Capstone Two Project: Genotyping SNP classification

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https://github.com/cabruck/DataScienceCapstoneTwo

Overview

In the interest of time, using this document to capture data cleaning steps, rather than implement all in Jupyter Notebook

Two primary input files:

- \git_repositories\DataScienceCapstoneTwo\raw_data\Output_allps.zip\Output_allps\genotype-inliers\filtered\Ps.performance.txt
- \git_repositories\DataScienceCapstoneTwo\raw_data\Output_allps.zip\Output_allps\CC_ignoreNC_probeset_CC.txt

The output file from this procedure:

- \git_repositories\DataScienceCapstoneTwo\data\data_cleaning_step1.zip\data_cleaning_step1.txt

The input “Ps.performance.txt” file contains standard metrics routinely generated by automated SNP quality control. Each row is summary statistics for one SNP (“probeset_id” is the unique identifier). rows can be grouped into different categories of markers:

- standard diploid probesets that measure exactly 2 alleles. This is large majority of observations in dataset.
- multiallelic probesets: measure more than 2 alleles.
- special chromosome probesets: statistics computed only only a subset of samples (only female for X, only male for Y),
- or only measure mitochondrial DNA, which has different probeset properties
- other probesets that can report more than standard 3 genotype calls (haploid and zero copy number calls)

Many of the measured features of the probesets are specific to these special categories of markers, which means that there is high missingness of data in many features that are only computed for some categories of markers. Ther,efore this file needs to be cleaned up.

The input “CC_ignoreNC_probeset_CC.txt” file contains observed accuracy metrics for a subset of probesets for which accuracy can be computed. The surrogate measurements of accuracy are various concordance metrics, of which the primary metric of interest is “CC” (overall concordance or agreement. for the probeset_id vs an independent technology prediction of the genotype calls). This file has some rows where CC is missing, and has other rows where the concordance calculation is based on limited data (“n” samples < 50, out of over 250 possible samples measured). Therefore this input file must also be cleaned.

The “CC” metric is the metric we’re trying to predict with a machine learning model, and so it must be joined with metrics in other table. Therefore, after cleaning both input tables (limited to deleting rows and columns at this time), an inner join is done on both tables.

Some derived columns are also computed to simplify selection of rows to filter, and also as potential new features to be used for modeling.

The processing steps described herein, and resulting visualizations, were performed with the TIBCO Spotfire Analysis desktop application. I haven’t paid extra to manage data in cloud, and to support interactive access of visualizations and filtering by another user.

Steps to clean the Ps.performance.txt file

Strategy of probeset rows to keep: diploid biallelic probesets where metrics computed on all samples.

Filter on these columns to retain these values:

- multiallelic = 0
- gender_metrics = "all" (all samples are used to compute feature values)
- only_diploid_calls = true (derived feature, which excludes remaining non-diploid calling probesets)

only_diploid_calls: true if sum of haploid calls is 0:

```
0 == ((If([n_A] is null,0,[n_A])) + (If([n_B] is null,0,[n_B])) + (If([n_CN0] is null,0,[n_CN0])))
```

keep = ([multiallelic]=0) And [only_diploid_calls] And ([gender_metrics]="all")

Following visualization is row counts grouped by 5 columns, on raw input data. Intent is to retain only rows where keep = True.

Row Count per multiallelic, only_diploid_calls, gender_metrics, specialSNP_chr, keep

(None)

multiallelic	only_diploid_calls	gender_metrics	specialSNP_chr	keep	(Row Count)
0	False	all	autosomal	False	760
			MT	False	8
		male	Y	False	7
	True	all	autosomal	True	836384
		female	X	False	42511
1	True	all	autosomal	False	4368
		diploid	autosomal	False	3
		female	X	False	117
Grand total					884158

5 columns

(Row Count)

Data table:
Ps.performance
Colors:
All values

Derived features for possible later use:

typical signal strength, the weighted average of each cluster's meanY:

meanY = ([n_AA]*[AA.meanY] + [n_AB]*[AB.meanY] + [n_BB]*[BB.meanY])/Sum([n_AA],[n_AB],[n_BB])

... and another computed filter that finds probesets with unusual differences in allele strengths (might indicate susceptibility to making bad calls)

Hom.meanY.delta = Abs([AA.meanY] - [BB.meanY])

Most of the deleted columns named later are deleted either because they always have the same value, or because their values are almost completely Null for retained rows. The values are mostly Null because these metrics are only computed for specific types of probesets that are being deliberately removed.

Notes on miscellaneous columns to toss:

Use “OriginalCT” instead of “ConversionType” since the latter is a function of multiple related rows, unlike former (it includes problematic OtherMA category).

H.W.chisquared.statistic is only computed on probesets where n_AA, n_AB, n_BB all are >=10. Related H.W.p-Value computed for all rows.

Maybe toss MMD (minimum Mahalanobis distance): only computed for probesets with three clusters. Should be correlated to FLD.

Data table 1: Ps.performance

```
1. Select Data > Add data...

    Source: Data loaded from file
```

Type: Text

Location: C:\Users\carsten.bruckner\OneDrive\Documents\Springboard\DataScienceCourse\7 Capstone Two\MVPEF\Output_allps\genotype-inliers\filtered\Ps.performance.txt

Data loaded at: 8/13/2021 5:57 AM

Data was added as a new data table

4. Data > Add calculated column...

Column name: only_diploid_calls

Expression: ((If([n_A] is null,0,[n_A])) + (If([n_B] is null,0,[n_B])) + (If([n_CN0] is null,0,[n_CN0])))=0

2. Data > Add calculated column...

Column name: keep

Expression: ([multiallelic]=0) And [only_diploid_calls] And ([gender_metrics]="all")

3. Data > Add calculated column...

Column name: same conversion type

Expression: [ConversionType]=[OriginalCT]

Data table 2: Ps.performance.trimmed

1. Select Data > Add data...

Source: Data table from current analysis

Data table: Ps.performance

Update behavior: Automatic

Added transformations

Transformation name: Filter rows

Expression: [keep]=TRUE

Transformation name: Exclude columns

Excluded columns:

HomFLD_hap

HomRO_hap

n_A

n_B

n_CN0

hemizygous

ConversionType

BestProbeset

BestandRecommended

A.meanX

A.meanY

B.meanX

B.meanY

CN0.meanX

CN0.meanY

count_ma_A

count_ma_B

count_ma_C

count_ma_D

count_ma_E

count_ma_F

FLD_MA

MinFLD_MA

HomFLD_MA

HetSO_MA

HomRO_MA

same conversion type

nSamples

nCalls

nAllelesTested

nAllelesDetected

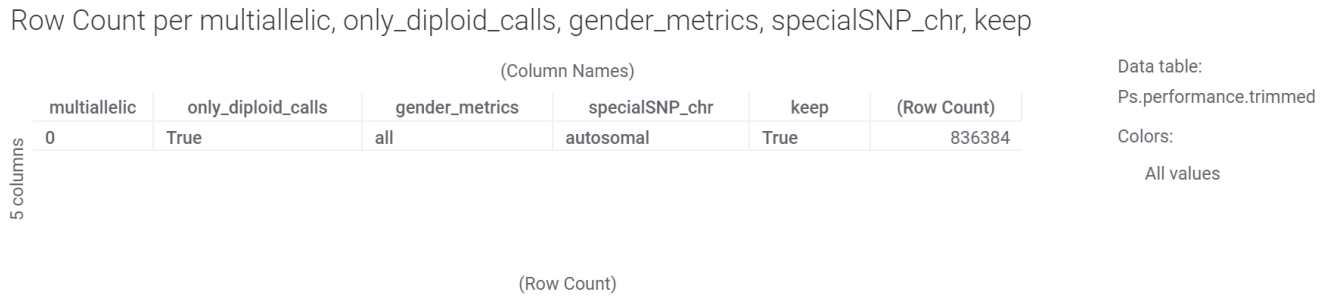
NHetClus

nMajorAlleles

```
            nMinorAlleles
            MAFall
            MAFmax
            HomCount
            MajorHomCount
            MinorHomCount
            HetCount
            HomMMA
            NC.meanX
            NC.meanY
            maxMinorAllele
            H.W.chisquared.statistic
            affy_snp_id
            multi_snp_id
            CopyNumIssue

    Data loaded at: 8/16/2021 11:59 AM
    Data was added as a new data table
2. Data > Add calculated column...
    Column name: meanY
    Expression: (([n_AA] * [AA.meanY]) + ([n_AB] * [AB.meanY]) + ([n_BB]
* [BB.meanY])) / Sum([n_AA],[n_AB],[n_BB])
3. Data > Add calculated column...
    Column name: Hom.meanY.delta
    Expression: Abs([AA.meanY] - [BB.meanY])
```

After this filtering step to create new Ps.performance.trimmed data table, repeat the previous visualization on new data table:



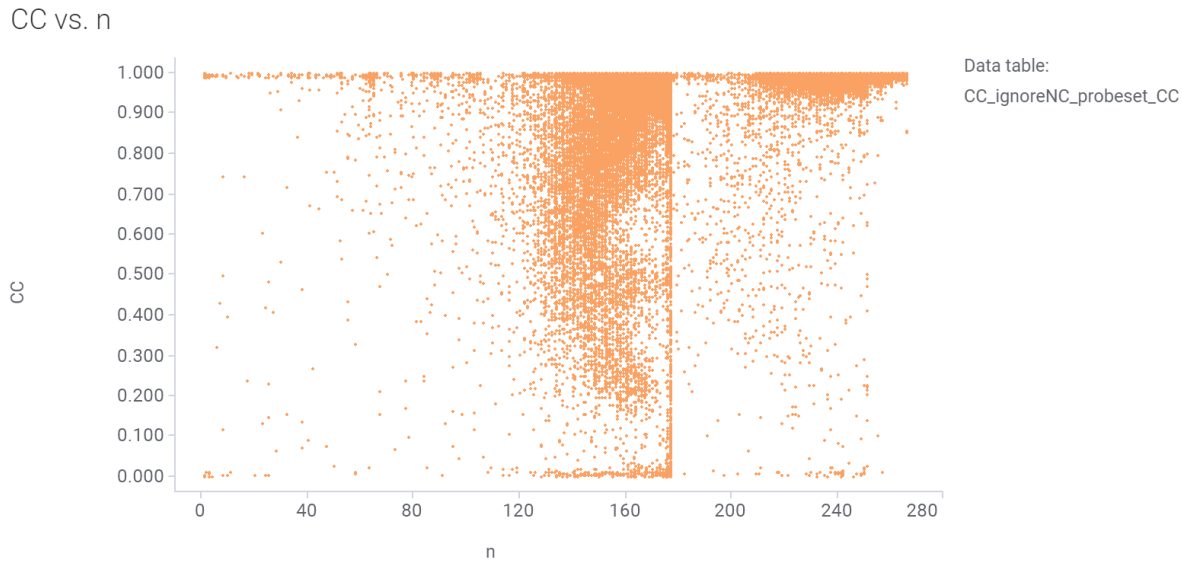
Starting table has 884158 rows, trimmed table has 836384 rows, so we retained about 95% of rows. Starting table has 86 imported columns, trimmed table has 43 columns (4 of which were derived).

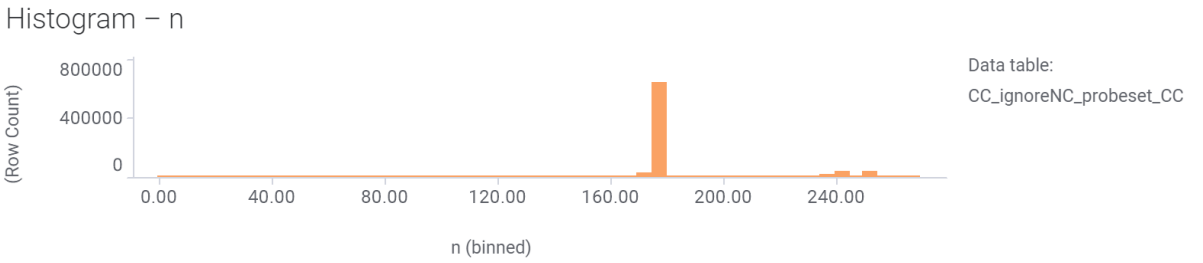
Steps to clean the CC_ignoreNC_probeset_CC.txt file

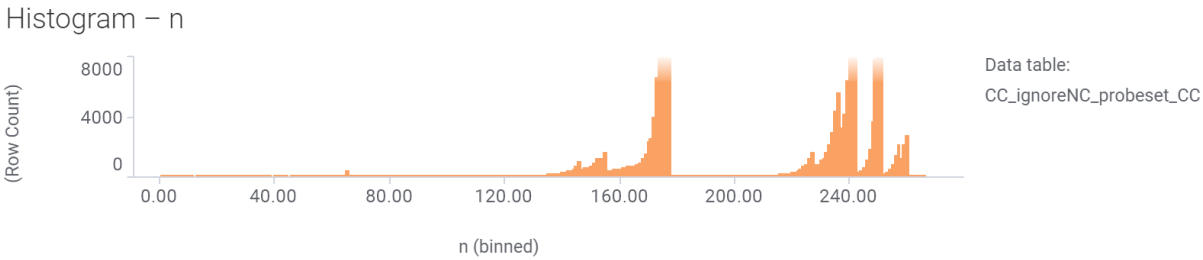
Other input file is observed Concordance (CC). This is the feature we're trying to predict by modeling of other features

Source file: CC_ignoreNC_probeset_CC.txt

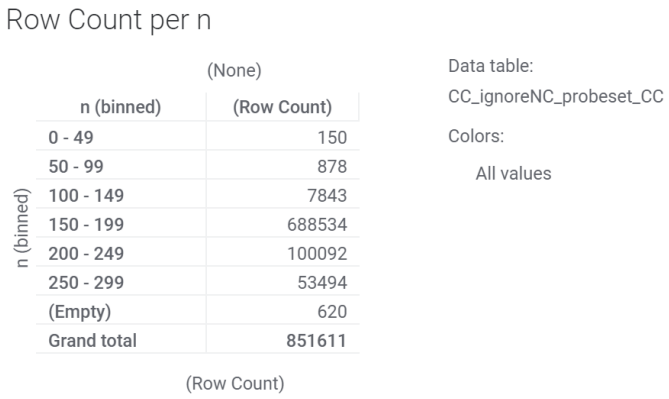
Concordance is computed over n samples (CC = 1 is best, 100% agreement with reference data). The larger the n, the more reliable the concordance calculation as a predictor of probeset performance. Here's a scatterplot of CC vs n, followed by a histogram of count of n, and a zoomed-in histogram:







Most CC measurements are computed over more than 160 samples (n > 160). Let's remove the small fraction of probesets where the CC predictor is less reliable (n<50, 150 probesets), or not even available (620 probesets):



Data cleaning: some CC values are empty. Exclude these probeset rows.

Some probesets (150) have <50 samples used to measure concordance, so these CC values are not as reliable. Exclude these probeset rows.

Actually, both row filtering steps can be accomodated by single filter: keep rows where n >= 50. Empty CC rows are also empty n rows, and are removed.

Data Table 3: Predictor features from different table:

“CC_ignoreNC_probeset_CC”:

1. Select Data > Add data...

    Source: Data loaded from file

    Type: Text

    Location: C:\Users\carsten.bruckner\OneDrive\Documents\Springboard\DataScienceCourse\7 Capstone Two\MVPEF\Output_allps\CC_ignoreNC_probeset_CC.txt

    Data loaded at: 8/16/2021 10:04 AM

    Data was added as a new data table

2. Data > Add calculated column...

    Column name: CC Binned

    Expression: BinBySpecificLimits([CC],0.899,0.949,0.959,0.969,0.979,0.989,1)

Data Table 4: filtered predictor features

"CC_ignoreNC_probeset_CC.trimmed"

1. Select Data > Add data...

    Source: Data table from current analysis

    Data table: CC_ignoreNC_probeset_CC

    Update behavior: Automatic

    Added transformations

        Transformation name: Change column names

        Columns to rename:

            n

            n_het

        Expression: [%C]&"_CC"

        Transformation name: Filter rows

        Expression: [n_CC]>=50

        Transformation name: Exclude columns

        Excluded columns:

```
        CC_major_hom
        CC_minor_hom
        n_major_hom
        n_minor_hom
        MAC
        n_refmaj_maj
        n_refmaj_het
        n_refmaj_min
        n_refmaj_nc
        n_refhet_maj
        n_refhet_het
        n_refhet_min
        n_refhet_nc
        n_refmin_maj
        n_refmin_het
        n_refmin_min
        n_refmin_nc
        minor_allele

Data loaded at: 8/16/2021 11:44 AM
Data was added as a new data table
```

The following table shows row counts by “n” bin (renamed to n_CC) after keeping only rows where n has a value and is at least 50. Compare to previous graphic.

Row Count per n_CC

(None)

n_CC (binned)	(Row Count)
50 - 99	878
100 - 149	7843
150 - 199	688534
200 - 249	100092
250 - 299	53494
Grand total	850841

n_CC (binned)

(Row Count)

Data table:
CC_ignoreNC_probeset_CC.trimmed

Colors:
All values

There are now 850841 rows, vs 851611 rows in original CC file, retaining almost all rows. The named columns that are excluded in trimmed table are detail metrics useful for understanding the kinds of discordances, and will not be used here. Screenshot of retained columns, some of which might be used later:

CC_ignoreNC_probeset_CC.trimmed

probeset_id	CC	n_CC	CC_het	n_het_CC	CC Binned
AX-100003653	0.996	248	1.000	56	0.989 < x ≤ 1.000
AX-100004573	0.953	172	0.000	1	0.949 < x ≤ 0.959
AX-100004941	1.000	177			0.989 < x ≤ 1.000
AX-100006840	0.975	244	0.793	29	0.969 < x ≤ 0.979
AX-100007392	0.996	240	1.000	21	0.989 < x ≤ 1.000
AX-100007701	0.963	241	0.989	94	0.959 < x ≤ 0.969
AX-100008742	0.989	177	0.000	2	0.979 < x ≤ 0.989
AX-100009026	1.000	177			0.989 < x ≤ 1.000
AX-100009110	1.000	177			0.989 < x ≤ 1.000
AX-100010733	1.000	177			0.989 < x ≤ 1.000
AX-101003880	0.990	101	0.800	5	0.989 < x ≤ 1.000

Notes for downstream feature engineering:

- As a predicted feature, due to skew in CC, maybe convert CC to two or three categorical bins, like:
    - if binary categories
        - "Suspect" = "no" if CC >=99
        - Suspect" = "yes" if not "no"
    - If ternary:
        - "Suspect" = "no" if CC=100
        - "Suspect" ="maybe" if not "no" and CC >=99
        - "Suspect" ="yes" if not "no" and not "maybe"

Join files, and remove bookkeeping columns

Data Table 5: inner join of independent and predictor features from both .trimmed tables

"inner_join"

```
1. Select Data > Add data...
    Source: Data table from current analysis
    Data table: CC_ignoreNC_probeset_CC.trimmed
    Update behavior: Automatic
    Data loaded at: 8/16/2021 11:48 AM
    Data was added as a new data table
2. Select Data > Add data...
    Source: Data table from current analysis
    Data table: Ps.performance.trimmed
    Update behavior: Automatic
    Data loaded at: 8/16/2021 11:59 AM
    Data was added as new columns in data table 'inner_join'
    Matching behavior: Tries to match the specified columns when data is
loaded
    Matched columns: probeset_id – probeset_id
    Added columns:
        CR
        FLD
        HomFLD
        HetSO
        HomRO
        nMinorAllele
        Nclus
        n_AA
        n_AB
        n_BB
```

n_NC

specialSNP_chr

gender_metrics

HomHet

AA.meanX

AA.meanY

AA.varX

AA.varY

AB.meanX

AB.meanY

AB.varX

AB.varY

BB.meanX

BB.meanY

BB.varX

BB.varY

AA.varX.Z

AA.varY.Z

AB.varX.Z

AB.varY.Z

BB.varX.Z

BB.varY.Z

MMD

MinorAlleleFrequency

H.W.p-Value

multiallelic

OriginalCT

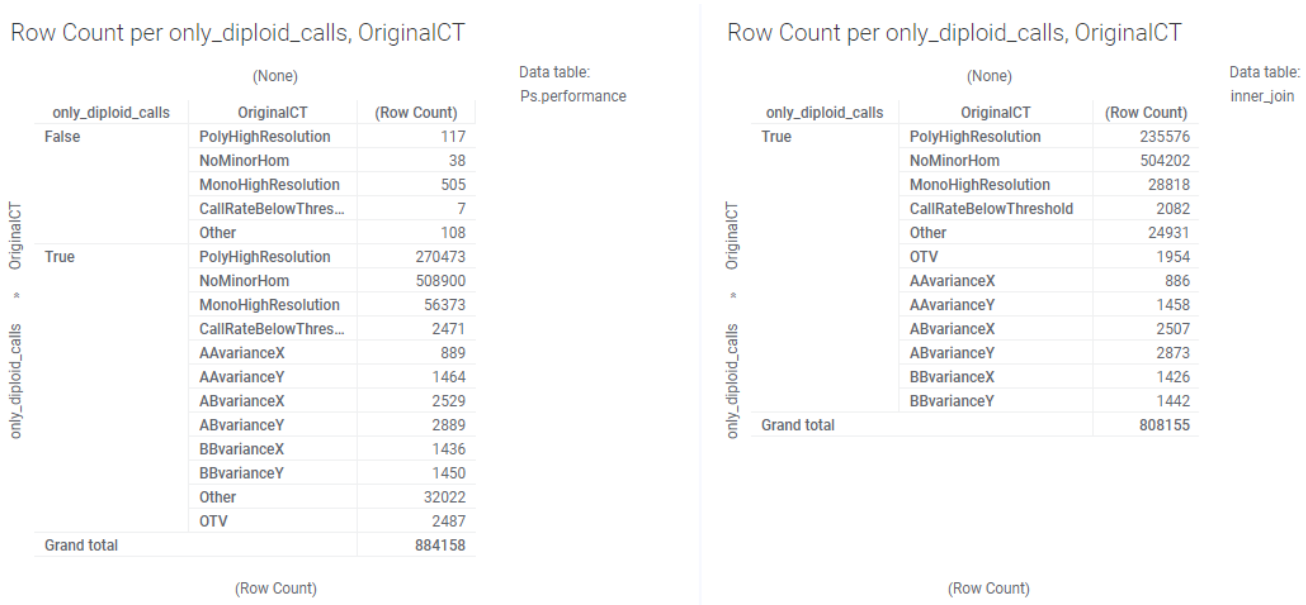
ordered_alleles

keep

only_diploid_calls

```
    meanY
    Hom.meanY.delta
Ignored columns: (None)
Join method: Inner join
Treat empty values as equal: No
```

The following visualization counts the probesets in original Ps.performance.txt and in final joined file, grouped by whether diploid probeset and automate Original Conversion Type (OriginalCT). Roughly 90% of original rows are still available for modeling. Some probesets in Ps.performance_filtered table were not available in CC table, so inner join removed them:



Row Count per only_diploid_calls, OriginalCT

(None)

Data table: Ps.performance

only_diploid_calls	OriginalCT	(Row Count)
False	PolyHighResolution	117
	NoMinorHom	38
	MonoHighResolution	505
	CallRateBelowThres...	7
	Other	108
True	PolyHighResolution	270473
	NoMinorHom	508900
	MonoHighResolution	56373
	CallRateBelowThres...	2471
	AAvarianceX	889
	AAvarianceY	1464
	ABvarianceX	2529
	ABvarianceY	2889
	BBvarianceX	1436
	BBvarianceY	1450
	Other	32022
	OTV	2487
Grand total		884158

OriginalCT * only_diploid_calls

(Row Count)

Row Count per only_diploid_calls, OriginalCT

(None)

Data table: inner_join

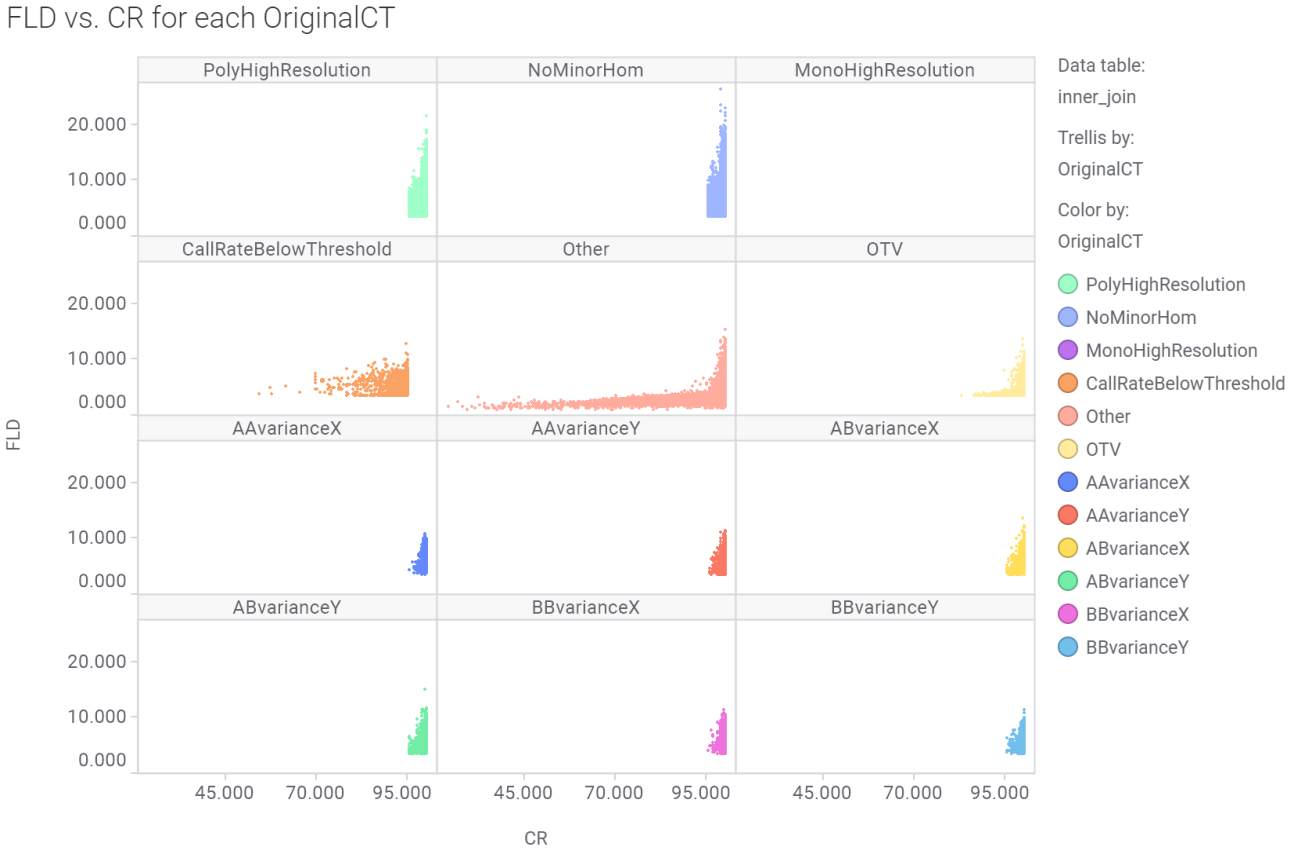
only_diploid_calls	OriginalCT	(Row Count)
True	PolyHighResolution	235576
	NoMinorHom	504202
	MonoHighResolution	28818
	CallRateBelowThreshold	2082
	Other	24931
	OTV	1954
	AAvarianceX	886
	AAvarianceY	1458
	ABvarianceX	2507
	ABvarianceY	2873
	BBvarianceX	1426
	BBvarianceY	1442
Grand total		808155

OriginalCT * only_diploid_calls

(Row Count)

“OriginalCT” is an automated categorization into recommended vs non-recommended probesets for end users to use in downstream steps. The only categories recommended for downstream use are “PolyHighResolution”, “NoMinorHom”, and “MonoHighResolution”. These category assignments have no knowledge of predicted concordance to another technology. As a reminder, the goal of this project is to see whether we can develop a model that predicts “good vs bad” concordance better than purely binning by “recommended vs non-recommended” categories.

The following visualization highlights the sparseness in the remaining table. Two valuable features that predict performance are Call Rate (CR, the % of samples returning a genotype call), and FLD (Fisher’s Linear Discriminant, a measure of cluster separation, which makes it easier to make a clear call).



The FLD metric is not computed for MonoHighResolution markers, which is why that pane of the trellis plot is empty. The various “variance” conversion types are only computed for probeset rows where CR >=95%. Apparently this supplemental computation is only performed on markers that might otherwise pass QC (appear in top three panes), and flags additional probesets into one of these 6 non-recommended conversion types.

Low FLD probesets are likely to have reduced call rate and lower calling accuracy.

Because some of the columns in inner_join table are used only for some visualizations and QC of filtering operations, the following are excluded from export to cleaned data file:

CC Binned

specialSNP_chr

gender_metrics

multiallelic

keep

only_diploid_calls

Summary stastics for table at end of this procedure

Columns with Count <808155 are sparse.

Column	Count	UniqueCount	Min	Median	Avg	Max	StdDev
probeset_id	808155	808155	AX-100003653			AX-98295645	
CC	808155	5563	0	1	0.993	1	0.054
CC_het	764300	1175	0	1	0.977	1	0.13
n_CC	808155	217	50	177	187.79	266	26.95
n_het_CC	764300	149	1	6	16.14	152	24.71
CR	808155	186	23.913	100	99.431	100	2.229
FLD	777314	86758	1.072	6.782	6.861	26.374	1.583
HomFLD	258881	109465	2.546	14.656	14.895	45.06	3.25
HetSO	777343	16299	-2.496	0.325	0.318	2.402	0.192
HomRO	808126	43673	-2.344	1.933	1.976	6.401	0.687
nMinorAllele	808155	277	0	9	29.17	276	49.62
Nclus	808155	3	1	2	2.28	3	0.53
n_AA	808155	277	0	2	99.72	276	122.08
n_AB	808155	251	0	9	21.85	276	30.34
n_BB	808155	277	0	237	152.86	276	124.66
n_NC	808155	186	0	0	1.57	210	6.15
HomHet	808155	2	0	1	0.64	1	0.48
AA.meanX	808155	42299	-2.635	2.389	2.394	6.54	0.614
AA.meanY	808155	37484	7.246	10.142	10.16	14.395	0.598
AA.varX	808155	6381	0.03	0.03	0.165	1.026	0.155
AA.varY	808155	4565	0.03	0.03	0.115	1.401	0.099
AB.meanX	808155	31431	-4.045	0.33	0.302	4.651	0.425
AB.meanY	808155	39838	7.469	10.501	10.486	14.641	0.594
AB.varX	808155	6242	0.03	0.157	0.152	1.01	0.108
AB.varY	808155	6152	0.03	0.134	0.134	1.748	0.097
BB.meanX	808155	41427	-8.06	-1.793	-1.84	2.344	0.625
BB.meanY	808155	40363	7.27	10.142	10.146	14.002	0.677
BB.varX	808155	5770	0.03	0.26	0.211	1.199	0.14
BB.varY	808155	5153	0.03	0.191	0.166	1.054	0.11
AA.varX.Z	246168	5782	-3.263	-0.716	-1.129	7.998	1.751
AA.varY.Z	246168	4131	-2.971	-0.721	-1.029	20.298	1.629
AB.varX.Z	246168	4763	-2.667	-0.199	-0.079	11.958	1.083
AB.varY.Z	246168	4654	-2.333	-0.209	-0.069	15.347	1.061
BB.varX.Z	246168	5151	-3.868	-0.467	-0.969	9.866	1.887
BB.varY.Z	246168	4550	-3.036	-0.504	-0.761	11.694	1.575
MMD	258516	179352	7.642	43.869	44.214	129.087	9.141
MinorAlleleFrequency	808155	4216	0	0.017	0.053	0.5	0.091

Column	Count	UniqueCount	Min	Median	Avg	Max	StdDev
H.W.p-Value	808155	34370	0	1	0.764204547	1	0.37719077
OriginalCT	808155	12	PolyHighResolution			BBvarianceY	
ordered_alleles	808155	855	-/A			T/TCTT	
meanY	808155	779856	7.246	10.134	10.147	14.384	0.69
Hom.meanY.delta	808155	19601	0	0.183	0.216	4.389	0.174

Known issues:

If n_AA = 0, might need to reset all AA.* metrics to Null, and same idea with n_AB=0, n_BB=0. The AA.* metrics currently report default values if there are no observations of AA cluster in dataset.