, the input concentration functions C_{pe} from $\mathbb{R}_+$ to $\mathbb{R}_+$ are Laplace-transformable. For $p \in \{1, \ldots, n\}$, $r_{pe} = \inf \left\{ r \in \mathbb{R} : \int_0^{+\infty} e^{-rt} C_{pe}(t) \, dt < +\infty \right\}$ will denote the abscissa of convergence of C_{pe}. Note that in practical applications, the input concentration functions are bounded so that they are Laplace-transformable and for $p \in \{1, \ldots, n\}$, $r_{pe} \leq 0$. The Laplace transform will be denoted by $\mathcal{L}$ and for $r \in \mathbb{R}$, we define $\mathbb{C}_r = \{ z \in \mathbb{C} : \Re e(z) > r \}$.

Lemma 2.10. *Consider a positive integer n, Laplace-transformable input concentration functions $\check{C} = (C_{pe})_{p \in \{1,\ldots,n\}} \in C^0(\mathbb{R}_+, \mathbb{R}_+)^n$, $\alpha \in \mathbb{R}_+^{*\,n}$ and exchange rates $K \in \mathbb{R}_+^{n^2+n}$. Then, for $\alpha \in \mathbb{R}_+^{*\,n}$, $\tilde{C} = \mathscr{C}^\alpha(\check{C})(K)$ is Laplace-transformable and its abscissa of convergence r verifies*

$$r \leq r_{\mathrm{m}} = \max \left(\{ r_{\mathrm{m}}^{\mathrm{e}} \} \cup \mathrm{sp}(M) \right), \tag{9}$$

where

$$r_{\mathrm{m}}^{\mathrm{e}} = \max \left(\{ r_{pe} : p \in \{1, \ldots, n\} \} \right), \tag{10}$$

and $\mathrm{sp}(M)$ denotes the spectrum of the matrix $M = \mathscr{M}(\hat{K})$. Moreover for all $z \in \mathbb{C}_{r_{\mathrm{m}}}$, we have

$$\mathcal{L}\tilde{C}(z) = \sum_{p=1}^{n} \alpha_p k_{pe} \frac{Q_p(z)}{P(z)} \mathcal{L} C_{pe}(z),$$

where the unitary polynomial P of degree n is the characteristic polynomial of M and for $p \in \{1, \ldots, n\}$, Q_p is a unitary polynomial of degree $n-1$ given by

$$Q_p(z) = \frac{\alpha^T \mathrm{adj}(zI_n - M)e_p}{\alpha_p},$$

where $\mathrm{adj}(zI_n - M)$ denotes the adjugate matrix of $zI_n - M$.

Proof. The first statement of the lemma is obvious. In addition, since $C = \mathscr{C}(\check{C})(K)$ verifies (2), for all $z \in \mathbb{C}_{r_{\mathrm{m}}}$, we have

$$\mathcal{L}\tilde{C}(z) = \sum_{p=1}^{n} k_{pe} \alpha^T (zI_n - M)^{-1} e_p \, \mathcal{L} C_{pe}(z).$$

Since

$$(zI_n - M)^{-1} = \frac{\mathrm{adj}(zI_n - M)}{\det(zI_n - M)} = \frac{\mathrm{adj}(zI_n - M)}{P(z)},$$

where P is the characteristic polynomial of M, we have

$$\mathcal{L}\tilde{C}(z) = \sum_{p=1}^{n} k_{p\mathrm{e}} \frac{\alpha^T \mathrm{adj}(zI_n - M)e_p}{P(z)} \mathcal{L}C_{p\mathrm{e}}(z).$$

Moreover, it can be easily remarked that the only cofactors of $zI_n - M$ of degree $n-1$ in z are the diagonal cofactors and that the coefficient of the monomial z^{n-1} in these cofactors is 1, so that for all $p \in \{1, \ldots, n\}$, the polynomial $\alpha^T \mathrm{adj}(zI_n - M)e_p$ in z is of degree $n-1$ and its leading coefficient is α_p. $\qquad\square$

For a positive integer n, we denote by $\mathscr{P}$ the function

$$\begin{aligned} \mathscr{P} : \mathbb{R}^{n^2} &\rightarrow \mathbb{R}[X] \\ H &\mapsto \det(XI_n - \mathscr{M}(H)), \end{aligned}$$

and for $\alpha \in \mathbb{R}_+^{*\,n}$, we denote by $\mathscr{Q}^\alpha$ the function

$$\begin{aligned} \mathscr{Q}^\alpha : \mathbb{R}^{n^2} &\rightarrow \mathbb{R}[X]^n \\ H &\mapsto \left(\frac{\alpha^T \mathrm{adj}(XI_n - \mathscr{M}(H))e_p}{\alpha_p} \right)_{p \in \{1,\ldots,n\}}. \end{aligned}$$

For $r \in \mathbb{R}$, we denote by $\mathcal{M}(\mathbb{C}_r)$ the field of meromorphic functions on $\mathbb{C}_r$ and by $\mathbb{R}(X)$ the field of rational fractions in the indeterminate X with coefficients in $\mathbb{R}$. In the following, for $r \in \mathbb{R}$, $\mathcal{M}(\mathbb{C}_r)$ will be regarded as a vector space over $\mathbb{R}(X)$. As an immediate consequence of lemma 2.10, we have

Corollary 2.11. *Consider a positive integer n and Laplace-transformable input concentration functions $\check{C} = (C_{p\mathrm{e}})_{p \in \{1,\ldots,n\}} \in C^0(\mathbb{R}_+, \mathbb{R}_+)^n$ such that $C_{p\mathrm{e}} = 0$ for $p \in \{1, \ldots, n\} \setminus \{p_\ell : \ell \in \{1, \ldots, k\}\}$, where $k \geq 1$ and $(p_\ell)_{\ell \in \{1,\ldots,k\}}$ are k distinct elements of $\{1, \ldots, n\}$. We recall that for exchange rates $K \in \mathbb{R}_+^{n^2+n}$, $\check{K}$ denotes the last n components of K, that is, for $p \in \{1, \ldots, n\}$, $\check{K}_p = k_{p\mathrm{e}}$. Consider $\alpha \in \mathbb{R}_+^{*\,n}$ and define $\tilde{C} = \mathscr{C}^\alpha(\check{C})$. If the functions $(\mathcal{L}C_{p_\ell \mathrm{e}})_{\ell \in \{1,\ldots,k\}}$ of $\mathcal{M}(\mathbb{C}_{r_\mathrm{m}^\mathrm{e}})$ are linearly independent over $\mathbb{R}(X)$, where r_m^e is defined by (10), then for $K \in \mathbb{R}_+^{n^2+n}$, the exchange rates $(\check{K}_{p_\ell \mathrm{e}})_{\ell \in \{1,\ldots,k\}}$ are uniquely determined by the function $\tilde{C}(K)$, that is, for all $K' \in \mathbb{R}_+^{n^2+n}$, we have $\tilde{C}(K') = \tilde{C}(K)$ only if $\check{K}_{p_\ell \mathrm{e}} = \check{K}'_{p_\ell \mathrm{e}}$ for all $\ell \in \{1, \ldots, k\}$. More precisely, we have $\tilde{C}(K') = \tilde{C}(K)$ if and only if the previous condition holds and for all $\ell \in \{1, \ldots, k\}$*

$$\frac{\mathscr{Q}^\alpha(K')_{p_\ell}}{\mathscr{P}(K')} = \frac{\mathscr{Q}^\alpha(K)_{p_\ell}}{\mathscr{P}(K)}.$$

Otherwise, in a more general case, we have

Corollary 2.12. *Consider a positive integer n and Laplace-transformable input concentration functions $\check{C} = (C_{p\mathrm{e}})_{p \in \{1,\ldots,n\}} \in C^0(\mathbb{R}_+, \mathbb{R}_+)^n$, then, there exist k distinct elements $(p_\ell)_{\ell \in \{1,\ldots,k\}}$ of $\{1, \ldots, n\}$, where $k \in \{0, \ldots, n\}$ ($k = 0$ if all input concentration functions are identically zero) such that the functions $(\mathcal{L}C_{p_\ell \mathrm{e}})_{\ell \in \{1,\ldots,k\}}$ of $\mathcal{M}(\mathbb{C}_{r_\mathrm{m}^\mathrm{e}})$ are linearly independent over $\mathbb{R}(X)$, where r_m^e is defined by (10), and such that for all $p \in \{1, \ldots, n\} \setminus \{p_\ell : \ell \in \{1, \ldots, k\}\}$, $\mathcal{L}C_{p\mathrm{e}} \in \mathrm{span}(\{\mathcal{L}C_{p_\ell \mathrm{e}} : \ell \in \{1, \ldots, k\}\})$. Consider*

$\alpha \in \mathbb{R}_+^{*\,n}$ *and denote by* $\tilde{C} = \mathscr{C}^{\alpha}(\check{C})$. *For all* $K \in \mathbb{R}^{n^2+n}$ *and* $z \in \mathbb{C}_{r_{\mathrm{m}}}$, *where* r_{m} *is defined by* (9), *we then have*

$$\mathcal{L}\tilde{C}(z) = \sum_{\ell=1}^{k} F_\ell^{\check{C},K,\alpha}(z)\mathcal{L}C_{p_\ell e}(z),$$

where for all $\ell \in \{1,\dots,k\}$, $F_\ell^{\check{C},K,\alpha} \in \mathbb{R}(X)$. *Moreover, for* $K, K' \in \mathbb{R}^{n^2+n}$, *we have* $\tilde{C}(K) = \tilde{C}(K')$ *if and only if for all* $\ell \in \{1,\dots,k\}$

$$F_\ell^{\check{C},K',\alpha} = F_\ell^{\check{C},K,\alpha}.$$

These are general, weak, results on identifiability of n-compartment systems; in the next sections, we will focus our study of identifiability on the 2-compartments and the 3-compartments catenary systems, and find a precise characterization of identifiability.

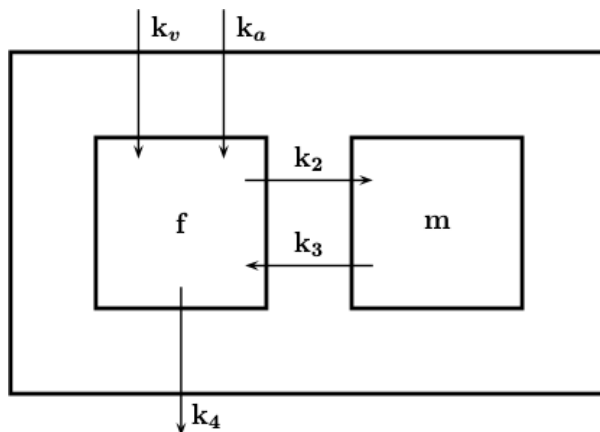## 3. Study of a 2-compartment catenary system

Figure 3. Generic 2-compartment catenary model.

We introduce now the case of a 2-compartment catenary system. The low degree of complexity of this 2-compartmental model, allows its daily clinical utilization, without high computational request. For this reason, this model gained high popularity over the last twenty years, and has been extensively used to analyze PET data. FDG-PET data are particularly favourable for the application of this model; it is indeed possible to simplify the metabolism of the tracer in two chemical phases: a free intracellular phase and a metabolized ones [9, 10, 27], that well suit a 2-compartment catenary model. We recall that the evolution equations in a 2-compartment catenary system as in Figure 3 are given by

$$\dot{C}_1 = -\left(k_{\mathrm{e}1} + k_{21}\right)C_1 + k_{12}C_2,$$
$$\dot{C}_2 = k_{21}C_1 - k_{12}C_2,$$

with initial conditions

$$C_1(0) = 0, \qquad C_2(0) = 0.$$

That is

$$\dot{C} = MC + W, \qquad C(0) = 0, \tag{11}$$

where $M \in M_2(\mathbb{R}), C \in C^1(\mathbb{R}_+, \mathbb{R})^2, W \in C^0(\mathbb{R}_+, \mathbb{R})^2$ are given by

$$M = \begin{pmatrix} -(k_{e1} + k_{21}) & k_{12} \\ k_{21} & -k_{12} \end{pmatrix}, \qquad C = \begin{pmatrix} C_1 \\ C_2 \end{pmatrix}, \qquad W = k_{1e} \begin{pmatrix} C_{1e} \\ 0 \end{pmatrix} = k_{1e} C_{1e} e_1.$$

PET-scan images allow to access $C^* = (1-V)(C_1 + C_2) + V C_{1e}$ where V is a fraction in $(0,1)$, represent the blood fraction in the tissue under examination, and in this analysis, as already observed, it is assumed to be known. Since C_{1e} is the concentration of tracer in blood, it is directly measurable [20, 28]. It is therefore possible to rewrite the previous equation as $\tilde{C} = (1-V)(C_1 + C_2)$, where $\tilde{C} = C^* - V C_{1e}$, which is measurable from PET-scans. The inverse problem consists in recovering $k_{1e}, k_{e1}, k_{21}, k_{12}$ from the knowledge of V, C_{1e} and

$$\tilde{C} = \alpha^T C, \qquad \text{where } \alpha = \begin{pmatrix} 1-V & 1-V \end{pmatrix}. \tag{12}$$

More generally, we will study the identifiability of this 2-compartment catenary system on $\Omega = \mathbb{R}_+^{*\,4}$. For sake of simplicity, in the following of the document, the exchange rates of the system are denoted by a, b, c, k where

$$a = k_{e1}, \qquad b = k_{21}, \qquad c = k_{12}, \qquad k = k_{1e}.$$

M and W are then rewritten

$$M = \begin{pmatrix} -(a+b) & c \\ b & -c \end{pmatrix}, \qquad W = k C_{1e} e_1.$$

We recall that according to theorem 2.8, M is diagonalizable and its eigenvalues are simple and negative. We suppose that C_{1e} is bounded and not identically zero. Hence, according to corollary 2.11, we first have the following lemma

Lemma 3.1. *k is uniquely determined by the knowledge of $\tilde{C}$.*

Now, in order to know the solutions of the inverse problem, we have to search for the matrices $M_x \in M_2(\mathbb{R})$

$$M_x = \begin{pmatrix} -(x_a + x_b) & x_c \\ x_b & -x_c \end{pmatrix},$$

where $x_a, x_b, x_c \in \mathbb{R}_+^*$, such that $F_x = F$, with $F = Q/P$ and $F_x = Q_x/P_x$, where P is the characteristic polynomial of M, P_x is the characteristic polynomial of M_x and Q, Q_x are defined by

$$Q(X) = \alpha^T \text{adj}(X - M) e_1, \qquad Q_x(X) = \alpha^T \text{adj}(X - M_x) e_1.$$

That is

$$P(X) = X^2 + (a + b + c)X + ac,$$
$$Q(X) = (1 - V)(X + b + c),$$
$$P_x(X) = X^2 + (x_a + x_b + x_c)X + x_a x_c,$$
$$Q_x(X) = (1 - V)(X + x_b + x_c).$$

First of all, we write the rational fraction by splitting the polynomial P

$$F(X) = \frac{(1-V)(X+b+c)}{(X-\lambda_1)(X-\lambda_2)},$$

where $\lambda_1 = -\frac{a+b+c+\sqrt{(a+b+c)^2-4ac}}{2}$ and $\lambda_2 = -\frac{a+b+c-\sqrt{(a+b+c)^2-4ac}}{2}$. Remark that in this simple example, we can easily verify the statement of theorem 2.8. Indeed, we have $0 < (a+b-c)^2 + 4bc = (a+b+c)^2 - 4ac < a+b+c$ so that λ_1 and λ_2 are real, negative and distinct. Moreover, we have $\lambda_1, \lambda_2 \neq -(b+c)$, hence, the rational fraction F is in its irreducible form. Since $\deg P_x = \deg P = 3$ and $\deg Q_x = \deg Q = 2$, we have $F_x = F$ only if the rational fraction F_x is irreducible too (but as we have just seen, since $x_a, x_b, x_c > 0$, it is always irreducible). In addition, since the leading coefficients of P_x and P are identical, as well as those of Q_x and Q, we have $F_x = F$ if and only if $P_x = P$ and $Q_x = Q$, that is

$$x_a + x_b + x_c = a + b + c,$$
$$x_a x_c = ac,$$
$$x_b + x_c = b + c.$$

Hence $F_x = F$ if and only if $x_a = a$, $x_b = b$, $x_c = c$, that is $M_x = M$. Consequently, we have the following theorem

Theorem 3.2. *The model of equations (11)-(12) is structurally globally identifiable.*

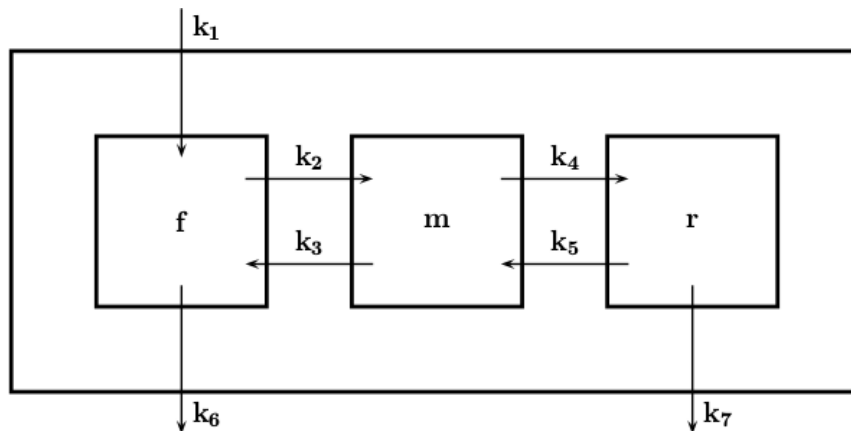## 4. Study of a 3-compartment catenary system

Figure 4. Generic 3-compartment catenary model.

We now introduce a 3-compartment catenary system [28]. This model is commonly used either in FDG-PET studies (and the third compartment accounts for the presence of a blood stream that carries tracer inside the organ under examination, approximated by C_{1e} in 2-compartment models) or in ^{11}C-PET studies, where the tracer has an intrinsic

three-status metabolism [18]. We recall that the evolution equations in a 3-compartment catenary system as in Figure 4 are given by

$$\dot{C}_1 = -\left(k_{e1} + k_{21}\right) C_1 + k_{12}C_2 + k_{1e}C_{1e},$$
$$\dot{C}_2 = k_{21}C_1 - \left(k_{12} + k_{32}\right) C_2 + k_{23}C_3,$$
$$\dot{C}_3 = k_{32}C_2 - k_{23}C_3,$$

with initial conditions

$$C_1(0) = 0, \qquad C_2(0) = 0, \qquad C_3(0) = 0.$$

That is

$$\dot{C} = MC + W, \qquad C(0) = 0, \tag{13}$$

where $M \in M_3(\mathbb{R}), C \in C^1(\mathbb{R}_+, \mathbb{R})^3, W \in C^0(\mathbb{R}_+, \mathbb{R})^3$ are given by

$$M = \begin{pmatrix} -(k_{e1} + k_{21}) & k_{12} & 0 \\ k_{21} & -(k_{12} + k_{32}) & k_{23} \\ 0 & k_{32} & -k_{23} \end{pmatrix},$$

$$C = \begin{pmatrix} C_1 \\ C_2 \\ C_3 \end{pmatrix}, \qquad W = k_{1e} \begin{pmatrix} C_{1e} \\ 0 \\ 0 \end{pmatrix} = k_{1e}C_{1e}e_1.$$

PET-scan images allow to access $\tilde{C} = VC_1 + (1 - V)(C_2 + C_3)$ where V is a fraction in $(0, 1)$, representing the blood fraction in the tissue under examination, and in this analysis, as already observed, it is assumed to be known. The inverse problem consists in recovering $k_{1e}, k_{e1}, k_{21}, k_{12}, k_{32}, k_{23}$ from the knowledge of V, C_{1e} and

$$\tilde{C} = \alpha^T C, \qquad \text{where } \alpha = \begin{pmatrix} V & 1 - V & 1 - V \end{pmatrix}. \tag{14}$$

More generally, we will study the identifiability of this 3-compartment catenary system on $\Omega = \mathbb{R}_+^{*\,6}$. For sake of simplicity, in the following of the document, the exchange rates of the system are denoted by a, b, c, d, e, k where

$$a = k_{e1}, \qquad b = k_{21}, \qquad c = k_{12}, \qquad d = k_{32}, \qquad e = k_{23}, \qquad k = k_{1e}.$$

M and W are then rewritten

$$M = \begin{pmatrix} -(a + b) & c & 0 \\ b & -(c + d) & e \\ 0 & d & -e \end{pmatrix}, \qquad W = kC_{1e}e_1.$$

We recall that according to theorem 2.8, M is diagonalizable and its eigenvalues are simple and negative. We suppose that C_{1e} is bounded and not identically zero. Hence, according to corollary 2.11, we first have the following lemma

Lemma 4.1. *k is uniquely determined by the knowledge of $\tilde{C}$.*

Using the properties of the n-compartment catenary systems given in theorem 2.8 and the corollary 2.11, we can write the following theorem, whose proof can be found in the appendix A.

Theorem 4.2. *If $V \geq 1/2$, the model of equations (13)-(14) is structurally globally identifiable. Otherwise, the model is neither structurally globally nor structurally locally identifiable. However, the model is locally identifiable at points $(a, b, c, d, e, k) \in \mathbb{R}_+^{*\,6}$ such that*

$$a \neq \frac{1 - 2V}{2V(1 - V)} \left((c + d + e)V + (1 - V)b \pm \sqrt{\Delta_Q} \right).$$

More precisely, in that case, the model is globally identifiable at points $(a, b, c, d, e, k) \in \mathbb{R}_+^{*\,6}$ such that one of the following exclusive conditions of lemma A.4 holds: 1, 2.1, 2.2.1, 2.2.2.1, 3.1.1, 3.1.2.1.1, 3.1.2.2, 3.2.1, 3.2.2.1, 3.2.2.2.1, 3.3.1.1, 3.3.2.1. Otherwise, the inverse problem has two distinct solutions. In the case where

$$a = \frac{1 - 2V}{2V(1 - V)} \left((c + d + e)V + (1 - V)b \pm \sqrt{\Delta_Q} \right),$$

the model is neither globally nor locally identifiable. More precisely, the set of solutions of the inverse problem is a curve of $\mathbb{R}^6$.

5. Conclusions

This paper describes the identifiability problem for a general n-compartment systems and provides some precise uniqueness results in the case of the two- and three-compartment catenary models. We think that the main advantage of our approach is its notable degree of generality, which allows a rather unified approach to the definition of the model and, particularly, to the proof of the uniqueness results. Further generalization of the identifiability results to n-compartment models, with $n > 3$, are certainly difficult although some uniqueness conditions can be probably formulated in the case of low dimension non-catenary models and catenary models with higher dimension.

A second paper concerned with two- and three-compartment catenary models is under preparation, which will address the inverse problem of numerically determining the tracer coefficients by means of a general Newton regularized scheme. In this paper applications concerning cerebral, hepatic, and renal functions will be considered, involving experimental measurements acquired by means of a PET system for small animals. Further investigation will deal with the formulation of a compartmental model in which the tracer coefficients are local parameters and therefore the numerical solution of the inverse problem leads to the construction of parametric images.

Acknowledgments

References

[1] Adams S, Baum R, Stuckensen T, Bitter T and Hoer G 1998 Prospective comparison of FDG-PET with conventional imaging modalities (CT, MRI, US) in lymph node staging of head and neck cancer *Eur. J. Nucl. Med* **25**

[2] Bateman T M, Heller G V, McGhie A I, Friedman J D, Case J A, Bryngelson J R, Hertenstein G K, Moutray K L, Reid K, Cullom S J 2006 Diagnostic accuracy of rest/stress ECG-gated Rb-82 myocardial perfusion PET: comparison with ECG-gated Tc-99m sestamibi SPECT *J. Nucl. Cardiol.* **13** 24–33

[3] Benning M, Kösters T, Wübbeling F, Schäfers K, and Burger M 2008 A nonlinear variational method for improved quantification of myocardial blood flow using dynamic H_2 ^{15}O PET *IEEE Nuclear Science Symposium Conference Record* 4472–4477

[4] Benning M, Heins P, Burger M 2010 A solver for dynamic PET reconstructions based on forward-backward-splitting *Aip Conference Proceedings* **1281** pp 1967

[5] Bergmann S R, Fox K A, and Rand A L 1984 Quantification of Regional Myocardial Blood Flow in Vivo with H_2 ^{15}O *Circulation* **70** 724–733

[6] Basu A, Basu R, Shah P, Vella A, Johnson C, Nair K, Jensen M, Schwenk W and Rizza R 1994 Evaluation of the effect of glucose ingestion and kinetic model configurations of FDG in the normal liver *J. Nucl. Med.* **35** 2055–2060

[7] Diederichs C, Staib L, Glatting G, Beger H and Reske S 1998 FDG PET: elevated plasma glucose reduces both uptake and detection rate of pancreatic malignancies *J. Nucl. Med.* **39** 1030–1033

[8] Evans N D, Errington R J, Chapman M J, Smith P J, Chappell M J and Godfrey K R 2005 Compartmental modelling of the uptake kinetics of the anti-cancer agent topotecan in human breast cancer cells *Internat. J. Adapt. Control Signal Process.* **19** 395–417 ISSN 0890-6327 URL http://dx.doi.org/10.1002/acs.856

[9] Garbarino S, Caviglia G, Brignone M, Massollo M, Sambuceti G and Piana M 2013 Estimate of FDG excretion by means of compartmental analysis and Ant Colony Optimization of nuclear medicine data *Comput. Math. Methods. Med.* **2013** 793142

[10] Garbarino S, Caviglia G, Sambuceti G, Benvenuto F and Piana M 2014 A novel description of FDG excretion in the renal system: application to metformin treated models *Phys. Med. Biol.* **59** 2469–2484

[11] Garbarino S, Vivaldi V, Delbary F, Caviglia G, Piana M, Marini C, Capitanio S, Calamia I, Buschiazzo A and Sambuceti G 2015 A new compartmental method for the analysis of liver FDG kinetics *European Journal of Nuclear Medicine and Molecular Imaging Research* **2015** 5-35

[12] Gunn R, Gunn S and Cunningham V 2001 Positron emission tomography compartmental models *J. Cereb. Blood Flow Metab.* **21** 635–652

[13] Gunn R, Gunn S, Turkheimer F, Aston J and Cunningham V 2002 Positron emission tomography compartmental models: a basis pursuit strategy for kinetic modeling *J. Cereb. Blood Flow Metab.* **22** 1425–1439

[14] Hearon J Z 1953 The kinetics of linear system with special reference to periodic reactions *Bull. Math. Biophys.* **16** 121–141

[15] Hearon J Z 1963 Theorems on Linear System *Ann. New York Acad. Sci.* **108** 36–68

[16] Hudson H and Larkin R 1994 Accelerated image reconstruction using ordered subsets of projection *IEEE Trans. Med. Imaging* **13** 601–609

[17] Ito H, Kanno I, Iida H, Hatazawa J, Shimosegawa E, Tamura H, Okudera T 2001 Arterial fraction of cerebral blood volume in humans measured by positron emission tomography *Ann. Nucl. Med.* **15** 111–116

[18] Koeppe R A, Holthoff V A, Frey K A, Kilbourn M R and Kuhl D E 1991 Compartmental Analysis of [11C]Flumazenil Kinetics for the Estimation of Ligand Transport Rate and Receptor Distribution Using Positron Emission Tomography *J. Cereb. Blood Flow Metab.* **11** 735–744

[19] Kostakoglu L, Schoder H and Johnson J 2012 Interim FDG PET imaging in stage I/II non bulky Hodgkin lymphoma: Would using combined PET and CT criteria better predict response than each test alone *Leuk. Lymphoma* **53** 2143–2150

[20] Kudomi N, Jarvisalo M, Kiss J, Borra R, Viljanen A, Viljanen T, Sauvunen T, Knuuti J, Iida H, Nuutila P and Iozzo P 2009 Non-invasive estimation of hepatic glucose uptake from [18F]FDG PET images using tissue-derived input functions *Eur. J. Nucl. Med. Mol. Imaging* **36** 2014–2026

[21] 2014 Meshkat N Identifiable reparametrizations of linear compartment models *J. Symbolic Computation* **63** 46–67

[22] Miao H, Xia X, Perelson A S and Wu H 2011 On Identifiability of Nonlinear ODE Models and Applications in Viral Dynamics *SIAM Rev.* **53** 3–39 ISSN 0036-1445 URL http://dx.doi.org/10.1137/090757009

[23] Natterer F 2001 Inversion of the attenuated Radon transform *Inverse Problems* **17** 113

[24] Ollinger J M and Fessler J A 1997 Positron-emission tomography *IEEE Sign. Proc. Mag.* **14** 43–55

[25] Onsager L 1931 Reciprocal Relations in Irreversible Processes I *Phys. Rev.* **37** 405–26

[26] Parter S 1960 On the eigenvalues and eigenvectors of a class of matrices *J. Soc. Indust. Appl. Math.* **8** 376–388

[27] Qiao H, Bai J, Chen Y and Tian J 2007 Kidney modelling for FDG excretion with PET *Int. J. Biomed. Imaging* **2007** 63234

[28] Rani S and Nemanich S and Fettig N and Shoghi K 2013 Kinetic analysis of FDG in rat liver: effect of dietary intervention on arterial and portal vein input *Nucl. Med. Biol.* **40** 537–546

[29] Reader A J, Sureau F C, Comtat C, Trébossen R, and Buvat I 2006 Joint estimation of dynamic PET images and temporal basis functions using fully 4D ML-EM *Phys. Med. Biol.* **51** 5455–5474

[30] Reader A J, Matthews J C, Sureau F C, Comtat C, Trébossen R, and Buvat I 2007 Fully 4D image reconstruction by estimation of an input function and spectral coefficients *IEEE Nuclear Science Symposium Conference Record*, 3260–3267

[31] Reips L, Burger M, and Engbers R, Towards Dynamic PET Reconstruction under Flow Conditions: Parameter Identification in a PDE Model *arXiv preprint* **arXiv:1411.5143v1**

[32] Rescigno A 1997 Clearance, turnover time, and volume of distribution *Pharm. Res.* **35** 189–193

[33] Rescigno A 2009 Compartmental Analysis and its Manifold Applications to Pharmacokinetics *The AAPS Journal* **12** 61–72

[34] Rida H, Kanno I, Takahashi A, Miura S, Murakami M, Takahashi K, Ono Y, Shishido F, Inugami A, and Tomura N 1988 Measurement of Absolute Myocardial Blood Flow with H_2 ^{15}O and Dynamic Positron-Emission Tomography. Strategy for Quantification in Relation to the Partial-Volume Effect *Circulation* **78** 104–115

[35] Schafers K P, Spinks T, Camici P G, Bloomfield P M, Rhodes C G, Law M P, Baker C S R, and Rimoldi O Absolute Quantification of Myocardial Blood Flow with H_2 ^{15}O and 3-Dimensional PET: An Experimental Validation *J. Nucl. Med.* **43** 1031–1040.

[36] Schmidt K 1999 Which Linear Compartmental Systems Can Be Analyzed by Spectral Analysis of PET Output Data Summed Over All Compartments? *J. Cereb. Blood Flow Metab.* **19** 560–569

[37] Shepp L and Vardi Y, Maximum likelihood reconstruction for emission tomography 1982 *IEEE Trans. Med. Imag.* **1** 113–122

[38] Wang W, Georgi J C, Nehmeh S A, Narayan M, Paulus T, Bal M and Humm J L 2009 Evaluation of a compartmental model for estimating tumor hypoxia via FMISO dynamic PET imaging *Phys. Med. Biol.* **10** 3083–3099

[39] Wernick M N and Aarsvold J N 2004 Emission Tomography: The Fundamentals of PET and SPECT *Elsevier Academic Press*

[40] Yan J, Planeta-Wilson B, and Carson R E 2008 Direct 4D list mode parametric reconstruction for PET with a novel EM algorithm *IEEE Nuclear Science Symposium Conference Record* 3625–3628

[41] Zhou Y, Resnick S and Wong F 2007 Using a reference tissue model with spatial constraint to quantify [11C] Pittsburgh compound B PET for early diagnosis of Alzheimer's disease

A. APPENDIX

In order to prove theorem 4.2 we first need to search for the matrices $M_x \in M_3(\mathbb{R})$

$$M_x = \begin{pmatrix} -(x_a + x_b) & x_c & 0 \\ x_b & -(x_c + x_d) & x_e \\ 0 & x_d & -x_e \end{pmatrix},$$

where $x_a, x_b, x_c, x_d, x_e \in \mathbb{R}_+^*$, such that $F_x = F$, with $F = Q/P$ and $F_x = Q_x/P_x$, where P is the characteristic polynomial of M, P_x is the characteristic polynomial of M_x and Q, Q_x are defined by

$$Q(X) = \alpha^T \mathrm{adj}(X - M)e_1, \qquad Q_x(X) = \alpha^T \mathrm{adj}(X - M_x)e_1.$$

That is

$$P(X) = X^3 + (a + b + c + d + e)X^2 + (ac + ad + ae + bd + be + ce)X + ace,$$
$$Q(X) = VX^2 + (V(c + d + e) + (1 - V)b)X + (Vce + (1 - V)(d + e)b),$$
$$P_x(X) = X^3 + (x_a + x_b + x_c + x_d + x_e)X^2$$
$$+ (x_a x_c + x_a x_d + x_a x_e + x_b x_d + x_b x_e + x_c x_e)X + x_a x_c x_e,$$
$$Q_x(X) = VX^2 + (V(x_c + x_d + x_e) + (1 - V)x_b)X + (Vx_c x_e + (1 - V)(x_d + x_e)x_b).$$

We first begin with some preliminary results about the polynomials P and Q and the rational fraction F. The discriminant of Q is given by

$$\Delta_Q = (V(c + d + e) + (1 - V)b)^2 - 4V(Vce + (1 - V)(d + e)b),$$
$$= ((-c + d + e)V - (1 - V)b)^2 + 4cdV^2,$$

thus $0 < \Delta_Q < V(c + d + e) + (1 - V)b$. Hence Q has two distinct real negative roots

$$\mu_q = -\frac{(c + d + e)V + (1 - V)b + (-1)^q\sqrt{\Delta_Q}}{2V}, \qquad q \in \{1, 2\},$$

Hence, the rational fraction F can be written as

$$F(X) = \frac{V(X - \mu_1)(X - \mu_2)}{(X - \lambda_1)(X - \lambda_2)(X - \lambda_3)},$$

where $\lambda_1 < \lambda_2 < \lambda_3 < 0$ are the eigenvalues of M. In the following, we will need to know the irreducible form of the rational fraction F, that is, the number of roots common to P and Q. For the moment, we have three possibilities.

① P and Q have no common root, *i.e.* they are coprime, so that F is irreducible,

② P and Q have one common root $\lambda_p = \mu_q, p \in \{1, 2, 3\}, q \in \{1, 2\}$, hence

$$F = \frac{V(X - \mu_{q'})}{(X - \lambda_{p'})(X - \lambda_{p''})}, \qquad \text{where } p', p'' \in \{1, 2, 3\} \setminus \{p\}, q' \in \{1, 2\} \setminus \{q\},$$

③ P and Q have two common roots, *i.e.* $Q|P$, $\mu_1 = \lambda_p, \mu_2 = \lambda_{p'}, p, p' \in \{1, 2, 3\}, p \neq p'$, hence

$$F = \frac{V}{X - \lambda_{p''}}, \qquad \text{where } p'' \in \{1, 2, 3\} \setminus \{p, p'\}.$$

We observe that P and Q are not coprime if and only if their resultant $\text{res}(P, Q)$ is 0. The resultant $\text{res}(P, Q)$ of P and Q is given by

$$\text{res}(P, Q) = -b^2 cd \left(V(1-V)^2 a^2 - (1-V)(1-2V)(V(c+d+e) + (1-V)b)a \right.$$
$$\left. + (1-2V)^2(Vce + (1-V)(d+e)b)\right).$$

In particular, we can see that if $V = 1/2$, $\text{res}(P, Q) = -a^2 b^2 cd/8 \neq 0$, otherwise, it can be easily remarked that

$$\text{res}(P, Q) = -b^2 cd(1-2V)^2 Q\left(-\frac{1-V}{1-2V}a\right).$$

Hence, for $V \neq 1/2$, $\text{res}(P, Q) = 0$ if and only if $-\frac{1-V}{1-2V}a$ is a root of Q. In particular, if $V > 1/2$, then $-\frac{1-V}{1-2V}a > 0$. However, the roots of Q are negative, thus $\text{res}(P, Q) \neq 0$. We recall that the same result holds for $V = 1/2$, thus we have the following lemma

Lemma A.1. *If $V \geq 1/2$, then P and Q are coprime so that F is irreducible.*

If now $V < 1/2$ and $-\frac{1-V}{1-2V}a$ is a root of Q, that is

$$a = \frac{1-2V}{2V(1-V)}\left((c+d+e)V + (1-V)b + (-1)^q \sqrt{\Delta_Q}\right), \qquad q \in \{1, 2\},$$

then $P(X) = (X - \mu_q)\breve{P}(X)$, where

$$\breve{P}(X) = X^2 + \frac{(2-3V)(c+d+e) + (1-V)b - (-1)^q\sqrt{\Delta_Q}}{2(1-V)}X + \frac{1-2V}{1-V}ce,$$

that is

$$\breve{P}(X) = X^2 + \left(-\frac{V}{1-2V}a + b - \frac{1-2V}{1-V}(c+d+e)\right)X + \frac{1-2V}{1-V}ce.$$

Since $Q(X) = (X - \mu_q)\breve{Q}(X)$, with

$$\breve{Q}(X) = V\left(X + \frac{(c+d+e)V + (1-V)b - (-1)^q\sqrt{\Delta_Q}}{2V}\right),$$

that is

$$\breve{Q}(X) = V\left(X - \frac{1-V}{1-2V}a + \frac{1-V}{V}b + c + d + e\right),$$

we have

$$F(X) = \frac{V\left(X - \frac{1-V}{1-2V}a + \frac{1-V}{V}b + c + d + e\right)}{X^2 + \left(-\frac{V}{1-2V}a + b - \frac{1-2V}{1-V}(c+d+e)\right)X + \frac{1-2V}{1-V}ce}.$$

Thus P and Q have two commons roots if and only if $\breve{P}(\mu_{q'}) = 0$ where $q' \in \{1, 2\} \setminus \{q\}$. However

$$\breve{P}(\mu_{q'}) = \frac{1-2V}{V^2}\left(bV + (1-V)d - \frac{V(1-V)}{1-2V}e\right),$$

$$= -\frac{1-2V}{2V^2}((-c+d+e)V - (1-V)b + (-1)^q\sqrt{\Delta_Q}).$$

Since $\Delta_Q = ((-c+d+e)V - (1-V)b)^2 + 4cdV^2$, we have $\sqrt{\Delta_Q} > |(-c+d+e)V - (1-V)b|$, hence $\breve{P}(\mu_{q'}) \neq 0$. We thus have the following lemma

Lemma A.2. *If $V < 1/2$, P and Q have at most one common root. This happens if and only if $-\frac{1-V}{1-2V}a$ is a root of Q, that is*

$$a = \frac{1-2V}{2V(1-V)}\left((c+d+e)V + (1-V)b + (-1)^q\sqrt{\Delta_Q}\right), \qquad q \in \{1,2\},$$

where

$$\begin{aligned}
\Delta_Q &= (V(c+d+e) + (1-V)b)^2 - 4V(Vbc + (1-V)(d+e)b), \\
&= ((-c+d+e)V - (1-V)b)^2 + 4cdV^2.
\end{aligned}$$

In this case, we have $F = \check{Q}/\check{P}$, where $\check{P}$ and $\check{Q}$ are coprime and

$$\check{P}(X) = X^2 + \left(-\frac{V}{1-2V}a + b - \frac{1-2V}{1-V}(c+d+e)\right)X + \frac{1-2V}{1-V}ce,$$

$$\check{Q}(X) = V\left(X - \frac{1-V}{1-2V}a + \frac{1-V}{V}b + c + d + e\right).$$

We are now ready to seek the solutions of the inverse problem and study the identifiability of the system. We first treat the case where P and Q are coprime and finish the study with the case where they are not.

A.1. Coprimality of P and Q

We suppose here that P and Q are coprime. Since F is irreducible and $\deg P_x = \deg P = 3$ and $\deg Q_x = \deg Q = 2$, $F_x = F$ only if the rational fraction F_x is irreducible too. In addition, since the leading coefficients of P_x and P are identical, as well as those of Q_x and Q, $F_x = F$ if and only if $P_x = P$ and $Q_x = Q$, that is

$$V(x_c + x_d + x_e) + (1-V)x_b = V(c+d+e) + (1-V)b, \tag{15a}$$
$$Vx_cx_e + (1-V)(x_d + x_e)x_b = Vce + (1-V)(d+e)b, \tag{15b}$$
$$x_a + x_b + x_c + x_d + x_e = a + b + c + d + e, \tag{15c}$$
$$(x_c + x_d + x_e)x_a + (x_d + x_e)x_b + x_cx_e = (c+d+e)a + (d+e)b + ce, \tag{15d}$$
$$x_ax_cx_e = ace. \tag{15e}$$

Doing (15a)$-V$(15c) to replace (15a), followed by $(1-2V)$(15c)$-$(15a) to replace (15c), then by $(1-V)$(15d)$-$(15b) to replace (15d), the system (15) is equivalent to

$$-Vx_a + (1-2V)x_b = -Va + (1-2V)b, \tag{16a}$$
$$Vx_cx_e + (1-V)(x_d + x_e)x_b = Vce + (1-V)(d+e)b, \tag{16b}$$
$$(x_c + x_d + x_e) + \frac{1-V}{1-2V}x_a = (c+d+e) + \frac{1-V}{1-2V}a, \tag{16c}$$
$$(x_c + x_d + x_e)\frac{1-V}{1-2V}x_a + x_cx_e = (c+d+e)\frac{1-V}{1-2V}a + ce, \tag{16d}$$
$$x_cx_e\frac{1-V}{1-2V}x_a = ce\frac{1-V}{1-2V}a. \tag{16e}$$

The equations (16c), (16d), (16e) are verified if and only if $\frac{x_c+x_d+x_e\pm\sqrt{(x_c+x_d+x_e)^2-4x_cx_e}}{2}$ and $\frac{1-V}{1-2V}x_a$ are the roots of the polynomial R of degree 3

$$R(X) = \left(X - \frac{1-V}{1-2V}a\right)\check{R}(X), \qquad \text{where } \check{R}(X) = X^2 - (c+d+e)X + ce.$$

Hence, the system (16) is equivalent to the one obtained by including the equation $R\left(\frac{1-V}{1-2V}x_a\right) = 0$, although the new system is redundant considering equations (16c), (16d), (16e) and the newly included one. The system (16) is then equivalent to

$$-Vx_a + (1-2V)x_b = -Va + (1-2V)b, \tag{17a}$$

$$Vx_cx_e + (1-V)(x_d+x_e)x_b = Vce + (1-V)(d+e)b, \tag{17b}$$

$$(x_c + x_d + x_e) + \frac{1-V}{1-2V}x_a = (c+d+e) + \frac{1-V}{1-2V}a, \tag{17c}$$

$$(x_c + x_d + x_e)\frac{1-V}{1-2V}x_a + x_cx_e = (c+d+e)\frac{1-V}{1-2V}a + ce, \tag{17d}$$

$$x_cx_e\frac{1-V}{1-2V}x_a = ce\frac{1-V}{1-2V}a, \tag{17e}$$

$$R\left(\frac{1-V}{1-2V}x_a\right) = 0. \tag{17f}$$

The solution $x_a = a$ to the equation (17f) leads to $x_b = b, x_c = c, x_d = d, x_e = e$, that is $M_x = M$. In addition, since $0 < (-c+d+e)^2 + 4cd = (c+d+e)^2 - 4ce < (c+d+e)^2$, the roots of $\check{R}$ are distinct, real and positive. However, for $V > 1/2$ and $x_a > 0$, we have $\frac{1-V}{1-2V}x_a < 0$, then $\check{R}\left(\frac{1-V}{1-2V}x_a\right) \neq 0$ and the unique solution of (17f) is $x_a = a$, so that the unique solution of the inverse problem is $M_x = M$. We recall that we had the same result for $V = 1/2$. In addition, we also recall that according to lemma A.1, P and Q are always coprime for $V \geq 1/2$, thus, we have the following lemma

Lemma A.3. *If $V \geq 1/2$, the inverse problem has a unique solution.*

Suppose now that $V < 1/2$, then (17f) has at least two distinct solutions since the roots of $\check{R}$ are distinct and at most three distinct solutions. Consider for the moment the solutions of (17) in $\mathbb{R}^5$ regardless of their sign and denote by $x_a^\pm = \frac{1-2V}{2(1-V)}\left(c+d+e \pm \sqrt{(c+d+e)^2 - 4ce}\right)$ the solutions of $\check{R}\left(\frac{1-V}{1-2V}x_a\right) = 0$. These solutions lead to two solutions $(x_a^\pm, x_b^\pm, x_c^\pm, x_d^\pm, x_e^\pm)$ to (17), provided $b + \frac{V}{1-2V}(x_a^\pm - a) \neq 0$ and $(1-2V)bc - (1-V)(x_a^\pm - a)\left(b - \frac{V}{1-2V}a\right) \neq 0$, they are given by

$$x_a^\pm = \frac{1-2V}{2(1-V)}\left(c+d+e \pm \sqrt{(c+d+e)^2 - 4ce}\right), \tag{18a}$$

$$x_b^\pm = b + \frac{V}{1-2V}(x_a^\pm - a), \tag{18b}$$

$$x_c^\pm = \frac{(1-2V)bc - (1-V)(x_a^\pm - a)\left(b - \frac{V}{1-2V}a\right)}{(1-2V)x_b^\pm}, \tag{18c}$$

$$x_d^\pm = \frac{bQ\left(-\frac{1-V}{1-2V}a\right)\left(\frac{1-2V}{1-V}c - x_a^\pm\right)}{(1-2V)x_b^{\pm 2}x_c^\pm}, \tag{18d}$$

$$x_e^{\pm} = a \left(\frac{1-V}{1-2V} \right)^2 \frac{x_a^{\mp}}{x_c^{\pm}}. \tag{18e}$$

Remark that if both solutions $(x_a^+, x_b^+, x_c^+, x_d^+, x_e^+)$ and $(x_a^-, x_b^-, x_c^-, x_d^-, x_e^-)$ exist, we have

$$x_c^+ x_d^+ x_c^- x_d^- = -16 cde^2 (1-V)^2 \frac{\Xi^2}{\Upsilon^2},$$

where

$$\Xi = a(c+d+e)(1-V)(1-2V)^2 - b(d+e)(1-V)(1-2V)^2 + ab(1-2V)(1-V)^2$$
$$- ceV(1-2V)^2 - a^2V(1-V)^2,$$

and

$$\Upsilon = ((c+d+e)V(1-2V) + 2b(1-V)(1-2V) - 2aV(1-V))^2$$
$$- V^2(1-2V)^2 \left((c+d+e)^2 - 4ce \right)^2.$$

Hence $x_c^+ x_d^+ x_c^- x_d^- \leq 0$ and we have $x_c^+ x_d^+ x_c^- x_d^- = 0$ if and only if $x_d^+ = 0$ or $x_d^- = 0$, otherwise $x_c^+ x_d^+ x_c^- x_d^- < 0$. Moreover, since $x_a^{\pm} > 0$, according to equation (17e), x_c^+ and x_e^+ have the same sign as well as x_c^- and x_e^-. In addition, x_c^+, x_d^+, x_e^+ are not all negative and x_c^-, x_d^-, x_e^- neither, since $\frac{x_c^{\pm} + x_d^{\pm} + x_e^{\pm} \pm \sqrt{(x_c^{\pm} + x_d^{\pm} + x_e^{\pm})^2 - 4x_c^{\pm} x_e^{\pm}}}{2}$ are roots of the polynomial R, thus positive. Hence, if $x_d^{\pm} \neq 0$, one and only one of x_c^+, x_d^+, x_c^-, x_d^- is negative so that we have one of the two exclusive cases: $x_c^+ > 0$ and $x_d^+ > 0$ or $x_c^- > 0$ and $x_d^- > 0$. Consequently, the inverse problem has at most two solutions. More precisely, considering (18) and the previous remark, we have the following lemma

Lemma A.4. *If $V < 1/2$ and the polynomials P and Q are coprime, that is*

$$a \neq \frac{1-2V}{2V(1-V)} \left((c+d+e)V + (1-V)b \pm \sqrt{\Delta_Q} \right),$$

then, we have one of the exclusive cases:
1) $\frac{V}{1-2V} x_a^+ \leq \frac{V}{1-2V} a - b$. Then the inverse problem has a unique solution: (a, b, c, d, e).
2) $\frac{V}{1-2V} x_a^- \leq \frac{V}{1-2V} a - b < \frac{V}{1-2V} x_a^+$ and
2.1) $(1-2V)bc - (1-V)(x_a^+ - a) \left(b - \frac{V}{1-2V} a \right) \leq 0$. Then the inverse problem has a unique solution: (a, b, c, d, e).
2.2) $0 < (1-2V)bc - (1-V)(x_a^+ - a) \left(b - \frac{V}{1-2V} a \right)$ and

2.2.1) $((-c+d+e)V - (1-V)b)^2 + 4cdV^2 < \left((c+d+e)V + (1-V)b - \frac{2V(1-V)}{1-2V} a \right)^2$.
Then the inverse problem has a unique solution: (a, b, c, d, e).
2.2.2) $\left((c+d+e)V + (1-V)b - \frac{2V(1-V)}{1-2V} a \right)^2 < ((-c+d+e)V - (1-V)b)^2 + 4cdV^2$ and

2.2.2.1) $a = x_a^+$. Then the inverse problem has a unique solution: (a, b, c, d, e).
2.2.2.2) $a \neq x_a^+$. Then the inverse problem has two solutions: (a, b, c, d, e) and $(x_a^+, x_b^+, x_c^+, x_d^+, x_e^+)$.
3) $\frac{V}{1-2V} a - b < \frac{V}{1-2V} x_a^-$ and
3.1) $b = \frac{aV(1-V)(x_a^+ - a)}{(1-2V)\left((1-V)(x_a^+ - a) - (1-2V)c \right)}$ and

3.1.1) $b - \frac{V}{1-2V}a \leq 0$. Then the inverse problem has a unique solution: (a, b, c, d, e).

3.1.2) $0 < b - \frac{V}{1-2V}a$ and

3.1.2.1) $((-c + d + e)V - (1 - V)b)^2 + 4cdV^2 < \left((c + d + e)V + (1 - V)b - \frac{2V(1-V)}{1-2V}a\right)^2$ and

3.1.2.1.1) $a = x_a^-$. Then the inverse problem has a unique solution: (a, b, c, d, e).

3.1.2.1.2) $a \neq x_a^-$. Then the inverse problem has two solutions: (a, b, c, d, e) and $(x_a^-, x_b^-, x_c^-, x_d^-, x_e^-)$.

3.1.2.2) $\left((c + d + e)V + (1 - V)b - \frac{2V(1-V)}{1-2V}a\right)^2 < ((-c + d + e)V - (1 - V)b)^2 + 4cdV^2$. Then the inverse problem has a unique solution: (a, b, c, d, e).

3.2) $b = \frac{aV(1-V)(x_a^- - a)}{(1-2V)\left((1-V)(x_a^- - a) - (1-2V)c\right)}$ and

3.2.1) $0 \leq b - \frac{V}{1-2V}a$. Then the inverse problem has a unique solution: (a, b, c, d, e).

3.2.2) $b - \frac{V}{1-2V}a < 0$ and

3.2.2.1) $((-c + d + e)V - (1 - V)b)^2 + 4cdV^2 < \left((c + d + e)V + (1 - V)b - \frac{2V(1-V)}{1-2V}a\right)^2$. Then the inverse problem has a unique solution: (a, b, c, d, e).

3.2.2.2) $\left((c + d + e)V + (1 - V)b - \frac{2V(1-V)}{1-2V}a\right)^2 < ((-c + d + e)V - (1 - V)b)^2 + 4cdV^2$ and

3.2.2.2.1) $a = x_a^+$. Then the inverse problem has a unique solution: (a, b, c, d, e).

3.2.2.2.2) $a \neq x_a^+$. Then the inverse problem has two solutions: (a, b, c, d, e) and $(x_a^+, x_b^+, x_c^+, x_d^+, x_e^+)$.

3.3) $b \neq \frac{aV(1-V)(x_a^\pm - a)}{(1-2V)\left((1-V)(x_a^\pm - a) - (1-2V)c\right)}$ and

3.3.1) $\left((c + d + e)V + (1 - V)b - \frac{2V(1-V)}{1-2V}a\right)^2 < ((-c + d + e)V - (1 - V)b)^2 + 4cdV^2$ and $0 < (1 - 2V)bd - (1 - V)(x_a^+ - a)\left(b - \frac{V}{1-2V}a\right)$ and

3.3.1.1) $a = x_a^+$. Then the inverse problem has a unique solution: (a, b, c, d, e).

3.3.1.2) $a \neq x_a^+$. Then the inverse problem has two solutions: (a, b, c, d, e) and $(x_a^+, x_b^+, x_c^+, x_d^+, x_e^+)$.

3.3.2) $((-c + d + e)V - (1 - V)b)^2 + 4cdV^2 < \left((c + d + e)V + (1 - V)b - \frac{2V(1-V)}{1-2V}a\right)^2$ and $0 < (1 - 2V)bd - (1 - V)(x_a^- - a)\left(b - \frac{V}{1-2V}a\right)$ and

3.3.2.1) $a = x_a^-$. Then the inverse problem has a unique solution: (a, b, c, d, e).

3.3.2.2) $a \neq x_a^-$. Then the inverse problem has two solutions: (a, b, c, d, e) and $(x_a^-, x_b^-, x_c^-, x_d^-, x_e^-)$.

A.2. Non-coprimality of P and Q

We suppose here that P and Q are not coprime. Then, according to lemma A.1, $V < 1/2$, moreover, according to lemma A.2, $-\frac{1-V}{1-2V}a$ is a root of Q, that is

$$a = \frac{1 - 2V}{2V(1 - V)}\left((c + d + e)V + (1 - V)b + (-1)^q\sqrt{\Delta_Q}\right), \qquad q \in \{1, 2\},$$

where

$$\Delta_Q = (V(c + d + e) + (1 - V)b)^2 - 4V((1 - V)(d + e)b + Vce),$$
$$= ((-c + d + e)V - (1 - V)b)^2 + 4cdV^2.$$

Moreover, $F = \breve{Q}/\breve{P}$ where $\breve{P}$ and $\breve{Q}$ are coprime and

$$\breve{P}(X) = X^2 + \left(-\frac{1 - 2V}{1 - V}(c + d + e) + b - \frac{V}{1 - 2V}a\right)X + \frac{1 - 2V}{1 - V}ce,$$

$$\breve{Q}(X) = V\left(X + c + d + e + \frac{1 - V}{V}b - \frac{1 - V}{1 - 2V}a\right).$$

$F_x = F$ only if P_x and Q_x are not coprime, that is $-\frac{1-V}{1-2V}x_a$ is a root of Q_x

$$x_a = \frac{1 - V}{2V(1 - 2V)}\left((x_c + x_d + x_e)V + (1 - V)x_b + (-1)^{q_x}\sqrt{\Delta_{Q_x}}\right), \qquad q_x \in \{1, 2\},$$

where

$$\Delta_{Q_x} = (V(x_c + x_d + x_e) + (1 - V)x_b)^2 - 4V((1 - V)(x_d + x_e)x_b + Vx_cx_e),$$
$$= ((-x_c + x_d + x_e)V - (1 - V)x_b)^2 + 4x_cx_dV^2.$$

So that, $F_x = \breve{Q}_x/\breve{P}_x$ where $\breve{P}_x$ and $\breve{Q}_x$ are coprime and

$$\breve{P}_x(X) = X^2 + \left(-\frac{1 - 2V}{1 - V}(x_c + x_d + x_e) + x_b - \frac{V}{1 - 2V}x_a\right)X + \frac{1 - 2V}{1 - V}x_cx_e,$$

$$\breve{Q}_x(X) = V\left(X + x_c + x_d + x_e + \frac{1 - V}{V}x_b - \frac{1 - V}{1 - 2V}x_a\right).$$

Since $\breve{Q}_x/\breve{P}_x$ and $\breve{Q}/\breve{P}$ are irreducible and the leading coefficients of $\breve{P}_x$ and $\breve{P}$ are identical, as well as those of $\breve{Q}_x$ and $\breve{Q}$, $F_x = F$ only if $\breve{P}_x = \breve{P}$ and $\breve{Q}_x = \breve{Q}$. Hence, $F_x = F$ if and only if

$$V\left(\frac{1 - V}{1 - 2V}x_a\right)^2 + ((1 - V)(x_d + x_e)x_b + Vx_cx_e)$$

$$-(V(x_c + x_d + x_e) + (1 - V)x_b)\frac{1 - V}{1 - 2V}x_a = 0, \tag{19a}$$

$$x_cx_e = ce, \tag{19b}$$

$$-\frac{1 - 2V}{1 - V}(x_c + x_d + x_e) + x_b$$

$$-\frac{V}{1 - 2V}x_a = -\frac{1 - 2V}{1 - V}(c + d + e) + x_b - \frac{V}{1 - 2V}a, \tag{19c}$$

$$V(x_c + x_d + x_e) + (1 - V)x_b$$

$$-\frac{V(1 - V)}{1 - 2V}x_a = V(c + d + e) + (1 - V)b - \frac{V(1 - V)}{1 - 2V}a. \tag{19d}$$

Hence, doing (19d)$-(1 - V)$(19c) to replace (19c), followed by $(1 - V)$(19d)$-V$(19c) to replace (19d), we get

$$V\left(\frac{1 - V}{1 - 2V}x_a\right)^2 + ((1 - V)(x_c + x_e)x_b + Vx_dx_e)$$

$$-(V(x_c + x_d + x_e) + (1 - V)x_b)\frac{1 - V}{1 - 2V}x_a = 0, \tag{20a}$$

$$x_c x_e = ce, \tag{20b}$$

$$x_c + x_d + x_e = c + d + e, \tag{20c}$$

$$(1 - 2V)x_b - V x_a = (1 - 2V)b - V a. \tag{20d}$$

Replacing x_a in (20a) by $a + \frac{1 - 2V}{V}(x_b - b)$ given by (20d), we get

$$(x_c + h)x_b = \frac{V}{1 - V}(h^2 + (x_c + x_d + x_e)h + x_c x_e), \tag{21a}$$

$$x_c x_e = ce, \tag{21b}$$

$$x_c + x_d + x_e = c + d + e, \tag{21c}$$

$$(1 - 2V)x_b - V x_a = (1 - 2V)b - V a, \tag{21d}$$

where $h = \frac{1 - V}{V}b - \frac{1 - V}{1 - 2V}a$. Then, replacing $x_c + x_d + x_e$ by $c + d + e$ and $x_c x_e$ by ce in (21a), we get

$$\left(x_c + \frac{1 - V}{V}b - \frac{1 - V}{1 - 2V}a\right)x_b = \left(c + \frac{1 - V}{V}b - \frac{1 - V}{1 - 2V}a\right)b, \tag{22a}$$

$$x_c x_e = ce, \tag{22b}$$

$$x_c + x_d + x_e = c + d + e, \tag{22c}$$

$$(1 - 2V)x_b - V x_a = (1 - 2V)b - V a. \tag{22d}$$

The set of solutions $(x_a, x_b, x_c, x_d, x_e)$ to (22) is a curve given by the intersection of two cylindrical hypersurfaces over hyperbolas (22a, 22b) and two hyperplanes (22c, 22d). If $c + \frac{1 - V}{V}b - \frac{1 - V}{1 - 2V}a = 0$, the cylindrical hypersurface given by (22a) degenerates into two hyperplanes whose respective equations are $x_b = 0$ and $x_c = c$ so that the set of solutions of (22) is composed of the line of equations $(1 - 2V)x_b - V x_a = (1 - 2V)b - V a, x_c = c, x_d = d, x_e = e$ and the hyperbola of equations $x_a = 0, x_b = 0, x_c + x_d + x_e = c + d + e, x_c x_e = ce$. Considering the inverse problem, we thus have the following lemma

Lemma A.5. *If $V < 1/2$ and the polynomials P and Q are not coprime*

$$P(X) = X^3 + (a + b + c + d + e)X^2 + (ac + ad + ae + bd + be + ce)X + ace,$$

$$Q(X) = V X^2 + (V(c + d + e) + (1 - V)b)X + (V ce + (1 - V)(d + e)b),$$

then, if $c + \frac{1 - V}{V}b - \frac{1 - V}{1 - 2V}a = 0$, the set of solutions $(x_a, x_b, x_c, x_d, x_e)$ to the inverse problem is given by the open half-line of $\mathbb{R}^5$ of parametric equation

$$t \mapsto (a + (1 - 2V)t, b + V t, c, d, e), \qquad t \in \left(-\frac{b}{V}, +\infty\right).$$

Otherwise, the set of solutions $(x_a, x_b, x_c, x_d, x_e)$ to the inverse problem is given by the curve of $\mathbb{R}^5$ of parametric equation

$$t \mapsto \left(a + \frac{(1 - 2V)(c - t)b}{V t + (1 - V)b - \frac{V(1 - V)}{1 - 2V}a}, \frac{c + \frac{1 - V}{V}b - \frac{1 - V}{1 - 2V}a}{t + \frac{1 - V}{V}b - \frac{1 - V}{1 - 2V}a}b, t, c + d + e - t - \frac{ce}{t}, \frac{ce}{t}\right),$$

where

$$t \in \begin{cases} \left(\beta^-, \min\left(\beta^+, \dfrac{1-V}{1-2V}a + \dfrac{(1-2V)bc}{(1-2V)b - Va} \right) \right), & \text{if } Va - (1-2V)b < 0, \\[3ex] \left(\max\left(\dfrac{1-V}{1-2V}a - \dfrac{1-V}{V}b, \beta^- \right), \beta^+ \right), & \text{if } 0 \le Va - (1-2V)b < (1-2V)Vc, \\[3ex] \left(\beta^-, \min\left(\beta^+, \dfrac{1-V}{1-2V}a - \dfrac{1-V}{V}b \right) \right), & \text{if } (1-2V)Vc < Va - (1-2V)b, \end{cases}$$

where

$$\beta^{\pm} = \frac{c + d + e \pm \sqrt{(c+d+e)^2 - 4ce}}{2}.$$