AN ALTERNATIVE ALGEBRAIC FORMALISM FOR GENOME REARRANGEMENTS

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Here we relate the recent theory of genome rearrangements to the theory of permutation groups in a new way and hope to set the ground for further advances in the area. This work was motivated by the fact that many arguments in genome rearrangements are of the form "look at the figure", and lack more formal algebraic derivation. We intend to give the area a strong algebraic formalism, much as analytic geometry provided an alternative geometric arguments based on pictures.

1 Introduction

In this paper we are concerned with the genome rearrangement problem viewed as a combinatorial problem. In the general formulation of this problem we are given two genomes (or parts of genomes), viewed as ordered lists of genes (or other markers), and a set of allowed mutation events (reversals, transpositions, etc). To solve the problem we must find the minimum number of events that lead from one genome to another. In general the solution is symmetric, that is, the same series of events, taken backward, will transform the second genome into the first. We will also restrict ourselves to the case of conservative events, that is, events that do not change the available gene pool. Thus events such as duplications or deletions will not be considered in this study.

Recent developments in this field include the polynomial solution to the signed reversal case (Hannenhalli and Pevzner, 1995), the NP-hardness of unsigned reversal distance (Caprara, 1996), and partial results for transposition distance (Bafna and Pevzner, 1995; Meidanis et al., 1997b), to name just a few. Many doctoral dissertations were devoted to this theme (see, for instance, the theses of Vergara (Vergara, 1997), Christie (Christie, 1998), and Walter (Walter, 1999)). Transposition distance seems to be a harder problem, that has eluded researchers for many years now. Its computational complexity is still unknown. We feel that new, more powerful formal tools are needed to successfully attack this problem.
The mathematical formalization of genome rearrangements usually begins by representing genomes as permutations. Thus, a genome \( \pi \) consisting of genes \( \pi_1, \pi_2, \pi_3, \ldots, \pi_n \) in this order is written as:

\[
\pi = (\pi_1 \pi_2 \pi_3 \ldots \pi_n)
\]

meaning that \( \pi \) is the function (permutations are functions):

\[
[1 \Rightarrow \pi_1, 2 \Rightarrow \pi_2, 3 \Rightarrow \pi_3, \ldots, n \Rightarrow \pi_n]
\]

that is, \( \pi \) maps 1 into \( \pi_1 \), 2 into \( \pi_2 \), and so on.

In this paper we will propose a different view of a genome as a permutation, namely, that Equation [1] denotes the function:

\[
[\pi_1 \Rightarrow \pi_2, \pi_2 \Rightarrow \pi_3, \ldots, \pi_{n-1} \Rightarrow \pi_n, \pi_n \Rightarrow \pi_1]
\]

that is, \( \pi \) maps \( \pi_1 \) into \( \pi_2 \), \( \pi_2 \) into \( \pi_3 \), and so on. Note that the last gene \( \pi_n \) is mapped into the first gene \( \pi_1 \). This is necessary, because permutations are functions that map each element into some other, and they cannot repeat images. However, this implies a circular character to our genome. But circular genomes do exist, and, as we will see in subsequent sections, the study of rearrangements of linear genomes is really not much different from circular ones.

Our goal in this note is to convince the reader that interpretation (2) is much more sensible, for a number of reasons. First, it allows us to directly apply many long known results from permutation group theory. Important tools such as breakpoints, the breakpoint graph, cycles, good cycles, bad cycles, gray edges, black edges, which served as basic building blocks for most of the advances in the field can be algebraically defined instead of graphically defined as they have been until now. Therefore, arguments that relied on pictures can now be expressed completely in algebraic terms. We consider this a powerful step towards a massive attack on such problems, much like analytic geometry is a powerful way of looking into geometric problems.

In Section 2 we briefly review the basics on permutation groups. Section 3 contains the first steps in redefining genome rearrangements under the new formalism that we propose. In the Section 4 we use theory just developed to show some results that have been proved based on pictures. Finally, we conclude in Section 5.

## 2 Permutation Groups

Permutations groups have been studied at least since the eighteenth century, when Galois wrote his much acclaimed theory for solving algebraic equations. Here we briefly recall a few classical results that are useful in genome rearrangements. For more information see references (Jacobson, 1985; MacLane and Birkhoff, 1971).

Given a base set \( E \), a permutation on \( E \) is a one-to-one function from \( E \) onto itself. Permutations are composed of one or more cycles. A cycle involving
elements $a$, $b$, $c$, for instance, is written:

$$(a\ b\ c)$$

meaning that $a$ is mapped into $b$, which is mapped into $c$, which in turn is mapped back into $a$. Cycles can be of any length. Cycles of length 1 are not explicitly written. Thus, if we write:

$$a = (a\ b\ c)$$

we implicitly mean that all other elements are left in place by $a$, that is, $a(x) = x$ for $x \neq a, b, c$. Note: $(a\ b\ c) = (b\ c\ a) = (c\ a\ b)$.

The product or composition of two permutations $\alpha$, $\beta$ is denoted by $\alpha \beta$. In general $\alpha \beta \neq \beta \alpha$, but when $\alpha$ and $\beta$ are disjoint cycles they commute: $\alpha \beta = \beta \alpha$. Every permutation can be written in an unique way as a product of disjoint cycles (apart from the order of the factors). We refer to this as the cycle decomposition of a permutation.

The identity permutation, that maps every element into itself, will be denoted by $1$. Every permutation $\alpha$ has an inverse $\alpha^{-1}$ such that $\alpha \alpha^{-1} = \alpha^{-1} \alpha = 1$. For cycles, the inverse is obtained reverting the order of the elements: $(a\ b\ c)$ is the inverse of $(c\ b\ a)$. For a general permutation, invert every cycle in its cycle decomposition.

To compute the product of $\alpha$ and $\beta$, $\alpha \beta$, we must keep in mind that $\beta$ will be applied first, and then $\beta$, as in $\alpha \beta(x) = \alpha(\beta(x))$. Therefore, to compute a product of nondisjoint cycles we need to proceed as follows. Take the example:

$$(a\ b\ c)(a\ b\ d)(c\ d\ b)$$

To compute this, we start with any element, say $a$, and compute its image. The element $a$ is fixed by the rightmost cycle, then is mapped into $b$ by the second cycle, and $b$ is mapped into $c$ by the leftmost cycle. So, the final destination of $a$ is $c$. We then write:

$$(a\ b\ c)(a\ b\ d)(c\ d\ b) = (a\ c\ \ldots)$$

and then proceed finding out the image of $c$: $c$ goes to $d$, $d$ goes to $a$, $a$ goes to $b$, respectively, by the rightmost, middle, and leftmost cycle, so $c$ is finally mapped into $b$. And so on. We reach the result:

$$(a\ b\ c)(a\ b\ d)(c\ d\ b) = (a\ c\ b)(d) = (a\ c\ b)$$

since singleton cycles do not need to be explicitly indicated.

One important operation is the conjugation. The conjugation of $\beta$ by $\alpha$ is the permutation $\alpha \beta \alpha^{-1}$. This results in a permutation with the same cycle structure of $\beta$ but the elements are changed by $\alpha$. For instance, if $\beta = (\beta_1\ \beta_2\ \ldots\ \beta_k)$ then:

$$\alpha \beta \alpha^{-1} = (\alpha(\beta_1)\ \alpha(\beta_2)\ \ldots\ \alpha(\beta_k))$$

If $\beta$ is a product of disjoint cycles, each one will be affected by $\alpha$ in the same way to form $\alpha \beta \alpha^{-1}$. Conjugations are so important that we will have a special notation for them: $\alpha \cdot \beta$ means the same as $\alpha \beta \alpha^{-1}$. 
2.1 Two- and Three-Cycles

A two-cycle, or 2-cycle, is a cycle of size 2. A three-cycle, or 3-cycle, is a cycle of order 3. It is important to know how products by 2- or 3-cycles affect an arbitrary permutation. It is simple, too.

Let \( a = (a \ b) \) be a 2-cycle. Its effect on an arbitrary permutation \( \beta \) can be described as follows. If \( a \) and \( b \) are in the same cycle in \( \beta \), this cycle is broken in two in \( a \beta \). If \( a \) and \( b \) are in two distinct cycles in \( \beta \), these two cycles become one in \( a \beta \). Here and in the rest of the paper we say “cycle in \( \beta \)” meaning “cycle in the unique cycle decomposition of \( \beta \)”.

The same results are valid for \( \beta a \). Notice that \( \beta a \) and \( a \beta \) are conjugates: \( a(\beta a)a^{-1} = a\beta \), and therefore have the same cycle structure.

Now take an arbitrary 3-cycle \( a = (a \ b \ c) \) and an arbitrary permutation \( \beta \). Three cases appear:

1. If \( a \), \( b \), and \( c \) are in three different cycles in \( \beta \), these three cycles become a single cycle in \( a \beta \).
2. If two of \( a \), \( b \), \( c \) are in the same cycle, and the third element is in a different cycle in \( \beta \), then these two cycles recombine into another two cycles in \( a \beta \). Thus, the total number of cycles is maintained.
3. If \( a \), \( b \), and \( c \) are all in the same cycle in \( \beta \), the result depends on the orientation they have in this cycle of \( \beta \). Selecting \( a \) as the starting point, this cycle can have the form \( (a \ldots b \ldots c \ldots) \) or \( (a \ldots c \ldots a \ldots) \). In the first case, the cycle becomes \( (a \ldots c \ldots b \ldots) \) in \( a \beta \). In the second case, the cycle breaks into \( (a \ldots)(b \ldots)(c \ldots) \) in \( a \beta \).

The same results (except for the exact format of the resulting cycles in case 3) are valid for \( \beta a \).

3 Genome Rearrangements

To formalize genome rearrangement problems we will use as base set for the permutations the set \( E_n = \{-1, +1, -2, +2, \ldots, -n, +n\} \), where \( n \) is the number of genes. Thus, we will be modeling both strands of the underlying DNA molecule. Each element \(+i\) or \(-i\) represents a marker on the \( i^{th} \) gene, with its opposite meaning a marker in the same location in the opposite strand. We will first model circular genomes, which conform more naturally to the formalism, and will later comment on the necessary adaptations for linear genomes.

To begin with, let \( \gamma \) be the permutation that maps each elements into its counterpart on the other strand. The permutation \( \gamma \) can be written as:

\[
\gamma = (-1 \ +1)(-2 \ +2)\ldots(-n \ +n)
\]

that is, a product of \( n \) disjoint 2-cycles. Notice that \( \gamma(a) \neq a \) for all \( a \in E_n \), and \( \gamma^2(a) = \gamma(\gamma(a)) = a \) for all \( a \in E_n \). In other words, \( \gamma^2 = 1 \) or, equivalently, \( \gamma^{-1} = \gamma \).
A cycle is *admissible* when it does not contain \(-i\) and \(+i\) for the same \(i\). Thus, \(\gamma\) is far from being an admissible cycle. An admissible cycle of size \(n\) is called a *genome strand*, because it models a strand of a genome formed by these \(n\) genes in some order. If we have an admissible cycle \(\alpha\), we can compute its reverse complement, as in the examples of the Table 1.

There is an algebraic way of obtaining the complement, though. If \(\alpha\) is an admissible cycle, \(\alpha^{-1}\) is its reverse; \(\gamma \cdot \alpha = \gamma \alpha \gamma\) is its complement. The reverse complement is when we do both: \((\gamma \cdot \alpha)^{-1}\) or \(\gamma \cdot (\alpha^{-1})\), which results in the same expression \(\gamma \alpha^{-1} \gamma\).

Given a genome strand \(\pi_1\), its reverse complement \(\pi_2 = \gamma \pi^{-1} \gamma\) forms the complementary strand of the same genome. We represent this genome as the product of the two strands: \(\pi = \pi_1 \pi_2\). Since the strands form two disjoint cycles it does not matter in which order we take the product: \(\pi_1 \pi_2 = \pi_2 \pi_1\). Also, it does not matter which strand we call \(\pi_1\); had we started with \(\pi_2\) we would have computed its reverse complement \(\pi_1\) and the final genome would have been the same. This is just as DNA should be: no matter which strand you pick, when you let it pair with its reverse complement, you get the same DNA molecule.

Formally, we define a *genome* as a permutation that can be written as \(\pi_1 \gamma \pi_1^{-1} \gamma\), for some genome strand \(\pi_1\). Notice that \(\gamma \pi \gamma = \pi^{-1}\) for every genome \(\pi\). The general genome rearrangement problem then becomes: given two genomes \(\pi\) and \(\sigma\) and a class of operations, find the minimum number of events (operations) that transform \(\pi\) into \(\sigma\). This minimum number is called the *distance* between \(\pi\) and \(\sigma\).

<table>
<thead>
<tr>
<th>(\alpha)</th>
<th>reverse complement</th>
</tr>
</thead>
<tbody>
<tr>
<td>((+3 \ -1 \ +7 \ +5))</td>
<td>((-5 \ -7 \ +1 \ -3))</td>
</tr>
<tr>
<td>((+2 \ +4 \ +6))</td>
<td>((-6 \ -4 \ -2))</td>
</tr>
</tbody>
</table>

Table 1: Examples of admissible cycles \(\alpha\) and their reverse complement.
gray edges in the same way. In the preceding example, we have:

\[
\gamma \pi = (-0 + 0)(-1 + 1)(-2 + 2)(-3 + 3)(-4 + 4)(-5 + 5) \\
+ (-0 + 3 + 2 - 5 - 4 + 1)(1 + 4 + 5 - 2 + 3 - 0) \\
= (+0 + 3)(-3 - 2)(+2 + 5)(-5 + 4)(-4 - 1)(+1 - 0),
\]

exactly the black edges. And \(\gamma \sigma\) will give the gray edges:

\[
\gamma \sigma = (+0 - 1)(+1 - 2)(+2 - 3)(+3 - 4)(+4 - 5)(+5 - 0).
\]

In the classical theory of genome rearrangements the cycle structure of the breakpoint graph plays an important role. Although we could not obtain the cycles themselves of the breakpoint graph, we derived an algebraic expression for the square of each cycles. This expression is just the product \((\gamma \pi)(\gamma \sigma) = \gamma \pi \gamma \sigma\). In the example, we have:

\[
\gamma \pi \gamma \sigma = (+0 - 4)(+3 - 1)(-3 + 5 + 1)(-2 - 0 + 2)(-5)(+4)
\]

For each cycle of breakpoint graph we have two cycles in \(\gamma \pi \gamma \sigma\). If the cycle in the breakpoint graph is \((a_1 a_2 \ldots a_{2k})\), we have \((a_1 a_3 \ldots a_{2k-1})\) and \((a_{2k} a_{2k-2} \ldots a_2)\) in \(\gamma \pi \gamma \sigma\). Therefore, this is not exactly the square of breakpoint cycle, because one of them is reversed. Strictly speaking, we cannot model as permutations the cycles of the breakpoint graph, since they have no orientation. This in part explains why one cycle in the square is reversed. Had we taken \(\gamma \pi \gamma \sigma\) the other cycle would have been reversed. Notice that \(\gamma \pi \gamma \sigma = \pi^{-1} \sigma\), and \(\gamma \sigma \gamma \pi = \sigma^{-1} \pi\).

In any case, this constructions allow us to rephrase technical properties of breakpoint graphs in algebraic terms. For instance, how many breakpoints \(\pi\) has with respect to \(\sigma\)? This is just the number of elements not fixed by \(\gamma \pi \gamma \sigma\), divided by 2:

\[
b(\pi, \sigma) = \frac{|\text{Supp}(\gamma \pi \gamma \sigma)|}{2}
\]
where the support $\text{Supp}(\alpha)$ of a permutation $\alpha$ is the set of elements not fixed by $\alpha$:

$$\text{Supp}(\alpha) = \{ x \in E_n | \alpha(x) \neq x \}$$

Likewise, the number of cycles in the breakpoint graph is half the number of cycles in $\pi^{-1} \sigma$. We can define also the length (size) of the cycles, good or bad cycles, cycle that can be broken by certain operations. We hope to be able to define interleaving cycles, hurdles, fortresses, all in algebraic terms.

### 3.1 Linear Genomes

The theory developed so far fits nicely with circular genomes. In this section we will briefly examine the case of linear genomes.

First, we must recognize that there are actually two kinds of linear genome: free and with fixed extremes. Let us define each kind, starting with the one with fixed extremes.

When we compare two regions of two different genomes, and these regions are flanked by conserved parts, we need to use the fixed-extreme case (Figure 2). In this case, we add an extra dummy gene $BA$, which represents the fixed extremities of the regions, and proceed as in the circular case.

When we compare two entire linear genomes, we need to take into account that there is a free reversal that can be applied, so the distance in this case becomes:

$$d_{\text{free}} = \min(d_{\text{fixed}}(\pi, \sigma), d_{\text{fixed}}(\gamma \cdot \pi, \sigma))$$

More details on the relationship between linear and circular genome rearrangement problems can be found in the references (Walter, 1999; Meidanis et al., 1997a).
Figure 4: A reversal $\rho$ applied to genome $\pi$.

### 3.2 Operations

We will define in this section the events (operations) of reversal, transposition (or block move), and block interchange, some of them in their signed and unsigned version. We will do a very detailed job for reversals, and then just state the results for the others, to save space.

Given a genome $\pi$, to perform a reversal (signed) on it we need to choose two distinct markers $u$ and $v$, in the same strand of $\pi$, and then replace the path from $u$ to $v$ (excluding $u$ but including $v$) by its reverse complement. Of course, a similar operation will be performed on the other strand, to make sure the final result is still a valid genome. Figure 4 shows what is meant.

We want to write the resulting genome $\sigma$ as $\pi\rho$, where $\rho$ is a permutation that will represent the reversal. With some work, we see that $\sigma$ differs from $\pi$ only in
the following mappings:

\[ \sigma u = \gamma v, \ \sigma v = \gamma u, \ \sigma \gamma \pi u = \pi v, \ \sigma \gamma \pi v = \pi u. \]

Therefore, \( \rho = \pi^{-1} \sigma \) maps:

\[ \rho u = \pi^{-1} \gamma v, \ \rho v = \pi^{-1} \gamma u, \ \rho \gamma \pi u = v, \ \rho \gamma \pi v = u \]

with all other elements fixed by \( \rho \). Noting that \( \pi^{-1} \gamma = \gamma \pi \) for every genome \( \pi \), we arrive at:

\[ \rho u = \gamma \pi v, \ \rho v = \gamma \pi u, \ \rho \gamma \pi u = v, \ \rho \gamma \pi v = u \]

or, written as a product of disjoint cycles:

\[ \rho = (u \ \gamma \pi v)(v \ \gamma \pi u). \]

This is then the general formula of a reversal applicable to \( \pi \), where \( u \) and \( v \) are two elements in same strand of \( \pi \). We say that \( \pi \) and \( \sigma \) differ by a reversal when there is such a reversal \( \rho \) with \( \sigma = \pi \rho \). Notice that the definition of a reversal depends on \( \pi \). There is no way to define a class of permutations that will be “the reversals”, valid for all genomes. Each genome has a particular set of reversals that can be applied to it, and this sets varies from one genome to another.

For this reason, we cannot view the genome rearrangement problem directly as a “group generators” problem, where a class of generators of the symmetric group is given and we seek the minimum number of generators to write a given permutation. Nevertheless, it can be view as a group generators problem. Details are given in the full version.

The reversal distance problem is: given two genomes \( \pi \) and \( \sigma \), find the minimum \( k \) such that there are genomes \( \delta_0, \delta_1, \ldots, \delta_k \) with \( \pi = \delta_0, \sigma = \delta_k \) and \( \delta_i \) differs from \( \delta_{i+1} \) by a reversal, for \( i = 0, \ldots, (k-1) \).

An unsigned reversal is defined similarly, but has the form:

\[ \rho = (u \ v)(\gamma \pi v \ \gamma \pi u) \]

where, as before, \( u \) and \( v \) are distinct elements of the same strand in \( \pi \).

A transposition (unsigned) is defined as:

\[ \tau = (u \ v \ w)(\gamma \pi w \ \gamma \pi v \ \gamma \pi u) \]

where \( u, v \) and \( w \) are three distinct elements in the same strand in \( \pi \), appearing in this order \( (u, v, w) \) in the strand.

A signed transposition is defined as:

\[ \tau = (u \ v \ \gamma \pi w)(w \ \gamma \pi v \ \gamma \pi u) \]

where \( u, v \) and \( w \) are distinct elements in the same strand in \( \pi \), appearing in this order \( (u, v, w) \) in this strand. A signed transposition models the event in which a
block detaches itself from a genome and reappears elsewhere, in the same strand but the block is reversed.

A block interchange is defined as:

\[ \beta = (u \, w)(\gamma \, \pi \, w \, \gamma \, \pi \, v)(v \, x)(\gamma \, \pi \, x \, \gamma \, \pi \, v) \]

where \( u, v, w \) and \( x \) are four distinct elements in the same strand of \( \pi \), appearing in the order \( (u, v, w, x) \) in this strand.

Each one (or a group of) of these types of events can be used to define a genome rearrangement problem: given two genomes \( \pi \) and \( \sigma \), find the minimum \( k \) such that there are genomes \( \delta_0, \delta_1, \ldots, \delta_k \) with \( \pi = \delta_0, \sigma = \delta_k \) and \( \delta_i \) differs from \( \delta_{i+1} \) by the specific operation (or a group of), for \( i = 0, \ldots, (k-1) \).

4 Using the Theory

We will use the theory developed to show two results whose proof was based on pictorial representations. The first result appears in Christie’s proof that a block interchange cannot create three cycles (Christie, 1997). The other result is that there is only one way for a transposition to break a cycle, proved by Walter & colleagues by reference to a picture (Walter et al., 1998).

**Theorem 1** Let \( \pi \) and \( \sigma \) be two genomes, and \( \beta \) a block interchange on \( \pi \). Then the number of cycles in \( (\pi \beta)^{-1} \sigma \) is not higher than \( 4 \) plus the number of cycles in \( \pi^{-1} \sigma \).

**Proof:** We have \( (\pi \beta)^{-1} \sigma = \beta^{-1} \pi^{-1} \sigma \), which differs from \( \pi^{-1} \sigma \) by a multiplication by \( \beta^{-1} \). The cycle structure of \( \beta^{-1} \) is the same as \( \beta \)'s: four 2-cycles. By the classical results about products by 2-cycles it is immediate that multiplying by four 2-cycles we cannot create more than \( 4 \) extra cycles. \( \square \)

**Theorem 2** Let \( \pi \) and \( \sigma \) be two genomes, and \( \tau = (u \, v \, w)(\gamma \, \pi \, w \, \gamma \, \pi \, v) \) a (unsigned) transposition on \( \pi \), where \( u, v, w \) appear in this order in the same cycle of \( \pi \). Then \( (\pi \tau)^{-1} \sigma \) has four more cycles than \( \pi^{-1} \sigma \) if and only if \( u, v, w \) are in the same cycle in \( \pi^{-1} \sigma \) and appear in the order \( (u, v, w) \) in this cycle.

**Proof:** Transpositions do not mix genome strands (at least unsigned transpositions, which is the kind we are using here), and therefore we know that the elements of a strand of \( \pi \) will form a strand in \( \pi \tau \) (possibly in different order). Let \( \pi_1 \) be the strand that contains \( u, v \) and \( w \), and \( \sigma_1 \), the corresponding strand in \( \sigma \). We then have \( \pi = \pi_1 \gamma \, \pi_1^{-1} \gamma, \sigma = \sigma_1 \gamma \, \sigma_1^{-1} \gamma, \) and \( \pi^{-1} \sigma = \pi_1^{-1} \sigma_1 (\gamma \, \pi_1 \gamma)(\gamma \, \sigma_1^{-1} \gamma) \). Then \( (\pi \tau)^{-1} \sigma = \pi^{-1} \pi^{-1} \sigma \) will be the product of disjoint permutations \( (w \, v \, u)(\pi_1 \, \pi_1^{-1} \sigma_1), \) and \( (\gamma \, \pi_1 \, \gamma \, \pi_1 \gamma)(\gamma \, \sigma_1^{-1} \gamma) \).

In the first component \( (w \, v \, u)(\pi_1^{-1} \sigma_1 \) we have a product of a 3-cycle by \( \pi_1^{-1} \sigma_1 \). We know from classical permutation group theory (see section 2.1) that this produces two extra cycles if and only if \( u, v, w \) appear in the same cycle of \( \pi_1^{-1} \sigma_1 \) in the order \( (u, v, w) \), as stated. \( \square \)
5 Conclusions

We propose a new way of looking of genomes as permutations, one that is more comfortable for those that have experience in permutation groups. Much remains do be done, but we feel this is the right way to attack difficult problems such as the transposition distance.

Acknowledgments

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