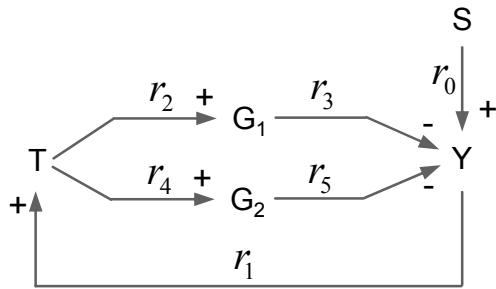


### Text S5. Negative feedback with multiple genes

In response to cellular stresses, the homeostatic gene regulatory network often drives the expression of more than one genes, which function collectively to counteract the perturbation and maintain the controlled variable within certain levels. For instance, in mammalian electrophilic stress response, there are a suite of genes including *Gclc*, *Gs*, *Gst*, et al, that are up-regulated. For a two-gene system as below, the systems-level gains for Y, T, and each of the two genes are as follows:



$$R_S^Y = \frac{r_0}{1 + |r_1(r_2r_3 + r_4r_5)|}, \quad (\text{S8})$$

$$R_S^T = \frac{r_0r_1}{1 + |r_1(r_2r_3 + r_4r_5)|}, \quad (\text{S9})$$

$$R_S^{G_1} = \frac{r_0r_1r_2}{1 + |r_1(r_2r_3 + r_4r_5)|}, \quad (\text{S10})$$

$$R_S^{G_2} = \frac{r_0r_1r_4}{1 + |r_1(r_2r_3 + r_4r_5)|}. \quad (\text{S11})$$

Equation S8 indicates that the inclusion of additional gene regulations can enhance the loop gain and thus reduce the systems-level gain for the controlled variable Y. Notably, local gain  $r_2$  and  $r_4$  has opposite influence on  $R_S^{G_1}$  and  $R_S^{G_2}$ . An increase in  $r_2$  augments  $R_S^{G_1}$ , but diminishes  $R_S^{G_2}$ . Alternatively, an increase in  $r_4$  augments  $R_S^{G_2}$ , but diminishes  $R_S^{G_1}$ . The two genes can be functionally related in several ways: 1)  $G_1$  and  $G_2$  can be the two subunits required to form a functional holo-enzyme catalyzing the removal of Y; 2) while  $G_1$  is the enzyme directly responsible for the removal of Y,  $G_2$  participates in a separate reaction which provides the cofactor or co-substrate for  $G_1$ -catalyzed reaction; 3)  $G_1$  and  $G_2$  may be two different enzymes involved in two separate reactions, but both of which directly remove Y (e.g., GPx and CAT all remove H<sub>2</sub>O<sub>2</sub>, but in two distinct reactions); 4)  $G_1$  and  $G_2$  may be two isoforms of the same enzyme family, which are co-expressed in the same cell. In either of these cases, as long as  $r_3$  and  $r_5$  are not zero, enhancing expression of either one of the two genes, by increasing local gain  $r_2$  or  $r_4$  respectively, would reduce the expression level of the other gene. Systems-level gains for gene regulatory networks with more than two genes and/or more than one transcription factors can be similarly derived.