Lecture 3: Genome Assembly

Student Handout & In-Class Exercises (with TikZ diagrams)

Course: BINF301 — Computational Biology
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1. Overview

This handout summarizes core ideas and adds inline diagrams:

- What genome assembly is and why it is difficult.
- Two graph-based strategies: Overlap-Layout-Consensus (OLC) and De Bruijn Graphs (DBG).
- Complexity considerations.
- Handling errors and graph imperfections.

[Slides referenced: OLC (5-12), DBG (13-25), non-perfect DBG (18), complexity (11, 19-25), error correction (27-38).]

2. Genome Assembly Basics

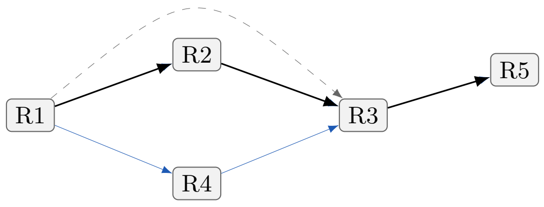
Definition & Challenges

Genome assembly combines sequencing reads into longer contiguous sequences (*contigs*). Key challenges:

- Repeats introduce ambiguity (multiple valid traversals).
- Sequencing errors introduce false paths/edges.
- Data volume drives graph size and cost.

3. Overlap-Layout-Consensus (OLC)

Idea. Reads are *nodes*; overlaps are *edges*. Reconstructing the genome corresponds (ideally) to a **Hamiltonian path** (visit each node/read once).



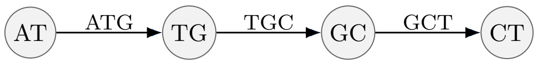
OLC sketch: nodes are reads (R1–R5), edges show overlaps. Dashed edge indicates a *transitive* overlap (can be removed).

Why transitive reduction? Removing transitive edges simplifies the graph and reduces ambiguity.

Solution. Nodes = reads; edges = overlaps. Transitive edges (e.g., R1→R3 implied by R1→R2 and R2→R3) are redundant; removing them clarifies structure and helps with repeats.

4. De Bruijn Graphs (DBG)

Idea. Nodes are $(k-1)$-mers; edges are k-mers. Reconstruction corresponds to an **Eulerian path** (visit each edge once). Under perfect sequencing (each genomic k-mer present exactly once), the graph is Eulerian.

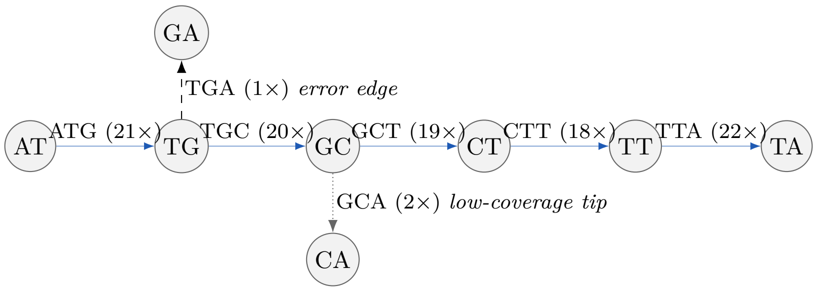


DBG sketch: nodes are $(k-1)$-mers, edges are k-mers; traversal uses each *edge* exactly once (Eulerian).

Solution. OLC vs DBG: OLC seeks a Hamiltonian path over reads (NP-hard); DBG seeks an Eulerian path over edges (linear-time). DBG avoids explicit all-to-all overlaps by indexing k-mers.

5. Non-perfect Sequencing in DBG (errors/repeats)

Errors, missing/duplicated k-mers create tips, bubbles, or spurious branches.



Non-perfect DBG. Top chain: high-frequency true k-mers (18–22×). Dashed branch: *TGA* (1×) is a sequencing error → novel, unsupported k-mer. Dotted tip: *GCA* (2×) may be real but insufficiently sampled → low-coverage artifact.

Solution. High coverage: true edges occur many times; erroneous edges are low-frequency and can be removed. Tip/bubble removal simplifies the graph.

6. Complexity (OLC vs DBG)

OLC. Building overlap graphs can be $O(N^2)$ in reads; graph can be large (especially for short reads). **DBG.** Construction scales with number of k-mers ($\approx O(N)$); more memory-efficient for high read counts, but sacrifices long-read continuity.

7. In-Class Exercises

Exercise 1 — Understanding OLC Overlap Graphs

Using OLC diagrams:

- Identify nodes vs edges.
- Find transitive edges (and say why to remove them).

Solution. Nodes = reads; edges = overlaps. Transitive edges are redundant (e.g., R1→R3 implied by R1→R2 and R2→R3). Removing them clarifies true structure.

Exercise 2 — Hamiltonian vs Eulerian

Reads: `ACTTTCTTCTGG`.

- In OLC: visit each *read* once (Hamiltonian).
- In DBG: traverse each *edge* once (Eulerian).
- Why is one NP-hard and the other linear-time?

Solution. OLC's Hamiltonian path problem is NP-hard; DBG's Eulerian path is linear-time. DBG avoids exhaustive overlap detection by working with k-mers.

Exercise 3 — DBG Error Scenario

Genome: `ATGCTTA` Reads ($k = 3$): `ATG, TGC, GCT, CTT, TTA, TGA` (*TGA* erroneous)

Tasks:

- Build the 3-mer DBG (nodes=2-mers; edges=3-mers).
- Identify the inconsistent edge.
- Explain coverage-based pruning.

Solution. Erroneous edge: *TGA* (TG→GA) forms a branch not on the main path. High coverage → true edges dominate counts; low-frequency error edges are pruned.

Exercise 4 — Choosing OLC vs DBG

- Why OLC for long reads and DBG for short reads?

Solution. Long reads reduce the number of nodes; overlaps are manageable ⇒ OLC good. Short reads produce massive graphs ⇒ OLC heavy; DBG compacts data into k-mers efficiently.