Human meiotic interference

Karl W Broman
James L Weber
Meiosis
Interference

- Strand choice
  → Chromatid interference

- Spacing
  → Chiasma (crossover) interference
Model organisms

• Lots of meioses
• A few linked markers
• Look at frequency of rare multiple recombination events

*Drosophila* data (Morgan et al 1935)

<table>
<thead>
<tr>
<th>Event</th>
<th>Count</th>
<th>Event</th>
<th>Count</th>
</tr>
</thead>
<tbody>
<tr>
<td>0000</td>
<td>10,431</td>
<td>1001</td>
<td>46</td>
</tr>
<tr>
<td>1000</td>
<td>771</td>
<td>0101</td>
<td>53</td>
</tr>
<tr>
<td>0100</td>
<td>1,579</td>
<td>0011</td>
<td>25</td>
</tr>
<tr>
<td>0010</td>
<td>1,221</td>
<td>1110</td>
<td>1</td>
</tr>
<tr>
<td>0001</td>
<td>1,994</td>
<td>1101</td>
<td>1</td>
</tr>
<tr>
<td>1100</td>
<td>4</td>
<td>1011</td>
<td>1</td>
</tr>
<tr>
<td>1010</td>
<td>7</td>
<td>0111</td>
<td>1</td>
</tr>
<tr>
<td>0110</td>
<td>4</td>
<td>1111</td>
<td>1</td>
</tr>
</tbody>
</table>
Human data

- [www.marshmed.org/genetics](http://www.marshmed.org/genetics)
- 8 CEPH families
  - three generations
  - 11 to 15 progeny
  - 92 meioses
- ~8,000 STRP markers
  - 90 ± 7 % typed
- Average spacing
  - female: 0.6 ± 1.2 cM
  - male: 0.4 ± 1.0 cM
  - sex-ave: 0.5 ± 0.9 cM
- Data cleaning
  - Removed 764/964,425 (~0.08%) genotypes resulting in tight double recombinants
• **Count-location model**

\[ n \sim (p_0, p_1, p_2, \ldots) \]

locations \( n \sim \text{iid uniform} \)

• **Gamma model**

\[ x_i \text{’}s \sim \text{stationary gamma renewal process} \]
\[ \text{shape} = \nu, \text{rate} = 2\nu \]

\[ y_i \text{’}s \sim \text{mixtures of gammas} \]
Model fitting

• Count-location model

\[ m_i = \# \text{ crossovers} \]
\[ n_i = \text{ underlying } \# \text{ chiasmata} \]

\[ n_i \sim (p_0, p_1, p_2, \ldots) \]
\[ m_i | n_i \sim \text{ binomial}(n_i, 1/2) \]

MLEs via a version of the EM algorithm
Model fitting

• Gamma model

\[ x_1, x_2, \ldots \sim f(\nu, 2\nu) \]
\[ x_0 \sim g = 2[1-F(\nu, 2\nu)] \]
\[ x_i \text{'s independent} \]

\[ y_1, y_2, \ldots \sim \sum \frac{1}{2} f(k\nu, 2\nu) \]
\[ y_0 \sim \frac{1}{2} g + \sum \frac{1}{2} (k+1) g \ast f(k\nu, 2\nu) \]
\[ y_i \text{'s independent} \]

• MLE of \( \nu \) using \( y_i \text{'s} \)
• \( g \) calculated numerically
• Convolutions calculated numerically
• Maximization performed using a quasi-Newton method
Distributions of \# XOs / chr

<table>
<thead>
<tr>
<th>Maternal chromosome 1</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5 &gt; 5</th>
<th>(X^2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Obs.</td>
<td>2</td>
<td>7</td>
<td>12</td>
<td>24</td>
<td>23</td>
<td>14</td>
<td>10</td>
</tr>
<tr>
<td>Pois.</td>
<td>3</td>
<td>9</td>
<td>17</td>
<td>20</td>
<td>17</td>
<td>12</td>
<td>14</td>
</tr>
<tr>
<td>C-L</td>
<td>2</td>
<td>7</td>
<td>14</td>
<td>22</td>
<td>23</td>
<td>16</td>
<td>9</td>
</tr>
<tr>
<td>Gamma</td>
<td>1</td>
<td>5</td>
<td>14</td>
<td>23</td>
<td>23</td>
<td>16</td>
<td>10</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Maternal chromosome 4</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5 &gt; 5</th>
<th>(X^2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Obs.</td>
<td>1</td>
<td>16</td>
<td>36</td>
<td>15</td>
<td>15</td>
<td>9</td>
<td>0</td>
</tr>
<tr>
<td>Pois.</td>
<td>7</td>
<td>18</td>
<td>23</td>
<td>20</td>
<td>13</td>
<td>7</td>
<td>4</td>
</tr>
<tr>
<td>C-L</td>
<td>4</td>
<td>16</td>
<td>26</td>
<td>25</td>
<td>15</td>
<td>6</td>
<td>1</td>
</tr>
<tr>
<td>Gamma</td>
<td>4</td>
<td>15</td>
<td>26</td>
<td>24</td>
<td>15</td>
<td>6</td>
<td>1</td>
</tr>
</tbody>
</table>

Evidence for interference:
maternal 3, 9, 12, 14, 15, 17
paternal 1, 4, 5, 9, 14
maternal chromosome 1
(n = 418, \( \hat{\nu} = 5.7 \))

paternal chromosome 1
(n = 285, \( \hat{\nu} = 4.9 \))
Discussion

• Approximations
  – Correct marker order
  – Correct genetic distances
  – All crossovers observed
  – Interval censoring unimportant
  – No individual variation in recombination
  – Interference constant across chromosome

• Conclusions
  – Gamma model fits well
  – Count-location model fits poorly
  – Gamma parameter, \( \hat{\nu} \approx 3–5 \)
    (stronger than Kosambi, \( \nu \approx 2.6 \))

• Further work
  – Interference across the centromere
  – Variation between chromosomes