Metabolic Perceptrons for Neural Computing in Biological Systems

Amir Pandi [1], Mathilde Koch* [1], Peter L. Voyvodic [2], **Paul Soudier** [1,3], Jerome Bonnet [2], Manish Kushwaha [1] & Jean-Loup Faulon [1,3,4]*

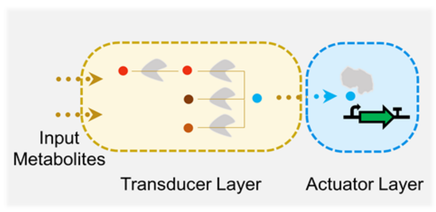
1.Micalis Institute, INRA, AgroParisTech, Université Paris-Saclay, Jouy-en-Josas, France
2. Centre de Biochimie Structurale, INSERM U1054, CNRS UMR 5048, University of Montpellier, Montpellier, France
3. iSSB Laboratory, Génomique Métabolique, Genoscope, Institut François Jacob, CEA, CNRS, Univ Evry, Université Paris-Saclay, 91057 Evry, France
4. SYNBIOCHEM Center, School of Chemistry, University of Manchester, Manchester, UK

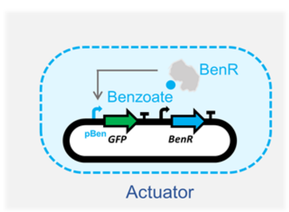
Background : digital & analog computation

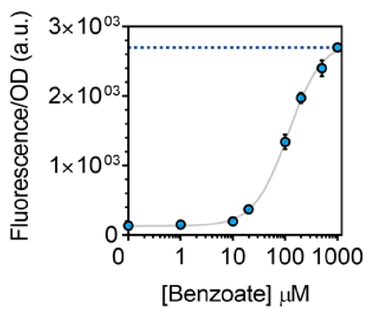
- Cells naturally perform analog computation but most of the synthetic systems created are digital[1]
- Metabolism can be used to perform computation on analog signals carried on metabolite concentrations[1]
- Metabolic circuitry allows fast & energy efficient computation in biological systems
- Bioinformatic tools (Retropath[2], sensipath[3]) enable rational design of such metabolic circuitry

Basic biological information processing device

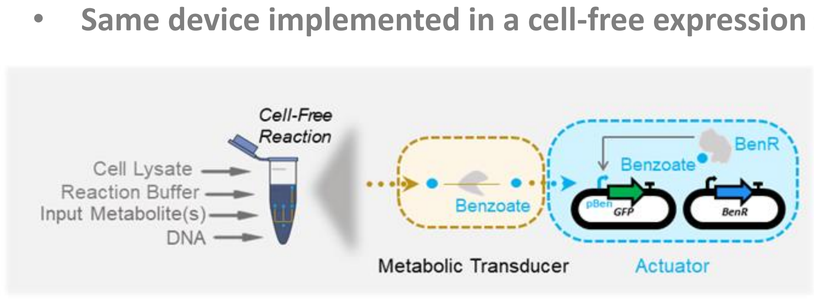
- Continuous metabolic concentrations can be used as analogic signals that can be actuated through whole cell and cell free biosensors[4]
- A benzoate sensing device in *Escherichia coli*

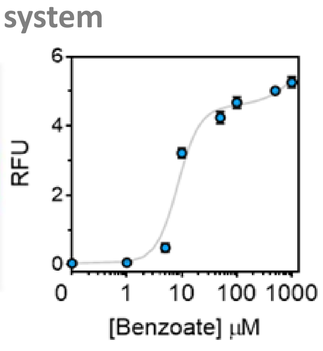




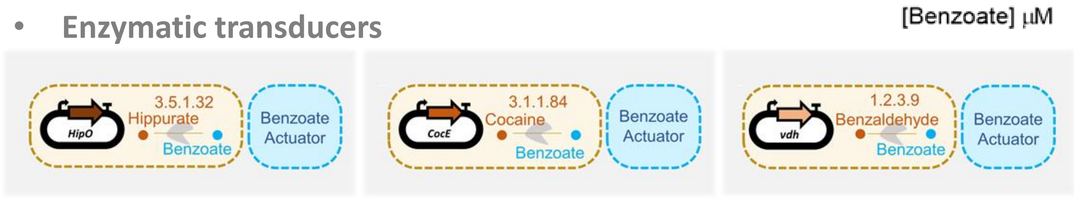


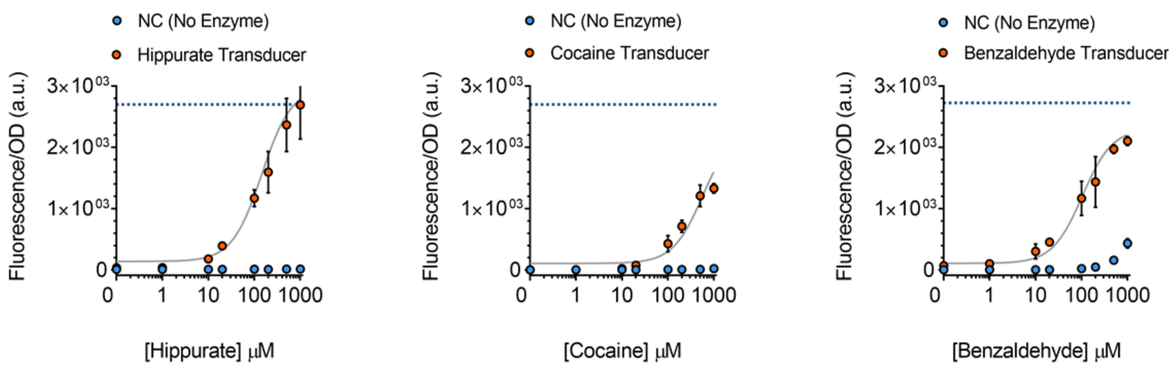
- Same device implemented in a cell-free expression system





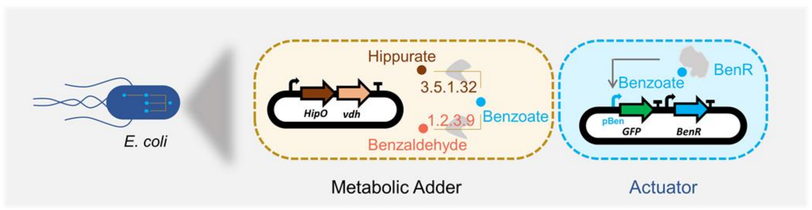
- Enzymatic transducers



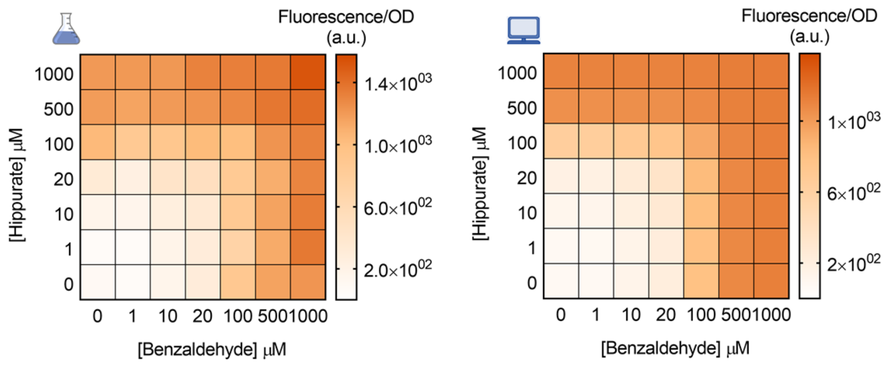


Whole Cell metabolic concentration adder

- Adders convert two metabolites into a common one

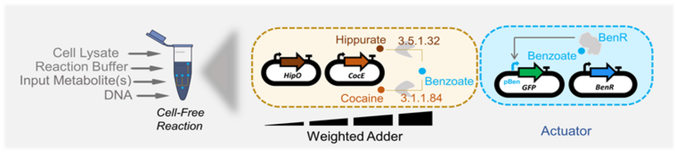


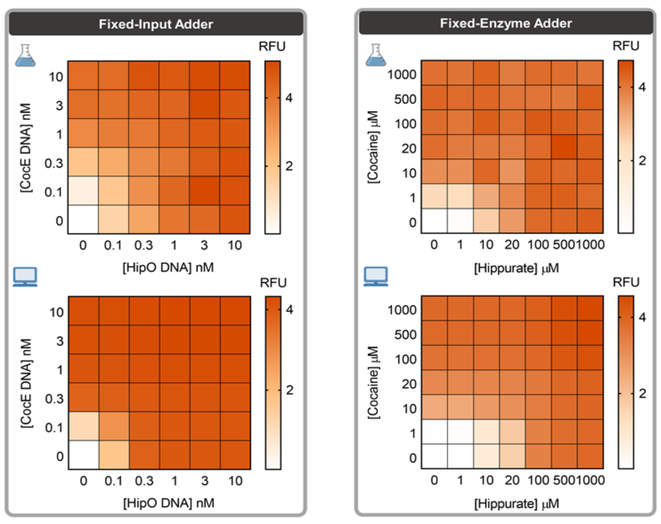
- Mathematical model captures behavior, including resource competition



PS is supported by PhD fellowship from ANR (Agence Nationale de la Recherche).

Cell Free weighted transducer and adders

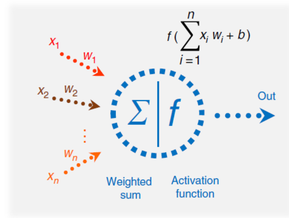


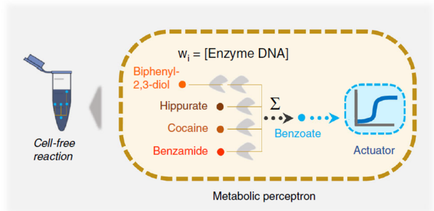


- In cell free ability to tune enzyme DNA concentration allows finer tuning
- Continuous [enzyme DNA] enables precise input weighting captured by our cell-free model

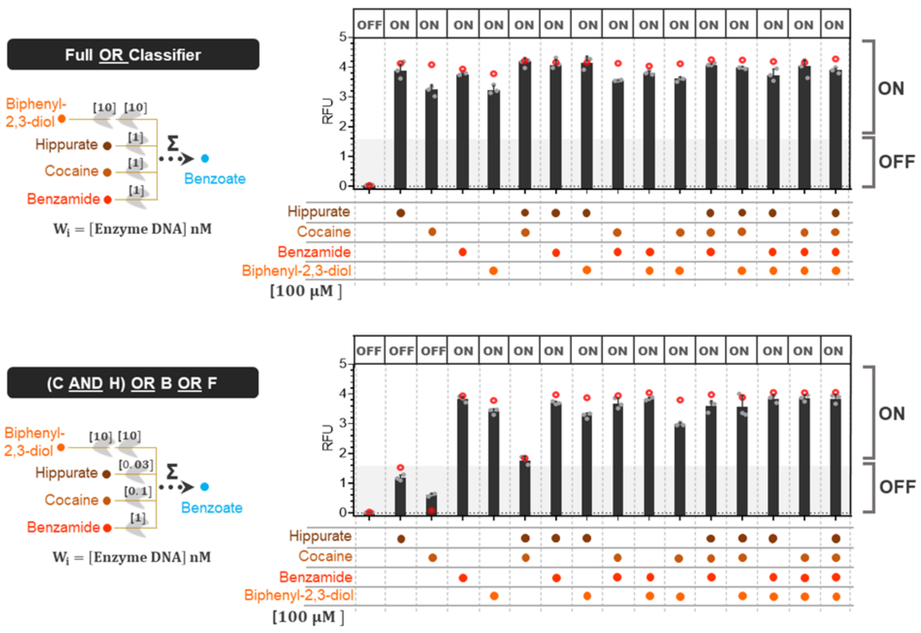
Perceptron implementation in cell free

- Our 4 input Perceptron design

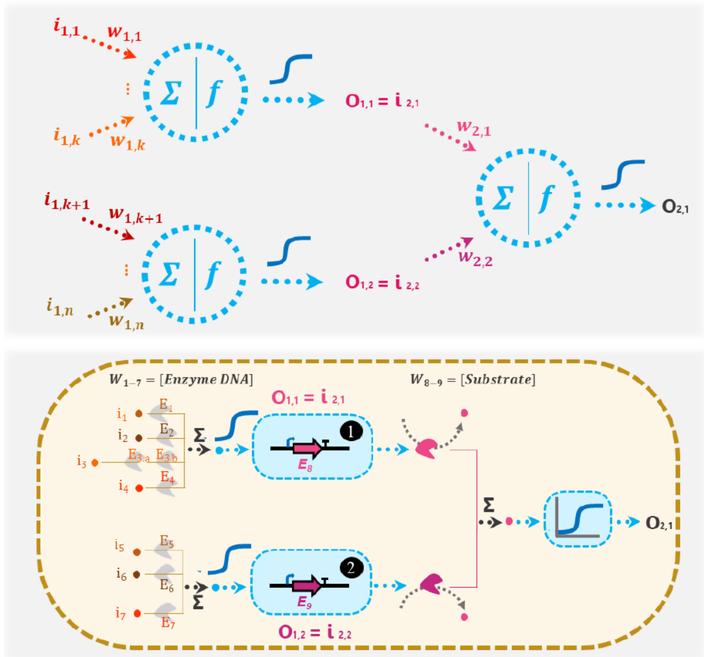




- Model based construction and validation of 2 binary classifiers



Strategies for a Multi-layer Perceptron



- Enzymes can be actuators weighted by inducer concentrations
- Intermediate perceptron layers use enzyme production as actuators
- More complex networks become possible

References

This work was published as : Pandi, A., Koch, M., Voyvodic, P. L., Soudier, P., Bonnet, J., Kushwaha, M., & Faulon, J. L. (2019). Metabolic perceptrons for neural computing in biological systems. *Nature communications*, 10(1), 3880.

1. Daniel, R., Rubens, J. R., Sarpeshkar, R., & Lu, T. K. (2013). Synthetic analog computation in living cells. *Nature*, *497*(7451), 619.
2. Delépine, B., Duigou, T., Carbonell, P., & Faulon, J. L. (2018). RetroPath2. 0: A retrosynthesis workflow for metabolic engineers. *Metabolic engineering*, *45*, 158-170.
3. Delépine, B., Libis, V., Carbonell, P., & Faulon, J. L. (2016). SensiPath: computer-aided design of sensing-enabling metabolic pathways. *Nucleic acids research*, *44*(W1), W226-W231.
4. Voyvodic, P. L., Pandi, A., Koch, M., Conejero, I., Valjent, E., Courtet, P., ... & Bonnet, J. (2019). Plug-and-play metabolic transducers expand the chemical detection space of cell-free biosensors. Nature communications, 10(1), 1697.