References (1)

Jeff (CHI-HSUAN HO)

Bioinformatics Analyses – Genotyping (GT), APT, CPT

Jeff (CHI-HSUAN HO)

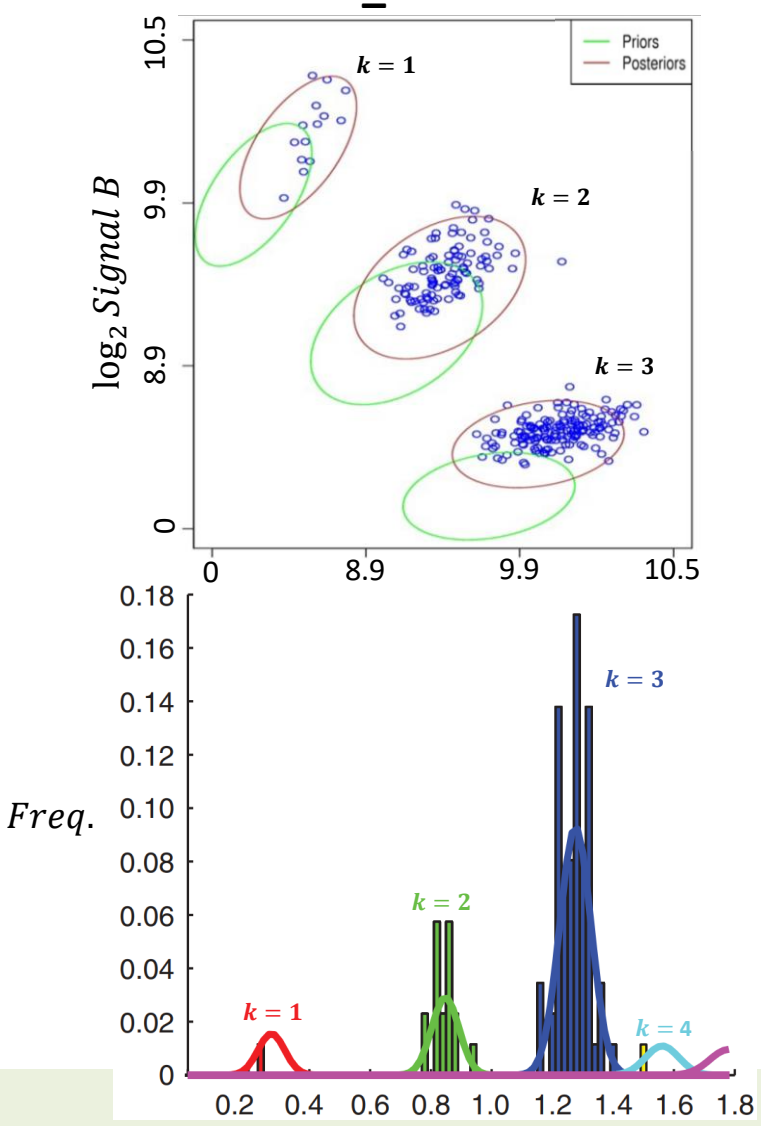
- Genotyping Procedure Documents for Each Chip

Algorithm	Array Type
BRLMM	Human Mapping 100K Array Human Mapping 500K Array
BRLMM-P	Genome-Wide Human SNP Array 5.0 Rat and Mouse Arrays
Birdseed v1 or Birdseed v2	Genome-Wide Human SNP Array 6.0

Axiom GT1 (BRLMM-P)	Axiom Arrays, including:
	• Axiom Human Arrays:
	  • Axiom Genome-Wide Human Arrays
	  • Axiom Genome-Wide CEU 1 Array
	  • Axiom Genome-Wide ASI 1 Array
	  • Axiom Genome-Wide YRI 1 Array set
	  • Axiom myDesign Custom Arrays
	• Axiom Genome-Wide BOS 1 Array

GTC v4.2 P/N 702982 Rev. 3

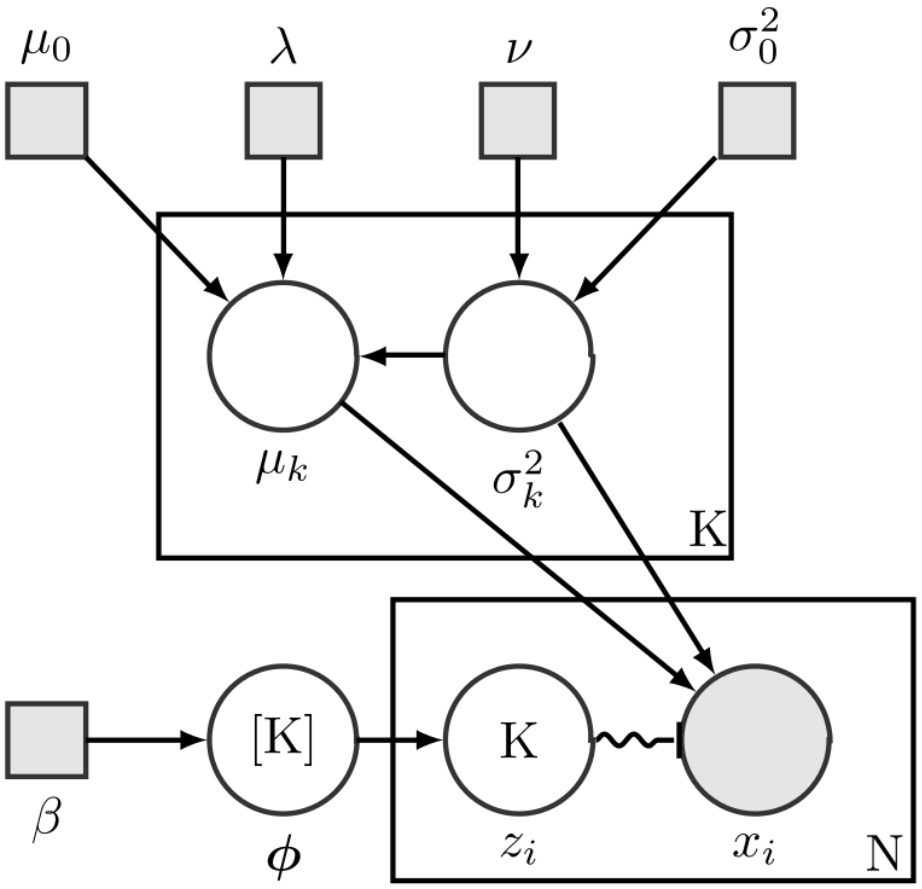
Gaussian Mixture Model (GMM)



- Bayesian framework clustering model
  - Prior → A guess (e.g. from HapMap)
  - Posterior → A correction of cluster membership
- Applications (Genotyping, CNV analysis):
  - Birdseed (2-D)
  - Brlmm-P (1-D)
  - Canary (1-D)
- Model: $p(\boldsymbol{x}|\Theta) = \sum_{k=1}^{K} w_k \cdot N(\boldsymbol{x}|\boldsymbol{\mu}_k, \Sigma_k)$,

  where $N(\cdot)$ = Gaussian (Normal) dist., w_k= the k_{th} cluster proportion
- Evaluation (Model-based, Domain knowledge):
  - Bayesian Information Criterion (BIC)
  - Resolution of posterior cluster centroids
  - Model reasonability (e.g. outlier cluster)
  - Similarity between posterior and prior (e.g. w_k, $\boldsymbol{\mu}_k$)
  - Biological insight (e.g. Hardy-Weinberg penalty)

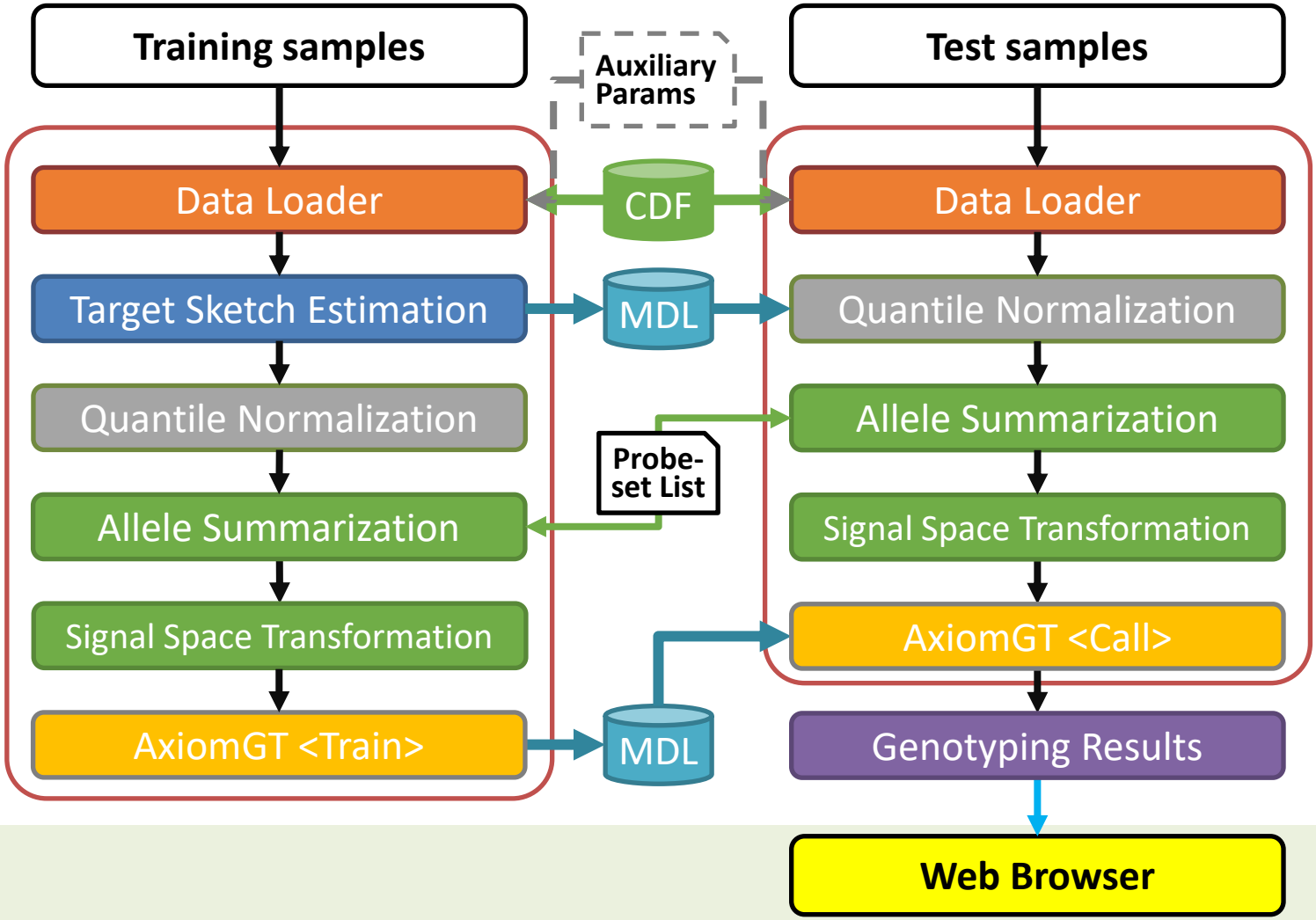
Bayesian Gaussian Mixture Model



- Model: $\sum_{k=1}^{K} \phi_k N(\mu_k, \sigma_k^2)$
- K = Number of mixture components
- σ_k^2 = Variance of component k,
  $\sigma_k^2 \sim$ Inverse-Wishart(ν, σ_0^2)
- μ_k = Mean of component k,
  $\mu_k \sim$ Normal$(\mu_0, \lambda\sigma_k^2)$
- N = Number of observations
- z_i = Component (category) of observation i,
  $z_i \sim$ Categorical(ϕ), $z_i \in \{1, 2, \ldots, k\}$
- ϕ_k = Mixture weight, i.e. prior probability of a particular component k,
  $\phi \sim$ Symmetric-Dirichlet(β),
  $\sum_k \phi_k = 1$
- x_i = Observation i,
  $x_i \sim$ Normal$(\mu_{z_i}, \sigma_{z_i}^2)$

Genotyping Analysis Development and Distribution

- AxiomGT Framework



Genotyping Analysis Development and Distribution

Auxiliary Params

Genotype

```
<?xml version="1.0" encoding="UTF-8" standalone="yes" ?>
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<Genohints_table>
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        <item>AFFX-SNP-000002</item>
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<Sample_names_for_col>
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        <item_version>0</item_version>
        <item>GSM2066668_206-001_CHB</item>
        <item>GSM2066669_206-003_CHB</item>
        <item>GSM2066670_206-004_CHB</item>
        <item>GSM2066671_206-014_CHB</item>
        <item>GSM2066672_206-015_CHB</item>
</Sample_names>
</boost_serialization>
```

Special SNPs

probeset_id	chr	copy_male	copy_female
AX-11086922	X	1	2
AX-11104190	MT	1	1
AX-11106959	Y	1	0
AX-11106974	PAR	2	2
AX-12524149	X	1	2

Meaning of the value: Theoretical copy number for each probeset and gen

- Explanation of the code in the chr column:

code	chr region
X	The non-pseudoautosomal region of the X chromosome
Y	The Y chromosome
MT	Mitochondrial SNPs
PAR	The pseudoautosomal region of the X chromosome

Genders

gender	sample_files
1	Sample01.CEN
1	Sample02.CEN
0	Sample03.CEN
0	Sample04.CEN
1	Sample05.CEN

Sex Probes

probe_id	channel_id
288	1
871	1
2014	1

Genotyping Analysis Development and Distribution

Genotyping Results

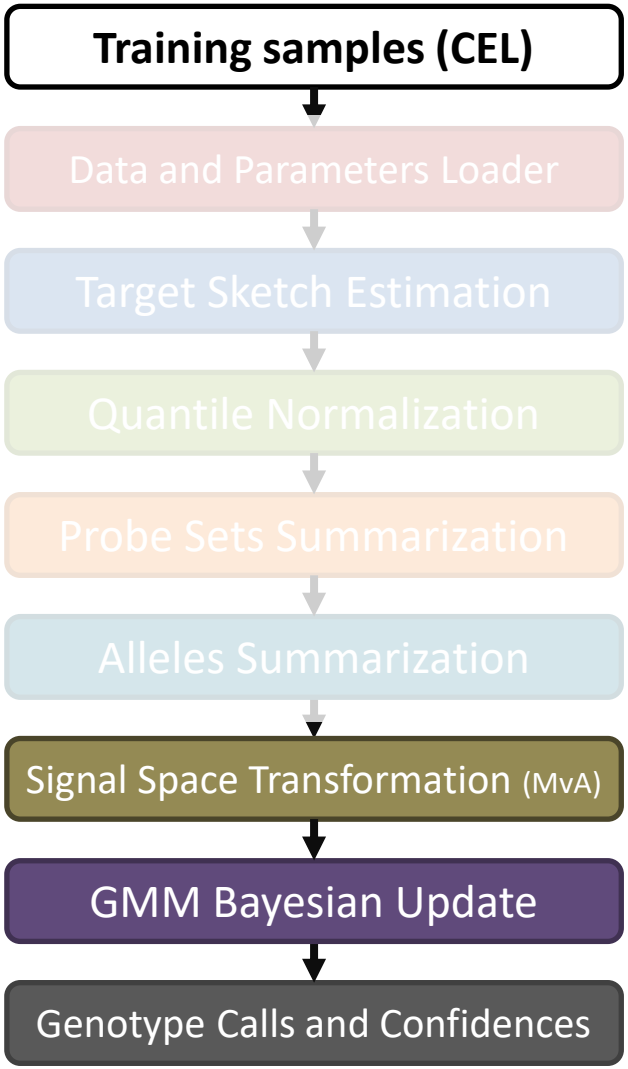
Call Rate

call_rate	sample_name
0.994788	GSM2066668_206-001_CHB
0.994555	GSM2066669_206-003_CHB
0.994841	GSM2066670_206-004_CHB
0.995426	GSM2066671_206-014_CHB
0.994742	GSM2066672_206-015_CHB
0.995266	GSM2066673_206-016_CHB
0.994938	GSM2066674_206-018_CHB
0.995377	GSM2066675_206-019_CHB
0.992347	GSM2066676_206-021_CHB
0.967893	GSM2066677_206-023_CHB
0.972985	GSM2066678_206-028_CHB
0.972951	GSM2066679_206-029_CHB
0.973976	GSM2066680_206-030_CHB
0.973856	GSM2066681_206-032_CHB
0.974752	GSM2066682_206-033_CHB
0.972898	GSM2066683_206-034_CHB

Genotype Inference Report

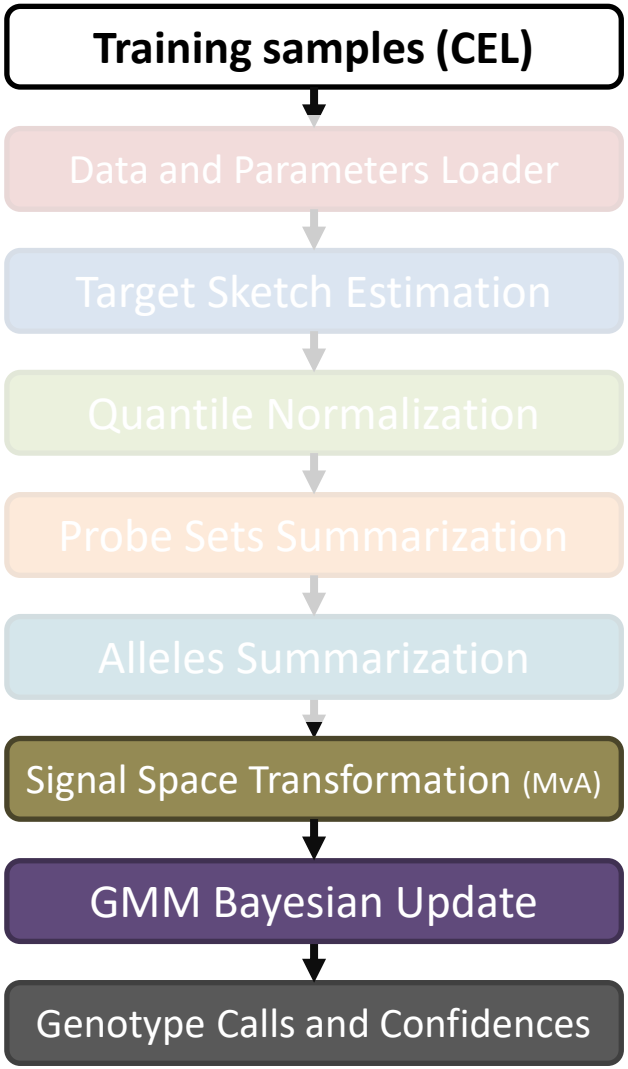
a_allele	b_allele	genotype	posterior	probeset_name	sample_name
-2.42229	9.69654	2	0.999972	AFFX-SNP-000001	GSM2066668_206-001_CHB
-0.213343	10.0077	1	0.999985	AFFX-SNP-000001	GSM2066669_206-003_CHB
2.62502	9.22009	0	0.999929	AFFX-SNP-000001	GSM2066670_206-004_CHB
-0.312298	9.95922	1	0.99998	AFFX-SNP-000001	GSM2066671_206-014_CHB
-0.264381	9.80488	1	0.999976	AFFX-SNP-000001	GSM2066672_206-015_CHB
0.0327307	10.0347	1	0.999982	AFFX-SNP-000001	GSM2066673_206-016_CHB
-2.92652	9.55797	2	0.999928	AFFX-SNP-000001	GSM2066674_206-018_CHB
-2.49338	9.65748	2	0.999975	AFFX-SNP-000001	GSM2066675_206-019_CHB
0.0407013	9.7349	1	0.999969	AFFX-SNP-000001	GSM2066676_206-021_CHB
-2.94063	9.34759	2	0.999895	AFFX-SNP-000001	GSM2066677_206-023_CHB
3.0863	9.23524	0	0.999049	AFFX-SNP-000001	GSM2066678_206-028_CHB
2.45937	9.3949	0	0.99994	AFFX-SNP-000001	GSM2066679_206-029_CHB
0.0585673	10.002	1	0.99998	AFFX-SNP-000001	GSM2066680_206-030_CHB
-0.260712	10.2414	1	0.999986	AFFX-SNP-000001	GSM2066681_206-032_CHB
-0.468117	9.97722	1	0.999958	AFFX-SNP-000001	GSM2066682_206-033_CHB
-3.29787	9.4166	2	0.996784	AFFX-SNP-000001	GSM2066683_206-034_CHB
-0.125064	10.003	1	0.999986	AFFX-SNP-000001	GSM2066684_206-038_CHB
-3.08476	9.3733	2	0.999697	AFFX-SNP-000001	GSM2066685_206-040_CHB
-0.0546291	9.93013	1	0.999983	AFFX-SNP-000001	GSM2066686_206-041_CHB
2.82779	9.32064	0	0.999878	AFFX-SNP-000001	GSM2066687_206-043_CHB
-2.80064	9.3799	2	0.99995	AFFX-SNP-000001	GSM2066688_206-044_CHB
-0.144338	9.56211	1	0.99996	AFFX-SNP-000001	GSM2066689_206-045_CHB
-2.77376	9.40567	2	0.999957	AFFX-SNP-000001	GSM2066690_206-048_CHB
-0.0830618	9.82269	1	0.99998	AFFX-SNP-000001	GSM2066691_206-049_CHB
-0.286435	10.002	1	0.999982	AFFX-SNP-000001	GSM2066692_206-054_CHB
-0.0575499	9.98275	1	0.999985	AFFX-SNP-000001	GSM2066693_206-056_CHB
-3.01959	9.36143	2	0.999822	AFFX-SNP-000001	GSM2066694_211-001_CHB
-2.95238	9.45029	2	0.999904	AFFX-SNP-000001	GSM2066695_211-003_CHB
-2.94825	9.37206	2	0.999895	AFFX-SNP-000001	GSM2066696_211-006_CHB
-3.12067	9.36538	2	0.999569	AFFX-SNP-000001	GSM2066697_211-009_CHB
-3.72513	9.12557	-1	0.123354	AFFX-SNP-000001	GSM2066698_211-010_CHB

Genotyping Analysis Development and Distribution



- AxiomGT1 Algo (bayes_label)
  - initialize_bins
    (x -> bins domain)
  - Integratebrlmmoverlabelings
    (bins domain)
  - labels_two_posterior
    (bins domain)
  - make_two_calls
    (bins domain params results
    -> x calls)

Genotyping Analysis Development and Distribution



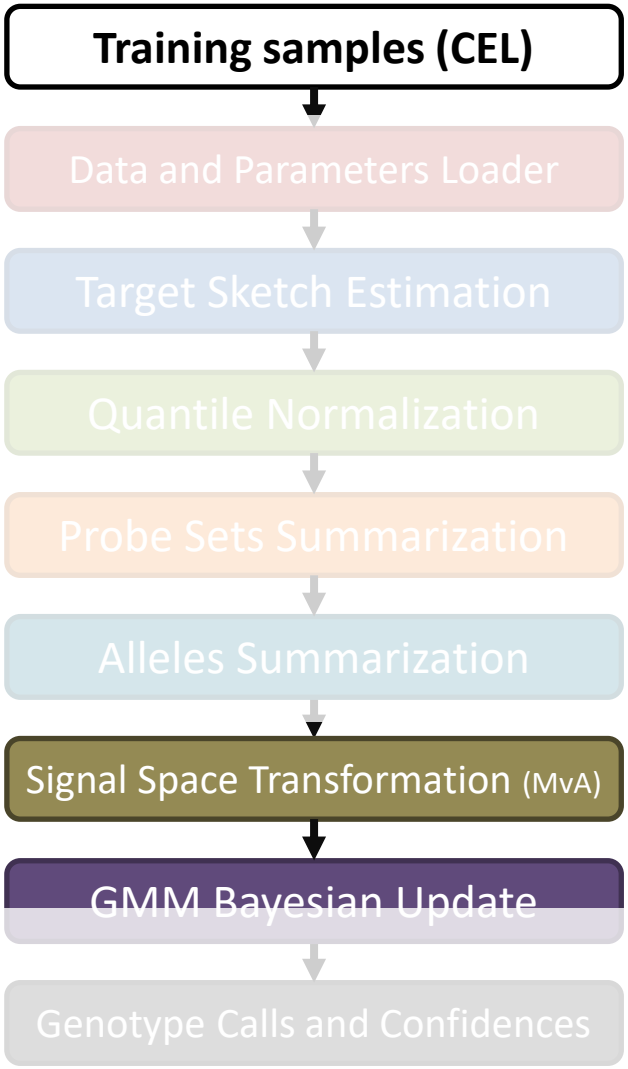
- Sort (x, y) and other related params by x (increasing order).
- Create bins data (setup_bins (x -> bins domain))

$$delta = \frac{Range(x)}{sp.bins + 1}, \qquad sp.bins = 100 \ (default)$$

  - Create a new bin and reset collected statistics if
    1. When current data point x lies outside current $boundary$ (previous $x + delta$) $\Rightarrow$ Create new $boundary$ by using current x.
    2. sp.bins = 0 (bins is turned off)
    3. When data points are fewer than bins.

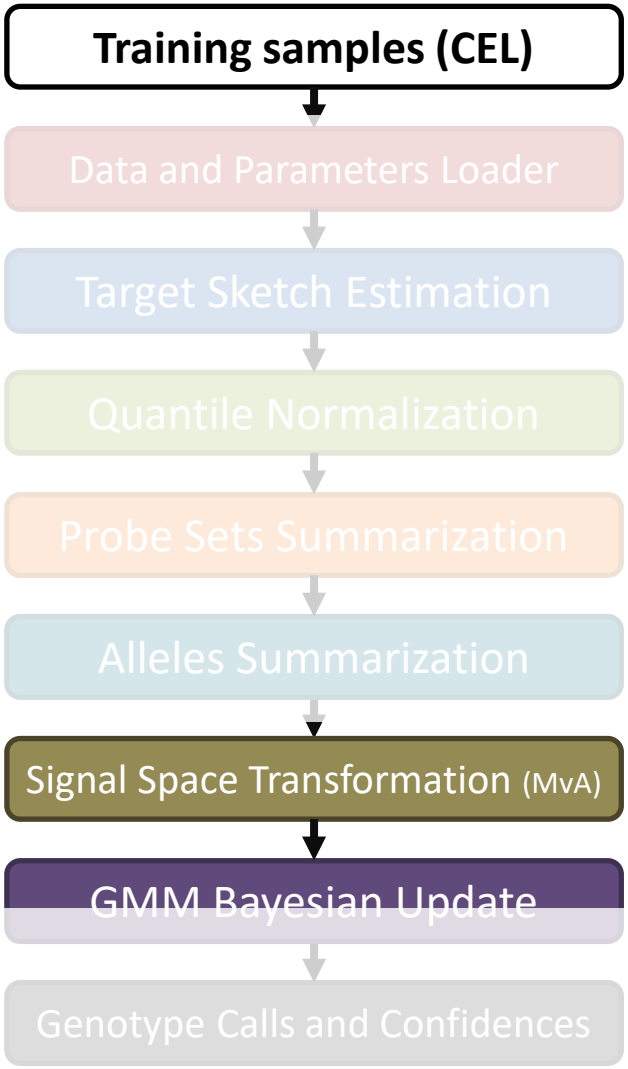
  - Statistics are collected and computed in the same bin:
    1. Data points number
    2. $x, x^2, y, y^2, x \cdot y$
    3. Penalty from each known genotype and inbreeding status (Only used in supervised mode)

Genotyping Analysis Development and Distribution



- **Compute Quality Score (Posterior Analog) (for each partition)**
  - **(sp.mix) mixture_penalty**
  - **(sp.bic) BIC (k*log(N) part)**
  - **1D (x) Log likelihood under posterior params**
  - **1D (x) Log prior probability of posterior params**
  - $\frac{1}{2} * \text{Quality Score Correction}$
  - **(sp.CSepPen) Geman-McClure transformed FLD penalty for non-well-separated clusters cases.**
- **Compute Relative Probability for (Each Partition) & (Each Data Point to Be Each Genotype) under Posterior Information.**

Genotyping Analysis Development and Distribution



- **Quality Score (Posterior Analog) (for each partition)**
  - **(sp.mix) mixture_penalty**

$$-\sum_{g=1}^{3} N_g * \log\left(\frac{(N_g + lambda)}{\sum_g (N_g + lambda)}\right), \qquad lambda = 1 \qquad g = 1\,(BB), 2\,(AB), 3\,(AA)$$

  - **(sp.bic) BIC (k*log(N) part)**

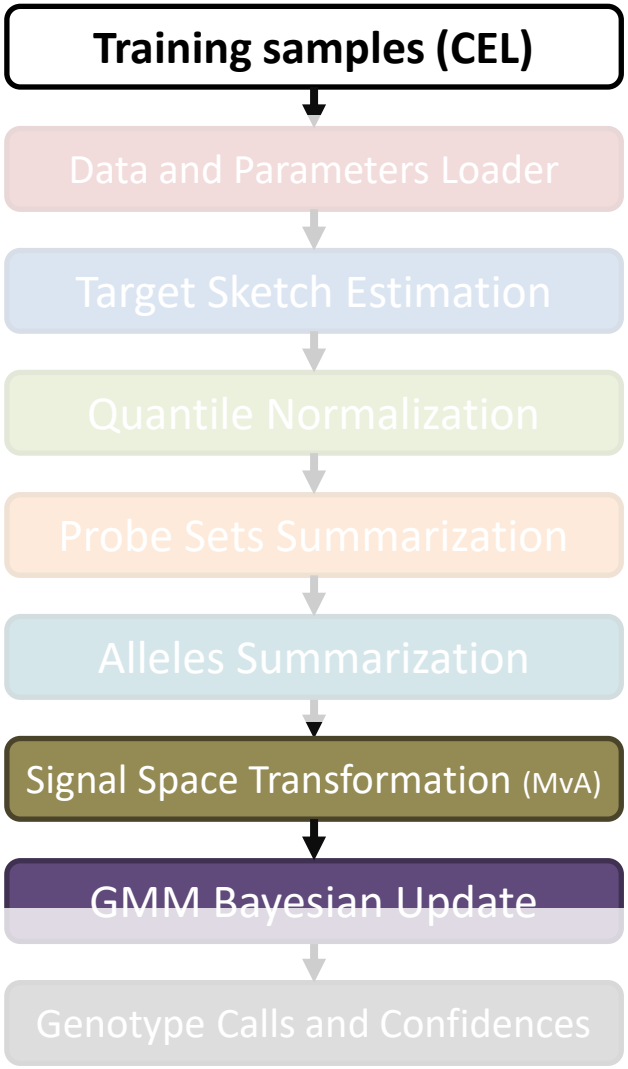
$$c * bic\_k * \log\left(\sum_g N_g\right), \qquad bic\_k = 2 \Rightarrow mean, var, \qquad c = 1,2,3$$

  - **1D (x) Log likelihood under posterior params**
    - $u'_{3x1} = \left(\boldsymbol{K_0^{-1}}_{3x3} + \boldsymbol{N'}_{3x3}\right)^{-1} * \left(\boldsymbol{K_0^{-1}}_{3x3} * u_{0\,3x1} + \boldsymbol{N}_{3x3} * m_{3x1}\right),$

$$\boldsymbol{K_0^{-1}}_{3x3} = \begin{bmatrix} \frac{k_{10}}{\sigma_{10}^2} & \frac{\sigma_{120}}{\sigma_{10}\sigma_{20}} & \frac{\sigma_{130}}{\sigma_{10}\sigma_{30}} \\ \frac{\sigma_{120}}{\sigma_{10}\sigma_{20}} & \frac{k_{20}}{\sigma_{20}^2} & \frac{\sigma_{230}}{\sigma_{20}\sigma_{30}} \\ \frac{\sigma_{130}}{\sigma_{10}\sigma_{30}} & \frac{\sigma_{230}}{\sigma_{20}\sigma_{30}} & \frac{k_{30}}{\sigma_{30}^2} \end{bmatrix}, \qquad \boldsymbol{N'}_{3x3} = \begin{bmatrix} \frac{N_1}{\sigma_{10}^2} & 0 & 0 \\ 0 & \frac{N_2}{\sigma_{20}^2} & 0 \\ 0 & 0 & \frac{N_3}{\sigma_{30}^2} \end{bmatrix}$$

$$u_{0\,3x1} = \begin{bmatrix} u_{10} \\ u_{20} \\ u_{30} \end{bmatrix}, \qquad m_{3x1} = \begin{bmatrix} \sum_i x_{1i} \\ \sum_i x_{2i} \\ \sum_i x_{3i} \end{bmatrix}, \qquad \boldsymbol{N}_{3x3} = \begin{bmatrix} \frac{1}{\sigma_{10}^2} & 0 & 0 \\ 0 & \frac{1}{\sigma_{20}^2} & 0 \\ 0 & 0 & \frac{1}{\sigma_{30}^2} \end{bmatrix}$$

Genotyping Analysis Development and Distribution



- **Quality Score (Posterior Analog) (for each partition)**
  - **1D (x) Log likelihood under posterior params**
    - $u'_{3x1} = \left(\boldsymbol{K_0}^{-1}_{3x3} + \boldsymbol{N'}_{3x3}\right)^{-1} * \left(\boldsymbol{K_0}^{-1}_{3x3} * u_{0\,3x1} + \boldsymbol{N}_{3x3} * m_{3x1}\right)$
    - (sp.hardshell) Isotonic Regression adjustment for cluster centers (separated by at least delta (0.75)). u'_{3x1}

$$w_g = N_g + k_{g0}, \quad g = 1,2,3$$

$$gamma = delta * \frac{w_1 - w_3}{w_1 + w_2 + w_3}$$

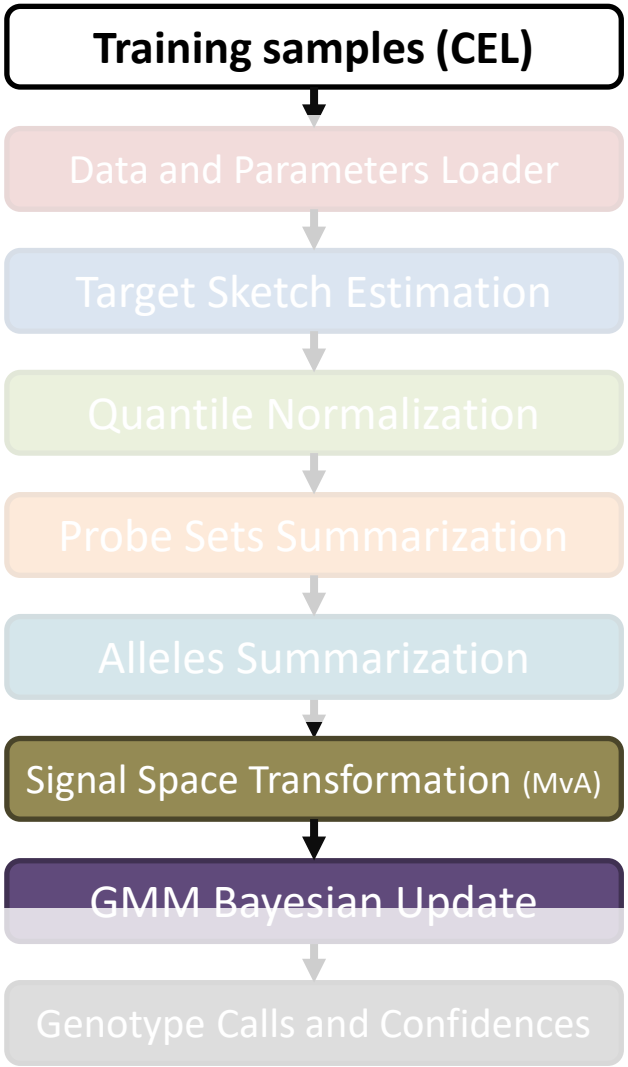
$$u'_{3x1} = \begin{bmatrix} u'_1 \\ u'_2 \\ u'_3 \end{bmatrix}, \quad \begin{aligned} u'_1 &= u'_1 + delta - gamma \\ u'_2 &= u'_2 - gamma \\ u'_3 &= u'_3 - delta - gamma \end{aligned}$$

Pool Adjacent-Violators (PAV) algo.

$$\begin{cases} u'_g, u'_{g+1}\ , & u'_g \le u'_{g+1} \\ u'_g, u'_{g+1} = \dfrac{\sum_{g \in A} w_g * u'_g}{\sum_{g \in A} w_g}, & A = \{g | u'_g > u'_{g+1}\}, g \\ = 1,2,3 \end{cases}$$

$$u'_{3x1} = \begin{bmatrix} u'_1 \\ u'_2 \\ u'_3 \end{bmatrix}, \quad \begin{aligned} u'_1 &= u'_1 - delta + gamma \\ u'_2 &= u'_2 + gamma \\ u'_3 &= u'_3 + delta + gamma \end{aligned}$$

Genotyping Analysis Development and Distribution



- **Quality Score (Posterior Analog) (for each partition)**
  - **1D (x) Log likelihood under posterior params**
    - $\mathrm{u}'_{3\mathrm{x}1} = \left(\boldsymbol{K_0}^{-1}_{3\mathrm{x}3} + \boldsymbol{N'}_{3\mathrm{x}3}\right)^{-1} * \left(\boldsymbol{K}^{-1}_{0\ 3\mathrm{x}3} * \mathrm{u}_{0\ 3\mathrm{x}1} + \boldsymbol{N}_{3\mathrm{x}3} * \mathrm{m}_{3\mathrm{x}1}\right),$
    - (sp.hardshell) Isotonic Regression adjustment for cluster centers (separated by at least delta (0.75)). $\mathrm{u}'_{3\mathrm{x}1}$
    - $\sigma'^{\,2}_g = \frac{v_{g0} * \sigma^2_{g0} + \sum_i (x_{gi} - \bar{x}_g)^2 + \frac{k_g * N_g}{k_g + N_g} * (\mathrm{u}'_g - \mathrm{u}_{g0})^2}{v_{g0} + N_g} \Rightarrow$
      $\frac{v_{g0} * \sigma^2_{g0} + \sum_i x^2_{gi} - \sum_i x_{gi} * \sum_i x_{gi} * \frac{1}{N_g + 0.0001} + \frac{k_g * N_g}{k_g + N_g} * (\mathrm{u}'_g - \mathrm{u}_{g0})^2}{v_{g0} + N_g}, \quad g = 1, 2, 3$
    - (sp.comvar) Ad-hoc shrinkage for $\sigma'^{\,2}_g$ of each cluster (controlled by mixing proportion (lambda) (1)).

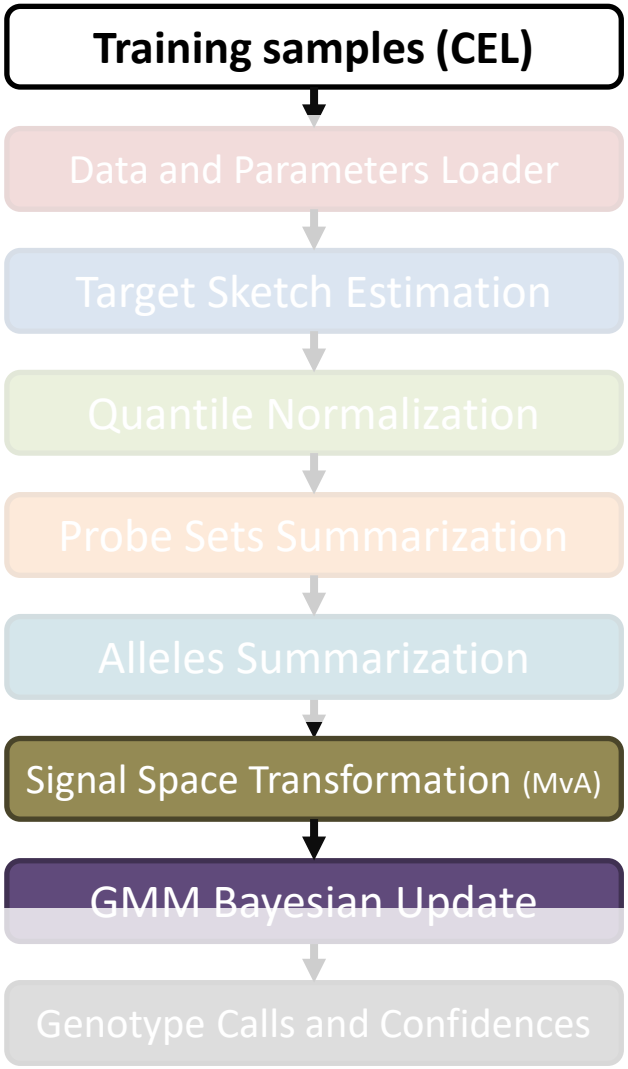
      Adjusted Pooled Variance.

      $w_g = N_g + v_{g0}, \qquad g = 1, 2, 3$

      $\sigma'^{\,2}_t = \frac{\sum_g w_g * \sigma'^{\,2}_g}{\sum_g w_g}, \qquad t = 1, 2, 3,$

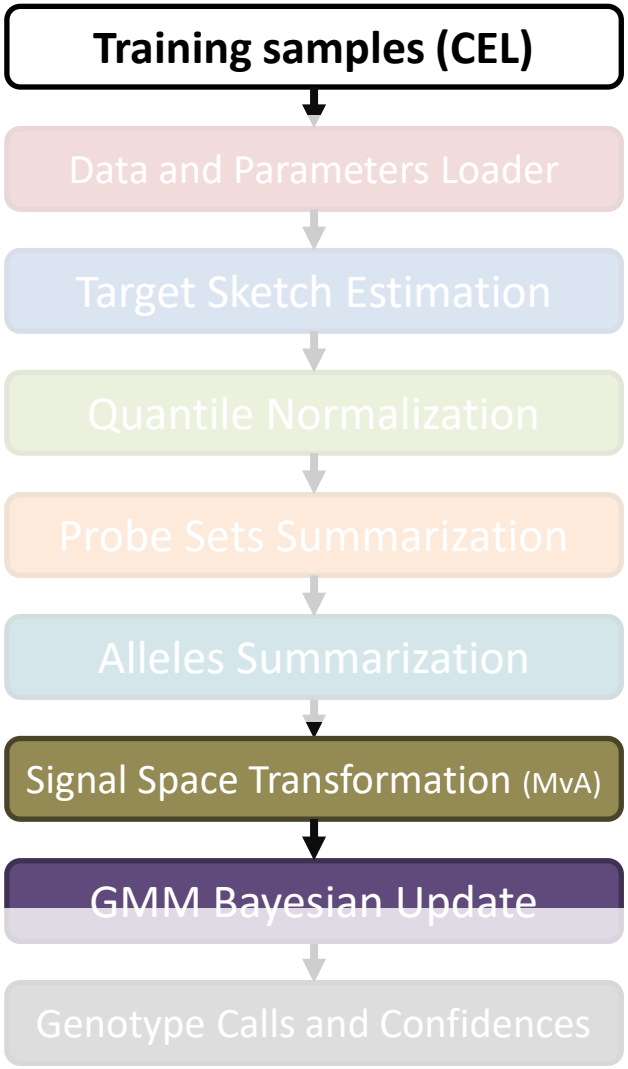
      $\Rightarrow \frac{(3 - 2 * lambda) * w_t * \sigma'^{\,2}_t + \sum_{g \neq t} lambda * w_g * \sigma'^{\,2}_g}{(3 - 2 * lambda) * w_t + \sum_{g \neq t} lambda * w_g}$

Genotyping Analysis Development and Distribution



- **Quality Score (Posterior Analog) (for each partition)**
  - **1D (x) Log likelihood under posterior params**
    - $\mathrm{u}'_{3\mathrm{x}1} = \left(\boldsymbol{K_0}^{-1}_{3\mathrm{x}3} + \boldsymbol{N}'_{3\mathrm{x}3}\right)^{-1} * \left(\boldsymbol{K_0}^{-1}_{3\mathrm{x}3} * \mathrm{u}_{0\ 3\mathrm{x}1} + \boldsymbol{N}_{3\mathrm{x}3} * \mathrm{m}_{3\mathrm{x}1}\right),$
    - (sp.hardshell) Isotonic Regression adjustment for cluster centers (separated by at least delta (0.75)). $\mathrm{u}'_{3\mathrm{x}1}$
    - $\sigma'^{2}_{g} = \frac{v_0 * \sigma^2_{g0} + \sum_i \left(x_{gi} - \bar{x}_g\right)^2 + \frac{k_g * N_g}{k_g + N_g} * \left(\mathrm{u}'_g - \mathrm{u}_{g0}\right)^2}{v_0 + N_g}, \quad g = 1, 2, 3$
    - (sp.comvar) Ad-hoc shrinkage for σ'^{2}_{g} of each cluster (controlled by mixing proportion (lambda) (1)).
    - $\ell = \log \prod_g \prod_{i=1}^{N_g} N\left(\mathrm{u}'_g,\ \sigma'^{2}_{g}\right) = \sum_g \sum_{i=1}^{N_g} \log\left(N\left(\mathrm{u}'_g,\ \sigma'^{2}_{g}\right)\right) \Rightarrow$
      $-\frac{1}{2}\left[\sum_g N_g \log\left(\sigma'^{2}_{g}\right) + \frac{1}{\sigma'^{2}_{g}}\left(\sum_{i=1}^{N_g} x_i^2 - 2\mathrm{u}'_g \sum_{i=1}^{N_g} x_i + N_g \mathrm{u}'^{2}_{g}\right)\right]$
      $\Rightarrow -2 * \ell$
      $= \sum_g N_g \log\left(\sigma'^{2}_{g}\right) + \frac{1}{\sigma'^{2}_{g}}\left(\sum_{i=1}^{N_g} x_i^2 - 2\mathrm{u}'_g \sum_{i=1}^{N_g} x_i + N_g \mathrm{u}'^{2}_{g}\right)$

Genotyping Analysis Development and Distribution

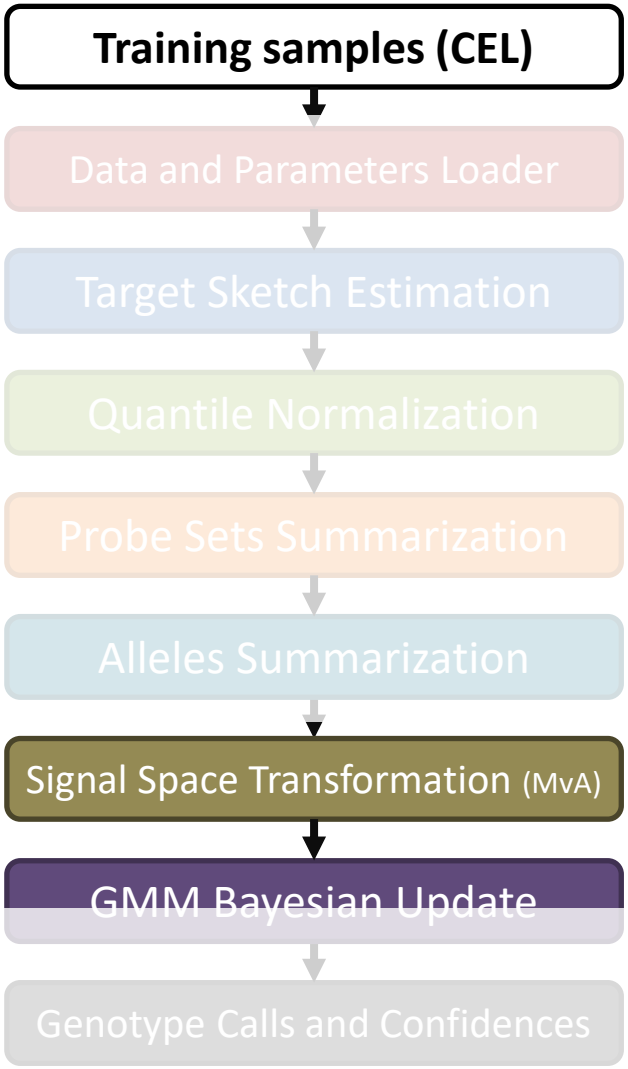


- **Quality Score (Posterior Analog) (for each partition)**
  - **1D (x) Log prior probability of posterior params**
    - $\ell = \log \prod_g N\left(u_{g0},\ \frac{\sigma_{g0}^2}{k_{g0}}\right) = \sum_g \log\left(N\left(u_{g0},\ \frac{\sigma_{g0}^2}{k_{g0}}\right)\right) \Rightarrow$
      $-\frac{1}{2}\left[\sum_g \log\left(\frac{\sigma_{g0}^2}{k_{g0}}\right) + \frac{k_{g0}}{\sigma_{g0}^2}\left(u'_g - u_{g0}\right)^2\right]$
      $\Rightarrow -2 * \ell = \sum_g \log\left(\frac{\sigma_{g0}^2}{k_{g0}}\right) + \frac{k_{g0}}{\sigma_{g0}^2}\left(u'_g - u_{g0}\right)^2$
    - $\ell = \log \prod_g IG\left(v_0,\ \sigma_{g0}^2\right) \Rightarrow -\ell = \sum_g \frac{\sigma_{g0}^2}{\sigma'^2_g} + (v_0 + 1) * \log\left(\sigma'^2_g\right)$
  - $\frac{1}{2} *$ **Quality Score**
  - **(sp.CSepPen) Geman-McClure transformed FLD penalty for non-well-separated clusters.**
    - $-CSepPen * \sum_{i,j,i\neq j} FLD'_{ij},\ i,j \in g = \{1,2,3\},$

$$FLD'_{ij} = \begin{cases} \dfrac{FLD_{ij}}{1 + \dfrac{FLD_{ij}}{CSepThr}} * \left(N_i + N_j\right), & other \\ \dfrac{FLD_{ij}}{1 + \dfrac{FLD_{ij}}{2 * CSepThr}} * \left(N_1 + N_3\right), & i = 1, j = 3 \end{cases},$$

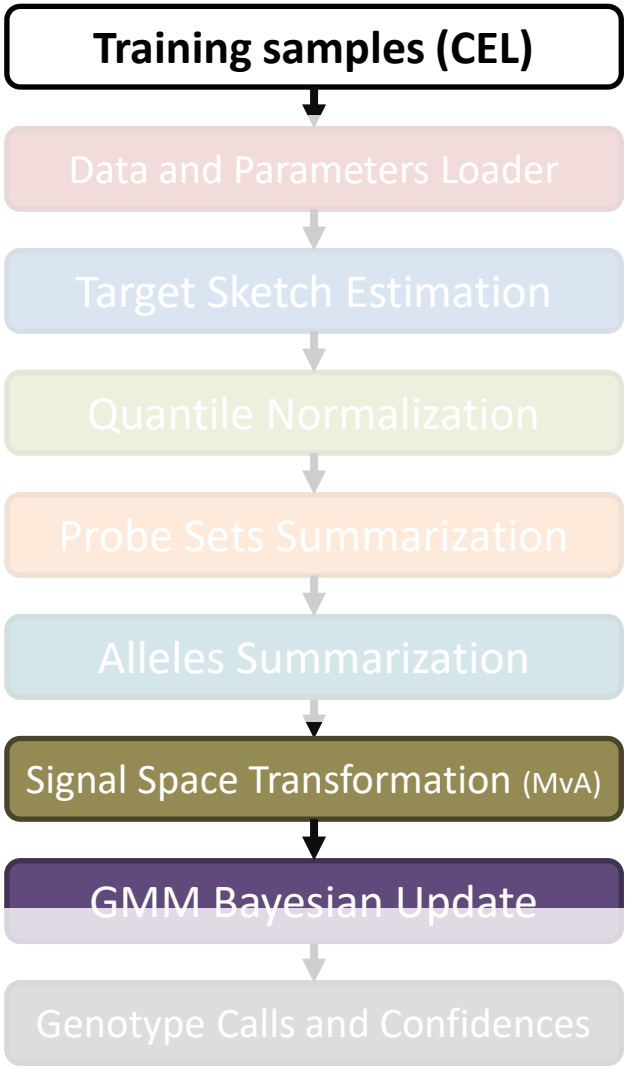
$$FLD_{ij} = FLD_{ji} = \frac{\left(u'_i - u'_j\right)^2}{\sigma'^2_i + \sigma'^2_j}, \qquad CSepPen = 0.1, \qquad CSepThr = 4$$

Genotyping Analysis Development and Distribution



- **Relative Probability for Each Partition under Posterior Information.**
  - Quality Score $Q_{i,j}$ for partition i, j
  - Relative Probability $q_{i,j} = \frac{\exp(-Q_{i,j})}{\exp(-\min Q_{i,j})} = \exp(\min Q_{i,j} - Q_{i,j})$
    $= \frac{Posterior\ Probability\ of\ Specified\ Partition\ (i,j)}{Maximal\ Posterior\ Probability}$

Genotyping Analysis Development and Distribution



- **Relative Probability for Each Data Point to Be Each Genotype under Posterior Information after dividing q...**

$q_{i,j}$

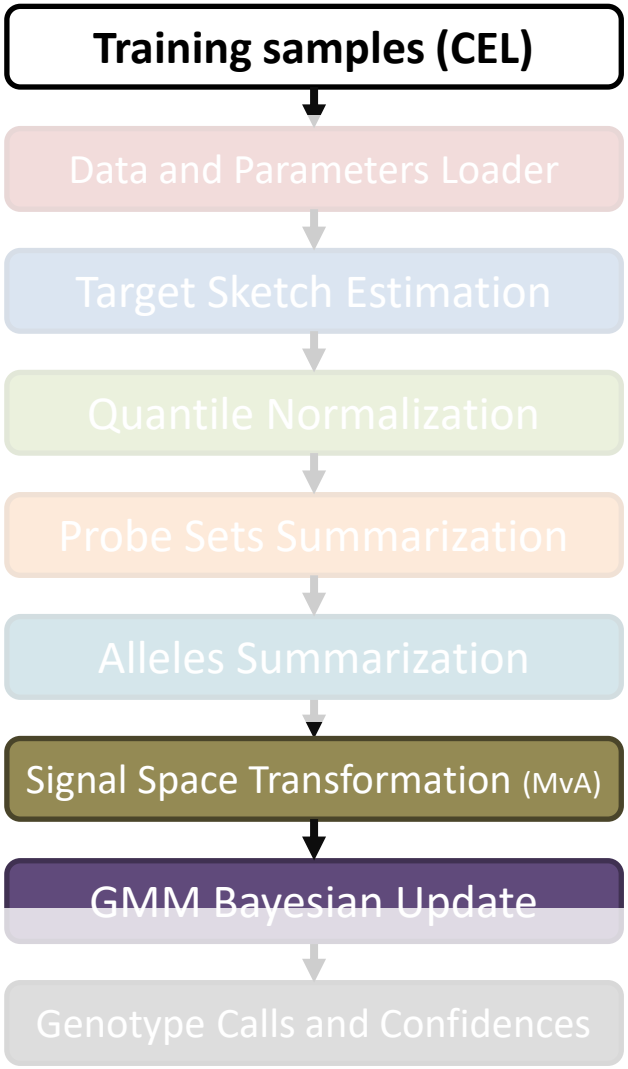
i \ j	0	1	2	3	4	$q_{i\cdot}$	$\sum_i q_{i\cdot}$	$q_{\cdot\cdot} - \sum_i q_{i\cdot}$
0	cccc	bccc	bbcc	bbbc	bbbb	$q_{0\cdot}$	$\sum_{i=0}^{0} q_{i\cdot}$	$\sum_{i=1}^{4} q_{i\cdot}$
1		accc	abcc	abbc	abbb	$q_{1\cdot}$	$\sum_{i=0}^{1} q_{i\cdot}$	$\sum_{i=2}^{4} q_{i\cdot}$
2			aacc	aabc	aabb	$q_{2\cdot}$	$\sum_{i=0}^{2} q_{i\cdot}$	$\sum_{i=3}^{4} q_{i\cdot}$
3				aaac	aaab	$q_{3\cdot}$	$\sum_{i=0}^{3} q_{i\cdot}$	$\sum_{i=4}^{4} q_{i\cdot}$
4					aaaa	$q_{4\cdot}$		
$q_{\cdot j}$	$q_{\cdot 0}$	$q_{\cdot 1}$	$q_{\cdot 2}$	$q_{\cdot 3}$	$q_{\cdot 4}$	$q_{\cdot\cdot}$		
$\sum_j q_{\cdot j}$	$\sum_{j=0}^{0} q_{\cdot j}$	$\sum_{j=0}^{1} q_{\cdot j}$	$\sum_{j=0}^{2} q_{\cdot j}$	$\sum_{j=0}^{3} q_{\cdot j}$				

The relative counts of Sth data point being genotype "a" after observing all data.

The relative counts of Sth data point being genotype "c" after observing all data.

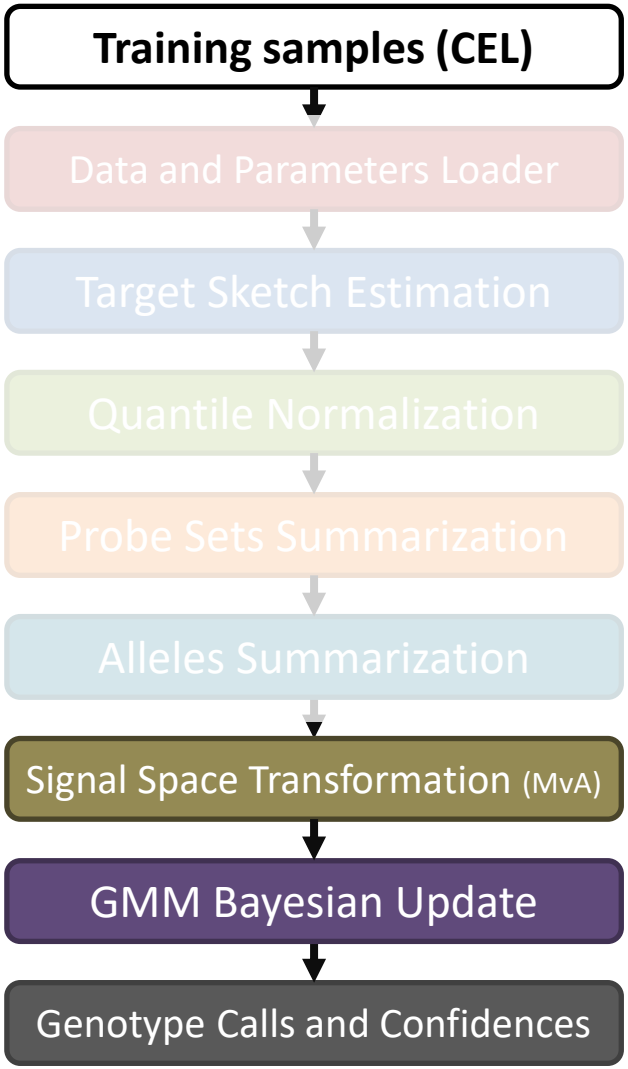
Let "a" ≡ BB genotype, "b" ≡ AB genotype, "c" ≡ AA genotype.

Genotyping Analysis Development and Distribution



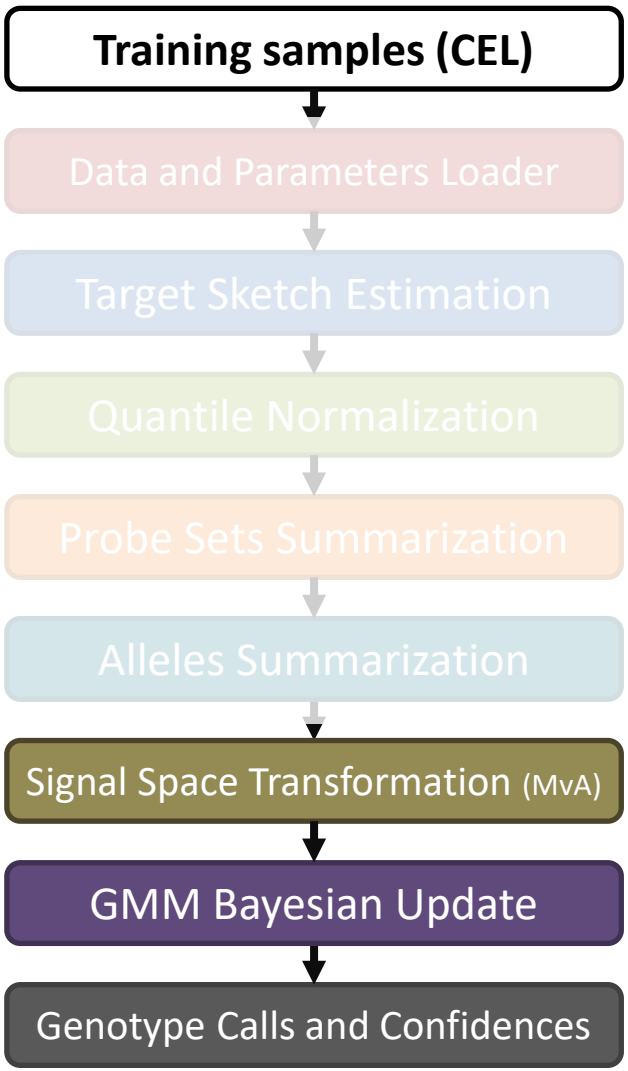
- **Relative Probability for Each Data Point to Be Each Genotype under Posterior Information.**
  - The relative probability for the S_{th} data point being AA genotype: $\frac{\sum_{j=0}^{S} q_{\cdot j}}{q_{\cdot\cdot}}$
  - The relative probability for the S_{th} data point being BB genotype: $1 - \frac{\sum_{i=0}^{S} q_{i\cdot}}{q_{\cdot\cdot}}$
  - The relative probability for the S_{th} data point being AB genotype: $1 - \left(1 - \frac{\sum_{i=0}^{S} q_{i\cdot}}{q_{\cdot\cdot}}\right) - \frac{\sum_{j=0}^{S} q_{\cdot j}}{q_{\cdot\cdot}} = \frac{\sum_{i=0}^{S} q_{i\cdot} - \sum_{j=0}^{S} q_{\cdot j}}{q_{\cdot\cdot}}$

Genotyping Analysis Development and Distribution



- Update 2D Data model parameters with soft assignment of each data bin
  - $u'_{6x1} = \left(\boldsymbol{K_0}^{-1}_{6x6} + \boldsymbol{N'}_{6x6}\right)^{-1} * \left(\boldsymbol{K_0}^{-1}_{6x6} * u_{0\ 6x1} + m_{6x1}\right),$
  - $\boldsymbol{K_0}^{-1}_{6x6} = \begin{bmatrix} k_{10} & \mathbf{0} & \sigma_{xx120} & \mathbf{0} & \sigma_{xx130} & \mathbf{0} \\ \mathbf{0} & k_{10} & \mathbf{0} & \sigma_{yy120} & \mathbf{0} & \sigma_{yy130} \\ \sigma_{xx120} & \mathbf{0} & k_{20} & \mathbf{0} & \sigma_{xx230} & \mathbf{0} \\ \mathbf{0} & \sigma_{yy120} & \mathbf{0} & k_{20} & \mathbf{0} & \sigma_{yy230} \\ \sigma_{xx130} & \mathbf{0} & \sigma_{xx230} & \mathbf{0} & k_{30} & \mathbf{0} \\ \mathbf{0} & \sigma_{yy130} & \mathbf{0} & \sigma_{yy230} & \mathbf{0} & k_{30} \end{bmatrix},$
  - $\boldsymbol{N}_{6x6} = \begin{bmatrix} \sum_i p_{1i} & \mathbf{0} & \cdots & \mathbf{0} \\ \mathbf{0} & \sum_i p_{1i} & & \\ & & \sum_i p_{2i} & \vdots \\ \vdots & & & \sum_i p_{2i} \\ & & & & \sum_i p_{3i} & \mathbf{0} \\ \mathbf{0} & & \cdots & \mathbf{0} & \sum_i p_{31} \end{bmatrix}$
  - $u_{0\ 6x1} = \begin{bmatrix} u_{x10} \\ u_{y10} \\ u_{x20} \\ u_{y20} \\ u_{x30} \\ u_{y30} \end{bmatrix}, \quad m_{6x1} = \begin{bmatrix} \sum_i x_{1i} \\ \sum_i y_{1i} \\ \sum_i x_{2i} \\ \sum_i y_{2i} \\ \sum_i x_{3i} \\ \sum_i y_{3i} \end{bmatrix}$

Genotyping Analysis Development and Distribution



- Update 2D Data model parameters with soft assignment of each data bin
  - $\mathrm{u}'_{6\mathrm{x}1} = \left(\boldsymbol{K}_{\boldsymbol{0}}^{-1}{}_{6\mathrm{x}6} + \boldsymbol{N}'_{6\mathrm{x}6}\right)^{-1} * \left(\boldsymbol{K}_{0}^{-1}{}_{6\mathrm{x}6} * \mathrm{u}_{0\ 6\mathrm{x}1} + \mathrm{m}_{6\mathrm{x}1}\right),$
  - $k'_g = k_{g0} + \sum_i p_{gi}\,, \quad g = 1,2,3$
  - (sp.hardshell) Isotonic Regression adjustment for cluster centers (separated by at least sp.shellbarrier (delta, 0.75)). $\mathrm{u}'_{x\ 3\mathrm{x}1}$

$$w_g = k'_g, \qquad g = 1,2,3$$

$$gamma = delta * \frac{w_1 - w_3}{w_1 + w_2 + w_3}$$

$$\mathrm{u}'_{x\ 3\mathrm{x}1} = \begin{bmatrix} \mathrm{u}'_{x1} \\ \mathrm{u}'_{x2} \\ \mathrm{u}'_{x3} \end{bmatrix}, \qquad \begin{aligned} \mathrm{u}'_{x1} &= \mathrm{u}'_{x1} + delta - gamma \\ \mathrm{u}'_{x2} &= \mathrm{u}'_{x2} - gamma \\ \mathrm{u}'_{x3} &= \mathrm{u}'_{x3} - delta - gamma \end{aligned}$$

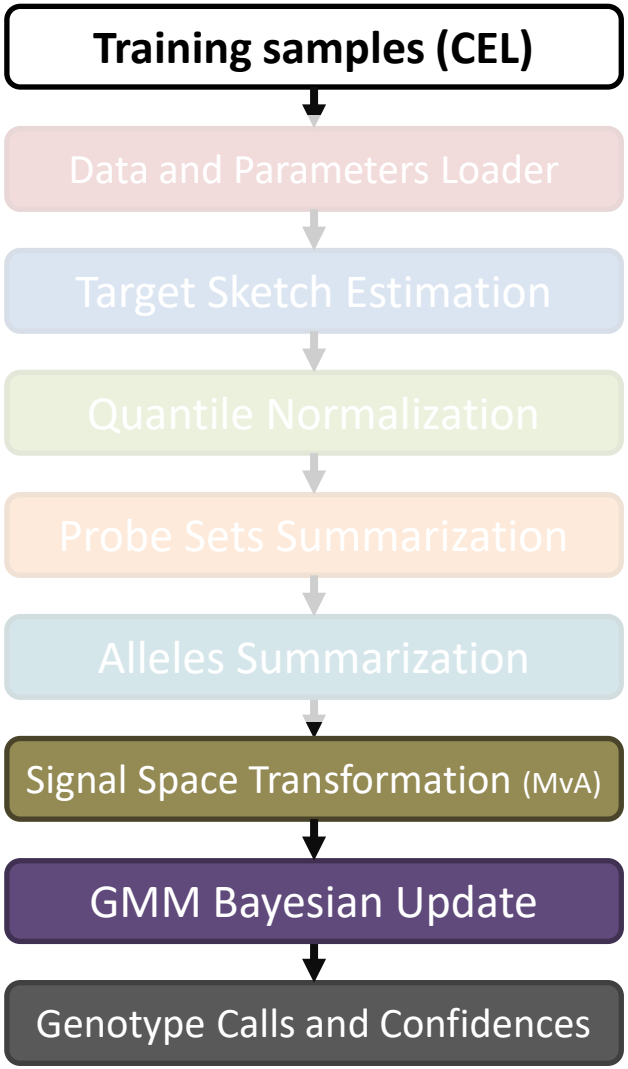
Pool Adjacent-Violators (PAV) algo.

$$\begin{cases} \mathrm{u}'_{xg}, \mathrm{u}'_{xg+1}\ , & \mathrm{u}'_{xg} \le \mathrm{u}'_{xg+1} \\ \mathrm{u}'_{xg}, \mathrm{u}'_{xg+1} = \dfrac{\sum_{g\in A} w_g * \mathrm{u}'_{xg}}{\sum_{g\in A} w_g}, & A = \left\{g \middle| \mathrm{u}'_{xg} > \mathrm{u}'_{xg+1}\right\}' \end{cases}$$

$$g = 1,2,3$$

$$\mathrm{u}'_{3\mathrm{x}1} = \begin{bmatrix} \mathrm{u}'_{x1} \\ \mathrm{u}'_{x2} \\ \mathrm{u}'_{x3} \end{bmatrix}, \qquad \begin{aligned} \mathrm{u}'_{x1} &= \mathrm{u}'_{x1} - delta + gamma \\ \mathrm{u}'_{x2} &= \mathrm{u}'_{x2} + gamma \\ \mathrm{u}'_{x3} &= \mathrm{u}'_{x3} + delta + gamma \end{aligned}$$

Genotyping Analysis Development and Distribution



- Update 2D Data model parameters with soft assignment of each data bin.
  - $\mathrm{u}'_{6\mathrm{x}1} = \left(\boldsymbol{K}_{\boldsymbol{0}}^{-1}{}_{6\mathrm{x}6} + \boldsymbol{N}'_{6\mathrm{x}6}\right)^{-1} * \left(\boldsymbol{K}_{0}^{-1}{}_{6\mathrm{x}6} * \mathrm{u}_{0\ 6\mathrm{x}1} + \mathrm{m}_{6\mathrm{x}1}\right),$
  - $k'_g = k_{g0} + \sum_i p_{gi}\,, \quad g = 1,2,3$
  - (sp.hardshell) Isotonic Regression adjustment for cluster centers (separated by at least sp.shellbarrier (delta, 0.75)). $\mathrm{u}'_{x\ 3\mathrm{x}1}$
  - $v'_g = v_{g0} + \sum_i p_{gi}\,, \quad g = 1,2,3$
  - $\sigma'^{\,2}_{xxg} \Rightarrow \frac{v_{g0} * \sigma^2_{xxg0} + \left(\sum_i p_{gi} x^2_{gi} - \sum_i p_{gi} x_{gi} * \sum_i p_{gi} x_{gi}\right) * \frac{1}{\sum_i p_{gi} + 0.001} + \frac{k_{g0} * \sum_i p_{gi}}{k_{g0} + \sum_i p_{gi}} * \left(\mathrm{u}'_{xg} - \mathrm{u}_{xg0}\right)^2}{v'_g}$
  - $\sigma'^{\,2}_{yyg} \Rightarrow \frac{v_{g0} * \sigma^2_{yyg0} + \left(\sum_i p_{gi} y^2_{gi} - \sum_i p_{gi} y_{gi} * \sum_i p_{gi} y_{gi}\right) * \frac{1}{\sum_i p_{gi} + 0.001} + \frac{k_{g0} * \sum_i p_{gi}}{k_{g0} + \sum_i p_{gi}} * \left(\mathrm{u}'_{yg} - \mathrm{u}_{yg0}\right)^2}{v'_g}$
  - $\sigma'^{\,2}_{xyg} \Rightarrow \frac{v_{g0} * \sigma^2_{xyg0} + \left(\sum_i p_{gi} xy_{gi} - \sum_i p_{gi} x_{gi} * \sum_i p_{gi} y_{gi}\right) * \frac{1}{\sum_i p_{gi} + 0.001} + \frac{k_{g0} * \sum_i p_{gi}}{k_{g0} + \sum_i p_{gi}} * \left(\mathrm{u}'_{yg} - \mathrm{u}_{yg0}\right) * \left(\mathrm{u}'_{xg} - \mathrm{u}_{xg0}\right)}{v'_g}$
  - Ad-hoc shrinkage for $\sigma'^{\,2}_{..g}$ of each cluster (controlled by mixing proportion (lambda) (1)).

    Adjusted Pooled Variance.

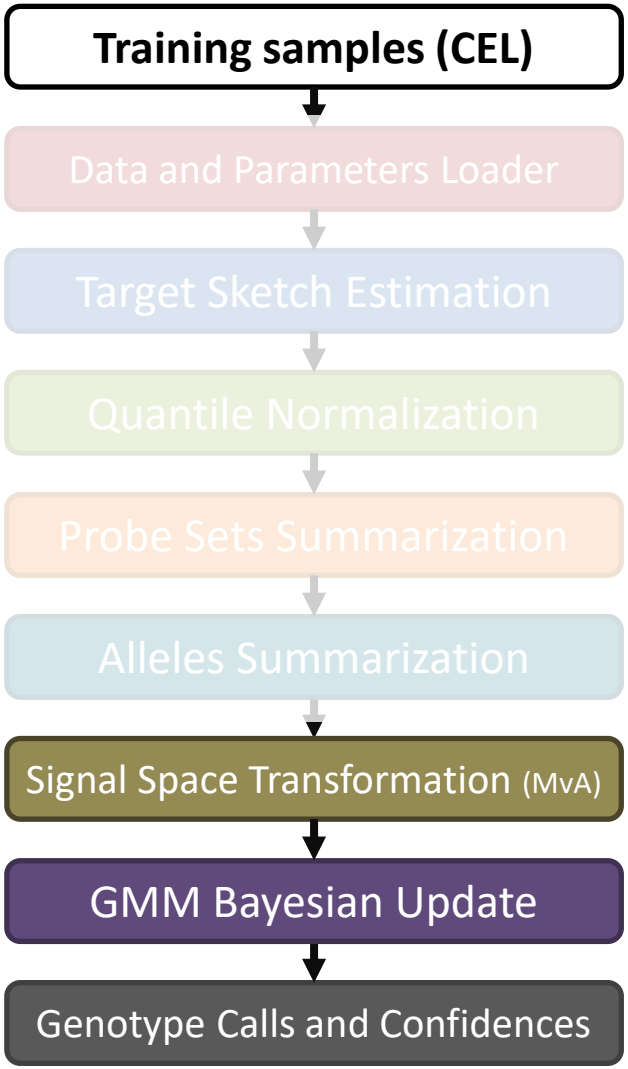
    $w_g = v_{g0} + \sum_i p_{gi}\,, \quad g = 1,2,3$

    $\sigma'^{\,2}_{xxt} = \frac{\sum_g w_g * \sigma'^{\,2}_{xxg}}{\sum_g w_g}\,, \quad \sigma'^{\,2}_{yyt} = \frac{\sum_g w_g * \sigma'^{\,2}_{yyg}}{\sum_g w_g}, \quad t = 1,2,3\,,$

    $\Rightarrow \frac{(3 - 2 * lambda) * w_t * \sigma'^{\,2}_{t} + \sum_{g \neq t} lambda * w_g * \sigma'^{\,2}_{g}}{(3 - 2 * lambda) * w_t + \sum_{g \neq t} lambda * w_g}$

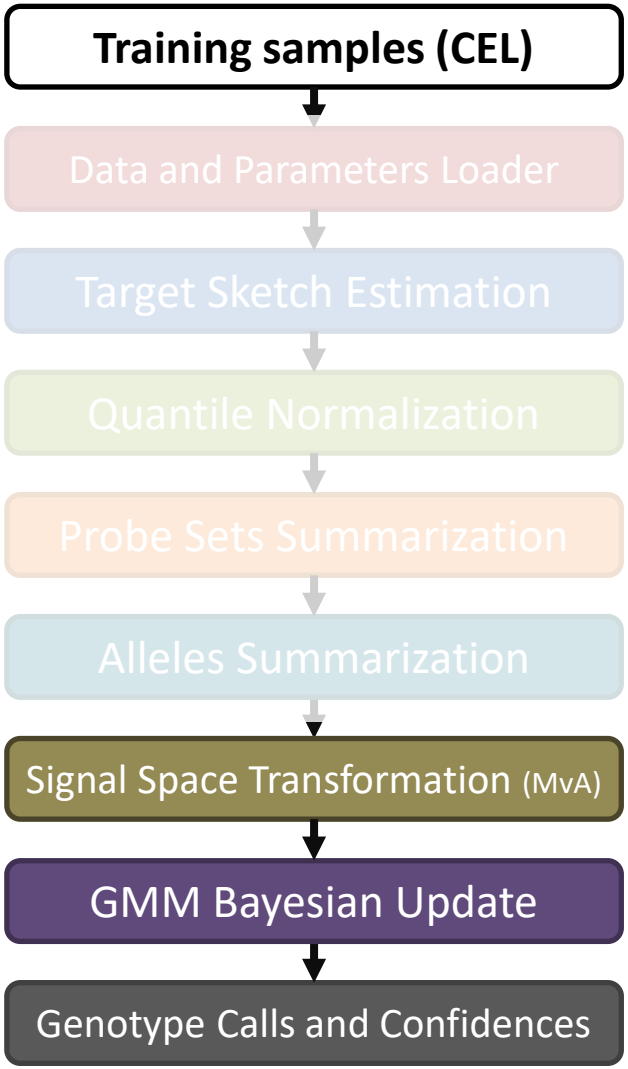
    $\sigma'^{\,2}_{xyt} = \left(\sigma'_{xxt} * \sigma'_{yyt}\right) * \frac{\sigma'_{xyg}}{\sigma'_{xxg} * \sigma'_{yyg}}, \quad t = 1,2,3\,, \quad g = t,$ means before shrinkage adjustment.

Genotyping Analysis Development and Distribution



- Update 2D Data model parameters with soft assignment of each data bin
  - $\mathrm{u}'_{6x1} = \left(\boldsymbol{K}_{\boldsymbol{0}}^{-1}{}_{6x6} + \boldsymbol{N}'_{6x6}\right)^{-1} * (\boldsymbol{K}_{0}^{-1}{}_{6x6} * \mathrm{u}_{0\ 6x1} + \mathrm{m}_{6x1})$,
  - $k'_g = k_{g0} + \sum_i p_{gi}\,, \quad g = 1,2,3$
  - (sp.hardshell) Isotonic Regression adjustment for cluster centers (separated by at least sp.shellbarrier (delta, 0.75)). $\mathrm{u}'_{x\ 3x1}$
  - $v'_g = v_{g0} + \sum_i p_{gi}\,, \quad g = 1,2,3$
  - σ'^{2}_{xxg}, σ'^{2}_{yyg}, σ'^{2}_{xyg}, $g = 1,2,3$
  - Ad-hoc shrinkage for $\sigma'^{2}_{..g}$ of each cluster (controlled by mixing proportion (lambda) (1)).
  - $\sigma'_{xx12} = \sigma_{xx120}$, $\sigma'_{xx13} = \sigma_{xx130}$, $\sigma'_{xx23} = \sigma_{xx230}$
    $\sigma'_{yy12} = \sigma_{yy120}$, $\sigma'_{yy13} = \sigma_{yy130}$, $\sigma'_{yy23} = \sigma_{yy230}$

Genotyping Analysis Development and Distribution



- (sp.mix, freqflag) compute the frequency of each cluster (AA, AB, BB)
  - $f_t = \frac{k'_t}{\sum_g k'_g}, t = 1,2,3$

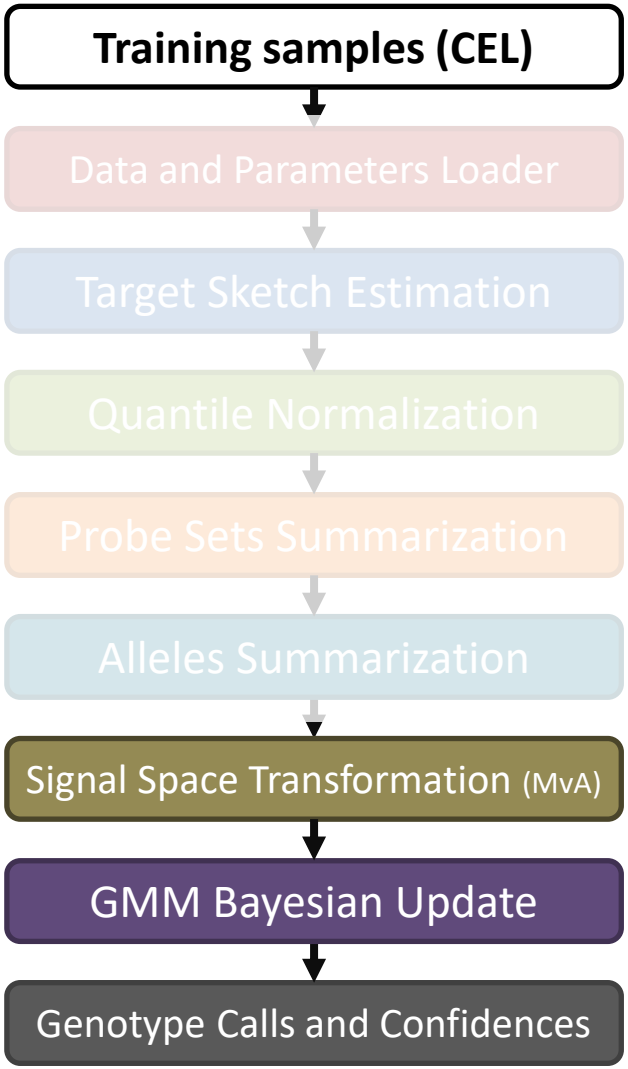
    $\Rightarrow \; logf_t = logk'_t - log\left(\sum_g k'_g\right)$

    $\Rightarrow \; -logf_t = -logk'_t + log\left(\sum_g k'_g\right)$
- For each point, compute the the probability that a data point X (x, y) belongs to each genotype.
  - $p(X \in t|X) = \frac{p(X \in t, X)}{p(X)} = \frac{p(X \in t)p(X|X \in t)}{ocean + \sum_g p(X \in g)p(X|X \in g)} =$

    $$\frac{f_t \cdot BVN\left(X \middle| \mathbf{u}'_t, \left(1 + \frac{inflatePRA}{k'_t}\right) \cdot \boldsymbol{\sigma}'_t\right)}{ocean + \sum_g f_g \cdot BVN\left(X \middle| \mathbf{u}'_g, \left(1 + \frac{inflatePRA}{k'_g}\right) \cdot \boldsymbol{\sigma}'_g\right)},$$

    $inflatePRA = 0\ (default),\ \ ocean = 0.00001\ (default)$
  - $logp(X \in t)p(X|X \in t) = \log\left(p(X \in t)\right) + \log\left(p(X|X \in t)\right)$
  - If copynumber=1, $p(X \in AB)p(X|X \in AB) = 0$

Genotyping Analysis Development and Distribution



- (sp.mix, freqflag) compute the frequency of each cluster (AA, AB, BB)
  - $f_t = \frac{k'_t}{\sum_g k'_g}, t = 1, 2, 3$
- For each point, compute the the probability that a data point X (x, y) belongs to each genotype.
  - $p(X \in t|X) = \frac{p(X \in t, X)}{p(X)} = \frac{p(X \in t)p(X|X \in t)}{ocean + \sum_g p(X \in g)p(X|X \in g)}, t = 1, 2, 3$
- For each point, make a call.
  - $\hat{t} = \underset{t}{\operatorname{argmax}}\, p(X \in t|X)$
  - $confidence = 1 - p(X \in \hat{t}|X)$
  - No call: If $confidence > MS$, $MS = 0.15$ (default) @ getGTypeCall()

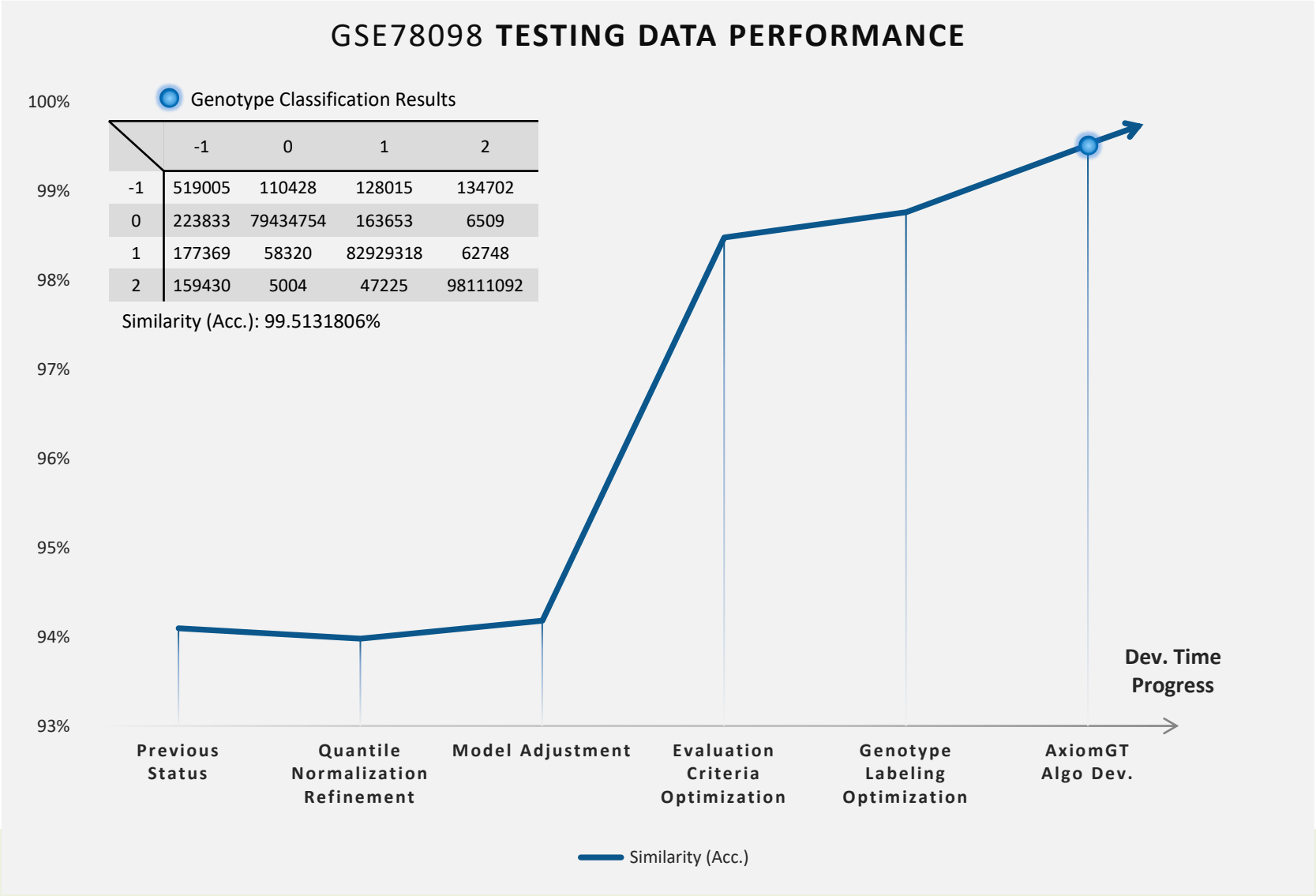
Genotyping Analysis Development and Distribution

- Evaluation Data: GSE78098
  - Platform: GPL21480 (Axiom_GW_Hu-CHB_SNP)
    - Focus on Chinese (Asian) people.
  - 420 human samples
  - 639653 Probe sets
  - Preprocessing and filter by DQC < 0.82
  - All 419 samples are picked.

- Evaluation Data: Dog Banff
  - Platform: B1C (Banff)
  - 187 dog samples
  - 48283 Probe sets
  - Preprocessing for channel name, vcf allele definition, and change the coordinate system for the Y axis of the heatmap.
  - QC filter by NP probes performance (e.g. NP call rate, NP call slope).
  - 155 dog samples are finally picked and used to build genotyping models.

- Manual, Reports & Results: Project-CPT/CPT.wiki/AxiomGT.md at main · jeff665547/Project-CPT (github.com)

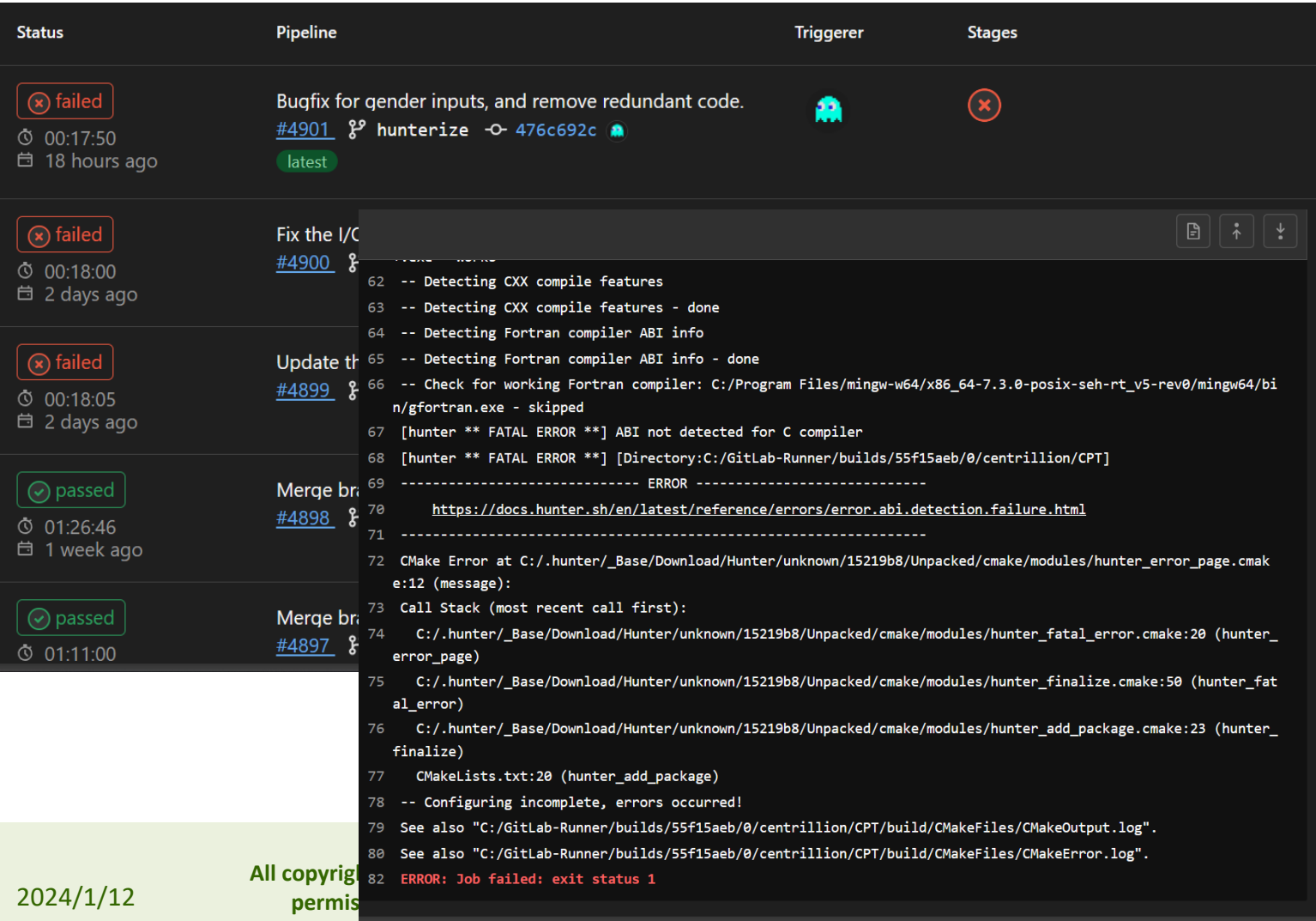
Genotyping Analysis Development and Distribution



	-1	0	1	2
-1	519005	110428	128015	134702
0	223833	79434754	163653	6509
1	177369	58320	82929318	62748
2	159430	5004	47225	98111092

Genotyping Analysis Development and Distribution

- Bugfix for the CI/CD error when deployment and distribution.



Genotyping Analysis Development and Distribution

- Successful deployment and distribution.

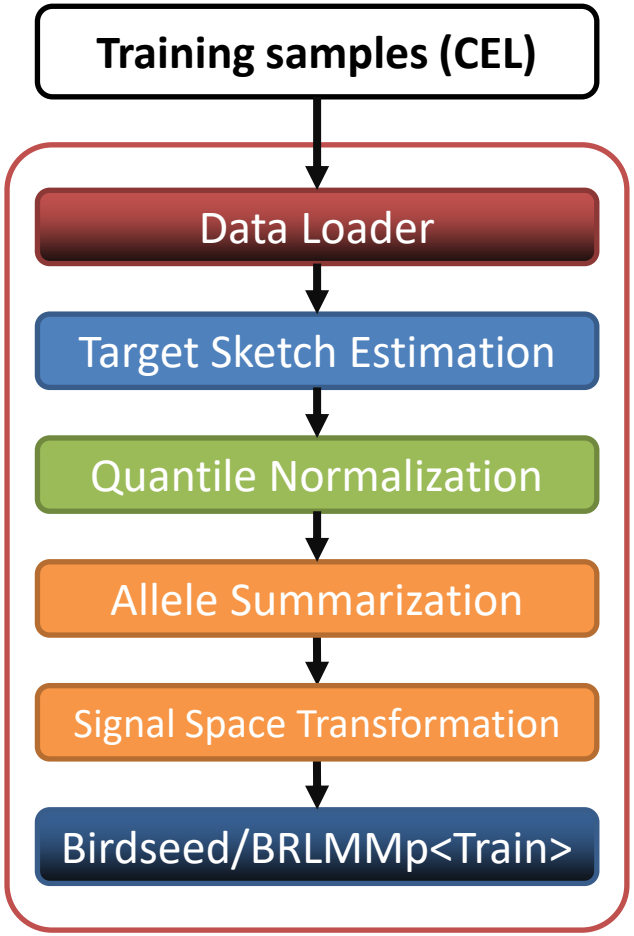
Status	Pipeline	Triggerer	Stages	
passed 01:33:52 15 hours ago	Bugfix for gender inputs, and remove redundant code. #4901 hunterize 476c692c latest			
passed 01:30:03 14 hours ago	Fix the I/O bug for the MvA Transformation. #4900 hunterize 99c7889d			
passed 01:30:22 12 hours ago	Update the logging system. #4899 hunterize 882600dc			
passed 01:26:46 1 week ago	Merge branch 'APT_AxiomGT1' into hunterize #4898 hunterize ba50e116			
passed 01:11:00 1 week ago	Merge branch 'APT_AxiomGT1' into hunterize #4897 hunterize 7a4dfac4			

Other Genotyping Models Research and Development

Jeff (CHI-HSUAN HO)

Progress Report and Future Work

- Birdseed Framework



TECHNICAL REPORTS

nature genetics

Integrated genotype calling and association analysis of SNPs, common copy number polymorphisms and rare CNVs

Joshua M Korn[1–5,10], Finny G Kuruvilla[1,4–6,10], Steven A McCarroll[1,4,5], Alec Wysoker[1], James Nemesh[1], Simon Cawley[7], Earl Hubbell[7], Jim Veitch[7], Patrick J Collins[7], Katayoon Darvishi[8], Charles Lee[8], Marcia M Nizzari[1], Stacey B Gabriel[1], Shaun Purcell[1,5], Mark J Daly[1,5,9] & David Altshuler[1,4,5,9]

- Birdseed: K-means training model

$Model_0$: *Gaussian Mixture Model* $-$ *GMM with K-Means centroid (Existing Model)*

$Model_1$: $Non-prbabilistic\ Model$

$$BIC = \frac{1}{\sigma^2}\sum_{j=1}^{K}\sum_{i=1}^{N_j} min\left\|\boldsymbol{X}_i - \hat{\boldsymbol{\mu}}_j\right\|^2 + Kd \cdot \ln(N)\,, \qquad \hat{\boldsymbol{\mu}}_j = \frac{\sum_{i=1}^{N_j}\boldsymbol{X}_i}{N_j}$$

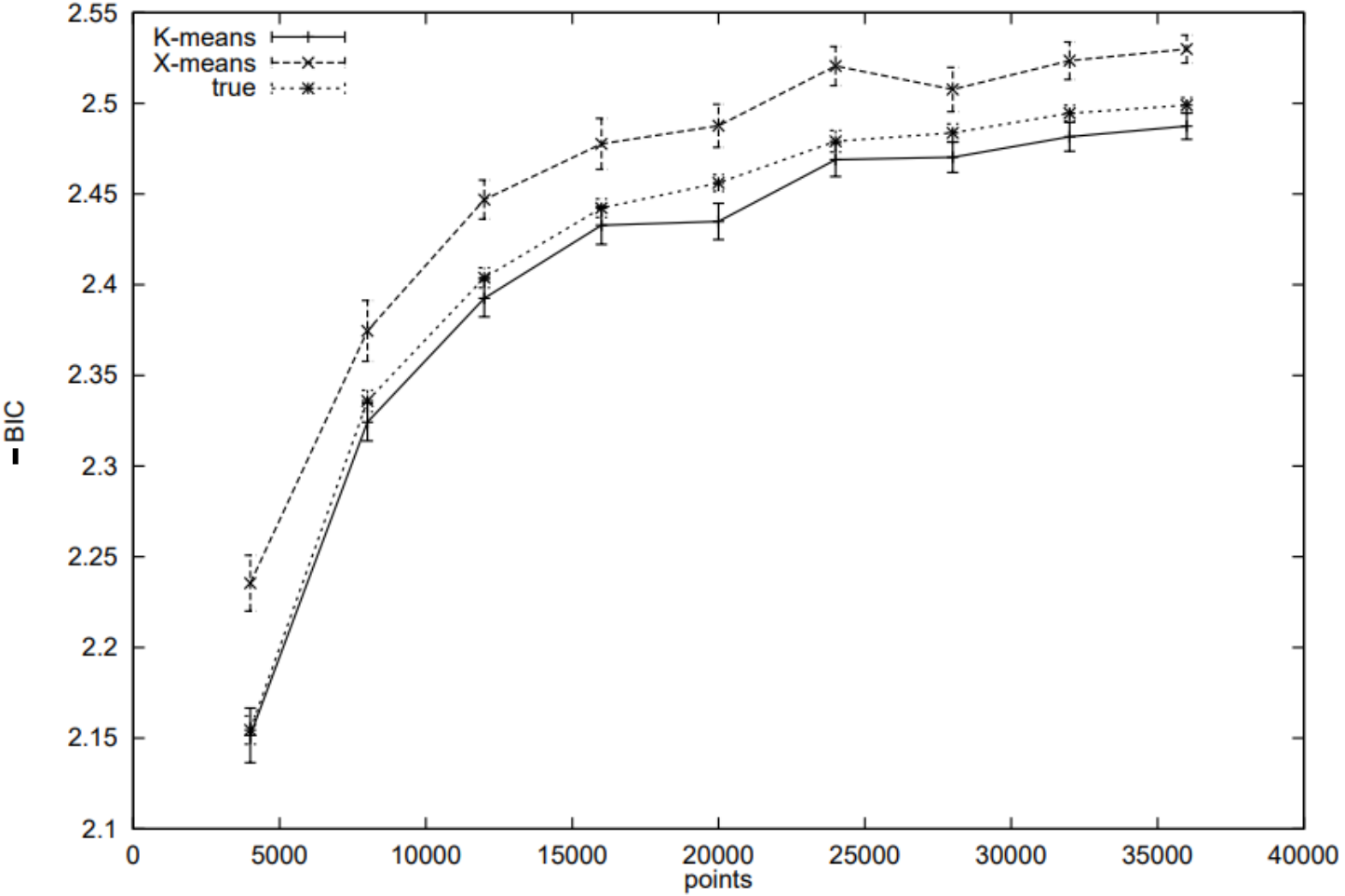
$$Model_2: f(x_i) = \pi_{ij} N\left(\boldsymbol{\mu}_j, \sigma^2 \cdot \boldsymbol{I}_d\right)$$

$$BIC = -2\sum_{j=1}^{K} N_j \ln\left(N_j\right) + 2N\ln(N) + \mathrm{dN}\ln(2\pi\hat{\sigma}^2) + dN + \ln(N)\cdot K(d+1),$$

$$where\ \hat{\sigma}^2 = \frac{1}{dN}\sum_{j=1}^{K}\sum_{i=1}^{N_j}\left\|\boldsymbol{X}_i - \hat{\boldsymbol{\mu}}_j\right\|^2, \qquad \hat{\boldsymbol{\mu}}_j = \frac{\sum_{i=1}^{N_j}\boldsymbol{X}_i}{N_j}$$

Genotyping Methods Evaluation and Simulation

$Model_2$



- Birdseed: K-means training model

$$Model_3\text{: } ANOVA\text{: } X_{it} = \mu_{it} + E_{it},\ \boldsymbol{\mu} \in \mathbb{R}^{nxd},\ \boldsymbol{E} \in \mathbb{R}^{nxd},\ E_{it} \sim iid\ N(0,\sigma^2),\ i = 1,2,\dots,N,\ t = 1,2,\dots,d$$

$$BIC = Nd \cdot \ln\left(\sum_{j=1}^{K}\sum_{i=1}^{N_j}\left\|\boldsymbol{X}_i - \hat{\boldsymbol{\mu}}_j\right\|^2\right) + Nd\left(1 + \ln\left(\frac{2\pi}{Nd}\right)\right)$$

$$+ \ln(Nd) \cdot \left[Kd + \frac{1}{\tilde{\sigma}}\sum_{j=1}^{K'}\sum_{i=1}^{\widetilde{N_j}}\sum_{t=1}^{d}\sum_{l\neq c(i)}\phi\left(\frac{X_{i,t} + \delta_l^{i,t} - \tilde{\mu}_{i,t}}{\tilde{\sigma}}\right) \cdot \lim_{\gamma \rightleftarrows \delta_l^{i,t}} \mathcal{M}\left(\boldsymbol{X} + \gamma \boldsymbol{e}_{i,t}\right)_{i,t}\right],$$

$$where\ \tilde{\sigma}^2 = \frac{1}{dN}\sum_{j=1}^{K'}\sum_{i=1}^{\widetilde{N_j}}\|\boldsymbol{X}_i - \tilde{\boldsymbol{\mu}}_i\|^2,\quad \tilde{\boldsymbol{\mu}} = \mathcal{M}(\boldsymbol{X}; K') \text{ for some } K' > K,$$

$\phi(\cdot)$ is the pdf of Normal (Gaussian) distribution,

$$\lim_{\gamma \rightleftarrows \delta_l^{i,t}} \mathcal{M}\left(\boldsymbol{X} + \gamma \boldsymbol{e}_{i,t}\right)_{i,t} = (-1)^{I_{\{\delta_l^{i,t}>0\}}}\left(\hat{\mu}_{c(i),t} - \frac{N_l}{N_l+1}\hat{\mu}_{l,t} - \frac{X_{i,t}}{N_l+1} + \delta_l^{i,t}\left(\frac{N_l+1-N_{c(i)}}{(N_l+1)\cdot N_{c(i)}}\right)\right),$$

$$c(i) = argmin_{l\epsilon\{1,2,\dots,K\}}\|\boldsymbol{X}_i - \hat{\boldsymbol{\mu}}_l\|^2,$$

$$\left(1 - \left(\frac{N_{c(i)}-1}{N_{c(i)}}\right)^2\right)\delta_l^{i,t\,2} + 2 \cdot \left(\left(X_{i,t} - \hat{\mu}_{l,t}\right) - \left(X_{i,t} - \hat{\mu}_{c(i),t}\right) \cdot \left(\frac{N_{c(i)}-1}{N_{c(i)}}\right)\right)\delta_l^{i,t} + \left(X_{i,t} - \hat{\mu}_{l,t}\right)^2 - \left(X_{i,t} - \hat{\mu}_{c(i),t}\right)^2 = 0$$

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$Model_3$

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Degrees of freedom and model selection for k-means clustering

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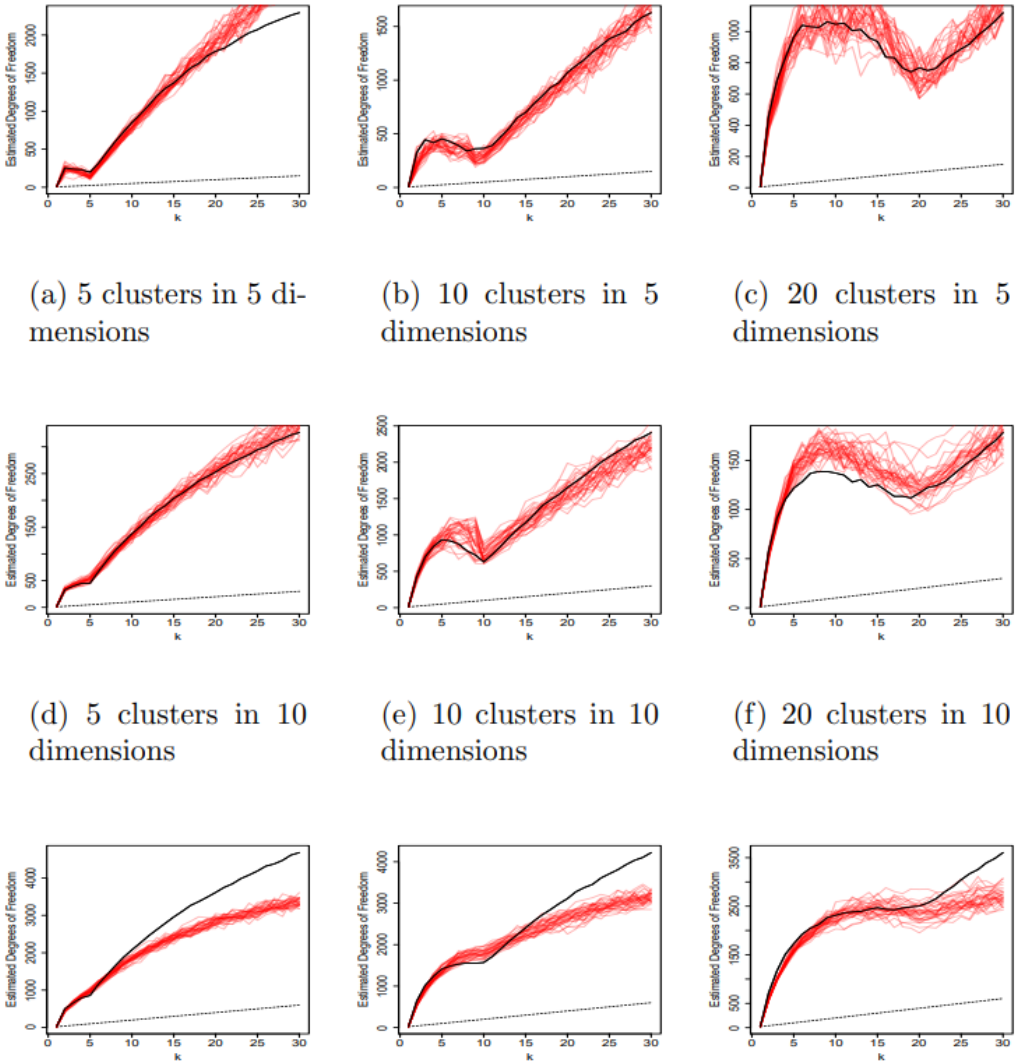
ABSTRACT

A thorough investigation into the model degrees of freedom in k-means clustering is conducted. An extension of Stein's lemma is used to obtain an expression for the effective degrees of freedom in the k-means model. Approximating the degrees of freedom in practice requires simplifications of this expression, however empirical studies evince the appropriateness of the proposed approach. The practical relevance of this new degrees of freedom formulation for k-means is demonstrated through model selection using the Bayesian Information Criterion. The reliability of this method is then validated through experiments on simulated data as well as on a large collection of publicly available benchmark data sets from diverse application areas. Comparisons with popular existing techniques indicate that this approach is extremely competitive for selecting high quality clustering solutions.



(a) 5 clusters in 5 dimensions

(b) 10 clusters in 5 dimensions

(c) 20 clusters in 5 dimensions

(d) 5 clusters in 10 dimensions

(e) 10 clusters in 10 dimensions

(f) 20 clusters in 10 dimensions

Genotyping Methods Evaluation and Simulation

- Birdseed: K-means training model

$Model_0$: $Equal\ weight\ Before\ scale$: 94.1908%
$Model_0$: $But\ differnet\ weight\ Before\ scale$
– $Default\ (trim\ BIC, trim\ Fan)$: 84.6841% $with\ very\ highly\ lose-classified\ rate.$
$Model_0$: $But\ differnet\ weight\ Before\ scale - no\ trim\ BIC$: 90.8778%
$Model_0$: $But\ differnet\ weight\ Before\ scale - no\ trim$ Fan: 0%
$Model_1$: $Before\ scale$
– $Default\ (trim\ BIC, trim\ Fan)$: 98.3863% $with\ very\ highly\ lose-classified\ rate.$
$Model_1$: $Before\ scale\ - no\ trim\ BIC$: 98.6603% → 98.7585% ($BIC\ under\ all\ data$)
$Model_1$: $Before\ scale\ - no\ trim$ Fan: 98.4763%
$Model_1$: $After\ scale$: 94.3179%

```
1   -    -2   -1   0    1    2    cen
2   -2   0    0    0    0    0
3   -1   0    0    68556     134030    87256
4   0    0    0    18744020       278090    4160
5   1    0    0    99968     19637894       134212
6   2    0    0    1485      255610    23149219
7   affy
8   acc : 0.987585
```

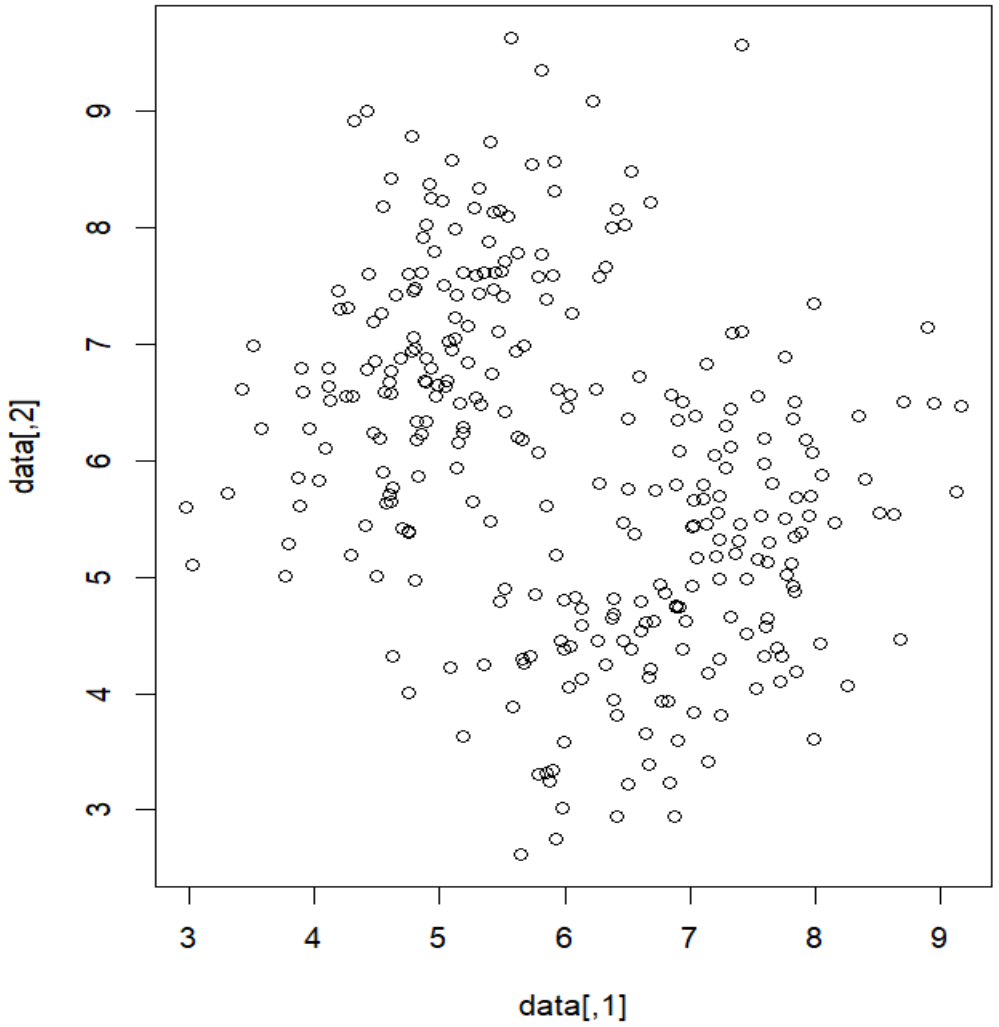
Genotyping Methods Evaluation and Simulation

- Simulation

`sol$k:` $Model_3$

`sol$k_:` $Model_1$: $Before\ scale$

```
> print(sol$k)
[1] 2
> print(sol$k_)
[1] 3
```



Ans: $k = 2$

Genotyping Methods Evaluation and Simulation

- Simulation

`sol$k:` $Model_3$

`sol$k_:` $Model_1$: $Before\ scale$

```
> print(sol$k)
[1] 3
> print(sol$k_)
[1] 3
```

Ans: $k = 3$