Comparative analysis of strategies for *in vivo* control of cellular populations

G. Perrino[1], G. Fiore[1], M. di Bernardo[2], and D. di Bernardo[1,2]

***Short Abstract* — Here we provide an *in silico* comparative analysis of two control strategies to regulate biological processes *in vivo*. In particular we analyse the model predictive control strategy (MPC) and the classical proportional-integral-derivative control strategy (PID) by assessing their performances in regulating the mathematical representation of the dynamics of two inducible promoters (pSTL1 and pGAL1) in yeast cells. Our results demonstrate that both the control strategies are able to accomplish the regulation tasks, however, unlike the MPC, the PID strategy does not require a model of the system to be controlled, thus being more generically applicable.**

***Keywords* — Control engineering, gene expression, yeast, negative feedback, gene networks.**

I. Introduction

A biological system can be modeled mathematically as a single equation or as a system of mathematical equations as any other physical phenomenon [1,2]; thus control engineering methods can be applied to steer the dynamic behavior of gene regulatory networks: a) *in silico*, by simulating the response of mathematical model to inputs calculated via negative feedback control schemes, b) *in vivo*, by applying control engineering principles to populations of living cells.

The *in vivo* control of cellular populations is a challenging task since all living conditions of cells should be guaranteed despite the external stimuli provided to them, moreover the sensing system outputs should be accurate enough to appreciate small variations in system outputs (e.g. cells' fluorescence, dimensions or shape); moreover genetically identical cells in the same environment show significant variations in phenotype thus even simple attributes, such as the concentration of proteins synthesized from a constitutively expressed gene, can vary greatly from cell to cell.

For this purpose several experimental platforms have been developed, each with its own characteristics [4,5]. Control algorithms that in general could be applied to control gene expression in living cells are presented. In particular, two control strategies are discussed: model predictive control (MPC) [6], and proportional-integral-derivative control (PID) [3]. Specifically, MPC has been applied to control expression of a fluorescent reporter protein from the pSTL1 promoter responsive to osmotic stress [4]. PID control has been applied to regulate expression of a fluorescent reporter protein from the pGAL1 promoter responsive to galactose/glucose [2,3,5]. These two control strategies have not been directly compared on the same promoter, therefore it is not possible to assess which one works better.

[1]Telethon Institute for Genetics and Medicine (TIGEM), Naples 80131, Italy. E-mail: dibernardo@tigem.it

[2]Department of Electrical Engineering and Information Technology, University of Naples Federico II, Naples 80125, Italy. E-mail: mario.dibernardo@unina.it

II. Methods

Here we compared the two strategies *in silico* on the mathematical models for both the pSTL1 and pGAL1 promoters driving a fluorescent reporter protein in yeast cells. We assessed the performance of the control strategies in maintaining a desired value of fluorescence in the face of biological noise and robustness to model parameters.

III. Results & Conclusions

The analysis proves that feedback control strategies can be applied successfully *in silico* for the regulation of gene expression in living cells' populations. In detail, when dealing the set-point regulation task, both control algorithms showed similar performances, whereas in the case of signal tracking regulation, the MPC strategy provided better results. However the MPC requires a mathematical model of the biological process to be controlled, whose parameters have to be accurately estimated. If the model is not correctly estimated, MPC performance will decrease below the PID performance.

References

[1] Cantone I, Marucci L, Iorio F (2009) "A yeast synthetic network for in vivo assessment of reverse-engineering and modeling approaches". *Cell* **137(1)**, 172-181.

[2] Fiore G, Menolascina F, di Bernardo D (2013) "An experimental approach to identify dynamical models of transcriptional regulation in living cells". *Chaos: An Interdisciplinary Journal of Nonlinear Science* **23(2)**, 025106.

[3] Menolascina F, di Bernardo M, di Bernardo D (2011) "Analysis, design and implementation of a novel scheme for in-vivo control of synthetic gene regulatory networks". *Automatica* **47(6)**, 1265-1270.

[4] Uhlendorf J, Miermont A, Delaveau T (2012) "Long-term model predictive control of gene expression at the population and single-cell levels". *PNAS* **109(35)**, 14271-14276.

[5] Menolascina F, Fiore G, di Bernardo D (in press) "In-vivo real-time control of protein expression from endogenous and synthetic gene networks". *PLOS Computational Biology*.

[6] Morari M, Lee J H (1999) "Model predictive control: past, present and future". *Computers & Chemical Engineering* **23(4)**, 667-682.