Cell Systems, Volume *3*

Supplemental Information

Analysis of Cell Lineage Trees by Exact Bayesian Inference Identifies Negative Autoregulation of Nanog in Mouse Embryonic Stem Cells

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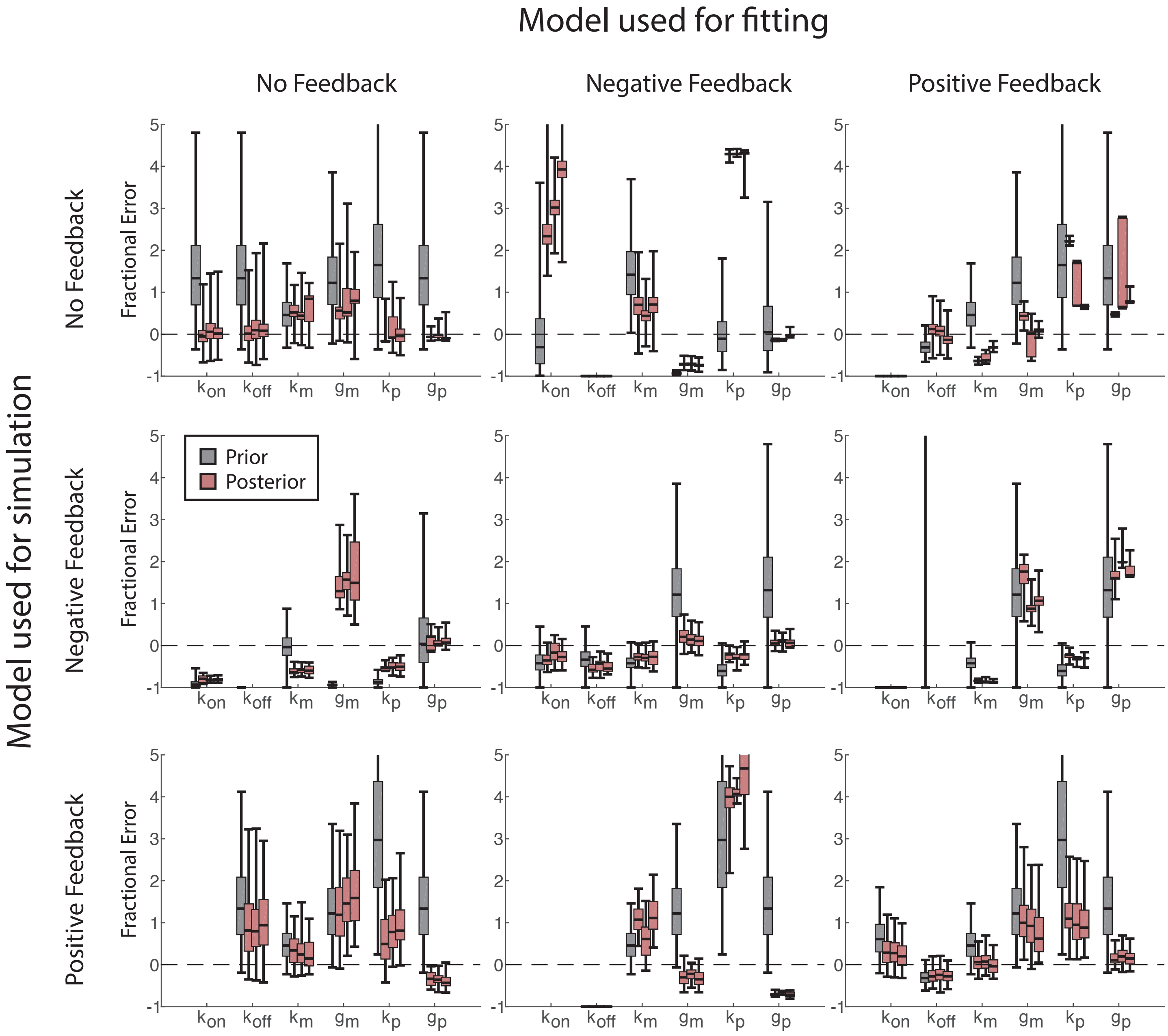
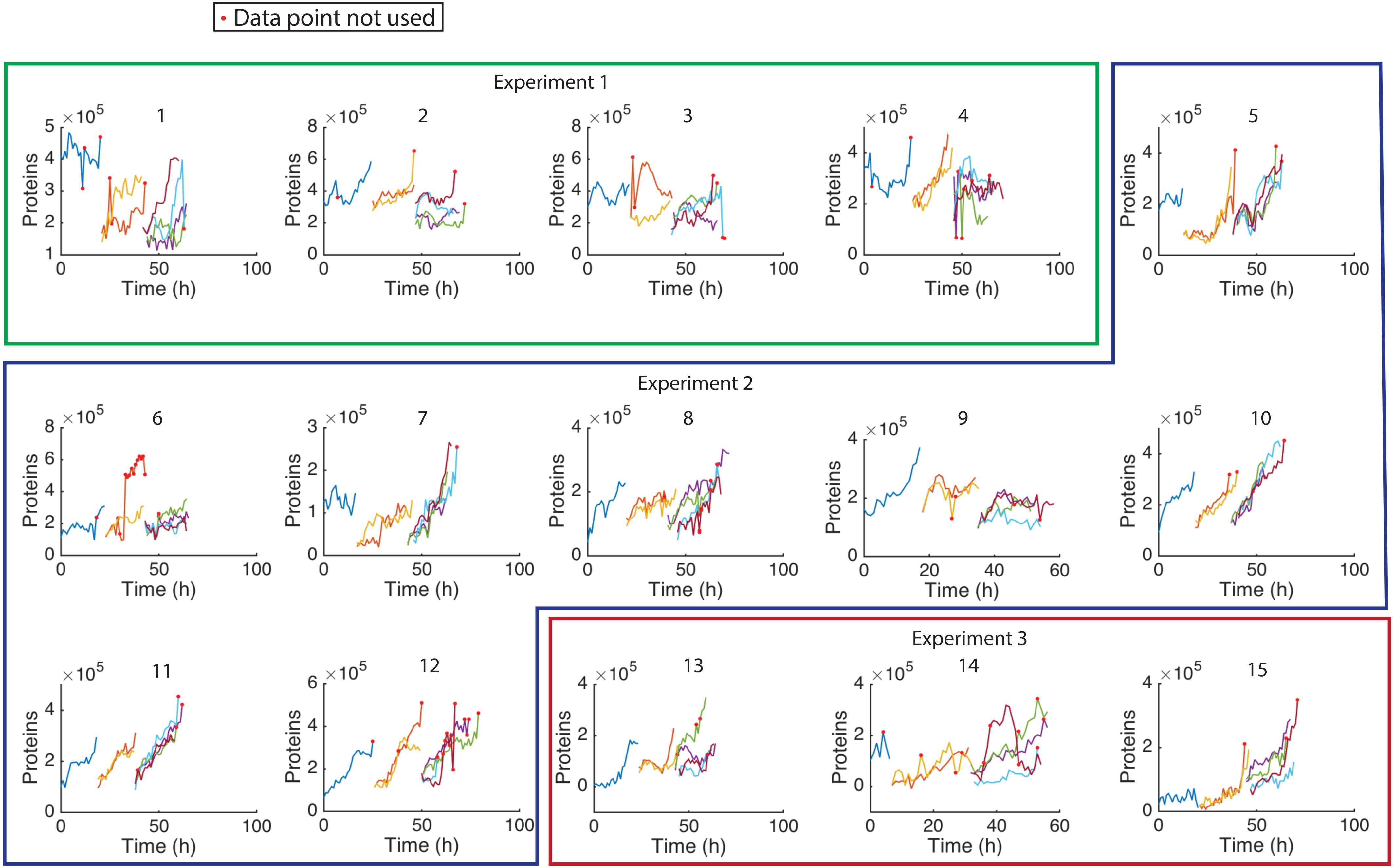
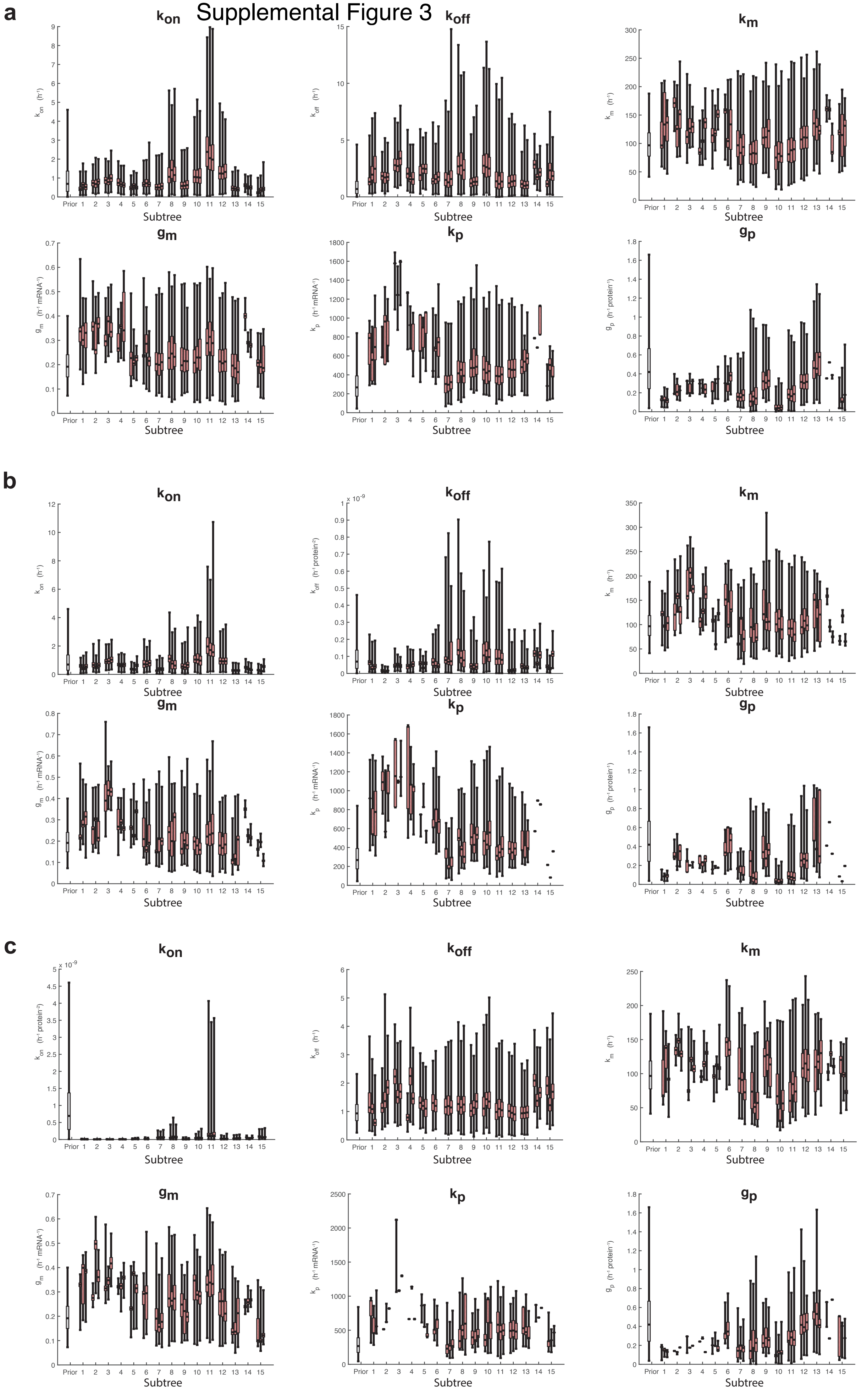
Supplemental Figure 1



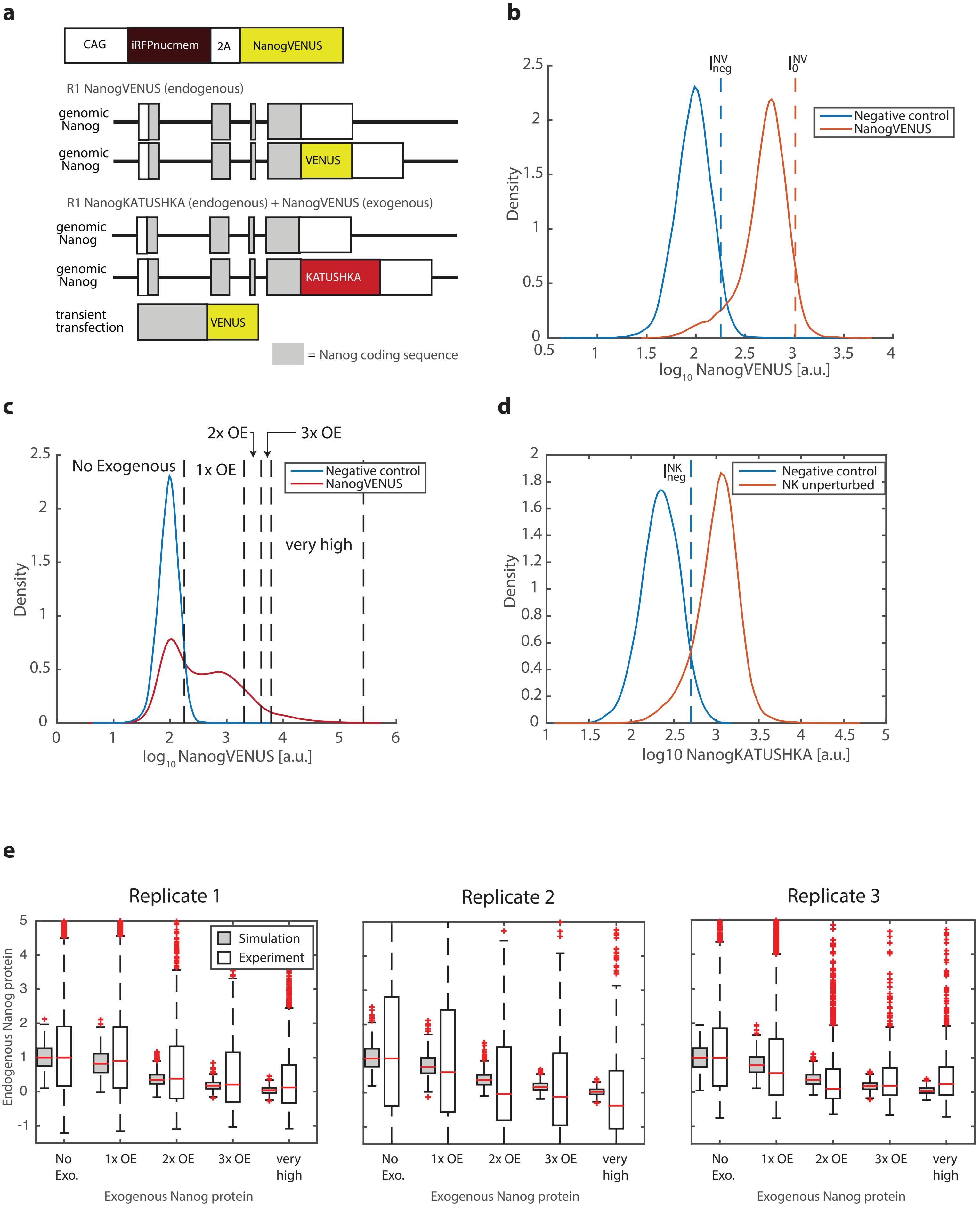
Supplemental Figure 2



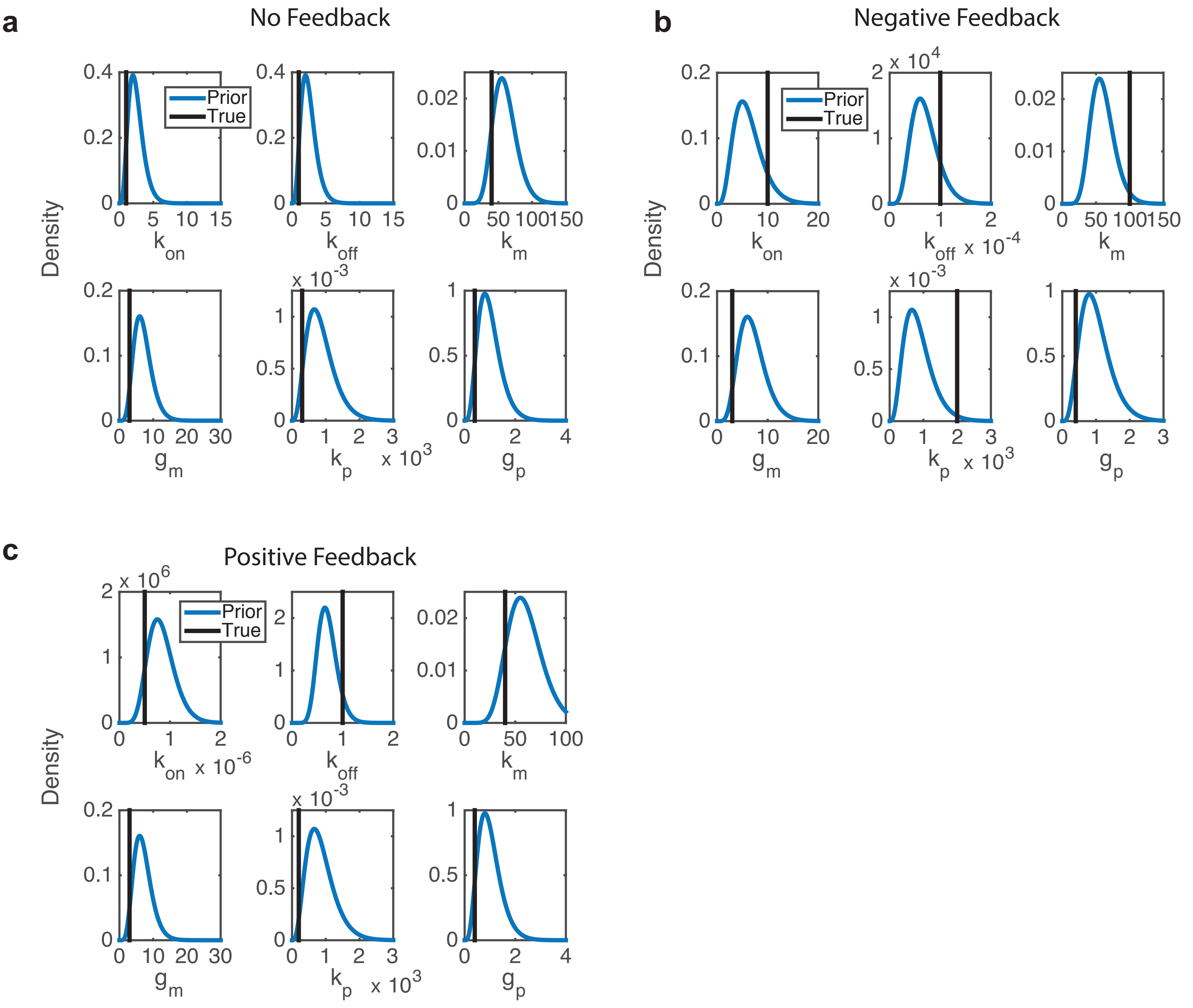
Supplemental Figure 3



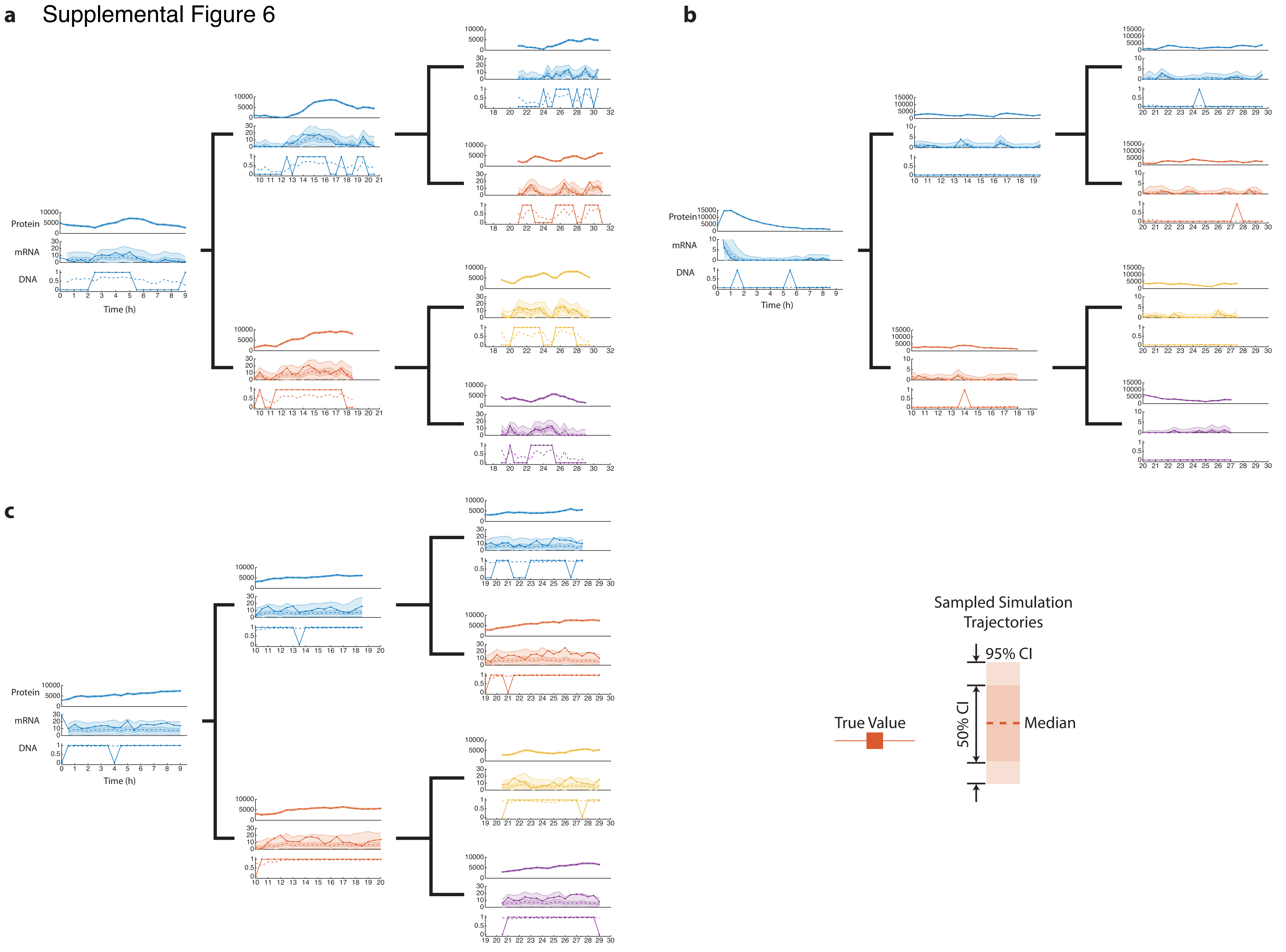
Supplemental Figure 4



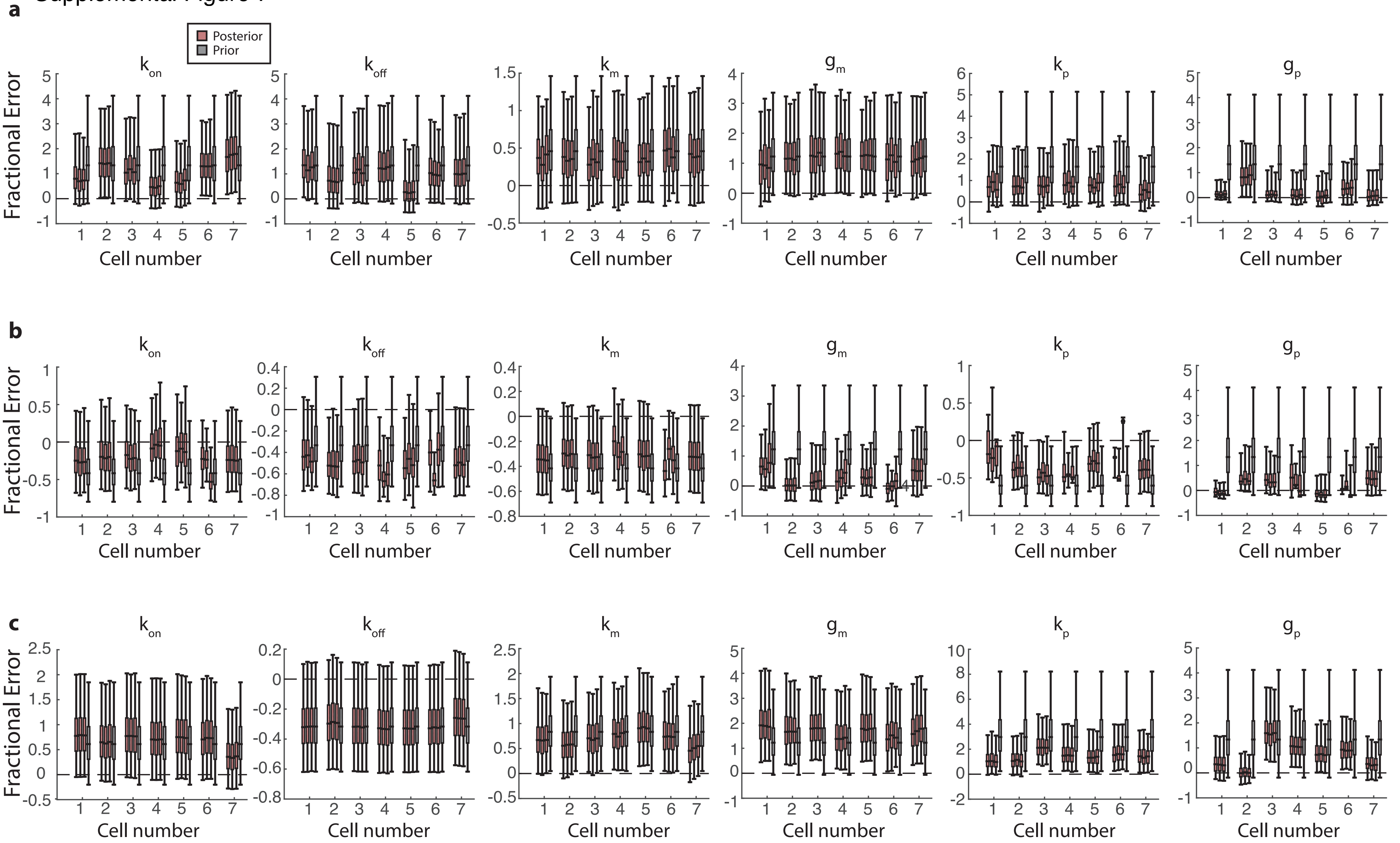
Supplemental Figure 5



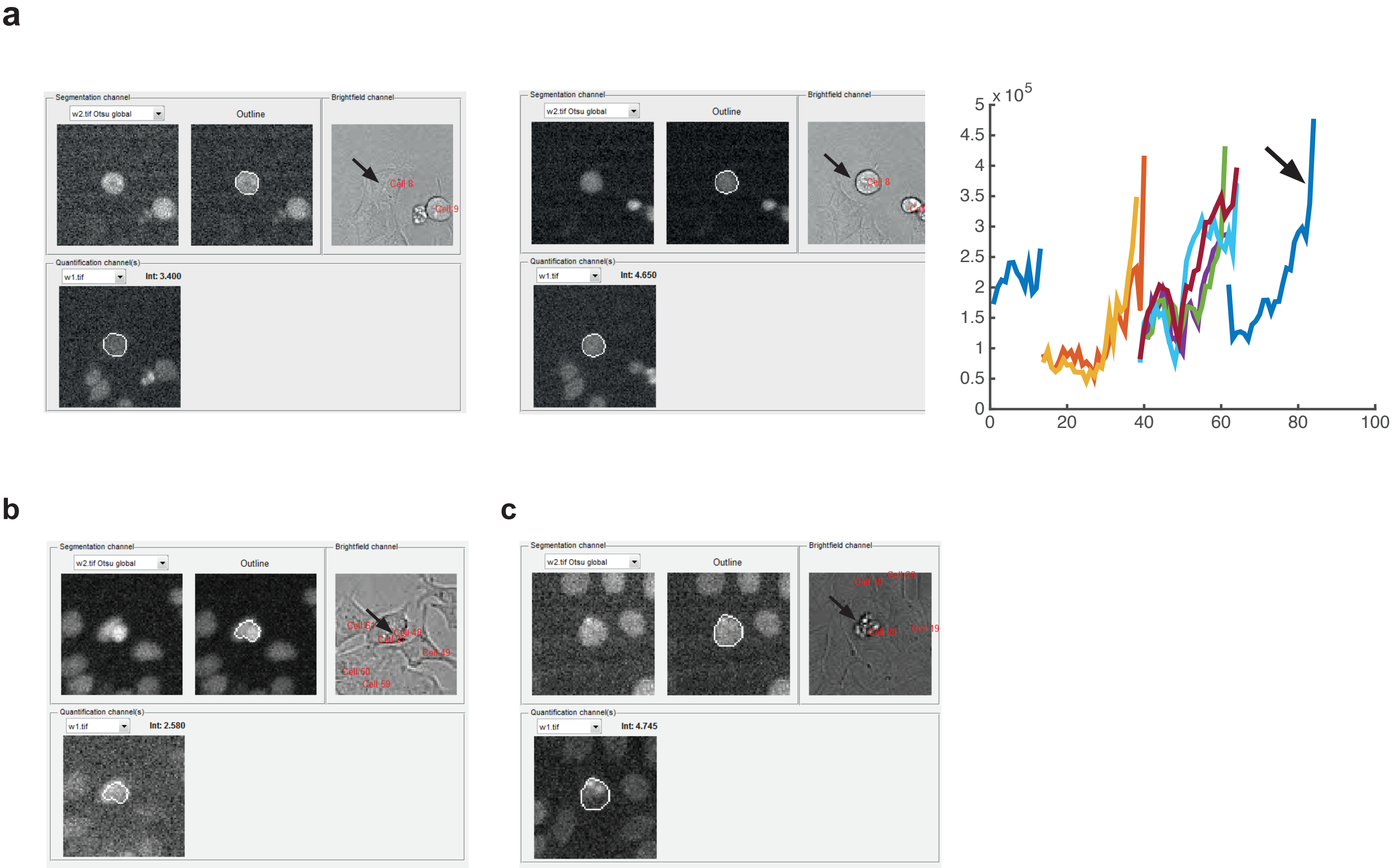
Supplemental Figure 6



Supplemental Figure 7



Supplemental Figure 8



a

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Quantification channel(s): w1.tif
Int: 3.400

Segmentation channel: w2.tif Otsu global
Quantification channel(s): w1.tif
Int: 4.650

b

Segmentation channel: w2.tif Otsu global
Quantification channel(s): w1.tif
Int: 2.580

c

Segmentation channel: w2.tif Otsu global
Quantification channel(s): w1.tif
Int: 4.745

Supplemental Table 1

		Reaction Propensity		
Reaction	**Description**	**No Feedback**	**Negative Feedback**	**Positive Feedback**
DNA ➔ DNA*	DNA activation	k_{on} D	k_{on} D	k_{on} D P^2
DNA* ➔ DNA	DNA inactivation	k_{off} D*	k_{off} D* P^2	k_{off} D*
DNA* ➔ DNA* + mRNA	Transcription	k_m D*		
mRNA ➔ Ø	Degradation of mRNA	g_m M		
mRNA ➔ mRNA + Protein	Translation	k_p M		
Protein ➔ Ø	Degradation of protein	g_p P		

Supplemental Table 2

Parameter	**Units**	**No Feedback**	**Negative Feedback**	**Positive Feedback**
k_{on}	h^{-1}	1	10	5×10^{-7} protein^{-2}
k_{off}	h^{-1}	1	10^{-4} protein^{-2}	1
k_m	h^{-1}	40	100	40
g_m	h^{-1} mRNA^{-1}	3	3	3
k_p	h^{-1} mRNA^{-1}	300	2000	200
g_p	h^{-1} protein^{-1}	0.4	0.4	0.4

Supplemental Table 3

	No Feedback				**Negative Feedback**				**Positive Feedback**			
parameter	**α**	**β**	**mean**	**variance**	**α**	**β**	**mean**	**variance**	**α**	**β**	**mean**	**variance**
k_{on}	5	2	2.5	1.25	5	0.8	4	3.2	10	1.2×10^{7}	8.33×10^{-7}	6.94×10^{-14}
k_{off}	5	2	2.5	1.25	7	10^{5}	7×10^{-5}	7×10^{-10}	14	20	0.7	0.035
k_m	12	0.2	60	300	12	0.2	60	300	12	0.2	60	300
g_m	7	1	7	7	7	1	7	7	7	1	7	7
k_p	4.3	0.005	860	1.72×10^{5}	4.3	0.005	860	1.72×10^{5}	4.3	0.005	860	1.72×10^{5}
g_p	5	5	1	0.2	5	5	1	0.2	5	5	1	0.2

Supplemental Table 4

Fitted Model

True Model

a No Feedback

Cell	No Feedback	Negative Feedback	Positive Feedback
1	0 (0.2105)	-9.3054 (0.2582)	-10.7013 (0.1581)
2	0 (0.1205)	-13.5696 (3.3602)	-5.935 (0.0862)
3	0 (0.0281)	-12.2594 (1.1507)	-7.3764 (0.1044)
4	0 (0.0909)	-15.0681 (1.3747)	-9.8305 (0.0782)
5	-1.1334 (0.121)	-33.2052 (6.1942)	0 (0.1186)
6	0 (0.0621)	-22.3497 (2.7166)	-6.9995 (0.141)
7	0 (0.0532)	-15.0969 (0.4353)	-5.1588 (0.1668)

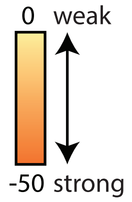
b Negative Feedback

Cell	No Feedback	Negative Feedback	Positive Feedback
1	-4.131 (0.3035)	0 (0.1548)	-26.3066 (0.8125)
2	-2.502 (0.014)	0 (0.0777)	-14.6629 (0.1774)
3	-1.3918 (0.0288)	0 (0.0425)	-11.957 (0.1156)
4	0 (0.0426)	-4.1386 (0.5486)	-1.0796 (0.0182)
5	0 (0.0477)	-1.0327 (0.0177)	-8.6714 (0.1402)
6	0 (0.0782)	-5.2632 (2.1421)	-5.0105 (0.0225)
7	-0.2432 (0.031)	0 (0.0186)	-8.7574 (0.1)

c Positive Feedback

Cell	No Feedback	Negative Feedback	Positive Feedback
1	-2.9141 (0.079)	-12.5306 (0.4929)	0 (0.0382)
2	-2.901 (0.243)	-14.1889 (1.3588)	0 (0.0643)
3	-0.9532 (0.0783)	-9.3542 (0.6612)	0 (0.021)
4	-4.4171 (0.0225)	-18.2459 (2.9465)	0 (0.0263)
5	-4.4039 (0.035)	-17.2991 (1.2285)	0 (0.0205)
6	-4.2933 (0.043)	-17.5176 (1.3442)	0 (0.0112)
7	-0.521 (0.0497)	-11.3935 (0.9244)	0 (0.0591)

log Bayes factor (fitted vs. true)



☐ Incorrect model preferred

Supplemental Table 5

parameter	No Feedback				Negative Feedback				Positive Feedback			
	α	β	mean	variance	α	β	mean	variance	α	β	mean	variance
k_{on}	1	1	1	1	1	1	1	1	1	1.00E+09	1.00E-09	1.00E-18
k_{off}	1	1	1	1	1	1.00E+10	1.00E-10	1.00E-20	5	5	1	0.2
k_m	10	0.1	100	1000	10	0.1	100	1000	10	0.1	100	1000
g_m	8	40	0.2	0.005	8	40	0.2	0.005	8	40	0.2	0.005
k_p	3	0.01	300	30000	3	0.01	300	30000	3	0.01	300	30000
g_p	2	4	0.5	0.125	2	4	0.5	0.125	2	4	0.5	0.125

Supplemental Table 6

a

Subtree	k_{on}	k_{off}	k_m	g_m	k_p	g_p
1	0.5278 [0.2494, 0.9398]	1.689 [0.7351, 4.511]	127.1 [78.92, 195.4]	0.3266 [0.1972, 0.4010]	631.0 [335.4, 946.9]	0.1194 [0.07609, 0.1619]
2	0.7527 [0.3644, 1.226]	1.773 [0.8402, 2.867]	151.4 [86.89, 186.7]	0.3576 [0.2147, 0.4256]	707.1 [511.8, 1197.]	0.2086 [0.1675, 0.2982]
3	0.8809 [0.4667, 1.480]	2.951 [1.637, 5.037]	123.3 [93.06, 156.3]	0.3290 [0.2600, 0.4308]	1577. [1037., 1600.]	0.3221 [0.1955, 0.3268]
4	0.6741 [0.3988, 1.222]	1.707 [0.8542, 3.393]	105.3 [77.71, 149.3]	0.3413 [0.2466, 0.5089]	925.8 [648.8, 1268.]	0.2494 [0.1907, 0.2978]
5	0.5151 [0.2867, 0.8555]	2.361 [0.9045, 3.830]	125.0 [84.33, 175.1]	0.2209 [0.1384, 0.4380]	900.7 [441.3, 1060.]	0.3004 [0.08873, 0.4757]
6	0.6729 [0.3785, 1.225]	1.531 [0.7032, 3.342]	129.2 [68.45, 191.0]	0.2371 [0.1616, 0.3400]	650.6 [440.0, 1026.]	0.3012 [0.1543, 0.4495]
7	0.5217 [0.2093, 1.108]	1.449 [0.4071, 4.034]	92.63 [48.80, 167.6]	0.2045 [0.1058, 0.3587]	305.8 [152.0, 629.9]	0.1582 [0.05890, 0.3708]
8	1.204 [0.3767, 2.897]	2.610 [0.8905, 6.009]	82.06 [43.07, 153.6]	0.2346 [0.1041, 0.4177]	424.7 [208.3, 845.9]	0.1415 [0.02042, 0.5670]
9	0.5972 [0.2088, 1.389]	1.288 [0.5685, 2.953]	112.3 [62.40, 174.2]	0.2107 [0.1001, 0.4172]	472.2 [293.4, 899.2]	0.3185 [0.1324, 0.5748]
10	1.039 [0.3801, 2.799]	2.624 [0.7105, 6.255]	78.47 [34.25, 140.3]	0.2228 [0.09231, 0.3958]	439.8 [192.4, 864.5]	0.04076 [0.007483, 0.1525]
11	2.117 [0.6500, 4.721]	1.279 [0.2285, 4.058]	86.36 [45.60, 151.0]	0.2964 [0.1400, 0.4712]	388.9 [213.9, 784.5]	0.1781 [0.04347, 0.4186]
12	1.265 [0.5667, 2.539]	1.318 [0.4152, 3.668]	109.2 [65.54, 173.2]	0.2106 [0.1093, 0.3523]	454.5 [252.9, 863.8]	0.3121 [0.1523, 0.6088]
13	0.4223 [0.1992, 0.7883]	1.047 [0.4126, 2.373]	126.5 [78.50, 188.6]	0.1841 [0.1059, 0.3924]	520.3 [295.5, 870.4]	0.4732 [0.1807, 0.8521]
14	0.5335 [0.3118, 0.8082]	2.197 [1.234, 3.664]	157.2 [78.65, 168.6]	0.2929 [0.2640, 0.4238]	787.9 [687.5, 1129.]	0.3869 [0.3505, 0.5219]
15	0.3360 [0.1189, 0.6724]	1.642 [0.6390, 3.694]	119.3 [62.50, 163.7]	0.1978 [0.08838, 0.2973]	379.8 [212.8, 699.0]	0.1083 [0.03755, 0.4625]

b

Subtree	k_{on}	k_{off}	k_m	g_m	k_p	g_p
1	0.5216 [0.2561, 0.9515]	4.298e-11 [1.557e-11, 9.163e-11]	106.0 [60.36, 153.3]	0.2690 [0.1902, 0.4101]	810.1 [404.9, 1270.]	0.09880 [0.05760, 0.1564]
2	0.5837 [0.3210, 1.103]	1.338e-11 [6.942e-12, 2.876e-11]	139.7 [85.37, 181.2]	0.2674 [0.1660, 0.3442]	970.5 [508.9, 1264.]	0.2763 [0.1884, 0.4132]
3	0.9452 [0.5632, 1.497]	4.652e-11 [2.616e-11, 7.961e-11]	181.8 [133.7, 238.5]	0.4255 [0.3186, 0.5778]	1142. [826.4, 1538.]	0.2336 [0.1308, 0.2553]
4	0.6609 [0.3540, 0.9702]	4.628e-11 [1.111e-11, 8.545e-11]	126.0 [90.44, 196.6]	0.2725 [0.1914, 0.3671]	1064. [538.2, 1688.]	0.2395 [0.1765, 0.3013]
5	0.4161 [0.2137, 0.8372]	5.105e-11 [2.087e-11, 8.602e-11]	108.1 [56.33, 128.1]	0.2621 [0.2113, 0.3567]	747.4 [574.9, 829.0]	0.1749 [0.1573, 0.1948]
6	0.7412 [0.3428, 1.605]	4.966e-11 [2.000e-11, 1.509e-10]	138.2 [90.45, 198.9]	0.1853 [0.1141, 0.3616]	680.4 [357.8, 1143.]	0.4410 [0.1867, 0.6021]
7	0.3325 [0.1459, 0.6193]	7.212e-11 [2.743e-11, 2.761e-10]	70.52 [42.53, 119.2]	0.1868 [0.1119, 0.2970]	288.2 [110.8, 572.0]	0.1729 [0.07847, 0.3784]
8	0.8374 [0.2208, 2.281]	1.069e-10 [2.630e-11, 2.868e-10]	89.63 [53.23, 183.0]	0.2486 [0.09213, 0.4080]	413.3 [208.7, 967.1]	0.08476 [0.01174, 0.3864]
9	0.5748 [0.1812, 1.248]	3.685e-11 [1.303e-11, 1.119e-10]	110.7 [64.29, 192.6]	0.1937 [0.1017, 0.3446]	519.9 [258.1, 922.1]	0.3357 [0.08823, 0.6580]
10	1.020 [0.2756, 2.094]	1.123e-10 [2.867e-11, 2.970e-10]	101.5 [58.06, 162.0]	0.1742 [0.08430, 0.2964]	477.7 [188.4, 1076.]	0.03097 [0.008924, 0.1029]
11	1.737 [0.7700, 3.662]	8.337e-11 [1.324e-11, 2.949e-10]	89.78 [46.99, 168.7]	0.2281 [0.1028, 0.4001]	347.2 [161.1, 699.9]	0.07673 [0.003671, 0.2667]
12	0.9256 [0.4466, 1.652]	1.662e-11 [5.536e-12, 5.604e-11]	100.8 [59.09, 168.0]	0.1763 [0.08528, 0.3408]	380.9 [206.5, 704.1]	0.2599 [0.1138, 0.5157]
13	0.2737 [0.1365, 0.4713]	3.652e-11 [1.547e-11, 7.865e-11]	129.3 [59.63, 176.9]	0.1145 [0.05830, 0.2794]	380.3 [292.6, 957.8]	0.3785 [0.2116, 1.031]
14	0.3892 [0.2049, 0.6660]	9.569e-11 [3.942e-11, 1.647e-10]	95.43 [71.45, 163.9]	0.2285 [0.2021, 0.3632]	855.0 [571.3, 896.3]	0.4089 [0.3231, 0.6574]
15	0.3224 [0.1348, 0.7100]	4.340e-11 [1.460e-11, 1.498e-10]	67.20 [62.15, 122.1]	0.1613 [0.1004, 0.2071]	215.9 [82.53, 360.3]	0.08336 [0.03257, 0.1947]

c

Subtree	k_{on}	k_{off}	k_m	g_m	k_p	g_p
1	6.886e-12 [2.954e-12, 1.471e-11]	0.9715 [0.4093, 2.277]	92.67 [60.86, 150.4]	0.3517 [0.2226, 0.4212]	556.2 [327.4, 937.7]	0.1426 [0.1011, 0.1874]
2	5.027e-12 [2.328e-12, 9.829e-12]	1.406 [0.7829, 2.520]	136.5 [119.1, 160.5]	0.3561 [0.2584, 0.5338]	620.6 [513.4, 885.8]	0.1407 [0.1056, 0.1780]
3	5.302e-12 [2.539e-12, 9.259e-12]	1.788 [1.045, 2.821]	108.1 [70.41, 134.6]	0.3488 [0.2918, 0.4864]	1297. [1078., 2120.]	0.1960 [0.1754, 0.2945]
4	6.147e-12 [3.108e-12, 1.223e-11]	1.420 [0.5834, 2.862]	113.9 [92.67, 135.8]	0.3295 [0.2706, 0.3730]	664.1 [662.9, 1139.]	0.2402 [0.1283, 0.2732]
5	1.663e-11 [6.825e-12, 3.256e-11]	1.220 [0.6440, 1.860]	107.7 [90.55, 116.8]	0.3163 [0.2170, 0.3908]	549.2 [406.9, 863.3]	0.1952 [0.1416, 0.2017]
6	2.025e-11 [7.966e-12, 3.563e-11]	1.241 [0.7099, 1.989]	139.6 [102.4, 187.9]	0.2931 [0.1781, 0.4633]	509.3 [422.3, 856.5]	0.3257 [0.2372, 0.7476]
7	5.906e-11 [2.106e-11, 1.312e-10]	1.160 [0.5538, 2.086]	84.12 [50.13, 173.5]	0.1665 [0.1004, 0.3294]	264.9 [147.0, 443.0]	0.1493 [0.04987, 0.2877]
8	5.981e-11 [1.226e-11, 1.922e-10]	1.221 [0.6068, 2.317]	55.71 [27.60, 129.7]	0.2676 [0.1772, 0.4457]	449.4 [229.6, 1096.]	0.1735 [0.04880, 0.4815]
9	1.189e-11 [4.586e-12, 2.646e-11]	1.167 [0.5575, 2.124]	120.3 [74.46, 158.9]	0.2148 [0.1126, 0.3142]	401.9 [177.8, 727.5]	0.2557 [0.08608, 0.4413]
10	4.621e-11 [1.046e-11, 1.002e-10]	1.327 [0.5909, 2.391]	54.64 [27.88, 118.7]	0.2915 [0.1673, 0.4019]	561.9 [215.8, 956.2]	0.1182 [0.01787, 0.2674]
11	1.166e-10 [3.985e-11, 8.070e-10]	1.037 [0.4213, 2.051]	75.01 [37.27, 141.5]	0.3333 [0.1868, 0.4987]	519.5 [270.6, 973.3]	0.2662 [0.1131, 0.5989]
12	2.835e-11 [1.141e-11, 6.291e-11]	0.9565 [0.4372, 1.764]	110.3 [56.11, 180.1]	0.2452 [0.1185, 0.3760]	494.2 [271.8, 885.7]	0.4192 [0.1828, 0.7191]
13	3.752e-11 [1.752e-11, 7.549e-11]	0.9486 [0.4921, 1.673]	117.6 [66.48, 157.8]	0.1416 [0.07264, 0.3531]	473.0 [295.5, 835.0]	0.4783 [0.2177, 0.8186]
14	5.410e-11 [1.021e-11, 8.397e-11]	1.706 [0.9723, 2.579]	110.5 [98.44, 135.7]	0.2563 [0.2290, 0.2876]	827.7 [685.3, 871.5]	0.6567 [0.2727, 0.6832]
15	7.041e-11 [3.459e-11, 1.396e-10]	1.608 [0.8168, 2.680]	97.04 [66.62, 130.4]	0.1095 [0.08600, 0.2696]	353.8 [187.5, 560.3]	0.2776 [0.07192, 0.5078]

Supplemental Table 7

Subtree	**No Feedback**	**Negative Feedback**	**Positive Feedback**
1	-1634.1 (0.4333)	-1636.3000 (0.9074)	-1641.6333 (0.8172)
2	-1814.7 (0.2646)	-1824.6000 (0.7211)	-1843.4667 (4.9320)
3	-1835.4 (0.5568)	-1834.6333 (1.1837)	-1865.3333 (4.3910)
4	-1700.3 (0.1528)	-1703.6333 (0.2906)	-1711.4000 (2.0075)
5	-1838.6 (0.4842)	-1843.9333 (1.5603)	-1848.7667 (2.1184)
6	-1597.1 (0.7126)	-1595.7000 (0.2000)	-1602.7858 (0.0231)
7	-1747.4 (0.1453)	-1753.1000 (0.7095)	-1754.5000 (0.1528)
8	-1820.4 (0.0882)	-1821.8667 (0.2603)	-1825.2333 (0.2333)
9	-1450.7 (0.0577)	-1454.8000 (0.1528)	-1453.7333 (0.2333)
10	-1554.4 (0.1732)	-1553.9000 (0.0000)	-1560.1000 (0.2517)
11	-1615.6 (0.0882)	-1615.1000 (0.0577)	-1617.6000 (0.1732)
12	-1591.0 (0.0577)	-1592.7333 (0.0667)	-1598.5333 (0.0882)
13	-1546.5 (0.1528)	-1551.8000 (0.1732)	-1554.8667 (0.6386)
14	-1714.6 (5.2129)	-1769.1000 (7.7253)	-1795.0667 (9.8660)
15	-1803.4 (0.4933)	-1832.0667 (0.2333)	-1810.9333 (0.7796)

Supplemental Table 8

Goodness-of-fit null distribution quantile

Experiment	Subtree number	No Feedback	Negative Feedback	Positive Feedback
1	1	0.2978 (0.1125)	0.2033 (0.0996)	0.0033 (0.0033)
	2	0.1811 (0.0804)	0.2578 (0.0617)	0 (0)
	3	0.5478 (0.0473)	0.1444 (0.0307)	0 (0)
	4	0.0167 (0.0058)	0.0944 (0.0195)	0 (0)
2	5	0.0567 (0.0291)	0.0467 (0.0158)	0 (0)
	6	0.0222 (0.004)	0.0044 (0.0022)	0 (0)
	7	0.9867 (0.0058)	0.8478 (0.0478)	0.0533 (0.019)
	8	0.7422 (0.0713)	0.5322 (0.0356)	0.0267 (0.0051)
	9	0.8389 (0.0879)	0.6122 (0.0695)	0.0067 (0)
	10	0.9044 (0.0292)	0.59 (0.0386)	0.0867 (0.0102)
	11	0.9956 (0.0011)	0.9267 (0.0133)	0.16 (0.0084)
	12	0.9756 (0.0048)	0.9267 (0.0315)	0.0078 (0.0011)
3	13	0.97 (0.0133)	0.6011 (0.083)	0.02 (0.0033)
	14	0.0089 (0.0022)	0 (0)	0 (0)
	15	0.9789 (0.0211)	0.3689 (0.1529)	0.08 (0.0058)

Reject ($p < 0.01$ or $p > 0.99$)
Marginal ($p < 0.025$ or $p > 0.975$)
Accept

Supplemental Figure Captions

Supplemental Figure 1. Related to Figure 2. Posterior distributions of model parameters are robustly estimated in most cases. We estimate the posterior distribution of each model parameter for every combination of model used for data generation and model used for inference. Each combination is fit three times (red boxes; whiskers show 95% confidence interval) to provide an estimation of the robustness of the inference procedure, and compared against the prior distribution (gray boxes).

Supplemental Figure 2. Related to Figure 3. We obtain 15 NanogVENUS subtrees of 7 cells each from 3 experiments. 15 NanogVENUS subtrees of 7 cells each are fit with each of the autoregulatory models. The subtrees are obtained from 7 microscopy positions from 3 independent experiments, obtained by dividing trees into non-overlapping subtrees of seven immediately-related cells (see Figure 3A). Unreliable data points (red) are censored (see Methods) and not used for inference.

Supplemental Figure 3. Related to Figure 3. We estimate the posterior distribution of all model parameters for every NanogVENUS subtree, fit with each of the three autoregulatory models. Inference for each model/dataset is performed in triplicate (red boxes) to assess robustness with respect to the stochastic nature of the inference procedure. Priors distributions are shown in gray. Each subtree was fit with the (A) No Feedback, (B) Negative Feedback and (C) Positive Feedback models.

Supplemental Figure 4. Related to Figure 4. We estimate autofluorescence and expression levels of endogenous Nanog reporters. (A) Top: Schematic Nanog overexpression construct. The NanogVENUS and RFPnucmem proteins are translated at similar levels. iRFPnucmem allows direct comparison of the construct with an empty vector (no NanogVENUS) and Nanog alone (without VENUS). CAG = constitutive promoter; 2A = sequence for protein "cleavage"; iRFP (targeted to nuclear membrane) and VENUS = fluorescent proteins. Bottom: Schematic representation of cell lines. Cells express a fluorescently labeled Nanog protein (either VENUS or KATUSHKA) from one endogenous allele. Exogenous NanogVENUS was transiently transfected 2 days before analysis. (B) We estimate the autofluorescence level of NanogVENUS (I_{neg}^{NV}) using wild-type mESCs. We also estimate the 0.95 quantile of endogenous NanogVENUS (I_0^{NV}) in unperturbed NV cells. (C) We measure NanogVENUS levels and define compartments of exogenous Nanog as either No Exogenous (below negative control levels); 1x, 2x, and 3x overexpression corresponding to up to 100%, 200% and 300%, respectively, of wild-type Nanog levels; and very high (> 300% wild-type Nanog expression). (D) We estimate the autofluorescence level (0.95 quantile) of NanogKATUSHKA (I_{neg}^{NK}) using the NanogVENUS cell line (blue). The intensity distribution of unperturbed NanogKATUSHKA mESCs is shown for comparison (red). (E) We compare simulated (gray) and measured (white) down-regulation relative to the median of the No Exogenous overexpression compartment, for three experimental replicates. Distributions are of the relative expression of individual cells for both experiment and simulation.

Supplemental Figure 5. Related to Figure 2. Prior distributions used for *in silico* testing. STILT was run using parameter prior distributions tailored to each model, chosen such that the true model parameters used for data generation are contained in the prior distribution, but not identical to the mode of the distribution. (A) No Feedback, (B) Negative Feedback and (C) Positive Feedback.

Supplemental Figure 6. Related to Figure 2. STILT provides estimates of the latent mRNA and DNA trajectories. Protein (top), mRNA (middle) and DNA (bottom) trajectories are estimated by STILT and show very good agreement with the true trajectories (solid lines) and the resampled trajectories. The 50% and 95% confidence intervals of the resampled trajectories are shown as band plots, along with the medians (dashed line). For DNA, the true value (solid line) is compared with the mean over the sampled histories (dashed line) . The trajectories for each cell of the simulated lineage are plotted separately for improved visibility. In each case the correct model is used for inference. Results are shown for the (A) No Feedback, (B) Negative Feedback and (C) Positive Feedback models.

Supplemental Figure 7. Related to Figure 2. Parameter inference without including cellular lineage trees fails to converge to the correct model parameters. Single-cell-based inference was performed for each of the seven cells from each of the three synthetic datasets. The fractional error of each posterior is plotted and compared to the prior for each model parameter and dataset. The posteriors are robustly estimated, across the repeats of the inference procedure. However, STILT's tree-based inference shows improved parameter convergence to the true value compared to the single-cell-based inference for most parameters (see supplemental Figure 1). Additionally, there is substantial variation between cells due to the difference in information content of their respective trajectories. (A) No Feedback, (B) Negative Feedback, and (C) Positive Feedback.

Supplemental Figure 8. Related to Figure 3. We pre-process quantified fluorescence lineage trees to remove inaccurate data. (A) Many cells show a substantial change in morphology, going from a flat (left) to round (middle) morphology just prior to division. This change often leads to an artificial jump in the quantified fluorescence intensity (right) at the last time point prior to division in many cells, and is thus censored (i.e. not used for inference). (B) Fluorescence signal at time points where cell nuclei overlap cannot be reliably quantified and are also censored. (C) Time points showing large fluctuations in fluorescence intensity due to contamination overlapping the segmented nuclei are likewise excluded.

Supplementary Table captions

Supplemental Table 1. Related to Figure 2. Propensity functions for the three autoregulation models (Negative, Positive, and No Feedback). Propensities depend on abundance of inactive DNA (D), active DNA (D*), mRNA (M) and protein (P). Each model is characterized by different DNA activation and inactivation reaction propensities. The remaining propensities for transcription, translation, and degradation of mRNA and protein are identical for the three models.

Supplemental Table 2. Related to Figure 2. Model parameters used for generating the synthetic datasets. Parameters differ slightly between the No Feedback, Negative Feedback, Positive Feedback models so as to provide similar order of magnitude of protein abundance between trajectories generated from each model.

Supplemental Table 3. Related to Figure 2. Parameters characterizing the gamma prior distributions used for inference of the synthetic datasets.

Supplemental Table 4. Related to Figure 2. Bayes Factor analysis shows that model selection is less robust for single-cell-based inference. The computed log Bayes Factors of each model indicate that the incorrect model is preferred (red boxes) for one cell in the (A) No Feedback dataset, and for 3 cells in the (B) Negative Feedback dataset. (C) The Positive Feedback model is inferred correctly for each of the Positive Feedback datasets. Each row indicates the difference of the marginal log likelihood (mean, s.d.; n=3 runs of the inference procedure) of each fitted model and the marginal log likelihood of the best model for that cell/dataset, i.e. a value of 0 indicates the best model for that cell/dataset.

Supplemental Table 5. Related to Figure 3. Parameters characterizing the gamma prior distributions used inference of the NanogVENUS subtrees.

Supplemental Table 6. Related to Figure 3. We estimate the median (95% confidence interval) of the posterior distributions of each model parameter for every NanogVENUS subtree using the (A) No Feedback, (B) Negative Feedback, and (C) Positive Feedback models.

Supplemental Table 7. Related to Figure 3. Evidence of each subtree/model combination. We estimate the evidence (marginal log likelihood) of each model applied to each dataset using STILT (mean, s.e., n=3).

Supplemental Table 8. Related to Figure 3. We use the goodness-of-fit test to determine which autoregulatory models are compatible with the NanogVENUS subtrees. For each subtree and model we estimate the null distribution of the average marginal log likelihood per transition using synthetic data (see Figure SI5). We use this distribution to compute the probability of a dataset having the same evidence as the real dataset if the model and model parameters are correct (mean, s.e.m., n=3 runs of the inference procedure). Each model is accepted if it is within the 95% confidence interval of the empirical distribution, marginally accepted if it is not accepted but is within the 98% confidence interval, and rejected otherwise.