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# Supporting Information for
## Identifying Regulation with Adversarial Surrogate

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# Supplementary Information for Identifying Regulation with Adversarial Surrogate

## SI1 Feedback control in biological system models

Let the observed system be a non-linear dynamical system formulated by the stochastic differential state space model,

$$dx = f(x, d)dt + \Xi(x, d)d\xi. \tag{S.1}$$

where both the deterministic term $f : \mathbb{R}^{n\times b} \to \mathbb{R}^n$ and the stochastic term $\Xi : \mathbb{R}^{n\times b} \to \mathbb{R}^n$ are a function of the state and an external input $d \in \mathbb{R}^b$. The term $d\xi$ is an increment of a Wiener process. For details on the formalization of continuous-time stochastic differential equations we refer the reader to Chapter 3 in [Åström, 2012].

Biological systems internally regulate some of the state variables, or, more generally, some combinations of the state variables. We denote such an internally regulated combination by $c(t) \in \mathbb{R}$ and denote by $c_{\text{set}}$ the set-point value of the regulation such that the biological system maintains a small deviation from the set-point value, namely $\|c(t) - c_{\text{set}}\|_2^2$ is small. Human-engineered systems are commonly represented by two separate entities – a plant and a controller. Biological systems, in contrast, are commonly modeled by a single dynamical equation. Therefore, the controlled objective and the control signal in a biological system model are implicit. Although control theory typically assumes the existence of a separate plant and controller (see Chapter 1.2 in [Åström and Murray, 2021]), most theoretical results and analysis tools, among them the analysis algorithm represented herein, do not require such a separation [Cosentino and Bates, 2011].

We do not observe the complete state of the system, but some function of the internal state that might be partial. Let $y \in \mathbb{R}^m$ be a vector of observables which is some instantaneous function of the internal state, the input and a white measurement noise $v \in \mathbb{R}^m$,

$$y = h(x, d, v). \tag{S.2}$$

Since we only have access to the observations $y$, we seek some regulated combinations of observations, which, assuming observability[1], should hold for the internal variables. In this study we present Identifying Regulation with Adverserial Surrogates (IRAS), a novel data analysis algorithm that receives a dataset of observed systems and yields regulated combinations that are jointly held by the observed system. These combinations are of two types: instantaneous combinations and combinations of measurements that are observed along a fixed-length time window.

# SI2 Notations

Dynamical systems

- $x^{(s)} \in \mathbb{R}^n$ - state of system $s$
- $\theta^{(s)}$ - parameter vector of system $s$
- $d^{(s)} \in \mathbb{R}^b$ - external input to system $s$
- $f_s : \mathbb{R}^{n \times b} \to \mathbb{R}^n$, $\Xi_s \in \mathbb{R}^{n \times n} \to \mathbb{R}^n$ - functions describing the deterministic and stochastic components of system $s$ such that $dx^{(s)} = f_s\left(x^{(s)}, d^{(s)}\right) dt + \Xi_s(x, d) d\xi^{(s)}$ where $dt$ is a time increment and $d\xi^{(s)}$ is the increment of a Weiner process.
- $y \in \mathbb{R}^m$ - observation obtained from system $s$
- $v \in \mathbb{R}^m$ - measurement noise in system $s$
- $h : \mathbb{R}^{n \times b \times m} \to \mathbb{R}^m$ - measurement equation of system $s$ such that $y^{(s)} = h(x^{(s)}, d^{(s)}, v^{(s)}; \theta_s)$

Dataset

- $z_k^{(s)} \in \mathbb{R}^{\tilde{m}}$, $\tilde{m} = m + b$ - concatenation of the external known input $d^{(s)}$ and the observation $y^{(s)}$ sampled at time $t_k^{(s)}$
- $z_{k:k+T}^{(s)} \in \mathbb{R}^{\tilde{m} \times T+1}$ - concatenation of $T$ samples, $z_{k:k+T}^{(s)} = \begin{bmatrix} z_k^{(s)} & z_{k+1}^{(s)} & \dots & z_{k+T}^{(s)} \end{bmatrix}$
- $z_{k,i}^{(s)} \in \mathbb{R}$ - the i$^{\text{th}}$ entry of $z_k^{(s)}$
- $N_s$ - number of samples ($z_k^{(s)}$) obtained from system $s$
- $M$ - number of observed systems

Regulated signal and combination

- $c_{set}^{(s)} \in \mathbb{R}$ - set-point value of system $s$

[1]Observability, in the sense of Control Theory, refers to the ability of determining the internal state of a system given measurements, e.g. Chapter 1.7. in [Simon, 2006]

- $c_k^{(T,a,s)} \in \mathbb{R}$ - the value of the most *regulated signal* of system $s$ at time $k$ over a time-scale of $T$ consecutive samples

- $g_T : \mathbb{R}^{\tilde{m}\times(T+1)} \rightarrow \mathbb{R}$ - the most *regulated combination* over a time-scale of $T$ consecutive samples for all $M$ observed systems such that $c_k^{(T,a,s)} = g_T\left(z_{k-T:k}^{(s)}; \theta^{(s)}\right)$

Algorithm variables

- $\Omega^{(T,\alpha,s)}$ - a set that consists of $N^{(T,\alpha,s)}$ members, $\alpha \in \{a, n, p\}$

- $z_k^{(T,\alpha,s)} \in \mathbb{R}^{\tilde{m}\times(T+1)}$ - a member of the set $\Omega^{(T,\alpha,s)}$

- $p_{\Omega^{(T,\alpha,s)}} : \mathbb{R}^{\tilde{m}\times(T+1)} \rightarrow \mathbb{R}$ - the distribution from which members were sampled to the set $\Omega^{(T,\alpha,s)}$

- $\hat{\theta}_t^{(s)} \in \mathbb{R}^l$ - estimated parameters of system $s$ in iteration $t$ of IRAS

- $\hat{g}_{T,\omega_t} : \mathbb{R}^{l+\tilde{m}\times(T+1)} \rightarrow \mathbb{R}$ - the estimated *regulated combination*, a function parameterized by the parameters vector $\omega_t$

- $\hat{c}_k^{(T,\alpha,s,t)} \in \mathbb{R}$ - estimated *regulated signal* of system $s$ at time $k$ in iteration $t$ of Algorithm 1 such that $\hat{c}_k^{(T,\alpha,s,t)} = \hat{g}_{T,\omega_t}\left(z_k^{(T,\alpha,s,t)}; \hat{\theta}_t^{(s)}\right)$

- $p_{\hat{c}^{(T,\alpha,s,t)}} : \mathbb{R} \rightarrow \mathbb{R}$ the distribution of $\hat{c}^{(T,\alpha,s,t)}$ such that $\hat{c}_k^{(T,\alpha,s,t)} = \hat{g}_{T,\omega_t}\left(z_k^{(T,\alpha,s,t)}; \hat{\theta}_t^{(s)}\right)$.

- $\hat{p}_b^{(T,\alpha,s,t)}$ - value of bin $b$ of the histogram of $\hat{c}_k^{(T,\alpha,s,t)}$ over all $k$; $B_b^{(T,s,t)}$ - set of values included in bin $b$

# SI3 Problem formulation

As described in section SI1, the systems we observe are non-linear stochastic dynamical systems. We analyze a dataset of observations of multiple similar systems, where the dynamic and observation equations of system $s$ are given by

$$dx^{(s)} = f_s\left(x^{(s)}, d^{(s)}\right) dt + \Xi_s(x, d) d\xi^{(s)} \quad ; \quad y^{(s)} = h_s(x^{(s)}, d^{(s)}, v^{(s)}). \tag{S.3}$$

**Discrete time formulation** Although we handle real-world systems that are by nature continuous time systems, we formulate the problem in discrete time so that the formulation is suitable for working on sampled data. At time $t_k^{(s)}$, let $z_k^{(s)} \in \mathbb{R}^{\tilde{m}}$, $\tilde{m} = m + b$, be the concatenation of the external known input $d^{(s)} \in \mathbb{R}^b$ and the observation $y^{(s)} \in \mathbb{R}^m$ sampled at time $t_k^{(s)}$ and let $z_{k,i}^{(s)}$ be the $i^{\text{th}}$ entry of $z_k^{(s)}$. Denote by $N_s$ the number of samples obtained from system $s$, and by $M$ the total number of observed systems. Figure SI 1 illustrates the notation.

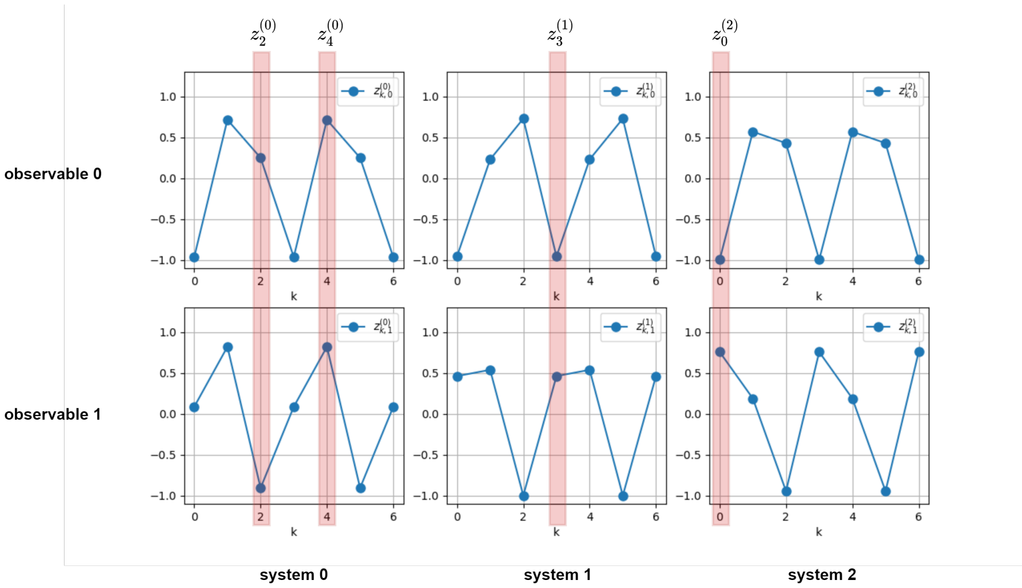


Figure SI 1: Observed data notations. The k$^{\text{th}}$ observation of system $s$ is noted by $z_k^{(s)} \in \mathbb{R}^{\tilde{m}}$ where the i$^{\text{th}}$ observable is noted by $z_{k,i}^{(s)} \in \mathbb{R}$. In this illustration the number of observed systems is $M = 3$, the number of samples obtained from each system is $N_s = 7$ for all systems $s = 0, \ldots, M-1$ and there are two observables, $\tilde{m} = 2$.

The methodology we hereby suggest for detecting regulated combinations is based on three key principles. *(i)* A combination that is regulated by the system has a time-dependent structure and is therefore sensitive to shuffles of the time-axis that decouple the components $z_{k,i}^{(s)}$ that when coupled form $z_k^{(s)}$; *(ii)* Different observed systems might regulate the same combination, yet about different set-points; *(iii)* A measure for the regulated combination must be universal in the sense that it is independent of physical units.

## SI3.1 Single player optimization

In what follows we construct the optimization algorithm in several methodological stages. *(i)* We begin by formulating a precise mathematical objective that follows the principles of a regulated combination mentioned above, and construct an optimization scheme that minimizes this objective. *(ii)* We then analyze the optimal solutions and show that they fail to capture the regulated combination. *(iii)* To address this shortcoming, in the final stage we construct a two-player optimization scheme that minimizes the same objective yet with respect to a dynamic selection of the observations;

Let $g_T : \mathbb{R}^{\tilde{m}\times(T+1)} \to \mathbb{R}$ be a function of $T+1$ consecutive observations, $T \geq 0$, parameterized by $\theta^{(s)}$. For $T = 0$ it is a function of the elements in a single observation. The vector $\theta^{(s)}$ consists of parameters which are specific to system $s$. We refer to $g_T(\cdot)$ as the *regulated combination* and to its output $c_k^{(T,a,s)}$ as the *regulated signal* such that for all $k \geq T$,

$$c_k^{(T,a,s)} + c_{set}^{(s)} = g_T\left(z_{k-T:k}^{(s)}; \theta^{(s)}\right) + c_{\text{set}}^{(s)} \, . \tag{S.4}$$

By not including the set-points $c_{set}^{(s)}$ in $g_T(\cdot)$ we follow the second key principle mentioned above, namely, allowing the systems to regulate the same combination, yet about different set-points for different systems. For the construction of an optimization criterion that derives the *regulated combination* (in the common cases when it is unknown) we should define an objective that obeys the key principles. Intuitively one expects the *regulated signal* to fluctuate about the set-point with 'small' deviations, a notion that requires a normalization scheme. A popular normalized measure for the fluctuations of a time-series is the coefficient of variation, CV, which is the standard deviation divided by the mean value. The CV measure does not consider time dependencies in the signal which is our first key principle for a regulated combination. As a result, in many cases one can obtain a combination of two independent observables having an extremely low CV value. In addition, CV is not invariant to the physical units in use as its value is changed by adding an offset (Celsius vs Fahrenheit), a violation of the third principle. We propose to measure the ratio of standard deviations between the *regulated signal* and a signal which is created by evaluating the *regulated combination* on time-shuffled observations.

We begin by examining the output of the *regulated combination* for two types of inputs. The first is the *authentic* input signal that consists of $T+1$ consecutive observations as in (S.4). The second input consists of non-consecutive, shuffled observations, that aim to impact the temporal correlations of the original data. We introduce these two sets for each system $s$, corresponding to the two input types. The sets are denoted by $\Omega^{(T,<\text{type}>,s)}$, and are constructed as follows.

The first, authentic dataset, consists of the original observed data,

$$\Omega^{(T,a,s)} = \left\{ z_k^{(T,a,s)} \triangleq z_{k:k+T}^{(s)} \right\}_{k=0}^{N^{(T,a,s)}-1} ,$$

where $N^{(T,a,s)} = N_s - T$. The second dataset, referred to as the *'naively shuffled dataset'*, and denoted by $\Omega^{(T,n,s)}$, is composed of elements $z_k^{(T,n,s)}$, each being a concatenation of non-consecutive bins. For $T > 0$, $z_k^{(T,n,s)}$ contains a sequence of $T$ consecutive bins from the original data, followed by a bin drawn uniformly from the time-series $z_{0:N_s-1}^{(s)}$. This destroys the correlations between the $(T+1)^{th}$ bin and the preceding $T$ bins. For $T=0$, $z_k^{(0,n,s)}$ has each and every entry $z_{k,i}^{(0,n,s)}$ drawn uniformly from $z_{0:N_s-1,i}^{(s)}$. Figure SI 2 illustrates the composition of these sets. Formally,

$$\Omega^{(T,n,s)} = \left\{ z_k^{(T,n,s)} \triangleq \begin{cases} \left[ z_{k_0,0}^{(s)}, z_{k_1,1}^{(s)}, \ldots, z_{k_{\tilde{m}-1},\tilde{m}-1}^{(s)} \right]' \mid k_i \sim \mathcal{U}[0, N_s-1], & \text{if } T=0 \\ \left[ z_{\tilde{k}:\tilde{k}+T-1}^{(s)}, z_{j_k}^{(s)} \right] \mid j_k \sim \mathcal{U}[0, N_s-1], & \text{if } T>0 \end{cases} \right\}_{k=0}^{N^{(T,n,s)}-1} , \tag{S.5}$$

where $\tilde{k} = \text{mod}(k, N_s - T)$ and $N^{(T,n,s)} \gg N^{(T,a,s)}$. Note that the dataset $\Omega^{(T,n,s)}$ is stochastic, and is thus not limited in size to $N^{(T,a,s)}$, the number of members in the authentic set. To obtain

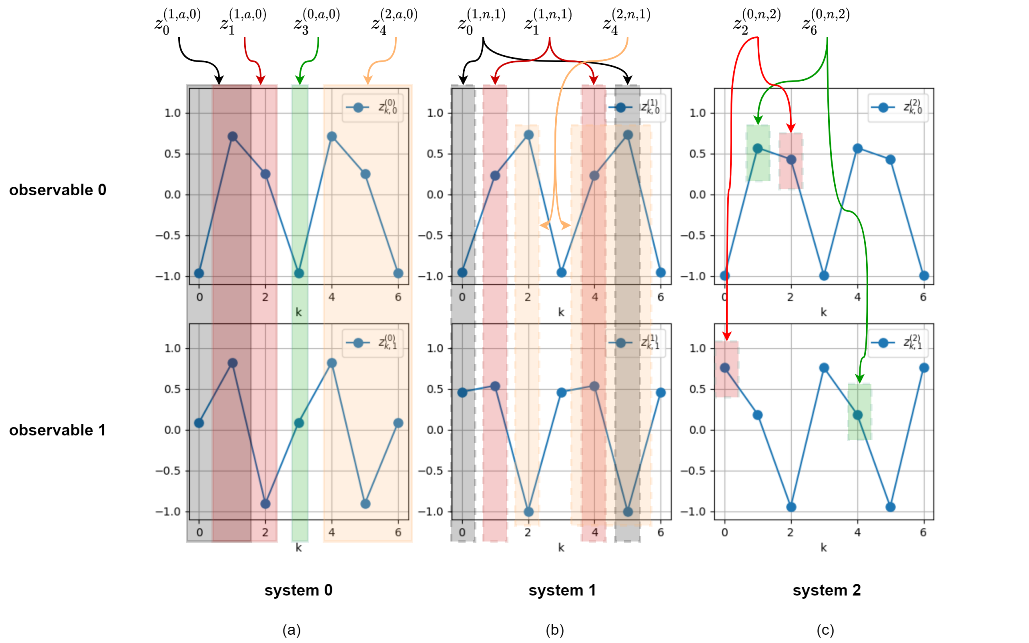


Figure SI 2: Illustration of the composition of the sets. **(a)** Examples of members $z_k^{(T,a,s)}$ of the *authentic sets* $\Omega^{T,a,s}$. A member $z_k^{(T,a,s)}$ has $T+1$ consecutive samples starting at sample $k$. **(b)** Example of members $z_k^{(T,n,s)}$ of the *naive shuffle sets* $\Omega^{T,n,s}$ for $T > 0$. A member $z_k^{(T,n,s)}$ has $T$ consecutive samples starting at sample $k$ followed by a sample from a random time point. **(c)** Example of members $z_k^{(0,n,s)}$ of the *naive shuffle sets* $\Omega^{0,n,s}$. A member $z_k^{(0,n,s)}$ has each observable from a random time point.

sufficient variety in the shuffled data we suggest setting $N^{(T,n,s)}$ to be an order of magnitude higher than $N^{(T,a,s)}$. Denote the distribution of members in the *authentic set* by $p_{\Omega^{(T,a,s)}}$, and of members in the *naive shuffle set* by $p_{\Omega^{(T,n,s)}}$, and note that by definition the support of $p_{\Omega^{(T,n,s)}}$ contains the support of $p_{\Omega^{(T,a,s)}}$, $\{z \mid p_{\Omega^{(T,n,s)}}(z) > 0\} \supseteq \{z \mid p_{\Omega^{(T,a,s)}}(z) > 0\}$.

We continue by examining the output of $g_T(\cdot)$, the *regulated combination*, for two types of inputs,

$$c_k^{(T,\alpha,s)} \triangleq g_T\left(z_k^{(T,\alpha,s)}; \theta^{(s)}\right) , \tag{S.6}$$

either when evaluated on members of the *authentic set* ($\alpha = a$) or when evaluated on members of the *naive shuffle set* ($\alpha = n$). Since $g_T(\cdot)$ is a *regulated combination*, and following the principle by which a regulated combination has a time-dependent structure, the time-series $c_k^{(T,a,s)}$ is expected to have a smaller standard deviation than the time-series $c_k^{(T,n,s)}$, in which the time dependency of the regulated signal was violated by the shuffle. Figure SI 3 illustrates the time-series at the output of the regulated combination $g_T(\cdot)$ in both cases. We can now form an optimization problem to obtain the combination that is most sensitive to the time shuffle with respect to the ratio of standard deviations. We refer to this optimization as the *'single player'* because it involves only the *'combination player'*. As is shown below this optimization

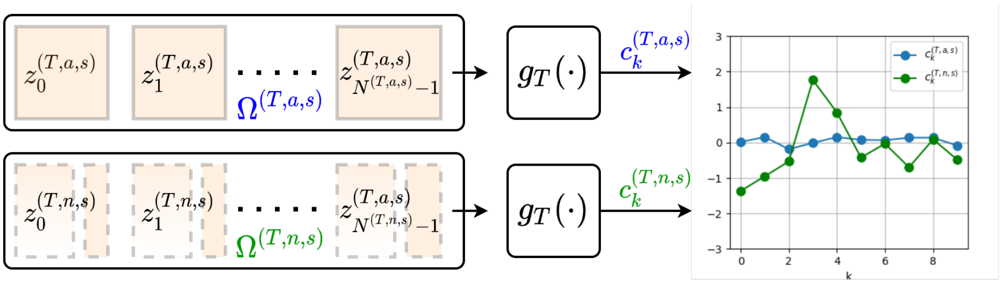


Figure SI 3: Illustrating the time-series at the output of the regulated combination $g_T(\cdot)$ when evaluated on members of the *authentic set* $\Omega^{(T,a,s)}$ and on the *naive shuffled set* $\Omega^{(T,n,s)}$. The shuffled data violates the relations between data-points resulting in an increased standard deviation of the corresponding time-series.

turns out not to yield a signal that the system regulates.

**Single-player formulation.** *Let $\hat{\theta}^{(s)} \in \mathbb{R}^l$, be a vector of estimated parameters of system s and let $\hat{g}_{T,\omega} : \mathbb{R}^{l+\tilde{m}\times(T+1)} \to \mathbb{R}$ be a function parameterized by the parameter vector $\omega$. The function $\hat{g}_{T,\omega^*}(\cdot)$ of the regulated combination is the solution of the optimization problem that is qualitatively written as,*

$$\begin{aligned} \omega^*, \phi^* &= \underset{\omega,\phi}{\operatorname{argmin}} \, \mathrm{E}_s \frac{\sigma\left(\hat{c}_k^{(T,a,s)} \sim p_{\hat{c}^{(T,a,s)}}\right)}{\sigma\left(\hat{c}_k^{(T,n,s)} \sim p_{\hat{c}^{(T,n,s)}}\right)} \\ s.t\ \hat{c}_k^{(T,\alpha,s)} &= \hat{g}_{T,\omega}\left(z_k^{(T,\alpha,s)}; \hat{\theta}_t^{(s)}\right), \quad \alpha \in \{a, n\} \\ z_k^{(T,\alpha,s)} &\sim p_{\Omega^{(T,a,s)}}, \\ \hat{\theta}_\phi^{(s)} &= \hat{\Theta}_\phi\left(p_{\Omega^{(T,a,s)}}\right), \end{aligned} \tag{S.7}$$

*and exactly, for a given dataset, as,*

$$\begin{aligned} \omega^*, \phi^* &= \underset{\omega,\phi}{\operatorname{argmin}} \sum_{s=0}^{M-1} \frac{\sigma(\hat{c}_{0:N^{(T,a,s)}-1}^{(T,a,s)})}{\sigma(\hat{c}_{0:N^{(T,n,s)}-1}^{(T,n,s)})} \\ s.t\ \hat{c}_k^{(T,\alpha,s)} &= \hat{g}_{T,\omega}\left(z_k^{(T,\alpha,s)}, \hat{\theta}_\phi^{(s)}\right), \quad \alpha \in \{a, n\} \\ \hat{\theta}_\phi^{(s)} &= \hat{\Theta}_\phi(\Omega^{(T,a,s)}), \end{aligned} \tag{S.8}$$

*where $\hat{\Theta}_\phi : \mathbb{R}^{(1+\tilde{m}(T+1))\times \max_s[N^{(T,a,s)}]} \to \mathbb{R}^l$ is a function parameterized by the parameters vector $\phi$.*

Optimization problem (S.8), illustrated in figure SI 4, has numerous different solutions that yield zero objective value, among which is the solution

$$\hat{g}_{T,\omega^*}\left(\tilde{z}; \hat{\theta}^{(s)}\right) = \begin{cases} 0, & \text{if } \tilde{z} \in \cup_s \Omega^{(T,a,s)} \\ 1, & \text{otherwise} \end{cases}. \tag{S.9}$$

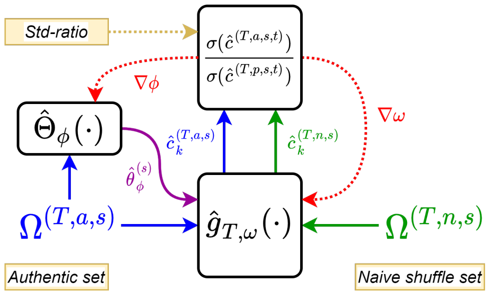


Figure SI 4: Block diagram of optimization (S.8). The function $\hat{g}_{T,\omega}(\cdot)$ is optimized to yield the minimal std-ratio, averaged over all systems $s$, between the time-series $\hat{c}_k^{(T,a,s)}$ and $\hat{c}_k^{(T,n,s)}$ which are its outputs when evaluated on members of the *authentic set* $\Omega^{(T,a,s)}$ and the *naive shuffle set* $\Omega^{(T,n,s)}$ respectively. The function $\hat{\Theta}_\phi$, depending on parameters $\phi$, is used to estimate the parameters $\hat{\theta}^{(s)}$ based on the authentic inputs. The gradients, $\nabla_\phi$ and $\nabla_\omega$, contribute to the learning process with respect to the std-ratio objective.

Solution (S.9) is far from representing a combination that yields a biologically-plausible regulated signal since it is simply $\hat{c}_k^{(T,a,s)} \equiv 0$. While we are looking for a combination that represents an active feedback mechanism, optimization (S.8) yields a solution that represents a feature that the authentic time-series always obeys while the time-shuffled series do not.

## SI3.2 Two player optimization

In Section SI3.1 we translated the principle by which a time-regulated combination has a structure that is sensitive to shuffles of the time axis to a single-objective optimization that seeks to minimize the ratio of the standard deviations, (S.8). We showed that this optimization scheme does not yield a combination that the system indeed regulates, but, rather, a combination that merely represents a feature that is always obeyed by the data. Analyzing its failure allows us to identify a way to correct it: if we constrain the time-shuffling to include only shuffles that are plausible in light of the data distribution, we may prevent the optimization algorithm from constructing artefact functions that rely solely on structural difference between the measured and shuffled ensembles. In what follows we construct an objective that yields a biologically plausible combination. We do so by constructing IRAS, a two-player algorithm (Algorithm 1) in which one player aims to minimize the ratio of standard deviations, while the second player seeks to keep the optimized combination biologically plausible. To do so we introduce an adaptive shuffle scheme based on the naive shuffle set introduced above.

Recall that in each iteration $t$ of the game, the *'naive shuffle set'*, $\Omega_t^{(T,n,s)}$, is constructed stochastically by (S.5) - Algorithm 1 line 8. To construct the new shuffle set, a *'shuffle player'* examines the *'naive shuffle set'*, and, according to some fixed policy $\Pi$ (to be described below), creates a subset, $\Omega_t^{(T,p,s)}$,

$$\Omega_t^{(T,p,s)} = \left\{ z_k^{(T,p,s,t)} \right\}_{k=0}^{N^{(T,p,s,t)}-1} = \Pi\left(\Omega_t^{(T,n,s)}\right), \tag{S.10}$$

**Algorithm 1** IRAS

1: **Input:** $\{z^{(s)}_{0:N_s-1}\}_{s=0}^{M-1}$, $T$, $l$, $\hat{g}_{T,\omega_0}(\cdot)$, $\hat{\Theta}_{\phi_0}(\cdot)$, $\eta$, `nEpochs`
2: **for** $s = 0, \dots, M-1$ **do**
3:     `Construct the` authentic set $\Omega^{(T,a,s)}$
4: **end for**
5: $t \leftarrow 0$ $t <$ `nEpochs`
6: **for** $s = 0, \dots, M-1$ **do**
7:     $\hat{\theta}^{(s)} \leftarrow \hat{\Theta}_{\phi_t}(\Omega^{(T,a,s)})$ {System parameters estimation}
8:     `Construct the` naive shuffle set $\Omega^{(T,n,s)}$ {A stochastic set}
9:     `Construct the` plausible shuffle set $\Omega^{(T,p,s)} \leftarrow \Pi(\Omega^{(T,n,s)})$ {Shuffle player}
10:     $\hat{c}^{(T,a,s)} \leftarrow \hat{g}_{T,\omega_t}(\Omega^{(T,a,s)}, \hat{\theta}^{(s)})$ {Combination player: regulated signal (authentic)}
11:     $\hat{c}^{(T,p,s)} \leftarrow \hat{g}_{T,\omega_t}(\Omega^{(T,p,s)}, \hat{\theta}^{(s)})$ {Combination player: regulated signal (shuffled)}
12: **end for**
13: $sr \leftarrow \mathrm{E}_s \frac{\sigma(\hat{c}^{(T,a,s)})}{\sigma(\hat{c}^{(T,p,s)})}$ {Std-ratio}
14: $\omega_{t+1} \leftarrow \omega_t - \eta \nabla_{\omega_t} sr$, $\phi_{t+1} \leftarrow \phi_t - \eta \nabla_{\phi_t} sr$ {Update step}
15: $t \leftarrow t + 1$
16: **return** $\omega_{nEpochs}, \phi_{nEpochs}$ {The parameters of the *regulated combination*}

which we refer to as the *'plausible shuffle set'*, and which has $N^{(T,p,s,t)}$ members denoted by $z_k^{(T,p,s,t)}$ - Algorithm 1 line 9. Once the *'plausible shuffle set'* set is created, a *'combination player'* has the objective of minimizing the mean (over all systems) of the ratio of standard deviations, as in (S.8), except that now the *regulated combination* is evaluated on members of the *'plausible shuffle set'*, $\Omega_t^{(T,p,s)}$, wheres in (S.8) it was evaluated on members of the *'naive shuffle set'*, $\Omega_t^{(T,n,s)}$. In Algorithm 1, lines $10-11$, the *combination player* evaluates the current combination $\hat{g}_{T,\omega_t}$ on the two sets, in line 13 it averages the std-ratio over all systems and in line 14 it updates the *regulated combination* to yield $\hat{g}_{T,\omega_{t+1}}(\cdot)$ and $\hat{\Theta}_{\phi t+1}(\cdot)$.

In Section SI3.1 we analyzed the case where the policy of the *shuffle player* is to leave the *naive shuffled set* untouched such that $\Omega_t^{(T,p,s)} = \Omega_t^{(T,n,s)}$, and showed that such a policy yields a combination that represents the feature that is most strongly maintained by the authentic time-series, while being violated by the shuffled time-series. To confront this problem, assume that the *combination player* has learned a combination $\hat{g}_{T,\omega_t}(\cdot)$ whose violation is biologically non-plausible, thus, a feature that the feedback controller in the system does not operate to maintain. The *combination player* has learned such a feature because the *naive shuffle set* contains members that violate it, that is, members that are not biologically plausible. To derive biologically plausible features, namely features that the controller actively works to regulate, we would like the *shuffle player* to *eliminate* the biologically non-plausible members from the *naive shuffle set*. This encourages the *combination player* to learn the combination that is actively maintained by the controller in the system. To do so we set the shuffle policy $\Pi$ such that the *plausible shuffle set* resembles the *authentic set* with respect to the combination $\hat{g}_{T,\omega}$ while maintaining the differences between the naive and authentic sets. Technically, the

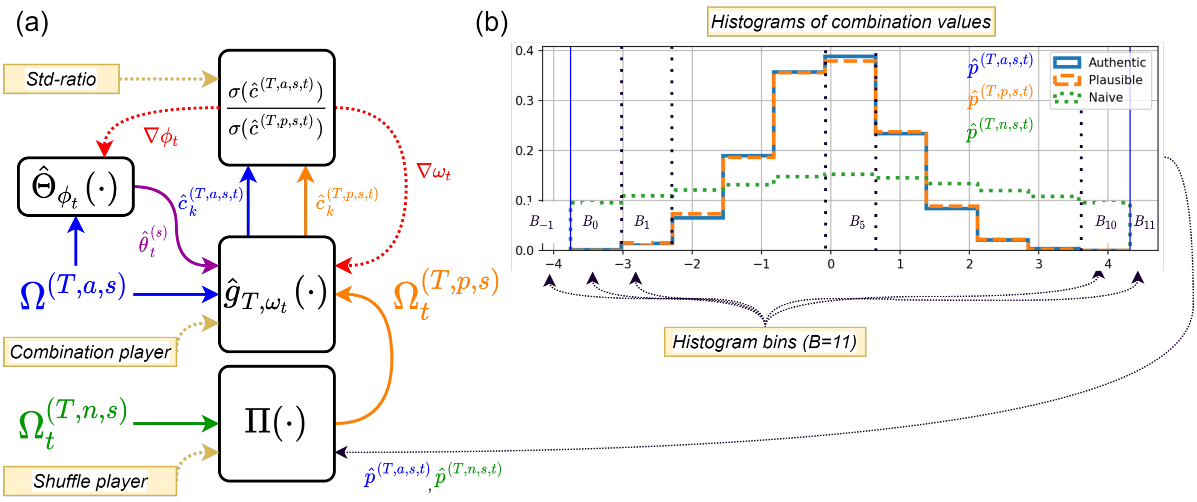


Figure SI 5: The optimization flow in iteration $t$. **(a)** The *shuffle player* examines the histograms $\hat{p}^{T,a,s,t}$ and $\hat{p}^{T,n,s,t}$ of combination values derived from the *authentic set* and the *naive shuffle set* respectively and constructs the *'plausible shuffle set'* $\Omega_t^{(T,p,s)}$. The combination player $\hat{g}_{T,\omega_t}$ calculates the time-series $\hat{c}_k^{(T,a,s,t)}$ and $\hat{c}_k^{(T,p,s,t)}$ and its weights, $\omega_t$, and the weights $\phi_t$ of the function $\hat{\Theta}_{\phi_t}(\cdot)$ (that estimates the system parameters $\hat{\theta}_t^{(s)}$) are updated as to minimize the std-ratio. **(b)** Histograms of 13 bins with borders according to (S.18). The histogram $\hat{p}^{(T,p,s,t)}$ of combination values evaluated on the *plausible shuffle set* resembles the histogram $\hat{p}^{(T,a,s,t)}$ of combination values evaluated on the *authentic set* while the histogram $\hat{p}^{(T,n,s,t)}$ that corresponds to the *naive shuffle set* is significantly wider.

shuffle player has an **information constraint** because it only has access to values under the combination $\hat{g}_{T,\omega}(z)$. Therefore, it outputs data-points distributed by $z \sim p_{\Omega^{(T,p,s)}}$ such that

$$p_{\Omega^{(T,p,s)}}(z) = p_{\Omega^{(T,n,s)}}(z)\zeta_\delta(\hat{g}_{T,\omega}(z)), \tag{S.11}$$

where $\zeta_\delta(\cdot) : \mathbb{R} \to \mathbb{R}$ is a function parameterized by $\delta$. Figure SI 5**a** illustrates the two-player optimization where the objective of the *combination player* is,

$$\begin{aligned}
\textbf{Combination player} \quad \omega^*, \phi^* &= \underset{\omega,\phi}{\operatorname{argmin}} \, \mathrm{E}_s \frac{\sigma\left(\hat{c}_k^{(T,a,s)} \sim p_{\hat{c}^{(T,a,s)}}\right)}{\sigma\left(\hat{c}_k^{(T,p,s)} \sim p_{\hat{c}^{(T,p,s)}}\right)} \\
\text{s.t } \hat{c}_k^{(T,\alpha,s)} &= \hat{g}_{T,\omega}\left(z_k^{(T,\alpha,s)}; \hat{\theta}_t^{(s)}\right), \quad \alpha \in \{a, n\} \\
z_k^{(T,\alpha,s)} &\sim p_{\Omega^{(T,a,s)}} \\
\hat{\theta}_\phi^{(s)} &= \hat{\Theta}_\phi\left(p_{\Omega^{(T,a,s)}}\right) \,.
\end{aligned} \tag{S.12}$$

The objective of the *shuffle player* is

$$\begin{aligned}
\textbf{Shuffle player} \quad & \delta^{(s)}(\omega,\phi) = \underset{\delta}{\operatorname{argmin}}\, D\left(p_{\hat{c}^{(T,a,s)}}, p_{\hat{c}^{(T,p,s)}}\right) \\
& \text{s.t } p_{\hat{c}^{(T,p,s)}}(c) = \int_{\{z|\hat{g}_{T,\omega}(z,\hat{\theta}_\phi^{(s)})=c\}} p_{\Omega^{(T,p,s)}}(z)dz \\
& p_{\Omega^{(T,p,s)}}(z) = p_{\Omega^{(T,n,s)}}(z)\zeta_\delta(\hat{g}_{T,\omega}(z,\hat{\theta}_\phi^{(s)})) \\
& \hat{\theta}_\phi^{(s)} = \hat{\Theta}_\phi\left(p_{\Omega^{(T,a,s)}}\right),
\end{aligned} \tag{S.13}$$

where $D(\cdot,\cdot)$ is a distributional distance metric and $\zeta_\delta(\cdot):\mathbb{R}\to\mathbb{R}$ is a function parameterized by $\delta$, as in (S.11). To solve the joint optimization problem (S.12-S.13) we use the iterative algorithm, Algorithm 1. Let the estimated combination be $\hat{g}_{T,\omega_t}(\cdot)$, a function parameterized by the vector $\omega_t$, where $t$ is the optimization-iteration index. For a given policy $\Pi$, a gradient-descent update step of the two-players optimization algorithm is given by,

$$\begin{aligned}
\begin{bmatrix}\omega_{t+1}\\ \phi_{t+1}\end{bmatrix} &= \begin{bmatrix}\omega_t\\ \phi_t\end{bmatrix} - \eta\nabla_{\begin{bmatrix}\omega_t\\ \phi_t\end{bmatrix}} \sum_{s=0}^{M-1} \frac{\sigma(\hat{c}^{(T,a,s,t)}_{0:N^{(T,a,s)}-1})}{\sigma(\hat{c}^{(T,p,s,t)}_{0:N^{(T,p,s,t)}-1})} \\
\text{s.t } \hat{c}_k^{(T,a,s,t)} &= \hat{g}_{T,\omega_t}\left(z_k^{(T,a,s)};\hat{\theta}_t^{(s)}\right) \\
\hat{c}_k^{(T,p,s,t)} &= \hat{g}_{T,\omega_t}\left(z_k^{(T,p,s,t)};\hat{\theta}_t^{(s)}\right) \\
\hat{\theta}_t^{(s)} &= \hat{\Theta}_{\phi_t}(\Omega^{(T,a,s)}).
\end{aligned} \tag{S.14}$$

We are left with describing the technical details of the policy $\Pi$ that creates the *plausible shuffle set* that resembles the *authentic set* with respect to the combination $\hat{g}_{T,\omega}$.

### SI3.2.1 Shuffle player

**Claim** The optimal solution to the shuffle player's optimization problem (S.13) is

$$\zeta_\delta(c) = \frac{p_{\hat{c}^{(T,a,s)}}(c)}{p_{\hat{c}^{(T,n,s)}}(c)}. \tag{S.15}$$

*Proof.*

$$
\begin{aligned}
p_{\hat{c}^{(T,p,s)}}(c) &= \int_{\{z|\hat{g}_{T,\omega}(z,\hat{\theta}_\phi^{(s)})=c\}} p_{\Omega^{(T,p,s)}}(z)dz \\
&\overset{(i)}{=} \int_{\{z|\hat{g}_{T,\omega}(z,\hat{\theta}_\phi^{(s)})=c\}} p_{\Omega^{(T,n,s)}}(z)\zeta_\delta(\hat{g}_{T,\omega}(z,\hat{\theta}_\phi^{(s)}))dz \\
&\overset{(ii)}{=} \int_{\{z|\hat{g}_{T,\omega}(z,\hat{\theta}_\phi^{(s)})=c\}} p_{\Omega^{(T,n,s)}}(z)\zeta_\delta(c)dz \\
&= \zeta_\delta(c)\int_{\{z|\hat{g}_{T,\omega}(z,\hat{\theta}_\phi^{(s)})=c\}} p_{\Omega^{(T,n,s)}}(z)dz \\
&= \zeta_\delta(c)p_{\hat{c}^{(T,n,s)}}(c) \\
&\overset{(iii)}{=} \frac{p_{\hat{c}^{(T,a,s)}}(c)}{p_{\hat{c}^{(T,n,s)}}(c)}p_{\hat{c}^{(T,n,s)}}(c) \\
&= p_{\hat{c}^{(T,a,s)}}(c)
\end{aligned}
\tag{S.16}
$$

where in $(i)$ we substitute (S.11), in $(ii)$ we inserted the projection, $\hat{g}_{T,\omega}(z,\hat{\theta}_\phi^{(s)}) = c$ and in $(iii)$ we substitute (S.15). It immediately follows that,

$$
D\left(p_{\hat{c}^{(T,a,s)}}, p_{\hat{c}^{(T,p,s)}}\right)\Big|_{\zeta_\delta(c)=\frac{p_{\hat{c}^{(T,a,s)}}(c)}{p_{\hat{c}^{(T,n,s)}}(c)}} = D\left(p_{\hat{c}^{(T,a,s)}}, p_{\hat{c}^{(T,a,s)}}\right) = 0. \tag{S.17}
$$

□

According to (S.13), the policy Π should perform changes to the *naive shuffle set* to obey the constraint by which the distributions of the authentic data and player-shuffled data, with respect to $\hat{g}_{T,\omega}$, are identical, as manifested in (S.17). To do so the *shuffle player* estimates these distributions by constructing 1D histograms, and then samples members from the *naive shuffle set* to obtain similar histograms. In each iteration, let the distributions of the combination values of each observed system be approximated by a histogram over the set of bins,

$$
B_b^{(T,s,t)} = \begin{cases} \{c \mid c \in (-\infty, \min_k \hat{c}_k^{(T,a,s,t)})\}, & \text{if } b=-1 \\ \{c \mid c \in \min_k \hat{c}_k^{(T,a,s,t)} + [bW_t,(b+1)W_t)\}, & \text{if } b=0,\dots,B-1 \\ \{c \mid c \in [\max_k \hat{c}_k^{(T,a,s,t)}, \infty)\} & \text{if } b=B \end{cases} \tag{S.18}
$$

where $W_t = \frac{1}{B}\left(\max_k \hat{c}_k^{(T,a,s,t)} - \min_k \hat{c}_k^{(T,a,s,t)}\right)$ is the width of a single bin in the histogram, and where the number of bins is a user-defined parameter. Then, the histograms of combination values of members in a set are given by,

$$
\hat{p}_b^{(T,\alpha,s,t)} = \frac{1}{N^{(T,\alpha,s,t)}} \sum_{k=0}^{N^{(T,\alpha,s,t)}-1} \mathcal{I}\left(\hat{c}_k^{(T,\alpha,s,t)} \in B_b^{(T,s,t)}\right), \tag{S.19}
$$

for $\alpha \in \{a, p, s\}$, where $\mathcal{I}(\cdot)$ is the indicator function. Figure SI 5**b** depicts the three 1D histograms of the combination $\hat{g}_{T,\omega_t}$, when evaluated on the different sets. In blue, the histogram of authentic data, in green, the naive shuffled data, and in orange, the histogram of player-shuffled data, the outcome of the policy $\Pi$ manifested in (S.15).

To block the biologically non-plausible pairs from entering the set of the *'plausible shuffled pairs'* we designed the policy $\Pi$ of the *shuffle player* to minimize $\sum_{b=0}^{B-1} |\hat{p}_b^{(T,p,s,t)} - \hat{p}_b^{(T,a,s,t)}|$, thus creating the *'plausible shuffle set'* such that the distribution of the combination values of its members resembles the distribution of combination values of members in the *'authentic set'*. The implementation of (S.15) is performed by by stochastically blocking a fraction of the members in the *naive shuffle set* from entering the player-shuffled set. This is done by estimating the fraction per each bin in the histogram.

For each combination value $c$, denote by $\beta(c)$ the index of the bin in which $c$ resides. For each member in the *naive shuffle set*, the *shuffle player* draws a Bernoulli distributed random variable such that,

$$P\left(z_k^{(T,n,s,t)} \in \Omega_t^{(T,p,s)}\right) = q_{\beta(\hat{c}_k^{T,n,s,t})}^{(T,s)} \tag{S.20}$$

where

$$q_b^{(T,s)} = \frac{\tilde{q}_b^{(T,s)}}{\max_b \tilde{q}_b^{(T,s)}}, \tag{S.21}$$

and

$$\tilde{q}_b^{(T,s)} = \begin{cases} 0, & \text{if } b = -1 \\ \frac{\hat{p}_b^{(T,a,s,t)}}{\hat{p}_b^{(T,n,s,t)}}, & \text{if } b = 0, \ldots, B-1 \\ 0, & \text{if } b = B. \end{cases} \tag{S.22}$$

Consider bin $B5$ in figure SI 5**b**. This bin has the highest ratio between authentic data (blue) and naive shuffled data (green) and thus it serves to normalize the Bernoulli parameters of all bins, (S.21). All members of the *naive shuffle set* that reside in bin $B5$ are transformed to the player-shuffled set since its corresponding Bernoulli parameter is $q_5^{T,s} = 1$. The Bernoulli parameters for all other bins is calculated by evaluating the ratio (S.22), between the blue and green histograms and normalizing by (S.21). We note that since $\Omega^{(T,n,s)} \supset \Omega^{(T,a,s)}$ it is guaranteed that $\tilde{q}_b^{(T,s)}$ is well defined.

# SI4 Implementation details

$\hat{g}_{T,\omega}(\cdot)$. The function $\hat{g}_{T,\omega}$ implemented as a feed-forward artificial neural network. The input, $\left[z_k^{(T,\ldots)}\right]$ or $\left[z_k^{(T,\ldots)} \quad \theta\right]$ when a parameter vector is estimated as well, is connected to all 32 neurons of the input layer which are themselves connected to a hidden layers having 16 neurons. The output layer has a single neuron which outputs the value of the regulated signal $\hat{c}_k^{(T,\ldots)}$ that corresponds the input. The activation function of all neurons is Leaky-ReLU except for the output neuron whose activation function is the Sigmoid function.

$\Theta_\phi(\cdot)$. The function $\Theta_\phi$ implemented as a feed-forward artificial neural network. The input consists of 100 time samples, $z_{100i:100(i+1)}$ for $i = 0, \ldots, \lfloor \frac{N}{100} \rfloor - 1$, is connected to all 128 neurons of the input layer which are themselves connected to two sequential hidden layers having 128 and 64 neurons each. The output layer has $l$ neurons (where $l$ is the user-defined number of parameters) which outputs the value $\theta_i$. The estimated parameters are given by $\theta = \frac{1}{\lfloor \frac{N}{100} \rfloor - 1} \sum_{i=0}^{\lfloor \frac{N}{100} \rfloor - 1} \theta_i$. The activation function of all neurons is Leaky-ReLU except for the output neurons which have no activation function.

We simultaneously train the networks as described in Algorithm 1 for a pre-defined fixed number of epochs (500) using the Stochastic-Gradient-descent optimizer with a momentum value of 0.9 and a learning rate of 0.01. See [Zhang et al., 2020] for a detailed explanation of feed-forward neural networks, activation functions and optimizers.

# SI5 Algorithm snapshots

Figure SI 6 is complementary to Figure 4 and displays the combination function and the sampling probability by the shuffle player in different iterations of the algorithm.

# SI6 Validation

## SI6.1 Steady states of the kinetic model

At steady state, $\dot{M}, \dot{P}, \dot{S}$ equal zero. Solving the equations gives the steady state

$$\begin{aligned} M_{ss} &= \frac{\gamma_P \gamma_S}{B_1} \frac{K}{F + B_2} \\ P_{ss} &= \frac{k_P \gamma_S}{B_1} \frac{K}{F + B_2} \\ S_{ss} &= \frac{k_S \gamma_P}{B_1} \frac{K}{F + B_2} \\ P_{ss} + S_{ss} &= \frac{K}{F + B_2} \end{aligned} \tag{S.23}$$

where $B_1 = k_P \gamma_S + k_S \gamma_P$ and $B_2 = \dfrac{\gamma_M \gamma_P \gamma_S}{B_1}$. For $F \gg B_2$, $P_{ss} + S_{ss}$ is robust to perturbations in the parameters while the steady states of the three proteins are sensitive to perturbations.

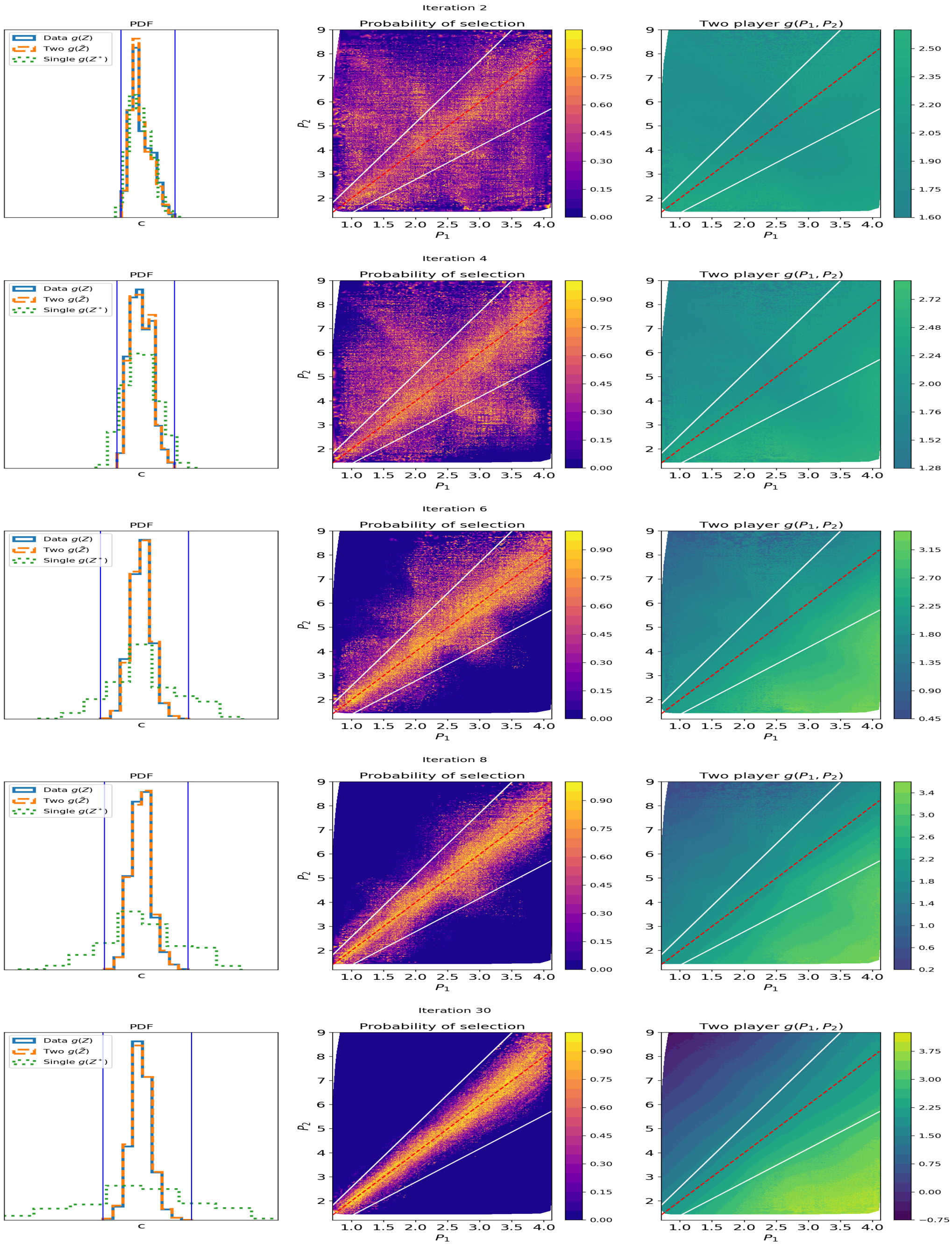


Figure SI 6: Iterations of the two-player algorithm for the example in Figure 4. The iterations shows a graduate identification of the data region followed by the identification of the control objective, within the region of the data.

## SI6.2 High and low perturbations in $\gamma_M$ give rise to The different output combinations

The most conserved combination in the kinetic model depends on the values of the parameters and the perturbations in them. We will consider the cases of low and high perturbations in $\gamma_M$ relative to the other parameters ($F$ and $K$ are constant). In the first case, the combination obtained incorporates the effect of $M$. In the second case, we get a behavior that is qualitatively similar to disabling the controller and a combination that reflects the resultant positive correlation between $S$ and $P$. The qualitatively different combinations obtained for high and low perturbations in $\gamma_M$ reflect the two ends of the spectrum of conserved combinations.

**Low perturbations in $\gamma_M$**

At steady state, and for a single parameter set, $\dot{M} = K - F(P + S) - \gamma_M M = 0$. Thus, $F(P_{\text{ss}} + S_{\text{ss}}) - \gamma_M M_{\text{ss}} = K$. For small perturbations in $\gamma_M$, a conserved combination that incorporates $M$ is obtained,

$$g(M, S, P) = F(P + S) - \overline{\gamma}_M M \approx K \tag{S.24}$$

where $\overline{\gamma}_M$ is the mean of $\gamma_M$ across all realizations. Figure SI 7A (left panel) shows that this combination is indeed conserved for low perturbations in $\gamma_M$. Running the algorithm for 30 realization of the model with low perturbations in $\gamma_M$ gives rise to the combination in (S.24). The output of the algorithm $g(M, S, P)$ overlaps with the combination in (S.24) (Fig. SI 7A right panel) with a Pearson correlation of $0.97 \pm 0.008$. Moreover, fitting the output of the network to a linear function of $M$, $S$ and $P$ using multivariate linear regression, yields the combination $g(M, S, P) = S + P + 0.15M$. Interestingly, the coefficient of $M$ in the linear combination is a very close approximation of the ratio $\overline{\gamma}_M/F = 0.16$.

**High perturbations in $\gamma_M$**

High perturbations in $\gamma_M$, relative to the other parameters, drives the change in M dominantly and in turn affects considerably $\dot{S}$ and $\dot{P}$. This results in a high positive correlation between S and P since they both follow similar first order kinetics and are both affected by the same source $M$ (Figure SI 7 B left panel). Thus, we expect the output of the algorithm to reflect this positive correlation.Indeed, the output of the algorithm for 30 realization of the model follows the combination $S - P$ (Figure SI 7 B right panel).The Pearson correlation between both combinations is $0.79 \pm 0.09$. Fitting the output of the network to a linear function of $M$, $S$ and $P$ using multivariate linear regression, yields the combination $g(M, S, P) = S - P - 0.06M$. In fact, this case resembles the case of disabling the controller where M induces the production of S and P without receiving a feedback of their sum.

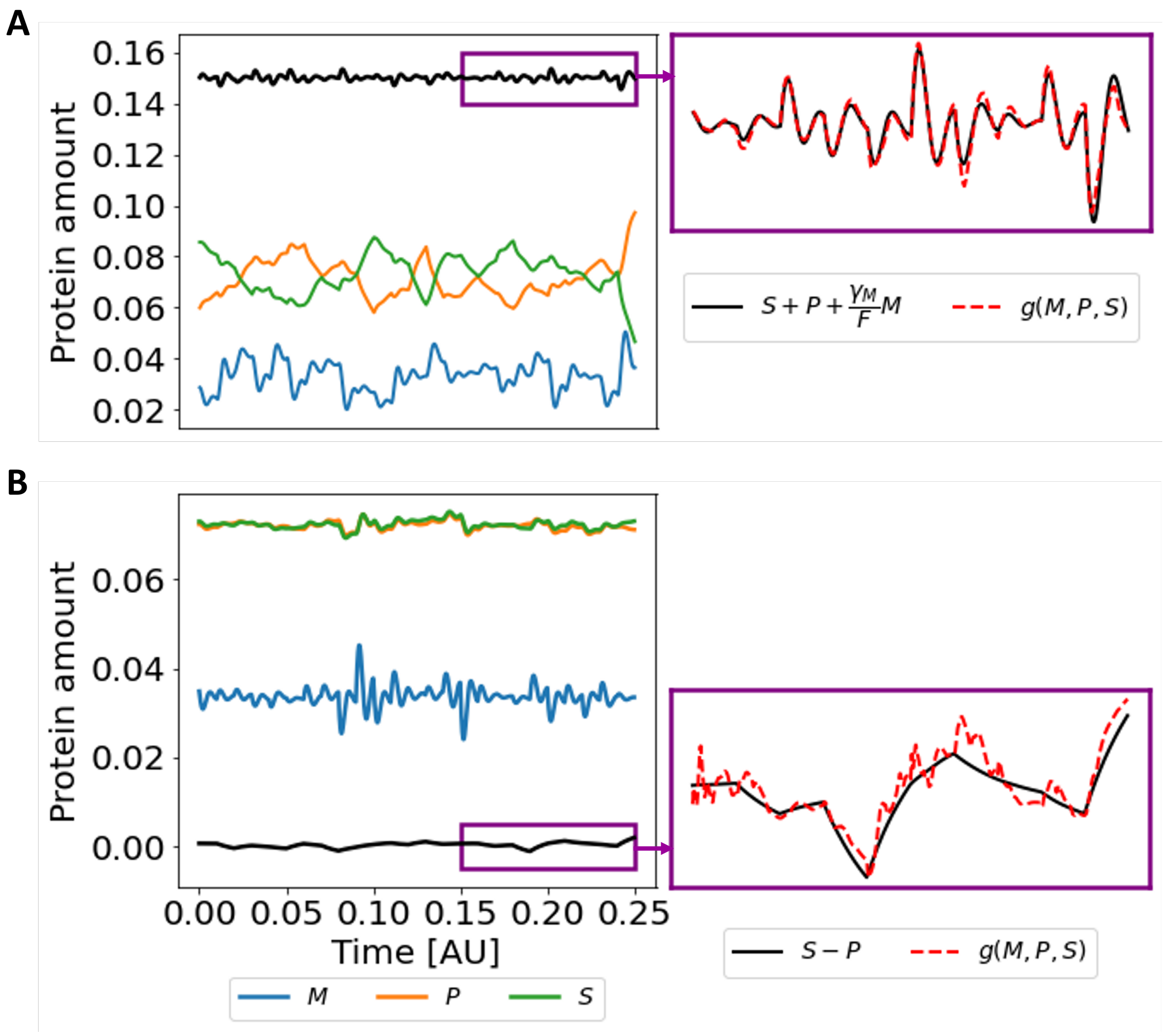


Figure SI 7: High and low perturbations in $\gamma_M$ give rise to different output combinations. (A) Low perturbations in $\gamma_M$ relative to the other parameters. Left Panel: The trajectories of the three proteins and the combination $P+S-\frac{\overline{\gamma}_M}{F}M$ over time. The perturbations in the parameters $\gamma_M, \gamma_S, \gamma_P, k_P$, and $K_S$ were created as described in Figure 5B, where $\gamma_M = 320 \pm 5, \gamma_S, \gamma_P = 70 \pm 15, k_S, k_P = 150 \pm 30$. Right Panel: A zoom-in for the combination $P+S-\frac{\overline{\gamma}_M}{F}M$ within the purple box along with the output of the algorithm. (B) High perturbations in $\gamma_M$ relative to the other parameters. Left Panel: The trajectories of the three proteins and the combination $S-P$ over time, where $\gamma_M = 320 \pm 100$, $\gamma_S, \gamma_P = 70 \pm 1, k_S, k_P = 150 \pm 1$. Right Panel: A zoom-in for the combination $S-P$ within the purple box along with the output of the algorithm. $F = 2000, K = 300$.

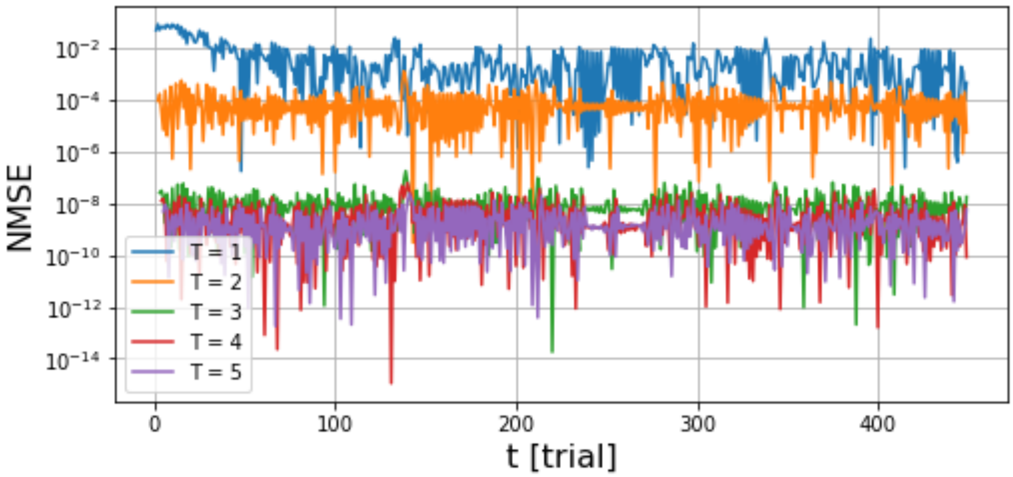


Figure SI 8: Normalized mean-square-errors of stimuli estimation values along a complete trial sequence. The stimuli estimation is obtained from the analytical expression of the feedback loop the algorithm detected. The estimation errors decrease monotonously up to $T = 5$ implying an effective time-scale of 5 trials.

## SI6.3 Relational dynamics in perception

The estimation errors along a complete trial sequence for various values of $T$ are depicted in figure SI 8. The corresponding mean estimation errors over all trials were depicted in Figure 6.

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