Observability of complex systems

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A quantitative description of a complex system is inherently limited by our ability to estimate the system’s internal state from experimentally accessible outputs. Although the simultaneous measurement of all internal variables, like all metabolite concentrations in a cell, offers a complete description of a system’s state, in practice experimental access is limited to only a subset of variables, or sensors. A system is called observable if we can reconstruct the system’s complete internal state from its outputs. Here, we adopt a graphical approach derived from the dynamical laws that govern a system to determine the sensors that are necessary to reconstruct the full internal state of a complex system. We apply this approach to biochemical reaction systems, finding that the identified sensors are not only necessary but also sufficient for observability. The developed approach can also identify the optimal sensors for target or partial observability, helping us to reconstruct selected state variables from appropriately chosen outputs, a prerequisite for optimal biomarker design. Given the fundamental role observability plays in complex systems, these results offer avenues to systematically explore the dynamics of a wide range of natural, technological, and socioeconomic systems.

The internal variables of a complex system are rarely independent of each other, as the interactions between the system’s components induce systematic interdependencies between them. Hence, a well-selected subset of variables can contain sufficient information about the rest of the variables, allowing us to reconstruct the system’s complete internal state, making the system observable. To address observability in quantitative terms, we focus on systems whose dynamics can be described by the generic state-space form

\[ x(t) = f(t, x(t), u(t)), \]

where \( x(t) \in \mathbb{R}^N \) represents the complete internal state of the system (e.g., the concentrations of all metabolites in a cell), and the input vector \( u(t) \in \mathbb{R}^K \) captures the influence of the environment. Observing the system means that we monitor a set of variables \( y(t) \in \mathbb{R}^M \) that depend on the time \( t \), the system’s internal state \( x(t) \), and the external input \( u(t) \),

\[ y(t) = h(t, x(t), u(t)). \]

Observability requires us to establish a relationship between the outputs \( y(t) \), the state vector \( x(t) \), and the inputs \( u(t) \) in a manner that we can uniquely infer the system’s complete initial state \( x(0) \). The observability criteria can be formulated algebraically for dynamical systems consisting of polynomial or rational expressions (1, 2) stating that [1] is observable if the Jacobian matrix \( J = \frac{\partial f}{\partial x} \mid _{x(1)=x(0)} \) has full rank,

\[ \text{rank } J = N, \]

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diagram of Fig. 1C contains three root SCCs, hence, we need at least three sensors to observe the system.

Results

The graphical approach (GA) described above reduces observability, a dynamical problem of a nonlinear system with many unknowns, to a property of the static map of the inference diagram, which is accurately mapped for an increasing number of unknowns, to a property of the static map of the inference diagram of Fig. 1C. Consequently any state observer, a dynamical device that aims to estimate the system’s internal state by monitoring the outputs (5), for full observability. However, the vast majority of systems of practical interest are not linear. Next, we offer a rather surprising result, showing that for several much-studied nonlinear dynamical systems the symmetries in state variables are extremely rare; therefore the sensor set predicted by GA is not only necessary but also sufficient for observability. Hence, for these systems we can provide the full solution to the observability problem, which is our second and main result.

Biochemical Reaction Networks. We apply GA to biochemical reaction networks, which, with their well-characterized wiring diagram and dynamics but largely unknown parameters (kinetic constants), represent an appropriate prototype of complex systems. Consider a biochemical reaction system of $N$ species $\{S_1, S_2, \ldots, S_N\}$ involved in $R$ reactions $\{R_1, R_2, \ldots, R_R\}$ with $R_j : \sum_{i=1}^N a_{ij}S_i \rightarrow \sum_{i=1}^N \beta_j S_i$, where $a_{ij} \geq 0$ and $\beta_j \geq 0$ are the stoichiometry coefficients. Under the continuum hypothesis and...
the well-mixed assumption (19) the system’s dynamics is described by \([1]\), where \(x_i(t)\) is the concentration of species \(S_i\) at time \(t\), the input vector \(u(t)\) represents regulatory signals or external nutrient concentrations, and the vector \(y(t)\) may capture the set of experimentally measurable species concentrations or reaction fluxes. The flux \(v_j(x)\) of reaction \(R_j\) follows mass-action kinetics \((20, 21)\)

\[
v_j(x) = k_j \prod_{i=1}^{N} x_i^{n_{ij}}
\]

with rate constants \(k_j > 0\). The system’s dynamics is therefore described by the balance equations

\[
\dot{x}_i = f_i(x) = \sum_{j=1}^{R} \Gamma_{ij} v_j(x),
\]

where \(\Gamma_{ij} = \beta_{ij} - \alpha_{ij}\) is the element of the \(N \times R\) stoichiometric matrix. The right-hand side of \([5]\) represents a sum of all fluxes \(v_j\) that produce and consume the species \(S_i\).

Assuming that the outputs \(y(t)\) are the concentrations of a particular set of sensor species, observability aims to identify a minimum set of sensor species from whose concentrations we can determine the concentration of all other species. The advantage of GA in this context is that it bypasses the need to know the system’s kinetic constants (which are largely unknown in vivo), and only requires accurate information about the topology of the inference diagram. In the context of metabolism or an arbitrary biochemical reaction system, this is uniquely provided by the full reaction list, which is relatively accurately known for several model organisms (22).

Applying GA to biochemical reaction systems leads to a number of results that elucidate the principles behind biochemical network observability:

- **a)** Species that are not reactants in any reaction, i.e., pure products, will be root SCCs of size 1; hence they are always sensors (e.g., \(S_5\) in Fig. 1C).
- **b)** For root SCCs of size larger than 1 (e.g., \(\{x_3, x_5\}\) and \(\{x_7, x_8, x_9\}\) in Fig. 1C), any node could be chosen as a sensor. For example, in Fig. 1C we can choose \(x_7, x_8, x_9\) as the sensor for the root SCC \(\{x_7, x_8, x_9\}\). Given that some root SCCs can be quite large, and we need only one node from each root SCC, this considerably reduces the number of sensor nodes (except some pathological cases discussed in SI Text, section II, B).
- **c)** The minimal number of sensor nodes that are necessary to observe a biochemical reaction system equals the number of root SCCs of its inference diagram. A minimum set of sensors consists of all pure products and one node from each root SCC with multiple species (e.g., \(\{x_5, x_6, x_7\}\) in Fig. 1C).
- **d)** As any node from a root SCC can be chosen as a sensor node, there are \(\Omega_i = \prod_{n_i=1}^{\infty} n_i\) equivalent sensor node combinations, representing the product of all root SCCs’ sizes. For example, in Fig. 1C we have three root SCCs with sizes \(n_1 = 1, 2, 3\); hence \(\Omega_i = 1 \times 2 \times 3 = 6\). This multiplicity offers significant flexibility in selecting experimentally accessible sensors.

The principles \(a-d\) allow us to formulate the second and main finding: In biochemical networks the minimum set of sensors identified by GA is not only necessary but also sufficient for observability (SI Text, section II, B). To demonstrate this we randomly generated 1,000 chemical reaction systems, testing each system’s observability using the rank criteria (3). We find that in all connected reaction networks the minimum set of sensors obtained by the GA achieves full observability for the whole system. This sufficiency is rooted in the fact that, when monitoring the GA-predicted minimum sensor set, the probability of developing symmetries in the state variables is close to zero. Indeed, we find that the only systems that fail sufficiency are those with isolated reactions, but such isolated reactions are not only useless from a biological perspective, but their chance of occurrence goes to zero exponentially as the number of species (or reactions) increases (SI Text, section II, B). Hence, apart from a few pathological cases, there are always algebraic relations between the system’s state variables and the successive derivatives of the outputs selected by GA, guaranteeing that the system is observable (5). In the following we discuss a series of
application of our main results, demonstrating its impact on the study of biological systems.

**Small Biochemical Networks.** We applied GA to two well-studied biochemical reaction systems, the simplified glycolytic reaction map and a model for ligand binding, confirming that each of these systems is observable through the minimum set of sensor nodes predicted by GA (Fig. 3). The simplified glycolytic reaction map (20) consists of 10 chemical species [glucose (Gluc); ADP; glucose 6-phosphate (G6P); ATP; glucose 1-phosphate (G1P); AMP; fructose 6-phosphate (F6P); fructose 2,6-biphosphate (F26BP); triose phosphate (TP); pyruvate (Pyr)] involved in nine reactions (see Fig. 3A and SI Text, section III, A for the balance equations). GA predicts that Pyr, which is the pure product of the system, forms the only root SCC of the inference diagram (Fig. 3B), hence the system should be observable by measuring Pyr only. We confirm this prediction by calculating the rank of the Jacobian matrix, finding that with sufficient data points on the Pyr concentration one can reconstruct all other metabolite concentrations in the system. The core model of erythropoietin (Epo) and Epo receptor (EpoR) interaction and trafficking (23) consists of six species involved in ligand binding: Epo, EpoR, Epo-EpoR complex, internalized complex Epo-EpoR_i, degraded internalized ligand dEpo_i, and degraded extracellular ligand dEpo_e (see Fig. 3C and SI Text, section III, B for the balance equations). GA predicts that the minimum sensor set contains two pure products, dEpo_i and dEpo_e (Fig. 3D), confirmed via the rank test of the Jacobian matrix.

**Exploring the Complete Metabolism.** The developed framework is not limited to small pathways, but allows us to study an organism’s genome-scale metabolism as well, involving hundreds of metabolites engaged in thousands of reactions. These systems are too large to identify the sensors via brute-force search or to explicitly verify observability via the rank condition [3]. However, we can efficiently identify the sensors using GA. We applied GA to the metabolic networks of three well-studied model organisms, *Escherichia coli*, *Saccharomyces cerevisiae*, and *Homo sapiens*, using their complete metabolic reconstruction (22) to identify the sensor nodes. We find that the sensor set necessary for observability of the genome-scale metabolisms represents ~5–10% of the total metabolites (Table 1). This is because the vast majority of metabolites (91% for *E. coli*, 88% for *S. cerevisiae*, and 83% for *H. sapiens*) are in a giant nonroot SCC. Overall, the GA predicts that in principle one can reconstruct the state of the whole metabolism from the concentration of a relatively small fraction of metabolites. We also find that this result is not very sensitive to the assignment of the reaction reversibility during genome-scale metabolic reconstructions (SI Text, section III, D).

**Target Observability.** Notwithstanding the fundamental importance of full observability, aiming to derive the state of each variable in a system, for most applications it is sufficient to infer the state of a certain subset of variables, that we call target variables, like the concentrations of metabolites whose activities are altered by a disease (24). If those target variables...
cannot be directly measured, we can invoke target observability, identifying the optimal sensor(s) that can infer the state of the target variables, thus discovering the optimal biomarkers for the respective disease. GA helps us select such optimal sensors as well, following these general principles, representing our third main result:

i) The state of a target node \( x_t \) can be observed from a sensor node \( x_s \) only if there is a directed path from \( x_s \) to \( x_t \) in the inference diagram. For example, in Fig. 1C, \( x_4 \) can only be inferred from \( x_5 \), whereas \( x_1 \) can be inferred from any other nodes.

ii) There are important differences in the complexity of the inference process, depending on the size of the subsystem we need to infer for a given sensor choice. The SCC decomposition of the inference diagram helps us formulate the following result: To observe \( x_t \) from \( x_s \), we need to reconstruct \( N_s = \sum_{i=1}^{n} N_i \) metabolite concentrations, where \( N_i \) denotes the set of all SCCs that are reachable from \( x_s \), and \( n \) is the size of the \( i \)-th SCC. This formula can be easily extended to multiple targets.

iii) To identify the optimal sensor node for any target node, we can minimize \( \sum_{x_s \in \Sigma} N_s \), representing the minimum amount of information required for the inference process. For example, if \( x_t \) is inside an SCC of size larger than 1 (e.g., \( x_1 \) in Fig. 1C), then the optimal sensor can be any other node in the same SCC (e.g., \( x_2 \) or \( x_3 \) in Fig. 1C). If no node in the same SCC is experimentally accessible, then the optimal sensor node belongs to the smallest SCC that points to \( x_t \) (e.g., \( x_6 \) in Fig. 1C).

Note that this minimization procedure can be implemented for any inference diagrams in polynomial time. Hence, GA can aid the efficient selection of optimal sensors for any targeted node, offering a potentially indispensable tool for biomarker design.

**Beyond Metabolism.** Although we illustrated GA on biochemical reaction systems, we emphasize that the inference diagram can be constructed for arbitrary nonlinear dynamical systems of form [1]; hence, GA can identify the necessary sensor set for arbitrary systems. Moreover, as general nonlinear dynamical systems lack symmetries in their state variables, we expect the GA-predicted sensor set to be sufficient for observability. To show this we have explicitly verified observability for several much-studied dynamical systems, such as Michaelis–Menten kinetics in reaction dynamics (SI Text, section III, C), Lotka–Volterra dynamics in ecological systems (SI Text, section V, A), and Hindmarsh–Rose model for neuronal systems (SI Text, section V, B), in each case finding that the sensors identified by GA are both sufficient and necessary for observability. Given the significant current efforts to elucidate the dynamics of complex systems (25), GA is bound to find applications in a wide range of natural, socioeconomic, or technological systems whose dynamics can be cast in the highly general form [1], helping identify optimal quantities to monitor their internal state.

### Materials and Methods

**Maximum Matching for Linear Systems.** We use the duality between controllability and observability to identify the minimum number of sensors sufficient for observability in a linear system (3, 4, 30). A linear time-invariant system \( x(t) = A x(t) + B u(t) \) is called a structured system if the state matrix \( A \) and the input matrix \( B \) are structured, i.e., their elements are either fixed zeros or independent free parameters. For a structured system with state matrix \( A \) representing the wiring diagram of its underlying directed weighted network \( G(A) \), the minimum number of inputs (or equivalently the minimum number of driver nodes which accept independent signals) required to fully control the system can be calculated by applying the maximum matching algorithm to \( G(A) \) (17). For a directed network, an edge subset \( M \) is matched if no two edges in \( M \) share a common starting node or a common ending node. A node is matched if it is an ending node of an edge in the matching. Otherwise, it is unmatched. A matching of maximum cardinality-size is called a maximum matching. The minimum set of driver nodes which accepts independent signals and enables us to fully control the

### Discussion

In many complex systems experimental access is often limited to only a subset of state variables. Hence, we need efficient tools to identify the variables that allow us to infer the state of the whole system. Otherwise, the experiments may waste resources on measuring system variables that are redundant. Our theoretical work helps us identify the necessary sensors for an arbitrary nonlinear dynamical system, serving as the lower bound of the number of system variables we need to monitor. We also show that for many biological systems the necessary sensors are actually sufficient. Hence, our results significantly narrow the candidate variables that one needs to monitor to ensure observability. Given the unprecedented rapid development of biotechnology in the last decade, driving the development of sensitive real-time monitoring tools, our results could have implications from metabolic engineering to synthetic biology and network medicine. For example, studying the role of the GA-identified sensors in cell communication or biomarker design might offer better diagnostic tools, as well as offer rational predictions for potential biomarkers. Moreover, if we consider those unknown system parameters \( \Theta \) as a special type of state variables with time derivative \( \dot{\Theta} = 0 \), we can extend the system to contain a larger set of state variables \( \{x(t), \Theta\} \). In this case we can study whether/how those system parameters can be reconstructed or identified from the input–output behavior of the extended system, using the framework of the observability problem developed here. This parameter identifiability problem has its own merit and deserves systematic study. We believe our results could shed light on this challenging problem as well.

**Work also raises a series of fundamental questions worthy of future pursuit. First, for general nonlinear systems GA cannot tell which node in a root SCC should be chosen as a sensor node. Hence in such cases identifying the sensor nodes requires detailed knowledge about the system dynamics. Second, currently the sufficiency of the predicted minimum sensor set can be checked only for rational dynamics (5), raising the need for tools capable of demonstrating the sufficiency for arbitrary complex dynamical systems, like that involved in the Kuramoto model describing synchronization in coupled oscillators (26). Furthermore, noise and measurement uncertainties will likely increase the number of sensors, the degree of which remains to be explored in the context of stochastic control (27, 28). Finally, observability only guarantees that the sensors have access to the necessary information to reconstruct the state of the whole system. To explicitly extract this information we need to construct observers, a well-developed subject in engineering control theory. We demonstrate the construction of such an observer for a linear reaction system in SI Text, section IV. However, the systematic adoption of these tools to natural and complex systems could open new avenues in our quest to understand complexity (29).**

### Table 1. Genome-scale metabolic networks

<table>
<thead>
<tr>
<th>Name*</th>
<th>N</th>
<th>L</th>
<th>R</th>
<th>NC</th>
<th>SC</th>
<th>NP</th>
<th>NDD</th>
<th>NS</th>
<th>Ni</th>
</tr>
</thead>
<tbody>
<tr>
<td>E. coli (iAF1260)</td>
<td>1,668</td>
<td>12,719</td>
<td>3,231</td>
<td>120</td>
<td>1,523</td>
<td>56</td>
<td>60</td>
<td>96</td>
<td></td>
</tr>
<tr>
<td>S. cerevisiae (iND750)</td>
<td>1,060</td>
<td>9,080</td>
<td>1,793</td>
<td>112</td>
<td>931</td>
<td>106</td>
<td>78</td>
<td>99</td>
<td></td>
</tr>
<tr>
<td>H. sapiens (Recon1)</td>
<td>2,763</td>
<td>21,026</td>
<td>5,283</td>
<td>335</td>
<td>2,290</td>
<td>166</td>
<td>144</td>
<td>293</td>
<td></td>
</tr>
</tbody>
</table>

*For each metabolic network we show the number of nodes (metabolites) \( N \), edges \( L \), number of elementary reactions \( R \) and the number of strongly connected components \( NC \), and the size of the giant SCC \( SC \), in the inference diagram. The table also lists the number of pure reactants \( NP \), pure products \( NDD \), which are always sensor nodes), and the minimum number of sensor nodes \( NS \) predicted by the graphical approach.
structured system is given by the set of unmatched nodes with respect to any maximum matchings (17). In case all nodes are matched, any single node can be chosen as the driver node. To assure controllability, each root SCC of $G[A]$ requires an input signal. If there is an unmatched node $i$ inside a root SCC $R$, then $R$ will be controlled by the same signal connected to node $i$. If all of the nodes inside a root SCC $R$ are matched, then $R$ can be controlled by any other signal connected to any other unmatched node in the network. Hence the number of actuator nodes, which directly accept signals, can be calculated by counting the unmatched nodes (i.e., the driver nodes) and the root SCCs inside which all of the nodes are matched. Note that by controlling those root SCCs with all nodes matched, we eliminate "inaccessibility" in the system. And, by controlling unmatched nodes, we eliminate all possible "dilations" in the system. A dilation occurs if there is a subset $S$ of the nodes such that its neighborhood set $T(S)$, i.e., the set of all nodes $j$ where a directed edge exists from $j$ to a node in $S$, has fewer nodes than $S$ itself (6). A structured system is controllable if and only if both inaccessibility and dilations are avoided. By invoking the duality between controllability and observability in linear systems, the actuators in system $G[A]$ are just the sensors in its dual (or transposed) system $G[A]^\top$, which is obtained by flipping the direction of all edges. By monitoring those sensors, the system $G[A]^\top$ is guaranteed to be observable.

**Observability Test of Rational Systems.** To perform the algebraic observability test of rational dynamic systems, we use Sedoglavic's algorithm with a Maple implementation (5). If a system is algebraically observable, then there are algebraic relations between the state variables and the successive derivatives of the system's inputs and outputs (1, 2). These algebraic relations guarantee that the system is observable and will forbid symmetries. A family of symmetries is equivalent to in finite relations guarantee that the system is observable and will forbid symmetries. There are algebraic relations between the state variables and the successive derivatives of the system. This algorithm certifies that a system is locally observable and its Jacobian matrix using the techniques of symbolic calculation (5).

**Analysis of Random Reaction Systems.** To perform the symbolic analysis of random reaction systems, we use the network representation of the Jacobian matrix using the techniques of symbolic calculation (5). This algorithm certifies that a system is locally observable and its answer for a nonobservable system is probabilistic with high probability of success. A predicted nonobservable system and its nonobservable variables can be further analyzed to find a family of symmetries, which then can confirm the result.

**Generation of Random Chemical Reaction Systems.** We generate random chemical reaction systems as follows. We assure each reaction is mass balanced, i.e., it is chemically feasible with respect to mass conservation—the sum of its substrate atoms equals the sum of its product atoms (31). To generate random reaction systems under the constraint of mass balance, we start with several initial chemical compounds, each being a few elementary, e.g., four, compounds. For each abundant elements in biological systems: carbon (C), hydrogen (H), nitrogen (N), oxygen (O), phosphorus (P), and sulfur (S). Each compound can be represented by a mass vector. For instance, the mass vector of glucose ($C_6H_{12}O_6$) is given by $mG = (6.21 \times 6.00 \times 5.80)$. From the initial compounds, we can generate new compounds through chemical reactions. The stoichiometry coefficients in the reactions are randomly chosen with the constraint that the mass balance is strictly preserved. This can be achieved by tracking the mass vectors of all of the compounds. For example, starting from two compounds $C_3H_7O_2$ and $C_7H_9O_8$, we may have the following reaction:

$$C_3H_7O_2 + C_7H_9O_8 \rightarrow C_8H_{15}O_{10}$$

where the number of each element is preserved. This is a very powerful method to generate new compounds from the initial compounds. For instance, we can start with just two compounds: $C_3H_7O_2$ and $C_7H_9O_8$. We can then generate new compounds using the above procedure to create 1,000 chemical reaction systems with up to 221 compounds involved in 121 mass-balanced reactions.

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