The incoherent feedforward loop can provide fold-detection in gene regulation

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Supplement

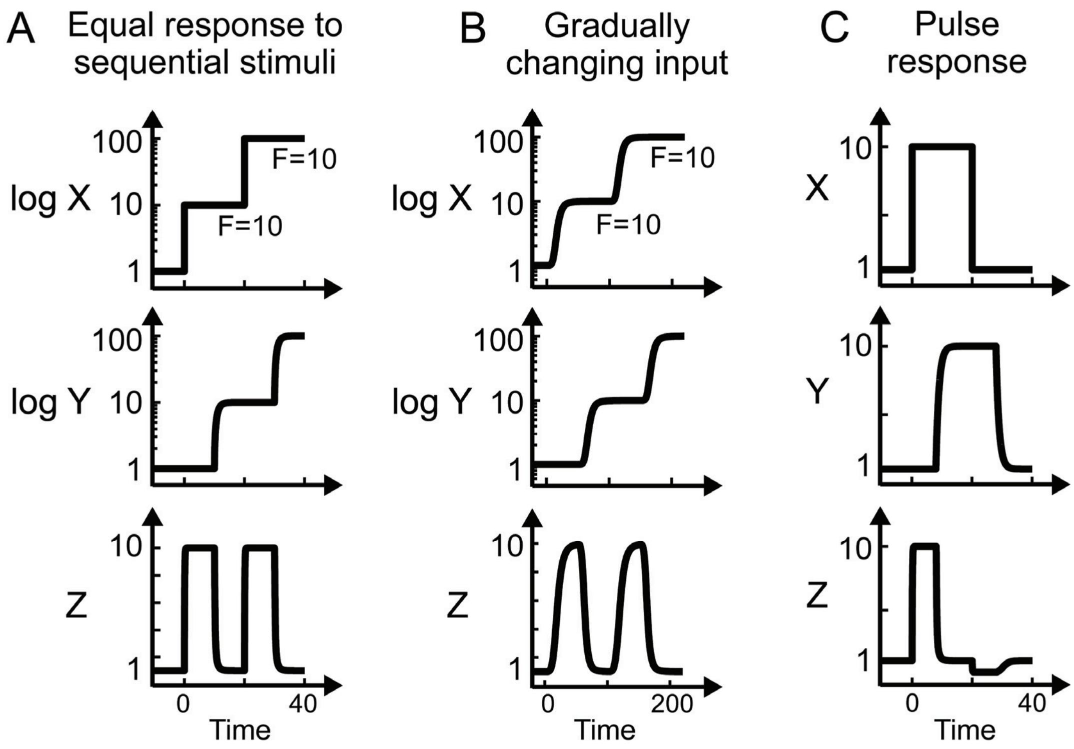
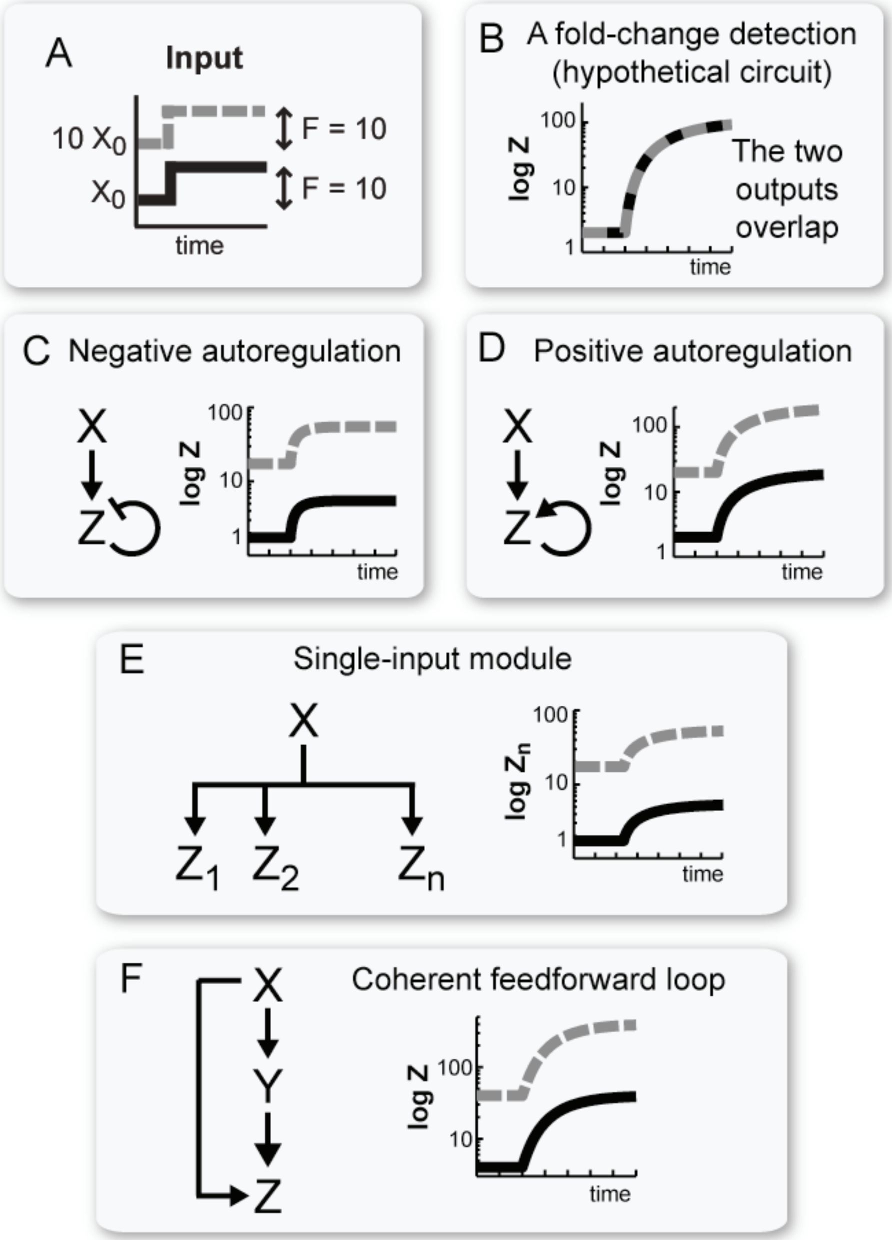


Figure S1. I1-FFL shows fold-change detection to sequential steps, gradually changing input, and pulses.

(A) The I1-FFL maintains identical response to sequential signal steps with the same fold-change. **(B)** The fold-change detection feature is maintained for any time varying form of input X(t). **(C)** The I1-FFL responds to a pulse showing undershoot of Z dynamics. Pulse signals are normally found in biological systems. A pulse-like signal also mimics a situation when after a period of signaling, signal degrades away or is actively removed to prepare cells for the next round of signaling. Removal of signal resets the memory Y (Y returns to the basal level) without affecting the transcription of Z significantly (if the basal transcription of Z is negligible).

Figure S2. Other common transcriptional network motifs show response that depends on the absolute levels of the input



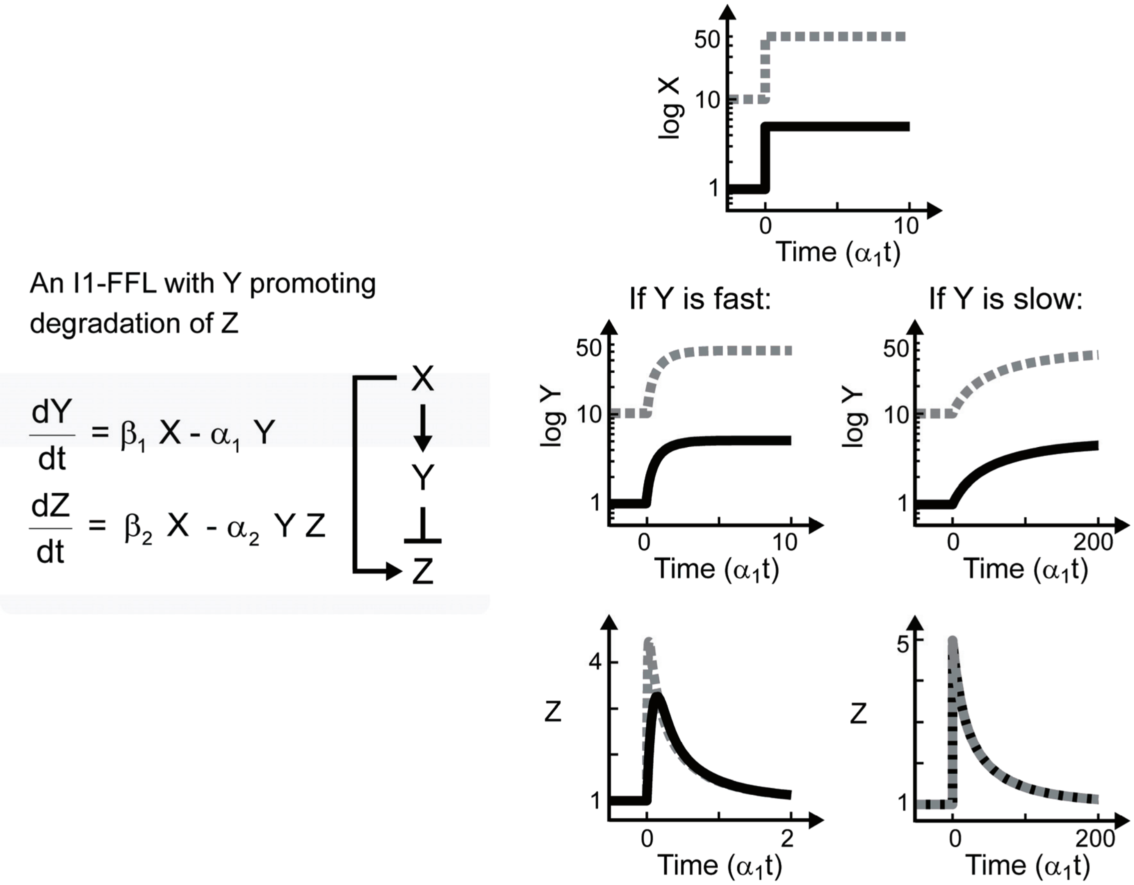
For illustration purposes, we stimulated network motifs with two step inputs of different absolute levels, but identical fold-changes **(A)**. If a circuit shows a response that depends on the fold-changes in the input, and not the absolute levels of the input, then the outputs to the two step stimuli would perfectly overlap **(B)**. All motifs, except for the incoherent FFLs, do not show fold-change detection: the dynamics and level of Z depends on the absolute level of the activator X.

Intuitively, fold-change detection first requires a memory of the basal level of the activator X. Recurrent network motifs such as positive autoregulation, negative autoregulation, and single-input module do not have a built-in memory of X. Consequently, they cannot provide fold-change detection **(C-E)**.

Another motif, the coherent feedforward loop **(F)**, resembles the incoherent feedforward loop, with one difference: the effect of Y on the output Z is coherent to the effect of X on Z (*i.e.*, Y activates Z instead of repressing it). This difference abolishes the fold-change detection behavior. Even though Y mimics the level of the activator X (hence acting as a memory of X), it no longer facilitates a temporal comparison between the basal level of X and the new level of X (because Y amplifies, and not opposes, the effects of X).

Mathematically, fold-change detection translates into a structural requirement of how Y appears in the differential equation describing the dynamics of Z.

Figure S3. I1-FFL connected in a different way can provide fold-change detection.



An I1-FFL where Y acts by degrading Z, rather than repressing the production of Z (Levchenko and Iglesias, 2002; Ma et al., 2009; Tyson et al., 2003) can provide fold-change detection in the limit where the dynamics of Y is very slow or delayed relative to the dynamics of Z. Under this condition, a quasi steady-state prevails: Z is at quasi steady-state, slaved by the slow dynamics of Y, $Z_{st} = \frac{\beta_2 X}{\alpha_2 Y(t,X)}$. Since Y also depends on X, this cancels the X-dependence of Z. In this limit, at all time, Z responds only to fold-changes in the activator X.

Analytical solution for the I1-FFL

As derived in Box in the main text, the dynamic equations for Y and Z are:

$$\frac{dY}{dt} = \beta_1 X - \alpha_1 Y \tag{1}$$

$$\frac{dZ}{dt} = \frac{\beta_2 X}{Y} - \alpha_2 Z \tag{2}$$

Let us define the following dimensionless variables,

$$y = \frac{Y}{\beta_1 \, X_0 / \alpha_1} \tag{3}$$

$$z = \frac{Z}{\beta_2 \, \alpha_1 / \beta_1 \, \alpha_2} \tag{4}$$

$$\tau = \frac{t}{1/\alpha_1} \tag{5}$$

$$f = \frac{X}{X_0} \tag{6}$$

where X_0 is the basal level of X, as depicted in Figure S4. Introducing the dimensionless variables into equations 1-2, we obtain the following dimensionless dynamic equations describing the I1-FFL,

$$\frac{dy}{d\tau} = f - y \tag{7}$$

$$r \frac{dz}{d\tau} = \frac{f}{y} - z \tag{8}$$

where the dimensionless group r is defined as follows,

$$r = \frac{\alpha_1}{\alpha_2} \tag{9}$$

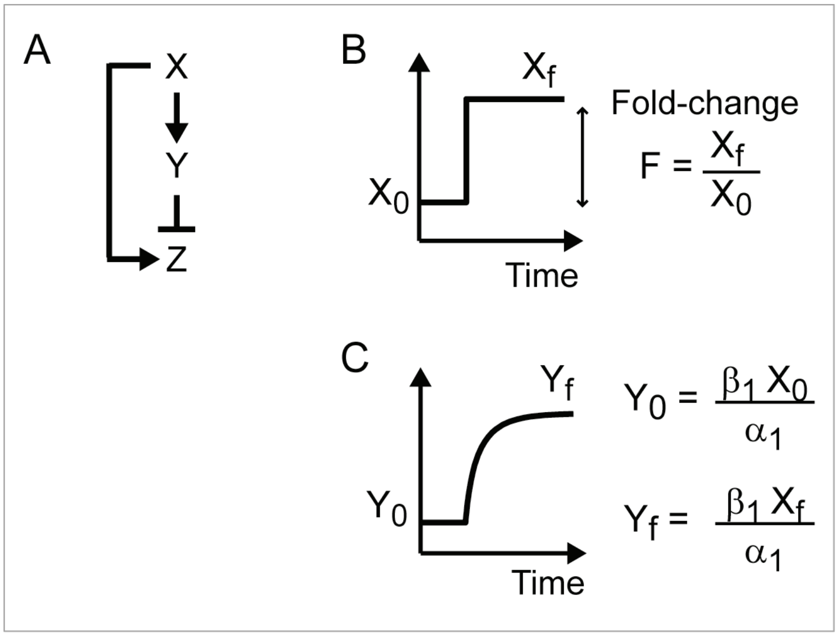


Figure S4. **(A)** The type-1 incoherent feedforward loop (I1-FFL). **(B)** The input to the circuit is the activator X. The **fold-change** in X is defined as the ratio of the new level of X to the previous level of X (**$F = X_f / X_0$**). **(C)** Y increases to a new steady-state level in response to a step change in the level of X.

Integrating equation 7 with the initial condition y(0)=1,

$$y = 1 + (f - 1)(1 - e^{-\tau}) \qquad (10)$$

Equation 10 describes how Y changes in time in response to a step increase in the activator X (Figure S4).

Substituting equation 10 into equation 8, we obtain a closed differential equation describing the dynamics of Z,

$$r\frac{dz}{d\tau} = \frac{f}{1 + (f - 1)(1 - e^{-\tau})} - z \qquad (11)$$

Equation 11 can be fully solved analytically when r=1 ($\alpha_1=\alpha_2$),

$$\frac{dz}{d\tau}=\frac{f}{1+(f-1)\left(1-e^{-\tau}\right)}-z \qquad (12)$$

Integrating equation 12 with the initial condition z(0)=1,

$$z=\left[e^{\tau}+\ln\left(f e^{\tau}-f+1\right)-\frac{1}{f}\ln\left(f e^{\tau}-f+1\right)\right]e^{-\tau} \qquad (13)$$

Equation 13 shows that the dynamics of Z, both during the transient time and steady state, responds only to the fold-changes in X (f), and not on the absolute level of X. The profile of Z is shown in Figure S5.

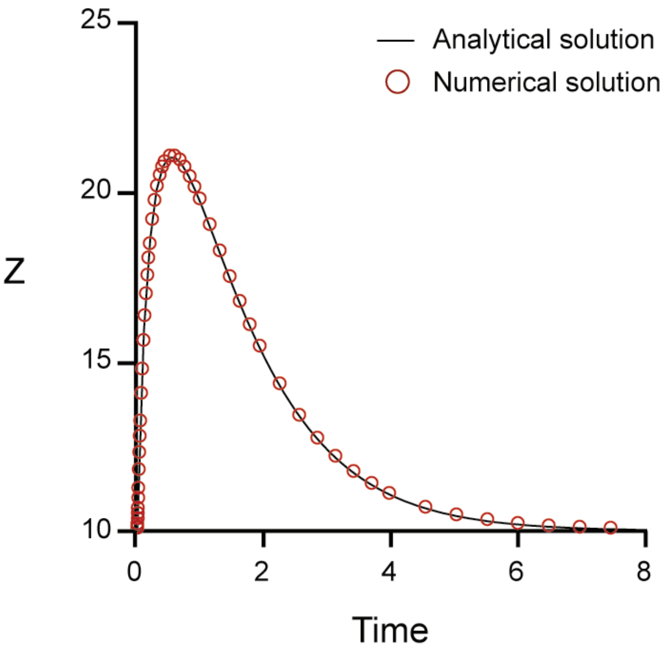


Figure S5. The dynamic of Z in response to a step increase in the activator X. The solid line depicts the analytical solution (equation 13); the circles depict the numerical solution (equation 2). The parameters used in this plot were: β_1=1, β2=10, $\alpha_1=\alpha_2$=1,

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