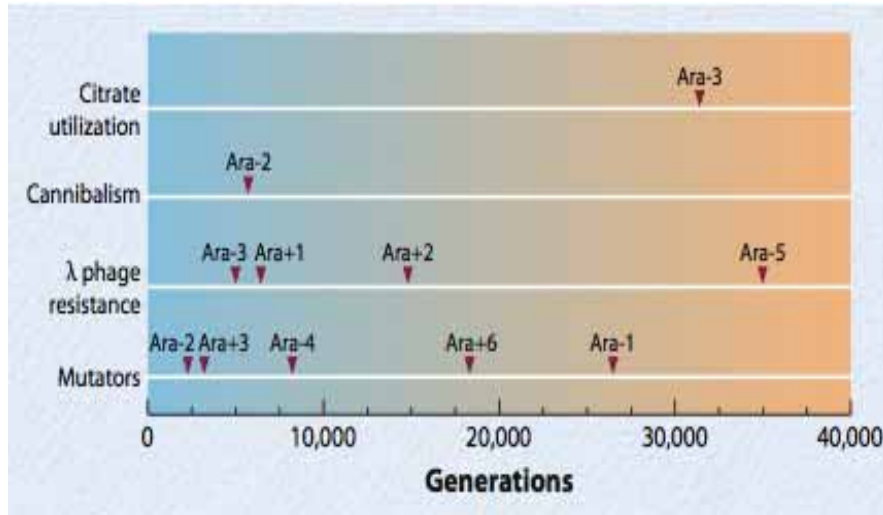


# **Evolving chromosomes and gene regulatory networks**

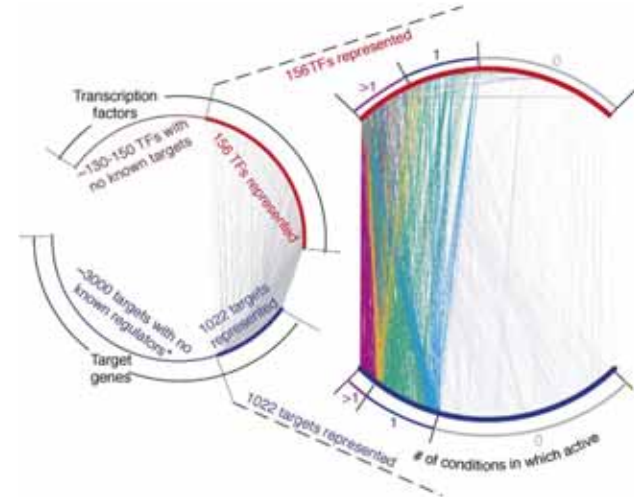
*Aswin Sai Narain Seshasayee  
National Centre for Biological Sciences  
Tata Institute of Fundamental Research  
Bangalore*

# Adaptation to changing environments



*Kussell. 2013*

**changing genomes**

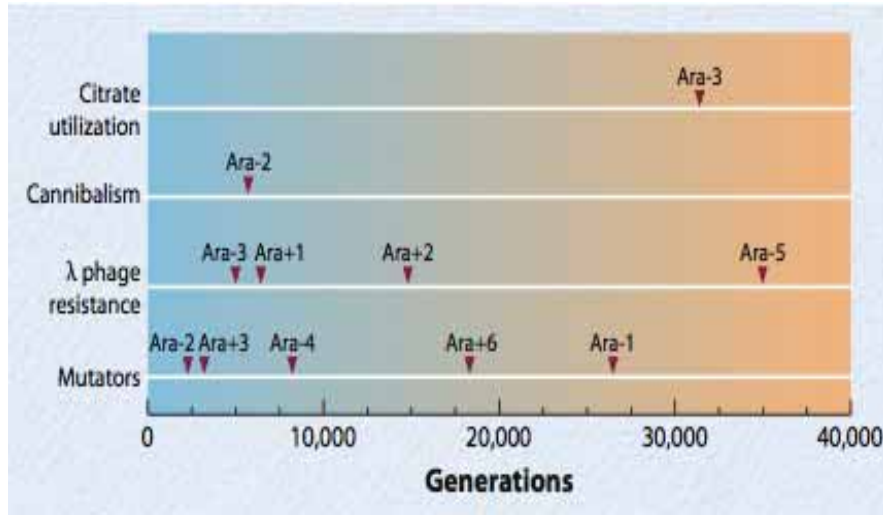


*Seshasayee et al. 2006*

**changing gene expression**

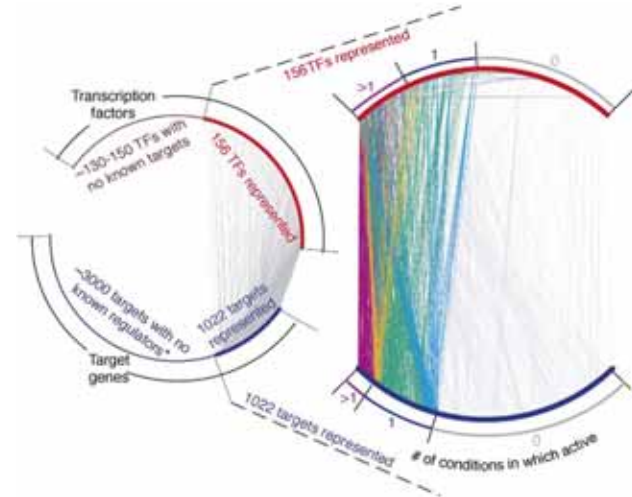
**typically operate over distinct time-scales**

# Adaptation to changing environments



*Kussell. 2013*

**changing genomes**



*Seshasayee et al. 2006*

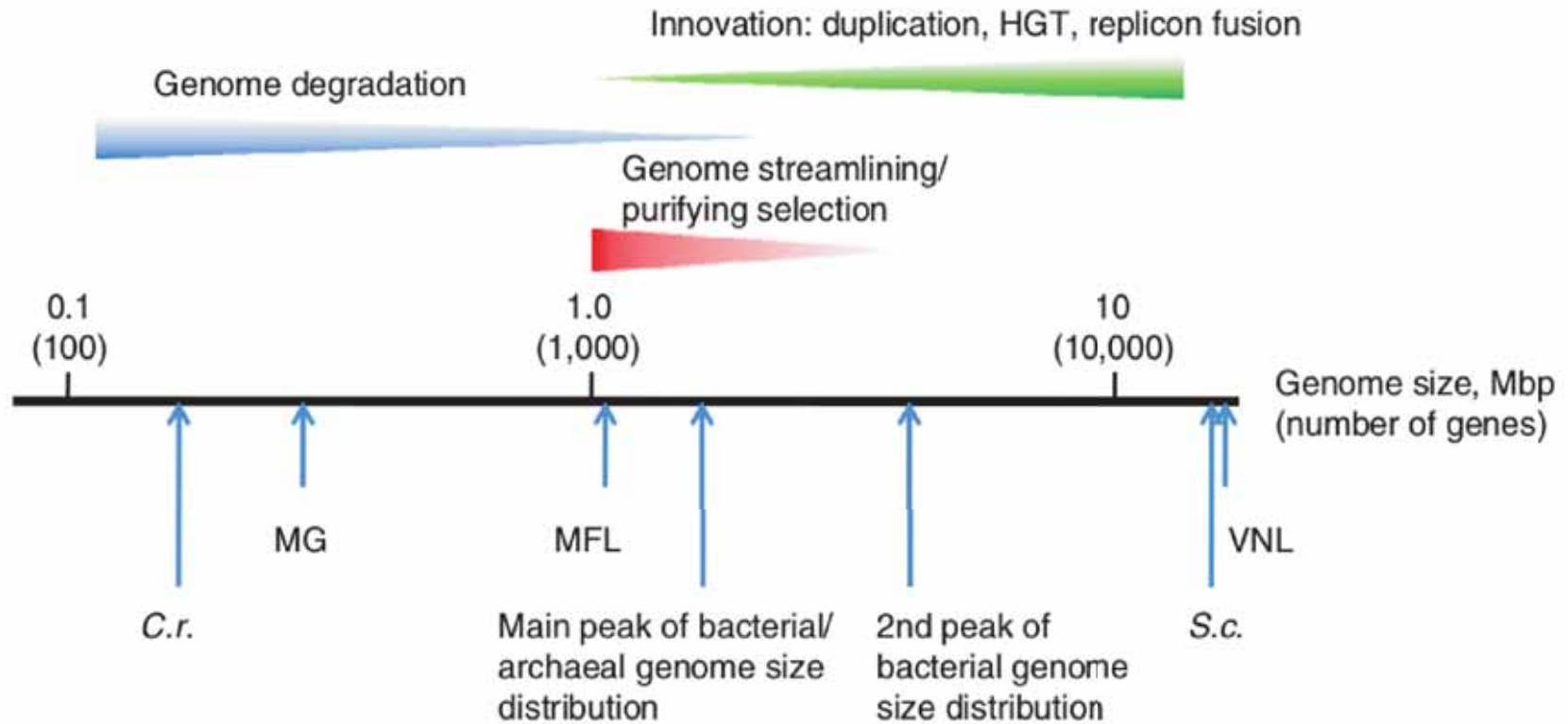
**changing gene expression**

**typically operate over distinct time-scales**

**how does one impact the other?**

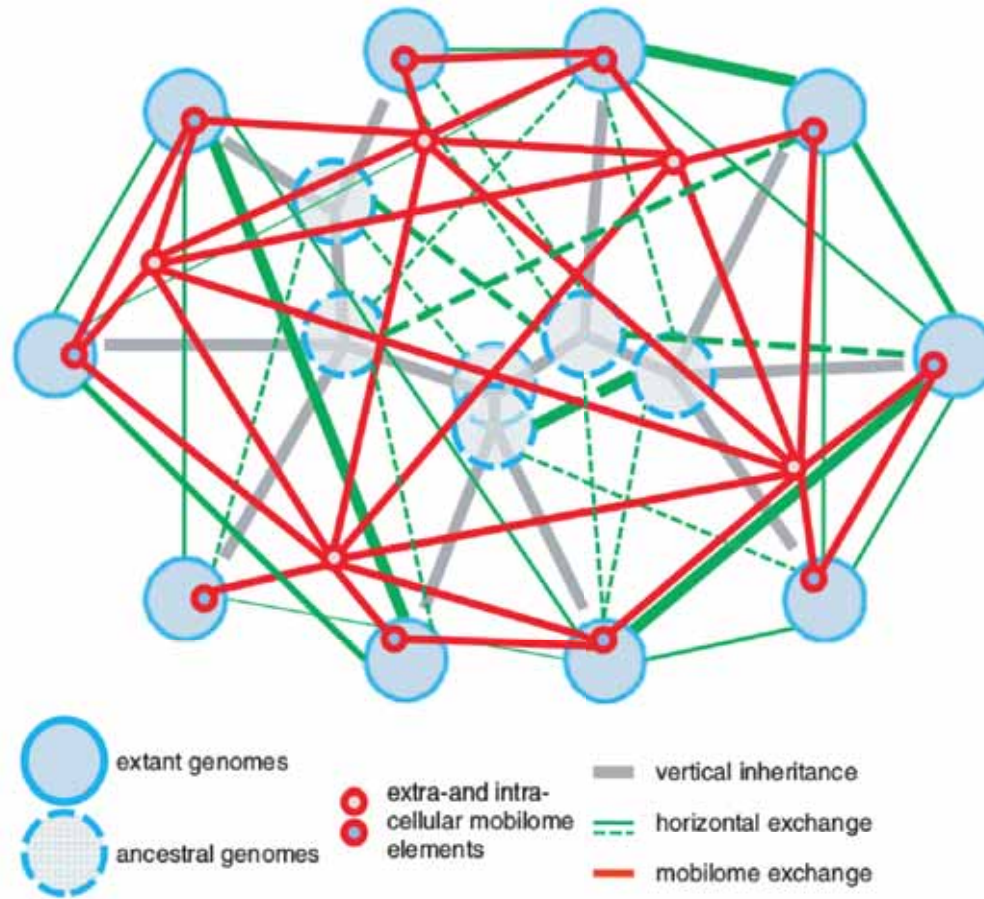
**do they converge?**

# Many processes change genomes



*Koonin and Wolf. 2008*

**.. including horizontal gene transfer**



*Koonin and Wolf. 2008*

# **Horizontal gene transfer**

**Drastic modification** of genetic material

Rapid exploration of **new niches and phenotypes**

# Horizontal gene transfer regulates

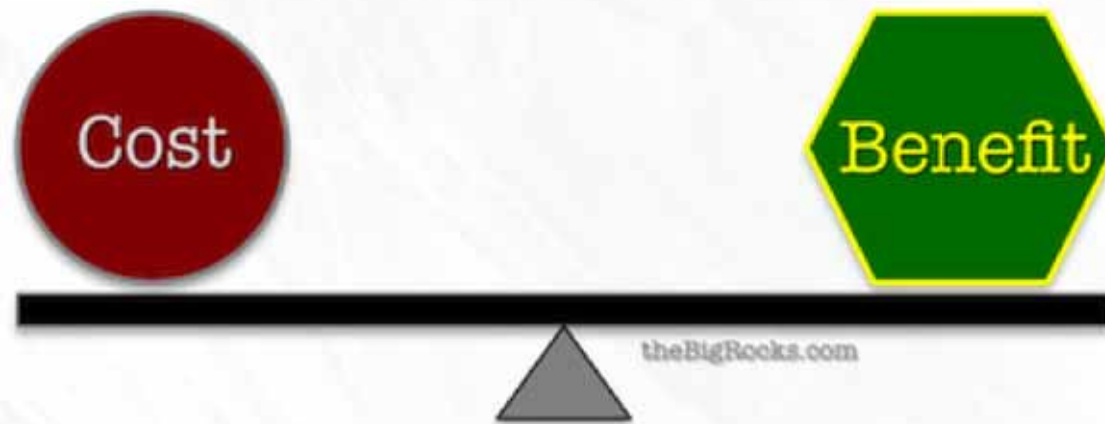
New selective forces for **gene addition / deletion**

Alterations in **genome architecture**

Network **rewiring**

# .. and is regulated at multiple levels

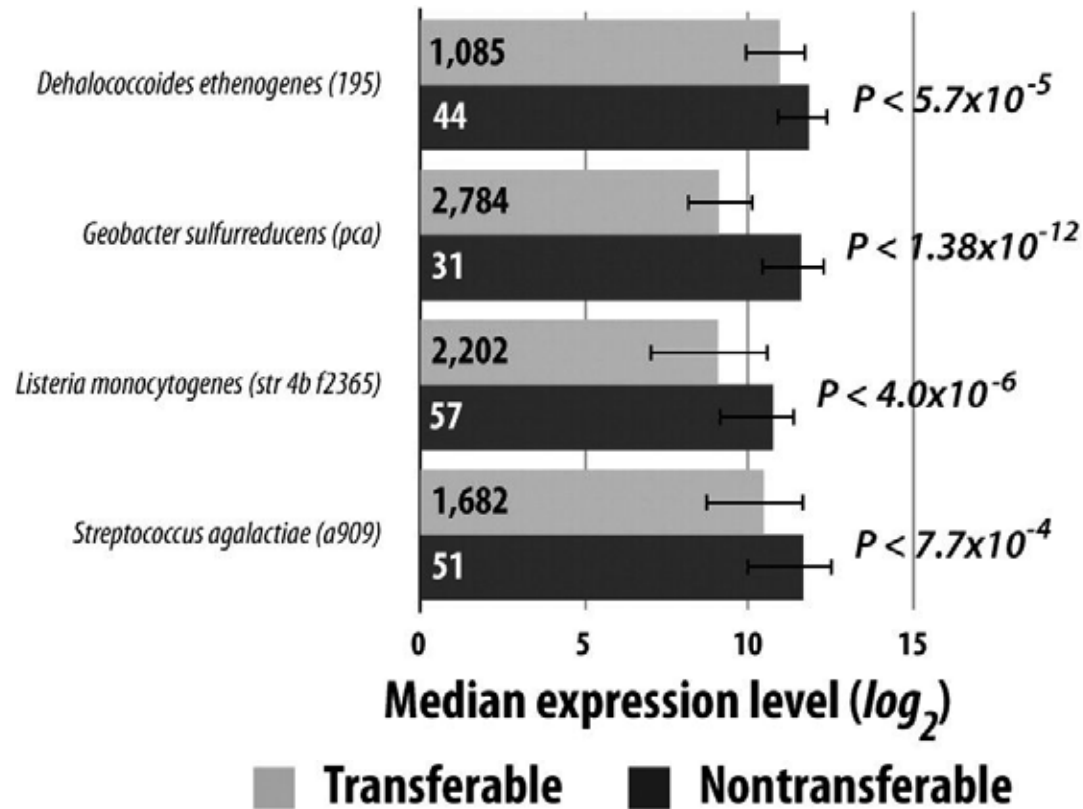
High gene expression is a barrier to horizontal transfer



**Balance** between  
selective **benefit** of acquired gene  
and  
**“cost”** of expressing it



# Gene silencing is important



Park and Zhang. 2012

**as high gene expression  
hampers horizontal transfer**

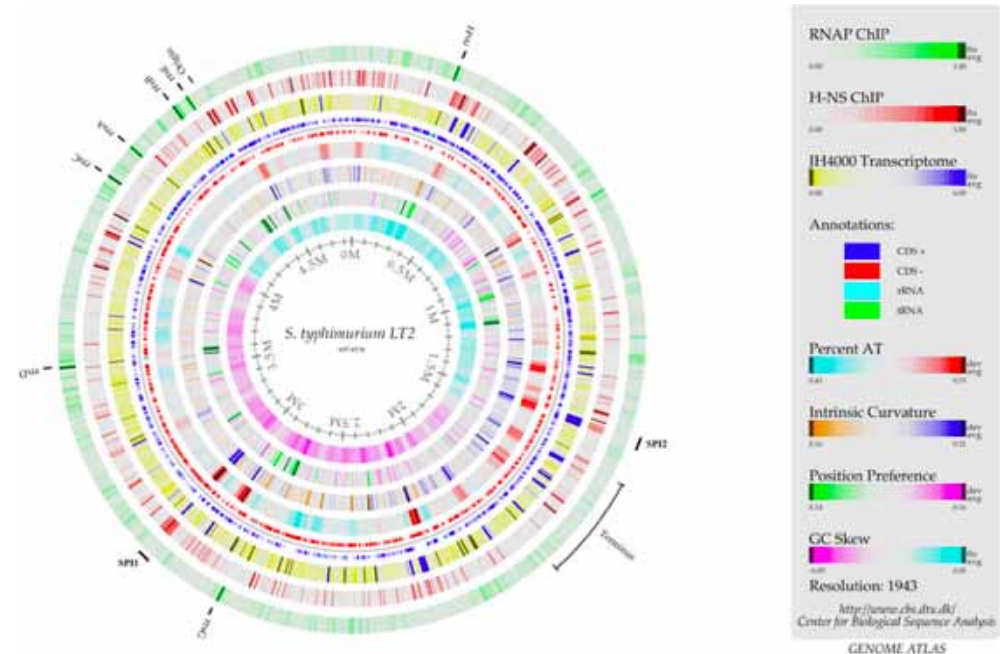
# H-NS

Binds to A+T-rich / intrinsically bent DNA / Holliday junctions

A global regulator

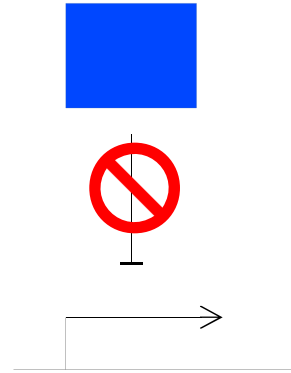
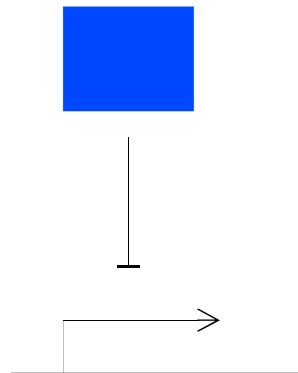
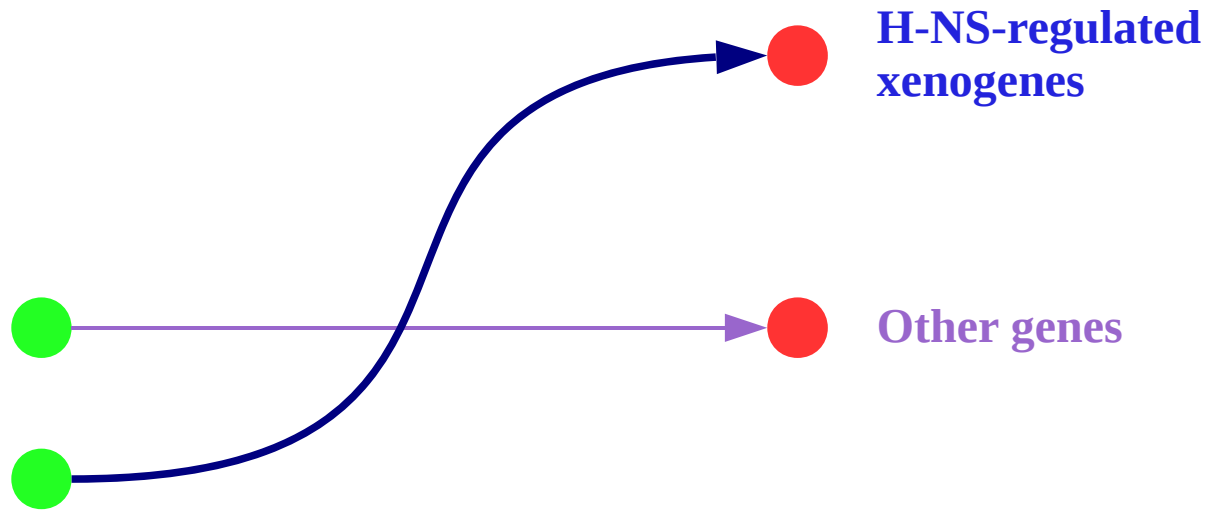
*Represses* gene expression

**Role in silencing horizontally-acquired genes**



Lucchini et al. PLoS Pathogens, 2006

Gene expression level ↑



If a role of H-NS is to keep  
***highly transcribable\**** genes silent..

At the sequence level:

***are H-NS binding sites more correlated with  
transcribability?***

At the network level:

***is the H-NS co-regulatory network designed to  
robustly target transcribable genes?***

***\*costly / wasteful***

If a role of H-NS is to keep  
***highly transcribable\**** genes silent..

At the sequence level:

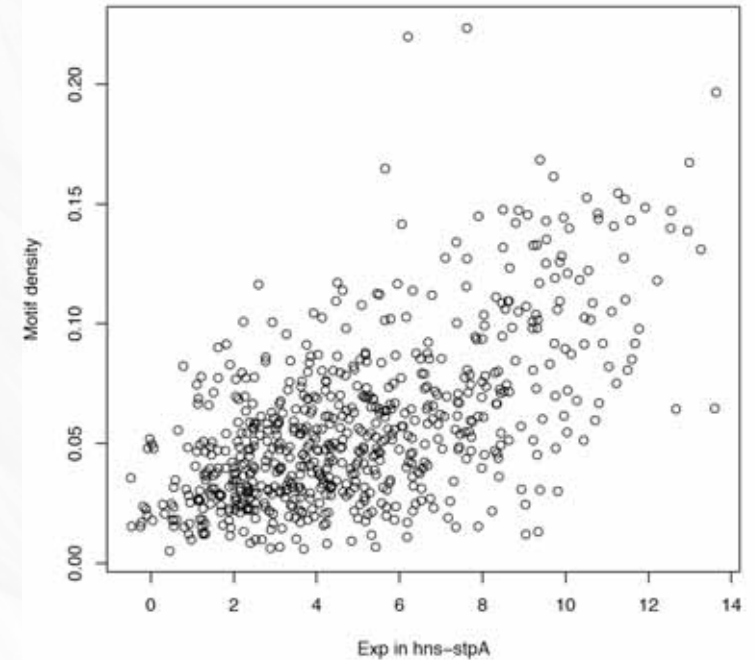
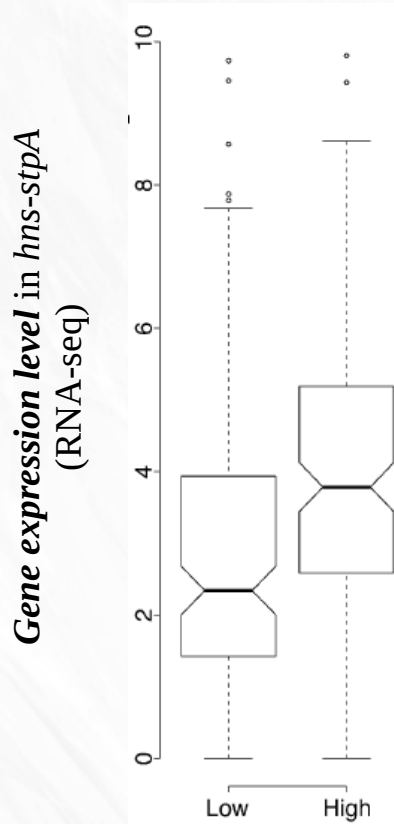
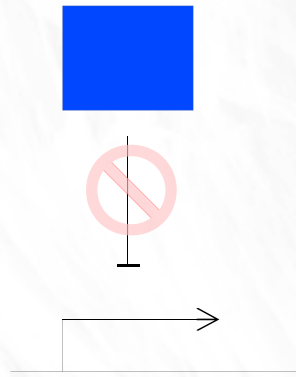
***are H-NS binding sites more correlated with  
transcribability?***

At the network level:

***is the H-NS co-regulatory network designed to  
robustly target transcribable genes?***

***\*costly***

# DNA binding affinities for H-NS v. Transcribability



(Raji Srinivasan; new data)

Higher the transcribability, greater the binding affinity to H-NS

The *DNA binding affinities* of H-NS are such that

**H-NS may be more likely to**

**silence highly transcribable genes**

If a role of H-NS is to keep  
***highly transcribable\**** genes silent..

At the sequence level:

*are H-NS binding sites more correlated with  
transcribability?*

At the network level:

***is the H-NS co-regulatory network designed to  
robustly target transcribable genes?***



# *H-NS has a homolog - StpA*

*A poorer cousin* to H-NS

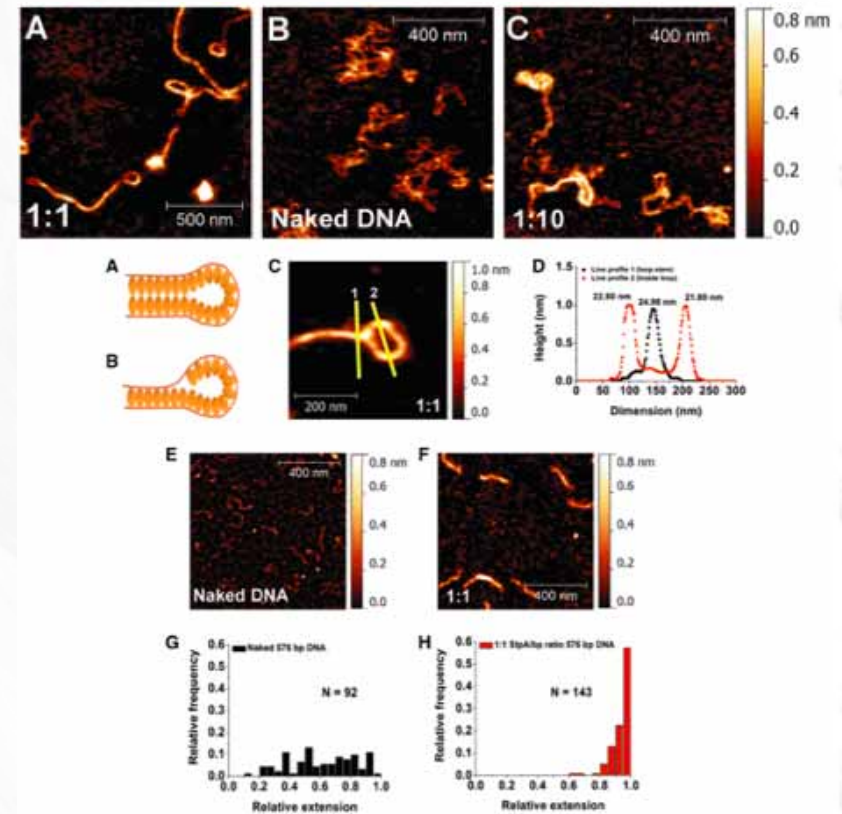
~70% sequence similarity

Can form heteromer with H-NS

Share binding sites with H-NS

Can silence gene expression

Can backup for H-NS



Lim et al. NAR, 2012

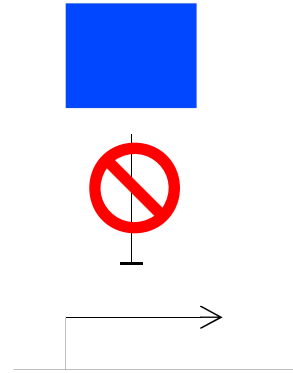
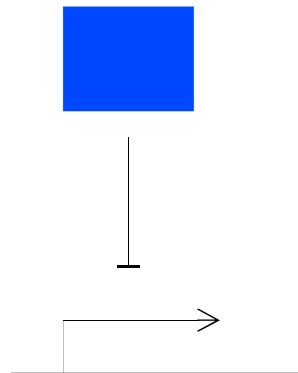
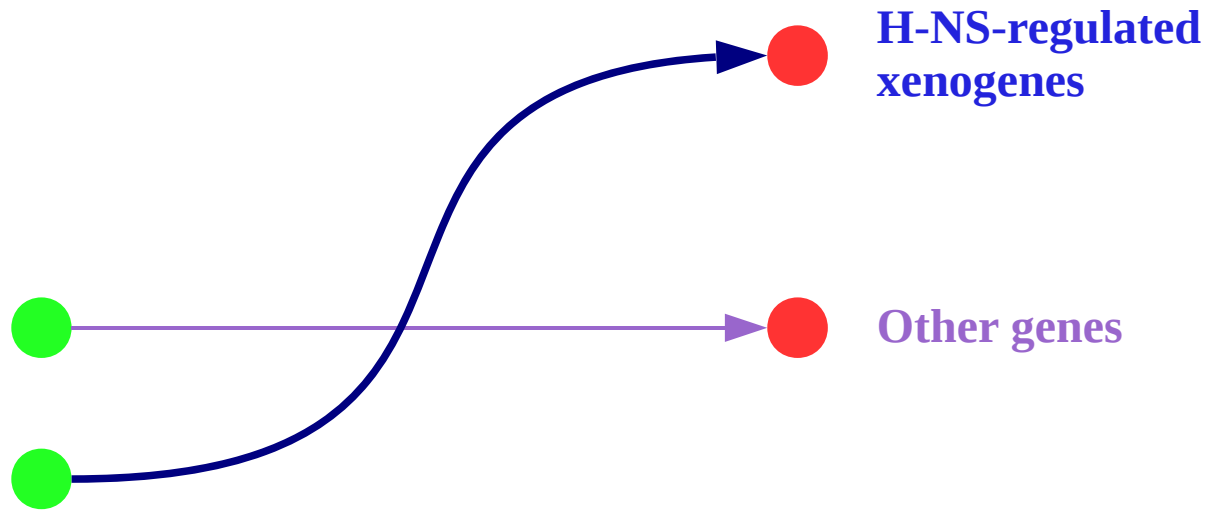
Genes under H-NS control can be

(a) *unilaterally* regulated by H-NS

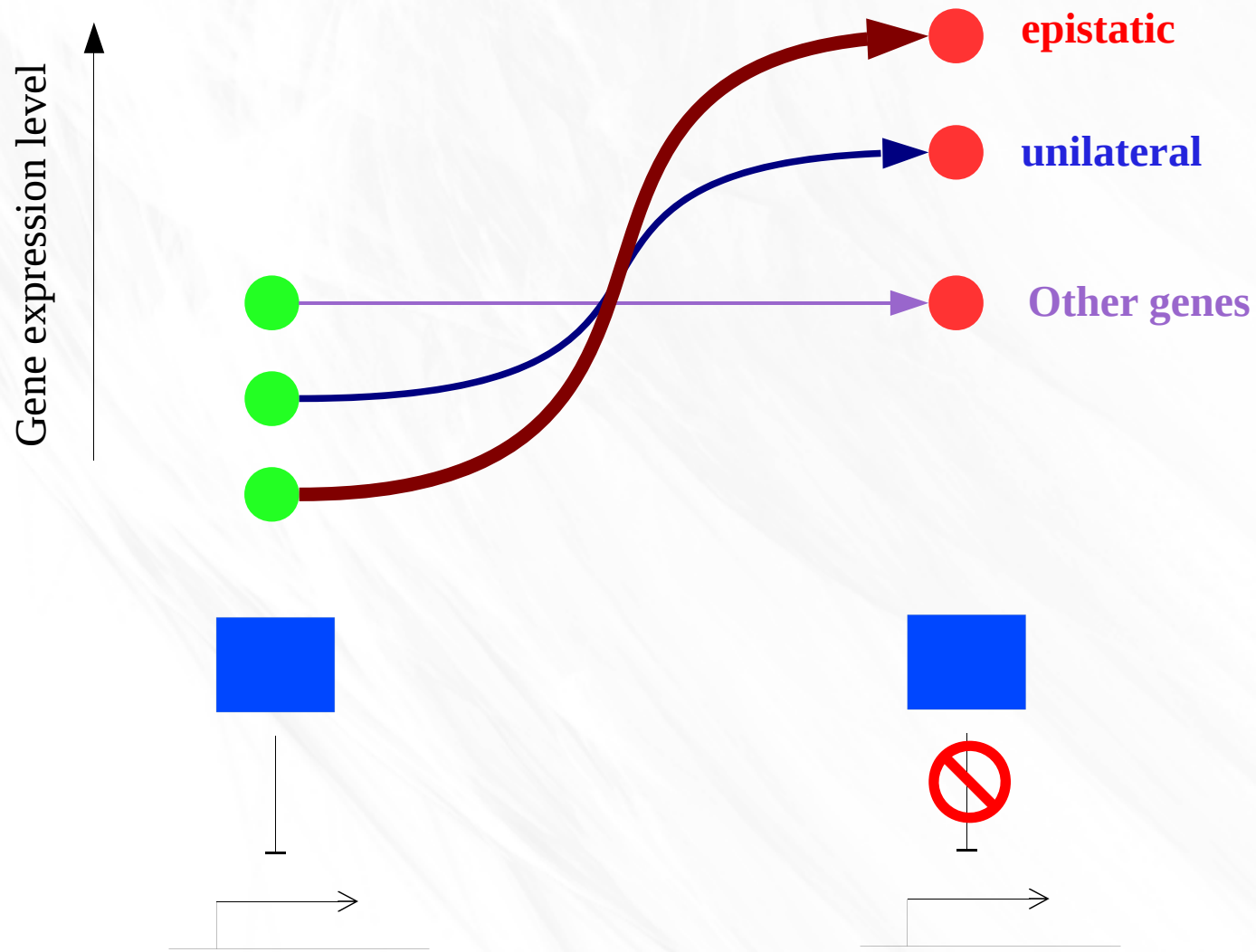
(b) *epistatically* regulated by H-NS and StpA

Because **backup by StpA is partial!**

Gene expression level ↑



... recollect: H-NS silences highly transcribable genes



H-NS and its regulatory network show  
selection for  
**preferential silencing**  
of  
**highly transcribable, dispensable genes**

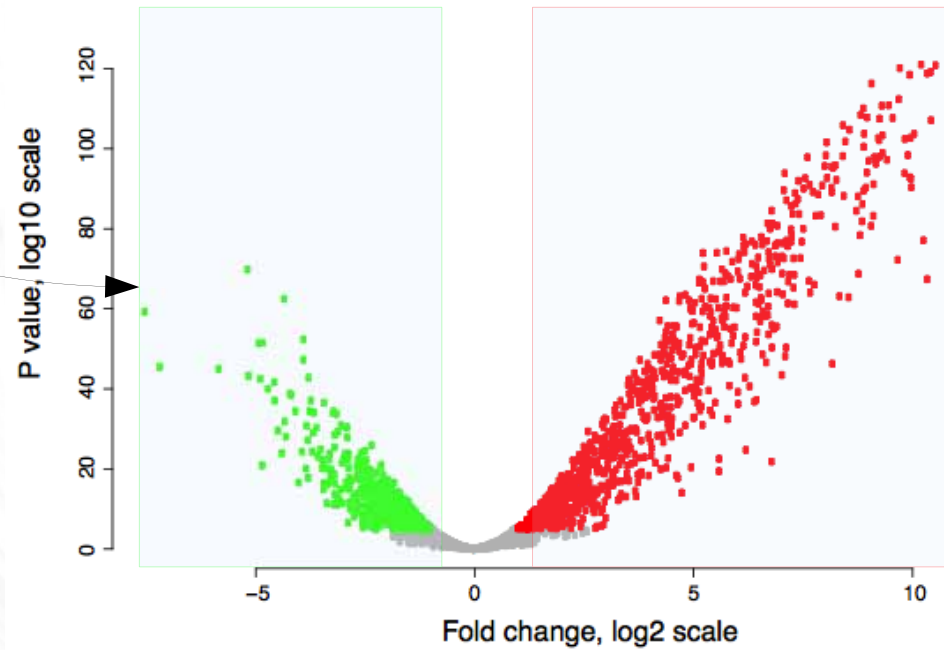
in  
multiple ways

*Potential selection* operating at the level of *target specificity*

*Epistatic control* by multiple homologous regulators

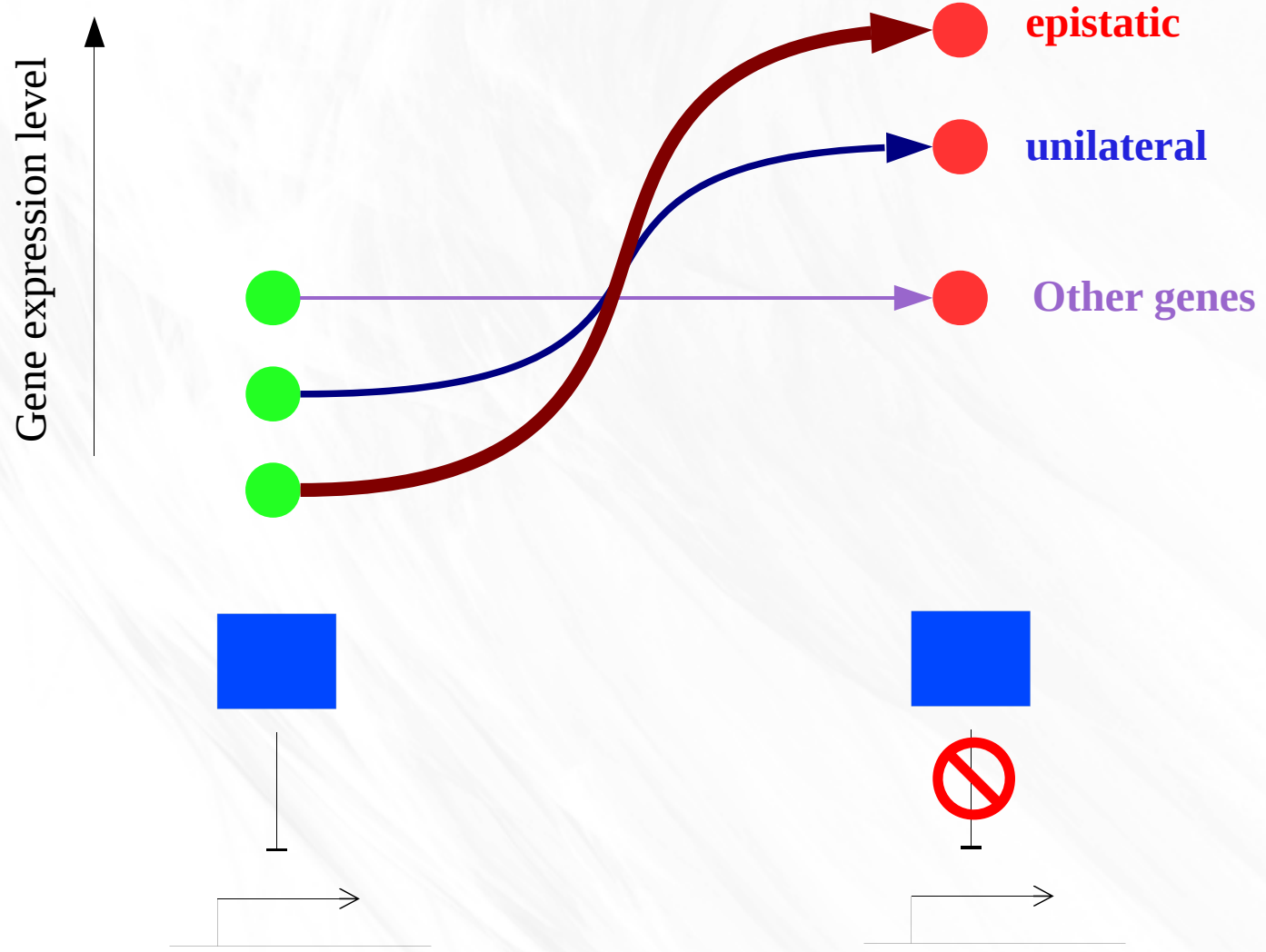
# It gets worse!

Indirect down-regulation  
of non-targets

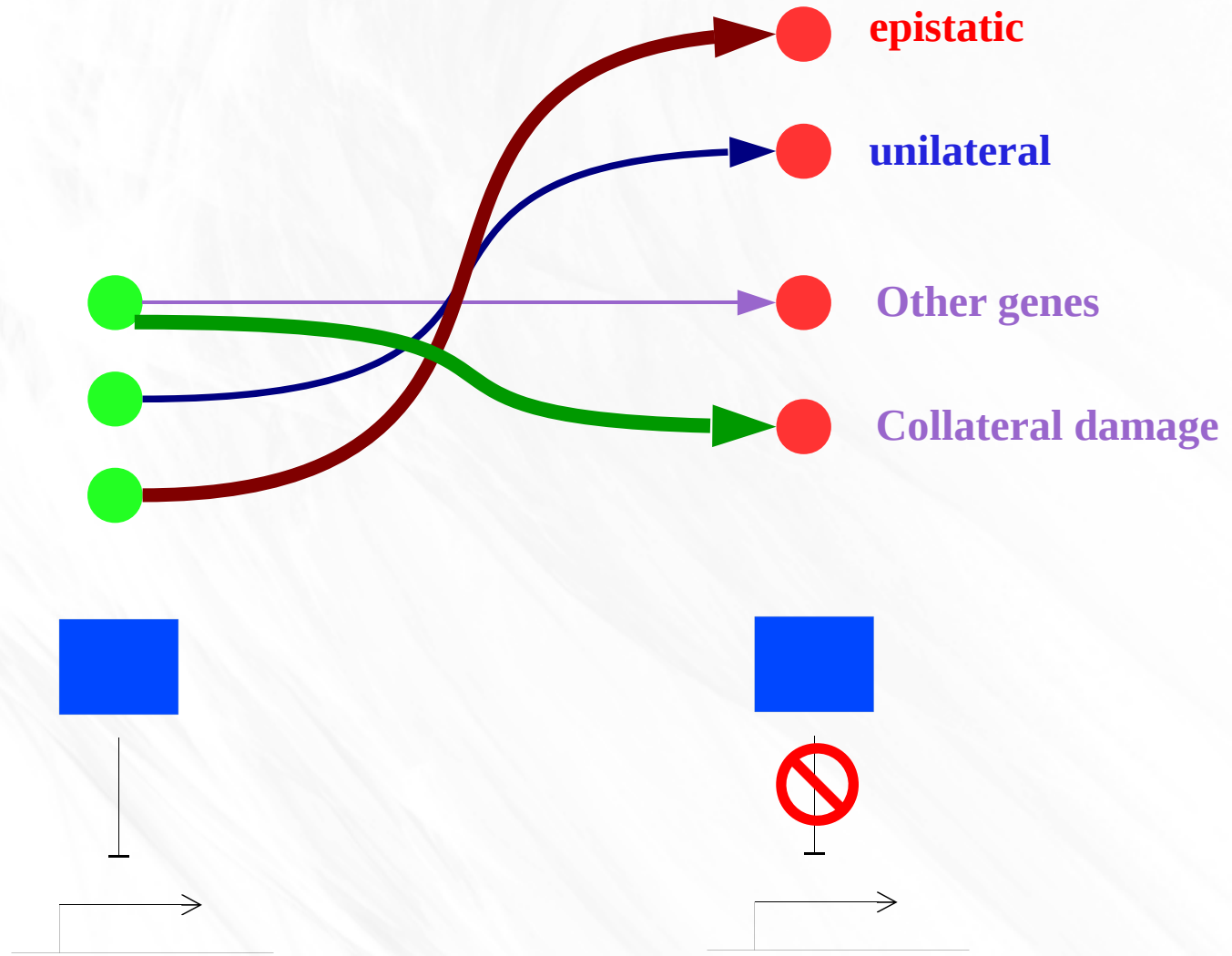


Direct up-regulation  
of targets

***Loss of gene silencing*** of horizontally-acquired genes  
results in an  
***indirect down-regulation*** of other genes

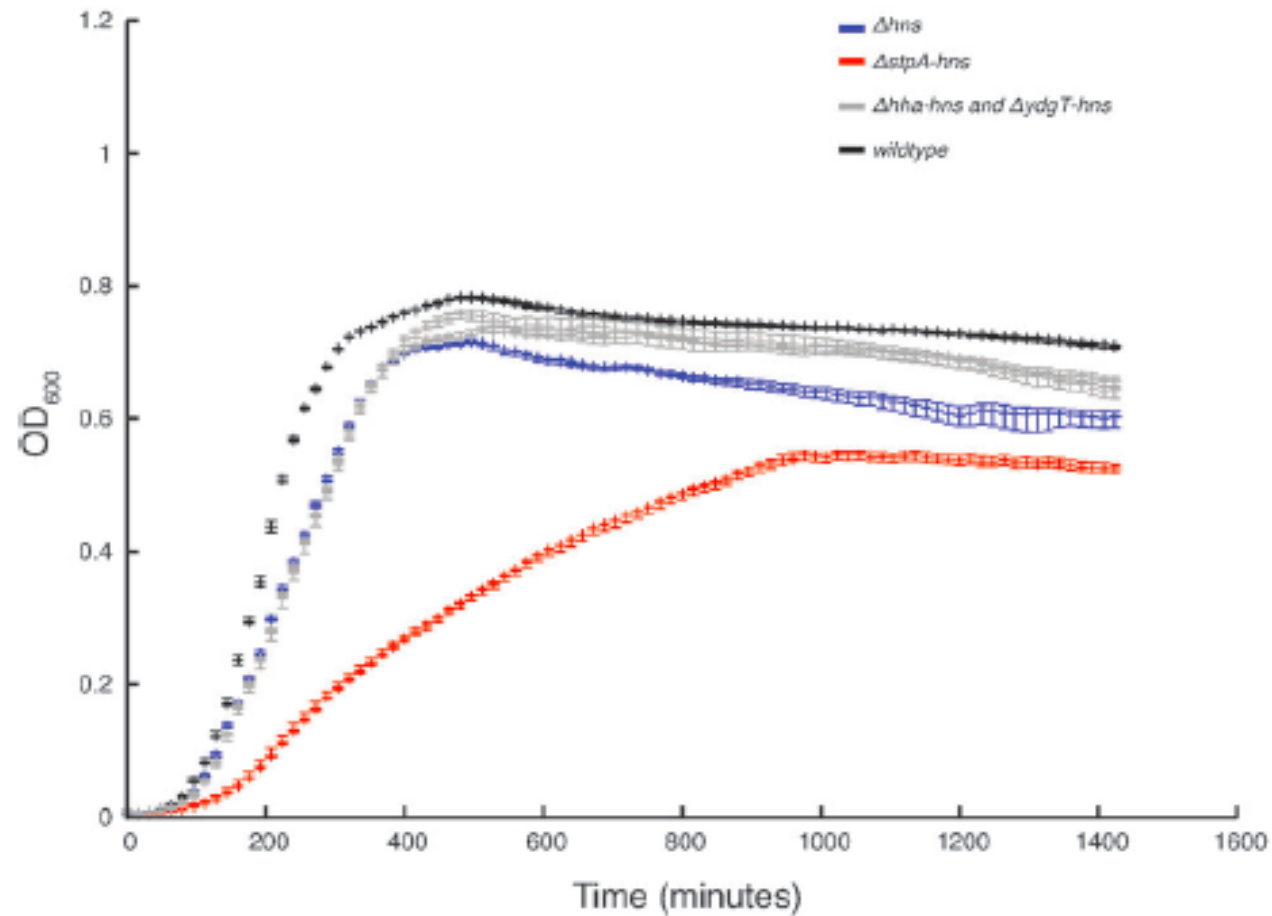


Gene expression level ↑





ok.. is there a phenotype?



***Yes, hns-stpA is sick***

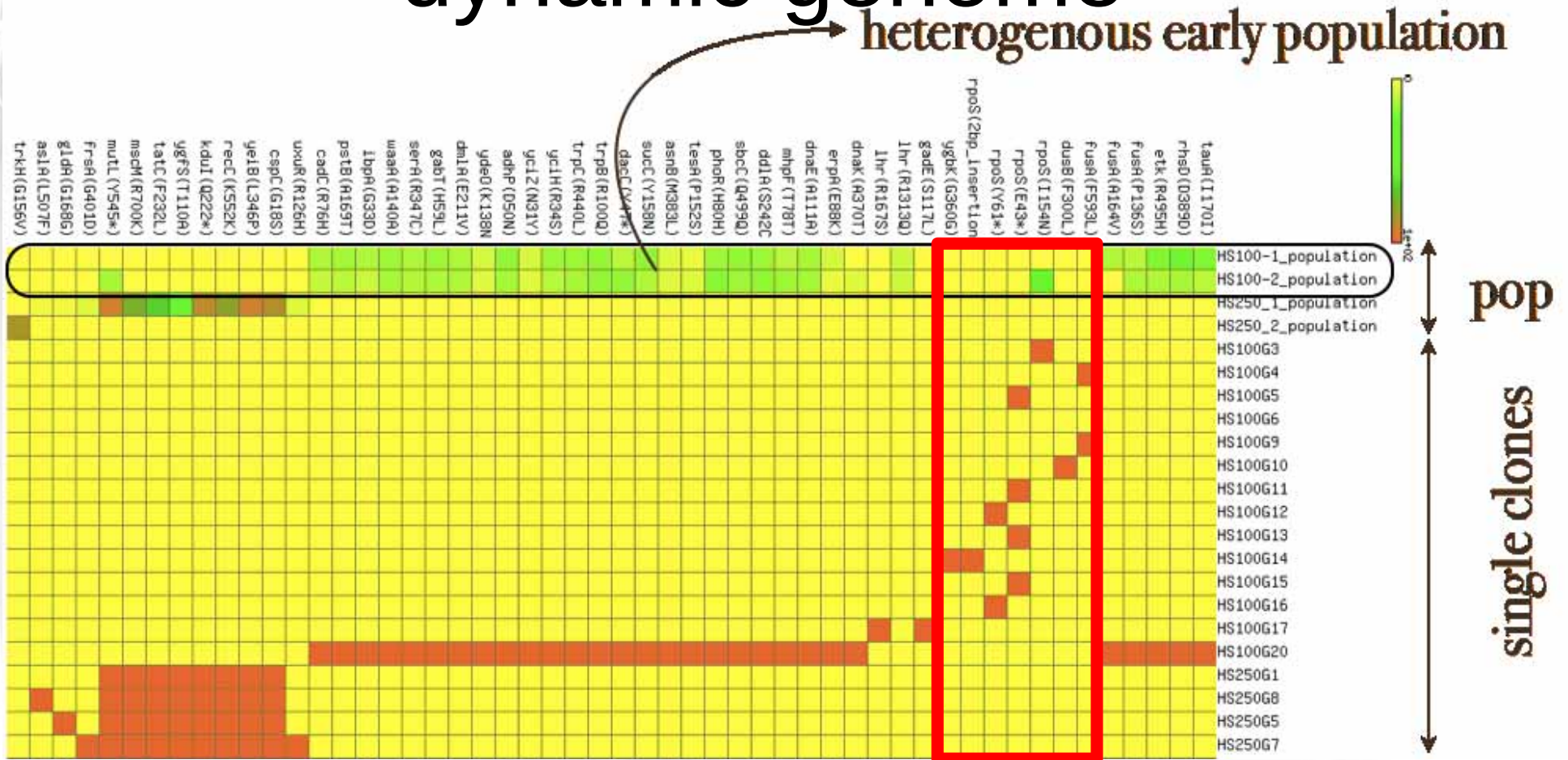
Can the regulatory network of

*E. coli*

***lacking the xenogene silencing*** system

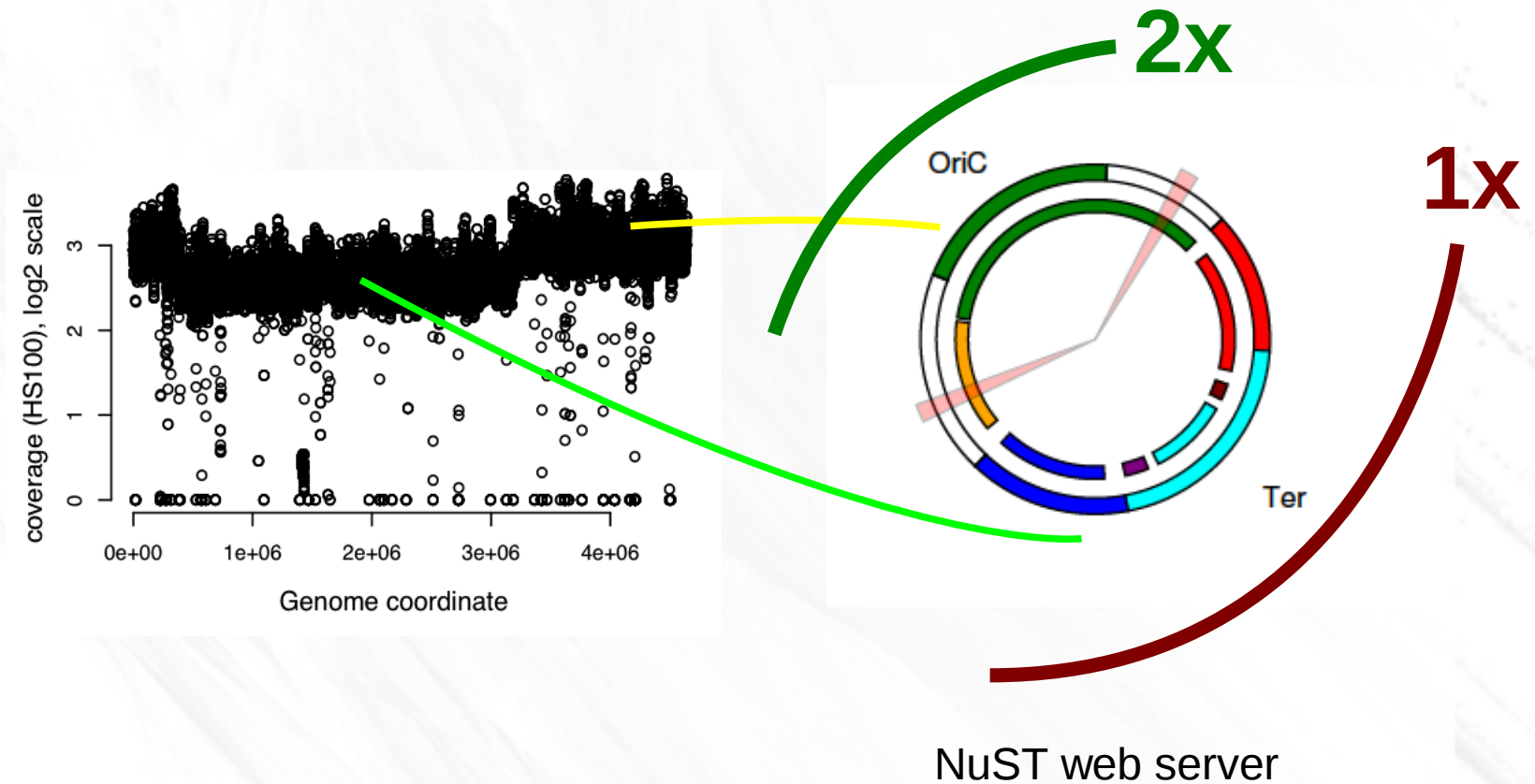
***evolve*** towards greater fitness?

# Many mutations emerge in a dynamic genome



Inactivation of the global regulatory network of RpoS

# A large segmental duplication increases growth rates

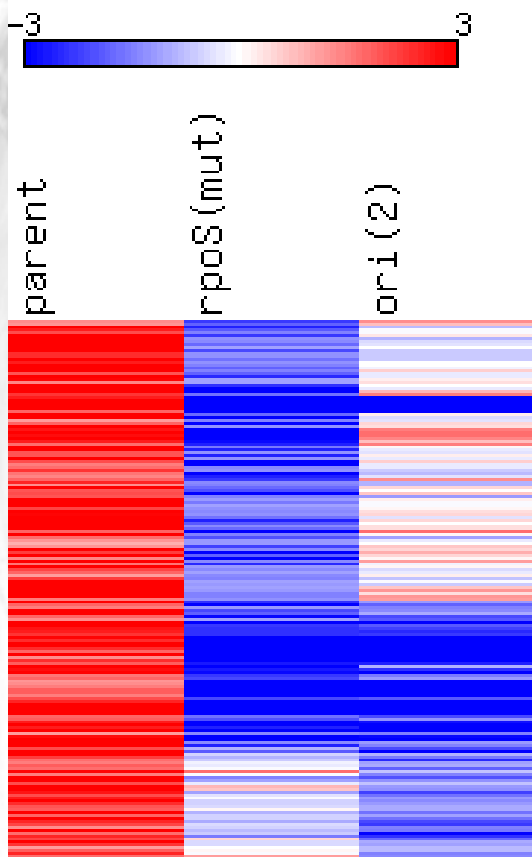


## **RpoS inactivation**

**What are the consequences of these mutations to gene expression?**

**Large segmental duplication  
around Ori**

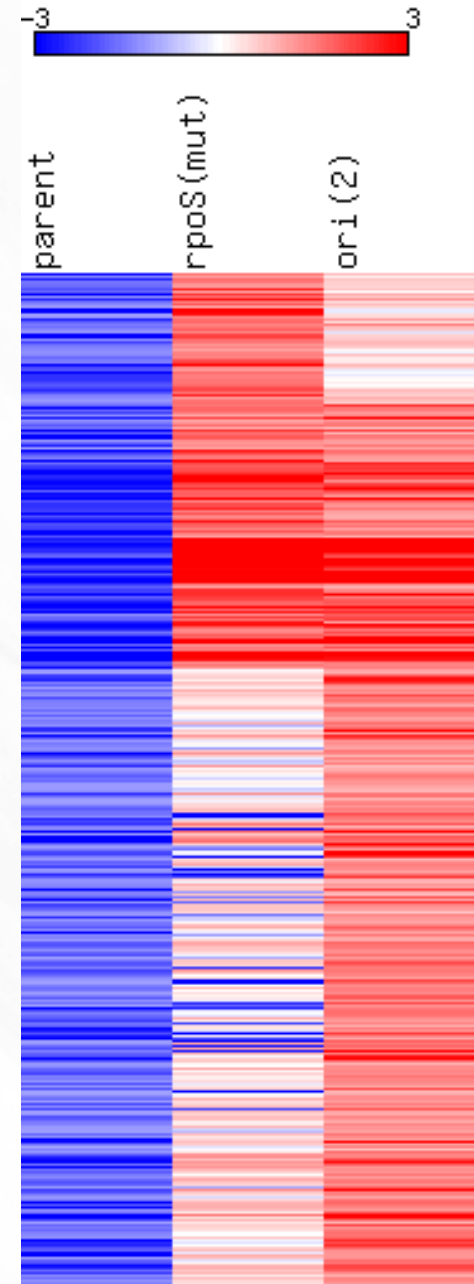




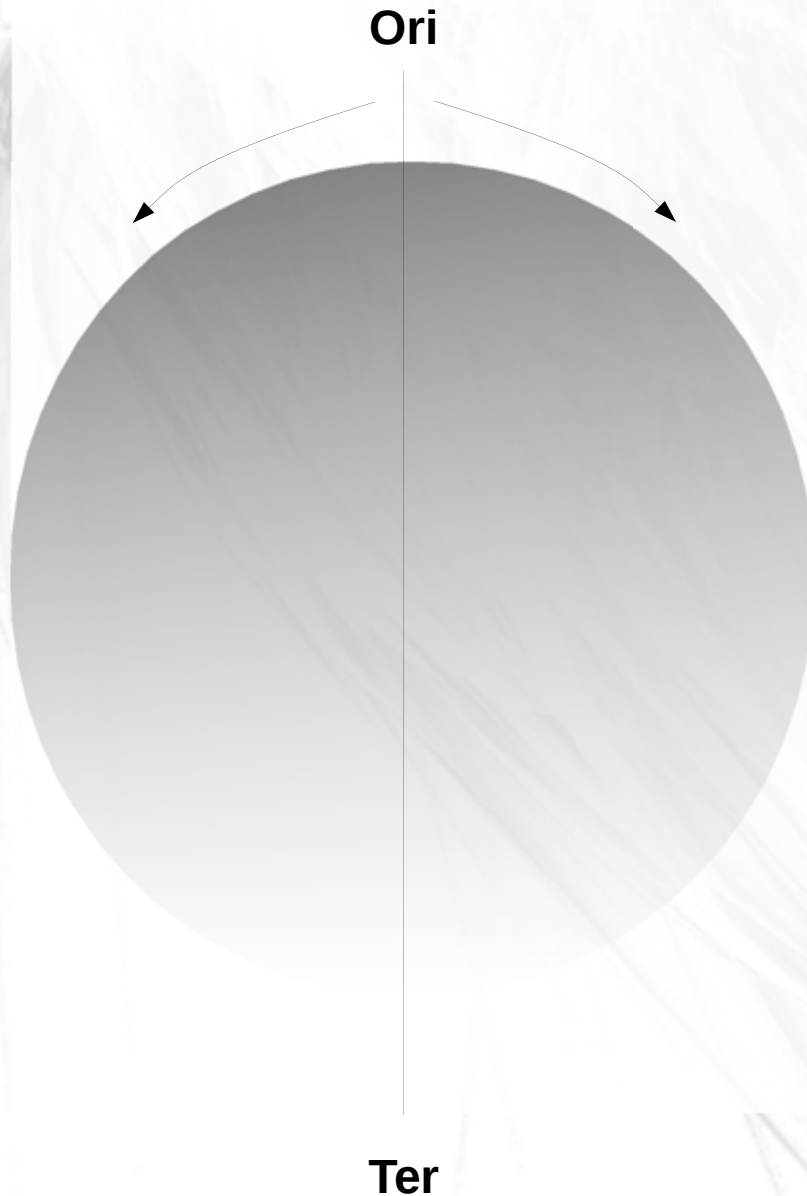
Inactivation of RpoS  
and  
segmental duplication of 40%  
of genome

**converge**

in **reversing disruption** of  
gene expression homeostasis



# A simple-minded view of bacterial chromosome architecture



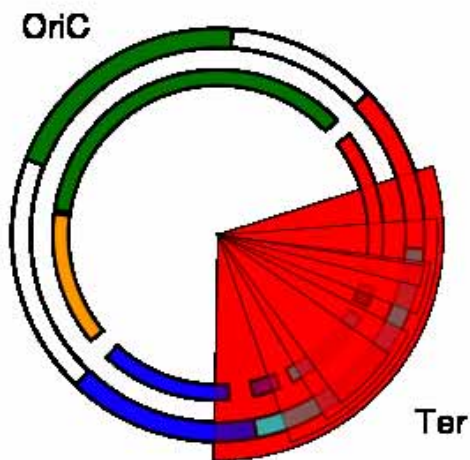
**Gradients down the axis:**

*Gene dosage and hence gene expression*

*Gene essentiality*

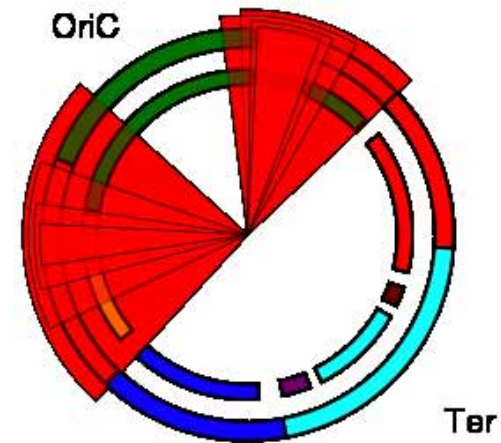
*Base composition*

# Polarity in gene organisation



Kahramanoglou et al. 2010.

H-NS targets enriched around the **terminus of replication**



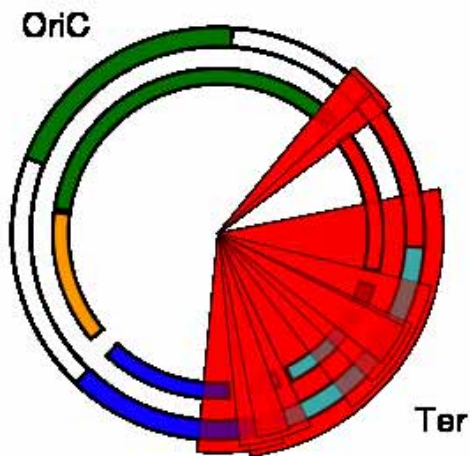
Keio knockout collection

Essential genes enriched around the **origin of replication**

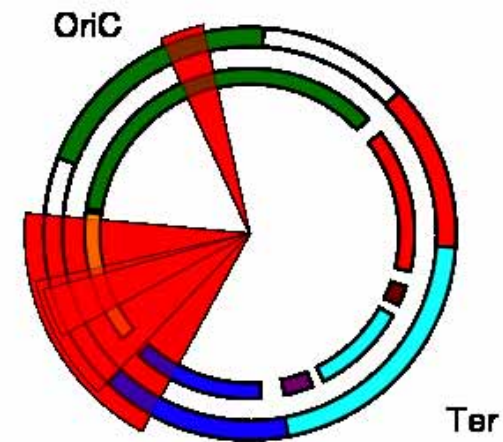
NuST server: <http://www.lgm.upmc.fr/nust>



# Polarity in gene organisation



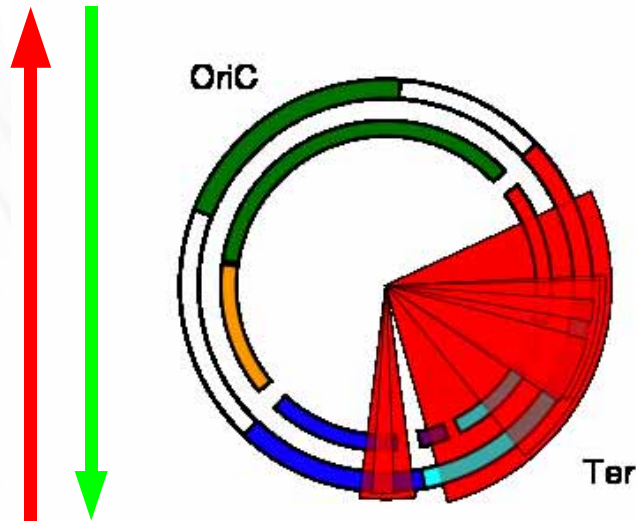
**Direct de-silencing** of  
gene expression around  
**terminus of replication**



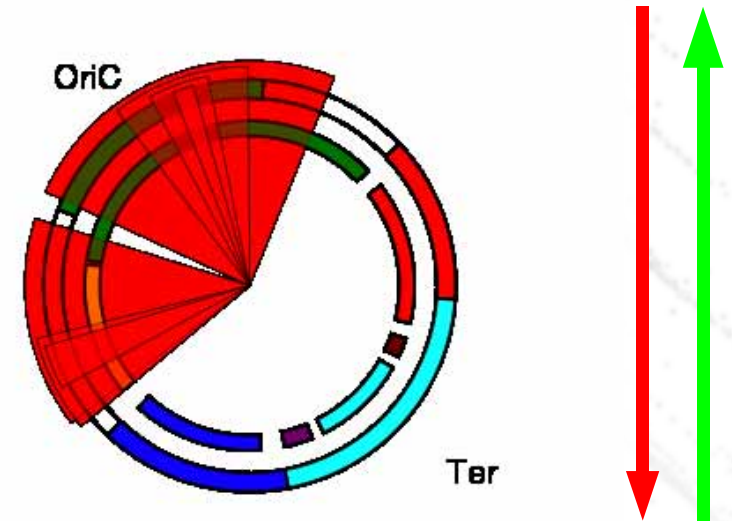
Indirect knock-on effect closer to  
**origin of replication**

# Segmental Duplication

## Reversal of the expression imbalance

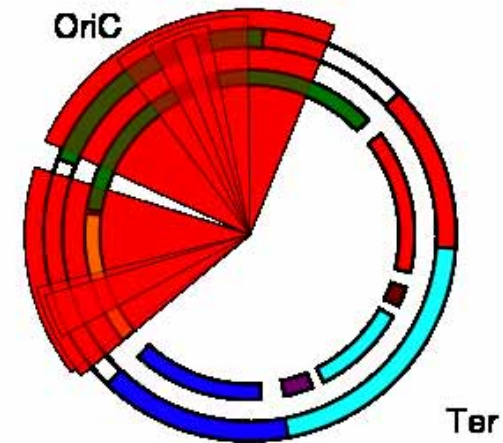
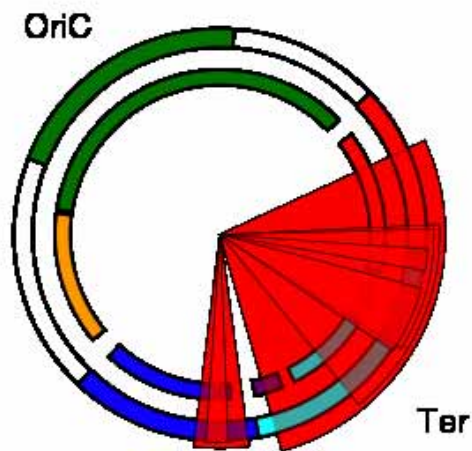


**Reversal of de-silencing  
around  
terminus**

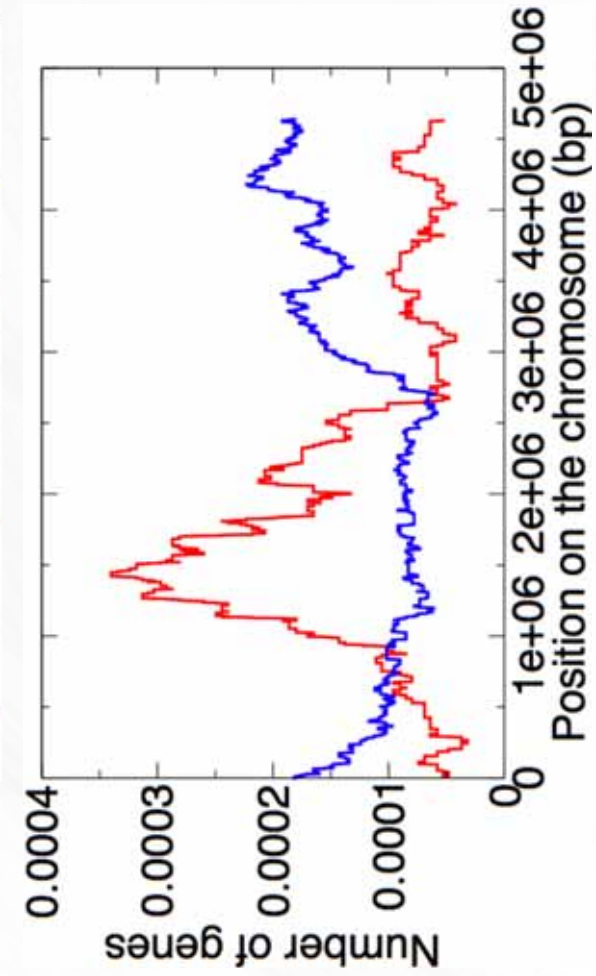
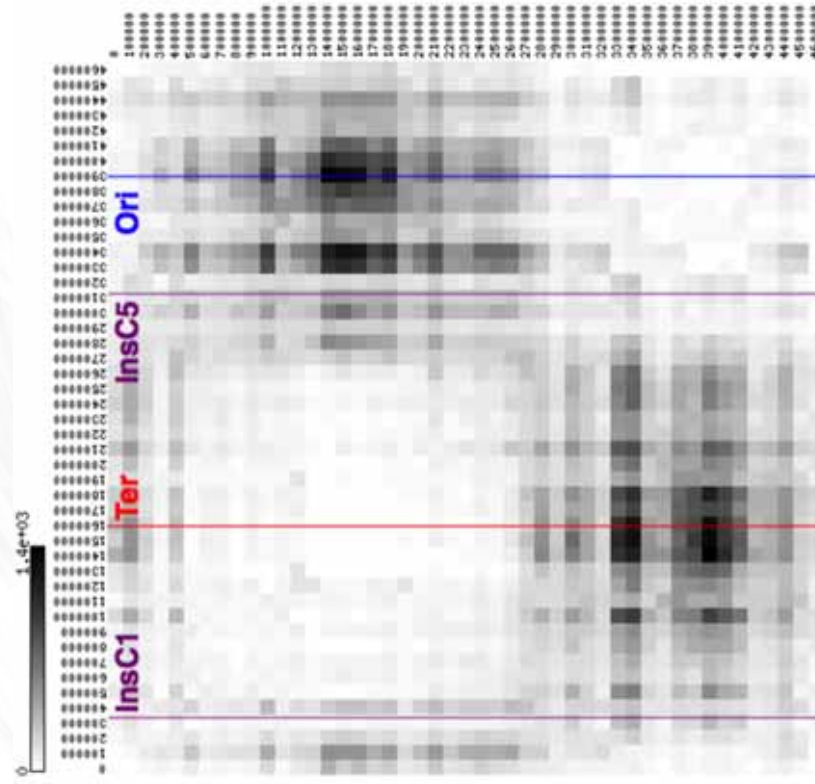


**Reversal of knock-on  
closer to  
origin**

# Taken together...



**Antagonistic gene expression** profiles  
**across the two halves** of the chromosome



**Two chromosomal domains of gene expression selected in evolution**

**In convergence with an accessible genomic variation**

There exists a  
**pattern to the organisation  
of horizontally-acquired genes**  
on the chromosome.



Loss of gene silencing of  
**horizontally-acquired genes**  
results in a  
**large-scale disruption**  
of **gene expression homeostasis.**



**Convergence**  
*of gene regulatory networks*  
**and chromosome architecture**

**Rajalakshmi Srinivasan**

**Vittore Scolari**

**Marco Cosentino  
Lagomarsino**

Aalap Mogre, Avantika  
Lal, Farhan Ali, Mohak  
Sharda, Parul Singh,  
Reshma TV, Revathy  
Krishamurthi, Savita Chib,  
Supriya Khedkar,  
Terrence Christie

**Credits!**

**Centre for Cellular and  
Molecular Platforms**

**Department of Science and Technology,  
Govt**

**NCBS Core Funding**

**CEFIPRA**