The TF binding mechanism role in the retroactivity impact

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***Short Abstract* — The effects of downstream loads in regulatory networks represent an issue for design in synthetic biology. Currently, retroactivity effects role in natural regulatory networks remains far from understood. A first step towards the understanding of such role is the dissection of biological systems where retroactivity is involved. In this work, we deal with different mechanisms that a transcription factor may use to bind to DNA and the impact that such downstream loads may have depending of the used mechanism.**

***Keywords* — retroactivity, transcription regulation, transcription factor.**

I. Introduction

Retroactivity is a signal that arises when connecting new elements to a biological system [1]. In a transcriptional regulation circuit, retroactivity is caused by the association of a transcription factor (TF) to its cognate binding sites in the genome.

The functional relevance of retroactivity still remains elusive, though multiple proposals regarding the potential functional roles of downstream loads have been posed as in [2] and [3], among others.

TFs bind their downstream targets by different mechanisms [4], [5]. These mechanisms are the steps needed for the transcription factor-binding site complex to drive downstream transcription. Here, we analyze four main binding mechanisms: simple monomer binding, dimerization prior to binding, two monomers' sequential binding, and sequential cooperative binding along with dimerization prior to binding. Our aim is to evaluate the impact of retroactivity in the system's behavior given that the transcription factor is regulating downstream sites with a specific mechanism.

II. Results

We analyze the change of three features due to interconnection: i) functional TF capable of binding downstream sites and ii) the total TF concentration, as this is easy to assess experimentally. We simulated our systems using ODE's and rule based models.

A. Deterministic models

The ODE's based modeling was curated using rule based models [6] and simulated using odeint in Python. Our models include whole tentative systems in two versions: original systems and retroactivity induced systems. Each one is simulated considering for the conditions of weak and strong association rate.

We assessed different degradation rates for each of the mechanism to analyze the extent at which they could be controlled.

B. Stochastic models

We simulated the stochastic versions of our systems using the Gillespie algorithm version included in BioNetGen to give further statistical support to the observed differences and gain insight in the noise role in this system.

III. Conclusion

Independently of the promoter strength, the sequential binding mechanism is conserved as the one with the most notorious difference between connected and disconnected cases, followed by sequential binding with dimerization. Regardless of the TF assessed (total or functional), the relation of connected vs. disconnected case seems to change in a way that is linearly dependent on the chosen degradation rate.

The prevalent change in variability upon interconnection, seems to be indicative of a side effect caused by downstream connections that makes the systems responses much more punctual in terms of the available TF. We find this interesting as it could have a role in fine tuning transcriptional responses.

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References

[1] Del Vecchio D, Ninfa AJ, and Sontag ED (2008) Modular Cell Biology: Retroactivity and Insulation. *Nature/EMBO Molecular Systems Biology*, 4:161

[2] Burger A, Walczak AM, Wolynes PG (2010) Abduction and asylum in the lives of transcription factors. *PNAS* 107 (9), 4016–4021.

[3] Jayanthi S, Nilgiriwala K S, Del Vecchio D (2013) Retroactivity controls the temporal dynamics of gene transcription. *ACS Synth. Biol* 2, 431–441.

[4] Keller AD, (1995) Model genetic circuits encoding autoregulatory transcription factors. *Journal of Theoretical Biology* 172, 169–185.

[5] Berger C, Piubelli L, Haditsch U, Rudolf Bosshard H, (1998) Diffusion–controlled DNA recognition by an unfolded, monomeric b-zip transcription factor. *FEBS Letters* 425, 14–18.

[6] Faeder JR, Blinov ML, Goldstein B and Hlavacek WS (2005) Rule-based modeling of biochemical networks. *Complexity,* 10, 22-41