

Research



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Author for correspondence:
 Yang-Yu Liu
 e-mail: yyli@channing.harvard.edu

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Fundamental limitations of network reconstruction from temporal data

Marco Tulio Angulo¹, Jaime A. Moreno², Gabor Lippner³,
 Albert-László Barabási^{4,5,6} and Yang-Yu Liu^{5,7,8}

¹Institute of Mathematics, Universidad Nacional Autónoma de México, Juriquilla 76230, México

²Institute of Engineering, Universidad Nacional Autónoma de México, CdMx 04510, México

³Department of Mathematics, and ⁴Center for Complex Networks Research, Northeastern University, Boston MA 02115, USA

⁵Center for Cancer Systems Biology, Dana-Farber Cancer Institute, Boston, MA 02115, USA

⁶Center for Network Science, Central European University, Budapest 1052, Hungary

⁷Channing Division of Network Medicine, Brigham and Women's Hospital, and ⁸Harvard Medical School, Boston, MA 02115, USA

MTA, 0000-0002-9802-8567; Y-YL, 0000-0003-2728-4907

Inferring properties of the interaction matrix that characterizes how nodes in a networked system directly interact with each other is a well-known network reconstruction problem. Despite a decade of extensive studies, network reconstruction remains an outstanding challenge. The fundamental limitations governing which properties of the interaction matrix (e.g. adjacency pattern, sign pattern or degree sequence) can be inferred from given temporal data of individual nodes remain unknown. Here, we rigorously derive the necessary conditions to reconstruct any property of the interaction matrix. Counterintuitively, we find that reconstructing any property of the interaction matrix is generically as difficult as reconstructing the interaction matrix itself, requiring equally informative temporal data. Revealing these fundamental limitations sheds light on the design of better network reconstruction algorithms that offer practical improvements over existing methods.

1. Introduction

Networks are central to the functionality of complex systems in physics, engineering, biology and medicine [1–3], often serving as a conduit to the system dynamics and fundamentally affecting their dynamic behaviour [4–10]. Network reconstruction (NR)—recovering properties of the underlying interconnection network of the system from temporal data of its nodes—thus provides a first step to understand, diagnose and control the dynamics of diverse networked systems [11–17]. Let $x_i(t) \in \mathbb{R}$ be the activity of node i —representing the concentration of a certain biomolecule, or the abundance of a certain species, etc.—in a networked system of n nodes. Assume that the system dynamics is dominated by pairwise interaction and can be described by a set of ordinary differential equations (ODEs)

$$\dot{x}_i(t) = \sum_{j=1}^n a_{ij} f_{ij}(x_i(t), x_j(t)) + u_i(t); \quad i = 1, \dots, n, \quad (1.1)$$

where the *coupling functions* $f_{ij} : \mathbb{R} \times \mathbb{R} \rightarrow \mathbb{R}$ specify how two nodes interact, and $u_i(t) \in \mathbb{R}$ represents some known signals. The *interaction matrix* $A = (a_{ij}) \in \mathbb{R}^{n \times n}$ captures direct interactions between nodes, defining the interconnection network of the system by associating a_{ij} to the directed edge $j \rightarrow i$. By appropriately choosing the coupling functions, equation (1.1) models a broad class of networked systems [18].

Given some function \mathcal{P} of the interaction matrix—which we call a *property*—NR aims to recover $\mathcal{P}(A)$ from given temporal data $\{x_i(t), u_i(t)\}_{i=1}^n, \forall t \in [t_0, t_1]$, and given knowledge of the coupling functions. Reconstructing the identity property (i.e. A itself) is equivalent to the classical *parameter* (PI) problem [19,20]. But

we can also reconstruct other properties of A , such as its *sign pattern* $S = [s_{ij}] = [\text{sign}(a_{ij})] \in \{-1, 0, 1\}^{n \times n}$, *connectivity pattern* $C = [c_{ij}] = [|s_{ij}|] \in \{0, 1\}^{n \times n}$, *adjacency pattern* $K = [k_{ij}] = [c_{ij}(1 - \delta_{ij})] \in \{0, 1\}^{n \times n}$ (δ_{ij} is the Kronecker delta) or *in-degree sequence* $d = [d_i] = [\sum_j c_{ij}] \in \mathbb{Z}^n$. Note the adjacency pattern is obtained from the connectivity pattern by ignoring self-loops. Many characteristics of networked systems such as sign stability [21], robustness [22], controllability [8,9,23], observability [10] and epidemic thresholds [24] can be determined from the above properties without knowing A . In general, $\mathcal{P}(A)$ cannot be reconstructed from correlation or association analysis, but requires more sophisticated NR algorithms [11–17,25,26]; see also electronic supplementary material 1 for a summary of existing NR algorithms. However, after a decade of extensive studies, some core problems in NR remain open [27–33]. In particular, we still lack an identifiability analysis characterizing the conditions on the temporal data and knowledge of the coupling functions that are necessary to reconstruct a desired property $\mathcal{P}(A)$ [34,35].

Our main contribution here is to derive such necessary conditions in the ideal case (i.e. all state variables are measured without any measurement noise), rendering fundamental limitations of NR in the sense that those conditions are necessary regardless of which NR algorithm is used. By checking these conditions, we can decide if an NR algorithm failing to recover $\mathcal{P}(A)$ is due to some design flaws, or due to limitations intrinsic to the available temporal data and/or our knowledge about the coupling functions. The relevance of our analysis is that we are able to establish, for the first time, if NR problems can be solved with less informative data than that required for solving the classical PI problem, which is one of the major motivations for using NR instead of PI algorithms. Indeed, our intuition suggests that this should be possible because we are recovering less information (e.g. K instead of A). But, is this true?

A property $\mathcal{P}(A)$ can be reconstructed if and only if (iff) any two interaction matrices $A_1, A_2 \in \mathbb{R}^{n \times n}$ with different properties $\mathcal{P}(A_1) \neq \mathcal{P}(A_2)$ produce different node trajectories $\{x_i(t)\}_{i=1}^n, t \in [t_0, t_1]$, a notion of *identifiability* or *distinguishability* [19]. Note that in case all state variables are measured (i.e. if the so-called ‘observation function’ satisfies $y = x$), an ODE model with parameters A is called *structurally identifiable* if any two distinct parameters $A_1 \neq A_2$ produce different right-hand sides of the ODEs [36]. Structural identifiability is a property of the considered model only, independent of the measured temporal data. Hence, the lack of structural identifiability can only be solved by modifying the model itself (e.g. by decreasing the number of unknown parameters). This is not the focus of our work, as we are concerned with the fundamental limitations governing which properties of the interaction matrix can be inferred from given temporal data. To make sure the system (1.1) is structurally identifiable, here we introduce a mild assumption that $\partial f_{ij}(x_i, x_j) / \partial x_j \neq 0$ for any j . Note that structural identifiability does not necessarily lead to identifiability, because indistinguishability may arise for particular temporal data.

Define the *interconnection vector* $\mathbf{a}_i = (a_{i1}, \dots, a_{in})^\top \in \mathbb{R}^n$ and *regressor vector* $\mathbf{f}_i(\mathbf{x}) = (f_{i1}(x_i, x_1), \dots, f_{in}(x_i, x_n))^\top$ of node i . Then, equation (1.1) can be rewritten as

$$\dot{x}_i(t) = \mathbf{f}_i^\top(\mathbf{x}(t))\mathbf{a}_i + u_i(t), \quad (1.2)$$

with $\mathbf{x}(t) = (x_1(t), \dots, x_n(t))^\top \in \mathbb{R}^n$ the state vector.

Distinguishing $\mathcal{P}(A)$ is then equivalent to the distinguishability of $\mathcal{P}(\mathbf{a}_i)$ for $i = 1, \dots, n$.

Often, the true coupling functions are unknown to us and we only know a *family* of regressors $\{\bar{f}_i\}$ to which the true regressor \mathbf{f}_i belongs. Such uncertainty inevitably produces indistinguishability of the interconnection vector, because the parameters a_{ij} in (1.1) are not uniquely determined. We model the members of $\{\bar{f}_i\}$ as *deformations* $\bar{f}_i(\mathbf{x}) = \mathbf{g}_i(\mathbf{f}_i(\mathbf{x}))$ of the true regressor $\mathbf{f}_i(\mathbf{x})$ obtained by applying some transformation $\mathbf{g}_i: \mathbb{R}^n \rightarrow \mathbb{R}^n$. Thus, $\{\bar{f}_i\}$ is characterized by the *group* \mathbf{G}_i^* of admissible transformations for node i . We consider that \mathbf{G}_i^* is the group of continuous functions that preserves pairwise interactions in (1.1). Characterizing the uncertainty of the coupling functions in this way provides us with a geometric interpretation of the fundamental limitations of NR. Let $\mathbf{G}_{i,\text{lin}}^*$ be the subgroup of admissible linear transformations (associated with non-singular matrices $G_i^\top \in \mathbb{R}^{n \times n}$ with non-zero entries only in its diagonal and i -th column; figure 1a; electronic supplementary material 2). Let $\mathbf{G}_{i,\text{lin}}$ denote the transpose of $\mathbf{G}_{i,\text{lin}}^*$, i.e. $G_i \in \mathbf{G}_{i,\text{lin}}$ if and only if $G_i^\top \in \mathbf{G}_{i,\text{lin}}^*$. Hereafter, we use the following observation: because $\mathbf{G}_{i,\text{lin}}^* \subset \mathbf{G}_i^*$, a *necessary* condition to reconstruct a property when $\mathbf{g}_i \in \mathbf{G}_i^*$ is that it can be reconstructed when $\mathbf{g}_i \in \mathbf{G}_{i,\text{lin}}^*$. Consequently, in order to characterize the fundamental limitations of network reconstruction, we focus on linear transformations only.

Two candidate interconnection vectors $\mathbf{v}_1, \mathbf{v}_2 \in \mathbb{R}^n$ are indistinguishable if

$$\mathbf{f}_i^\top(\mathbf{x}(t))\mathbf{v}_1 = \mathbf{f}_i^\top(\mathbf{x}(t))G_i\mathbf{v}_2, \quad \forall t \in [t_0, t_1], \quad (1.3)$$

for some matrix $G_i \in \mathbf{G}_{i,\text{lin}}$. Multiplying this equation by $\mathbf{f}_i(\mathbf{x}(t))$ from the left and integrating over $[t_0, t_1]$, we obtain

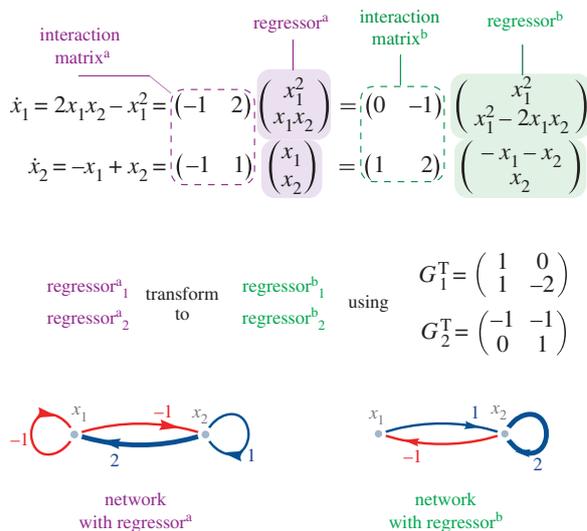
$$M_i(t_0, t_1)(\mathbf{v}_1 - G_i\mathbf{v}_2) = \mathbf{0}, \quad (1.4)$$

where $M_i(t_0, t_1) = \int_{t_0}^{t_1} \mathbf{f}_i(\mathbf{x}(t))\mathbf{f}_i^\top(\mathbf{x}(t)) dt$ is a constant $n \times n$ matrix. Condition (1.3) obviously implies (1.4), but the converse is not so obvious (proposition 1 of electronic supplementary material 3). Hereafter, we write M_i instead of $M_i(t_0, t_1)$, unless the specific time interval is important for the discussion. From (1.4), the set of all pairs of indistinguishable interconnection vectors for node i is

$$\Omega_i = \{(\mathbf{v}_1, \mathbf{v}_2) \in \mathbb{R}^n \times \mathbb{R}^n \mid \exists G_i \in \mathbf{G}_{i,\text{lin}} \text{ such that } (\mathbf{v}_1 - G_i\mathbf{v}_2) \in \ker M_i\}. \quad (1.5)$$

The above analysis reveals two classes of fundamental limitations of NR (figure 1). *First*, unknown coupling functions cause two vectors to be indistinguishable if they can be transformed to each other via some $G_i \in \mathbf{G}_{i,\text{lin}}$. This set of indistinguishable vectors is the partition \mathcal{O}_i of \mathbb{R}^n by the *orbits* of the group $\mathbf{G}_{i,\text{lin}}$ (figure 2a; electronic supplementary material 2). An orbit is considered to be low dimensional if its dimension is less than n (e.g. the purple, blue, green and brown orbits in figure 2a). The orbits in figure 2a show we can only distinguish the adjacency pattern (i.e. if \dot{x}_i depends on x_j for $j \neq i$, see proposition 2a and example 1 in electronic supplementary material 5). Other properties such as edge weights, connectivity pattern or degree sequence are indistinguishable and cannot be reconstructed (proposition 2b in electronic supplementary material 5). This is a consequence of the assumed prior knowledge of the coupling functions, because only the adjacency pattern is invariant to the transformations in \mathbf{G}_i^* , but other properties of A are not. *Second*, even if the coupling functions are exactly known,

(a) indistinguishability due to unknown coupling functions



(b) indistinguishability due to uninformative data

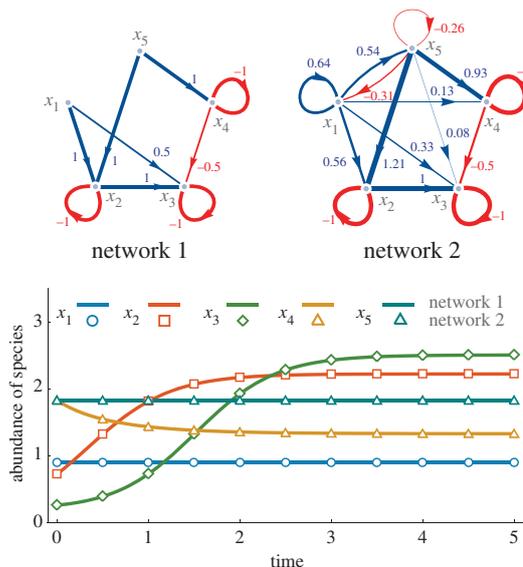


Figure 1. Two sources of indistinguishability. (a) The same dynamics can be characterized by two regressors with different coupling functions (purple and green), yielding indistinguishable networks that differ in their edge weights, sign patterns, connectivity patterns and degree sequences. (b) With the classical population dynamics described by the generalized Lotka–Volterra (GLV) model $\dot{x}_i = r_i x_i + \sum_j a_{ij} x_i x_j$, the two different networks shown in the top panel produce identical node trajectories $\mathbf{x}(t)$ (bottom panel). Here, the growth rate vector is $\mathbf{r} = (0, -0.5, 0.5, -0.5, 0)^T$ and initial abundance $\mathbf{x}(0) = (0.895349, 0.72093, 0.255814, 1.82558, 1.82558)^T$. (Online version in colour.)

indistinguishability will appear if the temporal data are not informative enough in the sense that different interaction matrices produce the same node trajectories (figure 2b); see, for example, [37,38] and references therein. Equation (1.4) shows that indistinguishability due to uninformative data appears when $\mathbf{v}_1 - \mathbf{v}_2 \in \ker M_i$ and $\ker M_i$ contains a subspace different from $\mathbf{0}$. In other words, when the endpoints of \mathbf{v}_1 and \mathbf{v}_2 can be joined by a hyperplane parallel to $\ker M_i$. Such hyperplanes are called *fibres* of the quotient space $\mathbb{R}^n / \ker M_i$.

Combining these two sources of indistinguishability, \mathbf{v}_1 is indistinguishable from \mathbf{v}_2 if it is possible to transform \mathbf{v}_2 using an element of $G_{i,\text{lin}}$ in a way that the hyperplane passing through \mathbf{v}_1 and $G_{i,\text{lin}}\mathbf{v}_2$ is a fibre (figure 2c). As orbits of $G_{i,\text{lin}}$ intersected by a fibre of $\mathbb{R}^n / \ker M_i$ become indistinguishable, we can ‘glue’ them together to form a partition $\mathcal{O}_i^{\ker M_i}$ of \mathbb{R}^n into sets of indistinguishable interconnection vectors (figure 2c). Consequently, $\mathcal{P} : \mathbb{R}^n \rightarrow \mathbb{Y}$ can be reconstructed only if all two sets in the collection $\mathcal{C}_{\mathcal{P}} = \{\mathcal{P}^{-1}(\mathbf{y}) \subseteq \mathbb{R}^n | \mathbf{y} \in \mathbb{Y}\}$ belong to different orbits $\mathcal{O}_i^{\ker M_i}$. If $\ker M_i$ is contained in low-dimensional orbits, then we can reconstruct the adjacency pattern of the interaction matrix (right panel of figure 2c). Otherwise $\mathcal{O}_i^{\ker M_i} = \mathbb{R}^n$ and all interconnection vectors are indistinguishable (left panel of figure 2c). Furthermore, once indistinguishability appears, there will always be indistinguishable interconnection vectors that are arbitrarily far from each other. Consequently, the reconstruction error of the edge weights and other properties such as sign pattern and adjacency pattern can always be maximal.

The matrix M_i in (1.4) is unknown when the true regressor \mathbf{f}_i is unknown. Indeed, choosing any $\bar{\mathbf{f}}_i = G_i^T \mathbf{f}_i$, $G_i \in G_{i,\text{lin}}$, gives

$$\bar{M}_i(t_0, t_1) = \int_{t_0}^{t_1} \bar{\mathbf{f}}_i(\mathbf{x}(t)) \bar{\mathbf{f}}_i^T(\mathbf{x}(t)) dt = G_i^T M_i(t_0, t_1) G_i.$$

Thus, $G_{i,\text{lin}}$ transforms $\ker \bar{M}_i$ into $\ker M_i$ (and vice versa), and

we can only know the orbit $G_{i,\text{lin}}(\ker M_i)$ corresponding to this subspace. For example, the condition $\ker \bar{M}_i = \{\mathbf{0}\}$ for some $G_i \in G_{i,\text{lin}}$ implies that

$$\ker M_i = \{\mathbf{0}\}, \quad (1.6)$$

because $G_{i,\text{lin}}(\mathbf{0}) = \mathbf{0}$ (i.e. $\mathbf{0} = G_i \mathbf{0}$ for any G_i). We can then tell if M_i is non-singular using any \bar{M}_i . Condition (1.6) is known as *persistent excitation* (PE) in the literature and it is necessary and sufficient to solve the PI problem [19,20]. In general, we can prove that $\mathcal{O}_i^{\ker \bar{M}_i} = \mathcal{O}_i^{\ker M_i}$ (lemma 1, electronic supplementary material 6), so we can build the partition of indistinguishable vectors using any \bar{M}_i .

The above analysis only depends on the group property of the transformations, hence it can be straightforwardly extended to any other linear group G_i , allowing us to shrink or enlarge $G_{i,\text{lin}}$ according to our uncertainty about the coupling functions. Thus, in order to reconstruct some property of the interaction matrix, it is necessary that (i) our uncertainty about the coupling functions is small enough (i.e. any two sets in $\mathcal{C}_{\mathcal{P}}$ belong to different orbits of G_i); and (ii) the measured temporal data are informative enough (i.e. hyperplanes parallel to $G_i(\ker M_i)$ do not glue orbits together). As an obvious example, in order to reconstruct the edge weights, it is necessary to know the coupling functions exactly (i.e. $G_i = \{I\}$) because only then do any two vectors belong to different orbits.

It is possible to reduce G_i to $\{I\}$ when we know the appropriate coupling functions to use (e.g. the generalized Lotka–Volterra equations for ecological systems, or linear functions if the system remains close to its steady state [18]). In this case indistinguishability emerges from uninformative data only. Consequently, a property $\mathcal{P}(\mathbf{a}_i)$ can be reconstructed iff all two sets in the collection $\mathcal{C}_{\mathcal{P}}$ can be separated by a fibre (electronic supplementary material, figure S1). A fibre is a hyperplane and thus partitions \mathbb{R}^n in two regions; we say it separates P_{y_1} from P_{y_2} if P_{y_1} belongs to one region

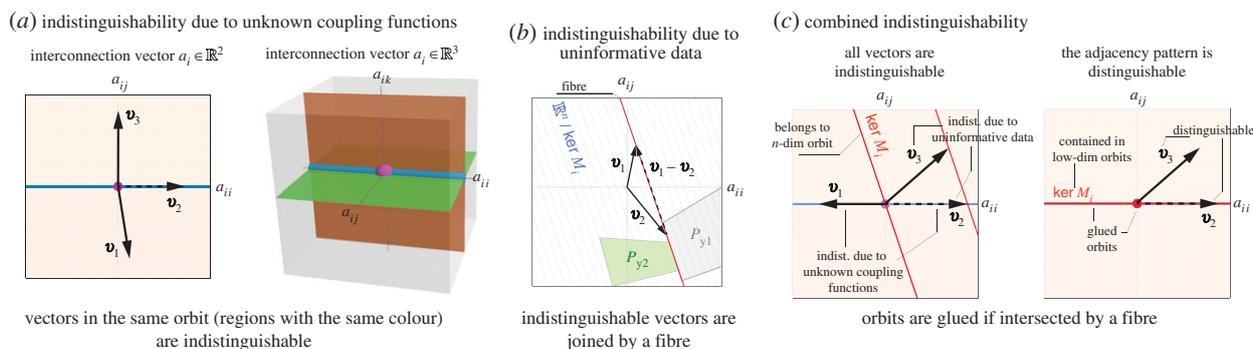


Figure 2. Indistinguishability of interconnection vectors. (a) Indistinguishable vectors due to unknown coupling functions can be transformed into each other using some transformation $G_i \in \mathcal{G}_{i,\text{lin}}$. Sets of those indistinguishable vectors are the partition of \mathbb{R}^n by the orbits \mathcal{O}_i of $\mathcal{G}_{i,\text{lin}}$, here shown in different colours for $n = 2$ and $n = 3$. Purple regions should be interpreted as points, and blue regions as lines. The grey region is another orbit. We can distinguish an interconnection vector in the blue orbit (e.g. \mathbf{v}_2 with component $a_{ij} = 0$) from an interconnection vector in the orange orbit (e.g. \mathbf{v}_1 or \mathbf{v}_3 with component $a_{ij} \neq 0$), illustrating that we can distinguish the adjacency of the interconnection vector (i.e. whether a_{ij} is zero or not for $j \neq i$). Nevertheless, as \mathbf{v}_1 and \mathbf{v}_3 belong to the same orbit and hence are indistinguishable, but they have different degree sequences and sign or connectivity patterns, these properties cannot be reconstructed. (b) Owing to uninformative measured temporal data, the interconnection vector \mathbf{v}_1 is indistinguishable from \mathbf{v}_2 because $\mathbf{v}_1 - \mathbf{v}_2 \in \ker M_i$, i.e. both vectors are joined by the red fibre. We can also separate the sets P_{y_1} and P_{y_2} with the particular orientation of the fibres. However, as there is no gap between these sets, any change in the orientation of the fibres will produce indistinguishable interconnection vectors that belong to different sets. This illustrates that the PE condition remains generically necessary if there is no gap between the sets in $\mathcal{C}_{\mathcal{P}}$. (c) Indistinguishable vectors in network reconstruction appear by combining both kinds of indistinguishable vectors, gluing together orbits of $\mathcal{G}_{i,\text{lin}}$ when they are intersected by a fibre of $\mathbb{R}^n / \ker M_i$. In the left panel, as $\ker M_i$ is not contained in low-dimensional orbits, all orbits are glued $\mathcal{O}_i^{\ker M_i} = \mathbb{R}^n$ and all vectors become indistinguishable (e.g. \mathbf{v}_1 is indistinguishable from \mathbf{v}_3). In the right panel, $\ker M_i$ is contained in low-dimensional orbits. We can then distinguish between \mathbf{v}_2 and \mathbf{v}_3 and hence reconstruct the adjacency pattern of the interaction matrix. (Online version in colour.)

and P_{y_2} belongs to the other region or the fibre (figure 2b). By specifying the coupling functions we can reconstruct more information such as the interaction matrix itself, if the PE condition (1.6) holds. Without PE it is still possible to distinguish, for example, the adjacency pattern of the interconnection vector when $\ker M_i$ is exactly ‘horizontally’ oriented. In fact, from the right panel of figure 2c, we can separate the sets P_y of vectors with different adjacency patterns (orange and red regions) using the same red region as the separating fibre. However, such a situation is *non-generic* (i.e. pathological) in the sense that an infinitesimal change in the fibre’s orientation will eliminate the distinguishability. Note also that other properties such as sign pattern, connectivity pattern or degree sequence are indistinguishable. Indeed, we can prove that there are only two generic cases (electronic supplementary material 7): (i) $\ker M_i = \{\mathbf{0}\}$ and indistinguishable vectors emerge only due to uncertain coupling functions (i.e. $\mathcal{O}_i^{\ker M_i} = \mathcal{O}_i$); and (ii) $\ker M_i$ is non-trivial and is contained in the n -dimensional orbit, so all interconnection vectors become indistinguishable (i.e. $\mathcal{O}_i^{\ker M_i} = \mathbb{R}^n$). This implies that, even if the coupling functions are well known, the PE condition (1.6) is generically necessary to reconstruct any property.

Next, we show that prior information of A is the only way to relax the PE condition. Consider, for the sake of clarity, that the coupling functions are exactly known. Prior information shrinks the domain of the property \mathcal{P} from \mathbb{R}^n to \mathbb{V} , i.e. $\mathcal{P} : \mathbb{V} \subseteq \mathbb{R}^n \rightarrow \mathbb{Y}$. Two typical cases are: (i) a_{ij} takes a finite number of values (e.g. binary interactions [25]) so $\mathbb{V} = \cup_y P_y$ is a discrete set as each P_y is a point (electronic supplementary material, figure S4a); and (ii) a_{ij} are bounded as $a_{ij} \in [-a_{\max}, -a_{\min}] \cup [-\epsilon, \epsilon] \cup [a_{\min}, a_{\max}]$ for some known constants $0 \leq \epsilon < a_{\min} < a_{\max}$. In this case $\mathbb{V} = \cup_y P_y$, where P_0 is an ϵ neighbourhood of zero and each of the $3^n - 1$ remaining sets lies in a different orthant of \mathbb{R}^n (associated with distinct sign patterns; see electronic supplementary material,

figure S4b). In case (i), A itself can be reconstructed without PE if we can separate each point composing \mathbb{V} with a fibre. If $\dim(\ker M_i) < n$, this is generically possible because an infinitesimal deformation will change any ‘pathological’ orientation that contains two points. In case (ii), the sign or connectivity pattern can be reconstructed without PE if there is a gap between the sets P_y such that a fibre can separate them (electronic supplementary material, figure S4b), but A itself cannot be reconstructed because it is impossible to separate two points inside one P_y . In electronic supplementary material 10, we illustrate our results in a basic NR problem using steady-state data, and in electronic supplementary material 4 we show how to use our analysis to build an NR method that correctly reconstructs the sign pattern of the interaction matrix. Note also that, if $\dim \ker M_i = d_i$, providing the value of $\mathcal{P}(a_{ij})$ for d_i entries of \mathbf{a}_i as prior information guarantees a correct reconstruction of $\mathcal{P}(\mathbf{a}_i)$. Sparsity of the interaction matrix can be equally effective prior information (electronic supplementary material 9).

Our analysis lays a firm theoretical basis to some fundamental limitations of network reconstruction that have been observed before via computer simulations—such as the role of the informativeness of the temporal data [34] and the fact that different networks may produce exactly the same temporal response [35]. A particular instance of our analysis is when different networks, such as those obtained from chemical reactions, produce the same dynamical model (i.e. they are structurally unidentifiable [37,39,40]) and hence they are indistinguishable for all temporal data. Indeed, despite the fact that the identifiability of the identity property has been studied in different disciplines including statistics and system identification [19,20,25,37,38], a similar analysis for all the other properties we can reconstruct using NR was lacking. The impact of uncertain coupling functions on the properties that can be reconstructed was unknown too. Our analysis can be straightforwardly extended to

higher-order interactions (e.g. $x_i x_j x_k$) and some nonlinear parametrizations, e.g. $x_i/(a_{ij} + x_j)$ (see electronic supplementary material 12). Note that, by contrast to the case of structural identifiability [40], nonlinearities in the coupling functions do not always enhance the distinguishability of a property for given temporal data (electronic supplementary material 14). We can also analyse the effect of noise and more general uncertainty of the coupling functions at the cost of less constructive results [41]. In such a case, the partition of indistinguishable interconnection vectors is given by a general equivalence relation; this makes it harder to characterize the fundamental limitations of NR, as the role of the uncertainty about the coupling functions and the informativeness of the temporal data cannot be disentangled anymore. The derived fundamental limitations for NR also apply in the case of noisy measurements, in the sense that the distinguishability of a property with noiseless data is a necessary condition for its distinguishability under noise. A more detailed analysis in the spirit of *practical identifiability* [42] would characterize the parameters a_{ij} and their properties that are more sensitive to noise. We note that the necessity of measuring all time-varying nodes in the network leads to another fundamental limitation in NR [43]; see also

electronic supplementary material 11. Our results indicate that, as in the case of PI [39], a better knowledge of the system's coupling functions and prior information of the interaction matrix are extremely useful for NR (even when some algorithms explicitly ignore all knowledge of the system [31,32]). Furthermore, the generic necessity of PE means it can also be a guideline to informative enough experiments for general NR problems, letting us take advantage of the existing theory for optimal experiment design [44–46]. This calls for the design of better algorithms that incorporate such information and provide a guarantee of correct NR under PE (electronic supplementary material 4).

Authors' contributions. M.T.A. conceived the project. Y.-Y.L. and M.T.A. designed the project. M.T.A. did the analysis with the help of G.L. and J.A.M. All authors analysed the results. M.T.A. and Y.-Y.L. wrote the manuscript.

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References

- Barabási A-L. 2016 *Network science*. Cambridge, UK: Cambridge University Press.
- Newman ME. 2003 The structure and function of complex networks. *SIAM Rev.* **45**, 167–256. (doi:10.1137/S003614450342480)
- Dorogovtsev SN, Goltsev AV, Mendes JFF. 2008 Critical phenomena in complex networks. *Rev. Mod. Phys.* **80**, 1275–1335. (doi:10.1103/RevModPhys.80.1275)
- Pastor-Satorras R, Vespignani A. 2001 Epidemic spreading in scale-free networks. *Phys. Rev. Lett.* **86**, 3200–3203. (doi:10.1103/PhysRevLett.86.3200)
- Cohen R, Erez K, ben Avraham D, Havlin S. 2000 Resilience of the internet to random breakdowns. *Phys. Rev. Lett.* **85**, 4626–4628. (doi:10.1103/PhysRevLett.85.4626)
- Nishikawa T, Motter AE, Lai Y-C, Hoppensteadt FC. 2003 Heterogeneity in oscillator networks: are smaller worlds easier to synchronize? *Phys. Rev. Lett.* **91**, 014101. (doi:10.1103/PhysRevLett.91.014101)
- Wang W, Slotine J-J. 2005 On partial contraction analysis for coupled nonlinear oscillators. *Biol. Cybernetics* **92**, 38–53. (doi:10.1007/s00422-004-0527-x)
- Liu Y-Y, Slotine J-J, Barabási A-L. 2011 Controllability of complex networks. *Nature* **473**, 167–173. (doi:10.1038/nature10011)
- Nepusz T, Vicsek T. 2012 Controlling edge dynamics in complex networks. *Nat. Phys.* **8**, 568–573. (doi:10.1038/nphys2327)
- Liu Y-Y, Slotine J-J, Barabási A-L. 2013 Observability of complex systems. *Proc. Natl Acad. Sci. USA* **110**, 2460–2465. (doi:10.1073/pnas.1215508110)
- Wang W, Bhargava B. 2004 Visualization of wormholes in sensor networks. In *Proc. of the 3rd ACM Workshop on Wireless Security (WISE '04), Philadelphia, PA, 1 October 2004*, pp. 51–60. New York, NY: ACM.
- Arianos S, Bompard E, Carbone A, Xue F. 2009 Power grid vulnerability: a complex network approach. *Chaos* **19**, 013119. (doi:10.1063/1.3077229)
- Stein RR, Bucci V, Toussaint NC, Buffie CG, Rättsch G, Pamer EG, Sander C, Xavier JB. 2013 Ecological modeling from time-series inference: insight into dynamics and stability of intestinal microbiota. *PLoS Comput. Biol.* **9**, e1003388. (doi:10.1371/journal.pcbi.1003388)
- Bonneau R. 2008 Learning biological networks: from modules to dynamics. *Nat. Chem. Biol.* **4**, 658–664. (doi:10.1038/nchembio.122)
- Tyson JJ, Chen K, Novak B. 2001 Milestones, network dynamics and cell physiology. *Nat. Rev. Mol. Cell Biol.* **2**, 908–916. (doi:10.1038/35103078)
- Kohanski MA, Dwyer DJ, Collins JJ. 2010 How antibiotics kill bacteria: from targets to networks. *Nat. Rev. Microbiol.* **8**, 423–435. (doi:10.1038/nrmicro2333)
- Chung M, Krueger J, Pop M. 2015 Robust parameter estimation for biological systems: a study on the dynamics of microbial communities. (<http://arxiv.org/abs/1509.06926>)
- Barzel B, Barabási A-L. 2013 Universality in network dynamics. *Nat. Phys.* **9**, 673–681. (doi:10.1038/nphys2741)
- Walter E, Pronzato L. 1997 *Identification of parametric models from experimental data*. Communications and Control Engineering. Berlin, Germany: Springer.
- Ljung L. 1998 *System identification*. Berlin, Germany: Springer.
- May RM. 1973 Qualitative stability in model ecosystems. *Ecology* **638**, 1389–1391.
- Shinar G, Feinberg M. 2010 Structural sources of robustness in biochemical reaction networks. *Science* **327**, 1389–1391. (doi:10.1126/science.1183372)
- Ruths J, Ruths D. 2014 Control profiles of complex networks. *Science (New York, NY)* **343**, 1373–1376. (doi:10.1126/science.1242063)
- Pastor-Satorras R, Vespignani A. 2001 Epidemic spreading in scale-free networks. *Phys. Rev. Lett.* **86**, 3200–3203. (doi:10.1103/PhysRevLett.86.3200)
- Yu D, Righero M, Kocarev L. 2006 Estimating topology of networks. *Phys. Rev. Lett.* **97**, 188701. (doi:10.1103/PhysRevLett.97.188701)
- Yu D, Parltz U. 2011 Inferring network connectivity by delayed feedback control. *PLoS ONE* **6**, e24333. (doi:10.1371/journal.pone.0024333)
- Bansal M, Belcastro V, Ambesi-Impombato A, Di Bernardo D. 2007 How to infer gene networks from expression profiles. *Mol. Syst. Biol.* **3**, 78. (doi:10.1038/msb4100120)
- He F, Balling R, Zeng A-P. 2009 Reverse engineering and verification of gene networks: principles, assumptions, and limitations of present methods and future perspectives. *J. Biotechnol.* **144**, 190–203. (doi:10.1016/j.jbiotec.2009.07.013)
- Prill RJ, Marbach D, Saez-Rodriguez J, Sorger PK, Alexopoulos LG, Xue X, Clarke ND, Altan-Bonnet G, Stolovitzky G. 2010 Towards a rigorous assessment of systems biology models: the DREAM3 challenges. *PLoS ONE* **5**, e9202. (doi:10.1371/journal.pone.0009202)
- Marbach D, Prill RJ, Schaffter T, Mattiussi C, Floreano D, Stolovitzky G. 2010 Revealing strengths and weaknesses of methods for gene network

- inference. *Proc. Natl Acad. Sci. USA* **107**, 6286–6291. (doi:10.1073/pnas.0913357107)
31. Villaverde AF, Banga JR. 2014 Reverse engineering and identification in systems biology: strategies, perspectives and challenges. *J. R. Soc. Interface* **11**, 20130505. (doi:10.1098/rsif.2013.0505)
 32. Timme M, Casadiego J. 2014 Revealing networks from dynamics: an introduction. *J. Phys. A Math. Theor.* **47**, 343001. (doi:10.1088/1751-8113/47/34/343001)
 33. Filosi M, Visintainer R, Riccadonna S, Jurman G, Furlanello C. 2014 Stability indicators in network reconstruction. *PLoS ONE* **9**, e89815. (doi:10.1371/journal.pone.0089815)
 34. Smith VA, Jarvis ED, Hartemink AJ. 2003 Influence of network topology and data collection on network inference. In *Pacific symposium on biocomputing* (eds RB Altman, AK Dunker, L Hunter, TA Jung, TE Klien), pp. 164–175. Singapore: World Scientific.
 35. Krishnan A, Giuliani A, Tomita M. 2007 Indeterminacy of reverse engineering of gene regulatory networks: the curse of gene elasticity. *PLoS ONE* **2**, e562. (doi:10.1371/journal.pone.0000562)
 36. Chis O-T, Banga JR, Balsa-Canto E. 2011 Structural identifiability of systems biology models: a critical comparison of methods. *PLoS ONE* **6**, e27755. (doi:10.1371/journal.pone.0027755)
 37. Craciun G, Pantea C. 2008 Identifiability of chemical reaction networks. *J. Math. Chem.* **44**, 244–259. (doi:10.1007/s10910-007-9307-x)
 38. Casadiego J, Timme M. 2015 Network dynamics as an inverse problem. In *Mathematical technology of networks*, pp. 39–48. Berlin, Germany: Springer.
 39. Szederkényi G, Banga JR, Alonso AA. 2011 Inference of complex biological networks: distinguishability issues and optimization-based solutions. *BMC Syst. Biol.* **5**, 177. (doi:10.1186/1752-0509-5-177)
 40. Vajda S, Rabitz H. 1994 Identifiability and distinguishability of general reaction systems. *J. Phys. Chem.* **98**, 5265–5271. (doi:10.1021/j100071a016)
 41. Picci G. 1977 Some connections between the theory of sufficient statistics and the identifiability problem. *SIAM J. Appl. Math.* **33**, 383–398. (doi:10.1137/0133025)
 42. Raue A, Kreutz C, Maiwald T, Bachmann J, Schilling M, Klingmüller U, Timmer J. 2009 Structural and practical identifiability analysis of partially observed dynamical models by exploiting the profile likelihood. *Bioinformatics* **25**, 1923–1929. (doi:10.1093/bioinformatics/btp358)
 43. Gonçalves J, Warnick S. 2008 Necessary and sufficient conditions for dynamical structure reconstruction of LTI networks. *IEEE Trans. Automat. Contr.* **53**, 1670–1674. (doi:10.1109/TAC.2008.928114)
 44. Pukelsheim F. 1993 *Optimal design of experiments*, vol. 50. Philadelphia, PA: SIAM.
 45. Pronzato L. 2008 Optimal experimental design and some related control problems. *Automatica* **44**, 303–325. (doi:10.1016/j.automatica.2007.05.016)
 46. Bandara S, Schlöder J, Eils R, Bock H, Meyer T. 2009 Optimal experimental design for parameter estimation of a cell signaling model. *PLoS Comput. Biol.* **5**, e1000558. (doi:10.1371/journal.pcbi.1000558)