**Supplementary Note 2 :** The upstream fluxes can balance much more quickly than the pathway response time.

Consider an enzyme E operating far below $V_{\text{max}}$ in a linear pathway. Assume that the flux upstream of the enzyme changed at time $t=0$. We estimate how long it takes for the flux through the enzyme to balance the upstream flux. The dynamics of the substrate $S$ of the enzyme, produced by the upstream flux, are governed by the equation

$$\frac{dS}{dt} = F_u - \frac{K_{\text{cal}} SE}{S+K_m},$$

where $F_u$ is the upstream flux, and the second term is the flux through the enzyme given by standard Michaelis-Menten kinetics. Under the assumption that the enzyme is operating far below $V_{\text{max}}$, that is, $S << K_m$, the equation reduces to

$$\frac{dS}{dt} = F_u - \frac{S}{\tau},$$

with the time constant $\tau = \frac{K_m}{K_{\text{cal}} E}$.

The solution to this equation is

$$S = F_u (S_0 - F_u) \exp(-t/\tau),$$

where $S_0$ is the initial concentration of the substrate. Thus the flux through the enzyme relaxes to the upstream flux $F_u$ exponentially with time constant $\tau$. To get an order of magnitude estimate of $\tau$, we use $K_m = 0.5 \text{ mM}$, $E = 10^4$ molecules/cell, which translates to about $0.3 \mu\text{M}$ assuming the cell volume is $50 \mu\text{m}^3$, and $K_{\text{cal}} = 600/\text{min}$. These parameters yield $\tau = 3$ minutes. Thus the time it takes to reach flux balance is much faster than the typical response time of the pathway.