

Context-Aware Technology Mapping in Genetic Design Automation Supporting Information

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A Comparison of Thermodynamic Library to Original Cello Library

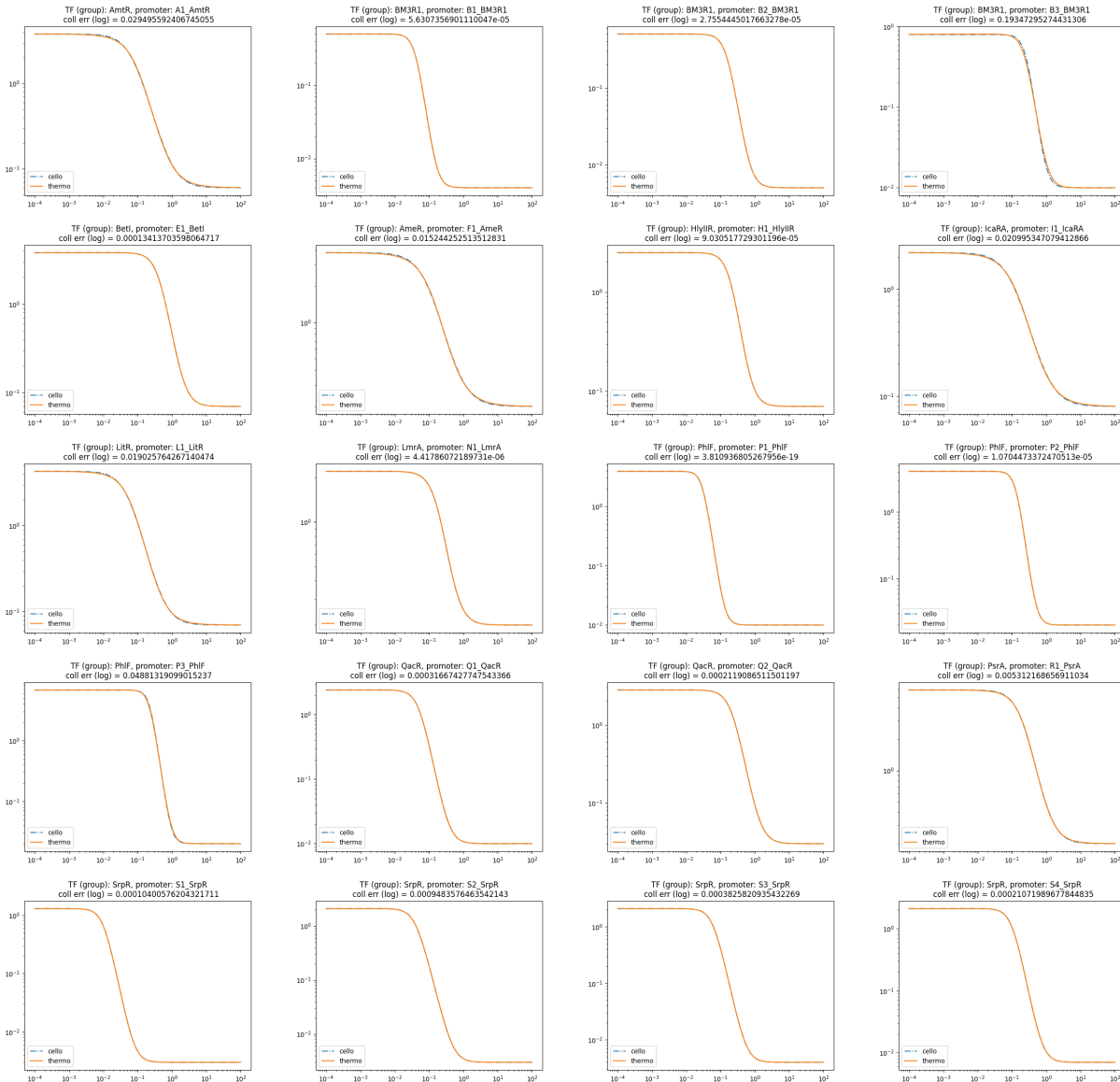


Figure S1: Plots comparing the original Cello transfer functions and the calibrated thermodynamic transfer functions.

B Proofs and Derivations

B.1 Proof of Transfer Function under Crosstalk

We start out with the equation from the main text

$$\mathbb{E}(X | f_1, \dots, f_K) = \frac{1}{1 + \frac{Z_0(p, f_1, \dots, f_K)}{Z_1(p, f_1, \dots, f_K)}}$$

What we did avoid before, we have to tackle now: the case, where we build the ratio of two implicitly completed multinomial coefficients with two arbitrary decrements. We thus seek to simplify

$$\begin{aligned} & \left[\begin{matrix} c \\ a_1, \dots, a_K \end{matrix} \right] / \left[\begin{matrix} c \\ a_1, \dots, a_m - 1, \dots, a_n - 1, \dots, a_K \end{matrix} \right] \\ &= \prod_{k=1}^K \binom{c - \sum_{l=1}^{k-1} a_l}{a_k} \\ & \quad / \left(\prod_{k=1}^{m-1} \binom{c - \sum_{l=1}^{k-1} a_l}{a_k} \binom{c - \sum_{l=1}^{m-1} a_l}{a_m - 1} \prod_{k=m+1}^{n-1} \binom{c - \sum_{l=1}^{k-1} a_l + 1}{a_k} \binom{c - \sum_{l=1}^{n-1} a_l + 1}{a_n - 1} \prod_{k=n+1}^K \binom{c - \sum_{l=1}^{k-1} a_l + 2}{a_k} \right) \\ &\approx \frac{c - \sum_{l=1}^{m-1} a_l}{a_m} \prod_{k=m+1}^{n-1} \frac{c - \sum_{l=1}^k a_l}{c - \sum_{l=1}^{k-1} a_l} \\ & \quad \times \left(\binom{c - \sum_{l=1}^{n-1} a_l}{a_n} \prod_{k=n+1}^K \binom{c - \sum_{l=1}^{k-1} a_l}{a_k} / \binom{c - \sum_{l=1}^{n-1} a_l + 1}{a_n - 1} \prod_{k=n+1}^K \binom{c - \sum_{l=1}^{k-1} a_l + 2}{a_k} \right) \end{aligned}$$

For the second line to simplify, we need to take a look at a combination of both formulas used before, i.e.

$$\binom{n-k+1}{m-1} \approx \frac{m}{n-k+1} \binom{n-k+1}{m} \approx \frac{m}{n-k+1} \frac{n-k}{n-k-m} \binom{n-k}{m} \approx \frac{m}{n-k-m} \binom{n-k}{m}$$

and thus

$$\binom{c - \sum_{l=1}^{n-1} a_l}{a_n} / \binom{c - \sum_{l=1}^{n-1} a_l + 1}{a_n - 1} \approx \frac{c - \sum_{l=1}^n a_l}{a_n}$$

The only thing that's left to derive is an expression for the two-times-increment. For this, we need to apply one of the formulas twice, i.e.

$$\binom{n-k+2}{m} \approx \frac{n-k+1}{n-k-m+1} \binom{n-k+1}{m} \approx \frac{n-k+1}{n-k-m+1} \frac{n-k}{n-k-m} \binom{n-k}{m} \approx \left(\frac{n-k}{n-k-m} \right)^2 \binom{n-k}{m}$$

and thus

$$\binom{c - \sum_{l=1}^{k-1} a_l}{a_k} \bigg/ \binom{c - \sum_{l=1}^{k-1} a_l + 2}{a_k} \approx \left(\frac{c - \sum_{l=1}^k a_l}{c - \sum_{l=1}^{k-1} a_l} \right)^2$$

This together then allows us to state

$$\begin{aligned} & \left[\begin{array}{c} c \\ a_1, \dots, a_K \end{array} \right] \bigg/ \left[\begin{array}{c} c \\ a_1, \dots, a_m - 1, \dots, a_n - 1, \dots, a_K \end{array} \right] \\ & \approx \frac{c - \sum_{l=1}^{m-1} a_l}{a_m} \prod_{k=m+1}^{n-1} \frac{c - \sum_{l=1}^k a_l}{c - \sum_{l=1}^{k-1} a_l} \frac{c - \sum_{l=1}^n a_l}{a_n} \prod_{k=n+1}^K \left(\frac{c - \sum_{l=1}^k a_l}{c - \sum_{l=1}^{k-1} a_l} \right)^2 \end{aligned}$$

and finally carry out the simplification of the expression for the expectation $\mathbf{E}(X \mid f_1, \dots, f_K)$, giving us

$$\begin{aligned} & \frac{Z_0(p, f_1, \dots, f_K)}{Z_1(p, f_1, \dots, f_K)} \\ & \approx \frac{w(p, f_1, \dots, f_K) \quad \dots}{\frac{p}{c} \prod_{n=1}^K \frac{c-p-\sum_{l=1}^{n-1} f_l}{c-p-\sum_{l=1}^n f_l} w(p-1, f_1, \dots, f_K) \quad \dots} \\ & \quad \dots \quad + \sum_{k=1}^K \frac{f_k}{c-p-\sum_{l=1}^{k-1} f_l} \prod_{n=k+1}^K \frac{c-p-\sum_{l=1}^{n-1} f_l}{c-p-\sum_{l=1}^n f_l} w(p, f_1, \dots, f_k - 1, \dots, f_K) \\ & \quad \dots \quad + \frac{p}{c} \sum_{k=1}^K \prod_{n=1}^{k-1} \frac{c-p-\sum_{l=1}^{n-1} f_l}{c-p-\sum_{l=1}^n f_l} \frac{f_k}{c-p-\sum_{l=1}^k f_l} \prod_{n=k+1}^K \left(\frac{c-p-\sum_{l=1}^{n-1} f_l}{c-p-\sum_{l=1}^n f_l} \right)^2 w(p-1, f_1, \dots, f_k - 1, \dots, f_K) \\ & \approx \frac{c}{p} \frac{w(p, f_1, \dots, f_K) + \sum_{k=1}^K \frac{f_k}{c} w(p, f_1, \dots, f_k - 1, \dots, f_K)}{w(p-1, f_1, \dots, f_K) + \sum_{k=1}^K \frac{f_k}{c} w(p-1, f_1, \dots, f_k - 1, \dots, f_K)} \\ & = \frac{c}{p} \frac{1 + \sum_{k=1}^K \frac{f_k}{c} \exp(-\beta(\varepsilon_{f_k} - \varepsilon_{c, f_k}))}{\exp(-\beta(\varepsilon_p - \varepsilon_{c,p})) + \sum_{k=1}^K \frac{f_k}{c} \exp(-\beta(\varepsilon_{p, f_k} - \varepsilon_{c,p} - \varepsilon_{c, f_k}))} \\ & = \frac{c}{p} \exp(-\beta(\varepsilon_{c,p} - \varepsilon_p)) \frac{1 + \sum_{k=1}^K \frac{f_k}{c} \exp(-\beta(\varepsilon_{f_k} - \varepsilon_{c, f_k}))}{1 + \sum_{k=1}^K \frac{f_k}{c} \exp(-\beta(\varepsilon_{p, f_k} - \varepsilon_p - \varepsilon_{c, f_k}))} \end{aligned}$$

Thus, we again obtain a formula for the NOT gate with imperfect competitiveness and arbitrary crosstalk from other TF's:

$$E(X | f_1, \dots, f_K) = \frac{1}{1 + \frac{1}{d} \frac{c}{p} \exp(-\beta(\varepsilon_{c,p} - \varepsilon_p))}$$

where the d factor is given by

$$d = \frac{1 + \sum_{k=1}^K \frac{f_k}{c} \exp(-\beta(\varepsilon_{p,f_k} - \varepsilon_p - \varepsilon_{c,f_k}))}{1 + \sum_{k=1}^K \frac{f_k}{c} \exp(-\beta(\varepsilon_{f_k} - \varepsilon_{c,f_k}))}$$

It is now a rather simple step to derive the final expression for the (N-input) NOR gate.

B.2 Worst-Case Titration Effect

In this section, we investigate the maximal effect of titration on the circuit response. In particular, we are interested in the limiting case, in which the concentration of non-cognate binding sites is small but the statistical weight of binding to these sites is extremely large. We will do so by looking at the original equation defined for counts of species members (positive integers) and rewrite it to involve concentrations in the end.

First, we consider an expression first derived in (1) and again presented in (2). The expression gives the fold-change $\phi(R)$ for the amount of (outgoing) product encoded in a single gene that is repressed by a single (incoming) TF available in absolute count R and in presence of an absolute amount of N_c non-cognate binding sites for the TF. For completeness, we introduce the positive real system volume $V \in \mathbb{R}_{\geq 0}$ and demand the absolute count of background binding sites $N \equiv Vc \in \mathbb{N}_0$, where c was our concentration of background binding sites. As a consequence, our TF concentration f from before then also relates to the count R by $R \equiv Vf$ and a concentration s of non-cognate binding sites is also available, where $N_c \equiv Vs$.

Then mentioned original expression is given by

$$\begin{aligned}
\phi(R) &\approx \frac{\sum_{k=0}^{\min(R, N_c)} \frac{R!}{N^k (R-k)!} \binom{N_c}{k} \exp(-\beta k \Delta \varepsilon_c)}{\sum_{k=0}^{\min(R, N_c)} \frac{R!}{N^k (R-k)!} \binom{N_c}{k} \exp(-\beta k \Delta \varepsilon_c) + \sum_{k=0}^{\min(R-1, N_c)} \frac{R!}{N^{(k+1)} (R-k-1)!} \binom{N_c}{k} \exp(-\beta (k \Delta \varepsilon_c + \Delta \varepsilon))} \\
&= \frac{\sum_{k=0}^{\min(R, N_c)} \frac{R!}{N^k (R-k)!} \binom{N_c}{k} \exp(-\beta k \Delta \varepsilon_c)}{\sum_{k=0}^{\min(R, N_c)} \left[1 + \frac{(R-k)}{N} \exp(-\beta \Delta \varepsilon) \right] \frac{R!}{N^k (R-k)!} \binom{N_c}{k} \exp(-\beta k \Delta \varepsilon_c)} \quad (1)
\end{aligned}$$

We can first rewrite (1) to become

$$\begin{aligned}
\phi(R) &\approx \left(1 + \frac{\sum_{k=0}^{\min(R, N_c)} \frac{(R-k)}{N} \exp(-\beta \Delta \varepsilon) \frac{R!}{N^k (R-k)!} \binom{N_c}{k} \exp(-\beta k \Delta \varepsilon_c)}{\sum_{k=0}^{\min(R, N_c)} \frac{R!}{N^k (R-k)!} \binom{N_c}{k} \exp(-\beta k \Delta \varepsilon_c)} \right)^{-1} \\
&= \left(1 + w(R, N_c) \frac{R}{N} \exp(-\beta \Delta \varepsilon) \right)^{-1} = \left(1 + w(R, N_c) \frac{f}{c} \exp(-\beta \Delta \varepsilon) \right)^{-1}
\end{aligned}$$

where we can simply insert $\frac{f}{c} = \frac{R}{N}$. The titration modifier $w : \mathbb{N}_0 \times \mathbb{N}_0 \rightarrow \mathbb{R}_{\geq 0}$ is thereby given by

$$\begin{aligned}
w(R, N_c) &= \frac{\sum_{k=0}^{\min(R, N_c)} \frac{(R-k)}{R} \frac{R!}{N^k (R-k)!} \binom{N_c}{k} \exp(-\beta k \Delta \varepsilon_c)}{\sum_{k=0}^{\min(R, N_c)} \frac{R!}{N^k (R-k)!} \binom{N_c}{k} \exp(-\beta k \Delta \varepsilon_c)} \\
&= \frac{R + \nu_1 (R-1) \exp(-\beta \Delta \varepsilon_c) + \dots + \nu_{N_c} (R - N_c) \exp(-\beta N_c \Delta \varepsilon_c)}{R + \nu_1 R \exp(-\beta \Delta \varepsilon_c) + \dots + \nu_{N_c} R \exp(-\beta N_c \Delta \varepsilon_c)}
\end{aligned}$$

We are now interested to investigate the limiting case, in which there is maximal titration to the host for a given amount of binding sites. Thus, we demand $\exp(-\beta \Delta \varepsilon_c) \gg 1$ and then deduce

$$w(R, N_c) \approx \frac{\nu_{N_c} (R - N_c) \exp(-\beta N_c \Delta \varepsilon_c)}{\nu_{N_c} R \exp(-\beta N_c \Delta \varepsilon_c)} = \frac{(R - N_c)}{R}$$

Plugging this into (1) gives the fold-change for this limiting scenario, i.e.

$$\begin{aligned} \phi(R) &\approx \left(1 + \frac{(R - N_c) R}{R N} \exp(-\beta\Delta\varepsilon)\right)^{-1} = \left(1 + \frac{(R - N_c)}{N} \exp(-\beta\Delta\varepsilon)\right)^{-1} \\ &= \left(1 + \frac{(f - s)}{c} \exp(-\beta\Delta\varepsilon)\right)^{-1} \end{aligned}$$

which is equivalent to an effective reduction of the available TF concentration f by a concentration of non-cognate binding sites s and thus a simple right-shift of the associated gate's transfer function.

C Genetic Gate Library Compatibility

The following figures detail the compatibility analysis of the used gate library from Cello.

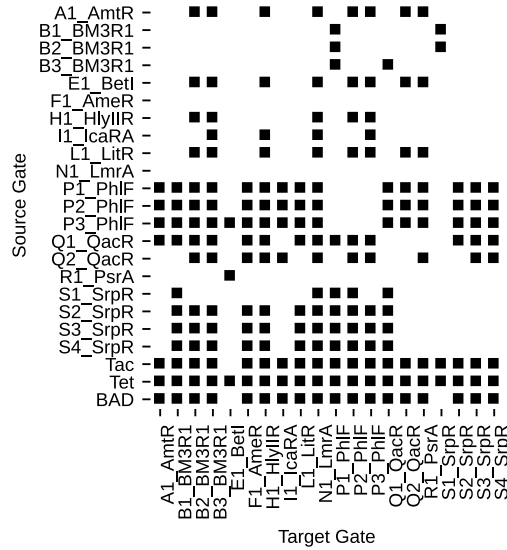


Figure S2: Pair-wise compatibility of gates according to the proposed compatibility constraint. Each dot represents a compatible pair of gates. This matrix is used for determining the compatibility of gates in the case of gates with only one input, i.e. NOT gates.

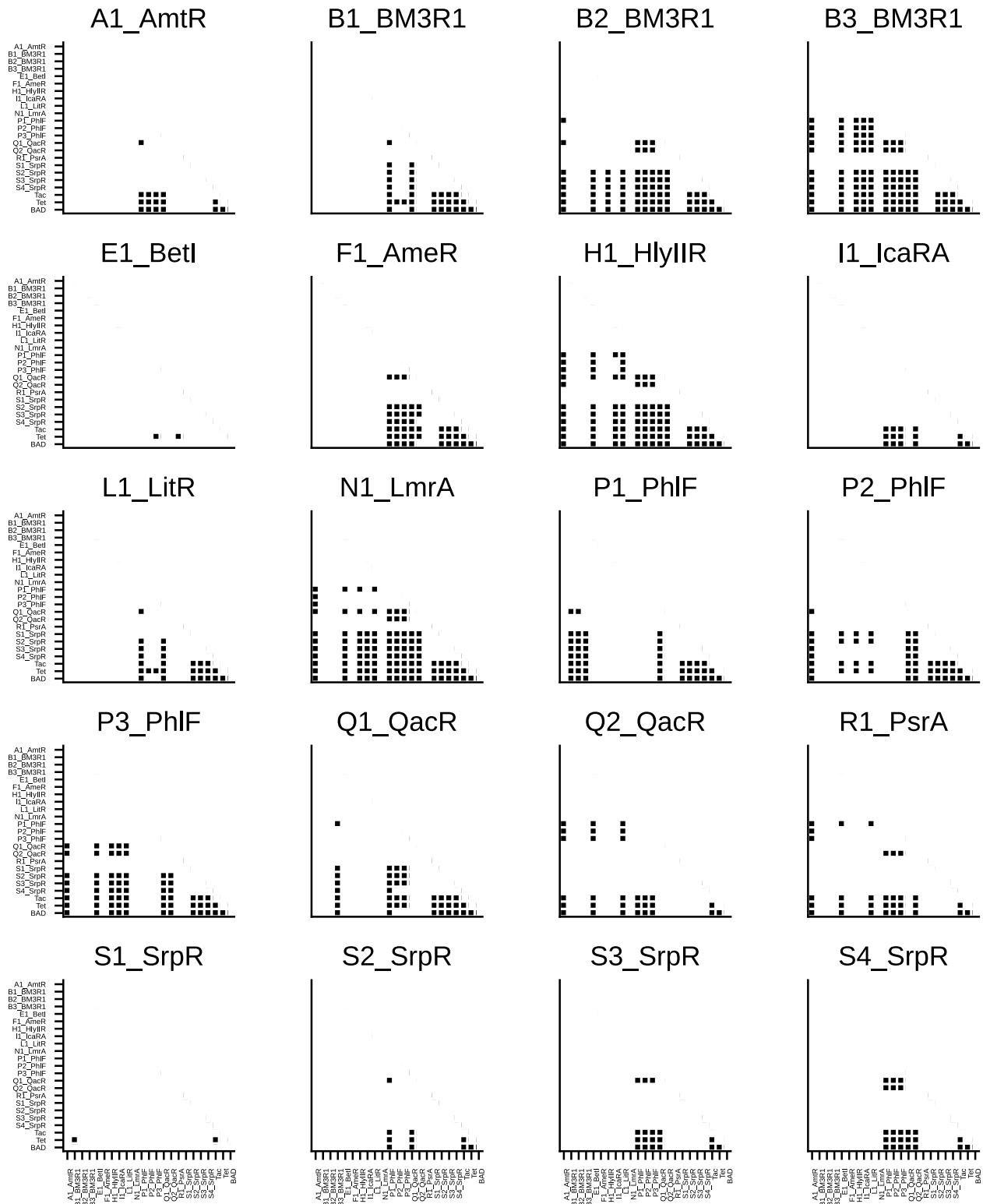


Figure S3: Detailed visualization of compatible gate triples. Each matrix shows the compatible pairs of input gates for one target gate.

References

1. Rydenfelt, M., Cox III, R., Garcia, H., and Phillips, R. (2014) Statistical mechanical model of coupled transcription from multiple promoters due to transcription factor titration. *Physical review. E, Statistical, nonlinear, and soft matter physics* 89, 012702.
2. Brewster, R. C., Weinert, F. M., Garcia, H. G., Song, D., Rydenfelt, M., and Phillips, R. (2014) The transcription factor titration effect dictates level of gene expression. *Cell* 156, 1312–1323.