Circadian Gene Symbol			
Acacb	Fads2	Tgfbr1	Fkbp5
Acadm	Fasn	Alas1	Usp2
Acly	Fgf15	Igfbp1	Amd1
Parp1	Insig1	Raet1c	Gck
Cyp2d9	Insig2	Rora	Hmgcr
Cyp7b1	Ldlr	Sult1e1	Lpin1
Arntl	Lipg	Fas	Saa4
Clock	Lpl	Rxra	Wee1
Cry2	Nr0b2	Cirbp	Nampt
Npas2	Nr1h2	Fus	Aco2
Per1	Nr1h3	Hsp90aa1	Akr7a5
Per2	Pctp	Hsph1	Aldh2
Per3	Scap	Ccrn4l	Bhmt
Acot1	Srebf1	Cpt1a	Cps1
Acot2	Srebf2	Pklr	Eef1d
Acot4	Apoc3	Slc2a2	Sord
Cyp4a10	Avpr1a	Slc37a4	Bhlhe41
Cyp4a14	Fkbp4	Ucp2	Nr1d1
Ak3	Hspd1	Aacs	Nr1d2
Rgs16	Tubb5	Acot3	Rorc
Ccnd1	Dbp	Apoa1	G6pc
Ddc	Hlf	Cyp7a1	Pck1
Hist1h1c	Nfil3	Elovl3	Ppara
Rell1	Tef	Elovl5	Ppard
Sbk1	Bhlhe40	Elovl6	Pparg
Smarcd1	Por	Fabp5	Id2

Non−circadian Gene Symbol			
Eif2a	Zkscan14	Trdmt1	Zfx
Utp6	Zfp1	Tsfm	Snx12
Rpl19	Slc26a11	Ercc6l2	Zfp524
Rplp0	Nkap	Smg8	Apbb3
Tbp	Mobkl2c	Commd5	Ppie
Eef1a1	Eya3	Ing5	Cops7b
Hmbs	Ddx27	Fam119a	Glmn
Tbcc	Asb6	Fam175a	Zfp592
Actb	Zfp451	Nvl	Nub1
Gapdh	Cln3	Rexo1	Zfp426
Ppib	Gpn2	Rngtt	Sertad3
Polr3f	Mtf1	Snapc3	Zfp414
Med6	Rab23	Cdkal1	Axin1
Tyw1	Lysmd1	Rrp9	Casz1
Vars2	Asb3	Utp15	Bcl2l1
Ell	Zfp397	Atpbd3	Telo2
Gtf2h3	Fam123b	Nsun5	Terf2ip
Polr1a	Zkscan6	Chd1	Rabl4
Ttf1	Adck2	Kdm4a	Dgcr8
Mrps5	Usp36	Men1	Cep110
Med23	Trib1	Kdm5d	Abcd4
Polr3h	Tfpt	Ankra2	Rad50
Patl1	Stam2	Bcor	Sesn2
Med24	E2f3	Rbm28	Gnptab
Tsr3	Zfp511	Kat2a	Gtf2ird2
Rprd2	Slc10a7	Gtpbp5	Zscan12
Tbc1d5	Vps33b	Mynn	Ino80b
Ttc15	Ppm1f	Sumf2	Smurf1
Mga			

Supplementary Table 1. Circadian and non-circadian genes in Mus muculus liver as gold standard. The 104 circadian gene list is extracted from Wu et al. (*J Biol Rhythms* 2014) and the 113 non-circadian gene list is obtained from Wu et al. (*PLoS One* 2012).

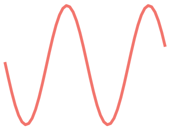
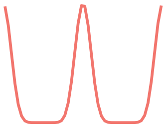
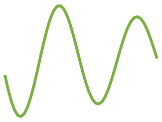
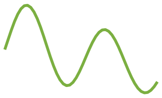
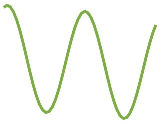
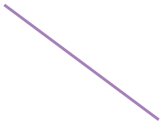
Method	Term	Count	Percent	*P*–Value	Benjamini
GRO–seq MC	mmu00260:Glycine, serine and threonine metabolism	3	11.5384615	1.408300e–03	4.812851e–02
Nascent–seq RAIN	mmu04710:Circadian rhythm	4	4.4943820	4.546934e–04	4.359144e–02
Nascent–seq eJTK	mmu04710:Circadian rhythm	5	5.8823529	1.448933e–05	1.259787e–03
RNA–seq JTK	mmu04710:Circadian rhythm	5	3.7037037	1.738213e–04	2.064430e–02
RNA–seq RAIN	mmu01100:Metabolic pathways	169	14.2978003	8.003523e–16	2.176037e–13
	mmu00982:Drug metabolism – cytochrome P450	25	2.1150592	1.644394e–11	2.302154e–09
	mmu00980:Metabolism of xenobiotics by cytochrome P450	24	2.0304569	5.798815e–11	5.412229e–09
	mmu00040:Pentose and glucuronate interconversions	16	1.3536379	2.901869e–09	2.031308e–07
	mmu05204:Chemical carcinogenesis	26	2.1996616	6.999948e–09	3.919970e–07
	mmu00860:Porphyrin and chlorophyll metabolism	16	1.3536379	1.012513e–07	4.725049e–06
	mmu00053:Ascorbate and aldarate metabolism	12	1.0152284	1.519743e–06	6.078791e–05
	mmu00983:Drug metabolism – other enzymes	16	1.3536379	2.527470e–06	8.845766e–05
	mmu04710:Circadian rhythm	11	0.9306261	5.067967e–05	1.575498e–03
	mmu00830:Retinol metabolism	19	1.6074450	7.641930e–05	2.137534e–03
	mmu01130:Biosynthesis of antibiotics	31	2.6226734	5.198836e–04	1.314962e–02
	mmu00480:Glutathione metabolism	13	1.0998308	5.774587e–04	1.338751e–02
	mmu04141:Protein processing in endoplasmic reticulum	26	2.1996616	6.167556e–04	1.320017e–02
	mmu00130:Ubiquinone and other terpenoid–quinone biosynthesis	6	0.5076142	7.081090e–04	1.406731e–02
	mmu04146:Peroxisome	16	1.3536379	1.041198e–03	1.925798e–02
	mmu00140:Steroid hormone biosynthesis	16	1.3536379	1.708722e–03	2.948479e–02
	mmu00270:Cysteine and methionine metabolism	10	0.8460237	2.213890e–03	3.584623e–02
RNA–seq eJTK	mmu01100:Metabolic pathways	321	12.2753346	5.097538e–24	1.478286e–21
	mmu00982:Drug metabolism – cytochrome P450	35	1.3384321	7.422532e–12	1.076264e–09
	mmu00980:Metabolism of xenobiotics by cytochrome P450	34	1.3001912	1.466155e–11	1.417289e–09
	mmu01130:Biosynthesis of antibiotics	70	2.6768642	3.479491e–10	2.522630e–08
	mmu00280:Valine, leucine and isoleucine degradation	27	1.0325048	2.296309e–08	1.331858e–06
	mmu05204:Chemical carcinogenesis	37	1.4149140	2.547489e–08	1.231285e–06
	mmu00071:Fatty acid degradation	25	0.9560229	3.356184e–08	1.390418e–06
	mmu01200:Carbon metabolism	40	1.5296367	7.604773e–07	2.756693e–05
	mmu00053:Ascorbate and aldarate metabolism	16	0.6118547	1.688110e–06	5.439322e–05
	mmu04146:Peroxisome	31	1.1854685	2.657397e–06	7.706165e–05
	mmu00040:Pentose and glucuronate interconversions	17	0.6500956	7.960225e–06	2.098393e–04
	mmu00860:Porphyrin and chlorophyll metabolism	19	0.7265774	1.246414e–05	3.011731e–04
	mmu00830:Retinol metabolism	31	1.1854685	1.338463e–05	2.985377e–04
	mmu03050:Proteasome	20	0.7648184	1.425353e–05	2.952102e–04
	mmu05012:Parkinson's disease	44	1.6826004	1.880681e–05	3.635357e–04
	mmu04932:Non–alcoholic fatty liver disease (NAFLD)	45	1.7208413	3.346485e–05	6.063766e–04
	mmu05010:Alzheimer's disease	49	1.8738050	3.797554e–05	6.476206e–04
	mmu04710:Circadian rhythm	15	0.5736138	7.954074e–05	1.280720e–03
	mmu01230:Biosynthesis of amino acids	26	0.9942639	1.084256e–04	1.653637e–03
	mmu04610:Complement and coagulation cascades	26	0.9942639	1.084256e–04	1.653637e–03
	mmu05230:Central carbon metabolism in cancer	23	0.8795411	1.339332e–04	1.940277e–03
	mmu00270:Cysteine and methionine metabolism	17	0.6500956	1.469660e–04	2.027621e–03
	mmu04919:Thyroid hormone signaling pathway	34	1.3001912	1.606747e–04	2.115913e–03
	mmu00190:Oxidative phosphorylation	39	1.4913958	1.987891e–04	2.503581e–03
	mmu01040:Biosynthesis of unsaturated fatty acids	13	0.4971319	3.111264e–04	3.752969e–03
	mmu05016:Huntington's disease	50	1.9120459	3.643095e–04	4.217841e–03
	mmu00983:Drug metabolism – other enzymes	19	0.7265774	3.704177e–04	4.123821e–03
	mmu01212:Fatty acid metabolism	19	0.7265774	3.704177e–04	4.123821e–03
	mmu00130:Ubiquinone and other terpenoid–quinone biosynthesis	8	0.3059273	3.795185e–04	4.068784e–03
	mmu00062:Fatty acid elongation	12	0.4588910	9.205811e–04	9.493629e–03
	mmu00480:Glutathione metabolism	19	0.7265774	1.038016e–03	1.033181e–02
	mmu00140:Steroid hormone biosynthesis	26	0.9942639	1.085668e–03	1.044556e–02
	mmu04914:Progesterone–mediated oocyte maturation	26	0.9942639	1.085668e–03	1.044556e–02
	mmu00380:Tryptophan metabolism	17	0.6500956	1.212200e–03	1.128268e–02
	mmu00650:Butanoate metabolism	12	0.4588910	1.339581e–03	1.207460e–02
	mmu04141:Protein processing in endoplasmic reticulum	42	1.6061185	1.425778e–03	1.246023e–02
	mmu00010:Glycolysis / Gluconeogenesis	21	0.8030593	1.643029e–03	1.392769e–02
	mmu00260:Glycine, serine and threonine metabolism	15	0.5736138	1.788668e–03	1.472418e–02
	mmu00410:beta–Alanine metabolism	13	0.4971319	2.595550e–03	2.071815e–02
	mmu00310:Lysine degradation	17	0.6500956	3.923485e–03	3.034227e–02
	mmu04976:Bile secretion	21	0.8030593	4.242325e–03	3.192383e–02
	mmu01210:2–Oxocarboxylic acid metabolism	9	0.3441683	4.810340e–03	3.522031e–02
	mmu00640:Propanoate metabolism	11	0.4206501	5.011554e–03	3.576970e–02
	mmu00340:Histidine metabolism	10	0.3824092	5.039932e–03	3.510736e–02
	mmu04915:Estrogen signaling pathway	26	0.9942639	6.271672e–03	4.251073e–02
	mmu00020:Citrate cycle (TCA cycle)	12	0.4588910	6.343808e–03	4.201208e–02
	mmu02010:ABC transporters	15	0.5736138	7.532058e–03	4.860982e–02
RNA–seq MC	mmu04710:Circadian rhythm	5	5.3191489	6.382092e–05	6.235130e–03
RNA–seq BC	mmu04710:Circadian rhythm	9	2.2842640	6.040930e–07	1.413478e–04
	mmu01100:Metabolic pathways	52	13.1979695	2.048620e–04	2.368628e–02

Category	Term	Count	Percent	*P*−Value	Benjamini
XR−seq RAIN	mmu01100:Metabolic pathways	230	10.1769912	5.399408e−09	1.538830e−06
	mmu04146:Peroxisome	29	1.2831858	7.423091e−07	1.057735e−04
	mmu04710:Circadian rhythm	15	0.6637168	1.013260e−05	9.621386e−04
	mmu04141:Protein processing in endoplasmic reticulum	43	1.9026549	1.257843e−05	8.958171e−04
	mmu03040:Spliceosome	36	1.5929204	2.050925e−05	1.168356e−03
	mmu03050:Proteasome	18	0.7964602	2.103473e−05	9.986614e−04
	mmu04152:AMPK signaling pathway	35	1.5486726	2.170888e−05	8.834807e−04
	mmu05169:Epstein−Barr virus infection	35	1.5486726	8.306604e−05	2.954976e−03
	mmu03013:RNA transport	41	1.8141593	8.816172e−05	2.788017e−03
	mmu00270:Cysteine and methionine metabolism	15	0.6637168	2.880869e−04	8.178035e−03
	mmu03010:Ribosome	35	1.5486726	3.128193e−04	8.073366e−03
	mmu04068:FoxO signaling pathway	33	1.4601770	3.284607e−04	7.771865e−03
	mmu04932:Non−alcoholic fatty liver disease (NAFLD)	37	1.6371681	3.354265e−04	7.327834e−03
	mmu01130:Biosynthesis of antibiotics	46	2.0353982	5.152173e−04	1.043622e−02
	mmu04920:Adipocytokine signaling pathway	21	0.9292035	5.603045e−04	1.059227e−02
	mmu04120:Ubiquitin mediated proteolysis	32	1.4159292	1.972447e−03	3.455766e−02
XR−seq eJTK	mmu01100:Metabolic pathways	153	10.1526211	2.637646e−06	7.356334e−04
	mmu04710:Circadian rhythm	12	0.7962840	2.807031e−05	3.908206e−03
	mmu04152:AMPK signaling pathway	25	1.6589250	1.780315e−04	1.642207e−02
	mmu03040:Spliceosome	25	1.6589250	3.253113e−04	2.243858e−02
	mmu03013:RNA transport	29	1.9243530	5.151755e−04	2.834473e−02
	mmu04120:Ubiquitin mediated proteolysis	25	1.6589250	8.709083e−04	3.970512e−02
	mmu04068:FoxO signaling pathway	24	1.5925680	8.906319e−04	3.489064e−02
	mmu03050:Proteasome	12	0.7962840	1.113533e−03	3.811088e−02
	mmu01130:Biosynthesis of antibiotics	33	2.1897810	1.190583e−03	3.625647e−02
XR−seq BC	mmu01100:Metabolic pathways	200	10.1781170	5.203804e−08	1.488277e−05
	mmu03013:RNA transport	42	2.1374046	1.096642e−06	1.568075e−04
	mmu03050:Proteasome	17	0.8651399	1.435104e−05	1.367207e−03
	mmu04152:AMPK signaling pathway	32	1.6284987	2.042087e−05	1.459042e−03
	mmu01212:Fatty acid metabolism	18	0.9160305	2.073602e−05	1.185410e−03
	mmu04146:Peroxisome	24	1.2213740	2.445182e−05	1.164872e−03
	mmu04141:Protein processing in endoplasmic reticulum	38	1.9338422	3.290665e−05	1.343590e−03
	mmu01130:Biosynthesis of antibiotics	45	2.2900763	3.714389e−05	1.327037e−03
	mmu04710:Circadian rhythm	13	0.6615776	6.531774e−05	2.073567e−03
	mmu04920:Adipocytokine signaling pathway	20	1.0178117	2.475823e−04	7.056713e−03
	mmu03040:Spliceosome	29	1.4758270	6.326819e−04	1.632029e−02
	mmu00071:Fatty acid degradation	15	0.7633588	6.711375e−04	1.587348e−02
	mmu03015:mRNA surveillance pathway	23	1.1704835	7.180379e−04	1.567830e−02
	mmu04530:Tight junction	22	1.1195929	7.323059e−04	1.485402e−02
	mmu04932:Non−alcoholic fatty liver disease (NAFLD)	32	1.6284987	1.041217e−03	1.966692e−02
	mmu04140:Regulation of autophagy	10	0.5089059	1.391158e−03	2.457719e−02
	mmu04120:Ubiquitin mediated proteolysis	29	1.4758270	1.823600e−03	3.024072e−02
	mmu05100:Bacterial invasion of epithelial cells	19	0.9669211	1.954260e−03	3.060334e−02
	mmu04068:FoxO signaling pathway	27	1.3740458	3.291902e−03	4.842192e−02

Supplementary Table 2. Pathway enrichment analysis of significantly cyclic genes from the light-dark datasets. Functional annotations (KEGG pathway mapping) of the significant genes (q-values ≤ 0.05) are carried out using the the DAVID Bioinformatics Resources (https://david.ncifcrf.gov/). The list only contains significantly enriched pathways with a 0.05 cutoff of the p-values adjusted by Benjamini Hochberg.

Method	Term	Count	Percent	*P*-Value	Benjamini
JTK	mmu04610:Complement and coagulation cascades	8	7.4074074	6.721172e–06	7.256256e–04
	mmu01100:Metabolic pathways	25	23.1481481	4.274151e–04	2.282092e–02
RAIN	mmu01100:Metabolic pathways	173	32.6415094	1.199819e–40	2.567613e–38
	mmu01130:Biosynthesis of antibiotics	56	10.5660377	3.862699e–25	4.133088e–23
	mmu01200:Carbon metabolism	36	6.7924528	9.865999e–19	7.037746e–17
	mmu00071:Fatty acid degradation	24	4.5283019	1.203313e–17	6.437722e–16
	mmu01212:Fatty acid metabolism	21	3.9622642	1.230112e–13	5.264900e–12
	mmu00620:Pyruvate metabolism	18	3.3962264	1.108719e–12	3.954248e–11
	mmu00280:Valine, leucine and isoleucine degradation	19	3.5849057	7.498068e–11	2.292267e–09
	mmu00020:Citrate cycle (TCA cycle)	15	2.8301887	1.088804e–10	2.912552e–09
	mmu04141:Protein processing in endoplasmic reticulum	31	5.8490566	8.613214e–10	2.048031e–08
	mmu00190:Oxidative phosphorylation	28	5.2830189	8.951829e–10	1.915691e–08
	mmu00830:Retinol metabolism	22	4.1509434	1.760418e–09	3.424813e–08
	mmu00640:Propanoate metabolism	13	2.4528302	1.948424e–09	3.474690e–08
	mmu04146:Peroxisome	21	3.9622642	2.917345e–09	4.802398e–08
	mmu01230:Biosynthesis of amino acids	20	3.7735849	3.764751e–09	5.754691e–08
	mmu03320:PPAR signaling pathway	20	3.7735849	9.469415e–09	1.350970e–07
	mmu05012:Parkinson's disease	26	4.9056604	8.303846e–08	1.110639e–06
	mmu00380:Tryptophan metabolism	14	2.6415094	3.196986e–07	4.024434e–06
	mmu00630:Glyoxylate and dicarboxylate metabolism	11	2.0754717	7.851021e–07	9.333951e–06
	mmu00140:Steroid hormone biosynthesis	18	3.3962264	1.153208e–06	1.298869e–05
	mmu05010:Alzheimer's disease	26	4.9056604	2.373644e–06	2.539770e–05
	mmu00062:Fatty acid elongation	10	1.8867925	2.743240e–06	2.795457e–05
	mmu00010:Glycolysis / Gluconeogenesis	15	2.8301887	3.714133e–06	3.612780e–05
	mmu05016:Huntington's disease	27	5.0943396	5.915296e–06	5.503662e–05
	mmu05204:Chemical carcinogenesis	17	3.2075472	1.158093e–05	1.032586e–04
	mmu01210:2–Oxocarboxylic acid metabolism	8	1.5094340	2.302407e–05	1.970689e–04
	mmu01040:Biosynthesis of unsaturated fatty acids	9	1.6981132	3.645856e–05	3.000424e–04
	mmu00650:Butanoate metabolism	9	1.6981132	3.645856e–05	3.000424e–04
	mmu04932:Non–alcoholic fatty liver disease (NAFLD)	21	3.9622642	1.093741e–04	8.665630e–04
	mmu00220:Arginine biosynthesis	7	1.3207547	2.420391e–04	1.848384e–03
	mmu03050:Proteasome	10	1.8867925	3.320438e–04	2.447661e–03
	mmu00982:Drug metabolism – cytochrome P450	12	2.2641509	3.996930e–04	2.847651e–03
	mmu00270:Cysteine and methionine metabolism	9	1.6981132	7.105099e–04	4.894536e–03
	mmu00310:Lysine degradation	10	1.8867925	1.009361e–03	6.730756e–03
	mmu00410:beta–Alanine metabolism	8	1.5094340	1.058989e–03	6.847468e–03
	mmu00980:Metabolism of xenobiotics by cytochrome P450	11	2.0754717	1.224984e–03	7.685233e–03
	mmu00072:Synthesis and degradation of ketone bodies	5	0.9433962	1.570289e–03	9.562728e–03
	mmu00053:Ascorbate and aldarate metabolism	7	1.3207547	1.875310e–03	1.109612e–02
	mmu00330:Arginine and proline metabolism	9	1.6981132	2.805579e–03	1.611835e–02
	mmu00591:Linoleic acid metabolism	9	1.6981132	3.196868e–03	1.787065e–02
	mmu00260:Glycine, serine and threonine metabolism	8	1.5094340	3.412465e–03	1.858201e–02
	mmu04964:Proximal tubule bicarbonate reclamation	6	1.1320755	4.066064e–03	2.156193e–02
	mmu00061:Fatty acid biosynthesis	5	0.9433962	4.223097e–03	2.184700e–02
	mmu00360:Phenylalanine metabolism	6	1.1320755	4.984794e–03	2.514080e–02
	mmu00400:Phenylalanine, tyrosine and tryptophan biosynthesis	4	0.7547170	5.857129e–03	2.881192e–02
	mmu00120:Primary bile acid biosynthesis	5	0.9433962	7.088942e–03	3.400906e–02
	mmu04612:Antigen processing and presentation	11	2.0754717	7.757074e–03	3.635568e–02
	mmu04142:Lysosome	14	2.6415094	8.139112e–03	3.730583e–02
	mmu00250:Alanine, aspartate and glutamate metabolism	7	1.3207547	9.639924e–03	4.314685e–02
	mmu04975:Fat digestion and absorption	7	1.3207547	1.097517e–02	4.801067e–02
MC	mmu04610:Complement and coagulation cascades	9	6.8702290	1.950814e–06	2.360209e–04
	mmu01100:Metabolic pathways	31	23.6641221	3.112798e–05	1.881500e–03
	mmu00140:Steroid hormone biosynthesis	7	5.3435115	4.272723e–04	1.708929e–02

Supplementary Table 3. Pathway enrichment analysis of significantly cyclic proteins. Functional annotations (KEGG pathway mapping) of the significant proteins (q-values ≤ 0.05) are carried out using the the DAVID Bioinformatics Resources (https://david.ncifcrf.gov/). The list only contains significantly enriched pathways with a 0.05 cutoff of the p-values adjusted by Benjamini Hochberg. KEGG metabolic pathways were enriched by all three methods.

Types	Waveforms	Equations	Examples
		amp = A pha = ϕ per = T	
Stationary (Periodic)	cosine	$A\cos\left(\frac{2\pi(t-\phi)}{T}\right)$	
	cosine 2	$\frac{A}{1.39}\cos\left(\frac{2\pi(t-\phi_1)}{T}\right)+0.5\cos\left(\frac{2\pi(t-\phi_2)}{T_2}\right)$ where $T_2=\frac{1}{3}T,\ \phi_1=\phi+\frac{0.215T}{\pi},\ \phi_2=(\phi_1+0.25T_2)\mod T$	
	cosine peak	$A\left(-1+2\left\lvert\cos\left(\frac{\pi(t-\phi)}{T}\right)\right\rvert^{10}\right)$	
Non-stationary (Periodic)	cosine damp	$A\cos\left(\frac{2\pi(t-\phi)}{T}\right)e^{-0.01t}$	
	trend exp	$5e^{-0.01t}+A\cos\left(\frac{2\pi(t-\phi)}{T}\right)e^{-0.01t}$	
	trend linear	$A\cos\left(\frac{2\pi(t-\phi)}{T}\right)+st$ where $s\sim U(-0.05,0)$	
Asymmetric (Periodic)	saw-tooth	$\frac{-2A}{\pi}\arctan\left(\frac{1}{\tan\frac{\pi(t-\phi)}{T}}\right)$	
Non-periodic	linear	st where $s\sim U(-0.05,0)$	
	flat	0	

Supplementary Table 4. In silico generated periodic v.s. non-periodic gene profiles. Three types of periodic waveforms are included: stationary, non-stationary, and asymmetric. The stationary and non-stationary subgroups consist of three forms of cosine curves. The asymmetric subgroup consists of a saw-tooth waveform. Flat or linear lines are adopted to generate non-periodic waveforms. The waveforms shown are constructed without noise. 'Amp', 'pha', and 'per' represent amplitude, phase and period, respectively.

Simulation group	Description	Period length	Amplitude	Phase shift	Waveforms	Noise levels	Sampling patterns & replicates	Sample size (profiles)
Group 1	The trade-off between time window and sampling frequency	24	Uniform Distribution (1-6)	Uniform Distribution (0-24)	Periodic: cosine, cosine 2, cosine peak Non-periodic: flat	N(0, 1)	4 h/1 day X 1 & 8 h/2 days X 1 3 h/1 day X 1 & 6 h/2 days X 1 2 h/1 day X 1 & 4 h/2 days X 1	12,000
Group 2	The trade-off between time window and replicates	24	Uniform Distribution (1-6)	Uniform Distribution (0-24)	Periodic: cosine, cosine 2, cosine peak Non-periodic: flat	N(0, 1)	4 h/1 day X 1 & 8 h/1 day X 2 3 h/1 day X 1 & 6 h/1 day X 2 2 h/1 day X 1 & 4 h/1 day X 2	12,000
Group 3	stationary, non-stationary and asymmetric curves	24	Uniform Distribution (1-6)	Uniform Distribution (0-24)	Periodic: Stationary (cosine, cosine 2, cosine peak) Nonstationary (cosine damp, trend exp, trend linear) Asymmetric (Saw-tooth) Non-periodic: flat, linear	N(0, 1)	4 h/ 1 day X 1 3 h/ 1 day X 1 2 h/ 1 day X 1	12,000
Group 4	Signal to Noise Ratio (SNR) 0.5:1, 1:1, 2:1, 3:1	24	sqrt(2*SNR)	Uniform Distribution (0-24)	Periodic: cosine Non-periodic: flat	N(0, 1)	4 h/ 1 day X 1 3 h/ 1 day X 1 2 h/ 1 day X 1	12,000
Group 5	Uneven sampling (1, 2, or 4 randomly selected timepoints removed)	24	Uniform Distribution (1-6)	Uniform Distribution (0-24)	Periodic: cosine, cosine 2, cosine peak Non-periodic: flat	N(0, 1)	4 h/ 1 day X 1 3 h/ 1 day X 1 2 h/ 1 day X 1	12,000
Group 6	Missing value (1%, 5%, 10% genes missing)	24	Uniform Distribution (1-6)	Uniform Distribution (0-24)	Periodic: cosine, cosine 2, cosine peak Non-periodic: flat	N(0, 1)	4 h/ 1 day X 1 3 h/ 1 day X 1 2 h/ 1 day X 1	12,000

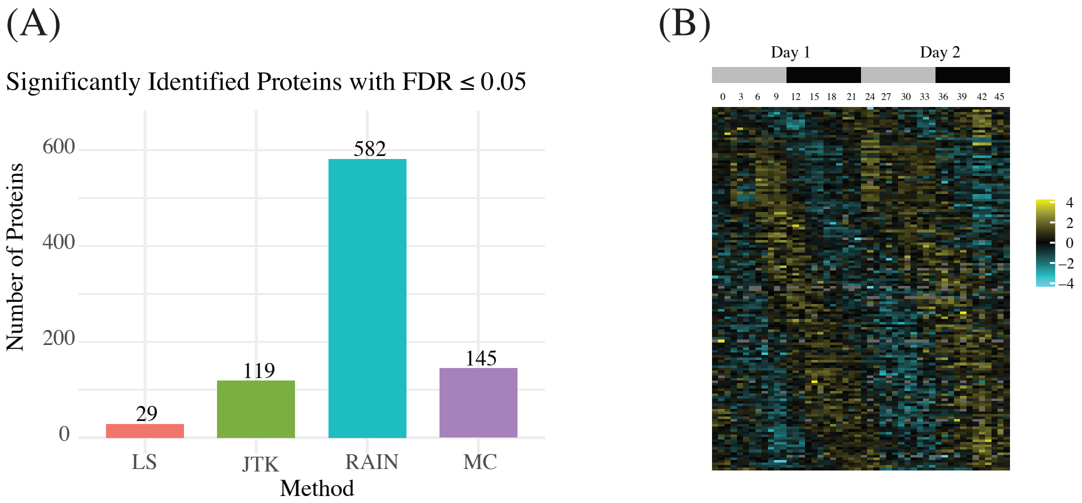
Supplementary Table 5. Details of simulation setup and parameters used to in silico generate periodic and non-periodic profiles. Each simulation run consists of 6,000 periodic and 6,000 non-periodic gene profiles. All simulated waveforms have a period length of 24, a phase shift that is uniformly distributed between 0 and 24, and a noise term with standard normal distribution. The amplitude is uniformly distributed between 1 and 6 for all groups except when testing for different signal-to-noise ratios (SNRs), which we define as the ratios of the empirical variances of the cosine function and the variances of the noise. Non-periodic profiles are sampled from a flat/linear function. “X 1” indicates no replicate and “X 2” indicates two replicates.

Methods	1 h/2 days	2 h/2 days	4 h/2 days
LS	13s	11s	11s
ARS	18s	13s	21s
JTK	30s	5s	2s
RAIN	729s	26s	4s
eJTK	98s	49s	29s
MC	61s	29s	34s
BC	16s	8s	7s

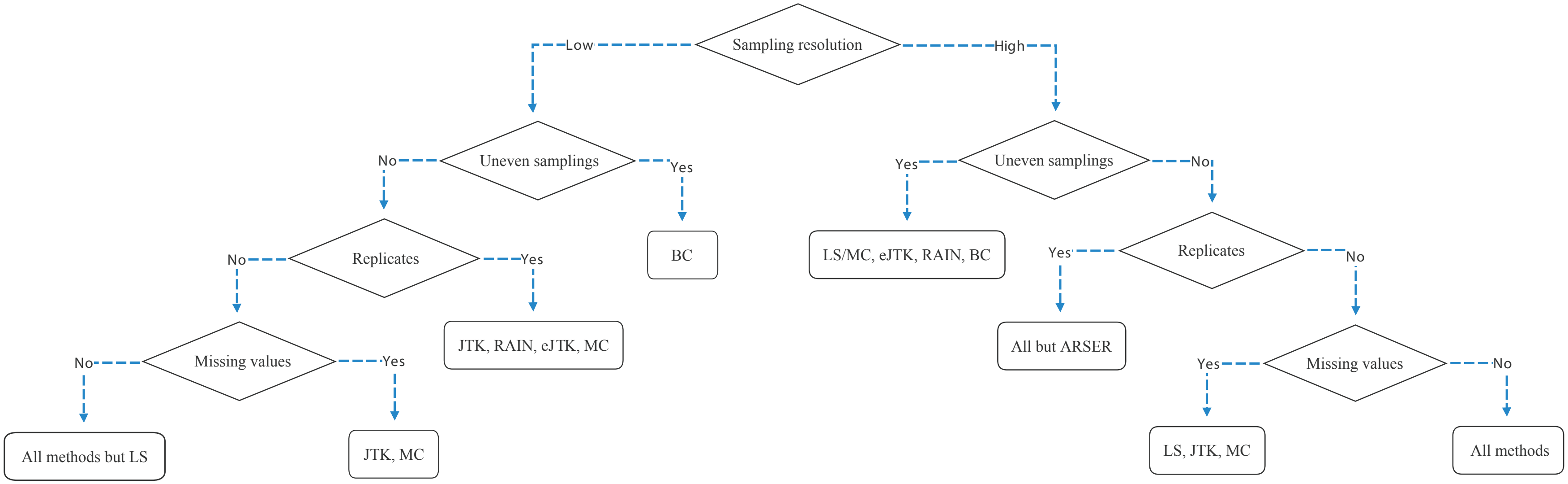
Supplementary Table 6. Evaluation of computational efficiency with different sampling rates. Each method is run on a dataset with a total of 6,000 genes. All programs are run on a Macbook Pro (15-inch, 2019) with 2.3 GHz 8-Core Intel Core i9 and 16 GB memory. Running time for MetaCycle is the sum of the runing time for LS, ARSER, and JTK_CYCLE. Running time for BIO_CYCLE does not include the time used to fit the deep neural network.

Method	5K	10K	50K	100K	500K
LS	0.5667	0.5599	0.6785	0.7467	0.8188
JTK	0.6329	0.6141	0.6958	0.7604	0.7934
RAIN	0.6220	0.6781	0.8243	0.8501	0.8666
eJTK	0.6388	0.6008	0.6880	0.7775	0.8410
MC	0.6068	0.5982	0.7045	0.7514	0.8085
BC	0.4578	0.4947	0.6525	0.7463	0.7998

Supplementary Table 7. Performance assessment of downsampled RNA-seq data. AUC values of downsampled RNA-seq datasets with varying sequencing depths were calculated. Existing methods suffer from low sequencing depths. The performance of RAIN exceeds that of all other methods in all sequencing depths with an exception at 5K, due to its large number of significant genes detected in general. BIO_CYCLE consistently ranks the lowest at all but the highest sequencing depth. The performances of LS, JTK_CYCLE, eJTK_CYCLE, and MetaCycle are comparable.



Supplementary Figure 1. Circadian rhythm detection of Mus musculus liver protemoic dataset. (A) Bar plot of the number of significant proteins detected by each method using an FDR threshold of 0.05. Only methods that are able to handle both replicates and missing values were applied and evaluated. (B) Heatmap of scaled measurements of oscillatory proteins identified by at least two methods. Proteins (rows) are ordered based on their inferred phases.



Supplementary Figure 2. Decision tree as user guidance on method selection. The decision tree has decision rules for sampling resolutions, uneven samplings, replicates, and missing values.