Maximally distant genomes under the DCJ operation

Manda Riehl

Permutation Patterns, 2010
Genomes

- Made of chromosomes.
Genomes

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- Made of genes.
Replication
Mouse and Human Genomes

90.2% of the human genome and 93.3% of the mouse genome lie in conserved syntenic segments.
Mouse and Human Genetic Similarities

Mouse chromosomes

Human chromosomes

Courtesy Lisa Stubbs
Oak Ridge National Laboratory
Chromosomes as Permutations

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Chromosomes as Permutations

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  - Direction matters:
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  - Even so, Christie (1996), Pevzner (1998), Labarre (2005) have also considered unsigned versions.
Chromosomes as SIGNED Permutations

1 2  −4  −3 indicates the substring 3  4 was attached to 1  2 "backwards".
Distances between permutations

Fundamental Question:
Given two genomes/permutations, how many mistakes/mutations/operations do we need to change one into the other?
Distances between permutations

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  Given two genomes/permutations, how many mistakes/mutations/operations do we need to change one into the other?

- Fundamental Answer:
  It depends on your operation.
(Note: Because in this talk, we are using a multichromosomal model, our signed permutations are more like “broken" permutations, or ordered set partitions)
Inversions: Reverse the order of a chromosome or part of the genome
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Interchanges: Switch two segments of the genome
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- Fissions: one segment is split into two
- Circularizations and Linearizations: Convert between linear and circular chromosomes
Double Cut and Join

- Includes them all!
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  - Pros: Very general
Double Cut and Join

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  - Cons: Very general
Definitions

- An *external vertex* or *telomere* is half an element of the signed permutation whose tail or head is not connected to any other element.
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Example: $2 1^- 4 3 5 C . . . $
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**Example:** 2 1 −4  3 5C... (2t), (4t), (3h), and (3t) are external vertices. (2h,1t), (1h,4h), and (5h,5t) are internal vertices.
Double Cut and Join

(Yancoupoulos 2005)
A DCJ operation involves making two cuts in a genome and rejoining the pieces in one of the following ways:

- Two internal vertices \((a,b)\) and \((c,d)\) can be replaced with two new internal vertices \((a,d)\) and \((c,b)\) or \((a,c)\) and \((b,d)\).
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- An internal vertex \((a,b)\) can be replaced by two external vertices \((a)\) and \((b)\).
The example below shows how a DCJ operation can transform one genome into another.
The DCJ distance between two genomes on the same set of genes is defined to be the fewest number of Double-Cut-and-Join operations that it takes to transform one genome into the other.
DCJ Distance

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- What for?
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What for?

Audience Poll: Which has a more recent common ancestor: humans and rabbits, humans and camels, or humans and pigs?
Adjacency/Breakpoint Graph

Any genome can be represented by a distinct arrangement of sets of internal vertices and external vertices. A bipartite adjacency graph is constructed with vertices corresponding to the sets of internal and external vertices of the two genomes. Two vertices are connected with an edge for every head or tail that they share.
Theorem

(Bergeron, Mixtacki, Stoye 2008) The DCJ distance between two genomes, A and B, defined on the same set of N genes is given by

\[ d_{DCJ}(A, B) = N - (C + I/2), \]

where \( C \) is the number of cycles and \( I \) is the number of odd paths in the adjacency graph of A and B.
Example

\[ d_{DCJ}(1 \ 2 \ 3 \ 4 \ 5, \ 1 \ -4 \ 2 \ 5 \ -3) \]
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Questions:
- Are “most” genomes near $A$ or far from $A$?
- What features of $A$ will this distribution depend on?
- Are there symmetry properties of this distribution?
Obvious Corollary to BMS: The maximum distance between two genomes is $N$ and occurs when $C + I/2 = 0$. 
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This means that there are no cycles and no odd paths in the adjacency graph of two maximally distant genomes.
Maximum Distance

By considering an arbitrary starting genome, $A$, defined on $N$ signed genes and counting the number of distinct adjacency graphs that could be created from it containing only even paths we showed:

**Theorem**

The number of maximally distant genomes is given by

$$G_{\text{max}}(m, n) = (2m - 1)!! \sum_{k=0}^{n} \binom{n + m - 1}{k} \binom{n}{k} 2^k k!,$$

where $2m$ is the number of telomeres, and $n$ is the number of adjacencies in $A$. 
Show me the values!

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<th></th>
<th></th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
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<td>4361</td>
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<td></td>
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<td>137025</td>
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<td>36893745</td>
<td>726753195</td>
</tr>
</tbody>
</table>
Theorem

\[ G(m, 1) = G(m + 1, 0) \]
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Conjecture: \( G(m, n) \neq G(s, t) \) otherwise.
Theorem

The exponential generating function for the sequence \( \{g_m\} \) is given by

\[
f_m(x) = (2m - 1)!! \frac{e^{x/(1-2x)}}{(1-2x)^m},
\]
Chromosomes as UNSIGNED permutations

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- The method of BMS breaks down thoroughly.
Chromosomes as UNSIGNED permutations

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- The method of BMS breaks down thoroughly.
- Python program to generate data.
Number of unsigned genomes distance $D$ from a single linear chromosome of length $N$

<table>
<thead>
<tr>
<th>$N \setminus D$</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
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<tbody>
<tr>
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<td>1</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>1</td>
<td>4</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>1</td>
<td>10</td>
<td>12</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
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<td>1</td>
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<td>64</td>
<td>39</td>
<td>1</td>
<td></td>
</tr>
<tr>
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<td>1</td>
<td>28</td>
<td>208</td>
<td>387</td>
<td>149</td>
<td>1</td>
</tr>
<tr>
<td>6</td>
<td>1</td>
<td>40</td>
<td>501</td>
<td>2096</td>
<td>2478</td>
<td>661</td>
</tr>
</tbody>
</table>

Column when $n = 1$ is A028552 in OEIS.
Strategy

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- Find a new data structure!
- Must incorporate the symmetries.
In progress

Consider the vertices of your two genomes as ordered pairs, with external vertices having a 0 in their pair.
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- Plot the vertices, and their reflections across the line $x = y$, on the upper right quarter plane.
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- Use circles for your start genome, crosses for your destination.
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- Plot the vertices, and their reflections across the line $x = y$, on the upper right quarter plane.
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- Imagine an infinite source of circles at $(0, 0)$. 
About the Game Board

- No more than 2 of the same symbol at each grid point.
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- Row and column restrictions arise from genome motivation.
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- Row and column restrictions arise from genome motivation.
- Want to abolish all crosses by moving circles on top of them.
Rules of the Game

- Take a circle, move it in its row or column.

Recording these moves gives a sequence of unsigned DCJ operations. When all crosses have been destroyed, you have reached your destination genome.
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- At a right angle to the new location, move the next circle an opposite move, if it exists.

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- (Do the reflection of this move simultaneously with the reflected circle.)
- At a right angle to the new location, move the next circle an opposite move, if it exists.
- OR: Take two circles \((0, a), (0, b)\) and create one circle \((a, b)\), or vice versa.

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Strategy of the Game

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- Do doubles when you can, and choose doubles to get the most doubles immediately.
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- Do doubles when you can, and choose doubles to get the most doubles immediately.
- A double is always better than a single.
- No single is better than any other!
In progress:

- Complicated proof by contradiction outlining why no single is better than any other.
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- Basically, large loops of dependencies terminate.
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- Complicated proof by contradiction outlining why no single is better than any other.
- Basically, large loops of dependencies terminate.
- Not only shows that the maximum distance is $n$, but also gives the sequences of DCJ’s.
Questions:
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Is there a better data structure that yields a distance without the work of finding the sequence of moves?
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The total number of these unsigned genomes is not known. Is there a smart way to count them?
Thank you to the organizers for allowing me to speak and all their hard work.
FIGURE 13.33. Gene order is conserved across wide evolutionary distances. The colored segments show blocks of genome that have maintained the same order between mouse and humans. Each color corresponds to a mouse chromosome, overlaid onto the human chromosomes. Note that gene content on the X chromosome is completely conserved (far right).