

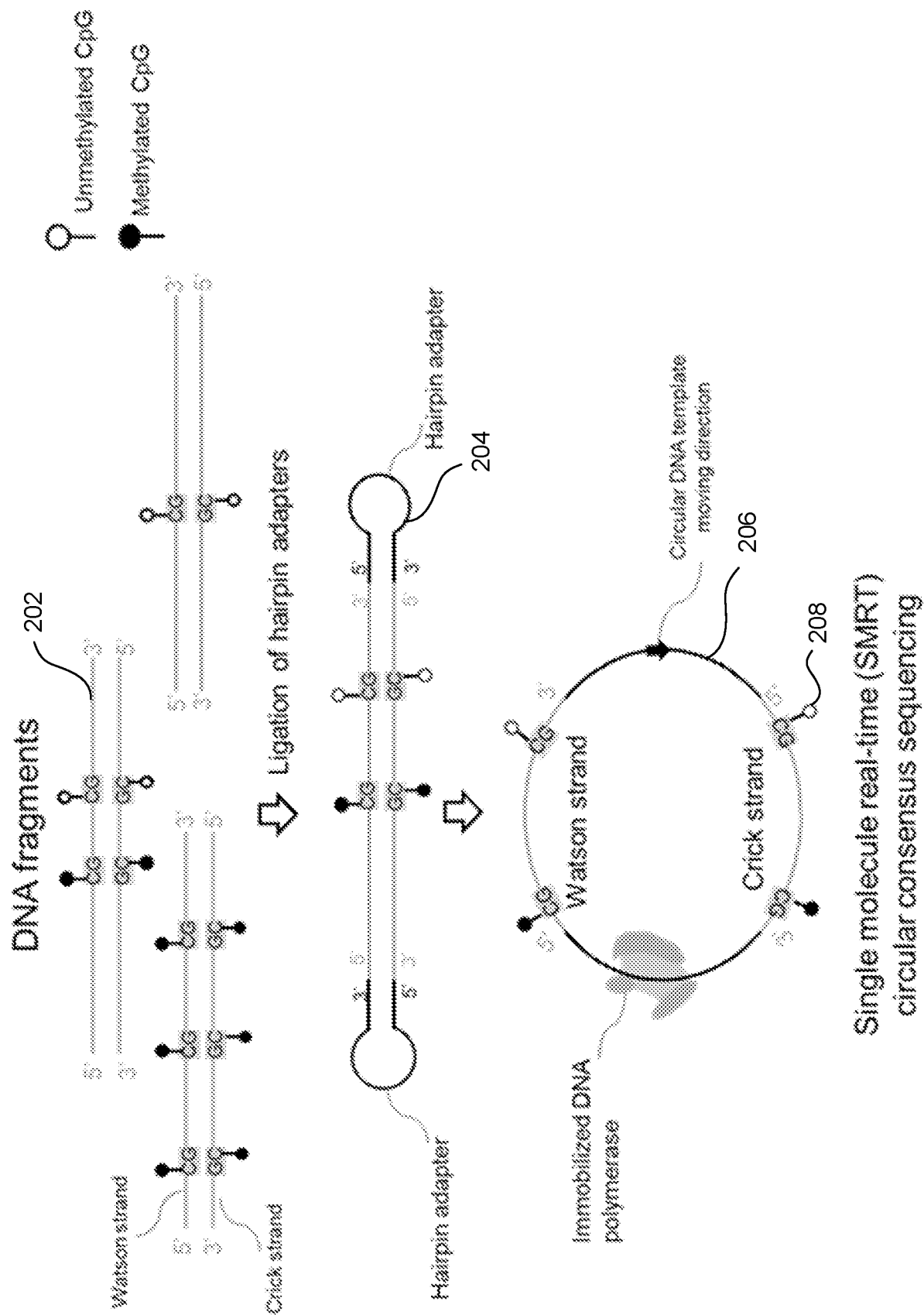


FIG. 2







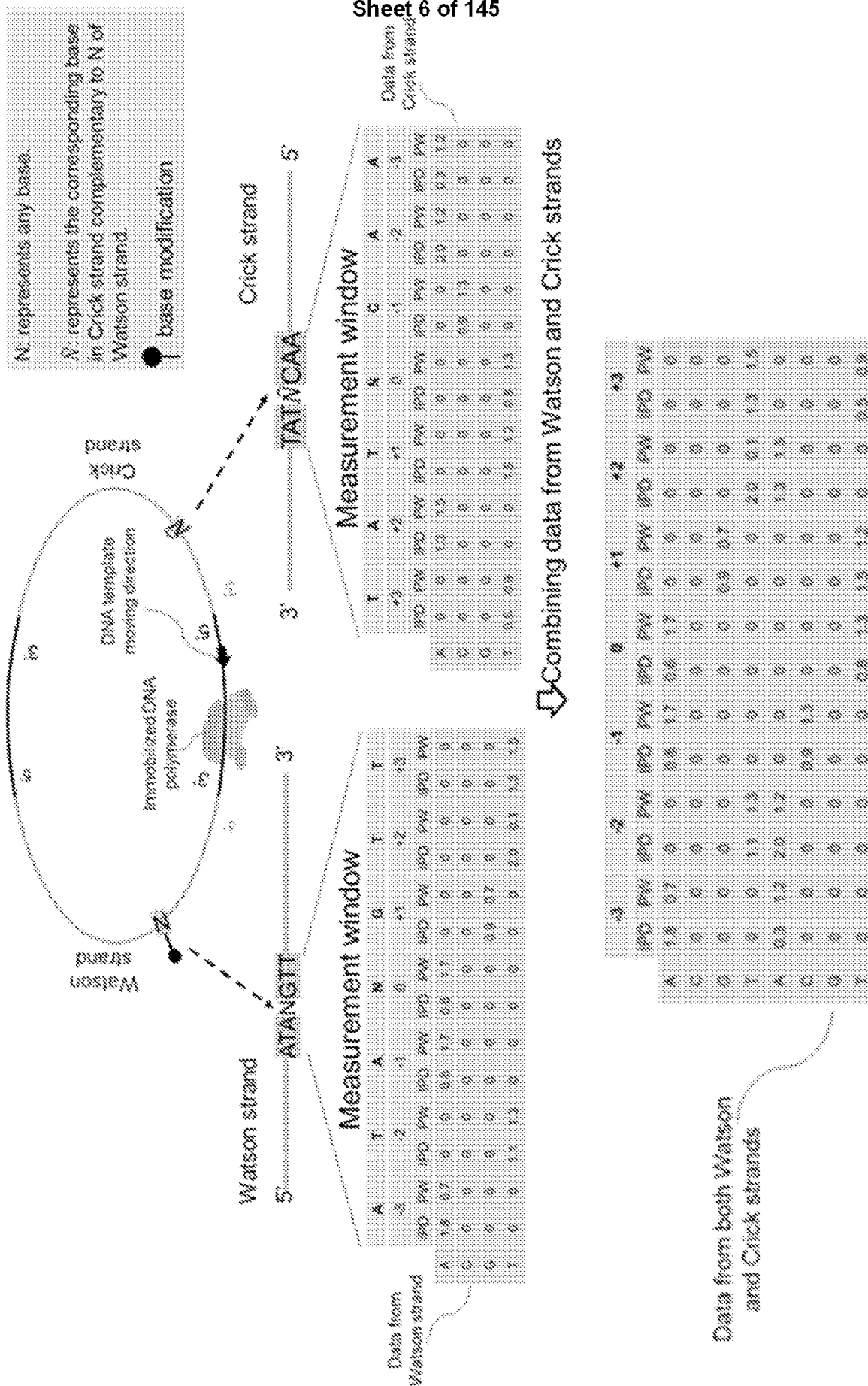


FIG. 6

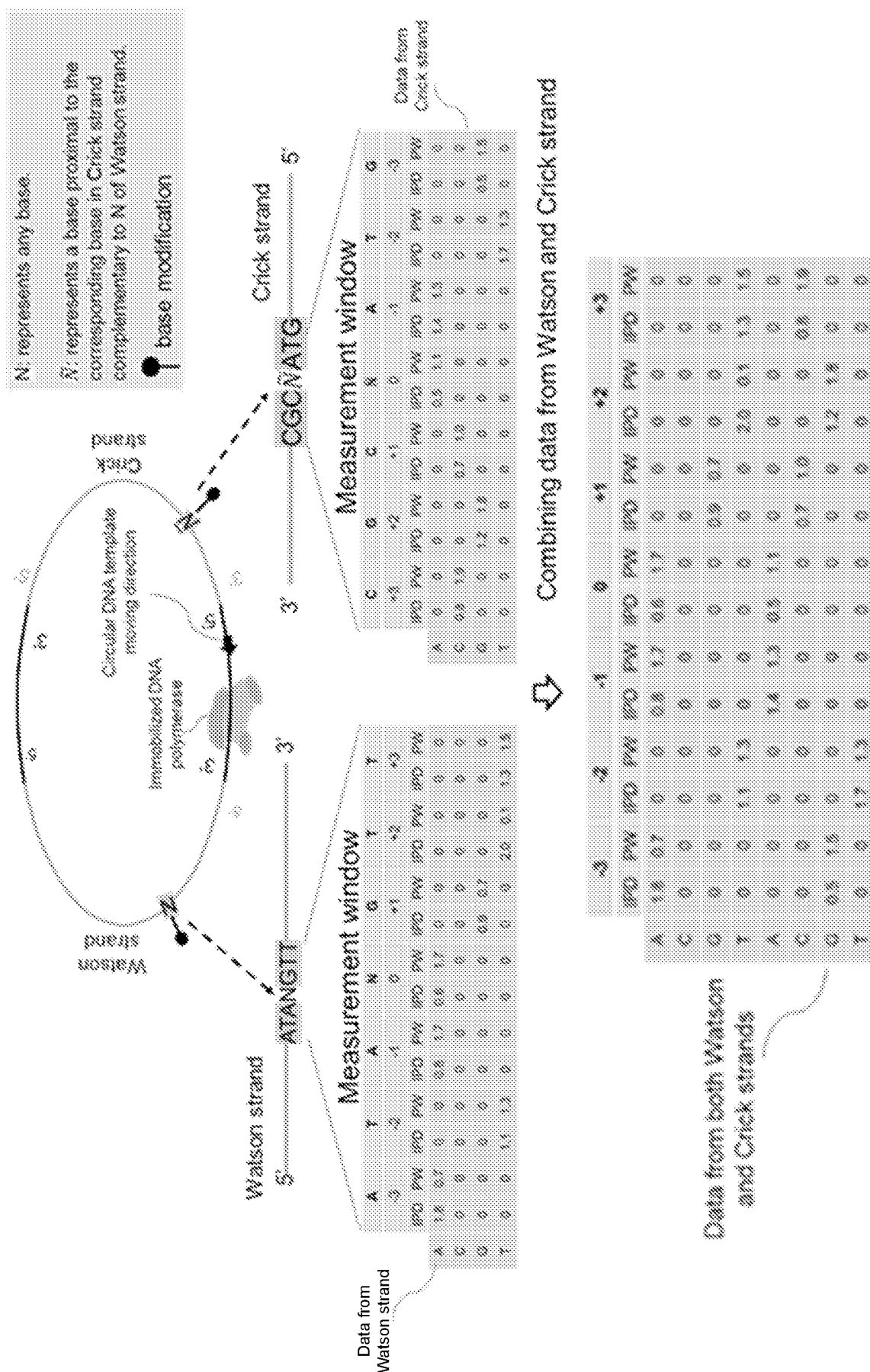


FIG. 7

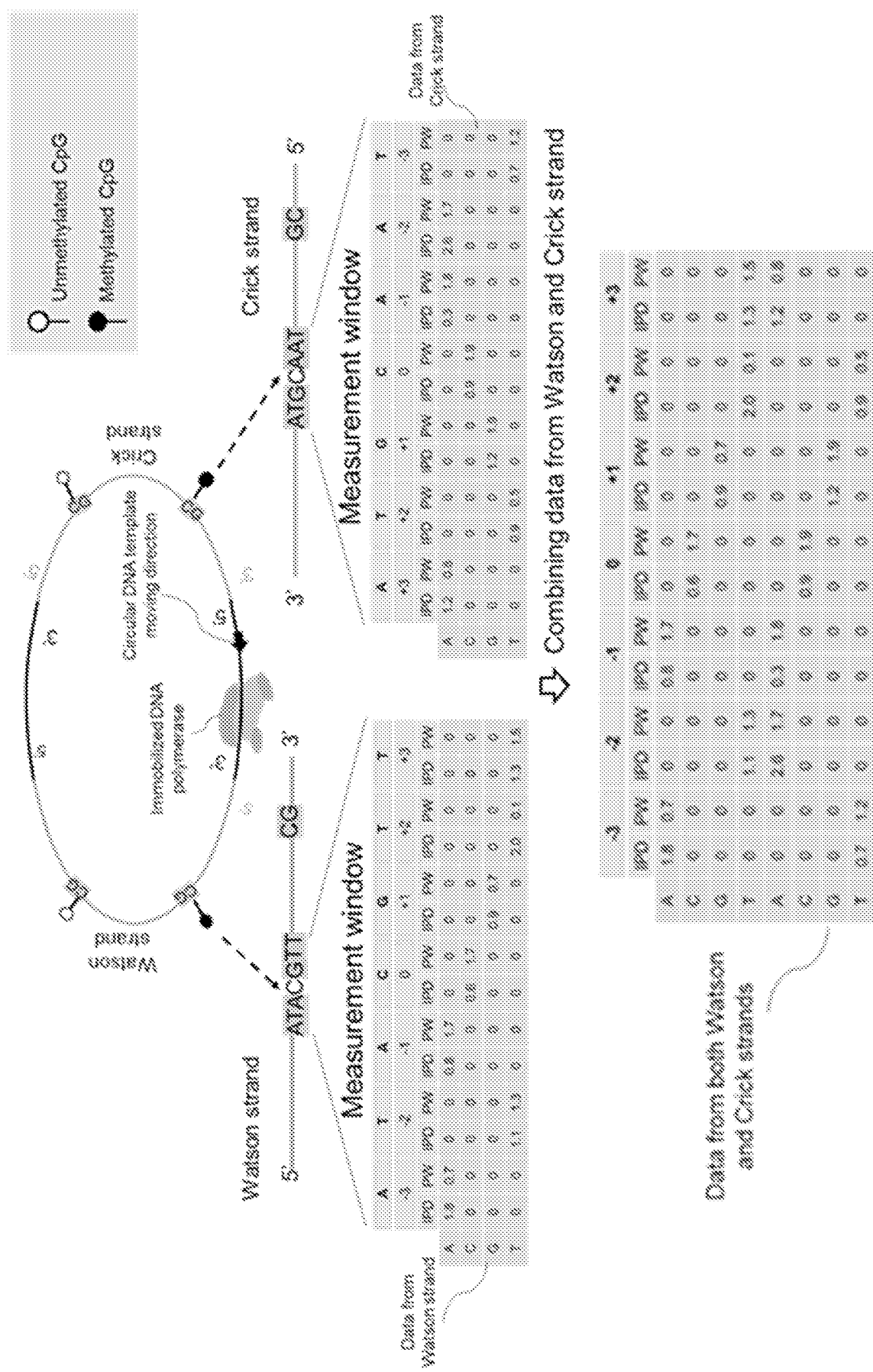


FIG. 8

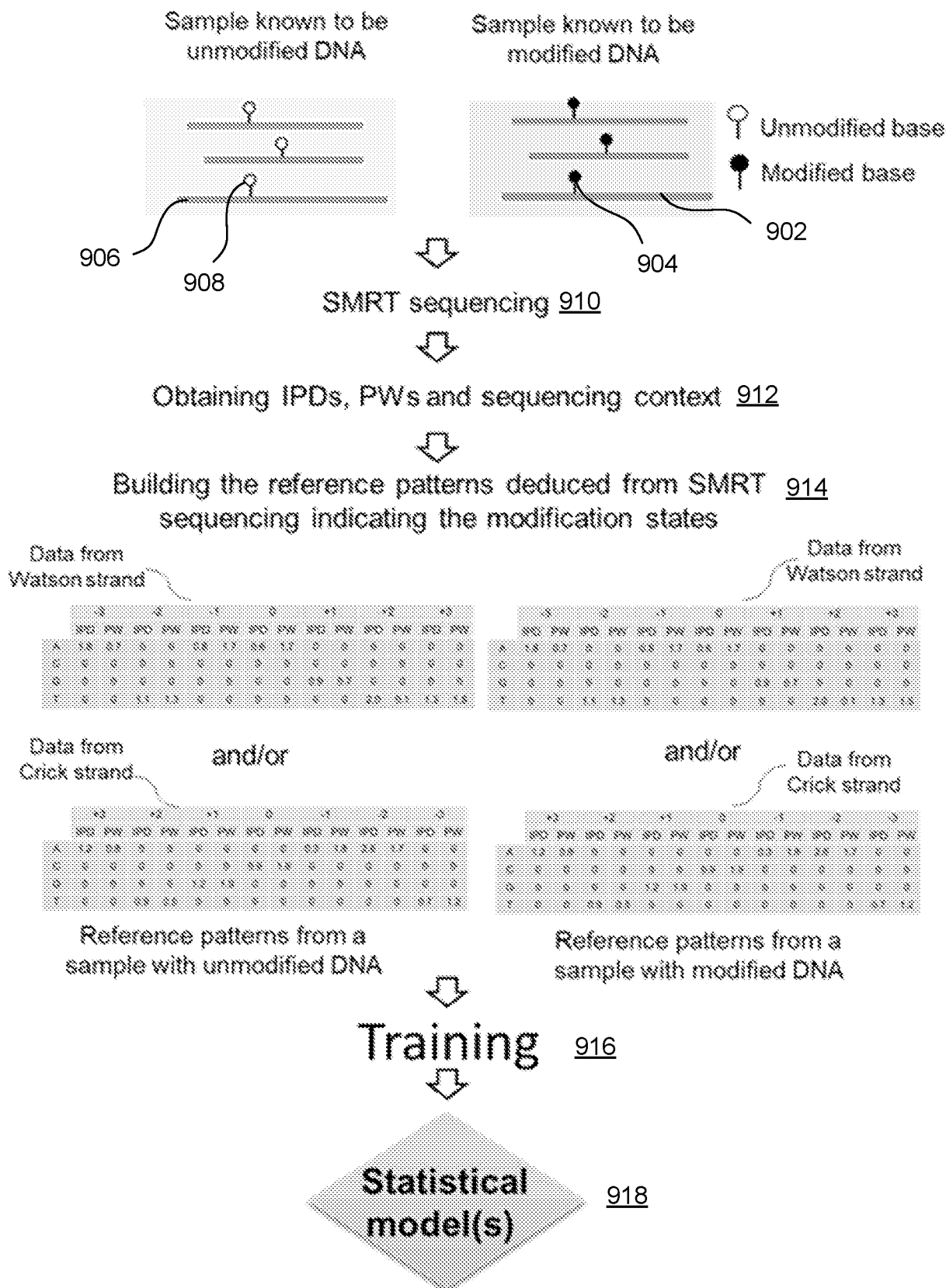


FIG. 9

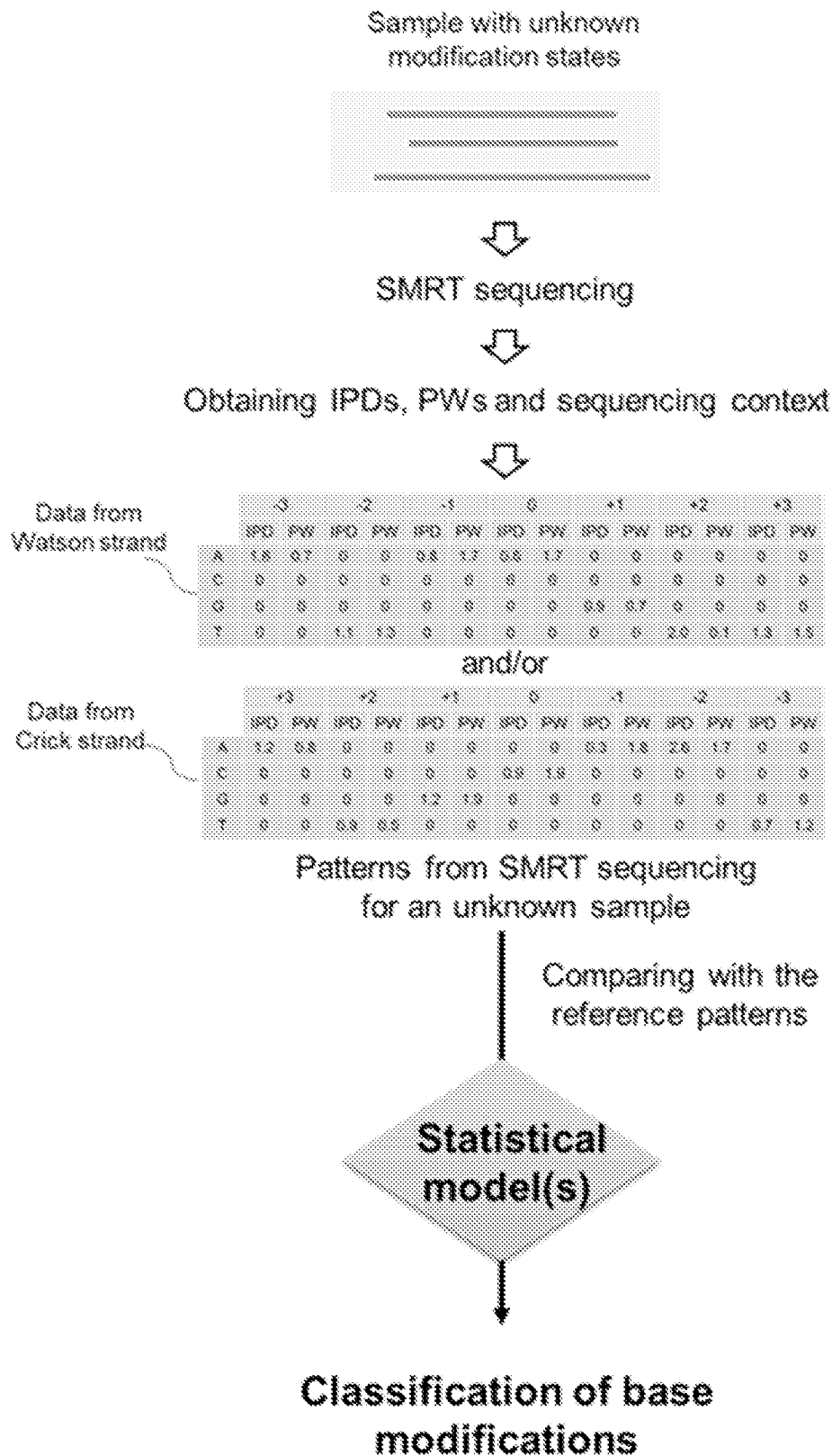


FIG. 10

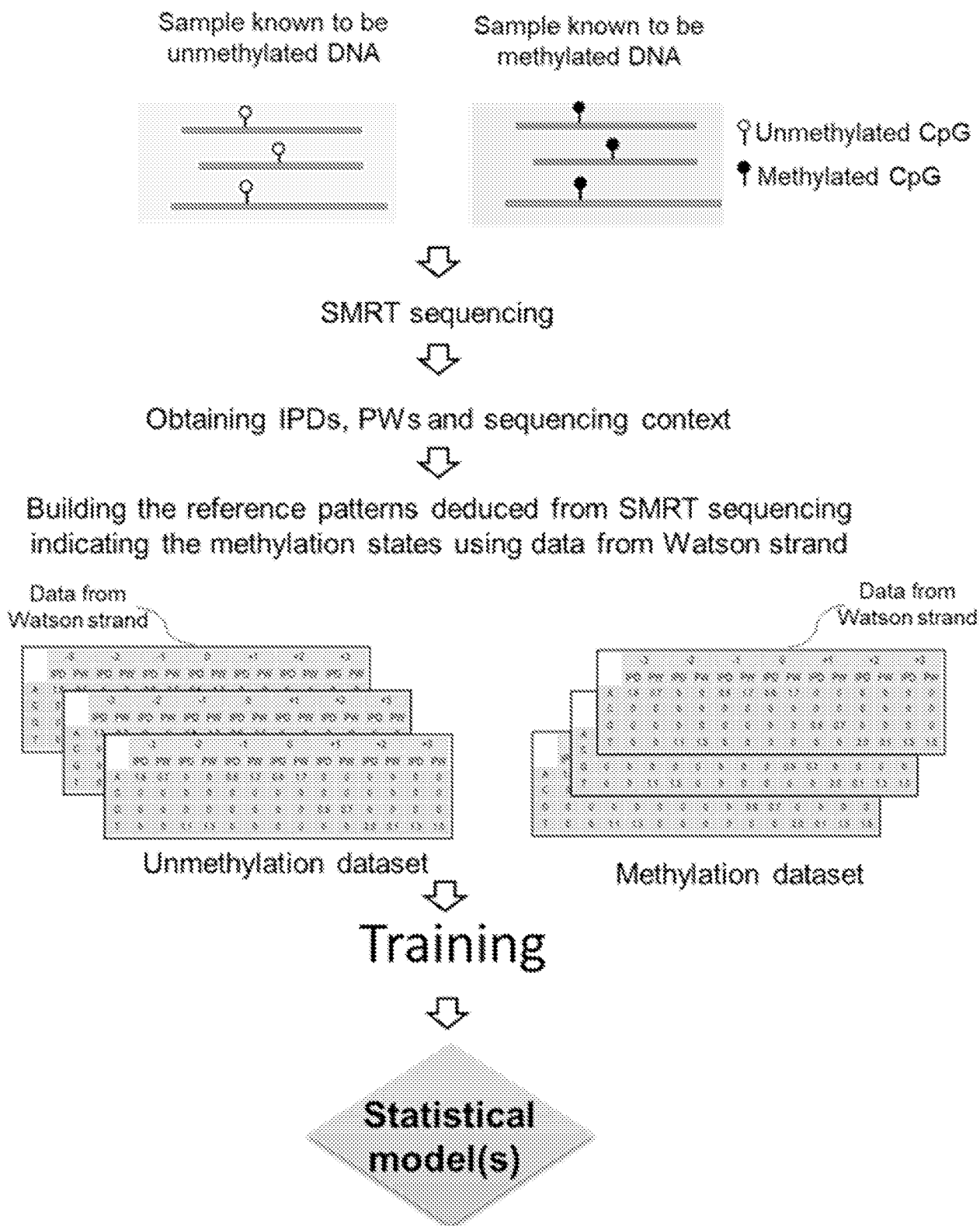
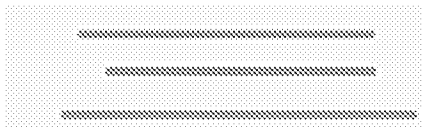


FIG. 11

Samples with unknown
methylation states



SMRT sequencing



Obtaining IPDs, PWs and sequencing context



Data from
Watson strand

	-3		-2		-1		0		+1		+2		+3	
	IPD	PW	IPD	PW	IPD	PW	IPD	PW	IPD	PW	IPD	PW	IPD	PW
A	1.8	0.7	0	0	0.8	1.7	0.6	1.7	0	0	0	0	0	0
C	0	0	0	0	0	0	0	0	0	0	0	0	0	0
G	0	0	0	0	0	0	0	0	0.9	0.7	0	0	0	0
T	0	0	1.1	1.3	0	0	0	0	0	0	2.0	0.1	1.3	1.5

Patterns from SMRT sequencing
for an unknown sample

Comparing with the
reference patterns

**Statistical
model(s)**



**Classification of
methylation states**

FIG. 12

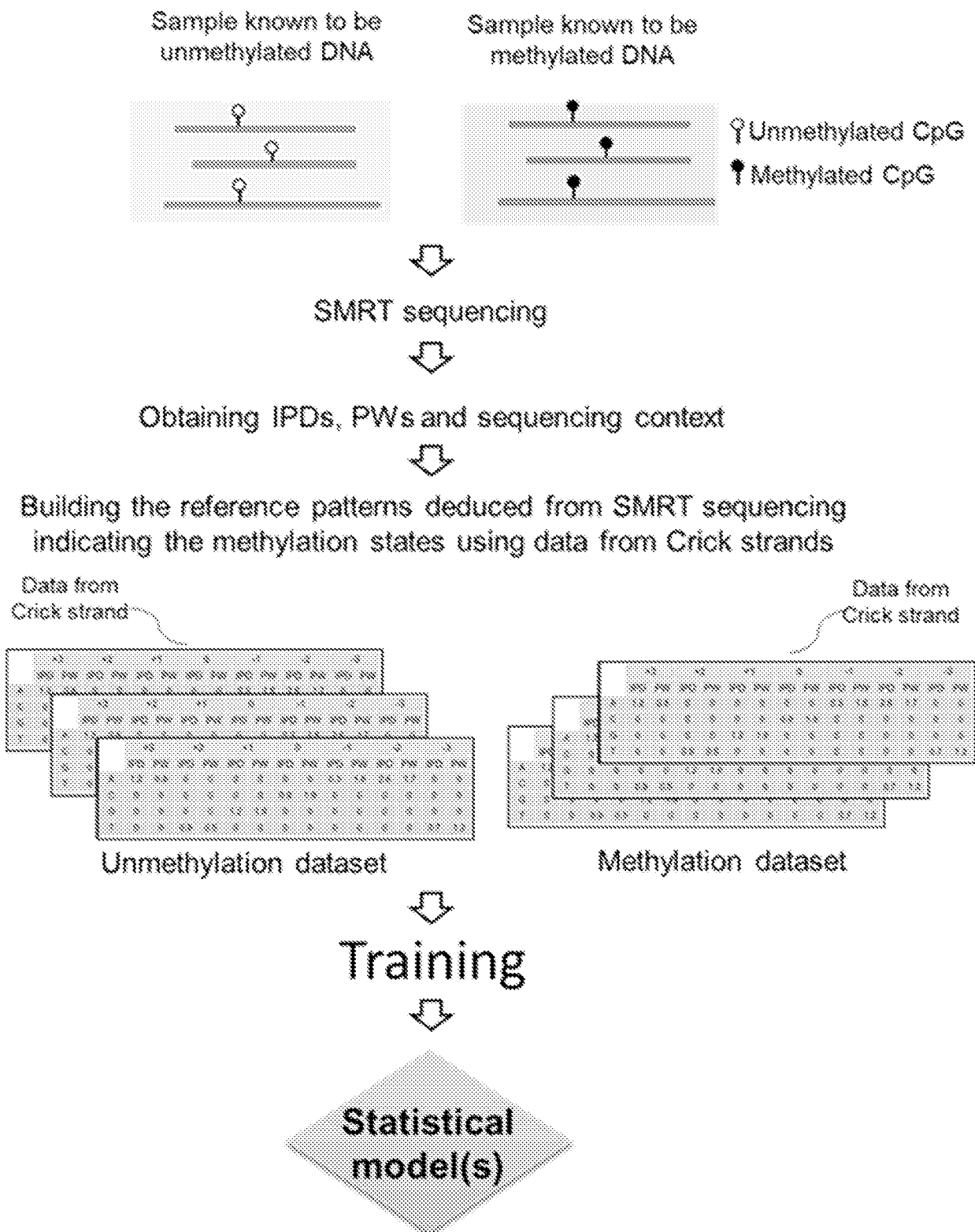
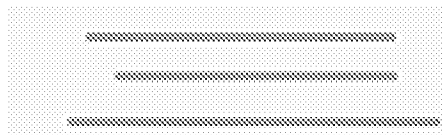


FIG. 13

Sample with unknown
methylation states



SMRT sequencing



Obtaining IPDs, PWs and sequencing context

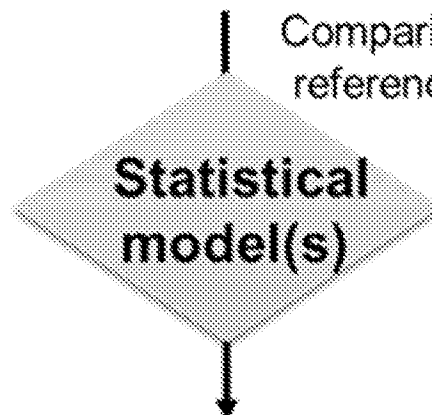


Data from
Crick strand

	+3		+2		+1		0		-1		-2		-3	
	IPD	PW	IPD	PW	IPD	PW	IPD	PW	IPD	PW	IPD	PW	IPD	PW
A	1.2	0.8	0	0	0	0	0	0	0.3	1.8	2.8	1.7	0	0
C	0	0	0	0	0	0	0.8	1.8	0	0	0	0	0	0
G	0	0	0	0	1.2	1.9	0	0	0	0	0	0	0	0
T	0	0	0.9	0.5	0	0	0	0	0	0	0	0	0.7	1.2

Patterns from SMRT sequencing
for an unknown sample

Comparing with the
reference patterns



Classification of
methylation states

FIG.14

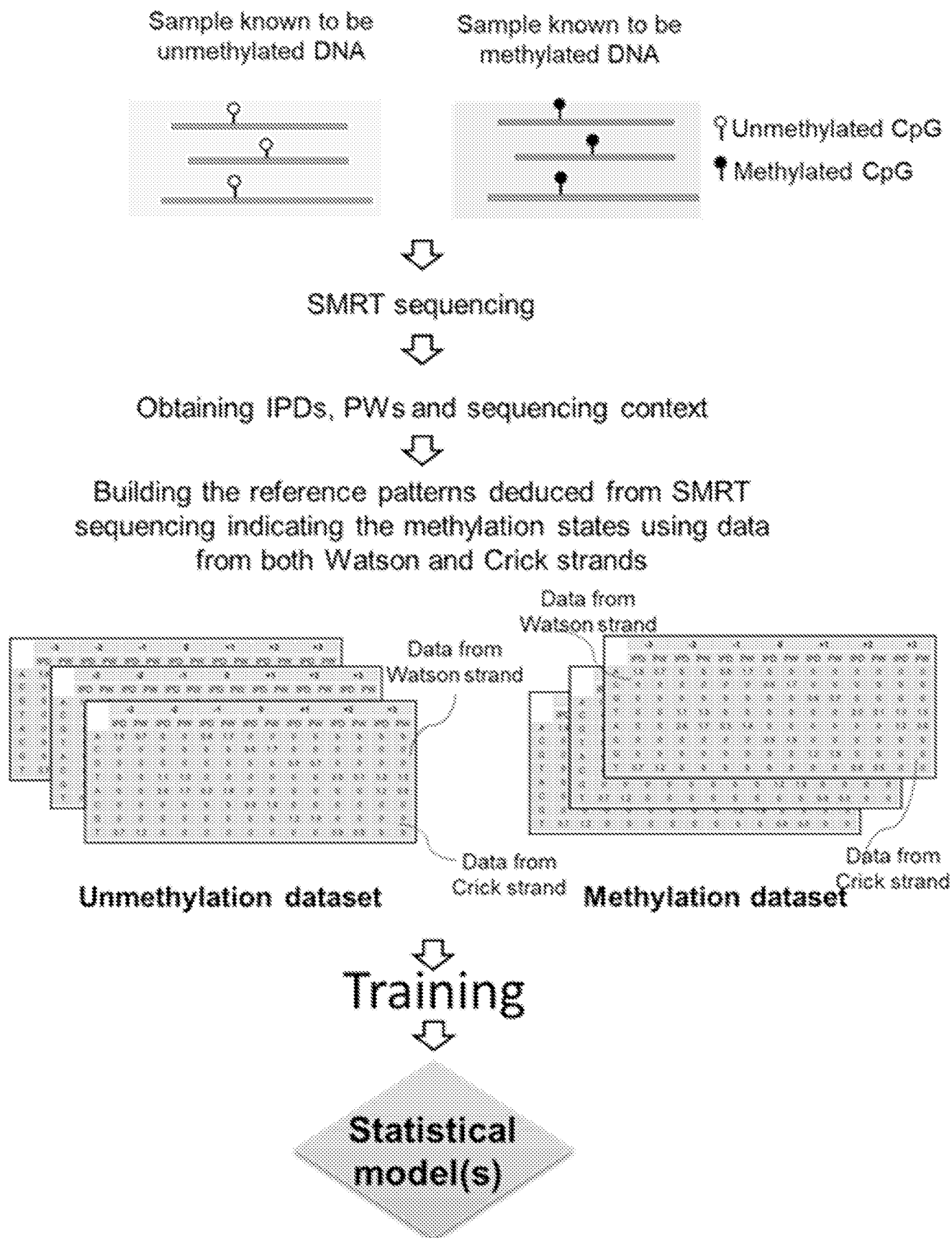


FIG. 15

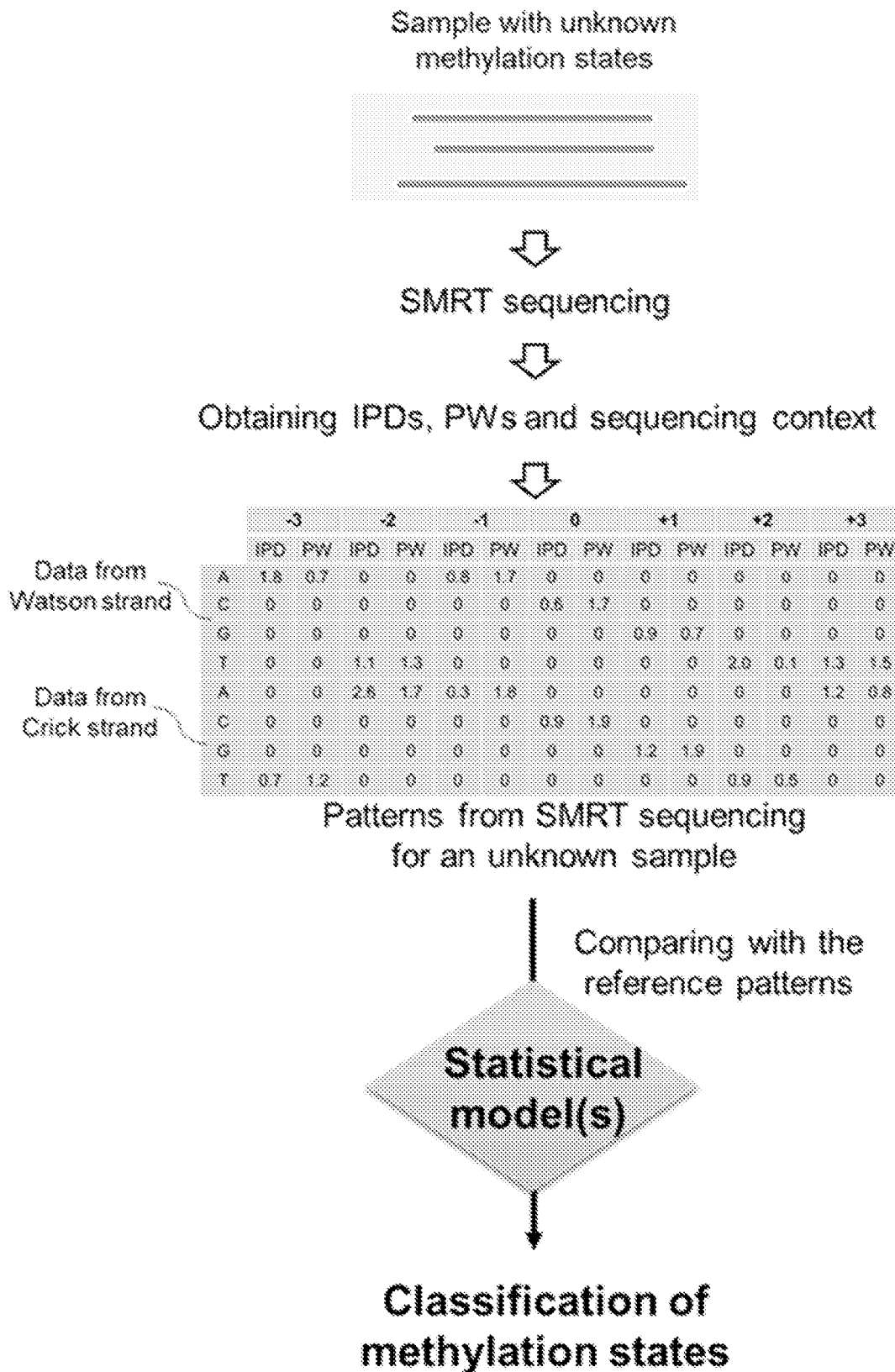


FIG. 16

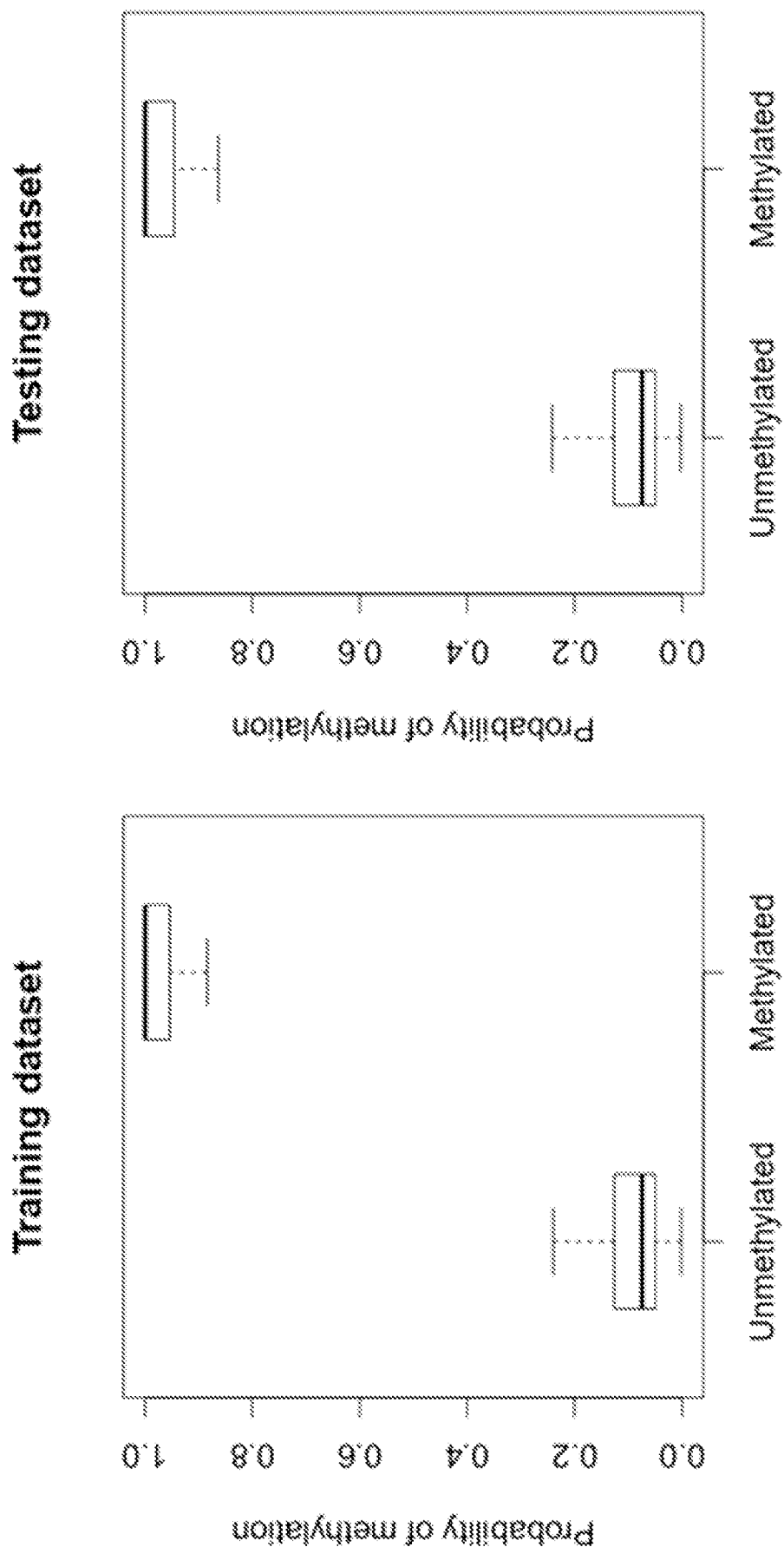


FIG. 17A

FIG. 17B

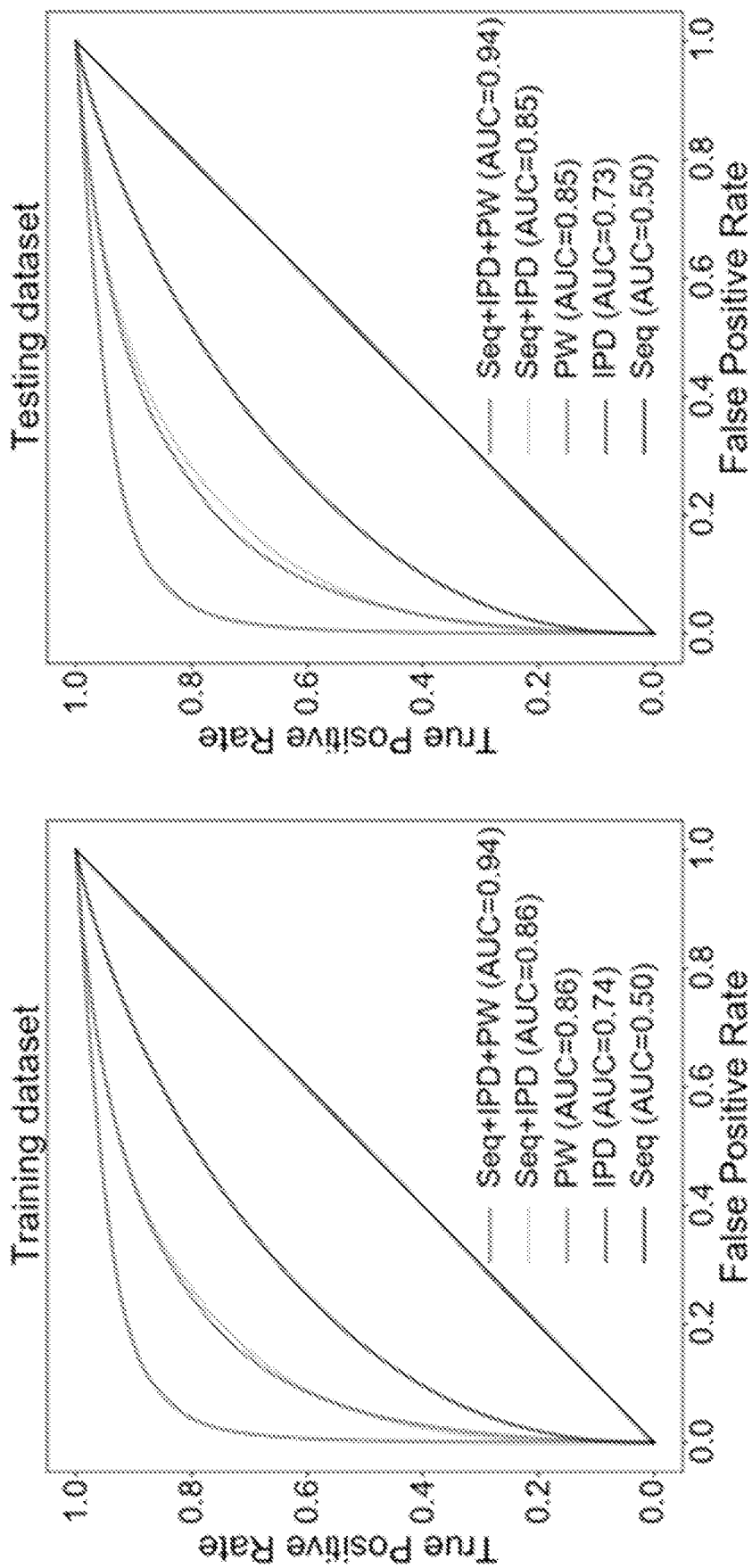


FIG. 18B

FIG. 18A

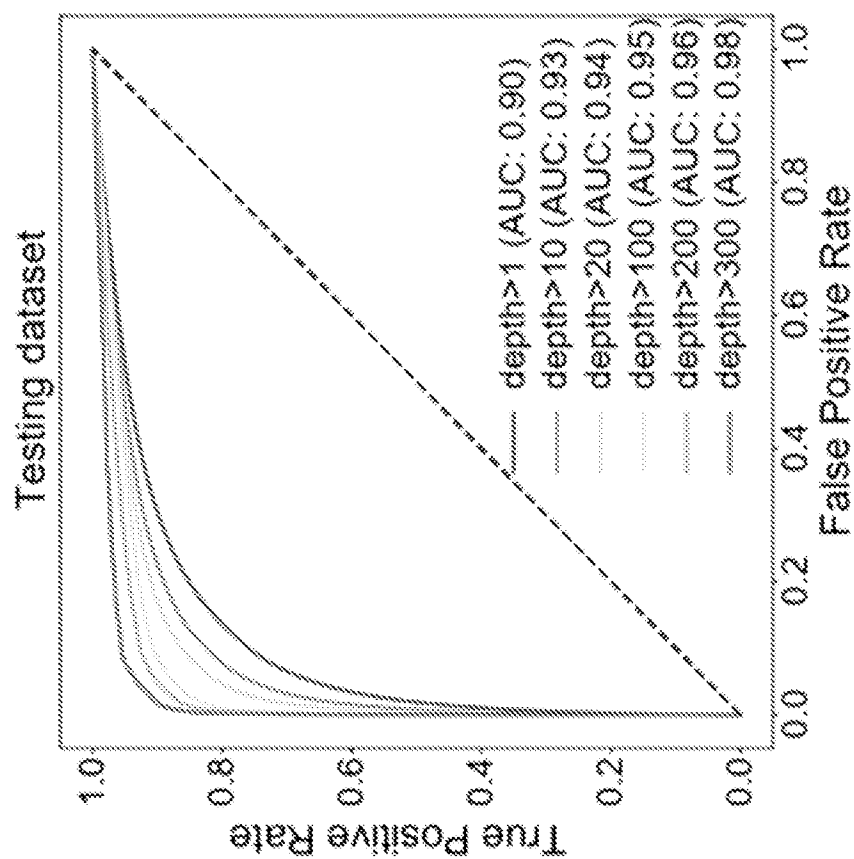


FIG. 19B

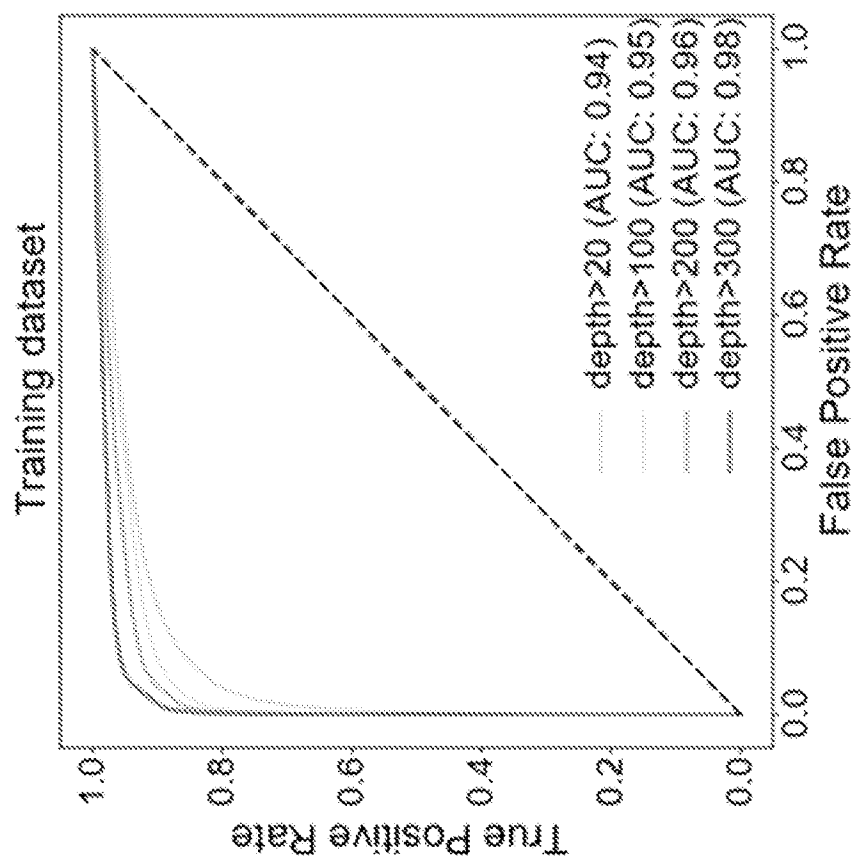


FIG. 19A

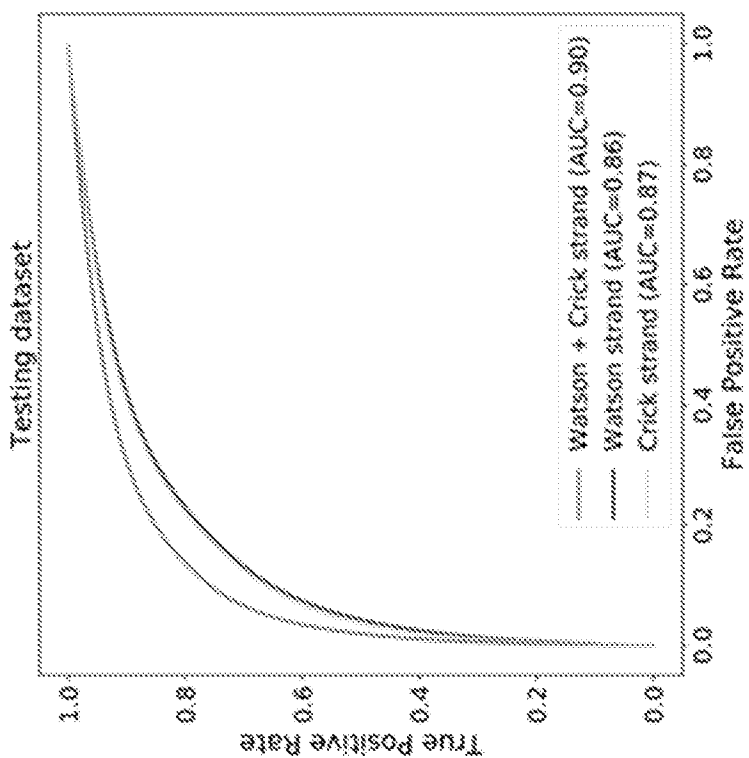


FIG. 20B

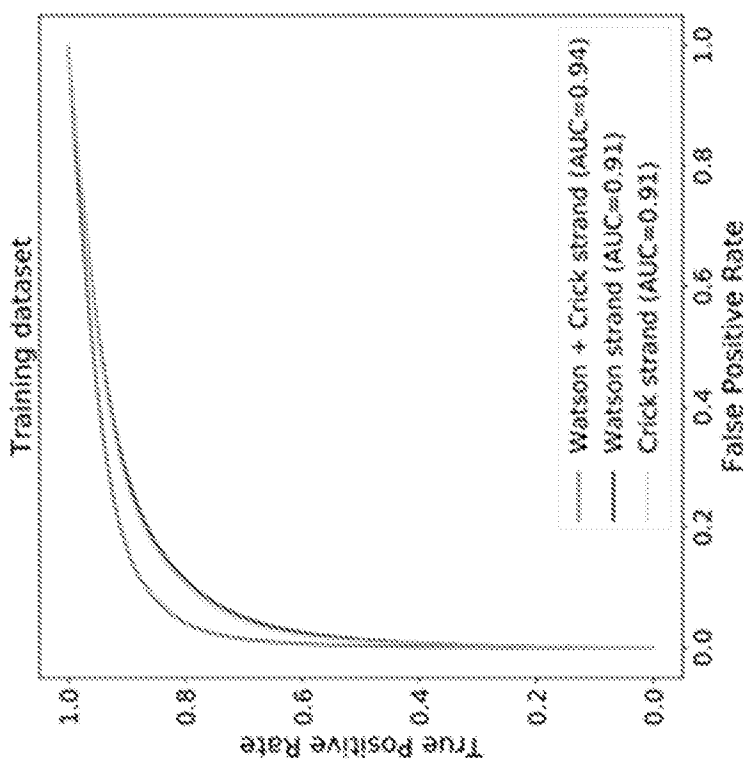


FIG. 20A

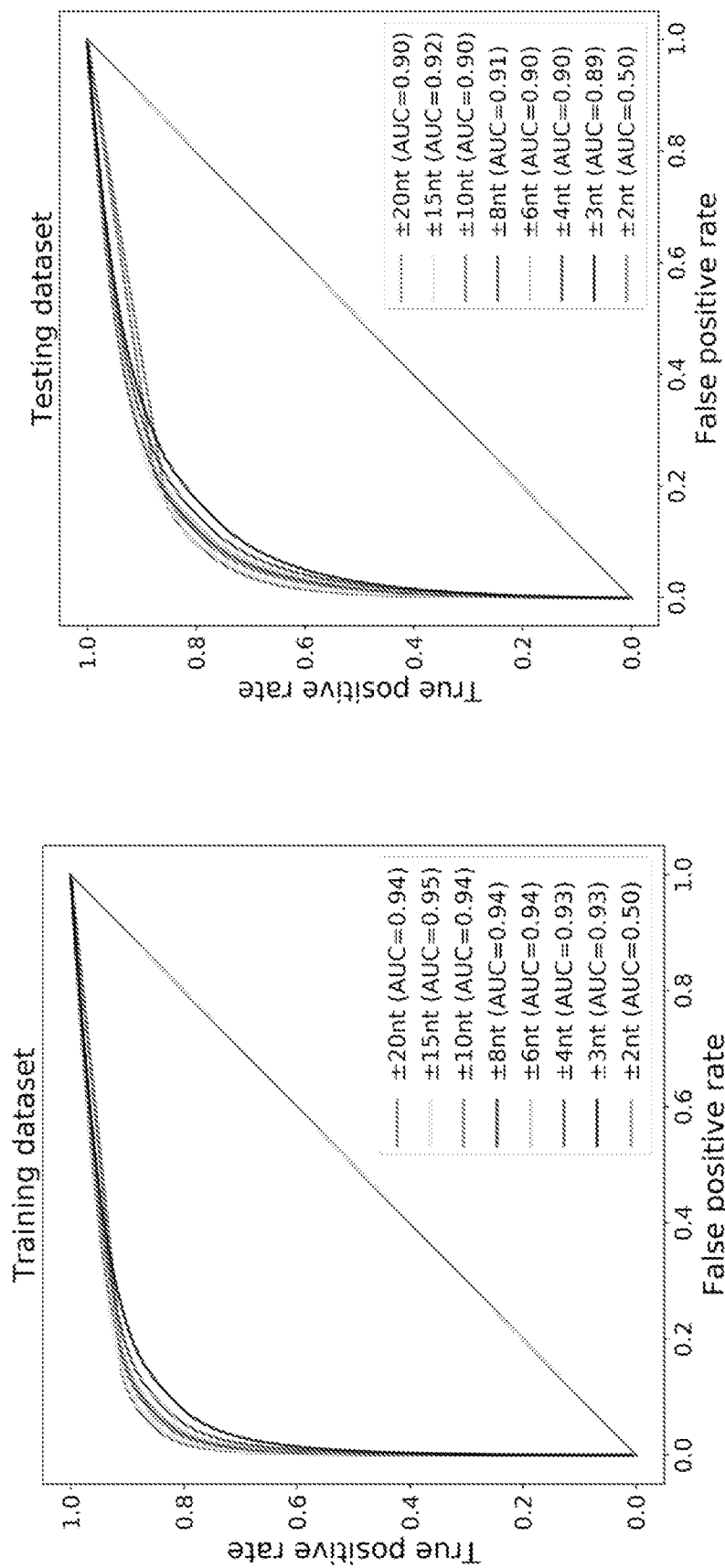


FIG. 21A

FIG. 21B

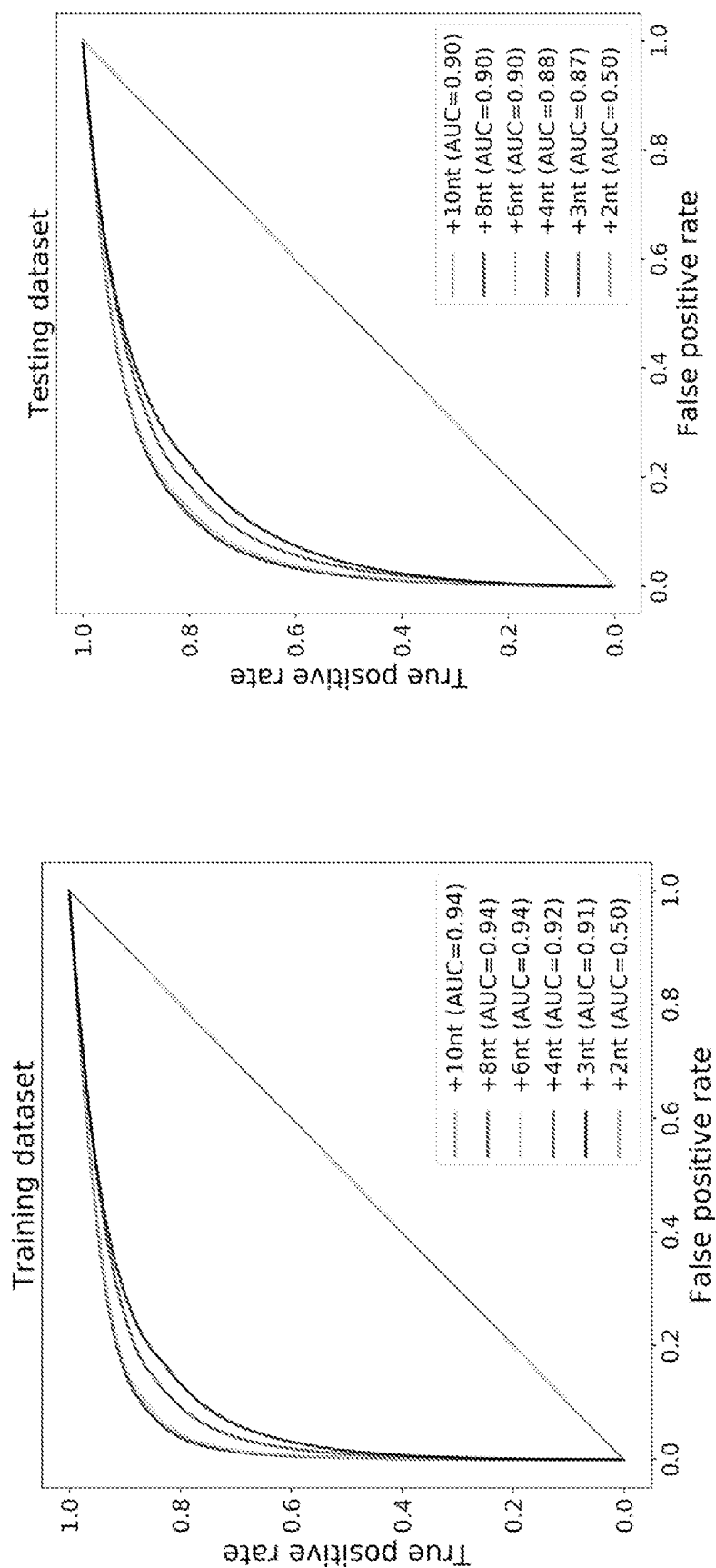


FIG. 22B

FIG. 22A

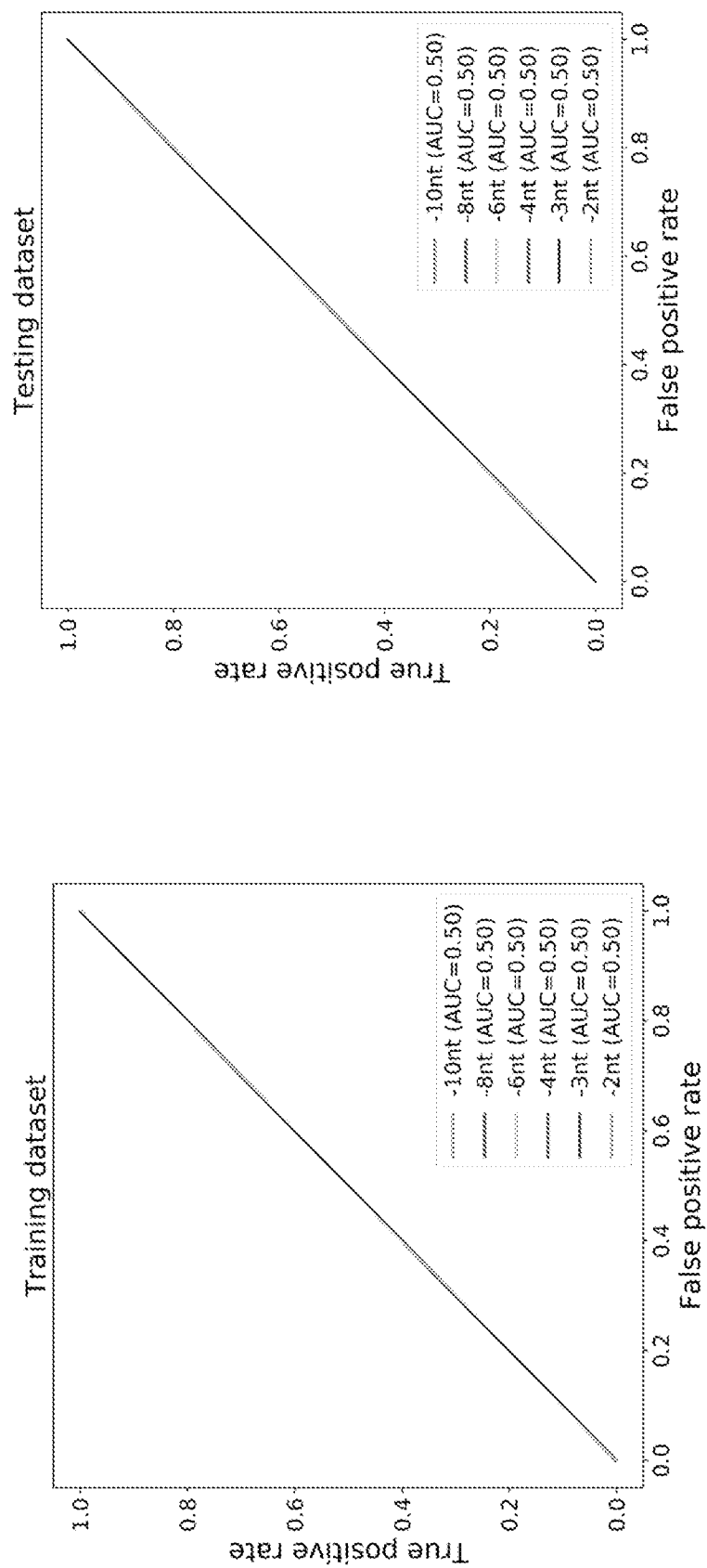


FIG. 23B

FIG. 23A

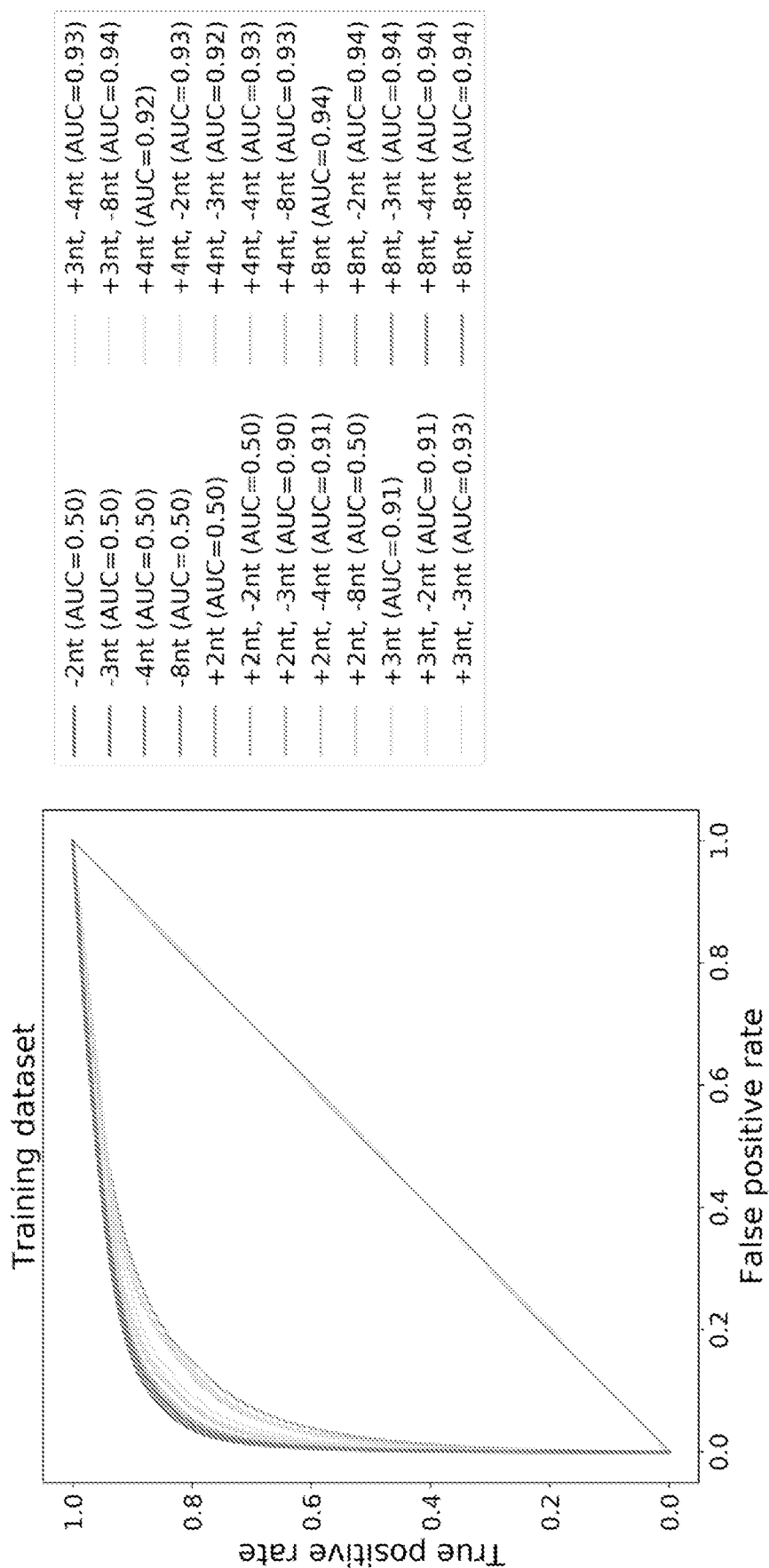


FIG. 24

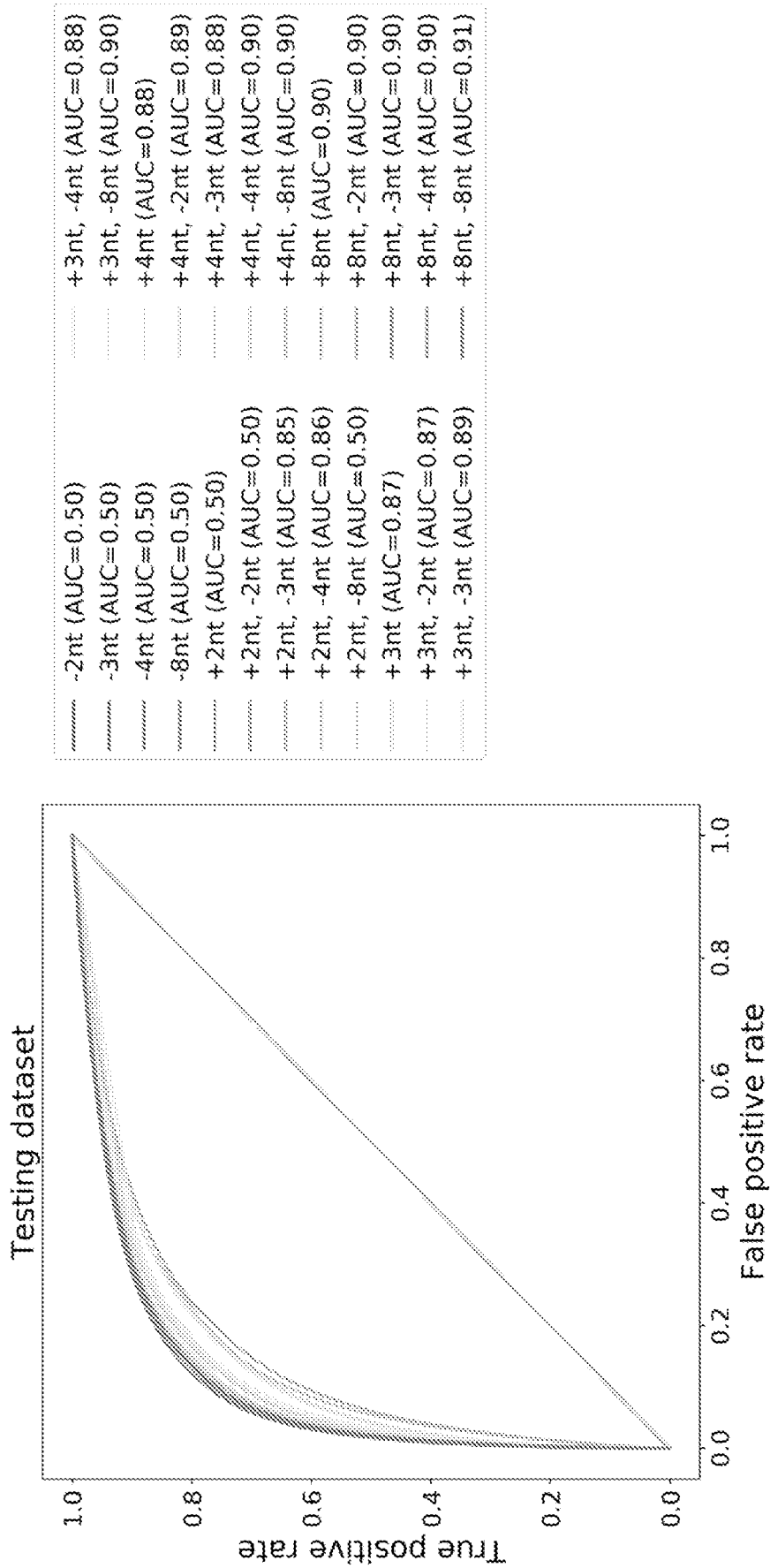


FIG. 25

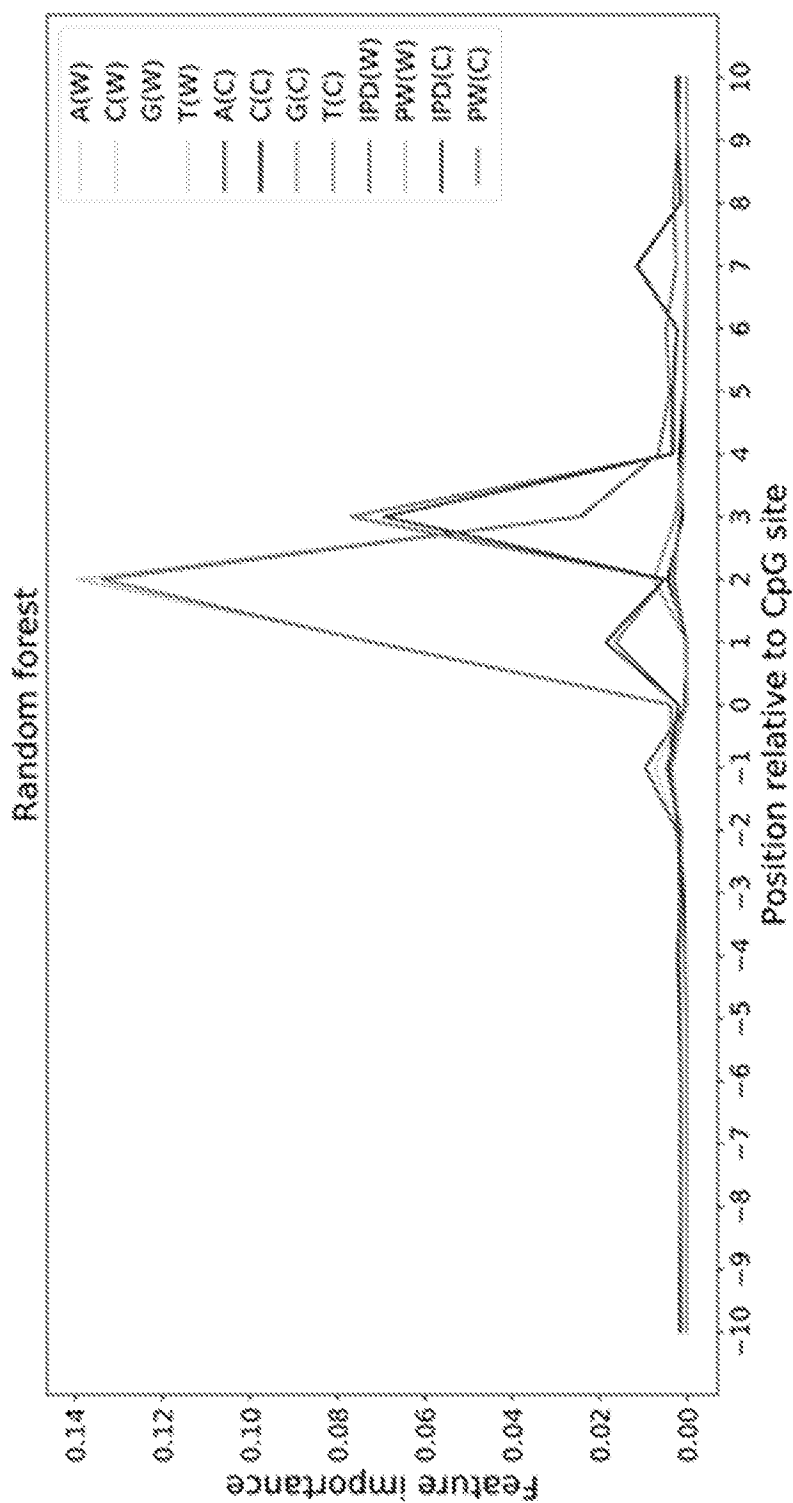


FIG. 26

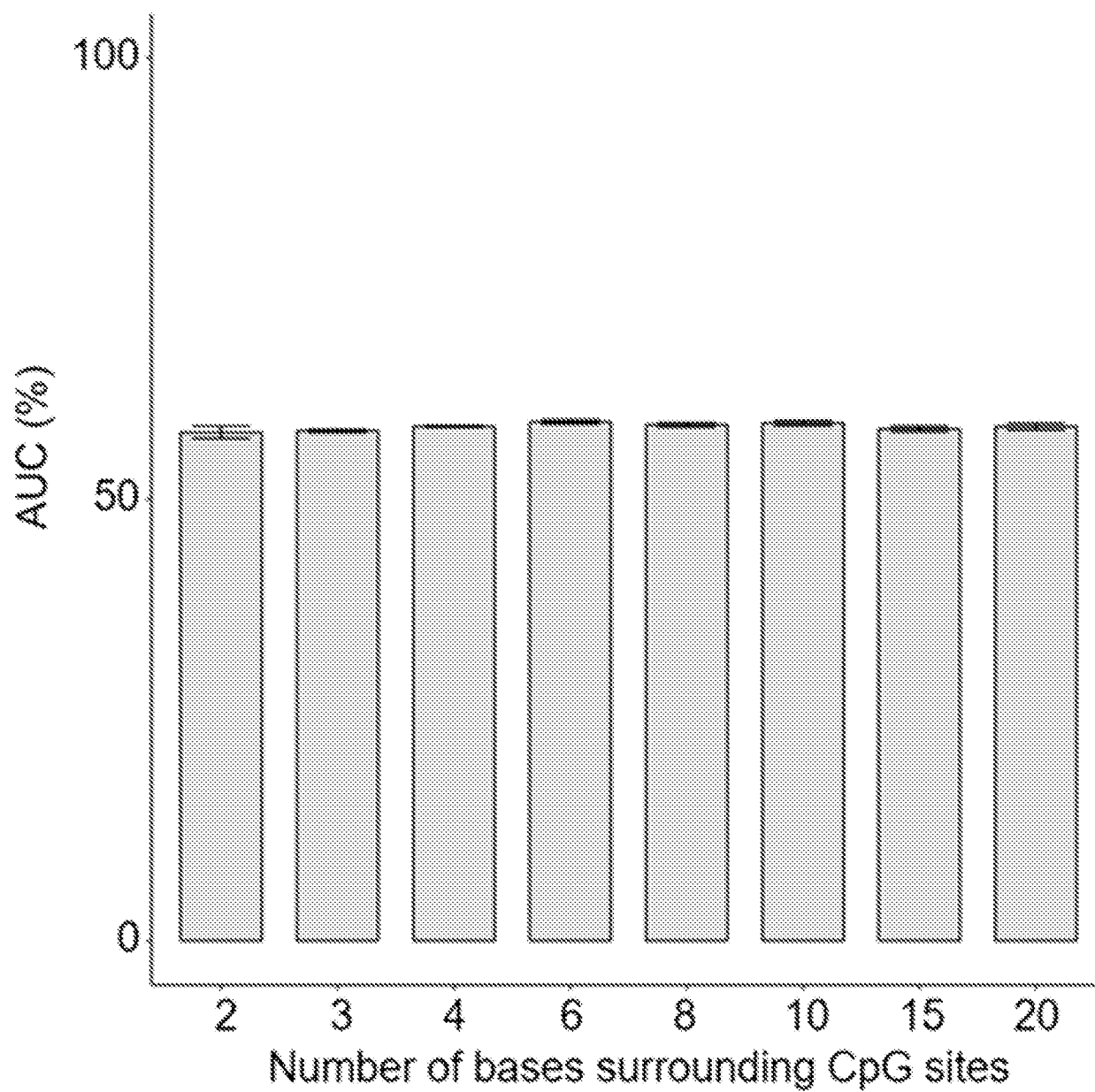


FIG. 27

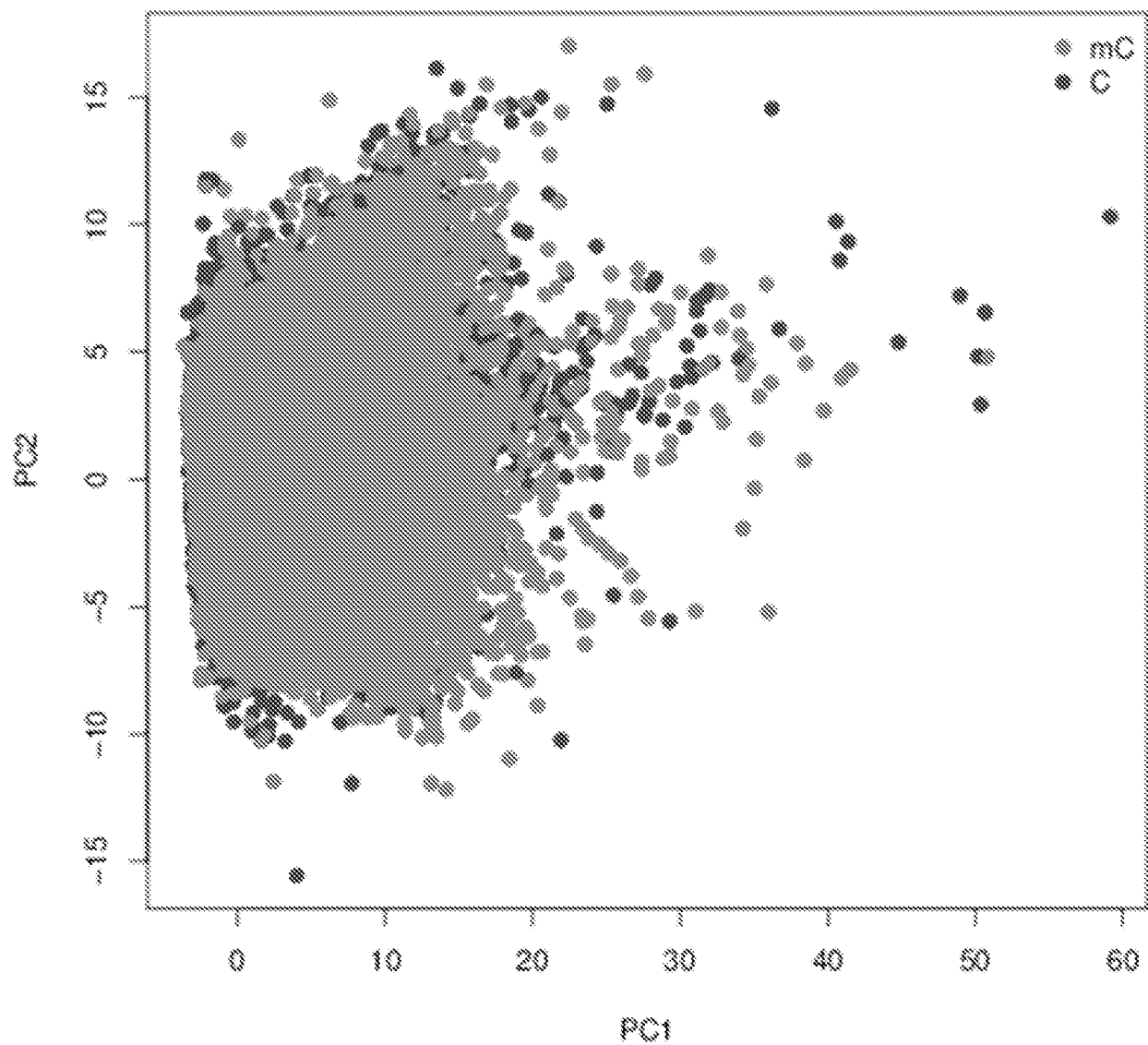


FIG. 28

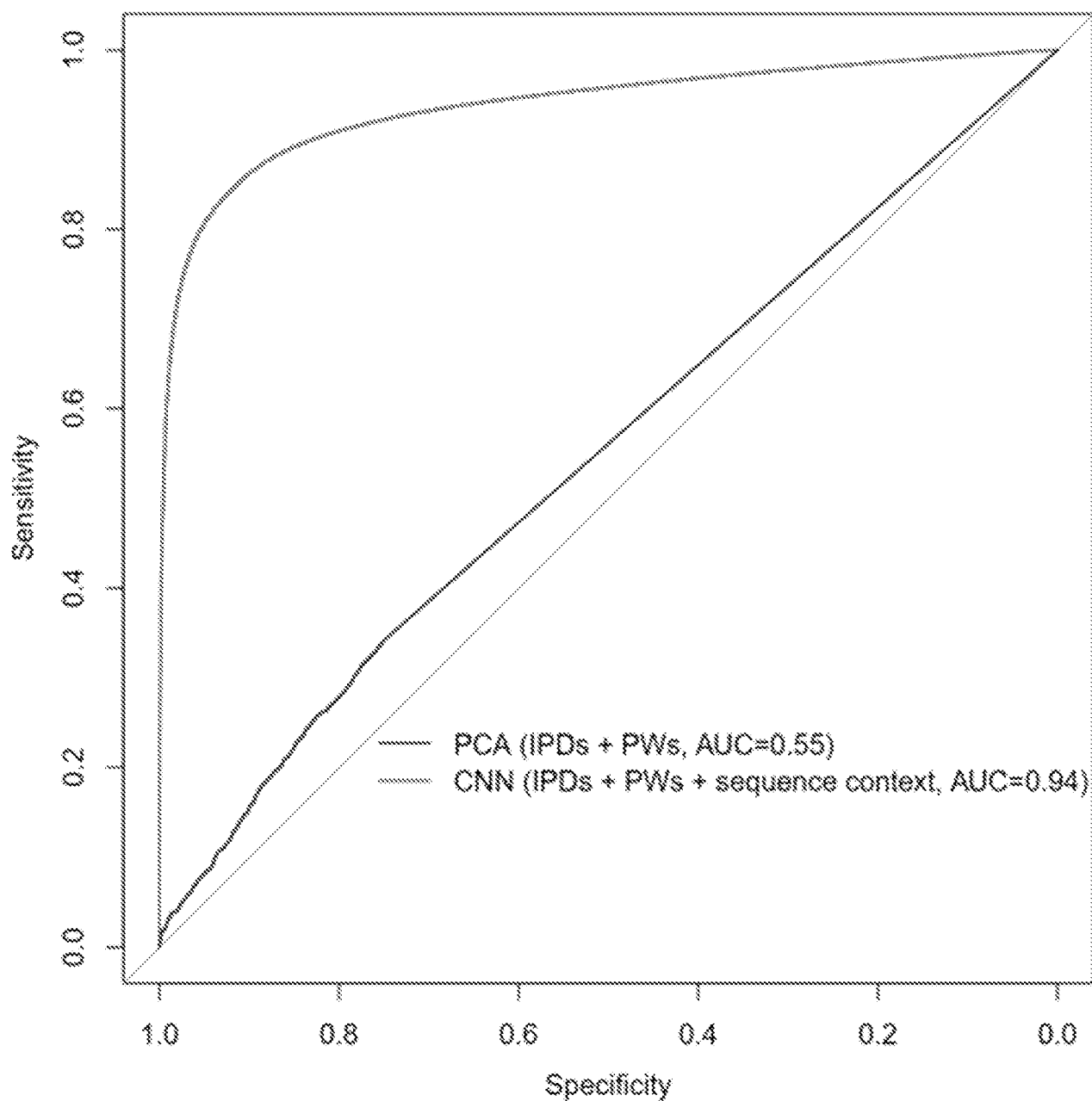


FIG. 29

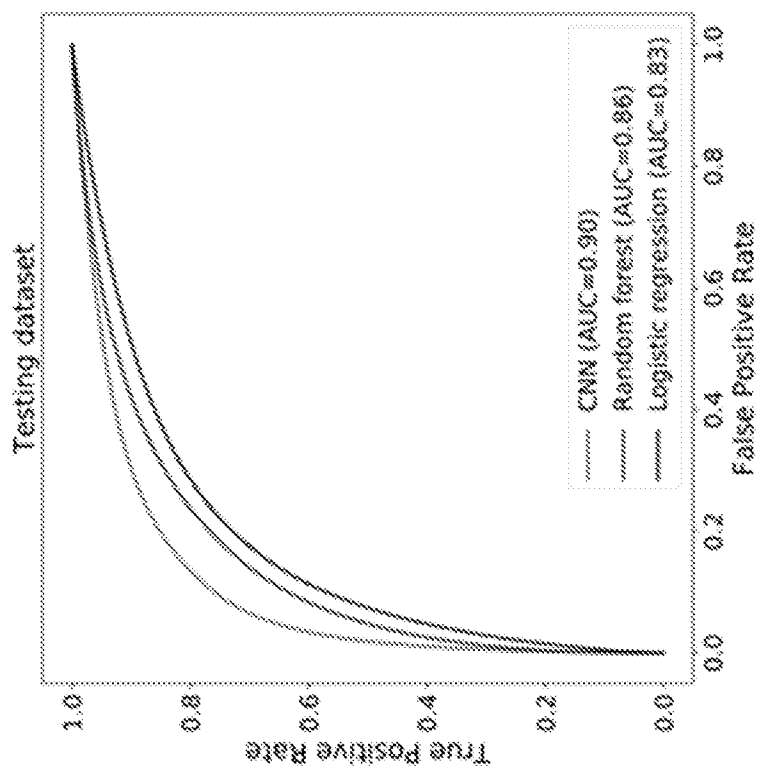


FIG. 30B

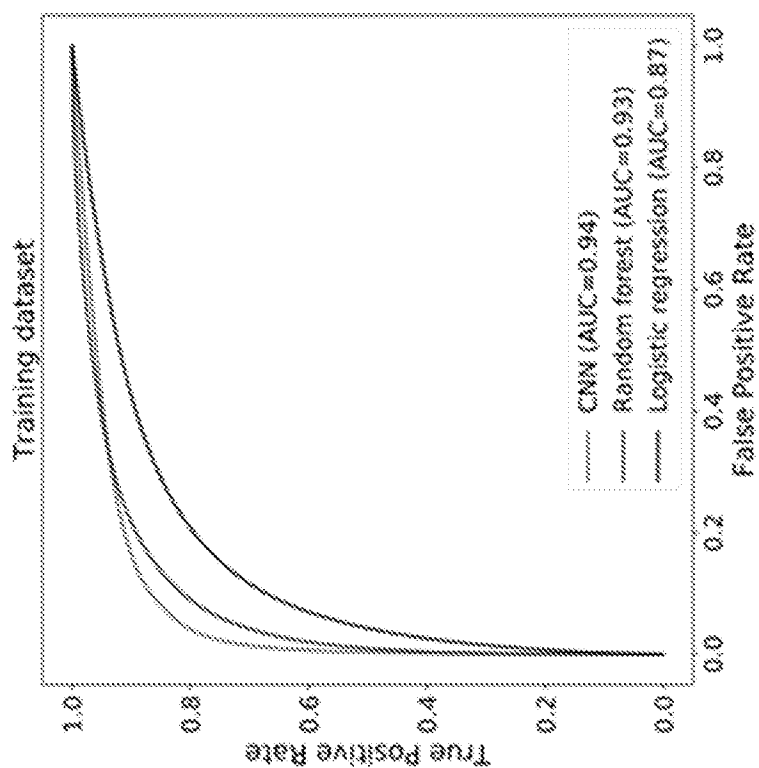
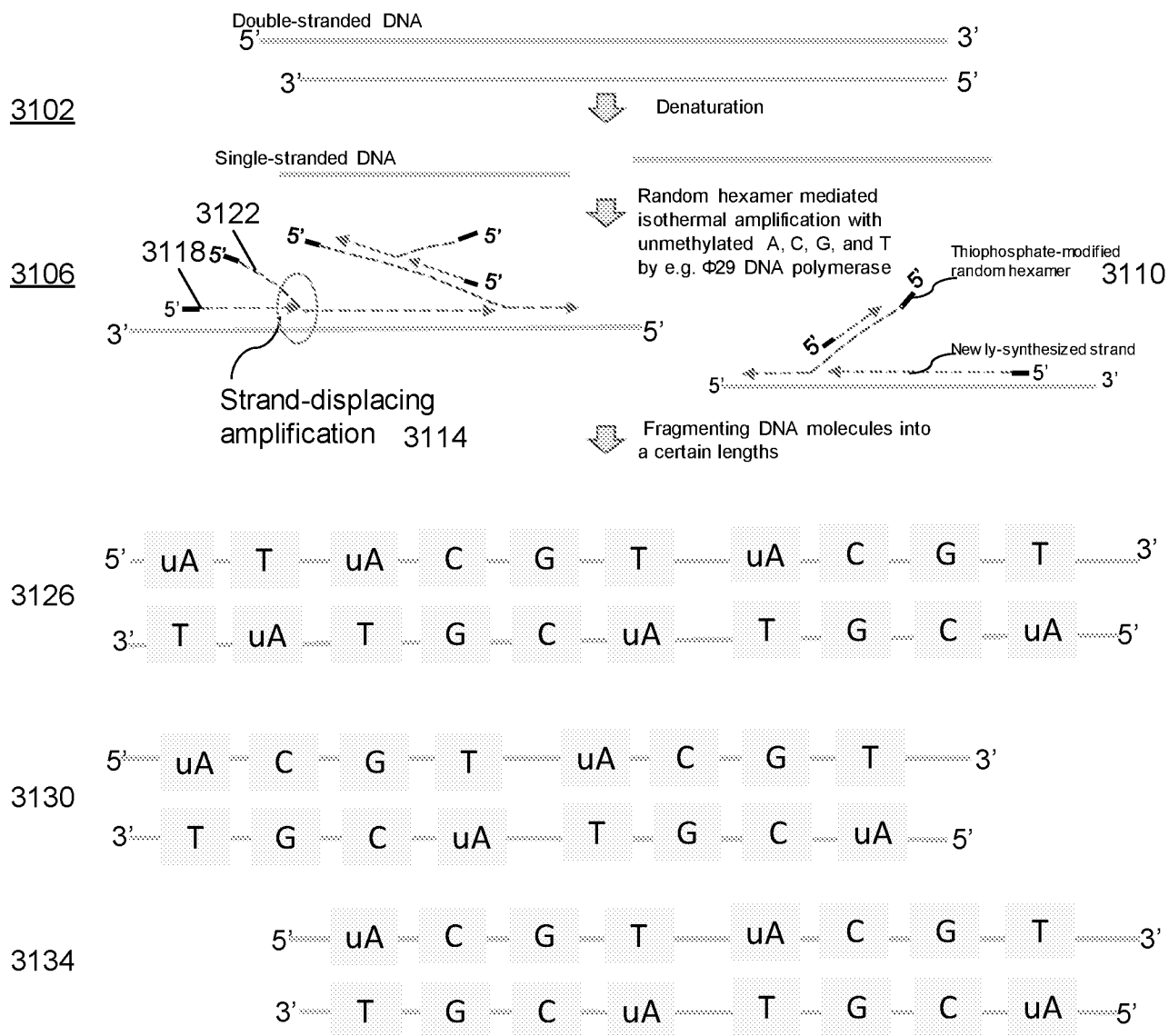
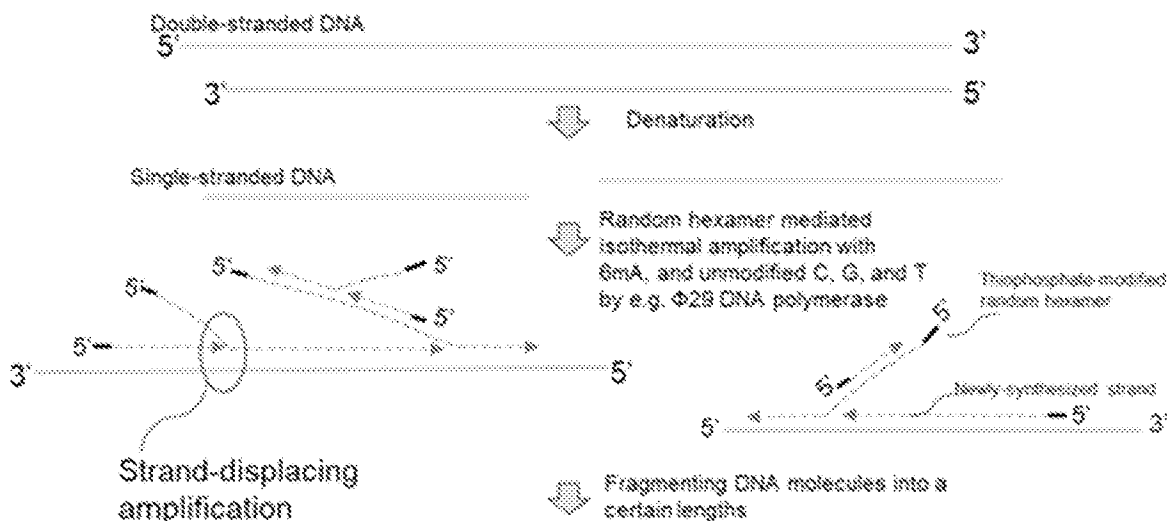
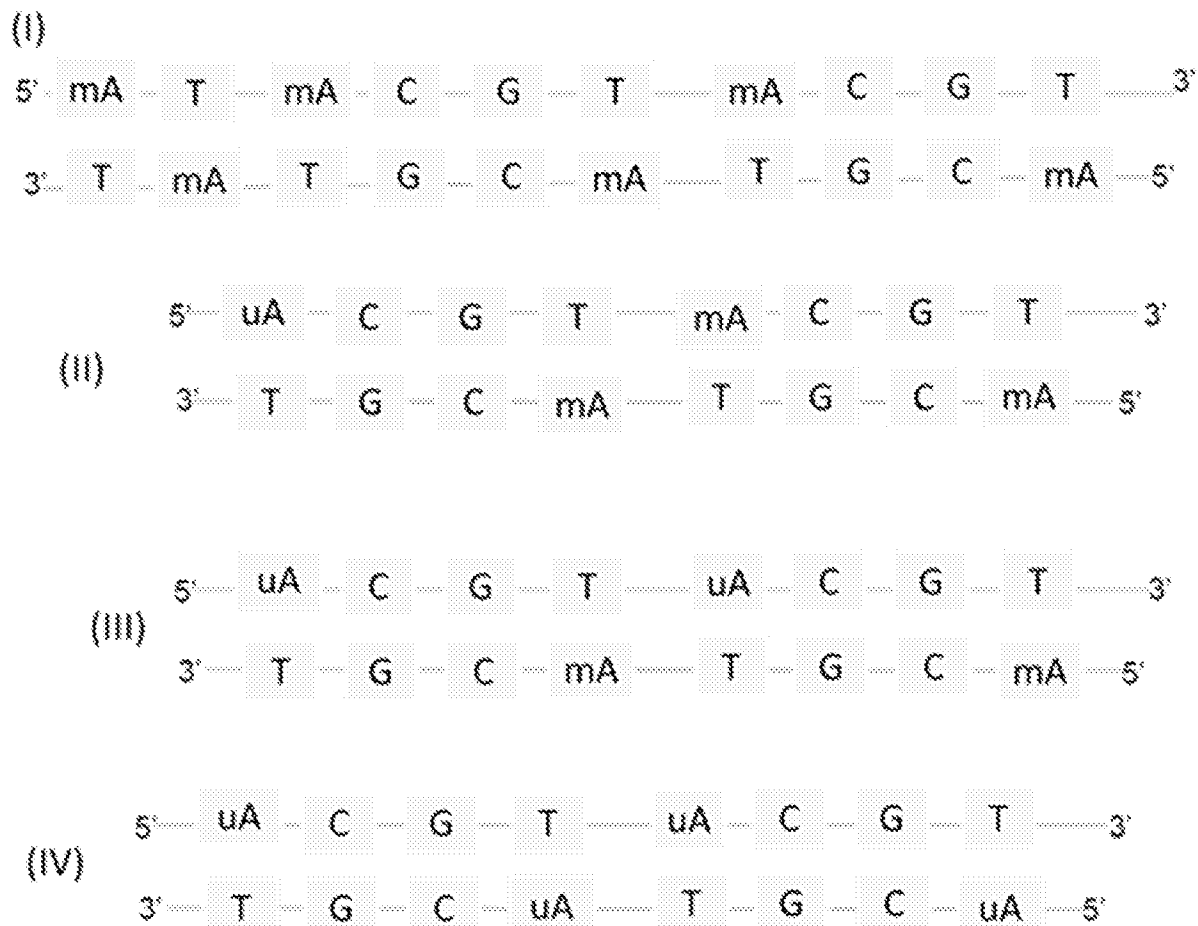


FIG. 30A



Whole-genome amplified DNA products

FIG. 31A



Whole-genome amplified DNA products

FIG. 31B

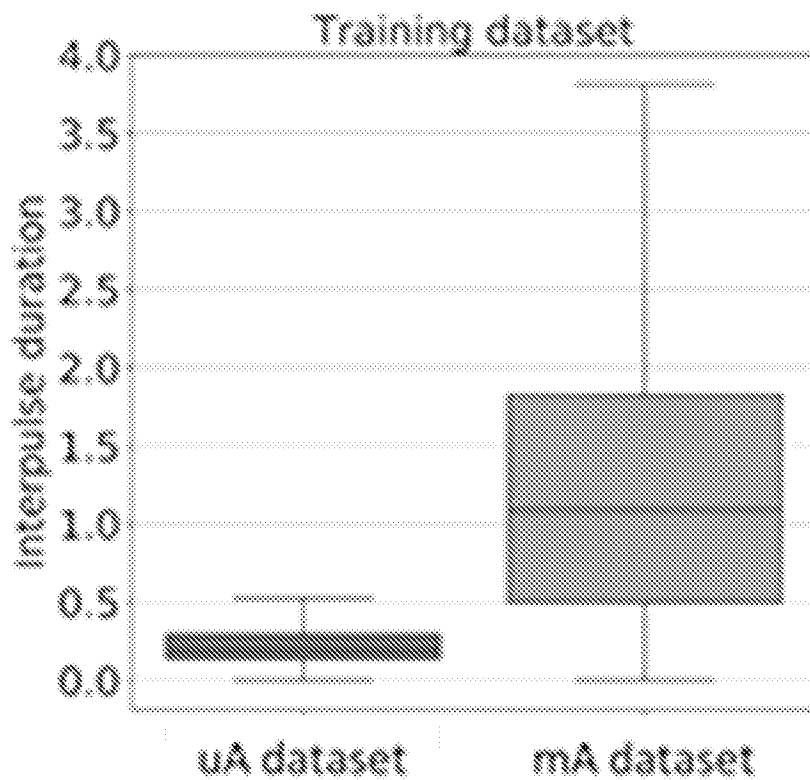


FIG. 32A

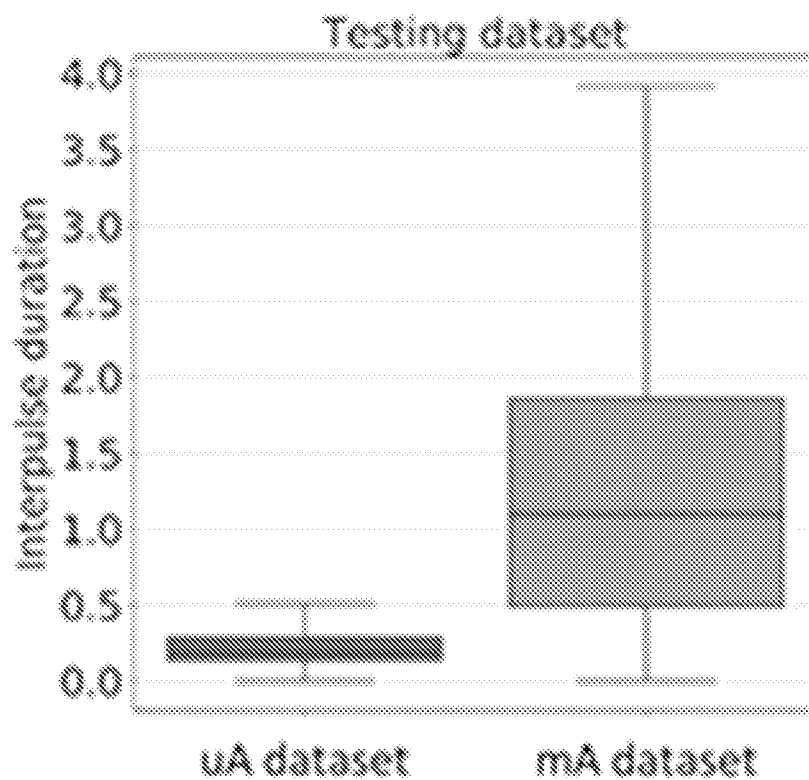


FIG. 32B

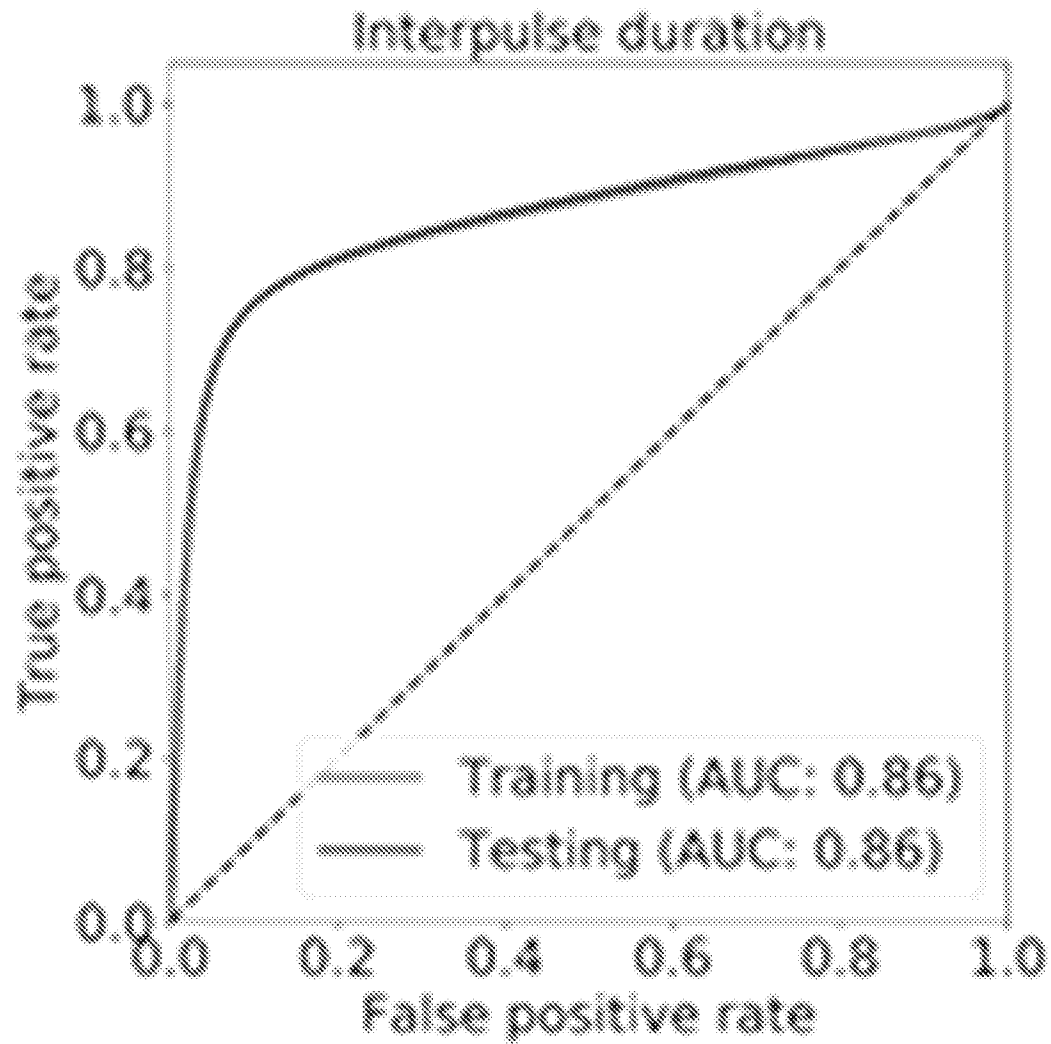


FIG. 32C

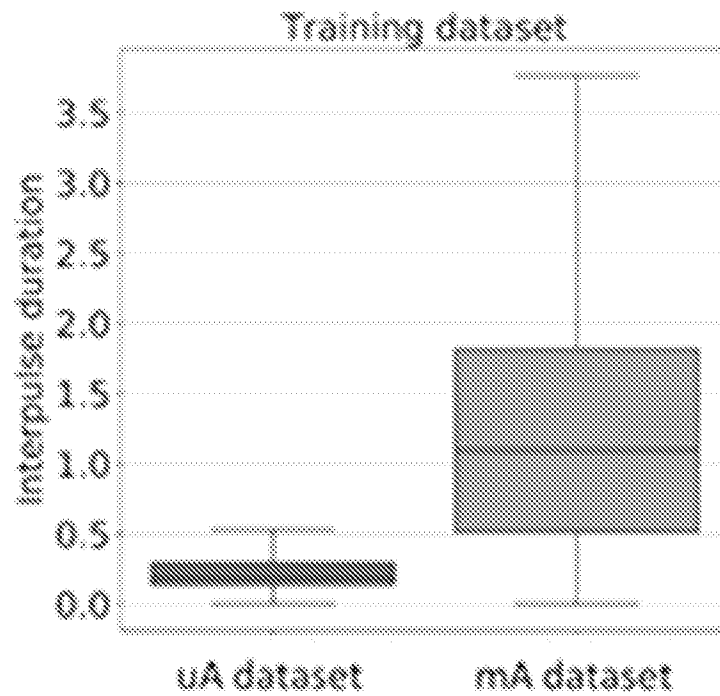


FIG. 33A

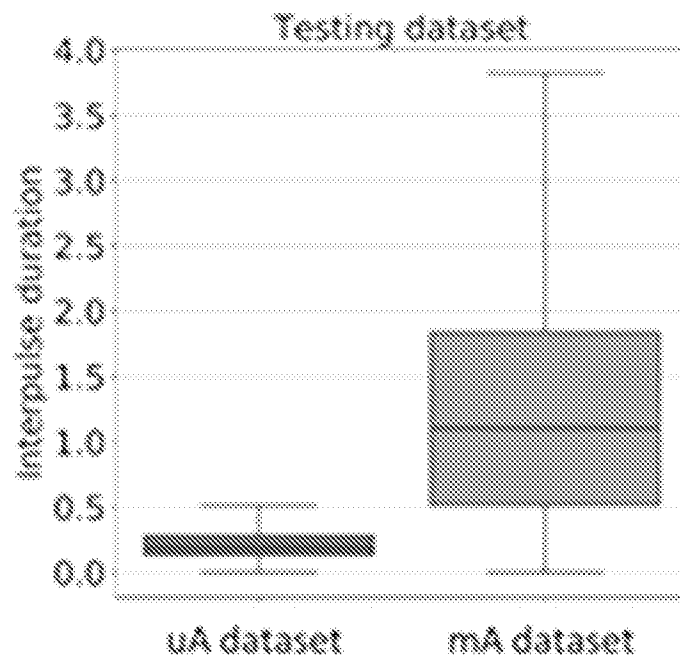


FIG. 33B

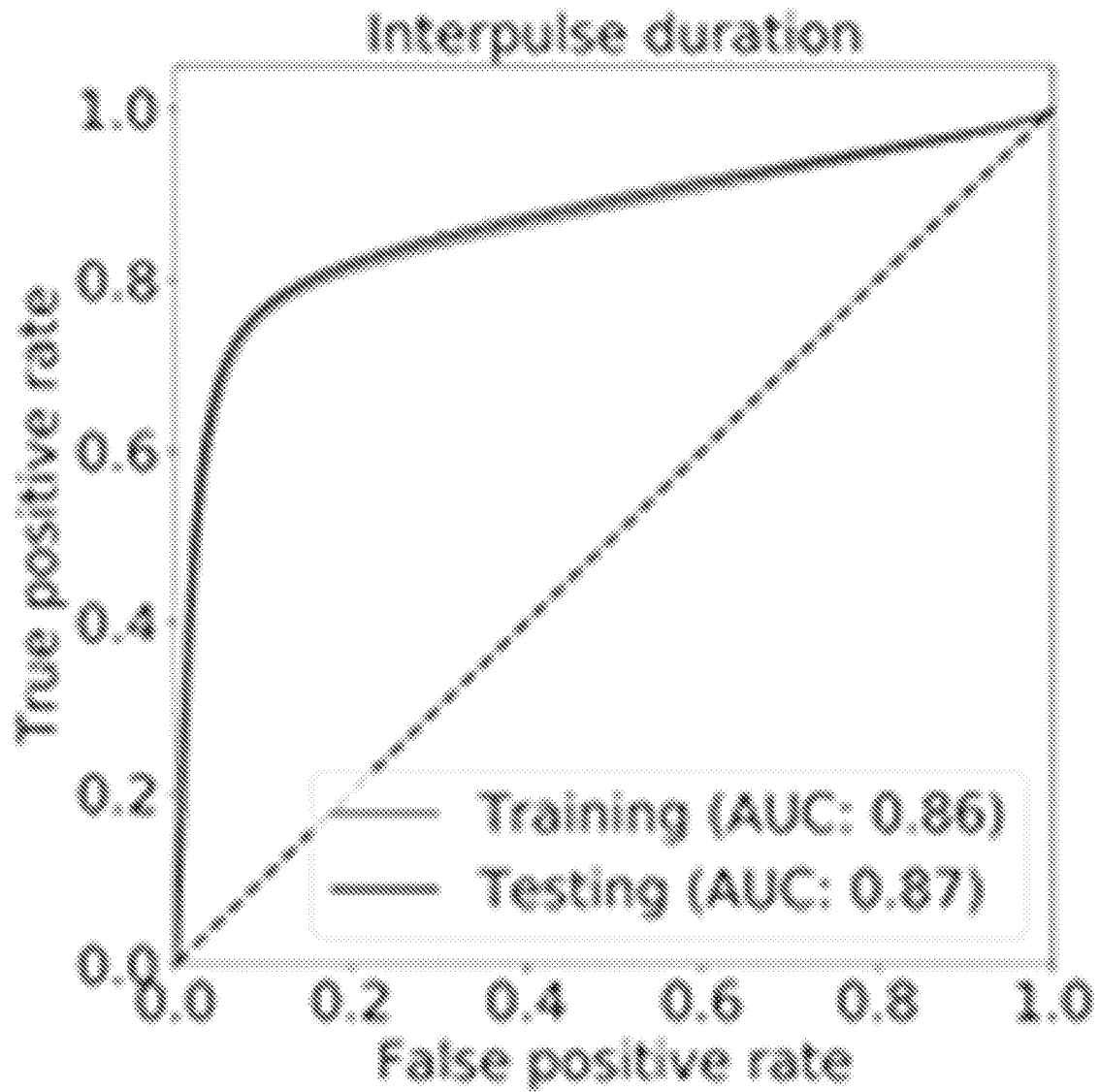


FIG. 33C

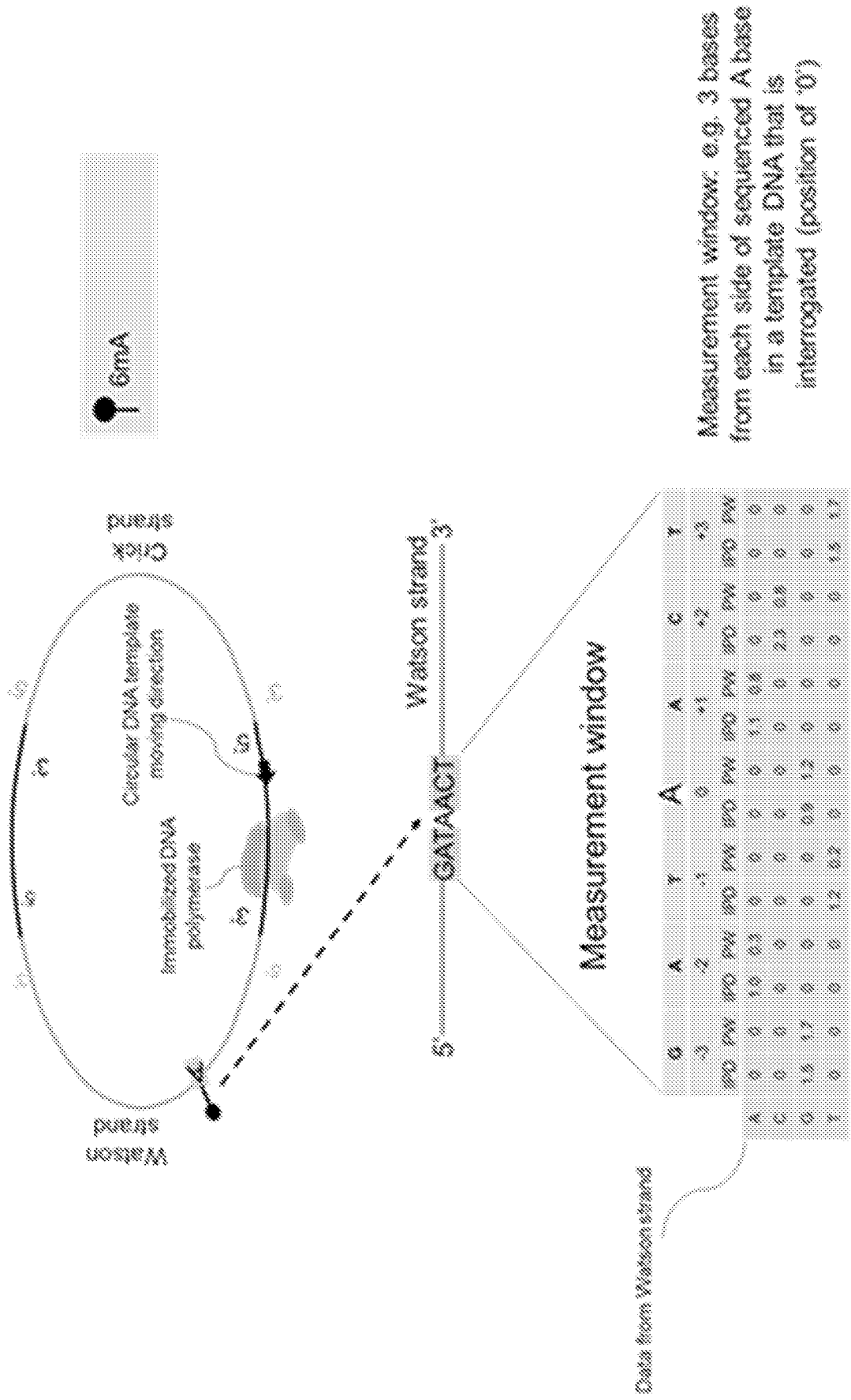


FIG. 34

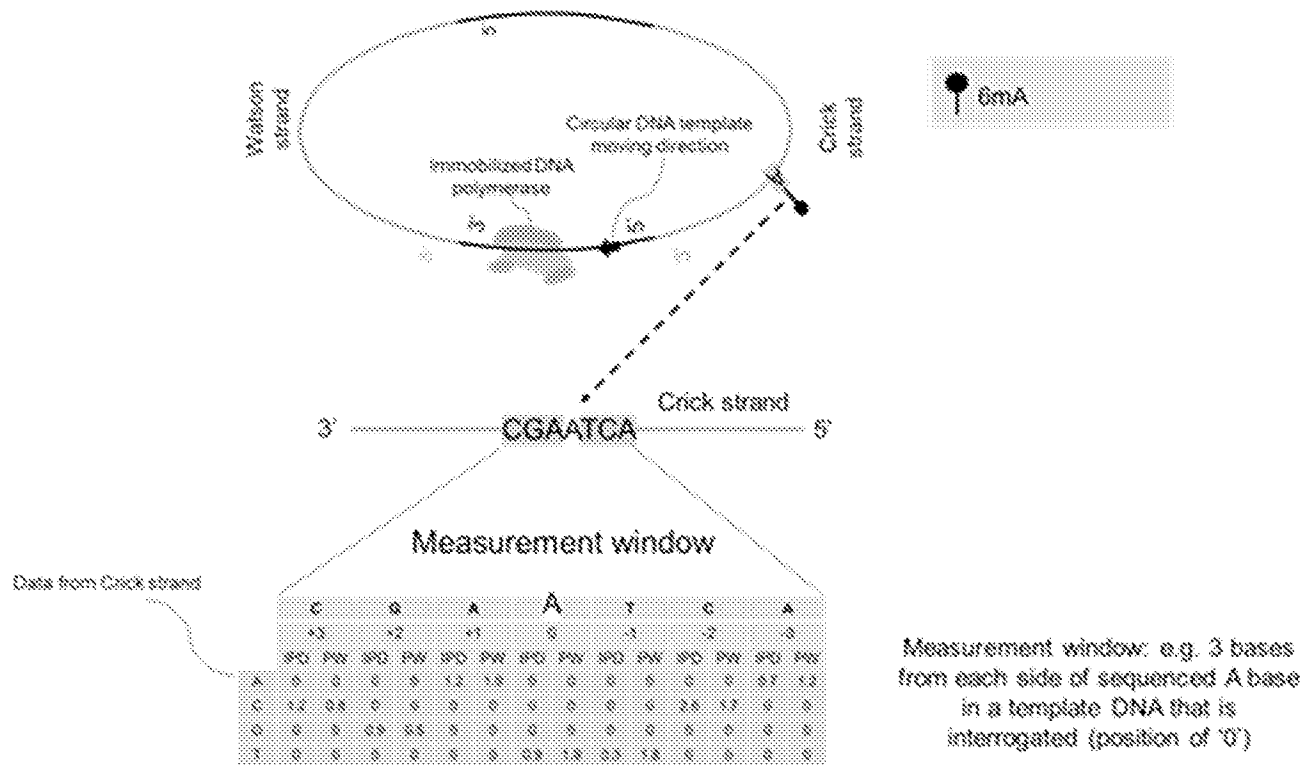


FIG.35

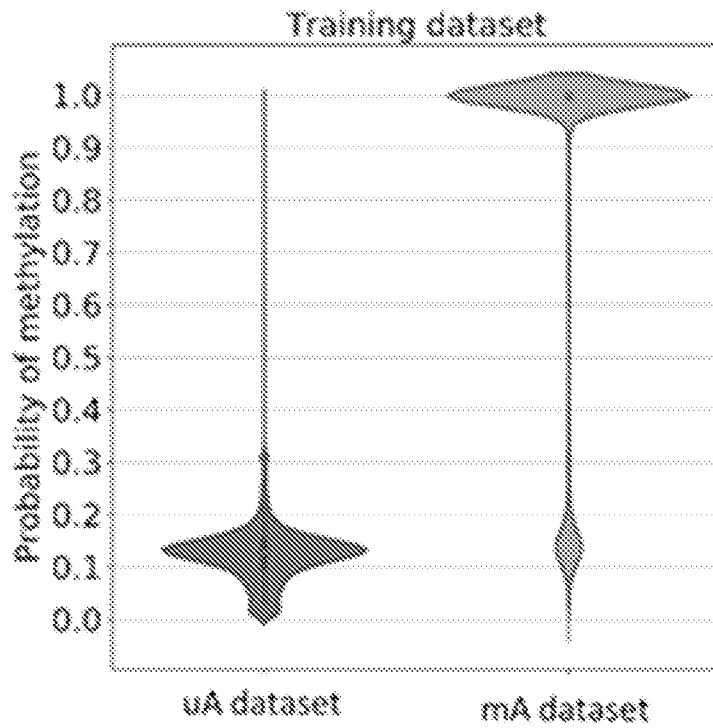


FIG. 36A

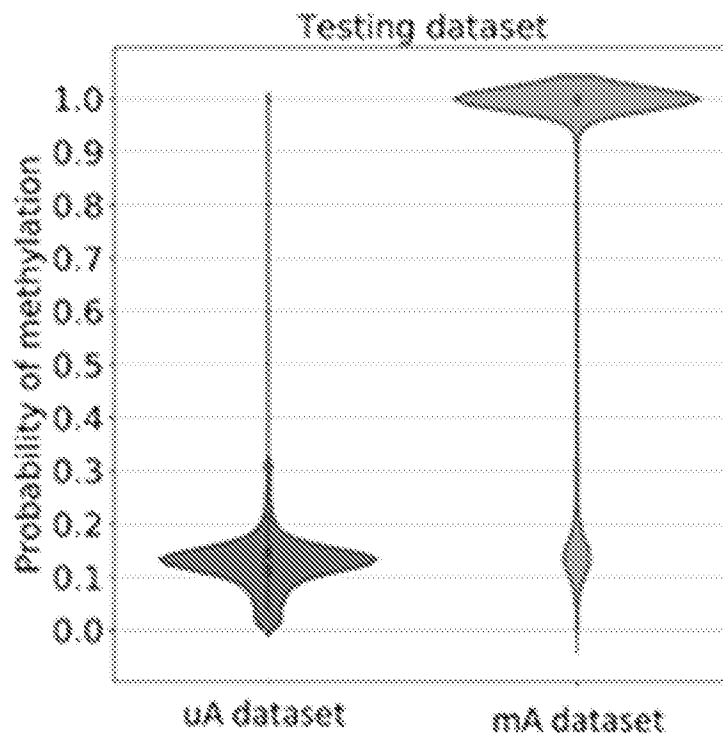


FIG. 36B

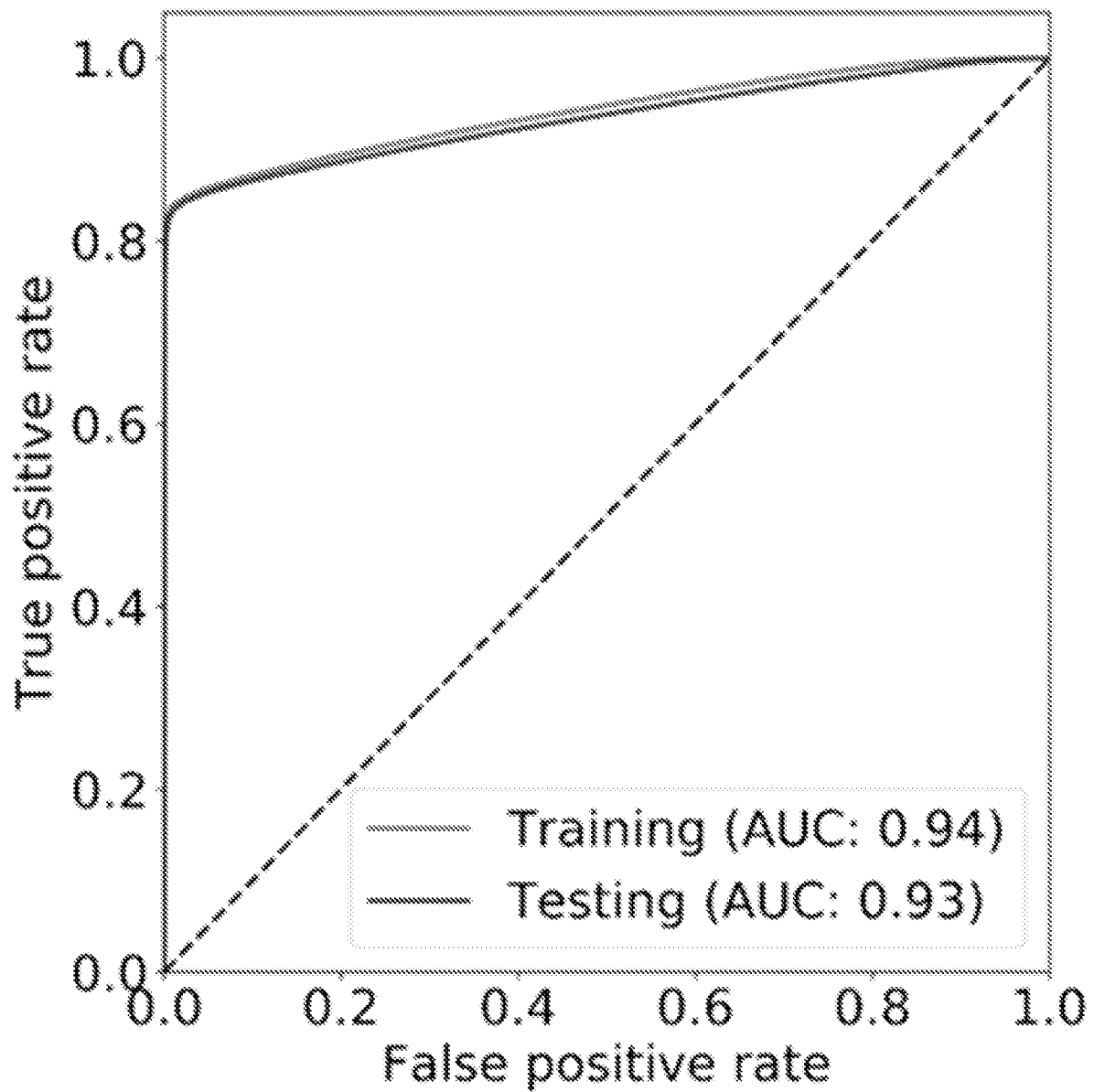


FIG. 37

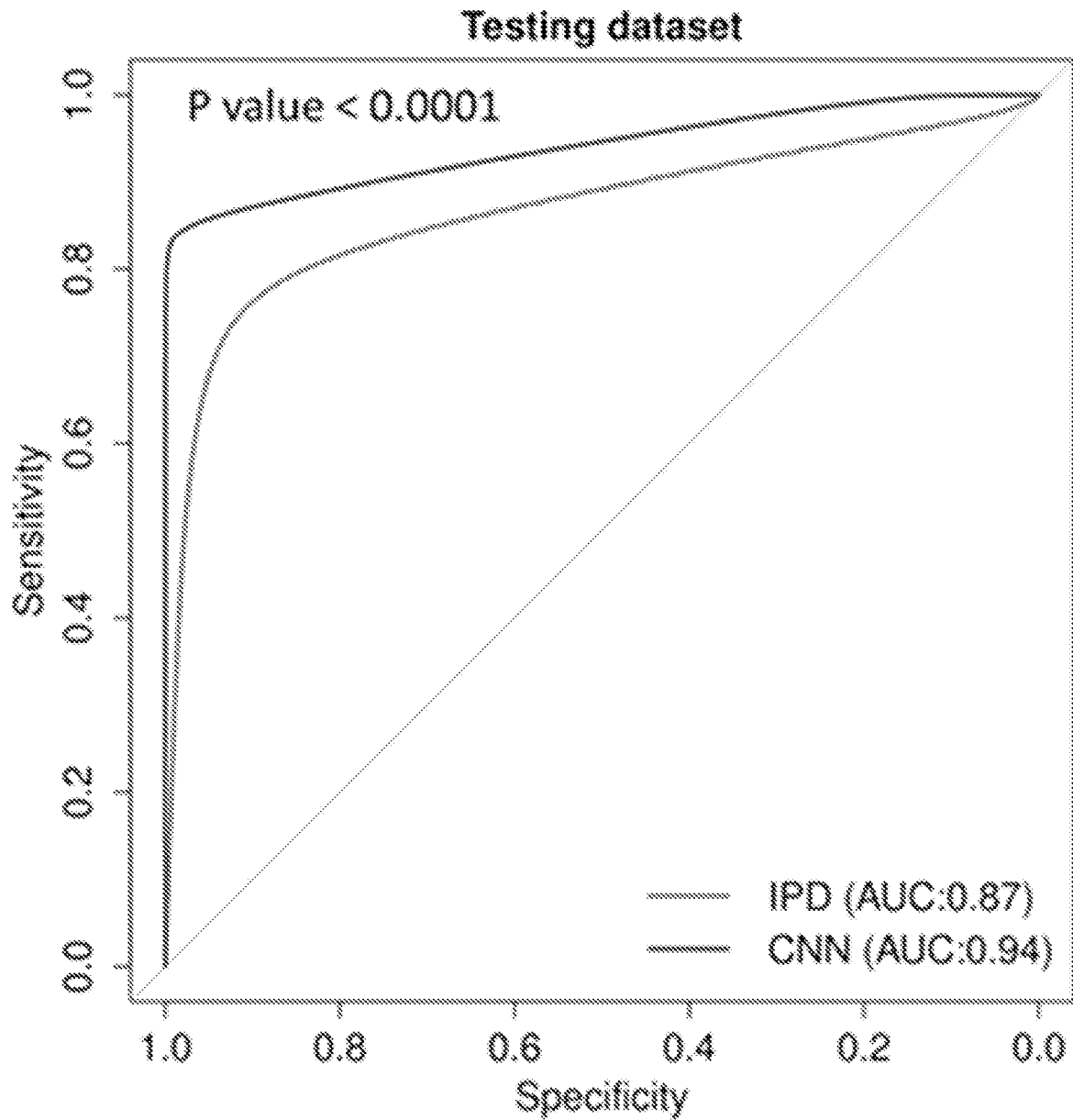


FIG. 38

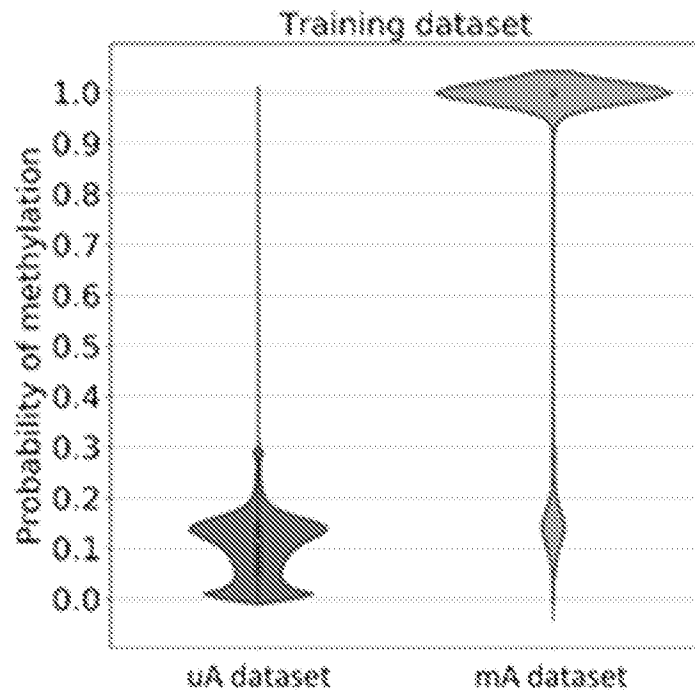


FIG. 39A

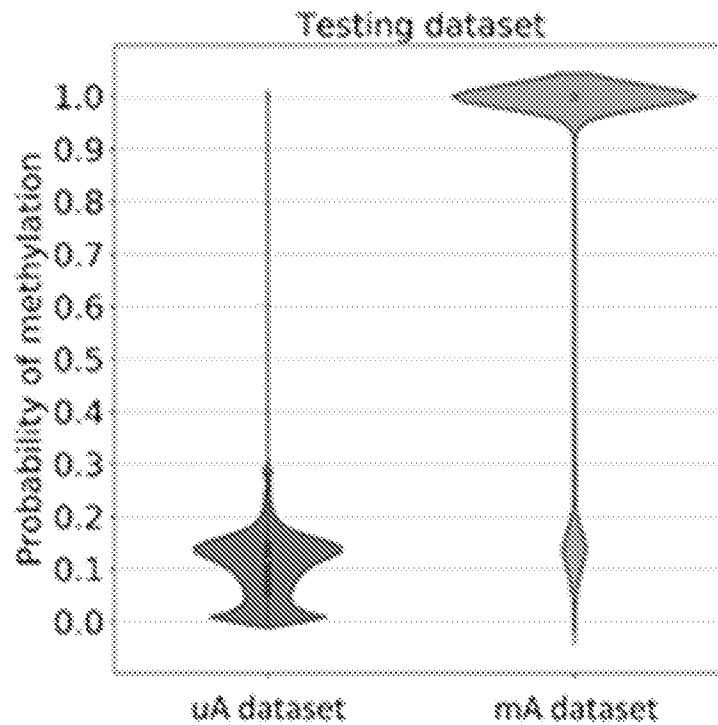


FIG. 39B

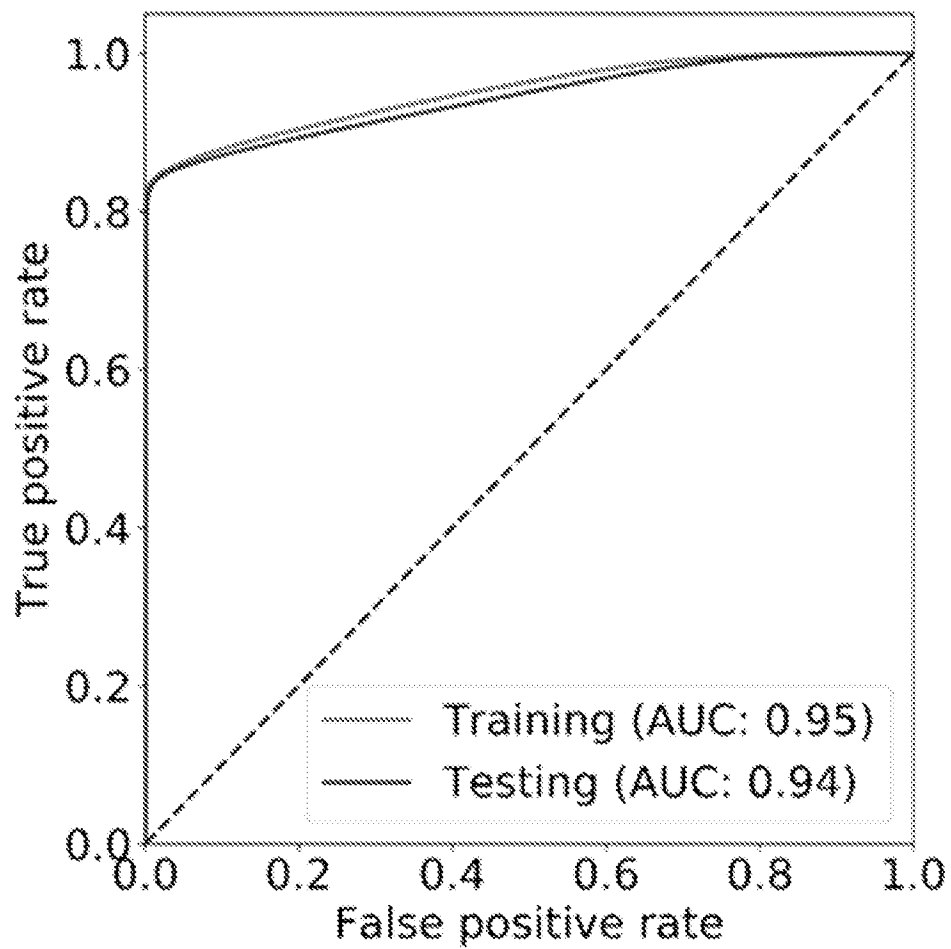


FIG. 40

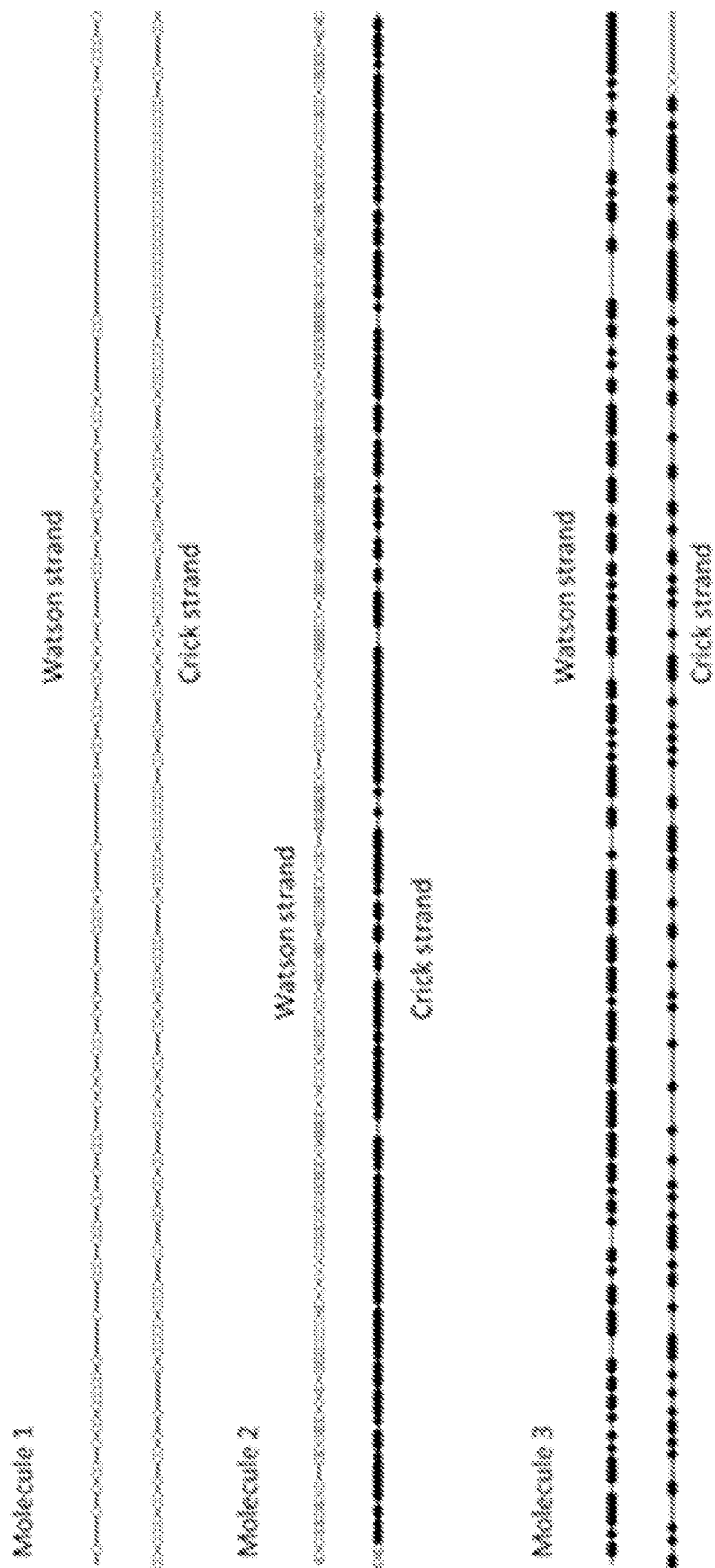


FIG. 41

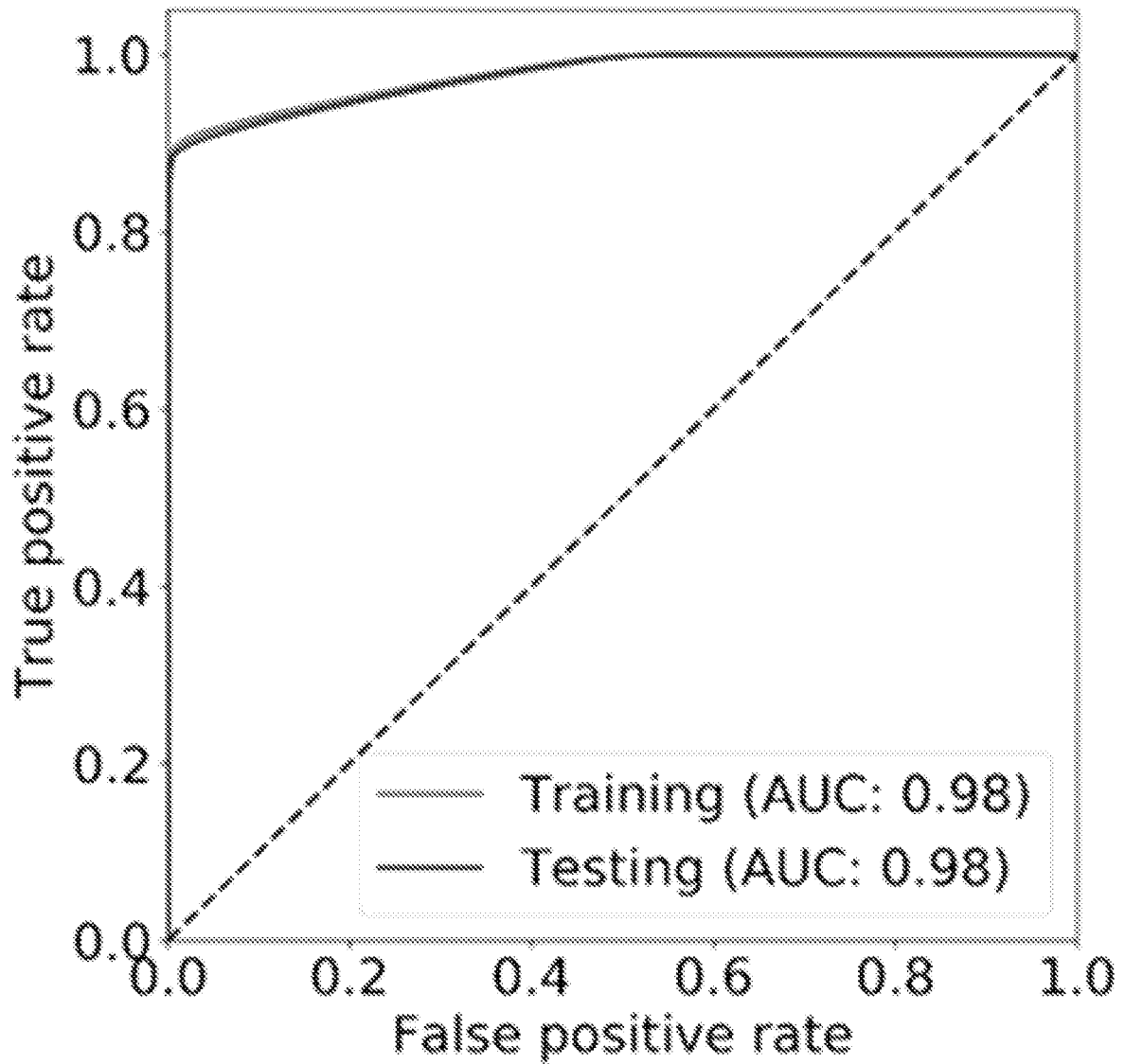


FIG. 42

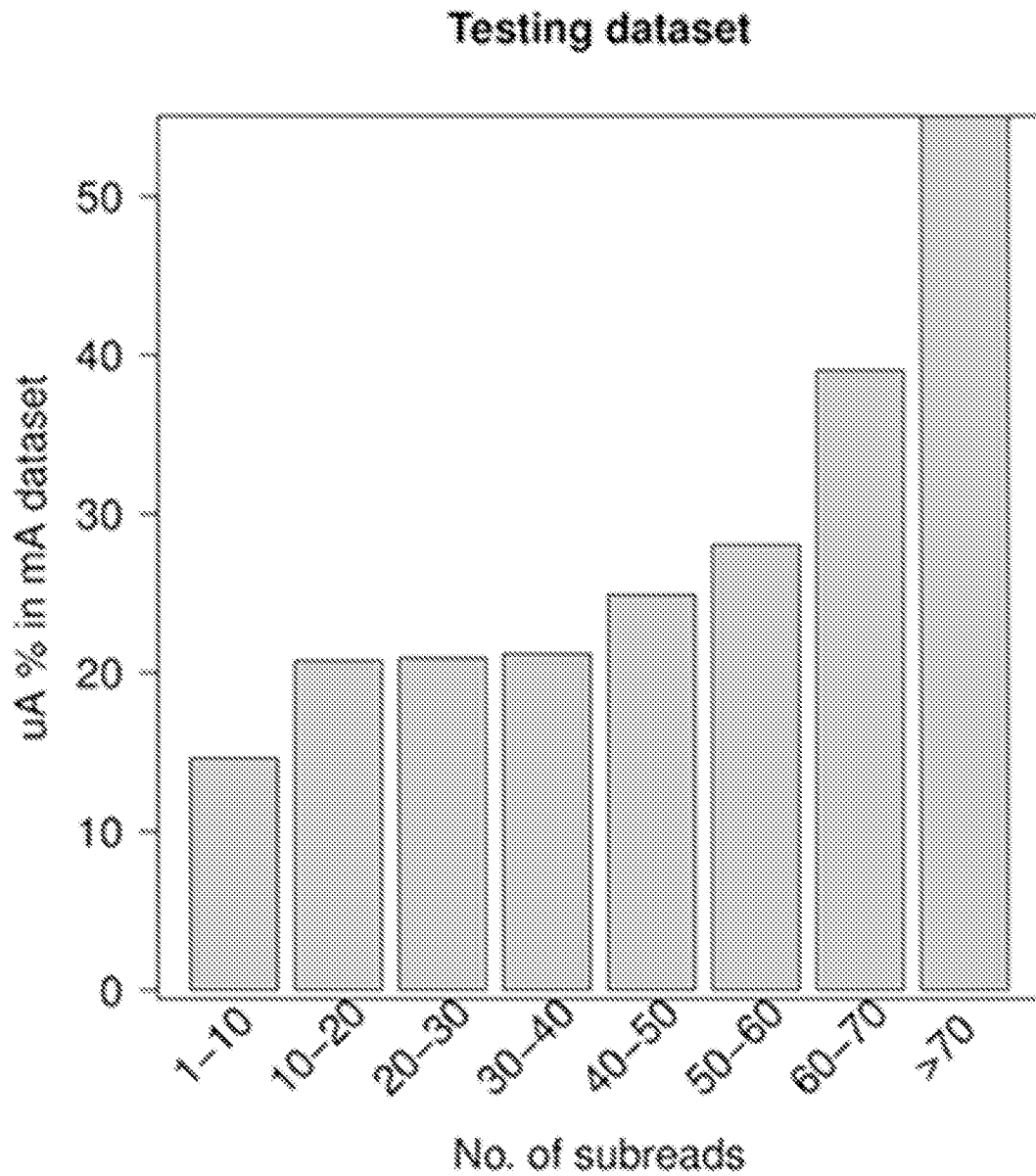


FIG. 43

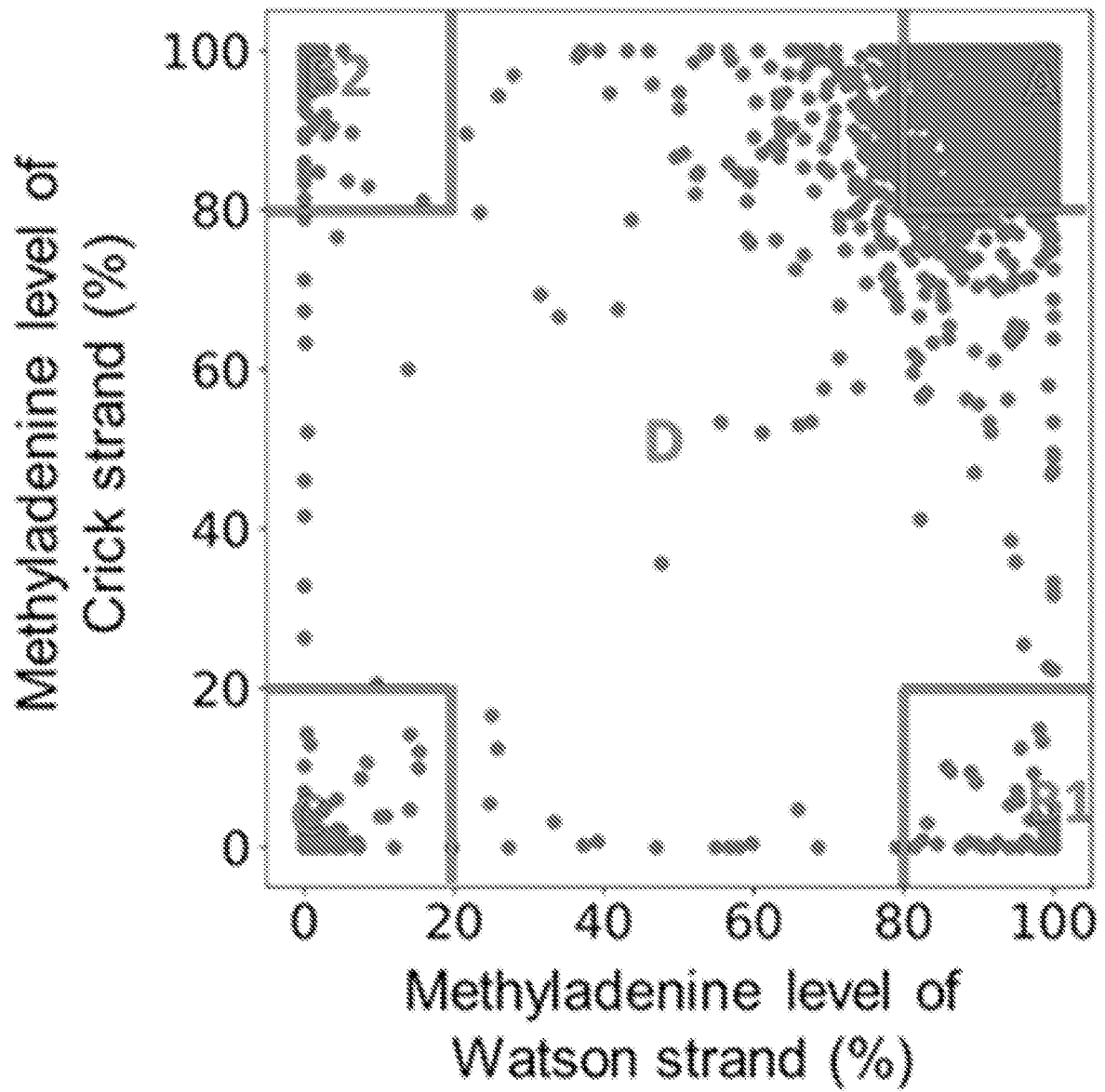


FIG.44

Categories	Training dataset	Testing dataset
Fully-unmethylated	283 (7.0%)	276 (7.0%)
Hemi-methylated	401 (10.0%)	389 (9.8%)
Fully-methylated	3194 (79.4%)	3142 (79.4%)
Interlacing methylation patterns	145 (3.6%)	148 (3.7%)

FIG. 45

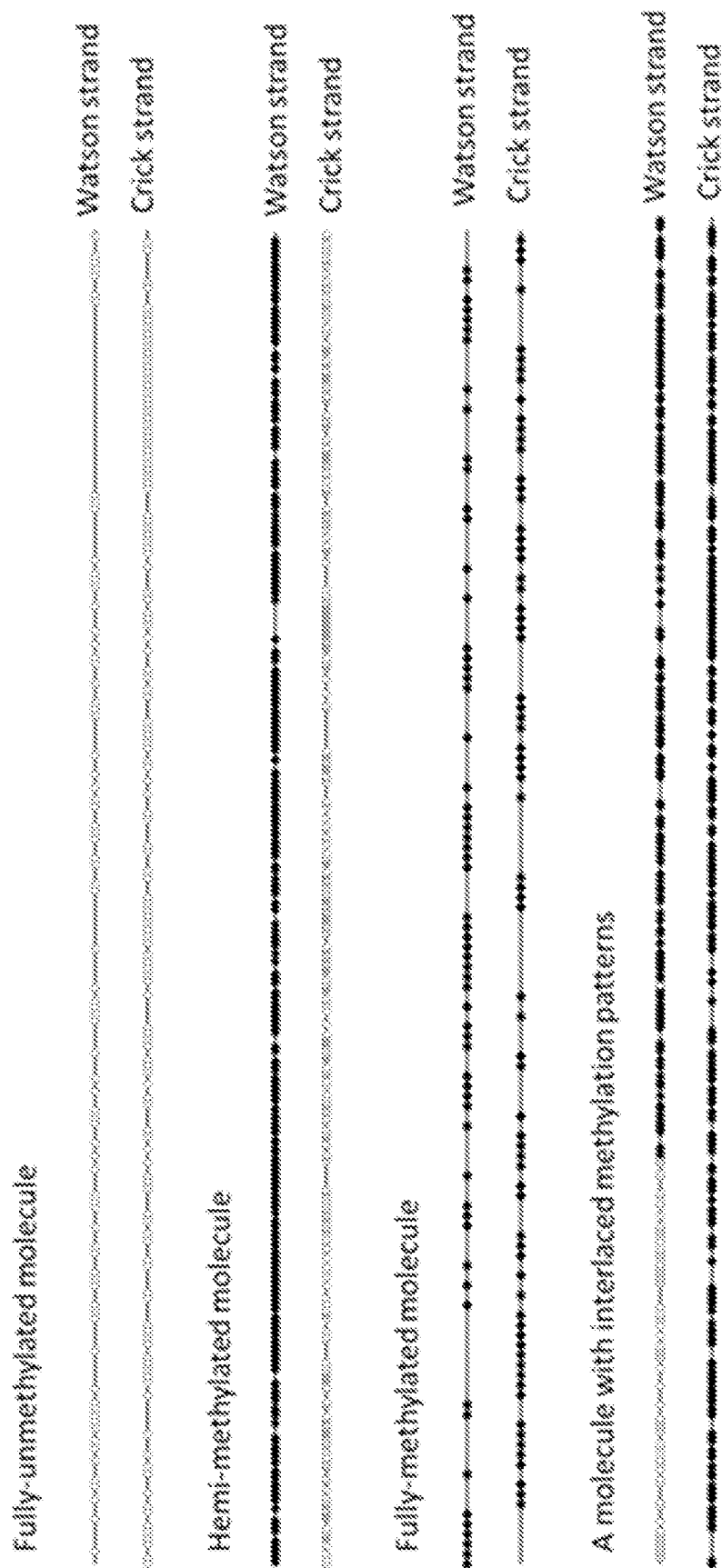


FIG. 46

ZMW hole number: m54276_180626_162240/40763503
Mapped location: chr1:113246546-113252811
Size: 6265

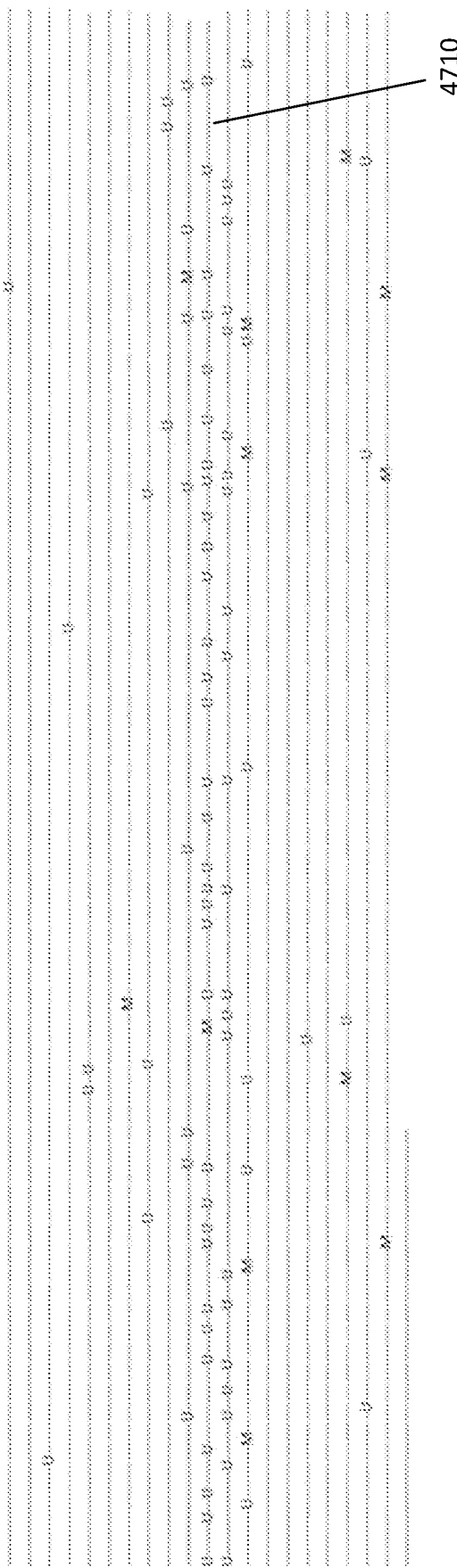


FIG. 47

FIG. 48

Methylation patterns present in a paternally imprinted region

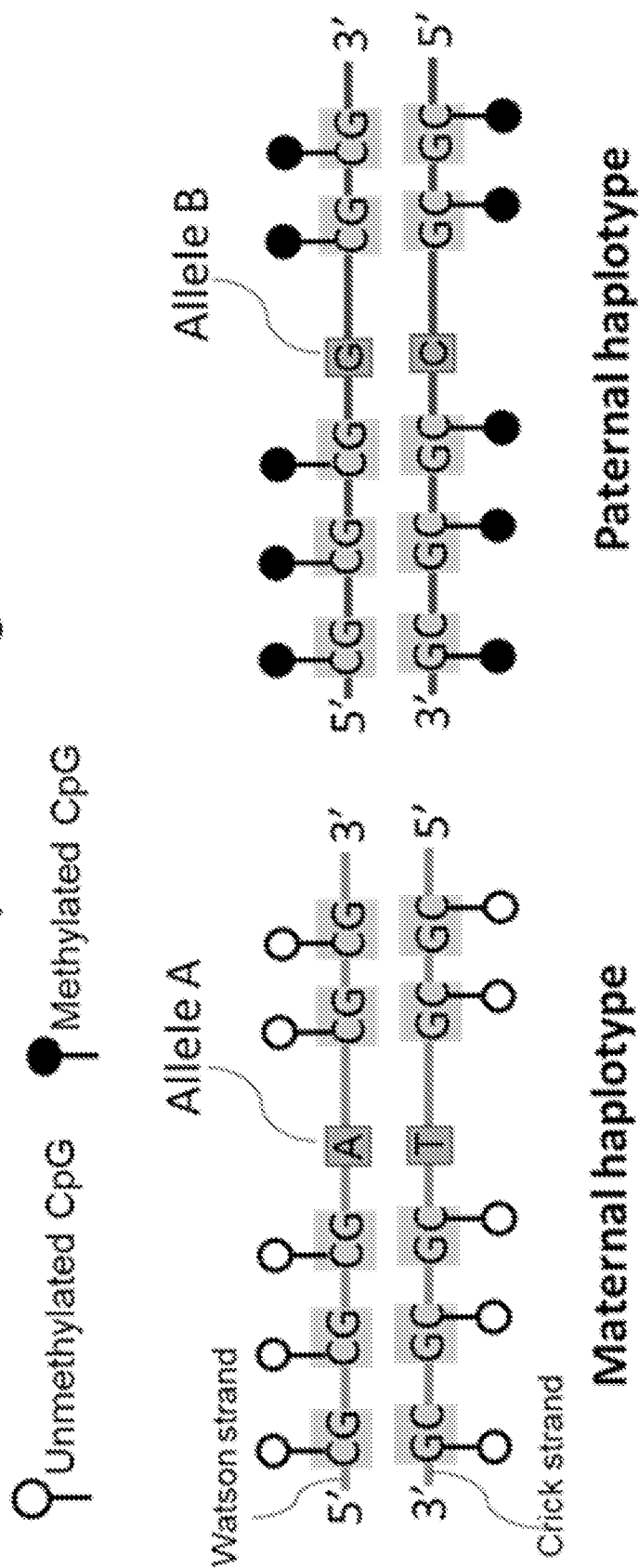


FIG. 49

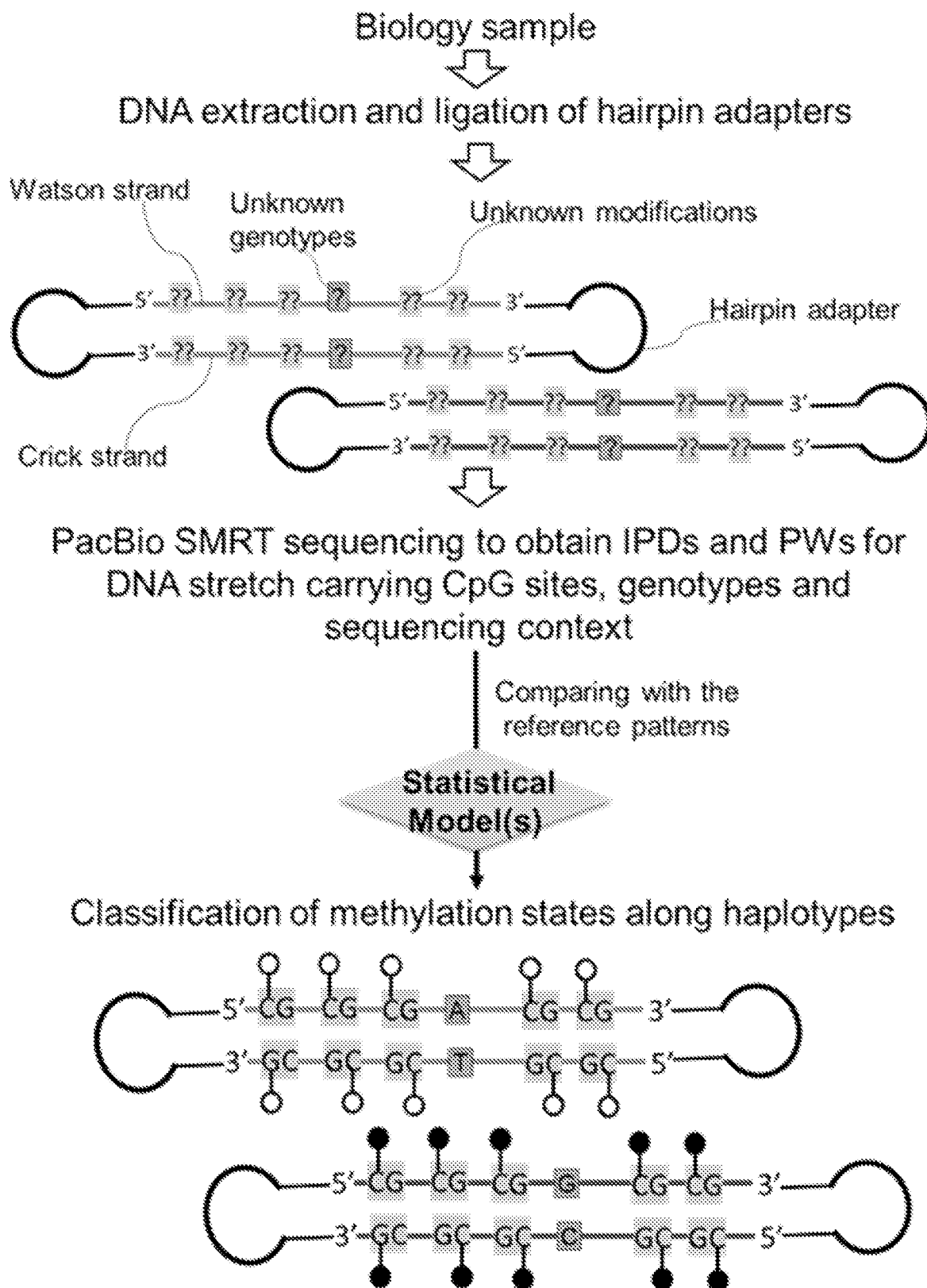


FIG. 50

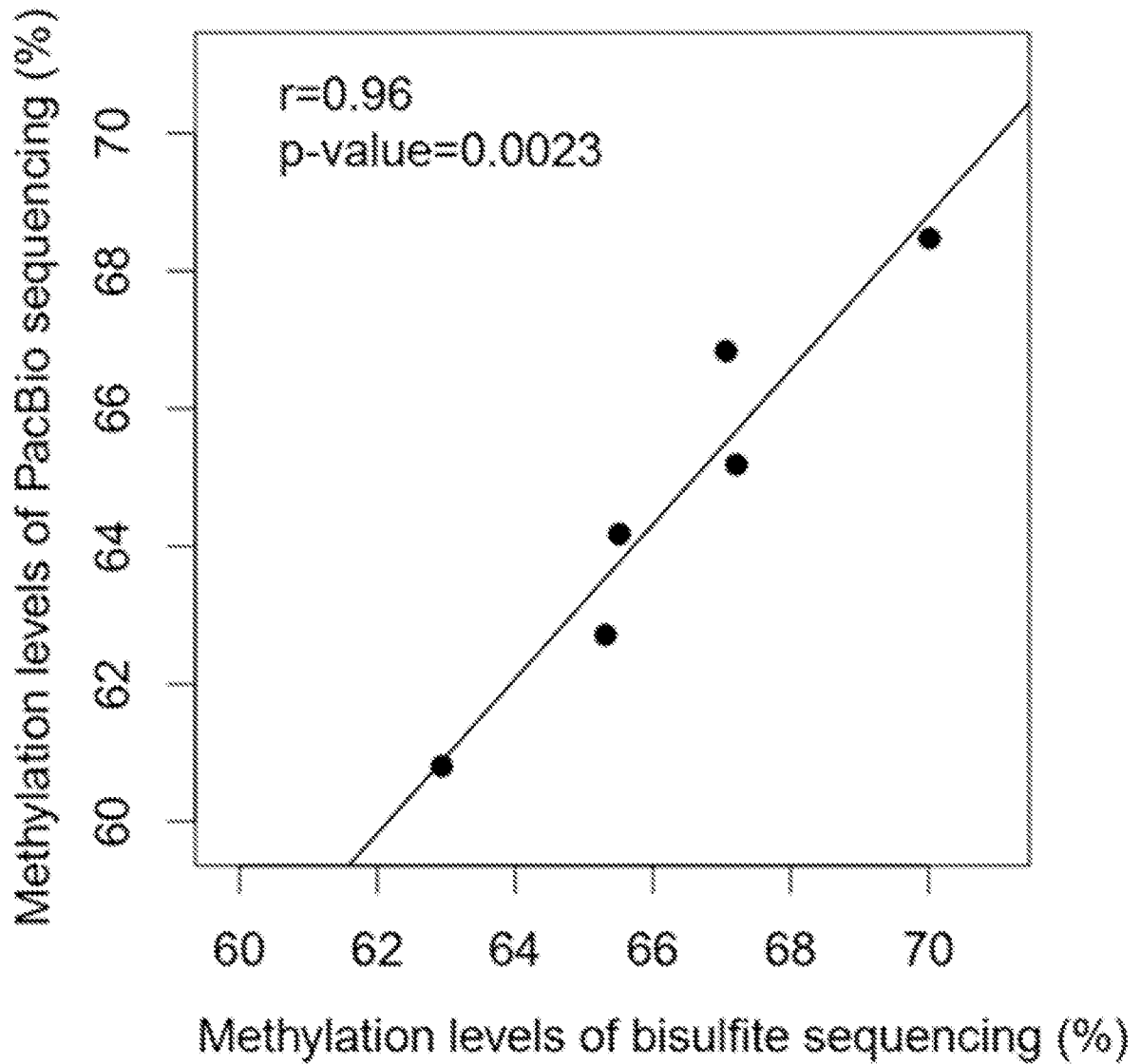


FIG. 51

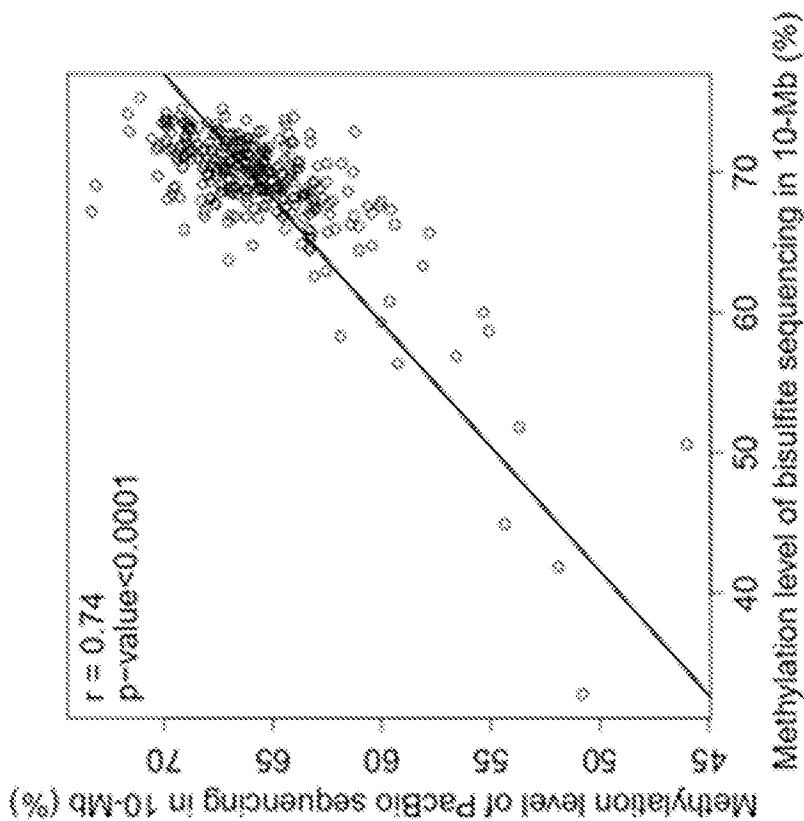


FIG. 52B

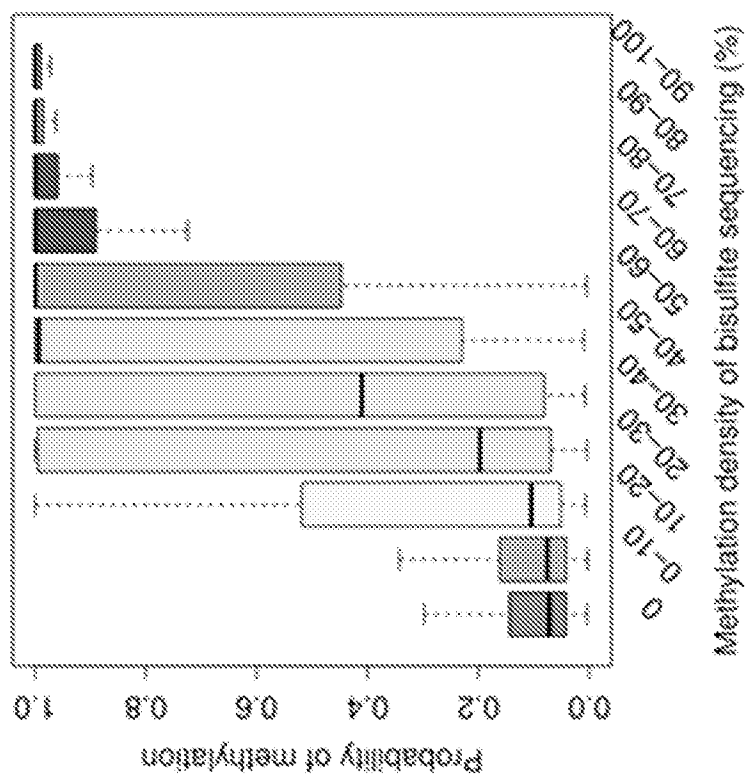


FIG. 52A

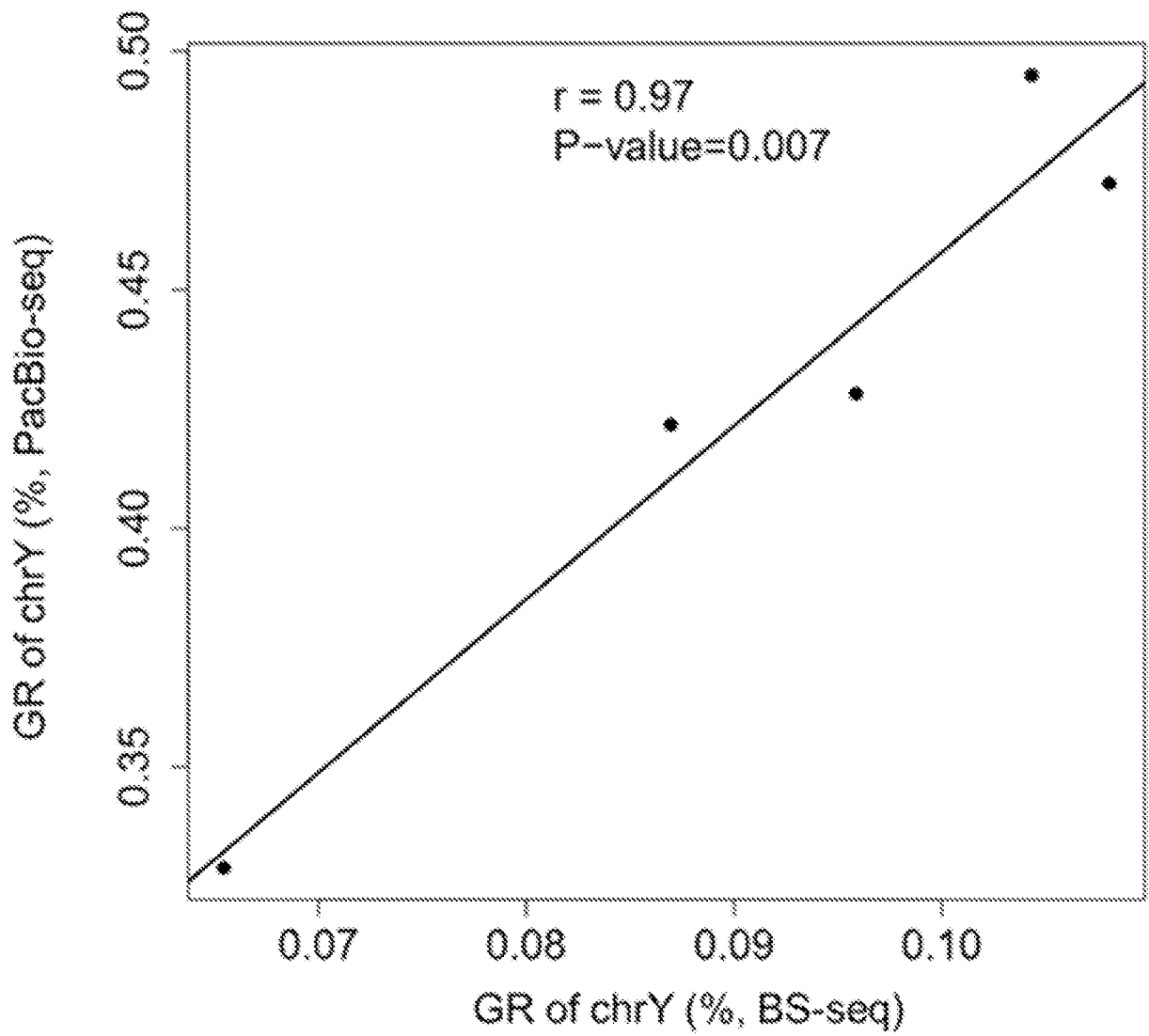


FIG. 53

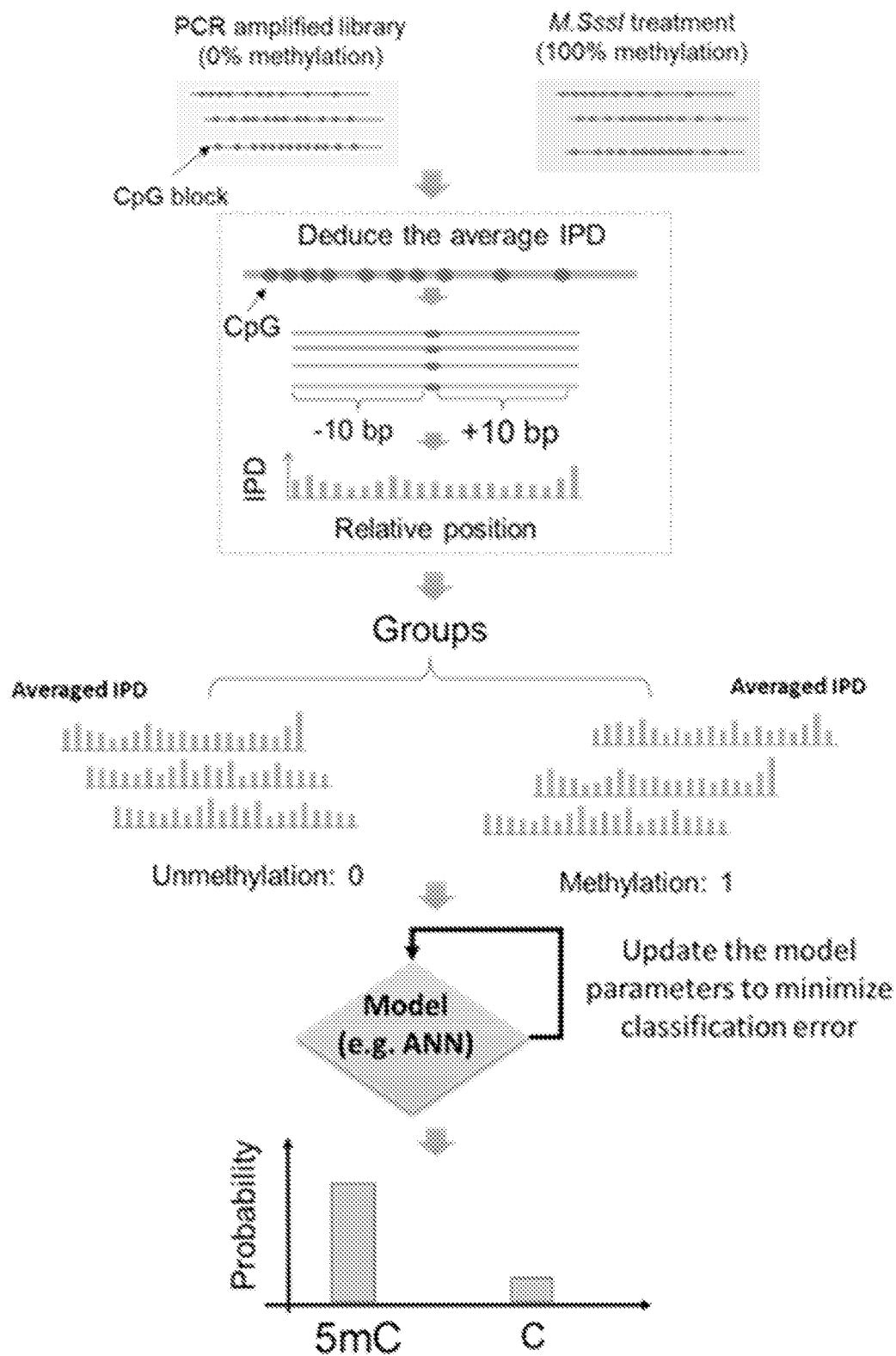


FIG. 54

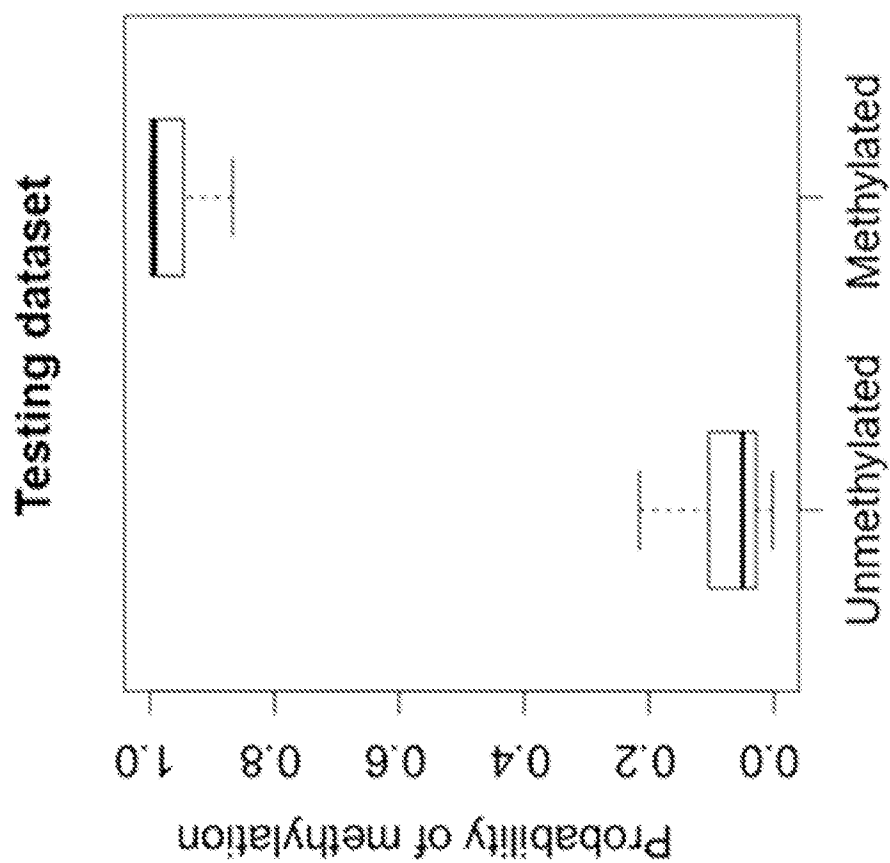


FIG. 55B

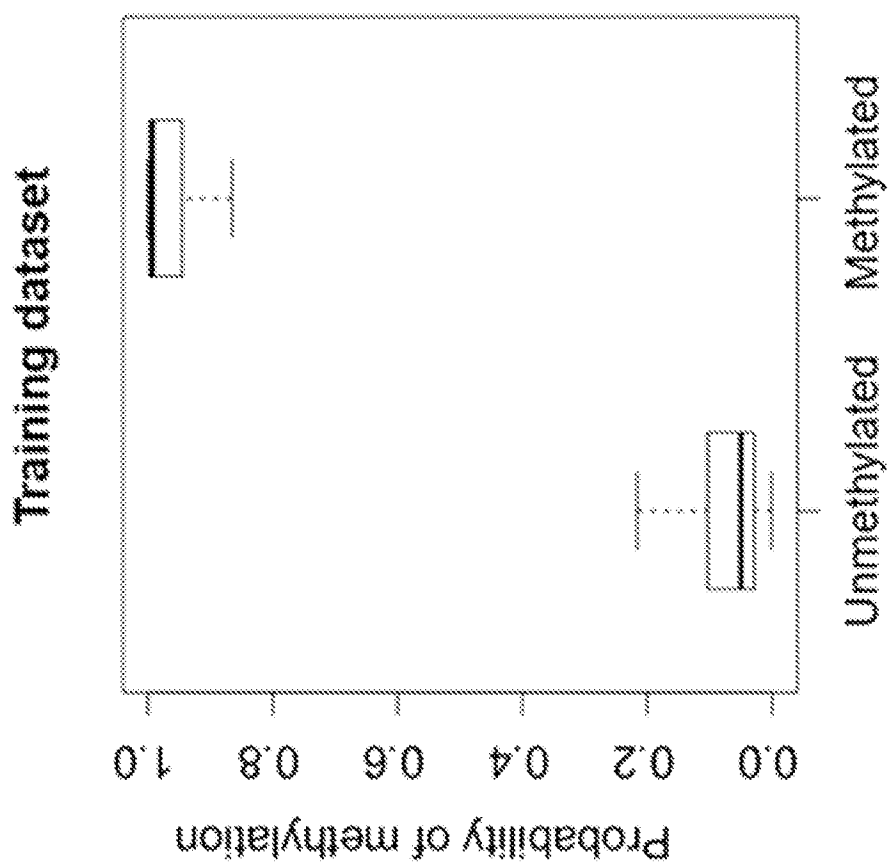


FIG. 55A

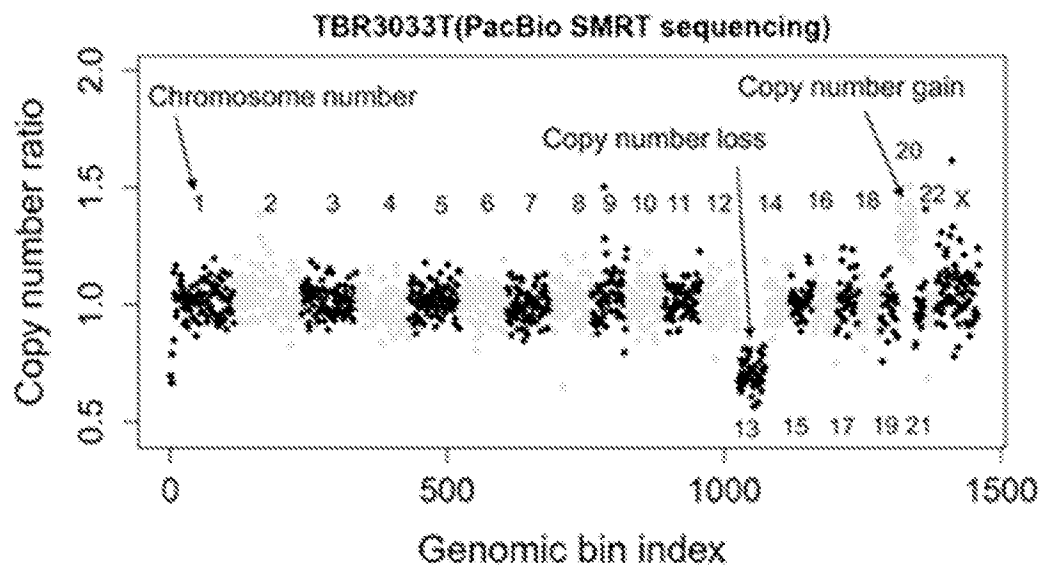


FIG. 56A

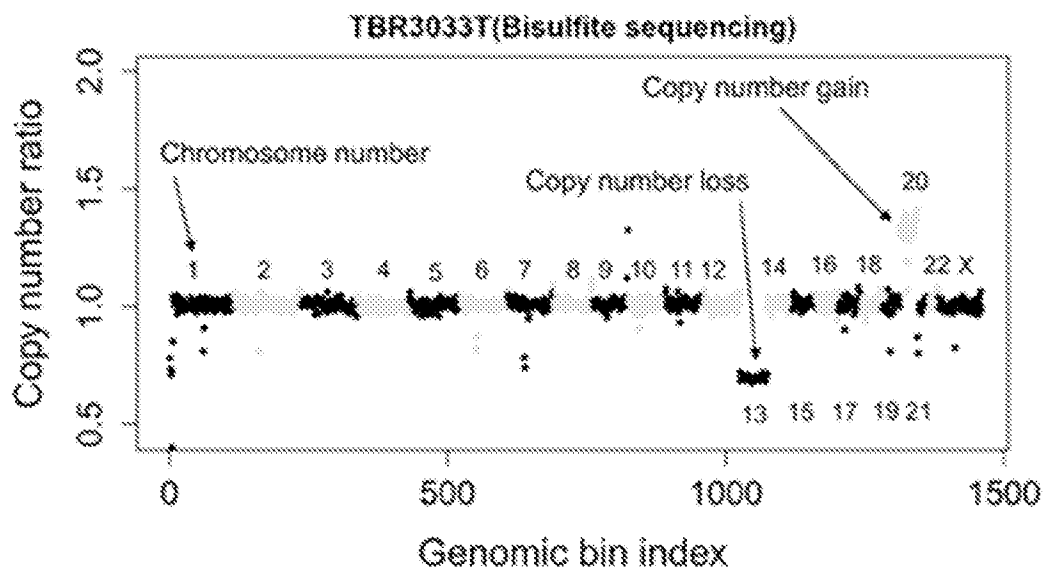


FIG. 56B

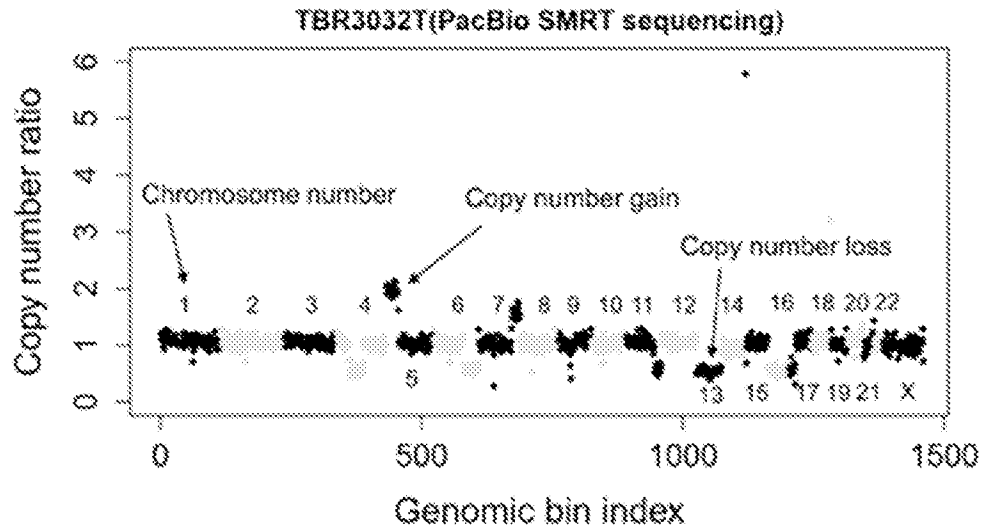


FIG. 57A

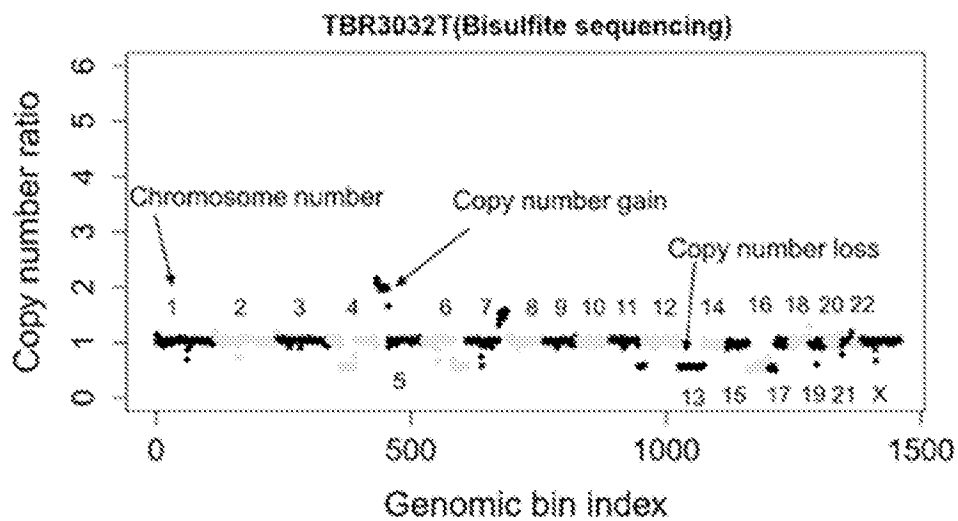


FIG. 57B

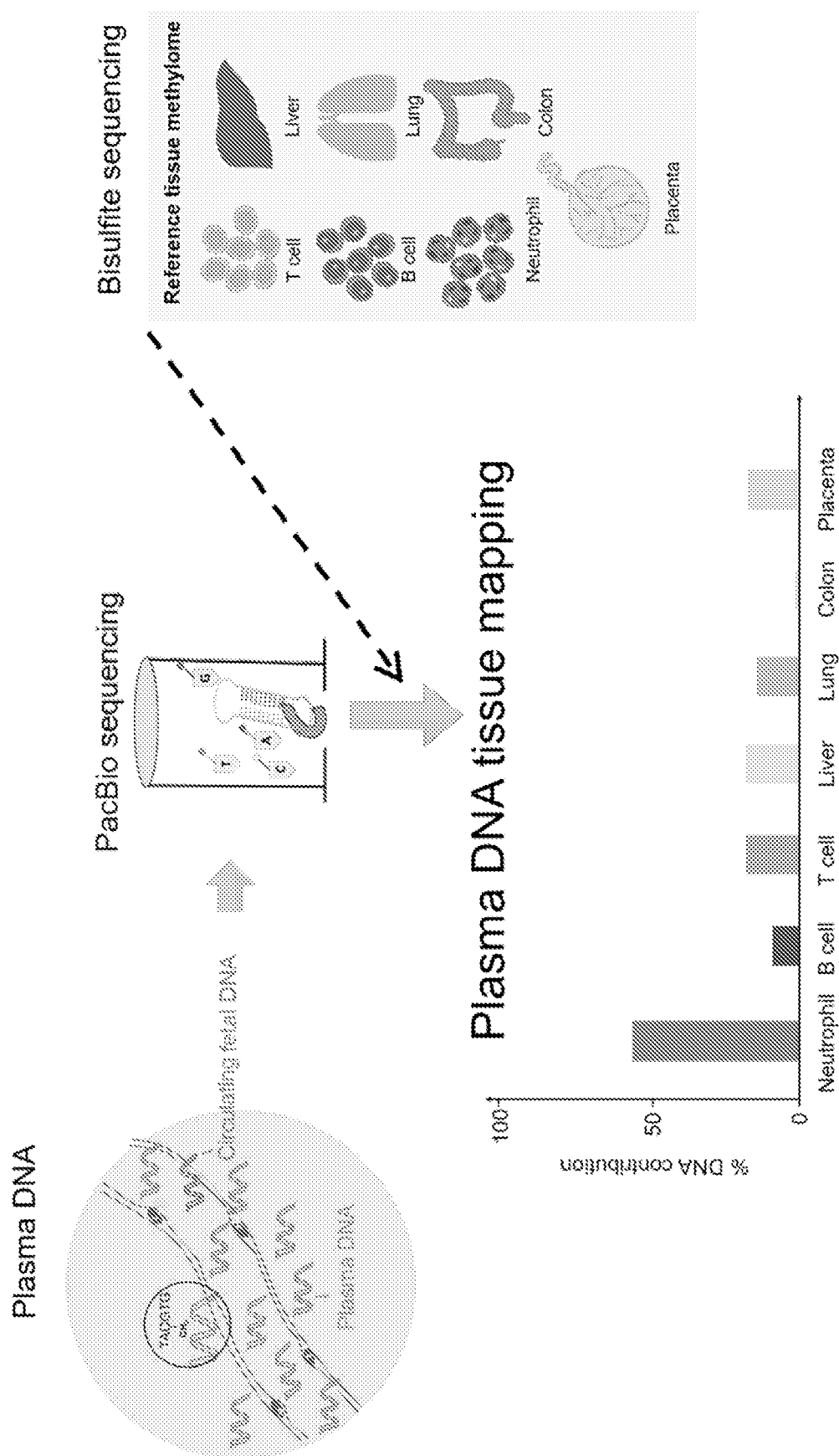


FIG. 58

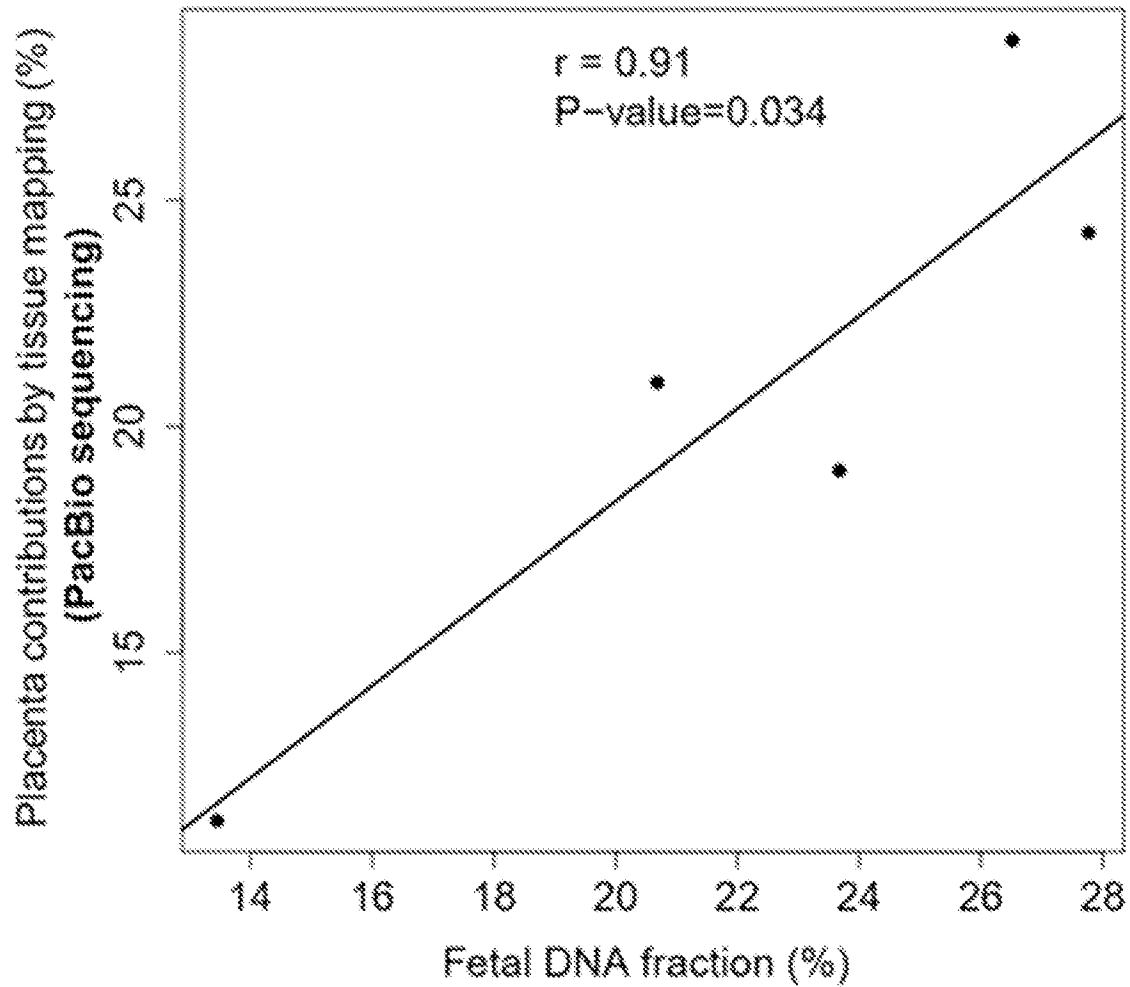


FIG. 59

Groups	Samples	Total subreads	Mapped subreads	Subread mappability (%)	Mean subread depth per SMRT well (x)	No. of SMRT wells	Mappable wells	Mappable well rate (%)
Maternal buffy coat	M13153w	38,008,460	30,673,525	78.6	13.4	3,157,310	2,295,002	72.7
	N13153	23,013,428	18,374,758	71.2	10.4	2,393,400	1,573,540	65.7
HCC tissues	TBR3032T	20,164,513	15,232,744	75.5	13.1	1,742,960	1,147,985	64.8
	TBR3033T	22,639,602	17,479,024	77.2	8.1	2,832,837	2,157,196	76.2
Adjacent normal tissues	TBR3033N	73,118,110	56,446,202	77.2	12.6	6,861,142	4,471,370	65.0
	TBR3032N	76,852,680	60,145,452	78.3	12.8	6,000,227	4,702,130	78.4
Buffy coat (healthy control subjects)	M1	44,777,423	28,325,567	63.3	7.7	7,316,000	3,859,966	50.0
	F2	48,840,758	32,984,845	68.2	8.6	7,215,112	3,823,329	53.0
	F1	40,012,804	24,717,289	61.8	6.5	7,301,768	3,800,392	52.0
	M2	152,530,411	88,596,520	58.1	7.7	21,794,606	11,563,500	53.1
HCC cell line	HepG2	47,308,982	34,581,721	73.1	7.3	6,220,000	4,750,581	76.4

FIG. 60

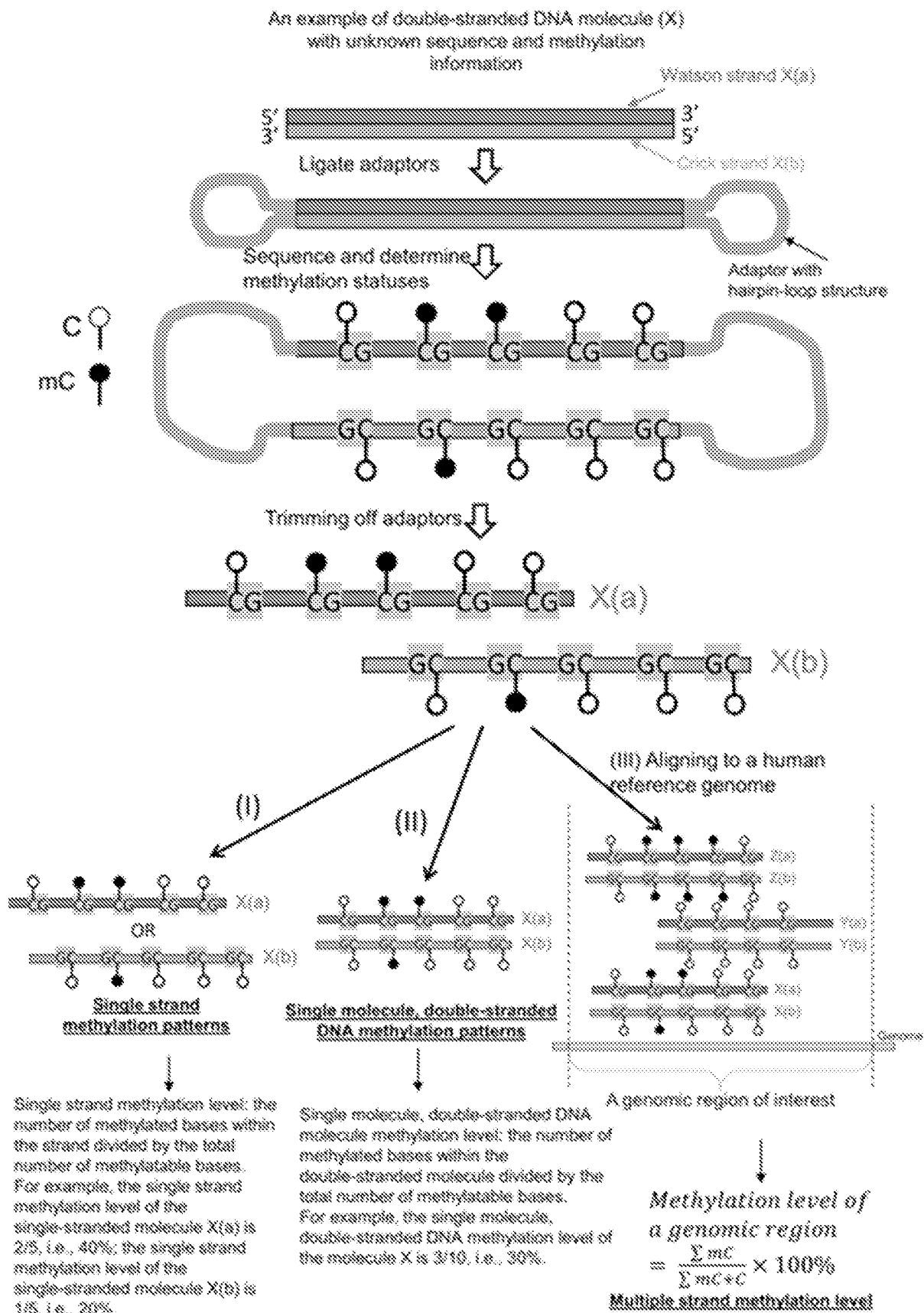


FIG. 61

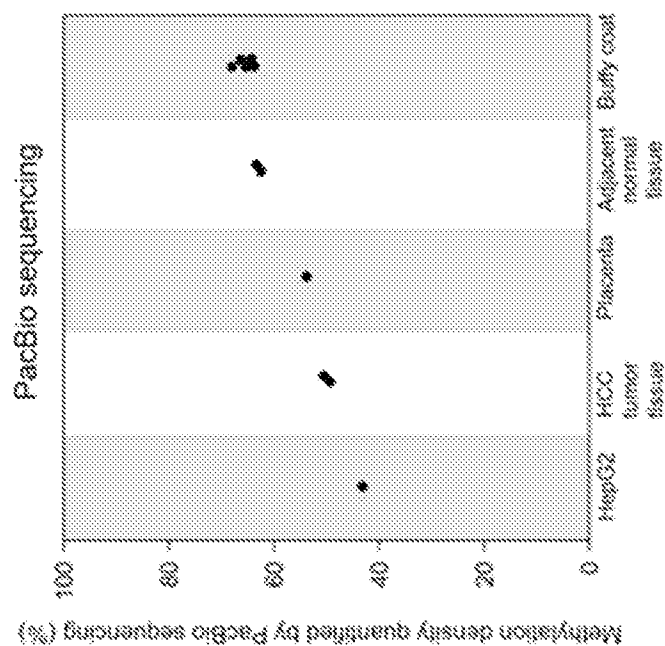


FIG. 62B

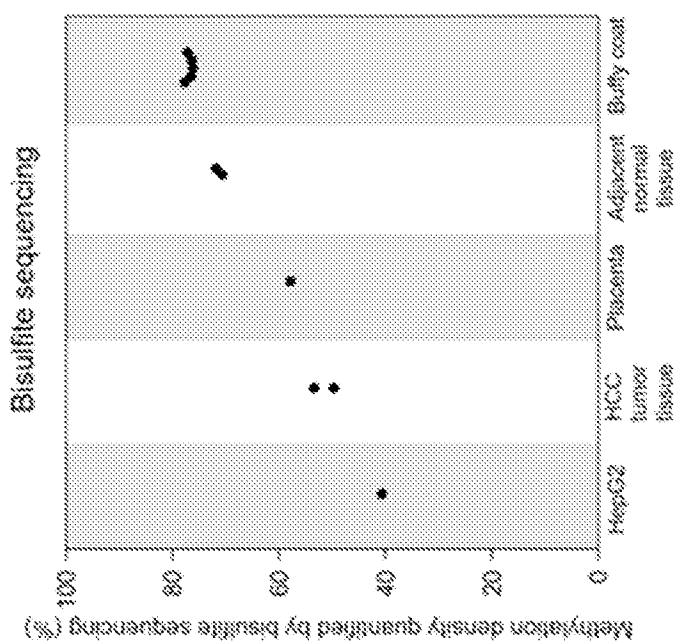


FIG. 62A

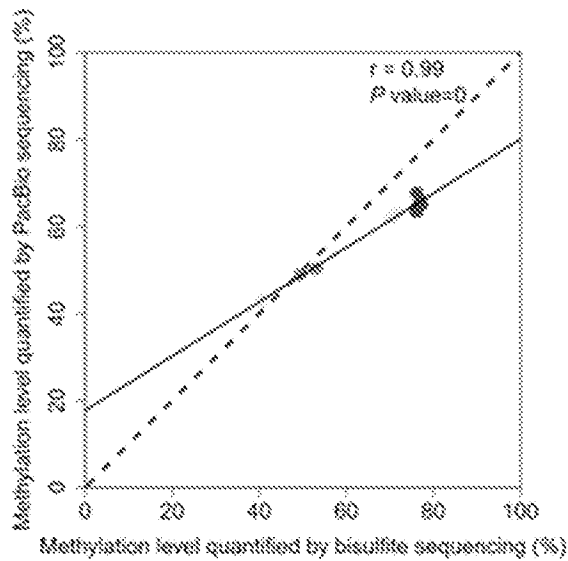


FIG. 63A

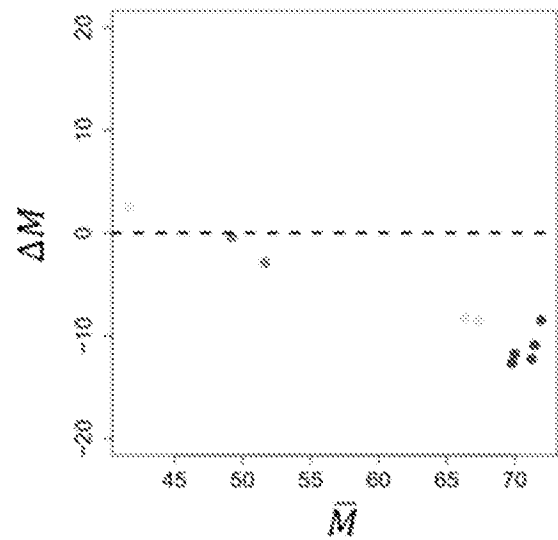


FIG. 63B

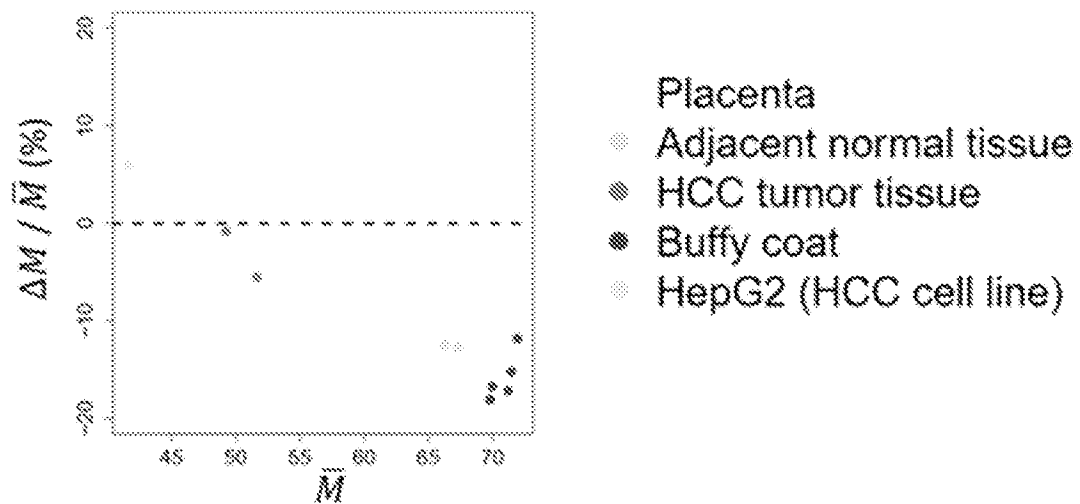


FIG. 63C

F2 (Buffy coat)

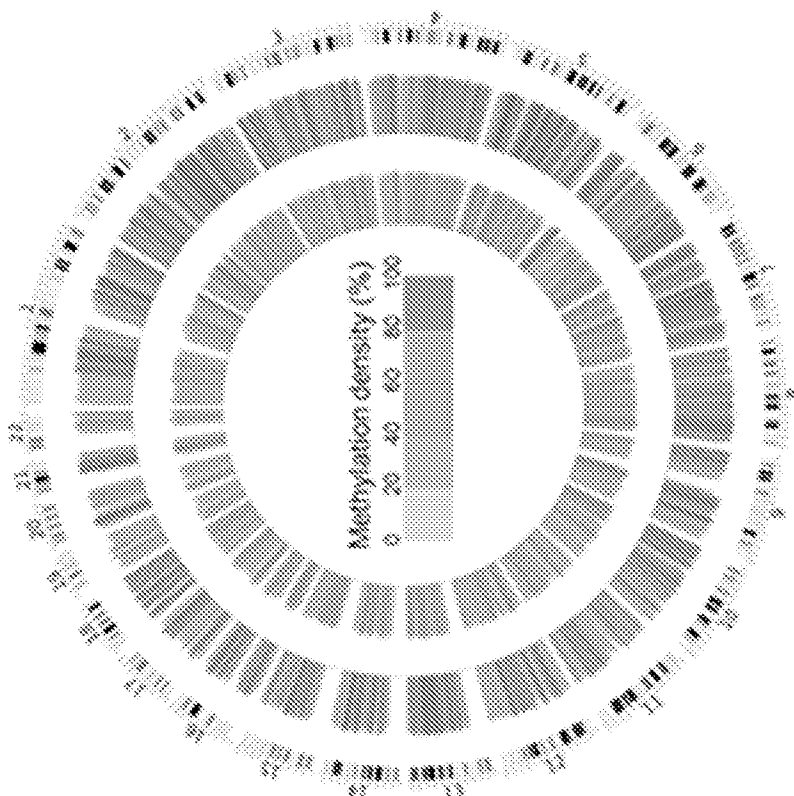


FIG. 64B

HepG2 (HCC cell line)

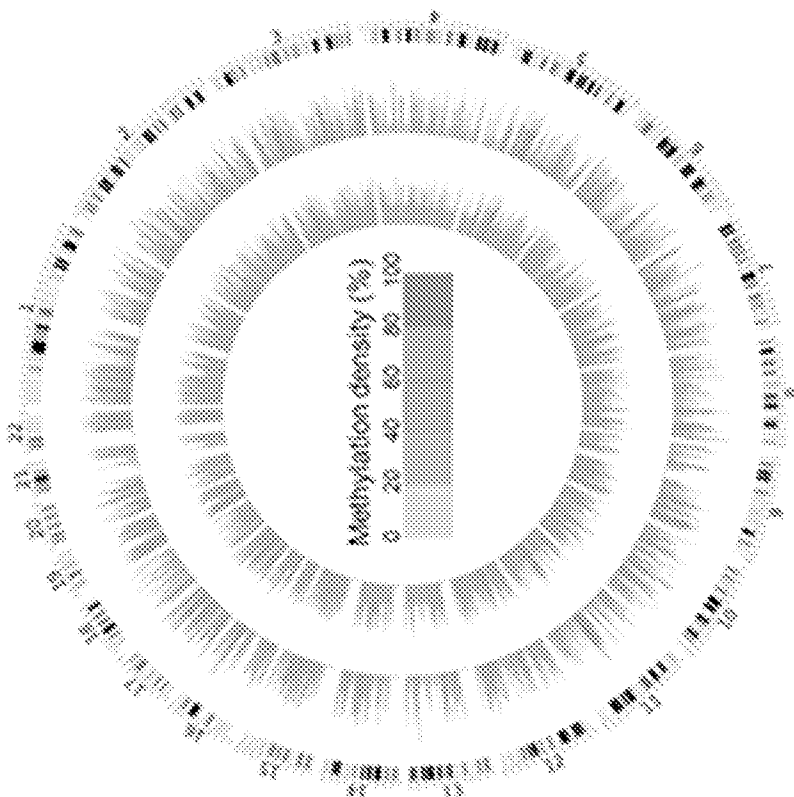


FIG. 64A

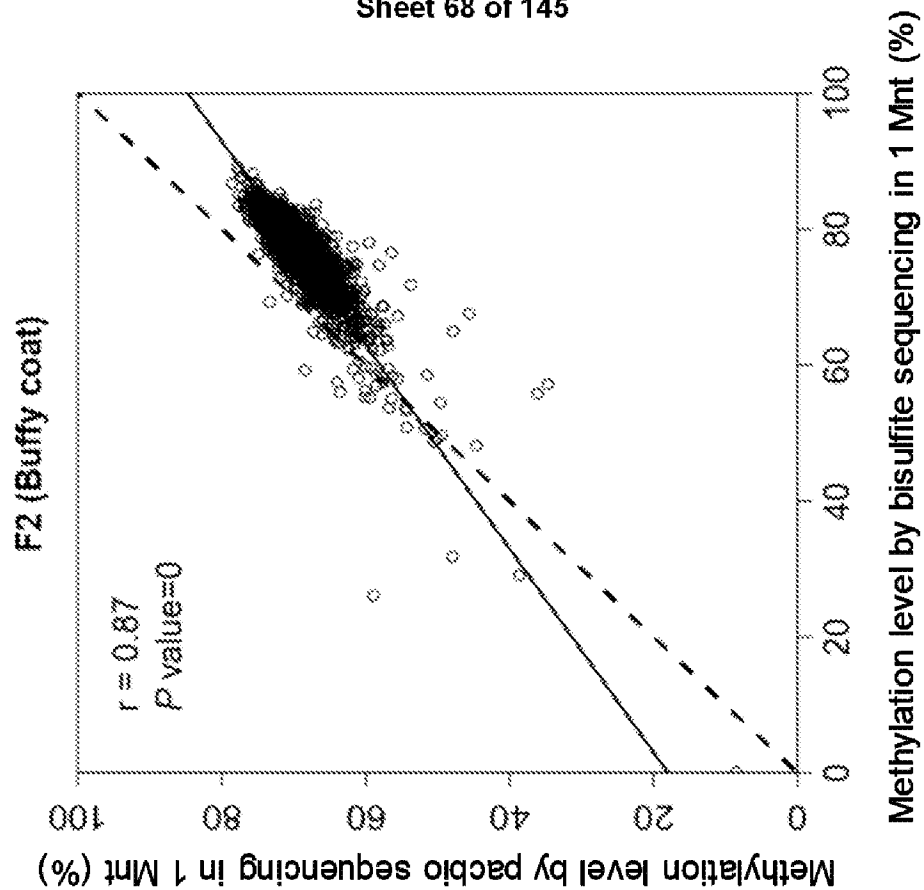


FIG. 65B

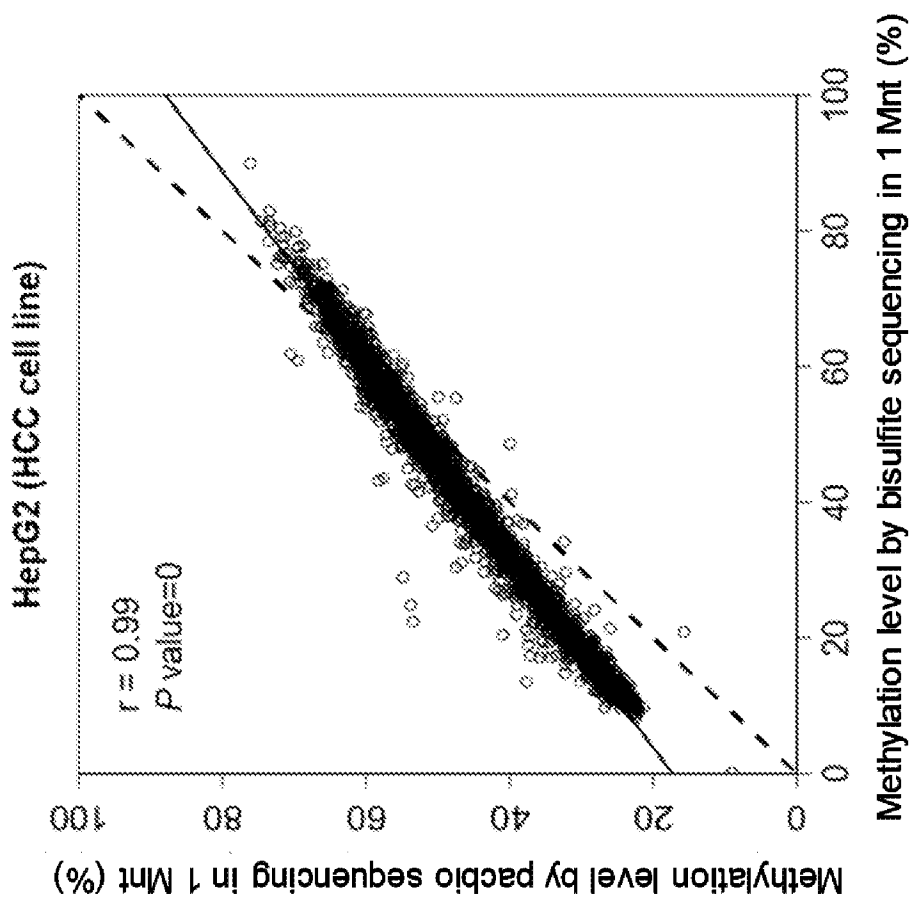


FIG. 65A

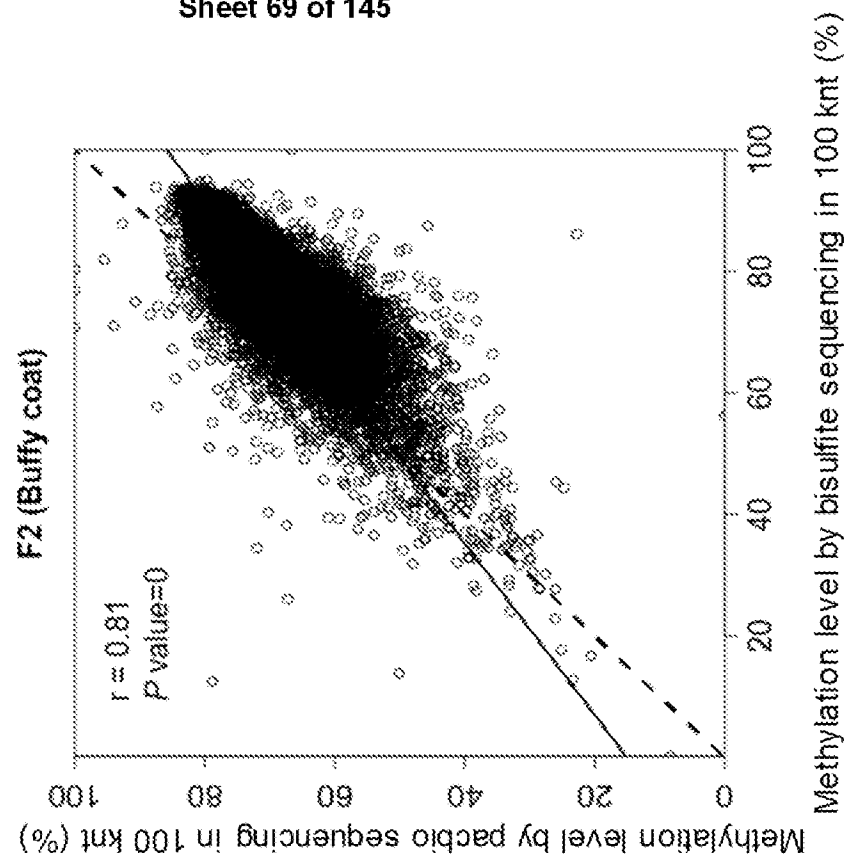


FIG. 66B

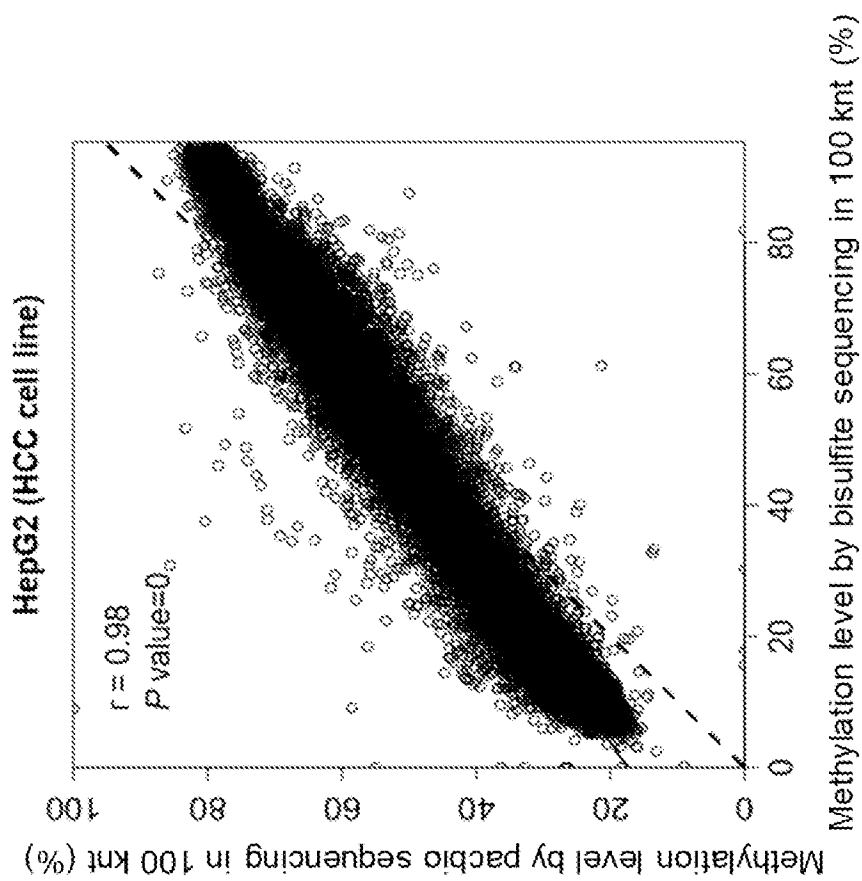


FIG. 66A

TBR3033N (Adjacent normal tissue)

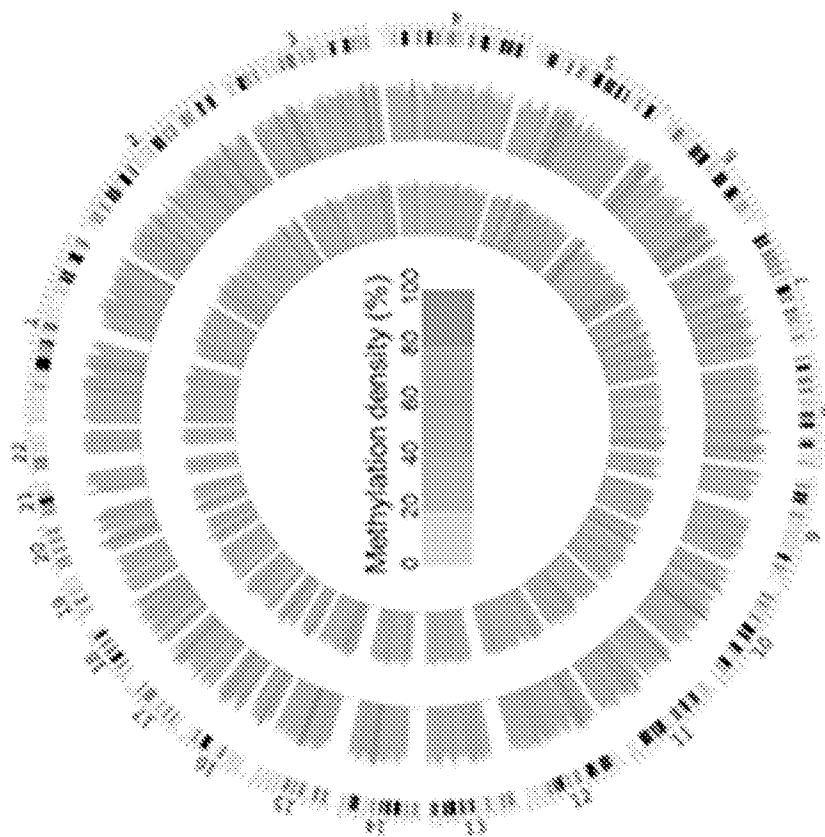


FIG. 67B

TBR3033T (HCC tumor)

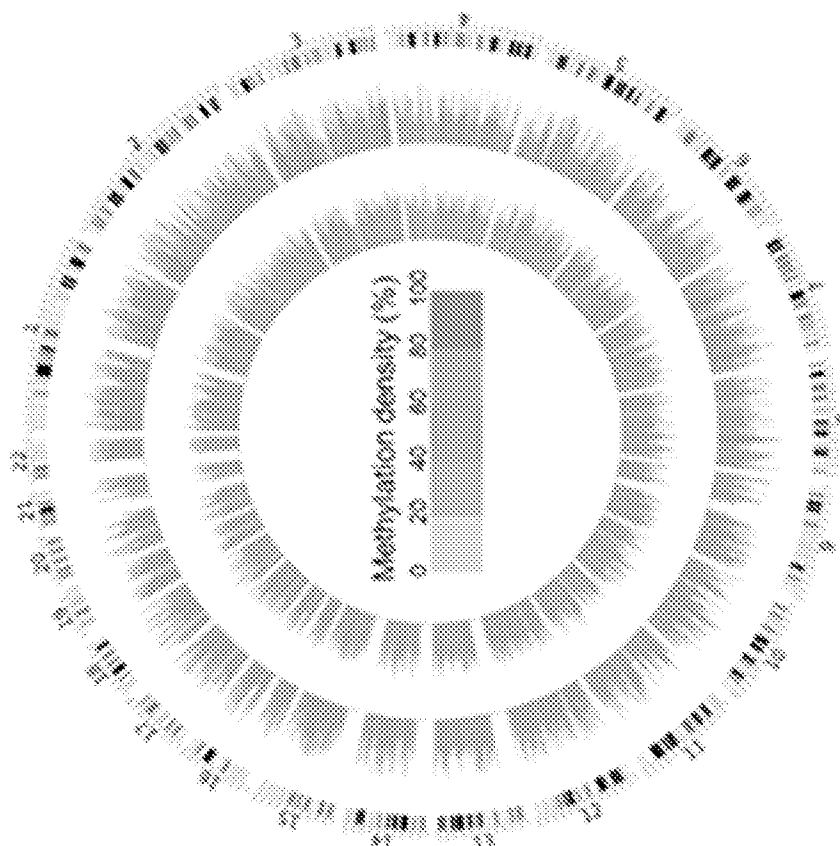


FIG. 67A

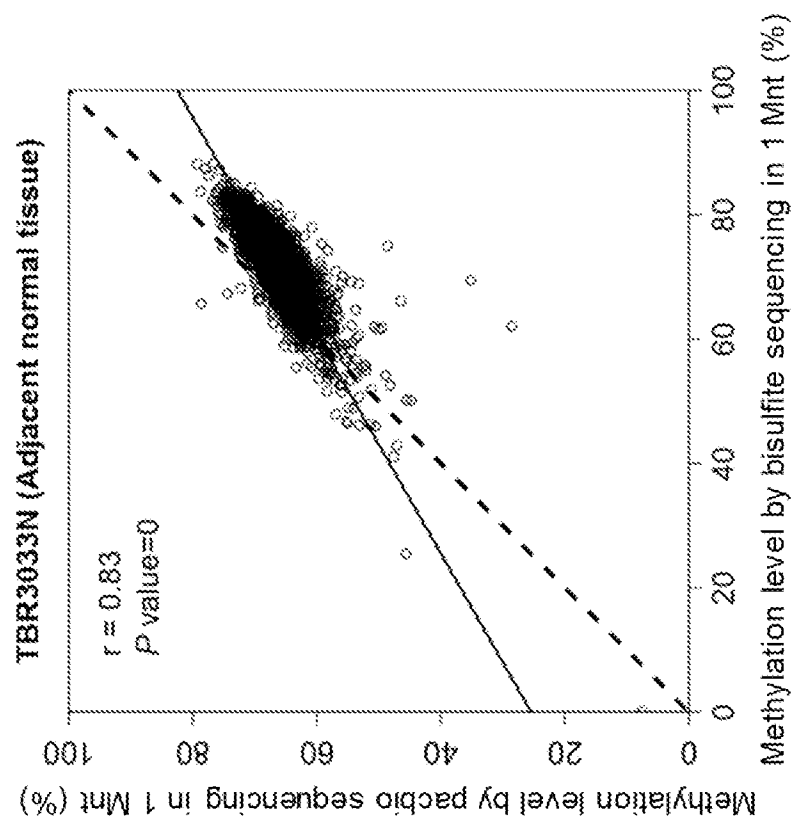


FIG. 68B

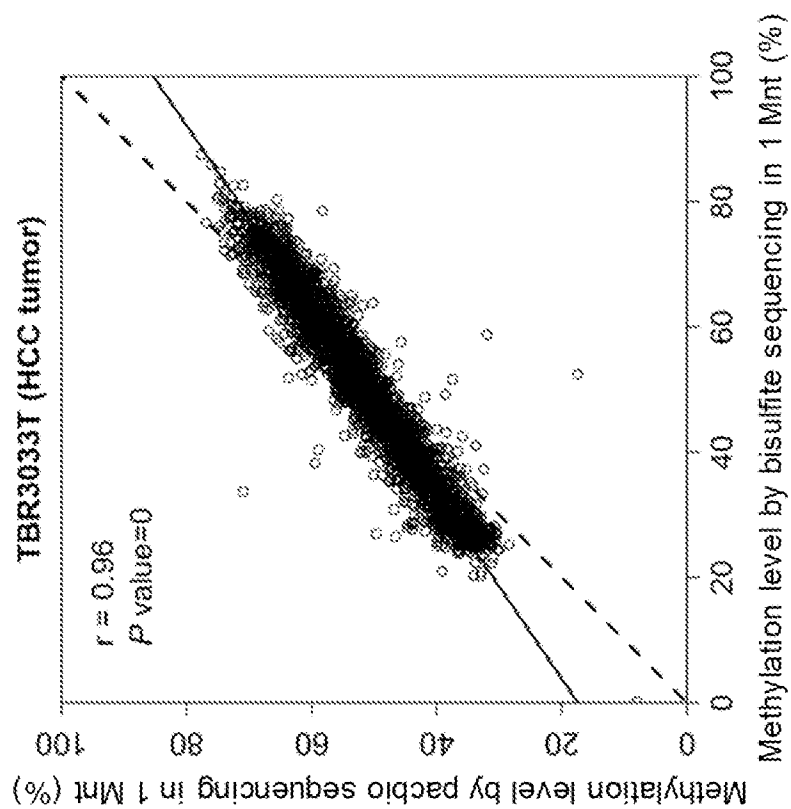


FIG. 68A

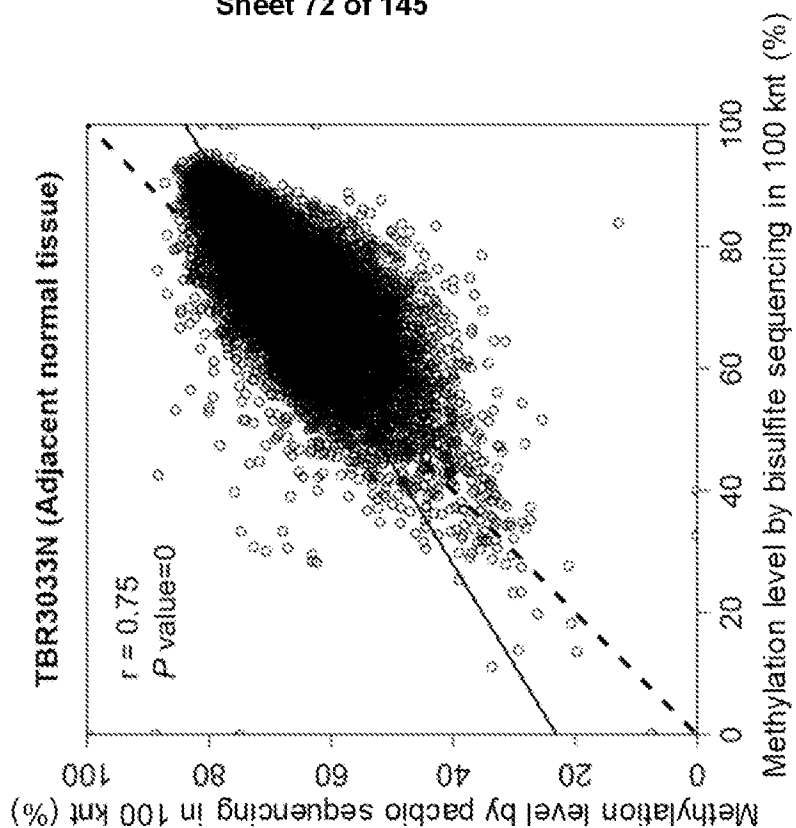


FIG. 69B

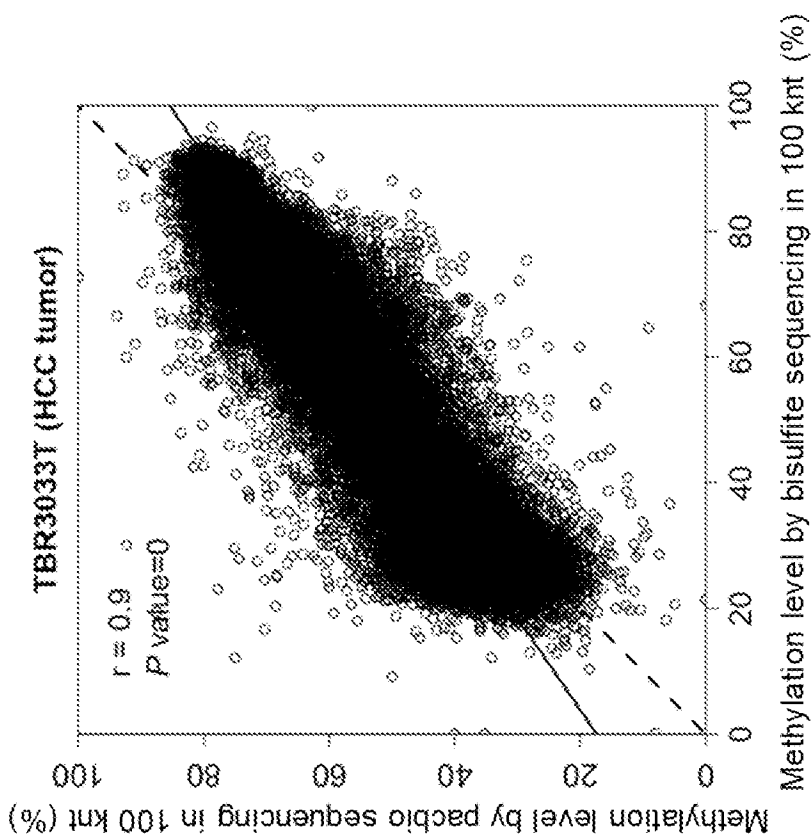


FIG. 69A

TBR3032N (Adjacent normal tissue)

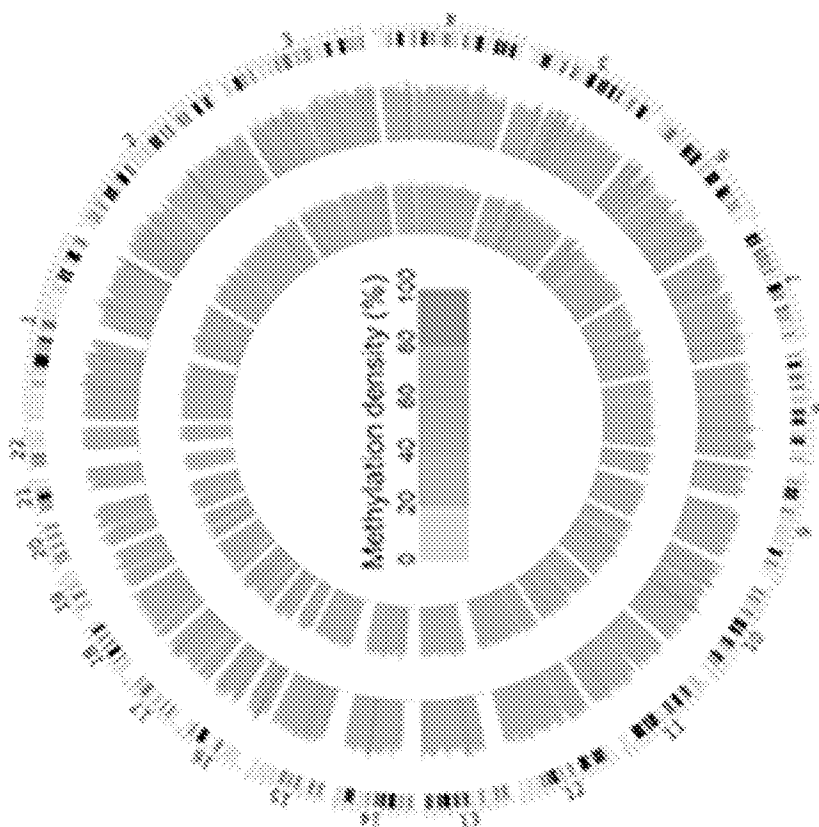


FIG. 70B

TBR3032T (HCC tumor)

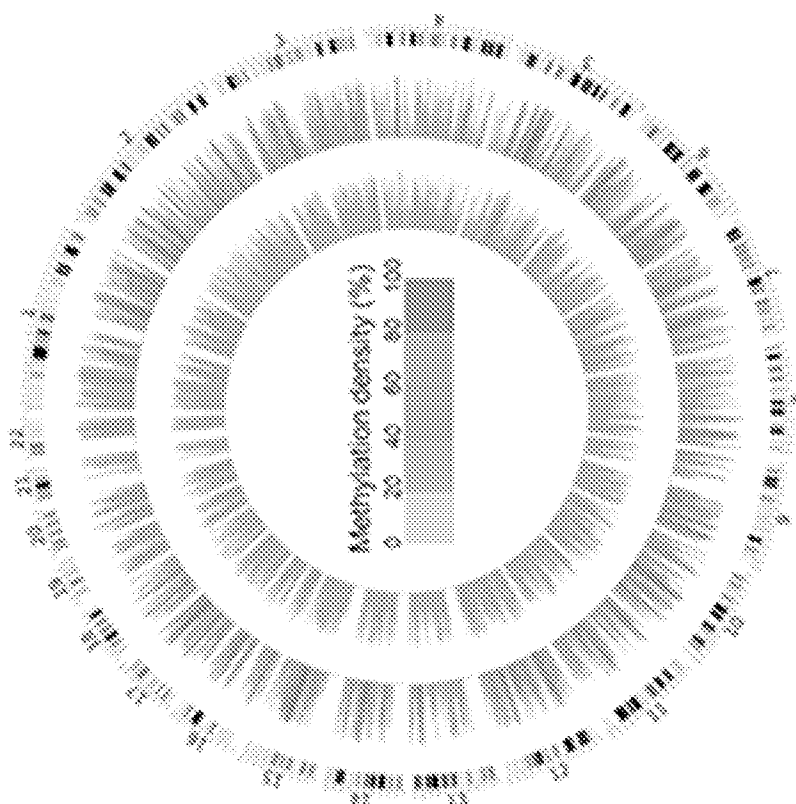


FIG. 70A

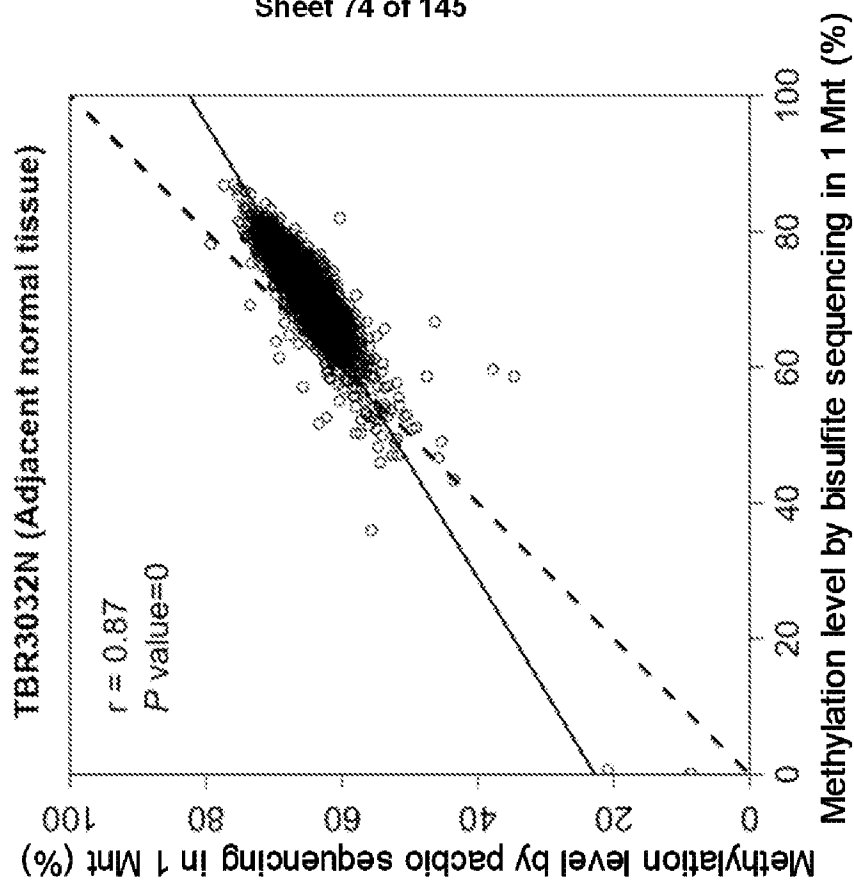


FIG. 71B

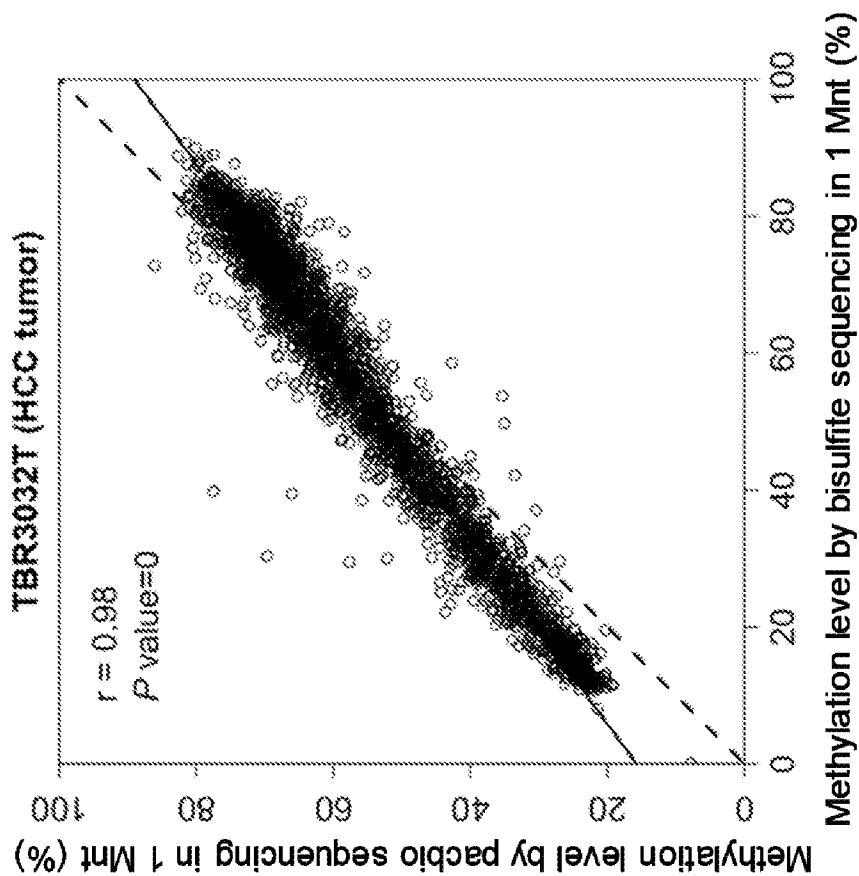


FIG. 71A

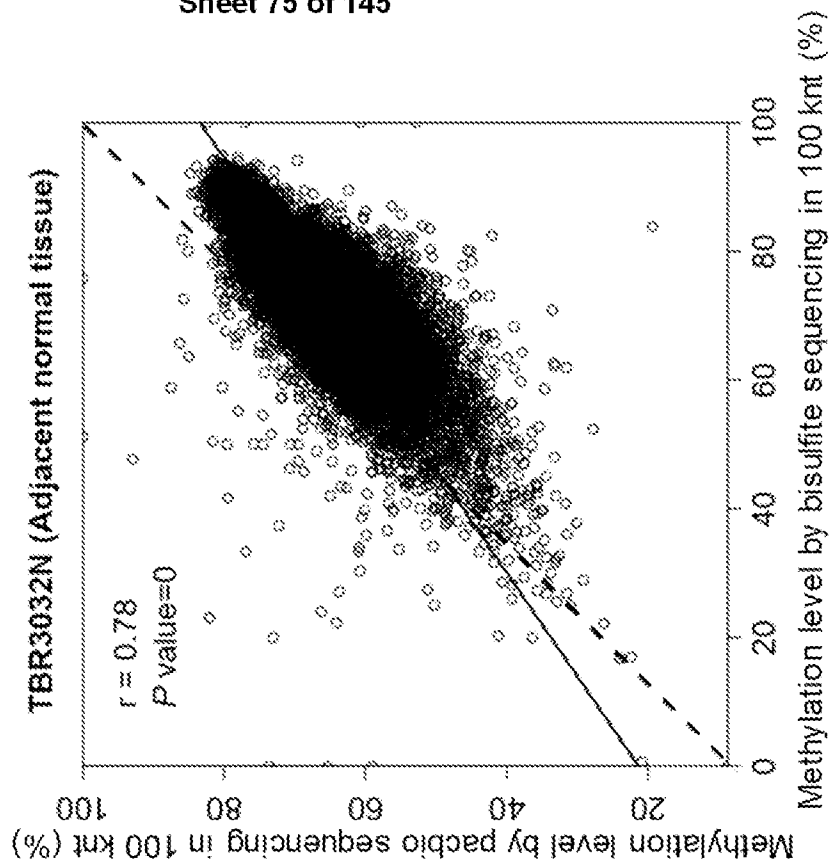


FIG. 72B

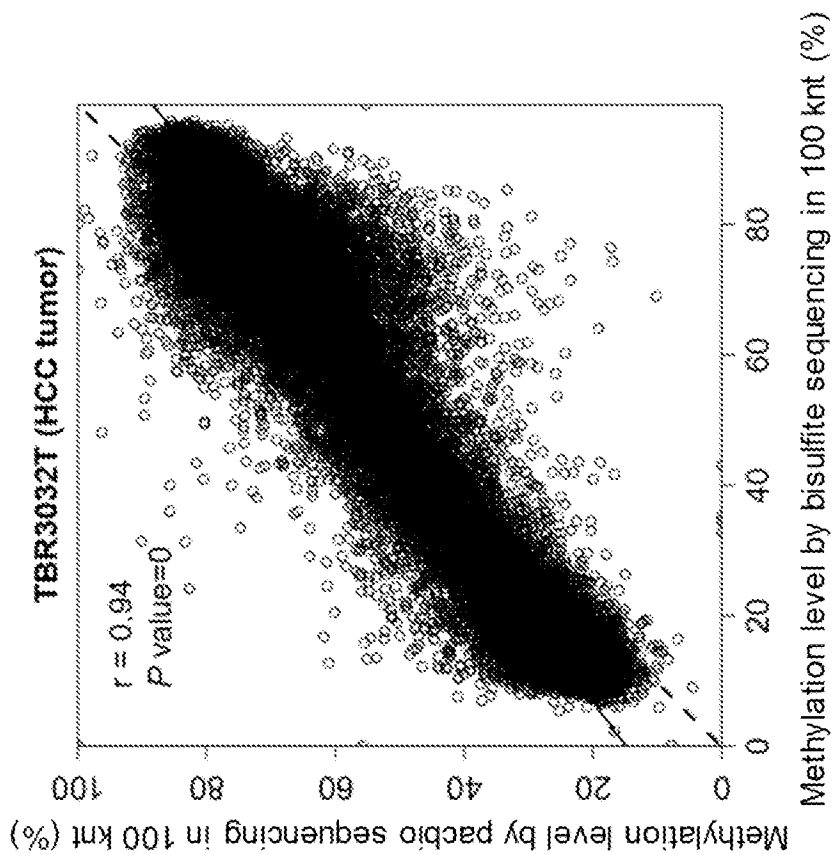


FIG. 72A

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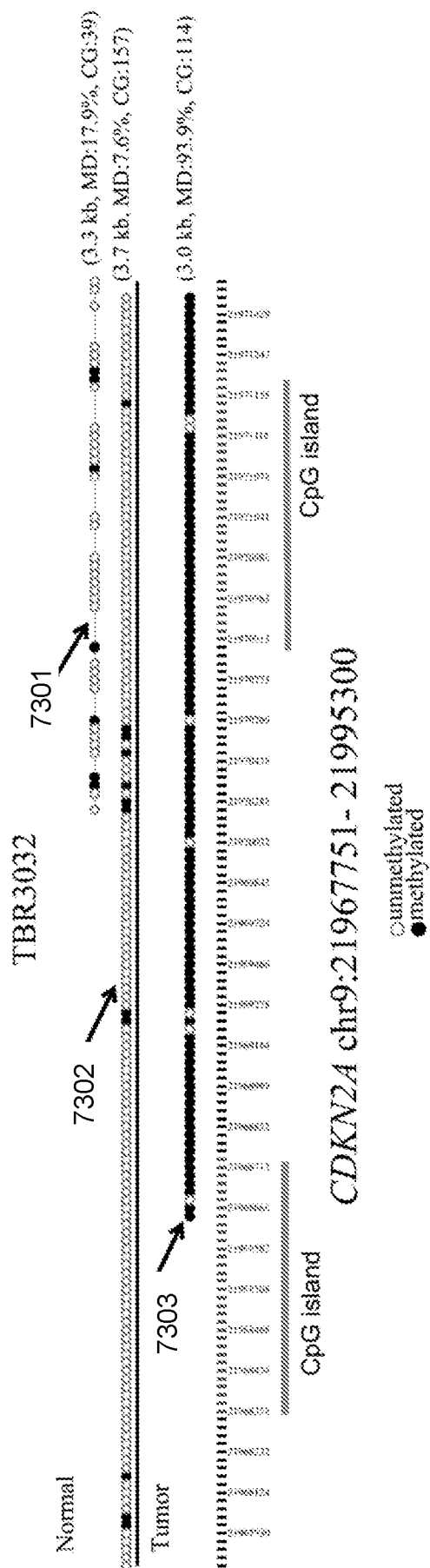


FIG. 73

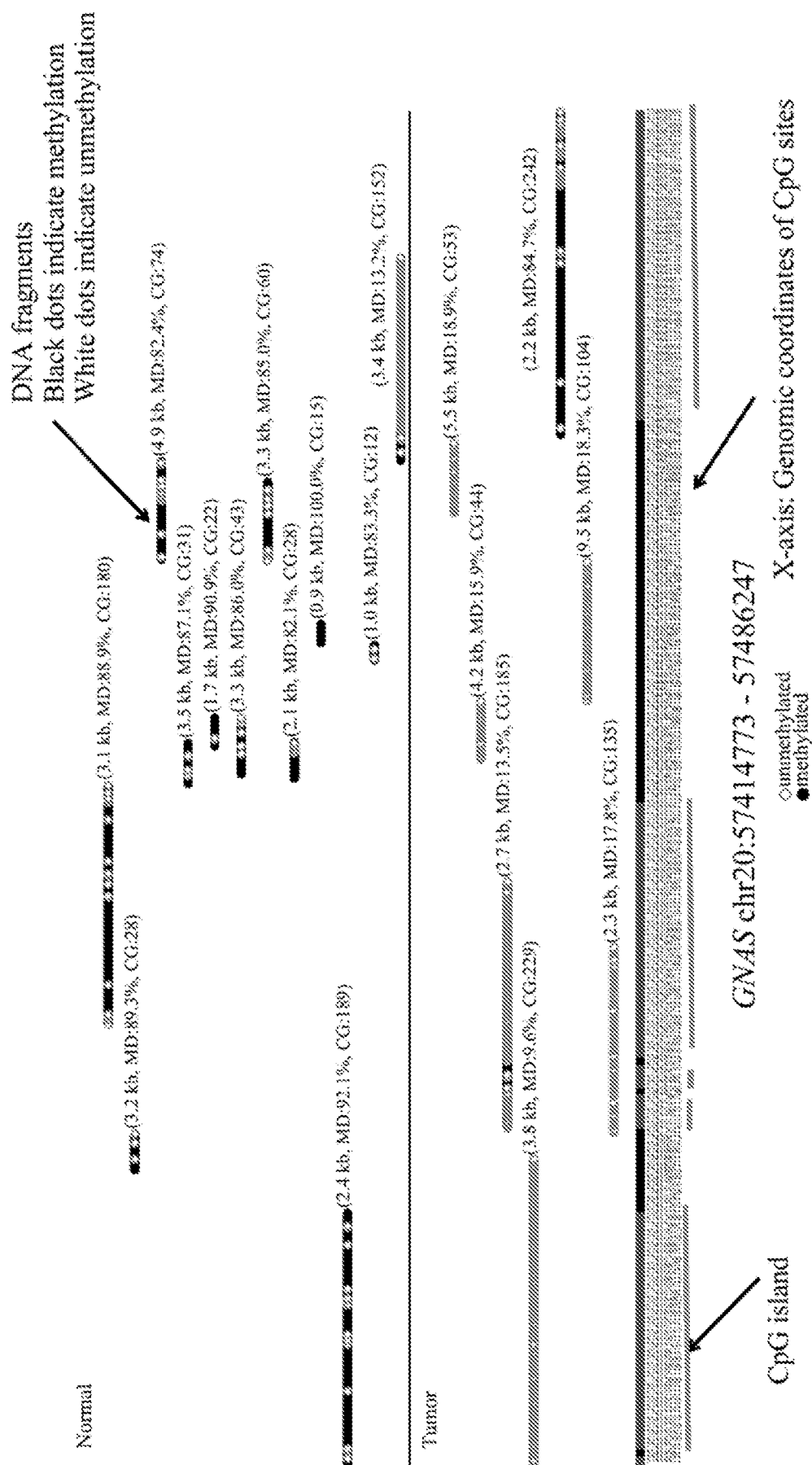


FIG. 74A

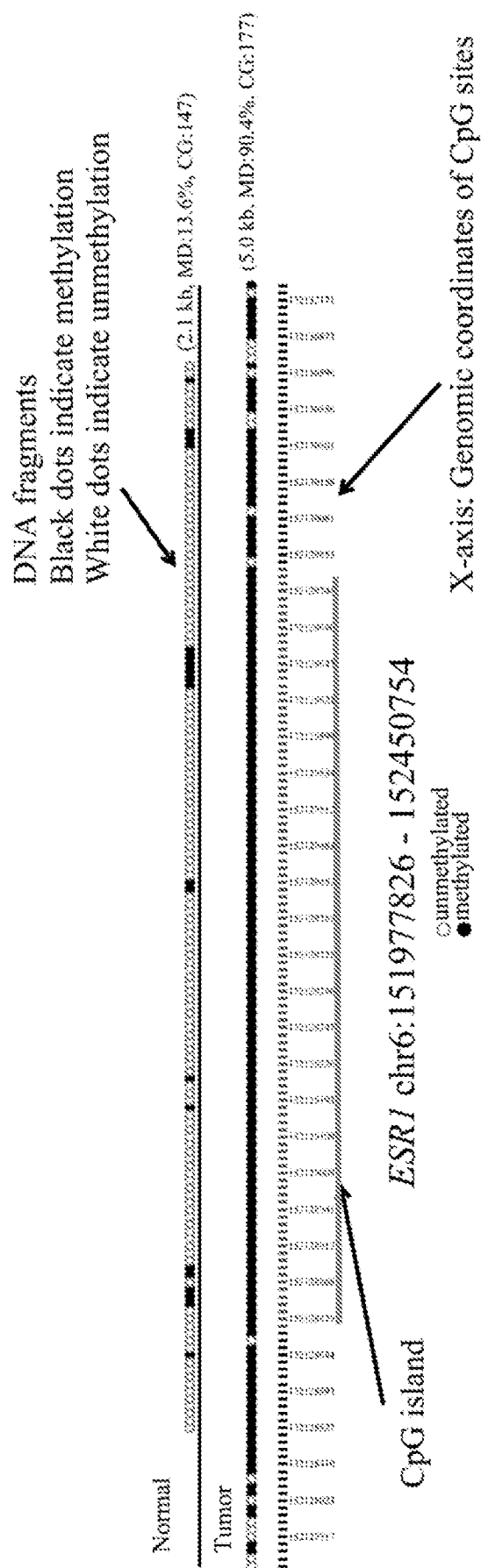


FIG. 74B

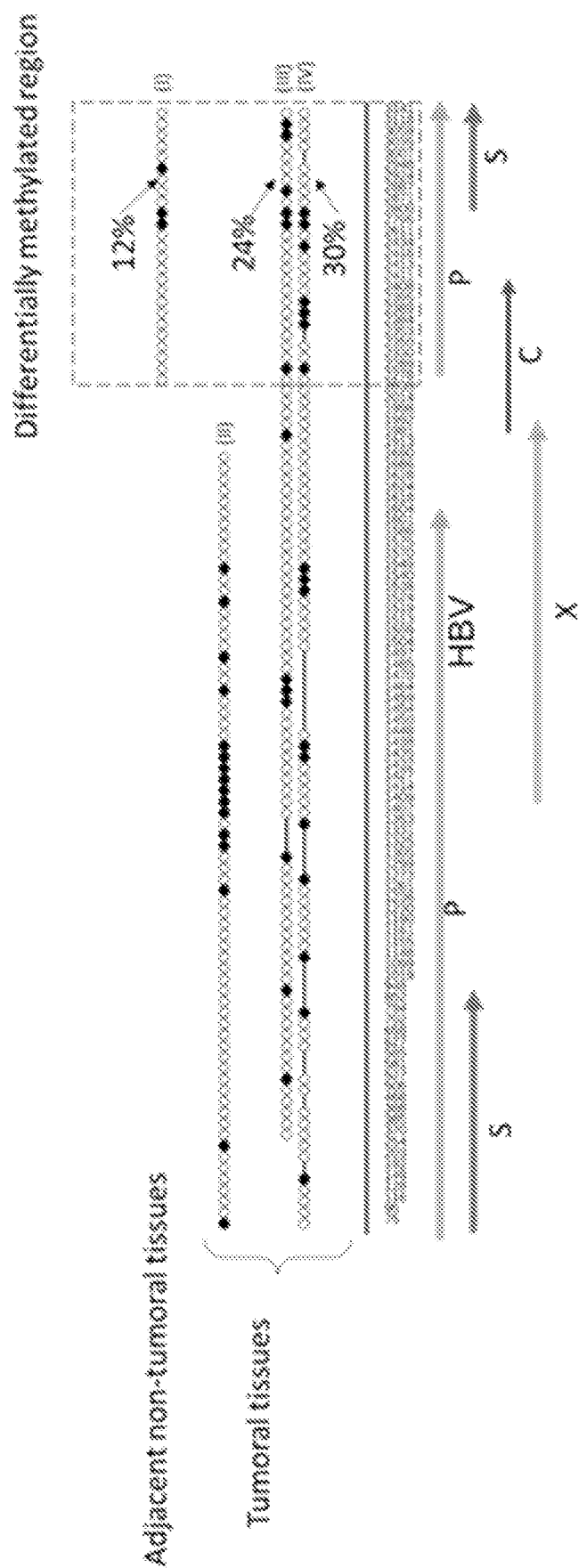


FIG. 75

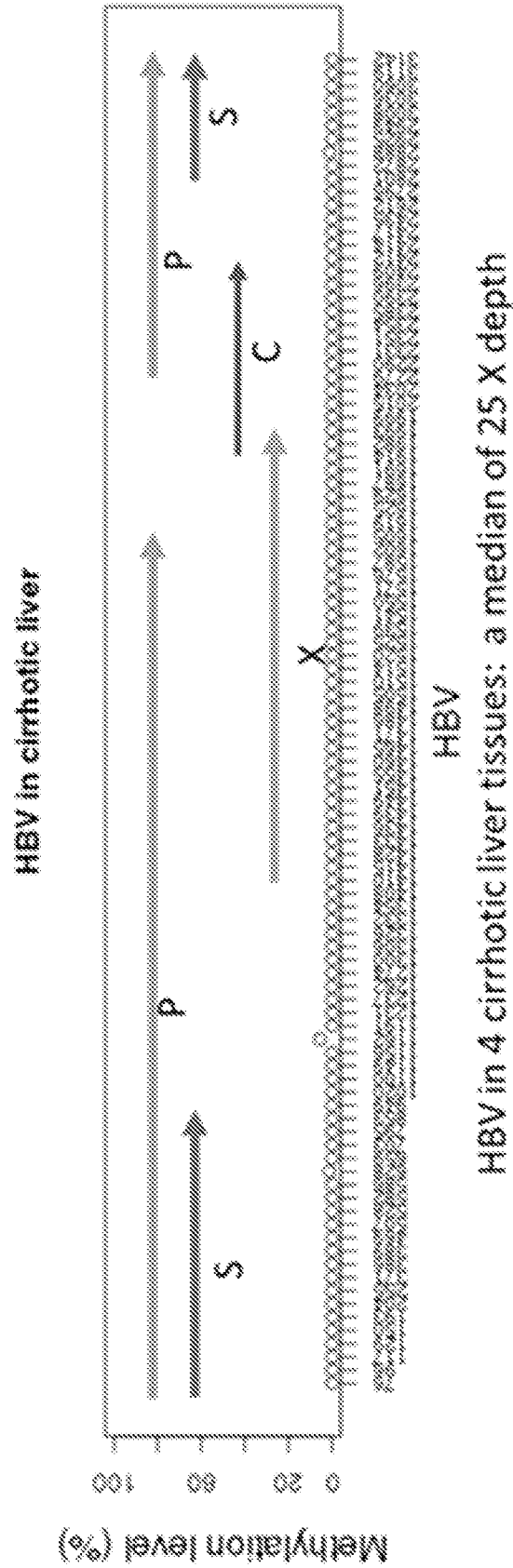


FIG. 76A

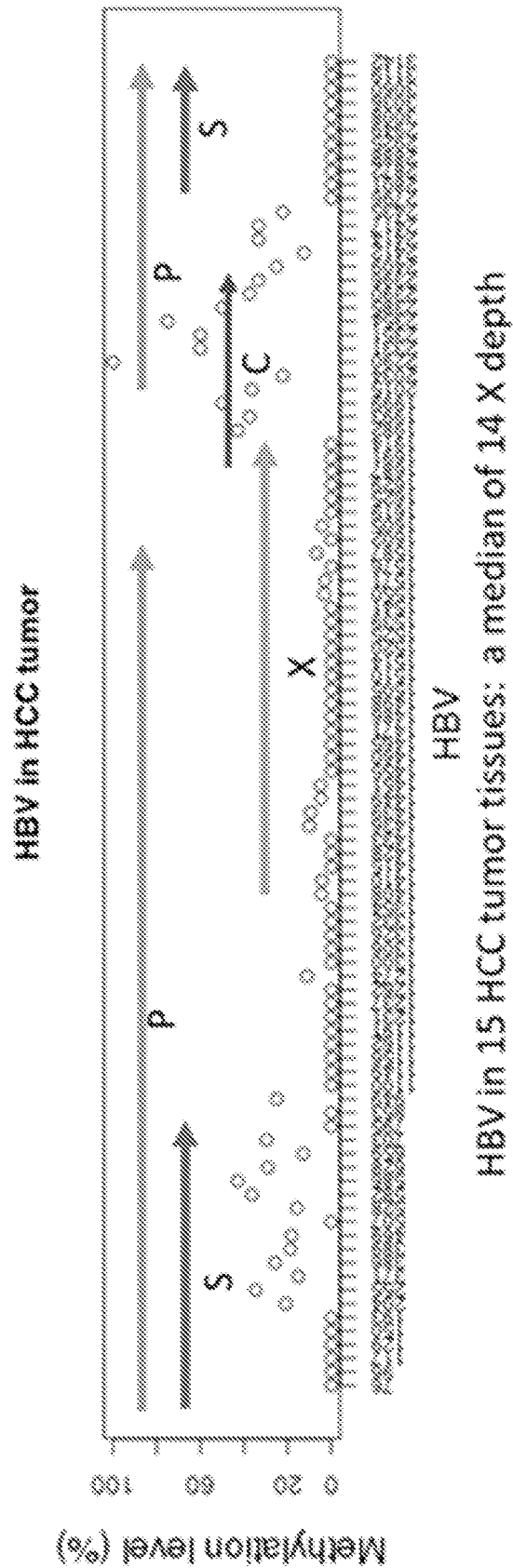


FIG. 76B

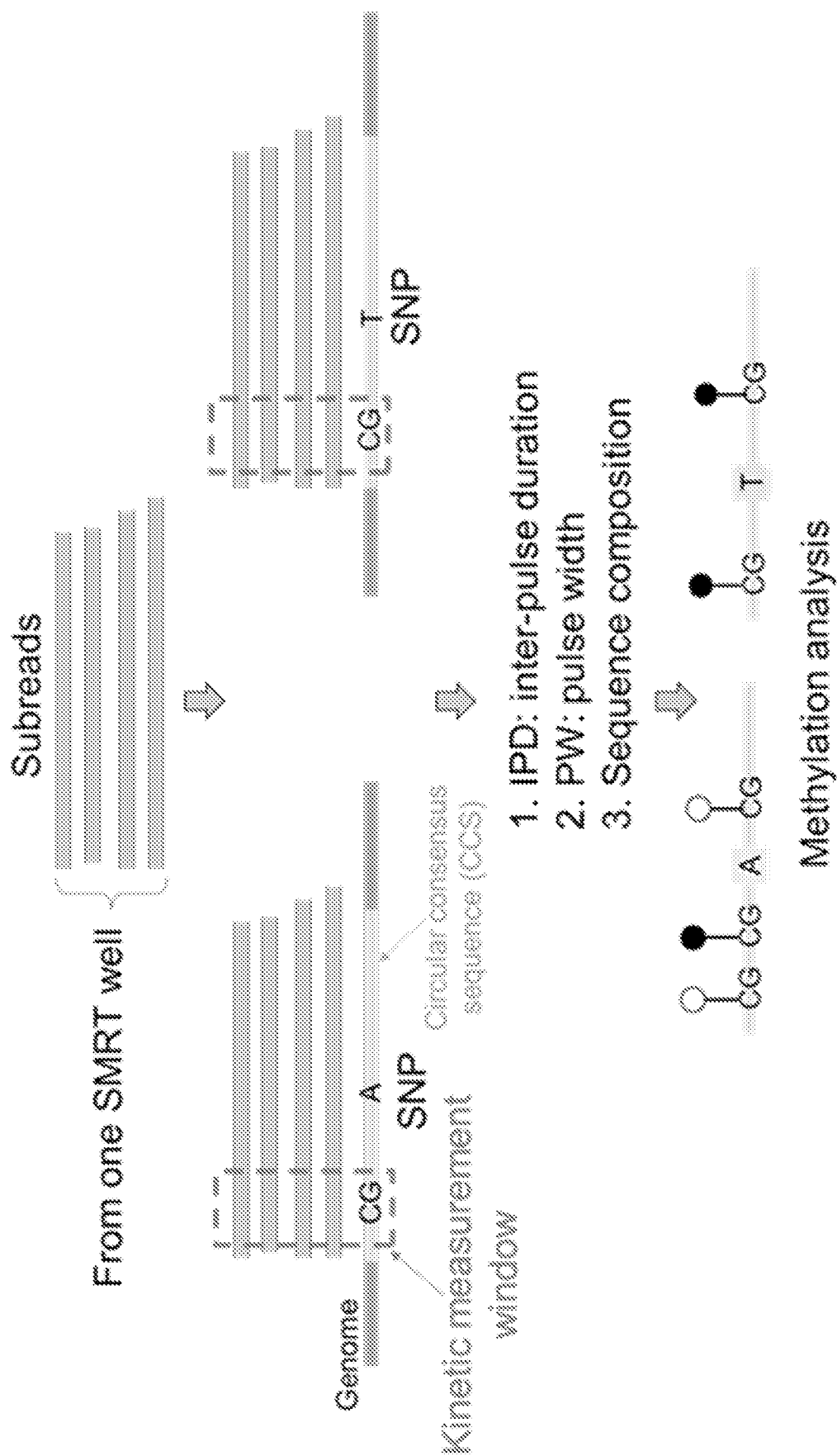


FIG. 77

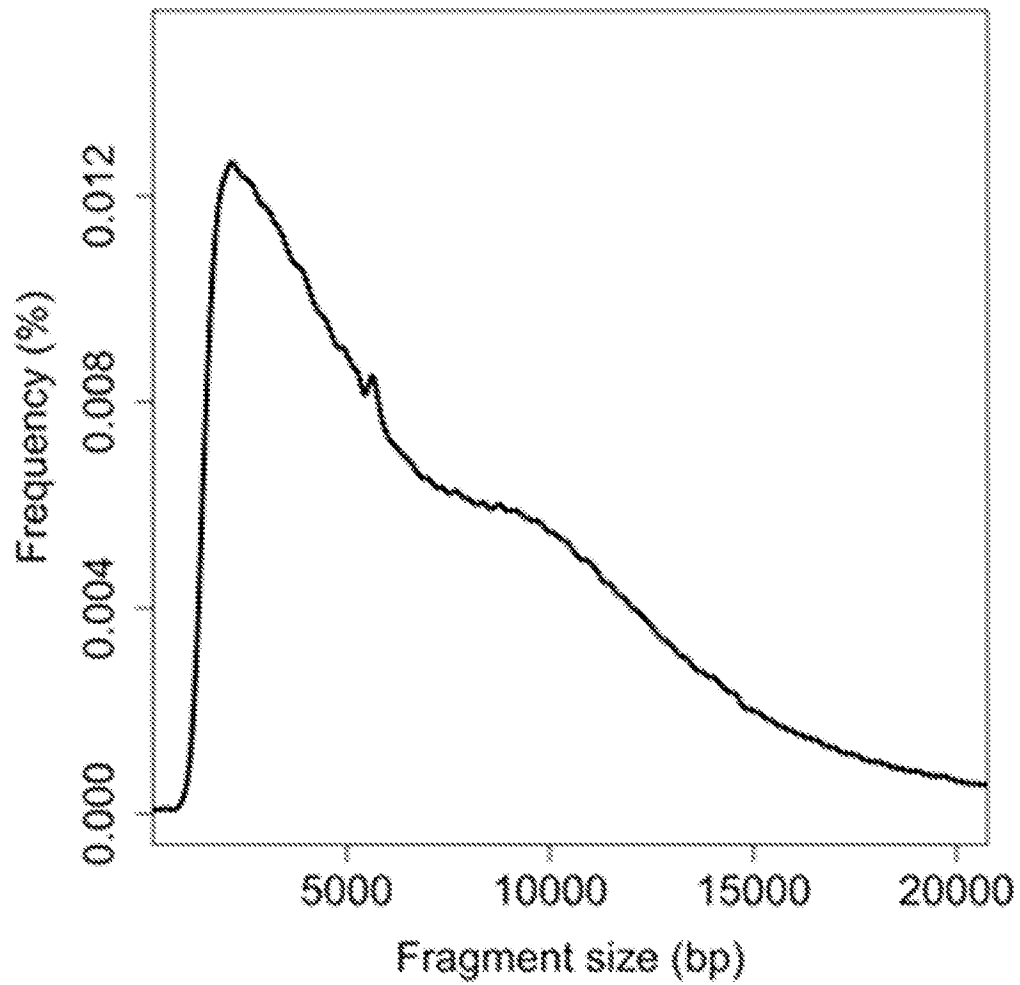


FIG. 78

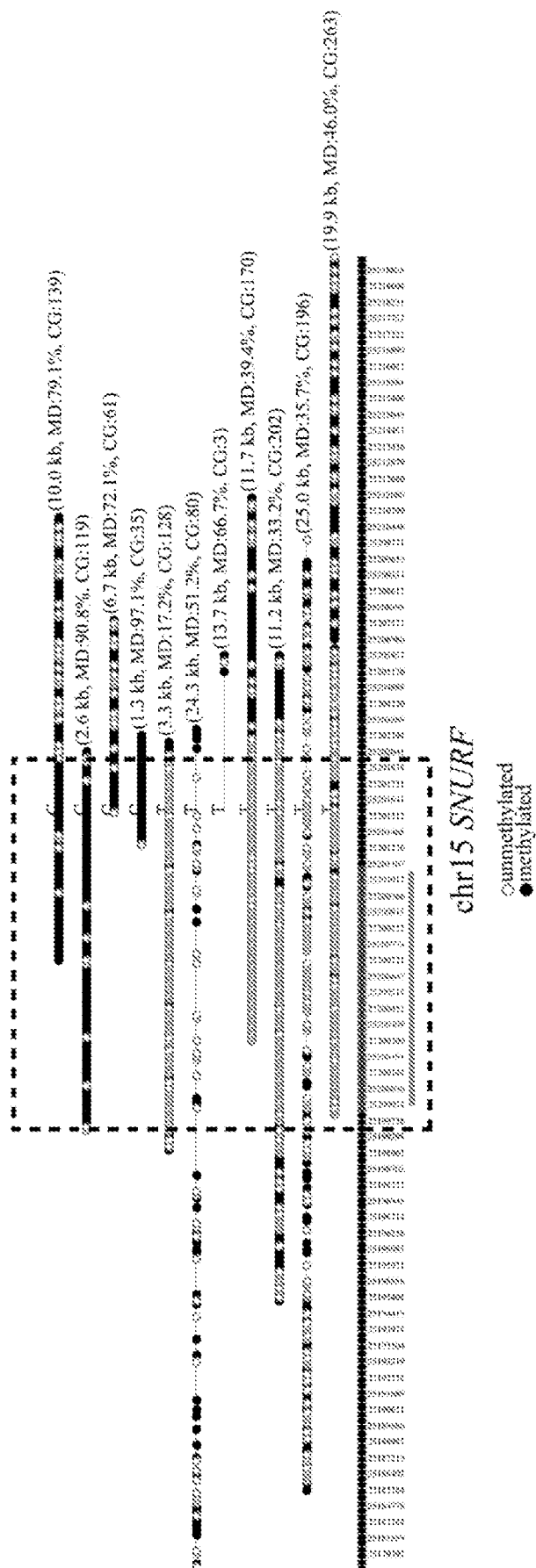
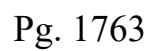


FIG. 79A



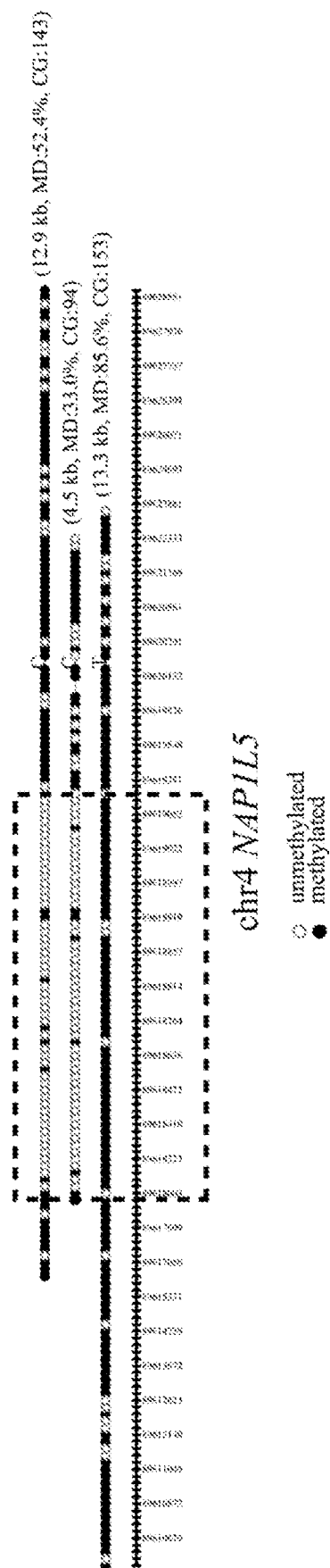


FIG. 79C

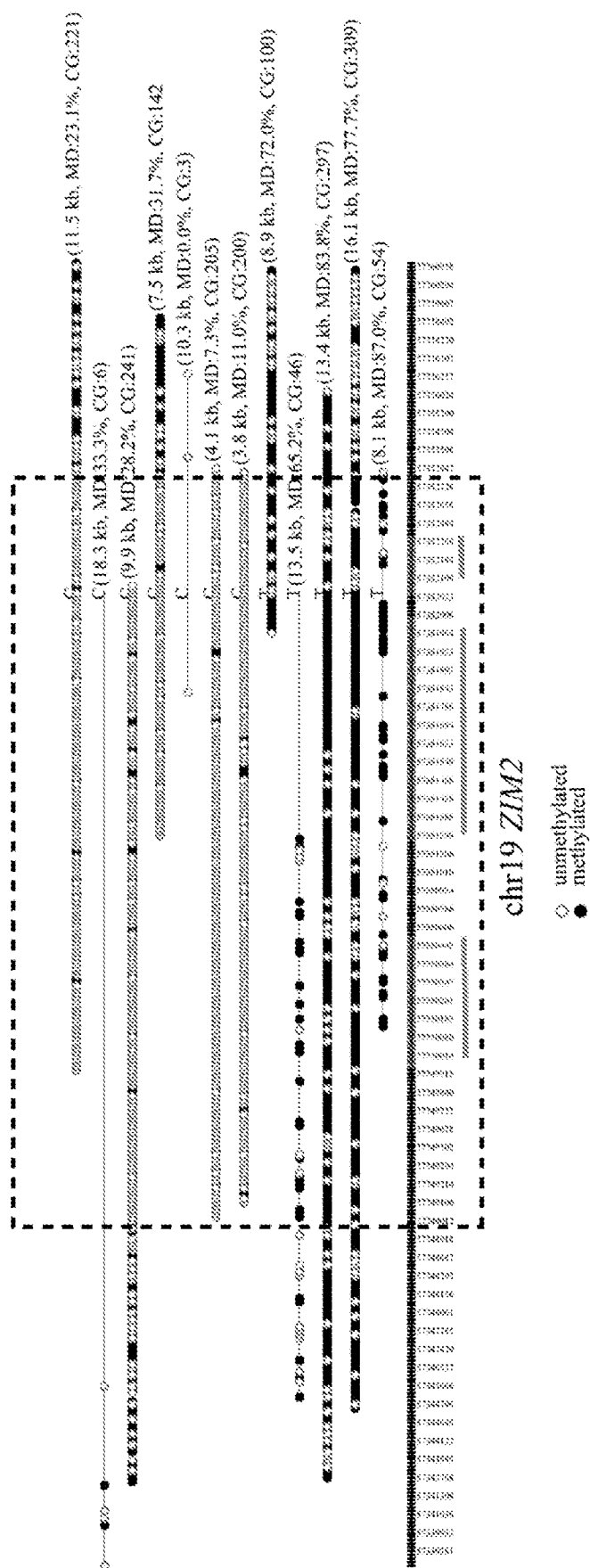


FIG. 79D

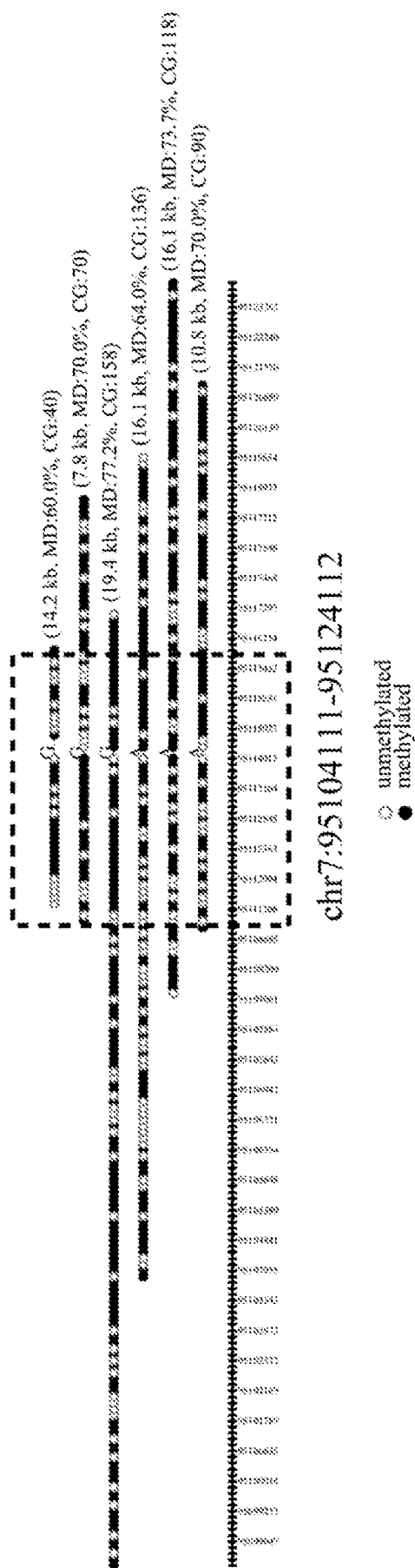


FIG. 80A

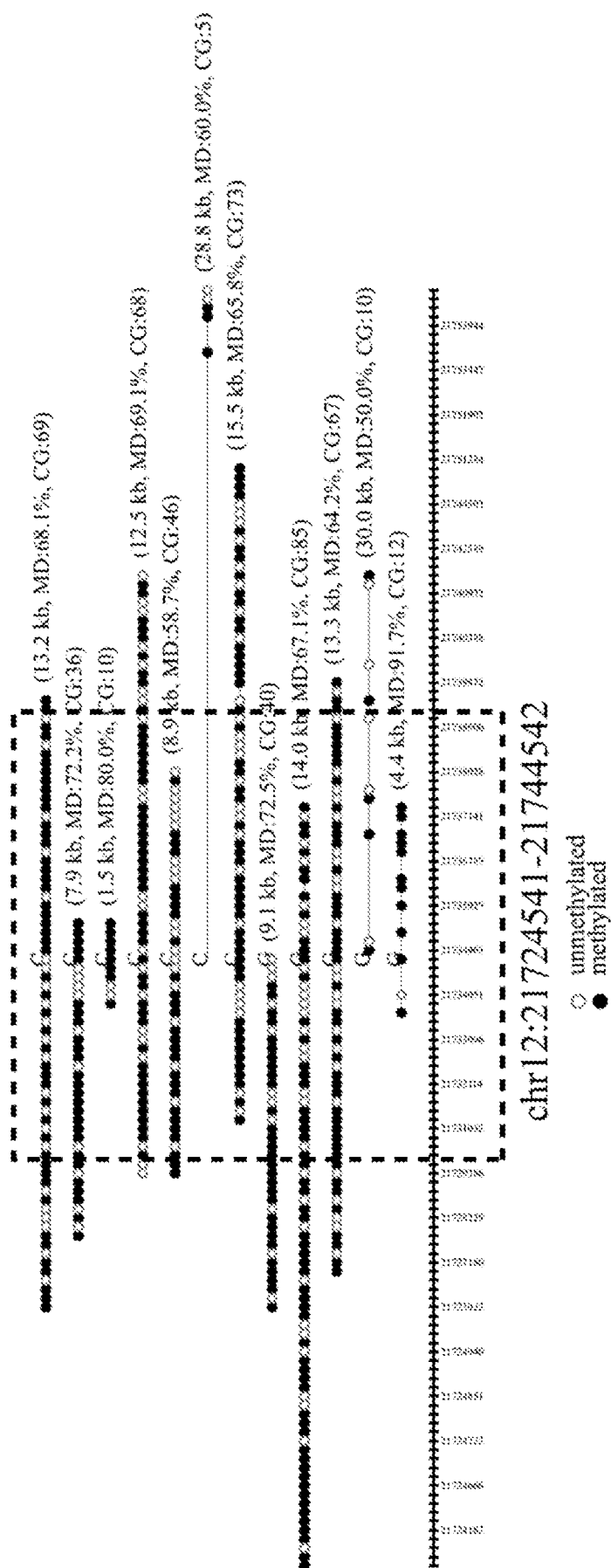


FIG. 80B

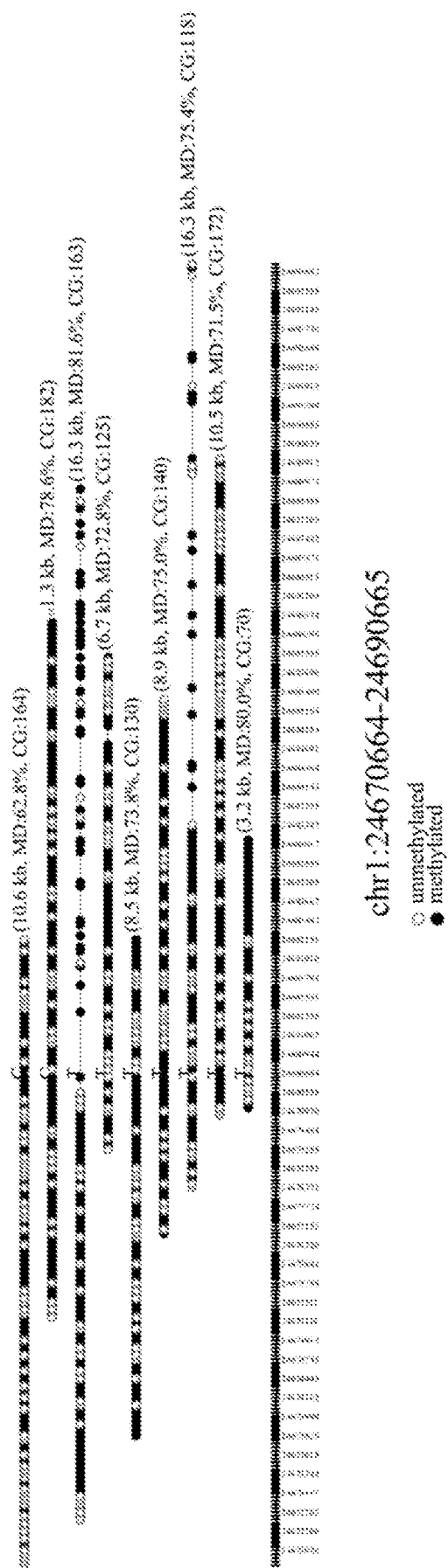


FIG. 80C

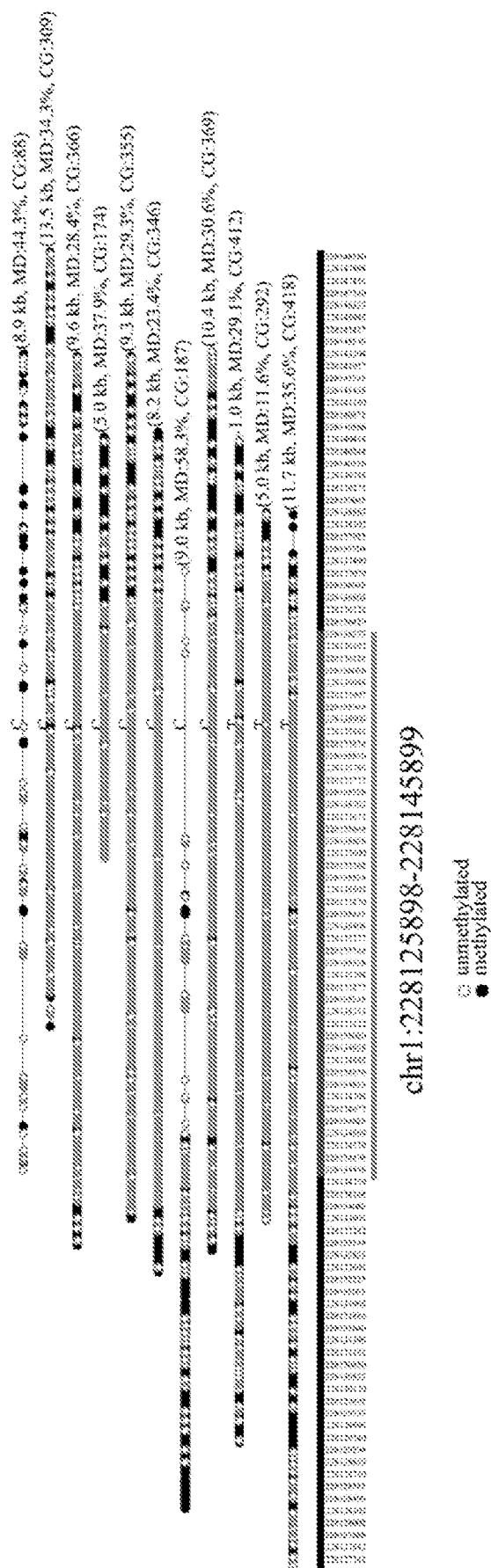


FIG. 80D

	Gene	Allele 1	Allele 2	Methylation level (%)	
				Allele 1	Allele 2
Imprinted genes	<i>SNURF</i>	T	C	15.73	89.37
	<i>PLAGL1</i>	T	C	7.56	89.41
	<i>NAP1L5</i>	C	T	12.5	91.07
	<i>ZIM2</i>	C	T	13	84.64
Randomly selected regions	Region 01	G	A	71.79	69.17
	Region 02	T	G	63.22	65.22
	Region 03	C	T	73.33	74.9
	Region 04	C	T	10.83	8.51

FIG. 81

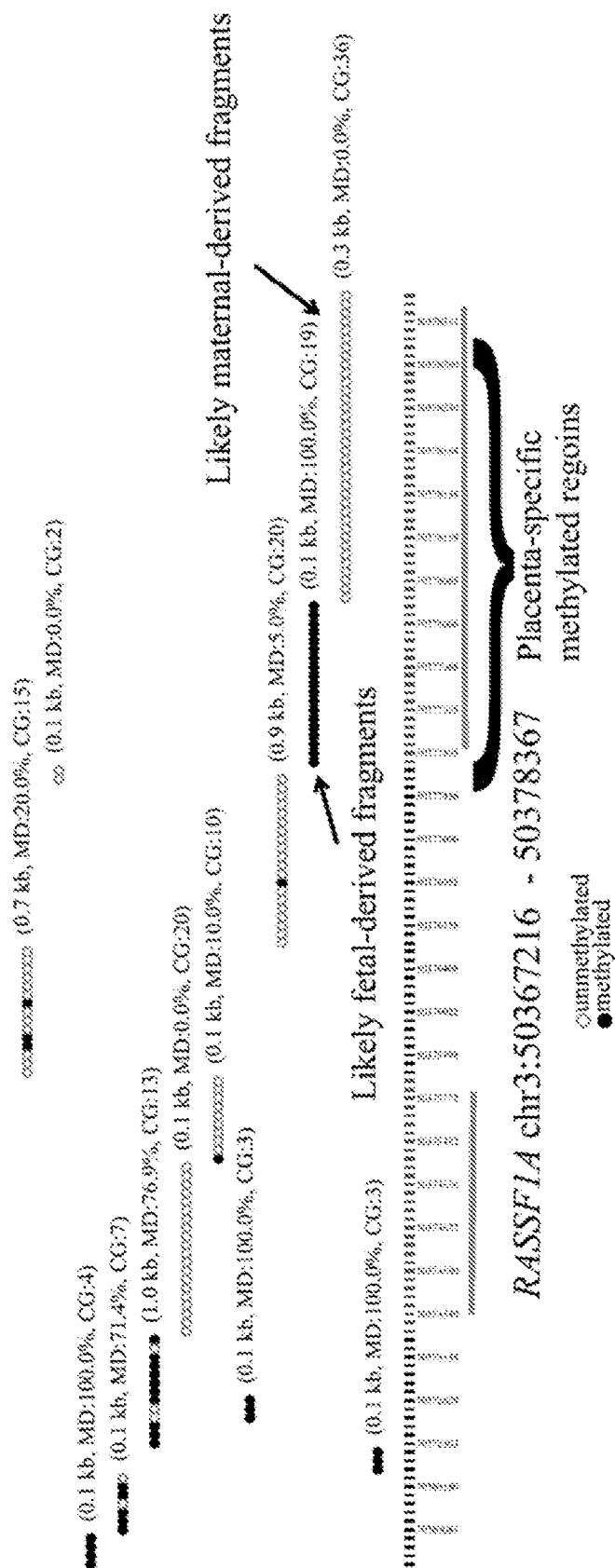


FIG. 82

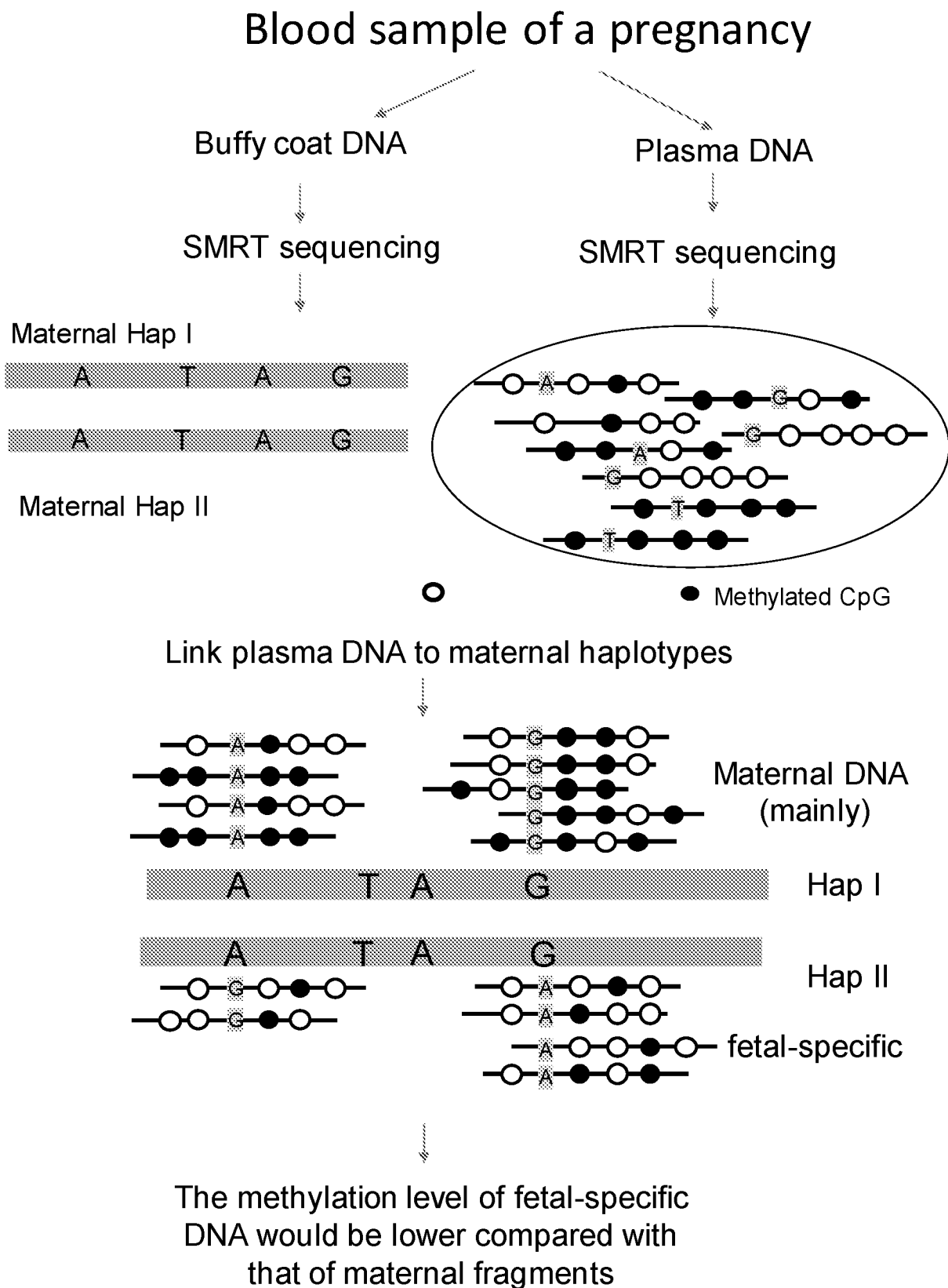


FIG. 83

Sequel Sequencing Kit 3.0

Training dataset

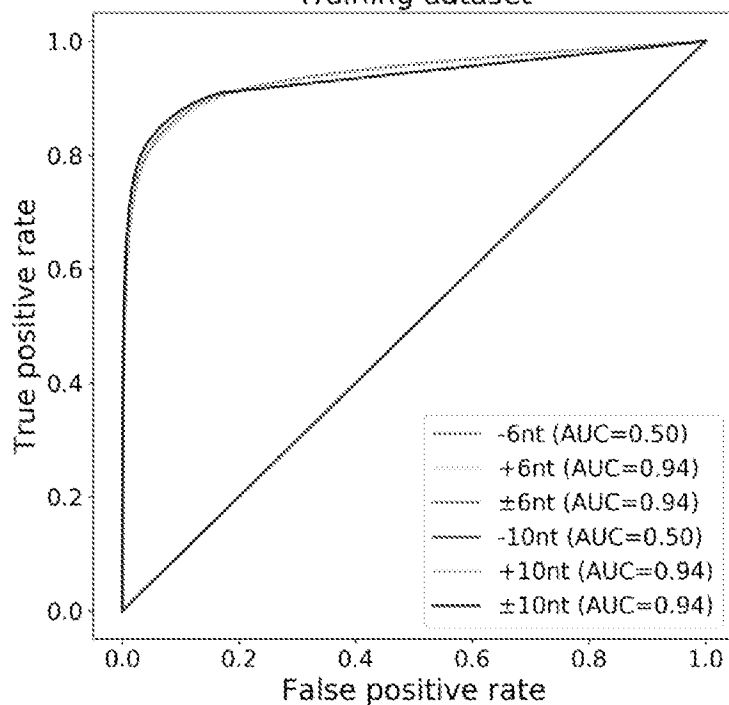


FIG. 84A

Sequel II Sequencing Kit 1.0

Training dataset

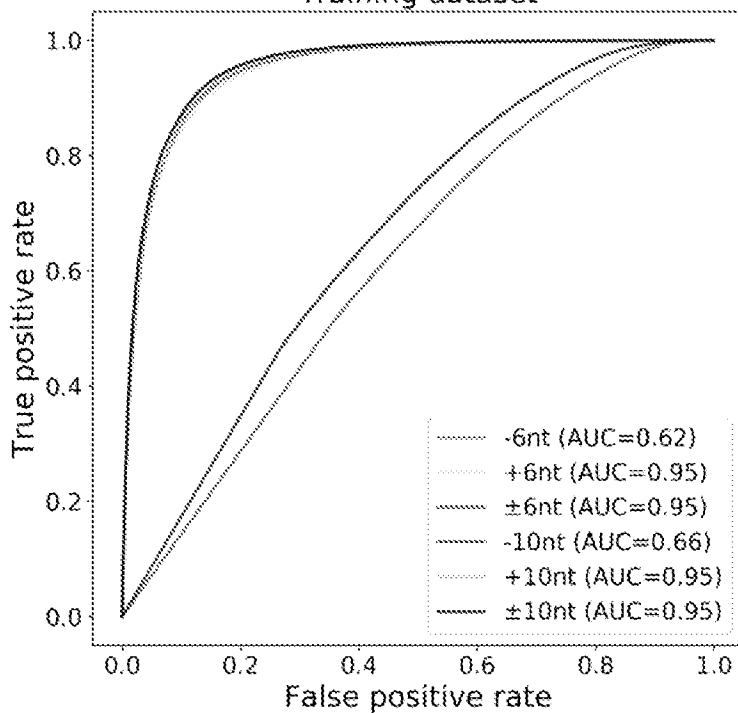


FIG. 84B

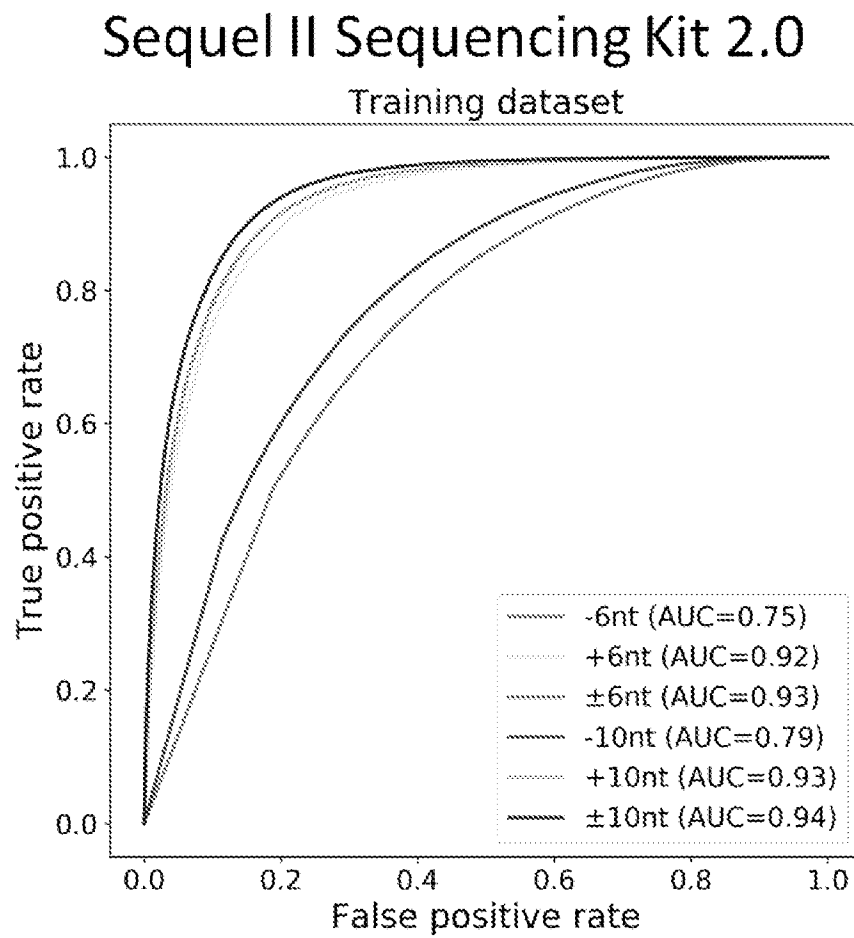


FIG. 84C

Sequel Sequencing Kit 3.0

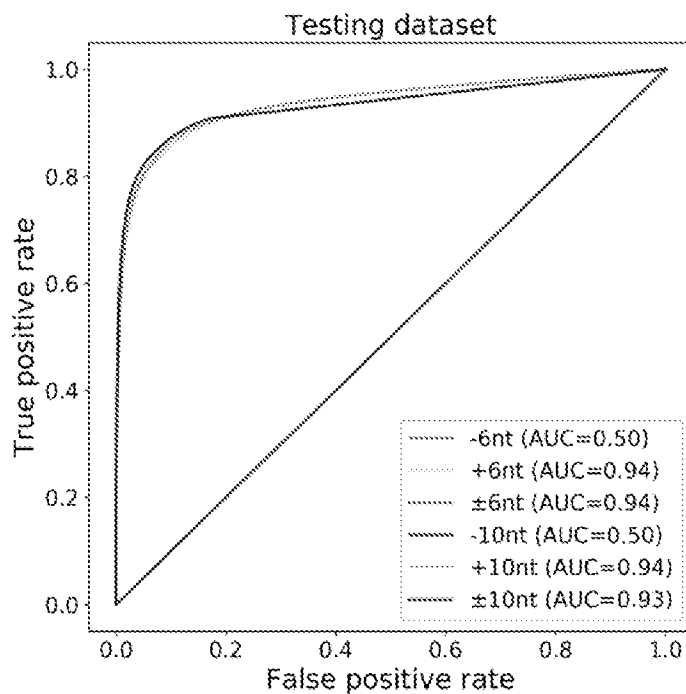


FIG. 85A

Sequel II Sequencing Kit 1.0

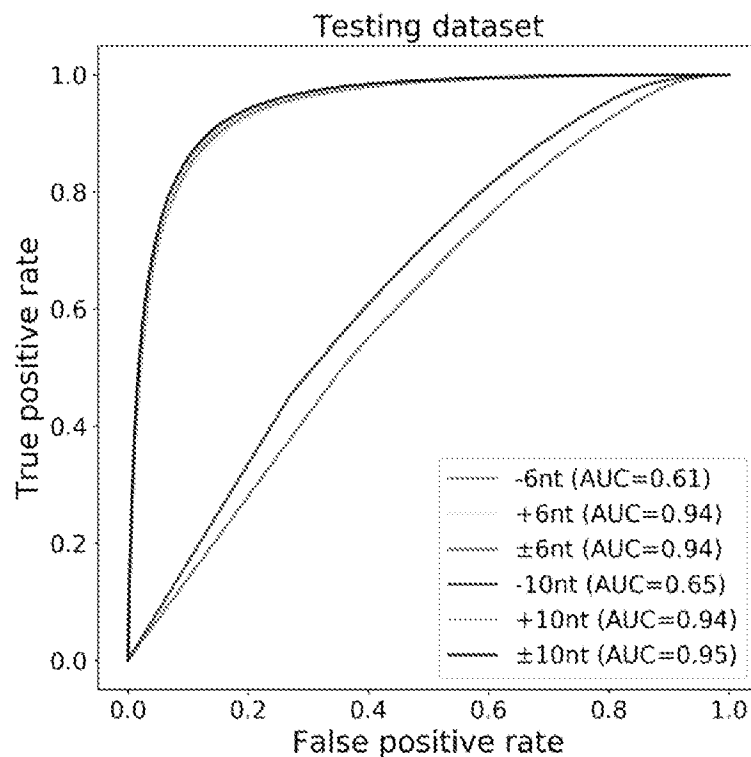


FIG. 85B

Sequel II Sequencing Kit 2.0

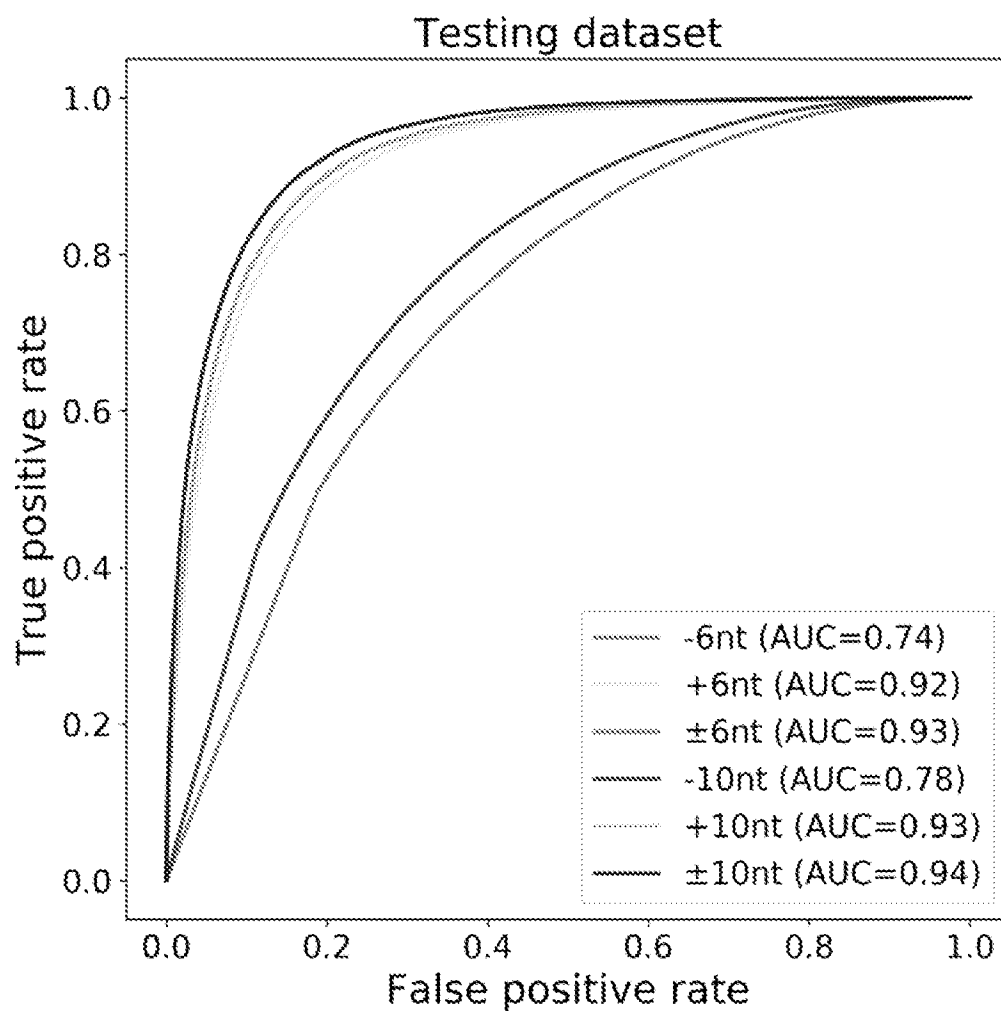


FIG. 85C

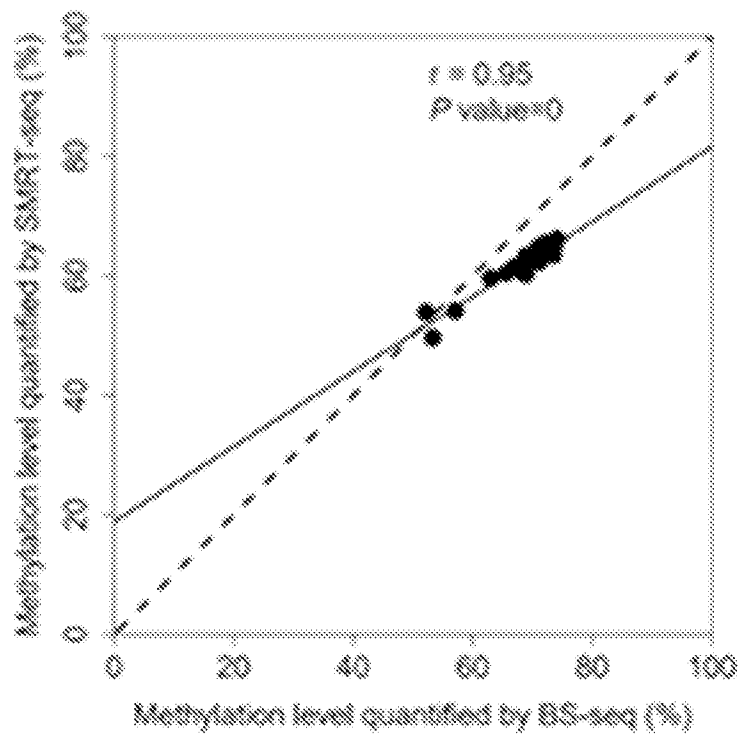


FIG. 86A

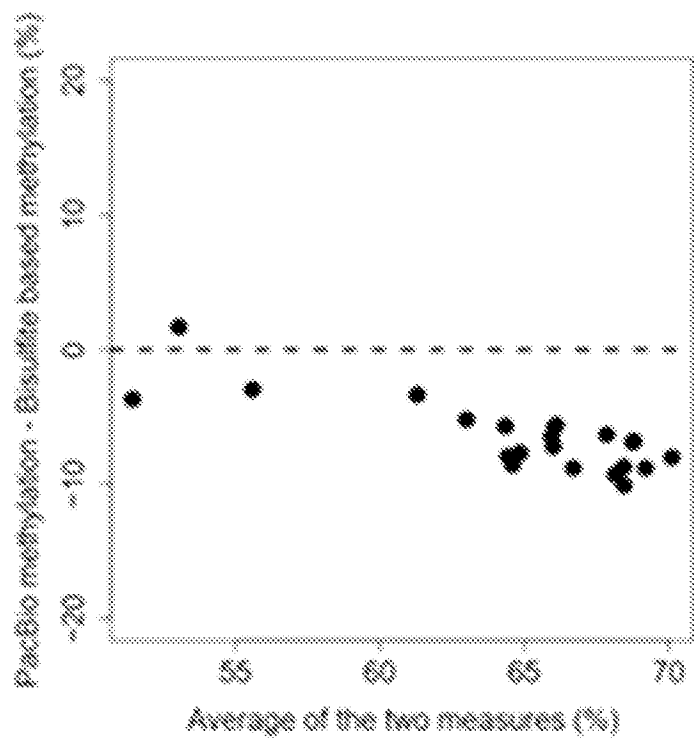


FIG. 86B

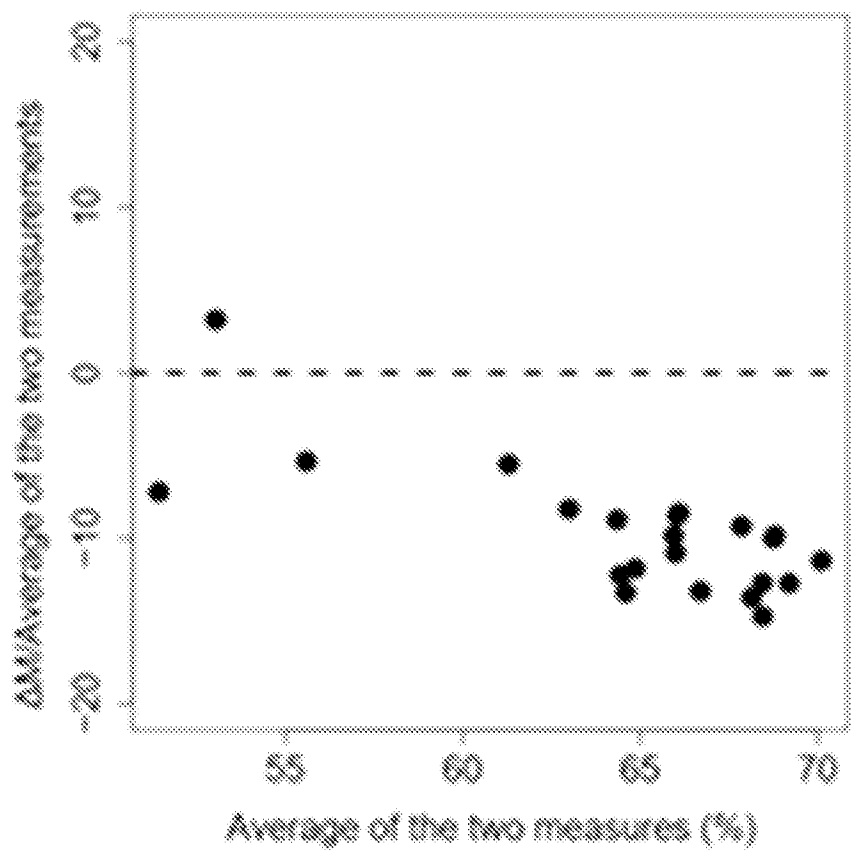


FIG. 86C

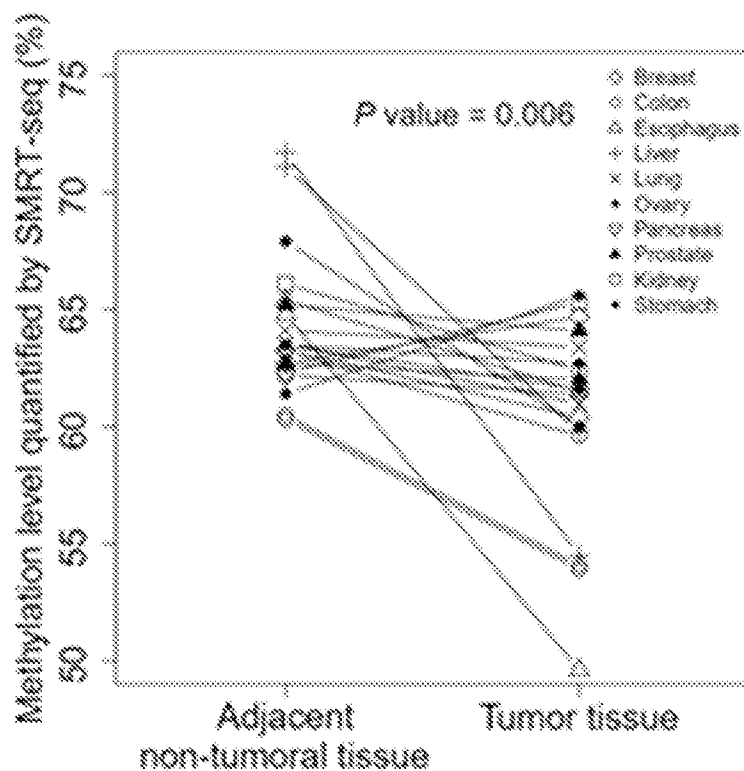


FIG. 87A

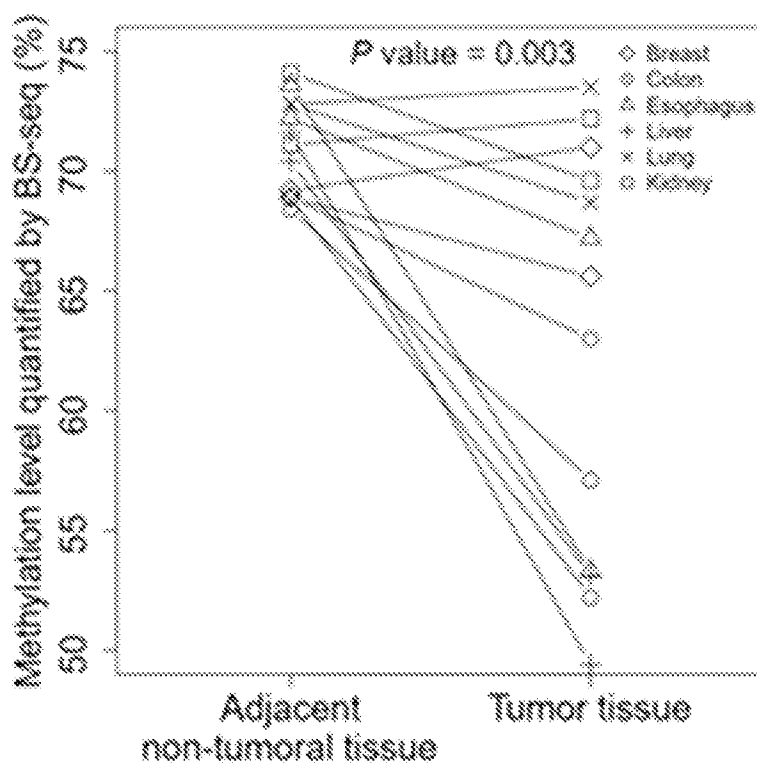


FIG. 87B

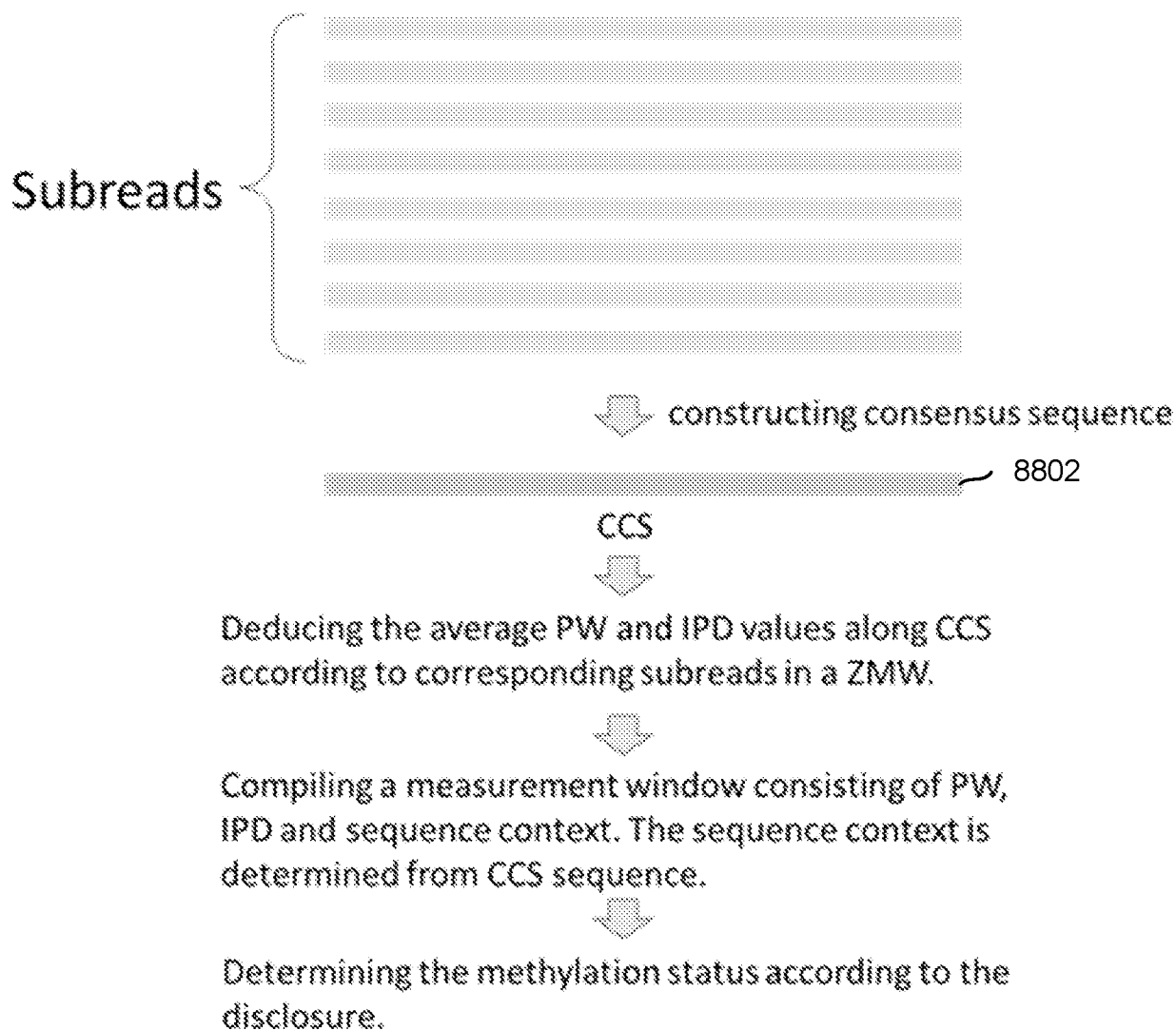


FIG. 88

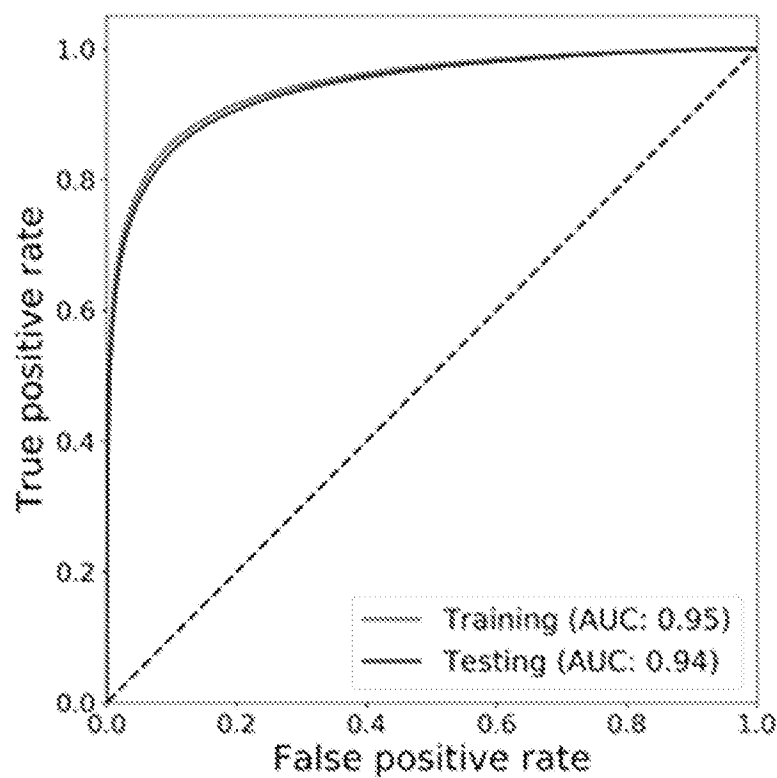


FIG. 89

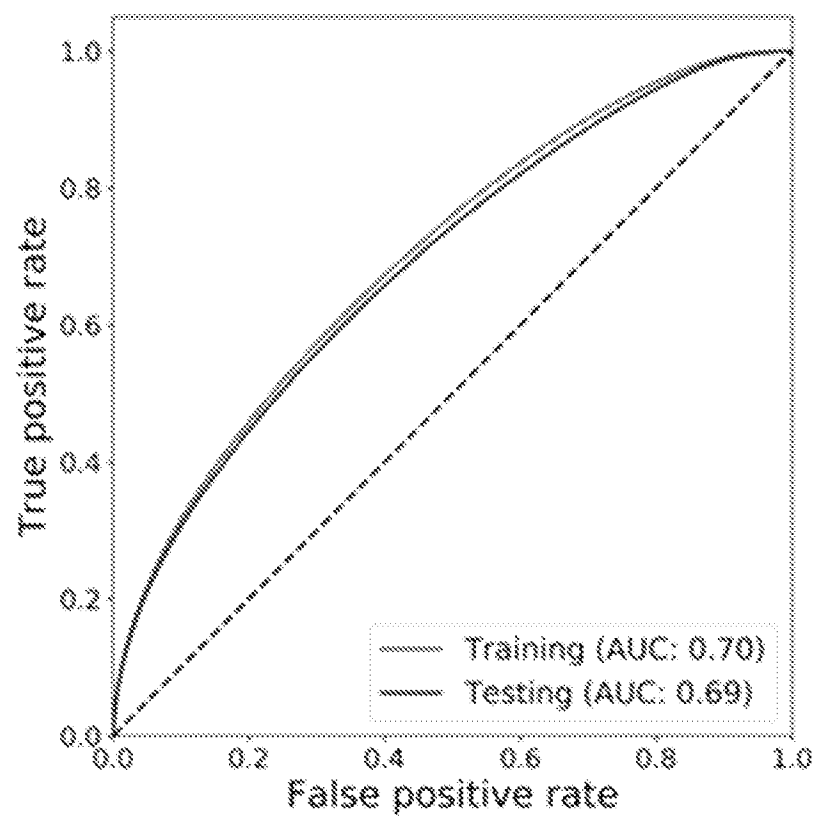


FIG. 90



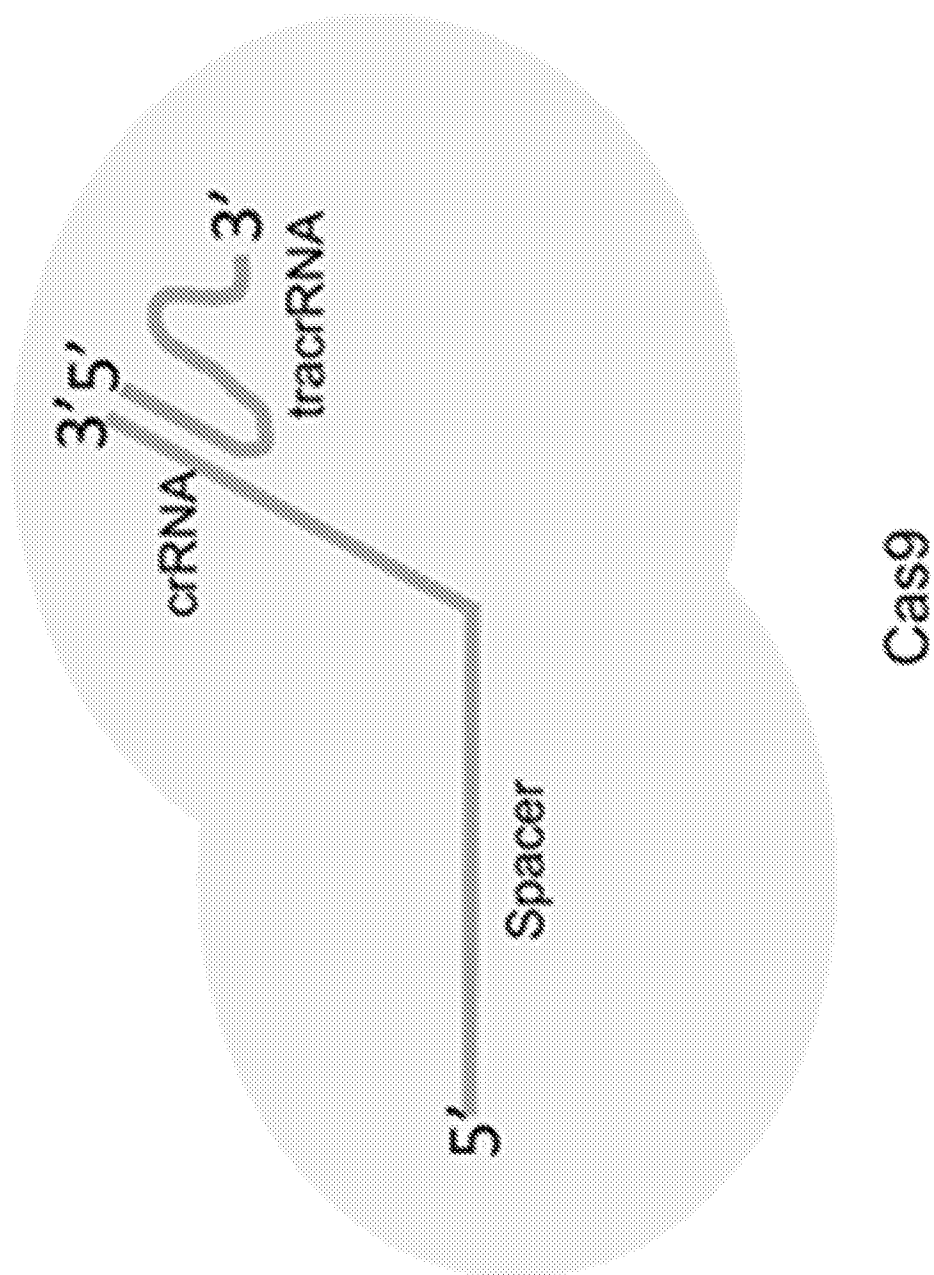


FIG. 92

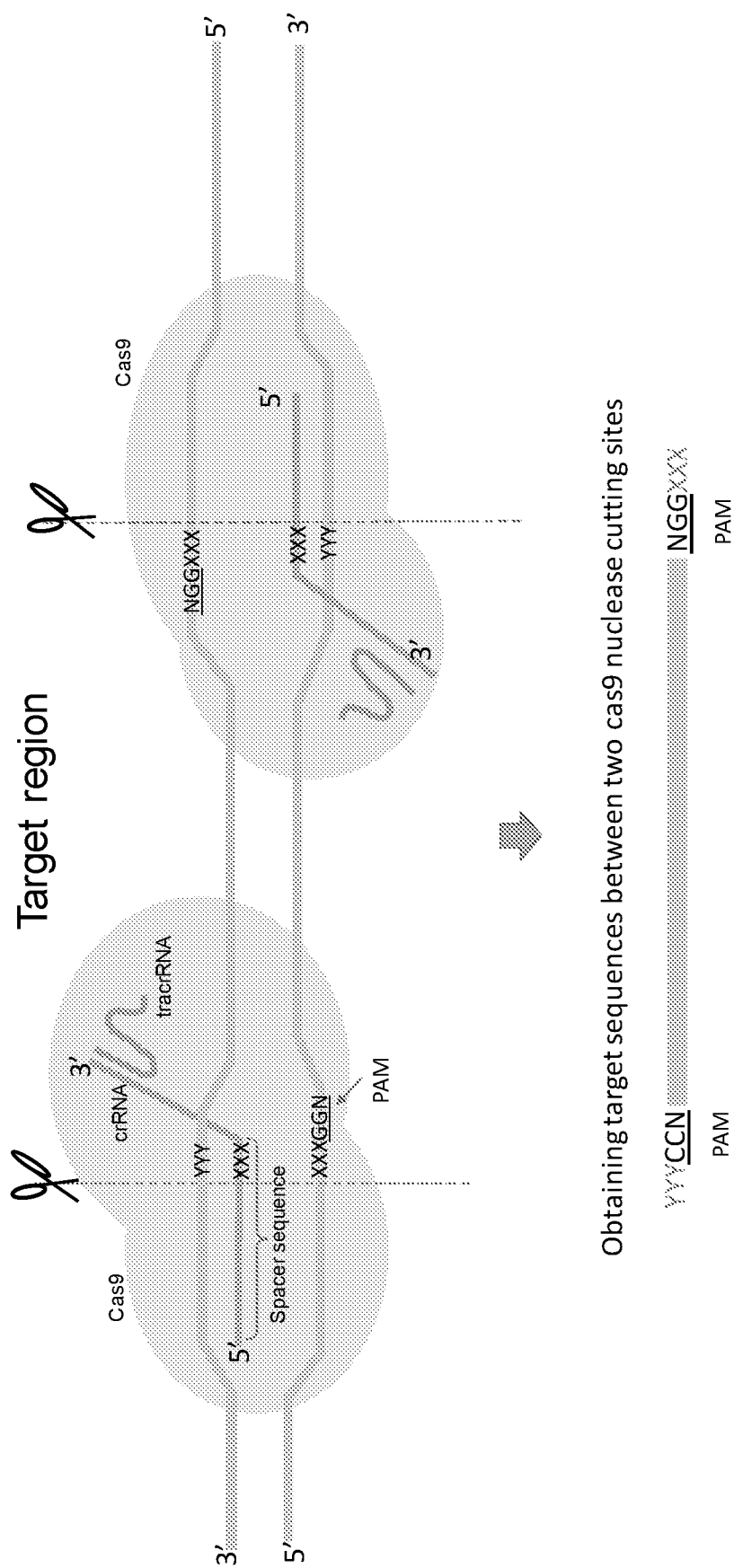


FIG. 93

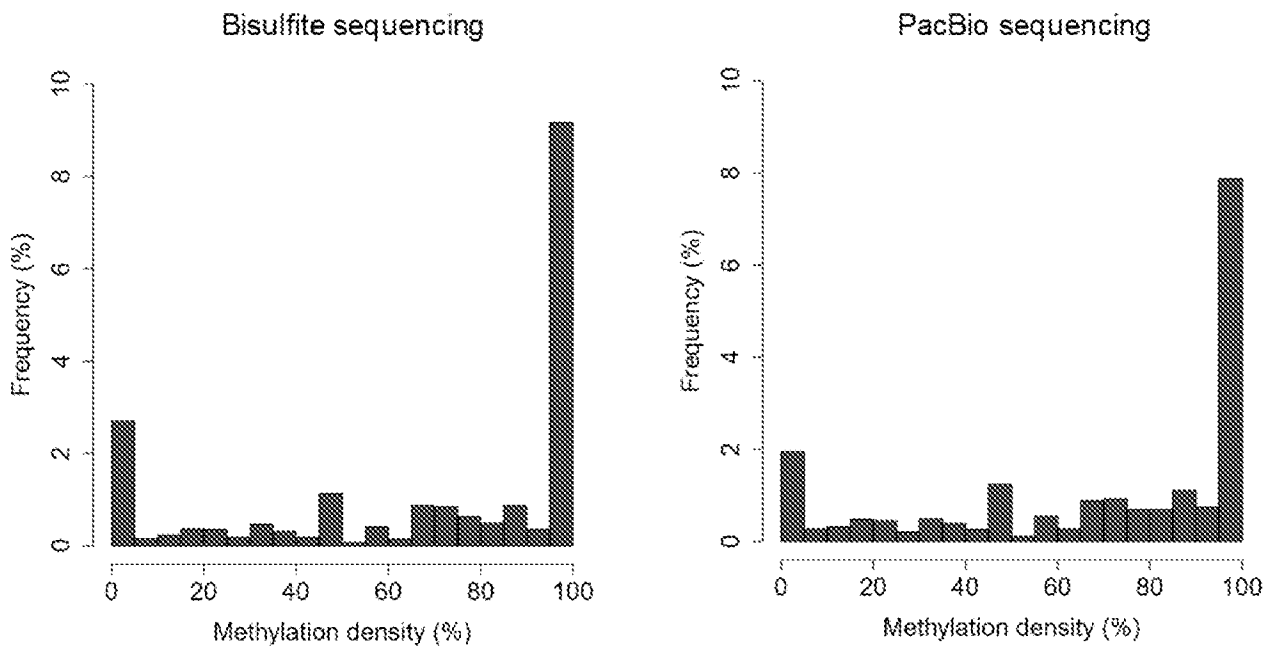


FIG. 94

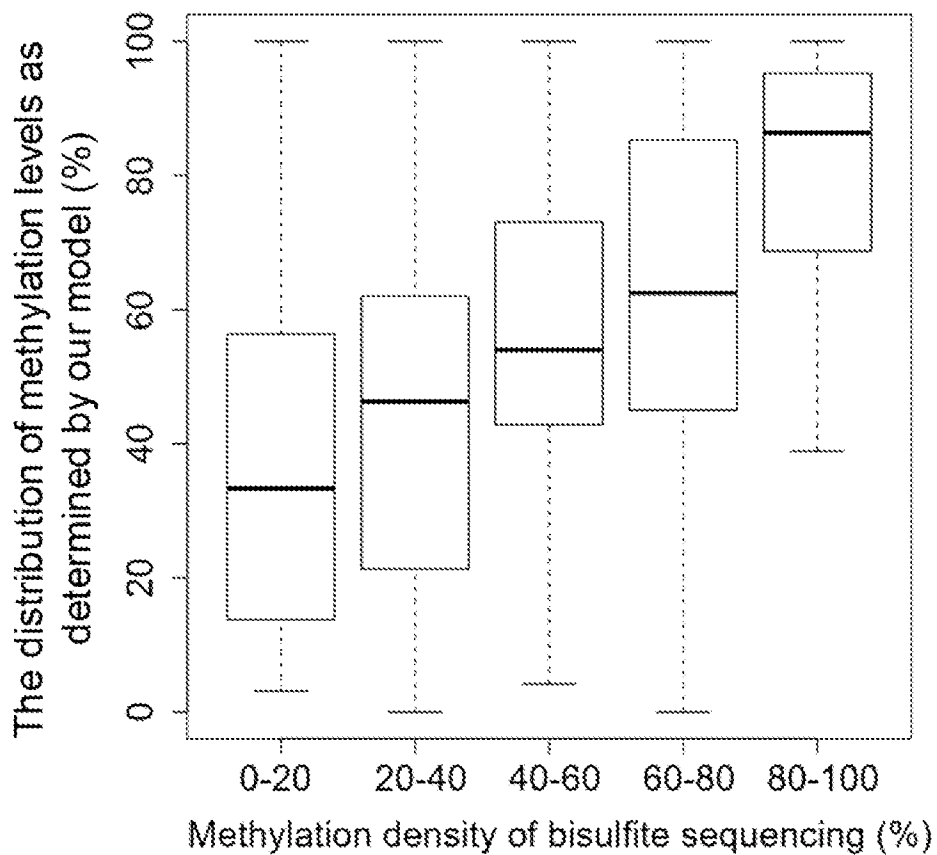


FIG. 95

Tissues	Methylation level of Alu (%)
Buffy coat	89.54
Liver	88.18
Colon	89.56
Lung	91.52
Small intestine	86.56
Adrenal gland	89.07
Adipose	91.44
Pancreas	85.82
Brain	91.79
HCC	76.74
Placenta	73.04



Cancer types
 BLCA: Bladder Urothelial Carcinoma
 BRCA: Breast invasive carcinoma
 OV: Ovarian serous cystadenocarcinoma
 PAAD: Pancreatic adenocarcinoma
 HCC: Liver hepatocellular carcinoma
 LUAD: Lung adenocarcinoma
 STAD: Stomach adenocarcinoma
 SKCM: Skin Cutaneous Melanoma
 UCS: Uterine Carcinosarcoma

FIG. 97

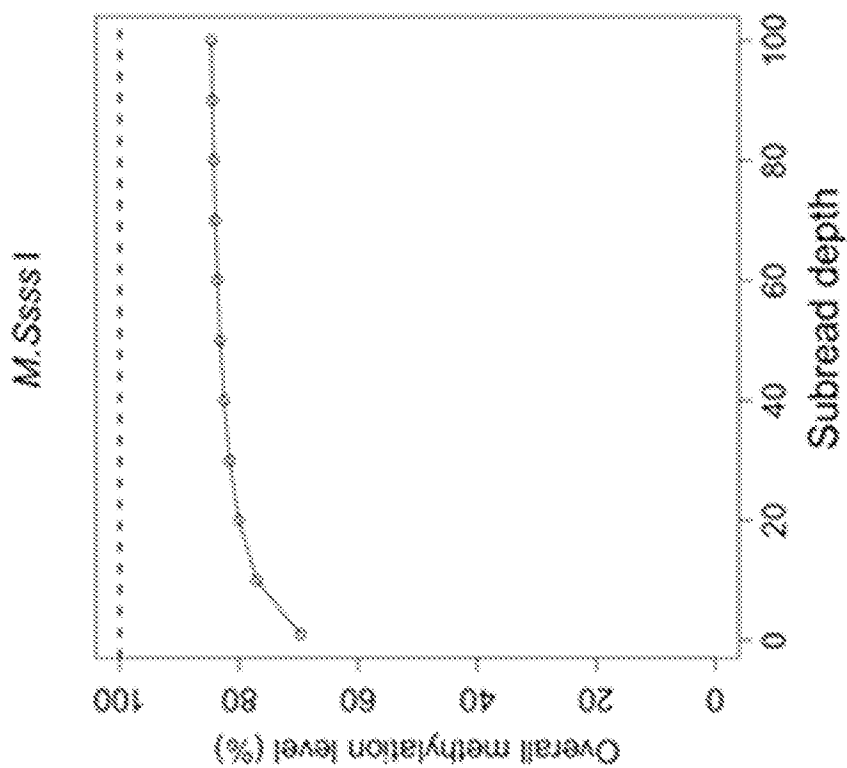


FIG. 98B

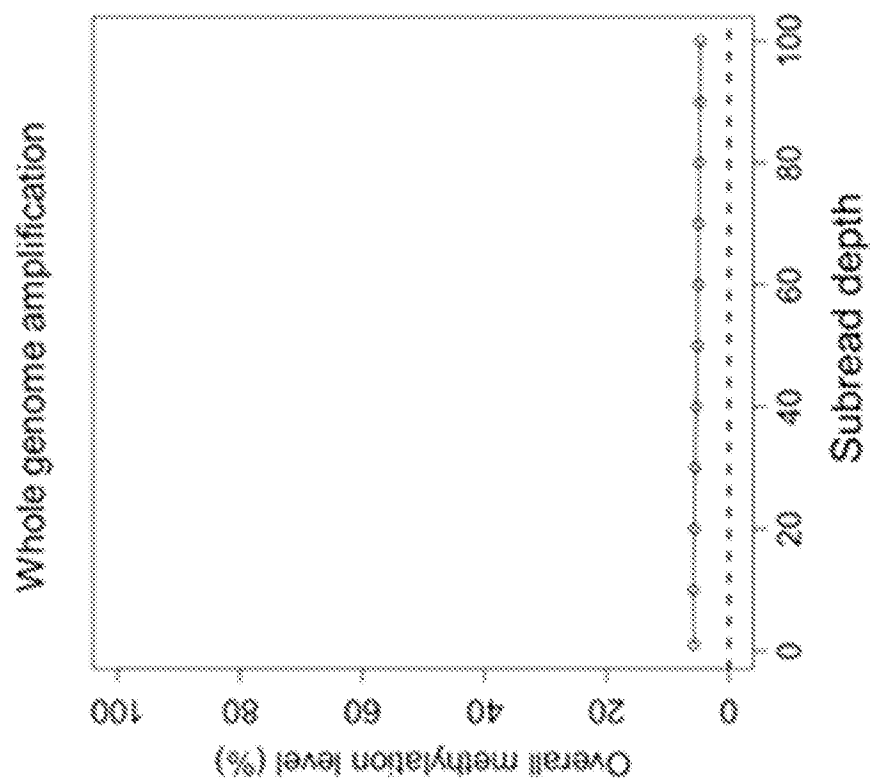


FIG. 98A

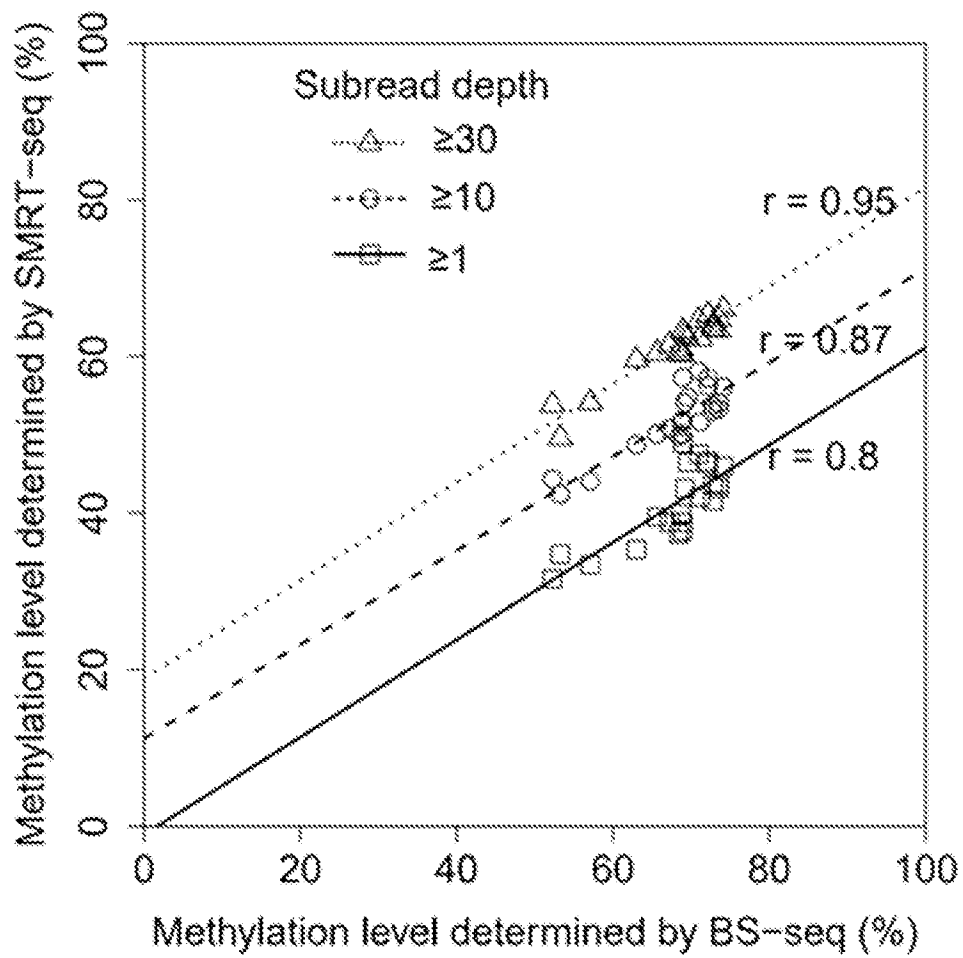


FIG. 99

Subread depth cutoffs $\geq$	Pearson's r (SMRT-seq vs BS-seq)	No. of CpG sites
1	0.797	25,606,068 (23,949,832-27,008,582)
10	0.873	21,668,418 (18,263,886-23,515,147)
20	0.933	14,276,212 (10,526,406-16,736,887)
30	0.952	6,736,890 (4,255,452-10,449,814)
40	0.948	3,420,790 (2,232,511-5,792,825)
50	0.941	1,684,871 (1,278,475-3,055,876)
60	0.929	911,961 (707,295-1,581,313)
70	0.917	532,422 (350,001-866,045)
80	0.907	284,375 (177,698-534,540)
90	0.906	150,974 (98,000-333,933)
100	0.875	89,788 (58,552-182,861)

FIG. 100

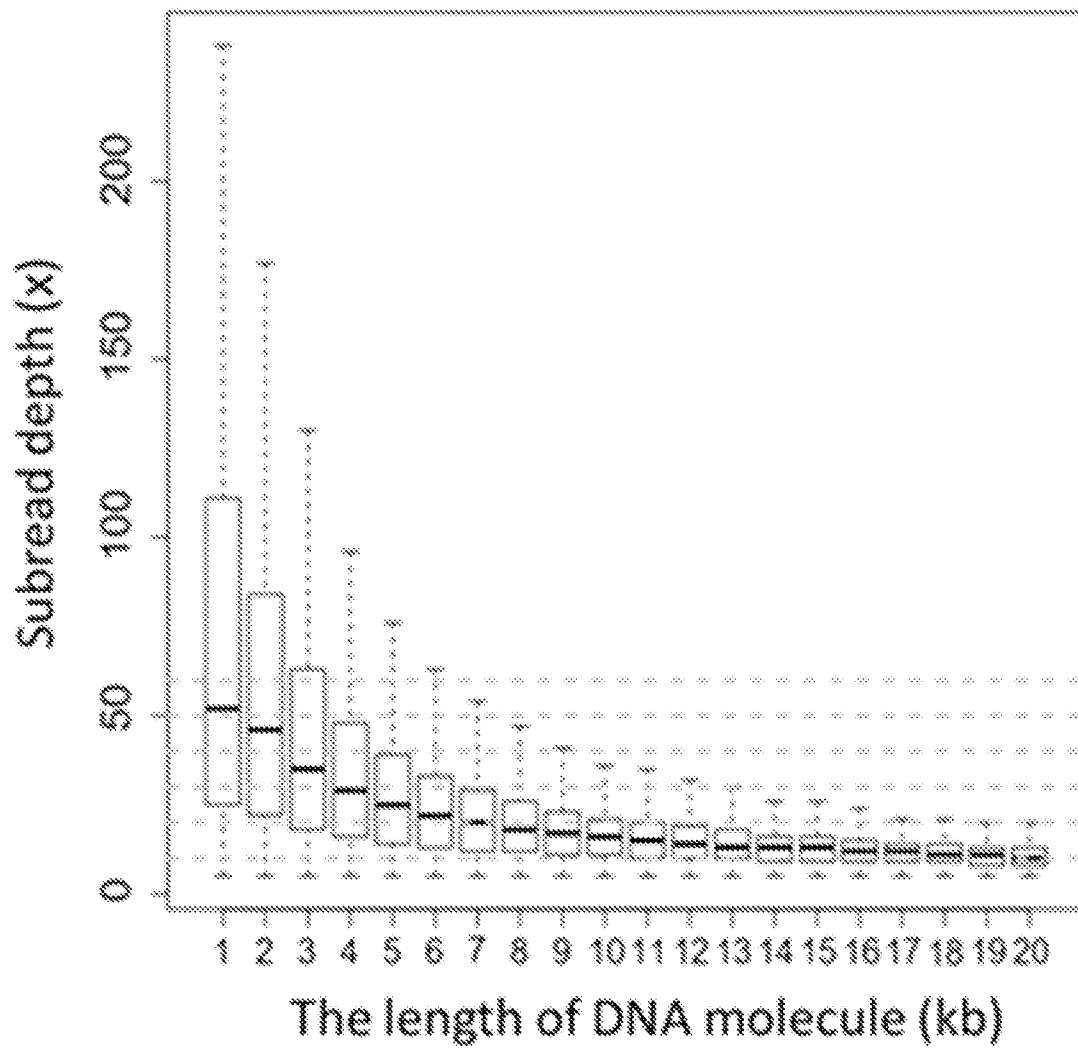


FIG. 101

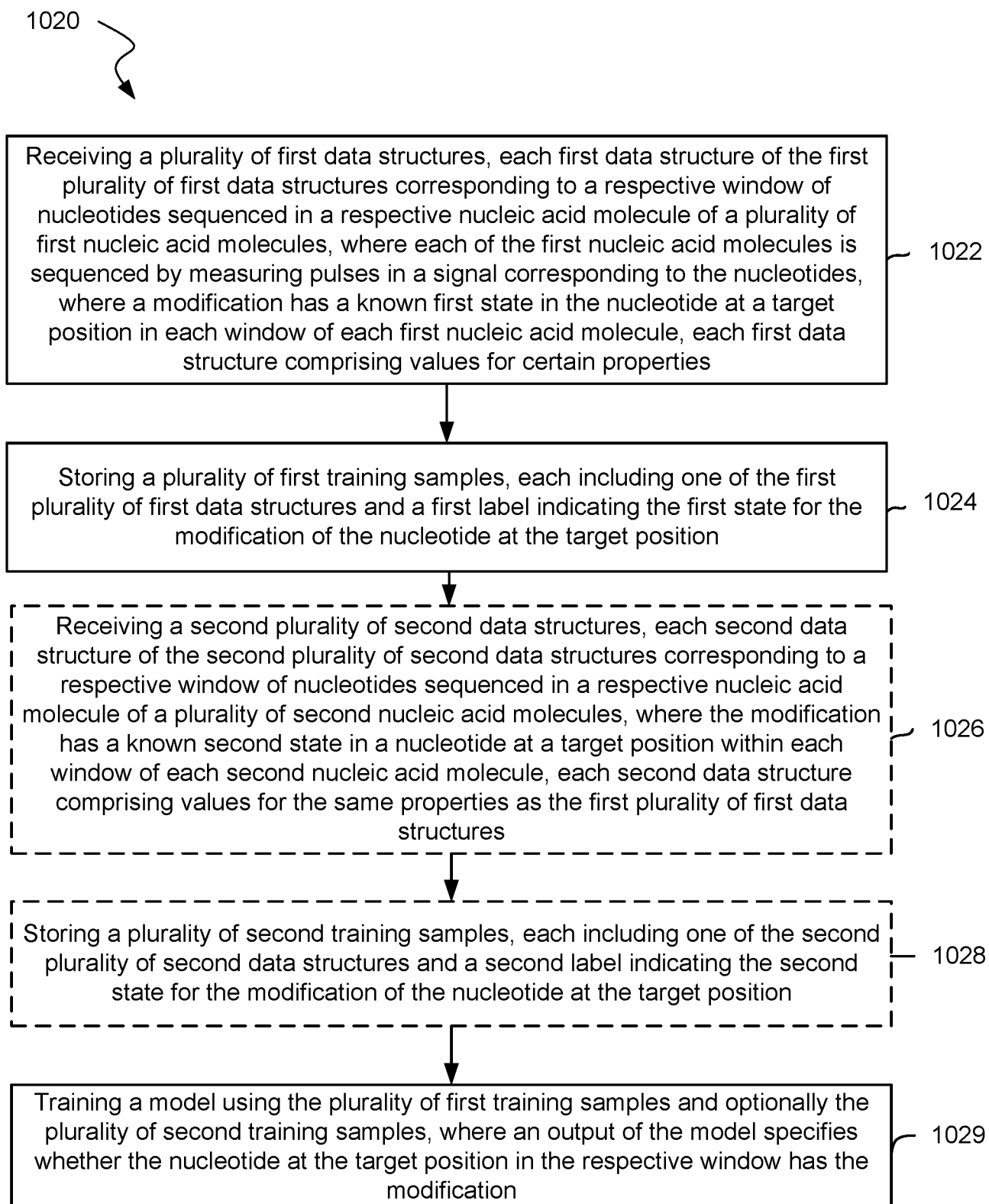


FIG. 102

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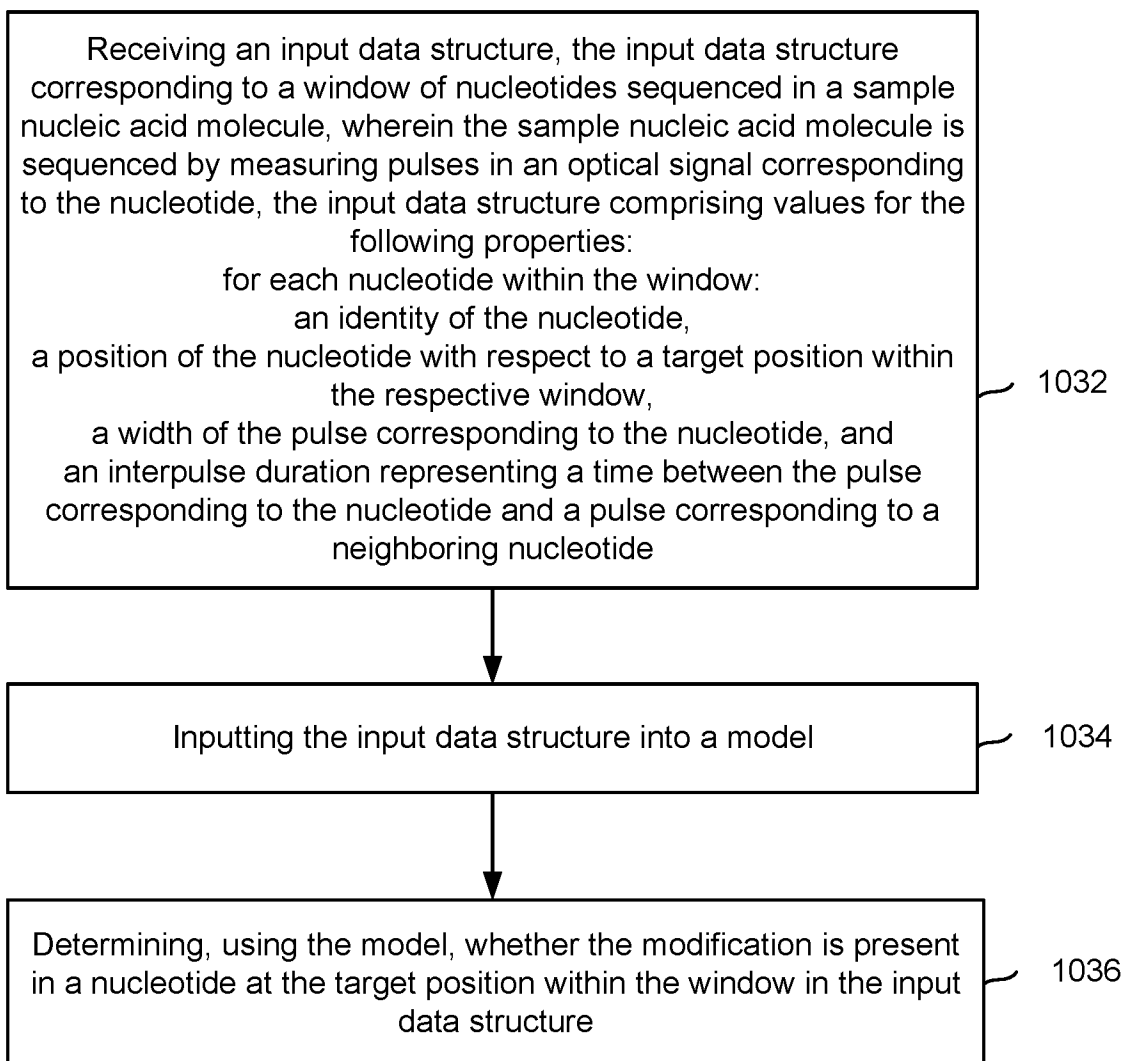


FIG. 103

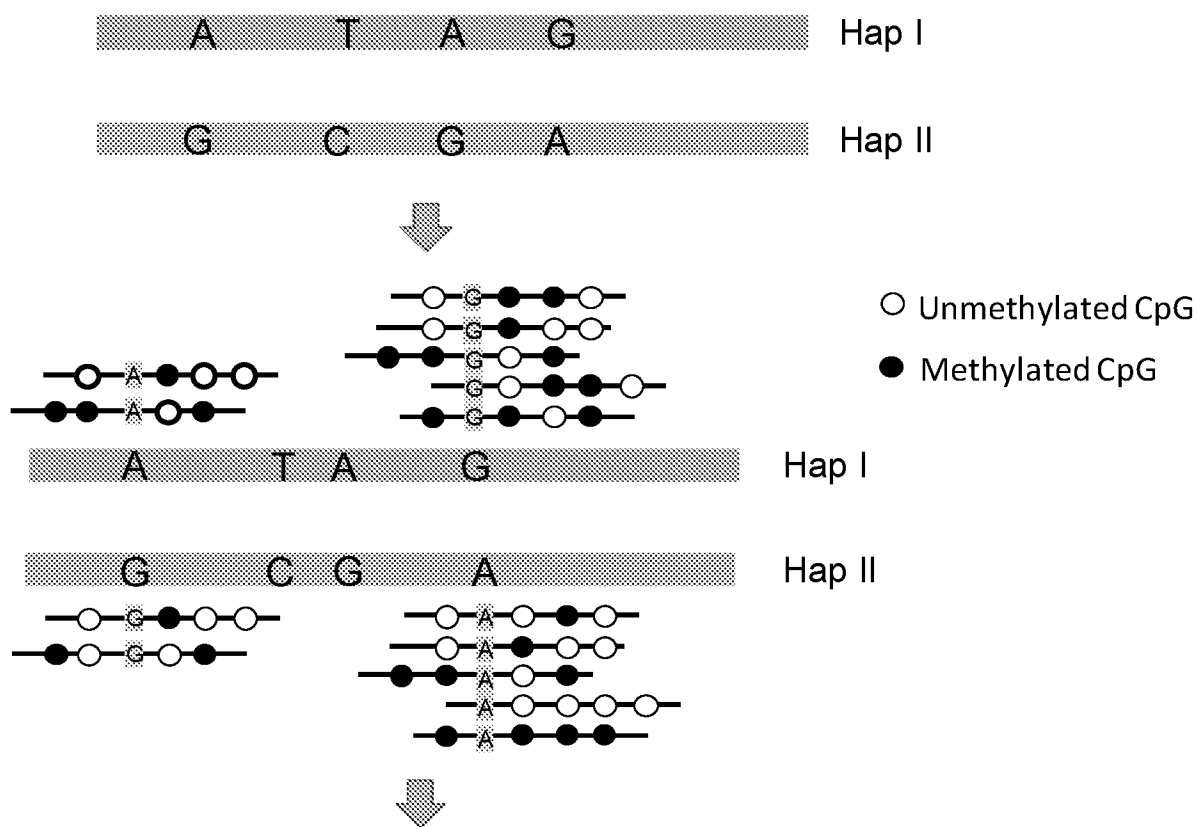


FIG. 104

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Chr	start	end	Length	Haplotype block id	PacBio sequencing			
					Methylation level in adjacent non- tumoral tissue		Methylation level in tumor tissue	
					Hap I	Hap II	Hap I	Hap II
chr1	56312395	56347696	35301	hap1927	68.2	67.4	60.3	23.5
chr1	194413819	194424806	10987	hap5953	52.8	49.5	48.8	9.3
chr1	220674478	220699011	24533	hap6863	63.0	64.5	50.4	17.3
chr10	113088792	113124248	35456	hap11838	62.7	63.4	38.1	5.7
chr11	5482746	5498801	16055	hap12904	70.3	75.0	16.3	51.7
chr11	42819351	42852772	33421	hap14385	54.6	54.9	65.3	17.8
chr11	57983961	58051078	67117	hap14930	67.3	66.4	58.2	18.6
chr11	60174708	60204209	29501	hap14990	58.4	59.8	49.6	10.8
chr12	128079419	128114656	35237	hap22249	60.0	58.3	12.1	45.2
chr15	20480575	20533464	52889	hap29631	64.7	69.1	27.7	59.3
chr15	94902853	94946231	43378	hap32161	74.1	74.5	74.9	15.8
chr15	96526684	96549225	22541	hap32221	70.8	68.8	28.9	64.4
chr16	31595372	31613277	17905	hap33499	55.9	59.3	46.3	14.4
chr16	80151778	80182097	30319	hap34821	71.1	71.0	11.5	51.8
chr16	82519715	82554191	34476	hap34920	71.3	66.5	47.4	13.0
chr17	21668593	21685572	16979	hap36049	50.3	47.8	67.4	19.6
chr17	44999177	45012087	12910	hap36640	47.1	45.2	81.6	35.1
chr17	69911623	69926625	15002	hap37435	67.3	63.0	37.8	5.2
chr18	11441122	11458521	17399	hap38335	65.5	66.8	65.9	22.4
chr18	23405569	23423387	17818	hap38673	66.3	61.7	3.3	48.1
chr18	68887284	68925031	37747	hap40390	63.0	61.0	22.0	53.4
chr18	69487809	69505470	17661	hap40414	74.5	74.1	33.3	72.2
chr2	41480394	41514135	33741	hap43972	54.0	54.0	14.9	77.8
chr2	114171214	114182880	11666	hap46226	72.4	68.8	79.7	16.7
chr2	123762541	123797629	35088	hap46589	66.7	68.1	24.0	54.5
chr2	125236882	125241950	5068	hap46673	58.9	59.2	10.7	46.4
chr2	130016110	130040331	24221	hap46835	54.6	50.8	5.6	41.6
chr2	137757638	137783716	26078	hap47090	61.8	61.4	13.5	69.2
chr2	144128597	144160845	32248	hap47343	65.8	66.6	9.3	50.3
chr20	15736792	15753459	16667	hap51505	78.9	74.3	45.8	77.3
chr20	26167979	26177235	9256	hap51868	55.0	52.2	38.5	68.6
chr20	44255808	44264190	8382	hap52246	57.4	56.1	9.7	50.6
chr20	59518410	59559273	40863	hap52761	61.0	62.4	30.0	72.8
chr21	21402034	21424129	22095	hap53197	63.5	67.3	25.0	75.5
chr21	24750027	24768793	18766	hap53333	68.2	64.6	3.4	38.9
chr21	26666833	26701575	34742	hap53418	62.1	66.5	47.6	16.7
chr3	2364024	2387896	23872	hap55539	67.4	67.8	54.9	10.9
chr3	21036965	21049451	12486	hap56223	54.8	51.4	53.1	21.1
chr3	56011690	56046642	34952	hap57346	64.2	61.2	71.2	22.6

FIG. 105A

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chr3	73330942	73371216	40274	hap57939	60.9	62.9	9.4	42.9
chr3	106372440	106401301	28861	hap59077	67.8	67.9	13.8	53.2
chr3	107772994	107807482	34488	hap59122	69.6	73.5	30.4	66.4
chr3	116742501	116776747	34246	hap59493	64.3	69.1	14.1	51.6
chr3	171076306	171100102	23796	hap61495	68.0	66.0	80.6	48.8
chr3	193058272	193080344	22072	hap62231	65.5	64.7	54.6	20.0
chr4	30411613	30432317	20704	hap63589	59.3	60.6	53.4	14.6
chr4	31304718	31338193	33475	hap63633	60.2	60.0	7.2	55.0
chr4	92003467	92030505	27038	hap65794	65.3	65.1	54.1	21.7
chr4	155224697	155250915	26218	hap68104	60.5	57.5	57.3	25.0
chr5	2281802	2299281	17479	hap69632	71.5	66.9	69.9	6.6
chr5	4624948	4664704	39756	hap69739	62.8	61.0	14.0	52.0
chr5	89593236	89606080	12844	hap72628	76.6	74.0	20.3	78.4
chr5	119214026	119233058	19032	hap73698	62.8	61.2	57.6	13.1
chr5	119940397	119972658	32261	hap73720	59.1	54.7	53.8	12.2
chr5	132859668	132877415	17747	hap74150	62.5	66.6	59.5	28.3
chr6	26914610	26936918	22308	hap76887	41.9	40.9	71.9	32.6
chr6	66879106	66957243	78137	hap78266	61.6	59.6	25.4	62.0
chr6	77349083	77377529	28446	hap78674	64.5	66.4	27.0	62.9
chr6	159738794	159751033	12239	hap81616	79.6	79.0	21.2	59.8
chr7	26585255	26641907	56652	hap83161	66.2	64.7	49.4	13.3
chr7	48214640	48248036	33396	hap84003	76.0	76.7	78.0	32.3
chr7	88558182	88575482	17300	hap85335	63.8	59.6	63.8	22.9
chr7	96588562	96607580	19018	hap85620	60.4	63.1	19.7	50.0
chr7	122942180	122956897	14717	hap86454	42.3	39.0	19.2	50.0
chr7	132321970	132344802	22832	hap86807	61.4	60.7	52.5	11.5
chr7	153296219	153302441	6222	hap87487	48.7	53.7	64.4	19.3
chr7	156356247	156371897	15650	hap87631	74.9	71.6	87.5	56.6
chr7	159091986	159119486	27500	hap87738	54.0	49.1	52.0	13.2
chr8	51530582	51550889	20307	hap89477	66.4	65.7	68.0	19.9
chr8	63513932	63537543	23611	hap89942	62.0	63.3	11.6	48.4
chr8	72373321	72398122	24801	hap90226	58.0	54.9	71.6	32.0
chr8	94100451	94141855	41404	hap90991	65.2	65.7	36.2	68.7
chr8	109300499	109326404	25905	hap91510	63.6	67.7	29.5	65.8

FIG. 105B

Chr	start	end	Length	Haplotype block id	PacBio sequencing			
					Methylation level in adjacent non- tumoral tissue		Methylation level in tumor tissue	
					Hap I	Hap II	Hap I	Hap II
chr9	27803548	27888202	84654	hap58508	64.2	60.9	20.6	75.4
chr6	242149	386636	144487	hap47880	62.3	63.3	77.4	32.2
chr5	28219159	28302858	83699	hap44666	59.3	58.0	16.8	58.2
chr5	18119943	18153743	33800	hap44475	61.6	65.0	53.2	21.7
chr7	24906307	25046195	139888	hap52069	69.3	68.7	44.0	76.2
chr15	27689897	27752573	62676	hap18337	65.9	61.9	64.8	20.5
chr12	42183870	42212433	28563	hap12045	63.5	68.4	19.4	51.2
chr21	9825597	9935752	110155	hap34175	54.3	53.5	60.9	29.1
chr2	118813055	118893366	80311	hap30060	62.6	62.3	77.0	38.6
chr6	90307702	90344869	37167	hap49779	69.1	66.4	84.7	53.9
chr7	107932914	108049376	116462	hap53838	67.2	62.9	43.8	76.4
chr7	137039327	137160933	121606	hap54447	59.5	60.9	22.9	72.0
chr17	21193754	21254930	61176	hap22633	59.2	54.3	69.7	31.6
chr12	11473697	11644714	171017	hap11451	62.8	66.4	35.5	75.9
chr5	129212299	129353349	141050	hap46632	50.9	54.5	45.5	14.0
chr11	93910738	94028887	118149	hap10288	67.6	63.6	36.6	74.2
chr3	131707434	132003636	296202	hap38642	57.8	55.9	17.9	60.2
chr3	43024004	43161785	137781	hap36769	69.1	66.5	46.1	80.2
chr3	190403156	190606658	203502	hap39947	60.9	61.6	36.9	72.7
chr15	40218970	40279780	60810	hap18606	53.4	57.5	79.1	47.4

FIG. 106

Tissue types	No. of haplotype blocks showing methylation imbalance between two haplotypes in tumor tissues	No. of haplotype blocks showing methylation imbalance between two haplotypes in paired adjacent non-tumoral tissues
Colon	92	47
Breast	57	13
Kidney	68	18
Lung	31	21
Prostate	26	19
Stomach	2	0

FIG. 107A

Tissue types	No. of haplotype blocks showing methylation imbalance between two haplotypes in tumor tissues	Tumor Staging information (TNM) available
Breast	18	T2
	57	T3
Kidney	68	T3a
	0	T2

FIG. 107B

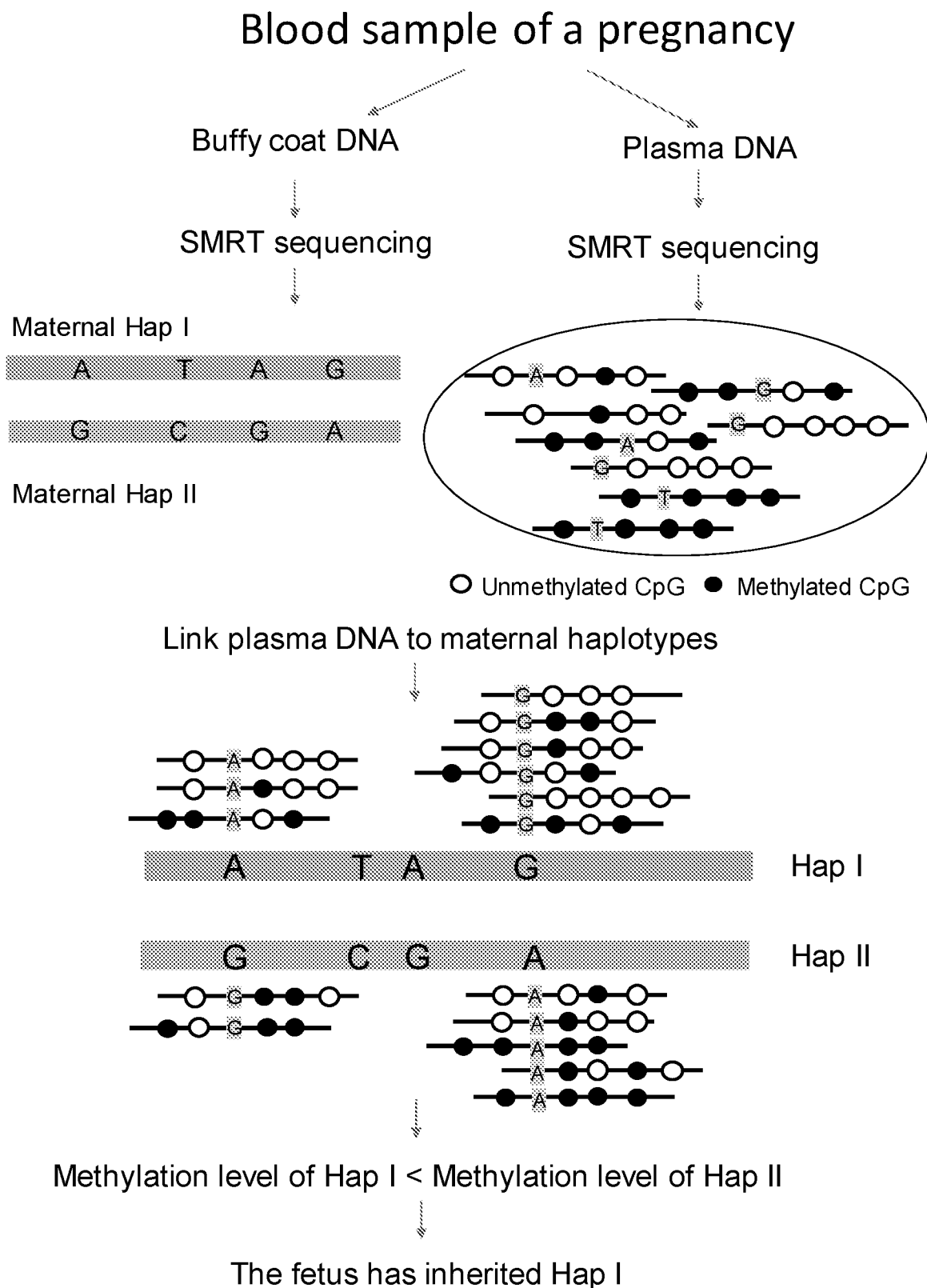


FIG. 108

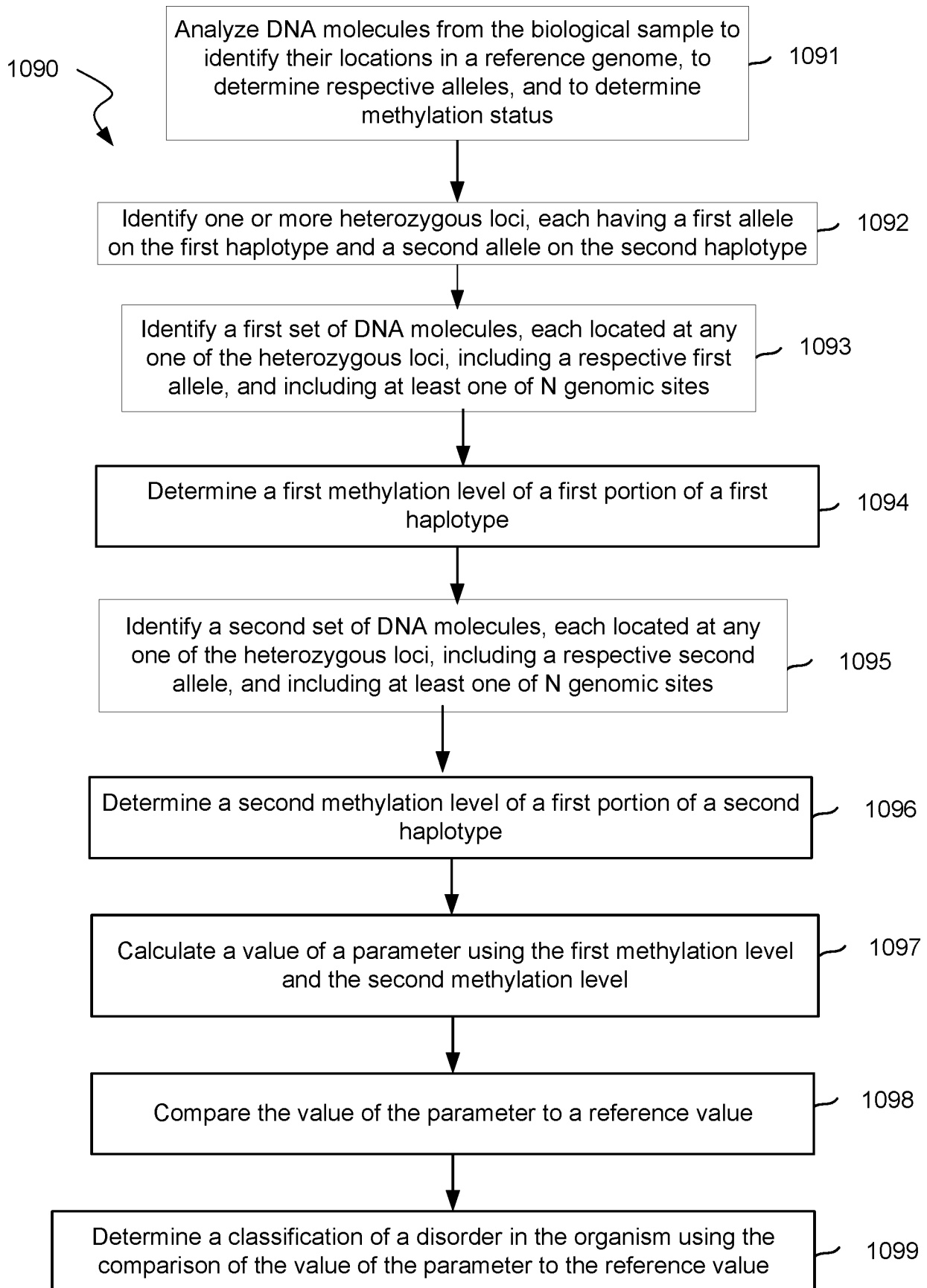


FIG. 109

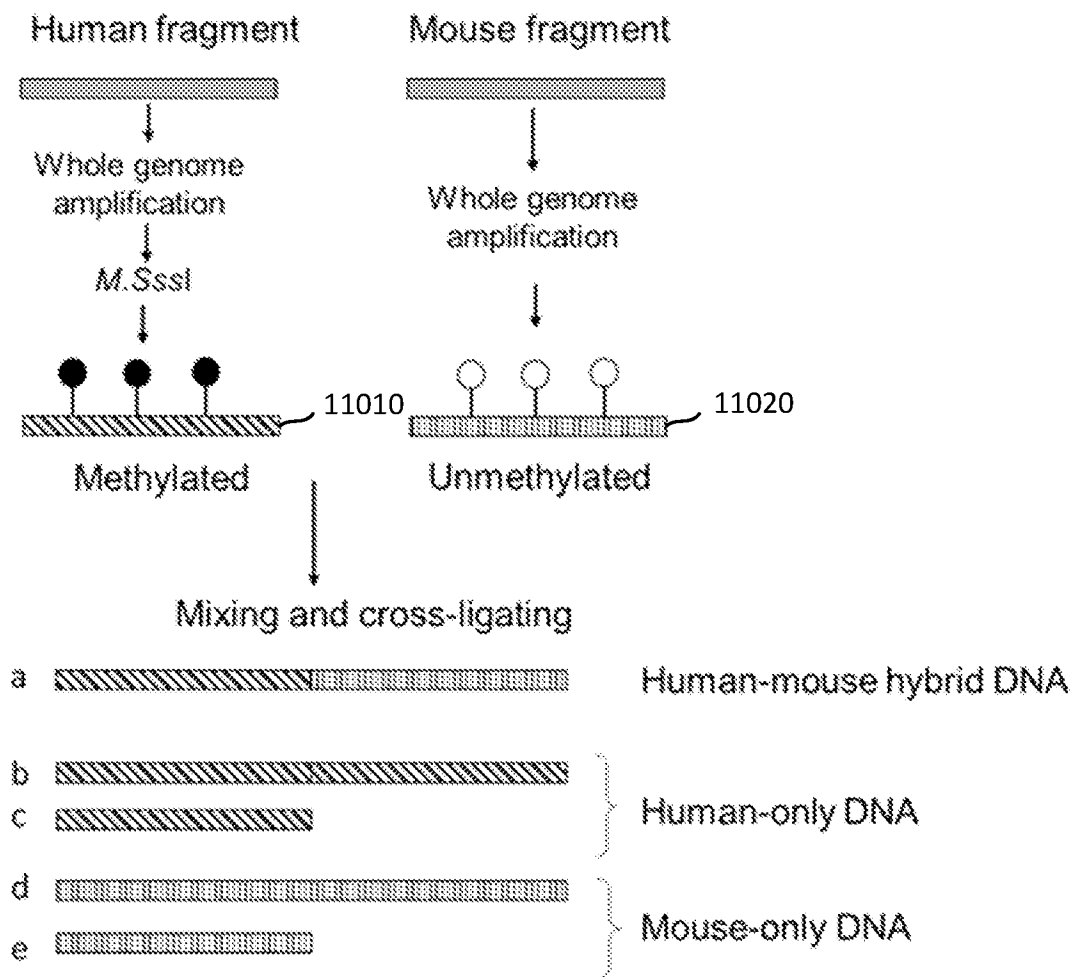


FIG. 110

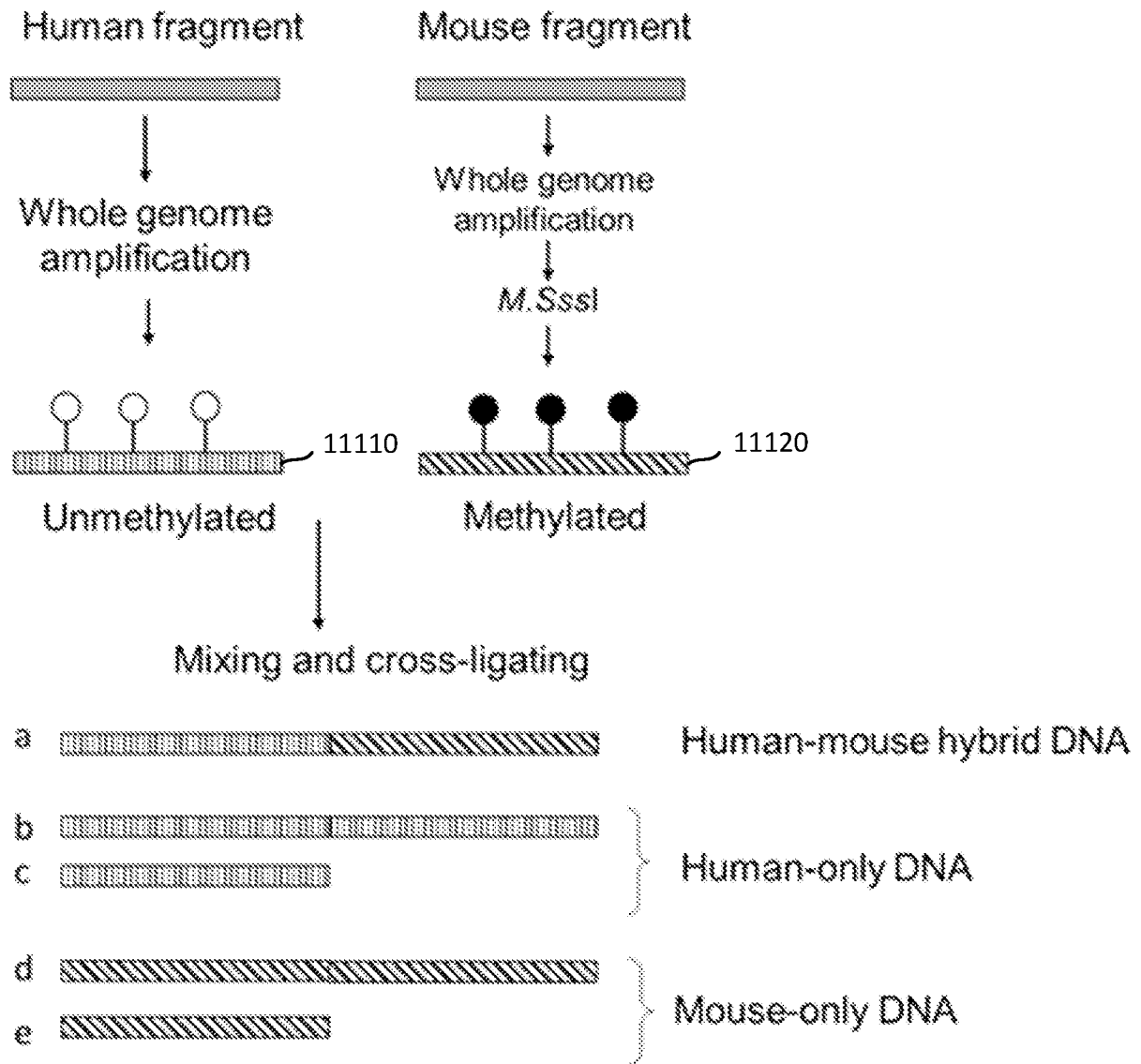


FIG. 111

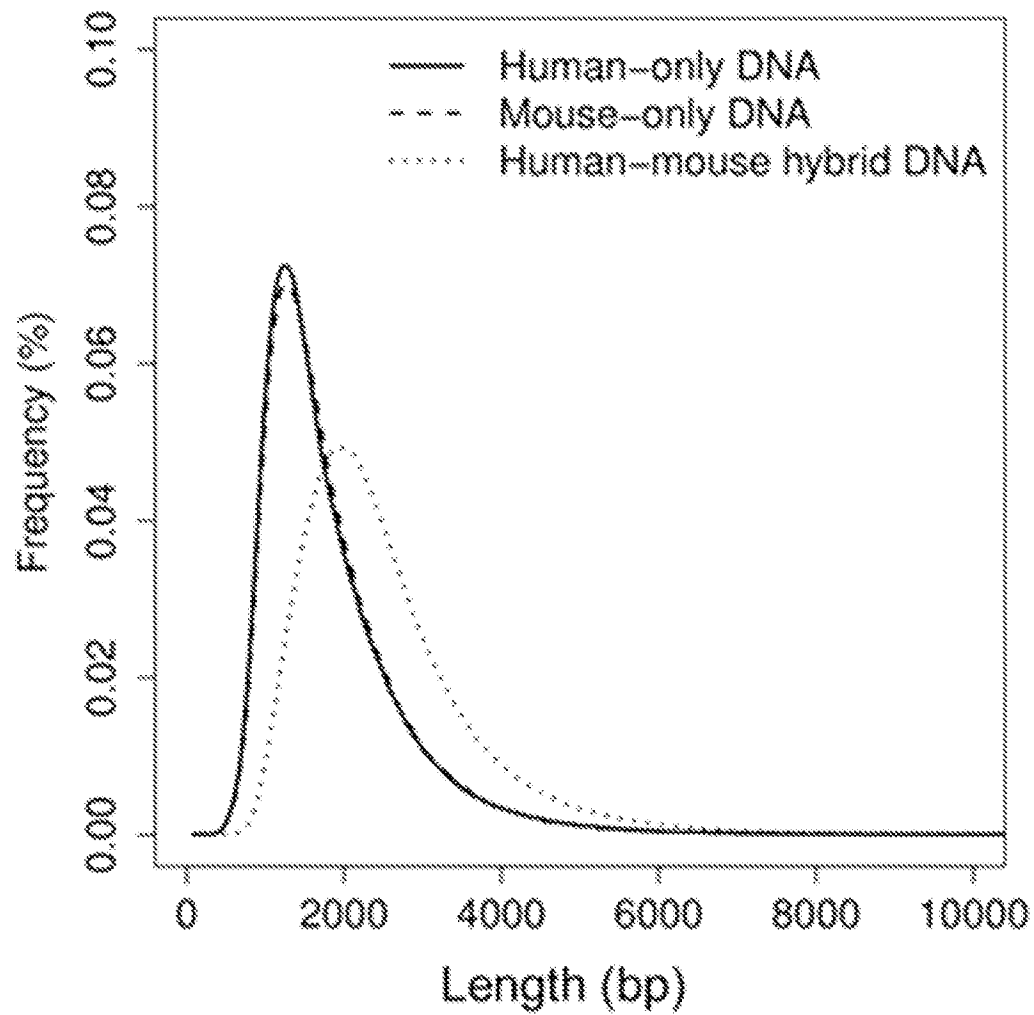


FIG. 112

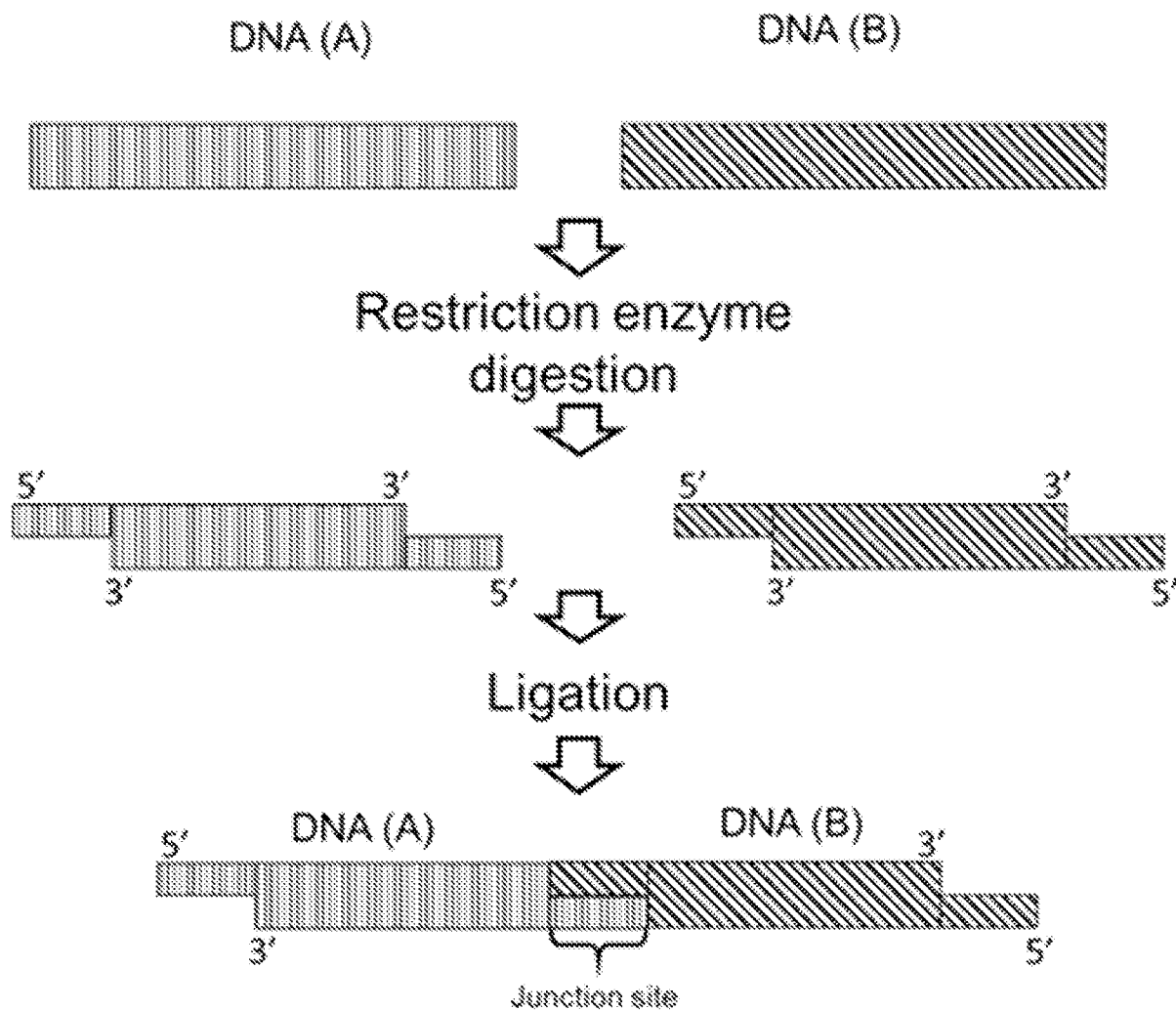


FIG. 113

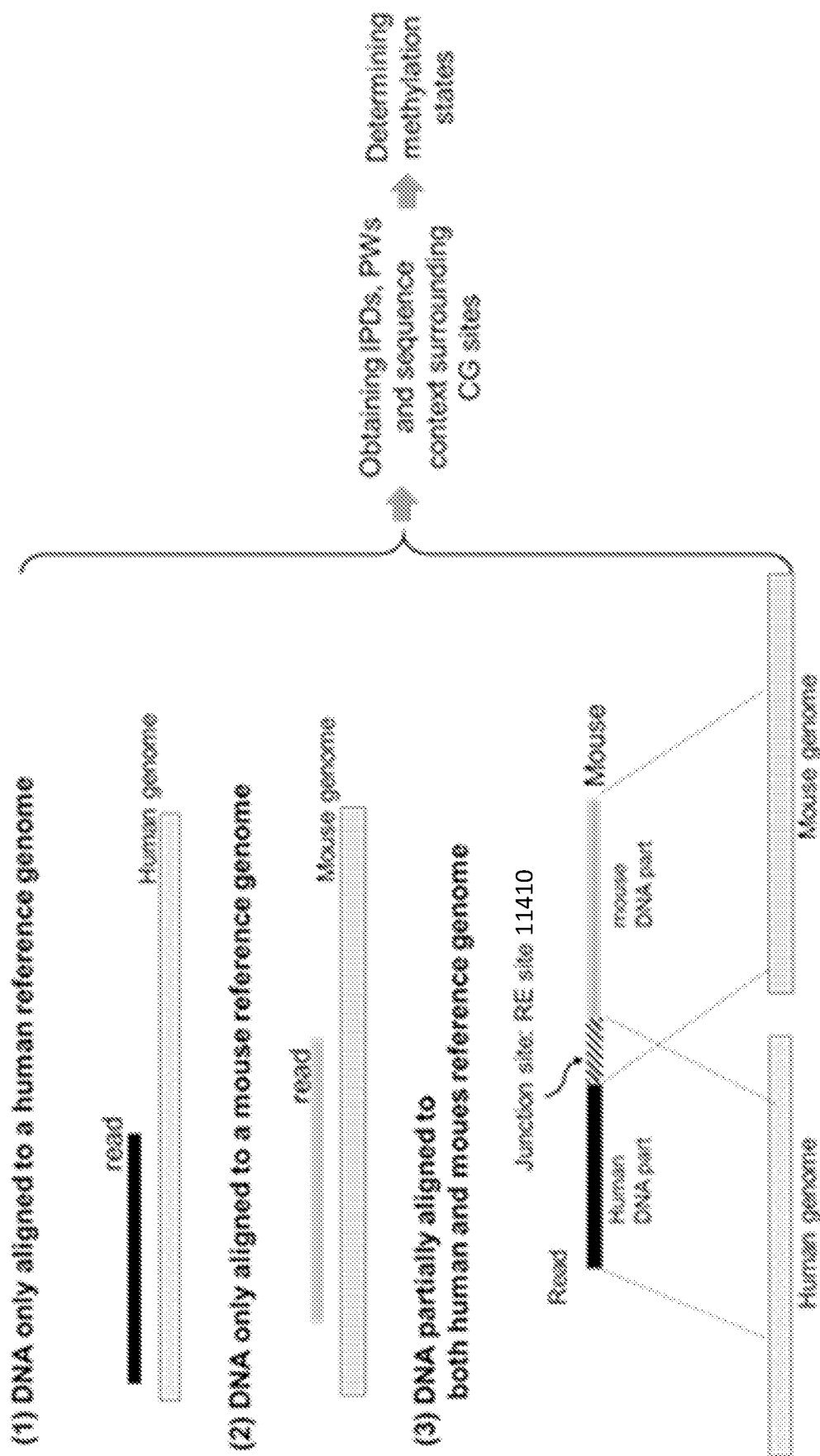


FIG. 114

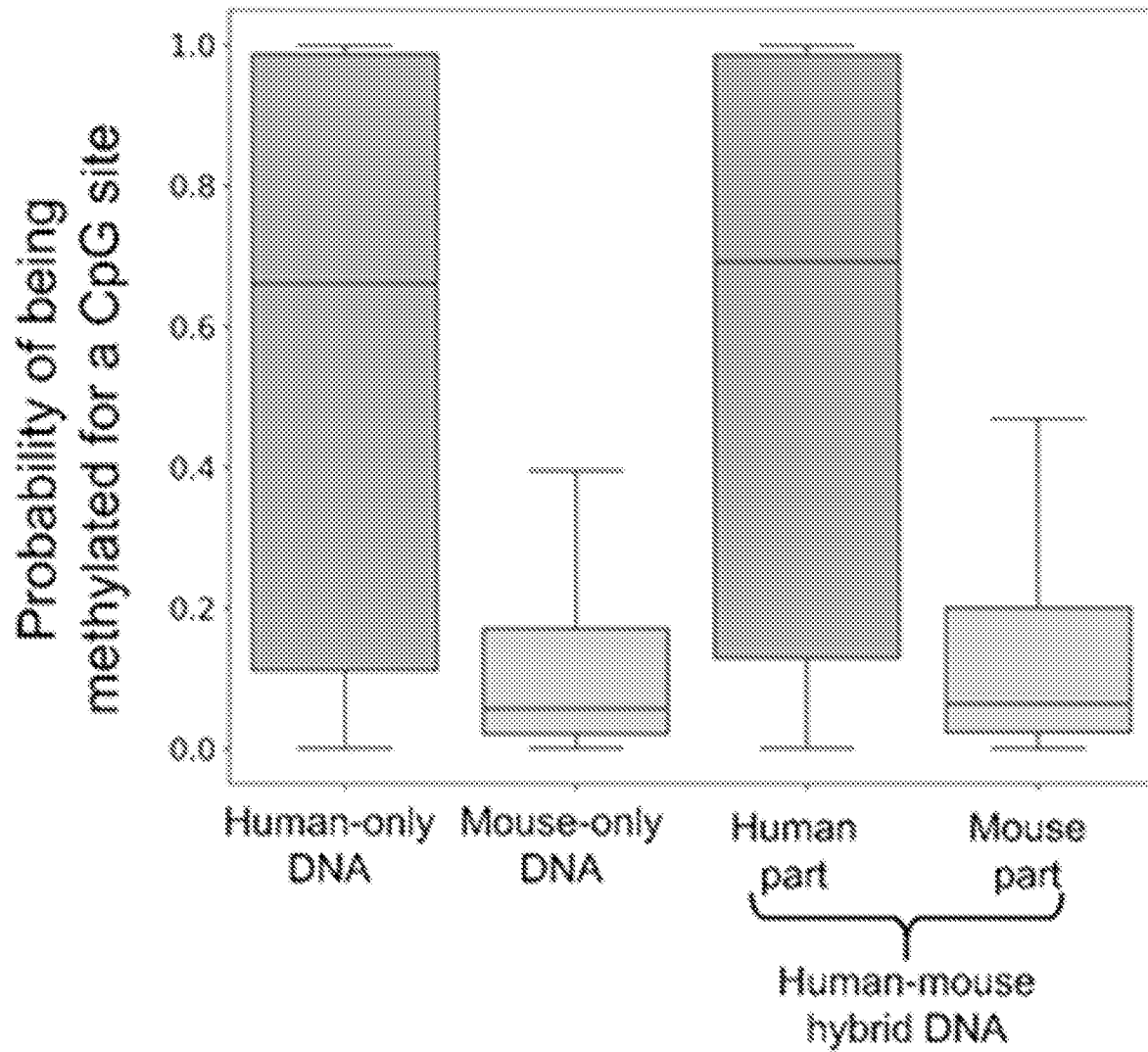


FIG. 115

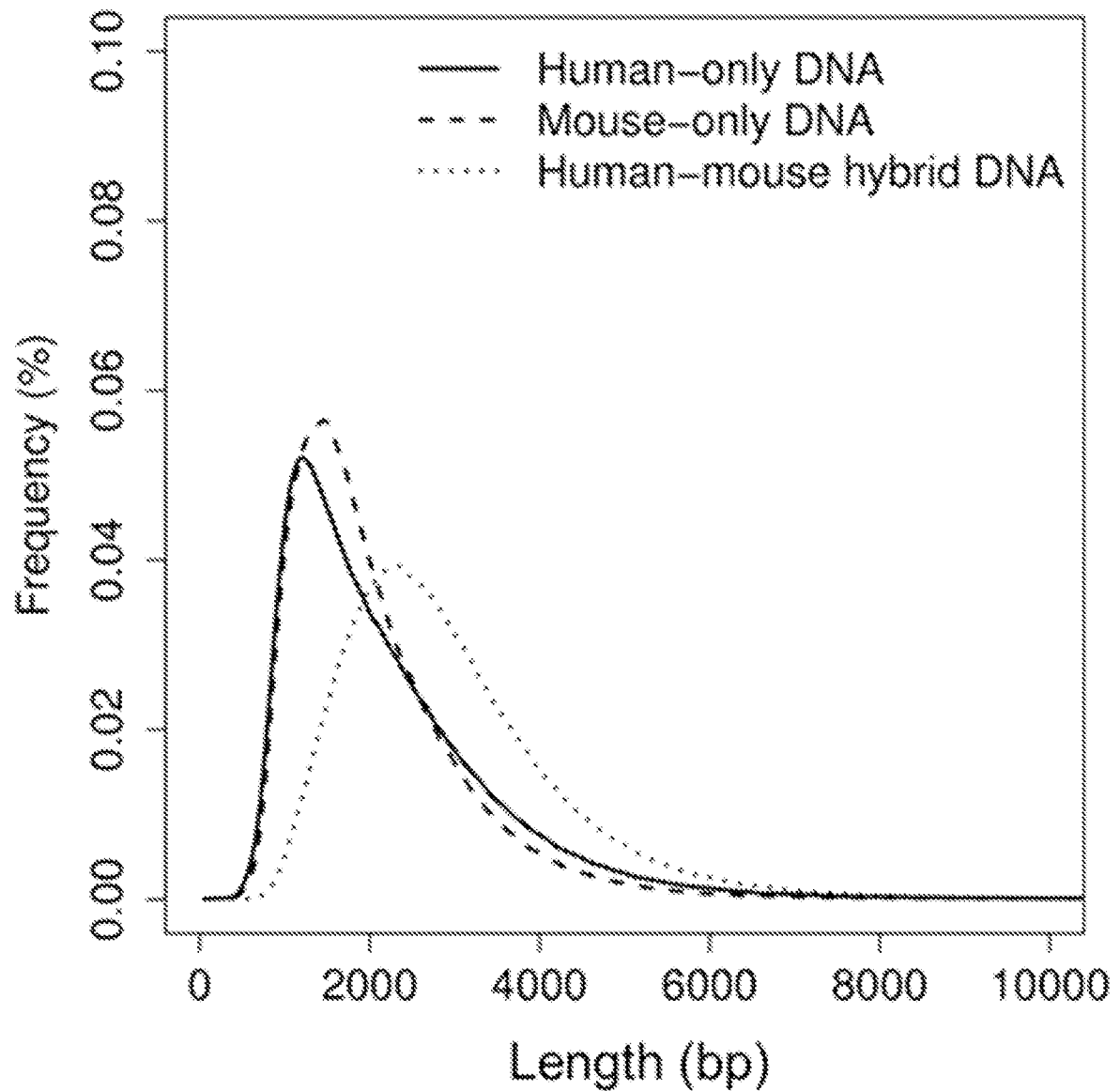


FIG. 116

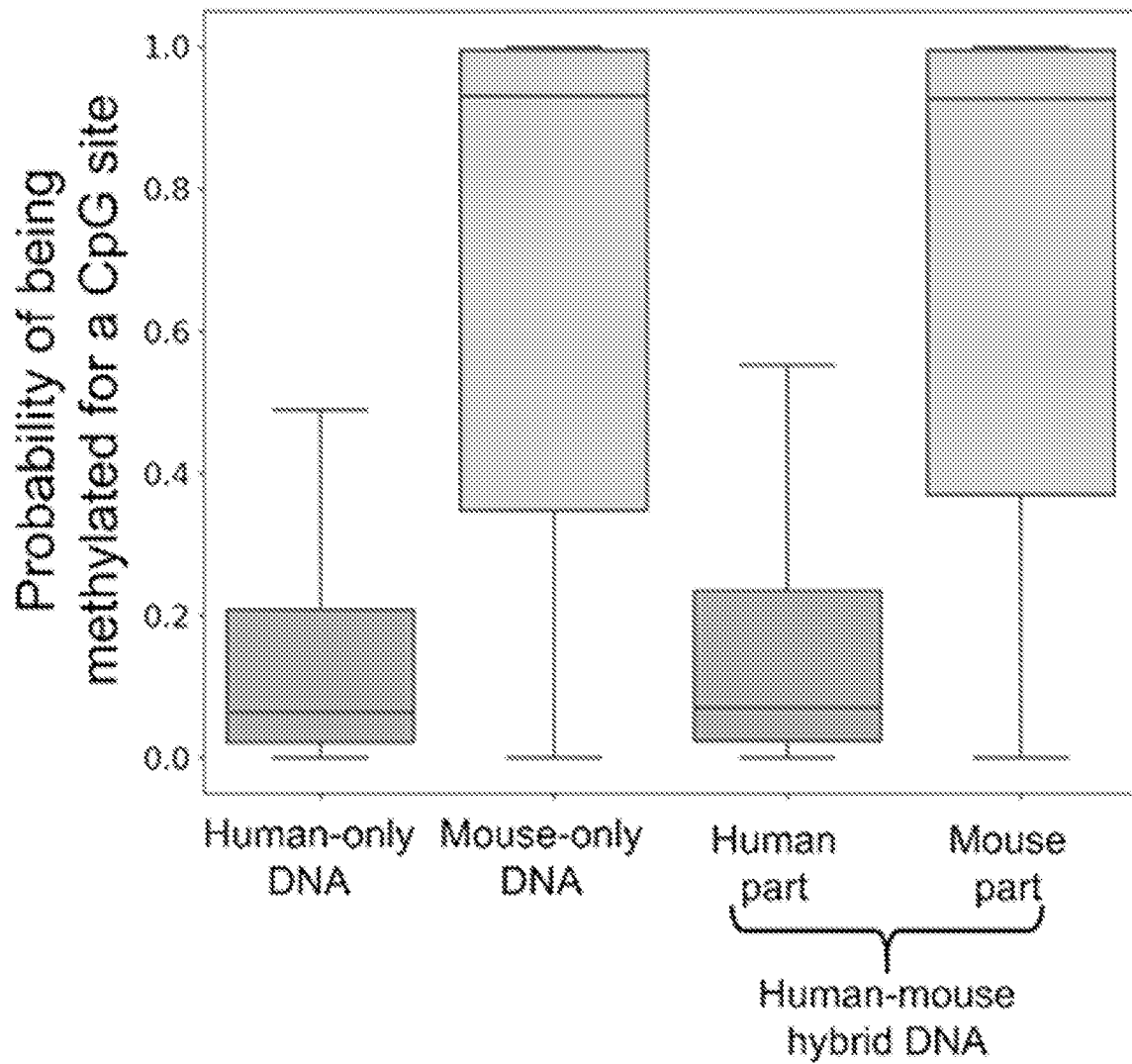


FIG. 117

	Bisulfite sequencing		PacBio sequencing	
	No. of CG sites	Methylation density (%)	No. of CG sites	Methylation density (%)
1) Human-only	2,230,407	41.4	16,226,014	56.0
2) Mouse-only	2,726,499	1.6	9,398,340	10.7
3) Human-mouse hybrid DNA	73,780	48.8	4,838,454	57.4
	76,312	2.3	4,385,046	12.1

FIG. 118

	Bisulfite sequencing		PacBio sequencing	
	No. of CG sites	Methylation density (%)	No. of CG sites	Methylation density (%)
1) Human-only	2,938,088	1.6	14,503,548	11.6
2) Mouse-only	1,513,971	62.4	11,348,555	71.5
3) Human-mouse hybrid DNA	67,371	1.8	5,824,379	13.1
	58,242	67.4	5,093,097	72.2

FIG. 119

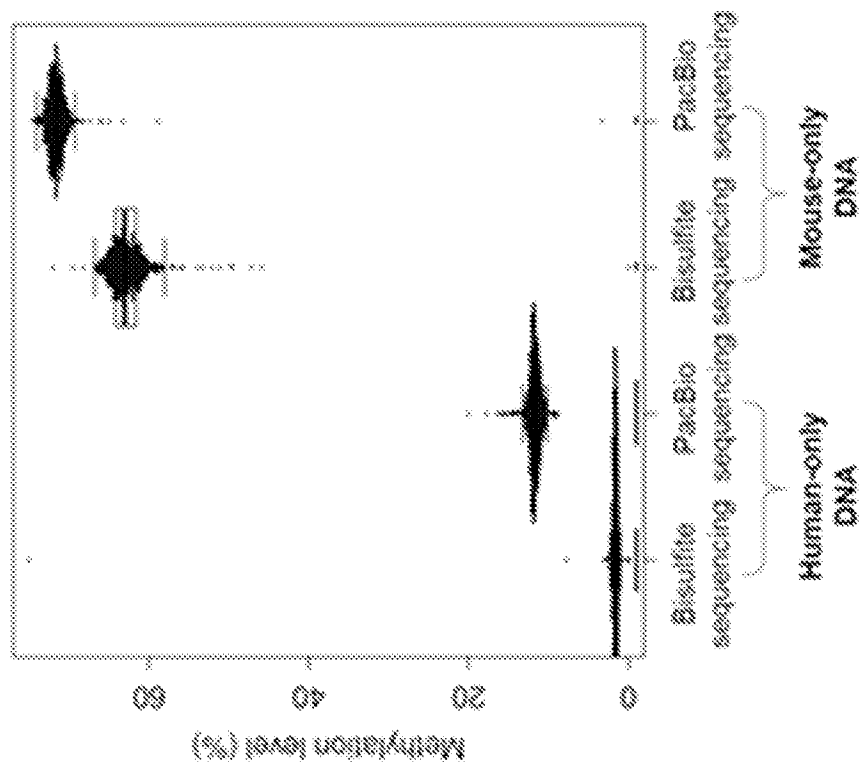


FIG. 120B

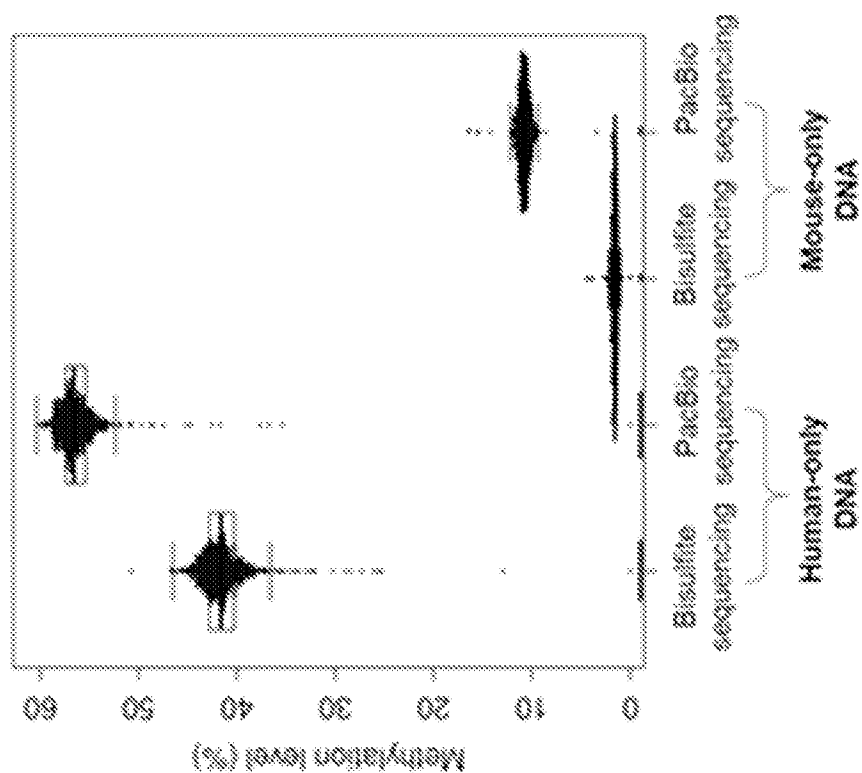


FIG. 120A

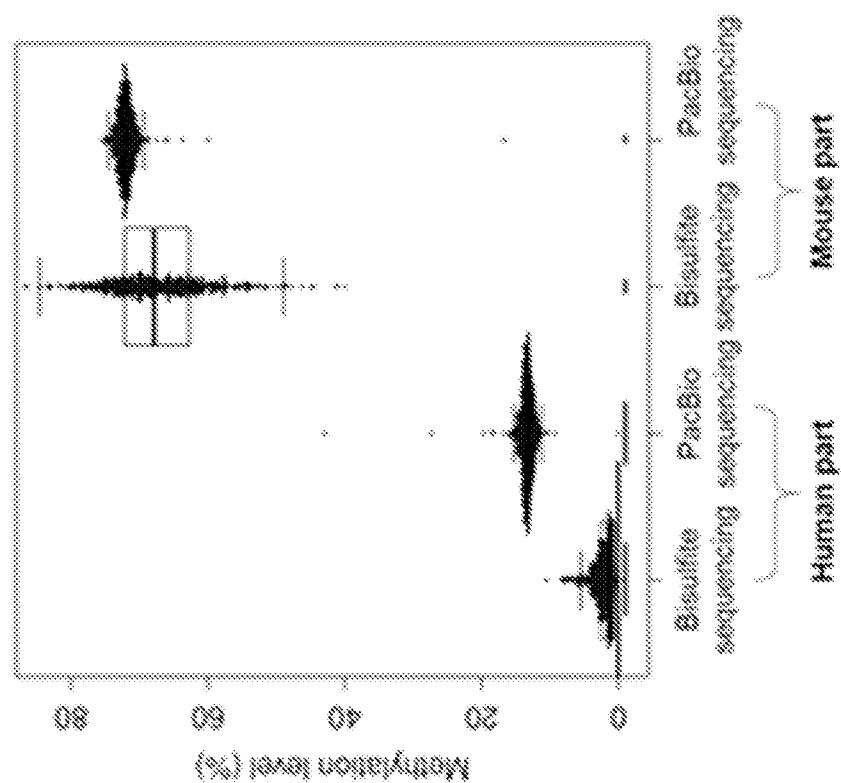


FIG. 121B

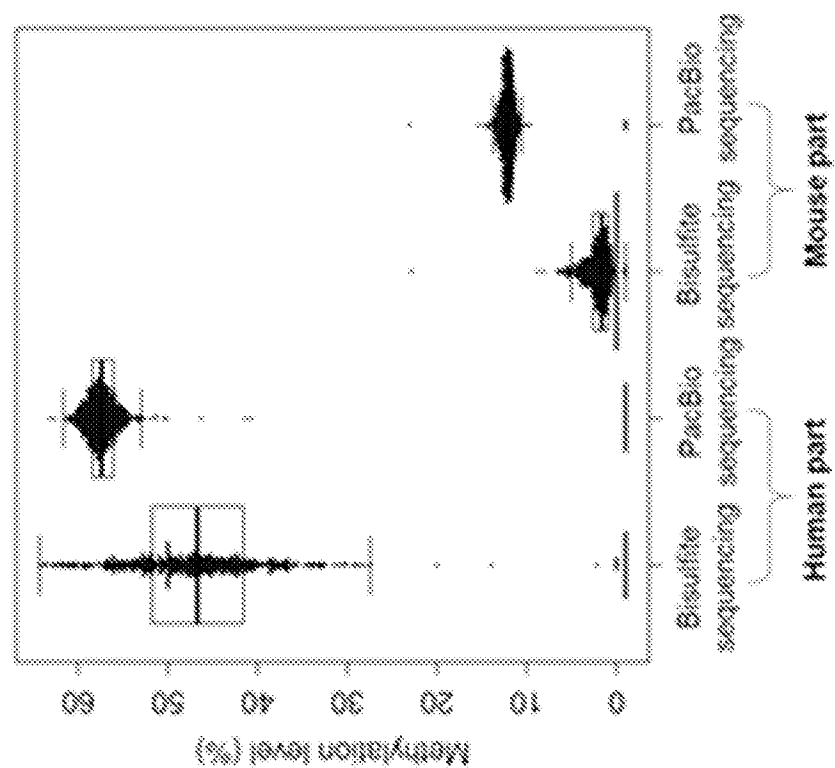


FIG. 121A

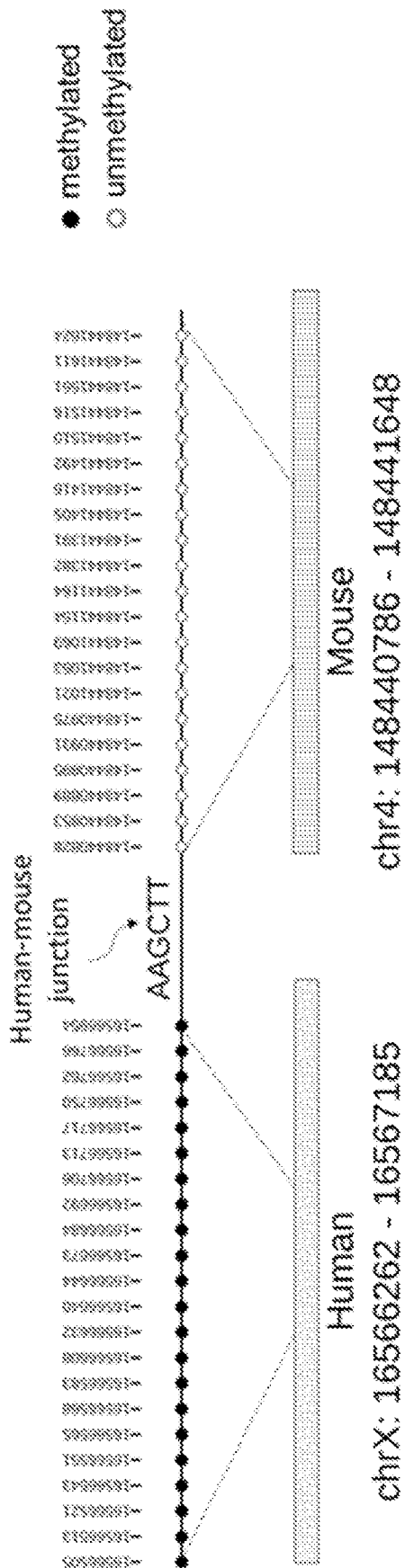


FIG. 122A

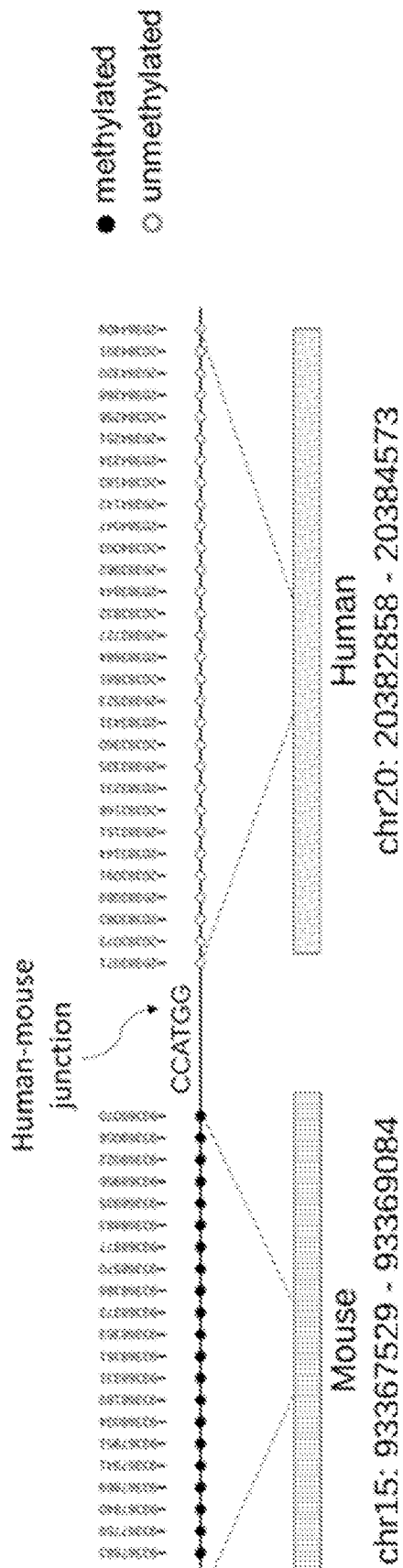


FIG. 122B

1230

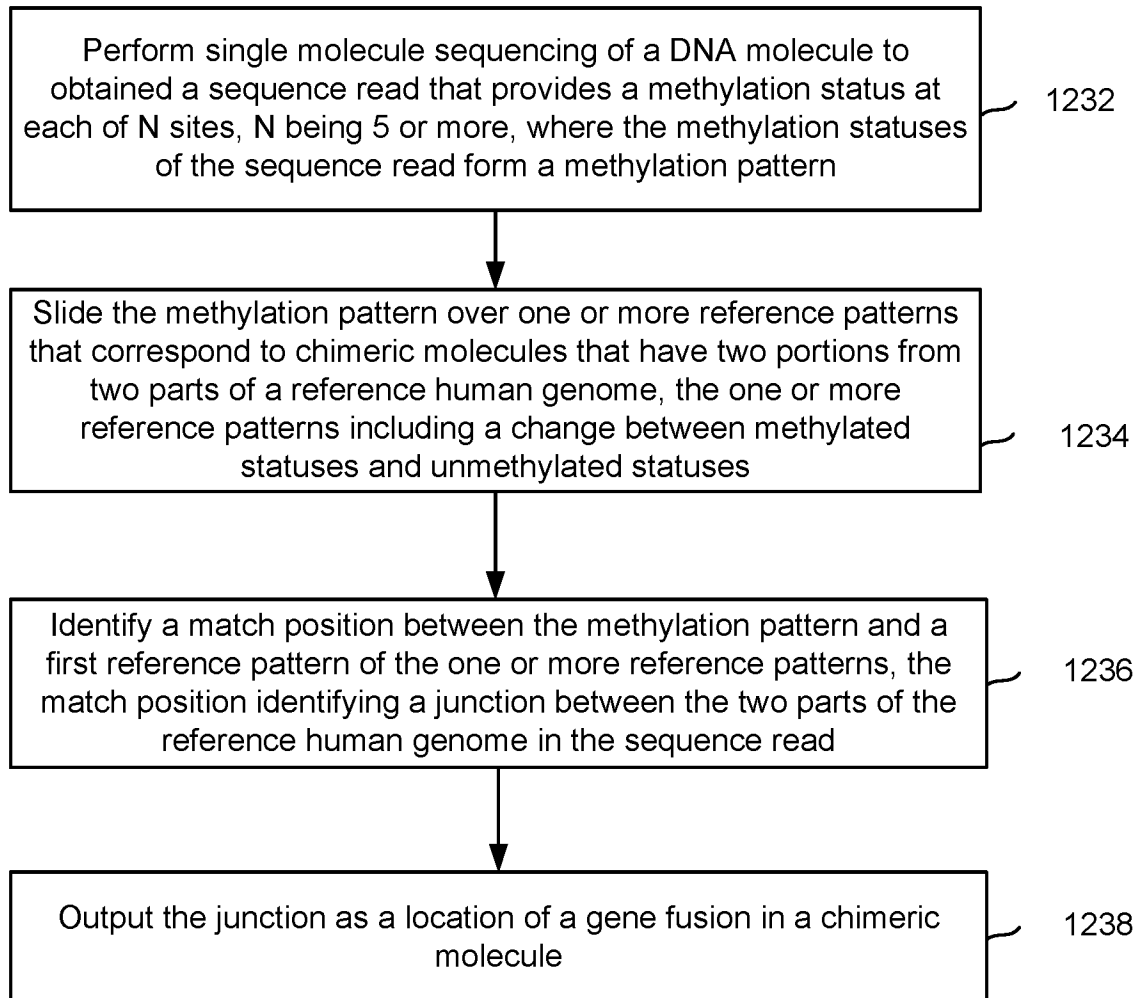


FIG. 123

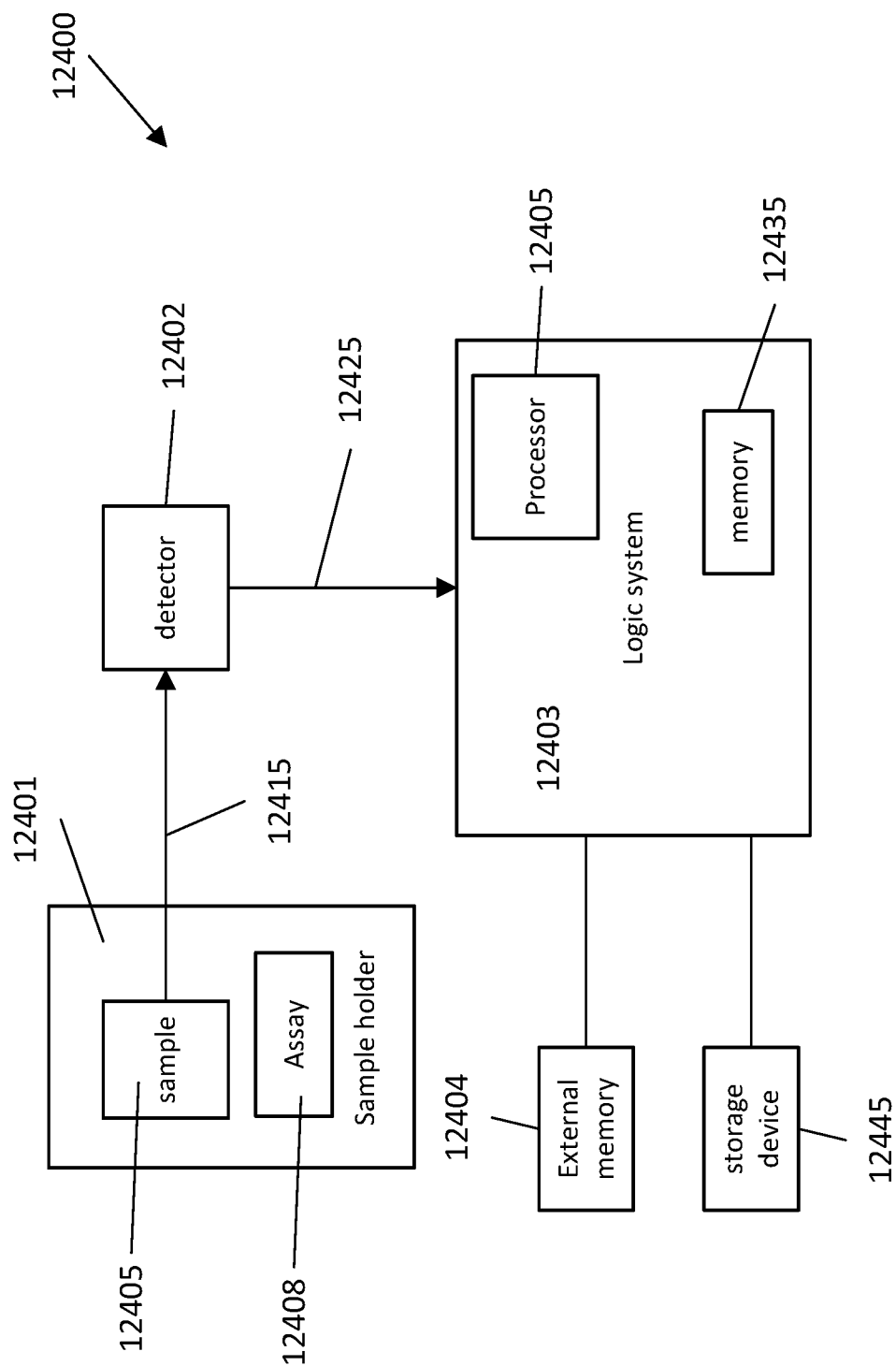


FIG. 124

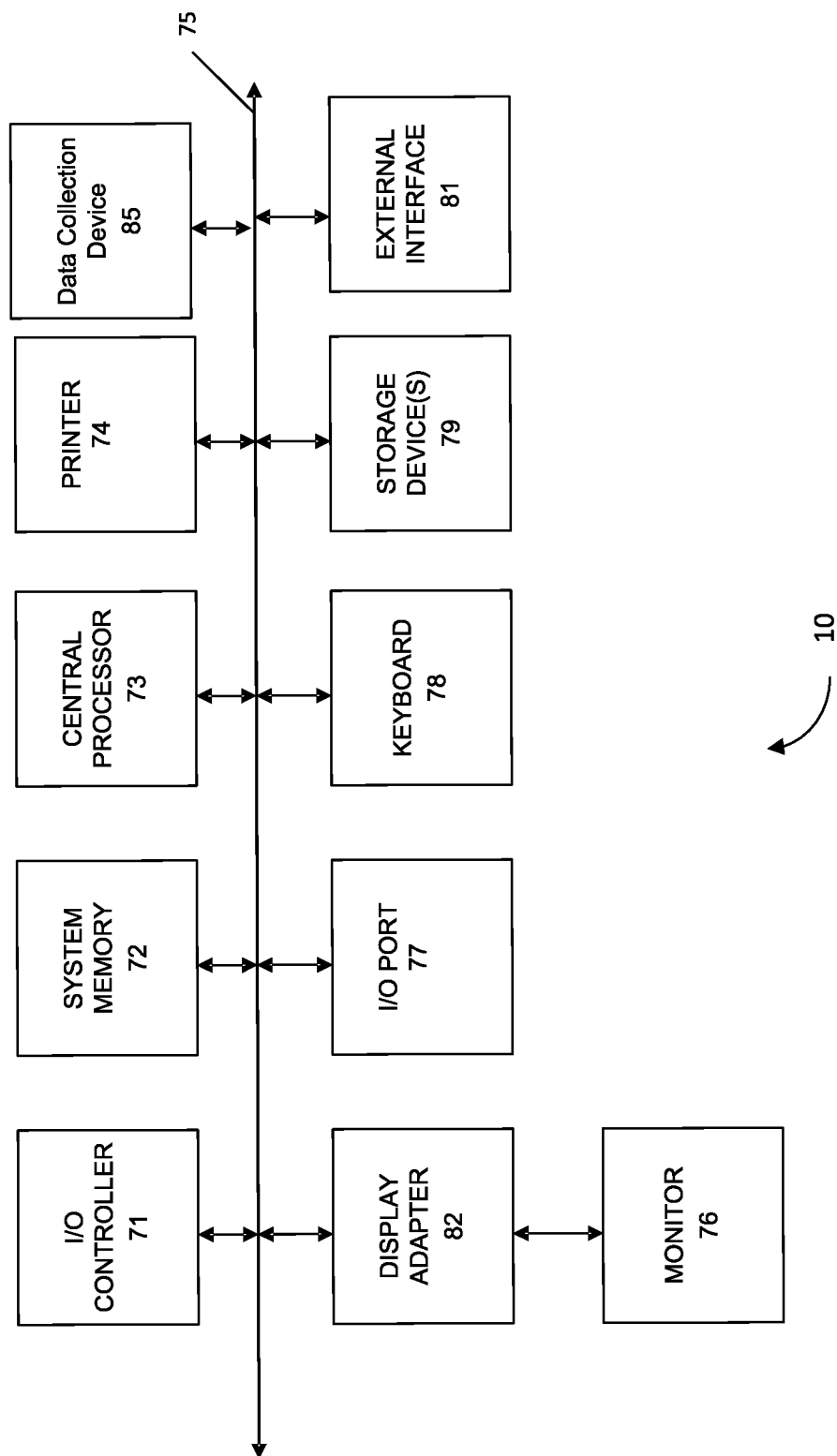


FIG. 125

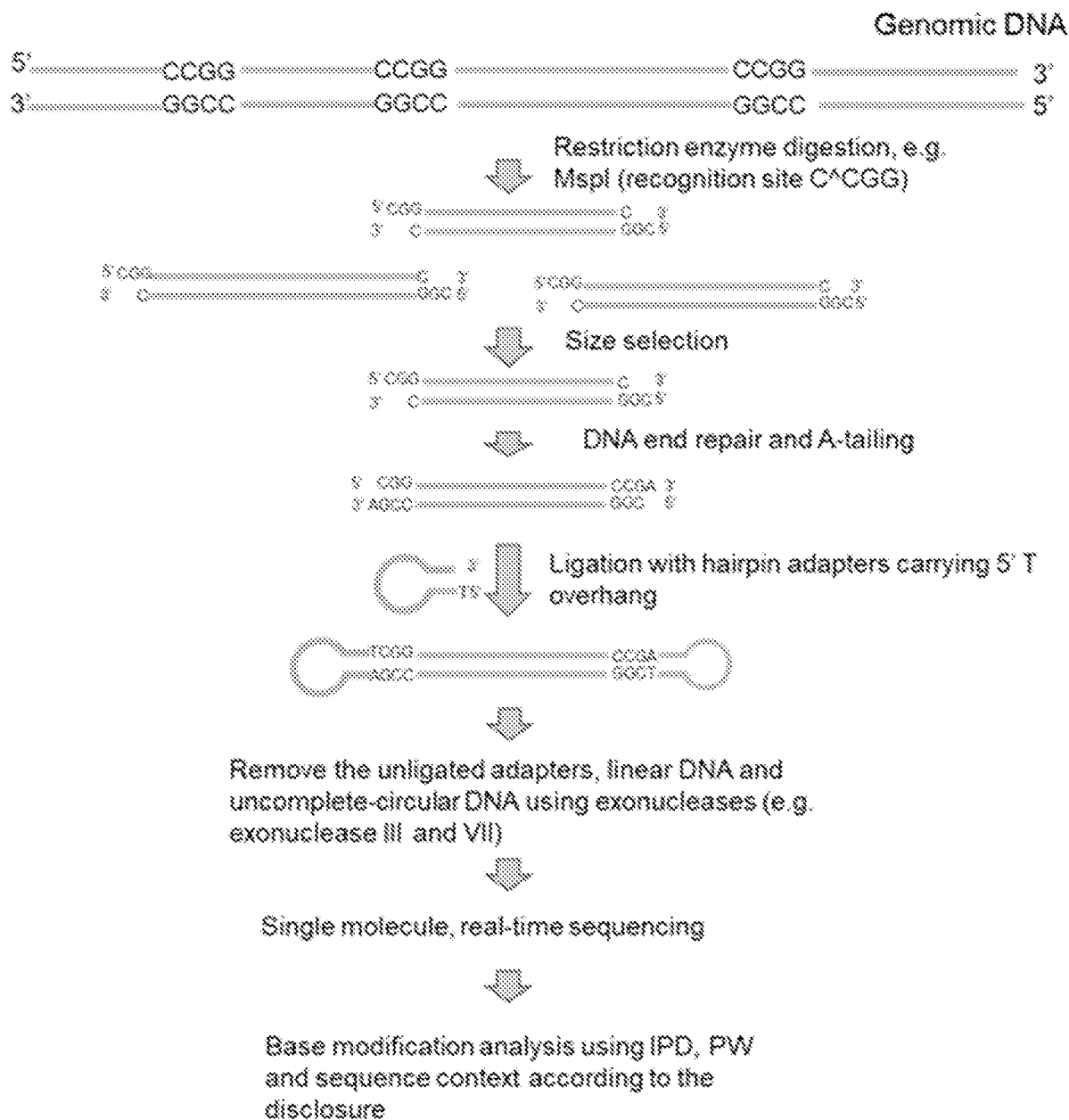


FIG. 126

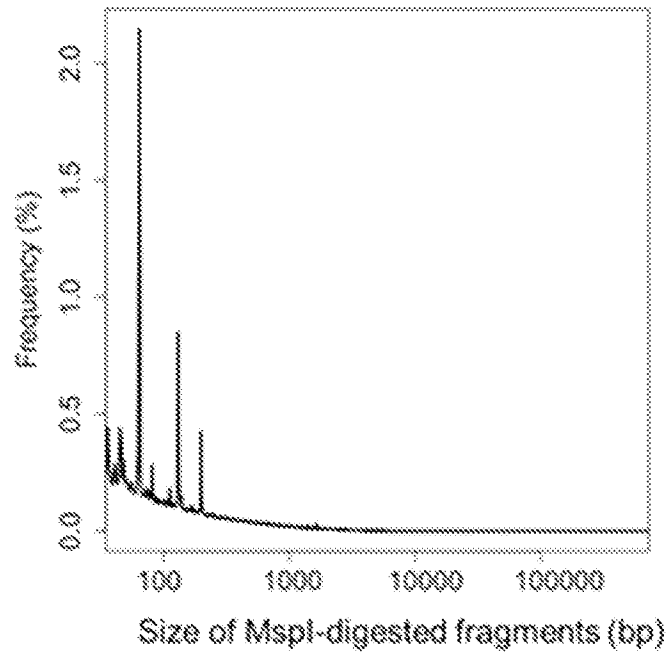


FIG. 127A

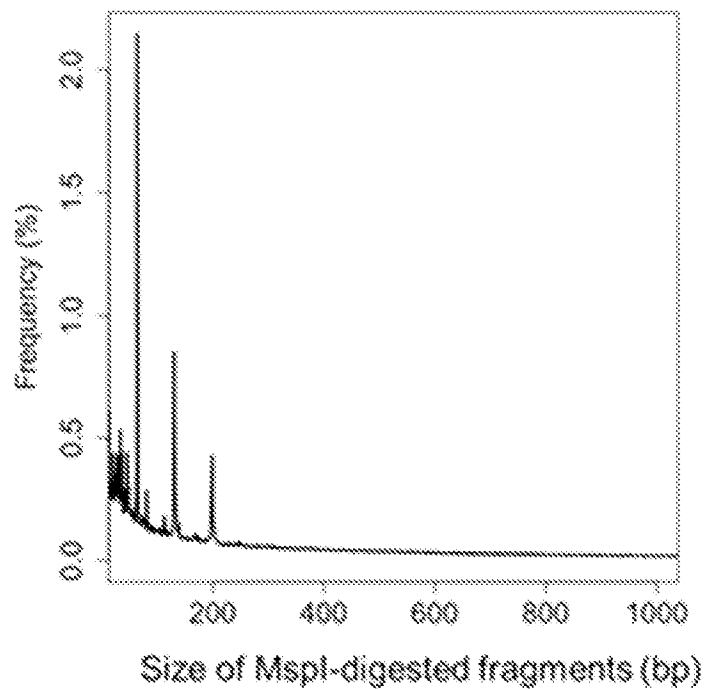


FIG. 127B

Size ranges (bp)	No. of molecules	Percentage of molecules within a size range relative to total fragments (%)	No. of molecules within a size range overlapping CpG islands	Percentage of molecules within a size range overlapping CpG islands (%)	No. of CpG sites being sequenced	No. of CpG sites falling within CpG islands	Percentage of CpG sites targeted by size selection and falling within CpG islands (%)
50-200	526,543	23.03	104,059	19.76	2,358,020	885,041	37.53
200-400	269,562	11.79	23,927	8.88	1,781,556	353,087	19.82
400-600	177,776	7.77	7,369	4.15	1,468,561	107,130	7.29
600-800	133,927	5.86	3,673	2.74	1,326,544	48,851	3.68
800-1000	104,976	4.59	2,168	2.07	1,193,233	25,821	2.16
1000-2000	311,596	13.63	4,596	1.47	4,610,504	58,288	1.26
2000-3000	149,468	6.54	1,771	1.18	3,036,951	25,106	0.83
3000-4000	86,760	3.79	809	0.93	2,165,171	10,785	0.50
5000-6000	36,931	1.62	266	0.72	1,242,712	3,412	0.27
6000-7000	25,027	1.09	202	0.81	947,874	3,354	0.35
7000-8000	17,597	0.77	86	0.49	736,830	791	0.11
8000-9000	12,658	0.55	76	0.60	583,680	993	0.17
9000-10000	9,184	0.40	48	0.52	461,935	591	0.13
10000-15000	20,790	0.91	97	0.47	1,255,731	2,003	0.16
15000-20000	5,111	0.22	16	0.31	414,400	163	0.04
20000-25000	1,441	0.06	6	0.42	147,731	34	0.02

FIG. 128

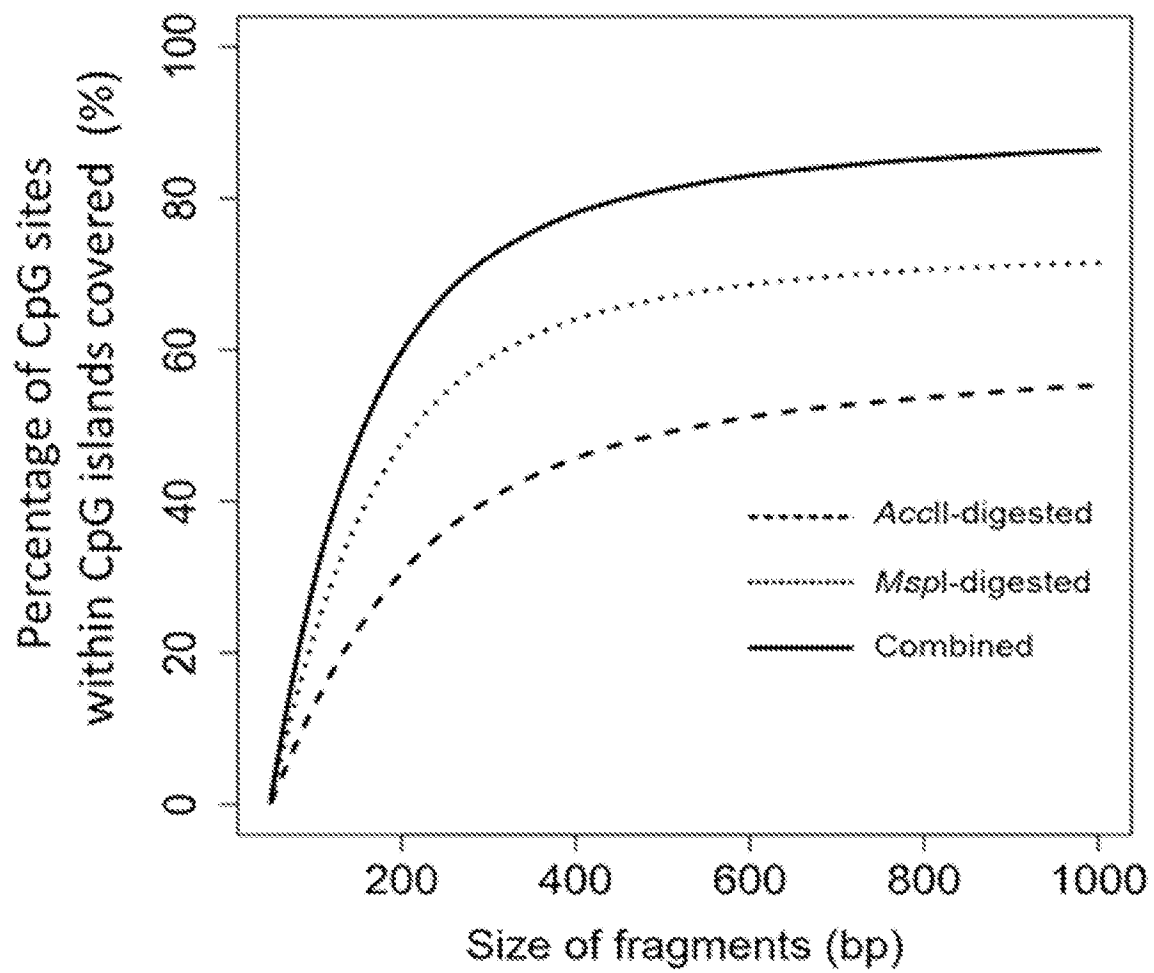


FIG. 129

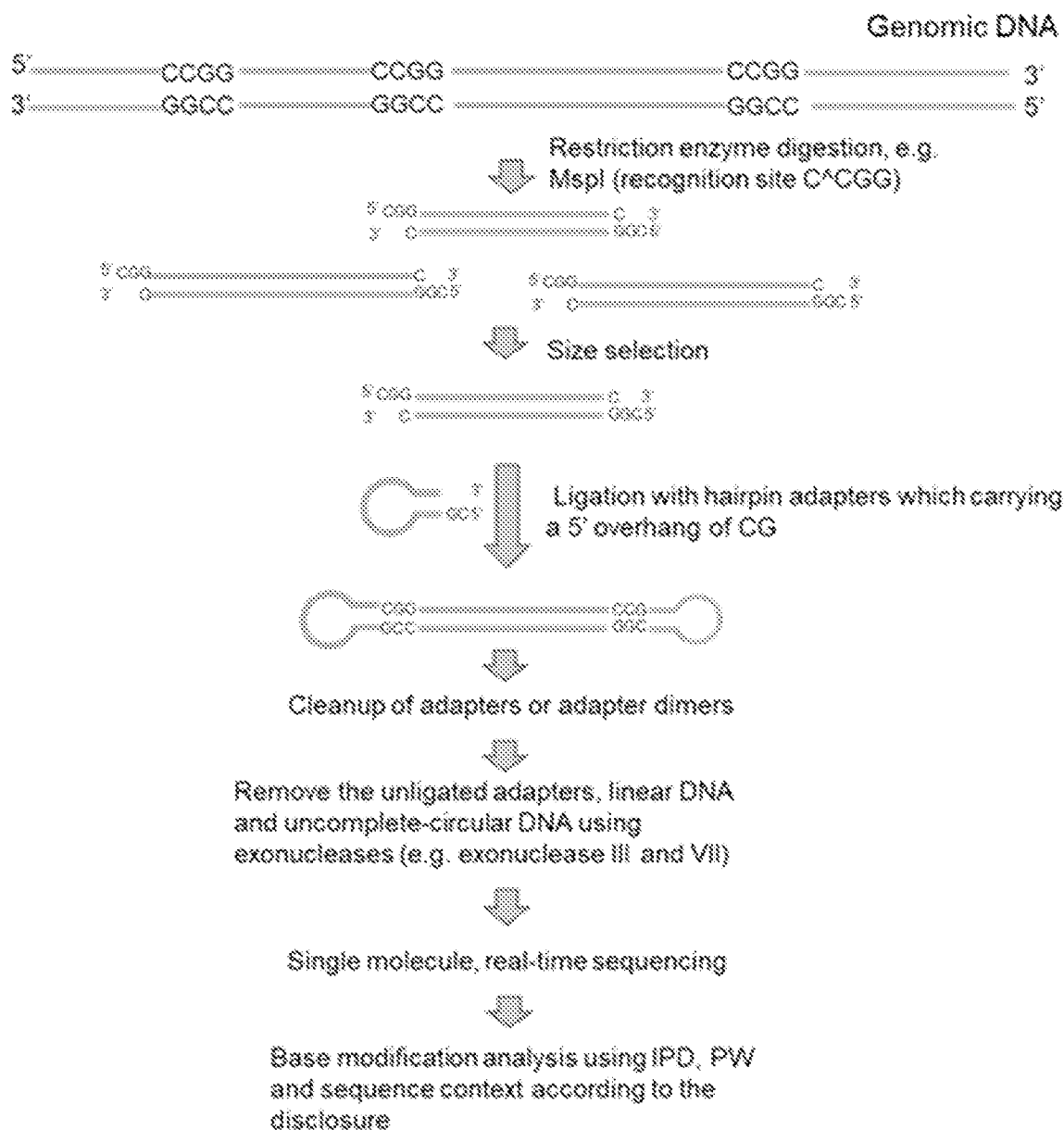


FIG. 130

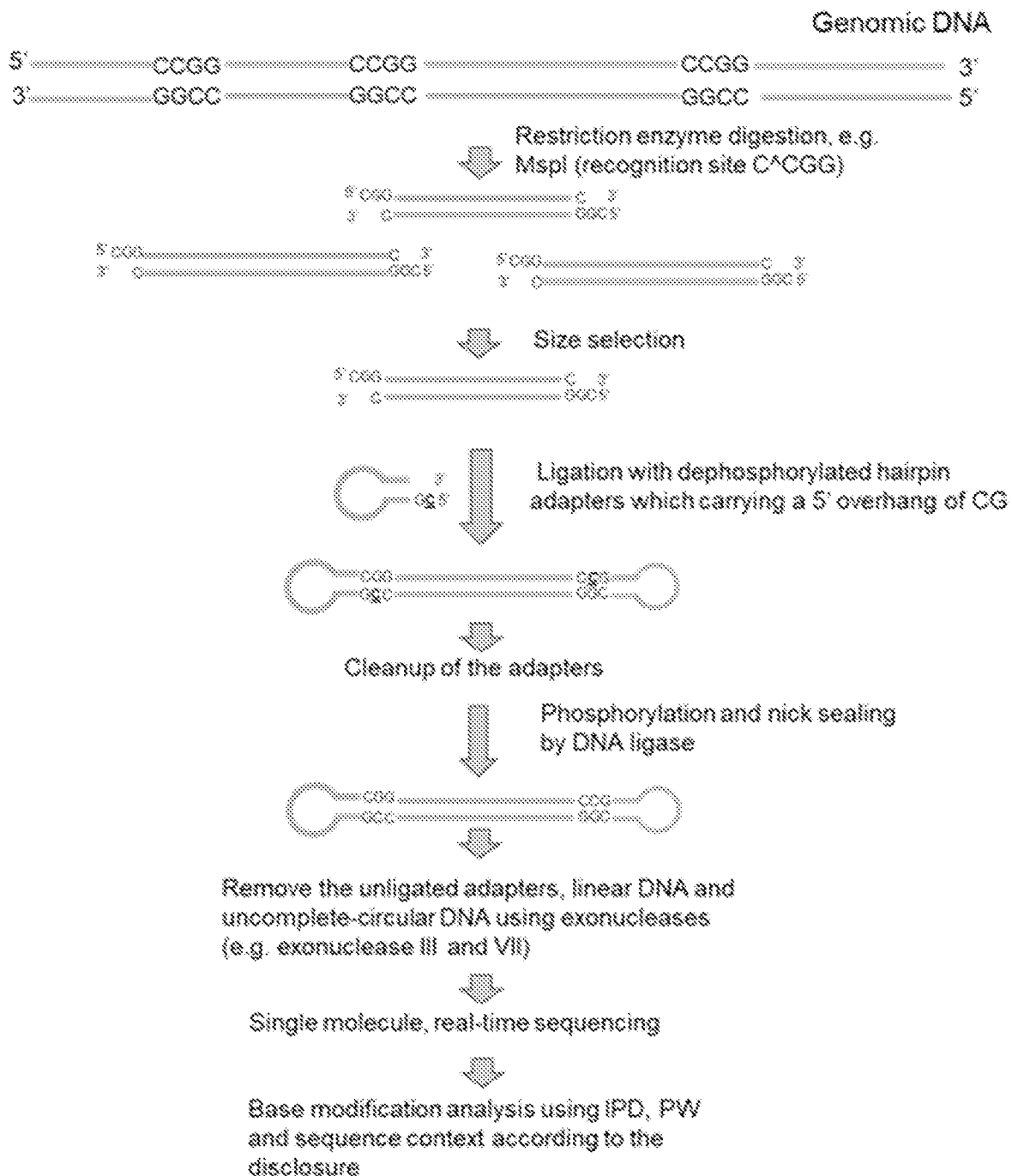


FIG. 131

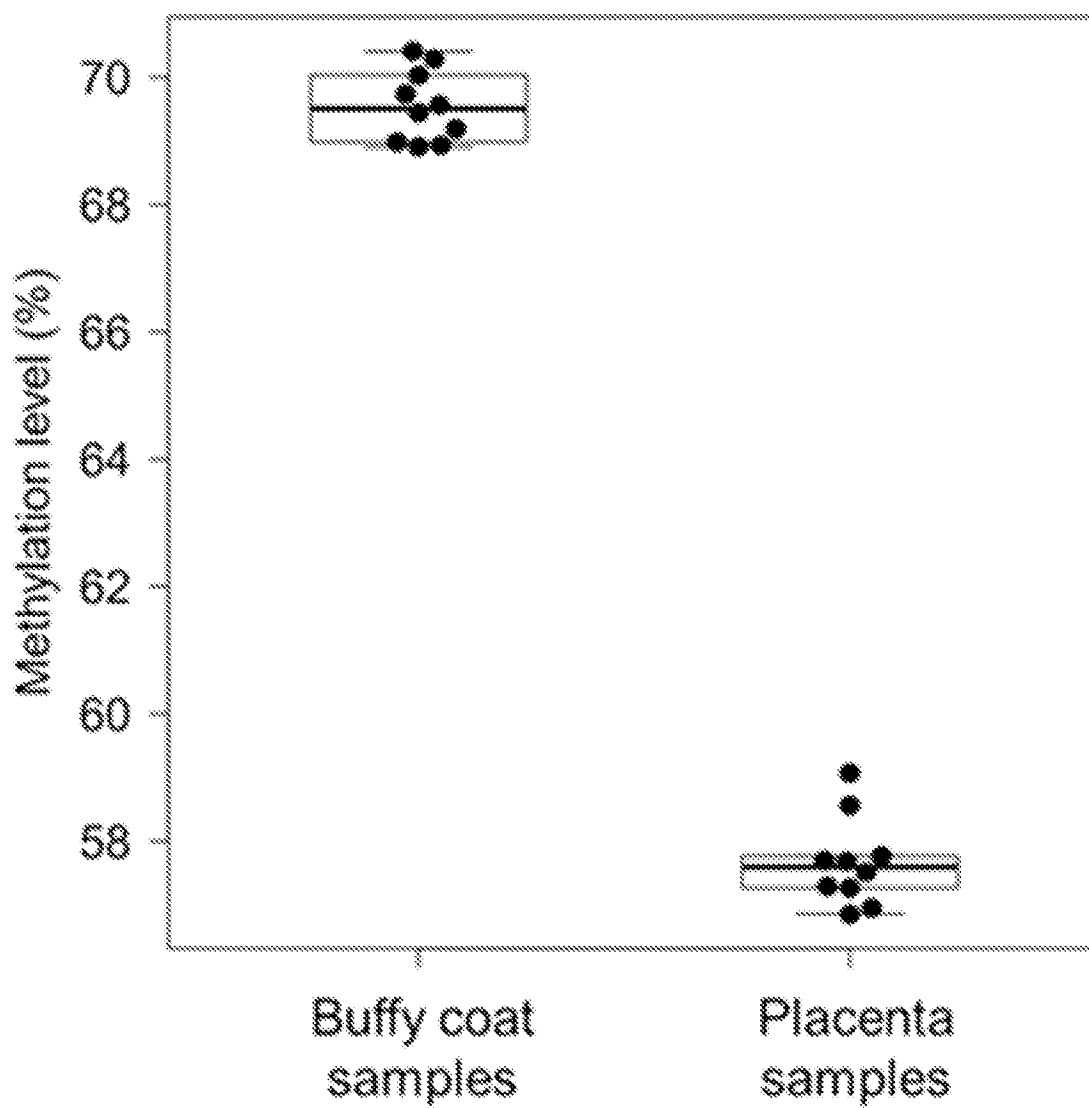


FIG. 132

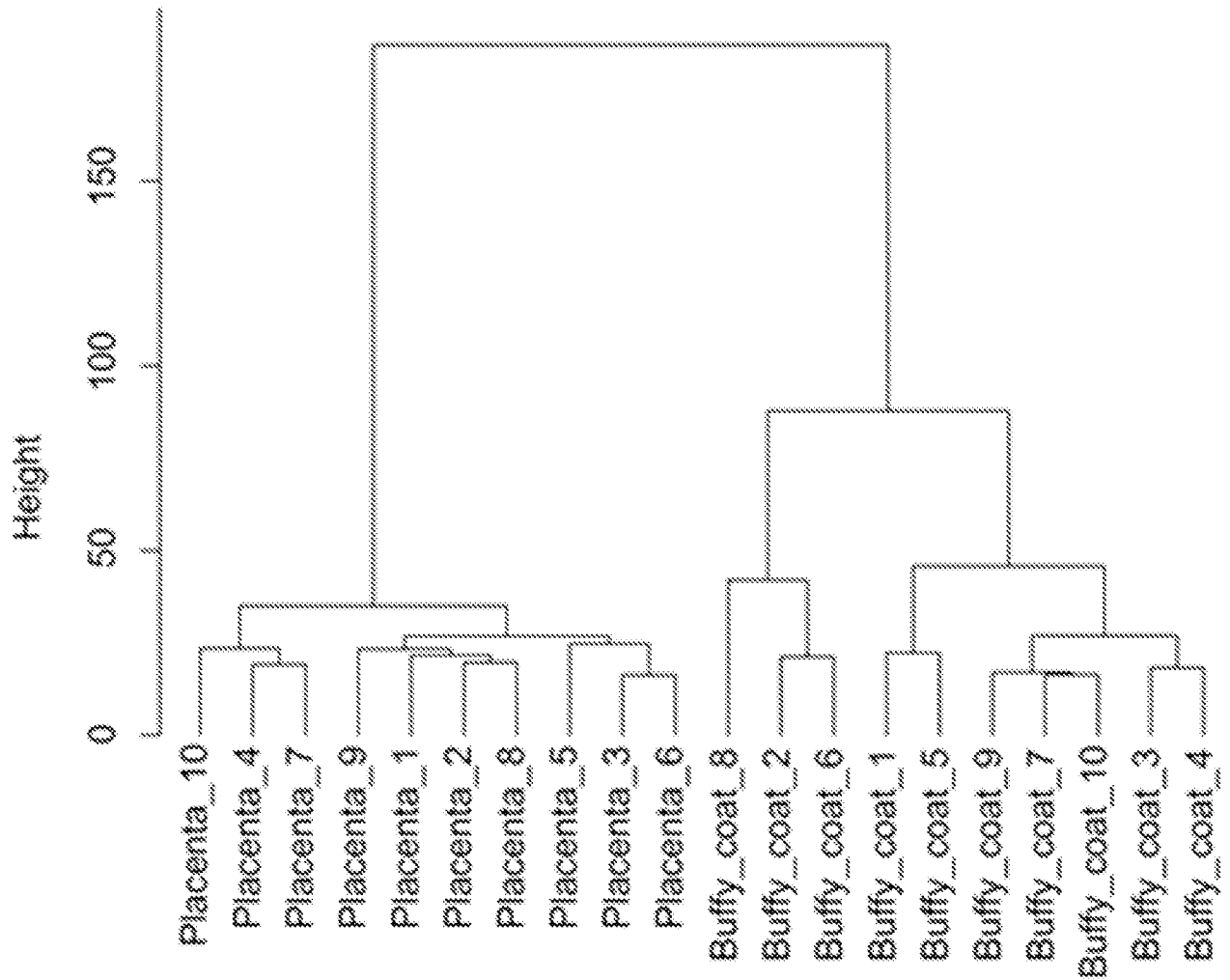


FIG. 133

**CERTIFICATION AND REQUEST FOR PRIORITIZED EXAMINATION
UNDER 37 CFR 1.102(e) (Page 1 of 1)**

First Named Inventor:	Yuk-Ming Dennis Lo	Nonprovisional Application Number (if known):	
Title of Invention:	DETERMINATION OF BASE MODIFICATIONS OF NUCLEIC ACIDS		

APPLICANT HEREBY CERTIFIES THE FOLLOWING AND REQUESTS PRIORITIZED EXAMINATION FOR THE ABOVE-IDENTIFIED APPLICATION.

1. The processing fee set forth in 37 CFR 1.17(i)(1) and the prioritized examination fee set forth in 37 CFR 1.17(c) have been filed with the request. The publication fee requirement is met because that fee, set forth in 37 CFR 1.18(d), is currently \$0. The basic filing fee, search fee, and examination fee are filed with the request or have been already been paid. I understand that any required excess claims fees or application size fee must be paid for the application.
2. I understand that the application may not contain, or be amended to contain, more than four independent claims, more than thirty total claims, or any multiple dependent claims, and that any request for an extension of time will cause an outstanding Track I request to be dismissed.
3. The applicable box is checked below:

I. ☒ Original Application (Track One) - Prioritized Examination under § 1.102(e)(1)

- i. (a) The application is an original nonprovisional utility application filed under 35 U.S.C. 111(a). This certification and request is being filed with the utility application via EFS-Web.
---OR---
(b) The application is an original nonprovisional plant application filed under 35 U.S.C. 111(a). This certification and request is being filed with the plant application in paper.
- ii. An executed inventor's oath or declaration under 37 CFR 1.63 or 37 CFR 1.64 for each inventor, or the application data sheet meeting the conditions specified in 37 CFR 1.53(f)(3)(i) is filed with the application.

II. ☐ Request for Continued Examination - Prioritized Examination under § 1.102(e)(2)

- i. A request for continued examination has been filed with, or prior to, this form.
- ii. If the application is a utility application, this certification and request is being filed via EFS-Web.
- iii. The application is an original nonprovisional utility application filed under 35 U.S.C. 111(a), or is a national stage entry under 35 U.S.C. 371.
- iv. This certification and request is being filed prior to the mailing of a first Office action responsive to the request for continued examination.
- v. No prior request for continued examination has been granted prioritized examination status under 37 CFR 1.102(e)(2).

Signature <u>/David D. Hsu/</u>	Date <u>8/19/2022</u>
Name (Print/Typed) <u>David D. Hsu</u>	Practitioner Registration Number <u>71,659</u>

Note: This form must be signed in accordance with 37 CFR 1.33. See 37 CFR 1.4(d) for signature requirements and certifications. Submit multiple forms if more than one signature is required.*

☒ *Total of 1 forms are submitted.

Privacy Act Statement

The **Privacy Act of 1974 (P.L. 93-579)** requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C. 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether disclosure of these records is required by the Freedom of Information Act.
2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.
3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.
4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).
5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.
6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (*i.e.*, GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspection or an issued patent.
9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

**DECLARATION (37 CFR 1.63) FOR UTILITY OR DESIGN APPLICATION USING AN
APPLICATION DATA SHEET (37 CFR 1.76)**

Title of Invention	DETERMINATION OF BASE MODIFICATIONS OF NUCLEIC ACIDS
-----------------------	--

As the below named inventor, I hereby declare that:

This declaration
is directed to: ☐ The attached application, or

☒ United States application or PCT international application number 16/995,607
filed on August 17, 2020

The above-identified application was made or authorized to be made by me.

I believe that I am the original inventor or an original joint inventor of a claimed invention in the application.

I hereby acknowledge that any willful false statement made in this declaration is punishable under 18 U.S.C. 1001
by fine or imprisonment of not more than five (5) years, or both.

WARNING:

Petitioner/applicant is cautioned to avoid submitting personal information in documents filed in a patent application that may contribute to identity theft. Personal information such as social security numbers, bank account numbers, or credit card numbers (other than a check or credit card authorization form PTO-2038 submitted for payment purposes) is never required by the USPTO to support a petition or an application. If this type of personal information is included in documents submitted to the USPTO, petitioners/applicants should consider redacting such personal information from the documents before submitting them to the USPTO. Petitioner/applicant is advised that the record of a patent application is available to the public after publication of the application (unless a non-publication request in compliance with 37 CFR 1.213(a) is made in the application) or issuance of a patent. Furthermore, the record from an abandoned application may also be available to the public if the application is referenced in a published application or an issued patent (see 37 CFR 1.14). Checks and credit card authorization forms PTO-2038 submitted for payment purposes are not retained in the application file and therefore are not publicly available.

LEGAL NAME OF INVENTOR

Inventor: Yuk-Ming Dennis Lo Date (Optional) : _____

Signature: _____

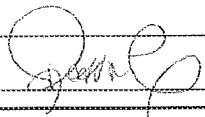
Note: An application data sheet (PTO/SB/14 or equivalent), including naming the entire inventive entity, must accompany this form.
Use an additional PTO/AIA/01 form for each additional inventor.

This collection of information is required by 35 U.S.C. 115 and 37 CFR 1.63. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 1 minute to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

DECLARATION (37 CFR 1.63) FOR UTILITY OR DESIGN APPLICATION USING AN
APPLICATION DATA SHEET (37 CFR 1.76)

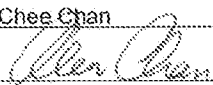
Title of Invention	DETERMINATION OF BASE MODIFICATIONS OF NUCLEIC ACIDS
<p>As the below named inventor, I hereby declare that:</p> <p>This declaration is directed to: ☐ The attached application, or</p> <p>☒ United States application or PCT international application number 16/995,607</p> <p>filed on August 17, 2020</p> <p>The above-identified application was made or authorized to be made by me.</p> <p>I believe that I am the original inventor or an original joint inventor of a claimed invention in the application.</p> <p>I hereby acknowledge that any willful false statement made in this declaration is punishable under 18 U.S.C. 1001 by fine or imprisonment of not more than five (5) years, or both.</p> <p style="text-align: center;">WARNING:</p> <p>Petitioner/applicant is cautioned to avoid submitting personal information in documents filed in a patent application that may contribute to identity theft. Personal information such as social security numbers, bank account numbers, or credit card numbers (other than a check or credit card authorization form PTO-2038 submitted for payment purposes) is never required by the USPTO to support a petition or an application. If this type of personal information is included in documents submitted to the USPTO, petitioners/applicants should consider redacting such personal information from the documents before submitting them to the USPTO. Petitioner/applicant is advised that the record of a patent application is available to the public after publication of the application (unless a non-publication request in compliance with 37 CFR 1.213(a) is made in the application) or issuance of a patent. Furthermore, the record from an abandoned application may also be available to the public if the application is referenced in a published application or an issued patent (see 37 CFR 1.14). Checks and credit card authorization forms PTO-2038 submitted for payment purposes are not retained in the application file and therefore are not publicly available.</p> <p>LEGAL NAME OF INVENTOR</p> <p>Inventor: <u>Rossa Wai Kwun Chiu</u> Date (Optional) : _____</p> <p>Signature: </p> <p>Note: An application data sheet (PTO/SB/14 or equivalent), including naming the entire inventive entity, must accompany this form. Use an additional PTO/AIA/01 form for each additional inventor.</p>	

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**DECLARATION (37 CFR 1.63) FOR UTILITY OR DESIGN APPLICATION USING AN
APPLICATION DATA SHEET (37 CFR 1.76)**

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Title of Invention	DETERMINATION OF BASE MODIFICATIONS OF NUCLEIC ACIDS
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As the below named inventor, I hereby declare that:

This declaration
is directed to: ☐ The attached application, or

☒ United States application or PCT international application number 16/995,607

filed on August 17, 2020

The above-identified application was made or authorized to be made by me.

I believe that I am the original inventor or an original joint inventor of a claimed invention in the application.

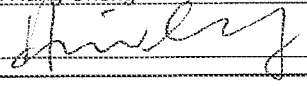
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LEGAL NAME OF INVENTOR

Inventor: Suk Hang Cheng Date (Optional) : _____

Signature: 

Note: An application data sheet (PTO/SB/14 or equivalent), including naming the entire inventive entity, must accompany this form.
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SCORE Placeholder Sheet for IFW Content

Application Number: 17891899

Document Date: 08/19/2022

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Since this was an electronic submission, there is no physical artifact folder, no artifact folder is recorded in PALM, and no paper documents or physical media exist. The TIFF images in the IFW record were created from the original documents that are stored in SCORE.

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