



**Figure S3.** Sampling of partitioned parameter space in a simplified two-component system model. (A) The model was simplified by eliminating as many variables as possible while retaining the capability for negative open-loop gain. (B) Distribution of negative and positive open-loop gain cases for fraction of exogenous phosphorylation flux  $J_E/(J_E + J_S)$ . Histogram bins containing more than  $10^5$  members were cut off for clarity. (C) Distribution of cases with feedback-induced overshoot  $> 10\%$  over the activated steady state. Intervals for parameter sampling were the same as Table S1 with the following exceptions:

$k'_{txn} \in [4.33 \times 10^{-5}, 100.]$ ;  $k'_{txnbasal} \in [4.33 \times 10^{-6}, 1.0]$ ;  $K_{mb} \in [10^{-4}, 10]$ .  $k'_{txnbasal}$  and  $k'_{txn}$  are derived from

dividing  $k_{txnbasal}$  and  $k_{txn}$  by  $k_{mRNAdeg}$ . Production rates of RR and SHK are  $k_{tsn} \left( \frac{k'_{txn} [RRP]^2}{K_{mtx}^2 + [RRP]^2} + k'_{txnbasal} \right)$

for  $k_{tsn} = k_{tsnRR}$ ,  $k_{tsnSHK}$ , respectively.