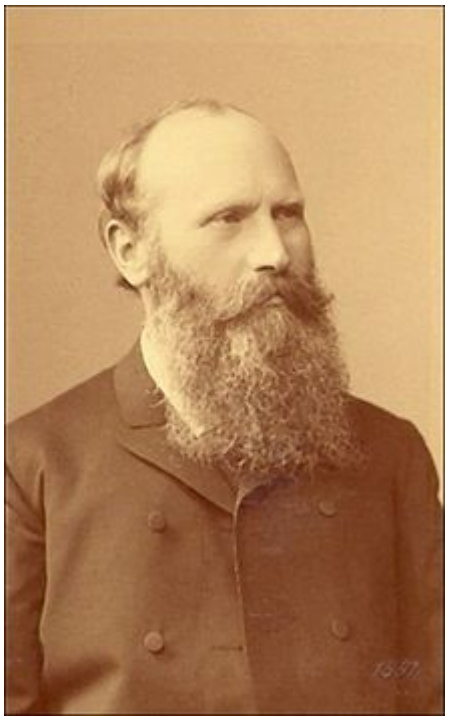
Modyfikacje histonów I ich rola w ustalaniu stanu chromatyny

Bartek Wilczyński

Wykład dla biotechnologów

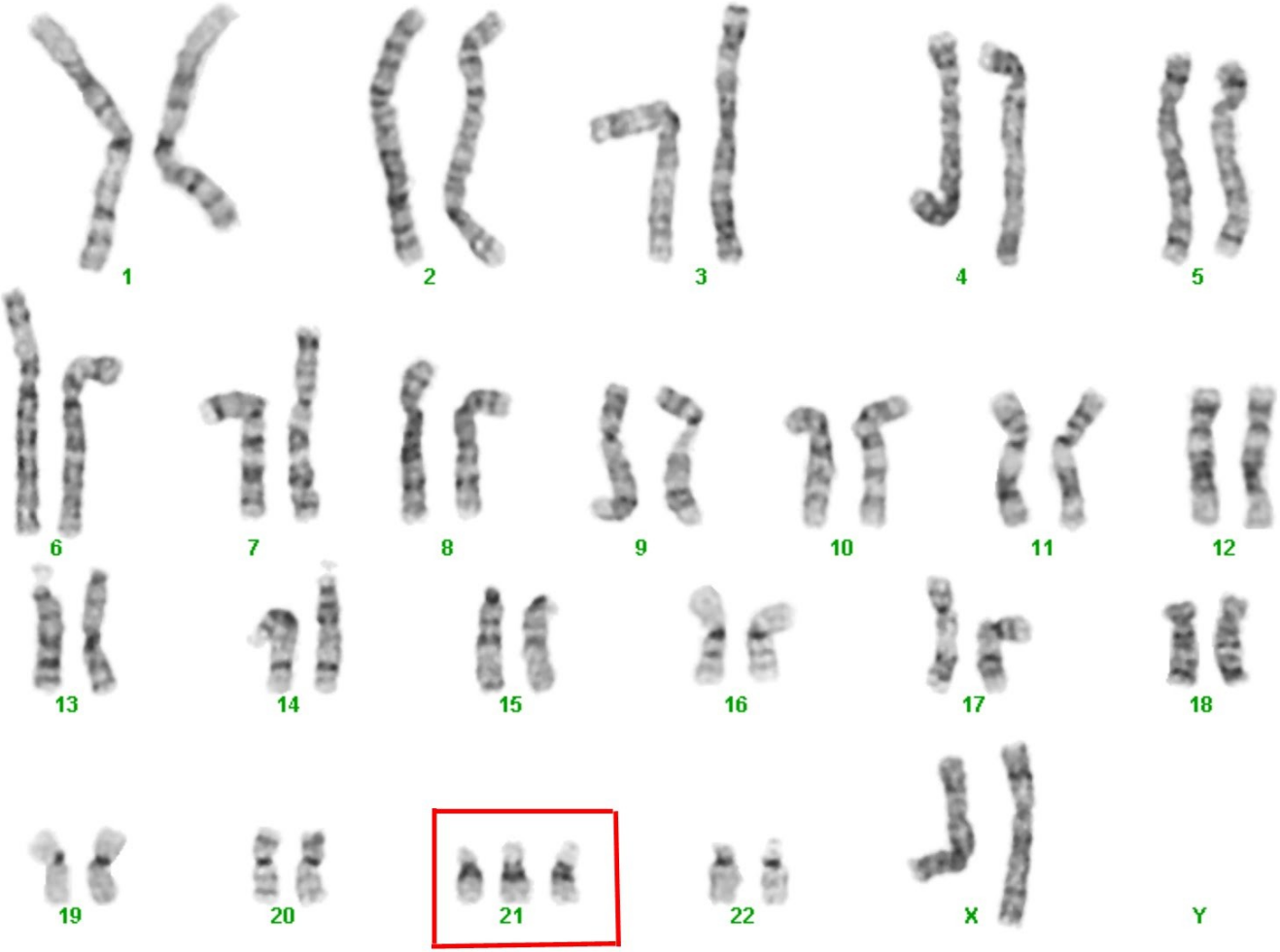
5 grudnia 2013

Chromatyna

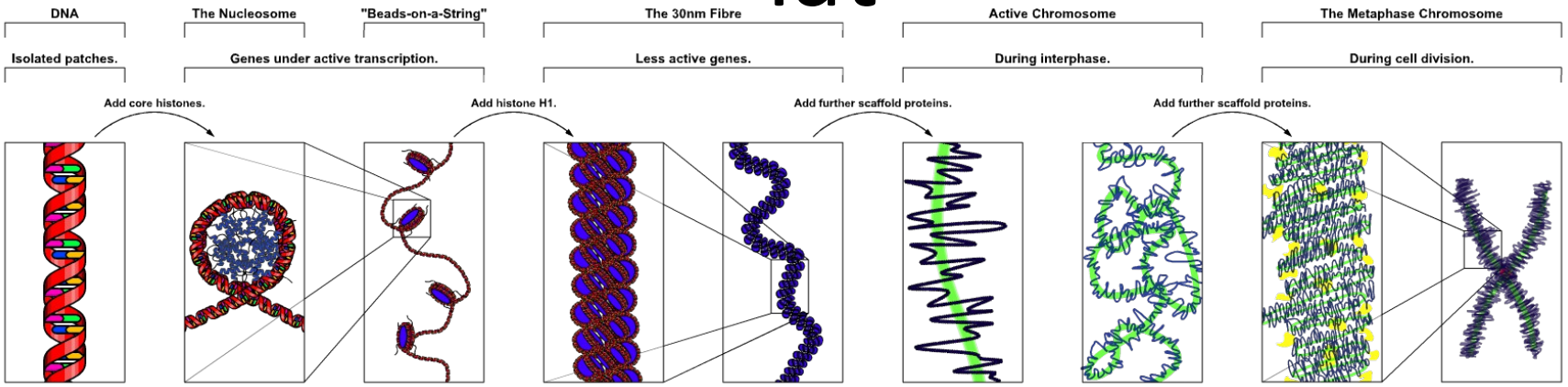


Heinrich Wilhelm Gottfried von Waldeyer-Hartz, 1891

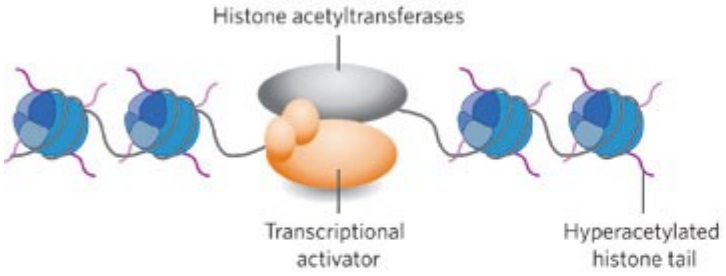
Nazwał chromatynę i chromosomy w 1888



Chromatyna przez następne 100 lat

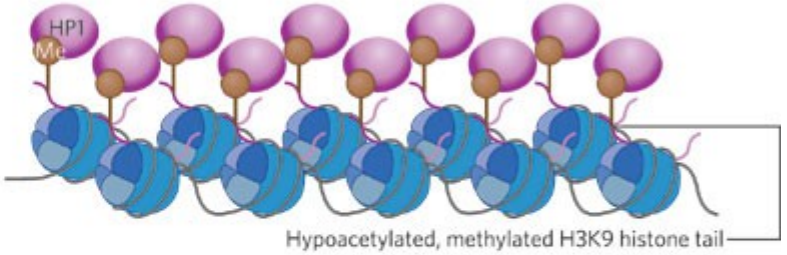


Euchromatin



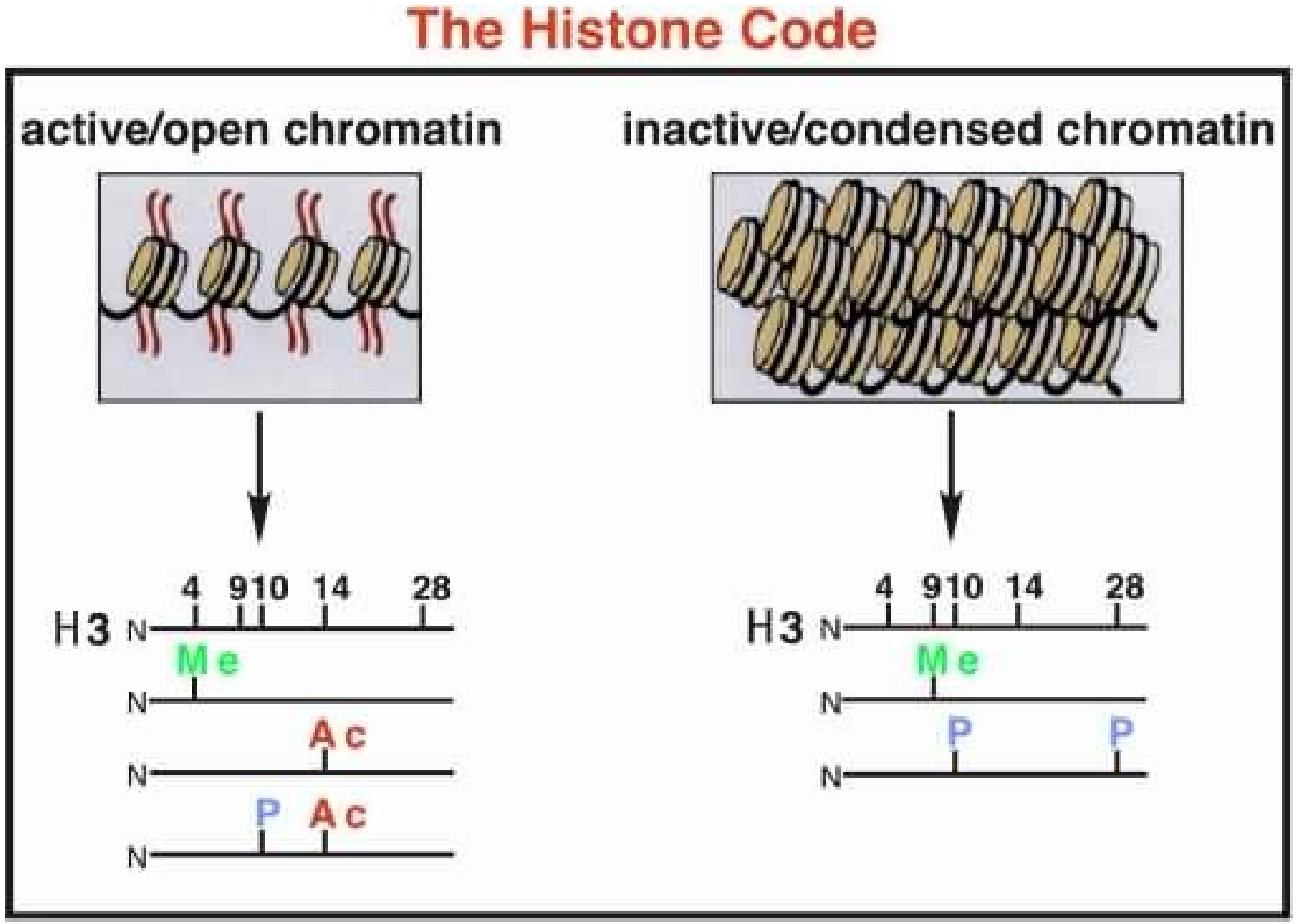
- Less condensed
- At chromosome arms
- Contains unique sequences
- Gene-rich
- Replicated throughout S phase
- Recombination during meiosis

Heterochromatin

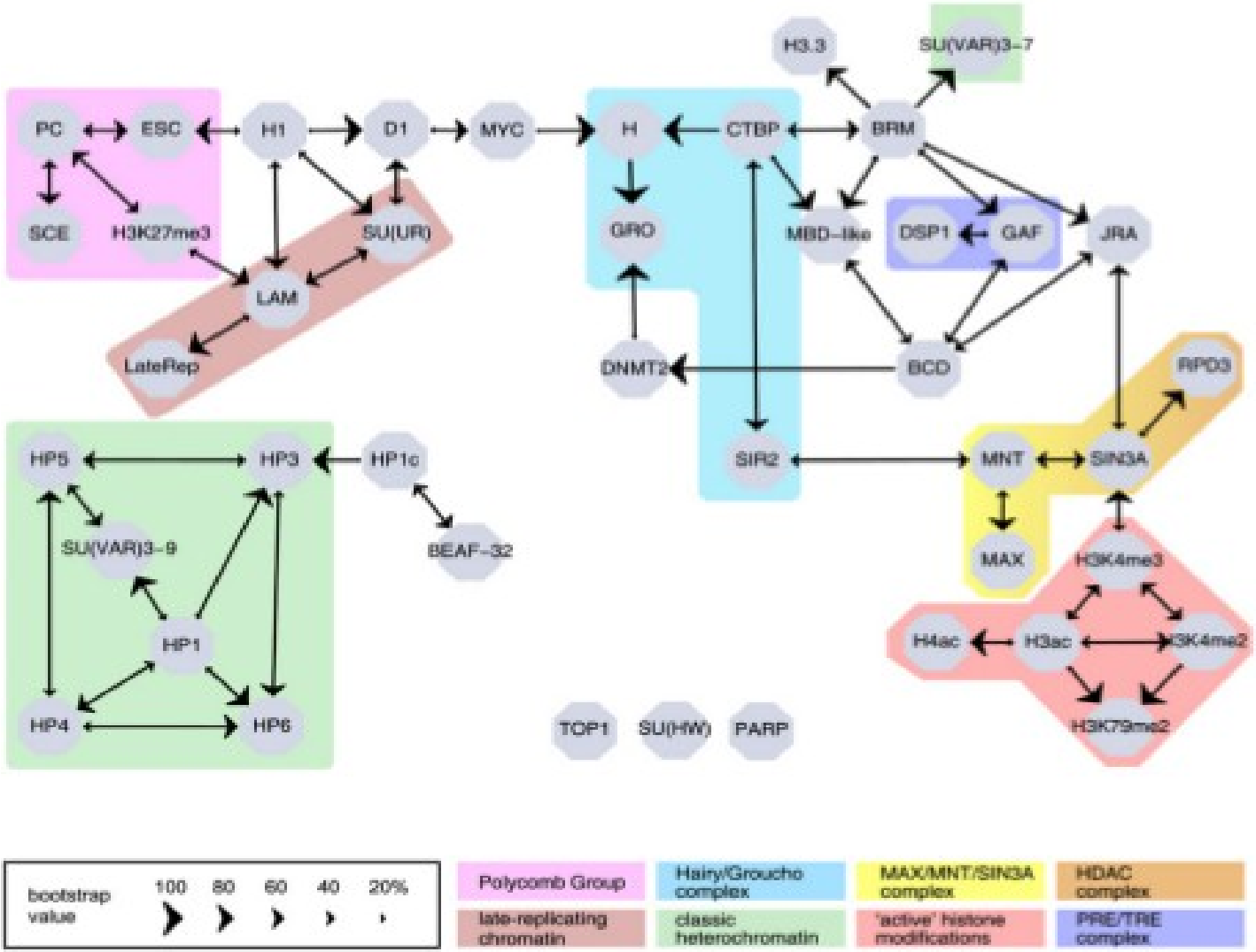


- Highly condensed
- At centromeres and telomeres
- Contains repetitious sequences
- Gene-poor
- Replicated in late S phase
- No meiotic recombination

Modyfikacje histonów a chromatyna



Sieci interakcji chromatynowych



Domeny chromatynowe

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PLoS GENETICS

Global Chromatin Domain Organization of the *Drosophila* Genome

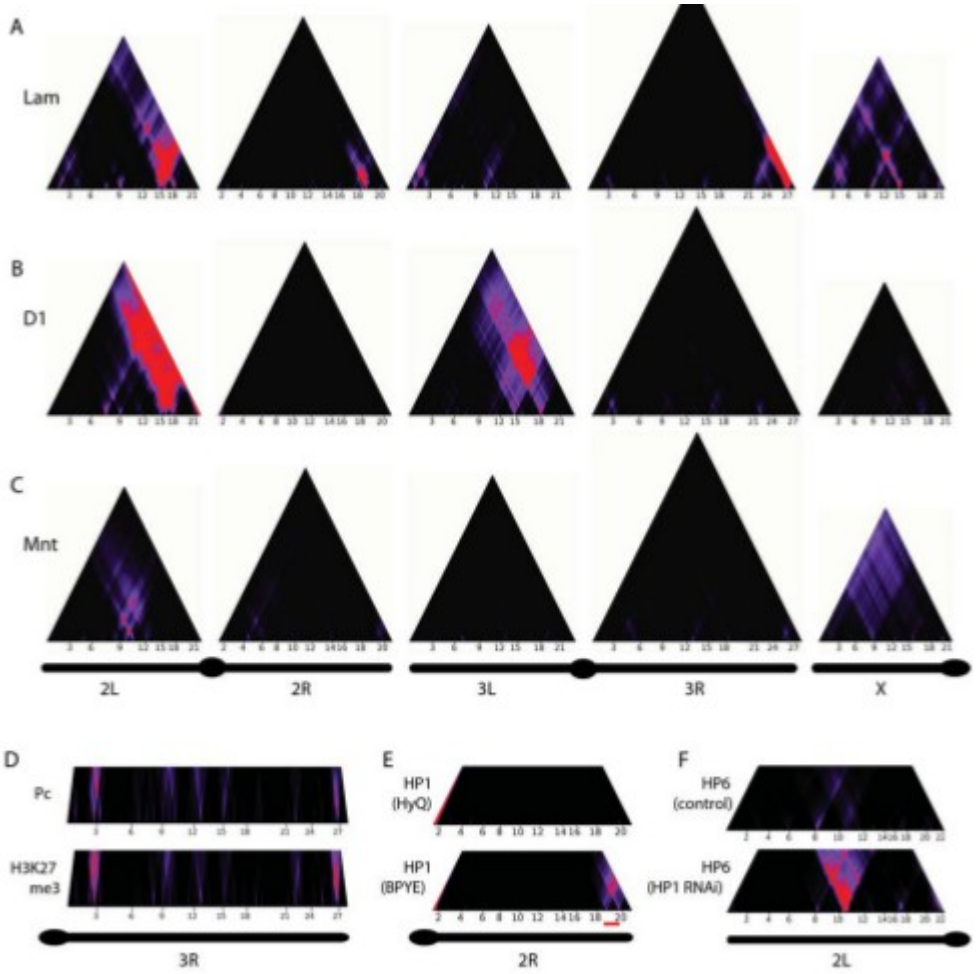
Elzo de Wit[1¤a], Ulrich Braunschweig[1], Frauke Greil[1¤b], Harmen J. Bussemaker[2*], Bas van Steensel[1*]

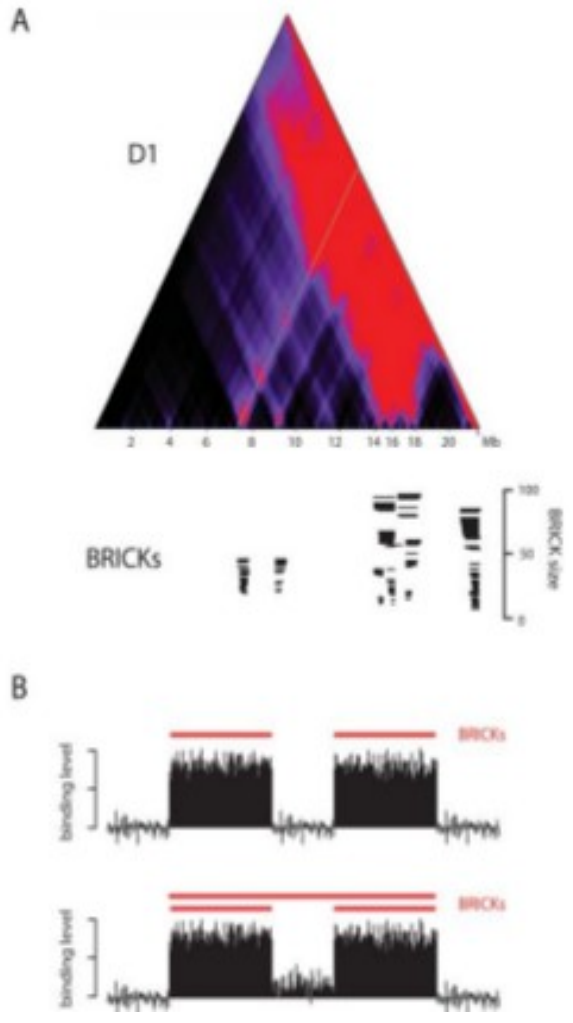
1 Department of Molecular Biology, Netherlands Cancer Institute, Amsterdam, The Netherlands, 2 Department of Biological Sciences, Columbia University, New York, New York, United States of America

Abstract

In eukaryotes, neighboring genes can be packaged together in specific chromatin structures that ensure their coordinated expression. Examples of such multi-gene chromatin domains are well-documented, but a global view of the chromatin organization of eukaryotic genomes is lacking. To systematically identify multi-gene chromatin domains, we constructed a compendium of genome-scale binding maps for a broad panel of chromatin-associated proteins in *Drosophila melanogaster*. Next, we computationally analyzed this compendium for evidence of multi-gene chromatin domains using a novel statistical segmentation algorithm. We find that at least 50% of all fly genes are organized into chromatin domains, which often consist of dozens of genes. The domains are characterized by various known and novel combinations of chromatin proteins. The genes in many of the domains are coregulated during development and tend to have similar biological functions. Furthermore, during evolution fewer chromosomal rearrangements occur inside chromatin domains than outside domains. Our results indicate that a substantial portion of the *Drosophila* genome is packaged into functionally coherent, multi-gene chromatin domains. This has broad mechanistic implications for gene regulation and genome evolution.

Wizualizacja domen chromatynowych





Stan chromatyny
a modyfikacje histonów

Vol 448|2 August 2007|doi:10.1038/nature06008 nature

ARTICLES

Genome-wide maps of chromatin state in pluripotent and lineage-committed cells

Tarjei S. Mikkelsen[1,2], Manching Ku[1,4], David B. Jaffe[1], Biju Issac[1,4], Erez Lieberman[1,2], Georgia Giannoukos[1], Pablo Alvarez[1], William Brockman[1], Tae-Kyung Kim[5], Richard P. Koche[1,2,4], William Lee[1], Eric Mendenhall[1,4], Aisling O'Donovan[4], Aviva Presser[1], Carsten Russ[1], Xiaohui Xie[1], Alexander Meissner[3], Marius Wernig[3], Rudolf Jaenisch[3], Chad Nusbaum[1], Eric S. Lander[1,3*] & Bradley E. Bernstein[1,4,6*]

We report the application of single-molecule-based sequencing technology for high-throughput profiling of histone modifications in mammalian cells. By obtaining over four billion bases of sequence from chromatin immunoprecipitated DNA, we generated genome-wide chromatin-state maps of mouse embryonic stem cells, neural progenitor cells and embryonic fibroblasts. We find that lysine 4 and lysine 27 trimethylation effectively discriminates genes that are expressed, poised for expression, or stably repressed, and therefore reflect cell state and lineage potential. Lysine 36 trimethylation marks primary coding and non-coding transcripts, facilitating gene annotation. Trimethylation of lysine 9 and lysine 20 is detected at satellite, telomeric and active long-terminal repeats, and can spread into proximal unique sequences. Lysine 4 and lysine 9 trimethylation marks imprinting control regions. Finally, we show that chromatin state can be read in an allele-specific manner by using single nucleotide polymorphisms. This study provides a framework for the application of comprehensive chromatin profiling towards characterization of diverse mammalian cell populations.

Kolory chromatyny

Cell

Systematic Protein Location Mapping Reveals Five Principal Chromatin Types in *Drosophila* Cells

Guillaume J. Filion,[1,5] Joke G. van Bemmel,[1,5] Ulrich Braunschweig,[1,5] Wendy Talhout,[1] Jop Kind,[1] Lucas D. Ward,[3,4,6] Wim Brugman,[2] Inês J. de Castro,[1,7] Ron M. Kerkhoven,[2] Harmen J. Bussemaker,[3,4] and Bas van Steensel[1,*]

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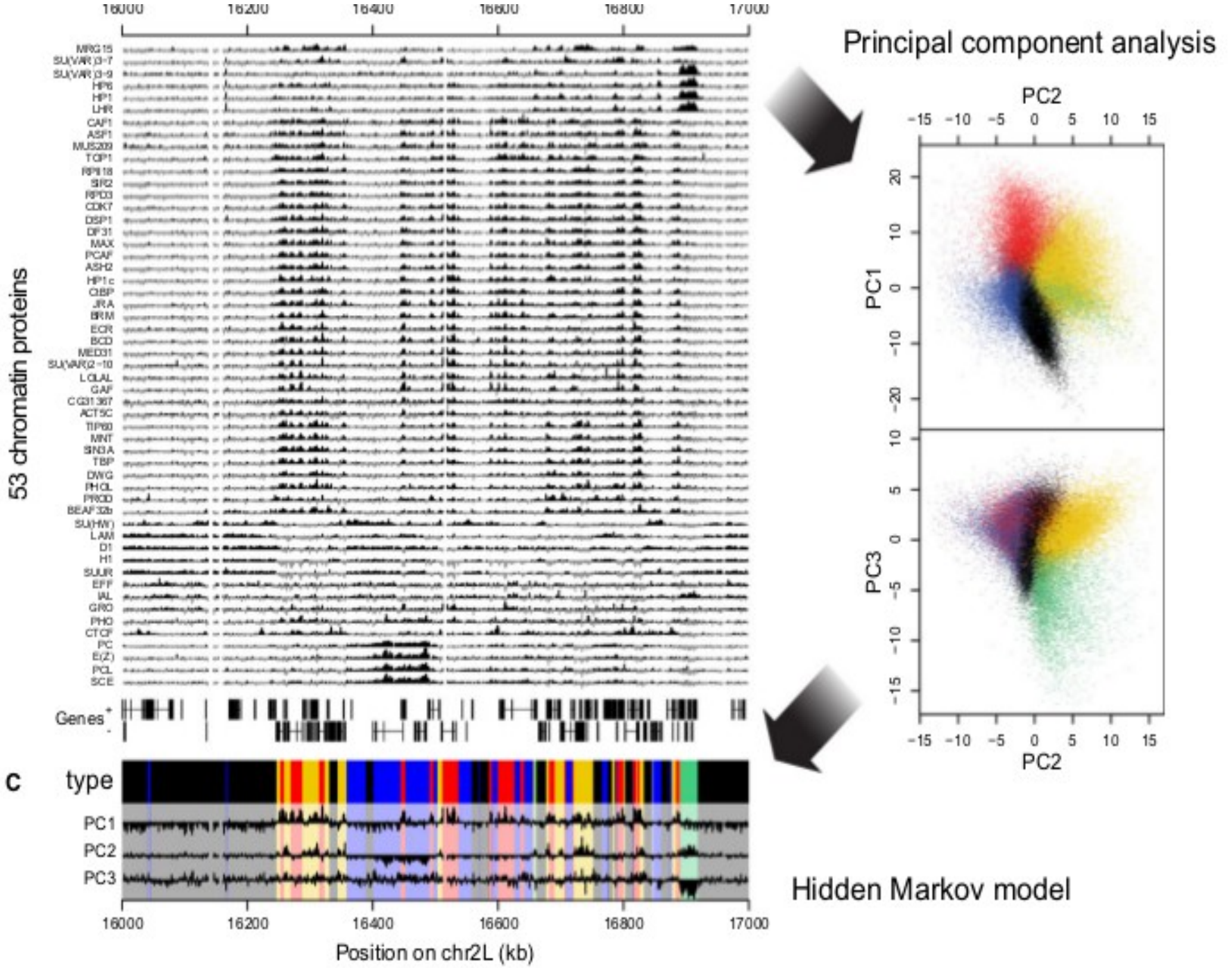
DOI 10.1016/j.cell.2010.09.009


53 chromatin proteins
Genes
c
type
PC1
PC2
PC3
16000
16200
16400
16600
16800
17000
Position on chr2L (kb)
Principal component analysis
PC2
PC1
PC3
Hidden Markov model

Ukryte stany chromatyny

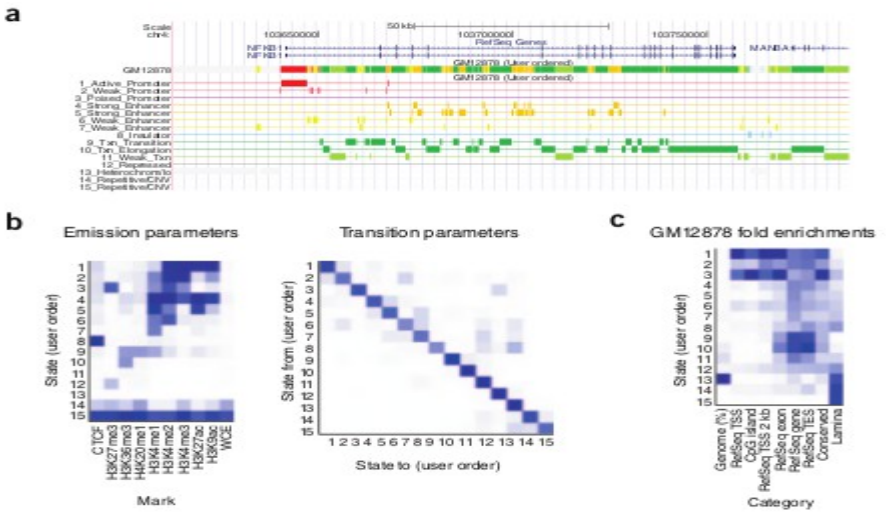
_computational BIOLOGY

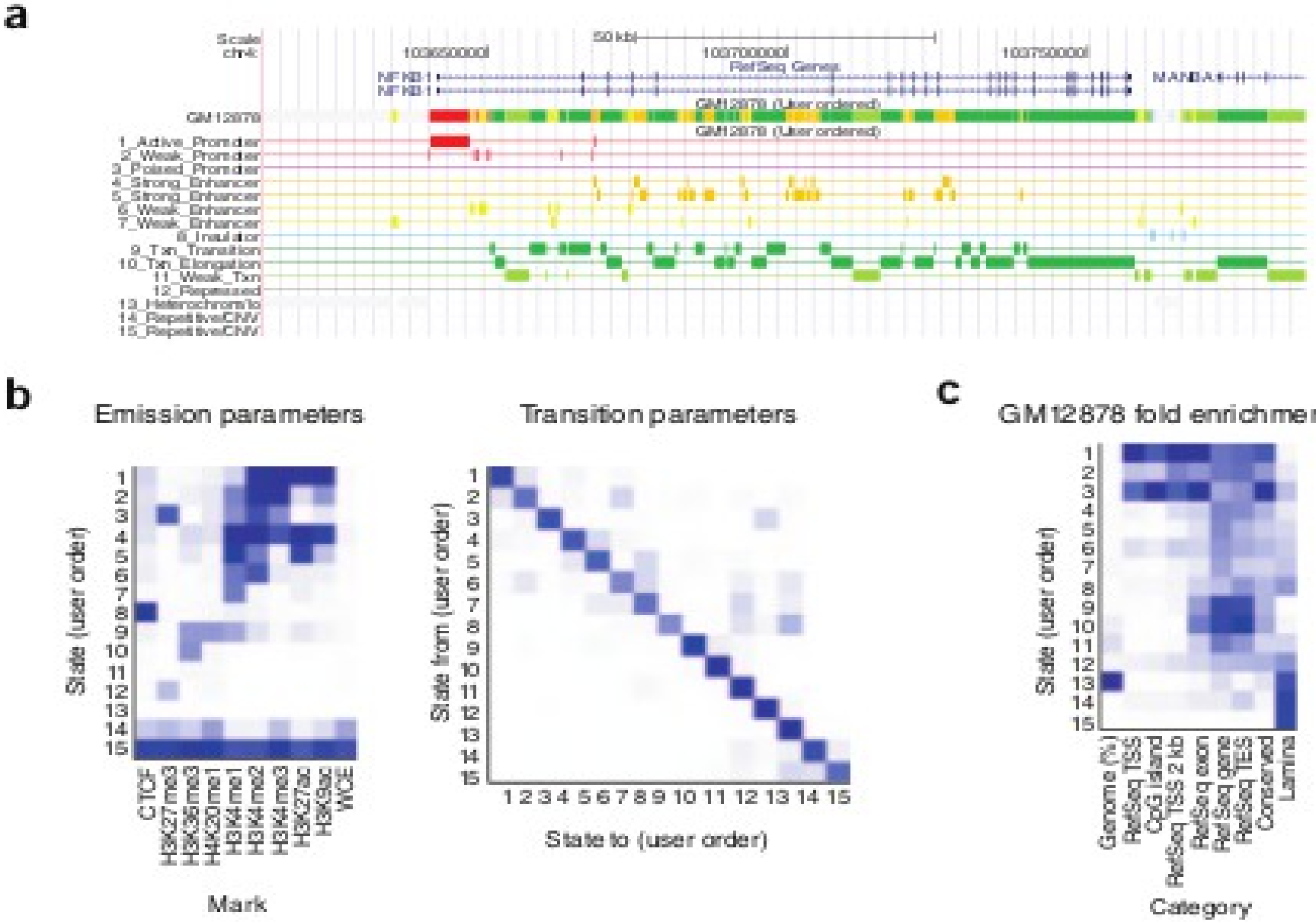
ANALYSIS

Discovery and characterization of chromatin states for systematic annotation of the human genome

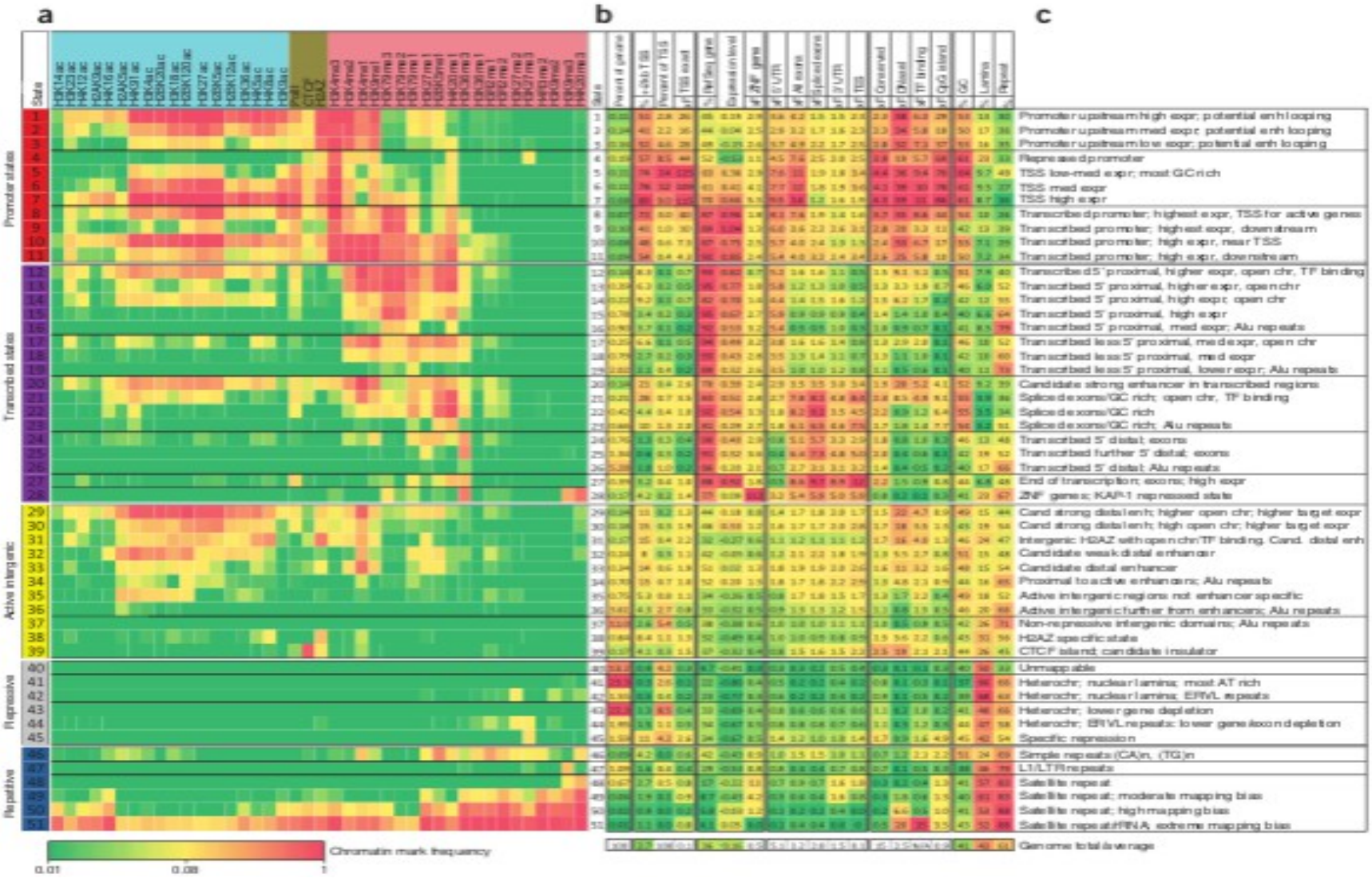
Jason Ernst[1,2] & Manolis Kellis[1,2]

A plethora of epigenetic modifications have been described in the human genome and shown to play diverse roles in ge regulation, cellular differentiation and the onset of disease. Although individual modifications have been linked to the activity levels of various genetic functional elements, their combinatorial patterns are still unresolved and their potenti for systematic *de novo* genome annotation remains untappe Here, we use a multivariate Hidden Markov Model to reveal 'chromatin states' in human T cells, based on recurrent and spatially coherent combinations of chromatin marks. We de 51 distinct chromatin states, including promoter-associate transcription-associated, active intergenic, large-scale repr and repeat-associated states. Each chromatin state shows specific enrichments in functional annotations, sequence motifs and specific experimentally observed characteristics suggesting distinct biological roles. This approach provides complementary functional annotation of the human genom that reveals the genome-wide locations of diverse classes o epigenetic function.

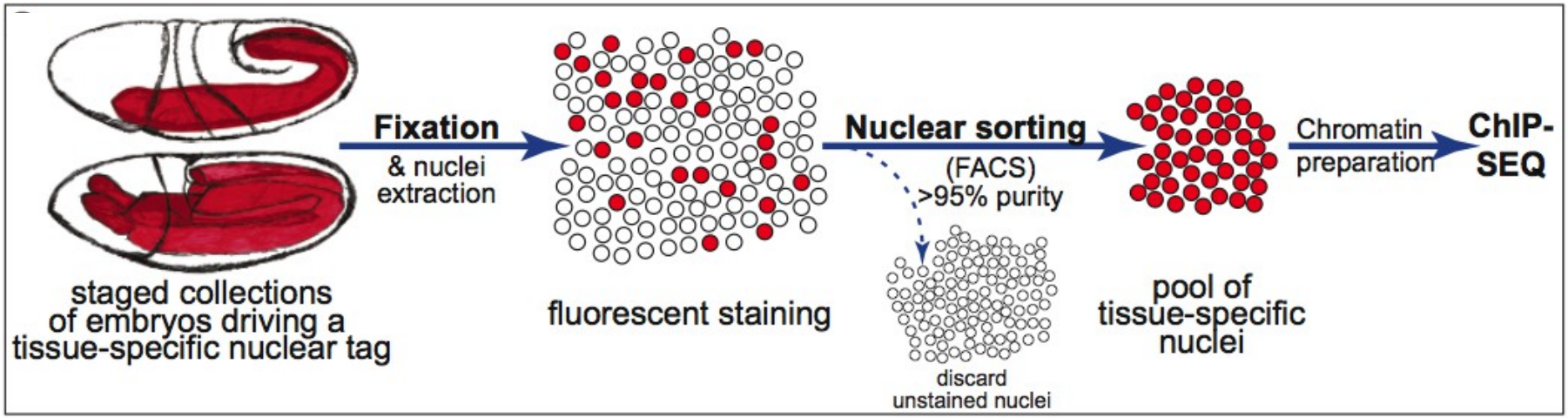


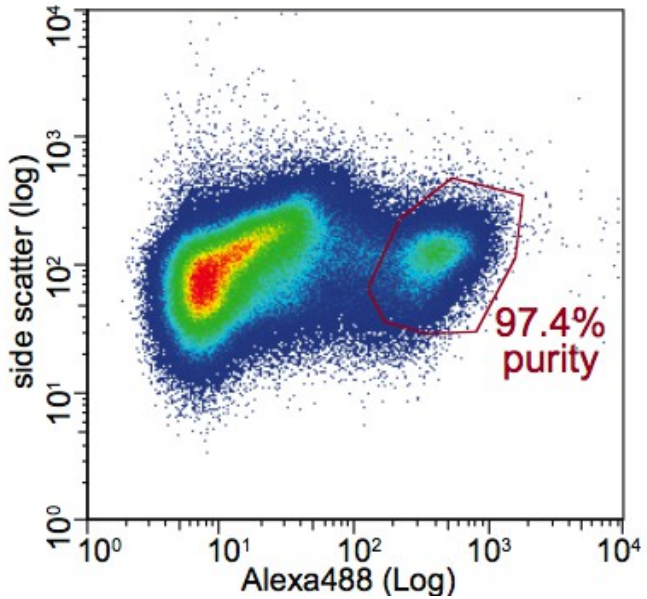

a
Scale
chr4:
50 kb
1006500000
1007000000
1007500000
RefSeq Genes
NFKB1
NFKB1
MANBAL
GM12878 (User ordered)
GM12878
GM12878 (User ordered)
1_Active_Promoter
2_Weak_Promoter
3_Poised_Promoter
4_Strong_Enhancer
5_Strong_Enhancer
6_Weak_Enhancer
7_Weak_Enhancer
8_Insulator
9_Txn_Transition
10_Txn_Elongation
11_Weak_Txn
12_Repressed
13_Heterochromatin
14_RepetitiveCNV
15_RepetitiveCNV
b
Emission parameters
State (user order)
CTCF
H3K27me3
H3K36me3
H4K20me1
H3K4me1
H3K4me2
H3K4me3
H3K27ac
H3K9ac
WCE
Mark
Transition parameters
State from (user order)
State to (user order)
c
GM12878 fold enrichments
State (user order)
Genome (%)
RefSeq TSS
CpG Island
RefSeq TSS 2 kb
RefSeq exon
RefSeq gene
RefSeq TES
Conserved
Lamina
Category

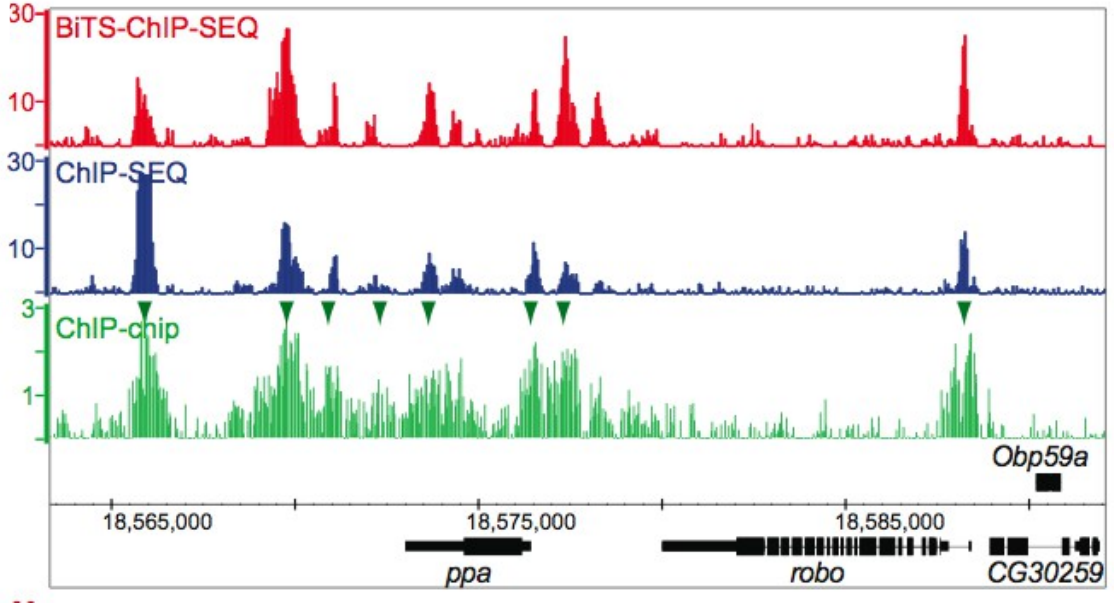
Korelacje ze znanymi anotacjami



Modyfikacje specyficzne dla tkanki







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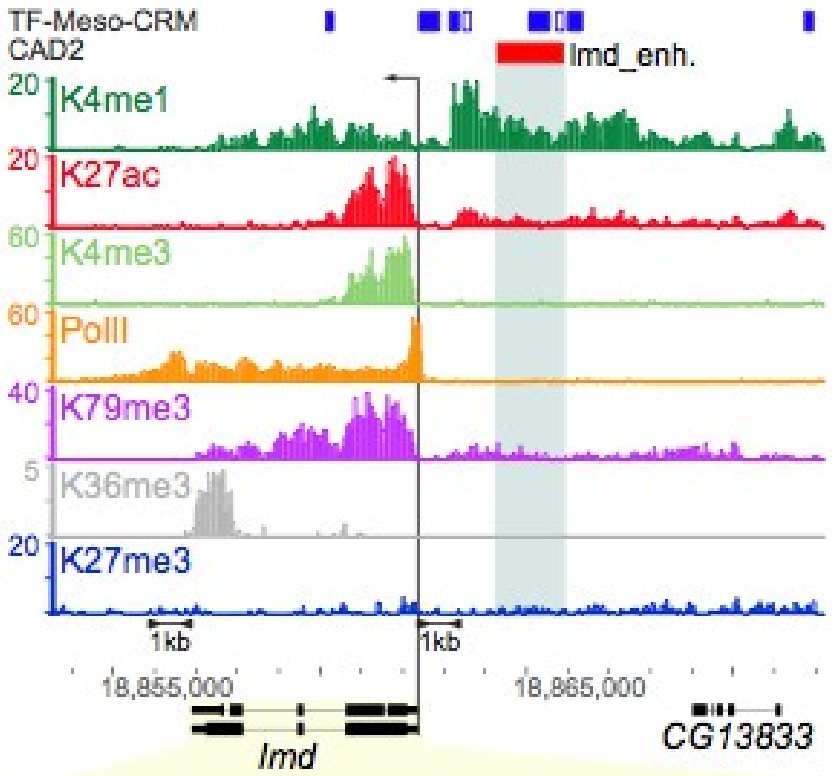
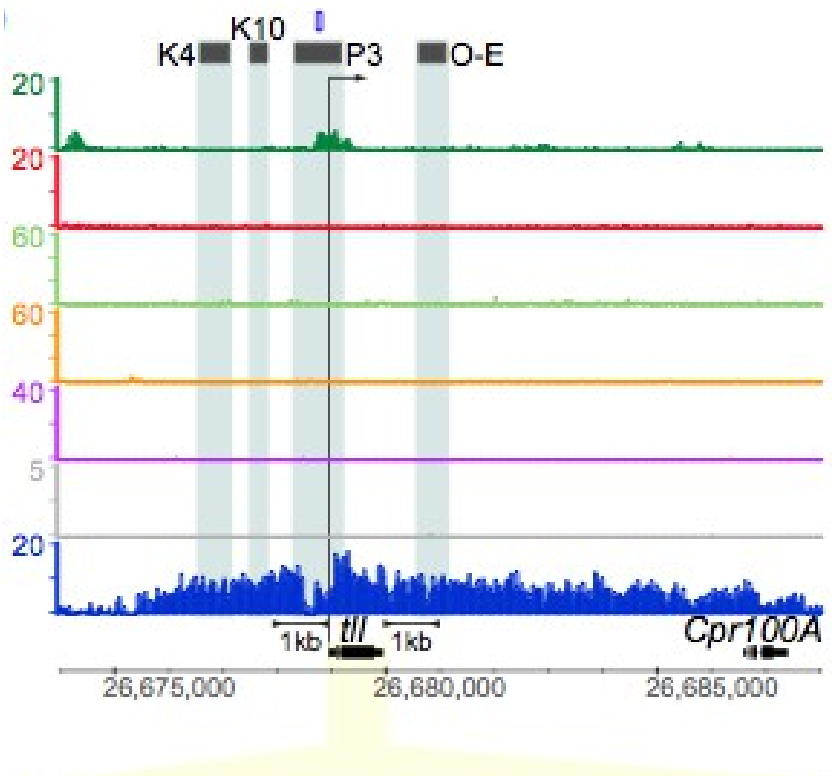
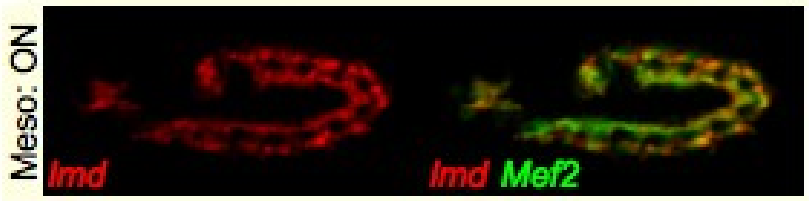
Jak wygląda obraz dla znanych genów







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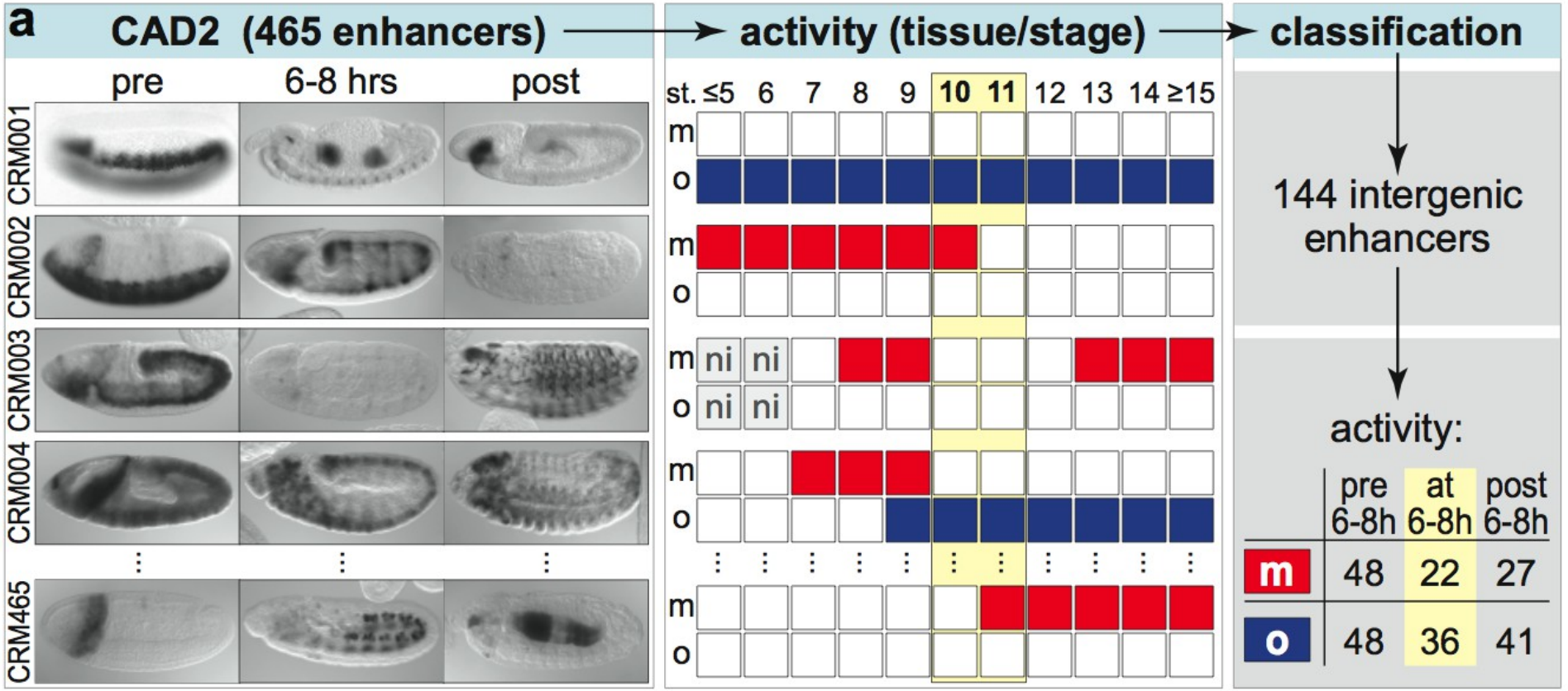
Konstrukcja zbioru uczącego



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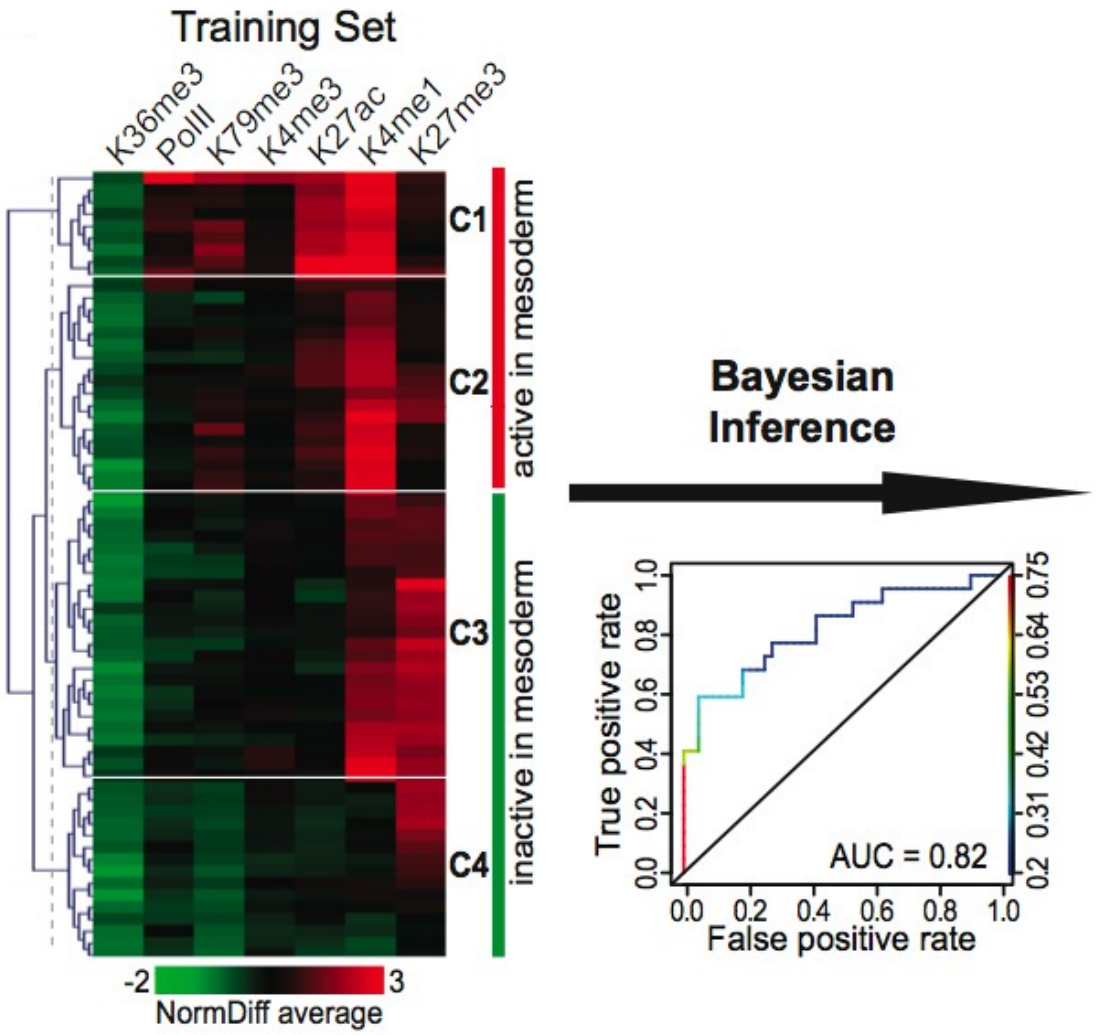
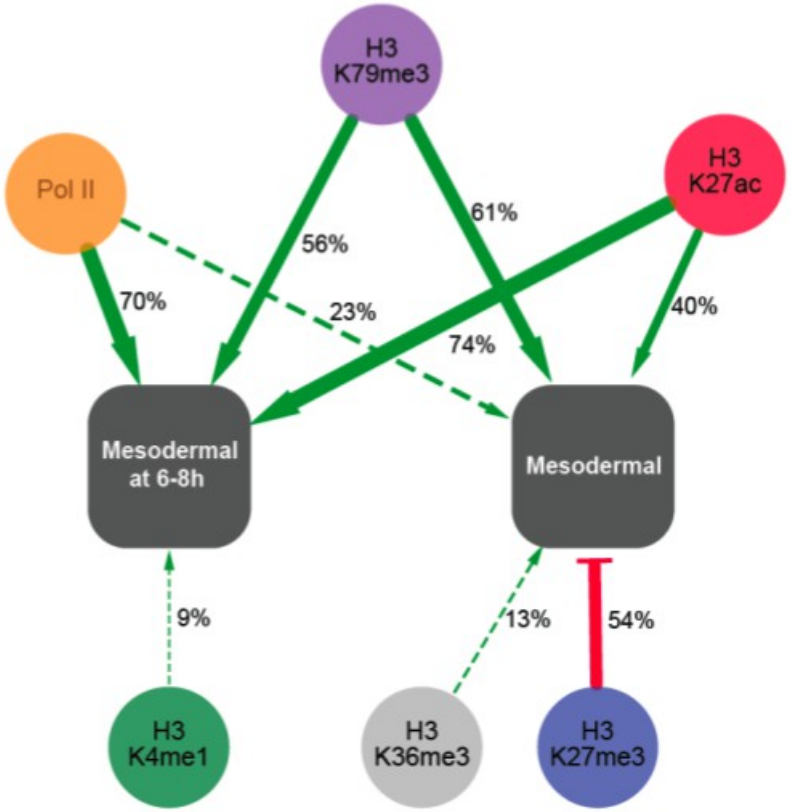
Stworzenie klasyfikatora





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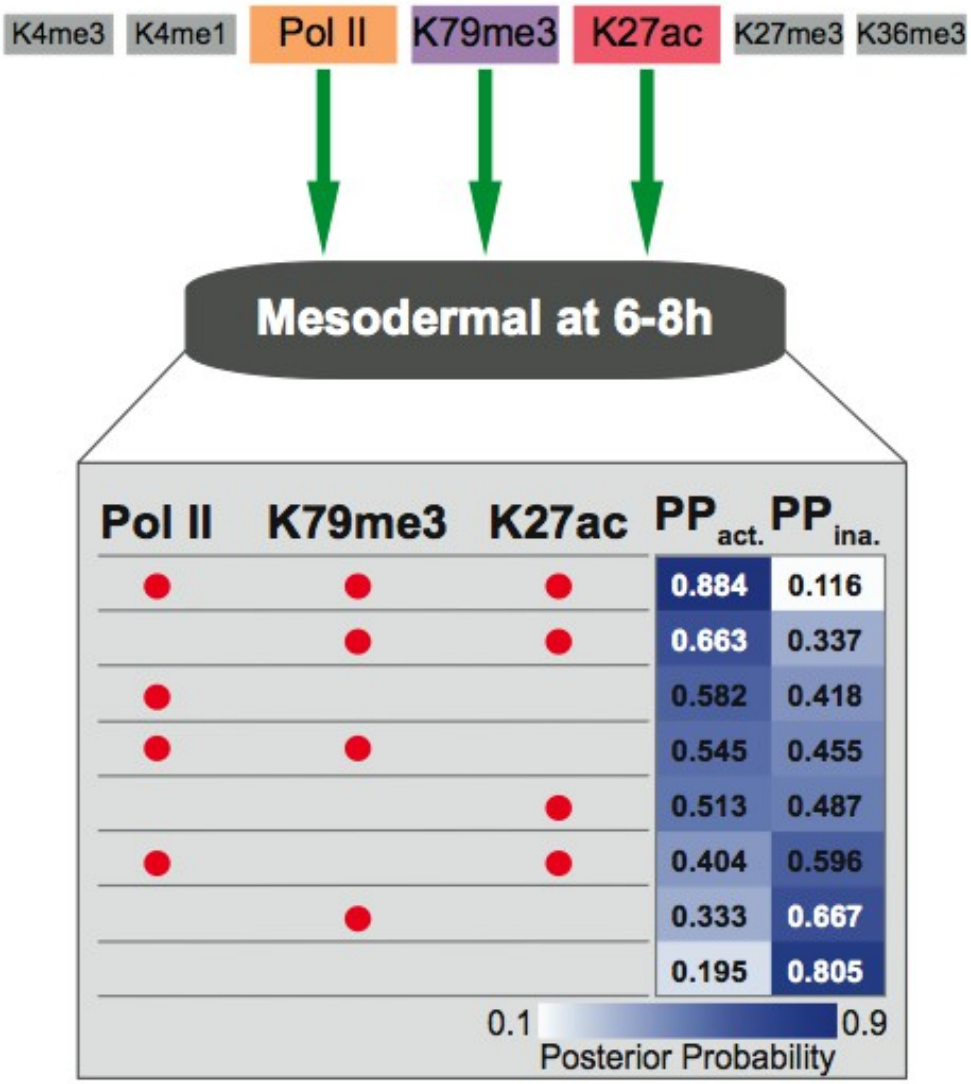
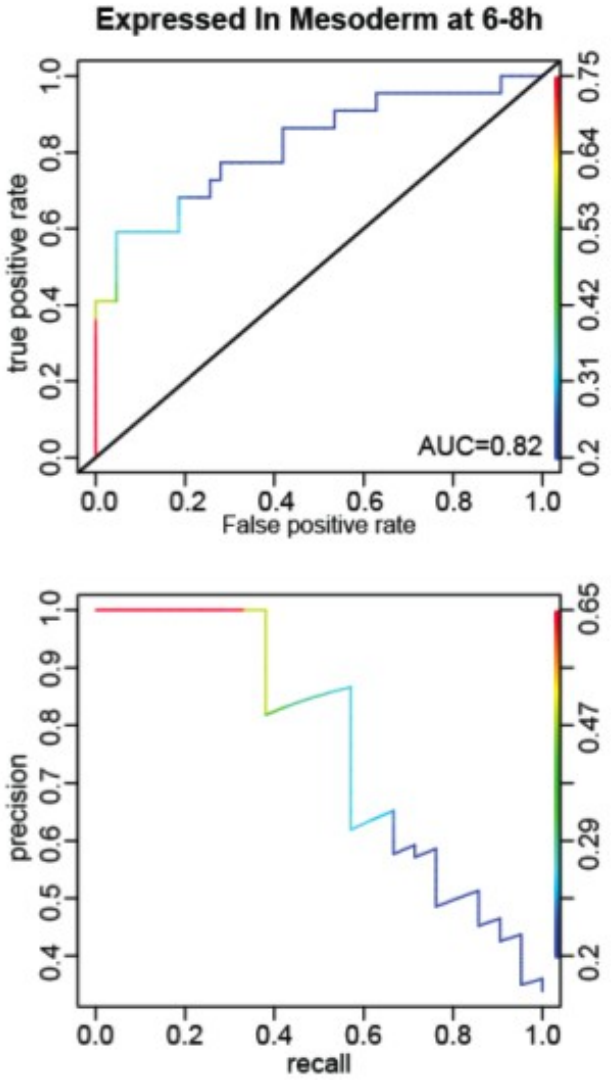
Jak działa klasyfikator





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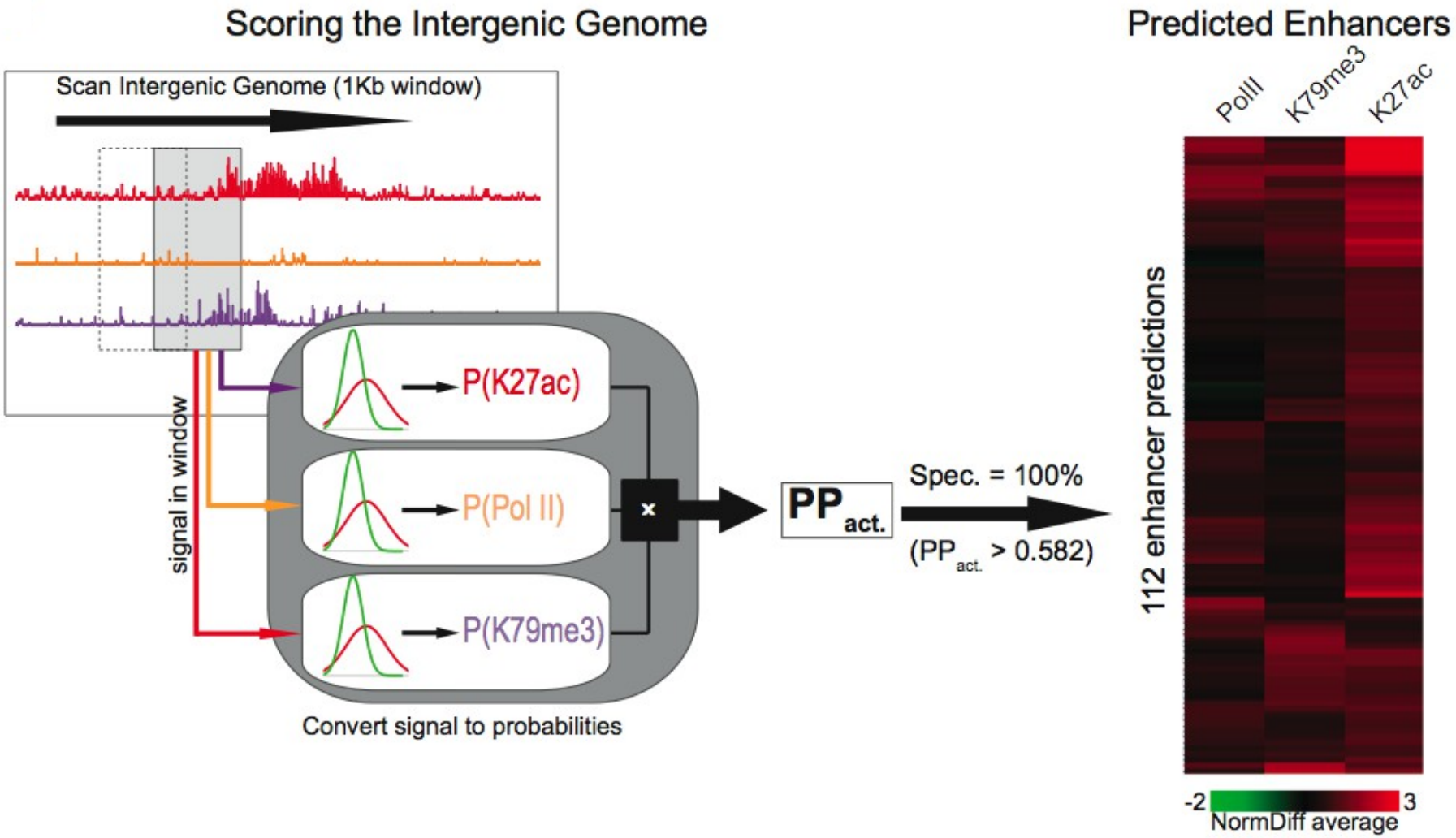
Generowanie predykcji poza zbiorem uczącym



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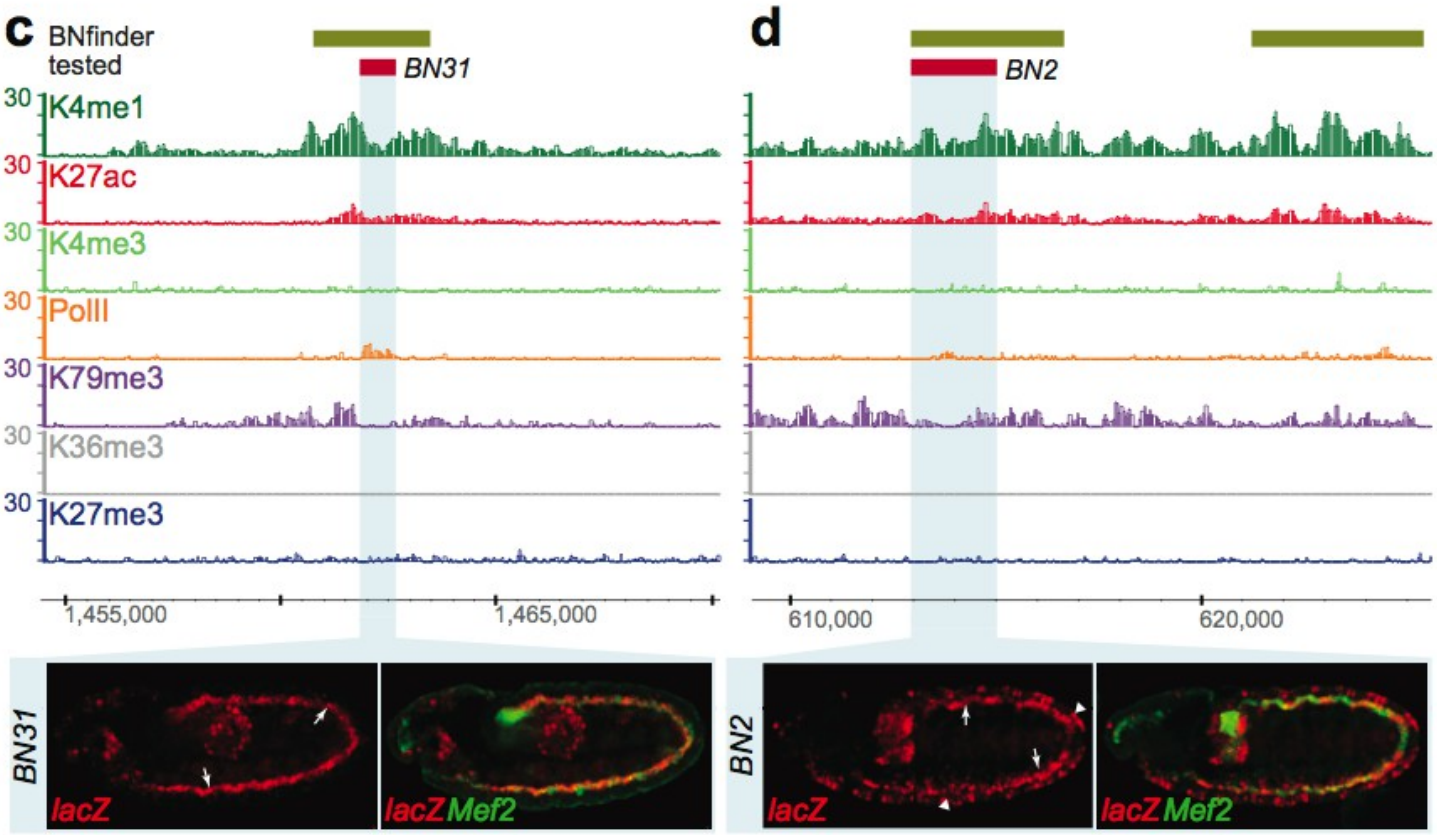
Weryfikacja eksperymentalna



- 12 pozytywnych i 4 negatywne predykcje
- >90% prawidłowo! (1 pozytywna pomyłka)

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Podsumowanie

- Stan chromatyny jest skojarzony z modyfikacjami histonowymi
- Nie jest jasne jakie są prawdziwe związki przyczynowo skutkowe pomiędzy histonami i aktywnością
- Metody „bez nadzoru” takie jak Ukryte modele Markowa (HMM), pozwalają na segmentację na domeny, ale nie działają w szczegółowych przypadkach
- Metody klasyfikacji pozwalają (na podstawie przygotowanego zbioru uczącego) stworzyć model elementów funkcjonalnych
- Takich modeli można użyć do przewidywania funkcji nowych obszarów genomu