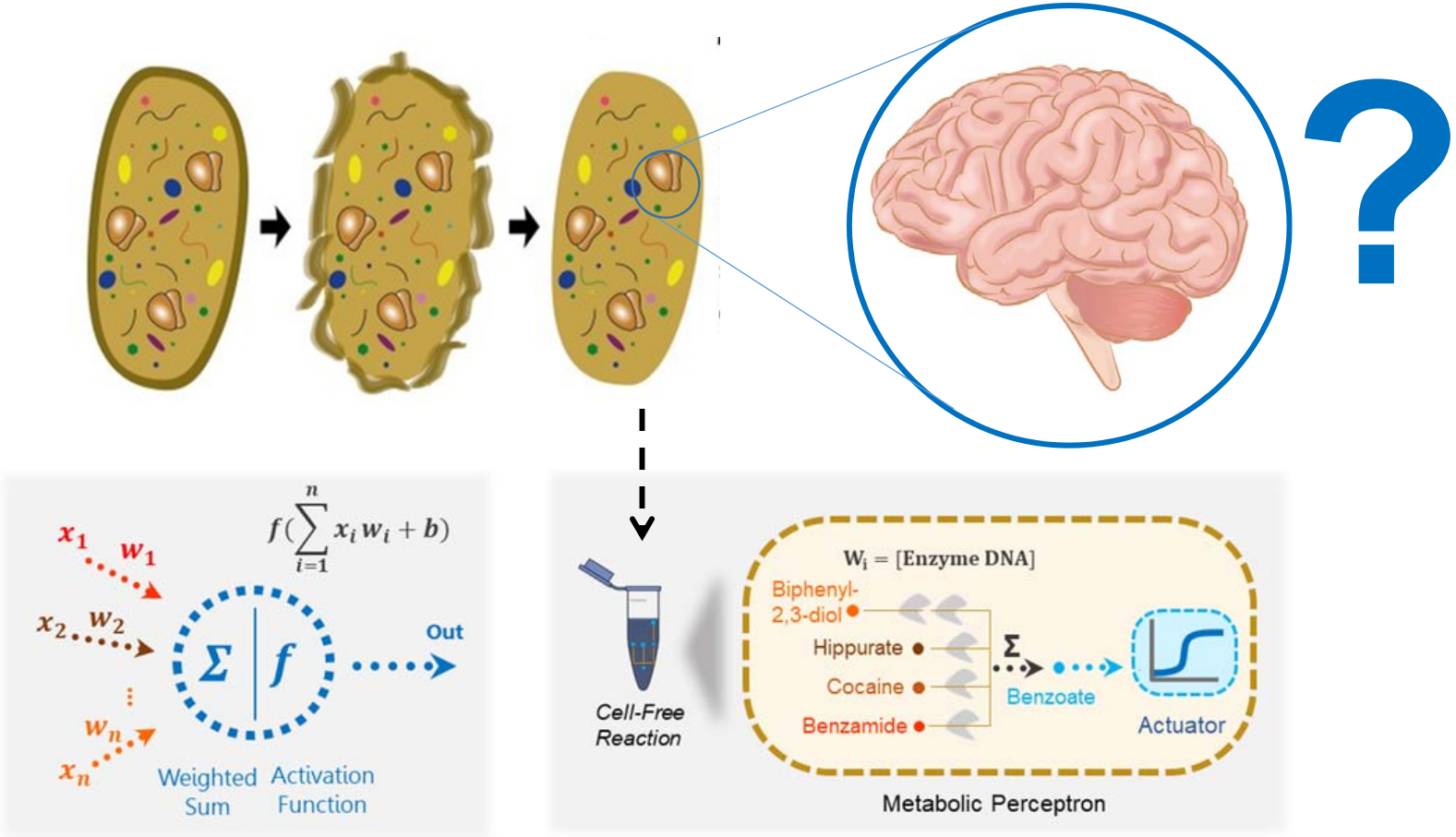
The Thinking Dead: using cell-free systems for decision-making circuits

Manish Kushwaha

The Thinking Dead: using cell-free systems for decision-making circuits



Manish Kushwaha

iGEM 2021 French Meetup

11 September 2021

Thinking is information processing

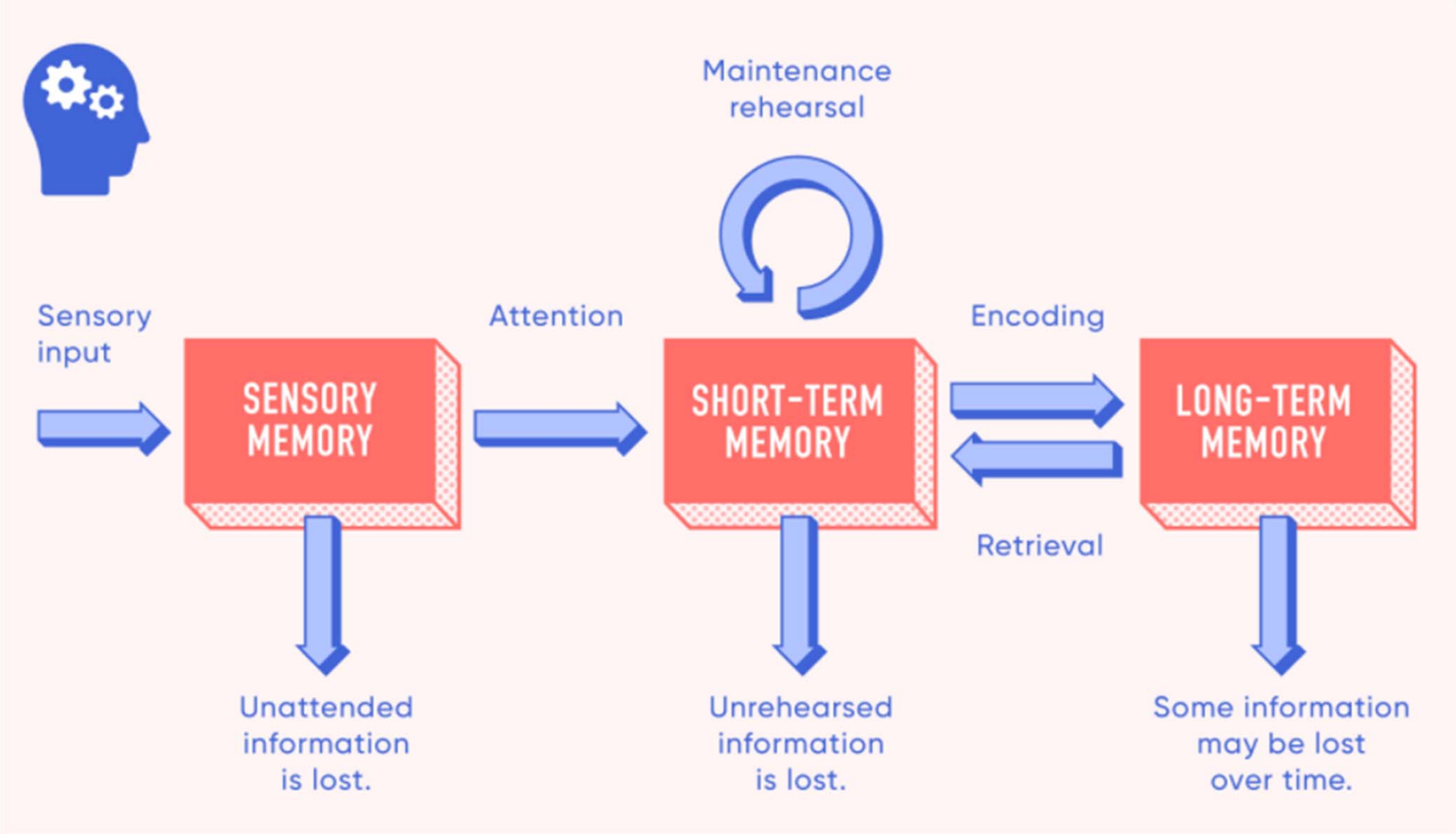


Image Credit: LearnUpon.com

Information Processing Theory (George Miller)

Learning = training to think

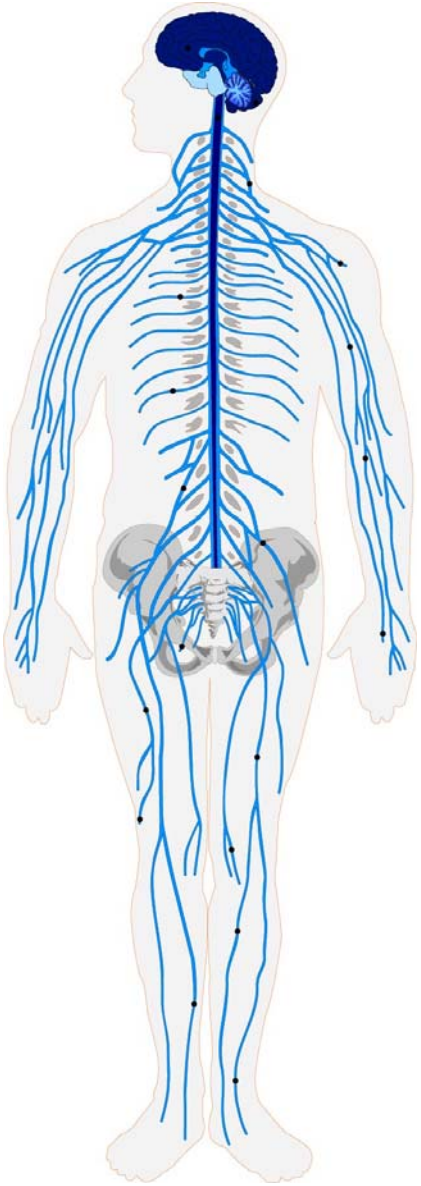
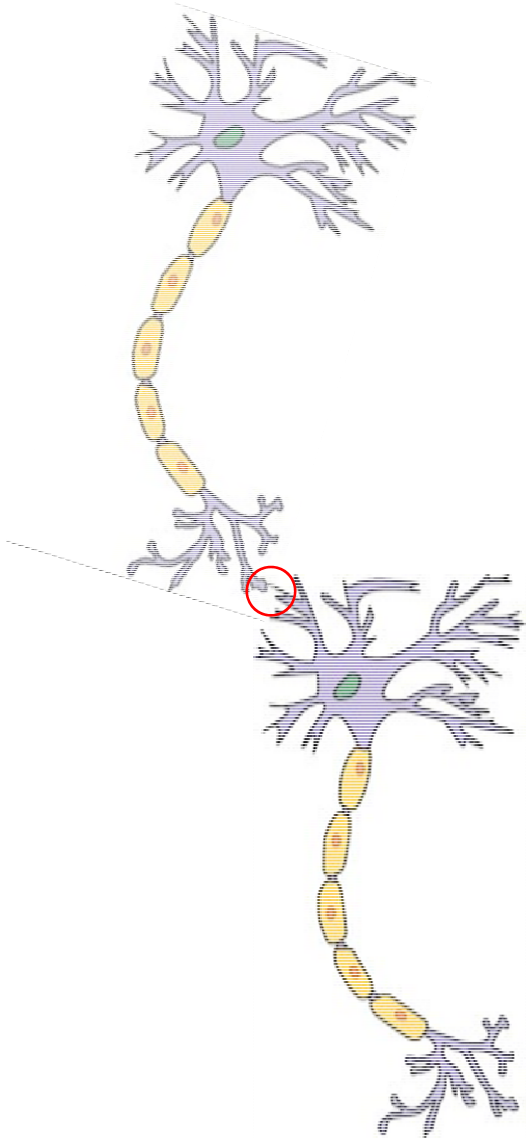
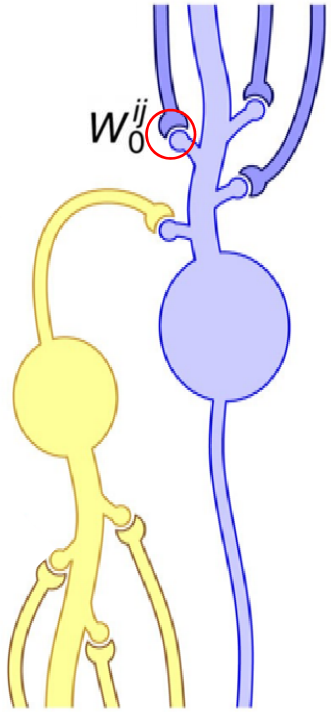


Image Credits: Wikipedia Commons

The Human Nervous System

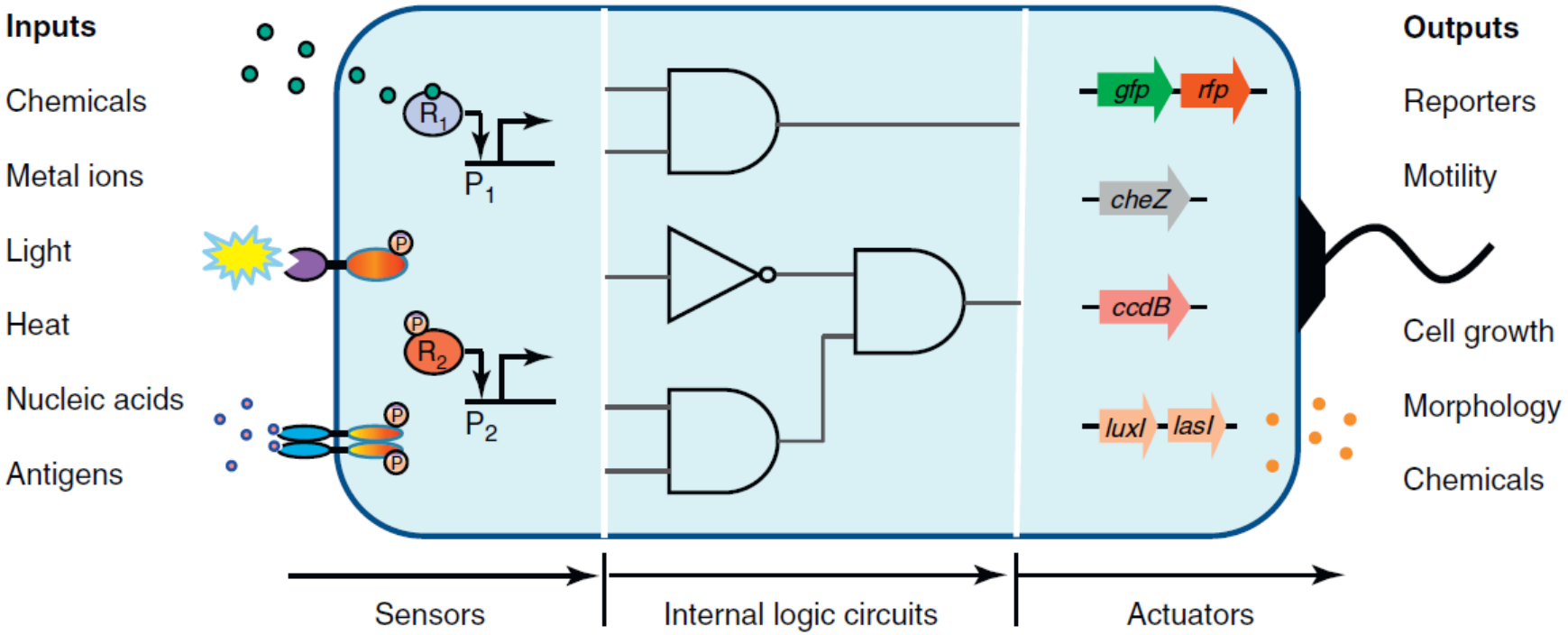


The Neurons



Lillicrap *et al.*, 2016. Nat Comm.

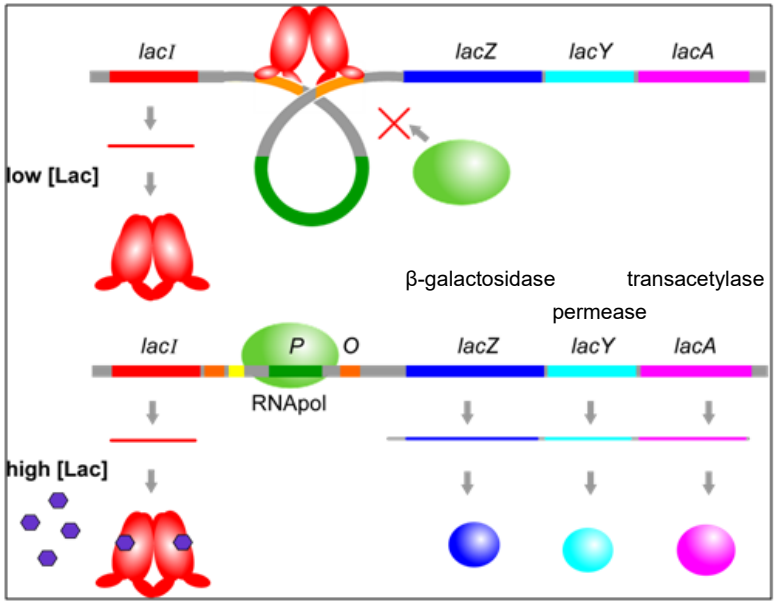
Cells process a diverse range of information



- Cells process a wide variety of extracellular and intracellular information.

(Wang & Buck, 2012. Trends in Microbiology)

Cells are like computers

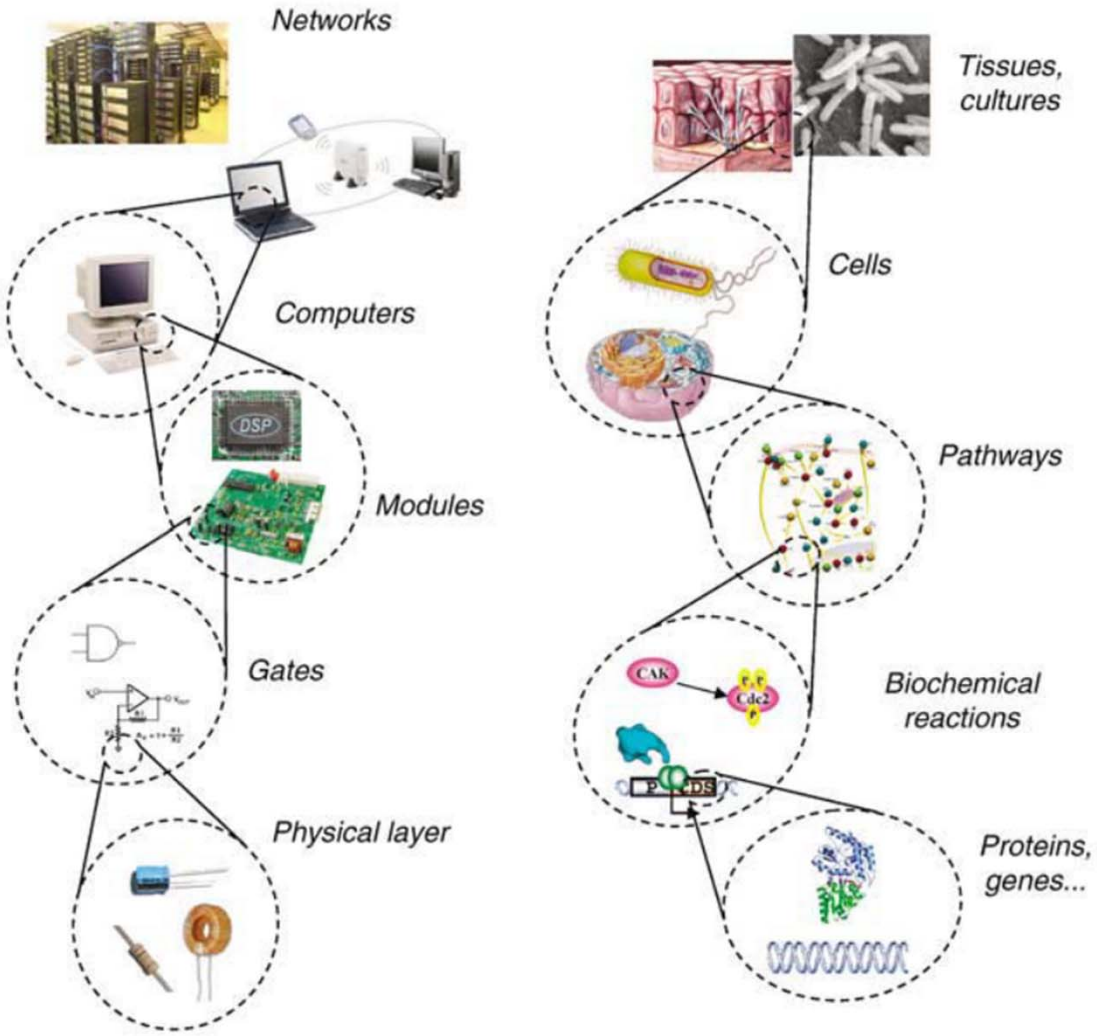


Deyholos-CC:AN

"... Thus the logic of this system is simple in the extreme: the repressor inactivates transcription; it is inactivated in its turn by the inducer. From this double negation results a positive effect, an "affirmation".... The logic of biological regulatory systems abides not by Hegelian laws but, like the workings of computers, by the propositional algebra of George Boole."

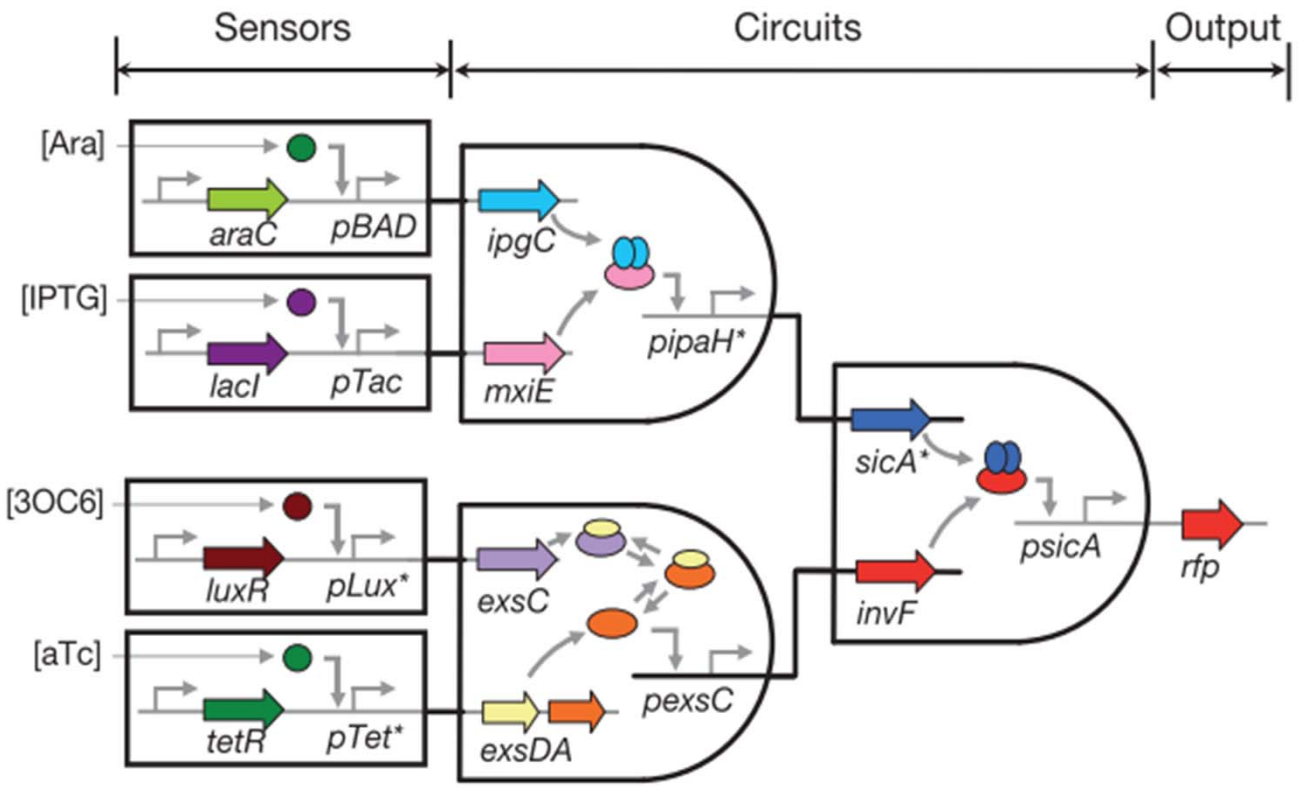
-Jacques Monod. *Chance and Necessity: An Essay on the Nature of Philosophy of Modern Biology*. Collins, London, 1972.

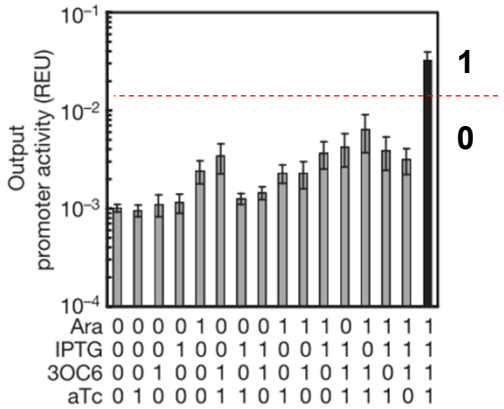
Parallels with the computational “parts” hierarchy

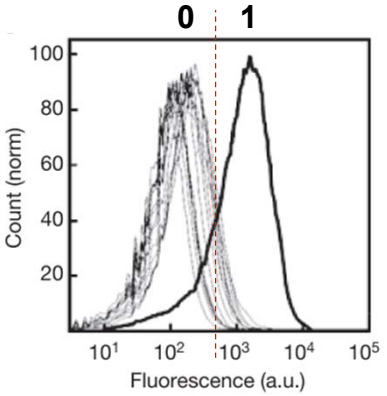


Andrianantoandro et al. (2006). Molecular systems biology.

Gene expression regulation for digital logic



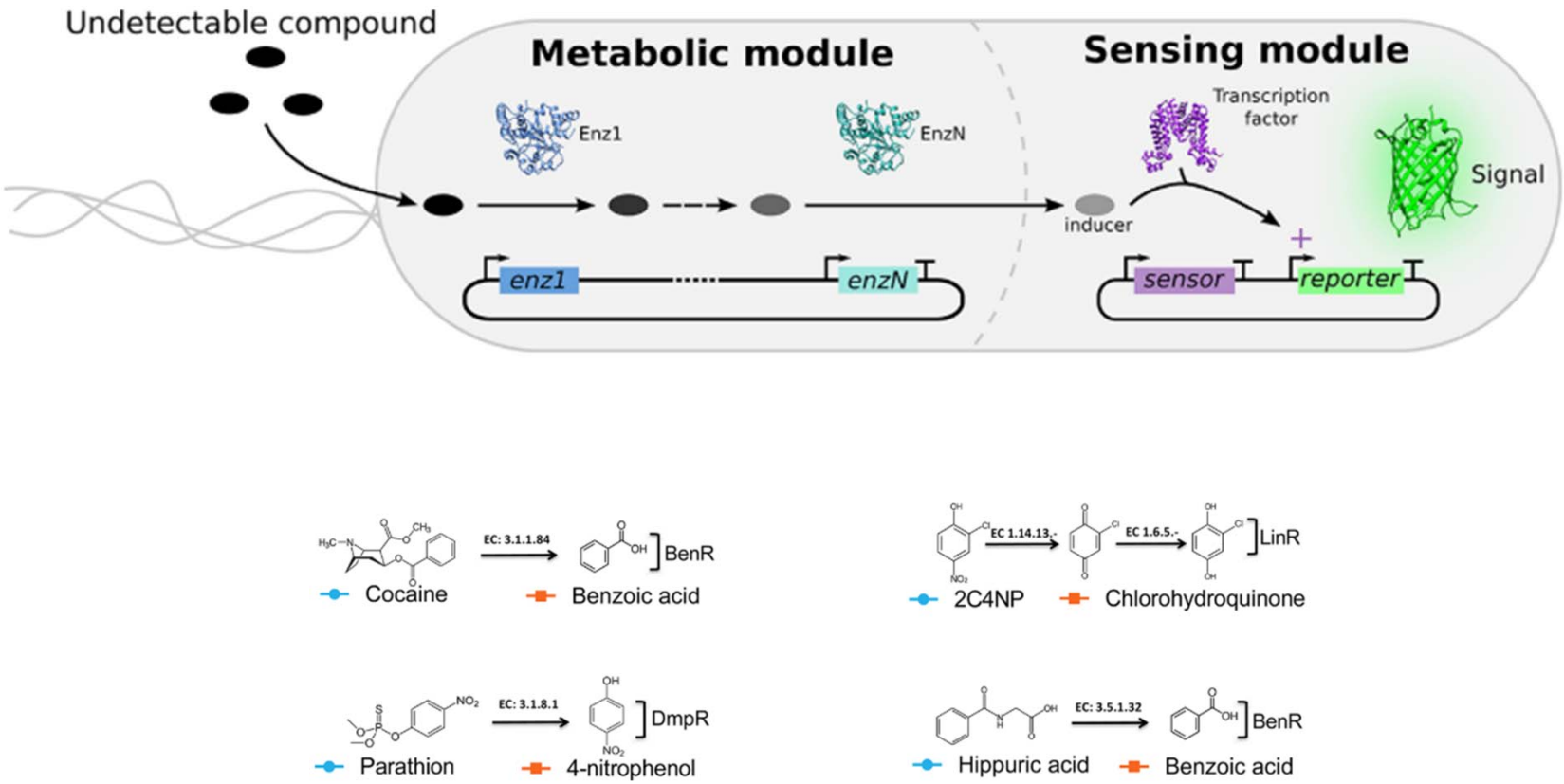




- Layered transcriptional regulation can be used for multi-input computational logic
- Continuous signals must be “discretized” in order to treat them as digital ‘0’ or ‘1’

(Moon *et al.*, 2012. Nature.)

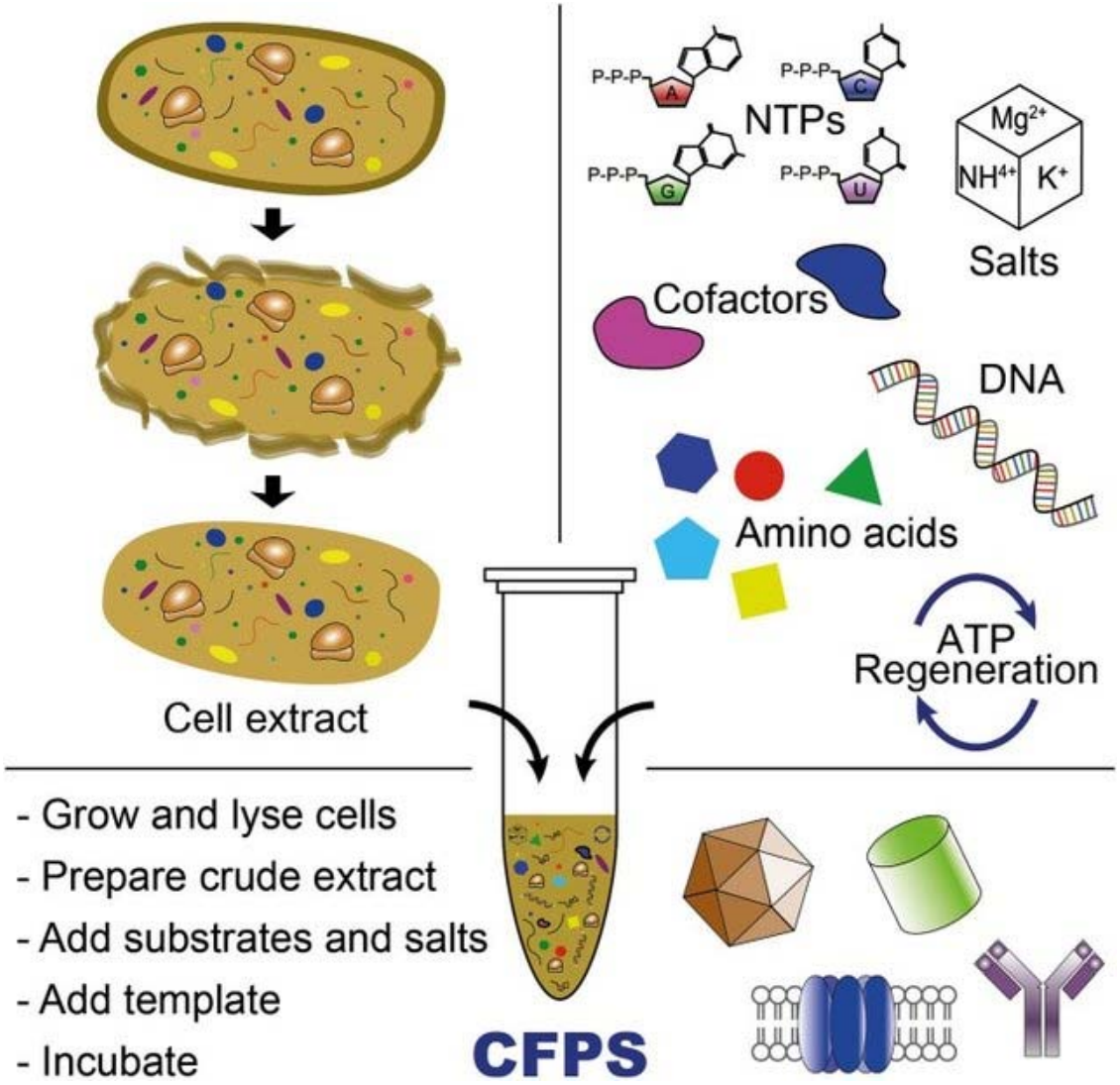
Sensing-enabling metabolic pathways (SEMP)



- Sensing-enabling metabolic pathways enable indirect sensing of molecules for which direct transcriptional regulators are unknown

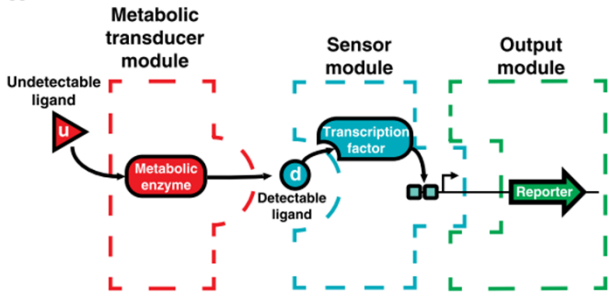
(Delepine *et al.*, 2016. NAR.
Libis *et al.*, 2016. ACS Synth. Biol.)

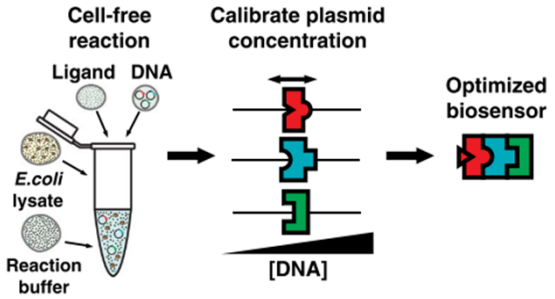
Re-energizing cellular lysates

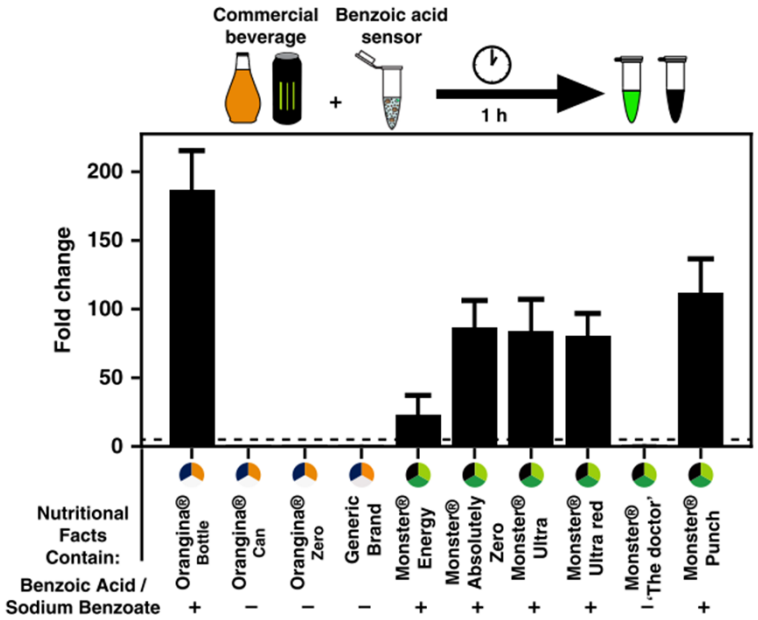


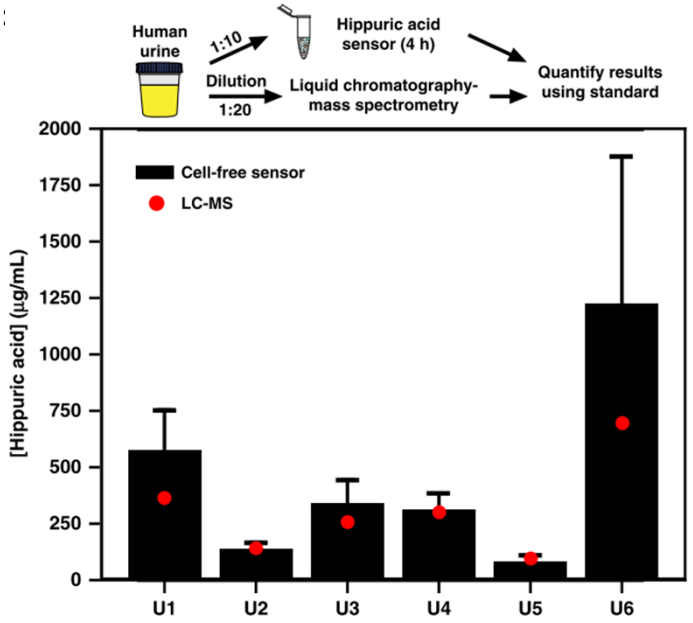
Hong *et al.*, 2014. Frontiers in Chemistry.

Sensing-enabling metabolic pathways in Cell Free Systems





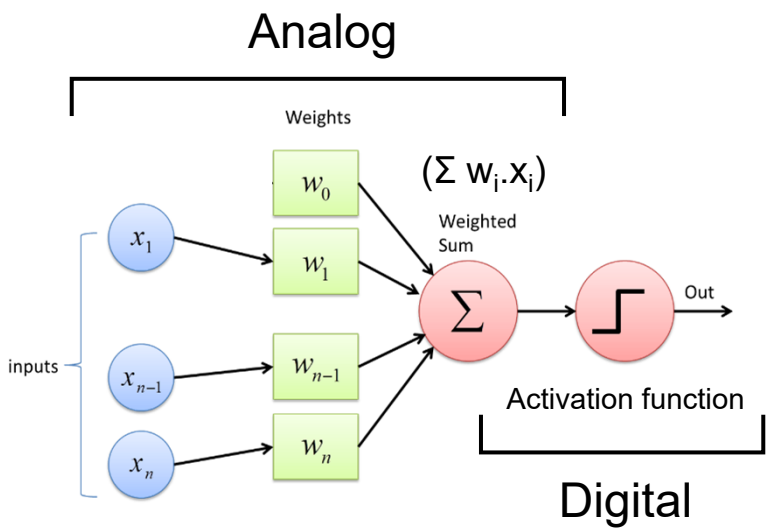


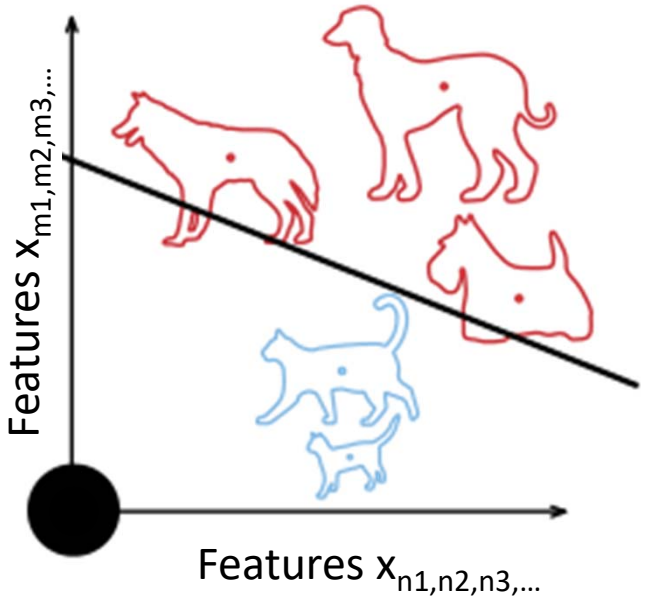


- Metabolic “transducers” convert undetectable molecules into a detectable ones, which in turn can be sensed by the “sensors”
- Cell Free Systems allow easier optimization of the biosensing system

(Voyvodic *et al.*, 2019. Nat. Commun.)

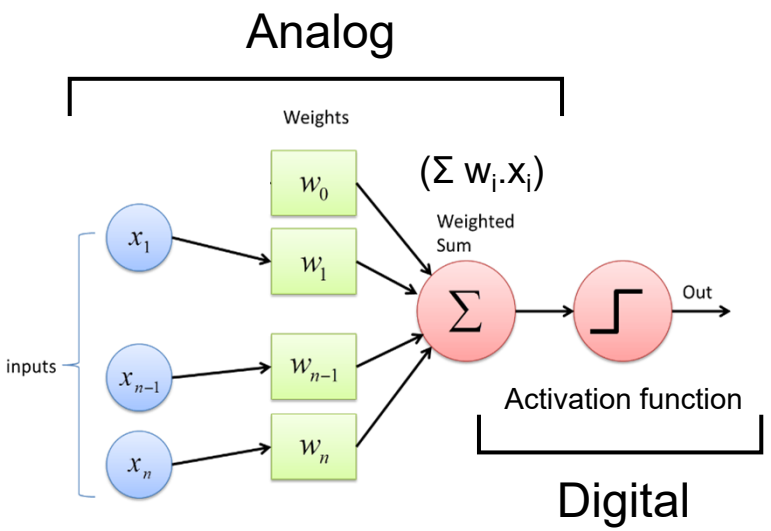
A Perceptron for multi-input sensing

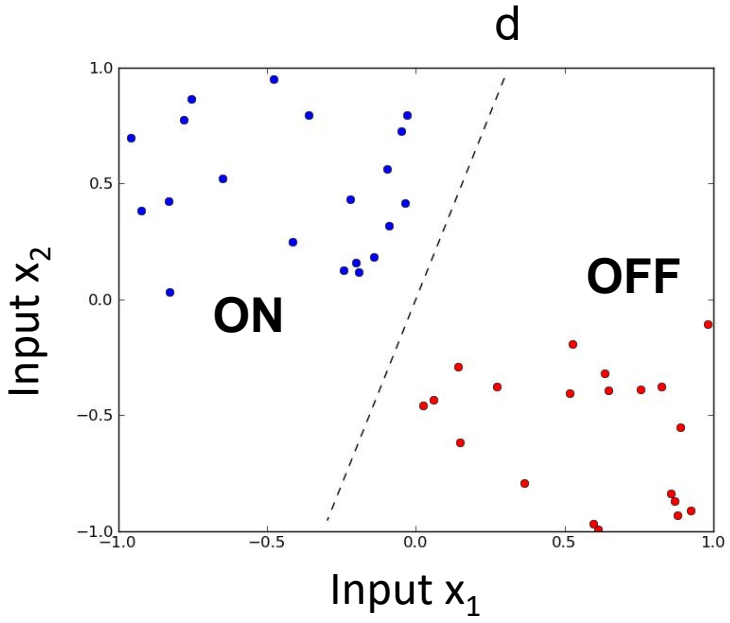




- The perceptron mimics the neuron's ability to process information
- It is a basic block of artificial neural networks

A Perceptron for multi-input sensing

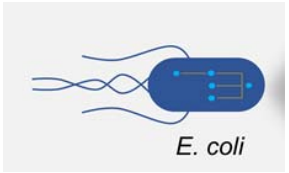


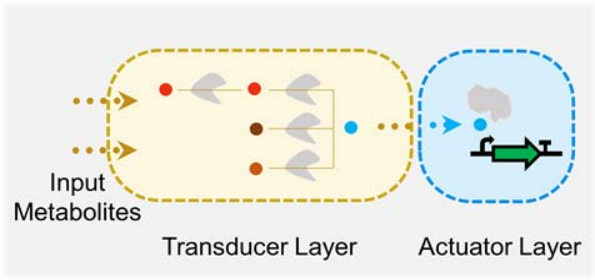


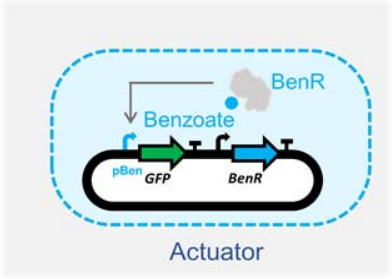
If $(\Sigma\ w_i.x_i) > d$, ON

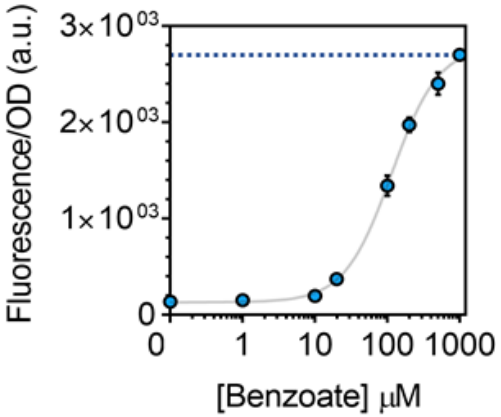
If $(\Sigma\ w_i.x_i) <= d$, OFF

Characterizing and modeling the benzoate actuator



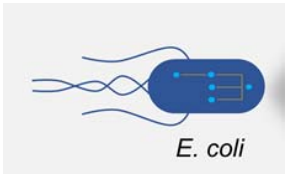


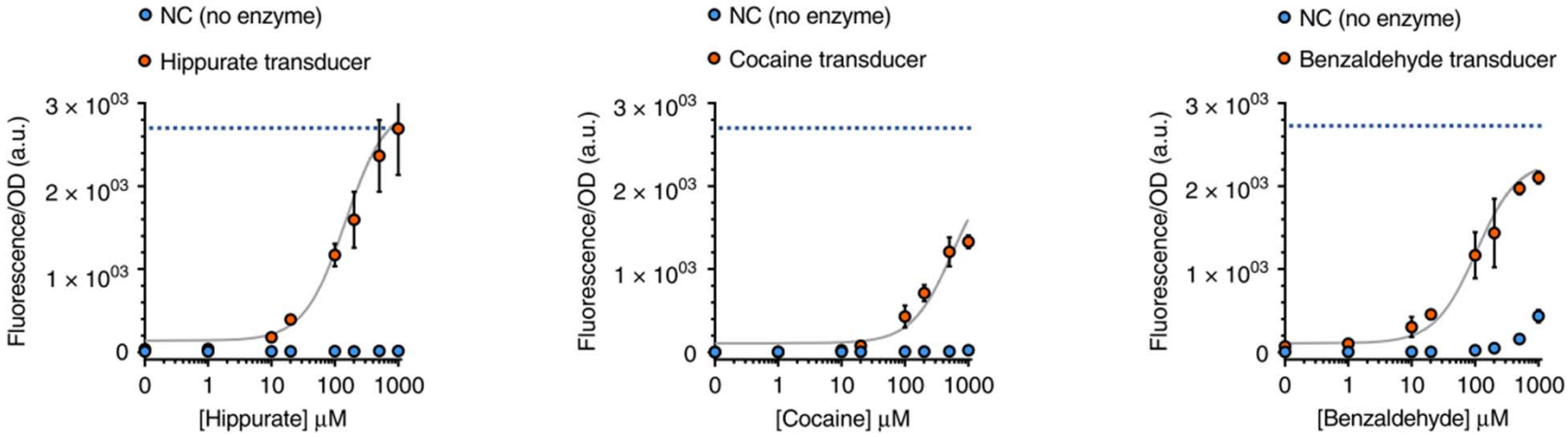




- The benzoate actuator device in *E. coli*

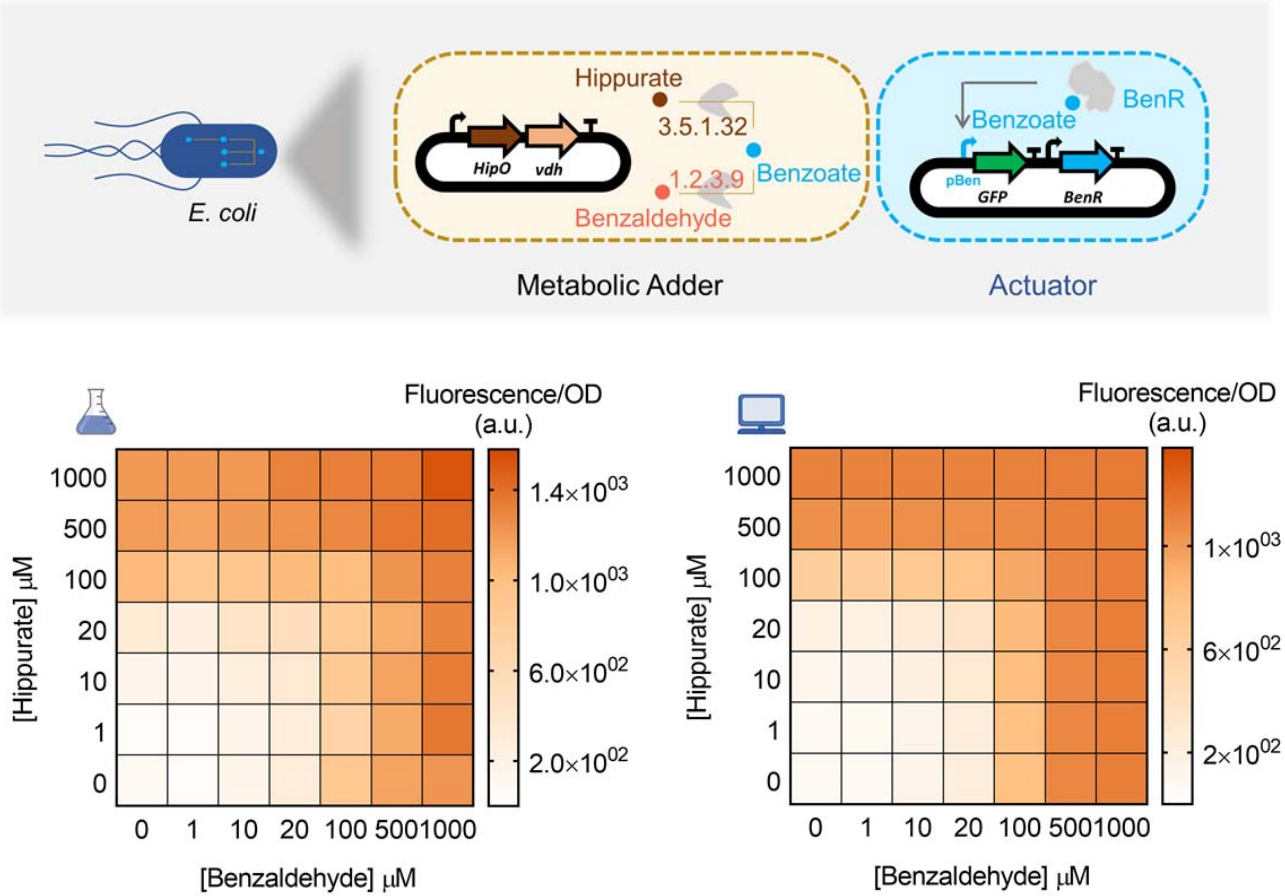
Characterizing and modeling the metabolic transducers





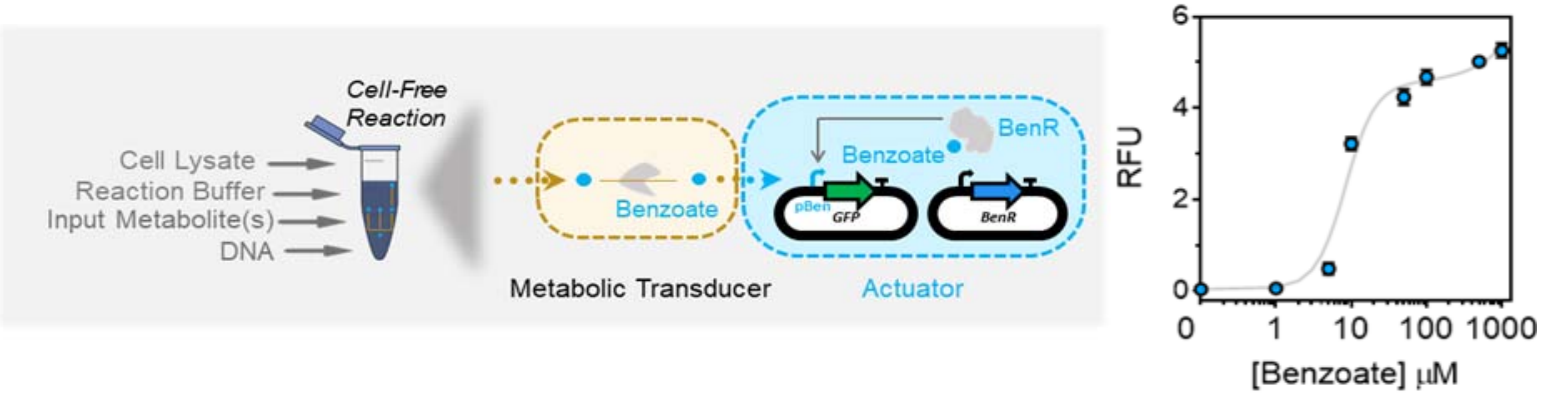
- Three metabolic transducers in *E. coli*

Characterizing and modeling the metabolic adders



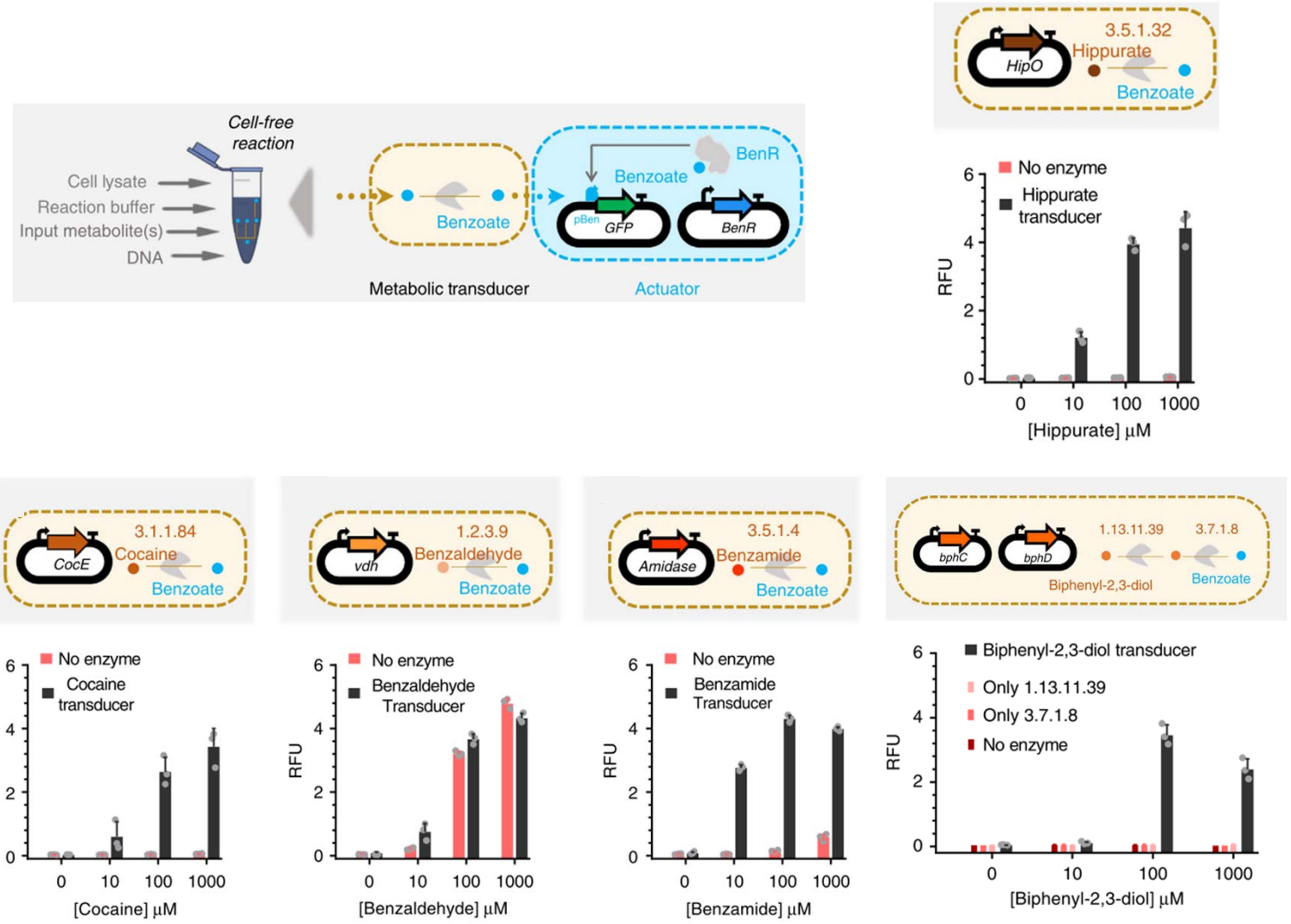
- Metabolic concentration adders in *E. coli*

Characterizing and modeling the benzoate actuator



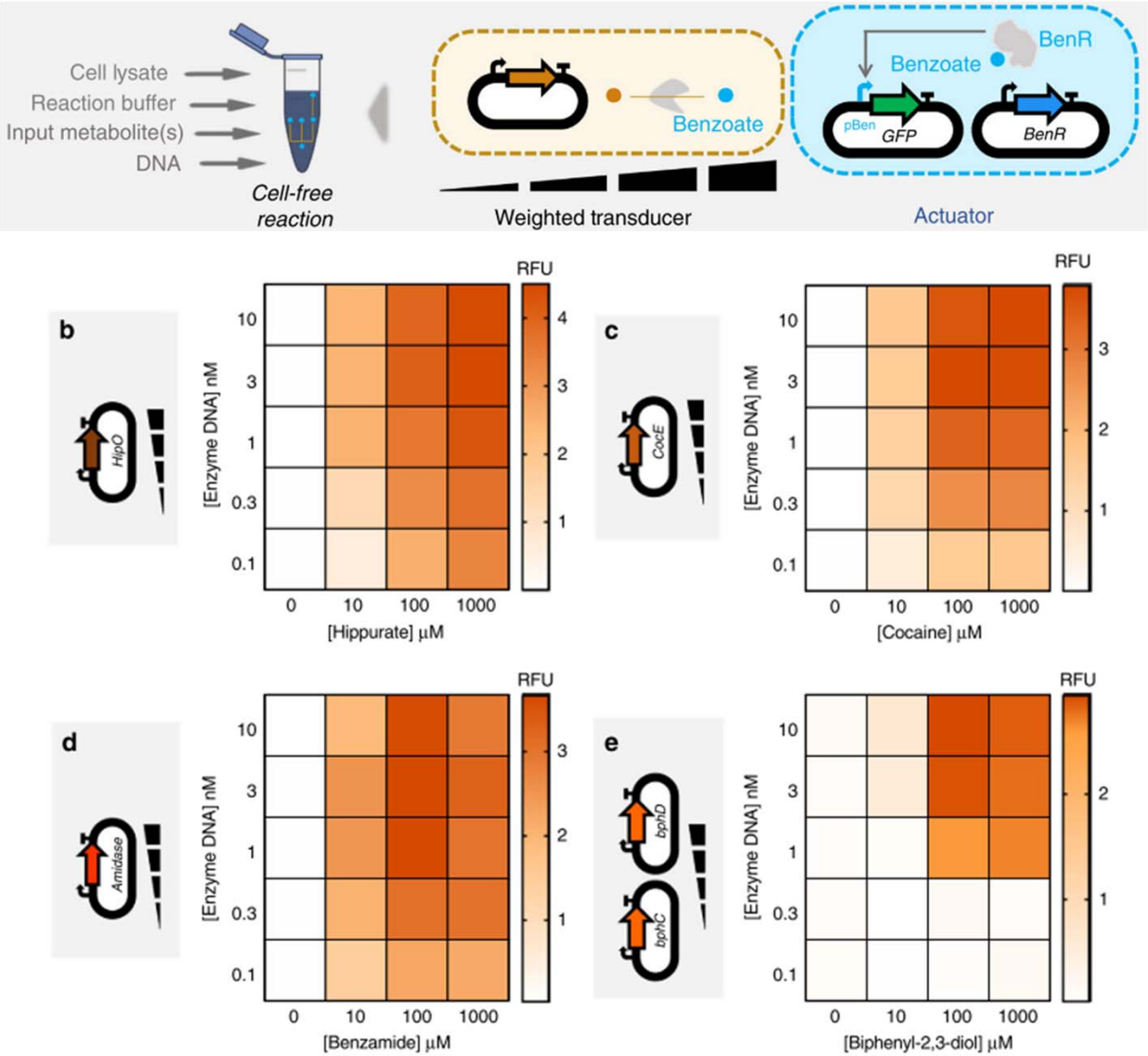
- The benzoate actuator device in Cell Free System

Characterizing and modeling the metabolic transducers



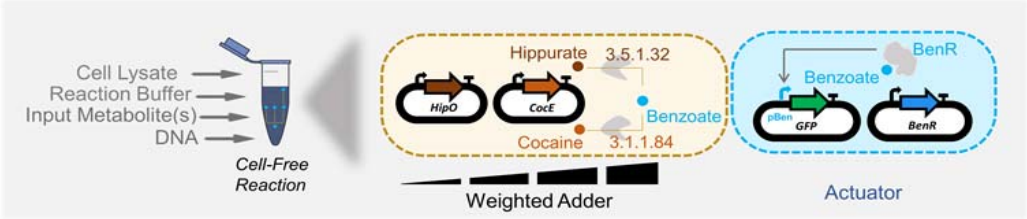
- Five metabolic transducers in Cell Free System

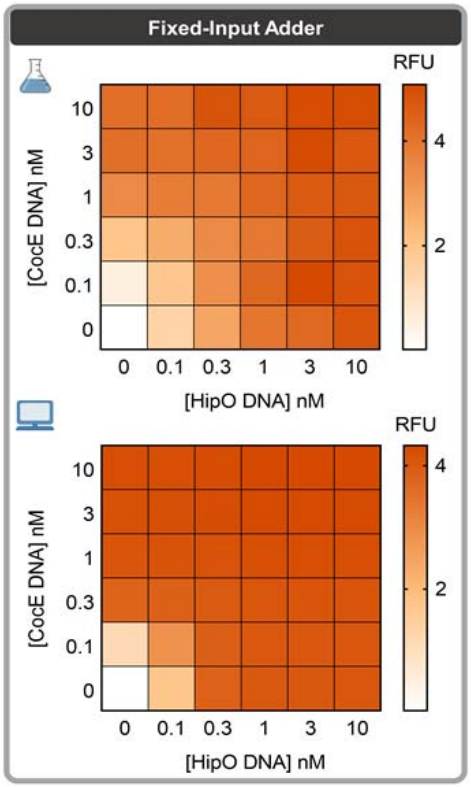
Building the Cell Free weighted transducers



- The weight of a traducer can be tuned by changing the amount of transducer DNA added

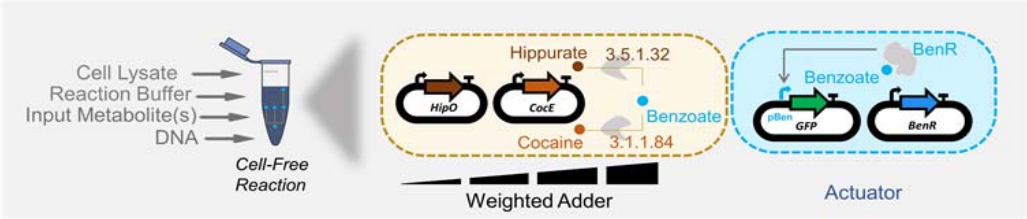
Characterizing and modeling the metabolic adders

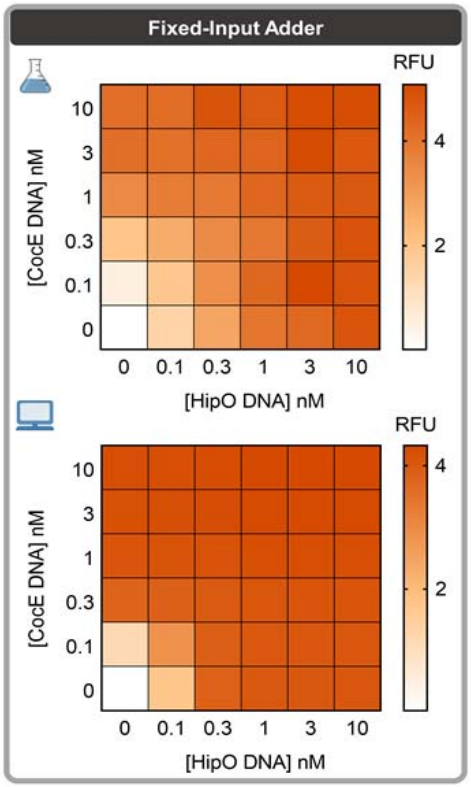


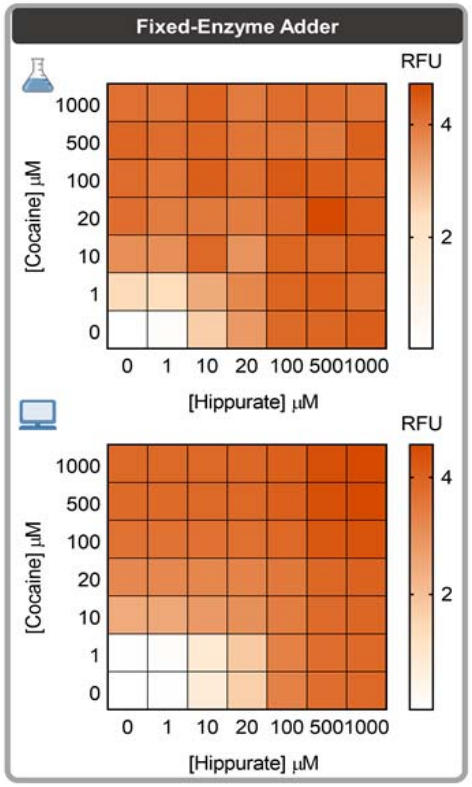


- Metabolic concentration weighted adders in Cell Free System

Characterizing and modeling the metabolic adders

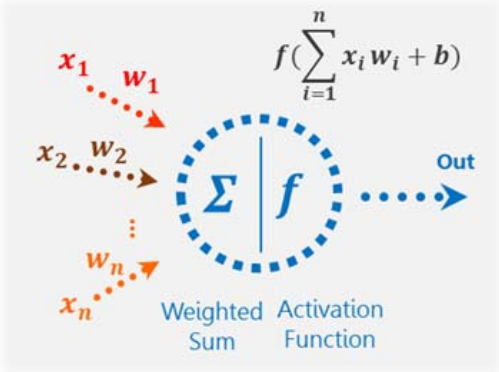


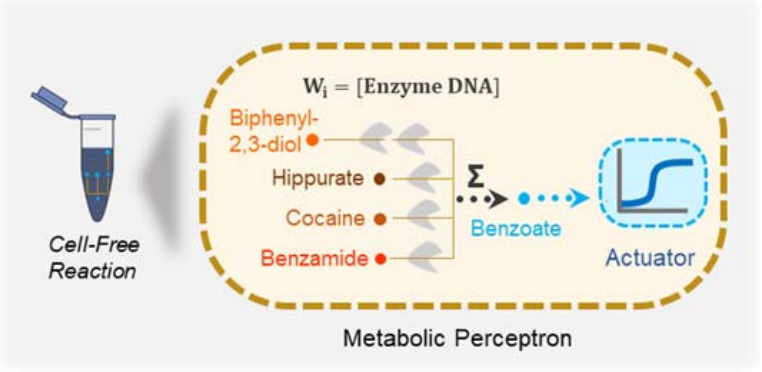


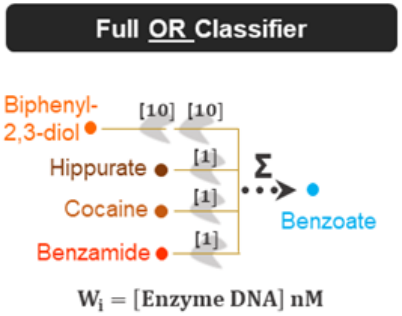


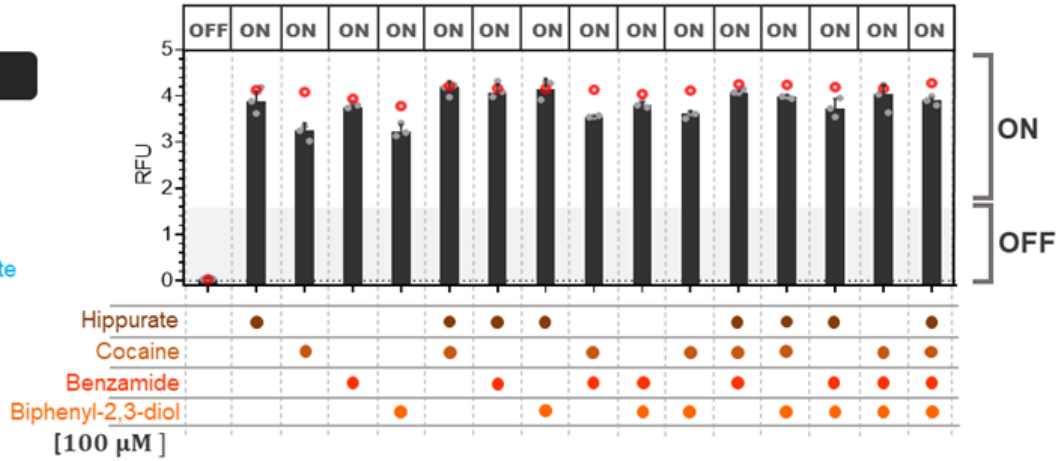
- Metabolic concentration weighted adders in Cell Free System

The Metabolic Perceptron: Classifier 1



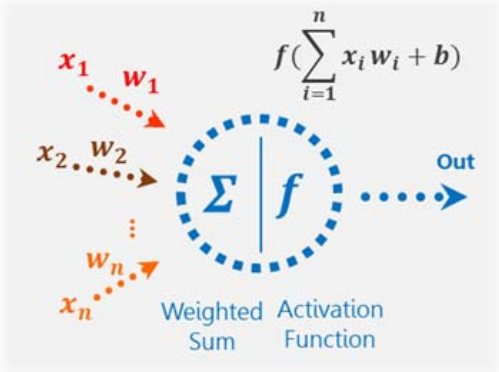


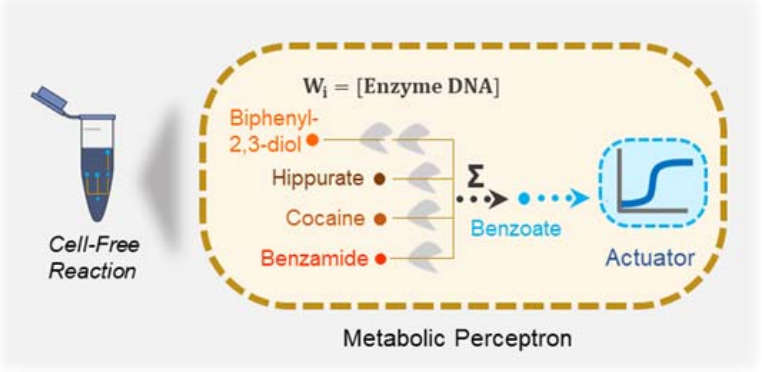


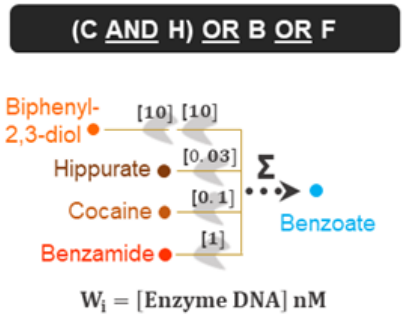


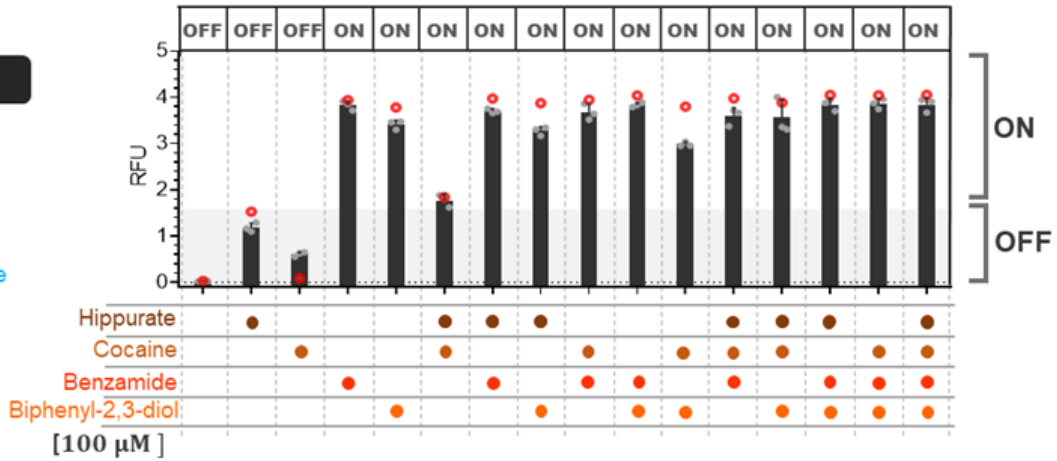
- Model based construction and validation of a binary classifiers
- The same metabolic circuit has different behaviors when used with different weights

The Metabolic Perceptron: Classifier 2









- Model based construction and validation of a binary classifiers
- The same metabolic circuit has different behaviors when used with different weights

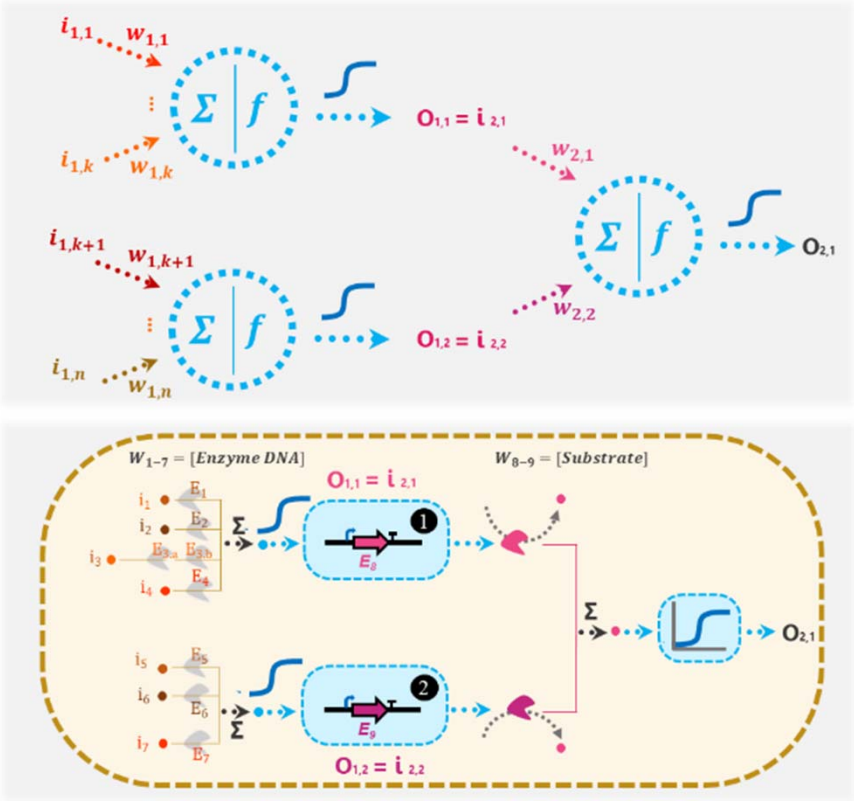
Future Perspectives

Metabolites

Nucleic acids (DNA, RNA)

Proteins

Multiple classes of input molecules



- By combining different types of inputs, diagnostic approaches can be dramatically improved
- Multi-layer metabolic perceptrons can classify complex patterns of metabolite concentrations in analytical samples

Acknowledgments

Amir Pandi
Mathilde Koch
Paul Soudier
Jean-Loup Faulon

Peter L. Voyvodic
Jerome Bonnet

Angelo Batista
Hadi Jbara
Ioana Popescu
Joan Herisson
Kenza Bazi-Kabbaj
Leon Faure
Mahnaz Sabeti-Azad
Thomas Duigou
Yorgo El-Moubayed

Thank You

Questions Welcome