The translational buffer: widespread polysomal suppression of transcriptional programs in mammalian cells

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Transcriptome analysis: “molecular portraits”

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Molecular portraits of human breast tumours

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Human breast tumours are diverse in their natural history and in their responsiveness to treatments[1]. Variation in transcriptional programs accounts for much of the biological diversity of human cells and tumours. In each cell, signal transduction and regulatory systems transduce information from the cell's identity to its environmental status, thereby controlling the level of expression of every gene in the genome. Here we have characterized variation in gene expression patterns in a set of 65 surgical specimens of human breast tumours from 42 different individuals, using complementary DNA microarrays representing 8,102 human genes. These patterns provided a distinctive molecular portrait of each tumour. Twenty of the tumours were sampled twice, before and after a 16-week course of doxorubicin chemotherapy, and two tumours were paired with a lymph node metastasis from the same patient. Gene expression patterns in two tumour samples from the same individual were almost always more similar to each other than either was to any other sample. Sets of co-expressed genes were identified for which variation in messenger RNA levels could be related to specific features of physiological variation. The tumours could be classified into subtypes distinguished by pervasive differences in their gene expression patterns.

We proposed that the phenotypic diversity of breast tumours might be accompanied by a corresponding diversity in gene expression patterns that we could capture using cDNA microarrays. Systematic investigation of gene expression patterns in human breast tumours might then provide the basis for an improved molecular taxonomy of breast cancers. We analysed gene expression patterns in grossly dissected normal or malignant human breast tissues from 42 individuals (36 infiltrating ductal carcinomas, 2 lobular carcinomas, 1 ductal carcinoma *in situ*, 1 fibroadenoma and 3 normal breast samples). Fluorescently labelled (Cy5) cDNA was prepared from mRNA from each experimental sample. We prepared cDNA, labelled using a second distinguishable fluorescent nucleotide (Cy3), from a pool of mRNAs isolated from 11 different

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Transcriptome analysis in signature discovery

- Judget an unbiased way of identifying differentially expressed genes by competitive and non-competitive comparisons
- Definition of potential **single gene markers** and **gene signatures**
- Potentially applicable to **cancer**, **multifactorial diseases**, **rare diseases**
- Few success cases
- Instability of signatures in oncology attributed to technical error, biological diversity, platform diversity
- *Is it the whole story?*

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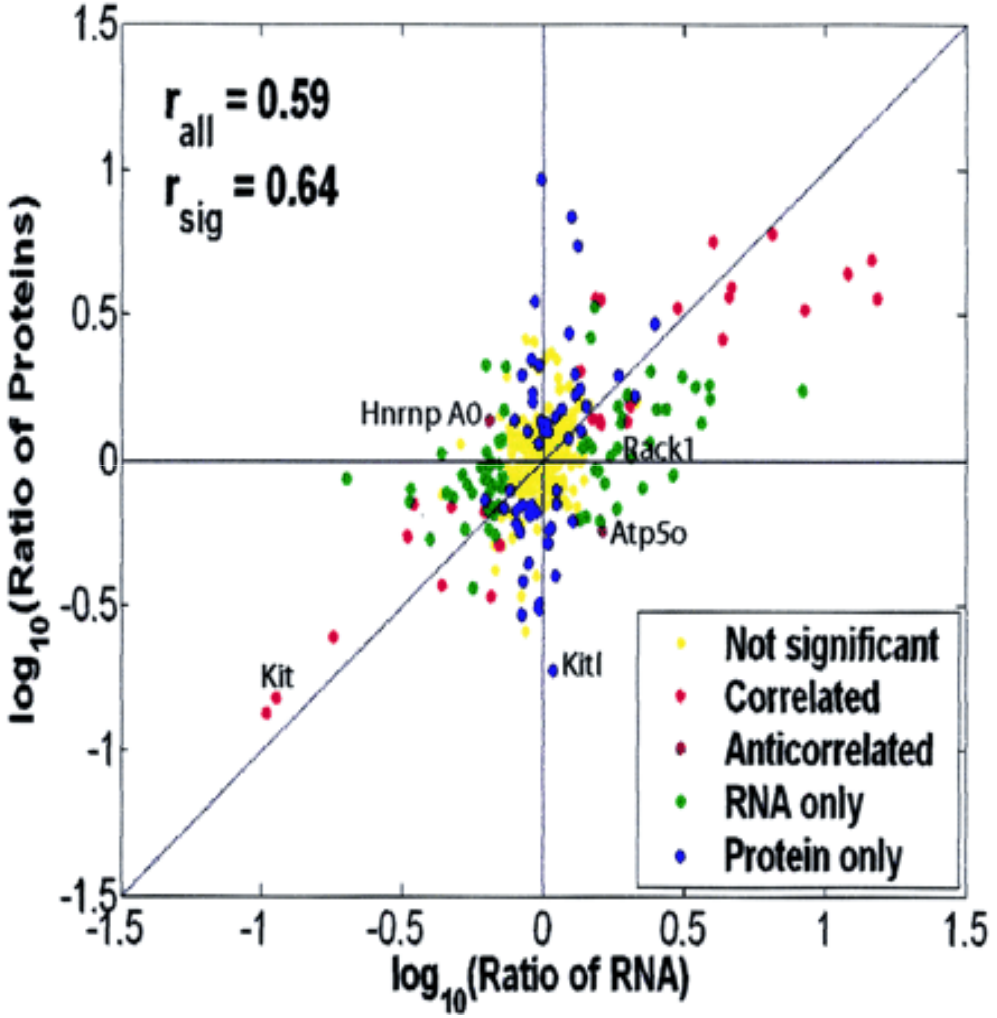
1.
Prologue:
what we are speaking of

Transcriptome/proteome early correlation studies

Myeloid differentiation (murine cell lines)



The differential expression of mRNA (up or down) can capture at most <u>40%</u> of the variation of protein expression

Tian et al., *Mol Cell Proteomics* 3:960, 2004

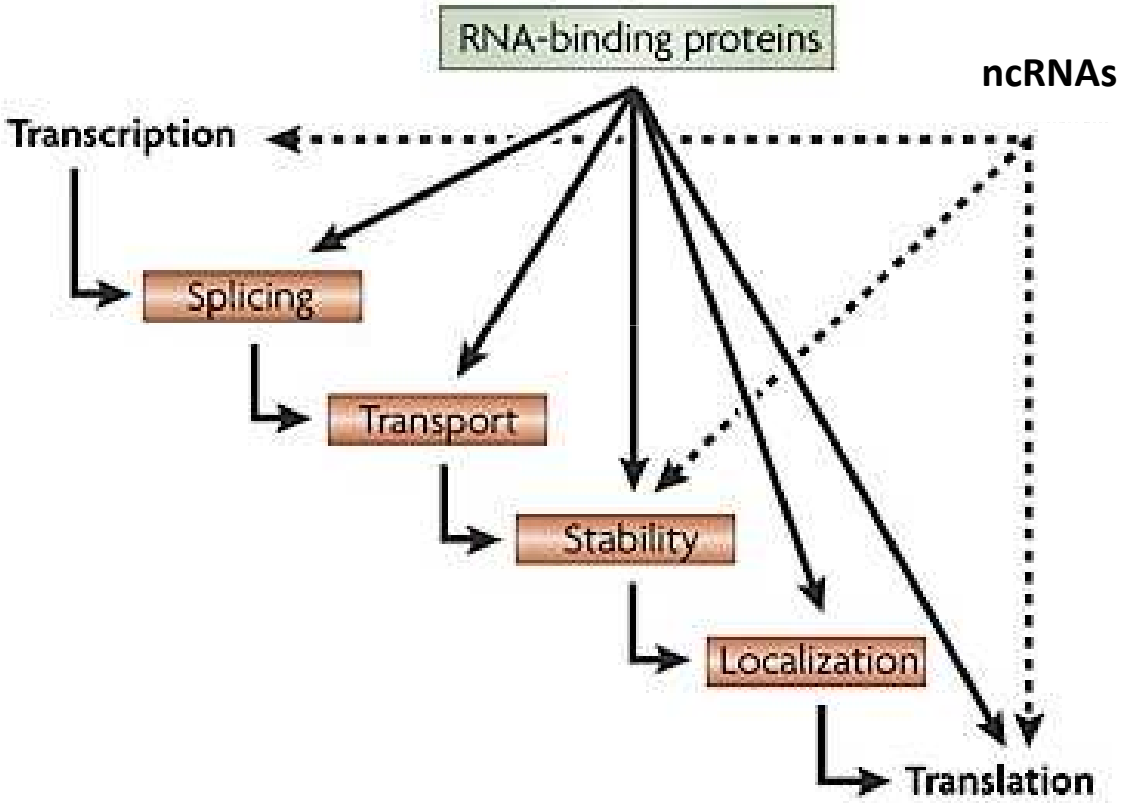
Transcriptome/proteome early correlation studies

CORRELATION COEFFICIENT	COMPARISON	AUTHOR	REFERENCE
r = 0.59	murine myeloid differentiation (cell lines)	Tian *et al.*	Mol Cell Proteomics 3:960, 2004
r = 0.66 nucleolus (r = 0.8) cell periphery (r = 0.74) mitochondria (r = 0.42) cell cycle (r = 0.71) cell rescue (r = 0.45)	yeast (various perturbations)	Greenbaum *et al.*	Genome Biology 4:117, 2003
r = 0,48	human liver/kidney	Anderson & Seilhamer	Electrophoresis 18:533, 1997

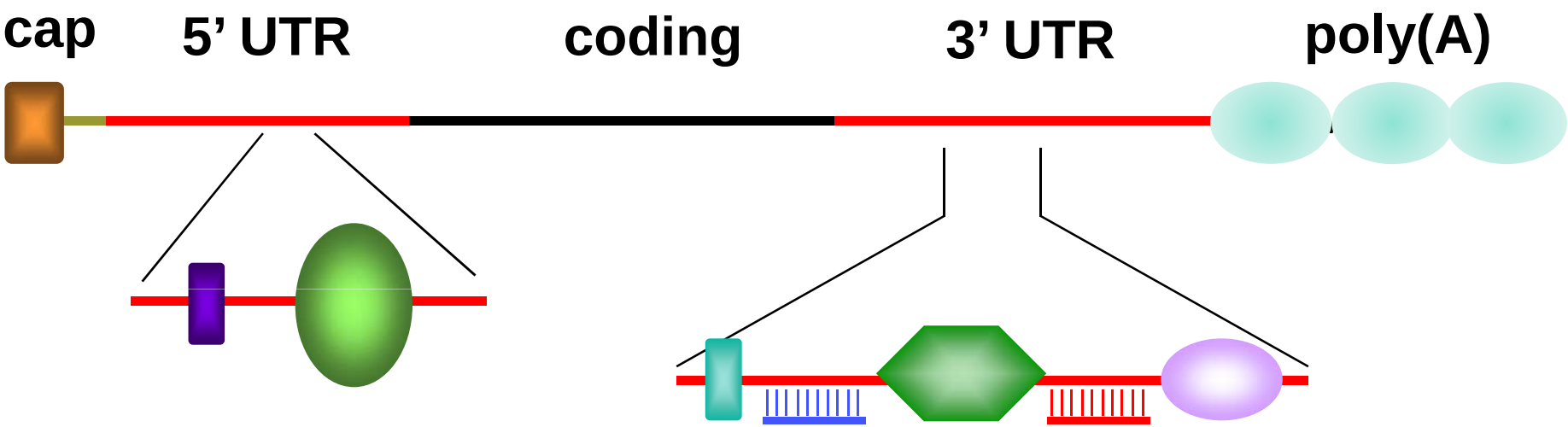
mRNA fate: determinants

mRNA possible fates:

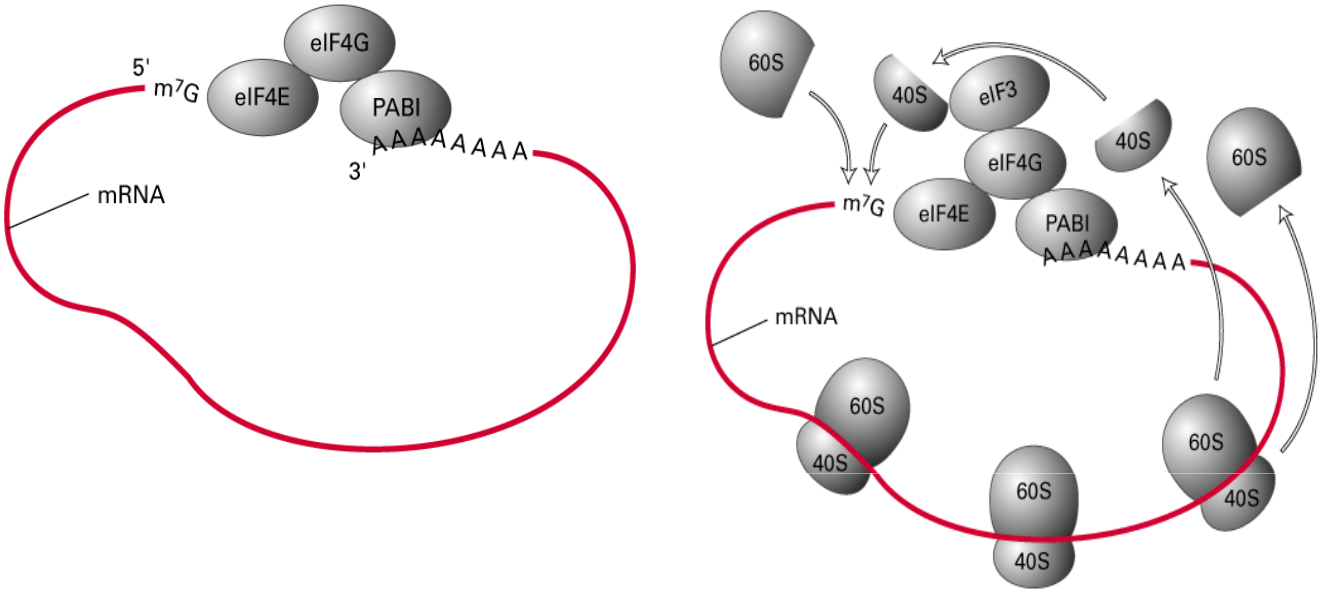
1. translation
2. degradation
3. silent storage

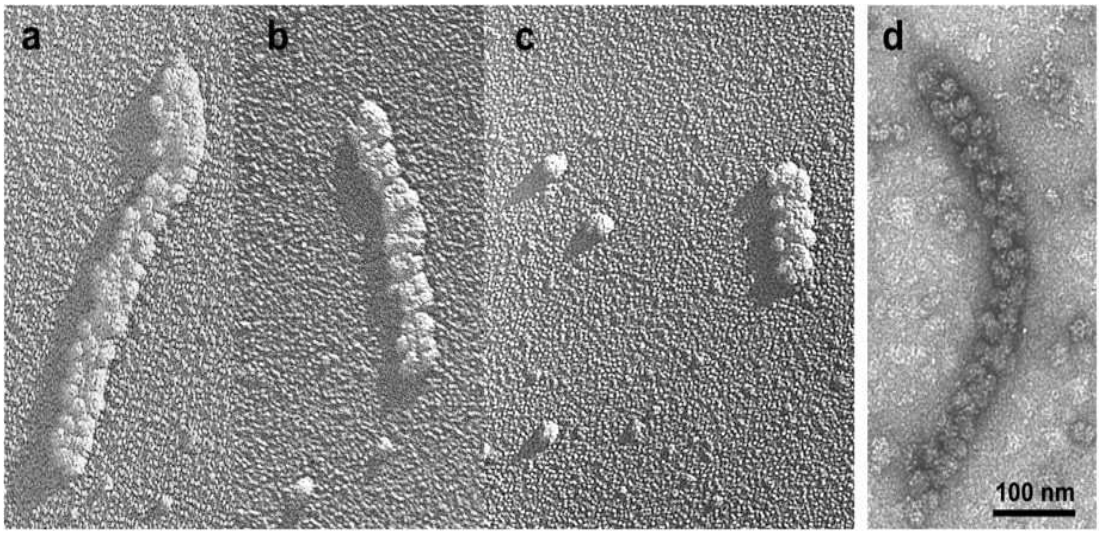


mRNA fate: determinants

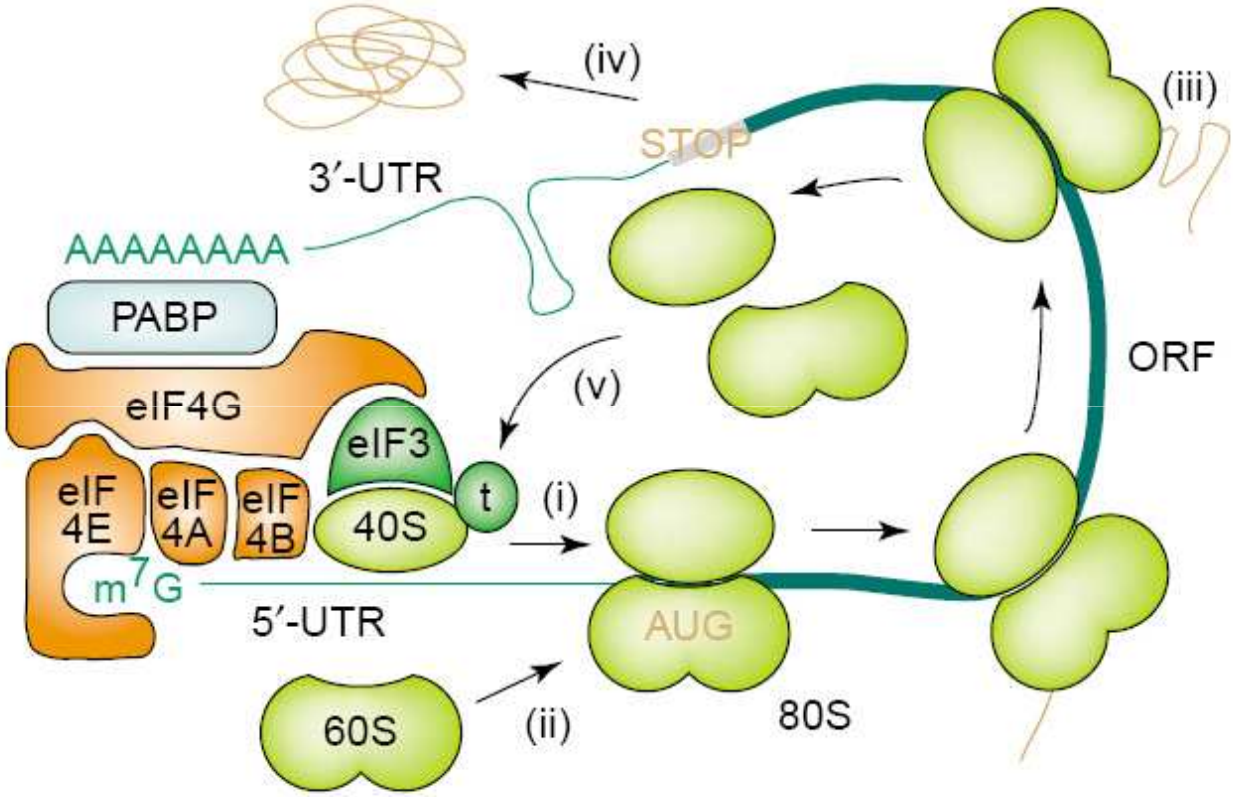


Polysomes or polyribosomes



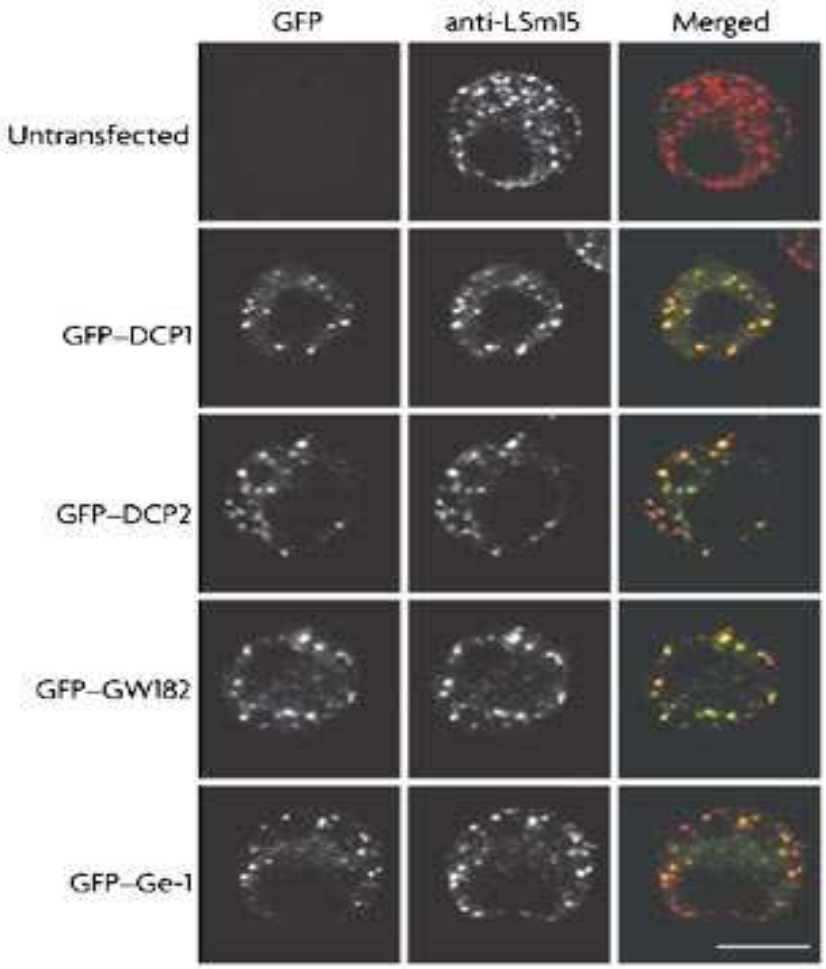


Polyribosomes



Mazumder *et al., Trends Biochem. Sci. 28:91, 2003*

P-bodies



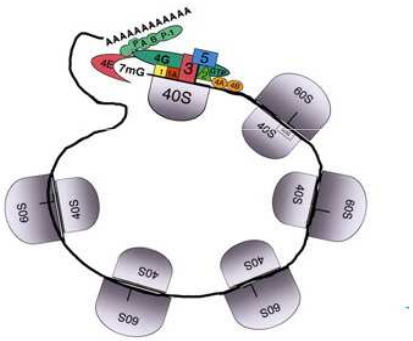
✓ discrete cytoplasmic domains where proteins involved in mRNA degradation, translational repression, mRNA surveillance and RNA-mediated gene silencing colocalize with their mRNA targets.

✓ phisical connection between post-transcriptional processes.

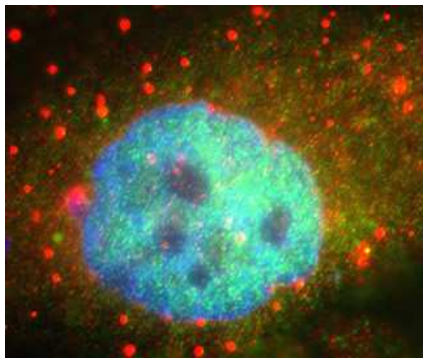
Eulalio *et al*., *Nature Rev. Mol. Cell Biol.* **8:**9, 2007

fate of cytoplasmic mRNA

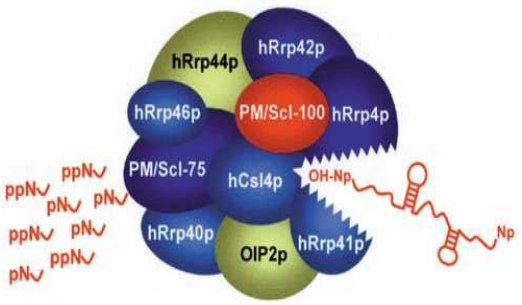
polysomes



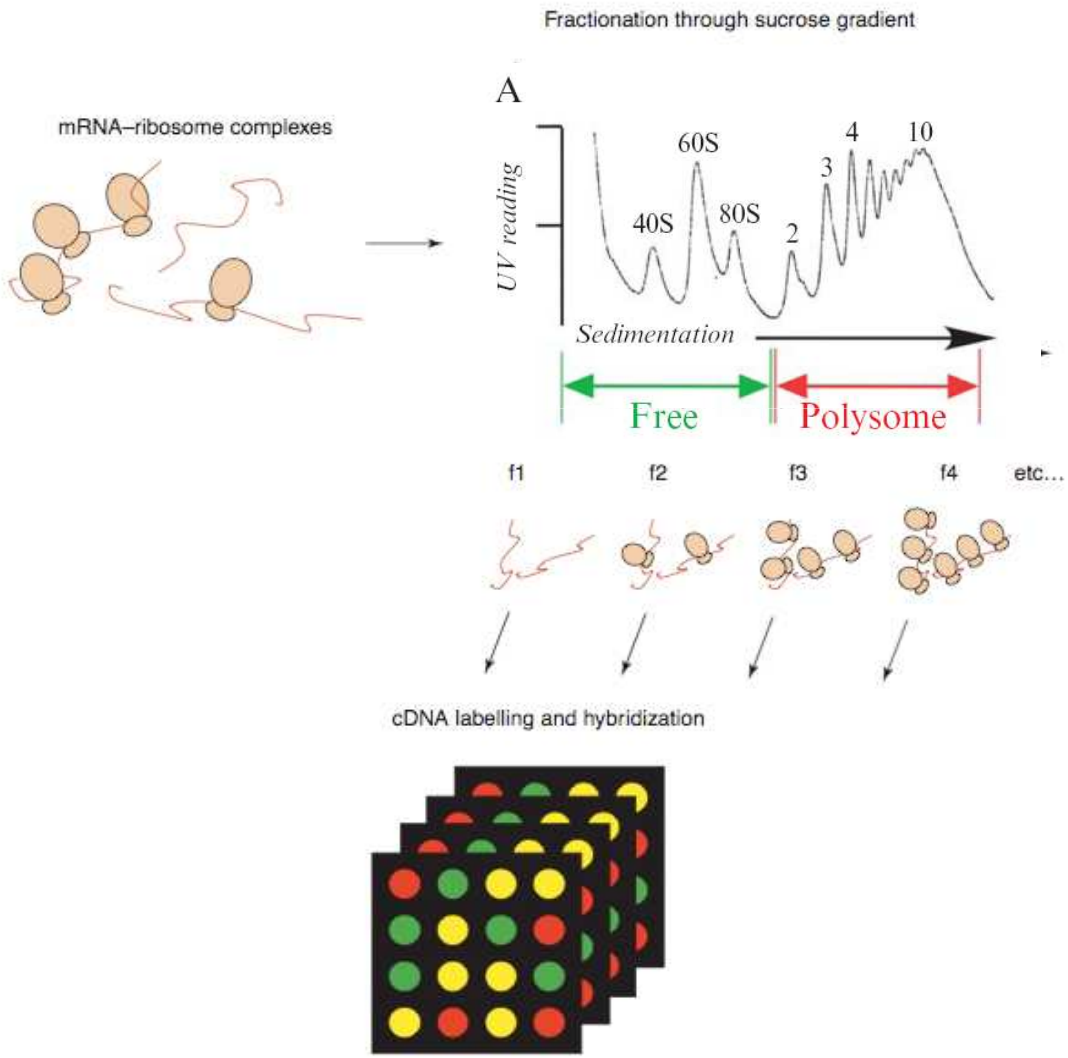
P-bodies/other granules



exosomes



Polysomal profiling



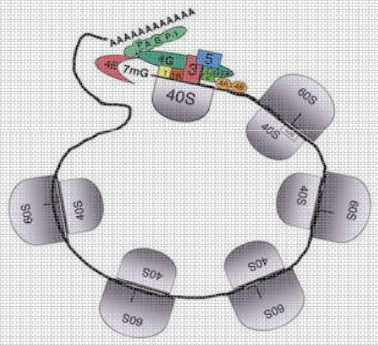
Fractionation of mRNA/ ribosomal complexes through sucrose gradient centrifugation.

✓ inefficiently translated fractions (corresponding to monosomes, free mRNAs and ribosomal subunits). *Sub-polysomal mRNA*

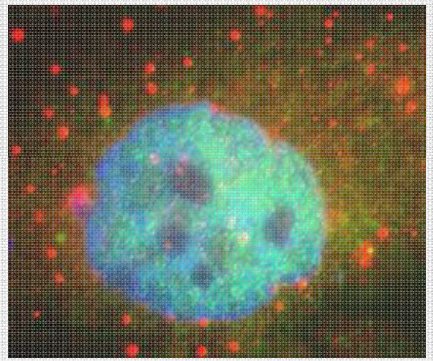
✓ efficiently translated fractions (corresponding to polysomes). *Polysomal mRNA*

Total mRNA profiling

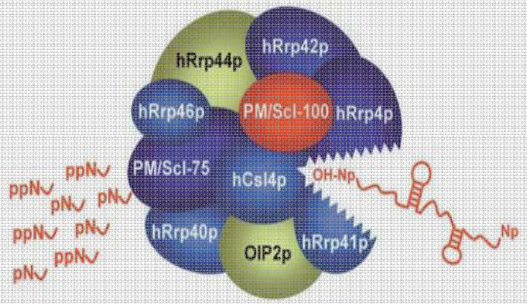
polysomes



P-bodies/other granules

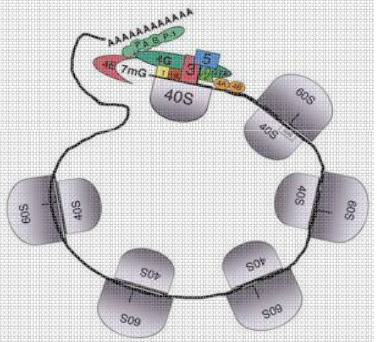


exosomes

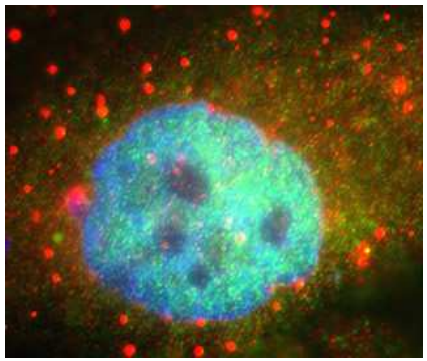


Polysomal mRNA profiling

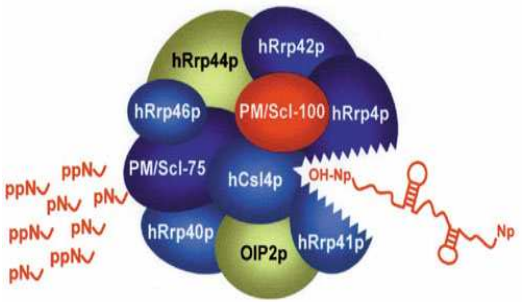
polysomes



P-bodies/other granules

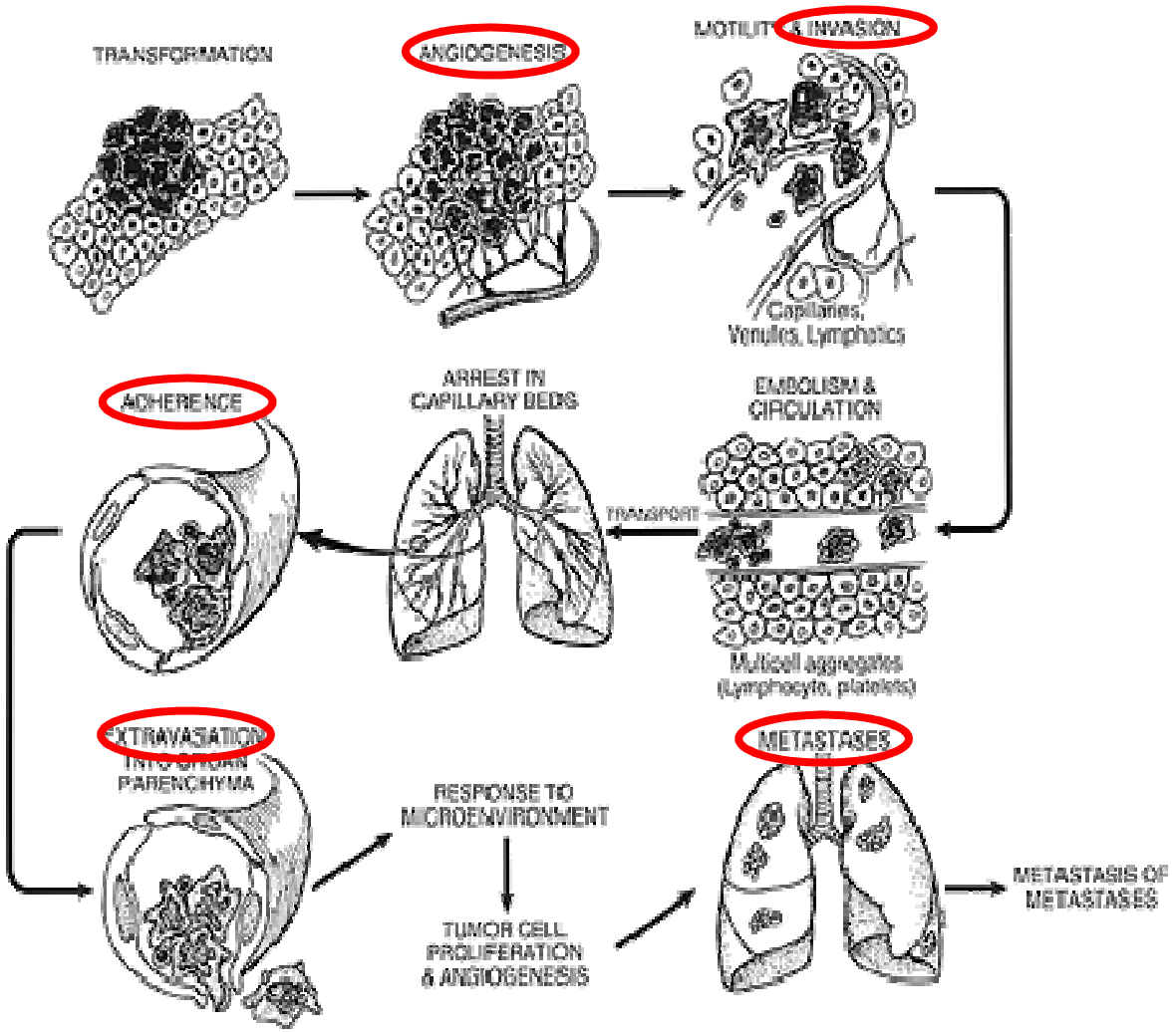


exosomes

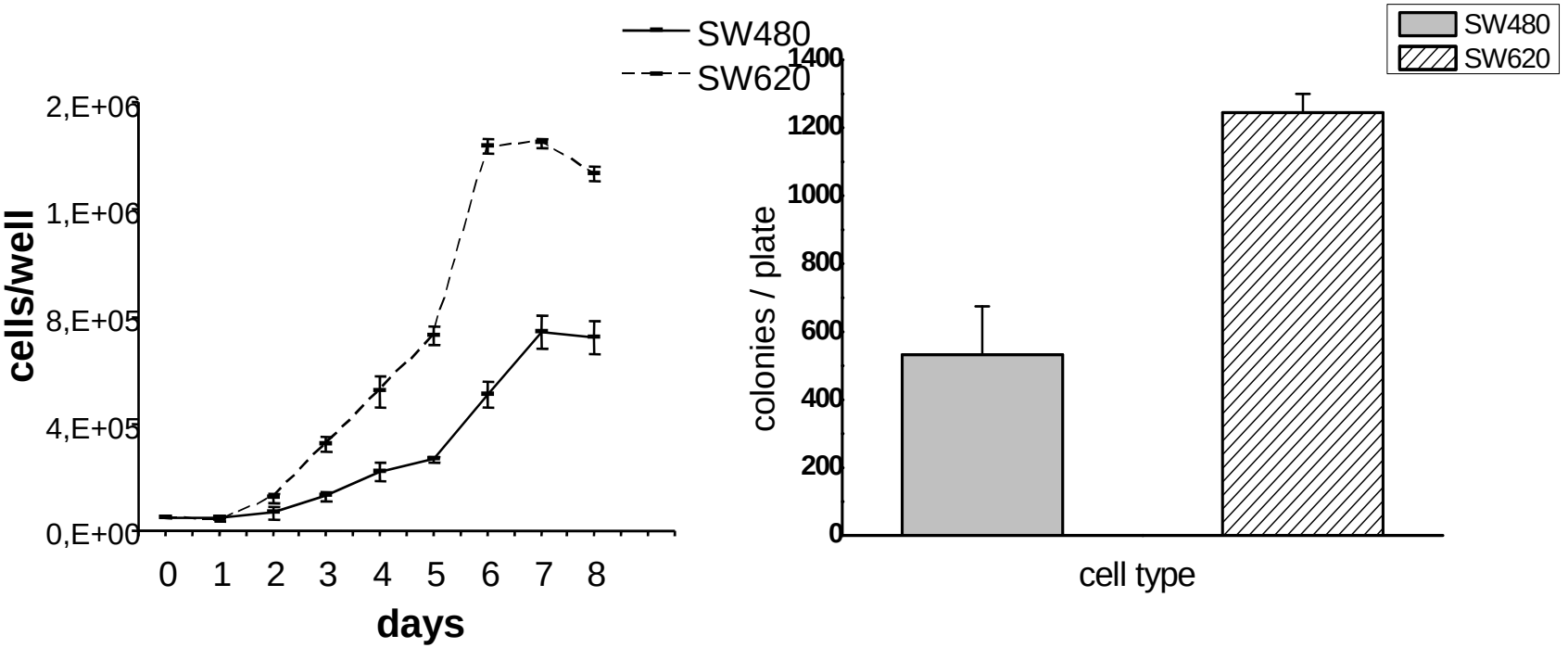


2.
A case:
combined molecular profiling of metastatic *vs* primary colorectal cancer cells

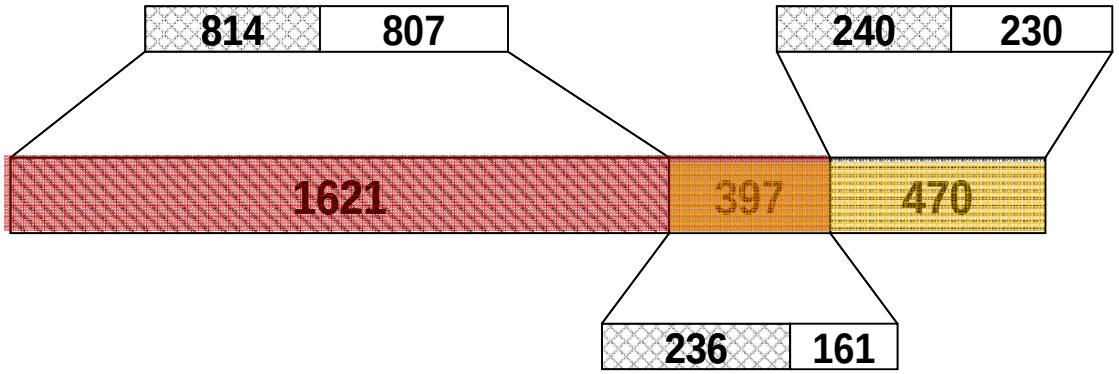
Metastasis


TRANSFORMATION
ANGIOGENESIS
MOTILITY & INVASION
Capillaries,
Venules, Lymphatics
EMBOLISM &
CIRCULATION
Multicell aggregates
(Lymphocyte, platelets)
TRANSPORT
ARREST IN
CAPILLARY BEDS
ADHERENCE
EXTRAVASATION
INTO SPECIFIC
PARENCHYMA
RESPONSE TO
MICROENVIRONMENT
TUMOR CELL
PROLIFERATION
& ANGIOGENESIS
METASTASES
METASTASIS OF
METASTASES

Phenotypic differences



Total to polysomal mRNA profiling



mRNAs in Total RNA

mRNAs in Polysomal RNA

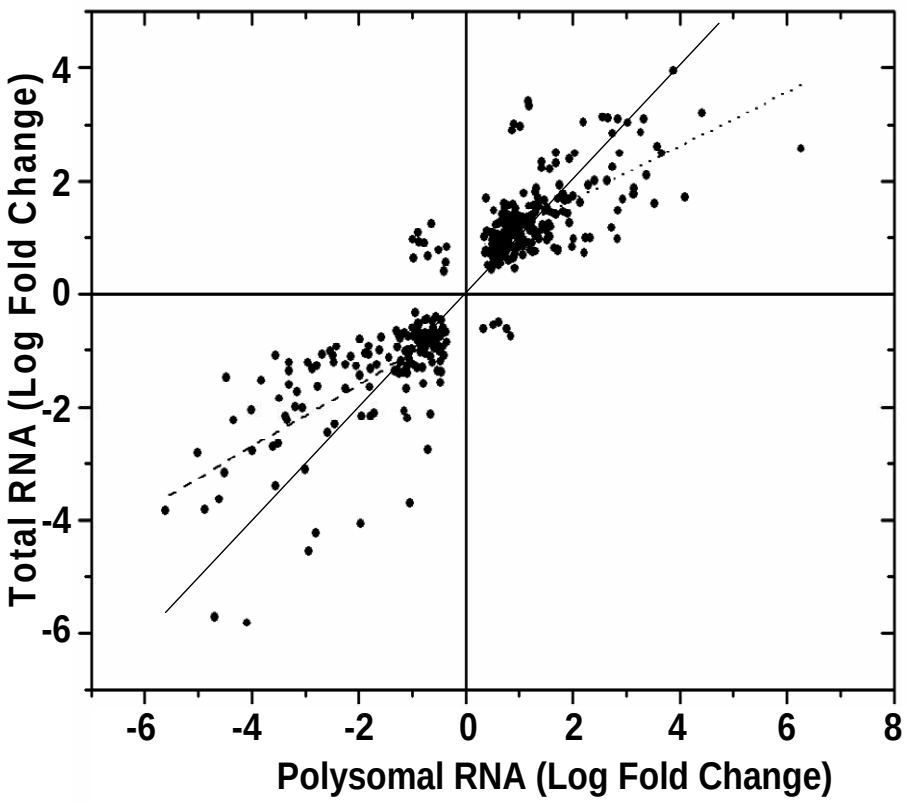
Common mRNAs

Up-regulated mRNAs

Down-regulated mRNAs

2018/867 = 2.5 : 1

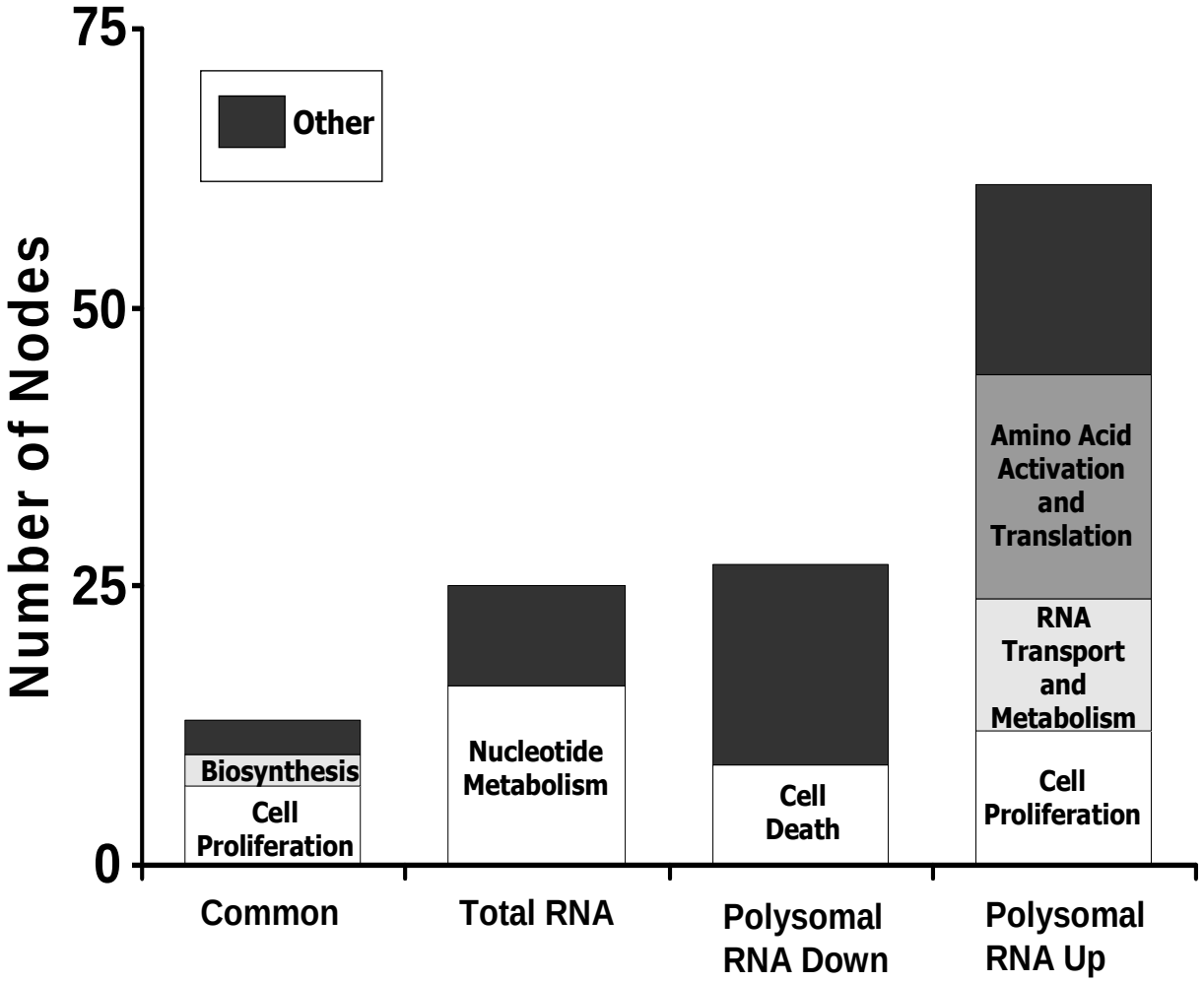
Commonly regulated genes



Genes
Fit on increased Genes
m=0.4742
r=0.63
p<0.0001
Fit on decreased Genes
m=0.5514
r=0.69
p<0.0001

Magnification: 4-fold

Ontologization: wrong information?



Many cases:
comparative analysis of total and polysomal mRNA profiles

Dataset collection

ID	Short name	Biological source	Perturbation type	Description	Ref.
9	starv.release.Mm	Mus musculus	environmental perturbation	Starvation release: data from primary mouse embryonic fibroblasts (MEF) early in response to serum (2h).	(Kenzelmann2007)
10a	LPS.Mm.1h	Mus musculus	environmental perturbation	LPS treatment (1h-0h): mouse macrophage cell line J774.1 before and after LPS stimulation	(Kitamura2008)
10b	LPS.Mm.2h	Mus musculus	environmental perturbation	LPS treatment (2h-0h): mouse macrophage cell line J774.1 before and after LPS stimulation	(Kitamura2008)
10c	LPS.Mm.4h	Mus musculus	environmental perturbation	LPS treatment (4h-0h): mouse macrophage cell line J774.1 before and after LPS stimulation	(Kitamura2008)
11	muscle.contr.Rn	Rattus norvegicus	environmental perturbation	Muscle contractions: response of rat muscle to acute resistance exercise (skeletal muscle hypertrophy)	(Chen2002)
13	carc.progr.Hs	Homo sapiens	genomic rearrangement	Carcinoma progression: comparison between colon cancer cell lines SW480, from primary cancer, and SW620, from lymphonode metastatic sites.	(Provenzani2006)
14	eIF4e.overexpr.Hs	Homo sapiens	genomic rearrangement	eIF4E overexpression: simulation of cancer translational deregulation by overexpression of eIF4E in primary human mammary epithelial cells.	(Larsson2007)
15	eIF4GI.depl.Hs	Homo sapiens	genomic rearrangement	eIF4GI depletion: comparison between control and eIF4GI silenced human immortalized breast epithelial cells MCF10A.	(Ramirez-Valle2008)
16	v-Ki-ras.transf.Hs	Homo sapiens	genomic rearrangement	v-Ki-ras transformation: identification of mRNAs under differential translational control in Ki-ras transformed 267B1 cells as compared to the parental cell line.	(Spence2006)
17a	hepat.diff.Hs	Homo sapiens	ontogenetic/homeostatic program	hepatocytic differentiation: comparison of transcriptional and translational regulation upon hepatocytic diffentiation	(Parent2008)
17b	mTOR.act.Hs.b	Homo sapiens	genomic rearrangement	hepatocytic proliferative cells: comparison between WT and. mTOR activated	(Parent2007)
17c	mTOR.act.Hs.c	Homo sapiens	genomic rearrangement	hepatocytic differentiated cells: comparison between WT and mTOR activated	(Parent2007)
17d	mTOR.act.Hs.d	Homo sapiens	ontogenetic/homeostatic program	hepatocytic mTOR activated cells: comparison between proliferative and differentiated	(Parent2007)
18a	testis.diff.Mm.17-22	Mus musculus	ontogenetic/homeostatic program	testis differentiation 17d-22d: analysis of testes from prepuberal and adult mice to characterize the translation state as spermatogenesis proceeds.	(Iguchi2006)
18b	testis.diff.Mm.17-70	Mus musculus	ontogenetic/homeostatic program	testis differentiation 17d-70d: analysis of testes from prepuberal and adult mice to characterize the translation state as spermatogenesis proceeds.	(Iguchi2006)
18c	testis.diff.Mm.22-70	Mus musculus	ontogenetic/homeostatic program	testis differentiation 22d-70d: analysis of testes from prepuberal and adult mice to characterize the translation state as spermatogenesis proceeds.	(Iguchi2006)
19	stem.cell.diff.Mm	Mus musculus	ontogenetic/homeostatic program	stem cell differentiation: comparison between embryonic stem cells (ESC) maintained in an undifferentiated state and day-5 Embryoid bodies (EB)	(Sampath2008)
20a	lung.diff.Rn.19-22	Rattus norvegicus	ontogenetic/homeostatic program	lungs differentiation FD19-FD22: expression data from perinatal rat lung to identify pre- or postnatally changes.	(Otulakowski2009)
20b	lung.diff.Rn.19-1	Rattus norvegicus	ontogenetic/homeostatic program	lungs differentiation FD19-P1: expression data from perinatal rat lung to identify pre- or postnatally changes.	(Otulakowski2009)
20c	lung.diff.Rn.22-1	Rattus norvegicus	ontogenetic/homeostatic program	lungs differentiation FD22-P1: expression data from perinatal rat lung to identify pre- or postnatally changes.	(Otulakowski2009)
21	EPO.release.Mm	Mus musculus	environmental perturbation	erythroid EPO deprivation release: l/11 and R10 erythroid progenitor cells EPO deprived for 4h	(Grech2008)

Data analysis

Expression levels and **fold changes**: Robust Multichip Average algorithm (RMA) from the *Affy package*, Bioconductor.

Significant **differentially expressed genes (DEGs)**: a statistical technique based on calculating gene rank products from replicate experiments, from the *RankProd package* , Bioconductor.

Principal component analysis (PCA): "uncoupling" measure. The first principal component pins down the ideal line on which polysomal and total fold changes are perfectly related. Uncoupling for each gene has been measured as the distance of its fold changes from the first principal component.

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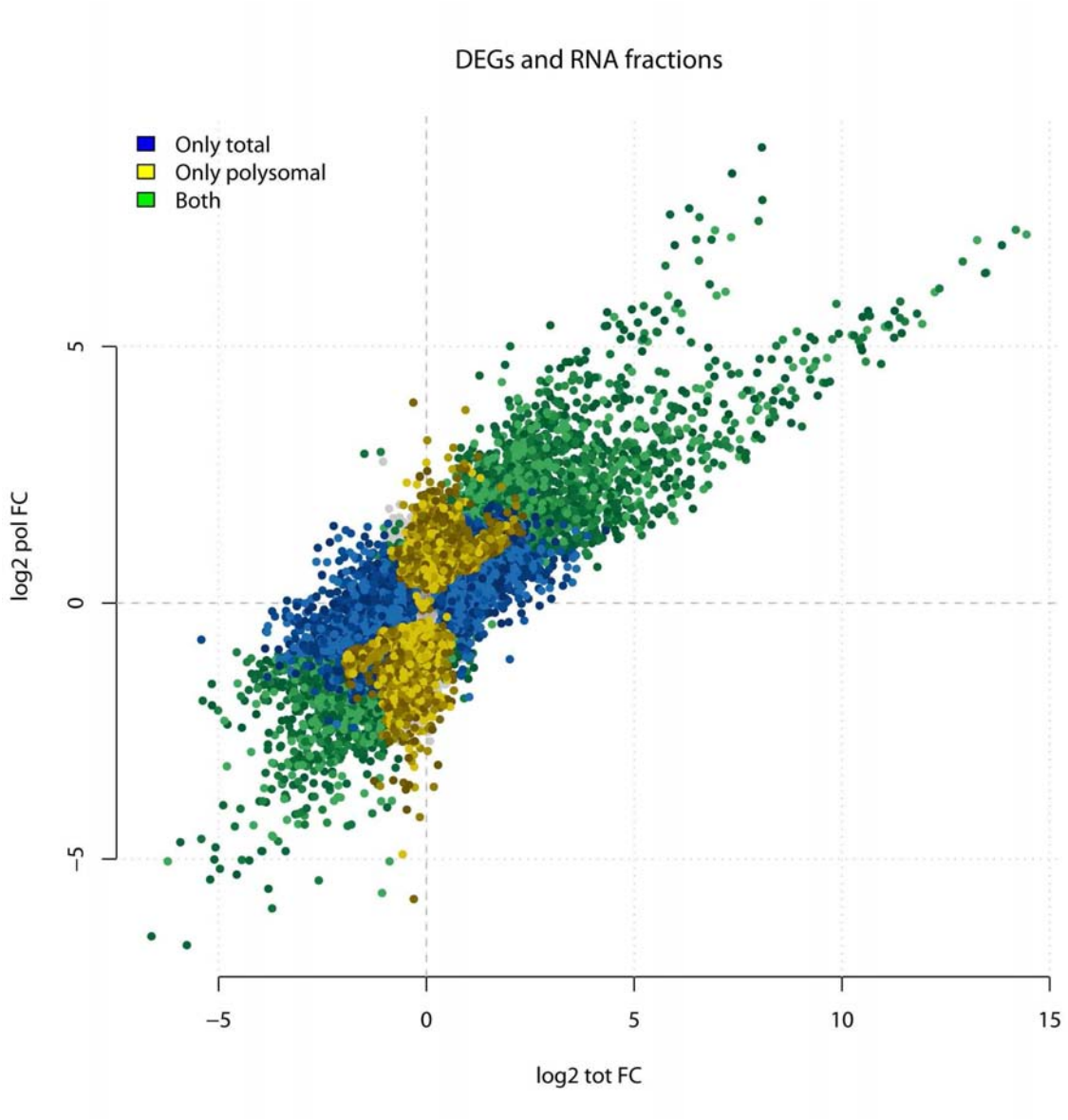
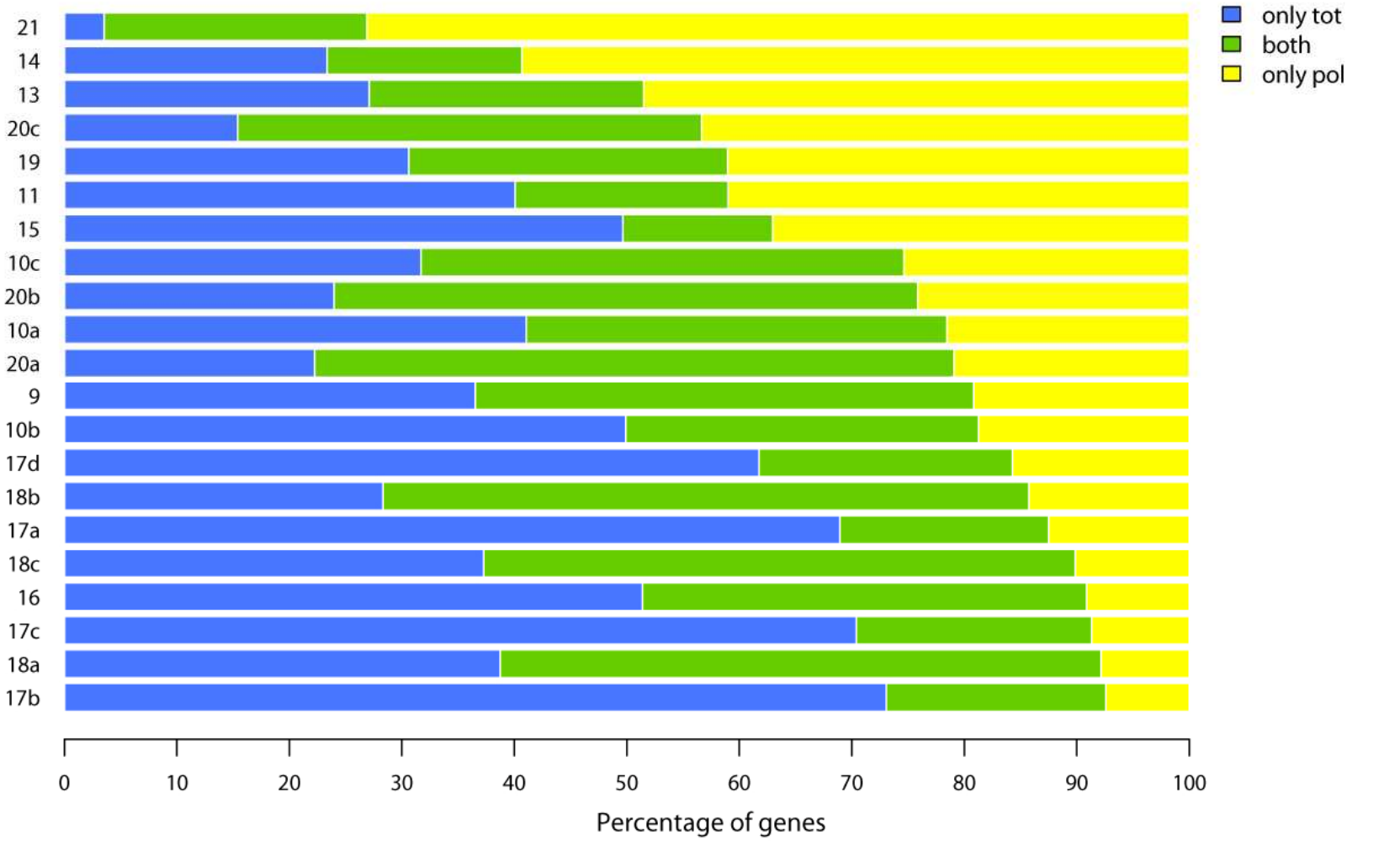
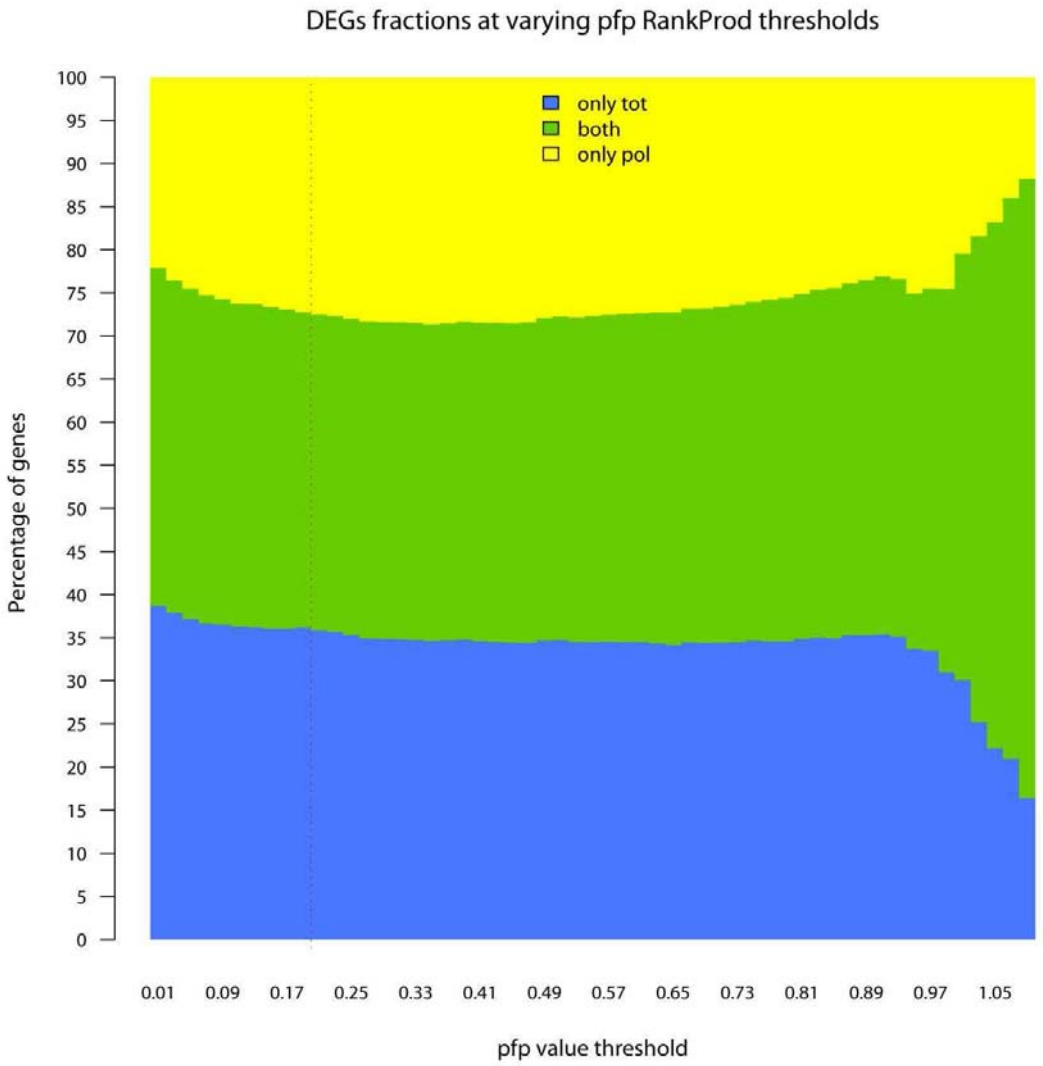
DEGs at the total and polysomal mRNA levels



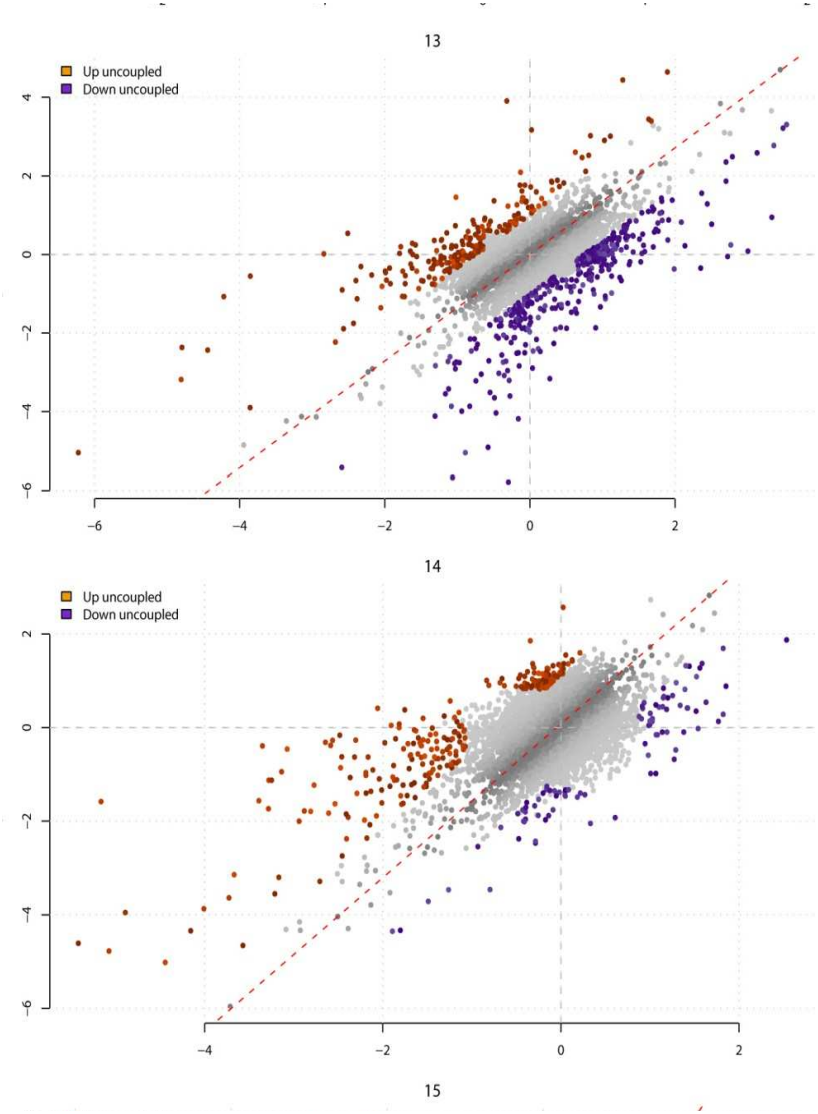
DEGs at the total and polysomal mRNA levels

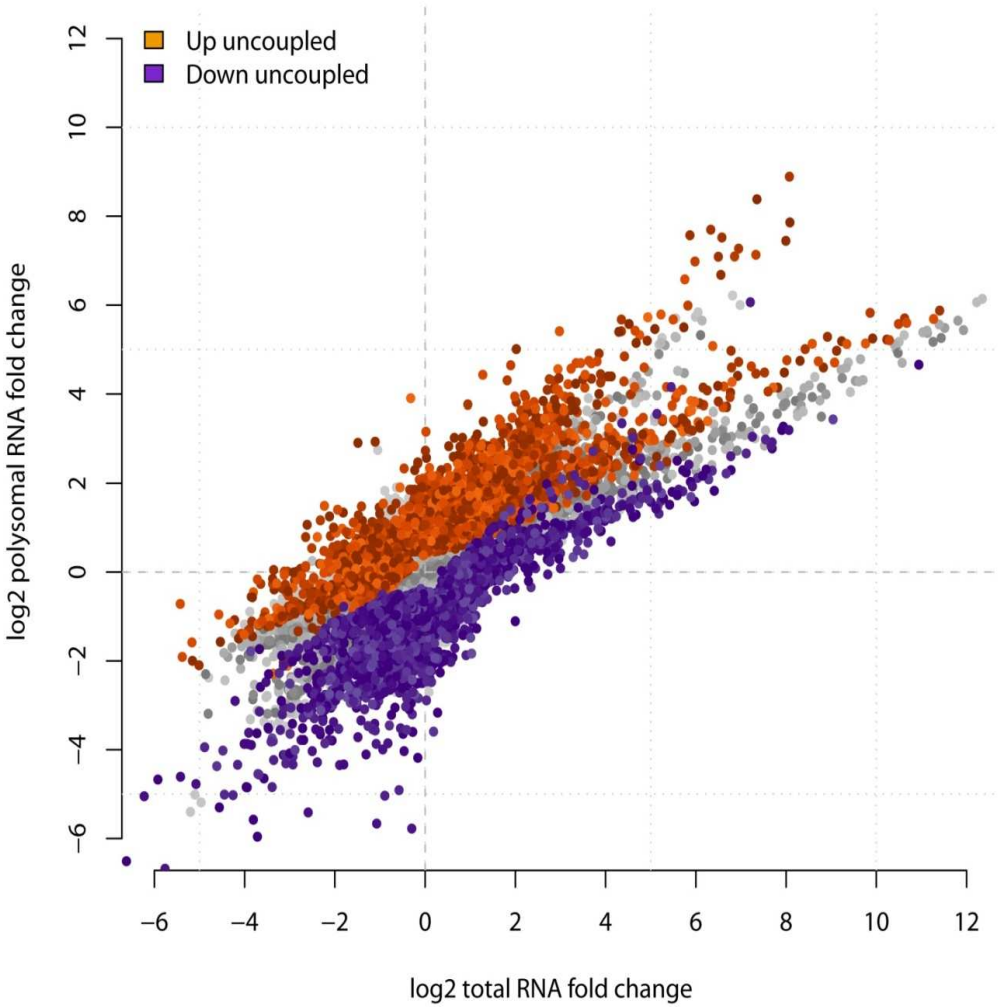


DEGs at the total and polysomal mRNA levels

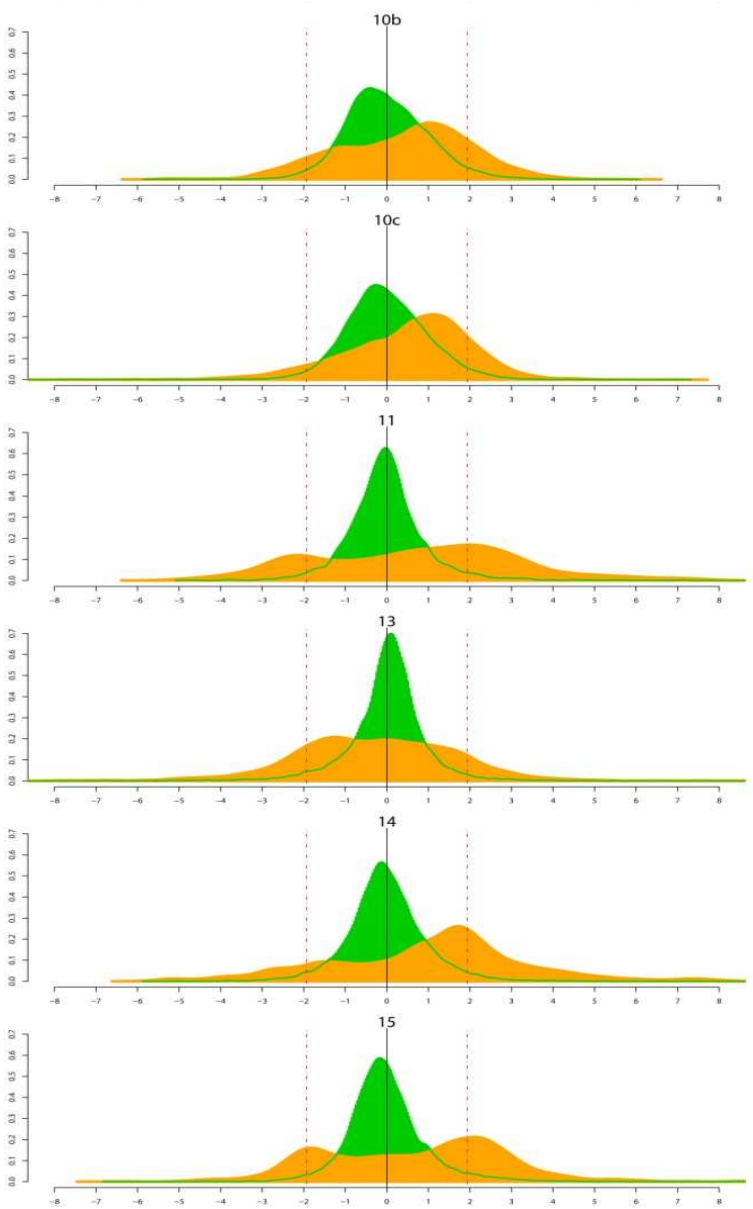


Analysis by PCA





Distribution of uncoupling residuals



Top uncoupled genes

Gene	Description
PDCD6	Programmed cell death protein 6 (Apoptosis-linked gene 2 protein)(Probable calcium-binding protein ALG-2)
DYRK4	Dual specificity tyrosine-phosphorylation-regulated kinase 4 (EC 2.7.12.1)
PRND	Prion-like protein doppel Precursor (PrPLP)(Prion protein 2)
CXCL10	C-X-C motif chemokine 10 Precursor (Small-inducible cytokine B10)(10 kDa interferon-gamma-induced protein)(Gamma-IP10)(IP-10)
NPC2	Epididymal secretory protein E1 Precursor (Niemann-Pick disease type C2 protein)(hE1)
FZD6	Frizzled-6 Precursor (Fz-6)(hFz6)
MT1H	Metallothionein-1H (MT-1H)(Metallothionein-IH)(MT-IH)(Metallothionein-0)(MT-0)
TGFA	Protransforming growth factor alpha Precursor [Contains Transforming growth factor alpha(TGF-alpha)(EGF-like TGF)(ETGF)(TGF type 1)]
FHOD1	FH1/FH2 domain-containing protein 1 (Formin homolog overexpressed in spleen 1)(FHOS)(Formin homology 2 domain-containing protein 1)
SPINK1	Pancreatic secretory trypsin inhibitor Precursor (Serine protease inhibitor Kazal-type 1)(Tumor-associated trypsin inhibitor)(TATI)
SPARC	SPARC Precursor (Secreted protein acidic and rich in cysteine)(Osteonectin)(ON)(Basement-membrane protein 40)(BM-40)
C11orf1	UPF0686 protein C11orf1
IL1F9	Interleukin-1 family member 9 (IL-1F9)(Interleukin-1 homolog 1)(IL-1H1)(Interleukin-1 epsilon)(IL-1 epsilon)(IL-1-related protein 2)(IL-1RP2)
PRDX3	Thioredoxin-dependent peroxide reductase, mitochondrial Precursor (EC 1.11.1.15)(Peroxiredoxin-3)(PRX III)(Antioxidant protein 1)(AOP-1)(Protein MER5 homolog)(HBC189)
TMEM176B	Transmembrane protein 176B (Protein LR8)

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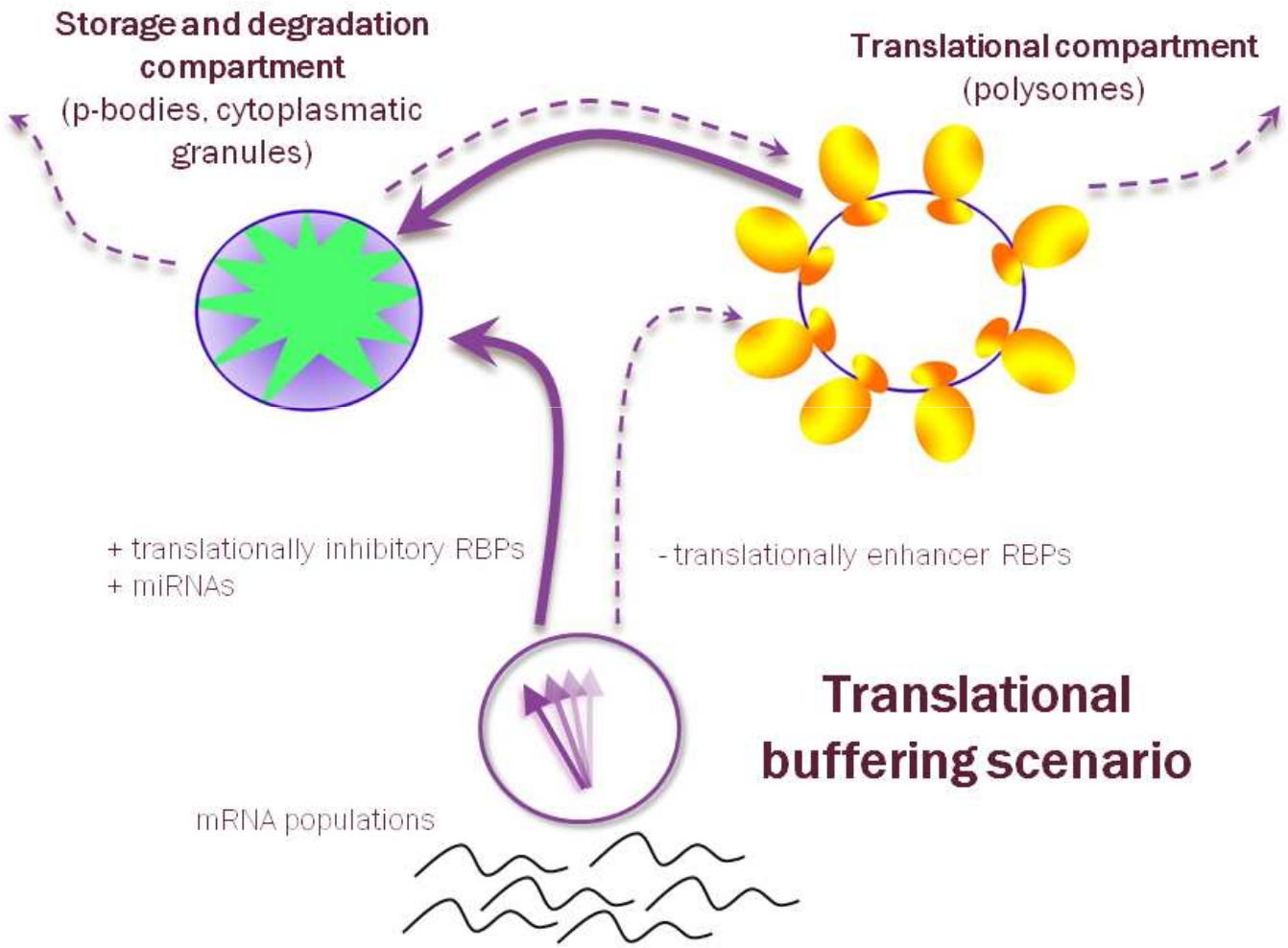
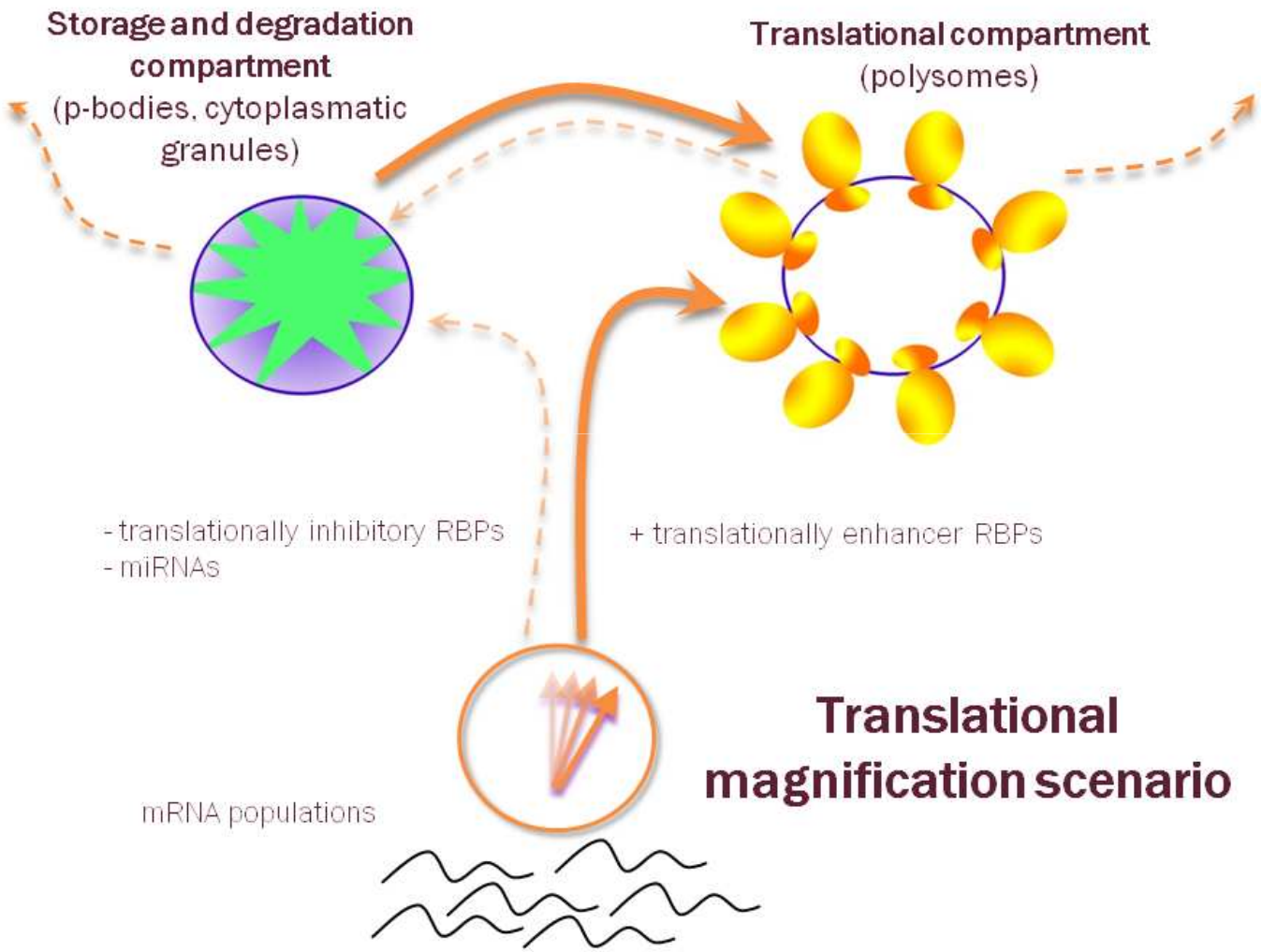
A possible model

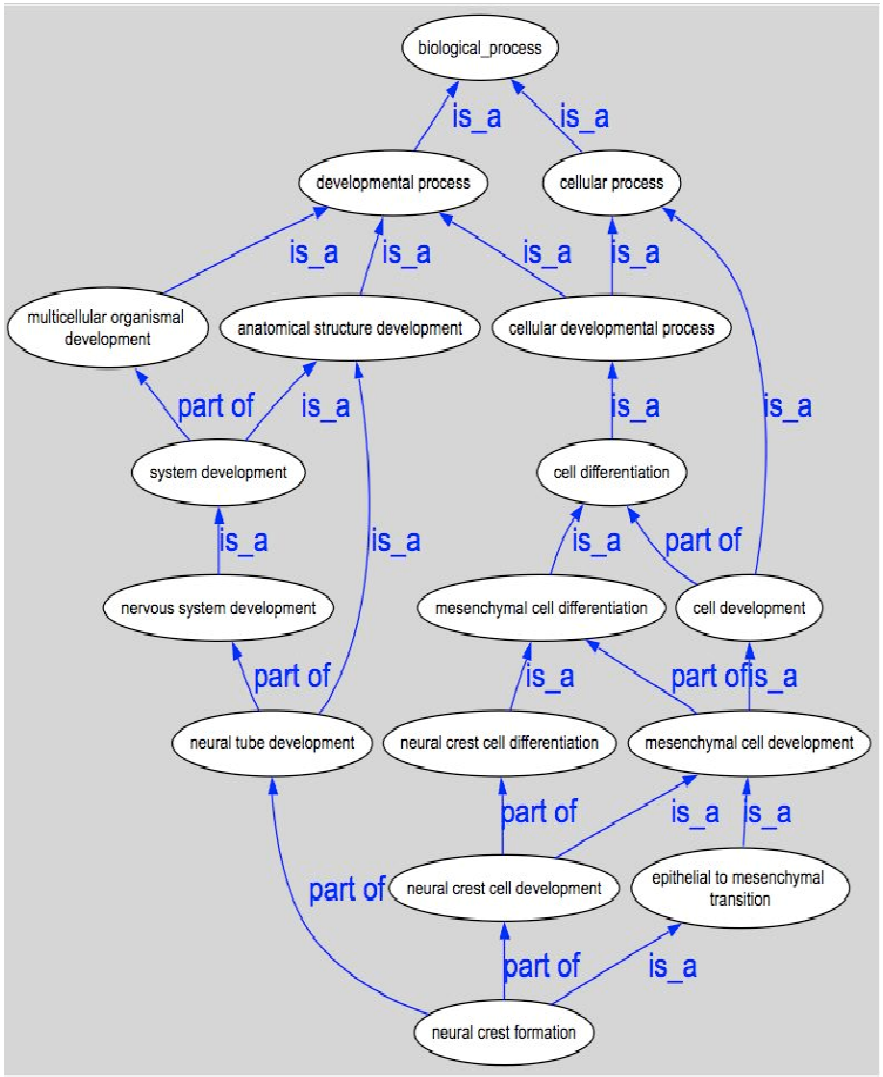


A possible model

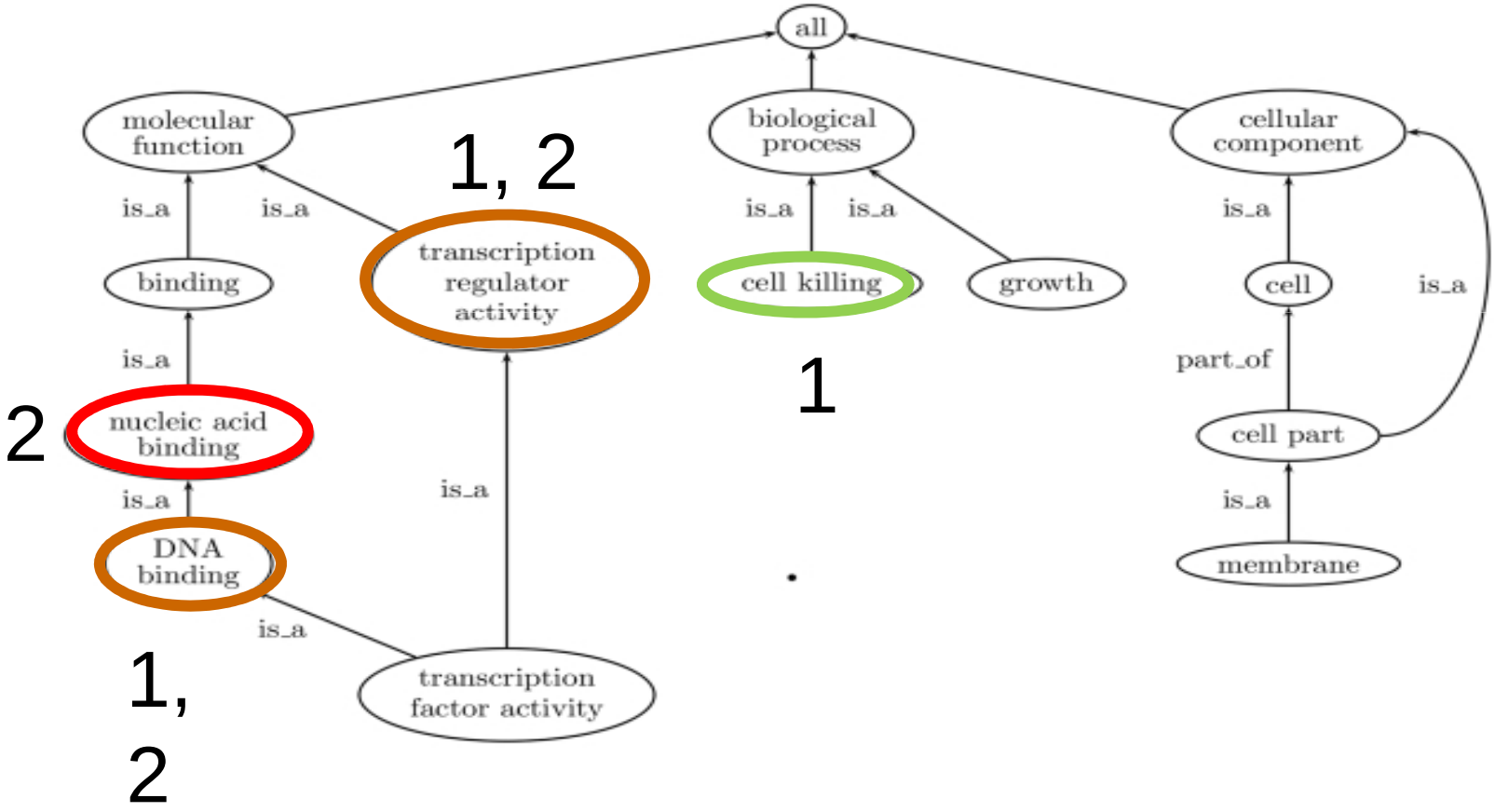


Epilogue:
molecular portraits of nothing

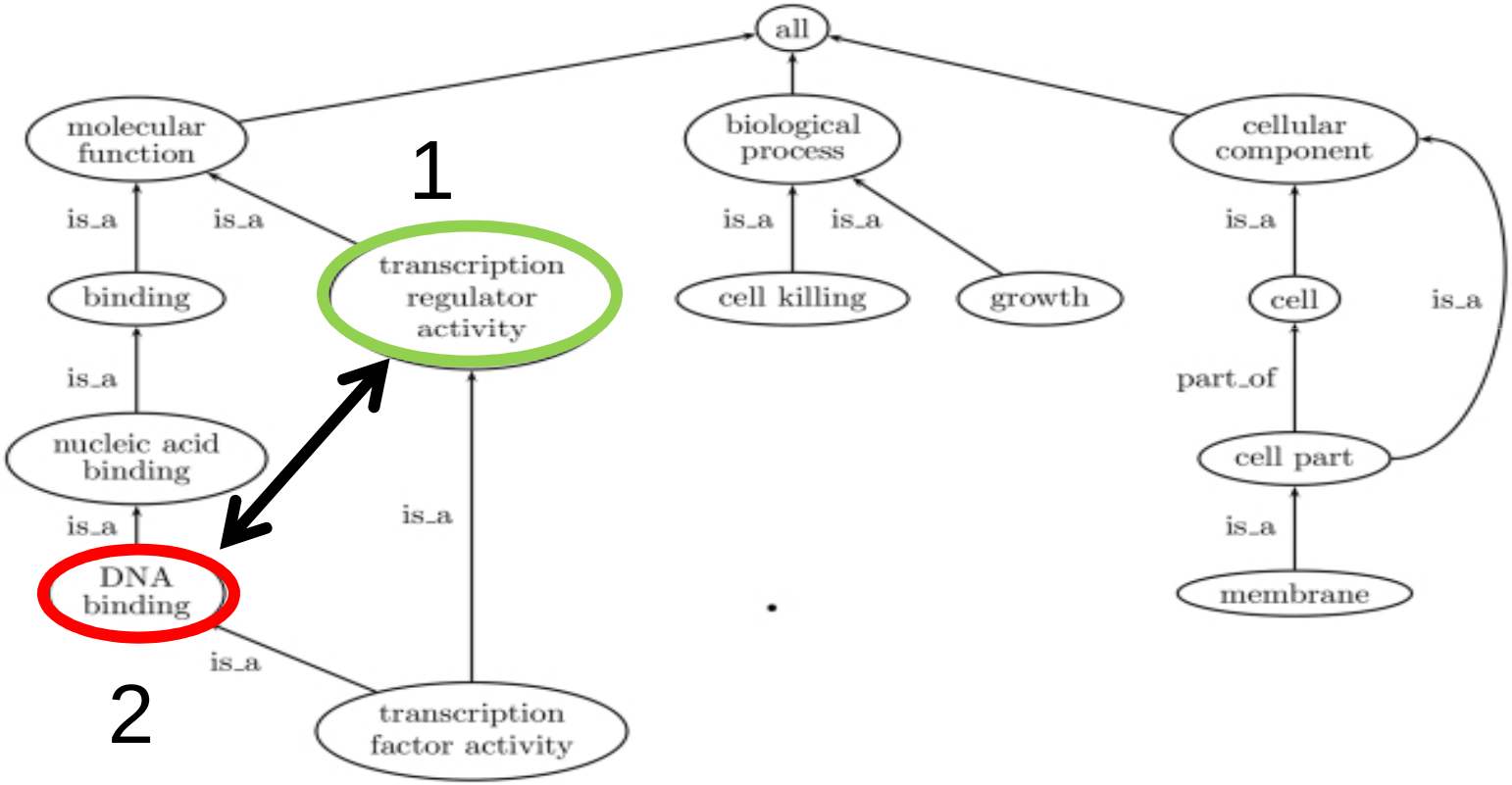
Biological ontologies



Measures of information distance: semantic *identity*



Measures of information distance: semantic *similarity*



Functional clustering of datasets

eIF4e.overexpr.Hs	*14*
eIF4GI.depl.Hs	*15*
v-Ki-ras.transf.Hs	*16*
mTOR.act.Hs.b	*17b*
mTOR.act.Hs.c	*17c*
hepat.diff.Hs	*17a*
mTOR.act.Hs.d	*17d*
testis.diff.Mm.P17-P22	*18a*
testis.diff.Mm.P17-P70	*18b*
testis.diff.Mm.P22-P70	*18c*
lung.diff.Rn.E19-E22	*20a*
lung.diff.Rn.E19-P1	*20b*
lung.diff.Rn.E22-P1	*20c*
stem.cell.diff.Mm	*19*
EPO.release.Mm	*21*
starv.release.Mm	*9*
LPS.Mm.1h	*10a*
LPS.Mm.2h	*10b*
LPS.Mm.4h	*10c*
muscle.contr.Rn	*11*
carc.progr.Hs	*13*

- Cluster 1: alterations of translational control
- Cluster 2: tissue differentiation
- Cluster 3: extracellular signalling
- Cluster 4: macrophage activation
- Cluster 5: muscle contraction
- Cluster 6: cancer progression

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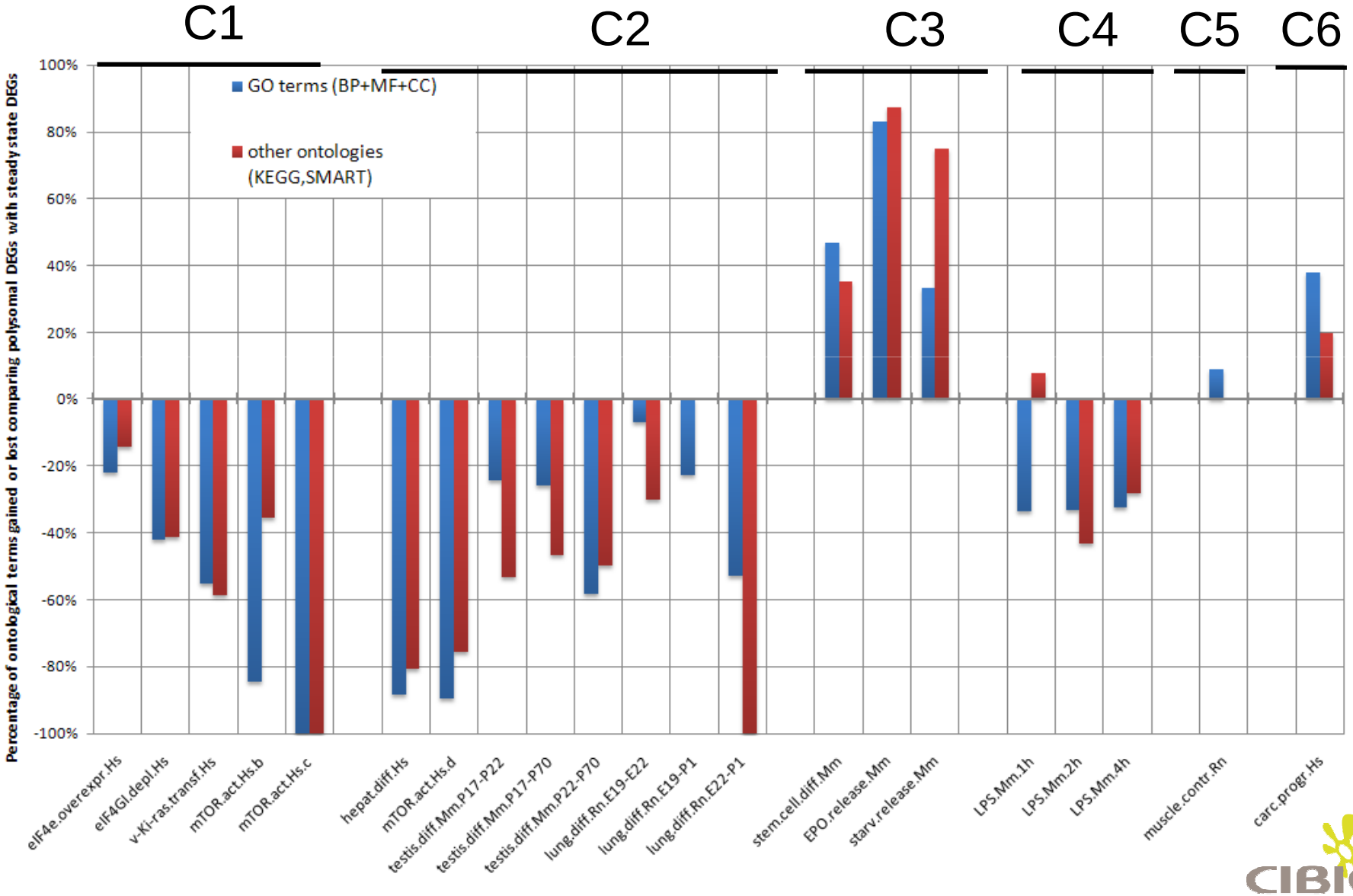
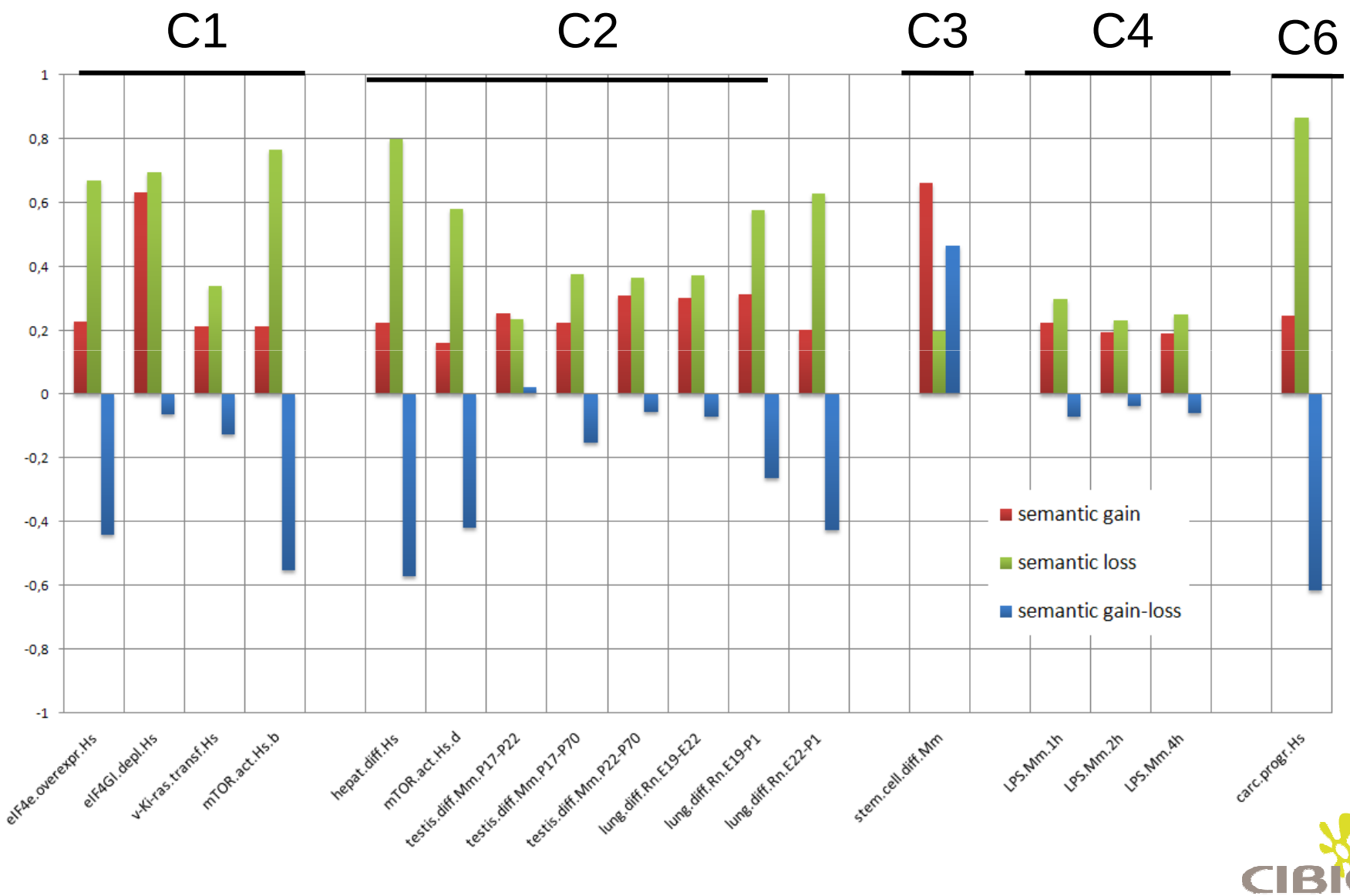
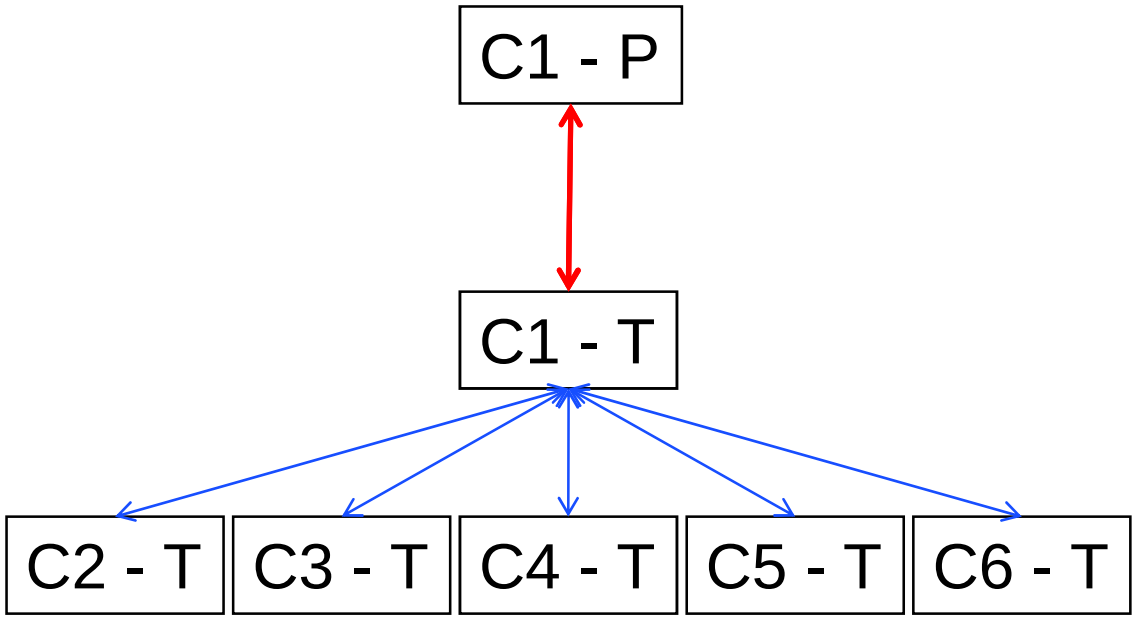
Semantic *identity*: information gain and loss at polysomes



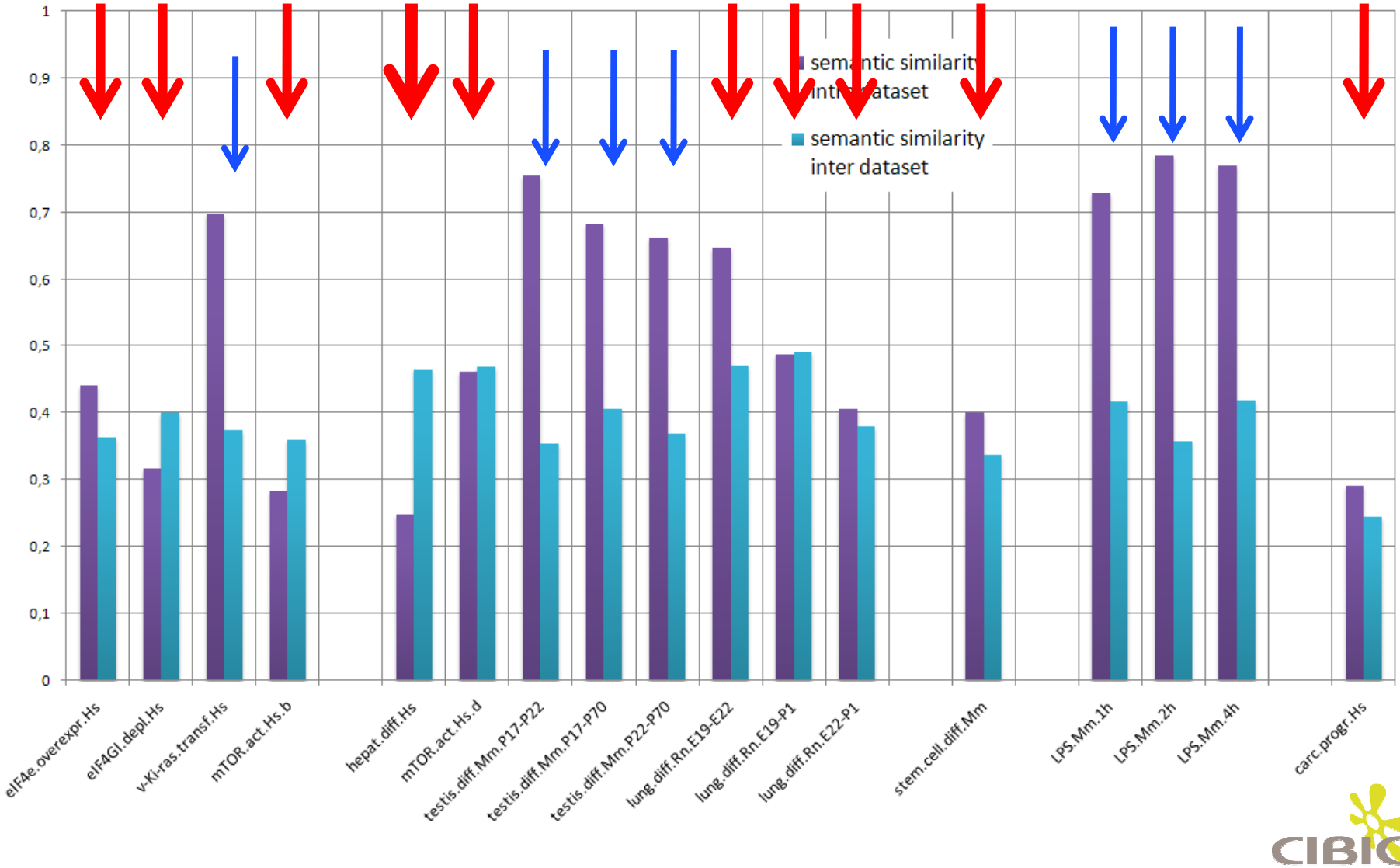
Semantic *similarity* information gain and loss at polysomes



How much is the t/p semantic distance?



Lack of phenotypic informativity of transcriptome profiling



Conclusions

- The degree of uncoupling between total and polysomal mRNA gene expression variation profiles in each experiment is very high. Only an always minor fraction of genes is coupled in each experiment.

- The semantic distance between the ontologizations of total and polysomal RNA profiles of the same dataset is in **10 cases out of 17** (58.8%) bigger than the average semantic distance between transcriptome profiles coming from completely different experiments.

- Any strategy aimed at the identification of a diagnostic/prognostic biomarker or signature based on transcriptome profiling will be ..... by the complete failure in representing the phenotype lack of this type of protrait of cell activity.

Credits

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