

# **Chronobiological analysis for the reliable identification of cell-cycle regulated genes from gene expression profiles.**

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Many biological processes are periodically regulated by intrinsic oscillators. Identifying such periodically co-regulated patterns from large-scale gene expression profiles can be used to reconstruct genetic regulatory networks. Simple cluster analysis with the following subjective visual inspection of the pattern periodicity was used to determine cell-cycle regulated clusters of genes. Cosinor analysis, which tests statistical significances of the cross-correlations between the temporal expression profiles and model-fitted cosine waves, can objectively determine the pattern periodicity with mesor and acrophase assignments at the individual expression profile level.

Cosinor analysis successfully identified 602 cell-cycle regulated ORFs showing significant cross-correlations between the temporal expression profiles and the model-fitted cosine curves among the 6,601 ORFs of the yeast cell-cycle data set from Cho *et al.* (1999). Acrophase of each ORF was evaluated for objective cell-cycle phase assignment. Comparison analysis of the objective phase assignments and functional annotations from MIPS and SGD showed high biological relevance. Detailed motif usage analysis showed that phase-specific motifs could be discovered not only in the G1, S, G2, M phases but also in all 10 minute interval groups. We could correct many mis-assigned ORFs by the previous investigators who have used simple cluster analysis that neglects temporal information of the time-series cell cycle data set and relies on subjective visual inspection. Interestingly, phase-shifted ORF-group analysis suggested that antagonistically-coregulated groups of motifs.

Utilizing temporal information and the objective determination of pattern periodicity are demonstrated to be essential in the reliable identification of cell-cycle regulated patterns and in reconstructing genetic regulatory networks.

## **50-word abstract:**

Chronobiological analysis can reliably identify periodical patterns from large-scale gene expression profiles. Objective determination of acrophase demonstrated high correlations between motifs-usage patterns and cell-cycle periodicity. Agonistic and antagonistic pairs of motifs are suggested and shown to be used to reconstruct genetic regulatory networks.

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