

1 **Supplementary Information: Signaling pathways have an inherent need for noise**  
2 **to acquire information**

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5 **Supplementary text 1**

6 We want to compute the mutual information  $I(S_0; O)$  of the two random variables  $S_0$ ,  
7 which represents the signal, and  $O$ , which represents the output.  $S_0$  is the initial number  
8 of signal molecules and takes on  $n$  values uniformly distributed in the interval  
9  $[N_{Smax}/n, N_{Smax}]$ , where  $N_{Smax}$  is the maximal number of signal molecules.  
10  $O = O_\infty$ , where  $O_t = S_0 - S_t$  and where  $S_t$  is a birth and death Markov process  
11 determined by the following set of infinitesimal generators

12

$$\lim_{h \rightarrow 0} \frac{p_{j,j+1}(h)}{h} = \lambda_j = k_d(S_0 - j)$$

$$\lim_{h \rightarrow 0} \frac{p_{j,j-1}(h)}{h} = \mu_j = k_a(R_0 - (S_0 - j))$$

$$\lim_{h \rightarrow 0} \frac{p_{j,j}(h)}{h} = \lambda_j + \mu_j$$

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14 with  $p_{i,j}(h) = P\{S_{t+s} = j | S_t = i\}$  for  $s \geq 0$ .  $R_0$  is an initial condition for the number of  
15 receptors, equal to the total number of receptor molecules. The birth and death  
16 process  $S_t$  depends on the parameters  $k_a$  and  $k_d$ . Let  $m = S_0 - R_0$  be the minimum  
17 value of  $O_t$  and let  $M = S_0 + O_0$  be the maximum value. Notice that by now we have four  
18 parameters  $k_a$ ,  $k_d$ ,  $R_0$  and  $O_0$  that govern the birth and death process. The process is  
19 described by the following set of Kolmogorov forward equations

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$$p'_{i,m}(t) = \mu_{m+1}p_{i,m+1}(t) - \lambda_m p_{i,m}(t)$$

$$p'_{i,j}(t) = \mu_{j+1}p_{i,j+1}(t) - (\lambda_j + \mu_j)p_{i,j}(t) + \lambda_{j-1}p_{i,j-1}(t)$$

$$p'_{i,M}(t) = -\mu_M p_{i,M}(t) + \lambda_{M-1}p_{i,M-1}(t)$$

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22

23 with the initial conditions  $p_{i,j}(0) = \delta_{ij}$ . If we let  $\pi_i = p_{i,j}(\infty)$  and let

24  $t \rightarrow \infty$  in the Kolmogorov forward equations, then  $p'_{i,j}(\infty) = 0$  and we obtain the

25 following set of algebraic equations

26

$$\pi_{m+1} = \frac{\lambda_m}{\mu_{m+1}} \pi_m, \quad \pi_{j+1} = \frac{\lambda_j + \mu_j}{\mu_{j+1}} \pi_j - \frac{\lambda_{j-1}}{\mu_{j+1}} \pi_{j-1}, \quad \pi_{m+1} = \frac{\lambda_{M-1}}{\mu_M} \pi_{M-1}$$

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28 where  $\lambda_j$  and  $\mu_j$  are as stated above. These equations can be solved recursively. The

29 set  $\{\pi_j: m \leq j \leq M\}$  determines the probability distribution of  $S_\infty$  and hence also of

30  $O_\infty = S - S_\infty$ .

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32 It is more expedient to write  $\pi_j(S_0)$  instead of  $\pi_j$ , since the above computations depend

33 on the value of  $S_0$ . To compute the mutual information  $I(S_0; O) = H(\Pr(O_\infty)) -$

34  $H(\Pr(O_\infty | S_0))$ , we must determine the marginal distribution of  $O = O_\infty$ . This marginal

35 distribution is given by

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$$P\{O_\infty = S_0 - j\} = \sum_{i=m}^M P\{S_\infty = j | S_0 = i\} P\{S_0 = i\} = \frac{1}{n} \sum_{i=m}^M \pi_j(S_0 = i)$$

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38 and allows us to compute mutual information, output range, and noise (Sup Fig 2).

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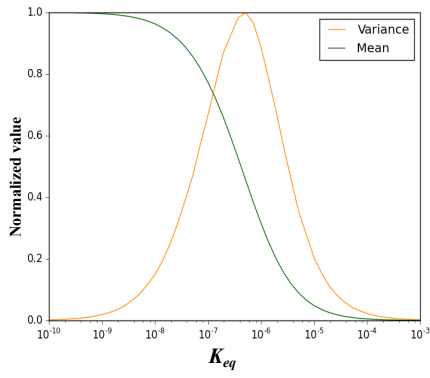
## 40 **Supplementary text 2**

41 In the model of a complete signaling pathway the signal-bound receptor molecules.  
42 Receptor-signal complexes act as TFs that associate and dissociate from a regulatory  
43 binding site on DNA ( $DNA_{bs}$ ). Once a receptor-signal- $DNA_{bs}$  complex is formed, mRNA is  
44 transcribed at rate  $k_1$ , and protein is produced from mRNA molecules at rate  $k_2$ . mRNA  
45 and protein are degraded at rates  $d_1$  and  $d_2$ .  $K_{eq_{R,S}}$  and  $K_{eq_{R,S,D}}$  describe the affinity of the  
46 receptor to the signal, and the affinity of the receptor-signal complex to the  $DNA_{bs}$ ,  
47 respectively. This model resembles nuclear receptor signaling pathways, where nuclear  
48 receptors directly regulate gene transcription (reviewed in (1)). Although many nuclear  
49 receptors act as dimers (e.g., (2)), we consider here for simplicity a receptor that acts as  
50 a monomeric transcriptional regulator.

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52 Based on our previous result we expected that both reversible binding interactions  
53 included in the model, namely the receptor-signal and the receptor-signal- $DNA_{bs}$   
54 interactions, should acquire and transmit information at intermediary affinity values,  
55 where both noise levels and the output range are high. At intermediary affinity values,  
56 the binding-unbinding dynamic of the receptor-signal with the  $DNA_{bs}$  should amplify the  
57 fluctuations in the number of proteins, thus increasing both noise and increasing  
58 information transmission. Our simulation shows that this is indeed the case. Information  
59 acquisition in this simple signaling model is maximized at intermediary affinity values of  
60 both binding interactions (Sup Fig 8).

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**Sup Fig 1.** Mean and variance of the number of receptor-signal complexes ( $\bar{N}_{RS}$ ) formed at different affinity values

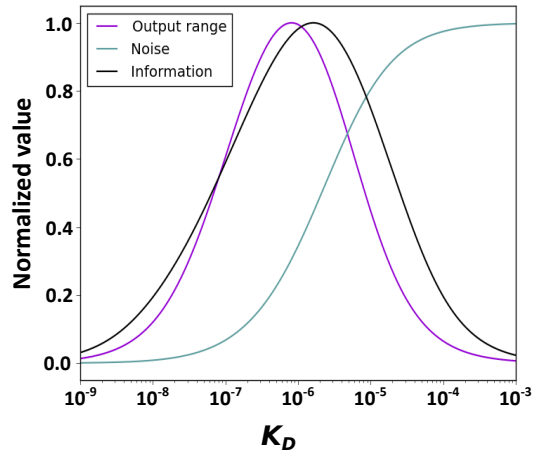
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( $K_{eq}$ ). The maximum number of receptor-signal complexes for this simulation is 50 (see Sup Table 1). For visualization

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purposes, mean and variance are normalized by their maximal value.

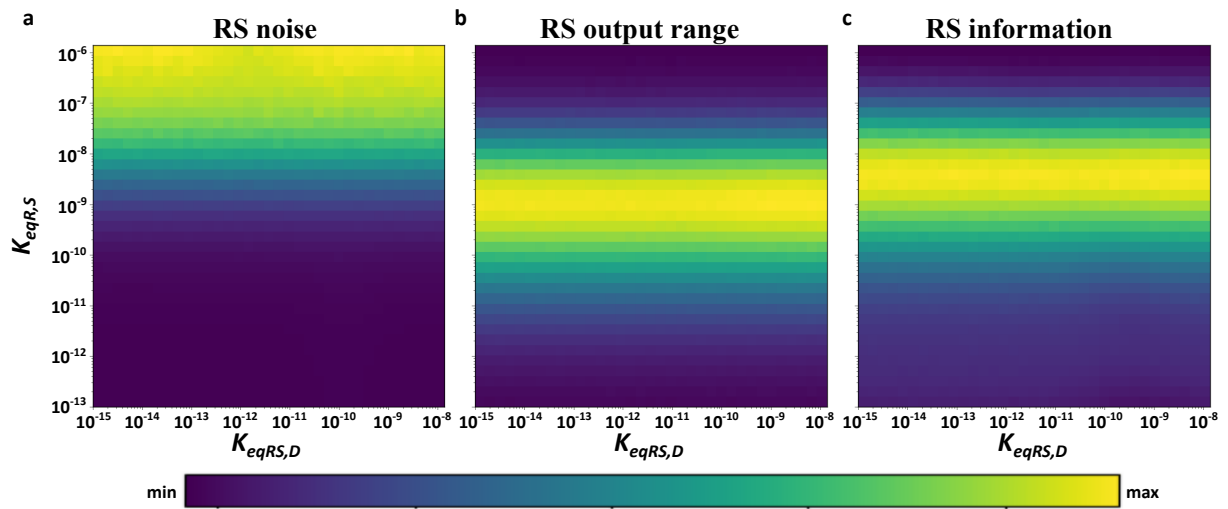
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68 **Sup Fig 2.** Analytic results of information, noise and output range in the receptor-signal system (see Sup Text 1).

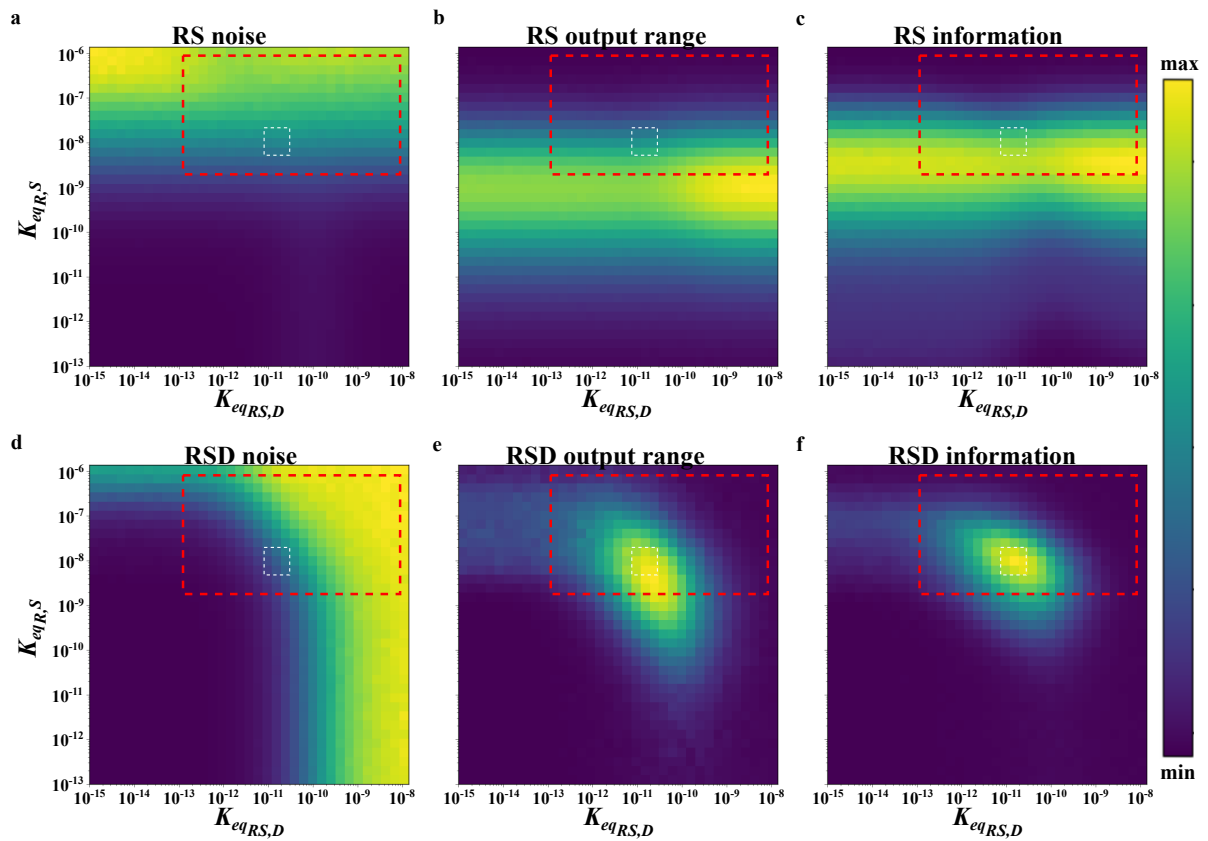
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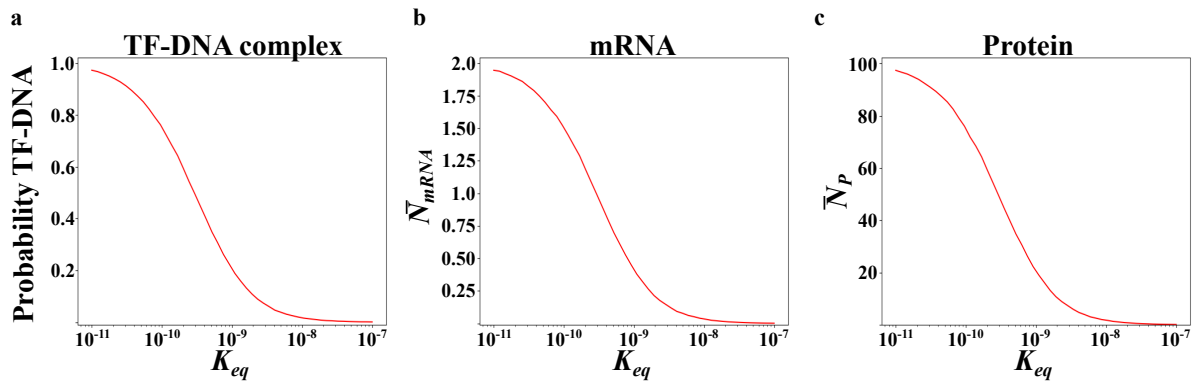
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71 **Sup Fig 3. Information, output range and noise in a pair of reversible binding interactions.** Contour plots of (a)  
 72 noise, (b) output range and (c) information acquisition in the receptor-signal complex (RS) as a function of the  
 73 affinities between both the receptor and the signal ( $K_{eqR,S}$ ), and the receptor-signal complex with the downstream  
 74 molecule ( $K_{eqRS,D}$ ). Acquired information, output range and noise are plotted from minimally to maximally observed  
 75 values, color-coded as indicated by the color bar (see Sup Table 2 for the parameters).

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78 **Sup Fig 4. Information, output range and noise in two consecutive binding interactions with ten DNA<sub>bs</sub>.**  
79 Contour plots of (a and d) noise, output range (b and e) and information acquisition (c and f) in the receptor-signal  
80 complex (*RS*; a-c) and in the receptor-signal-DNA<sub>bs</sub> complex (*RSD*; d-f) as a function of the affinities between both the  
81 receptor and the signal ( $K_{eq,R,S}$ ), and the receptor-signal complex with the downstream molecule ( $K_{eq,RS,D}$ ). Red-dashed  
82 rectangles circumscribe biologically sensible receptor-signal DNA affinities ( $[10^{-8}M, 10^{-13}M]$ ) and receptor signal  
83 affinities ( $[10^{-6}M, 10^{-9}M]$ ). White-dashed rectangles delineate the region of maximal information acquisition at the  
84 receptor-signal-DNA<sub>bs</sub> level. Acquired information, output range and noise are plotted from minimally to maximally  
85 observed values, color-coded as indicated by the color bar (see Sup Table 2 for the parameters).  
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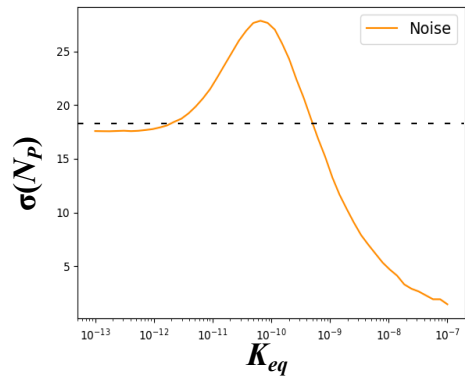
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**Sup Fig 5.** (a) Probability of TF-DNA binding, (b) mean number of mRNA molecules ( $\bar{N}_{mRNA}$ ), and (c) mean number of protein molecules ( $\bar{N}_P$ ), as a function of TF-DNA affinity ( $K_{eq}$ ). For the parameters we used (Sup Table 3), the expected mean number of mRNA and protein molecules produced from a constitutively expressed gene is 2 and 100, respectively.





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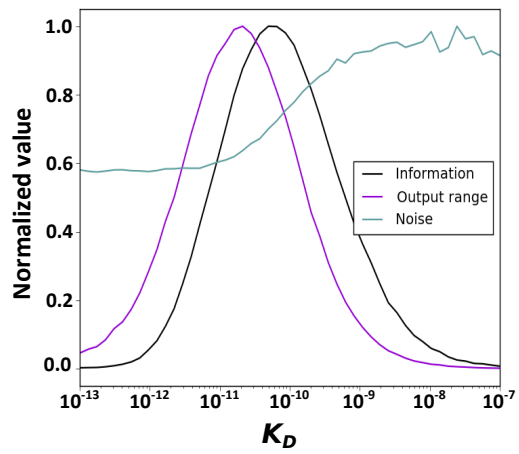
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**Sup Fig 6. Non-normalized values of standard deviation in the number of proteins.** The black line is the standard

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deviation expected for the parameters used in this simulation (Sup Table 3).

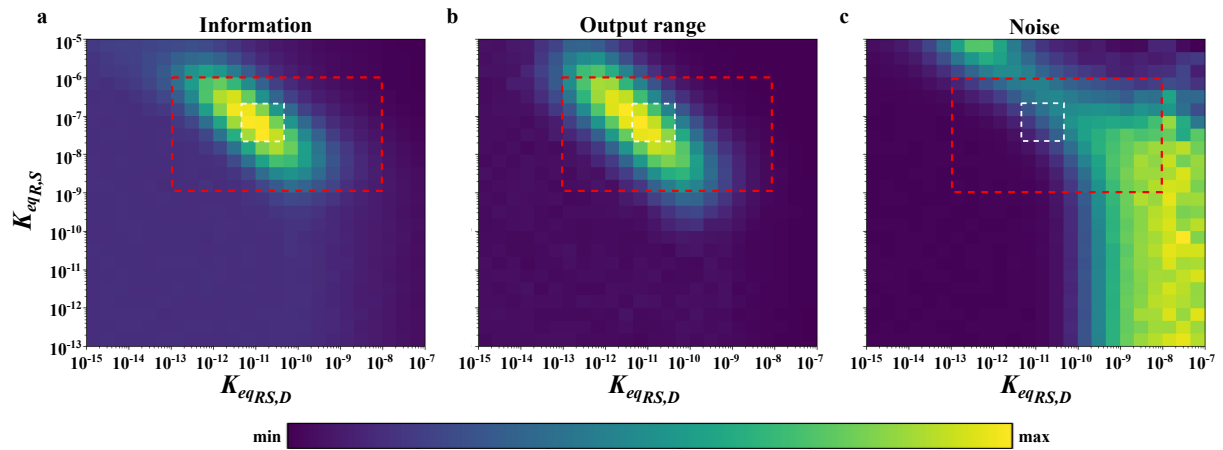
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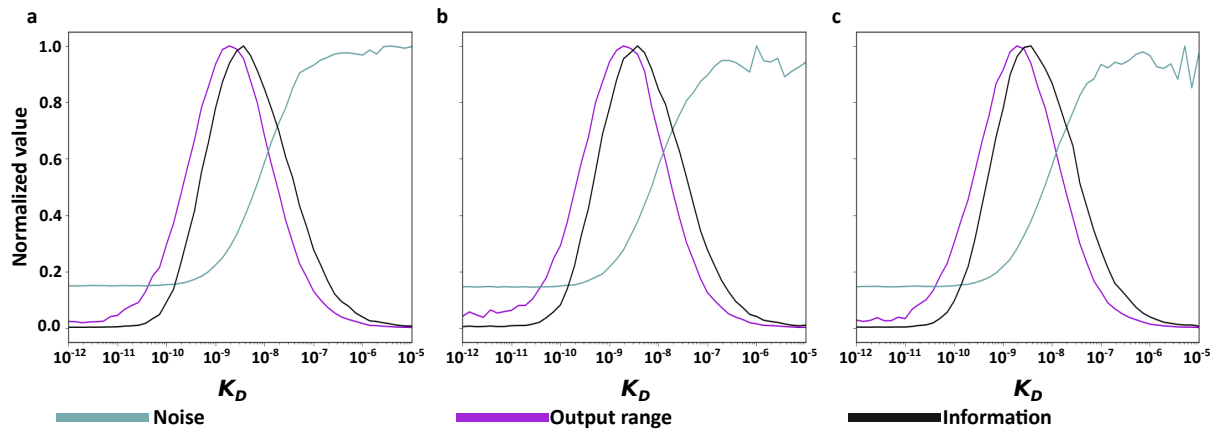
97 **Sup Fig 7.** Information, output range and noise in the gene regulation model for proteins with a half-life of ~12h (see Sup

98 Table 3).



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100 **Sup Fig 8. Contour plot of acquired information and noise in a complete signaling pathway.** (a) Information, (b)  
 101 output range, and (c) noise for different affinities between receptor and signal molecules ( $K_{eq,R,S}$ ,  $y$  axis), and receptor-  
 102 signal complexes with a DNA binding site ( $K_{eq,R,S,D}$ ,  $x$  axis) in a model of a simple lineal signaling pathway where a signal  
 103 bound receptor can bind DNA and regulate gene expression. The number of signal molecules constitute the input into  
 104 this pathway, and the number of protein molecules expressed from the regulated gene constitute the output. The red-  
 105 dashed rectangle show experimentally measured affinity values between receptors and signals ( $[10^{-6}\text{M}, 10^{-9}\text{M}]$ ) and  
 106 between transcriptional regulators and DNA ( $[10^{-8}\text{M}, 10^{-13}\text{M}]$ ). The amount of acquired information and noise level are  
 107 indicated in the color bar (see Sup Table 4 for the parameters).  
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**Sup Fig 9. Acquired information, output range, and noise in a gene regulation model that includes the binding of RNA polymerase subject to extrinsic noise.** Noise, output range, and information observed in numerical simulations of the gene expression system with added polymerase-DNA binding. The affinity between the polymerase and the TF-DNA is  $10^{-9}$ . The mean number of polymerase molecules is 10 times the maximal number of TF molecules (see  $N_{Tmax}$  in Sup Table 5) and has a standard deviation of (a) 0% (no extrinsic noise) (c) 10% and (d) 30%. Information, noise, and output range are normalized by their respective maximal values.

117 **Sup Table 1.** Parameter values used for the receptor-signal model.

	$k_d$ ( $s^{-1}$ )	$k_a$ ( $M^{-1}s^{-1}$ )	$N_{Smax}$	$N_{RT}$	Volume (L)	n
Fig 2 and Sup Fig 1 and 2	0.001	[10,10 <sup>7</sup> ]	5000	50	$8.3 \times 10^{-15}$	50
Fig 3a-c	0.001	[10 <sup>4</sup> ,10 <sup>7</sup> ]	[50,5000]	50	$8.3 \times 10^{-15}$	50
Fig 3d-f	0.001	[10,10 <sup>7</sup> ]	5000	50	[ $8.3 \times 10^{-17}$ , $8.3 \times 10^{-13}$ ]	50

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119 **Sup Table 2.** Parameter values used for the model of two consecutive reversible binding interactions.

	$k_{dRS}$ ( $s^{-1}$ )	$k_{aRS}$ ( $M^{-1}s^{-1}$ )	$k_{dRSD}$ ( $s^{-1}$ )	$k_{aRS,D}$ ( $M^{-1}s^{-1}$ )	$N_{Smax}$	$N_{RT}$	Volume (L)	n
Fig 4, Sup Fig 3 and 4	0.001	[10 <sup>2</sup> ,10 <sup>10</sup> ]	0.001	[10 <sup>2</sup> ,10 <sup>10</sup> ]	10 <sup>4</sup>	100	$1.66 \times 10^{-13}$	50

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121 **Sup Table 3.** Parameter values used for the gene expression model.

	$k_d$ ( $s^{-1}$ )	$k_a$ ( $M^{-1}s^{-1}$ )	$k_1$ ( $s^{-1}$ )	$k_2$ ( $s^{-1}$ )	$d_1$ ( $s^{-1}$ )	$d_2$ ( $s^{-1}$ )	$N_{TFmax}$	Volume (L)	n
Fig 5, Sup Fig 5 and 6	0.001	[10 <sup>4</sup> ,10 <sup>10</sup> ]	0.01	0.011	0.005	0.00022	10,000	$1.66 \times 10^{-14}$	50
Sup Fig 7	0.001	[10 <sup>4</sup> ,10 <sup>10</sup> ]	0.01	0.011	0.005	0.000022	10,000	$1.66 \times 10^{-14}$	50

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123 **Sup Table 4.** Parameter values used for the complete signaling pathway model.

	$k_{dRS}$ ( $s^{-1}$ )	$k_{aRS}$ ( $M^{-1}s^{-1}$ )	$k_{dRSD}$ ( $s^{-1}$ )	$k_{aRS,D}$ ( $M^{-1}s^{-1}$ )	$k_1$ ( $s^{-1}$ )	$k_2$ ( $s^{-1}$ )	$d_1$ ( $s^{-1}$ )	$d_2$ ( $s^{-1}$ )	$N_{Smax}$	$N_{RT}$	Volume (L)	n
Sup Fig 8	0.001	[10 <sup>2</sup> ,10 <sup>10</sup> ]	0.001	[10 <sup>4</sup> ,10 <sup>12</sup> ]	0.01	0.011	0.005	0.00022	5000	50	$8.3 \times 10^{-12}$	25

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125 **Sup Table 5.** Parameter values used for the extended gene expression model.

	$k_d$ ( $s^{-1}$ )	$k_a$ ( $M^{-1}s^{-1}$ )	$k_{dTPD}$ ( $s^{-1}$ )	$k_{aTD,P}$ ( $M^{-1}s^{-1}$ )	$k_1$ ( $s^{-1}$ )	$k_2$ ( $s^{-1}$ )	$d_1$ ( $s^{-1}$ )	$d_2$ ( $s^{-1}$ )	$N_{Tmax}$	$N_P$	Volume (L)	n
Sup Fig 9	0.001	10 <sup>6</sup>	0.001	0.0001	0.01	0.011	0.005	0.00022	100	NA	$1.66 \times 10^{-12}$	25

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## 127 **Supplementary References**

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