

# **Supplementary Information for $\tau_{OY}$ LIFE: a computational framework to study the multi-level organization of the genotype-phenotype map**

Clemente F. Arias<sup>1,2</sup>, Pablo Catalán<sup>1,2</sup>, Susanna Manrubia<sup>1,3</sup>, José A. Cuesta<sup>1,2,4,\*</sup>

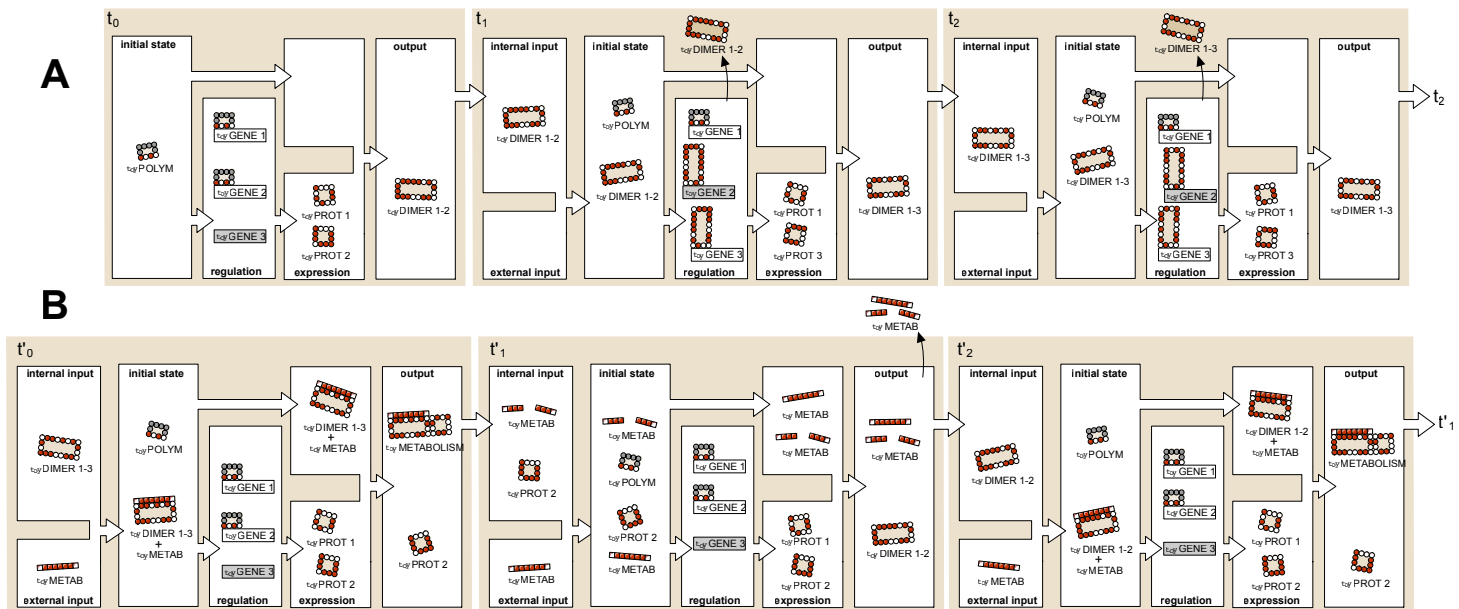
<sup>1</sup> Grupo Interdisciplinar de Sistemas Complejos (GISC), Madrid, Spain

<sup>2</sup> Dept. Matemáticas, Universidad Carlos III de Madrid, Leganés, Madrid, Spain

<sup>3</sup> Centro Nacional de Biotecnología (CSIC), Campus de Cantoblanco, Madrid, Spain

<sup>4</sup> Instituto de Biocomputación y Física de Sistemas Complejos (BIFI),  
Universidad de Zaragoza, Zaragoza, Spain

\* E-mail: Corresponding [cuesta@math.uc3m.es](mailto:cuesta@math.uc3m.es)



**Supplementary Figure S1. Summary of a metabolon activity in *toyLIFE*.** Consider the toyGRN of Figures 4 and 5 (A). Initially ( $t_0$ ) all three toyGenes are off. The toyPolymerase can bind to the promoter regions of toyGenes 1 and 2, expressing toyProteins 1 and 2, and toyDimer 1-2 forms. Thus, the internal input set for time step  $t_1$  contains toyDimer 1-2. At the regulation phase in  $t_1$  the toyPolymerase (which is always present) activates the expression of toyGene 1, and toyDimer 1-2 inhibits the expression of toyGene 2 and activates that of toyGene 3. As a result, toyDimer 1-3 forms. The input set for time step  $t_2$  then contains just toyDimer 1-3. At  $t_2$  toyDimer 1-3 again inhibits the expression of toyGene 2 and activates that of toyGene 3, and the internal input set for next time step will again only contain toyDimer 1-3. The toyGRN has reached a steady state. But if at this point a toyMetabolite is added to the input set, the behavior of the toyGRN changes (B). The toyMetabolite is such that it binds toyDimer 1-3, so the toyDimer is unable to participate in regulation, and the toyPolymerase activates the expression of toyGenes 1 and 2. toyProtein 1 is then able to bind to toyDimer 1-3 in the output phase, breaking it. The internal input set for time step  $t'_1$  is formed by toyProtein 2 and the rests of the broken toyMetabolite. Even if the toyMetabolite appears again as a external output, no molecule can bind it in the input phase, so this does not affect regulation. toyProtein 2 has no effect on regulation, and again toyProteins 1 and 2 are expressed, and toyDimer 1-2 is formed. As no molecule has bound the toyMetabolites, they will not be present in the internal input set of time step  $t'_2$ , which will only contain toyDimer 1-2. If a new toyMetabolite is provided as the external input, the toyDimer will bind to it, and the cycle begins again (however, note that from now on all metabolism will be due to toyDimer 1-2 instead of toyDimer 1-3).