The Lorry I. Lokey Interdisciplinary Center for Life Sciences and Engineering

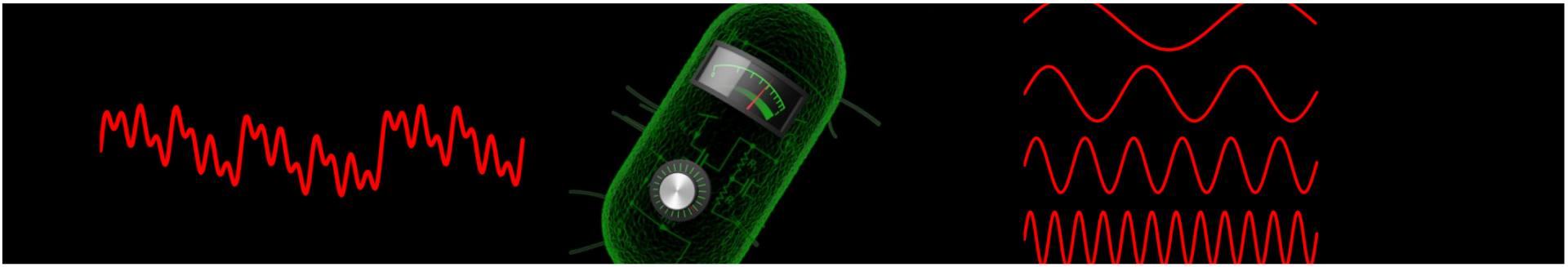
Technion
Israel Institute of Technology

Synthetic neuromorphic computing in living cells

Prof. Ramez Daniel

Laboratory of Synthetic Biology & Bioelectronics (LSB^2)

Biomedical Engineering , Technion



FENS BIOCOMPUTING **2024**

The Laboratory for Synthetic Biology & Bioelectronics (LSB^2)

Dr. Muna Habib

Luna Rizik

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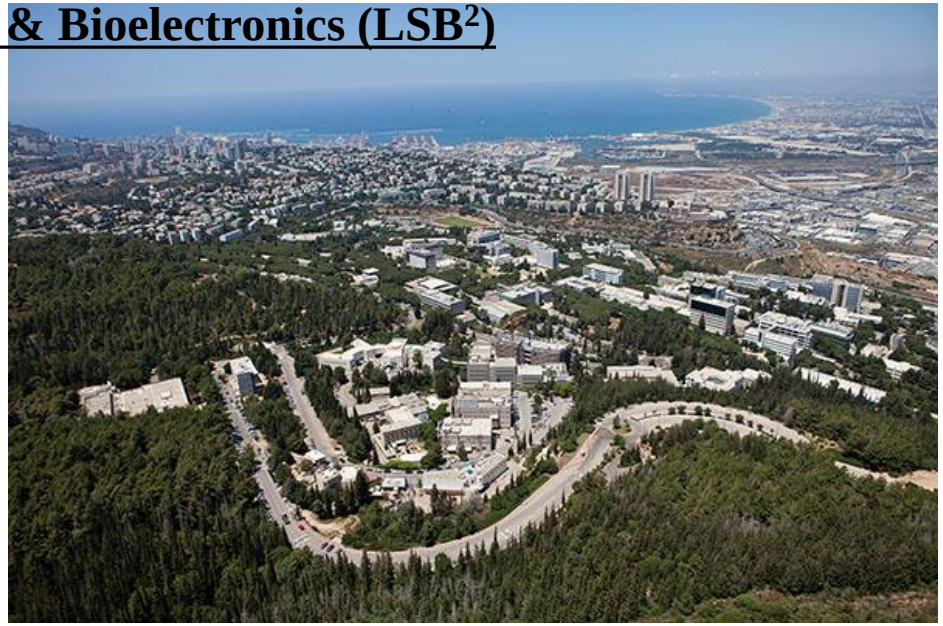

Dr. Ximing Li

Natali Barger

Phyana Litovco

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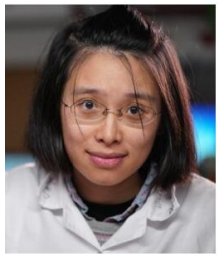
Ilan Oren

VISHESH GUPTA

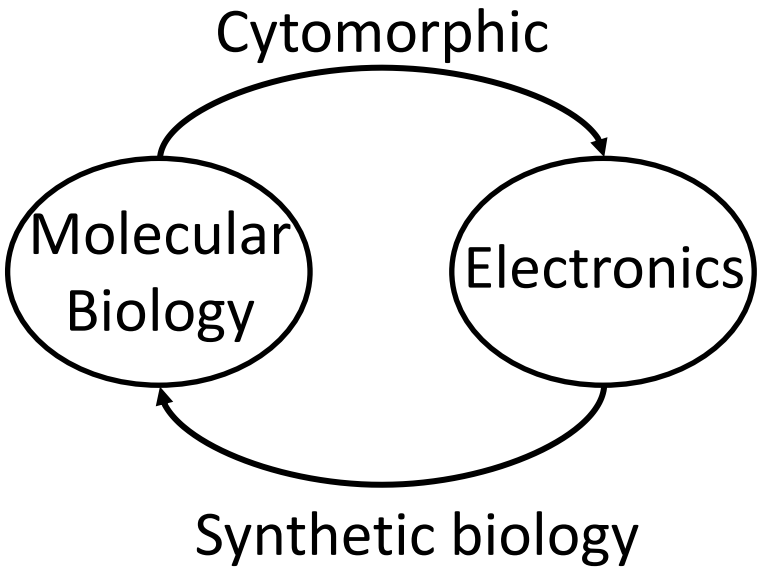
Valeriia Kravchik



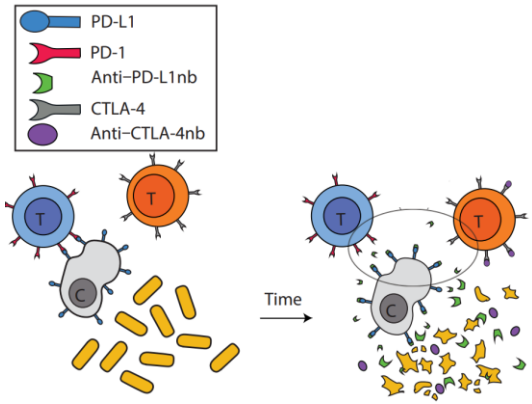
Rongying Huang

Cytomorphic engineering

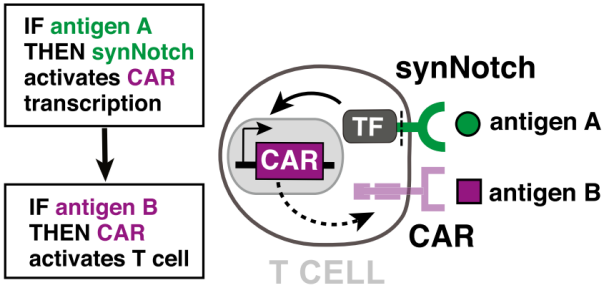
Neutrophil chasing bacterium (David Rogers 1950)



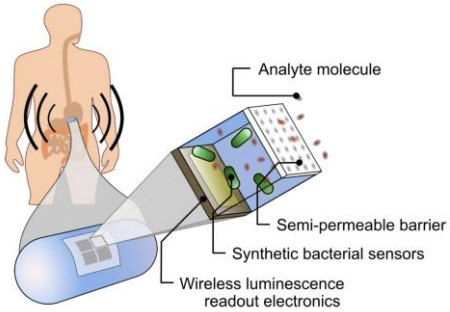
Our inputs and outputs are proteins



Gurbatri et al., 2020)

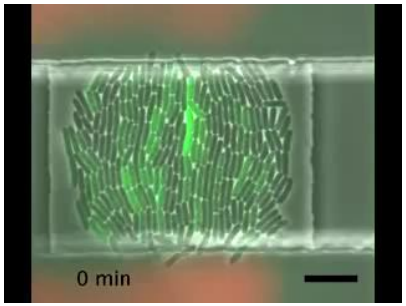


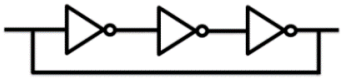
Roybal et al., 2016,



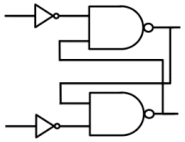
Mimee et al., 2018

Synthetic Gene circuits are numbers of biological elements that are connected according to design principles



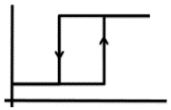


Gardner *et al. Nature* **2000** — **Toggle Switch**



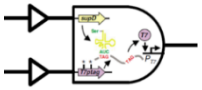
Elowitz *et al. Nature* **2000** — **Oscillator**

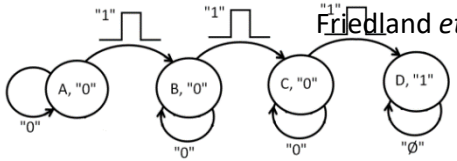
Ajo-Franklinr *et al.* Genes Dev. **2007** — **Memory**



Andersonr *et al Mol.Sys.Biol.* **2007** — **AND Gate**

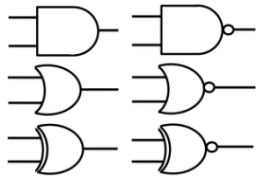
Nissim et al 2007





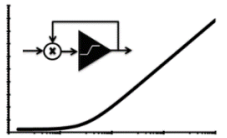
Friedland *et al. science* **2009** — **Counter, State machine**

Boolean Logic Gates & Memory Devices



Tamsir *et al. Nature* **2011**

Daniel et al. Nature **2013** — **Analog Circuits**



Nielsen et al. science **2016** — **Design automation for digital systems**

Li et al. Nat. Comm **2021** — **Neuromorphic circuits**

Molecular Networks Vs Neuron Networks

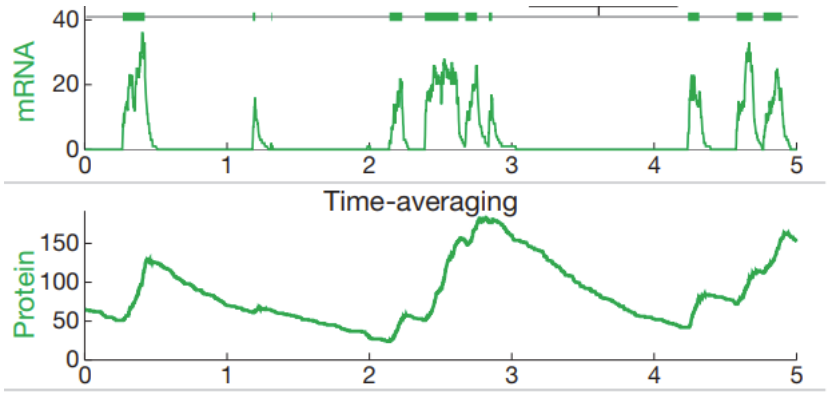
Both networks employ bitstream data-encoding pulses (such as spikes in neurons and mRNA transcripts in cell biology) for processing and transcommunication

Both networks utilize naturally graded signals for computation, exemplified by the post-synaptic potential in neurons and the translation of mRNA to protein

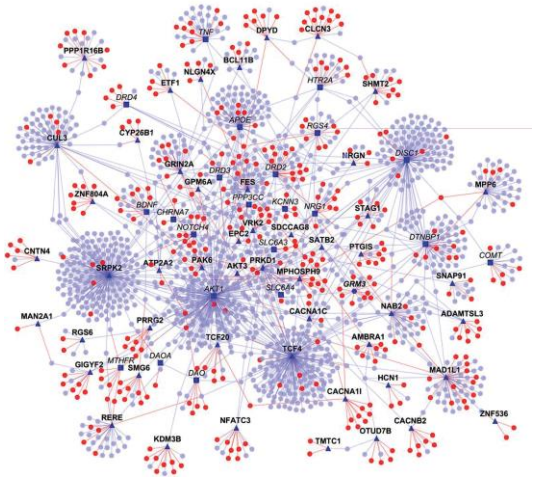
Both networks share analogous complex topologies, encompassing feed-forward structures, negative and positive feedback loops, and highly interconnected nodes.

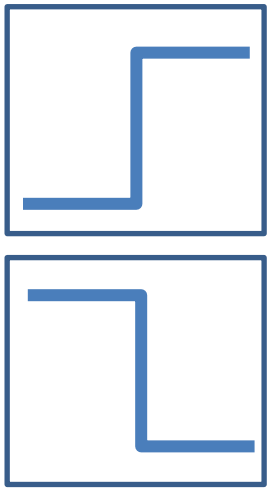
Both networks exhibit two types of excitability—activation, and repression

Both networks exhibit adaptability to new environmental conditions through learning and evolutionary mechanisms.



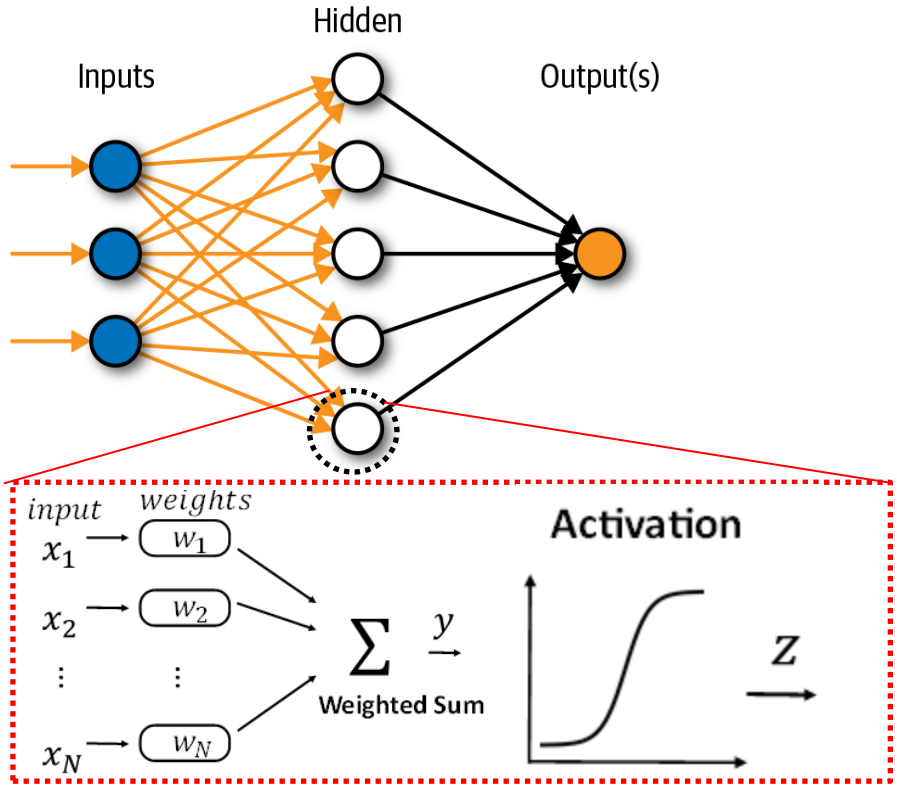
Eldar et al 2009

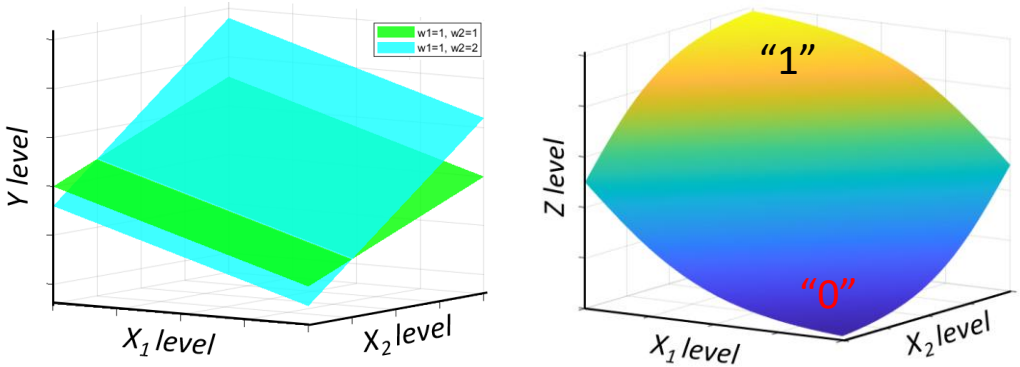




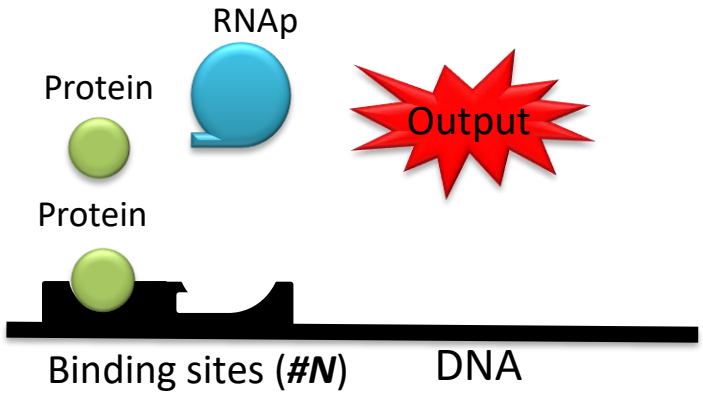
How cell science is getting an upgrade- Neuromorphic Computing

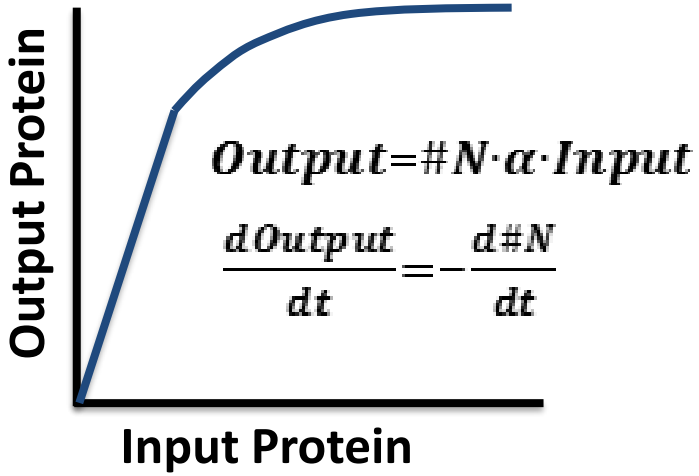
Neuromorphic Computing



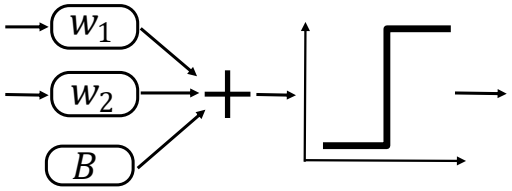


Cellular computing

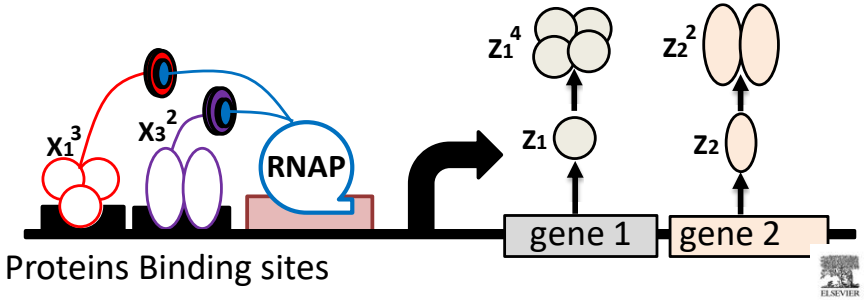




Neuromorphic Computing in living cells



Regulatory unit

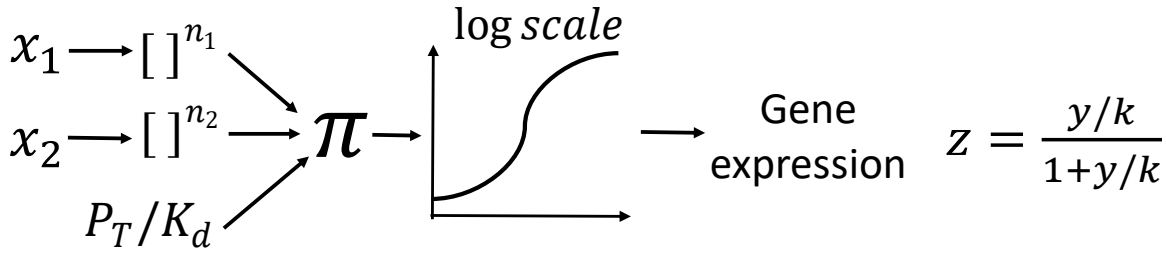


Proteins Binding sites

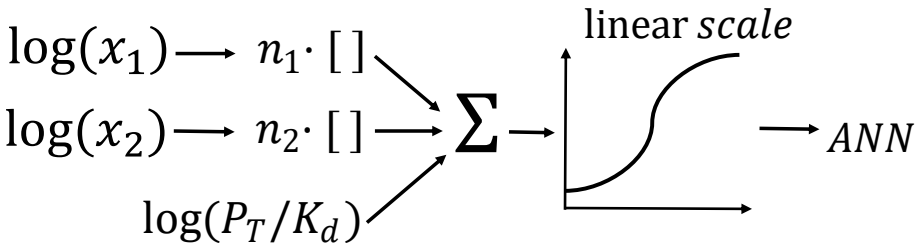
Transcriptional regulation by the numbers: models

Lacramioara Bintu[1], Nicolas E Buchler[2], Hernan G Garcia[3], Ulrich Gerland[4], Terence Hwa[5], Jané Kondev[1] and Rob Phillips[6]

Abstract model



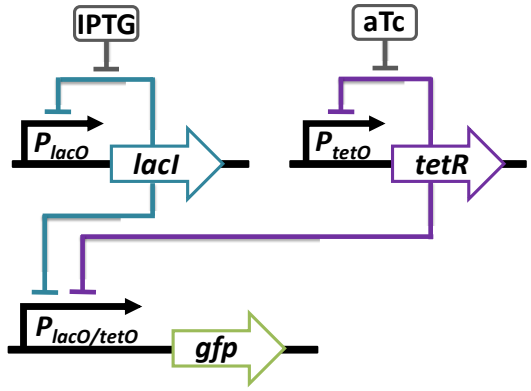
log-transform

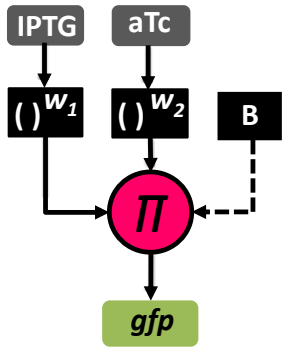


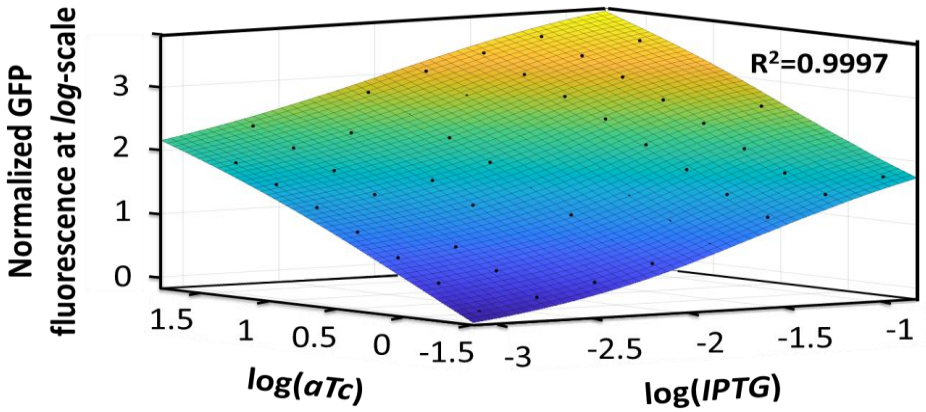
$$z = \frac{e^{y/k}}{1+e^{y/k}}$$

Weights, bias, activation functions, and optimization algorithms

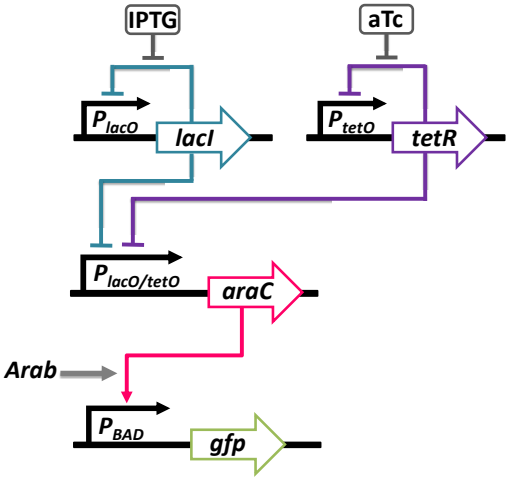
Neuromorphic Computing in genetic networks

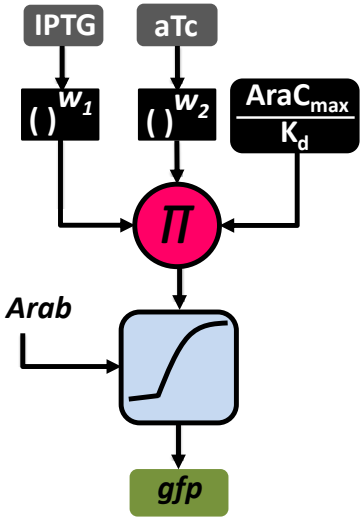


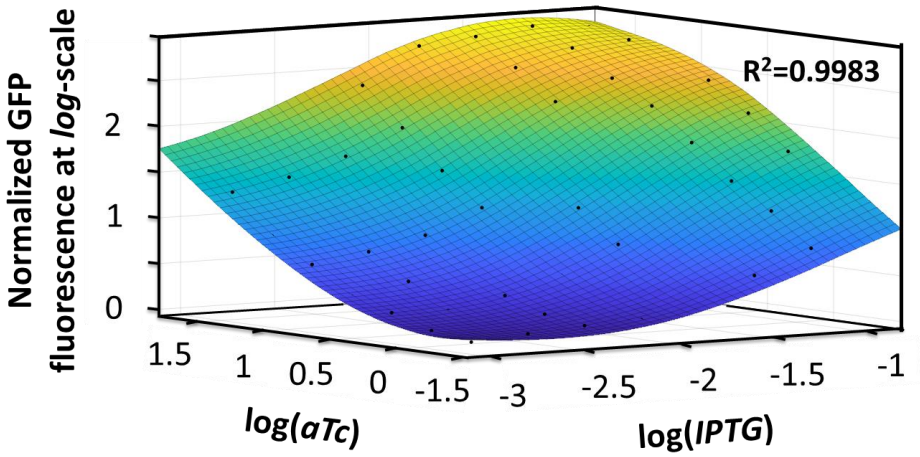




$$\log(GFP) = B + \frac{n_1 \cdot h_1}{n_1 + 1} \cdot log\left(\frac{IPTG}{K_{m1}}\right) + \frac{n_2 \cdot h_2}{n_2 + 1} \cdot log\left(\frac{aTc}{K_{m2}}\right)$$

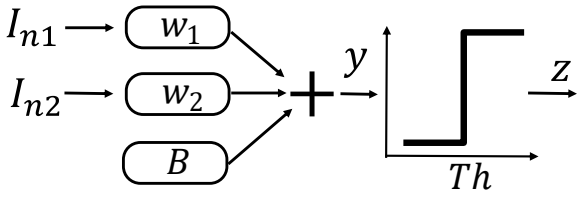






Rizik *et al., Nat. Comm 2022*

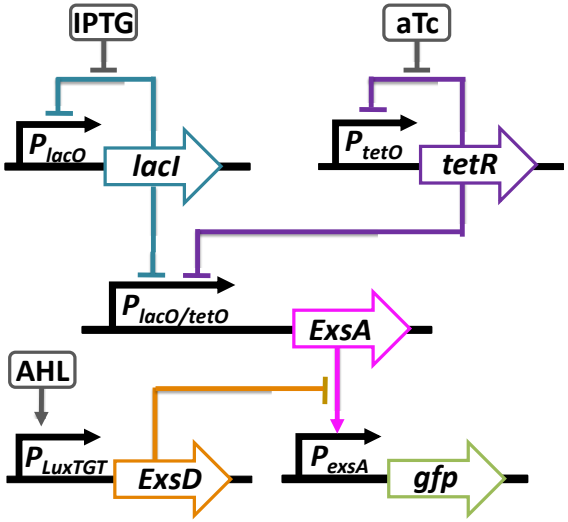
Adaptive gene circuits



I_{n1}	I_{2n}	Y	Z	Z
0	0	B	0	0
0	1	B+w_1	1	0
1	0	B+w_2	1	0
1	1	B+w_1+w_2	1	1

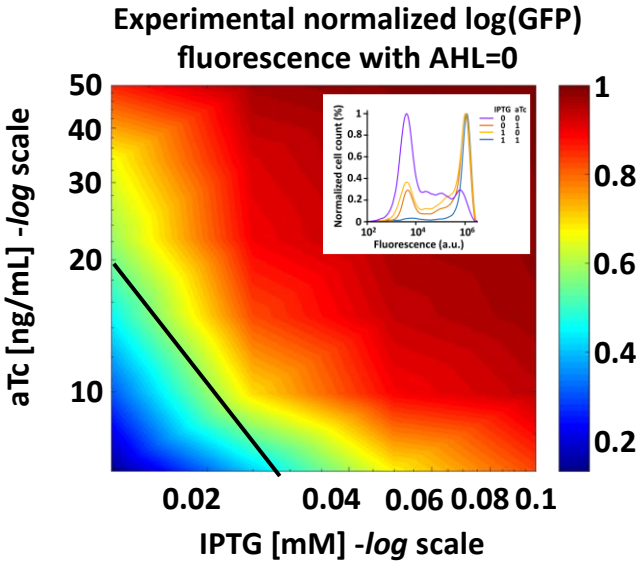
$$Y = w_1 \times I_{n1} + w_2 \times I_{n2} + \mathrm{B}$$

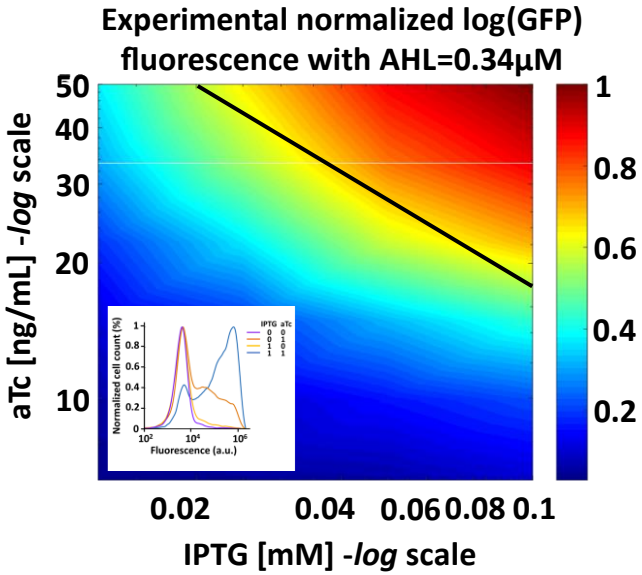
$$Z = \begin{cases} 0 & Y < Th \\ 1 & Y > Th \end{cases}$$



$$\boldsymbol{OR}: \quad (1)B + w > Th, (2)B < Th$$

$$\boldsymbol{AND}: (1)B + w < Th, (2)B + 2w > Th$$





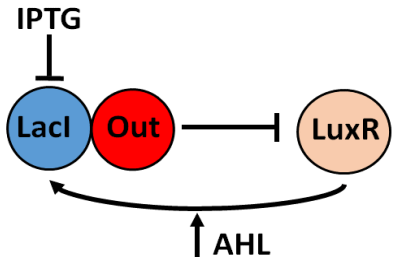
Dr. Muna Habib

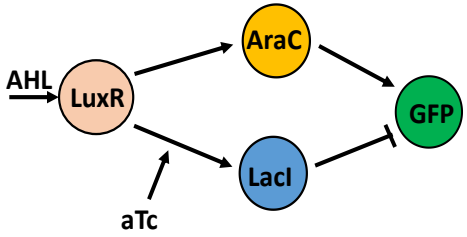
Rizik *et al., Nat. Comm 2022*

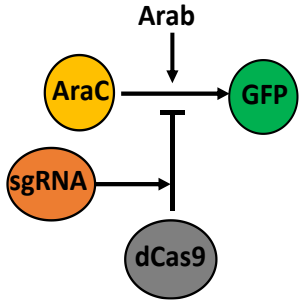
Design principles of molecular neuromorphic circuits

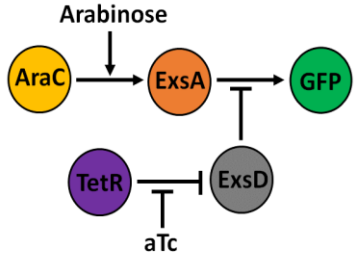
Weights and biases in neuromorphic circuits are determined by several factors:

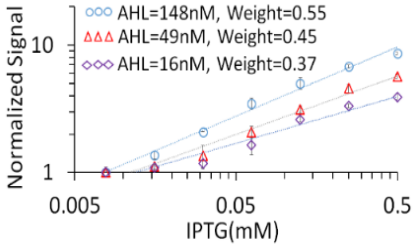
- Hill coefficients of small molecule inducers,
- Number and sequence of transcription factor binding sites,
- Negative feedback strength,
- Incoherent feedforward strength,
- Transcription factor sequestration
- Transcription factors that competitively inhibit expression via steric hindrance, operator sequence that controls binding affinity of transcription factor in open loop and positive feedback, activation via RNA-protein interactions , and protein structure (*e.g.*, dimerization and cooperativity)

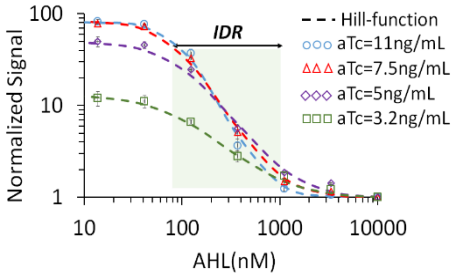


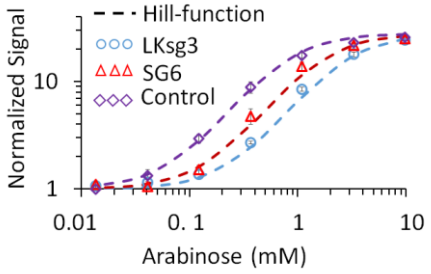


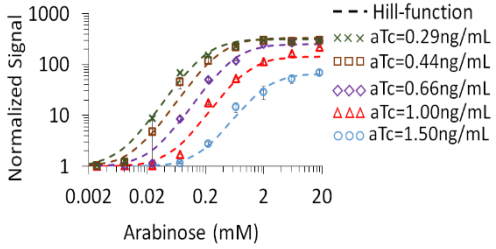




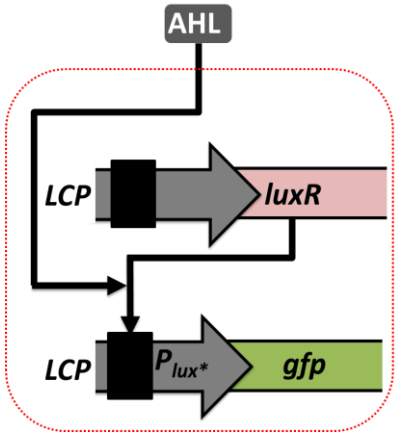




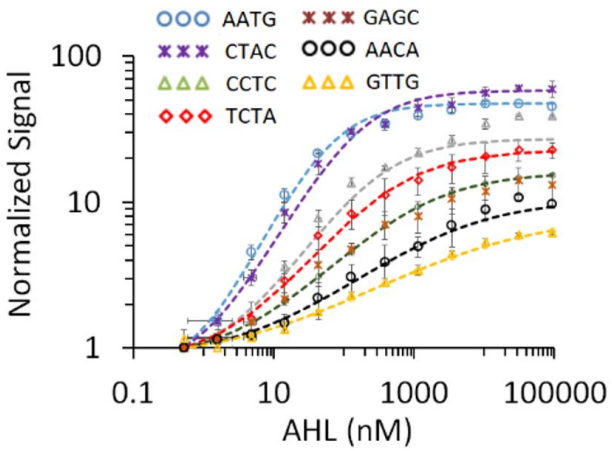


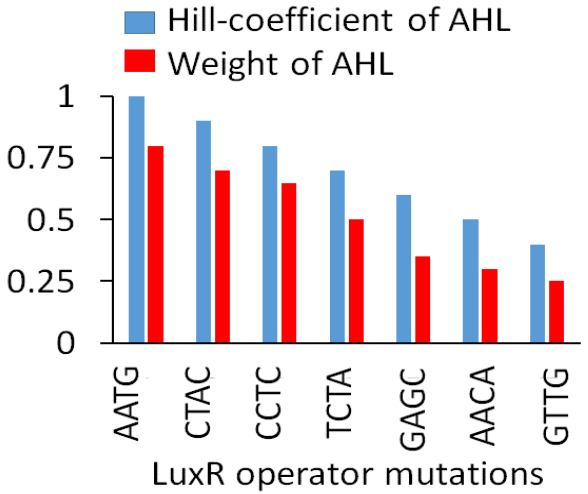


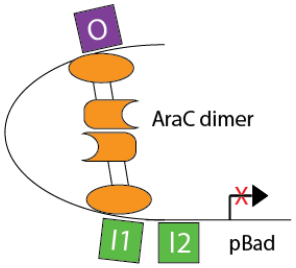
Control the design parameters

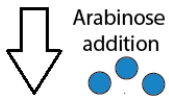


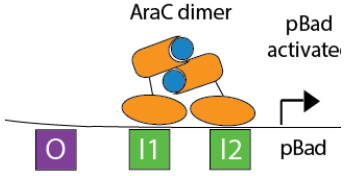
Open loop (OL)

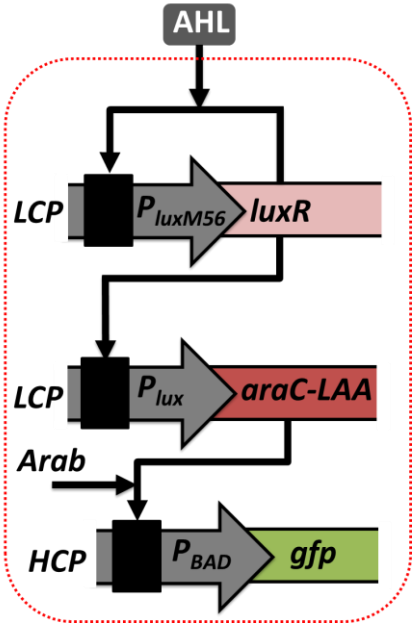


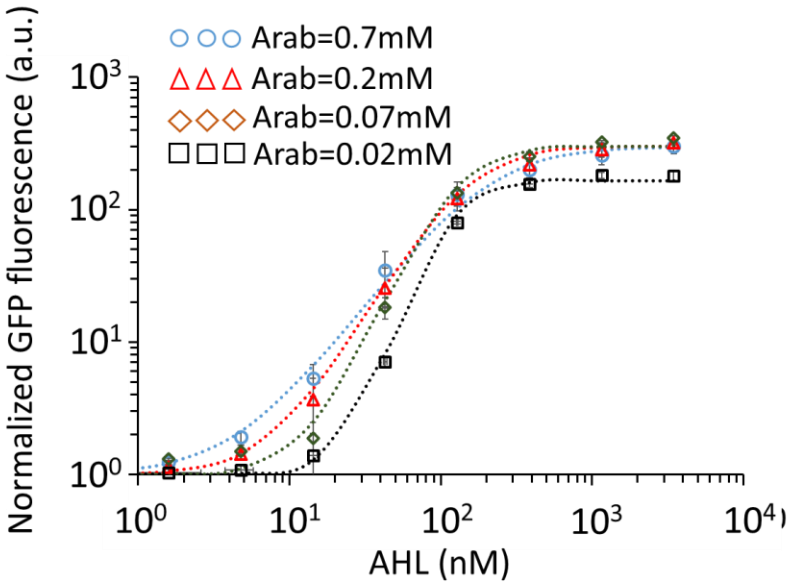






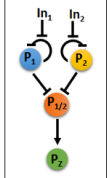
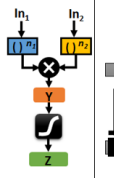
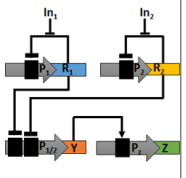
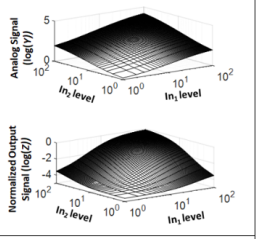




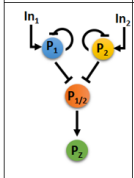
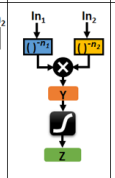
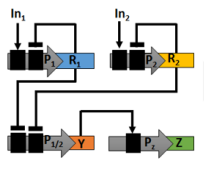
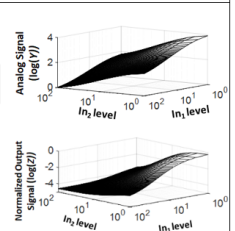


Design principles of genetic neuromorphic circuits

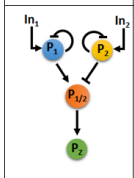
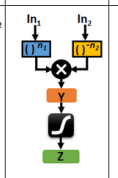
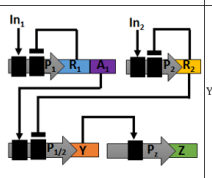
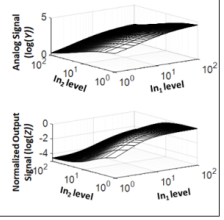
(a) Positive- weight perceptgene based dual repression system

Schematic design	Schematic block	Genetic design	Mathematical model at steady state	Simulation results
			$R_i = \frac{R_{Ti}}{\left(1+\left(\frac{In_i}{K_{mi}}\right)^{h_i}\right)}$ $R_{Ti} = \frac{\alpha_R \cdot \tau}{1+\left(\frac{R_i}{K_{di}}\right)^{n_i}}$ $Y = \frac{\alpha_Y \cdot \tau}{1+\left(\frac{R_1}{K_{d1}}\right)^{n_1}+\left(\frac{R_2}{K_{d2}}\right)^{n_2}+\left(\frac{R_1}{K_{d1}}\right)^{n_1}\cdot\left(\frac{R_2}{K_{d2}}\right)^{n_2}}$ $Z = \frac{\alpha_Z \cdot \tau \cdot \left(\left(\frac{Y}{K_d}\right)^m+\beta\right)}{1+\left(\frac{Y}{K_d}\right)^m}$ $K_{mi}=1,\ h_i=1.5, \alpha_R \cdot \tau=300, K_{di}=1,$ $n_i=1,\ m=2.5,\ \alpha_Y \cdot \tau=100, K_d=30, \beta=0.01$	

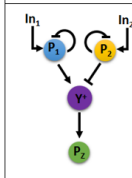
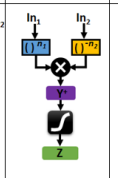
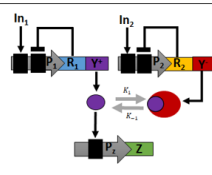
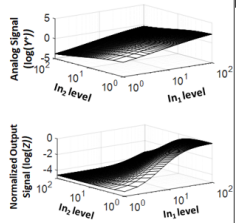
(b) Negative-weight perceptgene based dual repression

Schematic design	Schematic block	Genetic design	Mathematical model at steady state	Simulation results
			$R_i = \frac{\alpha_R \cdot \tau}{1+\left(\frac{R_i}{K_{di}}\right)^{n_i}} \cdot \frac{\left(\left(\frac{In_i}{K_{mi}}\right)^{h_i}+\beta_i\right)}{1+\left(\frac{In_i}{K_{mi}}\right)^{h_i}}$ $Y = \frac{\alpha_Y \cdot \tau}{1+\left(\frac{R_1}{K_{d1}}\right)^{n_1}+\left(\frac{R_2}{K_{d2}}\right)^{n_2}+\left(\frac{R_1}{K_{d1}}\right)^{n_1}\cdot\left(\frac{R_2}{K_{d2}}\right)^{n_2}}$ $Z = \frac{\alpha_Z \cdot \tau \cdot \left(\left(\frac{Y}{K_d}\right)^m+\beta\right)}{1+\left(\frac{Y}{K_d}\right)^m}$ $K_{mi}=100,\ h_i=1.5, \alpha_R \cdot \tau=300, K_{di}=1,$ $n_i=1,\ m=2.5,\ \alpha_Y \cdot \tau=100, K_d=30, \beta=0.01$	

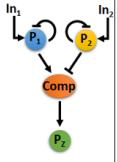
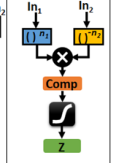
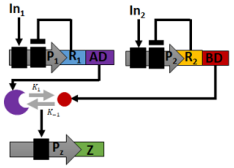
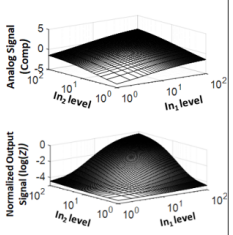
(c) Perceptgene based hybrid activation-repression system

Schematic design	Schematic block	Genetic design	Mathematical model at steady state	Simulation results
			$R_i = \frac{\alpha_R \cdot \tau}{1+\left(\frac{R_i}{K_{di}}\right)^{n_i}} \cdot \frac{\left(\left(\frac{In_i}{K_{mi}}\right)^{h_i}+\beta_i\right)}{1+\left(\frac{In_i}{K_{mi}}\right)^{h_i}}$ $A_1 = g_1 \cdot R_1$ $Y = \frac{\alpha_Y \cdot \tau \cdot \left(\left(\frac{A_1}{K_{da1}}\right)^{n_1}+\beta\right)}{1+\left(\frac{A_1}{K_{da1}}\right)^{n_1}+\left(\frac{R_2}{K_{d2}}\right)^{n_2}+\left(\frac{A_1}{K_{da1}}\right)^{n_1}\cdot\left(\frac{R_2}{K_{d2}}\right)^{n_2}}$ $Z = \frac{\alpha_Z \cdot \tau \cdot \left(\left(\frac{Y}{K_d}\right)^m+\beta\right)}{1+\left(\frac{Y}{K_d}\right)^m}$ $K_{mi}=100,\ h_i=1.5, \alpha_R \cdot \tau=300, g_1=1, K_{di}=1$ $n_i=1,\ m=2.5,\ \alpha_Y \cdot \tau=200, K_{da1}=5, K_d=30,$ $\beta=0.01$	

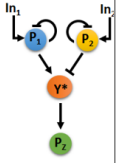
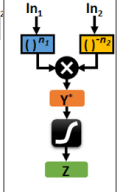
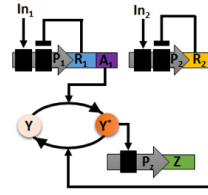
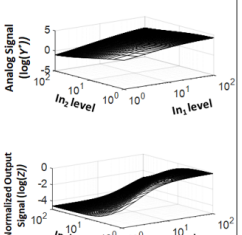
(d) Perceptgene based protein sequestration system

Schematic design	Schematic block	Genetic design	Mathematical model at steady state	Simulation results
			$R_i = \frac{\alpha_R \cdot \tau}{1+\left(\frac{R_i}{K_{di}}\right)^{n_i}} \cdot \frac{\left(\left(\frac{In_i}{K_{mi}}\right)^{h_i}+\beta_i\right)}{1+\left(\frac{In_i}{K_{mi}}\right)^{h_i}}$ $Y_T^+ = g_1 \cdot R_1$ $Y_T^- = g_2 \cdot R_2$ $C = \frac{K_{mc}+Y_T^++Y_T^-}{2} - \frac{\sqrt{(K_{mc}+Y_T^++Y_T^-)^2-4 \cdot Y_T^+ \cdot Y_T^-}}{2}$ $Y^+ = Y_T^+ - C$ $K_{mc} = K_{-1}/K_1$ $Z = \frac{\alpha_Z \cdot \tau \cdot \left(\left(\frac{Y^+}{K_d}\right)^m+\beta\right)}{1+\left(\frac{Y^+}{K_d}\right)^m}$ $K_{mi}=100,\ h_i=1.5, \alpha_R \cdot \tau=300, g_1=1,$ $g_2=15\ K_{di}=1,\ n_i=1, K_{mc}=$ $10,\ m=2.5, K_d=3, \beta=0.01$	

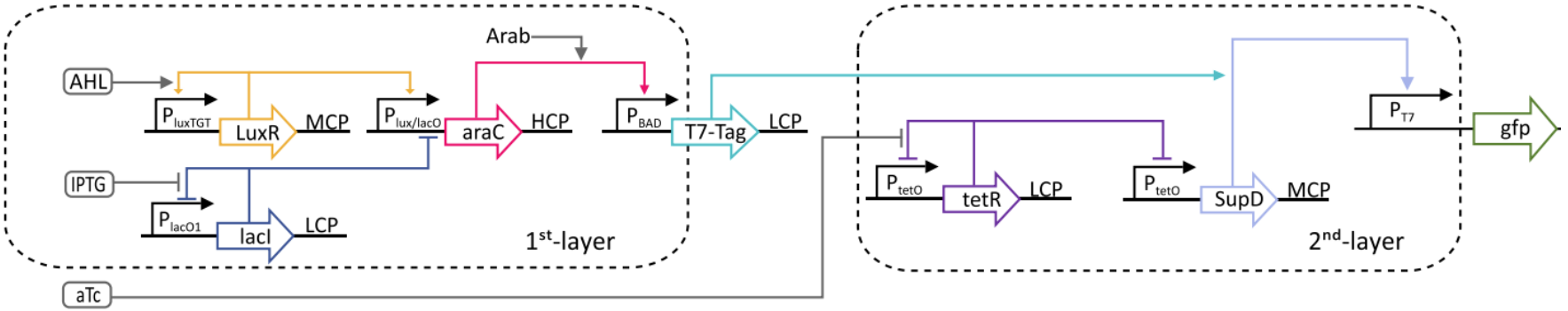
(e) Perceptgene based fusion protein system

Schematic design	Schematic block	Genetic design	Mathematical model at steady state	Simulation results
			$R_i = \frac{\alpha_R \cdot \tau}{1+\left(\frac{R_i}{K_{di}}\right)^{n_i}} \cdot \frac{\left(\left(\frac{In_i}{K_{mi}}\right)^{h_i}+\beta_i\right)}{1+\left(\frac{In_i}{K_{mi}}\right)^{h_i}}$ $AD_T = g_1 \cdot R_1$ $BD_T = g_2 \cdot R_2$ $Comp = \frac{K_m+AD_T+BD_T}{2} - \frac{\sqrt{(K_{mc}+AD_T+BD_T)^2-4 \cdot AD_T}}{2}$ $K_{mc} = K_{-1}/K_1$ $Z = \frac{\alpha_Z \cdot \tau \cdot \left(\left(\frac{C}{K_d}\right)^m+\beta\right)}{1+\left(\frac{C}{K_d}\right)^m}$ $K_{mi}=100,\ h_i=1.5, \alpha_R \cdot \tau=300,$ $g_1=1, g_2=1, K_{di}=1,\ n_i=1,$ $K_{mc}=10,\ m=2.5, K_d=3, \beta=0.01$	

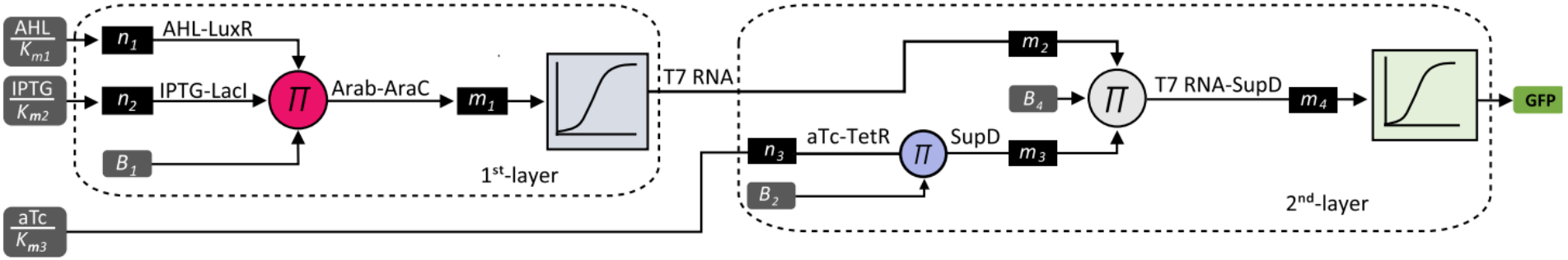
(f) Perceptgene based two-component regulatory system

Schematic design	Schematic block	Genetic design	Mathematical model at steady state	Simulation results
			$R_i = \frac{\alpha_R \cdot \tau}{1+\left(\frac{R_i}{K_{di}}\right)^{n_i}} \cdot \frac{\left(\left(\frac{In_i}{K_{mi}}\right)^{h_i}+\beta_i\right)}{1+\left(\frac{In_i}{K_{mi}}\right)^{h_i}}$ $A_i = g_i \cdot R_i$ $Y^* = Y_T \frac{\frac{A_1}{K_{a1}}\frac{A_2}{K_{a2}}}{\frac{A_1}{K_{a1}}\frac{A_2}{K_{a2}}+1}$ $K_{mc} = K_{-1}/K_1$ $Z = \frac{\alpha_Z \cdot \tau \cdot \left(\left(\frac{Y^*}{K_d}\right)^m+\beta\right)}{1+\left(\frac{Y^*}{K_d}\right)^m}$ $K_{mi}=100,\ h_i=1.5, \alpha_R \cdot \tau=300,$ $g_1=1, g_2=1, K_{di}=1,\ n_i=$ $1, Y_T=100, K_{mc}=10, m=2.5,$ $K_d=30, \beta=0.01$	

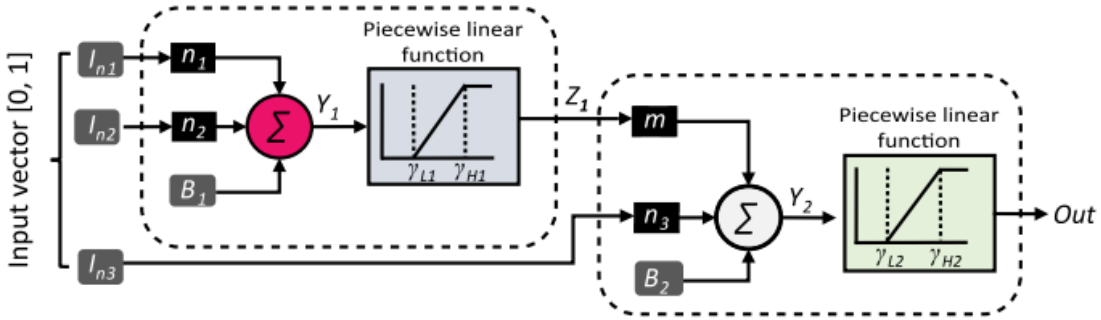
Multilayer networks



Neural network in log domain



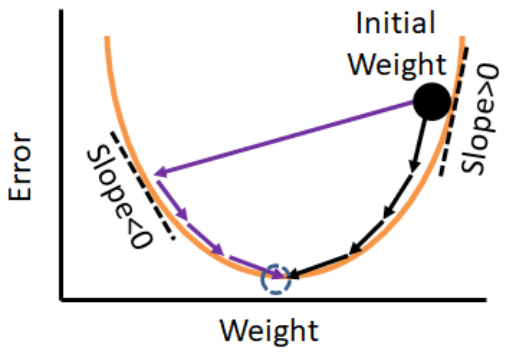
Neural network

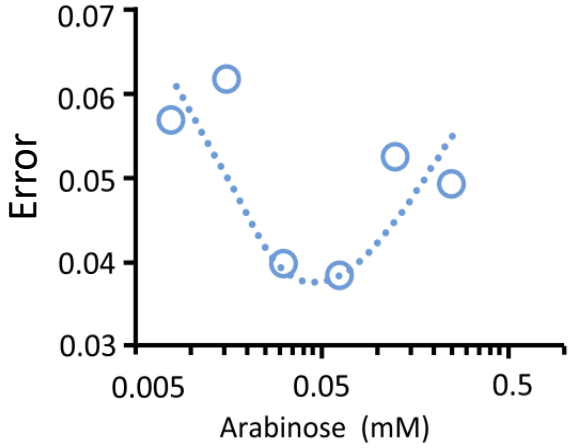


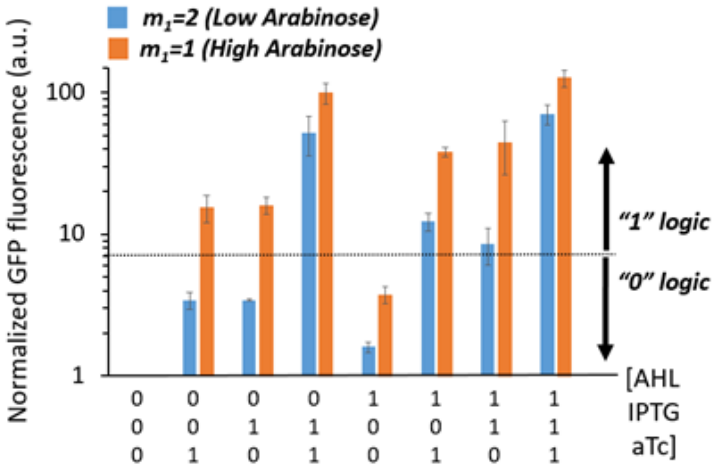
I_{n1}	I_{n2}	I_{n3}	Out
0	0	0	0
0	0	1	0
0	1	0	0
0	**1**	**1**	**1**
1	0	0	0
1	**0**	**1**	**1**
1	**1**	**0**	**1**
1	**1**	**1**	**1**

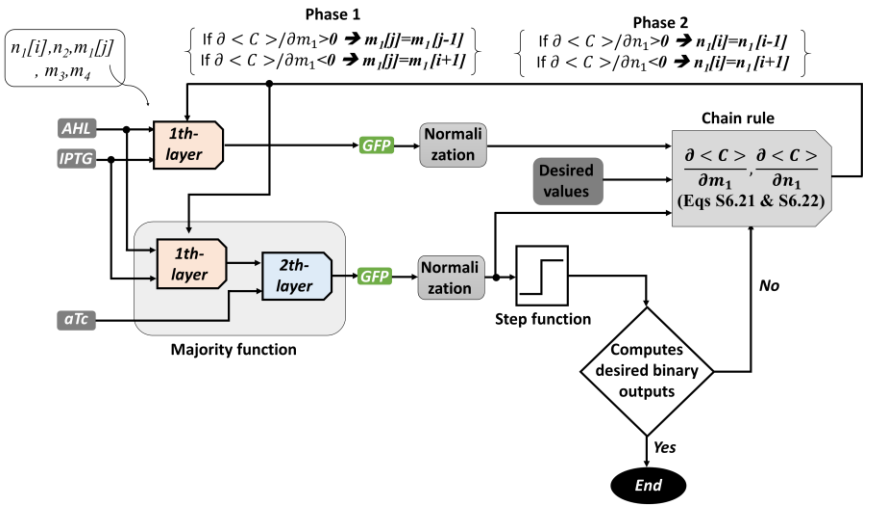
AI (optimization) algorithm

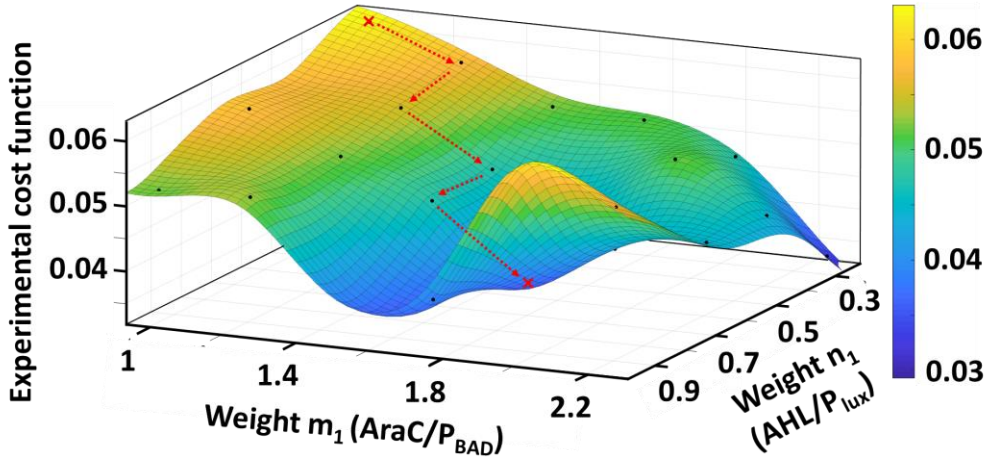
$$Error = \frac{(Meaured - Desired)^2}{2}$$





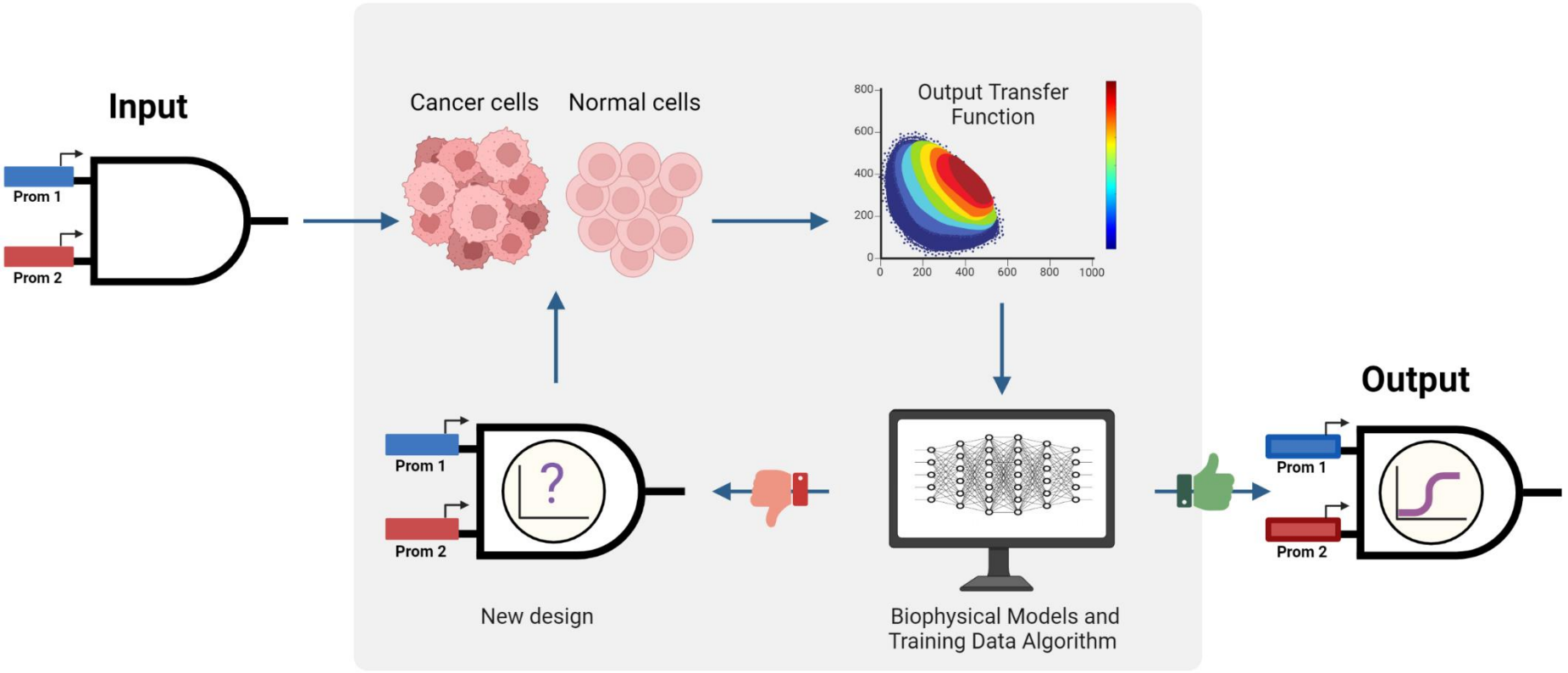






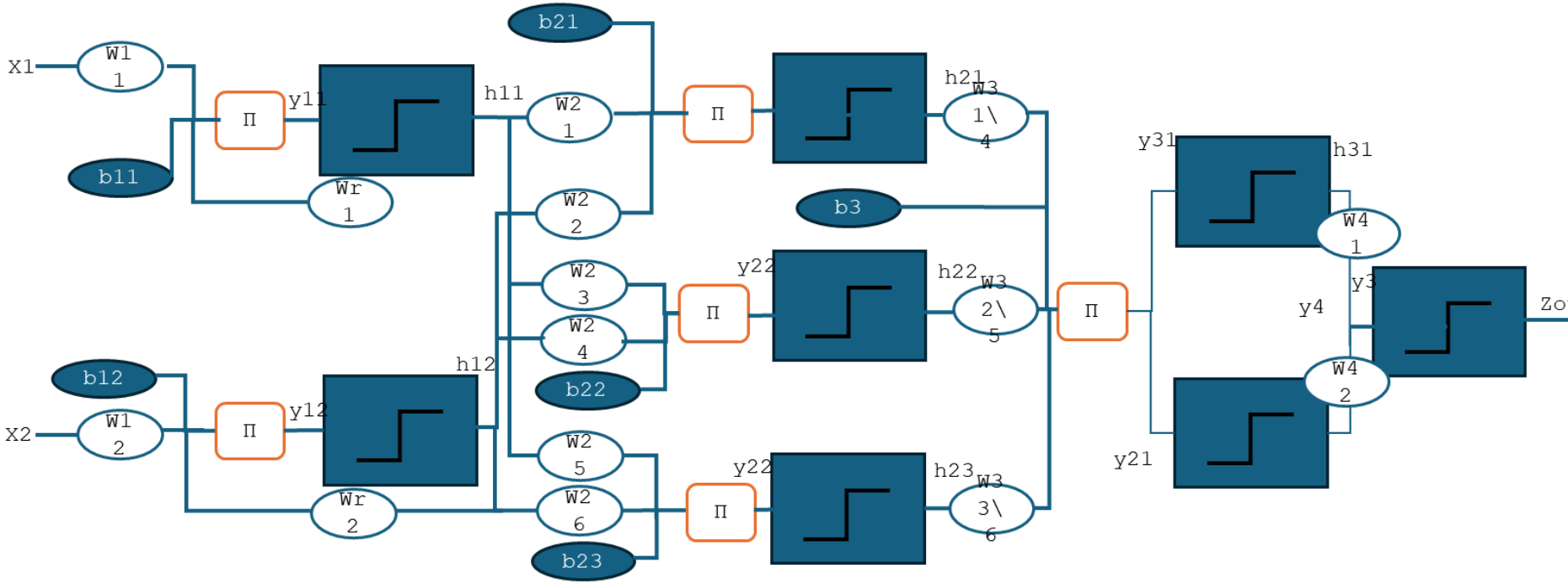
ARTIFICIAL NEURAL NETWORK (ANN) BASED DESIGNS:

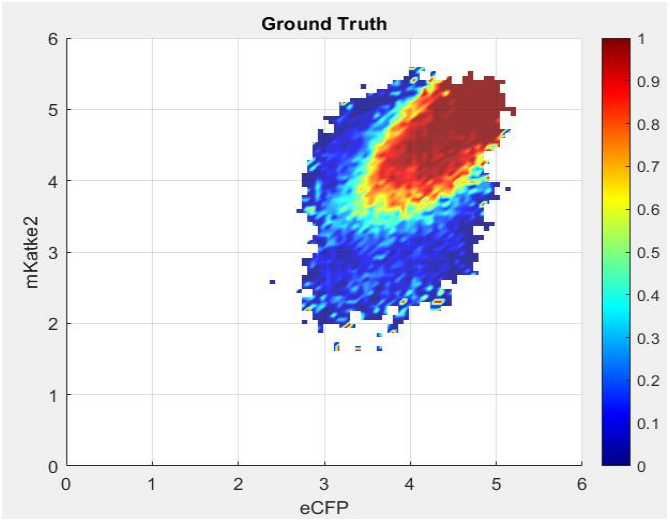
AI-based Optimization

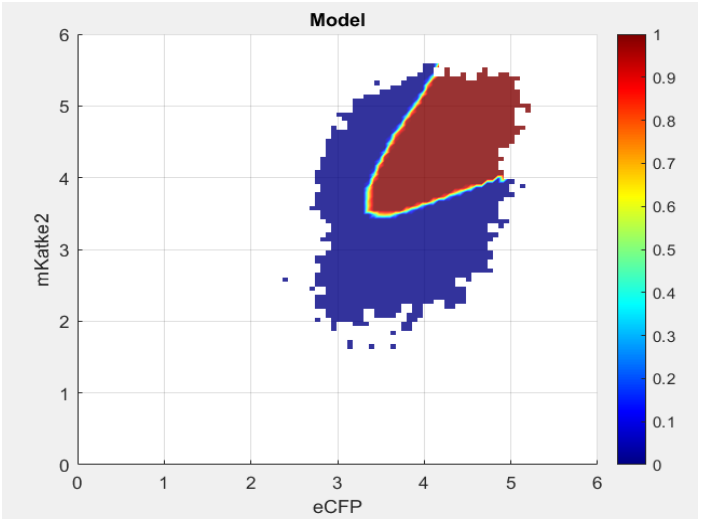


In Collaboration with Prof. Lior Nissim, Hebrew University

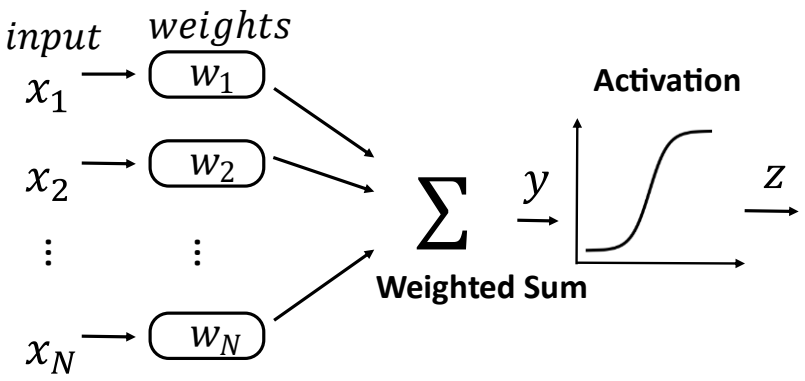
AI-based Optimization

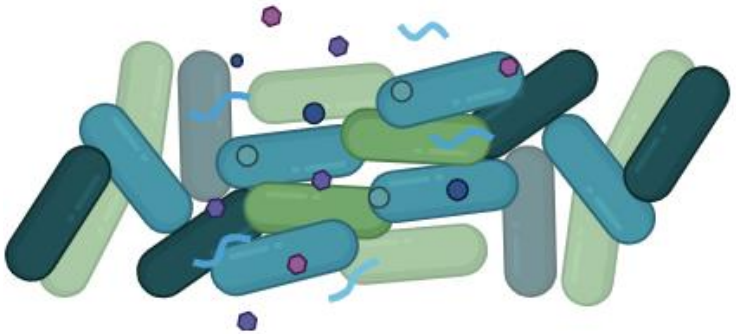






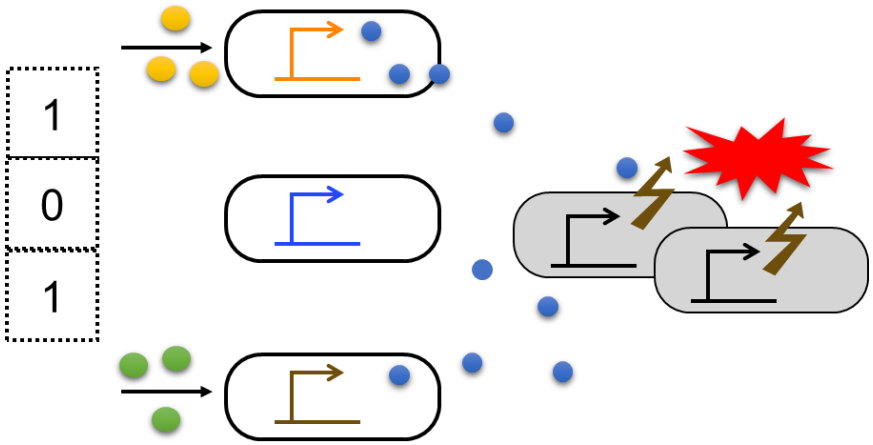
Bacteria consortia for classification of chemical patterns





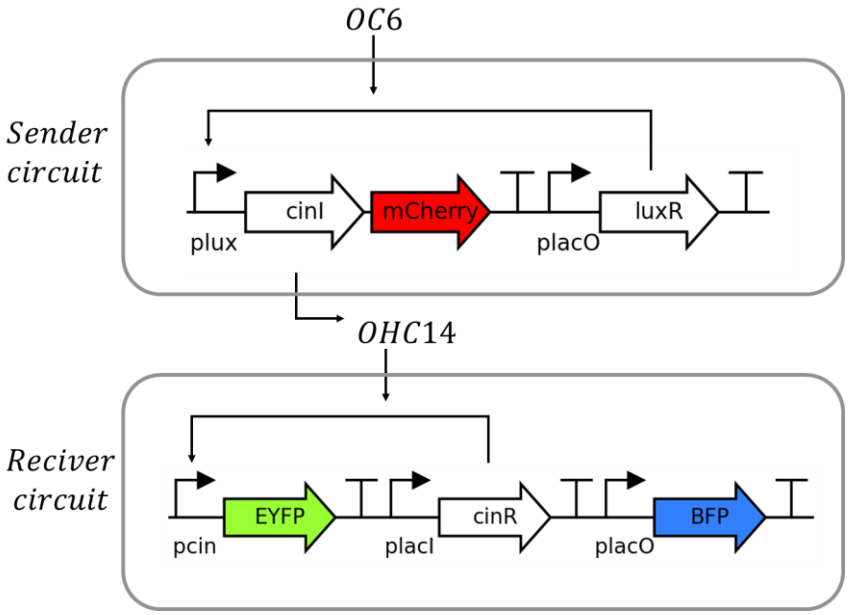
Dr. Ximing Li

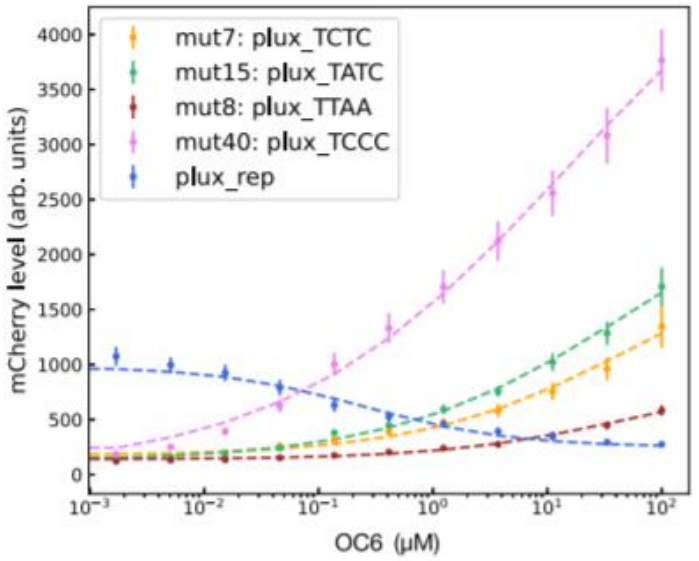
Quorum sensing is the way how bacterial cells communicate and coordinate with each other as an individual or several groups

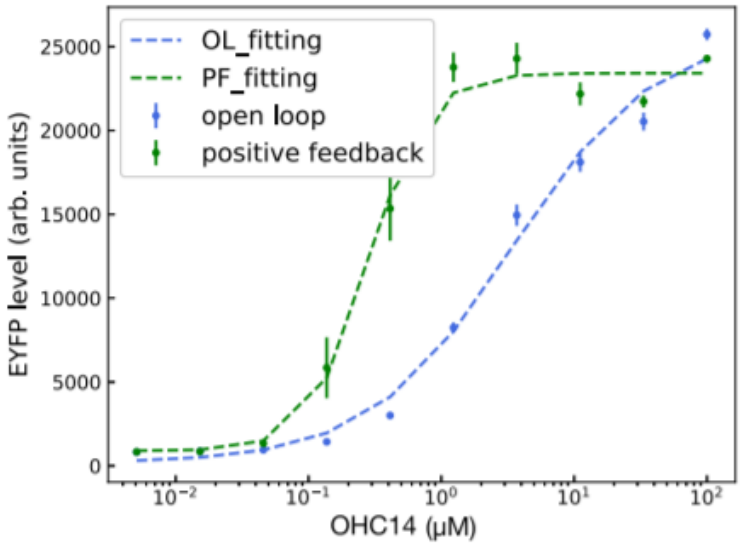


Ximing et al., Nat. Comm 2021,

Bacteria consortia for classification of chemical patterns

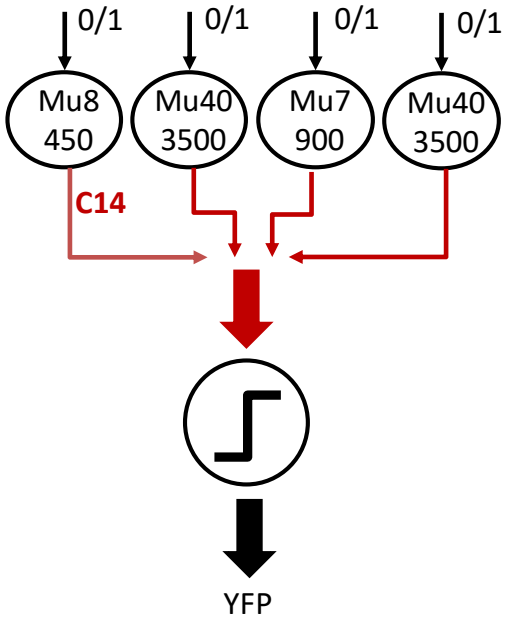






Ximing et al., Nat. Comm 2021

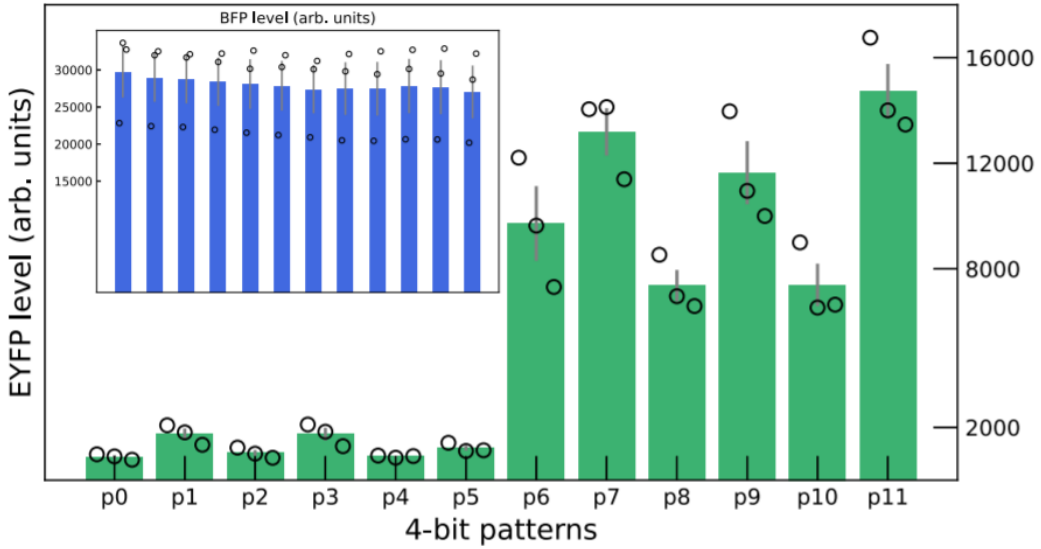
Bacteria consortia for classification of chemical patterns

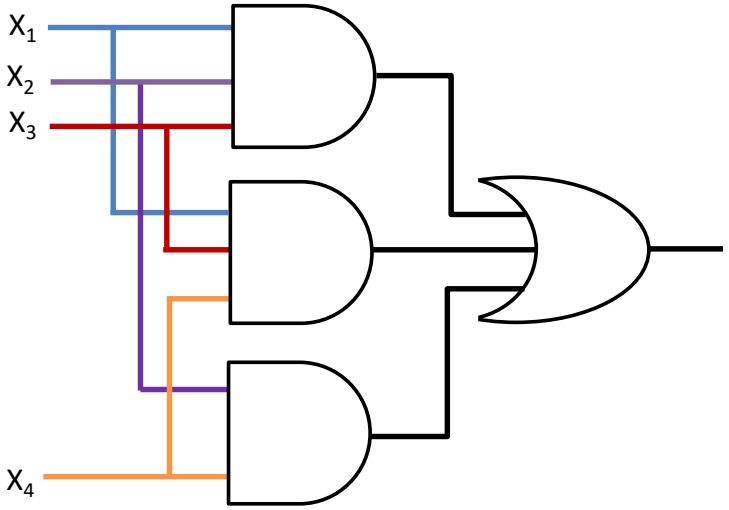


pattern set0		$\vec{w}^T \cdot \vec{p}$
p0 [0, 0, 0, 0]		0
p1 [0, 0, 0, 1]		3500
p2 [0, 0, 1, 0]		900
p3 [0, 1, 0, 0]		3500
p4 [1, 0, 0, 0]		450
p5 [1, 0, 1, 0]		1350

pattern set1		$\vec{w}^T \cdot \vec{p}$
p6 [0, 1, 0, 1]		7000
p7 [0, 1, 1, 1]		7900
p8 [1, 0, 1, 1]		4850
p9 [1, 1, 0, 1]		7450
p10 [1, 1, 1, 0]		4850
p11 [1, 1, 1, 1]		8350

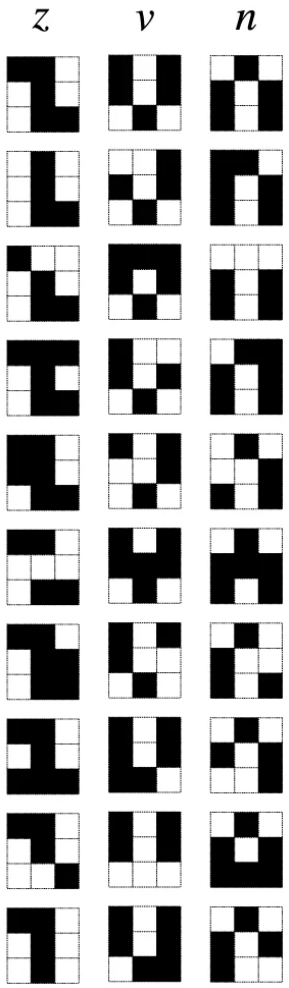
$\vec{w}$ = [450, 3500, 900, 3500]=[mut8, mut40, mut7, mut40]





Ximing et al., Nat. Comm 2021

Bacteria consortia for classification of chemical patterns 3×3



AI algorithm & Biophysical models

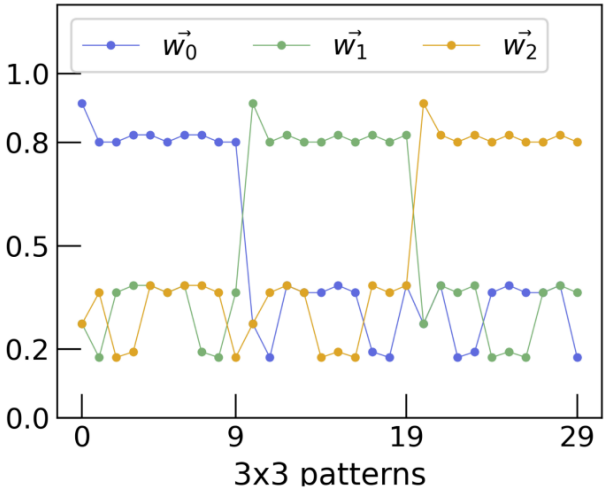
$\vec{w}_0 = [1906,\ 1906,\ -735,\ -735,\ 1906,\ -735,\ -735,\ 1906,\ 1906]$
$\vec{w}_1 = [1906,\ -735,\ 1906,\ 1906,\ -735,\ 1906,\ -735,\ 1906,\ -735]$
$\vec{w}_2 = [-735,\ 1906,\ -735,\ 1906,\ -735,\ 1906,\ 1906,\ -735,\ 1906]$

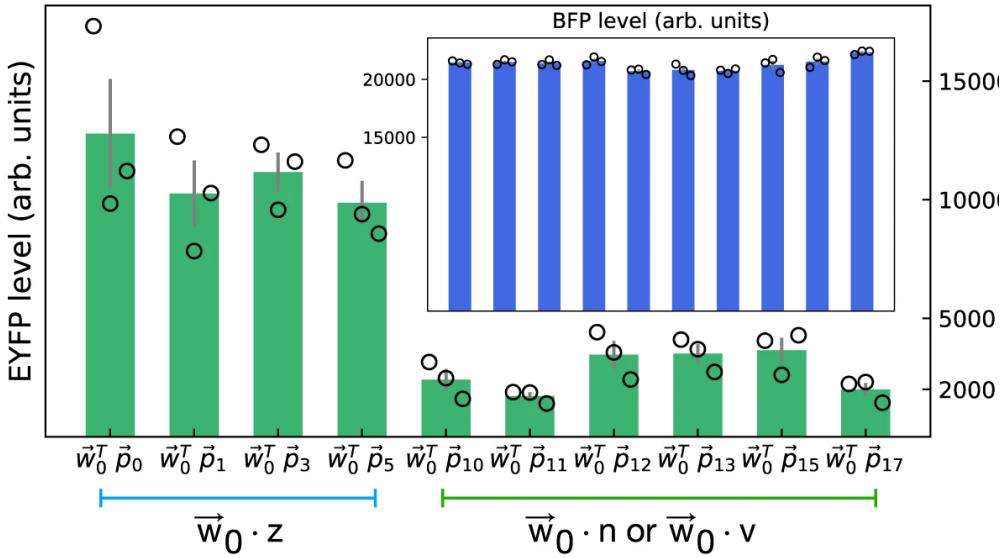
$P_j \times w_i$

$\vec{t}_0 = [H\,H\,H\,H\,H\,H\,H\,H\,H$
$L\,L\,L\,L\,L\,L\,L\,L\,L$
$L\,L\,L\,L\,L\,L\,L\,L\,L]$

$\vec{t}_1 = [L\,L\,L\,L\,L\,L\,L\,L\,L$
$H\,H\,H\,H\,H\,H\,H\,H\,H$
$L\,L\,L\,L\,L\,L\,L\,L\,L]$

$\vec{t}_2 = [L\,L\,L\,L\,L\,L\,L\,L\,L$
$L\,L\,L\,L\,L\,L\,L\,L\,L$
$H\,H\,H\,H\,H\,H\,H\,H\,H]$



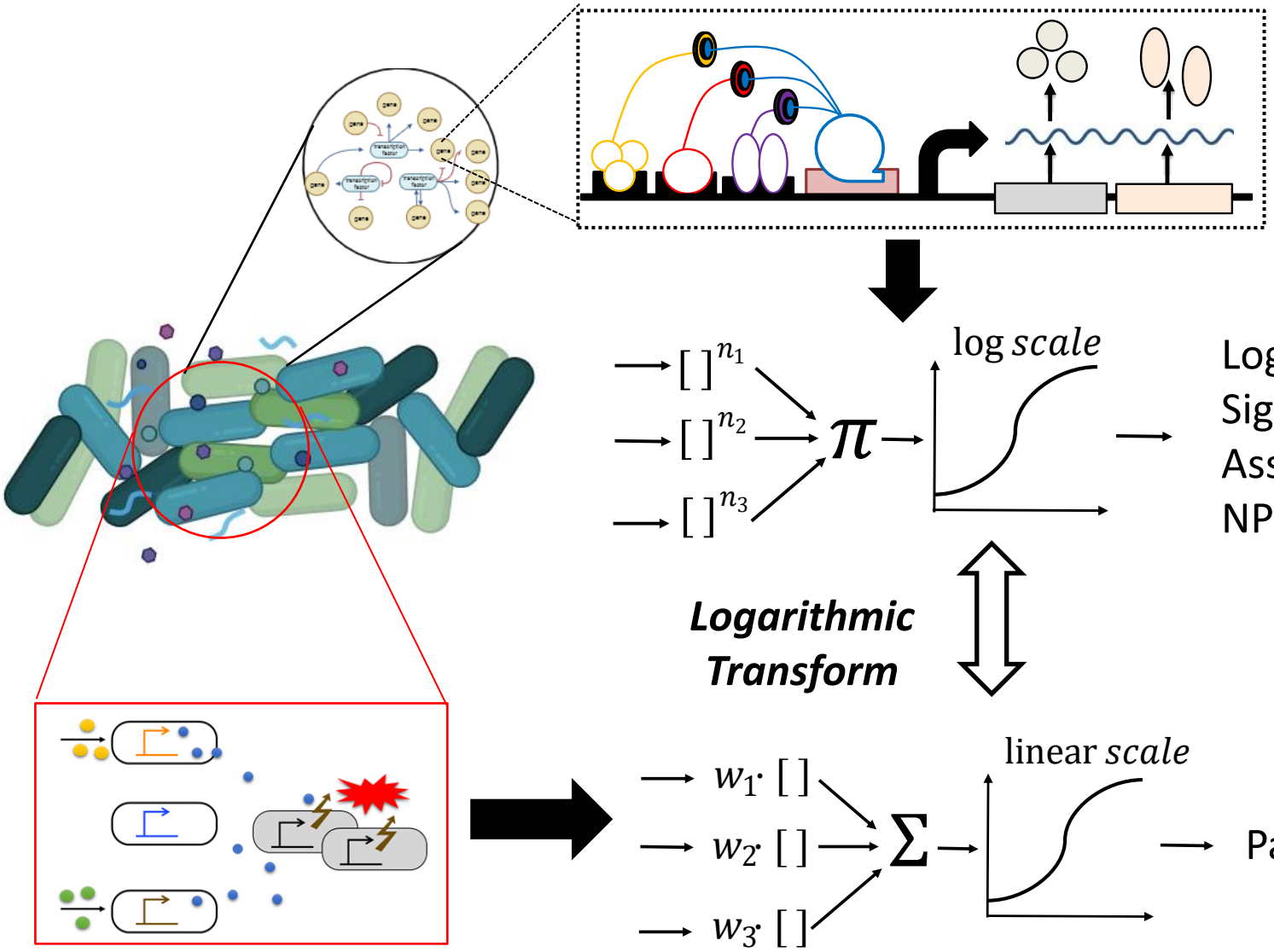


Ximing et al., Nat. Comm 2021,

Conclusions

Implementation of artificial neural networks into genetic circuits and cells

➔ Biological Intelligence (BI)



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