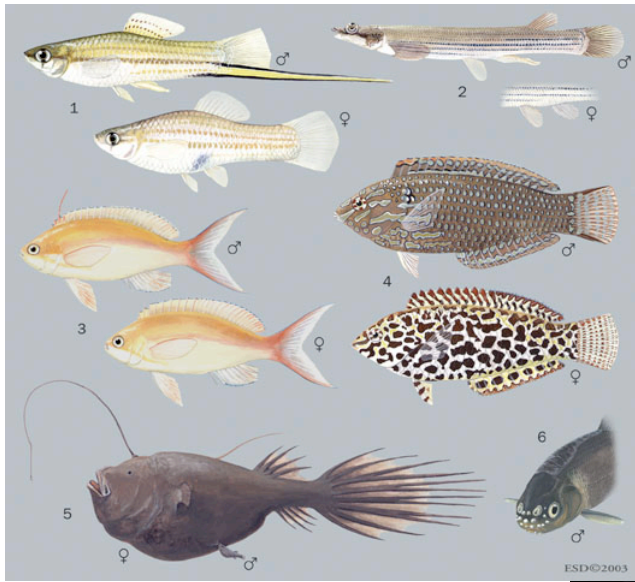


Transcriptional variation and regulatory feedback in *Saccharomyces*

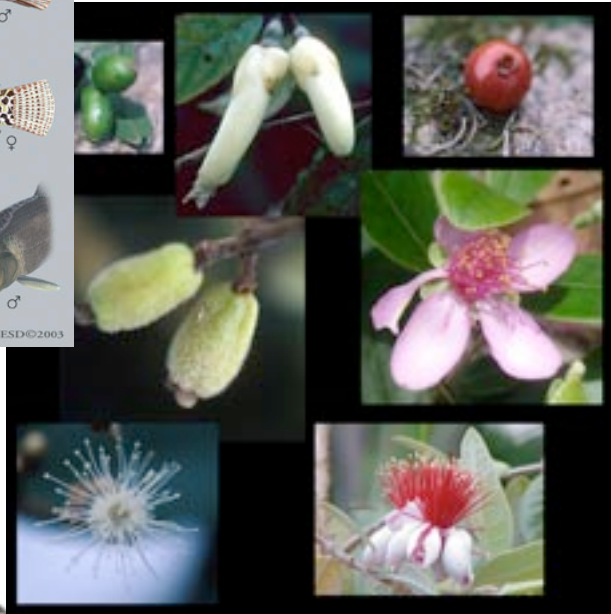
Rachel Brem
Department of Molecular and Cell Biology
University of California, Berkeley



A G A T T C G A C T T G A C G G T A C C A
A G C T T C G A T T T G G C G G T A T C A



www.keew.org/science/directory/teams/Myrtaceae/images/Myrtaceae.jpg



Expression and phenotype

Genetic and developmental basis of evolutionary pelvic reduction in threespine sticklebacks

A Single P450 Allele Associate with Insecticide Resistance in *Drosophila*

P. J. Daborn,¹ J. L. Yen,¹ M. R. Bogwitz,² G. Le Goff,¹ E. Feil,¹ S. Jeffers,² N. Tijet,⁴ T. Perry,² D. Heckel,² P. Batterham,² R. Feyereisen,⁵ T. G. Wilson,² R. H. French-Constant^{1*}

Michael Dolph
An IRF8-binding promoter variant and AIRE control *CHRNA1* promiscuous expression in thymus

Matthieu Giraud^{1,2}, Richard Taubert³, Claire Vandiedonck¹, Xiayi Ke⁴, Matthieu Lévi-Strauss¹, Franco Pagani², Francisco E. Baralle⁵, Bruno Eymard⁶, Christine Tranchant⁷, Philippe Gajdos⁸, Angela Vincent², Nick Willcox², David Beeson², Bruno Kyewski³ & Henri-Jean Garchon¹

Genetic variation in human *NR1* expression affects stress response and emotion

Zhifeng Zhou^{1*}, Guanshan Zhu^{1**†}, Ahmad R. Hariri², Mary-Anne Enoch³, Matti Virkkunen³, Deborah C. Mash⁶, Robert H. Lipsky¹, Xian-Zhang He⁴, Beata Buzas¹, Qiaoping Yuan¹, Pei-Hong Shen¹, Robert E. Ferrell⁵, Stepi Richard L. Hauger⁷, Christian S. Stohler⁸, Jon-Kar Zubieta³ & David Gol

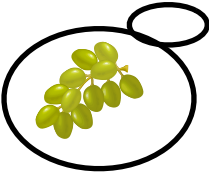
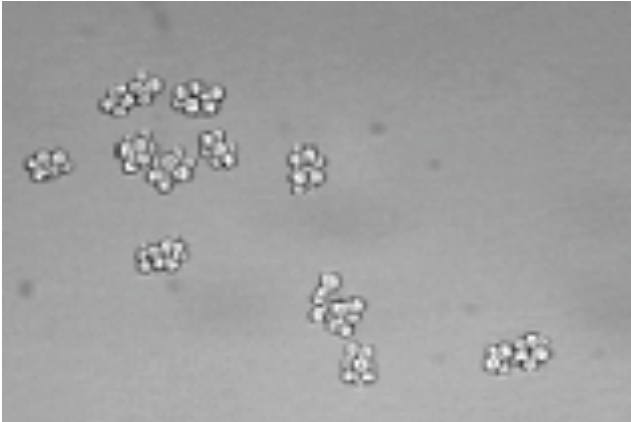
Morphological evolution through multiple *cis*-regulatory mutations at a single gene

A *cis*-acting regulatory mutation causes premature hair graying and susceptibility to melanoma in the horse

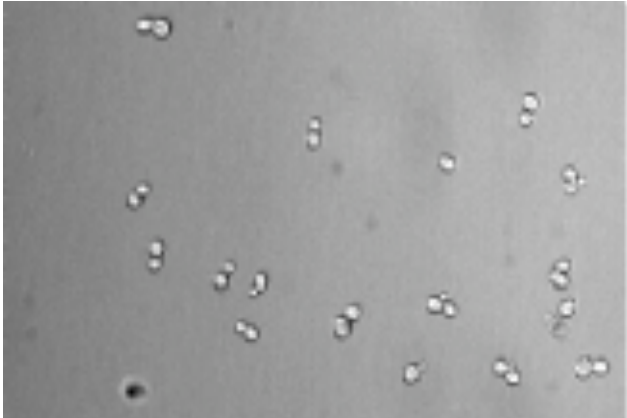
†, Isabelle Delon^{2†}, Jennifer Zanet², Dayalan G. Srinivasan¹,

Gerli Rosengren Pielberg¹, Anna Golovko^{1,12}, Elisabeth Sundström^{2,12}, Ino Curik³, Johan Lennartsson⁴, Monika H. Seltenthaler⁵, Thomas Druml⁶, Matthew Binns⁷, Carolyn Fitzsimmons¹, Gabriella Lindgren², Kaj Sandberg², Roswitha Baumung⁶, Monika Vetterlein⁸, Sara Strömberg⁹, Manfred Grabherr¹⁰, Claire Wade^{10,11}, Kerstin Lindblad-Toh^{1,10}, Fredrik Pontén⁹, Carl-Henrik Heldin⁴, Johann Sölkner⁶ & Leif Andersson^{1,2}

Expression variation between yeast strains



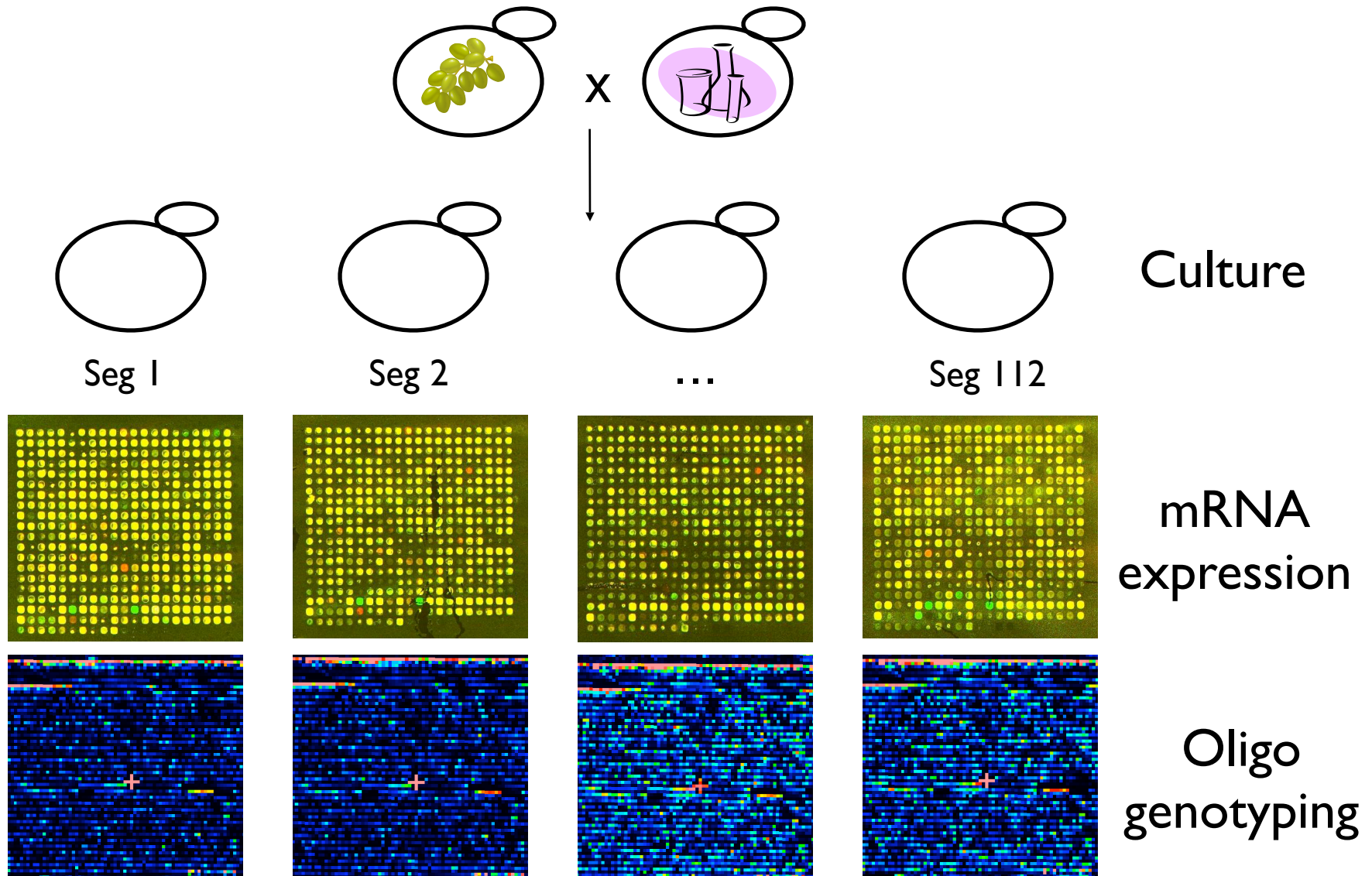
RM, vineyard



BY, lab

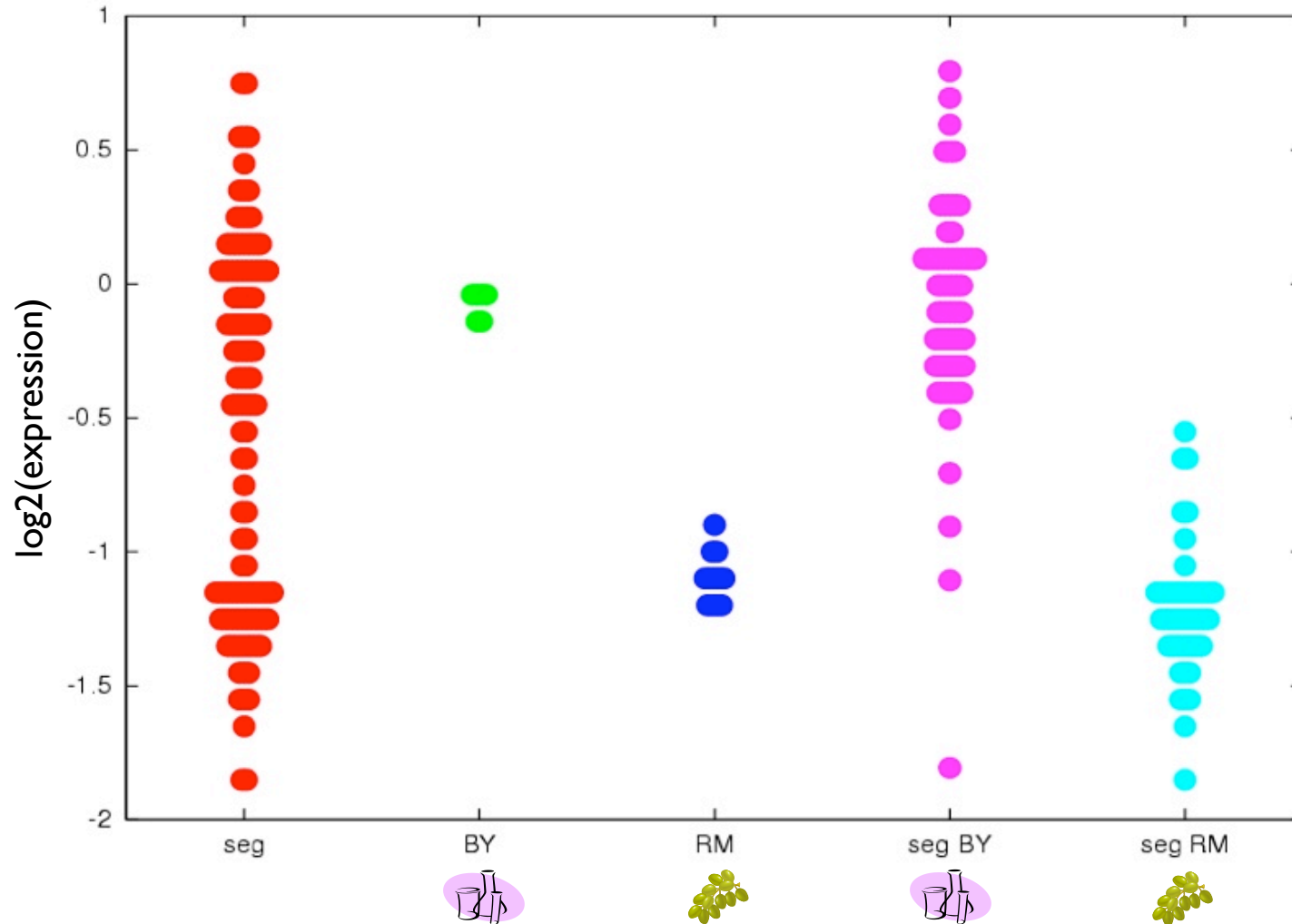
1% divergent

Mapping expression variation

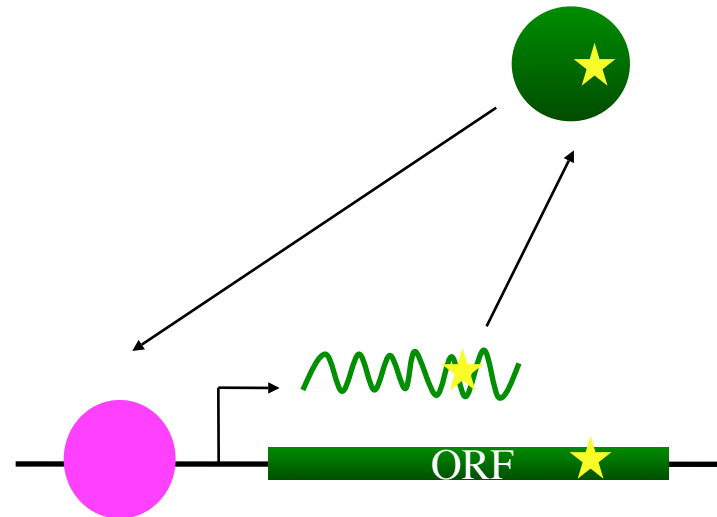
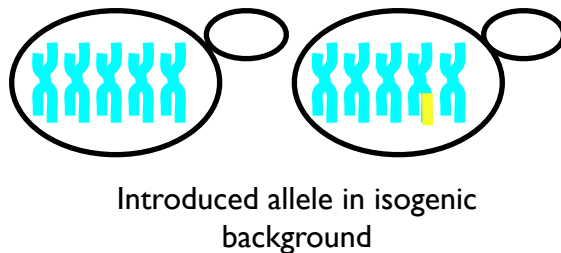
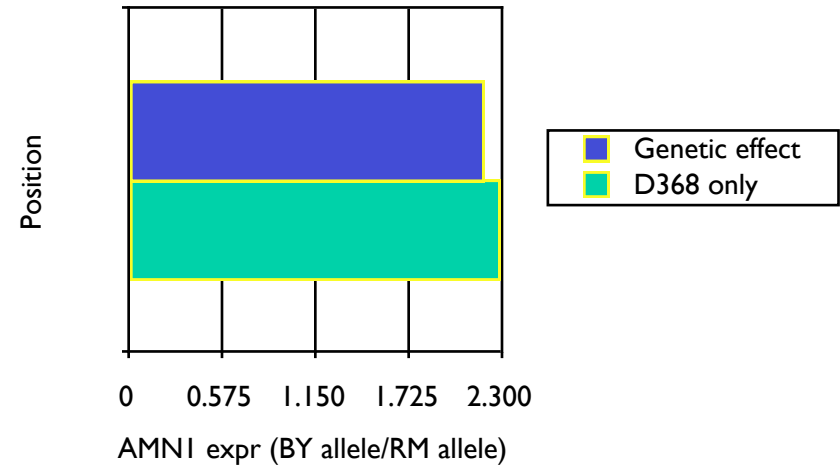
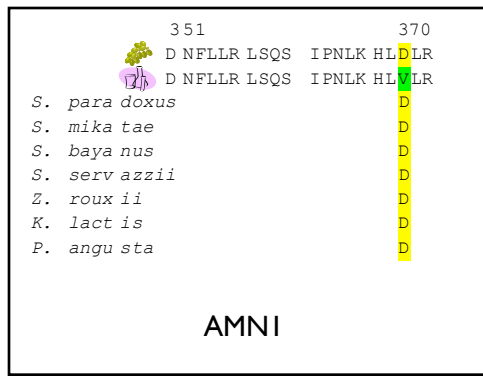


Gene expression as a mappable trait

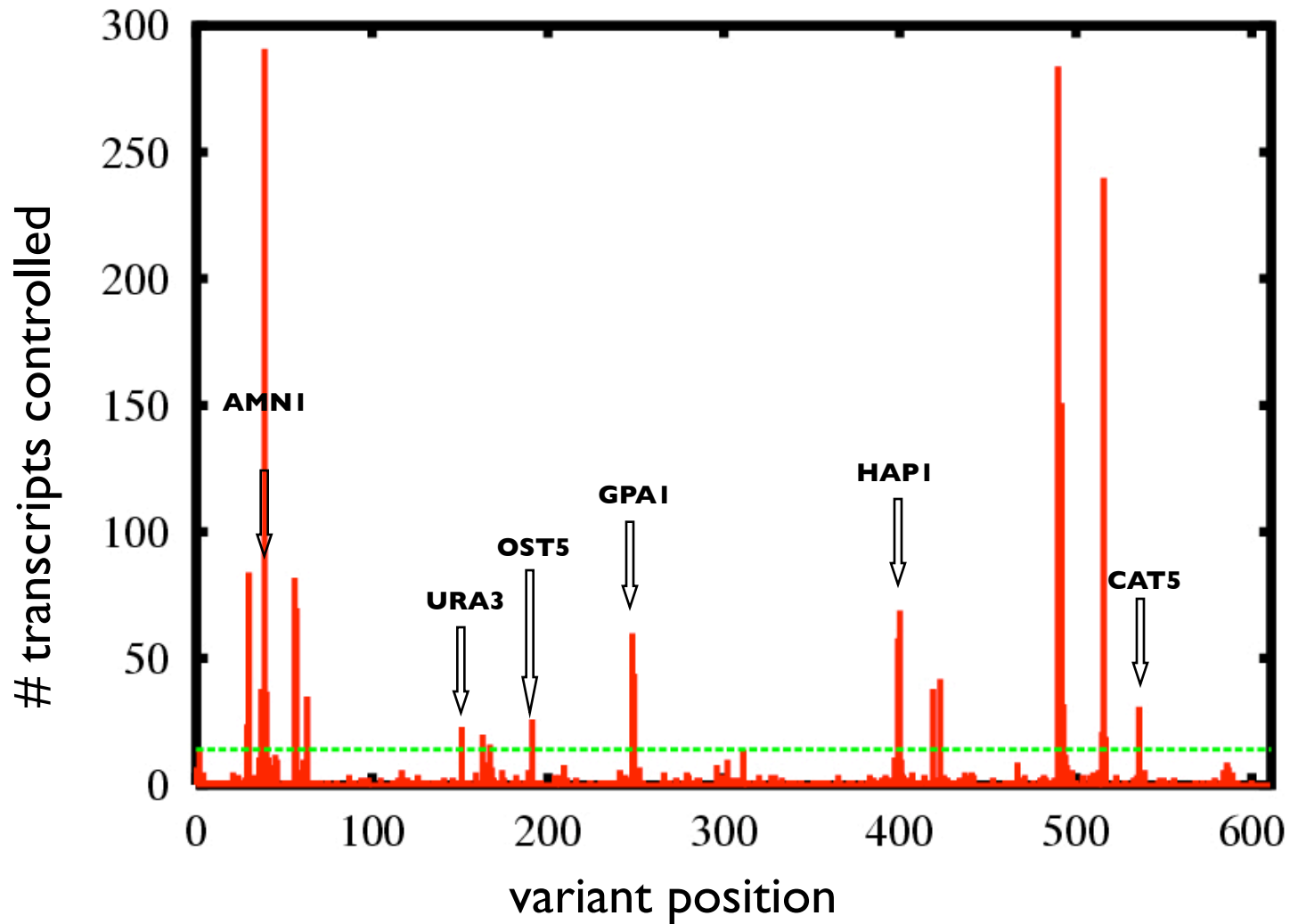
AMNI linking to intergenic marker, chrom II

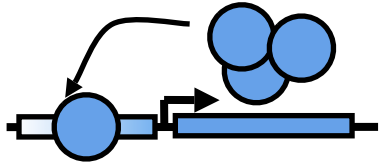


Variant affects its own expression: feedback



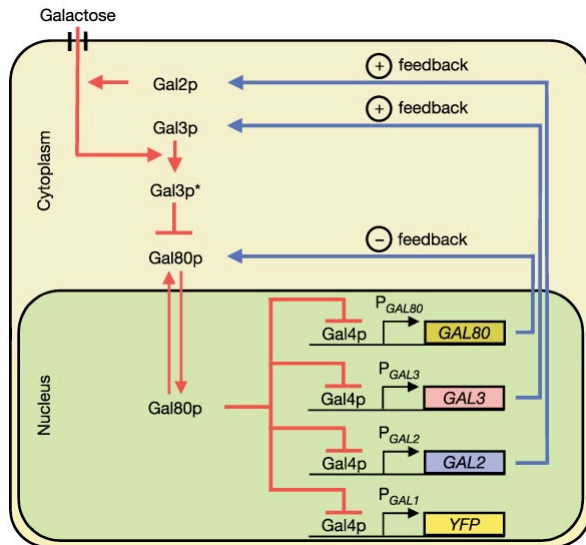
How common is feedback and why?





Feedback and quantitative behaviors

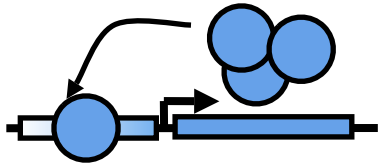
Genetic switch



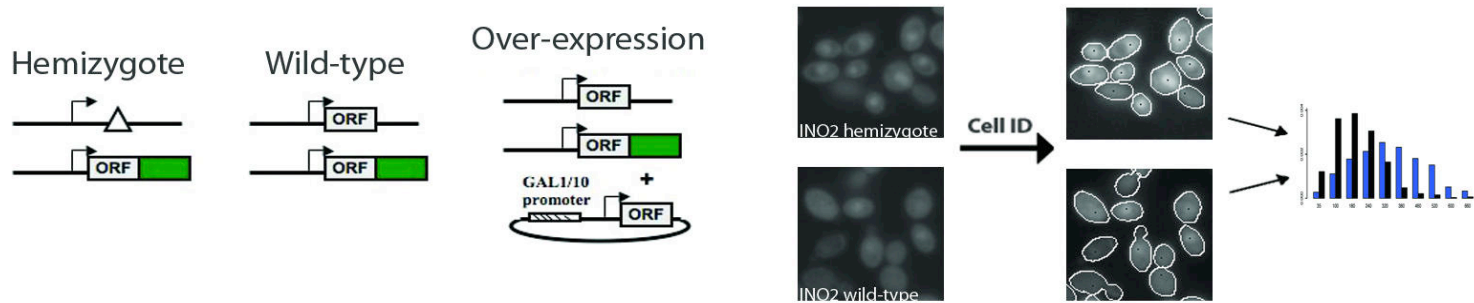
doi: 10.1038/nature03524

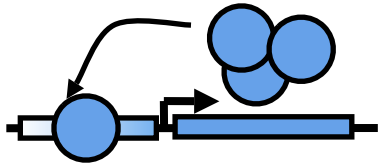
Other properties (synthetic circuits)

- Robustness to expression, input noise
- Homeostatic regulation
- Response timing
- Oscillation

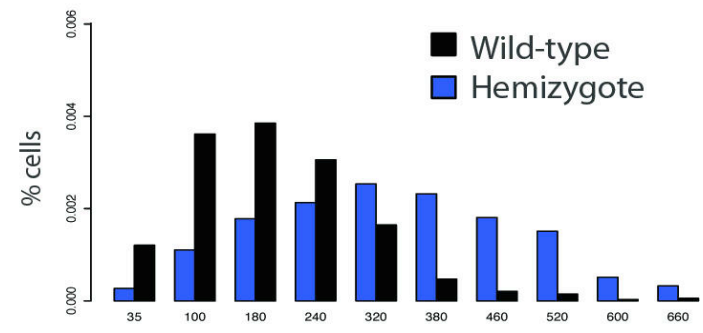
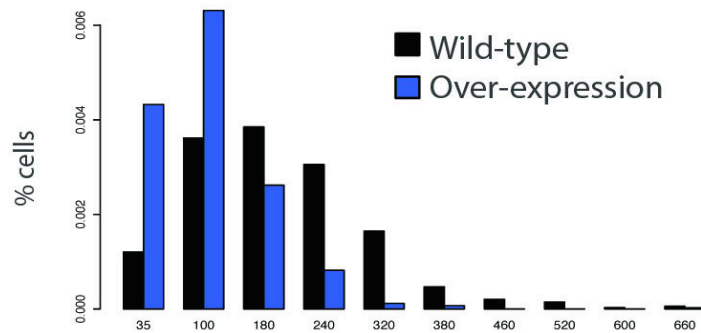
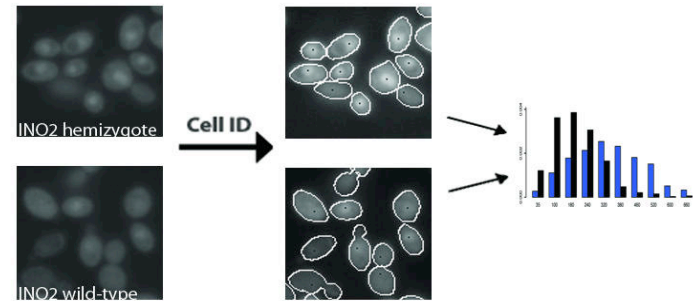
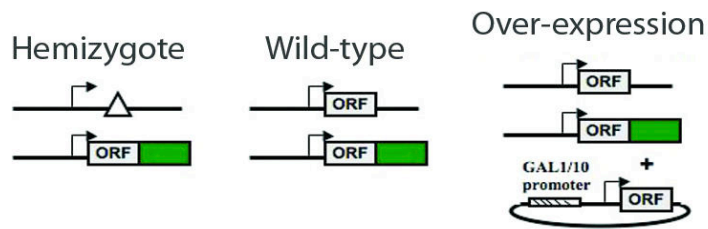


A screen for feedback across yeast TFs

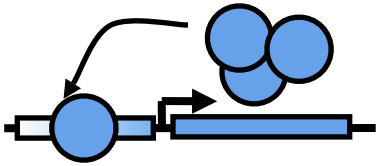




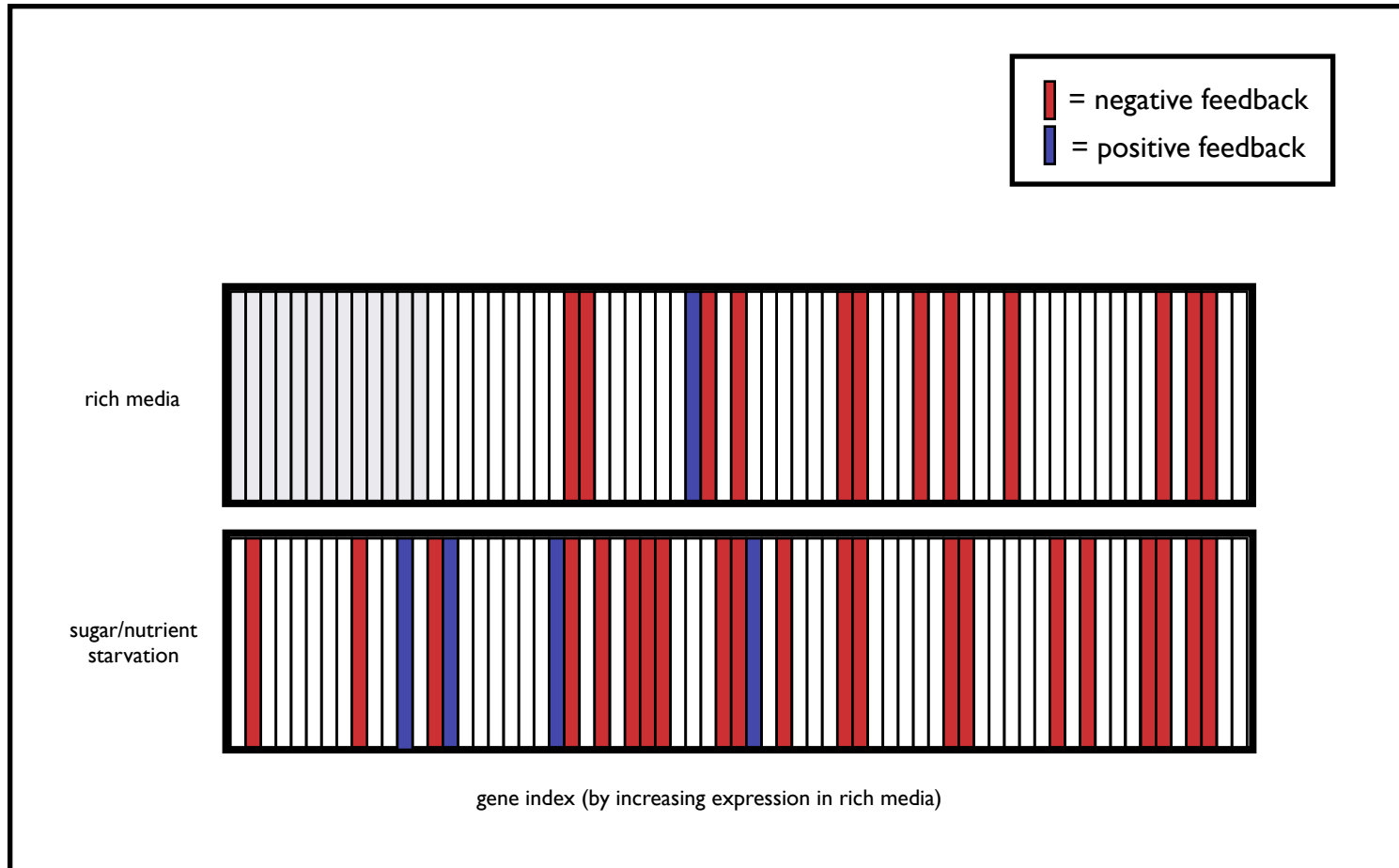
A screen for feedback across yeast TFs

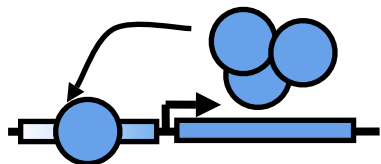


Ino2-GFP Fluorescence

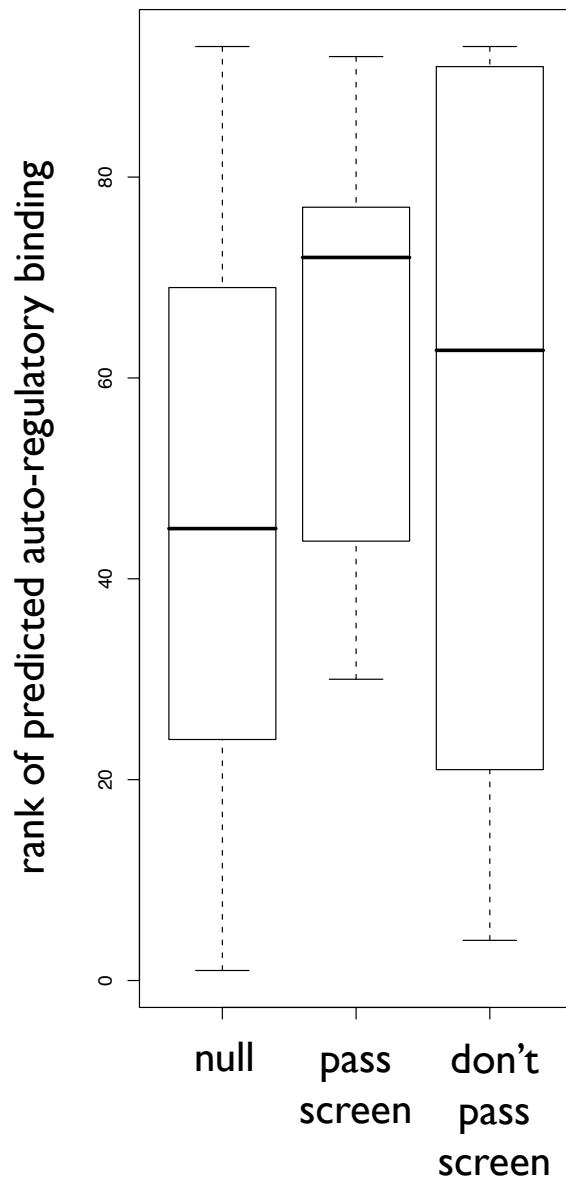
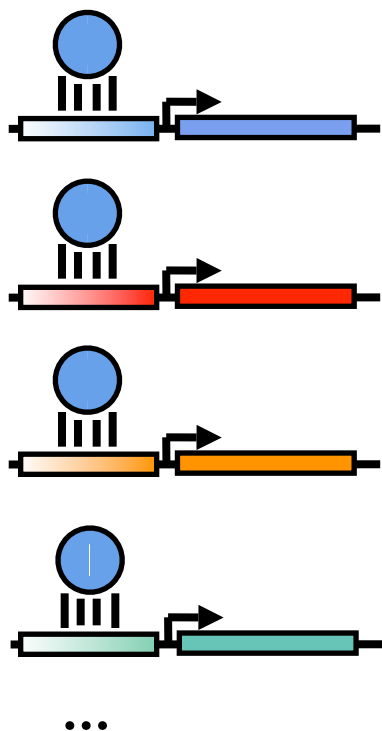


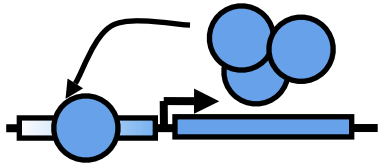
Widespread evidence for feedback



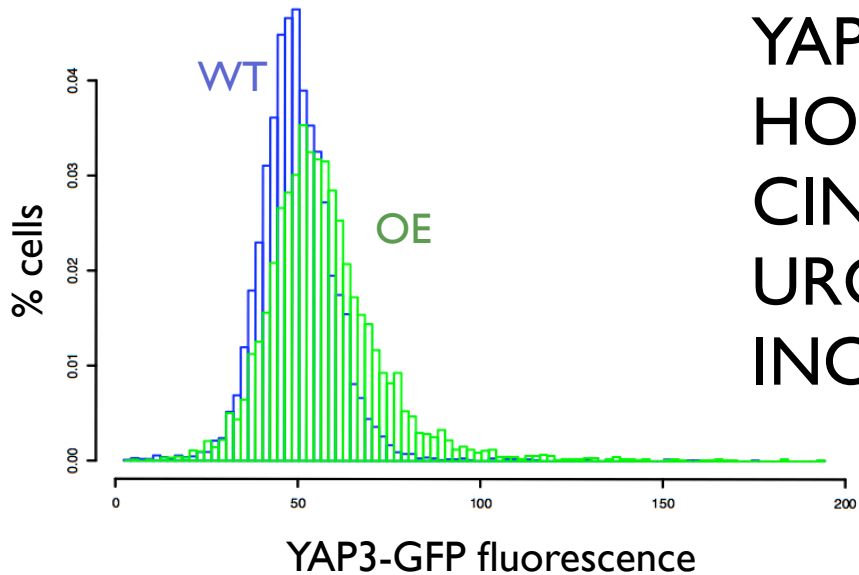


Most feedback is direct





Positive feedback and stress



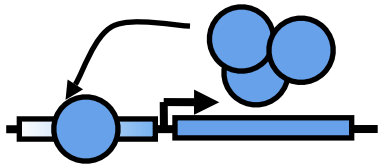
YAP3: nutrient starvation

HOG1: osmotic stress

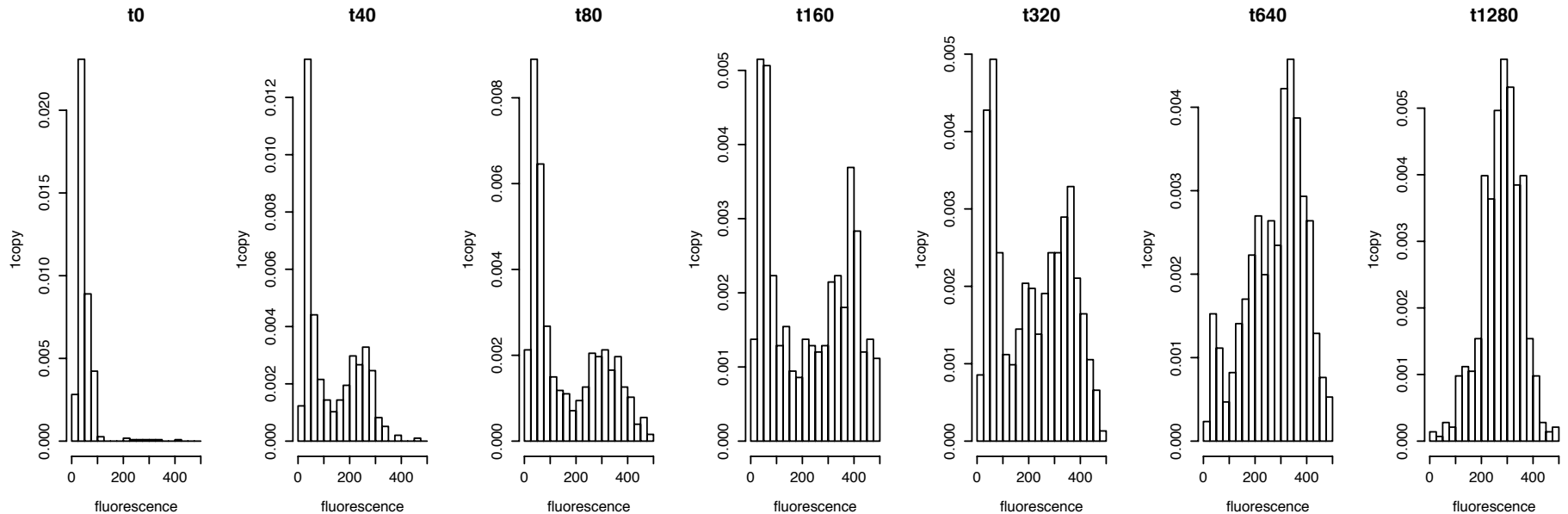
CIN5: osmotic stress

URC2: uracil catabolism

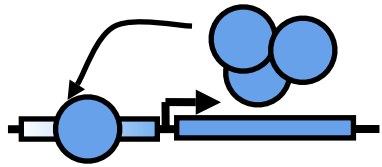
INO4: phospholipid metabolism



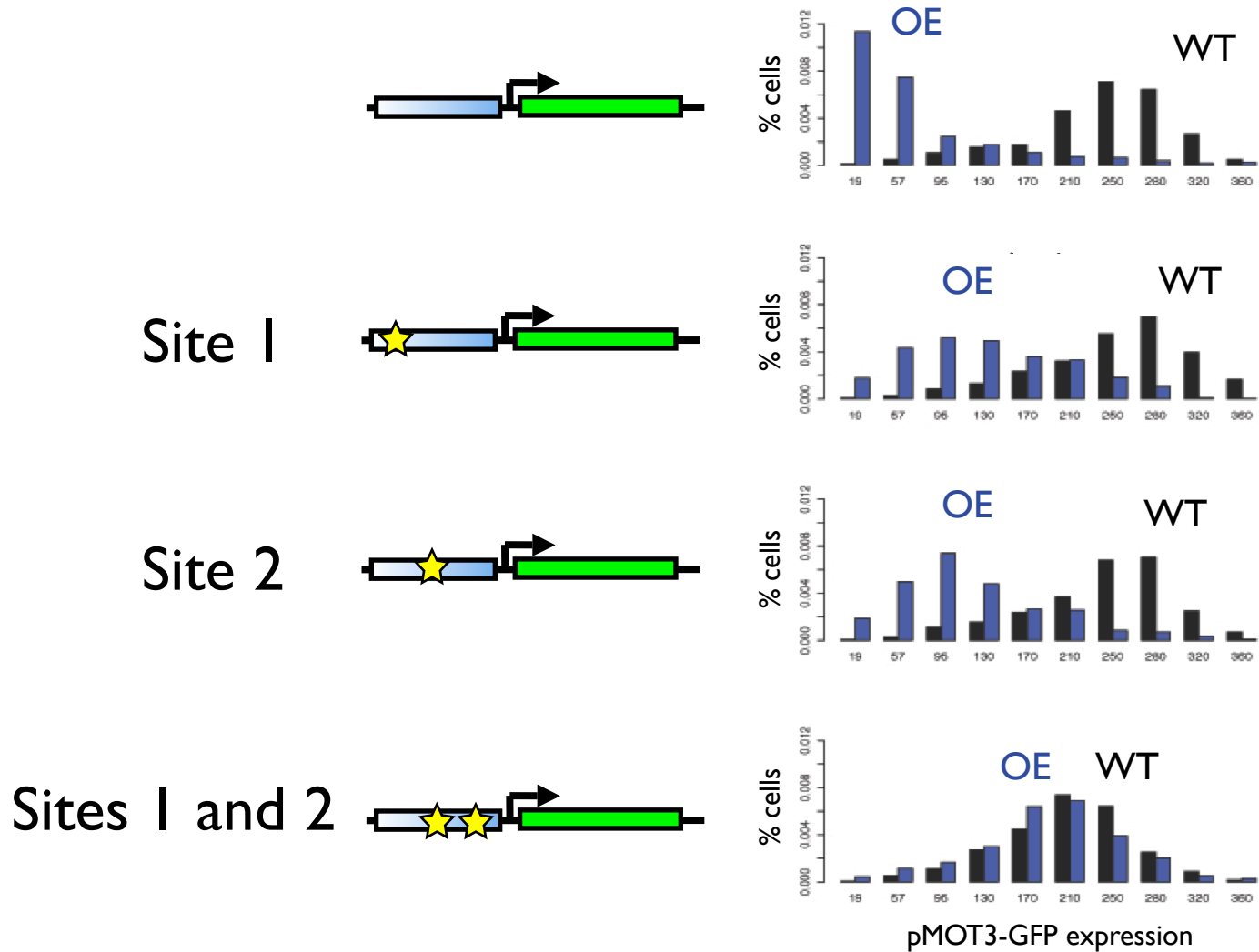
A genetic switch in *MOT3* expression



Transition from hypoxia: some cells “on,” some “off”

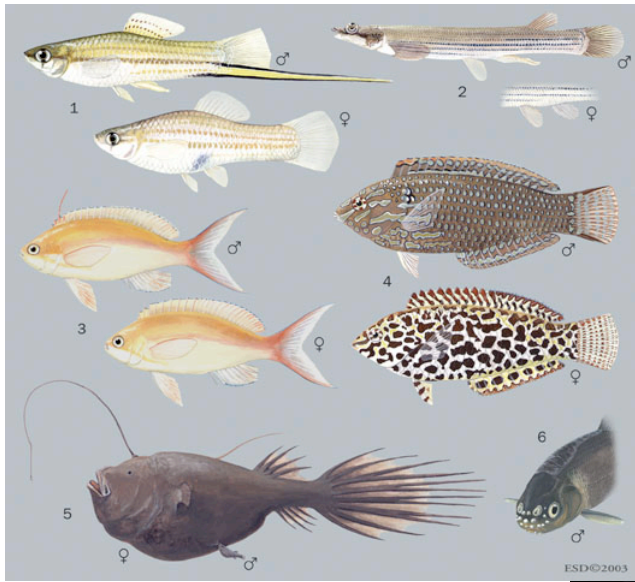


Confirming a novel feedback loop: *MOT3*

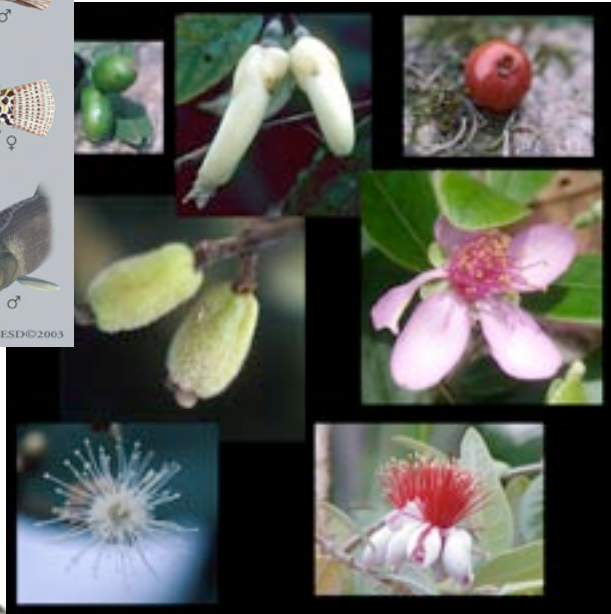




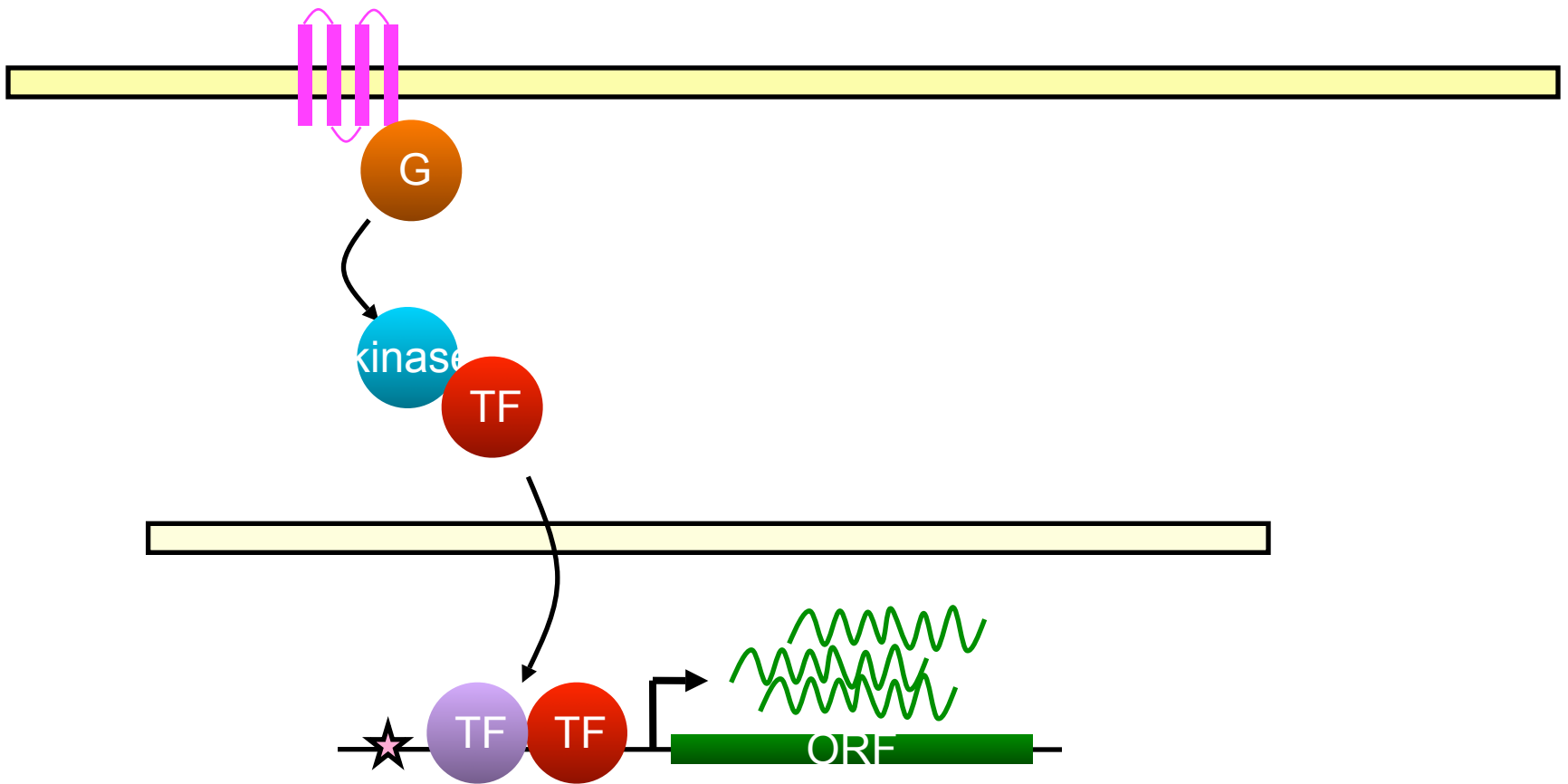
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 A G C T T C G A T T T G G C G G T A T C A



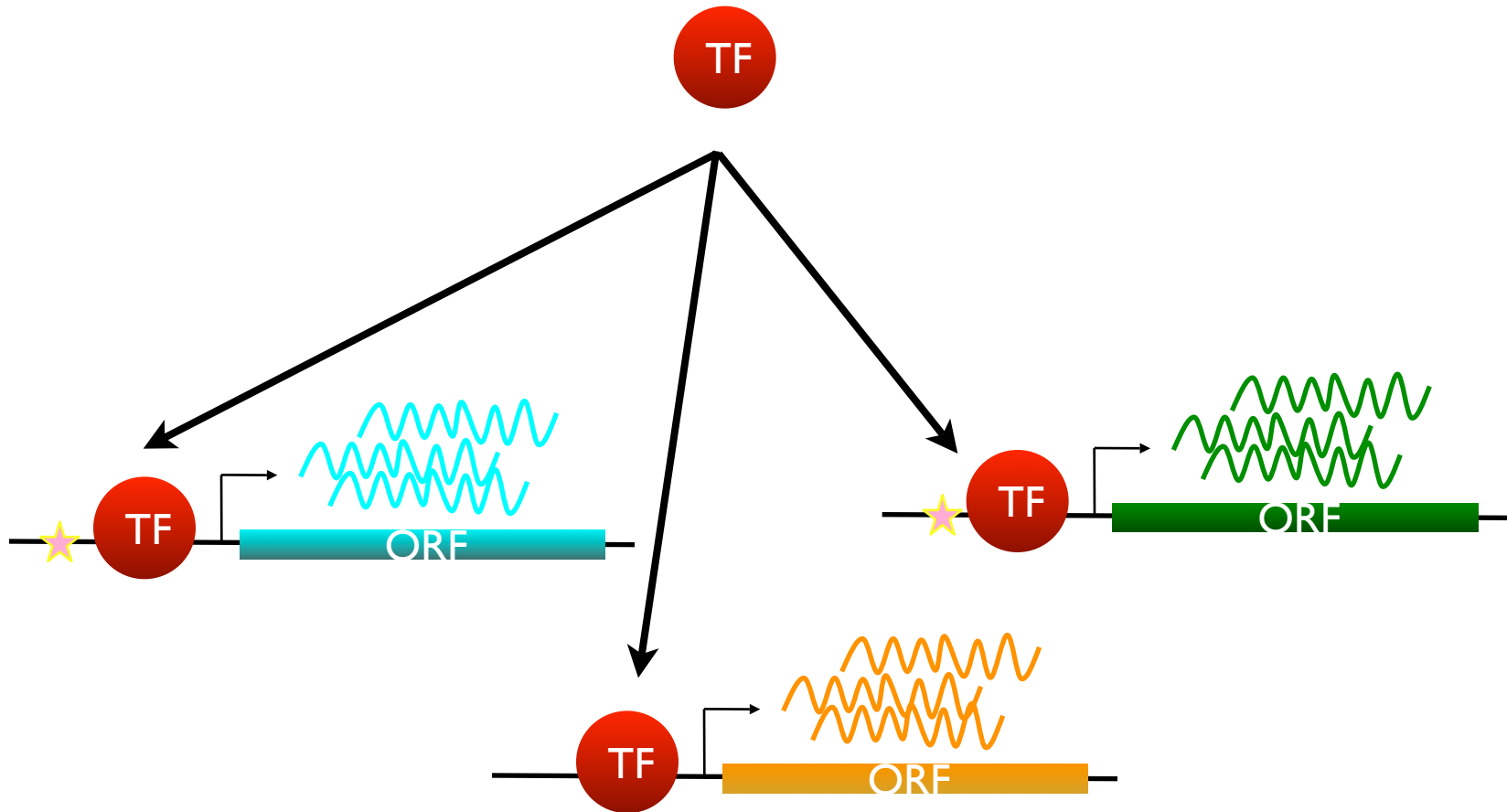
www.keew.org/science/directory/teams/Myrtaceae/images/Myrtaceae.jpg



Cis-acting variant

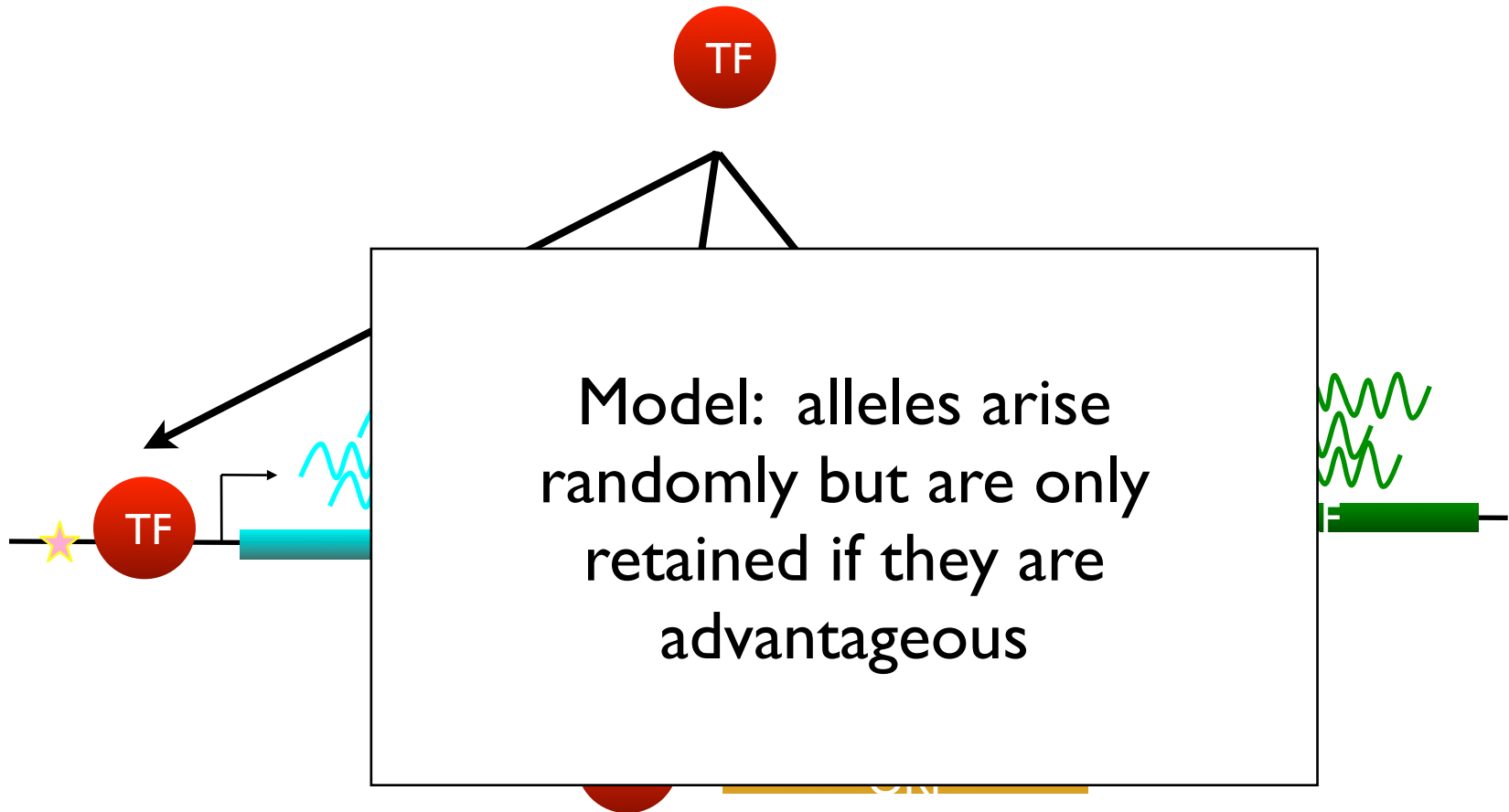


Adaptation *via cis-acting variation*?



Sign imbalance across genes of a pathway

Adaptation *via cis*-acting variation?



Sign imbalance across genes of a pathway

Expression variation between yeast species



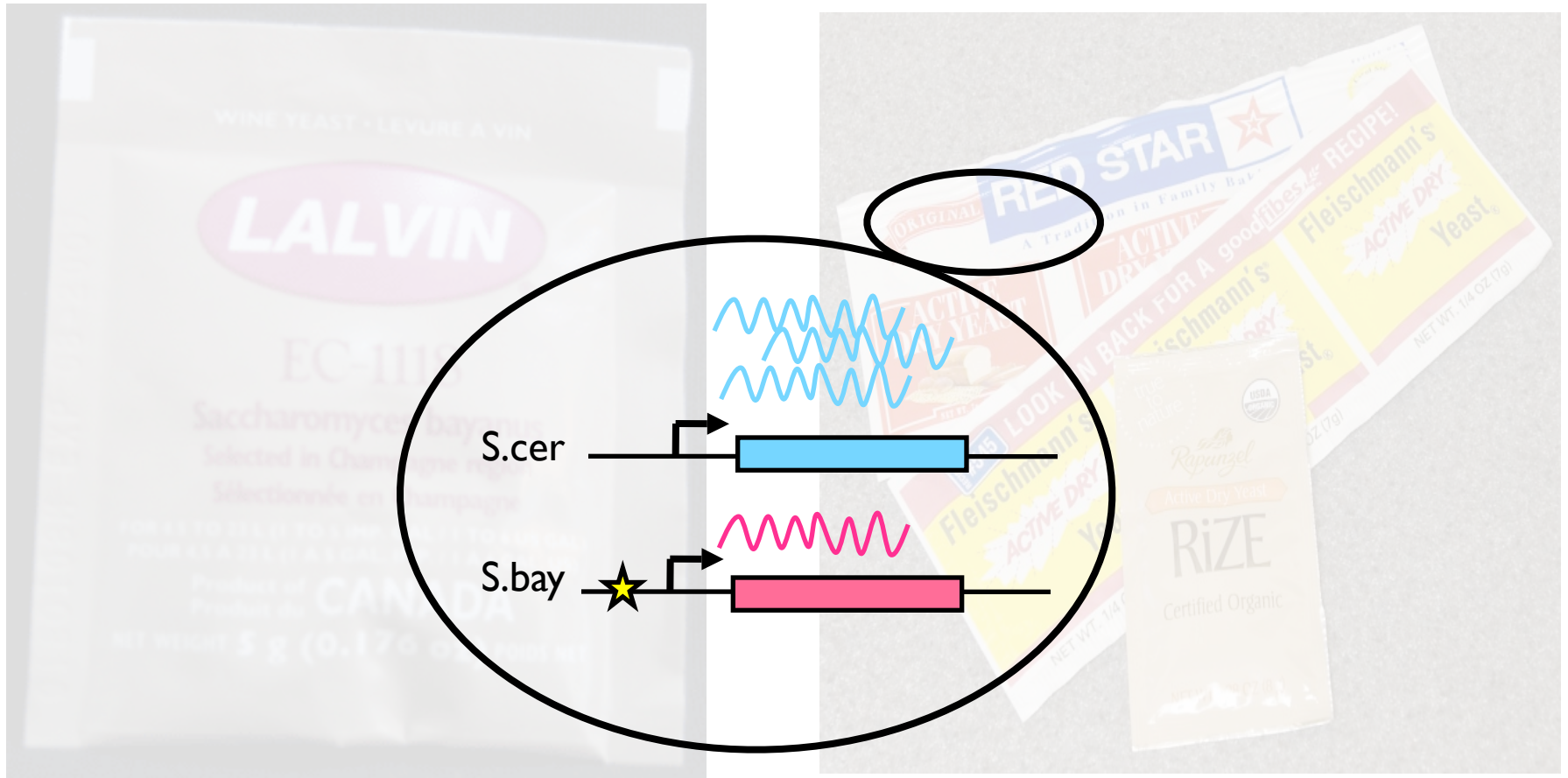
S. bayanus

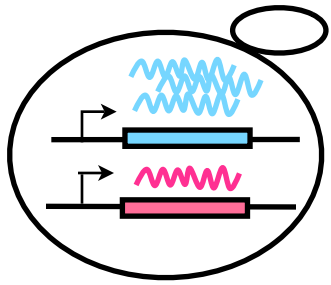


S. cerevisiae

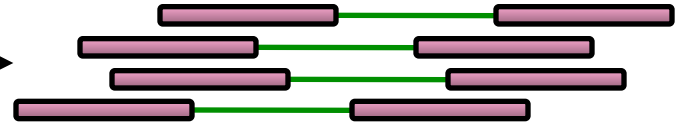
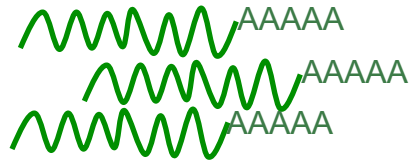
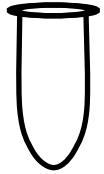
diverged 20 Mya

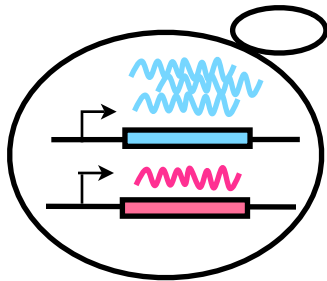
Expression variation between species



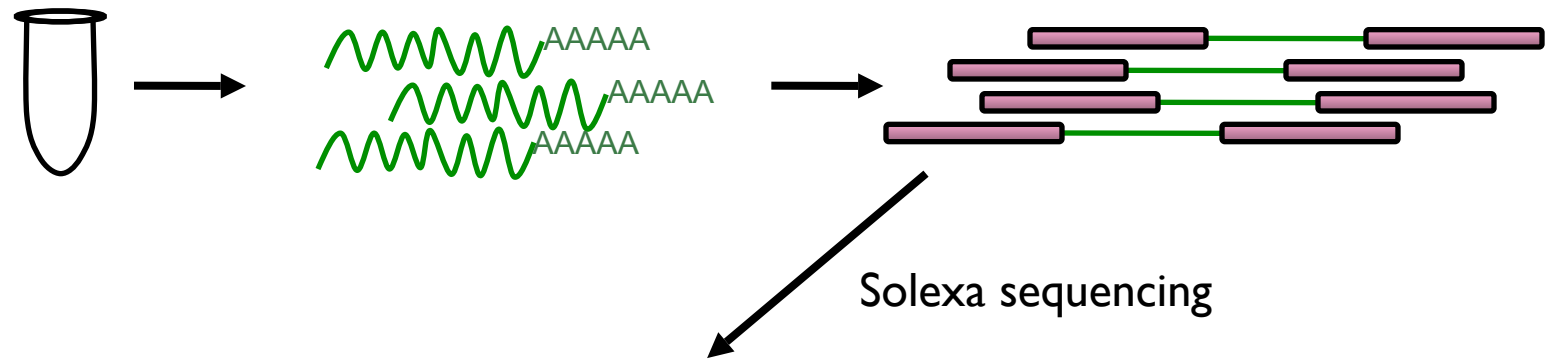


Allele-specific transcript profiling

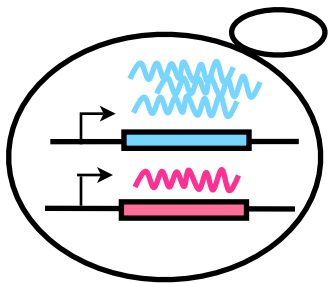




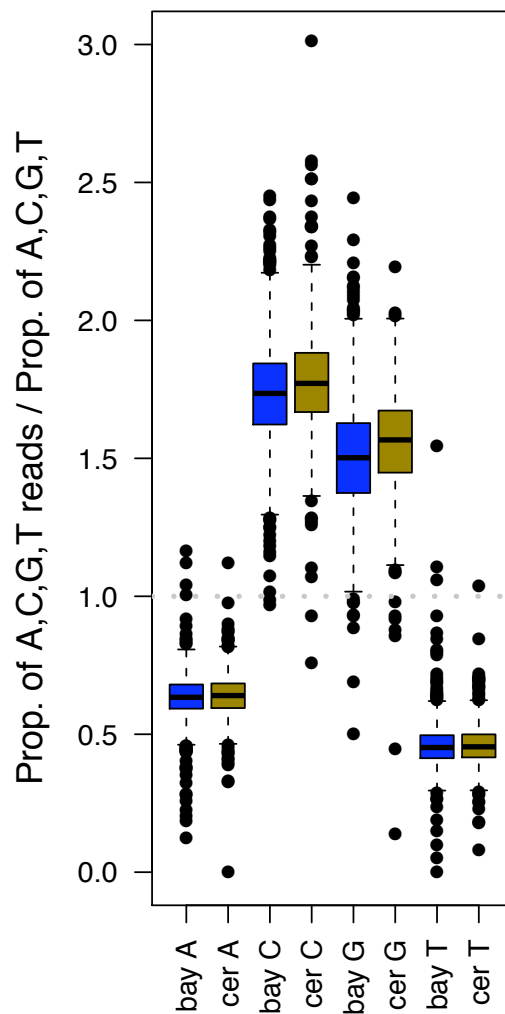
Allele-specific transcript profiling

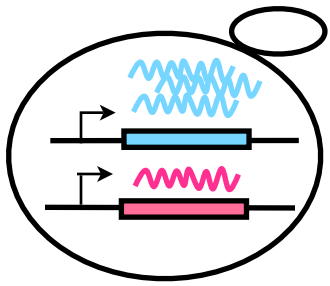


read name	strand	ORF	position	read	mismatches
HWI-EAS105_3_8_1_881_610	+	sbay_c671-g59.1	351	TACAAGGAAATTAGAGA	1
HWI-EAS105_3_8_1_881_610	+	sbay_c589-g15.1	300	TACAAGGAAATTAGAGA	1
HWI-EAS105_3_8_1_890_283	+	sbay_c600-g18.1	250	TACCCAATTATATCAAG	0
HWI-EAS105_3_8_1_331_398	+	sbay_c571-g5.1	1371	ATCAGATGGGGTTTGAA	1
HWI-EAS105_3_8_1_331_398	+	sbay_c672-g24.1	1371	ATCAGATGGGGTTTGAA	1
HWI-EAS105_3_8_1_461_139	+	sbay_c639-g33.1	720	GATAAAATGAAGAATGA	1
HWI-EAS105_3_8_1_461_139	+	YLR300W	720	GATAAAATGAAGAATGA	1
HWI-EAS105_3_8_1_531_314	+	sbay_c658-g10.1	2234	GTACGAATTACAAAAGG	0
HWI-EAS105_3_8_1_529_361	+	YGL103W	135	GATAAATACCATCCAGG	1
HWI-EAS105_3_8_1_529_361	+	sbay_c557-g11.1	135	GATAAATACCATCCAGG	1
HWI-EAS105_3_8_1_886_349	+	sbay_c667-g33.1	358	TTTACGAGATAGCCAAG	0
HWI-EAS105_3_8_1_259_961	+	YPL217C	2249	GTATGAACTACAGAAGG	0
.....					

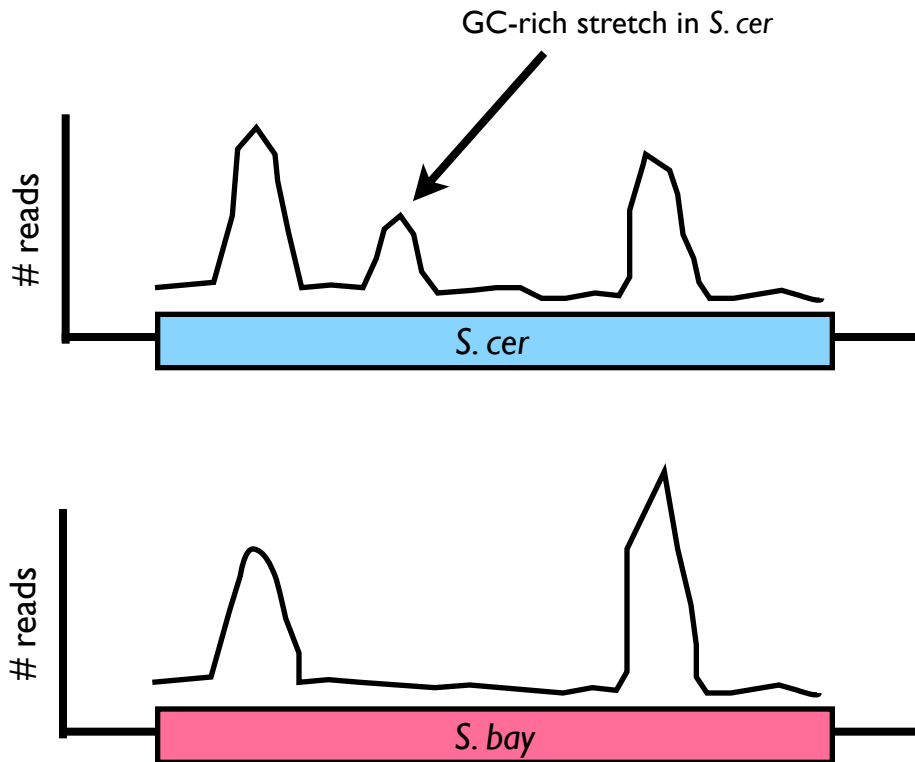


Solexa sequence dependence

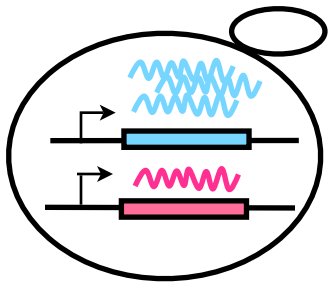




Solexa sequence dependence



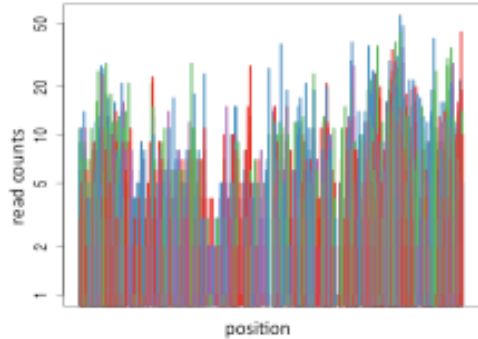
Expression fold-change
confounded
with sequencing
biases?



Assess differential expression

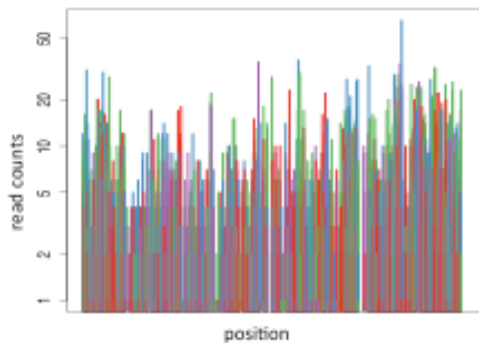
Observed read counts

$\pi_b(A) = .35$, $\pi_b(C) = .18$, $\pi_b(G) = .23$, $\pi_b(T) = .24$

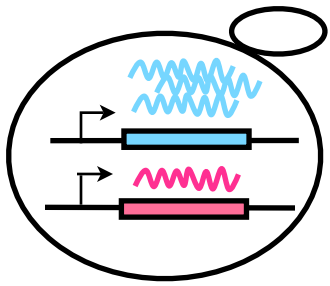


S. bayanus

$\pi_c(A) = .37$, $\pi_c(C) = .17$, $\pi_c(G) = .21$, $\pi_c(T) = .25$



S. cerevisiae

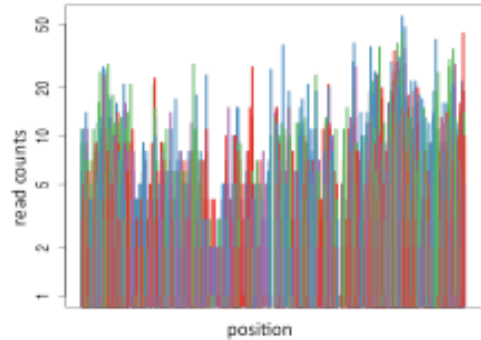


Assess differential expression

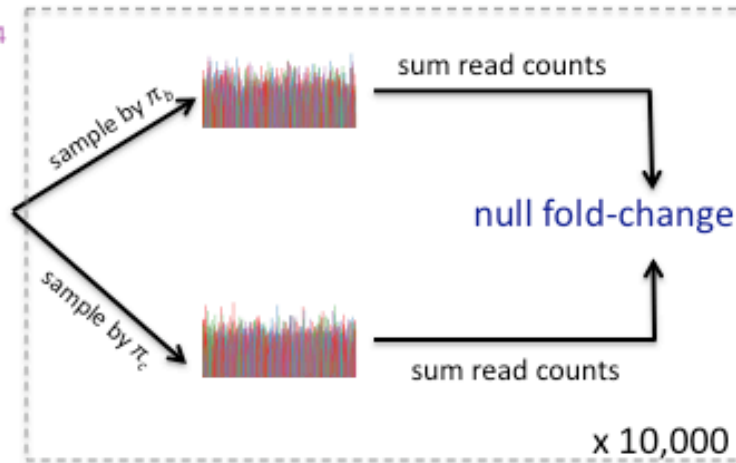
Observed read counts

Resampled read counts

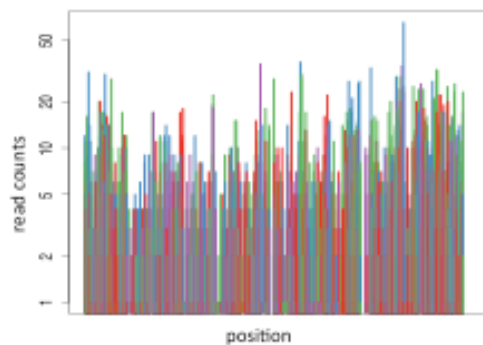
$\pi_b(A) = .35$, $\pi_b(C) = .18$, $\pi_b(G) = .23$, $\pi_b(T) = .24$



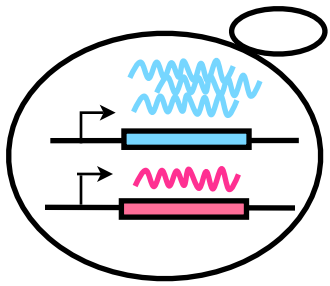
S. bayanus



$\pi_c(A) = .37$, $\pi_c(C) = .17$, $\pi_c(G) = .21$, $\pi_c(T) = .25$

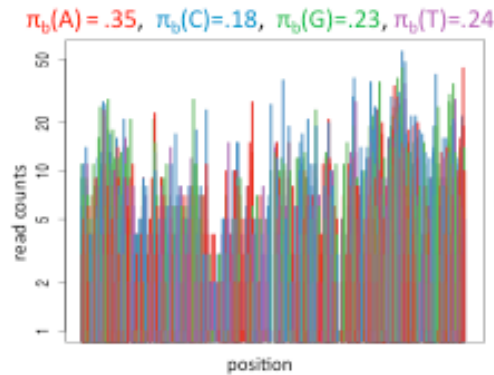


S. cerevisiae



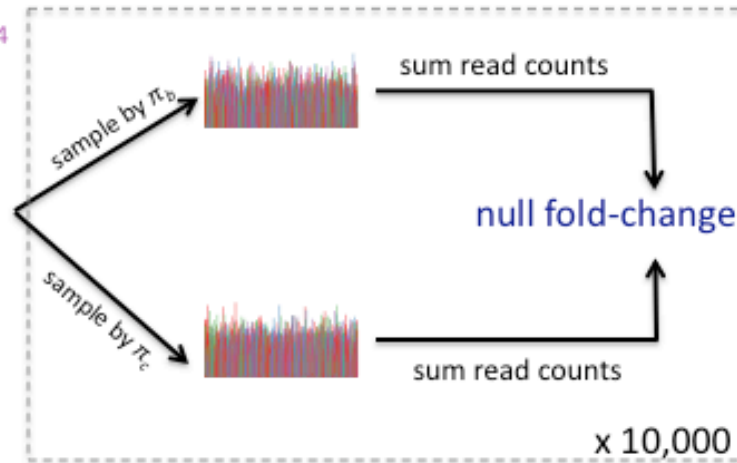
Assess differential expression

Observed read counts

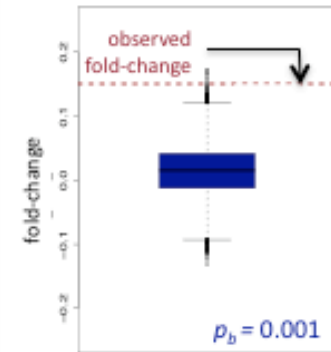


S. bayanus

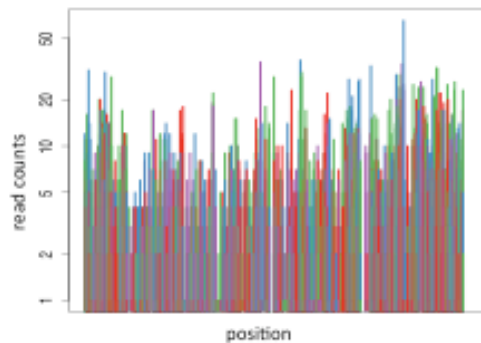
Resampled read counts



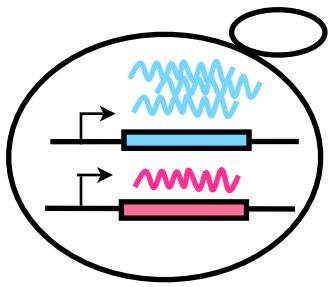
Null distribution of fold-change



$\pi_c(A) = .37, \pi_c(C) = .17, \pi_c(G) = .21, \pi_c(T) = .25$

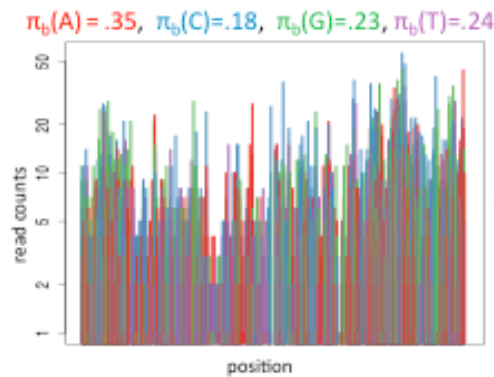


S. cerevisiae



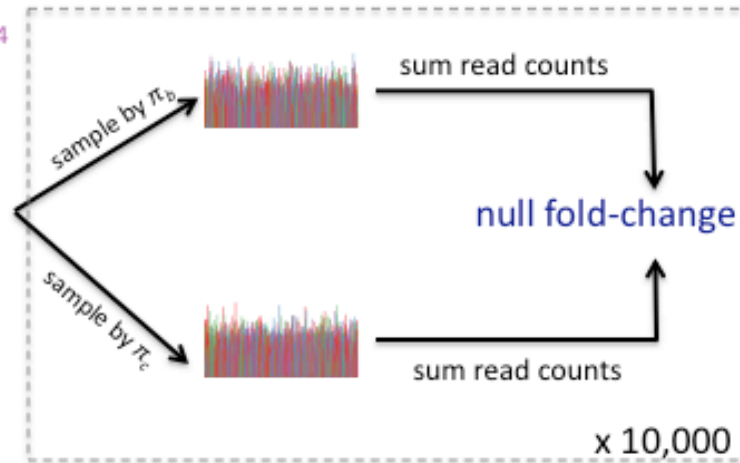
Assess differential expression

Observed read counts

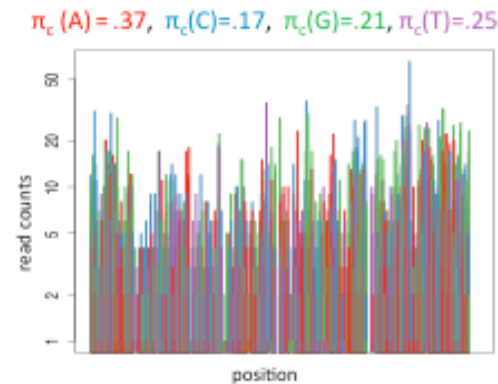
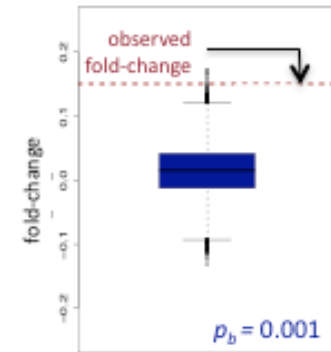


S. bayanus

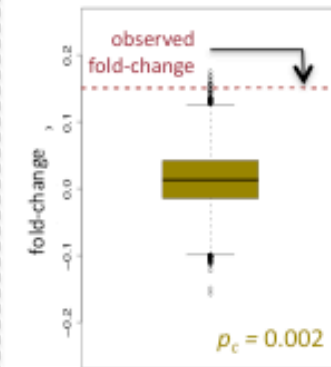
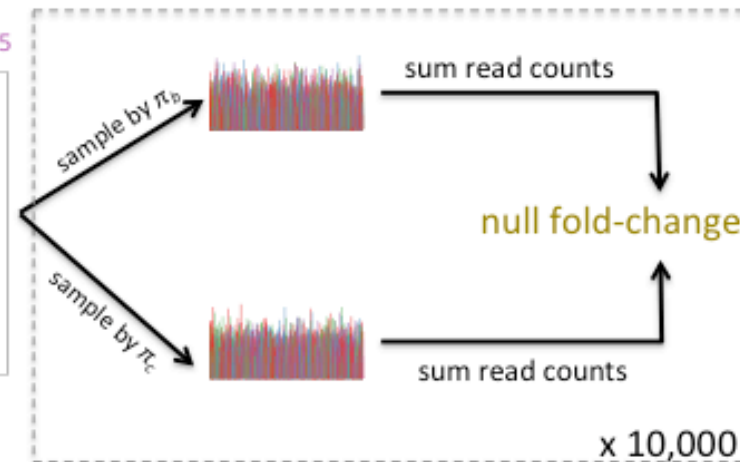
Resampled read counts

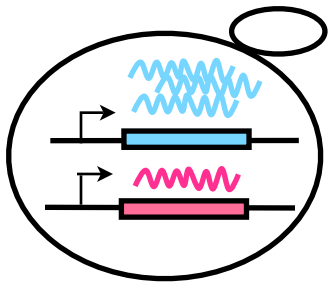


Null distribution of fold-change



S. cerevisiae





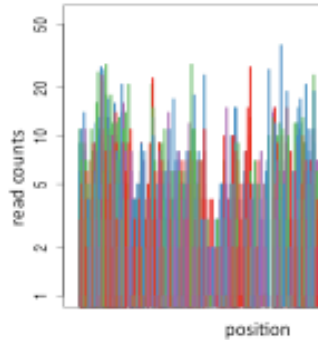
Assess differential expression

Observed read counts

Resampled read counts

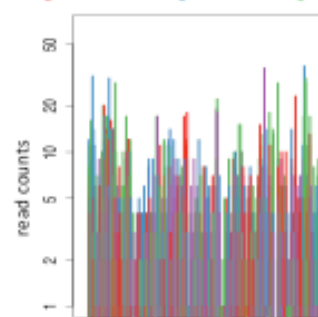
Null distribution of fold-change

$\pi_b(A) = .35, \pi_b(C) = .18, \pi_b(G) = .23, \pi_b(T) = .24$



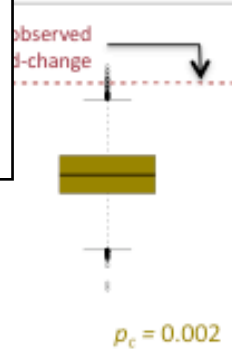
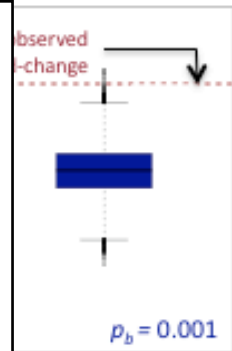
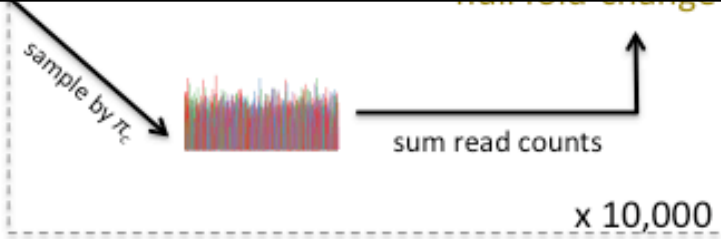
S. bayanus

$\pi_c(A) = .37, \pi_c(C) = .17, \pi_c(G) = .23, \pi_c(T) = .23$

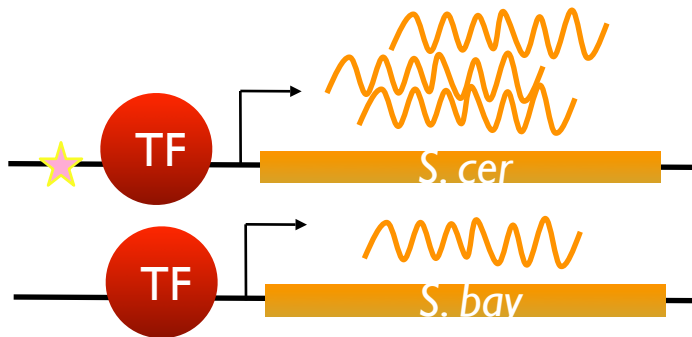
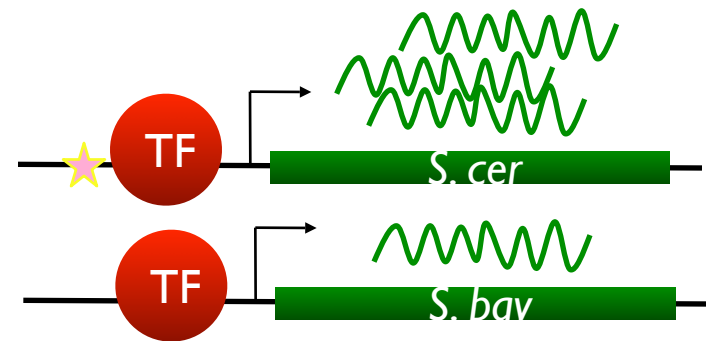
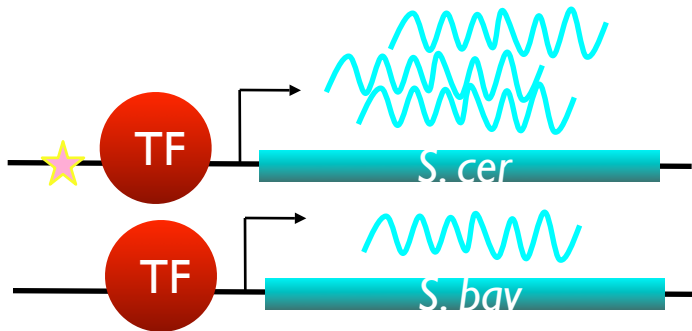


S. cerevisiae

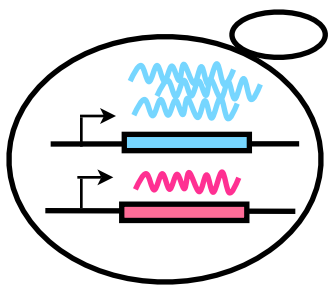
Result: a p -value assessing significance of difference between species, in the face of GC bias



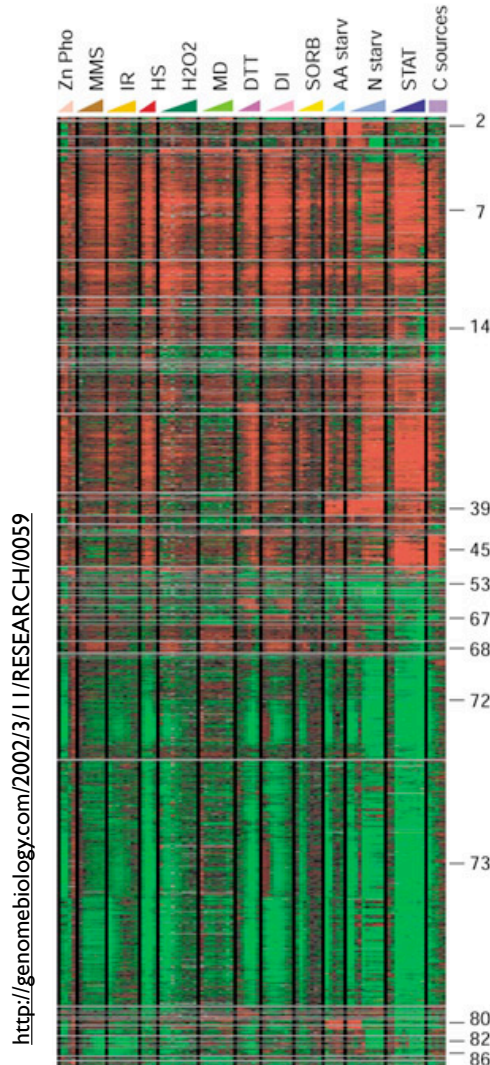
Adaptation *via cis-acting variation*?



Sign imbalance across genes of a pathway



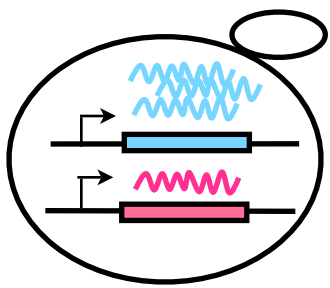
Use pre-defined gene clusters



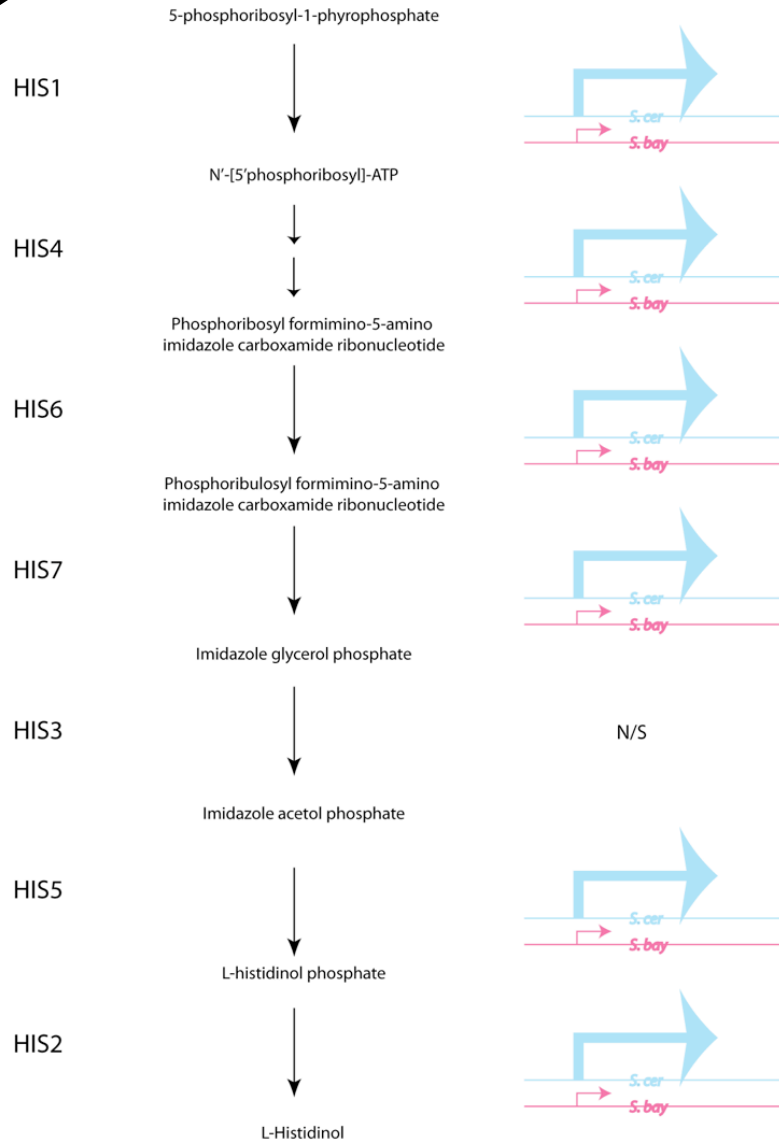
```

...
YER014W
YDR047W
YOR278W
Cluster_Histidine"c"
YER055C
YBR248C
YCL030C
YFR025C
YIL116W
YOR202W
YIL020C
YKR099W
Cluster_Isoleucine"c"
YJR148W
YHR208W
YMR108W
...

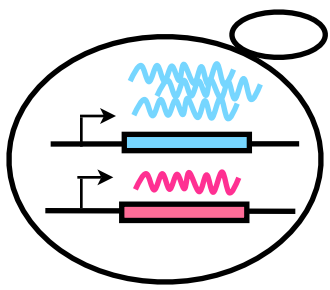
```



Sign imbalance in a pathway



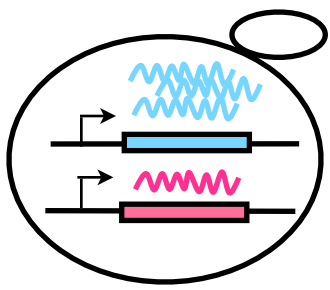
Sign sum over genes = -7



Significance of sign imbalance

Name	Sign sum	Group p	Annotation
Cluster_Histidine	-7	0.00007	Histidine biosynthesis
Cluster_NRG1	-7	0.0011	Stress-induced transport
Node 73	70	0.0016	Ribosome biogenesis
Cluster_adata-Respiration	-8	0.0057	Respiration
Cluster_Lysine	-5	0.0059	Lysine biosynthesis
Node 45	-9	0.0072	Respiration
Cluster_RTG1	-7	0.015	Ribosome and osmotic stress
Cluster_FKH1	8	0.018	Cell cycle
Cluster_RCS1	-5	0.028	Iron transport
Node 67	-6	0.031	Redox and secretion
Node 80	-4	0.044	AA biosynthesis
Node 68	-5	0.050	Proteasome

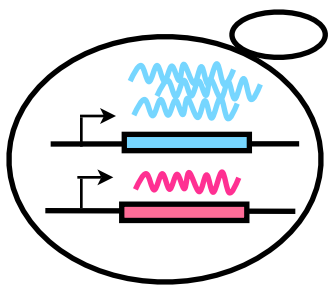
187 total
groups
tested



Significance of sign imbalance

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Node 80	-4	0.044	AA biosynthesis
Node 68	-5	0.050	Proteasome

187 total
groups
tested,
expect ~1
false

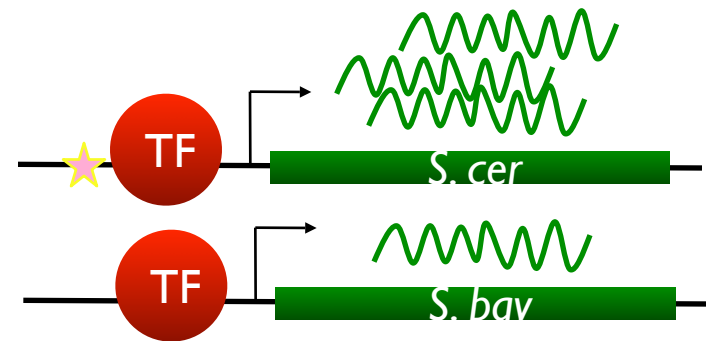
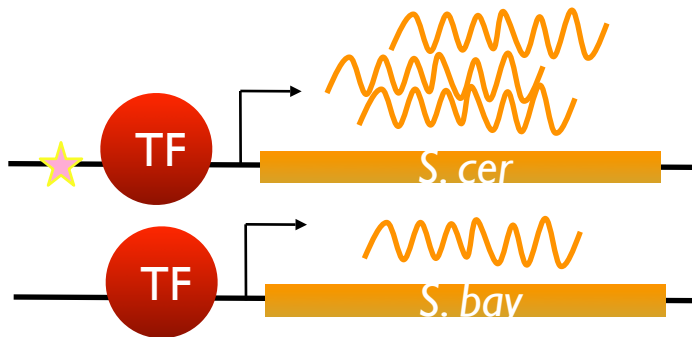
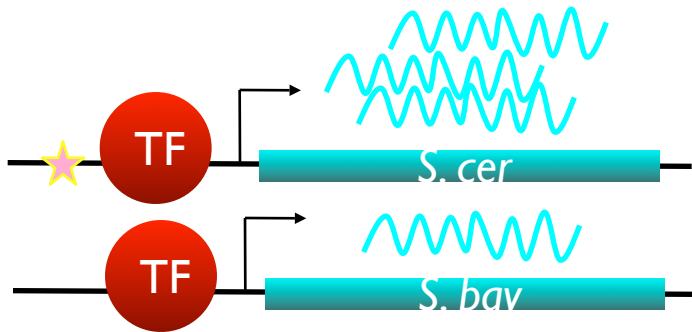


Repeat with Gene Ontology

Name	Sign sum	Group p	Annotation
GO:00042254	78	0.000001	Ribosome biogenesis
GO:0006725	-9	0.0074	Aromatic compound metabolism
GO:0016070	124	0.011	RNA metabolic process
GO:0006996	114	0.050	Organelle organization

38 total
groups
tested,
expect
~0.2 false

Adaptive tuning of gene expression



Thanks

Jackie Whittle
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HIP

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