

Gertz J, Siggia ED, Cohen BA, nature, vol 457, 8 january 2009

ANALYSIS OF COMBINATORIAL CIS-REGULATION IN SYNTHETIC AND GENOMIC PROMOTRES

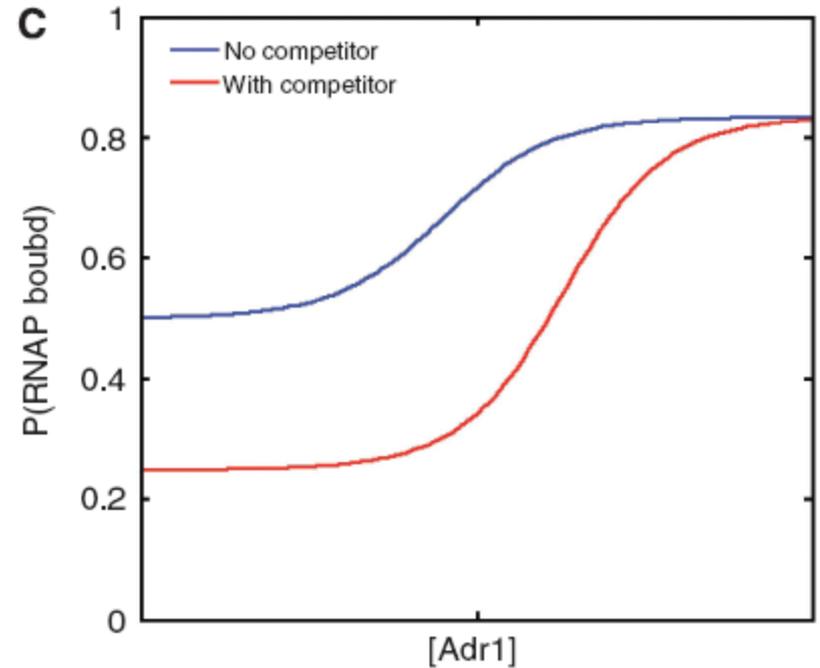
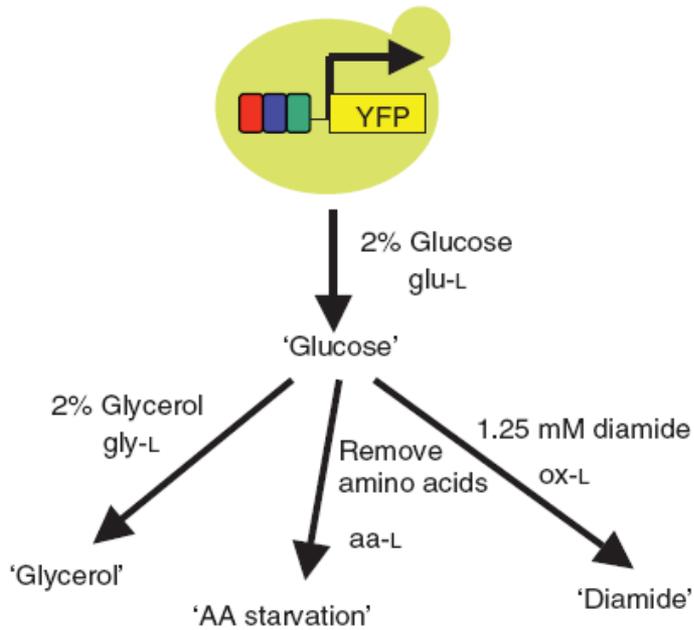
Summary

- Model
 - thermodynamical model based on Shea & Ackers
- Organism
 - S. cerevisiae*
- Assumptions
 - Gene regulation is completely controlled by DNA-protein/prot-prot binding
 - RNAP binding is directly proportional to fluorescence intensity

Parameters

- Model see Shea & Ackers
- Promoters:
 - 7 libraries à 80-600 promoters, $\Sigma = 2807$.
 - 18 building blocks
 - weak, strong, spacer
 - cooperativity
- Gene expression (FACS)
 - 25000 individual cells per promoter
 - Average FL : cell volume ratio

FACS: why volume against FL intensity?



Gertz J and Cohen BA, Mol Sys Biol, 2009

ENVIRONMENT-SPECIFIC COMBINATORIAL CIS-REGULATION IN SYNTHETIC PROMOTERS

Summary

- Basics: see Gertz et al. 2009
- Assumptions
 - Gene regulation is completely controlled by DNA-protein/protein-protein binding
 - RNAP binding is directly proportional to fluorescence intensity
- 4 Environments
 - + Glucose
 - + glycerol
 - amino acid
 - + diamide

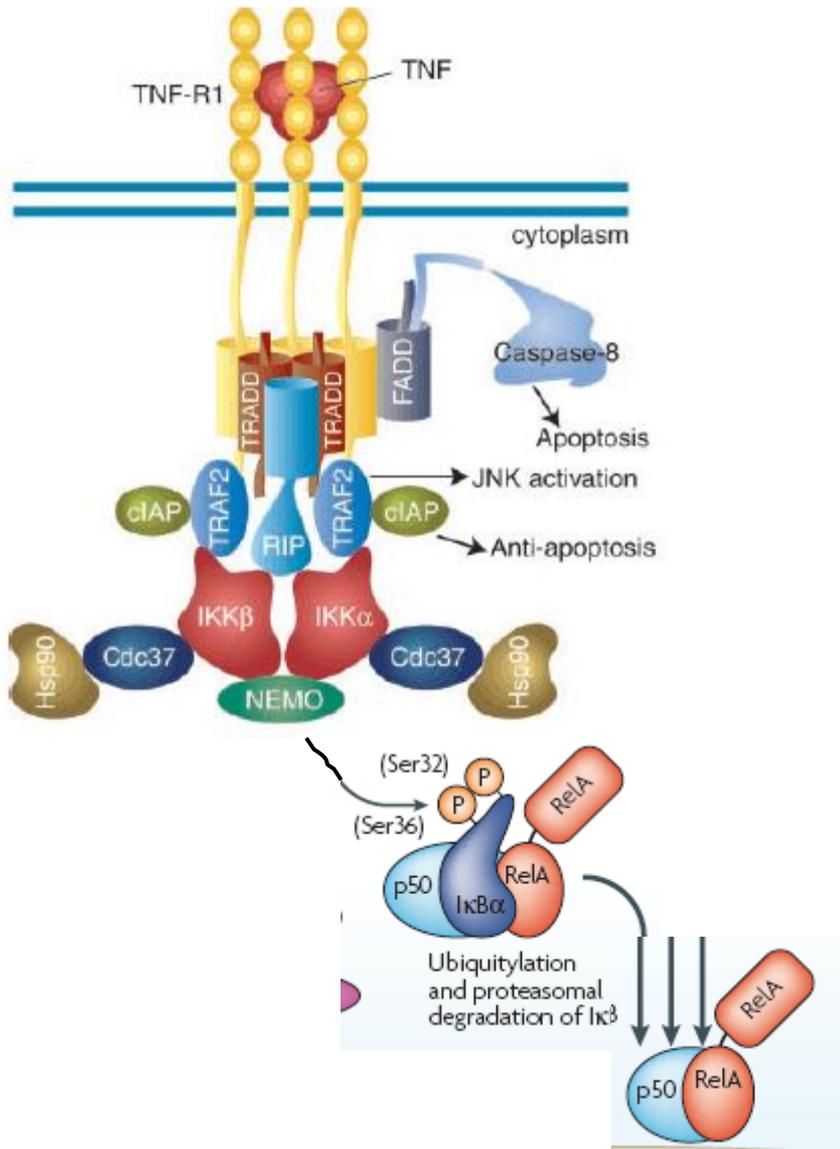
Parameters

- Model see Shea & Ackers
- Expression measurement: FACS
 - Mean fluorescence divided by electronic volume (25000 events)
 - Include plate effect
- TD model: explanation of expression variation
 - $R^2 \approx 0.4$ with $c(\text{TF}) = \text{const.}$
 - $R^2 \approx 0.6$ with differential TF concentration
 - Cross validation

Cross-validation?

Pathways

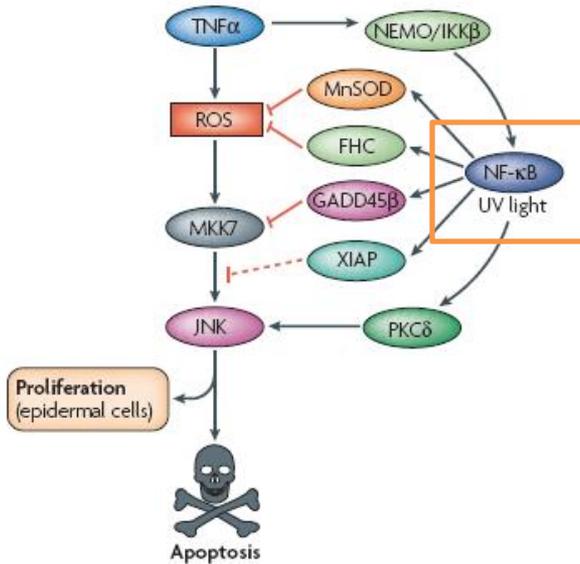
TNF α -pathway



Transcriptional activation
Transcriptional repression
Promoter selectivity

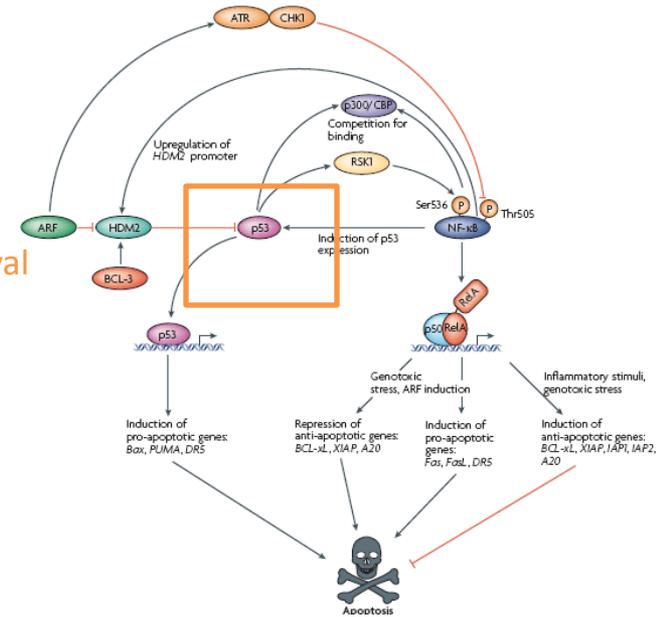
Cell proliferation
 α -apoptosis
pro-inflammatory

TNF α -pathway

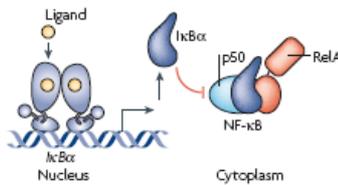


Crosstalk with DNA damage pathway!

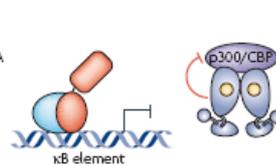
P53!
Leads to apoptosis & survival



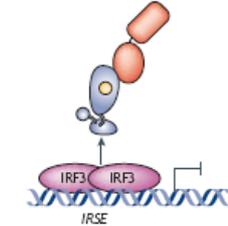
a Induction of I κ B α expression



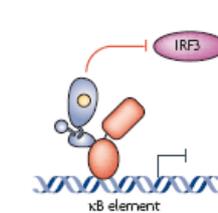
b Co-activator competition



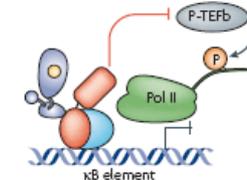
c Sequestration of NF-κB



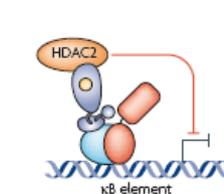
d Disruption of co-activator-complex formation



e Inhibition of RNA polymerase II hyperphosphorylation



f Recruitment of HDACs



Nuclear receptor pathways...

TNF α -pathway – simplify?

