Genotoul Biostat Bioinfo day
Toulouse, Dec 13, 2018

GeneNeighborhood

an R package to explore the direct neighbors of your favorite gene set

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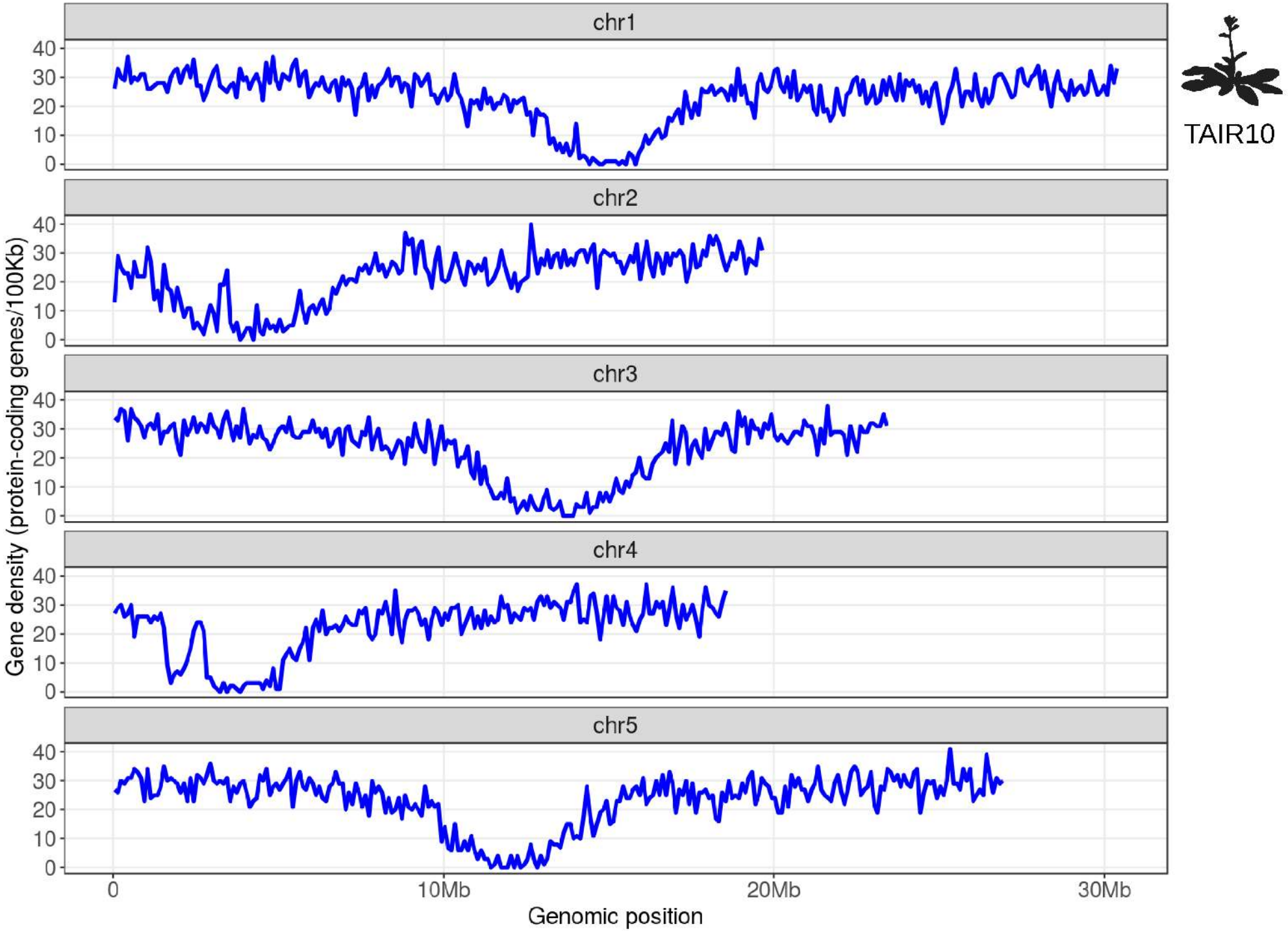
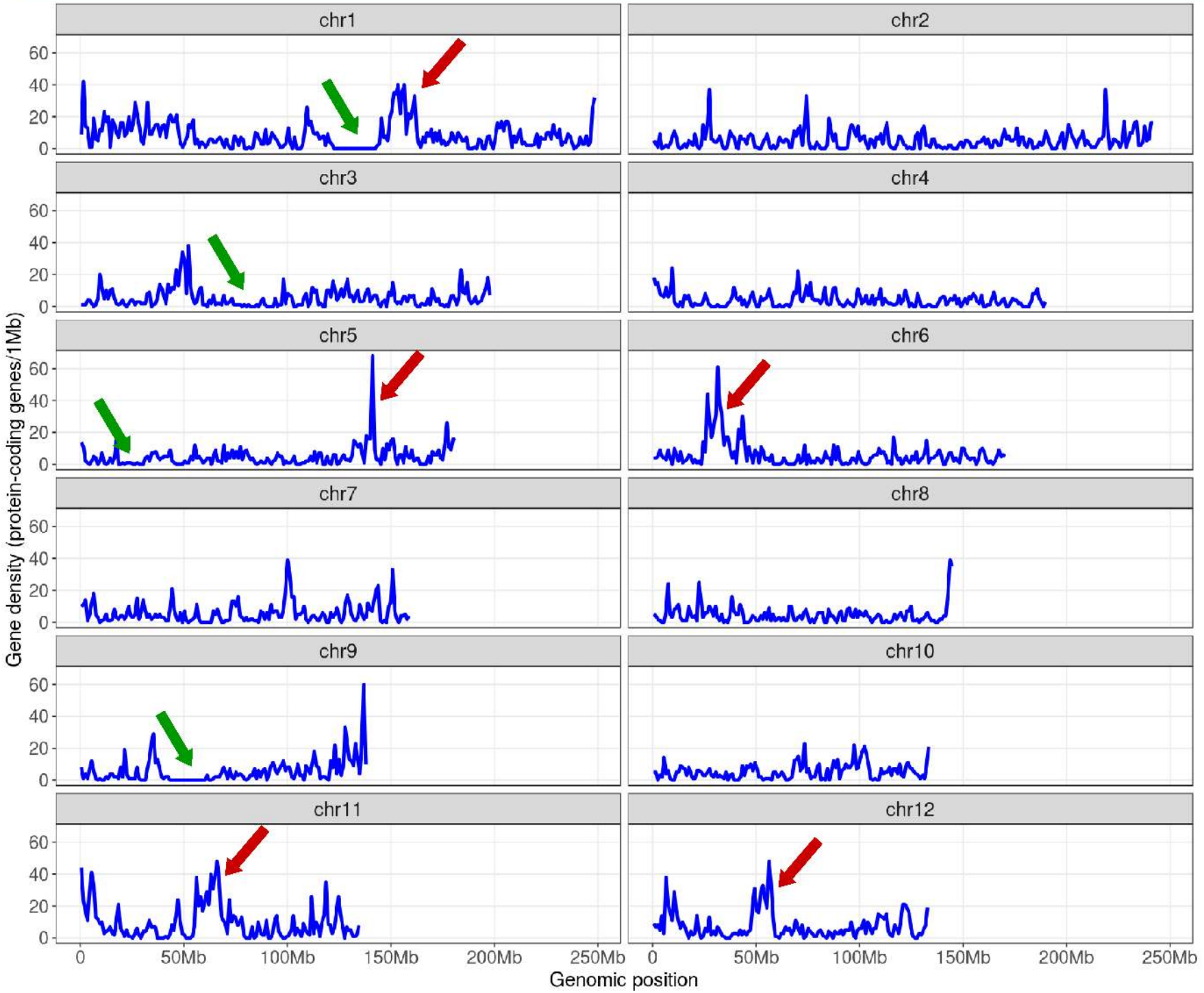
Genes are not randomly distributed in genomes

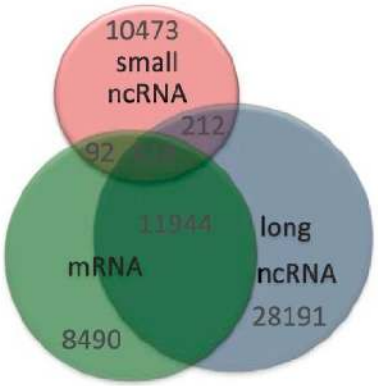


Genes are not randomly distributed in genomes

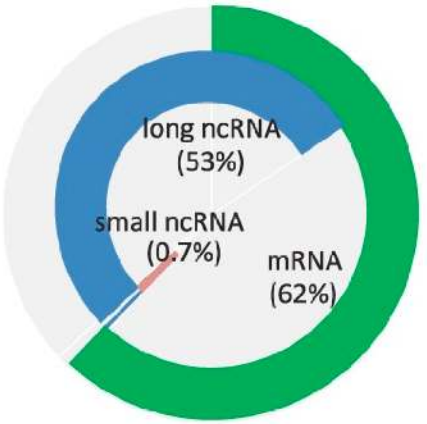
Gencode v28



A large fraction of the genome is transcribed

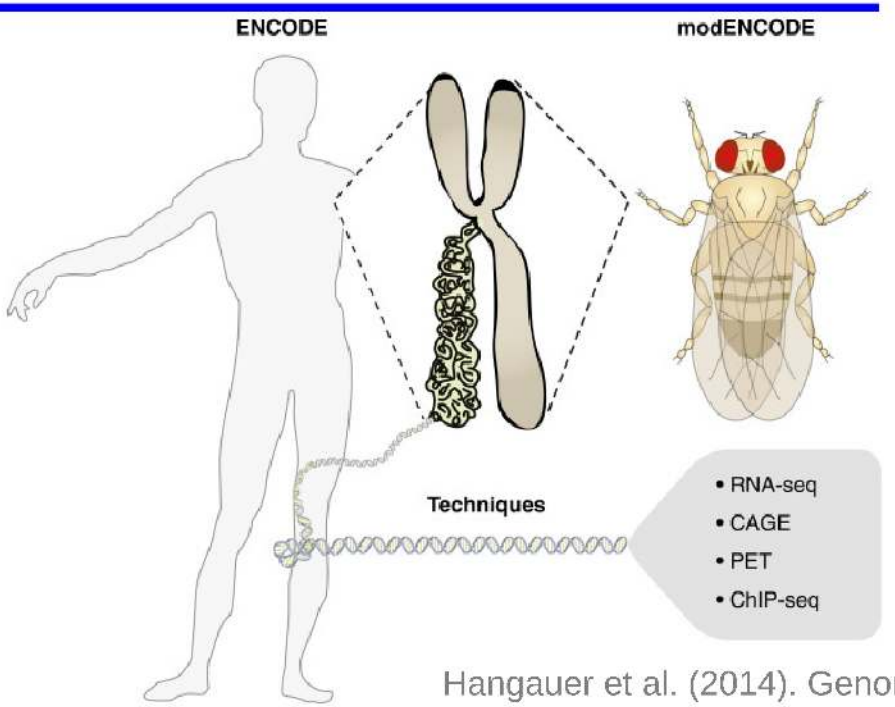


Number of loci



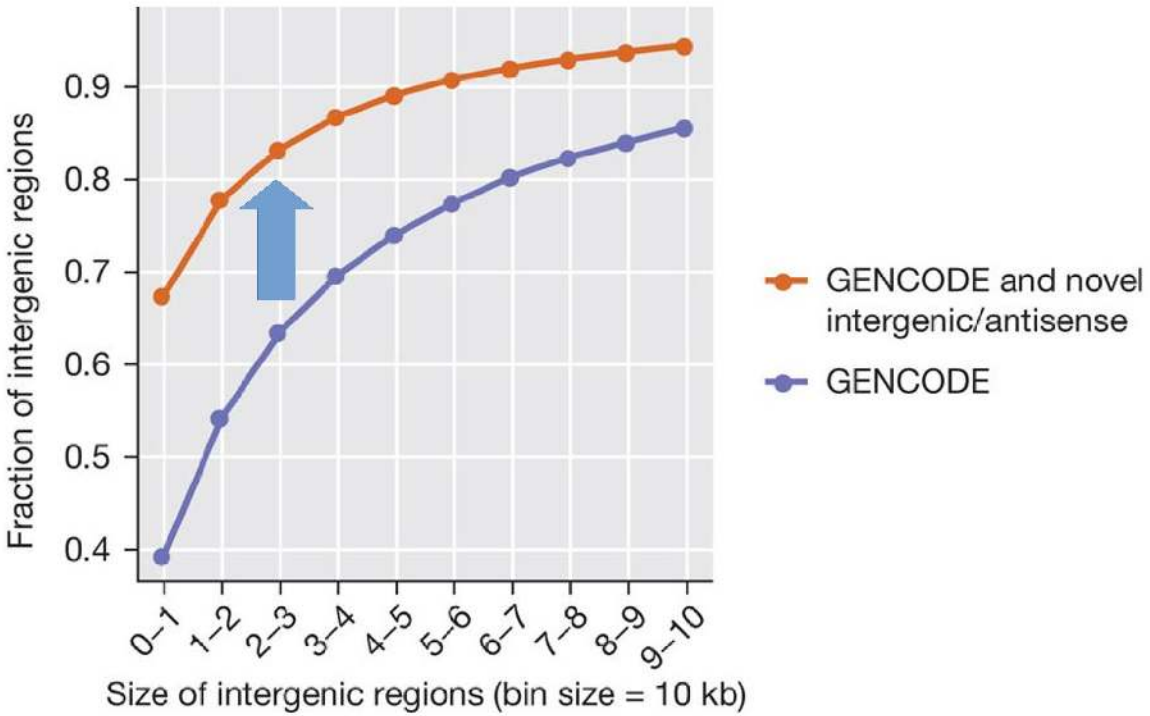
bp coverage of
the transcriptome

Pertea M. (2012). The human transcriptome. Genes.



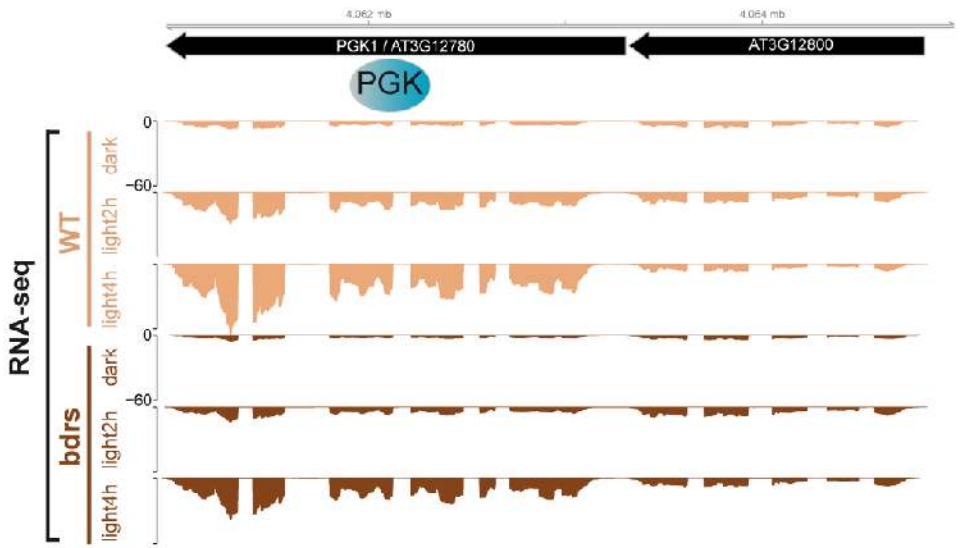
Hangauer et al. (2014). Genome Biol.

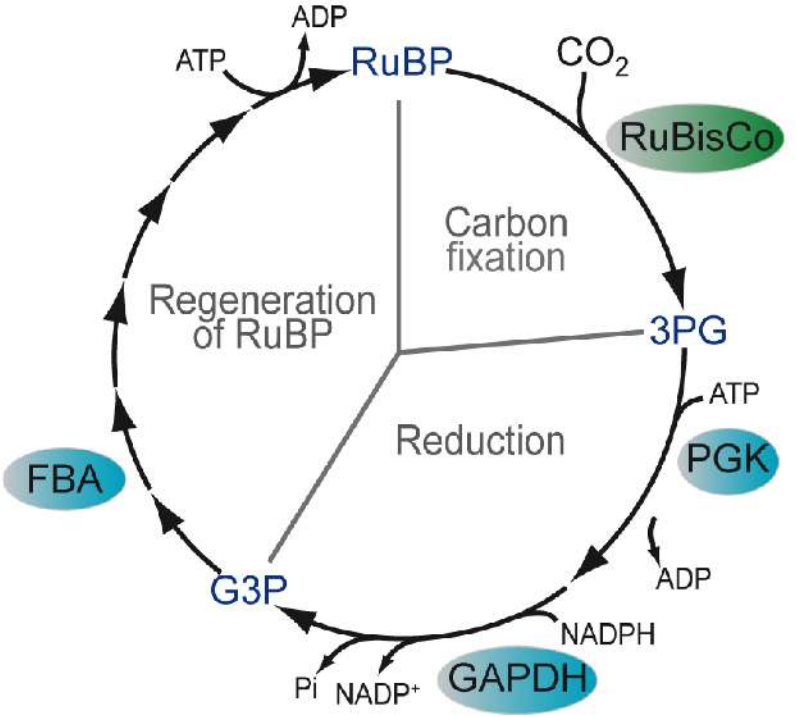
- ✔ enhancers
- ✔ promoters
- ✔ repetitive elements
- ✔ . . .

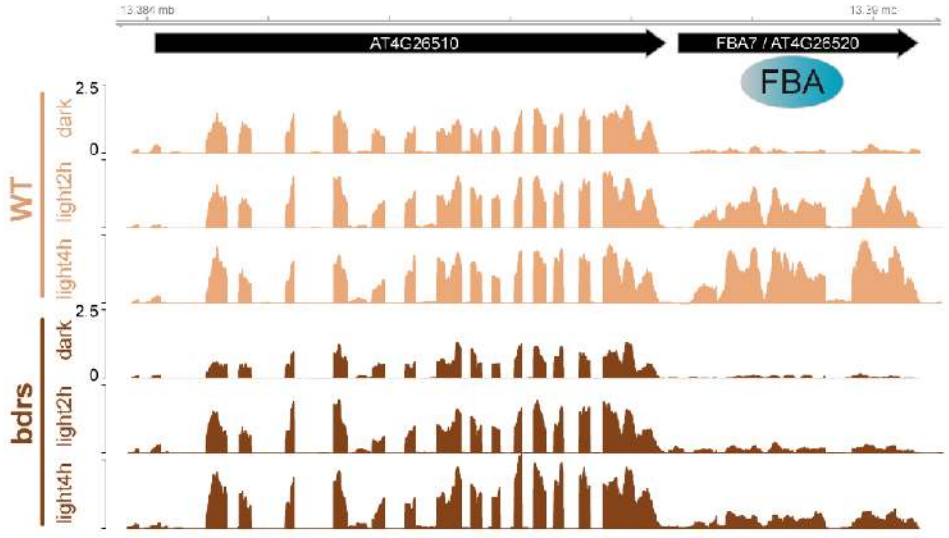


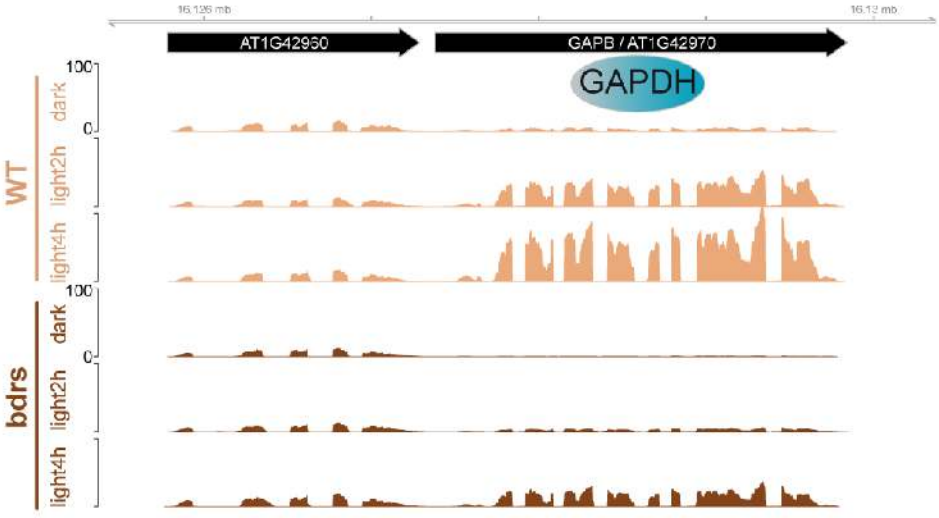
Djebali S et al. (2012) Landscape of transcription in human cells. Nature

with some functional consequences...



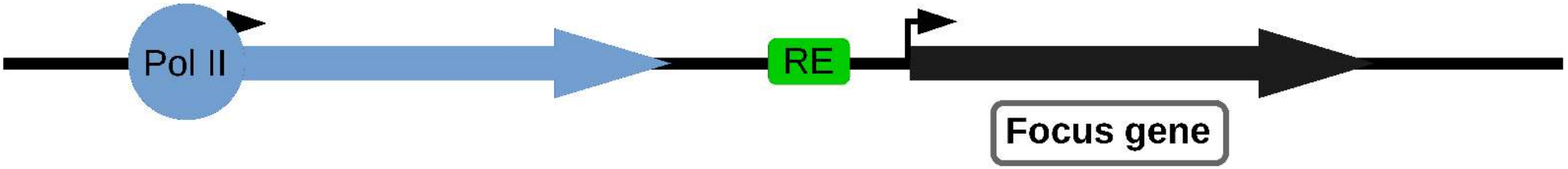






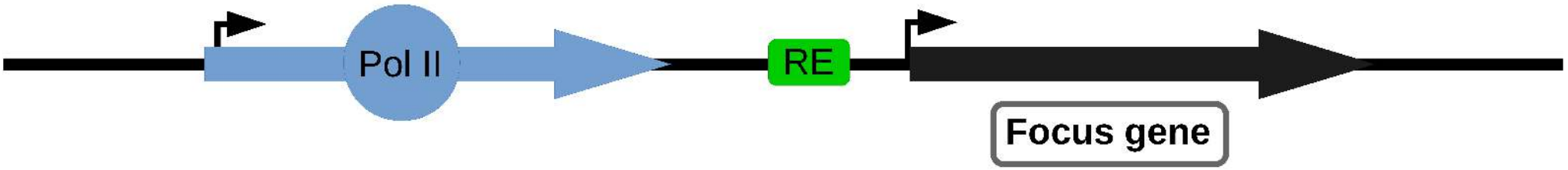
Transcriptional interferences

Shearwin et al., Trends Genet 2005



Transcriptional interferences

Shearwin et al., Trends Genet 2005



Transcriptional interferences

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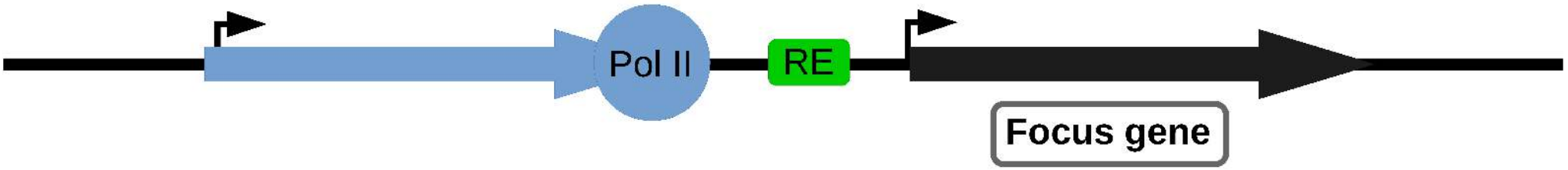

Transcriptional interferences

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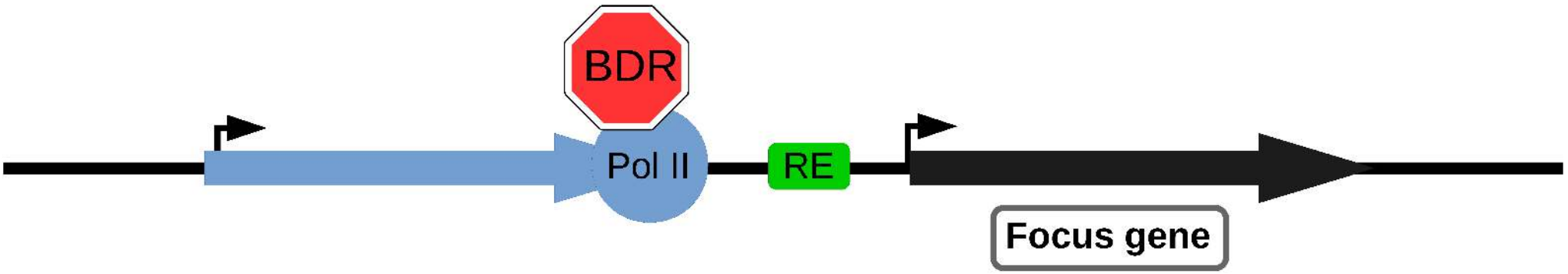
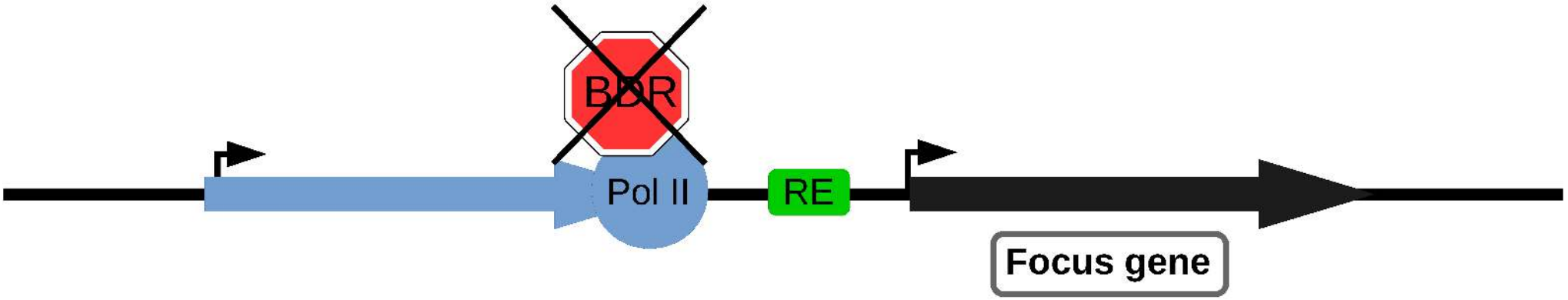


Transcriptional interferences

Shearwin et al., Trends Genet 2005



Transcriptional interferences

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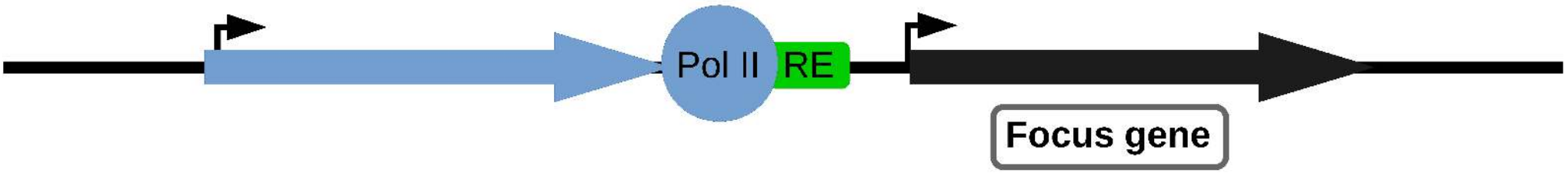

Transcriptional interferences

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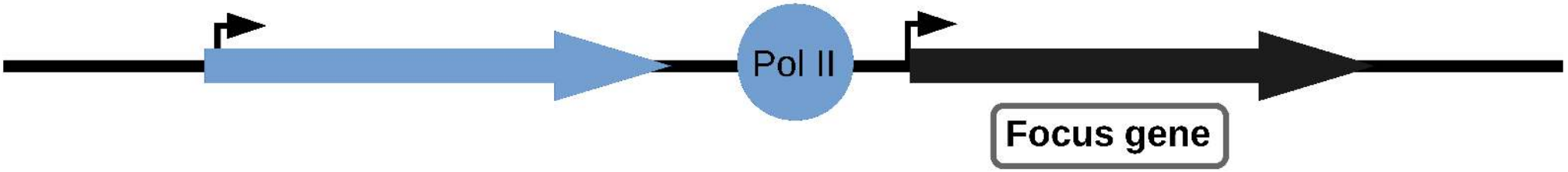
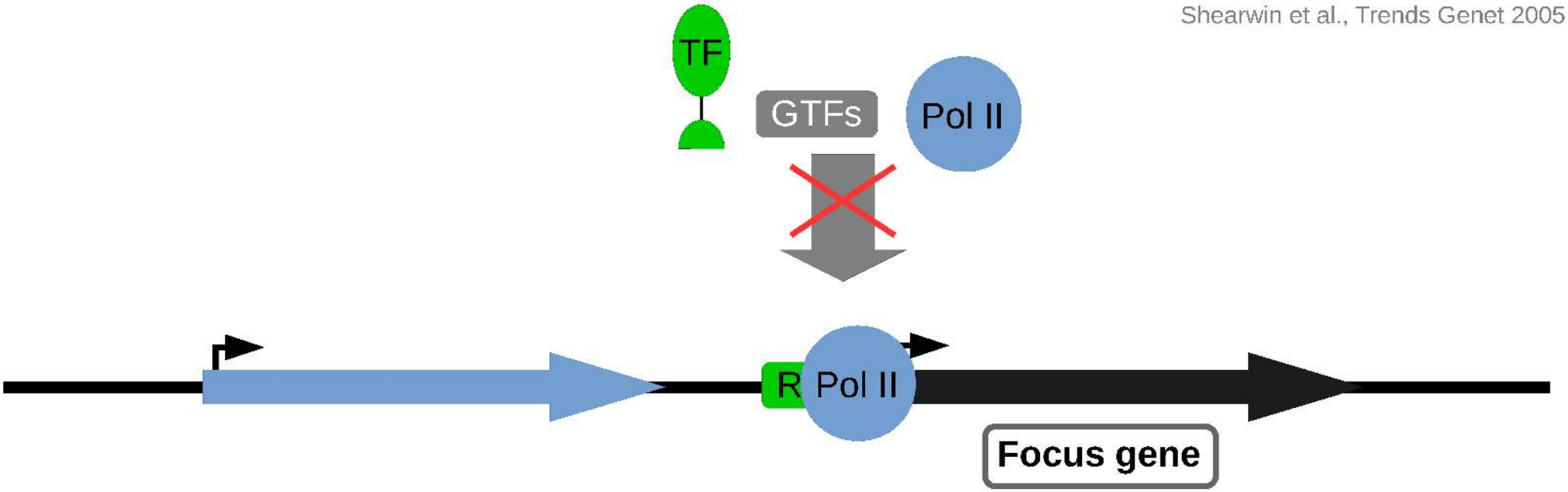


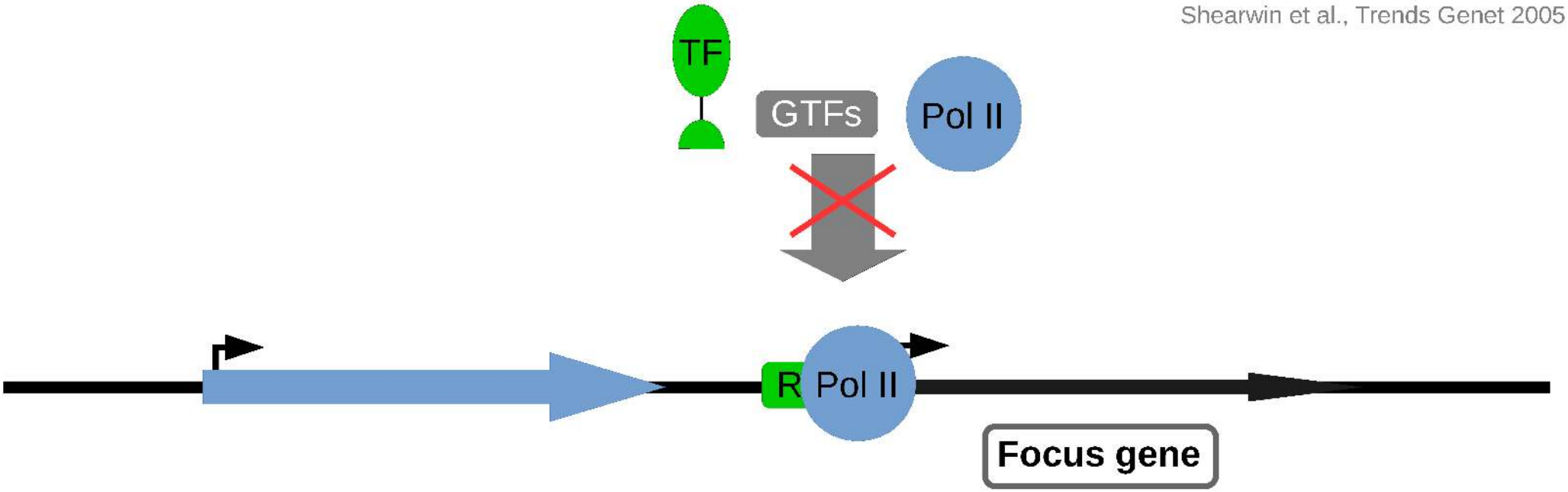
Transcriptional interferences

Shearwin et al., Trends Genet 2005

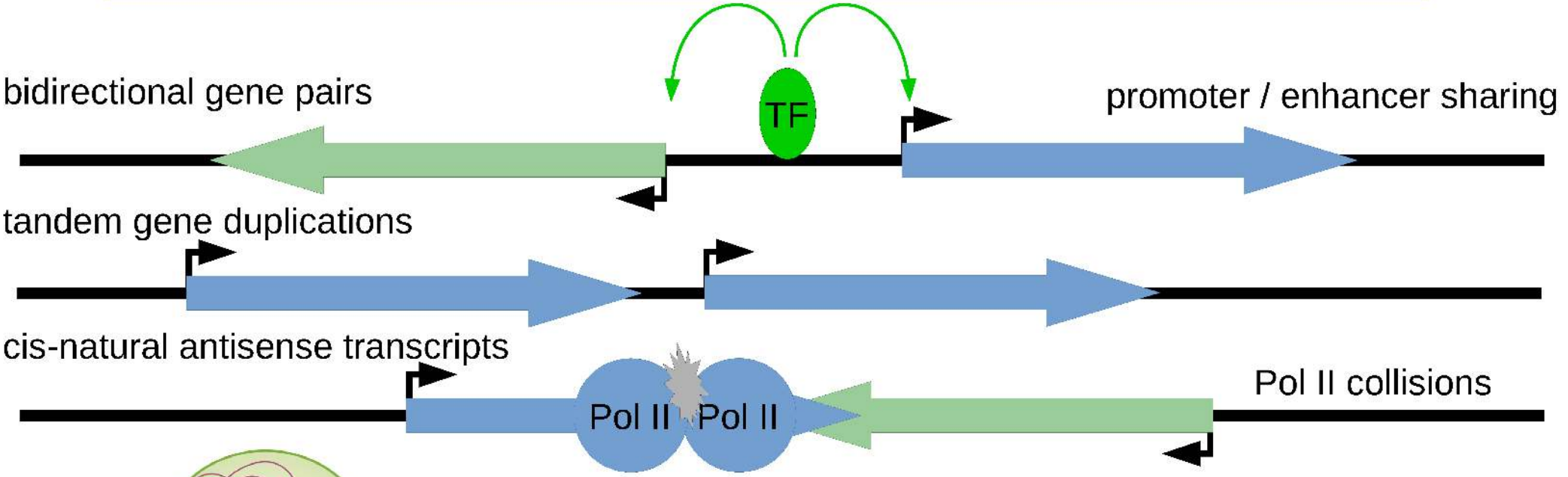


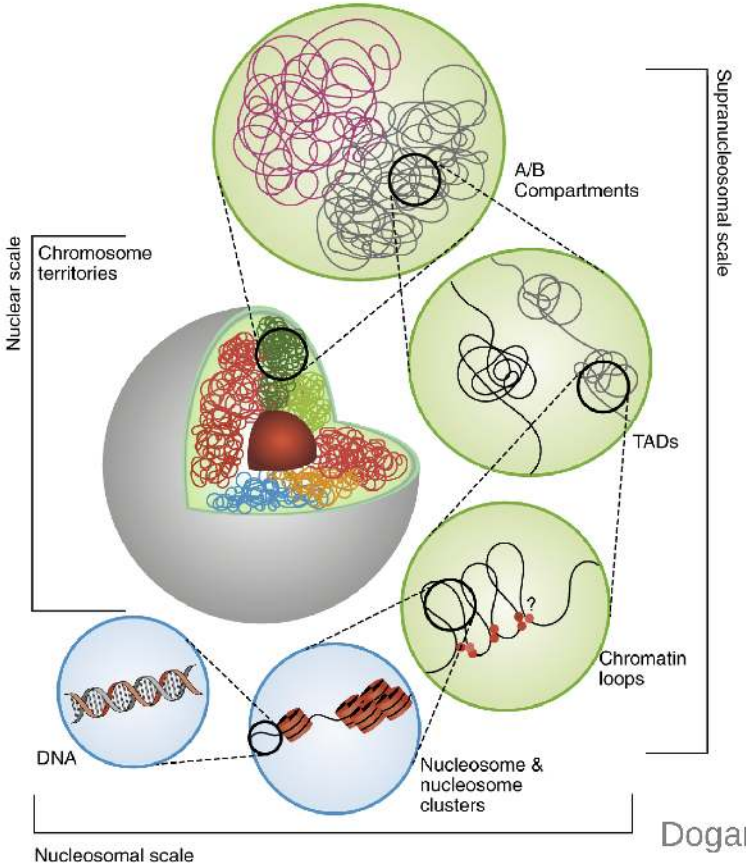
Transcriptional interferences

Shearwin et al., Trends Genet 2005



Other mechanisms associated with co-expression or interference





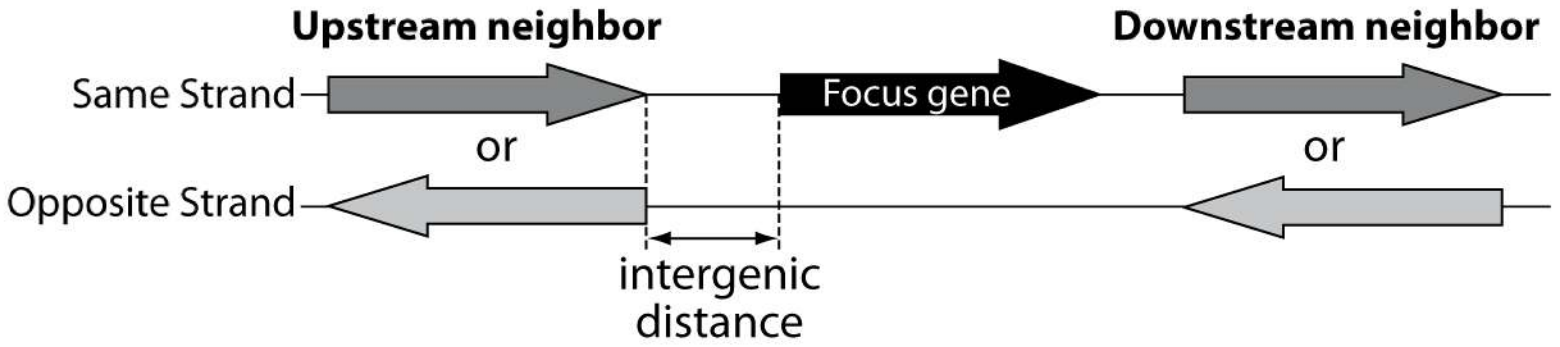
Dogan & Liu (2018) Nat Plants

Massively Parallel Reporter Assays

Akhtar et al. (2013) Cell

- enhancers / transcriptional activity
- chromatin state
- 3D position effects

Studying gene neighbors



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Gene sets:

- Differentially expressed
- Bound by a specific protein
- Present in a specific chromatin context
- Involved in a specific function
- . . .

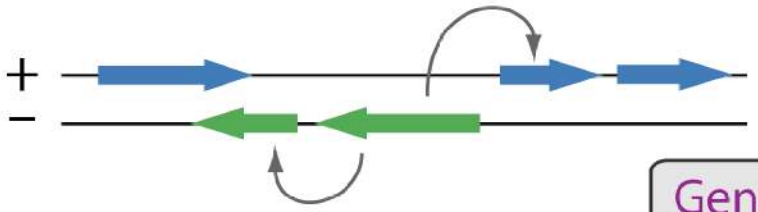
Specific neighborhood ?

- Orientation (incl. overlap) ?
- Specific proximity / distance ?

subgroups
Function / expression... of the neighbors ?

Generate hypothesis on how neighborhing genes interact

Package overview



Gene annotations

`getGeneNeighborhood()`

Gene neighbors annotations

Gene set(s)

DE analysis
TF binding
⋮

Neighbors orientation ?

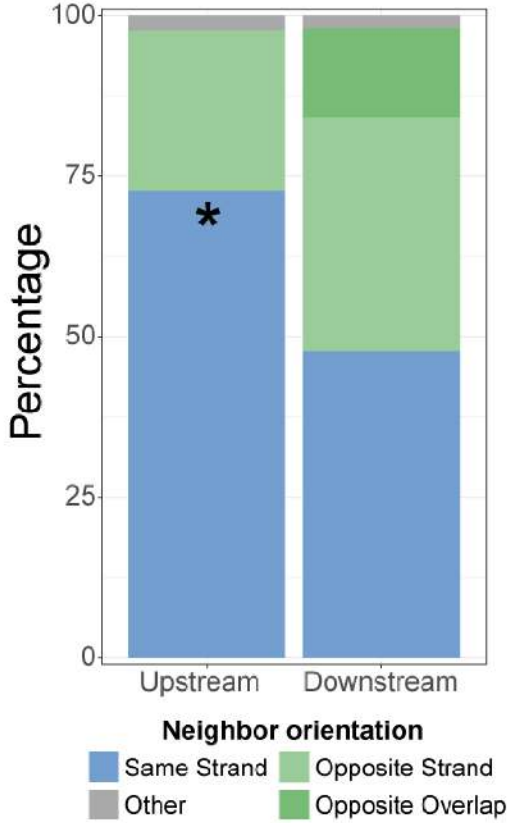
`analyzeNeighborsOrientation()`
`plotNeighborsOrientation()`

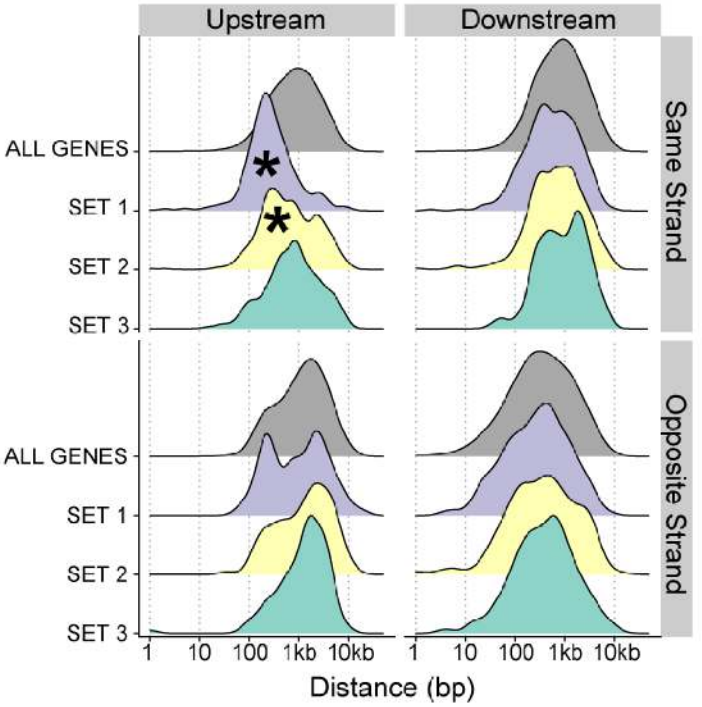
Neighbors distance ?

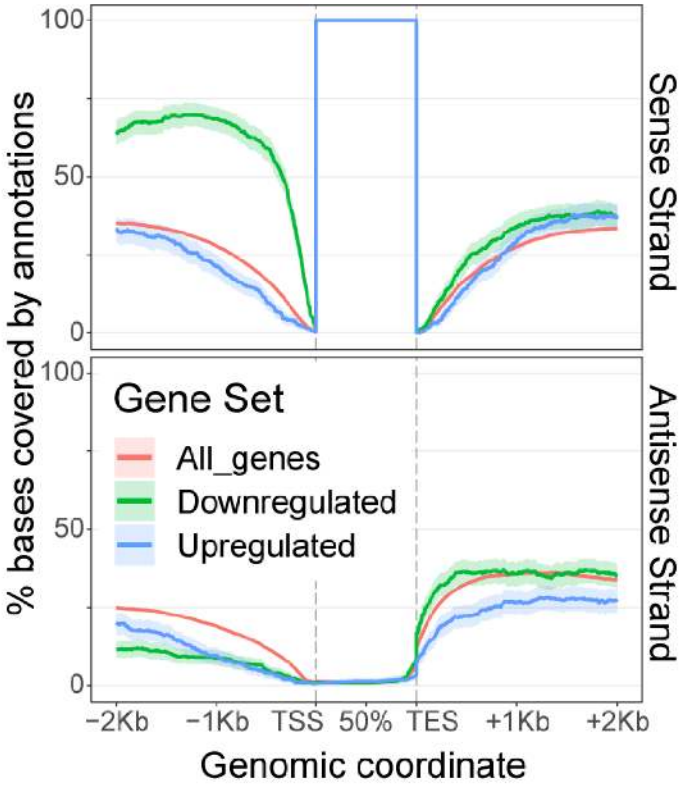
`analyzeNeighborsDistance()`
`plotDistanceDistrib()`

Metagene profiles

`annotationCoverageAroundFeatures()`
`getAvgProfileWithCI()`
`plotMetageneAnnotProfile()`







Defining Neighborhoods

Gene Neighborhood

Genes not overlapping with other genes:

UpstreamClass	Upstream	Focus gene	Downstream	DownstreamClass	Neighborclass
SameStrand	S		S	SameStrand	SS
SameStrand	S		O	OppositeStrand	SO
OppositeStrand	O		S	SameStrand	OS
OppositeStrand	O		O	OppositeStrand	OO

Genes overlapping with a single gene:

UPPER CASE: overlapping gene is on the same strand
lower case: overlapping gene is on the oppositre strand

UpstreamClass	Upstream	Focus gene	Downstream	DownstreamClass	Neighborclass	
SameOverlap	U		S or O	SameStrand or OppositeStrand	US / UO	U: upstream
OppositeOverlap	u		S or O	SameStrand or OppositeStrand	uS / uO	
SameStrand or OppositeStrand	S or O		D	SameOverlap	SD / OD	D: downstream
SameStrand or OppositeStrand	S or O		d	OppositeOverlap	Sd / Od	
SameStrand or OppositeStrand	S or O	I	S or O	SameStrand or OppositeStrand	I	I: identical (same start + same end)
SameStrand or OppositeStrand	S or O	i	S or O	SameStrand or OppositeStrand	i	
SameStrand or OppositeStrand	S or O	H	S or O	SameStrand or OppositeStrand	H	H: host
SameStrand or OppositeStrand	S or O	h	S or O	SameStrand or OppositeStrand	h	
other		G		other	G	G: guest
other		g		other	g	

Genes overlapping with a >1 gene:

UpstreamClass	Upstream	Focus gene	Downstream	DownstreamClass	Neighborclass
other	or any other situation with multiple overlaps			other	c

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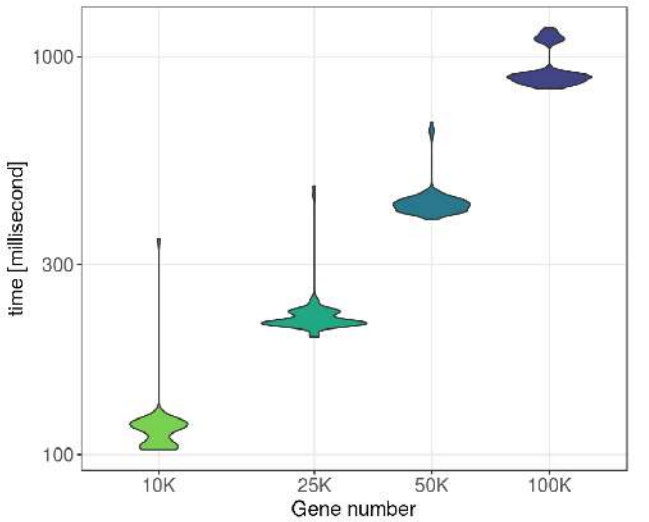
TxDb objects
ensembldb
GenomicFeatures package

Filter annotations
(expressed genes,
gene types, ...)

`getGeneNeighborhood()`

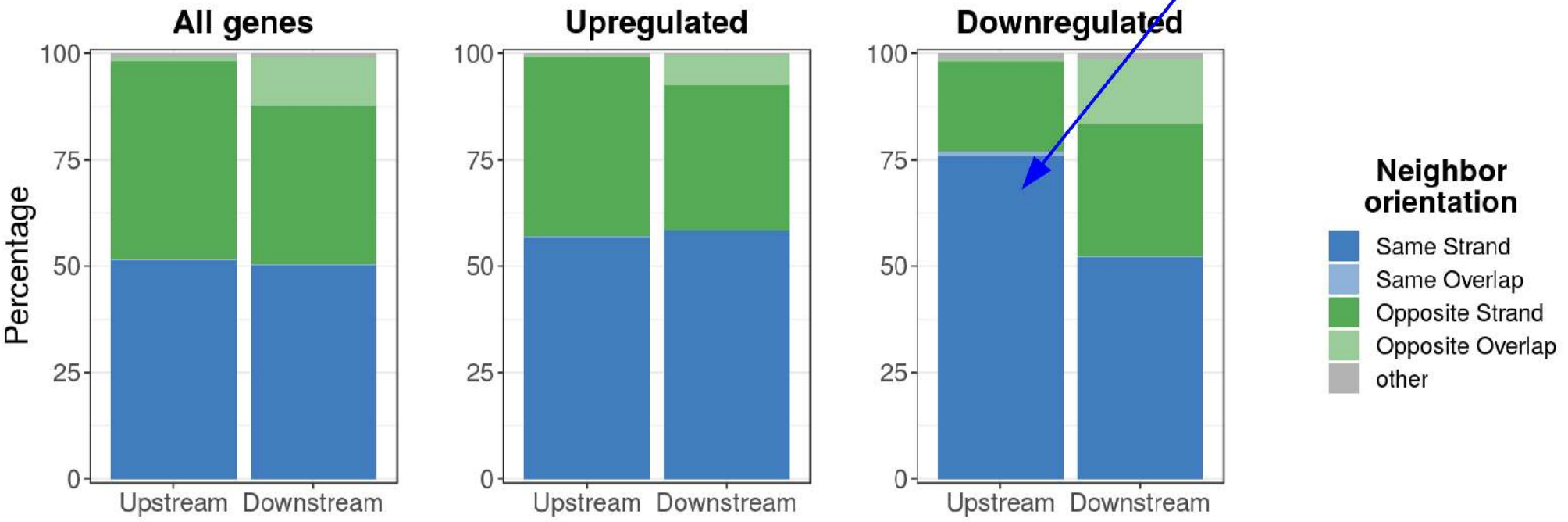


Analyzing neighbors orientations

`analyzeNeighborsOrientation()`

Side	Orientation	n	Percentage	n Universe	Percentage in Universe	p.value
Upstream	SameStrand	449	75.84	17068	51.23	**2,00E-35**
Upstream	SameOverlap	6	1.01	96	0.29	7,00E-03
Upstream	OppositeStrand	125	21.11	15267	45.82	1,00E+00
Upstream	OppositeOverlap	4	0.68	344	1.03	9,00E-01
Downstream	SameStrand	308	52.03	17099	51.32	4,00E-01
Downstream	SameOverlap	1	0.17	111	0.33	9,00E-01
Downstream	OppositeStrand	184	31.08	12708	38.14	1,00E+00
Downstream	OppositeOverlap	91	15.37	2857	8.57	**4,00E-08**

`plotNeighborsOrientation()`



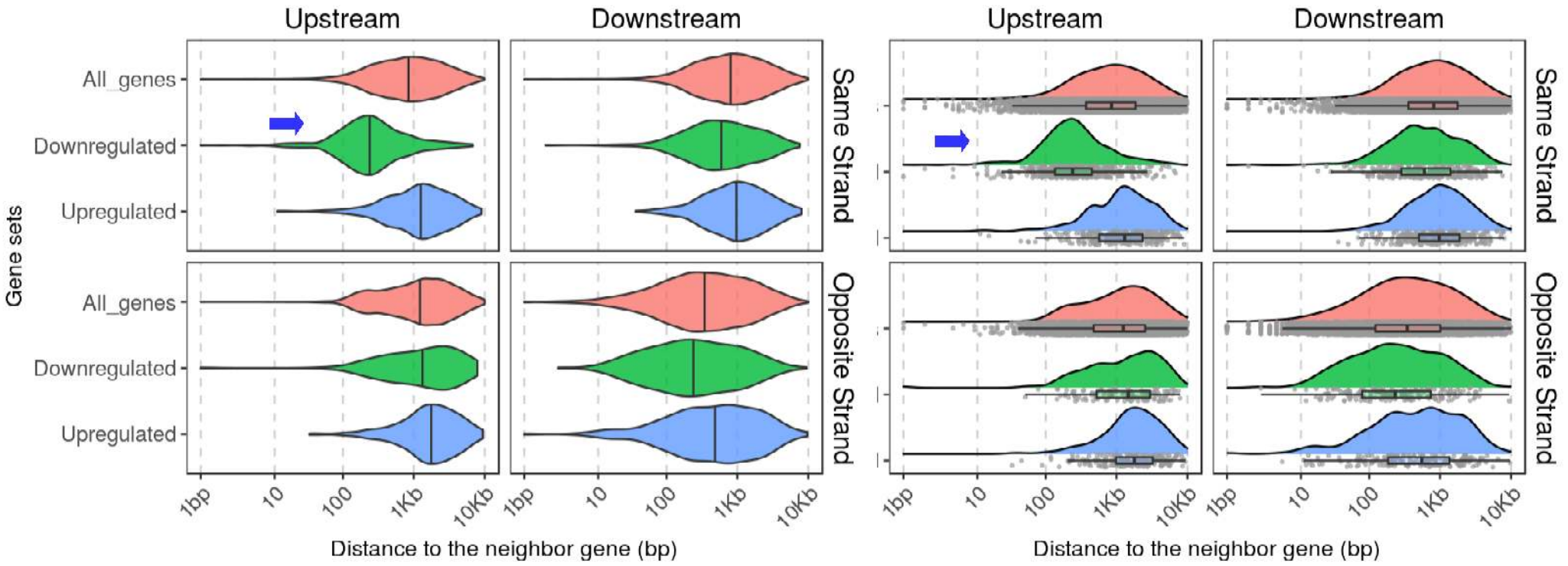
Analyzing neighbors distance

`analyzeNeighborsDistance()`

- Extract distances
- Descriptive statistics (mean, median, SD, 95 % CI, ...)
- Tests (KS, Mann-Whitney, permutation test of independence)

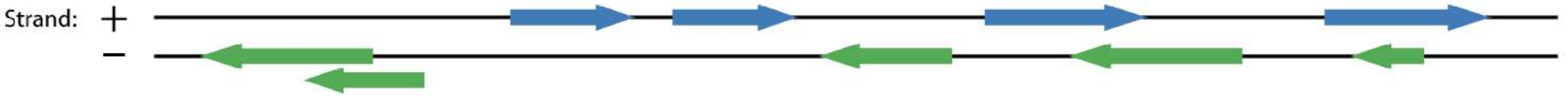
coin R package

`plotDistanceDistrib()`

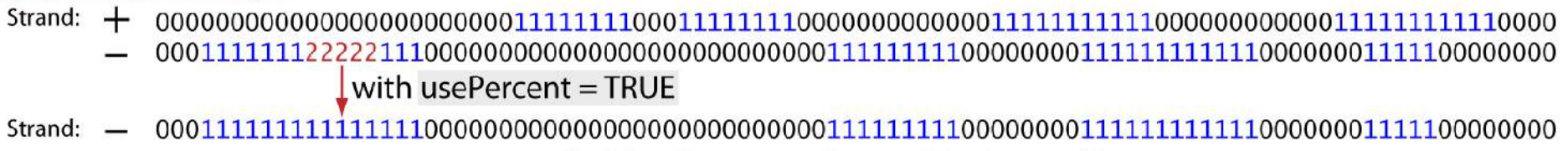


Metagene profiles

Gene annotations:

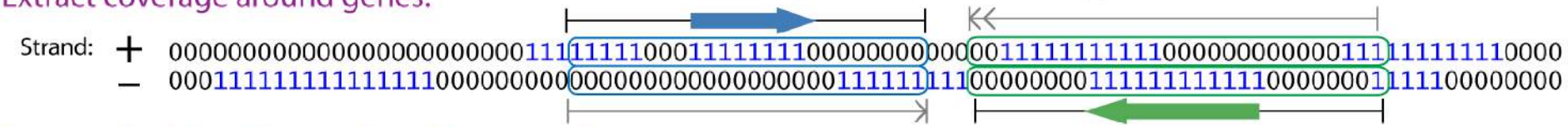


Annotation coverage:



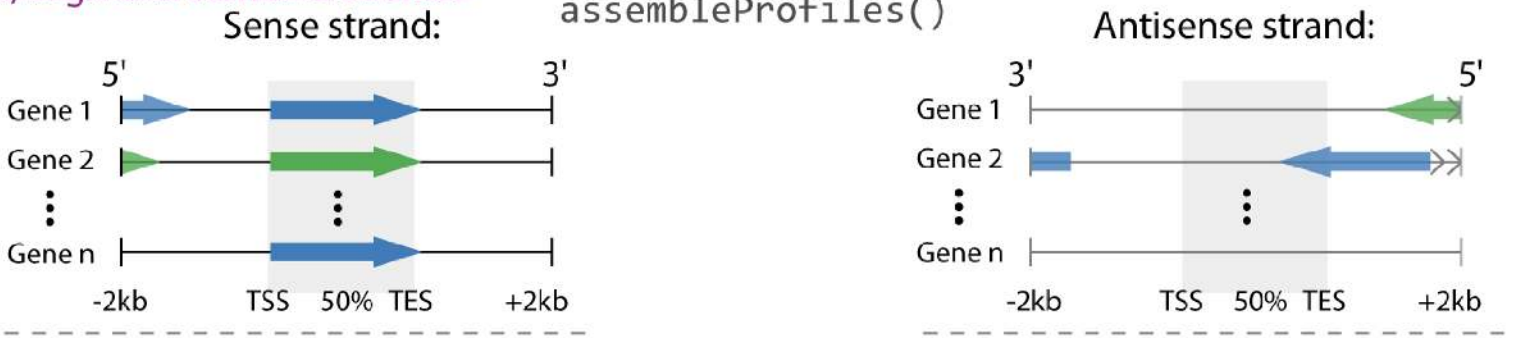
Extract coverage around genes:

annotationCoverageAroundFeatures()



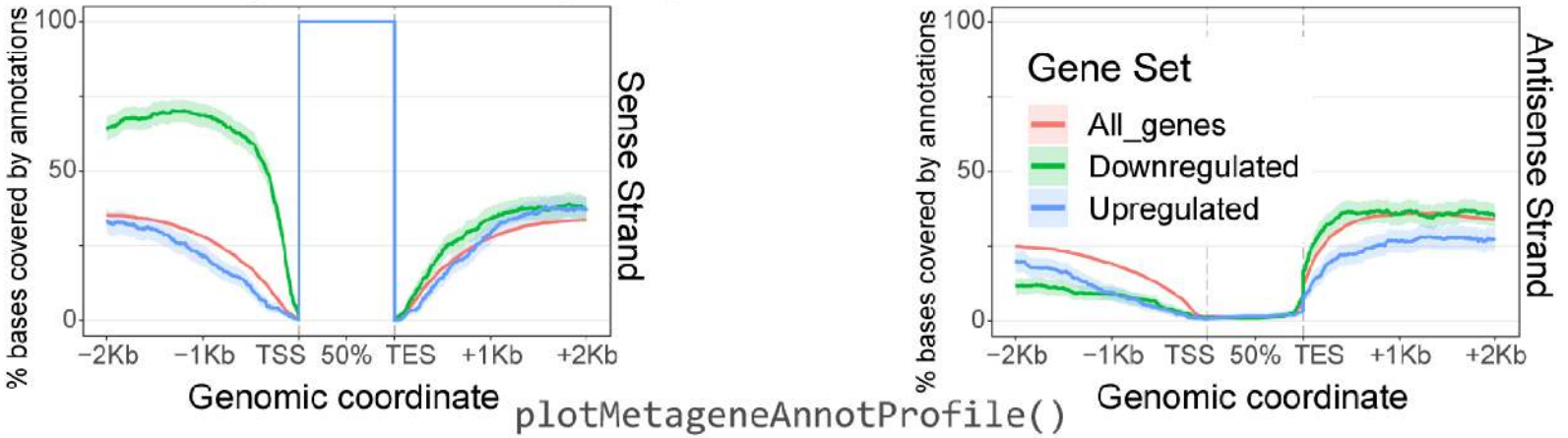
Bin gene bodies, align and combine strands:

assembleProfiles()



Average profiles for different gene sets:

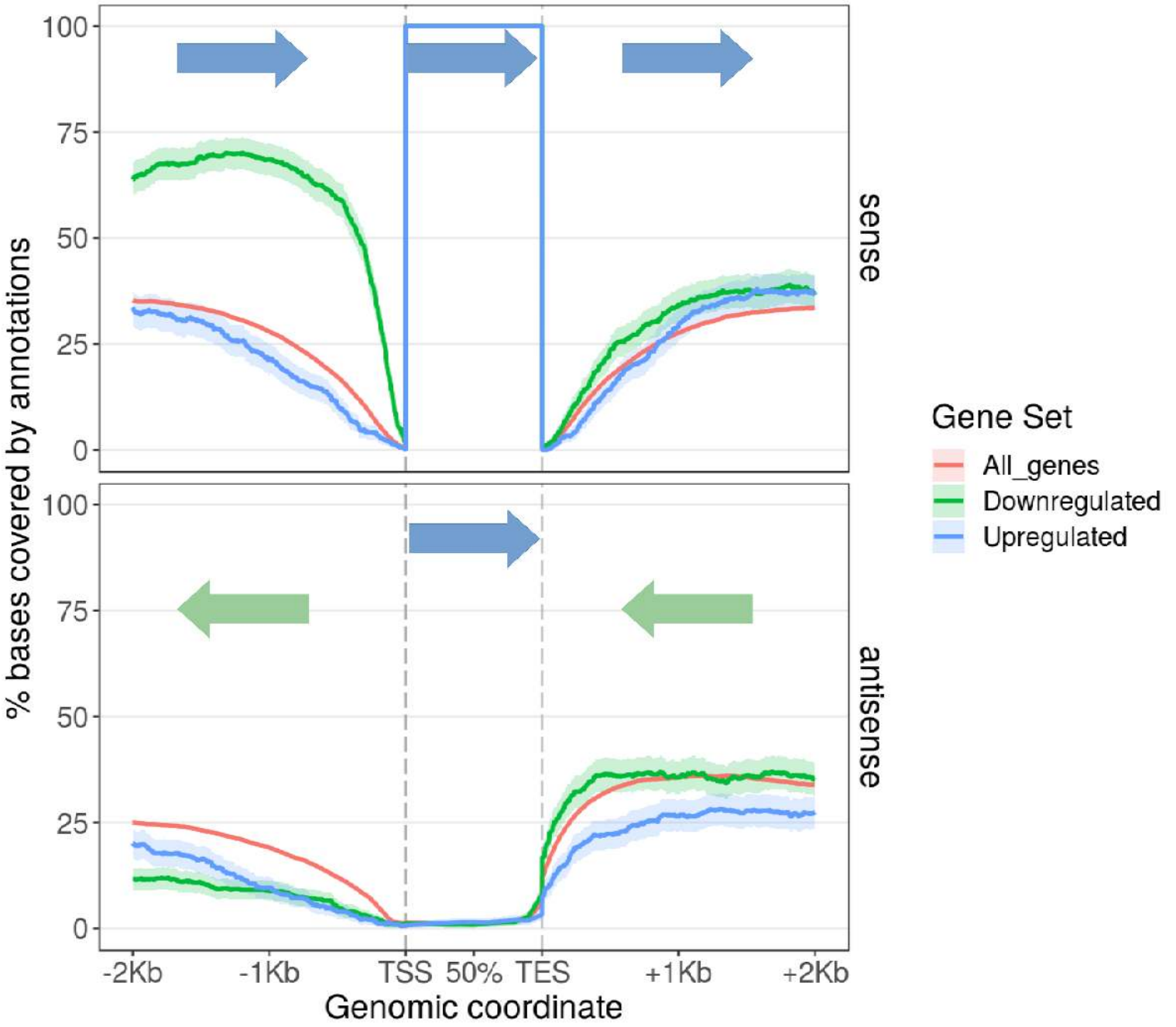
getAvgProfileWithCI()



plotMetageneAnnotProfile()

Metagene profiles

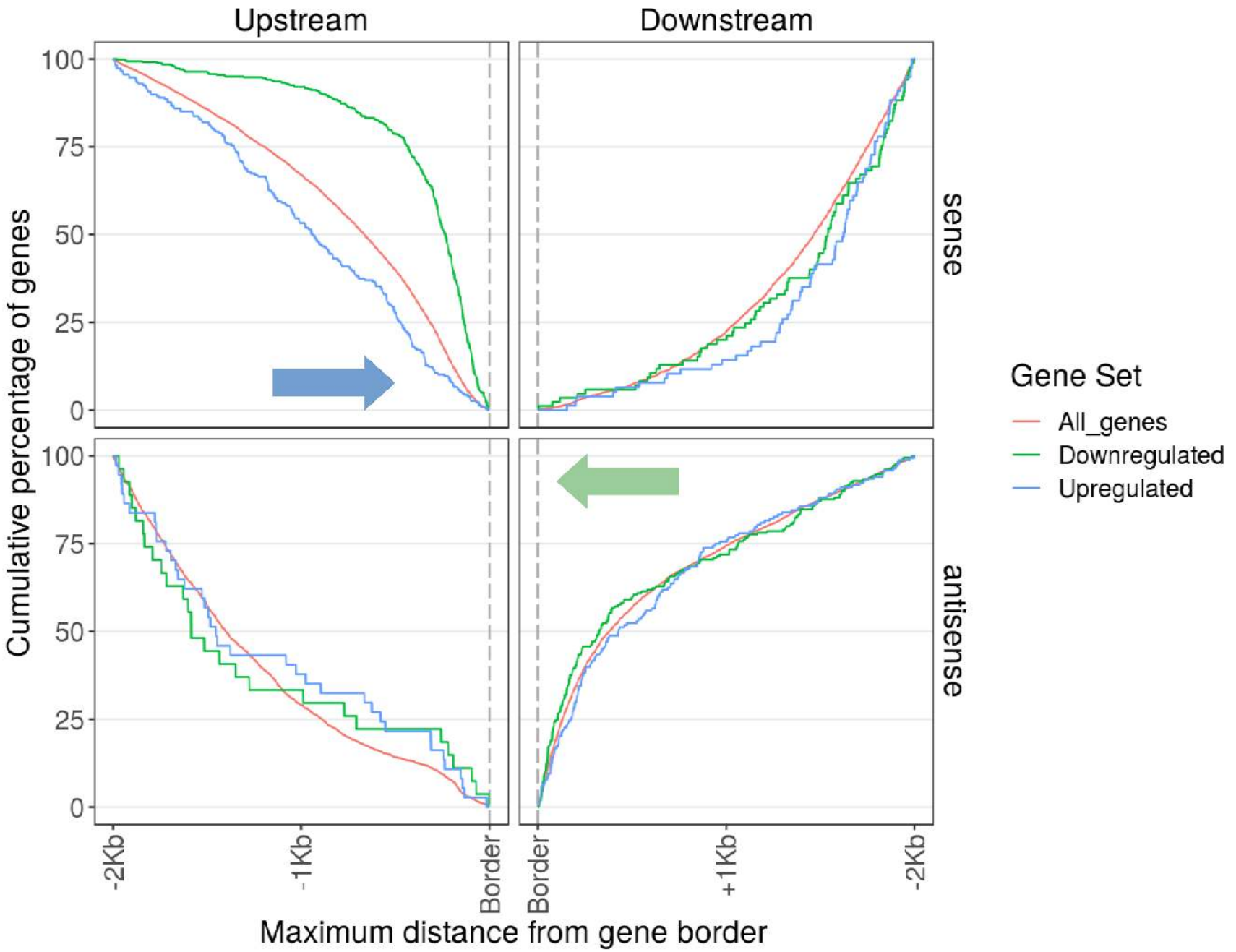
```
plotMetageneAnnotProfile()
```



Distances to single point features

`plotCumulPercentProfile()`

% of genes with a TES at less than X bp ?



Conclusion / future development

build passing build passing

github.com/pgpmartin/GeneNeighborhood

Neighbors orientation

- Facilitate the analysis of multiple gene sets

Neighbors distance

- Split analysis into 3 tasks :
  - extract distances
  - descriptive statistics
  - inference

Metagene profiles

- Add a wrapper to simplify the pipeline

+ Case studies in vignette → Submit to CRAN or BioC

Future development

- > 1 overlap
- Deal with a quantitative variable defining gene sets

Acknowledgements

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NIH

Xuhong Yu

Mathilde Gorieu

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AgreenSkills plus

Pathways for inventive researchers

Community help / forums:

R

Bioconductor

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Thank you for your attention !