Supplemental figures and captions

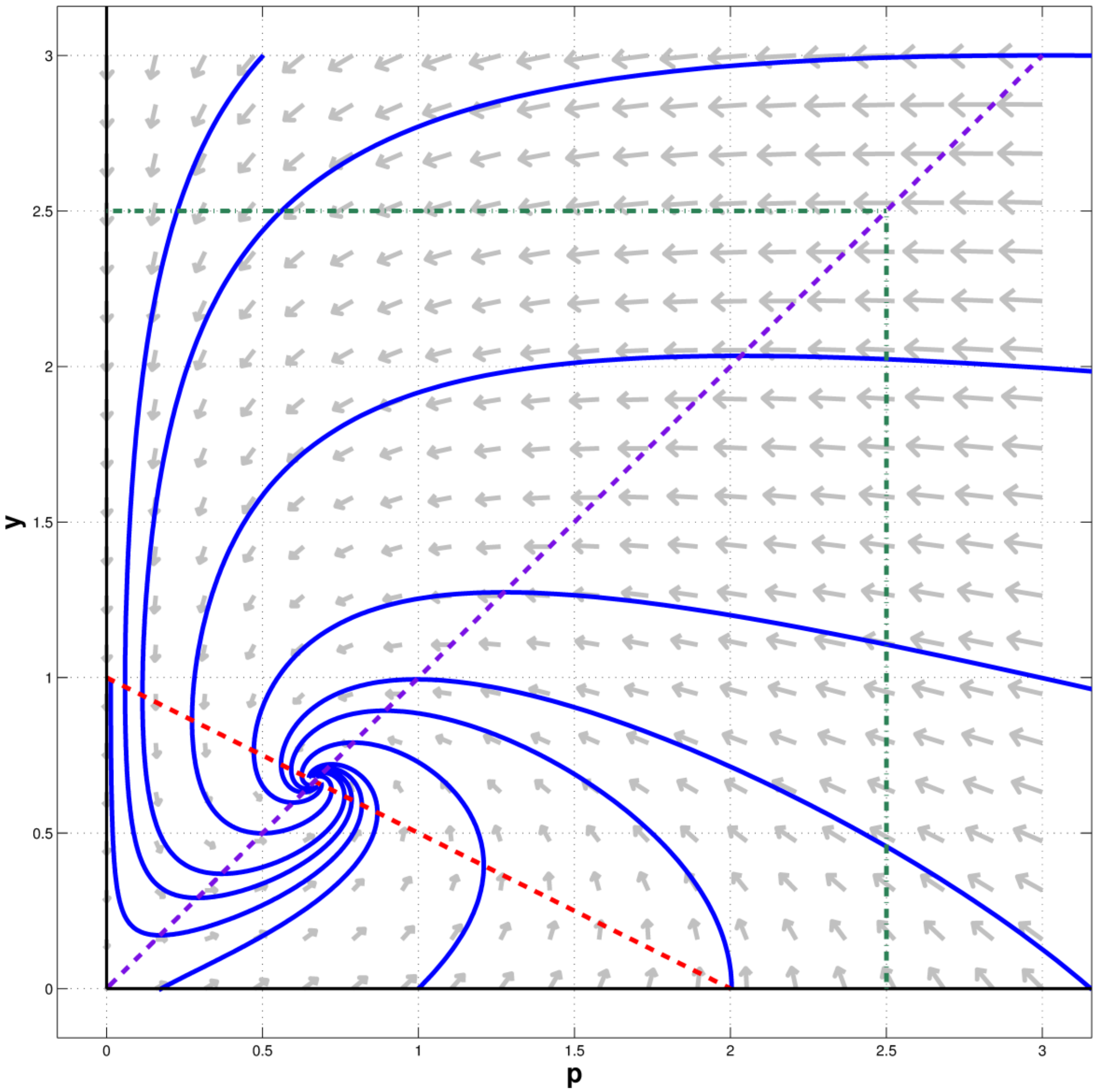

Figure S1. Related to the STAR Methods.

Phase plane for numerical example, with several representative trajectories plotted. Nullclines are the y *axis, corresponding to the stable manifold of* $(0,0)$*, and the lines given by* $y = (\delta_x + \lambda - \beta p)/\kappa$ *(dashed red line) and* $y = \mu p/\delta_y$ *(dashed magenta line). In this plot, we picked* $\delta_x = \beta = \mu = \lambda = \delta_y = 1$ *and* $\kappa = 2$*, but the qualitative picture is similar for all valid parameter values. With these values, trajectories converge to the equilibrium* $(\overline{p}, \overline{y}) = (2/3, 2/3)$*. Shown also is an invariant region* $[0, P] \times [0, Y]$ *with* $P = Y = 2.5$ *(green dash-dotted lines and axes).*

A

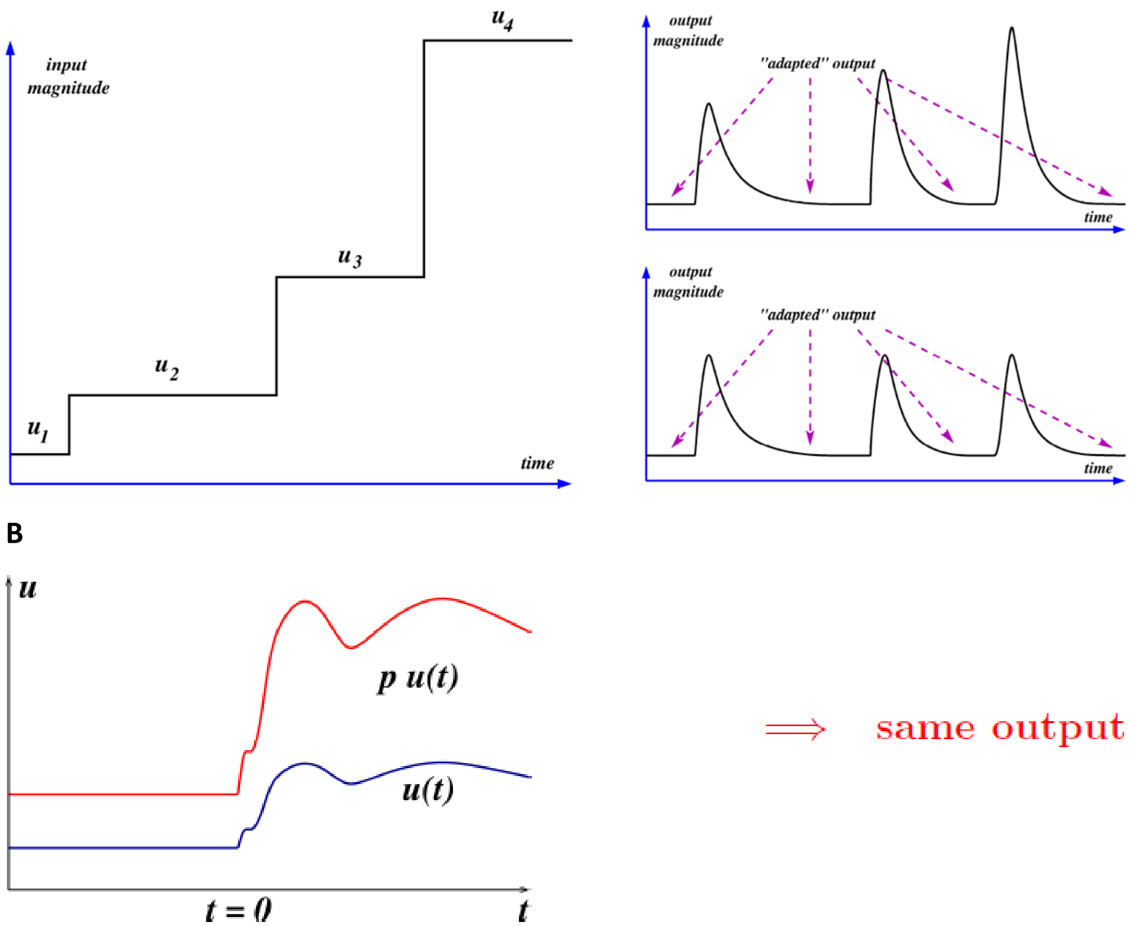

Figure S2. Related to the STAR Methods.

A. *In a perfectly adapting system, a step-wise input (left) gives rise to different responses that settle to the same basal level (top right). If the system has the scale invariance property, these responses are identical (bottom right).* ***B.*** *Scale invariance means that scaled signals should result in the same output, provided that the initial state is preadapted to the respective constant value for* $t < 0$

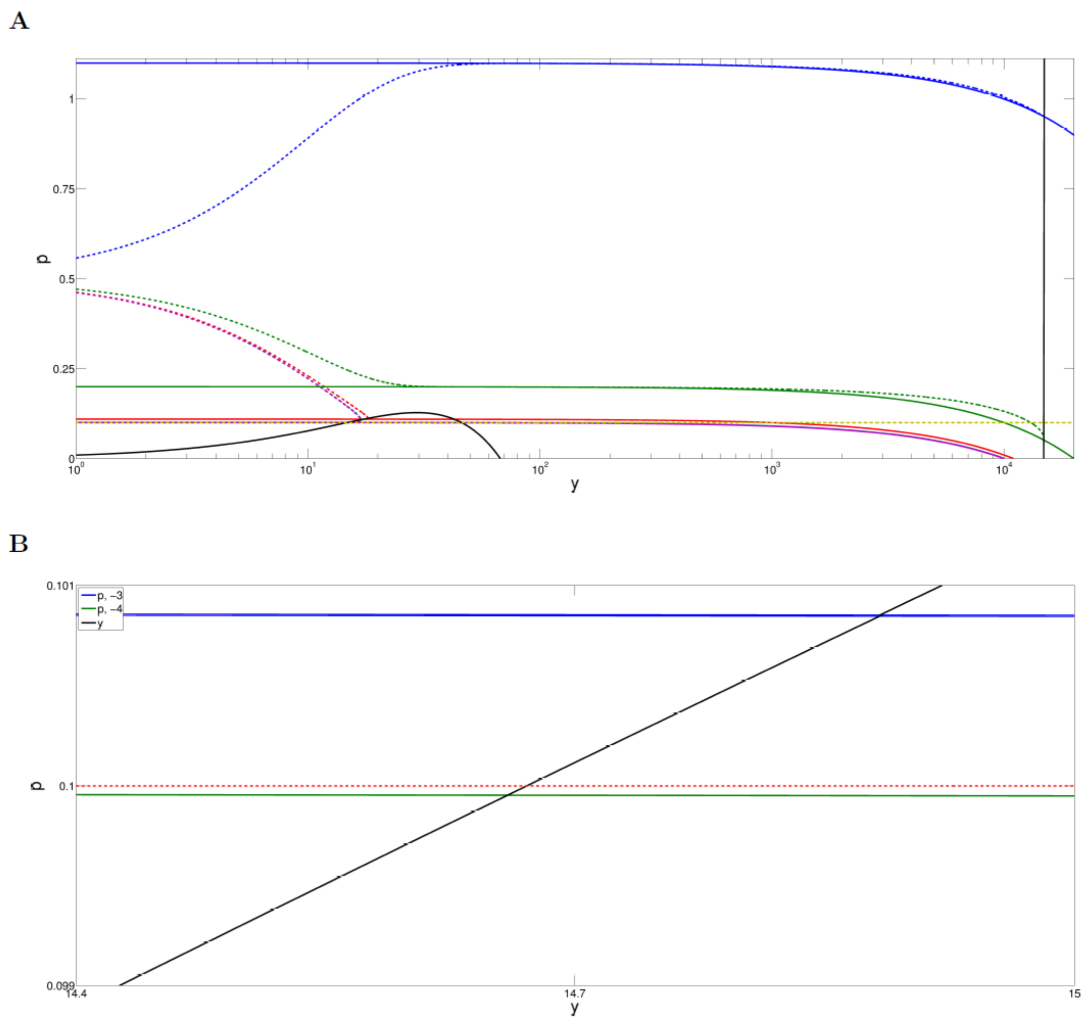

Figure S3. Related to the STAR Methods.

A. *Phase plane for the system described in the text. Shown are nullclines for several increasing values of* $\lambda = 10^i$, $i = -4, -3, -2, -1, 0$ *(bottom to top). Log scale in* y *is used in order to visualize behavior for different orders of magnitude in* λ*. Black curve is* y*-nullcline* $p = -(1/\mu)(Vy^2/(K+y) - \varepsilon y^2 - \delta_y y)$ *Solid color curves are* p*-nullclines* $p = (1/\beta)(d + \lambda - \kappa y)$ *(which look curved because of log scale), and* $p \equiv 0$*. Horizontal dashed line is threshold* $p = \delta_x/\beta$ *that determines if* $\lambda - \kappa y$ *is positive or negative. Dashed curves are trajectories, in same color as the respective nullclines. Initial state for simulation is in every case* $p(0) = 0.5$, $y(0) = 0$*, but only portion of plot for* $y \geq 10^0 = 1$ *is shown.* ***B.*** *Zoomed-in view of two nullclines, for* $\lambda = 10^{-4}$ *and* $\lambda = 10^{-3}$*, to show how steady state falls under/below threshold.*

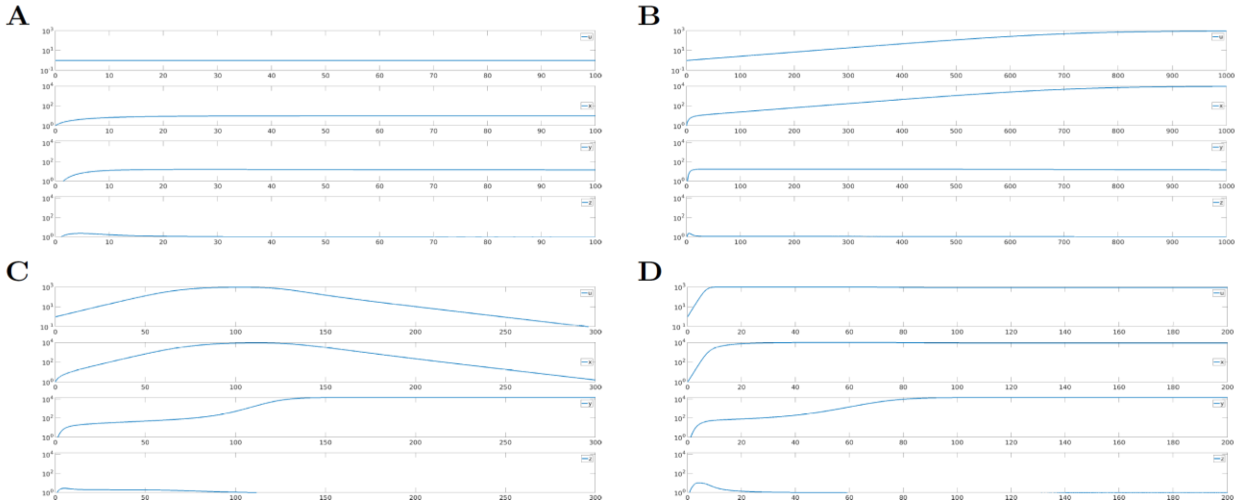

Figure S4. Related to the STAR Methods.

A-D. *Simulations of system with "helper" intermediate, for* $\lambda = 10^{-4}$, 10^{-2}, 10^{-1}, *and* 1. *(In* ***A****,* $u(t)$ *converges to zero as* $t \to \infty$*, but very slowly.) Parameters as described in text for Figure 3. Initial states are always* $u = 1$, $x = 1$, $y = 0$, $z = 0$. *Only noticeable difference with simpler model is a slight delay in activation of* y.