# Lecture 3: Genome Assembly
## Student Handout & In-Class Exercises

**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.

## 2. Genome Assembly Basics

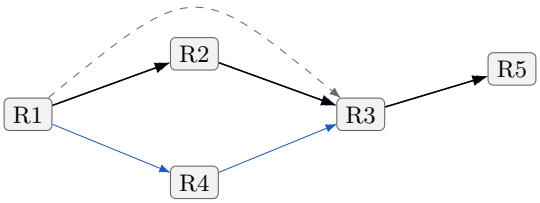
### Definition & Challenges

**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.

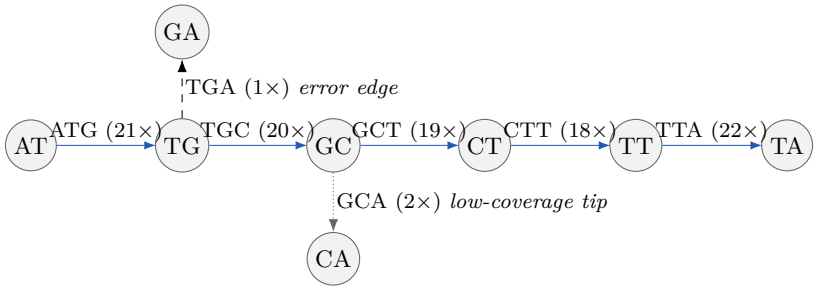
## 4. De Bruijn Graphs (DBG)

**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).

## 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.

## 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).

### 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?

### 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.

### Exercise 4 — Choosing OLC vs DBG

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