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Metabolic Perceptrons for Neural Computing in Cell Free Systems

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Amir Pandi, Mathilde Koch, Peter Voyvodic, Paul Soudier, Jerome Bonnet, et al.. Metabolic Perceptrons for Neural Computing in Cell Free Systems. AICHE Cell Free Systems Conference, American Institute of Chemical Engineers (AIChE), Dec 2019, Boston (MA), United States. hal-04563371

HAL Id: hal-04563371

<https://hal.inrae.fr/hal-04563371>

Submitted on 29 Apr 2024

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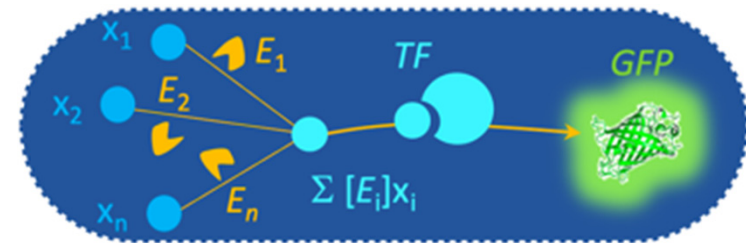
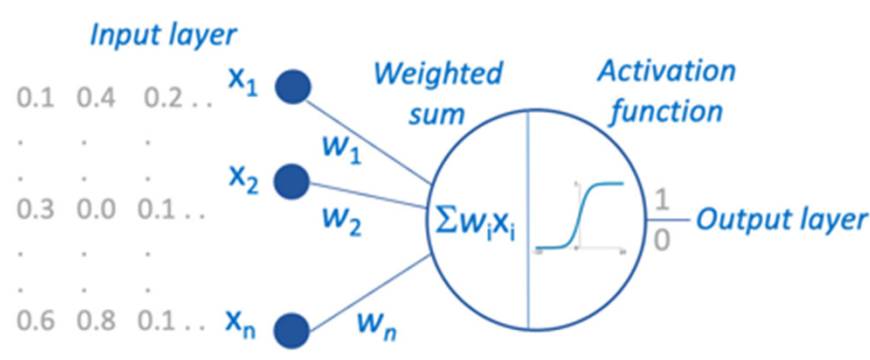
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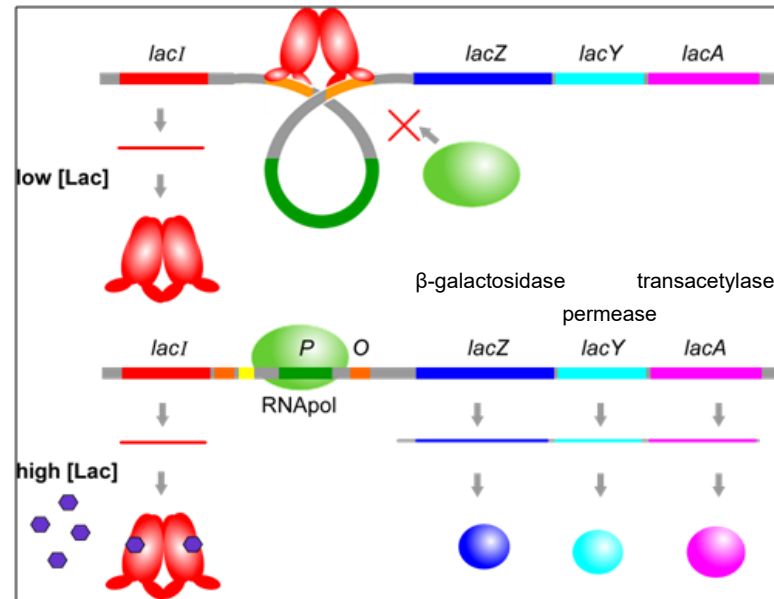
Metabolic Perceptrons for Neural Computing in Cell Free Systems

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Cell Free Systems Conference
4 December 2019, Boston

Do biological systems compute?

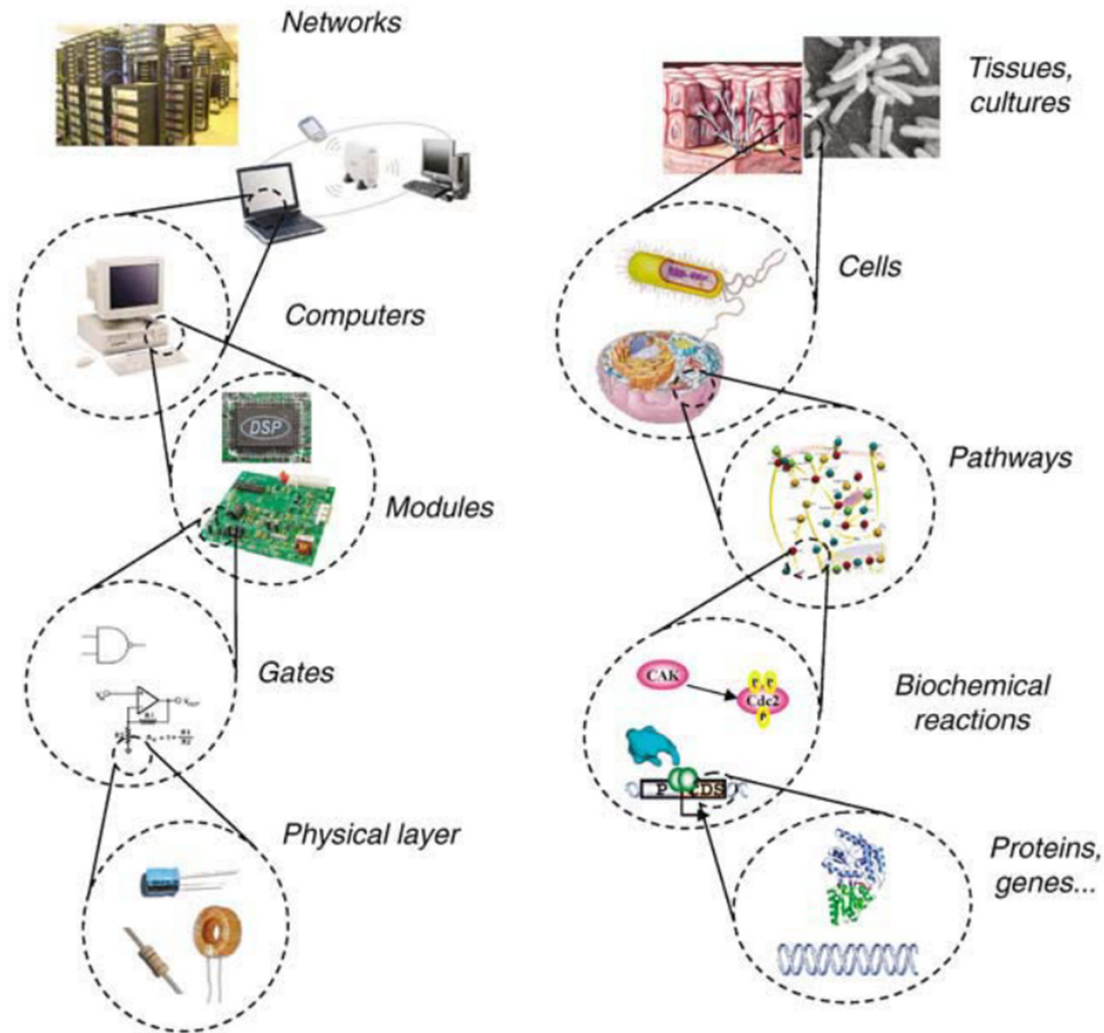


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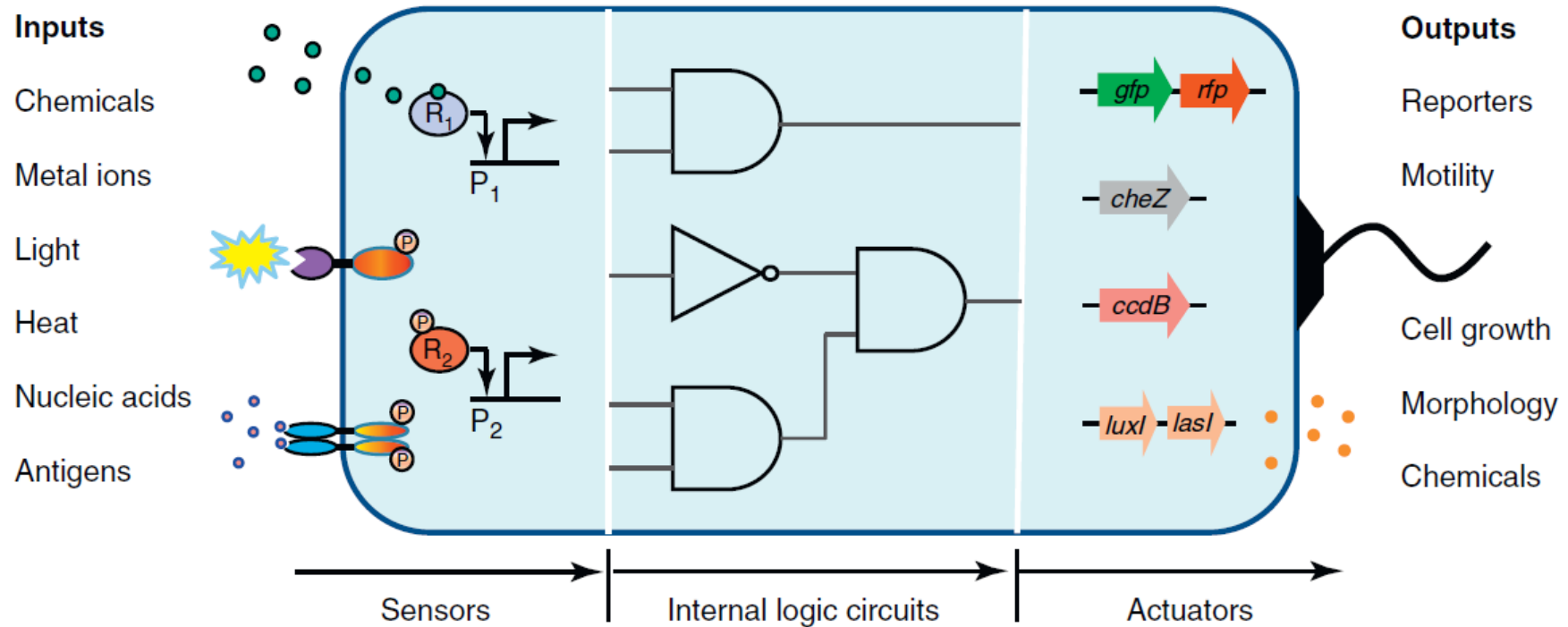
“... Thus the logic of this system is simple in the extreme: the repressor inactivates transcription; it is inactivated in its turn by the inducer. From this double negation results a positive effect, an "affirmation".... The logic of biological regulatory systems abides not by Hegelian laws but, like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

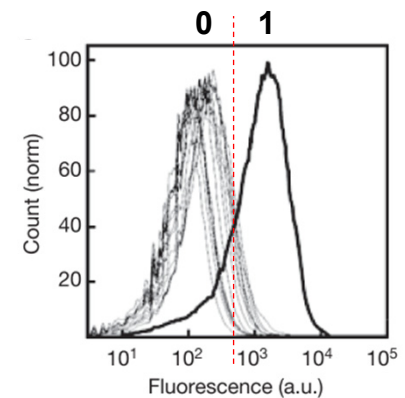
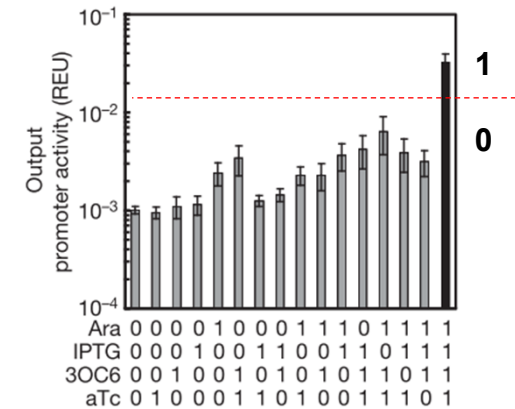
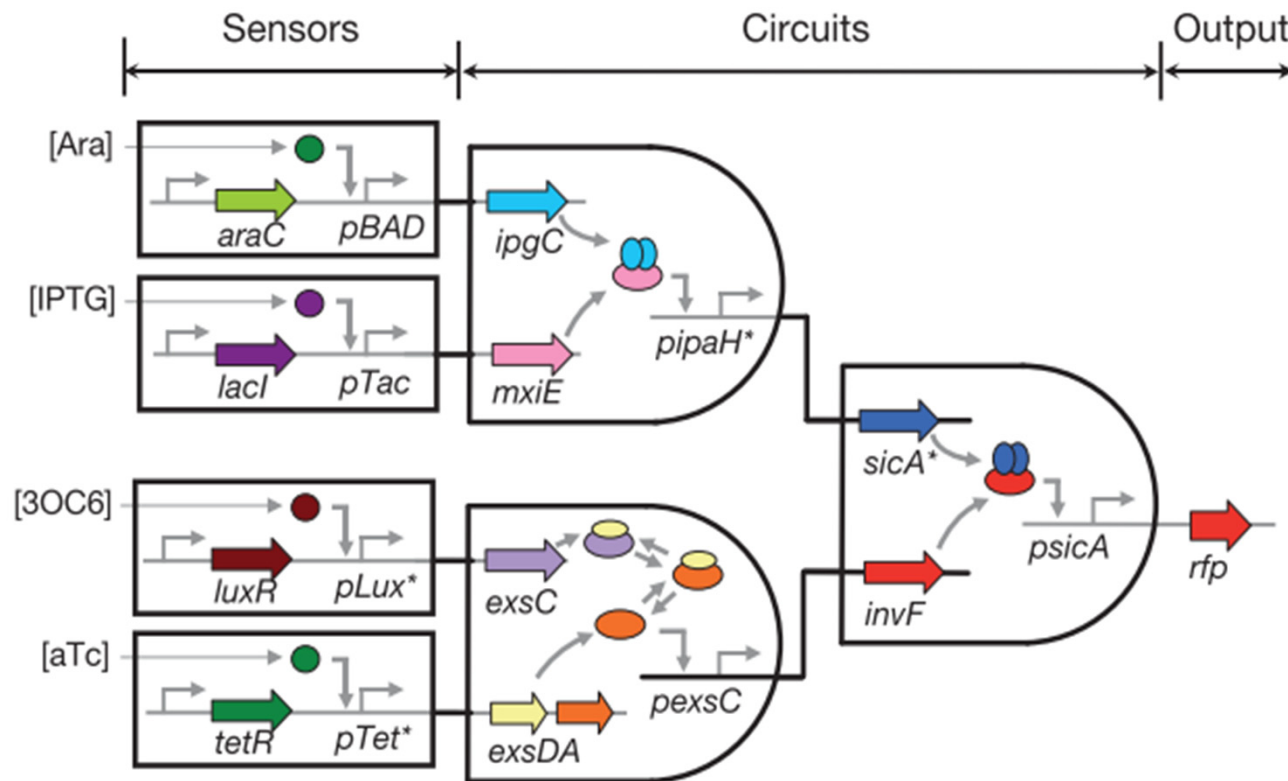


Cells process a diverse range of information



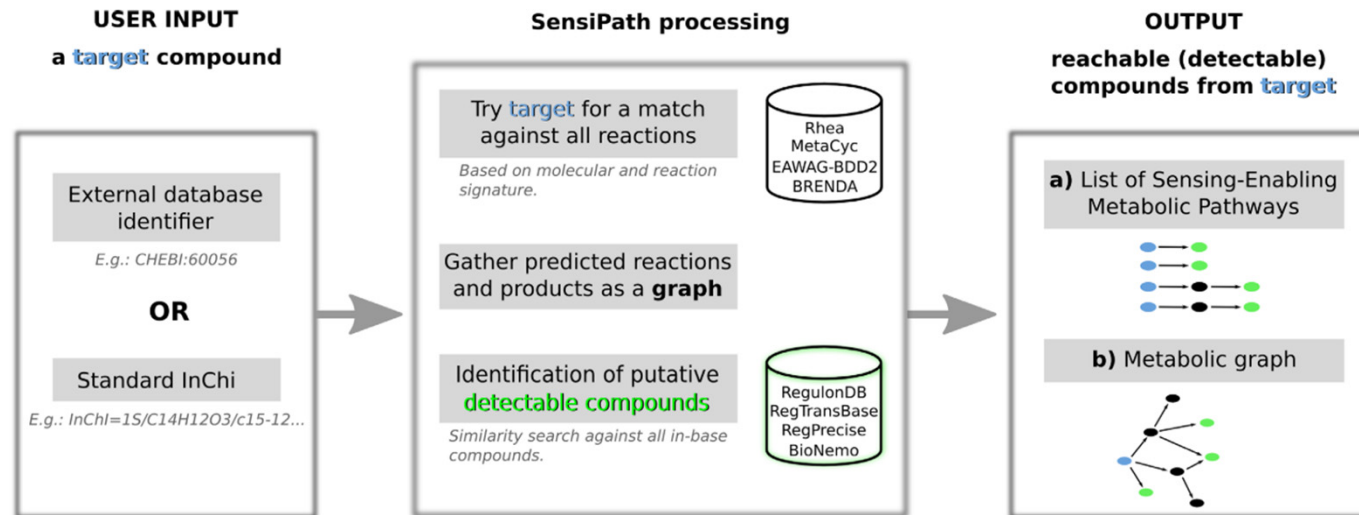
- Cells process a wide variety of extracellular and intracellular information.

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’

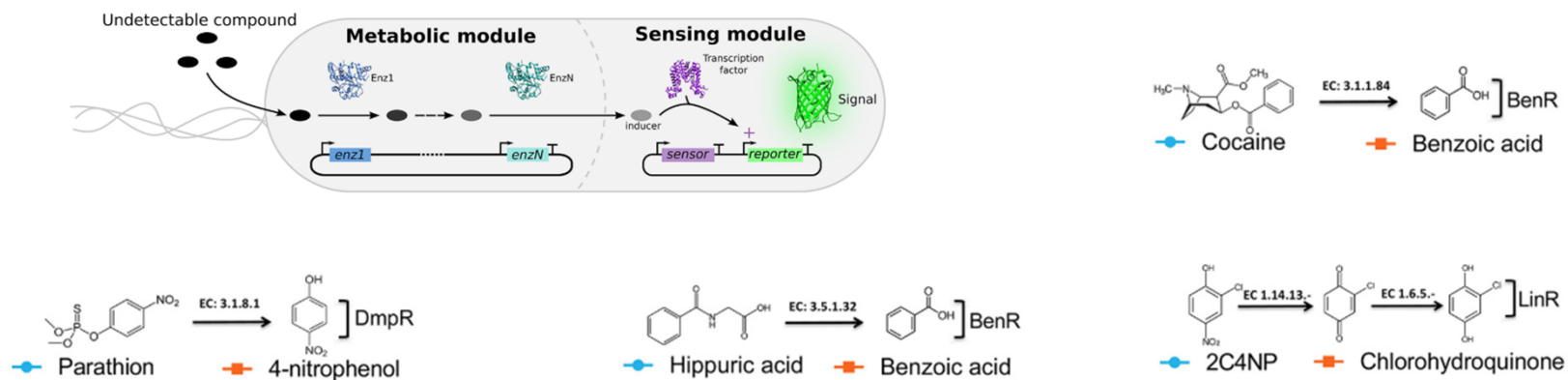
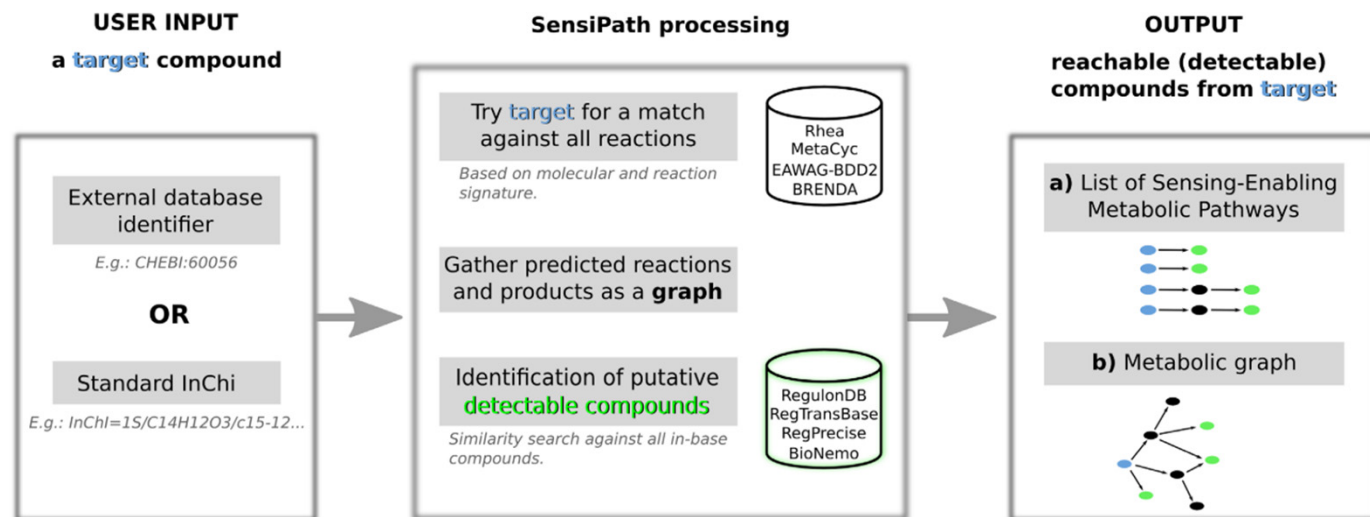
Sensing-enabling metabolic pathways (SEMP)



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

(Delepine *et al.*, 2016. NAR.

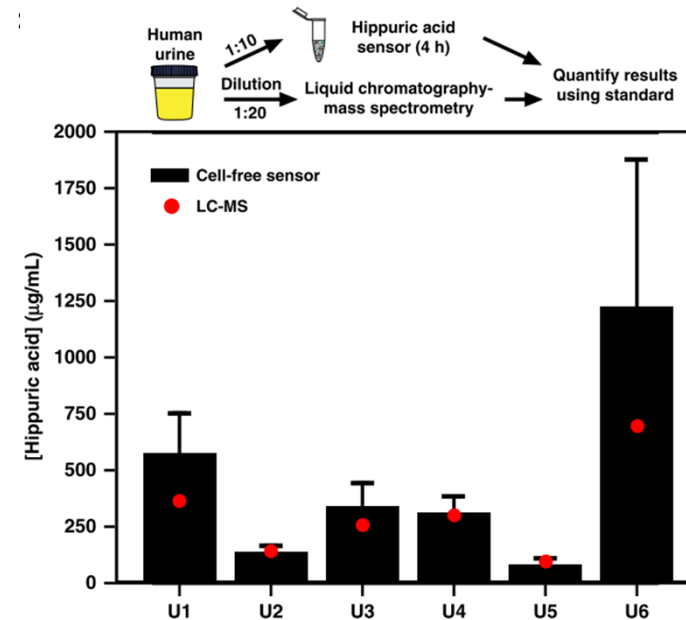
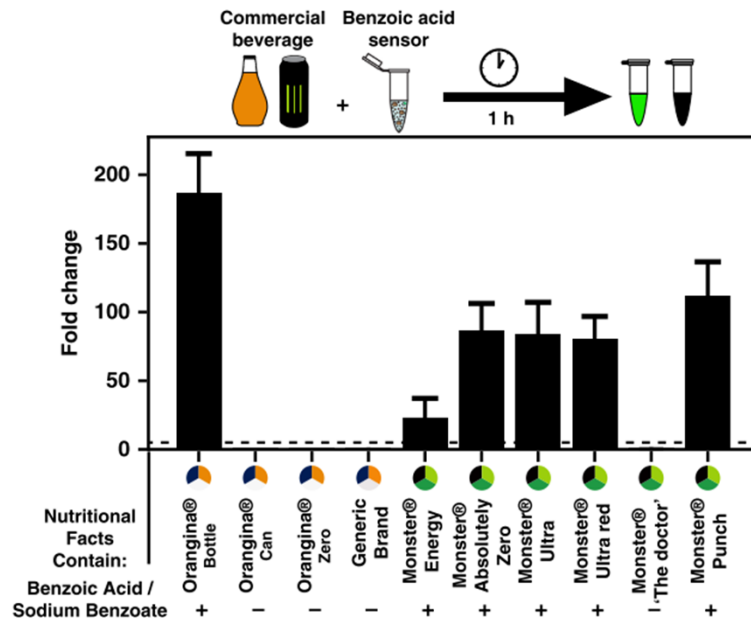
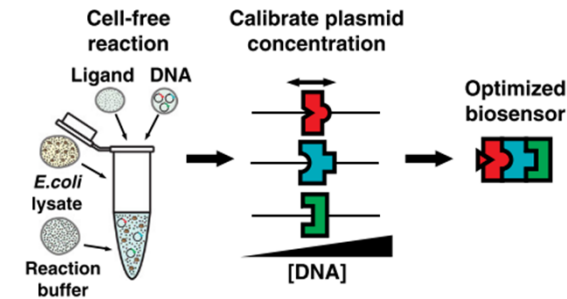
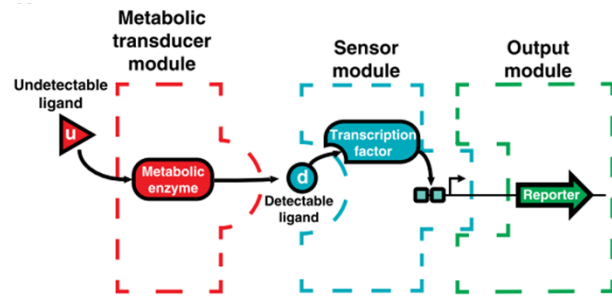
Sensing-enabling metabolic pathways (SEMP)



- 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.)

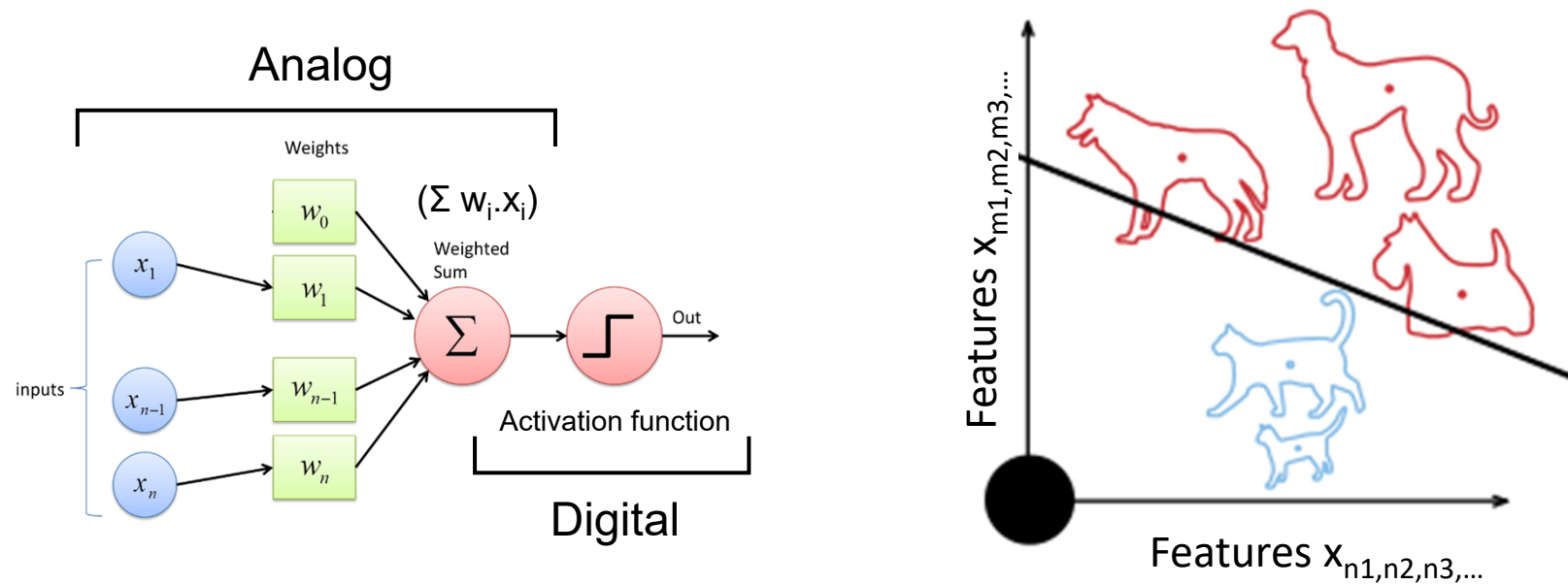
Sensing-enabling metabolic pathways in Cell Free Systems



- 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

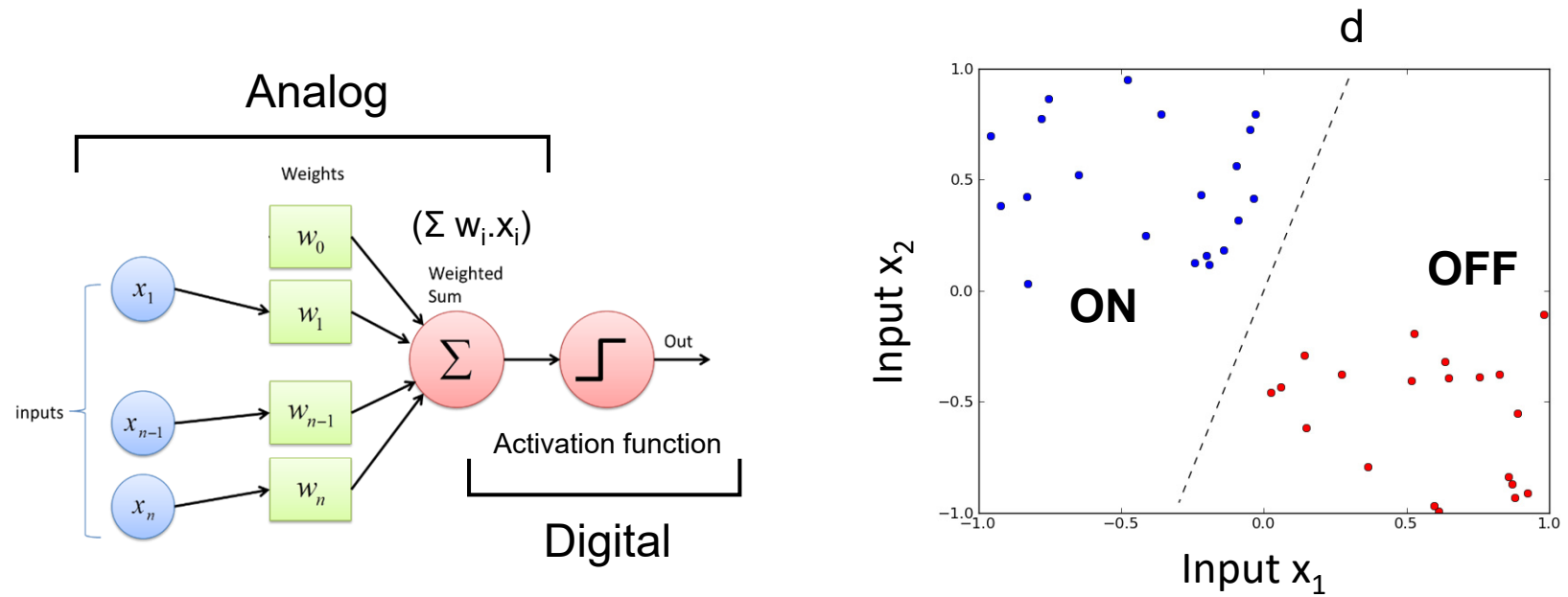
(Voyvodic *et al.*, 2019. Nat. Commun.)

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

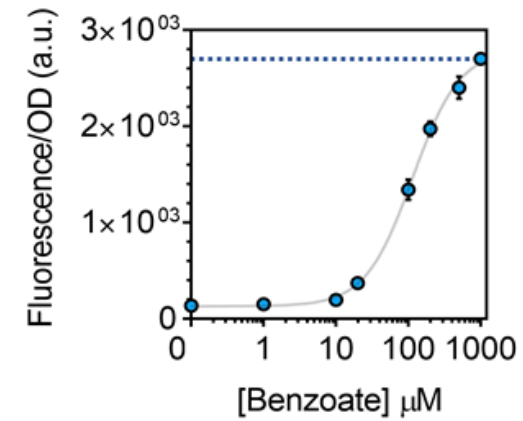
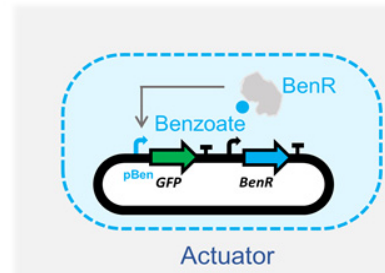
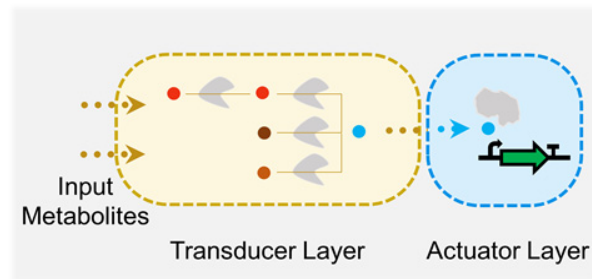
A Perceptron for multi-input sensing



If $(\sum w_i \cdot x_i) > d$, ON

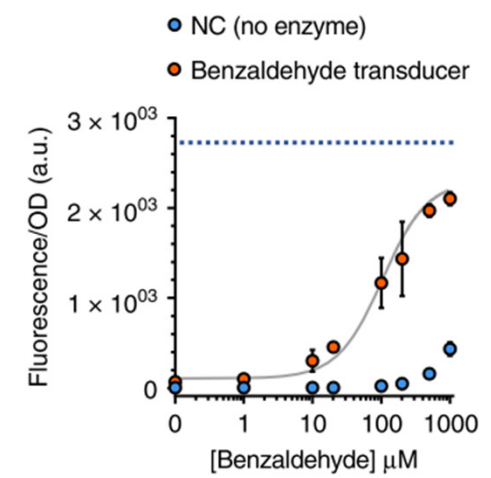
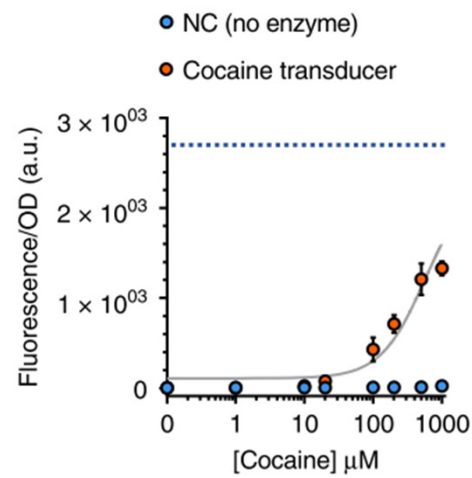
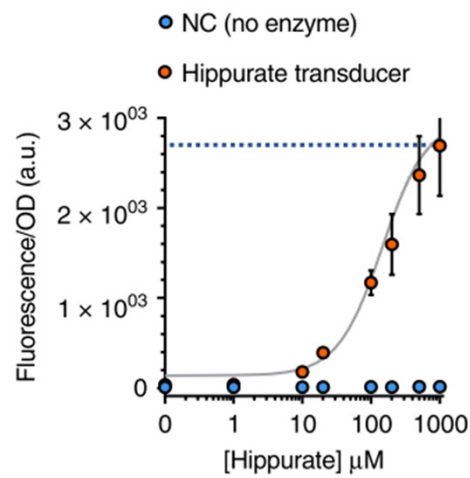
If $(\sum w_i \cdot x_i) \leq d$, OFF

Characterizing and modeling the benzoate actuator



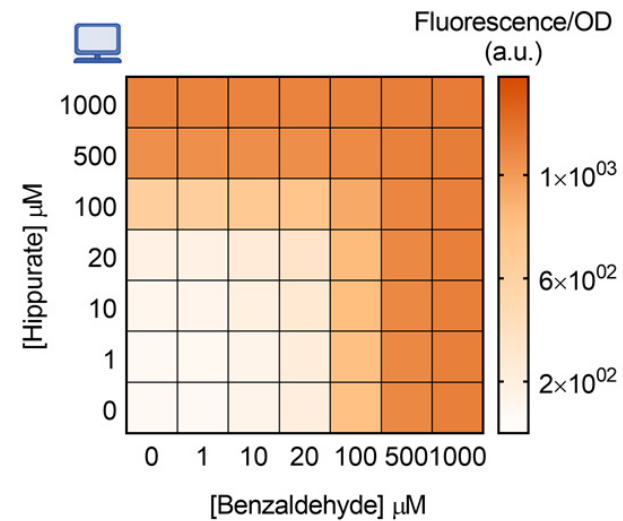
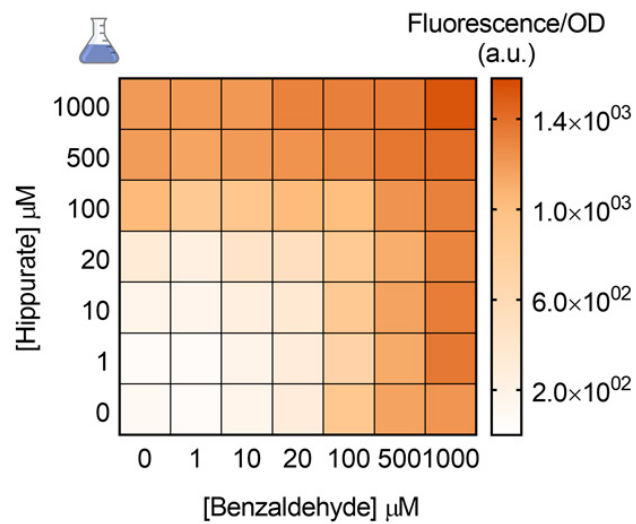
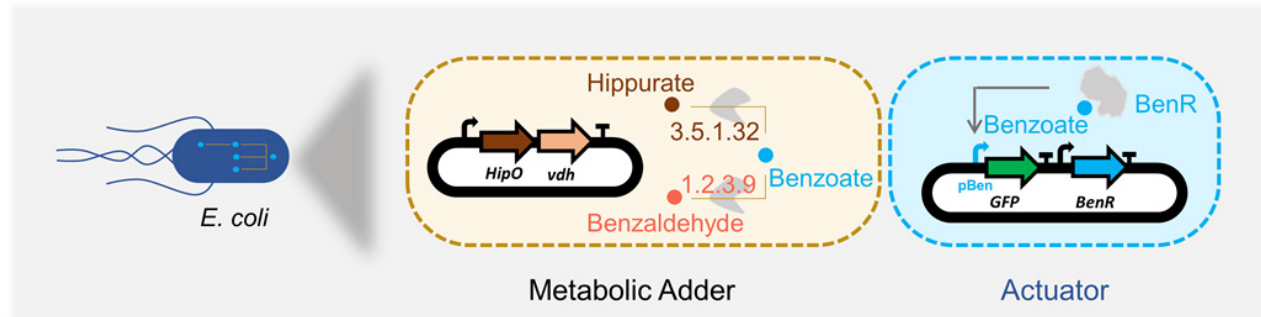
- The benzoate actuator device in *E. coli*

Characterizing and modeling the metabolic transducers



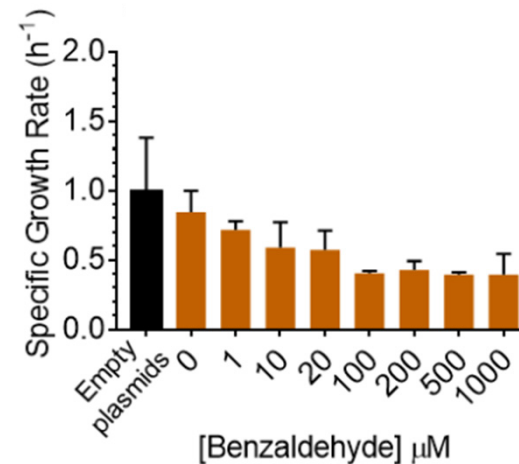
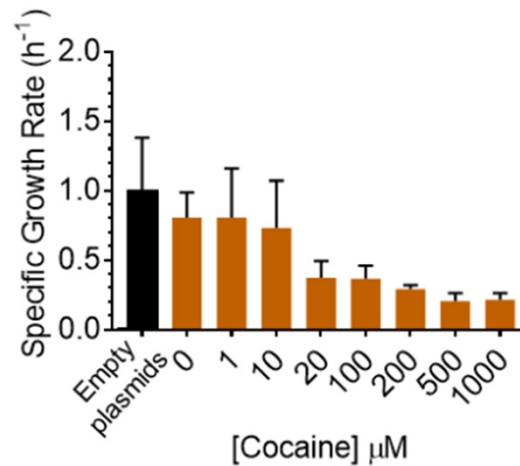
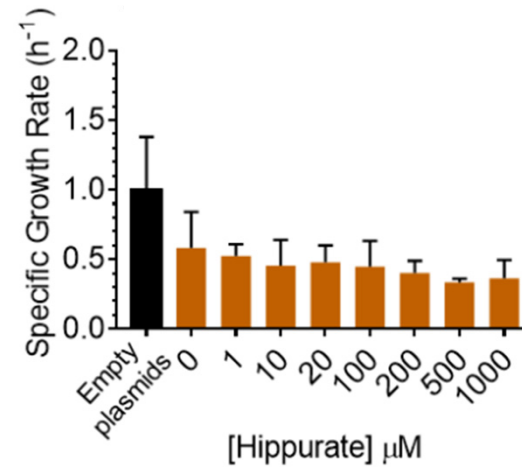
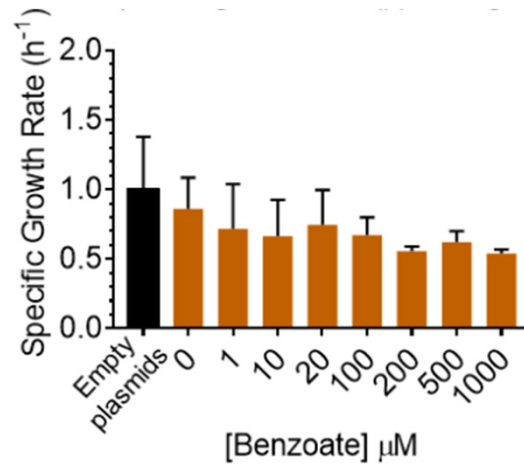
- Three metabolic transducers in *E. coli*

Characterizing and modeling the metabolic adders



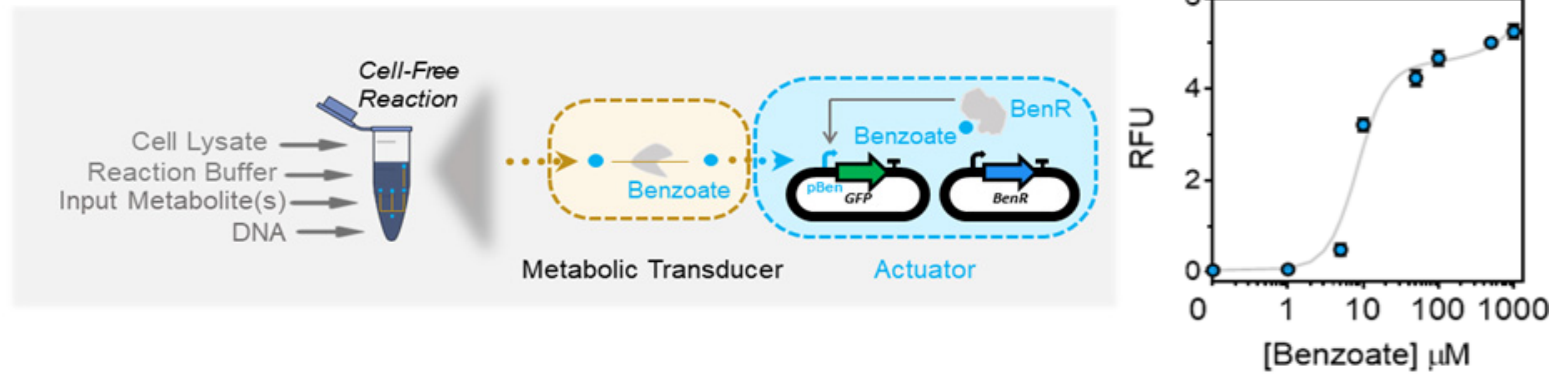
- Metabolic concentration adders in *E. coli*

Effect of input concentrations on *E. coli* growth



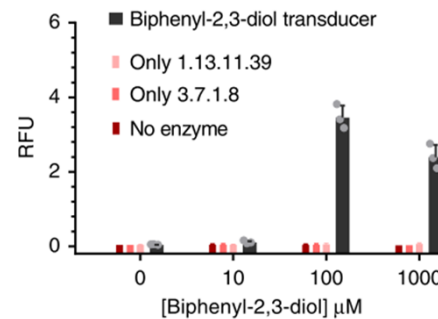
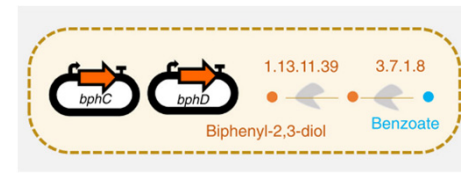
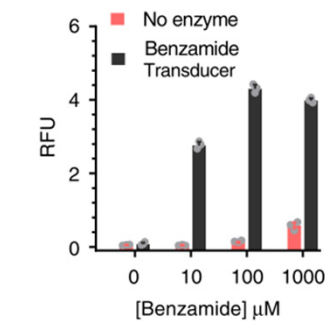
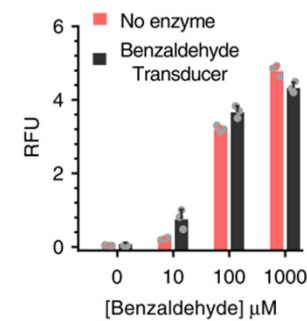
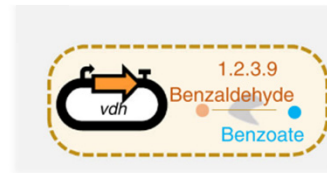
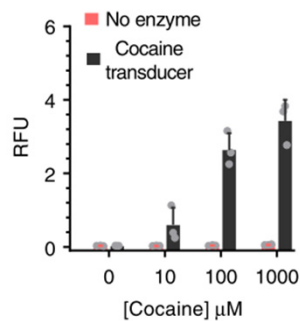
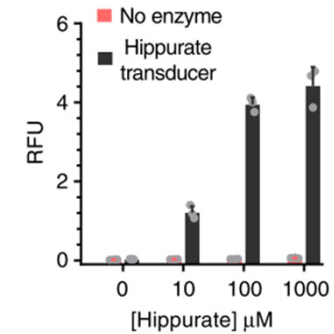
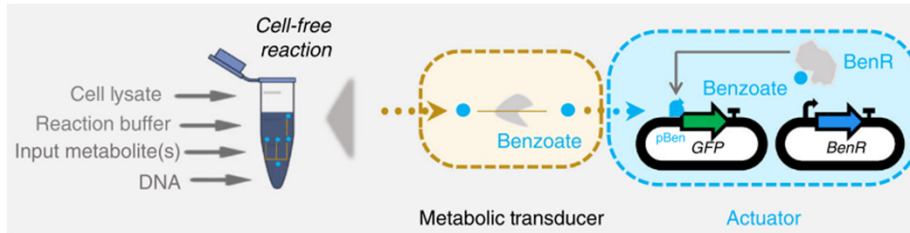
- Higher concentrations of input and intermediate molecules reduce growth in *E. coli*

Characterizing and modeling the benzoate actuator



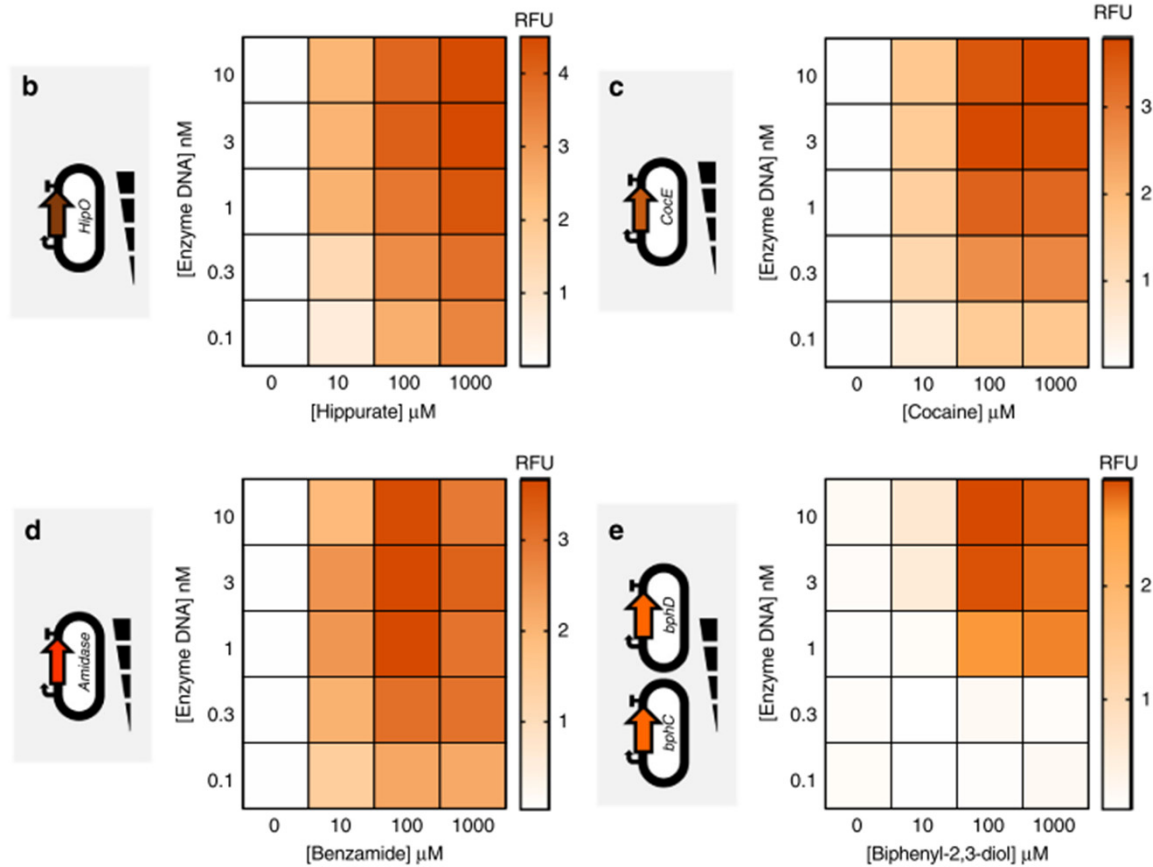
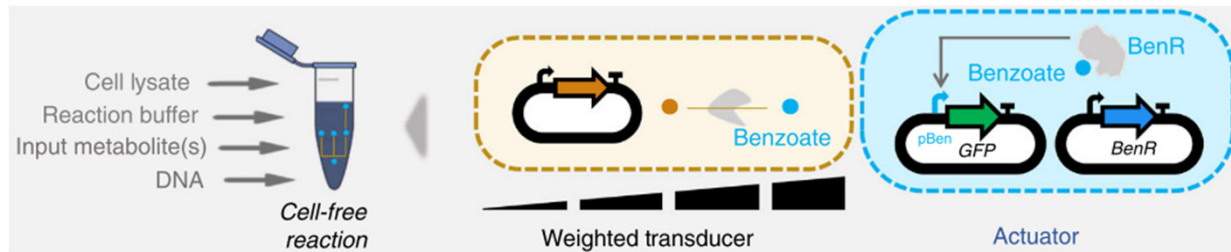
- The benzoate actuator device in Cell Free System

Characterizing and modeling the metabolic transducers



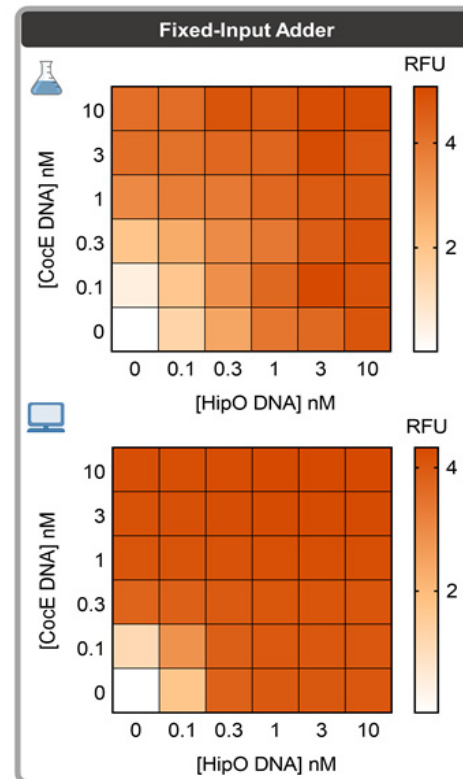
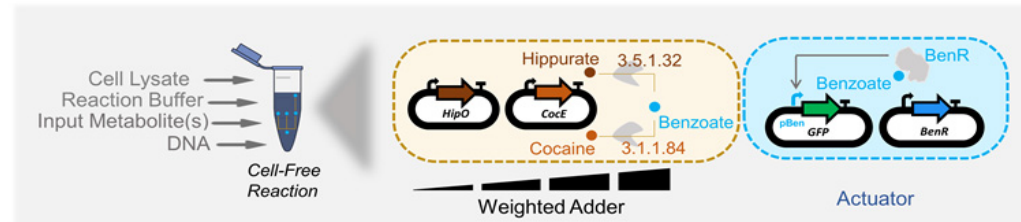
- Five metabolic transducers in Cell Free System

Building the Cell Free weighted transducers



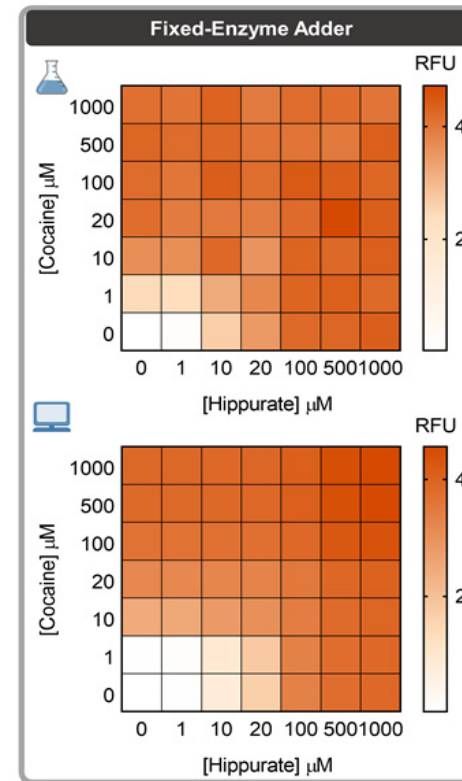
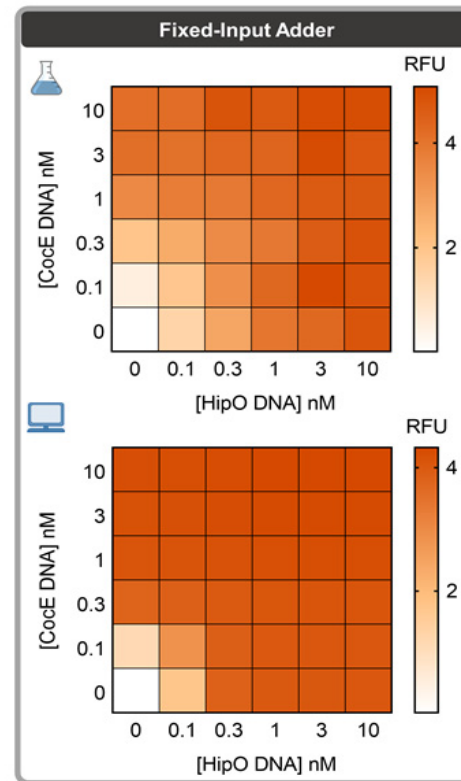
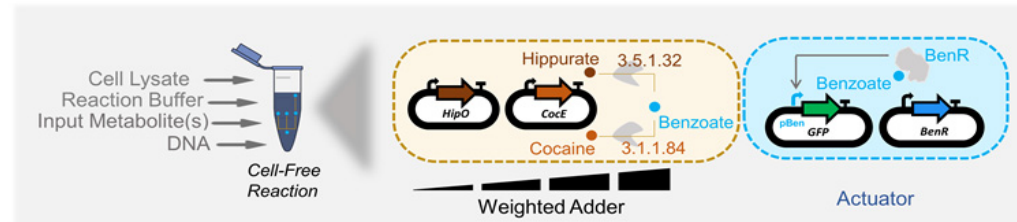
- The weight of a traducer can be tuned by changing the amount of transducer DNA added

Characterizing and modeling the metabolic adders



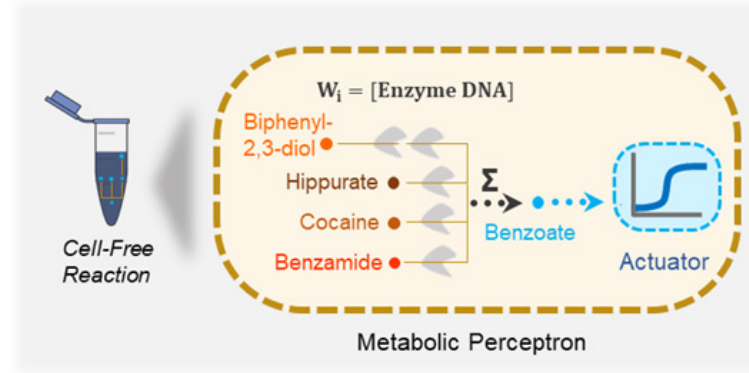
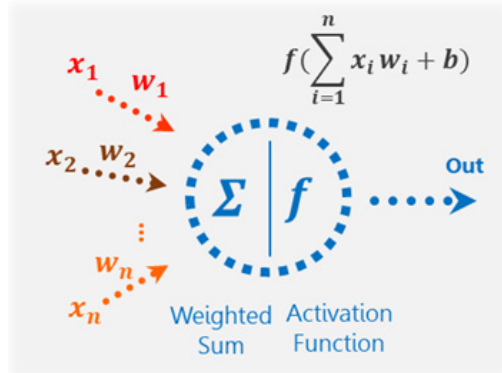
- Metabolic concentration weighted adders in Cell Free System

Characterizing and modeling the metabolic adders

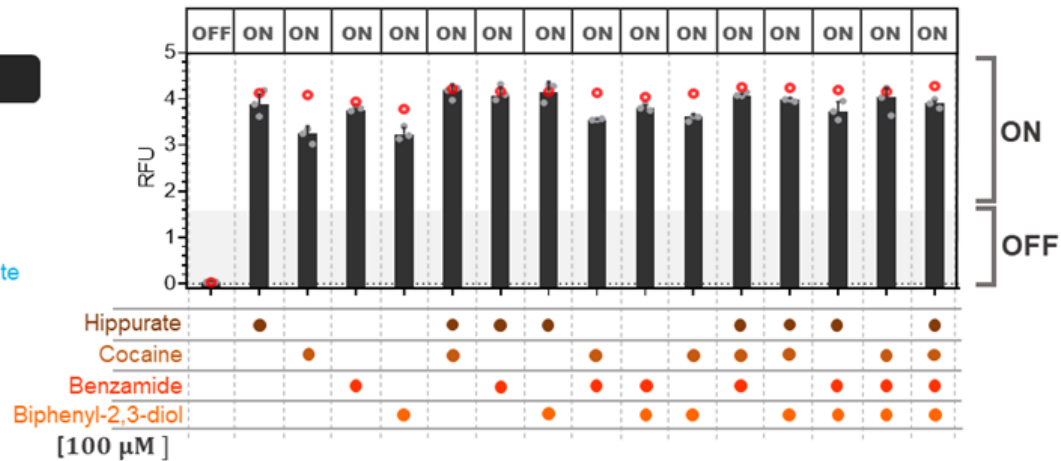
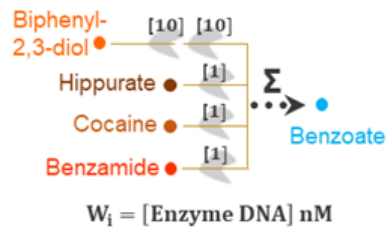


- Metabolic concentration weighted adders in Cell Free System

The Metabolic Perceptron: Classifier 1

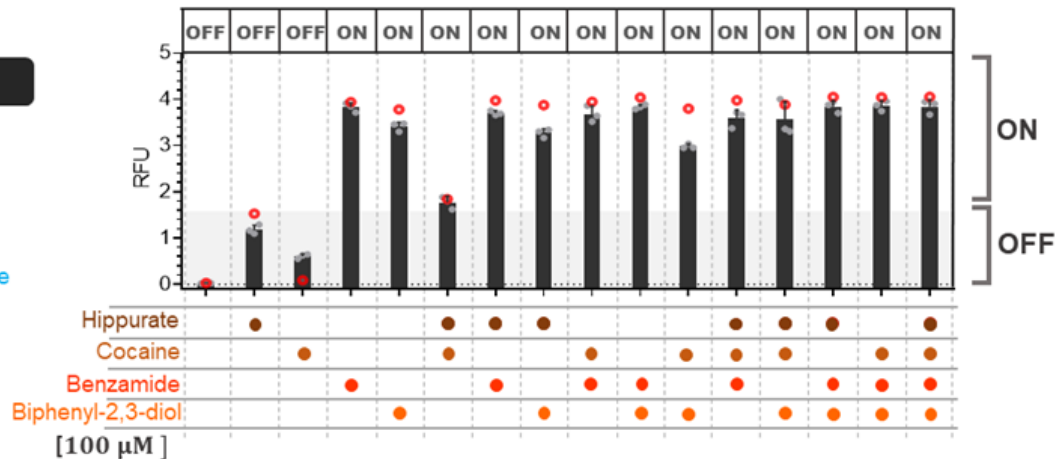
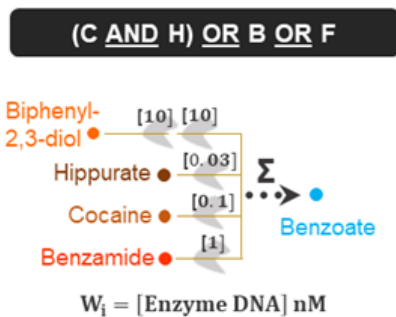
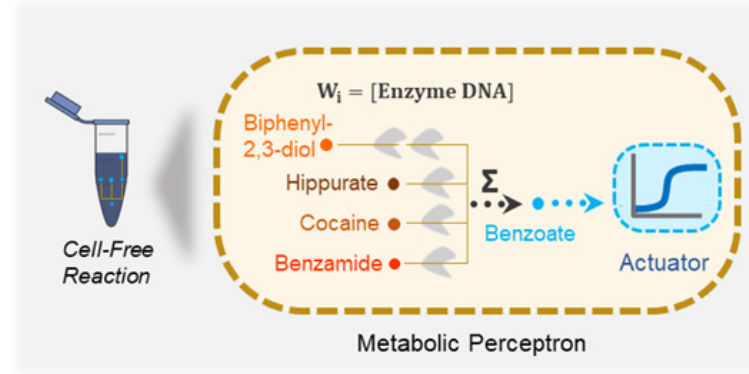
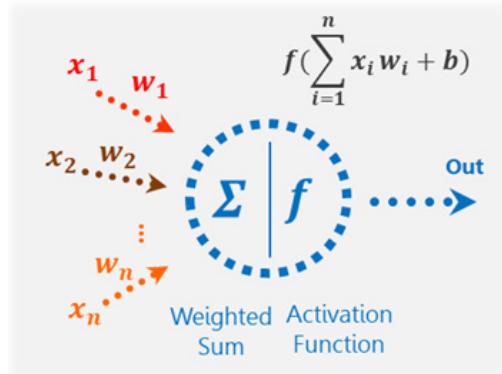


Full OR Classifier



- 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

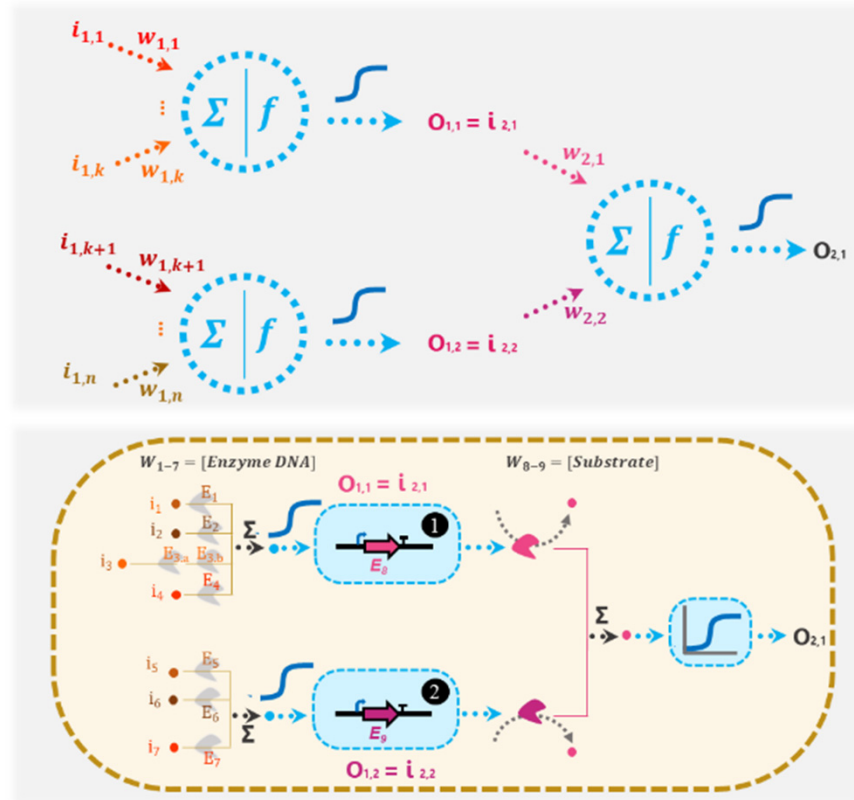


- Model based construction and validation of a binary classifiers
- The same metabolic circuit has different behaviors when used with different weights

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



Alexandra Zaharia
Angelo Batista
Bikash Samal
Ioana Popescu
Olivier Borkowski
Melchior Du-Lac
Thomas Duigou
Tristan Reif



Thank You

Questions Welcome