Electronic Supplementary Material (ESI) for Molecular BioSystems

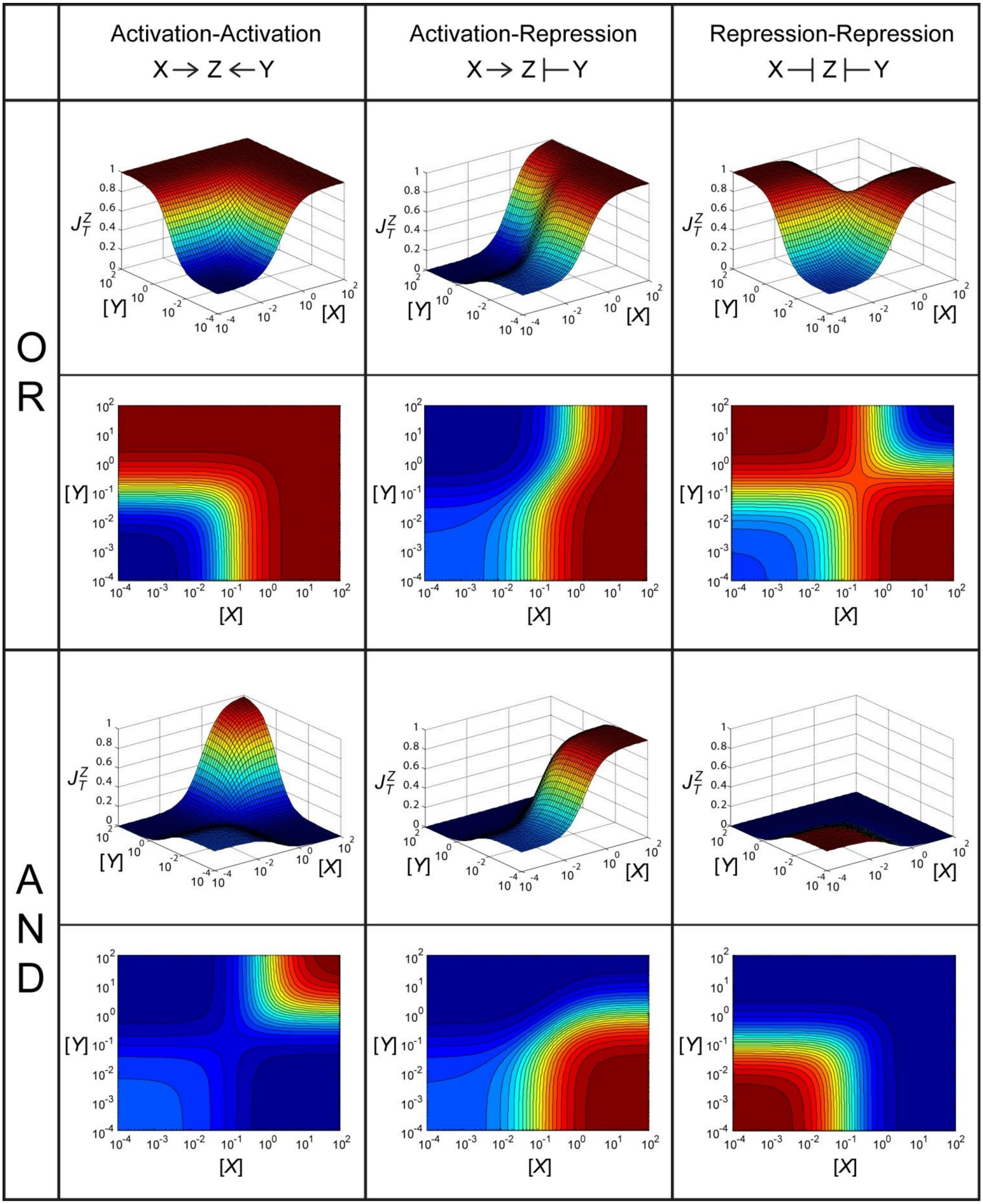
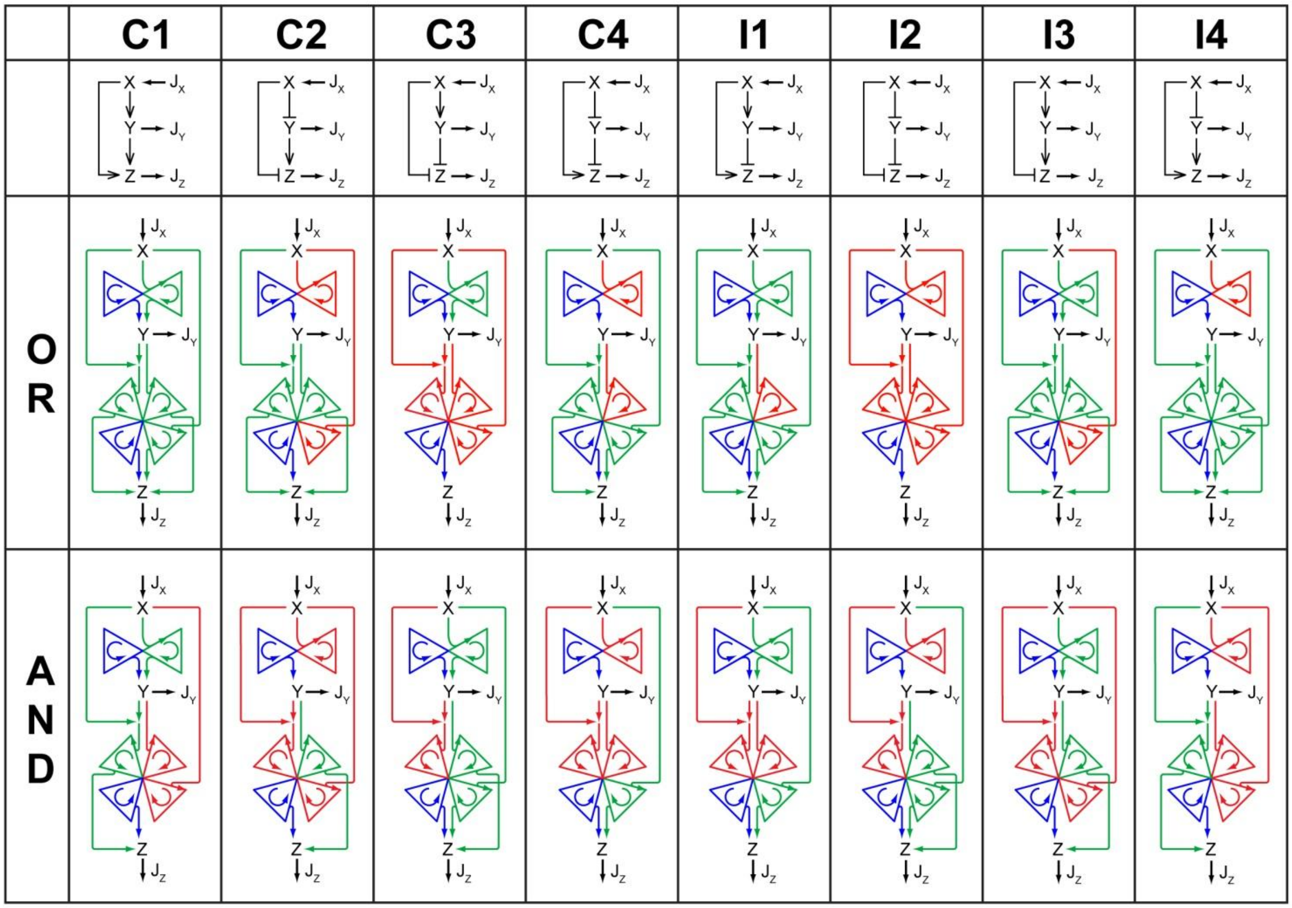


Figure S1: Transcription rate of *Z* when two transcription factors *X* and *Y* are present. The transcription surfaces and plane projections are shown for both *OR* and *AND* input logics in three different cases: activator-activator, activator-repressor and repressor-repressor. [*B*] = 0.02 [nM], $\beta^{ZI} = 1$ [nM·s^{-1}] and $\kappa^{ZI} = 0.08$ [nM], for *I* = *B*, *X*, *Y*, and *XY*.



Activation	YA	YX	ZB	ZX	ZY	ZXY OR	ZXY AND
k_1 [$s^{-1}nM^{-1}$]	2	222.2	1	20.2	2.02	10^{-8}	40.4
k_2 [s^{-1}]	2	2	1	1	1	10^{-4}	1
k_3 [s^{-1}]	10^3						
k_{-1} [s^{-1}]	10^{-6}						
k_{-2} [s^{-1}]	10^{-6}						
k_{-3} [$s^{-1}nM^{-2}$]	10^{-6}						
β [$nM\cdot s^{-1}$]	2	2	1	1	1	10^{-4}	1
κ [nM]	1	0.009	1	0.049	0.49	10^4	0.0247

Repression	YX	ZX	ZY	ZXY OR	ZXY AND
k_1 [$s^{-1}nM^{-1}$]	2.22	1.01	0.101	10^{-11}	40.4
k_2 [s^{-1}]	2	1	1	10^{-4}	1
k_3 [s^{-1}]	10^6				
k_{-1} [s^{-1}]	10^{-12}				
k_{-2} [s^{-1}]	10^{-12}				
k_{-3} [$s^{-1}nM^{-2}$]	10^{-12}				
β [$nM\cdot s^{-1}$]	2	1	1	10^{-4}	1
κ [nM]	0.898	0.989	9.89	10^7	0.0247

$T = 298$ [K], $[A] = 0.11$ [nM], $[B] = 0.01$ [nM], $[D_Y]_{tot} = [D_Z]_{tot} = 1$, $\alpha = 1$ [s^{-1}] (for all the species)

$J = 0$ (for all the co-activators), $10^{-4} \le [X],[Y],[Z] \le 1$ [nM], $J_Y, J_Z \le 10^{-5}$ [$nM\cdot s^{-1}$], $1.5\cdot 10^4 \le hdr \le 1.5\cdot 10^5$ [$J\cdot s^{-1}$]

Figure S2: Cyclic representation of the Feed Forward Loops (FFL) with input logics *AND* and *OR*. FFL Coherent Type 1 to 4 and Incoherent Type 1 to 4 are shown. Kinetic parameters for activation and repression, as well as the optimization parameters are shown here.

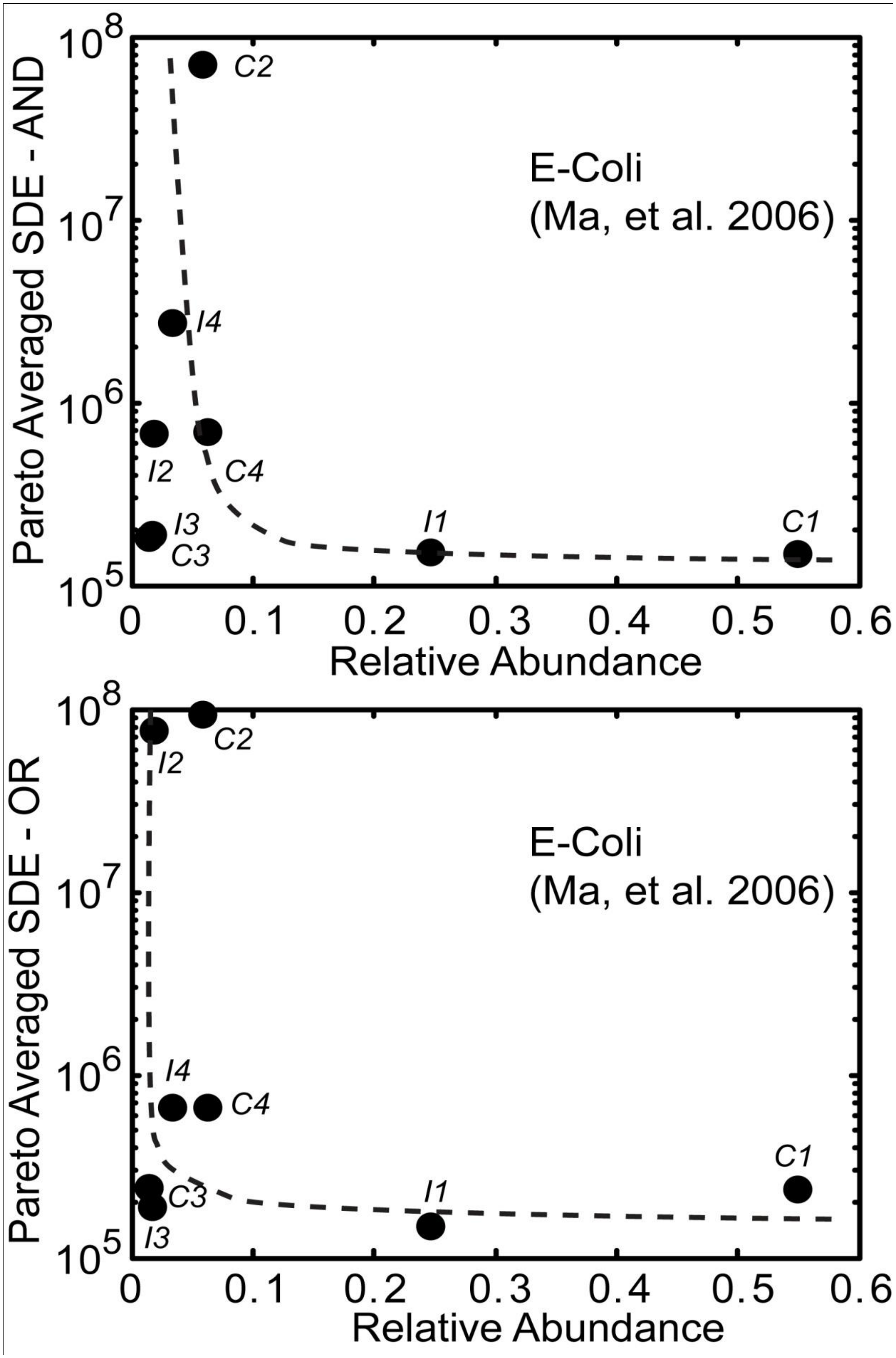


Figure S3: Correlation of averaged Pareto-optimal *SDE* with relative abundance of FFL motifs for *E. coli* and *S. cerevisiae* TRNs (Ma et. al, 2006 (10)).

Table S1: Normalized Constraint Method for *n*-objective

STEP	FUNCTIONS	FORMULATIONS
1	*Anchor points*	Obtain the anchor points, g^{i*} for $i \in \{1, 2,\ldots n\}$, by solving Problem PUi. Define hyperplane, as the one that comprises all the anchor points. This plane is called the *utopia hyperplane* (or, utopia plane).
2	*Objectives mapping/ normalization*	Compute the Nadir points and Utopia Points. Define L as $L = [\ell_1 \ell_2 \ldots \ell_n]^T = g^N - g^u$, that leads to the normalized design metrics as $\overline{g}_i = \dfrac{g_i - g_i\left(x^{i*}\right)}{\ell_i}$, $i = 1, 2, \ldots, n$
3	*Utopia plane vector*	Define the direction, $\overline{N}_k$ from $\overline{g}^{k*}$ to $\overline{g}^{n*}$ for $k \in \{1, 2,\ldots n\}$ as $\overline{N}_k = \overline{g}^{n*} - \overline{g}^{k*}$
4	*Normalized increments*	Compute a normalized increment, δ_k along the direction $\overline{N}_k$ for a prescribed number of solutions, m_k, along the associated $\overline{N}_k$ direction: $\delta_k = \dfrac{1}{m_k - 1}$ $(1 \le k \le n-1)$
5	*Generate utopia hyperplane points*	Evaluate a set of evenly distributed points on the Utopia hyperplane as $\overline{X}_{pj} = \sum_{k=1}^{n} \alpha_{kj} \overline{g}^{k*}$ where $0 \le \alpha_{kj} \le 1$ and $\sum_{k=1}^{n} \alpha_{kj} = 1$.
6	*Pareto points generation*	A set of well-distributed Pareto solutions in the normalized objective space. For each value of $\overline{X}_{pj}$ generated in Step 5, the corresponding Pareto solution is obtained by solving the following problem: Problem Pn $\min_x \{\overline{g}_n(x)\}$ Subject to: $f_j(x) \le 0$ $(1 \le j \le r)$
7	*Pareto design metrics values*	The design metrics values for the Pareto solutions obtained in Step 6 can be obtained using the equation $g_i = \overline{g}_i \ell_i + g_i\left(x^{i*}\right)$, $i = 1, 2, \ldots, n$