Supplement

1 Computational evolution

For evolutionary computations, we use the same formalism as in [3], with only transcriptional interactions and protein-protein interactions. Regulation of transcription of a protein B is modelled as a combination of Michaleis-Menten-Hill functions. If transcription factors A_1 and A_2 activate the expression of gene B and R represses it, the equation for B would then be :

$$\frac{dB}{dt} = \rho_B \max\left(\frac{A_1^{n_1}}{A_1^{n_1} + A_{1*}^{n_1}}, \frac{A_2^{n_2}}{A_2^{n_2} + A_{2*}^{n_2}}\right) \times \frac{R_*^{n_3}}{R^{n_3} + R_*^{n_3}} - \delta_B B \qquad (1)$$

A_{i*} and R_* are threshold concentrations in Hill functions, and n_i are Hill exponents accounting for cooperativity. Parameters are initialized and evolved randomly. Equation 1 says that we assume an "OR" combination between activators (i.e. one single activator is enough to activate trannscription) while repressors act multiplicatively.

Protein-protein interaction (PPI) are explicitly modelled using standard mass-action laws. For instance, if proteins A and B form a dimer C, the equations are :

$$\begin{aligned}
\frac{dA}{dt} &= -\rho AB + dC \\
\frac{dB}{dt} &= -\rho AB + dC \\
\frac{dC}{dt} &= \rho AB - dC
\end{aligned}$$

1.1 Evolutionary dynamics

Genetic networks are evolved by repeated rounds of selection, growth and mutation. Typically 40 networks constitute a population and are followed in parallel. At each step of the algorithm, equations corresponding to the networks are integrated, and the fitness functions are computed. The networks are then Pareto ranked as explained in the main text. Half the population with lowest ranks are discarded and one copy of each the remaining networks is mutated and returned to the population.

Mutations can either add or remove interaction or change parameters for existing interactions. The rates for parameter additions are generally 10-20% the rates for parameter changes. Lower rates for parameter additions, slow the convergence, i.e., one is oversampling the parameters. The rates to remove interactions are twice the rate for their addition, which keeps networks small and minimizes interactions that do not meaningfully improve fitness. The mutations are sampled according to their rates and approximately one mutation is made per generation per network.

In the equations for transcription and protein-protein interaction, we chose units of rate and concentration to be one. Then most parameters are sampled over a range of [0,1]. Exceptions are ρ_B which can vary from [0,10], which makes the overall transcription rate more comparable to the PPI rate. There is a lower limit of 0.1 on the decay rate δ, which prevents concentrations from going to infinity. The Hill exponent varies over [1,5]. In previous papers, ([2, 3, 1]) we experimented with various parameter ranges as well as ways of varying them (e.g. resample the range when mutating, or sample a region around the prior value), with no material change in the evolved networks. We have not repeated these experiments here, since our intent is just to present Pareto evolution.

References

[1] P François and E D Siggia. Predicting embryonic patterning using mutual entropy fitness and in silico evolution. *Development (Cambridge, England)*, 137(14):2385–2395, June 2010.

[2] Paul Francois, Vincent Hakim, and Eric D Siggia. Deriving structure from evolution: metazoan segmentation. *Molecular Systems Biology*, 3:9, December 2007.

[3] Paul Francois and Eric D Siggia. A case study of evolutionary computation of biochemical adaptation. *Physical Biology*, 5(2):26009, 2008.