Data-Driven Discovery with Deep Koopman Operators: Discovery of Novel Basis Functions and Operational Envelopes

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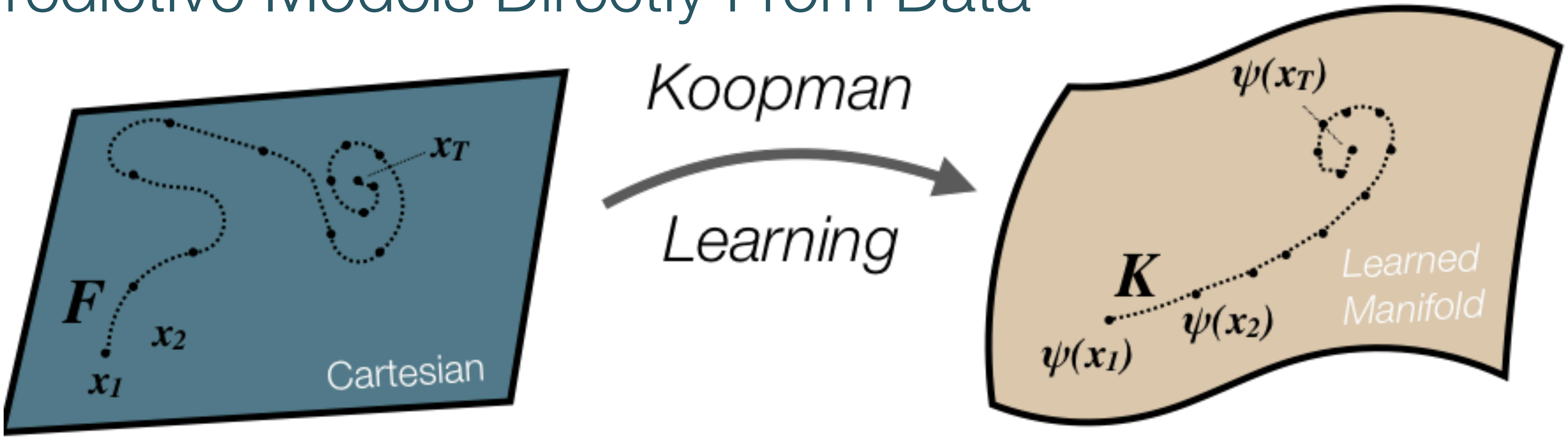
Koopman Operators Enable Discovery of Predictive Models Directly From Data



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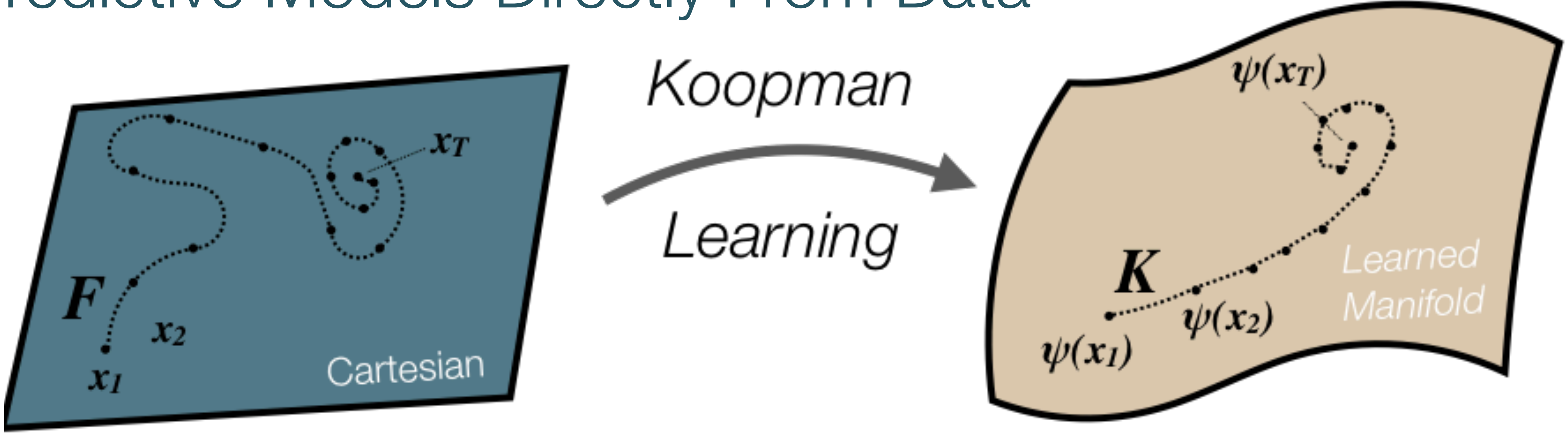

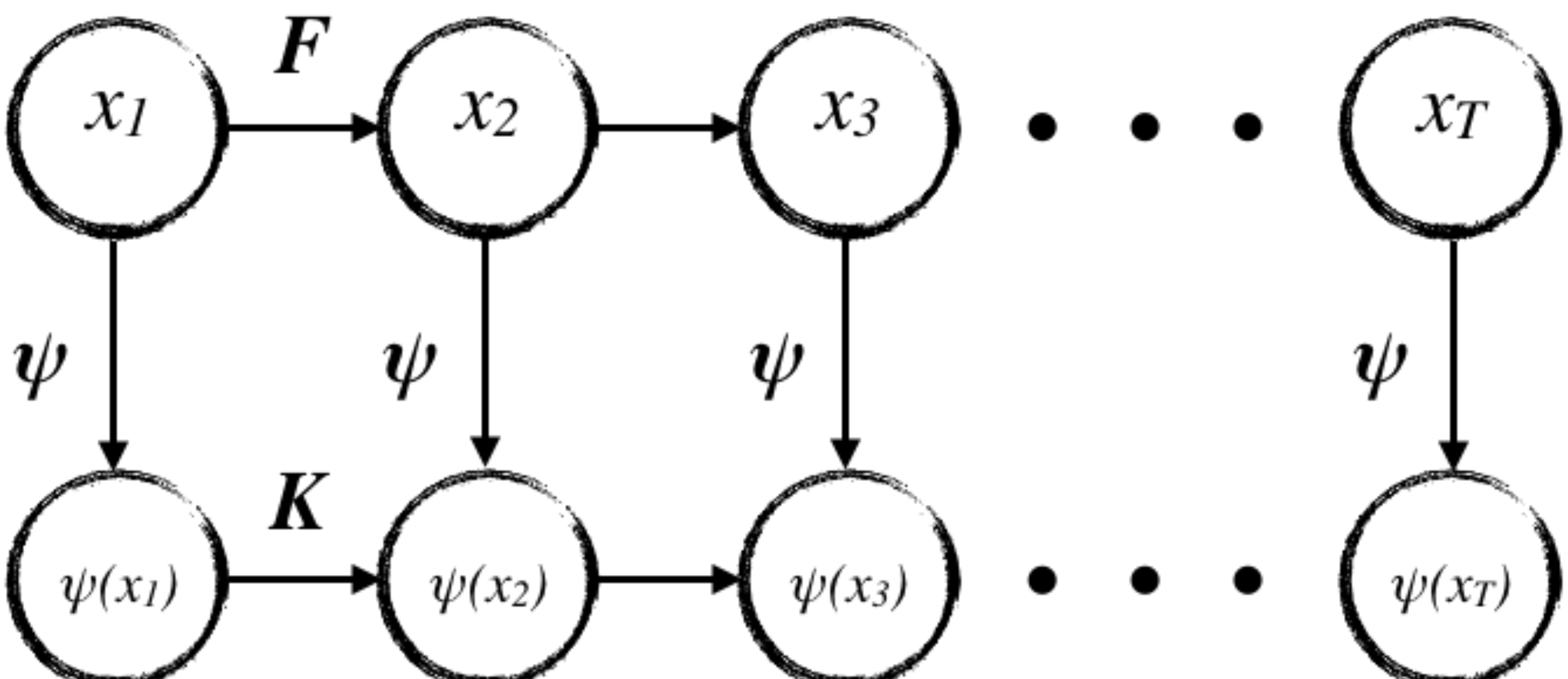

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Traditional Methods for Learning Koopman Operators Rely on Manual Dictionary Curation

Yeung et al., Deep Neural Network Representations for Koopman Operator Learning, 2017 arXiv/2018 ACC)

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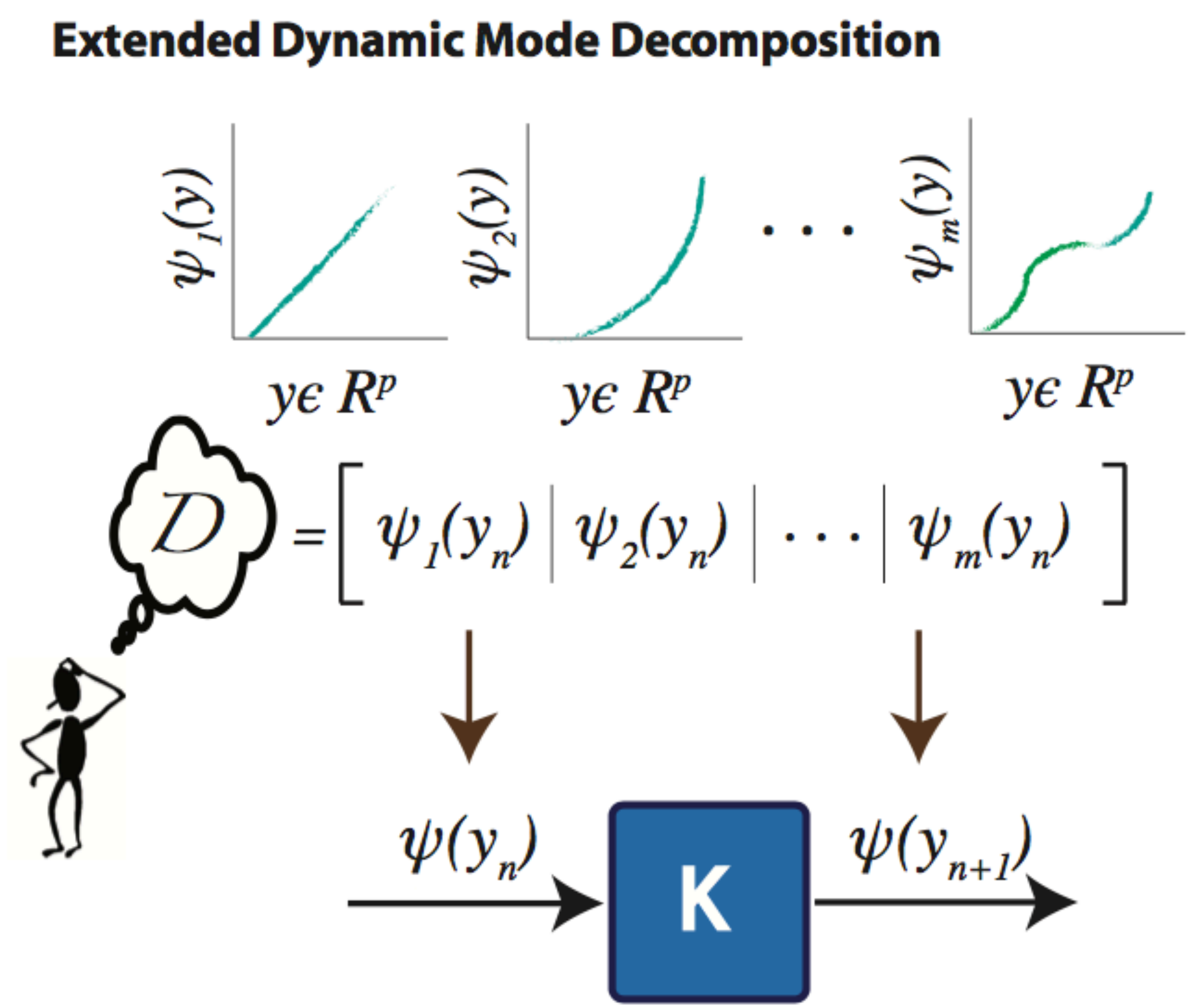

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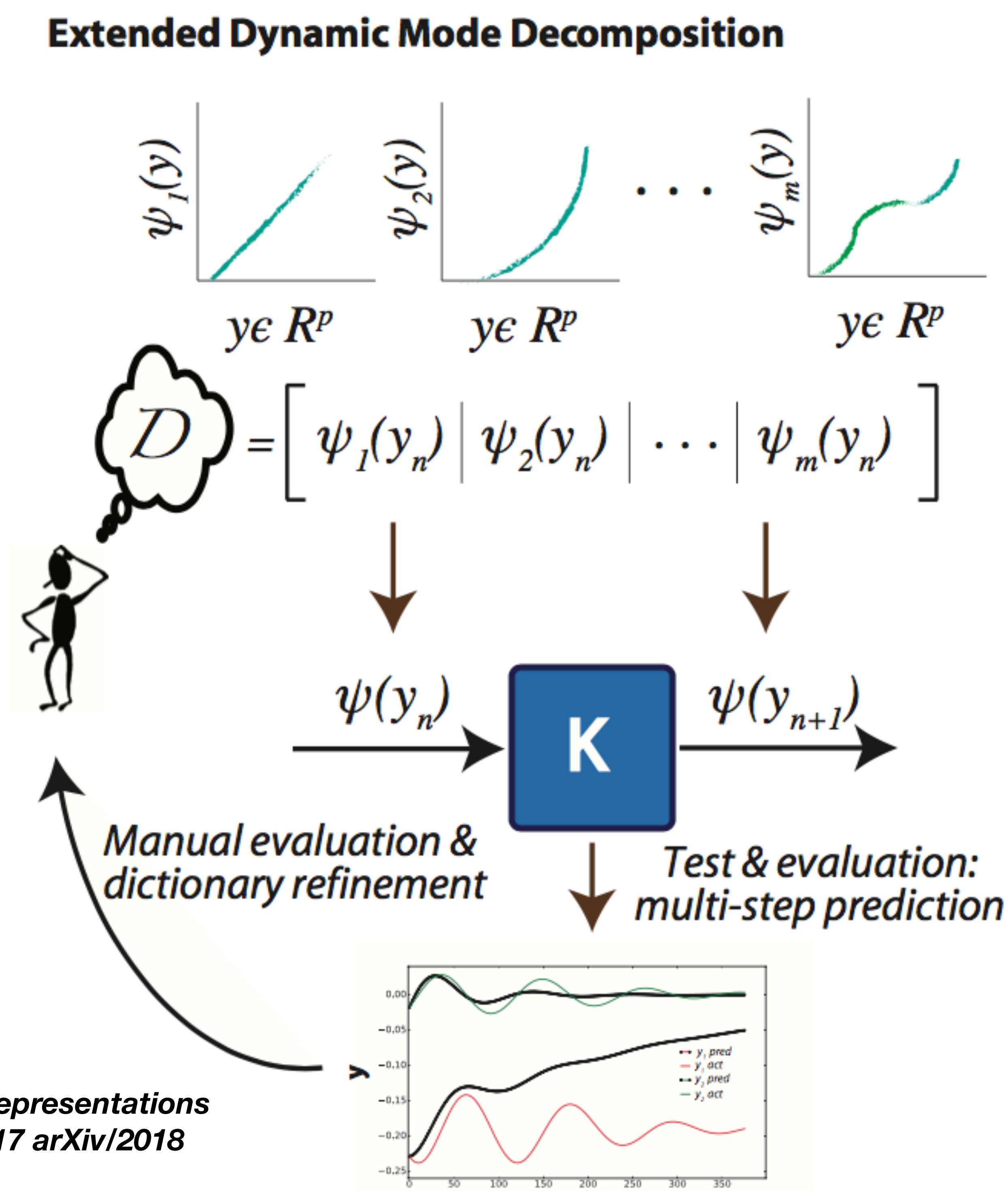

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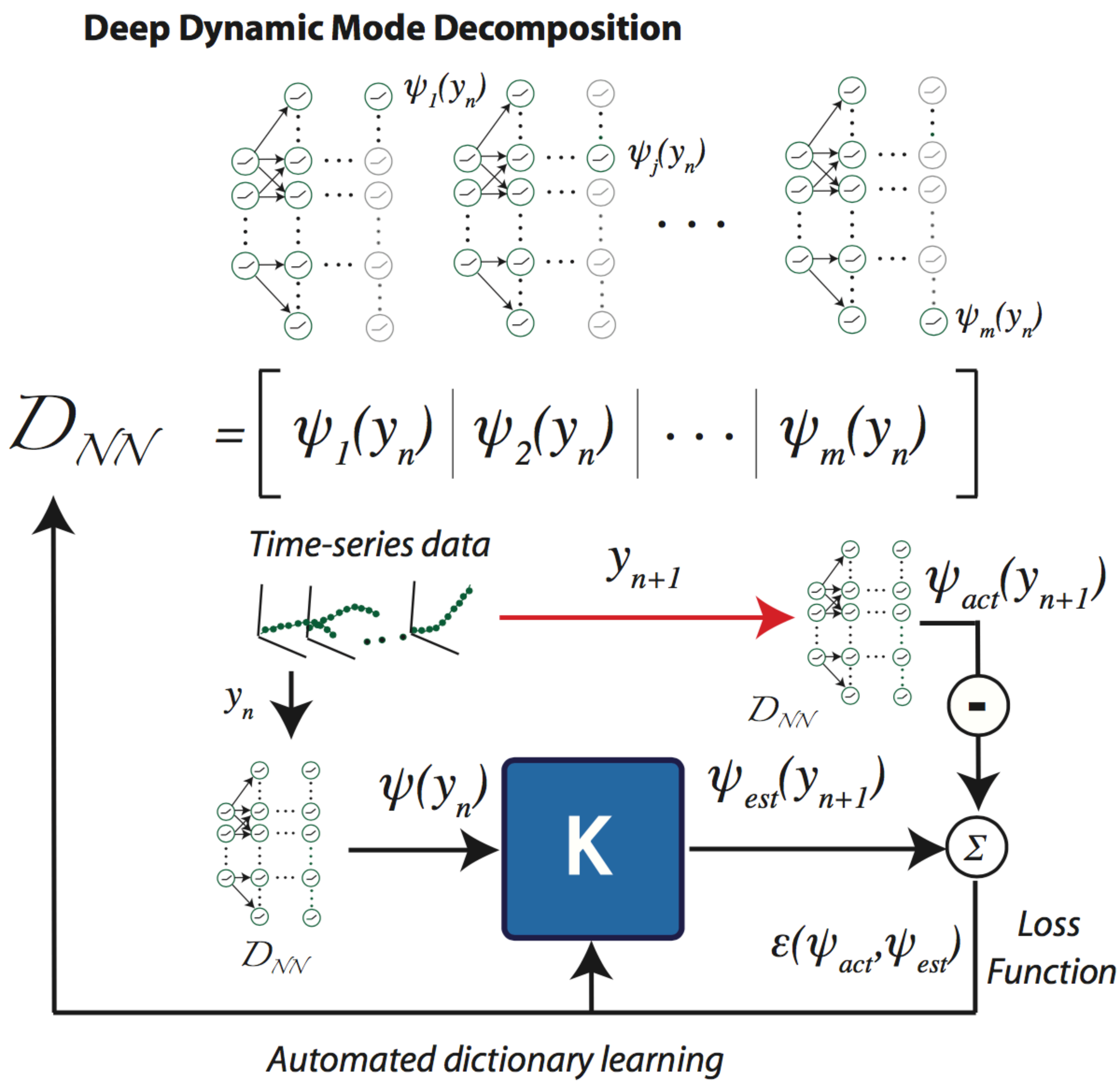
Our Proposed Approach: Deep Dynamic Mode Decomposition



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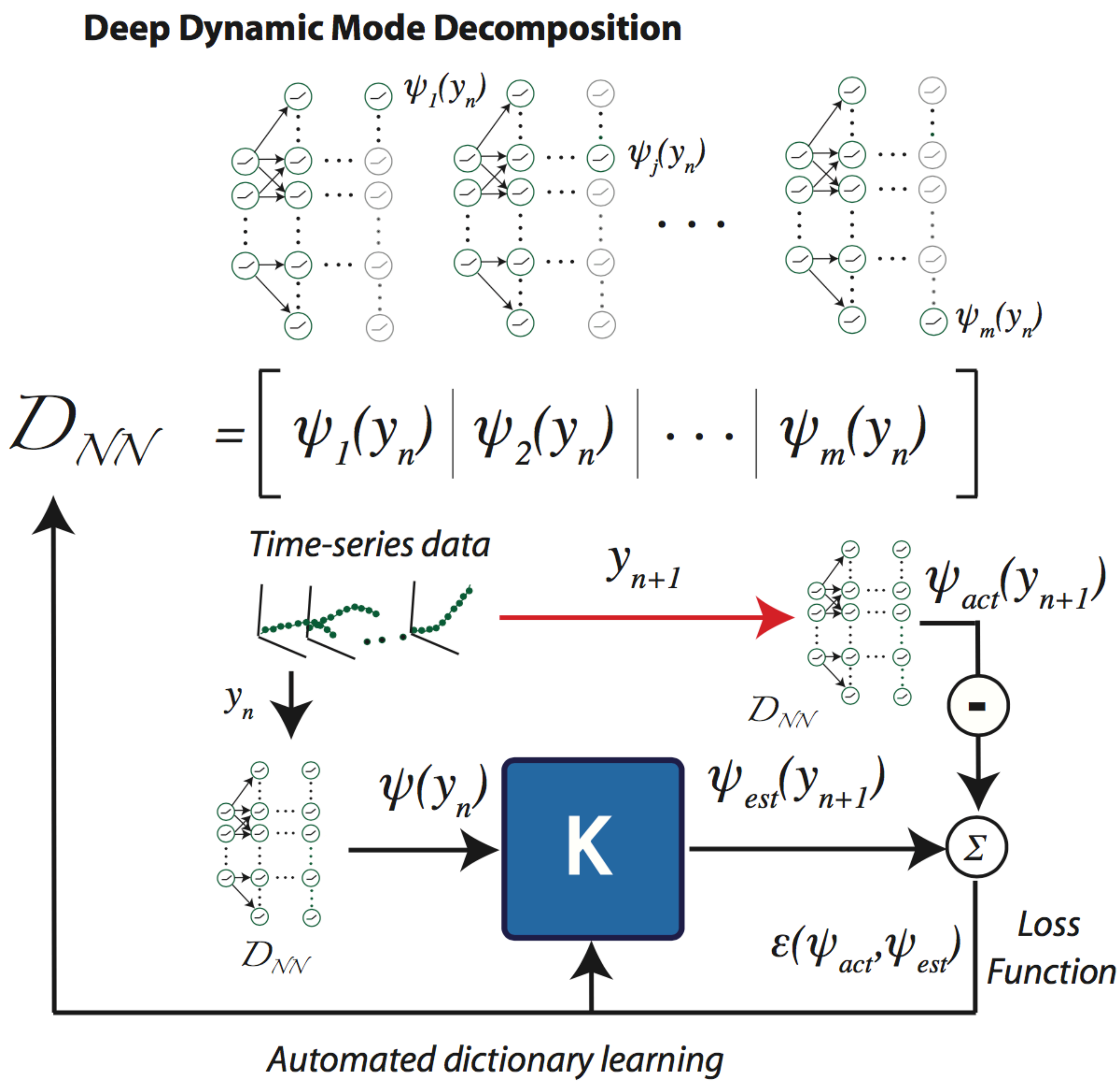
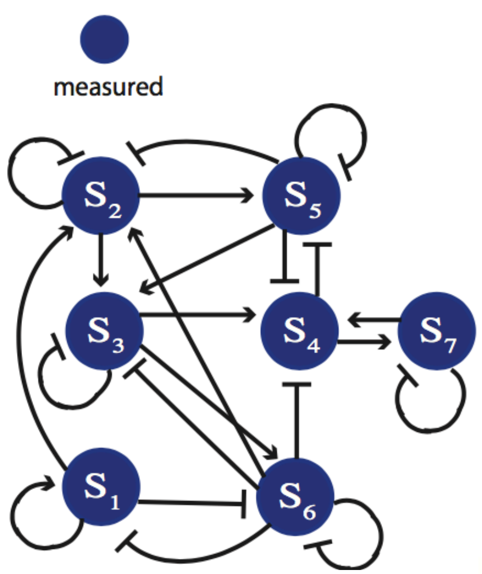


(see also Lorsch & Kutz, 2018)

Yeung et al., Deep Neural Network Representations for Koopman Operator Learning, (2017).

Deep Dynamic Mode Decomposition on the Glycolytic Oscillator

Glycolysis example:



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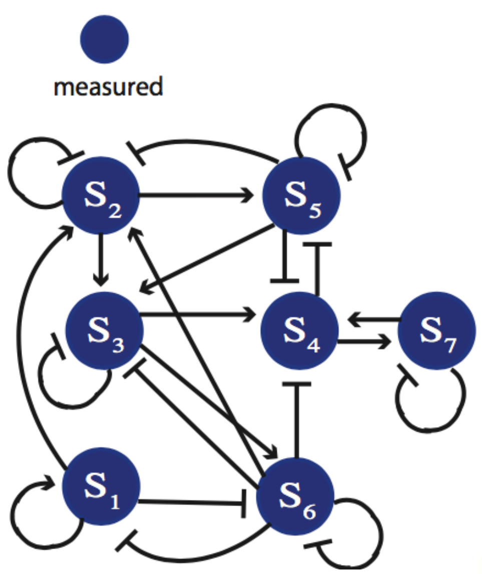

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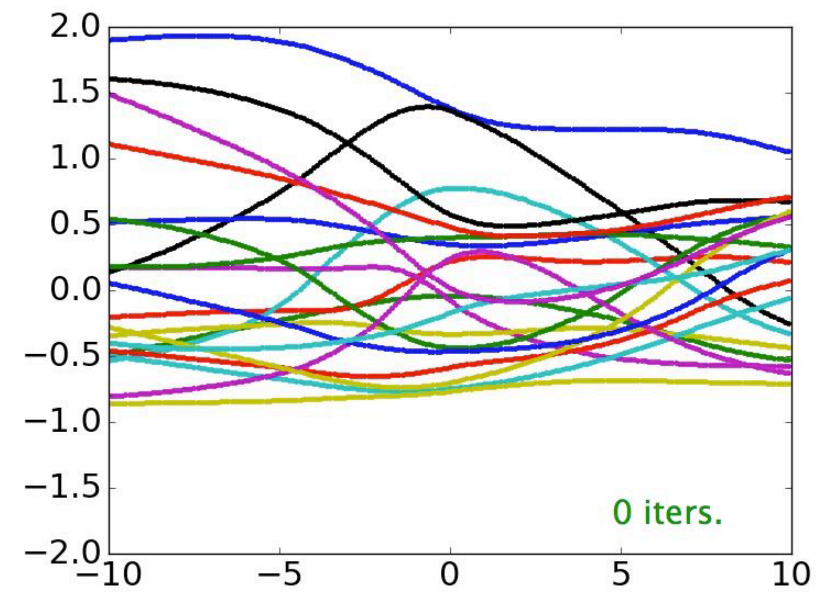
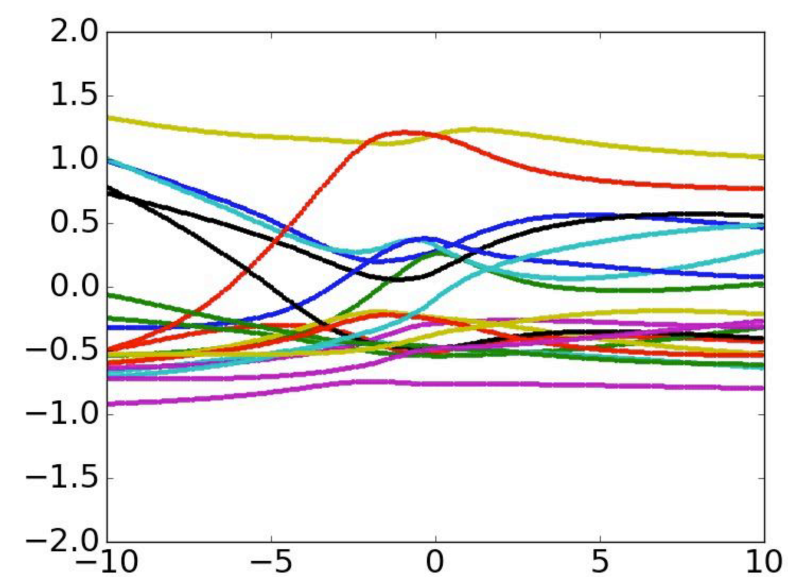


$u+\Delta e_1$



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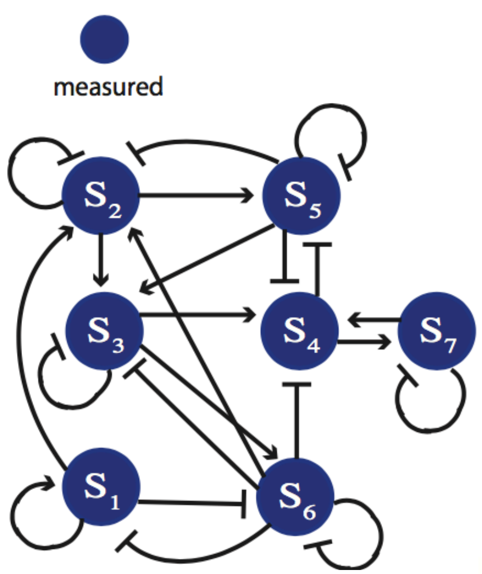

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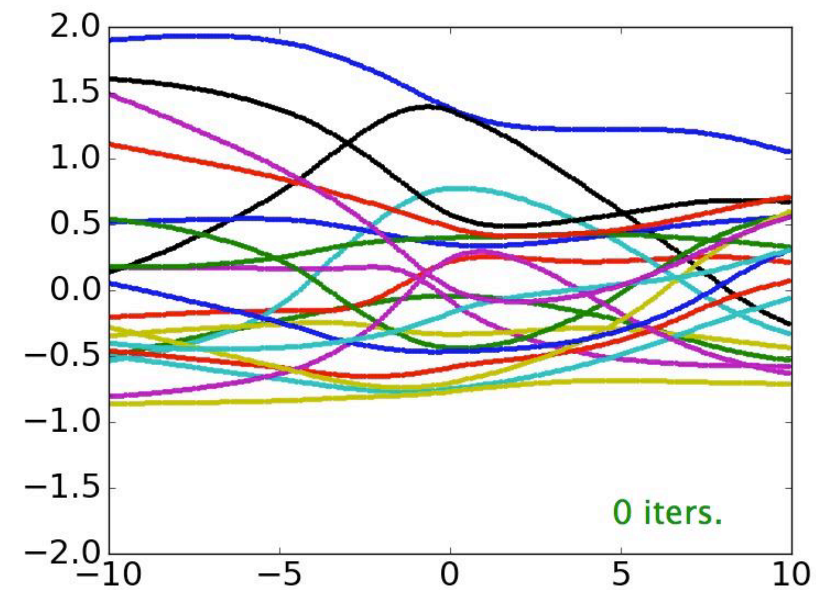
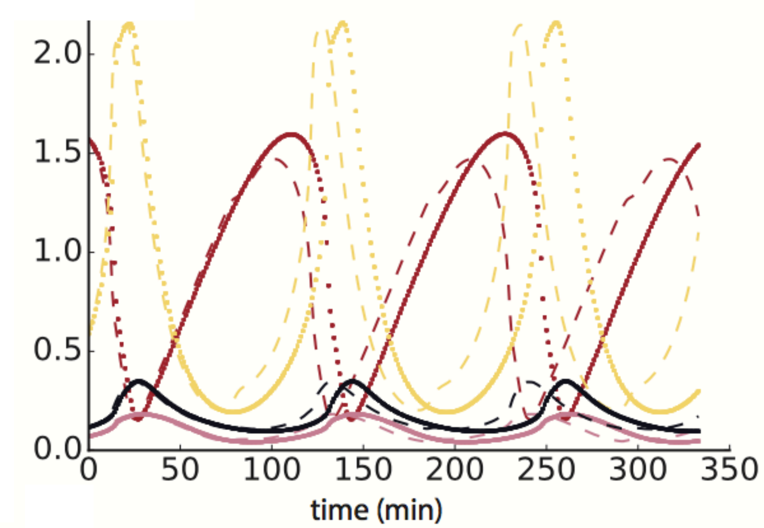
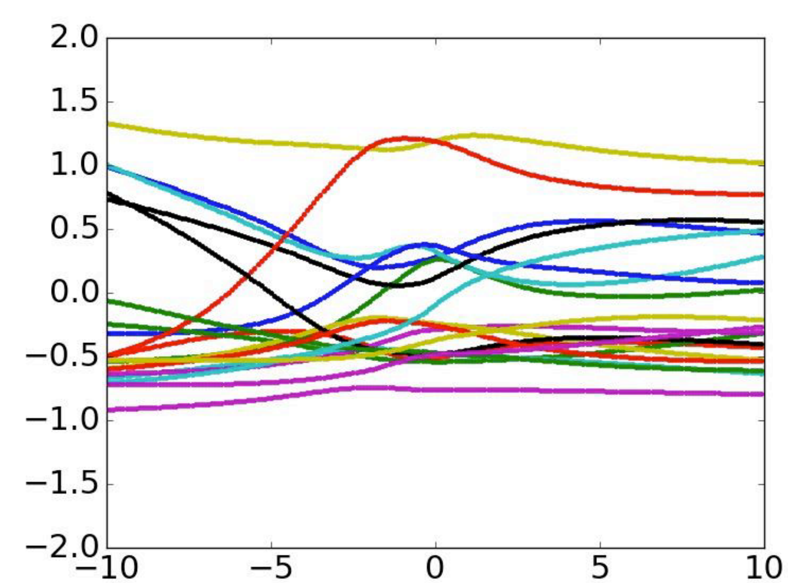


$u + \Delta e_1$

Deep DMD





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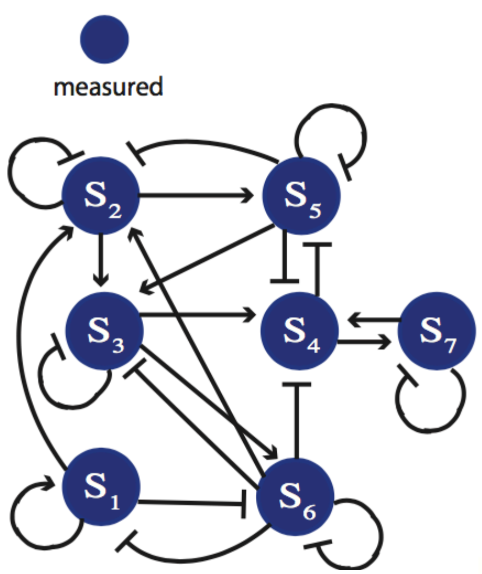

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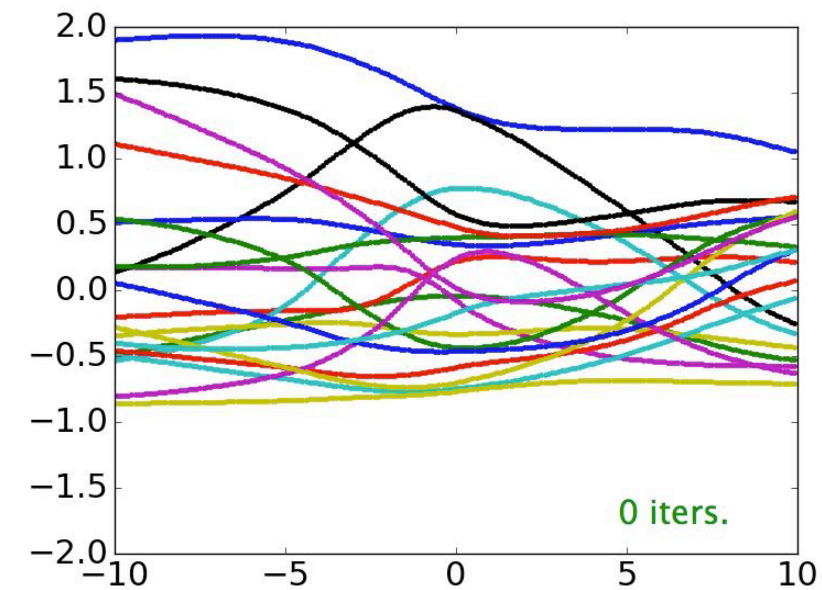
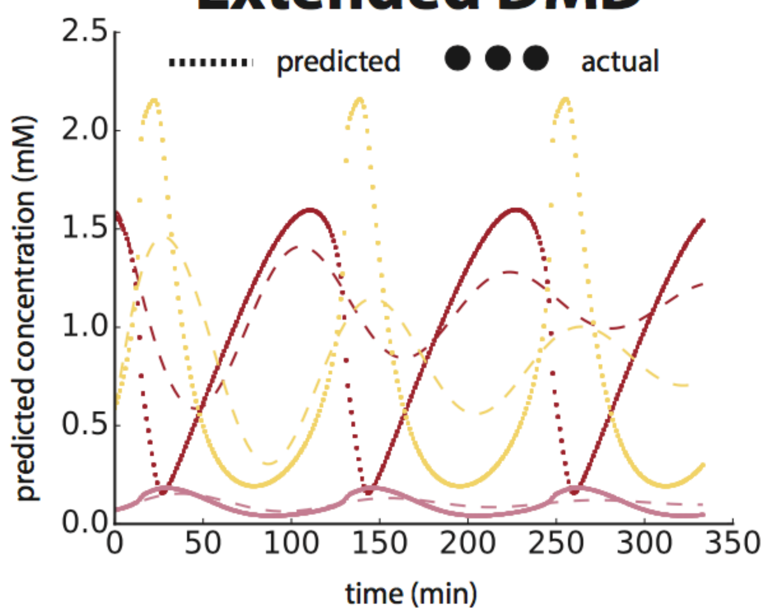
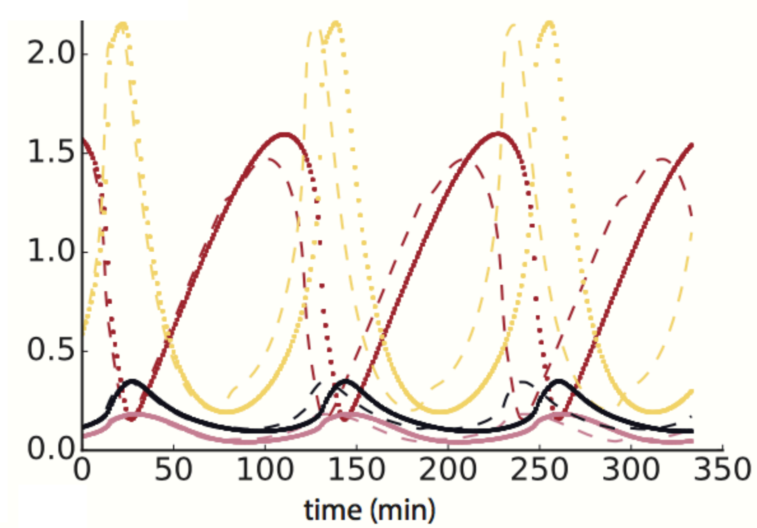


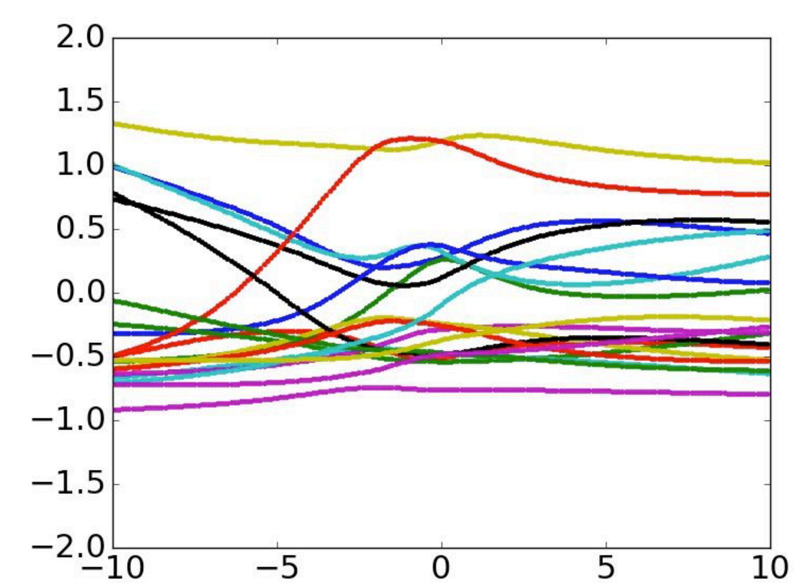
$u+\Delta e_1$

Extended DMD



Deep DMD





$u+\Delta e_2$

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The Appropriate Choice of Koopman Observables Lends Insight to Stability

We seek

$$\min_{\mathcal{K}_\mathcal{G},\psi\in\Psi} \left\| \frac{d\psi(x(t))}{dt} - \mathcal{K}_G \psi(x(t)) \right\|$$

such that we can learn about the stability of the underlying system.

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such that we can learn the spectral properties of the system

Theorem 1: Suppose that X is a forward invariant compact set and that the Koopman operator $U^t f = f \circ \varphi^t$ admits an eigenfunction $\phi_\lambda \in C^0(X)$ with the eigenvalue $\Re\{\lambda\} < 0$. Then the zero level set

$$M_0 = \{x \in X | \phi_\lambda(x) = 0\}$$

is forward invariant under φ^t and globally asymptotically stable.

(Mauroy & Mezic 2016)

The appropriate choice of observables can elucidate stability of the system.

Nuances to Constructing Koopman Observables

Not all liftings give insight into the underlying dynamical system's stability.

Consider the following system

$$\dot{x} = f(x)$$

with $f^{-1} \in \mathcal{L}_1 [0, \infty)$

Let $c \in \mathbb{R}$ be a constant. Let the functions

$$\{\mathcal{L}_1, \mathcal{L}_2, \ldots, \mathcal{L}_n | \mathcal{L}_i : \mathbb{R}^n \to \mathbb{R}, i \in \{1, 2, \ldots, n\}\}$$

be any bounded continuous function. Define the space of observables:

$$\mathcal{L}_i(x) = \int_0^\infty c f_i^{-1}(x(\tau)) d\tau$$

Johnson, Yeung, "A Class of Logistic Functions for State-Inclusive Koopman Operators" Proceedings of iEEE ACC (2017)

Nuances to Constructing Koopman Observables

Let the observable functions be defined as

$$\psi(x) \equiv \begin{bmatrix} \psi_1(x) \\ \vdots \\ \psi_n(x) \end{bmatrix} \equiv \begin{bmatrix} e^{\mathcal{L}_1(x)} \\ \vdots \\ e^{\mathcal{L}_n(x)} \end{bmatrix}$$

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It is straightforward to compute the Koopman operator for this choice of observables:

$$\frac{d}{dt}\psi(x(t)) = \frac{d}{dt}\begin{bmatrix} e^{\mathcal{L}_1(x)} \\ \vdots \\ e^{\mathcal{L}_n(x)} \end{bmatrix} = \begin{bmatrix} e^{\mathcal{L}_1(x)} \\ \vdots \\ e^{\mathcal{L}_n(x)} \end{bmatrix} cf^{-1}(x)f(x)$$

$$= cI \begin{bmatrix} e^{\mathcal{L}_1(x)} \\ \vdots \\ e^{\mathcal{L}_n(x)} \end{bmatrix} = K_G\psi(x)$$

Johnson, Yeung, "A Class of Logistic Functions for State-Inclusive Koopman Operators" Proceedings of iEEE ACC (2017)

State-Inclusive Liftings Lend Insight into the Stability of the System

When $\boldsymbol{x}$ is contained within the observable function, this **guarantees** the Koopman generator and its associated Koopman semigroup describe the time-evolution of observables and the system state.

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$$\psi(x) = (\psi_1(x), \psi_2(x), ..., \psi_{n_L}(x))$$

$\psi_j(x) = x$ for some ***j***.

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When

$$d\psi_j(x)/dt = f(x) \in \text{span}\{\psi_1, ..., \psi_{n_L}\}$$
$$d\psi(x)/dt = \mathcal{K}_{\mathcal{G}}\psi(x)$$

we say the system has ***finite*** exact closure.

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we say the system has ***finite*** exact closure.

This property does not hold for many nonlinear candidate observable functions.

State-Inclusive Liftings Lend Insight into the Stability of the System

Example **[Non-Finite Closure]**:

System of interest: $\dot{x} = f(x) = -x^2$

2nd-Degree Polynomial Lifting: $\psi(x) = \left(1, x, x^2\right)$

Non-Finite Closure: $\dot{\psi}(x) = \begin{bmatrix} 0 \\ -\psi_3(x) \\ -2\psi_2(x)\psi_3(x) \end{bmatrix}$

We would need to add an infinite number of polynomials to achieve convergence.

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Relaxing to Finite Approximate Closure

Since finite exact closure is hard, we consider a less stringent learning requirement on our liftings:

Definition 1: Let $\Psi(x) : M \to \mathbb{R}^{N_L}$ where $N_L < \infty$. We say $\Psi(x)$ achieves finite ϵ-closure or *finite approximate closure* with $O(\epsilon)$ error if and only if there exists an $\mathcal{K}_G \in \mathbb{R}^{n\times n}$ and $\epsilon > 0$ such that

$$\frac{d}{dt}\left(\Psi(x)\right) = \mathcal{K}_G \psi(x) + \epsilon(x). \quad (16)$$

What state-inclusive observable functions exhibit this property?

~~Radial basis functions,~~
~~Taylor/Legendre/Hermite polynomials,~~

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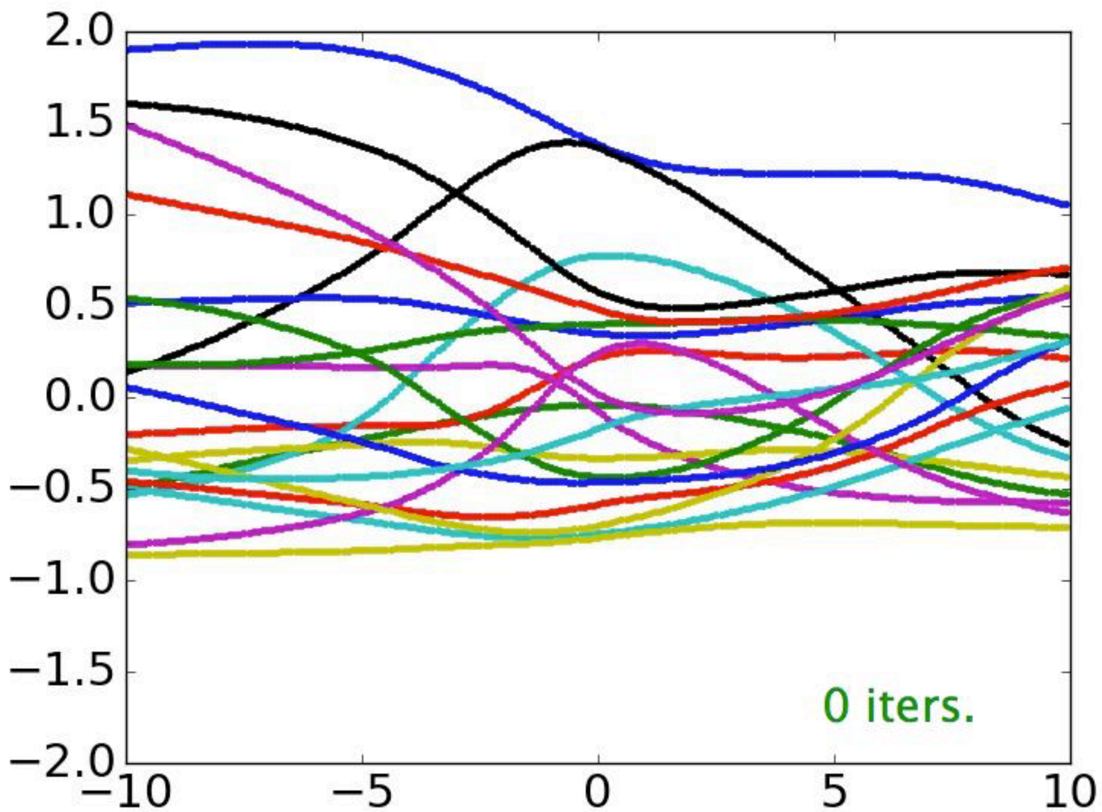
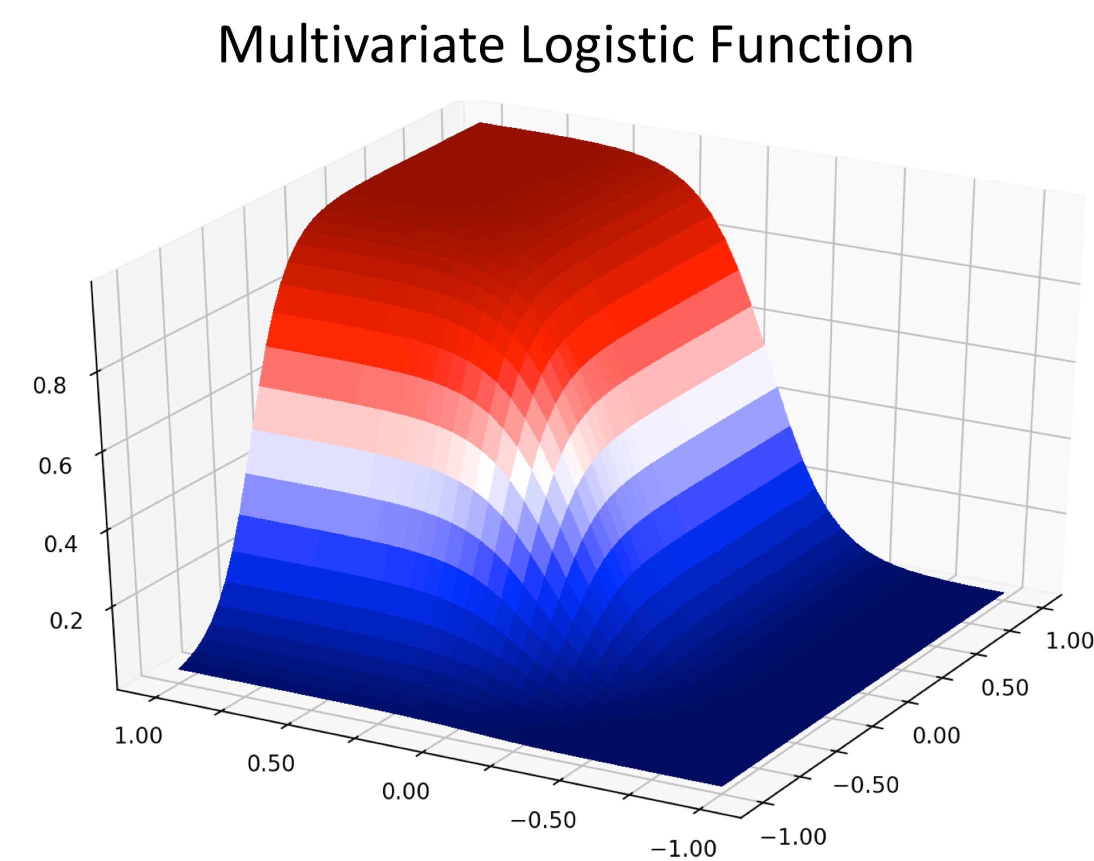
What about the functions discovered by deepDMD?

The dominant form is a logistic function:





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The SILL Observable Function:

Define the state inclusive logistic lifting **(SILL)** function:

$$\Lambda_{v_l}(x) \equiv \prod_{i=1}^{n} \lambda_{\mu_i}(x_i) \quad \text{where} \quad \lambda_\mu(x) \equiv \frac{1}{1+e^{-\alpha(x-\mu)}}$$

$$\psi(x) \equiv \begin{bmatrix} 1 \\ x \\ \Lambda \end{bmatrix} \quad \text{where} \quad \Lambda = [\Lambda_{v_1}, \Lambda_{v_2}, \ldots, \Lambda_{v_{N_L}}]^T(x)$$

Proposition: If there is a total order on the set of logistic functions

$$\Lambda_{v_1(x)}, \ldots, \Lambda_{v_{N_L}}(x)$$

Then the lifting $\psi(x)$ satisfies finite approximate closure.

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Finite Approximate Closure of the SILL Observable Function:

[Sketch of Proof]

Logistic functions are universal function approximators, therefore,

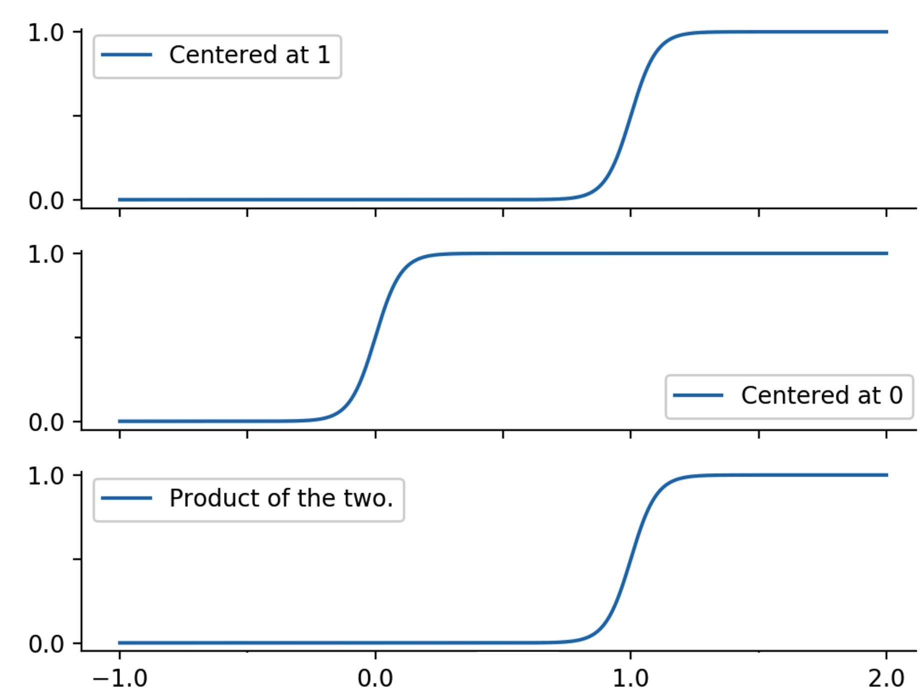
$$f(x) \approxeq \sum_{l=1}^{N_L} \mathbf{w}_l \Lambda_{v_l}(x)$$

The second property needed is closure w.r.t to differentiation and multiplication:

$$\frac{d\Lambda_{\mu_l}}{dt} = \sum_{i=1}^{n} \sum_{k=1}^{N_L} \alpha(1 - \lambda_{\mu_i^l}(x_i)) w_{ik} \Lambda_{v_l}(x) \Lambda_{v_k}(x)$$

$$\approxeq \sum_{i=1}^{n} \sum_{k=1}^{N_L} \alpha(1 - \lambda_{\mu_i^l}(x_i)) w_{ik} \Lambda_{v_{max}(l,k)}(x)$$

$$v_{max}(l,k) = \left(\max\{\mu_1^l, \mu_1^k\}, \ldots, \max\{\mu_n^l, \mu_n^k\}\right)$$



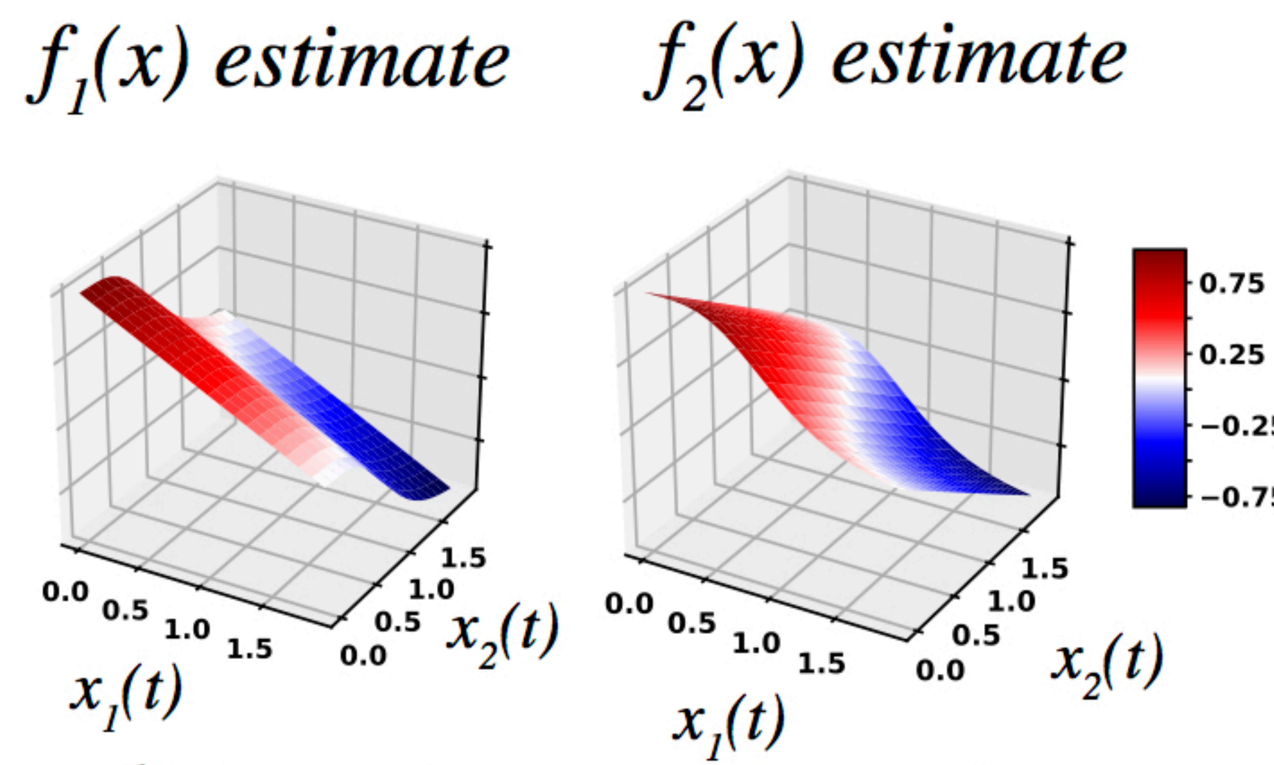
Illustrative Example: SILL Observables to Model Bistable Dynamics

System model:

$$\dot{x}_1 = \frac{\alpha_1}{1 + x_2^{n_1}} - \delta x_1$$
$$\dot{x}_2 = \frac{\alpha_2}{1 + x_1^{n_2}} - \delta x_2$$

x_1 - a repressor protein that represses x_2

x_2 - a repressor protein that represses x_1



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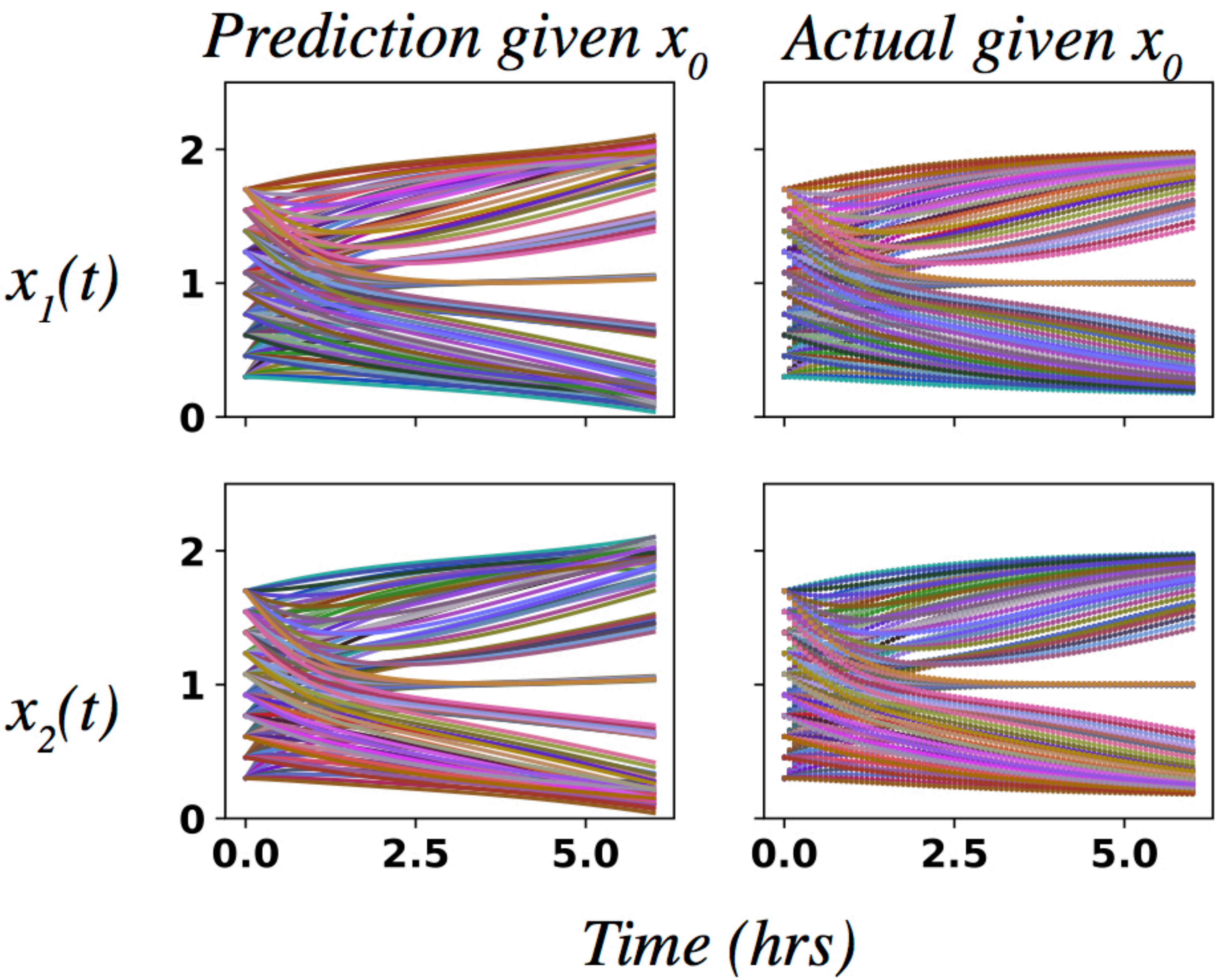
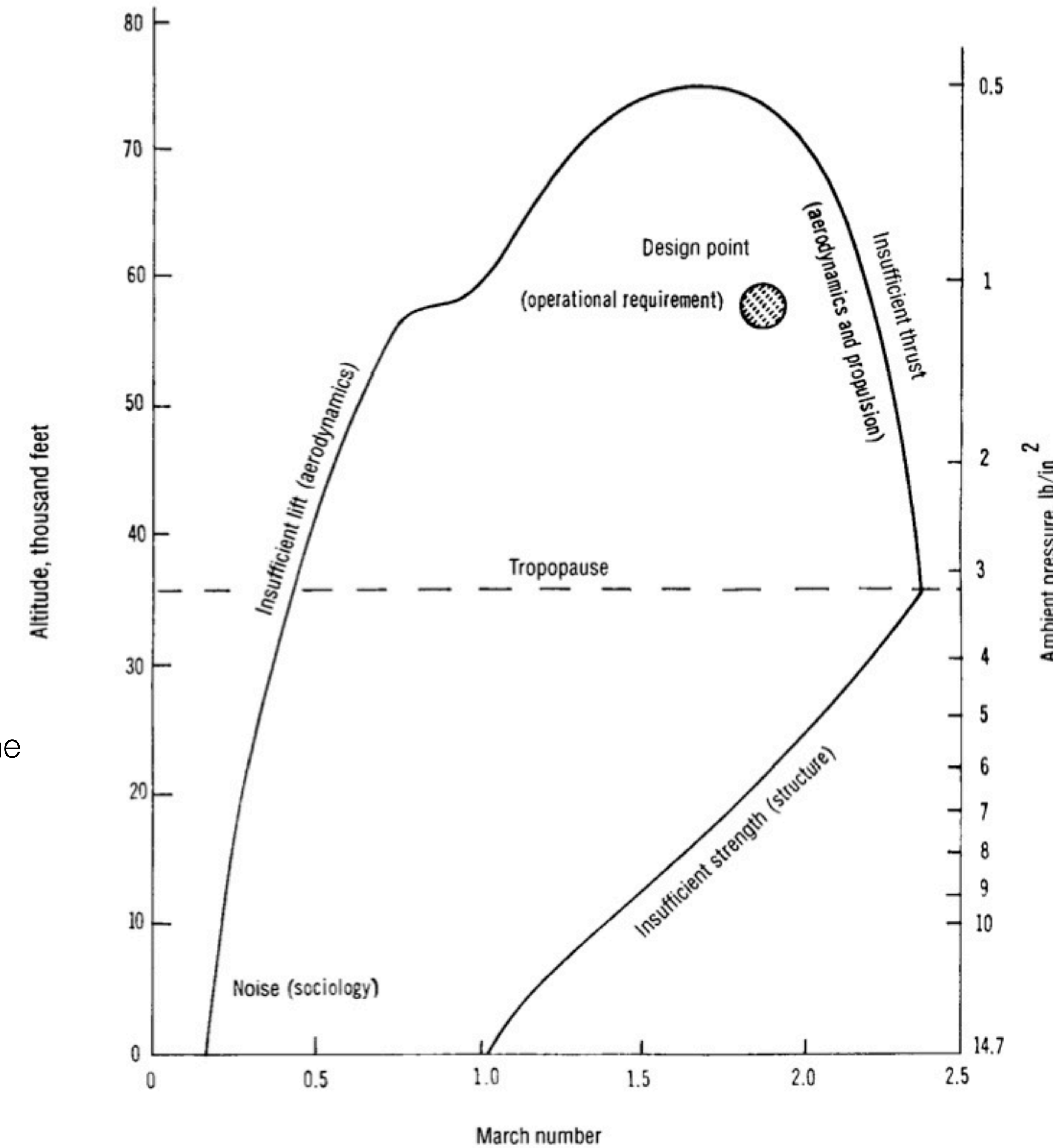


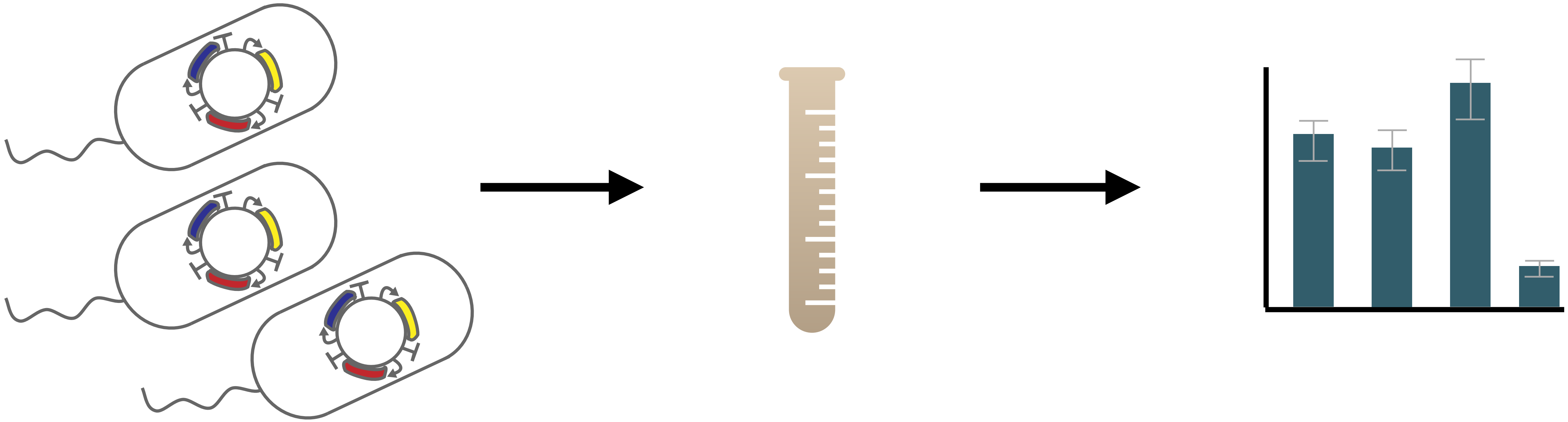
Operational Envelopes Define When and How Engineered Systems Work



- The outline of the envelope defines the limits of performance
- The design point is the target operational point for the airplane (well-insulated from the boundaries).
- Defined operational envelopes enable:
    - **A. Precise metrics for performance,**
    - **B. Index for improved design,**
    - **C. Specialization of design to different applications.**

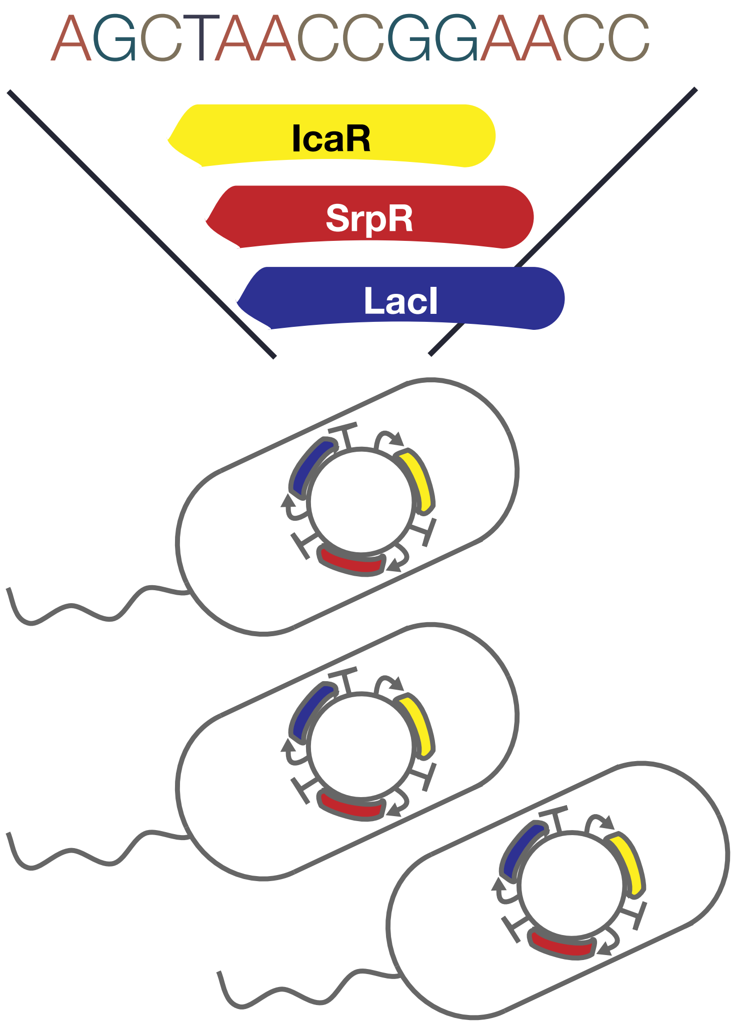
Yeung and Egbert "Discovery of Operational Envelopes for Synthetic Gene Networks" Winter qBio Meeting, 2018

Synthetic Biology Lacks Formal Methods for Defining and Characterizing Operational Envelopes



Yeung and Egbert "Discovery of Operational Envelopes for Synthetic Gene Networks" Winter qBio Meeting, 2018

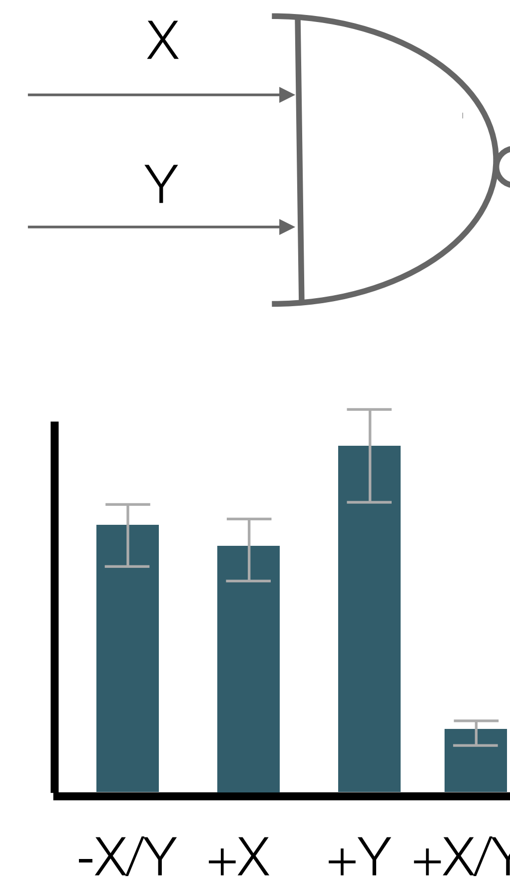
Engineering Novel Biological Function Involves Singleton Characterization (for a *Nature* paper)



Candidate Synthetic Design

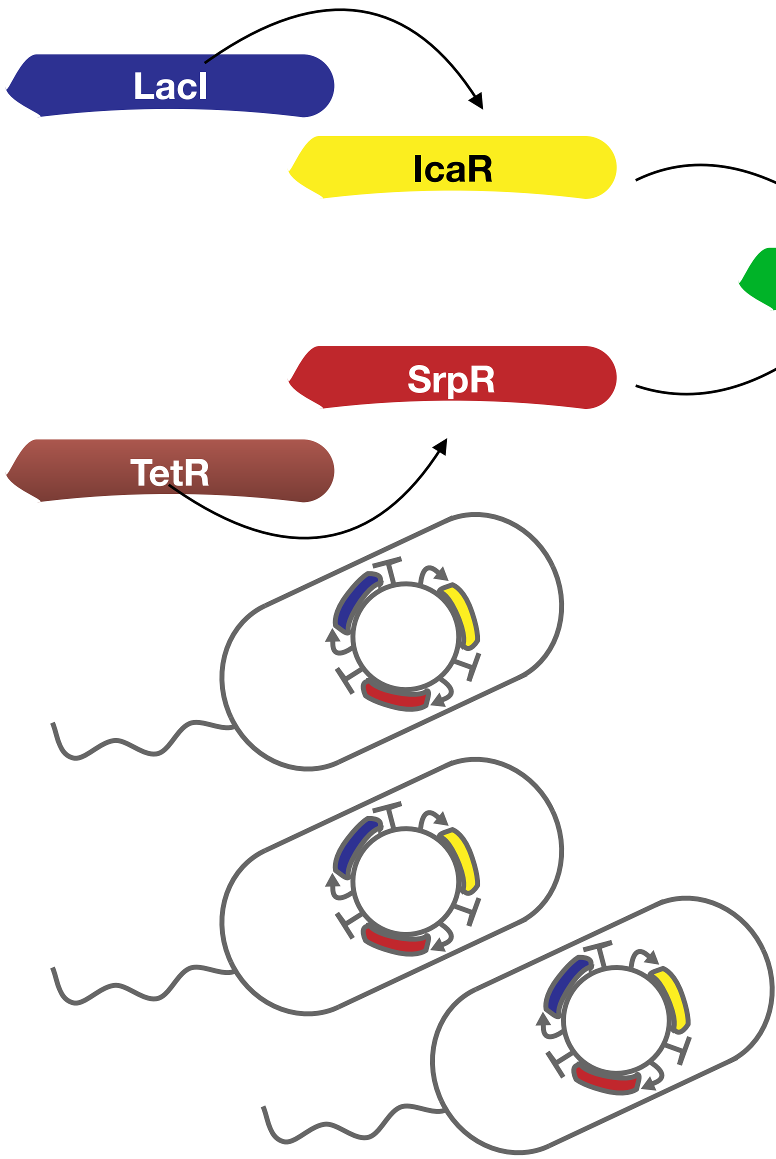
37°C
M9CA
0, 100 mM [X]
0, 100 mM [Y]
in MG1655Z1

Restricted Culturing Specifications



Functional Characterization of a Narrow Operating Condition

Discovering a Genetic Circuit's Operational Envelope Requires Robustness Characterization with ***Variables Independent of Design***



37°C
M9CA
0, 100 mM [X]
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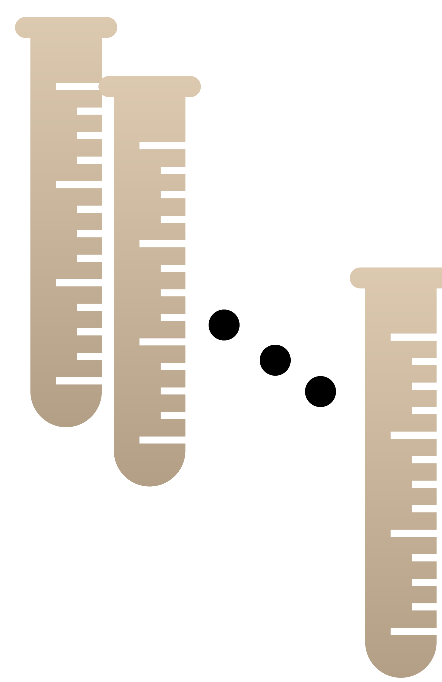
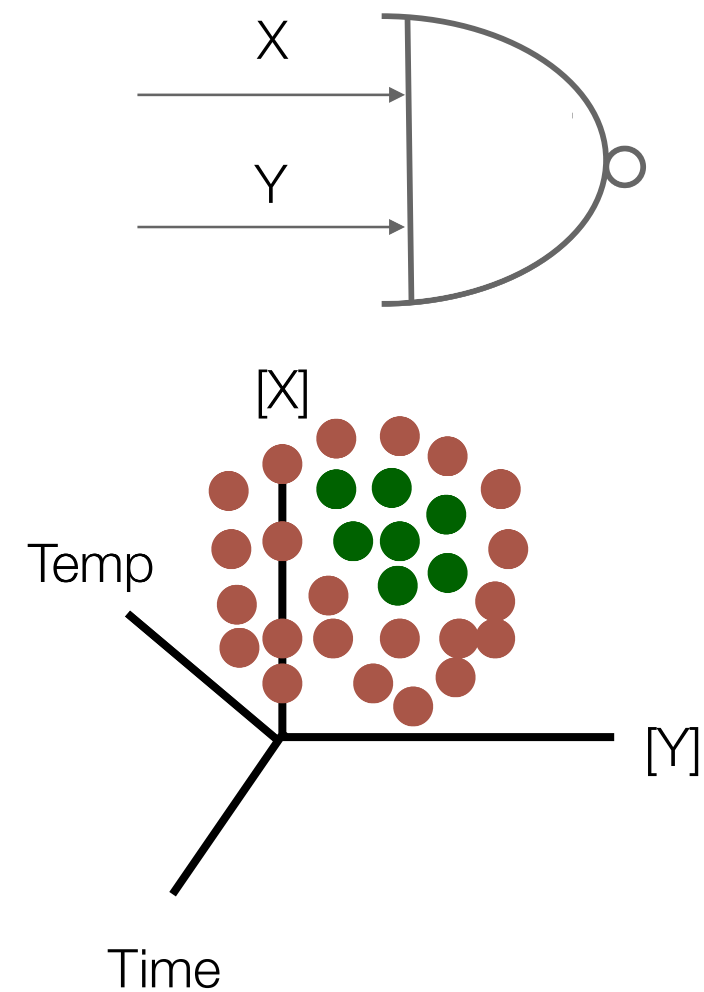
In MG1655Z1



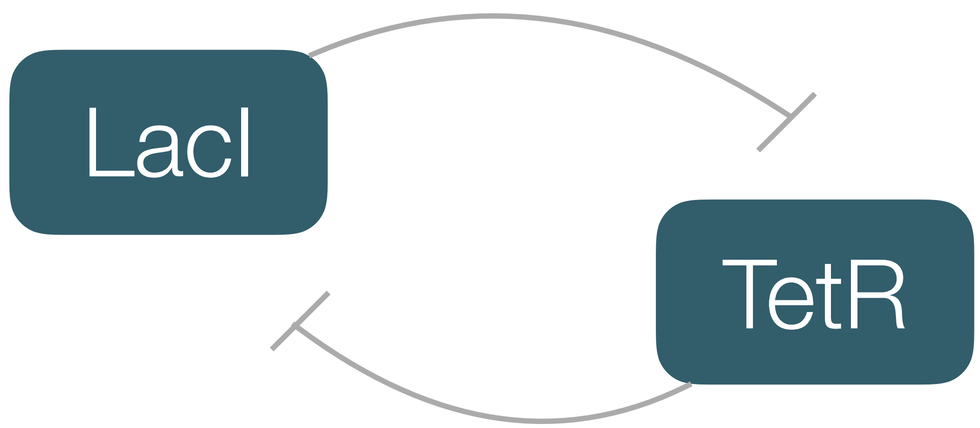


Proof-of-Concept Synthetic Design

Broad Culturing Specifications

Characterization of Operational Envelope

Discovering the Operational Envelope of the Genetic Toggle Switch



The Genetic Toggle Switch

[IPTG] > [aTc] → TetR (RFP) > LacI (GFP)

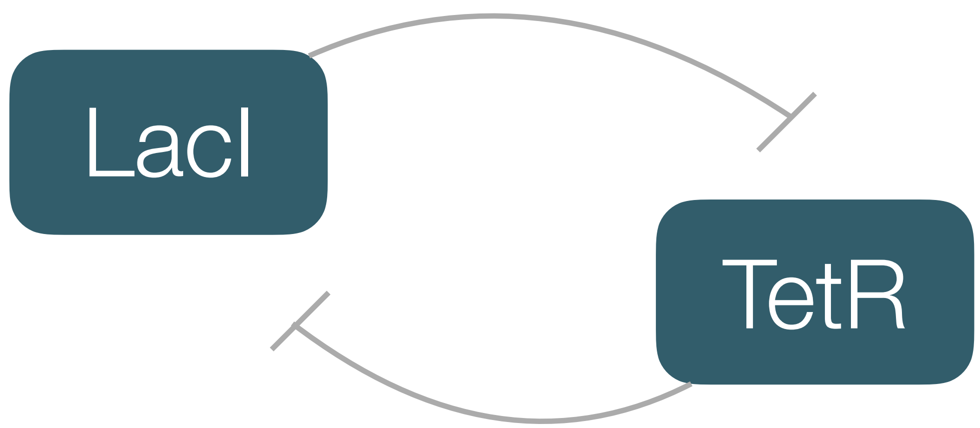
[aTc] > [IPTG] → LacI (GFP) > TetR (RFP)

Performance Specification

What are the conditions under which the toggle switch meets this specification?

- What temperatures?
- What range of input concentrations [IPTG], [aTc]?
- How soon and for how long (experimental time)?

Canonical Models for the Toggle Switch Are Underfitted & Context-Dependent



The Genetic Toggle Switch

$$\frac{du}{dt} = \frac{\alpha_1}{1+v^{\beta}} - u$$

$$\frac{dv}{dt} = \frac{\alpha_2}{1+u^{\gamma}} - v$$

Gardner-Collins Model

$$\mathrm{p_{Lac}} + \mathrm{LacI} \underset{k_r^L}{\overset{k_b^L}{\rightleftharpoons}} \mathrm{DNA{:}LacI} \qquad \mathrm{p_{Tet}} + \mathrm{TetR} \underset{k_r^T}{\overset{k_b^T}{\rightleftharpoons}} \mathrm{DNA{:}TetR}$$

$$\mathrm{p_{Lac}} \xrightarrow{k_{TX}} p_{Lac} + m_{TetR} \qquad \mathrm{p_{Tet}} \xrightarrow{k_{TX}} p_{Tet} + m_{LacI}$$

$$\mathrm{m_{TetR}} \xrightarrow{k_{TL}} m_{TetR} + TetR \qquad \mathrm{m_{LacI}} \xrightarrow{k_{TL}} m_{LacI} + LacI$$

$$\mathrm{m_{TetR}} \xrightarrow{\delta_m} \emptyset \qquad \mathrm{m_{LacI}} \xrightarrow{\delta_m} \emptyset$$

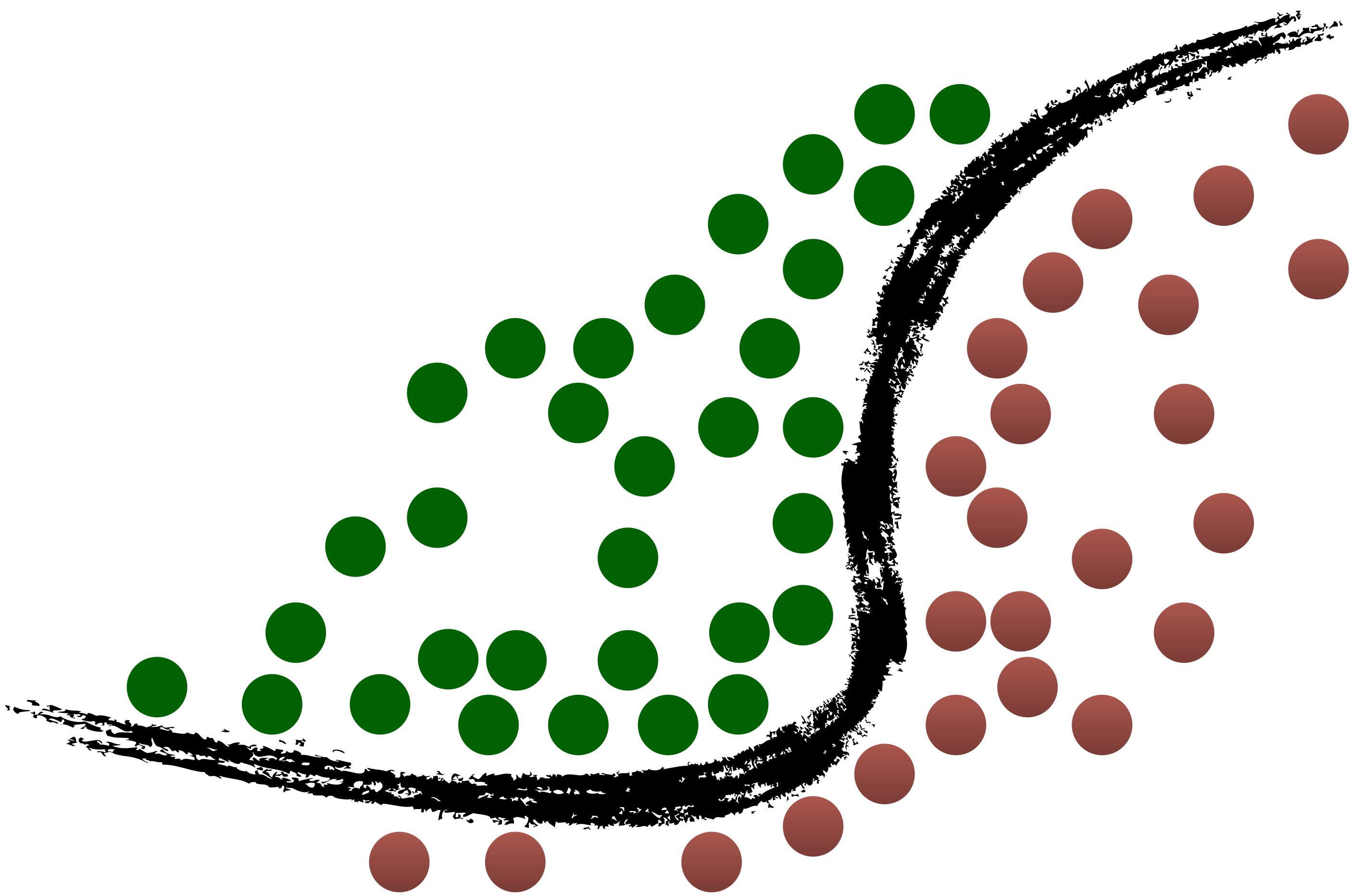
$$\mathrm{TetR} \xrightarrow{\delta_p} \emptyset \qquad \mathrm{LacI} \xrightarrow{\delta_p} \emptyset$$

Bilinear Mass Action Model

$$\begin{aligned}\sum_{x\in\mathcal{X}} \gamma_i(x)\frac{d}{dt}P(X(t)=x)) &= \frac{d}{dt}\mathbb{E}\left[\gamma_i(X(t))\right] \\ &= \sum_{x\in\mathcal{X}} \gamma_i(x)\left(\sum_{j=1}^{m}\alpha_j(x-\xi_j)P(X(t)=x-\xi_j)\right. \\ &\qquad \left. - \sum_{j=1}^{m}\alpha_j(x)P(X(t)=x)\right).\end{aligned}$$

Chemical Master Equation Model

What system variables determine the boundary of the operational envelope for a synthetic gene circuit?



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Input-Koopman Operators To Model The Effect of Experimental Conditions on A Synthetic Gene Network

Consider a system of the form:

$$x_{t+1} = F(x_t, w_t)$$

Assumptions:

1) $F(x_t, w_t)$ is analytic,
2) w_t are memoryless and independent of x_t

Conclusion:

There exists an input-Koopman representation for the system of the form:

$$\psi_x(x_{t+1}) = K_x \psi_x(x_t) + K_u \psi_u(u_t)$$

where u_t is a vector function consisting of univariate terms in w_t and multivariate w_t, x_t terms.

Yeung, Liu, Kundu, Hodas. "A Koopman Operator Approach for Computing and Balancing Gramians for Discrete Time Systems" in the Proceedings of the IEEE ACC (2017)

Modeling the Action of Inputs: A *Nonlinear* Master Equation Model for the Toggle Switch

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Two-State Toggle Switch Model

$$\dot{P}(x_1(t), x_2(t)) = \mathbf{A}P(x_1(t), x_2(t))$$

$$[\mathbf{A}]_{rc} \equiv \begin{cases} a_i(z_r = z_c - \xi_i) & \text{if } \exists i \in \{1, ..., m\} \text{ s.t. } z_r = z_c - \xi_i \\ -a_i(z_r = z_c) & \text{if } r = c \\ 0 & \text{otherwise.} \end{cases}$$

Toggle Switch Model with Inputs for Temperature & Chemical Inducers

$$\dot{P}(X(t), U(t)) = \mathbf{A}(\theta)P(X, U)$$

$$[\mathbf{A}]_{rc} \equiv \begin{cases} a_i(z_r = z_c - \xi_i, \theta) & \text{if } \exists i \in \{1, ..., m\} \text{ s.t. } z_r = z_c - \xi_i \\ -a_i(z_r = z_c, \theta) & \text{if } r = c \\ 0 & \text{otherwise.} \end{cases}$$

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Modeling the Action of Inputs: A *Nonlinear* Master Equation Model for the Toggle Switch

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Toggle Switch Model with Inputs for Temperature & Chemical Inducers

$$\dot{P}(X(t), U(t)) = \mathbf{A}(\theta)P(X, U)$$

$$\sum_{(x,u)\in\mathcal{X}} \gamma(x)\dot{P}(X, U) = \sum_{(x,u)\in\mathcal{X}} \gamma(x)\mathbf{A}(\theta, x)P(X, U)$$

$$\frac{d}{dt}\mathbb{E}_{P_t}\left[\gamma(x)\right] = \mathbb{E}_{P_t}\left[\gamma(x)\mathbf{A}(\theta, x)\right]$$

or more precisely . . .

$$\begin{aligned}\frac{d}{dt}\mathbb{E}_{P_t}\left[\gamma(x)\right] &= \sum_{(x,u)\in\mathcal{X}} \gamma(x)\left(\sum_{j=1}^{m} a_j(x-\xi_j, \theta)P\left(\begin{bmatrix}X(t)\\U(t)\end{bmatrix} = \begin{bmatrix}x\\u\end{bmatrix} - \xi_j\right) - \sum_{j=1}^{m} a_j(x, \theta)P\left(\begin{bmatrix}X(t)\\U(t)\end{bmatrix} = \begin{bmatrix}x\\u\end{bmatrix}\right)\right)\\ &= F(x(t), u(t), \theta)\end{aligned}$$

Yeung and Egbert "Discovery of Operational Envelopes for Synthetic Gene Networks" Winter qBio Meeting, 2018

Modeling the Action of Inputs: A *Nonlinear* Master Equation Model for the Toggle Switch

Toggle Switch Moment-Based Model with Inputs for Temperature & Chemical Inducers

$$\frac{d}{dt}\mathbb{E}_{P_t}\left[\gamma(x)\right] = \mathbb{E}_{P_t}\left[\gamma(x)\mathbf{A}(\theta, x)\right]$$

The input-Koopman equation is given by:

$$\psi_x(\mathbb{E}_{P_t}\left[\gamma(x)(t+\delta t)\right]) = K_x\psi_x(\gamma(x(t))) + K_u\psi_u(u(t), \theta)$$

We aim to discover the distribution moment dynamics of the form:

$$\Gamma(x) = (x_1, x_2, (x_1-\mu_1)(x_2-\mu_2), (x_1-\mu_1)^2, (x_2-\mu_2)^2)$$

Discovering the Operational Envelope of the Genetic Toggle Switch

Glycerol stock of optimized toggle switch

Overnight recovery (37 C)

Diluted to and maintained at OD 0.02 across 64 conditions, for 12 doubling times, for 3 different temperatures

Cell quenching and storage at 4C

Flow cytometry analysis

Time series data of 10,000 flow events x 3 different temperatures x 64 IPTG and aTc concentrations

Discovering the Operational Envelope of the Genetic Toggle Switch

Discovering the Operational Envelope of the Genetic Toggle Switch

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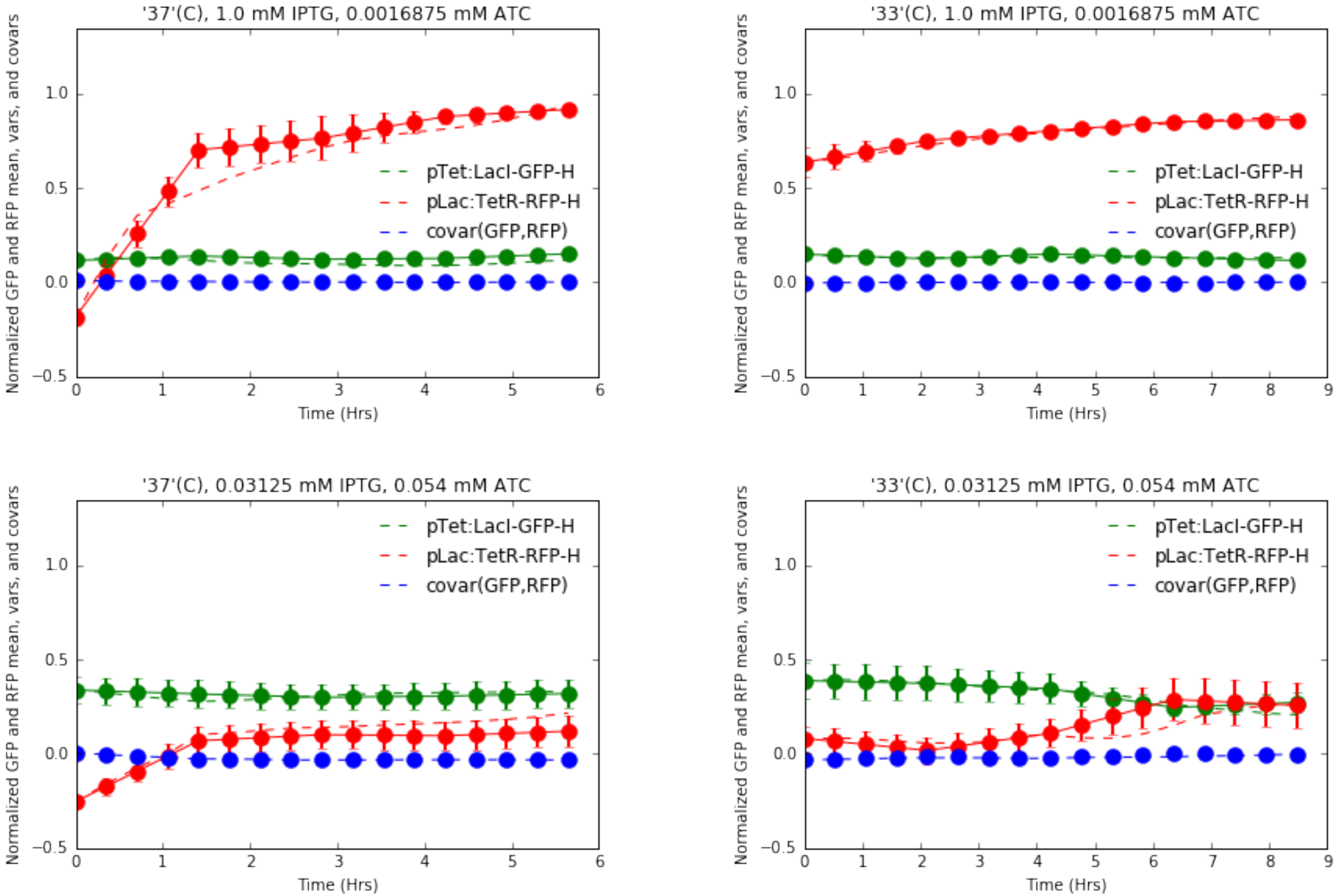
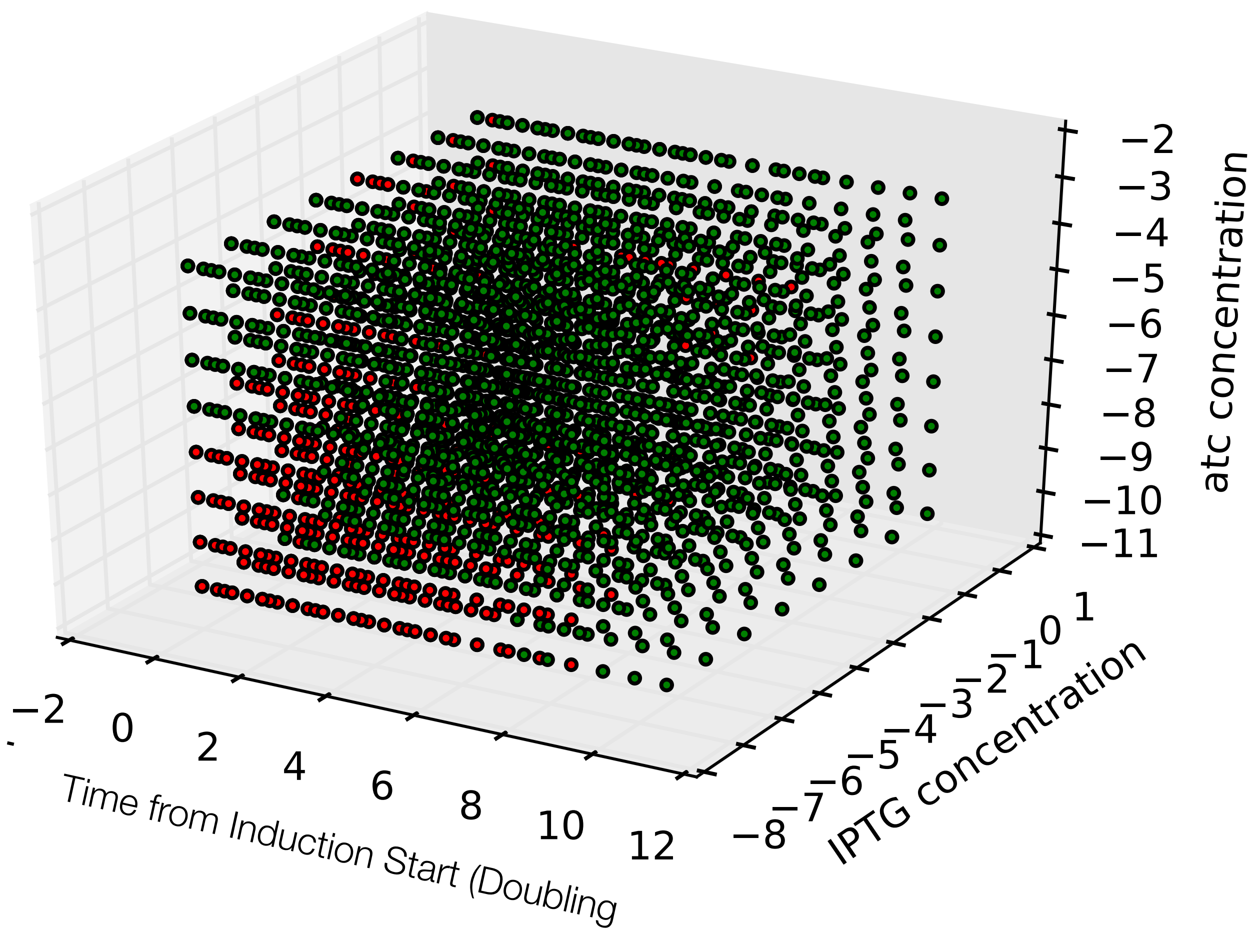
Deep Koopman Operators of Moment Dynamics: Forecasting with Learned Models

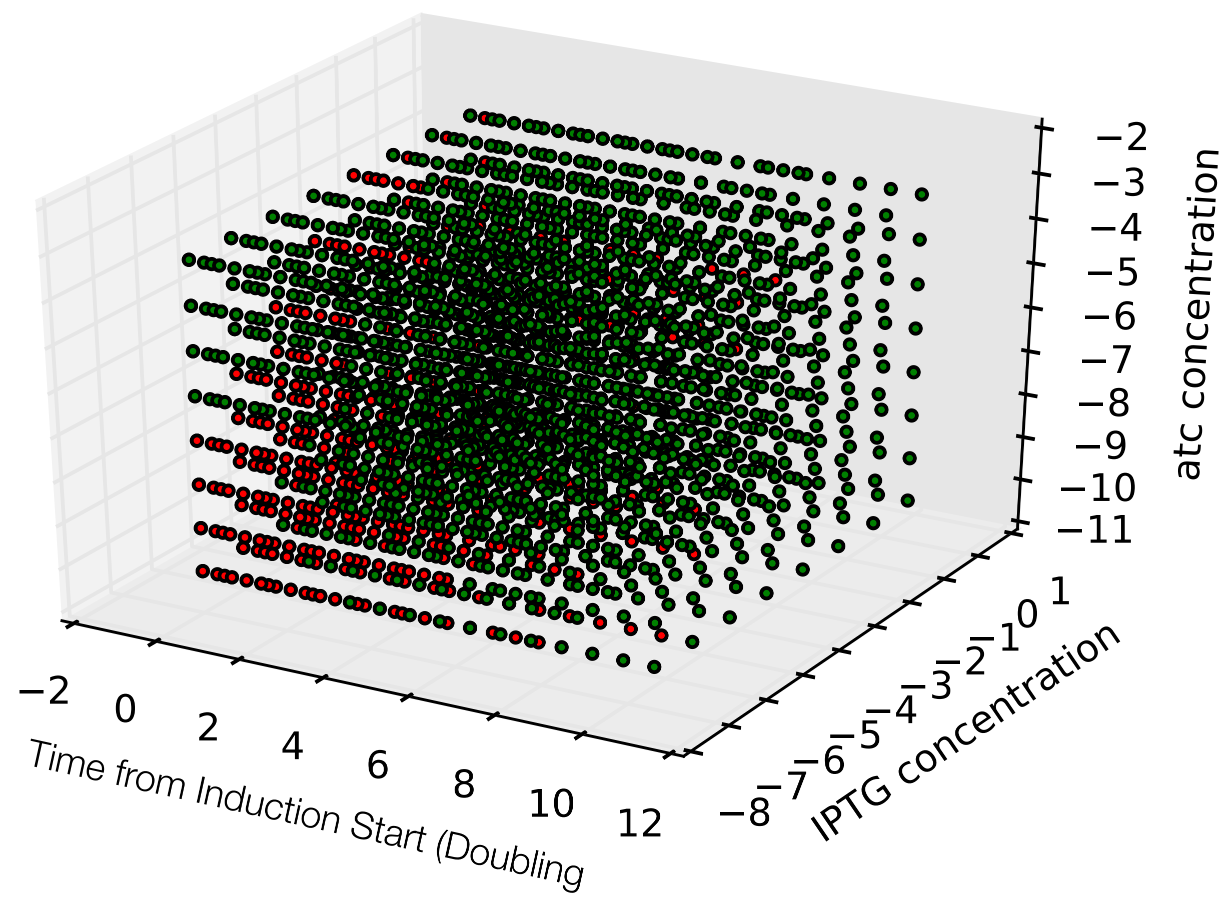


Discovering the Operational Envelope of the Genetic Toggle Switch (Training & Test Data)

Predicted



Actual



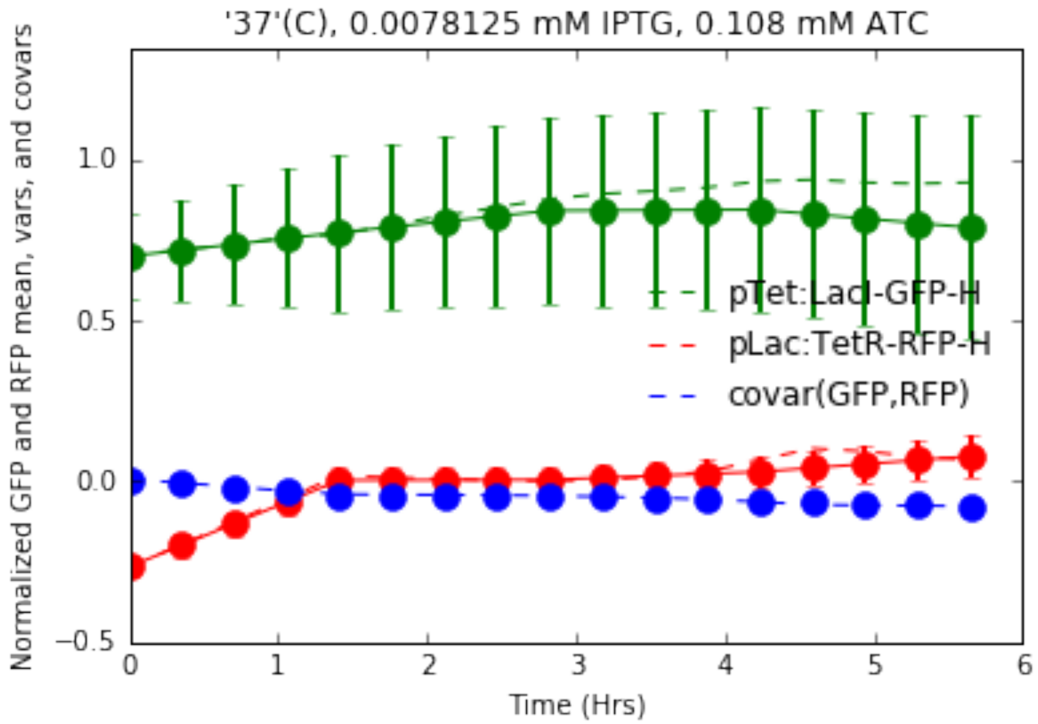
[IPTG] > [aTc] → TetR (RFP) > LacI (GFP)

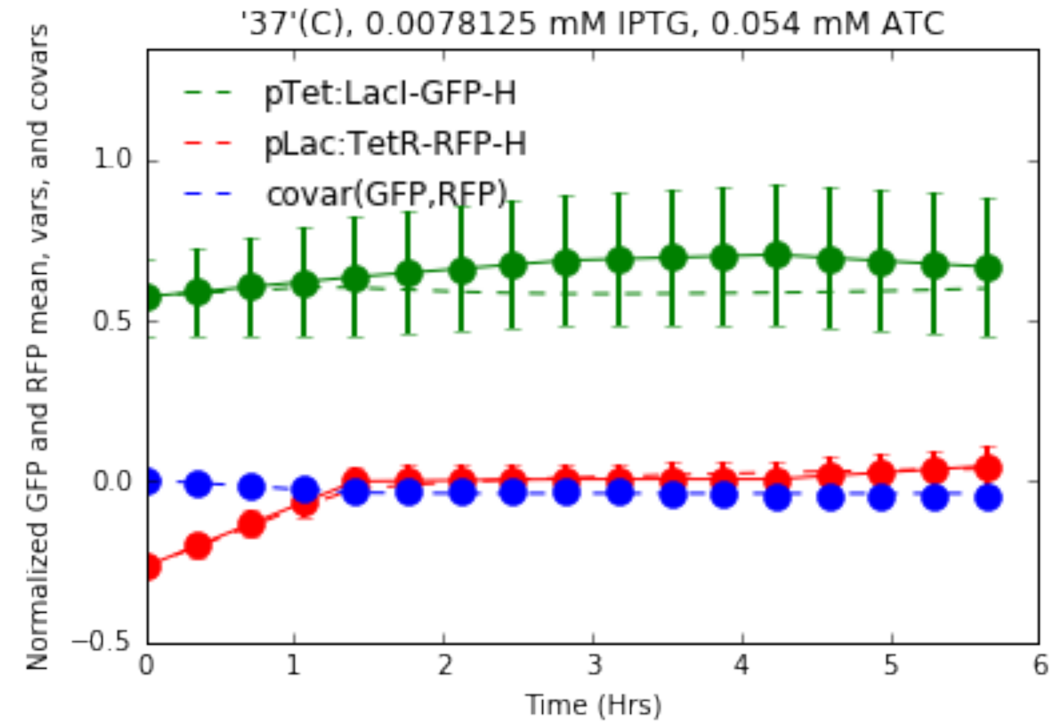
[aTc] > [IPTG] → LacI (GFP) > TetR (RFP)

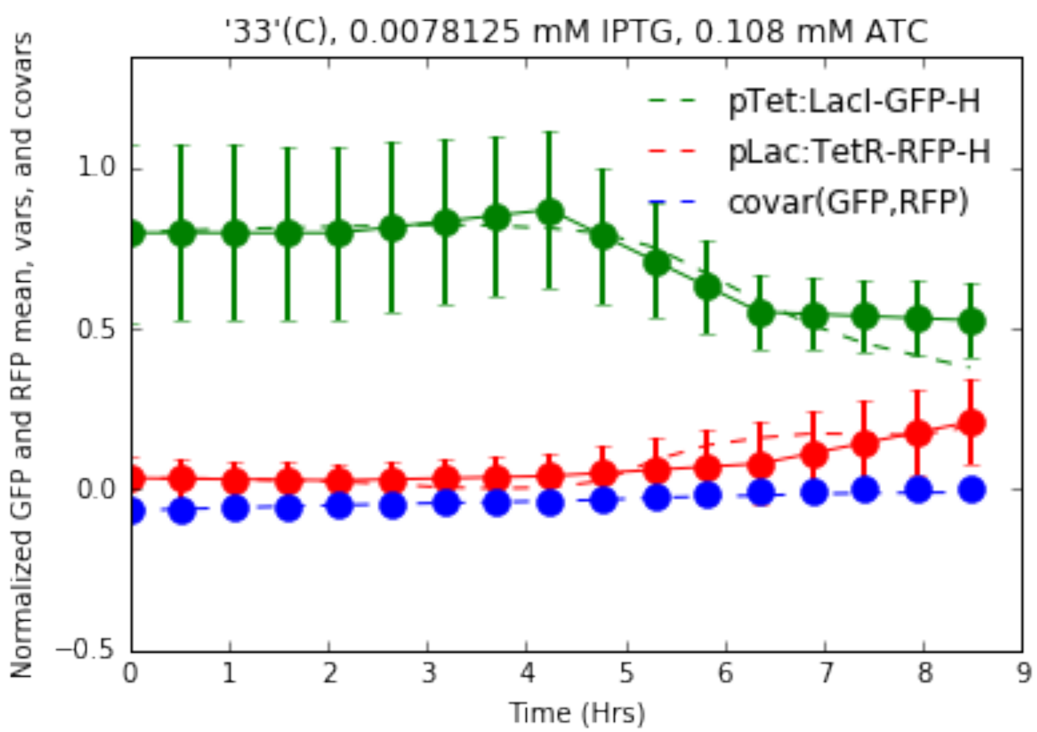
Performance Specification

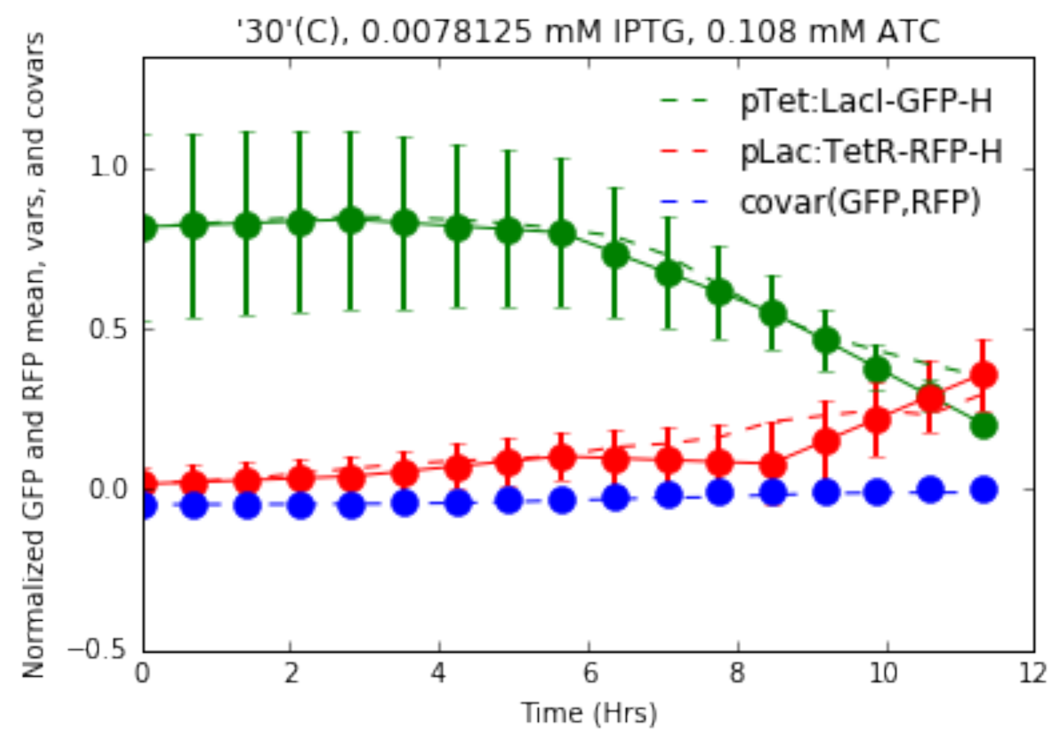
	Predicted	Actual
Functional	2428	2440
Dysfunctional	644	632

Deep Koopman Operators of Moment Dynamics: Discovery of High-Noise and State Flipping Modes









Discovering & Defining Operational Envelopes in Synthetic Biology