HIDEW: HIGH-SPEED DETERMINATION OF EPIGENETIC CODE RENDERED THROUGH A WEB APPLICATION

by

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(Under the direction of Jonathan Arnold)

Abstract

Histone modifications, especially methylations, play a vital role in transcriptional activation of genes within a human body. Hence, we created a web service to help users to study the local spatial structure of these modifications along a chromosome along with their patterns. We created four queries for this purpose. A memory mapping technique along with binary search was used to help obtain quick output results of these queries. We also created a tree representation to view the homogenous regions of these modifications as we walk through the chromosome. We not only show there is a large non-uniformity of the spatial distribution of epigenetic marks in these regions, but also that there are a large number of regions which are locally multinomial.

INDEX WORDS: High-Speed queries, Epigenetic code, Human genome, Histone modifications, Homogenous regions within a chromosome

HIDEW: HIGH-SPEED DETERMINATION OF

${\bf E} {\rm pigenetic}$ code rendered through a ${\bf W} {\rm eb}$ application

by

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A Thesis Submitted to the Graduate Faculty of The University of Georgia in Partial Fulfillment of the Requirements for the Degree

MASTERS OF SCIENCE

ATHENS, GEORGIA

2011

02011

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HiDEW: **H**igh-speed **D**etermination of **E**pigenetic code rendered through a **W**eb application

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May 2011

Acknowledgments

I gratefully acknowledge my advisor, Dr. Jonathan Arnold, whose expertise in this field helped me improve my knowledge and writing abilities. This thesis would not have been possible without him.

I extend a special thanks to my committee members Dr. Krzysztof Kochut and Dr. Rodney Canfield who helped me work through this thesis.

This work was supported by NSF grants DBI-0646315 and BES-0425762.

I would also like to thank my friends for the encouragement they have given me throughout this thesis.

Finally, I would like to thank my parents, who always have been a source of inspiration and support. I can never thank them enough for their love and sacrifice.

Contents

1	Pre	face for the Readers	6
	1.1	Human Genome	6
	1.2	DNA	6
	1.3	Histone Modification	8
	1.4	DNA Sequencing and Pattern Search	9
	1.5	Objectives of this thesis	9
2	Intr	oduction 1	1
3	Met	hods and Materials 1	4
	3.1	Data Source	4
	3.2	Hardware	4
	3.3	Software	5
	3.4	MySQL Database	5
	3.5	Data Structure	6
	3.6	Queries	7
		3.6.1 Query1: Find all (x,y)	8
		3.6.2 Query 2: Find p-mer in (x,y)	9
		3.6.3 Query 3: Find p-mer \geq Z in (x,y)	2
		3.6.4 Query 4: Find p-mer in (x,y) and not in (r,s)	3

	3.7	Search by Modification	26
	3.8	Partitioning Algorithm	27
	3.9	Graphical representation	29
	3.10	Web Process	30
4	Res	ults	31
	4.1	Query timings	31
	4.2	Coverage	32
	4.3	Run lengths	32
	4.4	Spacing	33
	4.5	Correlation Coefficient	34
	4.6	Total Modifications	35
	4.7	Multiple Test Correction	35
	4.8	Graphs	36
5	Disc	cussion	37
6	Con	clusion	39
	Refe	rences	40
	Appe	endix A	43
	Appe	endix B	44
	Appe	endix C	45
	Appe	endix D	46
	Appe	endix E	47

List of Figures

1.1	Overview of Chromosome and DNA in human body	7
1.2	Four Core Histones	8
3.1	Structure used for storing the data	16
3.2	Screenshot of first query	19
3.3	Screenshot of second query	21
3.4	Screenshot of third query	24
3.5	Screenshot of fourth query	26
3.6	Search for modification H3K4me1 on chr 5 between 60000 and 69000 \ldots	27
3.7	Architecture of the Web Application	30
4.1	Timing comparison for different range of search intervals in seconds \ldots .	31
4.2	Execution time comparison in seconds	32
4.3	Examples of Coverage	33
4.4	Examples of Run Lengths	33
4.5	Examples of Spacing	34
4.6	Correlation Coefficient formula	34
4.7	Total number of modifications per chromosome	35
1	Table showing the coverages for all the 23 modifications	43
2	The total run lengths for all the modifications for all the chromosomes \ldots	44

3	Table showing correlation coefficient of spacing and run lengths $\ldots \ldots \ldots$	45
4	Number of terminal nodes before and after applying the multiple test correction	46
5	graphical representation of the partitions on chromosome $1 \ \ldots \ \ldots \ \ldots$	47
6	graphical representation of the partitions on chromosome 2	48
7	graphical representation of the partitions on chromosome 3	49
8	graphical representation of the partitions on chromosome 4	50
9	graphical representation of the partitions on chromosome 5	51
10	graphical representation of the partitions on chromosome 6	52
11	graphical representation of the partitions on chromosome 7 $\ldots \ldots \ldots$	53
12	graphical representation of the partitions on chromosome 8 $\ldots \ldots \ldots$	54
13	graphical representation of the partitions on chromosome 9 $\ldots \ldots \ldots$	55
14	graphical representation of the partitions on chromosome 10 $\ldots \ldots \ldots$	56
15	graphical representation of the partitions on chromosome 11 $\ldots \ldots \ldots$	57
16	graphical representation of the partitions on chromosome 12 $\ldots \ldots \ldots$	58
17	graphical representation of the partitions on chromosome 13 $\ldots \ldots \ldots$	59
18	graphical representation of the partitions on chromosome 14 $\ldots \ldots \ldots$	60
19	graphical representation of the partitions on chromosome 15 $\ldots \ldots \ldots$	61
20	graphical representation of the partitions on chromosome 16 $\ldots \ldots \ldots$	62
21	graphical representation of the partitions on chromosome 17	63
22	graphical representation of the partitions on chromosome 18 $\ldots \ldots \ldots$	64
23	graphical representation of the partitions on chromosome 19 $\ldots \ldots \ldots$	65
24	graphical representation of the partitions on chromosome 20 $\ldots \ldots \ldots$	66
25	graphical representation of the partitions on chromosome 21 $\ldots \ldots \ldots$	67
26	graphical representation of the partitions on chromosome 22 $\ldots \ldots \ldots$	68
27	graphical representation of the partitions on chromosome X	69
28	graphical representation of the partitions on chromosome Y	70

Chapter 1

Preface for the Readers

1.1 Human Genome

Every living organism, including human beings, has a genome that comprises of all the biological information needed for the development and functioning of that organism. A human genome is subdivided into chromosomes which are present in the nucleus of every cell. In humans, there are 22 pair of chromosomes plus a pair of sex chromosomes (XX in females and XY in males). Each chromosome is made up of Deoxyribonucleic acid, DNA, which contains the biological information. This DNA molecule encodes genes, which consists of proteins that direct how a human body is built and maintained. A human genome consists of about 35,000 genes.

1.2 DNA

DNA is a double-stranded chemical structure, also known as a double-helix. The two strands in the double-helix are made up of an alternating sugar and phosphate backbone running parallel to each other, but in opposite directions. DNA is also made up of four chemical bases: adenine (A), guanine (G), cytosine (C), and thymine (T). It is the sequence of these bases, that determine the information available for the development and maintaining a human body. These bases pair up with each other, A with T and C with G, via hydrogen bonding, forming a base pair and are the steps o the helical staircase. On an average, a chromosome is 140 million base pairs long.

The DNA is wrapped around proteins known as histones. There are four primary types of histones: H2A, H2B, H3 and H4, as well as other variants like H2AZ. There are two copies of each of these histones, hence forming an octamer.





Figure 1.1: Overview of Chromosome and DNA in human body Source: http://creationwiki.org/File:Chromosome.png



Figure 1.2: Four Core Histones Source: http://www.nature.com/nrn/journal/v6/n2/fig_tab/nrn1604_F2.html

1.3 Histone Modification

Each of the four core histones has a tail which protrudes out of a nucleosome as shown in the figure 1.2. This tail is subject to a variety of chemical modifications because of the amino acid that is present in a modified histone protein. These modifications include acetylation, methylation, phosphorylation, ubiquitylation, and many more. The kind of modification and its location in a DNA sequence is called the epigenetic code. This epigenetic code in part decides how we look and who we are.

Among these methylations are a kind of modification which adds one or more methyl groups to an amino acid. Methylations are important because adding of a methyl group results in the "start" of a reaction which can eventually lead to the formation of a protein. Here, in this thesis, we study methylation modification.

1.4 DNA Sequencing and Pattern Search

The term DNA Sequencing is defined as the precise determination of the order of the bases - adenine, guanine, cytosine and thymine in a sample of DNA.

For example:

CATAAACCCTGGCGCGCGCGCGGGCCGGCACTCTTCTGGTCCATGG is a part of a DNA sequence.

The epigenetic code is determined by a new high-throughput method of genome sequencing. [4]

A pattern is defined as a cluster where nucleotides appear on the DNA. Hence a DNA Pattern Search accepts a search pattern and returns the number and positions of all the sites that match the pattern.

For example:

A pattern search for pattern 'CTACGATC' might return the following:

Match#1 from position 170 to 178

Match#2 from position 8000 to 8008

Match#3 from position 123861 to 123869

Match#4 from position 35638234 to 35638242 and so on

A review of how to do this can be found in[8]. This closely is related to the problem of finding epigenetic motifs. An epigenetic motif can be defined as a part of a DNA sequence which is recurring at various positions over the chromosome.

1.5 Objectives of this thesis

Barski et. al [1] studied twenty three histone modifications using a new Solexa 1G sequencing technology, and their data can be downloaded from [5]. We aim at determining a local spatial

structure in the occurrences of these modifications as we walk along a chromosome. To ascertain this, it is necessary to create a data structure that allows queries about the spatial locations of histone modifications in a DNA sequence quickly. Once this data structure is created, we can ascertain the spatial structure of the epigenetic code along a chromosome.

Chapter 2

Introduction

A human genome consists of 23 chromosomes, about 140 million base pairs long, on an average, and made up of DNA. DNA is wrapped around nucleosomes which are comprised of 4 core histones(H2A, H2B, H3 and H4). Histones are essential protein components of a chromatin and play a vital role in gene regulation. The amino-terminus of the core histones protrude out of the nucleosome. This is called a 'histone tail', and is subject to various post-translational modifications such as acetylation, methylation, phosphorylation, ubiquitylation, etc. The kind of modification and its location in a DNA sequence is called the epigenetic code. This epigenetic code determines in part how we look and who we are.

Among these modifications, methylations at lysine and arginine residues are very stable and are important for transcriptional activation of genes. Histone methylation is the modification of certain amino acids in a histone protein by the addition of one, two, or three methyl groups. There are many kinds of modifications that can be assayed in a genome.

Twenty three such histone modifications were studied closely by Barski et al.[1] using Solexa 1G sequencing technology.These include H2BK5me1, H3K4me1, H3K4me2, H3K4me3, H3K9me1, H3K9me2, H3K9me3, H3K27me1, H3K27me2, H3K27me3, H3K36me1, H3K36me3, H3K79me1, H3K79me2, H3K79me3, H3R2me1, H3R2me2, H4K20me1, H4K20me3, H4R3me2. Along with these, histone variant H2A.Z, RNA polymerase 2 and insulator binding protein CTCF were also examined.

The nomenclature for these modifications is as follows:

- 1. The name of the histone (e.g. H3)
- 2. The single letter amino acid abbreviation (e.g. K for Lysine, R for arginine) and the amino acid position in the protein, thereby specifying where the modification occurs on the histone.
- The type of histone methylation (me1: mono-methylation, me2: di-methylation, me3: tri methylation).

So H3K4Me1 denotes the mono-methylation of H3 on the 4th lysine from the start (N-terminal) of the histone protein.

Our task is to determine whether or not there is local spatial structure along a chromosome in the occurrence of these modifications. This work is motivated by [6]. To ascertain this, it is necessary to create a data structure that allows queries about the spatial location in a DNA sequence of histone modifications quickly.

Hence we created a data structure that consists of 3 parts - position, mark and count. position is the co-ordinate along the chromosome.

mark is a unique one letter code for the modification.

count is the number of modifications at a particular position. In other words, the count is the number of DNA sequence reads that cover a particular position on the human genome. To save space, we used a unique one letter code, a single alphabet, for each of the 23 modifications.

The chromosome data are stored in these data structures and written into files in a binary format, which are then stored on a Sun workstation as .bin files. As this project studies the pattern of modifications along each chromosome, the data from the original data files were broken down chromosome-wise which resulted in the creation of 24 binary files. (one for each chromosome, including chromosomes X and Y).

As these datasets are very large, there is a need to find an efficient way of accessing and retrieving the data. The binary files were memory mapped for this purpose. This resulted in quick recovery of the required data, as the memory map helps in array-like access to the data, which means that any row can be accessed directly by specifying its position on the array. This increased the speed tremendously which culminated in very quick queries.

Four queries were developed to help the users to study the spatial placement of these modifications on a chromosome. These queries then enabled the construction of graphical tree representation of spatial distribution of modifications along each chromosome, where the terminal nodes denote homogeneous subintervals on the chromosome. Within these subintervals, the distribution of 'modifications' appears locally multinomial.

Chapter 3

Methods and Materials

3.1 Data Source

The data used here can be downloaded from [5]. The data contains the 23 modifications, each having its corresponding reads over a DNA sequence of the human genome, randomly ordered, for all the chromosomes over the human genome.

3.2 Hardware

The web application which is developed for users to run the queries and view the distribution of modifications graphically is deployed on a Sun Solaris OS version 5.10 machine with an intel i386 processor.

MySQL and JDBC were used on a localhost having Mac OS X version 10.6.4 with 2.26 GHz Intel Core 2 Duo processor and 2 GB RAM.

3.3 Software

The web application has been hosted on an Apache2 Web sever. The front-end was developed in HTML and JavaScript. ClearSilver version 0.10.5 templating system was used for creating HTML templates to display the results to the users as per their input queries. Using these templates simplified the process of making any future changes to the HTML front-end, without affecting the rest of the application.

The 4 queries were coded in C++ version 3.4.3. These programs memory map the binary files, stored on the server. CgiCC version 3.1.5 has been used as an interface between the queries and the front-end HTML.

Java version 1.6.0_20 and MySQL version 5.5.3 were used heavily in the initial stages of this project. As the original files are very large, there was a necessity for an efficient way of storing these files. MySQL database was used initially for this purpose, but then was abandoned in favor of the binary files with data structure described in section 2.5. JDBC (Java Database Connectivity) API was used for finding coverages, run lengths, spacing and correlation coefficients.

3.4 MySQL Database

Early computation led to the creation of 24 MySQL tables, one for each chromosome.Each table consisted of all the modifications on that particular chromosome. Mainly, each table had 3 columns - position, mark and count. As these tables were large, above 100 million rows, high latency was observed when running queries on them. For this reason, the idea of using a MySQL database was discarded, and the binary files-memory mapping approach was adopted for efficiency and speed.

3.5 Data Structure

```
typedef struct {
    unsigned int pos;
    char mark;
    short int count;
} Marker;
Marker *rows;
```

Figure 3.1: Structure used for storing the data

Figure 3.1 shows the data structure "Marker" that has been used to store the data of a chromosome.

The data structure is of type 'struct' and consists of 3 datatypes to store the chromosome data - pos, mark and count. "pos" is of type 'unsigned int' since we know that positions don't have negative values. "mark" is of type 'char' since we have associated every modification with a single letter. "count" is the number of modifications of a particular type on that position of the chromosome and is of type 'short int'.

Every line of data in the file consists of the above mentioned three values and hence can be directly inserted into the structure.

An array of structs was created to store the necessary data, which was then written into a binary file. This process was carried out for each of the 24 chromosomes, thus creating 24 binary files with rows of data each containing the 3 data types. The binary files are then accessed and read in the query programs to generate a memory map for quick access of this data. "rows" is the pointer to an array of 'Marker' structs, as shown in fig 3.1. It points to the memory mapped contents from the binary file.

3.6 Queries

Four queries were created to help the user to observe the spatial pattern of modifications. Since the application created is a web-based application, the emphasis of this project was as much on speed as it was on the correctness of the results. Since, there was a huge amount of data to be queried, running large queries on this data was a slow process. This led to the creation of binary files with memory mapping for easy and quick access to the data.

To implement these queries, it was necessary to use a search algorithm which can quickly search for a particular position in a chromosome. Since the data is an ordered list of positions, binary search was opted for this process. Generally binary search returns the position of the key value being searched if it is present and a NULL value, if the key is not present. In this project however, there was a need to get a range of data between the start and end positions entered by the user. Hence, the nearest position to the key needs to be returned, if the key is not present in the data. The traditional algorithm of binary search was thus tweaked, so that it returned the nearest position, greater than the start position requested by the user.

The following is the pseudo code for the binary search used here.

begin

```
left = 0
right = number of lines in the file
key = value to be searched
while left ≤ right do
    mid = (left + right)/2
    if key == (rows[mid]→position) then
       return mid // found the value
    else if (key > (rows[mid]→position) then
       left = mid +1
    else
       right = mid +1
    end if
end while
// if not found
```

```
// move pointer to the nearest value greater than key
if (rows[mid]→position) ≥ key then
return mid;
else
return (mid+1)
end if
```

end

3.6.1 Query1: Find all (x,y)

The first query is implemented to allow users to be able to search between any two positions(x and y) in a DNA sequence for histone modifications. This is a basic query which will return the positions, modifications and their counts.

The pseudo code of this query is as follows

begin

//take user input values for the interval he wants to search start = start position of the intervalend = end position of the intervalresults = vector for holding the output $rows = memory_map(filehandle)$ // call the binary_search function $num_lines = number of lines in the file$ $bin_pos = \langle Binary_Search \rangle (0, num_lines-1, start)$ // due to repeated positions in the binary file, // binary search returns the position of the first match // move back until you encounter the first occurrence of the position being //searched while $bin_{pos} > 0$ do if rows[bin_pos] \rightarrow position \geq start then decrement bin_pos else break end if end while found_count = 0; // counter for number of positions found in the range while $(rows[bin_pos] \rightarrow position) \le end \&\& bin_pos \le (num_lines-1) do$ increment found_count insert rows $[bin_pos] \rightarrow position$ into results

```
increment bin_pos
end while
if found_count == 0 then
print "No modifications found"
else
display results //display positions,marks, and counts
end if
```

end

Position	Mark	Count
756780	H2BK5me1	1
756781	H2BK5me1	1
756782	H2BK5me1	2
756782	H3K79me1	1
756783	H2BK5me1	2
756783	H3K79me1	1
756784	H2BK5me1	2
756784	H3K79me1	1
756785	H2BK5me1	2
756785	H3K79me1	1

Figure 3.2: Screenshot of first query

Figure 3.2 shows a screenshot of the first query when searched between DNA positions 756780 and 756785.

3.6.2 Query 2: Find p-mer in (x,y)

The second query enables users to a find a sequence of modifications over a particular interval. We called this a 'p-mer'. A 'p-mer' is defined as a *particular sequence of modifications over a chromosome in a consecutive order*. For example a p-mer such as 'cst', in its one letter code, is a tri-mer since it consists of 3 histone modifications, c, s and t respectively for H2BK5me1, H3R2me2, and H4K20me1. All the modifications along with their one letter code can be viewed on the website. The following is the pseudo code for this query

begin

//take user input values for the sequence he wants to search start = start position of the search intervalend = end position of the search intervalmods = sequence of modificationsinputs = vector for holding the modifications entered by user pos = vector for storing single matched occurrenceinputs.push_back(mods) filehandle = open(binary file) $rows = memory_map(filehandle)$ // call the binary_search function $num_lines = number of lines in the file$ $bin_pos = \langle Binary_Search \rangle (0, num_lines-1, start)$ // due to repeated positions in the binary file, // binary search returns the position of the first match // move back until you encounter the first occurrence of the position being //searched while $bin_pos \ge 0$ do if rows[bin_pos] \rightarrow position \geq start then decrement bin_pos else break end if end while // counter for number of occurrences of the particular input pattern $occ_count = 0$ // counter for number of positions found in the range $found_count = 0$ $num_inputs = size of inputs$ while $(rows[bin_pos] \rightarrow position) \le end \&\& bin_pos \le (num_lines-num_inputs) do$ // store occurrence position since we need to list multiple occurrences $prev_occ = rows[bin_pos] \rightarrow position$ for j = 0 to num_inputs do mark_string = collect all marks from position //same as rows[bin_pos] \rightarrow position $non_inputs = characters other than input marks$ if (mark_string contains inputs[j]) && (mark_string does not contains non_inputs) then increment found_count insert rows[bin_pos]→position into pos end if end for

if $found_count = num_inputs$ then

// all input marks matched in the occurrence insert all values from pos into occurrence[occ_count] increment occ_count

end if

increment bin_pos // until next position value is encountered

end while

if $occ_count == 0$ then

print "No modifications found"

else

display occurrences //display only positions

end if

end

Occurrence	Position	
0	4000041	
Occurrence 0	4000042	
0	4000042	
Occurrence 1	4000043	
Occurrence 2	4000043	
	4000044	
Occurrence 3	4000044	
	4000045	
	4000045	
Occurrence 4	4000046	
0	4000046	
Occurrence 5	4000047	
0	4000047	
Occurrence 6	4000048	

Figure 3.3: Screenshot of second query

Figure 3.3 shows the result of the second query when searched for p-mer 'fk' between the interval 4000040 and 4000048. It shows that there are 7 occurrences of this p-mer in the specified interval.

3.6.3 Query 3: Find p-mer $\geq Z$ in (x,y)

This query will allow users to search for a p-mer which have counts above the specified threshold value, Z. In other words, Z is the number of reads associated with a modification, at a defined position in a DNA sequence.

The following is the pseudo code for this query

begin

//take user input values for the sequence he wants to search start = start position of the search intervalend = end position of the search intervalz=depth of the stack mods = sequence of modificationsinputs = vector for holding the modifications entered by user pos = vector for storing single matched occurrence inputs.push_back(mods) filehandle = open(binary file) $rows = memory_map(filehandle)$ // call the binary_search function $num_{lines} = number of lines in the file$ $bin_pos = \langle Binary_Search \rangle (0, num_lines-1, start)$ // due to repeated positions in the binary file, // binary search returns the position of the first match // move back until you encounter the first occurrence of the position being //searched while $bin_{pos} > 0$ do if rows[bin_pos] \rightarrow position \geq start then decrement bin_pos else break end if end while // counter for number of occurrences of the particular input pattern $occ_count = 0$ // counter for number of positions found in the range $found_count = 0$ $num_inputs = size of inputs$ while $(rows[bin_pos] \rightarrow position) \le end \&\& bin_pos \le (num_lines-num_inputs) do$

// store occurrence position since we need to list multiple occurrences prev_occ = rows[bin_pos] \rightarrow position for j = 0 to num_inputs do

mark_string = collect all marks from position //same as rows[bin_pos] \rightarrow position non_inputs = characters other than input marks if (mark_string contains inputs[j]) && (mark_string does not contains non_inputs) && (rows[bin_pos] \rightarrow count) > Z) then increment found_count insert rows[bin_pos]→position into pos end if end for if found_count = num_inputs then // all input marks matched in the occurrence insert all values from pos into occurrence[occ_count] increment occ_count end if increment bin_pos // until next position value is encountered end while if $occ_count == 0$ then print "No modifications found" else display occurrences //display only positions end if

end

Figure 3.4 shows the result of the third query when searched for p-mer 'cst' with $Z \ge 2$

between the interval 2930 and 2940. It shows that there are 6 occurrences of this p-mer in the specified interval.

3.6.4 Query 4: Find p-mer in (x,y) and not in (r,s)

This query allows users to find a p-mer in a interval(x,y) but not in another interval(r,s).

The following is the pseudo code for this query

begin

//take user input values for the sequence he wants to search start = start position of the search interval end = end position of the search interval r = start position of the second search interval s = end position of the second search interval mods = sequence of modifications inputs = vector for holding the modifications entered by user

Occurrence	Position	
	2933	
Occurrence 0	2934	
	2935	
	2934	
Occurrence 1	2935	
	2936	
	2935	
Occurrence 2	2936	
	2937	
	2936	
Occurrence 3	2937	
	2938	
	2937	
Occurrence 4	2938	
	2939	
	2938	
Occurrence 5	2939	
	2940	

Figure 3.4: Screenshot of third query

```
pos = vector for storing single matched occurrence
inputs.push_back(mods)
filehandle = open(binary file)
rows = memory_map(filehandle)
// call the binary_search function
num\_lines = number of lines in the file
bin_pos = \langle Binary_Search \rangle (0, num_lines-1, start)
// due to repeated positions in the binary file,
// binary search returns the position of the first match
// move back until you encounter the first occurrence of the position being
//searched
while bin_pos \ge 0 do
  if rows[bin_pos]\rightarrowposition \geq start then
    decrement bin_pos
  else
    break
```

end if end while

```
// counter for number of occurrences of the particular input pattern
  occ\_count = 0
  // counter for number of positions found in the range
  found\_count = 0
  num\_inputs = size of inputs
  while (rows[bin_pos] \rightarrow position) \le end \&\& bin_pos \le (num_lines-num_inputs) do
    // store occurrence position since we need to list multiple occurrences
    prev_occ = rows[bin_pos] \rightarrow position
    for j = 0 to num_inputs do
      mark_string = collect all marks from position //same as rows[bin_pos]\rightarrowposition
      non_inputs = characters other than input marks
      if (mark_string contains inputs[j]) && (mark_string does not contains non_inputs)
      then
         increment found_count
         insert rows[bin_pos]→position into pos
      end if
    end for
    if found_count = num_inputs then
       // all input marks matched in the occurrence
      insert all values from pos into occurrence[occ_count] except between 'r' and 's' insert
      all values from pos into occurrence[occ_count]
      increment occ_count
    end if
    increment bin_pos // until next position value is encountered
  end while
  if occ\_count == 0 then
    print "No modifications found"
  else
    display occurrences //display only positions
  end if
end
```

Figure 3.5 shows the result of the fourth query when searched for p-mer 'lh' between the interval 247199170 and 247199190 but not in the interval 247199180 to 247199185. It shows that there are 8 occurrences of this p-mer in the specified interval.

Your search is	between 247
Occurrence	Position
Occurrence 0	247199175
	247199176
	247199176
Occurrence 1	247199177
	247199177
Occurrence 2	247199178
	247199178
Occurrence 3	247199179
Occurrence 4	247199186
Occurrence 4	247199187
0	247199187
Occurrence 5	247199188
0	247199188
Occurrence o	247199189
	247199189
Occurrence /	247199190

Figure 3.5: Screenshot of fourth query

3.7 Search by Modification

Apart from searching by a chromosome, user also has the option to search by a modification. The second query, i.e Find p-mer in (x,y) can be used to search the occurrences of a particular modification in a given range or within the whole chromosome. A p-mer with a single modification, i.e a uni-mer, can be used in such a case.

For example the figure 3.6 shows the result of when a search is done for the modification 'd' (H3K4me1) on chromosome 5 between 60000 and 69000. It shows that there are 14 occurrences of the same. Similarly, a search can be made over the whole chromosome for a particular modification.

Occurrence	Position
Occurrence 0	67828
Occurrence 1	67829
Occurrence 2	67830
Occurrence 3	67831
Occurrence 4	68089
Occurrence 5	68090
Occurrence 6	68091
Occurrence 7	68092
Occurrence 8	68093
Occurrence 9	68094
Occurrence 10	68095
Occurrence 11	68096
Occurrence 12	68097
Occurrence 13	68098
Occurrence 14	68099

Figure 3.6: Search for modification H3K4me1 on chr 5 between 60000 and 69000

3.8 Partitioning Algorithm

A divide and conquer strategy is applied to break down an entire chromosome into three parts recursively, based on the frequency of modifications in each part[6]. A multiple test correction algorithm[7] is applied to reject parts of the chromosome that are significantly similar to each other.

Multiple Test Correction is a 2-pass algorithm. The first pass is essentially a simple chisquare test applied over the entire chromosome and the chromosome is broken down based on the chi-square being significant at the 0.05 level. The probability values are then sorted in ascending order and the following formula [Eq. 1] is applied over each of the probabilities to determine a cut-off probability value. The second pass of the multiple test correction consists of using this cut-off probability value as a threshold to reject further partitioning which denotes that the parts in the chromosome are closely similar in their composition. Let $P_1, P_2, \ldots P_m$ be the significant probabilities of the nodes sorted in ascending order. Let 'k' be the largest 'i' for which $P_{(i)} \leq \frac{i}{m}(0.05)$ Eq. 1 Then, we need to re-partition the nodes with probabilities $P_1, P_2, \ldots P_k$ and terminate partitioning for nodes with probabilities $P_{k+1}, P_{k+2}, \ldots P_m$.

If the three parts of the chromosome involved in the multiple test correction differ significantly, then the partition is enacted. If the 3 segments at any level of recursion have insignificant difference in composition, then the recursion is terminated. If the three segments are significantly different, then the segment is again broken down into three more segments and the process is repeated all over again. The result is a ternary tree.

The significance test is carried out as follows:

In any given segment, the positions and modifications are extracted using the first query. An additional piece of code has been used to count the number of modifications of each kind in that segment. These counts are then stored in the 1st row of a 2D array which will hold similar counts from the other two segments. Thus finally we create a 3 X 23 contingency table.

The homogeneity test is applied to this table. It is used to compute the chi-square statistic and the resulting value is compared against the critical value (0.05) for the significance level in the first pass. In the second pass, the critical value changes to the cut-off probability obtained from the first pass.

The partitioning algorithm used here is shown below.

1. Consider the entire chromosome as a single segment. Let the significant probability value, P_{sig} be 0.05.

2. Divide the segment into 3 subsegments.

3. For each subsegment, count the number of each type of modifications and create a row array of counts.

4. Create the 3 X 23 contingency table from the 3 segments.

5. Calculate the chi-square value for the table, and find the chi-square

probability value, given degrees of freedom is 44.

6. If the chi-square probability value is $\leq P_{sig}$, goto step 2, else stop the recursion.

7. List all the probabilities in ascending order.

8. Calculate a new probability as specified in Eq. 1

9. Now, let the new probability be assigned to P_{sig} , making it the new cut-off critical value for significance.

10. Start from Step 1 and run the recursive steps 2-6 with the new P_{sig} value.

11. When the chi-square probability value is > the new P_{sig} , stop the recursion and end the program.

3.9 Graphical representation

A tree-like representation is created which allows users to view all the homogeneous intervals within a chromosome. The partition algorithm mentioned in section 3.7 resulted in a ternary tree which is plotted using gnuplot [2]. Twenty four such trees are drawn, one for each chromosome. All these graphs can be viewed in Appendix E or on the website http://giles.genetics.uga.edu/~ankit/. We decided to represent each interval on the graph using its mid-point. The graphs are plotted with locations on the chromosome forming the 'x' co-ordinates and the levels in the tree forming the 'y' co-ordinates for the graph. The highest level in the graph shows all the homogeneous regions in the chromosome.



3.10 Web Process

Figure 3.7: Architecture of the Web Application

The web application can be accessed at http://giles.genetics.uga.edu/~ankit/. The application was created as a 3-tier architecture as shown in Figure 3.6. The presentation, application and the data storage have been separated into independent modules whose software and hardware specifications are described on section 2.2 and 2.3 respectively.

Chapter 4

Results

4.1 Query timings

	query1	query2	query3	query4
small (100 - 10000)	0.0048	0.0076	0.0058	0.0081
medium (10000 - 1000000)	1.0648	1.2824	2.1672	1.8256
large (1000000 - 100000000)	8.8345	12.6754	16.4024	13.5689

Figure 4.1: Timing comparison for different range of search intervals in seconds

Figure 4.1 shows the execution times, in seconds, for all the queries over small, medium and large intervals of search ranges. As shown in the table, small range is of interval (100-10000) means that the range of search can vary between 100 to 10000. Ex: A user can search either 100 to 500 (interval of 400) or he can search 350 - 10300 (interval of 9950). Similarly, a medium range is of interval (10000 - 1000000) and a large range is of interval (10000000 - 10000000).

The point to note here is that even though the queries run on huge search intervals, they run very fast and deliver results within seconds. This is largely a result of the memory mapping technique being employed in the queries. A more important benefit of using memory
mapping can be seen in figure 1.2.



Figure 4.2: Execution time comparison in seconds

Figure 4.2 shows a comparison of the timings when queries are executed at the beginning of the file, in the middle of the file and at the end of the file. As seen, the timings are very similar with only a few milliseconds of difference.

4.2 Coverage

Coverage is defined as the number of times a site was covered by n number of reads of a particular modification. Appendix A gives an overview on the coverages. As seen from the examples in figure 4.3, the coverage has a roughly exponential distribution.

4.3 Run lengths

A location can be defined as a position in nucleotides along a chromosome. A run is defined as a contiguous sequence of locations which consists of DNA reads. Run length is defined as the distance between start and end positions of these runs. There were cases when another run would start before the earlier run has ended. Such runs are known as overlapping runs and in this thesis, they are considered to be different.



Figure 4.3: Examples of Coverage



Figure 4.4: Examples of Run Lengths

If such overlapping sequences are considered to be the part of the same run, we would get an exponential curve as shown in figure 4.4 and in Appendix B.

4.4 Spacing

A space is a location with no DNA sequence reads. A run for each kind of modification will have a corresponding space which comprises of empty locations. Every space can be associated with a unique run. Similar to run lengths, even spacing has a exponential curve as shown in figure 4.5



Figure 4.5: Examples of Spacing

4.5 Correlation Coefficient

$$r = \frac{\sum (x_i - \overline{x})(y_i - \overline{y})}{\sqrt{\sum (x_i - \overline{x})^2 \sum (y_i - \overline{y})^2}}$$

Figure 4.6: Correlation Coefficient formula

A correlation between the run and the spaces was calculated by using the formula as shown in figure 4.6 where 'x' denotes the run and 'y' denotes the space.

The correlation coefficient, r , gave very low values as shown in Appendix C, which meant that the runs and spaces are nearly independent of each other.

As seen from Appendix C, many of the correlation coefficient values were negative, which indicates a negative correlation between the runs and spaces. This negative correlation is caused due to the fact that in many cases, the run lengths are longer than their respective spaces.

Chromosome	Total $\#$ of modifications					
chr1	303228071					
chr2	312668742					
chr3	250020056					
chr4	208347035					
chr5	218295125					
chr6	212288689					
chr7	190666723					
chr8	179008125					
chr9	145778656					
chr10	174430721					
chr11	175351822					
chr12	171317202					
chr13	115187991					
chr14	119236849					
chr15	109002079					
chr16	115784070					
chr17	121161507					
chr18	92984182					
chr19	95937678					
chr20	90337142					
chr21	45780610					
chr22	56506289					
chrX	101128973					
chrY	10165326					

Figure 4.7: Total number of modifications per chromosome

4.6 Total Modifications

Figure 4.7 shows the total number of modifications on every chromosome. These numbers do not count the overlapping sequences, as overlapping runs were considered to be different.

4.7 Multiple Test Correction

Using a multiple test correction reduced the number of terminal nodes by an average of 8%. A table showing this is given in appendix D. The table shows the chromosome number and the terminal nodes obtained before and after using the multiple test correction.

4.8 Graphs

The graphs are drawn with a tree-like representation with x-axis showing the locations on the chromosome and y-axis showing the levels in the tree. We see that there are a lot of non-uniform intervals. Most of the chromosomes get divided up to level 15 (i.e 3¹⁵ nodes in the tree) which suggest inhomogeneity with large number of intervals with respect to the modifications present within them. Most of the graphs have a big gap, which is likely to be the centromere.

Figure 5 in appendix E shows the graph drawn for chromosome 1. It shows all the homogeneous regions for that chromosome. Each region is denoted by a point representing the center of the homogenous interval. This graph, similar to all others, has been drawn using the partitioning algorithm as described in section 3.8. The x-axis shows the positions over the 1st chromosome from 0 to 250,000,000. The y-axis represents the levels of the tree, from 1 to 15. This denotes how deep the recursion went through. In this case, it went upto 15 levels. However, not all the homogenous regions are at level 15. Some of them have uniform intervals at lower levels too.

As seen from the graph, there is just one point on the graph at level 1, which represents the first mid-point in the chromosome. At level 2, there are 3 points on the graph and so on until level 15. However, due to lack of proper zooming, it is not possible to see distinct points on the graph at higher levels. So, it seems to be a straight line. There is also a huge gap or space in the graph where there are no points plotted on the graph. This represents the centromere of the chromosome. Hence, we do not see any points on the chromosome in that interval.

Chapter 5

Discussion

The main development here was to create a partition of each chromosome that was locally multinomial. The number of intervals in the partition varied from 200,000 - 6,500,000 within the chromosome. There was thus substantial spatial inhomogeneity in the marks. The graphs also show that the centromeres are apparent.

We have demonstrated some features of the distribution of epigenetic marks. The spacing and the run lengths have a roughly exponential distribution and appear uncorrelated. These observations provides some evidence of the independence in occurrences of the modifications. What remains to be specified is, 'what is determining the variation in probabilities of a modification along a chromosome'.

Another observation which can be noted from the coverages table in Appendix A is that, four modifications namely H3K36me1, H3K36me3, H3K79me1 and H3K79me2, have a peculiar distribution. But surprisingly the runs and spacing of these modifications is quite similar to the rest of the modifications. It would be interesting to find out the reason behind this. We decided to include these modifications in our further calculations as leaving them out would have results in different counts for our study with only 19 modifications.

We have created the partition for all the chromosomes in the human genome. It would

be desirable to identify characteristic motifs within elements of the partition and relate the elements of the partition by composition [9].

Here we have considered overlapping sequences of the same kind of modification as separate runs. We might have considered these overlapping sequences as a part of the same run, which would have eventually led us with comparatively less number of counts.

Before using the multiple test correction, Fishers exact test[3] along with chi-square test was used for the partition algorithm. But this process increased the number of terminal nodes by around 20-30%. A reason for this might be the size of the tables. The table size used here is 3 X 23 (i.e 69 entries). This might be a huge table for the Fishers exact test to calculate on due to which we might not get appropriate results. The reason for this can be researched in the future.

The partition algorithm used here results in a large number of terminal nodes. We might reduce the number of these terminal nodes, by say clustering on composition.

Another limitation of our procedure is optimizing the partition. Different approaches could have been used to create a better partition in some sense. For example, some kind of model averaging method could have been used to create the partition boundaries [6].

Chapter 6

Conclusion

Histones in a human nucleosome are subject to various post-translation modifications such as acetylation, methylation, phosporylation, etc. The modifications play a important role in gene regulation. The kind of modification and it location in a DNA sequence is called epigenetic code. The Epigenetic code is responsible in part for developing and maintaining a human body structure. This thesis deals with creating a web application for users to quickly find the epigenetic code along the human chromosomes. This thesis aims at finding a local structure of the histone modifications in a human genome.

To ascertain this, we created a data structure that can allow users to view quickly the spatial local locations of the histone modifications in a DNA sequence. The information about the histone modifications, i.e type of the modification, its location over the chromosome and their number of reads, were there stored in this data structure format which was then written in a binary files and stored on the server. A memory mapping technique and a binary search algorithm were used to search for a specific location in theses binary files. Over results show that this process very less time and works very efficiently.

Another aim of this thesis is to find all the homogeneous regions in the human chromosome. For this, we used a divide and conquer strategy with the partition algorithm as mentioned in 3.7. This resulted in a ternary tree which is represented with the chromosome positions on the x-axis and the levels in the trees on the y-axis. The graphs show that there are a large number of terminal nodes in the trees, which represent large non-uniformity in these regions. The graphs show that almost all the chromosomes get divided up to 15 levels and hence we infer that there are a large number of homogeneous regions in the partition of each chromosome.

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Appendix A

	H2AZ	H2BK5me1	H3K27me1	H3K27me2	H3K27me3	H3K36me1	H3K36me3	H3K4me1	H3K4me2	H3K4n	ne3 H3ł	(79me1	H3K79me2
1	109798608	116993291	190031557	175263995	169747591	0	7	125936644	91931056	176775	507	0	0
2	18220632	25226099	27334283	20261093	20672688	172207966	209642323	30179482	14391065	244254	468	0	0
3	10168001	6698090	3093975	1369626	1990376	0	15	9615427	2910658	48599	941	0	0
4	2043213	3479007	1197498	582363	585721	12547234	35735190	5645413	1479142	32793	172	0	0
5	818443	1351745	101574	27854	42241	0	0	2662477	468689	1869	579	1327	1378
6	1464953	937199	126539	48737	47426	914047	8891510	1961743	328746	15820	042	0	21
7	314500	427052	9164	7074	4762	0	0	1026748	108783	1125	540 93	944079	59716032
8	266629	341506	22342	9069	7394	88398	2995308	845745	95526	10040	073	0	0
9	351502	168198	3898	4014	2383	0	0	448014	30916	756	765	0	0
10	136647	150503	5871	3136	2637	18641	1230044	407018	35036	6964	497	155	70
11	77791	79926	2401	2334	1577	0	0	213218	9473	5374	451	0	0
12	161531	76504	2622	2024	1204	9691	577368	212886	13492	5056	696	0	49
13	45385	41686	1706	1705	1154	0	0	110743	3278	3939	998	0	12
14	47337	41788	1458	1381	1018	5953	302123	120193	6225	3773	368 14	376878	13440301
15	71931	24588	1375	1175	913	0	0	58765	1445	2946	691	9	1
16	30332	25027	1233	1110	805	4848	173597	70324	3142	287	721	0	0
17	18142	15981	1081	1067	772	0	0	33586	643	2272	229	0	17
18	47087	15759	814	701	566	3978	106611	43837	1563	226	310	0	0
19	12165	10488	765	867	429	0	0	20405	308	1782	247	0	0
20	14240	11093	648	769	528	3188	69494	27737	744	1793	398	0	2
21	24827	7493	645	636	349	0	0	12344	179	1414	453 2	695724	4337701
22	9944	8036	676	546	529	2450	49410	18290	532	144:	158	0	0
	H3K79me3	H3K9me1	H3K9me	2 H3K9me	3 H3R2m	e1 H3R2m	ne2 H4K20	me1 H4K20	me3 H4	3me2	Pol2	C	TCF
1	53220659	147058494	19429463	2 10691398	9 1803257	36 124673	775 105721	.161 7626	9644 1521	32578 6	56827464	435875	512
2	27171216	28180301	2454008	7 1417700	1 236284	54 170810	27619	464 1069	0274 95	49359	9965219	59769	906
3	6411826	6010807	199340	9 189108	1 20223	15 17990	9575 9575	282 191	8088 7	10353	2207077	9323	383
4	3488578	2821259	72290	3 74701	2 8851	14 7010	5636	880 95	9172 1	24035	753168	5602	259
5	1800198	732347	4553	16513	0 621	32 776	553 2773	023 40	9997	58874	346398	2760	033
6	1077778	512976	6229	3 12382	5 875	01 852	200 2014	767 31	6504	38179	187430	241:	181
7	642327	122393	956	2 3934	8 104	78 170	058 1120	829 19	2958	26733	110694	165	703
8	401362	128037	/ 1230	7 3779	6 156	01 187	774 909	169 16	6722	20884	70090	1484	121
9	251940	24810	491	5 1630	4 51	61 76	554 537	344 11	6732	15465	45685	107	705
10	161247	39354	382	1 1580	8 54	42 76	559 463	959 10	3937	11837	31229	1003	300
11	103891	6355	339	3 824	8 32	56 46	582 286	802 7	5362	9994	21901	740	025
12	68265	14579	287	5 796	2 29	91 44	421 257	375 6	9113	8324	15693	700	073
13	44488	2292	2 215	534	6 21	56 31	185 162	704 5	2769	6398	11526	517	758
14	30178	5706	5 192	3 548	3 19	98 30	099 153	131 5	1099	5695	8942	490	016
15	20173	1043	158	5 365	5 14	19 22	227 97	982 3	9962	4857	6884	354	175
16							04	270 2	0453	2000	5481	210	525
	13779	2590	138	3 324	5 16	63 22	277 94	270 3	8452	3990	5401	340	355
17	13779 9167	2590) 138 5 103	3 324 1 258	5 16 8 13	63 22 97 20	277 94 004 61	.297 2	8934	3594	4534	246	592
17 18	13779 9167 6388	2590 485 1137) 138 5 103 7 118	3 324 1 258 3 272	5 16 8 13 2 12	63 22 97 20 01 17	277 94 004 61 729 60	297 2 334 2	8934 8179	3594 3391	4534 3884	246	592 308
17 18 19	13779 9167 6388 4338	2590 485 1137 314	138 103 103 118 188	3 324 1 258 3 272 5 203	5 16 8 13 2 12 9 8	63 22 97 20 01 12 91 10	277 94 004 61 729 60 574 39	297 2 334 2 664 2	8934 8934 8179 2468	3594 3391 2624	4534 3884 3316	240 243 169	592 308 915
17 18 19 20	13779 9167 6388 4338 3067	2590 485 1137 314 657	138 103 103 118 118 180 180 180 180	3 324 1 258 3 272 5 203 1 171	5 16 8 13 2 12 9 8 6 10	63 22 97 20 01 17 91 16 52 13	277 94 004 61 729 60 574 39 369 40	270 3 297 2 334 2 664 2 201 2	8452 8934 8179 2468 2321	3594 3391 2624 2443	4534 3884 3316 2565	246 243 169 174	555 592 308 915 123
17 18 19 20 21	13779 9167 6388 4338 3067 2194	2590 485 1137 314 657 212	138: 103: 103: 118: 80: 80: 80: 80: 9:	3 324 1 258 3 272 5 203 1 171 4 143	5 16 8 13 2 12 9 8 6 10 2 8	63 22 97 20 01 17 91 16 52 13 36 17	277 94 004 61 729 60 574 39 369 40 296 26	297 2 334 2 664 2 201 2 233 1	8452 8934 8179 2468 2321 7943	3594 3594 3391 2624 2443 2131	4534 3884 3316 2565 2368	244 243 169 174 119	555 592 308 915 423 598

Figure 1: Table showing the coverages for all the 23 modifications

Appendix B

H2AZ	H2BK5me	L H3K27m	e1 H3K27	7me2 H3k	(27me3	НЗКЗб	ime1	H3K36m	e3 H	I3K4me1	H3K4me2	H3K4me3	НЗК7	9me1	H3K79me2
6449656	743340	97489	56 899	90667 8	3743975	802	8907	119882	96	9062443	5093850	11365689	49	38075	4160877
252144	24199	1 1461	10 7	78471	86375	5	7452	3914	64	432424	125221	628115	;	74048	161022
35118	2871	1 43	35	1648	1601		1295	307	'92	66507	9576	196763		2070	16645
7573	489	5 4	79	355	247		351	46	01	13288	979	84623		82	2454
1811	138	1 1	73	152	80		147	11	48	3329	151	35852		11	408
566	41	Ð	96	76	55		83	3	89	951	28	16079		4	118
192	18	7	61	37	34		47	1	59	299	12	7522		1	26
74	6	2	34	32	12		35	1	.02	107	2	3879		2	9
38	3	5	17	9	12		24		44	56	2	2037		2	1
22	2	2	17	9	5		16		23	20	1	1128		2	1
7	1	1	15	16	4		7		22	7	0	648		o	0
8		Э	10	8	2		9		11	10	1	336		0	0
4		8	7	5	2		10		13	4	0	233		0	0
1		3	8	2	3		8		6	3	0	135		0	0
2		3	4	0	1		2		5	7	0	99		0	0
1		0	1	1	2		1		0	3	0	50		0	0
1		2	1	1	0		2		6	2	0	32		o	0
0		1	6	2	1		3		5	1	0	23		0	0
0		2	0	1	1		2		4	0	0	11		0	0
0		<u> </u>	1	3	0	<u> </u>	1		2	0	0	8	<u> </u>	0	0
0		D	0	0	0		1		1	0	0	11		0	0
0		1	0	0	0		0		1	1	0	2		0	0
H3K7	9me3 H3	K9me1 H	I3K9me2	H3K9m	e3 H3	R2me1	НЗ	R2me2	Н4К	(20me1	H4K20me	3 H4R3	me2	Pol	2 СТСР
H3K7	9me3 H3 43848 8	K9me1 +	I3K9me2 9540738	H3K9m 59500	e3 H3	R2me1 239999	H3	R2me2 066335	H4K 8	(20me1 8254038	H4K20m 40275	H4R3	me2	Pol 362752	2 CTCF 3 2421267
H3K7 414	9me3 H3 43848 8 59295	K9me1 534215 250777	I3K9me2 9540738 123318	H3K9m 59500 872	e3 H3 82 9 35	R2me1 239999 132348	H3	R2me2 066335 36588	H4K 8	K20me1 8254038 557832	H4K20m 40275 1458	H4R3 24 7231 13 45	me2 1492 3 5811	Pol 362752 12330	2 CTCF 3 2421267 4 73877
H3K7 41	9me3 H3 43848 8 59295 17616	K9me1 534215 250777 17097	I3K9me2 9540738 123318 3616	H3K9m 59500 872 60	e3 H3 82 9 35 72	R2me1 9239999 132348 3806	H3 6	R2me2 066335 36588 1784	H4K 8	C20me1 8254038 557832 99102	H4K20m 40275 1458 280	H4R3 24 7231 13 45 21 3	me2	Pol 362752 12330 952	2 CTCF 3 2421267 4 73877 0 18768
H3K7 41	9me3 H3 43848 8 59295 17616 2910	K9me1 534215 250777 17097 1546	I3K9me2 9540738 123318 3616 519	H3K9m 59500 872 60 12	e3 H3 82 9 35 72 24	R2me1 9239999 132348 3806 566	H3 6	R2me2 066335 36588 1784 644	H4K 8	(20me1 8254038 557832 99102 25375	H4K20me 40275 1458 280 101	H4R3 24 7231 13 45 21 3 51 1	me2 1492 3 5811 3662 1398	Pol 362752 12330 952 220	2 CTCF 3 2421267 4 73877 0 18768 0 6326
H3K7 41/	9me3 H3 43848 8 59295 17616 2910 596	K9me1 H 534215 250777 17097 1546 201	I3K9me2 9540738 123318 3616 519 212	H3K9m 59500 872 60 12 4	e3 H3 82 9 35 72 24 18	R2me1 9239999 132348 3806 566 234	H3	R2me2 066335 36588 1784 644 261	H4K 8	(20me1 8254038 557832 99102 25375 8754	H4K20md 40275 1458 280 1010 44	H4R31 24 7231 13 45 21 3 51 1 11 1	me2 1492 3 5811 3662 1398 649	Pol 362752 12330 952 220 78	2 CTCF 3 2421267 4 73877 0 18768 0 6326 7 2531
H3K7 41-	9me3 H3 43848 8 59295 17616 2910 596 141	K9me1 H 534215 250777 17097 1546 201 51	I3K9me2 9540738 123318 3616 519 212 120	H3K9m 59500 872 60 12 4 1	e3 H3 82 9 35 72 24 18 85	R2me1 9239999 132348 3806 566 234 143	H3	R2me2 066335 36588 1784 644 261 164	H4K 8	K20me1 8254038 557832 99102 25375 8754 3458	H4K20md 40275 1458 280 1010 44 23	H4R3i 24 7231 13 45 21 3 51 1 11 1	me2 1492 3 5811 3662 1398 649 383	Pol 362752 12330 952 220 78 36	2 CTCF 3 2421267 4 73877 0 18768 0 6326 7 2531 4 1186
H3K7 41- 1:	9me3 H3 43848 8 59295 17616 2910 596 141 44	K9me1 F 534215 250777 17097 1546 201 51 24	3K9me2 9540738 123318 3616 519 212 120 74	H3K9m 59500 872 60 12 4 1	e3 H3 82 9 35 72 24 18 85 99	R2me1 9239999 132348 3806 566 234 143 79	H3 6	R2me2 066335 36588 1784 644 261 164 97	H4K 8	(20me1 8254038 557832 99102 25375 8754 3458 1593	H4K20me 40275 1458 280 1010 44 23 14	H4R31 24 7231 13 45 21 3 51 1 11 1 43 77	me2 1492 3 5811 3662 1398 649 383 188	Pol 362752 12330 952 220 78 36 18	2 CTCF 3 2421267 4 73877 0 18768 0 6326 7 2531 4 1186 4 470
H3K7 41	9me3 H3 43848 8 59295 1 17616 2 2910 5 596 1 141 1 44 15	K9me1 H 534215 250777 1 17097 1 1546 201 1 51 2 24 11	3K9me2 9540738 123318 3616 519 212 120 74 39	H3K9m 59500 872 60 12 4 1	e3 H3 82 9 35 72 24 18 85 99 48	R2me1 9239999 132348 3806 566 234 143 79 71	H3 6	R2me2 066335 36588 1784 644 261 164 97 49	H4K 8	(20me1 8254038 557832 99102 25375 8754 3458 1593 802	H4K20me 40275 1458 280 1010 44 23 1010 44 23 14	H4R31 24 7231 13 45 21 3 51 1 14 77 77 78	me2 1492 3 5811 3662 1398 649 383 188 150	Pol 362752 12330 952 220 78 36 18 12	2 CTCF 13 2421267 14 73877 0 18768 0 6326 7 2531 4 1186 4 470 0 264
H3K7 41	9me3 H3 43848 8 59295 17616 2910 596 141 4 15 5	K9me1 F 534215 250777 17097 1546 201 51 24 11 4	3K9me2 9540738 123318 3616 519 212 120 74 39 37	H3K9m 59500 872 60 12 4 1	e3 H3 82 9 35 72 24 18 85 99 48 56	R2me1 9239999 132348 3806 566 234 143 79 71 45	H3 6	R2me2 066335 36588 1784 644 261 164 97 49 38	H4K 8	(20me1 8254038 557832 99102 25375 8754 3458 1593 802 424	H4K20md 402753 14583 2800 1010 444 233 114 99 65	B3 H4R30 24 7231 13 45 21 3 51 1 14 77 77 78 30 9	1492 3 5811 3 3662 3 1398 3 649 3 188 1 150 88	Pol 362752 12330 952 220 78 36 18 12 12	2 CTCF 3 2421267 4 73877 0 18768 0 6326 7 2531 4 1186 4 4700 0 264 0 141
H3K7 41	9me3 H3 43848 8 59295 17616 2910 596 141 4 15 3	K9me1 F 534215 250777 17097 1546 201 51 24 11 4 5	35K9me2 9540738 123318 3616 519 212 120 74 39 37 22	H3K9m 59500 872 60 12 4 1	e3 H3 82 9 35 72 24 7 18 85 99 7 48 5 56 30	R2me1 2239999 132348 3806 566 234 143 79 71 45 22	H3 6	R2me2 066335 36588 1784 644 261 164 97 49 38 25	H4K 8	(20me1 8254038 557832 99102 25375 8754 3458 1593 802 424 237	H4K20md 402753 14583 2880 1010 444 233 144 99 66 33	B3 H4R30 24 7231 13 45 21 3 51 1 13 77 77 78 30 779	me2 1492 3 5811 3 662 3 1398 6 649 3 188 3 150 88 6 63 3	Pol 362752 12330 952 220 78 36 18 12 10 5	2 CTCF 3 2421267 4 73877 0 18768 0 6326 7 25531 4 1186 0 2640 0 2640 0 141 1 81
H3K7 41 1	9me3 H3 43848 8 59295 1 17616 2 2910 5 141 4 15 5 3 2	K9me1 F 534215 250777 17097 1546 201 51 24 11 4 5 5 24 24 22 22	35K9me2 9540738 123318 3616 519 212 120 74 39 37 22 15	H3K9m 59500 872 60 12 4 1	e3 H3 82 9 35 72 24 18 85 99 48 56 30 20	R2me1 2239999 132348 3806 566 234 143 79 71 45 222 17	H3 6	R2me2 066335 36588 1784 644 261 164 97 49 38 25 19	H4K 8	(20me1 8254038 557832 99102 25375 8754 3458 1593 802 424 237 155	H4K20ma 40275 1458 280 101 44 23 101 4 4 23 14 6 6 3 3 2 2	Page H4R30 24 7231 13 45 21 3 51 1 14 77 77 78 30 77 74 74	me2 1492 3 5811 3662 1398 649 383 188 150 888 63 41	Pol 362752 12330 952 220 78 36 18 12 10 5 4	2 CTCF 3 2421267 4 73877 0 18768 0 6326 7 2531 4 1186 4 470 0 264 1 811 2 52
H3K7 41. 1:	9me3 H3 43848 8 59295 1 17616 1 2910 1 596 1 141 1 44 1 5 3 2 1 1 1	K9me1 F 534215 250777 17097 1546 201 51 24 11 24 11 4 5 5 22 1	J3K9me2 9540738 123318 3616 519 212 120 74 39 37 37 222 15 6	H3K9m 59500 872 60 12 4 1	e3 H3 82 9 35 72 24 18 85 99 48 56 30 20 18 18	R2me1 2239999 132348 3806 566 234 143 79 71 45 222 17 15	H3 6	R2me2 066335 36588 1784 261 164 97 49 38 25 19 15	H4K 8	C20me1 8254038 557832 99102 25375 8754 3458 1593 802 424 237 1555 86	H4K20ma 40275 1458 280 101 44 23 101 4 4 23 14 14 9 9 3 3 3 2 2 2 2 2 2	Page H4R30 24 7231 13 45 21 3 51 1 141 1 77 78 30 79 74 09	me2 1492 5811 3662 1398 649 383 150 88 63 41 37	Pol 362752 12330 952 220 78 36 18 12 10 5 4 4 2	2 CTCF 3 2421267 4 73877 0 18768 0 6326 7 2531 4 1186 4 4700 0 2644 0 2644 1 811 2 522 2 333
H3K7 41- 1:	9me3 H3 43848 8 59295 1 17616 1 2910 1 596 1 141 1 44 1 5 3 3 2 1 0	K9me1 F 534215 250777 17097 1546 201 51 24 11 4 11 4 5 5 22 1 1 1	3K9me2 9540738 123318 3616 519 2212 120 74 39 37 322 15 6 6 7	H3K9m 59500 872 60 12 4 1	es H3 82 9 35 - 72 - 24 - 85 - 99 - 48 - 56 - 30 - 20 - 18 -	R2me1 239999 132348 3806 566 234 143 79 71 45 22 17 15 15	H3	R2me2 066335 36588 1784 644 261 164 97 49 38 38 25 25 19 15 12	H4K 8	C20me1 8254038 557832 99102 25375 8754 3458 1593 802 424 2375 866 61	H4K20ma 40275 1458 280 1010 44 23 1010 44 23 6 6 3 3 2 2 2 2 2 2 2 1	Page H4R30 24 7231 13 45 21 3 51 1 11 1 43 77 78 30 79 74 59 59	1492 3 5811 3 3662 3 1398 6 649 3 383 1 150 88 63 41 37 19	Pol 362752 12330 952 220 78 36 18 12 10 5 4 4 2 2 1	2 CTCF 3 2421267 4 73877 0 18768 0 6326 7 2531 4 1186 4 4700 0 264 0 141 1 81 2 52 3 0
H3K7 41- 1:	9me3 H3 43848 8 59295 1 2910 1 596 1 141 1 44 1 5 3 2 1 0 0	K9me1 F 534215 250777 17097 1546 201 51 24 11 4 5 5 5 5 2 2 4 11 2 4 11 2 1 2 2 1 1 2 2	3K9me2 9540738 123318 3616 519 2212 120 74 339 37 222 15 6 6 7 4	H3K9m 59500 872 60 12 4 1	es H3 82 9 35 - 72 - 24 - 85 - 99 - 48 - 56 - 30 - 20 - 18 - 13 -	R2me1 239999 132348 3806 566 234 143 79 71 45 227 15 15 15 9	H3	R2me2 066335 36588 1784 644 261 164 97 49 38 255 19 15 12 5	H4K 8	C2Ome1 8254038 557832 99102 25375 8754 3458 1593 802 424 2375 866 61 32	H4K20md 40275 1458 280 1010 44 23 114 99 66 33 3 22 22 22 11 11	Page H4R30 24 7231 13 45 21 3 51 1 11 1 43 77 78 30 79 74 59 30	me2 (492 (5811 (398 649 (383 1398 (49 (383 (19) (19	Pol 362752 12330 952 220 78 36 18 12 10 5 4 4 2 2 1 1 2 2	2 CTCF 3 2421267 4 73877 0 18768 0 6326 7 2531 4 1186 4 4700 0 264 0 141 1 81 2 522 2 333 0 222 0 13
H3K7 41- 1:	9me3 H3 43848 8 59295 1 17616 2 2910 5 596 1 44 1 5 3 2 1 0 0 0 0	K9me1 F 534215 250777 17097 1546 201 51 24 11 4 5 5 24 11 24 11 24 11 1 2 4 1 1 1 2 2 1 1 1 2 0	3K9me2 9540738 123318 3616 519 2212 120 74 339 337 222 15 6 77 4 4	H3K9m 59500 872 60 12 4 1	es H3 82 9 35 9 72 18 85 99 48 9 20 18 13 9 4 4	R2me1 3239999 132348 3806 566 234 143 79 71 45 22 17 15 15 15 9 9	H3	R2me2 066335 36588 1784 644 261 164 97 49 38 25 19 19 15 15 12 5 6	H4K 8	C2Ome1 8254038 557832 99102 25375 8754 3458 1593 802 424 237 155 661 322 201	H4K20md 40275 1458 2800 1010 444 233 144 99 66 33 22 20 20 11 11 11	B H4R30 24 7231 13 45 21 3 51 1 11 1 43 1 77 7 78 30 77 7 79 1 559 30 300 77	me2 5811 5813 5813 5813 5813 5813 583 649 588 649 50 60 60 60 60 60 60 60 60 60 6	Pol 362752 12330 952 2200 78 366 18 12 10 5 4 4 2 2 10 2 2 1 2 2 1 2 2 2 1 2 2 2 1 2 2 0 2 2 0 2 2 0 2 2 0 2 2 0 2 2 0 2 2 0 2	2 CTCF 3 2421267 44 73877 0 18768 0 6326 7 2531 4 1186 4 470 0 264 0 141 1 81 2 52 0 22 0 222 0 223 0 222 0 133 7 11
	9me3 H3 43848 8 59295	K9me1 F 534215 250777 17097 1546 201 51 24 11 4 5 2 1 1 1 4 5 2 1 1 2 0 1 1 1 1 1 1 1 1 1 1 1 1 1	3K9me2 9540738 123318 3616 519 212 120 74 39 37 222 15 6 6 7 7 4 4 4 4 4	H3K9m 59500 872 60 12 4 1	es H3 82 9 35 9 72 9 48 99 48 9 56 9 18 9 18 9 18 9 4 9	R2me1 3239999 132348 3806 566 234 143 79 71 45 22 17 15 9 7 3 3 3 3 3 4 3 3 4 5 6 3 4 5 6 5 6 6 7 7 7 7 7 7 7 7 7 7 7 7 7	H3	R2me2 066335 36588 1784 644 261 164 97 49 38 25 19 38 25 19 15 15 12 5 6 6	H4K 8	C2Ome1 8254038 557832 99102 25375 8754 3458 1593 802 424 237 155 86 322 201 322 201 323	H4K20md 40275 1458 2800 1001 444 234 144 99 66 33 22 20 20 10 11 11 11	B3 H4R31 24 7231 13 45 21 3 51 1 14 1 43 1 77 7 78 30 77 7 79 1 509 1 509 1	1492 3 3662 3 383 3 188 3 150 8 631 3 188 3 199 3 191 37 191 37 192 17 12 3	Pol 362752 12330 952 2200 78 366 18 12 10 5 4 4 2 2 10 2 2 1 1 2 2 1 1 2 2 1 1 2 2 1 1 2 1 2	2 CTCF 3 2421267 4 73877 0 18768 0 6326 7 2531 4 1186 4 470 0 264 0 141 1 81 2 52 0 22 0 22 0 22 0 213 7 111 3 8
	9me3 H3 43848 8 59295	K9me1 F 534215 250777 17097 1546 201 51 24 1 1 4 5 2 2 1 1 1 1 1 2 0 1 1 0 1 0 1 0 1 0 0 1 0 0 0 0 0 0 0 0 0 0 0 0 0	3K9me2 9540738 123318 3616 519 212 120 720 739 337 222 15 6 6 7 7 4 4 4 4 1 5	H3K9m 59500 872 60 12 4 1	es H3 82 9 35 - 72 - 24 - 18 - 99 - 48 - 56 - 30 - 20 - 18 - 13 - 4 - 4 - 4 -	R2me1 2239999 132348 3806 566 234 143 771 71 45 222 177 15 15 9 9 9 3 3 5	H3	R2me2 066335 36588 1784 644 261 164 97 49 38 25 19 15 12 5 6 6 2 6	H4K 8	C2Ome1 3254038 557832 99102 25375 8754 3458 1593 802 424 237 155 866 611 322 201 144 1393	H4K20ma 40275 1458 280 101 44 23 14 1 9 6 6 3 3 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2	A H4R3 24 7231 13 45 21 5 51 1 13 47 77 77 78 77 79 74 30 77 74 30 77 75 59 55 56	1492 3 3662 3 3683 3 1888 1 5011 3 649 3 383 3 150 3 649 3 150 3 41 3 19 2 17 12 7 7	Pol 362752 12330 952 220 78 36 18 12 10 5 4 4 22 11 2 1 1 1	2 CTCF 3 2421267 4 73877 10 18768 0 6326 7 2531 4 1186 0 6326 7 2531 4 4700 0 264 0 264 0 141 1 81 2 522 2 333 0 222 3 88 8
H3K7 41- 1: 	9me3 H3 43848 8 59295 1 17616 2 2910 596 141 4 15 5 3 - 1 0 0 - 0 - 0 - 0 - 0 - 0 - 0 - 0 - 0 - 0 - 0 - 0 - 0 - 0 - 0 - 0 -	K9me1 F 534215 250777 17097 1546 201 51 24 11 4 5 5 24 11 4 5 5 2 2 1 1 1 2 4 0 1 1 1 0 1 0 1 0 1	3K9me2 9540738 123318 3616 519 212 120 74 39 37 222 15 6 6 7 7 4 4 4 11 5 5	H3K9m 59500 872 60 12 4 1	es H3 82 9 35 - 72 - 24 - 18 - 99 - 48 - 56 - 30 - 20 - 18 - 13 - 4 - 4 - 4 - 5 -	R2me1 2239999 132348 3806 566 234 143 79 79 45 222 17 15 15 9 9 7 3 3 5 22 22 22 22 17 5 5 22 22 22 22 22 22 22 22 22 22 22 22	H31 6	R2me2 066335 36588 1784 644 261 164 97 49 38 25 19 38 25 19 15 12 5 6 6 2 2 6	H4K 8	C2Ome1 8254038 557832 99102 25375 8754 3458 1593 424 2337 1555 866 611 322 201 424 101 102	H4K20ma 40275 1458 280 1010 444 23 147 9 6 6 6 3 3 2 2 2 4 11 1 1 1 1 1 1 1 1 1 1 1 1 1 1	Page H4R3n 24 7231 13 45 21 3 51 1 13 45 51 1 143 77 77 78 30 77 74 79 53 77 53 77 53 59 54 59 55 55	me2 1492 5811 3662 1398 649 383 150 88 63 41 37 19 25 17 12 7 9	Pol 362752 12330 952 220 78 36 18 12 10 5 4 2 11 2 1 1 1 1 1 1	2 CTCF 3 2421267 44 73877 50 18768 60 6326 7 2531 4 1186 4 4700 0 264 0 264 1 81 2 522 3 33 3 88 2 3 3 33
H3K7 41- 1: 	9me3 H3 43848 8 59295 1 2910 - 596 - 141 - 44 - 15 - 3 - 2 - 1 - 0 -	K9me1 F 534215 250777 17097 1546 201 51 24 11 4 5 24 11 1 2 1 1 1 2 1 1 1 1 2 1 1 1 1 1 2 1 1 1 1 1 1 1 1 1 1 1 1 1	3K9me2 9540738 123318 3616 519 212 120 74 39 37 222 15 6 6 7 7 4 4 4 4 4 4 5 5 5 5 5 5	H3K9m 59500 872 60 12 4 1	es H3 82 9 35 9 72 9 18 9 48 5 50 9 10 9 11 9 120 10 13 9 4 10 4 10 5 10 4 10 5 10	R2me1 2239999 132348 3806 566 234 143 79 79 79 79 15 15 15 9 77 3 5 5 22 21 77 22 21 77 22 22 22 22 22 22 22 22 22 22 22 22		R2me2 066335 36588 1784 644 261 164 977 38 25 19 38 25 19 15 6 6 2 6 6 2 2 2 2 2	H4K 8	C2Ome1 3254038 557832 99102 25375 3458 1593 424 2337 1593 424 2337 1553 661 32 200 141 9 115	H4K20ma 40275 1458 280 1010 44 23 101 4 4 23 6 6 3 3 22 20 21 11 11 11 11 11 11 11 11 11 11 11 11	A H4R31 24 7231 13 45 21 3 51 1 13 77 77 77 78 30 79 74 59 74 59 59 56 59 57 59 58 34	me2 1492 5811 3662 1398 649 383 150 88 63 41 37 19 25 17 12 7 9 66	Pol 362752 12330 952 220 78 36 18 12 10 5 4 4 22 11 22 11 1 2 2 11	2 CTCF 3 2421267 4 73877 0 18768 0 6326 7 2531 4 11866 0 6326 7 2531 4 1186 0 264 1 81 2 522 0 222 0 222 0 222 0 133 8 22 3 33 2 4
H3K7 41- 1: 	9me3 H3 43848 8 59295 1 2910 - 596 - 141 - 5 - 3 - 2 - 1 - 0 -	K9me1 H 534215 250777 17097 1546 201 2 1546 2 11 4 5 2 11 4 5 2 11 4 5 2 1 1 2 0 1 2 0 1 0 1 0 1 0 2	3K9me2 9540738 123318 3616 519 212 120 74 37 37 22 15 6 6 7 7 4 4 4 4 4 4 4 5 5 5 5 1 1	H3K9m 59500 872 60 12 4 1	es H3 82 9 35 9 72 1 85 99 48 9 50 30 20 1 13 9 4 1 4 1 5 4 5 4 3 9	R2me1 2239999 132348 3806 566 234 143 79 71 455 222 177 15 15 9 7 3 5 2 2 2 2 3 3 2 2 3 3 3 3 4 5 5 5 5 5 5 5 5 5 5 5 5 5		R2me2 066335 36588 1784 644 261 164 97 497 38 25 19 12 5 6 2 6 2 6 2 2 2 2 2 2	H4K 8	C2Ome1 3254038 557832 99102 25375 3458 1593 424 237 1555 86 61 322 20 144 237 1553 866 611 322 200 144 90 14 90 11 33	H4K20ma 40275 1458 280 1010 44 23 101 4 4 23 101 4 9 20 20 20 20 20 20 20 20 20 20 20 20 20	Page H4R31 24 7231 13 45 21 3 51 1 13 77 77 78 30 79 77 78 30 79 77 78 30 79 77 78 30 79 77 79 78 30 79 74 59 59 50 59 53 59 54 28	1492 3 3811 3 3662 3 383 3 188 3 150 63 41 37 37 19 225 17 12 37 9 6 7 9 6 7	Pol 362752 12330 952 220 78 36 18 12 10 5 4 4 22 11 22 11 1 1	2 CTCF 3 2421267 4 73877 0 18768 0 6326 7 2531 4 11866 4 4700 0 2644 1 811 2 522 0 222 0 222 0 222 0 223 0 222 0 388 3 38 2 244 1 11
H3K7 41- 1)	9me3 H3 43848 8 59295 1 17616 - 2910 - 596 - 141 - 533 - 2 - 1 - 0 -	K9me1 H 534215 250777 17097 - 1546 - 201 - 51 - 24 - 51 - 24 - 11 - 5 - 2 - 1 - 2 - 0 - 1 - 0 - 1 - 0 - 1 - 0 - 1 - 0 - 2 - 0 - 2 - 0 - 2 - 0 - 2 - 0 - 0 - 0 - 0 - 0 -	3K9me2 9540738 123318 3616 519 212 120 74 337 222 15 6 6 7 7 4 4 4 4 1 5 5 5 5 1 1 1 1 1	H3K9m 59500 872 60 12 4 1	ea H3 82 9 35 9 72 1 85 9 94 9 56 30 20 1 113 9 4 1 5 1 4 1 5 1 4 1 5 1 3 1	R2me1 2239999 132348 3806 566 234 143 79 71 45 222 17 15 9 7 3 5 22 2 17 15 5 22 2 2 17 15 5 2 2 2 2 3 3 4 4 4 4 4 4 4 4 4 4 4 4 4		R2me2 066335 36588 1784 644 261 164 97 499 164 97 499 15 12 5 6 2 6 2 6 2 2 2 2 2 2 2 2 2 2 2 2 2	H4K 8	420me1 8254038 557832 99102 25375 8754 3458 1593 802 424 237 1555 866 611 322 200 14 10 91 11 32 33 6	H4K20ma 40275 1458 280 1010 444 233 144 99 6 33 22 20 20 11 11 11 12 11 12 12 12 12 12 12 12 12	Page H4R31 24 7231 13 45 21 33 51 1 11 1 43 77 77 78 30 77 79 74 79 74 79 74 79 74 79 74 79 74 79 74 79 74 79 74 77 75 78 30 77 75 73 75 74 77 77 75 77 75 73 75 74 75 75 75 76 75 73 75 74 75 75 75 75 75 75 75 75	1492 3 3811 3 3662 3 383 3 188 3 150 3 643 3 150 3 7 3 17 1 7 9 6 7 22 7 22 7 22 7 22 7	Pol 362752 12330 952 220 78 36 18 12 10 5 5 4 4 22 11 12 2 11 1 1	2 CTCF 3 2421267 4 73877 0 18768 0 6326 7 2531 4 1186 4 4700 0 2644 0 2644 1 81 2 522 0 222 0 222 0 222 0 133 7 111 3 8 2 244 1 11 3 8 2 4 1 11 3 3 3 3 3 4 1 1 6 1

Figure 2: The total run lengths for all the modifications for all the chromosomes

Appendix C

	chr1	chr2	chr3	chell	chr5	chr6	chr7	chr8	chr9	chr10	chr11	chr12				
H247	0.0078	-0.0132	-0.0080	-0.0113	-0.0118	-0.0126	-0.0117	-0.0102	-0.0020	-0.0120	-0.0116	-0.0227				
H2BK5me1	0.0678	-0.0115	-0.0037	-0.0124	-0.0113	-0.0100	-0.0104	-0.0102	-0.0018	-0.0107	-0.0098	-0.0187				
H2K27mo1	0.0054	0.0027	-0.0057	0.00224	-0.0022	0.0036	0.00104	0.0009	0.0077	0.0040	-0.0030	-0.0167				
H3K27me2	0.0145	-0.0016	-0.0026	-0.0019	-0.0016	0.0335	-0.0015	-0.0013	-0.0203	0.0107	-0.0013	-0.0031				
H3K27me3	0.0743	-0.0029	-0.0011	-0.0027	-0.0021	0.0327	-0.0023	-0.0022	-0.0005	-0.0028	-0.0015	-0.0031				
H3K36mo1	0.1792	0.0025	-0.0018	-0.0025	-0.0043	0.0015	-0.0011	-0.0022	0.0096	-0.0018	-0.0029	-0.0005				
H3K36me3	0.1833	0.0266	-0.0084	-0.0010	-0.0057	-0.0015	-0.0058	-0.0053	-0.0010	-0.0050	-0.0051	-0.0025				
H3K30me1	0.0845	-0.0154	-0.0046	-0.0156	-0.0147	-0.0097	-0.0135	-0.0033	-0.0010	-0.0139	-0.0115	-0.0773				
H3K4me2	0.0413	-0.0140	-0.0103	-0.0147	-0.0140	-0.0132	-0.0115	-0.0116	-0.0021	-0.0130	-0.0115	-0.0226				
H3K4me3	0.0127	-0.0150	-0.0093	-0.0140	-0.0137	-0.0064	-0.0132	-0.0116	-0.0022	-0.0140	-0.0127	-0.0268				
H3K79me1	0.0286	0.0122	-0.0102	-0.0121	-0.0104	-0.0087	-0.0092	-0.0096	-0.0017	-0.0096	-0.0084	-0.0154				
H3K79me2	-0.0017	-0.0217	-0.0074	-0.0127	-0.0216	-0.0180	-0.0182	-0.0182	-0.0031	-0.0191	-0.0169	-0.0315				
H3K79me3	0.0212	-0.0220	-0.0149	-0.0213	-0.0216	-0.0012	-0.0184	-0.0174	-0.0032	-0.0195	-0.0170	-0.0322				
H3K9me1	0.0203	-0.0105	-0.0145	-0.0110	-0.0100	-0.0093	-0.0079	-0.0084	-0.0015	-0.0094	-0.0079	-0.0162				
H3K9me2	-0.0017	0.0293	-0.0071	0.0079	-0.0012	-0.0016	-0.0015	0.0194	-0.0022	-0.0015	-0.0014	0.0088				
H3K9me3	-0.0005	-0.0052	-0.0010	-0.0037	-0.0042	0.0304	-0.0049	-0.0038	-0.0007	-0.0064	-0.0044	-0.0083				
H3R2me1	0.1694	-0.0018	-0.0032	-0.0018	-0.0011	-0.0014	-0.0014	-0.0010	-0.0027	-0.0022	0.0101	-0.0023				
H3R2me2	0.1413	-0.0023	-0.0012	-0.0018	-0.0079	-0.0015	0.0127	-0.0013	-0.0034	-0.0032	0.0037	-0.0023				
H4K20me1	0.0677	-0.0172	-0.0071	-0.0198	-0.0173	-0.0148	-0.0153	-0.0161	-0.0027	-0.0154	-0.0142	-0.0277				
H4K20me3	-0.0029	-0.0075	-0.0118	-0.0117	-0.0081	-0.0038	-0.0125	0.0033	-0.0014	-0.0141	-0.0055	-0.0246				
H4R3me2	0.0818	-0.0025	-0.0057	0.0384	-0.0012	-0.0012	-0.0029	0.0139	-0.0032	-0.0051	-0.0013	-0.0023				
Pol2	0.1532	-0.0118	-0.0039	-0.0080	-0.0103	-0.0036	-0.0107	-0.0083	-0.0018	-0.0107	-0.0104	-0.0194				
CTCF	0.0326	-0.0234	-0.0071	-0.0187	-0.0206	-0.0211	-0.0210	-0.0193	-0.0037	-0.0240	-0.0215	-0.0434				
	4413	1000	abot E	4-16	ab 17	aba10	ab-10	rh-20		4-22						
H2A7	chr13	chr14	chr15	chr16	chr17	chr18	chr19	chr20	chr21	chr22	chrX	chr¥				
H2AZ	chr13 -0.0445	chr14 -0.0728	chr15 -0.0421	chr16 -0.0035	chr17 -0.0556	chr18 -0.0153	chr19 0.0020	chr20 -0.0116	chr21 -0.0060	chr22 -0.0608	chrX -0.0131	chrY -0.0019				
H2AZ H2BK5me1	chr13 -0.0445 -0.0454	chr14 -0.0728 -0.0574	chr15 -0.0421 -0.0352	chr16 -0.0035 -0.0025	chr17 -0.0556 -0.0353	chr18 -0.0153 -0.0153	chr19 0.0020 -0.0023	chr20 -0.0116 0.0108	chr21 -0.0060 -0.0057	chr22 -0.0608 -0.0334	chrX -0.0131 -0.0101	chrY -0.0019 -0.0020				
H2AZ H2BK5me1 H3K27me1 H3K27me2	chr13 -0.0445 -0.0454 -0.0140 -0.0067	chr14 -0.0728 -0.0574 -0.0286 -0.0133	chr15 -0.0421 -0.0352 -0.0170	chr16 -0.0035 -0.0025 -0.0082	chr17 -0.0556 -0.0353 -0.0128	chr18 -0.0153 -0.0153 -0.0047	chr19 0.0020 -0.0023 -0.0010	chr20 -0.0116 0.0108 -0.0038	chr21 -0.0060 -0.0057 -0.0017	chr22 -0.0608 -0.0334 -0.0171	chrX -0.0131 -0.0101 -0.0025	chrY -0.0019 -0.0020 -0.0014				
H2AZ H2BK5me1 H3K27me1 H3K27me2 H3K27me3	chr13 -0.0445 -0.0454 -0.0140 -0.0067 -0.0110	chr14 -0.0728 -0.0574 -0.0286 -0.0133 -0.0194	chr15 -0.0421 -0.0352 -0.0170 -0.0064 -0.0090	chr16 -0.0035 -0.0025 -0.0082 -0.0039 -0.0008	chr17 -0.0556 -0.0353 -0.0128 -0.0084 -0.0144	chr18 -0.0153 -0.0153 -0.0047 -0.0026 -0.0027	chr19 0.0020 -0.0023 -0.0010 -0.0084 -0.0098	chr20 -0.0116 0.0108 -0.0038 -0.0015 -0.0022	chr21 -0.0060 -0.0057 -0.0017 -0.0013 -0.0011	chr22 -0.0608 -0.0334 -0.0171 -0.0030 -0.0088	chrX -0.0131 -0.0101 -0.0025 -0.0011 -0.0022	chrY -0.0019 -0.0020 -0.0014 -0.0015 -0.0011				
H2AZ H2BK5me1 H3K27me1 H3K27me2 H3K27me3 H3K36me1	chr13 -0.0445 -0.0454 -0.0140 -0.0067 -0.0110 -0.0031	chr14 -0.0728 -0.0574 -0.0286 -0.0133 -0.0194 -0.0073	chr15 -0.0421 -0.0352 -0.0170 -0.0064 -0.0090 -0.0058	chr16 -0.0035 -0.0025 -0.0082 -0.0039 -0.0008	chr17 -0.0556 -0.0353 -0.0128 -0.0084 -0.0144 0.0005	chr18 -0.0153 -0.0153 -0.0047 -0.0026 -0.0027 -0.0023	chr19 0.0020 -0.0023 -0.0010 -0.0084 -0.0098	chr20 -0.0116 0.0108 -0.0038 -0.0015 -0.0022 0.2497	chr21 -0.0060 -0.0057 -0.0017 -0.0013 -0.0011	chr22 -0.0608 -0.0334 -0.0171 -0.0030 -0.0088 -0.0053	chrX -0.0131 -0.0101 -0.0025 -0.0011 -0.0022 -0.0017	chrY -0.0019 -0.0020 -0.0014 -0.0015 -0.0011				
H2AZ H2BK5me1 H3K27me1 H3K27me2 H3K37me3 H3K36me1 H3K36me3	chr13 -0.0445 -0.0454 -0.0140 -0.0067 -0.0110 -0.0031 -0.0268	chr14 -0.0728 -0.0574 -0.0286 -0.0133 -0.0194 -0.0073 -0.0462	chr15 -0.0421 -0.0352 -0.0170 -0.0064 -0.0090 -0.0058 -0.0295	chr16 -0.0035 -0.0025 -0.0082 -0.0039 -0.0008 -0.0008	chr17 -0.0556 -0.0353 -0.0128 -0.0084 -0.0144 0.0005 -0.0241	chr18 -0.0153 -0.0153 -0.0047 -0.0026 -0.0027 -0.0023 -0.0083	chr19 0.0020 -0.0023 -0.0010 -0.0084 -0.0098 -0.0009	chr20 -0.0116 0.0108 -0.0038 -0.0015 -0.0022 0.2497 -0.0080	chr21 -0.0060 -0.0057 -0.0017 -0.0013 -0.0011 -0.0012 0.0092	chr22 -0.0608 -0.0334 -0.0171 -0.0030 -0.0088 -0.0053 -0.0247	chrX -0.0131 -0.0101 -0.0025 -0.0011 -0.0022 -0.0017 -0.0062	chrY -0.0019 -0.0020 -0.0014 -0.0015 -0.0011 -0.0011 -0.0012				
H2AZ H2BK5me1 H3K27me1 H3K27me2 H3K27me3 H3K37me3 H3K36me1 H3K46me1	chr13 -0.0445 -0.0454 -0.0140 -0.0067 -0.0110 -0.0031 -0.0268 -0.0561	chr14 -0.0728 -0.0574 -0.0286 -0.0133 -0.0194 -0.0073 -0.0462 -0.0705	chr15 -0.0421 -0.0352 -0.0170 -0.0064 -0.0090 -0.0058 -0.0295 -0.0472	chr16 -0.0035 -0.0025 -0.0082 -0.0039 -0.0008 -0.0047 -0.0014 -0.0029	chr17 -0.0556 -0.0353 -0.0128 -0.0084 -0.0144 0.0005 -0.0241 -0.0419	chr18 -0.0153 -0.0153 -0.0047 -0.0026 -0.0027 -0.0023 -0.0083 -0.0201	chr19 0.0020 -0.0023 -0.0010 -0.0084 -0.0098 -0.0009 -0.0025	chr20 -0.0116 0.0108 -0.0038 -0.0015 -0.0022 0.2497 -0.0080 0.0201	chr21 -0.0060 -0.0057 -0.0017 -0.0013 -0.0011 -0.0012 0.0092 -0.0066	chr22 -0.0608 -0.0334 -0.0171 -0.0030 -0.0088 -0.0053 -0.0247 -0.0412	chrX -0.0131 -0.0101 -0.0025 -0.0011 -0.0022 -0.0017 -0.0062 -0.0136	chrY -0.0019 -0.0020 -0.0014 -0.0015 -0.0011 -0.0011 -0.0012 -0.0018				
H2AZ H2BK5me1 H3K27me1 H3K27me3 H3K36me1 H3K36me3 H3K4me1 H3K4me1	chr13 -0.0445 -0.0454 -0.0140 -0.0067 -0.0110 -0.0031 -0.0268 -0.0561 -0.0465	chr14 -0.0728 -0.0574 -0.0286 -0.0133 -0.0194 -0.0073 -0.0462 -0.0705 -0.0537	chr15 -0.0421 -0.0352 -0.0170 -0.0064 -0.0098 -0.0295 -0.0472 -0.0384	chr16 -0.0035 -0.0082 -0.0082 -0.0009 -0.00047 -0.0014 -0.0014 -0.0024	chr17 -0.0556 -0.0353 -0.0128 -0.0084 -0.0144 0.0005 -0.0241 -0.0419 -0.0393	chr18 -0.0153 -0.0047 -0.0026 -0.0027 -0.0023 -0.0083 -0.0201 -0.0186	chr19 0.0020 -0.0023 -0.0010 -0.0084 -0.0098 -0.0029 -0.0025 -0.0028	chr20 -0.0116 0.0108 -0.0038 -0.0015 -0.0022 0.2497 -0.0080 0.0201 0.0407	chr21 -0.0060 -0.0057 -0.0017 -0.0013 -0.0011 -0.0012 -0.0066 -0.0063	chr22 -0.0608 -0.0334 -0.0171 -0.0030 -0.0083 -0.0053 -0.0247 -0.0412 -0.0337	chrX -0.0131 -0.0101 -0.0025 -0.0011 -0.0022 -0.0017 -0.0062 -0.0136 -0.0131	chrY -0.0019 -0.0020 -0.0014 -0.0015 -0.0011 -0.0012 -0.0018 -0.0023				
H2AZ H2BK5me1 H3K27me1 H3K27me2 H3K27me3 H3K36me1 H3K4me1 H3K4me2 H3K4me3	chr13 -0.0445 -0.0454 -0.0140 -0.0067 -0.0110 -0.031 -0.0268 -0.0566 -0.0465 -0.0606	chr14 -0.0728 -0.0574 -0.0286 -0.0133 -0.0194 -0.0073 -0.0462 -0.0705 -0.0537 -0.1151	chr15 -0.0421 -0.0352 -0.0170 -0.0064 -0.0098 -0.0295 -0.0472 -0.0384 -0.0619	chr16 -0.0035 -0.0082 -0.0082 -0.0009 -0.00047 -0.0014 -0.0014 -0.0024 -0.0024 -0.0024	chr17 -0.0556 -0.0353 -0.0128 -0.0084 -0.0144 0.0005 -0.0241 -0.0419 -0.0393 -0.0705	chr18 -0.0153 -0.0047 -0.0026 -0.0027 -0.0023 -0.0080 -0.0201 -0.0186 -0.0174	chr19 0.0020 -0.0023 -0.0010 -0.0084 -0.0098 -0.0026 -0.0026 -0.0028 -0.0028 -0.0028	chr20 -0.0116 0.0108 -0.0038 -0.0015 -0.0022 0.2497 -0.0080 0.0201 0.0407 0.0358	chr21 -0.0060 -0.0057 -0.0017 -0.0013 -0.0011 -0.0012 -0.0062 -0.0063 -0.0062	chr22 -0.0608 -0.0334 -0.0171 -0.0030 -0.0083 -0.0053 -0.0247 -0.0412 -0.0337 -0.0703	chrX -0.0131 -0.0010 -0.0025 -0.0011 -0.0022 -0.0017 -0.0062 -0.0131 -0.0174	chr¥ -0.0019 -0.0020 -0.0014 -0.0015 -0.0011 -0.0011 -0.0012 -0.0018 -0.0023 -0.0025				
H2AZ H2BK5me1 H3K27me1 H3K27me2 H3K27me3 H3K36me1 H3K36me3 H3K4me2 H3K4me2 H3K4me3 H3K79me1	chr13 -0.0445 -0.0454 -0.0140 -0.0067 -0.0110 -0.0268 -0.0561 -0.0465 -0.0666 -0.0606	chr14 -0.0728 -0.0574 -0.0286 -0.0133 -0.0194 -0.0073 -0.0462 -0.0705 -0.0537 -0.1151 -0.0309	chr15 -0.0421 -0.0352 -0.0170 -0.0064 -0.0090 -0.0295 -0.0472 -0.0384 -0.0384 -0.0619 -0.0013	chr16 -0.0035 -0.0025 -0.0082 -0.0039 -0.00047 -0.0014 -0.0029 -0.0024 -0.0024 -0.0019	chr17 -0.0556 -0.0353 -0.0128 -0.0084 -0.0144 -0.0241 -0.0241 -0.0419 -0.0393 -0.0705 -0.0188	chr18 -0.0153 -0.0047 -0.0026 -0.0027 -0.0023 -0.0083 -0.0201 -0.0186 -0.0158	chr19 0.0020 -0.0023 -0.0010 -0.0084 -0.0098 -0.0026 -0.0025 -0.0028 -0.0028 -0.0028 -0.0028	chr20 -0.0116 0.0108 -0.0038 -0.0015 -0.0022 0.2497 -0.0080 0.0201 0.0407 0.0358 0.0085	chr21 -0.0060 -0.0057 -0.0017 -0.0013 -0.0011 -0.0012 0.0092 -0.0066 -0.0063 -0.0062 -0.0061	chr22 -0.0508 -0.0334 -0.0171 -0.0030 -0.0088 -0.0053 -0.0247 -0.0412 -0.0337 -0.0703 -0.0703 -0.0703	chrX -0.0131 -0.0101 -0.0025 -0.0011 -0.0022 -0.0017 -0.0062 -0.0136 -0.0131 -0.0174 -0.0052	chr¥ -0.0019 -0.0020 -0.0014 -0.0015 -0.0011 -0.0011 -0.0012 -0.0018 -0.0018 -0.0018				
H2A2 H2BK5me1 H3K27me1 H3K27me2 H3K27me3 H3K36me1 H3K36me3 H3K4me2 H3K4me3 H3K79me1 H3K79me1	chr13 -0.0445 -0.0454 -0.0454 -0.0454 -0.0467 -0.0110 -0.031 -0.0268 -0.0561 -0.0465 -0.0606 -0.0018 -0.0034	chr14 -0.0728 -0.0574 -0.0286 -0.0133 -0.0194 -0.0073 -0.0462 -0.0705 -0.0537 -0.1151 -0.0309 -0.0582	chr15 -0.0421 -0.0352 -0.0170 -0.0064 -0.0090 -0.0295 -0.0472 -0.0384 -0.0384 -0.0619 -0.0013 -0.0028	chr16 -0.0035 -0.0025 -0.0082 -0.0039 -0.00047 -0.0014 -0.0029 -0.0024 -0.0024 -0.0039 -0.0019 -0.0043	chr17 -0.0556 -0.0353 -0.0128 -0.0084 -0.0144 -0.0419 -0.0393 -0.0705 -0.0188 -0.0397	chr18 -0.0153 -0.0047 -0.0026 -0.0027 -0.0023 -0.0083 -0.0201 -0.0176 -0.0174 -0.0158 -0.0174	chr19 0.0020 -0.0023 -0.0010 -0.0084 -0.0098 -0.0026 -0.0025 -0.0028 -0.0028 -0.0028 -0.0017 -0.0191	chr20 -0.0116 0.0108 -0.0038 -0.0015 -0.0022 0.2497 -0.0080 0.0201 0.0407 0.0407 0.0358 0.0085 -0.0157	chr21 -0.0060 -0.0057 -0.0017 -0.0013 -0.0011 -0.0012 -0.0066 -0.0063 -0.0063 -0.0063 -0.0081 0.0137	chr22 -0.0608 -0.0334 -0.0171 -0.0030 -0.0088 -0.0053 -0.0247 -0.0412 -0.0337 -0.0703 -0.0010 -0.0010	chrX -0.0131 -0.0025 -0.0011 -0.0022 -0.0017 -0.0062 -0.0136 -0.0131 -0.0174 -0.0052 -0.0186	chr¥ -0.0019 -0.0020 -0.0014 -0.0015 -0.0011 -0.0012 -0.0018 -0.0023 -0.0018 -0.0018 -0.0018 -0.0018 -0.0018				
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Figure 3: Table showing correlation coefficient of spacing and run lengths

Appendix	: D
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Chromosome #	Terminal nodes before	Terminal nodes after				
	multiple test	multiple test				
	correction	correction				
1	6985471	6501661				
2	7386077	6912765				
3	5652315	5149539				
4	4579833	4374105				
5	4700193	4421525				
6	4509073	4281157				
7	4135103	4009053				
8	4037995	3923059				
9	3928107	3852265				
10	3854737	3736259				
11	3865791	3747787				
12	3819251	3698983				
13	2862635	2705747				
14	2780659	2626505				
15	2507371	2365689				
16	2534539	2394211				
17	2577619	2437795				
18	2258731	2031463				
19	1890361	1757899				
20	1988487	1988487				
21	1057471	1008587				
22	1135587	1090799				
X	2920127	2707119				
Y	262679	229685				

Figure 4: Number of terminal nodes before and after applying the multiple test correction

Appendix E



Figure 5: graphical representation of the partitions on chromosome 1



Figure 6: graphical representation of the partitions on chromosome 2



Figure 7: graphical representation of the partitions on chromosome 3



Figure 8: graphical representation of the partitions on chromosome 4



Figure 9: graphical representation of the partitions on chromosome 5



Figure 10: graphical representation of the partitions on chromosome $6\,$



Figure 11: graphical representation of the partitions on chromosome $7\,$



Figure 12: graphical representation of the partitions on chromosome 8



Figure 13: graphical representation of the partitions on chromosome $9\,$



Figure 14: graphical representation of the partitions on chromosome 10



Figure 15: graphical representation of the partitions on chromosome 11



Figure 16: graphical representation of the partitions on chromosome 12



Figure 17: graphical representation of the partitions on chromosome 13



Figure 18: graphical representation of the partitions on chromosome 14



Figure 19: graphical representation of the partitions on chromosome 15



Figure 20: graphical representation of the partitions on chromosome 16



Figure 21: graphical representation of the partitions on chromosome 17



Figure 22: graphical representation of the partitions on chromosome 18



Figure 23: graphical representation of the partitions on chromosome 19



Figure 24: graphical representation of the partitions on chromosome 20



Figure 25: graphical representation of the partitions on chromosome 21


Figure 26: graphical representation of the partitions on chromosome $22\,$



Figure 27: graphical representation of the partitions on chromosome X



Figure 28: graphical representation of the partitions on chromosome Y