Effects of infinite parameter limits on the structural identifiability of linear compartment models*

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Abstract. Structural identifiability answers the theoretical question of which parameter combinations of a mathematical model can be uniquely recovered from ideal, noise-free input–output data. However, in many biological applications, systems may operate in near-limiting conditions (e.g. slow-fast systems). Structural identifiability has been long studied on biological systems, such as those represented by linear compartment models, but the effects of singular parametric limits on a model's structural identifiability have received less attention. In this work, we investigate how structural identifiability of linear compartment models is affected under singular limits in which a single parameter is sent to infinity. Such limits induce a collapse of the underlying graph that resembles an edge contraction and results in a reduced model, potentially changing the identifiability of the system in the process. Here, we show that for linear compartmental models, the limit and the transfer function commute—namely that the transfer function of the original model converges to the transfer function of the collapsed model under the infinite limit of a single parameter. From this result, we can identify which parameter combinations survive the singular limit and characterize the resulting changes to model identifiability, particularly the degeneracies that result and lead to parameter insensitivity. We illustrate these results on several families of linear compartment models, including mammillary, catenary, and cyclic networks, and discuss connections to model reduction and the geometry of parameter space under asymptotic limits.

Key words. linear compartmental models, structural identifiability, transfer function, singular parametric limits, graph theory

MSC codes. 37N25, 92C45, 93B30, 34A30, 34A55, 34C08

1. Introduction.

A central challenge in mathematical modeling of biological systems lies in parameter estimation. The parameters which govern a model's dynamics, such as rate constants or compartment volumes, are seldom directly observable and often must instead be inferred from experimental measurements of other variables from the dynamical system represented by the model. Before attempting to infer parameters, we must deduce whether the model structure allows parameters to be recovered from input-output data [5, 19, 44, 45]. This principle is known as *structural identifiability* [5, 19]. A model is (globally) structurally identifiable if its parameters are uniquely recoverable from ideal, noise-free input-output data. Structural identifiability is a prerequisite for practical identifiability, so evaluating whether or not a model is structurally identifiable is a necessary step in parameter estimation.

Many different approaches to structural identifiability analysis have been developed [6, 14].

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A successful approach to identifiability for polynomial and rational function ODE models is called the differential algebra approach [6]. The differential algebra approach can be used to determine a model's overall identifiability, as well as to determine the identifiable parameter combinations in the event that the model is unidentifiable. The differential algebra approach is a very general method for assessing a model's identifiability, with applicability to both linear and nonlinear models and assuming generic initial conditions. However, the symbolic calculations needed are often computationally expensive for larger models [6]. For linear models, identifiability can be determined globally via a transfer function approach and other linear algebraic methods [1, 14]. While the transfer function approach is more constrained than the differential algebra approach, namely due to its limited applicability to linear models and typical assumption of zero initial conditions, it can be a more accessible and quicker method from a computational perspective.

Compartment models enjoy a long history of providing a mathematical framework for an extremely wide range of applications [1, 35], and are often assessed for structural identifiability [2, 18, 20, 21, 22, 43], commonly utilized in fields such as pharmacokinetics [20], epidemiology [17, 29], and ecology [34, 37]. While identifiability has been explored in other mathematical settings, such as partial differential equations [12, 40], compartment models have been especially convenient and widely applicable to a broad array of biological contexts [17, 38]. Recent work has developed substantial advancements of the theory around the structural identifiability of linear compartment models [16, 31, 32], namely exploring the connections between the graph-theoretic structure of linear compartment models and the differential algebra approach [4, 8, 9, 13, 15, 23, 24, 30].

Structural identifiability is typically established for a fixed model. However, many linear compartment models arising in practice admit timescale separation or fast-slow dynamics. An example from pharmacokinetics involves the different timescales for drug absorption and drug distribution to peripheral compartments or elimination [1]. Practically, these systems often have singular limits, which may alter the model structure and, consequently, the identifiability of its parameters. Such changes are not always clear from the original model alone, and the relationship between these singular limits and the model's identifiability is not addressed in the current literature. It remains an open question how singular parametric limits affect a model's identifiability, and whether existing methods like the transfer function or differential algebra approach are compatible with these limiting processes.

Here, we examine this relationship between singular parametric limits and structural identifiability on linear compartment models. We utilize a graph-theoretic construction developed by Haque et al. [26, 27] within the linear framework, which produces a reduced graph that resembles the system under such singular limits. We show that the limit of the coefficients of the transfer function as a single parameter goes to infinity converge to those of the reduced graph. We exploit the transfer-function approach because its numerator and denominator are polynomial functions of the model parameters with explicit spanning-forest formulas. This setting provides a natural algebraic and combinatorial framework for studying connections between structural identifiability and graph operations. Furthermore, this rational function expression provides a more convenient mathematical setting to explore how identifiable combinations of parameters behave under singular limits. We then examine the effects of singular limits on catenary and mammillary models, classic classes of linear compartment models. We

begin below with some preliminaries that will establish the framework.

2. Background.

Consider a generic system of first order ODEs alongside an associated measurement equation:

$$\dot{\boldsymbol{x}}(t) = f(\boldsymbol{x}, t, \boldsymbol{p}, \boldsymbol{u}), \tag{2.1}$$

$$\boldsymbol{y}(t) = g(\boldsymbol{x}, t, \boldsymbol{p}), \tag{2.2}$$

where t represents time, $\boldsymbol{x}(t) \in \mathbb{R}^n$ is the vector of state variables, $\boldsymbol{u}(t) \in \mathbb{R}^m$ is the vector of experimental input functions, $\boldsymbol{y}(t) \in \mathbb{R}^r$ is the vector of output/measurement variables, and $\boldsymbol{p} \in \mathbb{R}^v$ is a vector of parameters. We denote $\boldsymbol{x}(0)$ as the initial condition of $\boldsymbol{x}(t)$, which as we will discuss below, we will assume for most of this paper to be equal to 0. Let us denote by $\boldsymbol{p}^\star$ an arbitrary point in parameter space $\mathbb{R}^v$. When talking generally about parameters of a model, we will sometimes refer to individual parameters within $\boldsymbol{p}$ as p. We assume f and g are rational functions of their arguments, and that $\boldsymbol{u}, \boldsymbol{y}$, and $\boldsymbol{x}$ are arbitrarily differentiable. Together, the collection of state equations, measurement equations, and any constraint equations comprises a *model* $M(t, \boldsymbol{x}, \boldsymbol{p}, \boldsymbol{u}, \boldsymbol{y})$. The model $M(t, \boldsymbol{x}, \boldsymbol{p}, \boldsymbol{u}, \boldsymbol{y})$ is *structurally identifiable* if it is possible to uniquely recover individual parameters $p \in \boldsymbol{p}$ from "perfect" (i.e. noiseless) data. That is, a model is structurally identifiable if the *model map* $\Phi : \boldsymbol{p} \mapsto \boldsymbol{y}$ is injective. We thus view the model output $\boldsymbol{y}$ as a function of the parameters $\boldsymbol{p}$ and inputs $\boldsymbol{u}$.

2.1. Structural identifiability.

We begin by providing formal definitions of identifiability:

Definition 2.1. *For a given model M with state equations $\dot{\boldsymbol{x}}$ and measurement equation $\boldsymbol{y}$, with initial condition $\boldsymbol{x}(0) = 0$, an individual parameter $p \in \boldsymbol{p}$ is* uniquely (or globally) structurally identifiable *if for almost every parameter value $\boldsymbol{p}^\star$, the equation $y(\boldsymbol{x}, t, \boldsymbol{p}^\star) = y(\boldsymbol{x}, t, \boldsymbol{p})$ (for all admissible inputs u) implies $p = p^\star$. A parameter $p \in \boldsymbol{p}$ is said to be* non-uniquely (or locally) structurally identifiable *if for almost any $p^\star$, the equation $y(\boldsymbol{x}, t, \boldsymbol{p}^\star) = y(\boldsymbol{x}, t, \boldsymbol{p})$ implies that p has a finite number of solutions.*

Definition 2.2. *For a given model M with state equations $\dot{\boldsymbol{x}}$ and measurement equation $\boldsymbol{y}$, with initial condition $\boldsymbol{x}(0) = 0$, an individual parameter $p \in \boldsymbol{p}$ is* unidentifiable *if for almost every parameter value $p^\star$, the equation $y(\boldsymbol{x}, t, \boldsymbol{p}^\star) = y(\boldsymbol{x}, t, \boldsymbol{p})$ (for all admissible inputs u) implies that p has an infinite number of solutions.*

Remark 2.3. We note that the above definition differs slightly from the usual definitions given in much of the literature based on the differential algebra approach [16]. Here, we assume initial conditions are specified to be zero, rather than being generic. This choice is to align with the typical practice using the transfer function approach, though we note that the generic initial condition case can be replicated here by assuming a delta function input to each compartment, multiplied by an unknown parameter, i.e. an input of the form $p_i\delta(t)$ to each compartment x_i.

Definition 2.4 ([16], Def. 2.2). *A model M with state equations $\dot{\boldsymbol{x}}$ and measurement equation $\boldsymbol{y}$ is* uniquely structurally identifiable *if every parameter $p \in \boldsymbol{p}$ is uniquely structurally identifiable. That is, the equation $y(\boldsymbol{x}, t, \boldsymbol{p}^\star) = y(\boldsymbol{x}, t, \boldsymbol{p})$ has exactly one solution $p = p^\star$. Equivalently, a model is uniquely structurally identifiable for a given output if and only if the map $\Phi : \boldsymbol{p} \mapsto \boldsymbol{y}$ is injective almost everywhere, i.e. if there exists a unique set of parameter values $\boldsymbol{p}^\star$ which yields a given trajectory $y(\boldsymbol{x}, t, \boldsymbol{p}^\star)$ almost everywhere.*

2.1.1. Indistinguishability. Next, we introduce a closely related concept that will be relevant to our work here, which illustrates the connection between uncertainty in the parameters, and uncertainty in the model structure itself. Let the set of output trajectories for a model given specified parameter values and inputs, but across all allowable initial conditions to be written as $\mathcal{S}(\mathbf{y})$.

Definition 2.5 ([16], Def. 3.1). *Two models* $M_1(t, \mathbf{u}_1, \mathbf{x}_1, \mathbf{y}_1, \mathbf{p}_1)$ *and* $M_2(t, \mathbf{u}_2, \mathbf{x}_2, \mathbf{y}_2, \mathbf{p}_2)$ *are said to be* input-output equivalent, or indistinguishable *if, given the same parameters and input functions, both models generate the same set of observed trajectories (for almost all parameter values). In other words,* M_1 *and* M_2 *are input-output equivalent if* $\mathbf{u_1} = \mathbf{u_2}, \mathbf{p_1} = \mathbf{p_2}$ *implies* $\mathcal{S}(\mathbf{y_1}) = \mathcal{S}(\mathbf{y_2})$. *We write this as* $M_1 \sim M_2$.

Lemma 2.6 ([16], Lem. 3.1). *Models that are input-output equivalent have the same identifiability (i.e., the same parameters are (globally or locally) identifiable or unidentifiable), and they have the same identifiable parameter combinations.*

2.1.2. Insensitivity. Here, we introduce an important concept that we will use throughout this work, which we term *unidentifiability by insensitivity*. Insensitivity has been discussed in previous work on identifiability and sensitivity analysis [1], and illustrates a particularly pathological form of unidentifiability which we will explore further below.

Definition 2.7. *A model is* unidentifiable by insensitivity *if it has a parameter or a collection of parameters that do not have any effect on the output of the model. That is, for all admissible inputs* u *and for all* t*, the output* $y(t)$ *remains constant as a single parameter* p *(or collection of parameters) varies. Equivalently,* $\partial y/\partial p = 0$ *identically for all* t *and all admissible inputs* u.

By the transfer function approach, where we assume zero initial conditions, a model being unidentifiable by insensitivity is equivalent to that parameter or collection of parameters being structurally unidentifiable and not participating in an identifiable combination with any other parameter. A model that is unidentifiable by insensitivity may also be known as being *state unobservable* [1]. In this context, we recall that systems of ODEs typically have one set of n linearly independent solutions, or modes. Any such set of solutions is a fundamental set. It is possible for an ODE system to have invisible or hidden modes. This means that not all modes are detectable from data because some modes may not be visible in a particular output $y(t)$ in response to an input $u(t)$.

If a linear compartment model is state unobservable, then this implies that the rank of the state variables is insufficient. That is, the solution contains fewer exponentials than the model has compartments. In most practical examples, if a linear compartment model is unidentifiable by insensitivity, then it is also state unobservable. The reverse is also typically true. However, there are some (usually trivial) examples where this may not be the case, e.g. if one has an identifiable model and appends a fully disconnected compartment with no parameters, then this model would be state unobservable but not unidentifiable by insensitivity.

2.2. Linear compartment models. We introduce linear compartment models through a commonly used graph theoretic framework [8, 9, 13, 23, 24, 32].

Definition 2.8. *A linear compartment model* $\mathcal{M} = (G, In, Out, Leak)$ *is a directed labeled*

graph $G = (V, E)$ with no multi-edges together with three sets, In, Out, $Leak \subseteq V$. Each vertex $i \in V$ corresponds to a compartment in the model, and each directed edge $j \to i \in E$ corresponds to a direct flow from compartment j to compartment i. Each edge $j \to i \in E$ is labeled with a parameter $a_{ij} \in \mathbb{R}_{\geq 0}$ with units time^{-1}. For each $i \in Leak$, $a_{0i} > 0$ denotes the leak rate from compartment i to the environment. The sets $In, Out, Leak \subseteq V$ represent sets of input compartments, output compartments, and leak compartments, respectively. We assume $Out \neq \emptyset$, as models without outputs are not identifiable.

It is often also useful to explicitly include the "0" compartment representing a common sink for all leaks in the graph, denoted the leak-augmented graph [23, 24]. We note that this additional "compartment" need not represent any real mechanistic process, but rather is often used for bookkeeping purposes when working with linear compartment models.

Definition 2.9. *A* leak-augmented graph $\widetilde{G}$ *is an auxiliary graph obtained from the graph G of a linear compartment model $\mathcal{M} = (G, In, Out, Leak)$ by adding a new node labeled by 0. We call this new node the leak node. For every $j \in Leak$, we redirect the former leak edges into 0; that is, the leak edges in G become edges $j \to 0$ in $\widetilde{G}$ with label a_{0j}.*

Linear compartment models are typically represented in matrix form:

Definition 2.10. *For an n-compartment linear compartment model $\mathcal{M} = (G, In, Out, Leak)$ (i.e. $\#V = n$), the compartmental matrix $A \in \mathbb{R}^{n \times n}$ is defined entry-wise as follows,*

$$A_{i,j} = \begin{cases} -a_{0i} - \sum_{k:i \to k \in E} a_{ki} & i = j, i \in Leak, \\ -\sum_{k:i \to k \in E} a_{ki} & i = j, i \notin Leak, \\ a_{ij} & i \neq j, (j,i) \in E, \\ 0 & i \neq j, (j,i) \notin E. \end{cases} \tag{2.3}$$

Definition 2.11 (Input–output linear compartment ODE system). *Given a linear compartment model $\mathcal{M} = (G, In, Out, Leak)$ with compartmental matrix $A \in \mathbb{R}^{n \times n}$, we consider the linear ODE system*

$$\dot{\boldsymbol{x}}(t) = A\boldsymbol{x}(t) + B\boldsymbol{u}(t), \tag{2.4}$$

$$\boldsymbol{y}(t) = C\boldsymbol{x}(t), \tag{2.5}$$

where $\boldsymbol{x}(t) \in \mathbb{R}^n$ is the state vector, $\boldsymbol{u}(t) \in \mathbb{R}^m$ is the input vector, $\boldsymbol{y}(t) \in \mathbb{R}^r$ is the output vector, $B \in \mathbb{R}^{n \times m}$ is the input matrix, and $C \in \mathbb{R}^{r \times n}$ is the measurement matrix.

The model in Def. 2.11 is written generally for a MIMO (multiple input multiple output) model. For a SISO (single input single output) model, we typically take B to have a single nonzero column corresponding to the single input vertex in In, and C as a single nonzero row vector corresponding to the single output vertex in $Out \subseteq V$. That is, $\#In = \#Out = 1$.

Example 2.12. Consider the cyclic model on the left side of Fig. 1. G is given by the complete graph on 3 vertices. Let $In = \{1\}$, $Out = \{1\}$, and $Leak = \{1, 2, 3\}$. All together, we write this linear compartment model as $\mathcal{M} = (G, \{1\}, \{1\}, \{1, 2, 3\})$. Because $\#In = 1$ and $\#Out = 1$, we call this model a single-input single-output (SISO) model. On the right side of Fig. 1, we illustrate the leak-augmented graph $\widetilde{G}$, which contains the new node 0 and

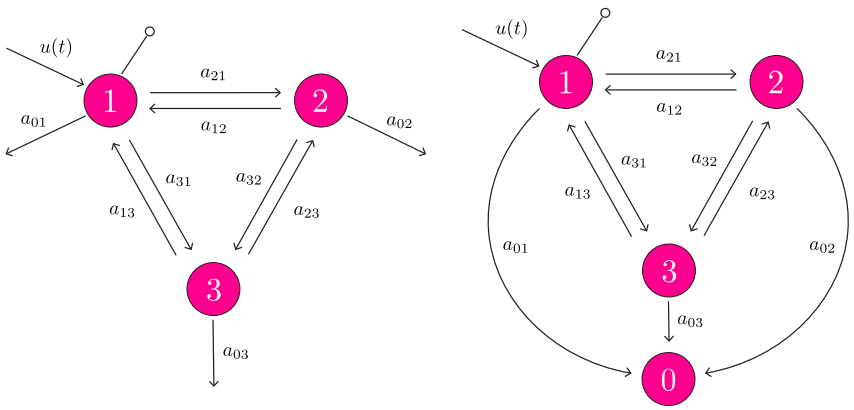


Figure 1: A three-compartment cyclic model with a fully reversible cycle, leaks from every compartment, and a time-varying input $u(t)$ and measurement function $y = x_1$. On the right, the leak-augmented graph.

all leaks in G are directed into 0. In this example, $m = 1$ and $r = 1$. With that in mind, we convert our ODE system into state form. For a SISO model, the matrices B and C are single column and row vectors, respectively. The compartmental matrix A is given below.

$$\begin{aligned}\dot{\boldsymbol{x}}(t) &= A\boldsymbol{x}(t) + Bu(t)\\ &= \begin{bmatrix} -(a_{01}+a_{21}+a_{31}) & a_{12} & a_{13} \\ a_{21} & -(a_{02}+a_{12}+a_{32}) & a_{23} \\ a_{31} & a_{32} & -(a_{03}+a_{13}+a_{23}) \end{bmatrix} \begin{bmatrix} x_1(t) \\ x_2(t) \\ x_3(t) \end{bmatrix} + \begin{bmatrix} 1 \\ 0 \\ 0 \end{bmatrix} u(t)\end{aligned}$$

$$y(t) = C\boldsymbol{x}(t), \implies y(t) = \begin{bmatrix} 1 & 0 & 0 \end{bmatrix} \begin{bmatrix} x_1(t) \\ x_2(t) \\ x_3(t) \end{bmatrix} = x_1(t)\,.$$

2.3. Transfer functions. For linear time-invariant systems, it is often convenient to replace the full state-space representation by a reduced description of the input-output behavior. From control theory and linear systems analysis, a common representation of this behavior is given by the *transfer function* [7]. The transfer function encodes the response of the system to inputs, under the assumption of zero initial conditions. While originally developed in engineering systems and signals applications, they have seen broad usage for assessing parameter identifiability in linear compartment models [1].

Definition 2.13 (Transfer function matrix). *Given an ODE system by Eqs.* (2.4)- (2.5)*, the* transfer function matrix *is given as,*

$$\mathcal{H}^{\mathcal{M}}(s) = C\,(sI - A)^{-1}\,B\,. \tag{2.6}$$

Remark 2.14. The transfer function is determined by the Laplace transform solution of the linear state space system, and lives in the Laplace domain in terms of the complex frequency parameter s. It is a rational function of the Laplace transform of the output $Y(s) = \mathscr{L}\{\boldsymbol{y}(t)\}$ divided by the Laplace transform of the continuous-time input signal $U(s) = \mathscr{L}\{\boldsymbol{u}(t)\}$,

$$\mathcal{H}(s) = \frac{Y(s)}{U(s)} = \frac{\mathscr{L}\{\boldsymbol{y}(t)\}}{\mathscr{L}\{\boldsymbol{u}(t)\}}\,. \tag{2.7}$$

2.3.1. Structural identifiability with transfer functions. The transfer function plays an analogous role to the model map; it directly encodes a map from inputs $\boldsymbol{u}$ to outputs $\boldsymbol{y}$. Once determined, a transfer function can be used to evaluate how the system will respond to any given input. Transfer functions also have great utility in evaluating identifiability for linear compartment models [1, 3, 36]. Each element of the transfer function matrix $\mathcal{H}_{r,q}(s)$ represents an *experiment* performed on the system at input compartment q and output compartment r [1]. Performing such an experiment on the system can be determined by analyzing the input-output pairs encoded by entries of $\mathcal{H}(s)$ [2, 1], and it can be shown rigorously that the coefficients of the transfer function encode the identifiable combinations of parameters [36].

The overall problem of structural identifiability is an inherently algebraic one, which motivates the development and implementation of the differential algebra approach. While the transfer function approach is more limited in its applicability, as it requires that the system be linear and assumes zero initial conditions, its compact structure can make assessments of a model's structural identifiability more accessible. A complete transfer-function identifiability calculation for a two-compartment model is provided in Sec. S2, and we show the calculation for the 3-compartment model below.

Example 2.15 (Transfer function approach to the full 3-compartment model).
From the cyclic model in Ex. 2.12, we obtain the transfer function matrix $\mathcal{H}^{\mathcal{M}}(s)$ directly from the ODE system in state space, $\mathcal{H}^{\mathcal{M}}(s) = C\,[sI - A]^{-1}\,B$. We can simplify the model equations with the following variable changes to represent the sums of outflows from each compartment, $a_{11} = a_{01} + a_{21} + a_{31}$, $a_{22} = a_{02} + a_{12} + a_{32}$, and $a_{33} = a_{03} + a_{13} + a_{23}$. Because the input $u_1(t)$ and output $y_1(t)$ are both localized to compartment 1, the transfer function for the cyclic model in Fig. 1 has a single entry, $\mathcal{H}^{\mathcal{M}}_{1,1}(s)$, which is given by,

$$\mathcal{H}^{\mathcal{M}}_{1,1}(s) = \frac{(a_{22}a_{33} - a_{23}a_{32}) - a_{22}a_{33}s - s^2}{\alpha_1 + \beta_1 s + \gamma_1 s^2 - s^3}\,, \tag{2.8}$$

where,

$$\begin{aligned}
\alpha_1 &= a_{13}a_{22}a_{31} + a_{12}a_{23}a_{31} + a_{13}a_{21}a_{32} + a_{11}a_{23}a_{32} + a_{12}a_{21}a_{33} - a_{11}a_{22}a_{33}\,,\\
\beta_1 &= a_{12}a_{21} - a_{11}a_{22} + a_{13}a_{31} + a_{23}a_{32} - a_{11}a_{33} - a_{22}a_{33}\,,\\
\gamma_1 &= -a_{11} - a_{22} - a_{33}\,.
\end{aligned}$$

Each transfer function $\mathcal{H}^{\mathcal{M}}_{r,q}(s)$ represents the results of the input-output experiment with input from compartment q and output from compartment r. The transfer function $\mathcal{H}^{\mathcal{M}}_{1,1}(s)$ reveals the identifiable parameter combinations of our model. For example, we can see from Eq. (2.8) that $\gamma_1 = -(a_{11} + a_{22} + a_{33})$ is an identifiable combination of parameters. α_1, β_1,

and γ_1 are all identifiable combinations of parameters for this model, as well as $a_{22}a_{33}$ and $a_{22}a_{33} - a_{23}a_{32}$. One can also see that α_1, β_1, and γ_1 are all symmetric polynomials that correspond to sums of principal minors.

This shows explicitly that each entry $\mathcal{H}^{\mathcal{M}}_{i,j}(s)$ is a ratio of a polynomial in s whose coefficients are polynomial functions of the parameters, divided by the characteristic polynomial. In particular, the parameter dependence of $\mathcal{H}^{\mathcal{M}}(s)$ is entirely encoded in the coefficients of these polynomials, which we will use to study structural identifiability.

2.3.2. Graph-theoretic interpretation of transfer function. While linear compartment models provide the standard framework to investigate structural identifiability, there are other graph-based models on which people have considered similar questions.

Definition 2.16. *A* rooted tree *is defined here as a directed graph in which each vertex except one has exactly one edge that exits it. The exception is the root vertex, from which no edges leave. A rooted tree also must contain a directed path to the root from each other vertex. A vertex is a trivial tree rooted in itself.*

Definition 2.17. *A* spanning rooted tree *of a directed graph is a subgraph which is a rooted tree and contains all vertices of the entire graph.*

Definition 2.18. *A* forest *is a disjoint union of rooted trees. Its weight is equal to the product of the weights of its trees. A* spanning forest *of a directed graph is a subgraph that is a forest and contains all vertices of the graph.*

Proposition 2.19 (Roelant et al. 2010 [39], Rule 1.). *Consider a linear compartment model $\mathcal{M} = (G, In, Out, Leak)$ with leak-augmented graph $\widetilde{G}$, compartment matrix A, a single input in compartment q and single output in compartment r. The transfer function $H_{r,q}(s)$ can be written as*

$$\mathcal{H}^{\mathcal{M}}_{r,q}(s) = \frac{N_{r,q}(\widetilde{G}, s)}{D(\widetilde{G}, s)} = \frac{\sum_{k=0}^{n-l_{r,q}-1} s^k \, n_k(\widetilde{G})}{\sum_{k=0}^{n} s^k \, d_k(\widetilde{G})}\,, \tag{2.9}$$

where the coefficients of D and $N_{r,q}$ are weighted sums of rooted spanning forests of G. We denote by $n = |V(G)|$, $l_{r,q}$ the length of a shortest directed path from q to r in $\widetilde{G}$. Each $d_k(\widetilde{G})$ is the weighted sum over spanning forests of $\widetilde{G}$ with $k+1$ trees and each $n_k(\widetilde{G})$ is the weighted sum of spanning forests with $k+2$ trees, one of which is rooted at q and contains r.

Remark 2.20 (Roelant et al. 2010 [39], Thms. 1 & 2). The polynomial $D(s)$ is monic and of order n,

$$D(s) = s^n + d_{n-1}s^{n-1} + \cdots + d_1 s + d_0\,, \tag{2.10}$$

and has all coefficients nonnegative. The polynomial $N_{r,q}$ has degree exactly $n - l_{r,q} - 1$, is monic,

$$\begin{aligned} N_{r,q}(s) &= s^{\,n-l_{r,q}-1} + n_{n-l_{r,q}-2}s^{\,n-l_{r,q}-2} + \cdots + n_1 s + n_0 \\ &= \sum_{k=0}^{n-l_{r,q}-1} n_k s^k, \qquad n_{n-l_{r,q}-1} = 1\,. \end{aligned} \tag{2.11}$$

and has all coefficients nonnegative.[1]

Remark 2.21. We note that the numerator and denominator as computed directly from $C(sI-A)^{-1}B$ follow the standard convention of DiStefano [1], which is derived from the control theory literature and where coefficients may carry negative signs. Expanding the coefficients in the original parameters a_{ij} recovers the nonnegative condition on the coefficients required by Prop. 2.19 and Rmk. 2.20

We now take a moment to prove the short lemma below, which discusses how a lack of paths in $\widetilde{G}$ from input to output results in a loss of identifiability.

Lemma 2.22. *Consider a linear compartment model $\mathcal{M} = (G, In, Out, Leak)$. Suppose that, in G, there is no directed path from any input vertex $q \in In$ to any output vertex $r \in Out$. Then, $\mathcal{H}^{\mathcal{M}}_{r,q} = 0$.*

Proof. By Prop. 2.19, $\mathcal{H}^{\mathcal{M}}_{r,q}(s) = N_{r,q}(s)/D(s)$, where each coefficient n_k of $N_{r,q}(s)$ is the weighted sum of spanning forests with $k+2$ trees in $\widetilde{G}$ such that one is rooted at q and contains r. Such a tree exists only if there is a directed path from q to r. By the assumptions of the Lemma, no such path exists in in $\widetilde{G}$. Thus, no forest contributes to any coefficient n_k and so $N_{r,q}(s) = 0$. Thus, $\mathcal{H}^{\mathcal{M}}_{r,q}(s) = 0$, as required. ∎

3. Results.

3.1. Asymptotic graphs and linear compartment models. Let $a_{ji} \in \mathbb{R}_{>0}$ be a single parameter of a linear compartment model, $\mathcal{M} = (G, In, Out, Leak)$. Suppose we take the limit $a_{ji} \to \infty$ while holding all other parameters fixed. We model this limit as a topological change in the underlying linear compartment model, just as described for linear framework graphs in Def. 3.1. This operation on the graph produces an edge-contracted graph along the edge $i \to j$ in G, where vertex i, along with all of its outgoing edges, is eliminated from G. We call this new graph an asymptotic graph $\mathcal{A}_{i,j}[G]$, consistent with the notation introduced in Haque et al. 2026 [27]. Here we define the same construction as applied to linear compartment models. The corresponding construction in the linear framework, together with the relationship between its Laplacian dynamics and linear compartment models, is reviewed in Sec. SM1 of the Supplementary Information.

Definition 3.1 (Haque 2024 [26], Haque et al. 2026 [27]). *Let $G = (V(G), E(G))$ be a finite directed graph with labeled edges, and let a_{ji} be the rate associated with the edge $i \to j \in E(G)$. The* asymptotic graph $\mathcal{A}_{i,j}[G]$ *obtained by sending $a_{ji} \to \infty$ is the graph on the vertices $\mathcal{V}(\mathcal{A}_{i,j}[G]) = \mathcal{V}(G) \setminus \{i\}$ whose labeled edges are defined from those of G as follows. Suppose $k \to_G m$. There are four mutually exclusive possibilities.*

- $\{k, m\} \cap \{i, j\} = \emptyset$. *Then $k \to_{\mathcal{A}_{i,j}[G]} m$ with rate a_{mk}, unchanged from G.*
- $\{k, m\} \cap \{i, j\} = \{j\}$. *There are two subcases.*
  - $k = j$. *Then $k \to_{\mathcal{A}_{i,j}[G]} m$ with rate a_{mk}, unchanged from G.*
  - $m = j$. *If there is no edge $k \to_G i$, then $k \to_{\mathcal{A}_{i,j}[G]} j$ with rate a_{jk}. If there is an edge $k \to_G i$, then $k \to_{\mathcal{A}_{i,j}[G]} j$ with rate $a_{jk} + a_{ik}$.*

[1] Roelant et al. prove formulation by way of an auxiliary *kinetic graph* $\mathcal{K}$, obtained from $\widetilde{G}$ by attaching an s-labeled arc from each vertex to the sink and using the All-Minors Matrix-Tree Theorem. We omit this intermediate construction since our results can be stated entirely in terms of $\widetilde{G}$.

- $\{k, m\} \cap \{i, j\} = \{i\}$. *There are two subcases.*
  - $k = i$. *The outgoing edges* $i \to_G m$ *do not give rise to any edges in* $\mathcal{A}_{i,j}[G]$.
  - $m = i$. *If there is no edge* $k \to_G j$, *then* $k \to_{\mathcal{A}_{i,j}[G]} j$ *with rate* a_{ik}. *If there is an edge* $k \to_G j$, *then* $k \to_{\mathcal{A}_{i,j}[G]} j$ *with rate* $a_{jk} + a_{ik}$.
- $\{k, m\} \cap \{i, j\} = \{i, j\}$. *The edges* $i \to j$ *and* $j \to i$ *do not give rise to edges in* $\mathcal{A}_{i,j}[G]$.

There are no other edges in $\mathcal{A}_{i,j}[G]$. *We refer to the step in which the rates* a_{ik} *and* a_{jk} *of the edges* $k \to i$ *and* $k \to j$ *in* G *are added to form the rate* $a_{jk} + a_{ik}$ *of the edge* $k \to j$ *in* $\mathcal{A}_{i,j}[G]$ *as* amalgamation.

Definition 3.2 (Asymptotic linear compartment model). *Let* $a_{ji} \in \mathbb{R}_{>0}$ *be a single parameter of a linear compartment model,* $\mathcal{M} = (G, In, Out, Leak)$. *We define here the* asymptotic linear compartment model $\mathcal{M}^\star = (\mathcal{A}_{i,j}[G], In^\star, Out^\star, Leak^\star)$. *The asymptotic graph* $\mathcal{A}_{i,j}[G]$ *is given by the operation described in Def. 3.1. For linear compartment models, we note some additional alterations this construction can induce on the structure of* G.

- *If* $i \in In$, *then* $a_{ji} \to \infty$ *eliminates* i *and redirects all incoming edges/flows into* j. *As a result,* $In^\star = (In \cup \{j\}) \setminus \{i\}$.
- *If* $i \in Out$, *then* $a_{ji} \to \infty$ *eliminates* i. *As a result,* $Out^\star = Out \setminus \{i\}$.
- *If* a_{ji} *is a leak (i.e.* $j = 0$*), then any edges incoming to* i *are redirected to the* 0 *vertex, which is included in the leak-augmented graph* $\widetilde{G}$. *In terms of* G, *any edges incoming to* i *either are augmented onto existing leaks or become leaks.*
- *If* $i \in Leak$ *but* $j \neq 0$, *then the edge* a_{0i} *is treated as an outgoing edge from* i *and is thus eliminated under* $a_{ji} \to \infty$. *Because the vertex* i *is eliminated, the leak-set of the resulting linear compartment model is* $Leak^\star = Leak \setminus \{i\}$.

Example 3.3. Let's consider again the 3-compartment model, and examine how the construction as defined by Def. 3.2 affects the graph depicted in Fig. 1 and its associated model $\mathcal{M}$ as $a_{12} \to \infty$. This step-wise application of the asymptotic construction is depicted in Fig. 2. If $a_{12} \to \infty$, then according to the construction, compartment 2 is eliminated and effectively merges with compartment 1. Now, we also eliminate the outgoing edges from compartment 2 in the reduced graph. Finally, according to the amalgamation step, the edge incoming to 2 from 3 gets combined with the already existing edges from 3 to 1, with the parameters summed together. Altogether, we obtain the resulting reduced graph. We obtained $\mathcal{A}_{1,2}[G]$ from G by taking $a_{12} \to \infty$, which is the graph for the "asymptotic" linear compartment model $\mathcal{M}^\star = (\mathcal{A}_{1,2}[G], In^\star, Out^\star, Leak^\star)$. Because $In = Out = \{1\}$, neither the input nor the output were altered by the asymptotic construction.

In conjunction with Lem. 2.22 and equipped with the asymptotic construction, we will now prove another short lemma about how sending a single parameter a_{ji} to ∞ results in a loss of identifiability in the case where $Out = \{i\}$.

Lemma 3.4. *If* $Out = \{i\}$ *and* $a_{ji} \to \infty$, *then* $\lim_{a_{ji} \to \infty} \mathcal{H}^{\mathcal{M}}_{i,q}(s) = 0$.

Proof. If Out is a singleton, then any paths from input vertices to output vertices are paths to i. By Def. 3.1, sending $a_{ji} \to \infty$ destroys vertex i. Since $Out = \{i\}$ and i is destroyed, then $Out^\star = \emptyset$ in $\mathcal{M}^\star$. Thus, there can be no path from any input vertex $q \in In^\star$ to any output vertex in $\mathcal{M}^\star$. By Lem. 2.22, this implies that $\lim_{a_{ji} \to \infty} \mathcal{H}^{\mathcal{M}}_{i,q}(s) = 0$. ∎

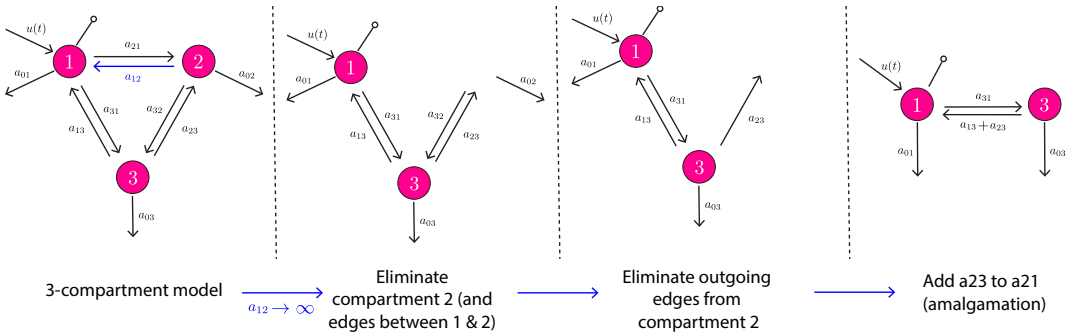


Figure 2: The asymptotic construction applied to the 3-compartment model. The parameter a_{12} is sent to ∞, and is marked in the original graph in blue.

3.2. Main result. The purpose of this work will be to understand how such a limiting procedure on linear compartment models affects its structural identifiability and how its identifiable combinations behave as a single parameter tends to infinity. We now are in a position to prove our main result, Thm. 3.5, which demonstrates how the identifiable parameter combinations of a linear compartment model $\mathcal{M}$ converge to those of the corresponding asymptotic linear compartment model $\mathcal{M}^\star$ under a singular parametric limit. We follow an argument similar in style to the main proof in S. J. Haque's thesis [26], which was used to demonstrate that the steady states of strongly connected linear framework graphs converge to those of its asymptotic graph under the appropriate singular parametric limit. The linear framework provides graph-theoretic formulas for Markovian quantities as rational algebraic functions in the edge labels of the graph. Because, by Prop. 2.19, we have a graph-theoretic formula for the transfer function of a similar structure, a similar logic will apply in our proof of the transfer function. It is worth noting that previous work derived graph-theoretic formulas for the coefficients of the input-output equation [8]. However, the rational structure of the transfer function is helpful to us here as we take singular parametric limits; applying the same procedure to the coefficients of the input-output equation would result in parametric blow-up. Thus, it will require more thought to consider how to investigate the relationship between singular limits and the differential algebra approach. We speculate on this further in the discussion.

Theorem 3.5. *Let $\mathcal{M} = (G, In, Out, Leak)$ be a linear compartment model with transfer function $\mathcal{H}^{\mathcal{M}}_{r,q}(s)$. Let $q \in In$ and $r \in Out$ be any input and output compartments, respectively. Let $a_{ji} \in \mathbb{R}_{>0}$ be a parameter of $\mathcal{M}$ corresponding to the edge $i \to j \in E(G)$. Let $a_{ji} \to \infty$ and let $\mathcal{M}^\star = (\mathcal{A}_{i,j}[G], In^\star, Out^\star, Leak^\star)$ denote the asymptotic linear compartment model with transfer function $\mathcal{H}^{\mathcal{M}^\star}_{r,q}(s)$. Suppose that:*

1. *$i \notin Out$, and*
2. *there exists at least one directed path from q to r in G that does not include any outgoing edge from i.*

Then,

$$\lim_{a_{ji}\to\infty} \mathcal{H}_{r,q}^{\mathcal{M}}(s) = \mathcal{H}_{r,q}^{\mathcal{M}^\star}(s)\,. \tag{3.1}$$

Proof. For ease of exposition, we will focus in this proof on the numerator coefficients n_k. Because $D(s)$ and $N_{r,q}(s)$ are both polynomials with nonnegative coefficients obtained from weighted sums of spanning forests of $\widetilde{G}$, then whatever we assert for the coefficients of $N_{r,q}(s)$ will also apply to those of $D(s)$. By Prop. 2.19, we can write the transfer functions of both $\mathcal{M}$ and $\mathcal{M}^\star$ as

$$\mathcal{H}_{r,q}^{\mathcal{M}}(s) = \frac{N_{r,q}(\widetilde{G},s)}{D(\widetilde{G},s)} = \frac{\sum_{k=0}^{n-l_{r,q}-1} n_k(\widetilde{G})s^k}{\sum_{k=0}^{n} s^k d_k(\widetilde{G})}\,, \tag{3.2}$$

and,

$$\mathcal{H}_{r,q}^{\mathcal{M}^\star}(s) = \frac{N_{r,q}(\mathcal{A}_{i,j}[\widetilde{G}],s)}{D(\mathcal{A}_{i,j}[\widetilde{G}],s)} = \frac{\sum_{k=0}^{(n-1)-l^\star_{r,q}-1} n_k(\mathcal{A}_{i,j}[\widetilde{G}])s^k}{\sum_{k=0}^{n-1} s^k d_k(\mathcal{A}_{i,j}[\widetilde{G}])}\,, \tag{3.3}$$

where $l^\star_{r,q}$ is shortest path length in $\mathcal{A}_{i,j}[\widetilde{G}]$. By assumptions (1) and (2), there exists a directed path from q to r that does not contain i, and hence survives in $\mathcal{A}_{i,j}[G]$. Since the asymptotic edge $i \to_G j$ can occur at most once in each spanning forest of $\widetilde{G}$, each weighted sum must be at most linear in its parameter a_{ji}. Let us separate the spanning forests of $\widetilde{G}$ into two sets: those that contain the edge $i \to_G j$ and those that do not. Let us define $\Theta_k^+(\widetilde{G})$ as the set of spanning forests in $\widetilde{G}$ with $k+2$ trees that contain the edge $i \to j$,

$$\Theta_k^+(\widetilde{G}) = \{F \in \Theta_k(\widetilde{G}) : i \to_F j\}\,,$$

and $\Theta_k^0(\widetilde{G})$ as the set of spanning forests in $\widetilde{G}$ with $k+2$ trees that do not contain $i \to_G j$,

$$\Theta_k^0(\widetilde{G}) = \{F \in \Theta_k(\widetilde{G}) : i \not\to_F j\}\,.$$

We can thus write each coefficient n_k as an affine sum,

$$n_k(\widetilde{G}) = n_k^+(\widetilde{G}) + n_k^0(\widetilde{G})\,, \tag{3.4}$$

where $n_k^+(\widetilde{G})$ is the weighted sum over $\Theta_k^+(\widetilde{G})$ and $n_k^0(\widetilde{G})$ is the weighted sum over $\Theta_k^0(\widetilde{G})$. Similarly, we can follow the same procedure to write d_k as an affine sum; however, we need to construct different sets of spanning forests that contain $k+1$ trees instead of $k+2$ trees. For the sake of completeness, let $\Psi_k^+(\widetilde{G})$ denote the set of spanning forests of $\widetilde{G}$ with $k+1$ trees that contain $i \to j$, and $\Psi_k^0(\widetilde{G})$ the set of spanning forests in $\widetilde{G}$ with $k+1$ trees that do not contain $i \to_G j$.

With Eq. 3.4, we can expand $N_{r,q}(\widetilde{G},s)$ as follows,

$$N_{r,q}(\widetilde{G},s) = \sum_{k=0}^{n-l_{r,q}-1} s^k \left(n_k^+(\widetilde{G}) + n_k^0(\widetilde{G})\right)\,, \tag{3.5}$$

and apply the same step to $D(s)$. From here, we return to our expression for $\mathcal{H}^{\mathcal{M}}_{r,q}(s)$ and plug these new expressions in,

$$\mathcal{H}^{\mathcal{M}}_{r,q}(s) = \frac{\sum_{k=0}^{n-l_{r,q}-1} s^k \left(n_k^+(\widetilde{G}) + n_k^0(\widetilde{G})\right)}{\sum_{k=0}^{n} s^k \left(d_k^+(\widetilde{G}) + d_k^0(\widetilde{G})\right)}\,. \tag{3.6}$$

Because each $n_k^+(\widetilde{G})$ and $d_k^+(\widetilde{G})$ is linear in a_{ji}, we can multiply $\mathcal{H}^{\mathcal{M}}_{r,q}(s)$ by $(1/a_{ji})/(1/a_{ji})$,

$$\mathcal{H}^{\mathcal{M}}_{r,q}(s) = \frac{\sum_{k=0}^{n-l_{r,q}-1} s^k \left(\hat{n}_k^+(\widetilde{G}) + \frac{n_k^0(\widetilde{G})}{a_{ji}}\right)}{\sum_{k=0}^{n} s^k \left(\hat{d}_k^+(\widetilde{G}) + \frac{d_k^0(\widetilde{G})}{a_{ji}}\right)}\,, \tag{3.7}$$

where $\hat{n}_k^+(\widetilde{G}) = n_k^+(\widetilde{G})/a_{ji}$. Now we take the limit of $\mathcal{H}^{\mathcal{M}}_{r,q}(s)$ as $a_{ji} \to \infty$:

$$\lim_{a_{ji}\to\infty} \mathcal{H}^{\mathcal{M}}_{r,q}(s) = \lim_{a_{ji}\to\infty} \frac{\sum_{k=0}^{n-l_{r,q}-1} s^k \left(\hat{n}_k^+(\widetilde{G}) + \frac{n_k^0(\widetilde{G})}{a_{ji}}\right)}{\sum_{k=0}^{n} s^k \left(\hat{d}_k^+(\widetilde{G}) + \frac{d_k^0(\widetilde{G})}{a_{ji}}\right)} = \frac{\sum_{k=0}^{n-l_{r,q}-1} s^k \hat{n}_k^+(\widetilde{G})}{\sum_{k=0}^{n} s^k \hat{d}_k^+(\widetilde{G})}\,. \tag{3.8}$$

By assumption (1), we know that $\lim_{a_{ji}\to\infty} \mathcal{H}^{\mathcal{M}}_{r,q}(s) \neq 0$ strictly due to destruction of the measurement. Furthermore, based on the definition of a spanning forest and because $i \to j$ is an edge in G, then there must be at least one spanning forest of $\widetilde{G}$ that contains the edge $i \to j$. Thus, $\Theta_k^+(\widetilde{G})$ and $\Psi_k^+(\widetilde{G})$ are nonempty and $\hat{n}_k^+(\widetilde{G}), \hat{d}_k^+(\widetilde{G}) \neq 0$. Therefore, the limit in Eq. (3.8) is well-defined. We conclude from this procedure that only those forests that contain the edge $i \to j$ in $\widetilde{G}$ contribute to $\lim_{a_{ji}\to\infty} \mathcal{H}^{\mathcal{M}}_{r,q}(s)$.

Let us denote the set $\emptyset \neq \Omega^+(\widetilde{G})$ the set of all forests of $\widetilde{G}$ that contain the edge $i \to j$. Note that if $F \in \Omega^+(\widetilde{G})$, then F cannot contain any other edge that leaves i. Hence, if we invoke the asymptotic construction on the forest F, it yields a spanning forest of $\mathcal{A}_{i,j}[\widetilde{G}]$. This defines a mapping,

$$\xi : \Omega^+(\widetilde{G}) \to \Omega(\mathcal{A}_{i,j}[\widetilde{G}])\,. \tag{3.9}$$

where $\Omega(\mathcal{A}_{i,j}[\widetilde{G}])$ is the set of all spanning forests of $\mathcal{A}_{i,j}[\widetilde{G}]$. Before we proceed, we must verify that the tree-count is preserved by this mapping. Suppose a forest $F \in \Omega^+(\widetilde{G})$ has $k+2$-trees on $n+1$ vertices (the n vertices of G, plus the leak vertex 0 in $\widetilde{G}$). It follows that F must have $n+1-(k+2) = n-k-1$ edges. Because each $F \in \Omega^+(\widetilde{G})$ contains the edge $i \to j$, i has no other outgoing edges. When the asymptotic construction acts on $F \in \Omega^+(\widetilde{G})$, it eliminates i and removes exactly one outgoing edge: $i \to j$. Therefore, a forest $\xi(F) \in \Omega(\mathcal{A}_{i,j}[\widetilde{G}])$ is defined on n vertices and has $n-k-2$ edges, and thus it has $n-(n-k-2) = k+2$ trees. This is precisely the tree-count for the coefficient $n_k(\mathcal{A}_{i,j}[\widetilde{G}])$, obtained by applying Prop. 2.19 to $\mathcal{A}_{i,j}[\widetilde{G}]$. We discuss what happens to forests under the mapping based on the amalgamation next.

We can see that any spanning forest $F' \in \Omega(\mathcal{A}_{i,j}[\widetilde{G}])$ can also be lifted back to a spanning forest in $\Omega^+(\widetilde{G})$ by reintroducing the vertex i, unraveling any redirection and amalgamation, and adding back the edge $i \to j$: thus, $\xi(F) = F'$. From this observation, we conclude that ξ is surjective. However, ξ is not injective. Because of the amalgamation in the asymptotic graph construction, it is not always true that $w(\xi(F)) = w(F)/a_{ji}$.

To examine how the amalgamation acts on forests of $\widetilde{G}$, let us first consider a single forest $F' \in \Omega(\mathcal{A}_{i,j}[\widetilde{G}])$ that contains amalgamated edges from $z_1, \ldots, z_m$. For each such z_k, a forest in the preimage $\xi^{-1}(F')$ contains either the edge $z_k \to_G i$ or the edge $z_k \to_G j$. That is, each $F \in \xi^{-1}(F')$ is chosen by picking independently for each z_k whether F contains $z_k \to_G i$ or $z_k \to_G j$. Therefore, it follows that the number of forests in $\Omega^+(\widetilde{G})$ that contribute to the amalgamated forest F' is $|\xi^{-1}(F')| = 2^m$. We see from the definition of $\mathcal{A}_{i,j}[\widetilde{G}]$ that ξ maps all the trees in $\xi^{-1}(F')$ to the same tree $F' \in \Omega(\mathcal{A}_{i,j}[\widetilde{G}])$. Let $\mu_k = \{a_{iz_k}, a_{jz_k}\}$. We can write the weight of each $F \in \xi^{-1}(F')$ as,

$$w(F) = a_{ji}\alpha\,(\mu_1 \cdots \mu_m)\,\beta\,,$$

where μ_k is either a_{iz_k} or a_{jz_k} and α and β are polynomials in the remaining parameters of $\mathcal{M}$, excluding a_{ji}. Any forest F can be modified by a simple surgery, which switches the edges $z_k \to_G i$ and $z_k \to_G j$. This forest surgery allows every possible combination of such edges to be achieved without altering any other edges in F. We sum over all 2^m preimages to obtain,

$$\sum_{F \in \xi^{-1}(F')} w(F) = \sum_{F \in \xi^{-1}(F')} a_{ji}\alpha\,(\mu_1 \cdots \mu_m)\,\beta = a_{ji}\alpha\beta \prod_{k=1}^{m} (a_{iz_k} + a_{jz_k})\,, \tag{3.10}$$

where we recognize that summing the products $\mu_1 \cdots \mu_m$ over all 2^m independent choices of$\mu_k \in \{a_{iz_k}, a_{jz_k}\}$ is precisely the expansion of $\prod_{k=1}^{m}(a_{iz_k} + a_{jz_k})$. Because each amalgamated edge $z_k \to j$ in $\mathcal{A}_{i,j}[\widetilde{G}]$ carries the label $a_{iz_k} + a_{jz_k}$, and F' contains no factor of a_{ji}, the weight of F' is

$$w(F') = \alpha\beta \prod_{k=1}^{m} (a_{iz_k} + a_{jz_k}) = \frac{w(\xi^{-1}(F'))}{a_{ji}}\,, \tag{3.11}$$

where the last equality comes from Eq.3.10. ξ is now surjective, and its fibers form a partition of $\Omega^+(\widetilde{G})$. To obtain the full expression for $n_k(\mathcal{A}_{i,j}[\widetilde{G}], s)$, we sum over all $F' \in \Omega(\mathcal{A}_{i,j}[\widetilde{G}])$,

$$n_k^+(\widetilde{G}) = \sum_{F'} \sum_{F \in \xi^{-1}(F')} w(F) = a_{ji} \sum_{F'} w\left(F'\right) = a_{ji} n_k(\mathcal{A}_{i,j}[\widetilde{G}]). \tag{3.12}$$

Thus, $\hat{n}_k^+(\widetilde{G}) = n_k(\mathcal{A}_{i,j}[\widetilde{G}])$, and identically, $\hat{d}_k^+(\widetilde{G}) = d_k(\mathcal{A}_{i,j}[\widetilde{G}])$. Substituting into Eq. (3.8) yields $\lim_{a_{ji}\to\infty} \mathcal{H}_{r,q}^{\mathcal{M}}(s) = \mathcal{H}_{r,q}^{\mathcal{M}^\star}(s)$, as required. ∎

Because we have demonstrated that each entry of $\mathcal{H}^{\mathcal{M}}$, under the assumptions of Thm. 3.5, converges asymptotically to the corresponding entry of $\mathcal{H}^{\mathcal{M}^\star}$, it is natural to consider the generalization of Thm. 3.5 and the relationship between the full transfer function matrices $\mathcal{H}^{\mathcal{M}}$ and $\mathcal{H}^{\mathcal{M}^\star}$. First, we must note that $\mathcal{H}^{\mathcal{M}}$ differs in dimension from $\mathcal{H}^{\mathcal{M}^\star}$. So, any

comparison between matrices must be between the appropriate submatrix of $\mathcal{H}^{\mathcal{M}}$ and $\mathcal{H}^{\mathcal{M}^\star}$. Recall that the transfer function matrix is indexed by the input and output sets of a given compartment model. Thus, we must consider the submatrix of $\mathcal{H}^{\mathcal{M}}$ indexed by the inputs and outputs of $\mathcal{H}^{\mathcal{M}^\star}$. Additionally, according to Def. 3.2, it is possible that $j \in In^\star$ while $j \notin In$. With these points in mind, we can state the following corollary.

Corollary 3.6. *Let $\mathcal{M}$ and $\mathcal{M}^\star$ be linear compartment models as defined in Thm. 3.5. Suppose the hypotheses of Thm. 3.5 hold for each input, output pair $(q, r) \in In^\star \times Out^\star$. Let us further suppose that $In^\star \subseteq In$ and $Out^\star \subseteq Out$. Let $\mathcal{H}^{\mathcal{M}}_{[Out^\star,\ In^\star]}$ denote the submatrix of $\mathcal{H}^{\mathcal{M}}$ with rows indexed by the set $Out^\star$ and columns indexed by the set $In^\star$. Then, it follows from Thm. 3.5 that $\lim_{a_{ji}\to\infty} \mathcal{H}^{\mathcal{M}}_{[Out^\star,\ In^\star]} = \mathcal{H}^{\mathcal{M}^\star}$.*

3.3. Topological and dynamical equivalence of linear compartment models. As we use Thm. 3.5 through the rest of the paper, it will be helpful to formally define concepts that allow us to compare different linear compartment models. It is possible for the underlying graphs of two linear compartment models to have the same topology, but differ in the way their edges are labeled. It is also possible for two linear compartment models with different underlying graph structures to have the same transfer function, and consequently, the same identifiability. We define these notions as *topological equivalence* and *dynamical equivalence*, respectively. It should be noted that dynamical equivalence adopts a different definition in other contexts, such as chemical reaction network theory [28]. The definition we give here is specific to the context in which we are investigating in this work.

Definition 3.7. *Two linear compartment models $\mathcal{M}_1$ and $\mathcal{M}_2$ are* topologically equivalent *if there exists a graph isomorphism $\phi : G_1 \to G_2$ that preserves the input, output, and leak structure. That is, $\mathcal{M}_1 \sim_{top} \mathcal{M}_2$ if $\phi(G_1) = G_2$, $\phi(In_1) = In_2$, $\phi(Out_1) = Out_2$, and $\phi(Leak_1) = Leak_2$.*

Definition 3.8. *Two linear compartment models $\mathcal{M}_1$ and $\mathcal{M}_2$ are* dynamically equivalent *if they have the same transfer function. That is, $\mathcal{M}_1 \sim_{dyn} \mathcal{M}_2$ if $\mathcal{H}^{\mathcal{M}_1}(s) = \mathcal{H}^{\mathcal{M}_2}(s)$.*

These definitions are independent: two models may be topologically equivalent without having the same transfer function, or dynamically equivalent despite having different underlying graph topologies. We will encounter both situations; see the Supplementary Information for an extended discussion on topological and dynamical equivalence. We further note that within a class of dynamically equivalent models, a linear compartment model's structural identifiability in the transfer function setting is invariant. This is not true of topological equivalence, although two models that are topologically equivalent will have related identifiability based on the graph isomorphism ϕ between them.

Remark 3.9. It should be noted that dynamical equivalence and topological equivalence are both closely related to input-output equivalence, or indistinguishability. Input-output equivalence implies dynamical equivalence, however the reverse can be untrue if one of the compared models contains parameters that are unidentifiable by insensitivity. Similarly, two models that are topologically equivalent may not be input-output equivalent, but will be indistinguishable based on the graph isomorphism ϕ between them.

To illustrate Thm. 3.5, we compare the transfer function of a linear compartment model

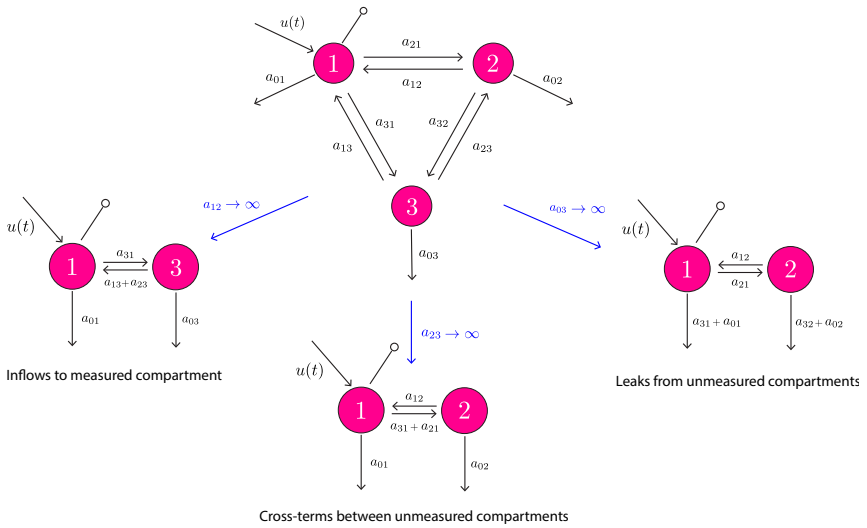


Figure 3: Illustration of the three canonical types of asymptotic compartment models obtained from taking different infinite parameter limits in the 3-compartment cyclic model.

$\mathcal{M}$ under the limit of a single parameter going to infinity and that of the corresponding asymptotic linear compartment model $\mathcal{M}^\star$ in the following example.

Example 3.10 (Ex. 2.15 continued). Having obtained the transfer function matrix $\mathcal{H}_{1,1}(s)$ in Ex 2.15, now we can explore sending different parameters to ∞ and compare the resulting transfer functions. From Lem. 3.4, we know that sending any parameter associated with an edge outgoing from 1 to ∞ will result in a transfer function of 0. Now, we consider what happens to the transfer function for this example when we take different singular parametric limits to ∞ (other than those outgoing from 1), illustrated in Fig. 3.

Inflows to measured compartment: We first select a rate attached to an edge that is an inflow to the measured compartment 1. Let us apply the asymptotic construction to the 3-compartment model via the parameter a_{12}. The resulting asymptotic linear compartment model $\mathcal{M}^\star_{a_{12}}$ is given in Fig. 3. We compute its transfer function,

(3.13)
$$\mathcal{H}_{1,1}^{\mathcal{M}^\star_{a_{12}}}(s) = \frac{a_{03}+a_{13}+a_{23}+s}{(a_{01}a_{03}+a_{01}a_{13}+a_{01}a_{23}+a_{03}a_{31})+(a_{01}+a_{03}+a_{13}+a_{23}+a_{31})s+s^2}\,.$$

To compare, let us recall the full transfer function for the 3-compartment model in Eq. (2.8). If we take the limit $a_{12}\to\infty$ of Eq. (2.8), we find that,

$$\mathcal{H}_{1,1}^{\mathcal{M}^\star_{a_{12}}}(s) = \lim_{a_{12}\to\infty} \mathcal{H}_{1,1}^{\mathcal{M}}(s)\,,$$

which matches the conclusion of Thm. 3.5.

Cross-terms between unmeasured compartments: Next, we consider the asymptotic construction applied to a rate associated with a cross-term between unmeasured compartments. Let us apply the asymptotic construction to the 3-compartment model along the

parameter a_{23}. The resulting asymptotic linear compartment model $\mathcal{M}^\star_{a_{23}}$ is given in Fig. 3. The transfer function for $\mathcal{M}^\star_{a_{23}}$ is given by,

$$\mathcal{H}_{1,1}^{\mathcal{M}^\star_{a_{23}}}(s) = \frac{a_{02}+a_{12}+s}{(a_{01}a_{02}+a_{01}a_{12}+a_{02}a_{21}+a_{02}a_{31})+(a_{01}+a_{02}+a_{12}+a_{21}+a_{31})s+s^2}\,. \tag{3.14}$$

Once again, we compare $\mathcal{H}_{1,1}^{\mathcal{M}^\star_{a_{23}}}(s)$ to the limit of $\mathcal{H}_{1,1}^{\mathcal{M}}(s)$ as $a_{23}\to\infty$. We find that,

$$\mathcal{H}_{1,1}^{\mathcal{M}^\star_{a_{23}}}(s) = \lim_{a_{23}\to\infty} \mathcal{H}_{1,1}^{\mathcal{M}}(s)\,,$$

which again matches the conclusion of Thm. 3.5.

Leaks from unmeasured compartments: Sending a leak to ∞ results in amalgamation along the other leaks in $\mathcal{M}$ for this example. When we send $a_{03}\to\infty$ in the full 3-compartment model, we obtain the asymptotic linear compartment model $\mathcal{M}^\star_{a_{03}}$, which is given in Fig. 3. The transfer function for $\mathcal{M}^\star_{a_{03}}$ is given by,

$$\mathcal{H}_{1,1}^{\mathcal{M}^\star_{a_{03}}}(s) = \frac{a_{02}+a_{12}+a_{32}+s}{a_{11}a_{22}+(a_{01}+a_{02}+a_{12}+a_{21}+a_{31}+a_{32})s+s^2}\,. \tag{3.15}$$

The identifiable combinations of parameters are:

$$\begin{aligned} &a_{11}a_{22}\,,\\ &a_{02}+a_{12}+a_{32}=a_{22}\,,\\ &a_{01}+a_{02}+a_{12}+a_{21}+a_{31}+a_{32}=a_{11}+a_{22}\,. \end{aligned}$$

Once again, if we compare $\mathcal{H}_{1,1}^{\mathcal{M}^\star_{a_{03}}}(s)$ to the limit of $\mathcal{H}_{1,1}^{\mathcal{M}}(s)$ as $a_{03}\to\infty$, we find that,

$$\mathcal{H}_{1,1}^{\mathcal{M}^\star_{a_{03}}}(s) = \lim_{a_{03}\to\infty} \mathcal{H}_{1,1}^{\mathcal{M}}(s)\,.$$

By Thm. 3.5, we know that $\mathcal{H}^{\mathcal{M}^\star_{a_{ji}}}(s) = \lim_{a_{ji}\to\infty}\mathcal{H}^{\mathcal{M}}(s)$ no matter which rate we select to send to ∞. The remaining singular limits and their transfer functions are listed in Sec. S3 of the Supplementary Information.

The six singular parametric limits of the 3-compartment cyclic model computed in Ex. 3.10 and in the Supplementary Information reveal a pattern organized by the *symmetry classes* of rates. For this example, we have the following symmetry classes of rates for $\mathcal{M}$:

- Inflows into compartment 1: $\{a_{12}, a_{13}\}$
- Cross-terms between unmeasured compartments: $\{a_{32}, a_{23}\}$
- Leaks out of unmeasured compartments: $\{a_{03}, a_{02}\}$.

Within each class, we observe that the construction appears to produce transfer functions of the same structural form, differing only by an exchange of the indices 2 and 3. Consider the inflow class $\{a_{12}, a_{13}\}$. Sending $a_{12}\to\infty$ yields a numerator $a_{03}+a_{13}+a_{23}+s$, while sending $a_{13}\to\infty$ yields $a_{02}+a_{12}+a_{32}+s$. These polynomials are identical under the exchange of indices $2\leftrightarrow 3$. That is, we find $a_{03}\leftrightarrow a_{02}$, $a_{13}\leftrightarrow a_{12}$, and $a_{23}\leftrightarrow a_{32}$. The same correspondence holds between the denominators, and for the transfer functions within each symmetry class.

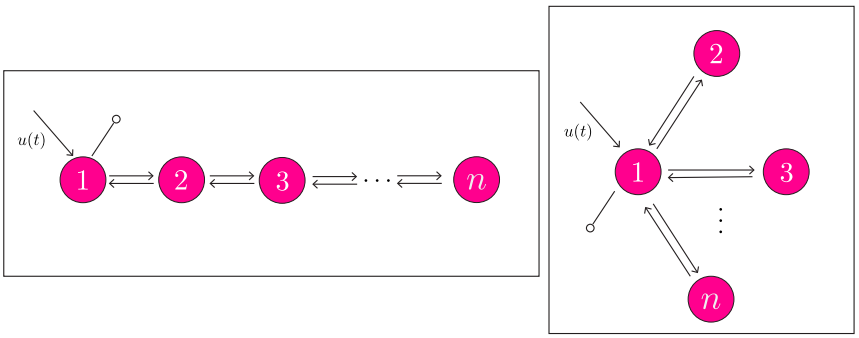


Figure 4: Generic catenary (left) and mammillary (right) models.

3.4. Asymptotic construction on linear compartment model families. Certain families of linear compartment models are especially well-studied in terms of their structural identifiability [43, 13]. One such class is the class of cyclic models, including the 3-compartment model we have used as a running example in this work. Two other well-studied model families are mammillary and catenary models, which we define below.

Definition 3.11. *Let $\mathcal{M} = (G, In, Out, Leak)$ be a linear compartment model. Here, the input and output is conventionally placed in compartment* 1.

- *$\mathcal{M}$ is a* mammillary model *if $G = (V, E)$ is a bidirectional star graph, where $V = \{1, \dots, n\}$ and $E = \{1 \leftrightharpoons 2, 1 \leftrightharpoons 3, \dots, 1 \leftrightharpoons n\}$. Here, 1 is designated the central compartment, which is connected to peripheral compartments $2, 3, \dots, n$.*
- *$\mathcal{M}$ is a* catenary model *if $G = (V, E)$ is a bidirectional path graph, where $V = \{1, \dots, n\}$ and $E = \{1 \leftrightharpoons 2, 2 \leftrightharpoons 3, \dots, n-1 \leftrightharpoons n\}$.*

Here, we investigate the effect of the asymptotic construction on these model families.

3.4.1. Mammillary models (star graphs). Because every edge in the directed graph of a mammillary model takes the form $1 \to k$ or $k \to 1$, where $k \in \{2, \dots, n\}$ and 1 is the central compartment, it follows that 1 must always be either i or j. It is also evident from the structure of the mammillary graph that no amalgamation takes place under the asymptotic construction (unless we consider leaks). We consider below a few different cases for how the asymptotic construction affects the identifiability of a generic mammillary model of the form depicted in Fig. 4.

Proposition 3.12. *Let $\mathcal{M} = (G, In, Out, Leak)$ be a n-compartment mammillary model with* 1 *as the central compartment and $2, \dots, n$ as peripheral compartments. Suppose $a_{ji} \to \infty$, where a_{ji} is the parameter associated with edge $i \to j$ in G. Let*

$$\mathcal{M}^\star = (\mathcal{A}_{i,j}[G], In^\star, Out^\star, Leak^\star)$$

be the resulting asymptotic compartment model. Let $i = 1$ and j be any peripheral compartment. Then, $\mathcal{M}^\star$ is no longer a mammillary model, as it has no outgoing edges from the central compartment j to any peripheral compartments.

Proof. For a mammillary model, all the edges in G are of the form $k \to 1$ or $1 \to k$, for any peripheral compartment k. Because 1 is the central node in the mammillary model, it has bidirectional edges to all other vertices in G. Because 1 is the source of the asymptotic edge, compartment 1 is deleted as a result of Def. 3.2. All other compartments remain in $\mathcal{A}_{i,j}[G]$; that is, the vertex set of $\mathcal{A}_{i,j}[G]$ is $V(\mathcal{A}_{i,j}[G]) = V(G) \setminus \{1\}$. As for the edge set of $\mathcal{A}_{i,j}[G]$, we can see from Def. 3.2 that every edge in G is affected by the asymptotic construction. All edges incoming to 1 are of the form $k \to 1$ for each peripheral compartment k. Each of these edges are redefined in $\mathcal{A}_{i,j}[G]$ as $k \to j$. There are no preexisting edges in G of the form $k \to j$ because peripheral compartments are not connected via direct edges in mammillary model graphs. The only edges incident to compartment j are $1 \to j$ and $j \to 1$, which are deleted by the construction as a result of $1 \to j$ being the asymptotic edge. Thus, the topology of $\mathcal{A}_{i,j}[G]$ is that of a unidirectional star graph on $n-1$ vertices where j is the central compartment. There are edges $k \to j$ for each peripheral compartment, as discussed above. There are no edges $j \to k$ because these edges did not exist in G. There are no other edges in $\mathcal{A}_{i,j}[G]$. ■

Note that if $i = 1 \in Out$, then the measurement gets destroyed as a consequence of Lem. 3.4.

Proposition 3.13. *Let $\mathcal{M} = (G, In, Out, Leak)$ be a n-compartment mammillary model with 1 as the central compartment and $2, \ldots, n$ as peripheral compartments. Suppose $a_{ji} \to \infty$, where a_{ji} is the parameter associated with edge $i \to j$ in G. Let*

$$\mathcal{M}^\star = (\mathcal{A}_{i,j}[G], In^\star, Out^\star, Leak^\star)$$

be the resulting asymptotic compartment model. Let $j = 1$ and i be any peripheral compartment. Then $\mathcal{M}^\star$ is a mammillary model with $n-1$ compartments, and j remains the central compartment. Additionally:

1. *Let $1 \in In$ and $1 \in Out$, and $i \notin In, Out$. Then $In^\star = In$ and $Out^\star = Out$ in $\mathcal{M}^\star$.*
2. *Let $i \notin Out$ and $i \in In$. Then $In^\star = (In \cup \{1\}) \setminus \{i\}$ and $Out^\star = Out$.*
3. *Let $1 \in In$ and $i \in Out$. Then $In^\star = In$ and $Out^\star = Out \setminus \{i\}$.*

Proof. As in Prop. 3.12, because $\mathcal{M}$ is a mammillary model, all edges in G are of the form $k \to 1$ or $1 \to k$ for any peripheral compartment k. Thus, $\mathcal{A}_{i,j}[G]$ maintains the mammillary model topology with vertex set $V(\mathcal{A}_{i,j}[G]) = V(G) \setminus \{i\}$ and $E(\mathcal{A}_{i,j}[G]) = E(G) \setminus \{1 \to i, i \to 1\}$. Applying the asymptotic construction on a mammillary model whose central compartment is the target of the asymptotic edge results in the elimination of the peripheral compartment i and the edges between i and 1. No amalgamation takes place, as there are no edges incoming to i other than $1 \to i$. No other edges in the graph are eliminated, as there are no edges outgoing from i other than $i \to 1$. That is, no other edges or compartments are affected by the asymptotic construction. What remains is a mammillary model, with central compartment at 1, with one fewer peripheral compartment. Thus, $\mathcal{M}^\star$ is a mammillary model with $n-1$ compartments.

We now consider how the input and output paths are affected by the asymptotic construction applied to the mammillary model. We first consider the case where $1 \in In$ and $1 \in Out$. Because 1 is not the source of the asymptotic edge, then by Def. 3.2, neither the input nor the output localized at 1 are affected by the asymptotic construction. Thus, $In^\star = In$ and

$Out^\star = Out$, as required. In the case where $1 \in Out$ and $i \in In$, as a consequence of Def. 3.2, the input at i moves to 1. Thus, $In^\star = (In \cup \{1\}) \setminus \{i\}$. The output at 1 is not affected by the asymptotic operation. $Out^\star = Out$ as $i \notin Out$. This proves the second assertion. Finally, in the case where $1 \in In$ and $i \in Out$, as a consequence of Def. 3.2, the output at i is eliminated from $\mathcal{M}^\star$. Thus, $Out^\star = Out \setminus \{i\}$. If $Out = \{i\}$, it follows that $Out^\star = \emptyset$. The input at 1 is unaffected by the asymptotic construction. Thus, $In^\star = In$, as required. ∎

Corollary 3.14. *Given the assumptions of Prop. 3.12, let us further assume that $In = \{i\}$ and $Out \neq \{i\}$. Then, as a result of applying the asymptotic construction on the edge $i \to 1$, $\mathcal{M}^\star$ is a $n-1$ compartment mammillary model with central compartment 1, $In^\star = \{1\}$, and $Out^\star = Out \neq \{i\}$.*

Proof. By Prop. 3.12, $\mathcal{M}^\star$ is a mammillary model with $n-1$ compartments. If $In = \{i\}$, then by Def. 3.2 the input at i moves to 1. Thus, $In^\star = \{1\}$. Out is unchanged as a result of the asymptotic construction, and so $Out^\star = Out$. This proves the corollary. ∎

A complete three-compartment mammillary example, including the corresponding transfer functions under each symmetry class of limits, is given in the Supplementary Information.

3.4.2. Catenary models. Unlike the cyclic and mammillary models, the catenary model lacks symmetry about the input and measurement compartment. Thus, the asymptotic construction has different implications on structural identifiability as measured by the transfer function for this class of models. A detailed three-compartment example illustrating the distinct catenary limits is provided in the Supplementary Information. We explore more generally the ways in which Thm. 3.5 impacts the identifiable combinations of catenary models below.

Proposition 3.15. *Let $\mathcal{M} = (G, In, Out, Leak)$ be a catenary model with $In = Out = \{1\}$. Let $2, \ldots, n$ comprise the remaining compartments. Let j be an interior compartment with neighboring compartments $i = j-1 \geq 2$ and $k = j+1 \leq n$. Suppose $j \in Leak$. Let $\mathcal{M}^\star_{a_{ij}}, \mathcal{M}^\star_{a_{kj}}, \mathcal{M}^\star_{a_{0j}}$ represent the asymptotic compartment models obtained from sending rates a_{ij}, a_{kj} and $a_{0j} \to \infty$, respectively. Then, the following statements hold:*

1. *Any parameters associated with compartment k through compartment n (not including any inflows to k from j) are unidentifiable by insensitivity in $\mathcal{M}^\star_{a_{ij}}, \mathcal{M}^\star_{a_{kj}}, \mathcal{M}^\star_{a_{0j}}$.*
2. *$\mathcal{M}^\star_{a_{kj}}$ and $\mathcal{M}^\star_{a_{0j}}$ are dynamically equivalent.*

The proof of Prop. 3.15 is included in the Supplementary Information, and it is illustrated for the 4-catenary model in Fig. 5.

3.5. Asymptotic construction's effect on structural identifiability of a model. Having established that the limit of the transfer function correctly captures the identifiability of the limiting model, the natural following question is whether such limiting cases can lead to a change in a model's identifiability. That is, can an unidentifiable model become identifiable, and vice versa? As we will show below, both are possible. When models become unidentifiable as a result of sending a parameter to infinity, that model often becomes unidentifiable due to insensitivity. We demonstrate these features with the following two examples.

Example 3.16 (Recovering identifiability under the asymptotic construction). Consider a variation on the 3-compartment catenary model $\mathcal{M}$ with $In = \{1\}$, $Out = \{3\}$, and $Leak = \{2\}$ in Fig. 6.

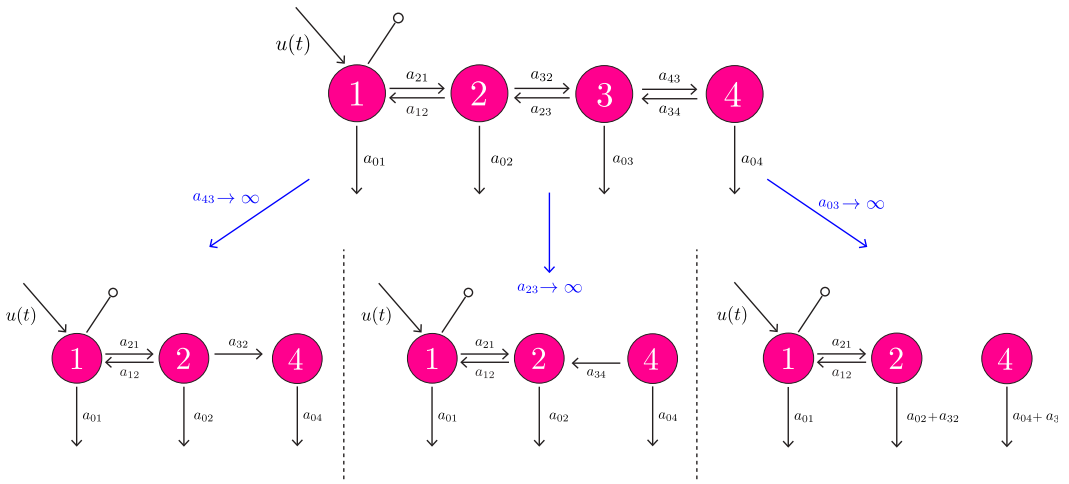


Figure 5: Prop. 3.15 on the 4-catenary model. We consider the asymptotic compartment models produced by sending different outflows from interior compartment 3 to ∞. From left to right: sending $a_{43} \to \infty$ eliminates compartment 3 and redirects the inflow $2 \to 3$ into compartment 4; sending $a_{23} \to \infty$ instead eliminates compartment 3 and redirects the inflow $4 \to 3$ into compartment 2; and sending the leak $a_{03} \to \infty$ eliminates compartment 3 and turns both of its inflows into leaks, amalgamated onto the existing leaks of 2 and 4; the resulting model $\mathcal{M}^\star_{a_{03}}$ has 2 and 4 disconnected.

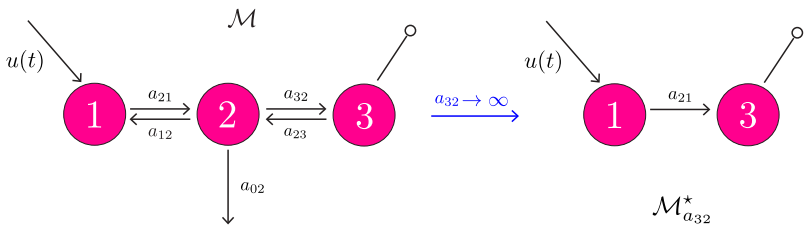


Figure 6: The asymptotic construction applied to an unidentifiable model may become identifiable in the limit. A variation of the 3-compartment catenary model $\mathcal{M}$, and the asymptotic compartment model corresponding to $a_{32} \to \infty$, $\mathcal{M}^\star_{a_{32}}$.

For completeness, we provide the full transfer function for $\mathcal{M}$ in the Supplementary Information. $\mathcal{M}$ is not structurally identifiable; none of its five parameters are identifiable, as the parameters a_{21} and a_{32} enter the numerator only through the product $a_{21}a_{32}$ and cannot be separated from the input-output data. When we send $a_{32} \to \infty$, we obtain the asymptotic compartment model $\mathcal{M}^\star_{a_{32}}$, depicted in Fig. 6. Its transfer function is,

$$\mathcal{H}_{3,1}^{\mathcal{M}^\star_{a_{32}}}(s) = \frac{a_{21}}{s^2 + a_{21}s}\,. \tag{3.16}$$

We can see that the asymptotic compartment model $\mathcal{M}^\star_{a_{32}}$ *is* structurally identifiable, as the

sole remaining parameter a_{21} appears in Eq. (3.16) and is recovered uniquely from the transfer function. It is worth considering the mechanism. In the original model's transfer function (see SI for the full expression), a_{21} and a_{32} are entangled in the numerator coefficient so neither can be identified individually. Sending $a_{32} \to \infty$ removes a_{32} from the model entirely. All the other outflows from 2 and the rates between 2 and 3 are also eliminated through the asymptotic construction, leaving a_{21} as the sole parameter in the model. Identifiability is thus recovered not by disentangling an unidentifiable combination, but by eliminating all but one parameter through the asymptotic construction.

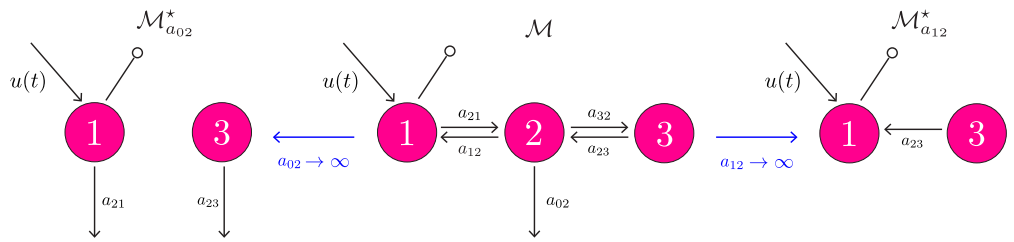


Figure 7: The asymptotic construction applied to an identifiable model may become unidentifiable in the limit. An identifiable 3-catenary model $\mathcal{M}$, and the asymptotic compartment models corresponding to $a_{02} \to \infty$ and $a_{12} \to \infty$, $\mathcal{M}^\star_{a_{02}}$ and $\mathcal{M}^\star_{a_{12}}$ respectively.

Example 3.17 (Rendering a model unidentifiable under the asymptotic construction). We now consider a variation on the identifiable catenary model $\mathcal{M}$, which is depicted in Fig. 7. Here, we consider two different infinite parameter limits of $\mathcal{M}$. The first limit is $a_{02} \to \infty$, which generates $\mathcal{M}^\star_{a_{02}}$. Its transfer function is given by,

$$\mathcal{H}_{1,1}^{\mathcal{M}^\star_{a_{02}}} = \frac{a_{23}+s}{(a_{21}+s)(a_{23}+s)} = \frac{1}{a_{21}+s}\,. \tag{3.17}$$

The second limit is $a_{12} \to \infty$, which produces $\mathcal{M}^\star_{a_{12}}$. Its transfer function is given by,

$$\mathcal{H}_{1,1}^{\mathcal{M}^\star_{a_{12}}} = \frac{a_{23}+s}{s(a_{23})+s^2} = \frac{1}{s}\,. \tag{3.18}$$

As evidenced by Fig. 7 and Eqs. (3.17)- (3.18), both asymptotic compartment models $\mathcal{M}^\star_{a_{02}}$ and $\mathcal{M}^\star_{a_{12}}$ are unidentifiable by insensitivity.

Through these examples, we have shown that it is possible for the asymptotic construction to recover identifiability from an unidentifiable linear compartment model. A larger four-compartment example exhibiting the same loss of identifiability by insensitivity is provided in the Supplementary Information. We have also shown that the asymptotic construction may render an identifiable linear compartment model unidentifiable. However, in both examples we displayed here, the model is not only unidentifiable but unidentifiable by insensitivity. The preceding examples suggest an interesting phenomenon: if an identifiable linear compartment model becomes unidentifiable when a parameter is sent to infinity, is this only possible if the model becomes unidentifiable by insensitivity? We state below a conjecture:

Conjecture 3.18. Let $\mathcal{M}$ be an identifiable linear compartment model. Suppose $\mathcal{M}^\star$ is the corresponding asymptotic linear compartment model obtained by sending $a_{ji} \to \infty$, where a_{ji} is the parameter associated with the edge $i \to j \in E(G)$. If $\mathcal{M}^\star$ is unidentifiable, then it must be unidentifiable by insensitivity.

As we have observed this phenomenon primarily through a collection of examples, it remains to be seen to what extent this conjecture holds in generality.

4. Discussion. Timescale separation or fast-slow dynamics are quite common in many modeling and mathematical biology applications [25, 33, 41], and are typically represented by considering infinite limits for parameters representing particular processes. However, while the implications for the identifiability of these infinite parametric limits are sometimes considered for individual models [11, 17], or for exploring practical identifiability and sloppiness [42], there has so far been little or no theoretical work exploring how structural identifiability is impacted for larger classes of models. Here, we explore this question for a commonly used class of models, linear compartment models, using graph-theoretic approaches developed in the setting of chemical reaction networks [39] and the linear framework [26, 27]. We show here that the transfer function for a linear compartment model, as well as its associated identifiability implications, will commute with the infinite parameter limit, enabling us to determine model identifiability for any limiting cases of the model directly from the original model transfer function. We then illustrate some of the implications of this theorem for a range of commonly used model classes, particularly mammillary and catenary models. Furthermore, we hypothesize that the construction limits the ways in which an identifiable model can become unidentifiable, through the concept of a model being unidentifiable by insensitivity.

The work here focuses on the transfer function approach to elucidate a linear compartment model's structural identifiability. Because the transfer function is a rational function that can be expressed in terms of polynomials of the parameters [39], it was especially ideal for taking limits of parameters and investigating the effect on the structural identifiability for classes of models. However, the transfer function often assumes the model to have zero initial conditions [1, 3]. A future goal will be to revisit this analysis with generic initial conditions, e.g. represented as delta function inputs to the compartments with an unknown scaling parameter. Another natural follow-up question to this work is how the analysis presented here will extend to the differential algebra approach to structural identifiability. Much work has been done using graph-theoretic approaches on linear compartment models as a setting to understand structural identifiability [8, 9, 10, 24], and even how network operations performed on linear compartment models affect a model's structural identifiability [23]. However, the key objects of the differential algebra approach, namely the input-output equations, are not rational functions like the transfer function, making them potentially more difficult to work with in the infinite limit setting. A future direction will be to explore connections to the differential algebra method and how single parametric limits affect the input-output equation.

Aside from the immediate extensions of our work, this paper opens up many other exciting areas of exploration related to structural identifiability and unidentifiability. Throughout this paper, we have included many examples of single-input single-output (SISO) models. One can imagine a host of additional results in the vein of Prop. 3.12, Prop. 3.13, and Prop. 3.15 that may emerge when considering multi-input multi-output (MIMO) models. It should be

noted that the results in this paper can naturally extend to MIMO models. However, there are patterns that can emerge in this setting that we do not observe in the SISO case. For example, if a limit splits a model into two pieces with one input-output in each portion, the cross terms of the transfer function (between the two portions) will now be zero. Proving patterns such as these is an interesting direction for future work. We have also introduced the topics of topological and dynamic equivalence, which are related to the well-characterized notion of indistinguishability in the identifiability literature [10, 16].

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