Inferring Ancestry in Admixed Populations using Microarray Probe Intensities

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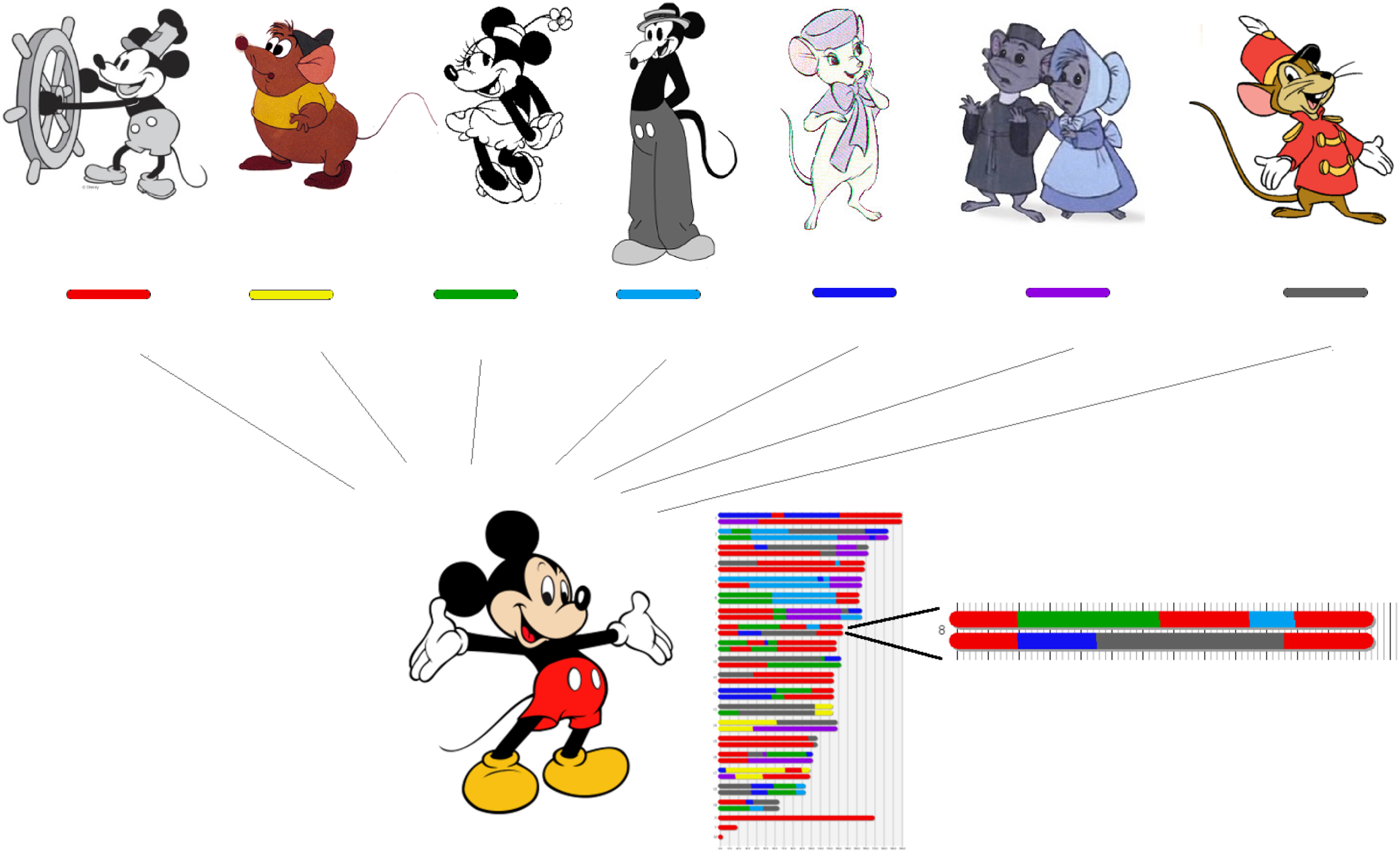
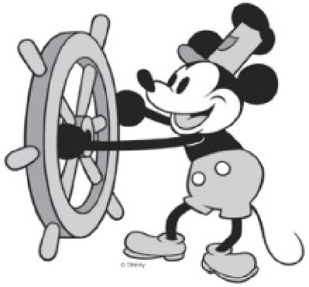
Ancestry Inference

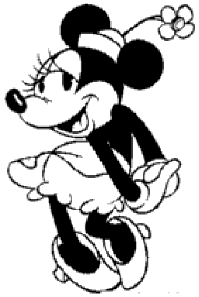


Existing Methods: Ancestry Inference w/ Biallelic SNPs



0000000000

0101010101



1010101010

0011001100

1100110011

0001110001

1111111111

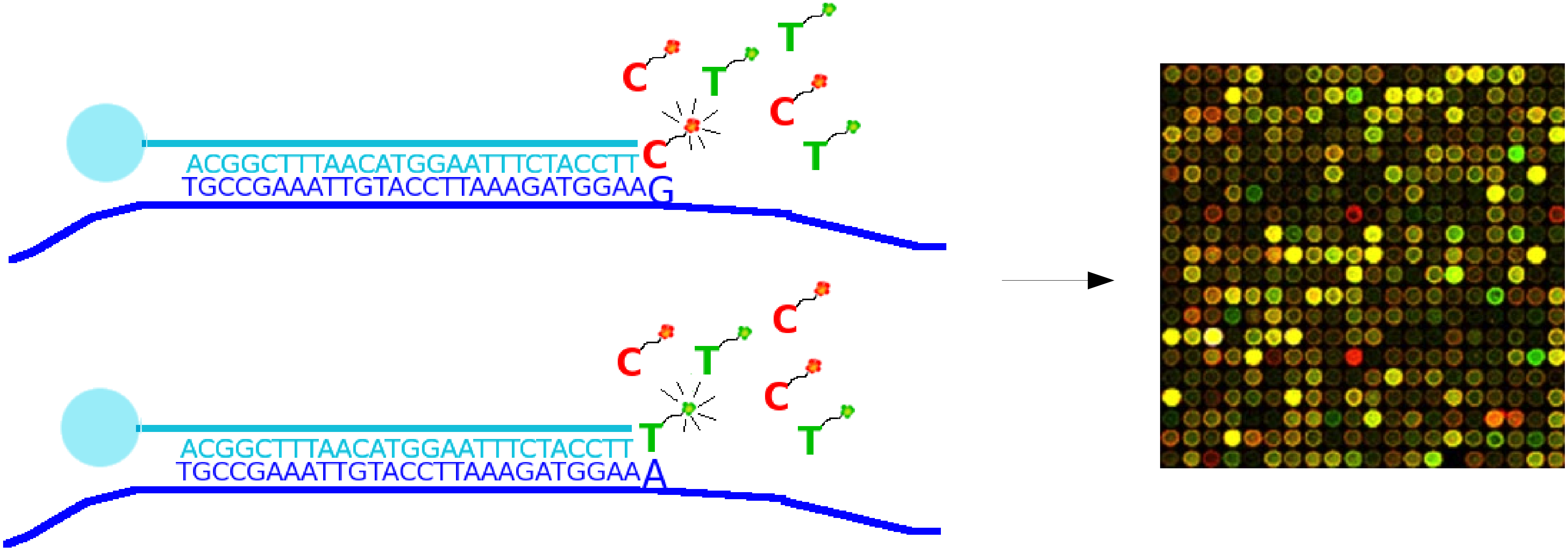
0001112200

↓

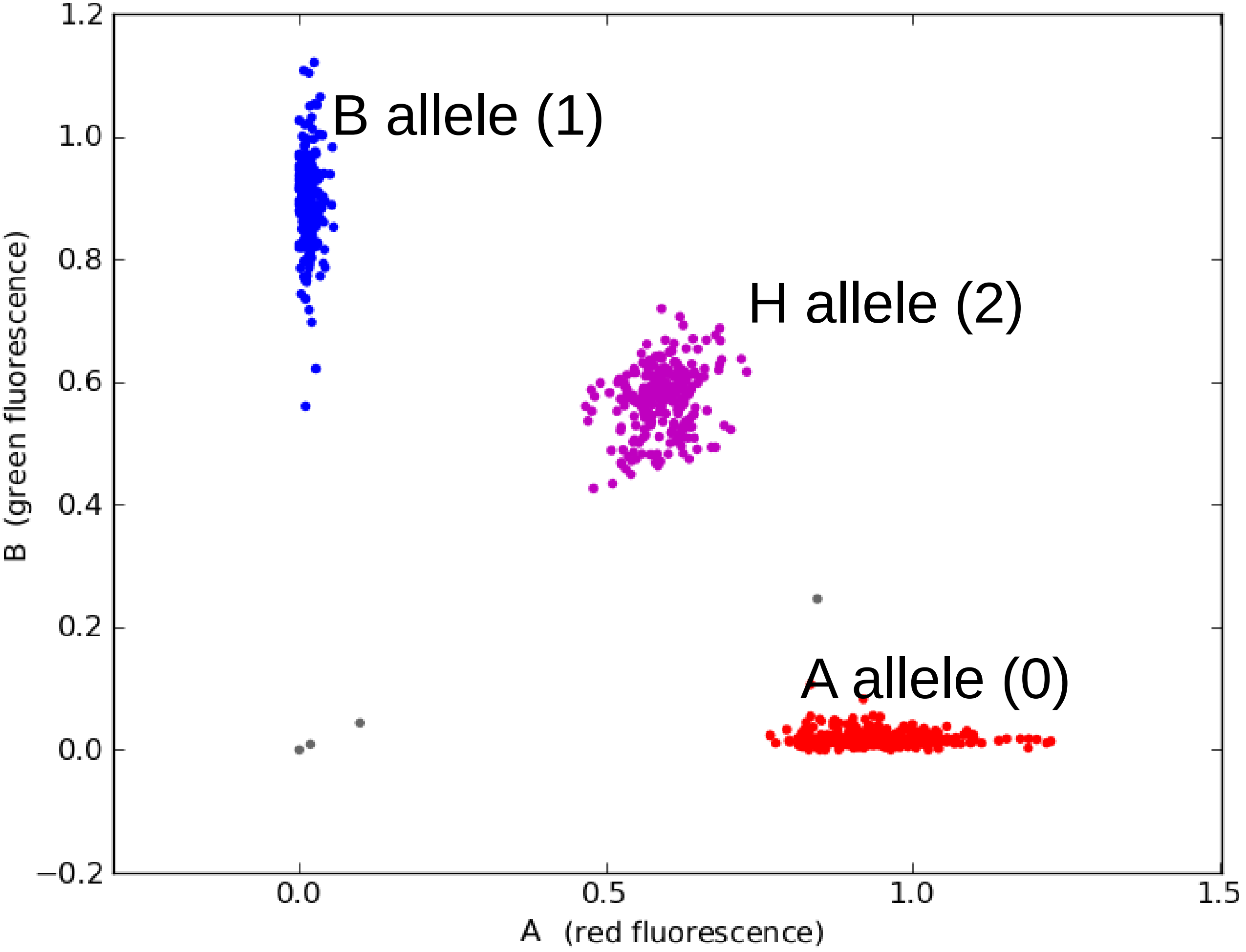
0001111100

0001110000

Biallelic SNPs from Genotyping Arrays


C
T
T
C
T
ACGGCTTTAACATGGAATTTCTACCTT C
TGCCGAAATTGTACCTTAAAGATGGAA G
C
C
T
C
T
ACGGCTTTAACATGGAATTTCTACCTT T
TGCCGAAATTGTACCTTAAAGATGGAA A

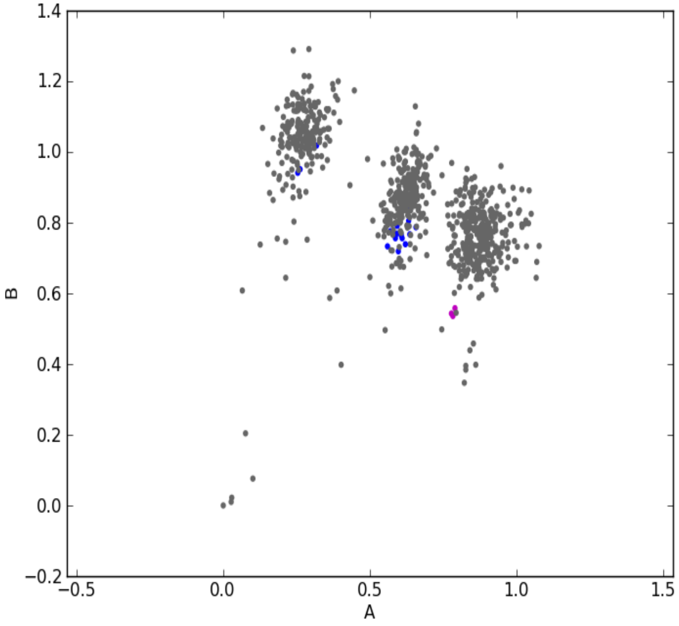
Converting Fluorescence into Genotype Calls



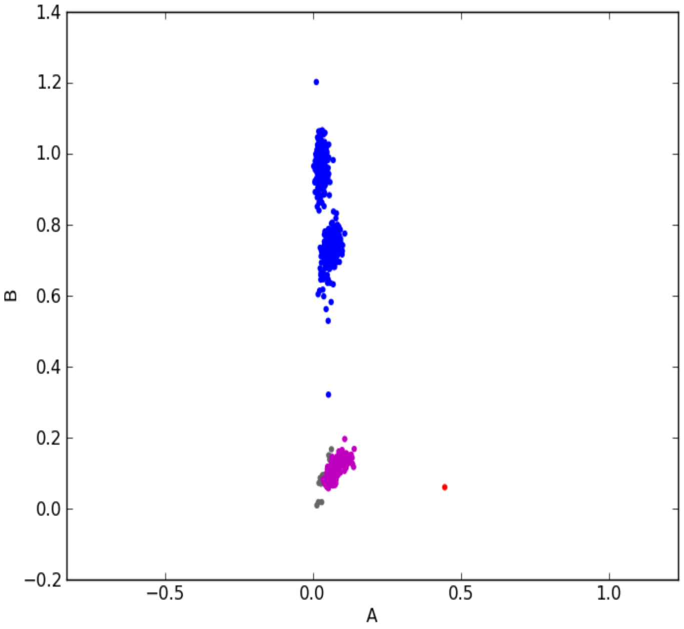
A B H N

Problems with Genotype-based Ancestry Inference

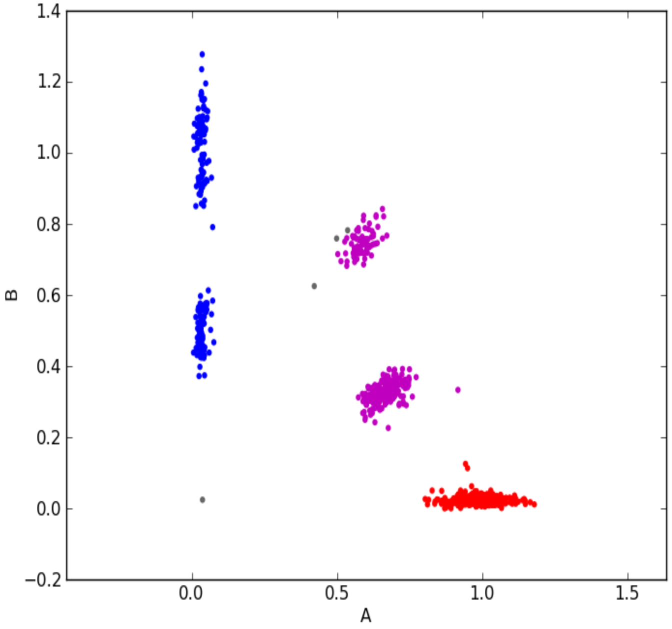
N calls → marker discarded from analysis



Erroneous calls → wrong ancestry inference



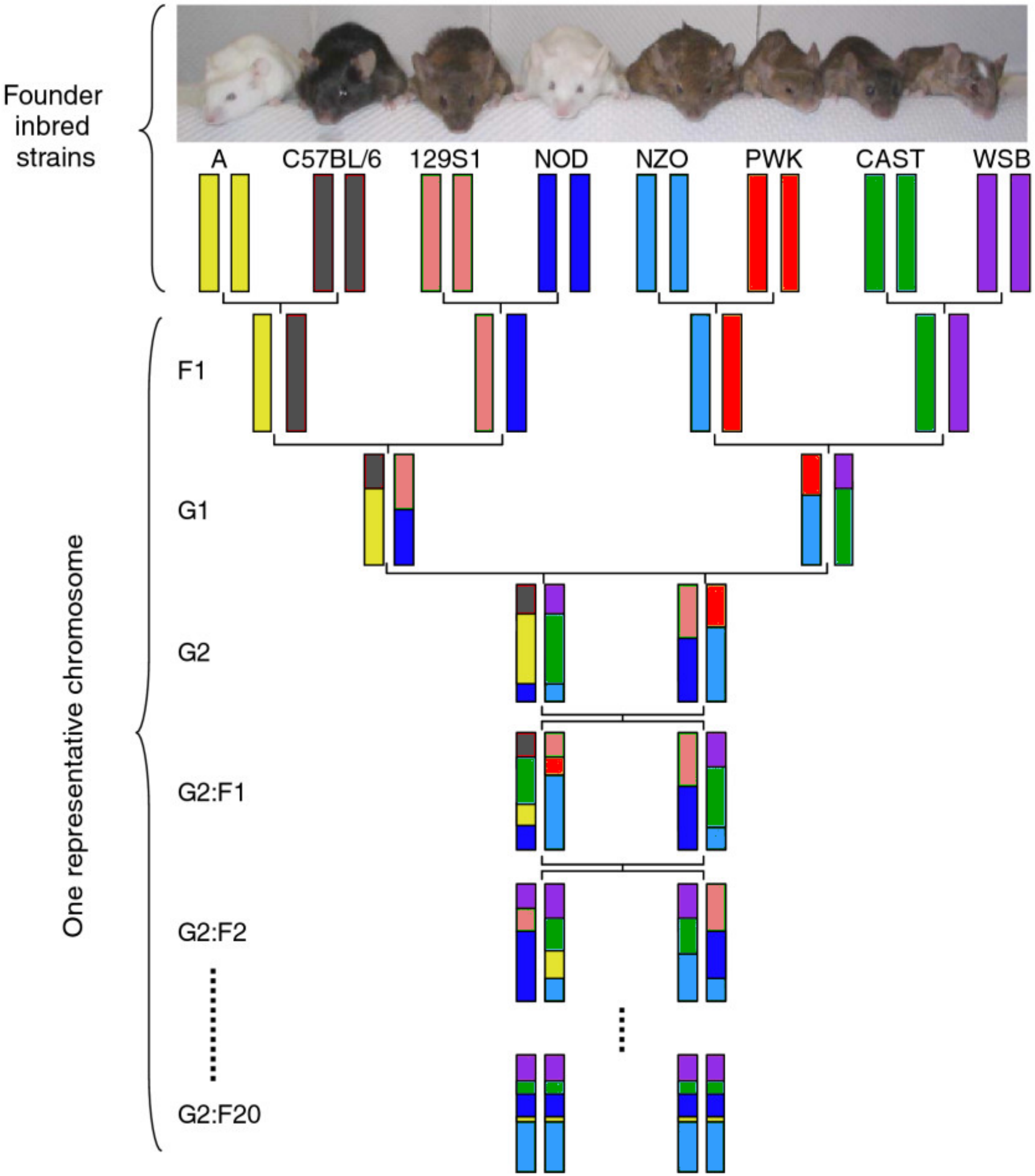
Unexpected variation → unexploited useful information



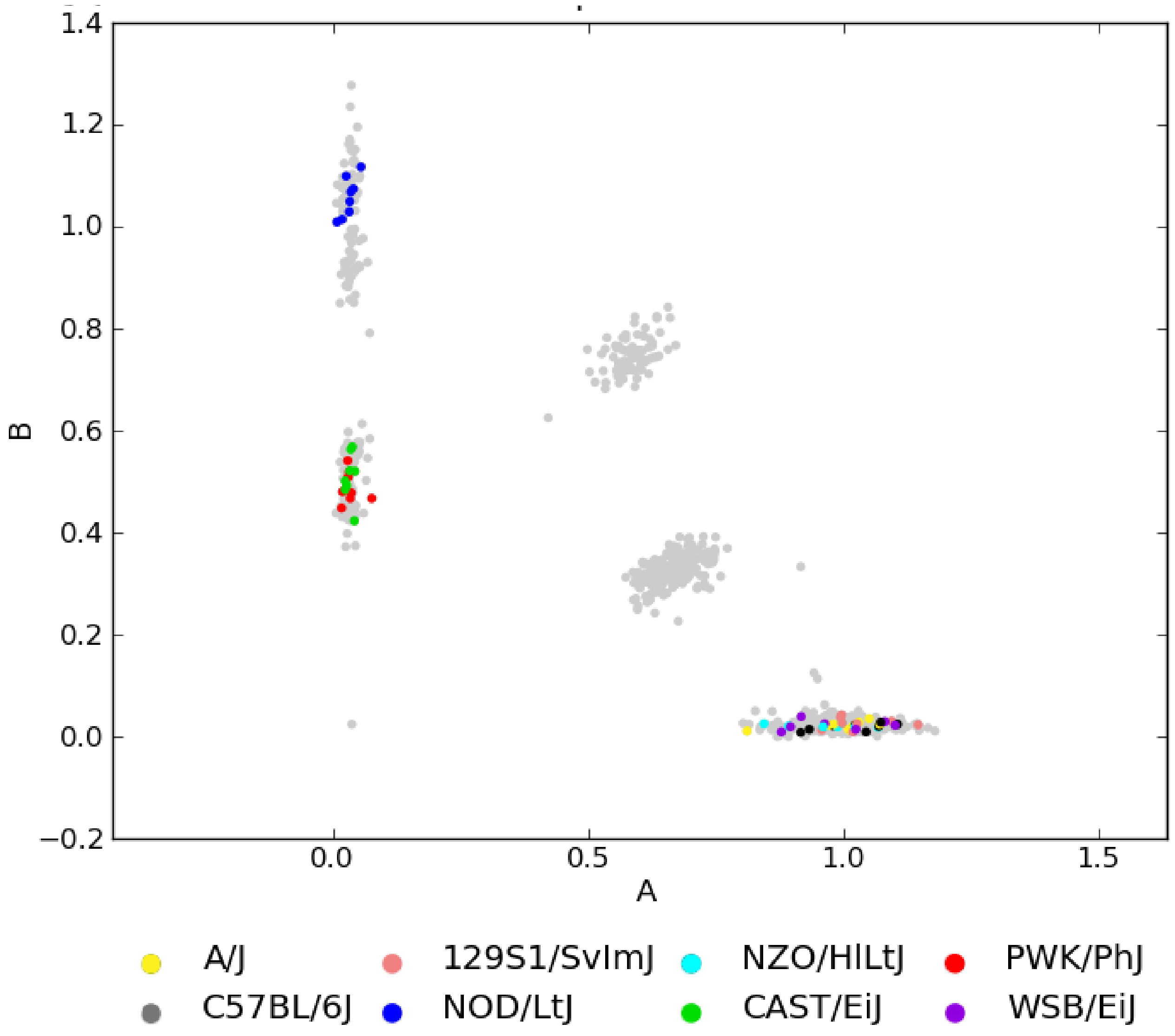
A B H N

Our Data

- Samples are from the Collaborative Cross (CC)
  - 8 inbred founders
  - Various stages of inbreeding
- Genotyped on the Mouse Universal Genotyping Array (MUGA)
  - 7,854 markers
  - Illumina Infinium platform
  - Designed to discriminate between CC founders

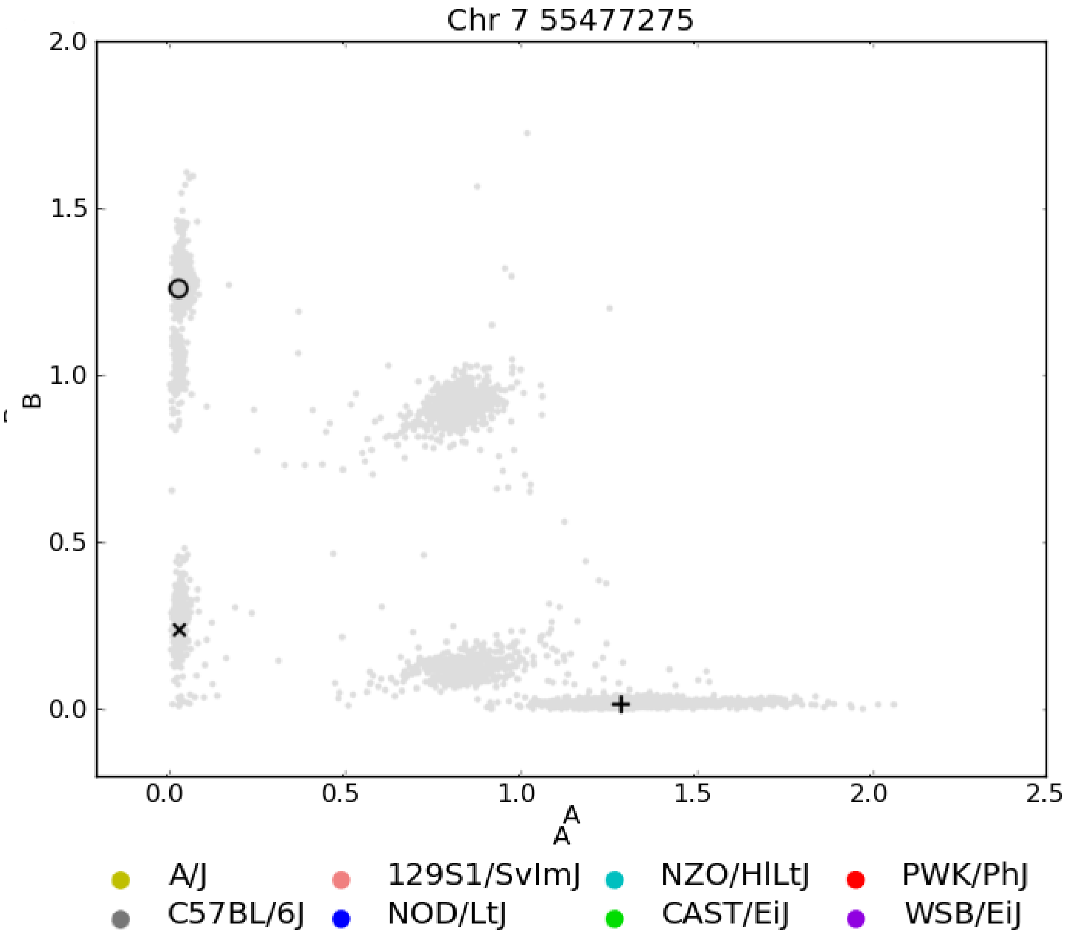


Our approach – use Intensities, not Genotypes



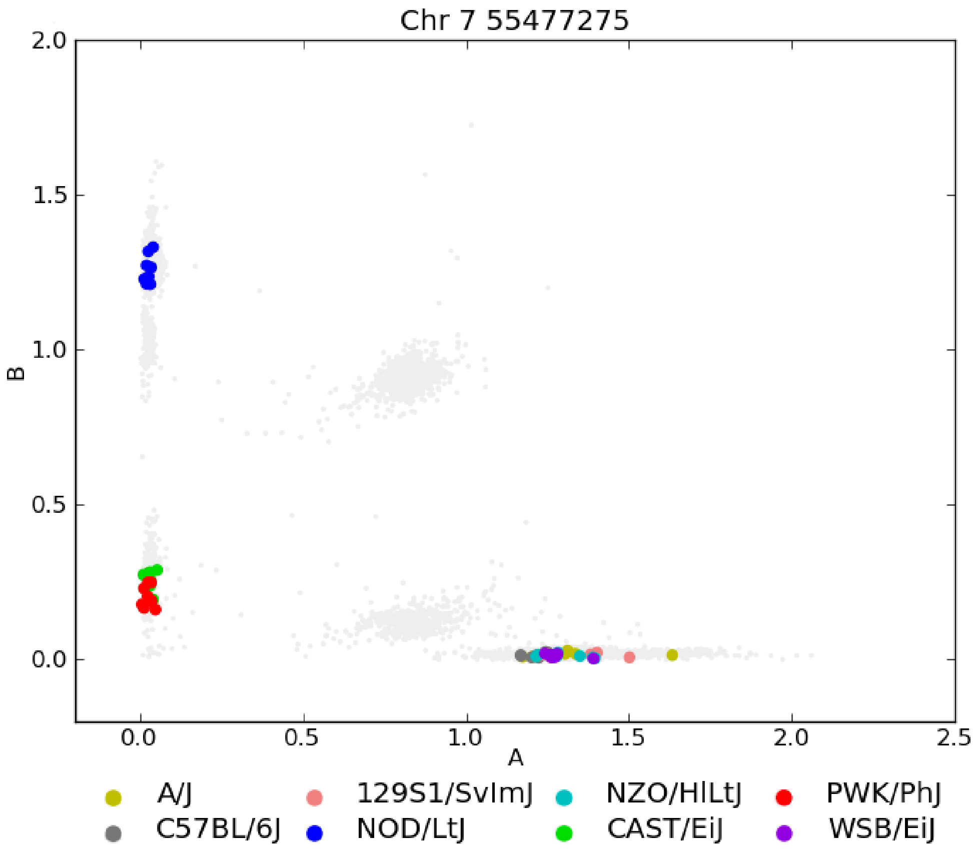
Cluster Similar Strains

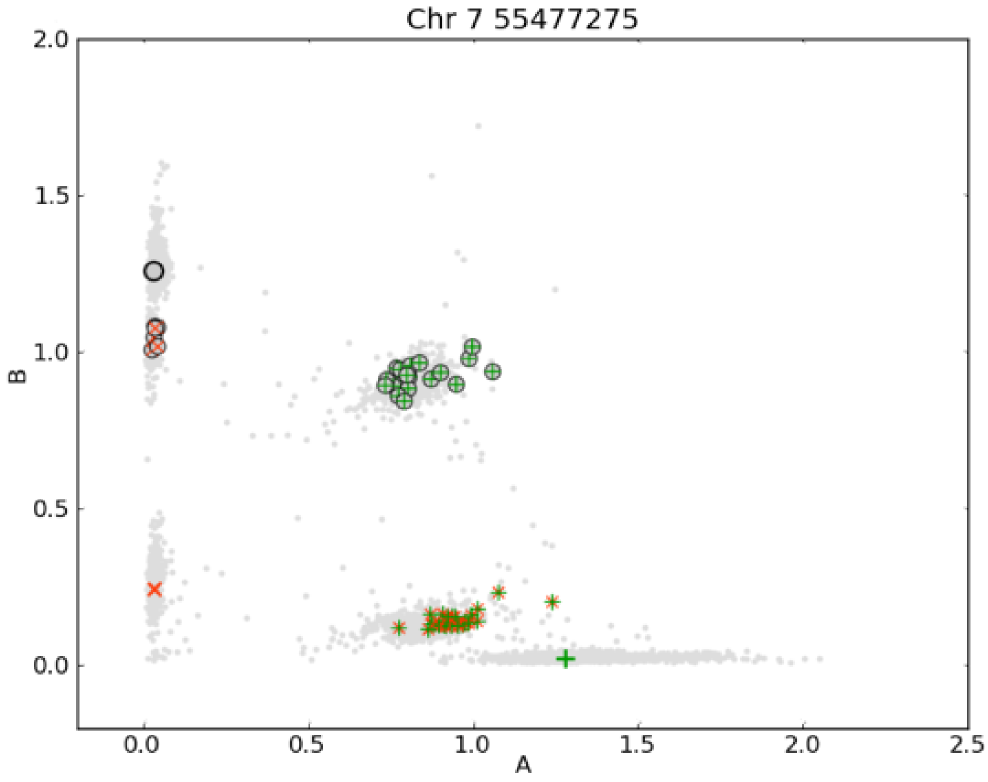
- 8-9 replicates of each inbred founder
  - All replicates of the same founder cluster together
- pool together founders that fall in the same cluster
  - Determined by Hotelling's T-squared test with $p \leq 0.001$
- Store cluster means and covariances as homozygous clusters for each SNP



Create Heterozygous Clusters

- Only have 2-4 samples for each of the ${}_8C_2$ = 28 possible F1 combinations
- Pool together F1s of all founders between pairs of homozygous clusters
- Store cluster means and covariances as heterozygous clusters for each SNP





Problem Statement

- Given:

m possible inbred ancestors generating m' ancestry states per marker, where $m' = m + {}_mC_2$. Call this state space F.

array with n markers arranged in genomic order

target strain's 2D intensities $x_1 \ldots x_i \ldots x_n$ for every marker, where x_i is the 2D intensity at marker i

cluster means and covariances for each state in F at every marker

Note: $m' \geq$ number of clusters at each marker (different ancestors may fall within the same cluster)

- Find:

sequence of most likely ancestry states $\{f_1, f_2 \ldots f_i \ldots f_n\}$ at every marker, where f is one of m' states in F

Distance Model

- Find the set of ancestor intensities closest to the target sample's intensities across the genome, without excessive transition between ancestor states

- At each marker. use Mahalanobis Distance

  $$D_M(x) = \sqrt{(x-\mu)^T S^{-1} (x-\mu)}$$

  as distance measure from the target intensity *x* to each ancestor cluster with mean μ and covariance *S*

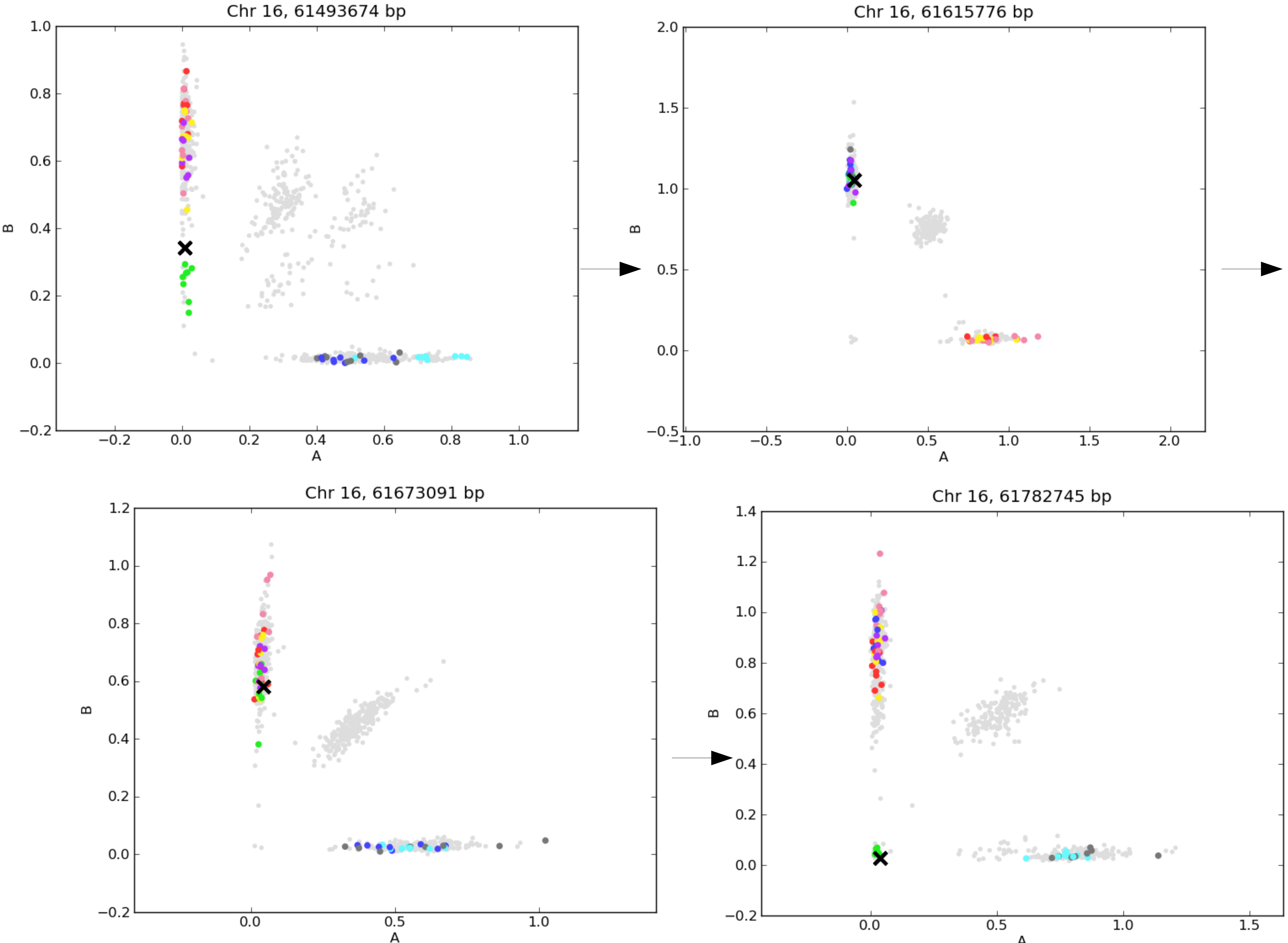
- Over each chromosome, choose $\{f_1, f_2 \ldots f_i \ldots f_n\}$, $f \in F$ so that

  $$D_M(x_1, cluster(f_1, 1)) + \sum_{i=2}^{n} D_M(x_i, cluster(f_i, i)) + penalty(f_{i-1}, f_i)$$

  is minimized,

  where $D_M(x_i, cluster(f_i, i))$ is distance from the target's intensity to state *f*$_i$'s intensity cluster at marker *i,*

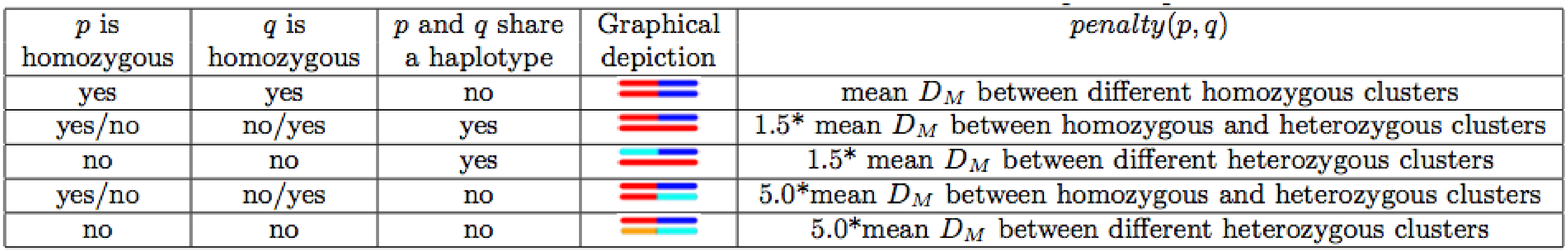
  and $penalty(f_{i-1}, f_i)$ is the transition penalty between the ancestry states at markers *i* and *i-1*


Chr 16, 61493674 bp
B
A
1.0
0.8
0.6
0.4
0.2
0.0
−0.2
−0.2
0.0
0.2
0.4
0.6
0.8
1.0
Chr 16, 61615776 bp
B
A
2.0
1.5
1.0
0.5
0.0
−0.5
−1.0
−0.5
0.0
0.5
1.0
1.5
2.0
Chr 16, 61673091 bp
B
A
1.2
1.0
0.8
0.6
0.4
0.2
0.0
−0.2
0.0
0.5
1.0
Chr 16, 61782745 bp
B
A
1.4
1.2
1.0
0.8
0.6
0.4
0.2
0.0
−0.2
0.0
0.5
1.0
1.5

Dynamic Programming Recurrence

$$\begin{aligned} dist_{f_i=p,f_{i+1}=q} =& D_M(x_{i+1}, cluster(q, i+1)) + penalty(p,q) \\ &+ min\{dist_{f_0=r,f_i=p} | \forall r \in F\}, \quad p, q \in F \end{aligned}$$

Transition penalties given by the following table:



p is homozygous	q is homozygous	p and q share a haplotype	Graphical depiction	$penalty(p,q)$
yes	yes	no		mean D_M between different homozygous clusters
yes/no	no/yes	yes		1.5* mean D_M between homozygous and heterozygous clusters
no	no	yes		1.5* mean D_M between different heterozygous clusters
yes/no	no/yes	no		5.0*mean D_M between homozygous and heterozygous clusters
no	no	no		5.0*mean D_M between different heterozygous clusters

Results

- We chose to compare with GAIN, a genotype-based inference algorithm designed for the CC
  - We had 6,750 informative markers (GAIN had 5,782)
  - 5,550 markers with 2 homozygous clusters, 1,200 markers with 3 or more homozygous clusters
  - 2.21 homozygous clusters/marker (genotype calls provide 2 – A, B)
  - 3.66 total clusters/marker (genotype calls provide 3 – A, B, H)

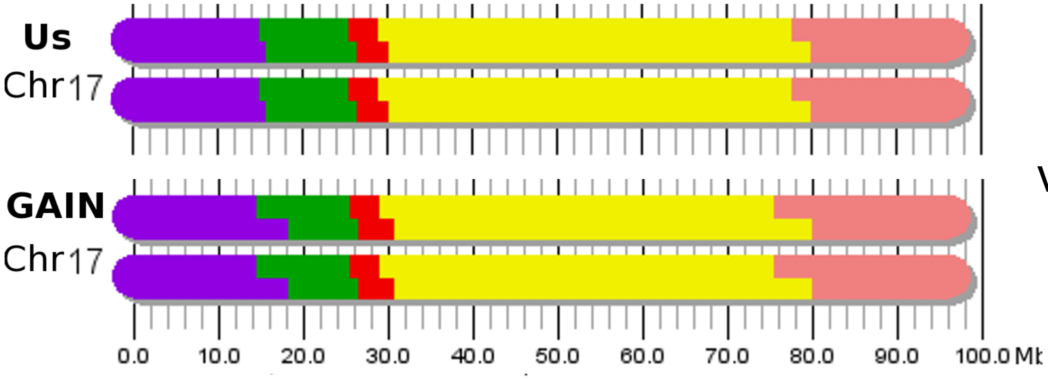
Results

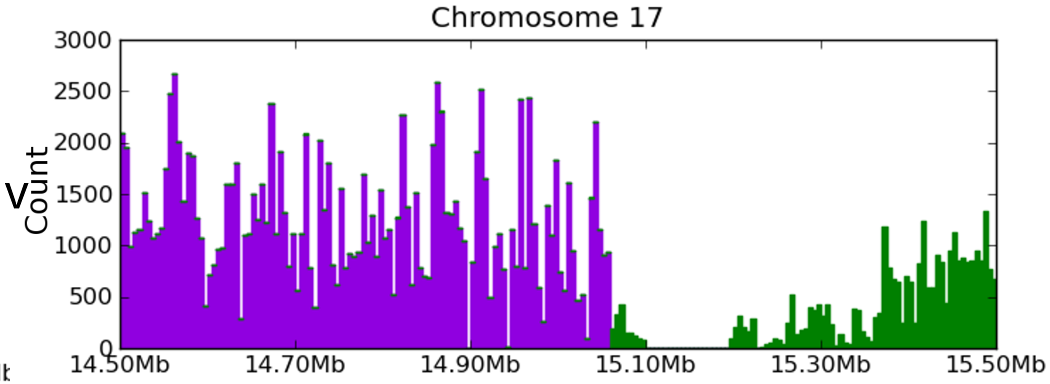
- Used whole-genome sequence data for verification
  - DNA sequence data available for 3 CC samples genotyped on MUGA
  - Ran our algorithm and GAIN on these 3 CC samples, then imputed SNPs using the Wellcome Trust's whole-genome sequences
  - When inference between us and GAIN differ, compare all imputed SNPs in the region with sequence data

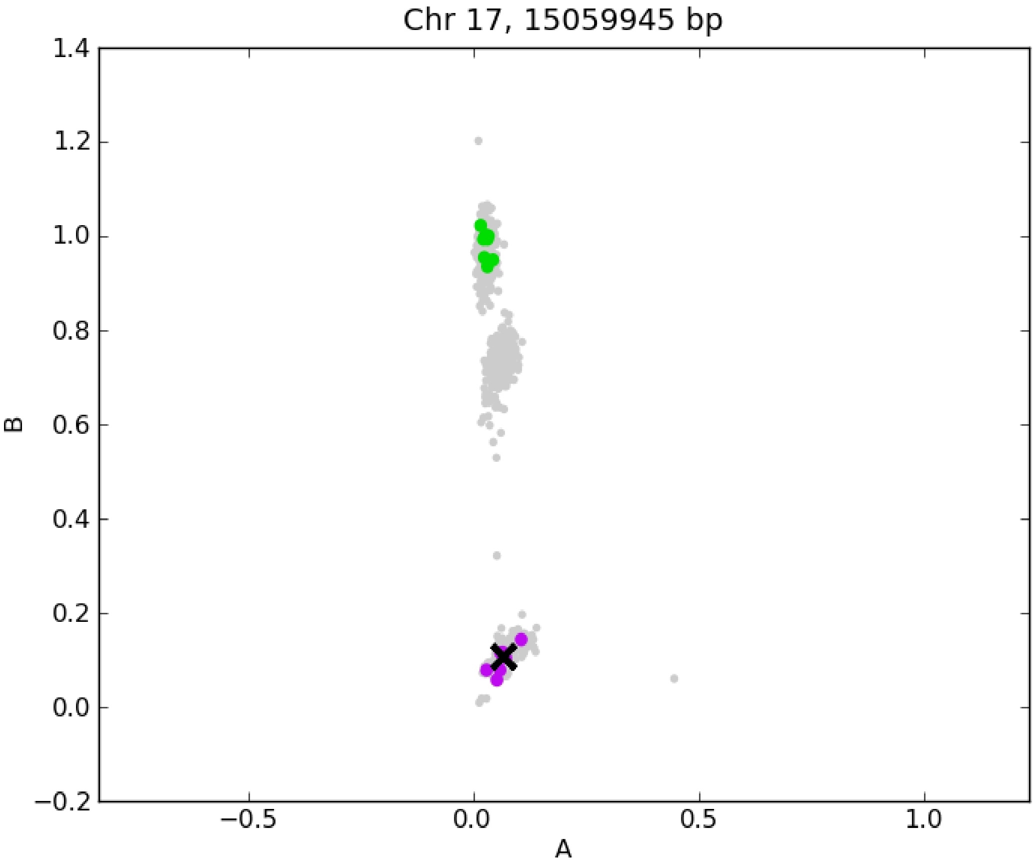
	# SNPs where we can GAN differ	SNPs where we agree with sequence	SNPs where GAIN agrees with sequence
OR867m532	33,026	24,092	8,934
OR1237m224	17,536	14,524	3,011
OR3067m352	38,621	23,095	15,526
Total	**89,183**	**52,144 (69.2%)**	**27,471 (30.8%)**

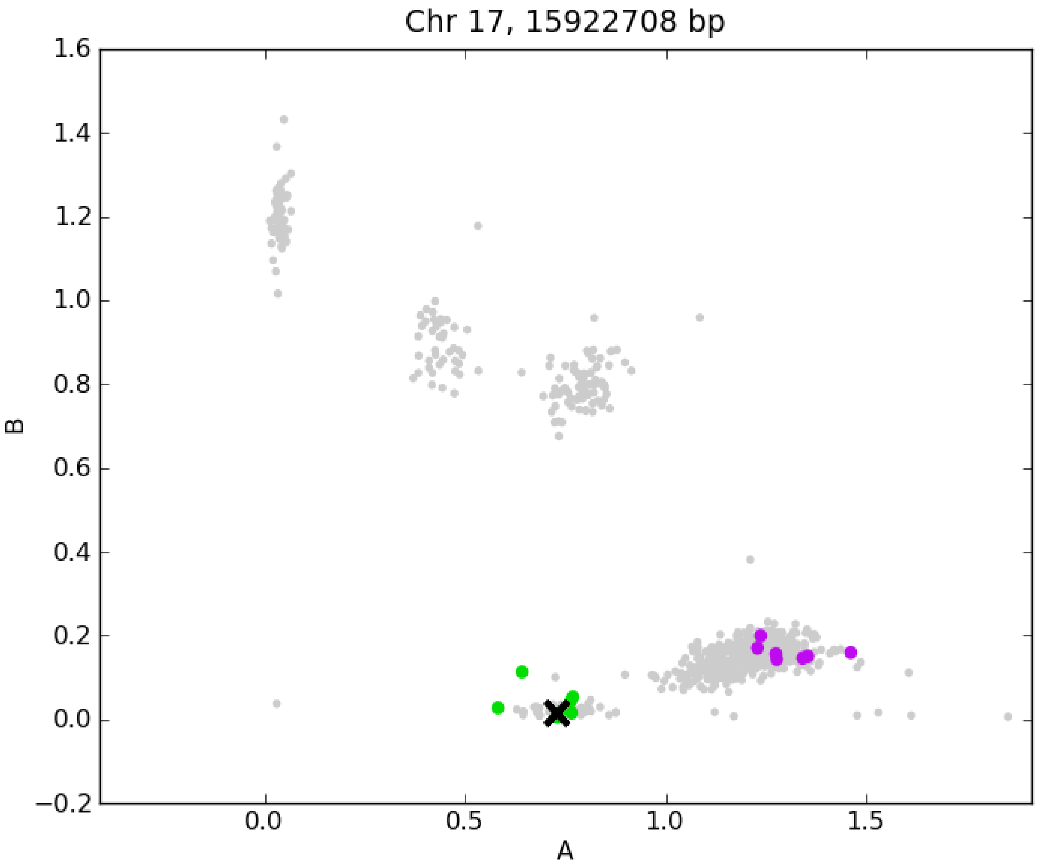
Results

We can refine breakpoints better



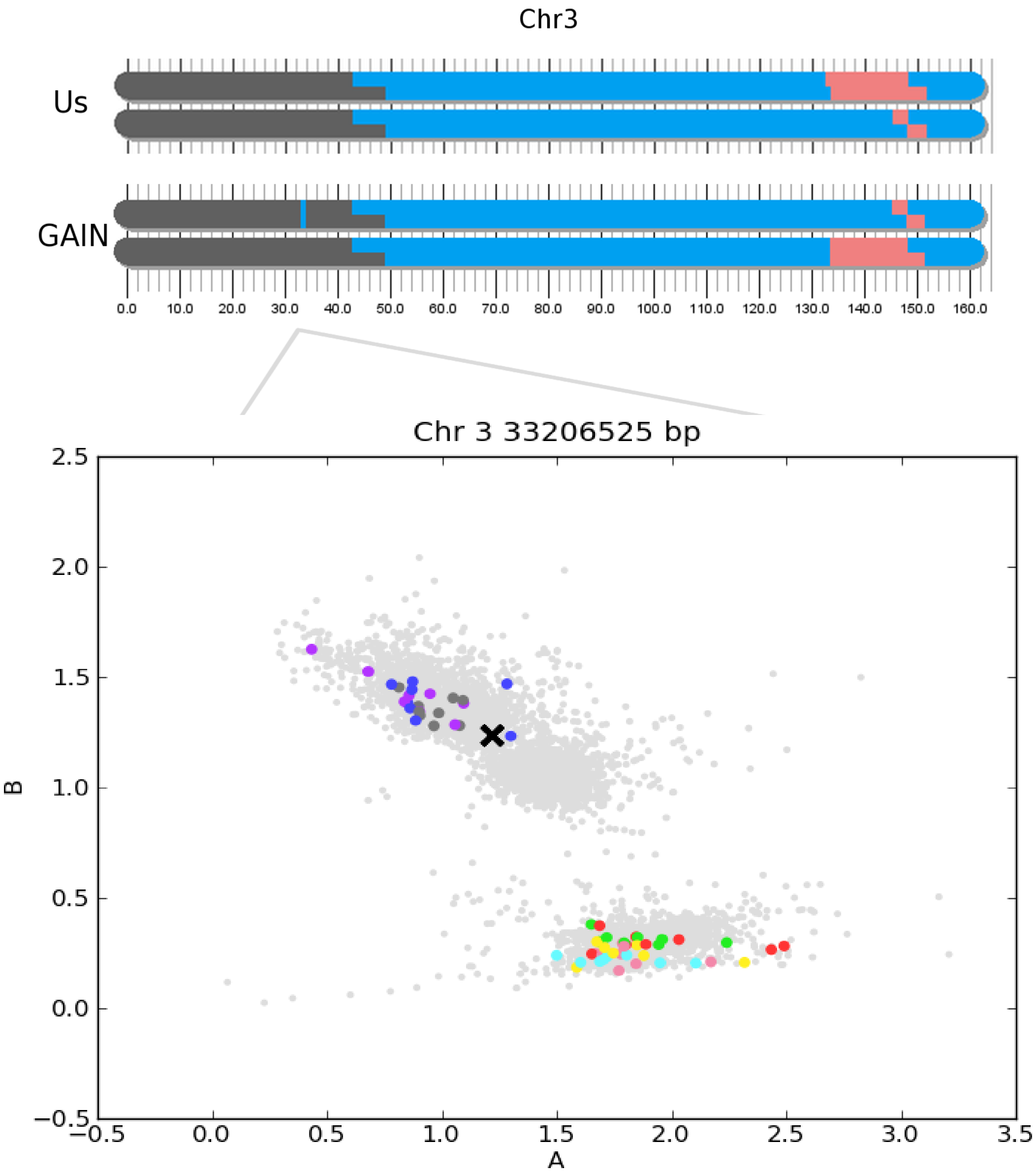


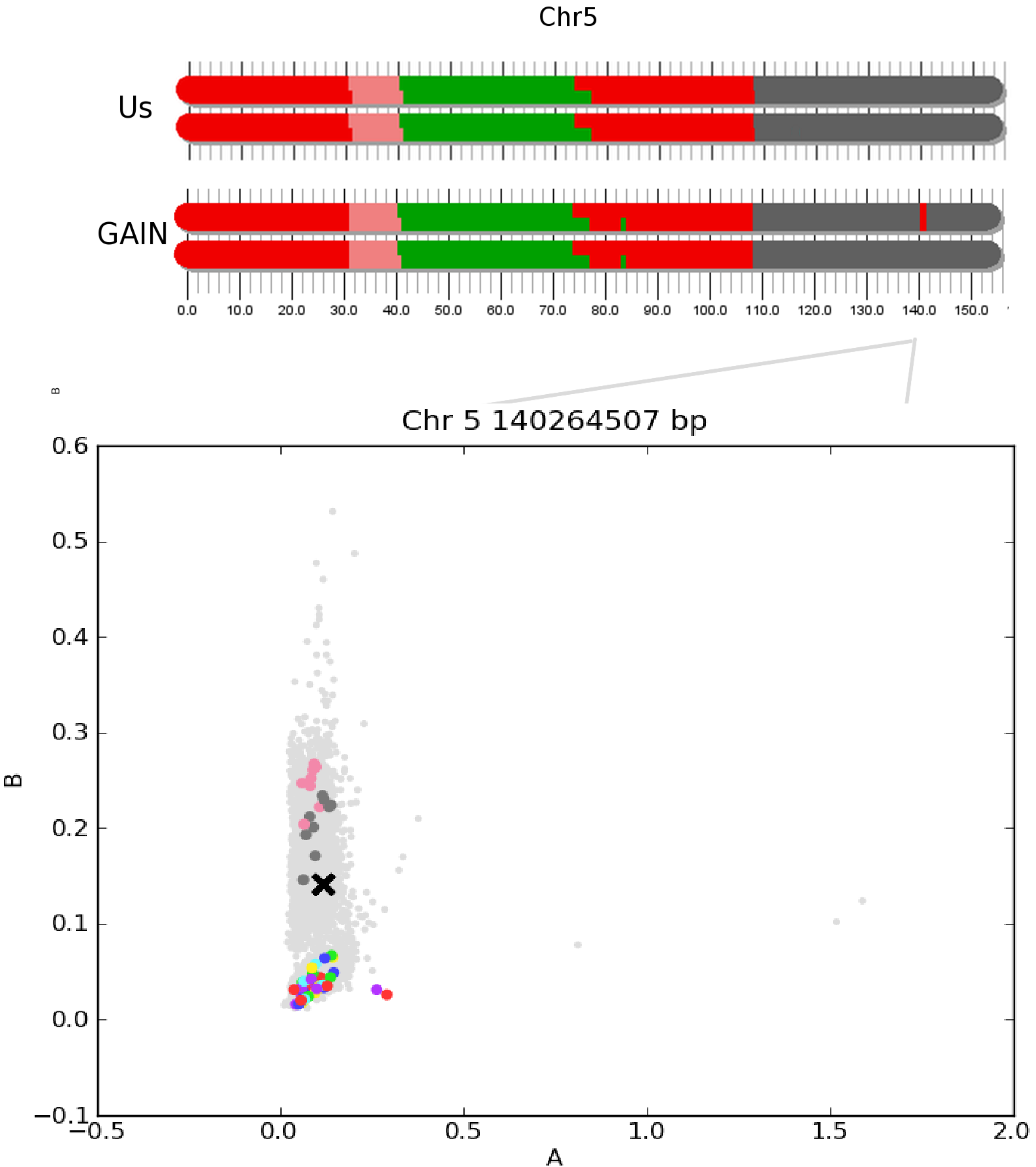




Results – Ancestry Inference

GAIN makes spurious transitions due to erroneous genotype calls, a problem which does not occur in our method





Conclusions

- We considered other distance measures – Euclidean, Manhattan, etc.
    - Mahalanobis distance most robust, but other distances useful when multiple replicates of ancestors are not available
- We applied our methods to different platforms and populations and found comparable results
- We will extend our model to an HMM – give a vector of probabilities at each marker
- Fluorescence intensity ranges vary between markers → we can move to a per-marker penalty model
- We should explore intensity-based methods for other applications (detecting structural variants, sexing, etc.)

THANK YOU!