TIRESIAS: Context-sensitive Approach to Decipher the Presence and Strength of MicroRNA Regulatory Interactions
Supplementary Material

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S1   Data scaling

The expression x_i used in this paper is the scaled one of the raw expression value x_i^r as follows:

$$x_i = \frac{x_i^r - E(x_i^r)}{\sqrt{Var(x_i^r)}} + o_x, \tag{1}$$

where $o_x > 0$ is an offset that is the same for all i. That is, the mean and variance of x_i are o_x and 1, respectively. The value of o_x is chosen large enough to make any sample of x_i likely to be positive. This is to ensure that a positive regulation weight means the up-regulation, and a negative one means the down-regulation.

On the other hand, the raw expression y_j^r is scaled as

$$y_j = \frac{y_j^r}{E(y_i^r)} + o_y, \tag{2}$$

where $o_y > 0$ is another offset that is the same for all j. That is, the mean of y_j is set to the same o_y, but the variance of y_j that we denoted by σ_j^2 is different across j. The non-uniform variance is intended to reflect the fact that in the first term of Equation (10), the relative importance of the cost related with y_j should decided by the scaling factor $1/\sigma_j^2$. Since we know

$$o_y + 1 = \mu_j + r_j(\boldsymbol{x}, \boldsymbol{s}) \tag{3}$$

from Equation (1), and $\mu_j > 0$ for any j, if o_y is too small, $r_j(\boldsymbol{x}, \boldsymbol{s})$ is difficult to be a positive value, possibly misleading an up-regulation case as a down-regulation case. Thus, the value of o_y is also chosen to be large enough to give room to model the up-regulation relationship properly.

S2   D'Agostino-Pearson omnibus tests

Normality test results for mRNAs using D'Agostino-Pearson omnibus tests are summarized in Tables S1, S2, and S3.

S3   Summary of interacting pairs predicted by Tiresias

We summarize the pairs of miRNAs and mRNAs that are predicted interacting by TIRESIAS in Tables S4, S5, and S6.
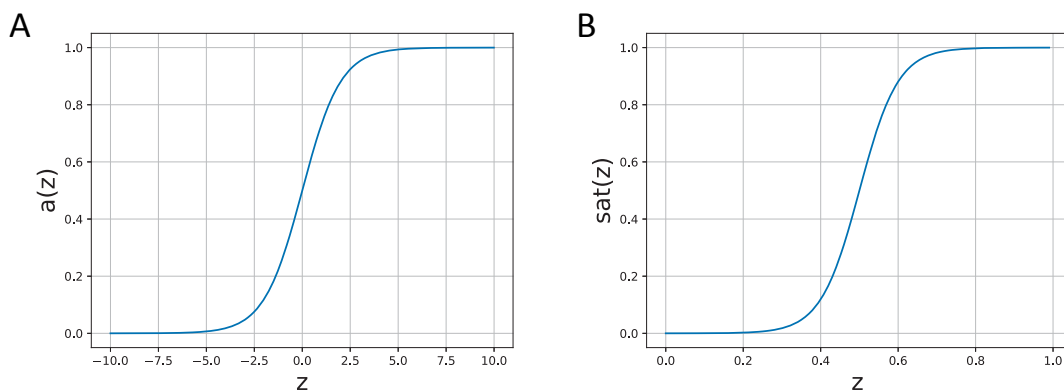
A

B

Figure S1: (A) Sigmoid activation function $a(z) = 1/(1 + \exp(-z))$. (B) Saturation function $\mathrm{sat}(z) = 0.5 \tanh(10(z - 0.5)) + 0.5$.

Table S1: D'Agostino-Pearson omnibus tests for mRNAs: TCGA-BRCA

mRNA	statistic	p-value
BCL2	458.7	2.50E-100
CCND1	1364.0	6.41E-297
DNMT3A	654.8	6.43E-143
ZNF652	2025.1	0
ZEB1	260.9	2.23E-57
ERBB2	1070.6	3.36E-233
TP53INP1	1054.4	1.10E-229
FSCN1	1632.4	0
ERBB3	156.7	9.53E-35
VEGFA	1096.5	7.72E-239
BMI1	909.0	4.11E-198
MSH2	663.2	9.89E-145
MMP2	603.2	1.06E-131
SATB1	2329.3	0
ATM	898.8	6.63E-196
RAB5A	444.0	3.79E-97
MTDH	553.1	8.04E-121
CSF1	991.4	5.22E-216
PTEN	309.0	8.06E-68

Table S2: D'Agostino-Pearson omnibus tests for mRNAs: TCGA-LUAD

mRNA	statistic	p-value
HMGA2	657.1	2.09E-143
MMP2	389.9	2.12E-85
YAP1	348.4	2.21E-76
E2F3	361.7	2.85E-79
PIK3R3	486.1	2.84E-106
SENP1	149.8	2.95E-33
PRKCA	363.8	1.01E-79
DAB2	184.6	8.08E-41
MMP14	372.1	1.60E-81

Table S3: D'Agostino-Pearson omnibus tests for mRNAs: TCGA-UCEC

mRNA	statistic	p-value
PLXNB1	284.4	1.71E-62
CUL5	124.5	9.40E-28
CDK2	368.0	1.20E-80
CCNA1	324.0	4.48E-71
IGF1R	388.7	3.89E-85
CHL1	542.7	1.46E-118
AKT1	668.0	8.70E-146
BCL2	509.7	2.05E-111

Table S4: Interacting pairs predicted by TIRESIAS ($|e_{ij}| > 0.01$): TCGA-BRCA.

miRNA	mRNA	e_{ij}	miRNA	mRNA	e_{ij}
hsa-miR-125a-5p	ERBB2	-0.16	hsa-miR-29b-3p	TP53INP1	0.158
hsa-miR-18a-5p	ERBB2	-0.09	hsa-miR-125a-5p	TP53INP1	0.069
hsa-miR-143-3p	ERBB3	-0.091	hsa-miR-101-3p	TP53INP1	-0.026
hsa-miR-125b-5p	ERBB3	-0.112	hsa-miR-30a-5p	TP53INP1	0.124
hsa-miR-205-5p	ERBB3	-0.021	hsa-miR-21-5p	SATB1	-0.233
hsa-miR-125a-5p	ERBB3	0.111	hsa-miR-155-5p	SATB1	0.023
hsa-miR-17-5p	ERBB3	-0.154	hsa-miR-34a-5p	SATB1	-0.072
hsa-miR-20b-5p	ERBB3	0.011	hsa-miR-17-5p	SATB1	0.207
hsa-miR-143-3p	DNMT3A	-0.093	hsa-miR-448	SATB1	-0.02
hsa-miR-30a-5p	DNMT3A	-0.105	hsa-miR-101-3p	SATB1	0.075
hsa-miR-101-3p	RAB5A	-0.05	hsa-miR-30a-5p	SATB1	-0.057
hsa-miR-34a-5p	CCND1	0.054	hsa-miR-20b-5p	SATB1	0.015
hsa-miR-17-5p	CCND1	-0.191	hsa-miR-20a-5p	VEGFA	0.118
hsa-let-7e-5p	CCND1	0.186	hsa-miR-200c-3p	VEGFA	0.056
hsa-miR-20b-5p	CCND1	-0.022	hsa-miR-205-5p	VEGFA	0.011
hsa-miR-29b-3p	MMP2	-0.15	hsa-miR-29b-3p	VEGFA	0.049
hsa-miR-17-5p	MMP2	-0.241	hsa-miR-21-5p	BCL2	-0.1
hsa-miR-20b-5p	MMP2	-0.037	hsa-miR-143-3p	BCL2	-0.11
hsa-miR-21-5p	MSH2	-0.067	hsa-miR-200c-3p	BCL2	-0.058
hsa-miR-18a-5p	ATM	-0.07	hsa-miR-143-3p	ZEB1	0.108
hsa-miR-128-3p	BMI1	-0.032	hsa-miR-200c-3p	ZEB1	-0.273
hsa-miR-101-3p	MTDH	-0.087	hsa-miR-205-5p	ZEB1	-0.051
hsa-miR-30a-5p	MTDH	-0.062	hsa-miR-143-3p	FSCN1	0.132
hsa-miR-128-3p	CSF1	-0.044	hsa-miR-200c-3p	FSCN1	0.172
hsa-miR-17-5p	CSF1	-0.094	hsa-miR-133a-3p	FSCN1	-0.045
hsa-miR-21-5p	PTEN	-0.09	hsa-miR-20a-5p	ZNF652	-0.256
hsa-miR-17-5p	PTEN	-0.089	hsa-miR-155-5p	ZNF652	-0.057
hsa-miR-20a-5p	TP53INP1	-0.207	hsa-miR-125b-5p	ZNF652	-0.085
hsa-miR-155-5p	TP53INP1	-0.033	hsa-miR-128-3p	ZNF652	-0.041
hsa-miR-205-5p	TP53INP1	-0.081	hsa-miR-448	ZNF652	-0.025

Table S5: Interacting pairs predicted by TIRESIAS ($|e_{ij}| > 0.01$): TCGA-LUAD.

miRNA	mRNA	e_{ij}	miRNA	mRNA	e_{ij}
hsa-miR-133a-3p	MMP14	-0.034	hsa-miR-29c-3p	SENP1	-0.075
hsa-miR-203a-3p	E2F3	-0.037	hsa-miR-133a-3p	SENP1	-0.071
hsa-miR-93-5p	E2F3	0.197	hsa-miR-7-5p	PIK3R3	-0.028
hsa-miR-203a-3p	PRKCA	-0.111	hsa-miR-93-5p	DAB2	-0.168
hsa-let-7b-5p	HMGA2	-0.098	hsa-miR-93-5p	MMP2	-0.153
hsa-let-7e-5p	HMGA2	0.236	hsa-miR-375	YAP1	-0.107
hsa-miR-93-5p	HMGA2	0.436			

Table S6: Interacting pairs predicted by TIRESIAS ($|e_{ij}| > 0.01$): TCGA-UCEC.

miRNA	mRNA	e_{ij}
hsa-miR-10a-5p	CHL1	0.086
hsa-miR-497-5p	PLXNB1	0.055
hsa-miR-143-3p	BCL2	0.369