On a Fundamental Structure of Gene Networks in Living Cells

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1. Surprisal analysis and the connectivity matrix

Surprisal analysis (1, 2) of microarray data provides an exact or at least a good approximation for the logarithm of the expression level of the transcripts. For gene *i* at the time point *T* we use the representation of its expression level (3, 4):

$$\ln X_i(t_T) = \ln X_i^o - \sum_{\alpha=1} G_{i\alpha}\, \lambda_\alpha(t_T) \qquad \text{[S.1]}$$

Surprisal analysis seeks to keep few terms in the sum in equation [S.1] while still providing an accurate representation of the experimental data.

The zeroth term, $\ln X_i^o$, is the 'secular', the time-invariant, part of the level of expression. This term is the gene expression level at maximal entropy (3, 4). It is definitely not a uniform distribution and different transcripts can have fold differences in their level. It is this variation of the zeroth order term as a function of the gene index, *i*, written as $-\ln X_i^o = G_{i0}\,\lambda_0$ and plotted in figure 2 of the main text that makes our work distinct from studies where entropy is used as a statistical measure.

The α = 1,2,.. terms in equation [S.1] reduce the entropy from its maximal value due to the presence of process constraints of the biology. $\alpha = 1,2,..$labels the different possible transcription patterns (= phenotypes) where $\lambda_\alpha(t_T)$ is the weight of the phenotype α at time point *T*. $G_{i\alpha}$ is the weight of gene *i* in the transcription pattern α. In technical terms, see scheme in (4), each transcription pattern is a constraint on the entropy. $\lambda_\alpha(t_T)$ is a measure of how much the entropy is reduced below its maximal value due to the constraint. We therefore index the successive terms in equation [S.1] such that the first, α =1, term is the major contribution. In the language of maximal entropy, it is the dominant constraint. Next is the α =2 term etc. As shown in(3, 4), keeping even the one, α = 1, dominant constraint term already provides a semi-quantitative representation for the expression level and its temporal evolution.

To determine the succession of terms for equation [S.1] all the way to an exact representation, we proceed as follows. Taking the microarray data in the form of expression levels $X_i(t_T)$ for gene *i* at the time *T* we take the logarithm of each entry. Say that there are A time points that were measured, *T* =1,2,..,A+1. We form the A+1 by A+1 symmetric connectivity matrix **C** such that its matrix elements are given

by $C_{T,T'} = \sum_i \ln(X_i(t_T))\ln(X_i(t_{T'}))$. If we introduce the N by A+1 matrix **Y** where $Y_{iT} = \ln(X_i(t_T))$ we can write the connectivity matrix as a matrix product

$$\mathbf{C} = \mathbf{Y}^{\mathrm{T}}\mathbf{Y} \qquad [S.2]$$

where the superscript T denotes the transpose of the matrix.

The matrix **C** is not quite but almost the covariance matrix of the information provided by the expression levels at two times.

C is a symmetric matrix and can be diagonalized. There are A+1 eigenvectors and eigenvalues. We here discuss the common case where all the eigenvalues of **C** are positive. Then the eigenvalue equations as

$$\mathbf{C}\,\mathbf{P}_\alpha = \omega_\alpha^2\,\mathbf{P}_\alpha \quad , \alpha = 0,1,2,..,\mathrm{A} \qquad [S.3]$$

The eigenvectors are normalized by the condition $\sum_{T=0}^{\mathrm{A}} P_{T\alpha}^2 = 1$.

To write the secular term in a manner analogous to the terms of the constraints we define

$$\begin{aligned} \ln X_i^o &= G_{i\alpha=0}\,\lambda_{\alpha=0} \\ \lambda_{\alpha=0} &= \omega_{\alpha=0} P_{T\alpha=0} \end{aligned} \qquad [S.4]$$

The secular expression level is, by definition, not time dependent.

The weights $\lambda_\alpha(t_T)$ of the different phenotypes are computed by an equation analogous to that for $\lambda_{\alpha=0}$ namely we write for each term $\lambda_\alpha(t_T)$

$$\lambda_\alpha(t_T) = P_{T\alpha}\omega_\alpha \qquad [S.5]$$

$G_{i\alpha}$, the weight of gene *i* in the transcription pattern *α* can also be determined by an eigenvalue equation for an N by N matrix $\mathbf{Y}\mathbf{Y}^{\mathrm{T}}$, (3, 4). In practice the vector $\mathbf{G}_\alpha$ whose components are the $G_{i\alpha}$'s can be computed with more modest computer storage requirements as

$$\mathbf{G}_\alpha = \omega_\alpha^{-1}\,\mathbf{Y}\,\mathbf{P}_\alpha \qquad [S.6]$$

We point out that the definition through equation [S.6] produces a vector that is

normalized: $\mathbf{G}_\alpha^{\mathrm{T}}\mathbf{G}_\alpha = \mathbf{P}_\alpha^{\mathrm{T}}\mathbf{Y}^{\mathrm{T}}\omega_\alpha^{-2}\,\mathbf{Y}\,\mathbf{P}_\alpha = \mathbf{P}_\alpha^{\mathrm{T}}\,\mathbf{P}_\alpha = 1$. In particular the vector $\mathbf{G}_0$ is normalized. This is important because normalization ensures that the individual components of the vector, the $G_{i0}'s$, have only a bounded scope for variation. As a rough guide $G_{i0}^2 \approx 1/\mathrm{N}$ where N is the number of transcripts. There are variations about the average, see figure 2 of the main text, but the estimate is useful for comparing arrays of different sizes.

The connectivity matrix as shown latter in Section 3 ,equation [S.8], follows from the definition by equation [S.2] and from equation [S.6]

$$\mathbf{C} = \sum_{\alpha=0}\omega_\alpha^2\mathbf{G}_\alpha^{\mathrm{T}}\mathbf{G}_\alpha = \omega_0^2\mathbf{G}_0^{\mathrm{T}}\mathbf{G}_0 + \sum_{\alpha=1}\omega_\alpha^2\mathbf{G}_\alpha^{\mathrm{T}}\mathbf{G}_\alpha \qquad [S.7]$$

This result is sometimes known as the spectral representation of a matrix.

2. G_{i0} distribution between functional groups

In the cellular models analyzed, transcripts with the lowest G_0 values (for example, below -0.0125 in HF1 cells, Figure S11, Table S7) belong to ribosome, protein translation and energy pathways' modules. The transcripts with mid G_{i0} values (-0.005-(-0.01) in HF1 cells, Figure S11) participate in the cell cycle and DNA/RNA metabolism (Table S8). The transcripts with the highest G_{i0} values (for example, greater than -0.0005 in HF1 cells, Figure S11) usually participate in signal transduction, morphogenesis and cell communication modules (Table S9). In addition, two additional examples of normal cells (TGFβ treated hematopoetic stem cells and dendritic differentiated cells) were analyzed. The distributions of the G_{i0} values between the functional groups of the steady state (Figure S12, Tables S10-S13) are found to be similar**.**

Moreover the scalar product between the stem and differentiated cells is $\sum_i G_{i0}^{(\mathrm{den})} G_{i0}^{(\mathrm{hemat})} = 0.973$ (see for details the section "Quantifying the conservation of the steady state pattern in different cells" of the manuscript). In contrast to the conservation of the steady state the transcription patterns that characterize the process of TGFβ treatment vary significantly between two cell types, $\sum_i G_{i1}^{(\mathrm{den})} G_{i1}^{(\mathrm{hemat})} = -0.18$**.**

In yeast a similar picture was observed in the lowest (less than -0.016) and mid G_{i0} (-0.012 to -0.015), Figure S9, Tables S14 and S15). There is a small number of significant categories for the transcripts with high G_{i0} (greater than -0.011) and among them sexual reproduction categories are present (Table S16). These categories include and are regulated by signal transduction and cell communication transcript, that extensively have been used by multicellular organisms. We see, for example, transcripts with high G_{0i}, as was revealed by KEGG analysis tool, participate in the MAPK signaling, whereas transcripts with low G_{0i} do not.

Lowest G_{i0} values and mid G_{i0} values in E.Coli included similar functional groups (lowest G_{i0} included translation and energy pathways, Table S19; mid G_{i0} included

RNA/DNA metabolism and cell cycle, Table 20) **.** Analysis of the high G_{0i} values in E. Coli did not show significant biological categories.

3. Stability of Transcripts Defines Connectivity

The connectivity matrix is determined by the means and correlations between the fold values, $Y_i = \ln X_i$, of the transcripts:

$$\underbrace{\overline{Y_i Y_j}}_{\text{connectivity}} = \underbrace{\overline{Y_i}\,\overline{Y_j}}_{\substack{\text{factored product} \\ \text{of two means}}} - \underbrace{\overline{\left(Y_i - \overline{Y_i}\right)\left(Y_j - \overline{Y_j}\right)}}_{\substack{\text{covariance between expression levels} \\ \text{of transcripts } i \text{ and } j}} \qquad [S.8]$$

$$= \sum_{\alpha=0} \omega_\alpha{}^2 G_{i\alpha} G_{j\alpha} = \omega_0^2 G_{i0} G_{j0} + \sum_{\alpha=1} \omega_\alpha{}^2 G_{i0} G_{j0}$$

A description of the derivation of equation [S.8] is provided in the Section 1 of the SI. ω_α determines the magnitude of λ_α ((3, 4) and Section 1 of the SI). As we saw, λ_0 is much larger than the other λ_α. Therefore the main contribution to the connectivity is defined by the steady state contribution $\omega_0^2 G_{i0} G_{j0}$. The overall weight is determined by the value of ω_0^2 while the connectivity of two transcripts is set by the product $G_{i0} G_{j0}$. Both G_{i0} and G_{j0} need to have a large value in order to be well connected. Therefore transcripts with stable gene expressions and low free energy are more connected.

The full connectivity, as shown in equation [S.8], also depends on the particular constraints of the biological process under study. But these terms are significantly smaller, see equation [1] of the main text, and represent a small perturbation of the robust steady state connectivity.

4. Tables

Table S1: Computed values of the weights, $\lambda_\alpha(t_T)$, for the trajectories 15781012,157811,157810, 15789,1578.

t_T	$\alpha=0$	$\alpha=1$	$\alpha=2$	$\alpha=3$	$\alpha=4$	$\alpha=5$
1	-407.6	-23.72	-10.31	2.74	-8.00	-8.05
5	-405.4	-22.42	-12.09	-0.80	6.78	8.70
7	-406.6	-21.34	23.12	-2.30	1.86	-0.67
8	-405.0	22.98	-0.56	12.54	8.51	-4.78
10	-406.9	21.59	3.34	5.17	-10.31	7.58
12	-404.7	23.09	-3.53	-17.40	1.25	-2.77
1	-407.8	-19.52	-10.77	4.69	-10.35	
5	-405.7	-17.42	-12.07	-3.96	10.52	
7	-406.8	-17.76	23.18	-0.58	0.46	
8	-404.8	28.24	0.48	12.24	3.37	
11	-403.9	26.80	-0.83	-12.44	-3.95	
1	-407.8	-19.49	10.36	7.04	-9.16	
5	-405.6	-18.75	11.81	-5.89	9.47	
7	-406.8	-16.51	-23.35	-1.85	-0.42	
8	-404.8	28.46	2.90	-9.89	-5.78	
10	-406.7	26.43	-1.69	10.51	5.92	
1	-407.9	18.85	-10.09	-5.34	10.76	
5	-405.6	19.25	-11.97	2.10	-10.62	
7	-406.8	16.88	23.24	2.77	-0.17	
8	-404.8	-26.71	-3.51	16.24	2.51	
9	-405.9	-28.47	2.30	-15.71	-2.52	
1	-408.1	-13.09	-10.71	-11.40		
5	-405.9	-11.74	-11.95	11.25		
7	-407.0	-11.08	23.26	0.52		
8	-404.4	36.15	-0.62	-0.31		

Table S2: Computed values of the weights, $\lambda_\alpha(t_T)$, for the TGFβ treated A549 cells. Cells were treated for 0 -72 hours as indicated in the table.

t_T	$\alpha=0$	$\alpha=1$	$\alpha=2$	$\alpha=3$	$\alpha=4$	$\alpha=5$	$\alpha=6$	$\alpha=7$	$\alpha=8$
0	1046.2	-39.4	-19.2	-15.2	-6.5	1.1	-7.5	6.2	-2.9
0.5	1046.8	-38.3	-10.6	-8.2	1.1	-6.0	9.0	-4.4	5.9
1	1048.9	-33.1	-1.5	5.6	3.5	8.9	-0.3	-9.1	2.2
2	1049.2	-30.4	6.1	14.7	14.7	-1.1	0.3	9.6	-1.4
4	1050.2	-14.0	17.6	10.3	-8.3	-5.4	-5.5	-6.8	-6.7
8	1049.4	10.7	22.1	-1.8	-13.4	3.6	7.6	6.5	-0.1
16	1049.8	40.5	15.1	-7.3	4.2	-1.1	-6.8	0.1	12.4
24	1047.6	49.4	0.7	-13.8	10.4	0.4	2.5	-2.9	-10.8
72	1048.2	54.5	-30.4	15.8	-5.7	-0.3	0.7	0.7	1.4

Table S3. Over-represented biological processes within the transcripts with the lowest G_{i0} value in trj 15781012 as identified by EASE software (5). Biological categories that are significantly over-represented (EASE score < 0.05) among the 500 transcripts with the lowest G_{i0}. Note that the biological processes are not autonomous and many of the categories overlap.(List hits, number of genes with particular GO term in the gene list; List total, number of genes in the gene list mapped to any GO term; Population hits, number of genes with particular GO term in the whole chip; Population total, number of genes in the whole chip mapped to any GO term; EASE score (a conservative variant of the one-tailed Fisher's exact probability), a level of confidence that particular GO term is over-represented in the gene list.

Gene Category	List Hits	List Total	Population Hits	Population Total	EASE score
protein biosynthesis	92	474	372	8049	5.15E-34
macromolecule biosynthesis	112	474	630	8049	6.80E-28
biosynthesis	116	474	753	8049	2.52E-23
protein metabolism	170	474	1670	8049	5.49E-15
translation	28	474	125	8049	2.35E-09
translational elongation	9	474	15	8049	5.98E-07
cytoplasm organization and biogenesis	37	474	291	8049	1.54E-05
main pathways of carbohydrate metabolism	15	474	68	8049	3.16E-05
ribosome biogenesis	11	474	37	8049	3.69E-05
ribosome biogenesis and assembly	11	474	38	8049	4.74E-05
energy pathways	26	474	184	8049	6.89E-05
glucose catabolism	11	474	41	8049	9.59E-05
metabolism	302	474	4489	8049	0.00021
ATP metabolism	8	474	23	8049	0.000249
actin cytoskeleton organization and biogenesis	12	474	56	8049	0.000343
alcohol catabolism	11	474	48	8049	0.000386
monosaccharide catabolism	11	474	48	8049	0.000386
hexose catabolism	11	474	48	8049	0.000386
actin filament-based process	12	474	57	8049	0.000403
cell organization and biogenesis	46	474	460	8049	0.000447
purine nucleoside triphosphate metabolism	9	474	34	8049	0.000626
ribonucleoside triphosphate metabolism	9	474	34	8049	0.000626
purine ribonucleoside triphosphate metabolism	9	474	34	8049	0.000626
energy derivation by oxidation of organic	17	474	111	8049	0.000717

compounds					
physiological process	420	474	6713	8049	0.000732
nucleoside phosphate metabolism	7	474	20	8049	0.000762
ATP biosynthesis	7	474	20	8049	0.000762
glycolysis	9	474	35	8049	0.00077
nucleoside triphosphate metabolism	9	474	36	8049	0.00094
glucose metabolism	12	474	64	8049	0.001119
group transfer coenzyme metabolism	8	474	29	8049	0.001164
purine ribonucleotide metabolism	10	474	46	8049	0.001213
purine nucleoside triphosphate biosynthesis	8	474	31	8049	0.001771
purine ribonucleoside triphosphate biosynthesis	8	474	31	8049	0.001771
ribonucleoside triphosphate biosynthesis	8	474	31	8049	0.001771
proton transport	10	474	49	8049	0.001933
ubiquitin-dependent protein catabolism	13	474	79	8049	0.002057
modification-dependent protein catabolism	13	474	79	8049	0.002057
nucleoside triphosphate biosynthesis	8	474	32	8049	0.002154
amino acid activation	9	474	42	8049	0.00269
tRNA aminoacylation for protein translation	9	474	42	8049	0.00269
tRNA aminoacylation	9	474	42	8049	0.00269
RNA modification	10	474	52	8049	0.002961
purine nucleotide metabolism	10	474	52	8049	0.002961
regulation of translation	10	474	53	8049	0.003386
ribonucleotide metabolism	10	474	53	8049	0.003386
hydrogen transport	10	474	53	8049	0.003386
coenzyme metabolism	11	474	63	8049	0.003424
carbohydrate catabolism	11	474	63	8049	0.003424
purine ribonucleotide biosynthesis	9	474	44	8049	0.003644
tRNA modification	9	474	45	8049	0.00421
obsolete biological process	34	474	349	8049	0.004374
organelle organization and biogenesis	26	474	246	8049	0.00506
purine nucleotide biosynthesis	9	474	48	8049	0.006318
ribonucleotide biosynthesis	9	474	49	8049	0.007174
protein transport	30	474	307	8049	0.007425

cytoskeleton organization and biogenesis	21	474	191	8049	0.008387
intracellular protein transport	28	474	291	8049	0.012018
antigen presentation\, endogenous antigen	4	474	9	8049	0.012978
oxidative phosphorylation	6	474	25	8049	0.013698
RNA metabolism	26	474	269	8049	0.015022
hexose metabolism	12	474	90	8049	0.015918
coenzyme biosynthesis	7	474	36	8049	0.017256
antigen processing\, endogenous antigen via MHC class I	4	474	10	8049	0.017742
nucleotide biosynthesis	11	474	80	8049	0.018181
monosaccharide metabolism	12	474	92	8049	0.018526
tRNA metabolism	9	474	58	8049	0.019266
muscle development	14	474	120	8049	0.023503
protein targeting	14	474	121	8049	0.02498
transition metal ion homeostasis	5	474	20	8049	0.026909
NADPH regeneration	3	474	5	8049	0.030604
pentose-phosphate shunt	3	474	5	8049	0.030604
intracellular transport	32	474	375	8049	0.033078
RNA processing	23	474	248	8049	0.034371
cell growth	11	474	90	8049	0.037695
nucleotide metabolism	12	474	105	8049	0.043694
NADPH metabolism	3	474	6	8049	0.044142
peroxidase reaction	3	474	6	8049	0.044142
coenzyme and prosthetic group metabolism	11	474	93	8049	0.045637
translational initiation	7	474	45	8049	0.046452

Table S4. In this experiment 3 stages of renal cancer metastasis were examined: normal, cancer, metastasis. Therefore 3 transcription patterns were identified (α =0,1,2). G_0 defines the steady state network, G_1, G_2 the patterns participating in the process of carcinogenesis. The scalar products $\sum_i G_{\alpha i} G_{\alpha i}$, α =0,1,2, between all the gene transcription patterns of the different patients were calculated.

patient1,2		p2		
	$G_{\alpha p1} * G_{\alpha p2}$	G_0	G_1	G_2
p1	G_0	**0.98**	0.023	0.00078
	G_1	0.02069	**0.43**	0.0114
	G_2	0.00677	-0.0377	0.026
patient1,3	$G_{\alpha p1} * G_{\alpha p3}$	p3		
		G_0	G_1	G_2
p1	G_0	**0.9775**	-0.03119	-0.01019
	G_1	0.030488	**0.33271**	-0.09
	G_2	0.000696	-0.01416	0.036051
patient 2,3	$G_{\alpha p2} * G_{\alpha p3}$	p3		
		G_0	G_1	G_2
p2	G_0	**0.98319**	-0.0051	0.024139
	G_1	0.035324	**0.38843**	-0.10307
	G_2	0.000386	-0.10678	0.034421

Table S4.A. In this experiment 3 stages of renal cancer metastasis were examined: normal, cancer, metastasis. G_1 is the major pattern participating in the process of carcinogenesis. Examples of G_{i1} values of the key signaling proteins, that belong to ~10% group of the most contributing, positively or negatively, proteins (have G_{i1} values less than -0.007 or more than 0.007) at least in one patient, are reported.

	G_1^{p1}	G_1^{p2}	G_1^{p3}
IGF1R	-0.002645	0.009486	0.00347
MAP2K7	0.002062	0.000639	0.011014
VEGFA	-0.009015	-0.007553	-0.004801
EGFR	-0.00406	-0.011398	-0.004444
PTEN	0.001558	0.007931	-0.000898
MAPK4	0.008391	0.003592	-0.001819
MAPK7	0.008151	-0.004993	0.00112
MAP2K7	0.002062	0.000639	0.011014
p38	0.000311	-0.003271	-0.007145
SRC	-0.009448	-0.000169	-0.000118
PDGFRA	0.010455	-0.000369	0.009453
NFKBIL2	0.001801	-0.0028	0.011662

Table S5. Three stages of colon cancer metastasis were examined: normal, cancer, metastasis. 3 transcription patterns were identified

		p2		
p1	$G_{\alpha p1} * G_{\alpha p2}$	G_0	G_1	G_2
	G_0	**0.995157**	-0.01612	-0.02213
	G_1	0.024807	**-0.25364**	0.168879
	G_2	-0.0317	-0.26787	**-0.26091**

Table S5.A. Three stages of colon cancer metastasis were examined: normal, cancer, metastasis. Examples of G_{i1} values of the key signaling proteins, that belong to ~10% group of the most contributing, positively or negatively, proteins (have G_{i1} values less than -0.007 or more than 0.007) at least in one patient, are reported.

	G_1^{p1}	G_1^{p2}
EGFR	-0.010989	-0.000497
EGFR	-0.008582	0.000998
MYC	-0.012846	0.008705
SMAD4	-0.015359	-0.002272
FOSB	0.002696	-0.017099
VEGFA	-0.012441	0.019198
MAPK3	0.008063	-0.005984
PDGFRA	-0.003558	-0.013948
PTEN	-0.000152	-0.00764
CASP6	0.009655	0.000439
IGF2R	-0.007799	0.003066
p38	-0.003906	0.006829

Table S6. Three stages of disease of prostate cancer metastasis were examined: basal, luminal, cancer. 3 transcription patterns were identified (α =0,1,2). The scalar product $\sum_i G_{i\alpha}G_{i\alpha}$, α =0,1,2, between all the gene transcription patterns of the different patients were calculated.

$G_{\alpha pi}*G_{\alpha pj}$	$G_{0\ p1}$	$G_{1\ p1}$	$G_{2\ p1}$	$G_{0\ p2}$	$G_{1\ p2}$	$G_{2\ p2}$	$G_{0\ p3}$	$G_{1\ p3}$	$G_{2\ p3}$	$G_{0\ p4}$	$G_{1\ p4}$	$G_{2\ p4}$
$G_{0\ p1}$	1.0	1.3E-07	1.0E-08	1.0E+00	-1.3E-02	2.0E-02	1.0E+00	2.6E-03	2.5E-02	1.0E+00	-6.0E-02	-4.1E-03
$G_{1\ p1}$	1.3E-07	1.0	6.9E-08	1.8E-02	3.7E-01	2.3E-02	1.1E-02	3.6E-01	-7.2E-02	-2.8E-02	1.5E-01	-5.0E-01
$G_{2\ p1}$	1.0E-08	6.9E-08	1.0	6.4E-04	1.7E-01	4.4E-02	6.6E-03	2.1E-01	-2.4E-02	-1.2E-02	7.1E-02	8.6E-01
$G_{0\ p2}$	1.0E+00	1.8E-02	6.4E-04	1.0	-6.9E-08	1.0E-07	1.0E+00	5.3E-03	1.7E-02	1.0E+00	-3.8E-02	-1.2E-02
$G_{1\ p2}$	-1.3E-02	3.7E-01	1.7E-01	-6.9E-08	1.0	1.6E-07	5.0E-03	3.7E-01	-3.2E-01	-1.2E-02	2.7E-01	-3.9E-02
$G_{2\ p2}$	2.0E-02	2.3E-02	4.4E-02	1.0E-07	1.6E-07	1.0	1.6E-02	4.6E-02	3.1E-02	6.9E-03	-1.8E-01	2.3E-02
$G_{0\ p3}$	1.0E+00	1.1E-02	6.6E-03	1.0E+00	5.0E-03	1.6E-02	1.0	-1.1E-07	9.0E-10	1.0E+00	-3.1E-02	-3.5E-03
$G_{1\ p3}$	2.6E-03	3.6E-01	2.1E-01	5.3E-03	3.7E-01	4.6E-02	-1.1E-07	1.0	8.7E-08	-1.6E-02	-1.8E-02	2.9E-03
$G_{2\ p3}$	2.5E-02	-7.2E-02	-2.4E-02	1.7E-02	-3.2E-01	3.1E-02	9.0E-10	8.7E-08	1.0	1.7E-02	-1.7E-01	1.3E-02
$G_{0\ p4}$	1.0E+00	-2.8E-02	-1.2E-02	1.0E+00	-1.2E-02	6.9E-03	1.0E+00	-1.6E-02	1.7E-02	1.0	-1.1E-08	-6.8E-08
$G_{1\ p4}$	-6.0E-02	1.5E-01	7.1E-02	-3.8E-02	2.7E-01	-1.8E-01	-3.1E-02	-1.8E-02	-1.7E-01	-1.1E-08	1.0	2.2E-07
$G_{2\ p4}$	-4.1E-03	-5.0E-01	8.6E-01	-1.2E-02	-3.9E-02	2.3E-02	-3.5E-03	2.9E-03	1.3E-02	-6.8E-08	2.2E-07	1.0

Table S7. Over-represented biological processes within the transcripts with the lowest G_{i0} in the HF1 cells as identified by EASE software (5). Biological categories that are significantly over-represented (EASE score < 0.05) among the 388 probes with the lowest G_{i0} values.

Gene Category	List Hits	List Total	Population	Population	EASE scor
protein biosynthesis	90	227	539	10937	3.10E-58
macromolecule biosynthesis	94	227	847	10937	4.43E-45
biosynthesis	95	227	1014	10937	2.93E-39
protein metabolism	108	227	2217	10937	2.62E-20
ribosome biogenesis	14	227	59	10937	1.55E-10
ribosome biogenesis and assembly	14	227	61	10937	2.42E-10
translation	20	227	195	10937	1.98E-08
translational elongation	8	227	22	10937	1.92E-07
metabolism	161	227	6063	10937	1.22E-06
cytoplasm organization and biogenesis	26	227	424	10937	2.20E-06
regulation of translational initiation	8	227	33	10937	3.96E-06
cell organization and biogenesis	32	227	635	10937	6.65E-06
translational initiation	9	227	56	10937	1.78E-05
physiological process	208	227	8954	10937	2.42E-05
regulation of translation	9	227	66	10937	6.01E-05
energy pathways	14	227	205	10937	0.00033
transition metal ion homeostasis	5	227	22	10937	0.000969
ectoderm development	8	227	80	10937	0.001295
glycolysis	6	227	44	10937	0.00203
glucose catabolism	6	227	53	10937	0.004618
energy derivation by oxidation of organi	9	227	130	10937	0.005512
alcohol catabolism	6	227	60	10937	0.007825
monosaccharide catabolism	6	227	60	10937	0.007825
hexose catabolism	6	227	60	10937	0.007825
proton transport	6	227	61	10937	0.008384
copper ion homeostasis	3	227	8	10937	0.010965
histogenesis	8	227	120	10937	0.012157
cell growth and/or maintenance	88	227	3436	10937	0.013402
epidermal differentiation	6	227	69	10937	0.013879
ATP biosynthesis	4	227	25	10937	0.01432
nucleoside phosphate metabolism	4	227	25	10937	0.01432
hydrogen transport	6	227	70	10937	0.014702
di-\, tri-valent inorganic cation homeost	5	227	51	10937	0.020798
carbohydrate catabolism	6	227	77	10937	0.021393
ATP metabolism	4	227	29	10937	0.021422
glucose metabolism	6	227	78	10937	0.022487
main pathways of carbohydrate metab	6	227	83	10937	0.028496
protein folding	7	227	113	10937	0.029596
metal ion homeostasis	5	227	57	10937	0.029897
cytoskeleton organization and biogenes	12	227	284	10937	0.033825
purine ribonucleoside triphosphate bios	4	227	36	10937	0.037698
ribonucleoside triphosphate biosynthes	4	227	36	10937	0.037698
nucleobase\, nucleoside\, nucleotide ar	4	227	36	10937	0.037698
purine nucleoside triphosphate biosynth	4	227	36	10937	0.037698
group transfer coenzyme metabolism	4	227	37	10937	0.040418
nucleoside triphosphate biosynthesis	4	227	37	10937	0.040418
binding to mRNA cap	2	227	2	10937	0.040902
purine ribonucleoside triphosphate met	4	227	40	10937	0.049154
ribonucleoside triphosphate metabolism	4	227	40	10937	0.049154
purine nucleoside triphosphate metabo	4	227	40	10937	0.049154

Table S8. Over-represented biological processes within the transcripts with the mid G_{i0} in the HF1 cells as identified by EASE software. Biological categories that are significantly over-represented (first 65 categories) among the 9900 probes with the mid G_{i0} values.

Gene Category	List Hits	List Total	Population	Population	EASE scor
metabolism	3534	5765	6063	10937	5.81E-39
nucleobase\, nucleoside\, nucleotide	1642	5765	2673	10937	1.65E-25
cell cycle	479	5765	690	10937	4.47E-20
DNA metabolism	354	5765	517	10937	1.25E-13
intracellular transport	349	5765	512	10937	4.93E-13
mitotic cell cycle	235	5765	329	10937	3.41E-12
transcription	1088	5765	1818	10937	1.71E-11
response to DNA damage stimulus	159	5765	211	10937	1.93E-11
cell proliferation	646	5765	1036	10937	4.58E-11
protein modification	597	5765	951	10937	5.59E-11
response to endogenous stimulus	159	5765	213	10937	6.82E-11
regulation of cell cycle	264	5765	384	10937	1.13E-10
transcription\, DNA-dependent	1048	5765	1756	10937	1.18E-10
protein metabolism	1302	5765	2217	10937	1.40E-10
RNA metabolism	264	5765	390	10937	1.30E-09
intracellular protein transport	255	5765	375	10937	1.31E-09
regulation of transcription	1011	5765	1704	10937	1.77E-09
RNA processing	247	5765	363	10937	2.22E-09
protein transport	268	5765	400	10937	4.57E-09
regulation of transcription\, DNA-depe	991	5765	1677	10937	8.78E-09
DNA replication and chromosome cy	136	5765	186	10937	1.76E-08
DNA repair	132	5765	180	10937	2.18E-08
chromatin modification	55	5765	64	10937	9.34E-08
Golgi vesicle transport	51	5765	59	10937	2.13E-07
physiological process	4821	5765	8954	10937	2.92E-07
S phase of mitotic cell cycle	108	5765	147	10937	4.17E-07
nucleocytoplasmic transport	76	5765	97	10937	4.36E-07
DNA replication	107	5765	146	10937	5.82E-07
nuclear division	106	5765	151	10937	1.66E-05
M phase	109	5765	157	10937	2.67E-05
negative regulation of cell cycle	56	5765	72	10937	2.84E-05
non-covalent chromatin modification	29	5765	32	10937	3.35E-05
chromatin remodeling	29	5765	32	10937	3.35E-05
negative regulation of transcription	74	5765	101	10937	4.22E-05
vesicle-mediated transport	195	5765	304	10937	4.67E-05
mitosis	86	5765	121	10937	5.78E-05
M phase of mitotic cell cycle	87	5765	123	10937	6.89E-05
protein-nucleus import	48	5765	61	10937	7.43E-05
regulation of gene expression\, epiger	48	5765	61	10937	7.43E-05
nuclear organization and biogenesis	127	5765	190	10937	8.62E-05
chromosome organization and bioger	124	5765	185	10937	8.77E-05
protein amino acid phosphorylation	293	5765	478	10937	9.72E-05
transcription from Pol II promoter	279	5765	454	10937	0.000113
regulation of transcription from Pol II p	154	5765	238	10937	0.000171
rRNA processing	29	5765	34	10937	0.000308
phosphorus metabolism	392	5765	662	10937	0.0004
phosphate metabolism	392	5765	662	10937	0.0004
cell organization and biogenesis	376	5765	635	10937	0.000532
coenzyme and prosthetic group biosy	64	5765	90	10937	0.000595
protein targeting	100	5765	150	10937	0.000613
ubiquitin-dependent protein catabolisr	71	5765	102	10937	0.000745
rRNA metabolism	31	5765	38	10937	0.000747
tRNA metabolism	77	5765	112	10937	0.000761
cell cycle checkpoint	29	5765	35	10937	0.000764
transcription initiation	34	5765	43	10937	0.00101
DNA dependent DNA replication	54	5765	75	10937	0.001119
modification-dependent protein catab	71	5765	103	10937	0.001134
RNA splicing	74	5765	108	10937	0.001137
phospholipid biosynthesis	28	5765	34	10937	0.001175
ER to Golgi transport	24	5765	28	10937	0.001176
coenzyme and prosthetic group meta	86	5765	129	10937	0.001556
establishment and/or maintenance of	103	5765	158	10937	0.001595
intracellular receptor-mediated signal	19	5765	21	10937	0.001643
cell growth and/or maintenance	1883	5765	3436	10937	0.001767

Table S9. Over-represented biological processes within the transcripts with the highest G_{i0} in the HF1 cells as identified by EASE software . Biological categories that are significantly over-represented (EASE score < 0.01) among the 410 probes with the highest G_{i0} values.

Gene Category	List Hits	List Total	Population	Population	EASE sco
cell-cell signaling	43	327	525	10937	4.14E-09
response to external stimulus	69	327	1263	10937	6.84E-07
cell communication	120	327	2791	10937	5.52E-06
neurogenesis	29	327	404	10937	2.84E-05
G-protein coupled receptor protein signalin	36	327	566	10937	3.21E-05
defense response	43	327	756	10937	6.32E-05
transmission of nerve impulse	20	327	240	10937	0.000102
immune response	39	327	682	10937	0.000137
development	76	327	1683	10937	0.000155
perception of external stimulus	23	327	315	10937	0.000186
response to biotic stimulus	44	327	821	10937	0.000195
synaptic transmission	19	327	232	10937	0.000199
organogenesis	46	327	901	10937	0.000394
morphogenesis	50	327	1010	10937	0.000417
cell surface receptor linked signal transduc	48	327	991	10937	0.000903
sensory perception	20	327	291	10937	0.001142
metal ion transport	19	327	283	10937	0.002045
homophilic cell adhesion	9	327	81	10937	0.002776
perception of abiotic stimulus	18	327	282	10937	0.004654
cyclic-nucleotide-mediated signaling	10	327	109	10937	0.005202
behavior	9	327	93	10937	0.00647
response to pest/pathogen/parasite	24	327	444	10937	0.007087
signal transduction	84	327	2196	10937	0.009705

Table S10. Over-represented biological processes within the transcripts with the lowest G_{i0} in the dendritic cells as identified by EASE software . Biological categories that were significantly over-represented (first 65 categories EASE score < 0.05) among the 1200 probes with the lowest G_{i0}.

Gene Category	List Hits	List Total	Population	Population	EASE scor
protein biosynthesis	131	1009	385	8120	2.79E-29
macromolecule biosynthesis	174	1009	630	8120	1.13E-26
biosynthesis	187	1009	756	8120	1.75E-22
protein metabolism	298	1009	1712	8120	1.08E-11
translation	47	1009	141	8120	2.08E-10
antigen processing	16	1009	22	8120	1.70E-09
nucleoside triphosphate metabolism	20	1009	37	8120	1.01E-08
proton transport	24	1009	53	8120	1.76E-08
antigen presentation	15	1009	22	8120	2.31E-08
ribonucleoside triphosphate metabolism	19	1009	35	8120	2.41E-08
purine ribonucleoside triphosphate metabolis	19	1009	35	8120	2.41E-08
purine nucleoside triphosphate metabolism	19	1009	35	8120	2.41E-08
purine nucleoside triphosphate biosynthesis	18	1009	32	8120	3.16E-08
purine ribonucleoside triphosphate biosynthe	18	1009	32	8120	3.16E-08
ribonucleoside triphosphate biosynthesis	18	1009	32	8120	3.16E-08
ATP metabolism	16	1009	26	8120	4.73E-08
nucleoside phosphate metabolism	15	1009	23	8120	5.23E-08
ATP biosynthesis	15	1009	23	8120	5.23E-08
nucleoside triphosphate biosynthesis	18	1009	33	8120	5.77E-08
physiological process	898	1009	6770	8120	5.97E-08
group transfer coenzyme metabolism	17	1009	30	8120	7.54E-08
response to biotic stimulus	135	1009	708	8120	1.28E-07
purine ribonucleotide metabolism	21	1009	47	8120	2.25E-07
hydrogen transport	24	1009	60	8120	2.79E-07
purine ribonucleotide biosynthesis	20	1009	44	8120	3.42E-07
purine nucleotide metabolism	22	1009	53	8120	4.80E-07
metabolism	642	1009	4602	8120	1.11E-06
ribonucleotide metabolism	21	1009	52	8120	1.57E-06
ribonucleotide biosynthesis	20	1009	48	8120	1.72E-06
purine nucleotide biosynthesis	20	1009	48	8120	1.72E-06
energy pathways	47	1009	184	8120	1.73E-06
response to pest/pathogen/parasite	80	1009	383	8120	2.23E-06
immune response	113	1009	596	8120	2.24E-06
translational initiation	19	1009	45	8120	2.69E-06
regulation of translation	21	1009	54	8120	3.14E-06
coenzyme biosynthesis	18	1009	42	8120	4.20E-06
oxidative phosphorylation	13	1009	23	8120	4.57E-06
regulation of translational initiation	14	1009	27	8120	5.76E-06
antigen presentation\, exogenous antigen	9	1009	11	8120	6.41E-06
antigen processing\, exogenous antigen via	9	1009	11	8120	6.41E-06
defense response	120	1009	656	8120	6.43E-06
RNA metabolism	63	1009	289	8120	7.78E-06
RNA processing	59	1009	267	8120	1.03E-05
coenzyme metabolism	23	1009	68	8120	1.31E-05
translational elongation	10	1009	15	8120	1.68E-05
energy derivation by oxidation of organic com	32	1009	119	8120	3.56E-05
main pathways of carbohydrate metabolism	23	1009	73	8120	4.55E-05
nucleotide metabolism	29	1009	107	8120	7.70E-05
ribosome biogenesis	16	1009	44	8120	0.00016
ribosome biogenesis and assembly	16	1009	45	8120	0.000213
aerobic respiration	7	1009	9	8120	0.000217
cellular respiration	7	1009	9	8120	0.000217
RNA splicing	26	1009	99	8120	0.000334
intracellular transport	72	1009	388	8120	0.000397
protein transport	60	1009	309	8120	0.000401
nucleotide biosynthesis	23	1009	84	8120	0.000434
intracellular protein transport	57	1009	291	8120	0.000457
response to external stimulus	163	1009	1030	8120	0.000462
ATP synthesis coupled electron transport (s	9	1009	17	8120	0.000474
ATP synthesis coupled electron transport	9	1009	17	8120	0.000474
carbohydrate catabolism	19	1009	64	8120	0.000562
protein-disulfide reduction	9	1009	18	8120	0.000761
response to stress	111	1009	667	8120	0.000778
mRNA metabolism	31	1009	134	8120	0.000826

Table S11. Over-represented biological processes within the transcripts with the lowest G_{i0} in the hematopoetic cells as identified by EASE software. Biological categories that are significantly over-represented (first 65 categories EASE score < 0.05) among the 1180 probes with the lowest G_{i0}.

Gene Category	List Hits	List Total	Population	Population	EASE scor
protein biosynthesis	142	971	385	8120	3.29E-38
macromolecule biosynthesis	190	971	630	8120	2.39E-37
biosynthesis	207	971	756	8120	4.37E-34
metabolism	684	971	4602	8120	5.60E-21
translation	56	971	141	8120	1.03E-16
protein metabolism	301	971	1712	8120	9.52E-15
RNA processing	77	971	267	8120	9.34E-14
RNA metabolism	80	971	289	8120	3.19E-13
physiological process	874	971	6770	8120	3.12E-10
translational initiation	23	971	45	8120	1.09E-09
purine nucleotide metabolism	25	971	53	8120	1.38E-09
purine nucleotide biosynthesis	23	971	48	8120	5.08E-09
regulation of translational initiation	17	971	27	8120	5.53E-09
regulation of translation	24	971	54	8120	1.30E-08
oxidative phosphorylation	15	971	23	8120	3.18E-08
nucleoside triphosphate metabolism	19	971	37	8120	4.03E-08
group transfer coenzyme metabolism	17	971	30	8120	4.35E-08
purine nucleoside triphosphate metabolism	18	971	35	8120	9.94E-08
purine ribonucleoside triphosphate metabolism	18	971	35	8120	9.94E-08
ribonucleoside triphosphate metabolism	18	971	35	8120	9.94E-08
purine ribonucleotide metabolism	21	971	47	8120	1.18E-07
purine nucleoside triphosphate biosynthesis	17	971	32	8120	1.42E-07
ribonucleoside triphosphate biosynthesis	17	971	32	8120	1.42E-07
purine ribonucleoside triphosphate biosynthesis	17	971	32	8120	1.42E-07
mRNA metabolism	39	971	134	8120	1.84E-07
purine ribonucleotide biosynthesis	20	971	44	8120	1.85E-07
RNA splicing	32	971	99	8120	2.24E-07
nucleoside triphosphate biosynthesis	17	971	33	8120	2.46E-07
ATP metabolism	15	971	26	8120	2.65E-07
nucleoside phosphate metabolism	14	971	23	8120	3.38E-07
ATP biosynthesis	14	971	23	8120	3.38E-07
energy pathways	47	971	184	8120	5.77E-07
ribonucleotide metabolism	21	971	52	8120	8.48E-07
ribonucleotide biosynthesis	20	971	48	8120	9.49E-07
translational elongation	11	971	15	8120	9.66E-07
proton transport	21	971	53	8120	1.21E-06
modification-dependent protein catabolism	27	971	81	8120	1.24E-06
ubiquitin-dependent protein catabolism	27	971	81	8120	1.24E-06
mRNA processing	34	971	120	8120	2.49E-06
nucleotide biosynthesis	27	971	84	8120	2.69E-06
nucleotide metabolism	31	971	107	8120	4.62E-06
ATP synthesis coupled electron transport	11	971	17	8120	4.99E-06
ATP synthesis coupled electron transport (sensu	11	971	17	8120	4.99E-06
ribosome biogenesis	18	971	44	8120	5.26E-06
RNA splicing\, via transesterification reactions wi	25	971	78	8120	7.26E-06
nuclear mRNA splicing\, via spliceosome	25	971	78	8120	7.26E-06
RNA splicing\, via transesterification reactions	25	971	78	8120	7.26E-06
ribosome biogenesis and assembly	18	971	45	8120	7.52E-06
protein-disulfide reduction	11	971	18	8120	1.00E-05
hydrogen transport	21	971	60	8120	1.10E-05
intracellular transport	75	971	388	8120	2.14E-05
main pathways of carbohydrate metabolism	23	971	73	8120	2.50E-05
coenzyme and prosthetic group biosynthesis	22	971	68	8120	2.52E-05
coenzyme and prosthetic group metabolism	27	971	96	8120	3.82E-05
energy derivation by oxidation of organic compou	31	971	119	8120	4.45E-05
RNA modification	20	971	61	8120	5.33E-05
coenzyme biosynthesis	16	971	42	8120	5.58E-05
tRNA modification	19	971	57	8120	6.82E-05
coenzyme metabolism	21	971	68	8120	8.47E-05
protein folding	25	971	90	8120	9.82E-05
mitochondrial electron transport\, NADH to ubiqu	9	971	15	8120	0.00012
amino acid activation	18	971	55	8120	0.000145
tRNA aminoacylation	18	971	55	8120	0.000145
tRNA aminoacylation for protein translation	18	971	55	8120	0.000145

Table S12. Over-represented biological processes within the transcripts with the mid G_{i0} in the hematopoetic cells as identified by EASE software . The similar results were obtained in the dendritic cells. Biological categories that were significantly over-represented (first 65 categories EASE score < 0.05) among the 5150 probes with mid G_{i0}.

Gene Category	List Hits	List Total	Population	Population	EASE scor
mitotic cell cycle	214	3844	280	8120	1.69E-23
cell cycle	395	3844	602	8120	1.11E-20
DNA replication and chromosome cycl	130	3844	158	8120	2.61E-19
metabolism	2375	3844	4602	8120	8.18E-19
DNA metabolism	274	3844	408	8120	2.25E-16
DNA replication	104	3844	125	8120	3.33E-16
nucleobase\, nucleoside\, nucleotide ar	1121	3844	2033	8120	3.53E-16
S phase of mitotic cell cycle	105	3844	127	8120	5.59E-16
protein modification	442	3844	758	8120	2.10E-10
DNA repair	112	3844	156	8120	9.95E-10
cell proliferation	516	3844	909	8120	1.42E-09
response to endogenous stimulus	126	3844	181	8120	1.90E-09
response to DNA damage stimulus	126	3844	181	8120	1.90E-09
DNA dependent DNA replication	57	3844	69	8120	6.50E-09
M phase of mitotic cell cycle	78	3844	104	8120	2.26E-08
mitosis	76	3844	102	8120	5.66E-08
protein amino acid phosphorylation	242	3844	405	8120	3.06E-07
physiological process	3288	3844	6770	8120	4.03E-07
M phase	91	3844	131	8120	5.13E-07
nuclear division	87	3844	125	8120	8.34E-07
regulation of cell cycle	212	3844	353	8120	1.08E-06
RNA metabolism	177	3844	289	8120	1.65E-06
phosphorus metabolism	320	3844	561	8120	1.72E-06
phosphate metabolism	320	3844	561	8120	1.72E-06
phosphorylation	258	3844	443	8120	2.28E-06
mRNA metabolism	90	3844	134	8120	5.48E-06
mRNA processing	82	3844	120	8120	5.60E-06
RNA processing	163	3844	267	8120	5.83E-06
intracellular transport	226	3844	388	8120	1.03E-05
transcription	724	3844	1379	8120	1.80E-05
protein metabolism	883	3844	1712	8120	5.22E-05
transcription\, DNA-dependent	698	3844	1336	8120	5.99E-05
RNA splicing	67	3844	99	8120	7.38E-05
regulation of transcription	681	3844	1304	8120	8.10E-05
cell growth and/or maintenance	1360	3844	2706	8120	0.000122
regulation of transcription\, DNA-depen	666	3844	1280	8120	0.000173
nuclear mRNA splicing\, via spliceosom	54	3844	78	8120	0.000177
RNA splicing\, via transesterification re	54	3844	78	8120	0.000177
RNA splicing\, via transesterification re	54	3844	78	8120	0.000177
protein transport	178	3844	309	8120	0.000221
intracellular protein transport	168	3844	291	8120	0.000291
cytokinesis	54	3844	79	8120	0.000292
mRNA-nucleus export	17	3844	18	8120	0.000295
ubiquitin cycle	43	3844	60	8120	0.000305
chromosome organization and biogene	92	3844	148	8120	0.000333
G2/M transition of mitotic cell cycle	29	3844	37	8120	0.000412
regulation of CDK activity	25	3844	31	8120	0.000607
G1/S transition of mitotic cell cycle	35	3844	48	8120	0.000809
chromatin modification	35	3844	48	8120	0.000809
nuclear organization and biogenesis	93	3844	153	8120	0.000897
nucleocytoplasmic transport	52	3844	78	8120	0.000946
transcription from Pol II promoter	221	3844	401	8120	0.001158
maintenance of fidelity during DNA dep	20	3844	24	8120	0.001448
mismatch repair	20	3844	24	8120	0.001448
establishment and/or maintenance of c	76	3844	123	8120	0.001504
transcription initiation	26	3844	34	8120	0.001717
regulation of transcription from Pol II pr	124	3844	215	8120	0.002045
RNA localization	19	3844	23	8120	0.002458
nucleic acid transport	19	3844	23	8120	0.002458
regulation of mitosis	19	3844	23	8120	0.002458
RNA transport	19	3844	23	8120	0.002458
RNA-nucleus export	19	3844	23	8120	0.002458
nucleotide-excision repair	17	3844	20	8120	0.002915
DNA packaging	80	3844	134	8120	0.004249

Table S13. Over-represented biological processes within the transcripts with the highest G_{oi} in the hematopoetic cells as identified by EASE software. Similar results were obtained in the dendritic cells. Biological categories that are significantly over-represented (EASE score < 0.05) among the 400 probes with the highest G_0 .

Gene Category	List Hits	List Total	Population	Population	EASE sco
organogenesis	60	314	775	8120	1.88E-07
morphogenesis	63	314	862	8120	6.52E-07
development	85	314	1352	8120	2.38E-06
cell surface receptor linked signal transduction	55	314	791	8120	1.85E-05
cell communication	122	314	2271	8120	1.95E-05
cell-cell signaling	32	314	450	8120	0.00113
cation transport	22	314	271	8120	0.001766
bile acid metabolism	4	314	7	8120	0.001769
cell adhesion	31	314	455	8120	0.002661
lymphocyte differentiation	6	314	26	8120	0.00278
lymphocyte activation	8	314	50	8120	0.002838
ion transport	27	314	381	8120	0.003206
T-cell activation	6	314	27	8120	0.003306
cellular process	198	314	4502	8120	0.003688
G-protein coupled receptor protein signaling pathway	29	314	425	8120	0.003711
signal transduction	89	314	1781	8120	0.005177
positive regulation of cell proliferation	11	314	102	8120	0.005781
cell activation	8	314	57	8120	0.005972
immune cell activation	8	314	57	8120	0.005972
metal ion transport	17	314	208	8120	0.006475
potassium ion transport	10	314	88	8120	0.006592
T-cell differentiation	4	314	11	8120	0.007433
circulation	10	314	95	8120	0.010734
transmembrane receptor protein tyrosine kinase signaling	10	314	96	8120	0.011457
monovalent inorganic cation transport	15	314	184	8120	0.011529
posttranslational membrane targeting	4	314	13	8120	0.012167
enzyme linked receptor protein signaling pathway	13	314	155	8120	0.016433
natural killer cell activation	3	314	7	8120	0.027355
heart development	4	314	18	8120	0.030124
hemopoiesis	6	314	48	8120	0.036453
cellular defense response	8	314	83	8120	0.04042
muscle development	10	314	120	8120	0.041785
cell-cell adhesion	11	314	140	8120	0.04372
neuropeptide signaling pathway	7	314	68	8120	0.046388
steroid metabolism	9	314	104	8120	0.047041

Table S14. Over-represented biological processes within the transcripts with the lowest G_0 in yeast as identified by DAVID software (6) Biological categories that are significantly over-represented (first 65 categories) among the 714 transcripts with the lowest (less than -0.016, Fig. S10) G_{i0}. Note that the biological processes are not autonomous and many of the categories overlap.(**Count**, number of genes with particular GO term in the gene list; **List total**, number of genes in the gene list mapped to any GO term; **Population hits**, number of genes with particular GO term in the whole chip; **Population total**, number of genes in the whole chip mapped to any GO term.

Term	Count	%	PValue	List Total	Pop Hits	Pop Total	Benjamini
GO:0006412~translation	222	31.66904	1.61E-45	657	677	4870	2.39E-42
GO:0055114~oxidation reduction	148	21.1127	3.85E-43	657	353	4870	2.86E-40
GO:0006417~regulation of translation	89	12.69615	8.11E-32	657	180	4870	4.01E-29
GO:0032268~regulation of cellular protein metabo	94	13.40942	3.18E-31	657	201	4870	1.18E-28
GO:0044271~nitrogen compound biosynthetic pro	122	17.40371	9.41E-31	657	317	4870	2.79E-28
GO:0010608~posttranscriptional regulation of gen	90	12.8388	5.93E-30	657	192	4870	1.46E-27
GO:0006091~generation of precursor metabolites	107	15.26391	4.76E-29	657	264	4870	1.01E-26
GO:0016053~organic acid biosynthetic process	77	10.98431	5.60E-24	657	172	4870	1.04E-21
GO:0046394~carboxylic acid biosynthetic proces	77	10.98431	5.60E-24	657	172	4870	1.04E-21
GO:0006119~oxidative phosphorylation	42	5.991441	3.69E-23	657	59	4870	6.09E-21
GO:0008652~cellular amino acid biosynthetic pro	62	8.844508	3.37E-20	657	134	4870	5.00E-18
GO:0009309~amine biosynthetic process	62	8.844508	1.20E-18	657	142	4870	1.62E-16
GO:0006811~ion transport	78	11.12696	1.62E-18	657	209	4870	2.00E-16
GO:0019320~hexose catabolic process	34	4.850214	1.32E-15	657	56	4870	1.52E-13
GO:0046365~monosaccharide catabolic process	35	4.992867	2.61E-15	657	60	4870	2.70E-13
GO:0006818~hydrogen transport	27	3.851641	8.15E-15	657	38	4870	8.01E-13
GO:0015992~proton transport	27	3.851641	8.15E-15	657	38	4870	8.01E-13
GO:0046164~alcohol catabolic process	36	5.135521	8.28E-15	657	65	4870	7.72E-13
GO:0044275~cellular carbohydrate catabolic proc	39	5.563481	1.39E-14	657	76	4870	1.21E-12
GO:0051186~cofactor metabolic process	70	9.985735	1.75E-14	657	203	4870	1.44E-12
GO:0008219~cell death	30	4.279601	1.33E-13	657	50	4870	1.04E-11
GO:0016265~death	30	4.279601	1.33E-13	657	50	4870	1.04E-11
GO:0016052~carbohydrate catabolic process	40	5.706134	1.38E-13	657	84	4870	1.02E-11
GO:0006007~glucose catabolic process	29	4.136947	1.18E-12	657	50	4870	8.34E-11
GO:0006163~purine nucleotide metabolic proces	37	5.278174	1.55E-12	657	78	4870	1.04E-10
GO:0015986~ATP synthesis coupled proton trans	22	3.138374	1.69E-12	657	30	4870	1.09E-10
GO:0015985~energy coupled proton transport, do	22	3.138374	1.69E-12	657	30	4870	1.09E-10
GO:0009150~purine ribonucleotide metabolic pro	35	4.992867	1.75E-12	657	71	4870	1.08E-10
GO:0019318~hexose metabolic process	48	6.847361	2.04E-12	657	122	4870	1.21E-10
GO:0006164~purine nucleotide biosynthetic proce	36	5.135521	2.13E-12	657	75	4870	1.21E-10
GO:0034220~ion transmembrane transport	27	3.851641	2.87E-12	657	45	4870	1.58E-10
GO:0009152~purine ribonucleotide biosynthetic p	34	4.850214	3.93E-12	657	69	4870	2.08E-10
GO:0005996~monosaccharide metabolic process	50	7.132668	1.24E-11	657	136	4870	6.36E-10
GO:0042775~mitochondrial ATP synthesis couple	20	2.853067	4.76E-11	657	28	4870	2.36E-09
GO:0042773~ATP synthesis coupled electron tra	20	2.853067	4.76E-11	657	28	4870	2.36E-09
GO:0015980~energy derivation by oxidation of org	58	8.273894	6.09E-11	657	178	4870	2.91E-09
GO:0022900~electron transport chain	32	4.564907	8.52E-11	657	68	4870	3.95E-09
GO:0034654~nucleobase, nucleoside, nucleotide	47	6.704708	1.50E-10	657	131	4870	6.73E-09
GO:0034404~nucleobase, nucleoside and nucleo	47	6.704708	1.50E-10	657	131	4870	6.73E-09
GO:0009259~ribonucleotide metabolic process	35	4.992867	1.67E-10	657	81	4870	7.28E-09
GO:0016129~phytosteroid biosynthetic process	18	2.56776	1.81E-10	657	24	4870	7.65E-09
GO:0006696~ergosterol biosynthetic process	18	2.56776	1.81E-10	657	24	4870	7.65E-09
GO:0006096~glycolysis	20	2.853067	2.89E-10	657	30	4870	1.19E-08
GO:0009206~purine ribonucleoside triphosphate b	26	3.708987	2.93E-10	657	49	4870	1.17E-08
GO:0009145~purine nucleoside triphosphate bios	26	3.708987	2.93E-10	657	49	4870	1.17E-08
GO:0009260~ribonucleotide biosynthetic process	34	4.850214	3.65E-10	657	79	4870	1.42E-08
GO:0006754~ATP biosynthetic process	25	3.566334	3.67E-10	657	46	4870	1.40E-08
GO:0009165~nucleotide biosynthetic process	44	6.276748	3.94E-10	657	121	4870	1.46E-08
GO:0006006~glucose metabolic process	39	5.563481	4.61E-10	657	100	4870	1.67E-08
GO:0009205~purine ribonucleoside triphosphate	26	3.708987	5.13E-10	657	50	4870	1.81E-08
GO:0009144~purine nucleoside triphosphate met	26	3.708987	5.13E-10	657	50	4870	1.81E-08
GO:0006084~acetyl-CoA metabolic process	21	2.99572	6.47E-10	657	34	4870	2.23E-08
GO:0046034~ATP metabolic process	25	3.566334	6.56E-10	657	47	4870	2.21E-08
GO:0015672~monovalent inorganic cation transp	27	3.851641	6.63E-10	657	54	4870	2.19E-08
GO:0009201~ribonucleoside triphosphate biosynt	26	3.708987	8.80E-10	657	51	4870	2.84E-08
GO:0045333~cellular respiration	43	6.134094	1.09E-09	657	120	4870	3.45E-08
GO:0008204~ergosterol metabolic process	18	2.56776	1.25E-09	657	26	4870	3.86E-08
GO:0016128~phytosteroid metabolic process	18	2.56776	1.25E-09	657	26	4870	3.86E-08
GO:0022904~respiratory electron transport chain	20	2.853067	1.41E-09	657	32	4870	4.26E-08
GO:0009199~ribonucleoside triphosphate metabo	26	3.708987	1.48E-09	657	52	4870	4.40E-08
GO:0009142~nucleoside triphosphate biosynthetic	26	3.708987	2.46E-09	657	53	4870	7.14E-08
GO:0006812~cation transport	46	6.562054	3.68E-09	657	138	4870	1.05E-07
GO:0006694~steroid biosynthetic process	20	2.853067	5.77E-09	657	34	4870	1.61E-07
GO:0016126~sterol biosynthetic process	20	2.853067	5.77E-09	657	34	4870	1.61E-07

Table S15. Over-represented biological processes within the transcripts with the mid G_{oi} in yeast as identified by DAVID software. Biological categories that were significantly over-represented (first 65 categories) among the 3000 probes with the mid G_{i0} (-0.012- (-0.015),Fig. S10).

Term	Count	PValue	List Total	Pop Hits	Pop Total	Benjamini
GO:0006350~transcription	382	1.00E-18	2483	5.59E+02	4870	2.42E-15
GO:0008104~protein localization	394	3.80E-15	2483	5.97E+02	4870	4.56E-12
GO:0045184~establishment of protein localizatio	361	4.02E-15	2483	5.40E+02	4870	3.22E-12
GO:0032774~RNA biosynthetic process	171	2.80E-13	2483	2.30E+02	4870	1.69E-10
GO:0015031~protein transport	333	3.14E-13	2483	5.02E+02	4870	1.52E-10
GO:0006351~transcription, DNA-dependent	169	6.19E-13	2483	2.28E+02	4870	2.50E-10
GO:0045449~regulation of transcription	420	8.17E-13	2483	6.57E+02	4870	2.82E-10
GO:0006366~transcription from RNA polymerase	132	9.98E-13	2483	1.70E+02	4870	3.02E-10
GO:0051301~cell division	233	3.90E-10	2483	3.47E+02	4870	1.05E-07
GO:0046907~intracellular transport	378	3.21E-09	2483	6.08E+02	4870	7.76E-07
GO:0016192~vesicle-mediated transport	246	5.27E-09	2483	3.76E+02	4870	1.16E-06
GO:0070727~cellular macromolecule localizatior	245	6.92E-09	2483	3.75E+02	4870	1.39E-06
GO:0051252~regulation of RNA metabolic proces	298	1.34E-08	2483	4.70E+02	4870	2.48E-06
GO:0006355~regulation of transcription, DNA-dep	292	2.24E-08	2483	4.61E+02	4870	3.87E-06
GO:0070271~protein complex biogenesis	165	2.72E-08	2483	2.41E+02	4870	4.39E-06
GO:0006461~protein complex assembly	165	2.72E-08	2483	2.41E+02	4870	4.39E-06
GO:0034613~cellular protein localization	235	3.45E-08	2483	3.62E+02	4870	5.20E-06
GO:0043933~macromolecular complex subunit c	323	5.20E-08	2483	5.19E+02	4870	7.40E-06
GO:0006886~intracellular protein transport	213	5.50E-08	2483	3.25E+02	4870	7.39E-06
GO:0051325~interphase	84	9.01E-08	2483	1.10E+02	4870	1.15E-05
GO:0034621~cellular macromolecular complex s	271	2.13E-07	2483	4.31E+02	4870	2.58E-05
GO:0051329~interphase of mitotic cell cycle	80	2.29E-07	2483	1.05E+02	4870	2.64E-05
GO:0016568~chromatin modification	130	2.67E-07	2483	1.87E+02	4870	2.94E-05
GO:0006354~RNA elongation	50	6.84E-07	2483	6.00E+01	4870	7.19E-05
GO:0006396~RNA processing	315	8.97E-07	2483	5.15E+02	4870	9.03E-05
GO:0006468~protein amino acid phosphorylation	99	9.44E-07	2483	1.38E+02	4870	9.13E-05
GO:0006338~chromatin remodeling	56	1.53E-06	2483	7.00E+01	4870	1.43E-04
GO:0006368~RNA elongation from RNA polymer	47	2.89E-06	2483	5.70E+01	4870	2.59E-04
GO:0006605~protein targeting	157	3.30E-06	2483	2.39E+02	4870	2.85E-04
GO:0043623~cellular protein complex assembly	89	3.57E-06	2483	1.24E+02	4870	2.98E-04
GO:0006357~regulation of transcription from RN	171	4.18E-06	2483	2.64E+02	4870	3.37E-04
GO:0000910~cytokinesis	82	4.66E-06	2483	1.13E+02	4870	3.63E-04
GO:0000278~mitotic cell cycle	196	5.99E-06	2483	309	4870	4.52E-04
GO:0000902~cell morphogenesis	105	7.09E-06	2483	152	4870	5.19E-04
GO:0042157~lipoprotein metabolic process	45	7.42E-06	2483	55	4870	5.27E-04
GO:0006367~transcription initiation from RNA po	39	7.57E-06	2483	46	4870	5.23E-04
GO:0006325~chromatin organization	145	9.18E-06	2483	221	4870	6.16E-04
GO:0042158~lipoprotein biosynthetic process	44	1.18E-05	2483	54	4870	7.71E-04
GO:0006497~protein amino acid lipidation	44	1.18E-05	2483	54	4870	7.71E-04
GO:0007010~cytoskeleton organization	143	3.13E-05	2483	221	4870	0.001991
GO:0016197~endosome transport	49	3.22E-05	2483	63	4870	0.001991
GO:0034470~ncRNA processing	207	3.83E-05	2483	335	4870	0.002312
GO:0048193~Golgi vesicle transport	121	4.87E-05	2483	184	4870	0.002865
GO:0006611~protein export from nucleus	31	5.25E-05	2483	36	4870	0.003014
GO:0065003~macromolecular complex assembl	242	6.19E-05	2483	400	4870	0.003476
GO:0002097~tRNA wobble base modification	24	6.23E-05	2483	26	4870	0.003418
GO:0002098~tRNA wobble uridine modification	24	6.23E-05	2483	26	4870	0.003418
GO:0031123~RNA 3'-end processing	55	8.35E-05	2483	74	4870	0.004474
GO:0006352~transcription initiation	50	8.58E-05	2483	66	4870	0.0045
GO:0008033~tRNA processing	75	8.70E-05	2483	107	4870	0.004462
GO:0051276~chromosome organization	234	8.83E-05	2483	387	4870	0.004438
GO:0007242~intracellular signaling cascade	113	9.57E-05	2483	172	4870	0.004707
GO:0006400~tRNA modification	51	1.11E-04	2483	68	4870	0.005339
GO:0032506~cytokinetic process	68	1.21E-04	2483	96	4870	0.005716
GO:0031124~mRNA 3'-end processing	33	1.38E-04	2483	40	4870	0.006374
GO:0016071~mRNA metabolic process	168	1.38E-04	2483	270	4870	0.006294
GO:0000086~G2/M transition of mitotic cell cycle	31	1.42E-04	2483	37	4870	0.006341
GO:0007049~cell cycle	362	2.23E-04	2483	627	4870	0.009761
GO:0007034~vacuolar transport	82	2.32E-04	2483	121	4870	0.009969
GO:0043044~ATP-dependent chromatin remode	28	2.34E-04	2483	33	4870	0.009869

Table S16. Over-represented biological processes within the transcripts with the highest G_{i0} in yeast as identified by DAVID software . Biological categories that were significantly over-represented (Benjamini< 0.05) among the 500 probes with the high G_{i0} greater than -0.011,Figure S10).

Term	Count	PValue	List Total	Pop Hits	Pop Total	Benjamini
GO:0019953~sexual reproduction	45	1.85E-06	376	2.77E+02	4870	0.002183
GO:0048610~reproductive cellular proce	40	5.82E-06	376	2.43E+02	4870	0.003426
GO:0007126~meiosis	33	7.73E-06	376	1.84E+02	4870	0.003032
GO:0051327~M phase of meiotic cell cyc	33	7.73E-06	376	1.84E+02	4870	0.003032
GO:0051321~meiotic cell cycle	33	1.54E-05	376	1.90E+02	4870	0.004525
GO:0043934~sporulation	36	2.19E-05	376	2.20E+02	4870	0.005157
GO:0030435~sporulation resulting in forn	36	2.19E-05	376	2.20E+02	4870	0.005157

Table S17. Over-represented biological processes within the transcripts with the highest G_{i1} in the HF1 cells as identified by EASE software . Biological categories that were significantly over-represented (EASE< 0.01) among the 1400 probes with the biggest absolute G_{i1} and mid G_{i0} (greater than -0.01 and less than -0.06, Figure S6).

Gene Category	List Hits	List Total	Population	Population	EASE sco
mitotic cell cycle	70	1077	329	10937	6.99E-10
cell cycle	114	1077	690	10937	2.08E-08
cell proliferation	156	1077	1036	10937	2.50E-08
DNA replication and chromosome cycle	40	1077	186	10937	3.72E-06
M phase	34	1077	157	10937	1.94E-05
nuclear division	33	1077	151	10937	2.17E-05
M phase of mitotic cell cycle	28	1077	123	10937	4.90E-05
mitosis	27	1077	121	10937	9.79E-05
regulation of cell cycle	61	1077	384	10937	0.000188
S phase of mitotic cell cycle	30	1077	147	10937	0.000197
cell cycle arrest	15	1077	52	10937	0.000362
DNA replication	29	1077	146	10937	0.00041
cell growth and/or maintenance	384	1077	3436	10937	0.00115
DNA metabolism	73	1077	517	10937	0.001412
cell growth	21	1077	108	10937	0.003979
G1 phase of mitotic cell cycle	7	1077	17	10937	0.004267
amine metabolism	48	1077	328	10937	0.00528
phenol metabolism	10	1077	35	10937	0.005587
regulation of catabolism	6	1077	13	10937	0.005989
mitotic anaphase	6	1077	13	10937	0.005989
coenzyme and prosthetic group biosynthesis	18	1077	90	10937	0.006189
regulation of proteolysis and peptidolysis	5	1077	9	10937	0.00783
mitotic chromosome segregation	5	1077	9	10937	0.00783

Table S18. Over-represented biological processes within the transcripts with the highest G_{i1} in the HF1 cells as identified by EASE software . Biological categories that are significantly over-represented (EASE< 0.01) among the 2830 probes with the largest absolute G_{i1} and high G_{i0} (greater than -0.06, Figure S6).

Gene Category	List Hits	List Total	Population	Population	EASE scor
development	412	1864	1683	10937	2.32E-17
organogenesis	241	1864	901	10937	2.39E-14
morphogenesis	263	1864	1010	10937	3.89E-14
cell communication	606	1864	2791	10937	7.89E-14
immune response	174	1864	682	10937	8.35E-09
response to external stimulus	289	1864	1263	10937	1.26E-08
cell adhesion	142	1864	542	10937	4.23E-08
defense response	185	1864	756	10937	7.35E-08
response to biotic stimulus	198	1864	821	10937	7.63E-08
neurogenesis	106	1864	404	10937	2.48E-06
cell-cell signaling	129	1864	525	10937	7.21E-06
signal transduction	443	1864	2196	10937	1.24E-05
cell surface receptor linked signal transduction	218	1864	991	10937	2.00E-05
circulation	38	1864	111	10937	2.06E-05
cellular process	1054	1864	5719	10937	3.24E-05
cell differentiation	51	1864	172	10937	5.57E-05
response to pest/pathogen/parasite	108	1864	444	10937	6.77E-05
cell-cell adhesion	54	1864	187	10937	7.13E-05
ion transport	122	1864	516	10937	8.29E-05
skeletal development	39	1864	125	10937	0.000153
pregnancy	19	1864	45	10937	0.000218
cation transport	91	1864	374	10937	0.000265
metal ion transport	71	1864	283	10937	0.000548
perception of external stimulus	76	1864	315	10937	0.001146
muscle development	38	1864	133	10937	0.001212
lymphocyte activation	20	1864	57	10937	0.002039
central nervous system development	32	1864	112	10937	0.00316
transmission of nerve impulse	58	1864	240	10937	0.004475
frizzled-2 signaling pathway	8	1864	14	10937	0.004636
G-protein coupled receptor protein signaling pat	121	1864	566	10937	0.004799
cartilage condensation	7	1864	11	10937	0.005135
response to light	43	1864	168	10937	0.005322
synaptic transmission	56	1864	232	10937	0.005378
response to abiotic stimulus	111	1864	516	10937	0.005687
potassium ion transport	35	1864	131	10937	0.006253
monovalent inorganic cation transport	58	1864	244	10937	0.006456
cell activation	21	1864	67	10937	0.006581
immune cell activation	21	1864	67	10937	0.006581
homophilic cell adhesion	24	1864	81	10937	0.007296
perception of pest/pathogen/parasite	8	1864	15	10937	0.007428
perception of biotic stimulus	8	1864	15	10937	0.007428
neuropeptide signaling pathway	25	1864	86	10937	0.007835
transmembrane receptor protein tyrosine kinase	31	1864	114	10937	0.007992
perception of abiotic stimulus	65	1864	282	10937	0.008034
response to wounding	61	1864	262	10937	0.00826
heterophilic cell adhesion	24	1864	82	10937	0.008545
respiratory gaseous exchange	9	1864	19	10937	0.008956
response to radiation	45	1864	183	10937	0.009212
histogenesis	32	1864	120	10937	0.00939
melanin biosynthesis	5	1864	6	10937	0.009411
melanin biosynthesis from tyrosine	5	1864	6	10937	0.009411
vision	40	1864	159	10937	0.00979
perception of light	41	1864	164	10937	0.009894

Table S19. Over-represented biological processes within the transcripts with the lowest G_{0i} in E.Coli as identified by DAVID software . Biological categories that were significantly over-represented (Benjamini p-value < 0.05) among the 490 transcripts with the lowest (less than -0.015) G_{0i} .

Term	Count	%	PValue	List Total	Pop Hits	Pop Total	Benjamini
GO:0006412~translation	50	15.33742	5.68E-42	236	253	16709	2.87E-39
GO:0006091~generation of precursor metabolites and energy	42	12.88344	4.92E-14	236	746	16709	1.24E-11
GO:0032268~regulation of cellular protein metabolic process	11	3.374233	2.44E-11	236	34	16709	4.11E-09
GO:0006417~regulation of translation	11	3.374233	2.44E-11	236	34	16709	4.11E-09
GO:0015980~energy derivation by oxidation of organic compounds	28	8.588957	4.21E-11	236	418	16709	5.32E-09
GO:0010608~posttranscriptional regulation of gene expression	11	3.374233	3.19E-10	236	43	16709	3.23E-08
GO:0045333~cellular respiration	25	7.668712	5.27E-10	236	371	16709	4.43E-08
GO:0009060~aerobic respiration	16	4.907975	6.61E-10	236	134	16709	4.77E-08
GO:0006084~acetyl-CoA metabolic process	14	4.294479	2.69E-09	236	105	16709	1.70E-07
GO:0046356~acetyl-CoA catabolic process	12	3.680982	2.88E-08	236	85	16709	1.62E-06
GO:0006099~tricarboxylic acid cycle	12	3.680982	2.88E-08	236	85	16709	1.62E-06
GO:0006090~pyruvate metabolic process	10	3.067485	4.02E-08	236	52	16709	2.03E-06
GO:0051187~cofactor catabolic process	12	3.680982	5.93E-08	236	91	16709	2.72E-06
GO:0009109~coenzyme catabolic process	12	3.680982	5.93E-08	236	91	16709	2.72E-06
GO:0009628~response to abiotic stimulus	12	3.680982	1.29E-07	236	98	16709	5.42E-06
GO:0009061~anaerobic respiration	14	4.294479	3.97E-07	236	159	16709	1.54E-05
GO:0006096~glycolysis	12	3.680982	4.64E-07	236	111	16709	1.67E-05
GO:0046164~alcohol catabolic process	16	4.907975	5.99E-07	236	222	16709	2.02E-05
GO:0044275~cellular carbohydrate catabolic process	16	4.907975	1.05E-06	236	232	16709	3.30E-05
GO:0046365~monosaccharide catabolic process	15	4.601227	1.26E-06	236	205	16709	3.75E-05
GO:0009386~translational attenuation	5	1.533742	1.29E-06	236	7	16709	3.62E-05
GO:0006351~transcription, DNA-dependent	9	2.760736	1.42E-06	236	58	16709	3.78E-05
GO:0032774~RNA biosynthetic process	10	3.067485	1.80E-06	236	80	16709	4.54E-05
GO:0006007~glucose catabolic process	14	4.294479	1.85E-06	236	182	16709	4.44E-05
GO:0019320~hexose catabolic process	14	4.294479	2.09E-06	236	184	16709	4.79E-05
GO:0016052~carbohydrate catabolic process	26	7.97546	2.43E-06	236	622	16709	5.33E-05
GO:0051186~cofactor metabolic process	27	8.282209	4.19E-06	236	684	16709	8.82E-05
GO:0016226~iron-sulfur cluster assembly	7	2.147239	2.86E-05	236	43	16709	5.78E-04
GO:0031163~metallo-sulfur cluster assembly	7	2.147239	2.86E-05	236	43	16709	5.78E-04
GO:0006006~glucose metabolic process	17	5.214724	3.92E-05	236	351	16709	7.61E-04
GO:0006970~response to osmotic stress	6	1.840491	3.98E-05	236	28	16709	7.44E-04
GO:0006353~transcription termination	4	1.226994	5.32E-05	236	6	16709	9.60E-04
GO:0006732~coenzyme metabolic process	19	5.828221	1.17E-04	236	468	16709	0.002033
GO:0006094~gluconeogenesis	6	1.840491	3.28E-04	236	43	16709	0.005512
GO:0019319~hexose biosynthetic process	6	1.840491	4.07E-04	236	45	16709	0.006614
GO:0046487~glyoxylate metabolic process	6	1.840491	4.07E-04	236	45	16709	0.006614
GO:0019318~hexose metabolic process	17	5.214724	6.15E-04	236	447	16709	0.009662
GO:0019402~galactitol metabolic process	5	1.533742	7.84E-04	236	30	16709	0.011932
GO:0006059~hexitol metabolic process	5	1.533742	7.84E-04	236	30	16709	0.011932
GO:0006081~cellular aldehyde metabolic process	6	1.840491	8.00E-04	236	52	16709	0.011816
GO:0043933~macromolecular complex subunit organization	9	2.760736	0.001346	236	151	16709	0.01925
GO:0009266~response to temperature stimulus	5	1.533742	0.002132	236	39	16709	0.029495
GO:0032984~macromolecular complex disassembly	4	1.226994	0.003471	236	22	16709	0.046354
GO:0022411~cellular component disassembly	4	1.226994	0.003471	236	22	16709	0.046354
GO:0034623~cellular macromolecular complex disassembly	4	1.226994	0.003471	236	22	16709	0.046354
GO:0043241~protein complex disassembly	4	1.226994	0.003471	236	22	16709	0.046354
GO:0043624~cellular protein complex disassembly	4	1.226994	0.003471	236	22	16709	0.046354

Table S20. Over-represented biological processes within the transcripts with the mid G_{0i} in E.Coli as identified by DADID software. Biological categories that were significantly over-represented (Benjamini p-value < 0.01) among the 5600 probes with the mid G_{0i} (-0.009-(-0.014).

Term	Count	PValue	List Total	Pop Hits	Pop Total	Benjamini
GO:0044271~nitrogen compound biosynthetic process	293	1.84E-34	2093	1164	16709	2.21E-31
GO:0016052~carbohydrate catabolic process	183	4.98E-30	2093	622	16709	2.99E-27
GO:0015949~nucleobase, nucleoside and nucleotide inte	43	2.14E-24	2093	61	16709	8.58E-22
GO:0009309~amine biosynthetic process	160	1.90E-21	2093	600	16709	5.70E-19
GO:0009061~anaerobic respiration	68	5.59E-21	2093	159	16709	1.34E-18
GO:0046394~carboxylic acid biosynthetic process	170	2.67E-19	2093	685	16709	5.34E-17
GO:0016053~organic acid biosynthetic process	170	4.24E-19	2093	688	16709	7.27E-17
GO:0008652~cellular amino acid biosynthetic process	145	5.08E-19	2093	550	16709	7.62E-17
GO:0016051~carbohydrate biosynthetic process	146	1.31E-14	2093	617	16709	1.75E-12
GO:0000271~polysaccharide biosynthetic process	132	2.08E-14	2093	540	16709	2.49E-12
GO:0007610~behavior	44	2.20E-13	2093	105	16709	2.40E-11
GO:0042330~taxis	44	2.20E-13	2093	105	16709	2.40E-11
GO:0007626~locomotory behavior	44	2.20E-13	2093	105	16709	2.40E-11
GO:0006023~aminoglycan biosynthetic process	38	4.52E-13	2093	83	16709	4.52E-11
GO:0009252~peptidoglycan biosynthetic process	38	4.52E-13	2093	83	16709	4.52E-11
GO:0006024~glycosaminoglycan biosynthetic process	38	4.52E-13	2093	83	16709	4.52E-11
GO:0010382~cellular cell wall macromolecule metabolic	39	4.82E-13	2093	87	16709	4.45E-11
GO:0070589~cellular component macromolecule biosynt	38	1.71E-12	2093	86	16709	1.47E-10
GO:0044038~cell wall macromolecule biosynthetic proce	38	1.71E-12	2093	86	16709	1.47E-10
GO:0005976~polysaccharide metabolic process	155	2.63E-12	2093	712	16709	2.11E-10
GO:0006091~generation of precursor metabolites and er	158	1.54E-11	2093	746	16709	1.16E-09
GO:0015980~energy derivation by oxidation of organic co	102	2.77E-11	2093	418	16709	1.96E-09
GO:0030258~lipid modification	21	4.14E-11	2093	32	16709	2.76E-09
GO:0009273~peptidoglycan-based cell wall biogenesis	38	4.16E-11	2093	94	16709	2.63E-09
GO:0042546~cell wall biogenesis	38	4.16E-11	2093	94	16709	2.63E-09
GO:0019395~fatty acid oxidation	20	9.16E-11	2093	30	16709	5.50E-09
GO:0034440~lipid oxidation	20	9.16E-11	2093	30	16709	5.50E-09
GO:0018130~heterocycle biosynthetic process	98	1.55E-10	2093	407	16709	8.85E-09
GO:0046377~colanic acid metabolic process	19	2.01E-10	2093	28	16709	1.10E-08
GO:0009242~colanic acid biosynthetic process	19	2.01E-10	2093	28	16709	1.10E-08
GO:0034654~nucleobase, nucleoside, nucleotide and nu	84	2.04E-10	2093	330	16709	1.07E-08
GO:0034404~nucleobase, nucleoside and nucleotide bio	84	2.04E-10	2093	330	16709	1.07E-08
GO:0045333~cellular respiration	91	2.67E-10	2093	371	16709	1.33E-08
GO:0006766~vitamin metabolic process	80	3.97E-10	2093	312	16709	1.90E-08
GO:0009108~coenzyme biosynthetic process	72	8.80E-10	2093	273	16709	4.06E-08
GO:0009116~nucleoside metabolic process	47	9.91E-10	2093	145	16709	4.40E-08
GO:0006790~sulfur metabolic process	70	1.44E-09	2093	265	16709	6.16E-08
GO:0006767~water-soluble vitamin metabolic process	72	1.47E-09	2093	276	16709	6.07E-08
GO:0009084~glutamine family amino acid biosynthetic pr	40	2.18E-09	2093	115	16709	8.70E-08
GO:0051188~cofactor biosynthetic process	102	2.82E-09	2093	452	16709	1.09E-07
GO:0009110~vitamin biosynthetic process	72	2.85E-09	2093	280	16709	1.07E-07
GO:0051186~cofactor metabolic process	139	5.08E-09	2093	684	16709	1.85E-07
GO:0042364~water-soluble vitamin biosynthetic process	64	1.05E-08	2093	244	16709	3.70E-07
GO:0034637~cellular carbohydrate biosynthetic process	105	1.06E-08	2093	481	16709	3.64E-07
GO:0042493~response to drug	48	1.32E-08	2093	161	16709	4.39E-07
GO:0006732~coenzyme metabolic process	102	1.91E-08	2093	468	16709	6.19E-07
GO:0019438~aromatic compound biosynthetic process	56	2.15E-08	2093	205	16709	6.78E-07
GO:0009066~aspartate family amino acid metabolic proc	37	1.19E-07	2093	116	16709	3.66E-06
GO:0008610~lipid biosynthetic process	104	1.32E-07	2093	498	16709	3.97E-06
GO:0009165~nucleotide biosynthetic process	64	1.34E-07	2093	260	16709	3.92E-06
GO:0009628~response to abiotic stimulus	33	1.61E-07	2093	98	16709	4.59E-06
GO:0009243~O antigen biosynthetic process	11	1.85E-07	2093	13	16709	5.17E-06
GO:0046402~O antigen metabolic process	11	1.85E-07	2093	13	16709	5.17E-06
GO:0033692~cellular polysaccharide biosynthetic proces	88	2.55E-07	2093	406	16709	6.95E-06
GO:0046128~purine ribonucleoside metabolic process	30	2.79E-07	2093	86	16709	7.45E-06
GO:0006308~DNA catabolic process	18	3.49E-07	2093	36	16709	9.09E-06
GO:0009119~ribonucleoside metabolic process	34	3.64E-07	2093	106	16709	9.30E-06
GO:0042278~purine nucleoside metabolic process	30	3.69E-07	2093	87	16709	9.23E-06
GO:0044264~cellular polysaccharide metabolic process	91	4.78E-07	2093	430	16709	1.17E-05
GO:0006928~cell motion	23	5.45E-07	2093	57	16709	1.31E-05
GO:0034660~ncRNA metabolic process	82	5.88E-07	2093	377	16709	1.38E-05
GO:0006457~protein folding	52	7.48E-07	2093	204	16709	1.73E-05
GO:0009067~aspartate family amino acid biosynthetic pr	35	7.49E-07	2093	114	16709	1.70E-05
GO:0044265~cellular macromolecule catabolic process	27	1.11E-06	2093	77	16709	2.46E-05

GO:0008360~regulation of cell shape	29	1.30E-06	2093	87	16709	2.85E-05
GO:0022604~regulation of cell morphogenesis	29	1.30E-06	2093	87	16709	2.85E-05
GO:0006631~fatty acid metabolic process	36	1.42E-06	2093	122	16709	3.05E-05
GO:0022900~electron transport chain	72	1.53E-06	2093	325	16709	3.22E-05
GO:0048870~cell motility	22	1.71E-06	2093	56	16709	3.54E-05
GO:0001539~ciliary or flagellar motility	22	1.71E-06	2093	56	16709	3.54E-05
GO:0051674~localization of cell	22	1.71E-06	2093	56	16709	3.54E-05
GO:0009432~SOS response	23	2.87E-06	2093	62	16709	5.83E-05
GO:0006113~fermentation	19	3.18E-06	2093	45	16709	6.36E-05
GO:0006220~pyrimidine nucleotide metabolic process	20	4.21E-06	2093	50	16709	8.29E-05
GO:0009991~response to extracellular stimulus	35	6.03E-06	2093	124	16709	1.17E-04
GO:0044272~sulfur compound biosynthetic process	47	6.47E-06	2093	190	16709	1.23E-04
GO:0042398~cellular amino acid derivative biosynthetic p	33	6.57E-06	2093	114	16709	1.23E-04
GO:0009103~lipopolysaccharide biosynthetic process	68	7.74E-06	2093	315	16709	1.43E-04
GO:0009226~nucleotide-sugar biosynthetic process	10	8.23E-06	2093	14	16709	1.50E-04
GO:0042558~pteridine and derivative metabolic process	26	8.55E-06	2093	80	16709	1.53E-04
GO:0042559~pteridine and derivative biosynthetic proces	26	8.55E-06	2093	80	16709	1.53E-04
GO:0006221~pyrimidine nucleotide biosynthetic process	19	9.34E-06	2093	48	16709	1.65E-04
GO:0006261~DNA-dependent DNA replication	38	1.03E-05	2093	143	16709	1.80E-04
GO:0008653~lipopolysaccharide metabolic process	69	1.06E-05	2093	324	16709	1.82E-04
GO:0006399~tRNA metabolic process	59	1.61E-05	2093	267	16709	2.72E-04
GO:0006022~aminoglycan metabolic process	51	2.21E-05	2093	222	16709	3.68E-04
GO:0030203~glycosaminoglycan metabolic process	50	2.47E-05	2093	217	16709	4.06E-04
GO:0000270~peptidoglycan metabolic process	50	2.47E-05	2093	217	16709	4.06E-04
GO:0007049~cell cycle	37	2.58E-05	2093	143	16709	4.18E-04
GO:0009415~response to water	8	4.06E-05	2093	10	16709	6.49E-04
GO:0009414~response to water deprivation	8	4.06E-05	2093	10	16709	6.49E-04
GO:0009269~response to desiccation	8	4.06E-05	2093	10	16709	6.49E-04
GO:0009451~RNA modification	45	4.32E-05	2093	192	16709	6.81E-04
GO:0000041~transition metal ion transport	47	5.77E-05	2093	206	16709	8.99E-04
GO:0000097~sulfur amino acid biosynthetic process	23	6.83E-05	2093	74	16709	0.001051
GO:0009070~serine family amino acid biosynthetic proce	20	8.21E-05	2093	60	16709	0.001247
GO:0015837~amine transport	62	8.59E-05	2093	301	16709	0.001288
GO:0009101~glycoprotein biosynthetic process	9	8.88E-05	2093	14	16709	0.001314
GO:0009100~glycoprotein metabolic process	9	8.88E-05	2093	14	16709	0.001314
GO:0055114~oxidation reduction	310	8.94E-05	2093	2037	16709	0.001307
GO:0042401~biogenic amine biosynthetic process	23	1.06E-04	2093	76	16709	0.001533
GO:0009310~amine catabolic process	44	1.34E-04	2093	195	16709	0.001909
GO:0009064~glutamine family amino acid metabolic proc	55	1.36E-04	2093	262	16709	0.001913
GO:0034470~ncRNA processing	61	1.43E-04	2093	300	16709	0.001997
GO:0009435~NAD biosynthetic process	14	1.82E-04	2093	35	16709	0.002501
GO:0019359~nicotinamide nucleotide biosynthetic proces	14	1.82E-04	2093	35	16709	0.002501
GO:0006596~polyamine biosynthetic process	14	1.82E-04	2093	35	16709	0.002501
GO:0019674~NAD metabolic process	14	1.82E-04	2093	35	16709	0.002501
GO:0019363~pyridine nucleotide biosynthetic process	15	2.15E-04	2093	40	16709	0.002928
GO:0033865~nucleoside bisphosphate metabolic proces	12	2.20E-04	2093	27	16709	0.002961
GO:0046942~carboxylic acid transport	77	2.42E-04	2093	409	16709	0.003216
GO:0015849~organic acid transport	77	2.42E-04	2093	409	16709	0.003216
GO:0006865~amino acid transport	57	2.58E-04	2093	281	16709	0.003397
GO:0019521~D-gluconate metabolic process	9	3.02E-04	2093	16	16709	0.003926
GO:0019520~aldonic acid metabolic process	9	3.02E-04	2093	16	16709	0.003926
GO:0000096~sulfur amino acid metabolic process	24	3.30E-04	2093	87	16709	0.004254
GO:0017004~cytochrome complex assembly	19	3.38E-04	2093	61	16709	0.004302
GO:0015936~coenzyme A metabolic process	10	3.41E-04	2093	20	16709	0.004294
GO:0015937~coenzyme A biosynthetic process	10	3.41E-04	2093	20	16709	0.004294
GO:0006811~ion transport	141	3.53E-04	2093	851	16709	0.004399
GO:0034621~cellular macromolecular complex subunit c	26	3.99E-04	2093	99	16709	0.004926
GO:0006575~cellular amino acid derivative metabolic pro	46	4.09E-04	2093	217	16709	0.004998
GO:0016042~lipid catabolic process	8	4.11E-04	2093	13	16709	0.004974
GO:0006071~glycerol metabolic process	17	4.23E-04	2093	52	16709	0.005069
GO:0006733~oxidoreduction coenzyme metabolic proces	35	4.30E-04	2093	151	16709	0.005093
GO:0046349~amino sugar biosynthetic process	10	5.30E-04	2093	21	16709	0.006219
GO:0009112~nucleobase metabolic process	29	6.39E-04	2093	119	16709	0.007423
GO:0006396~RNA processing	68	6.60E-04	2093	363	16709	0.007592
GO:0044036~cell wall macromolecule metabolic process	50	6.74E-04	2093	247	16709	0.007675

5. Identification of transcripts mostly contributing to the process of transformation

In order to analyse the transcripts strongly contributing to the major transcription pattern during process of transformation, we examine the change in the expression level between two time points. From equation [1] in the main text and noting that $G_{i\alpha}$, the weight of a transcript in the pattern α is not dependent on time, we calculate that:

$$\ln\left(X_i(t_T)\right) - \ln\left(X_i(t_{T'})\right) = -\sum_{\alpha=1} G_{i\alpha}\left(\lambda_\alpha(t_T) - \lambda_\alpha(t_{T'})\right)$$

The sign of $G_{i\alpha}$, the extent of participation of the transcript *i* in the pattern *α* can be either positive or negative (3, 4). Therefore in the same phenotype some transcripts in the pattern can be reduced while other can be induced and the surprisal analysis predicts which one does what (For examples see (3, 4)). HF1 model transformation system has 4 continous time points in the transformation route (K-normal cells, E-HPV16 immortalized cells at early stages, L- HPV16 immortalized cells at late stages, BP- benzo(a)pyren treated L cells, that able to form colonies in soft agar). The major transcription pattern switched its sign betweeen E and L time points. That means that the transcripts contributing to the early stages of transformation have a smaller contribution in the late stages of transformation and vice versa. For the analysis of the major transcription pattern in the HF1 transformation model we looked at 4647 transcrits (out of 22250) that mostly contributed , negatively and positively, to the major transcription pattern in the process of transformation and have a significant absolute dln value: $\ln(X_{i(BP)}) - \ln\left(X_{i(K)}\right) \geq 1.$

TGFβ treated lung cancer cells (A549) have 9 continous time points in the process of metastasis (the cells were treated by TGFβ for 0.5, 1, 2,4,8,16,24 and 72 hours). The major transcription pattern switched its sign betweeen 4 and 8 hours. For the analysis of the major transcription pattern in the TGFβ treated lung cancer cells we looked at 3416 transcrits (out of 54700) that mostly contributed , negatively and positively, to the major transcription pattern in the process of transformation and have a significant absolute dln value. $\ln(X_{i(72h)}) - \ln\left(X_{i(0h)}\right) \geq 0.7$

6. Stable transcripts of the steady state participate less in the process of transformation

Examination of the transcripts that contribute significantly (transcripts with the highest $G_{i1}\lambda_1$ (or G_{i1}) values), positively or negatively, to the major transcription pattern(α =1) during the transformation of HF1 cells revealed the majority of these transcripts have middle or high free energy values. Out of a total of ~22200 transcripts, 4647 have a non negligible weight, G_{i1} in the major transcription pattern. Of those, only 300 transcripts are also present in the core set of the steady state. (low G_{i0} value (< -0.01)). It is still however the case that because $\lambda_1 << \lambda_0$ the work done by the process hardly changes the free energy. About 1400 transcripts that belong to the α =1 pattern have a mid G_{i0} value (greater than -0.01 and less than -0.006, Fig. S6) and belong mostly to cell cycle process (Fig. S6, Table S17), while the transcripts in α =1 present in the steady state with the highest G_{i0} (greater than -0.006) belong to signal transduction, cell communication and morphogenesis categories (Table S18). The same results were obtained from the analysis of the TGFβ treated cells, the renal carcinoma metastasis model and fibroblast cancer model WI-38.

Experimental studies used in the manuscript:

1. WI-38 transformed fibroblasts (7):

The cancer model system follows the progression from the normal phenotype all the way to the onset of cancer. The WI-38 cellular system includes parental WI-38 fibroblasts in the young, senescent stages as well as the hTERT immortalized cells at the different stages . At a certain stage (Figure 1), p53 was inactivated by the expression of a dominant-negative peptide GSE56 , and the expression of oncogenic H-Ras was induced by infection at the indicated time points as shown in Figure 1. The genetic alterations were applied at different points as shown in Figure1 where the time points are labeled $T = 1,2,..,12$. It is important to note that different trajectories of the transformation process go through different time points. For example, we will compare the three trajectories 1-5-7-8-9, 1-5-7-8-11 and 1-5-7-8-10-12, which share a common process up to and including point 8. These are all continuous processes where each time point follows the preceding one and we will refer to such a sequence of stages as a trajectory. An opposite example is the trajectory 1-5-6-7 that cannot be considered as continuous since time point 7 does not experimentally follow point 6.

2. TGFβ treated lung cancer cells (8):

The goal of the experiment is to profile temporal gene expression changes during TGF-beta-induced epithelial-mesenchymal transition (EMT). During EMT cancer cells loose their epithelial specifc proteins and gain mesenchymal proteins to acquire migratory and invasive phenotype essential for metastasis. Human A549 lung adenocarcinoma cell line was treated with 5 ng/mL TGF-beta for 0, 0.5, 1, 2, 4, 8, 16, 24, and 72 h to induce EMT. The experiment was repeated 3 times. Samples were assayed using Affymetrix HG_U133_plus_2 arrays with 54675 probe-sets, using standard techniques.

3. Colon carcinoma development (9):

Paired tissues (normal colon, primary colorectal carcinoma, normal liver, liver metastasis of colorectal carcinoma) from 2 colorectal carcinoma patients in Taiwan were processed to generate total RNA, which was subsequently analyzed for gene expression using Affymetrix U133 plus 2.0 arrays.

4. Renal carcinoma development from (10):

In this study primary tumor, normal tissue and metastases with the aim of identifying similarities and differences between these tissues were compared. This comparison was performed for three patients on the level of the transcriptome using oligonucleotide microarrays. The quantitative results show that primary tumor is more similar to metastasis than to normal tissue, both on the level of HLA ligand presentation and mRNA.

5. Prostate cancer development:

Prostates taken from radical prostatectomy surgeries from 4 different patients (for removal of diseased tissue) were separated by a Urologic Pathologist into cancer and benign adjacent to cancer. Cancer and benign adjacent to cancer tissues were dissociated to single cells and highly purified populations of benign basal epithelial cells, benign luminal epithelial cells, and cancerous luminal cells were isolated by Fluorescence Activated Cell Sorting for subsequent RNA isolation and microarray analysis.

Gene expression in three epithelial cell-types, representing two stages of disease of prostate cancer, was examined using Human Genome U133 Plus 2.0 array. Basal cells represent the stem-like cell compartment in the benign epithelium of the prostate and are also cells-of-origin for prostate cancer. Luminal cells represent the mature compartment in benign prostate epithelium. Both basal cells and luminal cells were taken from benign tissues adjacent to cancer that were carefully separated from tumor under the guidance of the Urologic Pathologist following radical prostatectomy for removal of diseased prostate tissue. Cancer cells represent highly purified preparations of luminal cells taken from cancer glands in the prostate.

6. HPV16 transformed keratinocytes (11):

To identify early processes in carcinogenesis, we used an in vitro model, based on the initiating event in cervical cancer, human papillomavirus (HPV) transformation of keratinocytes. We compared gene expression in primary keratinocytes (K) and HPV16-transformed keratinocytes from early (E) and late (L) passages, and from benzo[a]pyrene treated L cells (BP). The transformed cells exhibit similar

transcriptional changes to clinical cervical carcinoma. We revealed a contraction in expression of the apoptotic network during HF1 cell transformation, which affected the ability of L and BP cells to execute apoptosis, but did not lead to resistance to apoptotic stimuli. The contraction in the apoptotic machinery during the process of transformation was accompanied by a switch from apoptosis to necrosis in response to CDDP. The shrinkage of the pro- and anti-apoptotic networks appears to be part of a general contraction in the number of genes transcribed in L and BP cells. We also identified a large group of genes with induced expression, which are involved in cell metabolism and cell cycle, suggesting increased investment of the transformed cell in cellular proliferation.

7. TGFβ treated hematopoetic stem cells and dendritic differentiated cells (12):

Analysis of dendritic cells (DCs) and hematopoetic stem cells at various time points up to 36 hours following treatment with TGF-beta1. DCs derived from CD34+ hematopoietic progenitor cells induced to differentiate in vitro. Results provide insight into the role of TGF-beta1 in DC development.

8. Phenelzine treated S. cerevisiae grown for 200 minutes (13):

Perturbation of the gated-synchrony system in the budding yeast *Saccharomyces*. *cerevisiae* with phenelzine, an antidepressant drug used in the treatment of affective disorders in humans, leads to a rapid lengthening in the period of the genome-wide transcriptional oscillation. Samples for Affymetrix expression array analysis were taken at 4-min intervals through four cycles of the oscillation. After one complete cycle of sampling, PZ was added at 1 mM at the different time points. Transcripts were classed according to their time of maximum expression in the cycle by scaling expression to the average of the first 10 samples (control cycle).

9. Development of carcinoma 31 mice (14):

Using an integrated linkage and genomic analysis of a mouse model of skin cancer that produces both benign tumors and malignant carcinomas, major changes in

germline control of gene expression during skin tumor development resulting from cell selection, somatic genetic events, and changes in the tumor microenvironment were documented. The number of significant expression Quantitative Trait Loci (eQTLs) is progressively reduced in benign and malignant skin tumors when compared to normal skin. However, novel tumor-specific eQTLs are detected for several genes associated with tumor susceptibility, including Interleukin 18, Granzyme E, Sprouty homolog 2, and MAP kinase kinase 4. Conclusions: the genetic architecture is substantially altered in tumors, and that eQTL analysis of tumors can identify host factors that influence the tumor microenvironment, MAP kinase signaling, and cancer susceptibility.

10. E. Coli grown on biofilms for 24 hours (15):

Analysis of Escherichia coli K-12 biofilms up to 24 hours of culturing. Biofilm bacteria predominate in nutrient-sufficient ecosystems. Temporal expression of biofilm and suspenion samples from E. coli wild type cultured on glass wool in LB medium. Samples removed after 4, 7, 15, and 24 hr of culturing. Results provide insight into the molecular mechanisms underlying biofilm development.

8. References

1. Laidler K (1996) A glossary of terms used in chemical kinetics, including reaction dynamics (IUPAC Recommendations 1996). *Pure & Appl. Chem* 68:149-192.
2. Levine RD (2005) Molecular Reaction Dynamics (Cambridge: The University Press).
3. Kravchenko-Balasha N, Remacle F, Gross A, Rotter V, Levitzki A, et al. (2011) Convergence of logic of cellular regulation in different premalignant cells by an information theoretic approach. *BMC Syst Biol* 5:42.
4. Remacle F, Kravchenko-Balasha N, Levitzki A, & Levine RD (2010) Information-theoretic analysis of phenotype changes in early stages of carcinogenesis. *Proc Natl Acad Sci USA* 107(22):10324-10329.
5. Hosack DA, Dennis G, Jr., Sherman BT, Lane HC, & Lempicki RA (2003) Identifying biological themes within lists of genes with EASE. *Genome Biol* 4(10):R70.
6. Huang da W, Sherman BT, & Lempicki RA (2009) Systematic and integrative analysis of large gene lists using DAVID bioinformatics resources. *Nat Protoc* 4(1):44-57.
7. Milyavsky M, Tabach Y, Shats I, Erez N, Cohen Y, et al. (2005) Transcriptional programs following genetic alterations in p53, INK4A, and H-Ras genes along defined stages of malignant transformation. *Cancer Res* 65(11):4530-4543.
8. Sartor MA, Mahavisno V, Keshamouni VG, Cavalcoli J, Wright Z, et al. (2010) ConceptGen: a gene set enrichment and gene set relation mapping tool. *Bioinformatics* 26(4):456-463.
9. Wang H & Tsai C (2009) Comparison of gene expression profiles between paired primary and metastasis colorectal carcinoma. (GEO database).
10. Stickel JS, Weinzierl AO, Hillen N, Drews O, Schuler MM, et al. (2009) HLA ligand profiles of primary renal cell carcinoma maintained in metastases. *Cancer Immunol Immunother* 58(9):1407-1417.
11. Kravchenko-Balasha N, Mizrachy-Schwartz S, Klein S, & Levitzki A (2009) Shift from apoptotic to necrotic cell death during human papillomavirus-

induced transformation of keratinocytes. *J Biol Chem* 284(17):11717-11727.

12. Ruau D, Ju XS, & Zenke M (2006) Genomics of TGF-beta1 signaling in stem cell commitment and dendritic cell development. *Cell Immunol* 244(2):116-120.
13. Li CM & Klevecz RR (2006) A rapid genome-scale response of the transcriptional oscillator to perturbation reveals a period-doubling path to phenotypic change. *Proc Natl Acad Sci USA* 103(44):16254-16259.
14. Quigley DA, To MD, Kim IJ, Lin KK, Albertson DG, et al. (2011) Network analysis of skin tumor progression identifies a rewired genetic architecture affecting inflammation and tumor susceptibility. *Genome Biol* 12(1):R5.
15. Domka J, Lee J, Bansal T, & Wood TK (2007) Temporal gene-expression in Escherichia coli K-12 biofilms. *Environ Microbiol* 9(2):332-346.

Figure S1

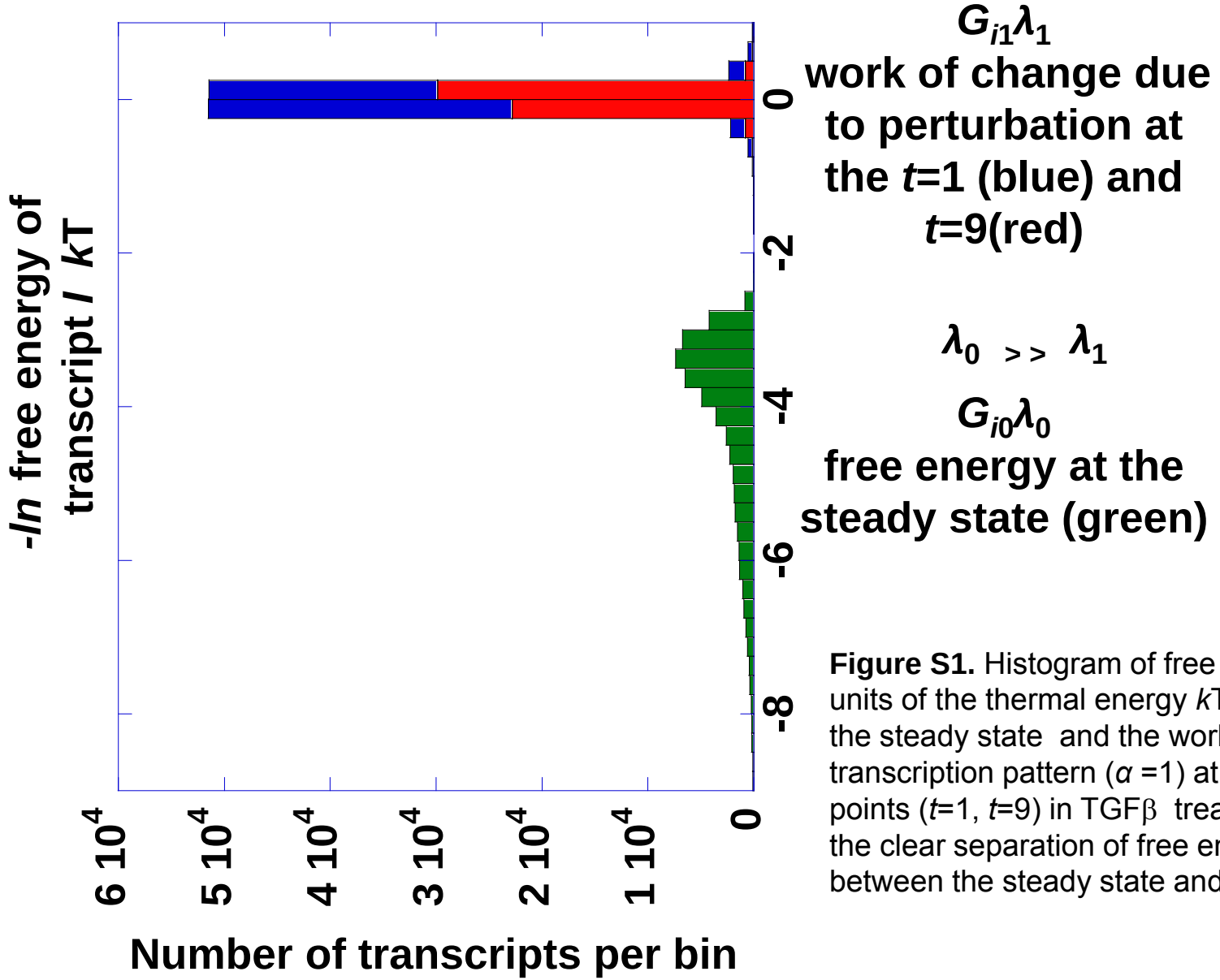
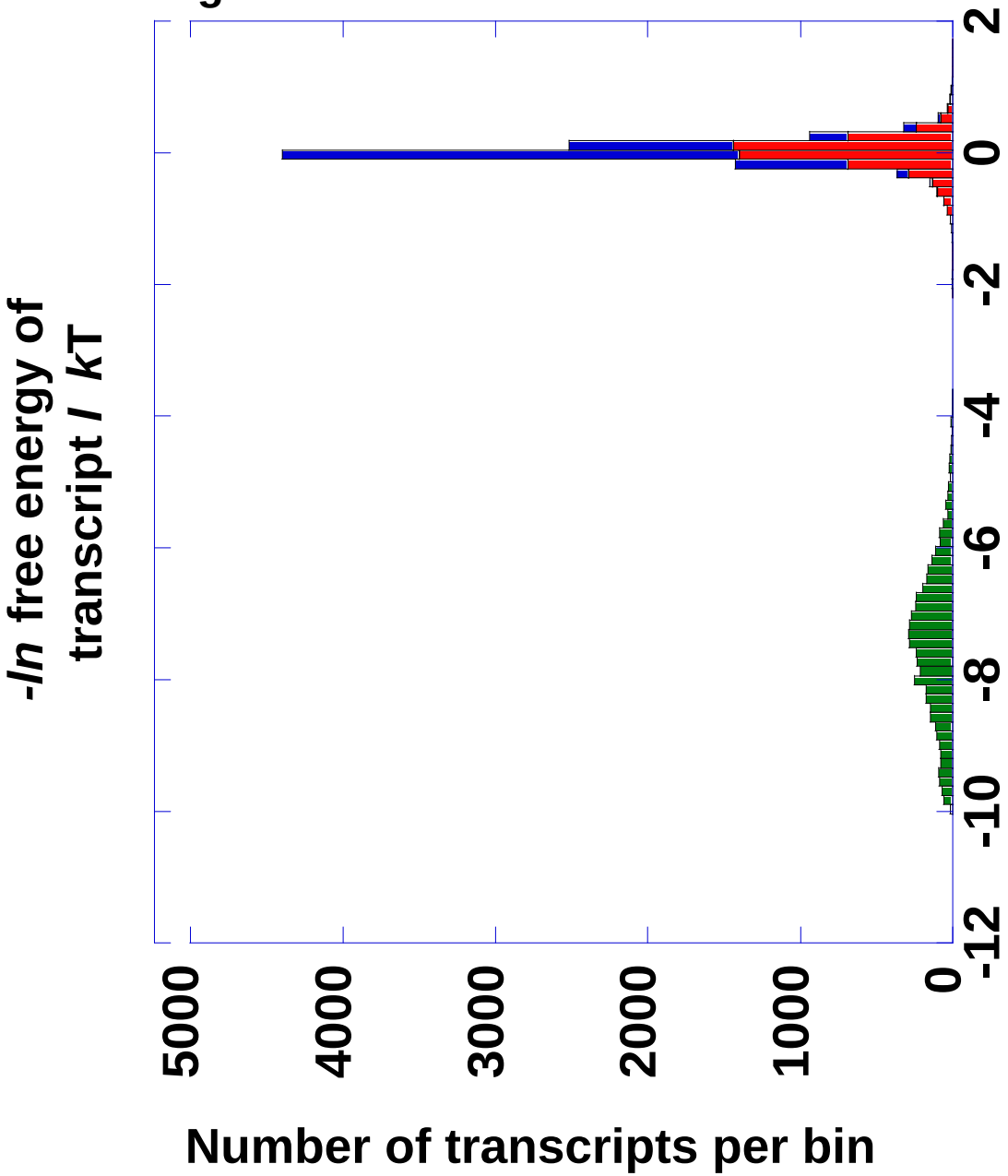


Figure S1. Histogram of free energy values, in units of the thermal energy *k*T, of the transcripts at the steady state and the work done by the major transcription pattern (α =1) at two opposite time points (*t*=1, *t*=9) in TGFβ treated A549 cells. Note the clear separation of free energy scales between the steady state and the perturbation..

Figure S2



$G_{i1}\lambda_1$
work of change due to perturbation the *t*=2 (blue) and *t*=8(red)

$\lambda_0 >> \lambda_1$

$G_{i0}\lambda_0$
free energy at the steady state (green)

Figure S2. Histogram of free energy values, in units of the thermal energy *k*T, of the transcripts at the steady state and the work done by the major transcription pattern (α =1) at two opposite time points (t=2, t=8) in yeast cells. Here too there is the clear separation of free energy scales between the steady state and the perturbation.

Figure S3

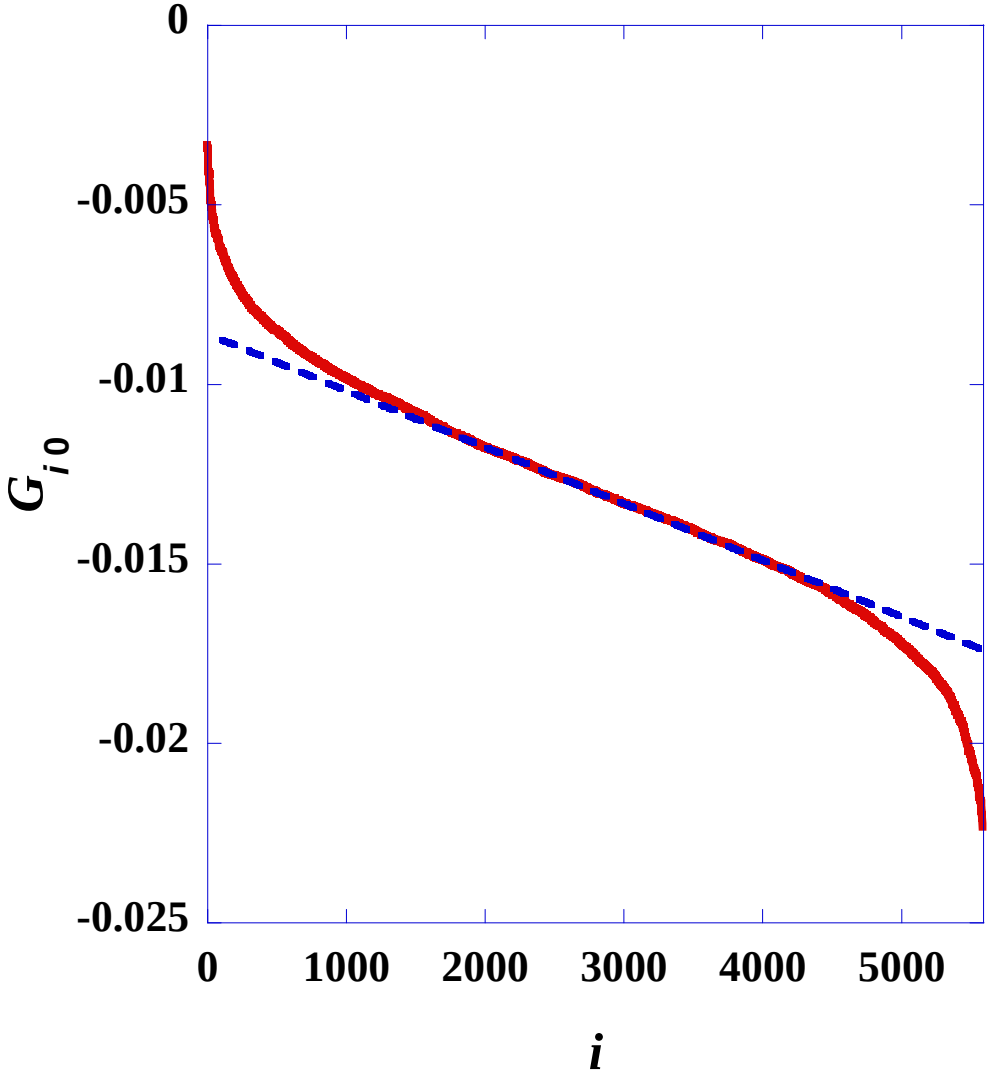


Figure S3. G_{i0} values sorted in decreasing magnitude vs. the transcript index determined in the cancer model system WI-38. The straight line is a fit to the linear part extended to the entire range emphasizing the rapidly varying entries at the two ends of the scale.

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Figure S4

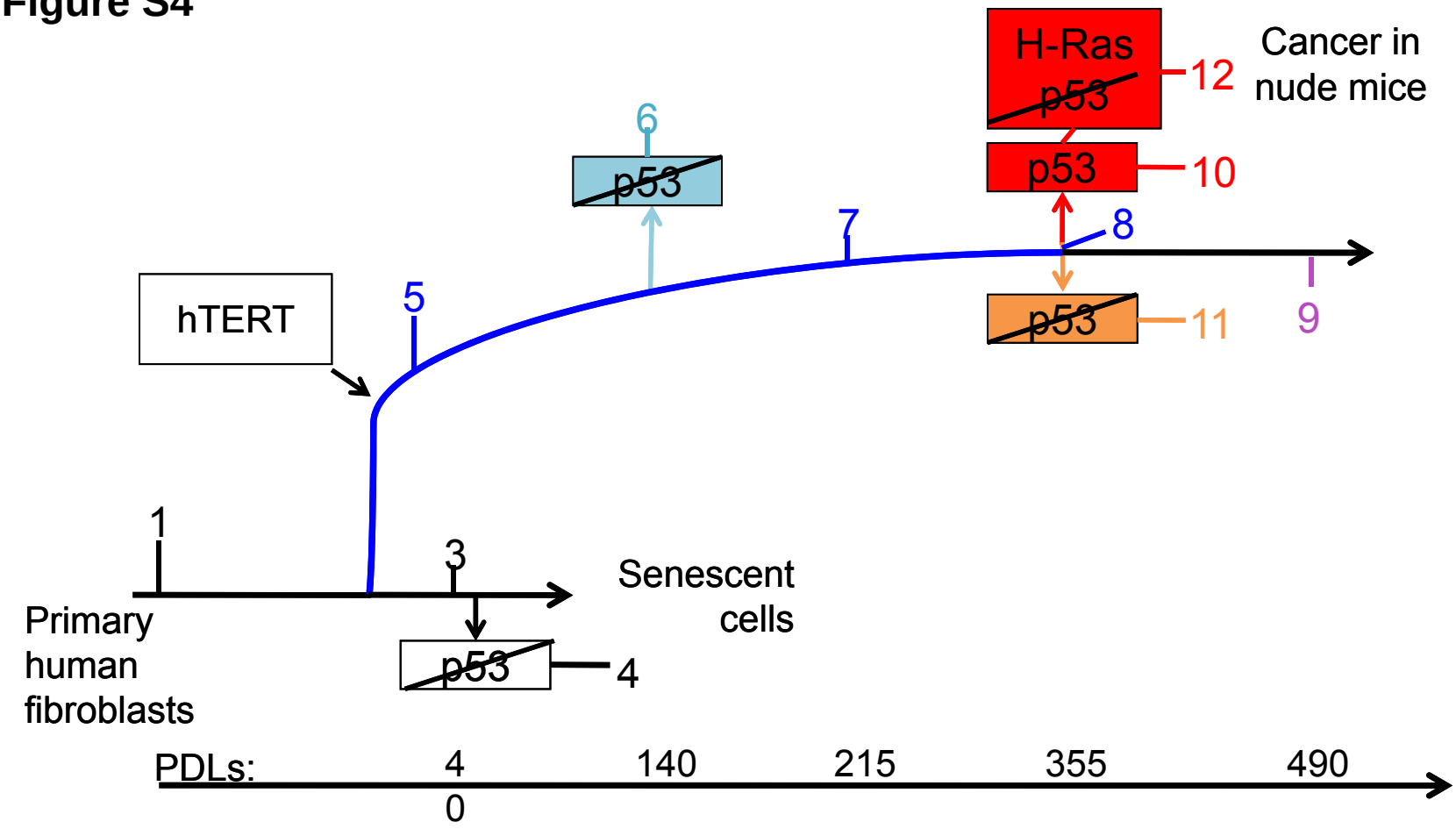


Figure S4. Schematic representation of the WI-38 cell model (adapted from (3)). Schematic representation of the physiological state (young, senescent, immortal, tumorigenic) and introduced modifications (hTERT, H-RAS, p53 inactivation) of the WI-38 cells along the process of malignant transformation. The stages chosen for the theoretical analyses can be arranged as several continuous trajectories where each sample follows the preceding one. A common route for many trajectories, the ones we highlight in the text, is represented by the blue color**.** The first branching occurs at the point 6 (pale blue) and generates the trajectory 156. The second branching occurs at the point 8 and generates 3 trajectories: 1-5-7-8-10-12 (red), 1-5-7-8-11 (yellow) and 1-5-7-8-9 (purple). There is an additional independent trajectory 1-3-4 (black). PDLs are the number of doublings since the cells primary isolation in vitro.

Figure S5

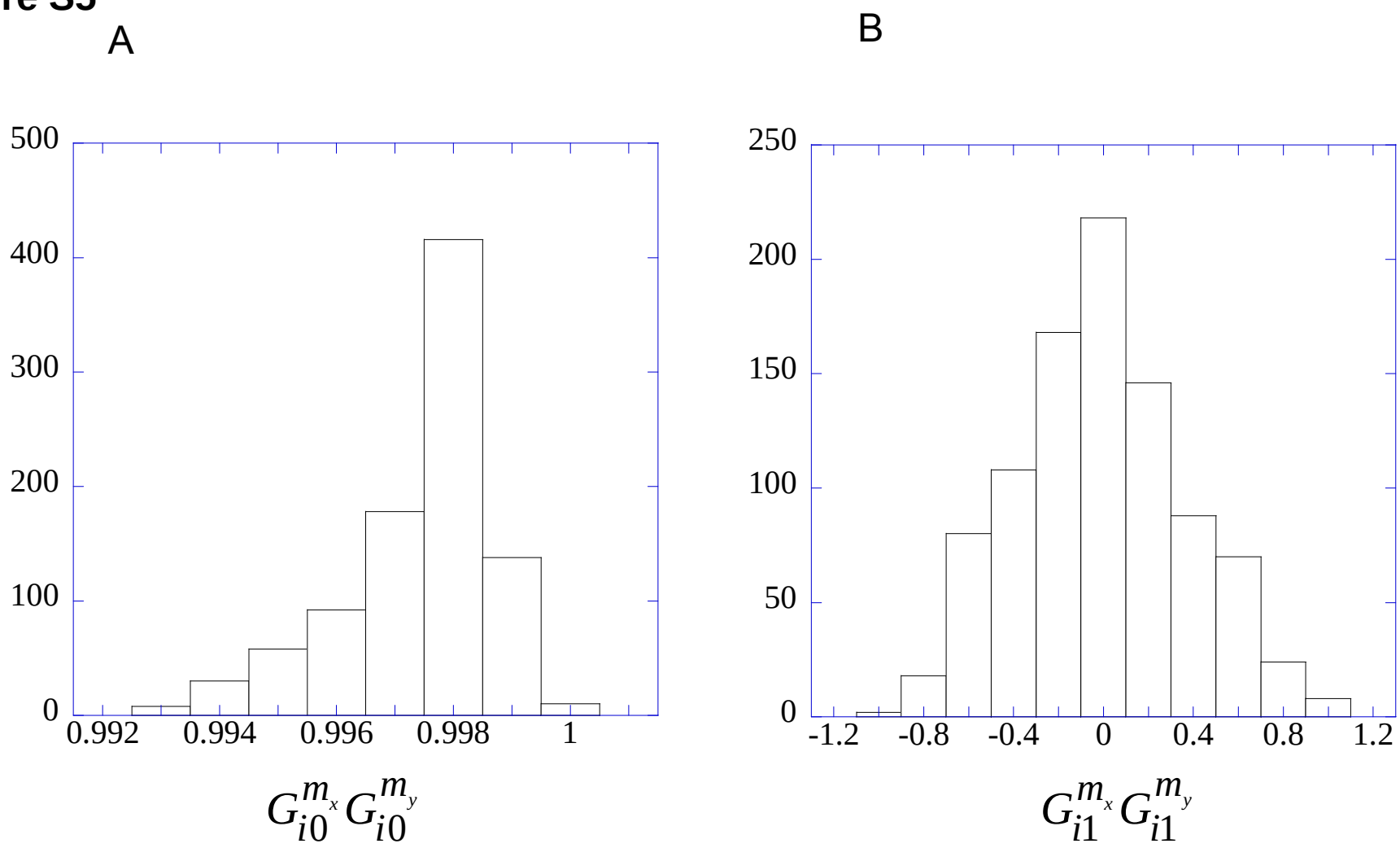


Figure S5. (A) Distribution of the scalar products $G_{i0}^{m_x} G_{i0}^{m_y}$ for all mouse pairs among 31 mice. (B) Distribution of the scalar products $G_{i1}^{m_x} G_{i1}^{m_y}$ for all mouse pairs.

Figure S6

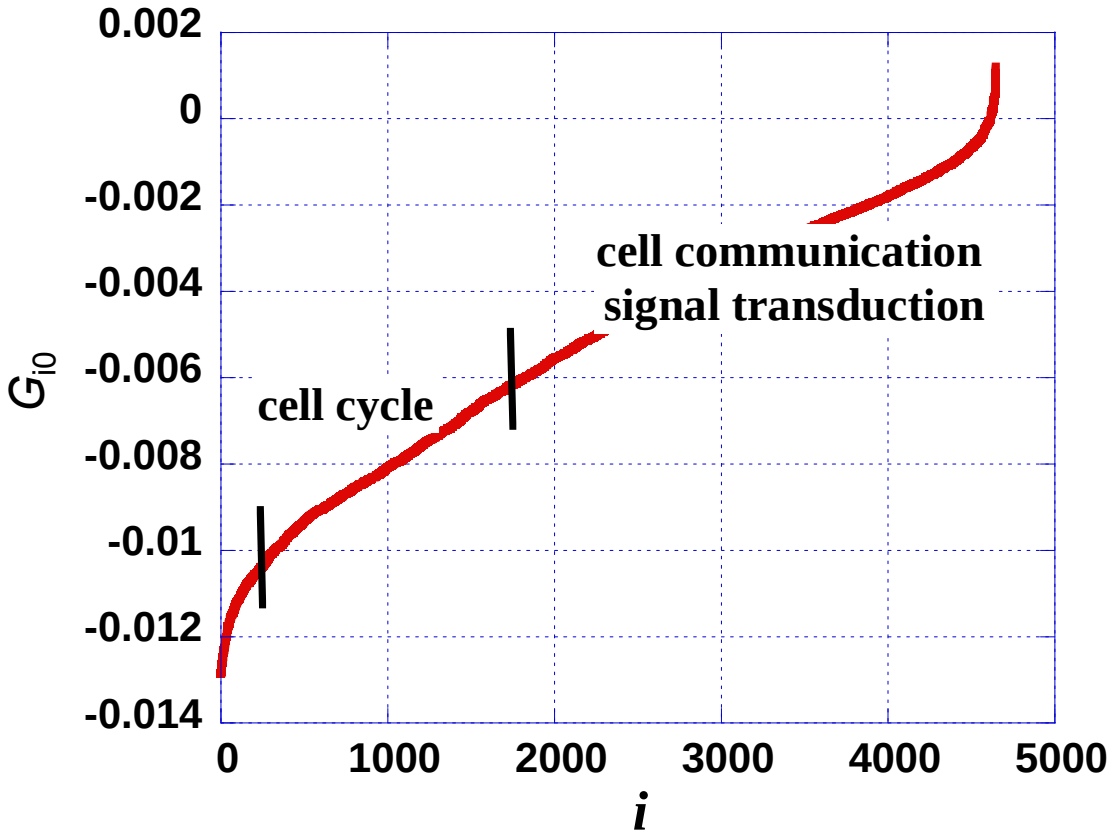


Figure S6. G_{i0} distribution of the transcripts in the trajectory 15781012 of the cancer model system WI-38 strongly contributing to α=1.

Figure S7

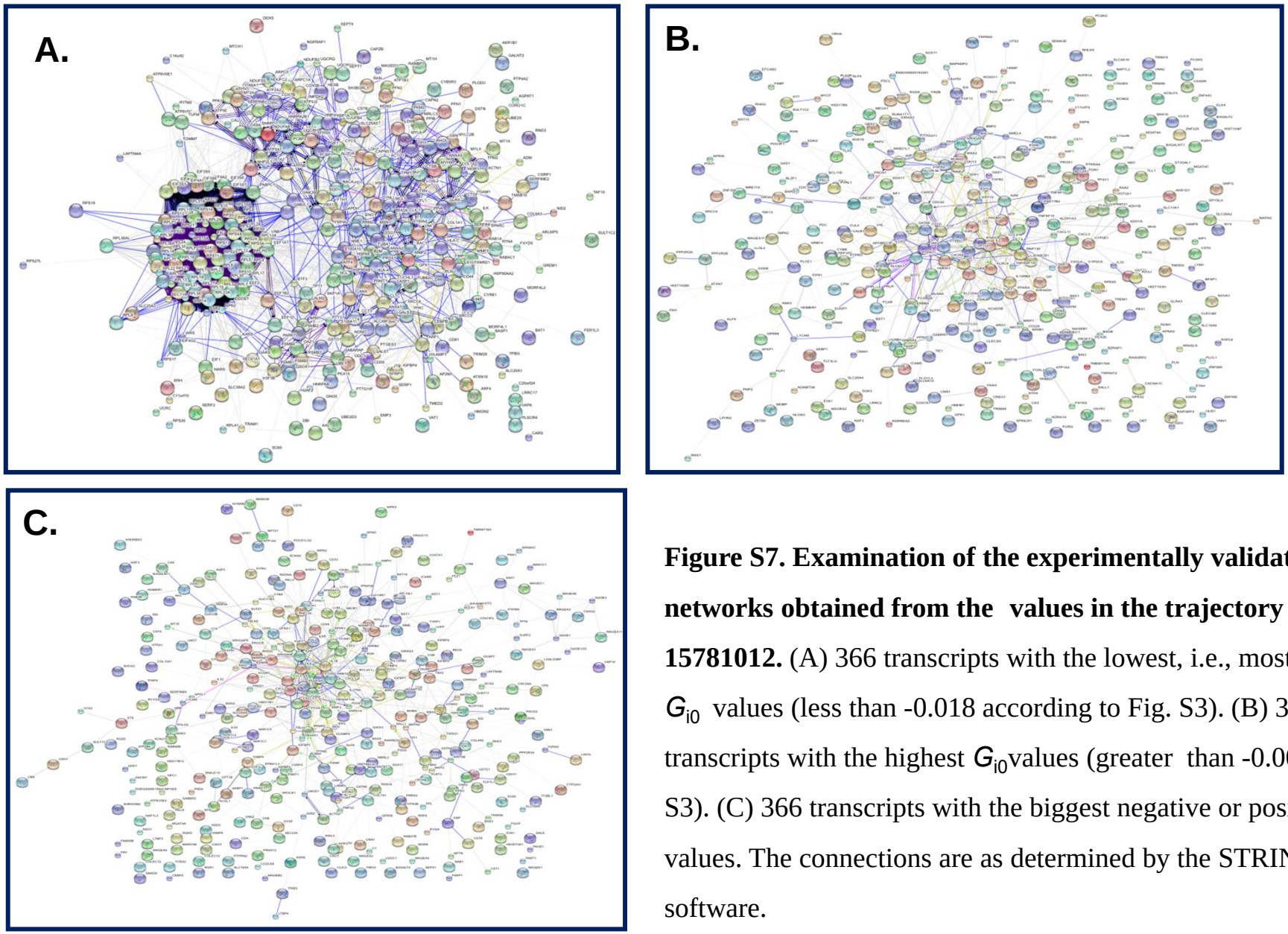


Figure S7. Examination of the experimentally validated networks obtained from the values in the trajectory 15781012. (A) 366 transcripts with the lowest, i.e., most stable, G_{i0} values (less than -0.018 according to Fig. S3). (B) 354 transcripts with the highest G_{i0} values (greater than -0.008, Fig. S3). (C) 366 transcripts with the biggest negative or positive G_{i1} values. The connections are as determined by the STRING software.

Figure S8

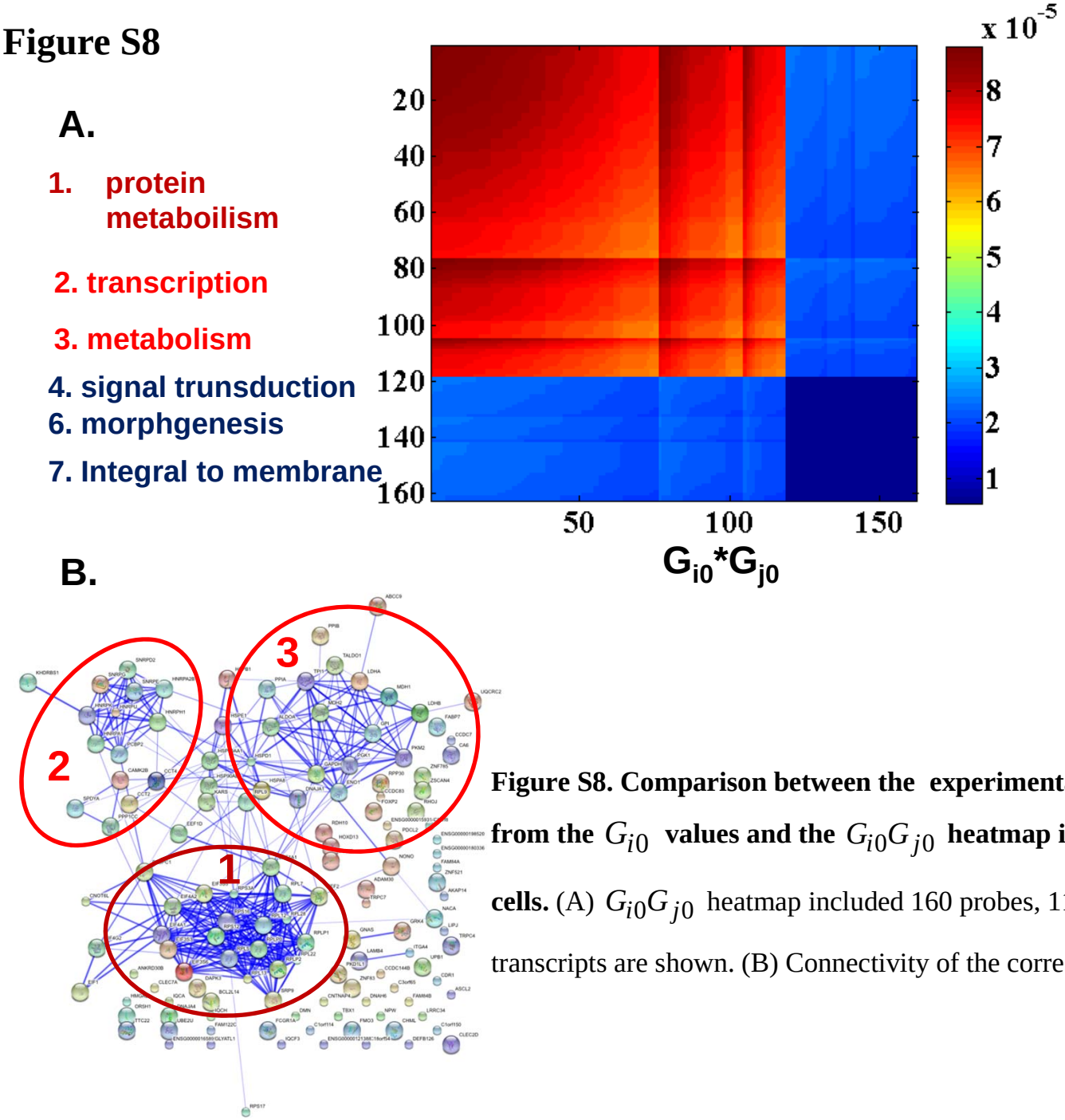
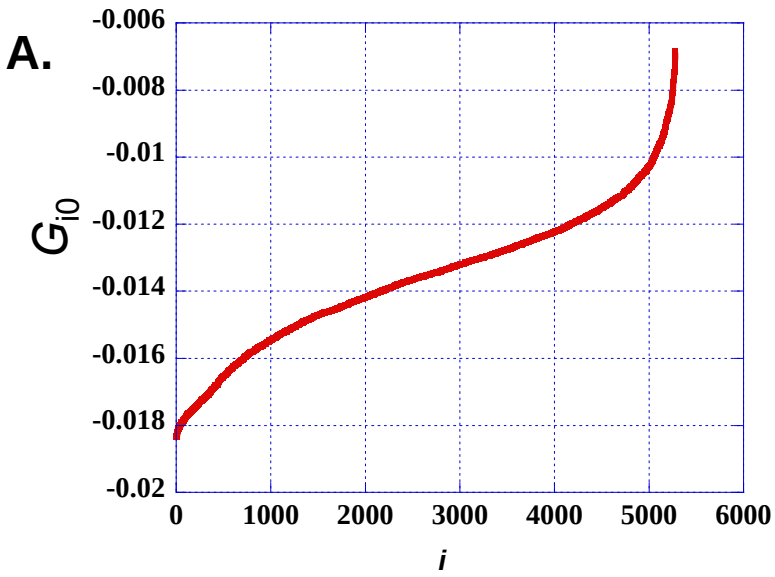
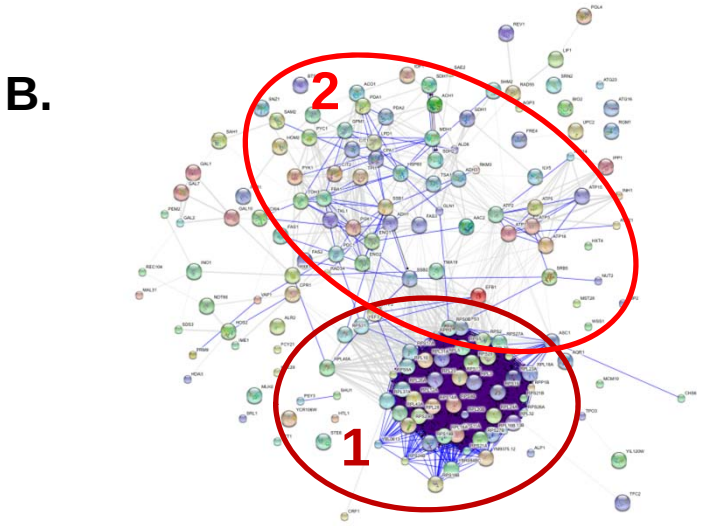


Figure S8. Comparison between the experimentally proved structure obtained from the G_{i0} values and the $G_{i0}G_{j0}$ heatmap in the TGFβ treated lung carcinoma cells. (A) $G_{i0}G_{j0}$ heatmap included 160 probes, 118 most stable and 42 least stable transcripts are shown. (B) Connectivity of the corresponding 160 probes are shown.

Figure S9





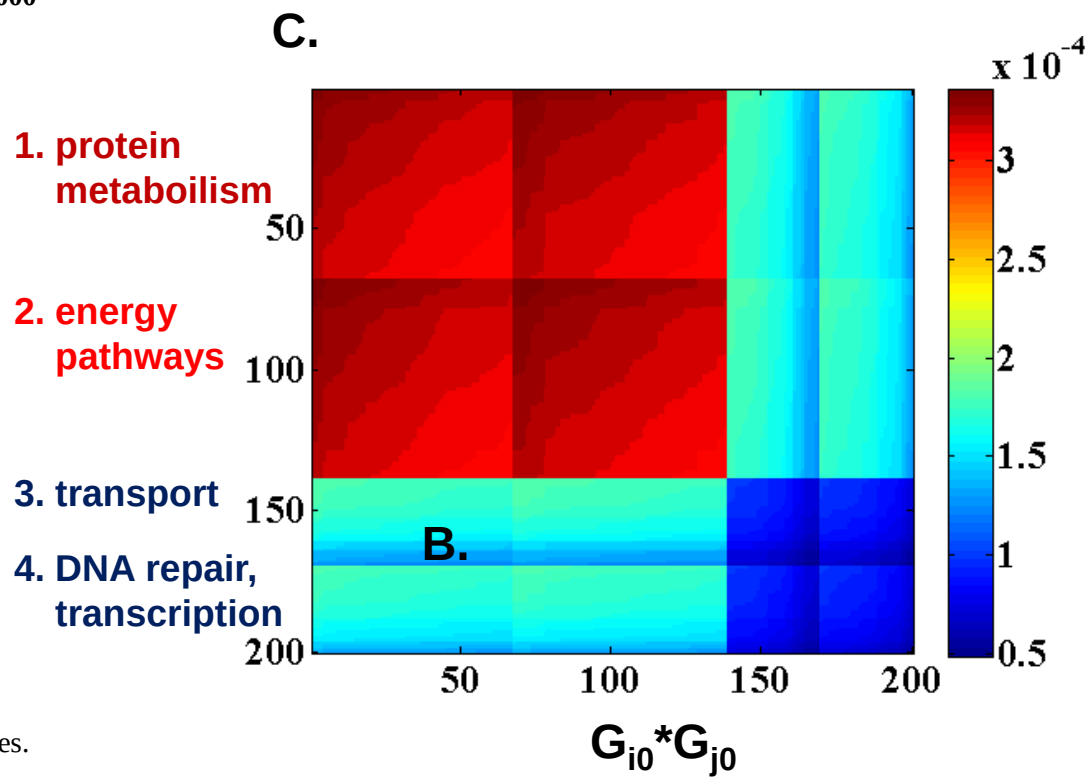


Figure S9. Comparison between the experimentally proved structure obtained from the G_{i0} values and the $G_{i0}G_{j0}$ heatmap in yeast.

(A) G_{i0} distribution (B) Connectivity of the 200 probes, 140 most stable and 60 least stable transcripts are shown. (C) A heatmap of the corresponding values. The transcripts are labeled according to Gene Ontology categories.

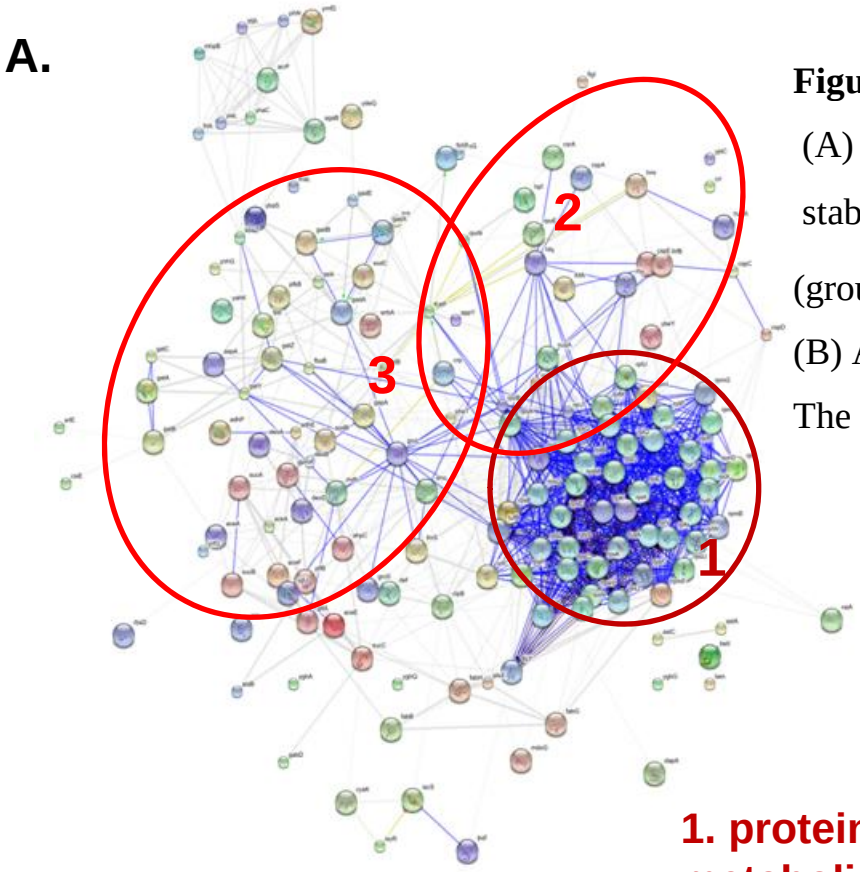


Figure S10. Predicting the connectivity of transcripts in E.Coli.
(A) Connectivity of 220 transcripts, 160 most stable and 60 least stable transcripts are shown. The transcripts with high G_{i0} (groups 4, 5 and 6) are sparsely connected.
(B) A heatmap of the corresponding values.
The transcripts are labeled according to Gene Ontology categories.

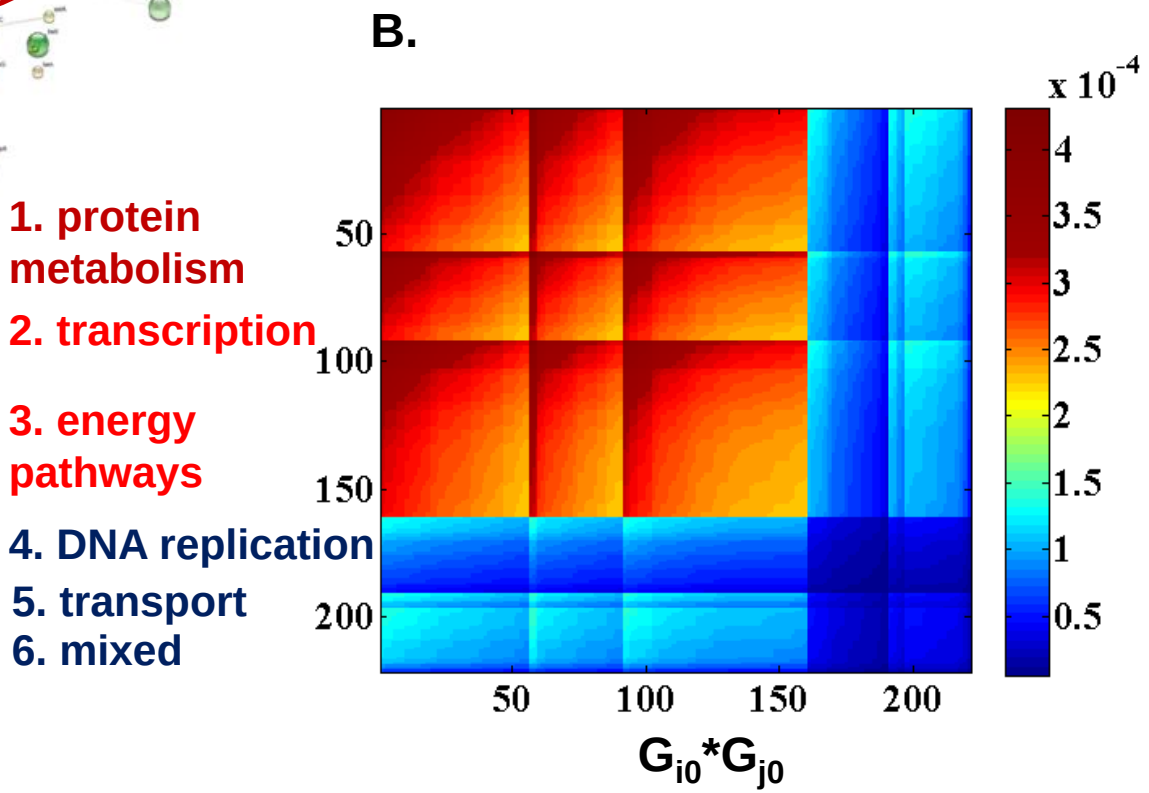


Figure S11

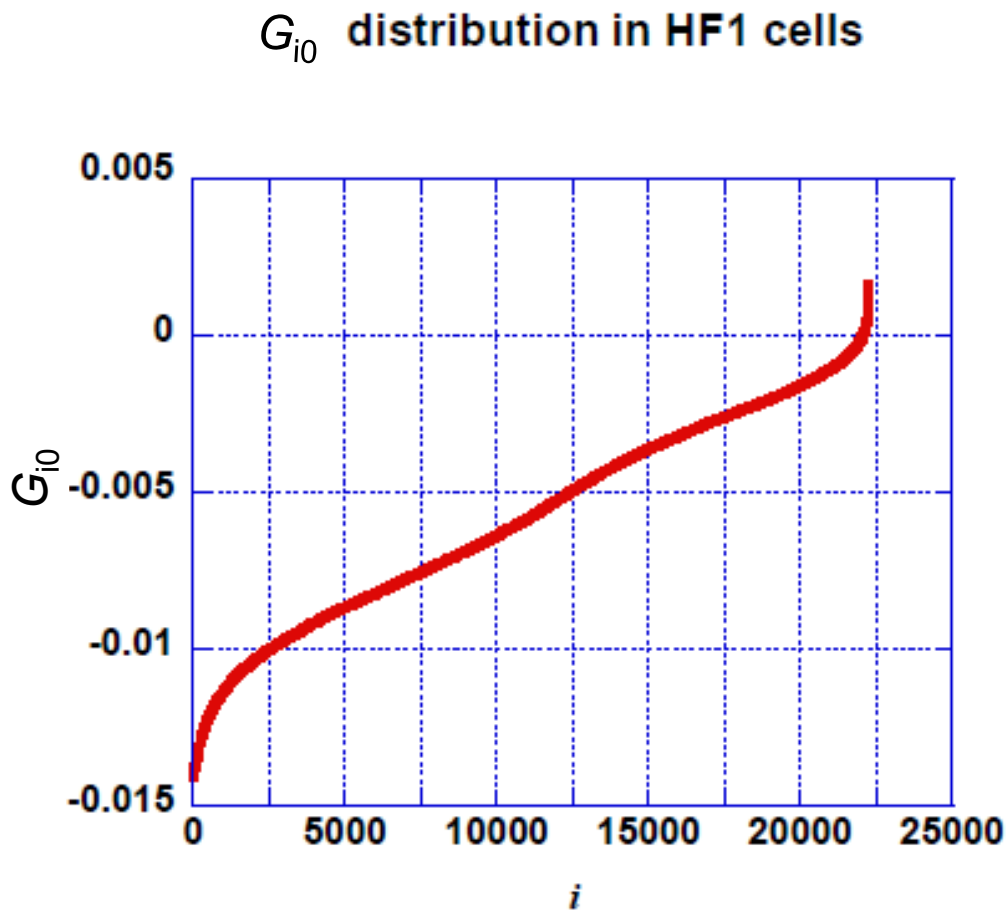


Figure S11. G_{i0} **distribution in the HF1 immortalized cellular model.**

Transcripts with the most negative values strongly contribute to the steady state.

Figure S12

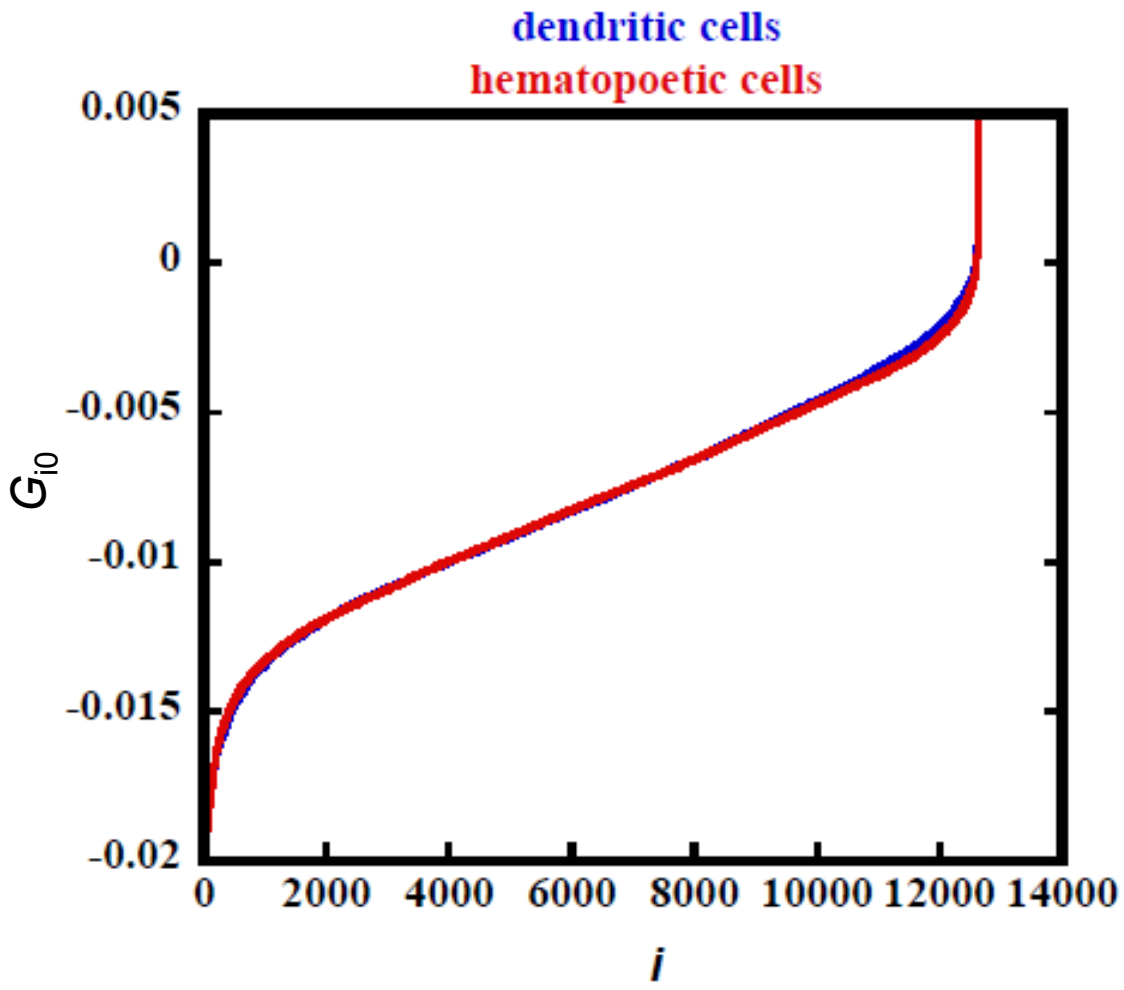


Figure S12. G_{i0} distribution in the dendritic (blue curve)/ hemapoetic (red curve) cells.