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by

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# Stress concentration in a transversely isotropic medium near a hyperboloid notch in pure shear and bending

<b>Stress</b>	iga doktorandi “parim sõber”
<b>concentration</b>	seal kus on, sinna tuleb juurde
<b>transversely</b>	<i>tranverse - (of an automotive engine) mounted with the crankshaft oriented sideways.</i>
<b>isotropic</b>	saun Saharas (iso = suur, tropic = kuum)
<b>medium</b>	<i>a person through whom the spirits of the dead are alleged to be able to contact the living</i>
<b>hyperboloid</b>	Insener Garini Hüperboloid “Öö on siin soe, ...”
<b>notch</b>	<i>to score, as in a game</i>
<b>pure</b>	<i>untainted with evil; innocent</i>
<b>shear</b>	<i>to divide, apportion, or receive equally.</i>
<b>bending</b>	<i>to force (an object, esp. a long or thin one) from a straight form into a curved or angular one</i>

Kokkuvõtvalt: üks süütu läheb Sahara kõrbes sumedas öös (suitsu)sauna, et vabaneda nädala jooksul kogunenud stressipunktidest nukkvõlli vibutava nõia abiga. Sauna aga koguneb rahvast juurde ning nõia leiliviskamise ajal tõmbavad kõik küüru selga ning naudivad ühtlast leili.

Ja seda kõike Springeris?!

# Dynamic Remodeling of Individual Nucleosomes Across a Eukaryotic Genome in Response to Transcriptional Perturbation

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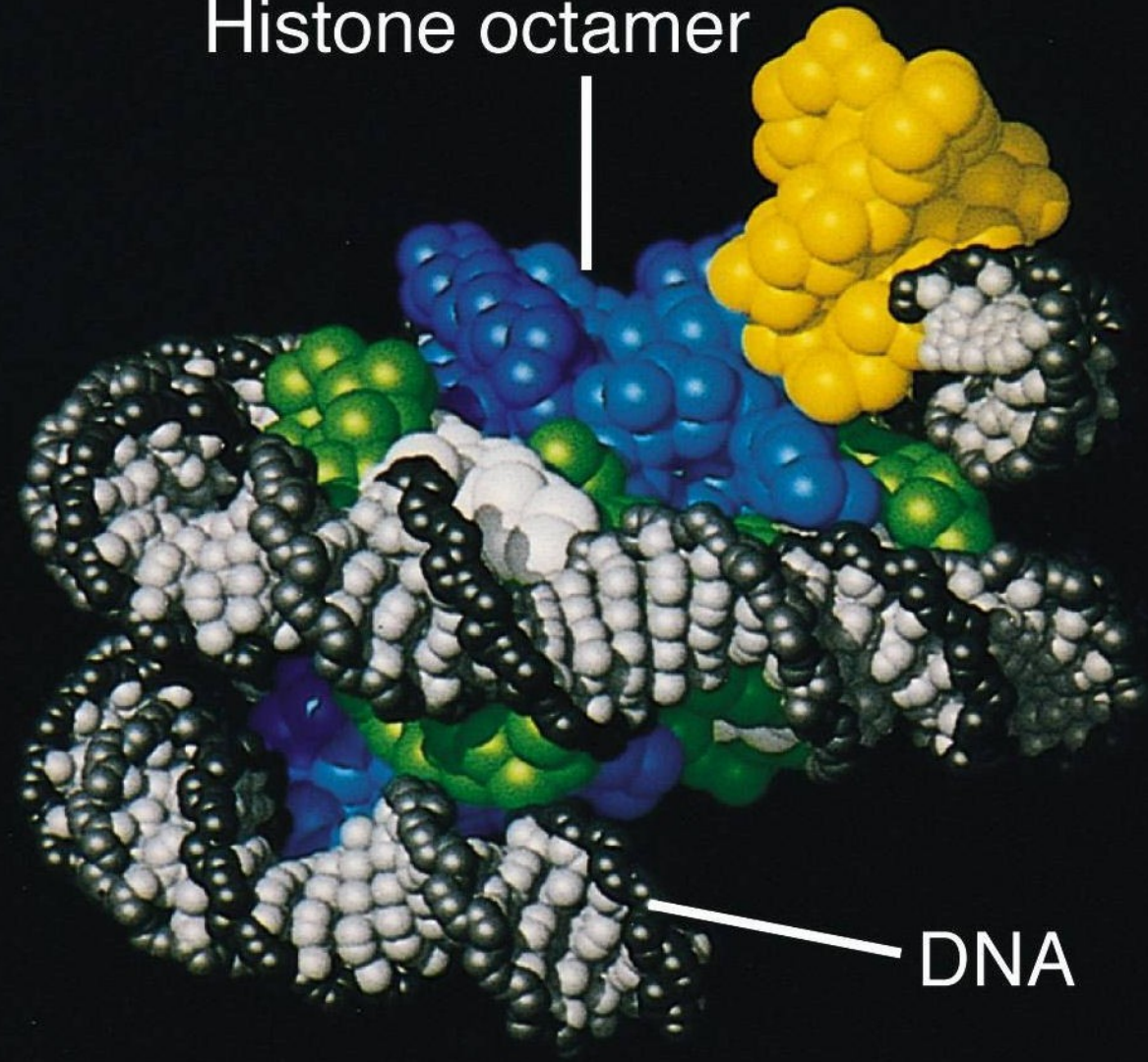
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**The eukaryotic genome is packaged as chromatin with nucleosomes comprising its basic structural unit, but the detailed structure of chromatin and its dynamic remodeling in terms of individual nucleosome positions has not been completely defined experimentally for any genome. We used ultra-high-throughput sequencing to map the remodeling of individual nucleosomes throughout the yeast genome before and after a physiological perturbation that causes genome-wide transcriptional changes. Nearly 80% of the genome is covered by positioned nucleosomes occurring in a limited number of stereotypical patterns in relation to transcribed regions and transcription factor binding sites. Chromatin remodeling in response to physiological perturbation was typically associated with the eviction, appearance, or repositioning of one or two nucleosomes in the promoter, rather than broader region-wide changes. Dynamic nucleosome remodeling tends to increase the accessibility of binding sites for transcription factors that mediate transcriptional changes. However, specific nucleosomal rearrangements were also evident at promoters even when there was no apparent transcriptional change, indicating that there is no simple, globally applicable relationship between chromatin remodeling and transcriptional activity. Our study provides a detailed, high-resolution, dynamic map of single-nucleosome remodeling across the yeast genome and its relation to global transcriptional changes.**

# Aim of the work

Map remodeling of individual nucleosomes before and after a physiological perturbation that causes genome-wide transcriptional changes in *S. cerevisiae*

Histone octamer



DNA

# Nucleosome positions

- influenced by the remodelers & transcriptional machinery
- determined by the intrinsic signals in genomic DNA (Segal et al)

# Positions mapped

- Previously used tiling arrays (5bp resolution)
- This study: Solexa high-throughput sequencing of nucleosome associated DNA ends (1bp resolution)
- Comparison of individual nucleosome positions in different biological conditions

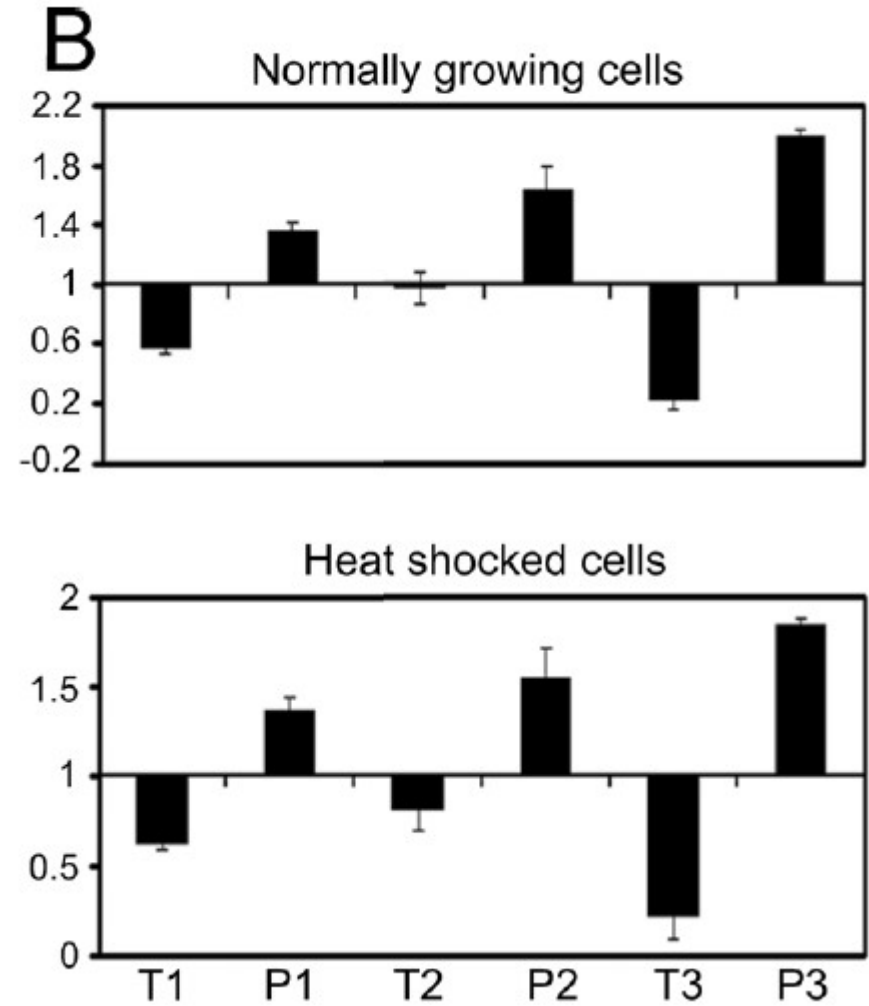
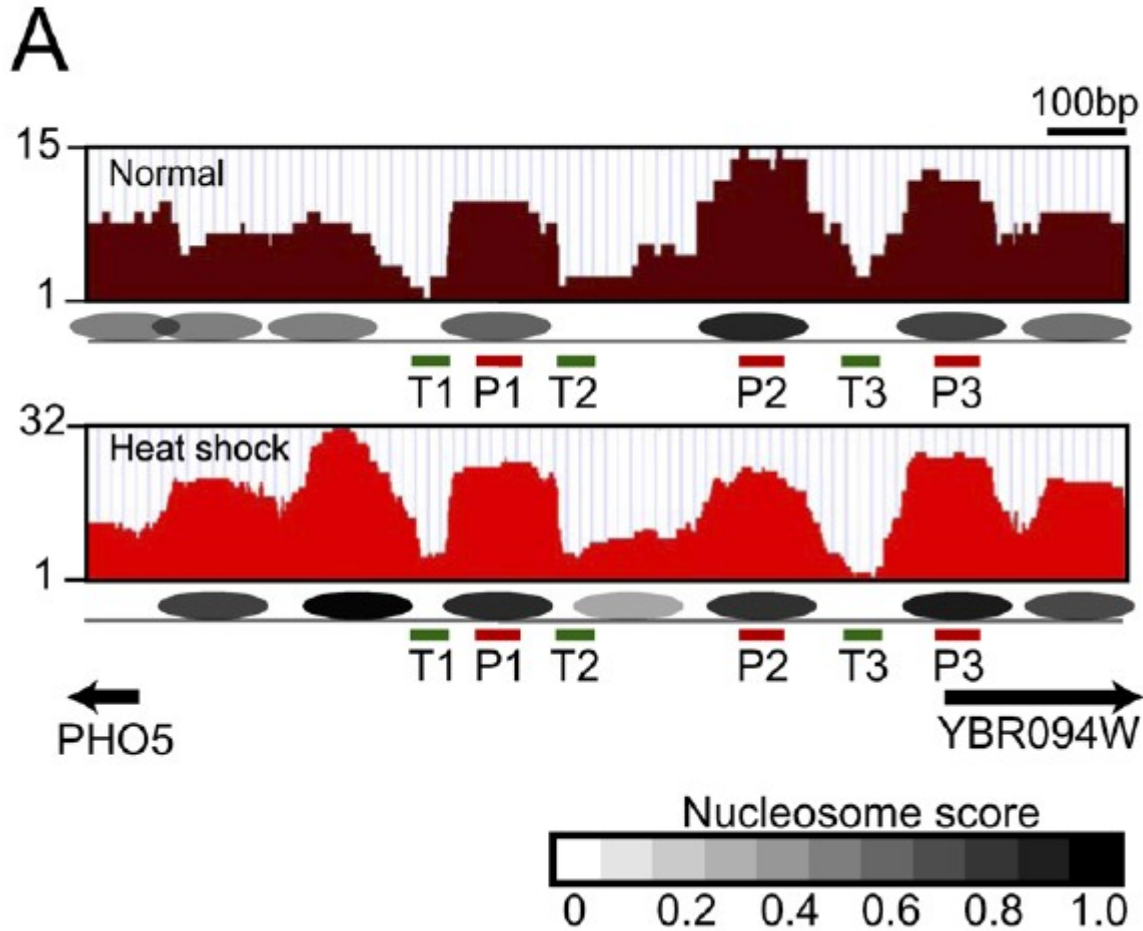
# Study build-up

- Normal condition vs heat-shock (15')
- Extract mononucleosome-associated DNA
- Sequence ends of the fragments
- Take only uniq reads
- Align reads to the genome
- Define peaks with width 146bp
- Score such peaks from 2 replicates

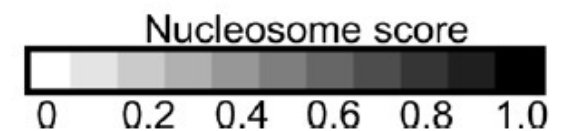
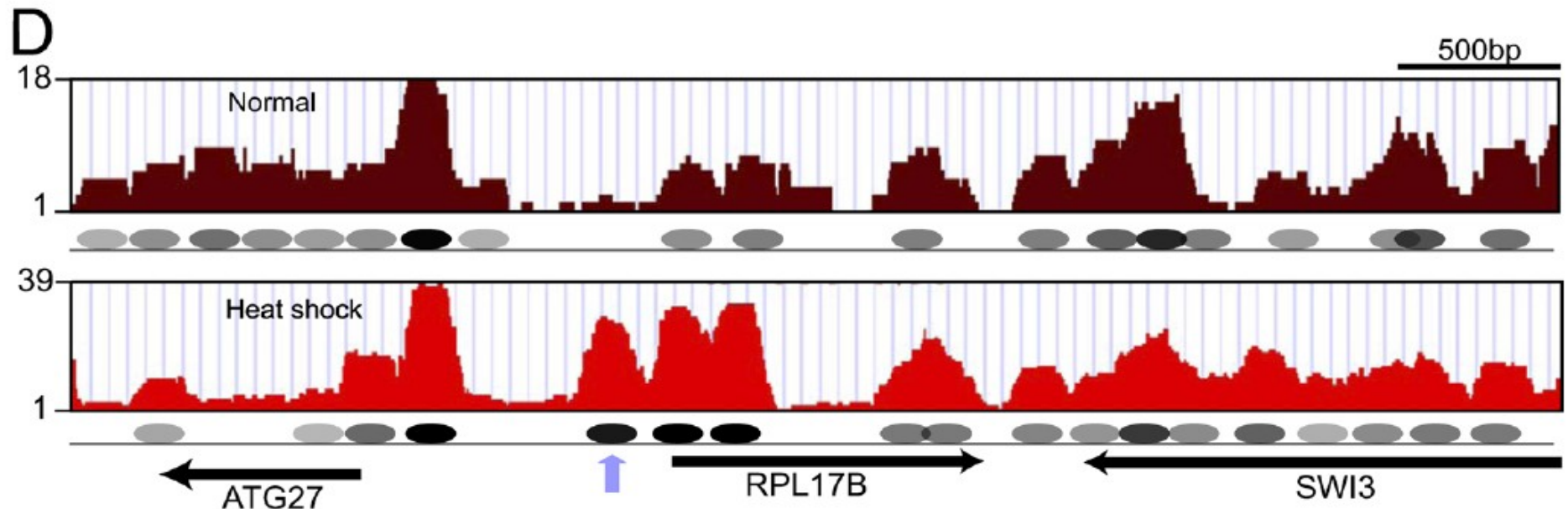
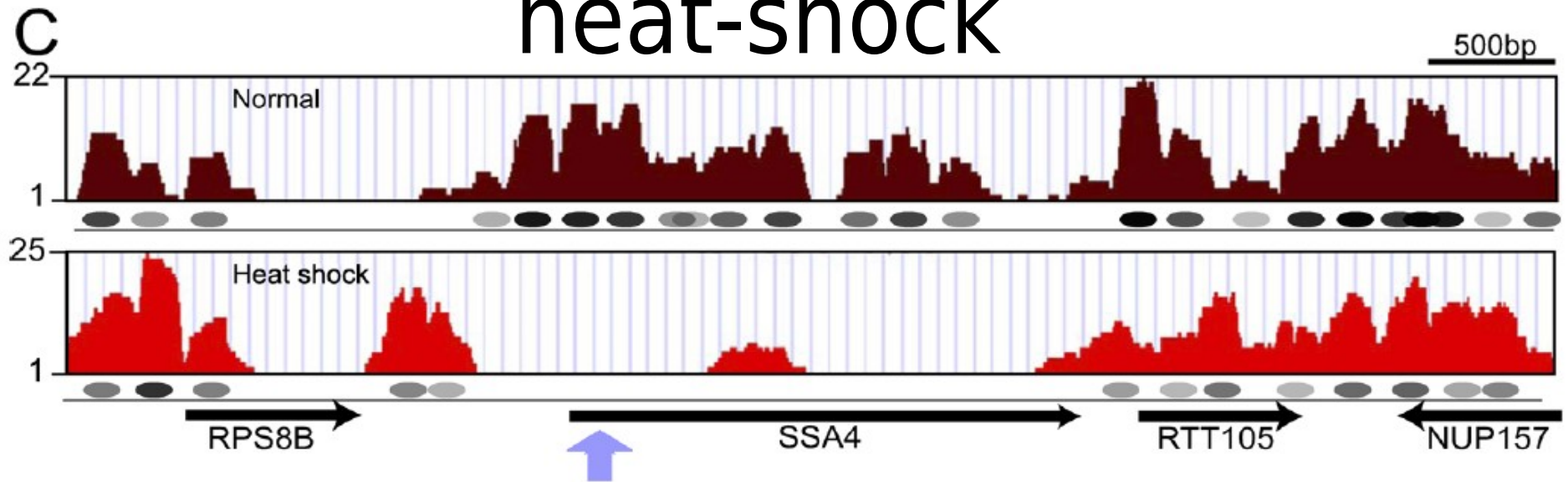


- Number of nucleosomes:
  - 49043 normal cells
  - 52817 heat-shocked cells
- 73% of yeast genome covered by a positioned nucleosome (estimation 78%)
- Mapped nucleosome positions overlap with other studies

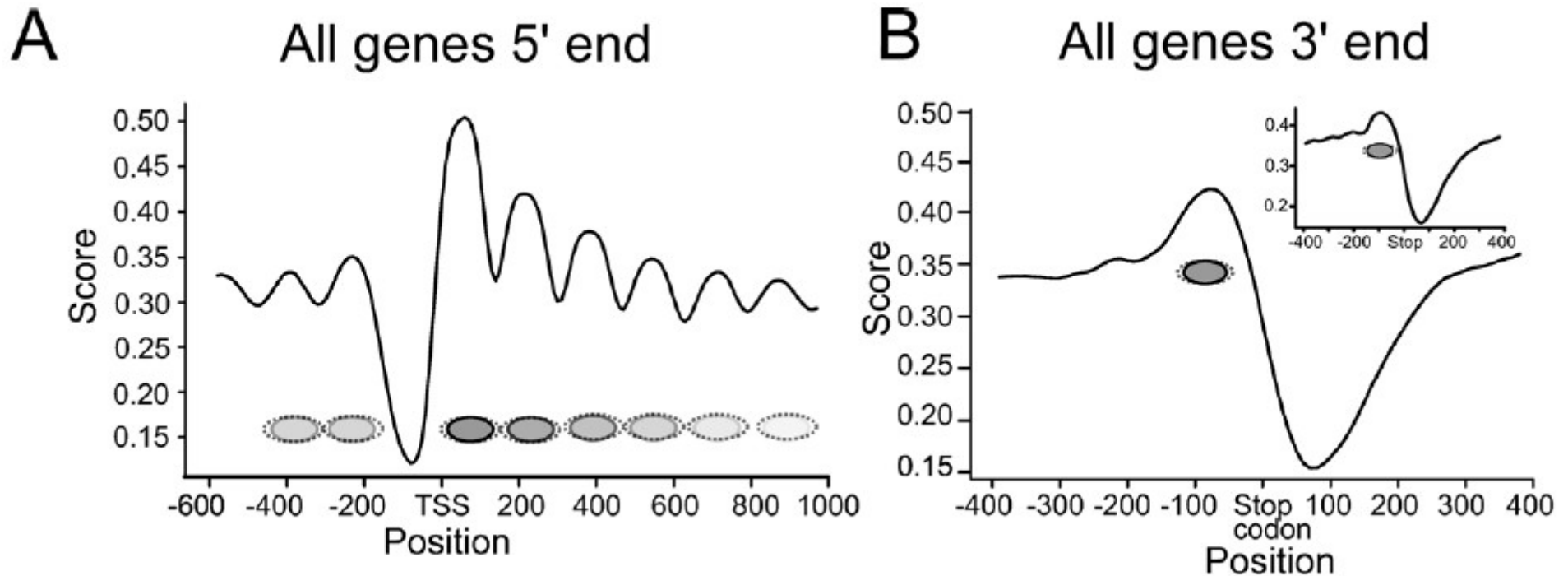
# Control (PHO5)



# Activation (C) and repression (D) by heat-shock



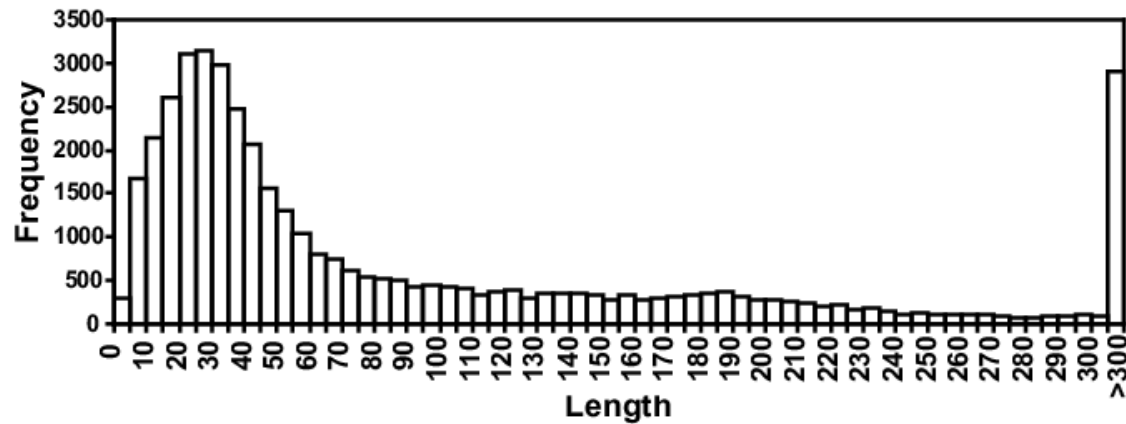
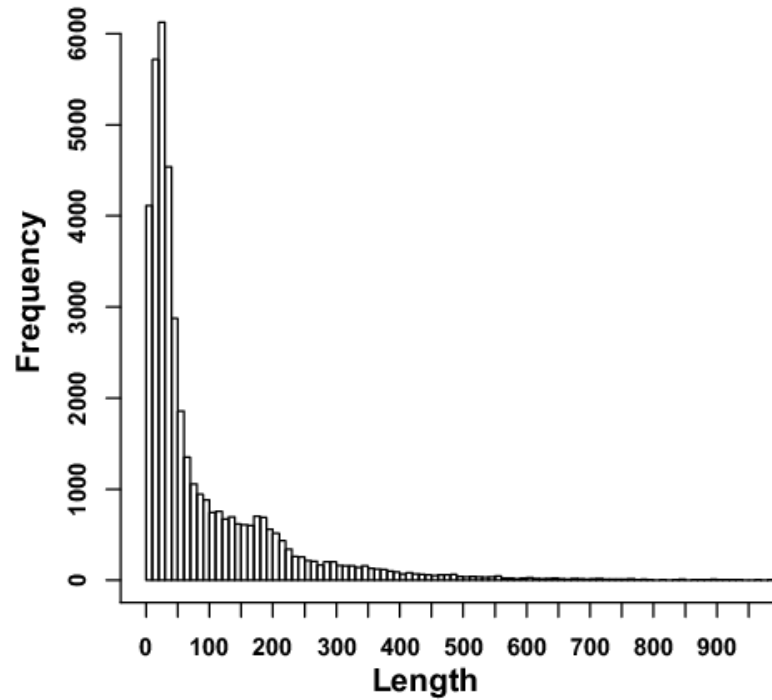
# Average nucleosome profile



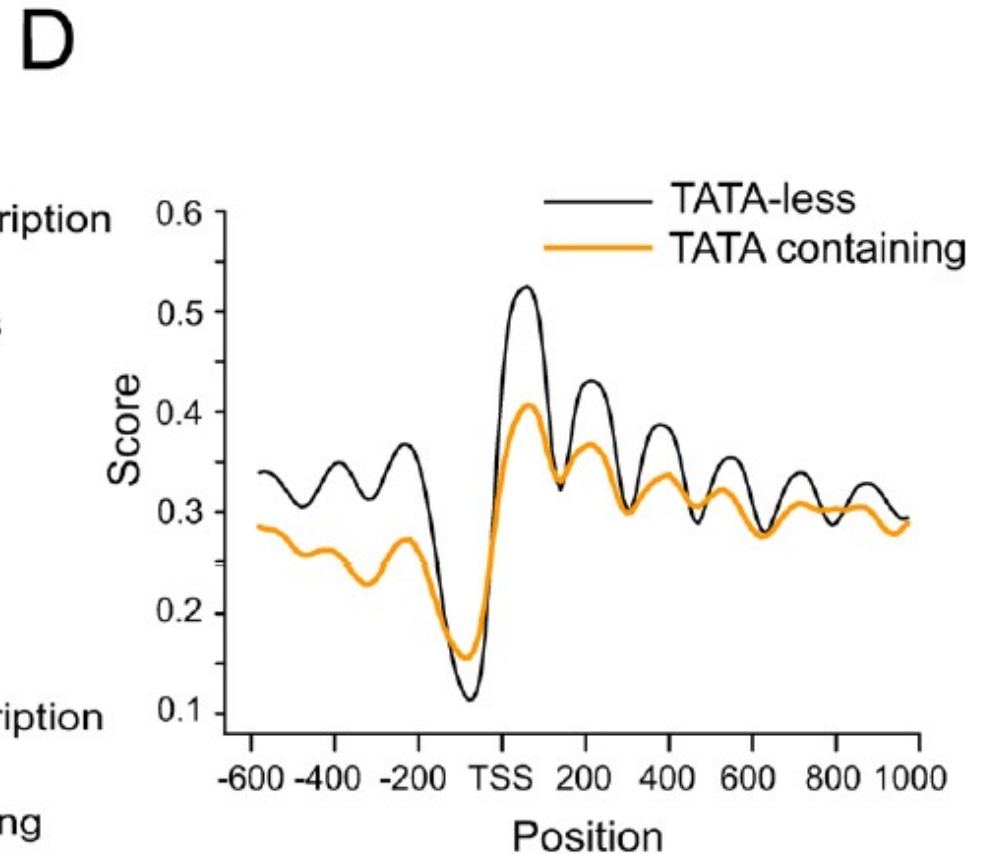
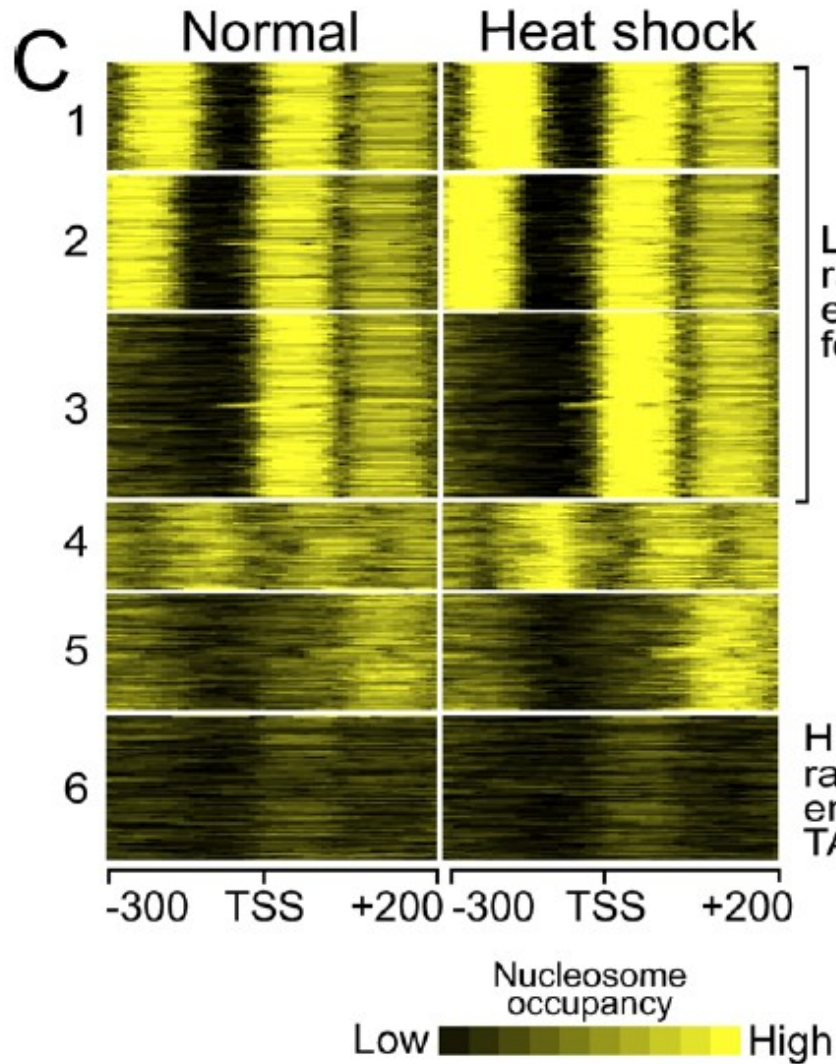
- Promoters have lower probability of nucleosomes
- Nucleosome free region before TSS is  $\sim 1$  nucleosome wide
- Strongly positioned nucleosome marking start of transcribed region
- Periodic intervals after TSS with decreasing probabilities
- Strongly positioned nucleosome at 3' end of coding region, followed by nucleosome-free region

# Distance between nucleosomes

Linker length distribution in the yeast genome



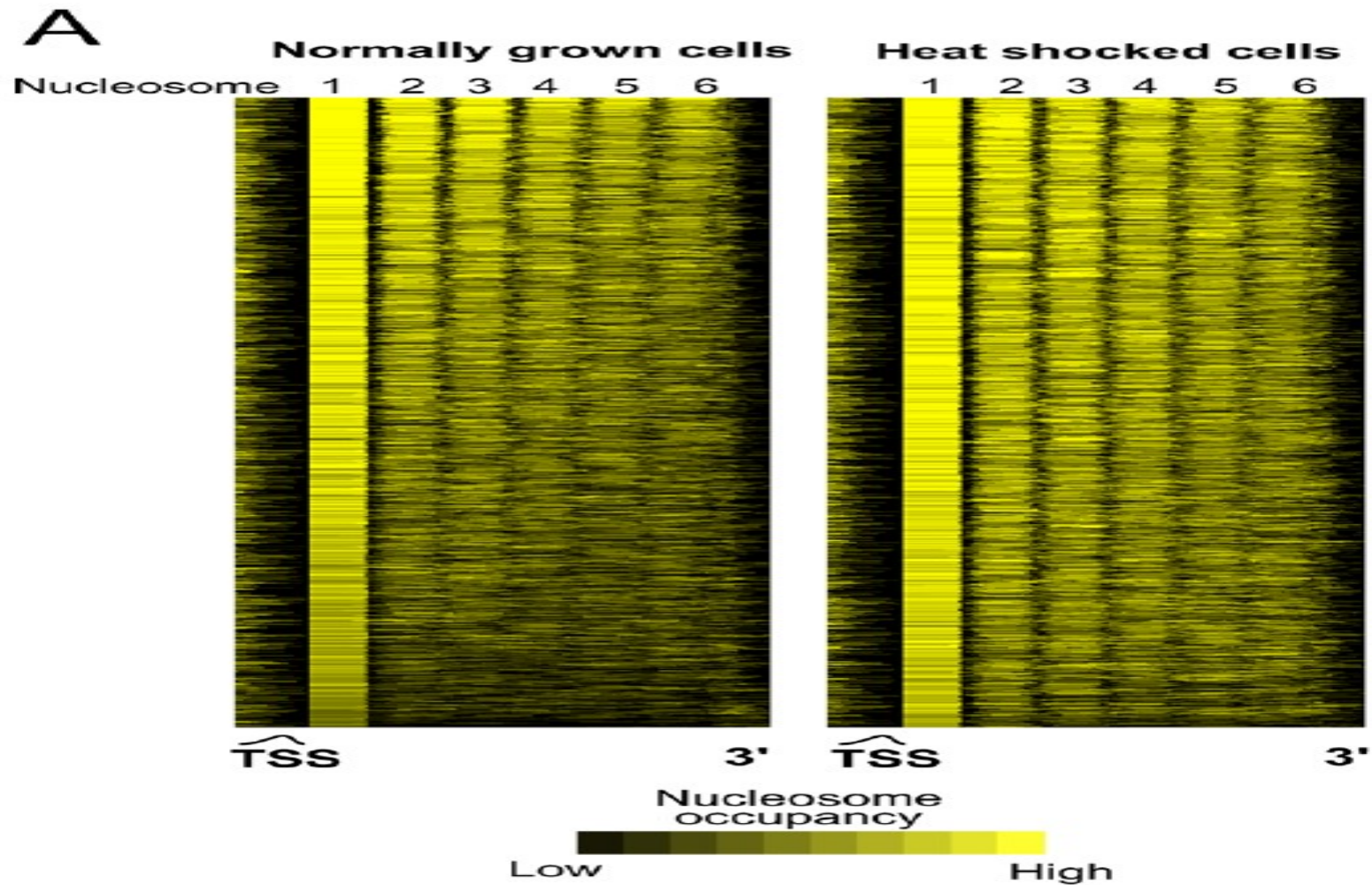
# TATA-box & transcription levels



# Position changes

- Majority of the nucleosomes do not change their positions
- 65% of nucleosomes from normal cells were had moved less than 30bp after heat-shock
- Less than 10% of nucleosomes were displaced more than 100bp after heat-shock

# Periodicity of nucleosomes in transcribed regions

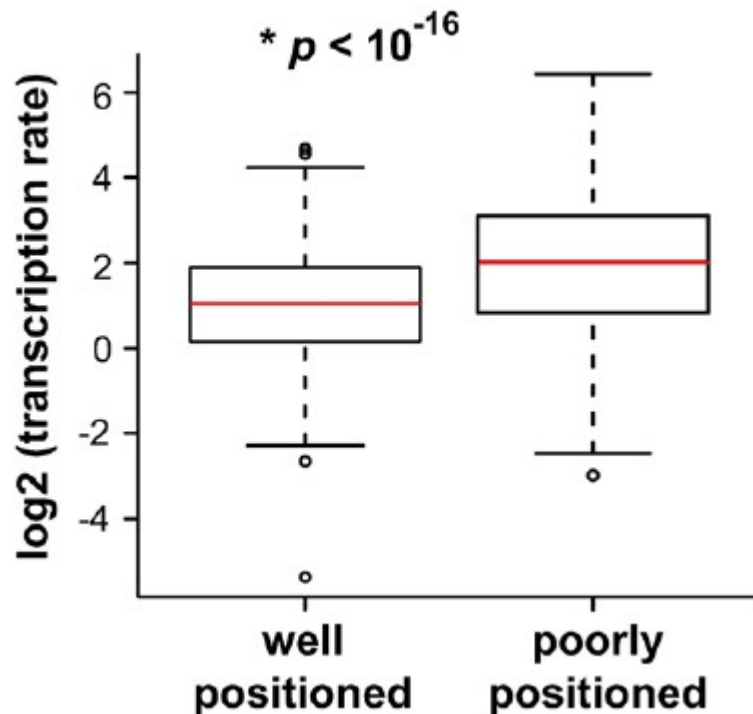




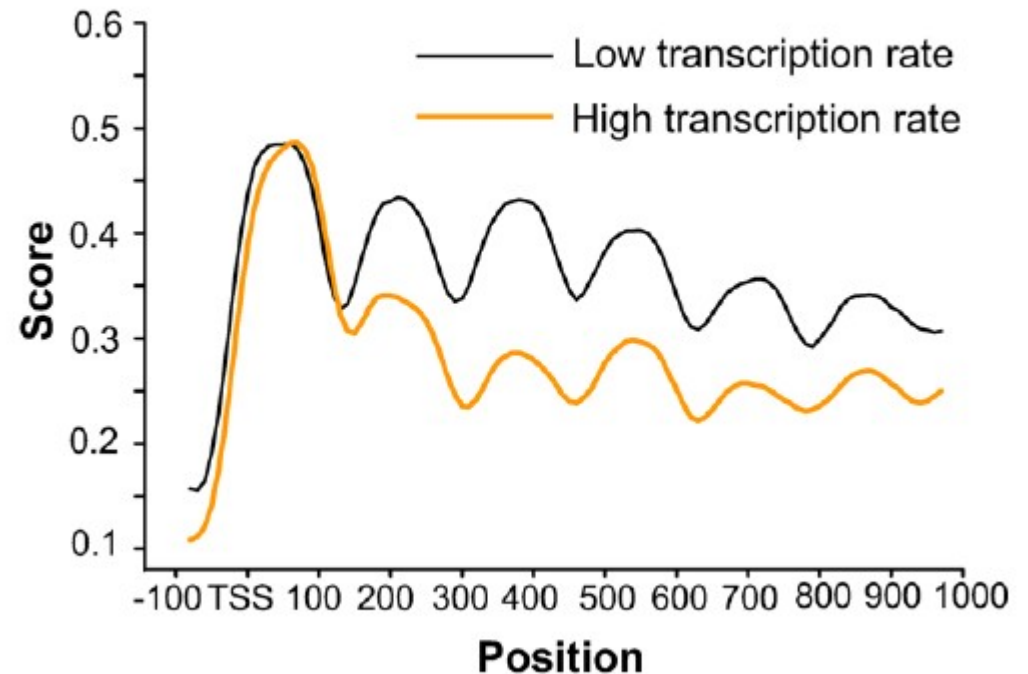
# Nucleosome position periodicity and transcription levels

- Strong periodicity in coding regions are transcribed in lower levels (& vice versa)

B



C

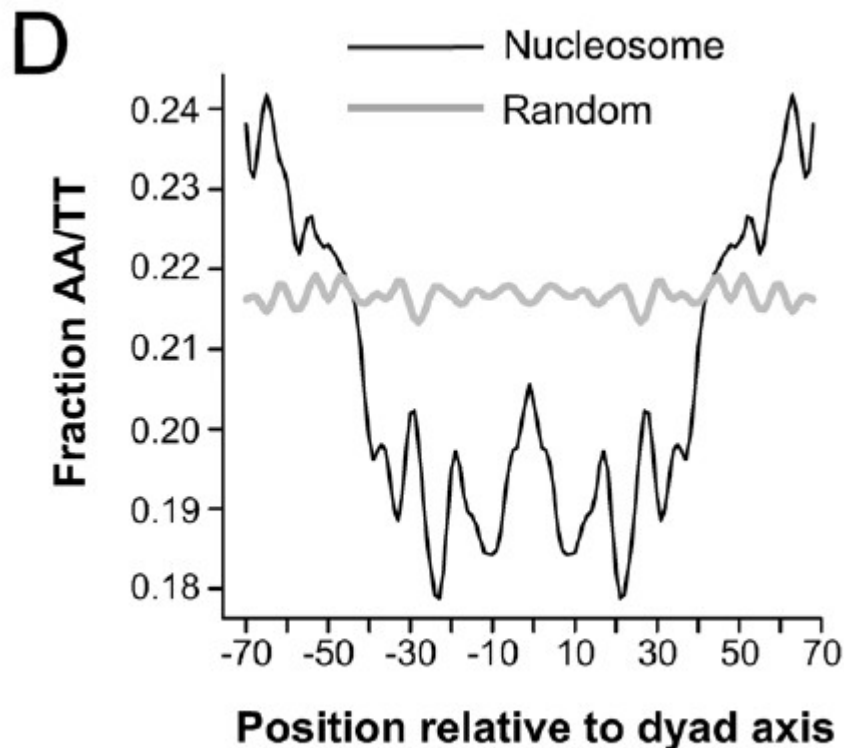


# Sequence dependent positioning

- old and partly proven idea: nucleosome positions are encoded in DNA
- further idea: when a nucleosome has strongly positioned “using” DNA encoded signals then adjacent nucleosomes will be “stacked” against it and there is no need for strong signal in DNA for the rest

# Nucleosome positioning sequence

- Profiles of AA/TT dinucleotide frequency
- Repeating pattern with approximate periodicity of 10bp indicating rotational positioning of the nucleosome

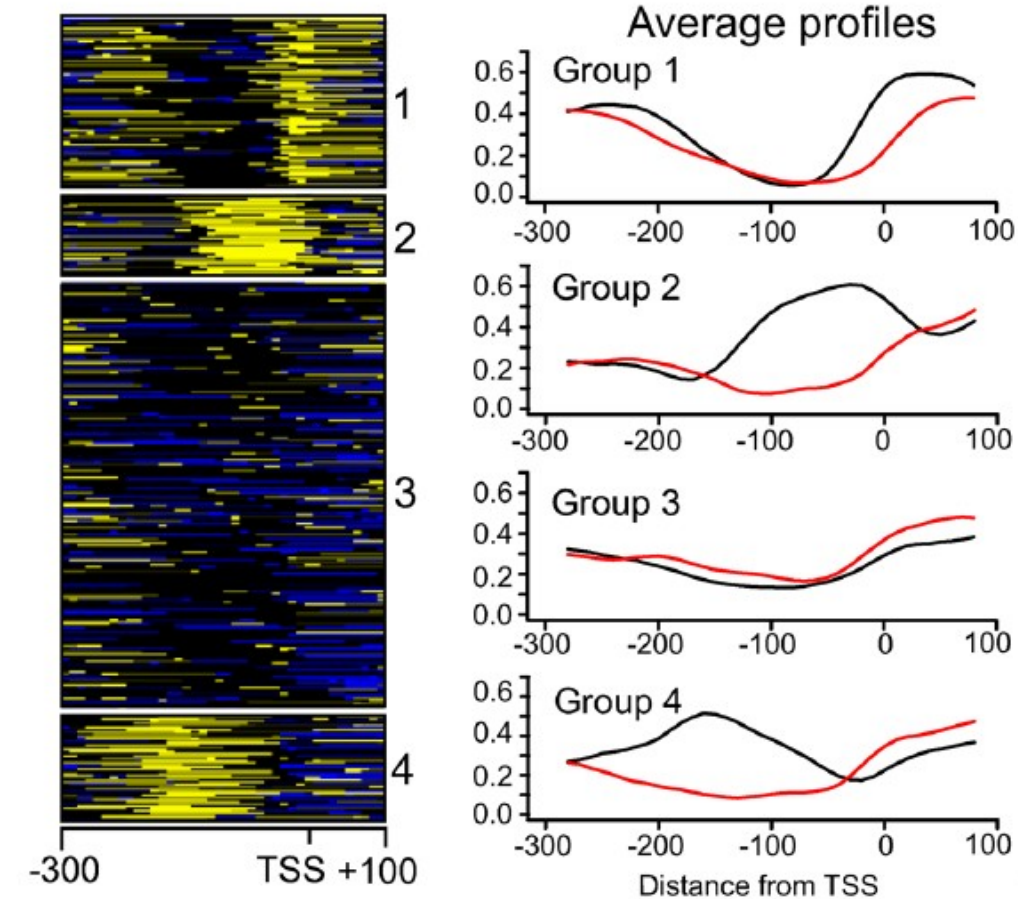


**E**

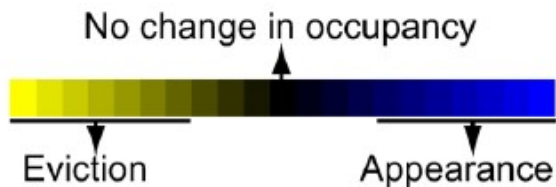
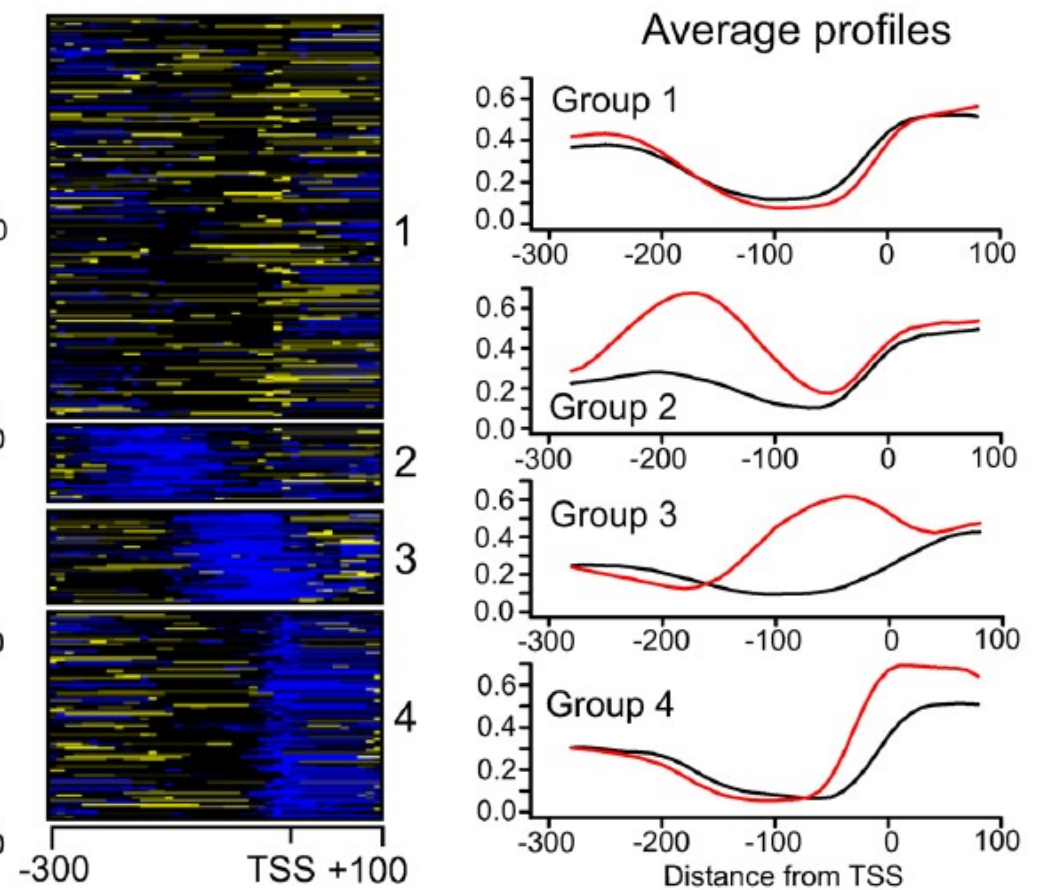
<b>Nucleosome</b>	<b>1</b>	<b>2</b>	<b>3</b>	<b>4</b>
Correlation	0.9	0.75	0.62	0.67

# Remodeling profiles

## A Activated genes



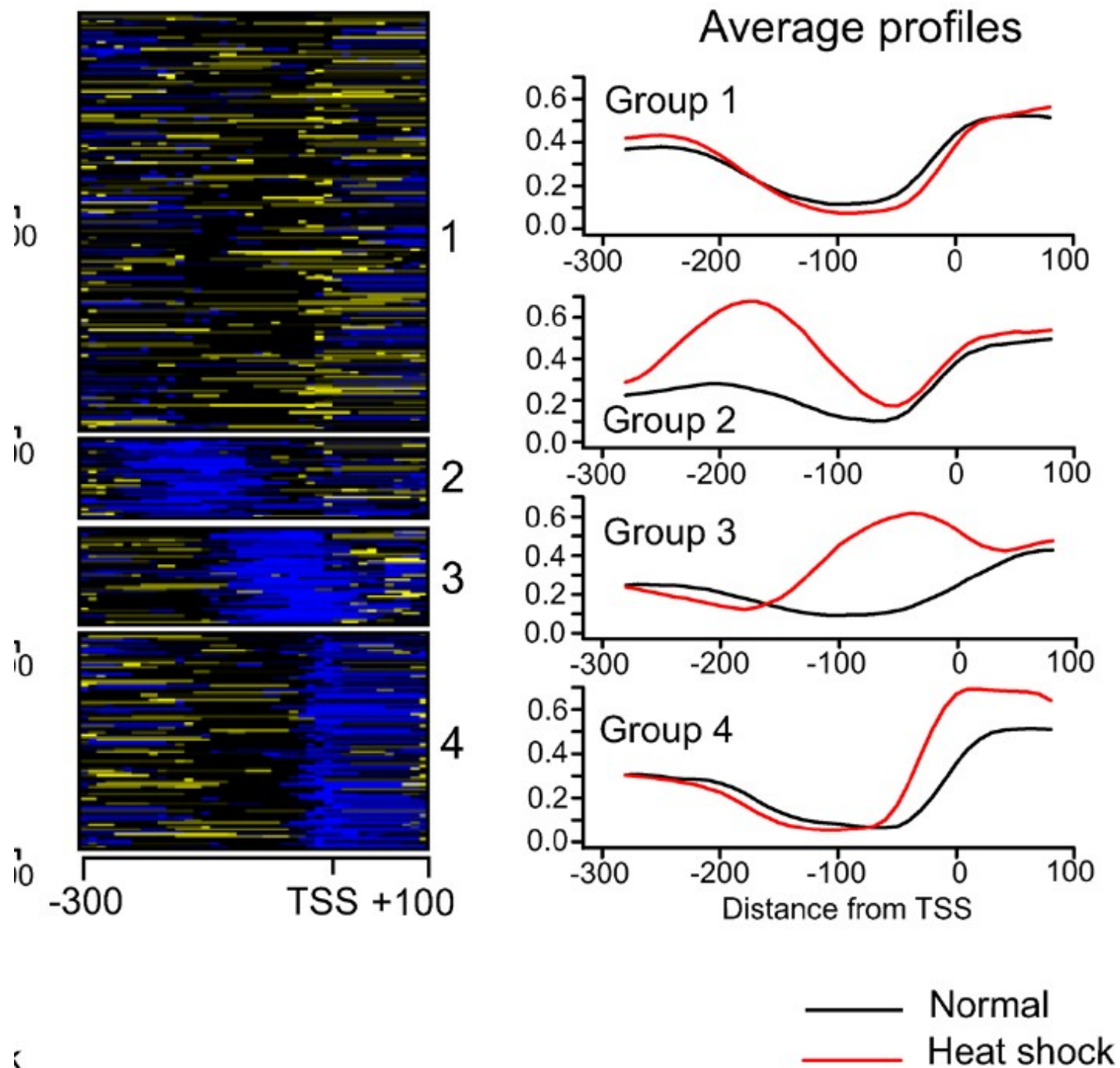
## B Repressed genes



— Normal  
— Heat shock

— Normal  
— Heat shock

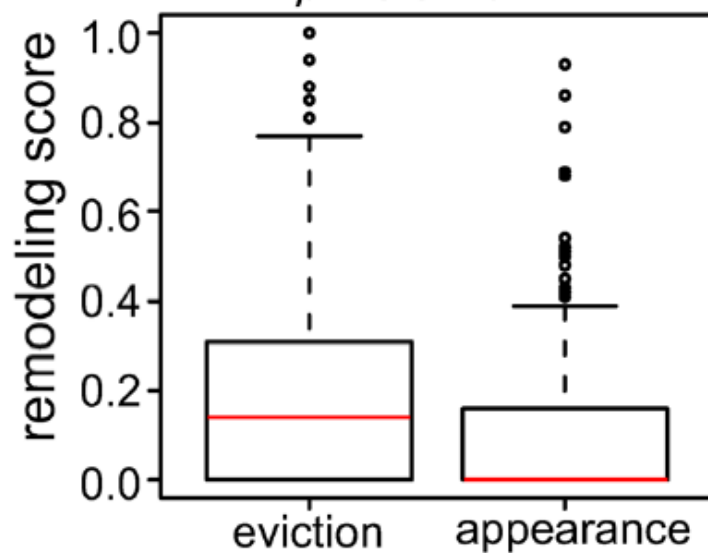
# B Repressed genes



# C

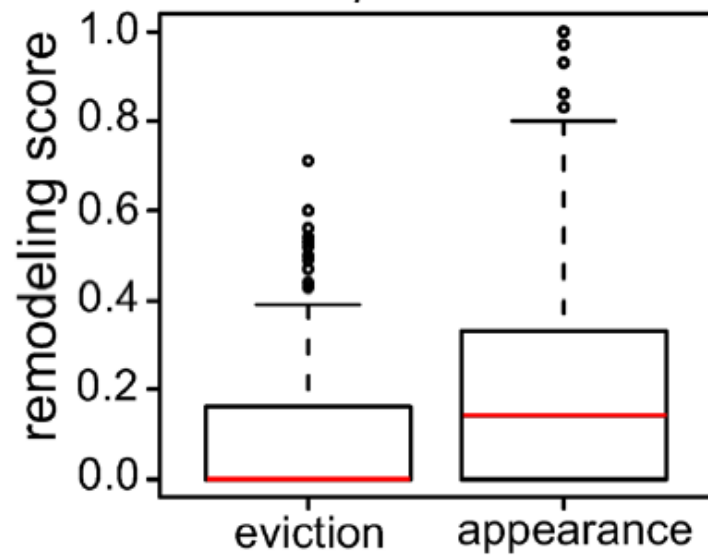
## Activated genes

$p < 3.5 \times 10^{-13}$



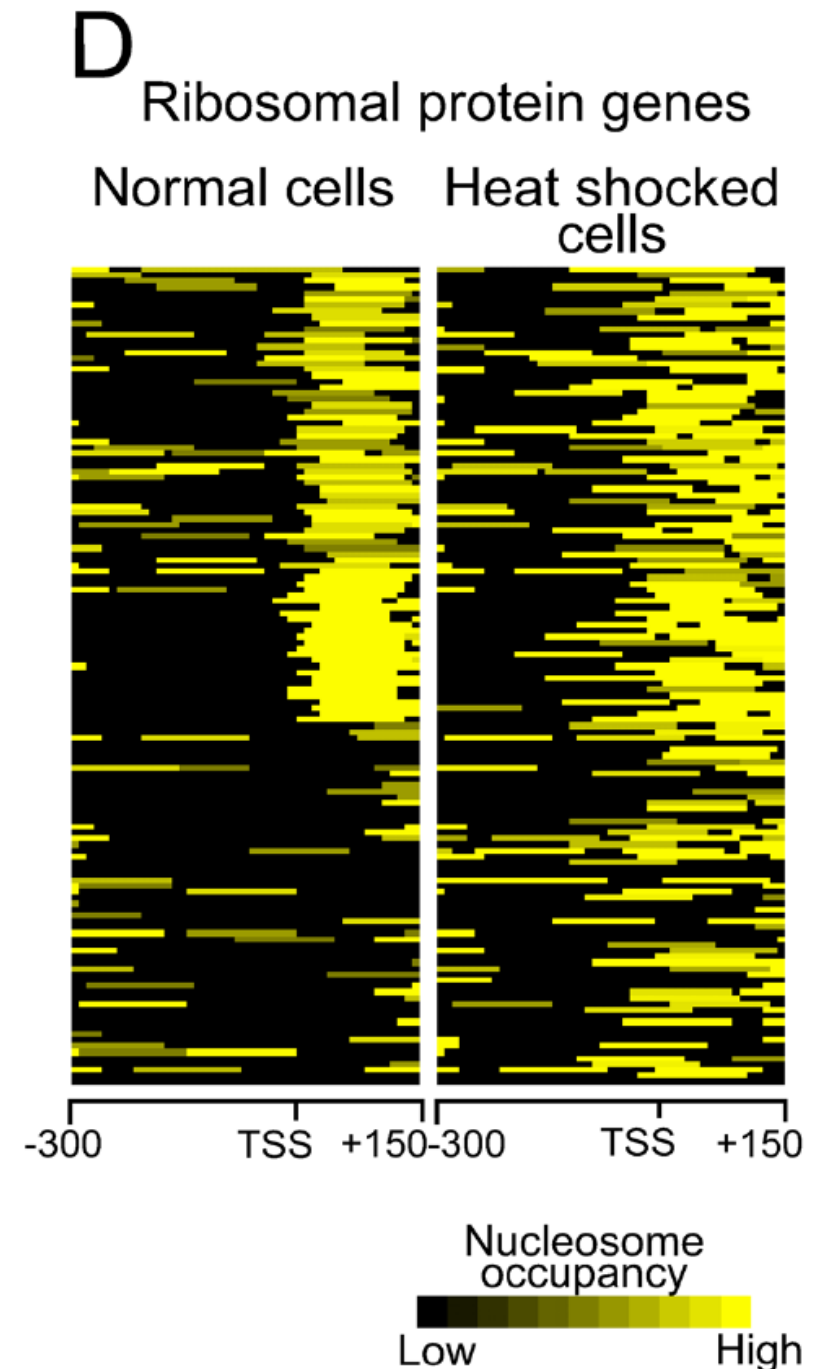
## Repressed genes

$p < 10^{-16}$

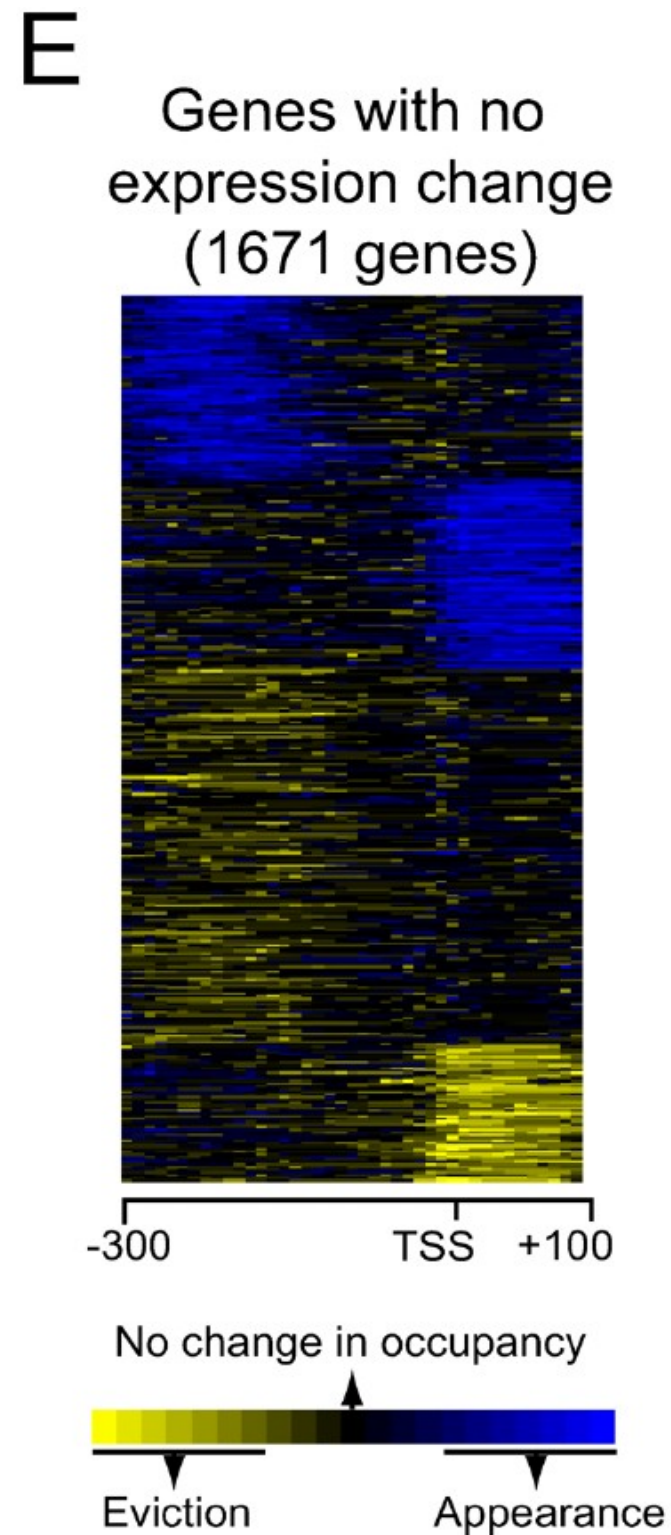


# Ribosomal genes are shut down after heat-shock

- Appearance of high-scoring nucleosomes between -200 and +100bp
- Chromatin remodeling involves only one or two nucleosomes



- Nucleosome disappearance and appearance are not only related with transcriptional changes

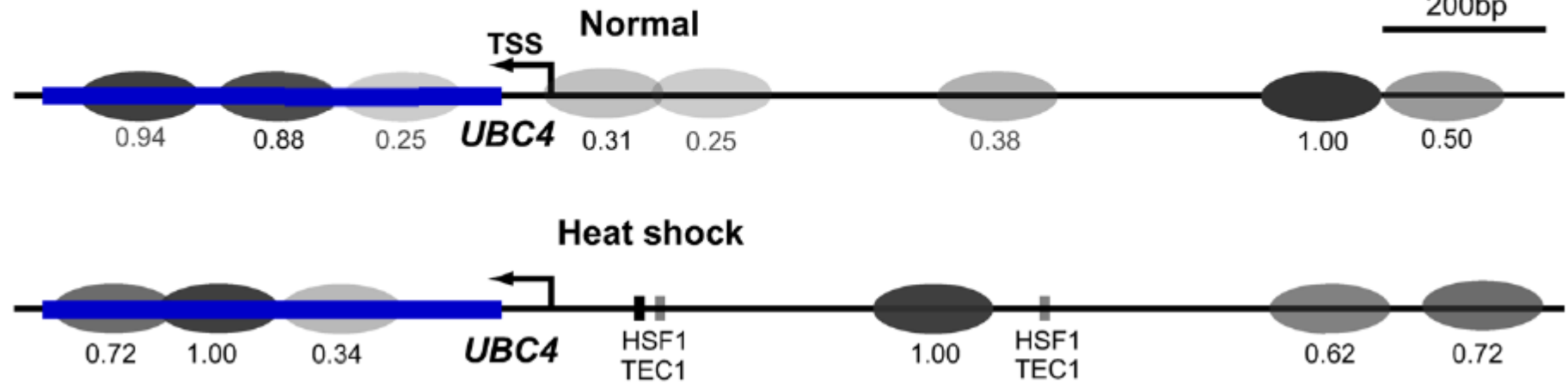




# Nucleosome positions affect TFBSs

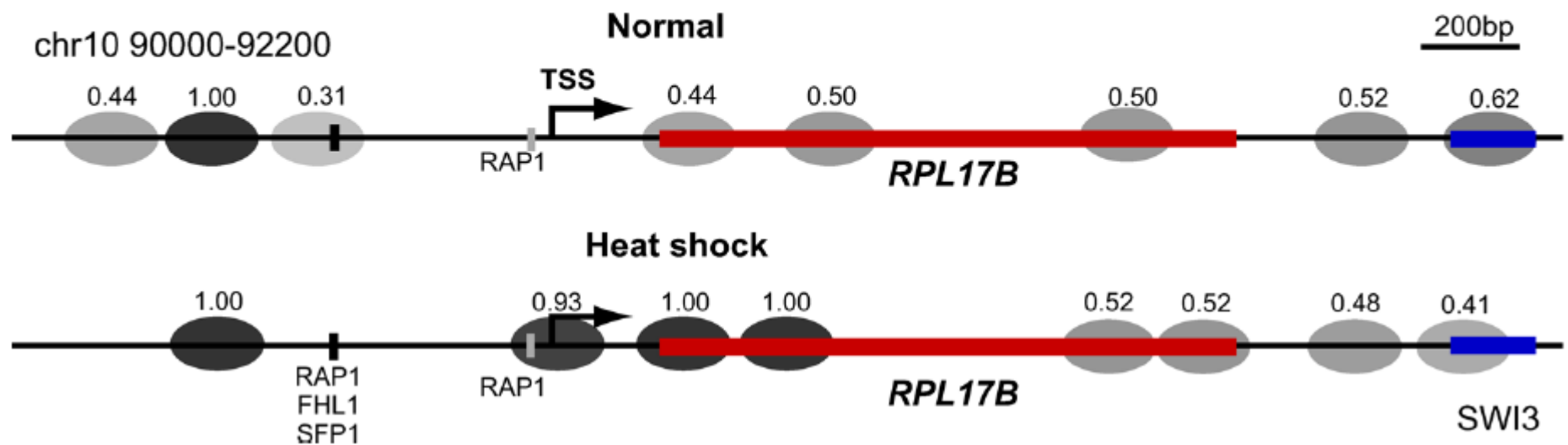
## A Hsf1 target gene

chr2 406600-408400



## B Rap1 target gene

chr10 90000-92200



# Nucleosomes on stress-related TF binding sites

- 55 transcription factors with functional binding sites identified by ChIP-chip
- 3 classes of TFs based on their BS accessibility after heat-shock

– increase

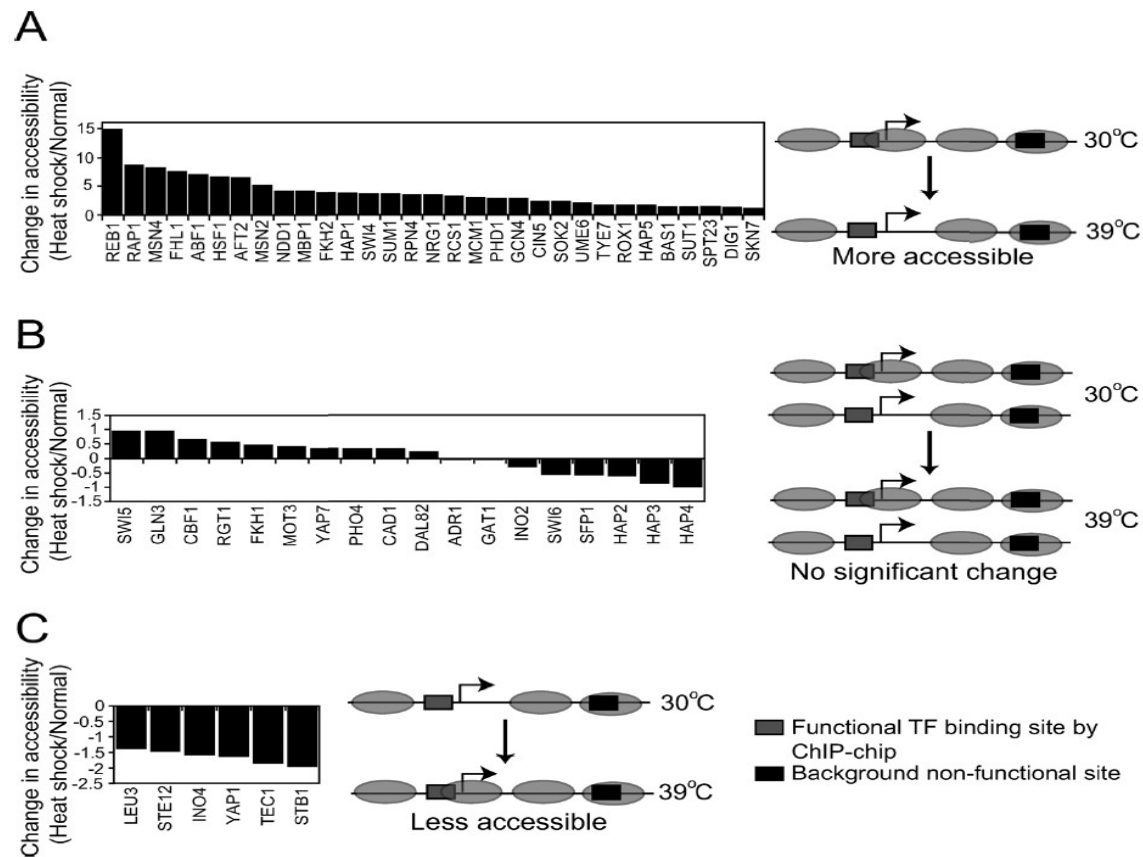
- stress-related Tfs

- ribosome TFs

– no change

- metabolic pathway regulators

– decrease



# Conclusions

- Strong nucleosome at TSS
- Well-positioned nucleosome at 3' end of coding region (New!)
- After heat-shock most nucleosomes did not change their positions
- Remodeling incorporates only one or two nucleosomes at promoters
- Remodeling not always leads to transcriptional change