Systems & Control Letters 208 (2026) 106309

Contents lists available at ScienceDirect

Systems & Control Letters

journal homepage: www.elsevier.com/locate/sysconle

System realizations by mammillary models with an application to propofol pharmacokinetics☆

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ARTICLE INFO

Keywords:
Positive systems
Positive realization
Pharmacokinetics
Mammillary models
Structured identification

ABSTRACT

This work addresses the problem of linear system realizations by mammillary and mammillary-like models, offering necessary and sufficient conditions under which a given transfer function can be represented in this form. Compartmental models, particularly mammillary ones, reflect the physiological dynamics of distribution and elimination. This is especially relevant in clinical pharmacology, where model parameters correspond to meaningful biological processes to support interpretability, personalization, and safe drug delivery, such as in total intravenous anesthesia. To conclude, an application to a propofol infusion model illustrates how mammillary realizations can support physiologically interpretable system representations.

1. Introduction

Compartmental systems are fundamental tools for modeling the dynamics of substance distribution and elimination within complex biological and pharmacological systems. They consist of a finite number of compartments that exchange material with each other. The transfer of material between compartments can be described by first-order ordinary differential equations, based on the principle of mass conservation. These models are commonly used to describe the distribution and elimination of a drug within a human body. In this context, a human body is modeled as a set of interconnected compartments, each representing regions or tissues of the body that behave similarly in terms of drug absorption, distribution, and elimination, with transfer rates characterizing the movement of the drug between compartments.

Such models are often designed under the assumption of mass conservation, meaning that any increase or decrease in the amount of substance within a compartment is fully accounted for by the flows between compartments and by explicit inputs or outputs (e.g., drug administration or elimination) [1].

Within this broad framework, mammillary compartmental models have emerged as especially significant [2]. These models are structured around a central compartment that interacts directly with peripheral compartments, which themselves do not exchange material directly. This configuration is highly relevant in pharmacokinetics, where mammillary models are widely employed to characterize drug absorption, distribution, and elimination, especially in clinical scenarios such as total intravenous anesthesia control [3,4].

1.1. Main results

Let

$$\begin{cases} \dot{x}(t) = Ax(t) + Bu(t) \\ y(t) = Cx(t), \end{cases} \tag{1}$$

be a continuous-time linear system with $A = (a_{ij}) \in \mathbb{R}^{n\times n}$, $B = (b_i) \in \mathbb{R}^{n\times 1}$, and $C = (c_j) \in \mathbb{R}^{1\times n}$. According to [1,2,5,6], (1) is said to be a *compartmental system* if, for $i, j \in \{1, \dots, n\}$,

$$b_i \geq 0 \quad c_j \geq 0 \tag{2}$$

$$a_{ij} \geq 0 \quad \text{for } i \neq j \tag{3}$$

$$a_{ii} + \sum_{j\neq i} a_{ji} \leq 0. \tag{4}$$

The usual physical interpretation is that, for $i \in \{1, \dots, n\}$, state variable $x_i(t)$ (the ith component of vector $x(t)$) represents the amount

☆ This work was supported by the PRIN 2022 Project "ACTIVA – Automatic Control of Total IntraVenous Anesthesia", funded by European Union – Next Generation EU under Grant CUP D53D23001180006.

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https://doi.org/10.1016/j.sysconle.2025.106309
Received 13 July 2025; Received in revised form 22 September 2025; Accepted 29 November 2025
Available online 3 December 2025

of resource present in the ith compartment at time t. Each diagonal element a_{ii} of matrix A represents the cumulative outgoing flows from the ith compartment, which accounts for material loss. Conversely, each off-diagonal element a_{ij}, for $i \neq j$, represents a constant incoming flow into the ith compartment coming from the jth one. Input $u(t)$ represents an external injection of material into the system and B determines how such material is distributed among the compartments. Output $y(t)$ represents the measured quantity of material in the system at time t, as determined by observation vector C. This reflects the amount of material present in one or more compartments, depending on which components of C are nonzero.

The following is a well-established property of compartmental systems (see, for instance, [7]).

Proposition 1.1. *Let A be the matrix associated with a compartmental system (i.e., let A satisfy (2)–(4)), and let λ be an eigenvalue of A. Then* $\mathrm{Re}(\lambda) \leq 0$.

A *mammillary model* is a compartmental system that consists of a central compartment connected to a set of peripheral ones. In this model, there is no material transfer between peripheral compartments, and all peripheral compartments exchange material with the central one.

In this work, we consider models with the following structure:

$$A = \left[\begin{array}{c|cccc} -k_{10} - \sum_{i=2}^{n} k_{1i} & k_{21} & k_{31} & \cdots & k_{n1} \\ \hline k_{12} & -k_{21} & 0 & \cdots & 0 \\ k_{13} & 0 & -k_{31} & \cdots & 0 \\ \vdots & \vdots & \vdots & \ddots & \vdots \\ k_{1n} & 0 & 0 & \cdots & -k_{n1} \end{array}\right] \in \mathbb{R}^{n\times n}, \tag{5}$$

$$B = [1, 0, \dots, 0]^T, \qquad C = B^T = [1, 0, \dots, 0].$$

We assume that all k_{i1}, with $i \in \{2, \dots, n\}$, are distinct.

Throughout this work, we assume that the parameters k_{i1}, for $i \in \{2, \dots, n\}$, are ordered so that $k_{21} < k_{31} < \cdots < k_{n1}$. Note that this ordering of the parameters is assumed without loss of generality, as there always exists a permutation of the states that realizes such an order.

For notational simplicity, let p be a vector collecting the parameters of A in (5) (i.e., the entries of A):

$$p := (k_{10}, k_{21}, \dots, k_{n1}, k_{12}, \dots, k_{1n}) \in \mathbb{R}^{2n-1}.$$

Observe that, if p is strictly positive, that is, if all its entries are strictly positive, then A, B, C in (5) satisfy conditions (2)–(4), and moreover, (5) is a mammillary model. On the other hand, if no positivity restrictions are imposed on p, we will refer to the system as *mammillary-like*.

The following property is known in the literature; however, for the sake of completeness, we provide a brief proof tailored to our specific case.

Proposition 1.2. *Let A be a matrix defined as in (5), with p strictly positive. If λ is an eigenvalue of A, then $\lambda \in \mathbb{R}$ and $\lambda \leq 0$.*

Proof. Since p is strictly positive, then A satisfies conditions (3) and (4), and, therefore, Proposition 1.1 holds. So we need only to prove that the eigenvalues of A are real.

Let D be a diagonal matrix of the following form

$$D = \begin{bmatrix} 1 & 0 & 0 & \cdots & 0 \\ 0 & \sqrt{k_{21}/k_{12}} & 0 & \cdots & 0 \\ 0 & 0 & \sqrt{k_{31}/k_{13}} & \cdots & 0 \\ \vdots & \vdots & \vdots & \ddots & \vdots \\ 0 & 0 & 0 & \cdots & \sqrt{k_{n1}/k_{1n}} \end{bmatrix}.$$

It is easy to compute $DAD^{-1} =: \tilde{A}$

$$\tilde{A} = \left[\begin{array}{c|cccc} -k_{10} - \sum_{i=2}^{n} k_{1i} & \sqrt{k_{21}k_{12}} & \sqrt{k_{31}k_{13}} & \cdots & \sqrt{k_{n1}k_{1n}} \\ \hline \sqrt{k_{21}k_{12}} & -k_{21} & 0 & \cdots & 0 \\ \sqrt{k_{31}k_{13}} & 0 & -k_{31} & \cdots & 0 \\ \vdots & \vdots & \vdots & \ddots & \vdots \\ \sqrt{k_{n1}k_{1n}} & 0 & 0 & \cdots & -k_{n1} \end{array}\right]. \tag{6}$$

Matrices $\tilde{A}$ and A are similar, therefore they have the same eigenvalues. Moreover, $\tilde{A}$ is symmetric, so all eigenvalues of $\tilde{A}$, and hence of A, are real. □

In the first part of this paper, we investigate a realization problem. Our objective is to derive necessary and sufficient conditions under which a given rational transfer function

$$H(s) := \frac{\beta(s)}{\alpha(s)},$$

with $\alpha(s) = s^n + \alpha_{n-1}s^{n-1} + \alpha_{n-2}s^{n-2} + \cdots + \alpha_1 s + \alpha_0$, $\alpha_i \in \mathbb{R}$, admits a realization of the form

$$H(s) = C(sI - A)^{-1}B,$$

where I denotes the $n \times n$ identity matrix, and A, B and C have the specific structure described in (5).

Note that we do not confine our analysis to the positive case, namely when p is strictly positive (mammillary case). Rather, we also extend the investigation to the setting where the structure is again given by (5), but without imposing positivity on p (mammillary-like case).

Recall that, in general,

$$C(sI - A)^{-1}B = \frac{C(sI - A)^{\mathrm{adj}}B}{\chi(s)},$$

where $\chi(s)$ denotes the characteristic polynomial of A, that is $\chi(s) = \det(sI - A)$.

Remark 1.3. Note that, if p is strictly positive, then it follows from Proposition 1.2 that all roots of $\chi(s)$ are real and non-positive.

The essential results regarding the realization problem described above are presented in the following two theorems. Theorem 1.4 addresses the general case, without imposing positivity on p, whereas Theorem 1.5 concerns the mammillary case, in which the positivity of p is required.

Theorem 1.4 (*Mammillary-like Case*)**.** *There exists a unique p such that*

$$C(sI - A)^{-1}B = H(s)$$

if and only if the following conditions hold:

1. *the relative degree of H is 1;*
2. *the numerator of H is a monic polynomial with simple, real, and nonzero roots.*

A consequence of Theorem 1.4 is the following.

Theorem 1.5 (*Mammillary Case*)**.** *There exists a unique, strictly positive p such that $H(s) = C(sI - A)^{-1}B$ if and only if the following conditions hold:*

1. *the relative degree of H is 1;*
2. *the numerator of H is a monic polynomial with simple, real, and strictly negative roots;*
3. *$H(0) > 0$;*
4. *the zeros and poles of H are interlacing.*

Moreover, Theorem 1.5 is equivalent to the following:

Theorem 1.6. *There exists a unique strictly positive p such that $T_p = H$ if and only if H is ZIP (Zeros-Interlacing-Poles).*

More precisely, following Definition 1 in [8], a transfer function

$$H(s) = K\frac{\prod_{j=1}^{n-1}(s+z_j)}{\prod_{i=1}^{n}(s+w_i)}, \text{ with } K>0,$$

is ZIP if and only if $0 < w_i < z_i < w_{i+1}$ for all $i \in \{1,\dots,n-1\}$.

As a consequence of Theorem 1.4, it is possible to derive an algorithm to determine the $2n-1$ parameters.

Algorithm for computing the parameters
Let $z_2 > z_3 > \cdots > z_n$ be the roots of $\beta(s)$.

$$k_{10} = \frac{\alpha(0)}{\beta(0)}$$
$$k_{i1} = -z_i, \qquad i \in \{2,\dots,n\}$$
$$k_{1i} = \frac{\alpha(z_i)}{\beta_i(z_i)}, \qquad i \in \{2,\dots,n-1\}.$$

Where

$$\beta_i(s) := z_i \cdot \widehat{\beta(s)}^{\,i}, \quad \widehat{\beta(s)}^{\,i} := \frac{\beta(s)}{s-z_i}.$$

In the last part of the paper, we apply this theoretical framework to the structured realization of a transfer function describing the intravenous infusion of propofol.

Specifically, in Section 3, starting from a generic transfer function, we will show – by employing techniques similar to those used in Section 1 and – that it is possible to construct a structured realization for the PK–PD model of propofol. This model consists of a third-order mammillary model of the form (5) (PK part), in cascade with a first-order filter (PD part) (see (23) for the structure of the model). In this case, however, we lose the uniqueness of the realization that is guaranteed in Theorems 1.4 and 1.5.

Following the approach used in the previous part, we first analyze the case without restrictions on the parameters (Theorem 3.1) and then consider the case where the parameters are strictly positive (Theorem 3.2), which reflects the actual characteristics of the propofol model.

Moreover, in Section 3.2, also in this case, we provide an algorithm to compute all possible positive realizations.

1.2. Literature review

In the context of continuous-time linear systems, a system of the form (1) is said to be *positive* if it satisfies conditions (2) and (3) alone (see, for instance, [9,10]). In literature, the Positive Realization Problem [11] is among the most studied and challenging issues in the field of positive systems. This problem deals with identifying necessary and sufficient conditions under which a given transfer function can be realized by a positive system (see, e.g., [12], Section 3 of [13], Section 5 of [14], and [15]).

Compartmental systems are a specific subclass within the broader category of positive systems (see, among others, [16–20]).

In particular, [5,21] focus on theorems that provide necessary and sufficient conditions under which a given transfer function corresponds to a compartmental system. For instance, Theorem 6 in [21] provides necessary and sufficient conditions for the realization of tree-compartmental systems.

Further results concerning more specific subclasses of positive systems can be found in [22–24]. Additionally, [25,26] provide necessary and sufficient conditions for a third-order transfer function with real poles to admit a third-order (minimal) positive realization. Further results on the positive realization problem can be found in [27–31]. For concise overviews of the established results on positive realization, see, for instance, the cornerstone Refs. [11,13], and [15]. Among various fields of application, positive realization theory has been recently applied to the study of Hessenberg forms of non-negative and Metzler matrices [32].

In this work, we focus on systems with the fixed structure (5). We analyze the realization problem both under the constraint that the parameters of A are strictly positive and without such a restriction. When no restriction is imposed on the parameters, the system will be referred to as *mammillary-like*. In the strictly positive case, the system is of mammillary type– a subclass of compartmental models – in which elimination occurs exclusively from the central compartment (the only elimination parameter is k_{10}, associated solely to the central compartment).

The case in which system (5) has all parameters strictly positive corresponds to a particular subclass of relaxation systems [8,33–39] which in turn are contained in the class of positive systems [11,13,15], themselves included in the more general class of externally positive systems [40–42]. The definition of relaxation systems is given in Definition 3 of [39], while that of externally positive systems can be found in Definition 3 of [42].

For a comparison with mammillary systems involving elimination from all compartments, see [43]. One may also consult [44] for a treatment of the identifiability problem in n-compartments linear mammillary and catenary models. Mammillary models are frequently adapted to describe the absorption, distribution, and elimination of drugs. For instance, they have been applied to model the pharmacokinetics of propofol, remifentanil, and rocuronium (see, e.g., [3,4,45,46]). Propofol and remifentanil are intravenous anesthetic agents commonly used for the induction and maintenance of general anesthesia (see, for instance, [3,4,45]) accounting for hypnosis and analgesia, respectively. Whilst rocuronium is a neuromuscular blocking agent used to facilitate endotracheal intubation and ensure muscle relaxation during surgical procedures (see, e.g., [46]). Additionally, mammillary models have been applied to the study of proteins metabolism kinetics in organisms, as shown in [47].

1.3. Statement of contribution

The proposed result addresses the realizability of a given transfer function with a specific model of the form (5).

We study the realizability problem under two different settings:

(i) (mammillary case) by requiring that all the parameters of the matrix A in (5) are strictly positive, which corresponds to a special case of the classical positive realization problem;

(ii) (mammillary-like case) without imposing such positivity constraints, that includes realizations with arbitrary real parameters.

For both problems, we provide necessary and sufficient conditions for realizability, and we prove that the corresponding realization is unique.

To the best of our knowledge, these results are novel and have not been previously explored in literature. Moreover, despite the demand of a quite specific system structure considered, the formulation of the necessary and sufficient conditions for realizability remains simple.

Recall that, in case (i), the considered mammillary system can be regarded as a subclass of relaxation systems (see Definition 3 in [39]), themselves included in the class of positive systems (they satisfy conditions (2) and (3)), and ultimately contained in the broader class of externally positive systems (see Definition 3 in [42]). Compared case (i) to existing results for relaxation, positive or externally positive systems, our conditions of realizability are more restrictive, reflecting the specific structure of the models under consideration.

The model considered in case (i) can also be viewed as a particular instance of compartmental systems. In particular, by comparing with [21], where the realization of tree-compartmental systems is discussed in Section V, it follows that Theorem 1.5 implies Theorem 6 of [21] in the case $n = 3$. This is not surprising, since we impose a specific mammillary structure, which is more restrictive than the general compartmental one, and therefore our conditions are correspondingly stronger.

A central contribution of our work is that, unlike previous results, especially on positive realizations, which typically ensure existence but not uniqueness, we establish that the realization is unique both for mammillary (i) and for mammillary-like systems (ii) of the form (5). Moreover, we present an explicit algorithm that uniquely computes the parameters of the realization.

Moreover, we prove necessary and sufficient conditions for obtaining a structured realization of the propofol PK–PD model, showing that, although uniqueness is lost, all possible realizations can be systematically computed through the algorithm we provide. We emphasize that the same reasoning and proofs developed, can be similarly applied to derive structured realizations of the remifentanil PK–PD model [3,45].

2. Proofs of the main results

Before proceeding to the proofs of Theorems 1.4 and 1.5 in the general case, we first focus on systems with 3 states. Although simpler and more intuitive, this case remains mathematically relevant and will play an important role in the development presented in Section 3.

2.1. The three-compartment case

We consider a continuous-time linear system of the form (5), in which $n = 3$:

$$A = \left[\begin{array}{c|cc} -k_{10}-k_{12}-k_{13} & k_{21} & k_{31} \\ \hline k_{12} & -k_{21} & 0 \\ k_{13} & 0 & -k_{31} \end{array}\right], \qquad (7)$$

$$B = [1,0,0]^T, \quad C = B^T = [1,0,0].$$

Notice again that if all the coefficients of A are strictly positive, the system represents a mammillary model (consisting of three compartments).

Let H be a given third order transfer function of the form $H(s) = \frac{\beta(s)}{\alpha(s)}$, where $\alpha(s) = s^3 + \alpha_2 s^2 + \alpha_1 s + \alpha_0$, with $\alpha_2, \alpha_1, \alpha_0 \in \mathbb{R}$. The goal is to find necessary and sufficient conditions under which H has a realization of the form $H(s) = C(sI - A)^{-1}B$, where I denotes the 3×3 identity matrix, and A, B, and C have the specific structure of (7).

This, in turn, will allow determining coefficients $k_{10}, k_{12}, k_{13}, k_{21}, k_{23}$, so that the following identity holds: $H(s) = C(sI - A)^{-1}B$.

In our case, we have that $C(sI - A)^{\text{adj}}B = \left(k_{21} + s\right)\left(k_{31} + s\right)$.

Moreover the denominator is given by

$$\chi(s) = \det \begin{bmatrix} k_{10}+k_{12}+k_{13}+s & -k_{21} & -k_{31} \\ -k_{12} & k_{21}+s & 0 \\ -k_{13} & 0 & k_{31}+s \end{bmatrix},$$

that is,

$$\begin{aligned}\chi(s) = s^3 &+ (k_{10}+k_{12}+k_{13}+k_{21}+k_{31})s^2 \\ &+ (k_{10}k_{21}+k_{13}k_{21}+k_{10}k_{31}+k_{12}k_{31}+k_{21}k_{31})s \\ &+ k_{10}k_{31}k_{21}.\end{aligned}$$

So

$$C(sI - A)^{-1}B = \frac{\left(k_{21} + s\right)\left(k_{31} + s\right)}{\chi(s)}. \qquad (8)$$

We now state a basic algebraic lemma, accompanied by a brief proof for the sake of completeness.

Lemma 2.1. *Two polynomials $p(x)$ and $q(x)$ of degree n are identically equal if and only if they coincide at least in $n+1$ distinct points.*

Proof. Let $r(x) = p(x) - q(x)$. Then $r(x)$ is a polynomial of degree at most n. Suppose $p(x_i) = q(x_i)$ for $n+1$ distinct points $x_1, x_2, \dots, x_{n+1}$. Then $r(x_i) = 0$, for all $i \in \{1, \dots, n+1\}$, that is, $r(x)$ has at least $n+1$ distinct zeros.

But a nonzero polynomial of degree at most n can have at most n distinct roots. Therefore, $r(x) \equiv 0$, and thus $p(x) \equiv q(x)$.

Conversely, if $p(x) \equiv q(x)$, then they clearly coincide at all points, including $n+1$ distinct ones. □

Corollary 2.2. *Two monic polynomials $p(x)$ and $q(x)$ of degree n are identically equal if and only if they coincide at least n distinct points.*

We now proceed to prove the following result in the case where (7) is a mammillary-like model, that is, without imposing restrictions on the signs of the coefficients of A.

Theorem 2.3. *There exist unique k_{10}, k_{12}, k_{13}, k_{21}, k_{23} such that $H(s) = C(sI - A)^{-1}B$, if and only if the following conditions hold:*

1. *the relative degree of H is 1;*
2. *the numerator β of H is a monic polynomial with simple, real, and nonzero roots.*

Proof.

(⇐) By hypothesis, $\beta(s) = (s - z_2)(s - z_3)$, where z_2 and z_3 are distinct, real and nonzero roots of $\beta(s)$. Without loss of generality, we assume $z_2 > z_3$. Clearly, $H(s) = C(sI - A)^{-1}B$ if and only if $\beta(s) = (k_{21} + s)(k_{31} + s)$ and $\alpha(s) = \chi(s)$. Equating the numerators, we get

$$k_{21} = -z_2 \quad \text{and} \quad k_{31} = -z_3. \qquad (9)$$

By Corollary 2.2, since both $\alpha(s)$ and $\chi(s)$ have leading coefficient equal to 1, to ensure that $\chi(s) = \alpha(s)$, we impose the following three conditions: $\chi(0) = \alpha(0)$, $\chi(z_2) = \alpha(z_2)$, and $\chi(z_3) = \alpha(z_3)$. From the first condition, we obtain $k_{10} = \frac{\alpha(0)}{k_{21}\,k_{31}}$, that is, by Eqs. (9),

$$k_{10} = \frac{\alpha(0)}{z_2\, z_3}. \qquad (10)$$

From the second condition we get $k_{12} = \frac{\alpha(z_2)}{k_{21}\,(k_{21} - k_{31})}$, that is, again, by (9),

$$k_{12} = \frac{\alpha(z_2)}{z_2\,\left(z_2 - z_3\right)}. \qquad (11)$$

From the third condition, we get $k_{13} = -\frac{\alpha(z_3)}{k_{31}\,(k_{21} - k_{31})}$, that is, again, by (9)

$$k_{13} = -\frac{\alpha(z_3)}{z_3\,\left(z_2 - z_3\right)}. \qquad (12)$$

(⇒) Condition (1) is trivial. Condition (2) is necessary for Eqs. (10), (11), and (12) to hold. □

Note that, from conditions (10)–(12), the five parameters of the model, $k_{10}, k_{12}, k_{13}, k_{21}$, and k_{23}, are uniquely determined.

For simplicity, we present the algorithm resulting from the previous proof to compute the coefficients.

Algorithm for computing the 5 parameters
Let $z_2 > z_3$ be the roots of $\beta(s)$.

$$k_{10} = \frac{\alpha(0)}{z_2 z_3},$$

$$k_{12} = \frac{\alpha(z_2)}{z_2\,\left(z_2 - z_3\right)}, \qquad k_{13} = -\frac{\alpha(z_3)}{z_3\,\left(z_2 - z_3\right)},$$

$$k_{21} = -z_2, \qquad k_{31} = -z_3.$$

The following result, which follows directly from Theorem 2.3 and is derived from Eqs. (9)–(12), concerns the case where (7) is a mammillary system, that is, when the coefficients of A are strictly positive.

Theorem 2.4. *There exist unique k_{10}, k_{12}, k_{13}, k_{21}, k_{23}, all positive, such that $H(s) = C(sI - A)^{-1}B$ if and only if the following conditions hold:*

1. *the relative degree of H is 1;*
2. *the numerator β of H is a monic polynomial with simple, real, and strictly negative roots;*
3. *$\alpha(0) > 0$, $\alpha(z_2) < 0$ and $\alpha(z_3) > 0$, where z_2 and z_3 are the roots of β, with $z_2 > z_3$.*

Observe that condition (3) implies that polynomial $\alpha(s)$ has real and negative roots, in agreement with Remark 1.3. Indeed, from condition (3) it follows that $\alpha(s)$ admits two distinct negative real roots: one located between 0 and z_2, and the other between z_2 and z_3.

Moreover, since $\alpha(s) = s^3 + \alpha_2 s^2 + \alpha_1 s + \alpha_0$, we have $\alpha(s) \to -\infty$ as $s \to -\infty$. Therefore, the third root of $\alpha(s)$ must also be a negative real number, lying to the left of z_3.

2.2. General case

We shall now address the general case, namely, consider the following system

$$A_p = \left[\begin{array}{c|cccc} -k_{10} - \sum_{i=2}^{n} k_{1i} & k_{21} & k_{31} & \cdots & k_{n1} \\ \hline k_{12} & -k_{21} & 0 & \cdots & 0 \\ k_{13} & 0 & -k_{31} & \cdots & 0 \\ \vdots & \vdots & \vdots & \ddots & \vdots \\ k_{1n} & 0 & 0 & \cdots & -k_{n1} \end{array}\right], \qquad (13)$$

$$B = [1, 0, \dots, 0]^T, \qquad C = B^T = [1, 0, \dots, 0].$$

where $p = (k_{10}, k_{2,1}, \dots, k_{n,1}, k_{1,2}, \dots, k_{1,n}) \in \mathbb{R}^{2n-1}$ is the set of parameters of (13). The transfer function of (13) is

$$T_p(s) = \frac{(s + k_{2,1})(s + k_{3,1}) \cdots (s + k_{n,1})}{\chi_p(s)},$$

where $\chi_p(s) = \det(sI - A_p)$.

Let $n_p(s) := (s + k_{2,1})(s + k_{3,1}) \cdots (s + k_{n,1})$ be the numerator of $T_p(s)$.

Moreover let $n_{p,i}(s) := -k_{i1}\, \widehat{n_p(s)}^{\,i}$, where $\widehat{n_p(s)}^{\,i}$ is merely the polynomial $n_p(s)$ without the factor $(s + k_{i1})$, that is, $\widehat{n_p(s)}^{\,i} := \frac{n_p(s)}{(s+k_{i1})}$.

With this in mind, it follows that

$$\chi_p(0) = n_p(0) k_{10}, \qquad (14)$$

and

$$\chi_p(-k_{i,1}) = k_{1i}\, n_{p,i}(s) \quad \text{with } i \in \{2, \dots, n\}. \qquad (15)$$

Now let $H(s) = \frac{\beta(s)}{\alpha(s)}$ be a given transfer function of order n, where $\alpha(s) = s^n + \alpha_{n-1} s^{n-1} + \alpha_{n-2} s^{n-2} + \cdots + \alpha_1 s + \alpha_0$, with $\alpha_i \in \mathbb{R}$, for $i \in \{0, 1, \dots, n-1\}$.

The generalization of Theorem 2.3 is the following one.

Theorem 2.5. *There exists unique p such that $T_p = H$ if and only if the following conditions hold:*

1. *the relative degree of H is 1;*
2. *the numerator of H is a monic polynomial with simple, real, and nonzero roots.*

Proof.

($\Leftarrow$) By assumption, the numerator of H is given by

$$\beta(s) = (s - z_2)(s - z_3) \cdots (s - z_n),$$

that is, $\beta(s)$ has $n-1$ distinct, real, and nonzero roots. Without loss of generality, we assume that the roots are ordered in the following way: $z_2 > z_3 > \cdots > z_n$. Clearly, $T_p = H$ holds if and only if the numerators and denominators are equal. So, set $k_{i1} = -z_1$, for $i \in \{2, 3, \dots, n\}$, where z_i are the roots of β, that is,

$$k_{21} = -z_2, \; k_{31} = -z_3, \; \dots \; k_{n1} = -z_n. \qquad (16)$$

Then, the numerator of T_p is equal to that of H.

Note that, by Corollary 2.2, $\alpha = \chi_p$ if and only if

$$\alpha(0) = \chi_p(0), \alpha(z_i) = \chi_p(z_i), \quad \text{for } i \in \{2, \dots, n\}.$$

From the first condition and by (14), it follows that

$$\beta(0) k_{10} = \alpha(0), \qquad (17)$$

whose solution provides

$$k_{10} = \frac{\alpha(0)}{\beta(0)}. \qquad (18)$$

From the remaining conditions and by (15), it follows that, for $i \in \{2, \dots, n\}$,

$$k_{1i} \beta_i(z_i) = \alpha(z_i), \qquad (19)$$

where

$$\beta_i(s) := z_i \widehat{\beta(s)}^{\,i} \qquad (20)$$

is a polynomial of degree $n-1$, and $\widehat{\beta(s)}^{\,i}$ is $\beta(s)$ without the factor $(s - z_i)$, that is

$$\widehat{\beta(s)}^{\,i} := \frac{\beta(s)}{(s - z_i)}.$$

The solution of (19) provides

$$k_{1,i} = \frac{\alpha(z_i)}{\beta_i(z_i)}, \quad \text{for } i \in \{2, \dots, n-1\}. \qquad (21)$$

Note that the denominators in (18) and (21) are nonzero because of the assumptions on β.

($\Rightarrow$) Condition (1) is trivial. Condition (2) is necessary to solve Eqs. (17) and (19). □

The following is a direct consequence of Theorem 2.5, taking into account Eqs. (16), (18) and (21).

Theorem 2.6. *There exists a unique, strictly positive p such that $T_p = H$ if and only if the following conditions hold:*

1. *the relative degree of H is 1;*
2. *the numerator of H is a monic polynomial with simple, real, and strictly negative roots;*
3. *$H(0) > 0$;*
4. *for any root z_i of β, $\frac{\beta_i(z_i)}{\alpha(z_i)} > 0$, where β_i is defined as in (20).*

Observe that if p is strictly positive, condition (3) $H(0) > 0$ is automatically satisfied. However, the requirement $H(0) > 0$ is necessary in order to obtain the converse implication of Theorem 2.6 (conditions (1), (2) and (4) alone do not imply that p is strictly positive).

Notice that condition (4) corresponds to the interlacing property of the poles and zeros of $H(s)$ in a ZIP system. Therefore, Theorem 2.6 can also be reformulated in its simpler version, as in Theorem 1.5.

Note that conditions (1)–(4) together are equivalent to stating that the system is ZIP.

Therefore, Theorem 2.6 is equivalent to the following result:

Theorem 2.7. *There exists a unique strictly positive p such that $T_p = H$ if and only if H is ZIP.*

3. Application to pharmacokinetic - pharmacodynamic models

3.1. Model formulation

Anesthesia is essential in modern medicine as it ensures that patients receive surgical procedures and invasive treatments without pain, anxiety, or fear, while also protecting them from physical and psychological trauma. Propofol is one of the most widely used hypnotic agents due to its potency, rapid redistribution, and metabolism, which ensures quick onset and short duration of action [4]. Additionally, when properly dosed, it causes minimal side effects [48].

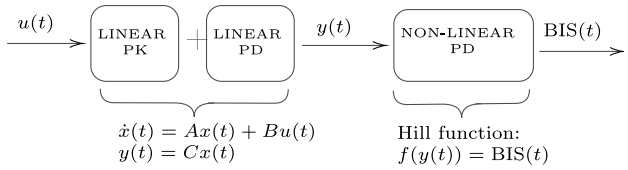

Fig. 1. Schematic representation of the PK–PD Wiener model of propofol.

To represent intravenously administered propofol, the considered model is a pharmacokinetic–pharmacodynamic (PK–PD) one with a Wiener structure, meaning it consist of a linear component (a mammillary model) followed by a static nonlinearity (a Hill function) [4]. The PK describes the drug concentration trajectory inside a human body, whereas the PD studies the physiological effects of the drug, and its mechanisms of action. Usually, the Hill function represents the Bispectral Index (BIS), which is a numerical value derived from electroencephalogram (EEG) signals. It is commonly used in anesthesiology and it quantifies a patient's level of consciousness, with values ranging from 100 (fully awake) to 0 (no cortical activity).

For a visual representation, consider the schematic diagram in Fig. 1.

The aspect of the model that we focus on in this work is its linear component. For propofol, the linear part of the Wiener model is represented by a mammillary model, more precisely, its infusion is accurately described by a three-compartment PK model of form (7), complemented by an additional effect-site compartment that captures the PD response.

The three compartments of the PK part are the primary, the fast, and the slow ones, each representing different physiological sites of drug distribution. The primary compartment encompasses the blood and liver, where the drug undergoes distribution and metabolism. The fast compartment corresponds to tissues with a rapid rate of drug uptake, such as muscles and viscera. The slow compartment represents tissues with a slower drug distribution, including fat and bones. The model can be represented by the following system of differential equations:

$$\begin{cases} \dot{q}_1(t) &= -(k_{10}+k_{12}+k_{13})q_1(t) \\ & \quad +k_{21}q_2(t)+k_{13}q_3(t)+u(t) \\ \dot{q}_2(t) &= k_{12}q_1(t)-k_{21}q_2(t) \\ \dot{q}_3(t) &= k_{13}q_1(t)-k_{31}q_3(t) \\ \dot{C}_e(t) &= k_{1e}\left(\frac{q_1(t)}{V_1}\right)-k_{e0}C_e(t). \end{cases} \tag{22}$$

Input u is the mass flow of the infused propofol, expressed in mg/s. Variables q_1, q_2 and q_3 are the drug masses, expressed in mg, in the primary, fast and slow compartments, respectively. Variable C_e is the drug concentration in the effect-site compartment, expressed in mg/L. The system has seven, strictly positive, patient-dependent parameters: k_{12}, k_{13}, k_{21}, k_{31}, k_{1e}, k_{10}, and k_{e0}. More precisely the drug transfer rates between compartments, expressed in 1/s, are k_{12}, k_{13}, k_{21}, k_{31}, and k_{1e}. The drug elimination rate from the primary compartment and from the effect-site compartment, expressed in 1/s, are k_{10} and k_{e0}, respectively. Finally V_1 is the volume, expressed in L, of the primary compartment.

System (22) can be rewritten in the continuous-time state-space form of (1), in which $x(t) = \left[q_1(t), q_2(t), q_3(t), C_e(t)\right]^T$ and $y(t) = C_e(t)$, where

$$A = \left[\begin{array}{ccc|c} -k_{10}-k_{12}-k_{13} & k_{21} & k_{31} & 0 \\ k_{12} & -k_{21} & 0 & 0 \\ k_{13} & 0 & -k_{31} & 0 \\ \hline k_{1e}/V_1 & 0 & 0 & -k_{e0} \end{array}\right] \in \mathbb{R}^{4\times 4}, \tag{23}$$

$$B = [1,0,0,0]^T \quad \text{and} \quad C = [0,0,0,1].$$

A schematic diagram of the linear part of the Wiener model of propofol is provided in Fig. 2.

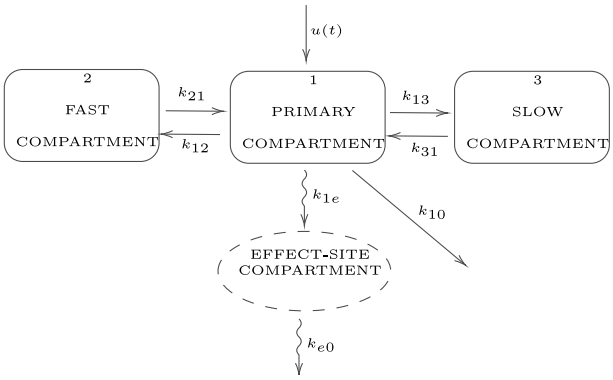

Fig. 2. Schematic representation of the linear PK–PD compartmental model of propofol.

Note that the upper-left 3×3 submatrix of A in (23):

$$A_{3\times 3} := \begin{bmatrix} -k_a & k_{21} & k_{31} \\ k_{12} & -k_{21} & 0 \\ k_{13} & 0 & -k_{31} \end{bmatrix}, \tag{24}$$

is of form (7).

A natural question that may arise is: why k_{1e} does not appear among the outgoing flows from the primary compartment? More specifically, why $a_{11} = -(k_{10}+k_{12}+k_{13})$, rather than $-(k_{10}+k_{12}+k_{13}+k_{1e})$?

The reason is that the effect-site compartment does not represent a PK compartment but rather serves as a PD extension designed to account for the lag in the effect of the drug. Notably, the drug entering the effect-site compartment is not eliminated from the body; instead, it remains available in the blood. Therefore, k_{1e} does not represent a loss of the drug from the primary compartment. This is why it does not appear in a_{11}.

In fact, only matrix $A_{3\times 3}$ of (24) characterizes the PK system consisting of three compartments: primary, fast, and slow.

3.2. Realization of the model

We consider the continuous-time linear system in (23). Let H be a given fourth order transfer function of the form $H(s) = \frac{\beta(s)}{\alpha(s)}$, where $\alpha(s) = s^4 + \alpha_3 s^3 + \alpha_2 s^2 + \alpha_1 s + \alpha_0$, with $\alpha_0, \alpha_1, \alpha_2 \in \mathbb{R}$.

Our aim is to find necessary and sufficient conditions under which H, admits a realization of the form $H(s) = C(sI - A)^{-1}B$, where I denotes the 4×4 identity matrix, and A, B, and C have the specific structure of (23). As a result, the coefficients $k_{10}, k_{12}, k_{13}, k_{21}, k_{23}, \frac{k_{1e}}{V_1}, k_{e0}$ of (23) can be determined so that $H(s) = C(sI - A)^{-1}B$. Observe that the following equality holds:

$$C(sI-A)^{-1}B = \frac{\frac{k_{1e}}{V_1}(s+k_{21})(s+k_{31})}{(s+k_{e0})(s^3+\mu_2 s^2+\mu_1 s+\mu_0)},$$

where

$$\mu_2 = k_{10}+k_{12}+k_{13}+k_{21}+k_{31}, \tag{25}$$

$$\mu_1 = k_{10}k_{21}+k_{13}k_{21}+k_{10}k_{31}+k_{12}k_{31}+k_{21}k_{31}, \tag{26}$$

$$\mu_0 = k_{10}k_{21}k_{31}. \tag{27}$$

To simplify the notation, we let

$$\chi(s) := (s+k_{e0})(s^3+\mu_2 s^2+\mu_1 s+\mu_0),$$
$$\Xi(s) := (s^3+\mu_2 s^2+\mu_1 s+\mu_0).$$

Notice that $C(sI - A)^{-1}B$ is nothing but the product of Eq. (8) and the transfer function of a first-order low-pass filter of the form $\frac{k_{1e}}{V_1}\frac{1}{(s+k_{e0})}$.

We first state the most general theorem, where no positivity assumptions are imposed on the parameters. We then consider, as a particular case, the model with strictly positive parameters that effectively reflects the structure of the propofol PK–PD model.

Theorem 3.1. *There exist k_{10}, k_{12}, k_{13}, k_{21}, k_{23}, $\frac{k_{1e}}{V_1}$, k_{e0} such that $H(s) = C(sI - A)^{-1}B$ if and only if the following conditions hold:*

1. *the relative degree of H is 2;*
2. *the numerator of H has simple, real, and nonzero roots;*
3. *the denominator of H has at least one real root.*

Proof.

($\Leftarrow$) By hypothesis, $\beta(s) = k(s-z_2)(s-z_3)$, where z_2 and z_3 are distinct, real and nonzero roots of $\beta(s)$. Without loss of generality, we assume $z_2 > z_3$.
Clearly, $H(s) = C(sI-A)^{-1}B$ if and only if $\beta(s) = \frac{k_{1e}}{V_1}(k_{21}+s)(k_{31}+s)$ and $\alpha(s) = \chi(s)$.
Equating the numerators, we get

$$\frac{k_{1e}}{V_1} = k, \quad k_{21} = -z_2, \quad \text{and} \quad k_{31} = -z_3. \tag{28}$$

Let z_0 be the real root of $\alpha(s)$, as stated in condition 3). This implies that $\alpha(s)$ can be written in the form $\alpha(s) = (s - z_0)\,a(s)$, where $a(s)$ is a monic polynomial of degree 3.
Equating the numerators, we get

$$k_{e0} = -z_0. \tag{29}$$

We still have to show that $a(s) = \Xi(s)$. By Corollary 2.2, since both $a(s)$ and $\Xi(s)$ are monic polynomials, to ensure that $a(s) = \Xi(s)$, we impose, as in Theorem 2.5 the following three conditions: $a(0) = \Xi(0)$, $a(z_2) = \Xi(z_2)$, and $a(z_3) = \Xi(z_3)$. From the first condition, we obtain $k_{10} = \frac{a(0)}{k_{21}\,k_{31}}$, that is, by Eqs. (28),

$$k_{10} = \frac{a(0)}{z_2\,z_3}. \tag{30}$$

From the second condition we get $k_{12} = \frac{a(z_2)}{k_{21}\,(k_{21}-k_{31})}$, that is, again by (28),

$$k_{12} = \frac{a(z_2)}{z_2\,\left(z_2 - z_3\right)}, \tag{31}$$

and, from the third condition, we get $k_{13} = -\frac{a(z_3)}{k_{31}\,(k_{21}-k_{31})}$, that is, again by (28),

$$k_{13} = -\frac{a(z_3)}{z_3\,\left(z_2 - z_3\right)}. \tag{32}$$

($\Rightarrow$) Condition (1) is trivial. Condition (2) is necessary for Eqs. (30)–(32) to hold. Condition (3) is necessary to get Eq. (29). □

The following result follows directly from Theorem 3.1, derived from Eqs. (28)–(32).

Theorem 3.2. *There exist k_{10}, k_{12}, k_{13}, k_{21}, k_{23}, $\frac{k_{1e}}{V_1}$, k_{e0} all positive such that $H(s) = C(sI - A)^{-1}B$ if and only if the following conditions hold:*

1. *the relative degree of H is 2;*
2. *the numerator of H has simple, real, negative, and nonzero roots, and its leading coefficient is positive;*
3. *the denominator $\alpha(s)$ of $H(s)$ has at least one real and negative root z_0, that is $\alpha(s) = (s - z_0)\,a(s)$;*
4. *$a(0) > 0$, $a(z_2) < 0$ and $a(z_3) > 0$, where z_2 and z_3 are the roots of β, with $z_2 > z_3$.*

Note that conditions (3) and (4) imply that denominator $\alpha(s)$ has only negative real roots. Thus, from condition (29), it can be observed that up to four different positive realizations are possible. This depends on which of the four roots of $\alpha(s)$ is assigned to z_0 and consequently to filter k_{e0}. Therefore, the parameters are not uniquely determined. In case of multiple positive realization, one could, for instance, choose the pole z_0 that is the closest to the one indicated in Schnider's model [4].

For the sake of completeness, we briefly report the algorithm to compute the parameters of the positive realizations.

Algorithm for computing the 7 parameters of all positive realizations

Let $\beta(s) = k(s - z_2)(s - z_3)$, with $z_2 > z_3$.

$$\frac{k_{1e}}{V_1} = k, \quad k_{21} = -z_2, \quad k_{31} = -z_3$$

For any pole z_0 of $H(s)$, let $\alpha(s) = (s - z_0)\,a(s)$ and set

$$k_{e0} = -z_0, \qquad k_{10} = \frac{a(0)}{z_2 z_3},$$

$$k_{12} = \frac{a(z_2)}{z_2(z_2 - z_3)}, \qquad k_{13} = -\frac{a(z_3)}{z_3(z_2 - z_3)}.$$

If k_{10}, k_{12}, k_{13} are all strictly positive, keep this solution, otherwise discard it.

Note that k_{10}, k_{12}, k_{13} are all strictly positive if and only if condition (4) of Theorem 3.2 holds.

3.3. Numerical example

From a practical perspective, all parameters of matrix A of (23) are strictly positive in the context of propofol infusion.

We consider a hypothetical female patient, aged 40 years, with a height of 163 cm and a weight of 54 kg. Using these data, we apply the Schnider model [4] to obtain the corresponding parameters

$$\begin{aligned}
\tfrac{k_{1e}}{V_1} &= 0.0018\\
k_{21} &= 0.0011\\
k_{31} &= 0.0001\\
k_{e0} &= 0.0077\\
k_{10} &= 0.0065\\
k_{12} &= 0.0063\\
k_{13} &= 0.0033,
\end{aligned}$$

and the corresponding transfer function $H(s)$, which is given by:

$$H(s) = \frac{0.001792s^2 + 2.099\times10^{-6}s + 1.168\times10^{-10}}{s^4 + 0.02482s^3 + 0.000143s^2 + 8.963\times10^{-8}s + 3.232\times10^{-12}}$$

We now aim to carry out the inverse process using Theorem 3.2: given the transfer function H, we seek to recover the patient-specific parameters. As we shall see, this procedure leads us back to the parameters of the Schnider model, but not exclusively, as the inversion is not unique. Let us proceed by verifying when H satisfies conditions (1), (2), (3), and (4) therein.

Rewriting H to explicitly express the roots of the numerator and the denominator, yields the following form:

$$H(s) = \frac{0.0018(s + 0.0001)(s + 0.0011)}{(s + 0.0165)(s + 0.0077)(s + 6.6830\times10^{-4})(s + 3.8401\times10^{-5})}$$

Condition (1) is trivial. The numerator of H has simple, real, and strictly negative roots, which, following the notation of the theorem, we denote by z_2 and z_3, with $z_2 > z_3$: specifically, $z_2 = -0.0001$ and $z_3 = -0.0011$. Moreover, its leading coefficient is positive: $k = 0.0018$. Therefore, condition (2) is satisfied.

The denominator of $H(s)$ has real negative roots: -0.0165, -0.0077, -6.6830×10^{-4}, and -3.8401×10^{-5}. Hence, it can be expressed in the form $\alpha(s) = (s - z_0)\,a(s)$, and depending on the choice of z_0, we must verify if condition (4) is satisfied.

We fix $z_0 = -0.0165$. Then, polynomial $a(s)$ is given by $a(s) = (s + 0.0077)(s + 6.6830 \times 10^{-4})(s + 3.8401 \times 10^{-5})$. We observe that

$$a(0) = 1.9632 \times 10^{-10} > 0,$$
$$a(z_2) = a(-0.0001) = -9.3239 \times 10^{-11} < 0,$$
$$a(z_3) = a(-0.0011) = 3.1266 \times 10^{-9} > 0.$$

Therefore, condition (4) is satisfied. From Eqs. (28)–(32), we then obtain:

$$\frac{k_{1e}}{V_1} = 0.0018,\ k_{21} = -z_2 = 0.0001,\ k_{31} = -z_3 = 0.0011,$$
$$k_{e0} = -z_0 = 0.0165, \qquad k_{10} = \frac{a(0)}{z_2\, z_3} = 0.0030,$$
$$k_{12} = \frac{a(z_2)}{z_2\,(z_2 - z_3)} = 0.0015, \quad k_{13} = -\frac{a(z_3)}{z_3\,(z_2 - z_3)} = 0.0027.$$

Proceeding in a similar manner, by fixing $z_0 = -0.0077$, condition (4) is again satisfied. And the resulting values are:

$$\frac{k_{1e}}{V_1} = 0.0018$$
$$k_{21} = 0.0001$$
$$k_{31} = 0.0011$$
$$k_{e0} = 0.0077$$
$$k_{10} = 0.0065$$
$$k_{12} = 0.0033$$
$$k_{13} = 0.0063.$$

Note that this solution yields exactly the parameters of the Schnider model, but with k_{21} exchanged with k_{31} and k_{12} exchanged with k_{13}. This arises from the initial assumption that $k_{21} < z_{31}$.

Remark 3.3. Note that, actually, if the assumed ordering $k_{21} < k_{31}$ is reversed, that is if we modify Eqs. (28) by setting $k_{31} = -z_2$ and $k_{21} = -z_3$, we obtain

$$\frac{k_{1e}}{V_1} = k, \quad k_{21} = -z_3, \quad k_{31} = -z_2, \quad k_{e0} = -z_0,$$
$$k_{10} = \frac{a(0)}{z_2\, z_3}, \quad k_{12} = -\frac{a(z_3)}{z_3\,(z_2 - z_3)}, \quad k_{13} = \frac{a(z_2)}{z_2\,(z_2 - z_3)}.$$

Hence, compared to the initial case, k_{21} and k_{31} as well as k_{12} and k_{13} are interchanged.

Instead, by fixing $z_0 = -6.6830 \times 10^{-4}$ or $z_0 = -3.8401 \times 10^{-5}$, condition (4) is not satisfied; therefore, a positive realization cannot be achieved. This is not so surprising since these two values are very far from the one indicated in the Schnider's model [4] for k_{e0}.

4. Conclusions

We studied the problem of linear systems realization through mammillary and mammillary-like models and derived necessary and sufficient conditions under which a given transfer function admits such a realization (that is unique). Compared to standard identification techniques, which may offer limited physical interpretability, mammillary models provide a structured framework aligned with the physiological mechanisms of material distribution and elimination. This property is particularly important in clinical contexts, where model interpretability and parameter meaning are essential for safe and personalized therapeutic interventions. The application to a propofol infusion model highlights the practical relevance of the proposed framework for obtaining physiologically meaningful models.

CRediT authorship contribution statement

Veronica Beltrami: Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Software, Resources, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Luca Consolini:** Writing – review & editing, Supervision, Methodology, Funding acquisition. **Mattia Laurini:** Writing – review & editing. **Marco Milanesi:** Writing – review & editing. **Michele Schiavo:** Writing – review & editing. **Antonio Visioli:** Writing – review & editing, Supervision, Funding acquisition.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

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