

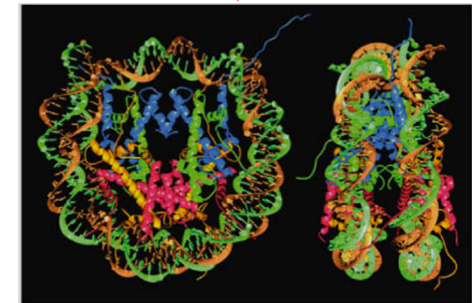
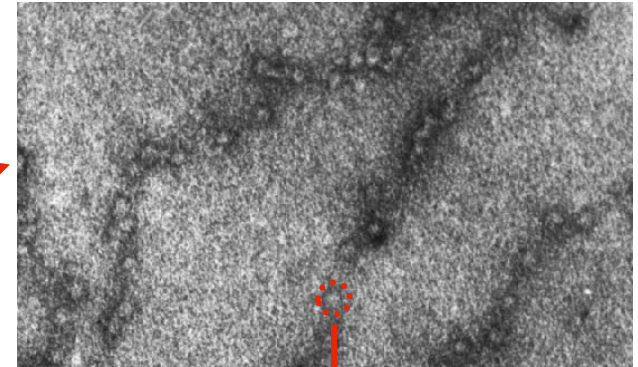
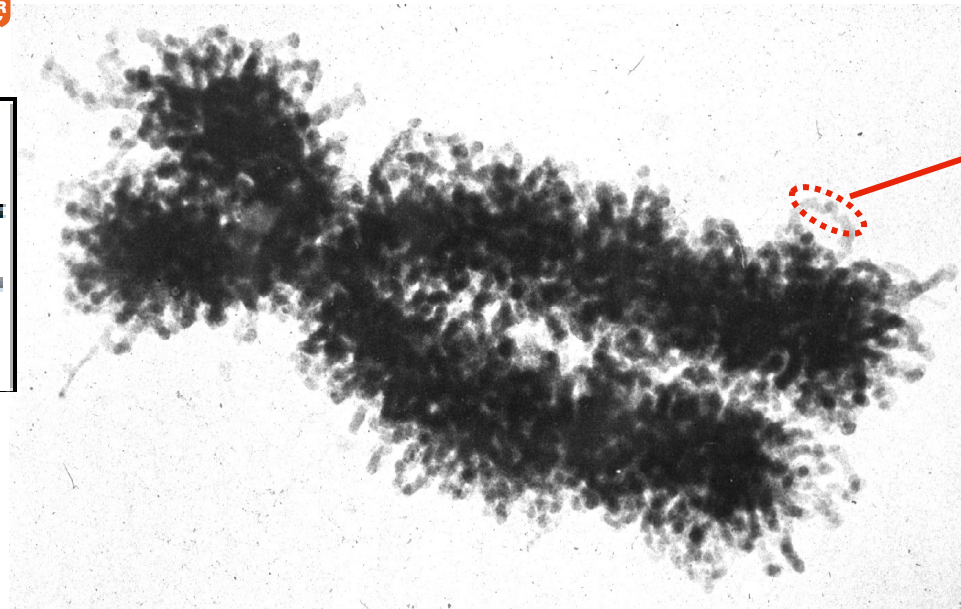
InnoMOL
GENOMICS & BIOINFORMATICS
WORKSHOP

Drosophila Epigenomics

Zagreb, November 2015

EPIGENETIC REGULATION OF CHROMATIN FUNCTIONS

Genetic information resides on DNA that, in eukaryotes, is packed into chromatin



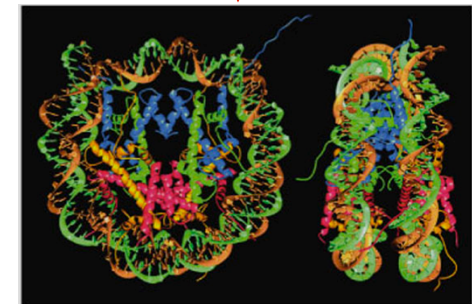
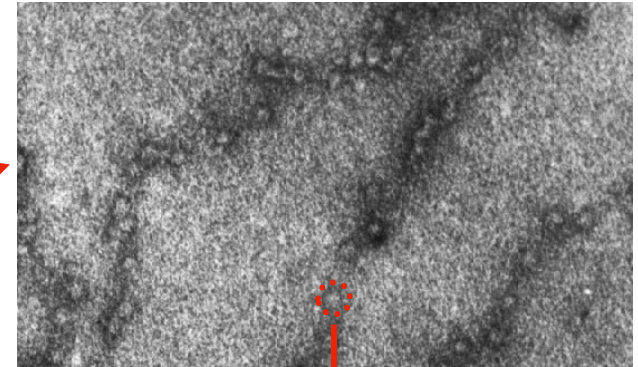
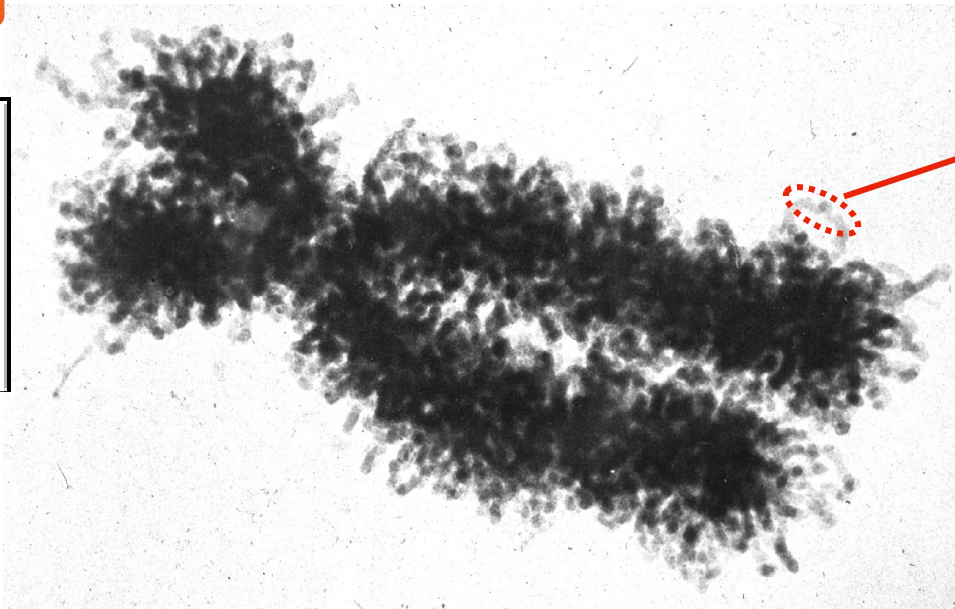
*“146bp of DNA wrapped around
a histone (H3.H4.H2A.H2B)₂ octamer”*

- > *Histone variants*
- > *Histone post-translational modifications*
- > *Non-histone regulatory proteins*
 - > *RNAs*
- > *DNA modifications*

EPIGENOME

EPIGENETIC REGULATION OF CHROMATIN FUNCTIONS

Genetic information resides on DNA that, in eukaryotes, is packed into chromatin



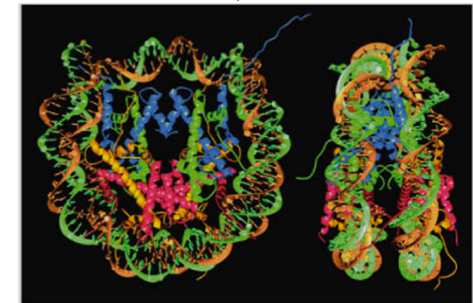
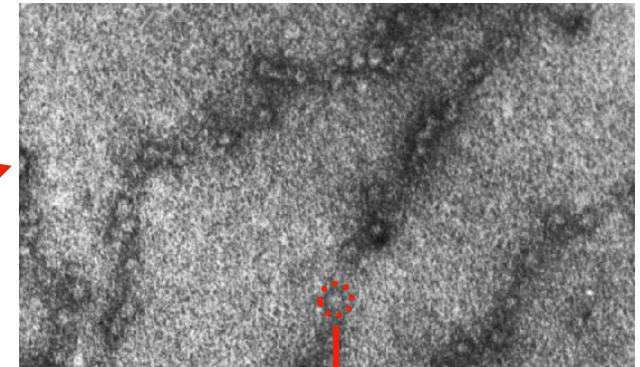
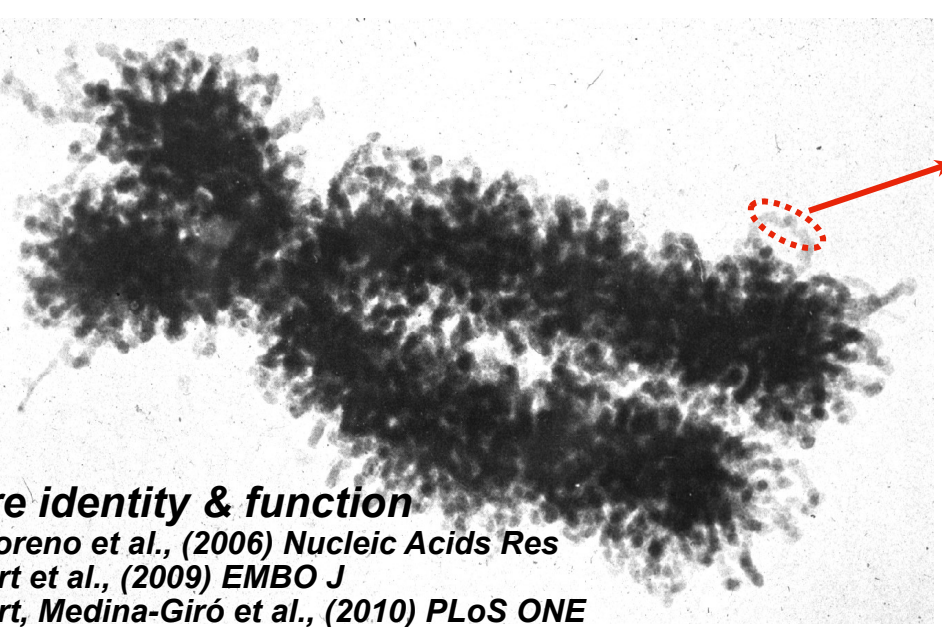
*“146bp of DNA wrapped around
a histone (H3.H4.H2A.H2B)₂ octamer”*

EPIGENETICS REGULATES “GENETICS”

**EPIGENETIC ALTERATIONS ARE ON THE BASIS
OF MULTIPLE DISEASES & AGING**

EPIGENETIC REGULATION OF CHROMATIN FUNCTIONS

Genetic information resides on DNA that, in eukaryotes, is packed into chromatin



“146bp of DNA wrapped around a histone (H3.H4.H2A.H2B)₂ octamer”

Centromere identity & function

*Moreno-Moreno et al., (2006) Nucleic Acids Res
Torras-Llort et al., (2009) EMBO J
Torras-Llort, Medina-Giró et al., (2010) PLoS ONE
Moreno-Moreno et al., (2011) Curr Biol
Medina-Giró, Torras-Llort et al., (2015) submitted*

Epigenetic regulation of transcription

*Lloret-Llinares et al., (2008) Nucleic Acids Res.
Font-Burgada et al., (2008) Genes Dev
Lloret-Llinares et al., (2013) Nucleic Acids Res.
Font-Burgada et al., (2014) Nucleic Acids Res.
Kessler et al., (2015) Nature Commun
Morán et al., (2015) Dev Biol*

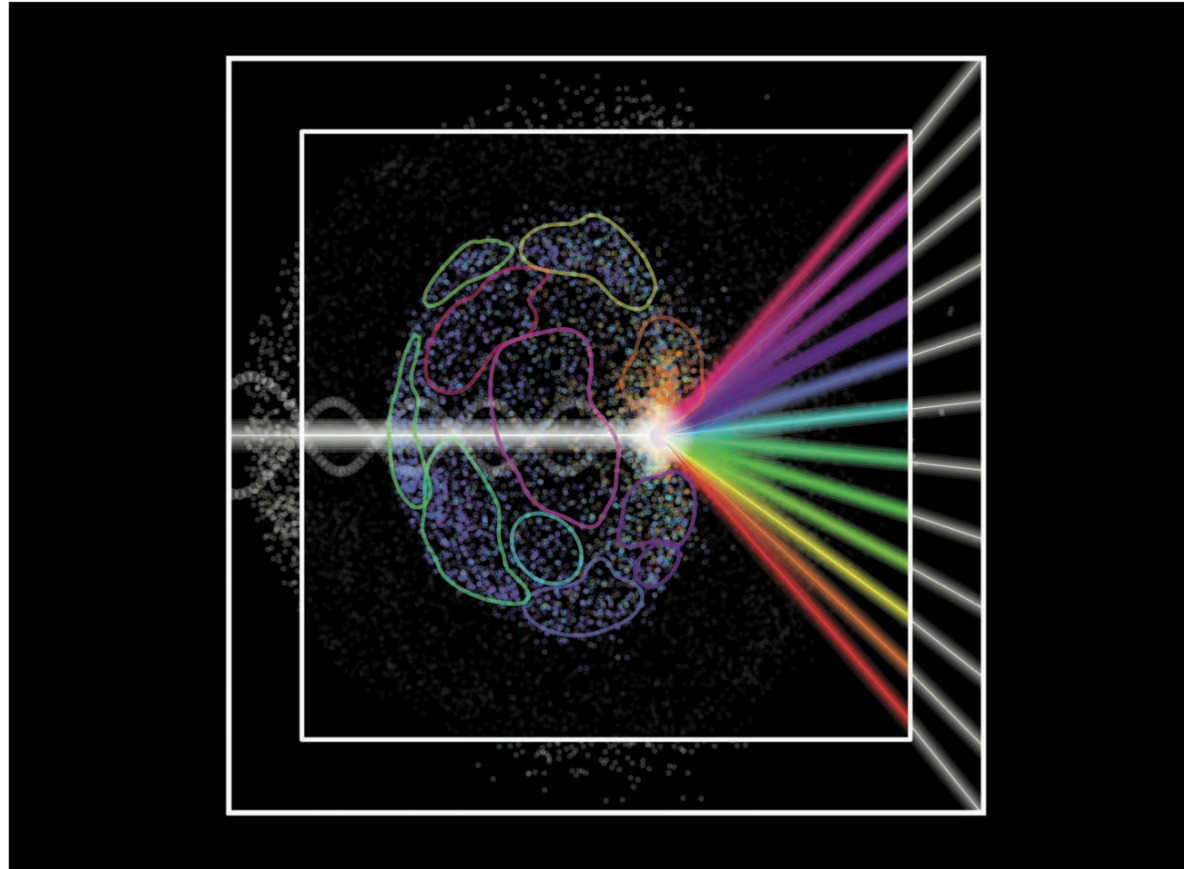
Higher-order chromatin organisation

*Aguilar-Arnal et al., (2008) EMBO J
Bonet et al., (2012) J Proteomics
Vujatovic et al., (2012) Nucleic Acids Res.
Pérez-Montero et al., (2013) Dev Cell
Cuartero et al., (2014) EMBO J*

Nucleic Acids Research

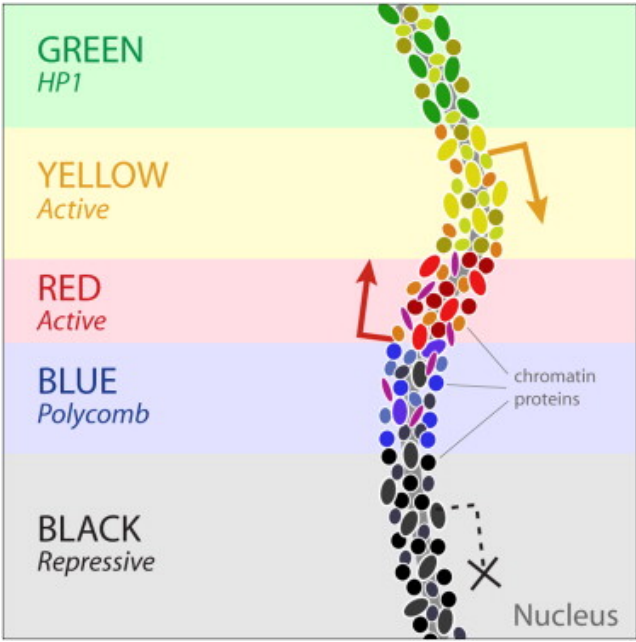
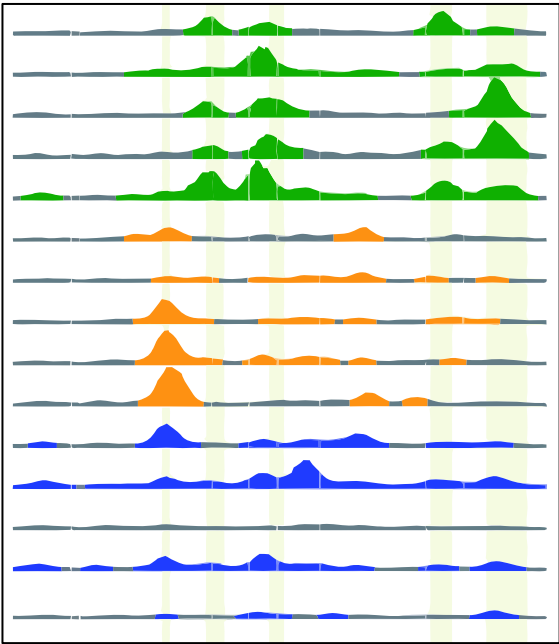
VOLUME 42 ISSUE 4 2014

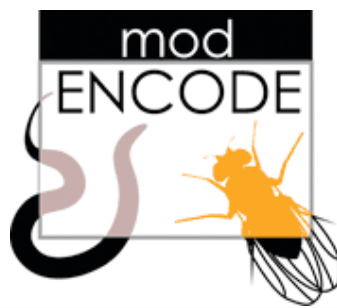
www.nar.oxfordjournals.org



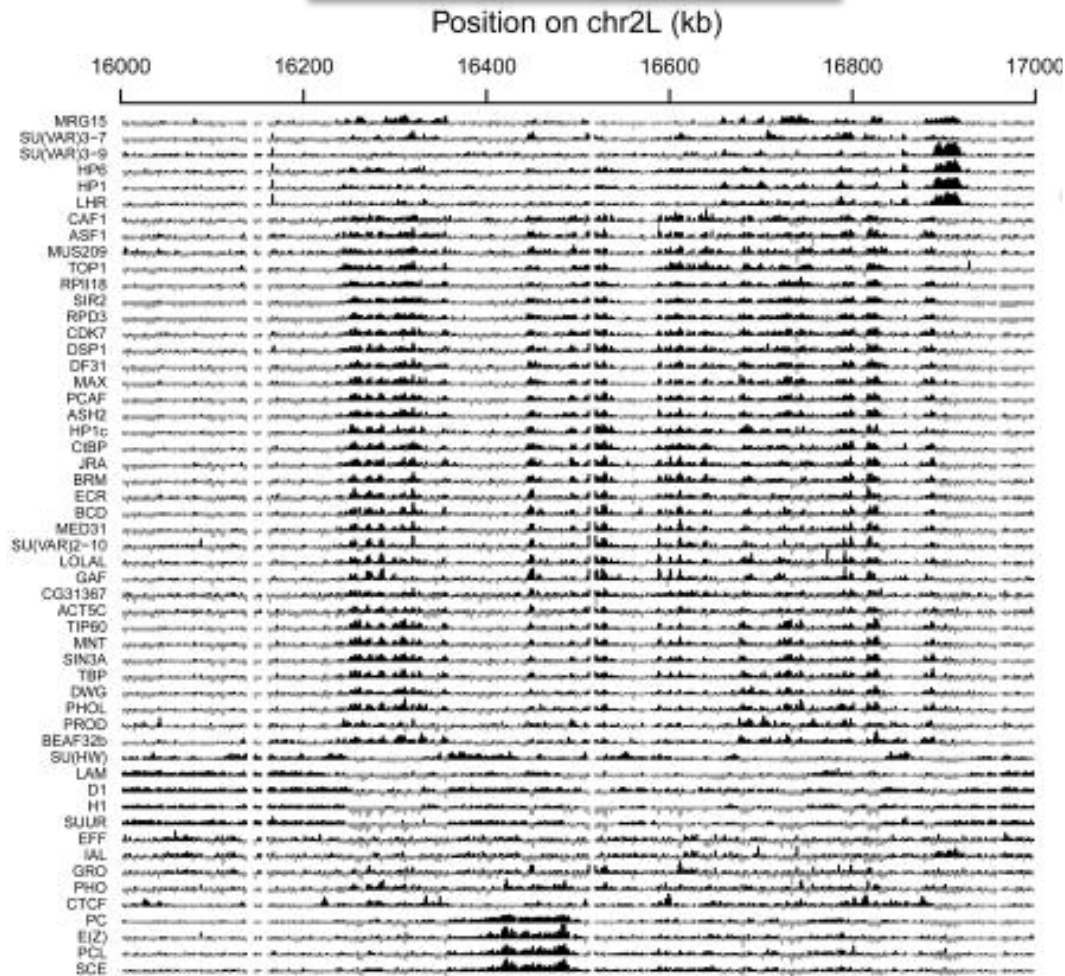
chroGPS
A GLOBAL CHROMATIN POSITIONING SYSTEM

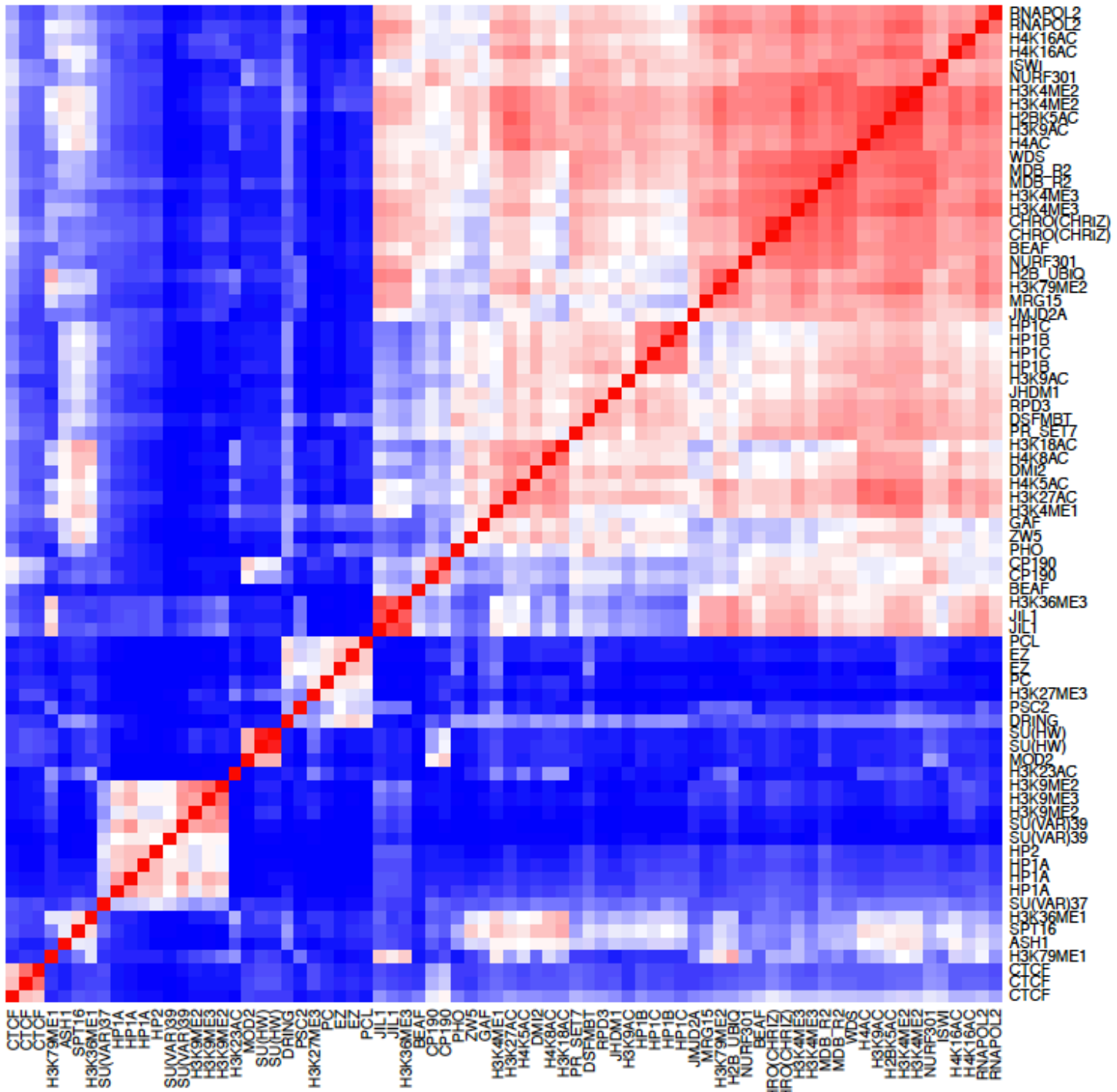
EPIGENOME





Drosophila S2 cells
>80 epigenetic factors





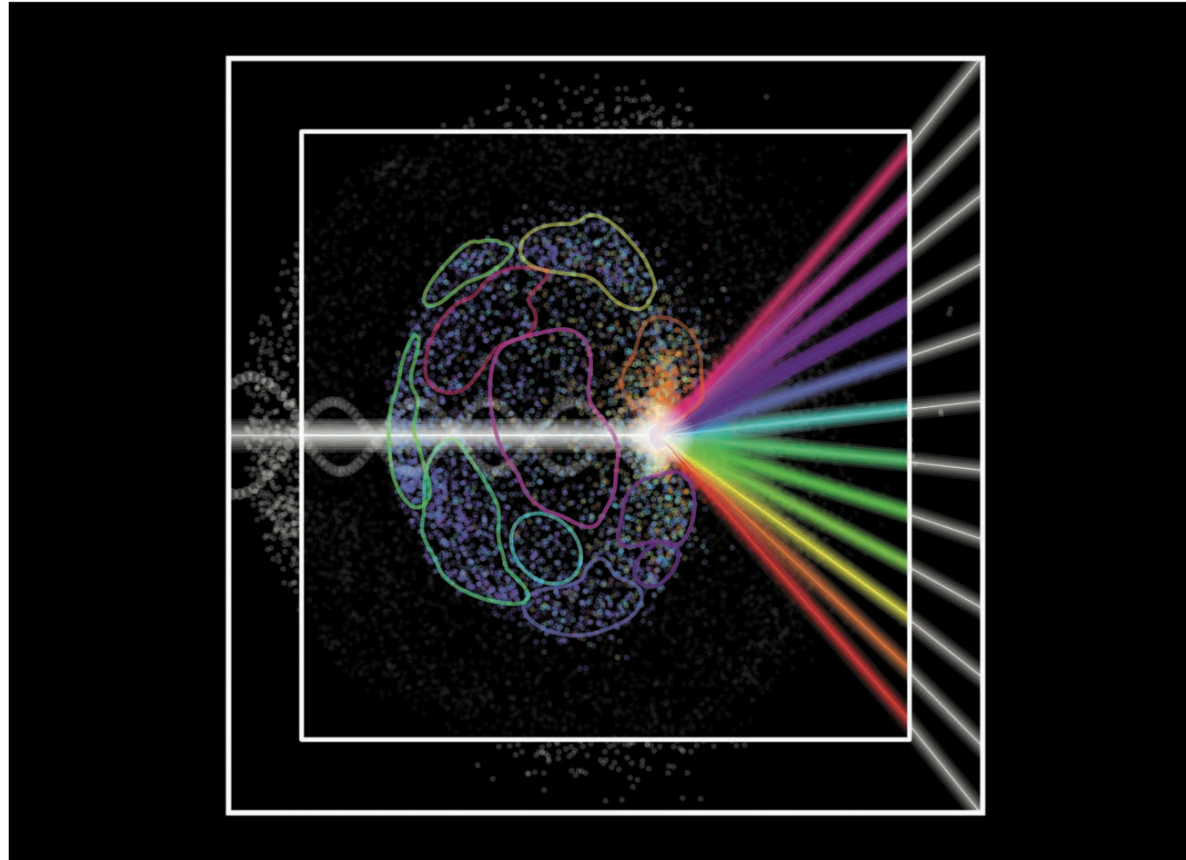
CTCF
CTCF
CTCF
H3K79ME1
ASH1
SPT16
SUVAR157
HP1A
HP1A
HP1A
HP2
SUVAR139
SUVAR139
H3K9ME2
H3K9ME3
H3K9ME2
H3K23AC
MOD2
SU(HW)
SU(HW)
SU(HW)
DRING
DRING
H3K27ME3
LO
LEZ
PCL
JIL1
JIL1
H3K36ME3
BEAF
CP190
CP190
PHO
PHO
ZNF5
ZNF5
GAF
GAF
GAF
H3K27AC
H4K8AC
DM12
H4K8AC
H3K18AC
PR_SET7
DSFMBT
DSFMBT
RPD3
JHDM1
H3K9AC
HP1B
HP1B
HP1B
HP1C
HP1C
HP1C
JMJD2A
JMJD2A
MRG15
MRG15
H3K79ME2
H2B_UBI1
H2B_UBI1
NURF301
NURF301
BEAF
BEAF
HPO(CHRIZ)
HPO(CHRIZ)
H3K4ME3
H3K4ME3
H3K4ME3
MDB_R2
MDB_R2
MDB_R2
VDS
VDS
H4AC
H3K9AC
H2BK5AC
H2BK5AC
H3K4ME2
H3K4ME2
H3K4ME2
NURF301
NURF301
ISWI
ISWI
H4K16AC
H4K16AC
RNAPOL2
RNAPOL2

RNAPOL2
RNAPOL2
H4K16AC
H4K16AC
ISWI
NURF301
H3K4ME2
H3K4ME2
H2BK5AC
H3K9AC
H4AC
WDS
MDB_R2
MDB_R2
H3K4ME3
H3K4ME3
HPO(CHRIZ)
HPO(CHRIZ)
BEAF
NURF301
H2B_UBI1
H2B_UBI1
H3K79ME2
MRG15
JMJD2A
HP1C
HP1B
HP1C
HP1B
H3K9AC
JHDM1
RPD3
DSFMBT
PR_SET7
H3K18AC
H4K8AC
DM12
H4K5AC
H3K27AC
H3K4ME1
GAF
ZNF5
PHO
CP190
CP190
BEAF
H3K36ME3
JIL1
JIL1
PCL
DRING
DRING
H3K27ME3
PSC2
DRING
SU(HW)
SU(HW)
SU(HW)
MOD2
H3K23AC
H3K9ME2
H3K9ME3
H3K9ME3
H3K9ME2
SU(VAR)39
SU(VAR)39
HP2
HP1A
HP1A
HP1A
SU(VAR)37
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SPT16
ASH1
H3K79ME1
CTCF
CTCF
CTCF

chroGPS

A GLOBAL CHROMATIN POSITIONING SYSTEM

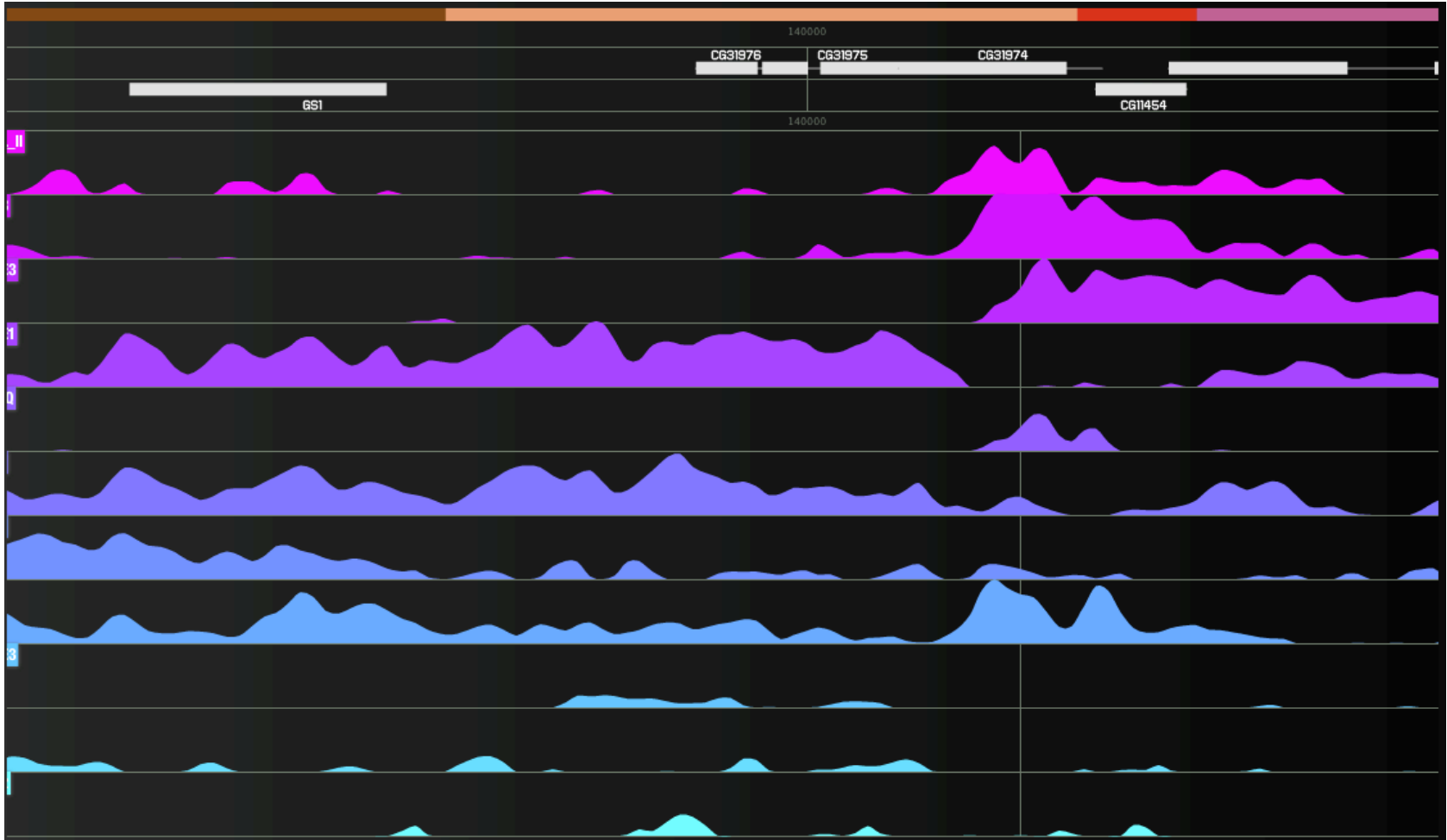
4 2014 PACIS 2099-2798



- > *define a metric to measure functional similarity/distance of factors*
- > *represent distances onto low-dimensional (2D/3D) “graphical” maps*

chroGPS

functionally related factors > similar genomic profiles



> metric to measure genomic overlap of factors

$$S_{ij}^T = \frac{\frac{1}{2} \left(\sum_{k=1}^{N_i} a_k + \sum_{k=1}^{N_j} b_k \right)}{N_i + N_j - \frac{1}{2} \left(\sum_{k=1}^{N_i} a_k + \sum_{k=1}^{N_j} b_k \right)},$$

iTanimoto

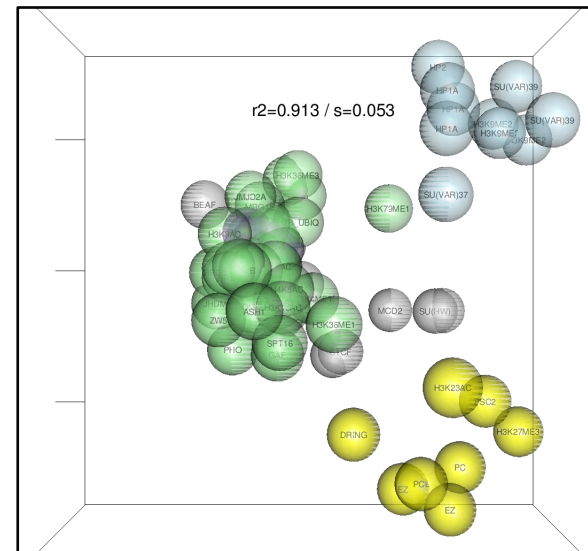
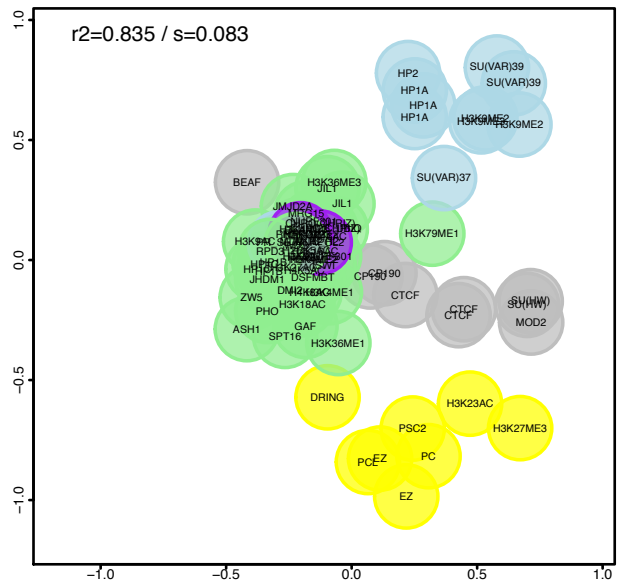
Font-Burgada et al., (2014) NAR

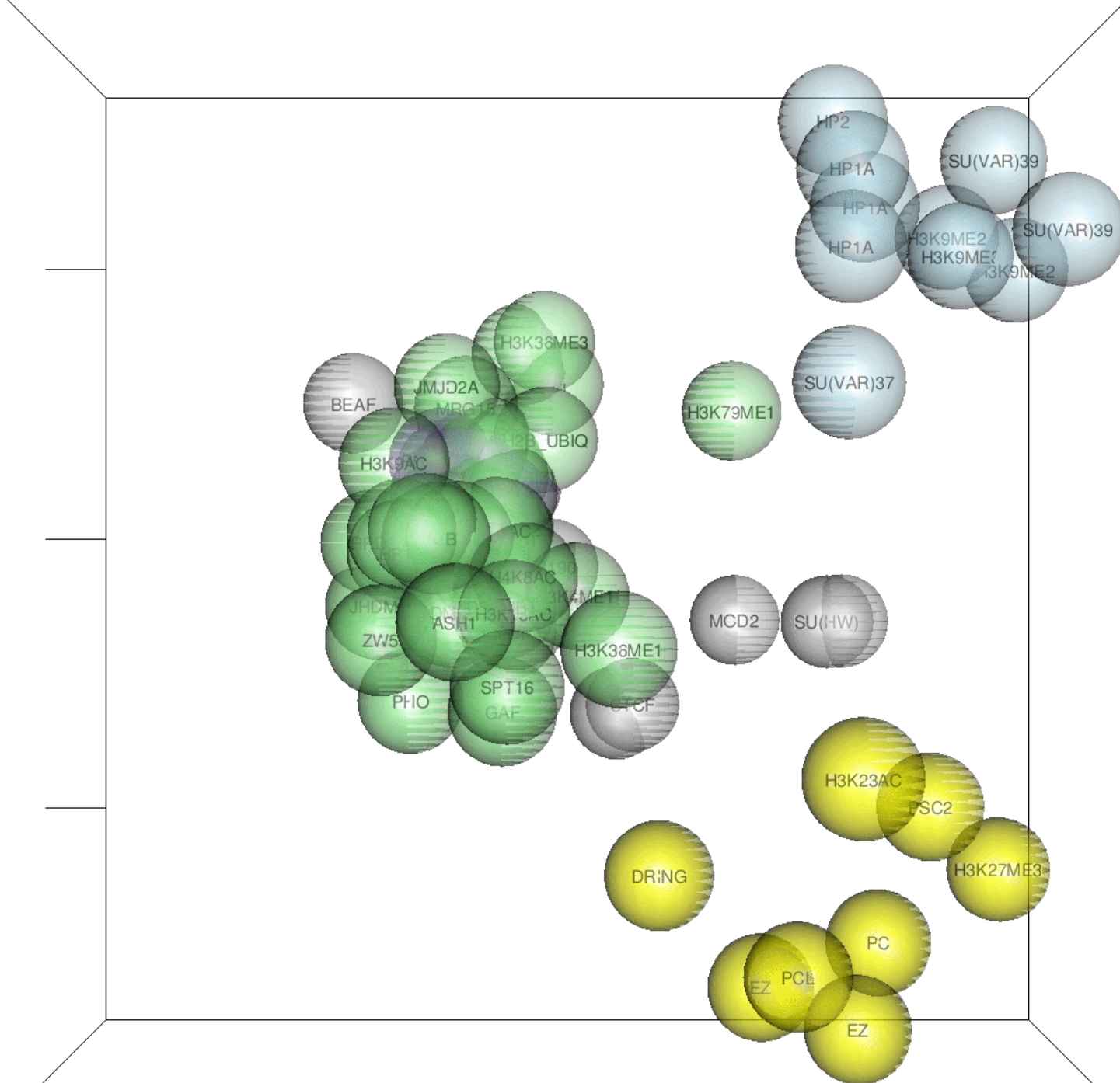
Similarity/Distance matrix

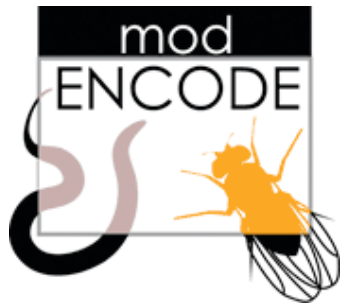
	BEAF-70.S2	BEAF-HB.S2	BRE1_Q2539.S2	Chro(Chriz)BR.S2	Chro(Chriz)WR.S2	CP190-HB.S2	CP190-VC.S2	CTCF-N_S2_ChIP-chip.do	CTCF-VC.S2
BEAF-70.S2	0.0000000	0.3873138	0.4423718	0.4036024	0.3988006	0.5952943	0.5396068	0.7456823	0.8879448
BEAF-HB.S2	0.3873138	0.0000000	0.3404092	0.2281914	0.2219629	0.4540323	0.4734651	0.5980498	0.7873931
BRE1_Q2539.S2	0.4423718	0.3404092	0.0000000	0.3119860	0.3181125	0.2450508	0.2011106	0.4885170	0.6176645
Chro(Chriz)BR.S2	0.4036024	0.2281914	0.3119860	0.0000000	0.0838671	0.4283438	0.4323009	0.5373341	0.7247709
Chro(Chriz)WR.S2	0.3988006	0.2219629	0.3181125	0.0838671	0.0000000	0.4479733	0.4428854	0.5627866	0.7588857
CP190-HB.S2	0.5952943	0.4540323	0.2450508	0.4283438	0.4479733	0.0000000	0.2670338	0.5338948	0.6456019
CP190-VC.S2	0.5396068	0.4734651	0.2011106	0.4323009	0.4428854	0.2670338	0.0000000	0.4880889	0.5849756
CTCF-N_S2_ChIP-chip.do	0.7456823	0.5980498	0.4885170	0.5373341	0.5627866	0.5338948	0.4880889	0.0000000	0.3756303
CTCF-VC.S2	0.8879448	0.7873931	0.6176645	0.7247709	0.7588857	0.6456019	0.5849756	0.3756303	0.0000000
dMi-2_Q2626.S2	0.6944491	0.4832453	0.5656321	0.5051546	0.5194891	0.5897217	0.6538882	0.7113578	0.8180009
dRING_Q3200.S2	0.9483883	0.7823768	0.8096109	0.8186688	0.8339729	0.8018512	0.8633946	0.8686896	0.8830726
Ez.S2	0.9833932	0.9191225	0.8967425	0.9235804	0.9334260	0.8934353	0.9027317	0.9175100	0.9028845
GAF.S2	0.8147613	0.6018410	0.6464975	0.6098805	0.6249339	0.6460412	0.7150134	0.7541072	0.8289878
H2B-ubiq (NR03).S2	0.5223125	0.3973741	0.4689453	0.3684410	0.3645971	0.6040529	0.5694651	0.6903108	0.8128053
H3K18ac.S2	0.7879481	0.5655329	0.6460000	0.5791774	0.6011717	0.6664849	0.7128233	0.7327470	0.8244540
H3K23ac.S2	0.9961489	0.9663235	0.9434764	0.9486231	0.9513682	0.9726831	0.9419391	0.9709932	0.9415850
H3K27Ac.S2	0.6262632	0.4024894	0.5092273	0.4079403	0.4176484	0.5787154	0.6145182	0.6874516	0.8147303
H3K27me3 (Abcam2).S2	0.9969899	0.9764218	0.9102040	0.9637222	0.9663998	0.9302341	0.8641556	0.9236113	0.8330153
H3K36me3.S2	0.6291223	0.4877882	0.5499882	0.3874824	0.3946344	0.7044055	0.6393722	0.7926125	0.8717958
H3K4me1.S2	0.7979625	0.4857548	0.5603993	0.4259234	0.4406708	0.6820029	0.6732947	0.7520504	0.7830191
H3K4me2-Millipore.S2.gff3	0.4307812	0.2644524	0.3869942	0.2597359	0.2601734	0.4777399	0.4981660	0.5752637	0.7763713
H3K4me2.ab.S2	0.4364097	0.2662582	0.3916688	0.2664065	0.2656822	0.4886827	0.5047900	0.5885575	0.7838972
H3K4me3_S2_ChIP-chip.do	0.4033140	0.2261853	0.3120696	0.2023114	0.1912824	0.4586444	0.4550273	0.6034595	0.8141389
H3K4me3(LP).S2	0.4180080	0.2442654	0.3509937	0.2158159	0.2084771	0.4731906	0.4870887	0.6079281	0.8042282
H3K79Me.S2	0.9509711	0.8019381	0.8083832	0.6384688	0.6557890	0.8978756	0.8405238	0.9079263	0.8817073
H3K79Me2.S2	0.5011225	0.3583639	0.4563429	0.3482140	0.3442775	0.5765942	0.5664691	0.6795912	0.8244267
H3K9ac.S2	0.4651772	0.2932414	0.4141149	0.3100038	0.3065687	0.5244091	0.5342881	0.6189867	0.8001291
H3K9acS10P (new_lot).S2	0.7158040	0.4867888	0.5564578	0.5010077	0.5057781	0.6536156	0.6848884	0.7783702	0.8927636
H3K9me2 antibody2.S2	0.9678685	0.9165412	0.9287151	0.8413661	0.8439145	0.9615702	0.9386201	0.9574055	0.9384848
H3K9me3.S2	0.9614119	0.9085998	0.9235325	0.8448014	0.8487009	0.9522748	0.9378957	0.9539212	0.9489948

> project onto low-dimensional (2D/3D) maps using MDS

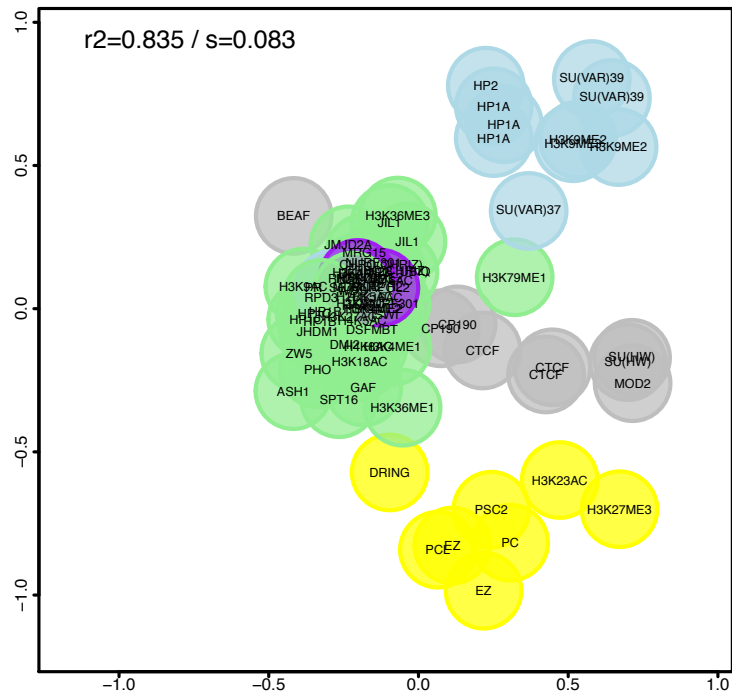
chroGPS^{factors} maps



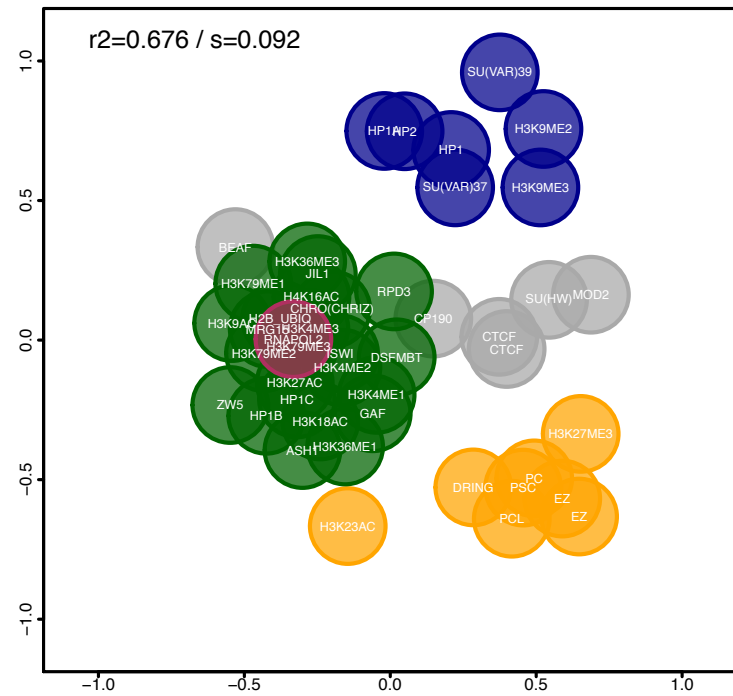




Drosophila S2 cells



Drosophila BG3 cells



A hint on Procrustes

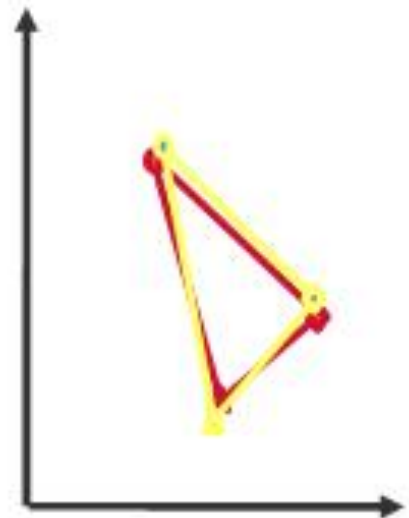
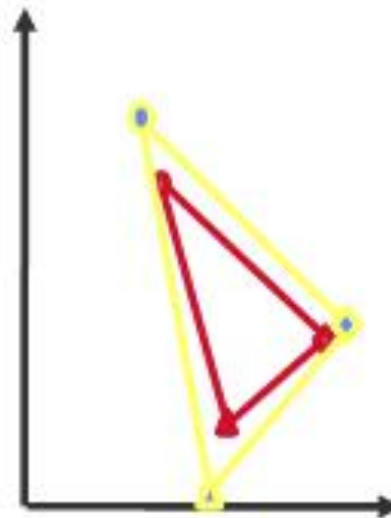
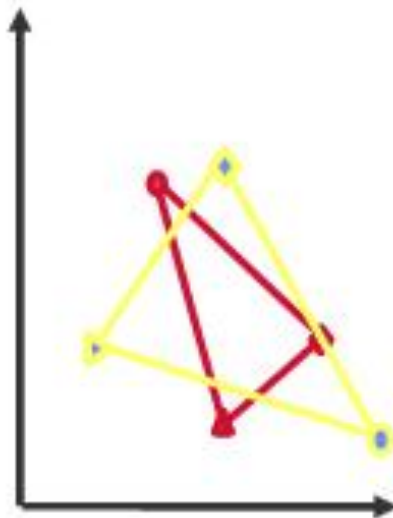
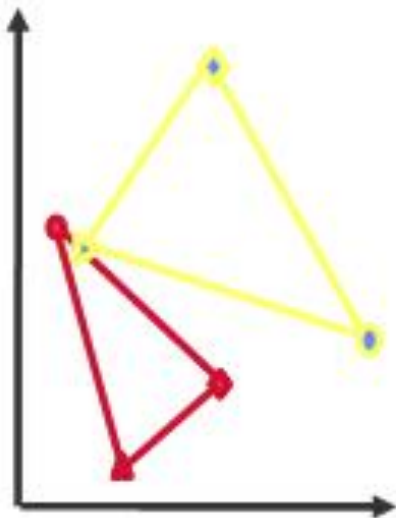


Initial configurations

Translation

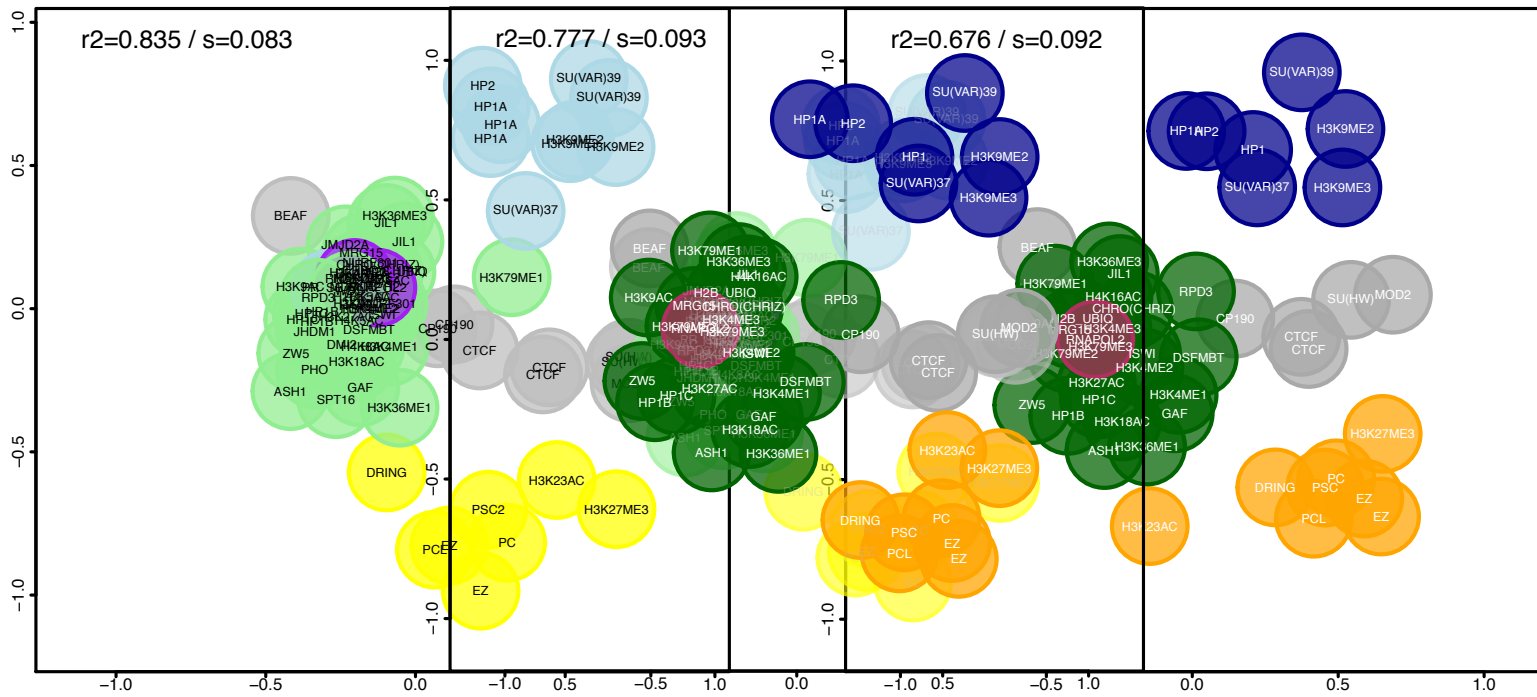
Rotation & Reflection

Scaling

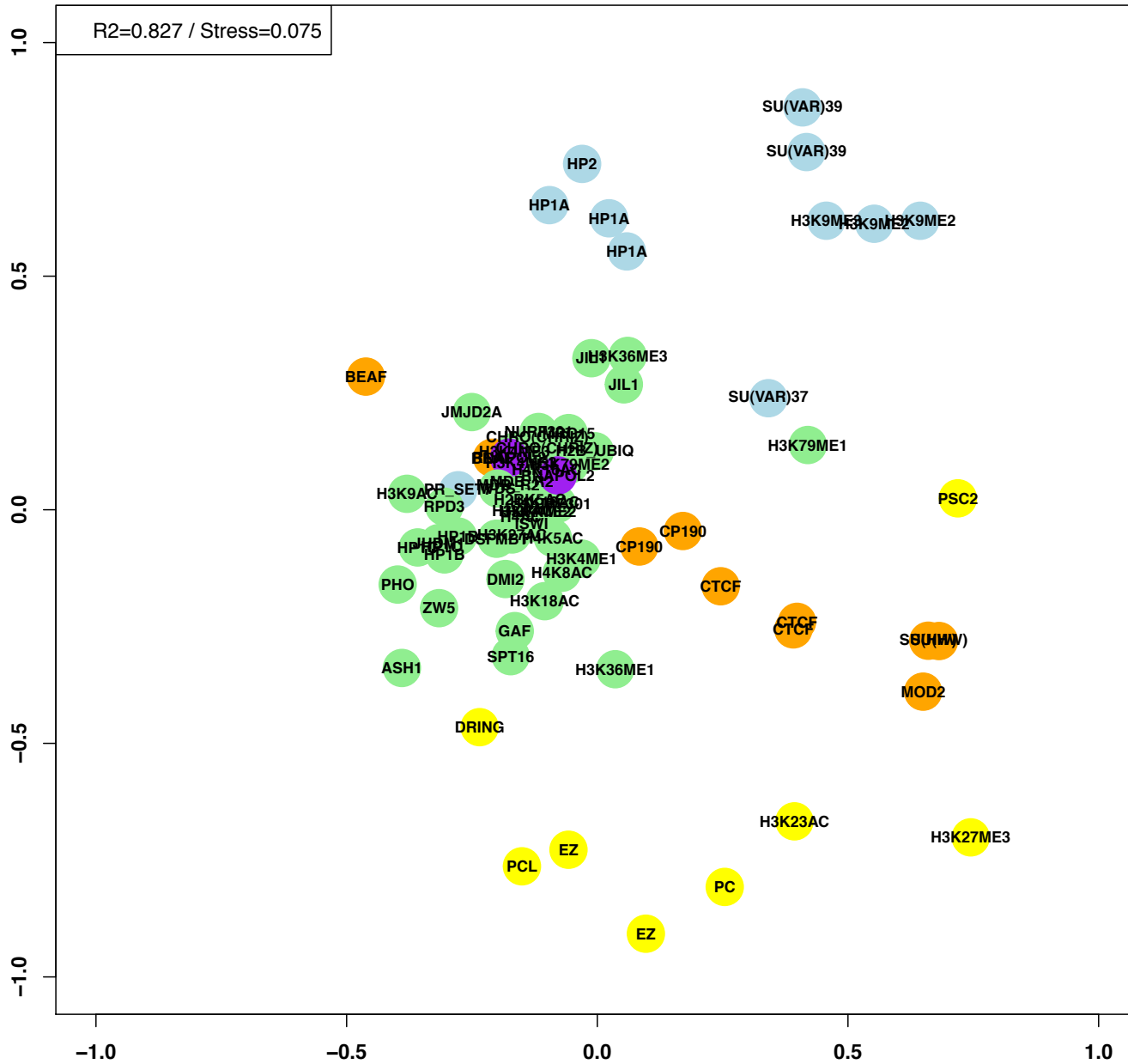




Drosophila S2 cell *Drosophila* S2/BG3 *Drosophila* BG3 cells

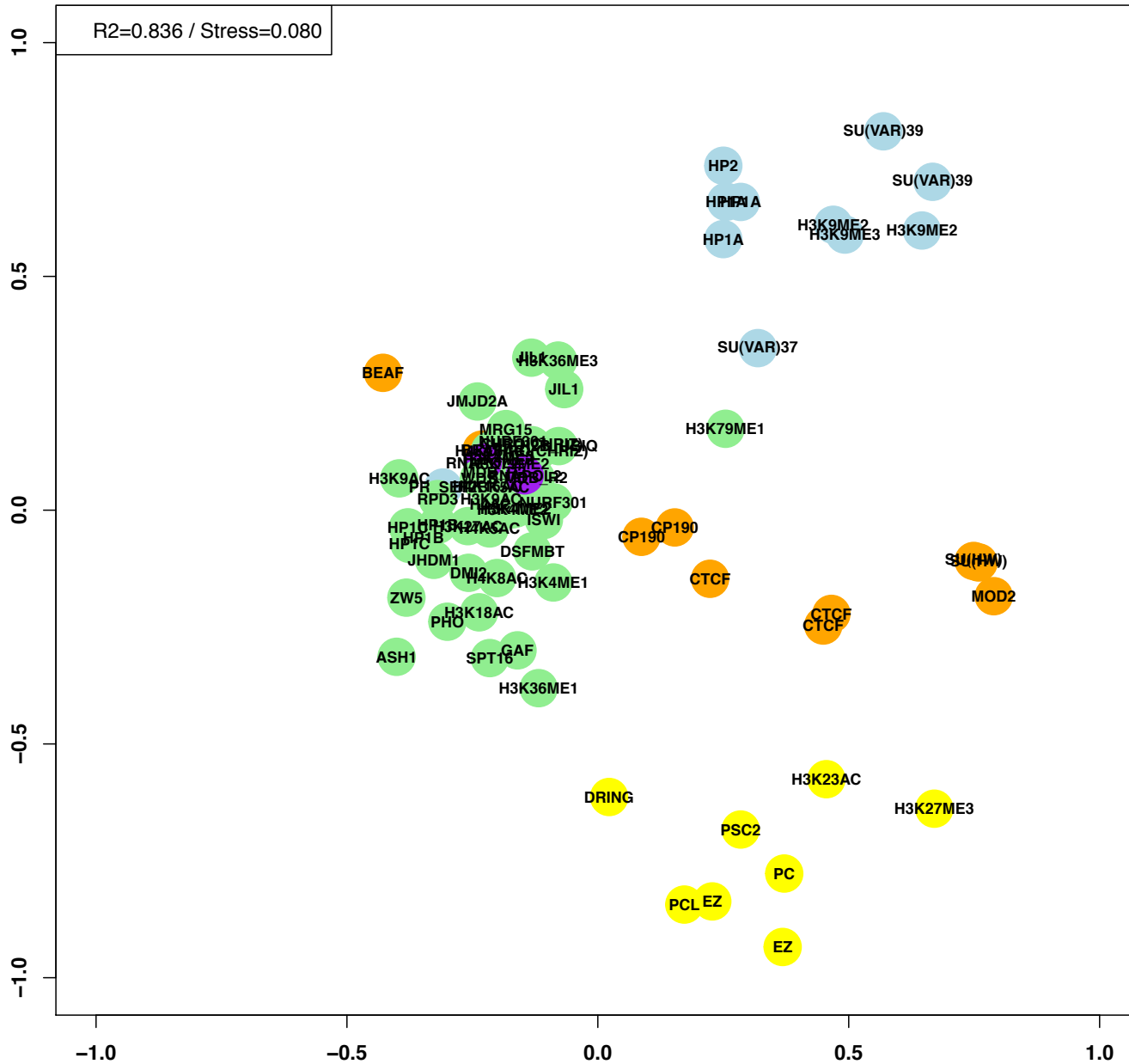


chroGPS^{origins}



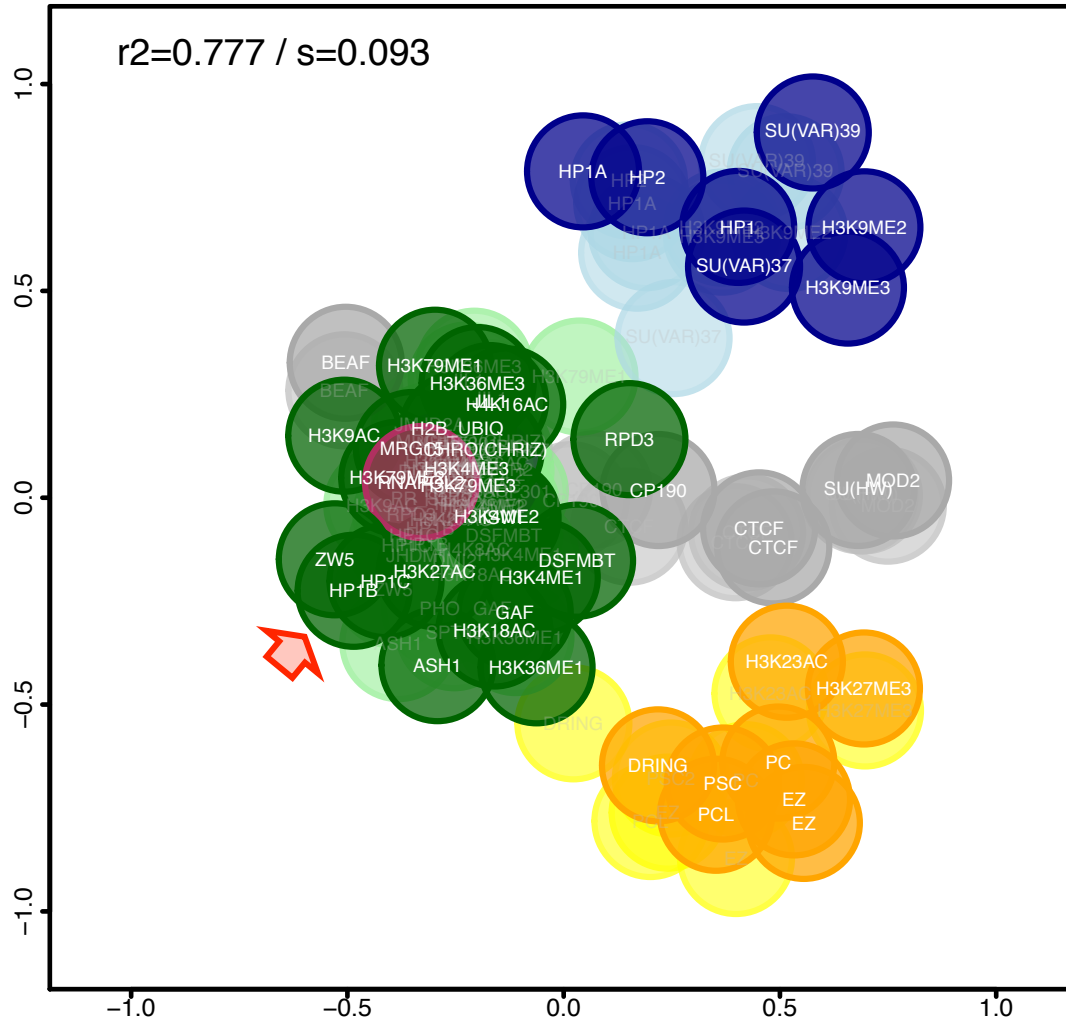
Early

chroGPS^{origins}





Drosophila S2/BG3



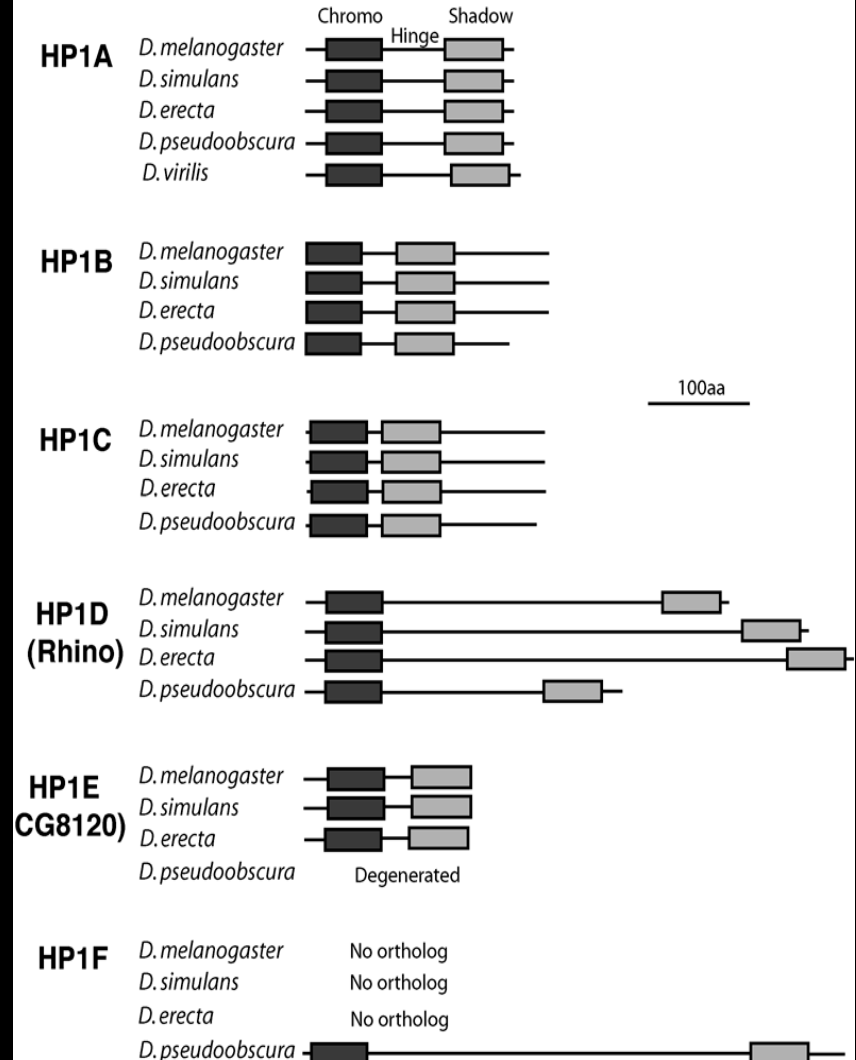
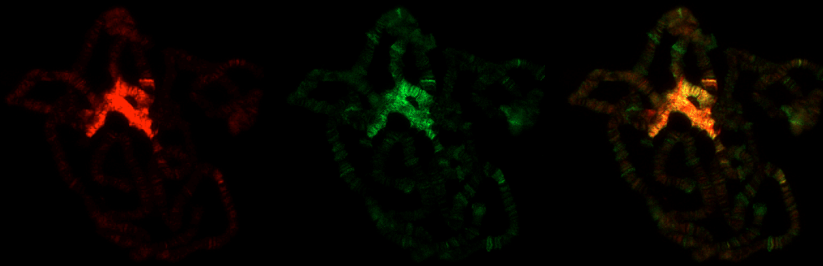
HP1 proteins in transcription regulation

Heterochromatin Protein 1 (HP1)

H3K9me2

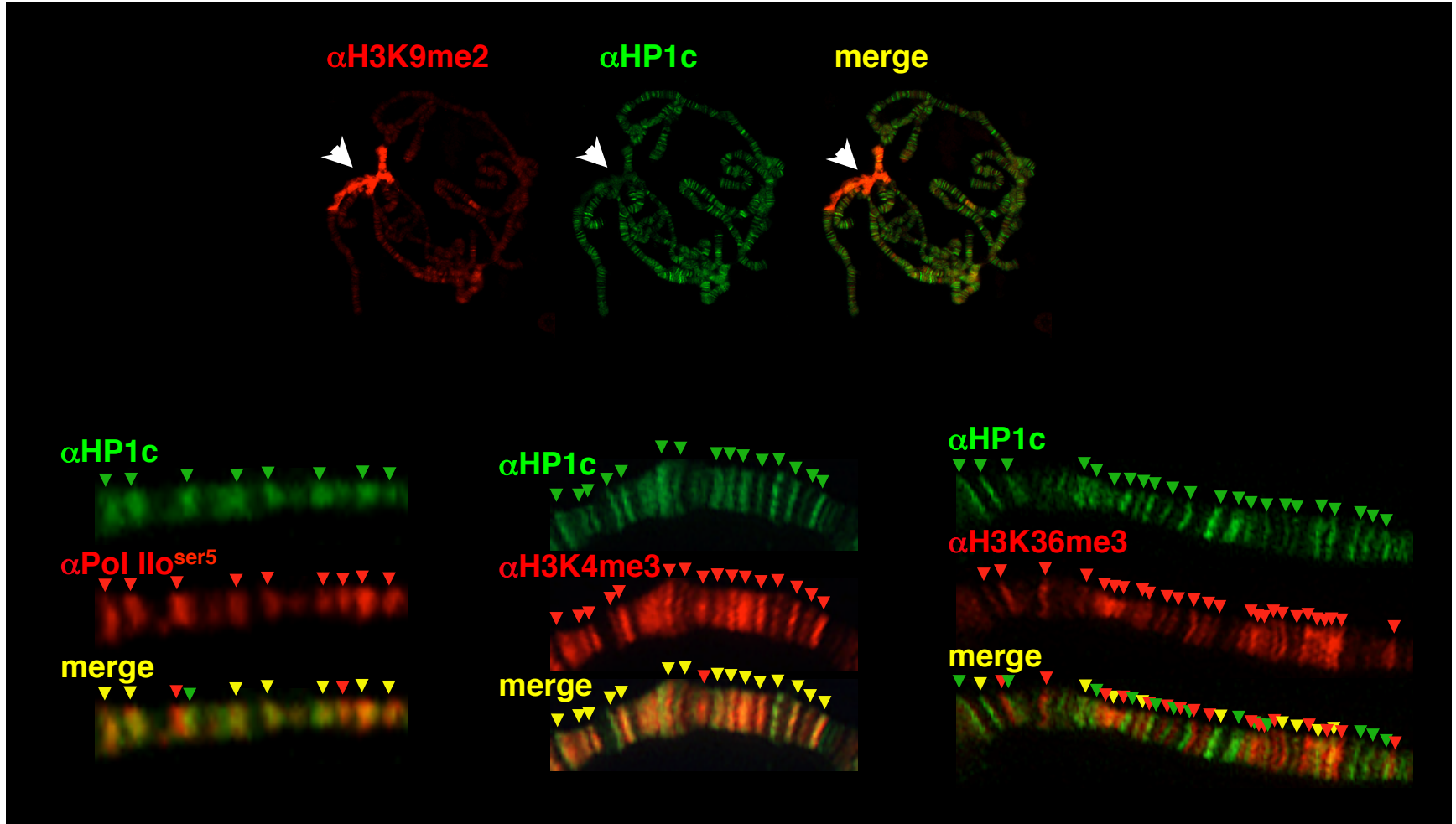
HP1

merge



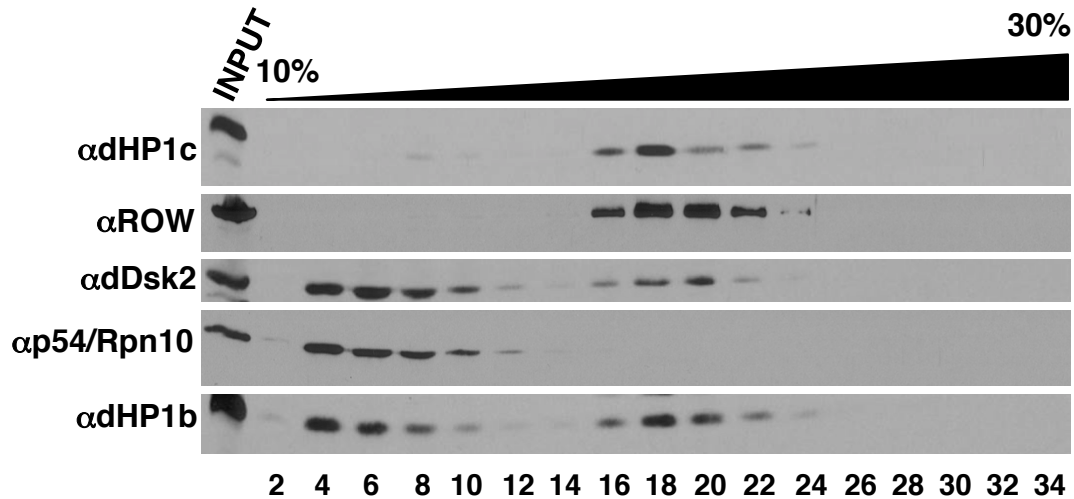
HP1 proteins in transcription regulation

> HP1c localizes to active chromatin domains



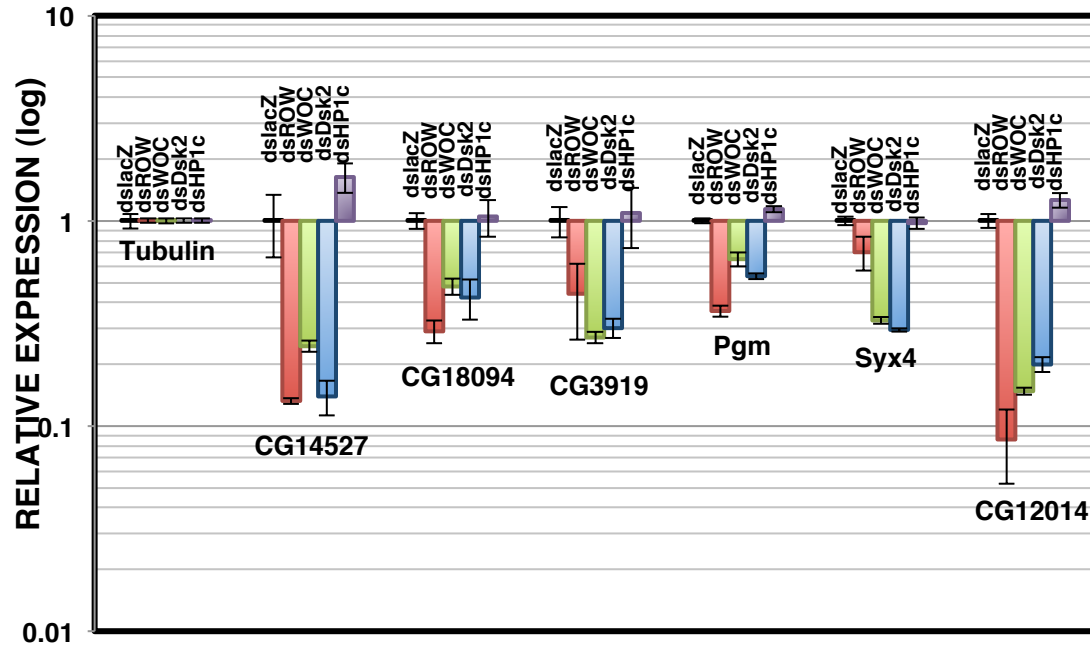
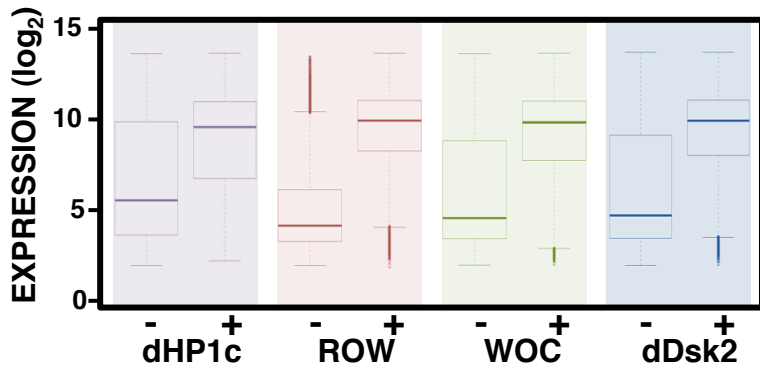
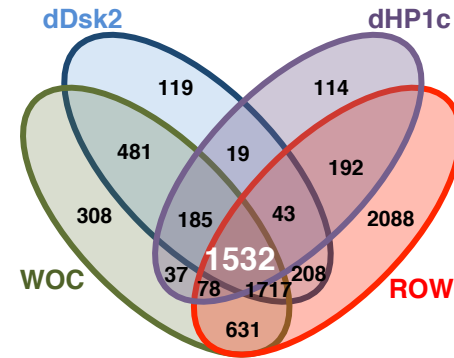
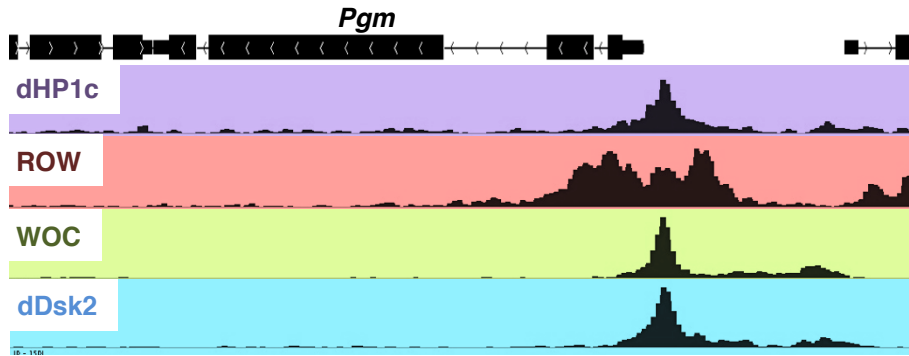
HP1 proteins in transcription regulation

- > *HP1c* localizes to active chromatin domains**
- > *HP1c* forms a complex with *HP1b*, the transcription factors *WOC* and *ROW*, and the ubiquitin receptor protein *Dsk2***

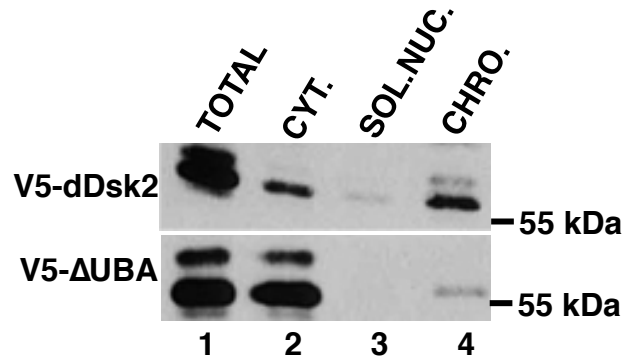
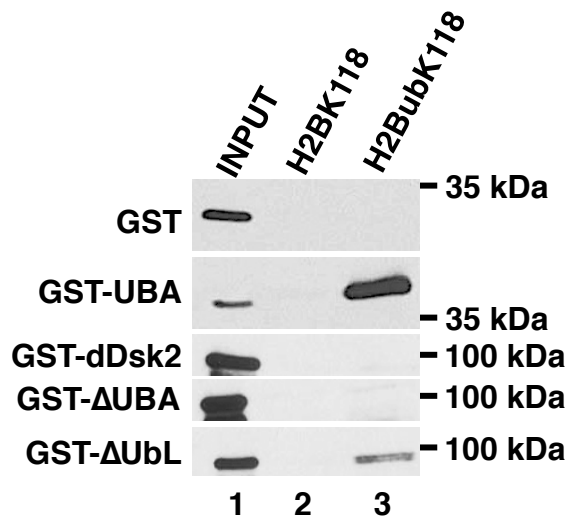
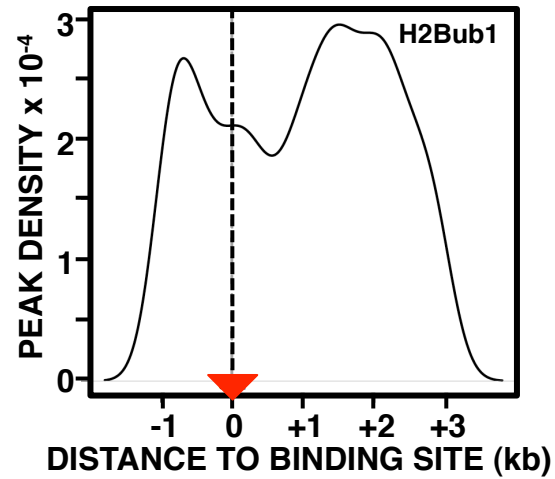


HP1 proteins in transcription regulation

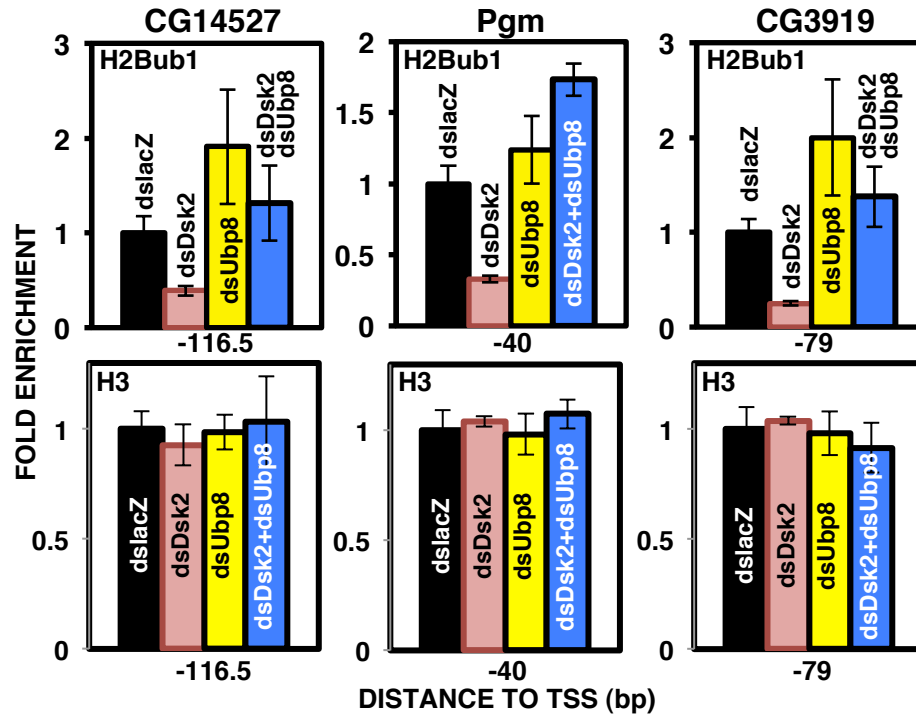
- > **HP1c localizes to active chromatin domains**
- > **HP1c forms a complex with HP1b, the transcription factors WOC and ROW, and the ubiquitin receptor protein Dsk2**
- > **The HP1/WOC/ROW/Dsk complex localizes at TSS of active genes and is required for transcription**



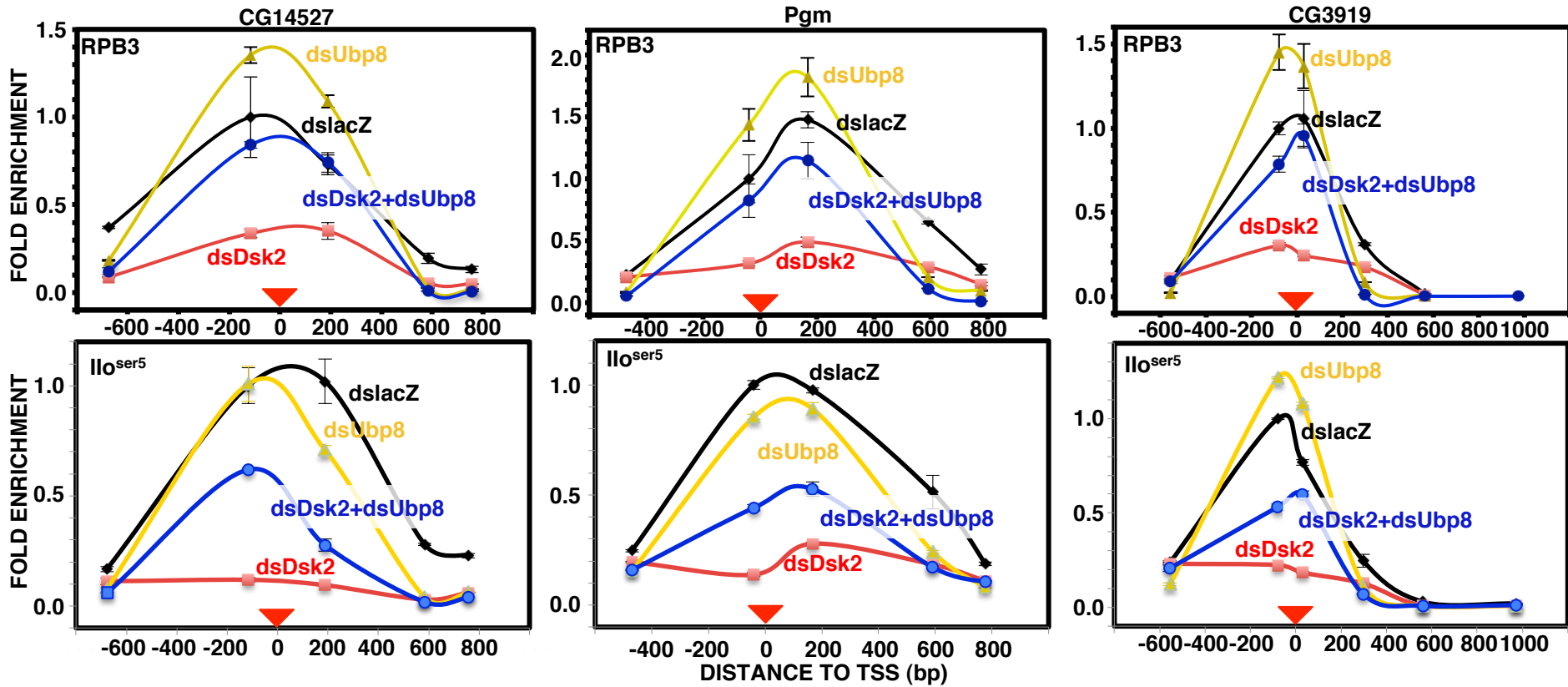
Dsk2 is an ubiquitin receptor protein



Dsk2 is an ubiquitin receptor protein

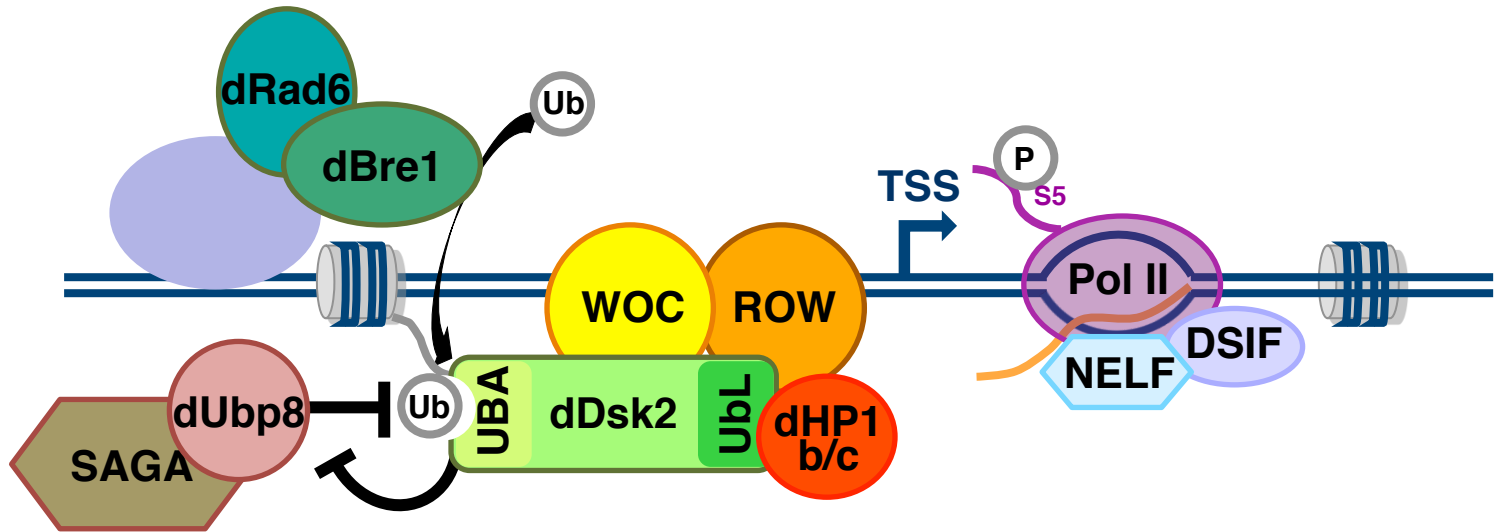


Dsk2 is an ubiquitin receptor protein



HP1 proteins in transcription regulation

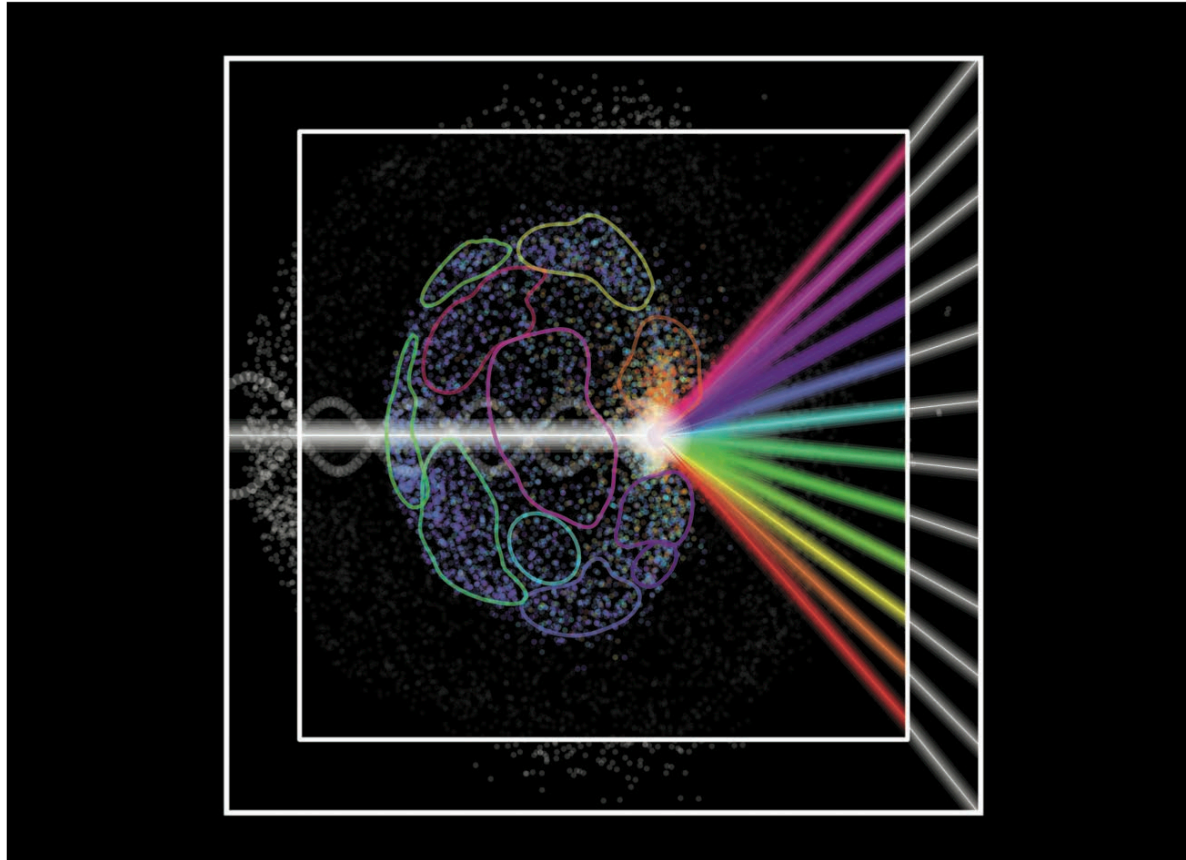
- > **HP1c localizes to active chromatin domains**
- > **HP1c forms a complex with HP1b, the transcription factors WOC and ROW, and the ubiquitin receptor protein Dsk2**
- > **The HP1/WOC/ROW/Dsk2 complex localizes at TSS of active genes and is required for transcription**
- > **Dsk2 binds H2Bub1, prevents its premature deubiquitylation by Ubp8 and regulates RNAPol II pausing**



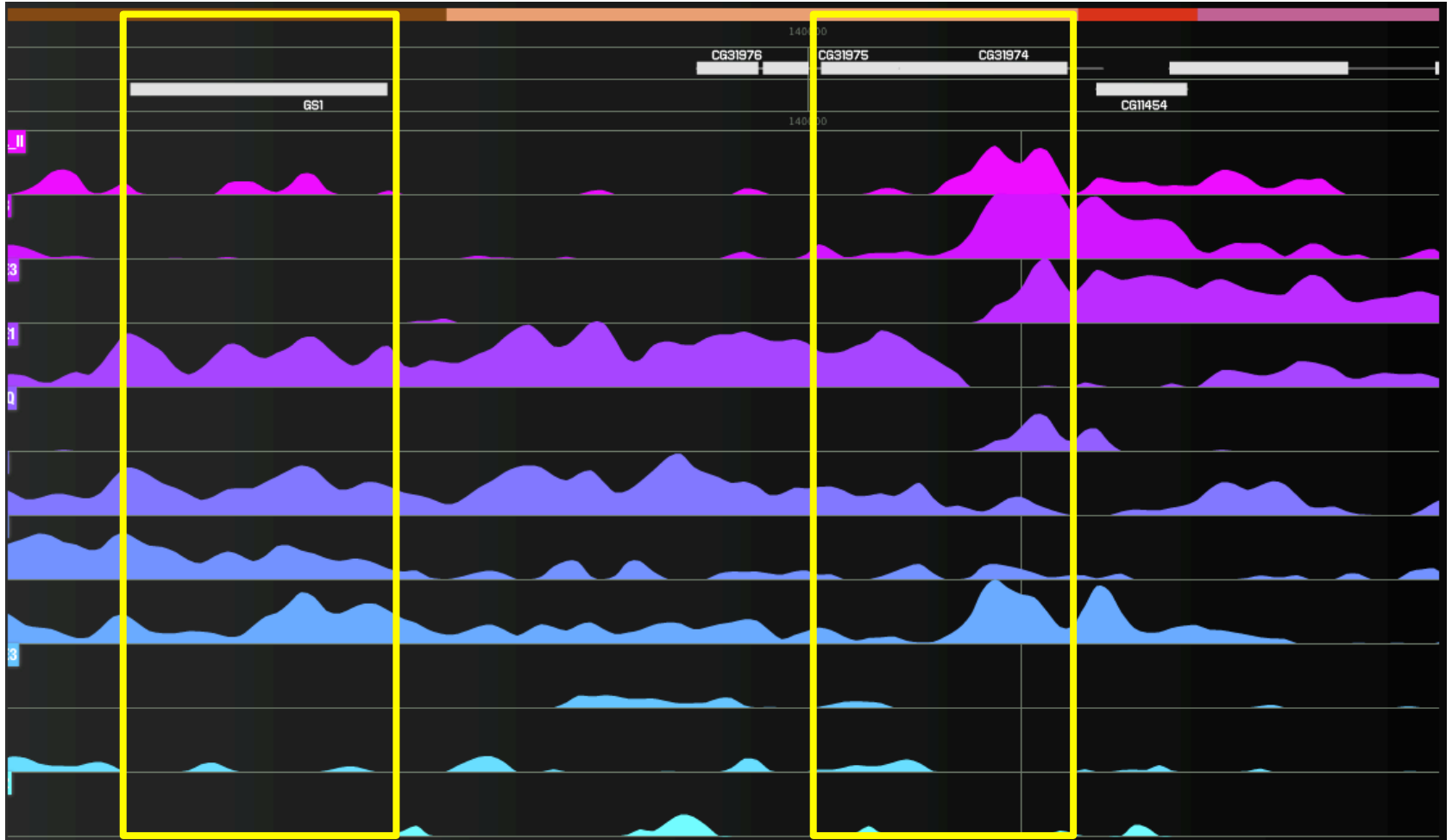
chroGPS^{genes}

Epigenetic states of genes

4 2014 PACIS 2099-2798

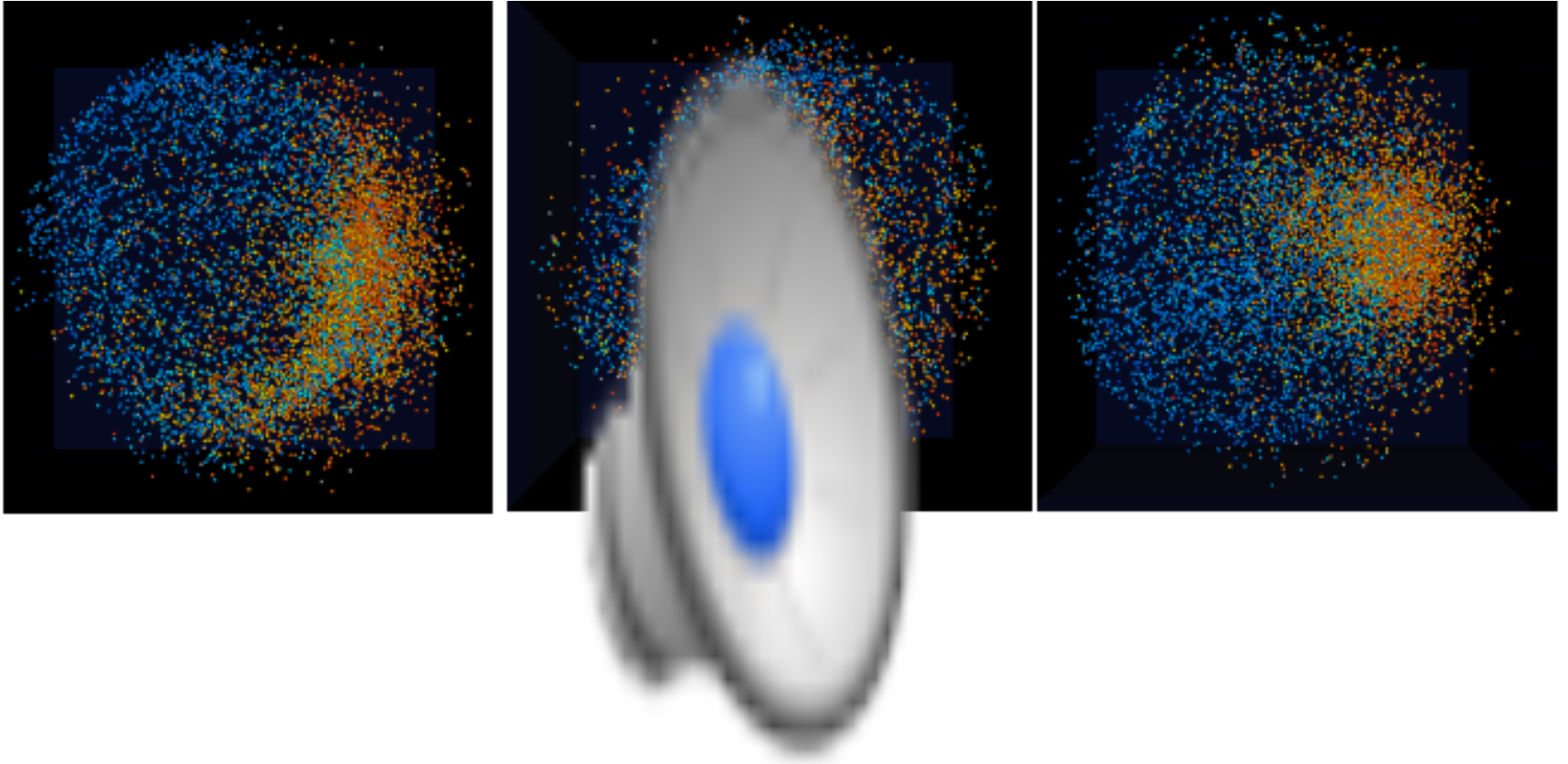


similar factors bound > similar epigenetic regulation (epigene)



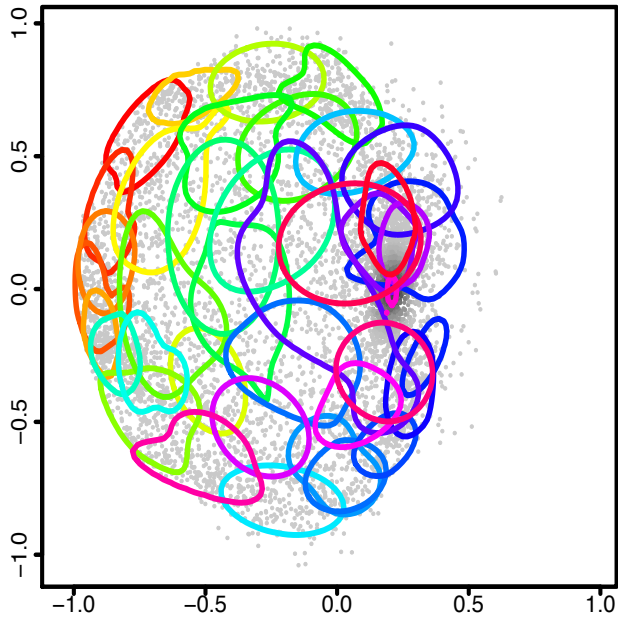
- > metric to measure epigenetic similarity/distance of genes based on factors shared
- > represent in 2D/3D maps using MDS

chroGPS^{genes} maps

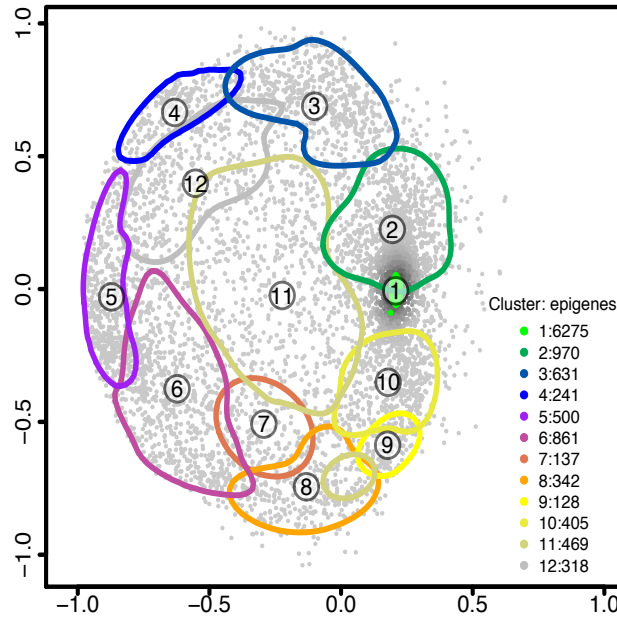


Drosophila S2 cells

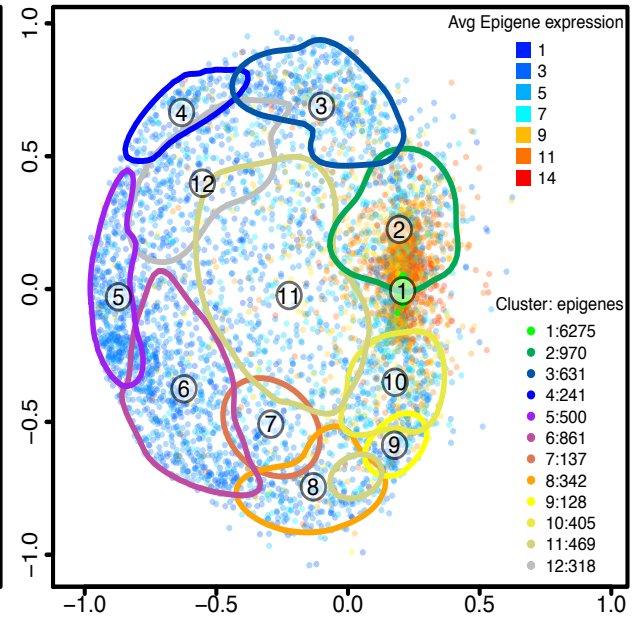
> hierarchical clustering



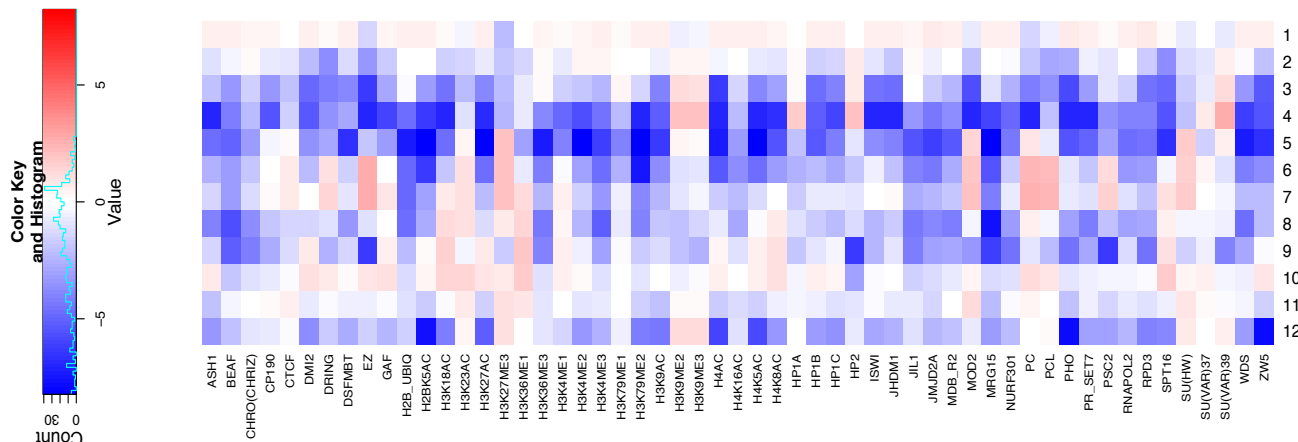
> cluster merge



> annotate expression

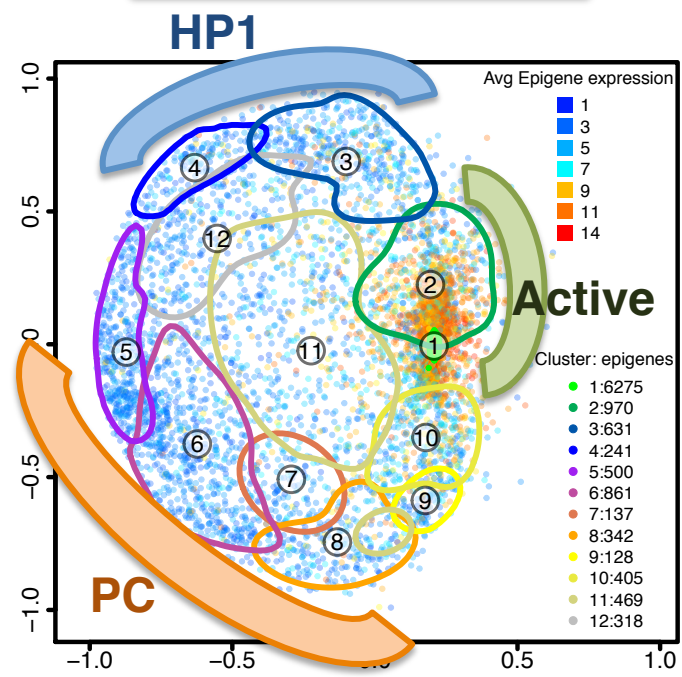


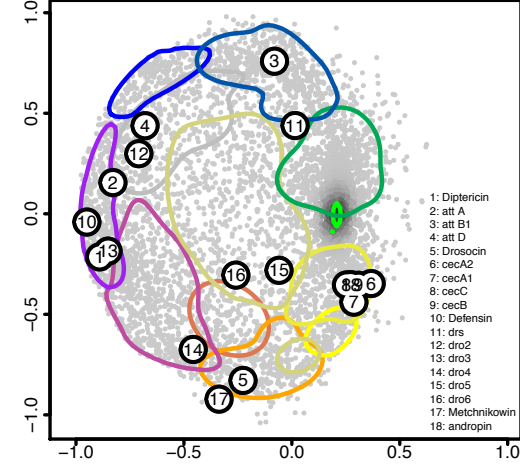
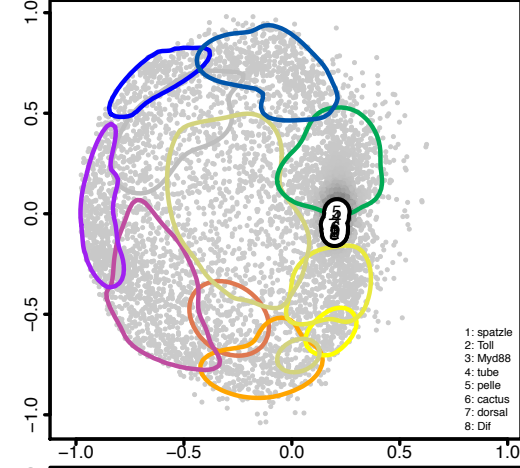
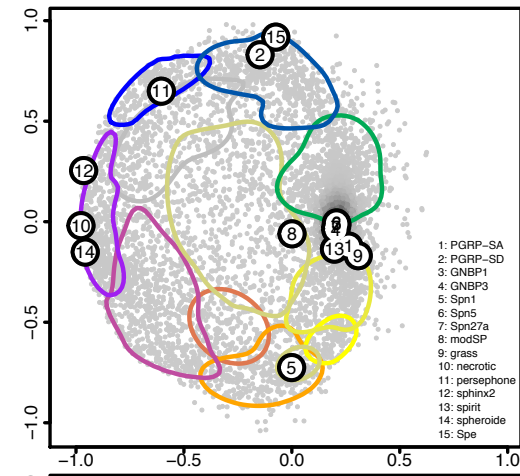
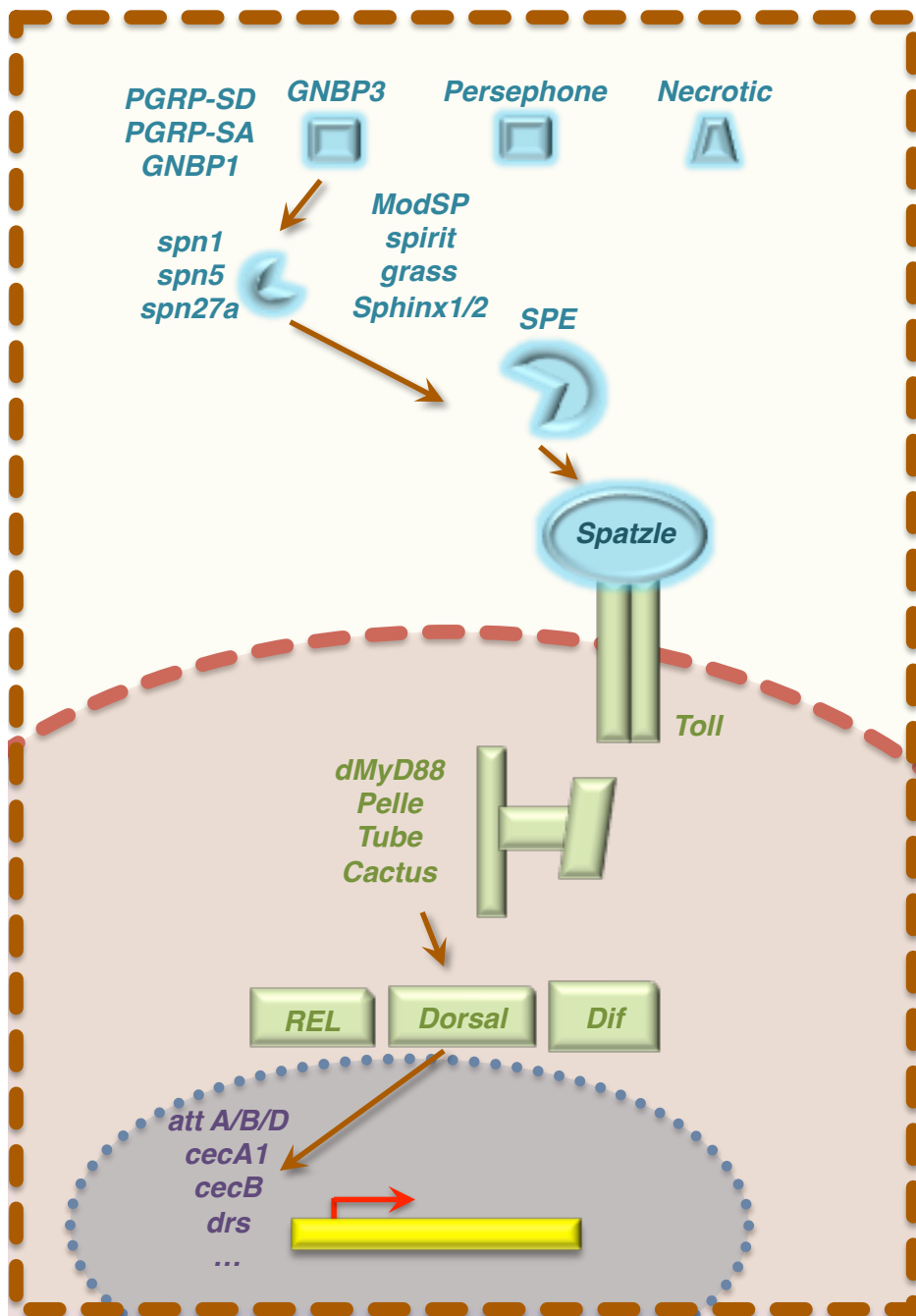
> annotate factor enrichment





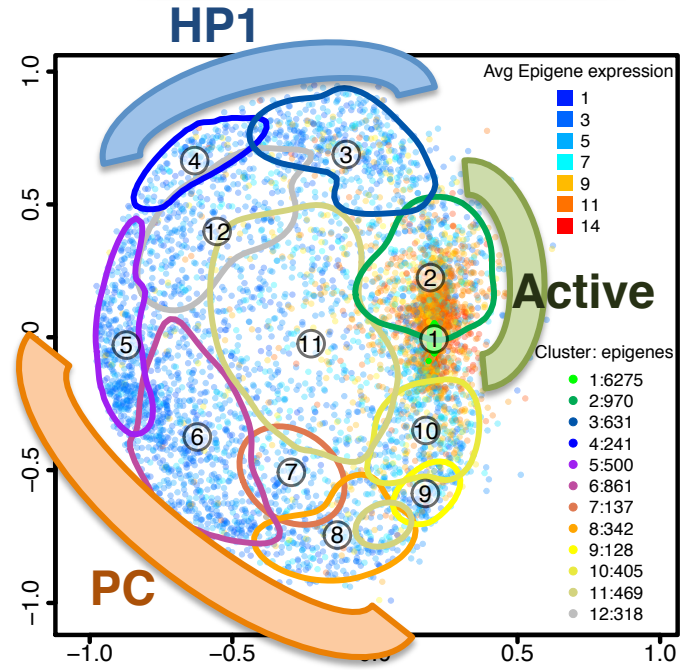
Drosophila S2 cells



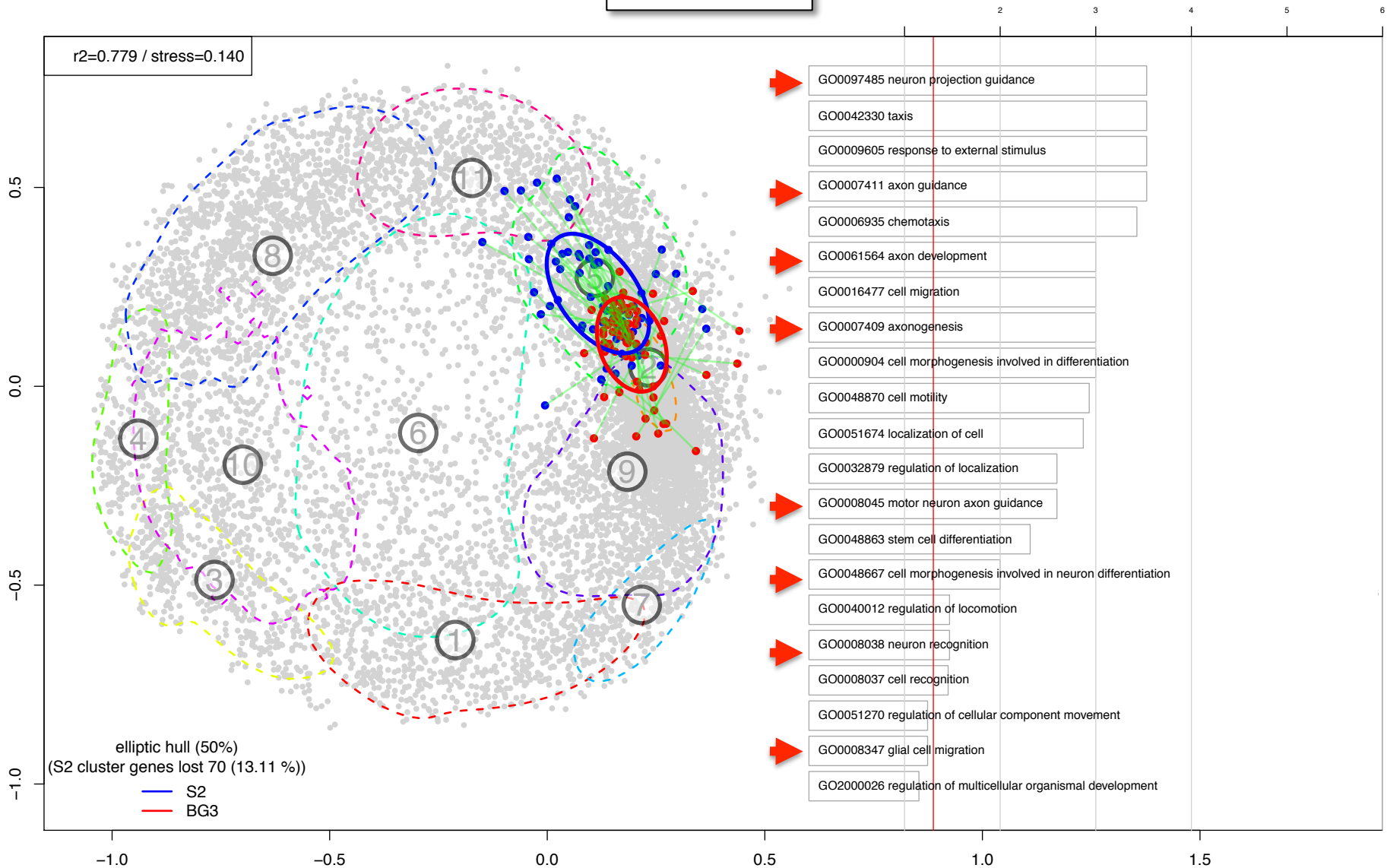




Drosophila BG3 cells

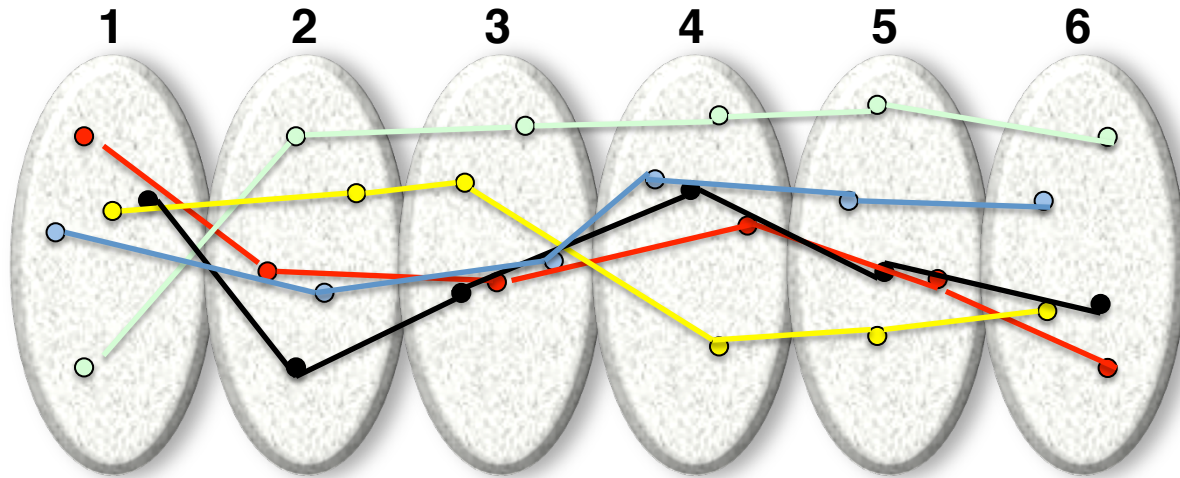


S2 vs BG3



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*Determine the complete set of genetic
&
epigenetic changes associated with a process*

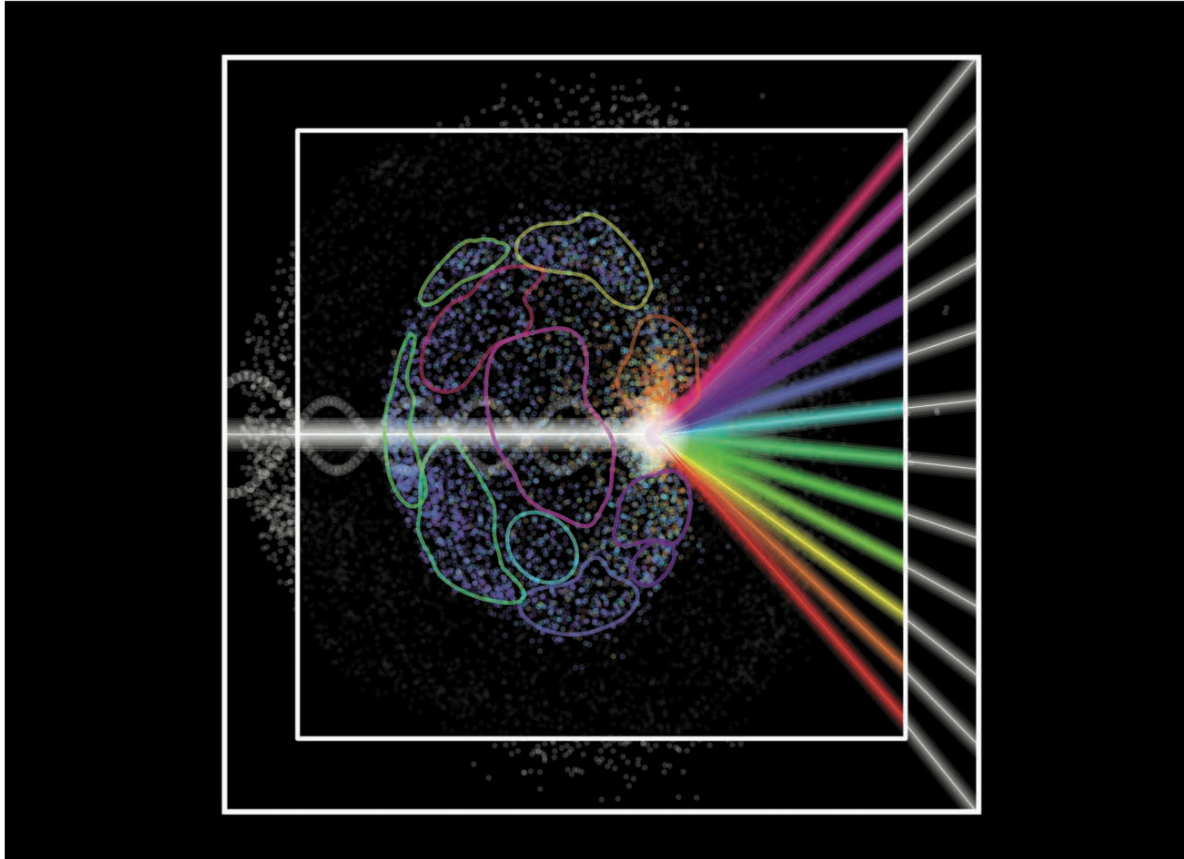


> development & differentiation

> reprogramming

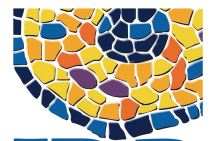
> cancer & disease conditions

chroGPS





CHROMATIN STRUCTURE & FUNCTION



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Postdoct & PhD opportunities!!!!