Identity Crisis: Preserving Identifiability in Linear Compartment Models by Removing Leaks, Moving Outputs, and in New Models

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Abstract

In this work, we address linear compartment model identifiability, and prove several cases where changing the model in preserves identifiability. We introduce a new family of models, which includes the Fin, Wing, Nemo, and Tweety-Bird models, and prove that each of these models is generically locally identifiable. We also prove that a conjecture of Gross, Meshkat, and Shiu (2019) holds for cycle, catenary, and mammillary models. Lastly, we examine a new kind of operation, moving the output, and show that it preserves identifiability in cycle models. Our proofs are aided by results on elementary symmetric polynomials and the theory of linear algebra for input-output equations of linear compartment models.

1 Introduction

Linear compartment models have become a staple in certain biological fields, including pharmacology, ecology, and cell biology. These models describe how something, whether it be drug concentration or toxins, move within a system. In this work, we focus on the *identifiability* of linear compartment models. Identifiability is the ability to recover flow parameters from a limited data set. This property is valuable for many reasons. Theoretically, the goal is to find simpler methods to identify parameters in a model. But, before the *how*, we must answer *can*: that is, before answering *how* to identify the parameters, we must answer if we *can*. The purpose of this work is answer when we *can*.

Previous research has investigated some operations which may or may not preserve identifiablity. That is, given a model that is identifiable, does changing the model in some

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way keep identifiability, or is the new model unidentifiable? Previous research investigated adding inputs, outputs, edges, and leaks, as well as deleting inputs, outputs, and edges. One of the open questions was leak deletion. Several of our results prove that, for certain models, deleting the leak *does preserve* identifiability, thereby giving further evidence that deleting a leak will always preserve identifiability.

Our first result analyzes elementary symmetric polynomials: they become essential in proving the later results. The second result addresses leak deletion in cycle, catenary, and mammillary models. We prove that deleting the leak preserves identifiability. Next, we prove that moving the output in a cycle model preserves identifiability. Our final result presents new models, the Fin, Wing, Nemo, and Tweety-Bird models, and prove they are identifiable.

This paper is structured as follows. The Section 2 examines previous results and sets up the necessary definitions and tools we use throughout the rest of the paper. Section 3 presents our main results: some cases where leak deletion preserves identifiability, and that moving the output in cycle models preserves identifiability. Finally, we present the new models and prove they are generically locally identifiable. Section 4 discusses avenues for further research as well as some notes which may help with future inquiry.

2 Background

We begin with some definitions and important preliminary results. We follow the definitions and notations used in [1]. Specifically, we focus on linear models and identifiability.

2.1 Linear Compartment Models

A *linear compartmental model* is defined as a directed graph, call it $G = (V, E)$, and three sets, *In, Out, Leak* $\subseteq V$, which are the Input, Output, and Leak compartments, respectively. A compartment is a vertex $i \in V$, and edges $j \to i$ represents the flow or transfer of material from the j^{th} compartment to the i^{th} compartment. Every input compartment has an external input, $u_i(t)$, which fuels the system. That is, the input compartment is the source of the material. The output compartments, on the other, are measureable: we are able to know the concentration in these compartments. A leak compartment $k \in Leak$ is a compartment where some rate of flow leaves the system. Input compartments are labeled with "in," and outputs are indicated by an edge with an empty circle at the end, also labeled with "out." Every edges has an associated parameter, indicated by k_{ij}, where i indicates the compartment where the flow is going *to*, and j indicates where the flowing is coming *from*. Furthermore, we attach a parameter to a leak, k_{0j}, where 0 indicates that the flow is leaving the system and j indicates which compartment the leak is located at. Figure 1 below represents a specific model, called a *cycle model* (which is a model we study).

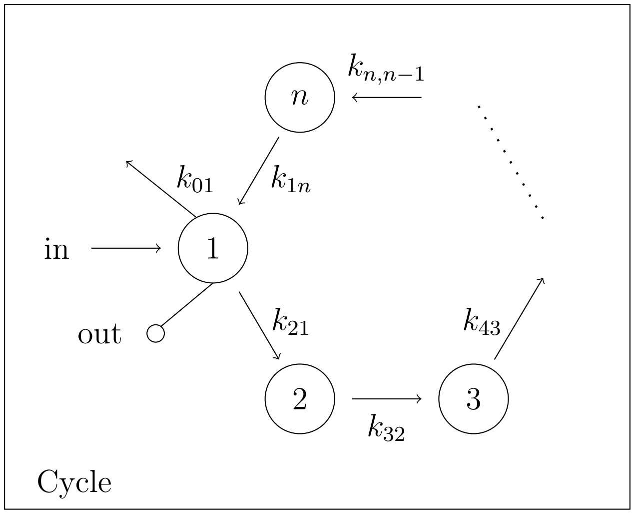

Figure 1: A cycle model

In this case, $In = Out = Leak = \{1\}$. (In general, the input, output, and leaks can be in any compartment.) We require that $In \neq \emptyset$ and $Out \neq \emptyset$, otherwise we would theoretically be unable to collect variable data. However, *Leak can* be the empty set.

To drive some intuition, an example of something that Figure 1 could model would be a drug injection. Compartment 1 would be the injection site, like an arm or thigh. The input would be the shot, where the drug concentration is known. The output would be some kind of measuring device which indicates how much drug is still in the injection site. The other compartments could represent organs, where the drug is going from the injection site, to the heart, to the lungs, to the kidneys, etc., and back to the injection site.

Now we develop some technical theory:

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

Essentially, Definition 2.1 is saying that in a strongly connected linear compartment model, there exists a sequence of edges that goes from a given compartment to any other compartment.

2.2 Input-Output Equations

For linear compartment models, *input-output equations* are equations which hold along any solutions of the ODE's, where only the parameters, the input variables u_i, and the output variables y_j and their derivatives are known. The general formulation of these equations was first presented by Meshkat, Sullivant, and Eisenberg [1]. Gross, Meshkat, and Shiu [2] proved a slightly different version, which we present here:

Proposition 2.1. *Let M=(G, In, Out, Leak) be a linear compartment model with n compartments and at least one input. Define ∂I to be the $n \times n$ matrix in which every diagonal* *entry is the differential operator d/dt and every off-diagonal entry is 0. Let A be the compartmental matrix, and let $(\partial I - A)_{ij}$ denote the $(n-1) \times (n-1)$ matrix obtained from $(\partial I - A)$ by removing row j and column i. Then, the following equations are input-output equations for M. For $i \in out$:*

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

From the input-output equation, we are able to derive a *coefficient map*. This map takes the parameters to the coefficients of the input-output equation. We denote a coefficient map as follows:

$$c : \mathbb{R}^{|E|+|Leak|} \mapsto \mathbb{R}^k. \tag{1}$$

Here, $|E|$ represents the number of non-leak parameters, or $k_{ij}s$, $i \neq 0$, and $|Leak|$ is the number of leaks, or $k_{0j}s$, (essentially, $|E| + |Leak|$ is the total number of parameters). As for the image, k represents the number of coefficients in the input-output equation. These coefficients are some polynomials of the parameters, (e.g. $k_{21}k_{43} + k_{01}k_{13}$). *A priori, there is no way to know for sure how many coefficients there will be. In fact, this is a driving question in our work.*

2.3 Identifiability

Next we turn to key property of a model. A model is *identifiable* if the parameters, the $k_{ij}s$, can be recovered from the data. That is, given two things, perfect input data and perfect output data, we can derive the parameters. Going off the injection analogy from the last section, the question is: if we know the amount of drug in the injection, and the amount of drug still present in the injection site, *can we figure out how much drug is being transferred from one organ to another after some time.* There are several kinds of identifiability, which we now define. Our work primarily focuses on local identifiability.

Definition 2.2. Let $M = (G, In, Out, Leak)$ be a linear compartment model. The *coefficient map* is the function $c : \mathbb{R}^{|E|+|Leak|} \mapsto \mathbb{R}^k$ that is the vector of all coefficient functions of the input-output equation (where k is the total number of coefficients). Then M is:

1. *globally identifiable* if c is one-to-one, and is *generically globally identifiable* if c is one-to-one outside a set of measure zero.

2. *locally identifiable* if around every point in $\mathbb{R}^{|E|+|Leak|}$ there is an open neighborhood U such that $C : U \mapsto \mathbb{R}^k$ is one-to-one, and is *generically locally identifiable* if, outside a set of measure zero, every point in $\mathbb{R}^{|E|+|Leak|}$ has such an open neighborhood U.

3. *unidentifiable* if c is infinite-to-one.

Lastly, we give a key result which is the work-horse of our results.

Proposition 2.2 (Meshkat, Sullivant, and Eisenberg (2015)). *A linear compartment model (G, In, Out, Leak) 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* $|E| + |Leak|$.

One important thing to note is that generically local identifiability *does not* guarantee the model with be identifiable. There may be values of certain parameters which make the model unidentifiable. For further reading on this issue, see [2].

3 Main Results

This section presents our main results. In Section 3.1, we discuss elementary symmetric polynomials, as they become important in proving the later results. In Section 3.2 we partially prove a conjecture from Gross, Harrington, Meshkat, and Shiu (2019) regarding leaks. Then, in Section 3.3, we address new kind of operation: moving the output, where we specifically focus on cycle models. Lastly, in Section 3.4, we introduce a new family of models and show they are generically locally identifiable.

3.1 Elementary Symmetric Polynomials

Our first set of results addresses elementary symmetric polynomials, for they become key to proving identifiability later on.

Lemma 3.1. *Let* e_j *be the* j^{th} *elementary symmetric polynomial on a set of variables* $X = \{x_1, ..., x_n\}$, *such that* $V := \{e_1, ..., e_n\}$. *Then the Jacobian matrix of* V *with respect to* $x_1, ..., x_n$ *has full rank.*

Proof. Let $X = \{x_1, ..., x_n\}$ be a set of n variables. Furthermore, let $\{\hat{i}\} := [n] \setminus \{i\}$ and $\{\hat{x}_i\} := X \setminus \{x_i\}$ Then, the m^{th} elementary symmetric polynomial on X can be rewritten as:

$$\text{f } e_m = \sum_{j_1<j_2<\cdots<j_m} x_{j_1}...x_{j_m} = \sum_{j_2<...<j_m} x_i(x_{j_2}...x_{j_m}) + \sum_{l_1<...<l_m} x_{l_1}...x_{l_m}$$

where $j_s, l_t \in \{\hat{i}\}$. Taking the partial derivative with respect to x_i yields:

$$\frac{\partial e_m}{\partial x_i} = \sum_{j_2<...<j_m} x_{j_2}...x_{j_m} =: e_{m-1}\{\hat{x_i}\}. \tag{2}$$

The expression $e_{m-1}\{\hat{x_i}\}$ represents the $(m-1)^{th}$ polynomial taken over the set $X \setminus \{x_i\}$. The Jacobian matrix is as follows:

$$J(V) = \begin{bmatrix} 1 & 1 & \cdots & 1 \\ e_1\{\hat{x_1}\} & e_1\{\hat{x_2}\} & & e_1\{\hat{x_n}\} \\ \vdots & & \ddots & \\ e_{n-1}\{\hat{x_1}\} & & \cdots & e_{n-1}\{\hat{x_n}\} \end{bmatrix}.$$

It will now suffice to show that $\det(J(V)) \neq 0$. We do so similarly as the proof of Theorem 5.1 in [2] by showing that $\det(J(V))$ equals the *Vandermonde polynomial* on X. In other words, we show the following equality, up to sign:

$$\det(J(V)) = \pm \prod_{1 \leq i < j \leq n} (x_i - x_j). \tag{3}$$

Both sides have the same degree: the determinant has degree $\sum_{i=1}^{n-1} i$, since each row increases degree by one, which is the degree of the Vandermonde polynomial. Lastly, we need to show that $(x_i - x_j)$ divides $\det(J(V))$. To do so, let $x_i = x_j$. Then the Vandermonde polynomial becomes zero. Since $x_i = x_j$, the i^{th} and j^{th} rows of $J(V)$ would coincide. Thus, the columns would be linearly dependent, and $\det(J(W)) = 0$. Therefore, $(x_i - x_j) | \det(J(V))$. So Equation (3) holds.

Now, since $x_i \neq x_j$, the Vadermonde polynomial is nonzero, and therefore $\det(J(v)) \neq 0$. Hence, the Jacobian matrix has full rank. □

Corollary 3.1. Every square submatrix of $Jac(V)$ in Lemma 3.1, where $V = \{e_1, ..., e_n\}$ has full rank.

Proof. Follows immediately from Lemma 3.1. □

3.2 Removing the Leak

Our next set of results addresses a conjecture posed by Gross, Meshkat, and Shiu [3]. We show that removing a leak in three specific models, defined in [2], preserves identifiability.

Conjecture 3.1 (Conjecture 4.5 (Gross, Meshkat, and Shiu (2017))**.** Let $\tilde{M}$ be a linear compartment model that is strongly connected and has at least one input and exactly one leak. If $\tilde{M}$ is generically locally identifiable from the coefficient map, then so is the model M obtained from $\tilde{M}$ by removing the leak.

Theorem 3.1. *Let $\tilde{M}$ be a catenary, cycle, or mammillary model that has exactly one input 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 [3] states catenary, cycle, and mammillary models, with no leaks, are locally identifiable from the coefficient map. Then, by Theorem 4.3 from [3], adding a leak preserves identifiability. Thus, both M and $\tilde{M}$ are generically locally identifiable. □

3.3 Moving the Output in a Cycle Model

Our next result is the first look at a new operation on linear compartment models: moving the output. Incidentally, for cycle models, moving the output is the same as moving the input. We assume that $Input = \{1\}$, but if $1 \notin Input$ (assuming we we only have one input), the model can be relabeled such that $1 \in Input$ (this property is special to the cycle model with one input and one output). We show that a cycle model with one input, one output, and one leak, is generically locally identifiable.

Theorem 3.2. *Assume $n \geq 3$. Let $\tilde{M}$ be an n-compartment cycle model with exactly one input, exactly one output, and exactly one leak. Then $\tilde{M}$ is generically locally identifiable and so is the model obtained by removing the leak.*

We prove Theorem 3.2 by first showing that moving the output preserves identifiability.

Theorem 3.3. *For an n-compartment cycle model with no leaks, input in compartment 1 only, and output in compartment p only, such that $p \neq 1$ (that is, the output is not in the same compartment as the input), the coefficients of the input-output equation are given by the coefficient map:*

$$c : \mathbb{R}^n \to \mathbb{R}^{n+p-2}$$

where

$$(k_{21}, ..., k_{1n}) \longmapsto (e_1, ..., e_{n-1}, \prod_{i=p+1}^{n+1} k_{i,i-1}e_0^*, ..., \prod_{i=p+1}^{n+1} k_{i,i-1}e_{p-2}^*)$$

where e_j is the j^{th} elementary symmetric polynomial on the set $E = \{k_{21}, ..., k_{n,n-1}, k_{1n}\}$ and e_q^* is the q^{th} elementary symmetric polynomial on the set $E^* = \{k_{32}, ..., k_{p,p-1}\}$.

Proof. Let p be the output compartment. Then, $2 \leq p \leq n$. In the indices, we let $n+1 := 1$.[1] According to Proposition 2.1, the input-output equation is

$$\det(\partial I - A)y_p = (-1)^{p+1} \det(\partial I - A)_{1p}u_1. \tag{4}$$

Let $A' = (\partial I - A)$. Then A' is the following $n \times n$ matrix:

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

By Equation (4), the LHS of the input-output equation is simply the determinant of the above matrix multiplied by y_p. Notice that changing the output compartment does not alter the matrix, and therefore the LHS is the same for all p. We compute the determinant by expanding along the first row:

$$\det(A') = \left(\frac{d}{dt} + k_{21}\right) \det(A'_1) + (-1)^n k_{1n} \det(A'_2) \tag{5}$$

where A'_1 is the submatrix (given below) obtained by deleting row 1 and column 1 of A'. A'_2

[1] The purpose of this relation is to be able to go from $(n, n-1)$ to $(1n)$ in the indices. We maintain this notation throughout

is the submatrix obtained by deleting row 1 and column n:

$$A_1' = \begin{bmatrix} \frac{d}{dt}+k_{32} & 0 & \dots & & 0 \\ -k_{32} & \frac{d}{dt}+k_{43} & & & \vdots \\ \vdots & & \ddots & & 0 \\ 0 & \dots & & -k_{n,n-1} & \frac{d}{dt}+k_{1n} \end{bmatrix}.$$

The A_1' matrix is a lower triangular matrix, therefore the determinant is the product of the diagonal entries. Then,

$$\det(A_1') = \prod_{i=2}^{n} \left(\frac{d}{dt} + k_{i+1,i} \right). \tag{6}$$

A_2' is the submatrix obtained by deleting row 1 and column n from A'.

$$A_2' = \begin{bmatrix} -k_{21} & \frac{d}{dt}+k_{32} & 0 & \dots & 0 \\ 0 & -k_{32} & & & \vdots \\ \vdots & & \ddots & & \\ & & & -k_{n-1,n-2} & \frac{d}{dt}+k_{n,n-1} \\ 0 & \dots & & 0 & -k_{n,n-1} \end{bmatrix}.$$

The A_2' matrix is an upper triangular matrix, and thus the determinant is the product of the diagonal entries as well:

$$\det(A_2') = \prod_{i=2}^{n} k_{i,i-1}. \tag{7}$$

Substituting (6) and (7) into (5) yields:

$$\det(A') = \left(\frac{d}{dt} + k_{21} \right) \prod_{i=2}^{n} \left(\frac{d}{dt} + k_{i+1,i} \right) - k_{1n} \prod_{i=2}^{n} k_{i,i-1}. \tag{8}$$

Recalling that e_j denotes the j^{th} elementary symmetric polynomial on E, (8) simplifies to the final form of the LHS:

$$\frac{d^n}{dt} e_0 + \frac{d}{dt}^{n-1} e_1 + \dots + \frac{d}{dt} e_{n-1}. \tag{9}$$

The left hand side coefficients for the coefficient map can easily be extracted: they are the first to $(n-1)^{th}$ elementary symmetric polynomials on E. This expression concludes the work on the LHS. We now turn our attention to the RHS.

By Proposition 2.1, the RHS is found by removing the first column and p^{th} row from A'. Call A^* the matrix generated by removing the first row and n^{th} column as well. Then, because the first row is $(0, 0, ..., -k_{1n})$, we get that $\det(\partial I - A_{1p}) = -k_{1n} \det(A^*)$, where

$$A^* = \begin{bmatrix} \frac{d}{dt}+k_{32} & \dots & & & & & 0 \\ -k_{32} & \ddots & & & & & \\ \vdots & & -k_{p-1,p-2} & \frac{d}{dt}+k_{p,p-1} & & & \vdots \\ & & 0 & 0 & -k_{p+1,p} & \frac{d}{dt}+k_{p+2,p+1} & \\ & & & & & \ddots & 0 \\ 0 & \dots & & & & 0 & k_{n,n-1} \end{bmatrix}.$$

A^* can be written as a block matrix:

$$A^* = \begin{bmatrix} B & 0 \\ 0 & C \end{bmatrix}$$

where B is a lower triangular matrix with the diagonal composed of terms of the form $(\frac{d}{dt} + k_{ij})$ and C is an upper triangular matrix with the diagonal composed of k_{ij}s. Then, $\det(A^*) = \det(B)\det(C - 0B^{-1}0) = \det(B)\det(C)$. Therefore:

$$-k_{1n}\det(A^*) = -k_{1n}\prod_{i=2}^{p-1}(\frac{d}{dt} + k_{i+1,i})\prod_{i=p+1}^{n} k_{i,i-1} \tag{10}$$

which can simplified to [2]:

$$\pm\prod_{i=2}^{p-1}(\frac{d}{dt} + k_{i+1,i})\prod_{i=p+1}^{n+1} k_{i,i-1}. \tag{11}$$

Similar to before, the product of the binomials is related to elementary symmetric polynomials. Define $E^* = \{k_{32}, ..., k_{p,p-1}\}$. Expansion of the binomial product then yields:

$$\frac{d}{dt}^{p-2} e_0^* + \frac{d}{dt}^{p-3} e_1^* + ... + e_{p-2}^*. \tag{12}$$

Combining (12) with (11), then (11) with (4) gives the final input-output equation:

$$\left(\frac{d}{dt}^{n}(e_0) + \frac{d}{dt}^{n-1} e_1 + \cdots + \frac{d}{dt}e_{n-1}\right) y_n = \left(\prod_{i=p+1}^{n+1} k_{i,i-1}\left(\frac{d}{dt}^{p-2} e_0^* + \frac{d}{dt}^{p-3} e_1^* + ... + e_{p-2}^*)\right)\right) u_1. \tag{13}$$

The coefficients can now easily be extracted. Let c_i represent the coefficients from the LHS and d_j the RHS.

$$\begin{aligned} c_i &= e_i && \text{for } i = 1, \dots, n-1 \\ d_j &= \prod_{i=p+1}^{n+1} k_{i,i-1} e_j^* && \text{for } j = 0, ..., p-2 \end{aligned}$$

[2]In the case of $p = 2$, the first product becomes the empty product, that is, 1.

□

Theorem 3.4. *Let M be an n-compartment cycle model with no leaks, exactly 1 input, and exactly one output. Then M is generically locally identifiable.*

Proof. Fix the input in the first compartment. If the input is not in the first compartment, then relabel the model such that it is. If $p = 1$ (that is, both input and output are in compartment-1), then the model is generically locally identifiable by Theorem 3.1.

Let $\prod_{i=p+1}^{n+1} k_{i,i-1} =: L$. By Proposition 2.2, a model is generically locally indentifiable if the Jacobian matrix of the coefficient map is full rank. By Theorem 3.3, the coefficients are as follows:

$$(e_1, e_2, ..., e_{n-1}, Le_0^*, Le_1^*, ..., Le_{p-2}^*)$$

The row dimension of $J(c)$ is $n-1+p-1 = n+p-2$. Observe that the first $n-1$ rows of the Jacobian matrix are derived from the LHS's elementary symmetric polynomials. There are n parameters, therefore in order to reach a full rank matrix, we need only one row who, when combined with the first $(n-1)$ rows, yields a nonzero determinant.

We select Le_0^*, and since $e_0^* = 1$, simplifies to L. Define the set set $\tilde{E} := \{k_{p+1,p}, ..., k_{1n}\}$. Then, $L = \tilde{e}_{n-p+2}$. Then, let

$$\frac{\partial}{\partial k_{p+1,p+i-1}} L = \frac{L}{k_{p+1,p+i-1}} =: \tilde{e}_{n-p+1}\{\hat{k}_{p+1,p}\}. \tag{14}$$

Note that $\tilde{E} \subset E$. The selected submatrix corresponding to rows specified above, $\tilde{J}$, of the full Jacobian matrix is:

$$\tilde{J} = \begin{bmatrix} 1 & 1 & \dots & 1 & 1 & \dots & 1 \\ e_1\{\hat{k}_{21}\} & e_1\{\hat{k}_{32}\} & \dots & e_1\{\hat{k}_{p,p-1}\} & e_1\{\hat{k}_{p+1,p}\} & \dots & e_1\{\hat{k}_{1n}\} \\ \vdots & & \ddots & & & & \vdots \\ e_{n-2}\{\hat{k}_{21}\} & e_{n-2}\{\hat{k}_{32}\} & \dots & e_{n-2}\{\hat{k}_{p,p-1}\} & e_{n-2}\{\hat{k}_{p+1,p}\} & \dots & e_{n-2}\hat{k}_{1n}\} \\ 0 & 0 & \dots & 0 & \tilde{e}_{n-p+1}\{\hat{k}_{p+1,p}\} & \dots & \tilde{e}_{n-p+1}\{\hat{k}_{1n}\} \end{bmatrix}$$

Now we only need to show that this matrix has a nonzero determinant. To do so, we do expansion on the bottom row. Let $\tilde{J}_i$ represent the submatrix generated by removing the bottom row and the column corresponding to $k_{i,i-1}$. Then, $\det(J)$, up to a sign [3], is:

$$\det \tilde{J} = \sum_{i=p+1}^{n+1} \pm \tilde{e}_{n-p+1}\{k_{i,i-1}\} \det(J_i). \tag{15}$$

Each $\tilde{e}_{n-p+1}\{\hat{k}_{i,i-1}\}$ is nonzero, and by Corollary 3.1, for the submatrix, $\tilde{J}_i$, generated by removing the last row and i^{th} column, each $\det(\tilde{J}_i)$ is nonzero. Thus, we need to only show that terms cannot cancel each other.

[3] The sign does not matter since the summation will not be zero

Observe that $\tilde{e}_{n-p+1}\{\hat{k}_{i,i-1}\}\det(\tilde{J}_i)$ cannot contain $k_{i,i-1}$. However, every other term *will* contain $k_{i,i-1}$ since they are still elementary symmetric polynomials on $\tilde{E}$ and E. Therefore, there can be no cancellation. Thus $\det(J) \neq 0$, and J is full rank. Thus, the model is generically locally identifiable. □

Proof of Theorem 3.2. By, Theorem (3.4) the model without the leak is generically locally identifiable. Then, by Theorem 4.3 from [3], adding the leak preserves identifiability. □

3.4 A new model: Fin and Wing Models

We introduce a new family of models: Fin, Nemo, Wing, and Tweety-Bird models. These models are a kind of hybrid between cycle and mammillary models. What relates each of these models to the others is their "skeletons" are a cycle model. These models are generated from a cycle model by adding what we term *interior edges*, or edges that go from compartment 1 to any other compartment, except for k_{21} and k_{21}. We term *returning edges* as interior edges that go *from* compartment n to compartment 1. Similarly, we term "outgoing" edges as interior edges that go *from* compartment 1 to compartment n. We begin by defining each of these new models. Figure 2 shows a Fin model.

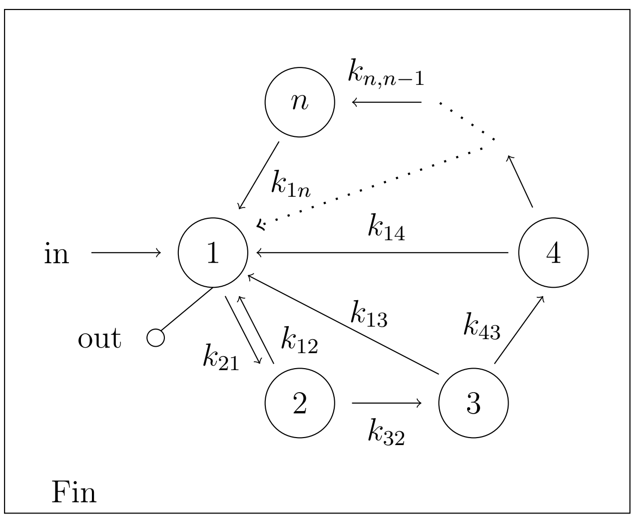

Figure 2: the $n-$compartment Fin model is obtained from the cycle model by adding all interior edges such that they are returning edges.

Nemo models are Fin models with deleted returning edges. Any number of returning edges can be removed. Just note that if all returning edges are removed, the model degenerates into a cycle model. Figure 3 shows an example of a Nemo model.

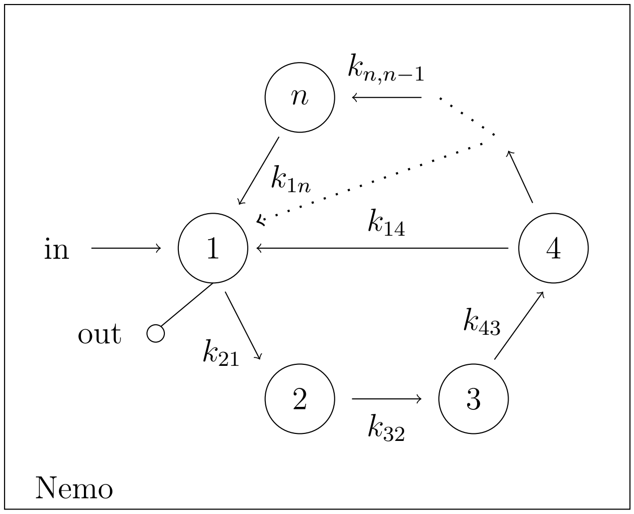

Figure 3: an example of an n-compartment Nemo model.

Next, we have *Wing* models. Wing models are just like Fin models, except instead of returning edges, the interior edges are out-going edges. Figure 4 shows an $n-$compartment Wing model.

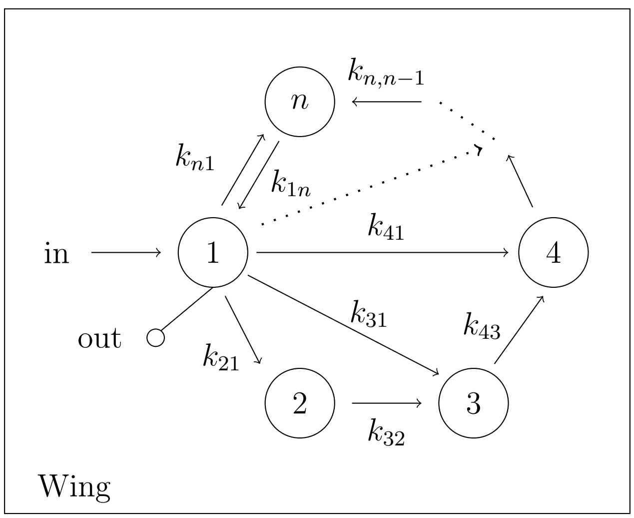

Figure 4: an example of an $n-$compartment Wing model.

Lastly, we define a Tweety-Bird model. Tweety-Bird models are to Wing models what Nemo models are to Fin models: some of the interior edges are deleted (in this case, they are out-going edges). As before, there is no order or set number of deleted edges, just note that if all of the interior edges are deleted, the model degenerates into a cycle model. Figure 5 shows a Tweety-Bird Model.

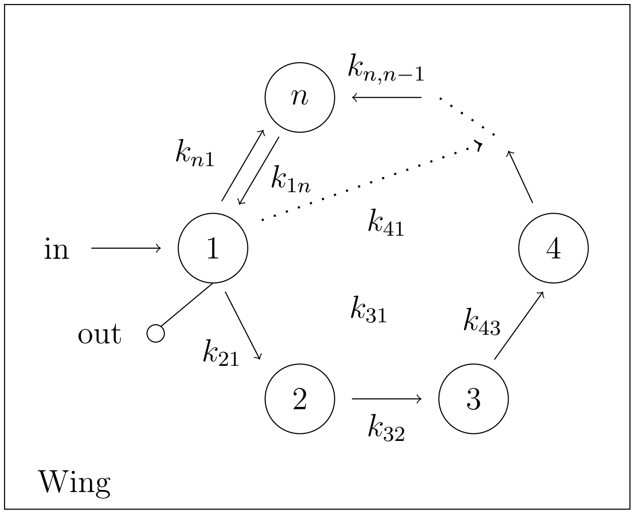

Figure 5: an example of an $n-$compartment Tweey-Bird Model.

Theorem 3.5. *Let $\tilde{M}$ be a Fin, Wing, Nemo, or Tweety Bird Model that has exactly one input and exactly one output in the first compartment only and exactly one leak. Then $\tilde{M}$ is generically locally identifiable and so is M obtained by removing the leak.*

We prove Theorem 3.5 by proving that each of the models, without a leak, are generically locally identifiable. We do so in pairs: Fin and Nemo models, then Wing and Tweety-Bird models.

3.4.1 Identifiability of Fin and Nemo Models

Theorem 3.6. *Assume $n \geq 3$. An $n-$compartment Fin model and any Nemo model generated by removing returning edges is generically locally identifiable.*

It is easier to prove the Nemo model is identifiable from a Fin model, and so we first prove that the Fin model is indentifiable.

Theorem 3.7. *Assume $n \geq 3$. For an n-compartment Fin model with no leaks, exactly one input and one output, both in compartment-1, the coefficients of the input-output equation are given by the coefficient map:*

$$c : \mathbb{R}^{2n-2} \to \mathbb{R}^{2n-1}$$

such that

$$(k_{12}, ..., k_{1n}, k_{21}, ..., k_{n,n-1}) \longmapsto (e'_1, ..., e'_{n-1}, e^*_1, e^*_2 + \sum_{i=2}^{2} P_i e^i_{2-i}, ..., e^*_j + \sum_{i=2}^{j} P_i e^i_{j-i}, ..., e^*_n + \sum_{i=2}^{n} P_i e^i_{n-i})$$

where $P_j = -k_{1j} \prod_{i=2}^{j} k_{i,i-1}$, and e^j_m is the m^{th} elementary symmetric on the set $E^j = \{k_{j+2,j+1}, ..., k_{n,n-1}, k_{1n}\}$, and e'_m is the m^{th} elementary symmetric polynomial on $E' = \{k_{32}, ..., k_{n,n-1}, k_{1n}\}$.

Proof. Let M be a Fin model as outlined in the theorem. The associated $(n \times n)$ matrix, A, is:

$$A = \begin{bmatrix} -k_{21} & k_{12} & k_{13} & \dots & k_{1n} \\ k_{21} & -k_{32} & 0 & & 0 \\ 0 & k_{32} & -k_{43} & & \\ \vdots & & & \ddots & \\ 0 & & \dots & k_{n,n-1} & -k_{1n} \end{bmatrix}.$$

Then, by Proposition 2.1, the input-output equation is:

$$\det(\partial I - A)y_1 = \det(\partial I - A_{11})u_1. \tag{16}$$

The RHS of Equation (16) is significantly easier to compute, so we'll begin there. By Equation (16), the RHS is derived, in part, by removing the first row and first column from A. The $(\partial I - A_{11})$ matrix, call it A_1, is:

$$A_1 = \begin{bmatrix} \frac{d}{dt} + k_{32} & 0 & \dots & & 0 \\ -k_{32} & \frac{d}{dt} + k_{43} & & & \vdots \\ \vdots & & \ddots & & 0 \\ 0 & \dots & & -k_{n,n-1} & \frac{d}{dt} + k_{1n} \end{bmatrix}.$$

A_1 is a lower triangular matrix, therefore the determinant is:

$$\prod_{i=2}^{n} \left(\frac{d}{dt} + k_{i+1,i} \right). \tag{17}$$

Recall that e'_j is the j^{th} elementary symmetric polynomials on E'. Then, the RHS can be written as:

$$\det(A_1)u_1 = \left(\frac{d}{dt}^{n-1} e'_0 + \frac{d}{dt}^{n-2} e'_1 + ... + \frac{d}{dt} e'_{n-2} + e'_{n-1} \right) u_1. \tag{18}$$

The coefficients of the RHS can now be extracted, specifically they are the elementary symmetric polynomials, $e'_0, e'_1, ..., e'_{n-2}, e'_{n-1}$ in Equation (18).

The LHS of Equation (16) is the determinant of the full $(\partial I - A)$ matrix. In computing the determinant, the first term in the row expansion of the first row is simply the product of the diagonal entries:

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

Let $E^* = \{k_{21}, k_{32}, ..., k_{n,n-1}, k_{1n}\}$, and let e^*_j denote the j^{th} elementary symmetric polynomial on E^*. Then, the product can be expanded to:

$$\frac{d}{dt}^{n} e^*_0 + \frac{d}{dt}^{n-1} e^*_1 + ... + \frac{d}{dt} e^*_{n-1} + e^*_n. \tag{19}$$

Then, for the k_{ij} term of the row expansion, the submatrix, denoted as A^j, is derived by removing the first row and the j^{th} column of $(\partial I - A)$:

$$A^j = \begin{bmatrix} -k_{21} & \frac{d}{dt}+k_{32} & 0 & \dots & & & 0 \\ 0 & -k_{32} & & & & & \vdots \\ \vdots & & & \ddots & & & \\ & & & & -k_{j,j-1} & 0 & \\ & & & & 0 & \frac{d}{dt}+k_{j+2,j+1} & \\ & & & & & \ddots & 0 \\ 0 & \dots & & & 0 & -k_{n,n-1} & \frac{d}{dt}+k_{1n} \end{bmatrix}.$$

This matrix can be rewritten as a block matrix:

$$A^j = \begin{bmatrix} B & 0 \\ 0 & C \end{bmatrix},$$

where B is a upper triangular matrix where the diagonal is composed of $k_{ij}s$ and C is a lower triangular matrix where the diagonal is composed of $\frac{d}{dt} + k_{ij}$. Thus, similarily as before, $\det(A^j) = \det(B)\det(C)$. Therefore, the row expansion for the $-k_{ij}$ term is:

$$-k_{1j}\prod_{i=2}^{j} k_{i,i-1} \prod_{i=j+1}^{n}\left(\frac{d}{dt} + k_{i+1,i}\right). \tag{20}$$

Recall that e^j_m is the m^{th} elementary symmetric polynomial on E^j. Finally, recall $P_j = -k_{1j}\prod_{i=2}^{j} k_{i,i-1}$. Then, Expression (20) can be rewritten as:

$$P_j\left(\frac{d}{dt}^{n-j} e^j_0 + \frac{d}{dt}^{n-j-1} e^j_1 + ... + \frac{d}{dt} e^j_{n-j_1} + e^j_{n-j}\right). \tag{21}$$

The determinant of A, then, is the sum of Expression (21) and Expression (19):

$$\frac{d}{dt}^n e^*_0 + \frac{d}{dt}^{n-1} e^*_1 + \frac{d}{dt}^{n-2}\left(e^*_2 + \sum_{i=2}^{2} \pm P_j e^i_{2-i}\right) + ... + \frac{d}{dt}^{n-j}\left(e^*_j + \sum_{i=2}^{j} \pm P_j e^j_{j-i}\right) + ... + \left(e^*_n + \sum_{i=2}^{n} P_i e^j_{j-i}\right).$$

This expression completes the computation for the LHS. The last coefficients can now be extracted and the full coefficient map is complete:

$$c : \mathbb{R}^{2n-2} \to \mathbb{R}^{2n-1}$$

such that

$$(k_{12}, ..., k_{1n}, k_{21}, ..., k_{n,n-1}) \longmapsto$$
$$(e'_1, ..., e'_{n-1}, e^*_1, e^*_2 + \sum_{i=2}^{2} P_i e^i_{2-i}, ..., e^*_j + \sum_{i=2}^{j} P_i e^i_{j-i}, ..., e^*_n + \sum_{i=2}^{n} P_i e^i_{n-i})$$

□

Theorem 3.8. *Assume $n \geq 3$. Let M be an n-compartment Fin model with no leaks, exactly one input and one output, both in compartment one. Then M is generically locally identifiable.*

Proof. According to Proposition 2.2, it suffices to show that the Jacobian is full rank. Then, by Theorem 3.7, there are $(2n-1)$ coefficients and only $(2n-2)$ parameters. Therefore, we only need a $(2n-2) \times (2n-2)$ submatrix of the full Jacobian matrix with a nonzero determinant. To do so, we shall use block matrices. Let $\tilde{J}(c)$ represent the submatrix, with block matrices W, X, Y, Z, where each block is $(n-1) \times (n-1)$:

$$\tilde{J}(c) = \begin{bmatrix} X & X \\ Y & Z \end{bmatrix}.$$

We are going to construct a few of matrices (as it will become apparent, we do not need to compute Y). We begin with W.

We are going to select specific coefficients to correspond to specific rows, and the same for parameters to columns. For W, the columns correspond to parameters $(k_{1n}, k_{32}, ..., k_{n,n-1})$, in that order. As for the rows, we selected the $(e'_1, e'_2, ..., e'_{n-1})$ coefficients. Observe that every parameter is a member of E'. Therefore, W is as follows:

$$W = \begin{bmatrix} 1 & 1 & \dots & 1 \\ e'_1\{k_{1n}\} & e'_1\{k_{32}\} & \dots & e'_1\{k_{n,n-1}\} \\ \vdots & & \ddots & \\ e'_{n-2}\{k_{1n}\} & e'_{n-2}\{k_{32}\} & \dots & e'_{n-2}\{k_{n,n-1}\} \end{bmatrix}.$$

By Lemma 3.1, $\det(W) \neq 0$. Therefore, the determinant of $\tilde{J}(c)$ is as follows:

$$\det(\tilde{J}(c)) = \det(W)\det(Z - YW^{-1}X). \tag{22}$$

Next we turn to X. However, since $k_{21} \notin E'$ and $k_{1j} \notin E'$ for $2 \leq j \leq n-1$, X is the zero matrix. Therefore, Equation (22) simplifies to:

$$\det(\tilde{J}(c)) = \det(W)\det(Z).$$

Thus, we need only show $\det(Z) \neq 0$, and so we construct Z. For the columns, we selected the remaining parameters in this order: $(k_{21}, k_{12}, ..., k_{1,n-1})$. As for the rows, we select the coefficients, in this order: $(e^*_1, e^* + \sum_{i=2}^{2} P_i e^i_{2-i}, ..., e^*_{n-1} + \sum_{i=1}^{n-1} P_i e^i_{n-1-i}$.

Since $k_{1i} | P_j$ when $i \leq j$, and $k_{1i} \notin E^* \bigcup E^j$, for $2 \leq j \leq n-1$, the partial derivative is as follows:

$$\frac{\partial}{\partial k_{1s}}(e^*_j + \sum_{i=2}^{j} P_i e^i_{j-i}) = \frac{P_i}{k_{1s}} e^s_{j-s} := \gamma^s_j. \tag{23}$$

When $i > j$, the partial derivative is zero. We can actually construct Z now:

$$Z = \begin{bmatrix} 1 & 0 & \dots & & & & 0 \\ & \gamma_2^2 & 0 & \dots & & & 0 \\ & & \gamma_3^3 & 0 & \dots & & 0 \\ & & & \ddots & & & \\ & & & & \gamma_j^j & \dots & 0 \\ & * & & & & \ddots & \\ & & & & & & \gamma_{n-1}^{n-1} \end{bmatrix}.$$

Therefore, Z is a lower triangular matrix, and $\det(Z)$ is the product of gammas. Since each gamma is nonzero, $\det(Z) \neq 0$. Therefore,

$$\det(\tilde{J}(c)) = \det(W)\det(Z) \neq 0.$$

Then, by Proposition 2.2, the model is generically locally identifiable. □

We are now ready to prove that Nemo Models are identifiable.

Proof of Theorem 3.6. Let N be the Nemo model derive from the $n-$compartment Fin model. Let S' be the set containing *all* of the returning edges. That is, $S' := \{k_{12}, k_{13}, ..., k_{1,n-1}\}$. Let S be the set containing the removed edges. Then, the set of returning edges remaining in the Nemo model is $\tilde{S} := S' - S$. (If $S = \emptyset$, then $\tilde{S}$ corresponds to a Fin model, and if $S = S'$, $\tilde{S}$ is a cycle model.)

Our approach is the same as before. We are going to keep the same Jacobian submatrix and the same parameters and coefficients set up. We are going to change a coefficient notation (it will become important in a moment).

Instead of $e_j^* + \sum_{i=2}^{j} P_i e_{j-i}^i$, we define it to be the following:

$$e_j^* + \sum_t P_t e_{j-t}^t. \tag{24}$$

for t such that $k_{1t} \in S'$

We are going to redefine a partial derivative as well:

$$\frac{\partial}{\partial k_{1s}} \left(e_j^* + \sum_t P_t e_{j-t}^t \right) = \frac{P_s}{k_{1s}} e_{j-s}^s := \tilde{\gamma}_j^s. \tag{25}$$

for $k_{1s} \in \tilde{S}$

Next we construct the Jacobian submatrix. Observe that e_j' is not changed when a returning edge is deleted, and since $(k_{1n}, k_{32}, ..., k_{n,n-1})$ are not returning edges, W *stays the same*, no matter which returning edges are deleted. Therefore:

$$\det(J(c)) = \det(W)\det(Z - YW^{-1}X). \tag{26}$$

Now, for every element of S, we do the following: Say $k_{1j} \in S$. For the X matrix, we remove the column corresponding to k_{1j}. Therefore, X is still a zero matrix.

Then, for the Z matrix, we again delete the column corresponding to k_{1j}. Thus, Z is no longer square. Therefore, we delete a row, specifically the row $e_s^* + \sum_t P_t e_{s-t}^t$, which brings Z to be the following:

$$\tilde{Z} = \begin{bmatrix} 1 & 0 & \dots & & & & 0 \\ & \tilde{\gamma}_2^2 & 0 & \dots & & & 0 \\ & & \ddots & & & & \vdots \\ & & & \tilde{\gamma}_{s-1}^{s-1} & 0 & \dots & 0 \\ & & & & \tilde{\gamma}_{s+1}^{s+1} & \dots & 0 \\ & & * & & & \ddots & \vdots \\ & & & & & & \tilde{\gamma}_{n-1}^{n-1} \end{bmatrix}.$$

Thus, Z is still a lower triangular matrix. Repeat this process for every element in S. Then, X will be a zero matrix, and Z is lower triangular with nonzero gammas. And thus, we have the following:

$$\det(\tilde{J}(c)) = \det(W)\det(Z - YW^{-1}X) = \det(W)\det(Z) \neq 0.$$

Thus, the model is generically locally identifiable. □

3.4.2 Identifiability of Wing and Tweety-Bird Models

Theorem 3.9. *Assume $n \geq 3$. The $n-$compartment Wing model and any $n-$compartment Tweety-Bird model generated by removing out-going edges of the Wing model are generically locally identifiable.*

Just as it was with Fin and Nemo models, it is easier to prove that Tweety-Bird models are identifiable after we show Wing models are identifiable.

Theorem 3.10. *Assume $n \geq 3$. For an n-compartment Wing model with no leaks and input and output in the first compartment only, the coefficient map is given by:*

$$c : \mathbb{R}^{2n-2} \mapsto \mathbb{R}^{2n-1}$$

such that

$$(k_{32}, ..., k_{1n}, k_{21}, k_{31}, ..., k_{n1}) \mapsto$$
$$(e_1', ..., e_{n-1}, e_2^* + \sum_{i=n}^{n} Q_i h_{n-i}^i, ..., e_j^* + \sum_{i=n-j+2}^{n} Q_i h_{n-i}^i, ..., e_n^* + \sum_{i=2}^{n} Q_i h_{n-i}^i)$$

where $Q =: k_{j1}k_{1n}\prod_{i=j+1}^{n} k_{i,i-1}$, $E' = \{k_{32}, k_{43}, ..., k_{n,n-1}, k_{1n}\}$ such that e_m' is the m^{th} elementary symmetric polynomial on E', $E^* =: \{k_{21}, ..., k_{1n}\}$ such that e_m^* is the m^{th} elementary symmetric polynomial on E^*, and $H^j =: \{k_{32}, k_{43}, ..., k_{j,j-1}\}$ such that h_m^j is the m^{th} elementary symmetric polynomial on H^j.

Proof. Let M be a wing model as outlined in the theorem. The associated $(n \times n)$ matrix, A, is:

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

Then, by Proposition 2.1, since the input and output are both in compartment one, the input-output equation is again given by Equation (16), but with the A matrix above. Then, the $(\partial I - A)$ matrix, call it A_1, is:

$$A_1 = \begin{bmatrix} \frac{d}{dt} + k_{21} & 0 & \dots & & 0 & -k_{1n} \\ -k_{21} & \frac{d}{dt} + k_{32} & 0 & \dots & & 0 \\ -k_{31} & -k_{32} & \frac{d}{dt} + k_{43} & & & \\ \vdots & & & & \ddots & \\ -k_{n1} & 0 & \dots & 0 & -k_{n,n-1} & \frac{d}{dt} + k_{1n} \end{bmatrix}.$$

Since the first row and first column are removed, the new matrix is same as matrix A_1 in Theorem 3.7, and the RHS is the same as in Equation (18). Therefore, the RHS coefficients are the elementary symmetric polynomials e'_j on E' from $1 \le j \le n$.

For the LHS, the first term of the column expansion (we are going along column one), is the same as in Equation (19). Then, for the k_{j1} term in the expansion, the matrix generated by removing the first column and j^{th} row, call it A^j is:

$$A^j = \begin{bmatrix} 0 & \dots & & & & & -k_{1n} \\ \frac{d}{dt} + k_{32} & 0 & \dots & & & 0 & \\ \vdots & & & & & & \\ 0 & \dots & -k_{j-1,j-2} & \frac{d}{dt} + k_{j,j-1} & \dots & & 0 \\ 0 & \dots & & & -k_{j+1,j} & \frac{d}{dt} + k_{j+2,j+1} & \dots \\ \vdots & & & & & \ddots & \\ 0 & \dots & & & 0 & -k_{n,n-1} & \frac{d}{dt} + k_{1n} \end{bmatrix}.$$

The determinant of A^j is the product of k_{1n} and the determinant of the matrix generated by removing the first row and last column of A^j. Call this new matrix A^j_*, which can be written as a block matrix:

$$A^j_* = \begin{bmatrix} M & N \\ O & P \end{bmatrix}.$$

Both N and O are the zero matrix. M is a lower triangular matrix where the diagonal is composed of $\frac{d}{dt} + k_{j+1,j}$, and P is an upper triangular matrix where the diagonal is composed of $k_{i,i-1}$. Thus,

$$\det(A^j) = -k_{1n} \prod_{i=j+1}^{n} k_{i,i-1} \prod_{i=2}^{j-1} \left(\frac{d}{dt} + k_{i+1,i} \right). \tag{27}$$

Then, combining Expression (27) and Equation (19) yields:

$$\det(A_1) = \frac{d}{dt}^{n} e_0^* + \frac{d}{dt}^{n-1} e_1^* + ... + \frac{d}{dt} e_{n-1}^* + e_n^* + \sum_{i=2}^{n} -k_{1i} \det(A^i). \tag{28}$$

Expanding the summation, and grouping by $\frac{d^j}{dt}$, the LHS of the input-output equation is:

$$\left(\frac{d}{dt}^{n} e_0^* + \frac{d}{dt}^{n-1} e_1^* + ... + \frac{d}{dt}^{n-j} \left(e_j^* + \sum_{i=n-j+2}^{n} Q_i h_{n-i}^i \right) + ... + e_n^* + \sum_{i=2}^{n} Q_i h_{n-i}^i \right) y_1 \tag{29}$$

for $2 \leq j \leq n$. Note that the superscript in Equation (3.10) can be rewritten as:

$$\frac{d}{dt}^{j-2} \left(e_{n-j+2}^* + \sum_{i=j}^{n} Q_i h_{n-i}^i \right).$$

We can now collect the coefficients from the RHS and the LHS and produce the coefficient map:

$$(k_{32}, ..., k_{1n}, k_{21}, k_{31}, ..., k_{n1}) \mapsto$$
$$(e_1', ..., e_{n-1}', e_2^* + \sum_{i=n}^{n} Q_i h_{n-i}^i, ..., e_j^* + \sum_{i=n-j+2}^{n} Q_i h_{n-i}^i, ..., e_n^* + \sum_{i=2}^{n} Q_i h_{n-i}^i)$$

□

Theorem 3.11. *Assume $n \geq 3$. Let M an n-compartment Wing model with no leaks and input and output in the first compartment only. Then M is generically locally identifiable.*

Proof. The proof follows similarly to Theorem 3.8. Once again, we pick $(2n-2)$ coefficients, and construct the $\tilde{J}(c)$ by using block matrices.

$$\tilde{J}(c) = \begin{bmatrix} W & X \\ Y & Z \end{bmatrix}$$

Once again, for W and X, we select the $(e_1', e_2', ..., e_{n-1}')$ coefficients from Theorem 3.10. For W, we pick the same parameters as in Theorem 3.8. Therefore, W is the same as in Theorem 3.8. Then, for X and Z, we select $(k_{21}, k_{n1}, k_{n-1,1}, ..., k_{31})$. Since all of these parameters are not in E', X is once again the zero matrix.

As for the Z matrix, the same idea holds. We select the coefficients $(e_1^*, e_2^* + \sum_{i=n}^{n} Q_i h_{n-i}^i, ..., e_{n-1}^* + \sum_{i=3}^{n} Q_i h_{n-i}^i$ in that order. Then, for k_{s1}, we calculate the partial derivative. Observe that $k_{j1} | Qi$ when $j = i$. When $i > j$, the partial derivative is zero. Then,

$$\frac{\partial}{\partial k_{s1}} \left(e_j^* + \sum_{i=n-j+2}^{n} Q_i h_{n-i}^i \right) = \frac{Q_s}{k_{s1}} h_{n-s}^s =: \zeta_j^s \tag{30}$$

Thus, Z can be written as:

$$Z = \begin{bmatrix} 1 & 0 & \dots & & 0 \\ & \zeta_2^n & 0 & \dots & 0 \\ & & \zeta_3^{n-1} & & 0 \\ & * & & \ddots & \vdots \\ & & & & \zeta_{n-1}^3 \end{bmatrix}$$

Therefore, Z is a lower triangular matrix with nonzero diagonal entries, and $\det(Z) \neq 0$. Thus, $\det(\tilde{J}(c)) \neq 0$. This computation completes the proof. □

Now we are ready to prove Tweety-Bird models are identifiable.

Proof of Theorem 3.9. The proof is similar to the proof of Theorem 3.6. Let S' be the set containing *all* of the out going edges. That is, $S' := \{k_{21}, k_{31}, ..., k_{n-1,1}\}$. Let S be the set containing the removed edges. Then, the set of outgoing edges remaining in the Tweety-Bird model is $\tilde{S} := S' - S$. Assume $k_{s1} \in S$. Removing k_{s1} does not change W. A column is removed from X, but is still the zero matrix. As for Z, we will show the altered coefficients. Instead of $e_j^* + \sum_{n-j+2}^{n} Q_i h_{n-i}^i$, we have:

$$e_j^* + \sum_t Q_t h_{n-t}^t \tag{31}$$

$$\text{for } t \text{ such that } k_{t1} \in \tilde{S}$$

We are going to make a similar adjustment to the partial derivatives. Let

$$\frac{\partial}{\partial k_{u1}} \left(e_j^* + \sum_t Q_t h_{j-t}^t \right) = Q_u h_{n-u}^t =: \tilde{\zeta}_j^u \tag{32}$$

$$\text{for } k_{u1} \in \tilde{S} \text{ and } u \leq j$$

Delete the column corresponding to k_{s1}, as well as the row corresponding to s as well (that is, $e_s^* + ...$). Thus, Z will be lower triangular. Repeat this process for every element of S. Thus, Z is lower diagonal with nonzero diagonal entries, and thus $\det(Z) \neq 0$. Therefore, $\det(Z) \neq 0$. This computation completes the proof. □

Proof of Theorem 3.5. By Theorems 3.6 and 3.9, the models without the leak are generically locally identifiable. Since each of these models are strongly connected, by Theorem 4.3 in [3], adding a leak to any compartment preserves identifiability. Thus, both $\tilde{M}$ and M are generically locally identifiable. □

4 Discussion

In this section, we discuss potential future research as well as some reflections on the methods used in this work.

4.1 Future Research

One immediate new project is what happens when an interior edge is *flipped* in a Fin (or Wing) model. That is, a returning (out-going) edge if flipped to an out-going (returning) edge. Call these models *Augmented Fin (Wing) models*. These models can have interior edges flipped or removed. However, note that doubling an edge, that is, to have both a returning edge and an out-going edge for for a given compartment, makes things a little tricky. We must ensure that we not have more than $2n-1$ parameters, otherwise the matrix cannot be full rank with respect to the parameters. Figure 6 gives an example, where the highlighted parameter has been flipped.

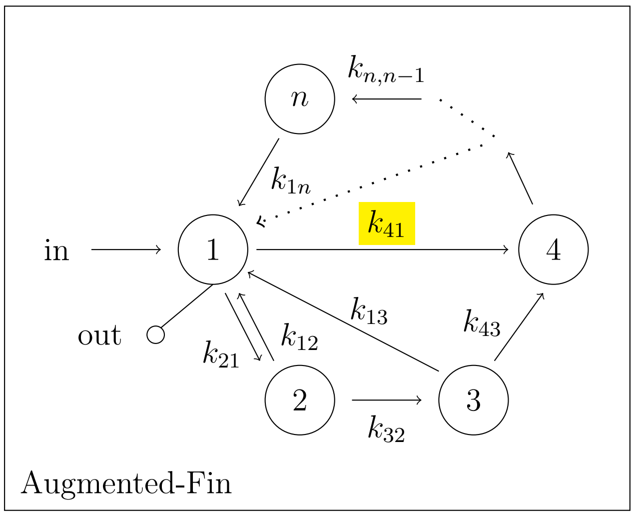

Figure 6

We believe that these models are identifiable, and so offer the following conjecture:

Conjecture 4.1. Assume $n \geq 3$. Let M be an n-compartment Augmented Fin(Wing) model with input and output located in compartment 1. M is generically locally identifiable.

The LHS of the input-output equation is the same as in Theorem 3.6. Thus, the W block matrix of the Jacobian submatrix, $\tilde{J}(c)$, is the same, and since none of the interior edges are in E', the X matrix remains the zero matrix. Therefore, one only need show that $\det(Z) \neq 0$. One further question to ask if what operations preserve identifiabilty with the new models, such as moving the output/input, or adding different components.

4.2 Reflections on the methods used

We relied heavily upon the theory of linear algebra. These methods allowed us to construct the Fin and wing models because we took advantage of a nice $(\partial I - A)$ matrix that produced triangular matrices in the computations. Thus, coefficient maps were fairly easy to obtain. However, the Jacobian matrices were still difficult: it took us a significant amount of time to find the correct arrangement of rows and columns for the Fin and Wing models. So, our methods did not necessarily produce nice Jacobians, and so identifiability is not necessarily easier to achieve with these methods. Still, it is difficult to find a Jacobian matrix without the coefficient map, and so our method is useful for finding the coefficient map.

We took advantage of triangular matrices because their determinants are easy to compute. If there are other matrices with easy determinants, models could be constructed according to nice $(\partial I - A$ matrices. However, identifiability may be tough to prove.

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References

[1] Nicolette Meshkat Seth Sullivant and Marisa Eisenberg. Identifiability results for several classes of linear compartmental models. *Bulletin of Mathematical Biology*, 77(8):1620–1651, 2015.

[2] Elizabeth Gross Nicolette Meshkat and Anne Shiu. Identifiability of linear compartment models: The singular locus. *arXiv:1709.10013v1*, 2017.

[3] Elizabeth Gross Heather Harrington Nicolette Meshkat and Anne Shiu. Linear compartmental models: The input-output equations and operations that preserve identifiability. *arXiv:1808.00335v2*, 2019.