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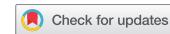
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Identifiability of linear compartmental models: the effect of moving inputs, outputs, and leaks

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ABSTRACT

A mathematical model is identifiable if its parameters can be recovered from data. Here we investigate, for linear compartmental models, whether (local, generic) identifiability is preserved when parts of the model – specifically, inputs, outputs, leaks, and edges – are moved, added, or deleted. Our results are as follows. First, for certain catenary, cycle, and mammillary models, moving or deleting the leak preserves identifiability. Next, for cycle models with up to one leak, moving inputs or outputs preserves identifiability. Thus, every cycle model with up to one leak (and at least one input and at least one output) is identifiable. Next, we give conditions under which adding leaks renders a cycle model unidentifiable. Finally, for certain cycle models with no leaks, adding specific edges again preserves identifiability. Our proofs, which are algebraic and combinatorial in nature, rely on results on elementary symmetric polynomials and the theory of input-output equations for linear compartmental models.

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1. Introduction

Linear compartmental models are a staple in many biological fields, including pharmacology, ecology, and cell biology. These models describe how something, whether it be drug concentration or toxins, moves within a system. In this work, we focus on the (local, generic) *identifiability* of linear compartmental models, that is, the ability to recover flow parameters from data.

Our motivation is the work of Gross, Harrington et al. [1], which investigated the effect on identifiability of adding or deleting some component – an input, output, leak, or edge – of a linear compartmental model. Two key problems that they raised are as follows. First, it is not well understood which edges can be added to a model so that identifiability is preserved [1, Table 2]. Second, the effect of removing a leak remains an open question: the authors conjectured that removing a leak from certain models preserves identifiability [1, Conjecture 4.5].

Here we address both problems: we resolve the leak-removal conjecture for three infinite families of models (Theorem 3.2), and prove that adding certain edges to a cycle model

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Table 1. Summary of results on operations preserving identifiability.

Linear compartmental model	Operation	Result
Catenary, cycle, or mammillary with $In = Out = \{1\}$, $Leak = \emptyset$	Add 1 leak	Theorem 3.2
Cycle with $ In = Out = 1$ and $Leak = \emptyset$	Add 1 leak, move input, move output	Theorem 3.4
	Add all incoming edges	Theorem 3.13
	Add all outgoing edges	
	Add 1 incoming edge	Theorem 3.17
	Add 1 or 2 outgoing edges	

Note: For a strongly connected linear compartmental model M with at least one input, if \tilde{M} is obtained from M by the specified operation, and M is identifiable, then \tilde{M} is identifiable. Related prior results, from [2], are summarized in Proposition 2.8. Results on how the operation of adding leaks causes identifiability to be lost appear in Section 3.3.

preserves identifiability (Theorems 3.13 and 3.17). We also analyze how the position and number of leaks affects identifiability (Theorem 3.10). Finally, by analyzing a new operation on models – namely, moving the output – we prove that every cycle model with up to one leak, at least one input, and at least one output (in any compartment) is identifiable (Theorem 3.4). Our main results are summarized in Table 1.

Our work fits into the larger goal of determining how properties of ODE systems defined by graphs are affected by operations on the graphs. See, for instance, recent work on a property closely related to identifiability, namely, observability [3].

Our proofs harness the theory of input-output equations for linear compartmental models [1, 4–8]. As a result, our analyzes are largely linear-algebraic and combinatorial. For instance, we apply results on elementary symmetric polynomials.

This paper is structured as follows. Section 2 introduces the definitions and tools we use throughout the rest of the paper. In Section 3, we state and prove our main results. We end with a discussion in Section 4.

2. Background

We begin with some definitions and important preliminary results, following the notation of [7]. Specifically, we focus on linear models and identifiability.

2.1. Linear compartmental models

A *linear compartmental model* consists of a directed graph $G = (V, E)$, and three sets, In , Out , $Leak \subseteq V$, which are the Input, Output, and Leak compartments, respectively (a *compartment* is a vertex $i \in V$). Each edge $j \rightarrow i$ in E represents the flow or transfer of material from the j th compartment to the i th compartment, with associated parameter (rate constant) k_{ij} . Each leak compartment $j \in Leak$ also has an associated parameter, k_{0j} , the rate constant for the outflow or degradation from that compartment.

Next, each input compartment has an external input, $u_i(t)$, which fuels the system. The output compartments, on the other hand, are measurable: we are able to know the concentration in these compartments. We always assume $Out \neq \emptyset$, as models without outputs are not identifiable.

Figure 1(a) depicts an n -compartment cycle model, with $In = Out = Leak = \{1\}$. The input compartment is labelled by ‘in’, the output is indicated by an edge with an empty circle at the end, also labelled with ‘out’, and the leak has an outgoing edge labelled by the

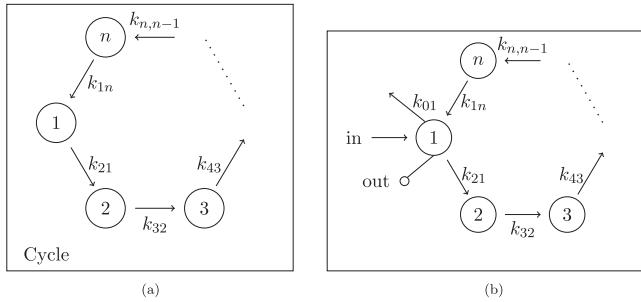


Figure 1. The cycle graph with n compartments (cf. [9, Figure 2]), and a linear compartmental model arising from this graph (with $In = Out = Leak = \{1\}$). (a) The cycle graph and (b) A cycle model.

leak parameter k_{01} . To drive some intuition, Figure 1(b) could model the flow of a drug in the body. Compartment 1 is the injection site, like an arm or thigh. The input is the shot. The output represents a device that measures how much drug is still in the injection site. The other compartments could represent organs; so, the drug goes from the injection site, to, e.g. the heart, the lungs, etc., and then back to the injection site.

We recall several more definitions:

Definition 2.1: (1) A directed graph is *strongly connected* if there exists a directed path from each vertex to every other vertex. A directed graph G with n vertices is *inductively strongly connected* with respect to vertex 1 if there exists a reordering of the vertices that preserves vertex 1, such that, for $i = 1, 2, \dots, n$, the induced subgraph $G_{\{1, 2, \dots, i\}}$ is strongly connected.
 (2) A linear compartmental model $(G, In, Out, Leak)$ is *strongly connected* (respectively, *inductively strongly connected* with respect to vertex 1) if G is strongly connected (respectively, inductively strongly connected with respect to vertex 1).

For instance, for $n \geq 3$, the cycle model in Figure 1(b) is strongly connected but not inductively strongly connected.

Definition 2.2: The *compartmental matrix* of a linear compartmental model $(G, In, Out, Leak)$ with n compartments is the $n \times n$ matrix A given by:

$$A_{ij} := \begin{cases} -k_{0i} - \sum_{p:i \rightarrow p \in E} k_{pi} & \text{if } i = j \text{ and } i \in \text{Leak} \\ -\sum_{p:i \rightarrow p \in E} k_{pi} & \text{if } i = j \text{ and } i \notin \text{Leak} \\ k_{ij} & \text{if } j \rightarrow i \text{ is an edge of } G \\ 0 & \text{otherwise} \end{cases}$$

Furthermore, a linear compartmental model defines the following system of linear ODE's, with inputs $u_i(t)$ and outputs $y_i(t)$, where $x(t) = (x_1(t), x_2(t), \dots, x_n(t))$ is the

vector of concentrations of the compartments at time t :

$$x'(t) = Ax(t) + u(t) \quad (1)$$

$$y_i(t) = x_i(t) \quad \text{for } i \in \text{Out}, \quad (2)$$

where $u_i(t) = 0$ for $i \notin \text{In}$.

Notation 2.1: Throughout this work, we let $(B)_{ji}$ denote the submatrix obtained from a matrix B by removing row j and column i .

2.2. Input-output equations

For linear compartmental models, *input-output equations* are equations that hold along every solution of (1)–(2), where only the parameters k_{ij} , the input variables u_i , the output variables y_j , and their derivatives are involved. The following general formulation of these equations comes from Meshkat et al. [7, Theorem 2] (see also [1, Remark 2.7]):

Proposition 2.3: *Let $M = (G, \text{In}, \text{Out}, \text{Leak})$ be a linear compartmental model with n compartments and at least one input. Define ∂I to be the $n \times n$ matrix in which each diagonal entry is the differential operator d/dt and each off-diagonal entry is 0. Let A be the compartmental matrix. Then, the following equations (for $i \in \text{Out}$) are input-output equations for M :*

$$\det(\partial I - A)y_i = \sum_{j \in \text{In}} (-1)^{i+j} \det((\partial I - A)_{ji}) u_j, \quad (3)$$

where $(\partial I - A)_{ji}$ is the matrix obtained from $(\partial I - A)$ by removing row j and column i .

From the input-output equations (3), we derive a *coefficient map*, denoted by $c : \mathbb{R}^{|E|+|\text{Leak}|} \rightarrow \mathbb{R}^m$, which evaluates each vector of parameters $(k_{ij})_{(j,i) \in E, \text{or } i=0 \text{ and } j \in \text{Leak}}$ at the vector of non-monic coefficients of the input-output equations. Here, m denotes the number of such coefficients. To give a formula for this number, directly from the model, remains an open question.

Example 2.4: For the cycle model shown in Figure 2, the compartmental matrix is:

$$A = \begin{bmatrix} -k_{21} & 0 & 0 & k_{14} \\ k_{21} & -k_{32} & 0 & 0 \\ 0 & k_{32} & -k_{43} & 0 \\ 0 & 0 & k_{43} & -k_{14} \end{bmatrix}.$$

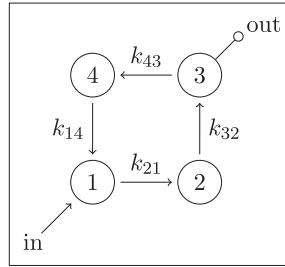


Figure 2. A 4-compartment cycle model with $In = \{1\}$, $Out = \{3\}$, and $Leak = \emptyset$.

We have $|Out| = 1$, so there is a single input-output equation (3):

$$\begin{aligned} & \det \left(\begin{bmatrix} \frac{d}{dt} + k_{21} & 0 & 0 & -k_{14} \\ -k_{21} & \frac{d}{dt} + k_{32} & 0 & 0 \\ 0 & -k_{32} & \frac{d}{dt} + k_{43} & 0 \\ 0 & 0 & -k_{43} & \frac{d}{dt} + k_{14} \end{bmatrix} \right) y_3 \\ &= \det \left(\begin{bmatrix} -k_{21} & \frac{d}{dt} + k_{32} & 0 \\ 0 & -k_{32} & 0 \\ 0 & 0 & \frac{d}{dt} + k_{14} \end{bmatrix} \right) u_1, \end{aligned}$$

which simplifies as follows:

$$\begin{aligned} & y_3^{(4)} + y_3^{(3)}(k_{14} + k_{21} + k_{32} + k_{43}) \\ &+ y_3^{(2)}(k_{14}k_{21} + k_{14}k_{32} + k_{21}k_{32} + k_{14}k_{43} + k_{21}k_{43} + k_{32}k_{43}) \\ &+ y_3^{(1)}(k_{14}k_{21}k_{32} + k_{14}k_{21}k_{43} + k_{14}k_{32}k_{43} + k_{21}k_{32}k_{43}) \\ &= u_1^{(1)}(k_{21}k_{32}) + u_1(k_{14}k_{21}k_{32}). \end{aligned}$$

Thus, the coefficient map $c : \mathbb{R}^4 \rightarrow \mathbb{R}^5$ is given by:

$$\begin{aligned} (k_{21}, k_{32}, k_{43}, k_{14}) \mapsto & (k_{14} + k_{21} + k_{32} + k_{43}, k_{14}k_{21} + k_{14}k_{32} + k_{21}k_{32} \\ &+ k_{14}k_{43} + k_{21}k_{43} + k_{32}k_{43}, \\ & k_{14}k_{21}k_{32} + k_{14}k_{21}k_{43} + k_{14}k_{32}k_{43} + k_{21}k_{32}k_{43}, k_{21}k_{32}, k_{14}k_{21}k_{32}). \end{aligned}$$

2.3. Identifiability

A model is (structurally) *identifiable* if all parameters k_{ij} can be recovered from data [10, 11]. More precisely, for an identifiable model, we can derive the values of the parameters

from perfect (noise-free) input-data and output-data (arising from generic initial conditions). Returning to the injection analogy from the last subsection, the question is: If we know the amount of injected drug and the amount of drug still present in the injection site at any time, *can we determine the rate at which the drug transfers from one organ to the next?*

There are several kinds of identifiability, but we focus on *generic local identifiability*. To determine whether a model is generically locally identifiable, we analyze coefficient maps. That is, the following definition of identifiability (for strongly connected models with at least one input) is equivalent to the definition above; this equivalence was proved

by Ovchinnikov et al. [8, Corollary 3.2].¹

Definition 2.5: Let $M = (G, In, Out, Leak)$ be a linear compartmental model that is strongly connected and has at least one input. Let $c : \mathbb{R}^{|E|+|Leak|} \rightarrow \mathbb{R}^m$ denote the coefficient map arising from the input-output equations (3). Then M is *generically locally identifiable* if, outside a set of measure zero, every point in $\mathbb{R}^{|E|+|Leak|}$ is in some open neighbourhood U such that the restriction $c|_U : U \rightarrow \mathbb{R}^k$ is one-to-one.

Next, we state some prior results that we will use. The following, due to Meshkat et al. [7, Proposition 2], is key to many of our proofs.

Proposition 2.6: A linear compartmental model $(G, In, Out, Leak)$, with $G = (V, E)$, is generically locally identifiable if and only if the rank of the Jacobian matrix of its coefficient map c , when evaluated at a generic point, is equal to $|E| + |Leak|$.

Example 2.7 (Example 2.4, continued): We show that the model from Example 2.4 is generically locally identifiable, by proving that the Jacobian matrix of its coefficient map generically has rank $|E| + |Leak| = 4$. Denote the first four non-monic coefficients as follows:

$$\begin{aligned} e_1 &= k_{14} + k_{21} + k_{32} + k_{43} \\ e_2 &= k_{14}k_{21} + k_{14}k_{32} + k_{14}k_{43} + k_{21}k_{32} + k_{21}k_{43} + k_{32}k_{43} \\ e_3 &= k_{14}k_{21}k_{32} + k_{14}k_{21}k_{43} + k_{14}k_{32}k_{43} + k_{21}k_{32}k_{43} \\ \kappa &= k_{21}k_{32}. \end{aligned}$$

For the (4×4) -submatrix of the Jacobian matrix arising from rows indexed by e_1, e_2, e_3, κ and columns $k_{21}, k_{32}, k_{43}, k_{14}$, the determinant is a nonzero polynomial in the k_{ij} 's:

$$-(k_{32} - k_{21})(k_{14} - k_{43}) \left((k_{14} - k_{32})(k_{32} - k_{43}) + k_{14}k_{21} - k_{21}^2 - k_{21}k_{32} + k_{21}k_{43} \right).$$

So, by Proposition 2.6, the model is generically locally identifiable.

The following result combines [1, Proposition 4.1, Proposition 4.6, and Theorem 4.3].

Proposition 2.8: Let M be a linear compartmental model that is strongly connected and has at least one input. Assume that one of the following holds:

- (1) M has no leaks, and \tilde{M} is a model obtained from M by adding one leak;

- (2) \tilde{M} is a model obtained from M by adding one input or one output; or
- (3) M has an input, an output, and a leak in a single compartment (and no other inputs, outputs, or leaks), and \tilde{M} is the model obtained from M by removing the leak.

Then, if M is generically locally identifiable, then so is \tilde{M} .

Remark 2.1: Most models we consider have at most one leak. So, by Proposition 2.8, to prove identifiability, it will suffice to analyze the input-output equations of models without leaks. For such models, in the left-hand side of the input-output equation (3), the constant term is 0 (e.g. see Example 2.4). Indeed, this term is, up to sign, the determinant of the compartmental matrix A , which (if there are no leaks) has 0 column sums.

We end this section by recalling from [7, 12] an important class of models that are identifiable when all leaks (or all but one) are removed (see Proposition 3.3).

Definition 2.9: A linear compartmental model $M = (G, In, Out, Leak)$, with $G = (V, E)$, is an *identifiable cycle model* if (1) G is strongly connected, (2) $In = Out = \{1\}$, (3) $Leak = V$, and (4) the dimension of the image of the coefficient map is $|E| + 1$.

When conditions (1)–(3) in Definition 2.9 hold, and also the equality $|E| = 2|V| - 2$, then a sufficient criterion for condition (4) to hold is that the graph G is inductively strongly connected with respect to vertex 1 [12] (c.f. [7, Remark 1]).

2.4. Elementary symmetric polynomials

We will use the following lemma to prove identifiability results in the next section.

Lemma 2.10: Let n be a positive integer. For $1 \leq m \leq n$, let e_m be the m th elementary symmetric polynomial on a set of variables $X = \{x_1, x_2, \dots, x_n\}$. Let $J(V)$ denote the Jacobian matrix of $V := \{e_1, e_2, \dots, e_n\}$ with respect to x_1, x_2, \dots, x_n . Then $\det J(V)$ is a nonzero polynomial in the x_i 's.

Proof: For $1 \leq m \leq n$, the m th elementary symmetric polynomial on X is as follows:

$$e_m = \sum_{j_1 < j_2 < \dots < j_m} x_{j_1} \dots x_{j_m} = \sum_{\substack{j_2 < \dots < j_m \\ j_k \neq i}} x_i(x_{j_2} \dots x_{j_m}) + \sum_{\substack{l_1 < \dots < l_m \\ l_k \neq i}} x_{l_1} \dots x_{l_m},$$

for any $1 \leq i \leq n$. Thus, taking the partial derivative with respect to x_i yields:

$$\frac{\partial e_m}{\partial x_i} = \sum_{\substack{j_2 < \dots < j_m \\ j_k \neq i}} x_{j_2} \dots x_{j_m} = e_{m-1}\{\hat{x}_i\}, \quad (4)$$

where $e_{m-1}\{\hat{x}_i\}$ is the $(m-1)$ -st elementary symmetric polynomial on the set $X \setminus \{x_i\}$. Hence, the Jacobian matrix of V is as follows:

$$J(V) = \begin{bmatrix} 1 & 1 & \dots & 1 \\ e_1\{\hat{x}_1\} & e_1\{\hat{x}_2\} & \dots & e_1\{\hat{x}_n\} \\ \vdots & \vdots & \ddots & \vdots \\ e_{n-1}\{\hat{x}_1\} & e_{n-1}\{\hat{x}_2\} & \dots & e_{n-1}\{\hat{x}_n\} \end{bmatrix}.$$

Finally, by Equation (5) in the proof of [7, Theorem 5.1], $\det(J(V))$ equals, up to sign, the *Vandermonde polynomial* on X , which is nonzero: $\det(J(V)) = \pm \prod_{1 \leq i < j \leq n} (x_i - x_j)$. ■

Remark 2.2: An alternate proof of Lemma 2.10 is as follows. The Jacobian matrix of n polynomials in n unknowns is nonzero if and only if the polynomials are algebraically independent [13, Theorem 2.3]. And the algebraic independence of the elementary symmetric polynomials is known [14, p. 20].

3. Results

In this section we present our main results. In Section 3.1, we recall a conjecture on removing leaks [1] and then prove the conjecture for three infinite families of models (Theorem 3.2). Next, in Section 3.2, we investigate a new operation: moving the input and output. We prove that every cycle model with up to one leak, at least one input, and at least one output is identifiable (Theorem 3.4). In Section 3.3, we give a partial converse to this result by analyzing how the number and location of leaks affects whether a cycle model is identifiable. Lastly, in Section 3.4, we show that adding certain edges to cycle models preserves identifiability (Theorem 3.17).

3.1. Adding or removing a leak

The following was posed by Gross et al. [1, Conjecture 4.5]:

Conjecture 3.1 (Removing a leak): Let \tilde{M} be a linear compartmental model that is strongly connected and has at least one input and exactly one leak. If \tilde{M} is generically locally identifiable, then so is the model M obtained from \tilde{M} by removing the leak.

The next result resolves Conjecture 3.1 for three infinite families of models, which we introduce now. A *catenary model* is a linear compartmental model $(G, In, Out, Leak)$ for which G is the catenary graph in Figure 3(a) (for some n). Similarly, a *cycle model* (respectively, a *mammillary model*) arises from the graph in Figure 1(a) (respectively, Figure 3(b)). All three families of models are among the most common in the literature [15–19].

Theorem 3.2: Let \tilde{M} be a catenary, cycle, or mammillary model that has exactly one input and exactly one output, both in the first compartment, and exactly one leak. Then \tilde{M} is generically locally identifiable and so is the model M obtained by removing the leak.

Proof: Proposition 4.7 from [1] states that the models M in the statement of the theorem, with no leaks, are generically locally identifiable. Then, by Proposition 2.8, adding a leak preserves identifiability. Thus, both M and \tilde{M} are generically locally identifiable. ■

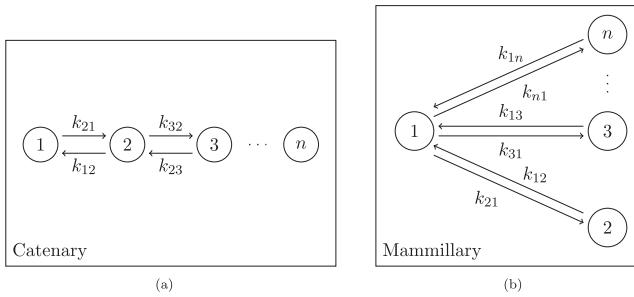


Figure 3. Two graphs with n compartments (cf. [9, Figures 1–2]). (a) The catenary graph and (b) The mammillary graph.

In other words, for every catenary, mammillary, or cycle model with input and output in the first compartment, identifiability is preserved when the leak is moved or deleted. Other models for which identifiability is preserved when the leak is moved, are those obtained by deleting all but one leak from an ‘identifiable cycle model’ [7, Theorem 1]. Also, for identifiability analysis of catenary and mammillary models where some of the parameters are already known, we refer the reader to [19].

Remark 3.1: For the part of Theorem 3.2 concerning models with one leak, another approach to the proof is via [12, Section 5] and [7, Theorem 1], or (for mammillary models) through [18, Theorem 5.1]. For the part of the theorem on catenary and mammillary models with no leaks, another proof is given in [20, Sections 3.1 and 4.1].

We end this subsection with a result that combines two prior results.

Proposition 3.3: *Let M be a linear compartmental model obtained from an identifiable cycle model by removing all leaks or removing all leaks except one. Then M is generically locally identifiable.*

Proof: Any such model with one leak is generically locally identifiable, by [7, Theorem 1]. In particular, the model with $\text{Leak} = \{1\}$ is identifiable (and strongly connected), and so Proposition 2.8.3 implies that removing the leak preserves identifiability. ■

3.2. Moving inputs and outputs

In the previous subsection, we investigated whether identifiability is preserved when a leak is moved or removed. Now we consider other operations: moving inputs and outputs. We show that these operations preserve identifiability in cycle models (in such models, moving the input is equivalent to moving the output). As a consequence, we obtain the main result of this subsection, Theorem 3.4, which states that every cycle model with at most one leak (and at least one input and at least one output) – such as those considered in Examples 2.4 and 2.7 – is identifiable.

Theorem 3.4: *Assume² $n \geq 3$. Let M be an n -compartment cycle model with at least one input, at least one output, and at most one leak. Then M is generically locally identifiable.*

In the next subsection, we prove a partial converse to Theorem 3.4 (see Theorem 3.7).

We prove Theorem 3.4 at the end of this subsection by using the next two propositions. For the proofs of those propositions, recall that $(A)_{ji}$ denotes the submatrix obtained by removing row j and column i from matrix A .

Proposition 3.5: *Assume $n \geq 3$. For an n -compartment cycle model with $In = \{1\}$, $Out = \{p\}$ for some $p \neq 1$, and $Leak = \emptyset$, the coefficient map $c : \mathbb{R}^n \rightarrow \mathbb{R}^{2n-p}$ is given by:*

$$(k_{21}, k_{32}, \dots, k_{1n}) \longmapsto (e_1, e_2, \dots, e_{n-1}, \kappa, e_1^* \kappa, \dots, e_{n-p}^* \kappa),$$

where $\kappa := \prod_{i=2}^p k_{i,i-1}$, and e_j and e_j^* denote the j th elementary symmetric polynomial on the sets $E = \{k_{21}, \dots, k_{n,n-1}, k_{1n}\}$ and $E^* = \{k_{p+2,p+1}, \dots, k_{n,n-1}, k_{1n}\}$, respectively.

Proof: In the indices, we let $n+1 := 1$. By Proposition 2.3, the input-output equation is

$$\det(\partial I - A)y_p = (-1)^{p+1} \det(\partial I - A)_{1p} u_1, \quad (5)$$

where A is the compartmental matrix. The $n \times n$ matrix $A' := (\partial I - A)$ is as follows:

$$A' = \begin{bmatrix} \frac{d}{dt} + k_{21} & 0 & \dots & 0 & -k_{1n} \\ -k_{21} & \frac{d}{dt} + k_{32} & 0 & \dots & 0 \\ 0 & \ddots & \ddots & & \vdots \\ \vdots & & -k_{i,i-1} & \frac{d}{dt} + k_{i+1,i} & \vdots \\ 0 & \dots & 0 & -k_{n,n-1} & \frac{d}{dt} + k_{1n} \end{bmatrix}. \quad (6)$$

We compute the determinant by expanding along the first row:

$$\begin{aligned} \det A' &= \left(\frac{d}{dt} + k_{21} \right) \det (A')_{11} + (-1)^{n-1} (-k_{1n}) \det (A')_{1n} \\ &= \left(\frac{d}{dt} + k_{21} \right) \prod_{i=2}^n \left(\frac{d}{dt} + k_{i+1,i} \right) - k_{1n} \prod_{j=2}^n k_{j,j-1} \\ &= \prod_{i=1}^n \left(\frac{d}{dt} + k_{i+1,i} \right) - \prod_{j=1}^n k_{j+1,j}. \end{aligned} \quad (7)$$

Here, we used the fact that the matrix $(A')_{11}$ is lower triangular and the matrix $(A')_{1n}$ is upper triangular, so each determinant is just the products of the diagonal entries.

Next, we simplify equation (7) by recalling that the e_j 's denote the elementary symmetric polynomial on E :

$$\det(A') = \frac{d^n}{dt^n} + e_1 \frac{d^{n-1}}{dt^{n-1}} + \cdots + e_{n-1} \frac{d}{dt}.$$

Thus, the left-hand side of the input-output equation (5) is:

$$\det(A')y_p = y^{(n)} + e_1 y_p^{(n-1)} + \cdots + e_{n-1} y_p^{(1)},$$

and so the first $(n - 1)$ coefficients stated in the proposition are correct.

We now turn our attention to the remaining coefficients, those on the right-hand side of the input-output equation (5). It is straightforward to check, using (6), that the matrix $(A')_{1p}$ can be written as a block matrix:

$$(A')_{1p} = \begin{bmatrix} B & 0 \\ 0 & C \end{bmatrix},$$

where B is an upper-triangular, $(p - 1) \times (p - 1)$ matrix with diagonal entries $-k_{21}, -k_{32}, \dots, -k_{p,p-1}$, and C is a lower-triangular, $(n - p) \times (n - p)$ matrix with the diagonal entries $\frac{d}{dt} + k_{p+2,p+1}, \dots, \frac{d}{dt} + k_{n,n-1}, \frac{d}{dt} + k_{1,n}$. Thus,

$$\det(A')_{1p} = (\det B)(\det C) = (-1)^{p-1} \left(\prod_{i=2}^p k_{i,i-1} \right) \prod_{j=p+1}^n \left(\frac{d}{dt} + k_{j+1,j} \right). \quad (8)$$

Similar to before, the product of the binomials in (8) can be expressed in terms of elementary symmetric polynomials, this time on E^* :

$$\prod_{j=p+1}^n \left(\frac{d}{dt} + k_{j+1,j} \right) = \left(\frac{d}{dt} \right)^{n-p} + e_1^* \left(\frac{d}{dt} \right)^{n-p-1} + \cdots + e_{n-p-1}^* \frac{d}{dt} + e_{n-p}^*. \quad (9)$$

Using (8) with (9), we obtain the right-hand side of the input-output equation (5):

$$(-1)^{p+1} \det(\partial I - A)_{1p} u_1 = \prod_{i=2}^p k_{i,i-1} \left(\frac{d}{dt}^{n-p} + e_1^* \frac{d}{dt}^{n-p-1} + \cdots + e_{n-p}^* \right) u_1. \quad (10)$$

By inspection, the coefficients of (10) match the last $(n - p + 1)$ coefficients stated in the proposition, and so this completes the proof. \blacksquare

Proposition 3.6: *Assume $n \geq 3$. Let M be an n -compartment cycle model with no leaks, exactly one input, and exactly one output. Then M is generically locally identifiable.*

Proof: By relabelling, we may assume that $In = \{1\}$. Let p denote the output compartment. If $p = 1$, then the model M is generically locally identifiable by Theorem 3.2.

Now assume $p \neq 1$. By Proposition 2.6, we must show that the Jacobian matrix of the coefficient map is generically full rank. By Proposition 3.5, the coefficient map $c : \mathbb{R}^n \rightarrow \mathbb{R}^{2n-p}$ is given by $(k_{21}, k_{32}, \dots, k_{n,n-1}, k_{1n}) \mapsto (e_1, e_2, \dots, e_{n-1}, \kappa, e_1^* \kappa, \dots, e_{n-p}^* \kappa)$, where

$\kappa := \prod_{i=2}^p k_{i,i-1}$. Thus, the Jacobian matrix of c is an $n \times (2n - p)$ matrix (with $2 \leq p \leq n$), and so we must show that an $(n \times n)$ submatrix has nonzero determinant.

To see this, it suffices to show (recall Remark 2.2) that $e_1, e_2, \dots, e_{n-1}, \kappa$ are algebraically independent. To start, the elementary symmetric polynomials e_1, e_2, \dots, e_{n-1} are algebraically independent (recall Remark 2.2). Now assume for contradiction that $\kappa = \prod_{i=2}^p k_{i,i-1}$ is algebraic over the field $\mathbb{F} := \mathbb{C}(e_1, e_2, \dots, e_{n-1})$. Then, by symmetry, the product of any $p-1$ distinct elements of the set $\{k_{21}, k_{32}, \dots, k_{n,n-1}, k_{1n}\}$ is also algebraic over \mathbb{F} . By a straightforward combinatorial argument, the product of all such products is $(e_n)^{\binom{n-1}{p-2}}$, so e_n is algebraic over $\mathbb{F} = \mathbb{C}(e_1, e_2, \dots, e_{n-1})$. This is a contradiction (see Remark 2.2). \blacksquare

We now prove the main result of this subsection.

Proof of Theorem 3.4: By Proposition 3.6, the models with no leaks, exactly one input, and exactly one output are generically locally identifiable. Also, by Proposition 2.8, adding one leak, one or more inputs, and/or one or more outputs preserves identifiability. \blacksquare

3.3. Adding leaks to a cycle model

In the previous subsection, we saw that cycle models with one input, one output, and at most one leak are identifiable (Theorem 3.4). Here we present a partial converse (Theorem 3.7), which we prove at the end of the subsection.

Theorem 3.7: *Assume $n \geq 3$. Let M be an n -compartment cycle model with input and output in the same compartment (and no other inputs or outputs). Then, M is generically locally identifiable if and only if $|\text{Leak}| \leq 1$.*

Our proof of Theorem 3.7 relies on an analysis of how the number and relative position of the leaks affects identifiability – even when the input and output compartments are distinct (see Theorem 3.10). We begin by computing the relevant coefficient map (Proposition 3.8), which can be viewed as the $\text{Leak} \neq \emptyset$ analogue of Proposition 3.5.

Proposition 3.8: *Assume $n \geq 3$. Let M be an n -compartment cycle model with $\text{In} = \{1\}$, $\text{Out} = \{p\}$ (for some $1 \leq p \leq n$), and $\text{Leak} = \{i_1, i_2, \dots, i_t\} \neq \emptyset$. Then the coefficient map $c : \mathbb{R}^{n+t} \rightarrow \mathbb{R}^{2n-p+1}$ is given by*

$$(k_{21}, k_{32}, \dots, k_{1,n}, k_{0,i_1}, k_{0,i_2}, \dots, k_{0,i_t}) \mapsto \left(e_1, e_2, \dots, e_{n-1}, e_n - \prod_{i=1}^n k_{i+1,i}, \kappa, e_1^* \kappa, \dots, e_{n-p}^* \kappa \right)$$

where $\kappa := \prod_{i=2}^p k_{i,i-1}$, and e_j and e_j^* denote the j th elementary symmetric polynomial on the sets $E = \{k_{\ell+1,\ell} \mid \ell \in \{1, \dots, n\} \setminus \text{Leak}\} \cup \{k_{\ell+1,\ell} + k_{0,\ell} \mid \ell \in \text{Leak}\}$ and $E^* = \{k_{\ell+1,\ell} \mid p+1 \leq \ell \leq n, \ell \notin \text{Leak}\} \cup \{k_{\ell+1,\ell} + k_{0,\ell} \mid p+1 \leq \ell \leq n, \ell \in \text{Leak}\}$, respectively.

Proof: The matrix $\partial I - A$ is obtained from the matrix (6) by adding, for each leak $\ell \in \text{Leak}$, the term $k_{0\ell}$ to the ℓ th diagonal entry. The rest of the proof is now completely analogous to the proof of Proposition 3.5. \blacksquare

It follows from Proposition 3.8 that a cycle model with too many leaks is unidentifiable.

Proposition 3.9: *Assume $n \geq 3$. Let M be an n -compartment cycle model with $In = \{1\}$ and $Out = \{p\}$ (for some $1 \leq p \leq n$). If $|Leak| \geq n - p + 2$, then M is not generically locally identifiable.*

Proof: Assume $|Leak| \geq n - p + 2$. It follows that $n + |Leak| > 2n - p + 1$, and so the coefficient map $\mathbb{R}^{n+|Leak|} \rightarrow \mathbb{R}^{2n-p+1}$ (from Proposition 3.8) is not finite-to-one, even outside a measure-zero set. Thus, by definition, M is not generically locally identifiable. ■

Similarly, the location of the leaks may make a cycle model unidentifiable.

Theorem 3.10: *Assume $n \geq 3$. Let M be an n -compartment cycle model with $In = \{1\}$ and $Out = \{p\}$ (for some $1 \leq p \leq n$). If there exist leaks $i, j \in \text{Leak}$ (with $i \neq j$) such that $i, j \geq p$, then M is not generically locally identifiable.*

Proof: For this model, the coefficient map $c : \mathbb{R}^{n+|Leak|} \rightarrow \mathbb{R}^{2n-p+1}$ is given in Proposition 3.8. Let J denote the $(2n - p + 1) \times (n + |Leak|)$ Jacobian matrix of c .

Assume that there exist two leaks $i, j \geq p$. It follows that $\kappa = \prod_{\ell=2}^p k_{\ell, \ell-1}$ does not contain any of the following as factors: $k_{i+1, i}, k_{0i}, k_{j+1, j}, k_{0j}$. Now it is straightforward to check from the coefficient map that, for each coefficient c_ℓ , except for the coefficient $e_n - \prod_{i=1}^n k_{i+1, i}$, the partial derivatives satisfy the following equalities:

$$\frac{\partial c_\ell}{\partial k_{i+1, i}} = \frac{\partial c_\ell}{\partial k_{0i}} \quad \text{and} \quad \frac{\partial c_\ell}{\partial k_{j+1, j}} = \frac{\partial c_\ell}{\partial k_{0j}}.$$

Thus, the columns of J corresponding to $k_{i+1, i}$ and k_{0i} , which we denote by $C_{i+1, i}$ and C_{0i} , respectively, are identical in every coordinate, except the one corresponding to the coefficient $e_n - \prod_{i=1}^n k_{i+1, i}$. Thus, the vector $C_{i+1, i} - C_{0i}$ has 0 in all but one coordinate. By the same argument, $C_{j+1, j} - C_{0j}$ is 0 in all but the same coordinate.

Thus, the four columns $C_{i+1, i}, C_{0i}, C_{j+1, j}, C_{0j}$ of the Jacobian matrix J are linearly dependent. We conclude that J is not full rank, and so the model M is not generically locally identifiable. ■

We end this subsection by analyzing two cases when identifiability of a cycle model is characterized by the number of leaks.

Corollary 3.11: *Assume $n \geq 3$. Let M be an n -compartment cycle model with Input = $\{i\}$ and Output = $\{i - 1 \bmod n\}$ (for some $1 \leq i \leq n$). Then M is generically locally identifiable if and only if $|Leak| \leq 1$.*

Proof: The backward direction (\Leftarrow) follows from Theorem 3.4. For the forward direction (\Rightarrow), we can relabel compartments so that $In = \{1\}$ and $Out = \{n\}$, so, by Proposition 3.9, $|Leak| \leq 1$. ■

Proof of Theorem 3.7: One direction (\Leftarrow) is immediate from Theorem 3.4. For the other direction (\Rightarrow), by relabelling, we may assume that $In = Out = \{1\}$, and so the desired result follows directly from Theorem 3.10. ■

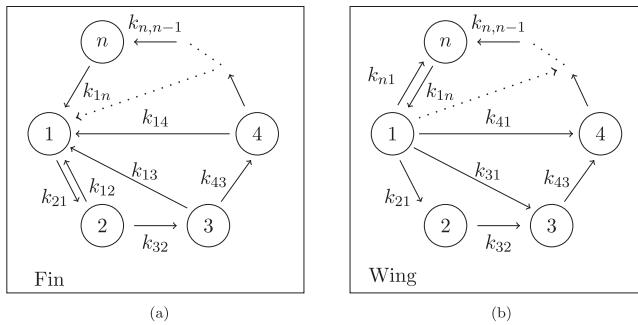


Figure 4. The Fin and Wing graphs with n compartments. (a) The Fin graph (Fin_n) and (b) The Wing graph (Wing_n).

3.4. Adding incoming and outgoing edges to cycle models

In this section, we introduce a new class of linear compartment models, which can be viewed as a hybrid between cycle and mammillary models, as they are constructed by adding certain ‘incoming’ or ‘outgoing’ edges (like those in the mammillary model) to a cycle model.

We prove that when all incoming edges or all outgoing edges are added, and there is at most one leak, the resulting model is identifiable (Theorem 3.13). Afterward, we consider the case of adding only a subset of the incoming edges or outgoing edges. Specifically, we compute the coefficient maps (Propositions 3.14 and 3.15) and assess identifiability (Theorem 3.17).

In what follows, we refer to an edge $j \rightarrow i$ by its edge-label parameter k_{ij} .

Definition 3.12: Consider an n -compartment model.

- (1) An *incoming edge* is an edge from compartment i to compartment 1, where $i \in \{2, 3, \dots, n-1\}$. The set of all incoming edges is $\{k_{12}, k_{13}, \dots, k_{1,n-1}\}$.
- (2) An *outgoing edge* is an edge from compartment 1 to compartment j , where $j \in \{3, 4, \dots, n\}$. The set of all outgoing edges is $\{k_{31}, k_{41}, \dots, k_{n1}\}$.

Fin and *Wing* models are obtained from cycle models by adding all incoming (respectively, outgoing) edges; see Figure 4 for the underlying graphs, denoted by Fin_n and Wing_n .

Theorem 3.13: Let $n \geq 3$, and let M be an n -compartment Fin model ($\text{Fin}_n, \text{In}, \text{Out}, \text{Leak}$) or Wing model ($\text{Wing}_n, \text{In}, \text{Out}, \text{Leak}$), with $\text{In} = \text{Out} = \{1\}$ and at most one leak. Then M is generically locally identifiable.

Proof: It is straightforward to check that, when all leaks are added to the Fin and Wing models, the resulting models are identifiable cycle models (Definition 2.9). In particular, condition (4) is satisfied because the graphs Fin_n and Wing_n satisfy $|E| = 2|V| - 2$ and are inductively strongly connected with respect to compartment 1 and the orderings $\{1, 2, \dots, n\}$ and $\{1, n, n-1, \dots, 2\}$, respectively [7, Remark 1]. So, by Proposition 3.3, M is generically locally identifiable. ■

When only *some* incoming (respectively, outgoing) edges are added, the resulting submodel of a Fin (respectively, Wing) model fails to be inductively strongly connected. Thus, to check whether such a model is an identifiable cycle model (Definition 2.9), we must compute and analyze the coefficient map. Accordingly, we next compute the coefficient maps of Fin and Wing models (Propositions 3.14 and 3.15) – the coefficient maps for submodels are then obtained by setting some rate constants to 0 – and then prove identifiability of submodels of Fin and Wing with only one or two incoming edges or outgoing edges (Theorem 3.17).

We begin by computing the coefficient maps for Fin and Wing models. The proofs are similar, but the differences are subtle enough that we must prove them separately.

Proposition 3.14 (Coefficient map for Fin): *Assume $n \geq 3$. For $2 \leq \ell \leq n - 1$, define the following expressions:*

- (1) $e_m^{[\ell]}$ is the m th elementary symmetric polynomial³ on $E^{[\ell]} := \{k_{1\ell} + k_{\ell+1,\ell}, k_{1,\ell+1} + k_{\ell+2,\ell+1}, \dots, k_{1,n-1} + k_{n,n-1}, k_{1n}\}$,
- (2) $P_\ell := k_{1\ell}(k_{21}k_{32} \cdots k_{\ell,\ell-1})$, and
- (3) $\phi_\ell := e_\ell^{[2]} + k_{21}e_{\ell-1}^{[2]} - \sum_{i=2}^{\ell} P_i e_{\ell-i}^{[i+1]}$.

Then, for the n -compartment model $(\text{Fin}_n, \text{In}, \text{Out}, \text{Leak})$ with $\text{In} = \text{Out} = \{1\}$ and $\text{Leak} = \emptyset$, the coefficient map $c : \mathbb{R}^{2n-2} \rightarrow \mathbb{R}^{2n-2}$ is given by

$$(k_{21}, k_{32}, k_{43}, \dots, k_{1n}, k_{12}, k_{13}, \dots, k_{1,n-1}) \mapsto \left(e_1^{[2]}, e_2^{[2]}, \dots, e_{n-1}^{[2]}, e_1^{[2]} + k_{21}, \phi_2, \phi_3, \dots, \phi_{n-1} \right). \quad (11)$$

Proof: The matrix $A' := (\partial I - A)$ is

$$A' = \begin{bmatrix} \frac{d}{dt} + k_{21} & -k_{12} & -k_{13} & \dots & -k_{1,n-1} & -k_{1n} \\ -k_{21} & \frac{d}{dt} + (k_{12} + k_{32}) & 0 & \dots & & 0 \\ 0 & -k_{32} & \frac{d}{dt} + (k_{13} + k_{43}) & & & \\ 0 & 0 & -k_{43} & \ddots & & \\ \vdots & \vdots & & & \frac{d}{dt} + (k_{1,n-1} + k_{n,n-1}) & 0 \\ 0 & 0 & \dots & 0 & -k_{n,n-1} & \frac{d}{dt} + k_{1n} \end{bmatrix}.$$

The matrix $(A')_{11}$ is lower triangular, with diagonal entries $(d/dt + k_{12} + k_{32}), (d/dt + k_{13} + k_{43}), \dots, (d/dt + k_{1,n-1} + k_{n,n-1}), (d/dt + k_{1n})$. Hence, the non-monic coefficients of the right-hand side of the input-output equation (3) are the elementary symmetric polynomials $e_1^{[2]}, e_2^{[2]}, \dots, e_{n-1}^{[2]}$ on $E^{[2]} = \{k_{12} + k_{32}, \dots, k_{1,n-1} + k_{n,n-1}, k_{1n}\}$, and these are the first $n-1$ coefficients in (11).

To obtain the left-hand side of (3), we expand along the first row of A' :

$$\begin{aligned}
 \det A' &= \left(\frac{d}{dt} + k_{21} \right) \det(A')_{11} + k_{12} \det(A')_{12} \\
 &\quad - k_{13} \det(A')_{13} + \cdots + (-1)^n k_{1n} \det(A')_{1n} \\
 &= \left(\frac{d}{dt} + k_{21} \right) \left(\left(\frac{d}{dt} \right)^{n-1} + \left(\frac{d}{dt} \right)^{n-2} e_1^{[2]} + \cdots + e_{n-1}^{[2]} \right) \\
 &\quad + \sum_{j=2}^n (-1)^j k_{1j} \det(A')_{1j}.
 \end{aligned} \tag{12}$$

Letting $K_j := k_{1j} + k_{j+1,j}$ (for $2 \leq j \leq n-1$) and $K_n := k_{1n}$, we obtain:

$$(A')_{1j} = \left[\begin{array}{cc|cc} -k_{21} & \frac{d}{dt} + K_2 & 0 & \cdots & 0 \\ 0 & -k_{32} & \ddots & & \vdots \\ \vdots & & \ddots & \frac{d}{dt} + K_{j-1} & \vdots \\ 0 & \cdots & -k_{j,j-1} & 0 & \cdots & 0 \\ \hline 0 & \cdots & 0 & \frac{d}{dt} + K_{j+1} & 0 & \cdots & 0 \\ \vdots & & \vdots & -k_{j+2,j+1} & \ddots & & \vdots \\ 0 & \cdots & 0 & & \ddots & \frac{d}{dt} + K_{n-1} & 0 \\ & & & & & -k_{n,n-1} & \frac{d}{dt} + K_n \end{array} \right].$$

We see that $(A')_{1j}$ is block diagonal, and both blocks are triangular, so we have:

$$\begin{aligned}
 \det(A')_{1j} &= (-1)^{j-1} (k_{21} k_{32} \cdots k_{j,j-1}) \cdot \left(\frac{d}{dt} + K_{j+1} \right) \left(\frac{d}{dt} + K_{j+2} \right) \cdots \left(\frac{d}{dt} + K_n \right) \\
 &= (-1)^{j-1} \frac{P_j}{k_{1j}} \left(\left(\frac{d}{dt} \right)^{n-j} + \left(\frac{d}{dt} \right)^{n-j-1} e_1^{[j+1]} + \cdots + e_{n-j}^{[j+1]} \right).
 \end{aligned}$$

Using the above expression, we compute a sum from (12):

$$\begin{aligned}
 \sum_{j=2}^n (-1)^j k_{1j} \det(A')_{1j} &= - \sum_{j=2}^n P_j \left(\left(\frac{d}{dt} \right)^{n-j} + \left(\frac{d}{dt} \right)^{n-j-1} e_1^{[j+1]} + \cdots + e_{n-j}^{[j+1]} \right) \\
 &= - \sum_{j=2}^n \left(\frac{d}{dt} \right)^{n-j} \sum_{i=2}^j P_i e_{j-i}^{[i+1]}.
 \end{aligned}$$

By substituting the above expression into equation (12), and collecting coefficients of powers of d/dt , it is straightforward to verify that the non-monic coefficients of the left-hand side of the input-output equation (3) match the final $n-1$ coordinates in (11). ■

Proposition 3.15 (Coefficient map for Wing): Assume $n \geq 3$. For the n -compartment model $(\text{Wing}_n, \text{In}, \text{Out}, \text{Leak})$ with $\text{In} = \text{Out} = \{1\}$ and $\text{Leak} = \emptyset$, the coefficient map $c : \mathbb{R}^{2n-2} \rightarrow \mathbb{R}^{2n-2}$ is given by

$$(k_{32}, k_{43}, \dots, k_{1n}, k_{21}, k_{31}, \dots, k_{n1})$$

$$\mapsto (e'_1, e'_2, \dots, e'_{n-1}, e'_1 + K, e'_2 + e'_1 K, \psi_3, \psi_4, \dots, \psi_{n-2}, e'_{n-1} K - \sum_{i=2}^n Q_i h_{i-2}^i), \quad (13)$$

where, for $3 \leq j \leq n-2$,

$$\psi_j := e'_j + e'_{j-1} K - \sum_{i=n-j+2}^n Q_i h_{i-n+j-2}^i,$$

and e'_m and h_m^j are the m th elementary symmetric polynomials⁴ on $E' := \{k_{32}, k_{43}, \dots, k_{n,n-1}, k_{1n}\}$ and $H^j := \{k_{32}, k_{43}, \dots, k_{j,j-1}\}$ (for $3 \leq j \leq n$), respectively, and $Q_j := k_{1n} k_{j1} (k_{j+1,j} k_{j+2,j+1} \dots k_{n,n-1})$ (for $2 \leq j \leq n$) and $K := k_{21} + k_{31} + \dots + k_{n1}$.

Proof: For this model, the matrix $A' := (\partial I - A)$ is as follows:

$$A' = \begin{bmatrix} \frac{d}{dt} + k_{21} + k_{31} + \dots + k_{n1} & 0 & \dots & 0 & -k_{1n} \\ -k_{21} & \frac{d}{dt} + k_{32} & 0 & \dots & 0 \\ -k_{31} & -k_{32} & \frac{d}{dt} + k_{43} & & \\ -k_{41} & 0 & -k_{43} & & \vdots \\ \vdots & \vdots & \ddots & \ddots & 0 \\ -k_{n1} & 0 & \dots & 0 & -k_{n,n-1} \frac{d}{dt} + k_{1n} \end{bmatrix}.$$

The matrix $(A')_{11}$ is lower triangular, with diagonal entries $(d/dt + k_{32})$, $(d/dt + k_{43})$, \dots , $(d/dt + k_{1n})$. Hence, the non-monic coefficients of the right-hand side of the input-output equation (3) are the elementary symmetric polynomials $e'_1, e'_2, \dots, e'_{n-1}$ on $E' := \{k_{32}, k_{43}, \dots, k_{n,n-1}, k_{1n}\}$, which match the first $n-1$ coordinates in (13).

Next, to obtain the left-hand side of (3), we expand along the first column of A' :

$$\begin{aligned} \det A' &= \left(\frac{d}{dt} + k_{21} + k_{31} + \dots + k_{n1} \right) \det(A')_{11} \\ &\quad + k_{21} \det(A')_{21} - k_{31} \det(A')_{31} + \dots + (-1)^n k_{n1} \det(A')_{n1} \\ &= \left(\frac{d}{dt} + K \right) \left(\left(\frac{d}{dt} \right)^{n-1} + \left(\frac{d}{dt} \right)^{n-2} e'_1 + \dots + e'_{n-1} \right) + \sum_{j=2}^n (-1)^j k_{j1} \det(A')_{j1}. \end{aligned} \quad (14)$$

Next, we compute:

$$(A')_{j1} = \left[\begin{array}{ccc|ccc|c} 0 & \dots & 0 & 0 & \dots & 0 & -k_{1n} \\ \frac{d}{dt} + k_{32} & 0 & \dots & 0 & 0 & \dots & 0 \\ -k_{32} & \ddots & & \vdots & \vdots & & \vdots \\ & \ddots & & 0 & & & \\ 0 & -k_{j-1,j-2} & \frac{d}{dt} + k_{jj-1} & 0 & \dots & 0 & 0 \\ \hline 0 & \dots & 0 & -k_{j+1,j} & \frac{d}{dt} + k_{j+2,j+1} & & 0 \\ \vdots & & \vdots & & \ddots & \ddots & \\ 0 & \dots & 0 & & -k_{n,n-1} & \frac{d}{dt} + k_{1n} & \end{array} \right]$$

We see that $\det(A')_{j1}$ is the product of the determinants of three block matrices: the (1×1) upper-right matrix, a $(j-2) \times (j-2)$ lower-triangular matrix with diagonal entries $(d/dt + k_{i,i-1})$, and an $(n-j) \times (n-j)$ upper-triangular matrix with diagonal entries $-k_{i+1,i}$:

$$\begin{aligned} \det(A')_{j1} &= (-1)^{j+1} k_{1n} (k_{j+1,j} k_{j+2,j+1} \dots k_{n,n-1}) \left(\frac{d}{dt} + k_{32} \right) \\ &\quad \times \left(\frac{d}{dt} + k_{43} \right) \dots \left(\frac{d}{dt} + k_{j,j-1} \right) \\ &= (-1)^{j+1} \frac{Q_j}{k_{j1}} \left(\left(\frac{d}{dt} \right)^{j-2} + h_1^j \left(\frac{d}{dt} \right)^{j-3} + \dots + h_{j-2}^j \right). \end{aligned}$$

Thus, we can compute a sum from (14):

$$\begin{aligned} \sum_{j=2}^n (-1)^j k_{j1} \det(A')_{j1} &= - \sum_{j=2}^n Q_j \left(\left(\frac{d}{dt} \right)^{j-2} + h_1^j \left(\frac{d}{dt} \right)^{j-3} + \dots + h_{j-2}^j \right) \\ &= - \sum_{j=2}^n \left(\frac{d}{dt} \right)^{n-j} \sum_{i=n-j+2}^n Q_i h_{i-n+j-2}^i. \end{aligned}$$

By substituting the above expression into equation (14), and collecting coefficients of powers of d/dt , it is straightforward to verify that the coefficients of the left-hand side of the input-output equation (3) match the final $n-1$ coordinates in (13). \blacksquare

Remark 3.2: In [9, Theorem 4.5], the authors give a formula for the coefficient map of any strongly connected model with $In = Out = \{1\}$ and *at least one leak*. This formula is in terms of spanning, incoming forests of subgraphs of the underlying graph G . This formula agrees with the coefficient maps we compute in Propositions 3.5, 3.14, and 3.15, even though those models have *no leaks* (where, in the notation of [9], we take $\tilde{G} = G$). This suggests that the result [9, Theorem 4.5] may generalize to models without leaks.

The coefficient maps of the Fin and Wing models (Proposition 3.14 and 3.15) are complicated, so analyzing the resulting Jacobian matrices (with the aim of assessing identifiability of submodels) is difficult. We therefore only conjecture that these submodels are identifiable.

Conjecture 3.16 (Submodels of Fin and Wing are identifiable): For $n \geq 3$, let G be a graph obtained from the n -compartment cycle graph in Figure 1(a) by adding one or more incoming edges or adding one or more outgoing edges. Then $(G, In, Out, Leak)$ with $In = Out = \{1\}$ and $Leak = \emptyset$, is generically locally identifiable.

Earlier, we proved the case of Conjecture 3.16 when all incoming or all outgoing edges are added (Theorem 3.13). Next, we obtain the following partial result toward Conjecture 3.16 (we can add one or two incoming or outgoing edges).

Theorem 3.17 (Adding edges to cycle model): Let $n \geq 3$. Let G be a graph obtained from the n -compartment cycle graph in Figure 1(a) by adding one incoming edge or adding one or (if $n \geq 4$) two outgoing edges. Let $In = Out = \{1\}$ and $Leak \subseteq \{1, 2, \dots, n\}$ with $|Leak| = 1$. Then the model $\tilde{M} = (G, In, Out, Leak)$ is generically locally identifiable, and so is the model M obtained by removing the leak.

Proof: By Proposition 2.8, it suffices to prove that the models M are identifiable.

First, we consider the case of a model M obtained by adding one incoming edge. Let $k_{1\ell}$ be the added edge (so, $2 \leq \ell \leq n-1$). The coefficient map $c : \mathbb{R}^{n+1} \rightarrow \mathbb{R}^{2n-2}$ is obtained from the coefficient map in Proposition 3.14 by setting $k_{1i} = 0$ and $P_i = 0$, for $i \in \{2, 3, \dots, n-1\} \setminus \{\ell\}$.

Therefore, $n+1$ of the coefficients are $\tilde{e}_1^2, \tilde{e}_2^2, \dots, \tilde{e}_{n-1}^2, \tilde{e}_1^2 + k_{21}, \tilde{\phi}_\ell$, where \tilde{e}_m^2 denotes the m th elementary symmetric polynomial on the following set:

$$\tilde{E}^2 := \begin{cases} \{k_{43}, \dots, k_{n,n-1}, k_{1n}, k_{12} + k_{32}\} & \text{if } \ell = 2 \\ \{k_{32}, k_{43}, \dots, k_{\ell,\ell-1}\} \cup \{k_{1\ell} + k_{\ell+1,\ell}\} \cup \{k_{\ell+2,\ell+1}, \dots, k_{n,n-1}, k_{1n}\} & \text{if } \ell \geq 3, \end{cases}$$

and $\tilde{\phi}_\ell := \tilde{e}_\ell^2 + k_{21}\tilde{e}_{\ell-1}^2 - P_\ell$.

Consider the $(n+1) \times (n+1)$ submatrix of the Jacobian matrix of c , with columns indexed by $k_{32}, k_{43}, \dots, k_{1n}, k_{21}, k_{1\ell}$ and rows indexed by $\tilde{e}_1^2, \tilde{e}_2^2, \dots, \tilde{e}_{n-1}^2, \tilde{e}_1^2 + k_{21}, \tilde{\phi}_\ell$. We call this matrix \tilde{J} , and we let R_1, R_2, \dots, R_{n+1} denote its rows. To show that $\det \tilde{J} \neq 0$, we first perform two row operations which do not change the determinant: (1) replace R_n by $(-1)R_1 + R_n$, and (2) replace R_{n+1} by $(-1)R_\ell + (-k_{21})R_{\ell-1} + R_{n+1}$.

The resulting matrix, which we denote by \bar{J} , is block upper-triangular, with upper-left block of size $(n-1) \times (n-1)$ and lower-right block of size (2×2) . For the upper-left block, after setting $k_{1\ell} = 0$, this matrix is the Jacobian matrix of the first through $(n-1)$ -st elementary symmetric polynomials (on $n-1$ variables) with respect to those variables, so by Lemma 2.10 the determinant is nonzero (and so is nonzero before setting $k_{1\ell} = 0$).

The lower-right 2×2 block of \bar{J} is the following matrix:

$$\begin{bmatrix} 1 & 0 \\ \tilde{e}_{\ell-1}^2 - \frac{\partial P_\ell}{\partial k_{21}} & -\frac{\partial P_\ell}{\partial k_{1\ell}} \end{bmatrix},$$

which has nonzero determinant $-\partial P_\ell / \partial k_{1\ell} = -P_\ell / k_{1\ell}$. Thus, $\det \tilde{J} = \det \bar{J} \neq 0$, and so, by Proposition 2.6, the model M is generically locally identifiable.

Next, we consider the case of adding outgoing edges. Let $k_{\ell 1}$ (with $3 \leq \ell \leq n$) or $\{k_{j1}, k_{\ell 1}\}$ (with $3 \leq j < \ell \leq n$) be the added edge(s). The coefficient map $c : \mathbb{R}^{n+1} \rightarrow \mathbb{R}^{2n-2}$ (or, respectively, $c : \mathbb{R}^{n+2} \rightarrow \mathbb{R}^{2n-2}$) is obtained from the coefficient map in Proposition 3.15 by:

- (1) setting $k_{i1} = 0$, for $i \in \{3, 4, \dots, n\} \setminus \{\ell\}$ (or, respectively, $i \in \{3, 4, \dots, n\} \setminus \{j, \ell\}$),
- (2) setting $Q_i = 0$, for $i \in \{1, 2, \dots, n\} \setminus \{\ell\}$ (or, respectively, $i \in \{1, 2, \dots, n\} \setminus \{j, \ell\}$), and
- (3) replacing K by $\tilde{K} := k_{21} + k_{\ell 1}$ (or, respectively, $\tilde{K} := k_{21} + k_{j1} + k_{\ell 1}$).

Consider the $(n+1) \times (n+1)$ (respectively, $(n+2) \times (n+2)$) submatrix of the Jacobian matrix of c , with columns indexed by $k_{32}, k_{43}, \dots, k_{1n}, k_{21}, k_{\ell 1}$ (respectively, an extra column for k_{j1}) and rows indexed by the coefficients $e'_1, e'_2, \dots, e'_{n-1}, e'_1 + \tilde{K}, e'_{n+2-\ell} + e'_{n+1-\ell} \tilde{K} - Q_\ell h_0^\ell$ (respectively, an extra row for $e'_{n+2-j} + e'_{n+1-j} \tilde{K} - Q_\ell h_{\ell-j}^\ell - Q_j h_0^j$). This matrix, which we call \tilde{J} , is block lower-triangular. The upper-left block, with size $(n-1) \times (n-1)$, has nonzero determinant by Lemma 2.10. The lower-right block is the following 2×2 matrix:

$$\begin{bmatrix} 1 & 1 \\ e'_{n+1-\ell} & e'_{n+1-\ell} - k_{1n}(k_{\ell+1,\ell} k_{\ell+2,\ell+1} \cdots k_{n,n-1}) \end{bmatrix},$$

which has nonzero determinant, or (respectively) the following 3×3 matrix:

$$\begin{bmatrix} 1 & 1 & 1 \\ e'_{n+1-\ell} & e'_{n+1-\ell} - k_{1n}(k_{\ell+1,\ell} k_{\ell+2,\ell+1} \cdots k_{n,n-1}) & e'_{n+1-\ell} \\ e'_{n+1-j} & e'_{n+1-j} & e'_{n+1-j} \\ -k_{1n}(k_{\ell+1,\ell} k_{\ell+2,\ell+1} \cdots k_{n,n-1}) h_{\ell-j}^\ell & -k_{1n}(k_{j+1,j} k_{j+2,j+1} \cdots k_{n,n-1}) & -k_{1n}(k_{j+1,j} k_{j+2,j+1} \cdots k_{n,n-1}) \end{bmatrix},$$

which has (nonzero) determinant $(Q_j Q_\ell) / (k_{\ell 1} k_{j1}) = k_{1n}^2 (k_{\ell+1,\ell} \cdots k_{n,n-1}) (k_{j+1,j} \cdots k_{n,n-1})$. Thus, $\det \tilde{J} \neq 0$. So, by Proposition 2.6, the model M is generically locally identifiable. \blacksquare

4. Discussion

Despite much progress, the following basic question remains open: Which linear compartmental models are identifiable? Here, we proved that certain infinite families belong to this class, including all cycle models with up to one leak and at least one input (and at least one output). We also showed that adding certain incoming or outgoing edges (for instance, all incoming edges or all outgoing edges) in cycle models also preserves identifiability.

Our results give rise to several open problems. First, for cycle models with two or more leaks, which are identifiable? We obtained results toward an answer in Section 3.3, but our knowledge is not yet complete. Next, consider cycle models with some incoming or outgoing edges added. We conjectured that identifiability is preserved when more than one or two incoming or outgoing edges are added (Conjecture 3.16). Next, is identifiability preserved when the input or output is moved? Finally, among models containing at least one incoming edge and at least one outgoing edge, which are identifiable?

In summary, as in [1], we view our work as a case study into the effect on identifiability of adding, removing, or moving parts of the model (input, output, edge, or leak). Indeed, we showed for many models that these operations preserve identifiability. Therefore, our work and further progress in this direction will help to resolve the fundamental problem of classifying and characterizing identifiable models.

Notes

1. Ovchinnikov *et al.* considered identifiability over \mathbb{C} , whereas we consider identifiability over \mathbb{R} , but these are equivalent in our setting (cf. the discussion in [21, § 3]).
2. This $n \geq 3$ assumption comes from the fact that the $n = 1$ and $n = 2$ cases reduce to catenary models.
3. By convention, $e_0^{[\ell]} := 1$.
4. By convention, $h_0^j := 1$

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