



SIXTH FRAMEWORK PROGRAMME

Specific Targeted Research Projects

PRIORITY 1

LIFE SCIENCES, GENOMICS AND BIOTECHNOLOGY FOR HEALTH

Contract no: LSHG-CT-2004-512143

DIAMONDS

Dedicated Integration And Modelling Of Novel Data and prior knowledge to enable Systems biology

EU Deliverable

D3.5

Sets of network modules and of cis-regulatory motifs

DIAMONDS Deliverable D3.5

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Version 1

Partner responsible: Søren Brunak (CBS)



Sets of network modules and of cis-regulatory motifs

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1 Executive Summary

Understanding the function and regulation of cell cycle related proteins by data integration is the main focus area of WP3. This deliverable report on the identification of a set of network modules and cis-regulatory motifs, as well as an investigation of the regulation of functional modules by extracting, mining, and integrating information from databases and large-scale expression data.

2 Background

The term module has been used with different meanings in biology, as explained in deliverable D3.4. Throughout this deliverable, the term network module will be used to refer to protein complexes, i.e. a collection of physically associated proteins.

Even though many studies in the last decades have investigated the functional role of single genes or proteins, it is well known that proteins work together in functional network modules. These protein complexes are thought to play a role in many, if not all, biological processes, and are known to be involved in all phases of the division process. Examples of known cell cycle complexes include the MCM complex, which is involved in DNA replication and the anaphase-promoting complex (APC) that play a crucial role in the mitotic phase of the division process.

The dynamic activation of protein complexes at just the right time in the division process is crucial to the cell's ability to complete an error-free duplication as the order in which processes are completed is essential, e.g. DNA replication must happen before cytokinesis. Consequently, understanding the regulation of protein complexes may be of great medical importance, especially since defects in the correct timing and execution of subprocesses during the cell cycle can lead to non-viable cells and tumors (Bartek *et al.*, 1999). The regulation of these functional modules can take place at many different levels, and transcriptional regulation, phosphorylation, and degradation have been found to play a major role in regulating the division process (Futcher,

2000). Assessing the transcriptional regulation of genes and proteins during the cell cycle is one of the key areas for the DIAMONDS project, and this can be achieved by taking samples from synchronously growing cell cultures and hybridized them to microarrays. By stringing together data points from the samples it is thus possible to obtain expression profiles for each gene in the genome. Subsequently, it is possible to determine if the gene is subjected to transcriptional regulation during the cell cycle by using computer algorithms to analyzing the expression profile is (see deliverable D3.3 for more details). This transcriptional regulation is partly governed by transcription factors that bind the upstream promoter region of a gene and exerts regulatory influence by either inhibiting or activating the transcription of the gene in question. The binding of transcription factors to the DNA is dependent on the presence of cis-regulatory motifs, ie nucleotide sequence patterns, and transcription factors are known to bind to rather specific motif. If a given motifs is found predominantly among genes that are regulated at transcriptional level during the cell cycle, the motif and the corresponding transcription factor is very likely to play a role in regulation the cell cycle. Information on the presence and absence of such cis-regulatory motifs would serve as a good starting point for expanding our current understanding of cell cycle regulation.

In the context of the DIAMONDS project, we have been mining literature and database for information regarding protein complexes and cis-regulatory motifs, as well as analyzed expression data to investigate the regulation of the cell cycle in general and the network modules in particular and compare it across organisms. We report here on this work.

3 Results

3.1 Functional modules

Decades of research has together with the availability of whole genomes made it clear that many of the core components involved in the cell cycle are conserved, both functionally and structurally, across eukaryotes. These proteins are organized in complexes and modules, which are activated or deactivated at specific stages during the cell cycle. In previous work, we have extracted potential and known protein complex from *S. cerevisiae* (de Lichtenberg *et al.* 2005), which can be seen as a rather elaborative catalog of functional modules of which only a subset is found in other organisms. In this deliverable, we have chosen to focus on annotating a set of cell cycle related protein complexes that are present in the four species of particular interest to the DIAMONDS consortium, *S. cerevisiae*, *S. pombe*, *A. thaliana*, and *H. sapiens*.

We chose protein complexes with a role in DNA replication, cohesion, and targeted degradation to avoid bias towards a particular cell cycle phase (Jensen *et al.*, 2006). The composition of the individual complexes as well as annotation of the individual subunits were manually extracted from articles and databases including Reactome (Vastrik *et al.*, 2007), UniProt (Uniprot consortium, 2007), ensembl (Hubbard *et al.*, 2007) , The Arabidopsis Information Resource (TAIR) (Rhee *et al.*, 2003). The composition of the protein complexes in each of the four organisms can be

found in Appendix A. We have made the complexes available in sif-format for the DIAMONDS consortium, such that integration of large-scale data on these complexes, such as expression data, can be done easily in Cytoscape, a publicly available data integration tool.

3.2 Regulation of functional modules during the cell cycle

The dynamic activation of the functional modules is key in securing a fully functional daughter cell. To investigate the activation of the functional modules as well as getting a starting point for finding important cell cycle regulatory motifs, microarray expression data from synchronously growing cell cultures of *S. cerevisiae* (Spellman *et al.*, 1998, Cho *et al.*, 1998), *S. pombe* (Rustici *et al.*, 2005, Oliva *et al.* 2006, Peng *et al.* 2006), *A. thaliana* (Menges *et al.*, 2003), and *H. sapiens* (Whitfield *et al.*, 2003) were analyzed with the state of the art analysis method (described in deliverable D3.4) and the quality of the analysis results were benchmarked (*H. sapiens* and *A. thaliana* benchmarks depicted in Figure 1).

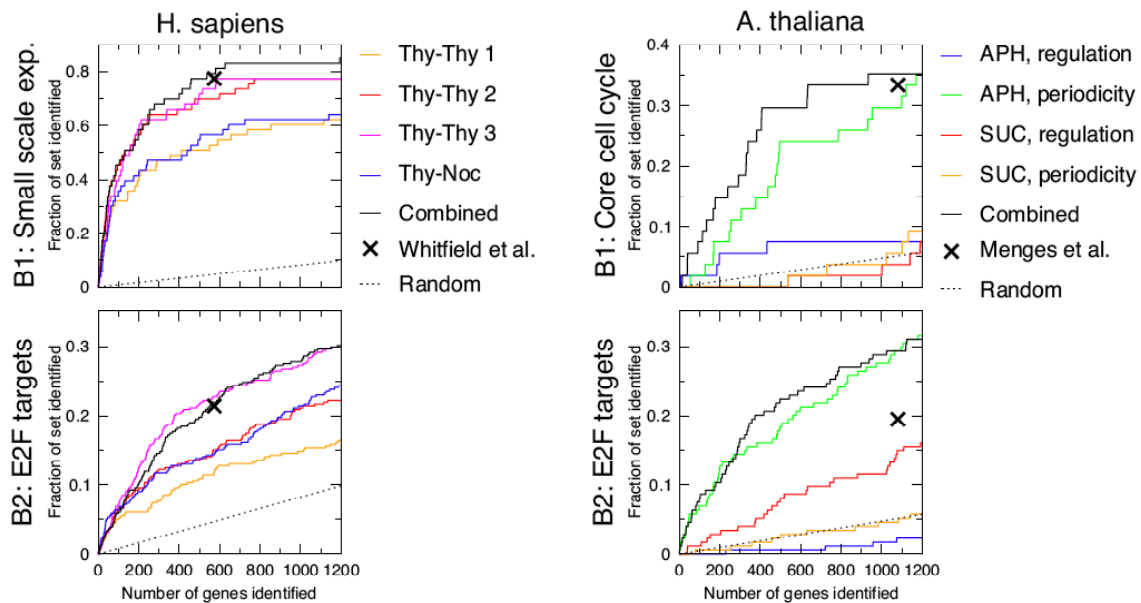


Figure 1: **Benchmarking of the proposed list of cell cycle regulated genes.** Based on array analysis, a ranked list of cell cycle regulated genes was proposed for each organism. These lists were benchmarked against lists of cell cycle regulated genes in each organism. The quality of the human data is fine while the data from *A. thaliana* is of poor quality.

In *S. cerevisiae*, three different experiments were analyzed and this lead to the identification of 600 cell cycle regulated genes (de Lichtenberg *et al.*, 2005), where as 500 genes were identified as cell cycle regulated in *S. pombe* based on ten cell cycle experiments (Marguerat *et al.*, 2006). Microarray data from four *H. sapiens* experiments were analyzed and 600 genes were subsequently identified as cell cycle regulated. Unfortunately, the expression data of *A. thaliana* was of poor quality, as can be seen from Figure 1, and the subset of 400 cell cycle regulated genes must be expected to be of similar quality (Jensen *et al.*, 2006).

For each of the cell cycle regulated genes the time of maximal expression, the peak time, was calculated. This peak time was averaged across the experiments and the average peak time is thus a measurement of when in the division cycle the gene is active. To investigate the dynamic activation of the functional modules, the peak time for the cell cycle regulated genes were mapped onto their corresponding proteins for *S. cerevisiae*, *S.pombe*, and *H. sapiens*. This integration revealed that only a subset of the proteins in a protein complex are regulated at transcriptional level, and the identity of which genes are regulated change across organisms. However, this change occurs in such a way that the dynamic activation of the entire protein complex is conserved (Jensen *et al.*, 2006) as depicted in Figure 2.

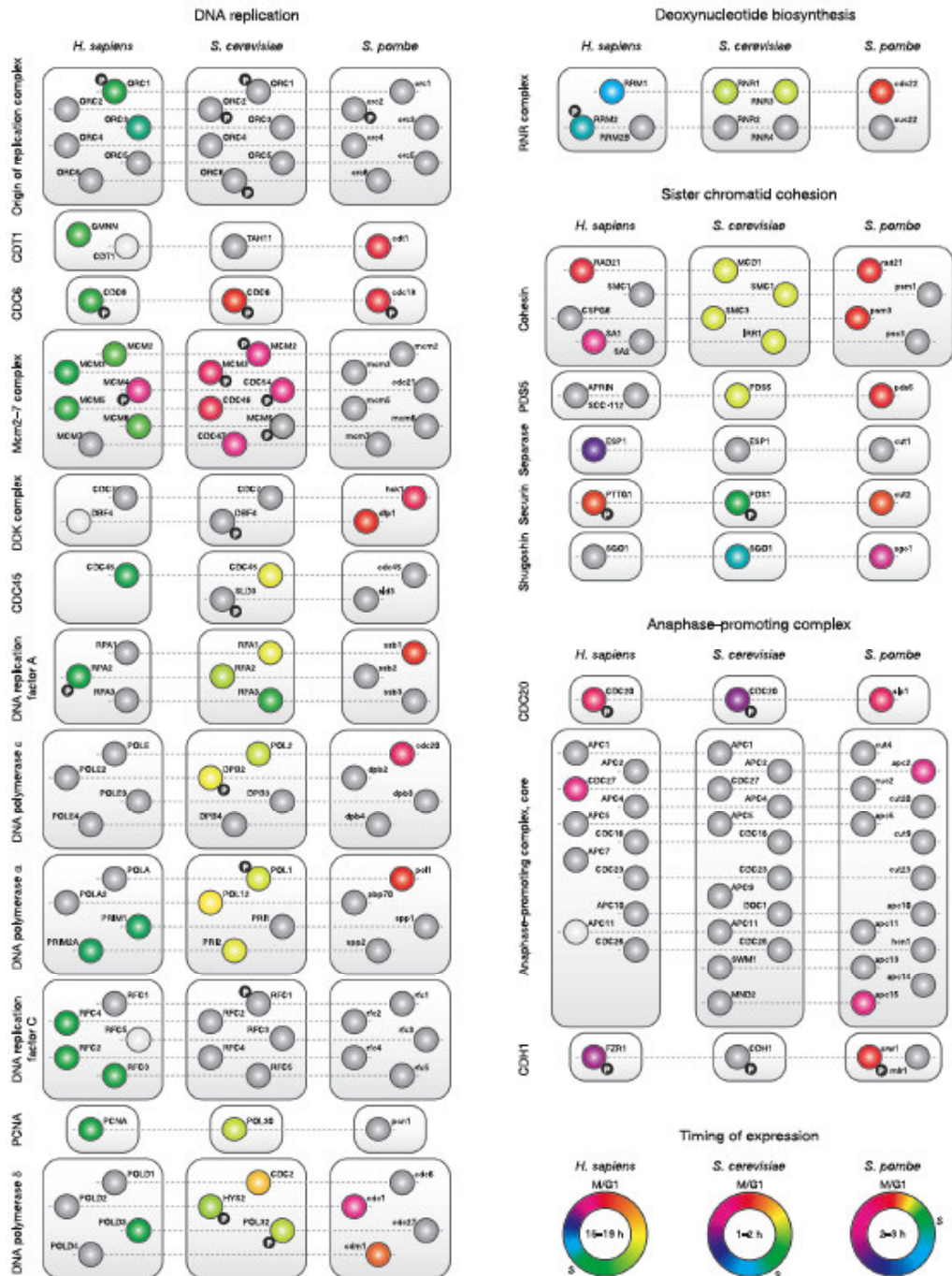


Figure 2: **Regulation of functional modules.** Different proteins in the functional modules are regulated at transcriptional level, but there appears to be conservation at the protein complex assembly level (Jensen *et al.*, 2006).

3.3 Cis-regulatory motifs

Expression data provides only indirect evidence on the regulatory mechanisms underlying the observed expression pattern, but can be used as a starting point for examining promoter motifs that are involved in regulation of the functional modules

and cell cycle genes in general. Transcription factors play an important part in temporally regulating mRNA levels of genes involved in the division process, and have a direct role in driving the cell cycle. Transcription factors and their binding motifs have been well studied in *S. cerevisiae*, whereas information about transcription factors in other species is severely lacking. In order to determine the factors involved in cell-cycle regulation, we did both a literature review and compared *S. cerevisiae* transcription factors and their targets to ortholog proteins in *S. pombe*.

Based on literature search and mining of databases (Matys *et al.*, 2006, Zhu *et al.*, 1999, Maclsaac *et al.*, 2006) we found a 12 transcription factors that are know to be involved in *S. cerevisiae* cell-cycle regulation (see below). We then mapped each of these to their respective *S. pombe* orthologs, giving nine likely transcription factors for *S. pombe* (V. Wood, 2006):

	<i>S. cerevisiae</i> Transcription Factor	<i>S. pombe</i> ortholog
1.	ACE2 (YLR131C)	ace2 (SPAC6G10.12C)
2.	FKH1 (YIL131C)	fkh2 (SPBC16G5.15C)
3.	FKH2 (YNL068C)	fkh2 (SPBC16G5.15C)
4.	MBP1 (YDL056W)	res2 (SPAC22F3.09C)
5.	MCM1 (YMR043W)	mbx1 (SPBC19G7.06) map1 (SPAC11E3.06)
6.	NDD1 (YOR372C)	
7.	RME1 (YGR044C)	
8.	SKN7 (YHR206W)	hsf1 (SPAC2E12.02) prr1 (SPAC8C9.14)
9.	STB1 (YNL309W)	
10.	SWI4 (YER111C)	res1 (SPBC725.16)
11.	SWI5 (YDR146C)	
12.	SWI6 (YLR182W)	cdc10 (SPBC336.12C)

The genomic binding sites of individual transcription factors for the 12 *S. cerevisiae* transcription factors have been determined from both ChIP-chip studies (Lee *et al.*, 2002, Harbison *et al.*, 2004) and small-scale studies. These experiments have lead to the identification of transcription factor specific consensus motifs (see Figure 3 for an example of a cis-regulatory motif) for many transcription factors, including the 12 cell cycle-related transcription factors listed above, which can be found in the appendix B.

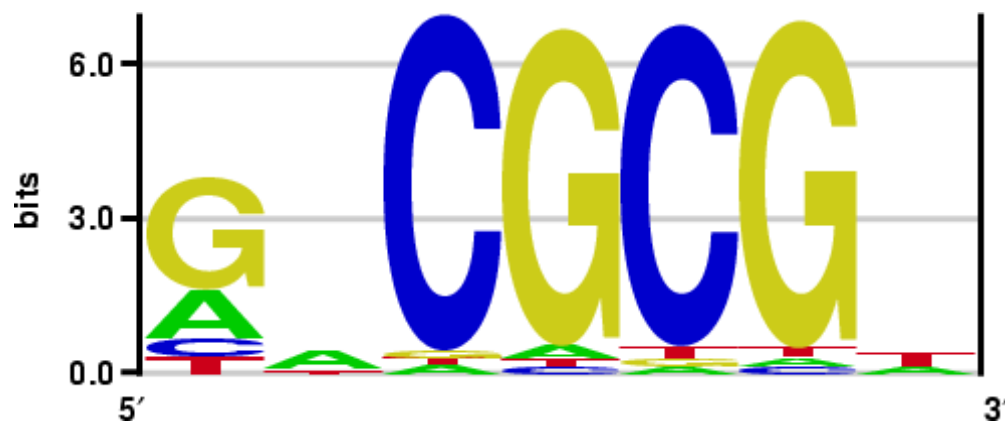


Figure 3. Cis-regulatory motif for the MBP1 transcription factor.

Unfortunately, transcription factor binding data, consensus sequences, and other cell-cycle transcript regulation data is not readily available for *S. pombe*. We applied motifs specific scoring matrices for each of the 12 transcription factors to the promoter region of cell cycle regulated genes in *S. cerevisiae* and *S. pombe*. These lists of cis-regulatory motifs for cell cycle regulated proteins in the two yeasts have been made available for the DIAMONDS consortium to provide a starting point for the DIAMONDS consortium to investigate the role of cis-regulatory motif and its conservation across the four species of interest.

4. Conclusions

A set of functional modules has been identified and their regulation during the cell cycle has been examined and compared across *H. sapien*, *S. cerevisiae*, and *S. pombe*. This comparison revealed that transcriptional regulation is not conserved on single gene level, but instead appears to be conserved at functional modules level, which we consider to be a major result for the DIAMONDS project. Furthermore, a set of cis-regulatory motifs has been identified in *S. cerevisiae* and a genome wide search of the presence of these motifs in *S. pombe* and *S. cerevisiae* have been conducted.

5. Publications and resources related to this deliverable

- **Co-evolution of transcriptional and posttranslational cell-cycle regulation, Jensen LJ, Jensen TS, de Lichtenberg U, Brunak S, Bork P, NATURE 443 (7111): 594-597 OCT 5 2006**
The paper presents the analysis of expression data, mapping of peak time, and comparison of the dynamic activation of functional modules across the three species.
- **The more the merrier: Comparison and integrative analysis of microarray studies on cell-cycle-regulated genes in schizosaccharomyces pombe, Marguerat, S, Jensen, TS, de Lichtenberg, U, Wilhelm, BT, Jensen, LJ and Bähler, J, Yeast, 2006, 3(4):261-77.**
This paper describes the combined analysis of all ten experiments in fission yeast performed in collaboration between partners 5 and 11.
- **www.cbs.dtu.dk/cellcycle.**
This website contains the results of our analyses in addition to benchmark sets and supplementary information on our work.

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Supplementary files:

[Human Cell Cycle complexes](#) (Cytoscape sif file)

[S. cer. cell cycle complexes](#) (Cytoscape sif file)

[S. cer. transcription factor motifs](#) (txt file)

[S. pombe cell cycle complexes](#) (Cytoscape sif file)

[S. pombe transcription factor motifs](#) (txt file)

Appendix A

Composition of the functional modules

Complex	H_sapiens	S_cerevisiae	S_pombe	A_thaliana
>GO:5664 nuclear origin of replication recognition complex				
Origin of replication complex subunit 1	ENSP00000262678	YML065W	SPBC29A10.15	AT4G14700/ AT4G12620
Origin of replication complex subunit 2	ENSP00000234296	YBR060C	SPBC685.09	AT2G37560
Origin of replication complex subunit 3	ENSP00000257789	YLL004W	SPAC3H1.01C	AT5G16690
Origin of replication complex subunit 4	ENSP00000338021	YPR162C	SPBP23A10.13	AT2G01120
Origin of replication complex subunit 5	ENSP00000297431	YNL261W	SPBC646.14C	AT4G29910
Origin of replication complex subunit 6	ENSP00000219097	YHR118C	SPBC2A9.12	AT1G26840
CDT1	ENSP00000301019	YJR046W	SPBC428.18	AT2G31270/ AT3G54710
CDC6	ENSP00000209728	YJL194W	SPBC14C8.07C	AT1G07270/ AT2G29680
>GO:42555 MCM complex				
MCM2 subunit	ENSP00000265056	YBL023C	SPBC4.04C	AT1G44900
MCM3 subunit	ENSP00000229854	YEL032W	SPCC1682.02C	AT5G46280
MCM4 subunit	ENSP00000336781	YPR019W	SPCC16A11.17	AT2G16440
MCM5 subunit	ENSP00000216122	YLR274W	SPAC1B2.05	AT2G07690
MCM6 subunit	ENSP00000264156	YGL201C	SPBC211.04C	AT5G44635
MCM7 subunit	ENSP00000307288	YBR202W	SPBC25D12.03C	AT4G02060
>GO:0031431 DDK (Dbf4-dependent protein kinase complex)				
CDC7	ENSP00000234626	YDL017W	SPBC776.12C	AT4G16970
DBF4	ENSP00000265728	YDR052C	SPCC550.13	
CDC45	ENSP00000263201	YLR103C	SPAC17D4.02	AT3G25100
>GO:5662 DNA replication factor A complex				
RFA subunit 1	ENSP00000254719	YAR007C	SPBC660.13C	AT2G06510/ AT4G19130/ AT5G45400
RFA subunit 2	ENSP00000263698	YNL312W	SPCC1753.01C	AT2G24490/ AT3G02920
RFA subunit 3	ENSP00000223129	YJL173C	SPCC23B6.05C	
>GO:8622 DNA polymerase epsilon complex				
DNA polymerase epsilon, subunit A/I,	ENSP00000322570	YNL262W	SPBC25H2.13C	AT1G08260/ AT2G27120

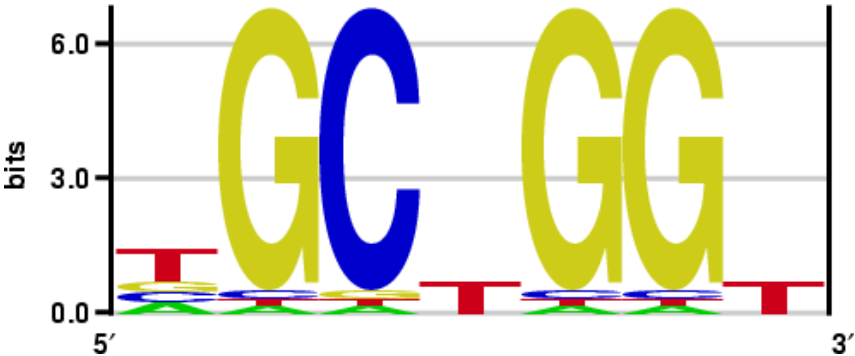
catalytic				
DNA polymerase epsilon, subunit B/II	ENSP00000216367	YPR175W	SPBP8B7.14C	AT5G22110
DNA polymerase epsilon, subunit C/III	ENSP00000277334	YBR278W	SPAC17G8.03C	
DNA polymerase epsilon, subunit D/IV	ENSP00000341370	YDR121W	SPBC3D6.09	AT2G27470
>GO:5658 DNA polymerase alpha primase complex				
DNA polymerase alpha catalytic subunit (pol1)	ENSP00000314415	YNL102W	SPAC3H5.06C	AT5G67100
DNA polymerase alpha B-subunit (pol12)	ENSP00000265465	YBL035C	SPCC553.09C	AT1G67630
DNA primase small subunit (pri1)	P49642	YIR008C	SPAC6B12.10C	AT5G41880
DNA primase large subunit (Pri2)	P49643	YKL045W	SPBC17D11.06	AT1G67320
>GO:5663 DNA replication factor C complex				
RFC subunit 1	ENSP00000340772	YOR217W	SPBC23E6.07C	AT5G22010
RFC subunit 2	ENSP00000296273	YJR068W	SPAC23D3.02	AT1G21690
RFC subunit 3	ENSP00000229043	YNL290W	SPAC27E2.10C	AT1G77470
RFC subunit 4	ENSP00000055077	YOL094C	SPAC1687.03C	AT1G63160
RFC subunit 5	ENSP00000255484	YBR087W	SPBC83.14C	AT5G27740
>PCNA				
PCNA, sliding clamp	ENSP00000254983	YBR088C	SPBC16D10.09	AT1G07370/ AT2G29570
>GO: 5659 DNA polymerase delta complex				
Pol III/delta subunit catalytic (p125)	ENSP00000262266	YDL102W	SPBC336.04	AT5G63960
Pol III/delta subunit 2 (p50)	ENSP00000223361	YJR006W	SPAC27E2.05	AT2G42120
Pol III/delta subunit 3 (p66)	ENSP00000263681	YJR043C	SPBC337.18C	AT1G78650
Pol III/delta subunit 4 (p12)	ENSP00000311368		SPBC12D12.02C	AT1G09815
>GO:5671 Ribonucleoside-diphosphate reductase complex				
RNR, large subunit	ENSP00000300738	YER070W		
	ENSP00000302955/	/YIL066C	SPAC1F7.05	AT2G21790
RNR, small subunit	ENSP00000251810	YJL026W/		AT3G23580/
		YGR180C	SPBC25D12.04	AT3G27060
>GO:0005680 anaphase-promoting complex				
Apc1	ENSP00000339109	YNL172W	SPBC106.09	AT5G05560
Apc2	ENSP00000314004	YLR127C	SPBP23A10.04	AT2G04660
	ENSP00000066544/			AT2G20000/
Apc3	ENSP00000339394	YBL084C	SPAC17C9.01C	AT3G16320

Apc4	ENSP00000318775	YDR118W	SPAC19G12.01C	AT4G21530
Apc5	ENSP00000261819	YOR249C	SPAC959.09C	AT1G06590
Apc6	ENSP00000252457	YKL022C	SPAC6F12.15C	AT1G78770
Apc7				ENSP00000 346363 N/I
Apc8	ENSP00000209827	YHR166C	SPAC6F12.14	AT3G48150
Apc9		YLR102C		
Apc10	ENSP00000310071	YGL240W	SPBC1A4.01	AT2G18290
Apc11	ENSP00000328790/ ENSP00000339695/ ENSP00000297808/ ENSP00000319439	YDL008W	SPAC343.03	AT3G05870
Cdc26		YFR036W	SPAC23C11.12	
Apc13		YDR260C	SPBC28E12.01C	
Apc14			SPAC27D7.05C	
Apc15	ENSP00000227618	YIR025W	SPBC83.04	
APC activators				
Cdc20	ENSP00000308450/ ENSP00000334322	YGL116W	SPAC821.08C	AT4G33260/ AT4G33270 AT4G11920/ AT4G22910/ AT5G13840
Cdh1	ENSP00000321800	YGL003C	SPAC144.13C/SP BC1198.12	
Ama1		YGR225W		

Appendix B

Regulatory motifs for cell cycle related *S. cerevisiae* transcription factors:

ACE2:



FKH1:



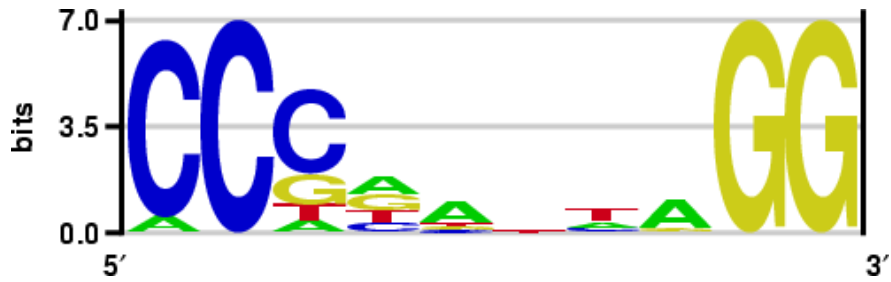
FKH2:



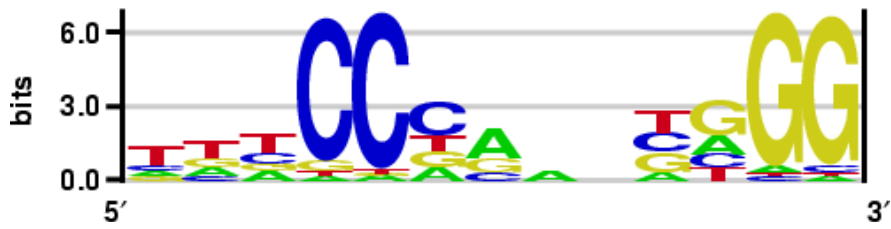
MBP1:



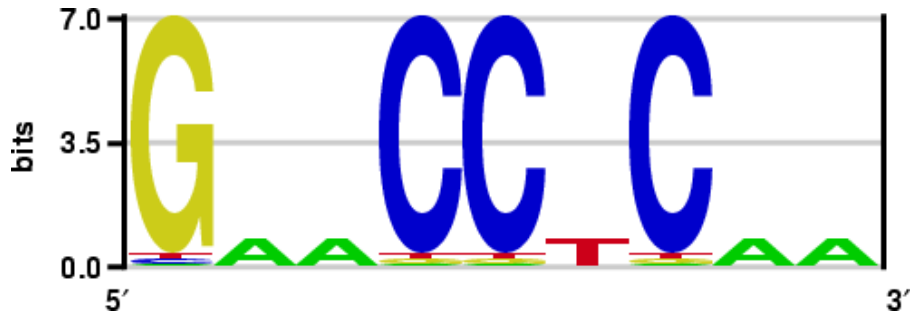
MCM1:



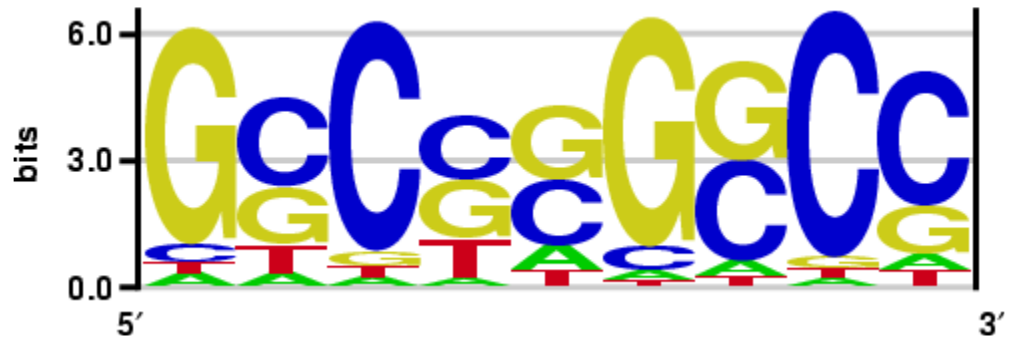
NDD1:



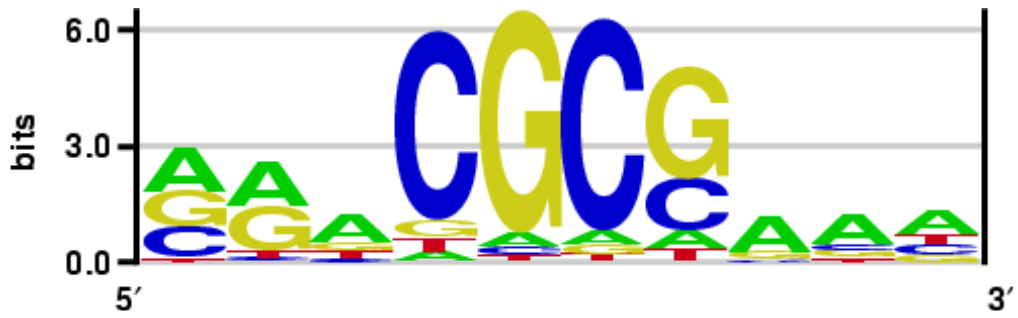
RME1:



SKN7:



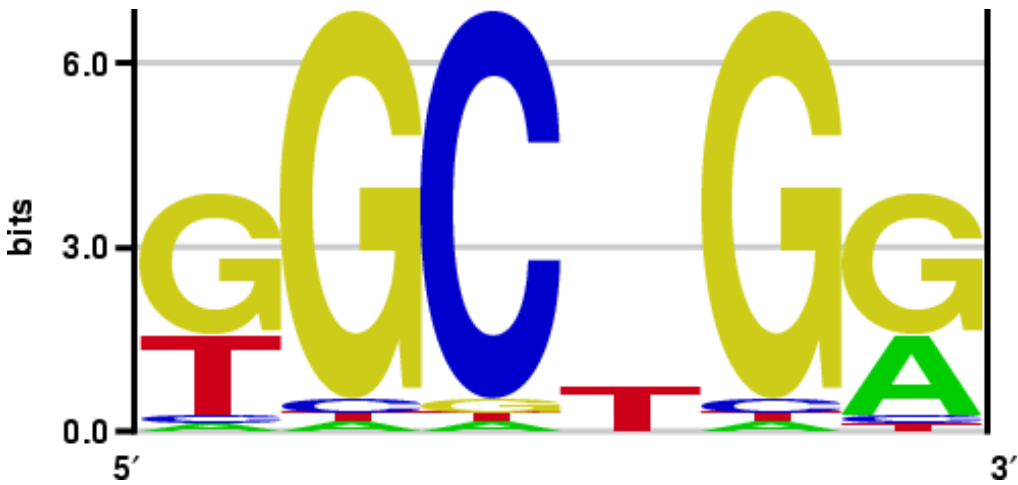
STB1:



SWI4:



SWI5:



SWI6:

