Deciphering the effect of nonlinearities induced by protein binding

Josep Mercadal[1,2], Nadja Bosch[3], Isabel Betegón-Putze[3], Ainoa Planas-Riverola[3], Ana I. Caño-Delgado[3], and Marta Ibañes[1,2]

[1]Department of Condensed Matter Physics, Universitat de Barcelona, 08028 Barcelona, Spain
[2]Universitat de Barcelona Institute of Complex Systems, Universitat de Barcelona, 08028 Barcelona, Spain
[3]Department of Molecular Genetics, Centre for Research in Agricultural Genomics (CRAG), CSIC-IRTA-UAB-UB, Campus UAB, Cerdanyola del Vallès, 08193 Barcelona, Spain

Deciphering and understanding the gene regulatory interactions that control biological processes is an active area of research, and one of the fundamental problems in modern biology. Mathematical and computational models have been helpful to investigate the emergent properties of such networks and circuits, as they often display behaviours which are only understood in the context of nonlinear dynamics, such as bistability, oscillations or excitability [1]. Yet, as more data are acquired, new layers of interactions are being included, such as epigenetic regulations and protein-protein interactions. Molecular titration, i.e., the formation of complexes, has been shown to induce ultrasensive responses in gene regulatory networks [2], a key behaviour in the cell's functional repertoire which allows decisive and fast responses when needed. For instance, protein interactions are though to play an important role in the regulation of quiescent states in stem cells of the *Arabidopsis thaliana* root [3].

Herein we study the effect of protein-protein interactions and how these influence the behaviour of gene expression, focusing on two genetic circuits which exhibit the same type of transcriptional response. These circuits involve only two genes, which mutually regulate each other's transcription. One of them involves only transcriptional regulations, while the other includes, beside transcriptional regulation, the formation of protein complexes through pair-wise interactions. The dynamics of the two protein types, x and y, are governed by the following two-dimensional dynamical system

$$\frac{dx}{dt} = g_x(x,y) - \lambda xy - x, \tag{1a}$$

$$\frac{dy}{dt} = g_y(x,y) - \lambda \epsilon xy - y, \tag{1b}$$

where the parameter λ, the rate of complex formation, is set to $\lambda = 0$ in the circuit without protein interactions (circuit B). The functions g_x and g_y encode all the transcriptional interactions, including possible self-activations and self-repressions as well as the cross-regulations between the two genes. We study how the parameters λ and ϵ, the ones quantifying the formation of complexes, affect the behaviour of circuit A with respect to circuit B over several circuit architectures. We also evaluate how the loss of function of proteins (mutant genotypes) alters the system's behaviour in the steady state, both in protein concentrations, measured by x and y, and transcriptional activity, measured by g_x and g_y. We find that different architectures can induce degeneracy in transcriptional responses, that is, generating the same behaviour from distinct interactions, but different behaviour in protein concentrations. This raises the question of how genetic interactions can be inferred only with transcriptional data.

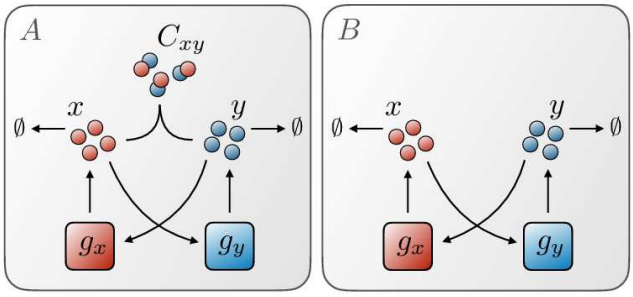

Fig. 1. Regulatory circuits may display the same kind of transcriptional responses eventhough their inherent architecture is different. In circuit A, two genes regulate each other and the product proteins can bind pair-wise to form complexes. In circuit B, no protein binding occurs, so the only relevant interactions are transcriptional. Cross-regulation arrows can indicate both transcriptional activation and repression.

We further study which is the role of stochasticity in our circuits. Both transcription and translation are inherently stochastic processes [5], and as such their dynamics can exhibit behaviours far from expected by their deterministic counterparts. These include, for example, noise induced transitions in bistable and excitable systems, which may play an important role as prime drivers of cellular differentiation.

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