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Learning stable and predictive structures in kinetic systems

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Learning kinetic systems from data is one of the core challenges in many fields. Identifying stable models is essential for the generalization capabilities of data-driven inference. We introduce a computationally efficient framework, called CausalKinetiX, that identifies structure from discrete time, noisy observations, generated from heterogeneous experiments. The algorithm assumes the existence of an underlying, invariant kinetic model, a key criterion for reproducible research. Results on both simulated and real-world examples suggest that learning the structure of kinetic systems benefits from a causal perspective. The identified variables and models allow for a concise description of the dynamics across multiple experimental settings and can be used for prediction in unseen experiments. We observe significant improvements compared to well-established approaches focusing solely on predictive performance, especially for out-of-sample generalization.

Results

Predictive Models versus Causal Models. Established methods mostly focus on predictability when inferring biological structure from data by selecting models. This learning principle, however, does not necessarily yield models that generalize well to unseen experiments, since purely predictive models remain

Significance

Many real-world systems can be described by a set of differential equations. Knowing these equations allows researchers to predict the system’s behavior under interventions, such as manipulations of initial or environmental conditions. For many complex systems, the differential equations are unknown. Deriving them by hand is infeasible for large systems, and data science is used to learn them from observational data. Existing techniques yield models that predict the observational data well, but fail to explain the effect of interventions. We propose an approach, CausalKinetiX, that explicitly takes into account stability across different experiments. This allows us to draw a more realistic picture of the system’s underlying causal structure and is a first step toward increasing reproducibility.

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Data deposition: Well-documented R and python code and data are available at http://CausalKinetiX.org. Code is also available as an open-source R package on CRAN (http://cran.r-project.org/web/packages/CausalKinetiX).

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agnostic with respect to changing environments or experimental settings. Causal models (22, 23) explicitly model such changes by the concept of interventions. The principle of autonomy or modularity of a system (24, 25) states that the mechanisms which are not intervened on remain invariant (or stable). This is why causal models are expected to work more reliably when predicting under distributional shifts (26–28).

Causality through Stability. In most practical applications the causal structure is unknown, but it may still be possible to infer the direct causes of a target variable $Y$, say, if the system is observed under different, possibly unspecified experimental settings. For nondynamical data, this can be achieved by searching for models that are stable across all experimental conditions; i.e., the parameter estimates are similar. Covariates that are contained in all stable models, i.e., in their intersection, can be proved to be causal predictors for $Y$ (17, 29).

The intersection of stable models, however, is not necessarily a good predictive model. In this work, we propose a method for dynamical systems that combines stability with predictability, we show that the inferred models generalize to unseen experiments, and we formalize its relation to causality (Materials and Methods).

CausalKinetiX: Combining Stability and Predictability. The observed data consist of a target variable $Y$ and covariates $X$ measured at several time points across different experimental setups and are assumed to be corrupted with observational noise (Fig. 1, Top).

Our proposed method, CausalKinetiX, exploits the assumption that the model governing the dynamics of $Y$ remains invariant over the different experiments. We assume there is a subset $S^*$ of covariates, such that for all $n$ repetitions, and $\frac{d}{dt} Y_t$ depends on the covariates in the same way; i.e.,

$$\frac{d}{dt} Y_t^{(i)} = f \left( X_t^{S^*,(i)} \right), \text{ for all } i = 1, \ldots, n.$$  \[1\]

The covariates are allowed to change arbitrarily across different repetitions $i$. Instead of fitting based only on predictive power, CausalKinetiX explicitly measures and takes into account violations of the invariance in [1].

Fig. 1. The framework of CausalKinetiX. The data for target variables $Y$ and predictors $X$ come from different experiments; we rank models according to their ability to fit the target well in all experiments; the top-ranked model is then fitted to the data; it allows us to predict the target in an unseen experiment.
provide a theoretical guarantee under which the top-ranked variables are indeed contained in the true causal model (Materials and Methods).

We compare the performance of this ranking on a simulation study based on a biological ordinary differential equation system from the BioModels Database (32) which describes reactions in heated monosaccharide–casein systems (SI Appendix, section 4). (In fact, the example in Fig. 2 comes from this model, with Y and X being the concentrations of Melanoidin and AMP, respectively.) We compare our method to dynamic Bayesian networks (33) based on conditional independence (DBN-CondInd), gradient matching (GM), and an integrated version thereof, which from now on we refer to as difference matching (DM); the last 2 methods both use \( \ell_1 \) penalization for regularization (SI Appendix, section 4). Fig. 3A shows median receiver operator curves (ROCs) for recovering the correct causal parents based on 500 simulations for all 4 methods. CausalKinetiX has the fastest recovery rate and, in more than 50% of the cases, it is able to recover all causal parents without making any false discoveries (Fig. 3C). The recovery of the causal parents as a function of noise level is given in Fig. 3B. On the x axis, we plot the relative size of the noise, where a value of 1 implies that the size of the noise is on the same level as the target dynamic and the signal is very weak. For all noise levels, CausalKinetiX is better at recovering the correct model than all competing methods. More comparisons can be found in SI Appendix, section 4.

 Numerical Stability, Scalability, and Misspecified Models. The method CausalKinetiX builds on standard statistical procedures, such as smoothing, quadratic programming, and regression. As opposed to standard nonlinear least squares, it does not make use of any numerical integration techniques. This avoids computational issues that arise when the dynamics result in stiff systems (34). For each model, the runtime is less than cubic in the sample size, which means that the key computational cost is the exhaustive model search. We propose to use a screening step to reduce the number of possible models (SI Appendix, section 3C), which allows applying the method to systems with hundreds of variables (e.g., Experiment on Metabolic Network below). Moreover, it does not require any assumptions on the dynamics of the covariates. In this sense, the method is robust with respect to model misspecifications on the covariates that can originate from hidden variables or misspecified functional relationships. Consistency of the proposed variable ranking (SI Appendix, section 3), for example, requires only the model for the target variable to be correctly specified. Simulation experiments show that this robustness can be observed empirically (SI Appendix, section 4). Finally, there is empirical evidence that incorporating invariance can be interpreted as regularization preventing overfitting and that the method is robust against correlated measurement error (SI Appendix, section 4).

Generalization in Metabolic Networks. We apply the proposed method to a real biological dataset of a metabolic network (Materials and Methods). Ions counts of one target variable and cell concentrations of 411 metabolites are measured at 11 time points across 5 different experimental conditions, each of which contains 3 biological replicates. The experiments include both up- and downshifts of the target variable; i.e., some of the conditions induce an increase of the target trajectory, compared to its starting value, and other conditions induce a decrease.

We compare the performance of CausalKinetiX with the performance of nonlinear least squares (NONLSQ). To make the methods feasible for such a large dataset, we combine them with a screening based on DM. We thus call the method based
Fig. 3. (A) Median ROCs for recovering the correct causal parents based on 500 simulations. CausalKinetiX has the fastest recovery rate. (B) Median area under the receiver operator curve (AUROC) for different relative noise levels. CausalKinetiX outperforms all other methods. (C) Number of recoveries before all correct variables enter the model. In the majority of cases, CausalKinetiX has no false discovery.

on nonlinear least squares DM-NONLSQ; its parameters are estimated using the software Data2Dynamics (d2d) (14), which uses CVODES of the SUNDIALS suite (35) for numerical integration.

Fig. 4.4 shows the models’ ability to describe the dynamics in the observed experiments (in-sample performance). DM-NONLSQ directly optimizes the RSS and therefore fits the data better than CausalKinetiX, which takes into account stability, as well. The RSS for DM-NONLSQ-10 (based on 10 terms) is lower (0.83) compared to CausalKinetiX (0.96) averaged over all in-sample experiments. The plot contains diagnostics for analyzing kinetic models. The integrated dynamics are shown jointly with a smoother (blue) through the observations (gray). At the observed time points, the predicted derivatives (red lines) are also shown using smoothed X and Y values. Model fits that explain the data reasonably well in the sense that the integrated trajectory is not far from the observations may predict derivatives (short red lines) on the smoother that do not agree well with the data: They fail to explain the underlying dynamics. For an example, see the in-sample fit of DM-NONLSQ-10 in Fig. 4.4. We regard plotting a smoothing spline and the predicted derivatives for the fitted values as a highly informative tool when analyzing models for kinetic systems.

Pooling data across heterogeneous experiments, as, for example, done by DM-NONLSQ, is already a natural regularization technique; if there is sufficient heterogeneity in the data, the causal model is the only invariant model. Finite many experiments, however, exhibit only limited heterogeneity and one can benefit from focusing specifically on invariant models. To compare the out-of-sample performance of the methods, we consider the best-ranked model from Fig. 4.4, hold out 1 experiment, fit the parameters on the remaining 4 experiments, and predict the dynamics on the held-out experiment. While DM-NONLSQ-10 explains the observations well in-sample, it does not generalize to the held-out experiments, and neither does DM-NONLSQ-3 (based only on 3 terms), which avoids overfitting. The average RSS of the held-out experiments are 1.41, 2.95, and 3.45 for CausalKinetiX, DM-NONLSQ-10, and DM-NONLSQ-3, respectively (Fig. 4B). Another comparison, when the methods are fully agnostic about one of the experimental conditions, is provided in SI Appendix, section 4. By trading off invariance and predictability, CausalKinetiX yields models that perform well on unseen experiments that have not been used for parameter estimation.

Discussion

In the natural sciences, differential equation modeling is a widely used tool for describing kinetic systems. The discovery and verification of such models from data have become a fundamental challenge of science today. Existing methods are often based on standard model selection techniques or various types of sparsity enforcing regularization; they usually focus on predictive performance and sometimes consider stability with respect to resampling (36, 37). In this work, we develop methodology for structure search in ordinary differential equation models. Exploiting ideas from causal inference, we propose to rank models not only by their predictive performance, but also by taking into account invariance, i.e., their ability to predict well in different experimental settings. Based on this model ranking, we construct a ranking of individual variables reflecting causal importance. It provides researchers with a list of promising candidate variables that may be investigated further by performing interventional experiments, for example. Our ranking methodology (both for models and for variables) comes with theoretical asymptotic guarantees and with a clear statement of the required assumptions. Extensive experimental evaluation on simulated data shows that our method is able to outperform current state-of-the-art methods. Practical applicability of the procedure is further illustrated on a not yet published biological dataset. Our implementation is readily available as an open-source R package (38).

The principle of searching for invariant models opens up a promising direction for learning causal structure from realistic, heterogeneous datasets. The proposed CausalKinetiX framework is flexible in that it can be combined with a wide range of dynamical models and any parameter inference method. This is particularly relevant when the differential equations depend nonlinearly on the parameters. Future extensions may further include the extension to stochastic, partial, and delay
differential equations and the transfer to other areas of application like robotics, climate sciences, neuroscience, and economics.

Materials and Methods

In this section, we provide additional details about data format, methodology, and the experiments. We further prove that our method is statistically consistent; i.e., it infers correct models when the sample size grows toward infinity.

Data Format. The data consist of \( n \) repetitions of discrete time observations of the \( d \) variables \( X \) (or their noisy version \( Y \)) on the time grid \( t = (t_1, \ldots, t_L) \). Each of the repetitions is part of an experiment \( \{e_1, \ldots, e_m\} \). The experiments should be thought of as different states of the system and may stem from different interventions. One of the variables, \( X^I \), say, is considered as the target, and we write \( Y_I^{(0)} = X^I \). We further assume an underlying dynamical model (which then results in various statistical dependencies between the variables and different time points).

Mass-Action Kinetic Models. Many ordinary differential equation-based systems in biology are described by the law of mass-action kinetics. The resulting ordinary differential equation models are linear combinations of various orders of interactions between the predictor variables \( X \). Assuming that the underlying ordinary differential equation model of our target \( Y = X^I \) is described by a version of the mass-action kinetic law, the derivative \( Y_I := \frac{d}{dt} Y_I \) equals

\[
Y_I = g_I(X) = \sum_{k=1}^d \theta_{0,k} X^k + \sum_{i=1}^d \sum_{k=1}^d \theta_{i,k} X^k X^i,
\]

where \( \theta = (\theta_{0,1}, \ldots, \theta_{0,d}, \theta_{1,1}, \ldots, \theta_{d,d}) \in \mathbb{R}^{(d^2+d)/2+d} \) is a parameter vector. We denote the subclass of all such linear models of degree 1 consisting of at most \( p \) terms \( (i.e., p \) nonzero terms in the parameter vector \( \theta \) \) by \( \mathcal{M}_p \) and call these models exhaustive linear models of degree 1. A more detailed overview of different collections of models is given in SI Appendix, section 2.

Model Scoring. For each model \( M \) the score \( T = T(M) \) is computed using the following steps. They include fitting 2 models to the data: one in \( M_3 \) and the other one in \( M_4 \) and \( M_5 \).

M1) Input: Data are as described above and a collection \( \mathcal{M} = \{M^1, M^2, \ldots, M^p\} \) of models over \( d \) variables is assumed to be rich enough to describe the desired kinetics. In the case of mass-action kinetics, e.g., \( M = M^{\text{exhaustive}} \).

M2) Screening of predictor terms (optional): For large systems, reduce the search space to fewer predictor terms. Essentially, any variable reduction technique based on the regression in step M4 can be used. We propose using \( \ell_1 \)-penalized regression (SI Appendix, section 2).

M3) Smooth target trajectories: For each repetition \( i \in \{1, \ldots, n\} \), smooth the (noisy) data \( Y_I^{(0)}, Y_I^{(0)} \) using a smoothing spline

\[
y_i^{(0)} := \arg\min_{y \in \mathcal{H}_C} \sum_{i=1}^L \left( Y_i^{(0)} - y(t_i) \right)^2 + \lambda \int y(s)^2 \, ds.
\]

where \( \lambda \) is a regularization parameter, which in practice is chosen using cross-validation; \( \mathcal{H}_C \) contains all smooth functions \( [0, T] \rightarrow \mathbb{R} \), for which values and first 2 derivatives are bounded in absolute value by \( C \). We denote the resulting functions by \( \hat{y}_i^{(0)} \), \( i \in \{1, \ldots, n\} \). For each of the \( m \) candidate target models \( M \in \mathcal{M} \) perform steps M4 to M6.

M4) Fit candidate target model: For each \( i \in \{1, \ldots, n\} \), find the function \( \hat{g} \in \mathcal{G} \) such that
\[ \hat{y}_t^0 = g' \left( \hat{X}_t^0 \right) \]  

is satisfied as well as possible for all \( t \in T \) and for all repetitions \( k \) belonging to a different experiment than repetition \( i \). Below, we describe 2 procedures for this estimation step resulting in estimates \( \hat{g}' \). For each repetition \( i \in \{1, \ldots, n\} \), this yields \( L \) fitted values \( g' \left( \hat{X}_t^0 \right), \ldots, g' \left( \hat{X}_t^L \right) \). Leaving out the repetition of experiment \( i \) ensures that only an invariant model leads to a good fit, as these predicted derivatives are reasonable only if the dynamics generalize across experiments.

M5) Smooth target trajectories with derivative constraint: Refit the target trajectories for each repetition \( i \in \{1, \ldots, n\} \) by constraining the smooth to these derivatives; i.e., find the functions \( \hat{y}_t^0 : [0, T] \to \mathbb{R} \) which minimize

\[ \hat{y}_t^0 : = \arg \min_{y \in \mathcal{H}} \frac{1}{n} \sum_{i=1}^{L} \left( \hat{y}_t^0 - y(t_i) \right)^2 + \lambda \int y'(s)^2 \, ds \]

such that \( y(t_i) = g' \left( \hat{X}_t^0 \right) \) for all \( t = 1, \ldots, L \).

M6) Compute score: If the candidate model \( M \) allows for an invariant fit, the fitted values \( g' \left( \hat{X}_t^0 \right), \ldots, g' \left( \hat{X}_t^L \right) \) computed in M4 will be reasonable estimates of the derivatives \( \hat{y}_t^0, \ldots, \hat{y}_t^L \). This, in particular, means that the constrained fit in M5 will be good, too. If, conversely, the model \( M \) does not allow for an invariant fit, the estimates produced in M4 will be poor. We thus score the models by comparing the fitted trajectories \( \hat{y}_t^0 \) and \( \hat{y}_t^L \) across repetitions as

\[ T(M) = -\frac{1}{n} \sum_{i=1}^{L} \frac{\text{RSS}_0^0 - \text{RSS}_a^0}{\text{RSS}_0^0} \]

where \( \text{RSS}_0^0 = \frac{1}{L} \sum_{i=1}^{L} \left( \hat{y}_t^0(t_i) - y(t_i) \right)^2 \). If there is a reason to believe that the observational noise has similar variances across experiments, the division in the score can be removed to improve numerical stability.

The scores \( T(M) \) induce a ranking on the models \( M \in \mathcal{M} \), where models with a smaller score have more stable fits than models with larger scores. Below, we show consistency of the model ranking.

Variable Ranking. The following method ranks individual variables according to their importance in obtaining invariant models. We score all models in the collection \( \mathcal{M} \) based on their stability score \( T(M) \) (see [6]) and then rank the variables according to how many of the top-ranked models depend on them. This can be summarized in the following steps:

V1) Input: Same as in M1.

V2) Compute scores: For each model \( M \in \mathcal{M} \) compute the noninvariance score \( T(M) \) as described in [6]. Denote by \( M_{\text{top}} \) the K top-ranked models, where \( K \in \mathbb{N} \) is chosen to be the number of expected invariant models in \( \mathcal{M} \).

V3) Score variables: For each variable \( j \in \{1, \ldots, d\} \), compute the following score:

\[ s_j := \frac{|\{k \in \{1, \ldots, K\} | M_{\text{top}} \text{ depends on } j\}|}{K} \]  

Here, “\( M_{\text{top}} \) depends on \( j \)” means that the variable \( j \) has an effect in the model \( M_{\text{top}} \) (SI Appendix, section 2). If there are \( K \) invariant models, the above score represents the fraction of invariant models that depend on variable \( j \). It equals 1 for variable \( j \) if and only if every invariant model depends on that variable.

These scores \( s_j \) are similar to what is referred to as inclusion probabilities in Bayesian model averaging (31). Below, we construct hypothesis tests for the test whether a score is significantly higher than if the models are ranked randomly.

A natural choice for the parameter \( K \) should equal the number of invariant models. This may be unknown in practice, but our empirical studies found that the method's results are robust to the choice of \( K \). In particular, we propose to choose a small \( K \) to ensure that it is smaller than the number of invariant models (SI Appendix, section 2).

Fitting Target Models (M4). In step M4, for every \( i \in \{1, \ldots, n\} \), we perform a regression to find a function \( g' \in M \) such that [4] is optimized across all repetitions \( k \) belonging to different experiments than \( i \). This task is difficult for 2 reasons. First, the derivative values \( \hat{y}_t^0 \) are not directly observed and, second, even if we had access to (noisy and unbiased versions of) \( \hat{y}_t^0 \), we are dealing with an error-in-variables problem. Nevertheless, for certain model classes it is possible to perform this estimation consistently and since the predictions are used only as constraints, one expects estimates to work as long as they preserve the general dynamics. We propose 2 procedures: 1) a general method that can be adapted to many model classes and 2) a method that performs better but assumes the target model to be linear in parameters.

The first procedure estimates the derivatives and then performs a regression based on the model class under consideration. That is, one fits the smoother \( \hat{y}_t^0 \) from M3 and then computes its derivatives. When using the first derivative of a smoothing spline, it has been argued that the penalty term in [3] contains the third rather than the second derivative of \( y \) (39). We then regress the estimated derivatives on the data. As a regression procedure, one can use ordinary least squares if the models are linear or random forests, for example, if the functions are highly nonlinear.

The second method works for models that are linear in the parameters, i.e., for models that consist of functions of the form \( g_k(x) = \sum_{j=1}^{g_k} \beta_j g_j(x) \), where the functions \( g_1, \ldots, g_p \) are known transformations. This yields

\[ Y_{t_k} - \hat{y}_t^0 = \sum_{j=1}^{p} \beta_j \int_{t_{k-1}}^{t_k} g_j(\hat{X}_t^0) \, ds \]

This approach does not require estimation of the derivatives of \( Y \) but instead uses the integral of the predictors. It is well known that integration is numerically more stable than differentiation (40). Often, it suffices to approximate the integrals using the trapezoidal rule; i.e.,

\[ \int_{t_{k-1}}^{t_k} g_j(\hat{X}_t^0) \, ds \approx \frac{g_j(\hat{X}_{t_k}^0) + g_j(\hat{X}_{t_{k-1}}^0)}{2} \]

since the noise in the predictors is often stronger than the error in this approximation. The resulting bias is then negligible.

As mentioned above, most regression procedures have difficulties with errors in variables and therefore return biased results. Sometimes it can therefore be helpful to use smoothing or averaging of the predictors to reduce the impact of this problem. Our procedure is flexible in the sense that other fitting procedures, e.g., inspired by refs. 28, 41, and 42, could be applied, too.

Experiment on Metabolic Network. Defining the auxiliary variable \( Z_i := Z - Y_i \), we expect that the target species \( Y_i \) and \( Z_i \) are tightly related: \( Y_i \approx Z_i \), i.e., \( Y_i \) is formed into \( Z_i \) and vice versa. We therefore expect models of the form

\[ Y_i = \theta_1 Z_i X_i^0 + \theta_2 Z_i X_i^0 Z_i X_i^0 \]

\[ Z_i = -\theta_3 Z_i X_i^0 - \theta_3 Z_i X_i^0 + \theta_4 Y_i X_i^0 \]

where \( j, k, p, q, r, s \in \{1, \ldots, 411\} \) and \( \theta_1, \theta_2, \theta_3, \theta_4 \geq 0 \). By the conservation of mass both target equations mirror themselves, which makes it sufficient to learn only the model for \( Y_i \). More precisely, we use the model class consisting of 3-term models of the form \( Z_i X_i^0 Y_i, X_i^0 Y_i, Y_i X_i^0 Z_i, Z_i X_i^0, Y_i X_i^0 \), or \( Y_i X_i^0 \), where the sign of the parameter is constrained to being positive or negative depending on whether the term contains \( Z_i \) or \( Y_i \), respectively.

We constrain ourselves to 3 terms, as this found to be the smallest number of terms that results in sufficiently good in-sample fits. Given sufficient computational resources, one may include more terms, too, of course. The sign constraint can be incorporated into our method by performing a constrained least-squares fit instead of OLS in step M4. This constrained regression can then be solved efficiently by a quadratic program with linear constraints.

As the biological data are high dimensional, our method first screens down to 100 terms and then searches over all models consisting of 3 terms. To get more accurate fits of the dynamics, we pool and smooth over the 3 biological replicates and work only with the smoothed data.

Significance of Variable Ranking. We can test whether a given score \( s_j \), defined in [7], is significant in the sense that the number of top-ranked models depending on variable \( j \) is higher than one would expect if the
ranking of all models in \( M \) was random. More precisely, consider the null hypothesis

\[ H_0 : \ \text{the top-ranked models } M_{(1)}, \ldots, M_{(k)} \text{ are drawn uniformly from all models in } M. \]

It is straightforward to show that under \( H_0 \) it holds that \( K - s_i \) follows a hypergeometric distribution with parameters \( |M| \) (population size), \( n \) (number of draws), and \( K \) (number of draws). For each variable we can hence compute a \( p \) value to assess whether it is significantly important for stability.

**Theoretical Consistency Guarantees.** We prove that both the model ranking and the proposed variable ranking satisfy theoretical consistency guarantees. More precisely, under suitable conditions and in the asymptotic setting where both the number of realizations \( n \) and the number of time points \( T \) converge to infinity, every invariant model will be ranked higher than all noninvariant models. Given sufficient heterogeneity of the experiments it additionally holds that the variable score \( s_i \) defined in [7] tends to one if and only if \( j \in S^* \) (see [1]). Details and proofs are provided in SI Appendix, section 3.


**Relation to Causality.** Causal models enable us to model a system’s behavior not only in an observational state, but also under interventions. There are various ways to define causal models ([22, 23]). The concept of structural causal models is well suited for the setting of this paper and its formalism can be adapted to the case of dynamical models (SI Appendix, section 1). If the experimental settings correspond to different interventions on variables other than \( Y \), choosing \( S^* \) as the set of causal parents of \( Y \) satisfies [1]. If the settings are sufficiently informative, no other set satisfies [1].

**Code and Data Availability.** Well-documented code is available as an open-source R package on CRAN ([38]). It includes the ordinary differential equation models used in the simulations, e.g., the Maillard reaction. All further code and data are available at http://CausalKinetiX.org. The exact parameter settings for the simulations can be found in SI Appendix, section 4. The data underlying the metabolic network experiment will be made available upon reasonable request.

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