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Likelihood Ratios for Mixtures: Continuous Approach

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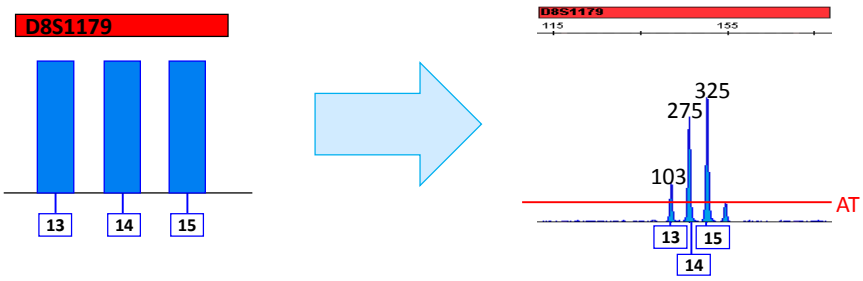
Disclaimer

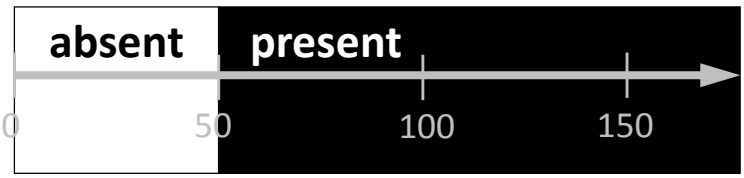
Points of view in this presentation are mine and do not necessarily represent the official position or policies of the National Institute of Standards and Technology.

From Semi-continuous to Continuous



Discrete vs. Continuous

- The observed peaks as a **discrete** variable:



- The observed peaks as a **continuous** variable:

Discrete vs. Continuous

The observed peak as a **discrete** variable:

$Pr(peak\ absent) = \bar{C}[(1-p_{15}) + p_{15}D]$

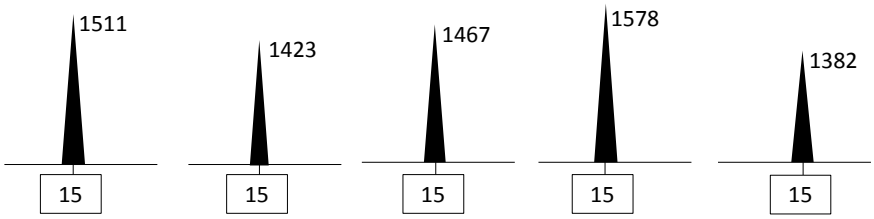
no drop-in and donor has no 15
or
no drop-in, donor has 15 and drop-out

$Pr(peak\ present) = p_{15}\bar{D} + (1-p_{15})Cp_{15}$

donor has 15 and no drop-out
or
donor has no 15 and drop-in of 15

Discrete vs. Continuous

The observed peaks as a **continuous** variable:

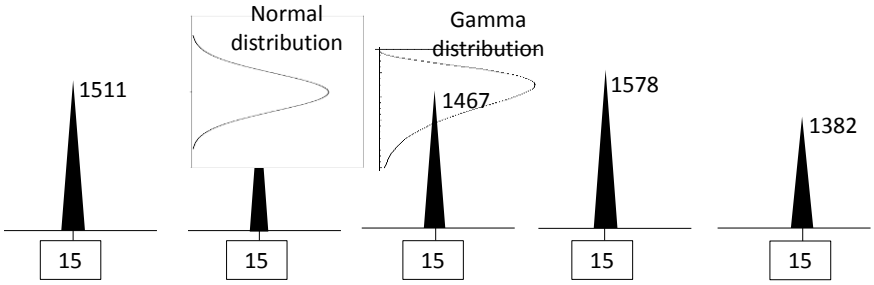


$Pr(peak\ is\ 1511rfu)$ $Pr(peak\ is\ 1467rfu)$ $Pr(peak\ is\ 1382rfu)$

$Pr(peak\ is\ 1423rfu)$ $Pr(peak\ is\ 1578rfu)$

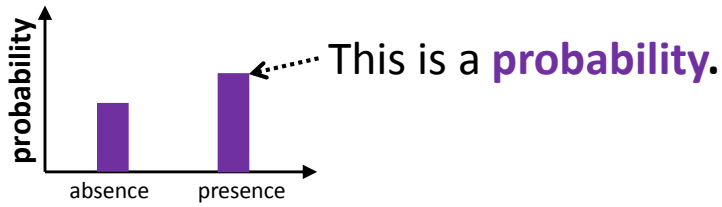
Discrete vs. Continuous

The observed peaks as a **continuous** variable:

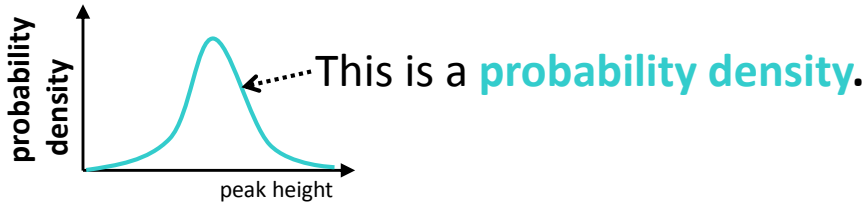


Discrete vs. Continuous

- The observed peaks as a **discrete** variable:



- The observed peaks as a **continuous** variable:



Likelihood Ratio: from semi-continuous to continuous

$$LR = \frac{\sum_{genotype\ sets|H_p} weight \times genotype\ match\ prob.}{\sum_{genotype\ sets|H_d} weight \times genotype\ match\ prob.}$$

stays the same

(Hardy-Weinberg Law, NRC II recommendation 4.1, NRC II recommendation 4.2)

Likelihood Ratio: from semi-continuous to continuous

$$LR = \frac{\sum_{genotype\ sets|H_p} weight \times genotype\ match\ prob.}{\sum_{genotype\ sets|H_d} weight \times genotype\ match\ prob.}$$

changes

semi-continuous weight: any value between 0 and 1, including 0 and 1, assigned using probabilities of drop-out and drop-in

continuous: a **probability density**, generally assigned based on the results of simulations that attempt to reproduce the observed peak heights

Likelihood Ratio

$$LR = \frac{\sum_{j=1}^{m} \mathrm{f}(G_{CS}|S_j)\Pr(S_j|G_K, H_p, I)}{\sum_{j=1}^{m} \mathrm{f}(G_{CS}|S_j)\Pr(S_j|G_K, H_d, I)}$$

match probabilities

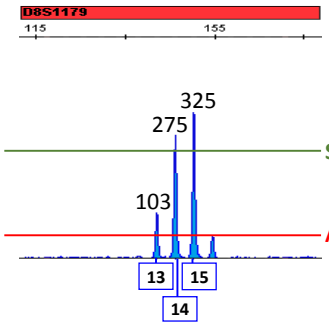
the probability of genotype set S_j given that we have observed genotypes G_K and that the contributors are as specified in H_p or H_d

Likelihood Ratio

$$LR = \frac{\sum_{j=1}^{m} \mathrm{f}(G_{CS}|S_j)\Pr(S_j|G_K, H_p, I)}{\sum_{j=1}^{m} \mathrm{f}(G_{CS}|S_j)\Pr(S_j|G_K, H_d, I)}$$

weights

the probability of obtaining these DNA typing results for genotype set S_j



Probabilistic Genotyping

weight

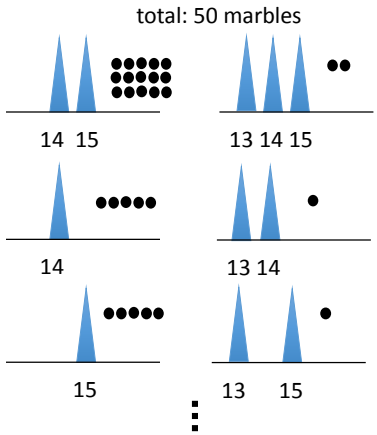
Major	Minor	*w*	*match prob*$_{\cdot major}$	*match prob*$_{\cdot minor}$
14,15	12,13		$2p_{14}p_{15}$	$2p_{12}p_{13}$
14,15	13,13		$2p_{14}p_{15}$	p_{13}^2
14,15	13,14		$2p_{14}p_{15}$	$2p_{13}p_{14}$
14,15	13,15		$2p_{14}p_{15}$	$2p_{13}p_{15}$
14,15	13,16		$2p_{14}p_{15}$	$2p_{13}p_{16}$
14,15	13,17		$2p_{14}p_{15}$	$2p_{13}p_{17}$

Concept of weights

the probability of obtaining these DNA typing results for a particular genotype set

Concept of weights

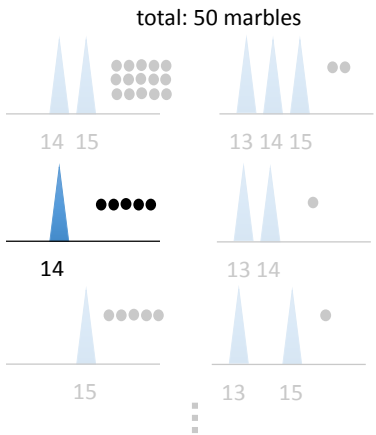
single source:



genotype = {14,15}

Concept of weights

single source:



genotype = {14,15}

$$\text{weight} = \frac{5}{50}$$

Concept of weights

how large or small a weight is depends on:

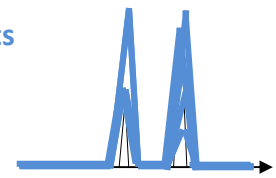
- possibility of allele drop-out
- possibility of allele drop-in
- amount of template DNA
- possibility of degradation
- possibility of oversized stutter peaks

⋮

Continuous Model: short explanation

Simulations attempt to reproduce the observed peak heights by varying a set of parameters.

simulated peak heights



observed peak heights

The better S_j and the set of parameters explain G_{CS}, the greater the probability density $f\left(G_{CS}|S_j\right)$ assigned to that genotype set.

Continuous model: longer explanation

1) Randomly choose a genotype set and values for all of the parameters that are necessary to model the expected peak heights.

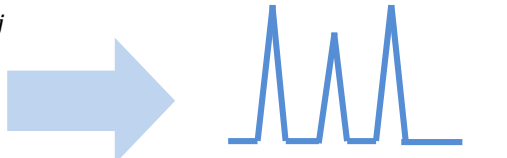
genotype set S_j
parameter 1
parameter 2
parameter 3
⋮

Markov Chain Monte Carlo (MCMC) sampling

Continuous model: longer explanation

2) Model the expected peak heights given the chosen genotype set S_j and parameter values.

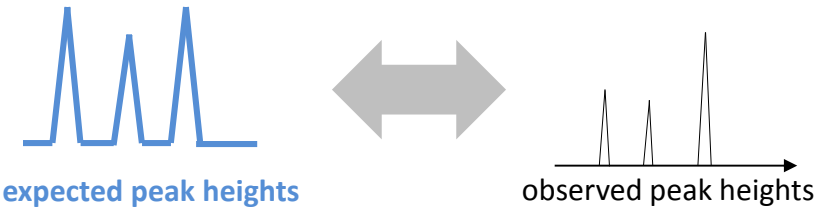
genotype set S_j
parameter 1
parameter 2
parameter 3
⋮



expected peak heights

Continuous model: longer explanation

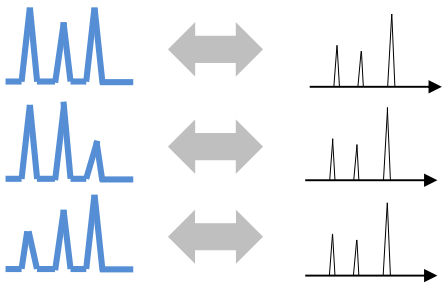
3) Compare the expected peak heights with the observed peak heights. How similar are they?



Assign a probability density for the observed peak heights given the expected peak heights.

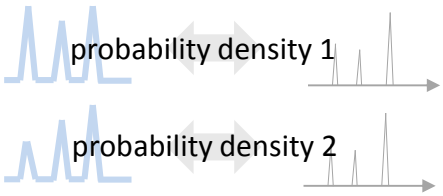
Continuous model: longer explanation

4) Repeat steps 1) through 3) a large number of times. A large number of simulations are performed that randomly vary the genotype set and the parameter values.



Continuous model: longer explanation

3) Compare the expected peak heights with the observed peak heights. How similar are they?
4) Repeat steps 1) through 3) a large number of times. A large number of simulations are performed that randomly vary the genotype set and the parameter values.

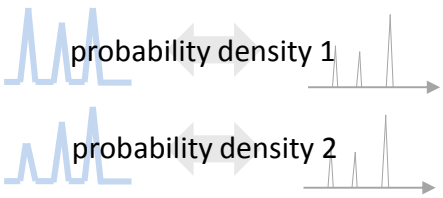


If *probability density 2* $\geq$ *probability density 1*, save S_j and the parameter values of simulation 2.

If *probability density 2* < *probability density 1*, save S_j and the parameter values of simulation 2 only some of the times. The probability of saving the values is equal to $\frac{probability\ density\ 2}{probability\ density\ 1}$.

Continuous model: longer explanation

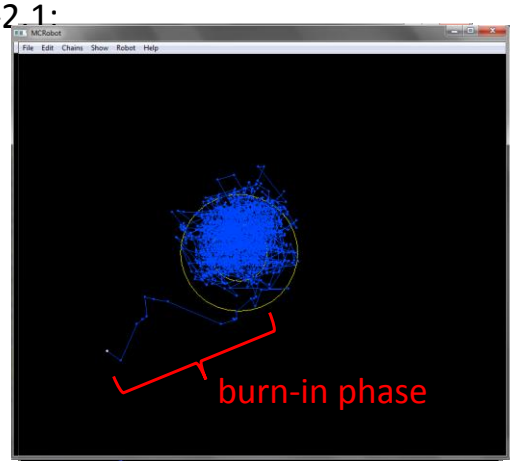
3) Compare the expected peak heights with the observed peak heights. How similar are they?
4) Repeat steps 1) through 3) a large number of times. A large number of simulations are performed that randomly vary the genotype set and the parameter values.



Metropolis-Hastings algorithm

Continuous model: longer explanation

MCRobot-2_1:



after taking 200 samples

384

Continuous model: longer explanation

5) Assign the weight $f(G_{CS}|S_j)$ based on the saved simulation results.

discard burn-in

saved simulation results:		
Genotype set	*Parameter 1*	*Parameter 2*
~~6,7 and 8,9~~		
~~6,7 and 8,8~~		
~~7,7 and 6,8~~		
6,7 and 8,8		
6,7 and 8,8		
6,8 and 7,8		
6,7 and 8,8		
6,7 and 8,8		
6,8 and 7,8		

Continuous model: longer explanation

5) Assign the weight $f(G_{CS}|S_j)$ based on the saved simulation results.

The weight $f(G_{CS}|S_j)$ is assigned as the proportion of genotype sets S_j among the saved genotype sets.

Example: S_j = 6,7 and 8,8

→ $f(G_{CS}|S_j) = \frac{4}{6}$

saved simulation results:		
Genotype set	*Parameter 1*	*Parameter 2*
~~6,7 and 8,9~~		
~~6,7 and 8,8~~		
~~7,7 and 6,8~~		
6,7 and 8,8		
6,7 and 8,8		
6,8 and 7,8		
6,7 and 8,8		
6,7 and 8,8		
6,8 and 7,8		

Continuous model: longer explanation

simulations

1) Randomly choose a genotype set S_j and values for all of the parameters that are necessary to model the expected peak heights.
2) Model the expected peak heights given the chosen genotype set S_j and parameter values.
3) Compare the expected peak heights with the observed peak heights. How similar are they?
4) Repeat steps 1) through 3) a large number of times. A large number of simulations are performed that randomly vary the genotype set S_j and the parameter values.
5) Assign the weight $f(G_{CS}|S_j)$ based on the saved simulation results.

Summary of main points

- The **peak heights** are a **continuous variable**.
- Mathematically speaking, $f\left(G_{CS}|S_j\right)$ is the **probability density** for the observed peak heights given the genotype set S_j.
- The probability densities $f\left(G_{CS}|S_j\right)$ are assigned based on the results of simulations that attempt to reproduce the observed peak heights by varying a set of parameters.