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 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. 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.

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 identifiability of linear compartmental models, that is, the ability to recover flow parameters from data.

Our motivation is the work of Gross, Harrington, Meshkat, and Shiu 8, 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. Second, the effect of removing a leak remains an open question: the authors conjectured that removing a leak from certain models preserves identifiability.

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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 preserves identifiability (Theorem 3.12). 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 proofs harness the theory of input-output equations for linear compartmental models \[1, 2, 6, \ldots, 13\]. As a result, our analyses 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 \[11\]. 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(b) depicts an \(n\)-compartment cycle model, with \(In = Out = Leak = \{1\}\). The input compartment is labeled by “in,” the output is indicated by an edge with an empty circle at the end, also labeled with “out,” and the leak has an outgoing edge labeled by the 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 continue with several more definitions:

**Definition 2.1.** A directed graph is **strongly connected** if there exists a directed path from each vertex to every other vertex. A linear compartmental model \((G, In, Out, Leak)\) is **strongly connected** if \(G\) is strongly connected.

For instance, the cycle model in Figure 1(b) is strongly connected.
Figure 1: The cycle graph with $n$ compartments (cf. [9, Figure 2]), and a linear compartmental model arising from this graph (with $In = Out = Leak = \{1\}$).

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:

$$A_{ij} := \begin{cases}  
-k_{0i} - \sum_{p:i\to p \in E} k_{pi} & \text{if } i = j \text{ and } i \in Leak \\
-k_{0j} - \sum_{p:j\to p \in E} k_{pi} & \text{if } i = j \text{ and } i \not\in Leak \\
0 & \text{if } j \rightarrow i \text{ is an edge of } G \\
k_{ij} & \text{otherwise}
\end{cases}$$

Furthermore, a linear compartmental model defines the following system of linear ODE’s, with inputs $u_i(t)$ and outputs $y_i(t)$, where $x(t) = (x_1(t), x_2(t), \ldots, x_n(t))$ is the vector of concentrations of the compartments at time $t$:

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

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

where $u_i(t) = 0$ for $i \not\in In$.

Notation 2.3. Throughout this paper, 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, Sullivant, and Eisenberg [11, Theorem 2] (see also [8, Remark 2.7]):
Proposition 2.4. Let $M = (G, In, Out, Leak)$ be a linear compartmental model with $n$ compartments and at least one input. Define $\partial I$ to be the $n \times n$ matrix in which each diagonal entry is the differential operator $\frac{d}{dt}$ and each off-diagonal entry is 0. Let $A$ be the compartmental matrix. Then, the following equations (for $i \in Out$) are input-output equations for $M$:

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

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 $c: \mathbb{R}^{|E| + |Leak|} \to \mathbb{R}^m$, which evaluates each vector of parameters $(k_{ij})_{(j,i) \in E}$, or $i=0$ and $j \in Leak$ 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 2.5. For the cycle model shown in Figure 2, the compartmental matrix is:

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

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

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

which simplifies as follows:

$$y_3^{(4)} + y_3^{(3)} (k_{14} + k_{21} + k_{32} + k_{43}) + y_3^{(2)} (k_{14} k_{21} + k_{14} k_{32} + k_{21} k_{32} + k_{14} k_{43} + k_{21} k_{43} + k_{32} k_{43}) + y_3^{(1)} (k_{14} k_{21} k_{32} + k_{14} k_{21} k_{43} + k_{14} k_{32} k_{43} + k_{21} k_{32} k_{43}) = u_1^{(1)} (k_{21} k_{32}) + u_1 (k_{14} k_{21} k_{32}).$$
Thus, the coefficient map \( c : \mathbb{R}^4 \to \mathbb{R}^5 \) is given by:

\[
(k_{21}, k_{32}, k_{43}, k_{14}) \mapsto (k_{14} + k_{21} + k_{32} + k_{43}, \ k_{14}k_{21} + k_{14}k_{32} + k_{21}k_{32} + k_{14}k_{43} + k_{21}k_{43} + k_{32}k_{43}, \ k_{14}k_{21}k_{32} + k_{14}k_{21}k_{43} + k_{14}k_{32}k_{43} + k_{21}k_{32}k_{43}, \ k_{21}k_{32}, \ k_{14}k_{21}k_{32}).
\]

### 2.3 Identifiability

A model is (structurally) **identifiable** if all parameters \( k_{ij} \) can be recovered from data \([3, 12]\). 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 is equivalent to the definition above; this equivalence was proved by Ovchinnikov, Pogudin, and Thompson [13, Corollary 3.2].

**Definition 2.6.** Let \( M = (G, In, Out, Leak) \) be a linear compartmental model that is strongly connected and has at least one input. Let \( c : \mathbb{R}^{|E|+|Leak|} \to \mathbb{R}^m \) 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 neighborhood \( U \) such that the restriction \( c|_U : U \to \mathbb{R}^k \) is one-to-one.

Next, we state some prior results that we will use. The following, due to Meshkat, Sullivant, and Eisenberg [11, Proposition 2], is key to many of our proofs.

**Proposition 2.7.** 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 2.8 (Example 2.5 continued)**. We show that the model from Example 2.5 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:

\[
\begin{align*}
e_1 &= k_{14} + k_{21} + k_{32} + k_{43}, \\
e_2 &= k_{14}k_{21} + k_{14}k_{32} + k_{14}k_{43} + k_{21}k_{32} + k_{21}k_{43} + k_{32}k_{43}, \\
e_3 &= k_{14}k_{21}k_{32} + k_{14}k_{21}k_{43} + k_{14}k_{32}k_{43} + k_{21}k_{32}k_{43}, \\
\kappa &= k_{21}k_{32}.
\end{align*}
\]

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

\[
-(k_{32} - k_{21})(k_{14} - k_{43})((k_{14} - k_{32})(k_{32} - k_{43}) + k_{14}k_{21} - k_{21}^2 - k_{21}k_{32} + k_{21}k_{43}).
\]

So, by Proposition 2.7, the model is generically locally identifiable.
The following result combines Proposition 4.1 and Theorem 4.3.

**Proposition 2.9.** 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; or
2. $\tilde{M}$ is a model obtained from $M$ by adding one input or one output.

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

**Remark 2.10.** The models considered here have at most one leak. So, in light of Proposition 2.9, to prove identifiability, it suffices 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., as in Example 2.5). Indeed, this term is, up to sign, the determinant of the compartmental matrix $A$, which (when there are no leaks) has 0 column sums.

### 2.4 Elementary Symmetric Polynomials

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

**Lemma 2.11.** 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 $X = \{x_1, x_2, \ldots, x_n\}$. Let $J(V)$ denote the Jacobian matrix of $V := \{e_1, \ldots, e_n\}$ with respect to $x_1, x_2, \ldots, x_n$. 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:

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

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

$$\frac{\partial e_m}{\partial x_i} = \sum_{\substack{j_2 < \ldots < j_m \ni j_k \neq i}} x_{j_2} \ldots x_{j_m} = e_{m-1}\{\hat{x}_i\},$$

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:

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

Finally, by equation (5) in the proof of [11, Theorem 5.1], $\det(J(V))$ equals, up to sign, the Vandermonde polynomial on $X$, which is nonzero: $\det(J(V)) = \pm \prod_{1 \leq i < j \leq n} (x_i - x_j).$
3 Results

In this section we present our main results. In Section 3.1, we recall a conjecture on removing leaks [8] 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). Lastly, in Section 3.3, we show that adding certain edges to cycle models preserves identifiability (Theorem 3.12).

3.1 Adding or Removing a Leak

The following was posed by Gross, Harrington, Meshkat, and Shiu [8, Conjecture 4.5]:

Conjecture 3.1. 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 [5, 7, 14, 15, 16].

![Catenary Graph](image1.png)

(a) The catenary graph.

![Mammillary Graph](image2.png)

(b) The mammillary graph.

Figure 3: Two graphs with \( n \) compartments (cf. [9, Figures 1–2]).

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 [8] states that the models \( M \) in the statement of the theorem, with no leaks, are generically locally identifiable. Then, by Proposition 2.9, adding a leak preserves identifiability. Thus, both \( M \) and \( \tilde{M} \) are generically locally identifiable. \( \square \)
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” \[11, \text{Theorem 1}\]. Also, for identifiability analysis of catenary and mammillary models where some of the parameters are already known, we refer the reader to \[16\].

**Remark 3.3.** For the part of Theorem 3.2 concerning models with one leak, another approach to the proof is via \[10, \text{Section 5}\] and \[11, \text{Theorem 1}\], or (for mammillary models) through \[15, \text{Theorem 5.1}\]. For the part of the theorem on catenary and mammillary models with no leaks, another proof is given in \[4, \text{Sections 3.1 and 4.1}\].

### 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 the 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 the one considered in Examples 2.5 and 2.8 – is identifiable.

**Theorem 3.4.** Assume \(n \geq 3\). Let \(\tilde{M}\) be an \(n\)-compartment cycle model with at least one input, at least one output, and at most one leak. Then \(\tilde{M}\) is generically locally identifiable.

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 \((A)_{ij}\) 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 \(\text{In} = \{1\}\), \(\text{Out} = \{p\}\) for some \(p \neq 1\), and \(\text{Leak} = \emptyset\), the coefficient map \(c : \mathbb{R}^n \to \mathbb{R}^{2n-p}\) is given by:

\[
(k_{21}, k_{32}, \ldots, k_{1n}) \mapsto (e_1, e_2, \ldots, e_{n-1}, \kappa, e_1^\ast \kappa, \ldots, e_{n-p}^\ast \kappa),
\]

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

**Proof.** In the indices, we let \(n + 1 := 1\). By Proposition 2.4 the input-output equation is

\[
\det(\partial I - A)y_p = (-1)^{p+1} \det(\partial I - A)_{1p}u_1,
\]

\(^1\)This \(n \geq 3\) assumption comes from the fact that the \(n = 1\) and \(n = 2\) cases reduce to catenary models.
where $A$ is the compartmental matrix. The $n \times n$ matrix $A' := (\partial I - A)$ is as follows:

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

(6)

We compute the determinant by expanding along the first row:

$$\det A' = \left( \frac{d}{dt} + k_{21} \right) \det (A')_{11} + (-1)^{n-1} (-k_{1n}) \det (A')_{1n}$$  

(7)

$$= \left( \frac{d}{dt} + k_{21} \right) \prod_{i=2}^{n} \left( \frac{d}{dt} + k_{i+1,i} \right) - k_{1n} \prod_{j=2}^{n} k_{j,j-1}$$

$$= \prod_{i=1}^{n} \left( \frac{d}{dt} + k_{i+1,i} \right) - \prod_{j=1}^{n} k_{j+1,j}.$$  

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:

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

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

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

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

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

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

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

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

**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 relabeling, 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 2.7, we must show that the Jacobian matrix of the coefficient map is generically full rank. By Theorem 3.5, the coefficient map $c : \mathbb{R}^n \to \mathbb{R}^{2n-p}$ is given by $(k_{21}, k_{32}, \ldots, k_{n,n-1}, k_{1n}) \mapsto (e_1, e_2, \ldots, e_{n-1}, \kappa, e_1^* \kappa, \ldots, e_{n-p}^* \kappa)$, where $\kappa := \prod_{i=2}^{n-p} k_{i,i-1}$. 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.

Let $\widetilde{J}$ denote the $(n \times n)$ submatrix of $J(c)$ with rows indexed by the first $n$ coefficients $(e_1, e_2, \ldots, e_{n-1}, \kappa)$ and columns indexed by $k_{21}, k_{32}, \ldots, k_{1n}$. It is straightforward to compute $\widetilde{J}$, and we obtain:

$$\widetilde{J} = \begin{bmatrix}
1 & 1 & \cdots & 1 & 1 & \cdots & 1 \\
e_1 \{k_{21}\} & e_1 \{k_{32}\} & \cdots & e_1 \{k_{p,p-1}\} & e_1 \{k_{p+1,p}\} & \cdots & e_1 \{k_{1n}\} \\
e_{n-2} \{k_{21}\} & \cdots & \cdots & \cdots & \cdots & \cdots & \cdots \\
k_{32} k_{43} \cdots k_{p,p-1} & k_{32} k_{43} k_{54} \cdots k_{p,p-1} & \cdots & k_{21} k_{32} k_{43} \cdots k_{p-1,p-2} & 0 & \cdots & 0 \\
\end{bmatrix},$$

where $e_i \{k_{\ell+1,\ell}\}$ denotes the elementary symmetric polynomial on $\{k_{21}, k_{32}, \ldots, k_{1n}\} \setminus \{k_{\ell+1,\ell}\}$.

Now consider what happens to $\widetilde{J}$ when $k_{21} = 0$. Notice that the bottom row of $\widetilde{J}_{|k_{21}=0}$ is $(k_{32} k_{43} \ldots k_{p,p-1}, 0, \ldots, 0)$. Also, it is straightforward to check that the matrix $(\widetilde{J}_{n1})_{|k_{21}=0}$ – that is, the upper-right $(n-1) \times (n-1)$ submatrix of $\widetilde{J}_{|k_{21}=0}$ – is the Jacobian matrix of the first through $(n-1)$-st elementary symmetric polynomials on the size-$(n-1)$ set $\{k_{32}, k_{43}, \ldots, k_{1n}\}$. Thus, by expanding along the bottom row of $\widetilde{J}_{|k_{21}}$, together with the proof of Lemma 2.11, we obtain:

$$\det \widetilde{J}_{|k_{21}=0} = (-1)^{n-1} (k_{32} k_{43} \ldots k_{p,p-1}) \det(\widetilde{J}_{n1})_{|k_{21}=0}$$

$$= \pm (k_{32} k_{43} \ldots k_{p,p-1}) \prod_{2 \leq i < j \leq n} (k_{j+1,j} - k_{i+1,i}) .$$
Thus, \( \det \tilde{J} \) is a nonzero polynomial, and this completes the proof.

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 2.9, adding one leak, one or more inputs, and/or one or more outputs preserves identifiability.

### 3.3 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 edges (like those in the mammillary model) to a cycle model. We compute the coefficient maps (Propositions 3.8 and 3.9) and assess identifiability (Theorem 3.12).

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

**Definition 3.7.** Consider an \( n \)-compartment model.

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

The *Fin* and the *Wing* models are obtained from the cycle model with \( \text{In} = \text{Out} = \{1\} \) and \( \text{Leak} = \emptyset \), by adding all incoming (respectively, outgoing) edges; see Figure 4.

![Diagram of the n-compartment Fin and Wing models](image)

Figure 4: The *n*-compartment Fin and Wing models.

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

1. \( e^\ell_m \) is the \( m \)th elementary symmetric polynomial on \( E^\ell := \{ k_{1\ell} + k_{\ell+1,\ell}, k_{1,\ell+1} + k_{\ell+2,\ell+1}, \ldots, k_{1,n-1} + k_{n,n-1}, k_{1n} \} \).
2. \( P_\ell := k_{1\ell}(k_{2\ell}k_{3\ell} \cdots k_{\ell,\ell-1}) \), and
3. \( \phi_\ell := e^\ell_1 + k_{2\ell} e^\ell_{\ell-1} - \sum_{i=2}^\ell P_i e^\ell_{\ell-i} \).

Then, for the \( n \)-compartment Fin model in Figure 4(a), the coefficient map \( c : \mathbb{R}^{2n-2} \to \mathbb{R}^{2n-2} \) is given by

\[
(k_{32}, k_{43}, \ldots, k_{1n}, k_{21}, k_{31}, \ldots, k_{1n}) \mapsto \left( e^2_1, e^2_2, \ldots, e^2_{n-1}, e^2_1 + k_{21}, \phi_2, \phi_3, \ldots, \phi_{n-1} \right) .
\]  

(11)

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

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

The matrix \((A')_{11}\) is lower triangular, with diagonal entries \((d/dt + k_{12} + k_{32}), (d/dt + k_{13} + k_{43}), \ldots, (d/dt + k_{1,n-1} + k_{n,n-1}), (d/dt + k_{1n})\). Hence, the non-monic coefficients of the right-hand side of the input-output equation (3) are the elementary symmetric polynomials \( e^2_1, e^2_2, \ldots, e^2_{n-1} \) on \( E^2 = \{ k_{12} + k_{32}, \ldots, k_{1,n-1} + k_{n,n-1}, k_{1n} \} \), 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 \( A' \):

\[
\det A' = \left( \frac{d}{dt} + k_{21} \right) \det (A')_{11} + k_{12} \det (A')_{12} - k_{13} \det (A')_{13} + \cdots + (-1)^n k_{1n} \det (A')_{1n}
\]

\[
= \left( \frac{d}{dt} + k_{21} \right) \left( \left( \frac{d}{dt} \right)^{n-1} + \left( \frac{d}{dt} \right)^{n-2} e^2_1 + \cdots + e^2_{n-1} \right) + \sum_{j=2}^n (-1)^j k_{1j} \det (A')_{1j} .
\]

(12)

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

\textsuperscript{2}By convention, \( e^2_0 := 1 \).
\[(A')_{1j} = \begin{bmatrix} -k_{21} & \frac{d}{dt} + K_2 & 0 & \cdots & 0 \\ 0 & -k_{32} & \cdots & \cdots \\ \vdots & \vdots & \ddots & \vdots \\ 0 & \cdots & \frac{d}{dt} + K_{j-1} & 0 & \cdots & 0 \\ 0 & \cdots & 0 & \frac{d}{dt} + K_{j+1} & 0 & \cdots & 0 \\ \vdots & \vdots & \vdots & \vdots \\ 0 & \cdots & 0 & -k_{j+1,j+2} & \cdots & \vdots \\ 0 & \cdots & 0 & 0 & \cdots & \frac{d}{dt} + K_n \\ -k_{n,n-1} & 0 & \cdots & \cdots & \frac{d}{dt} + K_n \end{bmatrix} \]

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

\[
\det (A')_{1j} = (-1)^{j-1} (k_{21}k_{32}\cdots k_{j-1}) \left( \frac{d}{dt} + K_{j+1} \right) \left( \frac{d}{dt} + K_{j+2} \right) \cdots \left( \frac{d}{dt} + K_n \right)
\]

\[
= (-1)^{j-1} \frac{P_j}{k_{1j}} \left( \left( \frac{d}{dt} \right)^{n-j} + \left( \frac{d}{dt} \right)^{n-j-1} e_{i+1} + \ldots + e_{i+1} \right).
\]

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

\[
\sum_{j=2}^{n} (-1)^{j} k_{1j} \det (A')_{1j} = - \sum_{j=2}^{n} P_j \left( \left( \frac{d}{dt} \right)^{n-j} + \left( \frac{d}{dt} \right)^{n-j-1} e_{i+1} + \ldots + e_{i+1} \right)
\]

\[
= - \sum_{j=2}^{n} \left( \frac{d}{dt} \right)^{n-j} \sum_{i=2}^{j} P_i e_{i+1}.
\]

By substituting the above expression into equation (12), and collecting coefficients of powers of \(\frac{d}{dt}\), 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 3.9 (Coefficient map for Wing).** Assume \(n \geq 3\). For the \(n\)-compartment Wing model in Figure 4(b), the coefficient map \(c : \mathbb{R}^{2n-2} \rightarrow \mathbb{R}^{2n-2}\) is given by

\[
(k_{32}, k_{43}, \ldots, k_{1n}, k_{21}, k_{31}, \ldots, k_{n1}) \Rightarrow (e'_1, e'_2, \ldots, e'_{n-1}, e'_1 + K, e'_2 + e'_1K, \psi_3, \psi_4, \ldots, \psi_{n-2}, e'_{n-1}K - \sum_{i=2}^{n} Q_i h_{i-2}^i),
\]

where, for \(3 \leq j \leq n-2\),

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

\[
\psi_{n-1} := e'_{n-1}K - \sum_{i=n+1}^{n} Q_i h_{n+i-1}^i.
\]
and \( e'_m \) and \( h'_m \) are the \( m^{th} \) elementary symmetric polynomials\(^3\) on \( E' := \{k_{32}, k_{43}, \ldots, k_{n,n-1}, k_{11}\} \) and \( H^j := \{k_{32}, k_{43}, \ldots, k_{j,j-1}\} \) (for \( 3 \leq j \leq n \)), respectively, and \( Q_j := k_{1n}k_{j1}(k_{j+1,j}k_{j+2,j+1}\ldots k_{n,n-1}) \) (for \( 2 \leq j \leq n \)) and \( K := k_{21} + k_{31} + \cdots + k_{n1} \).

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

\[
A' = \begin{bmatrix}
\frac{d}{dt} + k_{21} + k_{31} + \cdots + k_{n1} & 0 & \cdots & 0 & -k_{1n} \\
-k_{21} & \frac{d}{dt} + k_{32} & 0 & \cdots & 0 \\
-k_{32} & -k_{32} & \frac{d}{dt} + k_{43} & & \\
-k_{43} & 0 & -k_{43} & \ddots & \\
\vdots & \vdots & \ddots & \ddots & 0 \\
-k_{n1} & 0 & \cdots & 0 & -k_{n,n-1} \frac{d}{dt} + k_{1n}
\end{bmatrix}
\]

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

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

\[
\det A' = \left( \frac{d}{dt} + k_{21} + k_{31} + \cdots + k_{n1} \right) \det(A')_{11}
+ k_{21} \det(A')_{21} - k_{31} \det(A')_{31} + \cdots + (-1)^n k_{n1} \det(A')_{n1}
= \left( \frac{d}{dt} + K \right) \left( \left( \frac{d}{dt} \right)^{n-1} + \left( \frac{d}{dt} \right)^{n-2} e'_1 + \cdots + e'_{n-1} \right) + \sum_{j=2}^{n} (-1)^j k_{j1} \det(A')_{j1}.
\]

Next, we compute:

\[
(A')_{j1} = \begin{bmatrix}
0 & \cdots & 0 & 0 & \cdots & 0 & -k_{1n} \\
\frac{d}{dt} + k_{32} & 0 & \cdots & 0 & 0 & \cdots & 0 \\
-k_{32} & \ddots & \vdots & \vdots & \vdots & \ddots & \vdots \\
\ddots & \ddots & 0 & \frac{d}{dt} + k_{j,j-1} & 0 & \cdots & 0 \\
0 & \cdots & 0 & -k_{j-1,j-2} \frac{d}{dt} + k_{j,j-1} & 0 & \cdots & 0 \\
\vdots & \vdots & \ddots & \ddots & \ddots & \ddots & \vdots \\
0 & \cdots & 0 & 0 & -k_{j+1,j} \frac{d}{dt} + k_{j+2,j+1} & 0 & \cdots & 0 \\
0 & \cdots & 0 & 0 & \cdots & \ddots & \ddots & \vdots \\
0 & \cdots & 0 & 0 & 0 & \cdots & \ddots & -k_{n,n-1} \frac{d}{dt} + k_{1n}
\end{bmatrix}
\]

We see that \( \det(A')_{j1} \) is the product of the determinants of three block matrices: the \((1 \times 1)\) upper-right matrix, a \((j - 2) \times (j - 2)\) lower-triangular matrix with diagonal entries

\(^3\)By convention, \( h'_0 := 1 \)
\[
(d/dt + k_{i,i-1}), \text{ and an } (n-j) \times (n-j) \text{ upper-triangular matrix with diagonal entries } -k_{i+1,i}:
\]
\[
\det(A')_{j1} = (-1)^{j+1}k_{1n} (k_{j+1,j}k_{j+2,j+1} \ldots k_{n,n-1}) \left( \frac{d}{dt} + k_{32} \right) \left( \frac{d}{dt} + k_{43} \right) \ldots \left( \frac{d}{dt} + k_{j,j-1} \right)
\]
\[
= (-1)^{j+1}Q_{j1} \left( \left( \frac{d}{dt} \right)^{j-2} + h_{j1}^j \left( \frac{d}{dt} \right)^{j-3} + \cdots + h_{j-2}^j \right).
\]

Thus, we can compute a sum from (14):
\[
\sum_{j=2}^{n} (-1)^j k_{j1} \det(A')_{j1} = - \sum_{j=2}^{n} Q_{j1} \left( \left( \frac{d}{dt} \right)^{j-2} + h_{j1}^j \left( \frac{d}{dt} \right)^{j-3} + \cdots + h_{j-2}^j \right)
\]
\[
= - \sum_{j=2}^{n} \left( \frac{d}{dt} \right)^{n-j} \sum_{i=n-j+2}^{n} Q_{j} h_{i-n+j-2}.
\]

By substituting the above expression into equation (14), and collecting coefficients of powers of \( \frac{d}{dt} \), 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).

Remark 3.10. 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, 3.8, and 3.9, 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 3.8 and 3.9) are complicated, so analyzing the resulting Jacobian matrices (with the aim of assessing identifiability) is difficult. We therefore only conjecture that these models are identifiable.

Conjecture 3.11 (Fin and Wing are identifiable). For \( n \geq 3 \), the \( n \)-compartment Fin and Wing models (Figure 4) are generically locally identifiable.

We obtain the following partial result toward Conjecture 3.11 (we can add one or two incoming or outgoing edges, but not all).

Theorem 3.12 (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 \( Leak \subseteq \{1,2,\ldots,n\} \) 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 2.9, 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 \( c : \mathbb{R}^{n+1} \to \mathbb{R}^{2n-2} \) is
obtained from the coefficient map in Proposition 3.8 by setting \( k_{1i} = 0 \) and \( P_i = 0 \), for \( i \in \{2, 3, \ldots, n - 1\} \setminus \{\ell\} \). Therefore, \( n + 1 \) of the coefficients are \( \tilde{e}_1^2, \tilde{e}_2^2, \ldots, \tilde{e}_{n-1}^2, \tilde{e}_1^2 + k_{21}, \tilde{\phi}_\ell \), where \( \tilde{e}_m^2 \) denotes the \( m \)th elementary symmetric polynomial on the following set:

\[
\tilde{E}_2 := \begin{cases} \{k_{43}, \ldots, k_{n,n-1}, k_{1n}, k_{12} + k_{32}\} & \text{if } \ell = 2 \\ \{k_{32}, k_{43}, \ldots, k_{\ell-1}\} \cup \{k_{1\ell} + k_{\ell+1,\ell}\} \cup \{k_{\ell+2,\ell+1}, \ldots, k_{n,n-1}, k_{1n}\} & \text{if } \ell \geq 3 \end{cases}
\]

and \( \tilde{\phi}_\ell := \tilde{e}_1^2 + k_{21}\tilde{e}_\ell^2 - P_\ell \).

Consider the \((n + 1) \times (n + 1)\) submatrix of the Jacobian matrix of \( c \), with columns indexed by \( k_{32}, k_{43}, \ldots, k_{1n}, k_{21}, k_{1\ell} \) and rows indexed by \( \tilde{e}_1^2, \tilde{e}_2^2, \ldots, \tilde{e}_{n-1}^2, \tilde{e}_1^2 + k_{21}, \tilde{\phi}_\ell \). We call this matrix \( \tilde{J} \), and we let \( R_1, R_2, \ldots, R_{n+1} \) 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 \( R_{\ell+1} \) by \((-1)R_\ell + (-k_{21})R_{\ell-1} + R_{n+1} \).

The resulting matrix, which we denote by \( \tilde{J} \), is block upper-triangular, with upper-left block of size \((n - 1) \times (n - 1)\) and lower-right block of size \((2 \times 2)\). 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 2.11, the determinant is nonzero (and so is nonzero before setting \( k_{1\ell} = 0 \)).

The lower-right \( 2 \times 2 \) block of \( \tilde{J} \) is the following matrix:

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

which has nonzero determinant \(-\frac{\partial P_{\ell}}{\partial k_{1\ell}} = -P_\ell/k_{1\ell} \). Thus, \( \det \tilde{J} = \det \tilde{J} \neq 0 \), and so, by Proposition 2.7, the model \( M \) is generically locally identifiable.

Next, we consider the case of adding outgoing edges. Let \( k_{1\ell} \) (with \( 3 \leq \ell \leq n \)) or \( \{j, k_{1\ell}\} \) (with \( 3 \leq j < \ell \leq n \)) be the added edge(s). The coefficient map \( c : \mathbb{R}^{n+1} \to \mathbb{R}^{2n-2} \) (or, respectively, \( c : \mathbb{R}^{n+2} \to \mathbb{R}^{2n-2} \)) is obtained from the coefficient map in Proposition 3.9 by:

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

Consider the \((n + 1) \times (n + 1)\) (respectively, \((n + 2) \times (n + 2)\)) submatrix of the Jacobian matrix of \( c \), with columns indexed by \( k_{32}, k_{43}, \ldots, k_{1n}, k_{21}, k_{1\ell} \) (respectively, an extra column for \( k_{j1} \)) and rows indexed by the coefficients \( e'_1, e'_2, \ldots, e'_{n-1}, e'_1 + \tilde{K} , e'_{n+2-\ell} + e'_{n+1-\ell} - \tilde{K} - Q_\ell h'_0 \) (respectively, an extra row for \( e'_{n+2+s j} + e'_{n+1-s j} - \tilde{K} - Q_\ell h'_{\ell-j} - Q_\ell h'_0 \)). 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 2.11. The lower-right block is the following \( 2 \times 2 \) matrix:

\[
\begin{bmatrix} 1 & \frac{1}{k_{1n}(k_{\ell+1,\ell} k_{\ell+2,\ell+1} \cdots k_{n,n-1})} \\ e'_{n+1-\ell} & 1 - k_{1n}(k_{\ell+1,\ell} k_{\ell+2,\ell+1} \cdots k_{n,n-1}) \end{bmatrix},
\]
which has nonzero determinant, or (respectively) the following 3 × 3 matrix:

\[
\begin{bmatrix}
1 & e'_n & 1 \\
e'_n & e'_n & e'_n - k_1 n (k_{\ell + 1} k_{\ell + 2} \cdots k_n) \\
e'_n & e'_n & e'_n - k_1 n (k_{j + 1} k_{j + 2} \cdots k_n) \frac{k_{\ell + 1} \cdots k_n}{k_{j + 1} \cdots k_n}
\end{bmatrix},
\]

which has (nonzero) determinant \( (Q_j Q_\ell) / (k_1 k_{\ell + 1} \cdots k_n) (k_{j + 1} \cdots k_n) \).

Thus, \( \det \tilde{J} \neq 0 \). So, by Proposition 2.7, the model \( M \) is generically locally identifiable.

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 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? 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 3.11). 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 [8], 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.

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