

**Supplementary Figure 1.** DREM result. DREM found three clusters (green, gray and brown lines from the top). Three TFs are predicted to target a cluster colored in gray. Gene symbols (entrez IDs) of the TFs are FOXF2 (2295), NF1 (4763), SRF (6722).

Pathway	Pathway name	DEAP	TimeClip	SPIA	TRAP	
					pORA	pPERT
hsa00140	Steroid hormone biosynthesis	-	0.005	-	-	-
hsa00330	Arginine and proline metabolism	-	0.032	-	-	-
hsa00450	Selenocompound metabolism	-	0.016	-	-	-
hsa00830	Retinol metabolism	-	0.044	-	-	-
hsa04010	MAPK signaling pathway	-	-	-	0.000	0.035
hsa04014	Ras signaling pathway	-	0.047	-	-	-
hsa04015	Rap1 signaling pathway	-	0.006	-	0.000	0.043
hsa04022	cGMP-PKG signaling pathway	-	-	-	0.000	0.000
hsa04060	Cytokine-cytokine receptor interaction	-	-	-	0.000	0.000
hsa04062	Chemokine signaling pathway	-	-	-	0.000	0.046
hsa04080	Neuroactive ligand-receptor interaction	-	0.028	-	0.000	0.005
hsa04110	Cell cycle	-	0.032	-	-	-
hsa04115	p53 signaling pathway	-	0.036	-	-	-
hsa04270	Vascular smooth muscle contraction	-	-	-	0.000	0.001
hsa04340	Hedgehog signaling pathway	-	0.039	-	-	-
hsa04350	TGF-beta signaling pathway	-	-	0.002	-	-
hsa04370	VEGF signaling pathway	-	0.010	-	-	-
hsa04512	ECM-receptor interaction	-	0.030	0.002	0.000	0.001
hsa04540	Gap junction	-	-	-	0.006	0.013
hsa04611	Platelet activation	-	-	-	0.000	0.003
hsa04622	RIG-I-like receptor signaling pathway	-	0.015	-	-	-
hsa04630	Jak-STAT signaling pathway	-	0.021	0.002	-	-
hsa04668	TNF signaling pathway	-	-	-	0.030	0.000
hsa04720	Long-term potentiation	-	-	-	0.000	0.028
hsa04721	Synaptic vesicle cycle	0.000	-	-	-	-
hsa04723	Retrograde endocannabinoid signaling	-	-	-	0.000	0.000
hsa04724	Glutamatergic synapse	-	-	-	0.000	0.047
hsa04730	Long-term depression	-	-	-	0.001	0.002
hsa04740	Olfactory transduction	-	-	-	0.000	0.000
hsa04744	Phototransduction	-	-	-	0.000	0.048
hsa04912	GnRH signaling pathway	-	-	-	0.000	0.035
hsa04960	Aldosterone-regulated sodium reabsorption	-	0.048	-	-	-
hsa04970	Salivary secretion	-	-	-	0.000	0.001
hsa04971	Gastric acid secretion	-	0.019	-	0.000	0.000
hsa05010	Alzheimer's disease	-	-	-	0.000	0.002
hsa05133	Pertussis	-	-	-	0.000	0.010
hsa05134	Legionellosis	-	-	-	0.000	0.001
hsa05140	Leishmaniasis	-	-	-	0.000	0.000
hsa05143	African trypanosomiasis	-	-	-	0.000	0.034
hsa05144	Malaria	-	-	-	0.000	0.000
hsa05146	Amoebiasis	-	-	-	0.000	0.001
hsa05215	Prostate cancer	-	-	-	0.000	0.029
hsa05222	Small cell lung cancer	-	0.046	0.002	-	-
hsa05321	Inflammatory bowel disease (IBD)	-	-	-	0.000	0.019
hsa05323	Rheumatoid arthritis	-	-	-	0.000	0.006
hsa05412	Arrhythmogenic right ventricular cardiomyopathy (ARVC)	-	0.047	-	-	-

**Supplementary Table 1.** Pathways detected by other representative tools and not detected by TimeTP. Pathways with p-value over 0.05 are denoted as '-'.

Cluster	# of genes	Pathway	P-value	TF
Gray	71	NA	NA	FOXF2, NF1, SRF
Green	132	Focal adhesion	4.30E-04	
		Arrhythmogenic right ventricular cardiomyopathy (ARVC)	5.10E-03	
		Regulation of actin cytoskeleton	1.30E-02	
		Leukocyte transendothelial migration	2.30E-02	
		Pathways in cancer	2.90E-02	
		Small cell lung cancer	4.20E-02	
		ECM-receptor interaction	4.20E-02	
		Hypertrophic cardiomyopathy (HCM)	4.30E-02	
		Hematopoietic cell lineage	4.40E-02	
Brown	197	Phosphatidylinositol signaling system	2.60E-02	
		Taste transduction	7.40E-02	
		Inositol phosphate metabolism	7.90E-02	

**Supplementary Table 2.** Clustering result of DREM. Pathway analysis (Fisher's exact test) is performed by DAVID (Huang *et al.*, 2008).

## Reference

Huang, D. W., Sherman, B. T., & Lempicki, R. A. (2008). Systematic and integrative analysis of large gene lists using DAVID bioinformatics resources. *Nature protocols*, 4(1), 44-57.

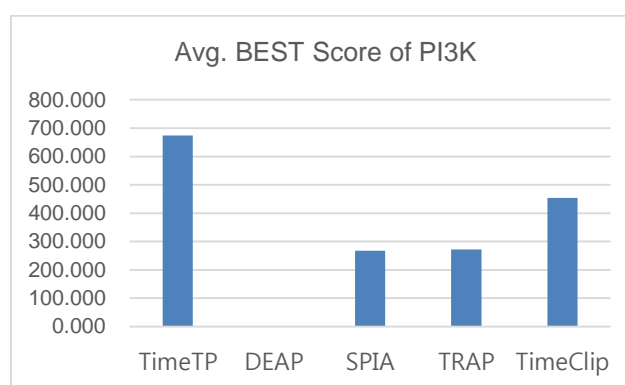
<b>Tool</b>	<b>TimeTP</b>	<b>DEAP</b>	<b>timeClip</b>	<b>SPIA</b>	<b>TRAP</b>
Time (s)	906.767 (408.862)	1776.885	94.989	398.474	1125.961

**Supplementary Table 3.** Running time of TimeTP and other pathway analysis tools using MCF10a dataset with 6 time points (Kiselev et al., 2015). Different from other tools, TimeTP include an additional process for regulator analysis in addition to pathway analysis. The number in brackets is the running time measured for pathway analysis only. (Intel(R) Xeon(R) CPU E7-4850 2.00GHz, CentOS 5.8. Python 2.7.3. for TimeTP, DEAP and TRAP. R 3.2.2 for timeClip and SPIA.)

Tool	pathwayID	pathwayName	Avg. BEST Score of PI3K
<b>TimeTP</b>	hsa04012	ErbB signaling pathway	34.417
	hsa04068	FoxO signaling pathway	39.465
	hsa04114	Oocyte meiosis	17.719
	hsa04151	PI3K-Akt signaling pathway	5888.045
	hsa04310	Wnt signaling pathway	203.205
	hsa04510	Focal adhesion	455.123
	hsa04520	Adherens junction	81.145
	hsa04666	Fc gamma R-mediated phagocytosis	0.000
	hsa04810	Regulation of actin cytoskeleton	21.974
	hsa04921	Oxytocin signaling pathway	0.000
<b>DEAP</b>	hsa04721	Synaptic vesicle cycle	0.000
<b>SPIA</b>	hsa04350	TGF-beta signaling pathway	7.100
	hsa04510	Focal adhesion	455.123
	hsa04512	ECM-receptor interaction	14.104
	hsa04630	Jak-STAT signaling pathway	135.708
	hsa05222	Small cell lung cancer	725.022
<b>TRAP</b>	hsa04010	MAPK signaling pathway	550.741
	hsa04015	Rap1 signaling pathway	4.825
	hsa04022	cGMP-PKG signaling pathway	8.847
	hsa04060	Cytokine-cytokine receptor interaction	12.712
	hsa04062	Chemokine signaling pathway	11.871
	hsa04080	Neuroactive ligand-receptor interaction	3.869
	hsa04151	PI3K-Akt signaling pathway	5888.045
	hsa04270	Vascular smooth muscle contraction	2.536
	hsa04510	Focal adhesion	455.123
	hsa04512	ECM-receptor interaction	14.104
	hsa04540	Gap junction	69.789
	hsa04611	Platelet activation	143.910
	hsa04668	TNF signaling pathway	1.459
	hsa04720	Long-term potentiation	74.123
	hsa04723	Retrograde endocannabinoid signaling	0.000
	hsa04724	Glutamatergic synapse	5.982
	hsa04730	Long-term depression	25.106
	hsa04740	Olfactory transduction	3.396
	hsa04744	Phototransduction	2.279
	hsa04912	GnRH signaling pathway	2.167
	hsa04921	Oxytocin signaling pathway	0.000
	hsa04970	Salivary secretion	0.190
	hsa04971	Gastric acid secretion	2.988
	hsa05010	Alzheimer's disease	287.818
	hsa05133	Pertussis	115.092
	hsa05134	Legionellosis	0.000
	hsa05140	Leishmaniasis	17.211
	hsa05143	African trypanosomiasis	0.000
	hsa05144	Malaria	20.215
	hsa05146	Amoebiasis	0.577
	hsa05215	Prostate cancer	967.044
	hsa05321	Inflammatory bowel disease (IBD)	93.237
	hsa05323	Rheumatoid arthritis	183.177
<b>TimeClip</b>	hsa00140	Steroid hormone biosynthesis	3.001
	hsa00330	Arginine and proline metabolism	0.000
	hsa00450	Selenocompound metabolism	0.000
	hsa00830	Retinol metabolism	0.000
	hsa04014	Ras signaling pathway	121.478
	hsa04015	Rap1 signaling pathway	4.825
	hsa04080	Neuroactive ligand-receptor interaction	3.869

hsa04110	Cell cycle	1795.028
hsa04115	p53 signaling pathway	54.785
hsa04151	PI3K-Akt signaling pathway	5888.045
hsa04310	Wnt signaling pathway	203.205
hsa04340	Hedgehog signaling pathway	51.371
hsa04370	VEGF signaling pathway	60.658
hsa04510	Focal adhesion	455.123
hsa04512	ECM-receptor interaction	14.104
hsa04622	RIG-I-like receptor signaling pathway	0.000
hsa04630	Jak-STAT signaling pathway	135.708
hsa04960	Aldosterone-regulated sodium reabsorption	0.000
hsa04971	Gastric acid secretion	2.988
hsa05222	Small cell lung cancer	725.022
hsa05412	Arrhythmogenic right ventricular cardiomyopathy (ARVC)	0.000

Avg BEST Score of PI3K	
<b>TimeTP</b>	674.109
<b>DEAP</b>	000.000
<b>SPIA</b>	267.412
<b>TRAP</b>	271.771
<b>TimeClip</b>	453.296



**Supplementary Table 4.** Pathways detected by TimeTP and other pathway analysis tools and their relevance to PI3K. Relevance to PI3K is evaluated using a state of the art context-aware literature search tool, BEST (<http://best.korea.ac.kr/>).