# High Throughput Sequencing Assembly: Information and Computation

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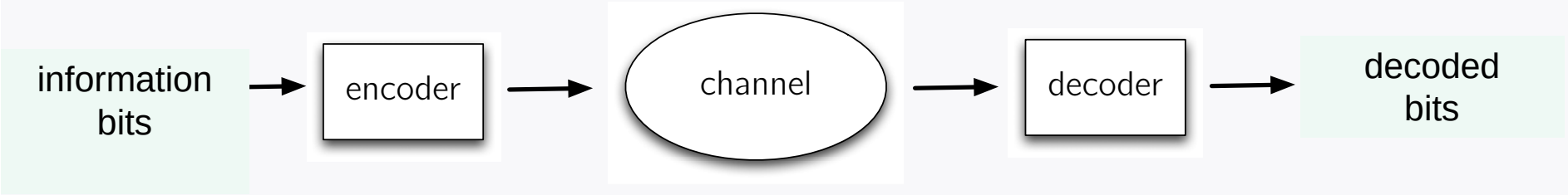
# A 60 year old quest in information theory




- In 1948, Claude Shannon showed that every channel has a capacity C.
- His method to achieve capacity uses random codes and very long block lengths.
- It took 60 years, but efficient capacity-achieving codes were finally found.

# Information and computation

C.E. Shannon

A.M. Turing

What is the information limit for communication?

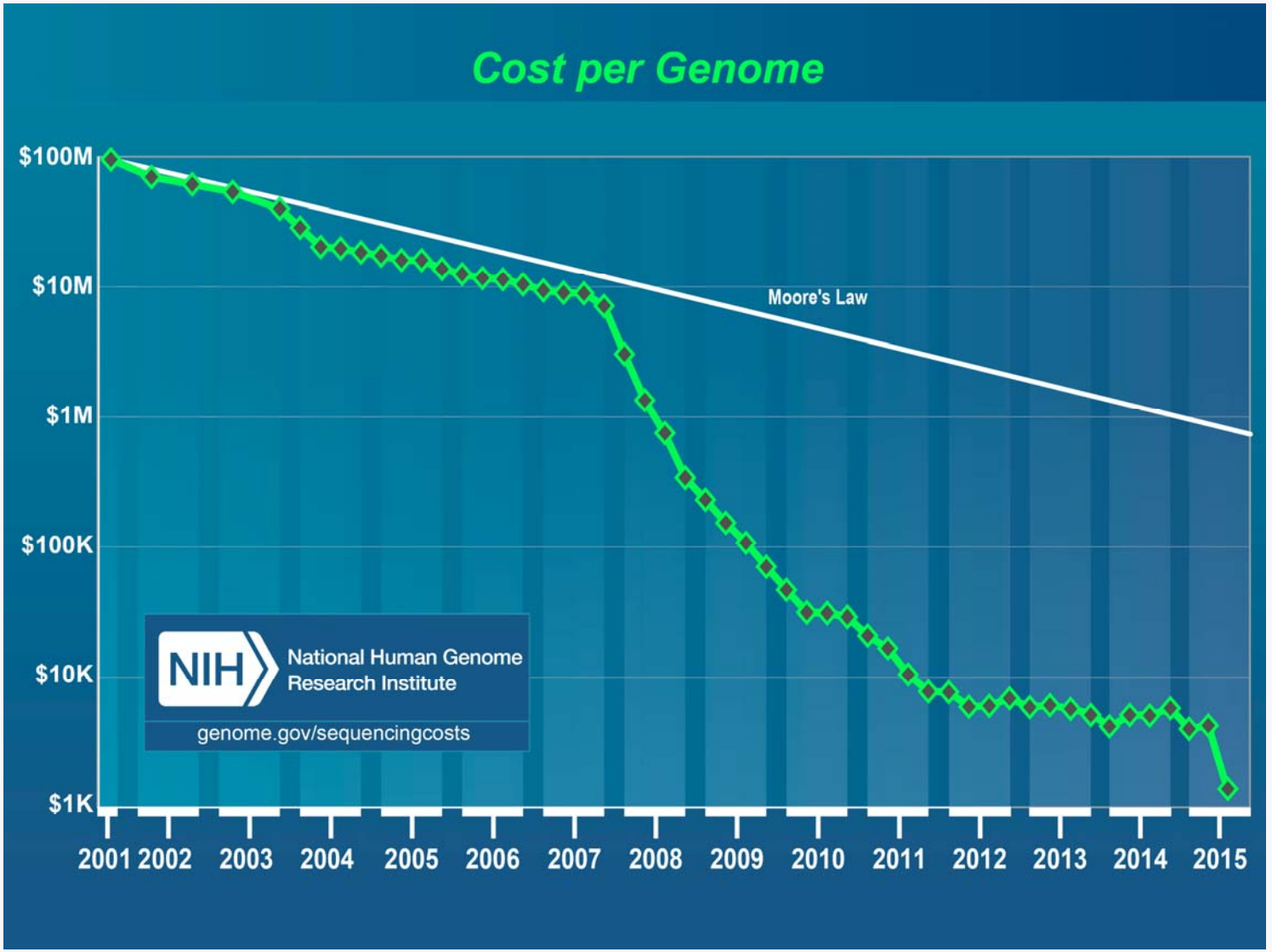
I only care about problem instances that matter.

But optimal decoding of general codes is NP-hard!

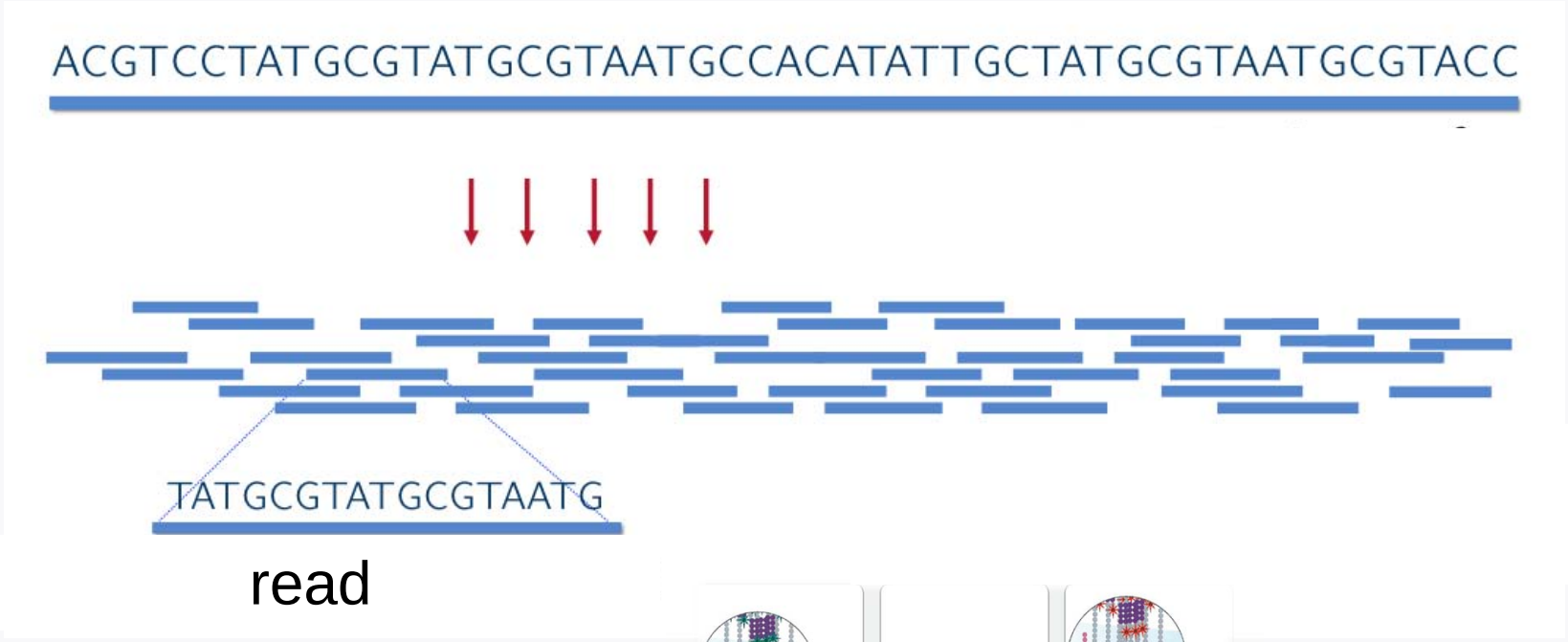
# Beyond communication

Can this way of thinking be broaden to other fields?

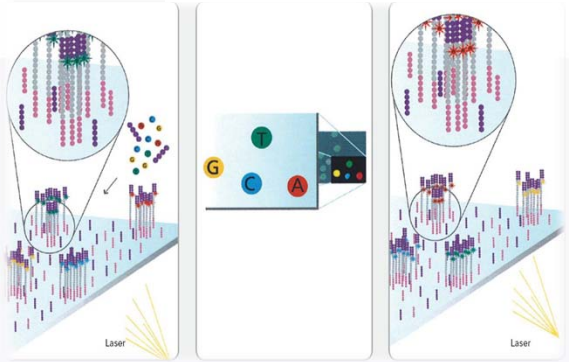
# High throughput sequencing revolution



# Shotgun sequencing




read



# The assembly problem: a gigantic jigsaw puzzle


A single sequencing experiment can generate 100's of millions of reads, 10's to 100's gigabytes of data.

# Computational complexity view

- Formulate the assembly problem as a combinatorial optimization problem.
- Typically NP-hard and even hard to approximate.
- Does not address the question of when the solution reconstructs the ground truth.

# Information theoretic view

**Basic question:**

How much read data is needed to reliably reconstruct?

# Key challenge: repeats

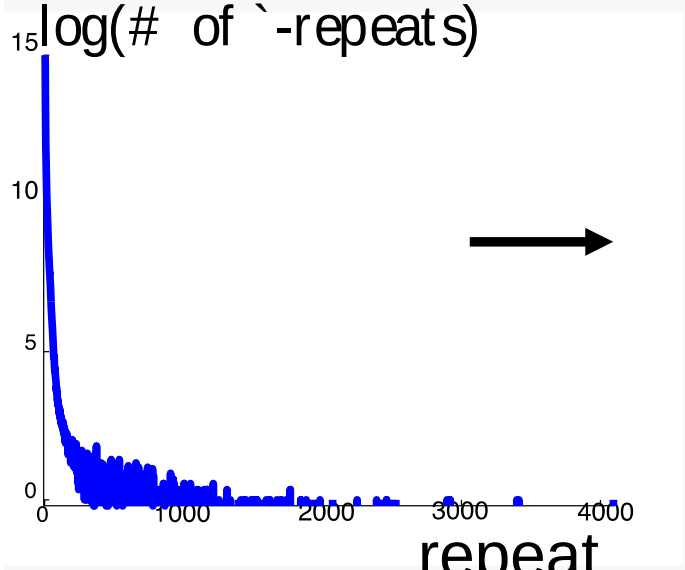
harder jigsaw puzzle

easier jigsaw puzzle

How exactly do the fundamental limits depend on repeat statistics?

# Information limit of assembly

(Bresler, Bresler & T. BMC Bioinformatics 13)




$\frac{N}{N_{LW}}$

information limit

$L_{critical}$

Lander-Waterman coverage

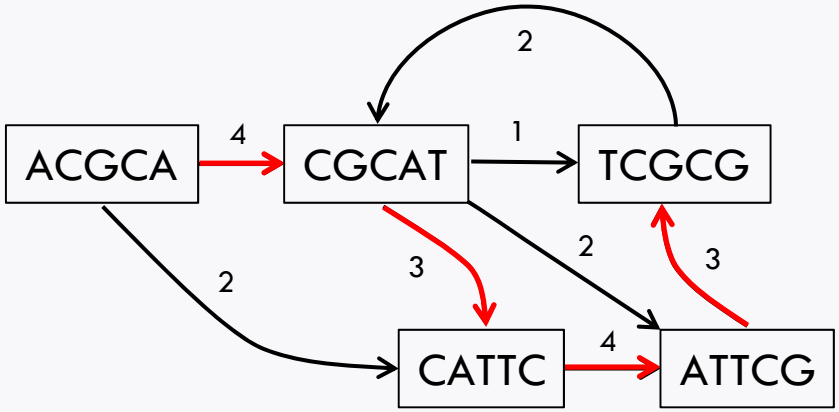
read length $L$

Human Chr 19
Build 37

# The assembly problem

(Shomorony, Courtade & T. 15)

- Formulated on a read-overlap graph

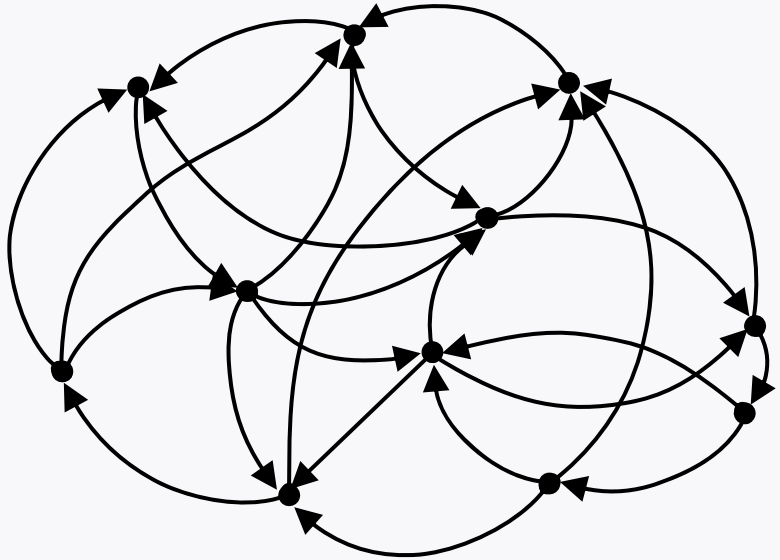



ACGCATTCGCG

- Sequence is a path that visits every node.
  - (Generalized) Hamiltonian Path
  - Finding shortest GHP is NP-hard

# The assembly problem

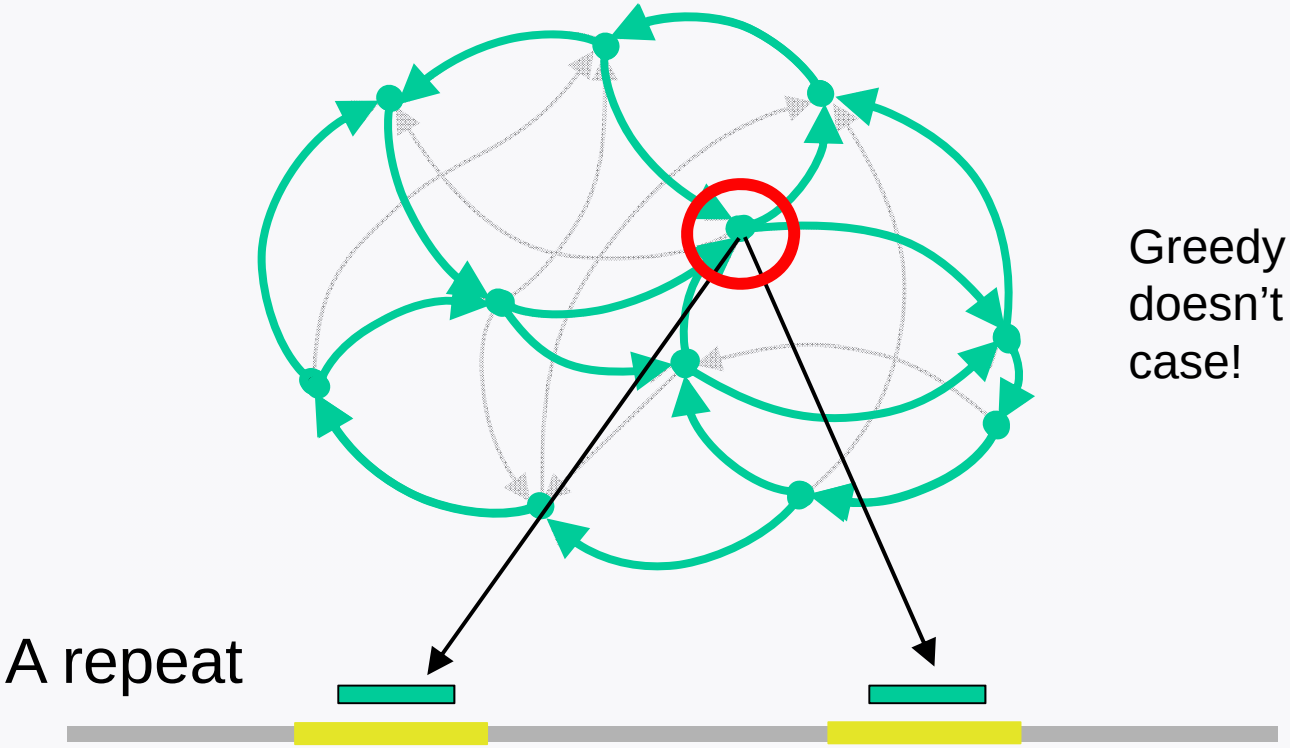
- Formulated on a read-overlap graph



- Sequence is a path that visits every node
  - (Generalized) Hamiltonian Path
  - Finding shortest GHP is NP-hard

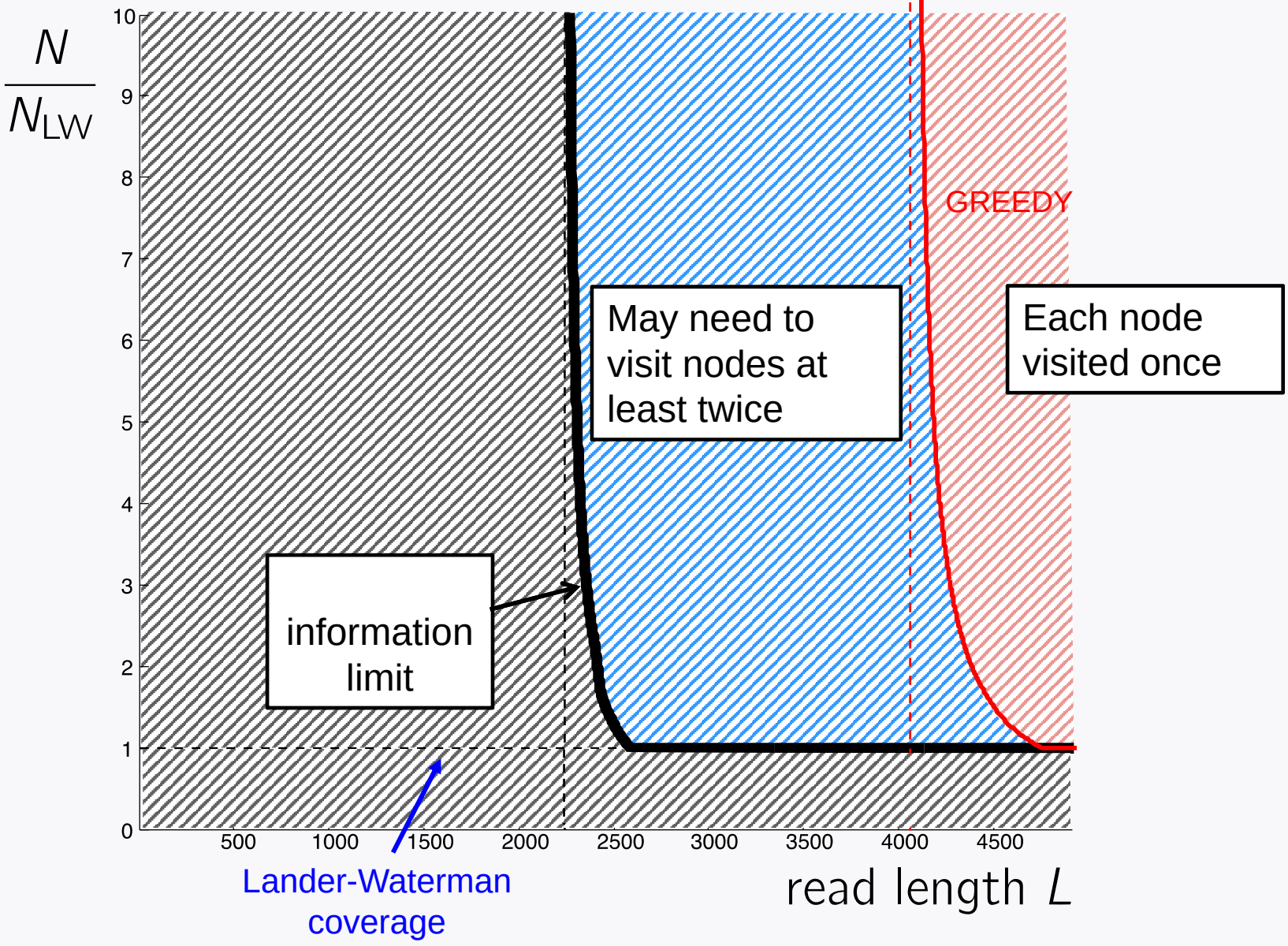
# How well does a greedy algorithm do?

- For each node, go to node with largest overlap.



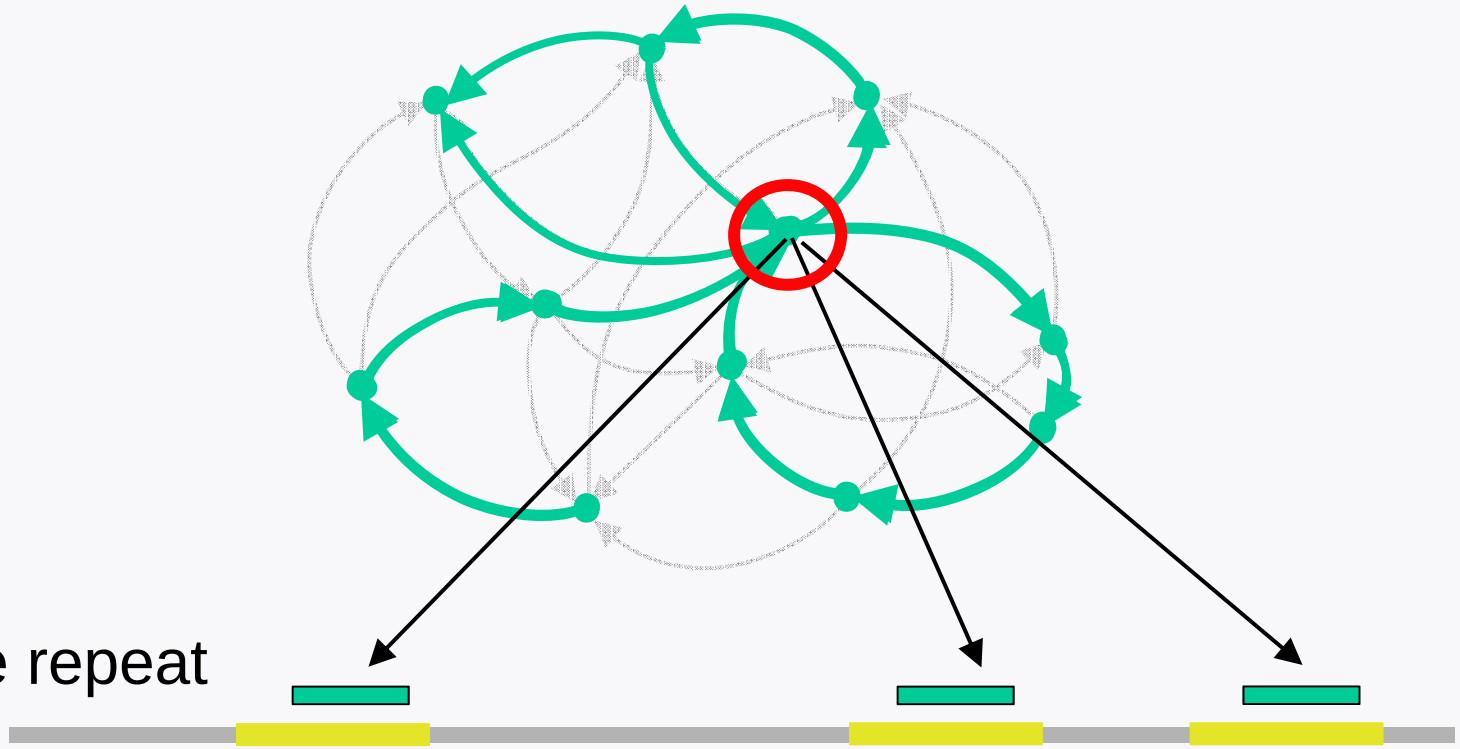

- What if true path visits a node twice?

# Information limit



# Do we need to visit nodes 3 or more times?

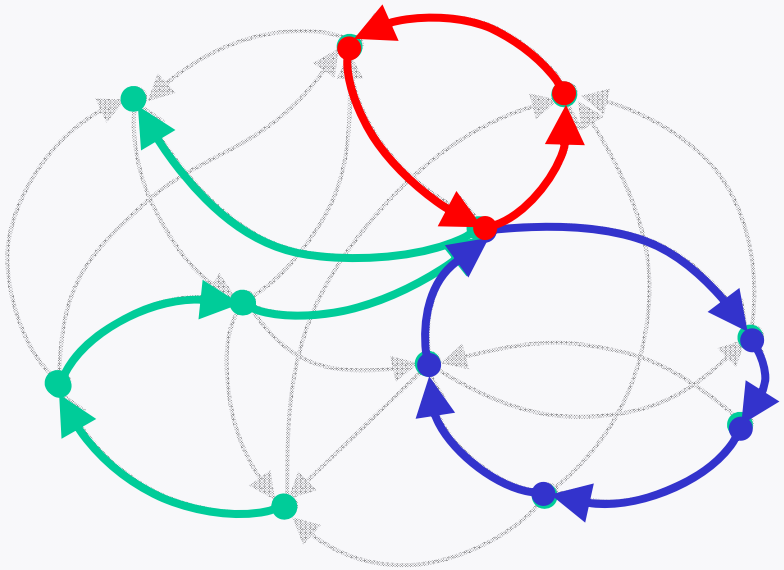
- What if true path visits a node three times?



A triple repeat

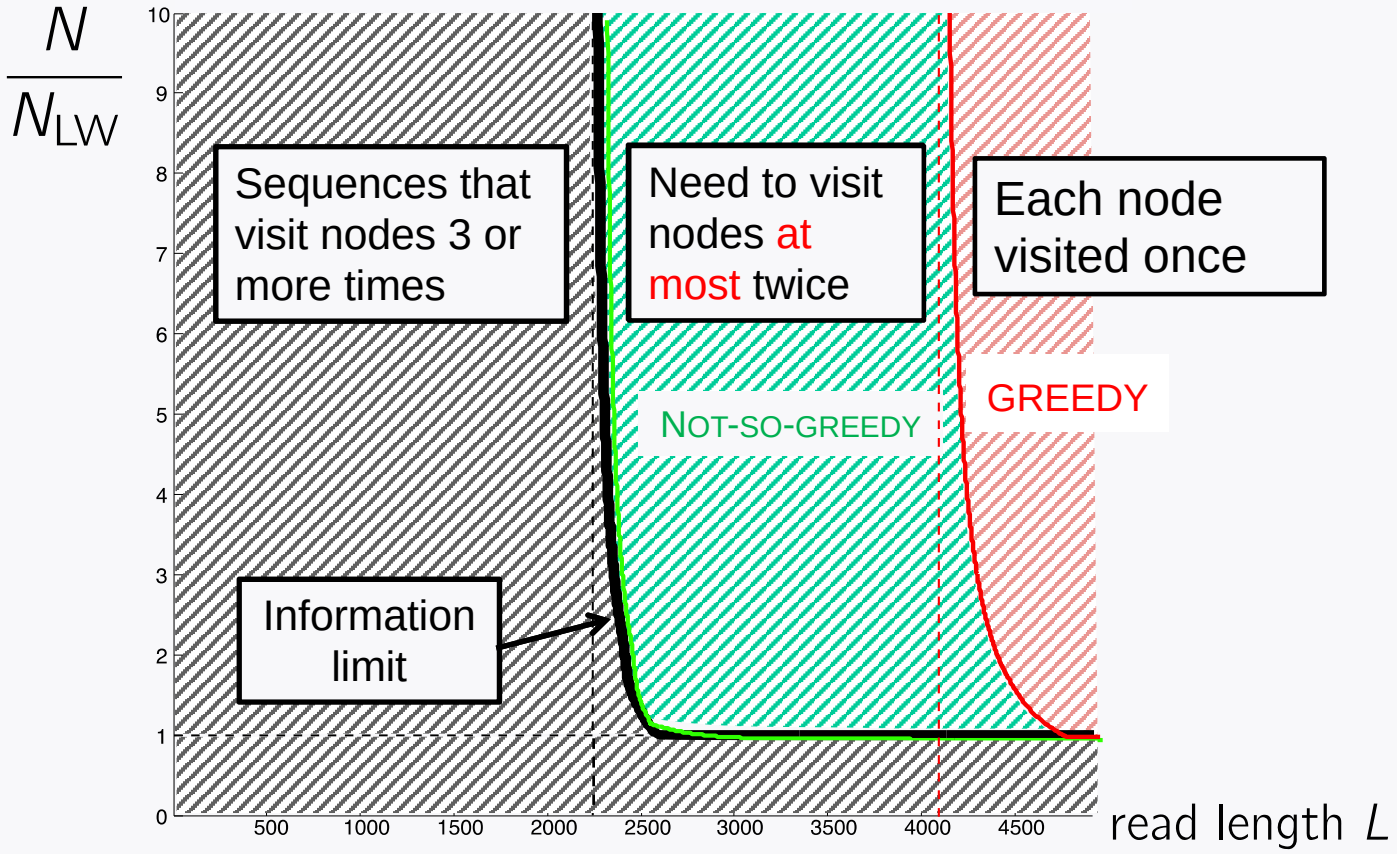
# Do we need to visit nodes > 2 times?

- What if true path visits a node three times?



- Both paths have the same likelihood!

# Information limit

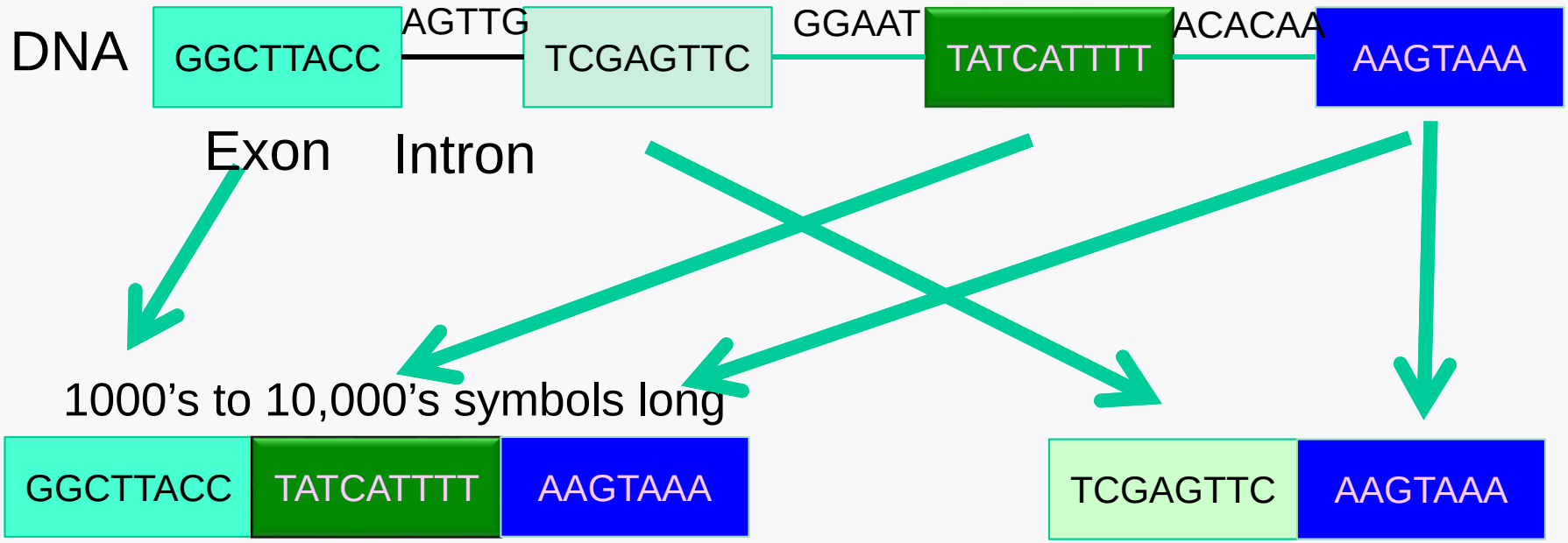



- "Not-so-greedy" algorithm (Shomorony, Courtade & T. 2015)
  - Only uses two best extensions.
  - With further pruning, complexity linear in number of reads.

# Information then computation

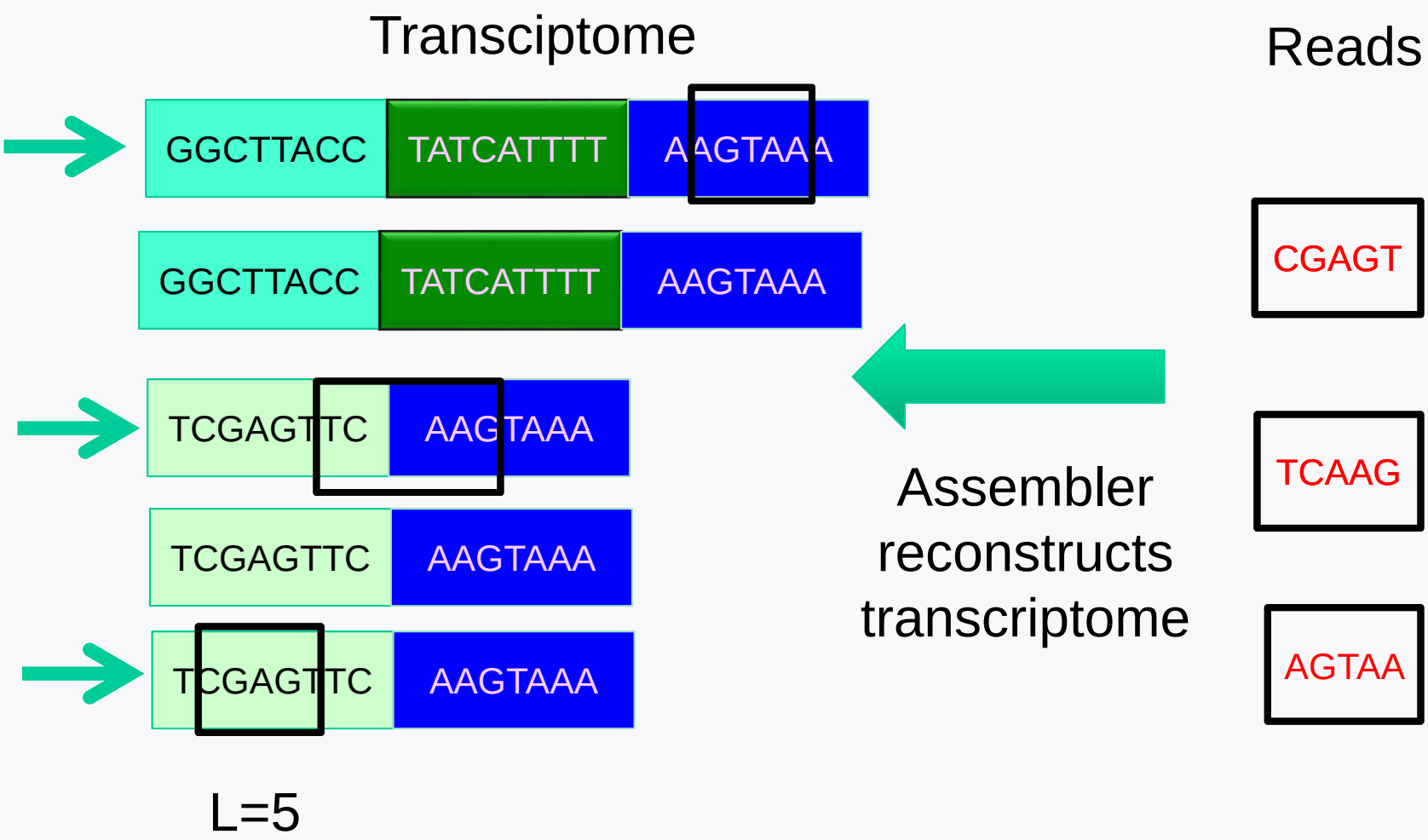
- NP-hardness is a worst-case measure of complexity over all problem instances.
- But we only care about the instances where there is enough data to reconstruct.
- It happens that those instances are also efficiently solvable.

# From DNA to RNA




The human transcriptome has 10,000's of such transcripts from 20,000 genes.

# RNA-Seq assembly




Both intra and inter-transcript repeats.

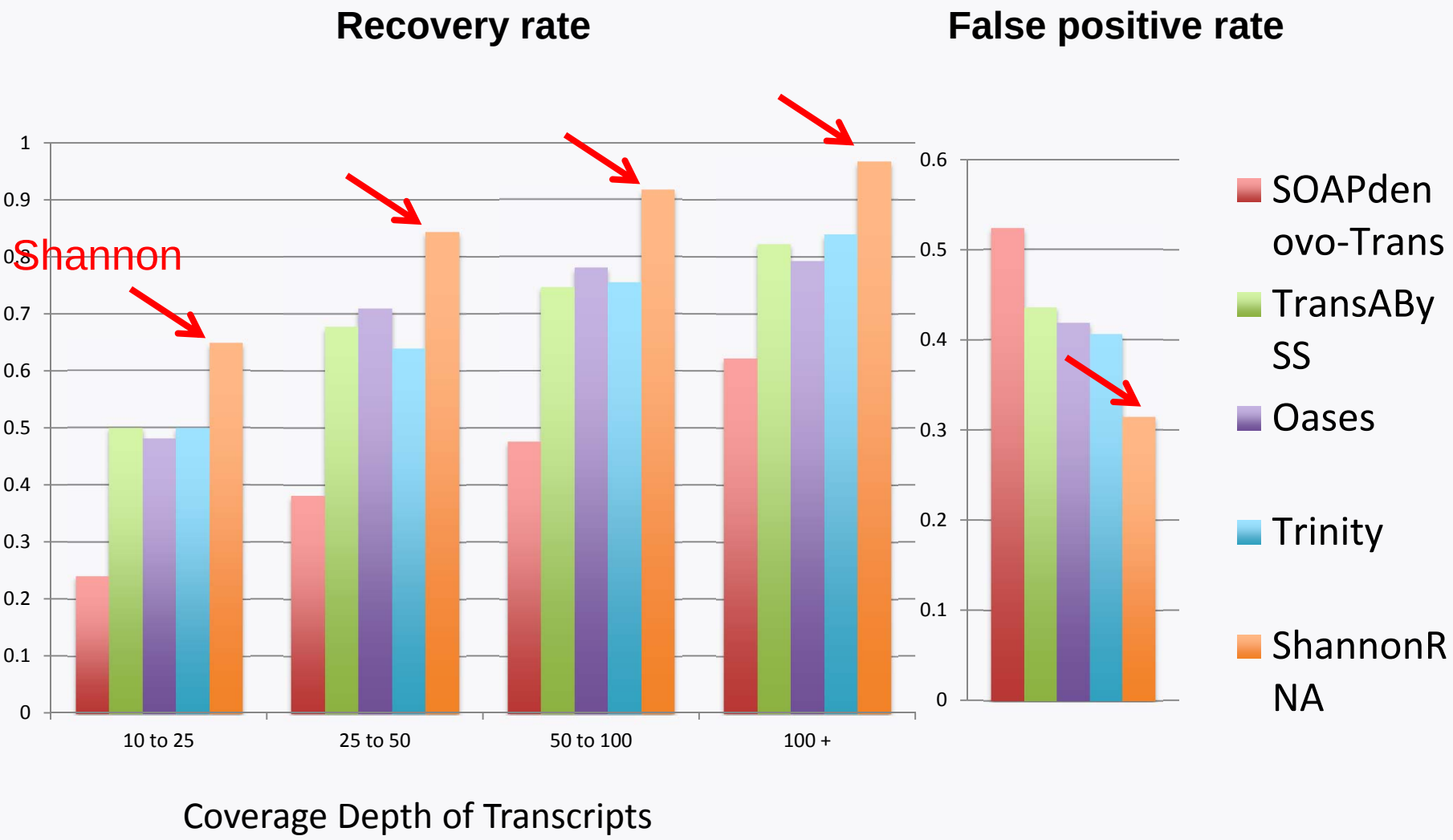
# RNA assembler: Shannon

Kannan, Pachter & T. 15

- Characterized information limit due to both intra and inter-transcript repeats.
- Intra-transcript repeats resolved using an algorithm similar to DNA assembly.
- Inter-transcript repeats resolved using an algorithm that finds sparsest flow in a graph.
- Sparsest flow is NP-hard, but we show that the reconstructible instances can be computed in linear time.

# Shannon: evaluation on real data

Read length=50, 135 Million reads, human embryonic stem cell (Au et al, PNAS 2013)



# Conclusion

- Information theory is about fundamental limits.
- It is also a constructive theory.
- It overcomes computationally intractable problems by focusing on tractable instances.