

From Genetic Feedback Control to AI-Designed Biomolecular Networks

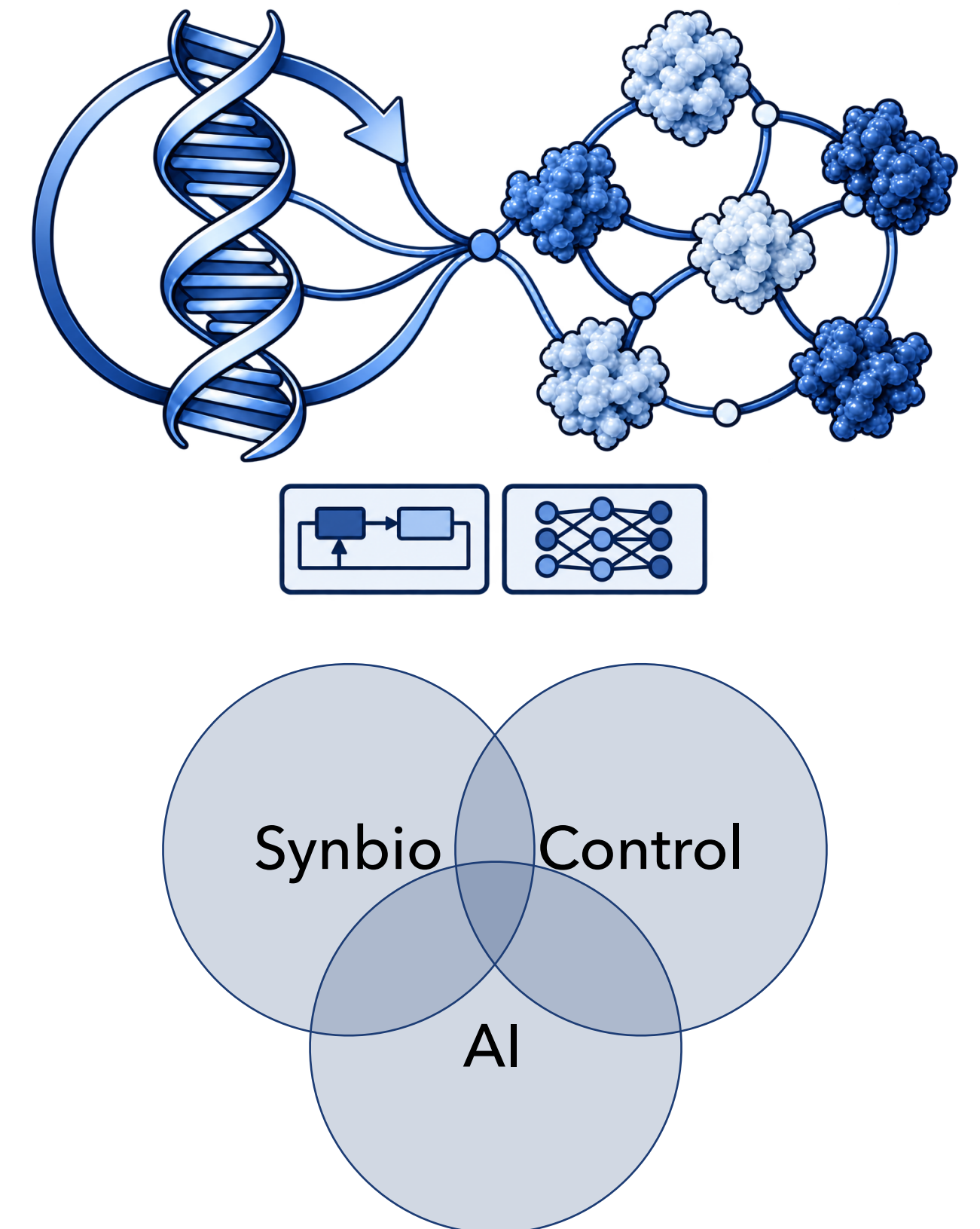
Maurice Filo

Assistant Professor, Department of Engineering



UNIVERSITY OF
CAMBRIDGE

Division F Conference, October 2026



What is synthetic biology?

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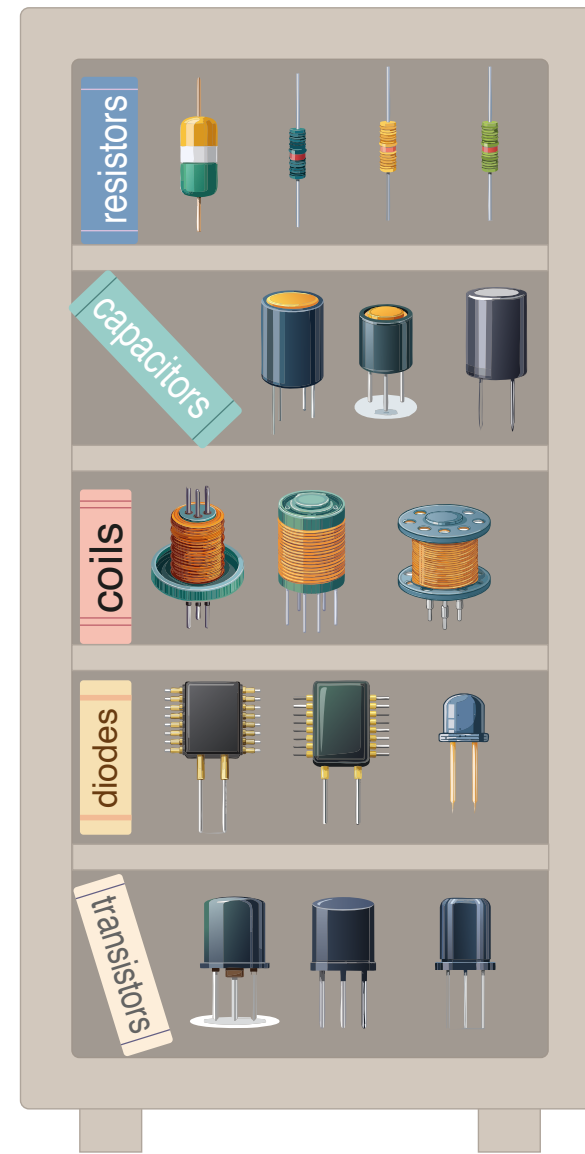
Goal:

Build an
electric
device to
perform a
function

What is synthetic biology?

Goal: Parts Library

Build an **electric** device to perform a function

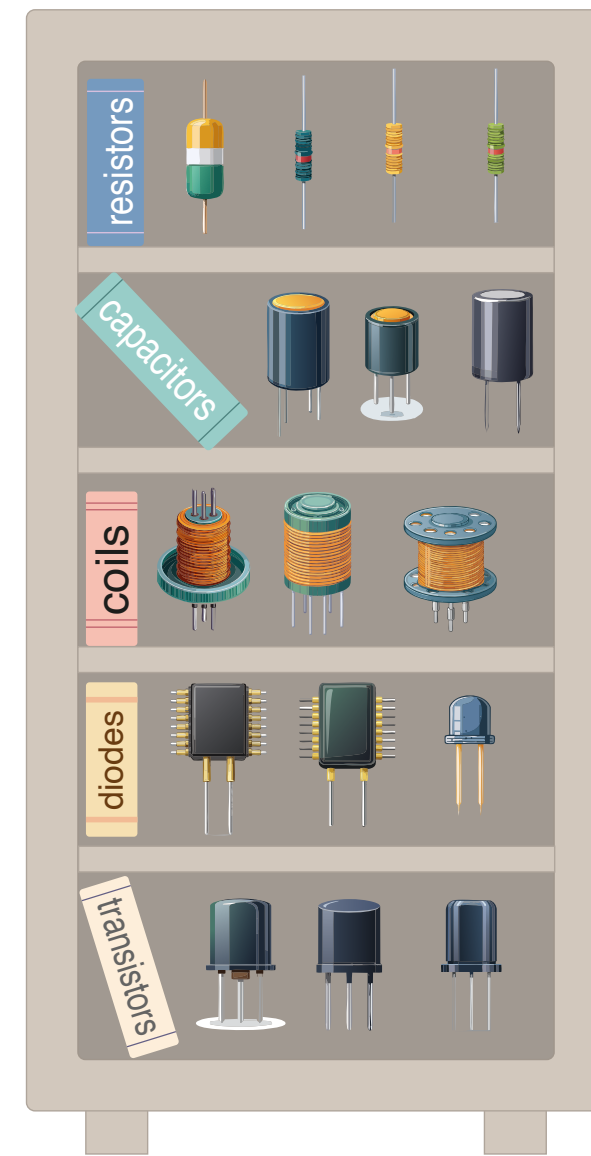


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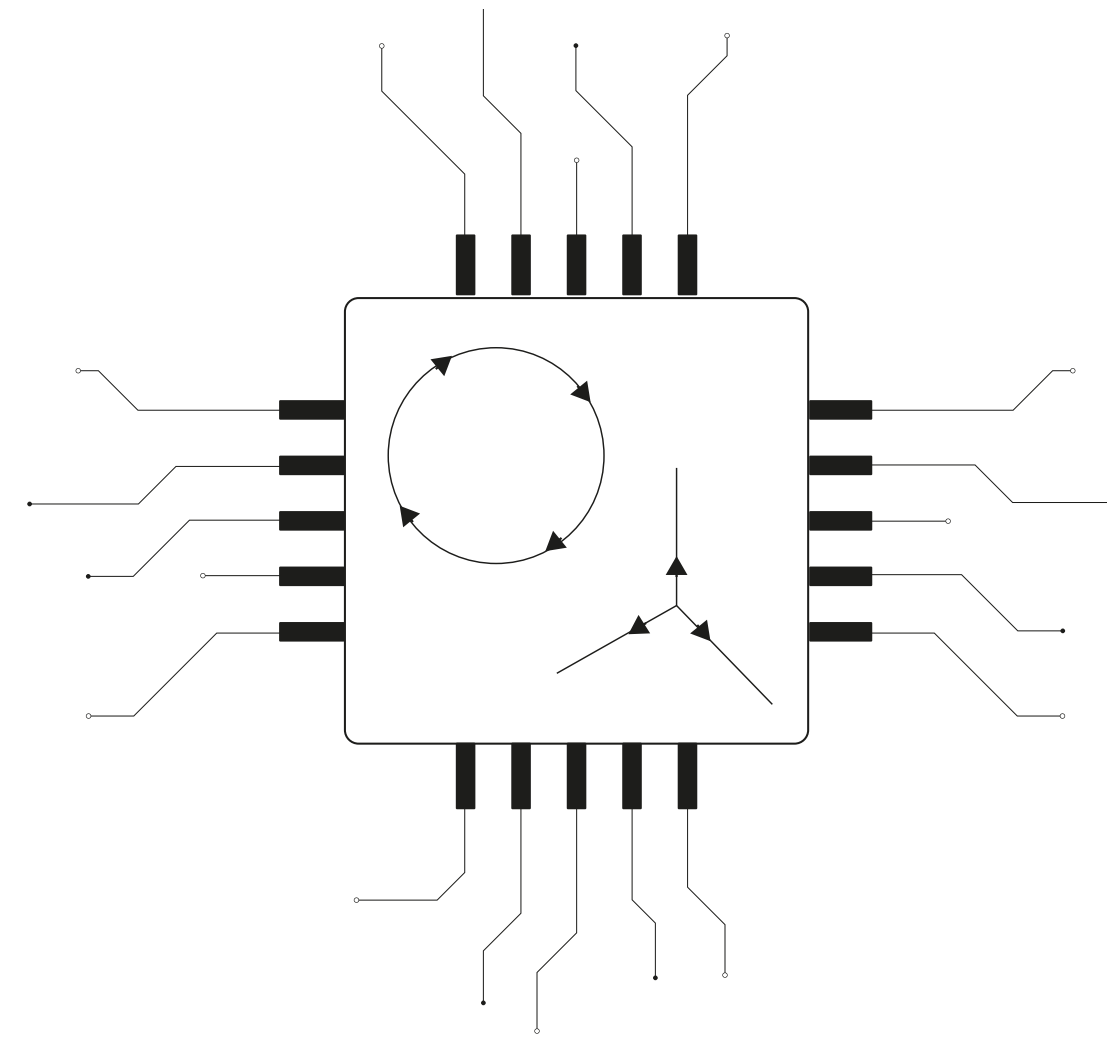
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Parts Library



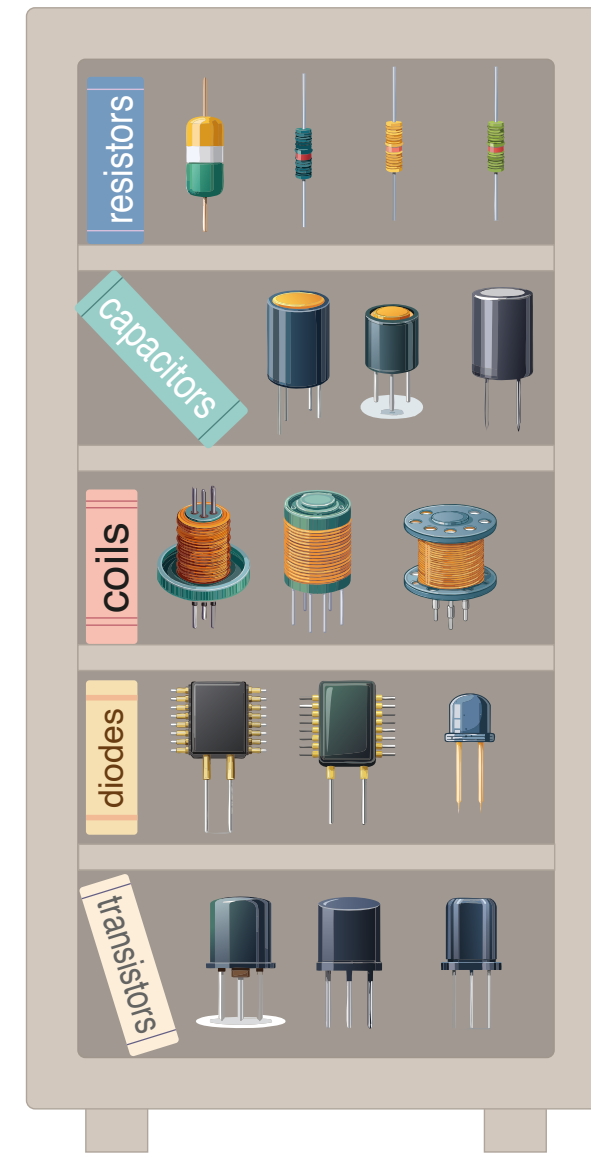
Circuit Theory



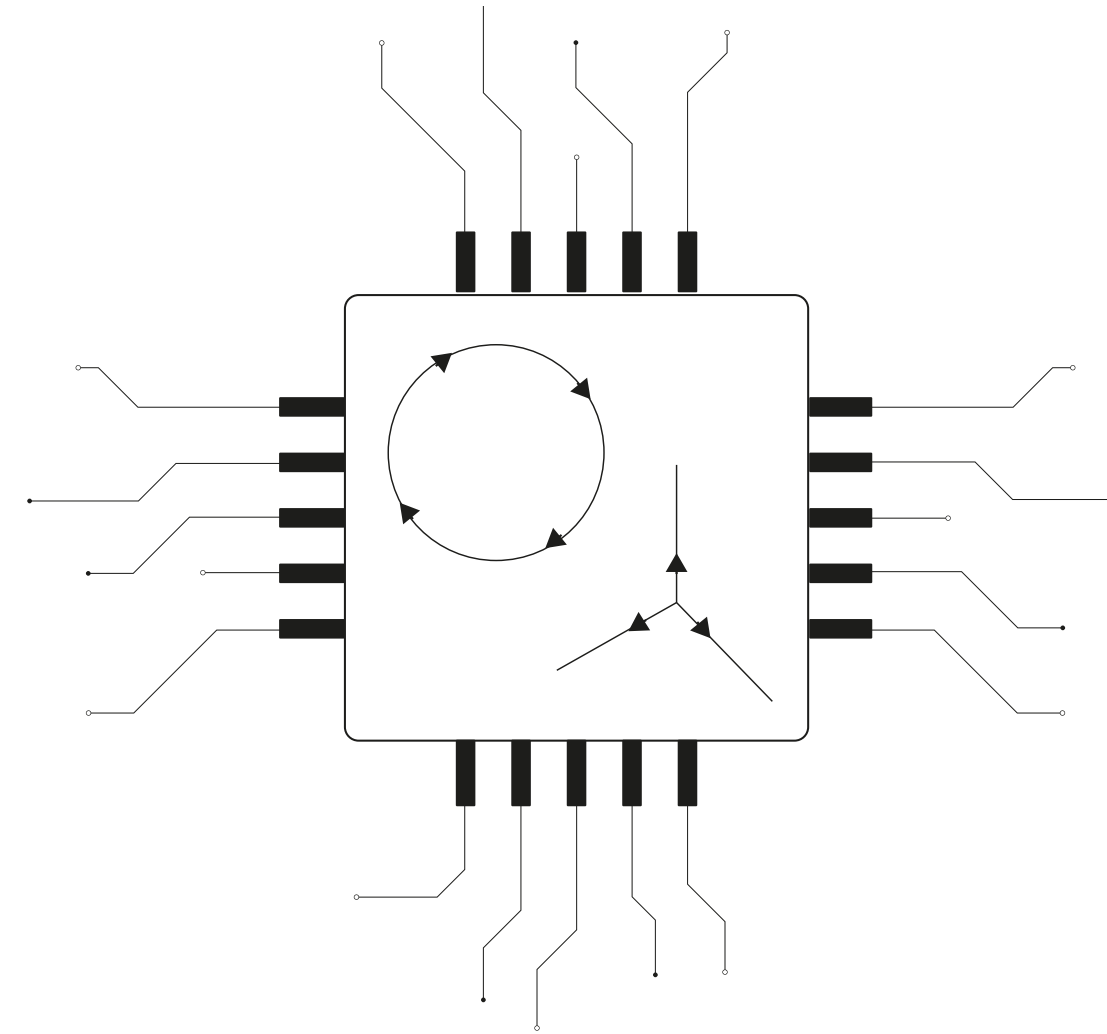
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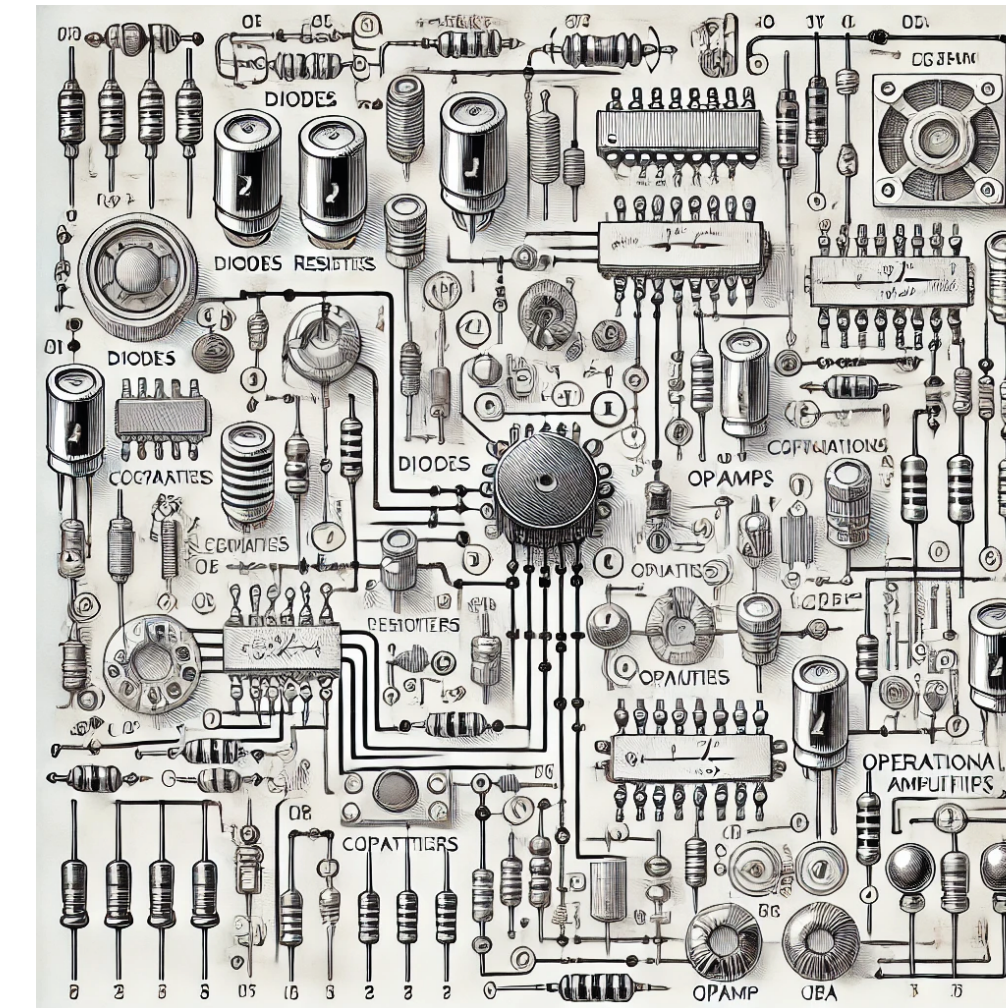
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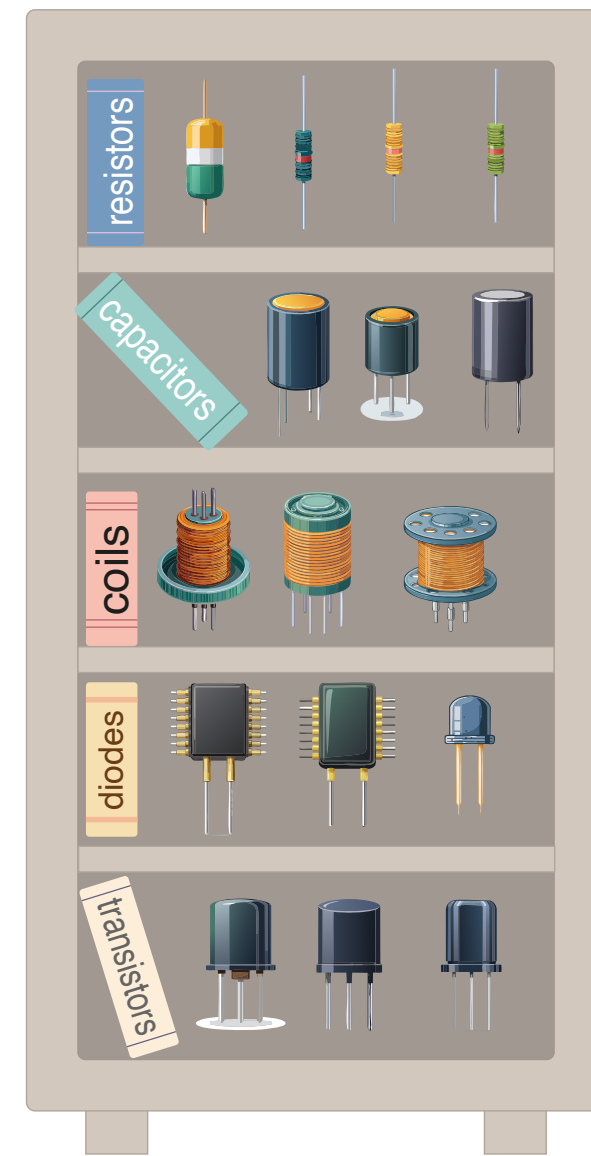
Electric Circuit



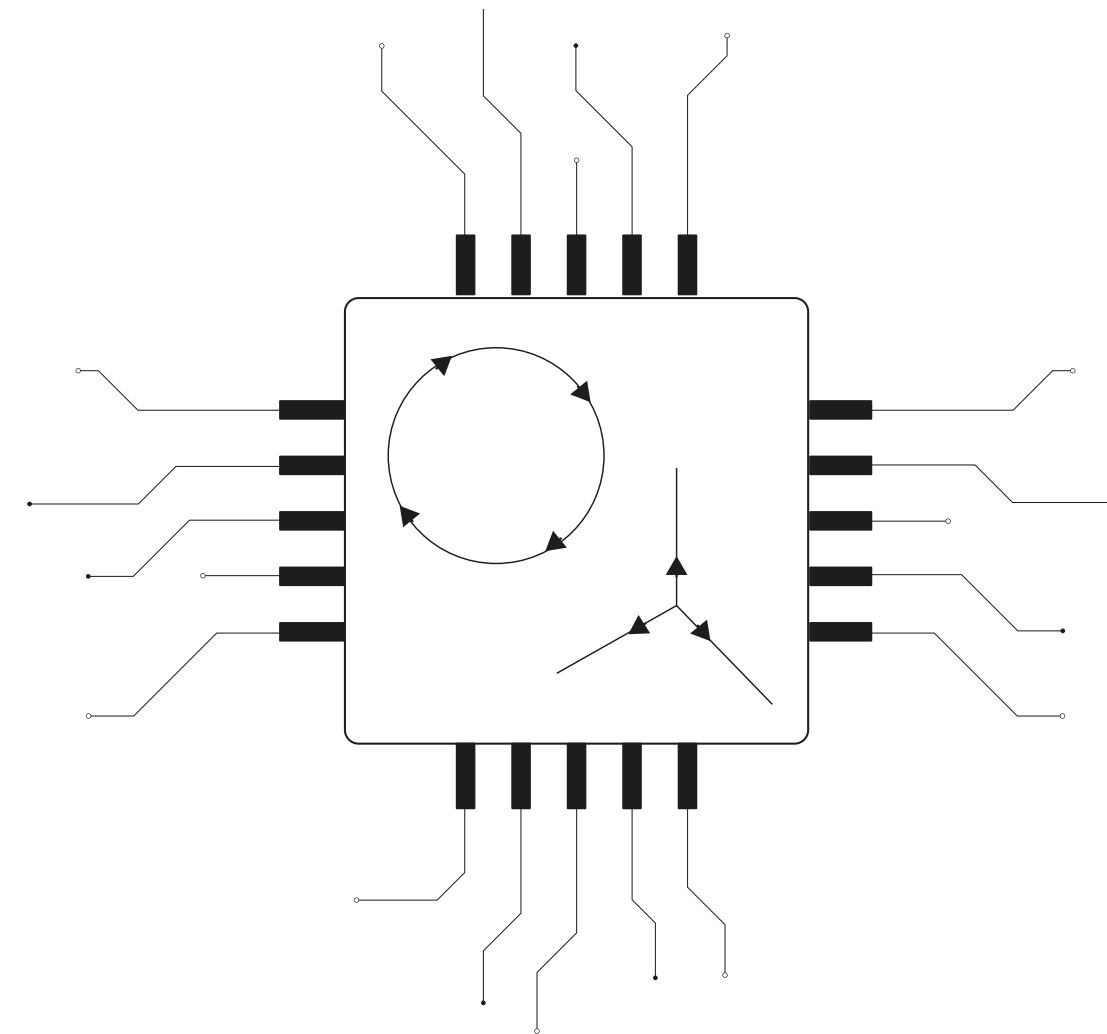
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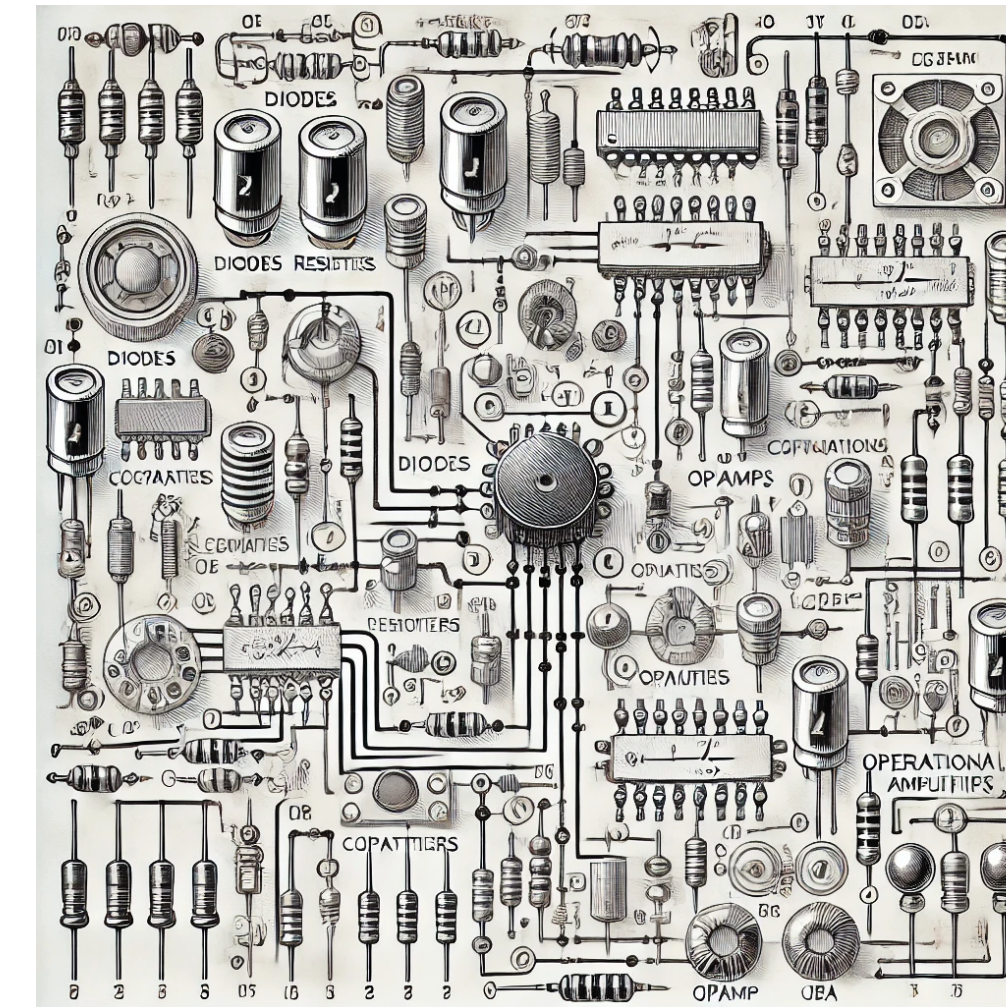
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Circuit Theory



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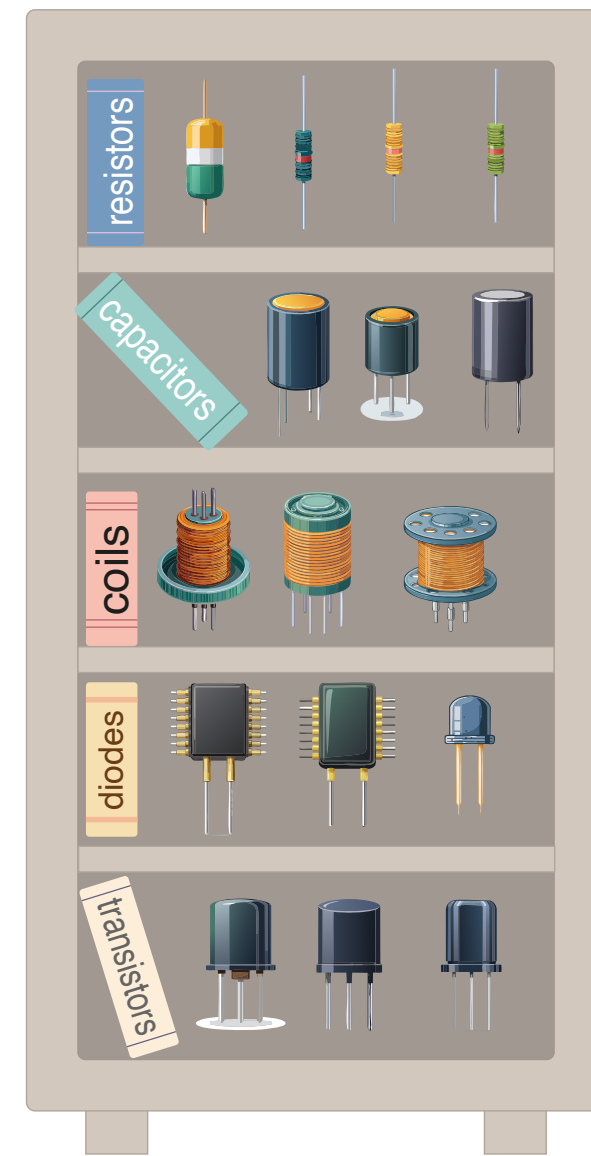


Build an **biological** device **inside the cell** to perform a function

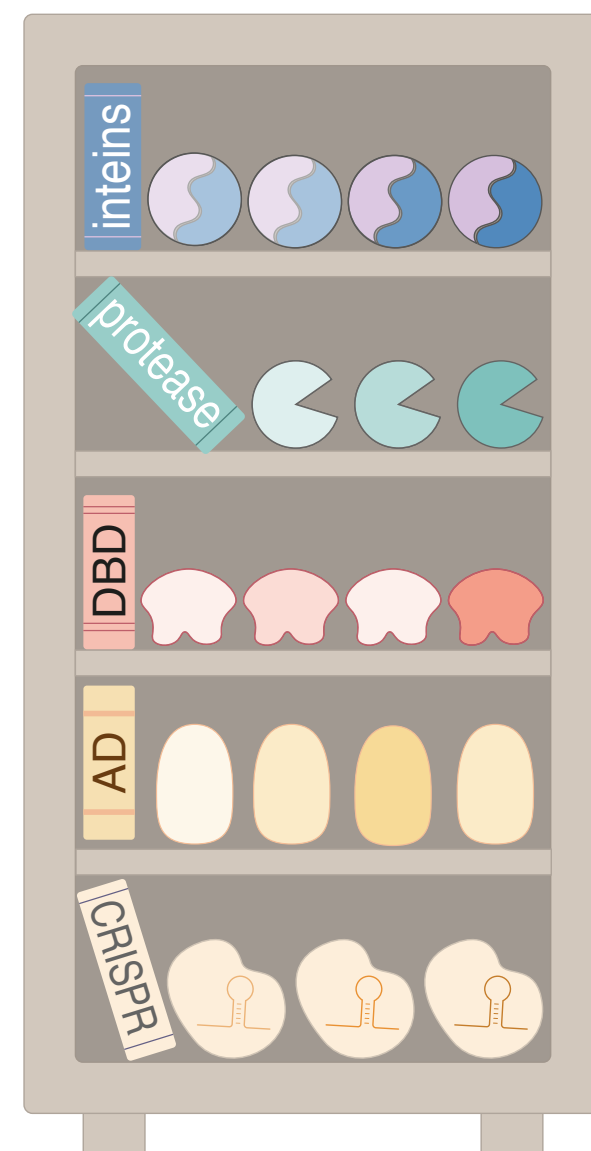
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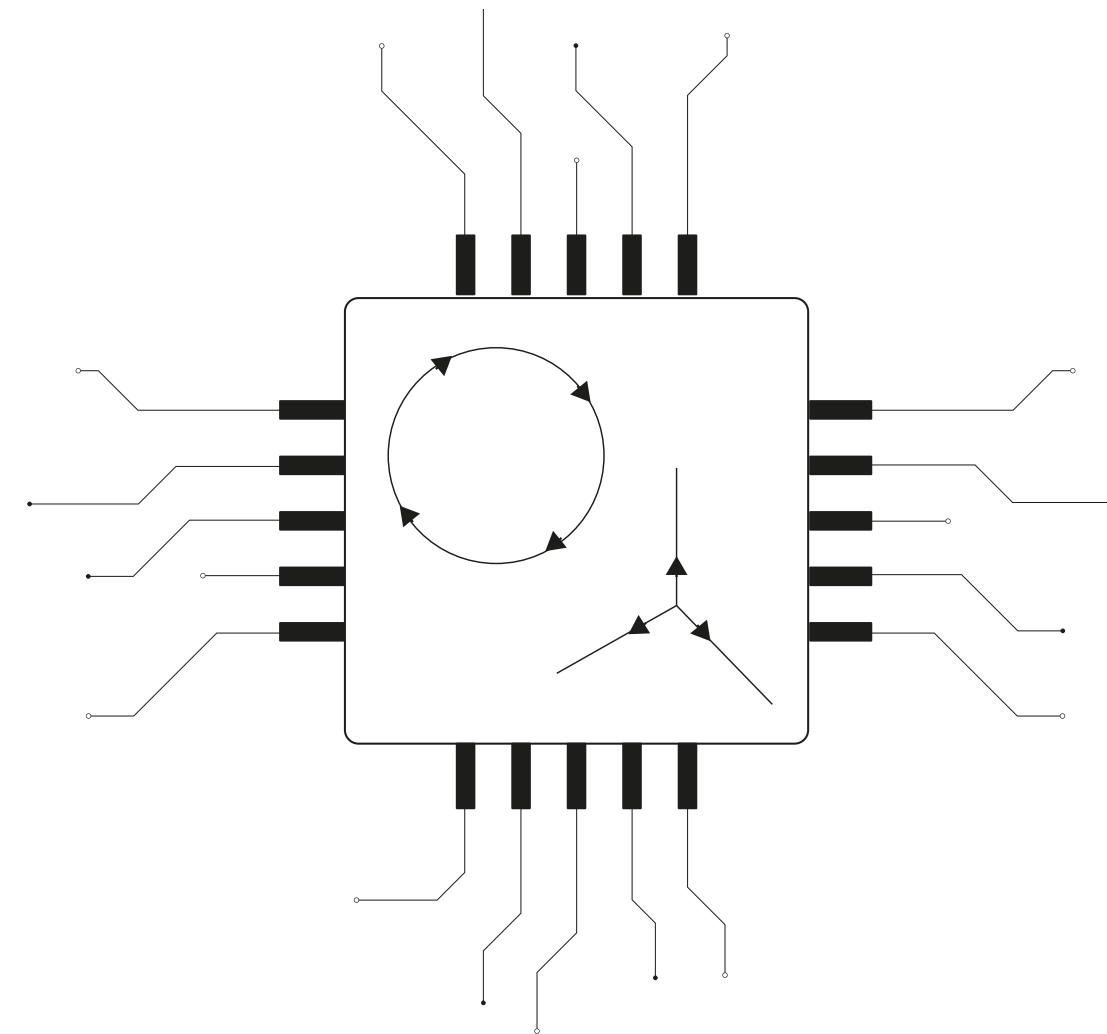
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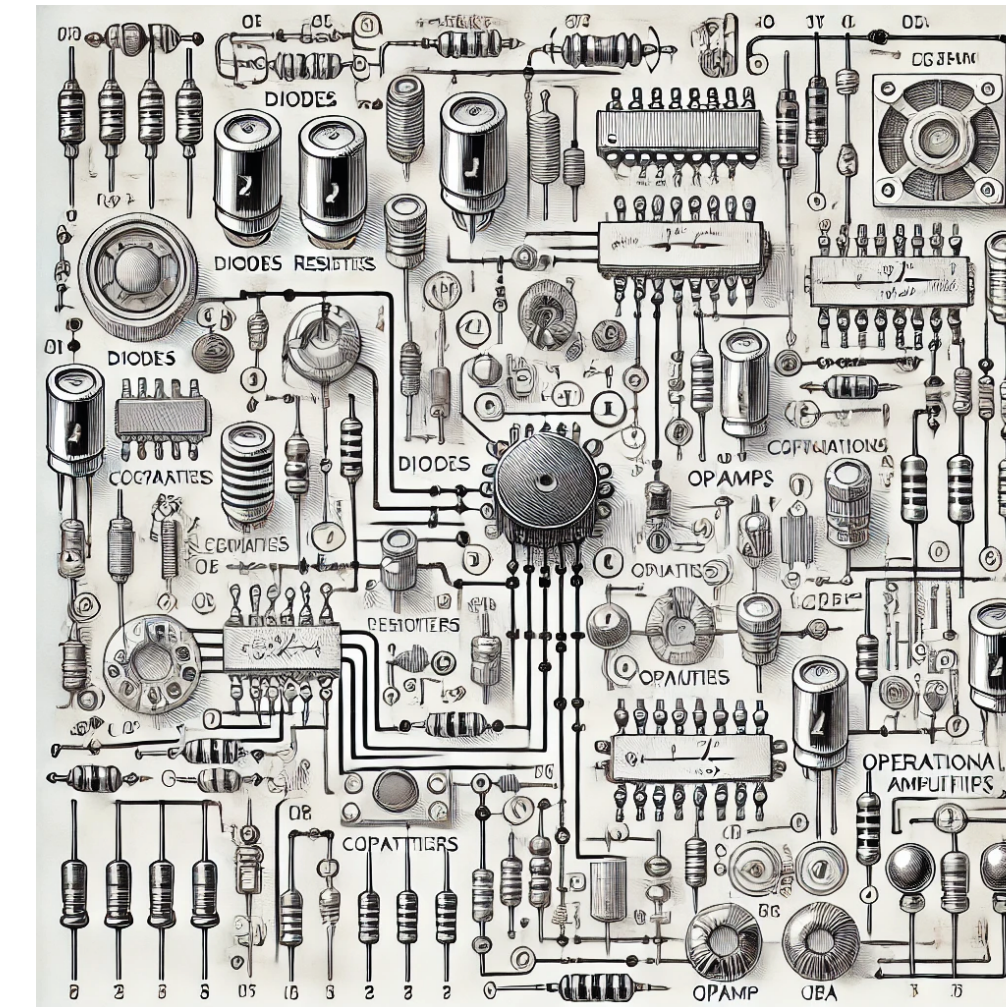
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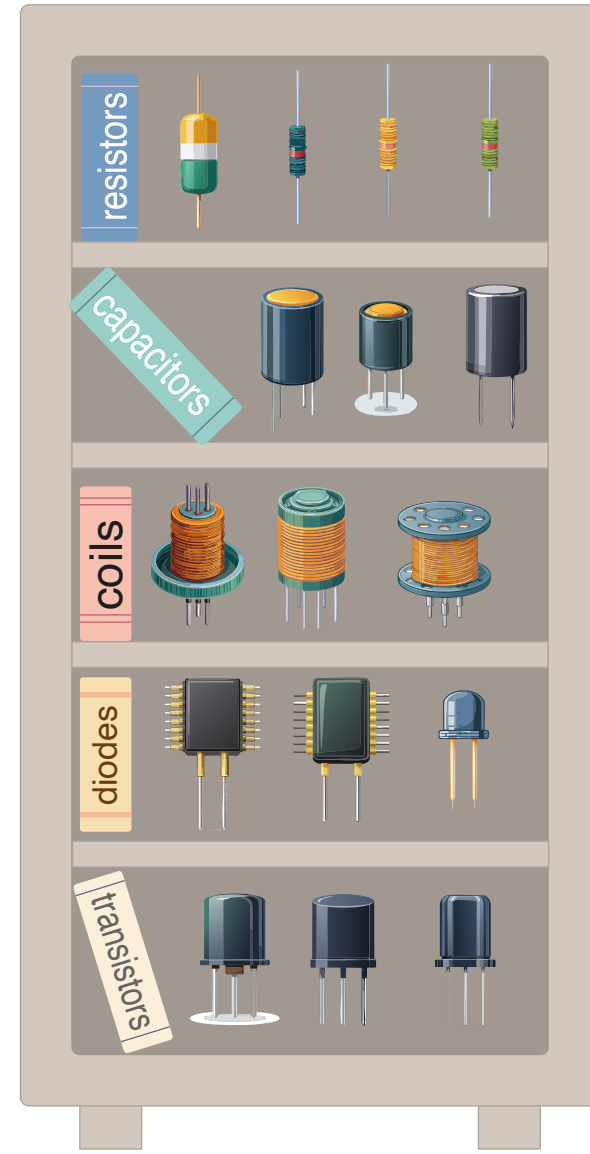
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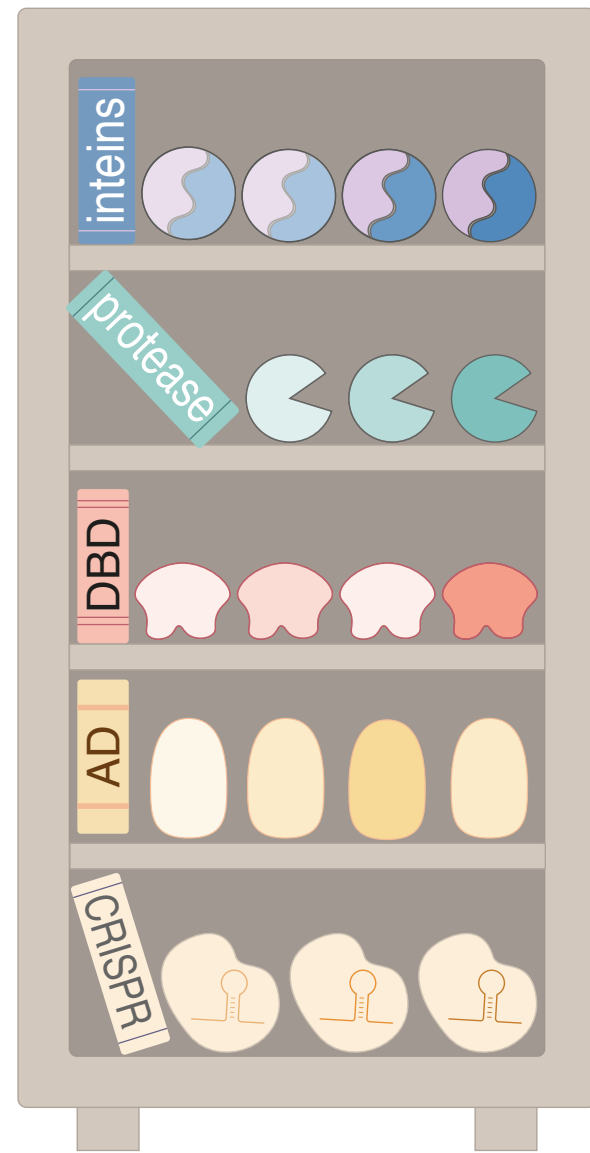
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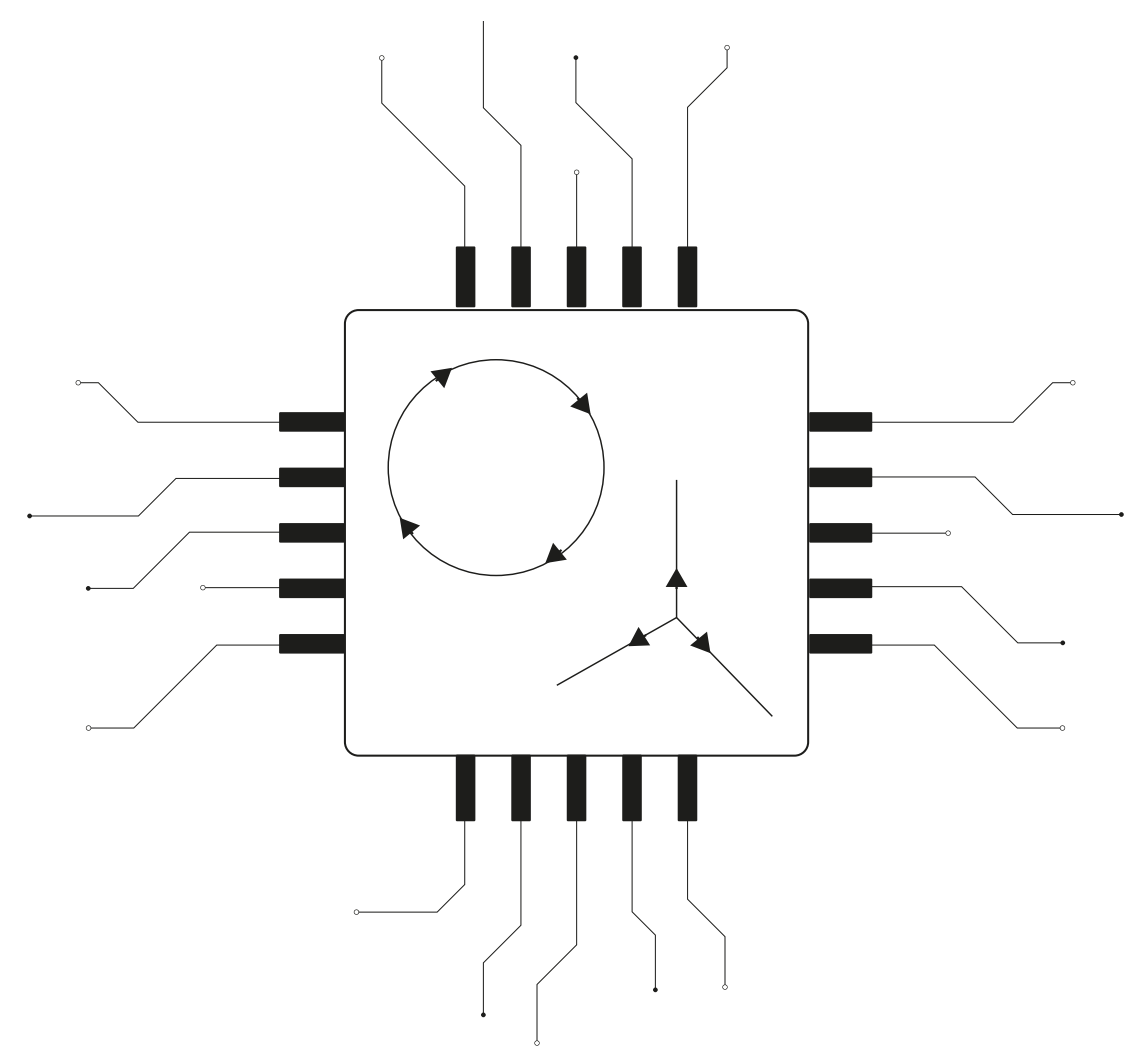
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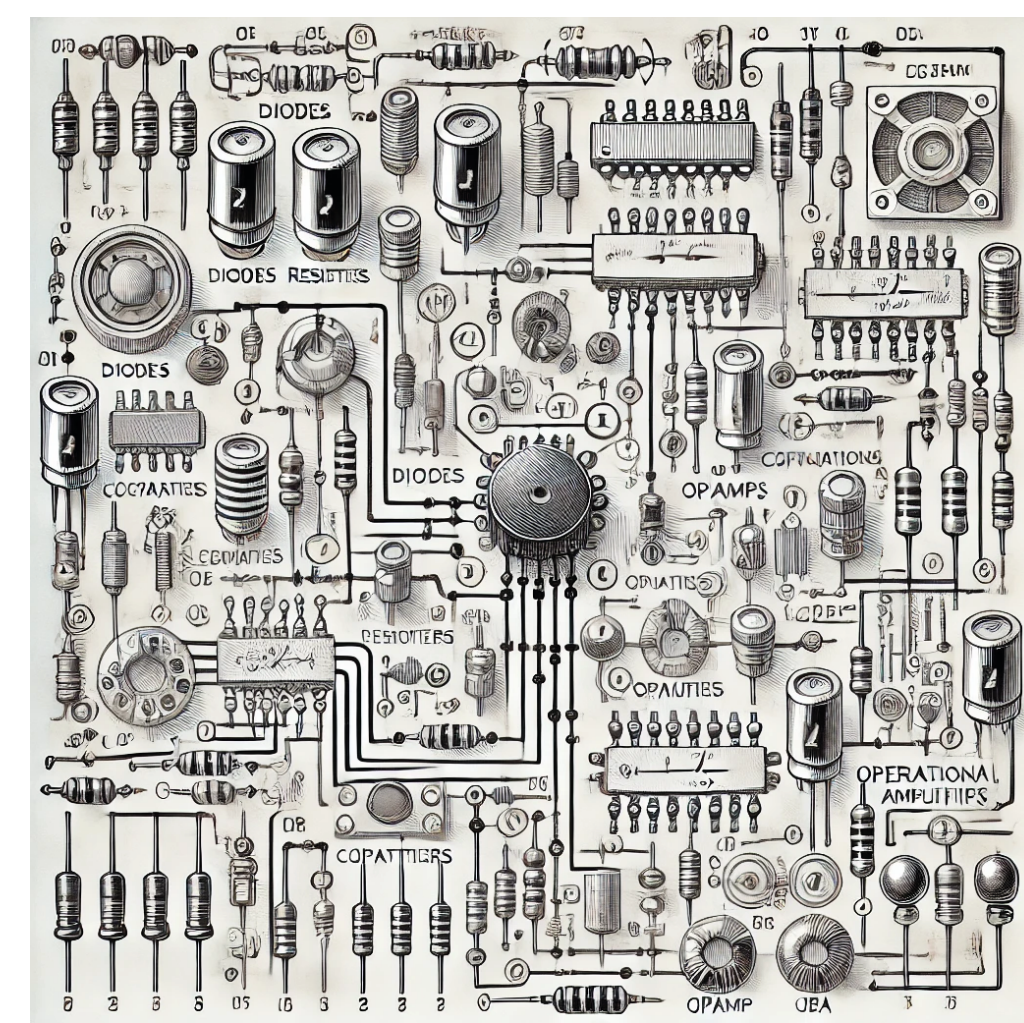
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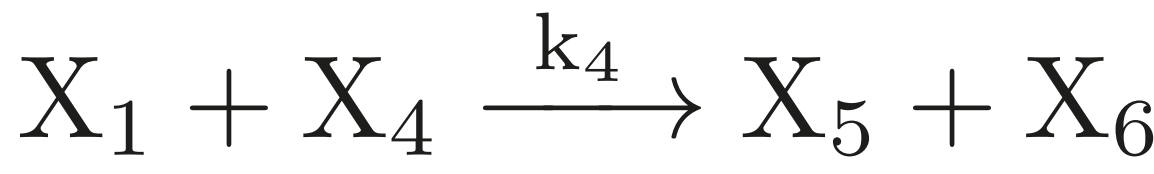
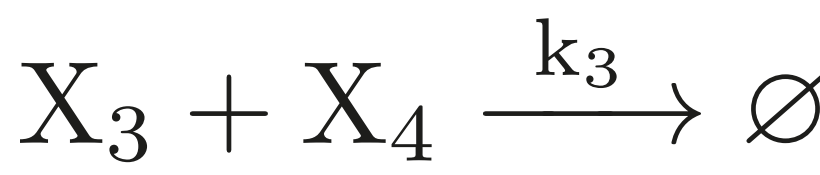
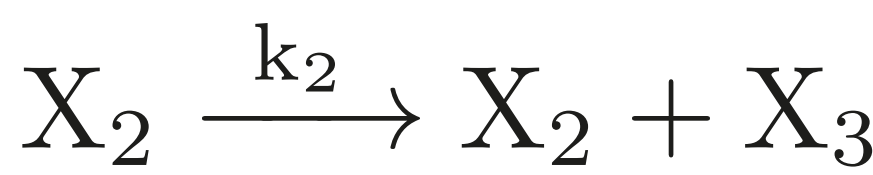
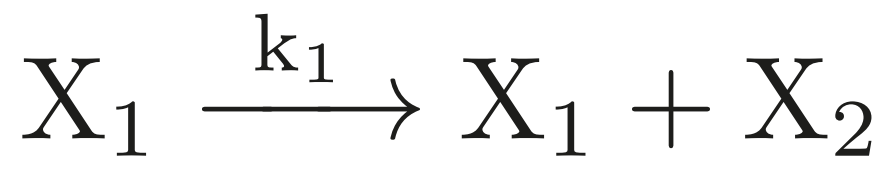
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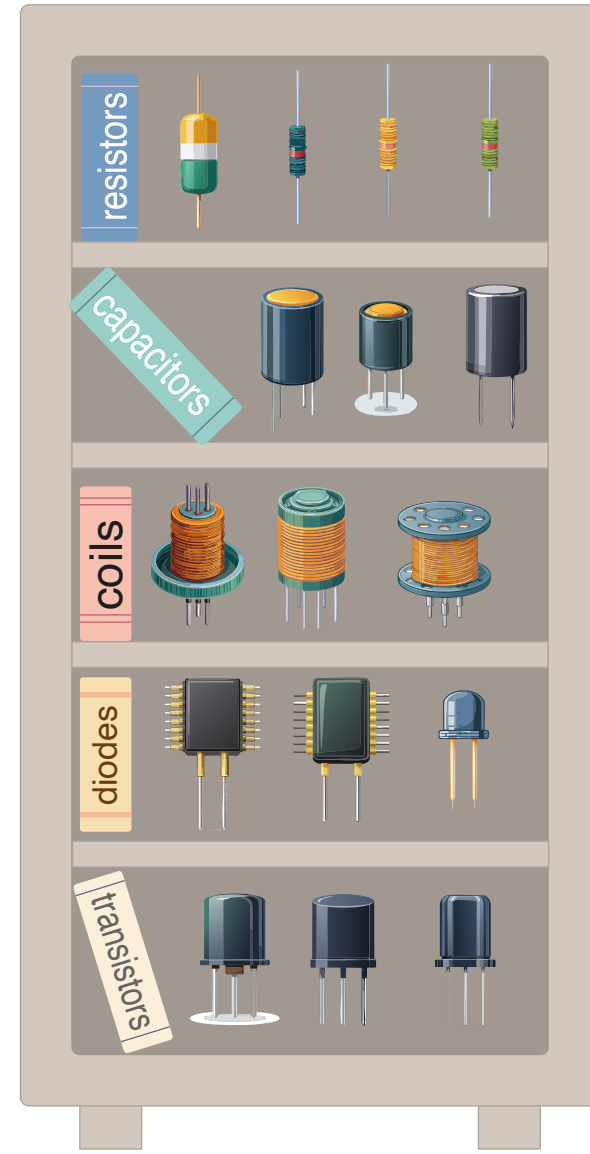
Chemical Reaction Network Theory



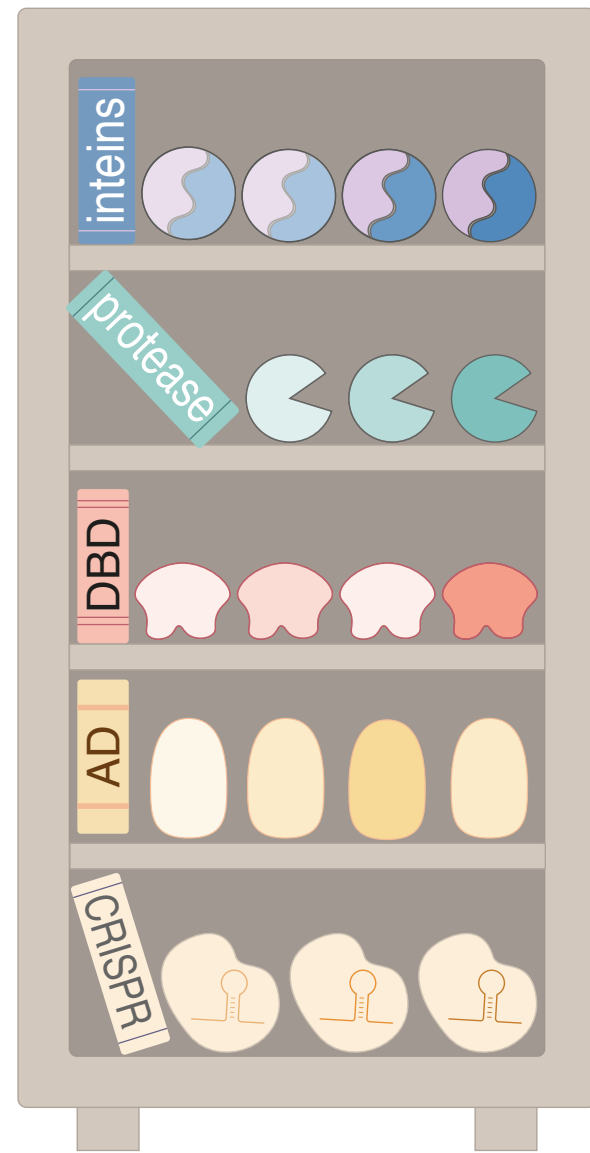
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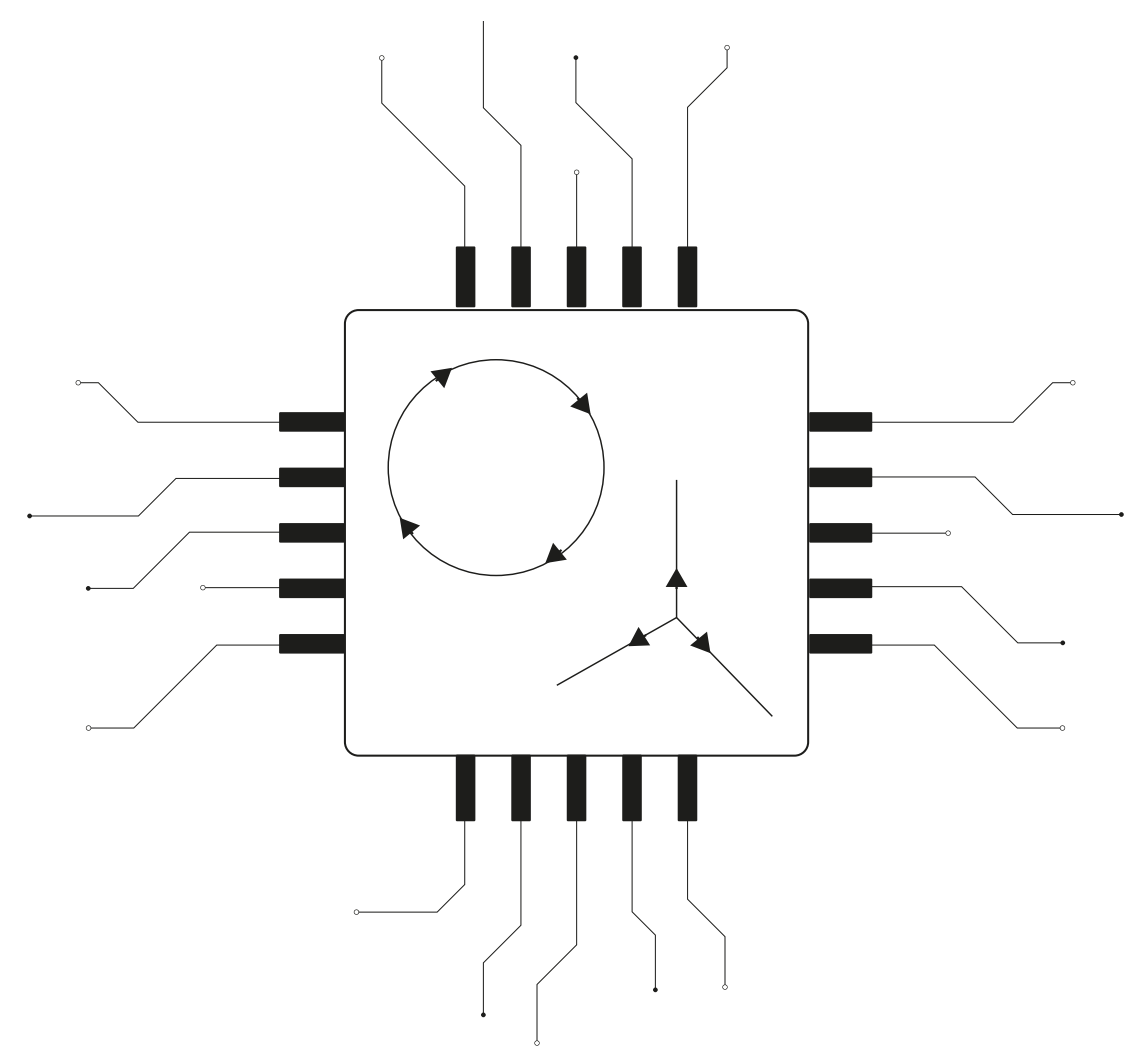
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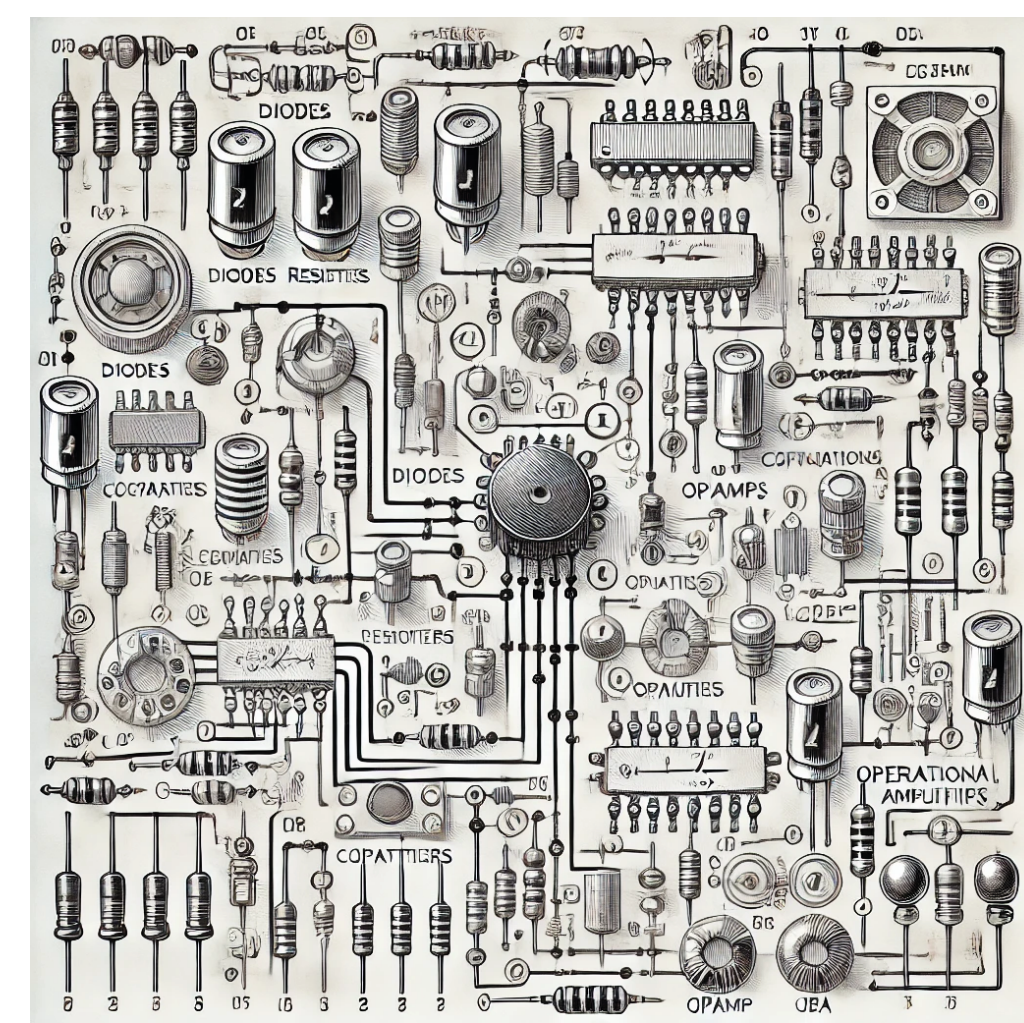
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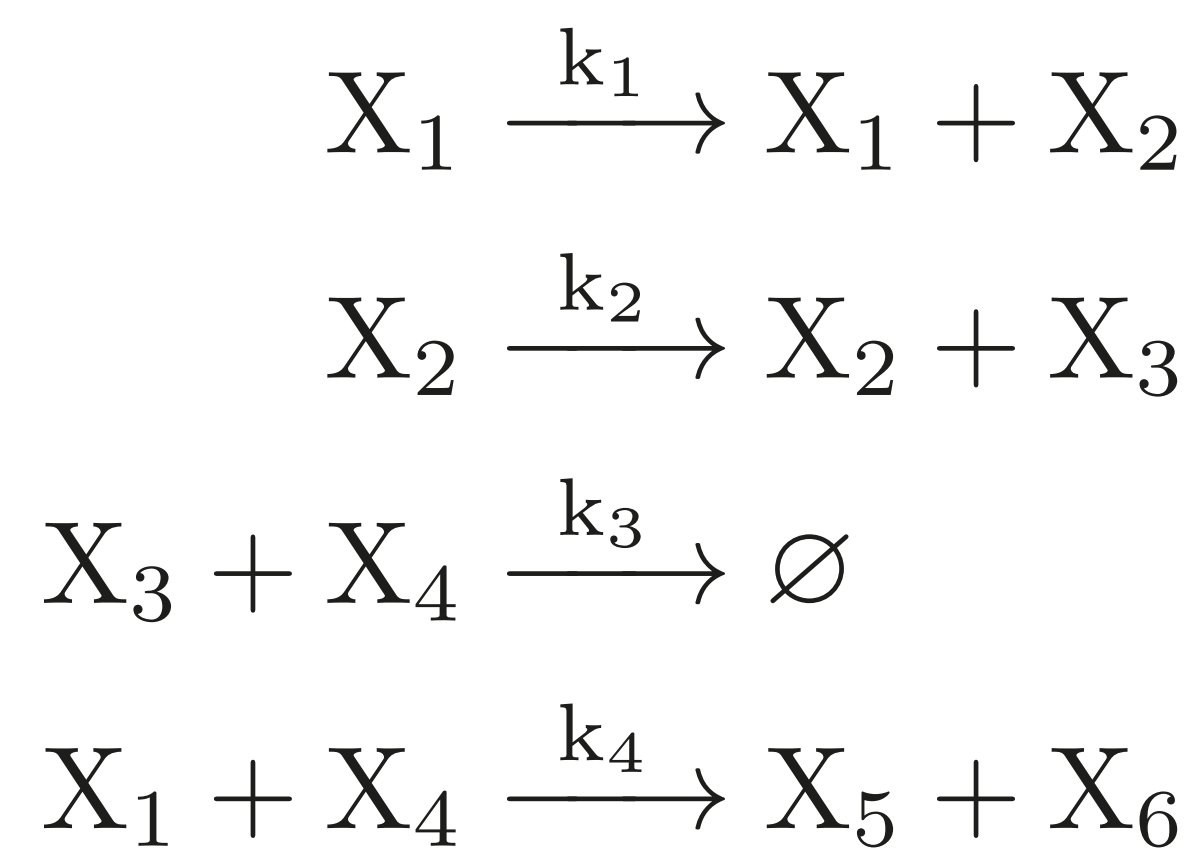
Circuit Theory



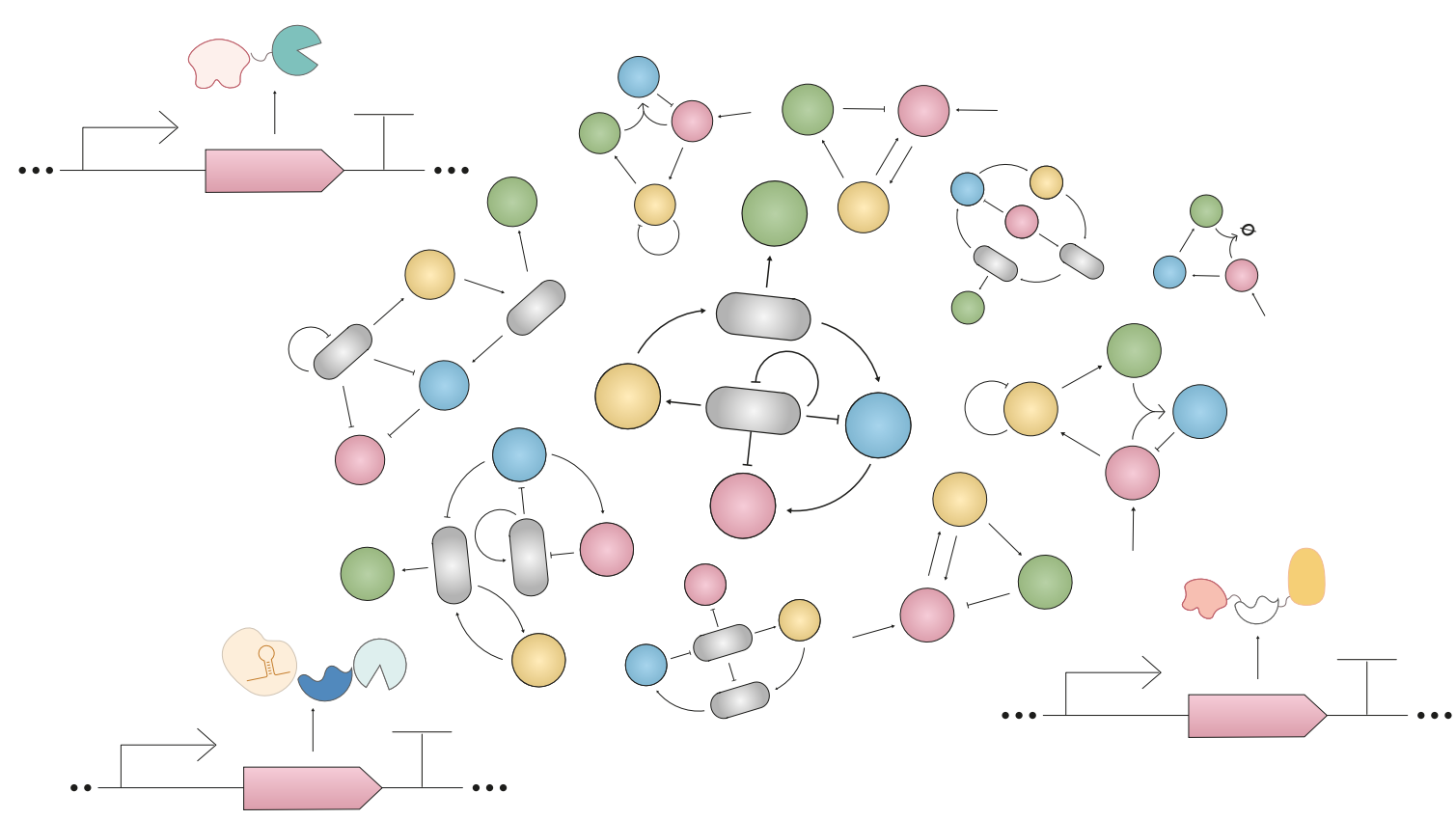
Electric Circuit



Chemical Reaction Network Theory



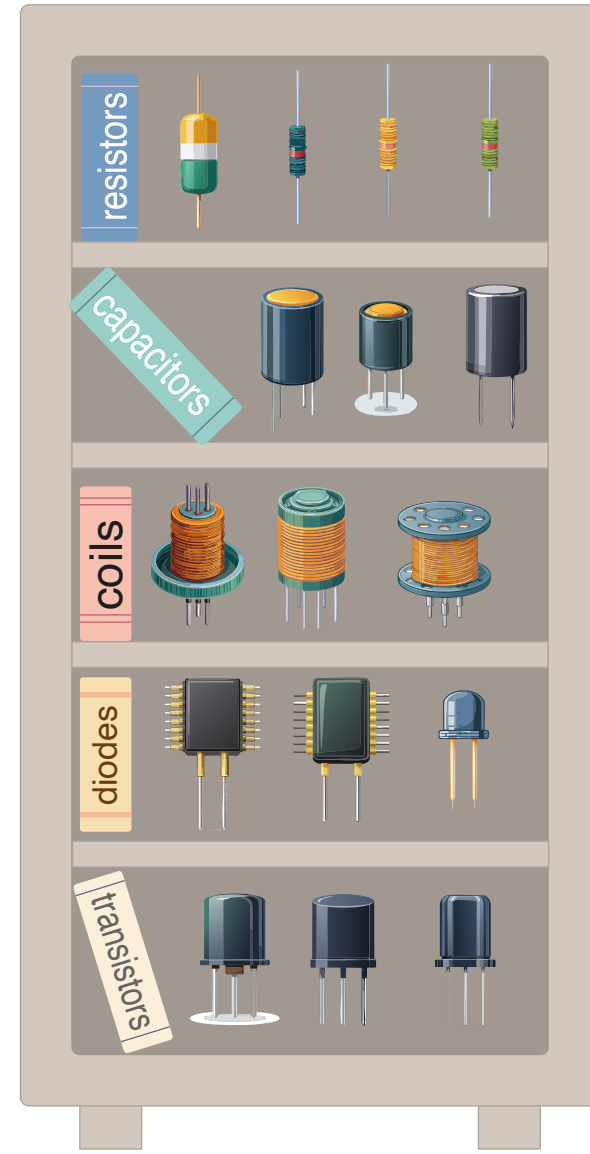
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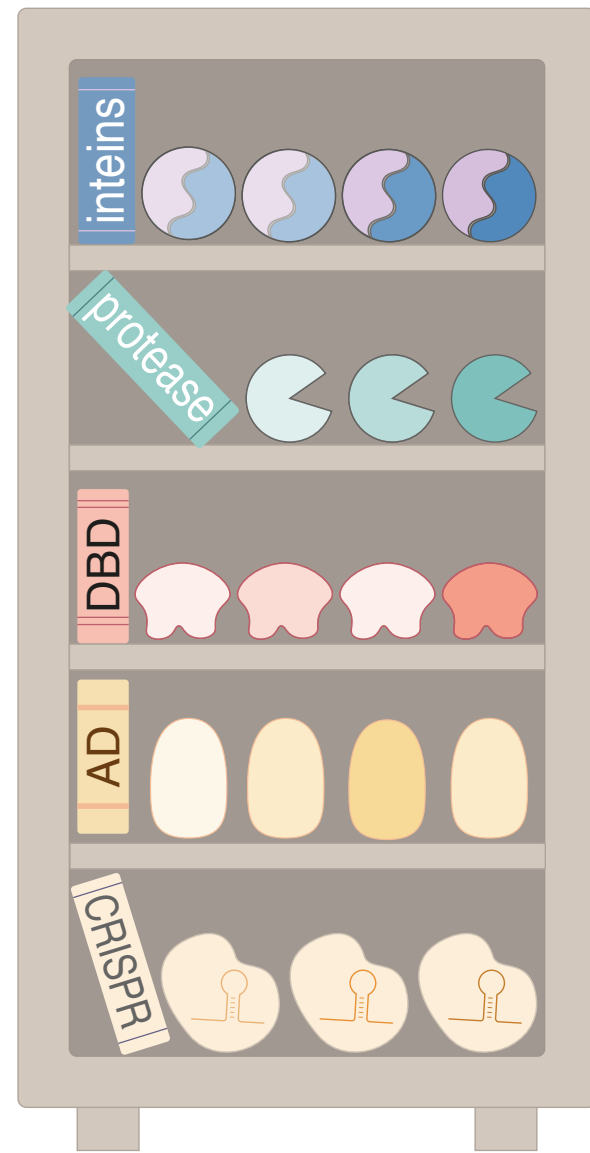
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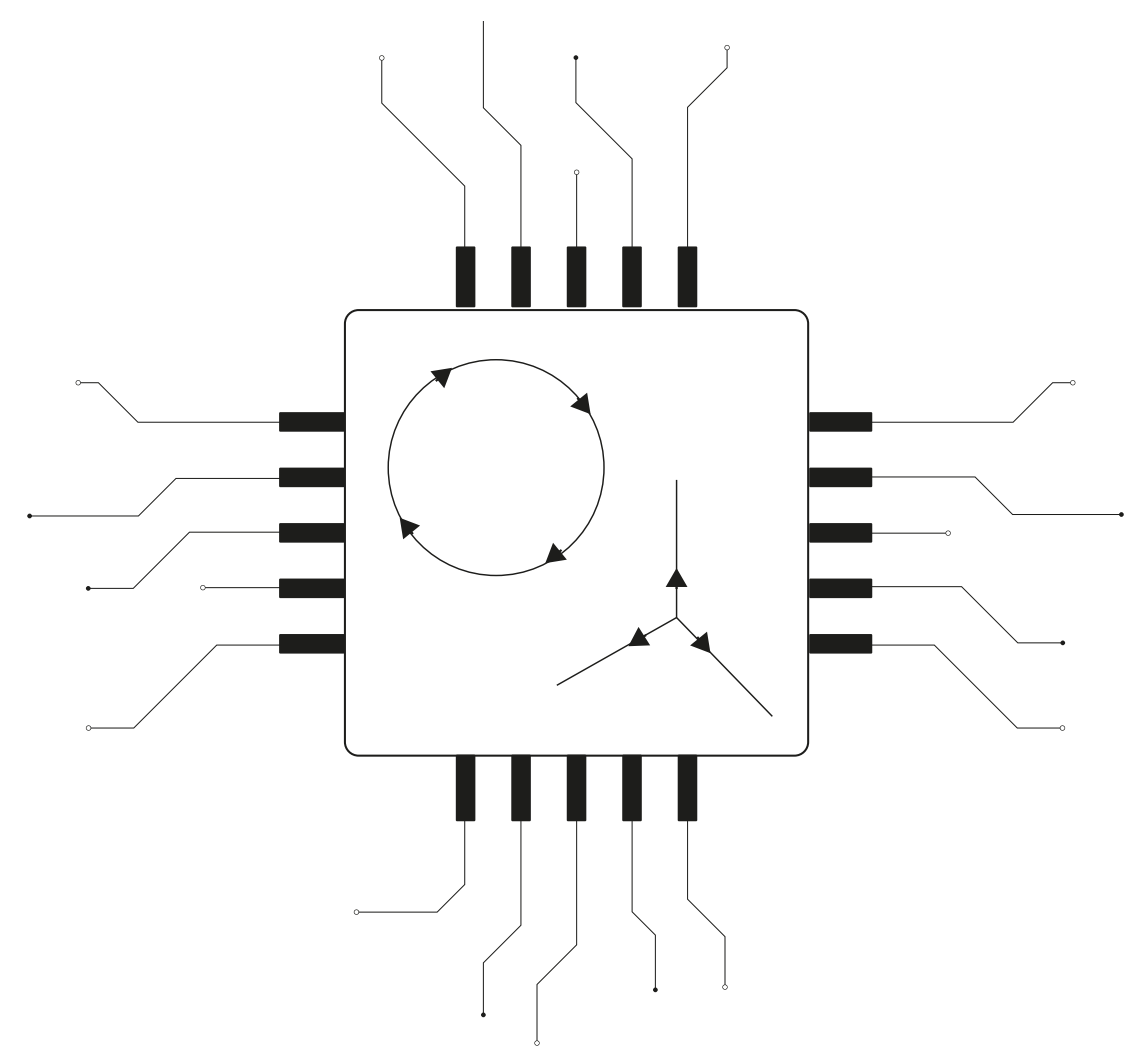
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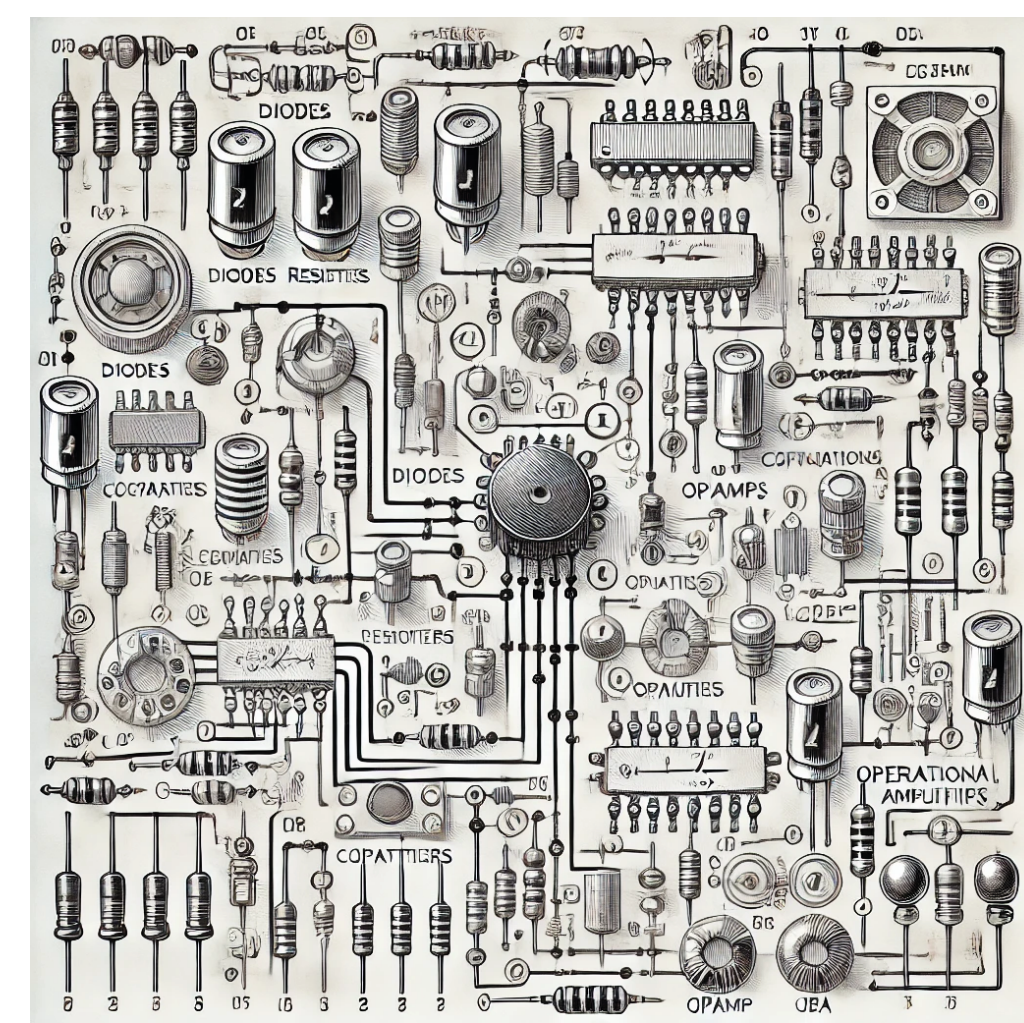
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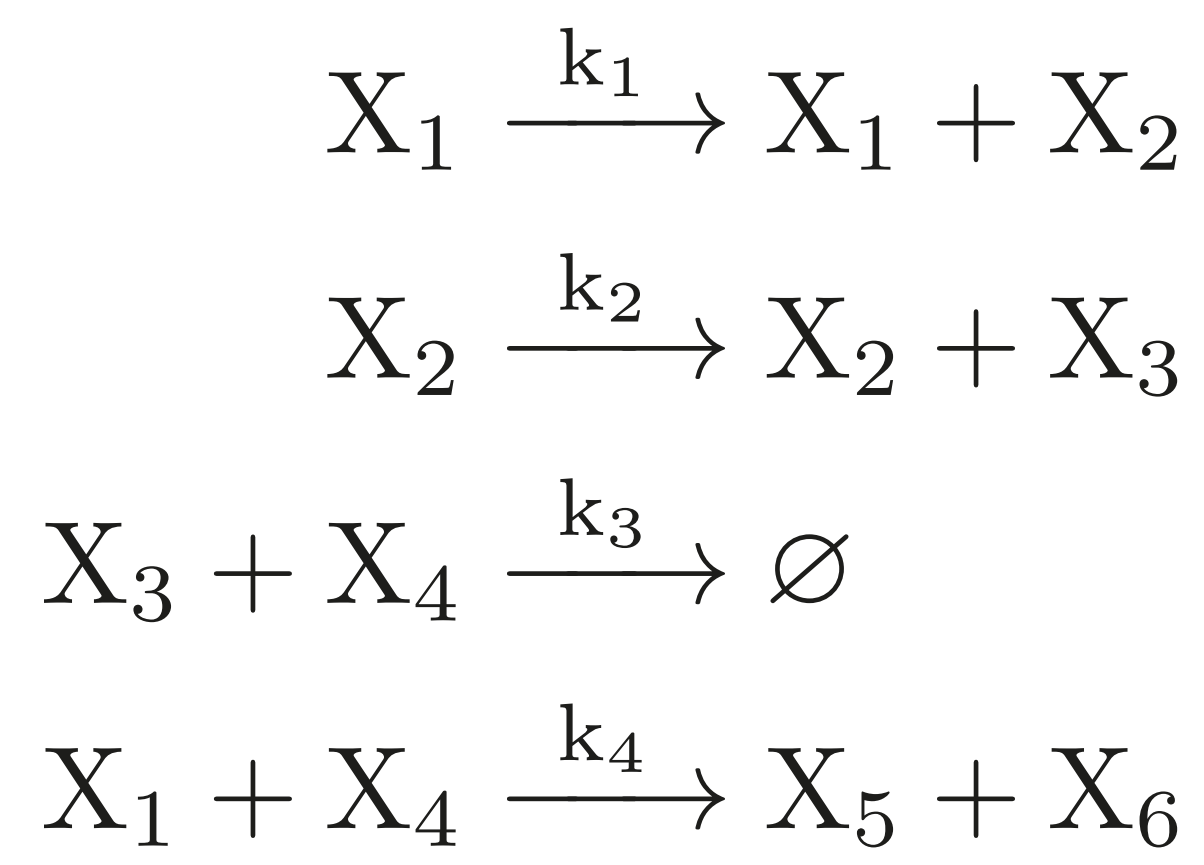
Electric Circuit



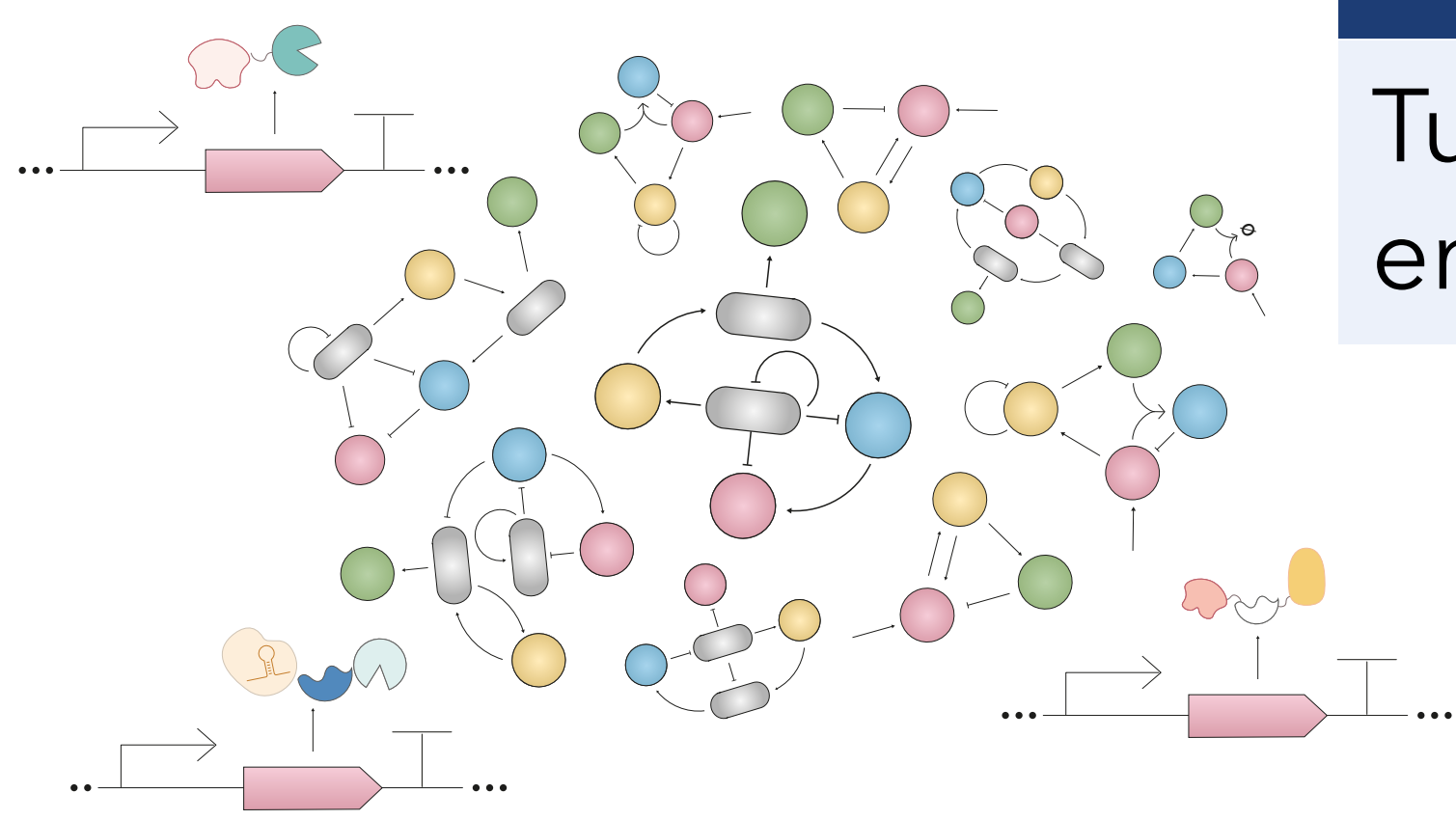
Silicon



Chemical Reaction Network Theory



Genetic Circuit



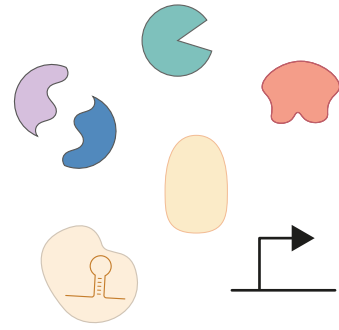
DNA

Synthetic Biology
Turning DNA into an engineering substrate

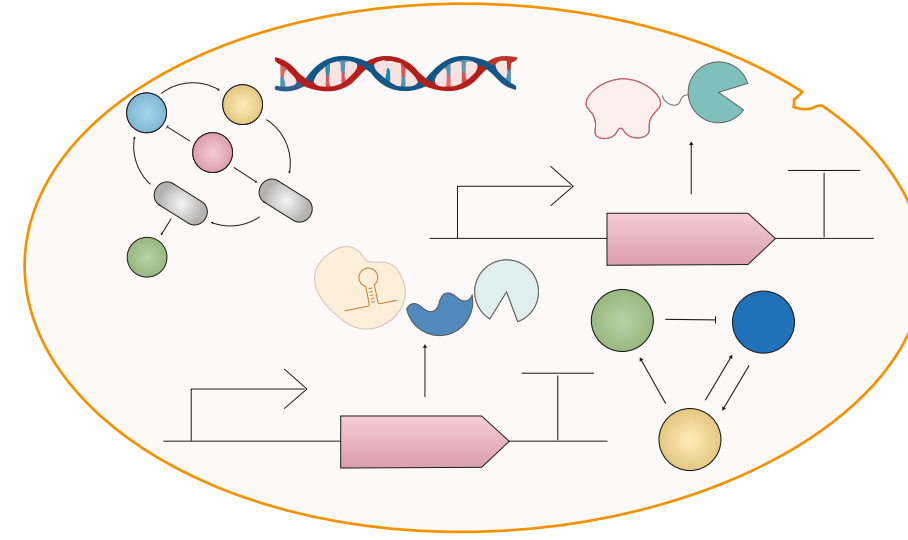
Programming cells enables bio-devices across domains

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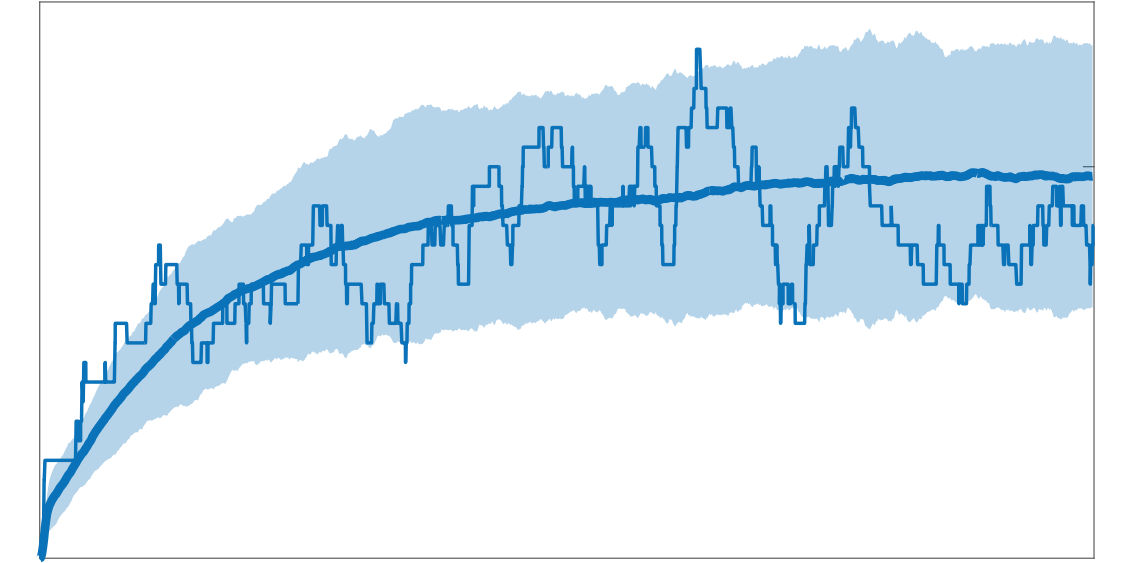
genetic parts



genetic circuits

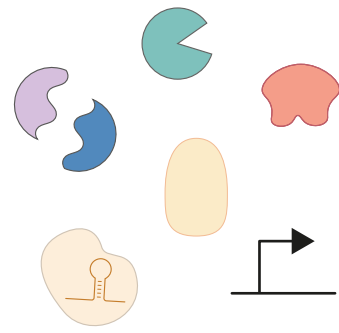


cell behaviour

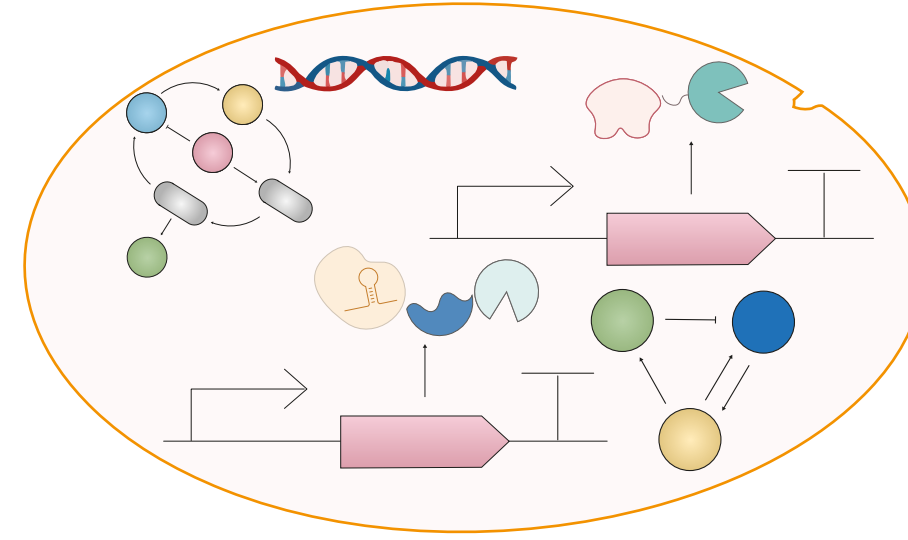


Programming cells enables bio-devices across domains

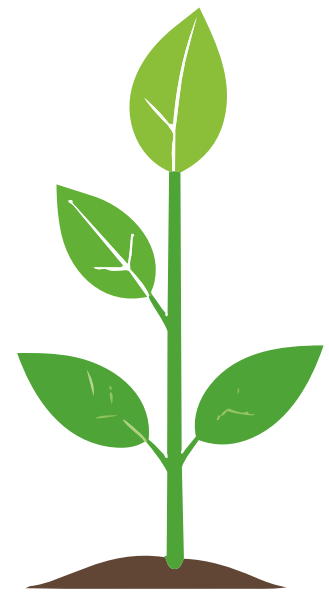
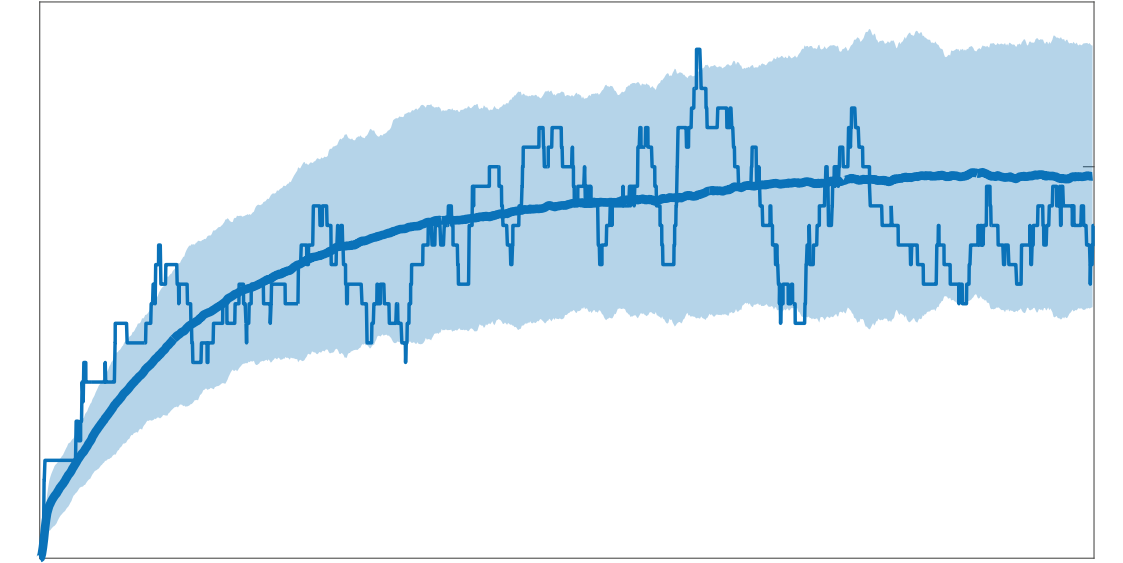
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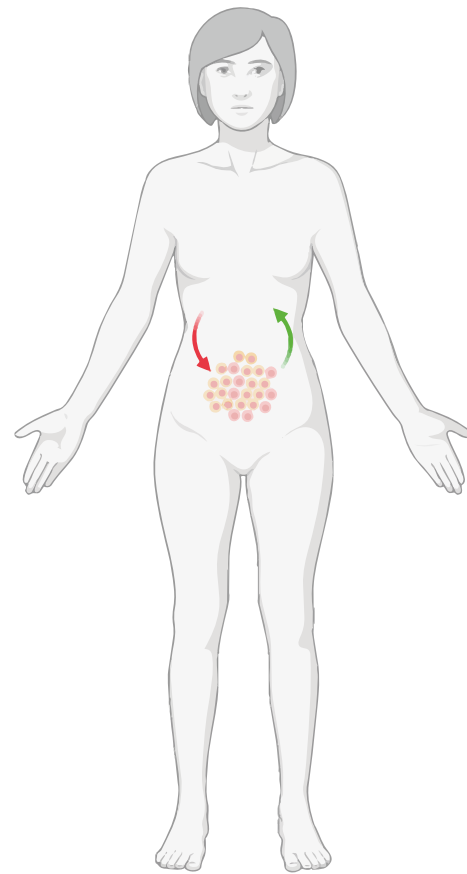
genetic circuits



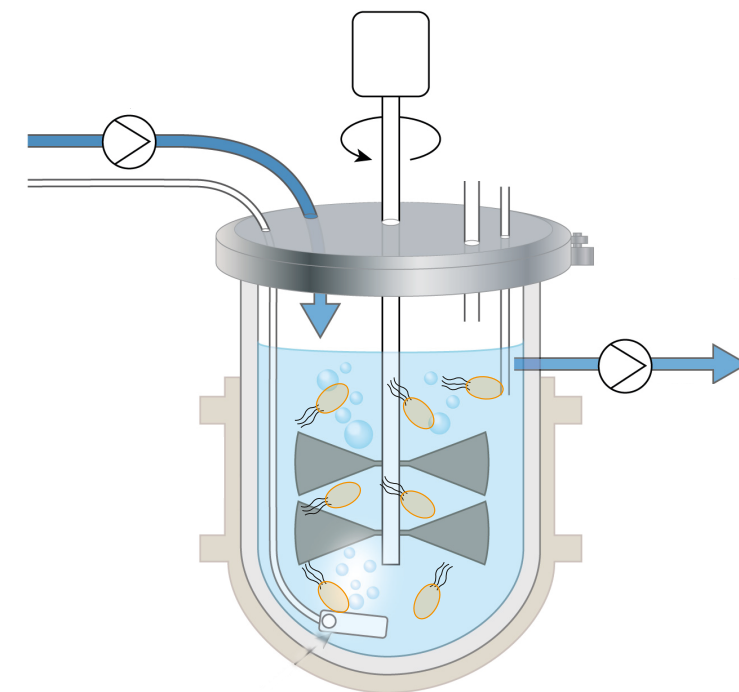
cell behaviour



Agriculture



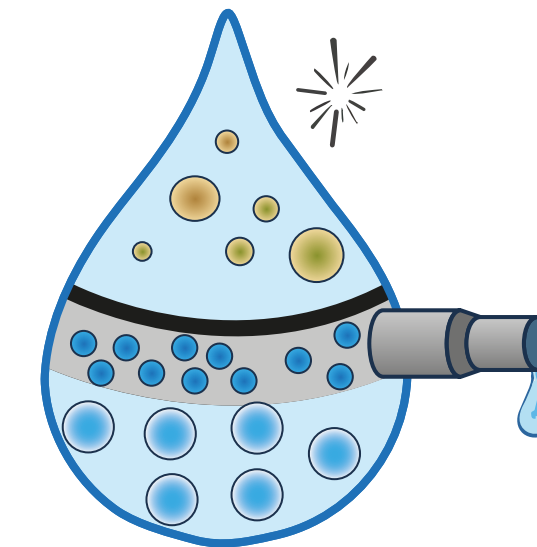
Therapeutics



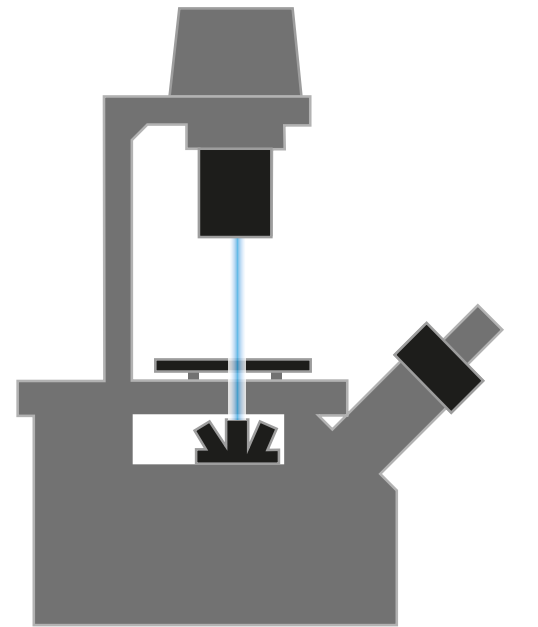
Biomanufacturing



Biofuels



Environmental
Remediation



Deeper
Understanding
of Biology

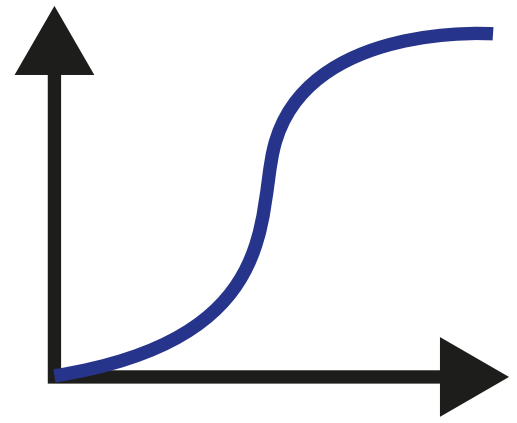
Cybergenetics: bringing control theory to synbio

Many genetic circuits fail outside the design environment.

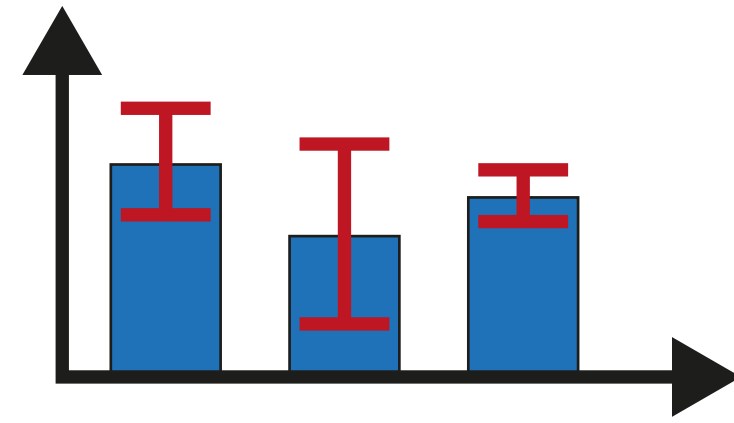
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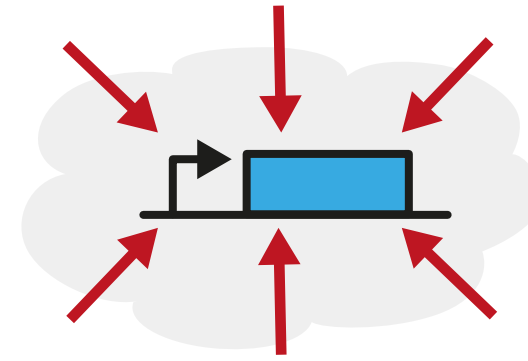
nonlinearity



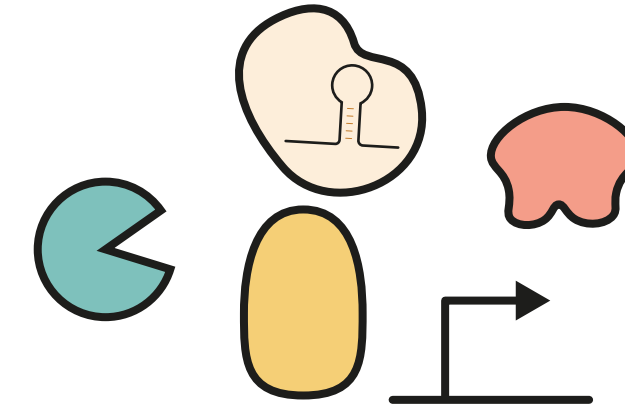
uncertainty



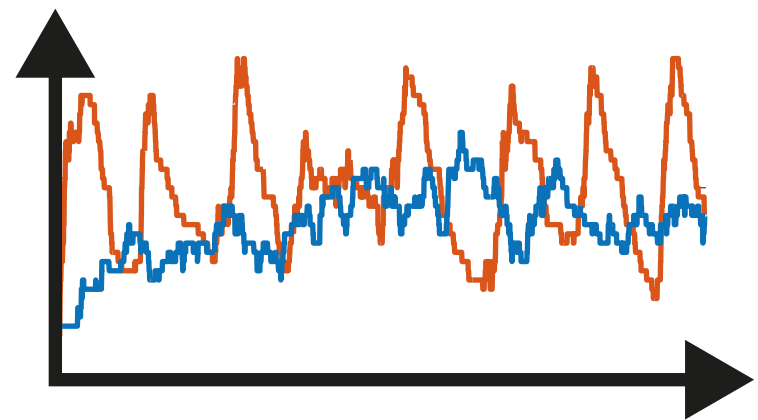
context dependence



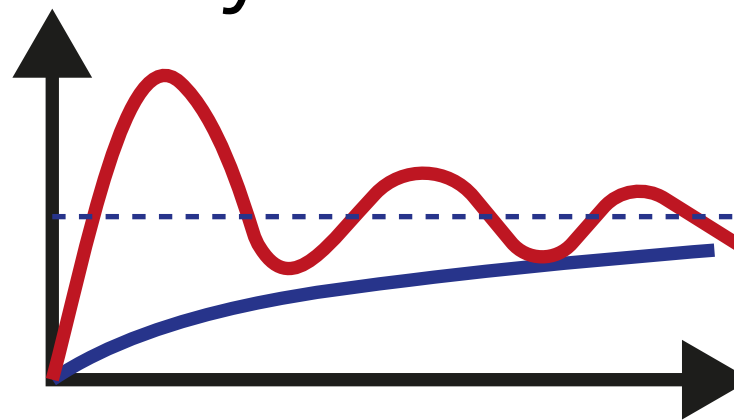
implementability



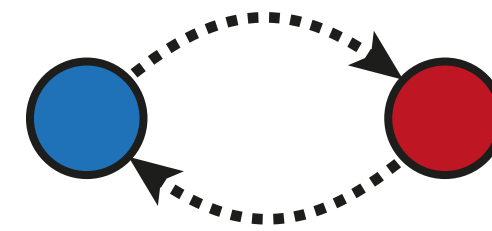
stochasticity



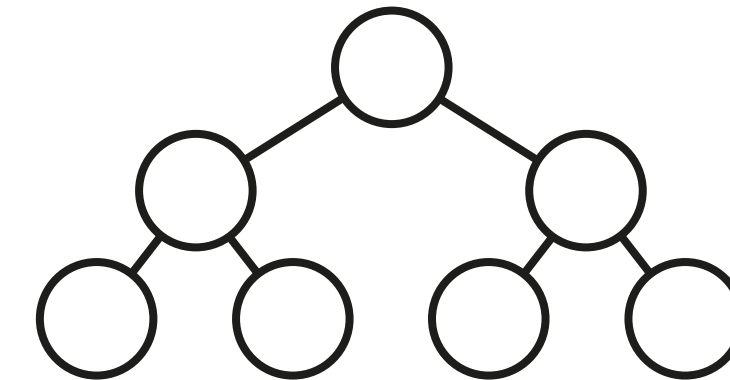
poor transient dynamics



cross-talk



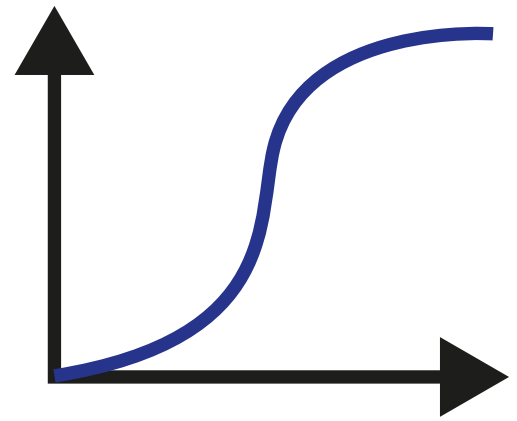
large design space



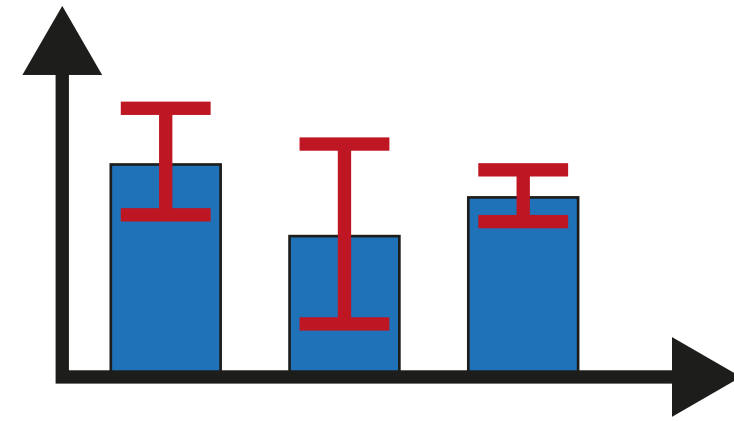
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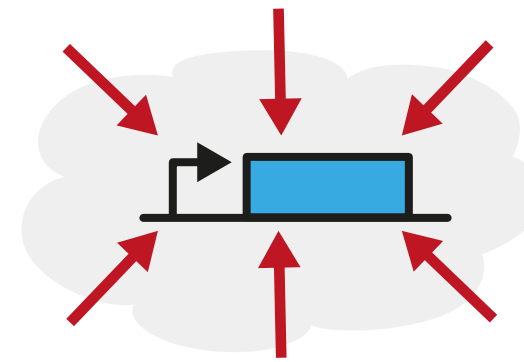
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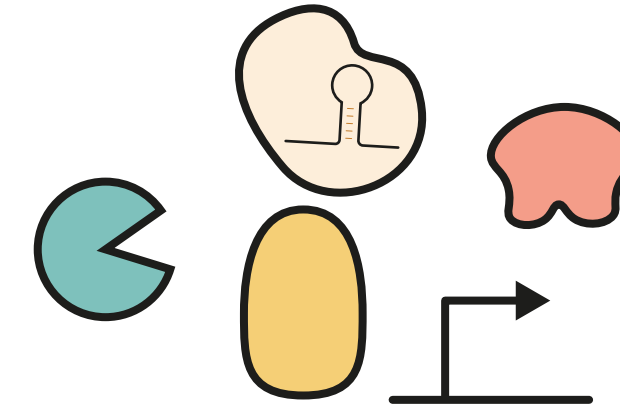
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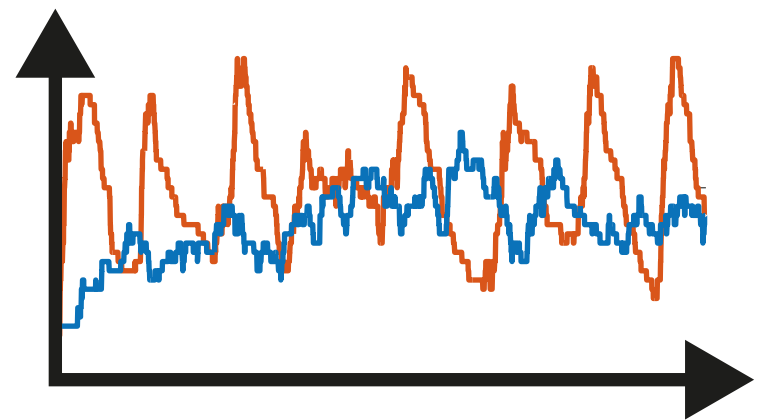
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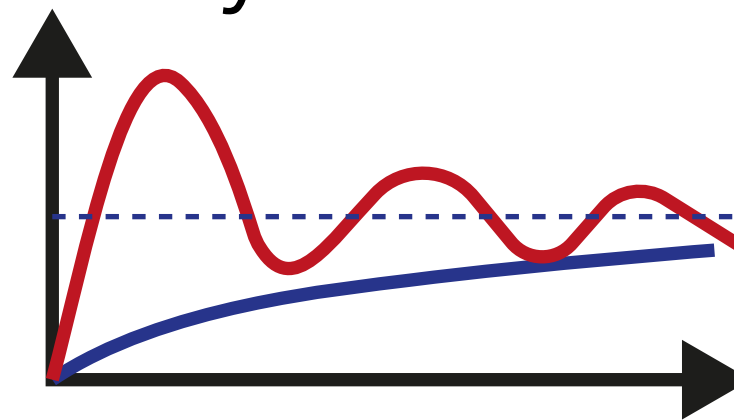
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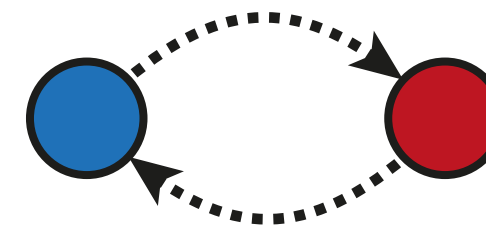
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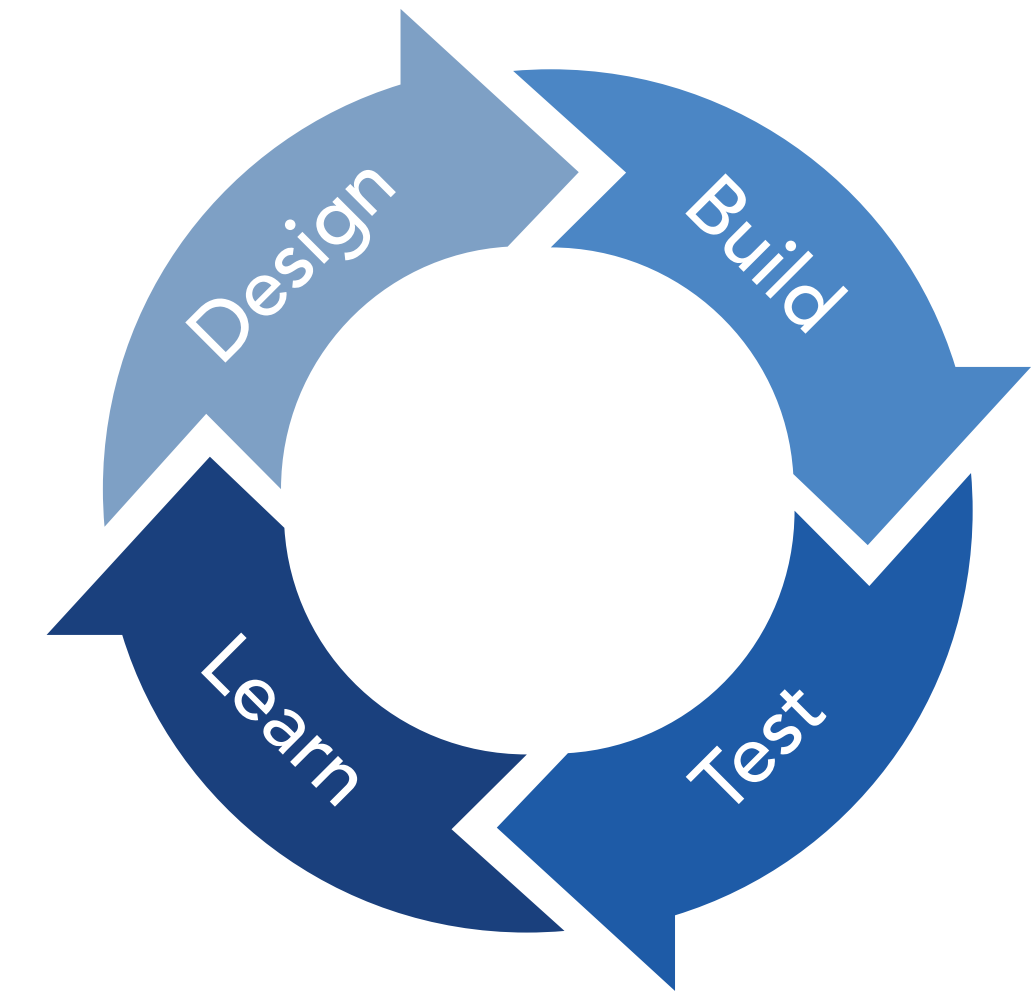
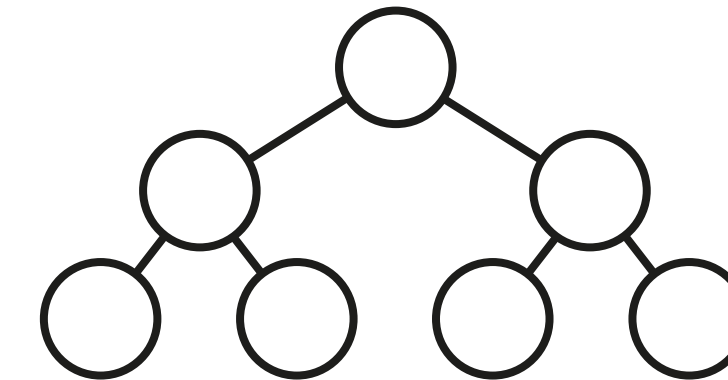
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Theory & computation enable rational circuit design

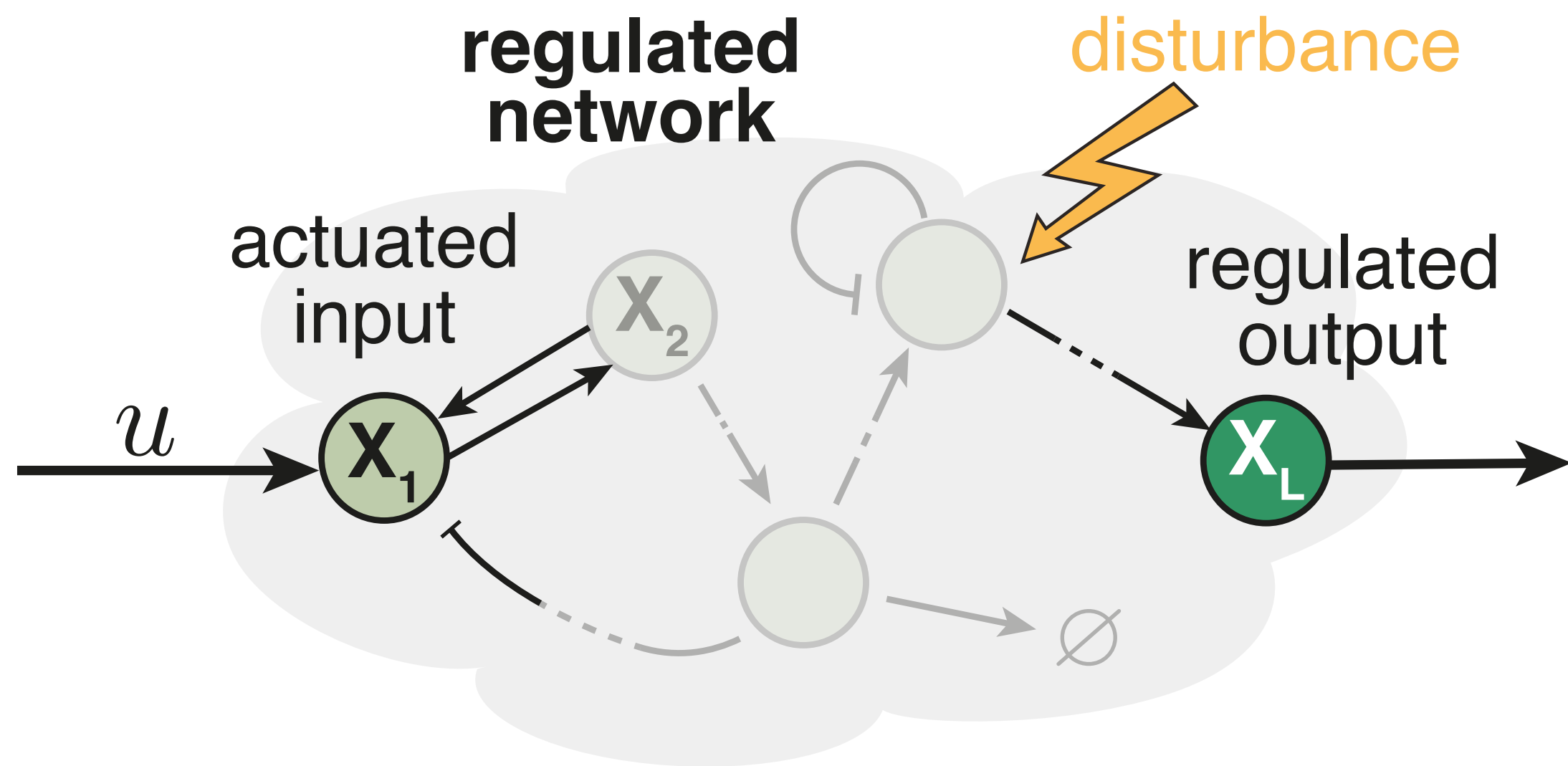
Control theory + synthetic biology



Cybergenetics

The mathematical language: Chemical Reaction Networks (CRNs)

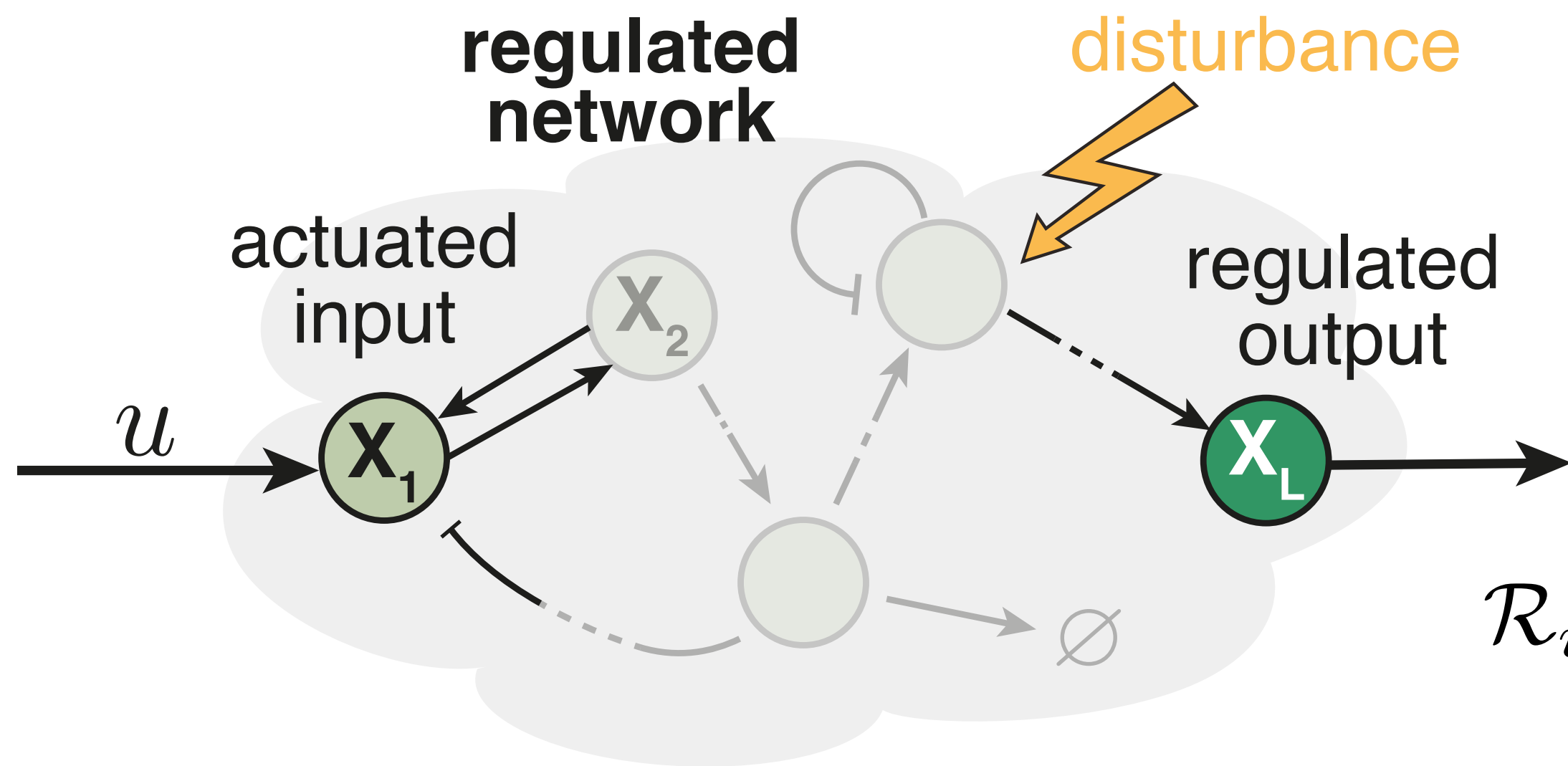
The mathematical language: Chemical Reaction Networks (CRNs)



Species: $\mathbf{X} \triangleq \{\mathbf{X}_1, \mathbf{X}_2, \dots, \mathbf{X}_L\}$

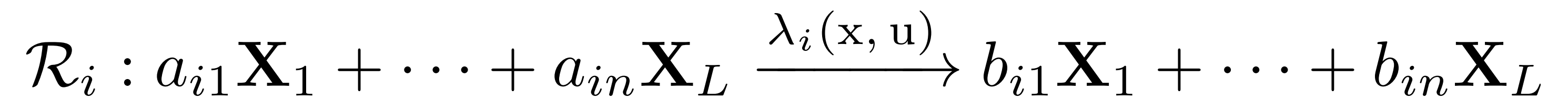
Reactions: $\mathcal{R} \triangleq \{\mathcal{R}_1, \mathcal{R}_2, \dots, \mathcal{R}_n\}$

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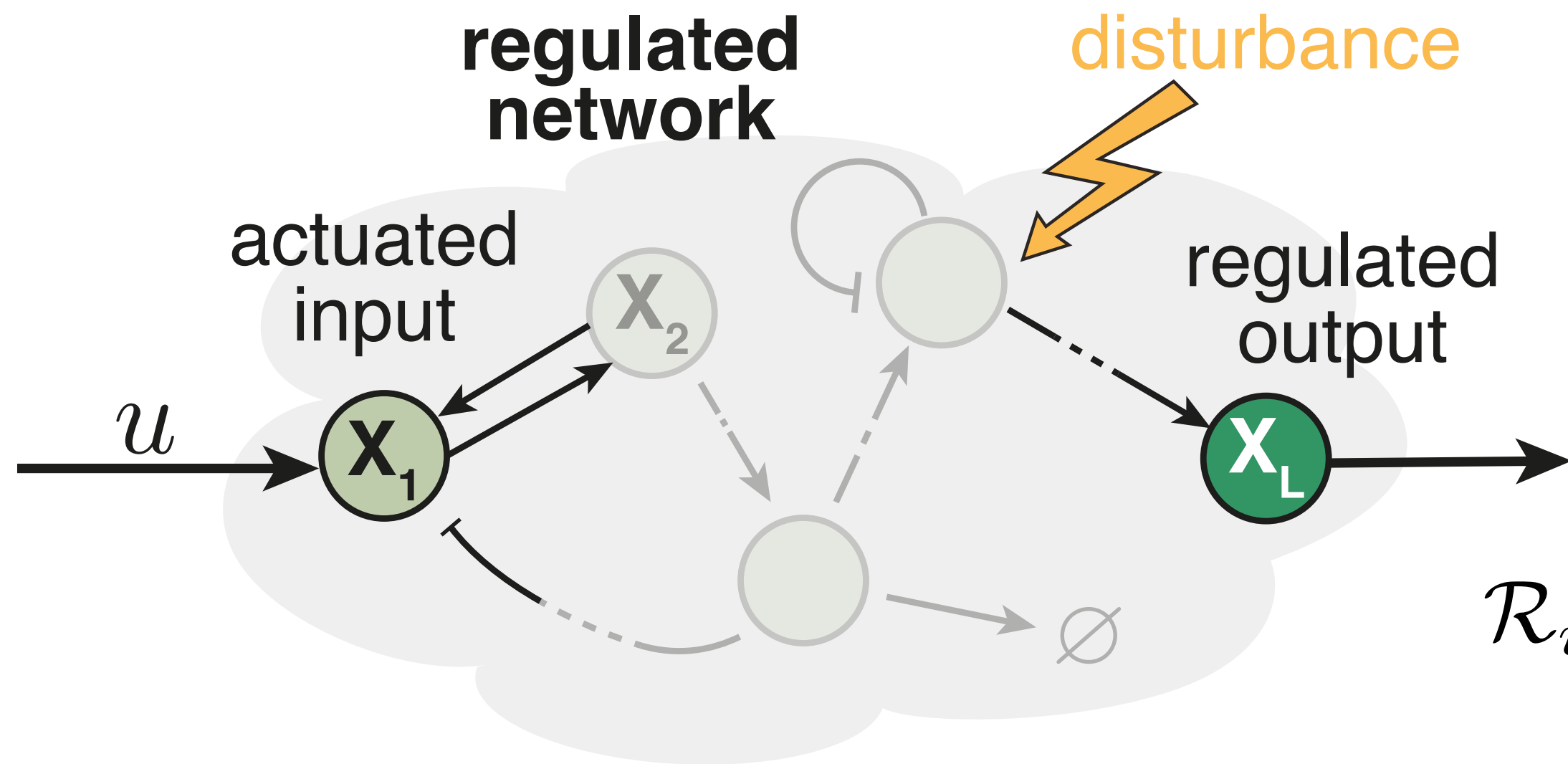


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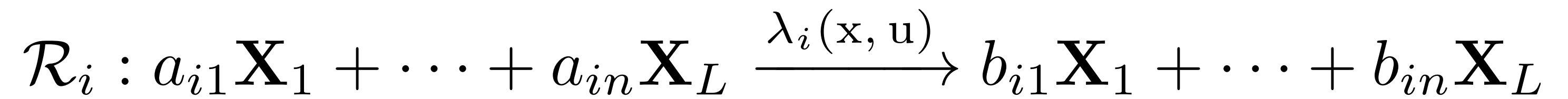


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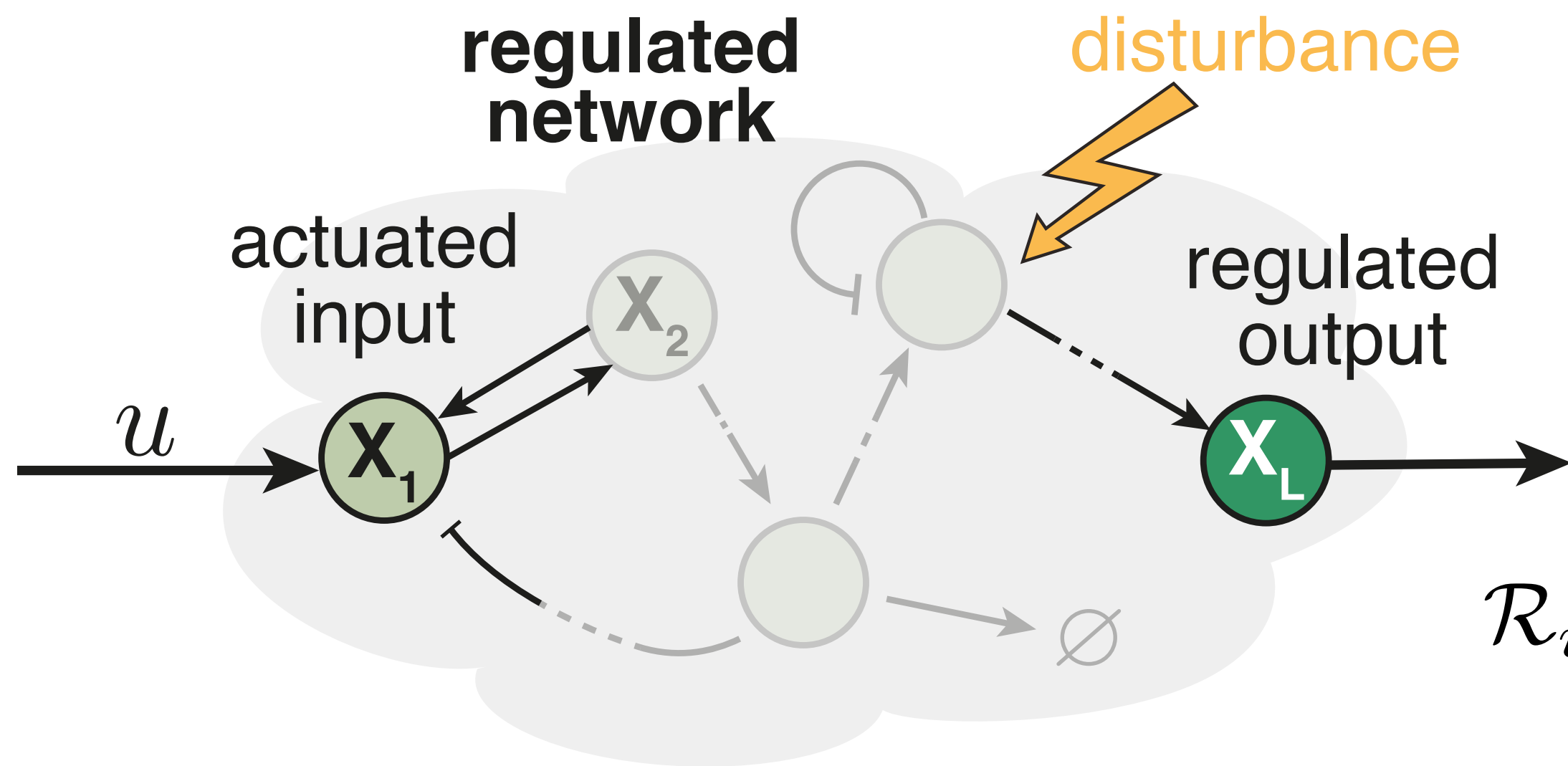
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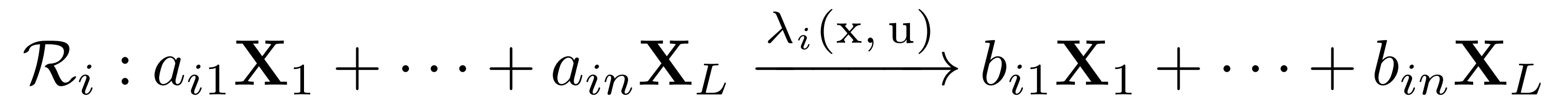
Vector form: $a_i\mathbf{X} \xrightarrow{\lambda_i(\mathbf{x}, \mathbf{u})} b_i\mathbf{X}$

The mathematical language: Chemical Reaction Networks (CRNs)



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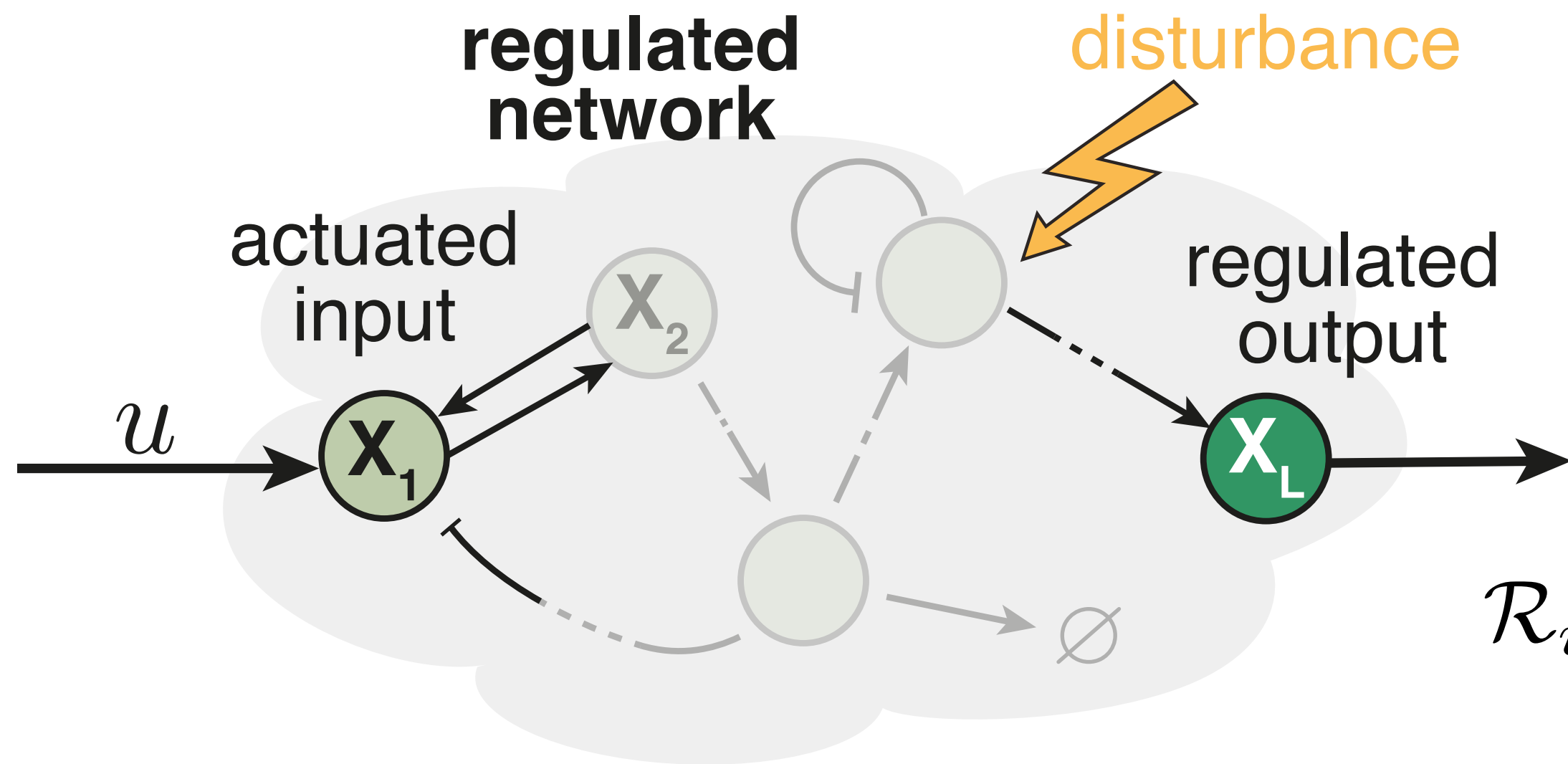


Vector form: $a_i\mathbf{X} \xrightarrow{\lambda_i(\mathbf{x}, u)} b_i\mathbf{X}$

Stoichiometry vector:

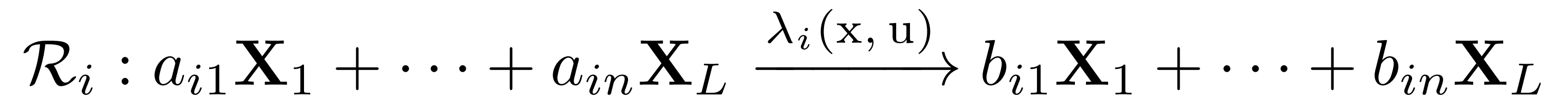
Propensity function:

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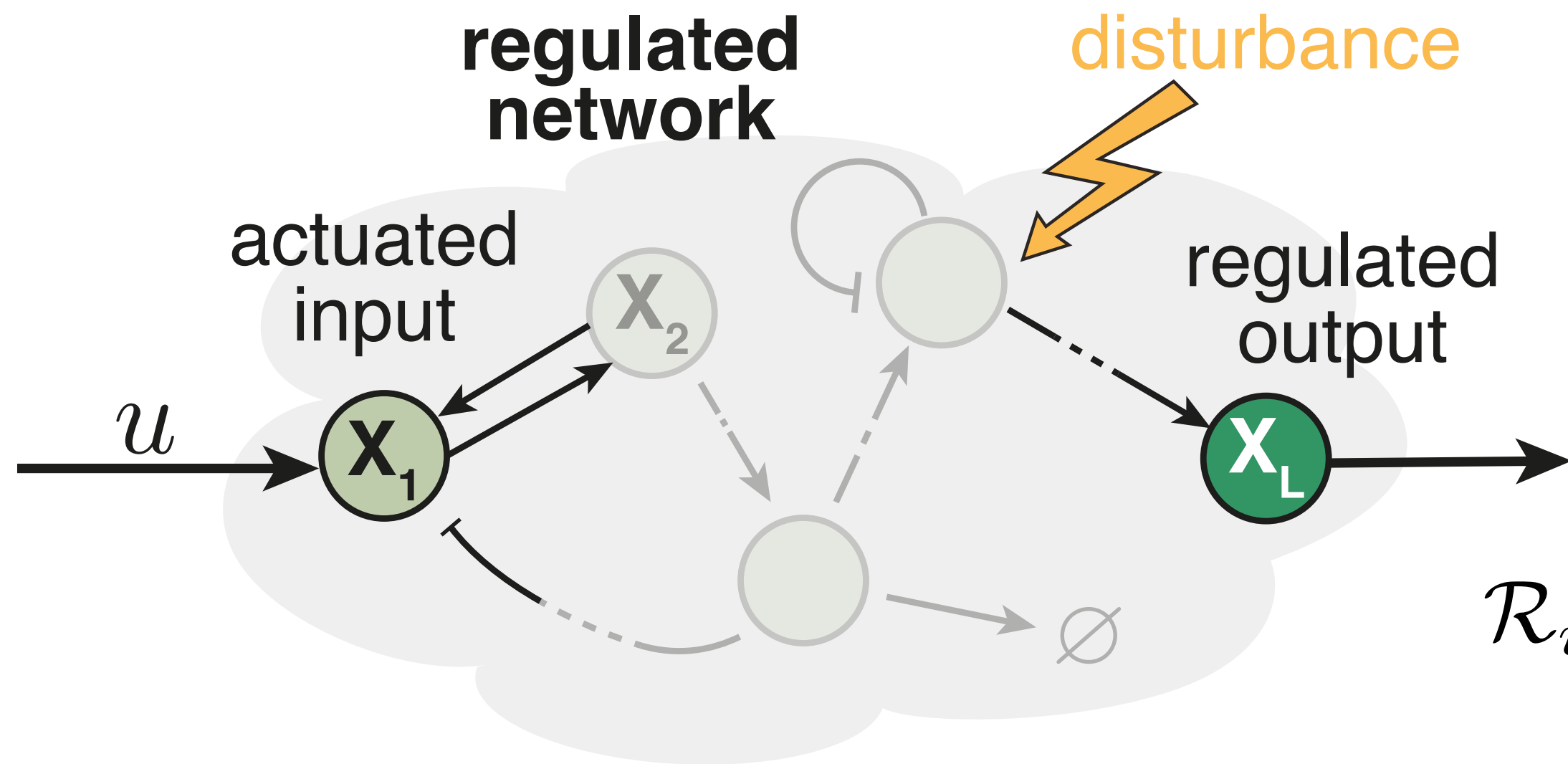


Vector form: $a_i\mathbf{X} \xrightarrow{\lambda_i(\mathbf{x}, \mathbf{u})} b_i\mathbf{X}$

Stoichiometry vector: $s_i \triangleq b_i - a_i \in \mathbb{N}^L$

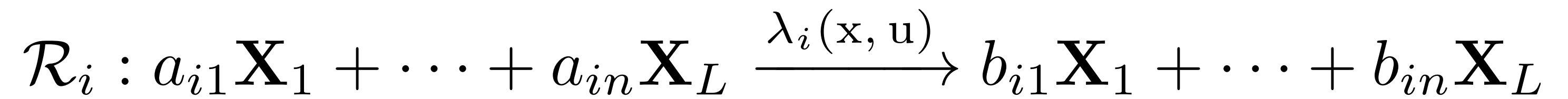
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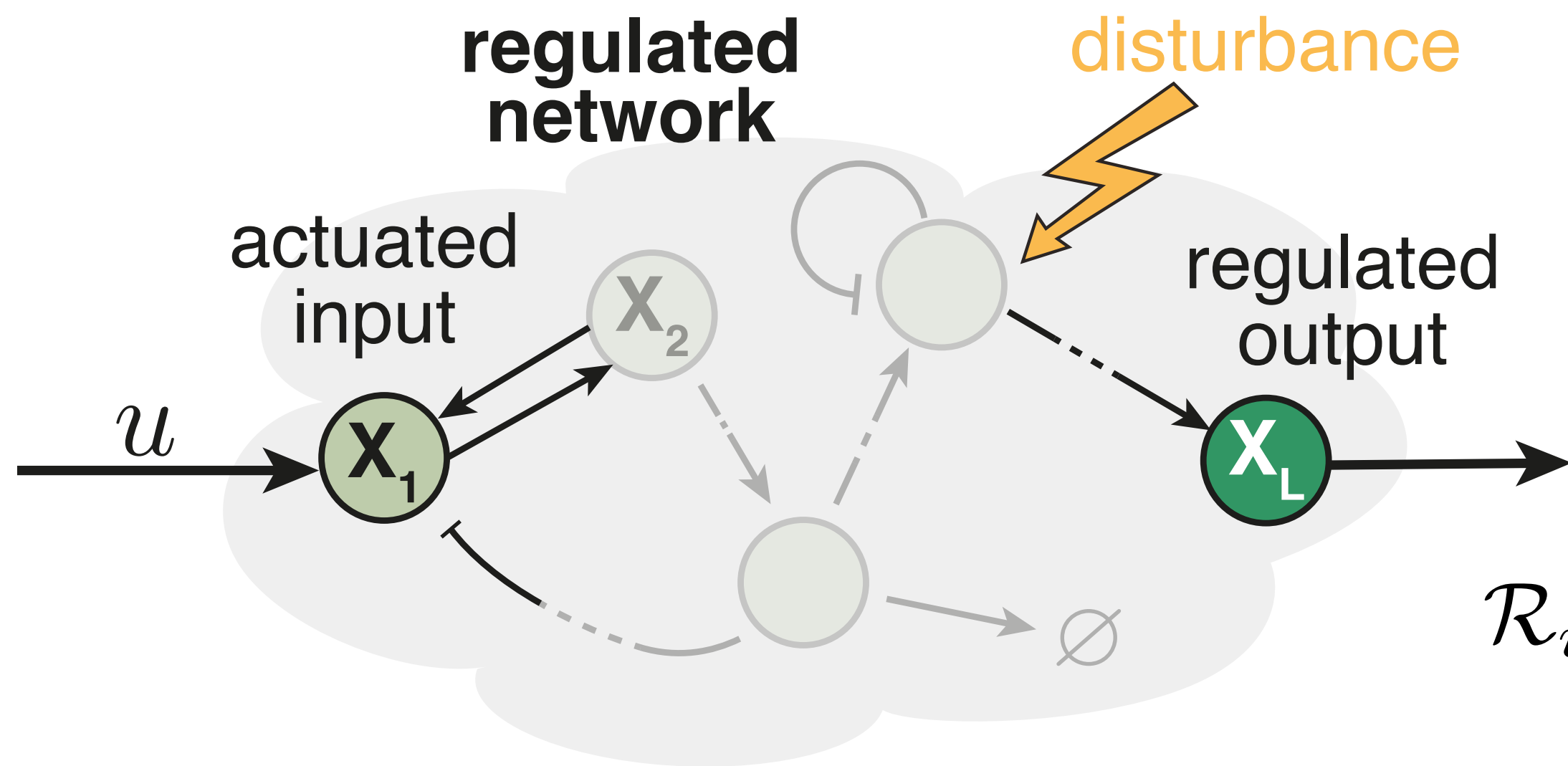


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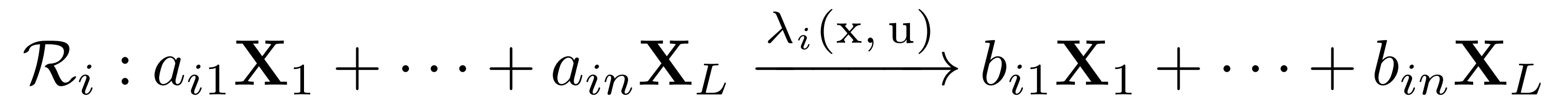
Propensity function: $\lambda_i : \mathbb{R}_+^L \times \mathbb{R}_+ \rightarrow \mathbb{R}_+$

The mathematical language: Chemical Reaction Networks (CRNs)



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Reactions: $\mathcal{R} \triangleq \{\mathcal{R}_1, \mathcal{R}_2, \dots, \mathcal{R}_n\}$



Vector form: $a_i\mathbf{X} \xrightarrow{\lambda_i(\mathbf{x}, \mathbf{u})} b_i\mathbf{X}$

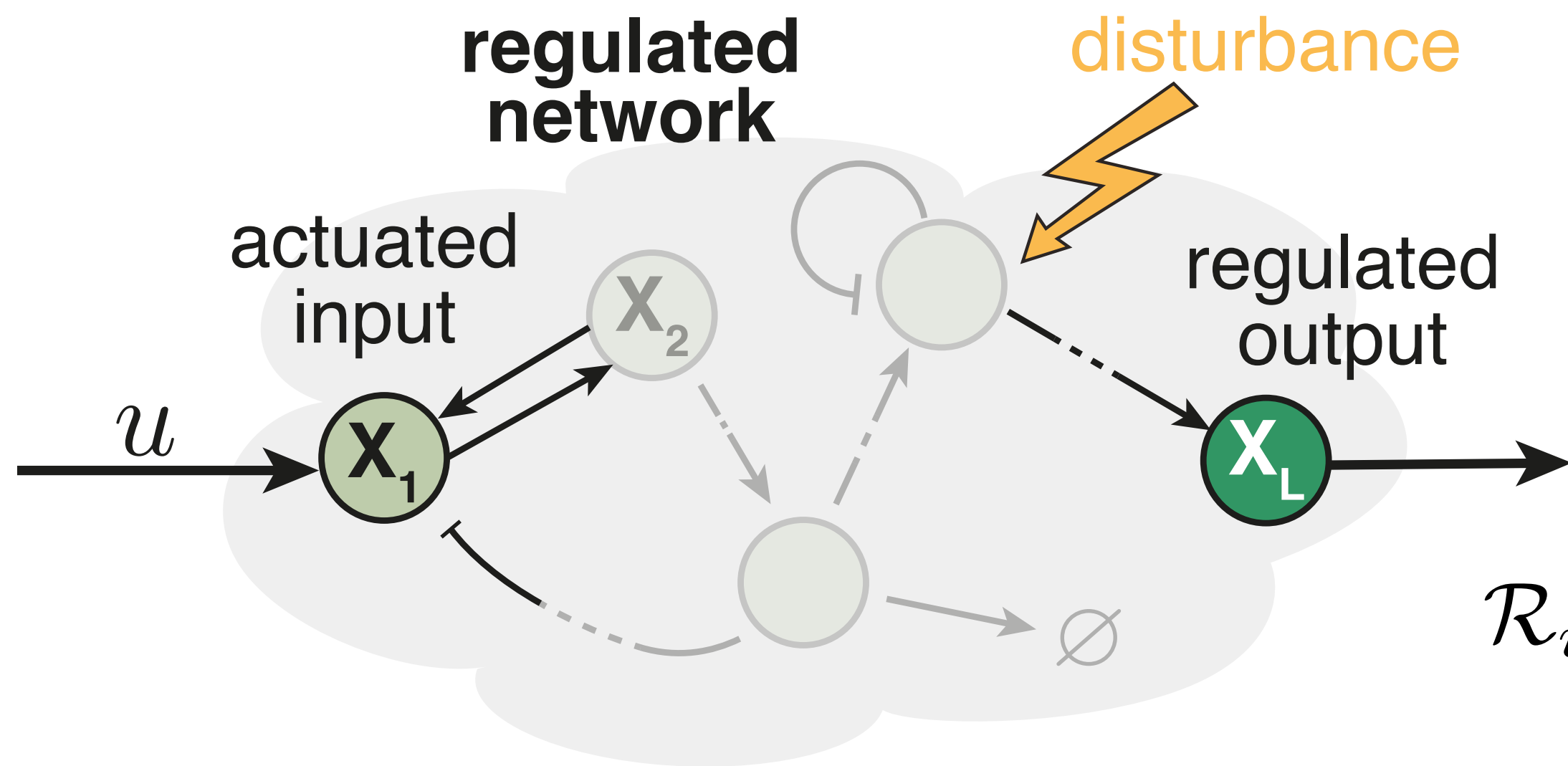
Stoichiometry vector: $s_i \triangleq b_i - a_i \in \mathbb{N}^L$

Propensity function: $\lambda_i : \mathbb{R}_+^L \times \mathbb{R}_+ \rightarrow \mathbb{R}_+$

Deterministic: $\dot{x} = \sum_{i=1}^n s_i \lambda_i(x, u)$

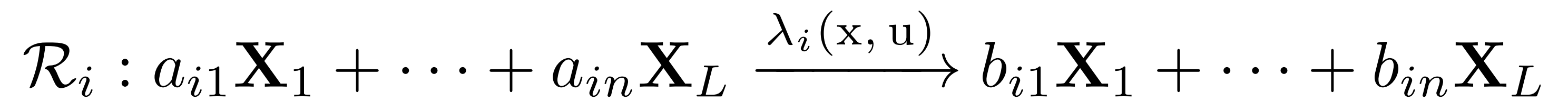
$(x \in \mathbb{R}_+)$ Nonlinear ODEs

The mathematical language: Chemical Reaction Networks (CRNs)



Species: $\mathbf{X} \triangleq \{\mathbf{X}_1, \mathbf{X}_2, \dots, \mathbf{X}_L\}$

Reactions: $\mathcal{R} \triangleq \{\mathcal{R}_1, \mathcal{R}_2, \dots, \mathcal{R}_n\}$



Vector form: $a_i\mathbf{X} \xrightarrow{\lambda_i(\mathbf{x}, \mathbf{u})} b_i\mathbf{X}$

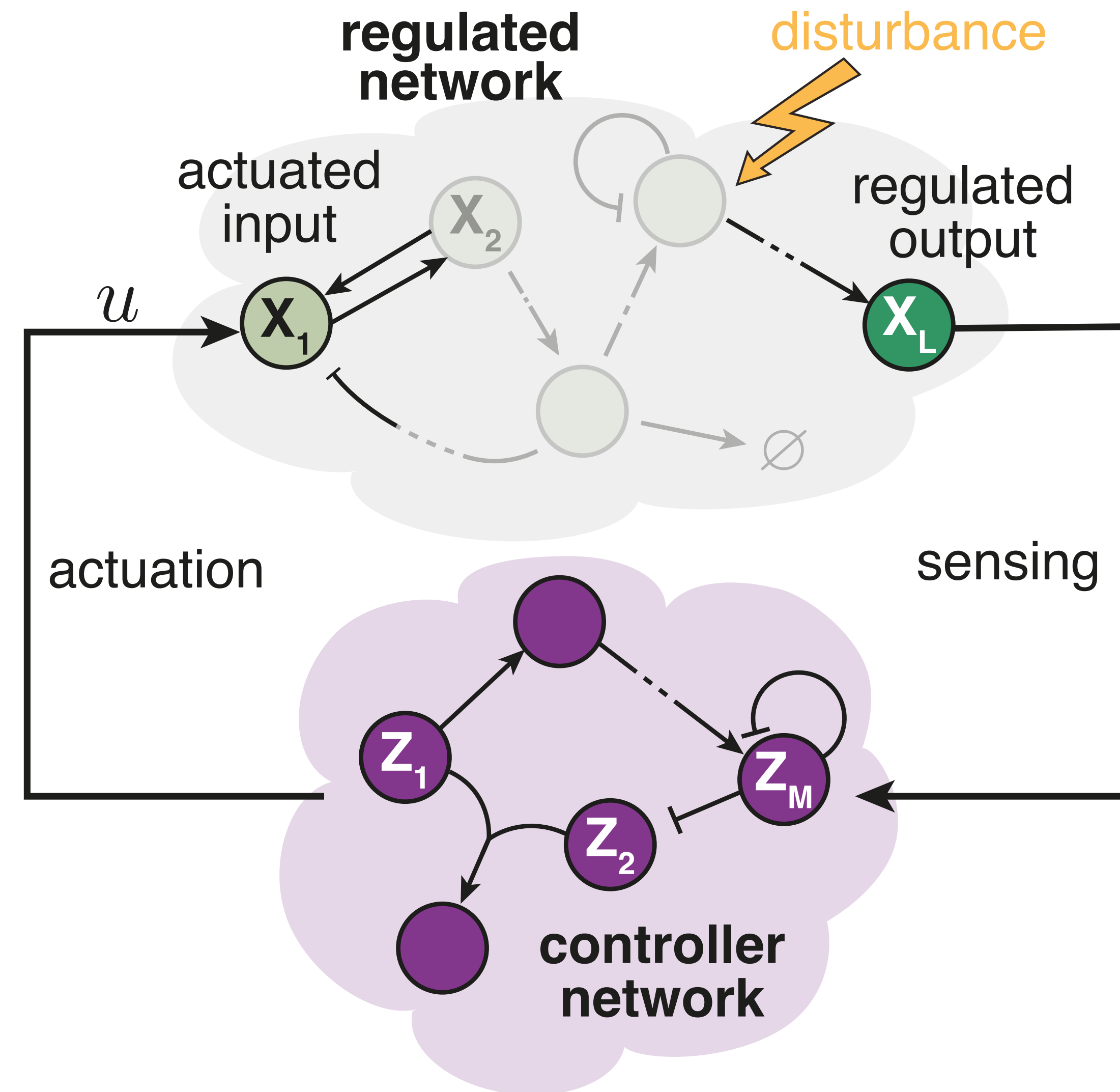
Stoichiometry vector: $s_i \triangleq b_i - a_i \in \mathbb{N}^L$

Propensity function: $\lambda_i : \mathbb{R}_+^L \times \mathbb{R}_+ \rightarrow \mathbb{R}_+$

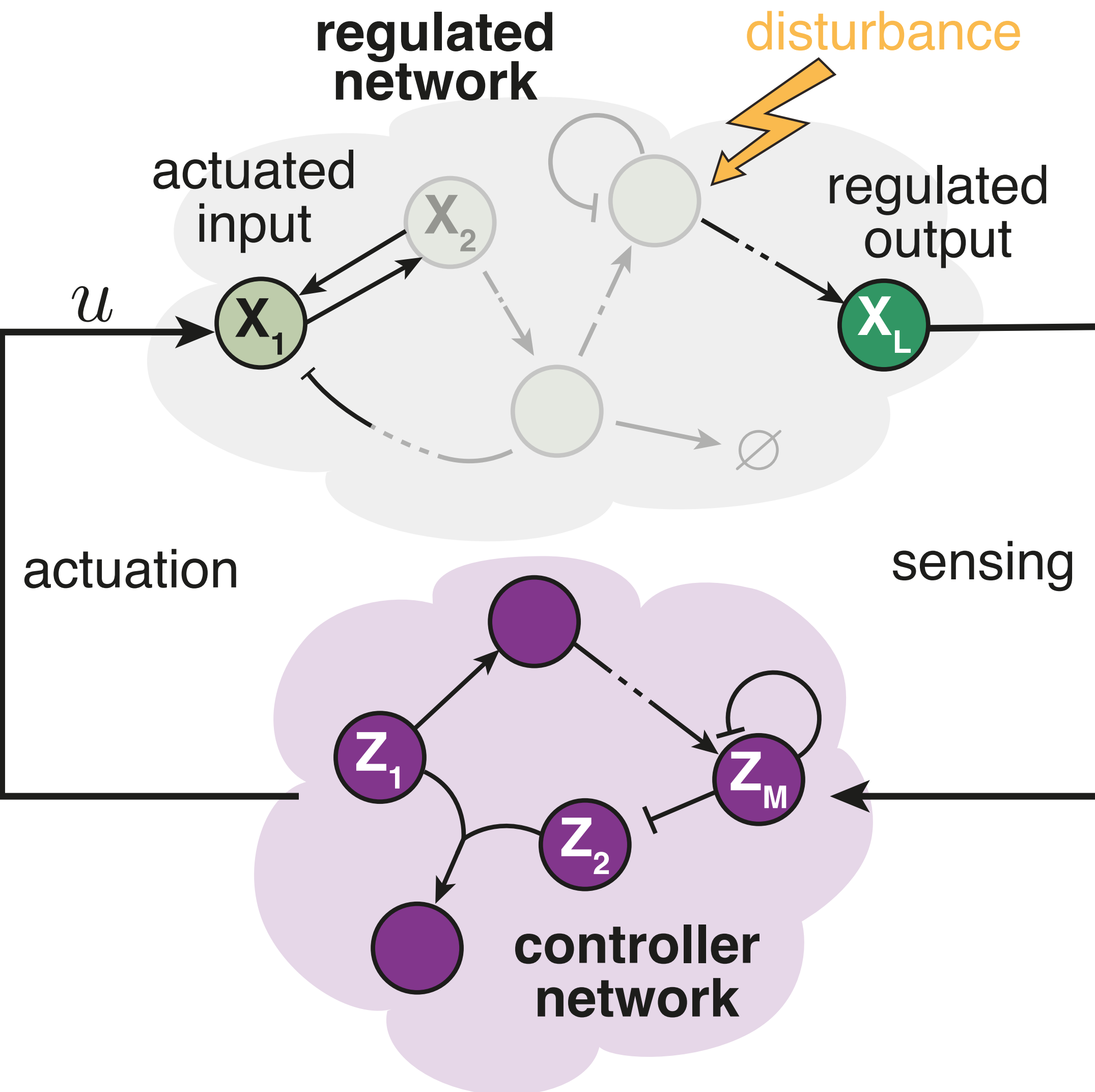
Deterministic: $\dot{x} = \sum_{i=1}^n s_i \lambda_i(x, u)$ ($x \in \mathbb{R}_+$) Nonlinear ODEs

Stochastic: $\dot{p}_x(t) = \sum_{i=1}^n \lambda_i(x - s_i, u)p_{x-s_i}(t) - \lambda_i(x, u)p_x(t)$ ($x \in \mathbb{N}_+$) Chemical Master Equation (for a CTMC)

A framework for biomolecular feedback controllers



A framework for biomolecular feedback controllers



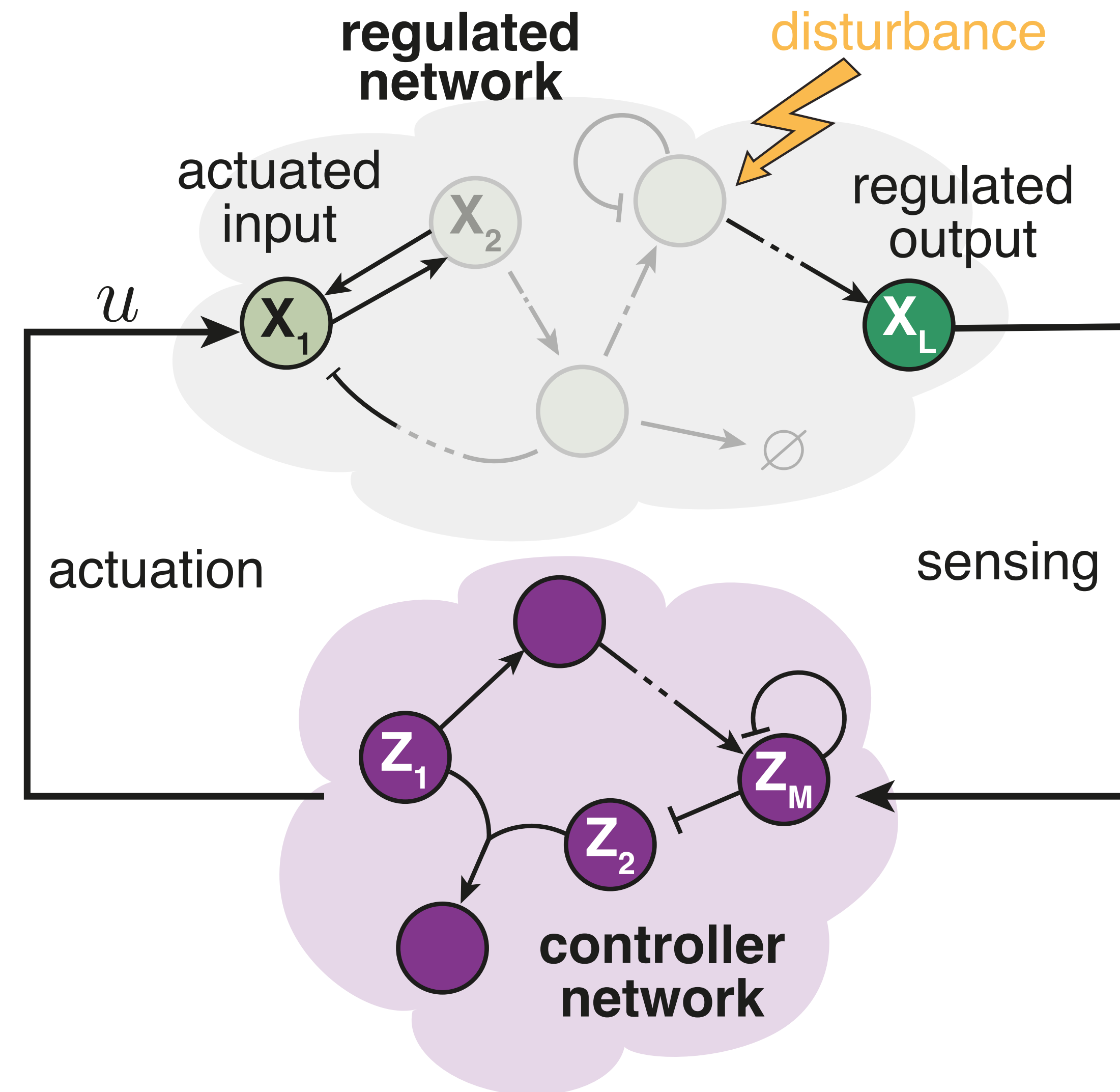
Questions:

(1) What reaction network structure in the controller achieves **robust steady-state tracking**?

Despite:

- ✦ Disturbances
- ✦ Unknown initial conditions
- ✦ Uncertain regulated network
- ✦ Stochastic noise

A framework for biomolecular feedback controllers



Questions:

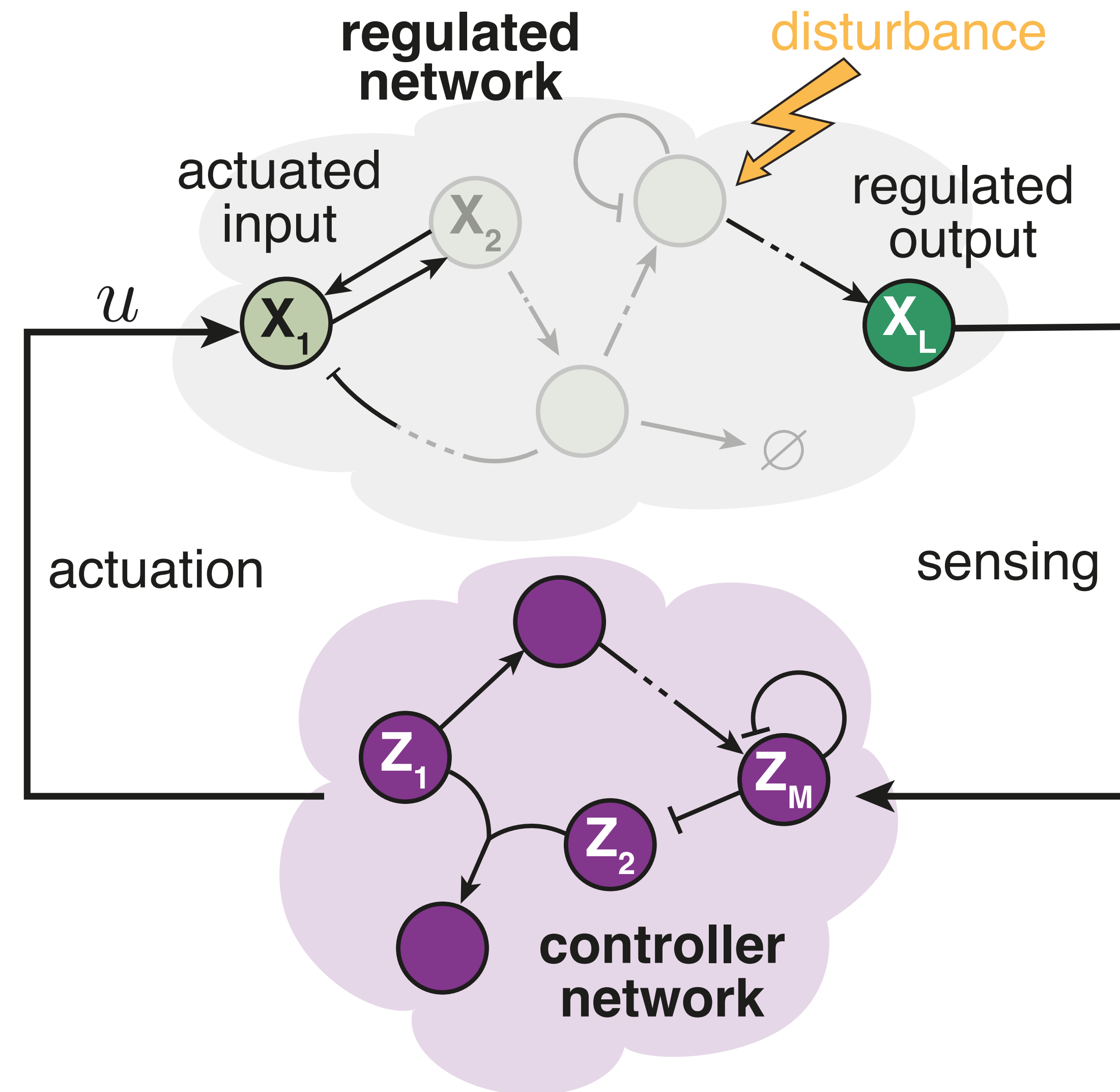
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a.k.a. **Robust Perfect Adaptation (RPA)**

A framework for biomolecular feedback controllers



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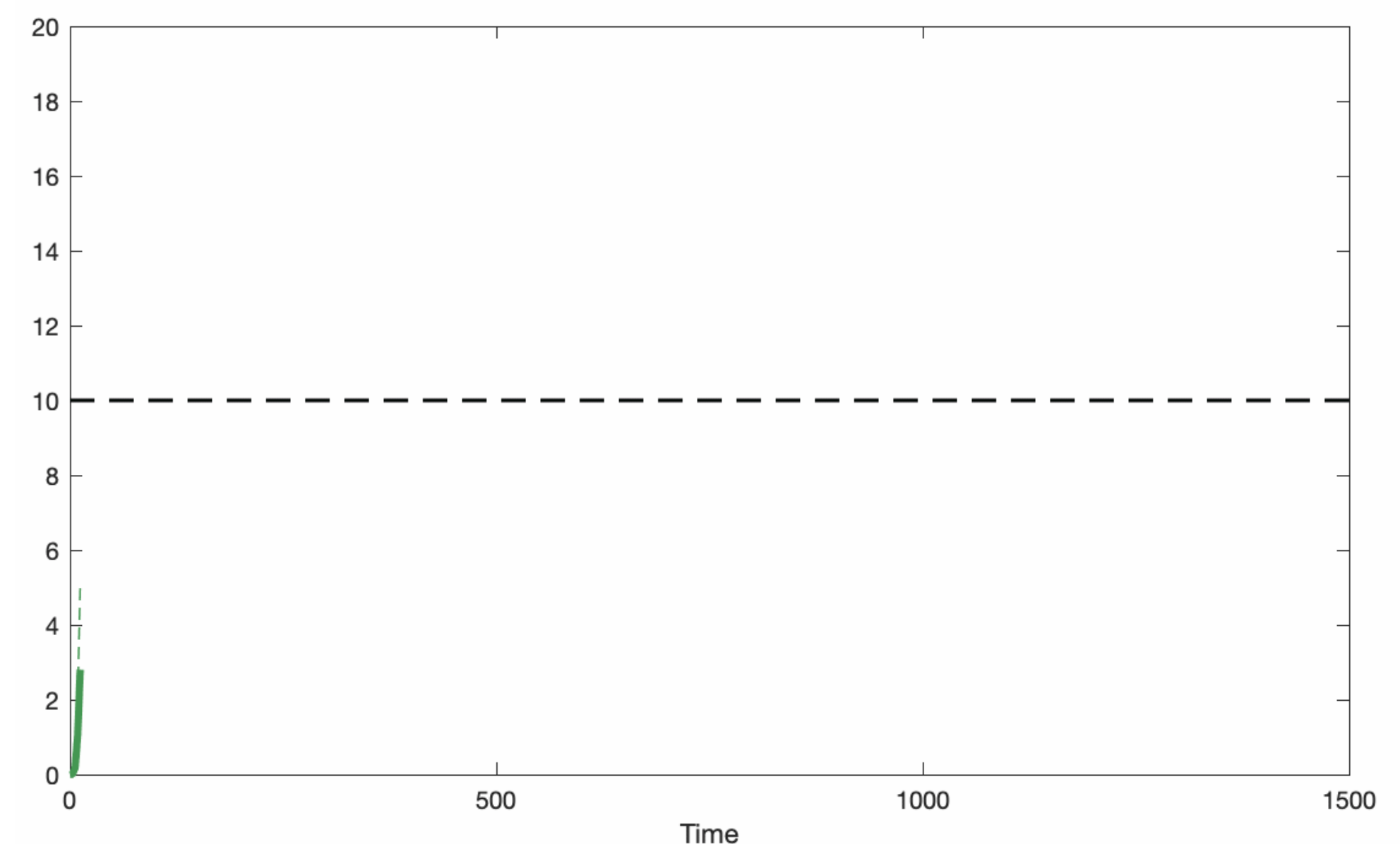
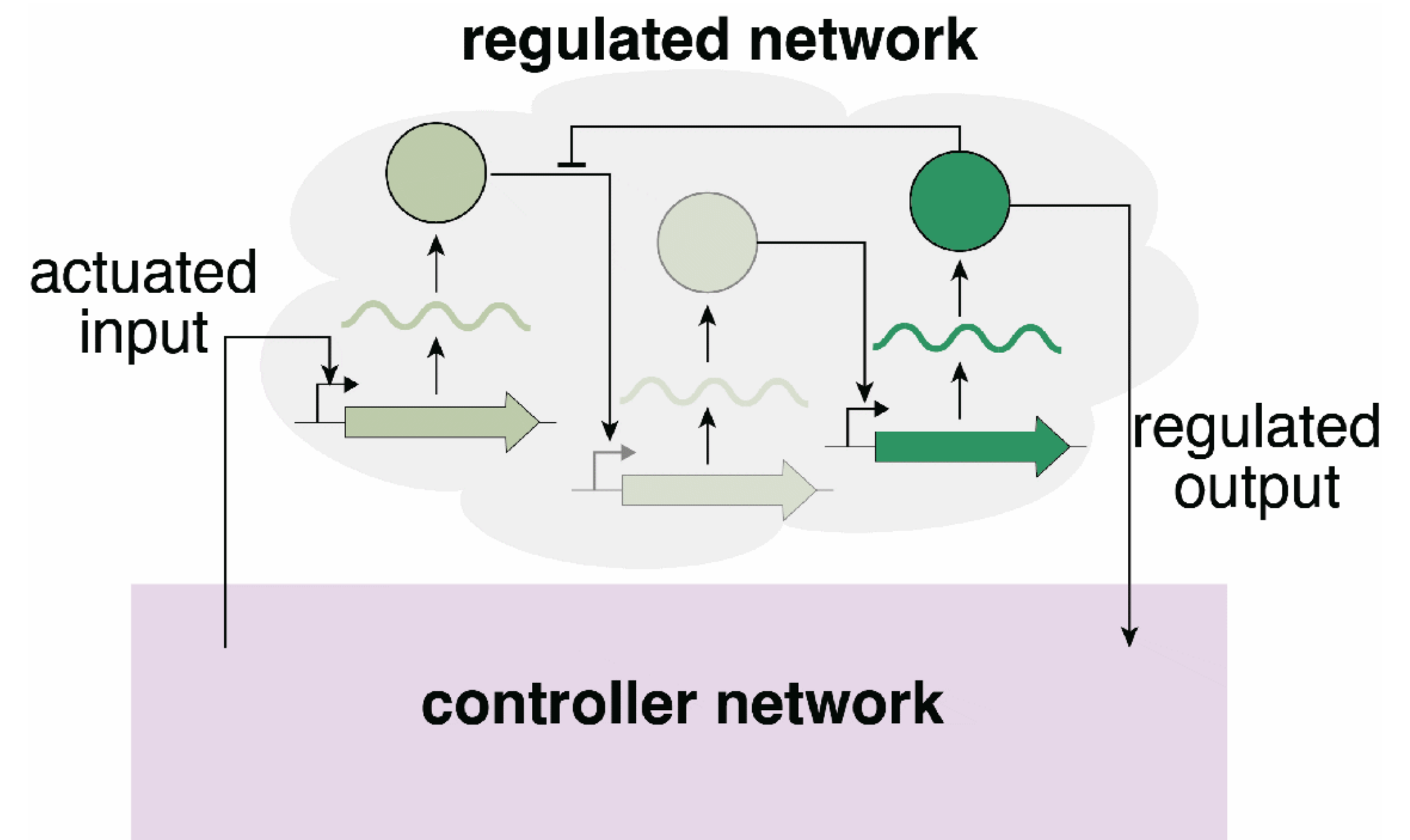
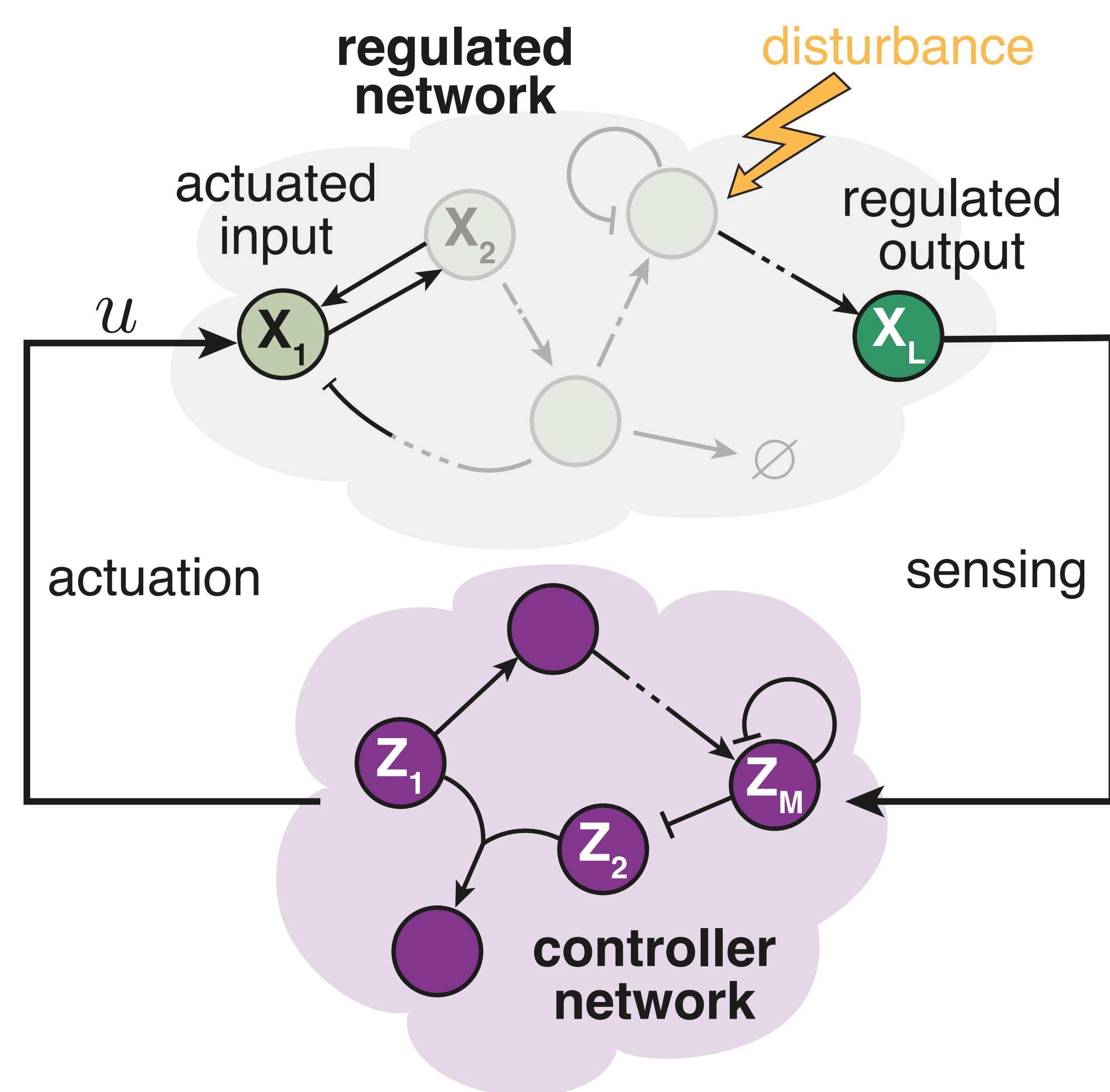
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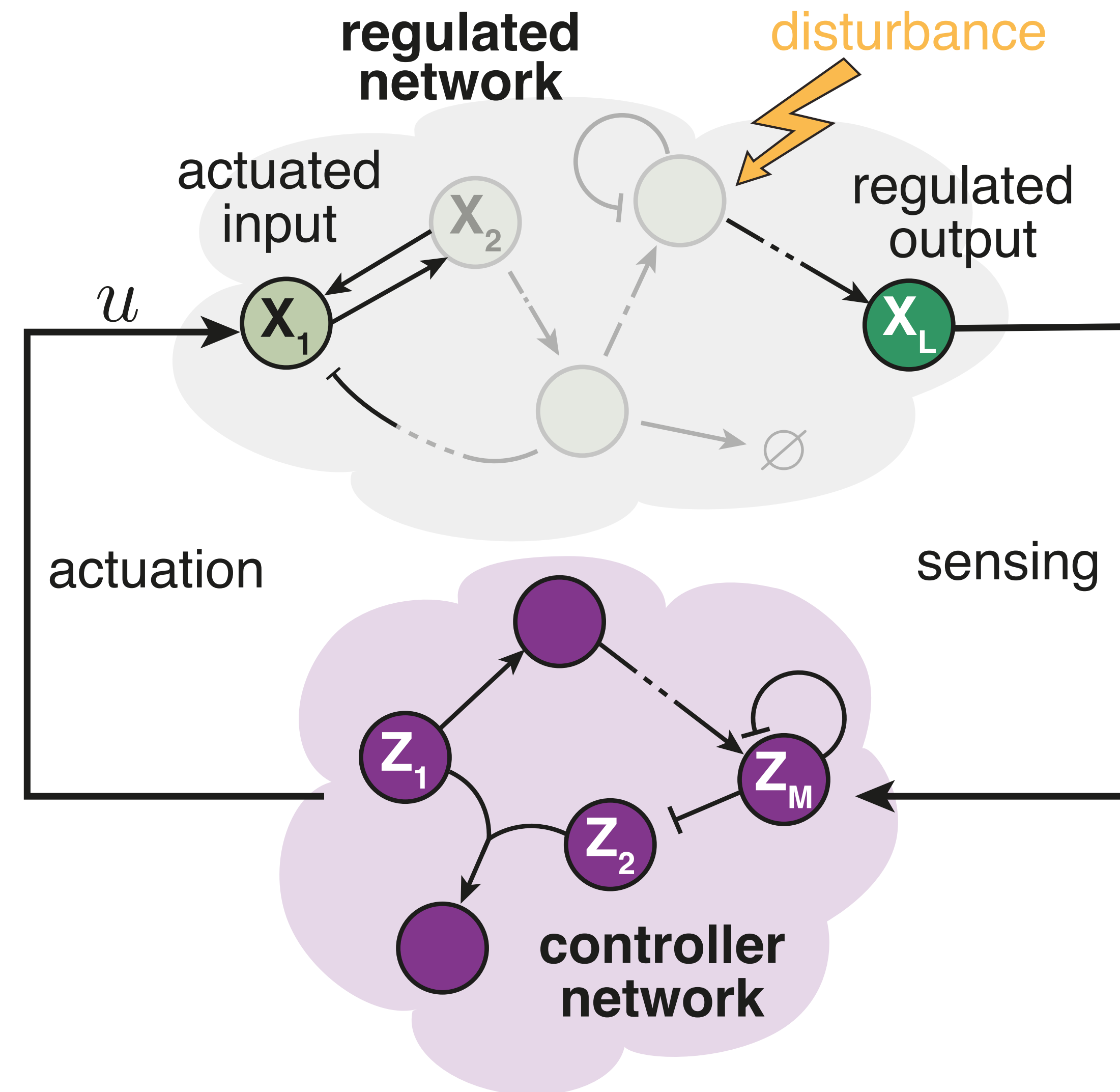
a.k.a. **Robust Perfect Adaptation (RPA)**

(2) What reaction network structure in the controller enhances **dynamic performance**?

A framework for biomolecular feedback controllers



A framework for biomolecular feedback controllers



Questions:

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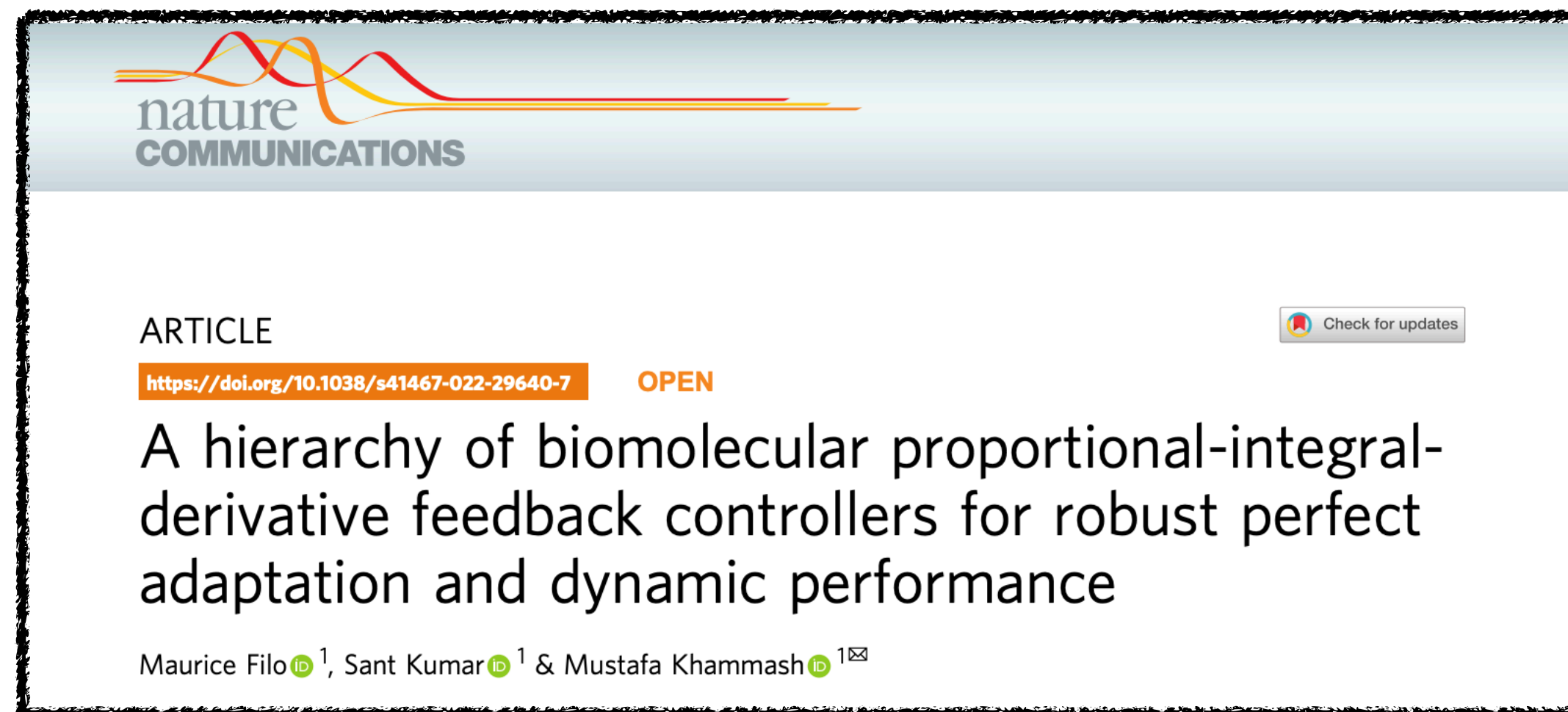
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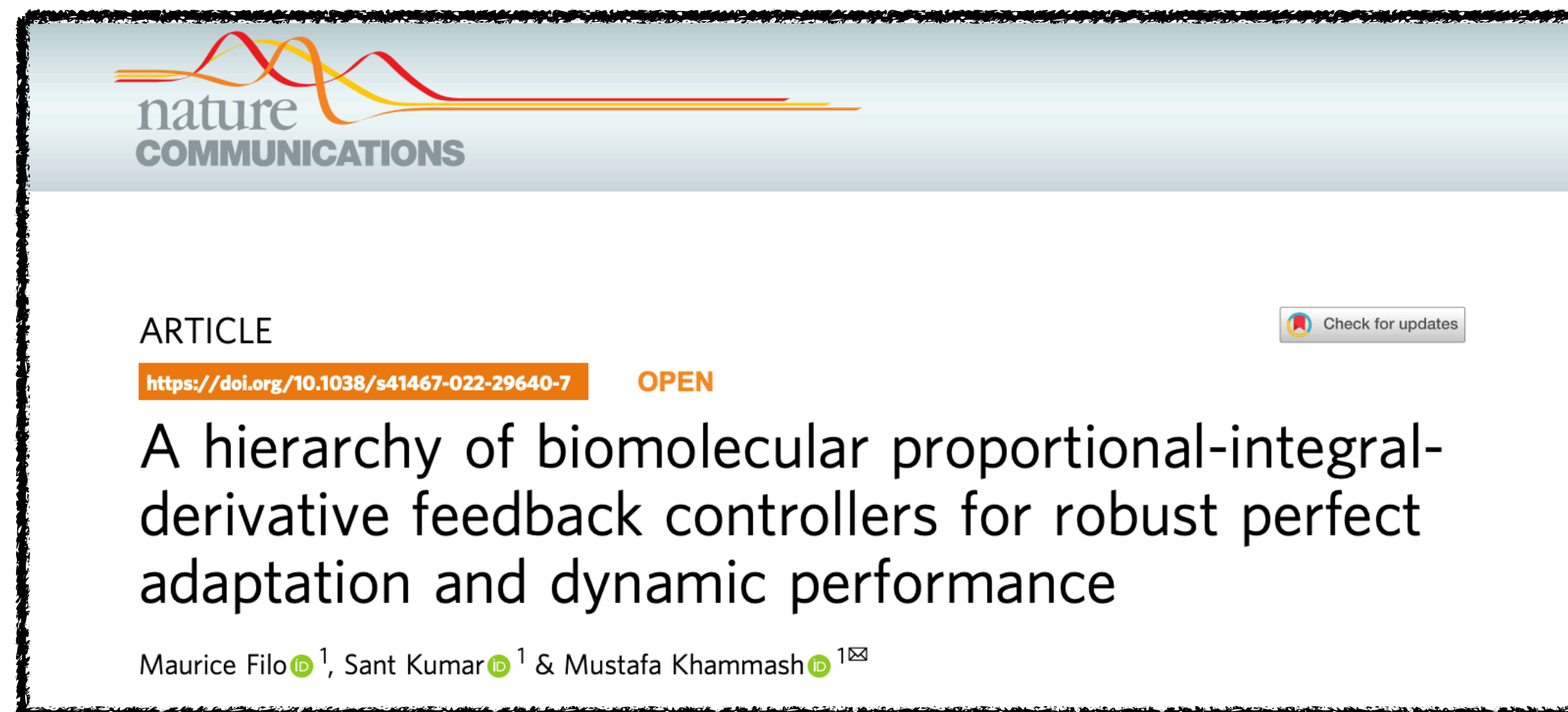
(2) What reaction network structure in the controller enhances **dynamic performance**?

(3) What **genetic parts** can implement such network inside the living cells?

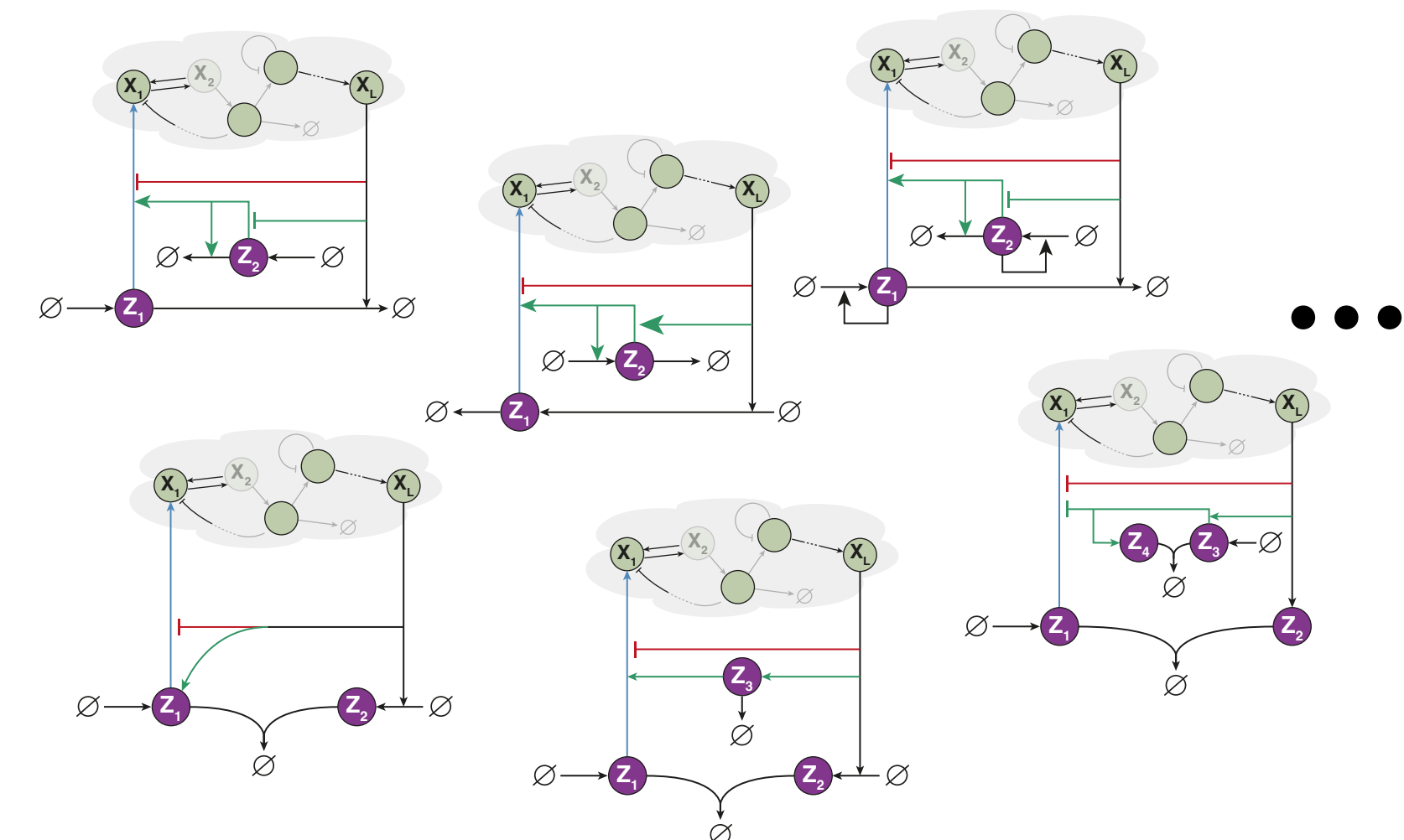
Can we design molecular PID controllers?



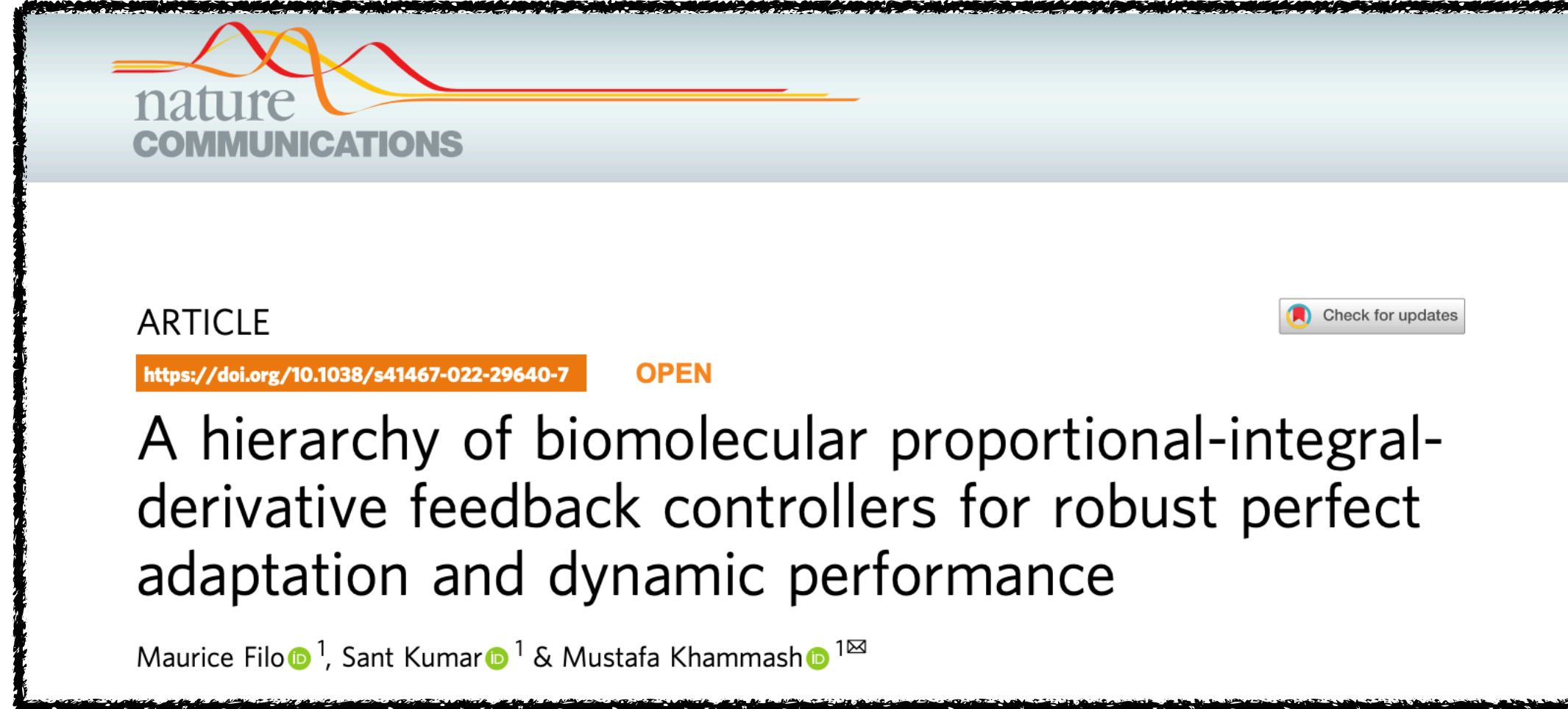
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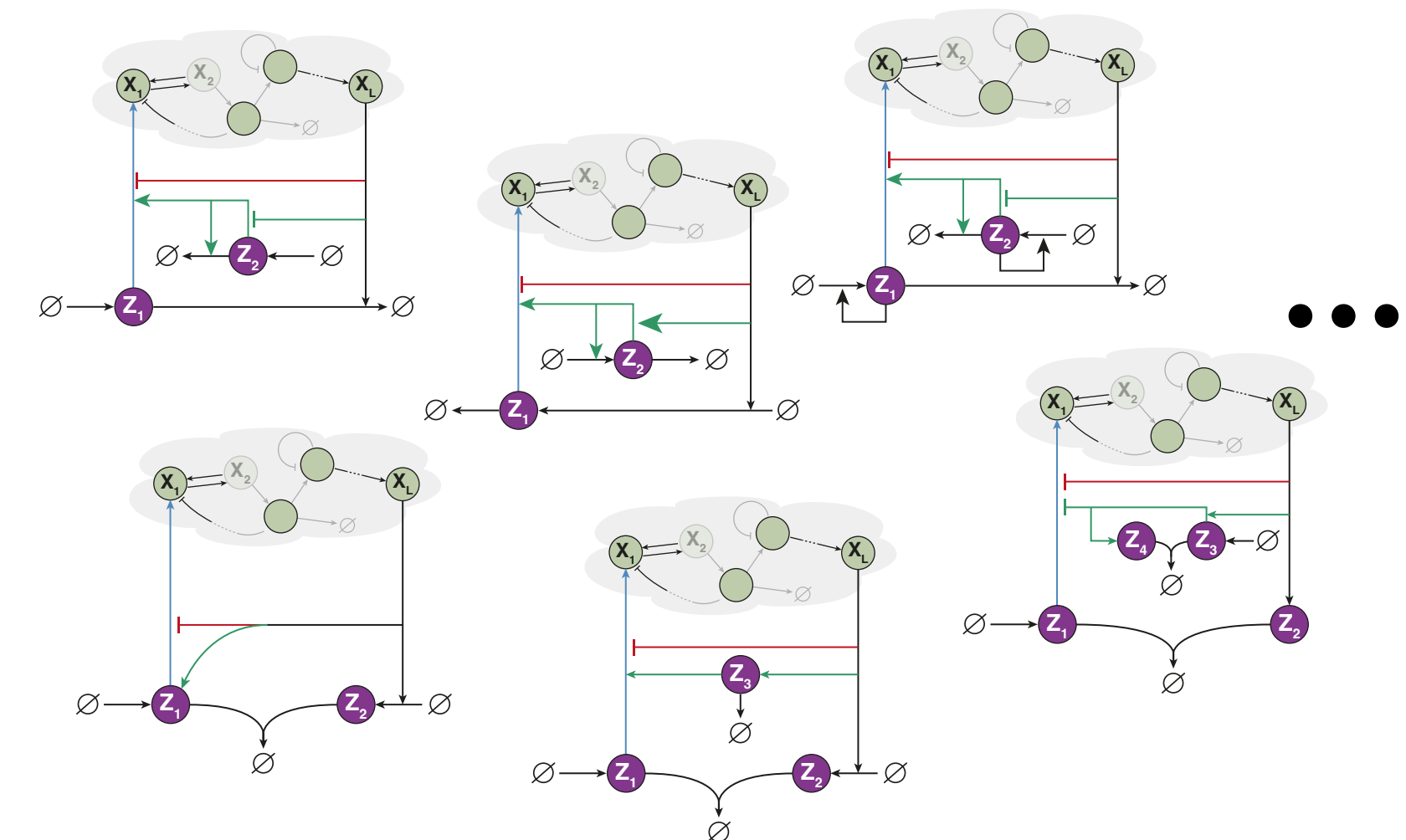
- Tailored control-theoretic tools to biology $\longrightarrow$ family of biological PIDs



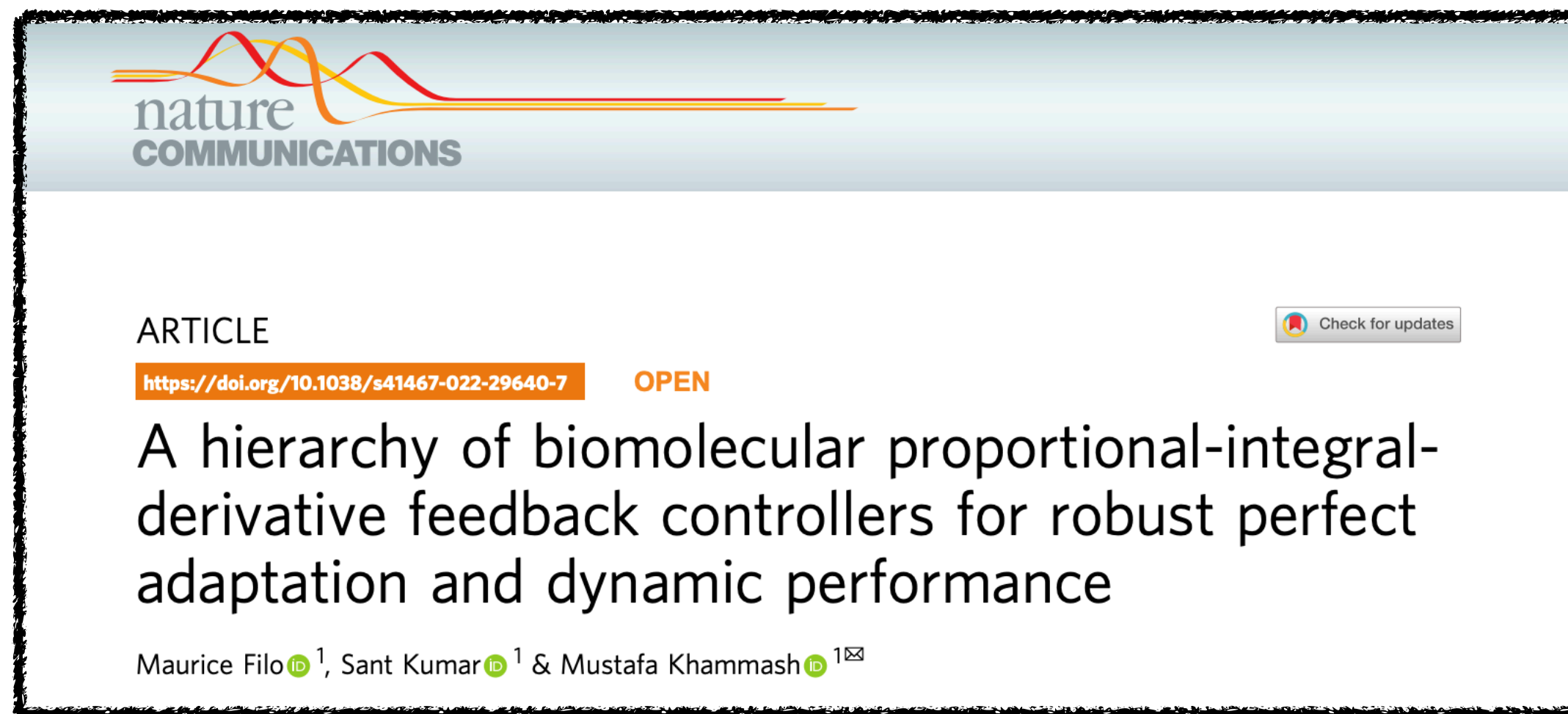
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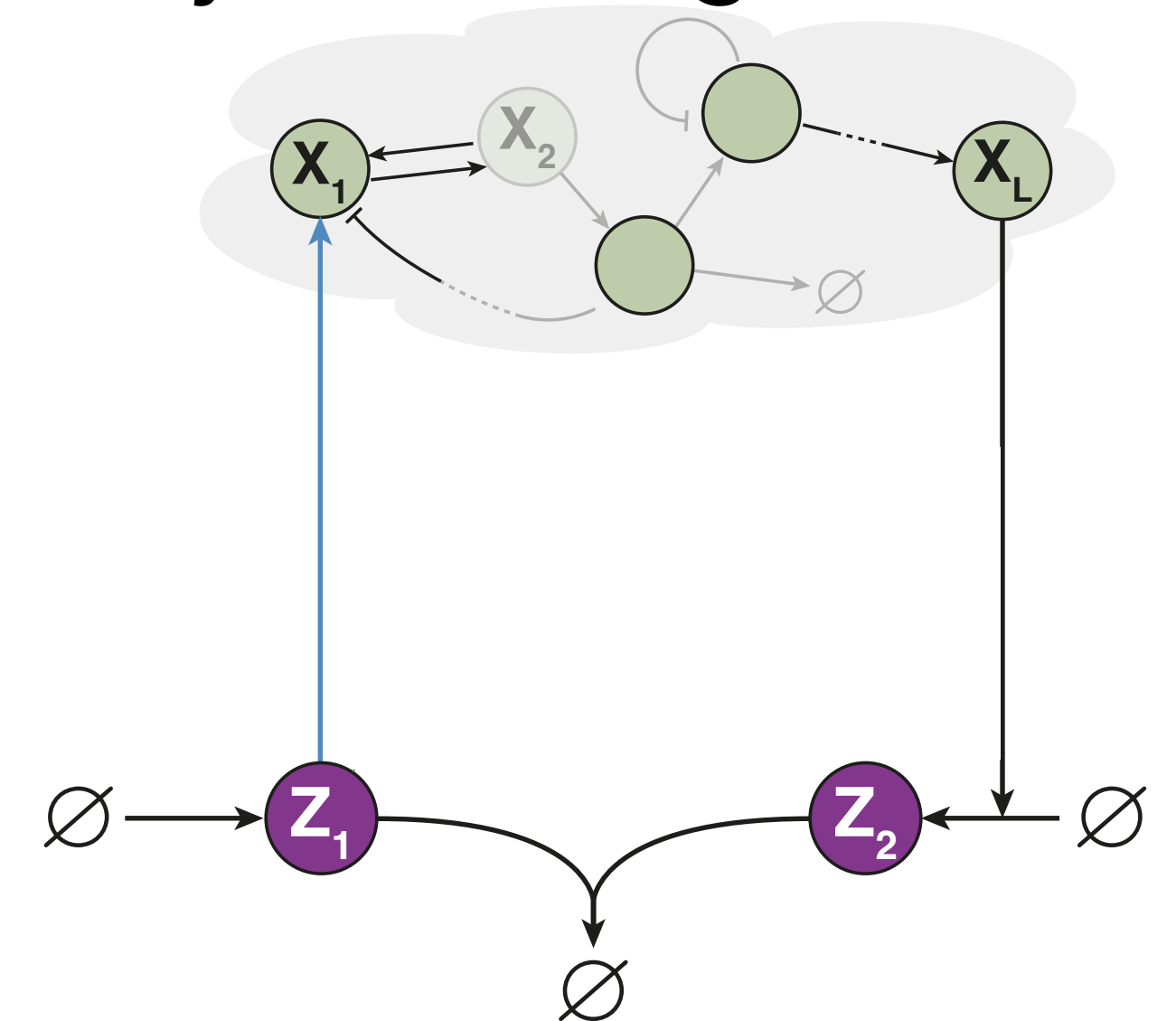
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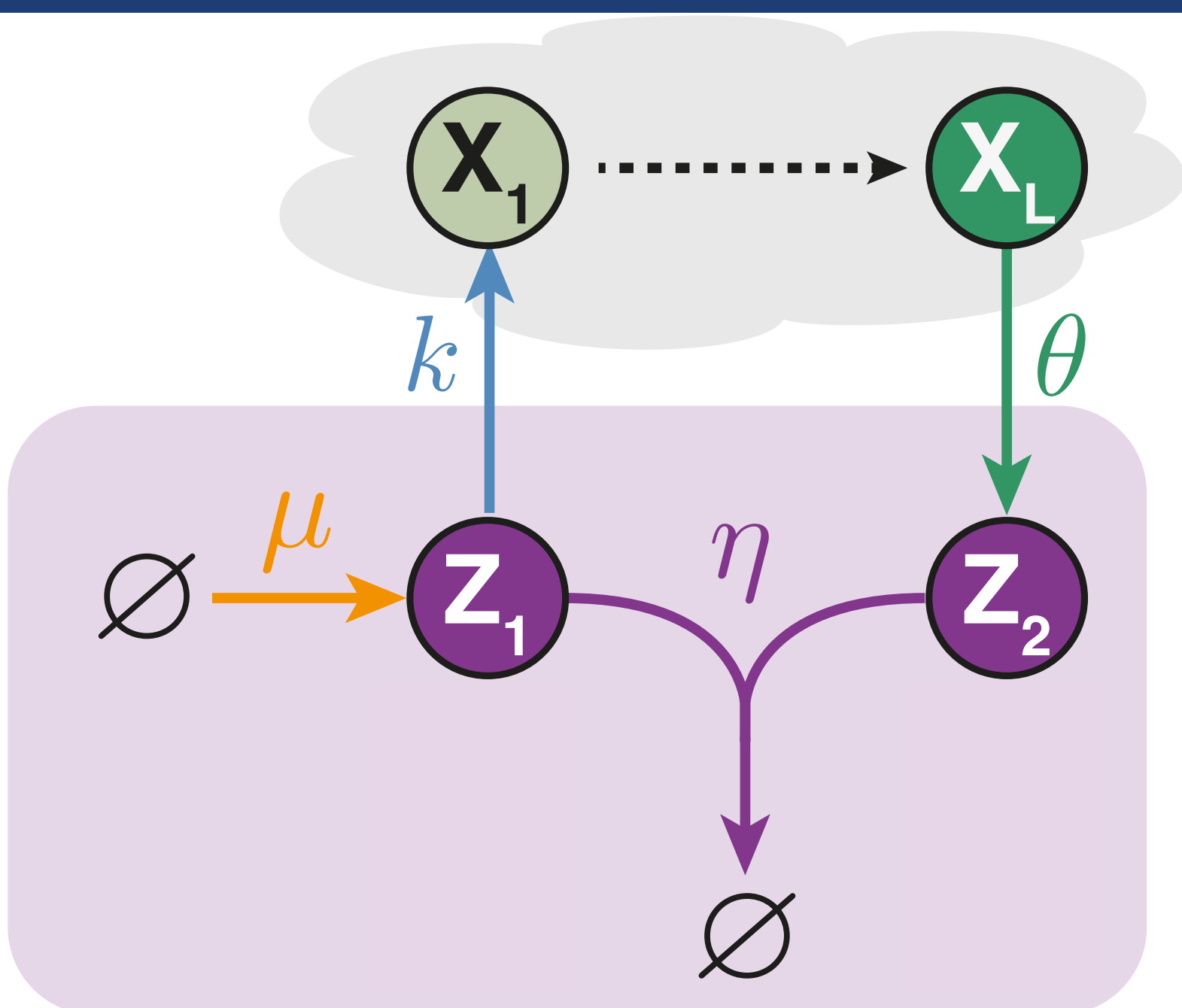


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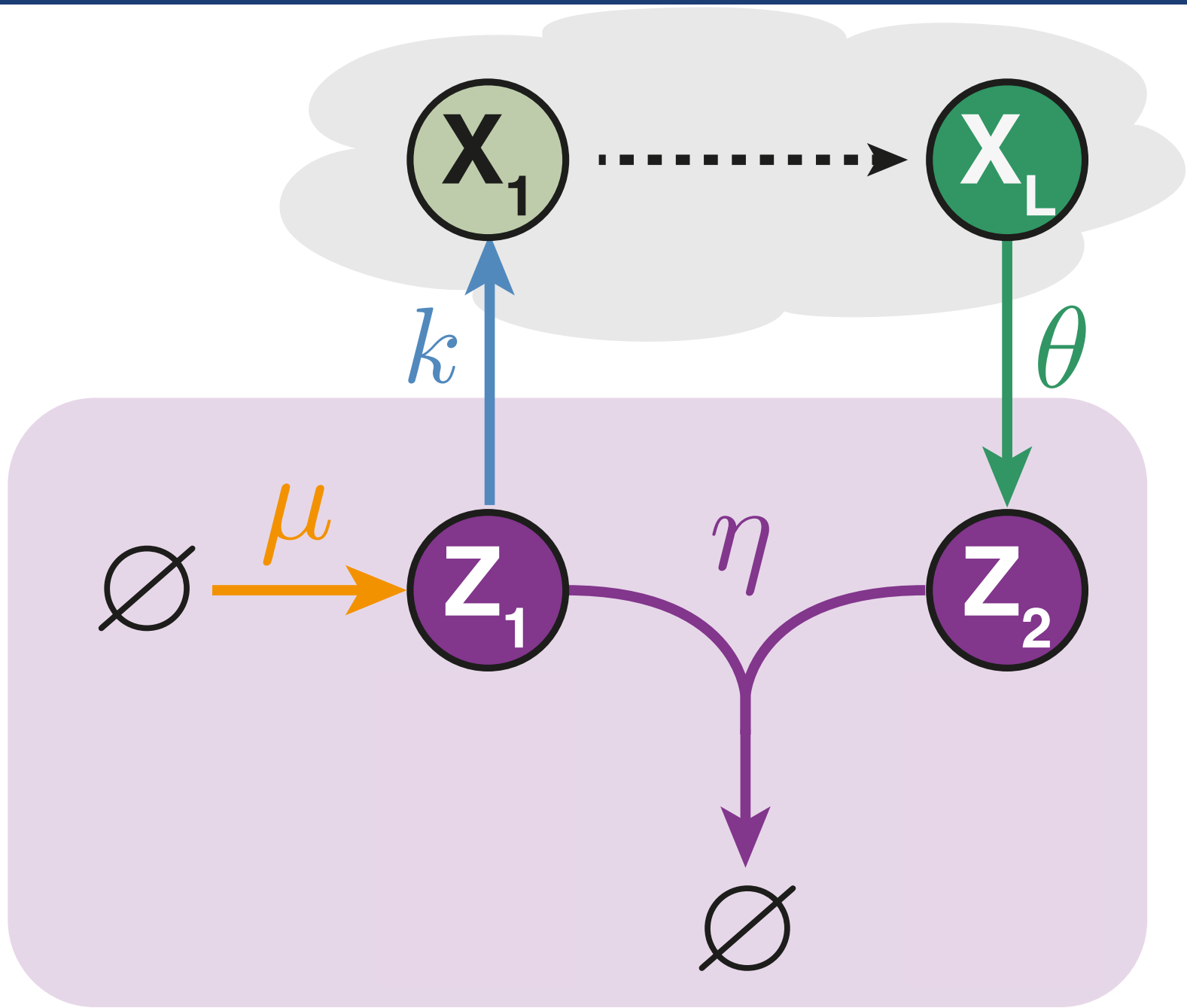
C. Briat*, A. Gupta*, M. Khammash. Cell Systems (2016)

Molecular integral feedback controller



Setpoint	$\emptyset \xrightarrow{\mu} \mathbf{z}_1$
Actuation	$\mathbf{z}_1 \xrightarrow{k} \mathbf{z}_1 + \mathbf{x}_1$
Sequestration	$\mathbf{z}_1 + \mathbf{z}_2 \xrightarrow{\eta} \emptyset$
Sensing	$\mathbf{x}_L \xrightarrow{\theta} \mathbf{x}_L + \mathbf{z}_2$

Molecular integral feedback controller

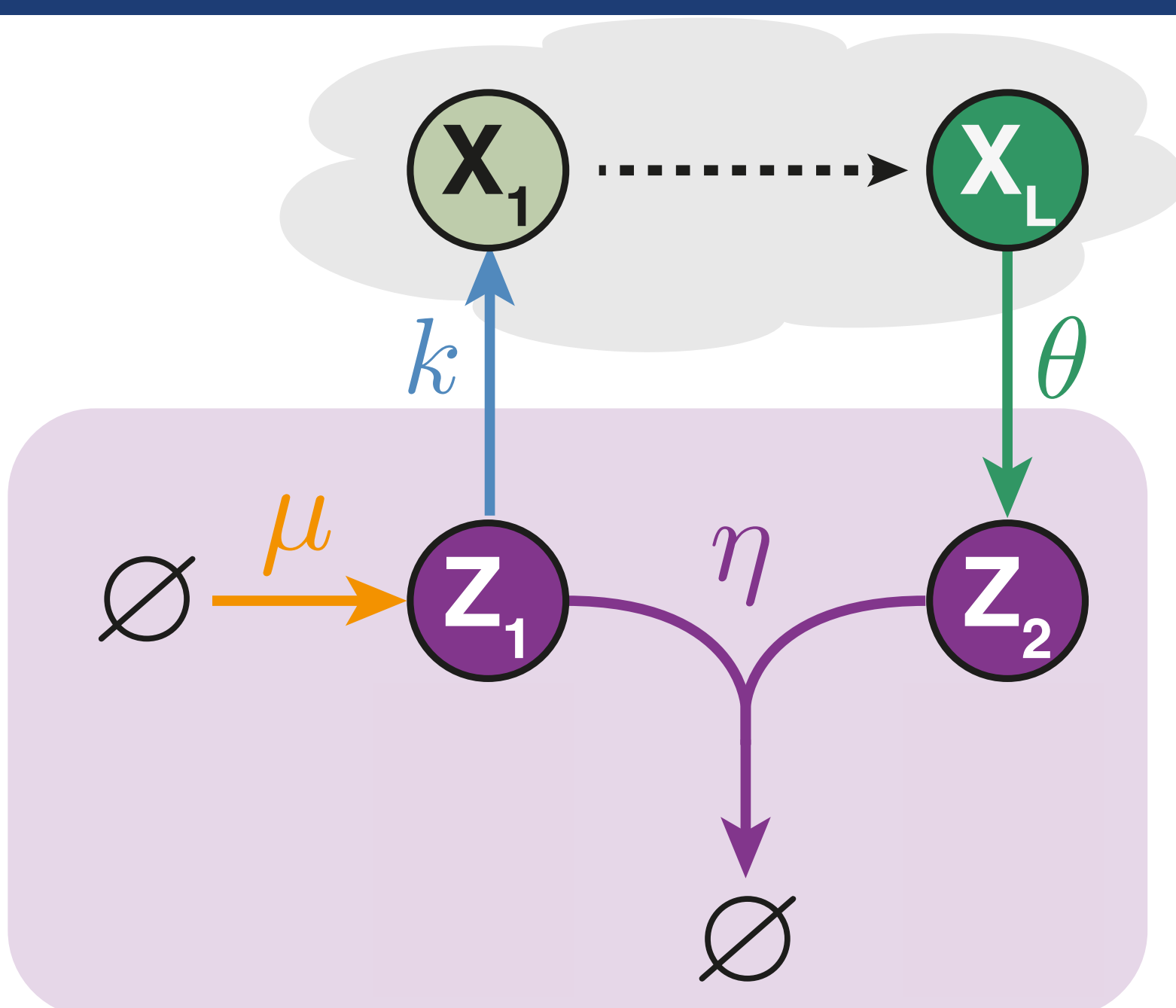


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Deterministic:

$$\begin{cases} \dot{z}_1 = \mu - \eta z_1 z_2 \\ \dot{z}_2 = \theta x_L - \eta z_1 z_2 \end{cases}$$

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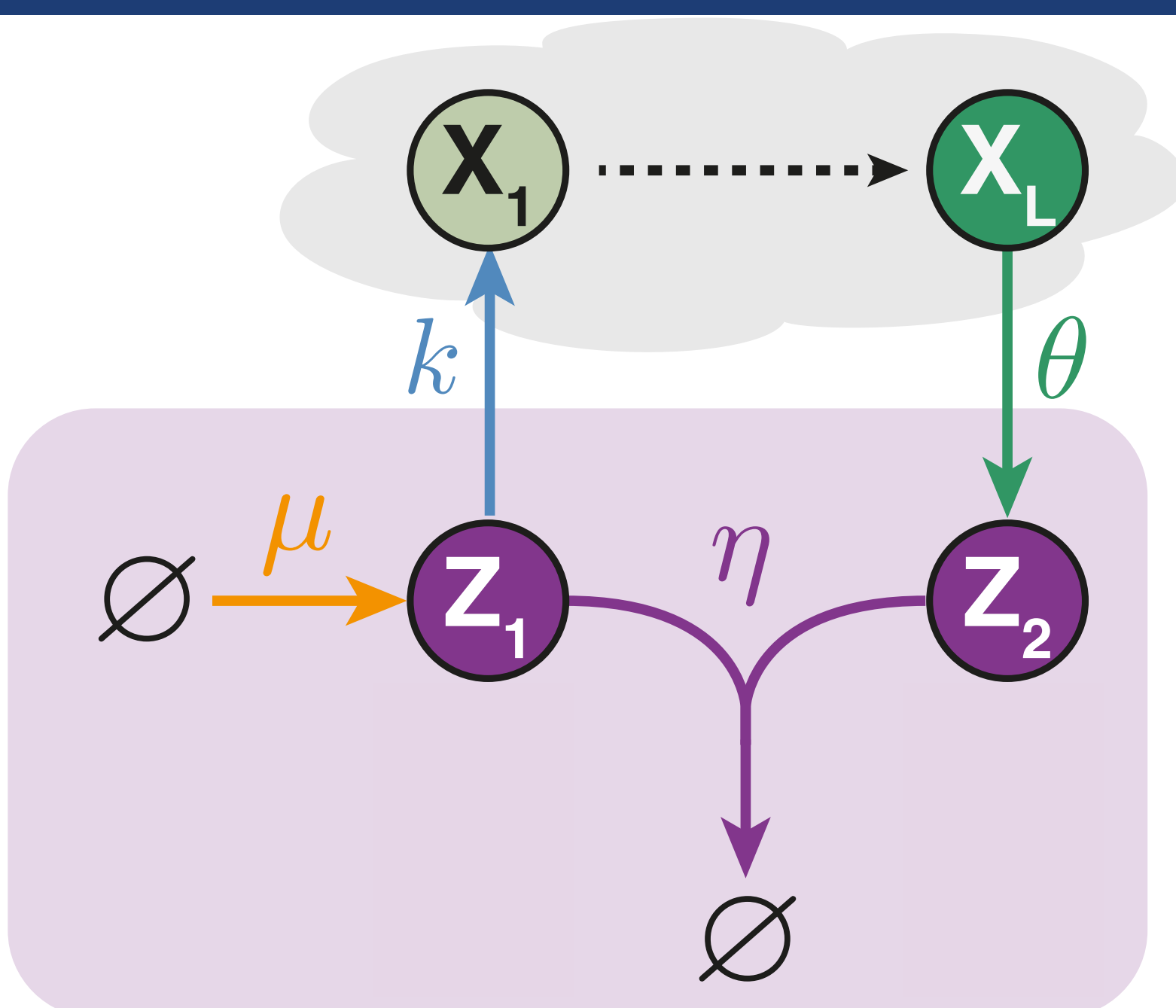
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Integrated Variable:

$$z \triangleq z_1 - z_2$$

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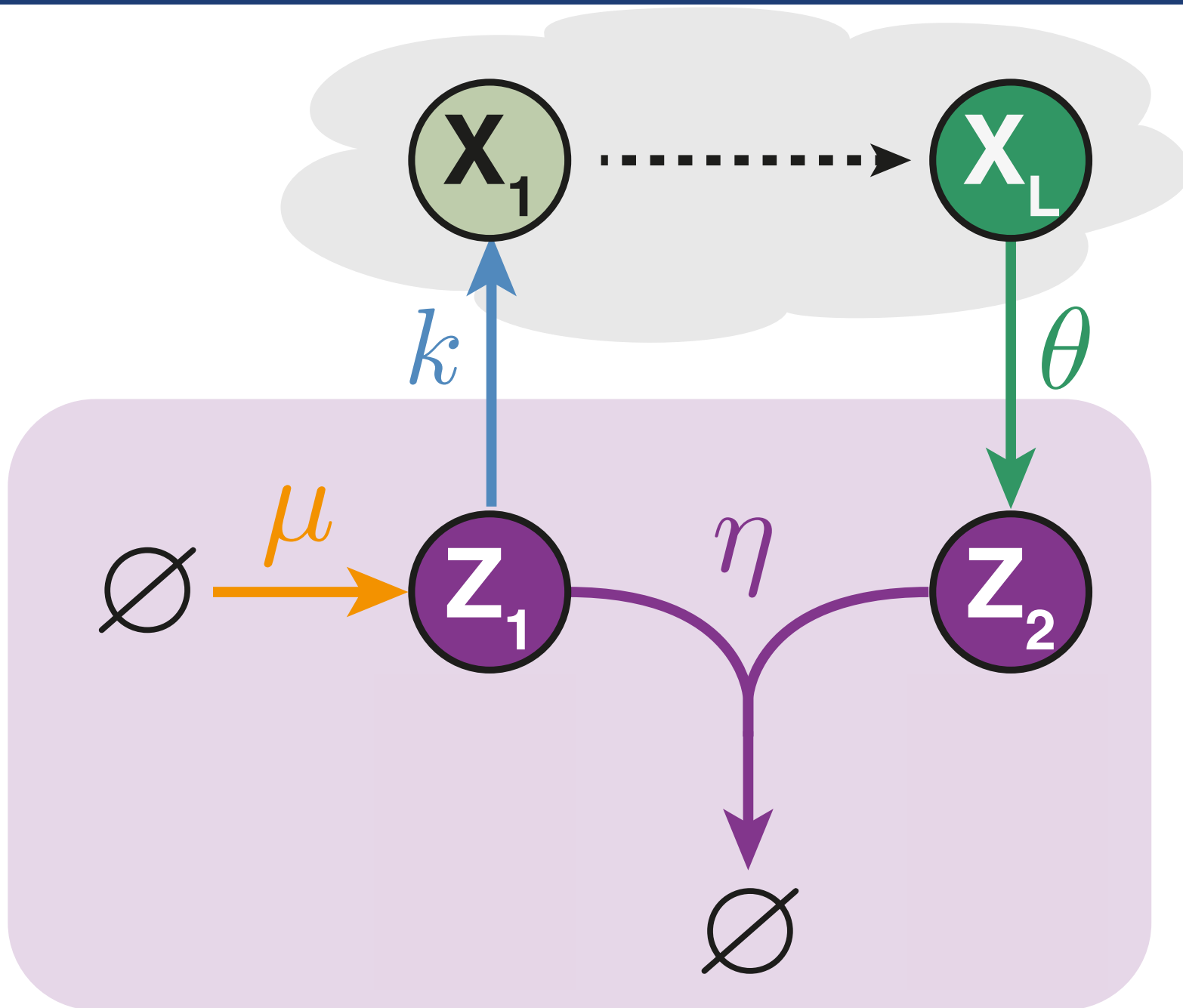
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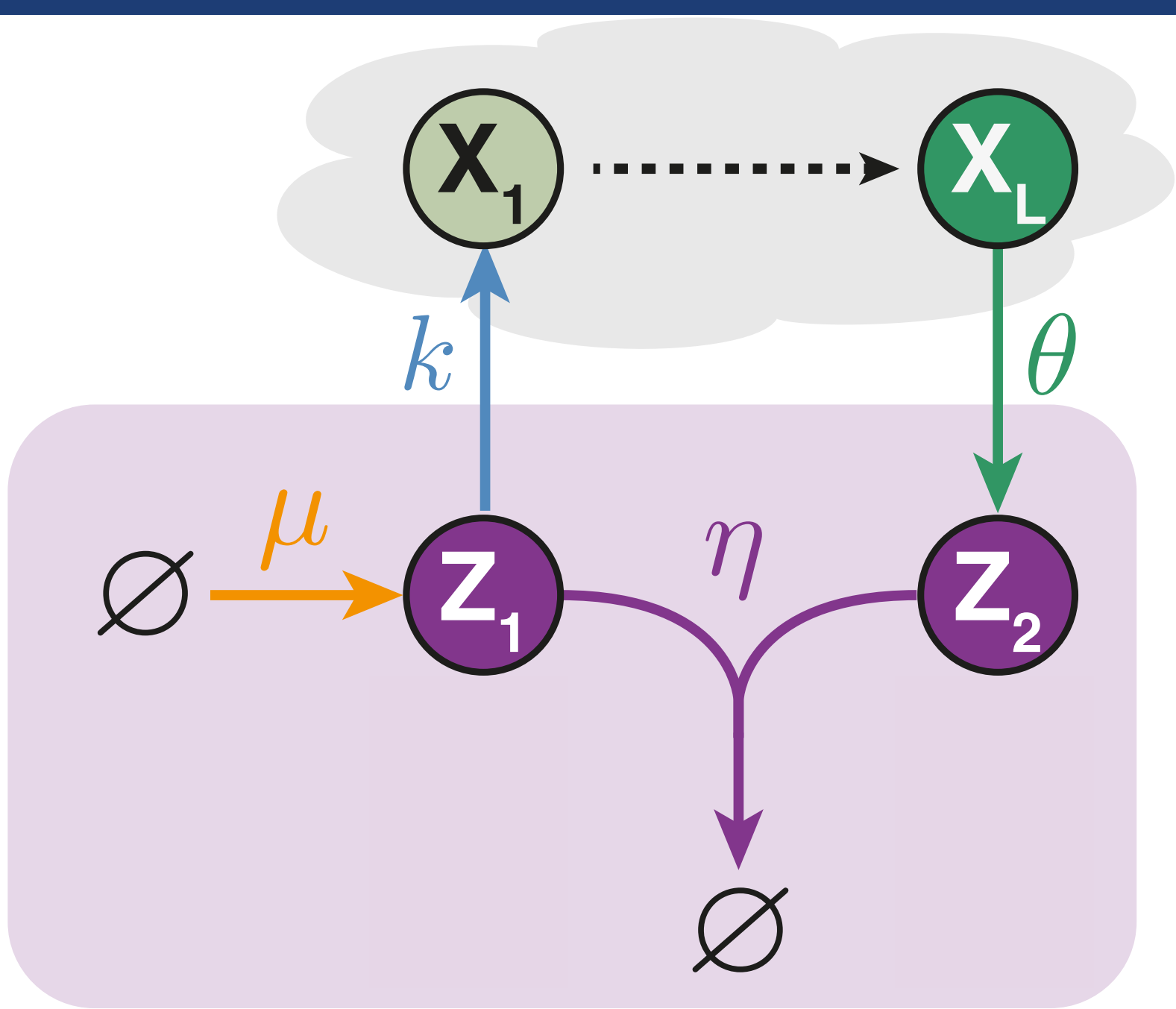
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Integrated Variable:

$$z \triangleq z_1 - z_2 \\ \implies \dot{z} = \mu - \theta x_L$$

$$z(t) = \int_0^t (\mu - \theta x_L(\tau)) d\tau$$

Molecular integral feedback controller



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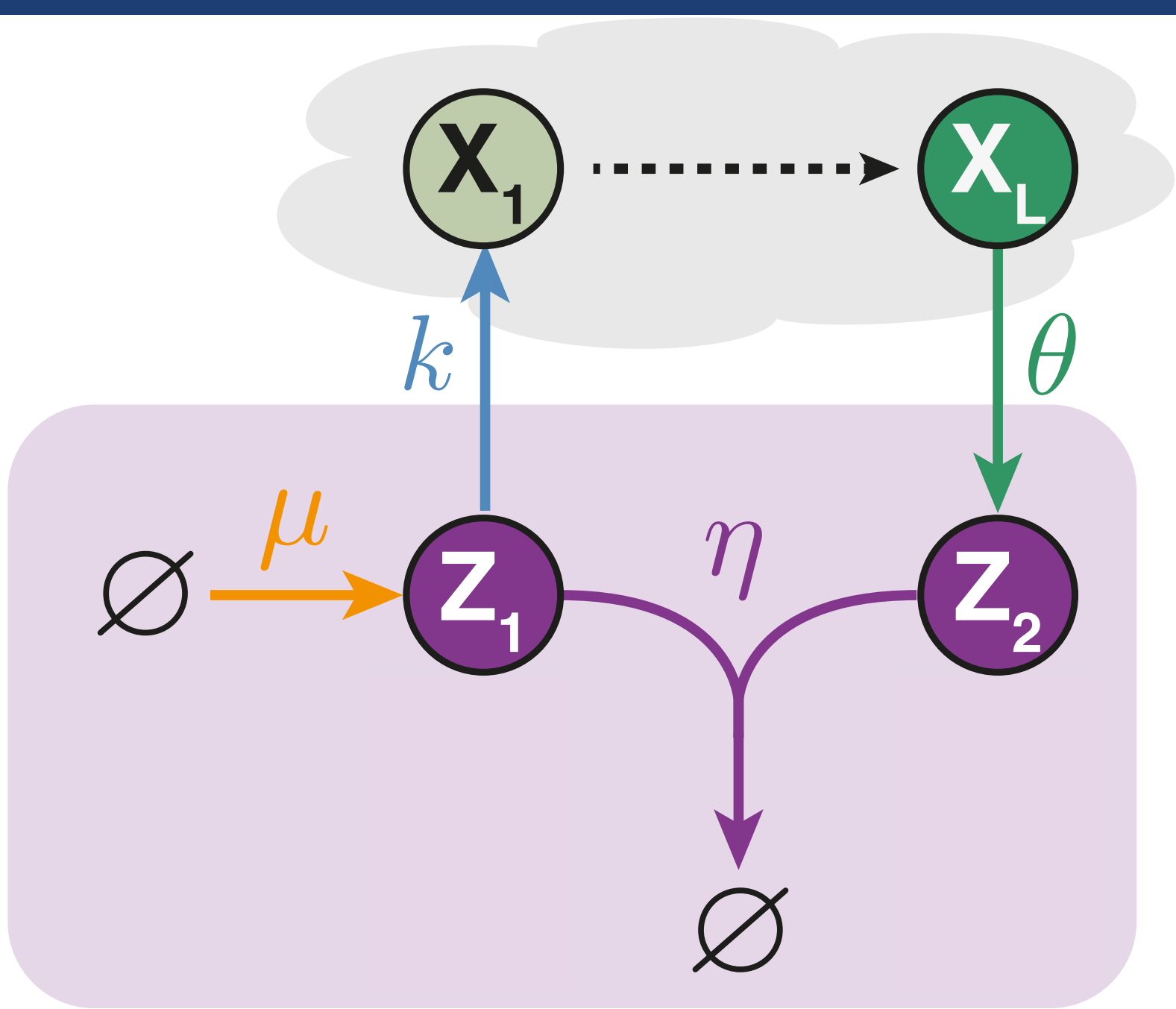
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$$\implies \dot{z} = \mu - \theta x_L$$

$$z(t) = \int_0^t (\mu - \theta x_L(\tau)) d\tau \quad \text{Stability} \implies x_L \xrightarrow[t \rightarrow \infty]{} \frac{\mu}{\theta} \quad \text{RPA!}$$

Molecular integral feedback controller



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Stability

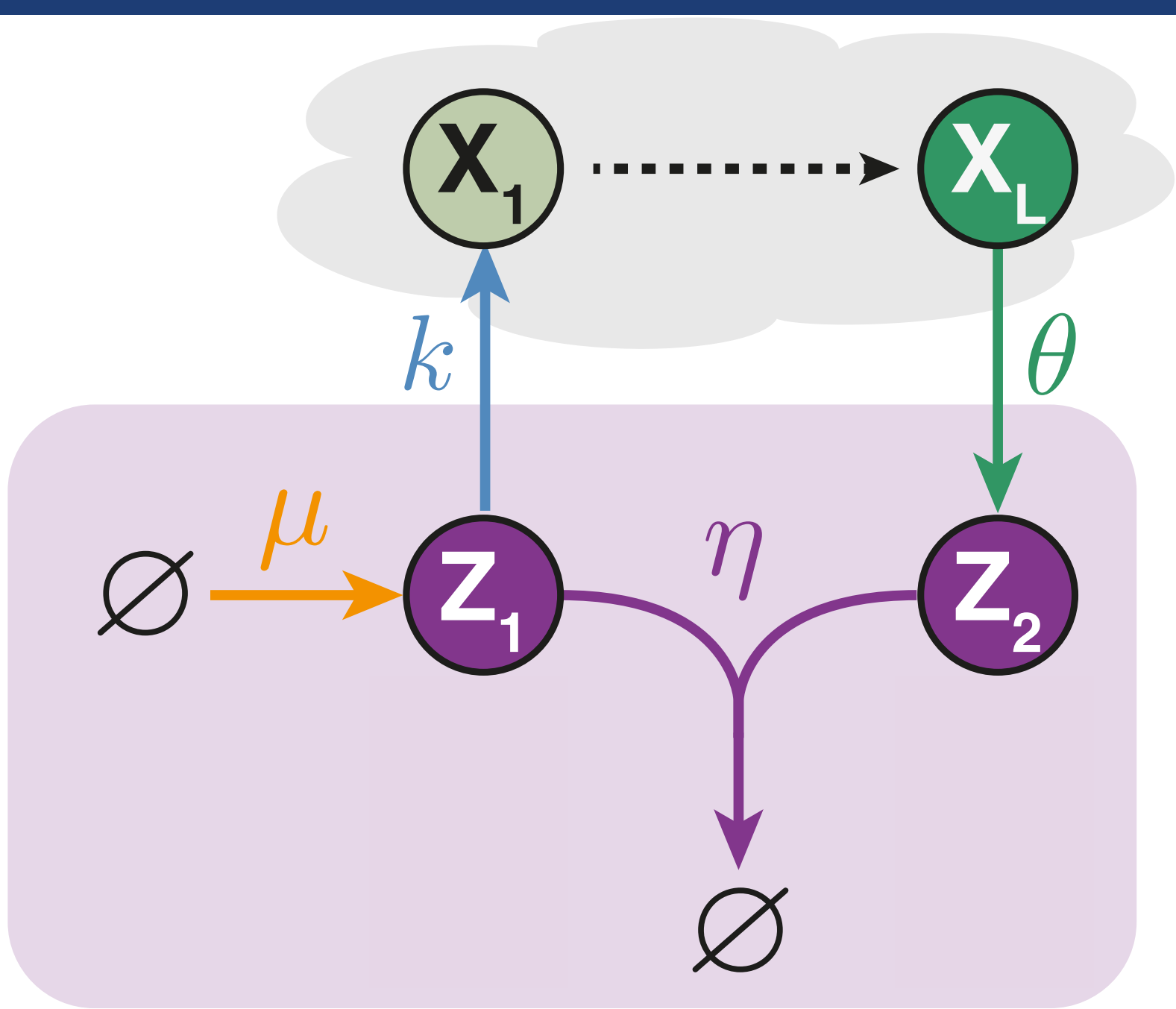
$$\implies x_L \xrightarrow[t \rightarrow \infty]{} \frac{\mu}{\theta}$$

RPA!

Stochastic:

$$\begin{cases} \dot{\mathbb{E}}[Z_1] = \mu - \eta \mathbb{E}[Z_1 Z_2] \\ \dot{\mathbb{E}}[Z_2] = \theta \mathbb{E}[X_L] - \eta \mathbb{E}[Z_1 Z_2] \end{cases}$$

Molecular integral feedback controller



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$$\text{Ergodicity} \implies \mathbb{E}[X_L] \xrightarrow[t \rightarrow \infty]{} \frac{\mu}{\theta} \quad \text{RPA!}$$

From the birth of Synbio to genetic feedback control

2000

2009

2012

2016

2018 2019

2026

2000

2000

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2019-2026

Birth of Synthetic Biology

Integral Feedback in Nature

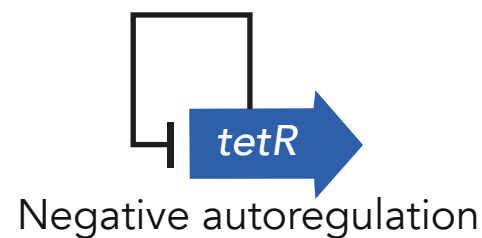
Motifs for Robust Adaptation

Zero-Order & Autocatalytic Integral Feedback

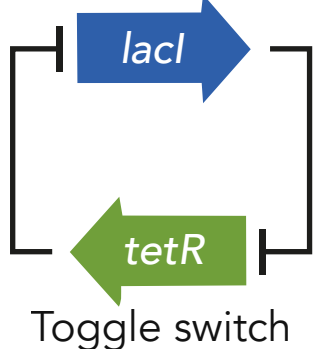
Antithetic Integral Feedback

Molecular PIDs

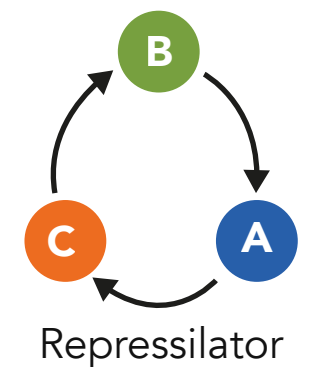
Genetic Implementation



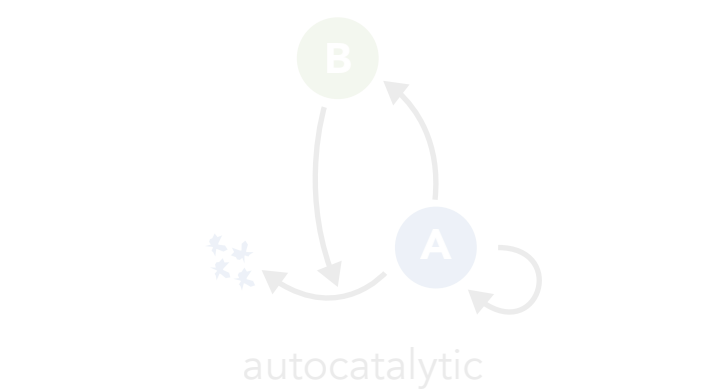
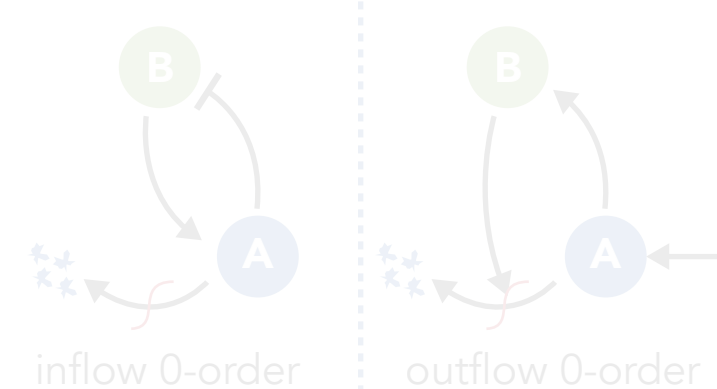
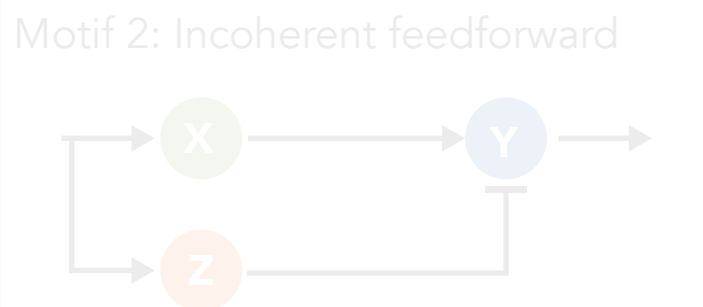
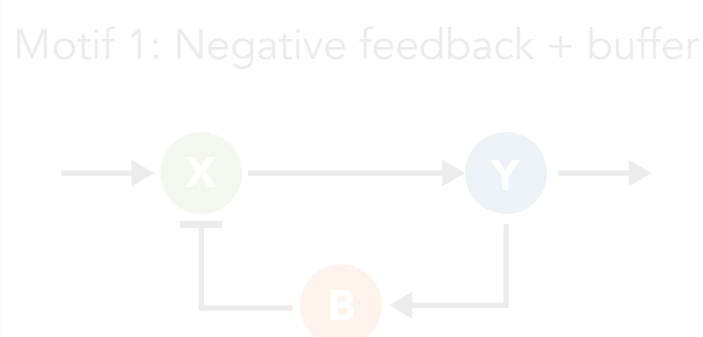
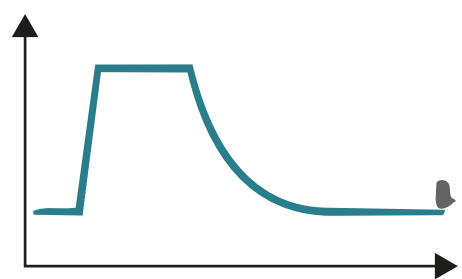
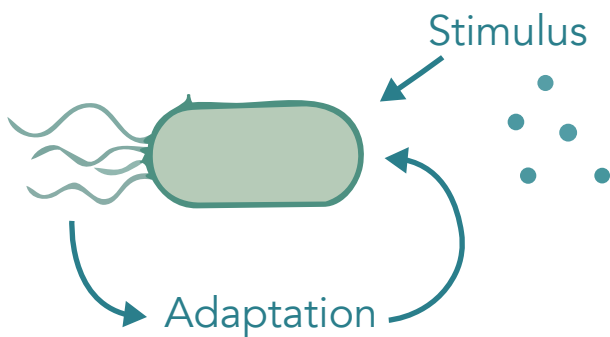
Negative autoregulation



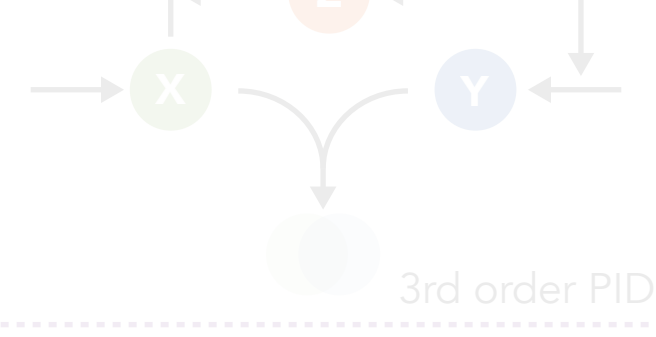
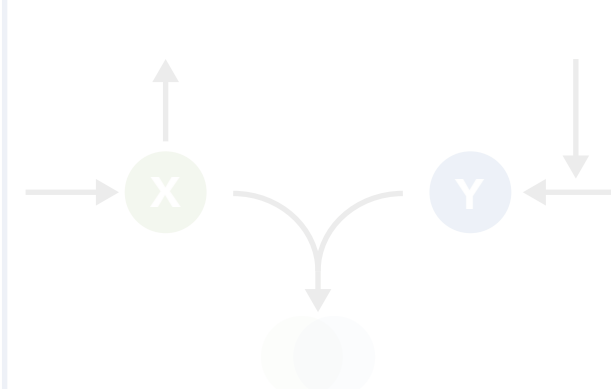
Toggle switch



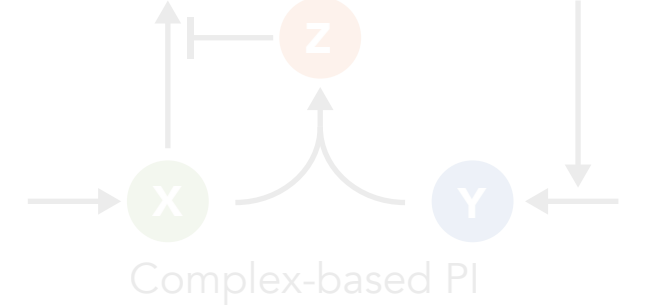
Repressilator



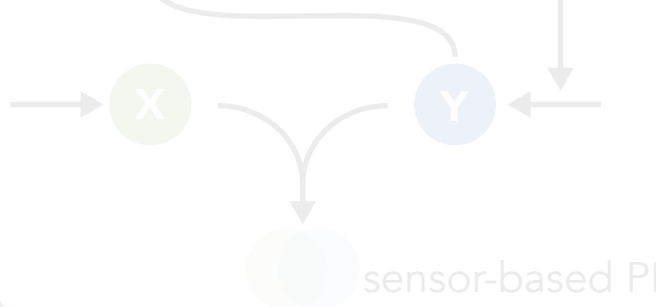
autocatalytic



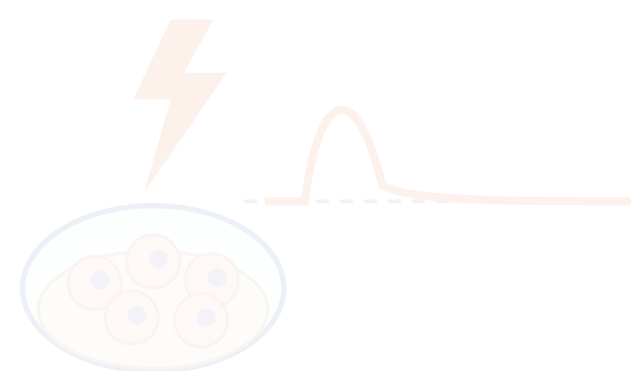
3rd order PID



Complex-based PI



sensor-based PI



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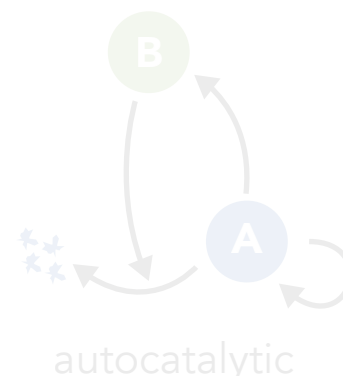
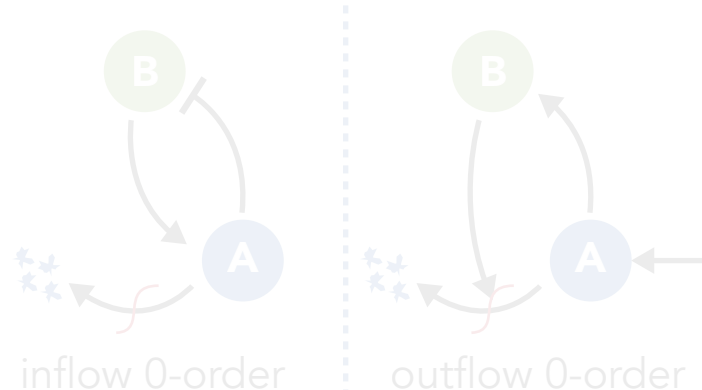
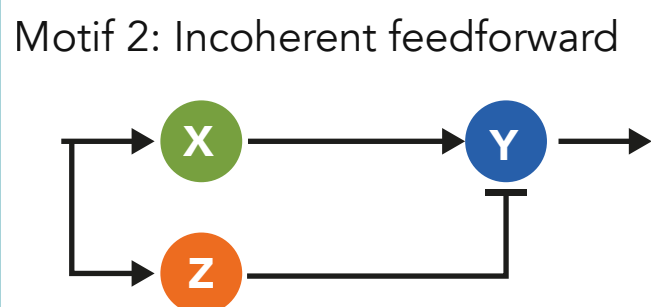
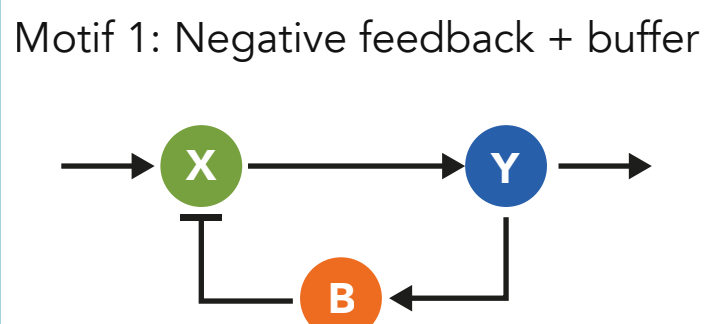
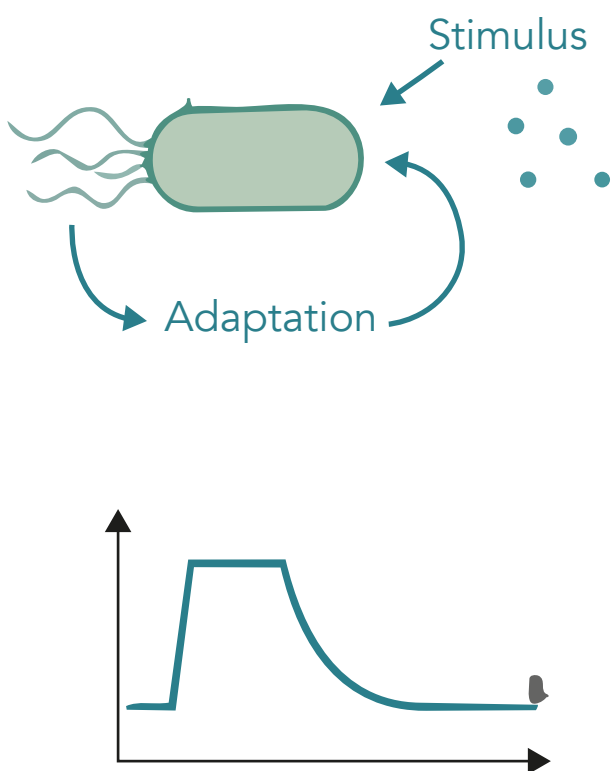
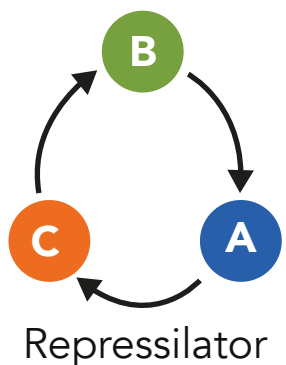
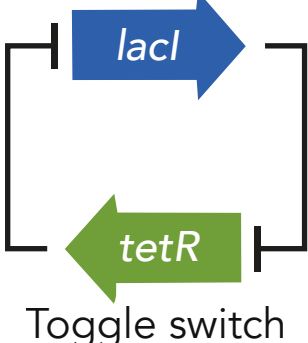
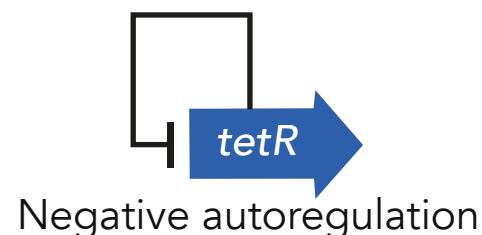
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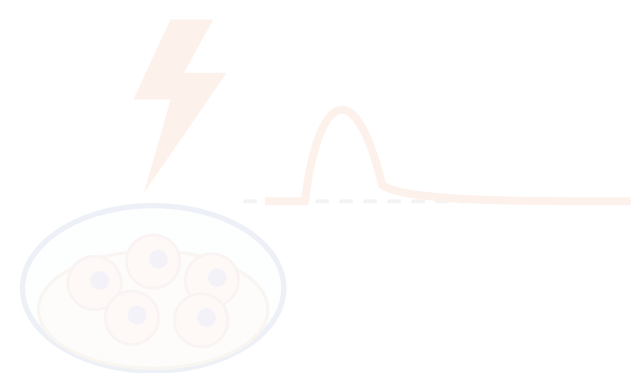
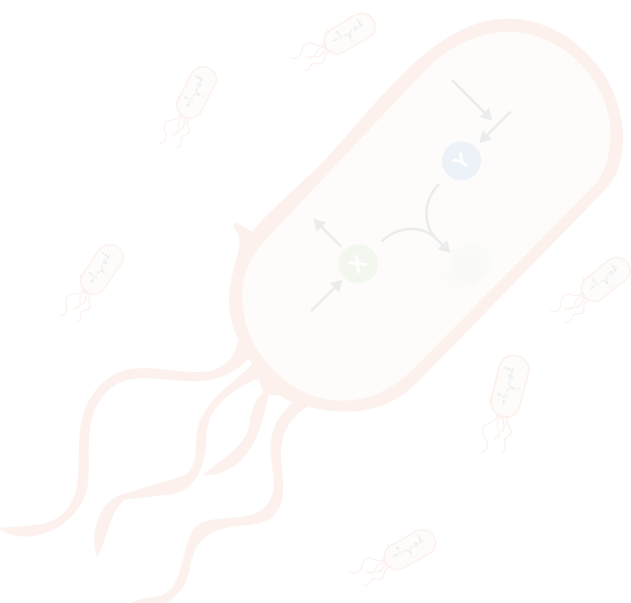
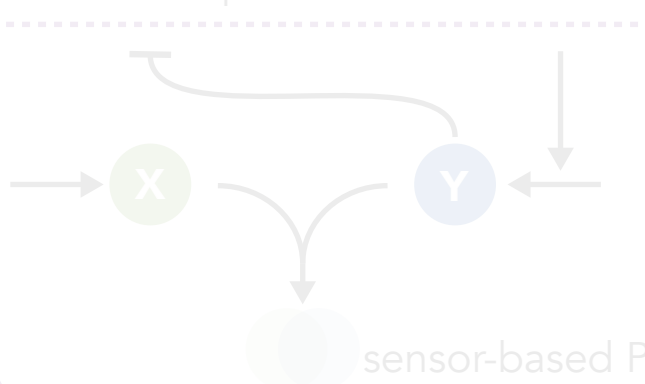
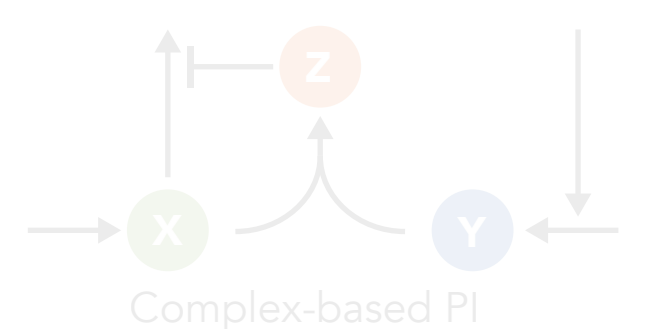
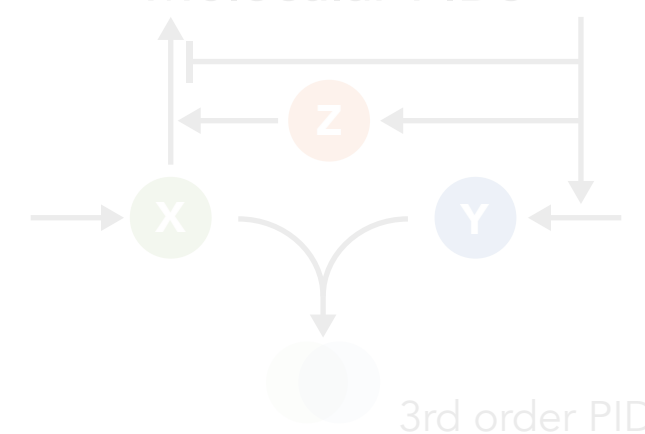
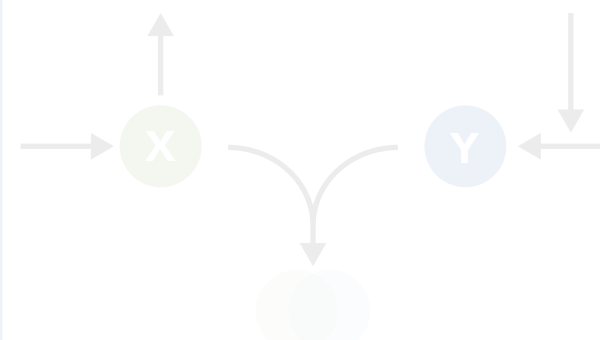
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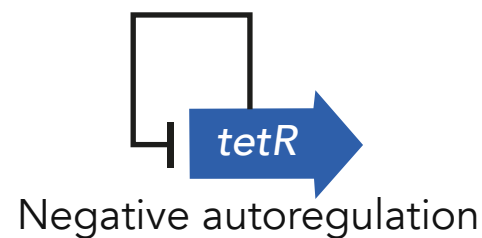
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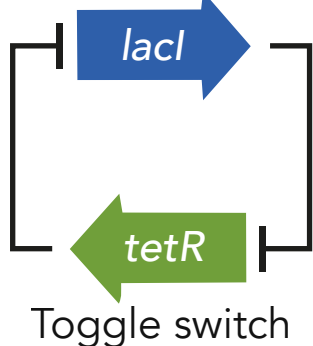
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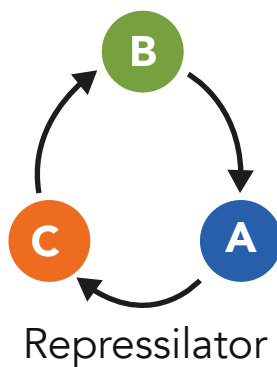
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Negative autoregulation



Toggle switch



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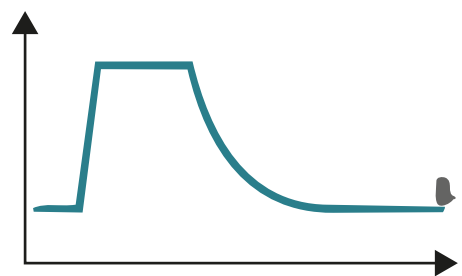
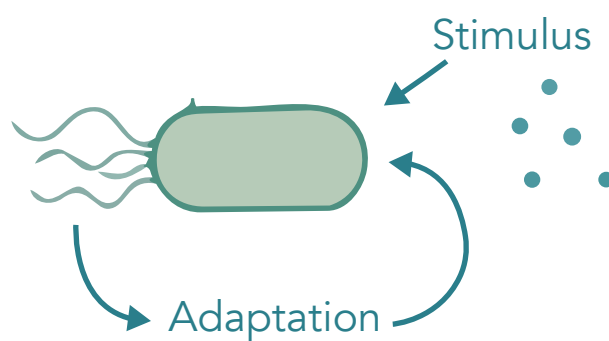
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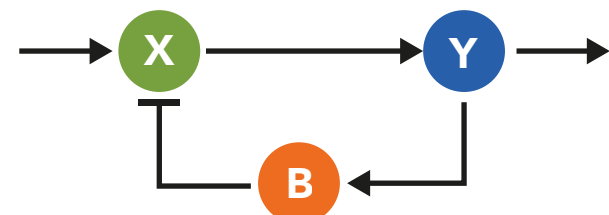
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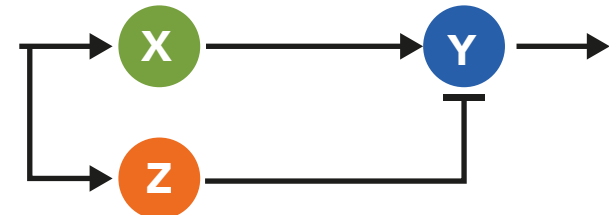
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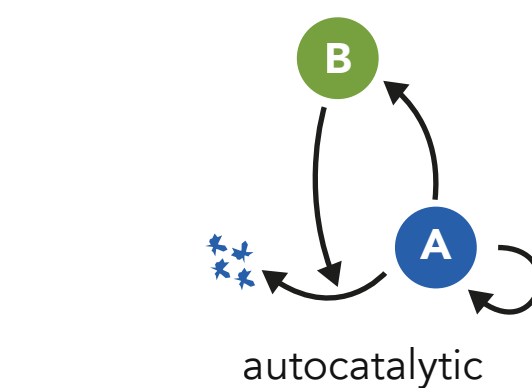
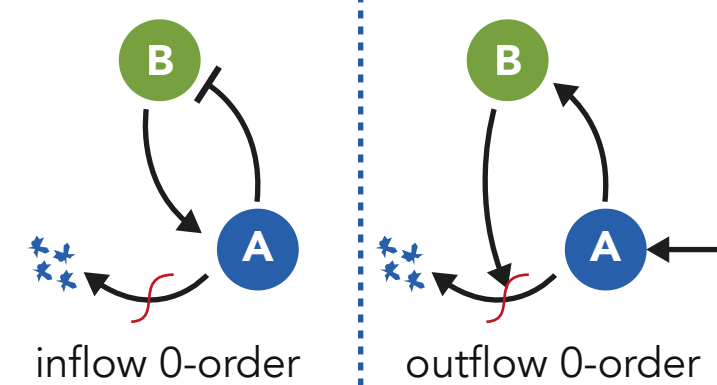


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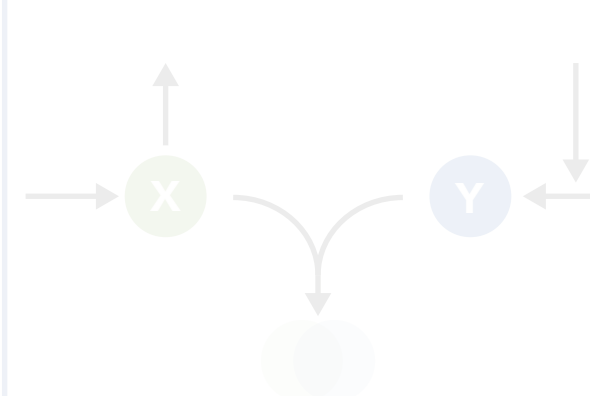
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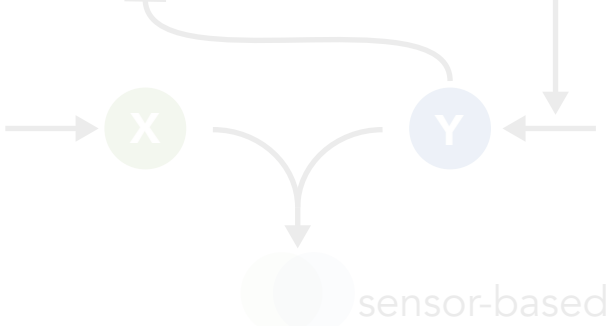
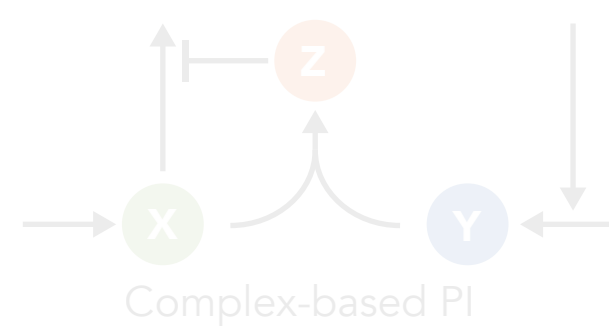
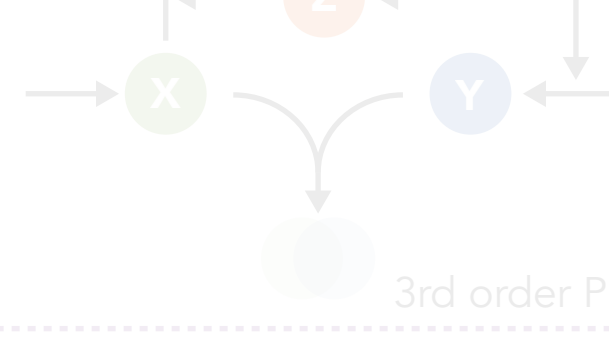


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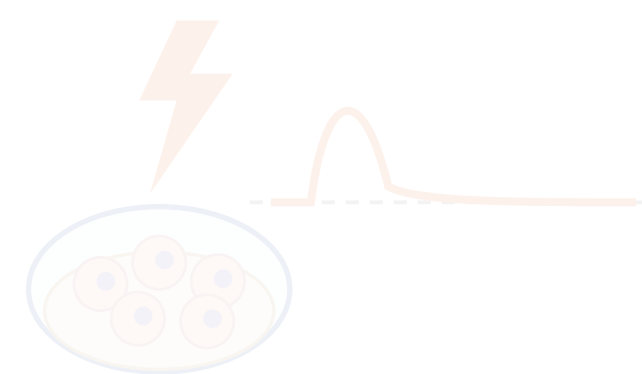
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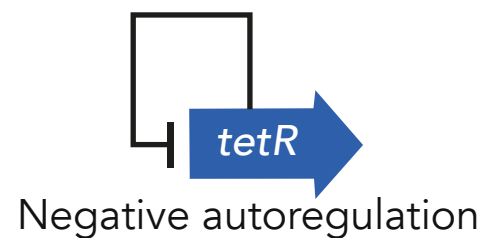
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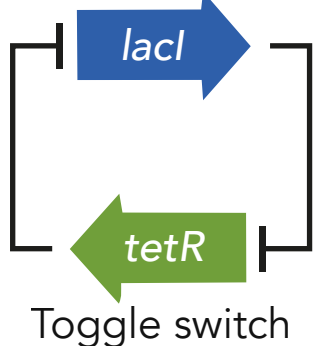
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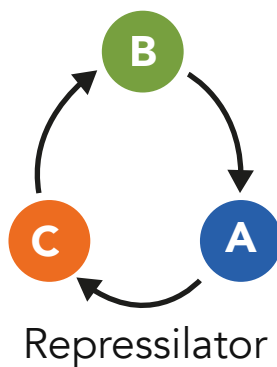
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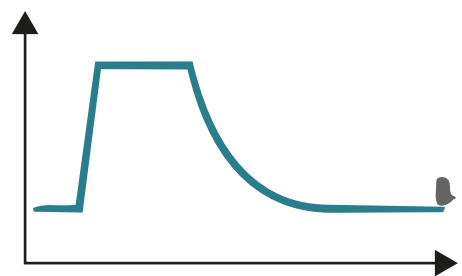
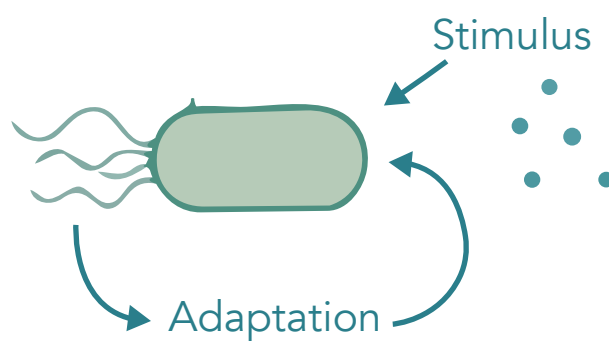
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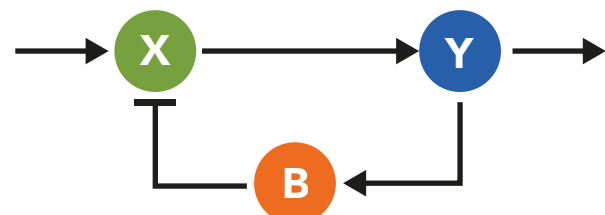
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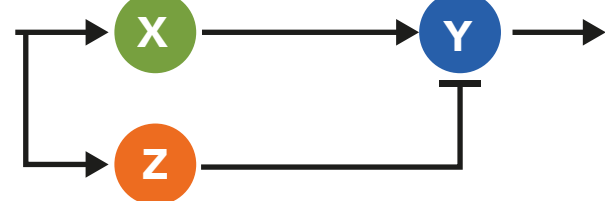
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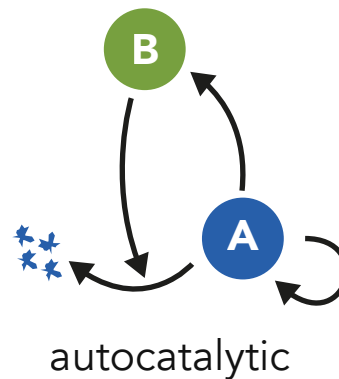
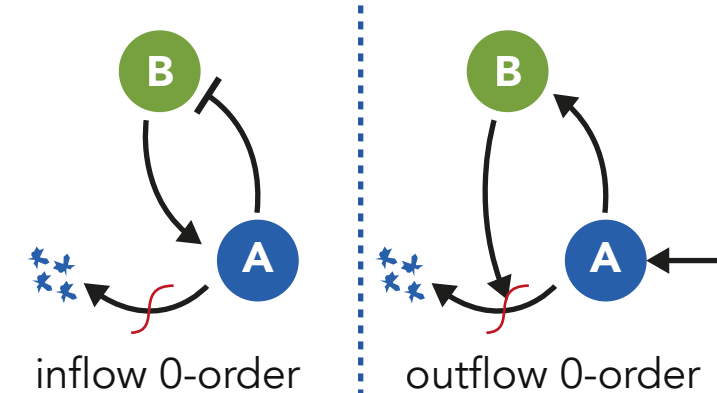


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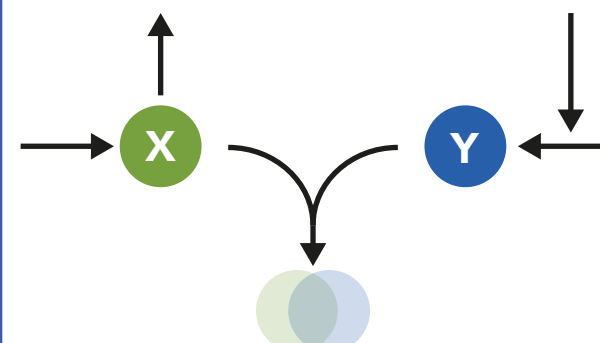
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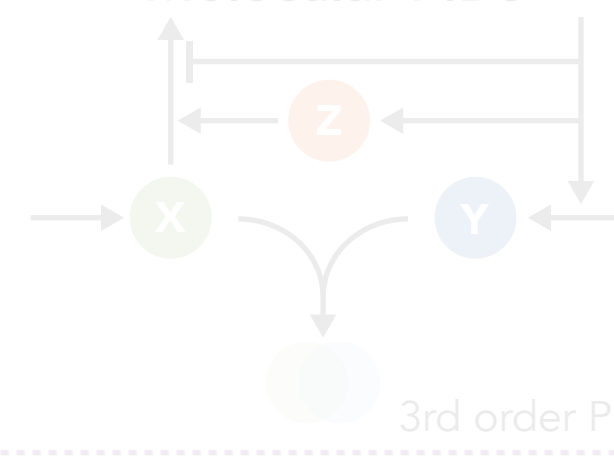


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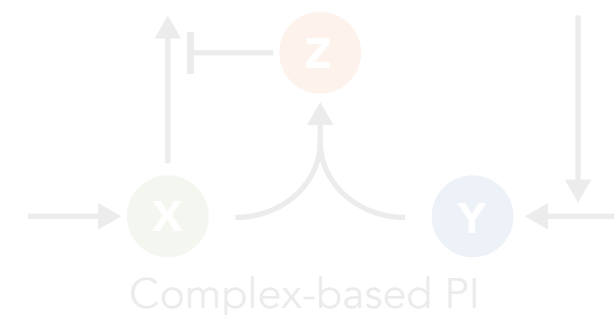
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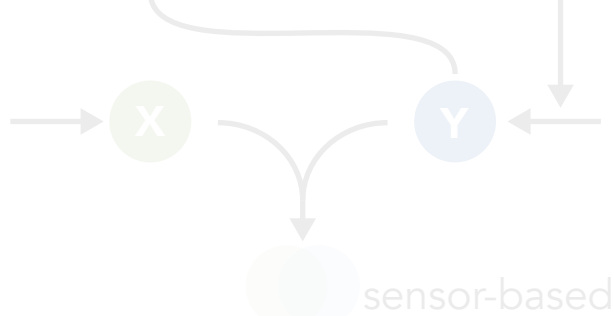
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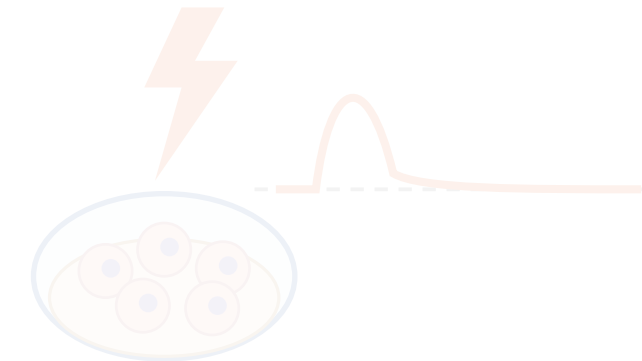
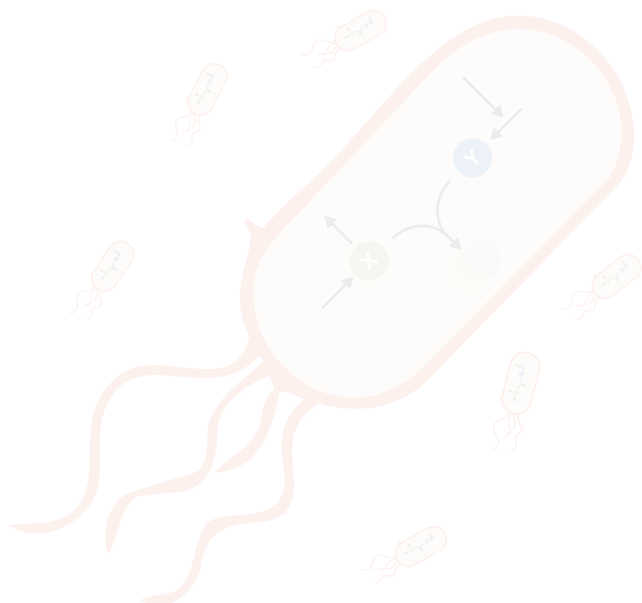
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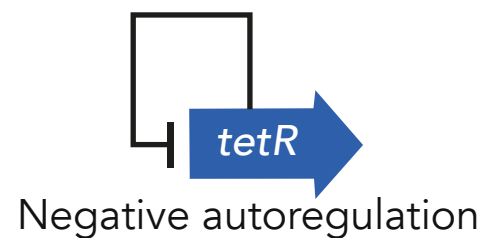
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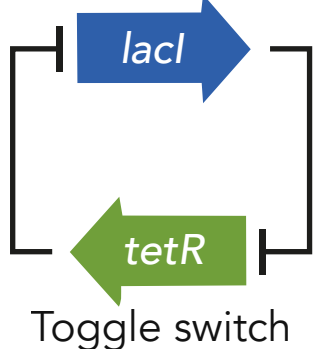
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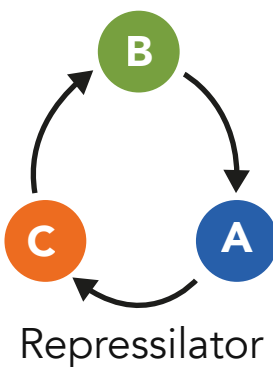
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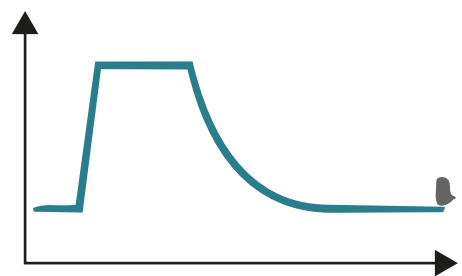
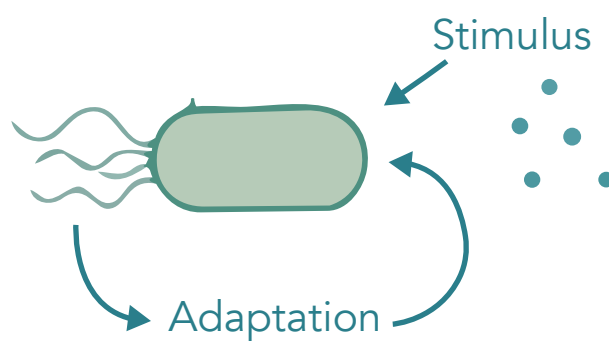
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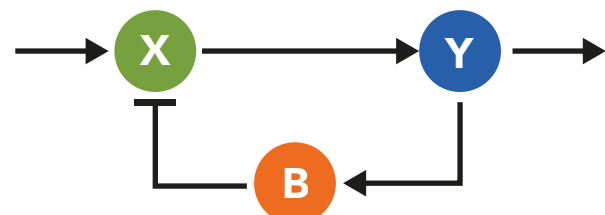
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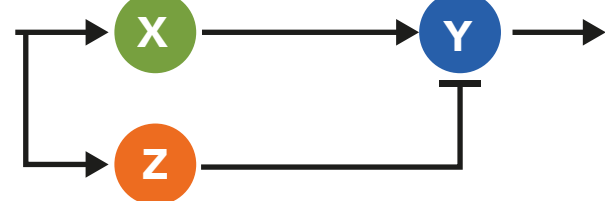
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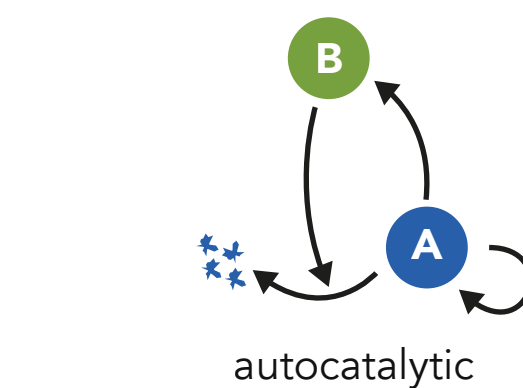
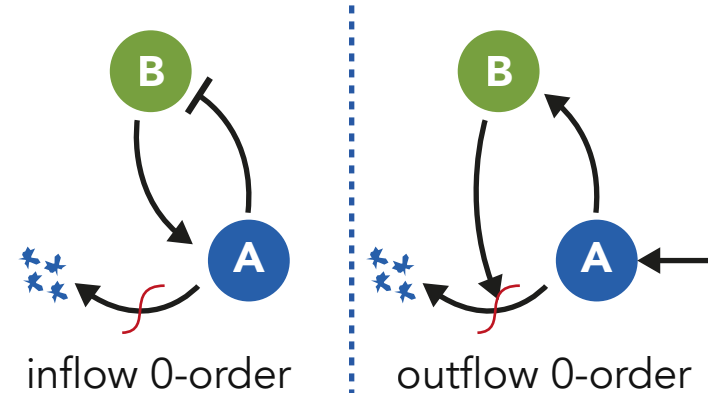


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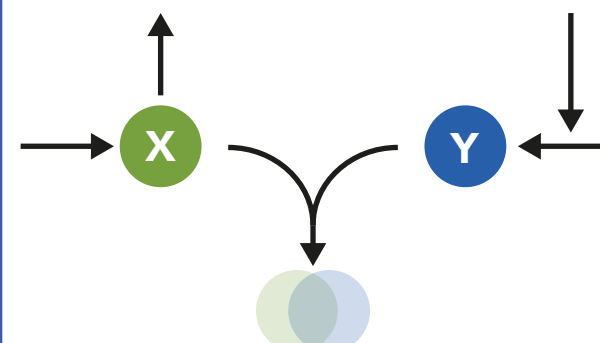
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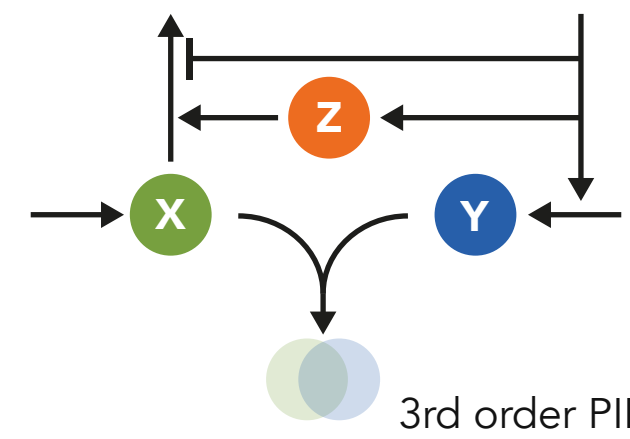


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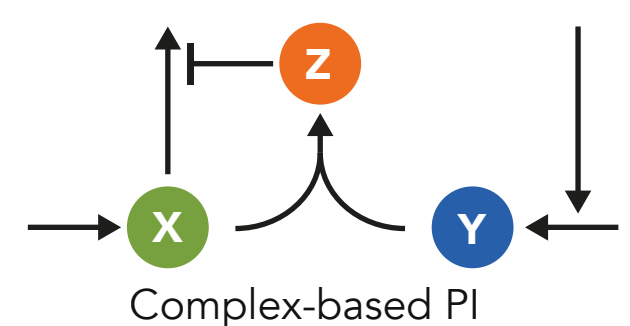
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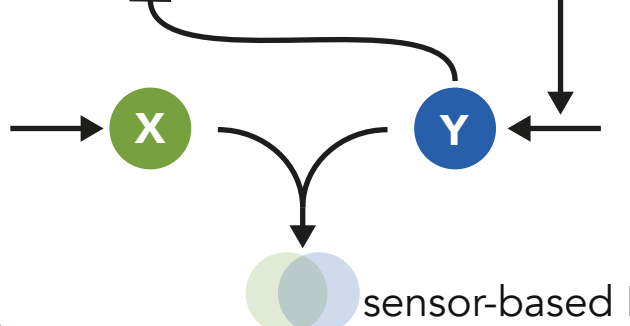
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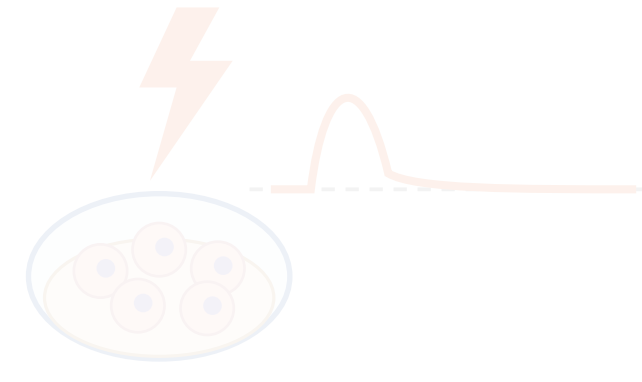
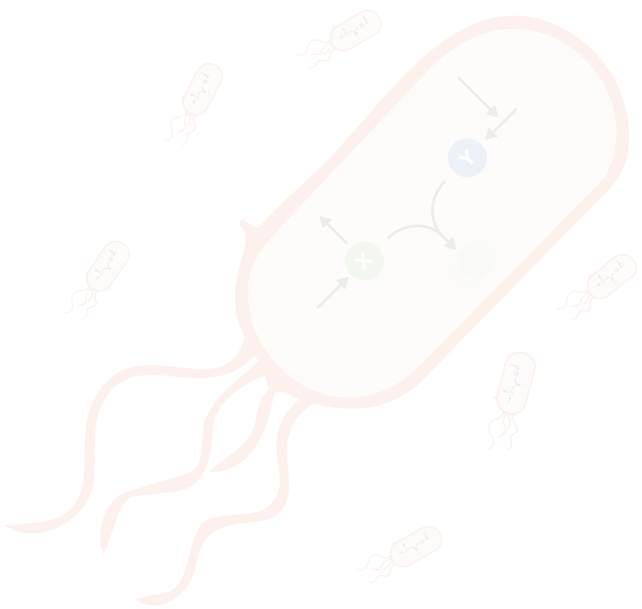
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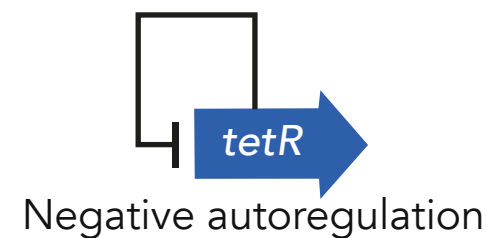
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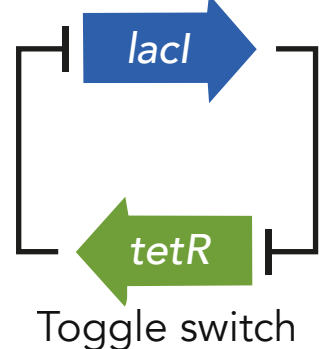
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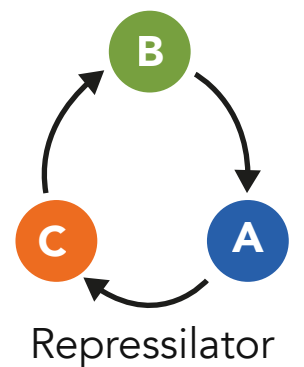
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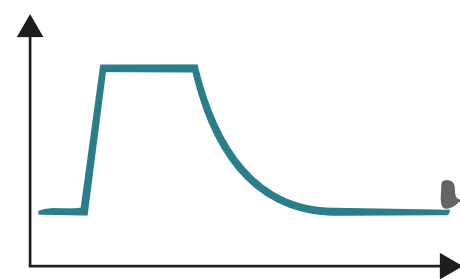
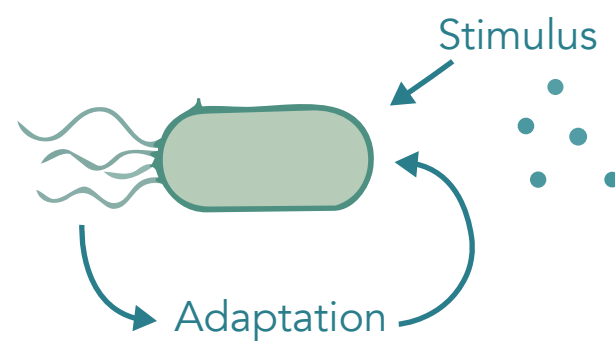
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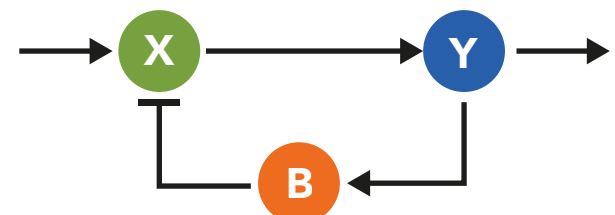
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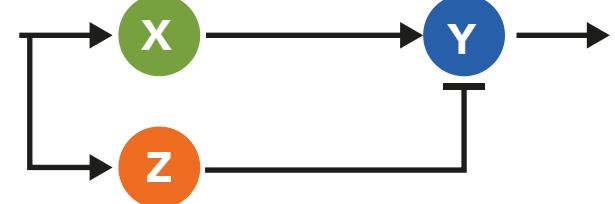
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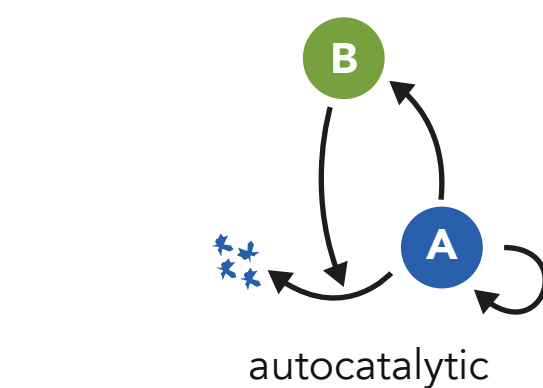
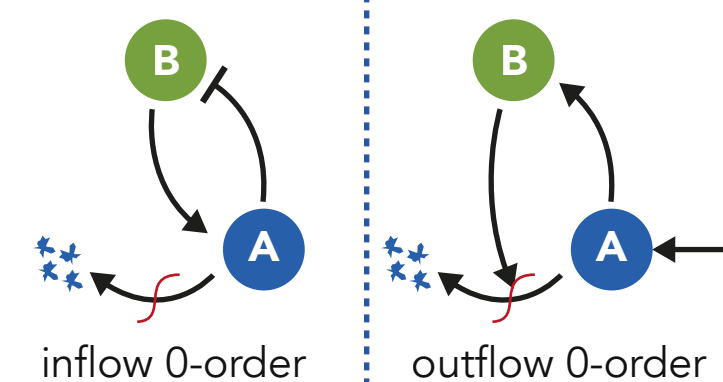


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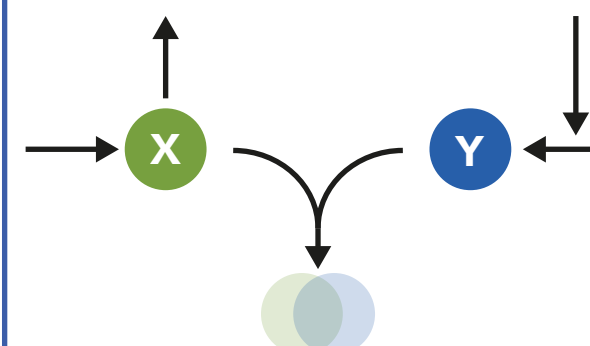
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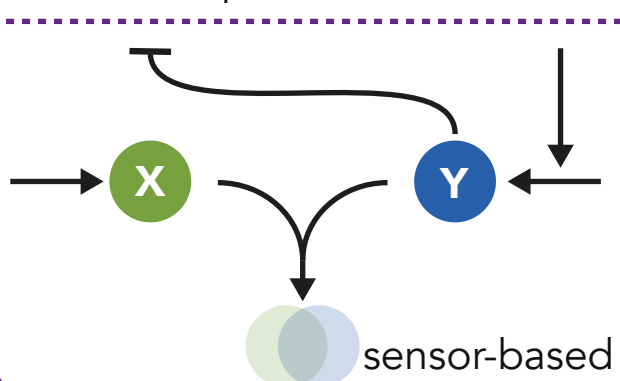
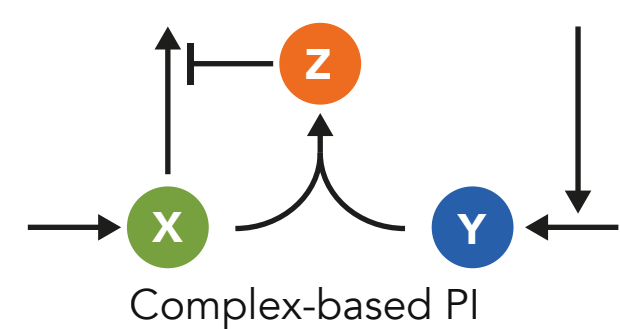
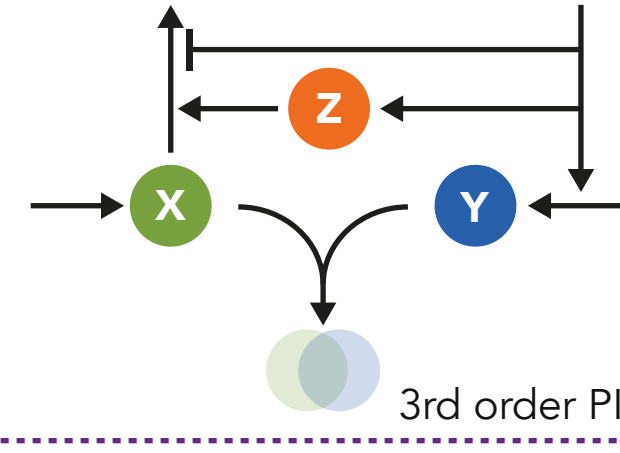


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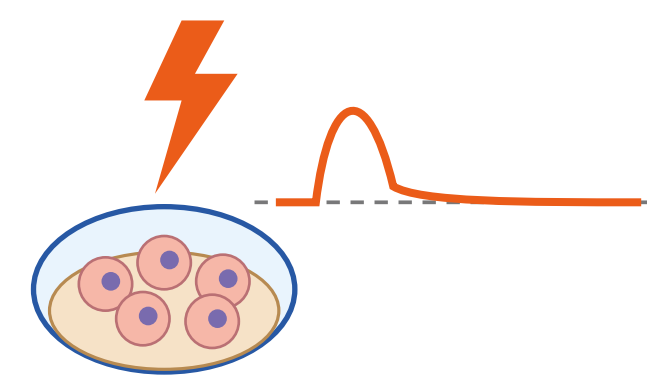
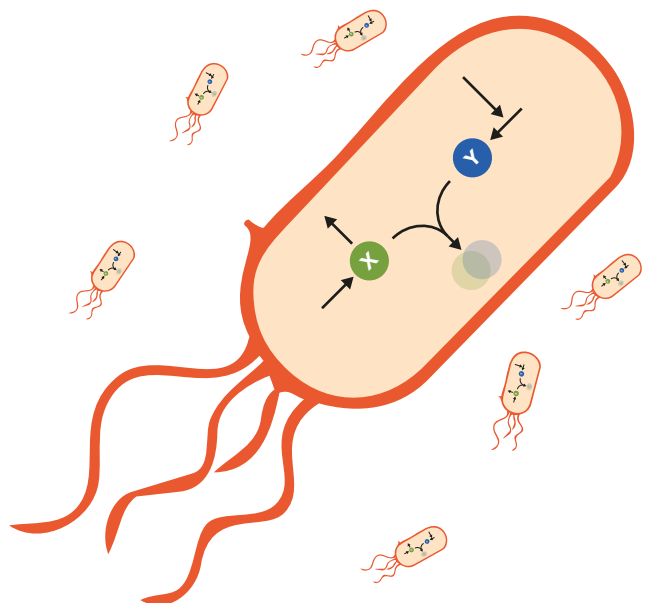
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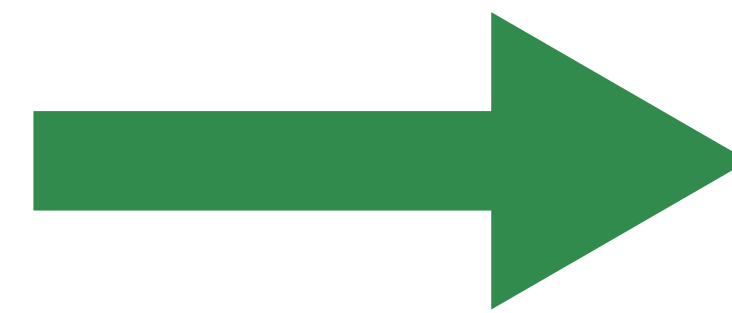
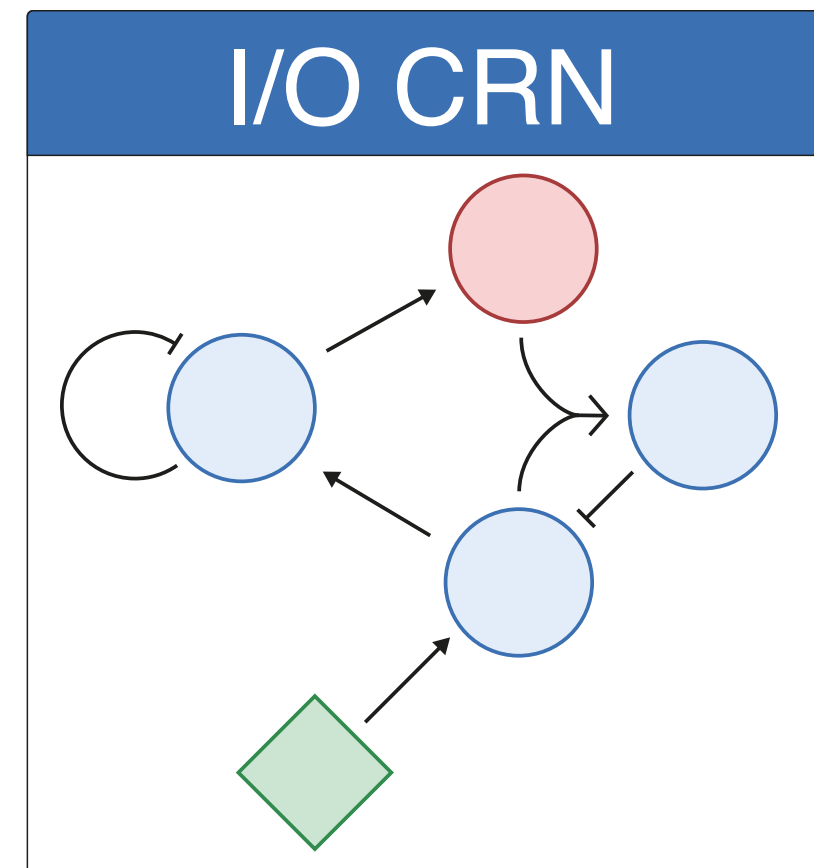
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The design of Input/Output Chemical Reaction Networks

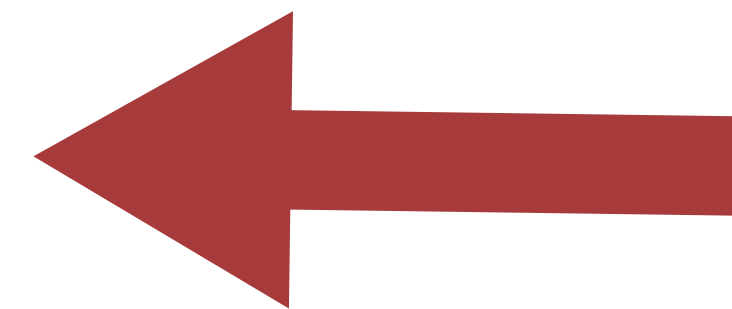
forward:



behavior

(easy)

inverse:



behavior

(hard)

Introducing GenAI-Net

SCIENCE ADVANCES | RESEARCH ARTICLE

SYNTHETIC BIOLOGY

GenAI-Net: A generative AI framework for automated biomolecular network design

Maurice Filo^{1†}, Nicolò Rossi^{1†}, Zhou Fang^{2†}, Mustafa Khammash^{1*}

Biomolecular networks underlie both natural biological processes and engineered cellular technologies, from intracellular regulation and ecological dynamics to biomanufacturing, smart therapeutics, and cell-based diagnostics. However, designing chemical reaction networks (CRNs) that implement a desired dynamical function remains a challenging task. Although candidate networks can be evaluated by simulation, the inverse problem of discovering networks from behavioral specifications remains difficult. It requires navigating vast spaces of topologies and kinetic parameters governed by nonlinear and potentially stochastic dynamics. Here, we introduce GenAI-Net, a generative artificial intelligence framework that automates CRN design by coupling reaction proposal to simulation-based evaluation defined by a user-specified objective. GenAI-Net efficiently produces topologically diverse solutions across design tasks, including dose-response shaping, complex logic gates, classifiers, oscillators, habituation, robust perfect adaptation, and noise reduction in stochastic settings. By turning specifications into families of circuit candidates, GenAI-Net provides a route to programmable biomolecular circuit design and accelerates translation from desired function to implementable mechanisms.

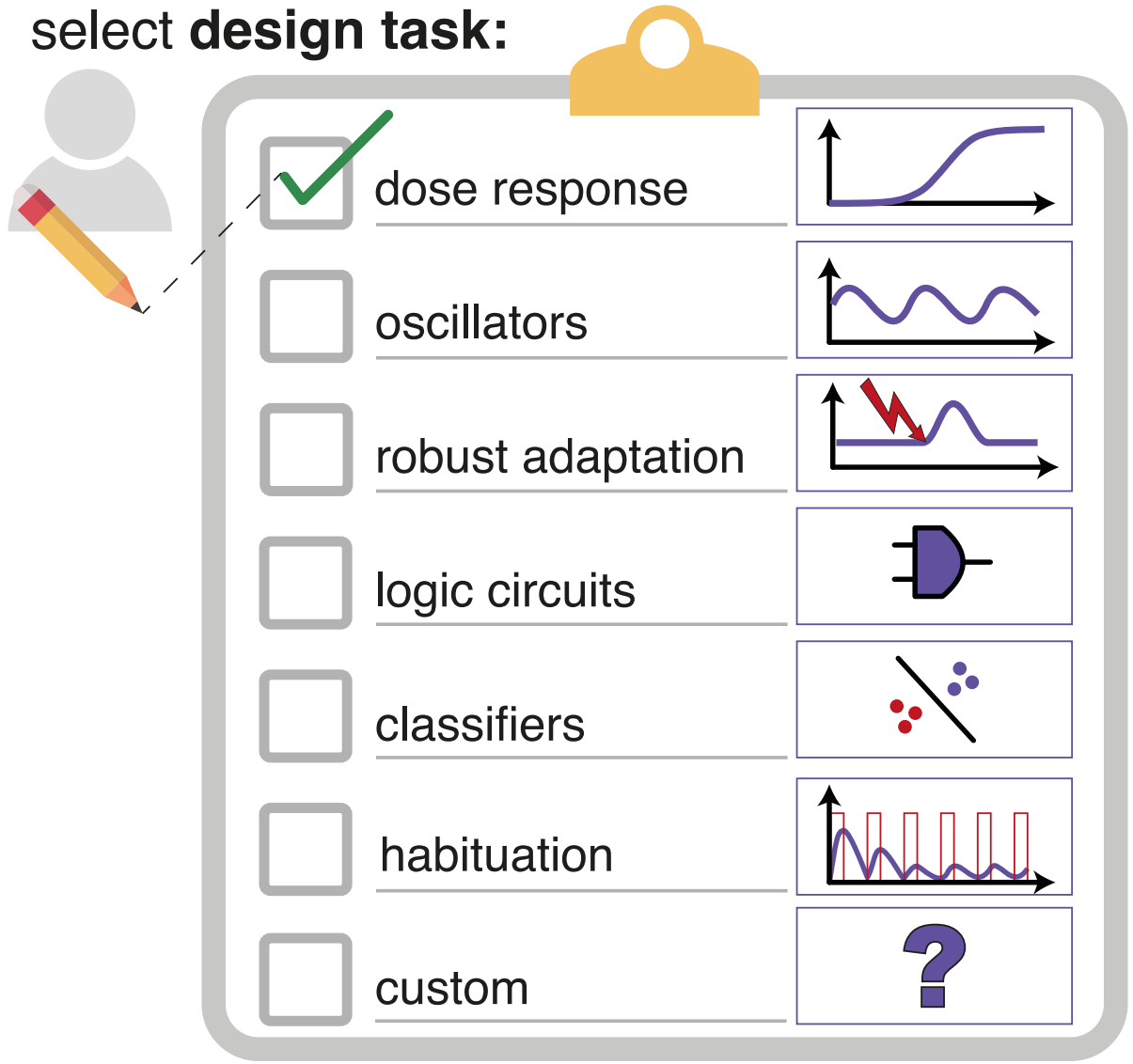
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Introducing GenAI-Net

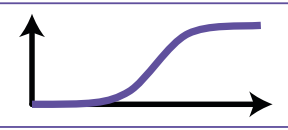
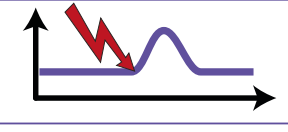
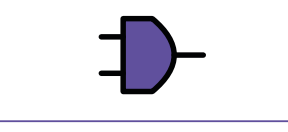
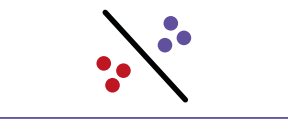
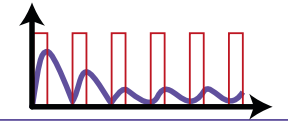
Introducing GenAI-Net

User Specifications

select design task:



A user interface for selecting a design task. It features a clipboard icon at the top left and a yellow pushpin at the top right. The form contains a list of tasks with checkboxes and corresponding icons:

Task	Icon
☒ dose response	
☐ oscillators	
☐ robust adaptation	
☐ logic circuits	
☐ classifiers	
☐ habituation	
☐ custom	

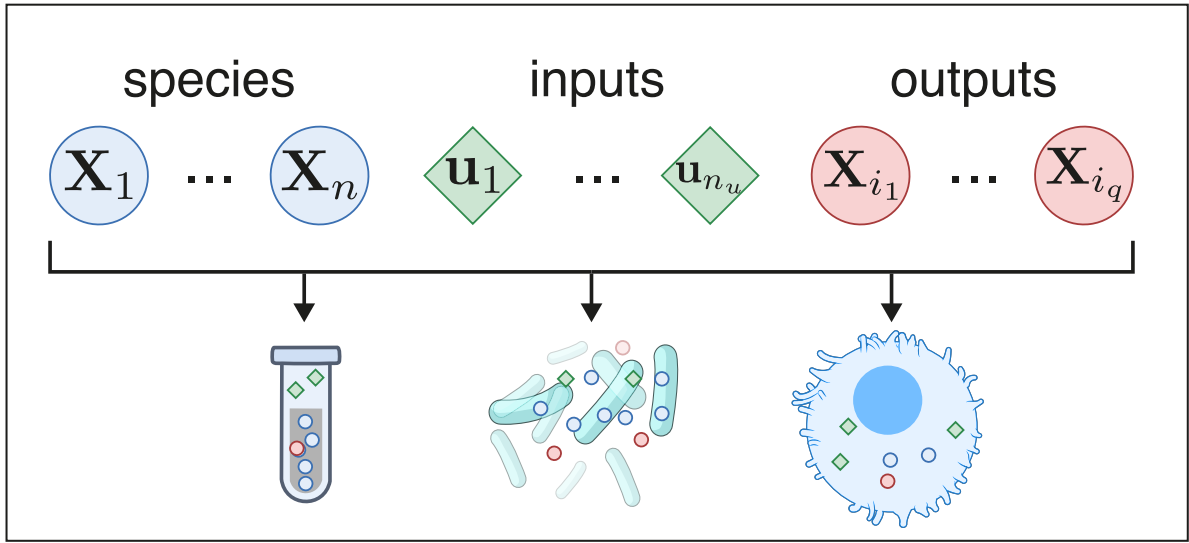
Introducing GenAI-Net

User Specifications

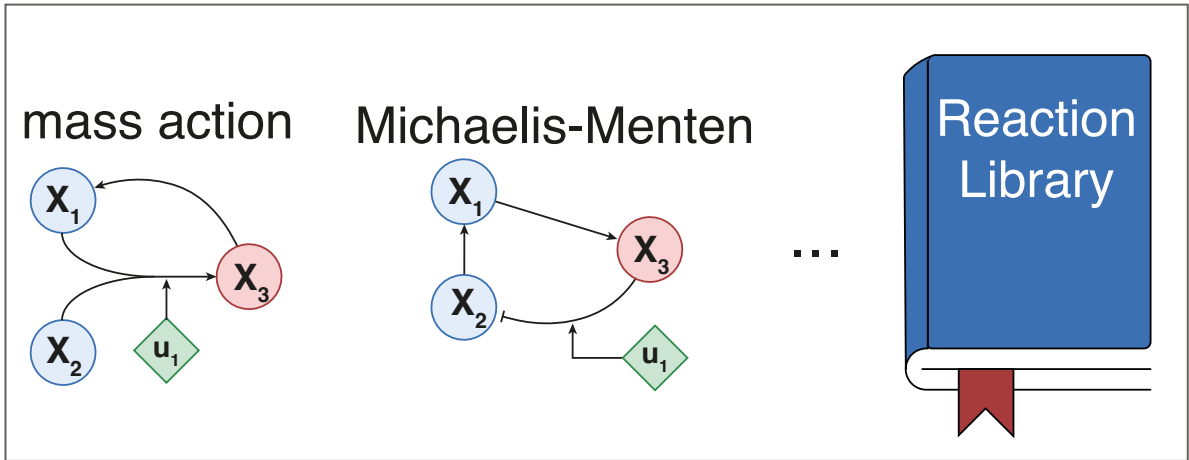
select **design task**:

☒	dose response	
☐	oscillators	
☐	robust adaptation	
☐	logic circuits	
☐	classifiers	
☐	habituation	
☐	custom	

specify **(bio)chemical environment**:



specify **kinetics**:



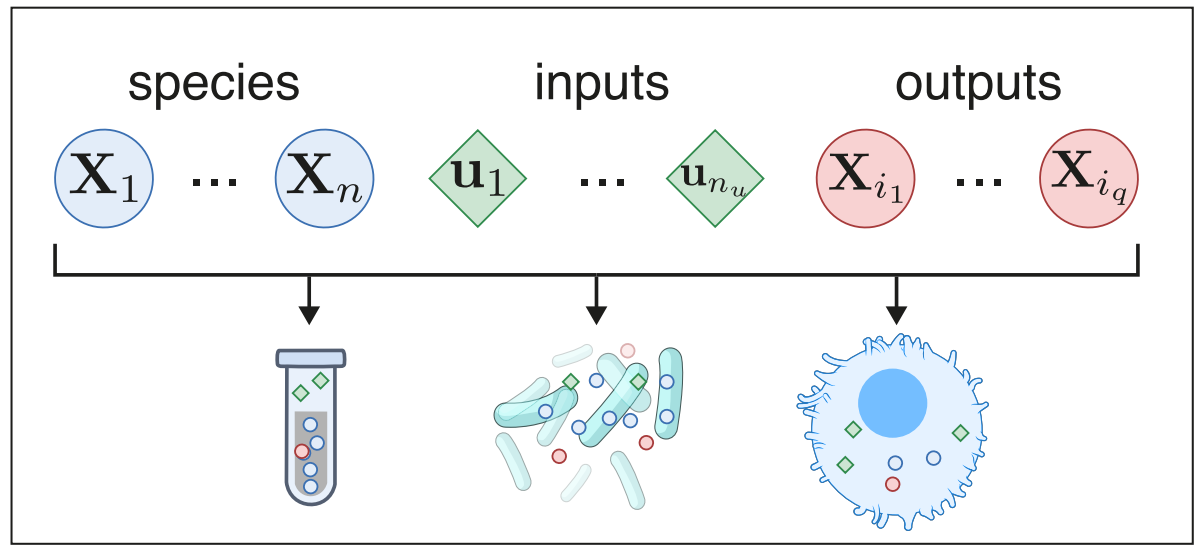
Introducing GenAI-Net

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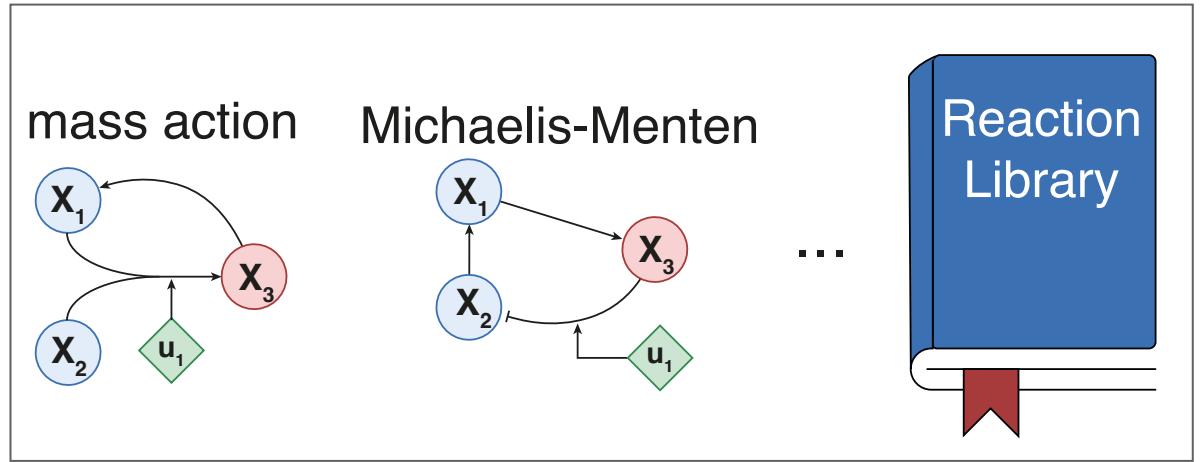
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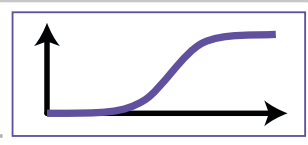
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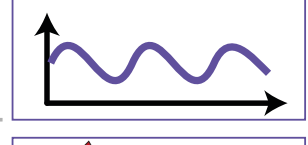
select design task:



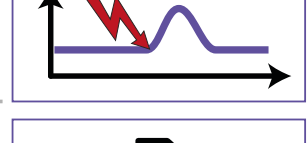
☒ dose response



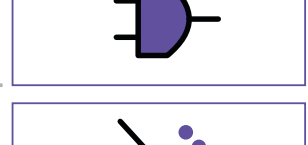
☐ oscillators



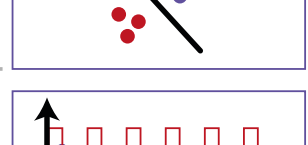
☐ robust adaptation



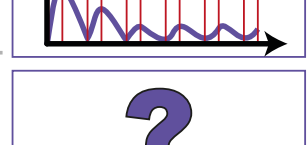
☐ logic circuits



☐ classifiers



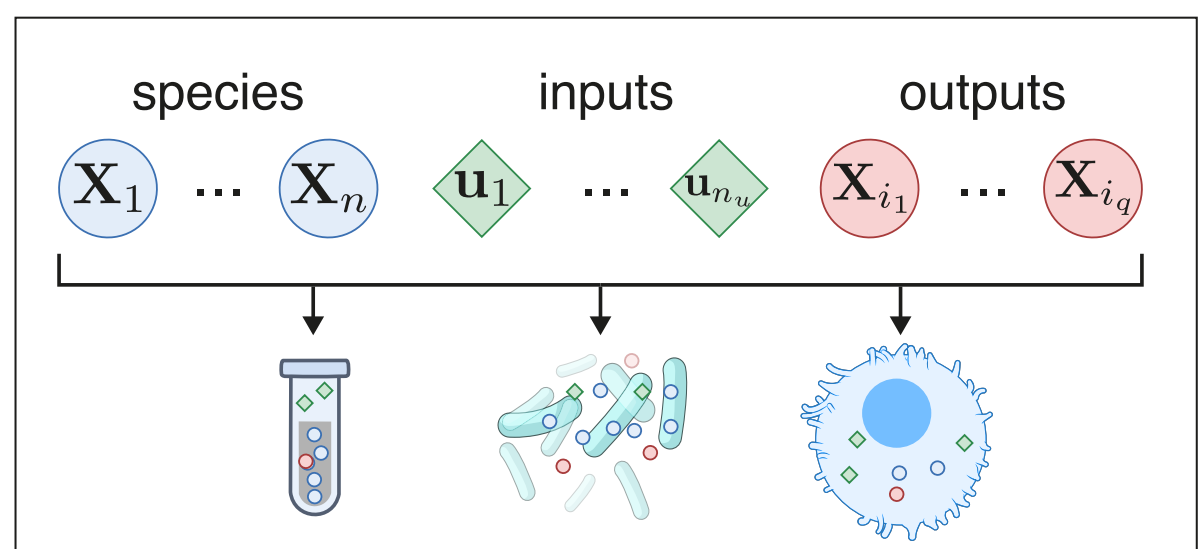
☐ habituation



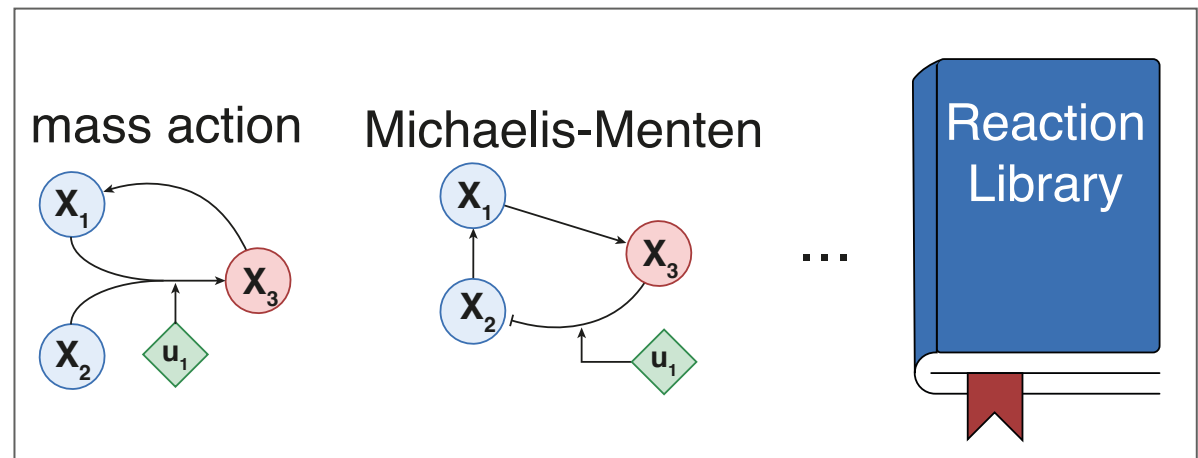
☐ custom



specify (bio)chemical environment:



specify kinetics:



Mass-Action Kinetics: Second Order



Species : $X_1, X_2, \dots, X_n$

Library size : $\frac{(n-1)n(n+1)(n+2)}{4}$

#parameters/rxn : 1

$\mathcal{R}_0 :$ $X_1 + X_1 \longrightarrow X_1 + X_2$ $[rx_1^2]$

$\mathcal{R}_1 :$ $X_1 + X_1 \longrightarrow X_1 + X_3$ $[rx_1^2]$

$\vdots$

$\mathcal{R}_{n-2} :$ $X_1 + X_1 \longrightarrow X_1 + X_n$ $[rx_1^2]$

$\mathcal{R}_{n-1} :$ $X_1 + X_2 \longrightarrow X_1 + X_1$ $[rx_1x_2]$

$\vdots$

$\mathcal{R}_{\dots} :$ $X_n + X_n \longrightarrow X_n + X_{n-1}$ $[rx_n^2]$

Mass-Action Kinetics: up to Order o



Species : $X_1, X_2, \dots, X_n$

Library size : $C_o^{n+o} (C_o^{n+o} - 1) + 1, o > 1$

#parameters/rxn : 1

$\mathcal{R}_0 :$ $\emptyset \longrightarrow \emptyset$ $[r]$

$\mathcal{R}_1 :$ $\emptyset \longrightarrow X_1$ $[r]$

$\vdots$

$\mathcal{R}_{\dots} :$ $X_1 \longrightarrow X_2$ $[rx_1]$

$\vdots$

$\mathcal{R}_{\dots} :$ $X_1 + X_n \longrightarrow X_2 + X_3$ $[rx_1x_n]$

$\vdots$

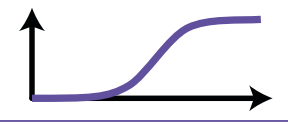
$\mathcal{R}_{\dots} :$ $X_1 + X_2 + \dots + X_i \longrightarrow X_2 + X_3 + \dots + X_j$ $[rx_1x_2 \dots x_i]$

Propensity function: $r \prod_{i=1}^n x_i^{s_i}$

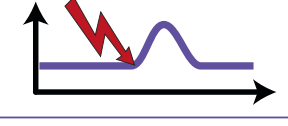
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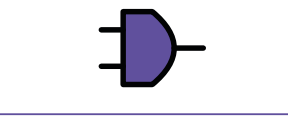
User Specifications

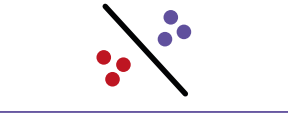
select design task:

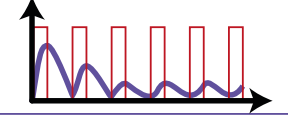
☒ dose response 

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☐ robust adaptation 

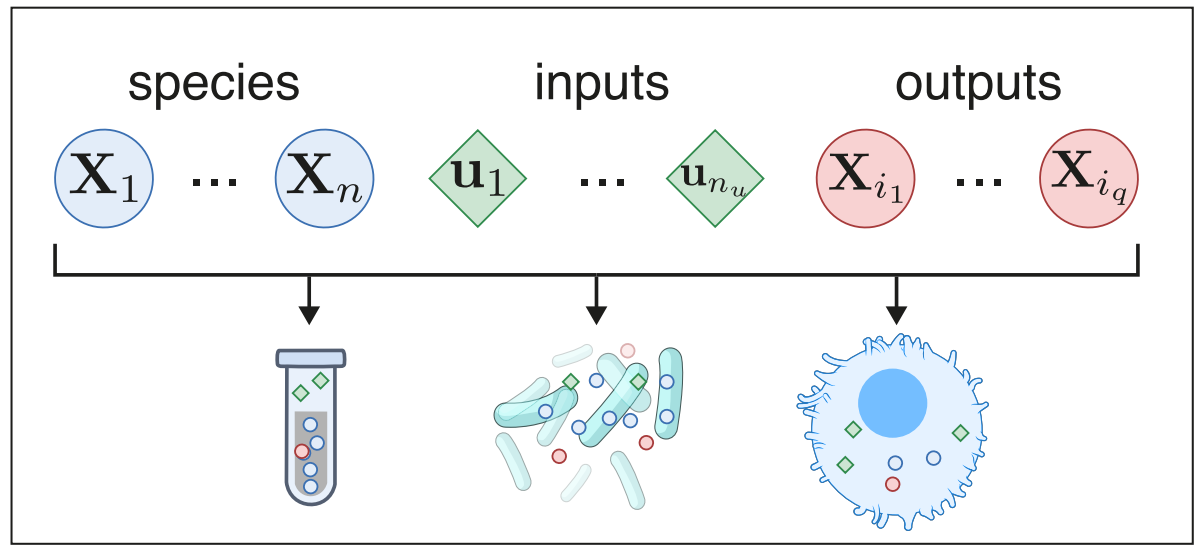
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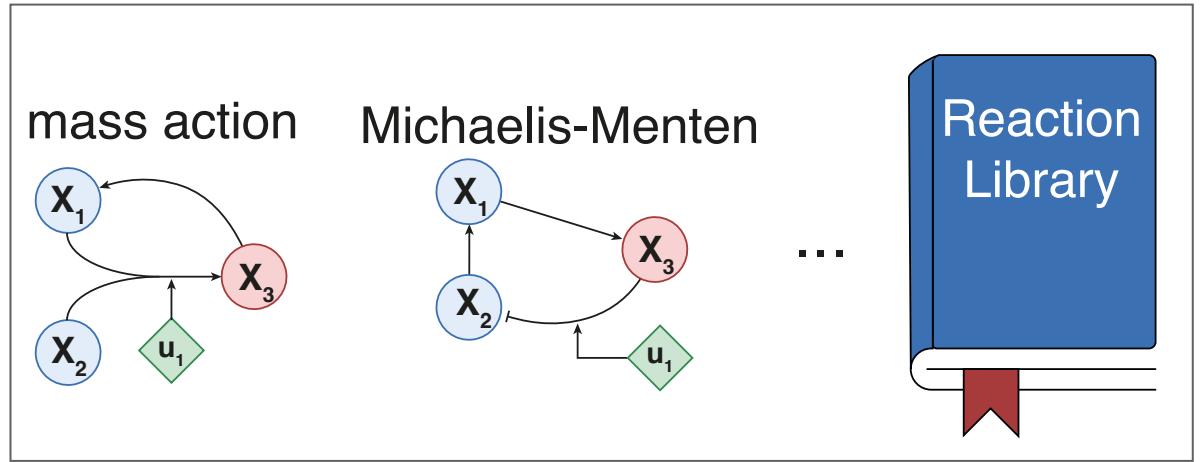
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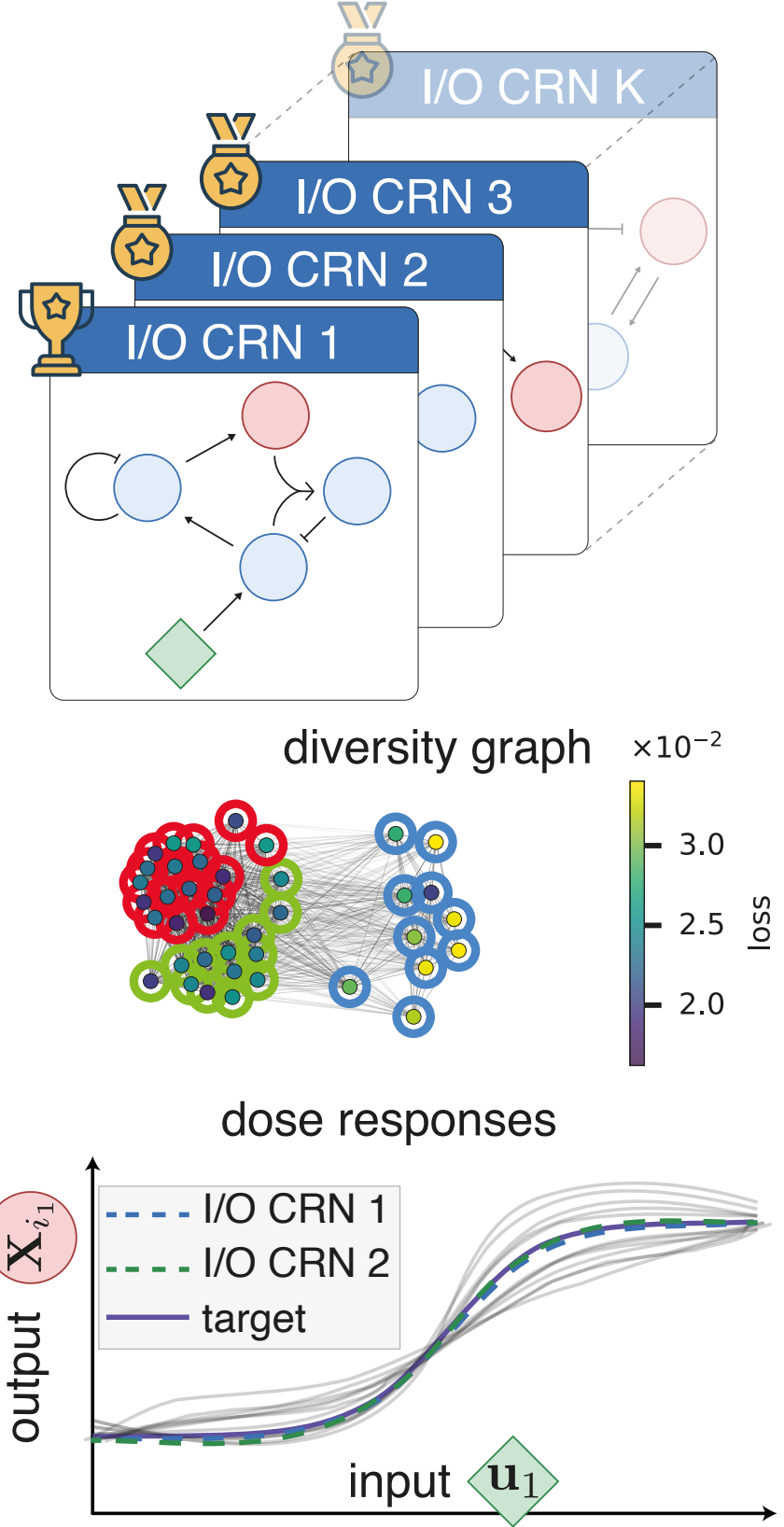
specify (bio)chemical environment:



specify kinetics:



Generated I/O CRNs

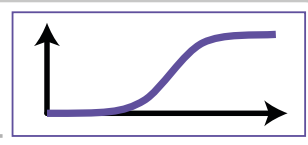
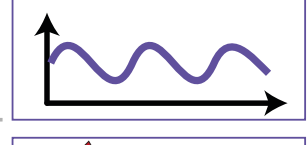
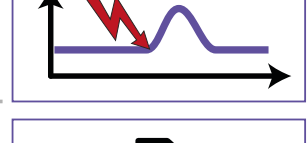
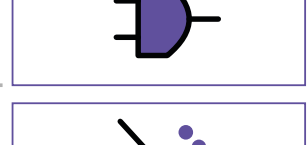
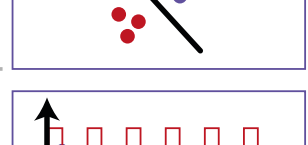
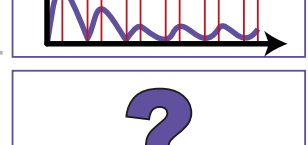


Introducing GenAI-Net

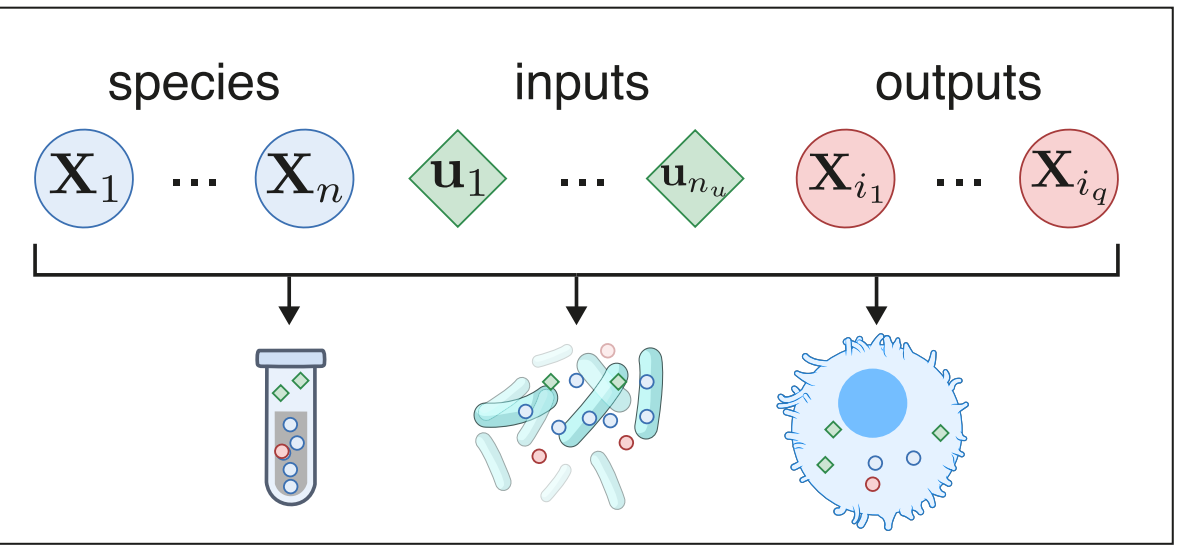
User Specifications

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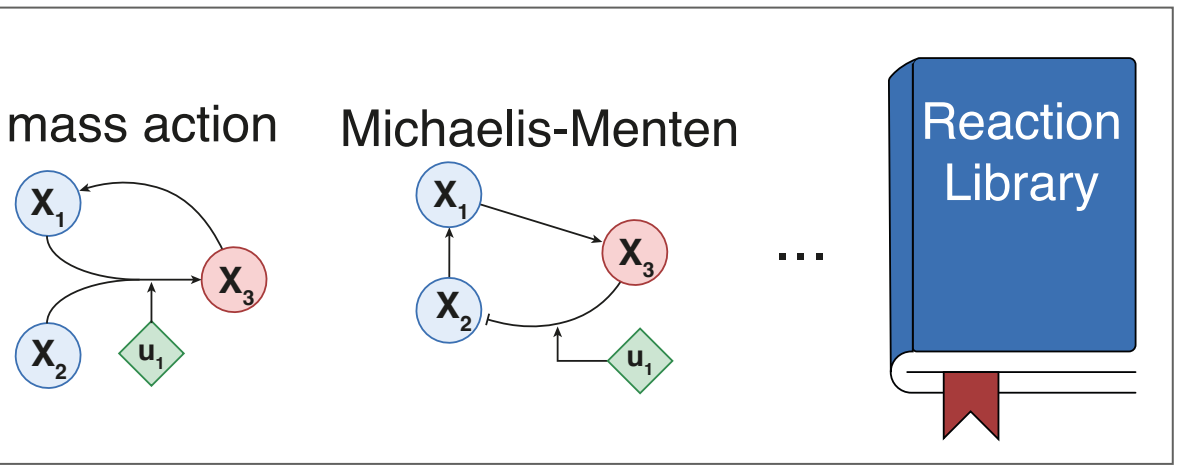


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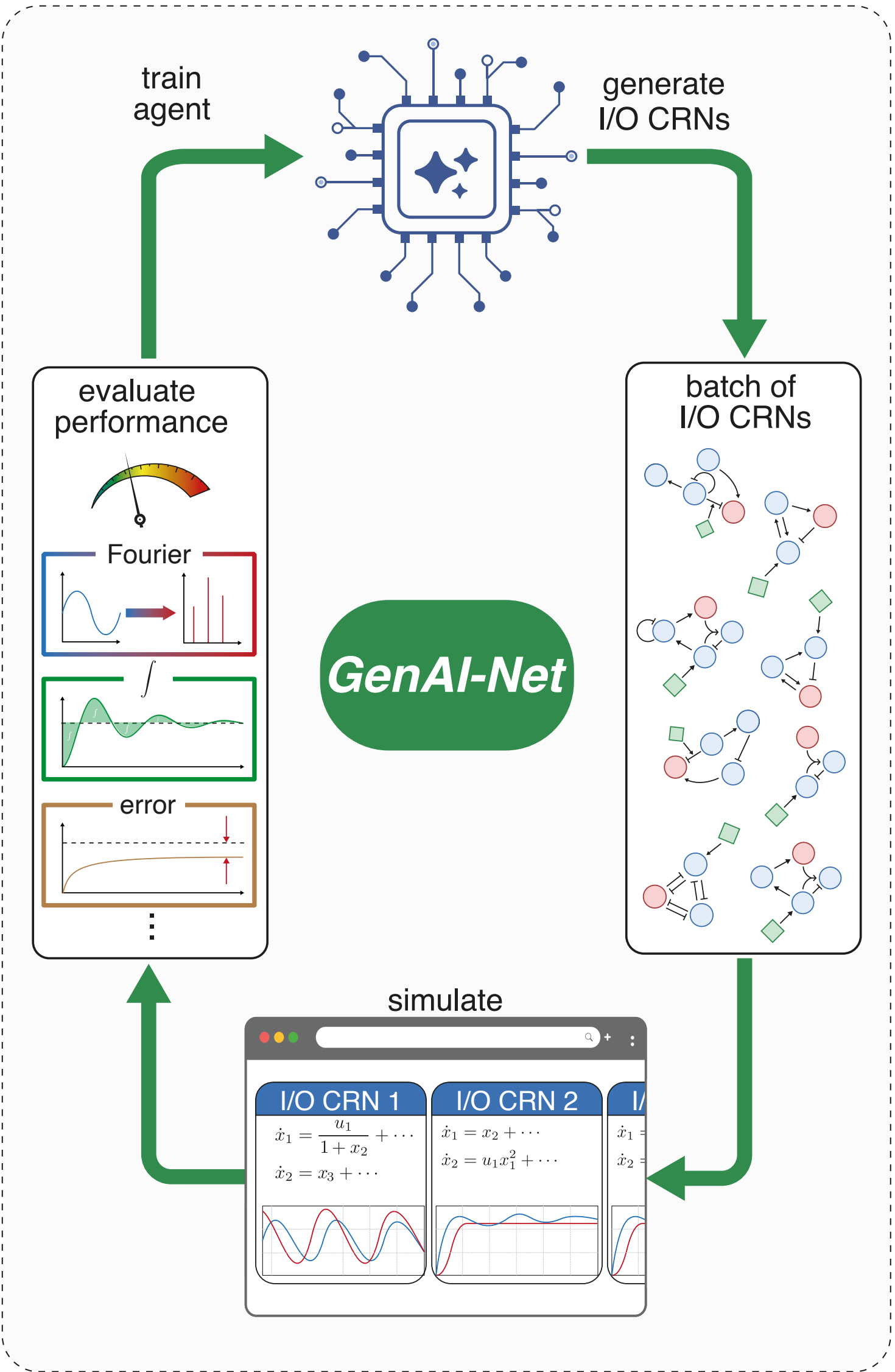
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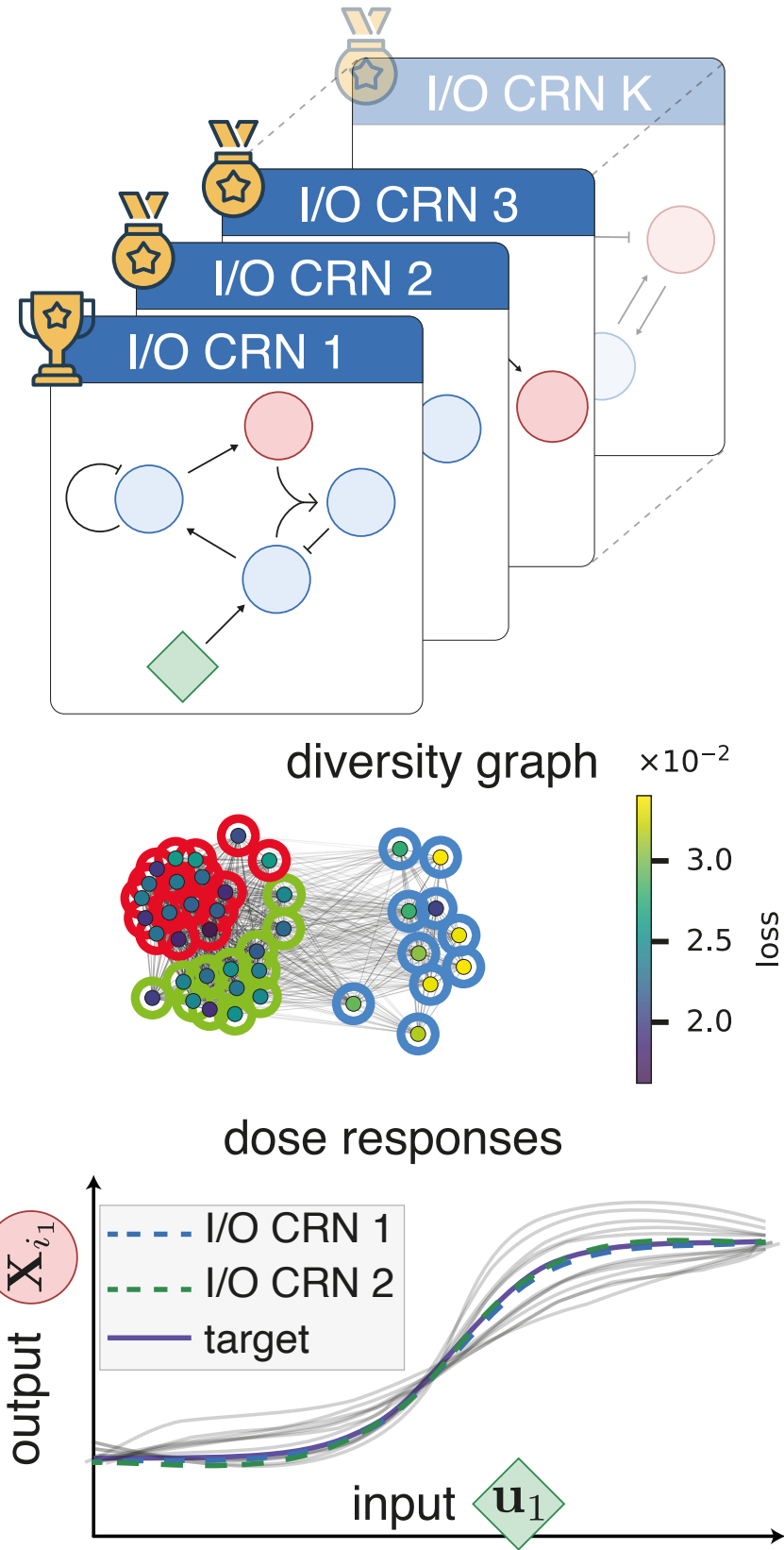
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AI Agent in the Loop



Generated I/O CRNs



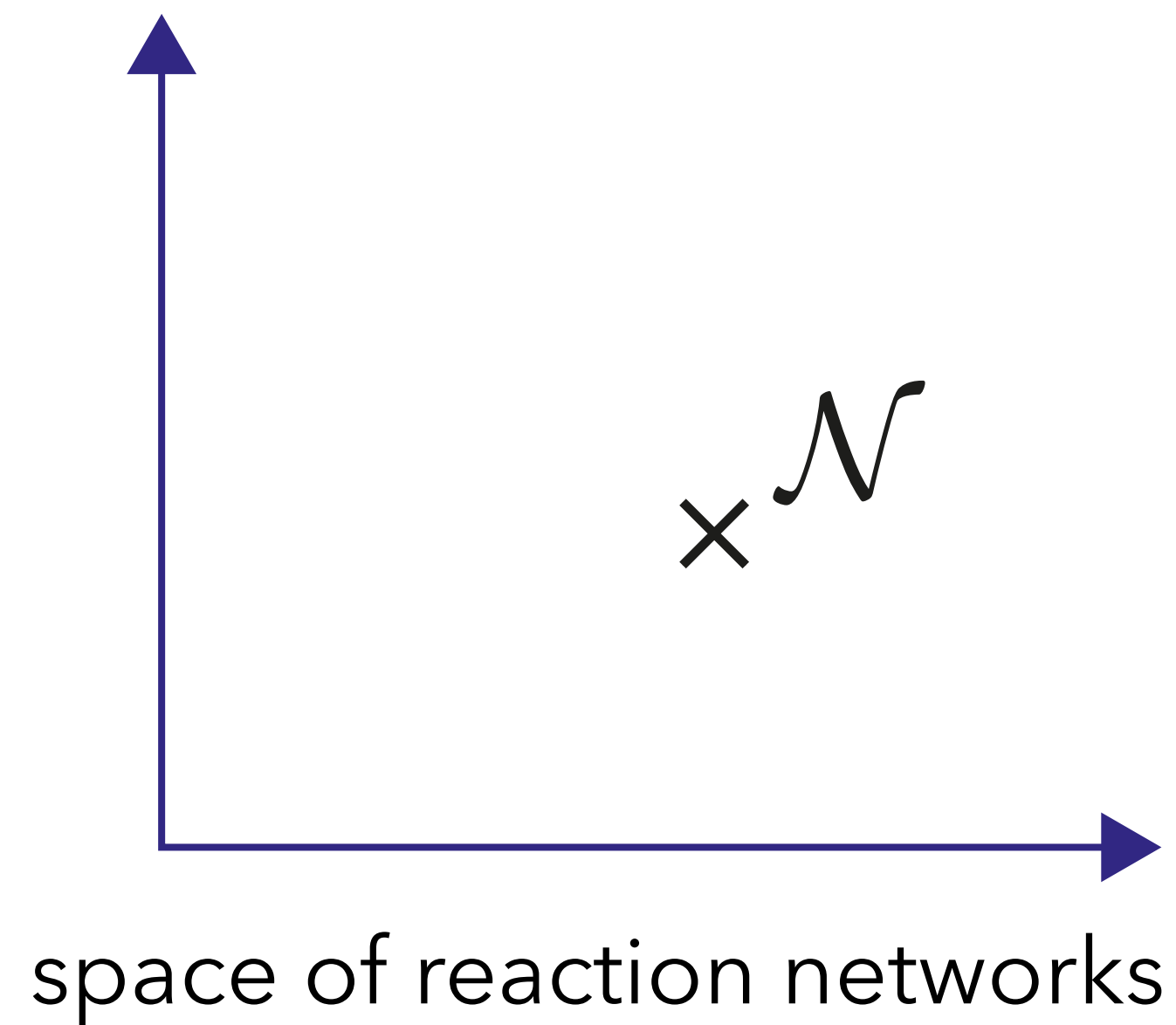
The high-level mathematical idea

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I/O CRN $\mathcal{N}$ is a random variable

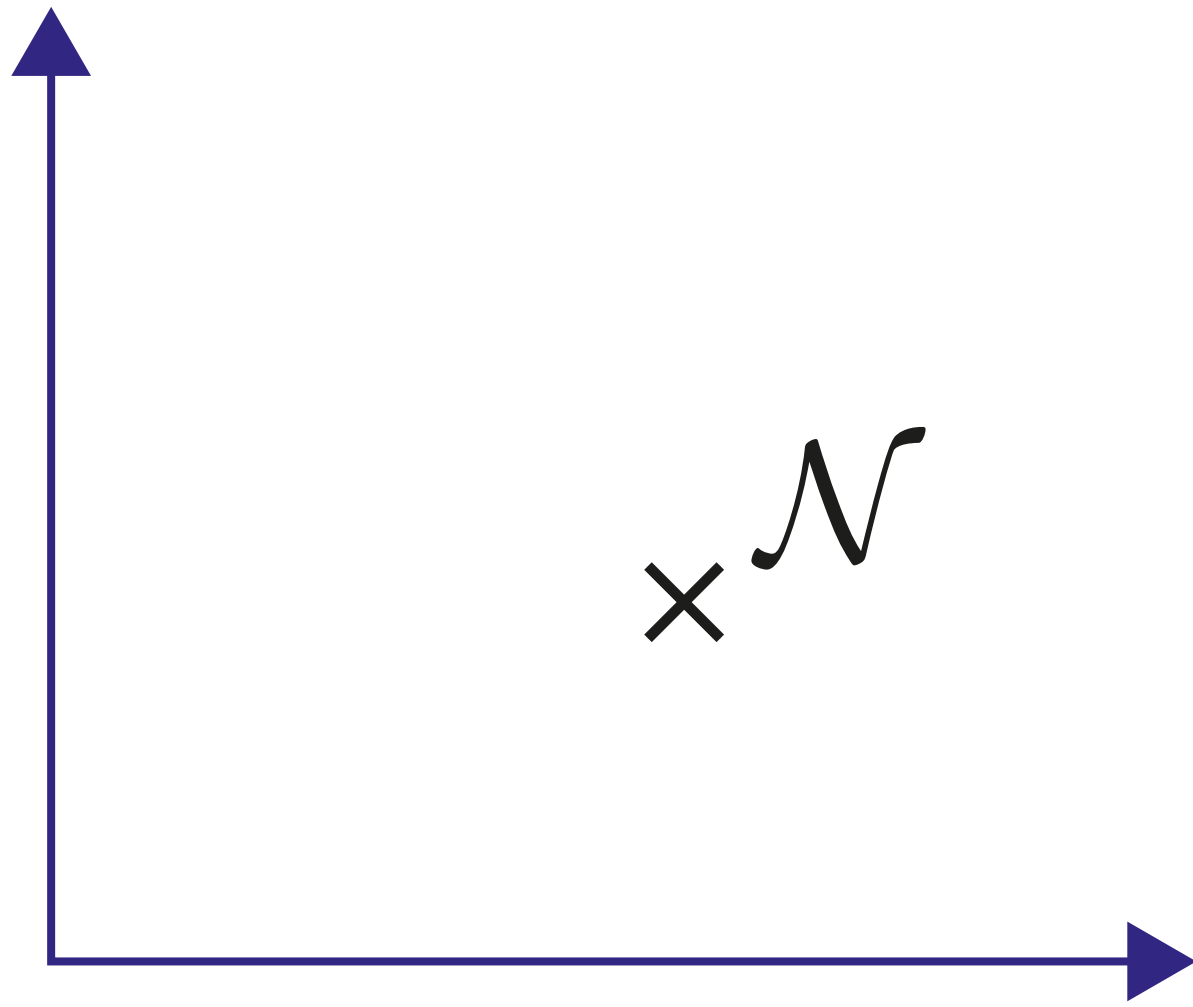
The high-level mathematical idea

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I/O CRN $\mathcal{N}$ is a random variable



space of reaction networks

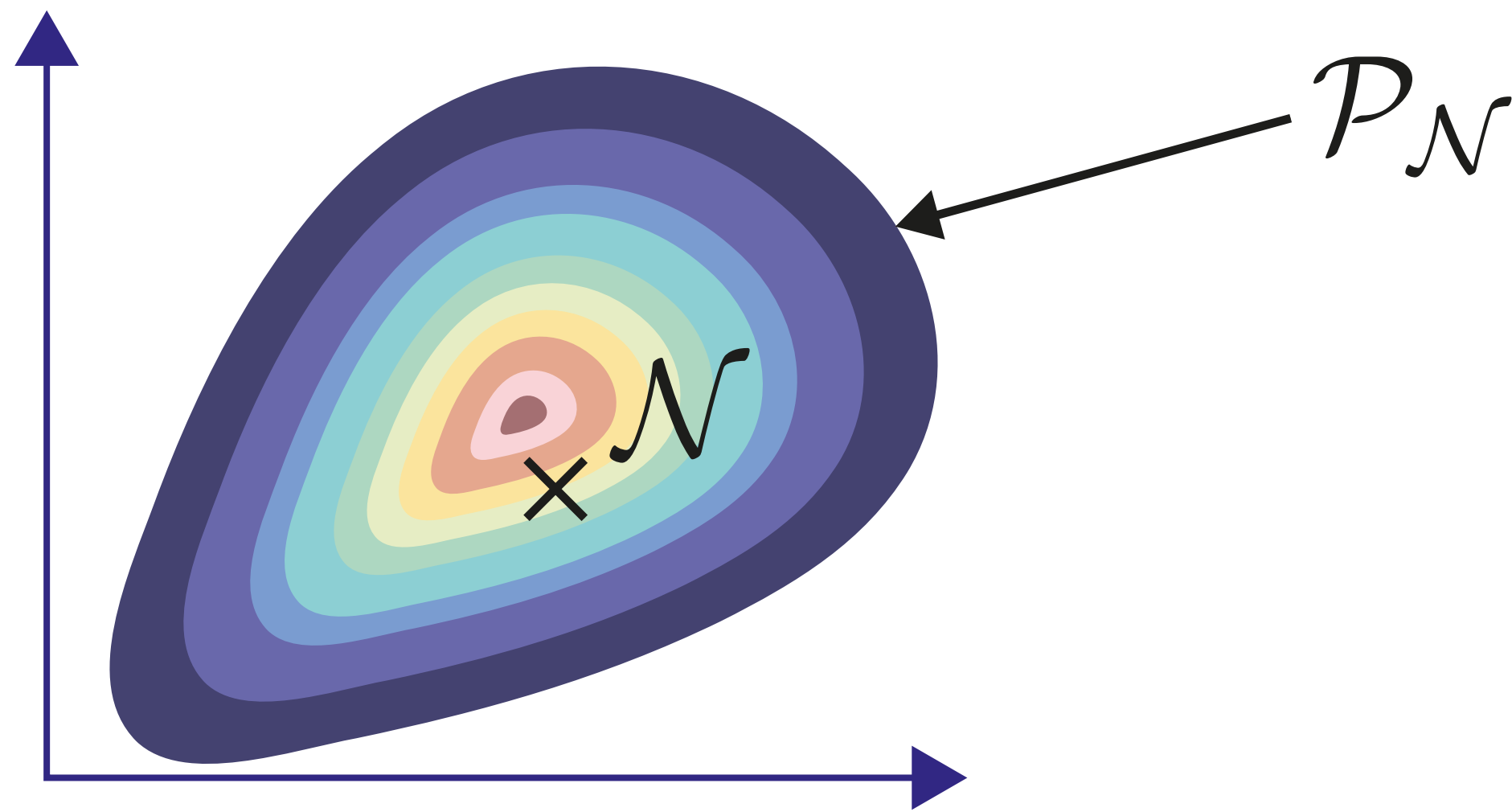
hybrid space:

- discrete: topologies
- continuous: parameters

The high-level mathematical idea

I/O CRN $\mathcal{N}$ is a random variable

with unknown probability distribution $\mathcal{P}_{\mathcal{N}}$



space of reaction networks

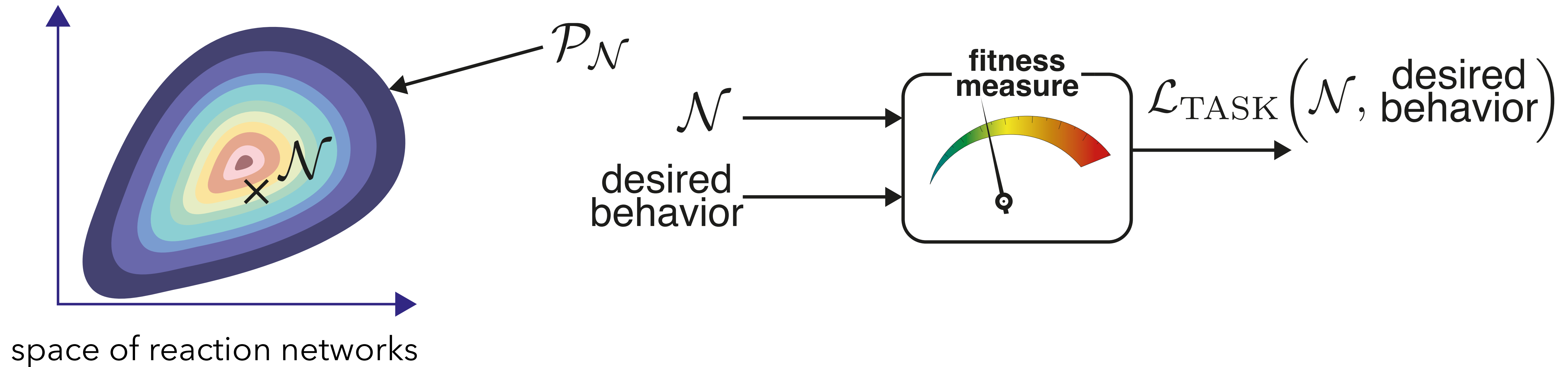
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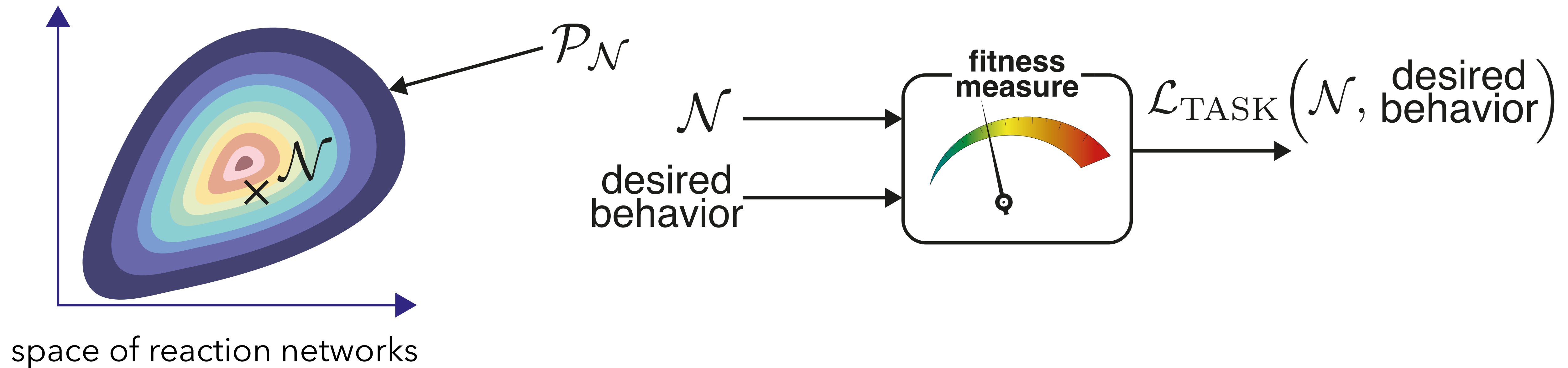
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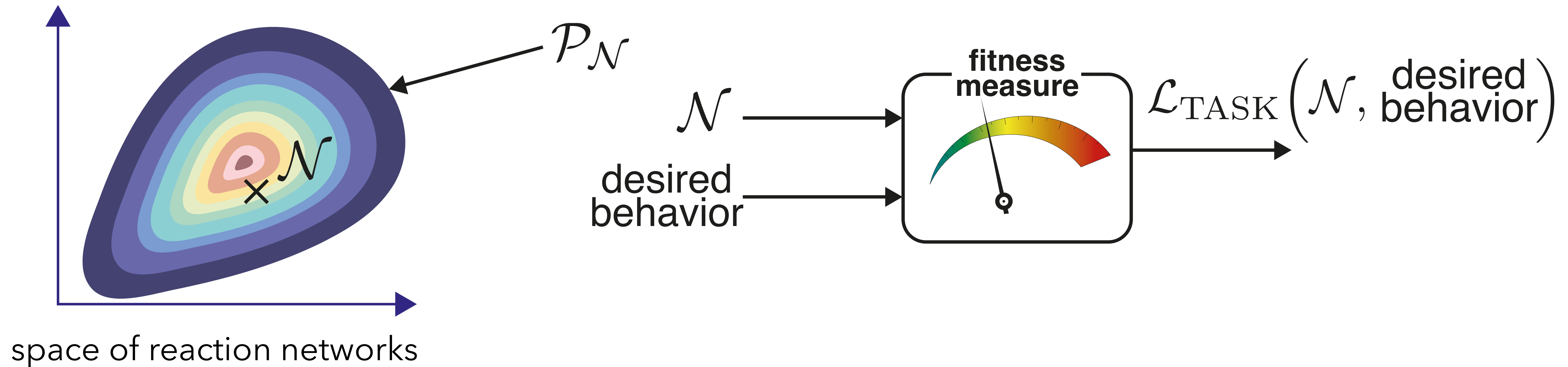
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$$\mathcal{P}_{\mathcal{N}}^* = \underset{\mathcal{P}_{\mathcal{N}}}{\operatorname{argmin}} \mathbb{E}_{\mathcal{N} \sim \mathcal{P}_{\mathcal{N}}} \left[\mathcal{L}_{\text{TASK}} \left(\mathcal{N}, \text{desired behavior} \right) \right]$$

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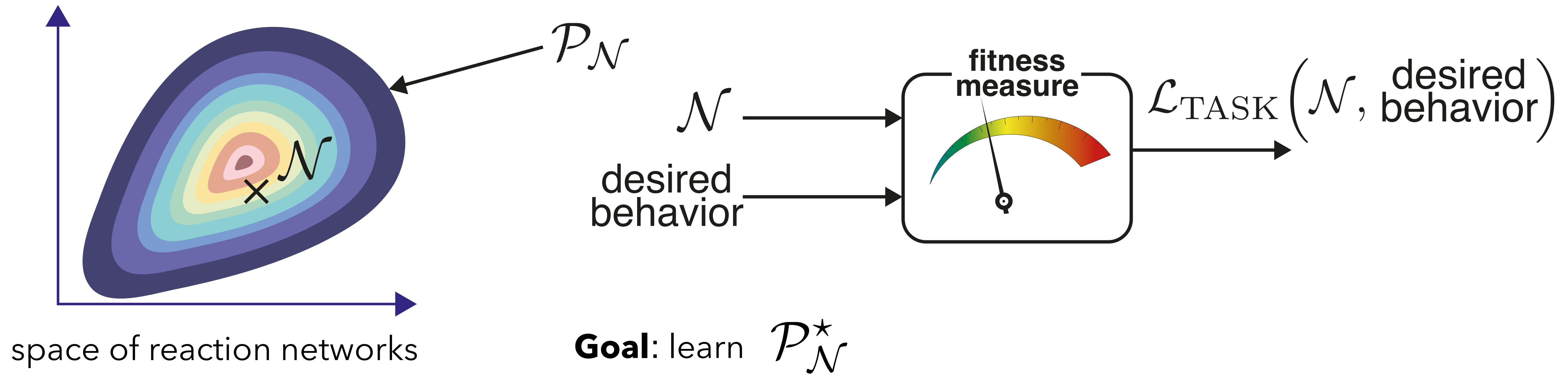
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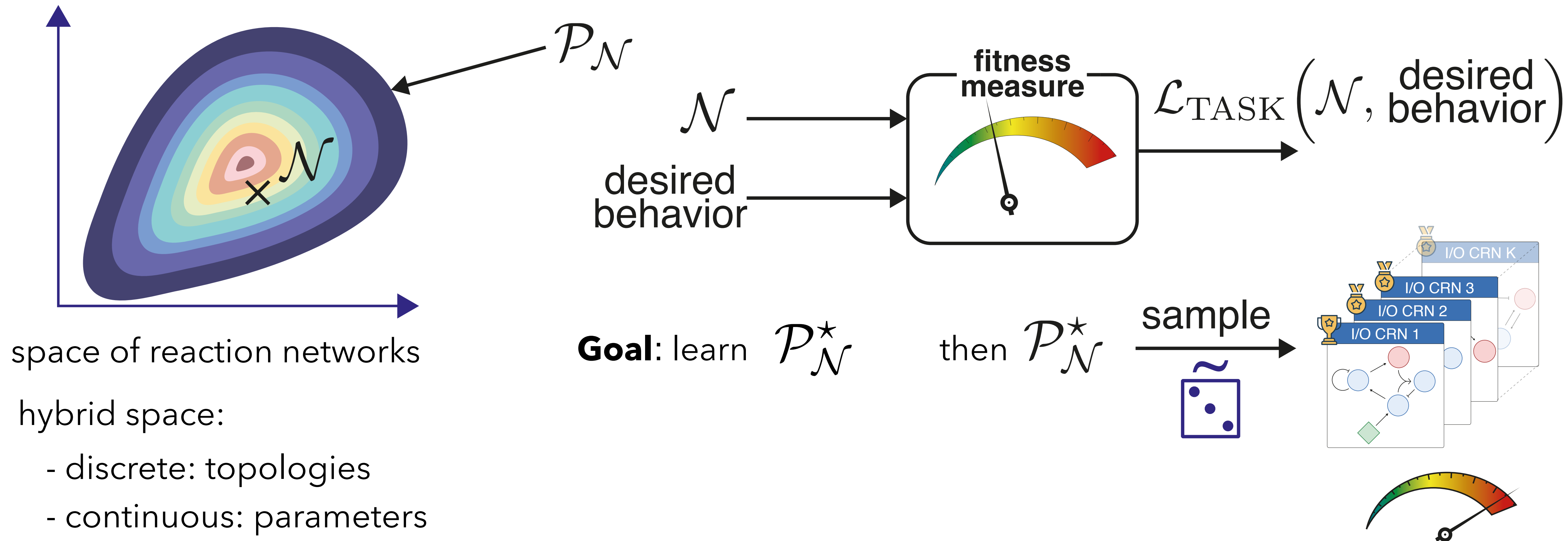
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Casting as a Reinforcement Learning problem

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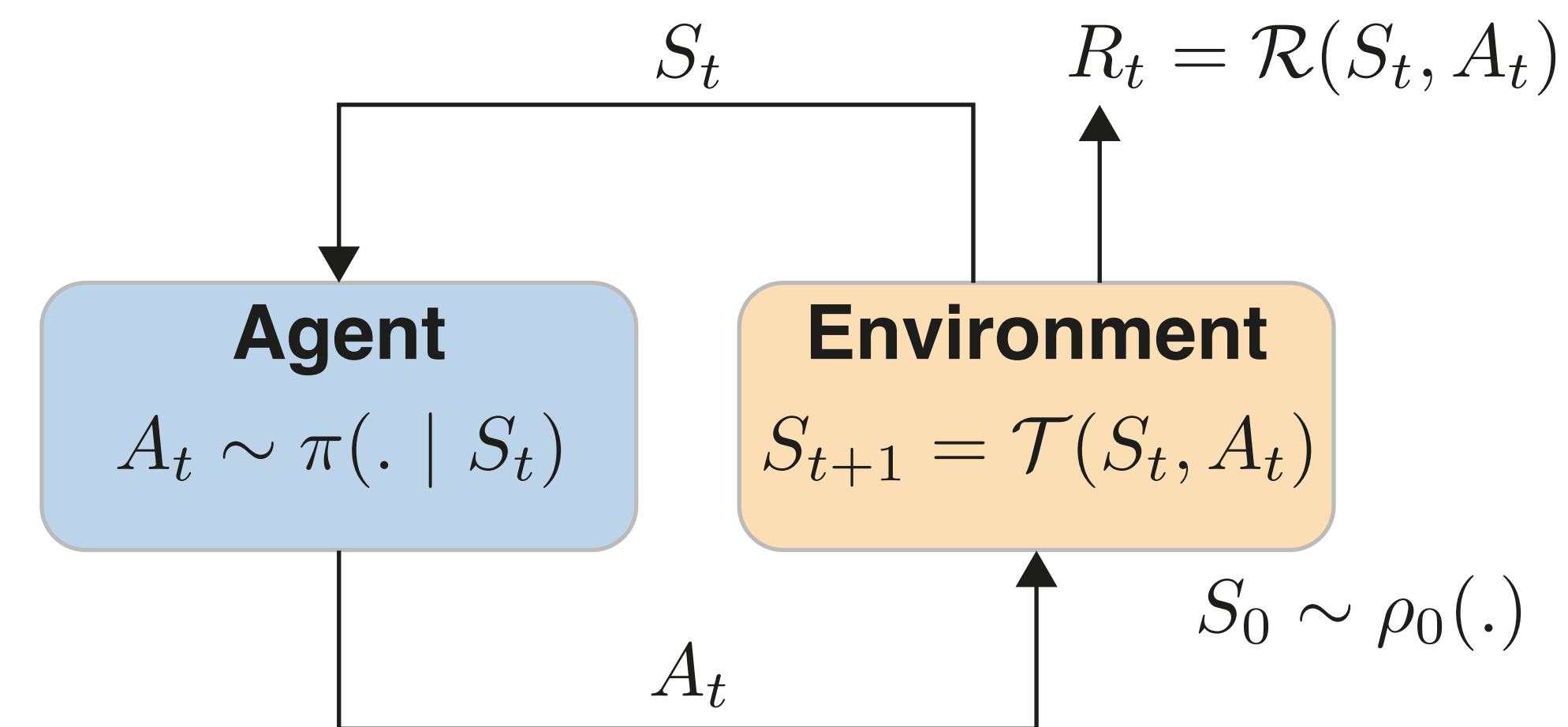
We can think of the process of building an I/O CRN, one reaction at a time, as a Markov Decision Process characterised by the tuple $(\mathcal{S}, \mathcal{A}, \mathcal{T}, \pi, \mathcal{R}, \rho_0)$

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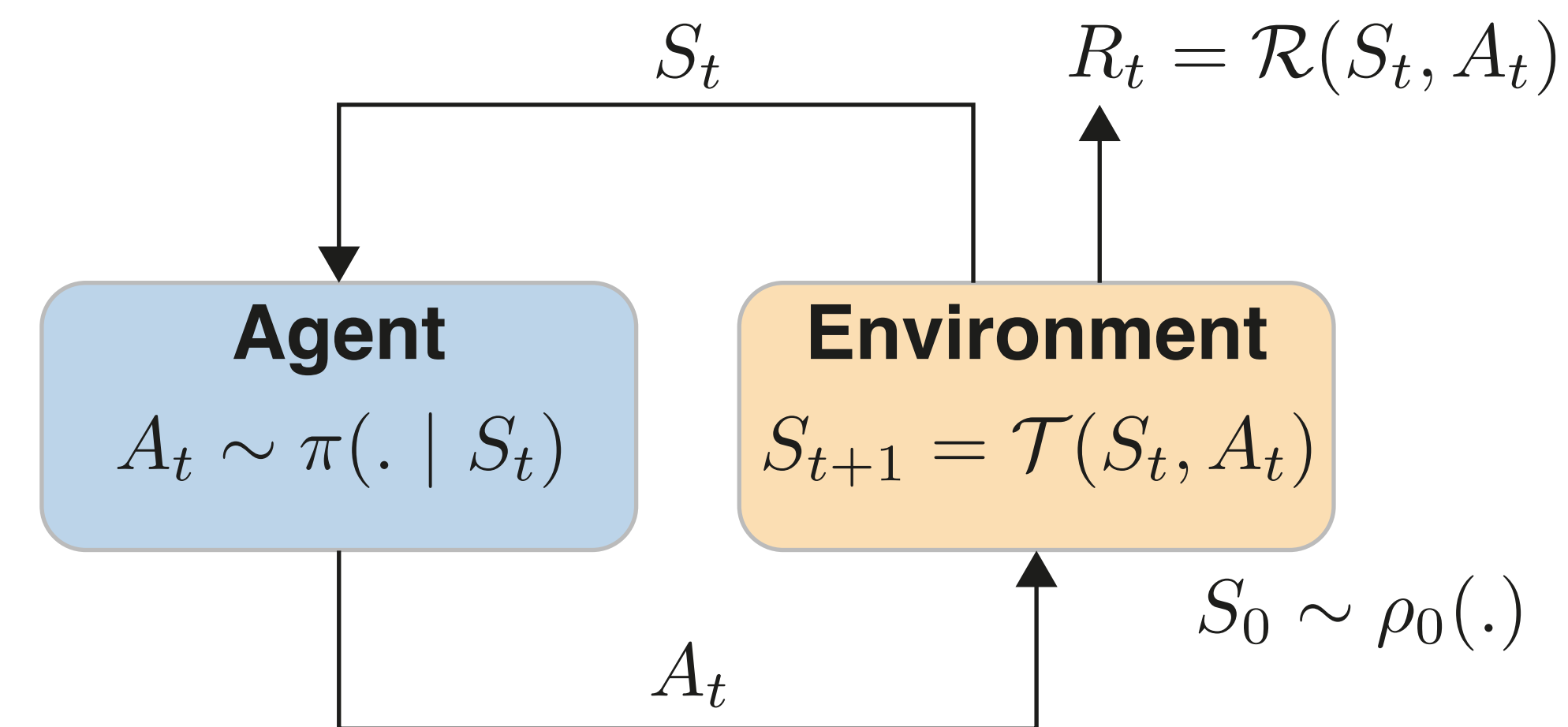
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Casting as a Reinforcement Learning problem

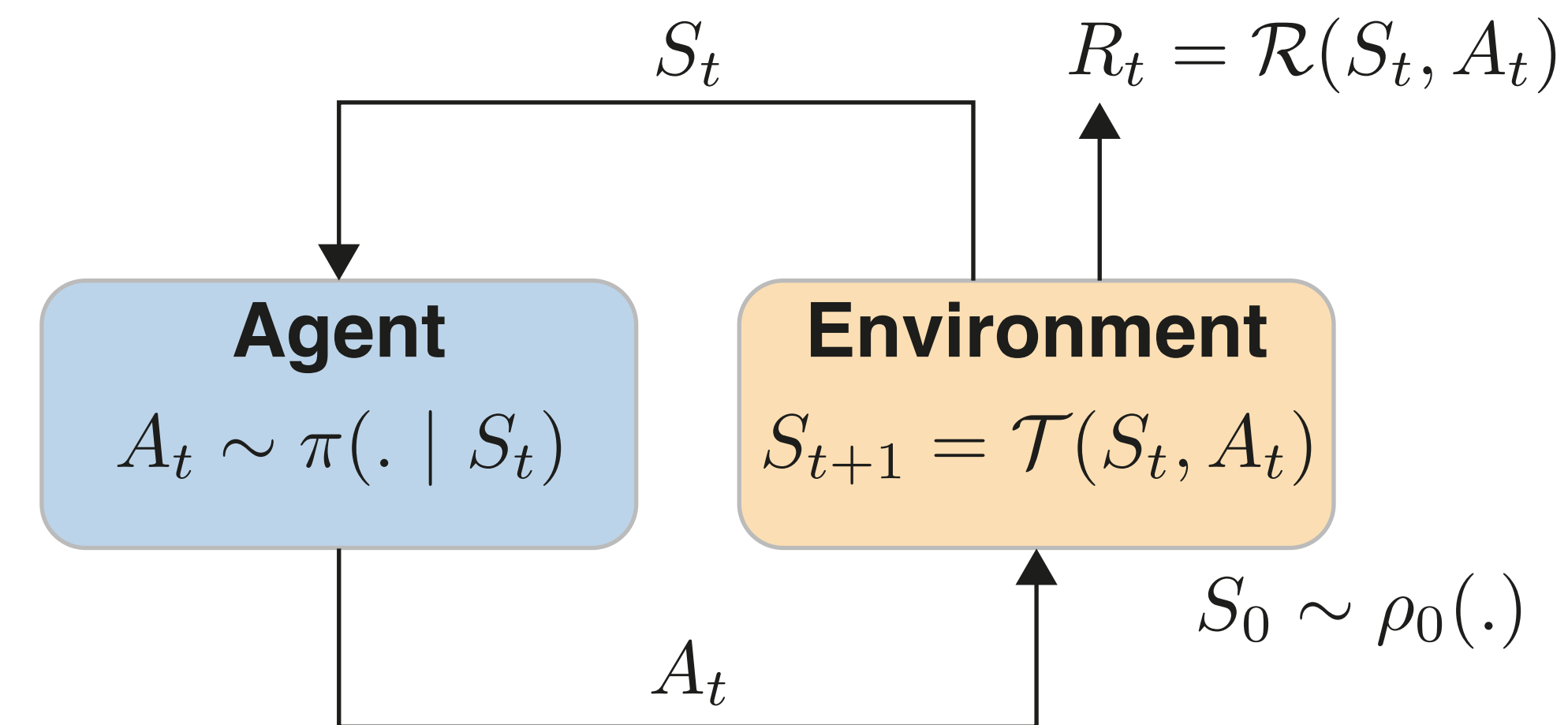
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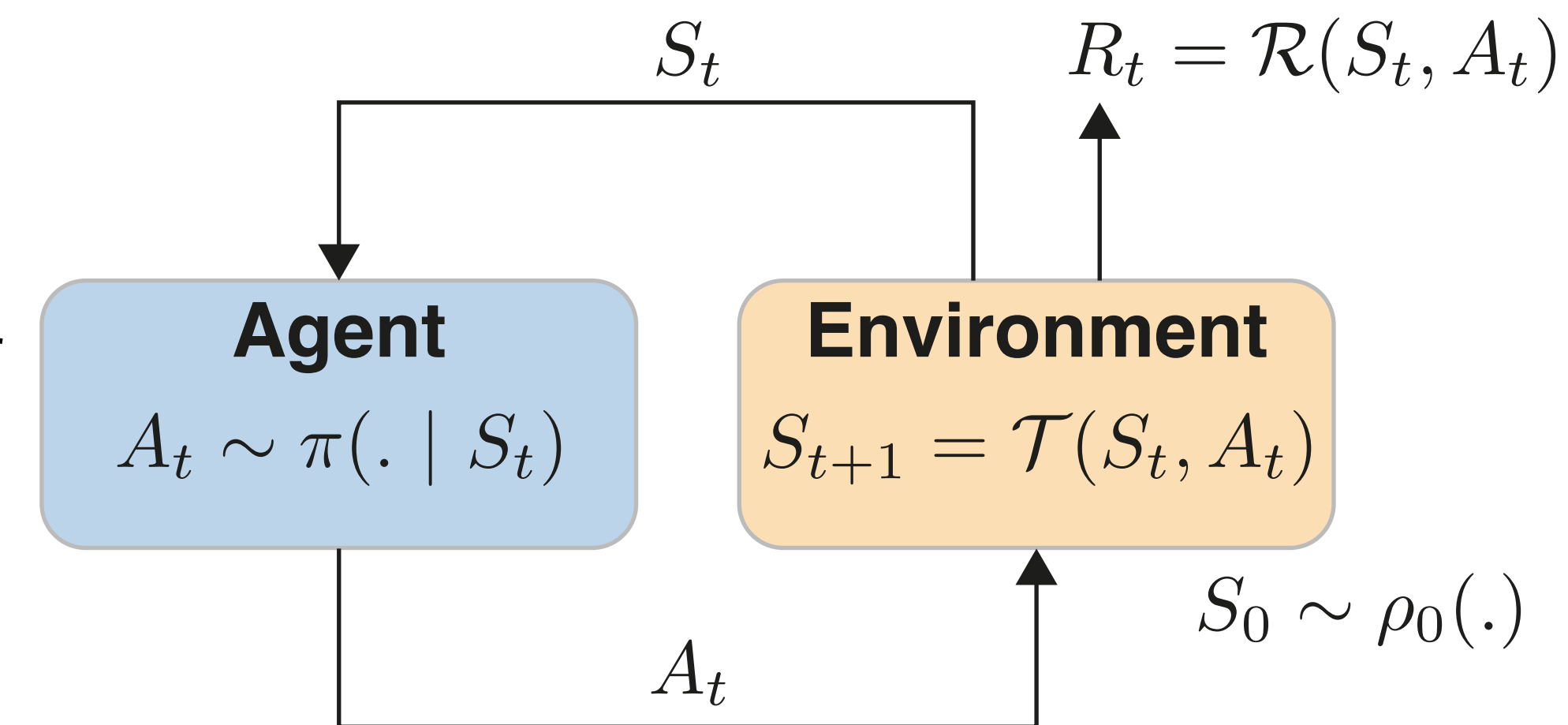
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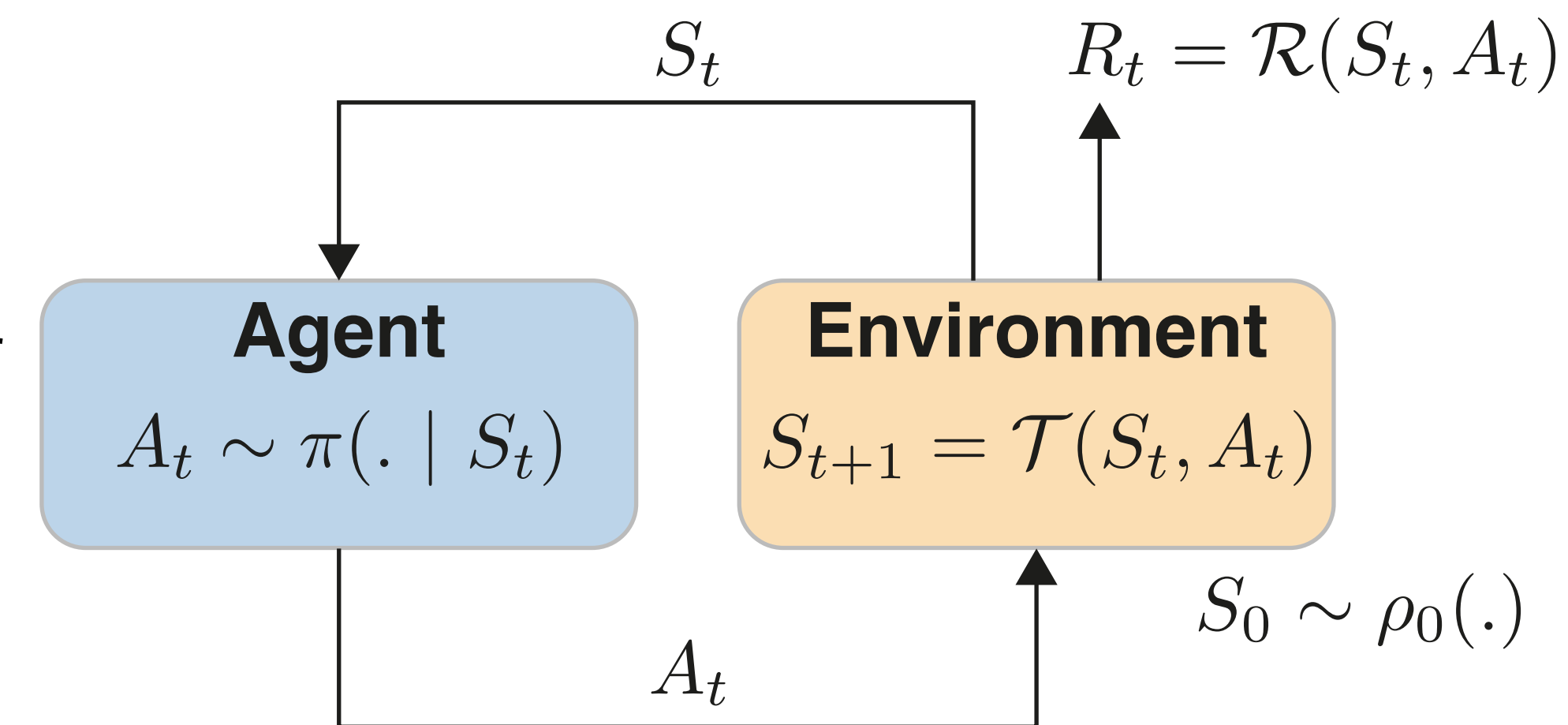
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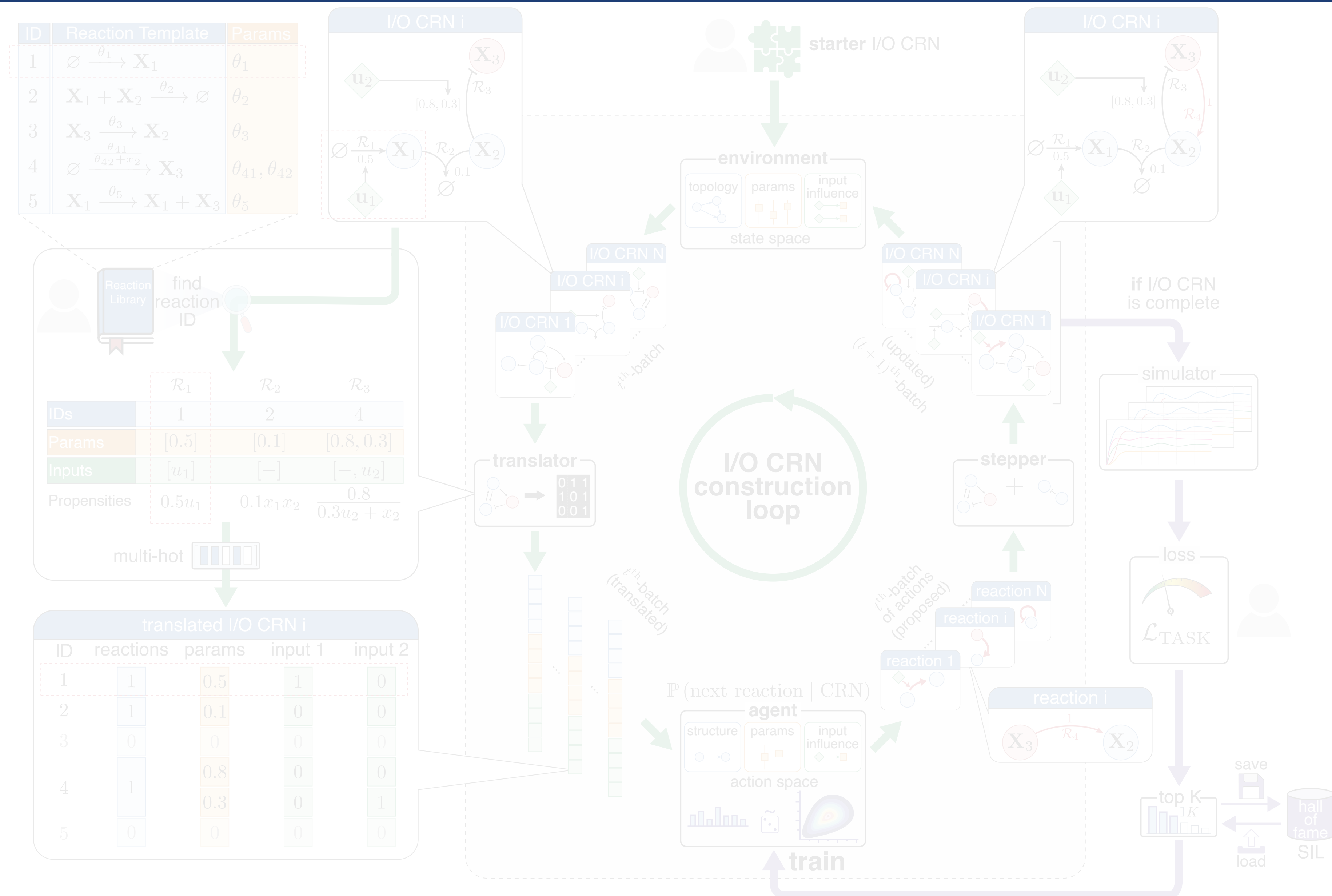
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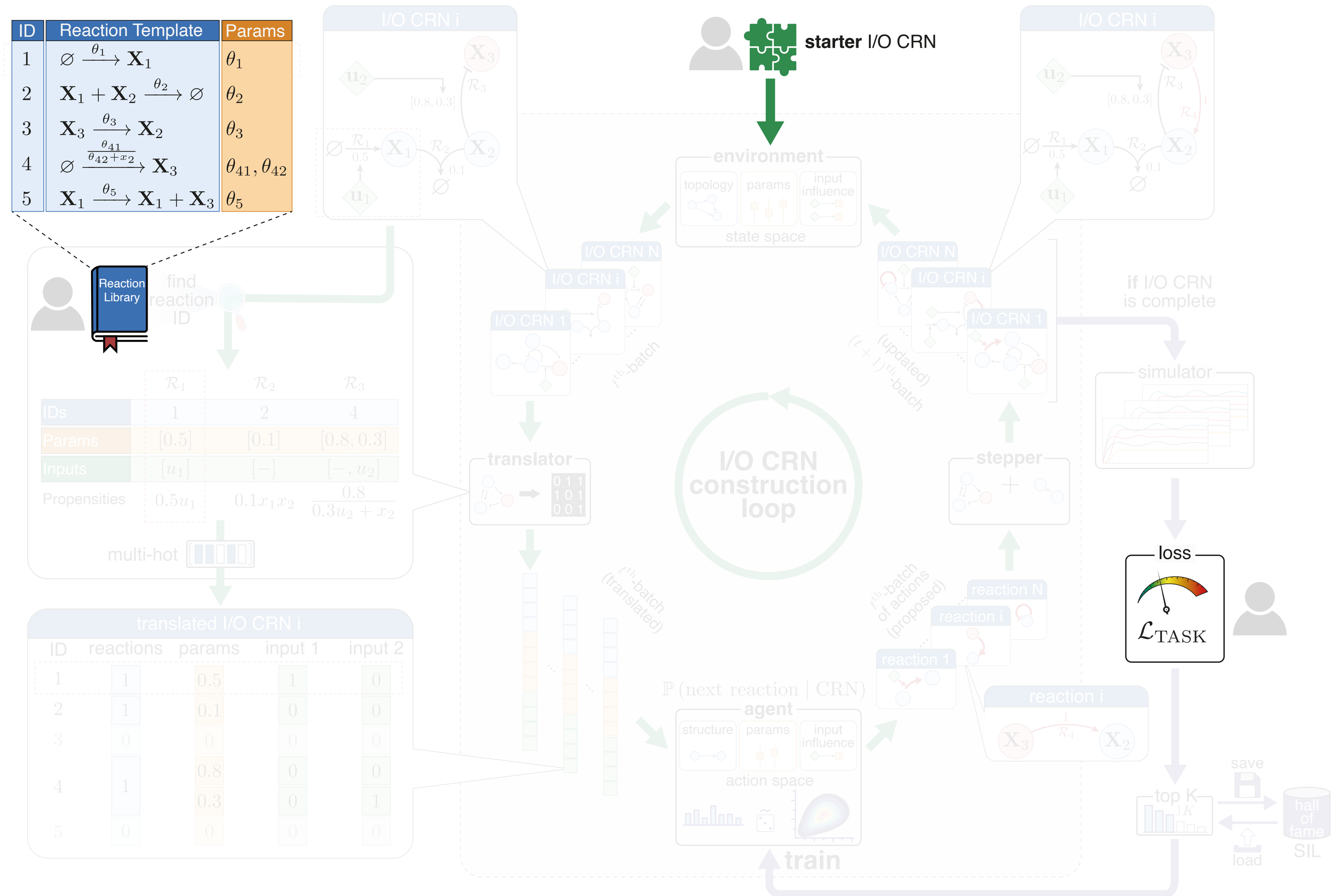
$\rho_0(\cdot)$ is the distribution of initial states s_0



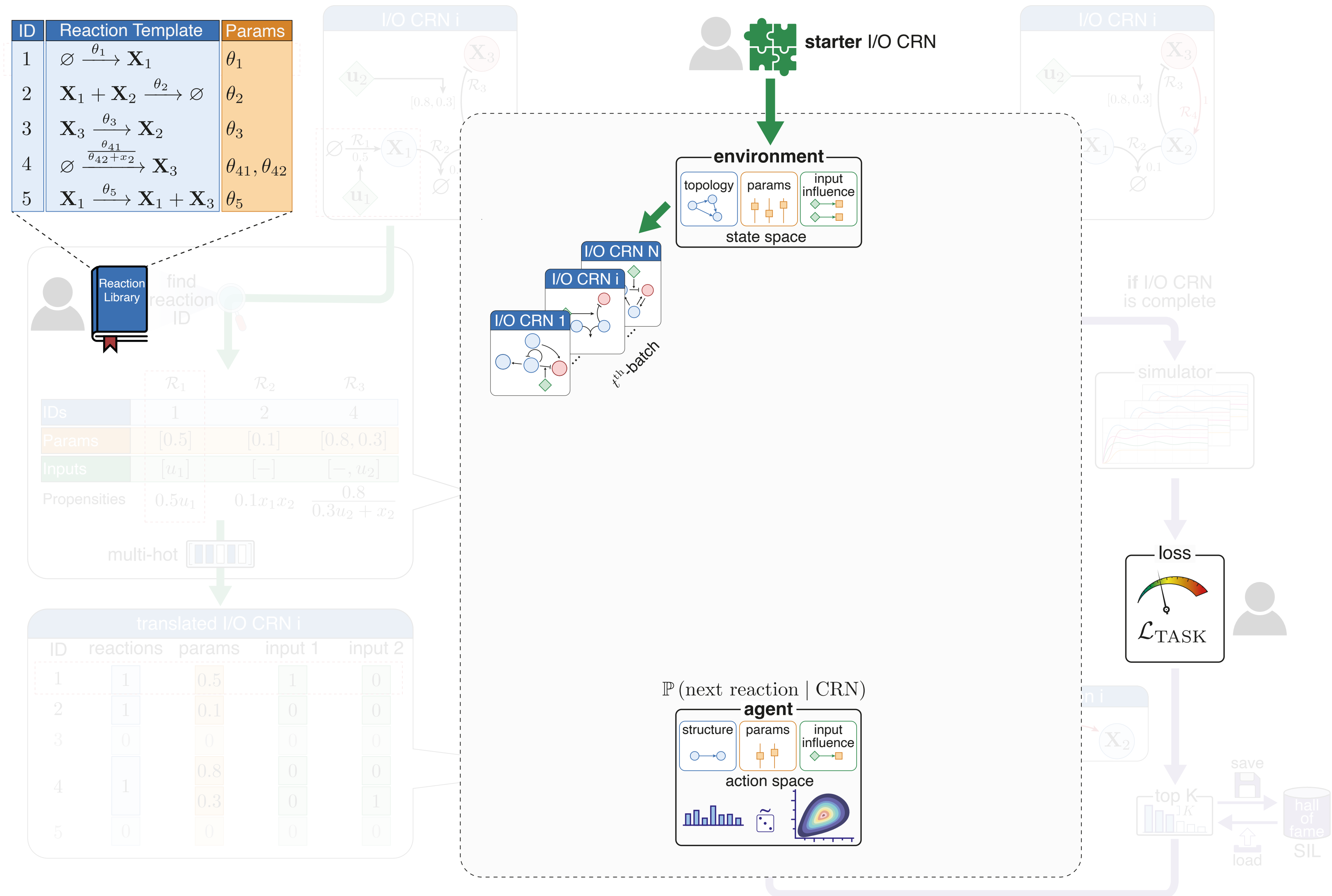
GenAI-Net: how it works



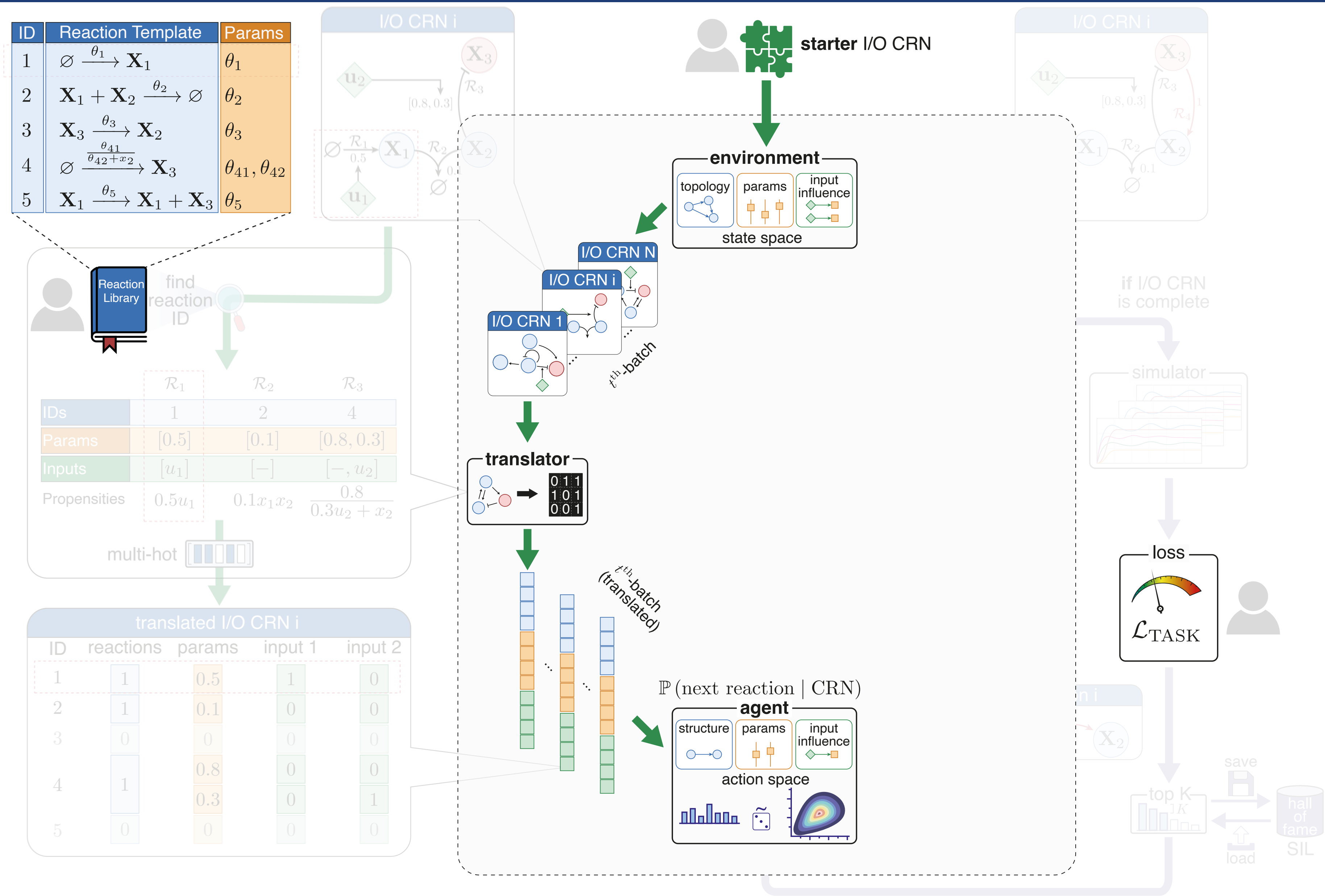
GenAI-Net: how it works



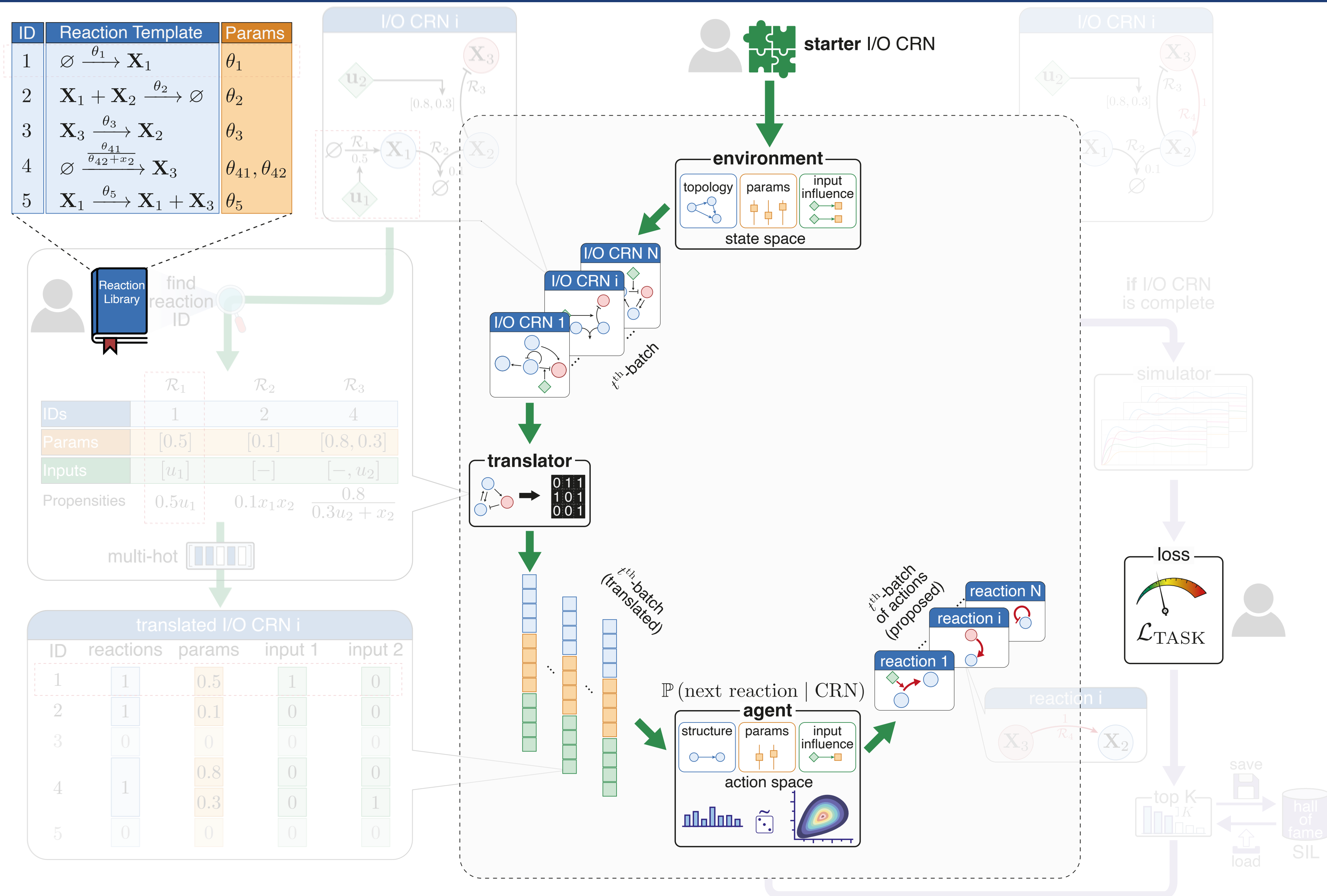
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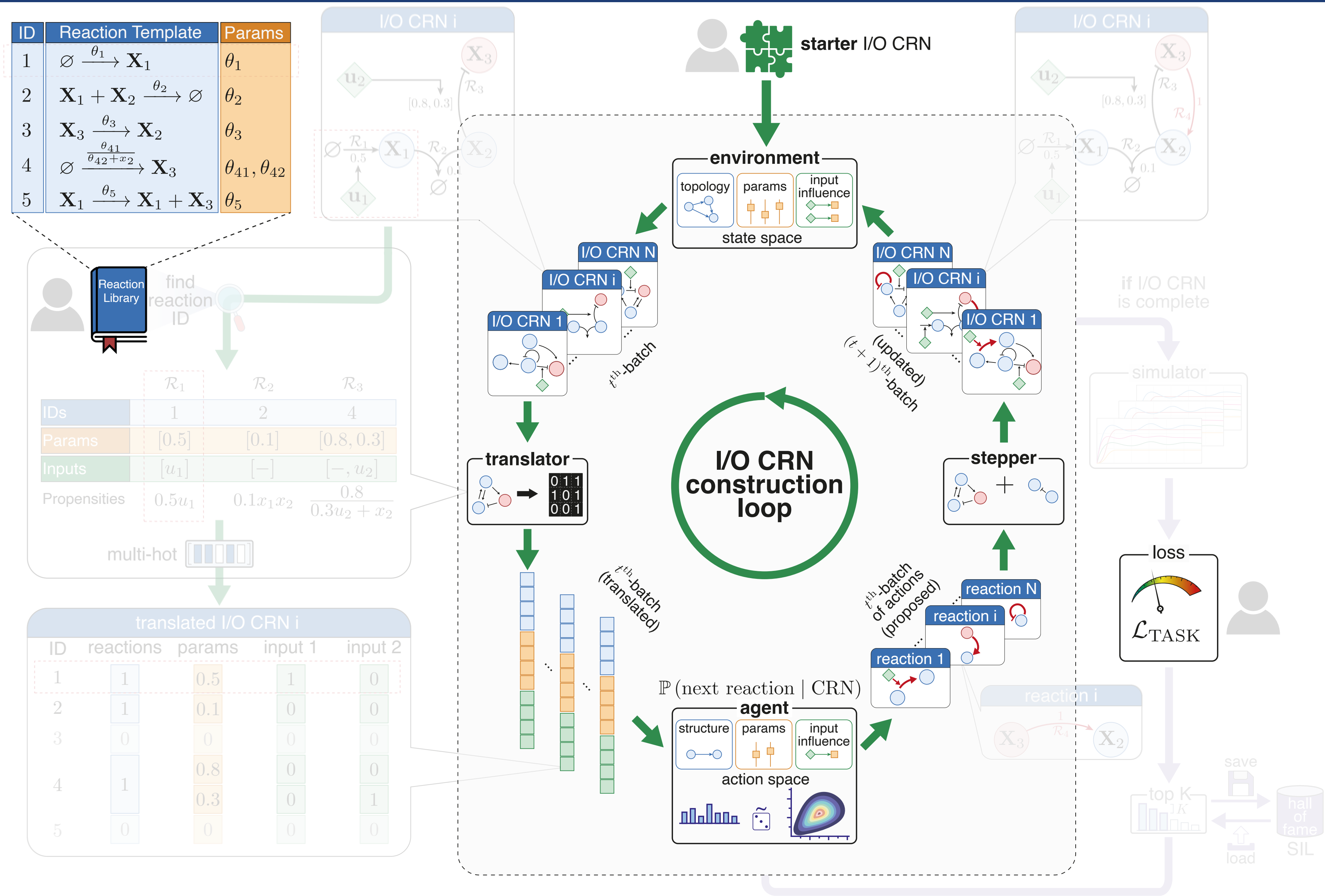
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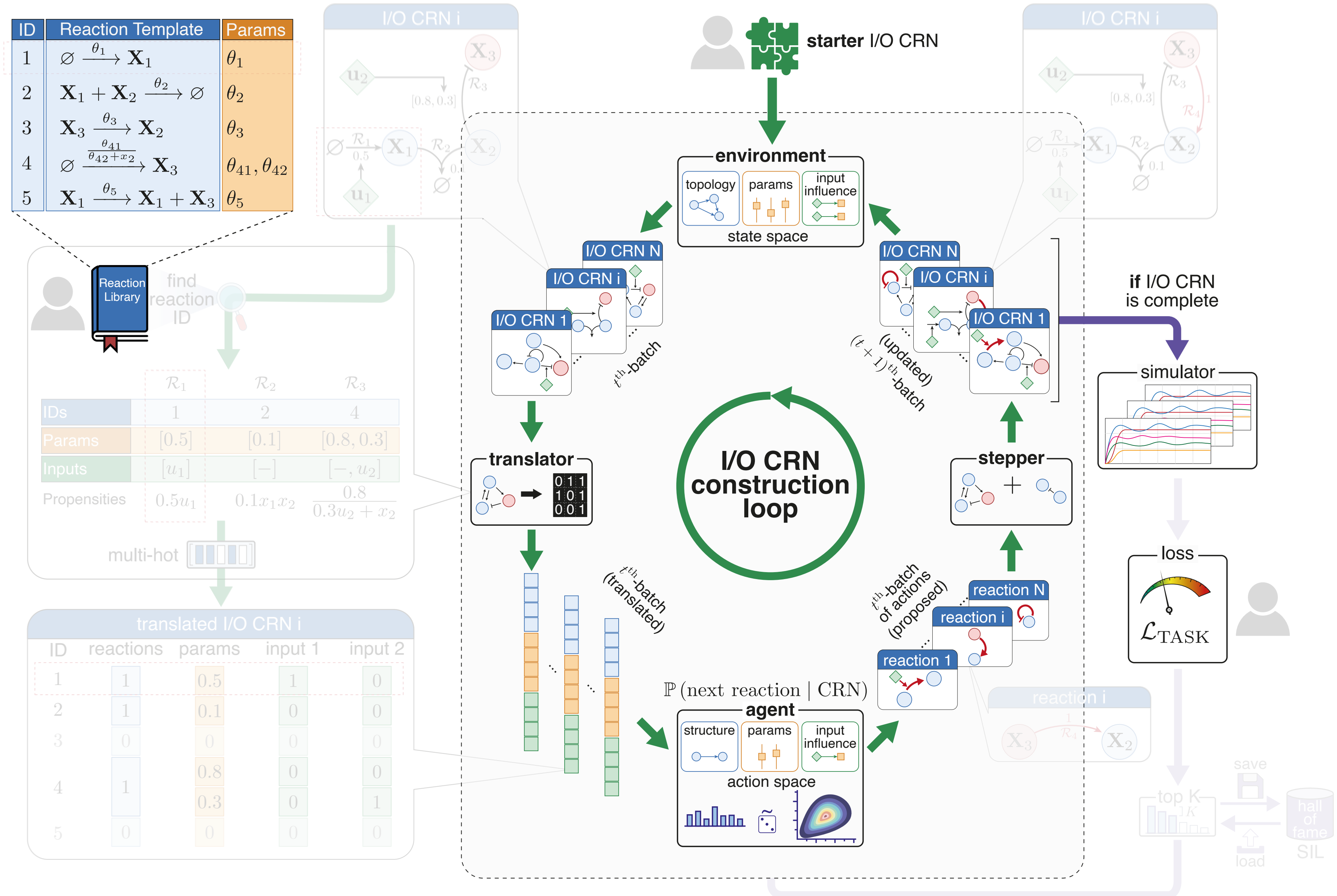
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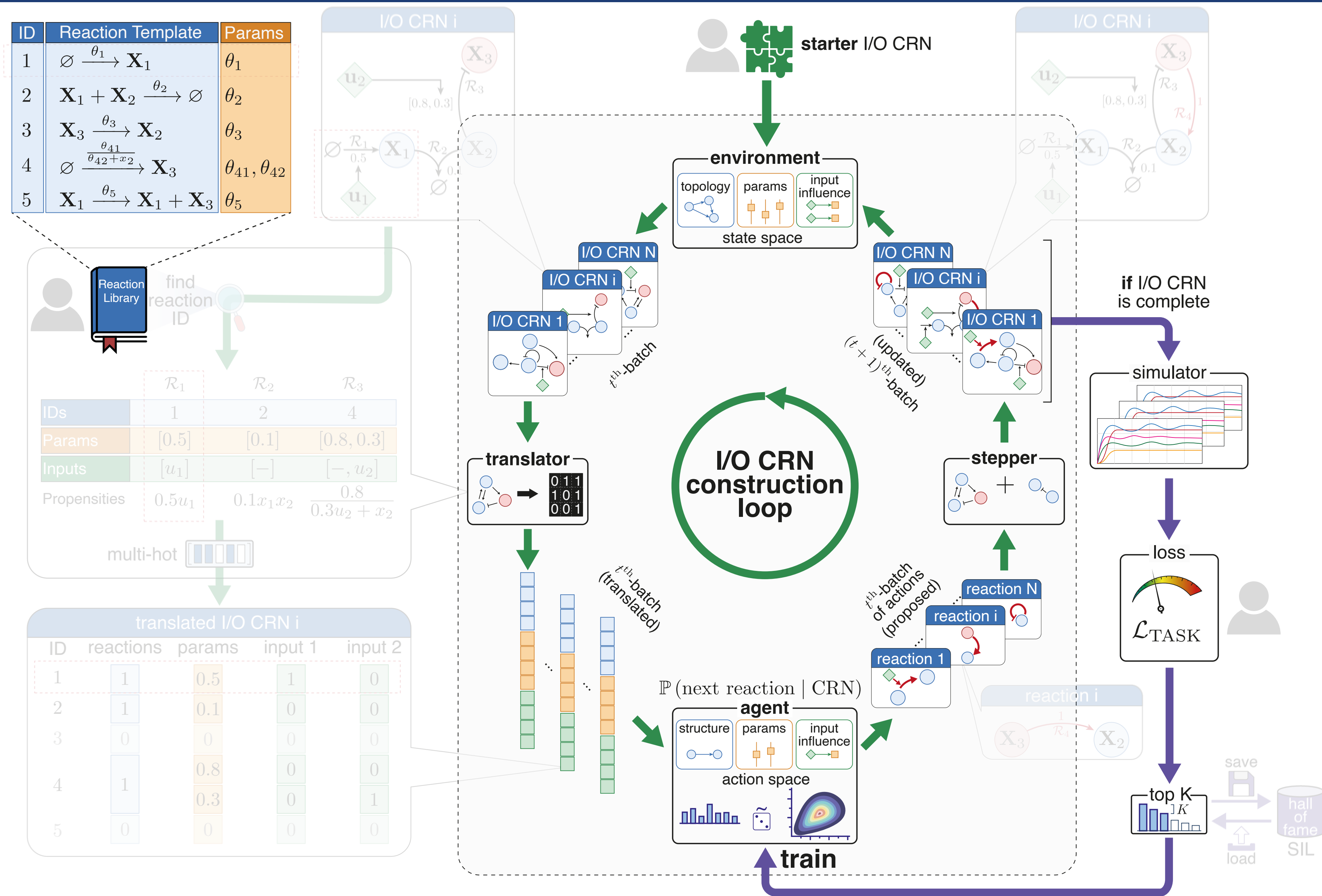
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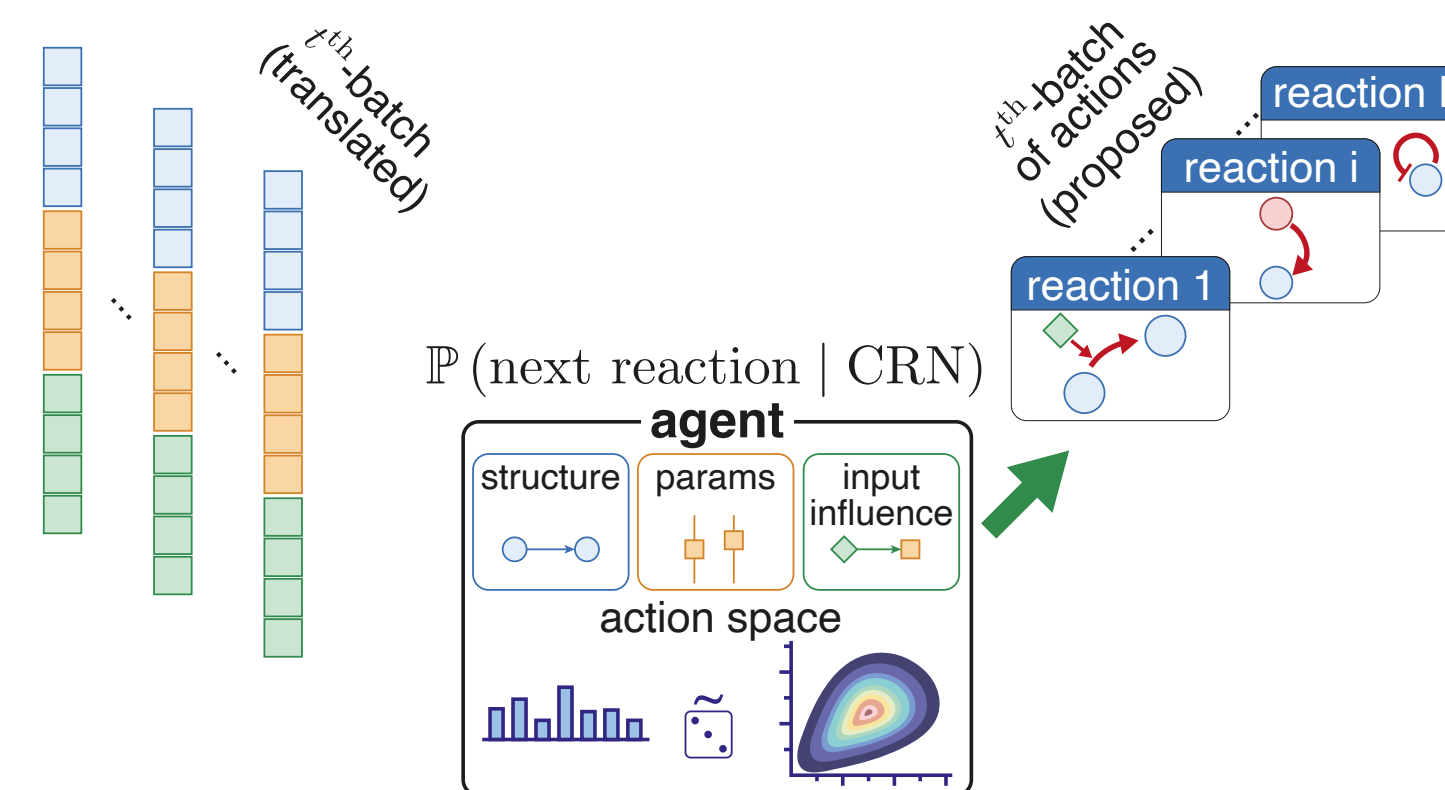
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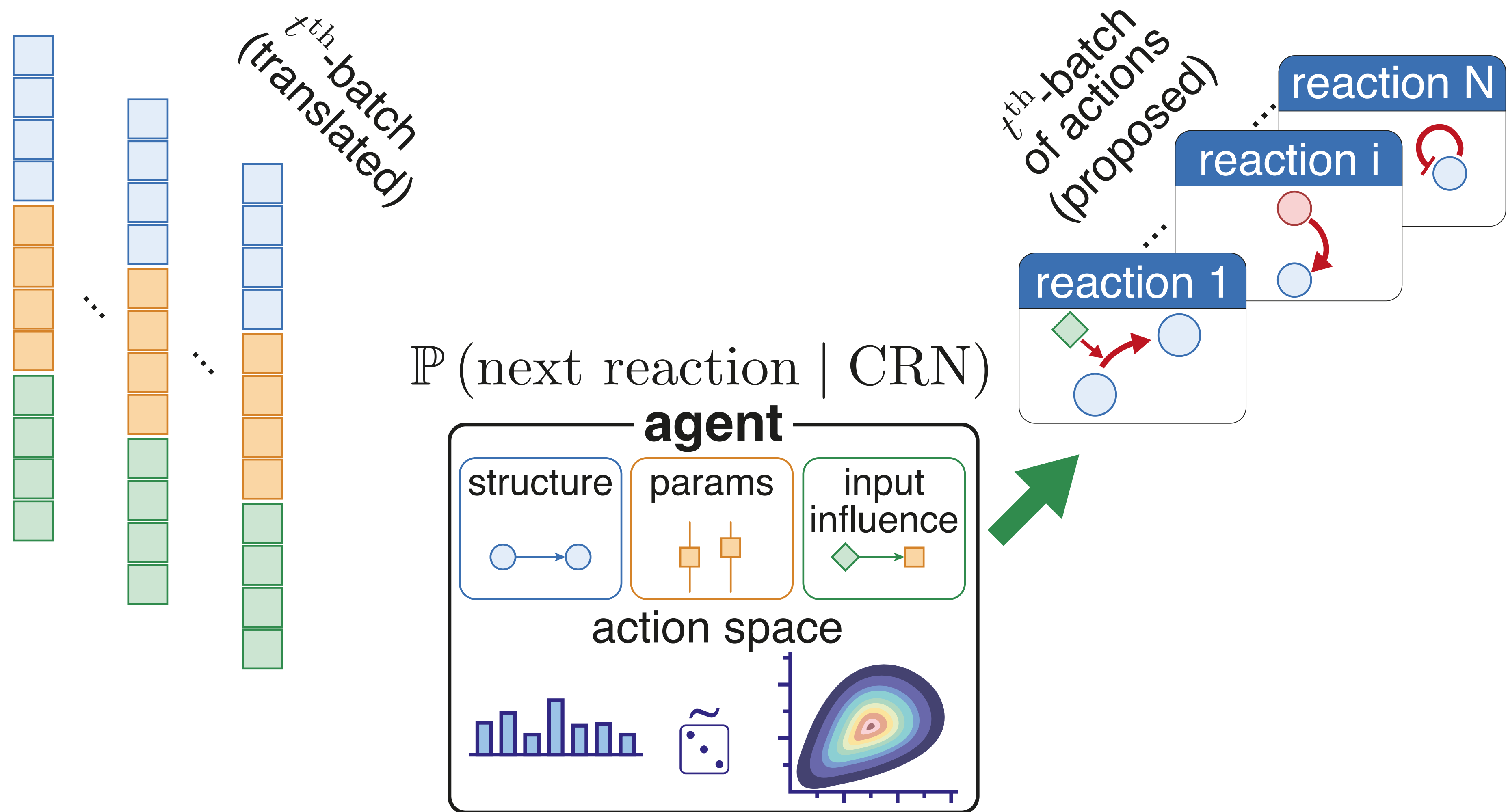
GenAI-Net: how it works



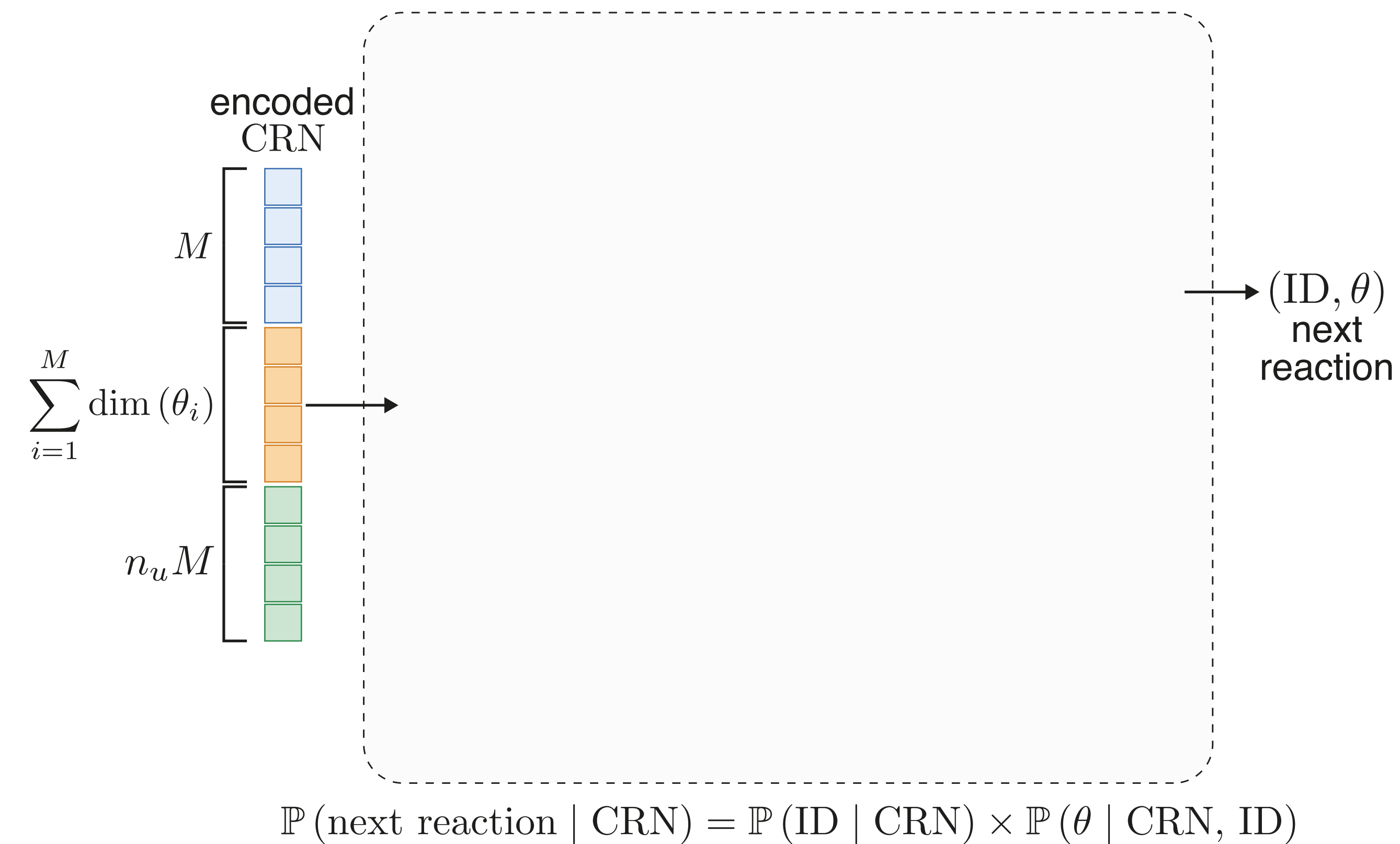
GenAI-Net: the agent architecture



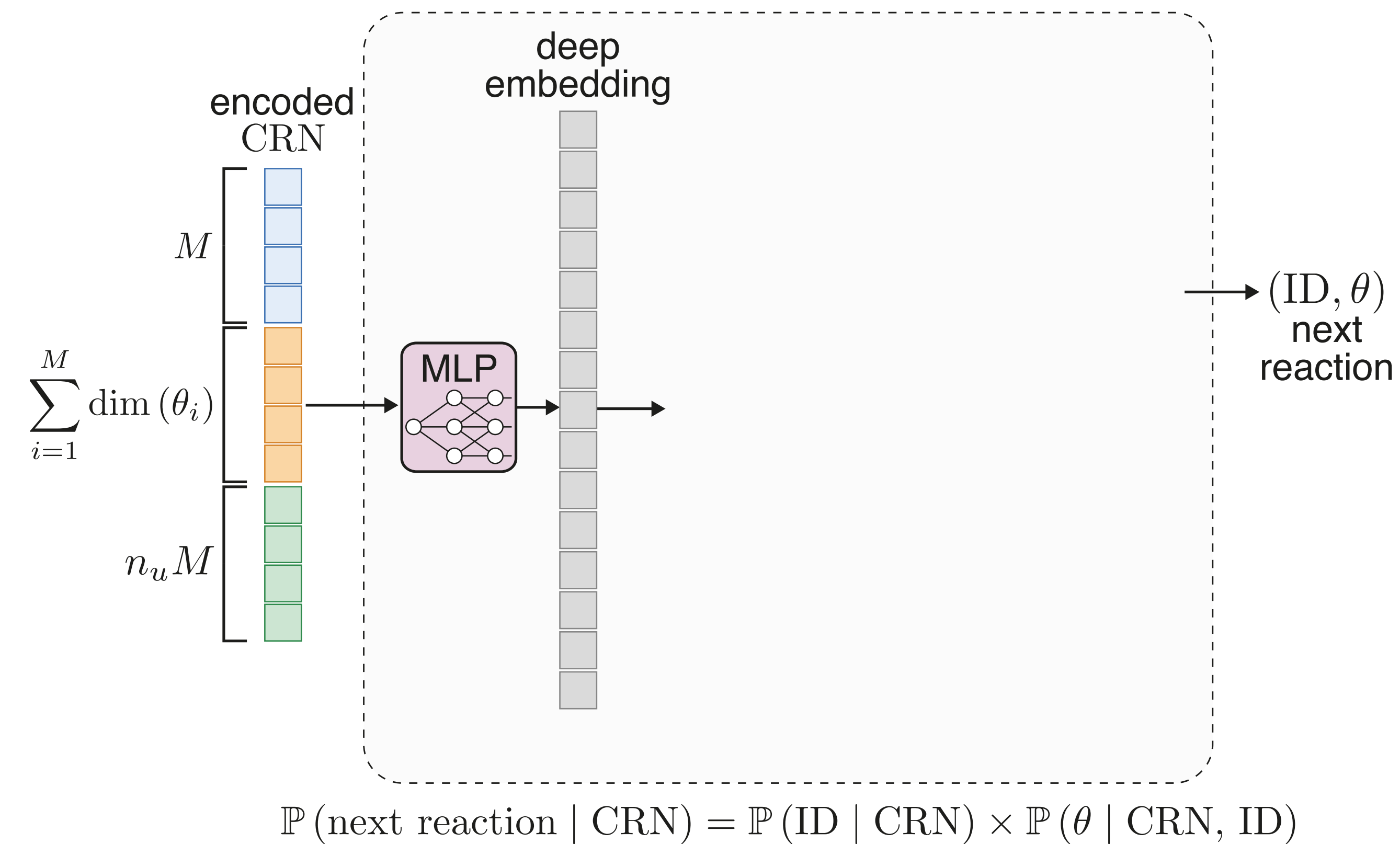
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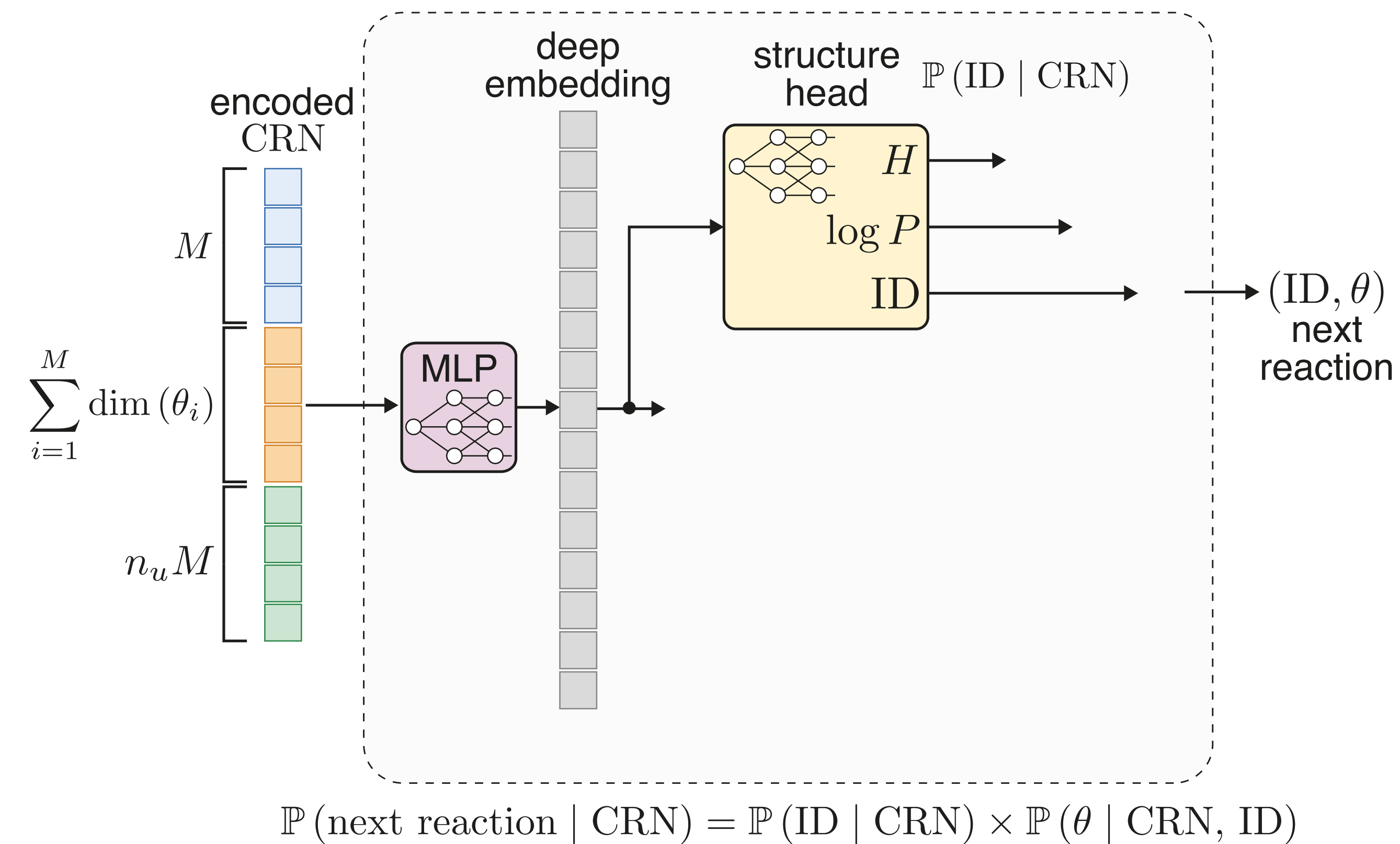
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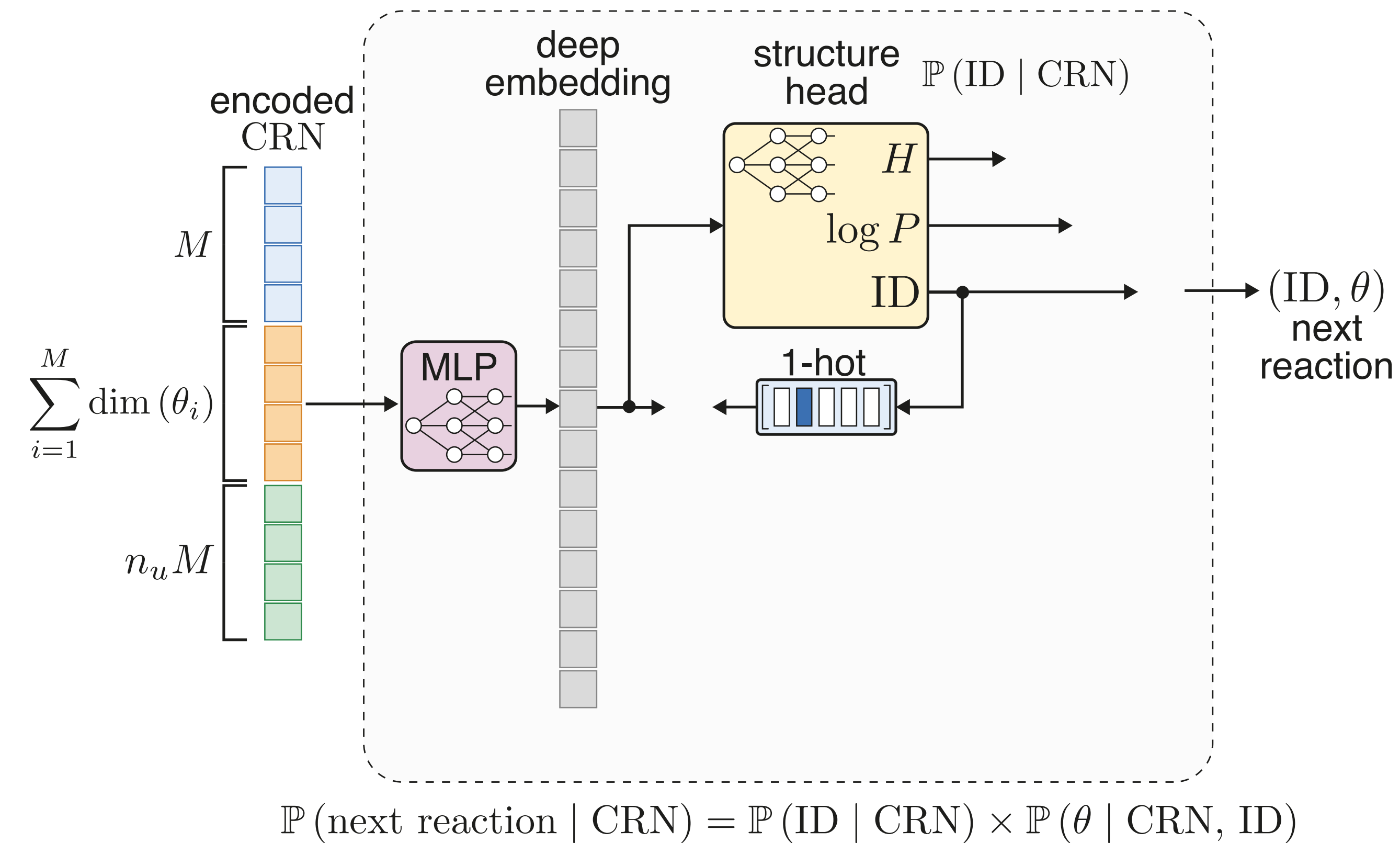
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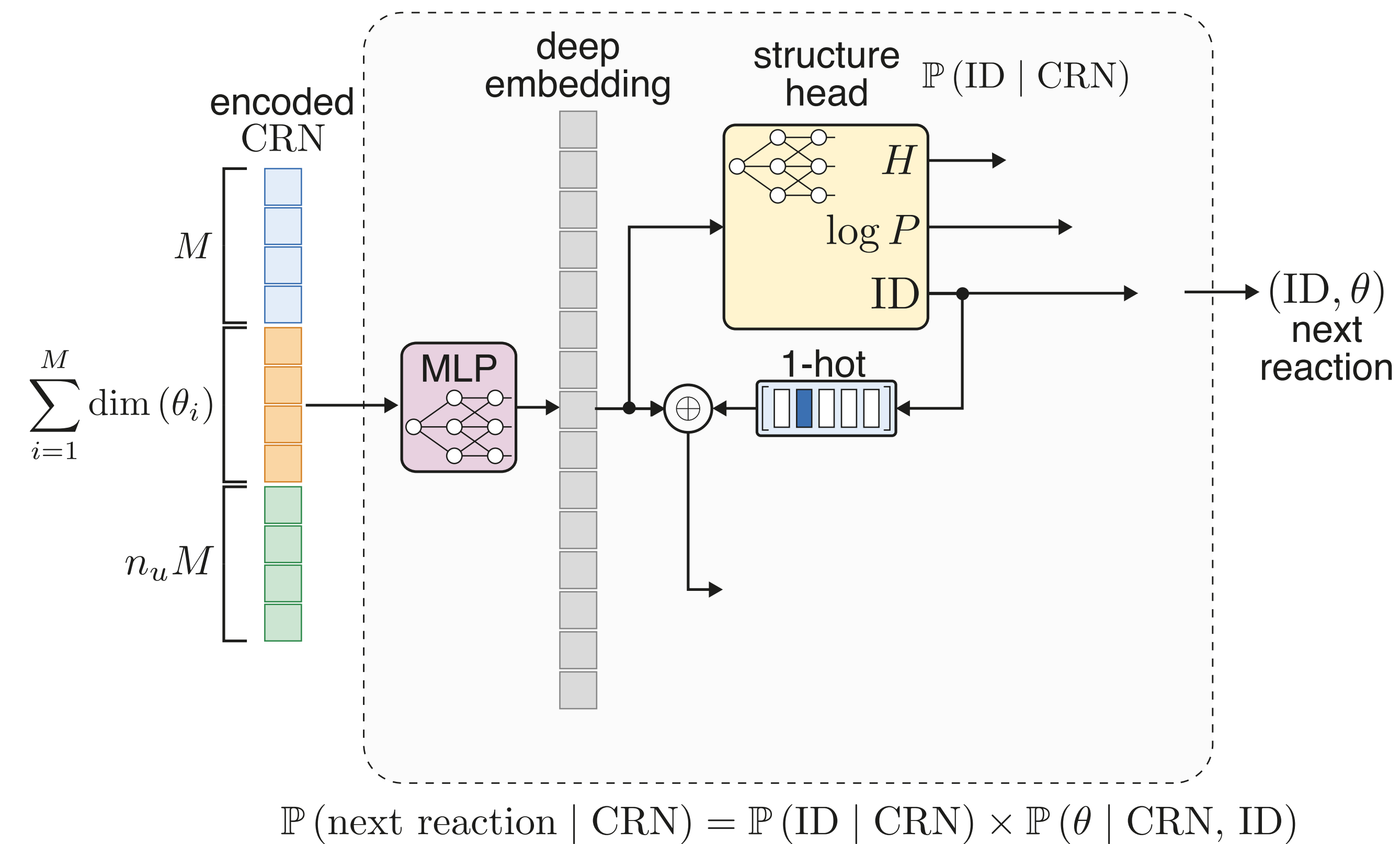
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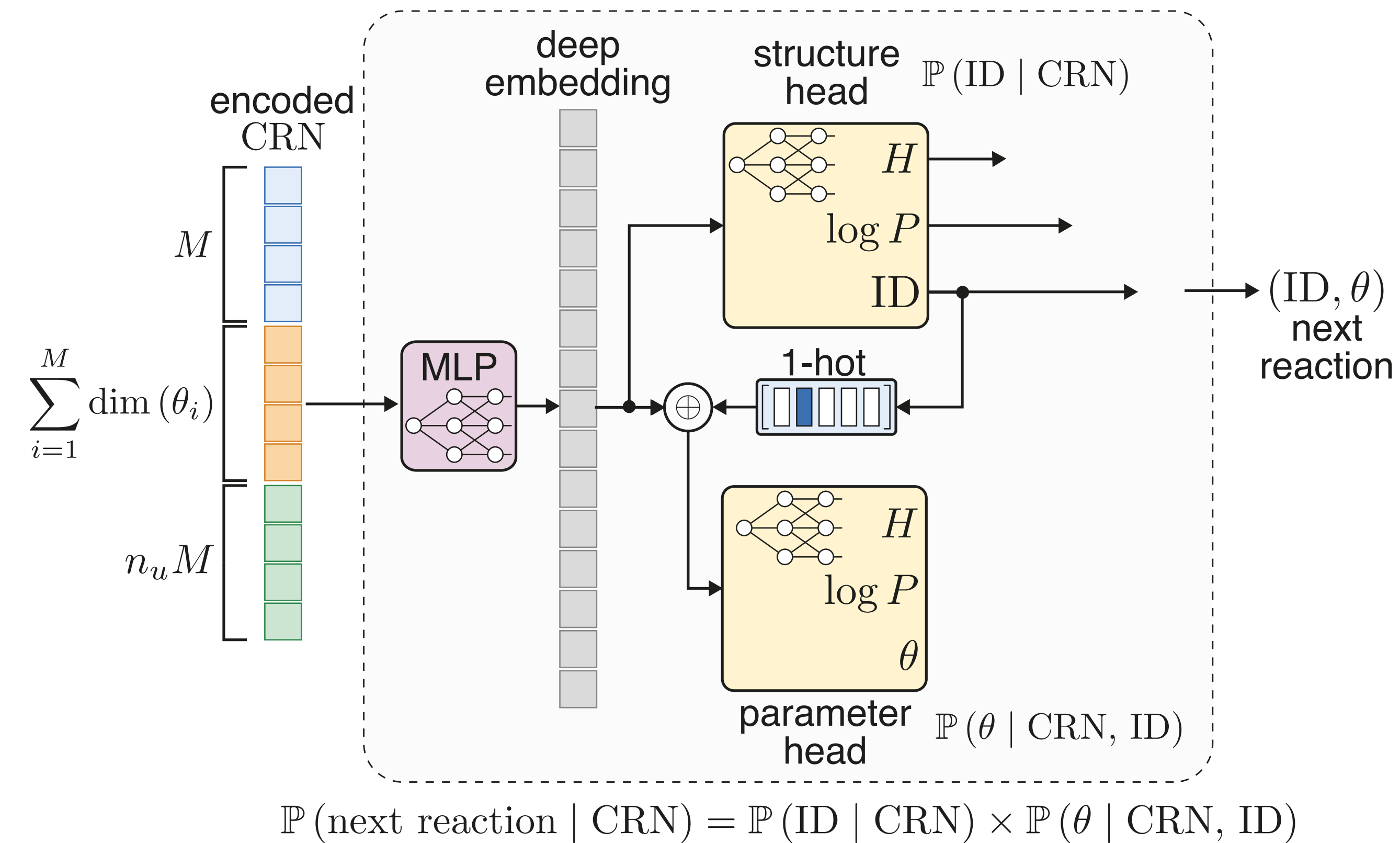
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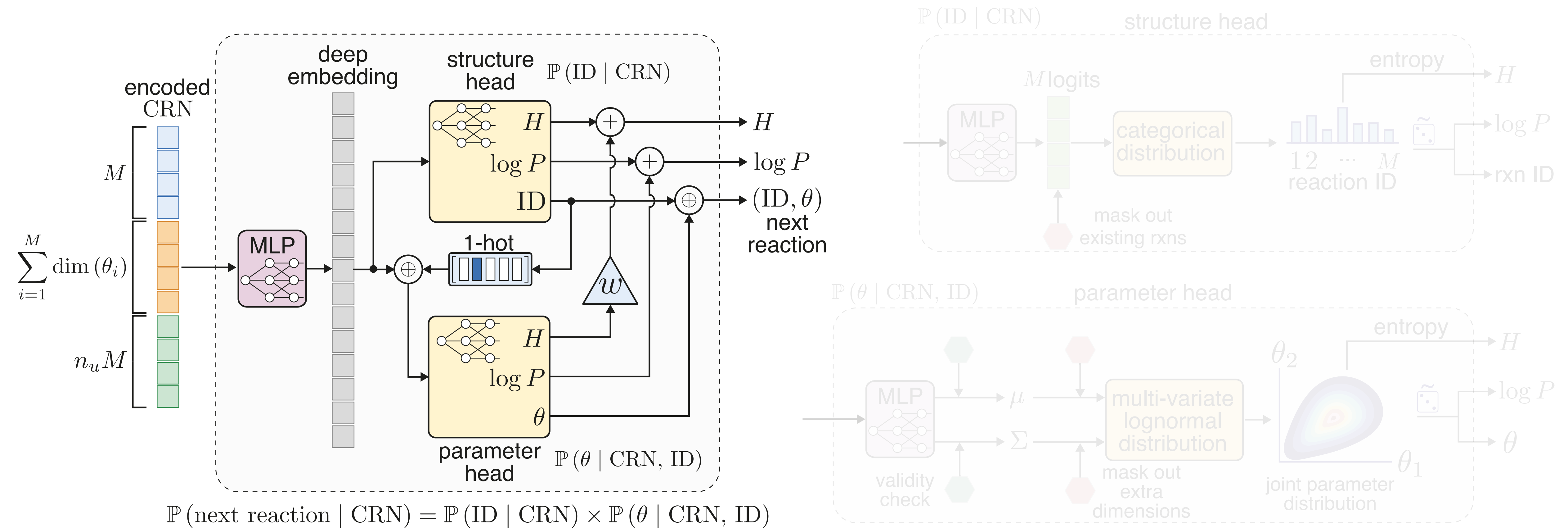
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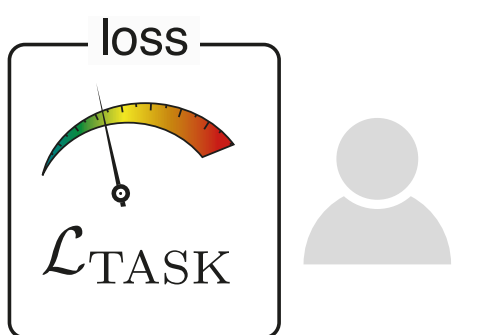
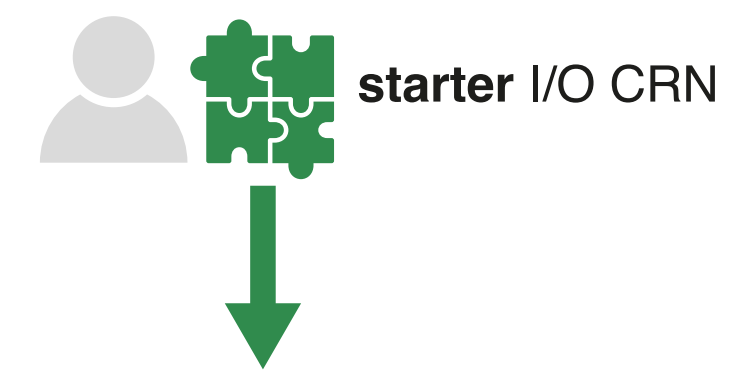
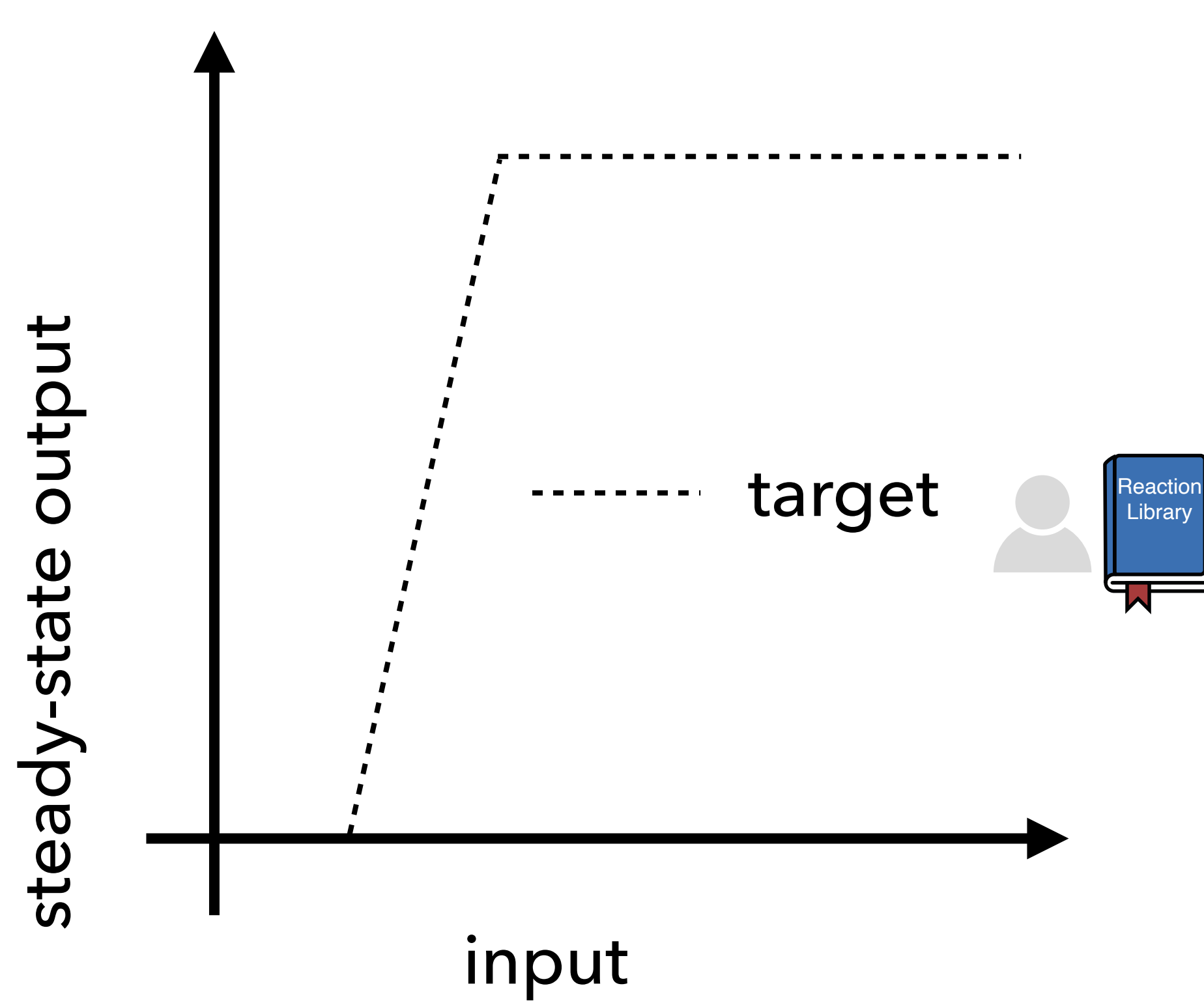
GenAI-Net: the agent architecture



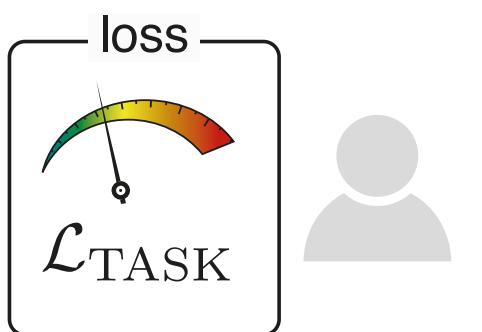
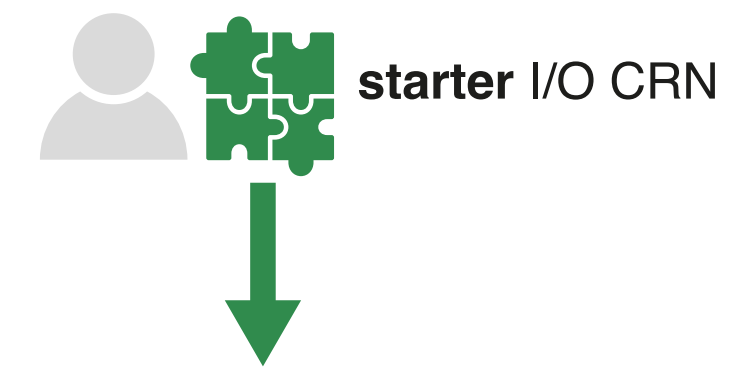
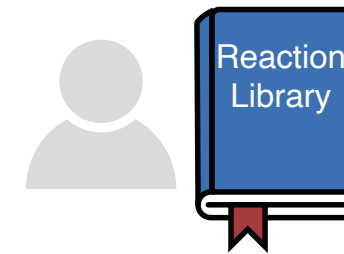
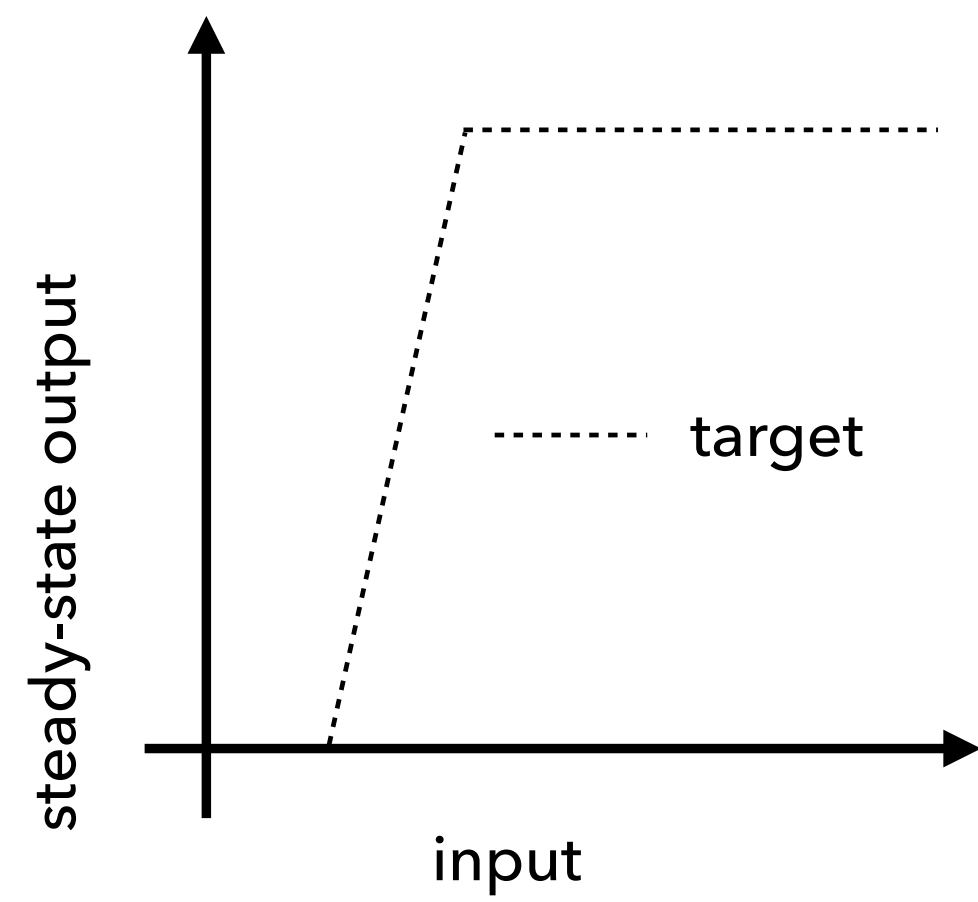
GenAI-Net: the agent architecture



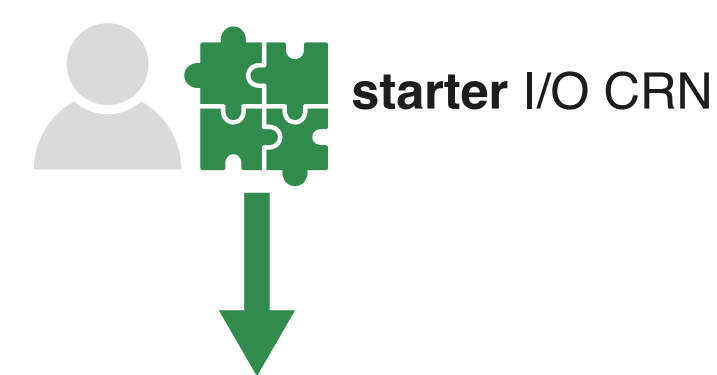
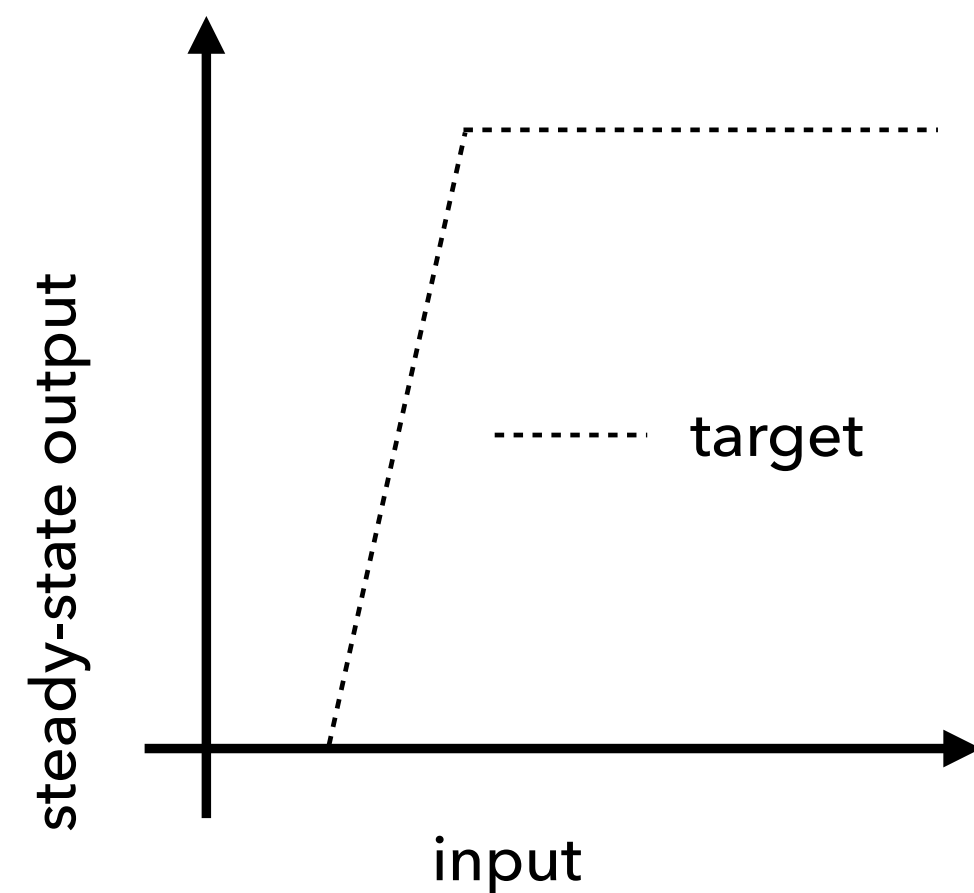
Dose response shaping - ultra sensitivity



Dose response shaping - ultra sensitivity



Dose response shaping - ultra sensitivity



Mass-Action Kinetics: Second Order

Species : $X_1, X_2, \dots, X_n$
Library size : $\frac{(n-1)n(n+1)(n+2)}{4}$
#parameters/rxn : 1

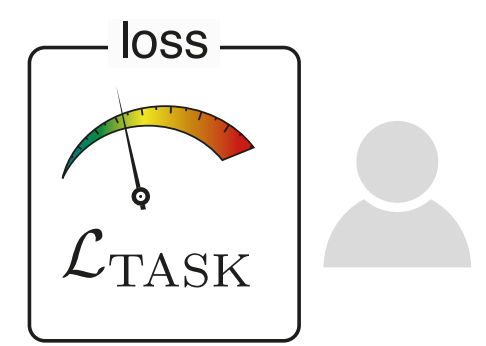
$\mathcal{R}_0 : X_1 + X_1 \longrightarrow X_1 + X_2 \quad [rx_1^2]$
 $\mathcal{R}_1 : X_1 + X_1 \longrightarrow X_1 + X_3 \quad [rx_1^2]$
 $\vdots$
 $\mathcal{R}_{n-2} : X_1 + X_1 \longrightarrow X_1 + X_n \quad [rx_1^2]$
 $\mathcal{R}_{n-1} : X_1 + X_2 \longrightarrow X_1 + X_1 \quad [rx_1x_2]$
 $\vdots$
 $\mathcal{R}_{...} : X_n + X_n \longrightarrow X_n + X_{n-1} \quad [rx_n^2]$

Mass-Action Kinetics: up to Order o

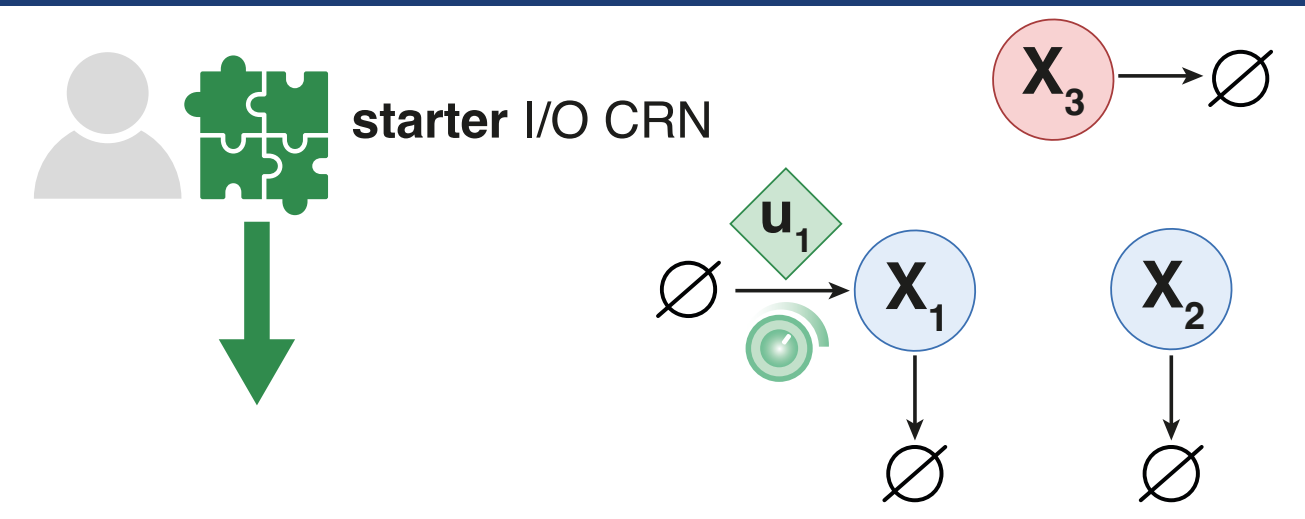
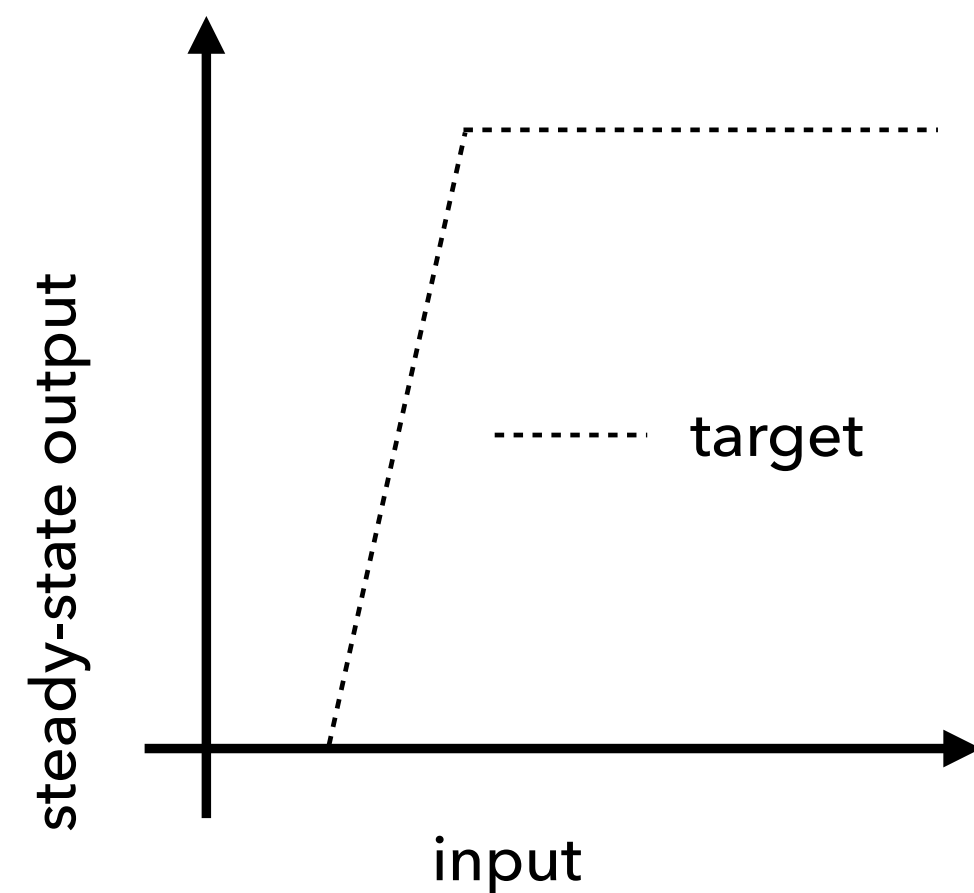
Species : $X_1, X_2, \dots, X_n$
Library size : $C_o^{n+o} (C_o^{n+o} - 1) + 1, o > 1$
#parameters/rxn : 1

$\mathcal{R}_0 : \emptyset \longrightarrow \emptyset \quad [r]$
 $\mathcal{R}_1 : \emptyset \longrightarrow X_1 \quad [r]$
 $\vdots$
 $\mathcal{R}_{...} : X_1 \longrightarrow X_2 \quad [rx_1]$
 $\vdots$
 $\mathcal{R}_{...} : X_1 + X_n \longrightarrow X_2 + X_3 \quad [rx_1x_n]$
 $\vdots$
 $\mathcal{R}_{...} : X_1 + X_2 + \dots + X_i \longrightarrow X_2 + X_3 + \dots + X_j \quad [rx_1x_2 \dots x_i]$

Propensity function: $r \prod_{i=1}^n x_i^{s_i}$



Dose response shaping - ultra sensitivity



Mass-Action Kinetics: Second Order

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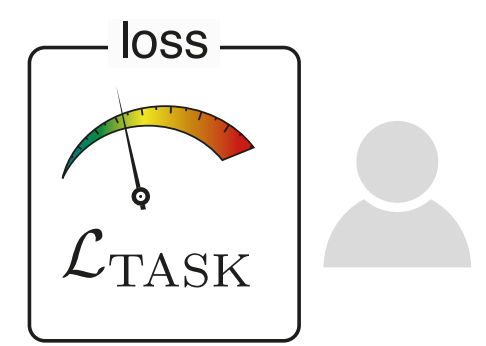
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 $\mathcal{R}_{n-1} : X_1 + X_2 \longrightarrow X_1 + X_1 \quad [rx_1x_2]$
 $\vdots$
 $\mathcal{R}_{\dots} : X_n + X_n \longrightarrow X_n + X_{n-1} \quad [rx_n^2]$

Mass-Action Kinetics: up to Order o

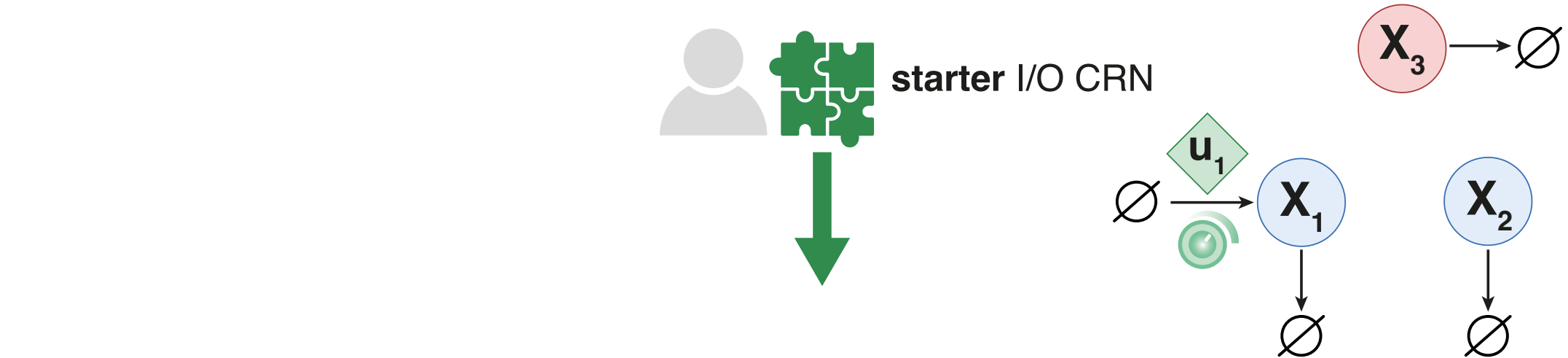
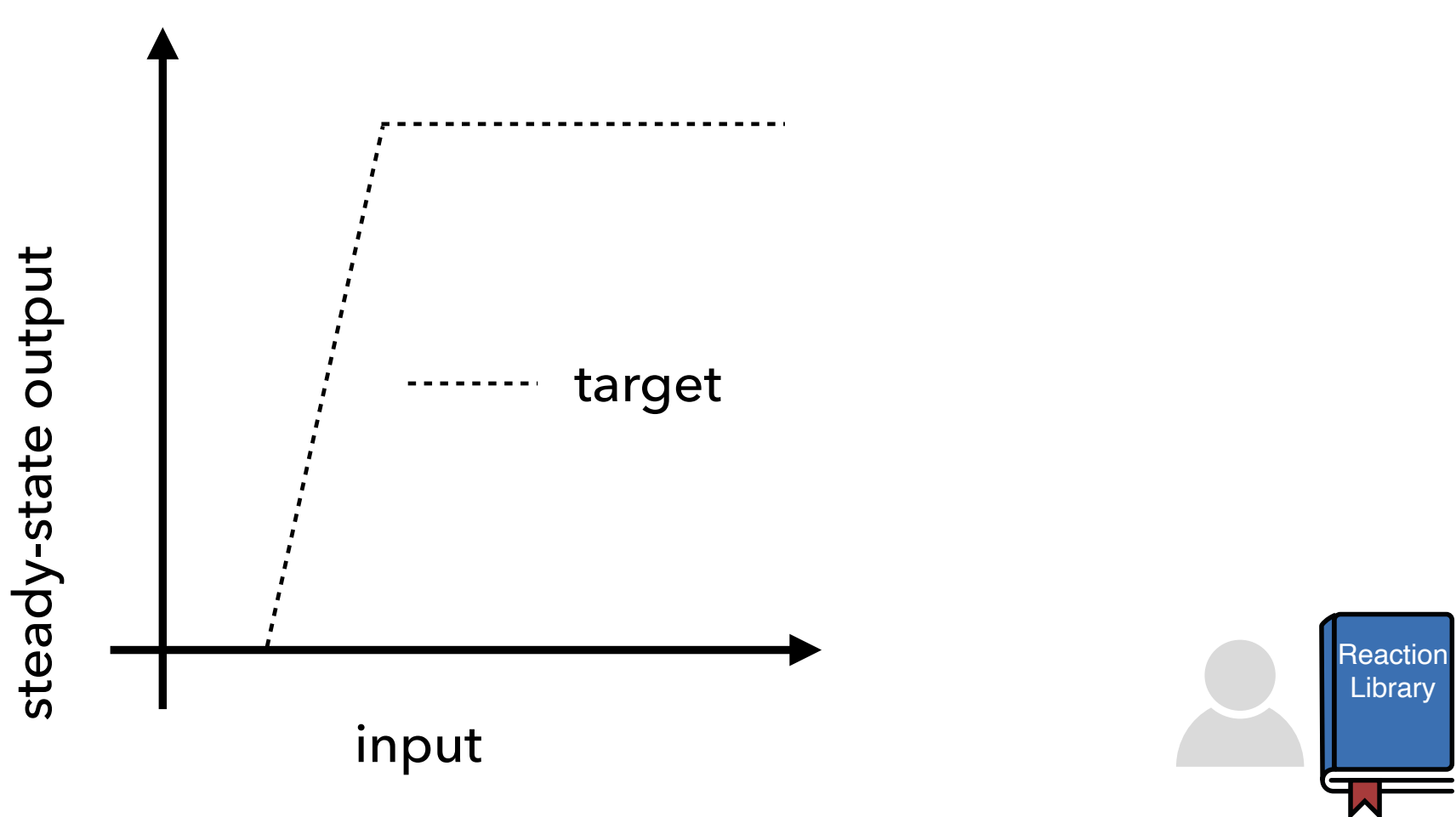
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Propensity function: $r \prod_{i=1}^n x_i^{s_i}$

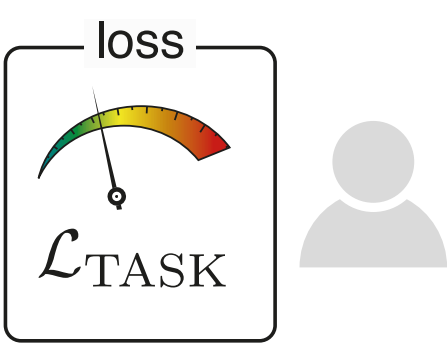
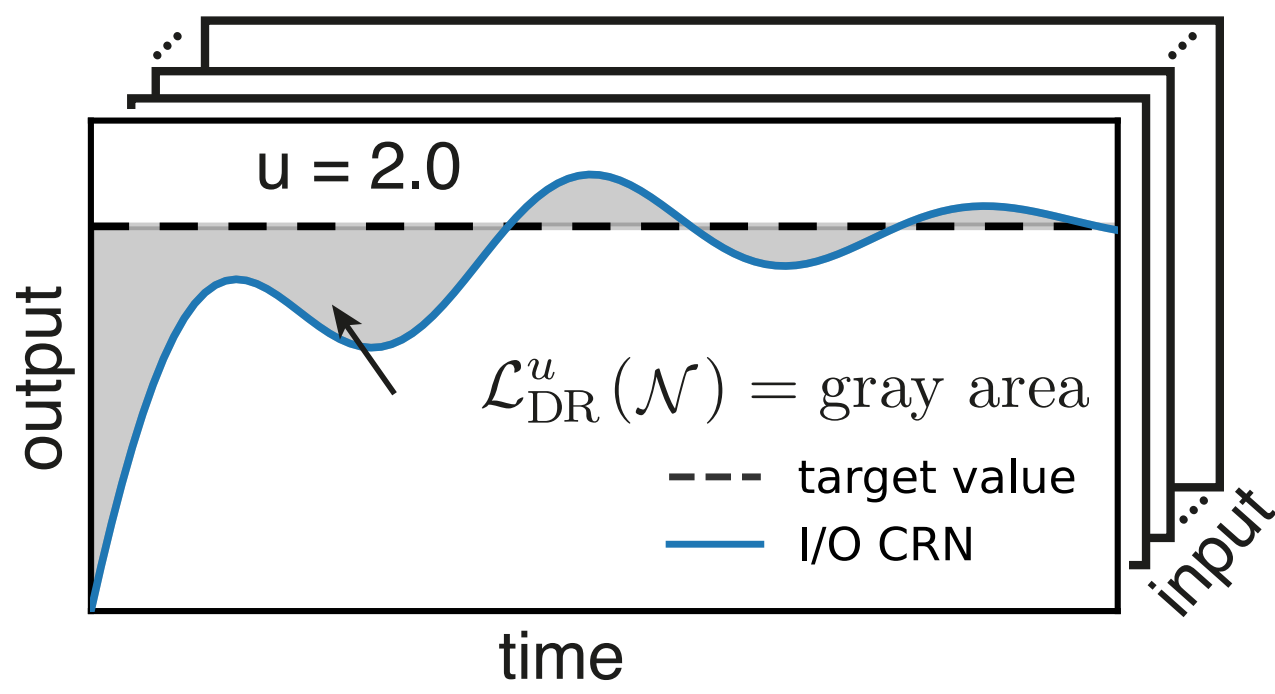


Dose response shaping - ultra sensitivity



$$\forall u \in \mathcal{U} \quad \mathcal{L}_{\text{DR}}^u(\mathcal{N}) \triangleq \int_0^{t_f} w_d(t) |y(t; u) - r(u)| dt$$

$$\mathcal{L}_{\text{DR}}(\mathcal{N}) \triangleq \frac{1}{|\mathcal{U}|} \sum_{u \in \mathcal{U}} \mathcal{L}_{\text{DR}}^u(\mathcal{N})$$



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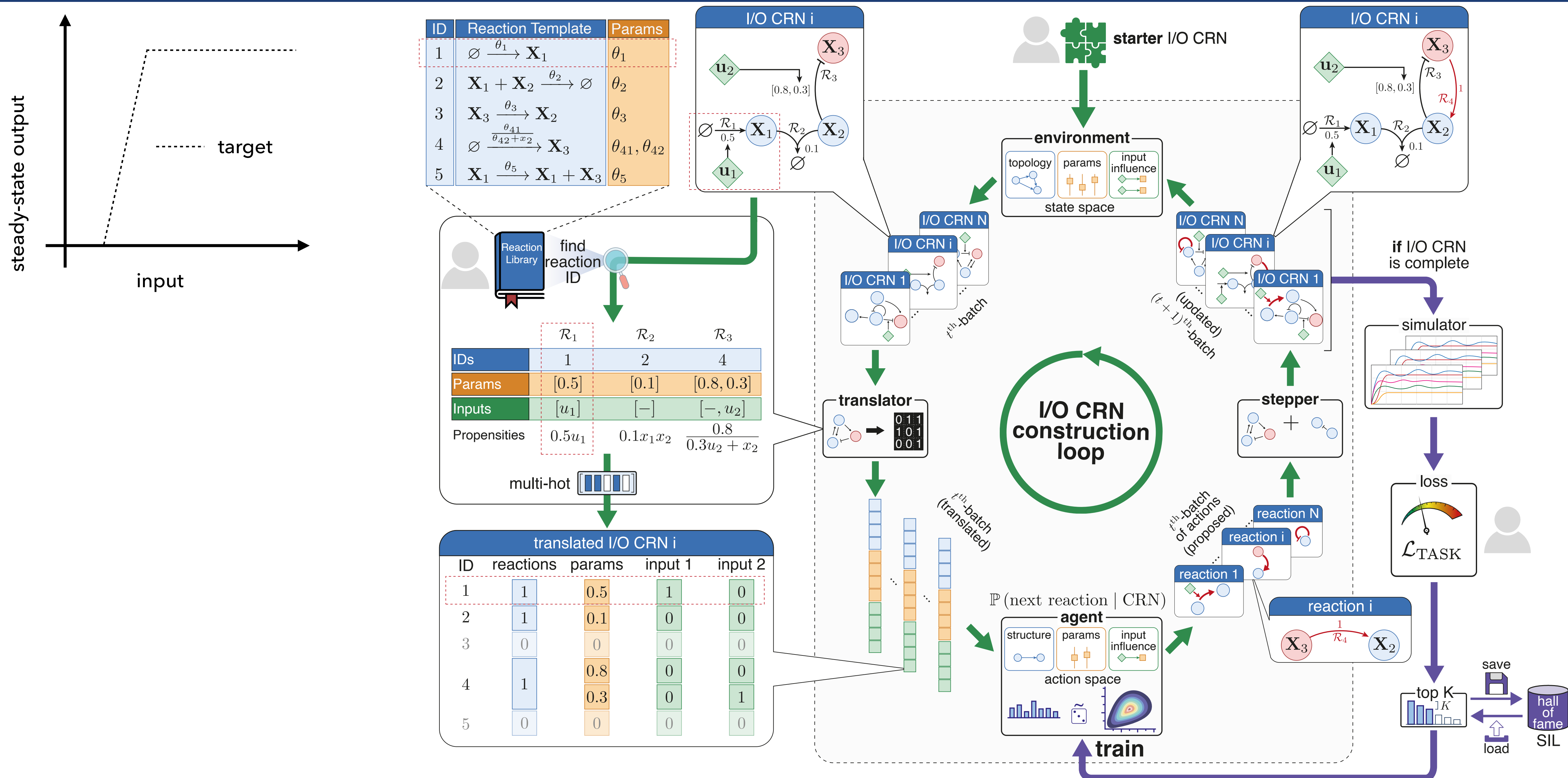
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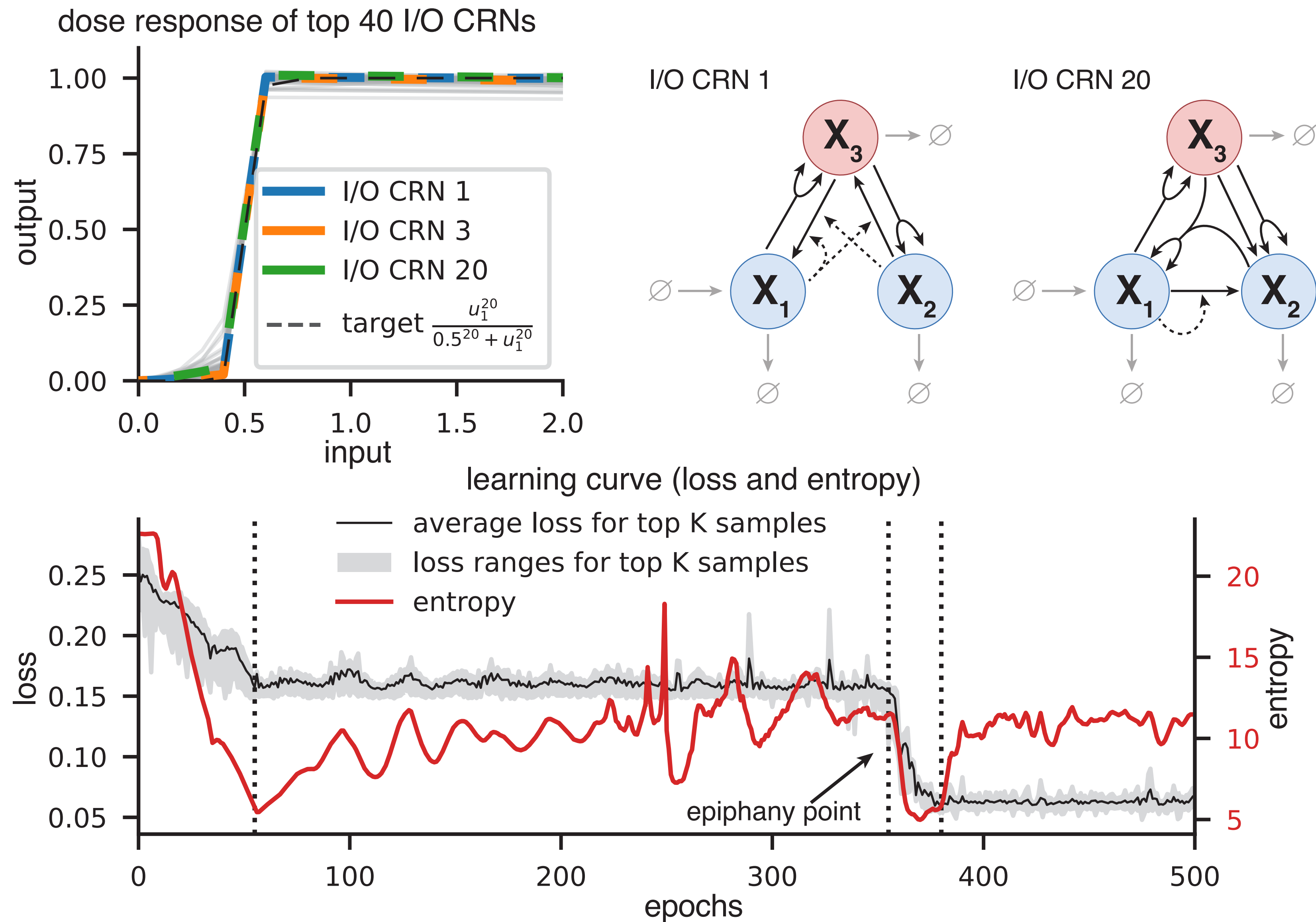
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 $\vdots$
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Dose response shaping - ultra sensitivity

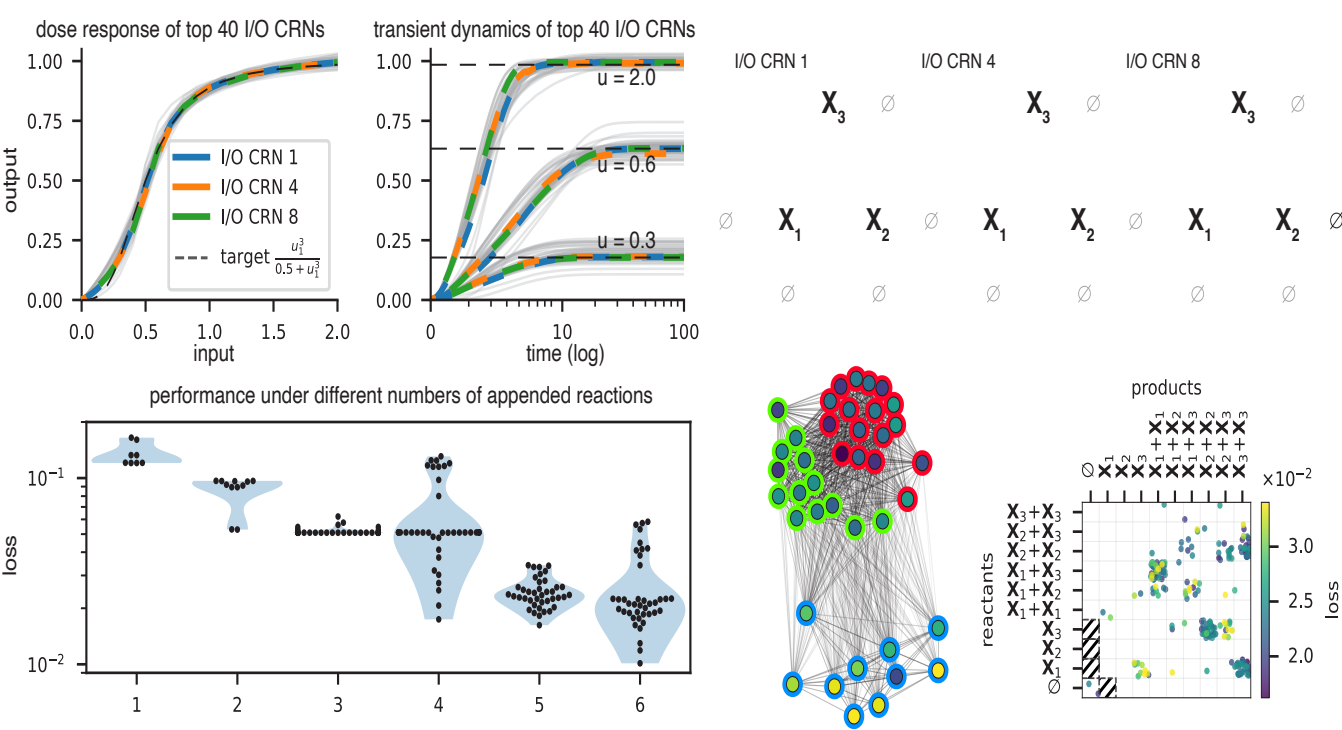


Dose response shaping - ultrasensitive response

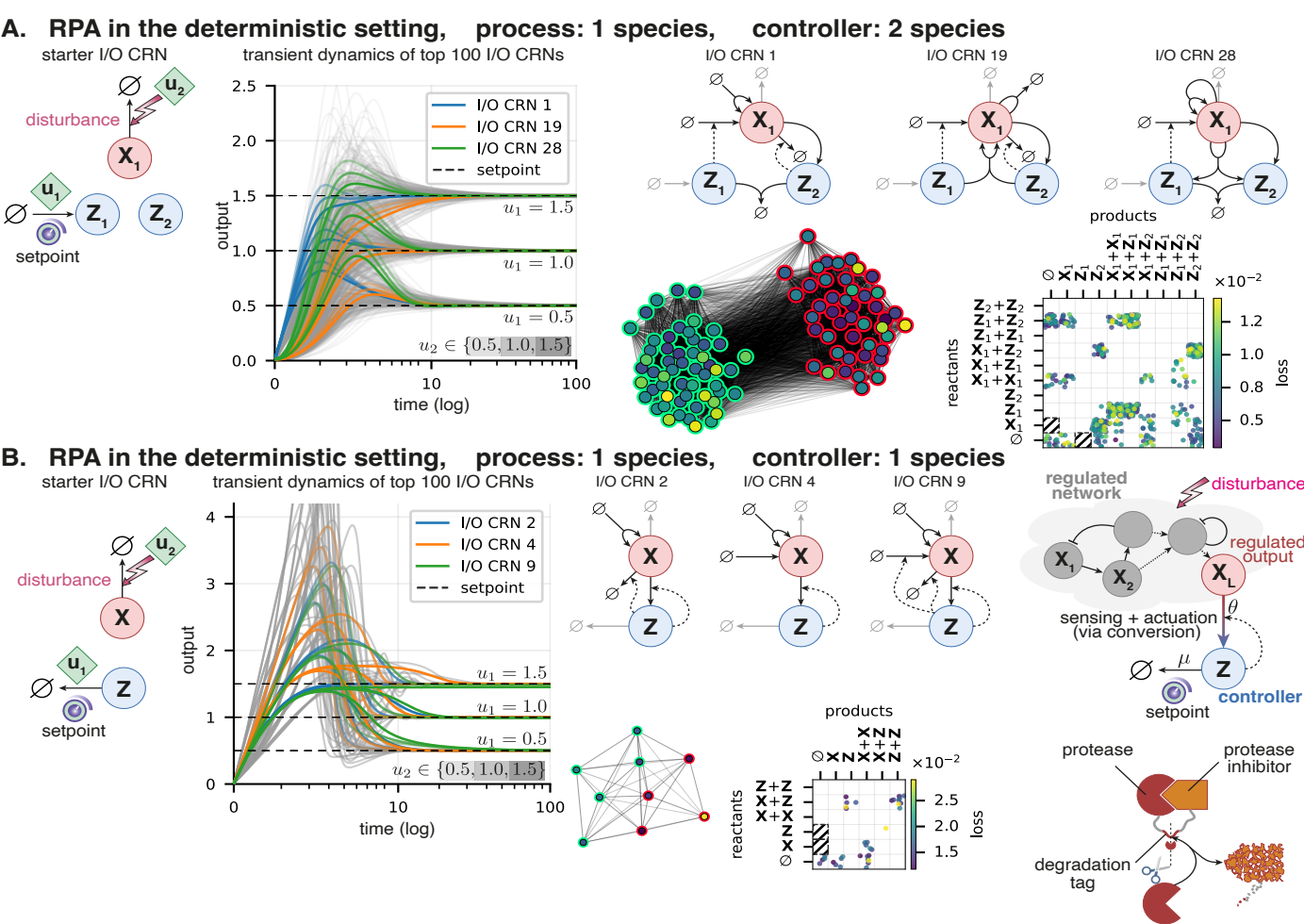


Discovered new topologies across diverse applications

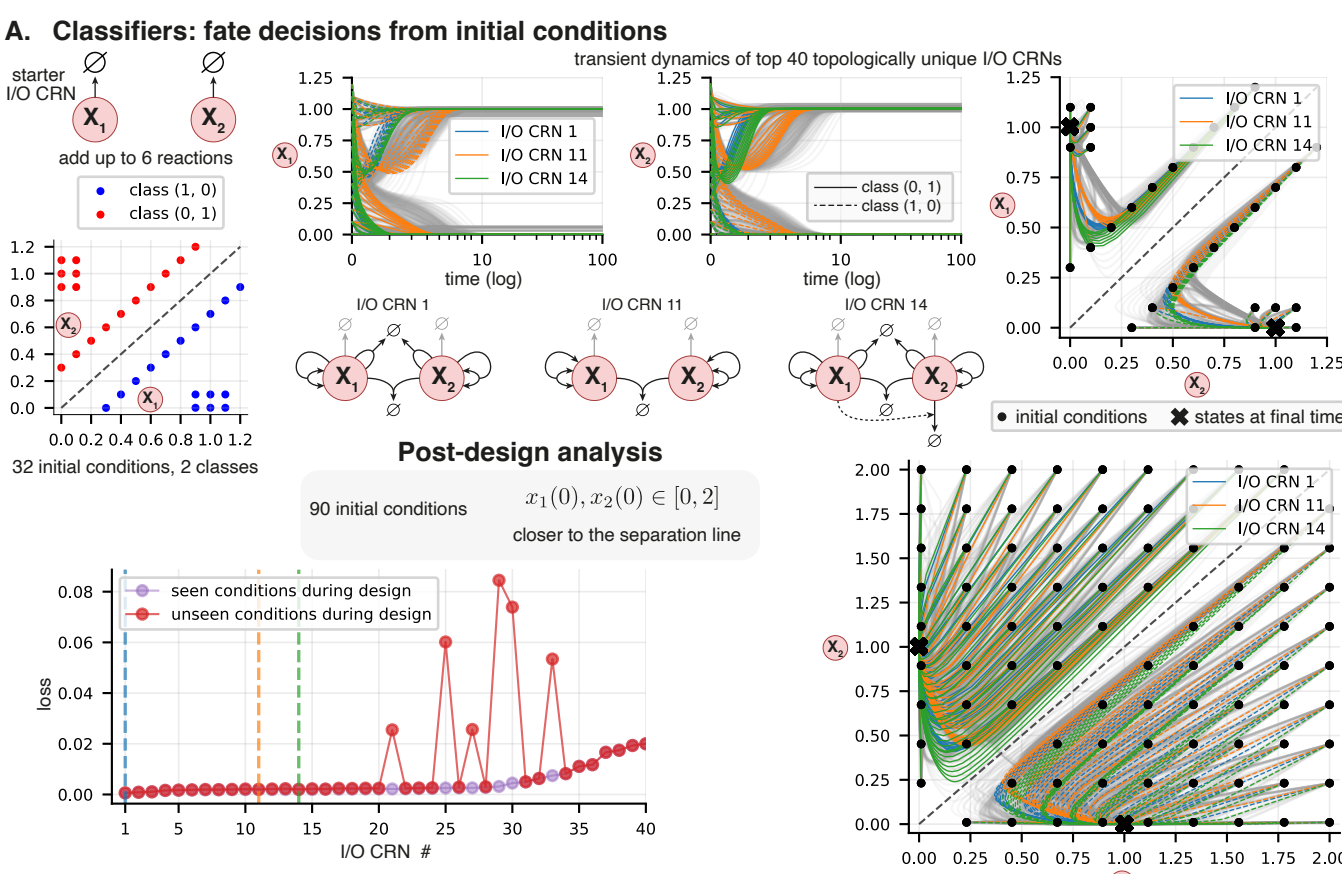
Dose Response Shaping



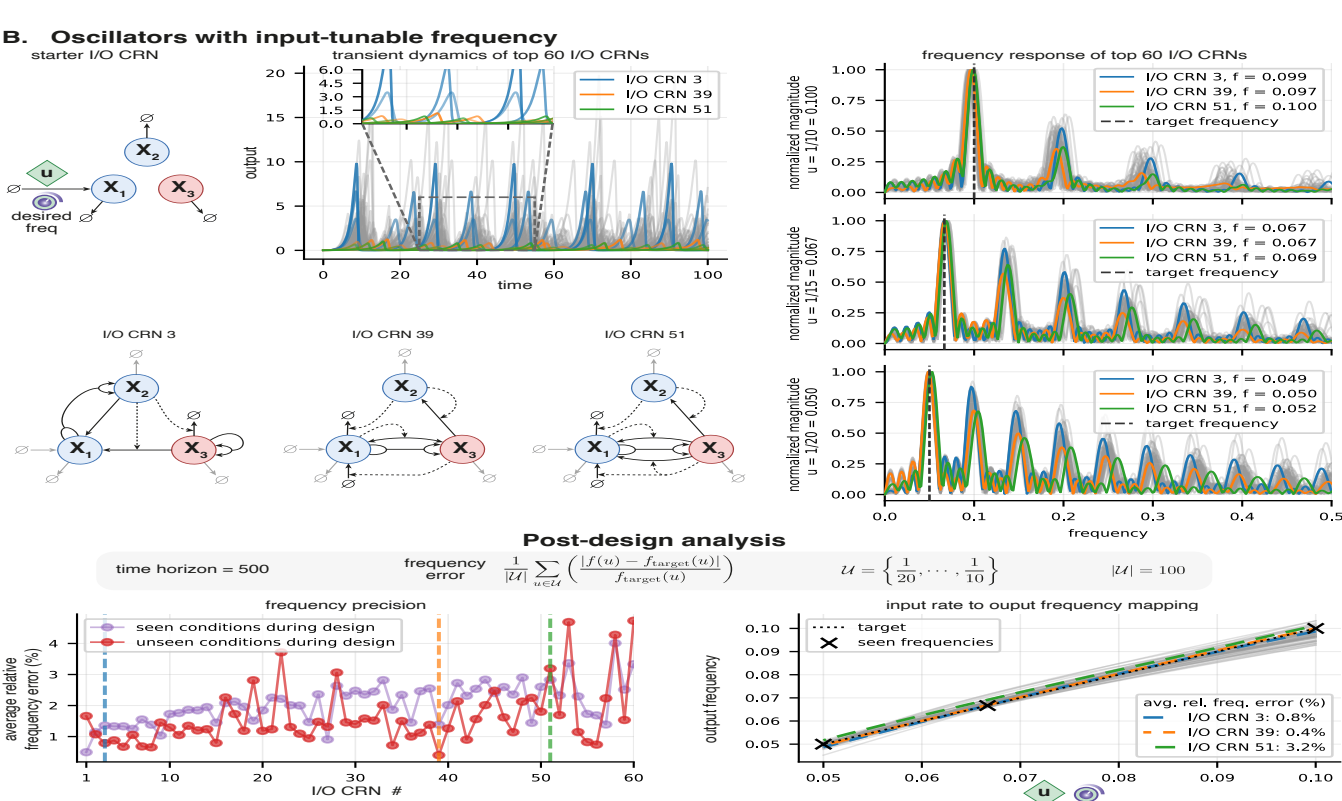
Robust Controllers



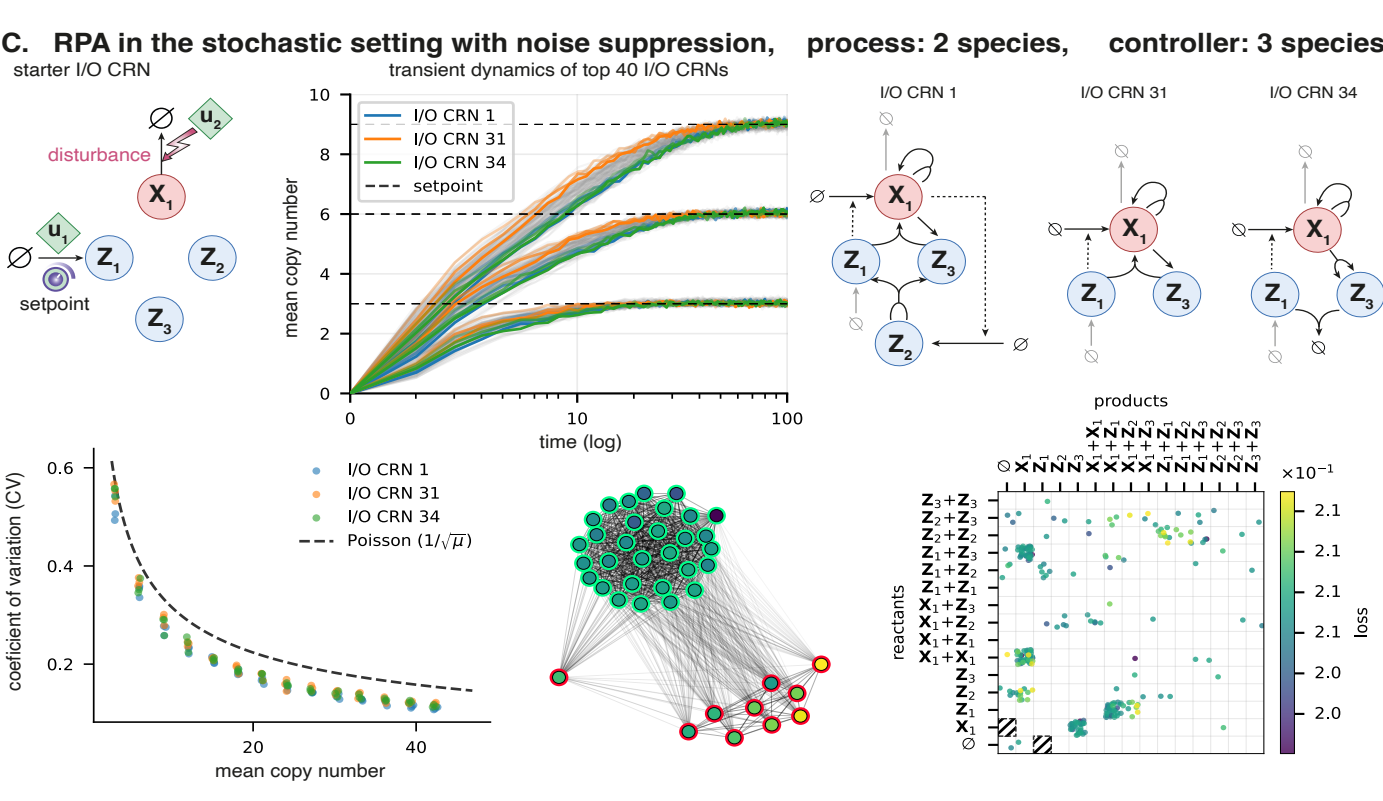
Classifiers



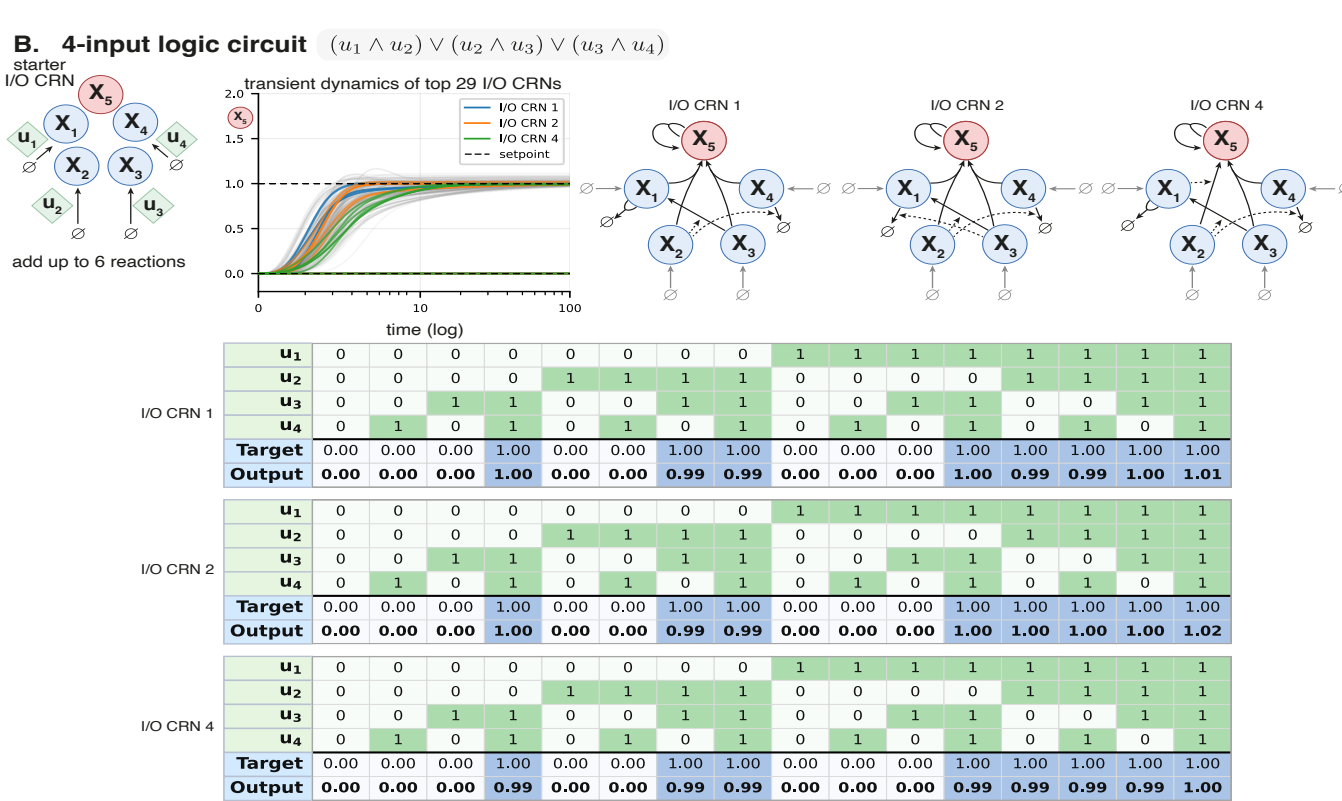
Biological Oscillators



Controllers w. Noise Attenuation

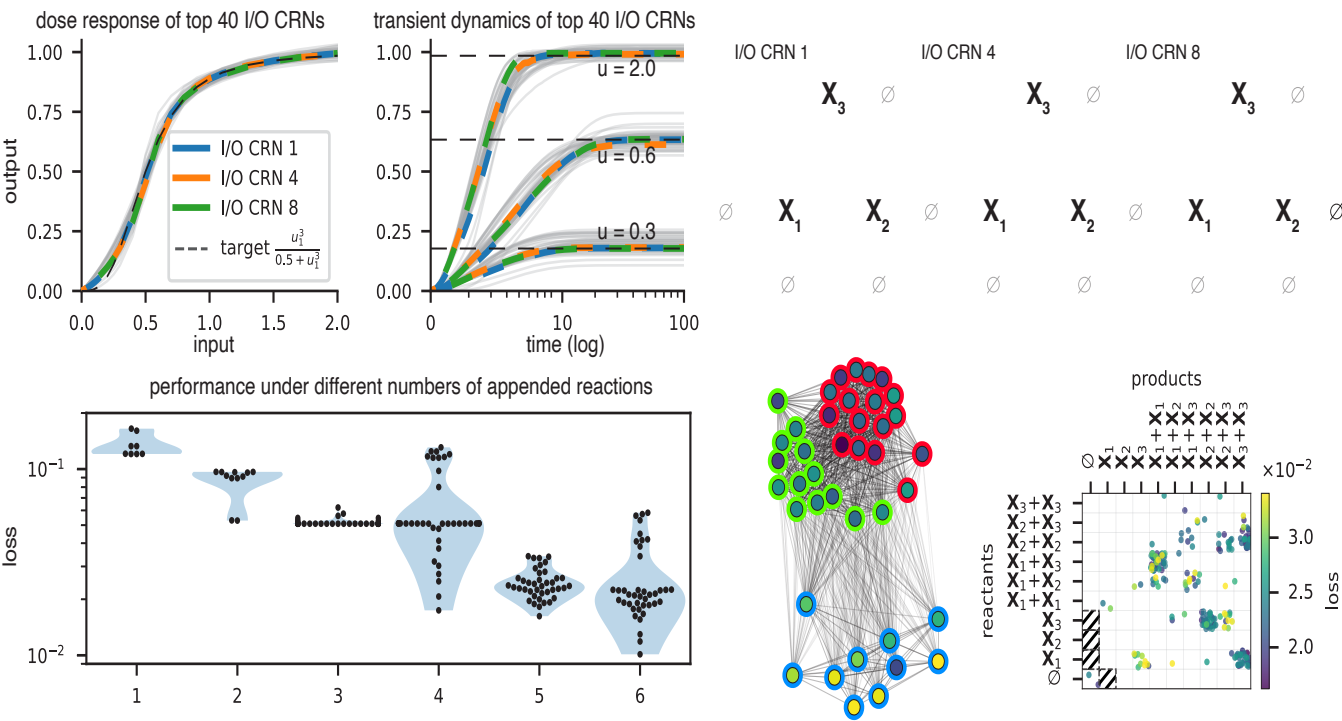


Logic Gates

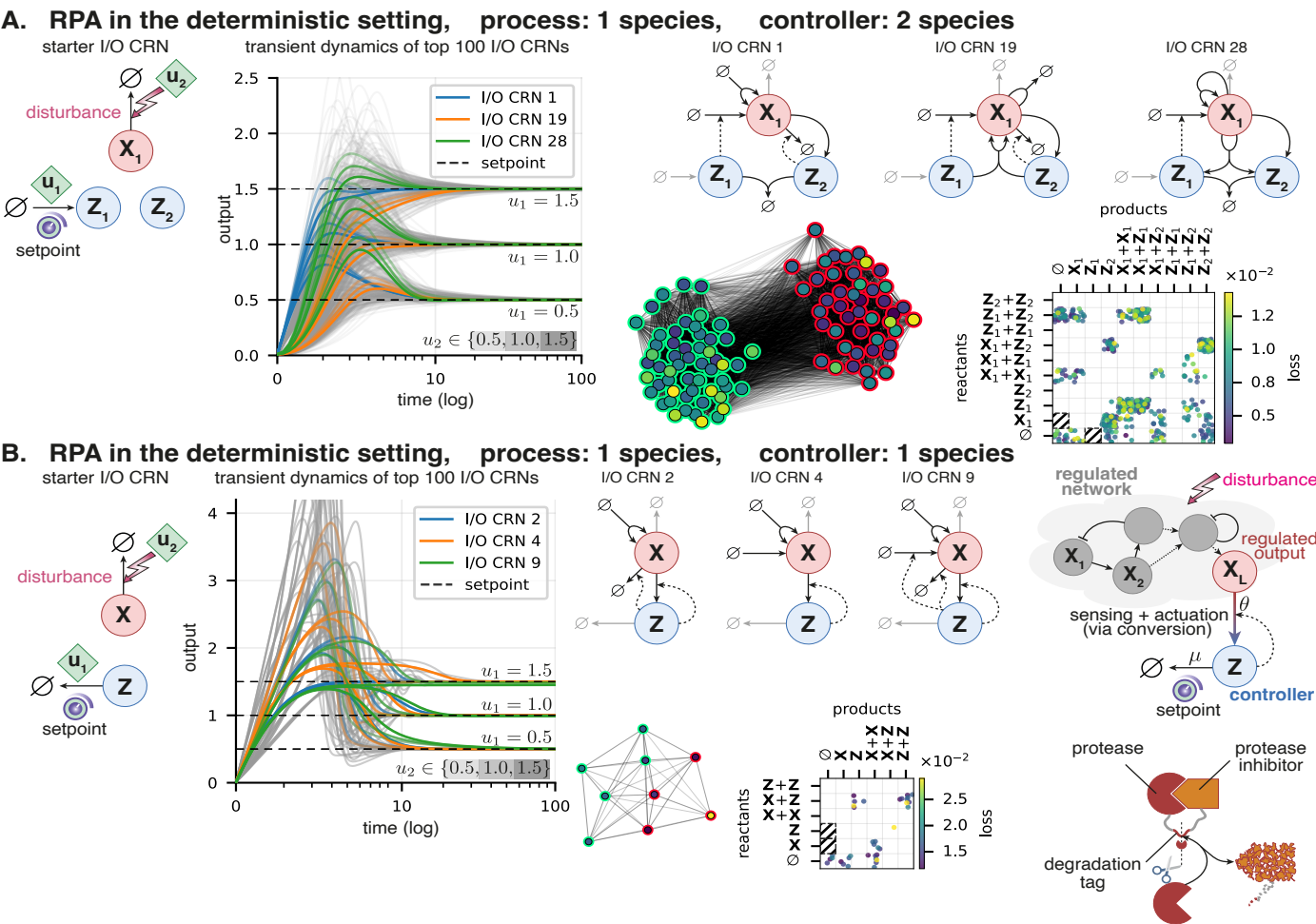


Robust molecular controllers

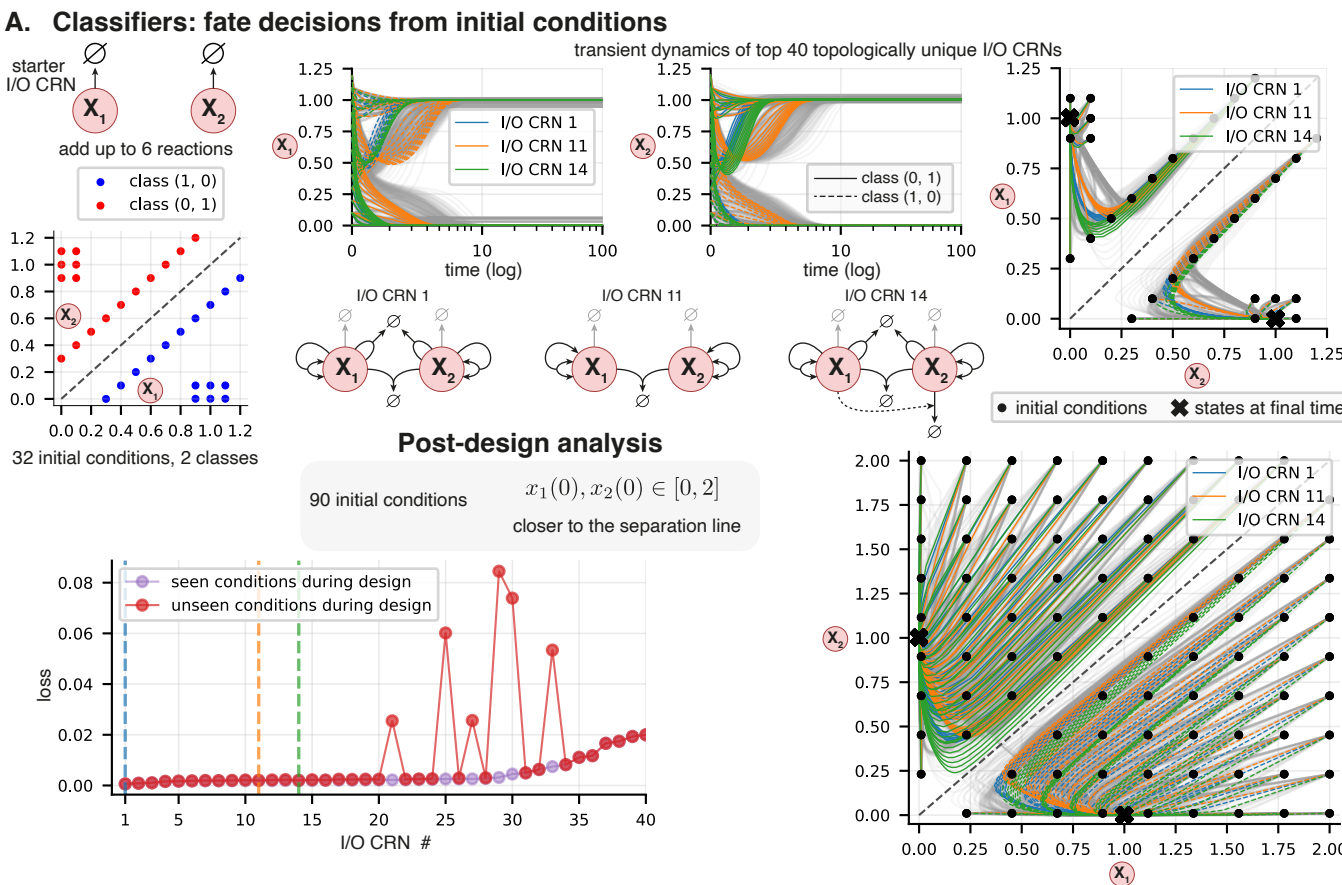
Dose Response Shaping



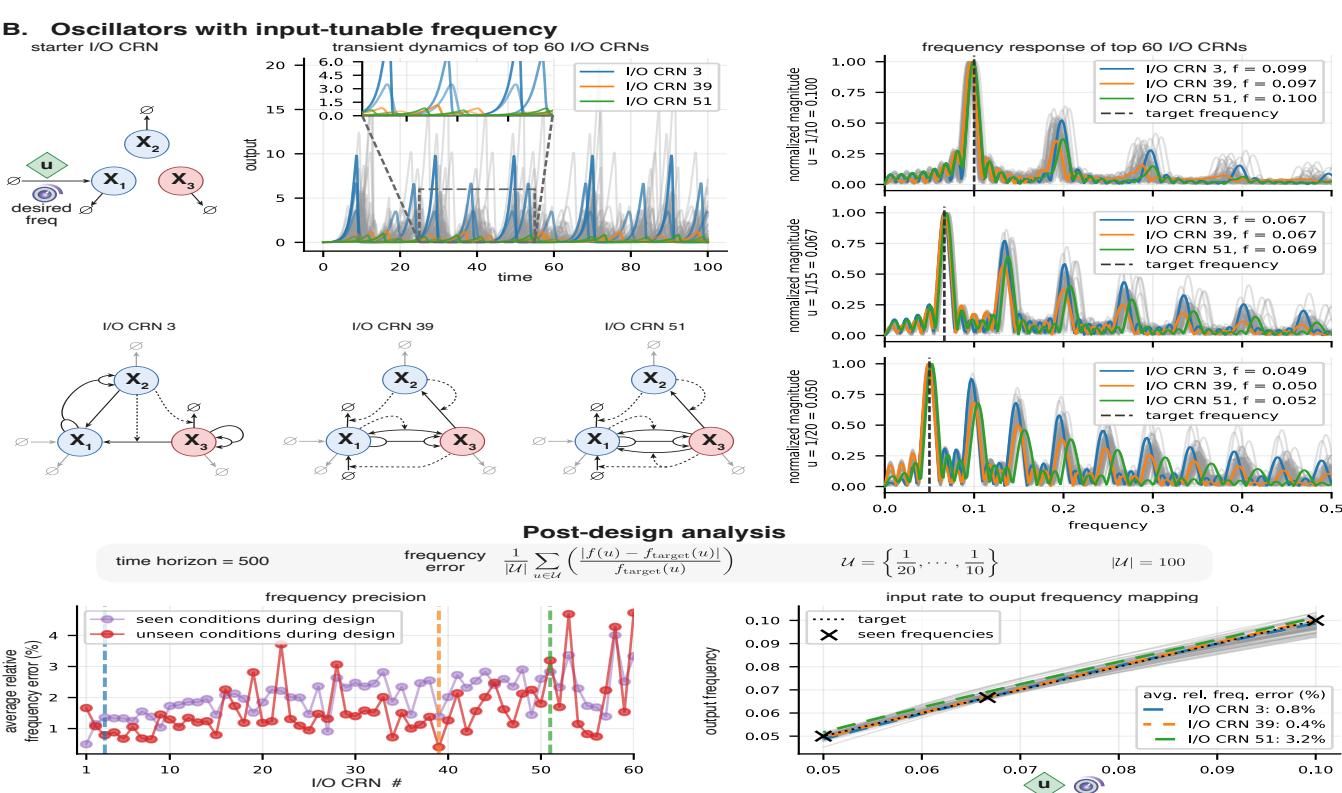
Robust Controllers



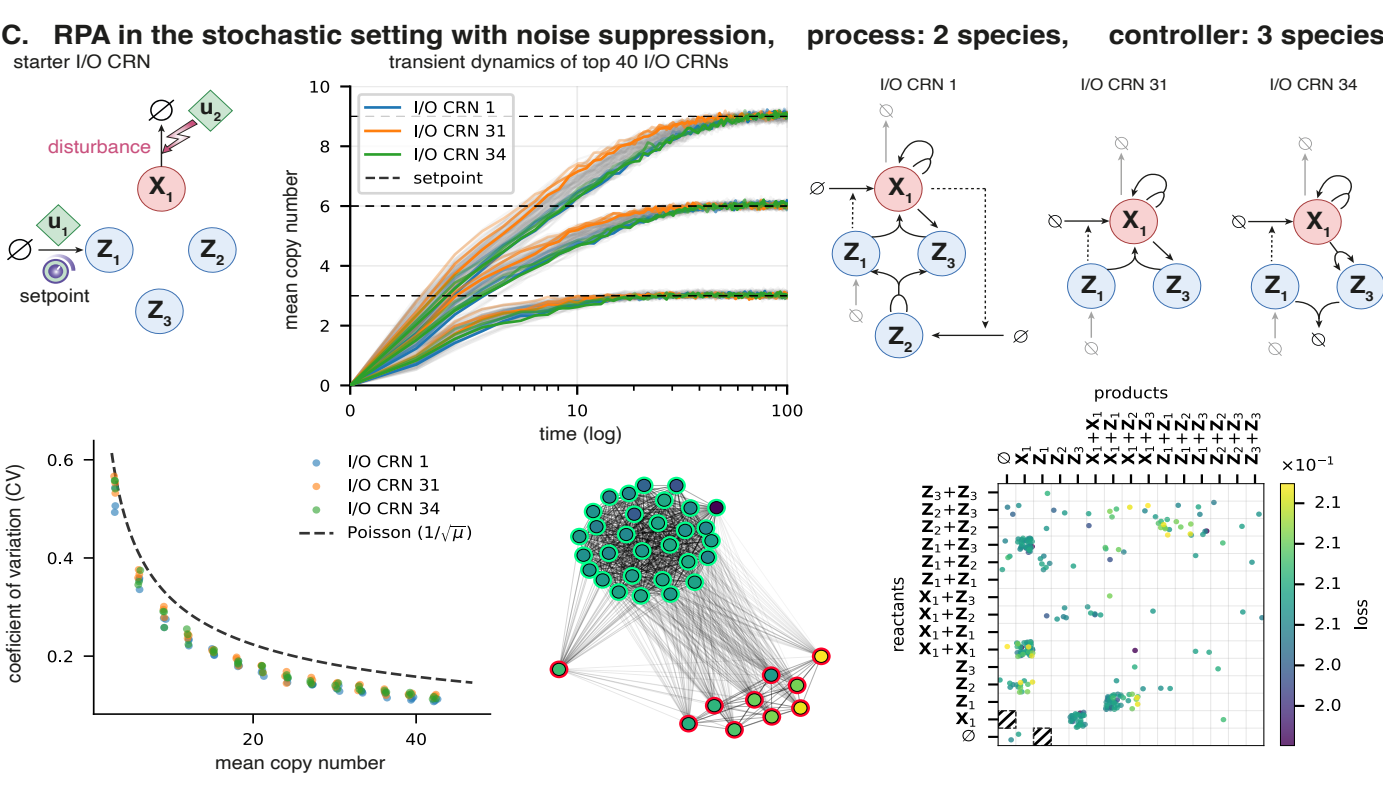
Classifiers



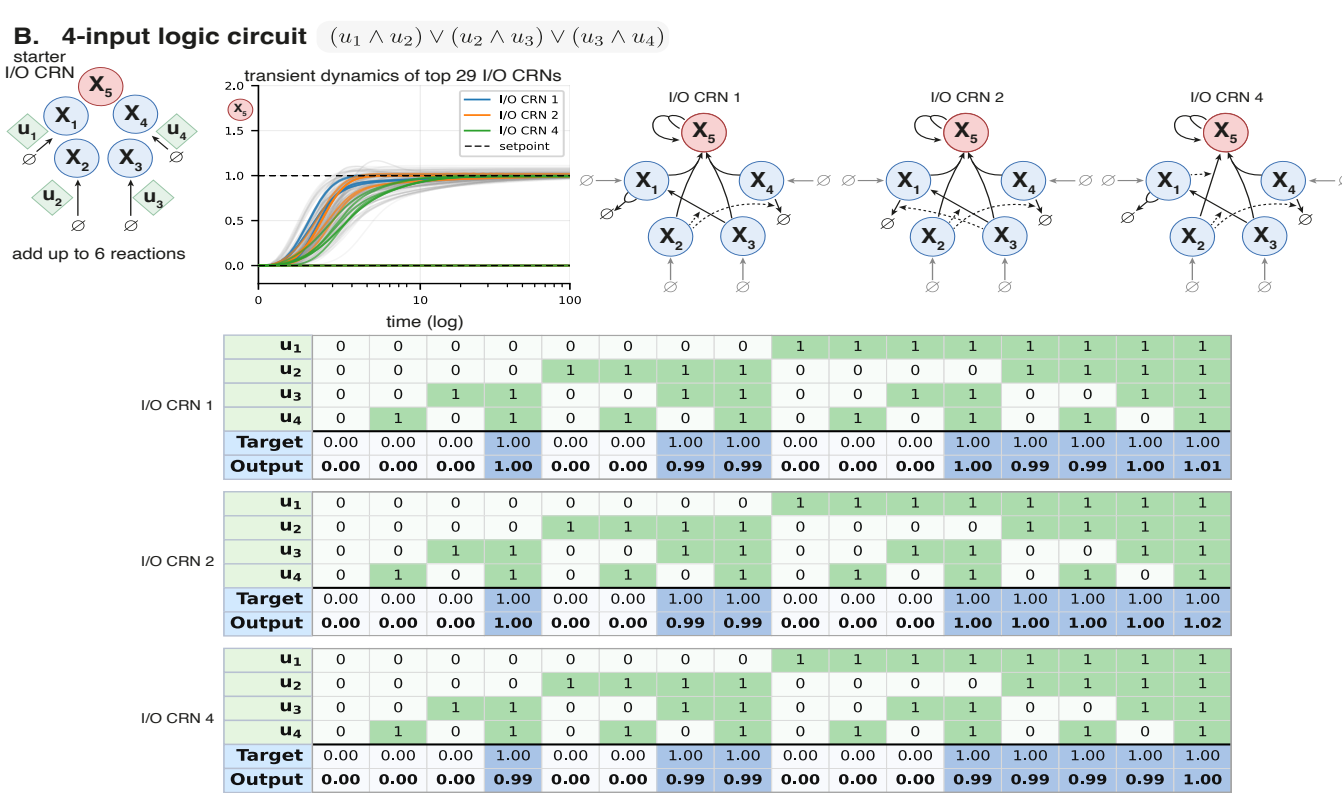
Biological Oscillators



Controllers w. Noise Attenuation

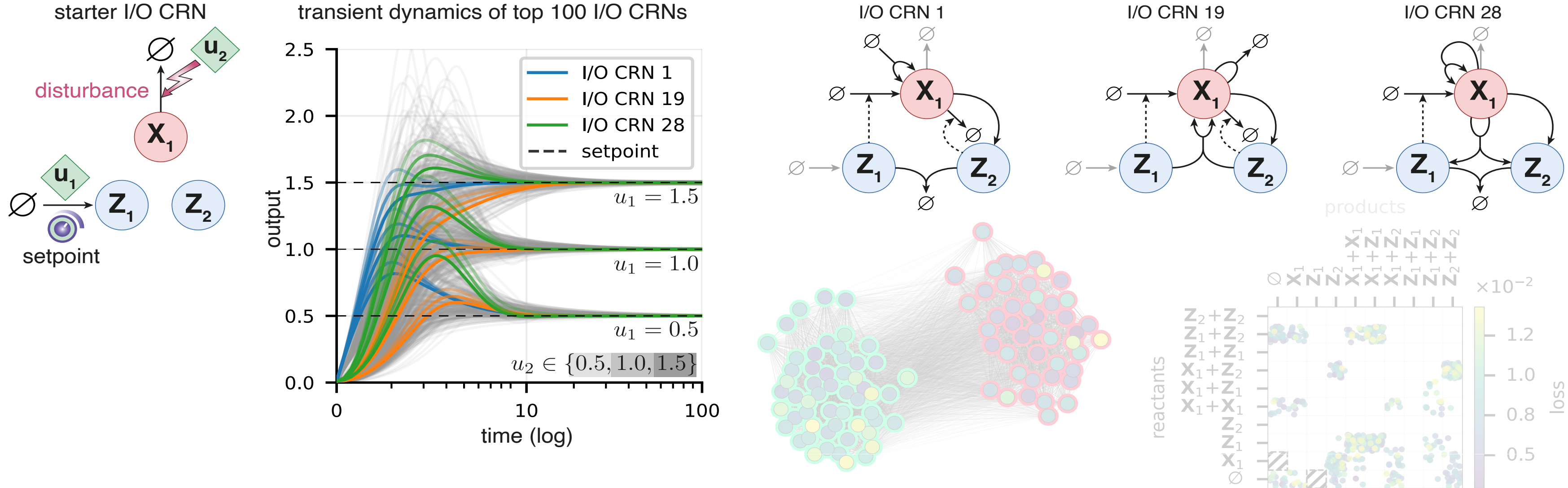


Logic Gates

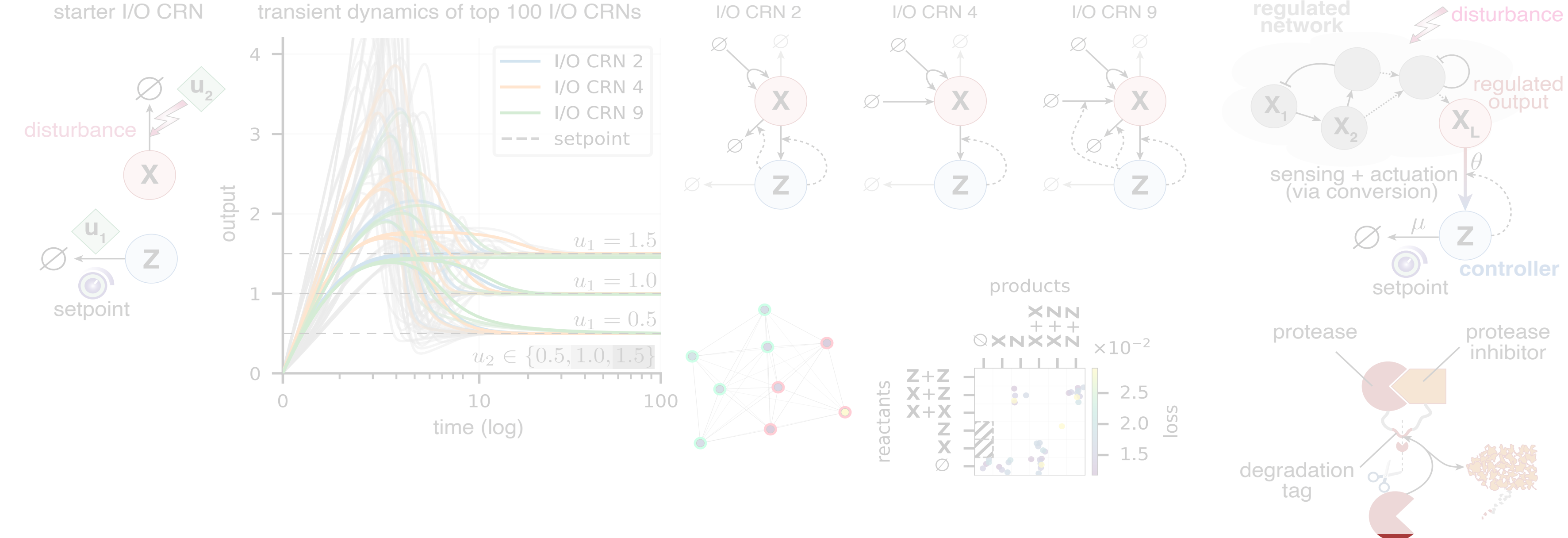


Robust molecular controllers

A. RPA in the deterministic setting, process: 1 species, controller: 2 species

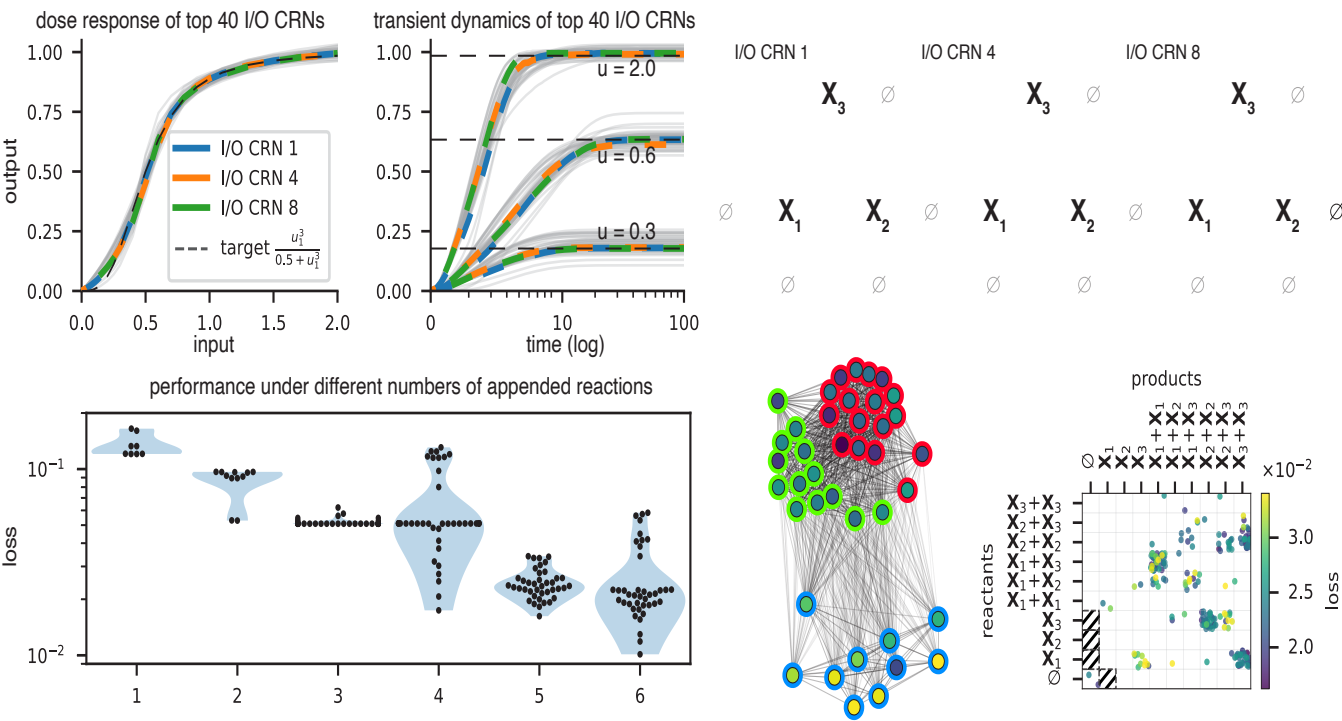


B. RPA in the deterministic setting, process: 1 species, controller: 1 species

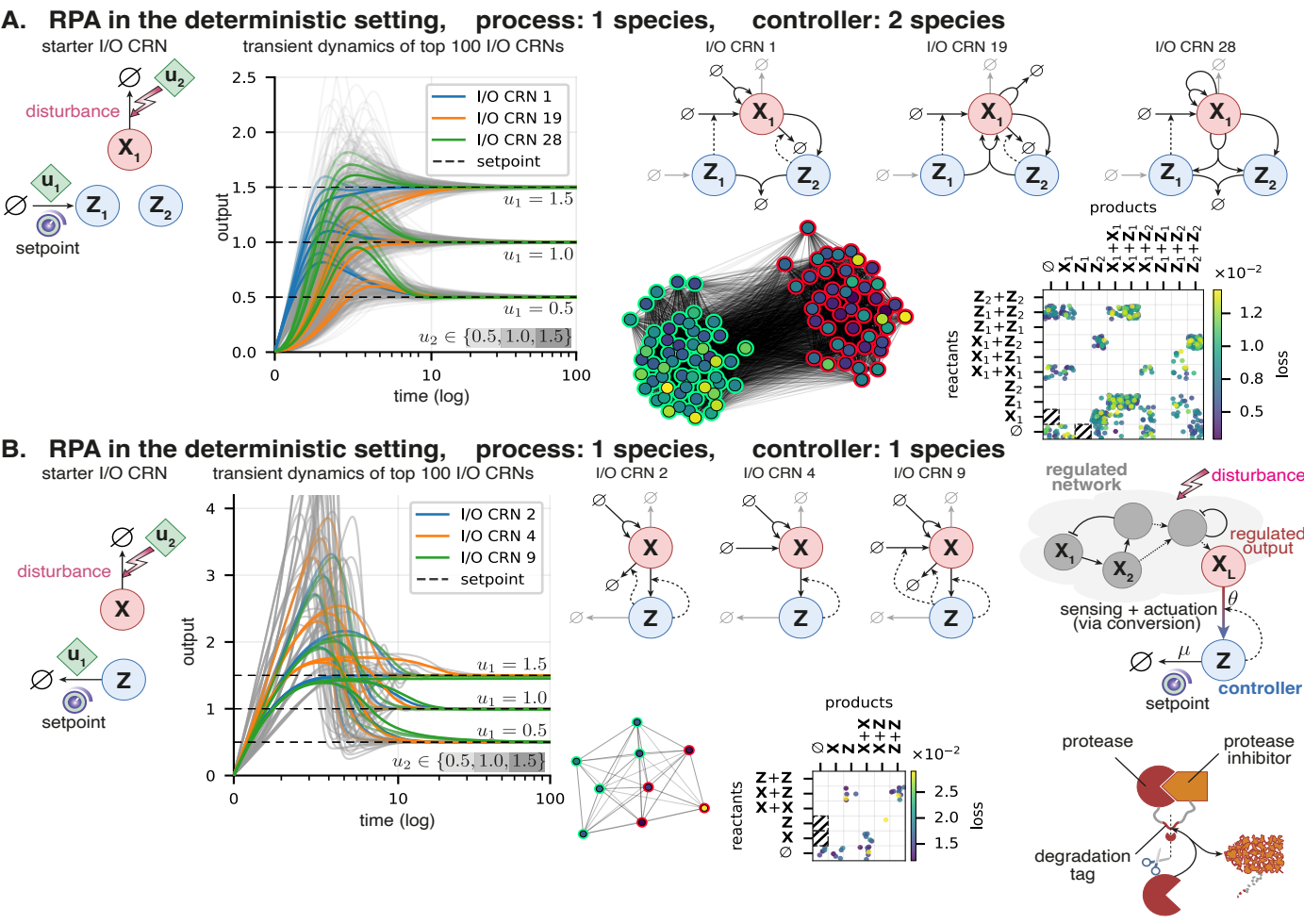


Classifiers

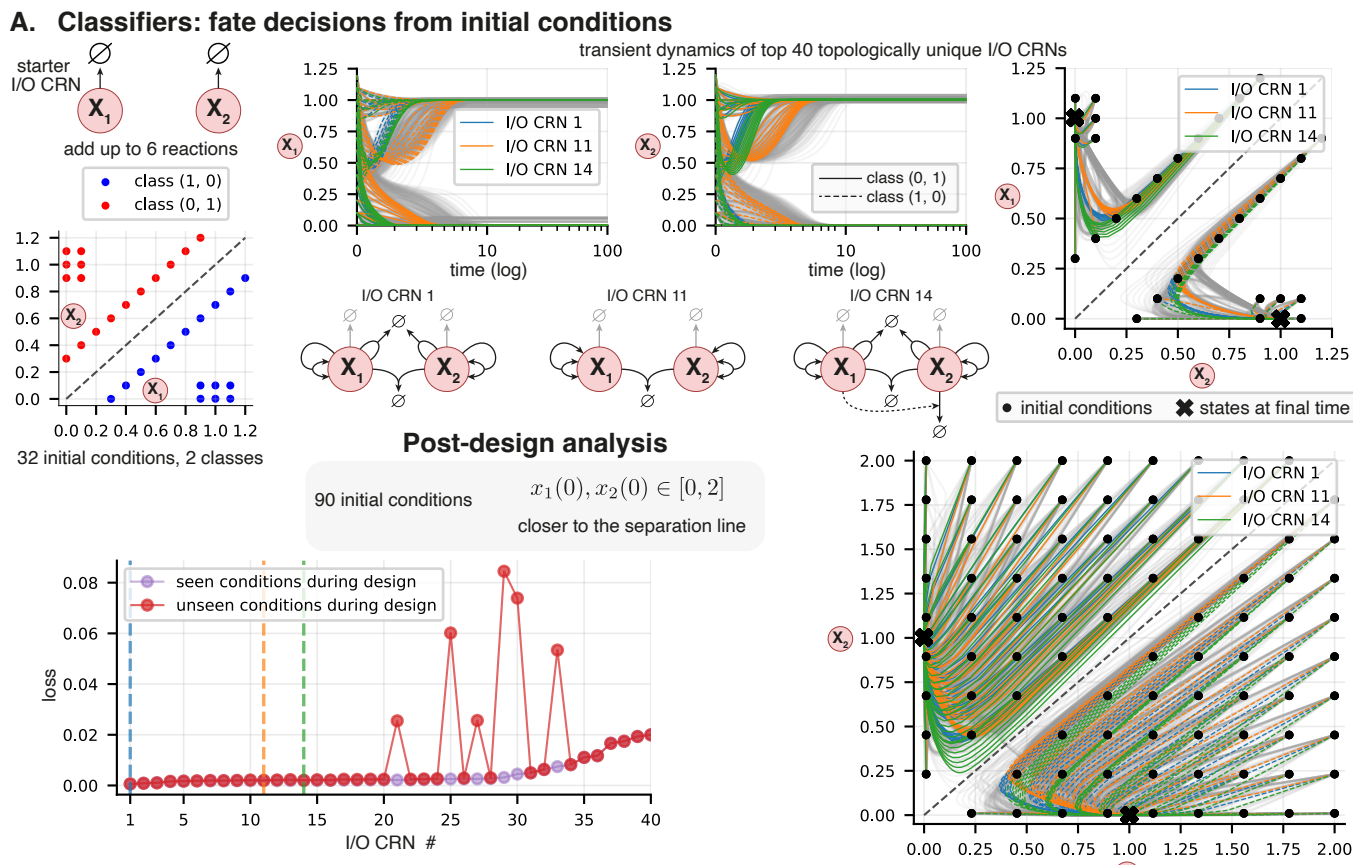
Dose Response Shaping



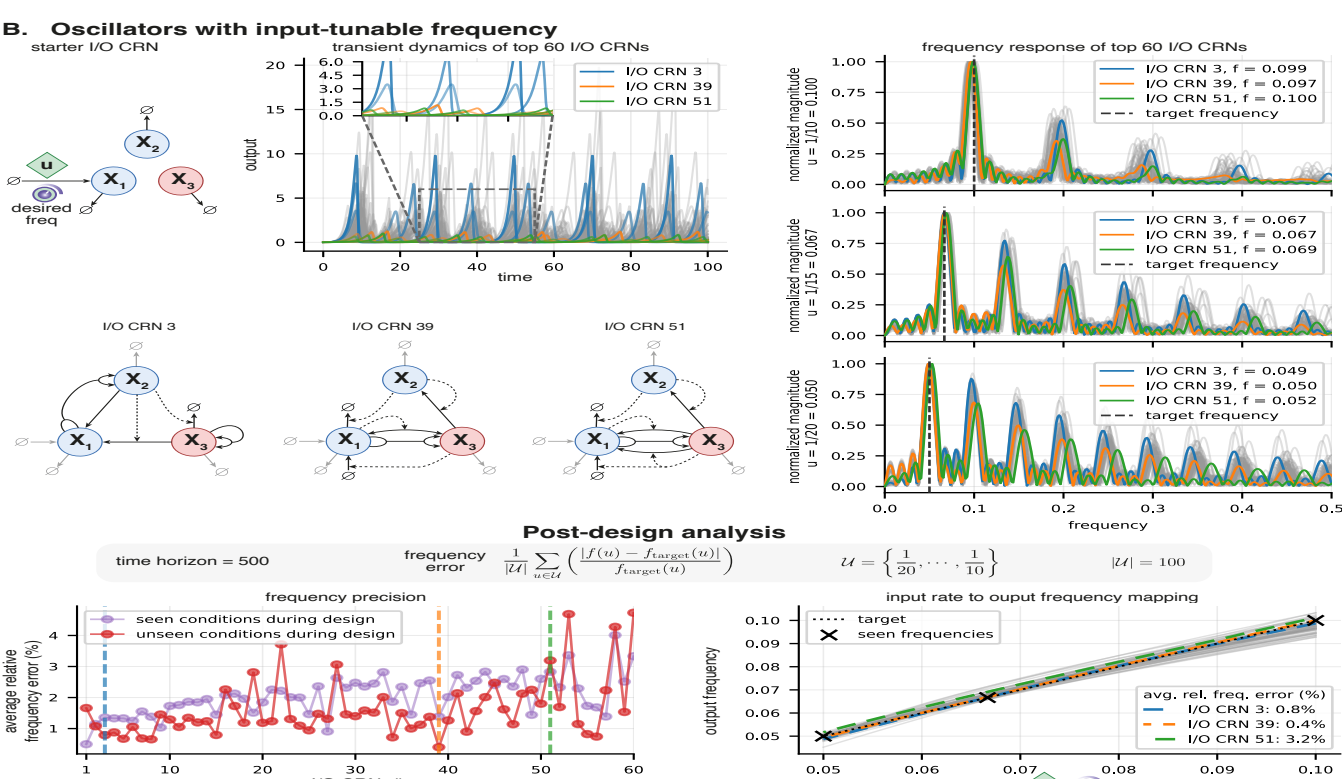
Robust Controllers



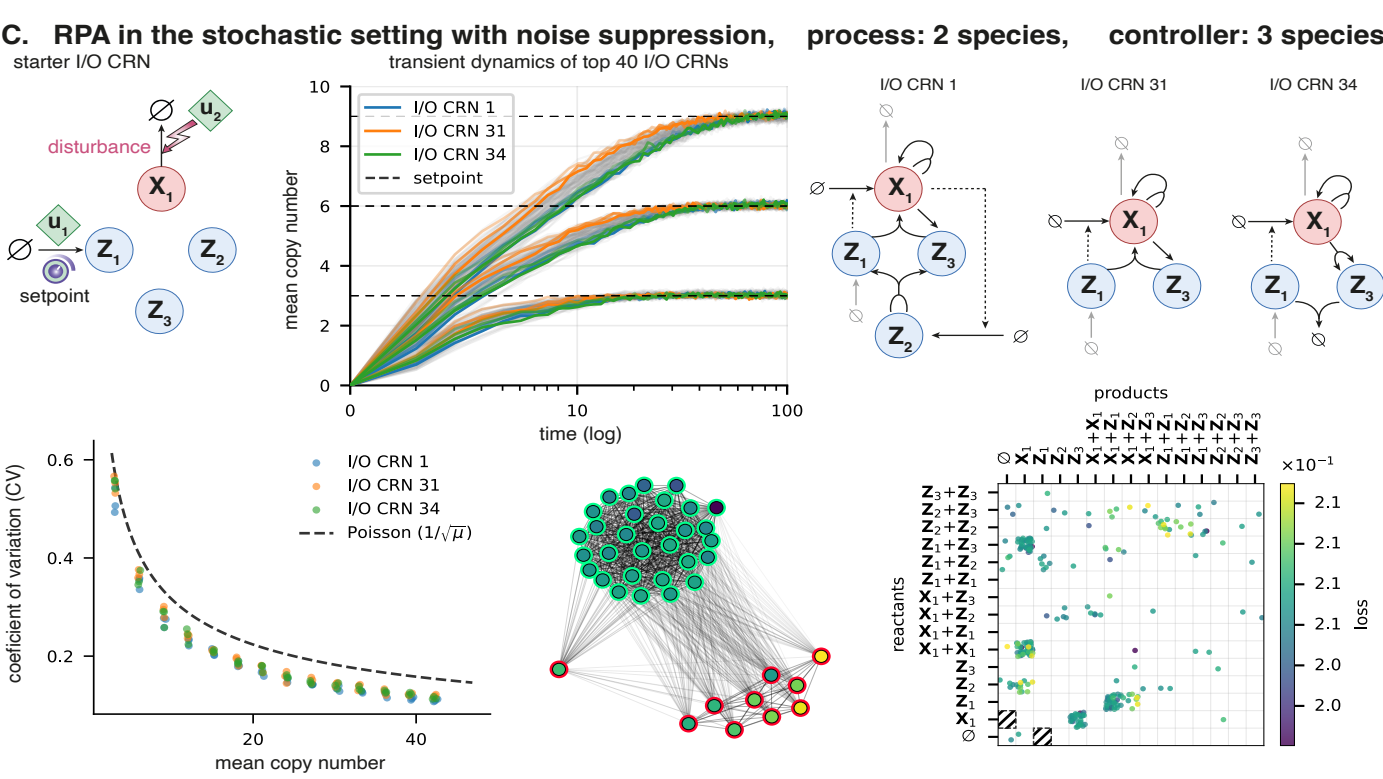
Classifiers



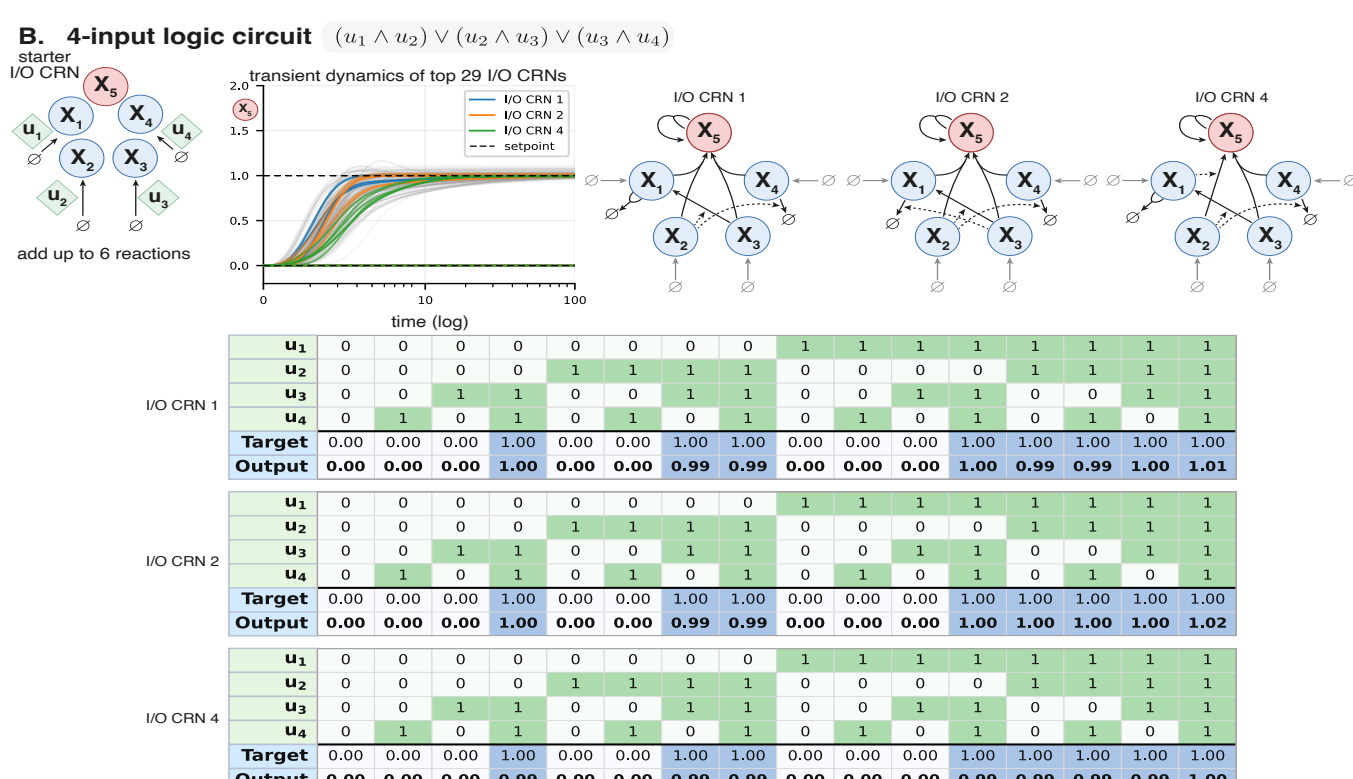
Biological Oscillators



Controllers w. Noise Attenuation

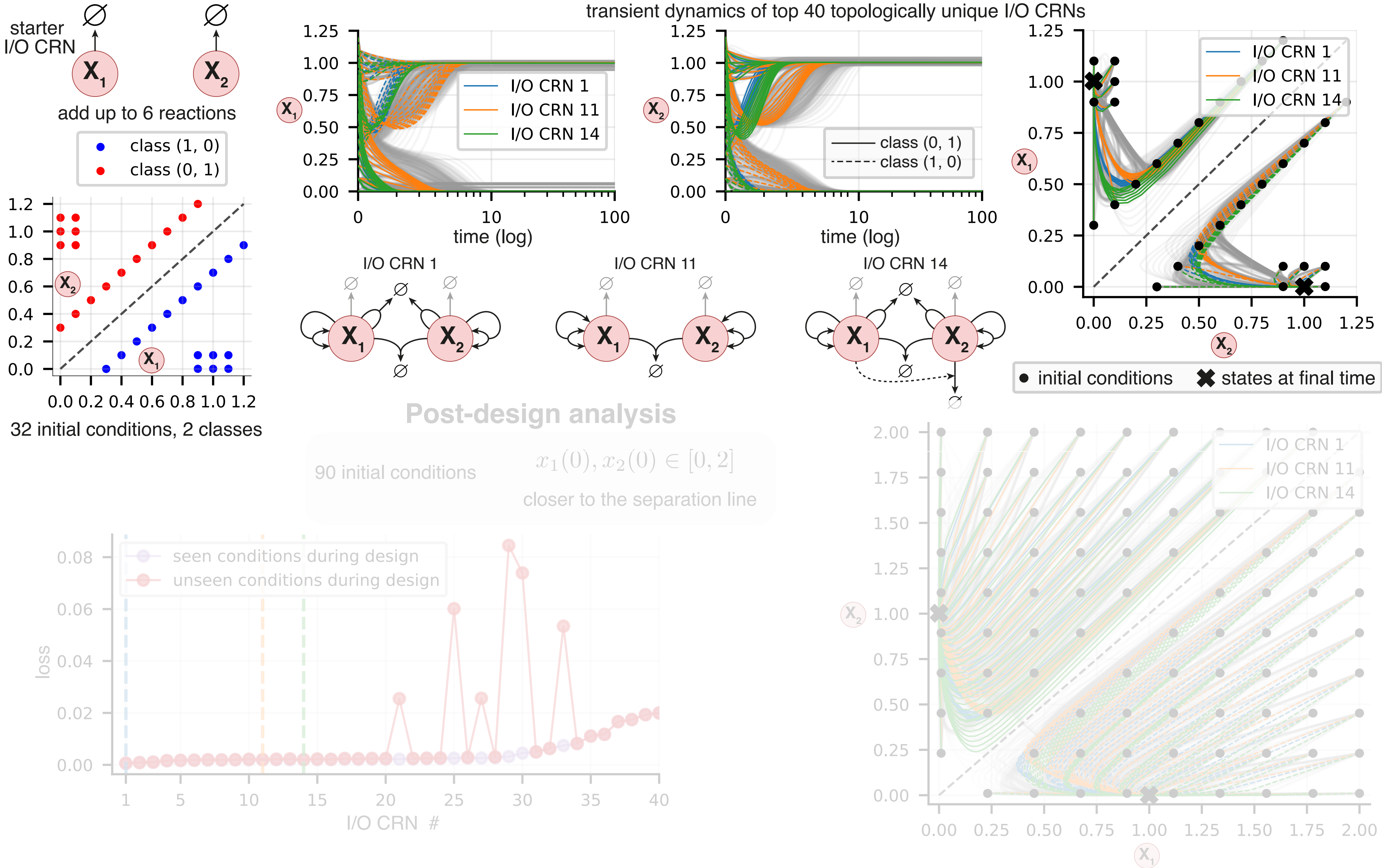


Logic Gates



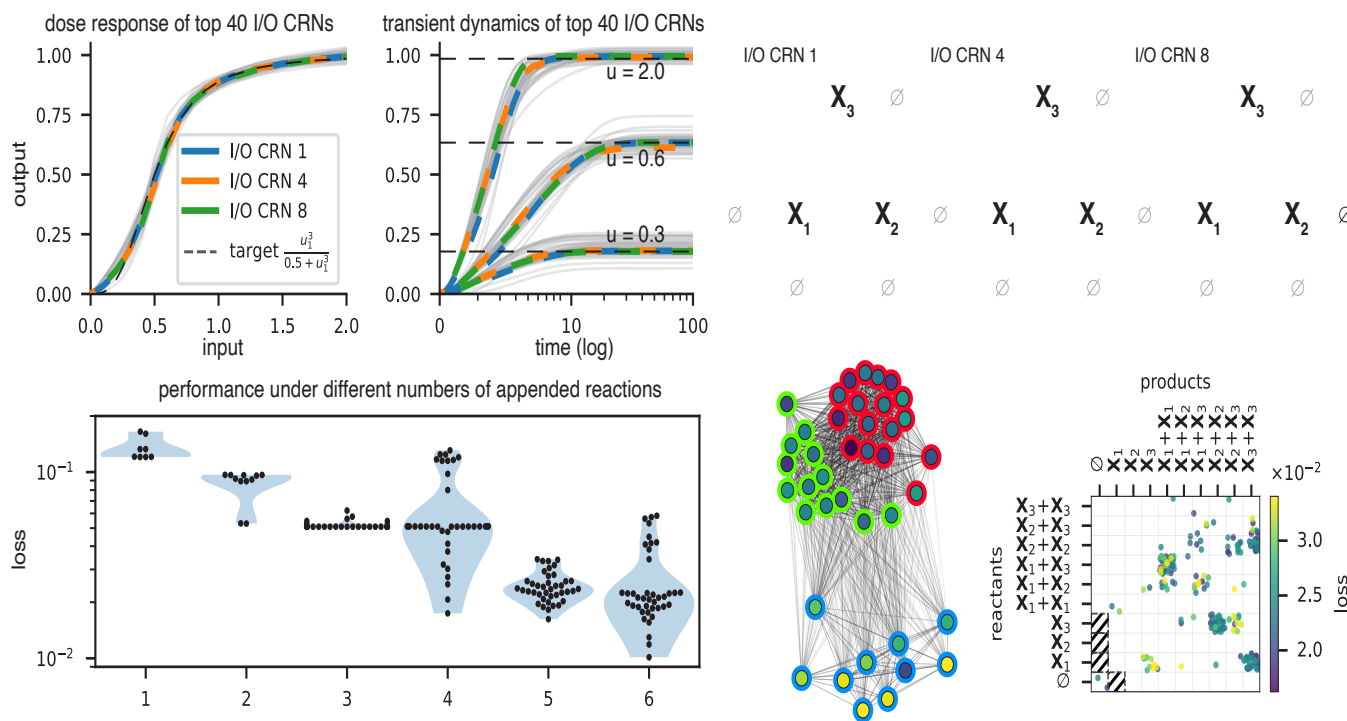
Classifiers

A. Classifiers: fate decisions from initial conditions

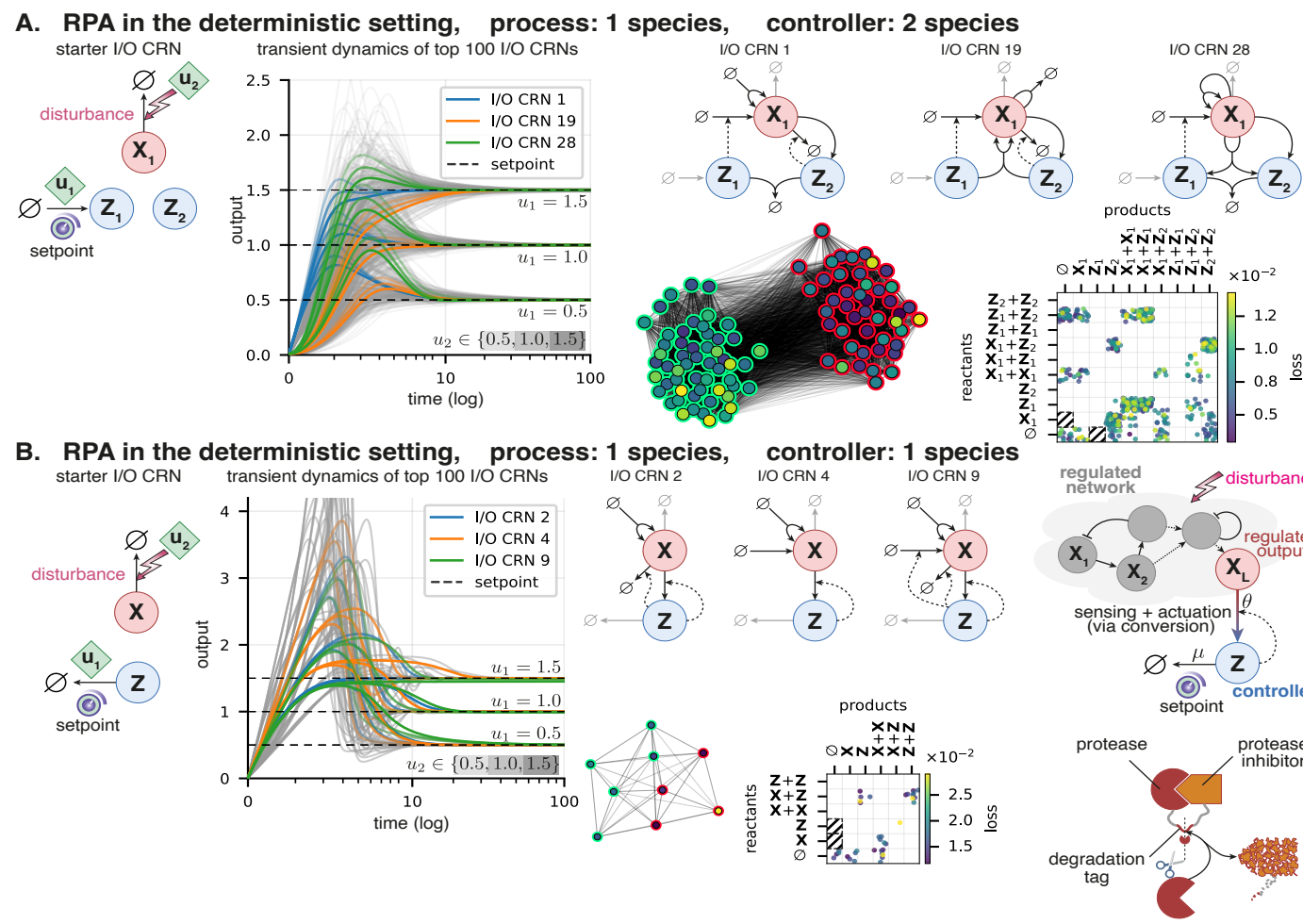


Molecular oscillators

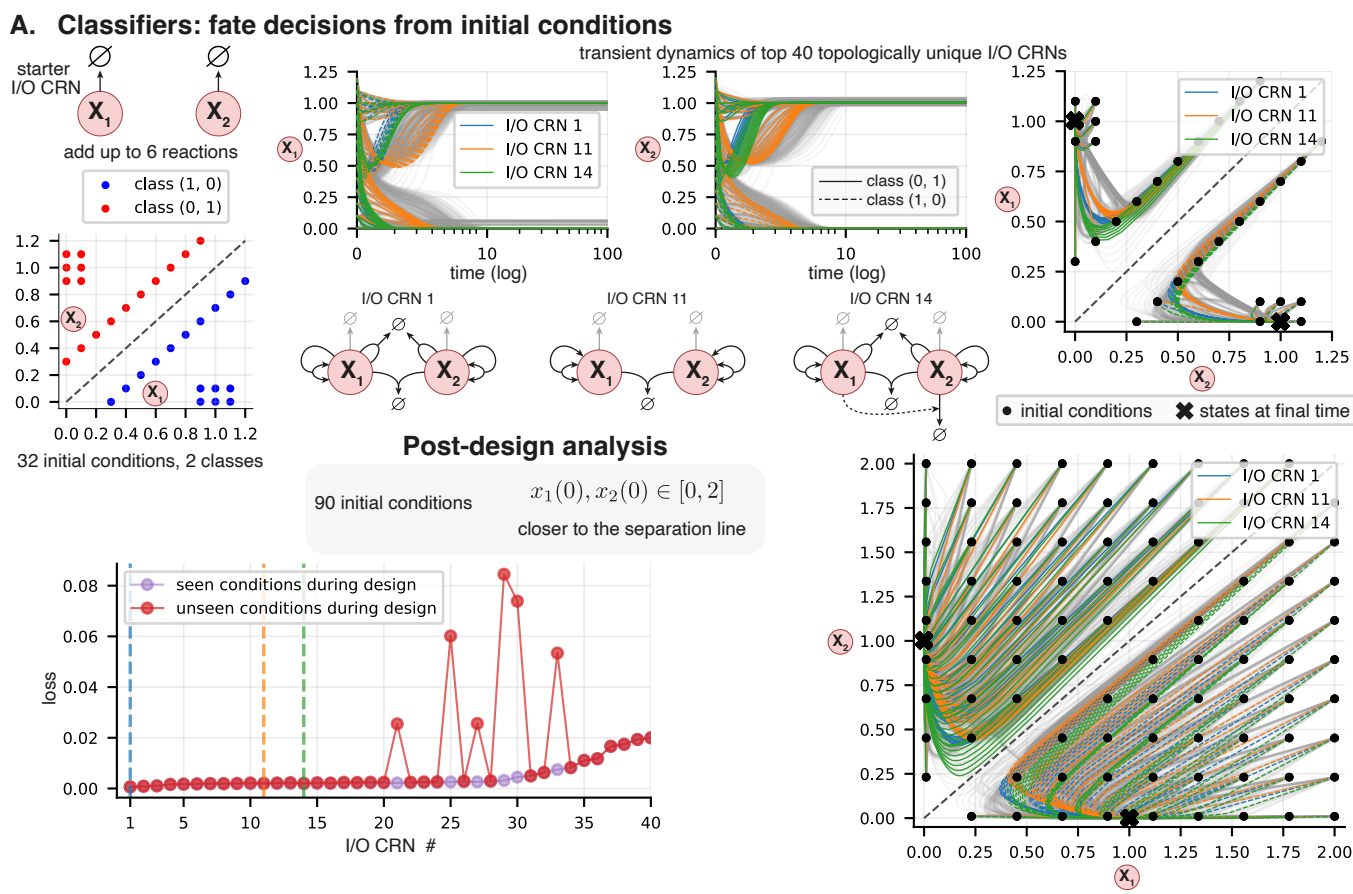
Dose Response Shaping



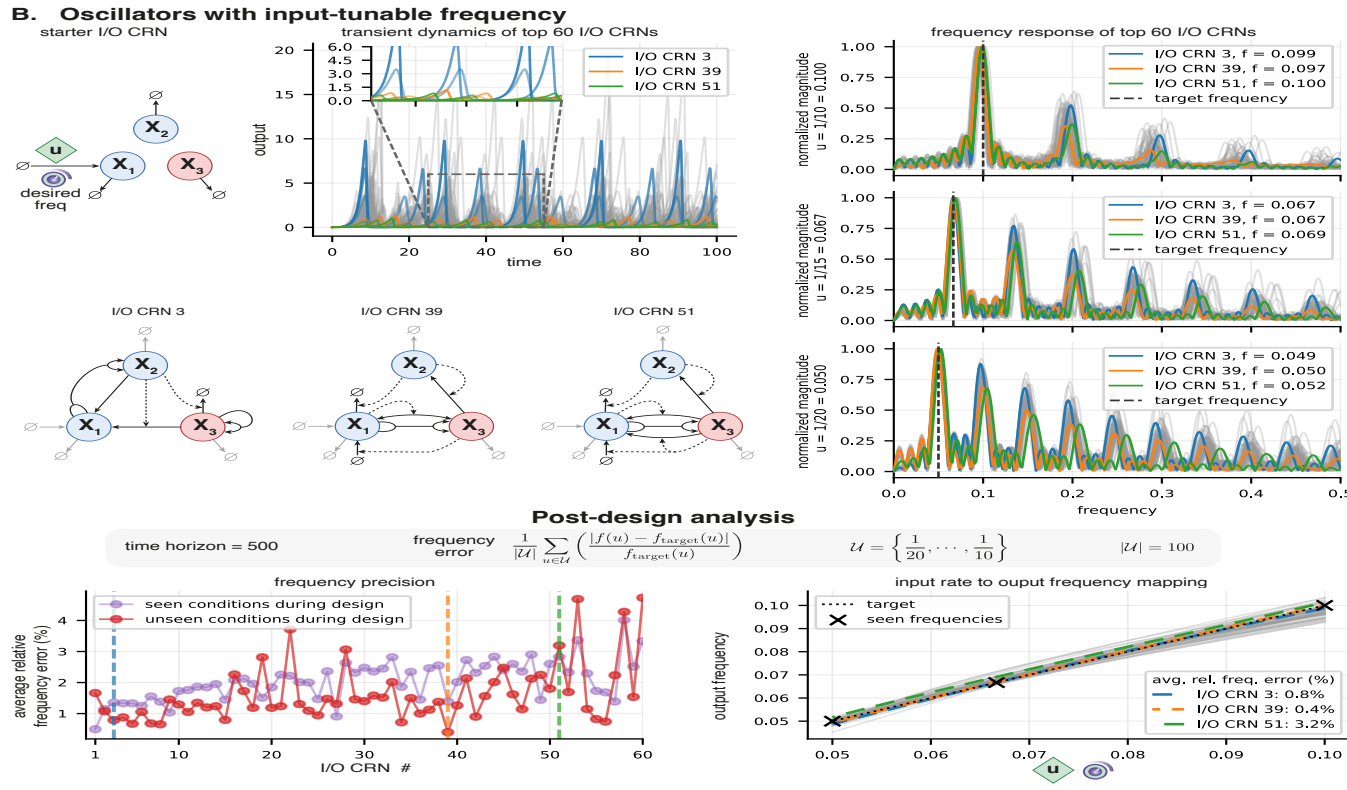
Robust Controllers



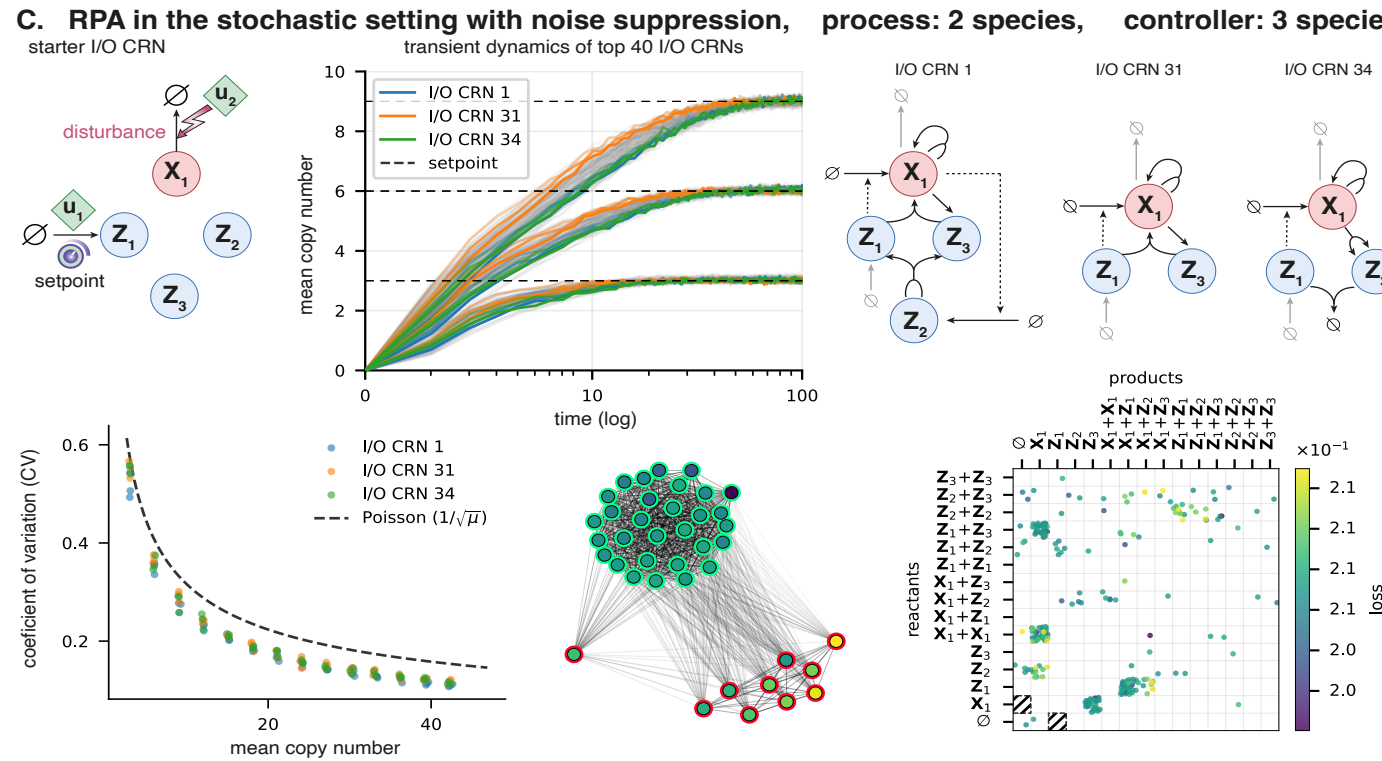
Classifiers



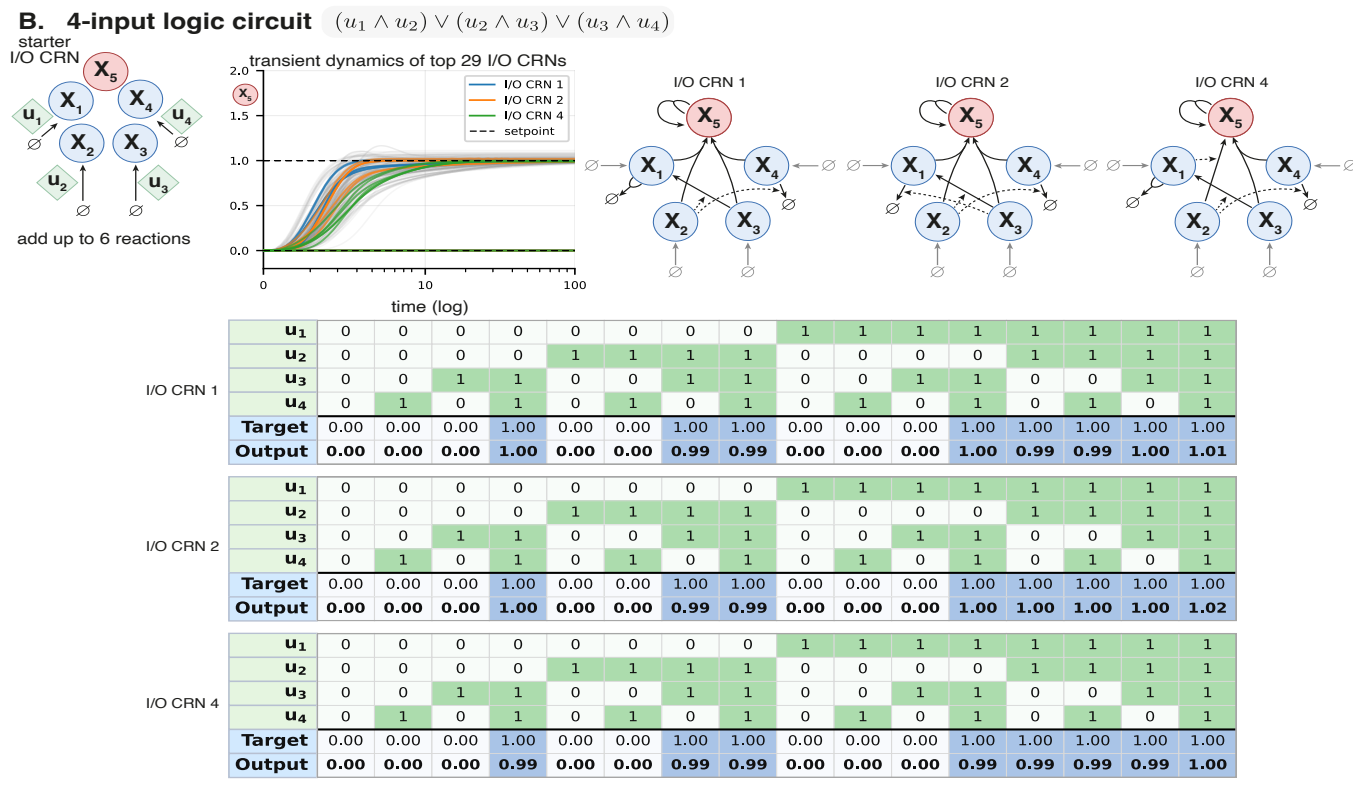
Biological Oscillators



Controllers w. Noise Attenuation

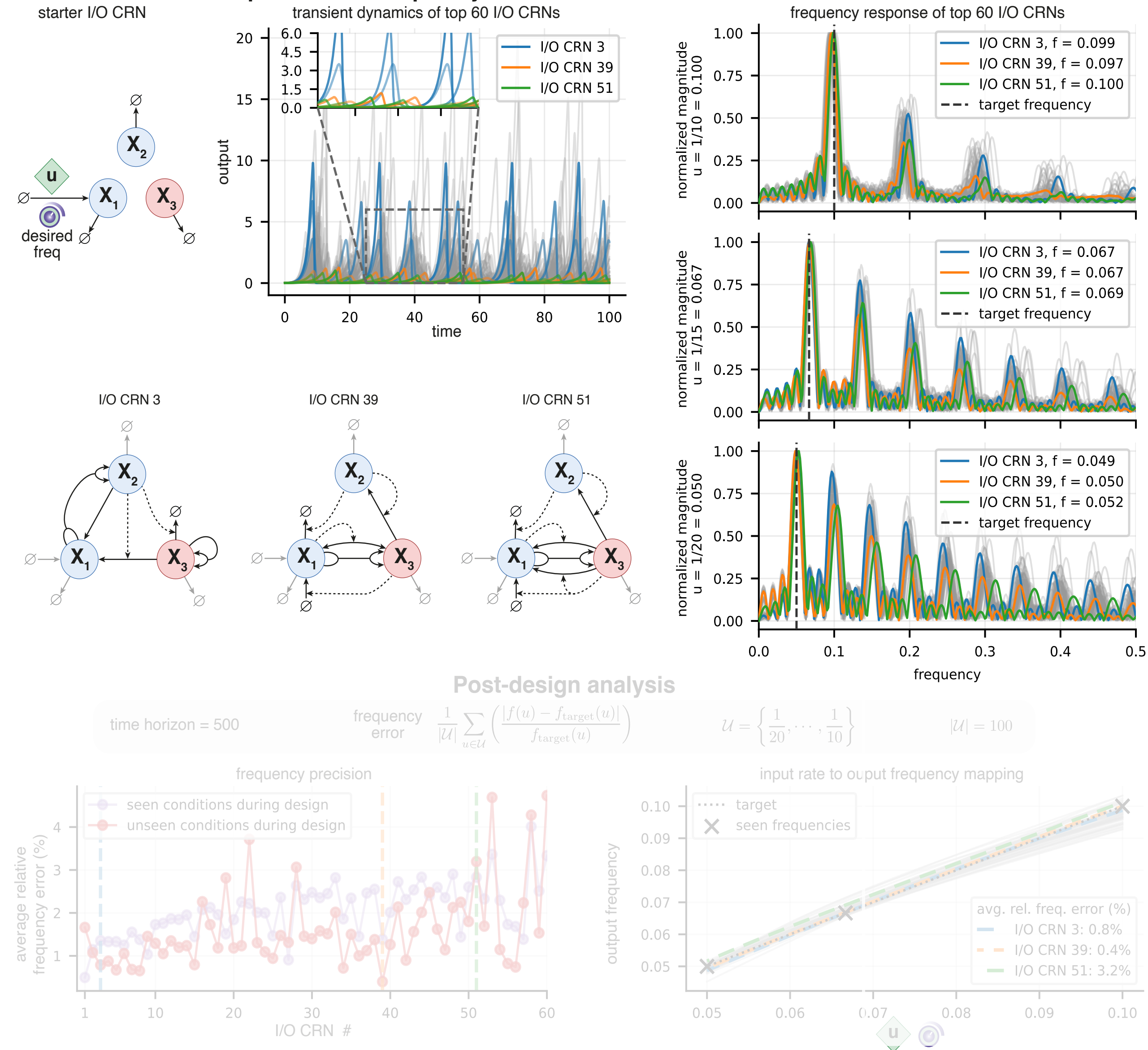


Logic Gates



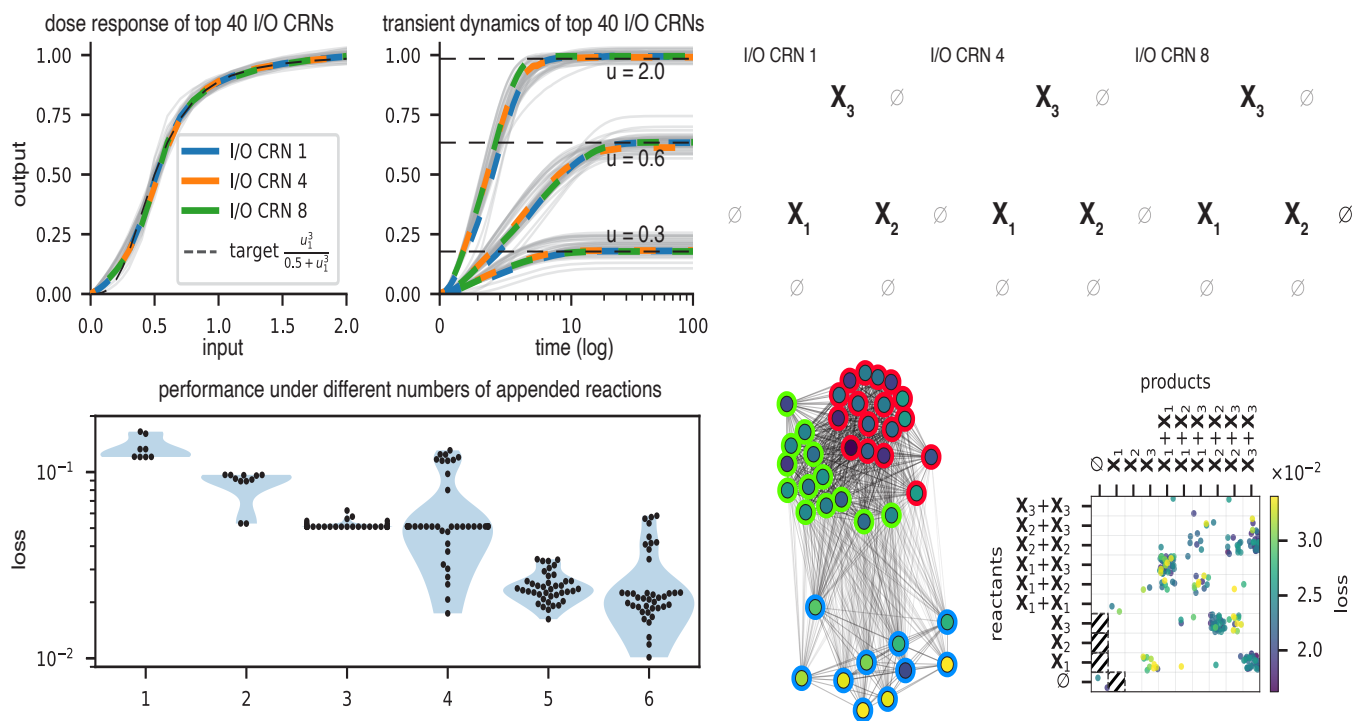
Molecular oscillators

B. Oscillators with input-tunable frequency

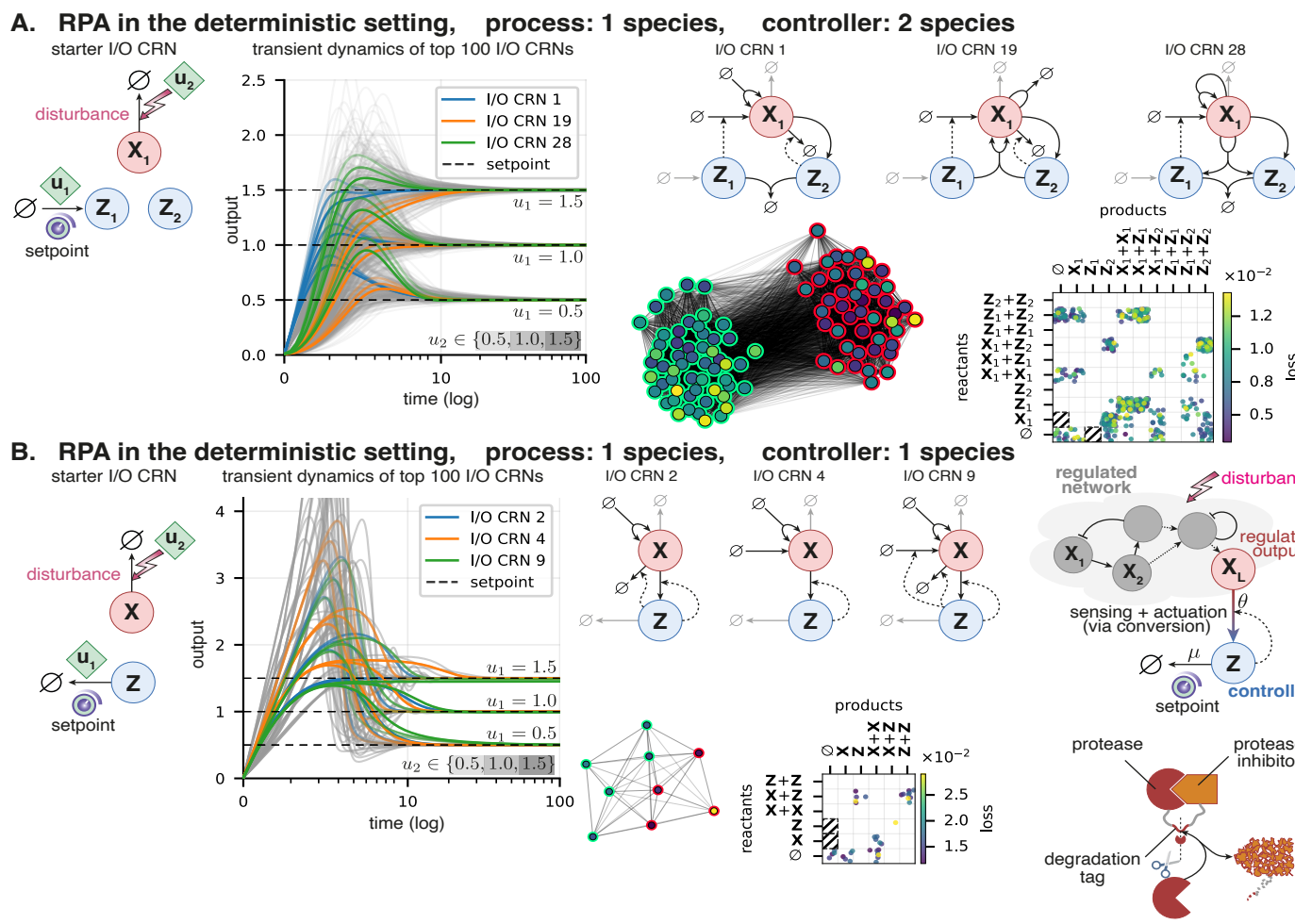


Molecular logic gates

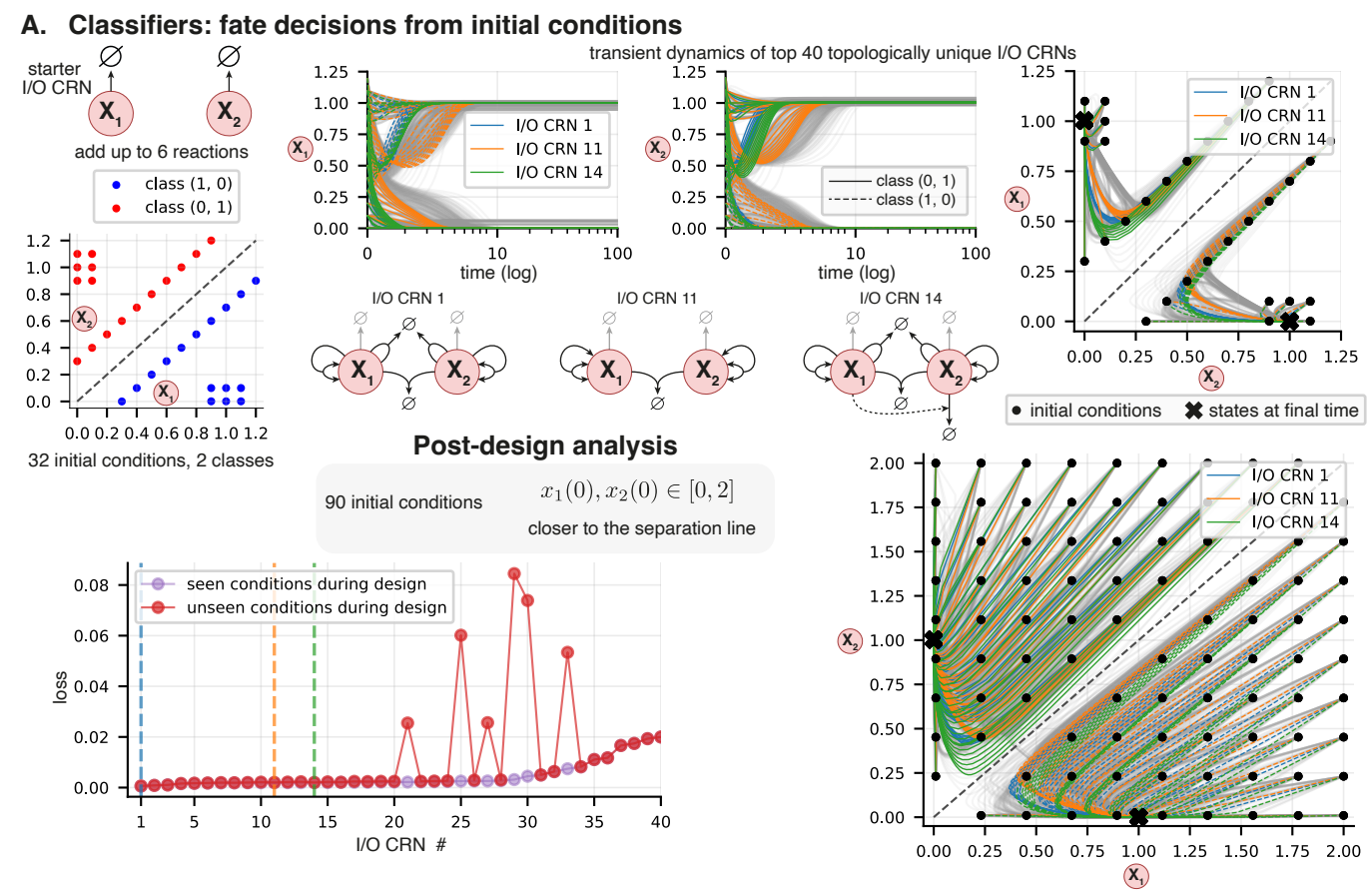
Dose Response Shaping



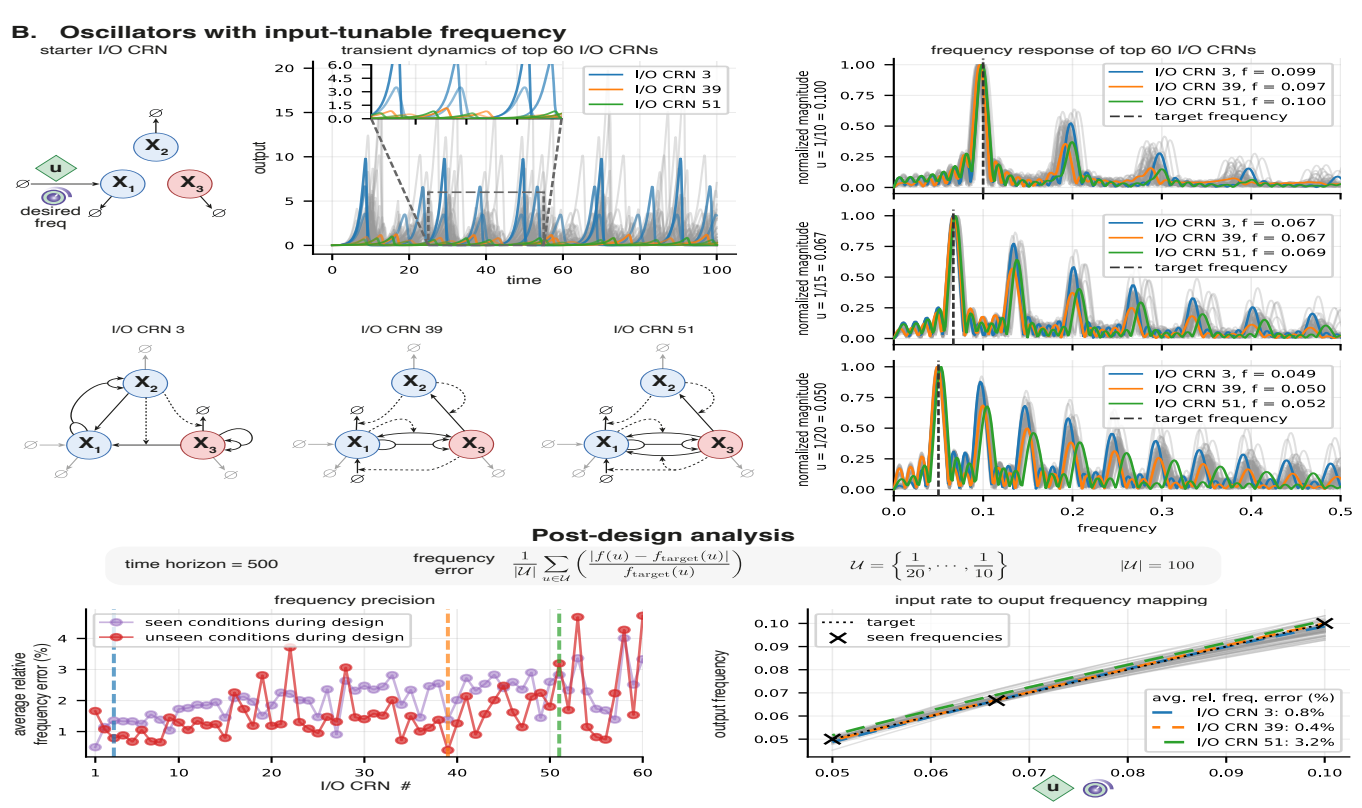
Robust Controllers



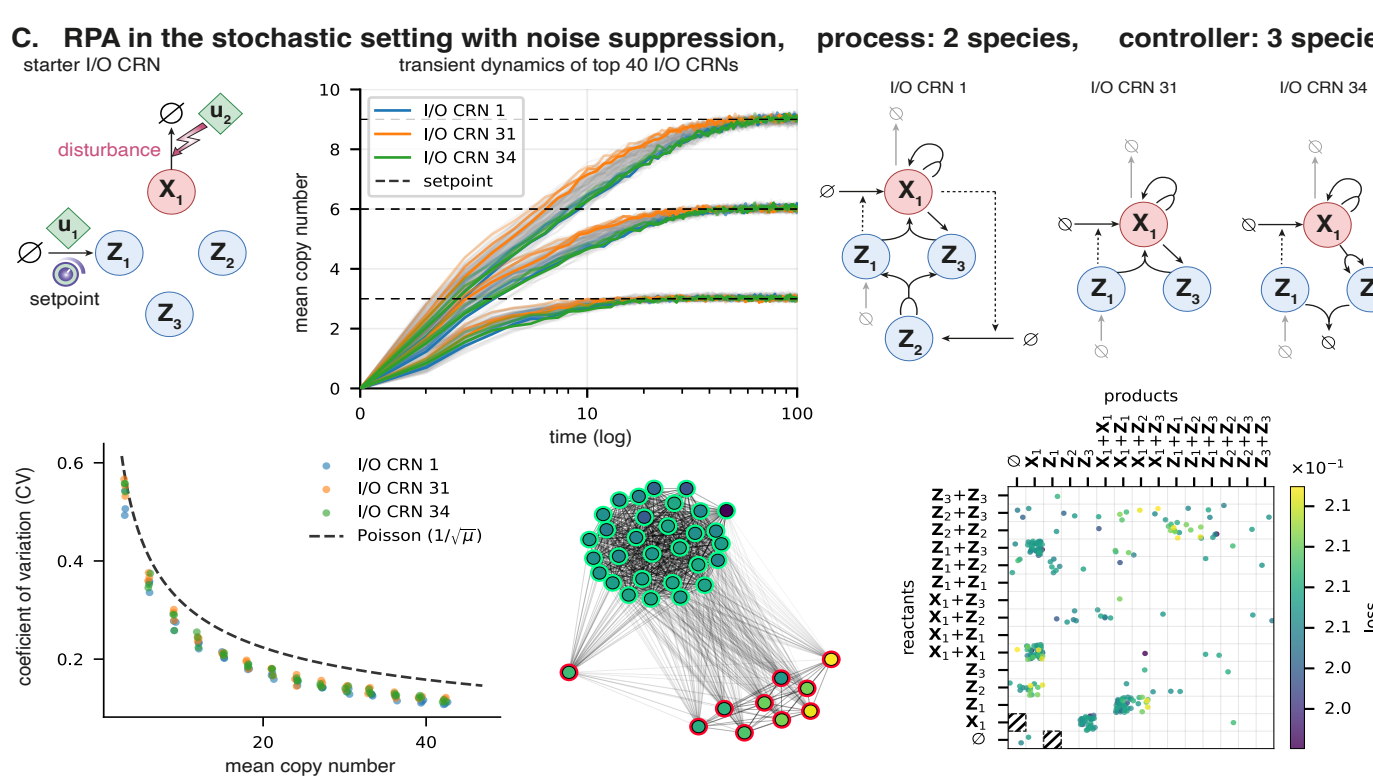
Classifiers



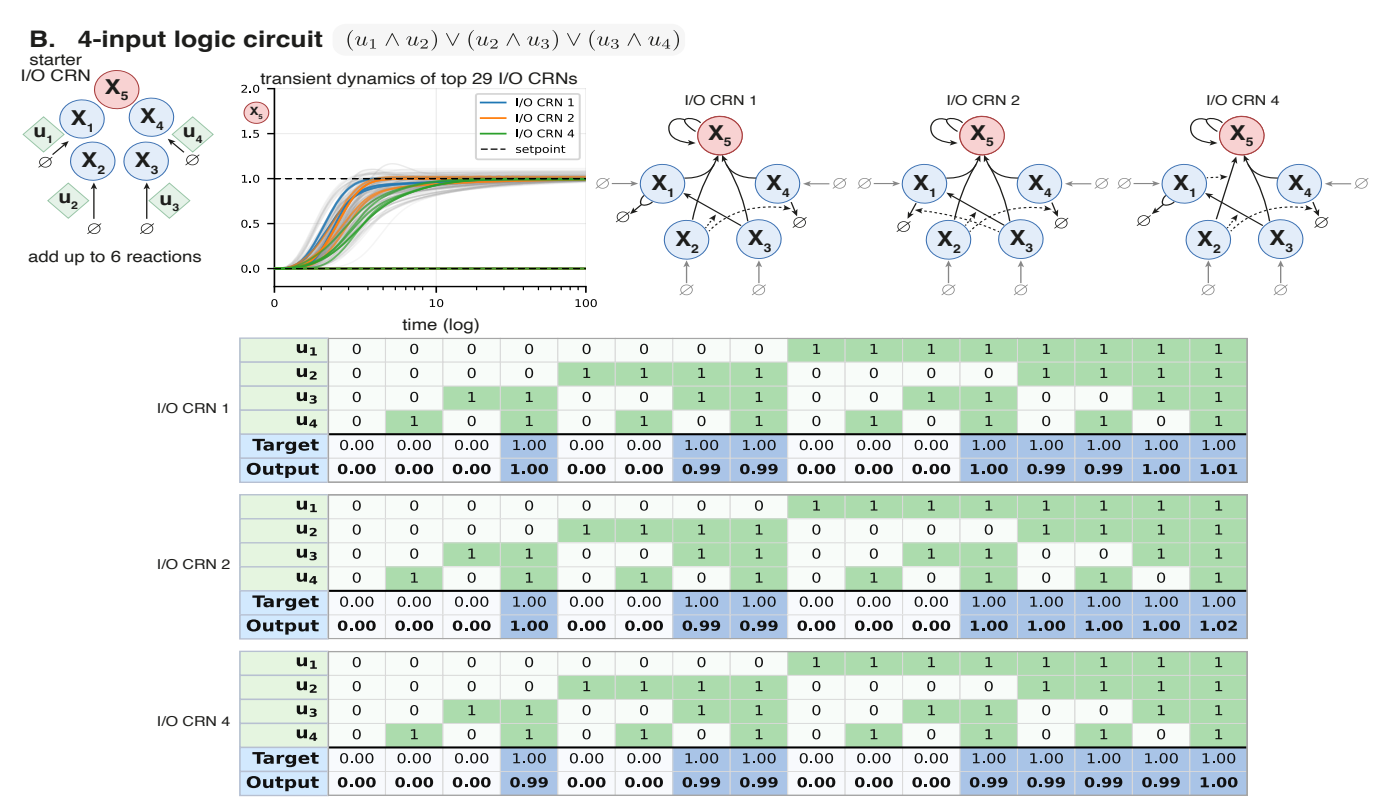
Biological Oscillators



Controllers w. Noise Attenuation

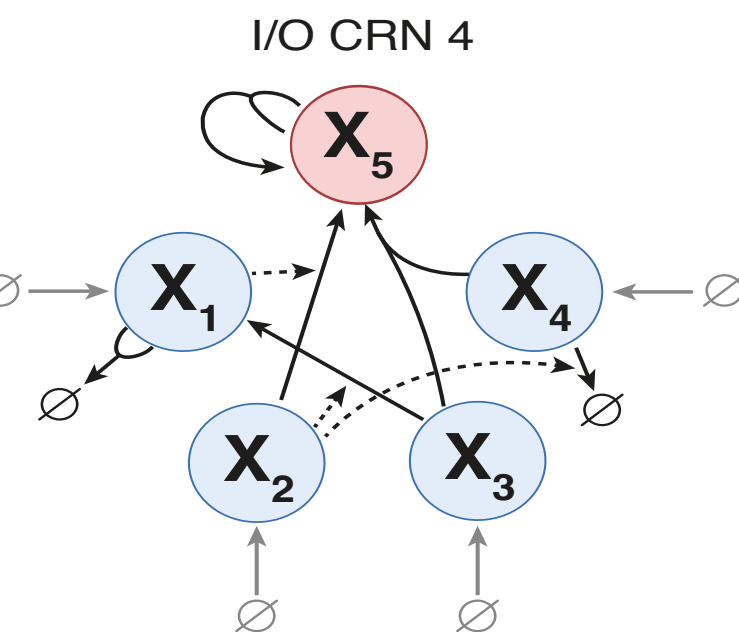
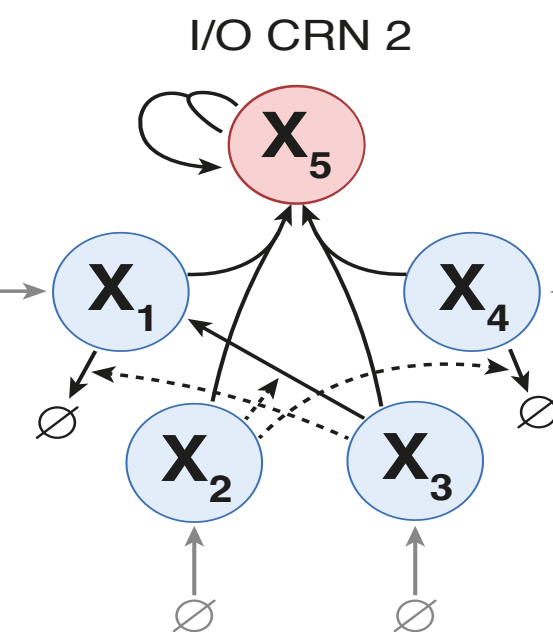
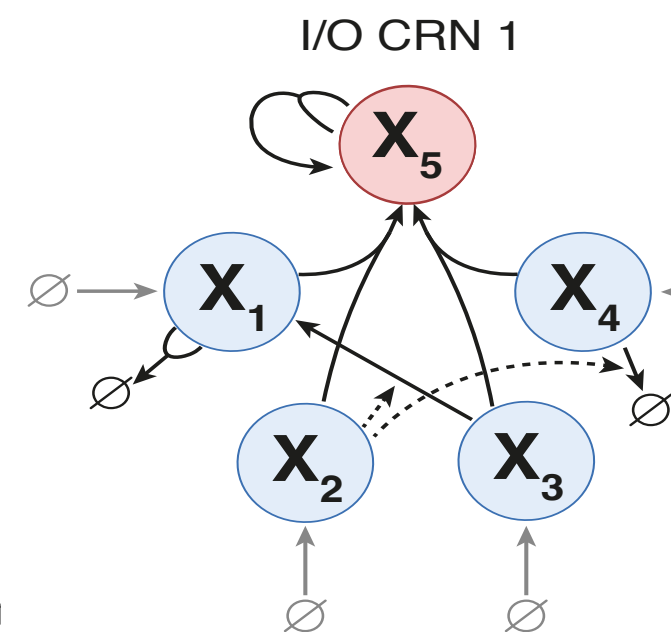
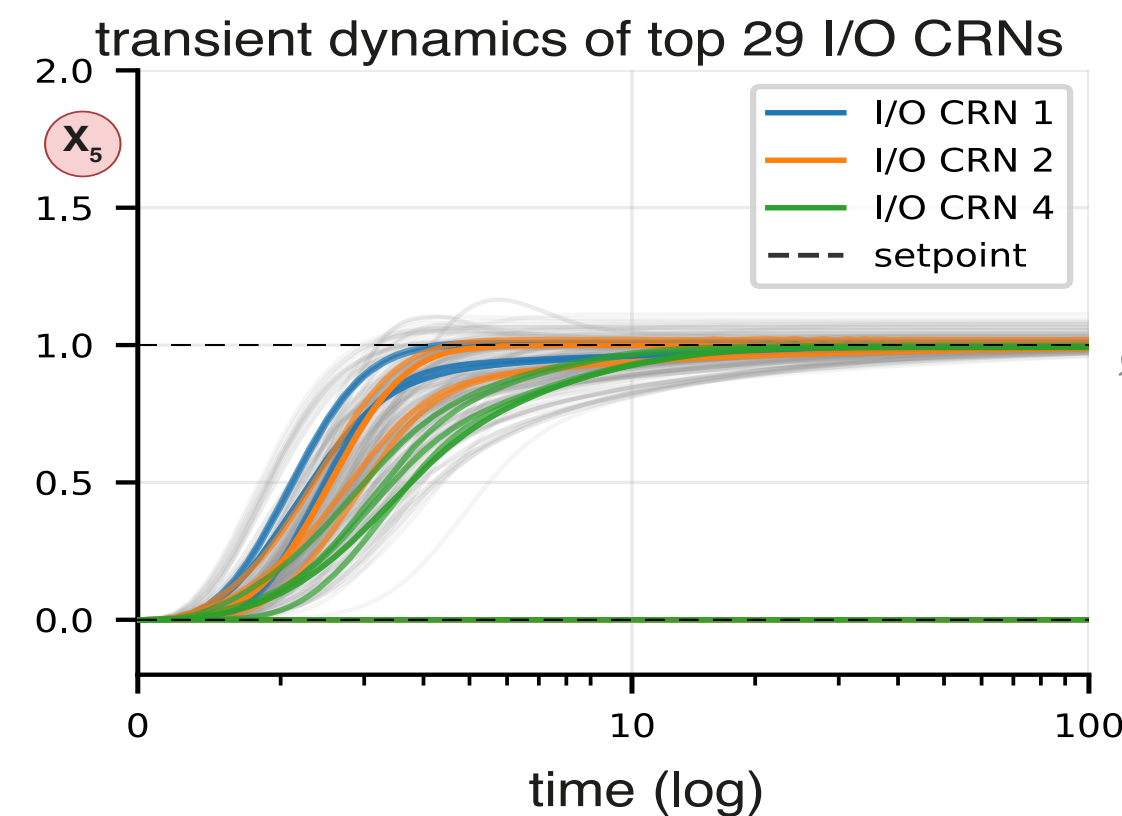
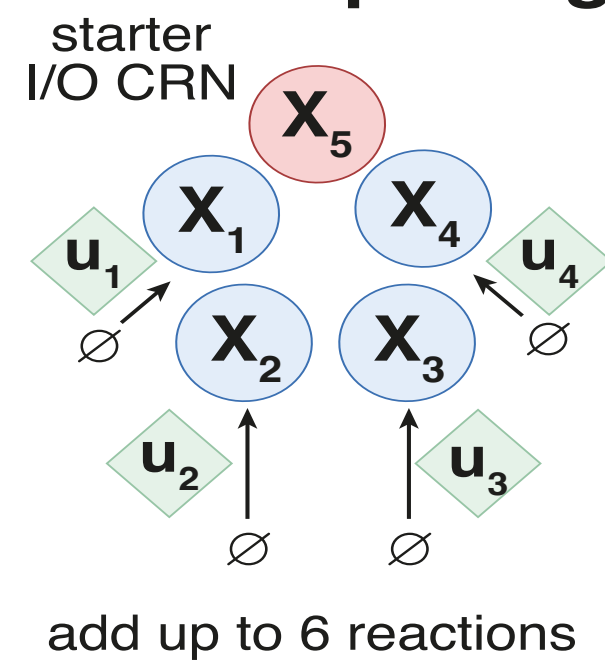


Logic Gates



Molecular logic gates

B. 4-input logic circuit $(u_1 \wedge u_2) \vee (u_2 \wedge u_3) \vee (u_3 \wedge u_4)$

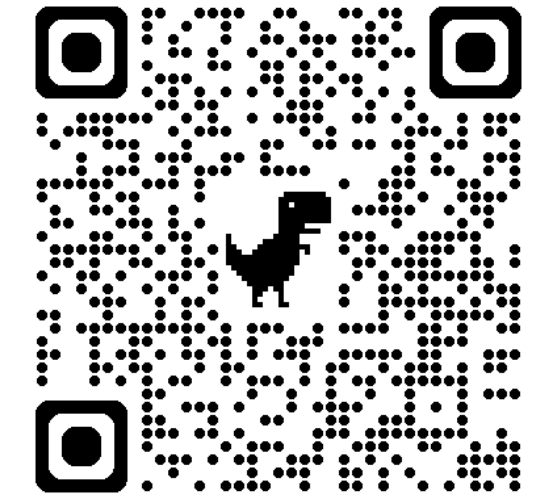


I/O CRN 1	u_1	0	0	0	0	0	0	0	0	1	1	1	1	1	1	1
	u_2	0	0	0	0	1	1	1	1	0	0	0	0	1	1	1
	u_3	0	0	1	1	0	0	1	1	0	0	1	1	0	0	1
	u_4	0	1	0	1	0	1	0	1	0	1	0	1	0	1	0
	Target	0.00	0.00	0.00	1.00	0.00	0.00	1.00	1.00	0.00	0.00	0.00	1.00	1.00	1.00	1.00
	Output	0.00	0.00	0.00	1.00	0.00	0.00	0.99	0.99	0.00	0.00	0.00	1.00	0.99	0.99	1.01
I/O CRN 2	u_1	0	0	0	0	0	0	0	0	1	1	1	1	1	1	1
	u_2	0	0	0	0	1	1	1	1	0	0	0	0	1	1	1
	u_3	0	0	1	1	0	0	1	1	0	0	1	1	0	0	1
	u_4	0	1	0	1	0	1	0	1	0	1	0	1	0	1	0
	Target	0.00	0.00	0.00	1.00	0.00	0.00	1.00	1.00	0.00	0.00	0.00	1.00	1.00	1.00	1.00
	Output	0.00	0.00	0.00	1.00	0.00	0.00	0.99	0.99	0.00	0.00	0.00	1.00	1.00	1.00	1.02
I/O CRN 4	u_1	0	0	0	0	0	0	0	0	1	1	1	1	1	1	1
	u_2	0	0	0	0	1	1	1	1	0	0	0	0	1	1	1
	u_3	0	0	1	1	0	0	1	1	0	0	1	1	0	0	1
	u_4	0	1	0	1	0	1	0	1	0	1	0	1	0	1	0
	Target	0.00	0.00	0.00	1.00	0.00	0.00	1.00	1.00	0.00	0.00	0.00	1.00	1.00	1.00	1.00
	Output	0.00	0.00	0.00	0.99	0.00	0.00	0.99	0.99	0.00	0.00	0.00	0.99	0.99	0.99	1.00

Conclusion & Outlook

- Control theory provides a principled framework for engineering biological feedback systems
- AI can help speed up the design and motivate new theory.
- How to tailor the search space to make the CRNs genetically implementable by construction?

<https://maurice-filo.github.io/>



- Filo, M., Kumar, S., & Khammash, M. (2022). A hierarchy of biomolecular PID feedback controllers for robust perfect adaptation and dynamic performance. *Nature communications*.
- Filo*, M., Rossi*, N., Fang*, Zhou, & Khammash, M. GenAI-Net (2026): A Generative AI Framework for Automated Biomolecular Network Design. *Science Advances*.
- Anastassov, S.*, Filo, M.*, Chang, C. H., & Khammash, M. (2023). A cybergenetic framework for engineering intein-mediated integral feedback control systems. *Nature Communications*.
- Filo, M., Chang, C. H., & Khammash, M. (2023). Biomolecular feedback controllers: from theory to applications. *Current Opinion in Biotechnology*.
- Filo*, M., Aoki*, S.K., Hou*, Mucun, Anastassov, & Khammash, M (2026). Engineering Genetic Controllers to Accelerate Adaptation and Attenuate Cellular Noise. *Cell Systems*.
- Filo, M.*, Gupta, A.*, & Khammash, M. (2024). Anti-windup strategies for biomolecular control systems facilitated by model reduction theory for sequestration networks. *Science Advances*.
- Frei, T., Chang, C. H., Filo, M., Arampatzis, A., & Khammash, M. (2022). A genetic mammalian proportional-integral feedback control circuit for robust and precise gene regulation. *PNAS*.