

Cell regulation and multicellular control for applications in Synthetic Biology

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Synthetic Biology aims at engineering biological systems with new functionalities, with applications ranging from health treatments to bioremediation, production of biofuels and drugs in bioreactors. This is made possible by embedding artificial genetic circuits into living cells, such as bacteria, yeast, and fungi, modifying their natural behavior; that is, by synthetically modifying when and how much genes are expressed to produce proteins or other chemicals of interest. In this talk we will briefly present the work that we have done at the University of Naples in the context of the project COSY-BIO funded by the European Union, which finished last year, and some of the ongoing research. Our work has been focused on the exploitation of the so-called “genetic toggle-switch”, which is a fundamental component in Synthetic Biology as it plays a key role in cell differentiation and decision making. Its importance comes from its ability to endow host cells with memory of previous stimuli allowing them to completely change their behavior in response. Specifically, we present how, thanks to its characteristics, the genetic toggle-switch can be used either to regulate the expression of two proteins of interest to some intermediate level [1-2] or as a reversible memory mechanism allowing cells to differentiate and balance labor in multicellular applications [3-4]. Moreover, we present some recent results on the control of the ratio and the growth rate of cell populations for biomedical and industrial applications [5-7].

[1] D. Fiore, A. Guarino, M. di Bernardo – “Analysis and control of genetic toggle switches subject to periodic multi-input stimulation”, *IEEE Control Systems Letters* (2018)

[2] A. Guarino, D. Fiore, D. Salzano, M. di Bernardo – “Balancing cell populations endowed with a synthetic toggle switch via adaptive pulsatile feedback control”, *ACS Synthetic Biology* (2020)

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[4] D. Salzano, D. Fiore, M. di Bernardo – “Ratiometric control for differentiation of cell populations endowed with synthetic toggle switches”, *Proc. of the 58th IEEE Conference on Decision and Control* (2019)

[5] D. Fiore, F. Della Rossa, A. Guarino, M. di Bernardo – “Feedback ratiometric control of two microbial populations in a single chemostat”, *IEEE Control Systems Letters* (2021)

[6] V. Fusco, D. Salzano, D. Fiore, M. di Bernardo – “Embedded control of cell growth using tunable genetic systems”, *International Journal of Robust and Nonlinear Control* (2022)

[7] G. Perrino, S. Napolitano, F. Galdi, A. La Regina, D. Fiore, T. Giuliano, M. di Bernardo, D. di Bernardo – “Automatic synchronisation of the cell cycle in budding yeast through closed-loop feedback control”, *Nature Communications* (2021)

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