SUTTA

Scoring-and-Unfolding Trimmed Tree Assembler

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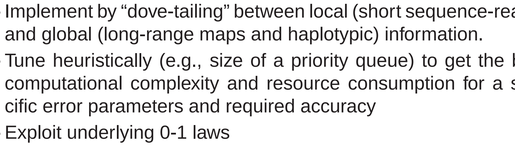
Sequence Assembly Problem

Definition [Genome Sequence Assembly Problem] *Given a set of fragments/reads* $F = \{f_1, f_2, \ldots, f_n\}$ *find a reconstruction* R *and a valid layout of the reads* L *such that the following set of properties (oracles) are satisfied :*

- *The observed distribution of fragment reads start point,* D_{obs}*, has the minimum deviation from the source distribution* D_{src}
- *The distance between mated reads must be consistent with the size of the fragments generated.*
- *The observed distribution of restriction enzyme sites,* C_{obs} *is consistent with the distribution of experimental optical map data* C_{src}*.*



History and Motivations

1. Single Molecule Methods such as Optical Mapping.
2. Next Generation Sequencers.
3. SMASH (Single Molecule Approach to Sequencing by Hybridization) combining:
   (a) Optical Mapping
   (b) Binary Maps (with PNA probes)
   (c) Positional Sequencing by Hybridization (using a Beam Search Algorithm)

SUTTA provides a more general approach for haplotypic whole genome sequencing.

SUTTA assembler

Main Ingredients

- Exhaustive
  - Not a greedy algorithm.
  - Avoid getting stuck with a locally best solution

Implementation

- Use Branch-and-Bound (or Beam-Search) algorithm to improve algorithmic complexity.
  - Provide bounds and allow pruning of unpromising regions/directions.
  - Implement by "dove-tailing" between local (short sequence-reads) and global (long-range maps and haplotypic) information.
  - Tune heuristically (e.g., size of a priority queue) to get the best computational complexity and resource consumption for a specific error parameters and required accuracy
  - Exploit underlying 0-1 laws
  - Parallelize in a straight-forward way

Scoring

- Use a "score" function to choose the best global solution.
  - Achieve high accuracy
  - Model the "error processes" in the score, consisting of Bayesian likelihood and penalty functions
  - Use side-information (e.g., optical maps, mated pairs, base-content, homologous reference sequences, diluted sequencing, low complexity representation, etc.) to sharpen the score function
  - Use empirical-Bayes method to decide the statistics (null-model, threshold, p-values, base- or sequence-quality)
  - Agnostic to the underlying short- and long-range technologies, while being able to mix-and-match technologies

Pseudo-Code

Algorithm 1: SUTTA - pseudo code
Input: Set of N reads
Output: Set of contigs

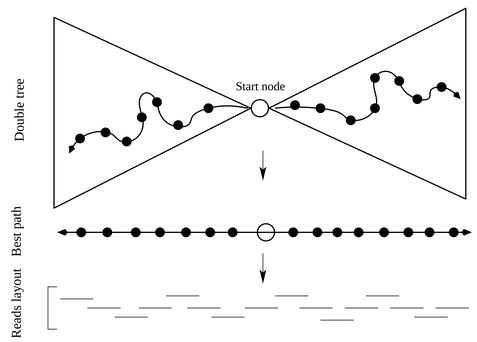
```
1  F := ∅;                                   /* Forest of trees */
2  C := ∅;                                   /* Set of contigs */
3  B := ⋃_i^N R_i;                           /* All the available reads */
4  while (B ≠ ∅) do
5      R := B.getNextRead();
6      if ( !R.isUsed() && !R.isContained() ) then
7          DT := create_double_tree(R);
8          F.add(DT);
9          Contig CTG := create_contig(DT);
10         C.add(CTG);
11         CTG.layout(); /* Compute layout of the contig */
12         B := B \ {CTG.reads};             /* Remove used reads */
13     else
                                             /* jump to next available read */
14     end
15 end
16 return C
```

Node expansion

1. Start with a random read (It will be the root of a tree; Use only the read that has not been "used" in a contig yet, or that is not "contained")
2. Create RIGHT Tree: Start with an unexplored leaf node (a read) with the best score-value; Choose all its non-contained "right"-overlapping reads and expand the node by making them its children; Compute their scores. (Add the "contained" nodes along the way, while including them in the computed scores; Check that no read occurs repeatedly along any path of the tree). STOP when the tree cannot be expanded any further.
3. Create LEFT Tree: Symmetric to previous step.

Contig Construction

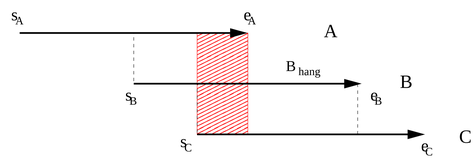
- The expand node routine is applied twice to generate LEFT and RIGHT trees for the start read.
- Next, the best LEFT path is concatenated with the root and the best RIGHT path to create a globally optimal contig.



Overlap Score

- "Weighted transitivity" score that formulates the following intuition: if read A overlaps read B, and read B overlaps read C, we will score those overlaps strongly if in addition A and C also overlap. This scoring approach implicitly assumes that the coverage is higher than 3.

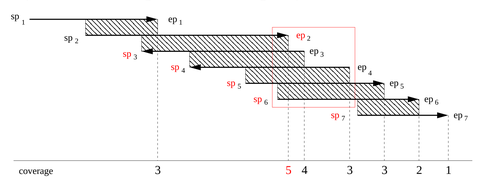
$$\texttt{if}(\pi_{(A,B)} \wedge \pi_{(B,C)})\texttt{then}\{S_{\pi_{(A,B,C)}} = S_{\pi_{(A,B)}} + S_{\pi_{(B,C)}} + (\pi_{(A,C)} ? S_{\pi_{(A,C)}} : 0)\} \quad (1)$$



- A simple generalization for higher coverage is obvious.
- This score cannot resolve repeats or haplotypic variations. Solution: augment the score with information for optical map alignment or mated-pair distances to put an appropriate reward/penalty term.

Dynamic Coverage Score

- **Observation**: compressed (expanded) regions are characterized by an increase (decrease) in the depth of coverage compared to the expected average coverage of the shotgun process.
- **Idea**: penalize solutions whose observed coverage deviates from the expected coverage of the shotgun process.



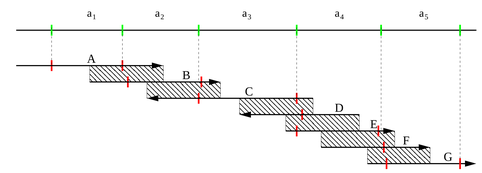
Optical Map Score

- **Observation**: restriction enzymes cut at precise locations in the genome. Let $< a_1, a_2, \ldots, a_n >$ be the *restriction map* obtained by a restriction enzyme digestion process.
- **Idea**: Organize the restriction sizes a_i into n-tuples. Build a hash table according to:

$$\mathcal{H}(a, b_1, \ldots, b_n) = < \left\lfloor \frac{b_1}{a} \times \alpha \right\rfloor, \left\lfloor \frac{b_2}{a} \times \alpha \right\rfloor, \ldots, \left\lfloor \frac{b_n}{a} \times \alpha \right\rfloor > \quad (2)$$

store a in the corresponding slot (with possible collisions).

- Create an in-silico map of the candidate solution and score it according to the number of *hits* that its n-tuples have in the hash table.



Streptococcus suis strain P1/7

Shotgun data from Sanger Institute (2,007,491 bp)

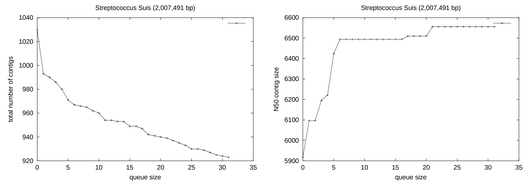


Figure 1: Queue size analysis

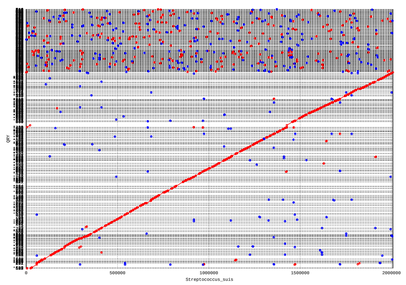


Figure 2: DotPlot

References

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[3] Adam M Phillippy et al. Genome assembly forensics: finding the elusive mis-assembly. *Genome Biology* (2008) vol. 9 (3) pp. R55