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A Closed-Loop Identification Protocol for Nonlinear Dynamical Systems

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A previous work introduced an optimal identification (OI) technique for reliably extracting model parameters of biochemical reaction systems from tailored laboratory experiments. The notion of optimality enters through seeking an external control in the laboratory producing data that leads to minimum uncertainties in the identified parameter distributions. A number of algorithmic and operational improvements are introduced in this paper to OI, aiming to build a more practical and efficient closed-loop identification protocol/procedure (CLIP) for nonlinear dynamical systems. The improvements in CLIP include (a) inversion cost function modification to preferably search for the upper and lower boundaries of the parameter distributions consistent with the observed data, (b) dynamic search range updating of the unknown parameters to better exploit the information from the prior iterative experiments, (c) replacing the control genetic algorithm by the simplex method to enable better balance between operational cost and inversion quality, and (d) utilizing virtual sensitivity optimization techniques to further reduce the laboratory costs. The workings of CLIP utilizing these new algorithms are illustrated in indentifying a simulated tRNA proofreading model, and the results demonstrate enhanced performance of CLIP in terms of algorithmic reliability and efficiency.

1. Introduction

Inferring mathematical models of dynamical systems from laboratory or field observations has always been a subject of interest in science and engineering. An important subdivision of this field addresses the identification of nonlinear systems, which pose problems and require solutions distinct from their linear counterparts. For linear system identification,[2] unique solutions normally exist for overdetermined problems where there are more equations than the unknown parameters, and the error distribution of the extracted parameters usually can be calculated from the measurement error. Similar principles have been employed in several recent studies for identifying nonlinear dynamical systems.[3−9] Complexities can arise in the latter case, however, because multiple solutions can exist even when the system is overdetermined, due to the nonlinearity, the limited amount of laboratory data, and the data noise. In addition, the error propagation from the laboratory data to the inverted model parameters is also generally nonlinear and usually cannot be explicitly determined. Consequently, obtaining one solution for the set of model parameters can often be unreliable and may result in erroneous model predictions, especially under conditions different from those involved in the identification.

A previous study presented an optimal identification (OI) procedure for reliably extracting the model parameters of biochemical reaction networks from tailored laboratory data.[1] OI differs from traditional approaches in two general aspects. First, it aims at recovering the full family of parameter values consistent with the laboratory data. Second, it integrates appropriate computational algorithms with the experimental capabilities in a closed-loop fashion to search for the optimal laboratory controls/perturbations and observations that result in maximal reduction of the uncertainties in the extracted parameters. The operation of OI was simulated in the identification of a tRNA proofreading system,[10,11] where OI yielded better accuracy and reliability compared with traditional inversion methods.

A potential concern when implementing OI is its laboratory and computational costs. The determination of the optimal laboratory controls was achieved using a genetic algorithm (GA).[12,13] The GA provides favorable global search ability, but it normally requires a large number of laboratory experiments to converge. In the system inversion following each experiment, a large population of parameter sets was usually needed to define

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the full parameter family consistent with the data, which can be computationally very expensive, especially when integrated with the iterative process of laboratory control optimization by the GA.

To address these issues, this article introduces various improvements to OI's operational procedure and algorithmic components. The resultant closed-loop identification protocol (CLIP) serves not only as an enhancement to OI for identifying biochemical reaction models but also more importantly as an algorithmic platform containing a growing suite of user-selectable modular components that can perform reliably in more general nonlinear system identifications. As an alternative to the GA, the control module of CLIP employs the Nelder−Mead simplex algorithm[17,18] to search for the optimal laboratory controls, thereby allowing for a favorable balance between lowering the number of experiments and maintaining a high-dimensional search capability. CLIP's inversion module also includes an enhanced inversion algorithm with (a) cost function modification for better extraction of the parameter distributions and (b) dynamic updating of the parameter search ranges to provide elevated inversion quality and algorithmic efficiency. Last, a virtual sensitivity optimization algorithm is introduced to CLIP's analysis module to estimate the best laboratory controls before the iterative inversion process, thus enabling further reduction of the identification cost. The performance of CLIP is demonstrated in the identification of the same tRNA proofreading model,[10,11] and the comparison with the original OI method suggests that the algorithmic improvements can enable more reliable and cost-effective parameter identification for nonlinear dynamical systems.

2. Concepts and Algorithms

2.1. The Optimal Identification Algorithm (OI). This section will summarize the OI algorithm as it forms the foundation of CLIP. One special feature of OI is its ability to recover the full family of model parameter values consistent with the laboratory measurements. More importantly, OI operates in a closed-loop fashion to guide the experiments so that the breadth of the distribution for the consistent parameter families can be best reduced from the information contained in the optimal control-measurements, thus leading to maximal reliability in parameter inversion and subsequent model predictions. The utilization of closed-loop experiment optimization is well established in linear system identification.[2,19] For nonlinear system identification, however, most efforts are still focused on extracting model parameters from a given/specific data set,[20−24] instead of further optimizing the experiments whose resultant data can lead to enhanced achievable inversion quality. In this context, OI specifically aims to exploit closed-loop experiment optimization for nonlinear dynamical system identification.

Figure 1 shows the three general components (i.e., the analysis module, the control module, and the inversion module) of the OI procedure for identifying the unknown parameter vector $\mathbf{k} = (k_1, ..., k_m, ..., k_M)$ of a specified ODE model representing a nonlinear dynamical system

$$\frac{dx_n}{dt} = f_n(\mathbf{x},\mathbf{k}) + u_n(t) \qquad n = 1, 2, ..., N \tag{1}$$

where $x_n \in \mathbf{x}$ is the nth component of the system and $u_n(t) \in \mathbf{u}_c(t)$ is the time-dependent external control flux associated with x_n. Utilizing available semiquantitative or qualitative knowledge about the system and incorporating other relevant information

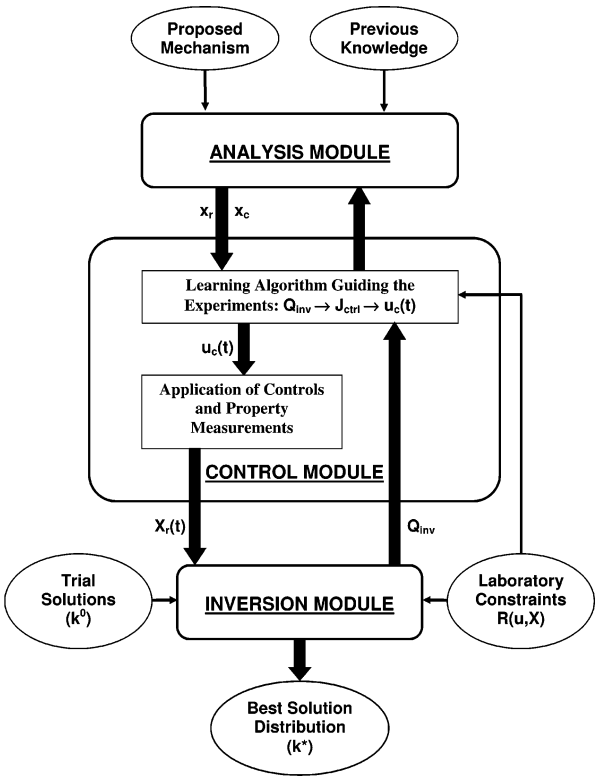

Figure 1. General operational procedure of OI and CLIP for identifying model parameters of nonlinear dynamical systems, adopted from Figure 1 of ref 1. The proposed mechanism and previous knowledge of the target system is provided to the analysis module, which estimates the best system components for controlling the system ($\mathbf{x}_c$) and recording its responses ($\mathbf{x}_r$). In the control module, time-dependent trial controls $\mathbf{u}_c(t)$ are applied and the system's behavior $\mathbf{X}_r(t)$ is measured. The inversion module extracts the full distribution of parameters $\mathbf{k}$ consistent with the laboratory data and calculates its inversion quality Q_{inv}, which is then returned to the control module to calculate the control cost J_{ctrl} for selecting new experiments, with the purpose of achieving better inversion quality. This iterative operation continues until the best attainable quality is achieved for all the model parameters under any laboratory constraints $R(\mathbf{u},\mathbf{X})$. The analysis module of CLIP also involves a virtual sensitivity optimization technique for estimating the best control $\mathbf{u}_c^*(t)$ before the iterative inversion process, to further reduce the laboratory cost (section 2.2.3).

such as laboratory capabilities, the analysis module employs system-dependent sensitivity analysis algorithms to estimate the best targets $\mathbf{x}_r$ for monitoring the system's dynamics and the best targets $\mathbf{x}_c$ for controlling (disturbing) the system.[1,25,26]

On the basis of the estimates from the analysis module, the control module applies a set of I trial control vectors ($\mathbf{u}_c^1(t)$, ..., $\mathbf{u}_c^i(t)$, ..., $\mathbf{u}_c^I(t)$) in the laboratory to $\mathbf{x}_c$ and records the response of $\mathbf{x}_r$ to each control vector at multiple times. The parameter vector $\mathbf{a}^i$ characterizing the ith control vector $\mathbf{u}_c^i(t)$ and the system's response $\mathbf{X}_r^i(t)$ are then forwarded to the inversion module, which returns the inversion quality Q_{inv}^i representing the breadth of the distribution for the extracted parameter family consistent with the observed data $\mathbf{X}_r^i(t)$ (see eq 4). The cost function J_{ctrl}^i for $\mathbf{u}_c^i(t)$ is calculated as

$$J_{ctrl}^i = Q_{inv}^i + wR[\mathbf{u}_c^i(t),\mathbf{X}_r^i(t)] \tag{2}$$

where $R[\mathbf{u}_c^i(t),\mathbf{X}_r^i(t)]$ is a positive semidefinitive functional representing the costs associated with any additional constraints for the controls $\mathbf{u}_c^i(t)$ and the laboratory measurements $\mathbf{X}_r^i(t)$, and w is a positive weight parameter. J_{ctrl}^i is used by a genetic

algorithm[12,13] (referred to as the control GA) to optimize $\mathbf{u}_c^i(t)$ in an iterative fashion until one or a few control vectors are found to achieve optimal reduction of Q_{inv}^i (hence optimal reduction of the uncertainties in $\mathbf{k}$).

Similar to traditional identification methods, the inversion module seeks the model parameters $\mathbf{k}$ that minimize the norm $||\mathbf{X}_r^{obs} - \mathbf{X}_r^{cal}||$ of the difference between observed and calculated temporal responses of the target system. Unlike most other methods that provide only one or a few solutions for $\mathbf{k}$, OI searches globally within a predefined domain of high-dimensional parameter space $[\mathbf{k}^L, \mathbf{k}^U]$ (with $\mathbf{k}^L$ and $\mathbf{k}^U$ being the corresponding lower and upper limits, respectively), aiming to recover the full family of $\mathbf{k}$ vectors consistent with the laboratory data. This treatment maximally avoids false convergence to local minima in the search process, which can be especially important in the presence of large laboratory noise. The global inversion is achieved by another GA (the inversion GA), which utilizes a cost function that compares the calculated system response to the experimental measurements, such as

$$J_{inv}^{i,p} = \frac{1}{N_r}\sum_{n=1}^{N_r}\frac{1}{T}\sum_{t=t_1}^{t_T}\begin{cases} 1 & : \ |X_{n,t}^{i,obs} - X_{n,t}^{i,p,cal}| \le \epsilon_n^i \\ \dfrac{|X_{n,t}^{i,obs} - X_{n,t}^{i,p,cal}|}{\epsilon_n^i} & : \ |X_{n,t}^{i,obs} - X_{n,t}^{i,p,cal}| > \epsilon_n^i \end{cases} \quad (3)$$

where $J_{inv}^{i,p}$ represents the "fitness" of the pth trial parameter vector $\mathbf{k}^{i,p}$ for the ith control vector $\mathbf{u}_c^i(t)$, N_r is the number of system components $\mathbf{x}_r$ selected for recording the system's response at the T time points (t_1, ..., t_T), and ϵ_n^i is the measured or estimated experimental error. The inversion GA iterates until a sufficient number S of $\mathbf{k}^{i,s}$ ($s = 1, 2, ..., S$) solutions with satisfactory $J_{inv}^{i,s}$ values are obtained to constitute a convergent sample ($\mathbf{k}^{i,1}$, ..., $\mathbf{k}^{i,s}$, ..., $\mathbf{k}^{i,S}$) of the distribution of the consistent parameters. The inversion quality Q_{inv}^i corresponding to the distribution of $\mathbf{k}^{i,s}$ can be calculated as

$$Q_{inv}^i = \frac{1}{M}\sum_{m=1}^{M}\left(\frac{k_{m,max}^{i,s} - k_{m,min}^{i,s}}{w_m}\right) \quad (4)$$

where $k_{m,max}^{i,s}$ and $k_{m,min}^{i,s}$ are the extracted upper and lower bounds, respectively, of the distribution of $k_m^{i,s}$ for the control $\mathbf{u}_c^i(t)$, and w_m is the normalization parameter for k_m. Because a smaller Q_{inv}^i value corresponds to a narrower $\mathbf{k}^{i,s}$ distribution, minimization of Q_{inv}^i is sought by the control module (using eq 2 as the cost function) over the evolving OI iterations. The inversion quality measure in eq 4 is very conservative, as it uses only the lowest and the highest parameter values found to be consistent with the data. Other measures (e.g., the distribution width or entropy) could be used as well.[1,14−16] It is notable that, although the control term $u_n(t)$ enters eq 1 linearly in this work, it is not a general requirement, because the operation of the inversion GA requires only knowledge of the input parameters (trial rate constants $\mathbf{k}^{i,p}$) and the corresponding cost function values ($J_{inv}^{i,p}$), which does not depend on the detailed mathematical form of the model as long as $J_{inv}^{i,p}$ is computable from the model equations.

2.2. The Closed-Loop Identification Protocol (CLIP). Two practical issues may impede OI's real-world applicability. In the inversion module, a large population (hundreds to even thousands) of $\mathbf{k}^{i,s}$ solutions are normally needed to provide a convergent parameter distribution for the control $\mathbf{u}_c^i(t)$. This requirement imposes a heavy computational burden with the inversion GA, which possesses the global search capability crucial to the algorithm's reliability but lacks in convergence efficiency. In the control module, the control vectors $\mathbf{u}_c^i(t)$ are optimized by another GA, whose convergence can require a large number of (sometimes expensive) experiments together with the associated increment of computational cost. These two problems can be increasingly serious for large nonlinear systems, when algorithmic scalability also needs to be taken into account.

A number of modifications are implemented to all three modules of OI to address the above issues. The goal is to form a foundation of CLIP that can incorporate particular computational algorithms to satisfy specific identification requirements. Suitable algorithmic components of CLIP will be selected on this basis to treat practical nonlinear system identification problems reliably and efficiently. This work focuses on the implementation of several algorithmic improvements for identification along with their application in simulated ODE systems. However, the principles and basic operational procedure of CLIP should be readily applicable to the identification of nonlinear dynamical systems represented in other mathematical forms, such as PDEs or stochastic equations, although the computational cost in the latter cases may be much higher.

2.2.1. Improvements in the Inversion Module. The cost function of the inversion GA (eq 3) indicates that, in the parameter inversion process, all trial parameter vectors $\mathbf{k}^{i,p}$ are weighted equally as long as they result in identical values for the norm of the difference between measured and calculated system behavior. Using this cost function, the inversion GA aims at recovering a discrete sampling/approximation of the full distribution of the consistent parameters $\mathbf{k}^i$. In certain cases, however, obtaining the full distribution function may not be critical for characterizing the inversion quality Q_{inv}^i. In eq 4, for example, Q_{inv}^i for $\mathbf{u}_c^i(t)$ is determined only by the maximum ($k_{m,max}^{i,s}$) and minimum ($k_{m,min}^{i,s}$) values of the distribution for $k_m^{i,s}$. Generally, the inversion GA, using eq 3 as its cost function, does not preferably search for $k_m^{i,s}$ solutions near $k_{m,max}^{i,s}$ or $k_{m,min}^{i,s}$, and much computational time is spent in identifying $k_m^{i,s}$ values lying in the middle of the solution distribution, which are not used for calculating Q_{inv}^i represented by eq 4.

An alternative algorithm is introduced to the inversion module of CLIP to enhance the computational efficiency in obtaining $k_{m,max}^{i,s}$ and $k_{m,min}^{i,s}$ values when the full consistent parameter distribution is not needed.[27] This algorithm utilizes two inversion GAs that search separately for $k_m^{i,s}$ solutions near the upper and lower edges of k_m's predefined search ranges. This capability is achieved by appropriate modification of the cost functions for the GA search. While functions of various forms can be selected as the inversion cost function, in the present work the following forms are used:

$$J_U^{i,p} = J_{inv}^{i,p}\left[\prod_{m=1}^{M}\left(\frac{k_m^U - k_m^{i,p} + c_m}{k_m^U - k_m^L + c_m}\right)^w\right] \quad (5)$$

and

$$J_L^{i,p} = J_{inv}^{i,p}\left[\prod_{m=1}^{M}\left(\frac{k_m^{i,p} - k_m^L + c_m}{k_m^U - k_m^L + c_m}\right)^w\right] \quad (6)$$

where k_m^U and k_m^L are the upper and lower search ranges for k_m, respectively, $J_{inv}^{i,p}$ is calculated from eq 3, and w is a user-

selected weight parameter. On the right-hand side of eqs 5 and 6, $J_{\text{inv}}^{i,p}$ serves to minimize the difference between the calculated system behavior and the laboratory measurements, whereas the additional multiplicative term guides the GA search of $\mathbf{k}^{i,p}$ toward the upper or lower edges of $[\mathbf{k}^L,\mathbf{k}^U]$. In eqs 5 and 6, $k_m^{\text{U}} - k_m^{\text{L}}$ is incremented by a positive, user-selected constant c_m to avoid potential singular behavior when $k_m^{\text{U}} - k_m^{\text{L}}$ is very small.

The second added feature in the inversion module of CLIP involves a dynamic updating of the parameter search ranges, in which the initial parameter boundaries k_m^{U} and k_m^{L} are replaced by $k_{m,\max}^{i,s}$ and $k_{m,\min}^{i,s}$, respectively, obtained from the parameter inversion after each control experiment $\mathbf{u}_c^i(t)$. This update allows the inversion process with the next trial control $\mathbf{u}_c^{i+1}(t)$ to operate within a reduced search range; thus, it utilizes information from the preceding control experiments with $\mathbf{u}_c{}^1(t)$, ..., $\mathbf{u}_c^i(t)$, resulting in improved algorithmic performance.

When the modified inversion GA is employed together with the dynamic search range updating, the inversion quality can be calculated alternatively as

$$Q_{\text{inv}}^i = \frac{1}{M}\sum_{m=1}^{M}\frac{\sqrt{\frac{1}{S}\sum_{s=1}^{S}(k_m^{i,s,\text{u}} - \overline{k_m^{i,s,\text{u}}})^2} + \sqrt{\frac{1}{S}\sum_{s=1}^{S}(k_m^{i,s,\text{l}} - \overline{k_m^{i,s,\text{l}}})^2}}{k_{m,\max} - k_{m,\min} + c_m} \quad (7)$$

where $k_m^{i,s,\text{u}}$ represents the sth consistent solution when eq 5 is used as the GA cost function to search for the upper boundary of k_m with the control $\mathbf{u}_c^i(t)$. $\overline{k_m^{i,s,\text{u}}}$ corresponds to the mean of $k_m^{i,s,\text{u}}$. $k_m^{i,s,\text{l}}$ and $\overline{k_m^{i,s,\text{l}}}$ are counterparts of $k_m^{i,s,\text{u}}$ and $\overline{k_m^{i,s,\text{u}}}$, respectively, in searching for the lower boundary of k_m. This measure reflects the normalized standard deviation of the extracted parameter distributions for both $\mathbf{k}^{i,s,\text{u}}$ and $\mathbf{k}^{i,s,\text{l}}$ and we find it more accurate and convenient in defining the inversion quality when using the modified inversion GA with the dynamic search range updating.

2.2.2. Improvements in the Control Module. As illustrated in ref 1, the nature of the control GA enables a global search for controls $\mathbf{u}_c^i(t)$ providing maximal information content in the data for retrieving the highest-quality model parameters, but this property may also lead to an undesired increase in the number of iterative experiments. To alleviate this disadvantage when the laboratory cost is a major concern, CLIP incorporates alternative local search/optimization algorithms in its control module to replace the control GA in OI. A good choice is the Nelder−Mead simplex method,[17,18,28,29] which is more efficient in exploring the complex high-dimensional control space while retaining some global search capability. The logic for utilizing such algorithms whose exploration part is deterministic resides in the fact that, in many cases, it suffices to identify a control $\mathbf{u}_c^i(t)$ that is "good enough" for retrieving a parameter distribution of $\mathbf{k}^{i,s}$ with adequate inversion quality Q_{inv}^i, because finding the globally optimal control with algorithms featuring stochastic exploration (such as the GA) requires many more experiments and may not provide much gain in Q_{inv}. As a result, the simplex method can often provide a better balance between operational cost and inversion quality. The simplex algorithm is not employed in the inversion module because the global search ability of the GA is crucial for extracting the full family of consistent parameters. The simplex algorithm can operate with eq 2 being the cost function and eq 4 or 7 representing the inversion quality Q_{inv}^i.

2.2.3. Improvements in the Analysis Module. Previous studies have shown that the identifiability and the inversion quality of unknown model parameters are directly associated with the experimental sensitivity coefficients L_{mn}, defined as the sensitivity of the nth experimental observable (X_n in eq 1) with respect to the mth model parameter to be inferred (k_m in eq 1).[30,31] This observation suggests that the laboratory controls that optimize L_{mn} (i.e., maximize the magnitude of L_{mn}) may also result in favorable inversion quality for the model parameters $\mathbf{k}$. Consequently, sensitivity optimization can be employed in CLIP's analysis module (prior to the iterative inversion process among the control and the inversion modules) to estimate the control(s) $\mathbf{u}_c^*(t)$ that may result in maximal or at least enhanced inversion quality Q_{inv}^*.

The experimental sensitivity coefficient $L_{\text{mn}}^i(t)$ for the control $\mathbf{u}_c^i(t)$ at time t can be calculated in different ways depending on the circumstances. If the search ranges of k_m and the variations in $X_n^i(t)$ are sufficiently small, $L_{\text{mn}}^i(t)$ can be determined by a partial derivative $\partial \ln X_n^i(t)/\partial \ln k_m$.[30,31] In cases where either term is large, global sensitivity measures become more appropriate. One convenient way to obtain the global sensitivity coefficient $L_{\text{mn}}^i(t)$ is to randomly sample the model parameters within their search ranges $[\mathbf{k}^{\text{L}},\mathbf{k}^{\text{U}}]$ and calculate the system's response $X_{n,t}^{z,i}$ for each sample $\mathbf{k}^z$ ($z = 1, 2, ..., Z$). $L_{\text{mn}}^i(t)$ can then be determined as a standard deviation

$$L_{\text{mn}}^i(t) = \left[\frac{\sum_{z=1}^{Z}(X_{n,t}^{z,i} - \langle X_{n,t}^i\rangle)^2}{Z}\right]^{1/2} \quad (8)$$

where $\langle X_{n,t}^i\rangle$ is the mean of the $X_{n,t}^{z,i}$ values averaged over the Z samples. This measure is directly associated with classical Monte Carlo integration and has been used elsewhere.[25] Note that all the M parameters k_m are randomly sampled simultaneously in calculating the global sensitivity. A normalized sum of these global sensitivity terms can be used to compute the cost function J_{sens}^i for optimizing (usually maximizing) $\mathbf{u}^i(t)$, such as

$$J_{\text{sens}}^i = \frac{1}{T}\sum_{t=t_1}^{t_T}\frac{1}{N_r}\sum_{n=1}^{N_r}[\alpha_n L_{\text{mn}}^i(t)] \quad (9)$$

where $\alpha_n \geq 0$ weights the role of X_n.

The importance of this sensitivity optimization approach lies in its ability to save in the number of laboratory experiments. Calculating and optimizing J_{sens}^i does not require any laboratory experiments because the search ranges of $\mathbf{k}$ and the model ODEs are both prespecified. In principle, if there exists an exact correspondence between Q_{inv}^i and J_{sens}^i for the control $\mathbf{u}_c^i(t)$, only one run of laboratory perturbations and measurements is necessary for extracting the best-quality model parameters $\mathbf{k}$ after the sensitivity optimization. Additionally, global search algorithms, such as the GA can be implemented inexpensively for the sensitivity optimization, which can provide further advantages in terms of its reliability.

In typical applications, the control $\mathbf{u}_c^*(t)$ that optimizes J_{sens} may not be the exact one that optimizes Q_{inv}, because (a) the two measures may not have perfect correspondence, and (b) the sensitivity measure J_{sens} is calculated from random samples $\mathbf{k}^z$ within the pre-defined search range $[\mathbf{k}^{\text{L}},\mathbf{k}^{\text{U}}]$, whereas the $\mathbf{k}^s$ solutions consistent with the laboratory data evidently lie in a subdomain of $[\mathbf{k}^{\text{L}},\mathbf{k}^{\text{U}}]$. Two methods are introduced to address this issue, both integrating the sensitivity optimization algorithm

in CLIP's analysis module with the rest of the package. The first method utilizes the fact that the control $\mathbf{u}_c^*(t)$ obtained from the sensitivity optimization usually provides better inversion quality than the random trial controls $\mathbf{u}_c^0(t)$ used in the identification without sensitivity optimization. Therefore, iterative parameter identification is initiated with $\mathbf{u}_c^*(t)$ being the first trial control and most probably it will take less experiments to converge. The second method also applies $\mathbf{u}_c^*(t)$ experimentally and extracts the resultant consistent parameter distribution [$\mathbf{k}_{min}^*$, $\mathbf{k}_{max}^*$]. This information is then fed back to the analysis module, which peforms another round of sensitivity optimization from this reduced parameter range to update $\mathbf{u}_c^*(t)$. This closed-loop process continues until satisfactory parameter distributions are obtained or J_{sens} can no longer distinguish different control candidates within the laboratory errors.

3. Illustration

Similar to the original OI algorithm, the operation of CLIP is simulated for the identification of a tRNA proofreading mechanism.[10,11] The model contains 10 chemical species, 16 reaction rate constants, and 10 kinetic equations as shown below:

$$\frac{dX_1}{dt} = k_{-3}X_5 + k_{-4}X_6 + (k_7 + k_1)X_7 + (k_8 + k_2)X_8 - k_3X_1X_3 - k_4X_1X_4 - k_{-7}X_1X_9 - k_{-8}X_1X_{10}$$

$$\frac{dX_2}{dt} = (k_{-5} + k_1)X_7 + (k_{-6} + k_2)X_8 + k_9X_9 + k_{10}X_{10} - k_5X_2X_5 - k_6X_2X_6$$

$$\frac{dX_3}{dt} = f_1 + k_{-3}X_5 + k_1X_7 - k_3X_1X_3$$

$$\frac{dX_4}{dt} = f_2 + k_{-4}X_6 + k_2X_8 - k_4X_1X_4$$

$$\frac{dX_5}{dt} = k_3X_1X_3 + k_{-5}X_7 - k_{-3}X_5 - k_5X_2X_5$$

$$\frac{dX_6}{dt} = k_4X_1X_4 + k_{-6}X_8 - k_{-4}X_6 - k_6X_2X_6$$

$$\frac{dX_7}{dt} = k_5X_2X_5 + k_{-7}X_1X_9 - (k_{-5} + k_7 + k_1)X_7$$

$$\frac{dX_8}{dt} = k_6X_2X_6 + k_{-8}X_1X_{10} - (k_{-6} + k_8 + k_2)X_8$$

$$\frac{dX_9}{dt} = k_7X_7 - k_{-7}X_1X_9 - k_9X_9$$

$$\frac{dX_{10}}{dt} = k_8X_8 - k_{-8}X_1X_{10} - k_{10}X_{10}$$

The details of the model and the physical meaning of the species are described in refs 1, 10, and 11. In this illustration, six rate constants (k_1, k_2, k_5, k_{-5}, k_6, k_{-6}) are selected for extraction by CLIP and its algorithmic performance is compared with OI. On the basis of the previous work,[1] x_4 is selected by the analysis module as the optimal component for disturbing/controlling the system (i.e., $\mathbf{x}_c = (x_4)$ and $\mathbf{u}_c(t) = (u_{x4}(t))$), and x_8 and x_{10} are the best for recording the system's dynamic response (i.e., $\mathbf{x}_r = (x_8, x_{10})$ and $N_r = 2$ in eq 3). Similar to the previous work, each time-dependent control flux $u_{x4}(t)$ is expressed as a sum of four Gaussians

$$u_{x_4}(t) = \sum_{l=1}^{4} a_{1,l} \exp[-(t - a_{2,l})^2/a_{3,l}] \quad (10)$$

Because the l^{th} Gaussian is encoded by three control parameters ($a_{m,l}$ with $m = 1$, 2, and 3), a total of 12 control parameters are optimized in searching for the best control $u_{x_4}(t)$ that leads to an extracted $\mathbf{k}^{i,s}$ distribution with the highest inversion quality Q_{inv}^i. The coefficient $a_{1,l}$ is confined to positive values considering the biological nature of the system. The weight w in eq 2 is set to zero, and rapidly varying structures in the controls are prevented by setting appropriate boundaries to the control parameters $a_{m,l}$. The error ϵ_n^i represents the sum of all sources of laboratory errors (e.g., observables, controls, etc.) and is simulated as ±10% around the steady-state values of the corresponding system components. All rate constants are transformed to a logarithmic scale to ensure a more thorough sampling over the large parameter space and better normalization across different rate constants.

To assess the performance of the inversion module with and without the modified cost function (sections 2.1 and 2.2.1), 50 random controls $u_{x_4}^i(t)$ ($i = 1$, 2, ..., 50) are introduced to the system. After applying each control, the response of x_8 and x_{10} is recorded at $T = 10$ time points and the data ($X_8^i(t)$, $X_{10}^i(t)$, and $a_{m,l}^i$) are forwarded to the inversion module, which searches for $\mathbf{k}^{i,s}$ solutions that achieve satisfactory agreement between the computational and the simulated experimental data within the data error. For both algorithms, a solution $\mathbf{k}^{i,s}$ is considered satisfactory and saved when $J_{inv}^{i,s} = 1$. Equation 3 serves as the cost function for the inversion GA in OI, and eqs 5 and 6 (with $c_m = 1$ and $w = 1$) guide the two modified inversion GAs in CLIP. The search continues until convergence is reached for the distribution of $\mathbf{k}^{i,s}$, corresponding to the Q_{inv}^i value in eq 4 (OI) or eq 7 (CLIP) being stable. 500 to 1000 $\mathbf{k}^{i,s}$ solutions (i.e., $S = 500$ to 1000) are normally needed to reach convergence in OI, whereas only 100−200 are necessary for each GA to converge in CLIP. Most of the $k_m^{i,s}$ solutions recovered in CLIP locate near the upper and lower edges of the corresponding distribution, whereas they are much more scattered in OI (data not shown here). These results clearly confirm the postulate that considerable computational time can be wasted in OI by searching for $\mathbf{k}^{i,s}$ values lying in the middle of the solution distribution, whereas the modified inversion cost function of CLIP can enable more efficient recovery of the defining characteristics of the $\mathbf{k}^{i,s}$ distribution.

Figure 2 compares the inversion quality Q_{inv}^i for the 50 random controls between OI and CLIP. It can be seen that OI and CLIP perform comparably for the "bad" controls (i.e., controls that result in large Q_{inv}^i values), whereas CLIP tends to yield larger Q_{inv}^i values for the "good" controls than OI does. Note that the ideal goal of the inversion module is to extract the full family of $\mathbf{k}^{i,s}$ solutions consistent with the laboratory data for any $\mathbf{u}_c^i(t)$, thus a larger value of Q_{inv}^i for the same control (note that in the tests with the 50 random controls, there is no attempt at minimizing Q_{inv}^i) means a better approximation of the true solution family, which will maximize the value of Q_{inv}^i for $\mathbf{u}_c^i(t)$. This indicates that the modified inversion algorithm is also more reliable in extracting the full family of parameters consistent with the observed data.

The performance of CLIP with both the new inversion module and the new control module is also tested (without incorporating the sensitivity optimization algorithm in section 2.2.3). Figure 3 shows the evolution of the normalized solution distribution (calculated from eq 4) over the iterative experiments of OI and

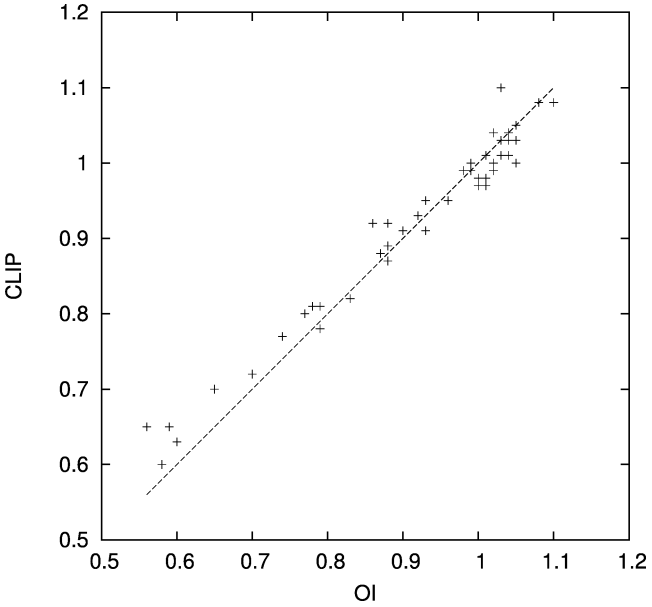

Figure 2. Inversion quality Q_{inv} obtained from OI and CLIP for 50 random controls. Q_{inv} is calculated by using eq 4 with $w_m = 1$ and $M = 6$ (six unknowns).

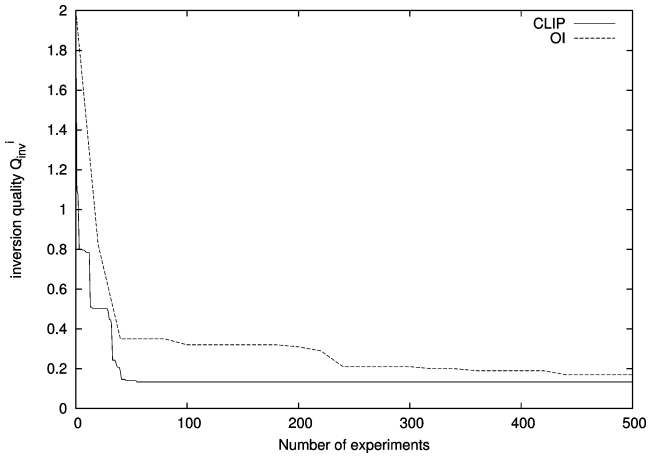

Figure 3. Evolution of the normalized solution distribution (calculated from eq 4 with $w_m = 1$ and $M = 6$) against the number of iterative experiments of OI and CLIP for inverting the six rate constants.

CLIP for inverting the six rate constants. Note that eq 7 is used to calculate the inversion quality in CLIP, but the corresponding value calculated from eq 4 is plotted in Figure 3 to provide for a fair comparison with OI. OI converges after ~450 control experiments and CLIP converges after ~50 experiments. The upper ($k^*_{m,max}/k_m$) and lower ($k^*_{m,min}/k_m$) limits of the final rate constant distributions relative to the corresponding true values k_m are shown in Figure 4 for OI and CLIP. Both algorithms extract rate constant distributions that include the true values. The final inversion quality is comparable for the two methods: OI recovers slightly narrower distributions for k_5 and k_{-5}, whereas CLIP provides better inversion quality for k_1, k_6, and k_{-6}.

Figure 5 shows the final controls found by OI and CLIP when the narrowest rate constant distribution is achieved. It needs to be emphasized that the best control identified by OI actually yields better inversion quality compared with that achieved by CLIP's final control *alone* (see Figure 4), but OI and CLIP's final inversion qualities are comparable. This phenomenon results from two differences between CLIP and OI. First, the control GA in OI is a better global search algorithm than the

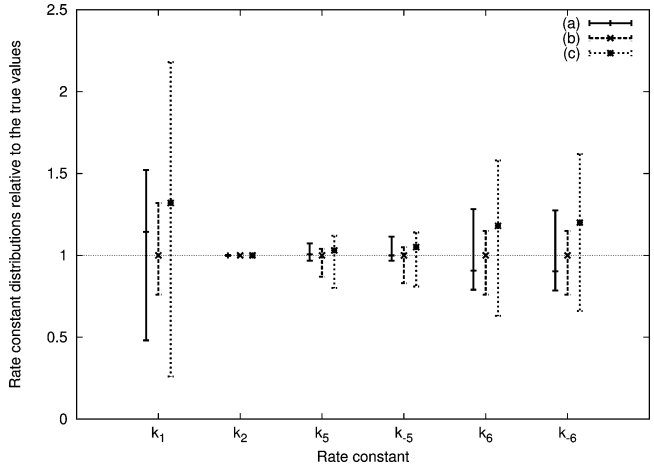

Figure 4. Solution distributions for the six rate constants relative to their true values, extracted by using (a) the optimal control experiment found by OI, (b) all the iterative control experiments of CLIP, and (c) the final control experiments of CLIP alone. The difference between (b) and (c) is illustrated in section 3. The true rate constants have relative value 1. The respective mean value of each distribution is also marked.

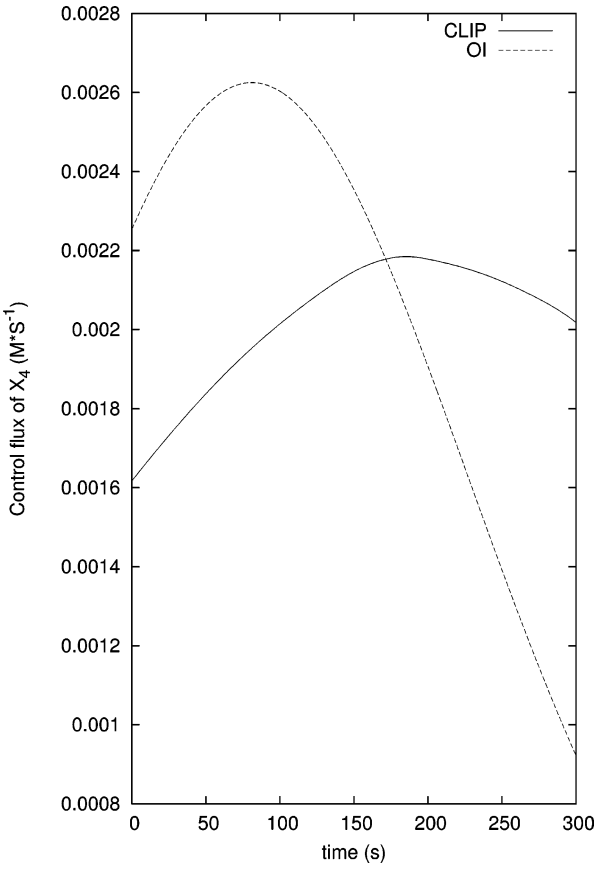

Figure 5. Control fluxes that give the best inversion quality, found by the OI and CLIP operations.

simplex in CLIP (section 2.2.2); thus in principle OI will find a control that, when applied alone, can lead to better inversion quality. However, CLIP updates the parameter search ranges [k^L_m, k^U_m] by [$k^i_{m,min}$, $k^i_{m,max}$] after each control $\mathbf{u}^i_c(t)$ (section 2.2.1); thereby it indirectly utilizes the information from *all* previous experiments and becomes a more efficient algorithm.

The performance of CLIP's sensitivity optimization algorithm (section 2.2.3) is also assessed. A GA is employed to search globaly for the best control $u^*_{X_4}(t)$ that maximizes the normalized sensitivity of $X_8(t)$ and $X_{10}(t)$ with respect to random

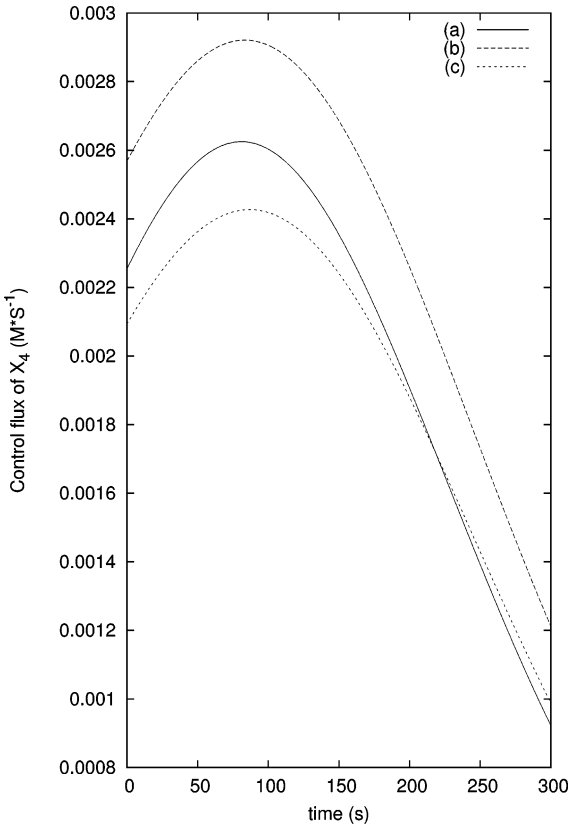

Figure 6. (a) Control flux that results in the best inversion quality obtained by OI. (b) Best control flux $\mathbf{u}_c^*(t)$ found by the virtual sensitivity optimization algorithm in CLIP's analysis module. (c) Last control obtained from CLIP's iterative inversion algorithm guided by the simplex algorithm, starting from $\mathbf{u}_c^*(t)$ instead of random controls $u_c^0(t)$.

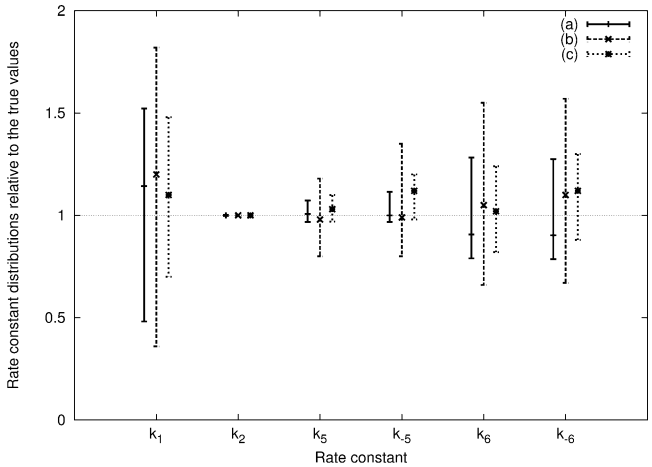

Figure 7. Solution distributions for the six rate constants relative to their true values, extracted from the three corresponding methods in Figure 6.

variations in the six rate constants, utilizing the eq 9 (with $\alpha_n = 1$) as its cost function. Figure 6 shows that $u_{x_4}^*(t)$ is similar to the best control found by OI, which is obtained by directly minimizing the inversion quality Q_{inv}^i through iterative rounds of laboratory control optimization and parameter inversion. The rate constant distributions corresponding to $u_{x_4}^*(t)$ are slightly wider, meaning slightly lower inversion quality, than those recovered from OI (Figure 7), which is also expected for reasons mentioned in section 2.2.3. Because the sensitivity optimization provides $u_{x_4}^*(t)$ without any laboratory experiments, its advantage is evident, especially when high-resolution identification is not necessary or the experiments are very expensive.

Starting from the control $u_{x_4}^*(t)$ identified by the sensitivity optimization, standard CLIP inversion is implemented with the guidance of the simplex algorithm. After ~25 closed-loop experiments (i.e., an additional laboratory cost reduction of 50% from using the simplex algorithm with random trial controls $\mathbf{u}_c^0(t)$ as with CLIP in Figure 4), convergence is reached and the parameter distribution is comparable with OI (Figure 7) and CLIP's performance in Figure 4. Additional iterative rounds of sensitivity optimization (to provide new controls $u_{x_4}^*(t)$) and parameter inversion (to update $[\mathbf{k}_{\text{min}}^*, \mathbf{k}_{\text{max}}^*]$) was also carried out. Only moderate improvement in the inversion quality was achieved upon the convergence of the procedure, with the main gain coming from the initial sensitivity optimization to yield $u_{x_4}^*(t)$.

4. Conclusion

A previous work developed a general optimal identification (OI) technique for reliable inversion of biochemical reaction networks.[1] A number of algorithmic modifications are introduced to OI in this paper to form the foundations of a closed-loop identification package (CLIP) for nonlinear dynamical systems. Simulation results clearly demonstrate that the algorithms in CLIP not only can reduce experimental and computational costs but also can increase reliability, inversion quality, and exploitation of all available information.

It needs to be emphasized that CLIP does not replace, but encompasses and enriches, the original OI technique. The original algorithms in OI should not be considered as obsolete, as the added methods in CLIP are not necessarily superior under all circumstances. For example, the simplex algorithm may not always behave better than a GA in the control module, because when dealing with highly complex problems, the global search ability of GA may be necessary for finding a good control. In addition, CLIP should not be considered as a system-independent, black-box method. The users will inevitably benefit from proper usage of the existing knowledge about the target system, careful design of the control and measurement experiments, and judicious selection of the computational algorithms and cost functions.

Despite the significant improvements, additional strategies can be introduced to further reduce CLIP's operational costs. For example, most of the computational time is spent on integrating the ODEs for the trial solutions $\mathbf{k}^{i,p}$. Suitable mapping techniques can be implemented to reliably interpolate the relationship between $\mathbf{k}^{i,p}$ and the system's behavior $\mathbf{X}_r^i(t)$, thus avoiding the need for ODE integration for every trial $\mathbf{k}^{i,p}$.[32−34]

We have successfully applied concepts and algorithms similar to those for CLIP in inverting quantum-mechanical observations.[35,36] Future research will aim to address specific problems that may arise in identifying other networks. One issue is how precise the target system needs to be identified. This issue is especially relevant to bionetwork identification because biological systems can be very robust to most small changes in its internal parameters (e.g., neutral gene mutations), which implies that (a) high-precision values may not be necessary for many parameters and (b) integration of robust system theory and techniques may assist the identification of these systems.

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