Phillip Compeau
@PhillipCompeau

This is the best video to introduce a computational biology course. There will never be a better one

From **Shashank**

3:02 PM · Jun 28, 2023 · **536.3K** Views

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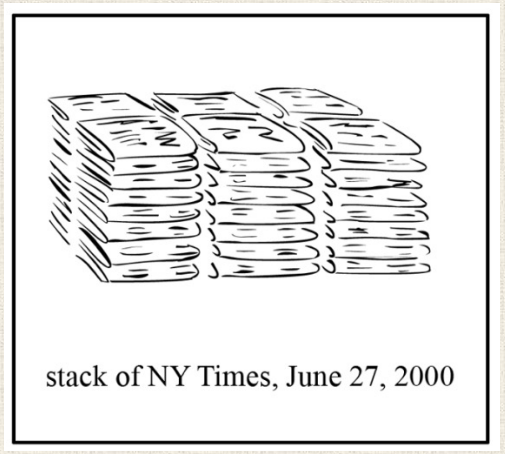
Assembling Genomes

Eternity II: The Highest-Stakes Puzzle in History

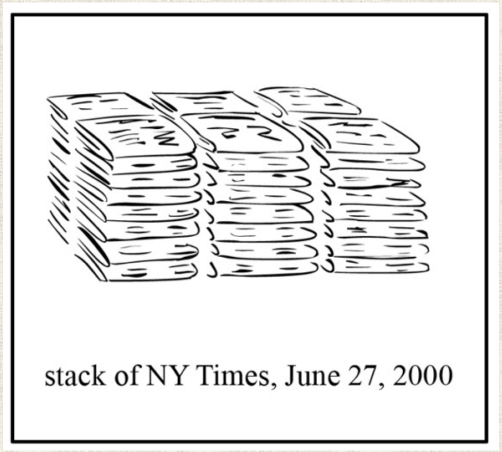
Courtesy: Matej Bat'ha

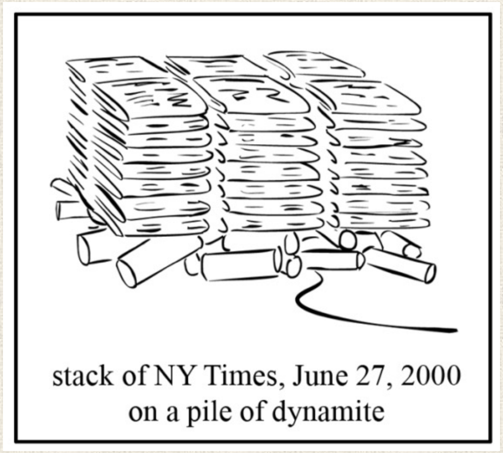
AN INTRODUCTION TO GENOME SEQUENCING

The Newspaper Problem


stack of NY Times, June 27, 2000

The Newspaper Problem





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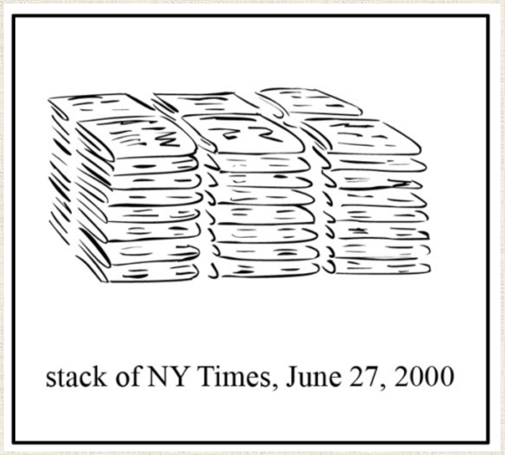

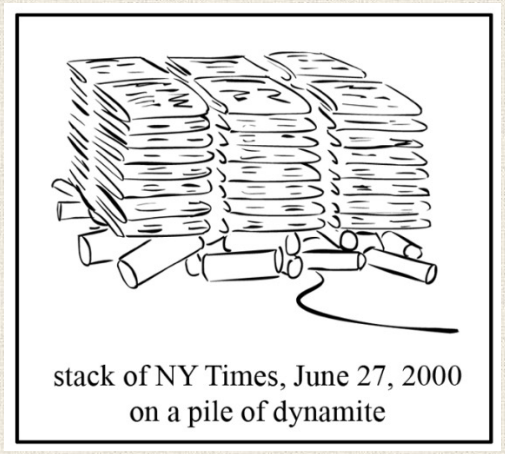

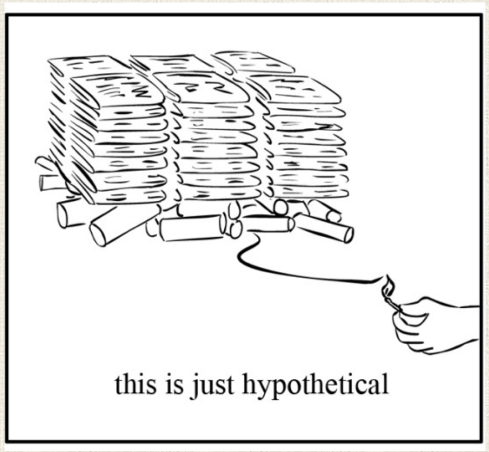

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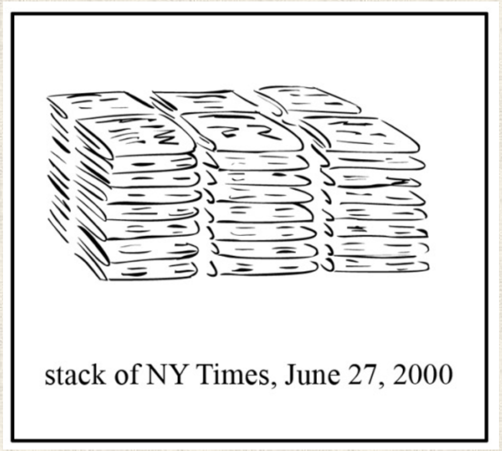

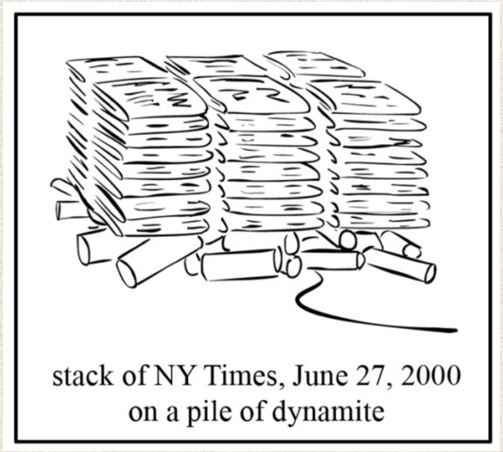

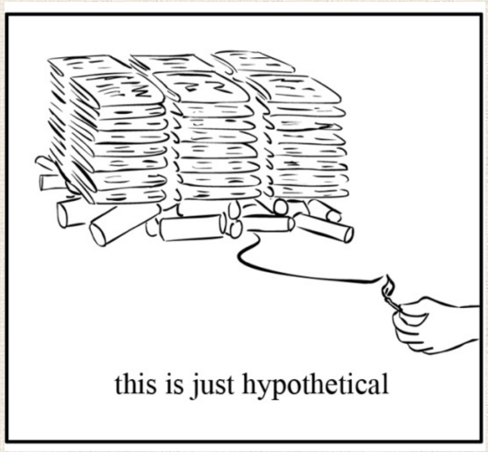

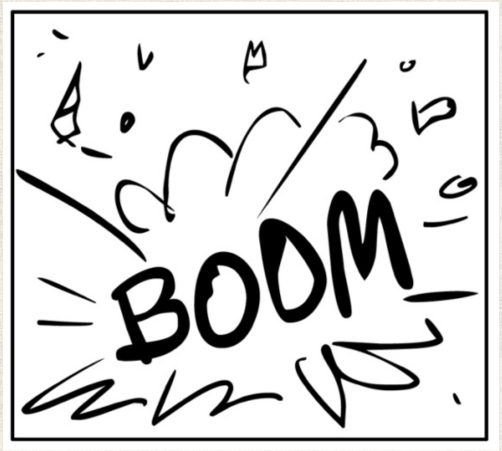

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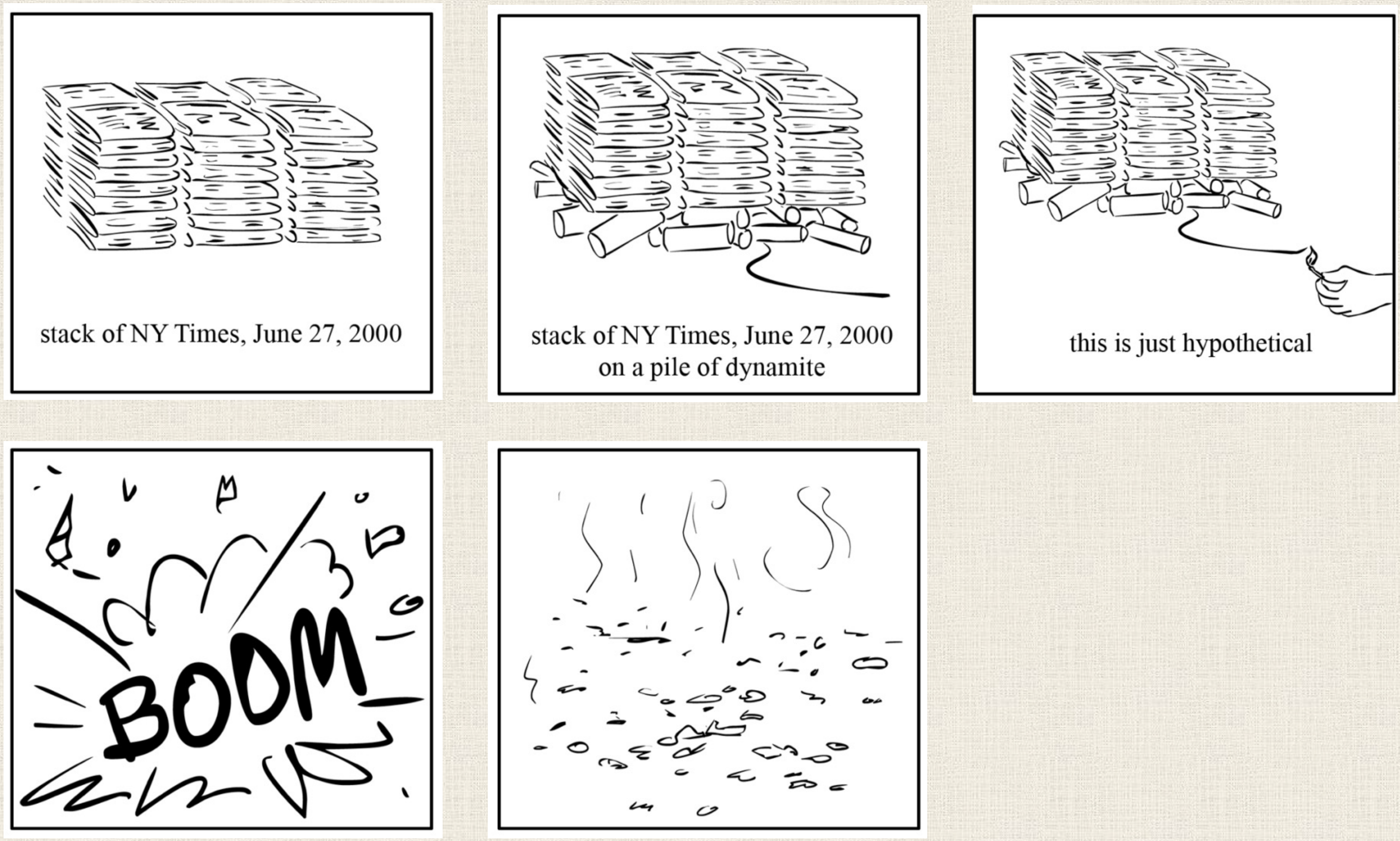
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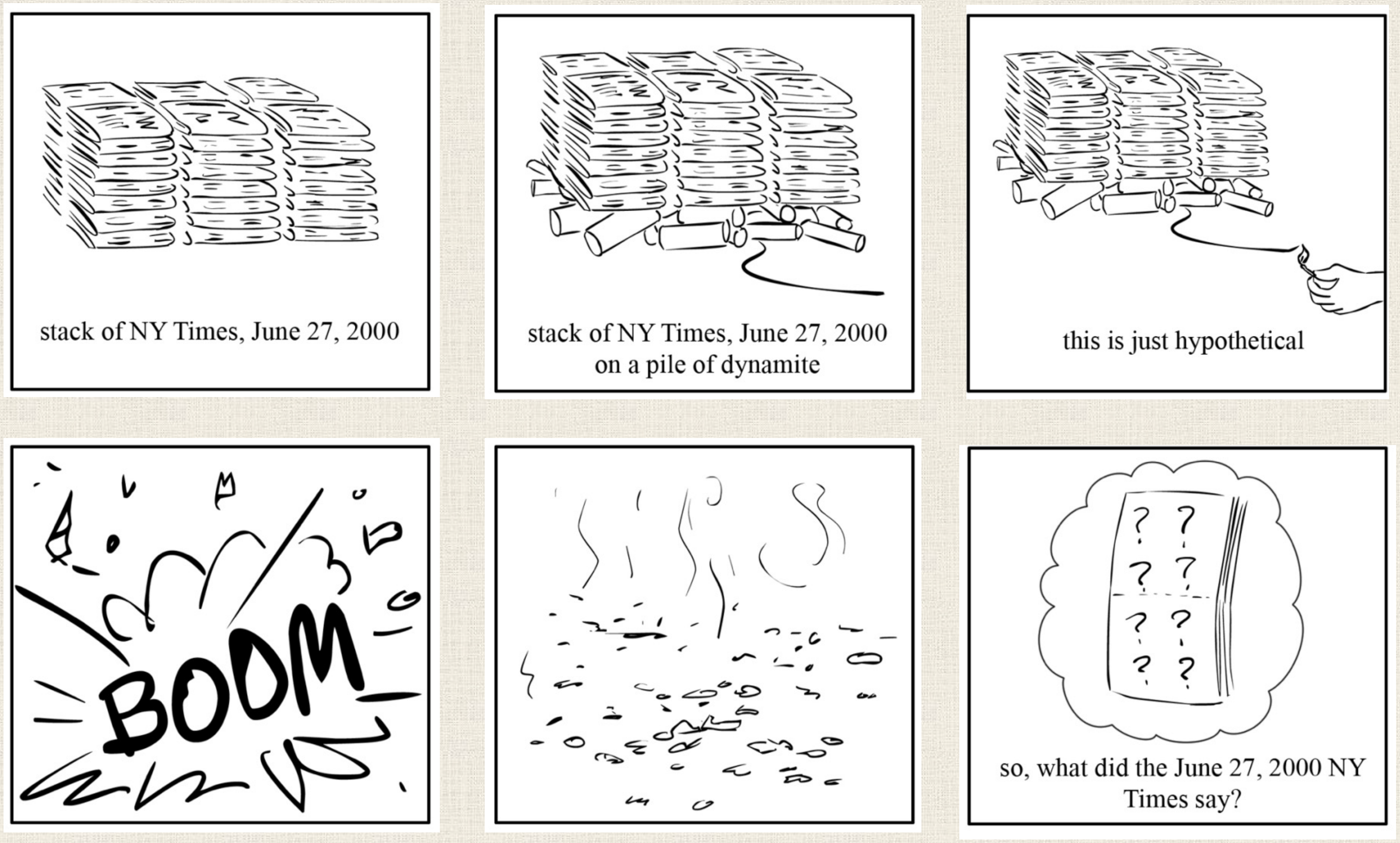
stack of NY Times, June 27, 2000 on a pile of dynamite
this is just hypothetical
BOOM

The Newspaper Problem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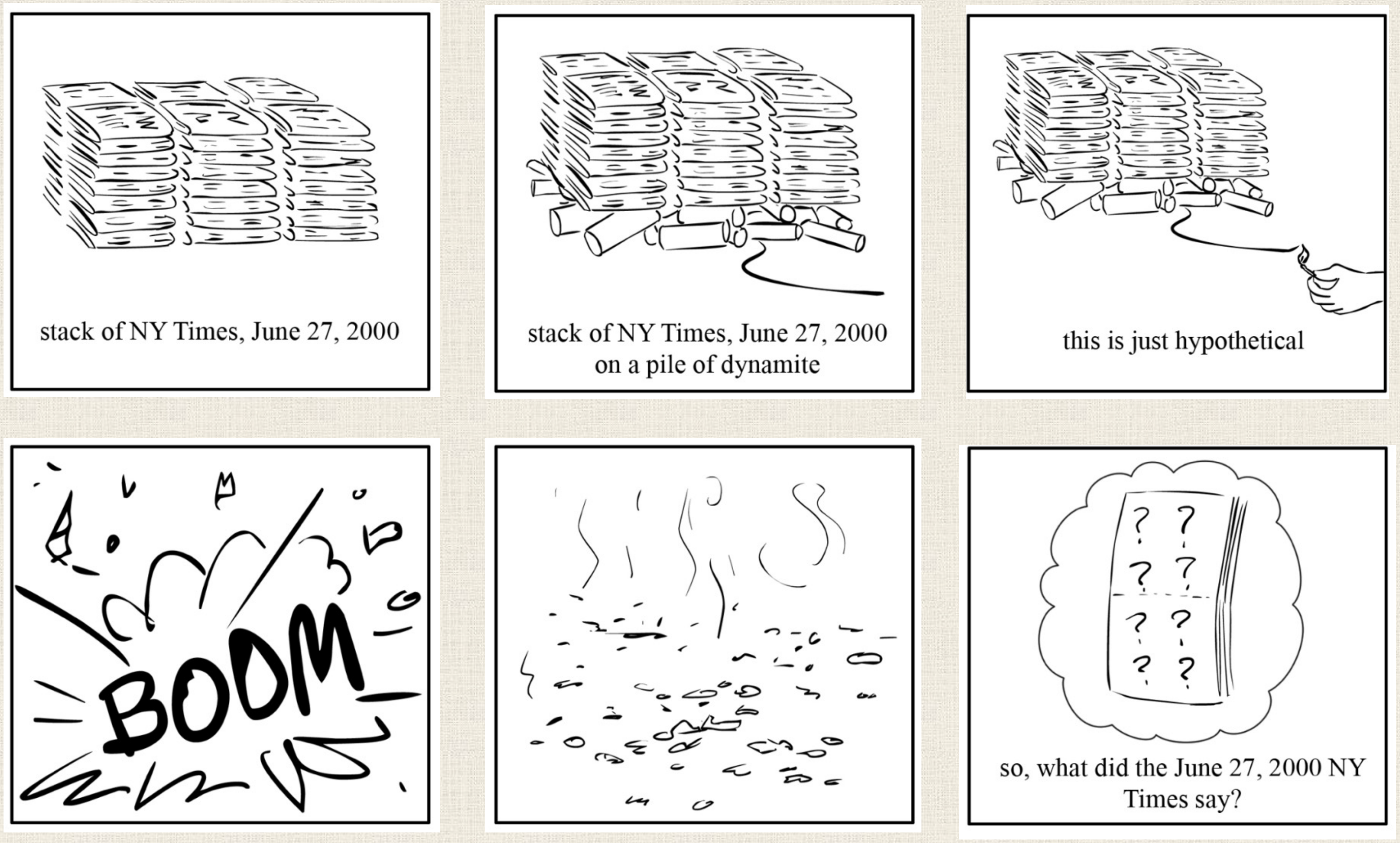
so, what did the June 27, 2000 NY Times say?

The Newspaper Problem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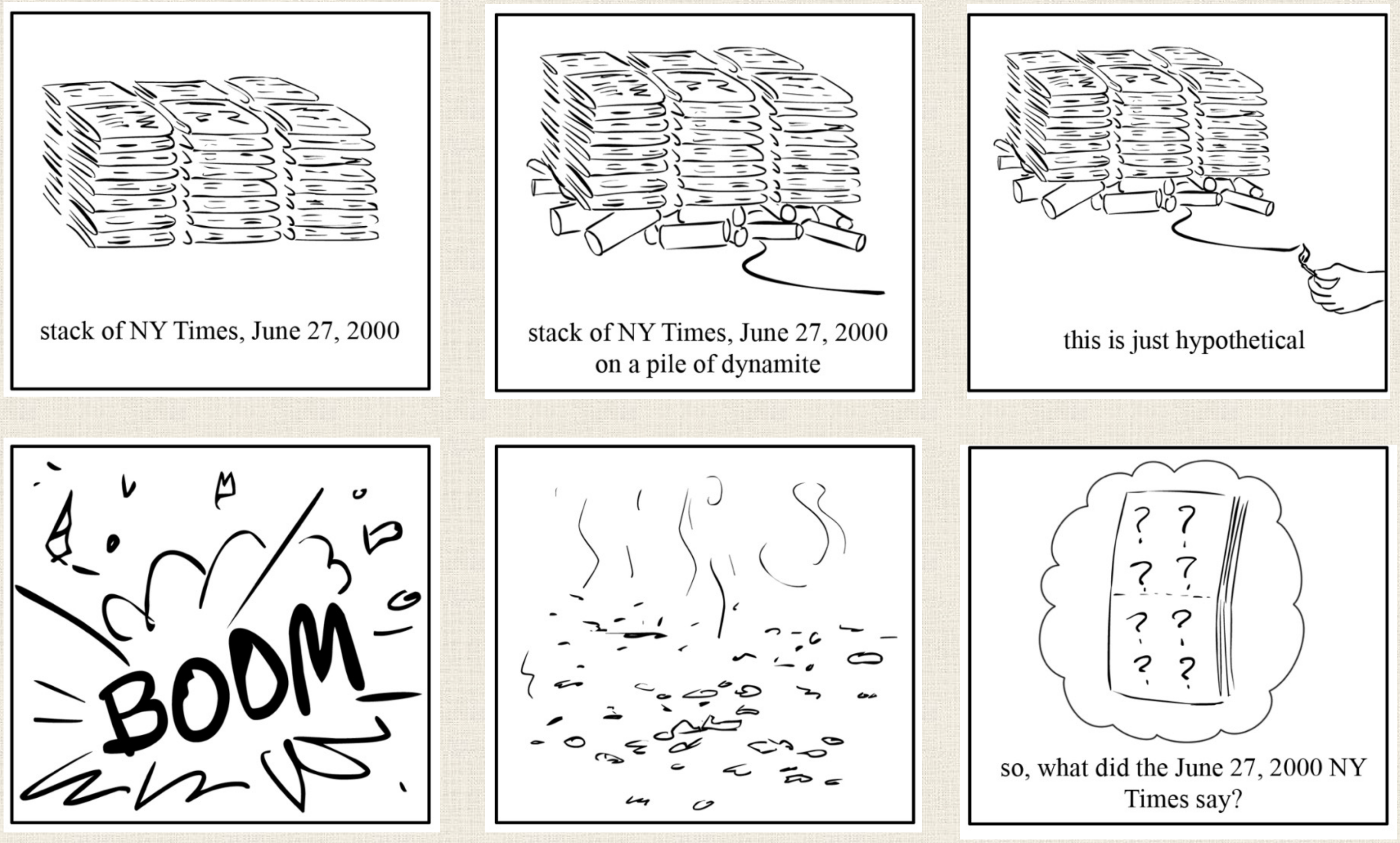
? ? ? ? ? ? ? ?
so, what did the June 27, 2000 NY Times say?

STOP: How would you reconstruct the news?

The Newspaper Problem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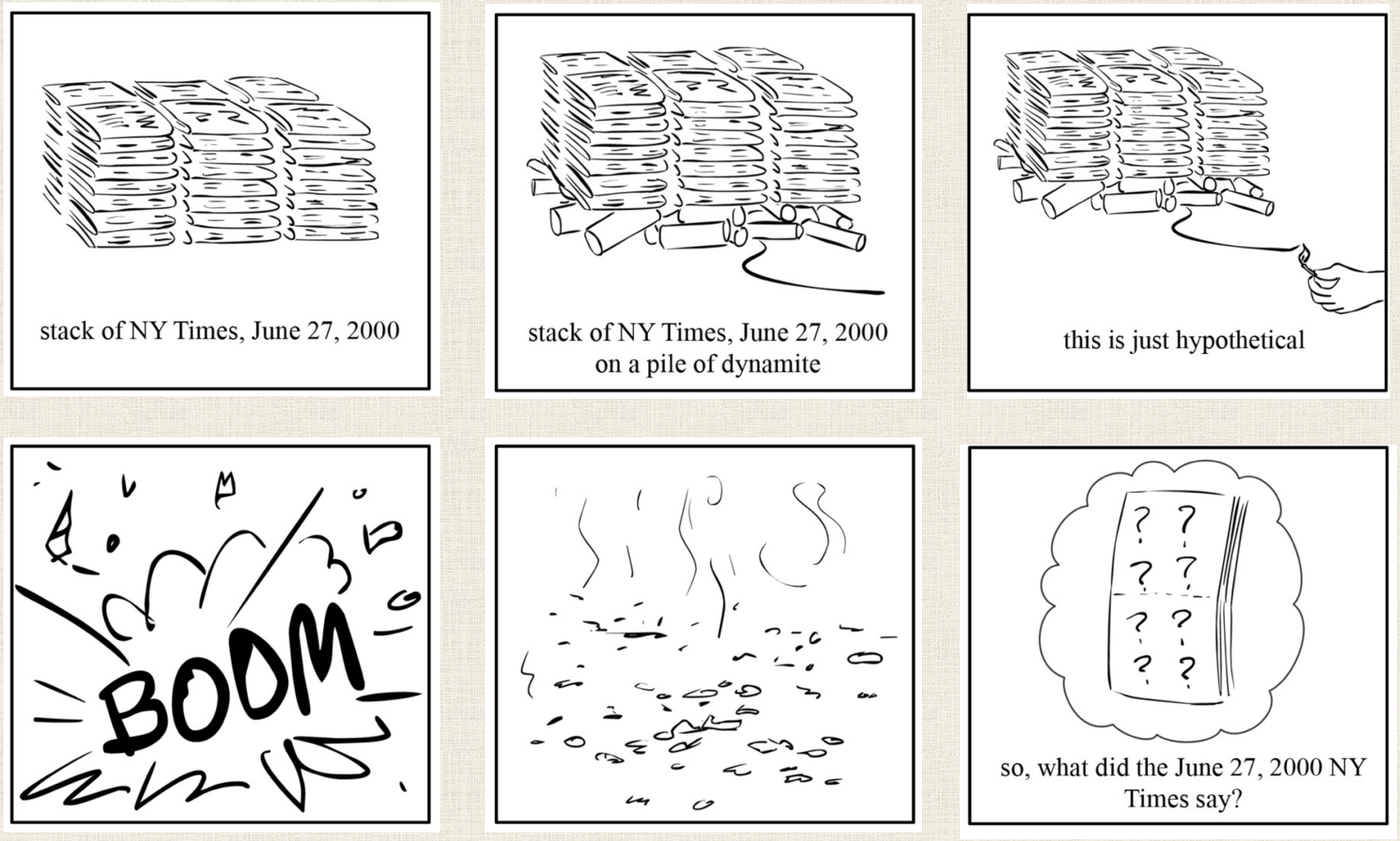
The Newspaper Problem is an **overlap puzzle**.

The Newspaper Problem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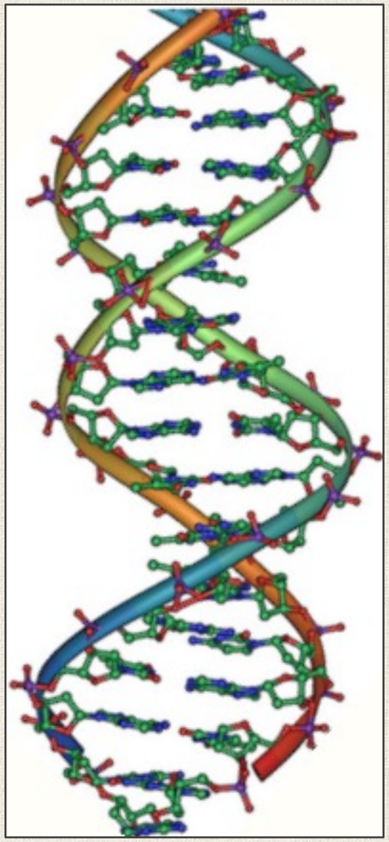
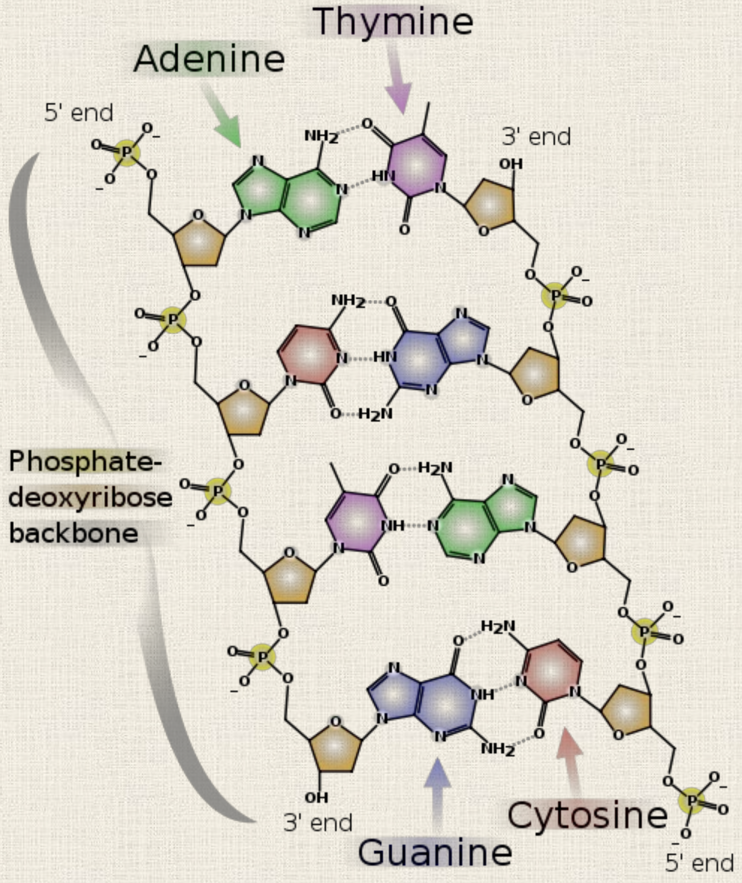
But what does this have to do with biology?

DNA is a Double Helix of Nucleotide Strands


DNA's Double Helix (1953)



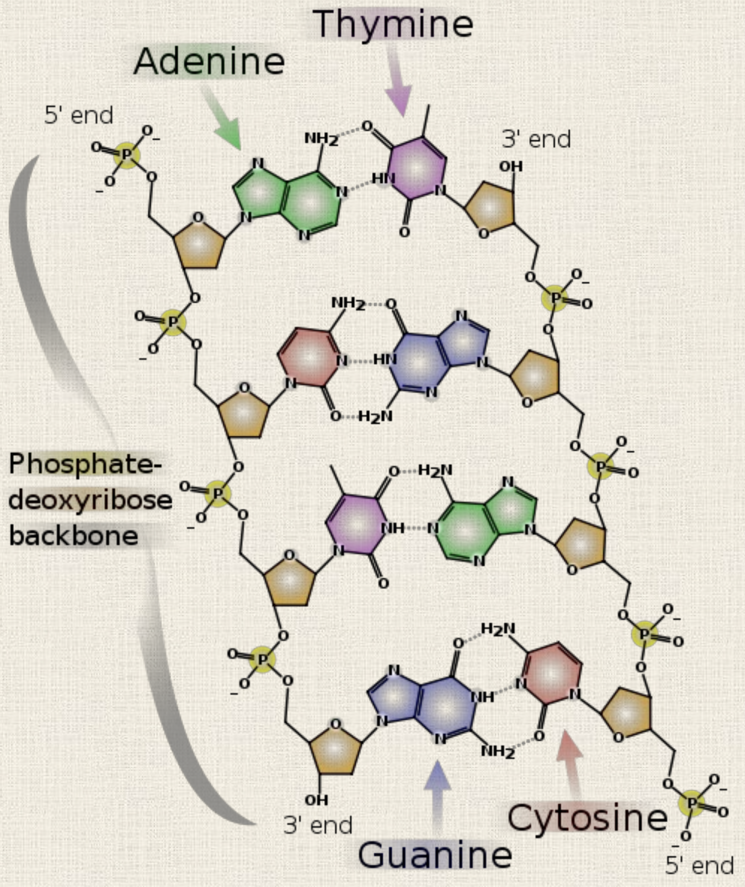
DNA's Molecular Structure
Courtesy: Madprime, Wikimedia Commons

The Order of Nucleotides Determines Genetics

Nucleotide: Half of one "rung" of DNA.

Four choices for the nucleic acid of a nucleotide:

1. Adenine (`A`)
2. Cytosine (`C`)
3. Guanine (`G`)—bonds to `C`
4. Thymine (`T`)—bonds to `A`



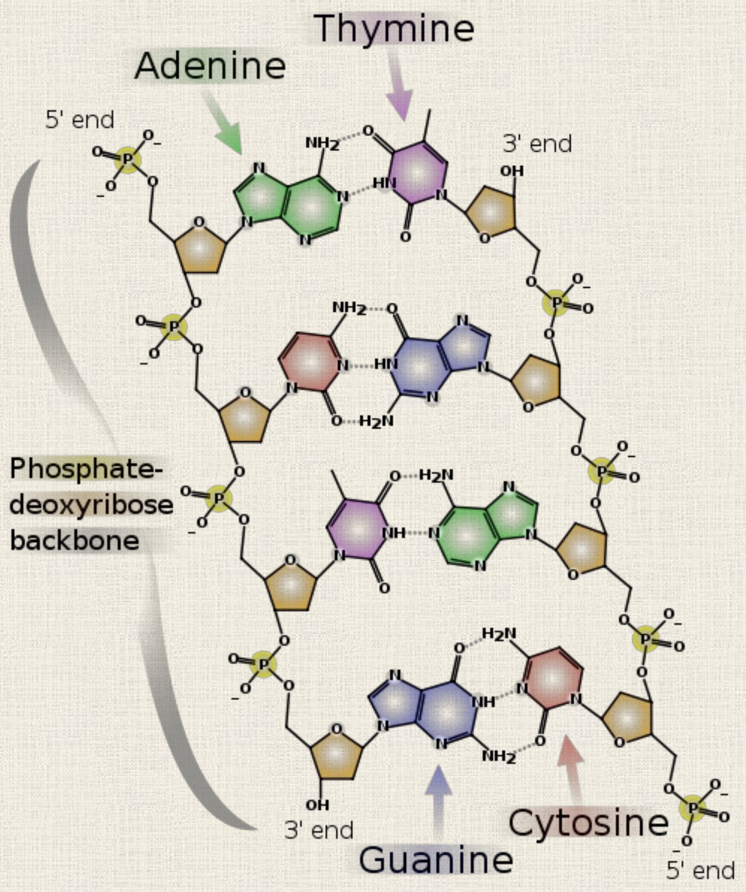
DNA's Molecular Structure

Courtesy: Madprime, Wikimedia Commons

The Order of Nucleotides Determines Genetics

Nucleotide: Half of one "rung" of DNA.

Key point: if we know one strand of DNA, we get the other strand for free because of this "complementarity".



DNA's Molecular Structure

Courtesy: Madprime, Wikimedia Commons

Genome “Sequencing” Means “Reading” the Genome

Genome: The nucleotide sequence read down one side of an organism’s chromosomal DNA. A human genome has about 3 billion letters.

```
…CCGTAGTCGCATGGAACAGTATACGAGACAGTACAGATACGATACGATACGATCATTAACCGAGAGTACCAGATTCCAGATCATACG
TTACGCTTAGCTACGGACGTACGATACCCAGATTACGATCCATATAGATATAACCGGTGTGTCTTGCTAATACGTAACGGGGTGCCT
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CTAGACTAGCGTATGCCTCTTATGATCGTCCCGATCGAGTCGCGTGCTCAGAAAAGCTACGATACGATACCCGATACTAGACCATAG…
```

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```
…CCGTAGTCGCATGGAACAGTATACGAGACAGTACAGATACGATACGATACGATCATTAACCGAGAGTACCAGATTCCAGATCATACG
TTACGCTTAGCTACGGACGTACGATACCCAGATTACGATCCATATAGATATAACCGGTGTGTCTTGCTAATACGTAACGGGGTGCCT
TCGATAGGTCAGAATACCAGATCTCTCGATCTTCTTACAGATACTACGATCCCCAGATACTACCCCTACTGACCCATCGTACGGGTA
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CTAGACTAGCGTATGCCTCTTATGATCGTCCCGATCGAGTCGCGTGCTCAGAAAAGCTACGATACGATACCCGATACTAGACCATAG…
```

Polychaos dubium (an amoeba) has one of the longest known genomes: 670 billion nucleotides.

Genome "Sequencing" Means "Reading" the Genome

Genome: The nucleotide sequence read down one side of an organism's chromosomal DNA. A human genome has about 3 billion letters.

```
…CCGTAGTCGCATGGAACAGTATACGAGACAGTACAGATACGATACGATACGATCATTAACCGAGAGTACCAGATTCCAGATCATACG
TTACGCTTAGCTACGGACGTACGATACCCAGATTACGATCCATATAGATATAACCGGTGTGTCTTGCTAATACGTAACGGGGTGCCT
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CTAGACTAGCGTATGCCTCTTATGATCGTCCCGATCGAGTCGCGTGCTCAGAAAAGCTACGATACGATACCCGATACTAGACCATAG…
```
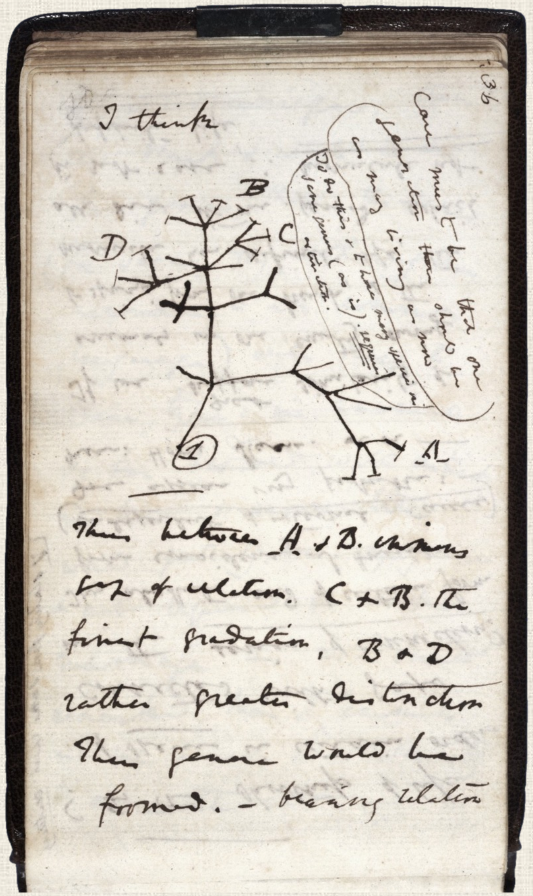

Key Point: DNA is submicroscopic! How do we read something that we cannot see?

We Sequence a Species's Genome to Unlock its Genetic Identity



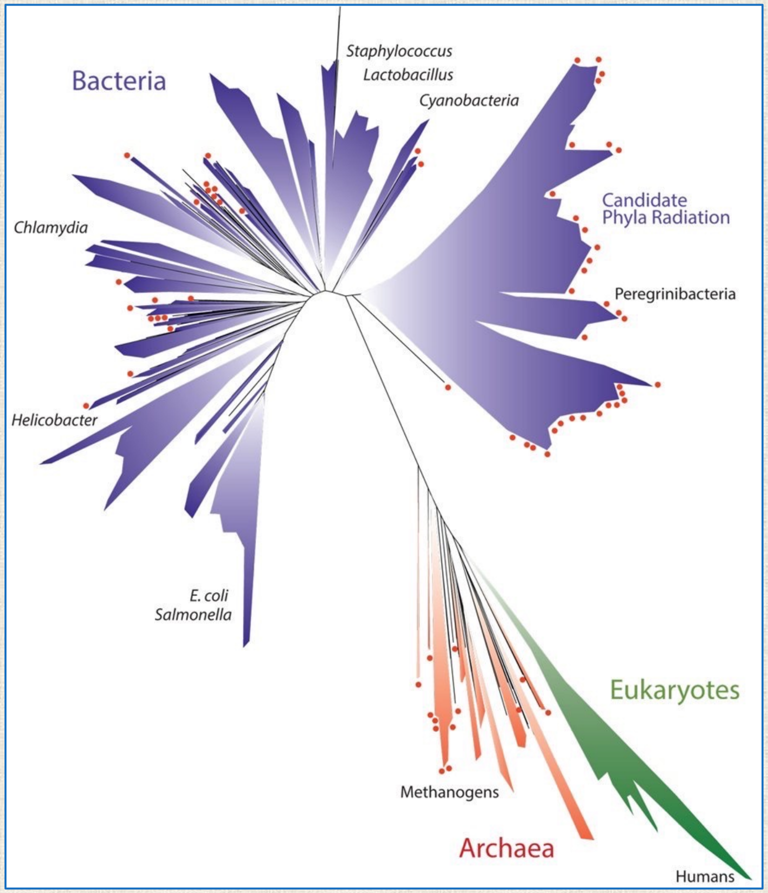
36

I think

Case must be that one generation then should be as many living as now. To do this & to have many species in same genus (as is). requires extinction.

Thus between A & B. immense gap of relation. C & B. the finest gradation, B & D rather greater distinction. Thus genera would be formed. — bearing relation

Darwin's notebook c. 1837

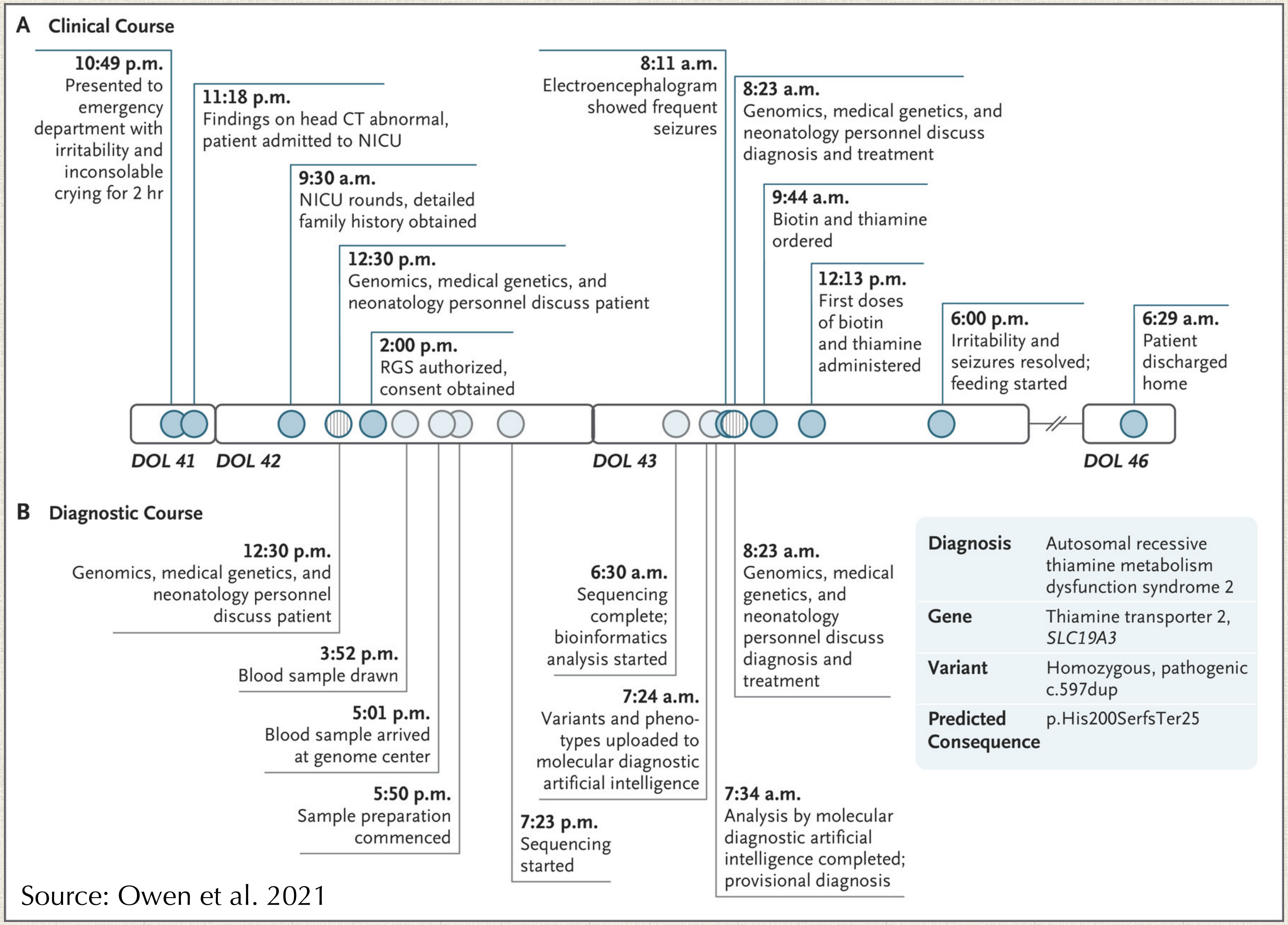


Hug et al., 2016
Nature Biotechnology, Discovery Magazine

We Sequence an Individual's Genome to Find What Makes them Unique

2011: First person whose life was saved because of genome sequencing.

Ten years later, genome sequencing saves a life in 13 hours


A Clinical Course
10:49 p.m. Presented to emergency department with irritability and inconsolable crying for 2 hr
11:18 p.m. Findings on head CT abnormal, patient admitted to NICU
9:30 a.m. NICU rounds, detailed family history obtained
12:30 p.m. Genomics, medical genetics, and neonatology personnel discuss patient
2:00 p.m. RGS authorized, consent obtained
8:11 a.m. Electroencephalogram showed frequent seizures
8:23 a.m. Genomics, medical genetics, and neonatology personnel discuss diagnosis and treatment
9:44 a.m. Biotin and thiamine ordered
12:13 p.m. First doses of biotin and thiamine administered
6:00 p.m. Irritability and seizures resolved; feeding started
6:29 a.m. Patient discharged home
DOL 41
DOL 42
DOL 43
DOL 46
B Diagnostic Course
12:30 p.m. Genomics, medical genetics, and neonatology personnel discuss patient
3:52 p.m. Blood sample drawn
5:01 p.m. Blood sample arrived at genome center
5:50 p.m. Sample preparation commenced
7:23 p.m. Sequencing started
6:30 a.m. Sequencing complete; bioinformatics analysis started
7:24 a.m. Variants and phenotypes uploaded to molecular diagnostic artificial intelligence
7:34 a.m. Analysis by molecular diagnostic artificial intelligence completed; provisional diagnosis
8:23 a.m. Genomics, medical genetics, and neonatology personnel discuss diagnosis and treatment

Diagnosis	Autosomal recessive thiamine metabolism dysfunction syndrome 2
Gene	Thiamine transporter 2, *SLC19A3*
Variant	Homozygous, pathogenic c.597dup
Predicted Consequence	p.His200SerfsTer25

Source: Owen et al. 2021

History of Genome Sequencing

Late 1970s: Walter Gilbert and Frederick Sanger develop independent sequencing methods.

```
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CCTGCA
```
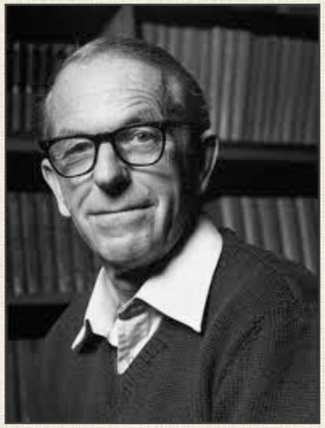

Bacterial phage PhiX174 genome (5,386 nucleotides)

Walter Gilbert

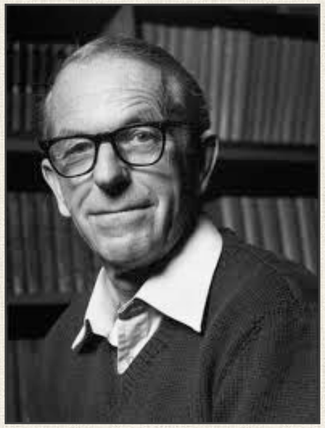

Frederick Sanger

History of Genome Sequencing

Late 1970s: Walter Gilbert and Frederick Sanger develop independent sequencing methods.

1980: They share the Nobel Prize in Chemistry.

Walter Gilbert


Frederick Sanger

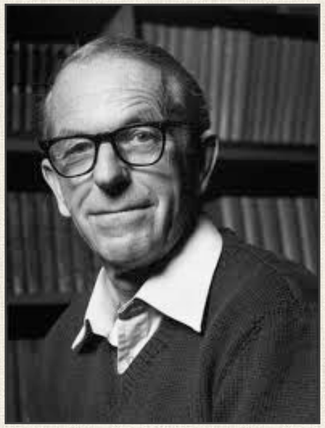
History of Genome Sequencing

Late 1970s: Walter Gilbert and Frederick Sanger develop independent sequencing methods.

1980: They share the Nobel Prize in Chemistry.

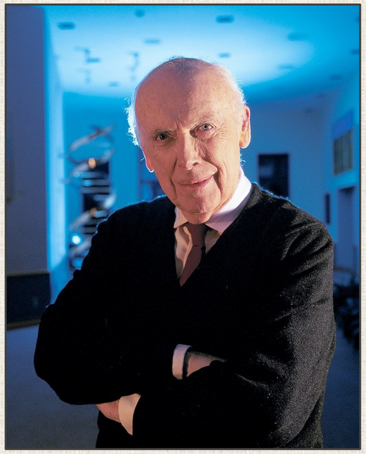
However, their approaches cost about $1 per nucleotide.

Walter Gilbert


Frederick Sanger

The Race to Sequence the Human Genome

1990: Human Genome Project given $3 billion to sequence human genome.


James Watson

The Race to Sequence the Human Genome

1990: Human Genome Project given $3 billion to sequence human genome.

1992: James Watson resigns, replaced by Francis Collins.

Francis Collins

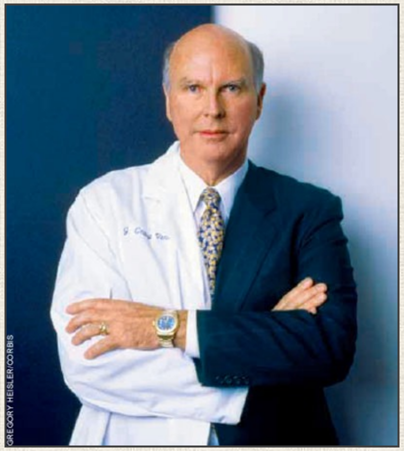
The Race to Sequence the Human Genome

1990: Human Genome Project given $3 billion to sequence human genome.

1992: James Watson resigns, replaced by Francis Collins.

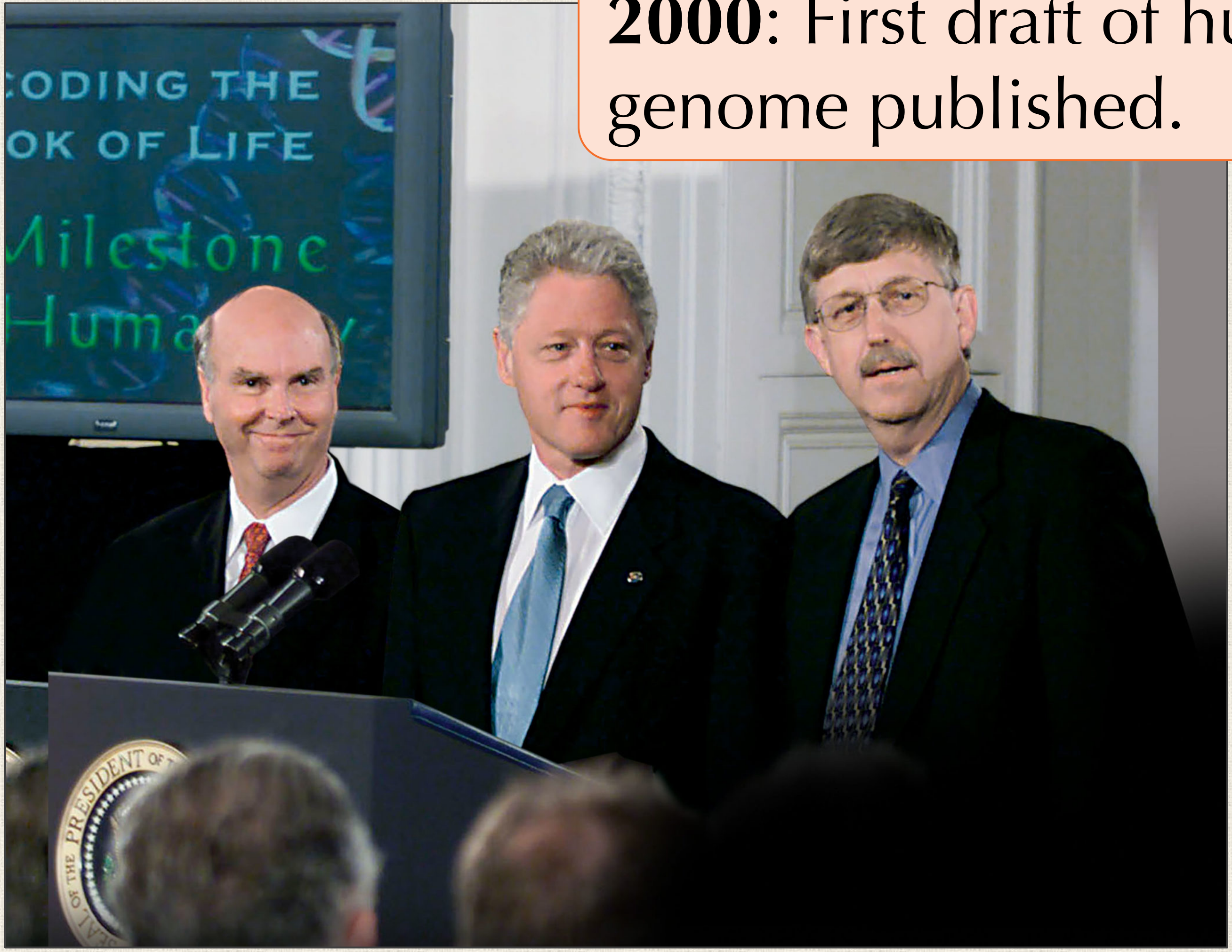
1997: Craig Venter founds Celera Genomics with same goal.

Francis Collins



Craig Venter

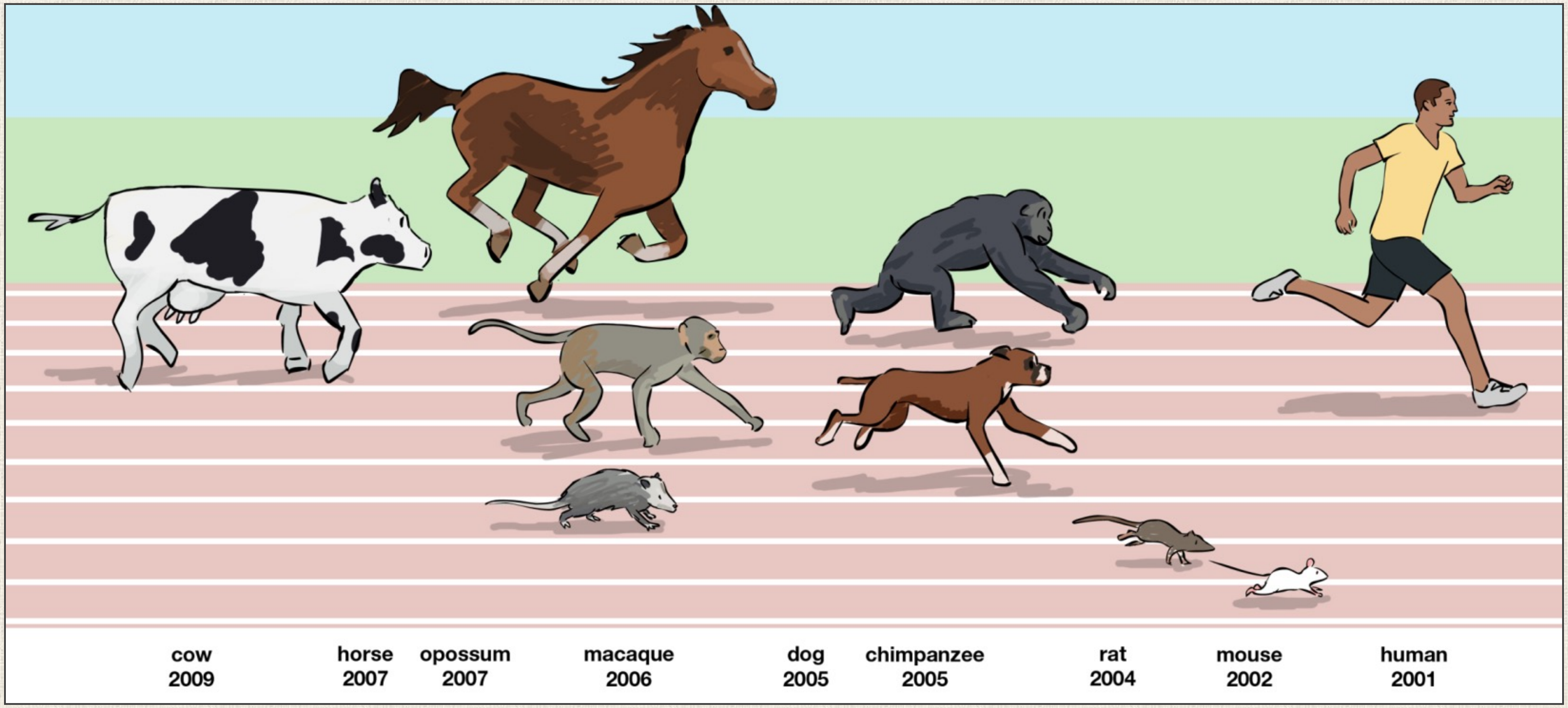
The Race to Sequence the Human Genome



2000: First draft of human genome published.

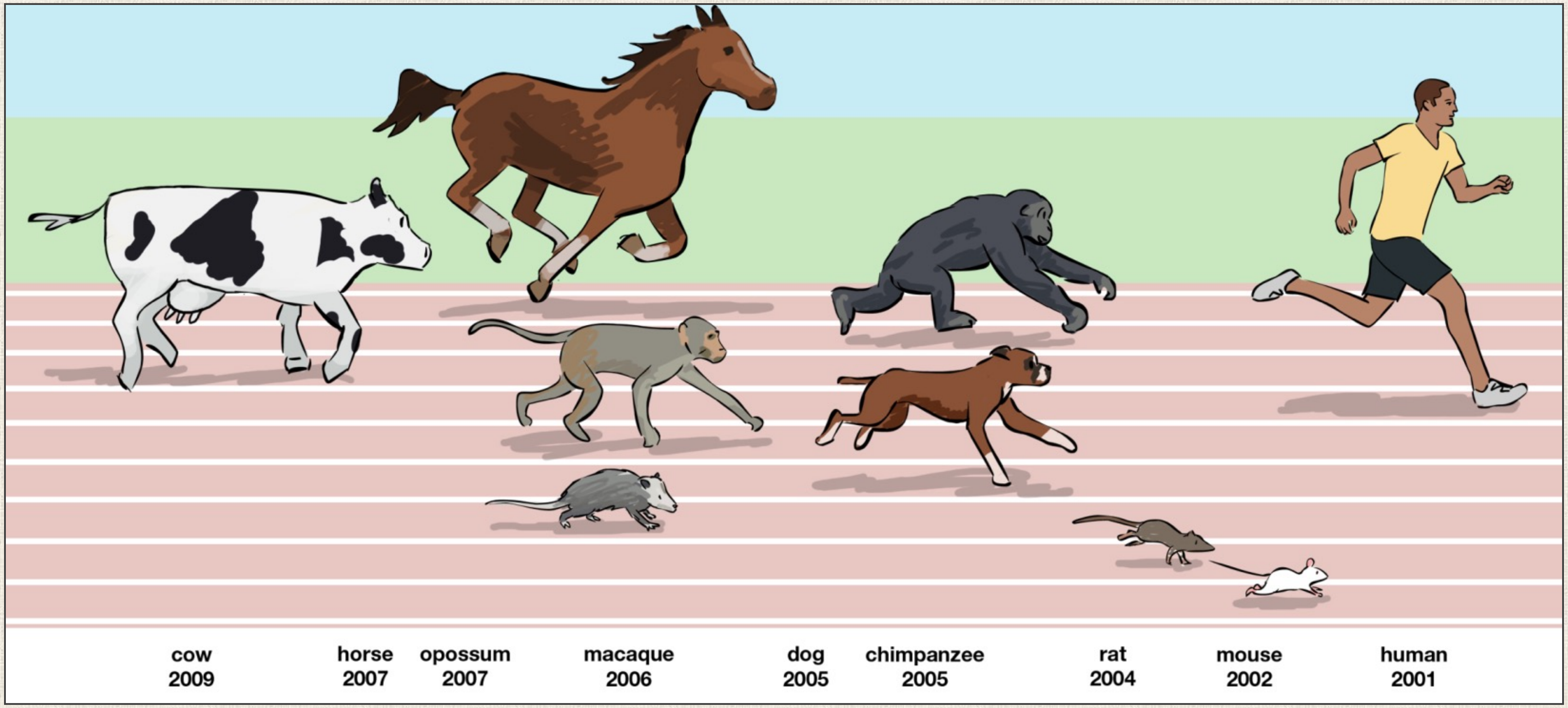
From One Mammal Genome to Many

Early 2000s: Many more mammalian genomes are sequenced using Sanger's approach.

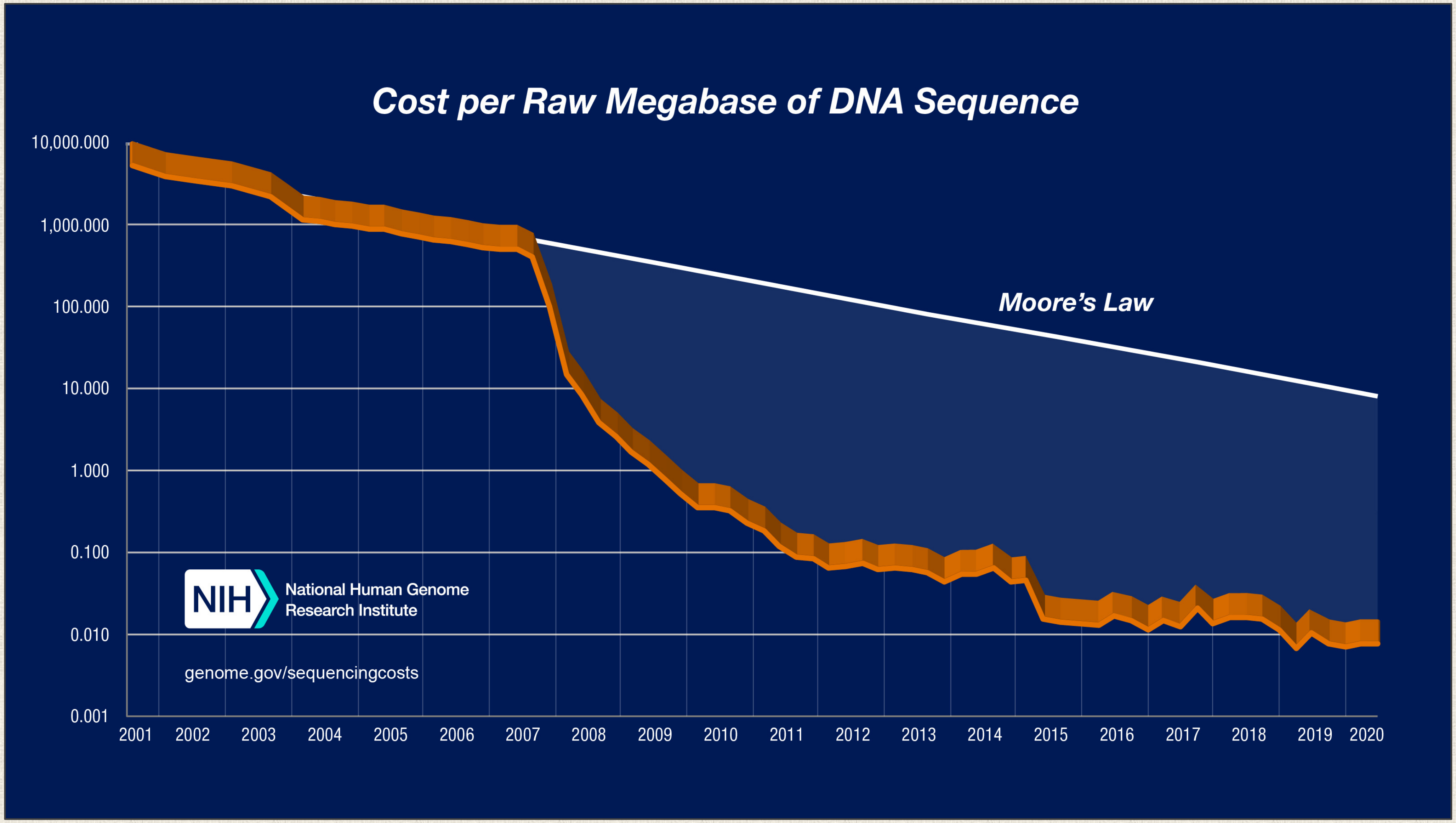


From One Mammal Genome to Many

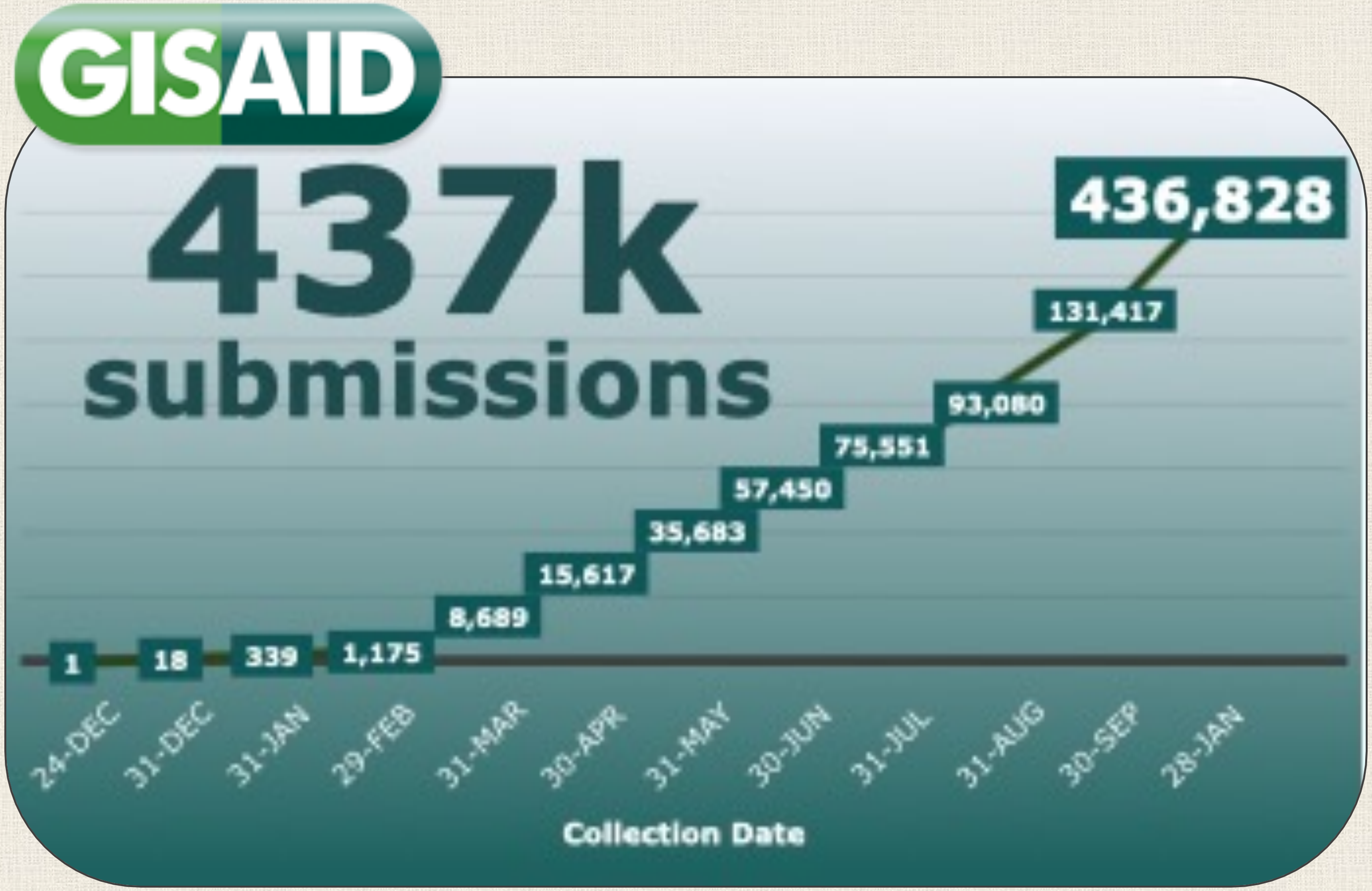
Problem: This approach was just too expensive to scale to thousands of species.



Sequencing Cost Has Fallen Faster than Moore's Law

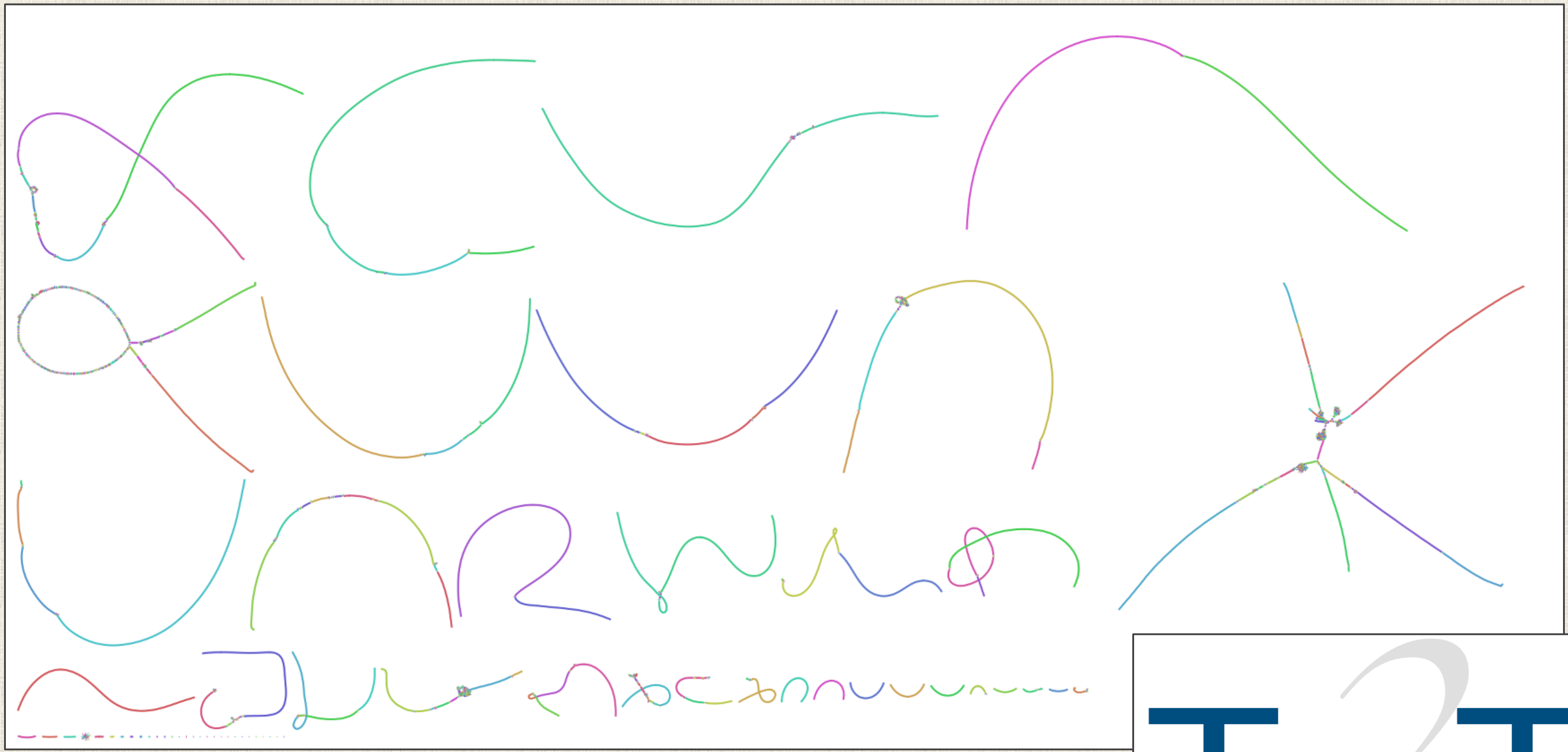


GISAID collects ~~400k~~ 2 Million SARS-CoV-2 Genomes in ~~One Year~~ Two Years



Scientists aim to sequence 1.5M eukaryotes before 2030

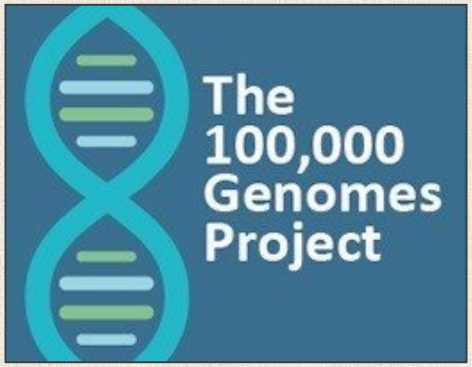
Dark Secret: The First *Full* Human Genome Wasn't Sequenced Until 2020!



TELOMERE-TO-TELOMERE CONSORTIUM

We Now Have Over 2 Million Human Genomes

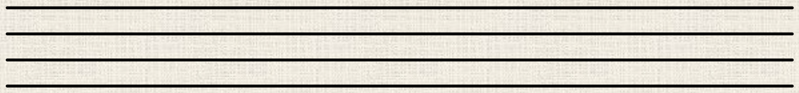
100,000 Genomes: Sequenced 100,000 UK resident genomes (2012-2018).



TELOMERE-TO-TELOMERE CONSORTIUM
TOWARDS A COMPLETE REFERENCE OF HUMAN GENOME DIVERSITY
HUMAN PANGENOME

Overview of Genome Sequencing

Multiple identical copies of a genome



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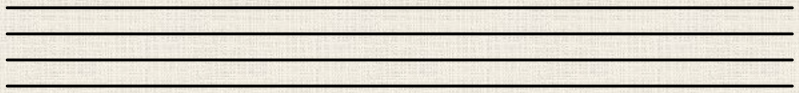
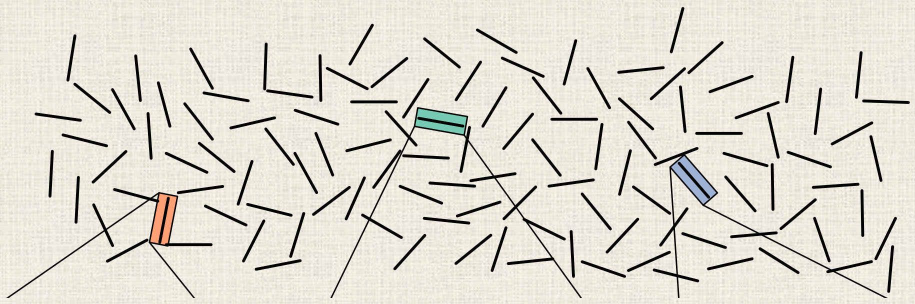
Multiple identical copies of a genome



Shatter the genome into reads



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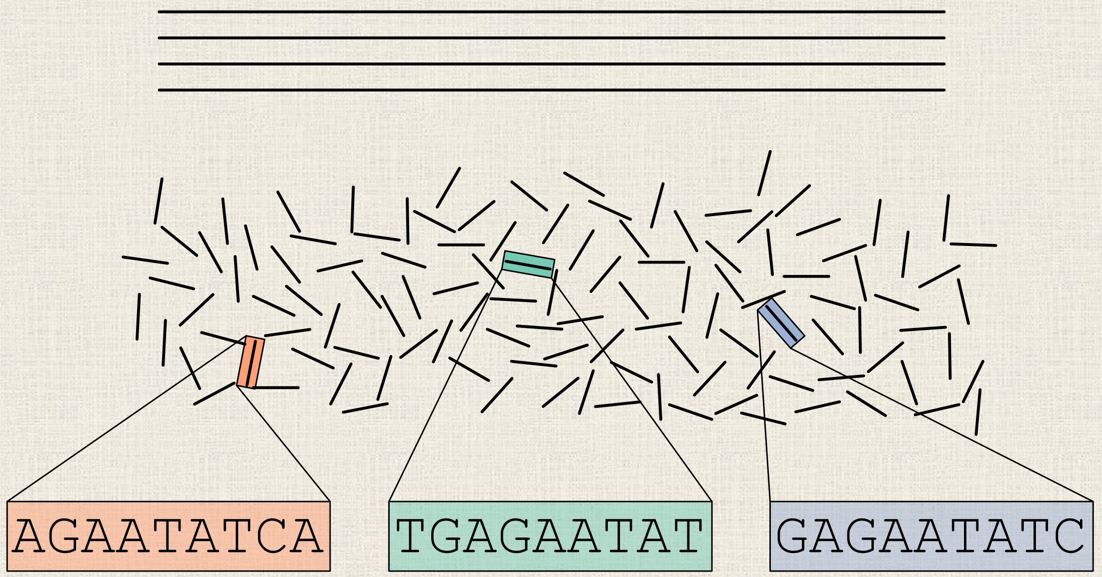
Sequence the reads

(Lab)



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(Lab)

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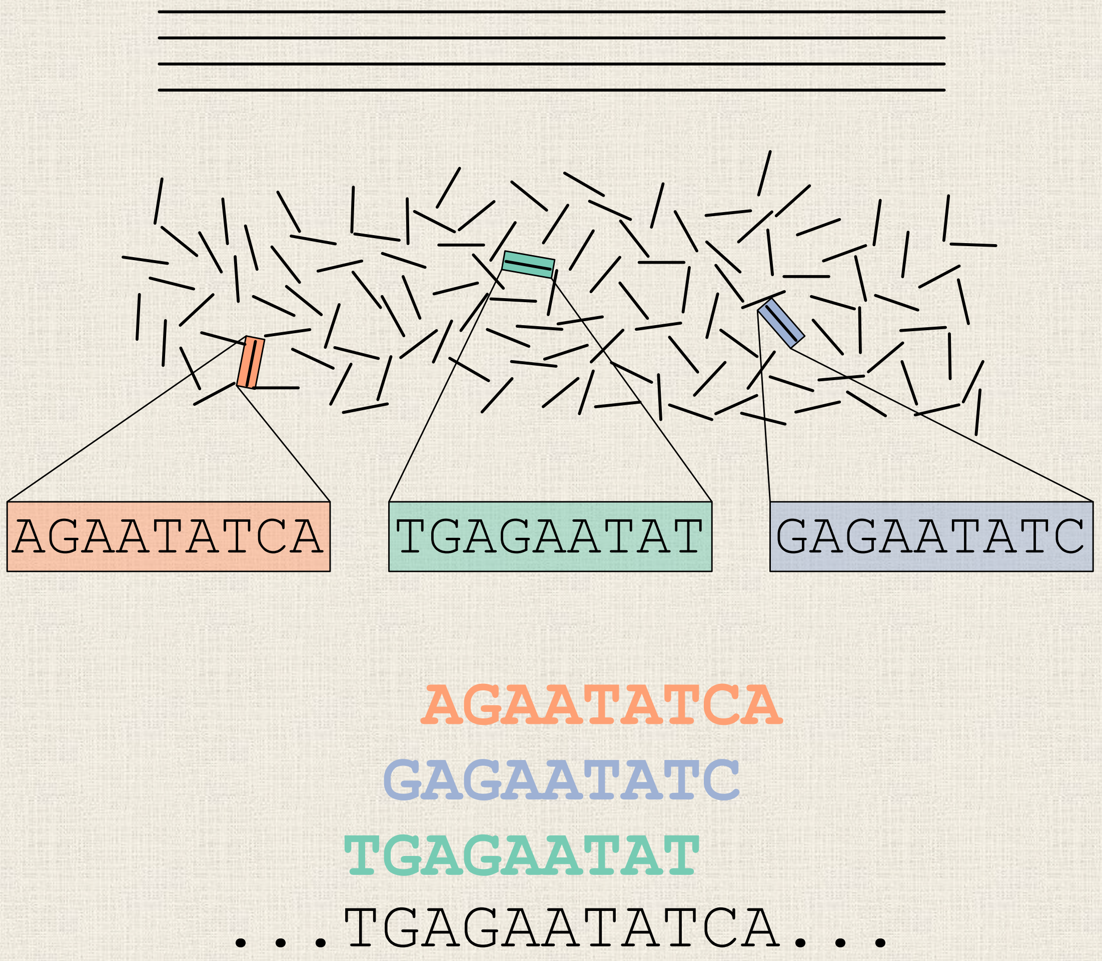
(Computational)



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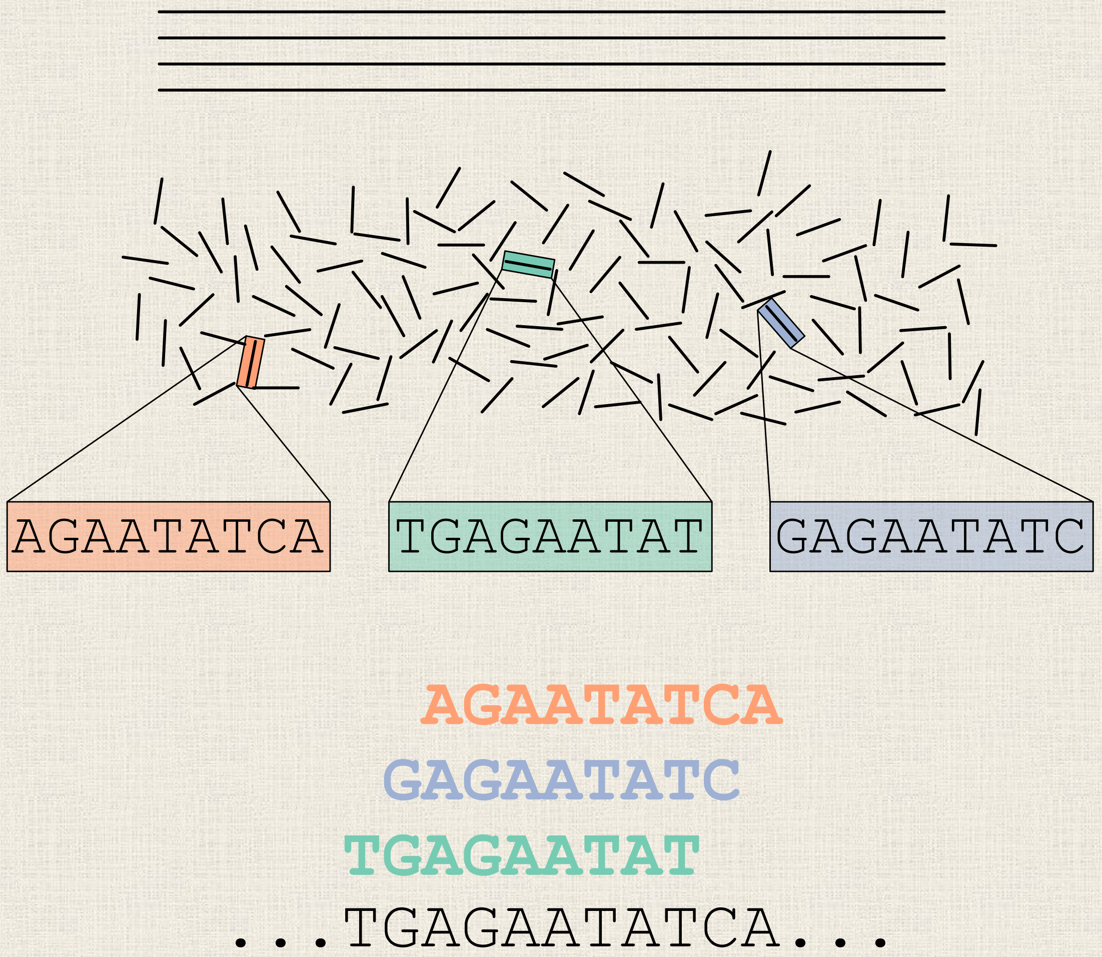
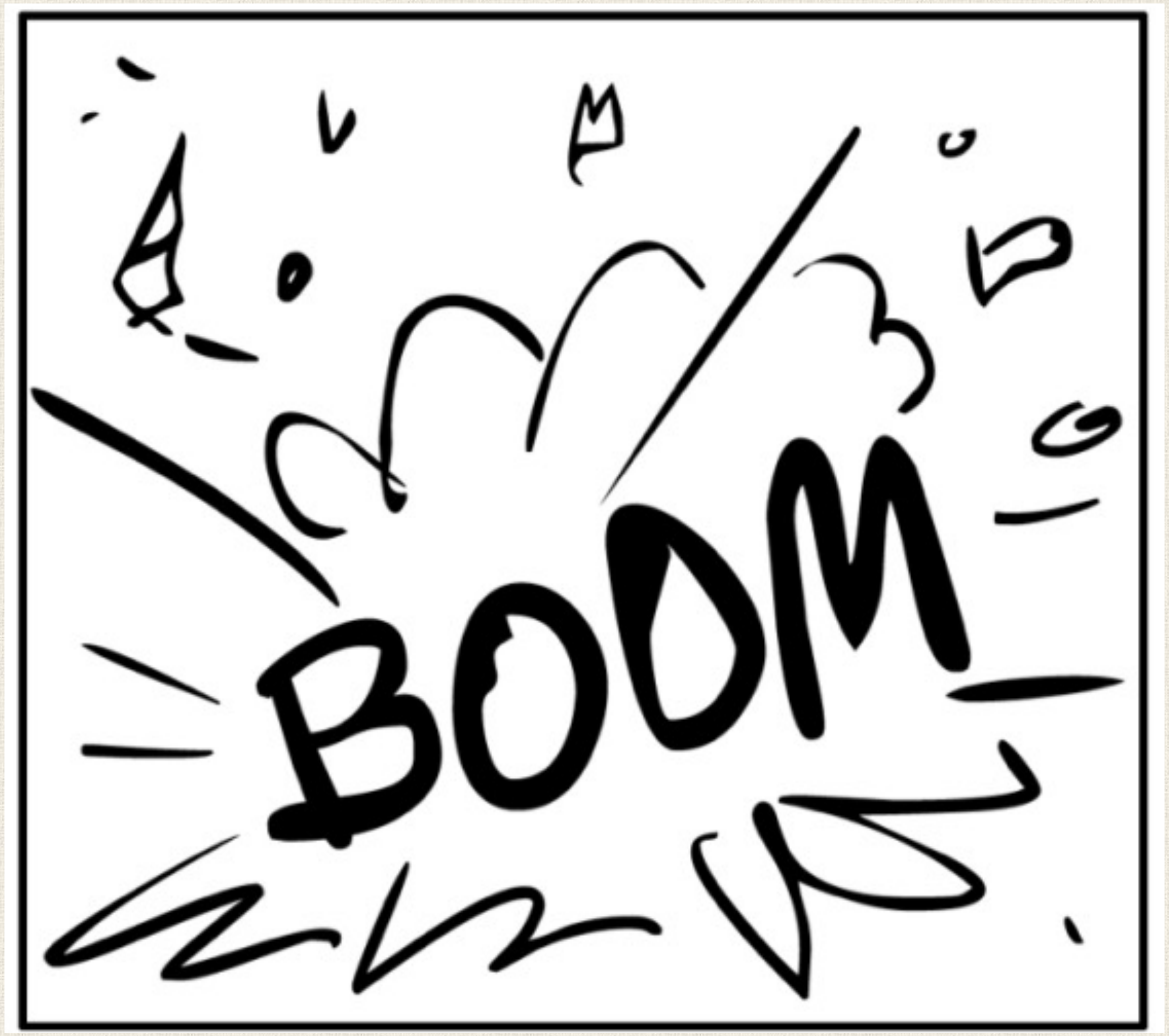
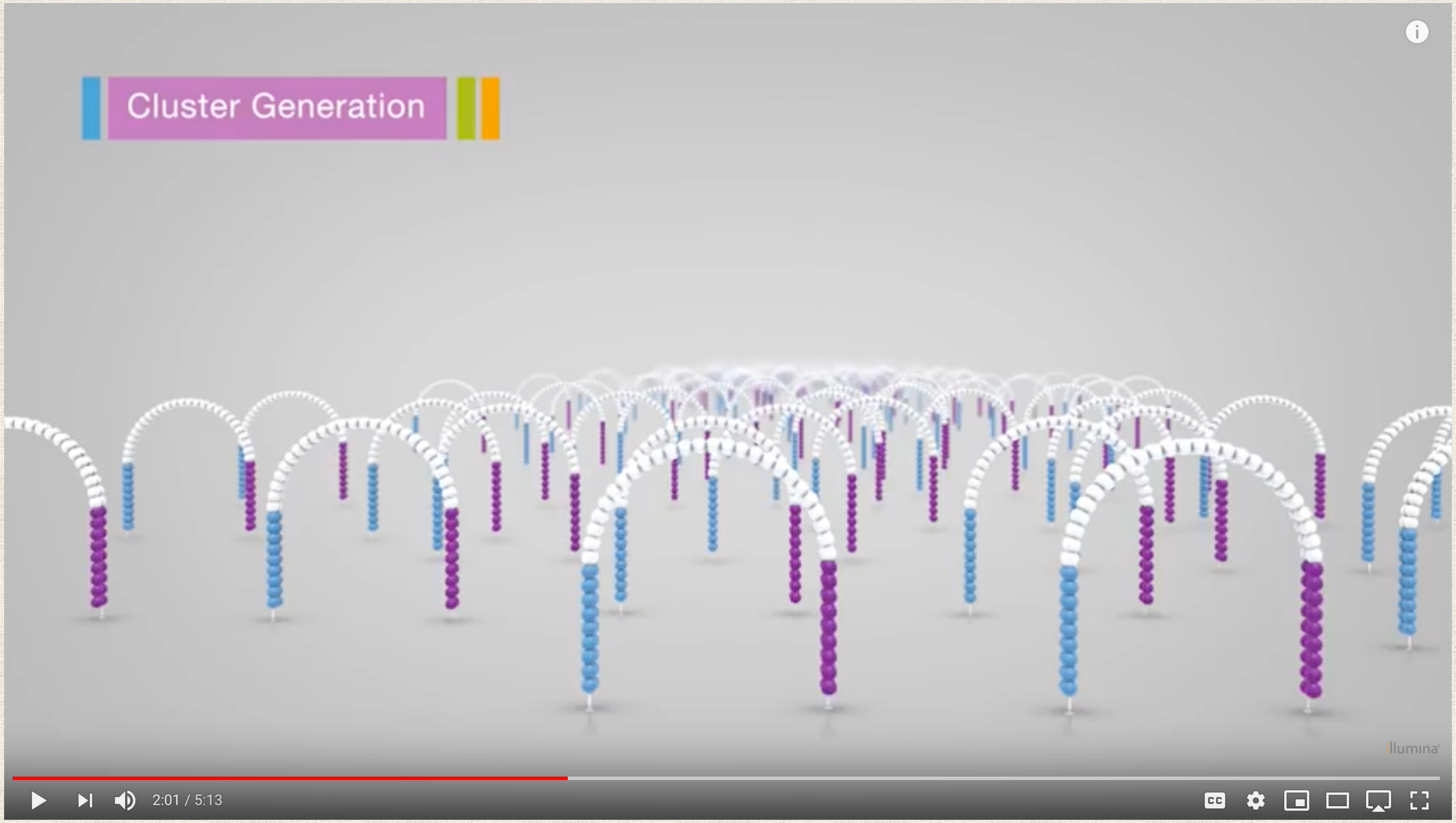


What does genome sequencing remind you of?

Genome Assembly = Overlap Puzzle



Interlude: How Are Reads Sequenced?



https://www.youtube.com/watch?v=fCd6B5HRaZ8

A COMPUTATIONAL PROBLEM FOR GENOME ASSEMBLY

Practical Sequencing Complications

1. DNA may be divided over **multiple chromosomes**.

2. Reads have **imperfect "coverage"** of the underlying genome – there may be some regions that are not covered by any reads.

3. Sequencing machines are **error-prone**.

4. DNA is **double-stranded**.

Making Some Assumptions is OK!

1. A genome consists of a **single chromosome**.

2. Reads have **perfect "coverage"** of the underlying genome –every possible starting position gets sampled by the sequencer.

3. Sequencing machines are **error-free**.

4. DNA is **single-stranded**.

Formulating a Computational Problem for Genome Assembly

Genome Assembly Problem

- **Input:** A collection of strings *Reads*.
- **Output:** A string *Genome* reconstructed from *Reads*.

Formulating a Computational Problem for Genome Assembly

Genome Assembly Problem
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STOP: Is this a well-defined problem?

Formulating a Computational Problem for Genome Assembly

Genome Assembly Problem

- **Input:** A collection of strings *Reads*.
- **Output:** A string *Genome* reconstructed from *Reads*.

STOP: Is this a well-defined problem?

Answer: No! We have no sense of what it means to "reconstruct" a genome.

Formulating a Computational Problem for Genome Assembly

The ***k*-mer composition** of a string *Text*, denoted *Composition$_k$*(*Text*), is the collection of all *k*-mer substrings of *Text* (including repeats).

```
NANABANANA
NAN
 ANA
  NAB
   ABA
    BAN
     ANA
      NAN
       ANA
```

3-mer composition

Toward a Computational Problem

We want to solve the *reverse* problem: given a collection of strings, find a string having this collection as its *k*-mer composition.

String Reconstruction Problem

- **Input:** A collection of strings *patterns* and an integer *k*.
- **Output:** A string *Text* whose *k*-mer composition is equal to *Patterns*.

Toward a Computational Problem

STOP: Now is this a well-defined computational problem?

String Reconstruction Problem

- **Input:** A collection of strings *patterns* and an integer *k*.
- **Output:** A string *Text* whose *k*-mer composition is equal to *Patterns*.

Toward a Computational Problem

STOP: Now is this a well-defined computational problem?

Answer: Not quite … what if *Patterns* = {`AAA`, `ZZZ`}?

Toward a Computational Problem

STOP: Now is this a well-defined computational problem?

Answer: Not quite … what if *Patterns* = {`AAA`, `ZZZ`}?

String Reconstruction Problem

- **Input:** A collection of strings *patterns* and an integer *k*.
- **Output:** A string *Text* whose *k*-mer composition is equal to *Patterns* (if such a string exists).

SOLVING THE STRING RECONSTRUCTION PROBLEM?

Toward an Algorithm for Genome Assembly

Exercise: Reconstruct the string corresponding to the following 3-mer composition.

```
AAT   ATG   GTT   TAA   TGT
```

Toward an Algorithm for Genome Assembly

Exercise: Reconstruct the string corresponding to the following 3-mer composition.

```
AAT   ATG   GTT   TAA   TGT
```

```
TAA
 AAT
  ATG
   TGT
    GTT
TAATGTT
```

Toward an Algorithm for Genome Assembly

"Greedy" algorithm: for each *k*-mer, look for the *k*-mer of maximum overlap in each direction.

```
TAA
 AAT
  ATG
   TGT
    GTT
TAATGTT
```

Toward an Algorithm for Genome Assembly

"Greedy" algorithm: for each *k*-mer, look for the *k*-mer of maximum overlap in each direction.

Genome assembly is trivial! We can pack up and go home.

Toward an Algorithm for Genome Assembly

"Greedy" algorithm: for each *k*-mer, look for the *k*-mer of maximum overlap in each direction.

Genome assembly is trivial! We can pack up and go home.

Exercise: Apply this algorithm to the 3-mer composition at right.

```
AAT
ATG
ATG
ATG
CAT
CCA
GAT
GCC
GGA
GGG
GTT
TAA
TGC
TGG
TGT
```

Toward an Algorithm for Genome Assembly

```
AAT
ATG
ATG
ATG
CAT
CCA
GAT
GCC
GGA
GGG
GTT
TAA
TGC
TGG
TGT
```

Toward an Algorithm for Genome Assembly

TAA

AAT
ATG
ATG
ATG
CAT
CCA
GAT
GCC
GGA
GGG
GTT
TAA
TGC
TGG
TGT

TAA

Toward an Algorithm for Genome Assembly

```
TAA                                    AAT
 AAT                                   ATG
                                       ATG
                                       ATG
                                       CAT
                                       CCA
                                       GAT
                                       GCC
                                       GGA
                                       GGG
                                       GTT
                                       TAA
                                       TGC
                                       TGG
TAAT                                   TGT
```

Toward an Algorithm for Genome Assembly

```
TAA
 AAT
  ATG
```

```
TAATG
```

```
AAT
ATG
ATG
ATG
CAT
CCA
GAT
GCC
GGA
GGG
GTT
TAA
TGC
TGG
TGT
```

STOP: Which one should we choose?

Toward an Algorithm for Genome Assembly

```
TAA                                          AAT
 AAT                                         ATG
  ATG                                        ATG
   TGC                                       ATG
                                             CAT
                                             CCA
                                             GAT
                                             GCC
                                             GGA
                                             GGG
                                             GTT
                                             TAA
                                             TGC
                                             TGG
TAATGC                                       TGT
```

Toward an Algorithm for Genome Assembly

```
TAA                                   AAT
 AAT                                  ATG
  ATG                                 ATG
   TGC                                ATG
    GCC                               CAT
                                      CCA
                                      GAT
                                      GCC
                                      GGA
                                      GGG
                                      GTT
                                      TAA
                                      TGC
                                      TGG
TAATGCC                               TGT
```

Toward an Algorithm for Genome Assembly

```
TAA                                  AAT
 AAT                                 ATG
  ATG                                ATG
   TGC                               ATG
    GCC                              CAT
     CCA                             CCA
                                     GAT
                                     GCC
                                     GGA
                                     GGG
                                     GTT
                                     TAA
                                     TGC
                                     TGG
TAATGCCA                             TGT
```

Toward an Algorithm for Genome Assembly

```
TAA                                                  AAT
 AAT                                                 ATG
  ATG                                                ATG
   TGC                                               ATG
    GCC                                              CAT
     CCA                                             CCA
      CAT                                            GAT
                                                     GCC
                                                     GGA
                                                     GGG
                                                     GTT
                                                     TAA
                                                     TGC
                                                     TGG
TAATGCCAT                                            TGT
```

Toward an Algorithm for Genome Assembly

```
TAA                                                AAT
 AAT                                               ATG
  ATG                                              ATG
   TGC                                             ATG
    GCC                                            CAT
     CCA                                           CCA
      CAT                                          GAT
       ATG                                         GCC
                                                   GGA
                                                   GGG
                                                   GTT
                                                   TAA
                                                   TGC
                                                   TGG
TAATGCCATG                                         TGT
```

Toward an Algorithm for Genome Assembly

```
TAA                                                                 AAT
 AAT                                                                ATG
  ATG                                                               ATG
   TGC                                                              ATG
    GCC                                                             CAT
     CCA                                                            CCA
      CAT                                                           GAT
       ATG                                                          GCC
        TGG                                                         GGA
                                                                    GGG
                                                                    GTT
                                                                    TAA
                                                                    TGC
                                                                    TGG
TAATGCCATGG                                                         TGT
```

Toward an Algorithm for Genome Assembly

```
TAA
 AAT
  ATG
   TGC
    GCC
     CCA
      CAT
       ATG
        TGG
         GGA

TAATGCCATGGA
```

```
AAT
ATG
ATG
ATG
CAT
CCA
GAT
GCC
GGA
GGG
GTT
TAA
TGC
TGG
TGT
```

Toward an Algorithm for Genome Assembly

```
TAA                                               AAT
 AAT                                              ATG
  ATG                                             ATG
   TGC                                            ATG
    GCC                                           CAT
     CCA                                          CCA
      CAT                                         GAT
       ATG                                        GCC
        TGG                                       GGA
         GGA                                      GGG
          GAT                                     GTT
                                                  TAA
                                                  TGC
                                                  TGG
TAATGCCATGGAT                                     TGT
```

Toward an Algorithm for Genome Assembly

```
TAA                                  AAT
 AAT                                 ATG
  ATG                                ATG
   TGC                               ATG
    GCC                              CAT
     CCA                             CCA
      CAT                            GAT
       ATG                           GCC
        TGG                          GGA
         GGA                         GGG
          GAT                        GTT
           ATG                       TAA
                                     TGC
                                     TGG
TAATGCCATGGATG                       TGT
```

Toward an Algorithm for Genome Assembly

```
TAA                                                AAT
 AAT                                               ATG
  ATG                                              ATG
   TGC                                             ATG
    GCC                                            CAT
     CCA                                           CCA
      CAT                                          GAT
       ATG                                         GCC
        TGG                                        GGA
         GGA                                       GGG
          GAT                                      GTT
           ATG                                     TAA
            TGT                                    TGC
                                                   TGG
TAATGCCATGGATGT                                    TGT
```

Toward an Algorithm for Genome Assembly

```
TAA                                        AAT
 AAT                                       ATG
  ATG                                      ATG
   TGC                                     ATG
    GCC                                    CAT
     CCA                                   CCA
      CAT                                  GAT
       ATG                                 GCC
        TGG                                GGA
         GGA                           ??? GGG
          GAT                              GTT
           ATG                             TAA
            TGT                            TGC
             GTT                           TGG
TAATGCCATGGATGTT                           TGT
```

Toward an Algorithm for Genome Assembly

```
TAA                                                 AAT
 AAT                                                ATG
  ATG                                               ATG
   TGC                                              ATG
    GCC                                             CAT
     CCA                                            CCA
      CAT                                           GAT
       ATG                                          GCC
        TGG                                         GGA
         GGA                                ???     GGG
          GAT                                       GTT
           ATG                                      TAA
            TGT                                     TGC
             GTT                                    TGG
TAATGCCATGGATGTT                                    TGT
```

STOP: Why did our algorithm fail?

Toward an Algorithm for Genome Assembly

```
TAA                                        AAT
 AAT                                       ATG
  ATG                                      ATG
   TGC                                     ATG
    GCC                                    CAT
     CCA                                   CCA
      CAT                                  GAT
       ATG                                 GCC
        TGG                                GGA
         GGA                         ???   GGG
          GAT                              GTT
           ATG                             TAA
            TGT                            TGC
             GTT                           TGG
TAATGCCATGGATGTT                           TGT
```

Answer: Repeated substrings!

Repeats Make Eternity II Unsolvable …

Courtesy: Matej Bat'ha

… Even a 16-piece “Triazzle” Can Take a Human Hours to Solve…

Courtesy: Dan Gilbert

… and Repeats Complicate Genome Assembly Too ☹

Repeats are very common in genomes; the 300-nucleotide **Alu repeat** occurs over a million times (with minor changes) in every human genome.

… and Repeats Complicate Genome Assembly Too ☹

Repeats are very common in genomes; the 300-nucleotide **Alu repeat** occurs over a million times (with minor changes) in every human genome.

So what hope do we have of assembling a genome?

GENOME ASSEMBLY AS A HAMILTONIAN PATH PROBLEM

Solution to Previous Exercise

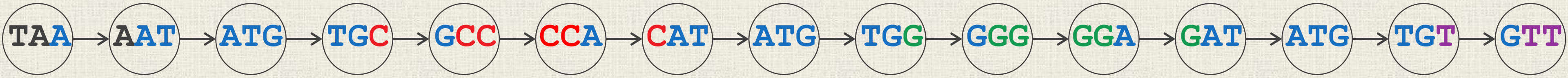
STOP: Is this the only solution?

```
TAA
 AAT
  ATG
   TGC
    GCC
     CCA
      CAT
       ATG
        TGG
         GGG
          GGA
           GAT
            ATG
             TGT
              GTT
TAATGCCATGGATGTT
```

```
AAT
ATG
ATG
ATG
CAT
CCA
GAT
GCC
GGA
GGG
GTT
TAA
TGC
TGG
TGT
```

We Can View a Genome as a "Path" in a Graph

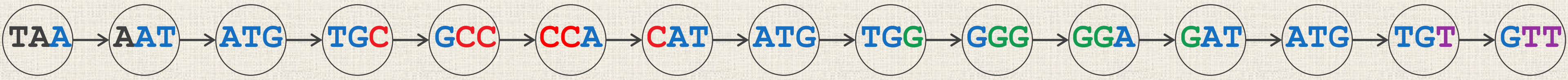
Genome path: assign each read to a node, connect adjacent reads with edges.



We Can View a Genome as a "Path" in a Graph

Genome path: assign each read to a node, connect adjacent reads with edges.

STOP: Can you still see the genome?



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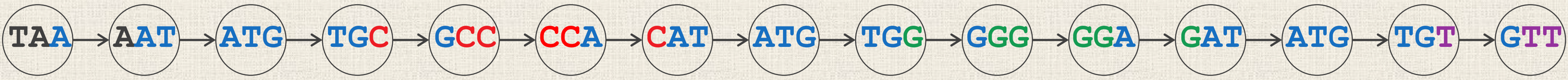

$$\begin{tikzcd}\text{TAA} \arrow[r] & \text{AAT} \arrow[r] & \text{ATG} \arrow[r] & \text{TGC} \arrow[r] & \text{GCC} \arrow[r] & \text{CCA} \arrow[r] & \text{CAT} \arrow[r] & \text{ATG} \arrow[r] & \text{TGG} \arrow[r] & \text{GGG} \arrow[r] & \text{GGA} \arrow[r] & \text{GAT} \arrow[r] & \text{ATG} \arrow[r] & \text{TGT} \arrow[r] & \text{GTT}\end{tikzcd}$$

STOP: Could you construct the genome path if you only knew the 3-mer composition?

We Can View a Genome as a "Path" in a Graph

Genome path: assign each read to a node, connect adjacent reads with edges.

STOP: Can you still see the genome?

$$\begin{tikzcd}
\text{TAA} \arrow[r] & \text{AAT} \arrow[r] & \text{ATG} \arrow[r] & \text{TGC} \arrow[r] & \text{GCC} \arrow[r] & \text{CCA} \arrow[r] & \text{CAT} \arrow[r] & \text{ATG} \arrow[r] & \text{TGG} \arrow[r] & \text{GGG} \arrow[r] & \text{GGA} \arrow[r] & \text{GAT} \arrow[r] & \text{ATG} \arrow[r] & \text{TGT} \arrow[r] & \text{GTT}
\end{tikzcd}$$

Answer: No … we need to know the order of the *k*-mers.

A Graph Can Represent All Overlapping Strings

- **Prefix:** First *k* – 1 letters in a *k*-mer.
- **Suffix:** Last *k* – 1 letters in a *k*-mer.

$$\begin{tikzcd}
\text{TAA} \arrow[r] & \text{AAT} \arrow[r] & \text{ATG} \arrow[r] & \text{TGC} \arrow[r] & \text{GCC} \arrow[r] & \text{CCA} \arrow[r] & \text{CAT} \arrow[r] & \text{ATG} \arrow[r] & \text{TGG} \arrow[r] & \text{GGG} \arrow[r] & \text{GGA} \arrow[r] & \text{GAT} \arrow[r] & \text{ATG} \arrow[r] & \text{TGT} \arrow[r] & \text{GTT}
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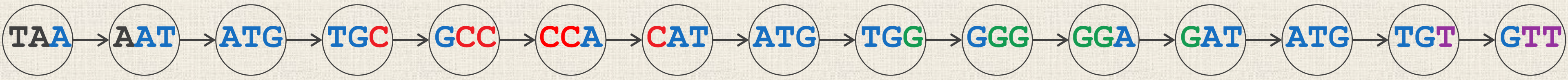
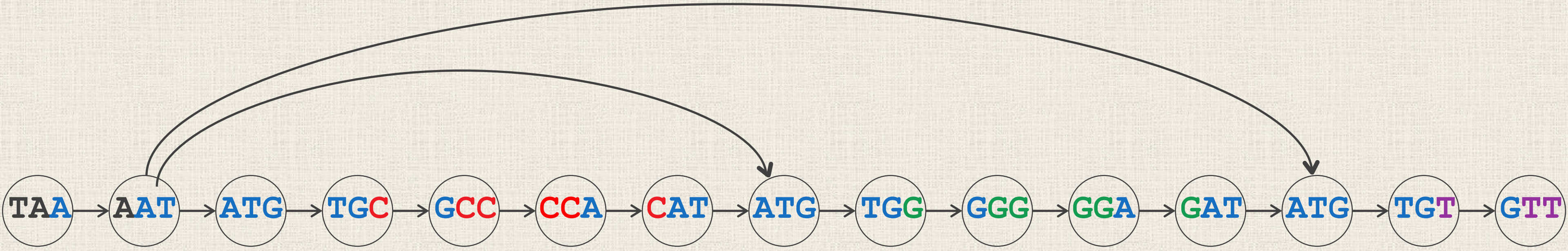


Overlap Graph: Form a node for each read in *Patterns*, then connect *x* to *y* if *Suffix*(*x*) = *Prefix*(*y*).

A Graph Can Represent All Overlapping Strings

- **Prefix:** First $k-1$ letters in a k-mer.
- **Suffix:** Last $k-1$ letters in a k-mer.



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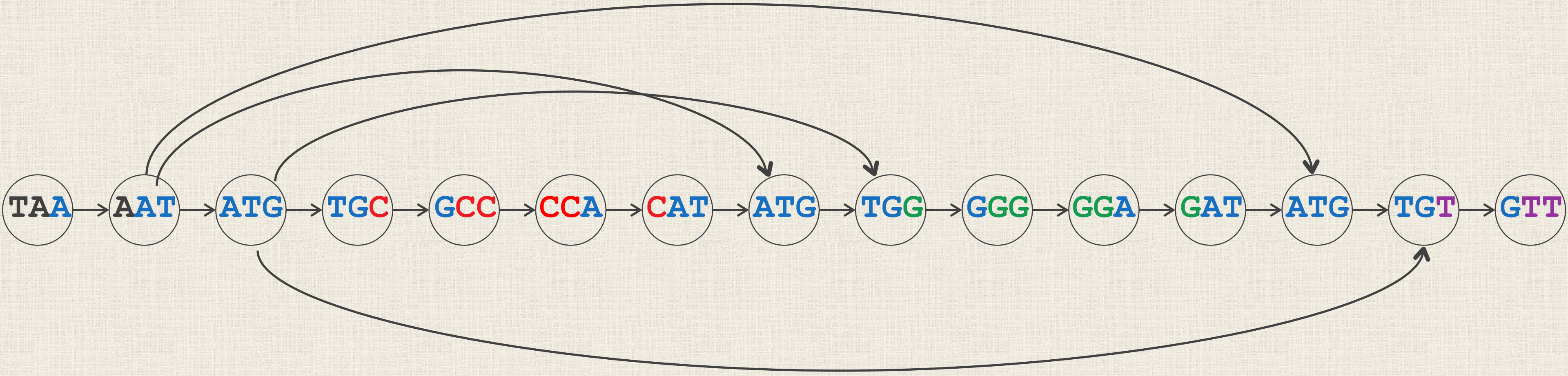
- **Suffix:** Last *k* – 1 letters in a *k*-mer.



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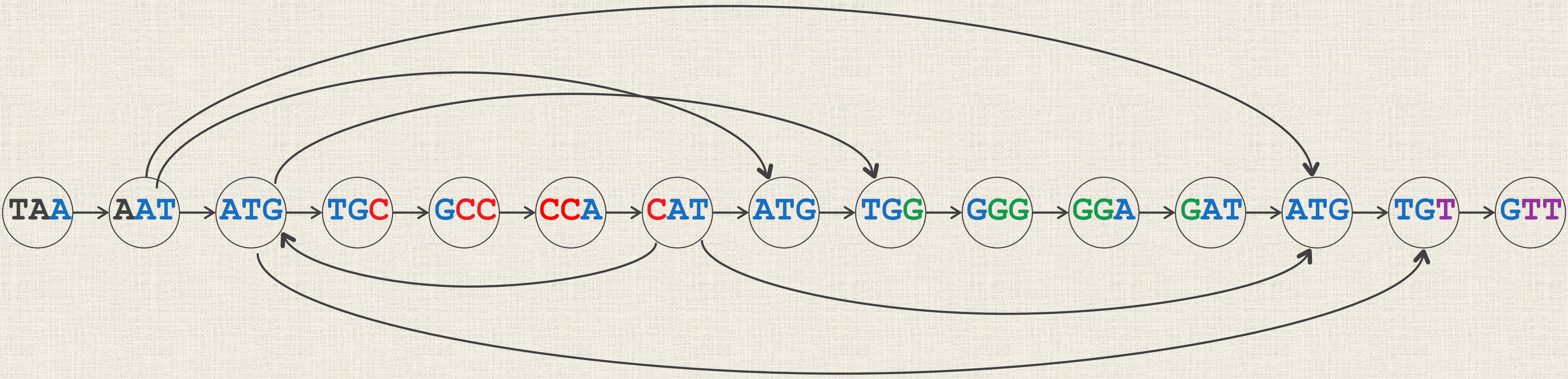

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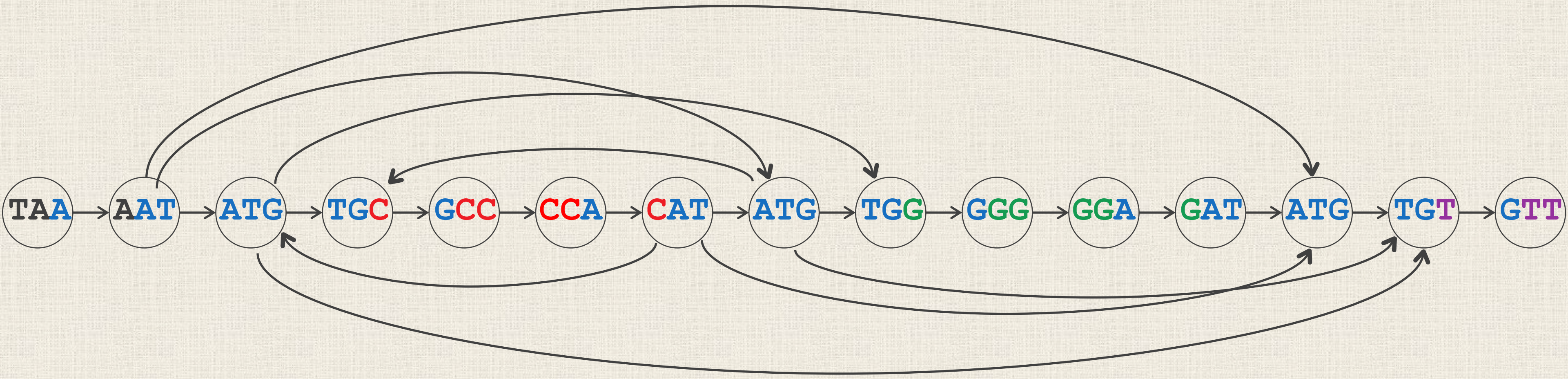

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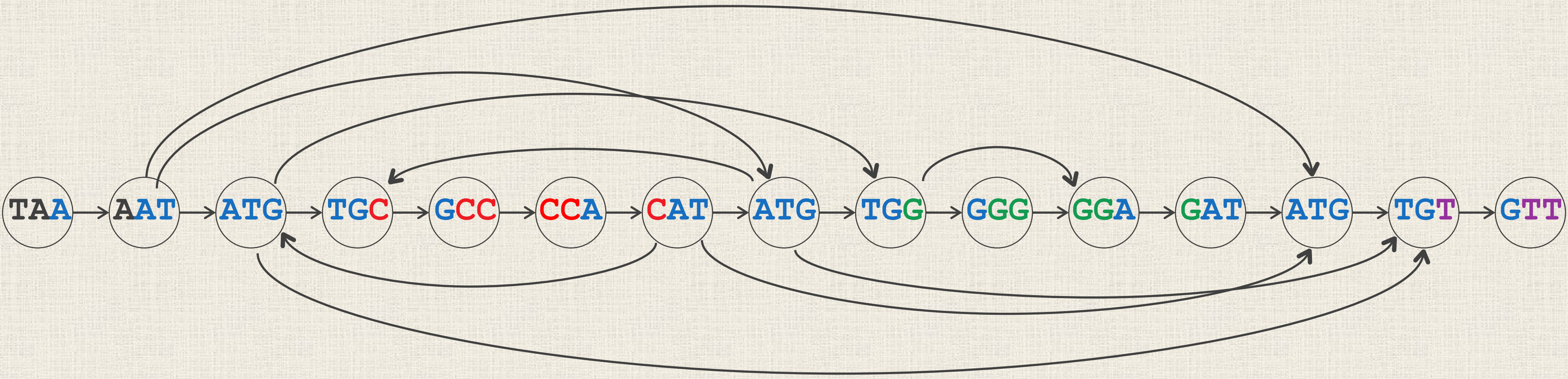

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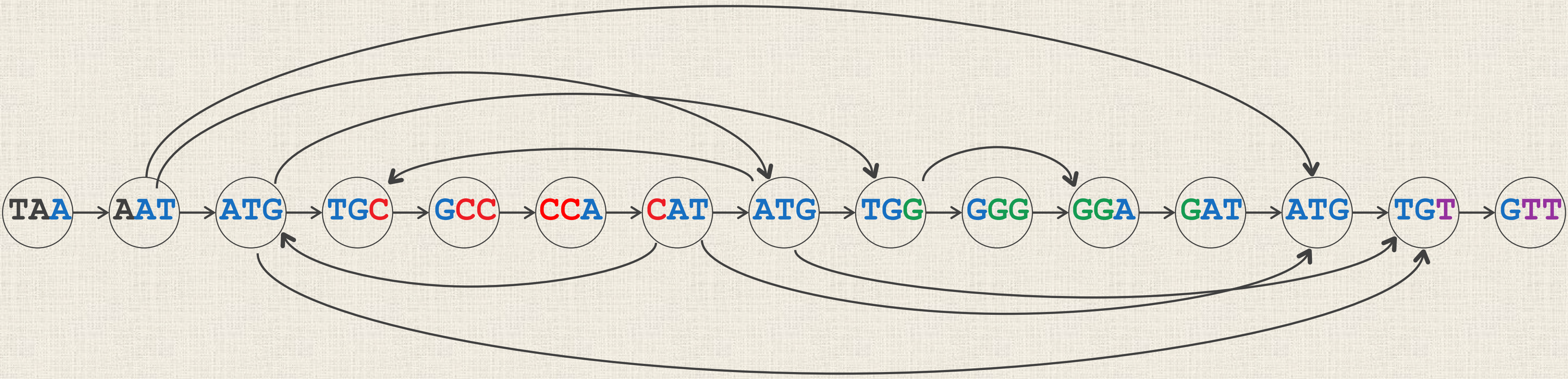
- **Suffix:** Last *k* – 1 letters in a *k*-mer.



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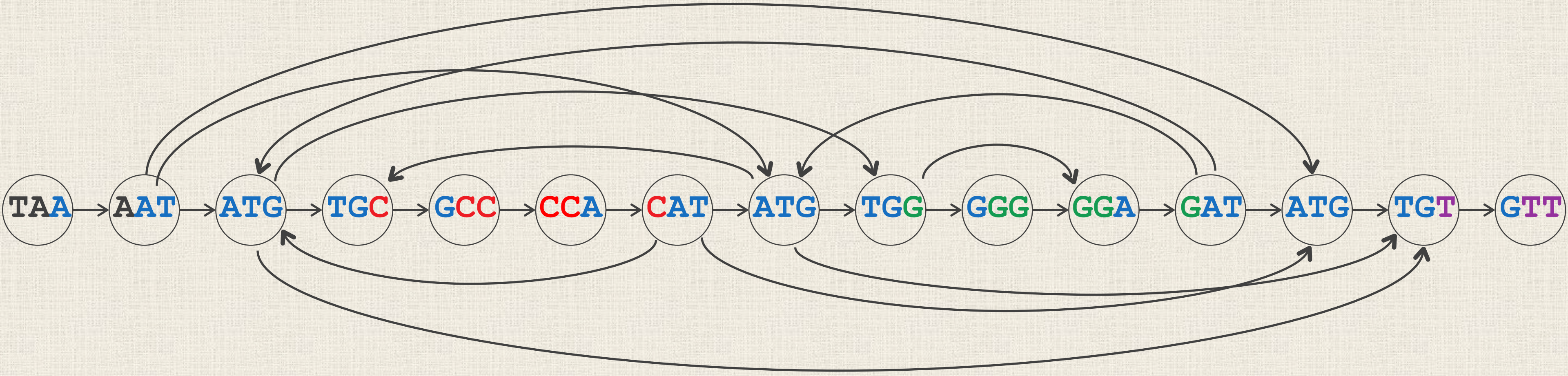

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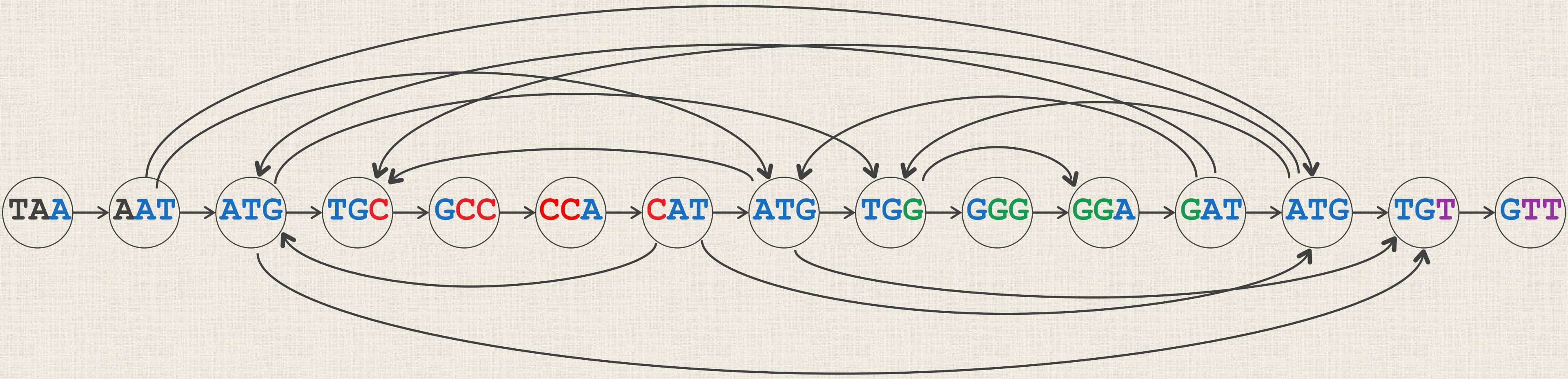
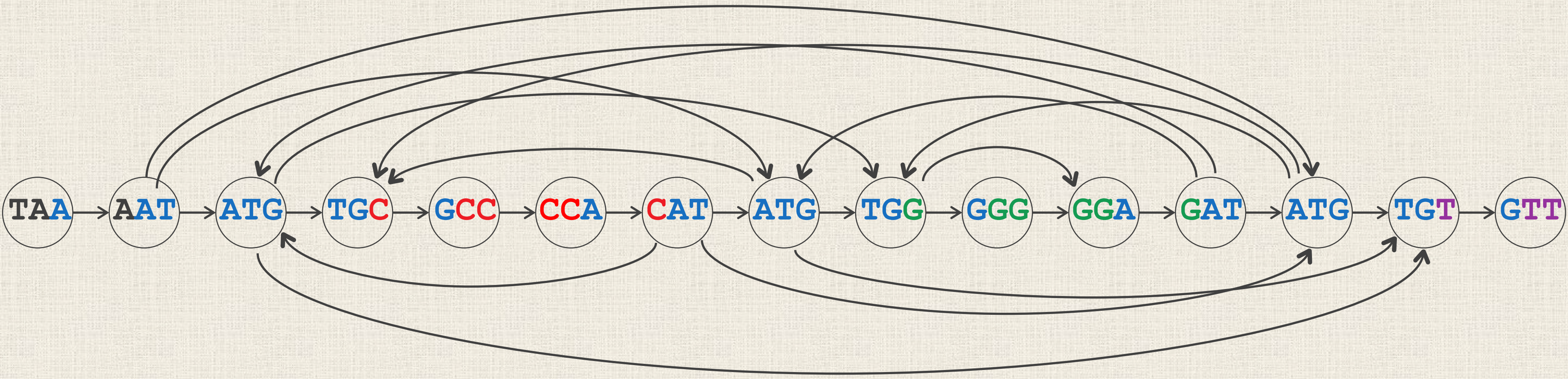
- **Prefix:** First *k* – 1 letters in a *k*-mer.
- **Suffix:** Last *k* – 1 letters in a *k*-mer.



Overlap Graph: Form a node for each read in *Patterns*, then connect *x* to *y* if *Suffix*(*x*) = *Prefix*(*y*).

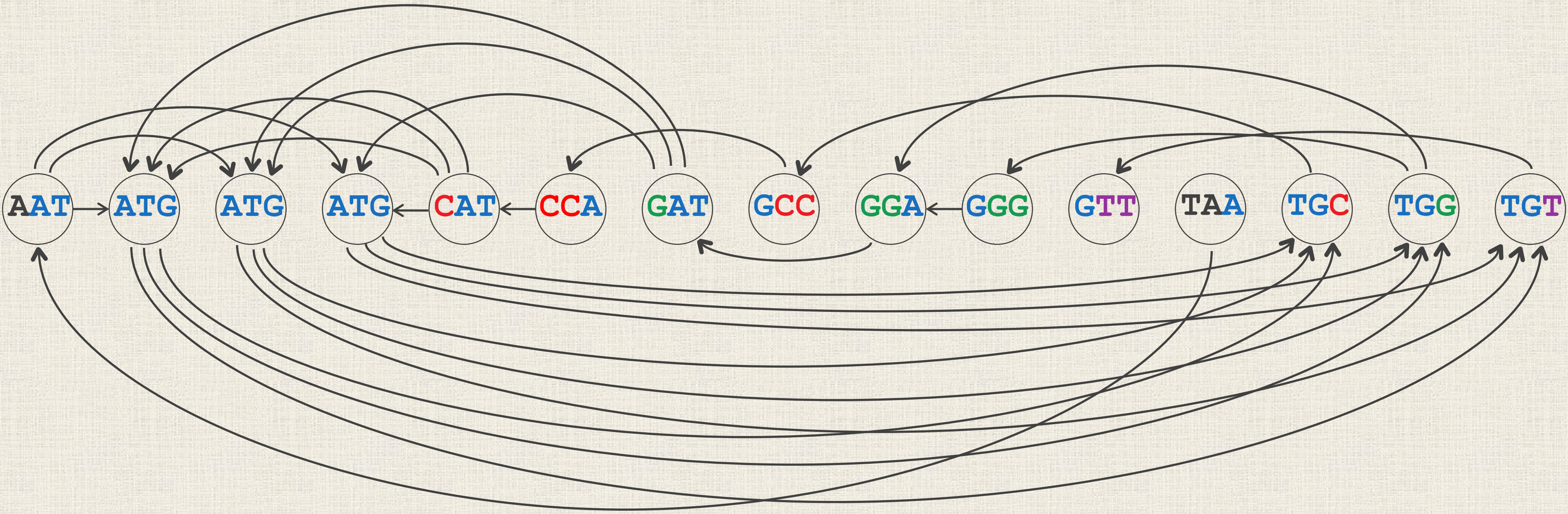
A Graph Can Represent All Overlapping Strings

Note: we can still see the genome path, but we wouldn't if we don't know the order of *k*-mers …



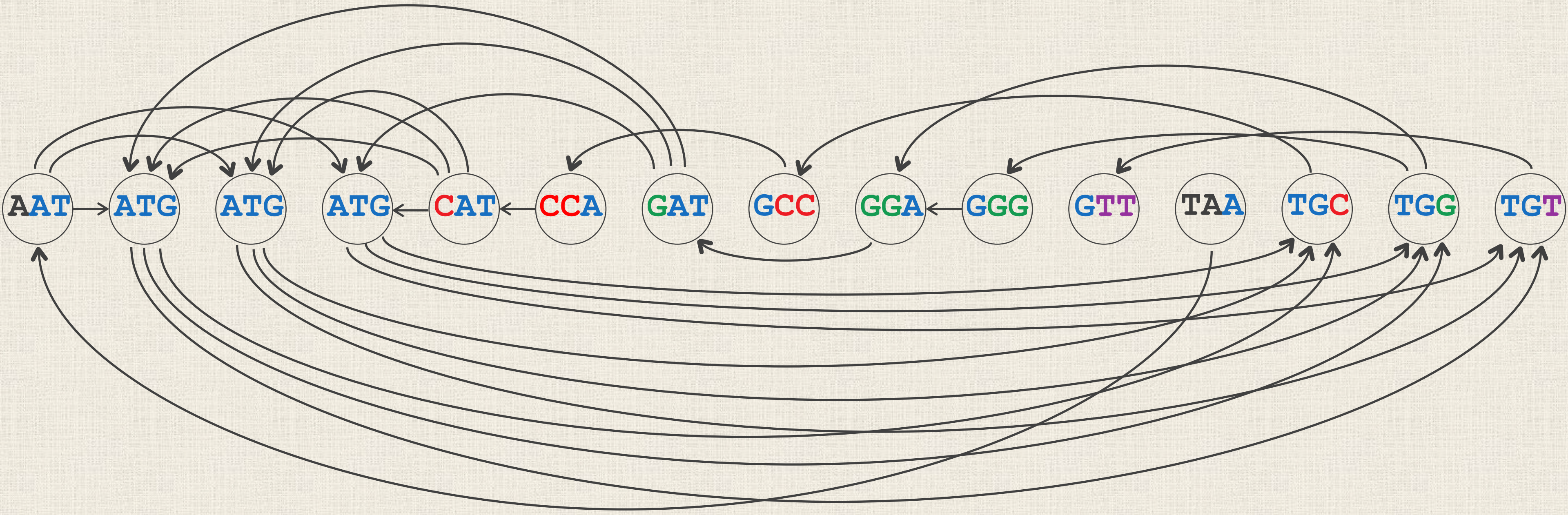
Overlap Graph: Form a node for each read in *Patterns*, then connect *x* to *y* if *Suffix*(*x*) = *Prefix*(*y*).

Arranging *k*-mers Lexicographically Makes Genome Vanish



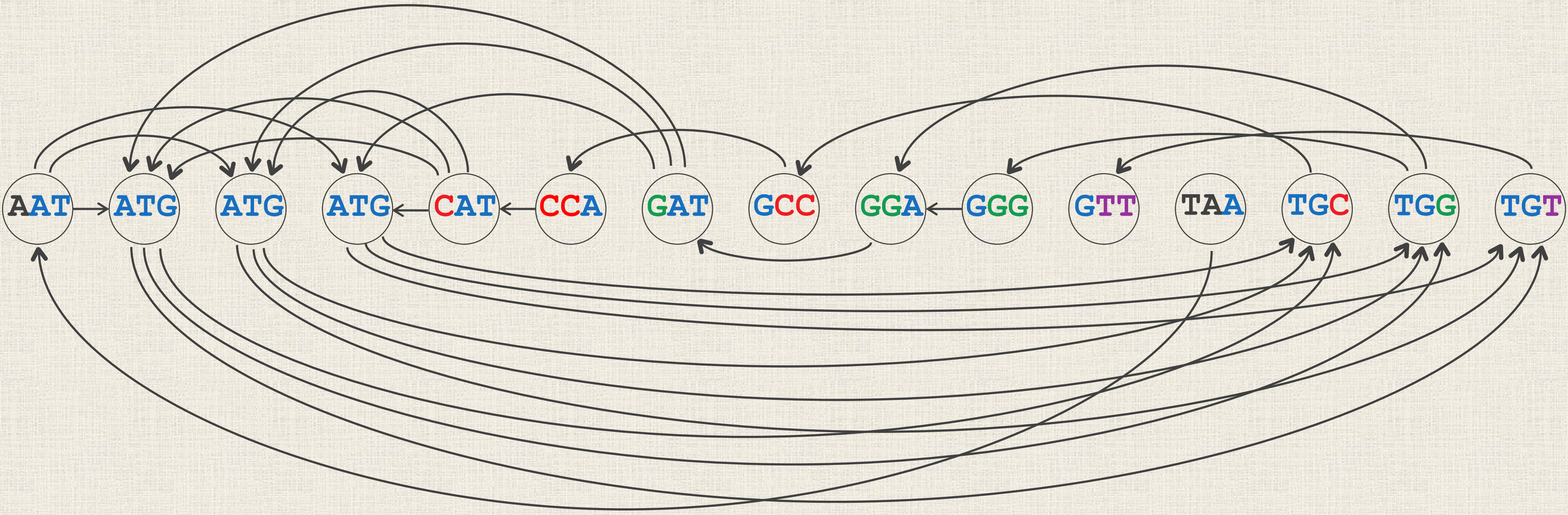
Arranging *k*-mers Lexicographically Makes Genome Vanish

STOP: If we gave you this graph, what would you look for to find the genome?



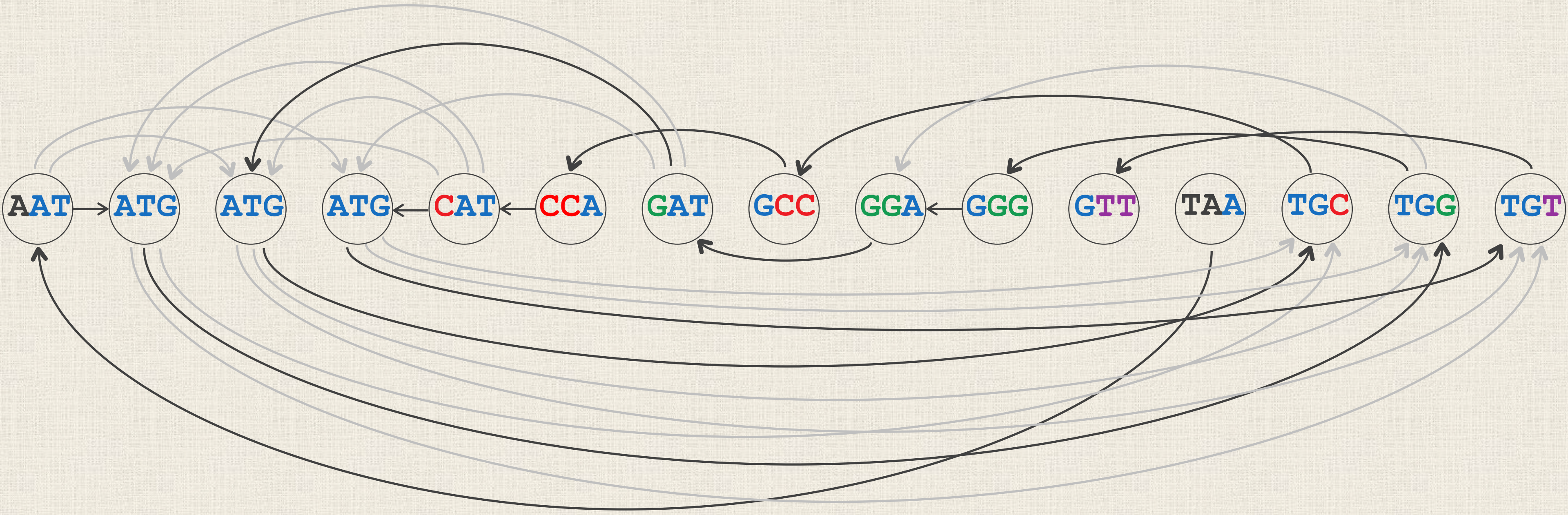
We are Looking for a Hamiltonian Path in the Overlap Graph

Hamiltonian path: A path through a graph that touches each node exactly once.



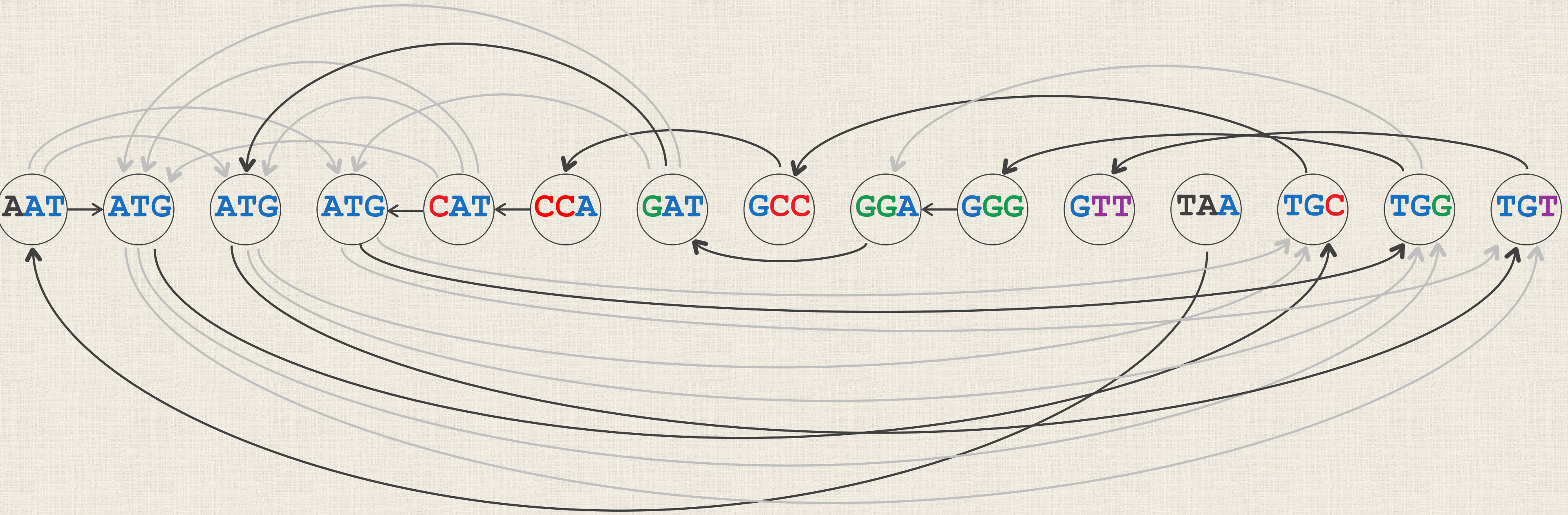
Here's One Solution

STOP: What genome does the highlighted path reconstruct?



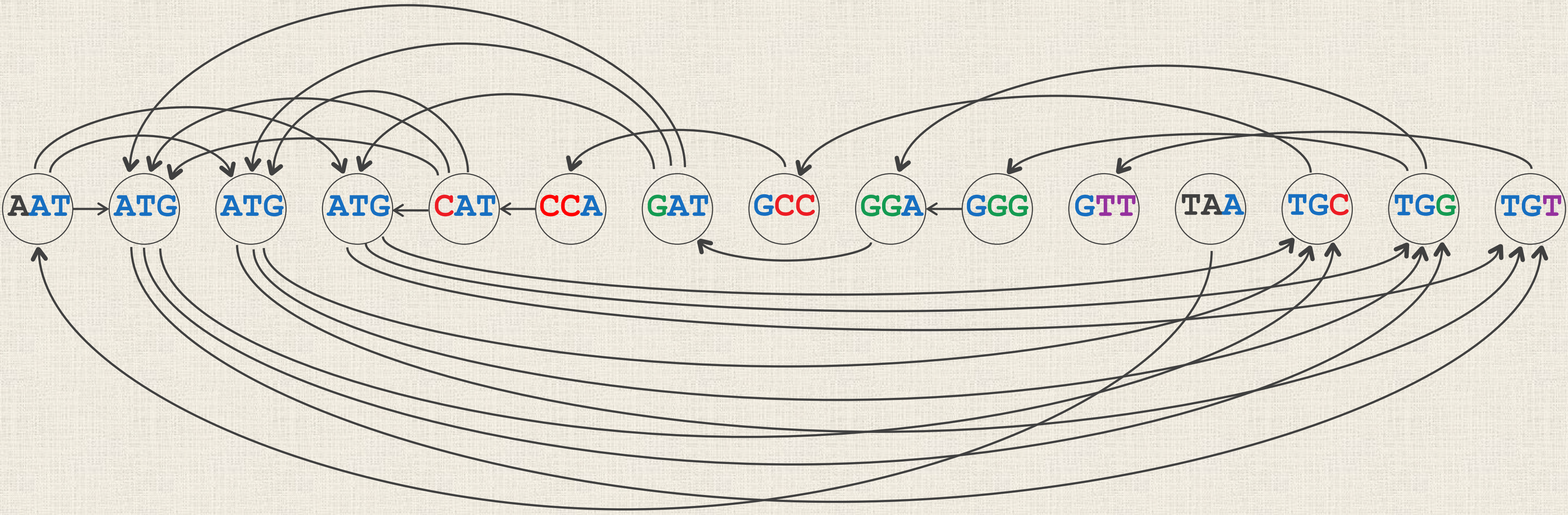
And Here's Another Solution

STOP: How about this highlighted path?



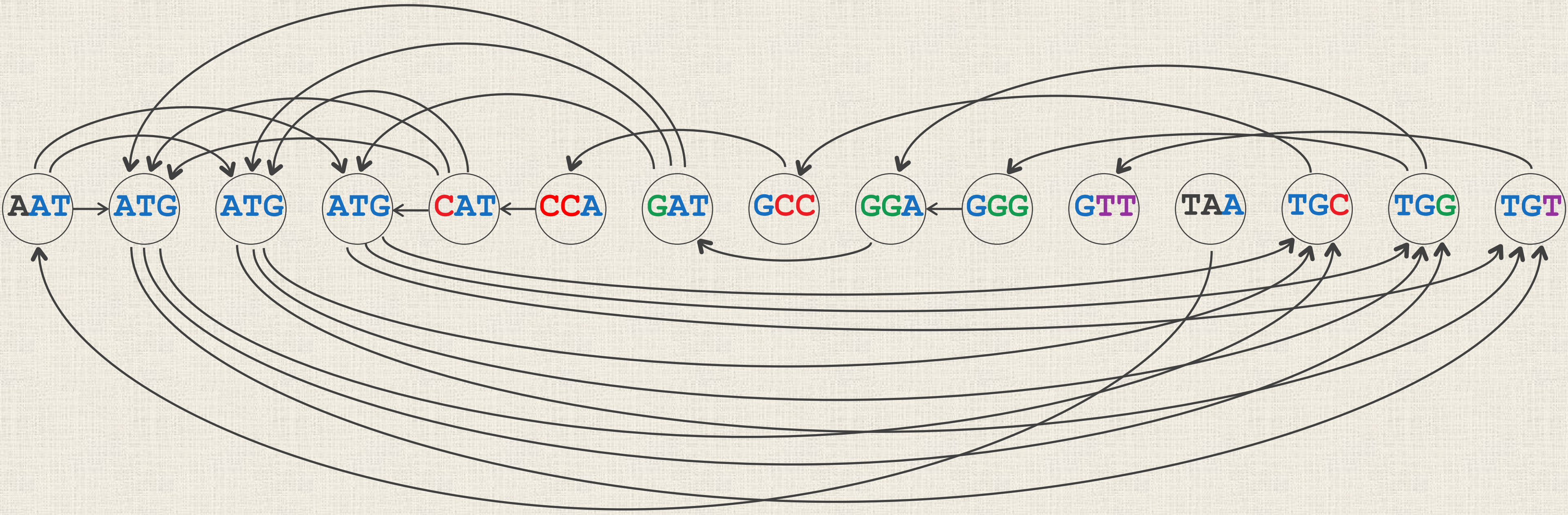
We are Looking for a Hamiltonian Path in the Overlap Graph

Note: The graph organizes our reads, but we don't have an *algorithm* for finding a Hamiltonian path.



We are Looking for a Hamiltonian Path in the Overlap Graph

STOP: What does the overlap graph look like if there are many repeats? What if there are none?

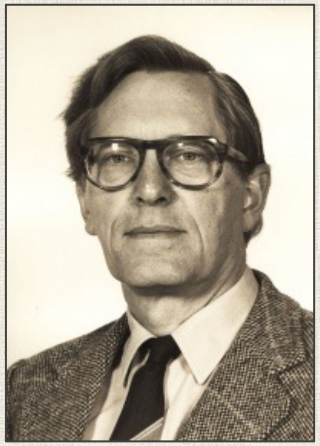


Aside 1: de Bruijn and Good

A binary string is ***k*-universal** if it contains every binary *k*-mer once.

Exercise: Find a 3-universal string.

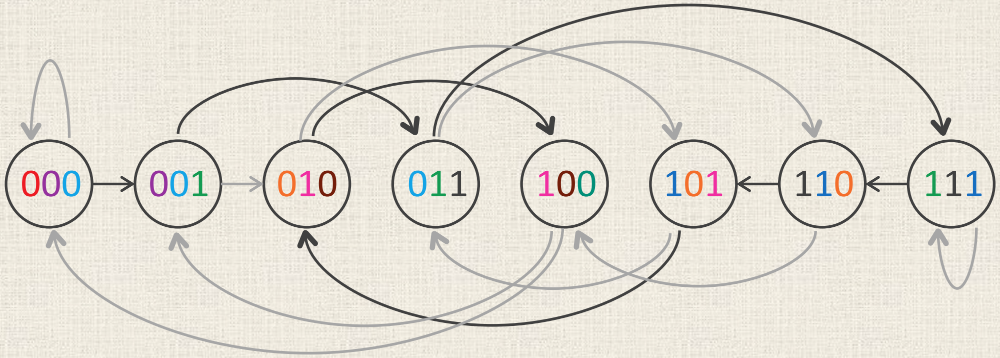
Jack Good


Nicolaas de Bruijn

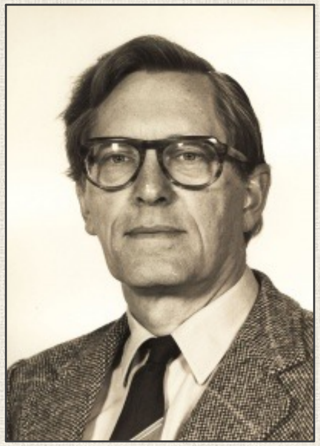
Aside 1: de Bruijn and Good

A binary string is ***k*-universal** if it contains every binary *k*-mer once.

Note: a *k*-universal string corresponds to a Hamiltonian path in the following overlap graph.



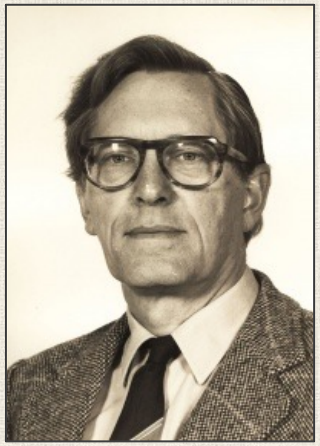
Jack Good

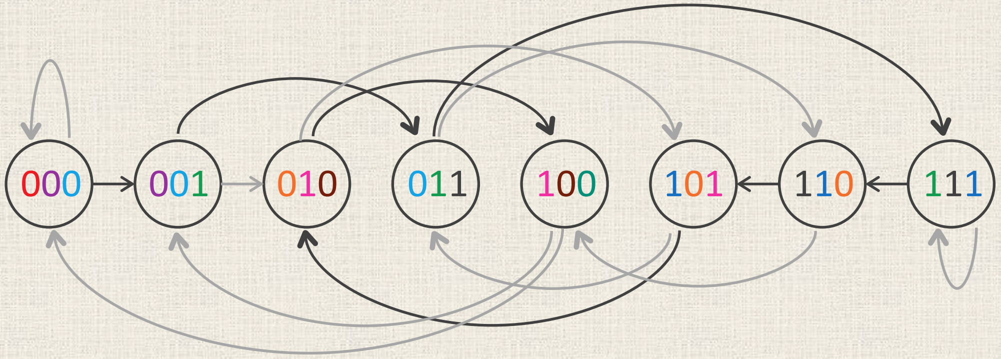

Nicolaas de Bruijn

Aside 1: de Bruijn and Good

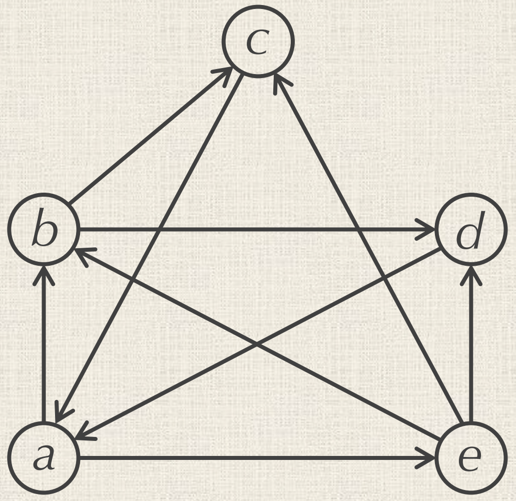
1946: Good and de Bruijn independently discover a way to find *k*-universal strings. They cannot imagine that their approach will one day power genome sequencing.

Jack Good


Nicolaas de Bruijn



Aside 2: Two Ways to Represent Graphs Computationally



Adjacency Matrix

	a	**b**	**c**	**d**	**e**
a	0	1	0	0	1
b	0	0	1	1	0
c	1	0	0	0	0
d	1	0	0	0	0
e	0	1	1	1	0

Adjacency matrix: $A_{i,j} = 1$ if there is an edge connecting node i to node j; $A_{i,j} = 0$ otherwise.

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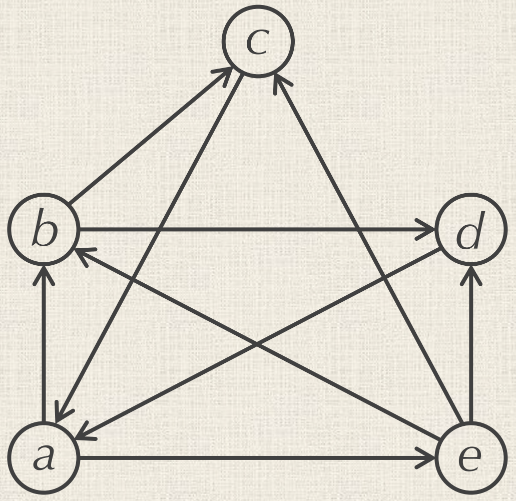

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c	1	0	0	0	0
d	1	0	0	0	0
e	0	1	1	1	0

Adjacency List

a	*b, e*
b	*c, d*
c	*a*
d	*a*
e	*b, c, d*

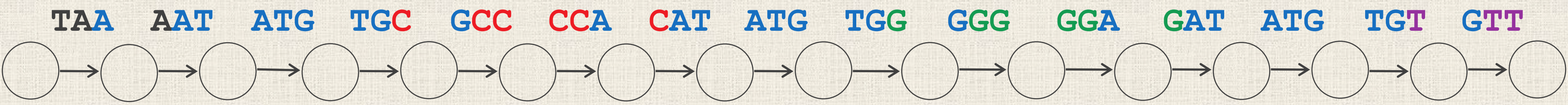
Adjacency matrix: $A_{i,j} = 1$ if there is an edge connecting node *i* to node *j*; $A_{i,j} = 0$ otherwise.

Adjacency list: Dictionary; "key" node *i*;"value" is list of nodes that *i* is connected to.

GENOME ASSEMBLY AS AN EULERIAN PATH PROBLEM

Assigning *k*-mers to *Edges* Instead of *Nodes*

We start again with a "genome path" corresponding to TAATGCCATGGGATGTT.



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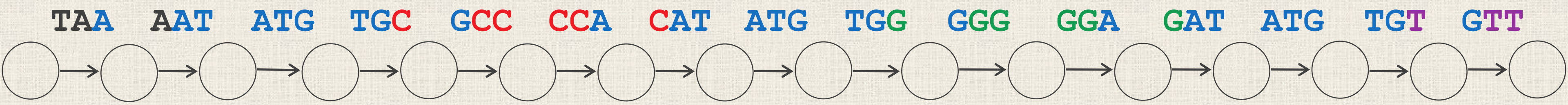

STOP: How should we label the nodes?

Assigning *k*-mers to *Edges* Instead of *Nodes*

Each node represents the (k – 1)-mer corresponding to the *overlap* between adjacent edges.

$$\begin{tikzcd}[column sep=small]
\mathrm{TA} \arrow[r, "\mathrm{TAA}"] & \mathrm{AA} \arrow[r, "\mathrm{AAT}"] & \mathrm{AT} \arrow[r, "\mathrm{ATG}"] & \mathrm{TG} \arrow[r, "\mathrm{TGC}"] & \mathrm{GC} \arrow[r, "\mathrm{GCC}"] & \mathrm{CC} \arrow[r, "\mathrm{CCA}"] & \mathrm{CA} \arrow[r, "\mathrm{CAT}"] & \mathrm{AT} \arrow[r, "\mathrm{ATG}"] & \mathrm{TG} \arrow[r, "\mathrm{TGG}"] & \mathrm{GG} \arrow[r, "\mathrm{GGG}"] & \mathrm{GG} \arrow[r, "\mathrm{GGA}"] & \mathrm{GA} \arrow[r, "\mathrm{GAT}"] & \mathrm{AT} \arrow[r, "\mathrm{ATG}"] & \mathrm{TG} \arrow[r, "\mathrm{TGT}"] & \mathrm{GT} \arrow[r, "\mathrm{GTT}"] & \mathrm{TT}
\end{tikzcd}$$

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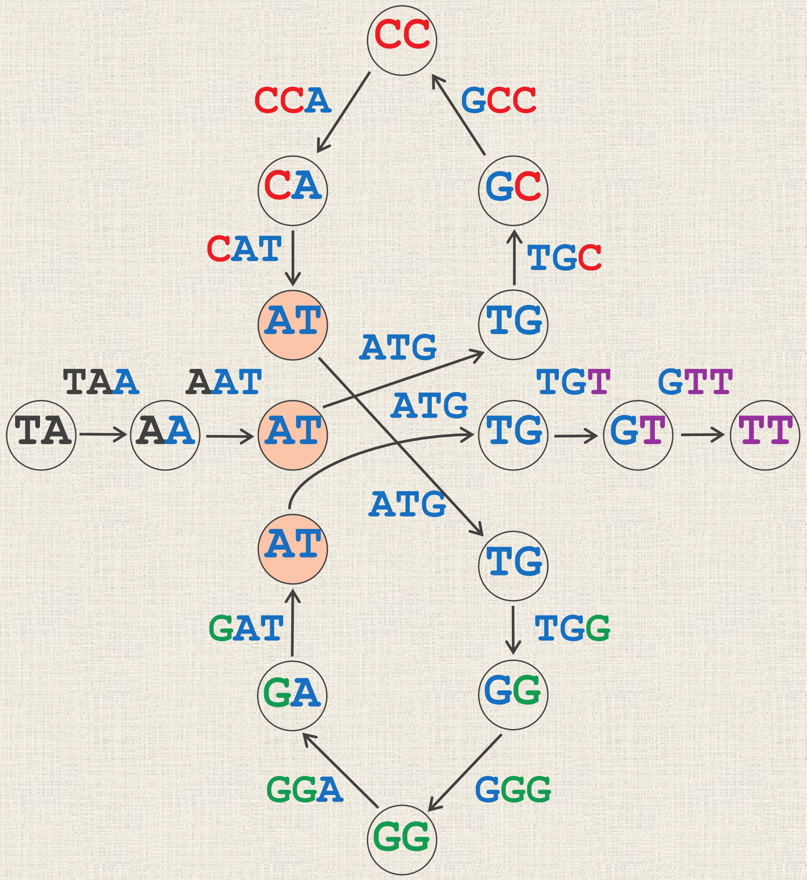
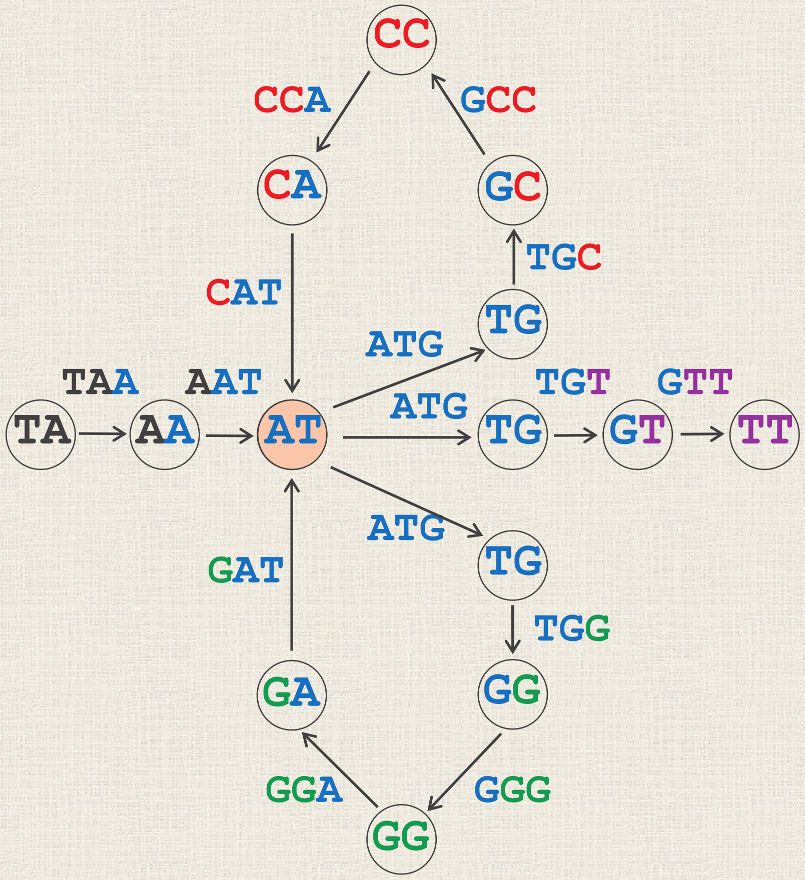
\text{TA} \arrow[r, "\text{TAA}"] & \text{AA} \arrow[r, "\text{AAT}"] & \text{AT} \arrow[r, "\text{ATG}"] & \text{TG} \arrow[r, "\text{TGC}"] & \text{GC} \arrow[r, "\text{GCC}"] & \text{CC} \arrow[r, "\text{CCA}"] & \text{CA} \arrow[r, "\text{CAT}"] & \text{AT} \arrow[r, "\text{ATG}"] & \text{TG} \arrow[r, "\text{TGG}"] & \text{GG} \arrow[r, "\text{GGG}"] & \text{GG} \arrow[r, "\text{GGA}"] & \text{GA} \arrow[r, "\text{GAT}"] & \text{AT} \arrow[r, "\text{ATG}"] & \text{TG} \arrow[r, "\text{TGT}"] & \text{GT} \arrow[r, "\text{GTT}"] & \text{TT}
\end{tikzcd}$$

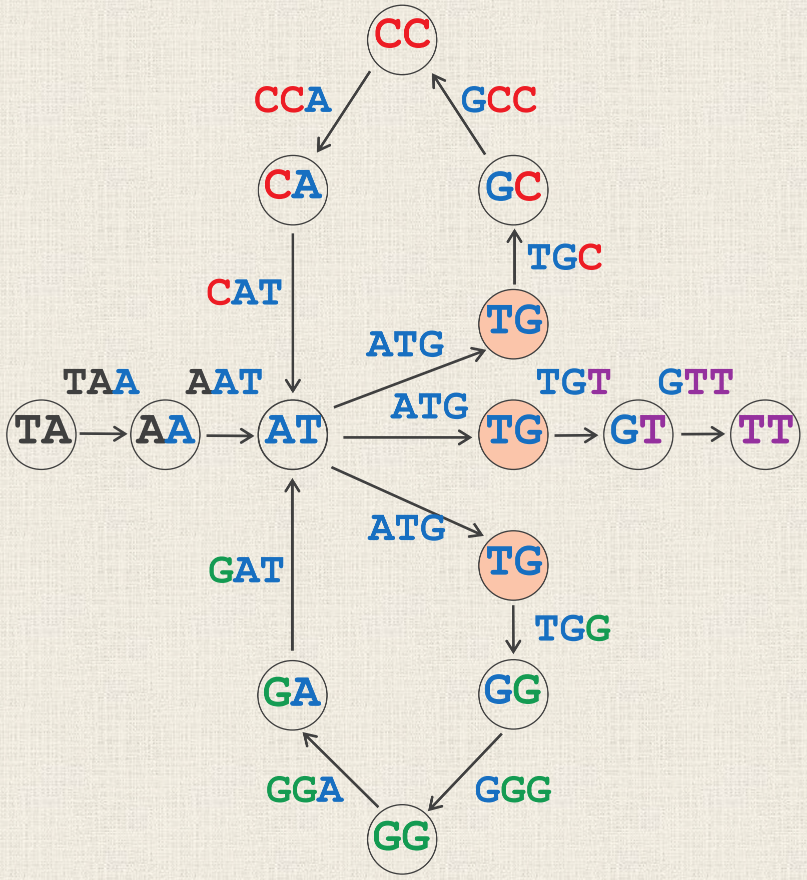
Unlike with the overlap graph, we will *glue* together nodes that have the same label.

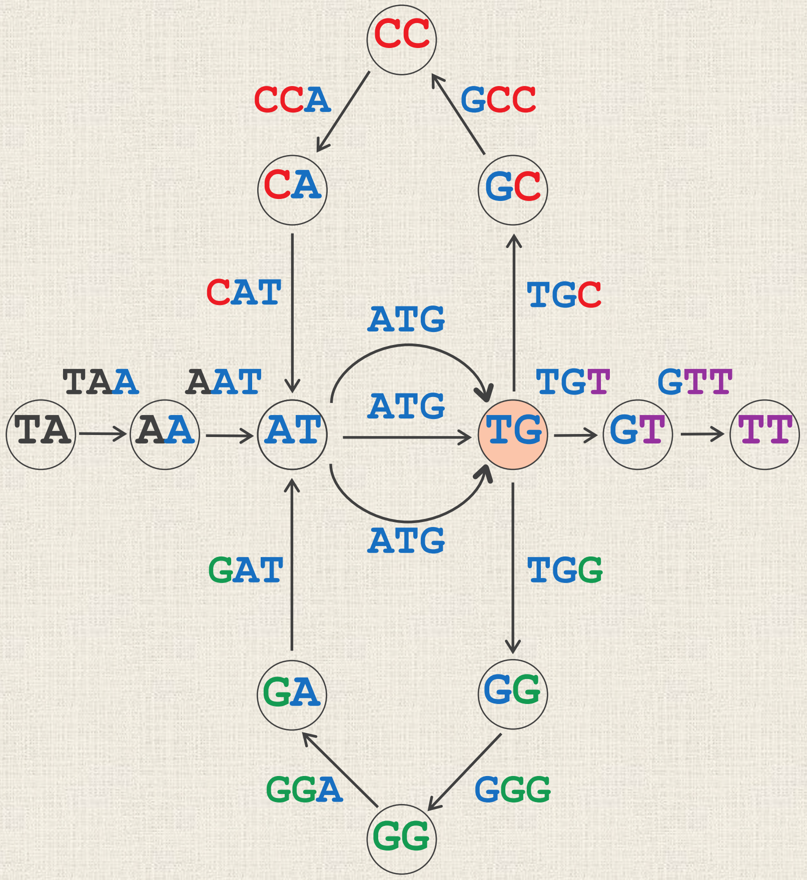
First: Gluing AT Together



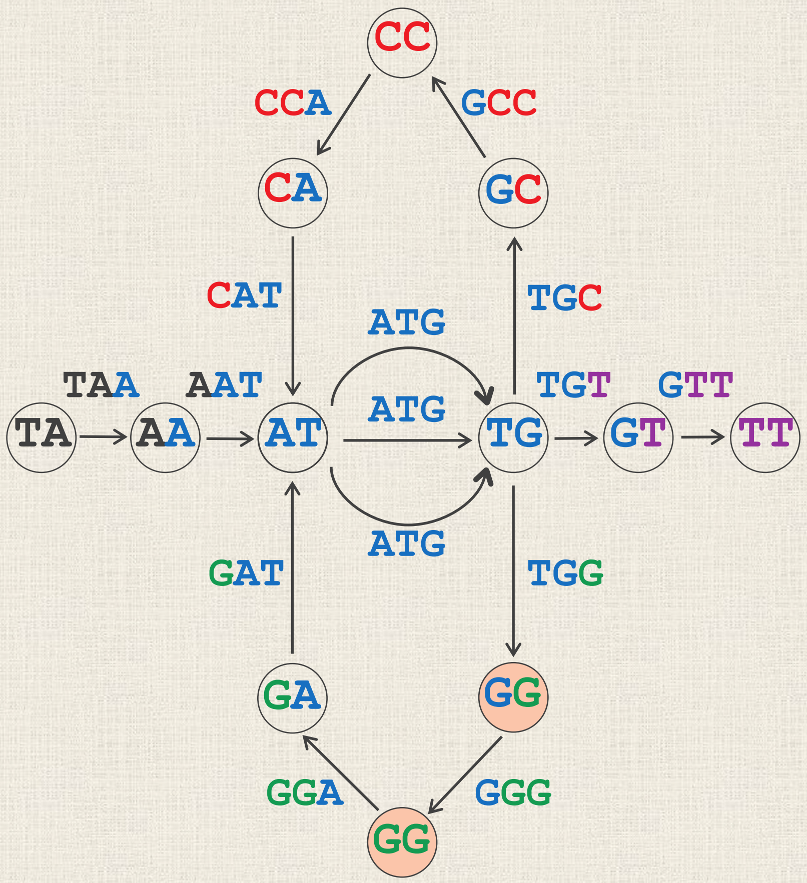


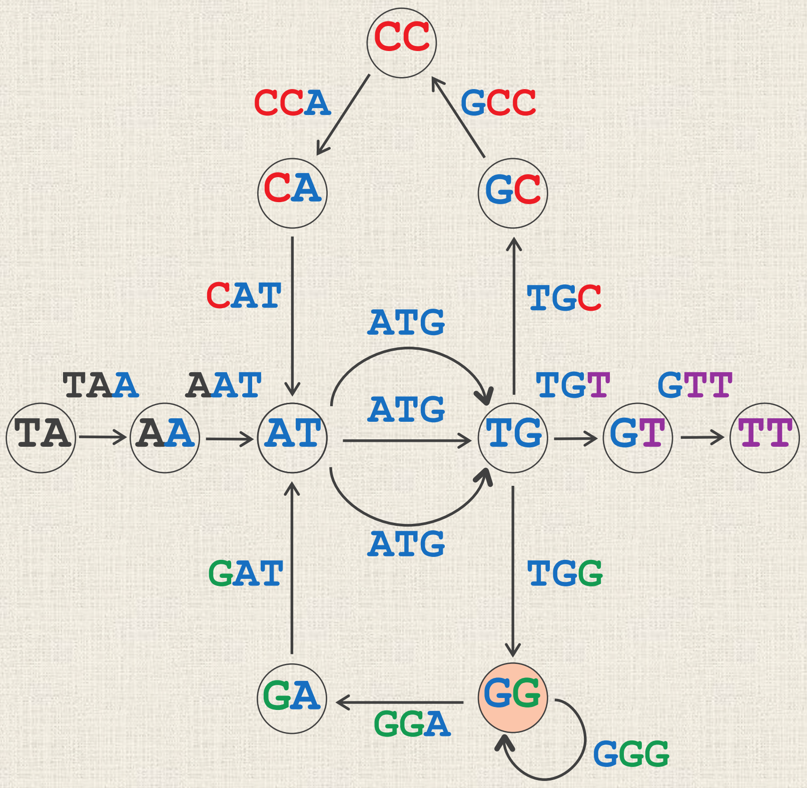
Next: Gluing TG Together





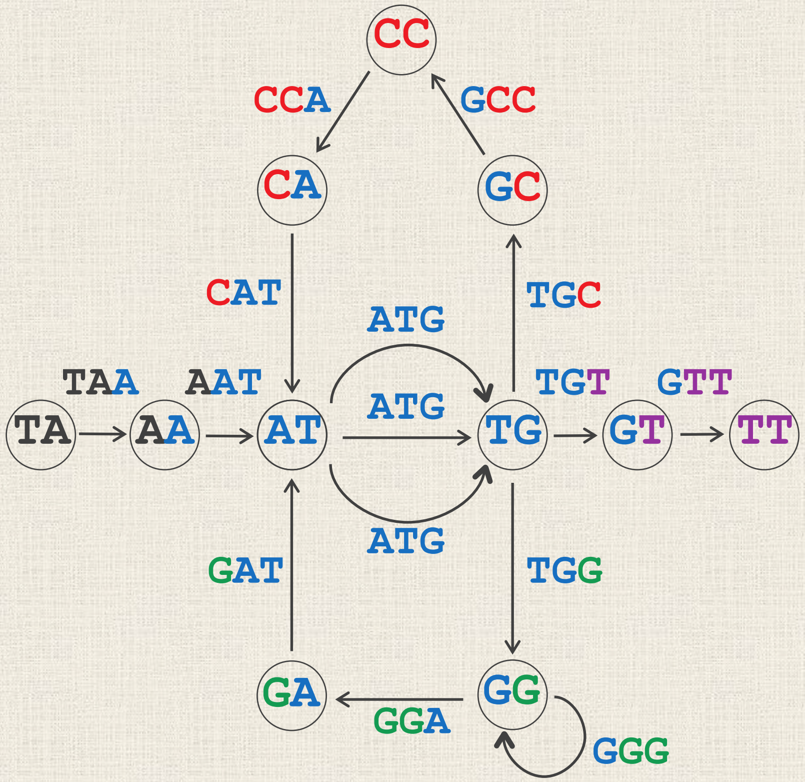
Gluing GG Produces a “Loop”





Gluing GG Produces a "Loop"

This graph is called the **de Bruijn graph** of *Text* = `TAATGCCATGGGATGTT` for *k* = 3.



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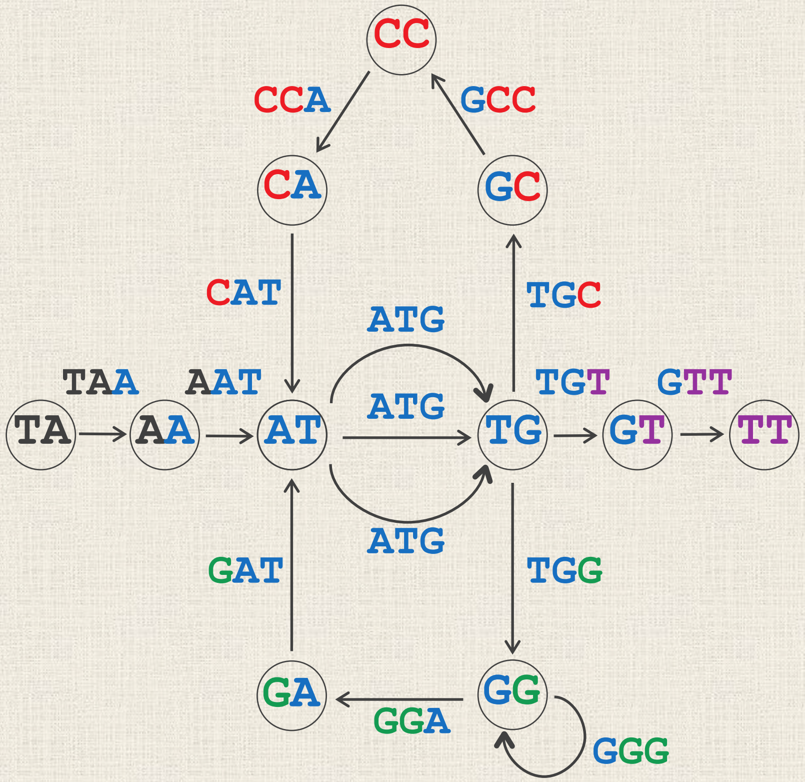
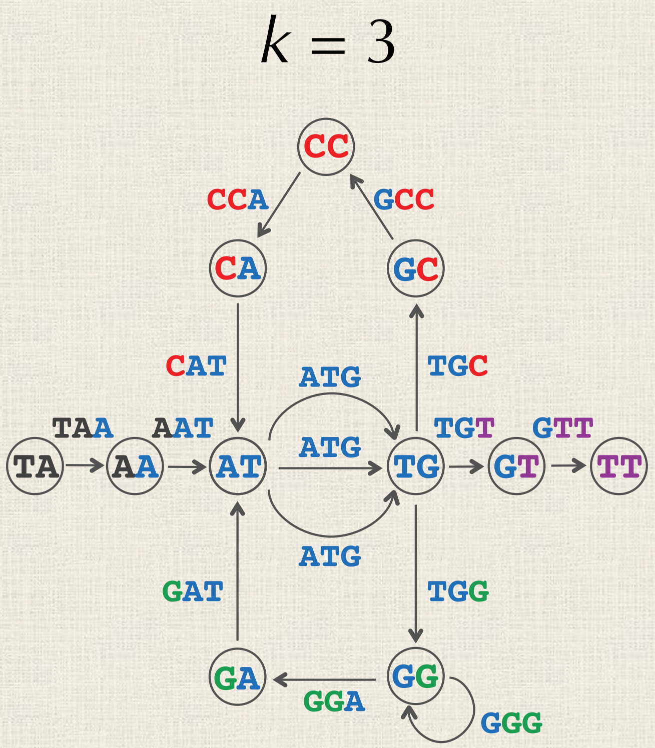
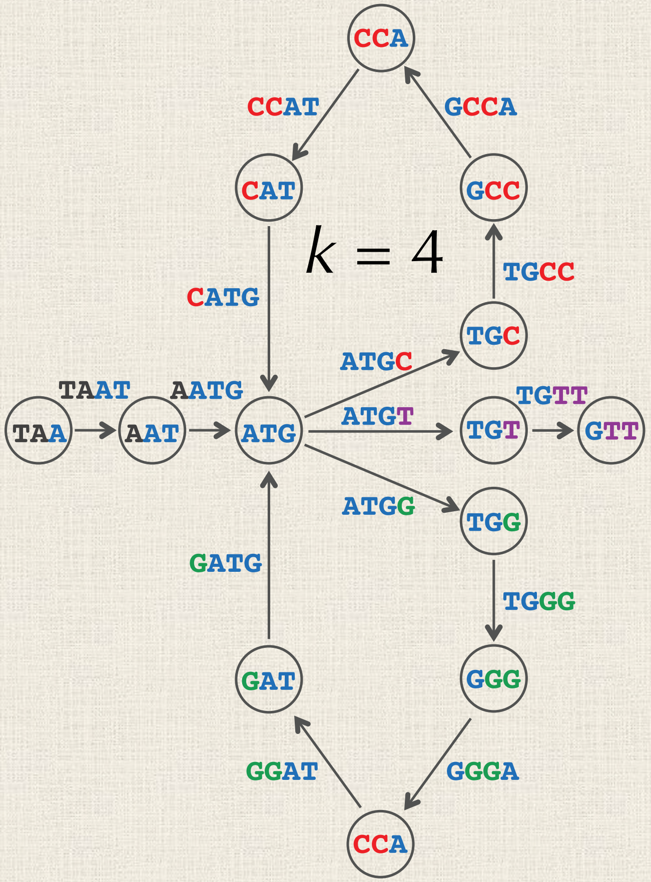
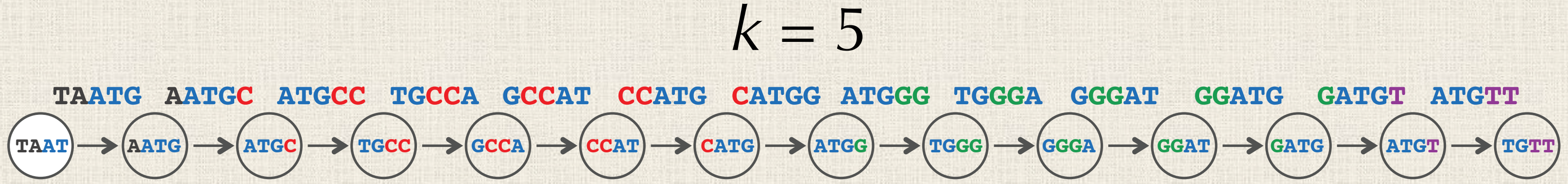


Exercise: Construct the de Bruijn graphs for $k = 4$ and $k = 5$. How do they differ from $k = 3$?

de Bruijn Graph Becomes Less "Tangled" as *k* Increases (fewer repeats)







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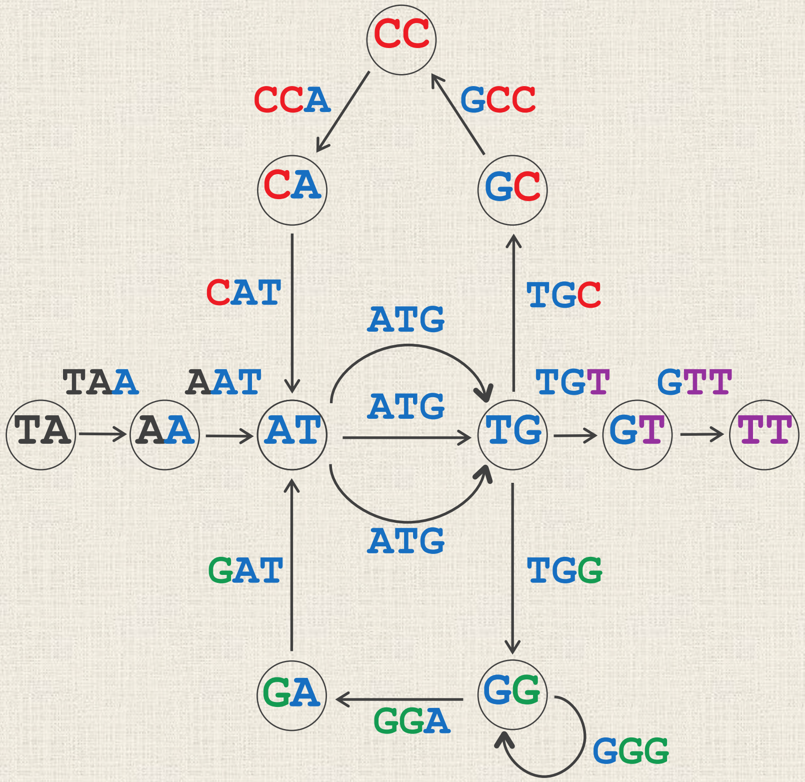
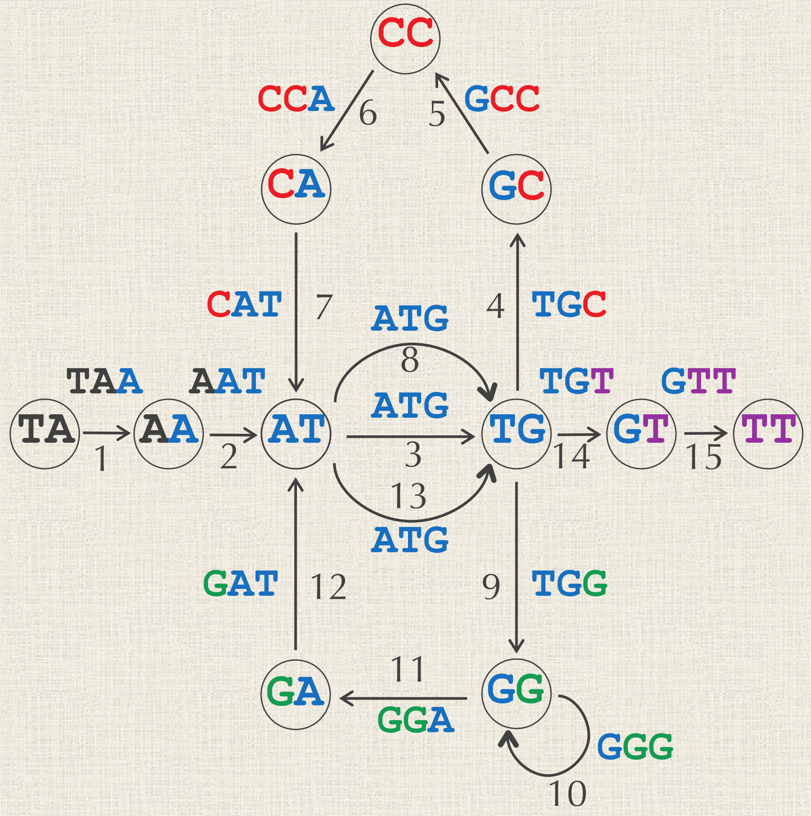


STOP: If we gave you this graph, could you reconstruct *Text*? How?

The Genome Path is Still There

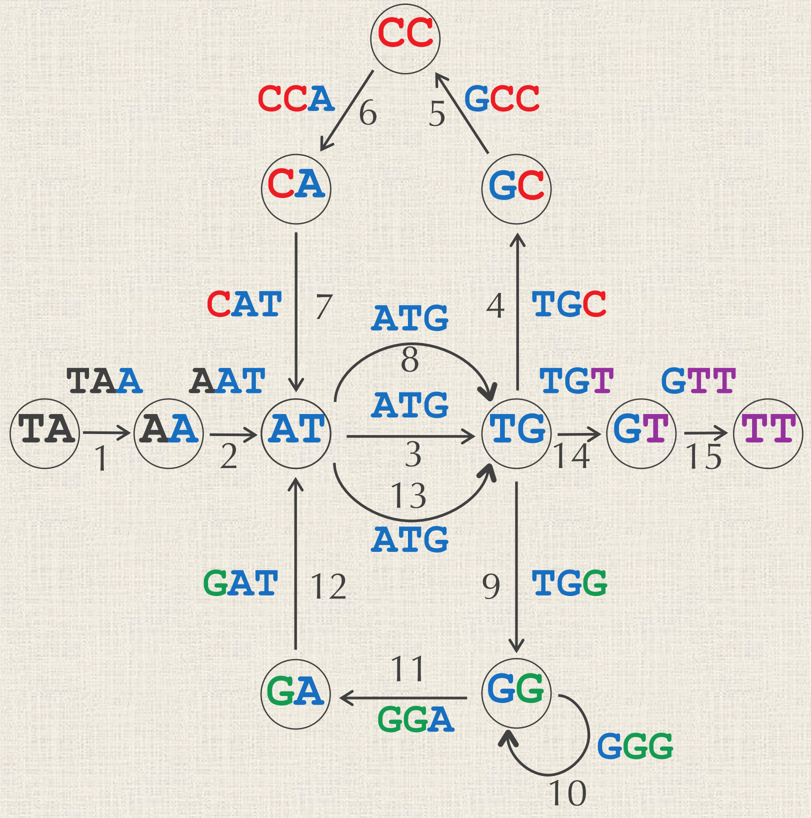
The genome path is an **Eulerian path** in the de Bruijn graph, or a path that uses every edge exactly once.



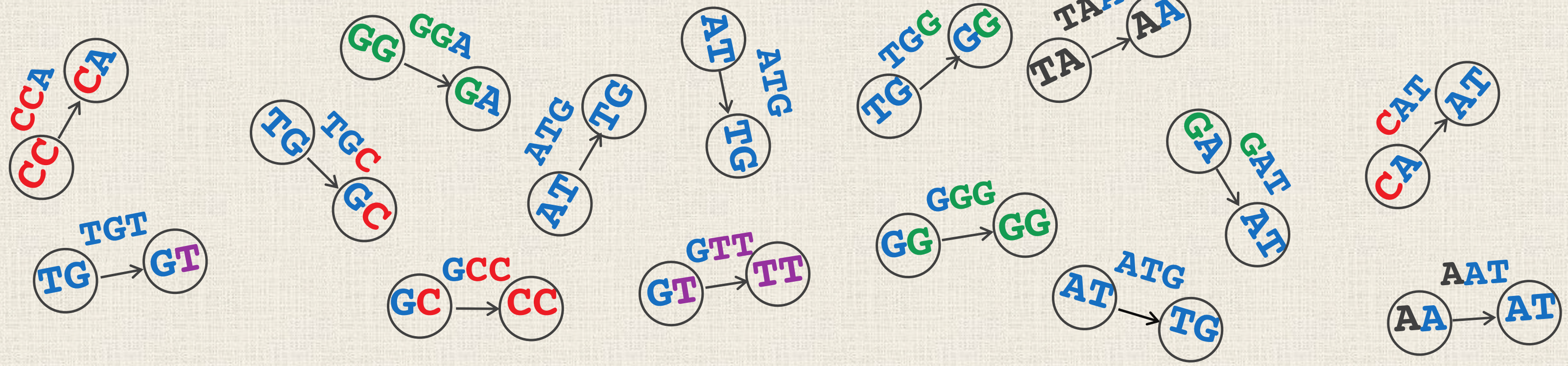
The Genome Path is Still There

The genome path is an **Eulerian path** in the de Bruijn graph, or a path that uses every edge exactly once.

STOP: Can you construct the de Bruijn graph if you don't already know *Text*?

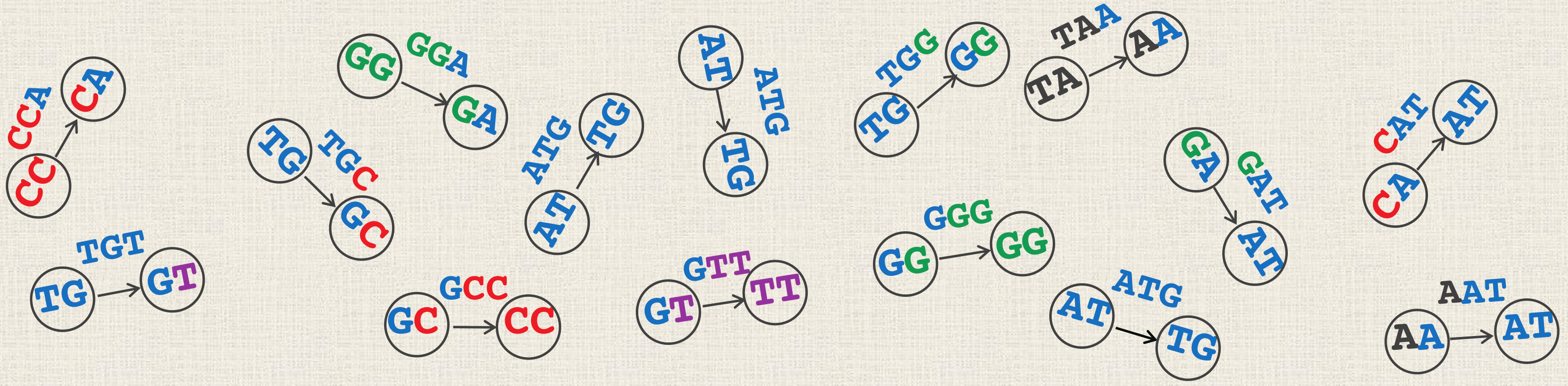


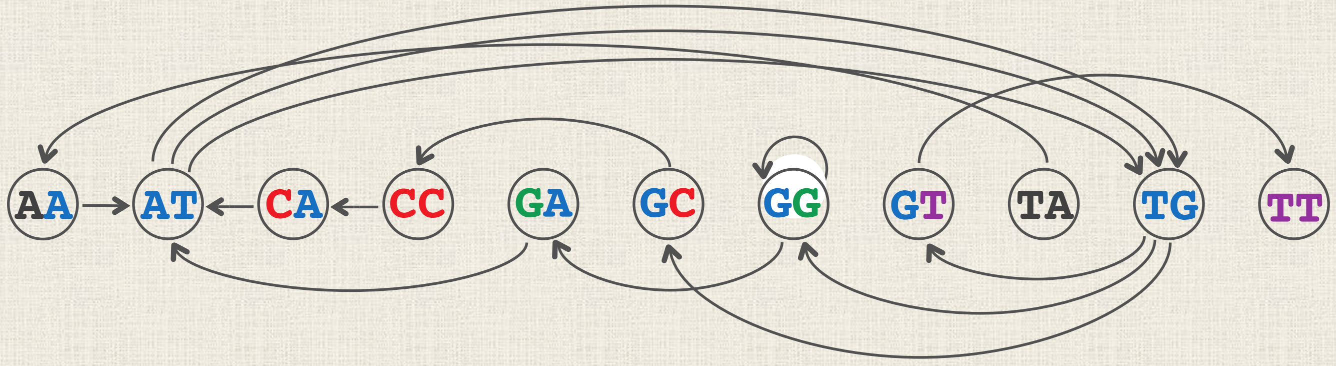
Forming de Bruijn Graph from *k*-mers



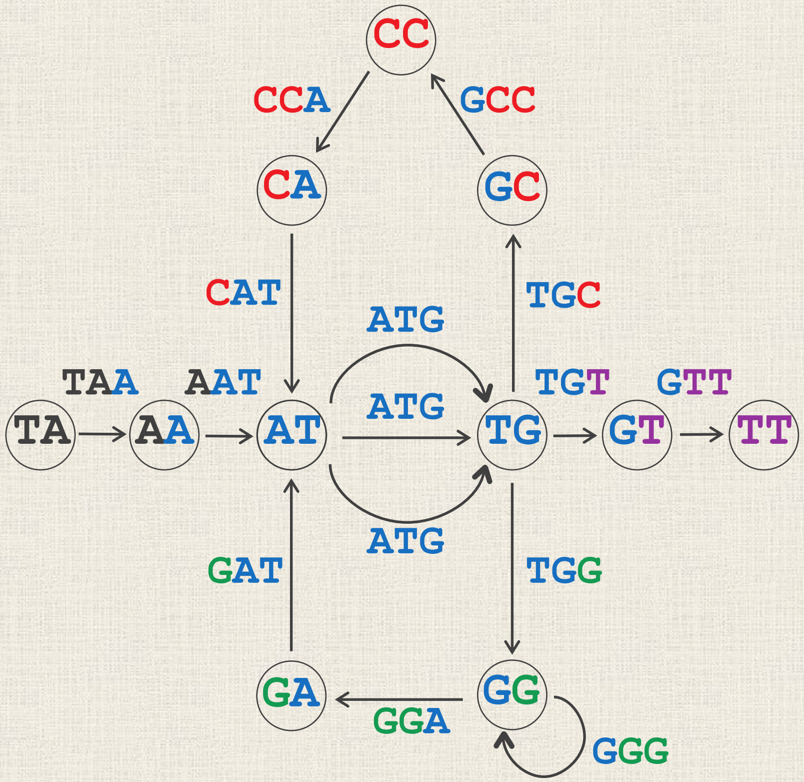
Exercise: Here are the 3-mers from our original dataset represented as *isolated edges*. By gluing nodes together, what do you obtain?

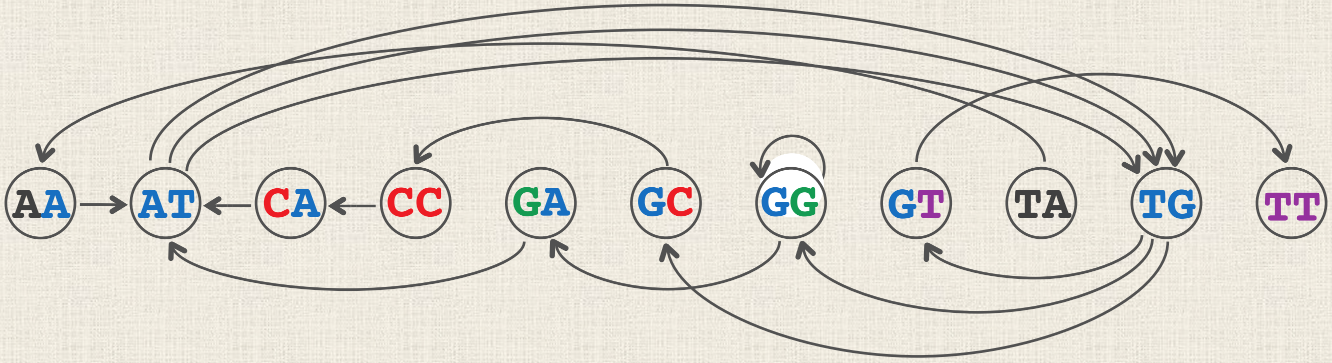
Forming de Bruijn Graph from *k*-mers





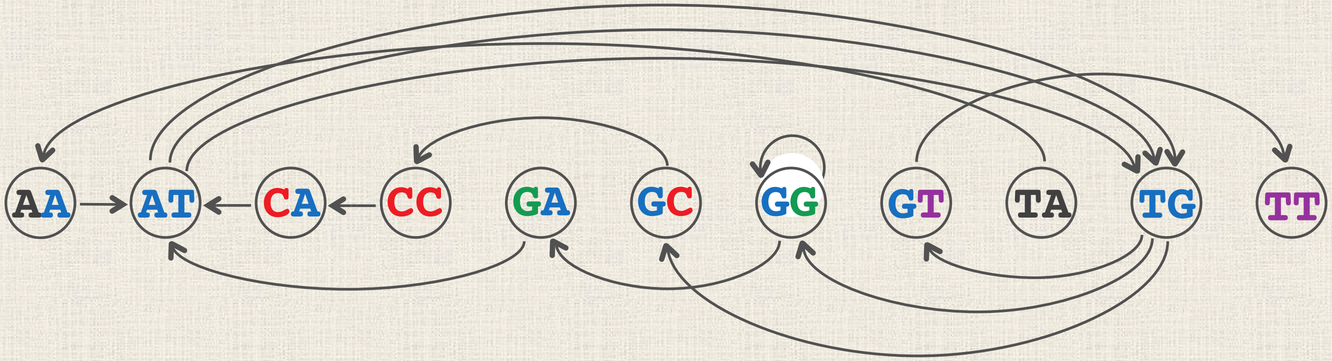
It's the Same Graph…





Approach for Constructing de Bruijn Graph

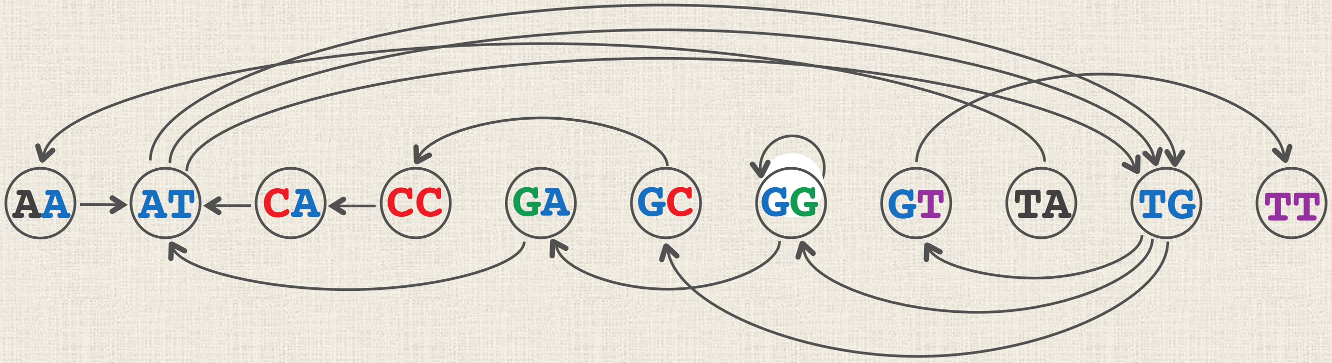
1. Form a node for every (k – 1)-mer appearing as a prefix/suffix in *Patterns*.
2. For every string in *Patterns*, connect its prefix to its suffix.



Approach for Constructing de Bruijn Graph

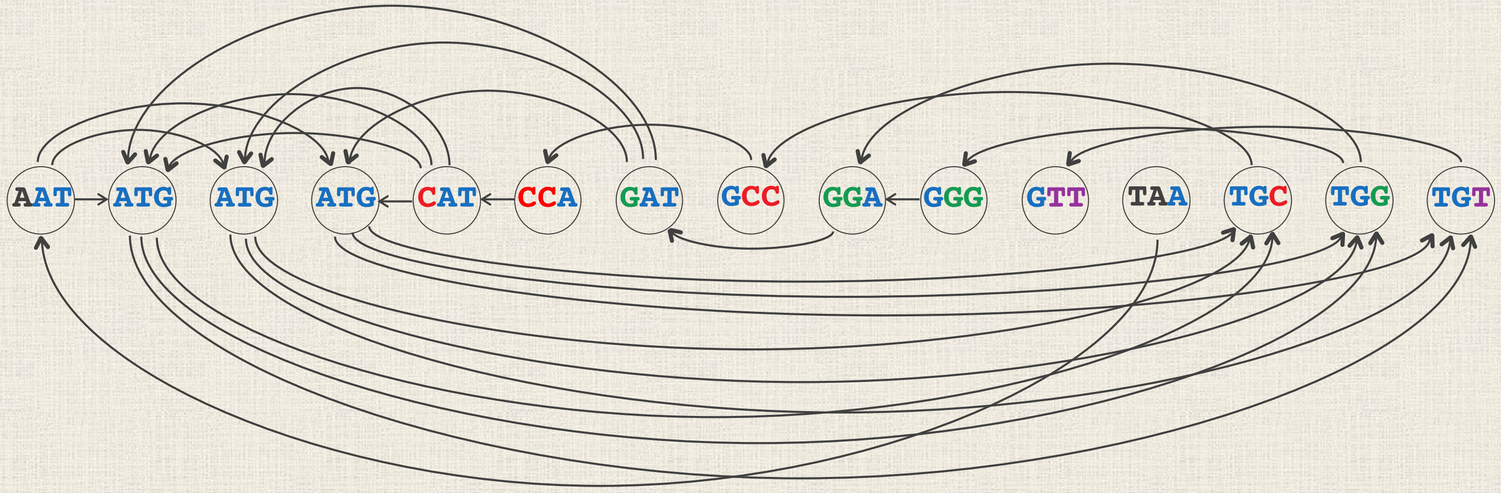
1. Form a node for every (k – 1)-mer appearing as a prefix/suffix in *Patterns*.
2. For every string in *Patterns*, connect its prefix to its suffix.

STOP: Verify this approach for *Patterns* = {`AAT ATG ATG ATG CAT CCA GAT GCC GGA GGG GTT TAA TGC TGG TGT`}.

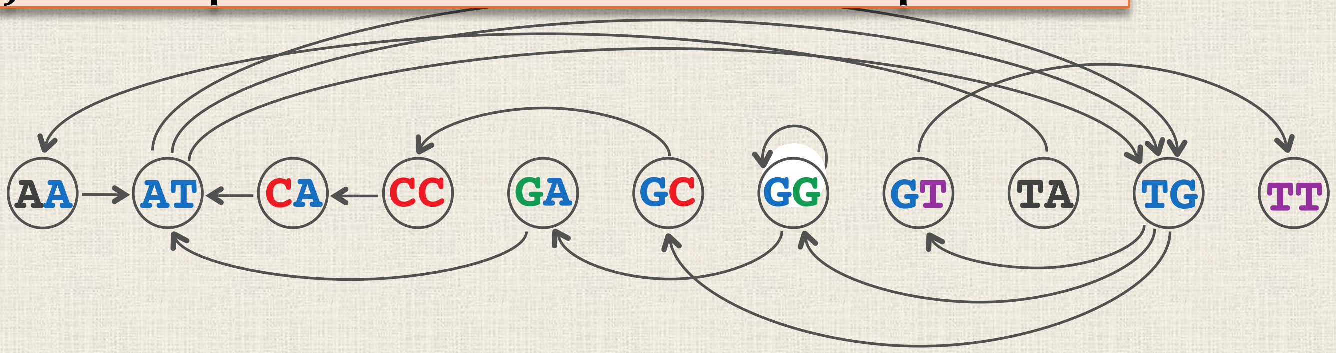


Which Graph Would You Rather Use?

Overlap Graph – find a Hamiltonian path



de Bruijn Graph – find an Eulerian path

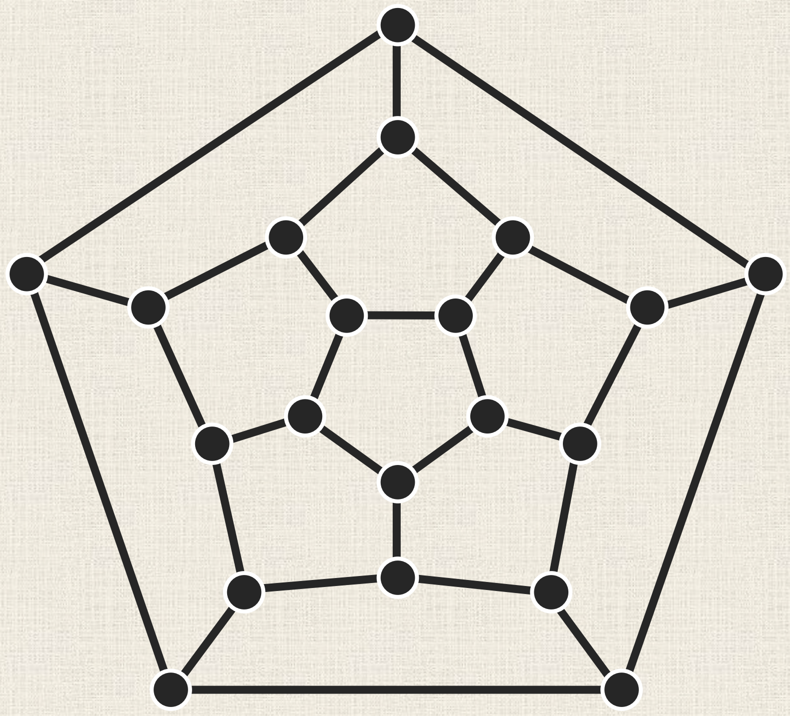


THE ICOSIAN GAME AND THE BRIDGES OF KONIGSBERG

The Origin of "Hamiltonian" Path/Cycle

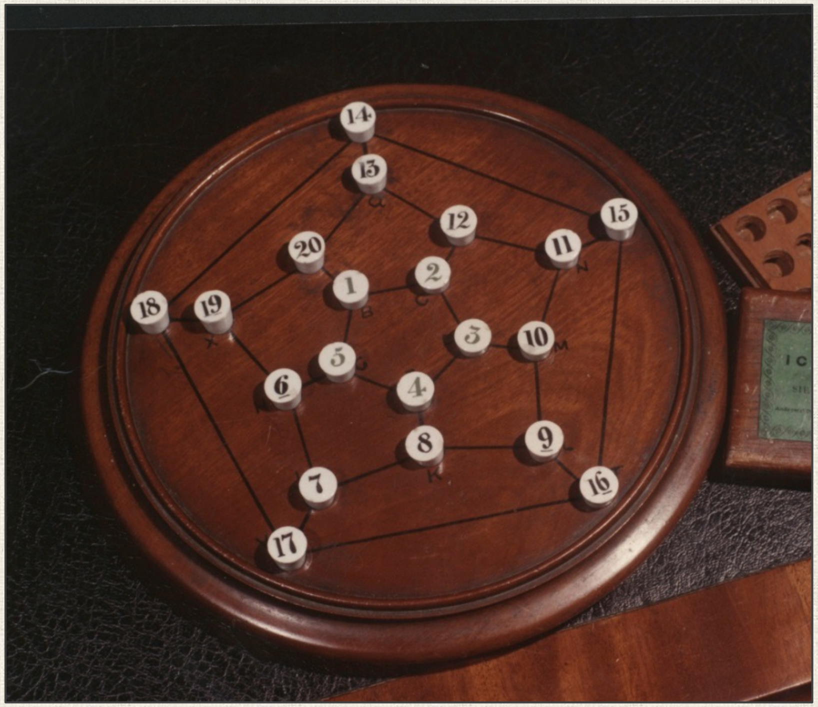
Hamiltonian cycle: A Hamiltonian path that returns to its starting node.

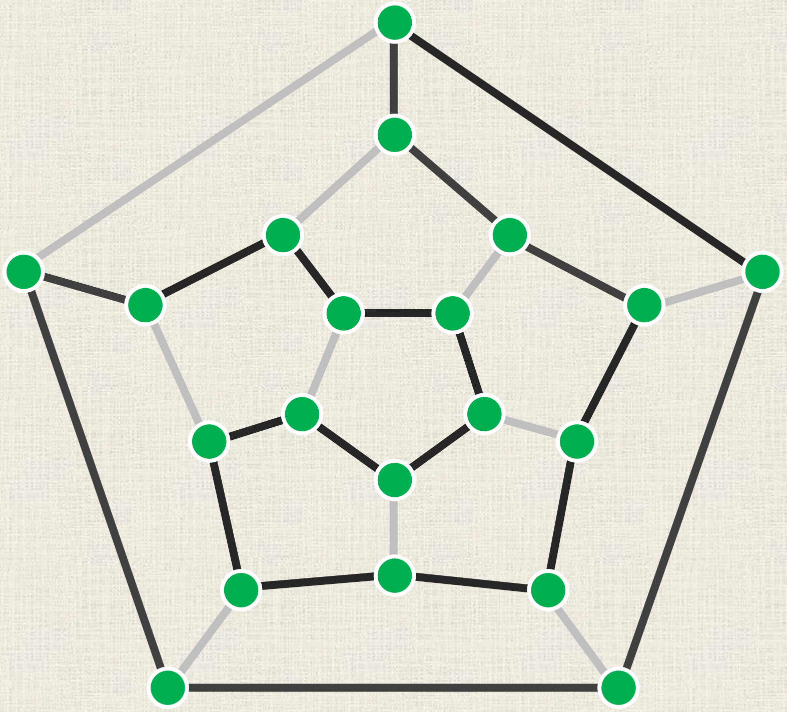
Exercise: Can you find a Hamiltonian cycle in this graph? (What algorithm did you use?)



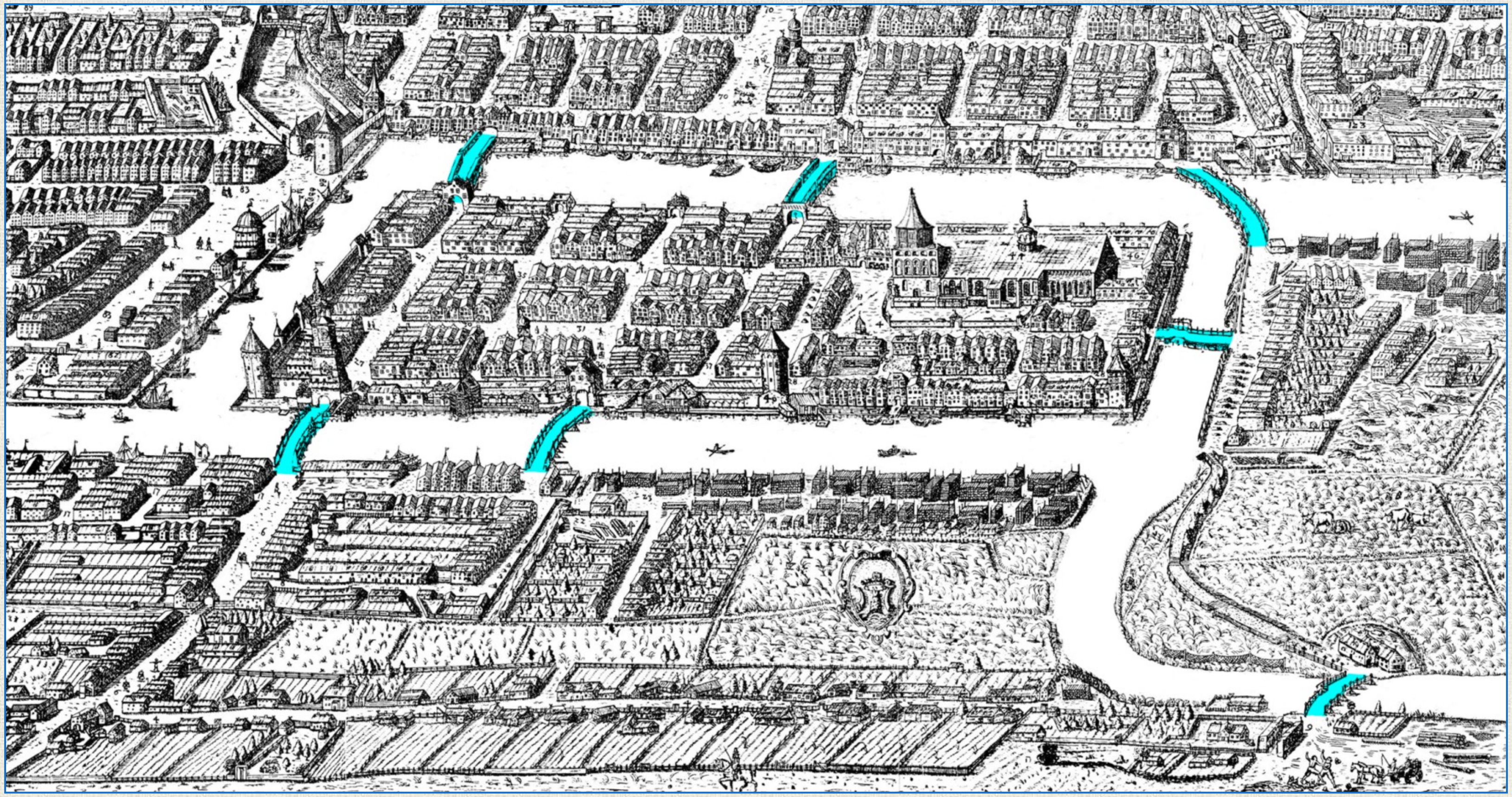
The Origin of "Hamiltonian" Path/Cycle

Icosian game: William *Hamilton,* 1857. Objective is to place pegs 1-20 one at a time in adjacent holes.





The Bridges of Königsberg

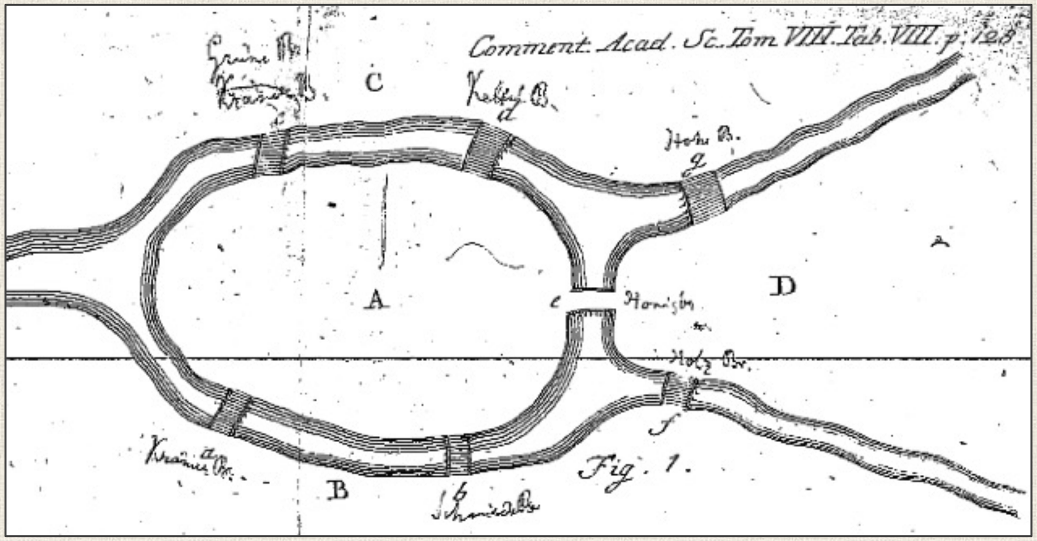


STOP: Is it possible to walk across each bridge *exactly once* and return to the starting point?

Leonhard Euler's Insight (1735)

Define a graph:

- Nodes = 4 land masses
- Edges = 7 bridges



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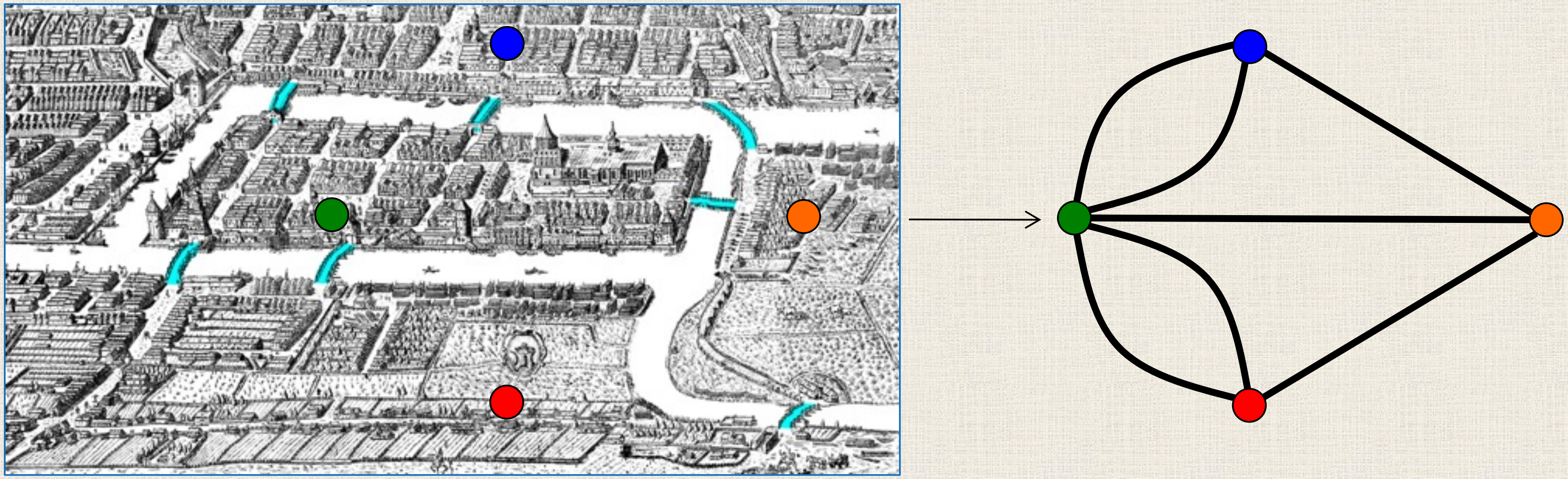
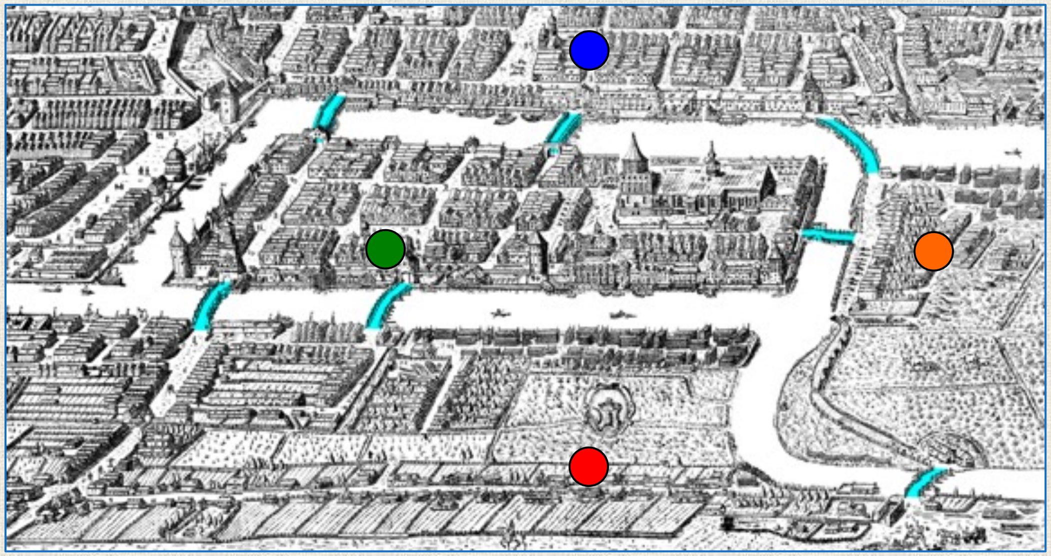
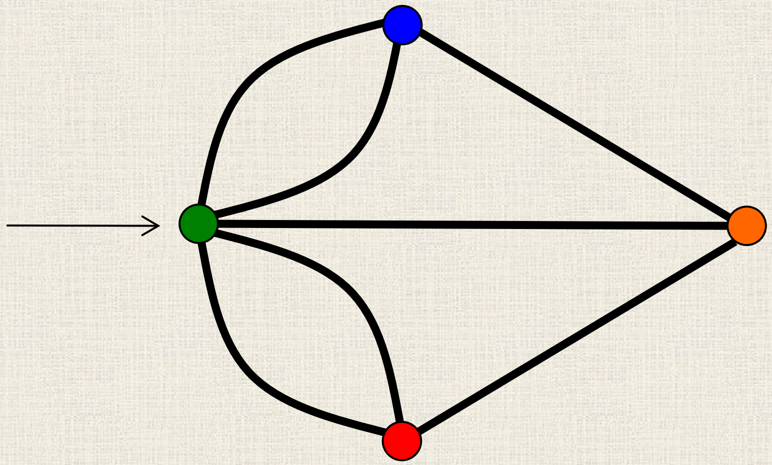


Leonhard Euler's Insight (1735)

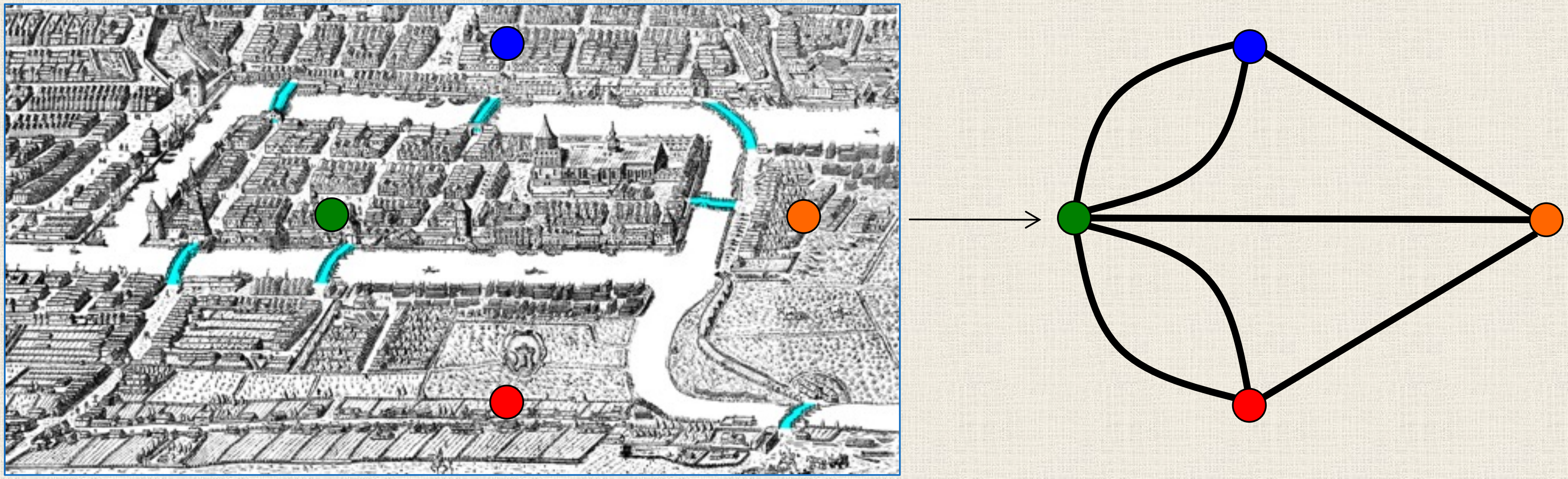
Note: The Bridges of Königsberg question has a solution when this graph has an *Eulerian* cycle.





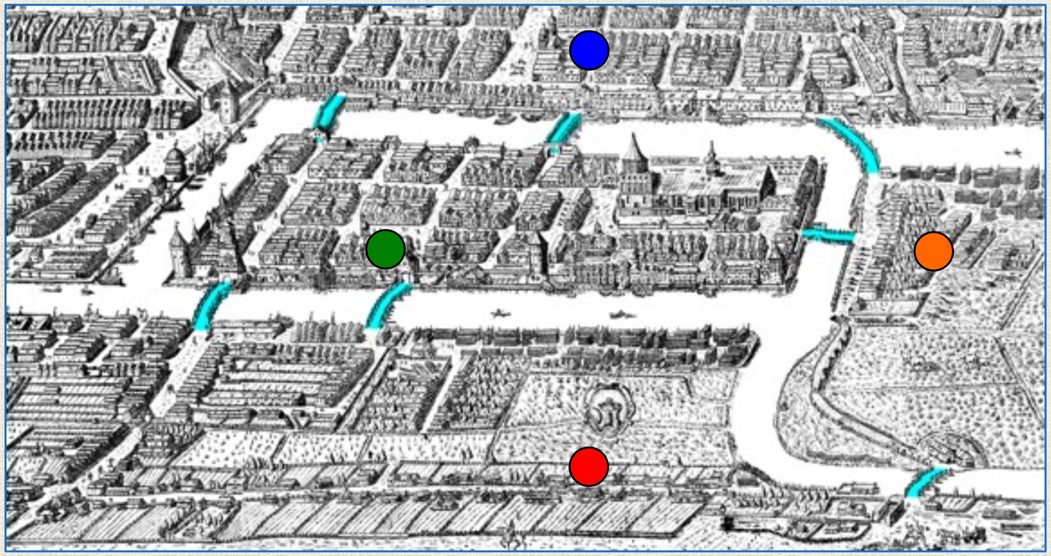
Leonhard Euler's Insight (1735)

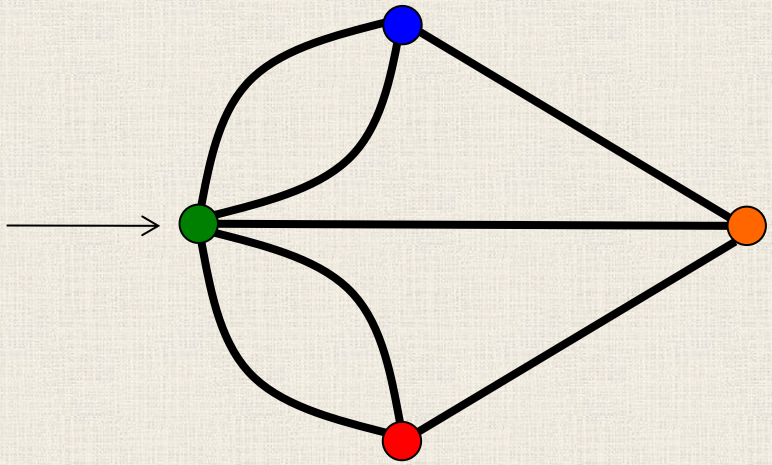
STOP: Does this graph help you solve the original question?



Leonhard Euler's Insight (1735)

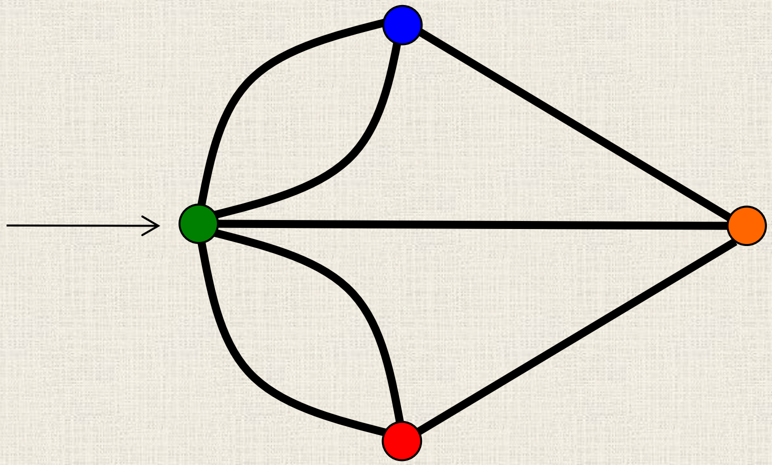
Answer: There is *no* solution because some nodes have an *odd* degree (number of incident edges).





Leonhard Euler's Insight (1735)

Even better, Euler would *prove* how to quickly determine whether a graph has an Eulerian cycle.



Intractable Problems

Even better, Euler would *prove* how to quickly determine whether a graph has an Eulerian cycle.

Key Point: And yet no one has ever found a polynomial-time algorithm to find a Hamiltonian cycle in a graph!

Similar Problems with Different Fates

Hamiltonian Cycle Problem ***NP-Complete***

Input: a network with *n* nodes.

Output: "Yes" if there is a cycle visiting every ***node*** in the network; "No" otherwise.

Eulerian Cycle Problem ***Polynomial***

Input: a network with *n* nodes.

Output: "Yes" if there is a cycle visiting every **edge** in the network; "No" otherwise.

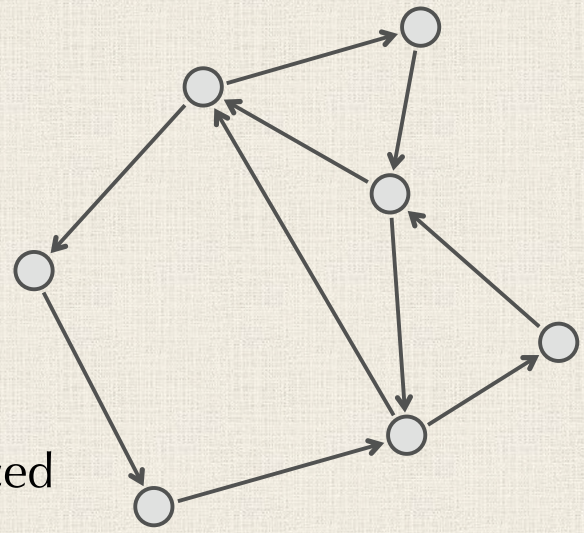
FROM EULER'S THEOREM TO AN ALGORITHM FOR GENOME ASSEMBLY

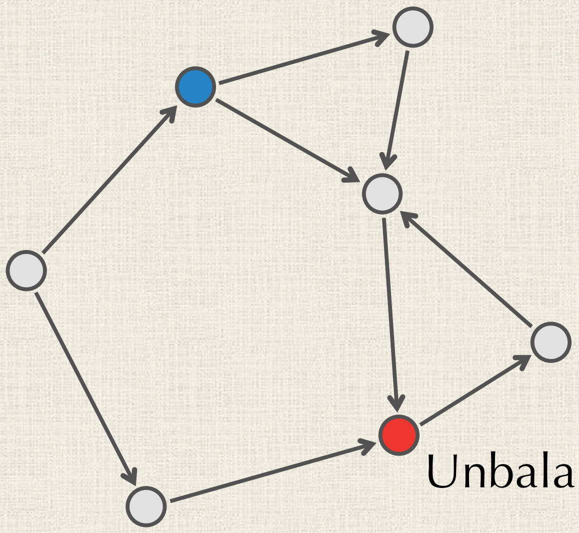
Euler's Theorem for Directed Graphs

Indegree: Number of edges leading into a node.

Outdegree: Number of edges leading out of a node.

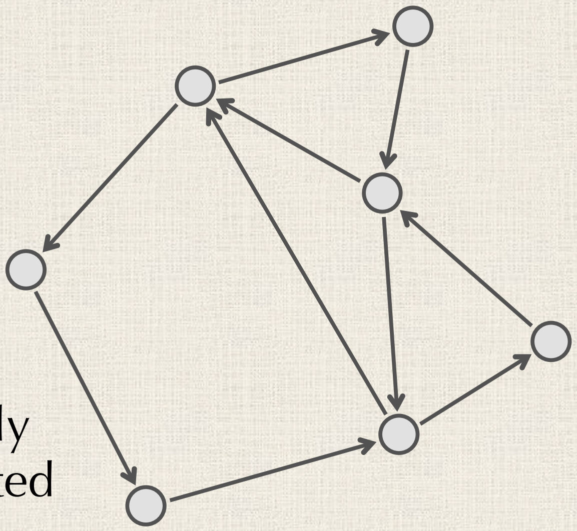
Balanced graph: Every node has indegree equal to outdegree.


Balanced

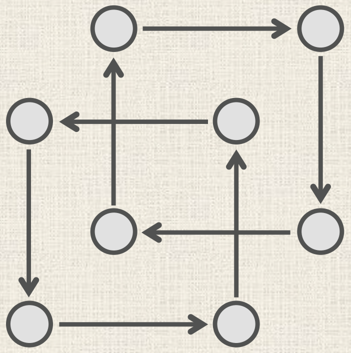

Unbalanced

Euler's Theorem for Directed Graphs

Strongly connected graph: A graph where it is possible to reach every node from any other node.



Strongly connected

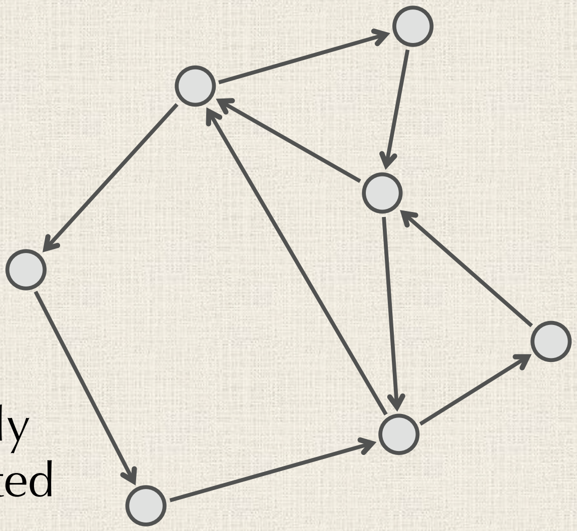


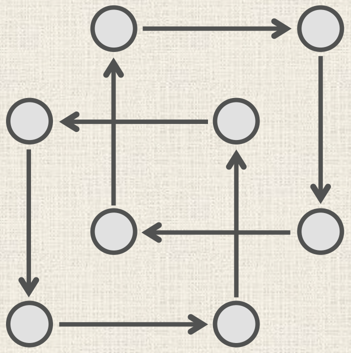
Disconnected

Euler's Theorem for Directed Graphs

Strongly connected graph: A graph where it is possible to reach every node from any other node.

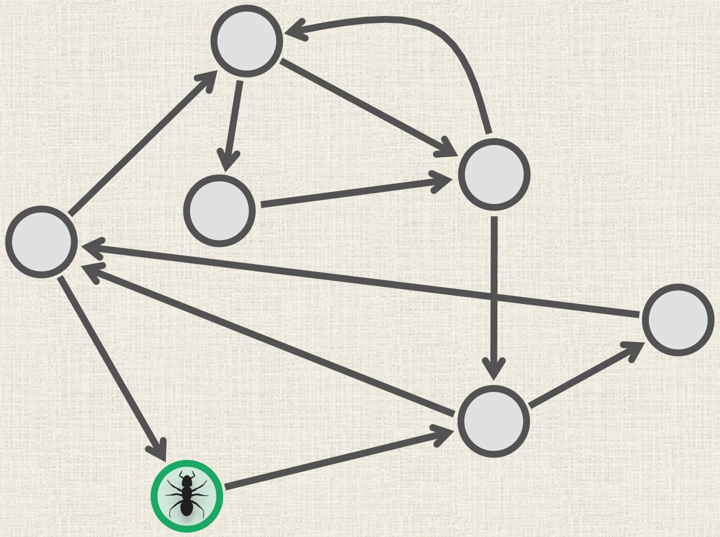
Euler's Theorem: Every balanced, strongly connected graph has an Eulerian cycle.


Strongly connected


Disconnected

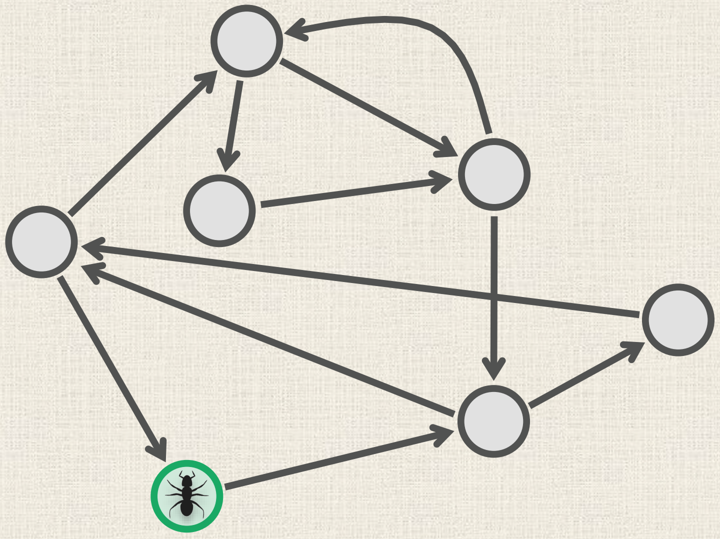
Proof of Euler's Theorem

Take an arbitrary balanced, strongly connected network, place an ant on any starting node v_0, and let it walk randomly.



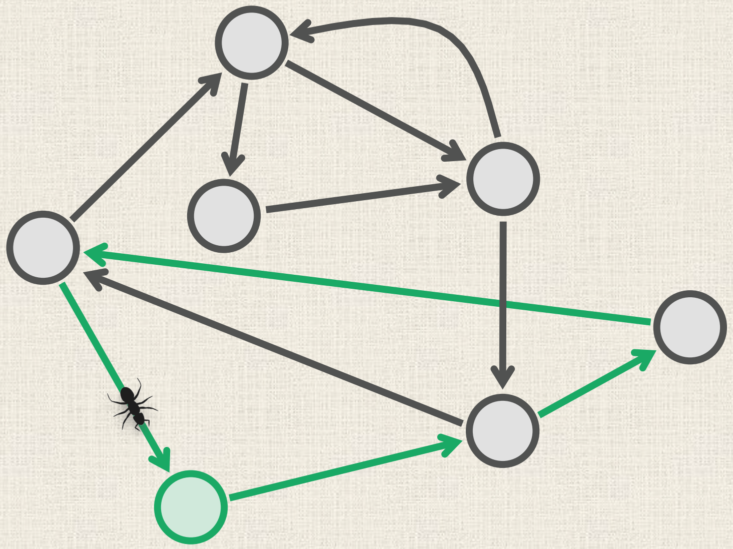
Proof of Euler's Theorem

STOP: What must eventually happen when the ant "gets stuck"?



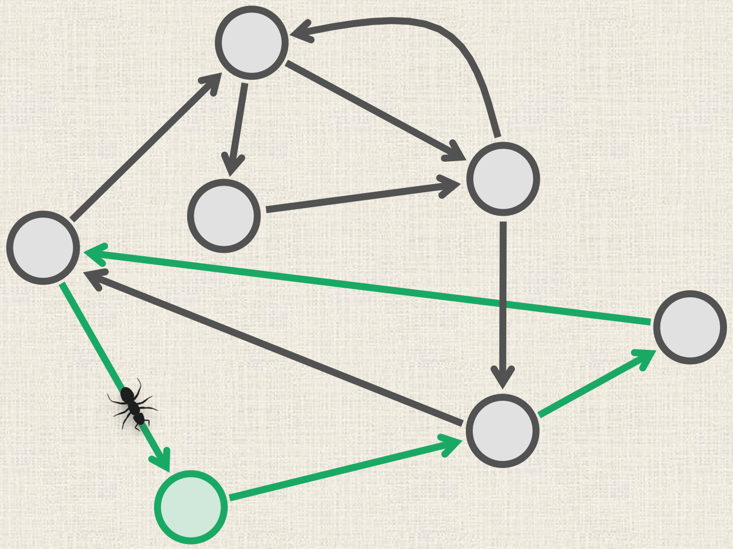
Proof of Euler's Theorem

Answer: Because the graph is balanced, the ant must eventually get stuck at v_0!



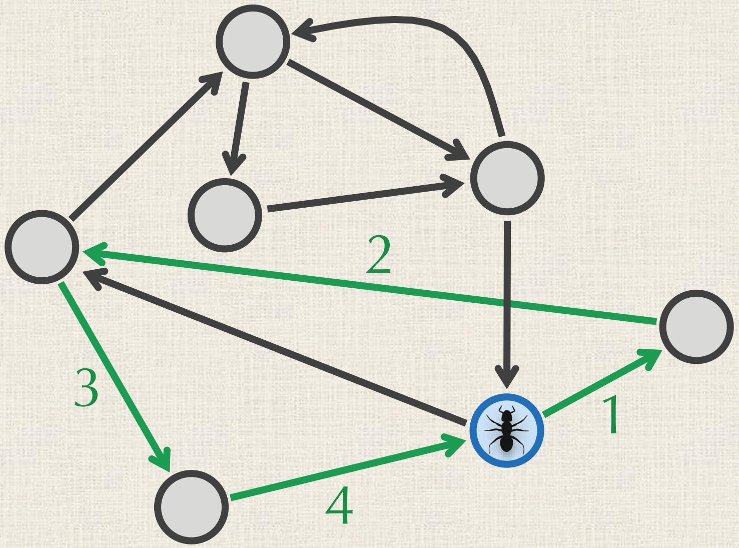
Proof of Euler's Theorem

If this cycle, which we call $Cycle_0$, is Eulerian, then we stop. Otherwise, move the ant to a node on $Cycle_0$ that still has unused edges, called v_1.



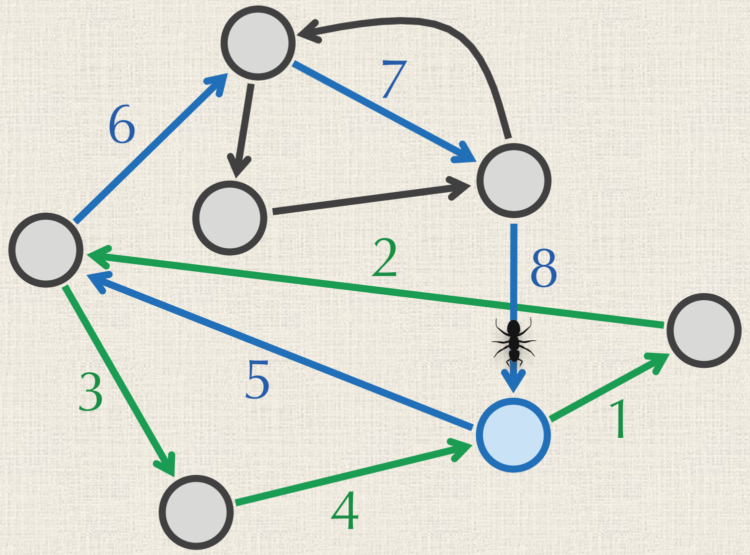
Proof of Euler's Theorem

Make the ant traverse all of *Cycle*$_0$ first, then explore unused edges.



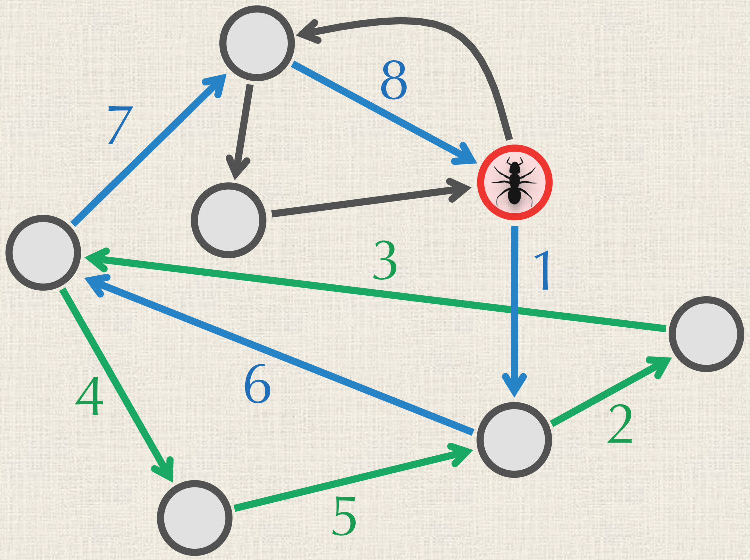
Proof of Euler's Theorem

The same reasoning implies that the ant will eventually get stuck at v_1, creating *Cycle*$_1$.



Proof of Euler's Theorem

We simply iterate this procedure until we are out of unused edges, when we have an Eulerian cycle!



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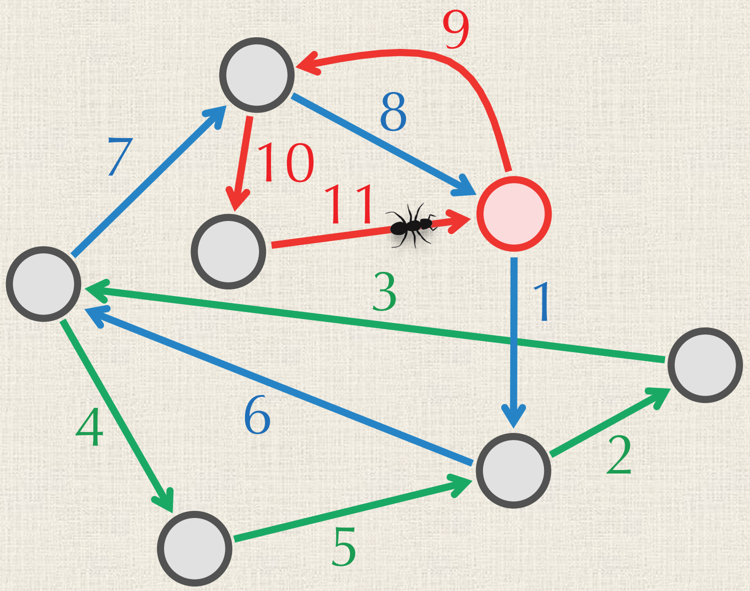
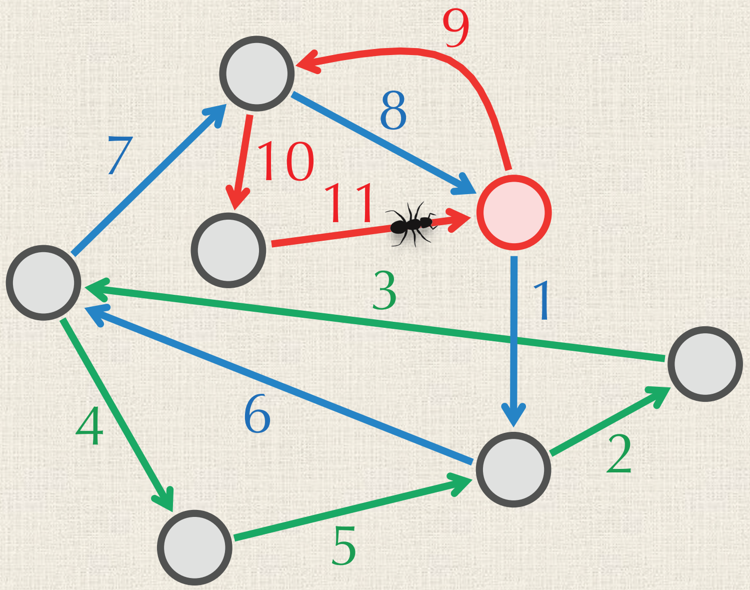


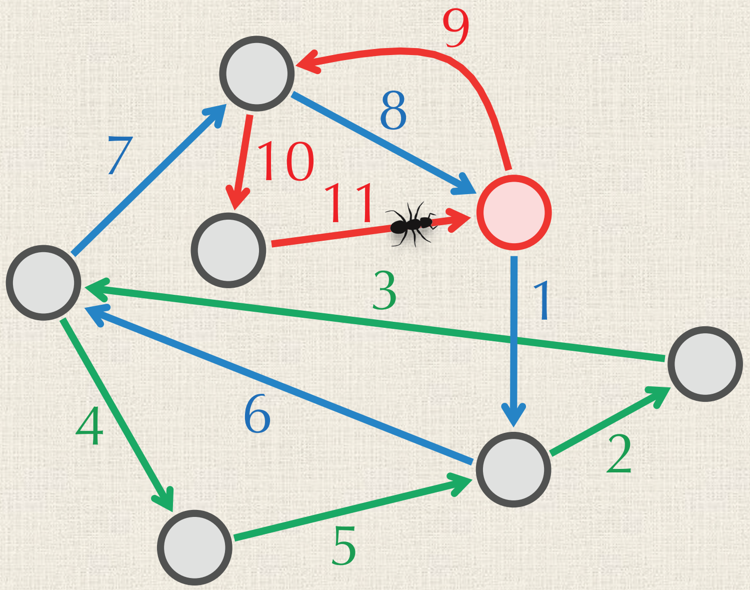
Proof of Euler's Theorem

STOP: Why can we be sure that this process will use all the edges?



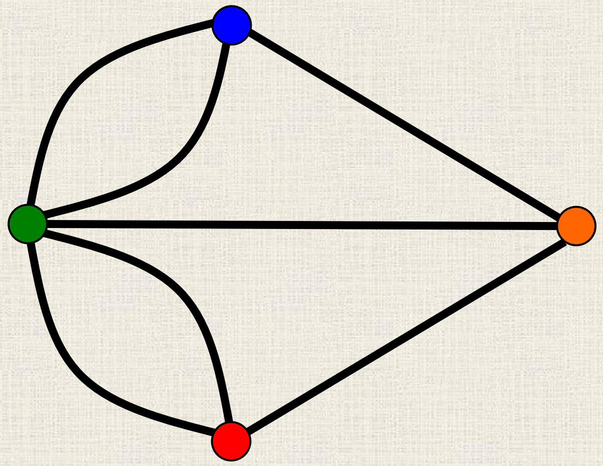
Proof of Euler's Theorem

Answer: Because the graph is strongly connected! So note that we have used both conditions in the theorem (balanced and strongly connected).



Proof of Euler's Theorem

Exercise: When will an "undirected" graph have an Eulerian cycle?



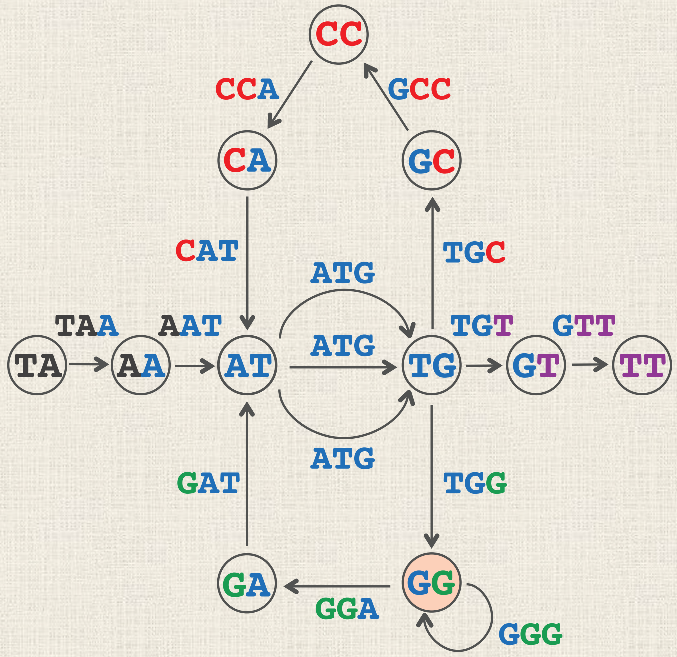
Euler's Theorem is "Constructive"

Key Point: This is a "constructive proof", meaning it implies an algorithm for finding an Eulerian cycle.

```
EulerianCycle(Graph)
    v ← arbitrary node in Graph
    Cycle ← randomly walk starting at v (don't revisit edges) until cycle
    while there are unexplored edges in Graph
        newStart ← node in Cycle with unexplored edges
        Cycle' ← cycle formed by traversing Cycle (starting at newStart)
            and then randomly walking
        Cycle ← Cycle'
    return Cycle
```

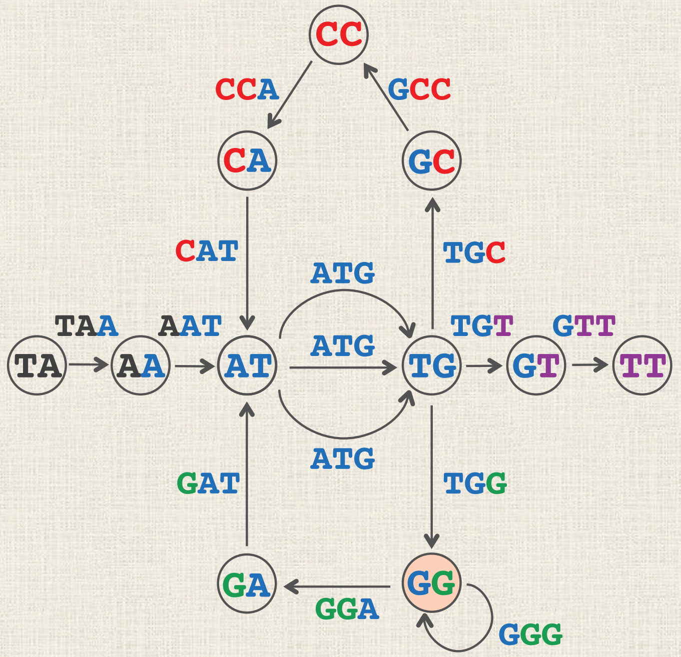
From Eulerian Cycles to Paths

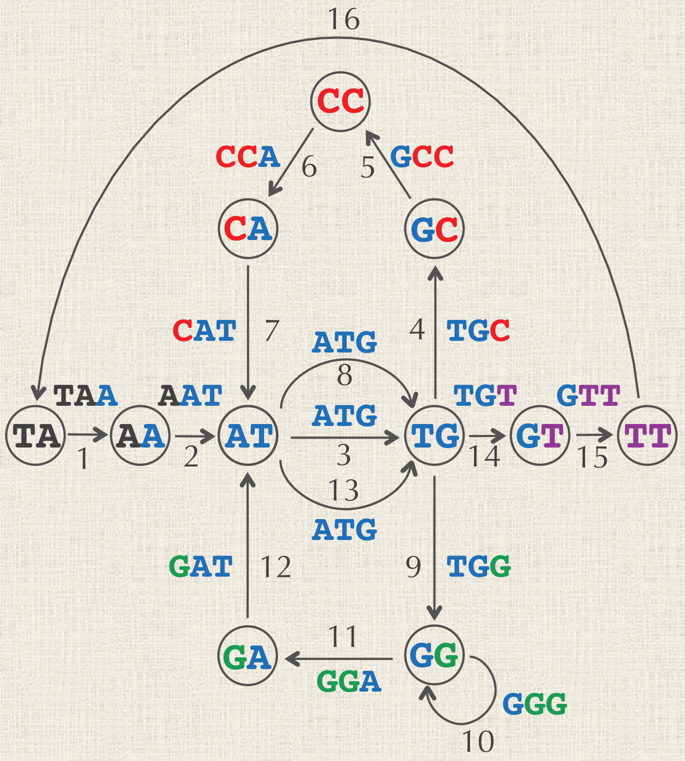
STOP: How do we find an Eulerian *path* in this graph?



From Eulerian Cycles to Paths

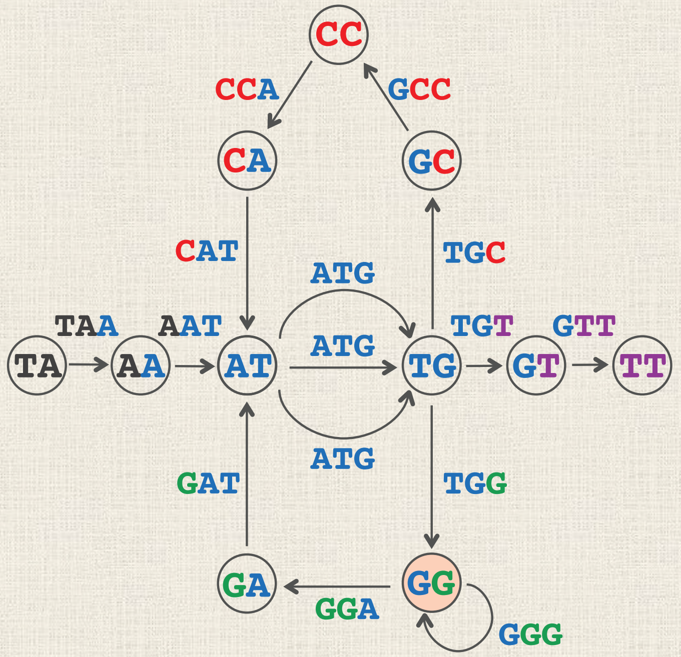
Answer: Simply draw an edge connecting the two unbalanced nodes to form a balanced graph. Eulerian cycle on right = Eulerian path on left.

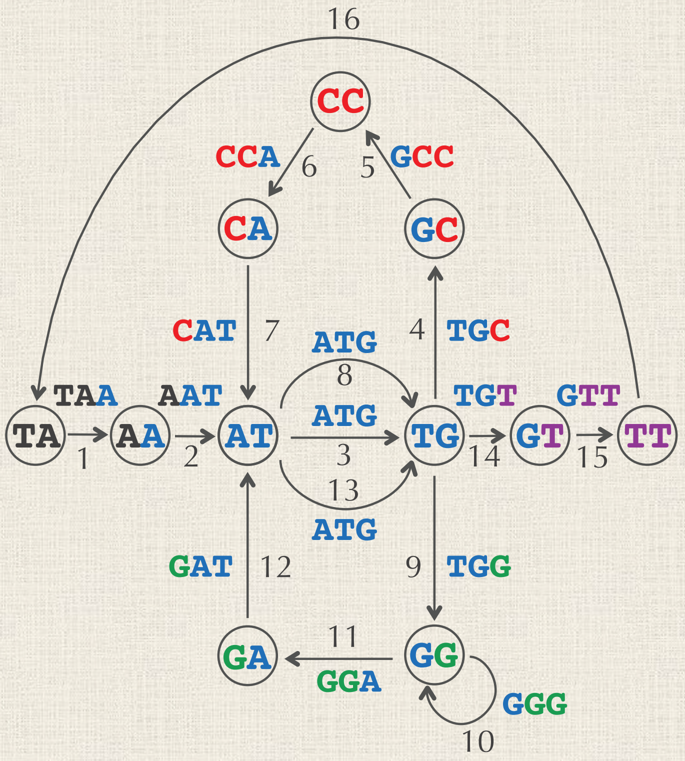




From Eulerian Cycles to Paths

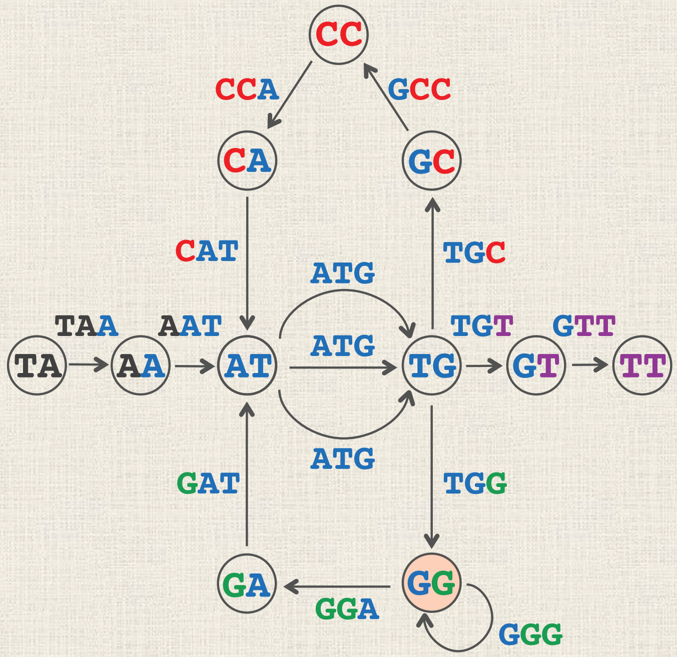
STOP: Why will the augmented de Bruijn graph on the right be balanced for any collection of strings *Patterns*?

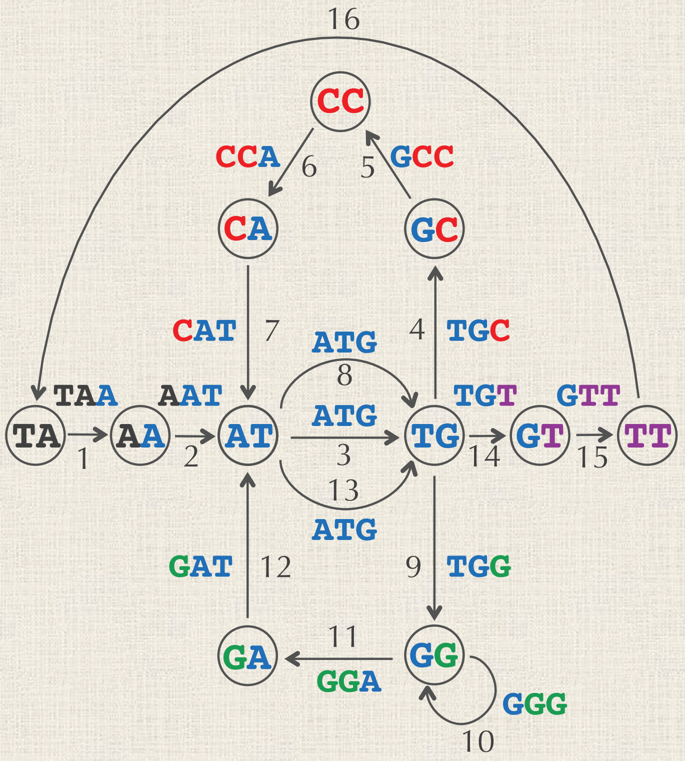




From Eulerian Cycles to Paths

Answer: For every node *v* in de Bruijn graph, Indegree(*v*) and Outdegree(*v*) are both equal to # of patterns containing *v* as prefix/suffix, respectively.





We Can Assemble a Genome!

String Reconstruction Problem: *Reconstruct a string from its k-mer composition.*

Input: An integer *k* and a collection *Patterns* of *k*-mers.

Output: A string *Text* with *k*-mer composition equal to *Patterns* (if such a string exists).

1. Form de Bruijn graph *G* from *Patterns*.

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3. Find Eulerian cycle in G'.

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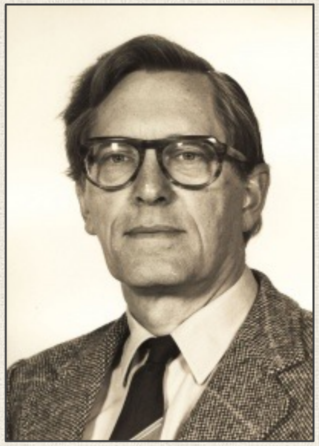
5. Convert "genome path" into string *Text*.

Aside: De Bruijn/Good's Question

Recall: a binary string is ***k*-universal** if it contains every binary *k*-mer once.

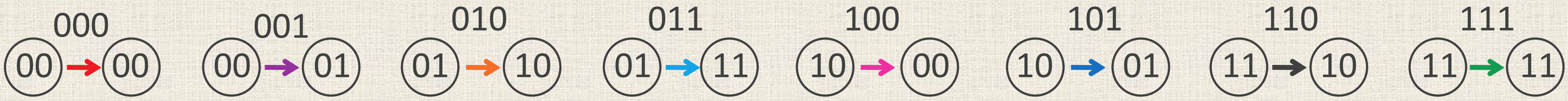
STOP: How can we find a *k*-universal binary string?

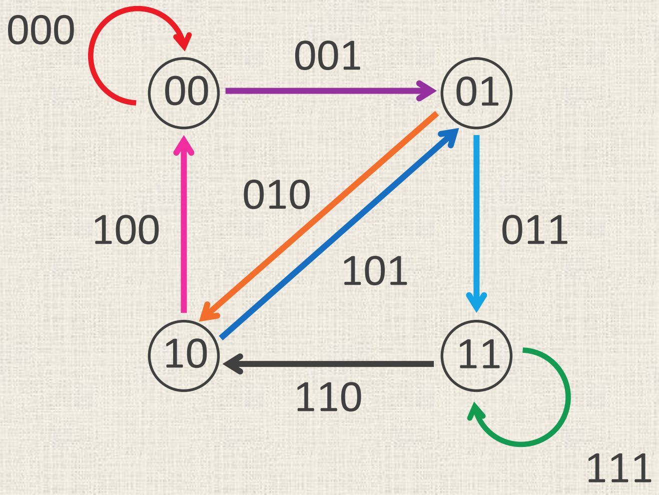
Jack Good


Nicolaas de Bruijn

Aside: De Bruijn/Good's Question

Answer: Construct the "de Bruijn graph" for *Patterns* = all binary *k*-mers; find Eulerian path.





DE BRUIJN GRAPHS FACE HARSH PRACTICAL REALITIES

Practical Sequencing Complications

1. DNA may be divided over **multiple chromosomes**.

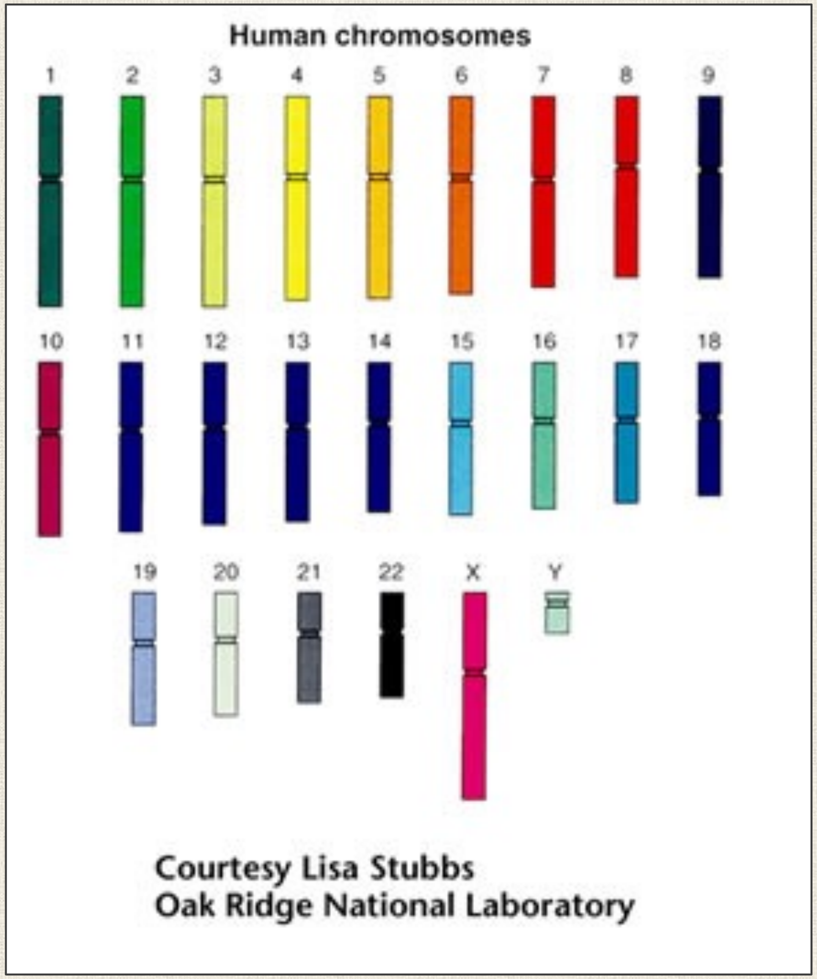
2. Reads have **imperfect "coverage"** of the underlying genome – there may be some regions that are not covered by any reads.

3. Sequencing machines are **error-prone**.

4. DNA is **double-stranded**.

Genomes May Have Multiple Chromosomes

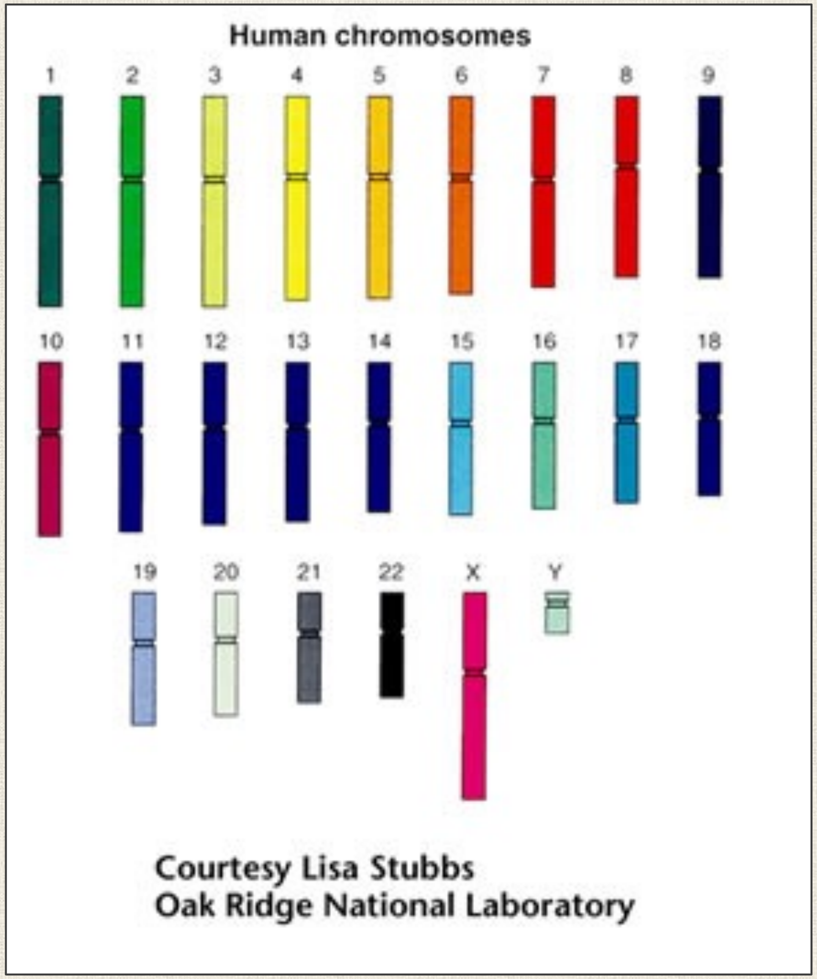
STOP: Any ideas for assembling a genome with multiple chromosomes?



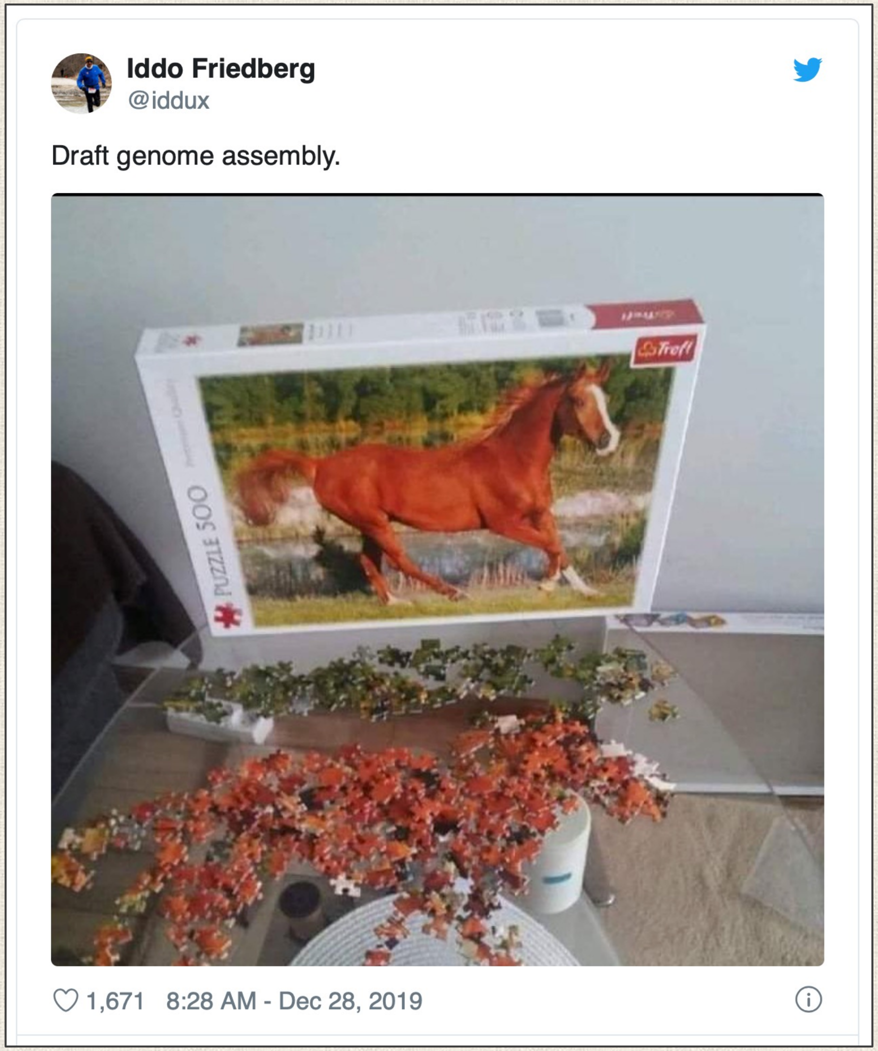
Genomes May Have Multiple Chromosomes

STOP: Any ideas for assembling a genome with multiple chromosomes?

Answer: In theory, we just find an Eulerian path in *n* different de Bruijn graphs…



Read Coverage is Never Perfect



Iddo Friedberg
@iddux

Draft genome assembly.

1,671 8:28 AM - Dec 28, 2019

Boosting Coverage through Read Breaking

```
ATGCCGTATGGACAACGACT
ATGCCGTATG
  GCCGTATGGA
     GTATGGACAA
          GACAACGACT
```

Note that these reads don't overlap perfectly, so building a de Bruijn graph will fail.

Boosting Coverage through Read Breaking

```
ATGCCGTATGGACAACGACT          ATGCCGTATGGACAACGACT
ATGCCGTATG                    ATGCC
  GCCGTATGGA                   TGCCG
     GTATGGACAA                 GCCGT
          GACAACGACT             CGTAT
                                  GTATG
```

Read breaking: Split each read into all its *k*-mer substrings (for a smaller value of *k*).

Boosting Coverage through Read Breaking

```
ATGCCGTATGGACAACGACT
ATGCCGTATG
  GCCGTATGGA
     GTATGGACAA
          GACAACGACT
```

```
ATGCCGTATGGACAACGACT
ATGCC
 TGCCG
  GCCGT
   CGTAT
    GTATG
     TATGG
      ATGGA
```

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```
ATGCCGTATGGACAACGACT
ATGCCGTATG
  GCCGTATGGA
     GTATGGACAA
          GACAACGACT
```

```
ATGCCGTATGGACAACGACT
ATGCC
 TGCCG
  GCCGT
   CGTAT
    GTATG
     TATGG
      ATGGA
       TGGAC
        GGACA
         GACAA
```

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```
ATGCCGTATGGACAACGACT
ATGCCGTATG
  GCCGTATGGA
     GTATGGACAA
          GACAACGACT
```

```
ATGCCGTATGGACAACGACT
ATGCC
 TGCCG
  GCCGT
   CGTAT
    GTATG
     TATGG
      ATGGA
       TGGAC
        GGACA
         GACAA
          ACAAC
           CAACG
            AACGA
             ACGAC
              CGACT
```

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```
ATGCCGTATGGACAACGACT
ATGCCGTATG
  GCCGTATGGA
     GTATGGACAA
          GACAACGACT
```

```
ATGCCGTATGGACAACGACT
ATGCC
 TGCCG
  GCCGT
   CGTAT
    GTATG
     TATGG
      ATGGA
       TGGAC
        GGACA
         GACAA
          ACAAC
           CAACG
            AACGA
             ACGAC
              CGACT
```

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```
ATGCCGTATGGACAACGACT
ATGCCGTATG
  GCCGTATGGA
     GTATGGACAA
          GACAACGACT
```

```
ATGCCGTATGGACAACGACT
ATGCC
 TGCCG
  GCCGT
   CGTAT
    GTATG
     TATGG
      ATGGA
       TGGAC
        GGACA
         GACAA
          ACAAC
           CAACG
            AACGA
             ACGAC
              CGACT
```

STOP: What are the trade-offs in choosing a value of *k*?

Boosting Coverage through Read Breaking

```
ATGCCGTATGGACAACGACT
ATGCCGTATG
  GCCGTATGGA
     GTATGGACAA
          GACAACGACT
```

```
ATGCCGTATGGACAACGACT
ATGCC
 TGCCG
  GCCGT
   CGTAT
    GTATG
     TATGG
      ATGGA
       TGGAC
        GGACA
         GACAA
          ACAAC
           CAACG
            AACGA
             ACGAC
              CGACT
```

Answer: The smaller the value of *k*, the higher our coverage will be, but also the more repeats and the more "tangled" our graph.

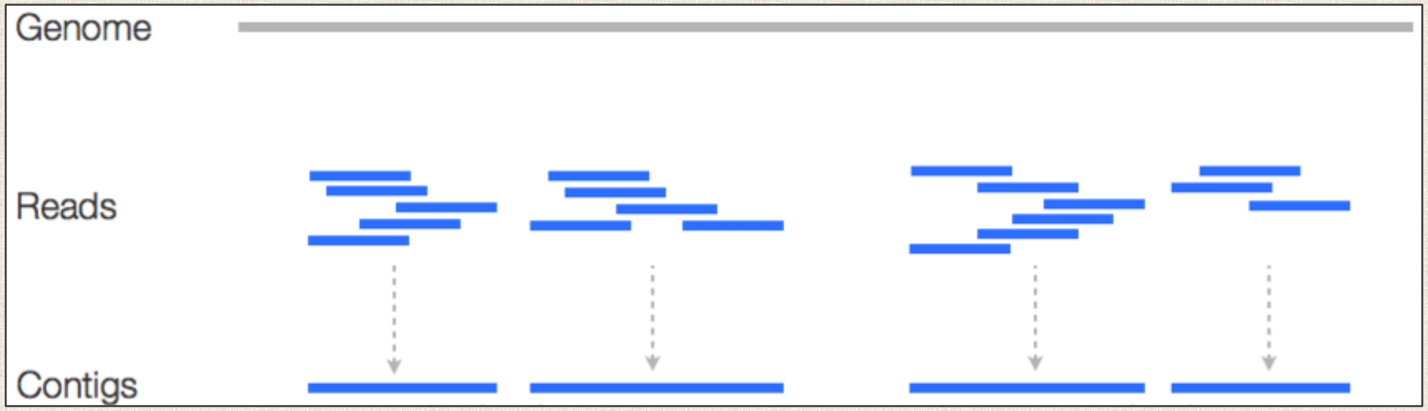
Assembling Contigs

Even after read breaking, most assemblies have gaps in their coverage, and we will not have a true Eulerian path in the de Bruijn graph.

Assembling Contigs

Even after read breaking, most assemblies have gaps in their coverage, and we will not have a true Eulerian path in the de Bruijn graph.

Real assembly software instead tries to infer (a small number of) **contigs:** contiguous genome segments.



Contigs Lurking in the de Bruijn Graph

A path in a graph is called **non-branching** if InDegree(*v*) = OutDegree(*v*) = 1 for each "intermediate" node *v* in the path.

Contigs Lurking in the de Bruijn Graph

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A **maximal non-branching path** is a non-branching path that cannot made longer in either direction.

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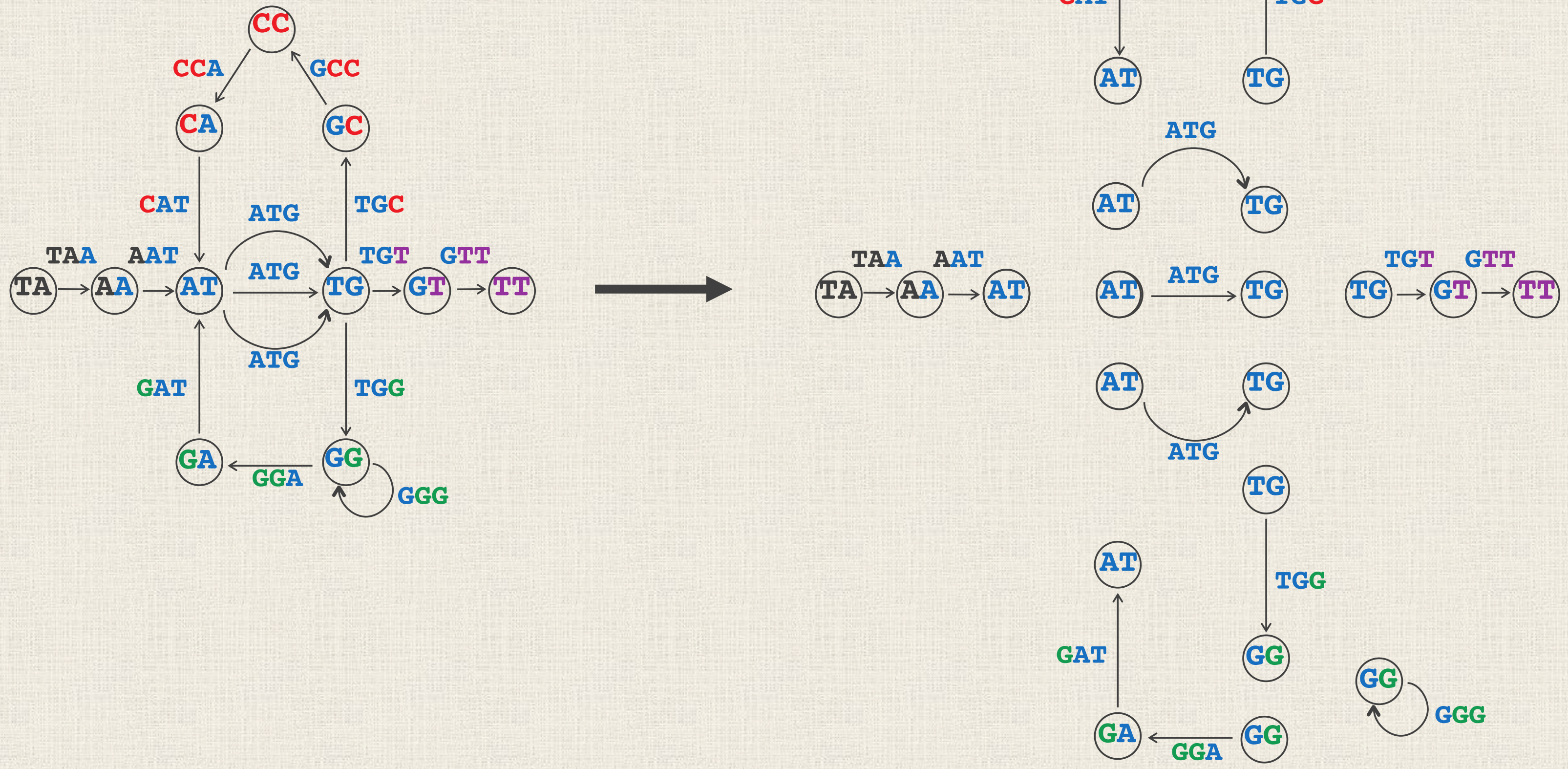
A **maximal non-branching path** is a non-branching path that cannot made longer in either direction.

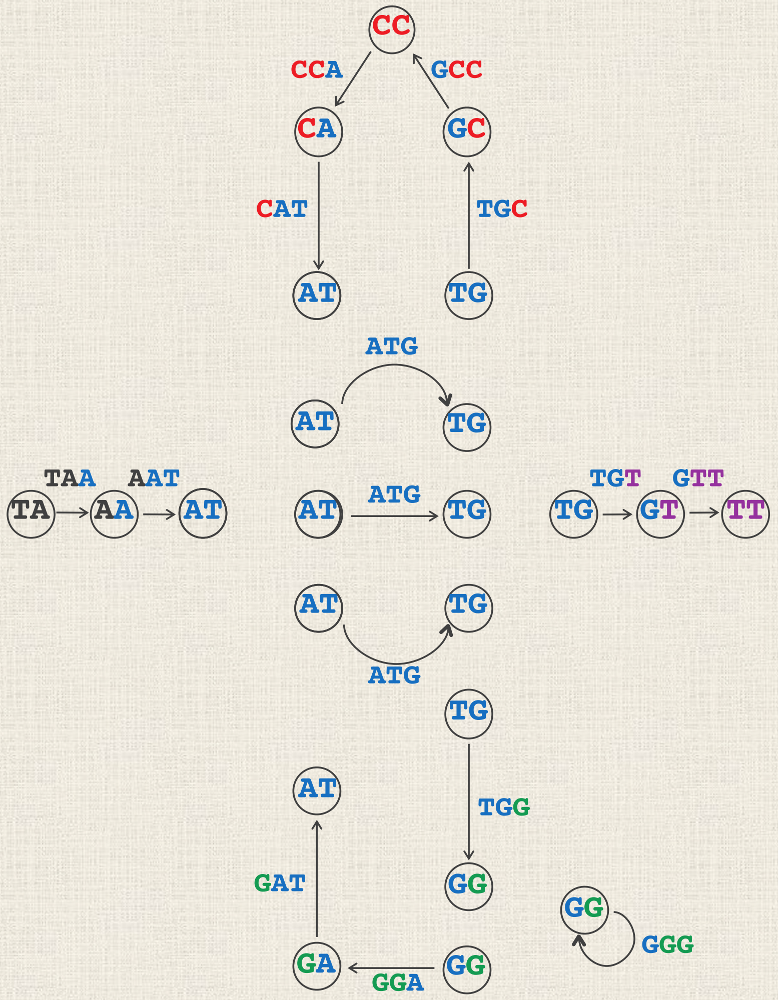
Note: In mathematics, "maximum" means "global maximum"; "maximal" means "local maximum".

Transforming dB Graph into Paths



Transforming dB Graph into Paths

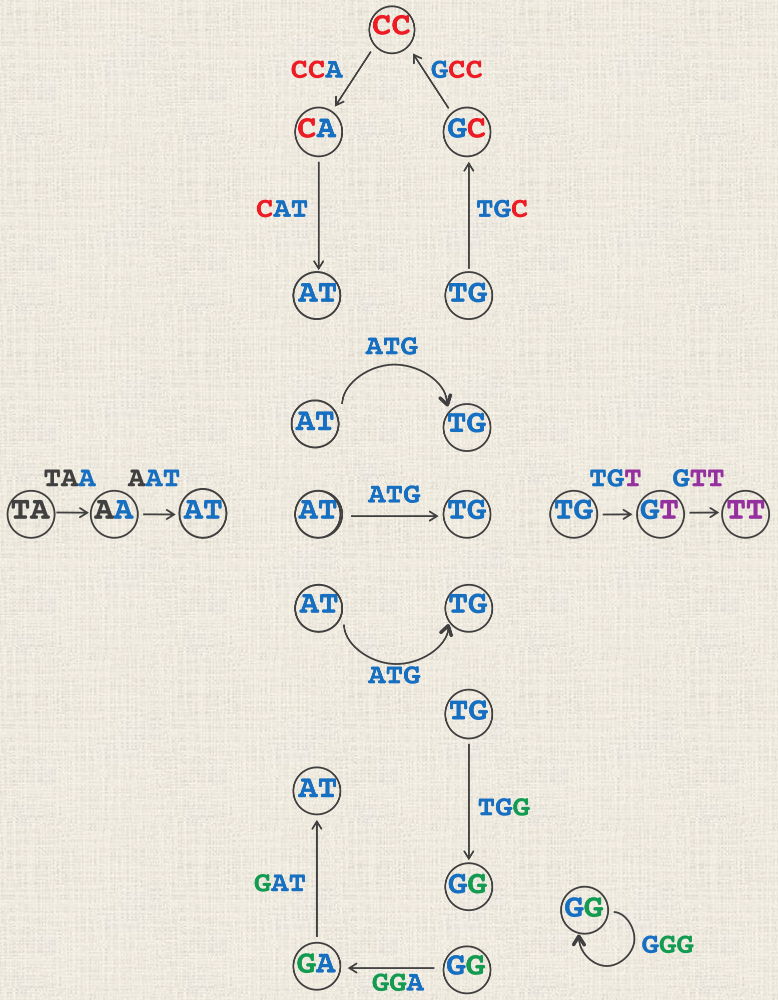
STOP: Why do you think we are interested in maximal non-branching paths in genome assembly?



Transforming dB Graph into Paths

STOP: Why do you think we are interested in maximal non-branching paths in genome assembly?

Answer: They represent "subpaths" that must be present in *any* assembly, and so we can be confident in them.



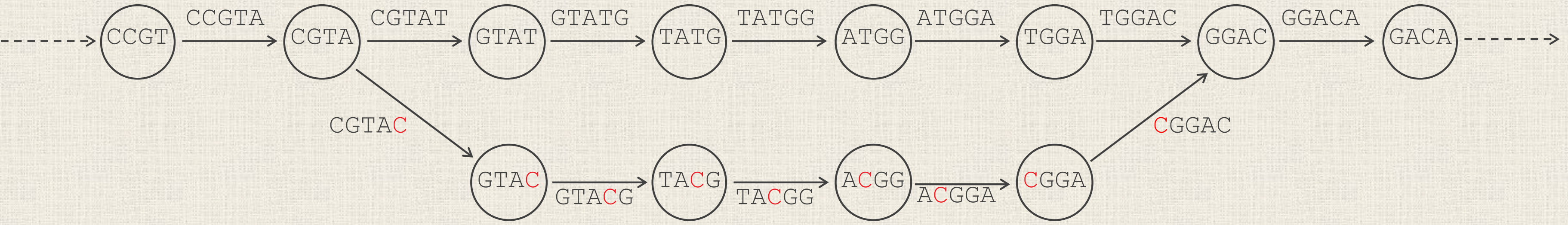
Assembling Error-Prone Reads

STOP: Say we sequence both the correct read `CGTATGGACA` and the incorrect read `CGTACGGACA`. What will we see in the de Bruijn graph after read breaking for $k = 5$?

Assembling Error-Prone Reads

STOP: Say we sequence both the correct read `CGTATGGACA` and the incorrect read `CGTACGGACA`. What will we see in the de Bruijn graph after read breaking for $k = 5$?

Answer: A "bubble"!



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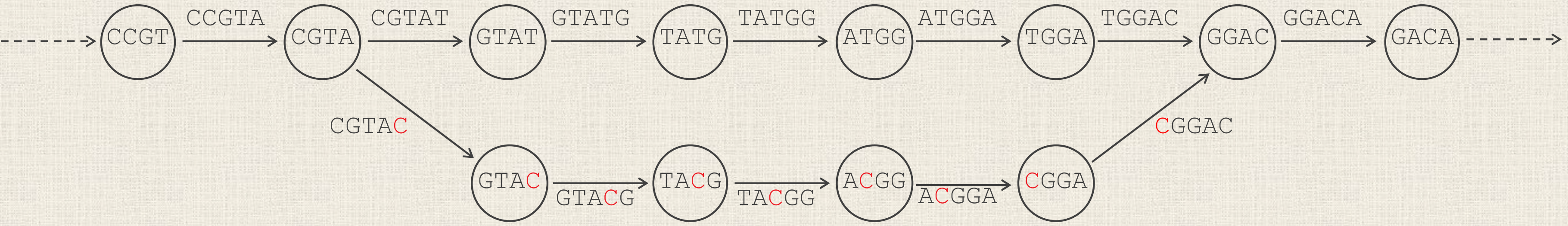
Popping Bubbles

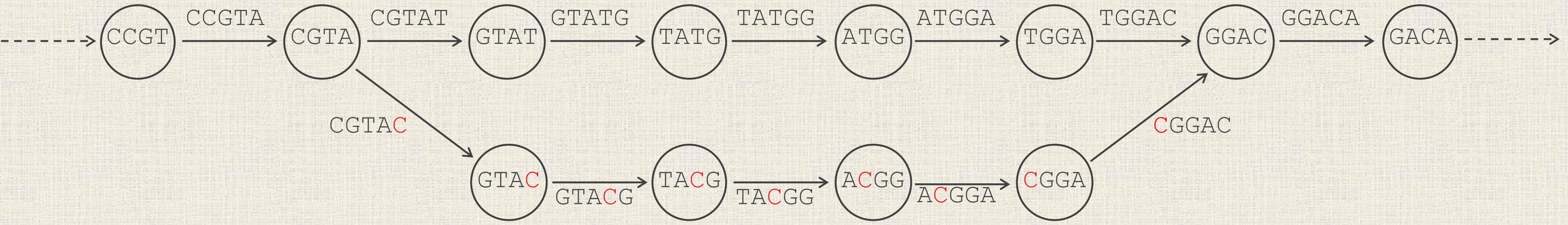
Bubble: Two disjoint short path (less than some threshold length) connecting the same pair of nodes in the de Bruijn graph.



Popping Bubbles

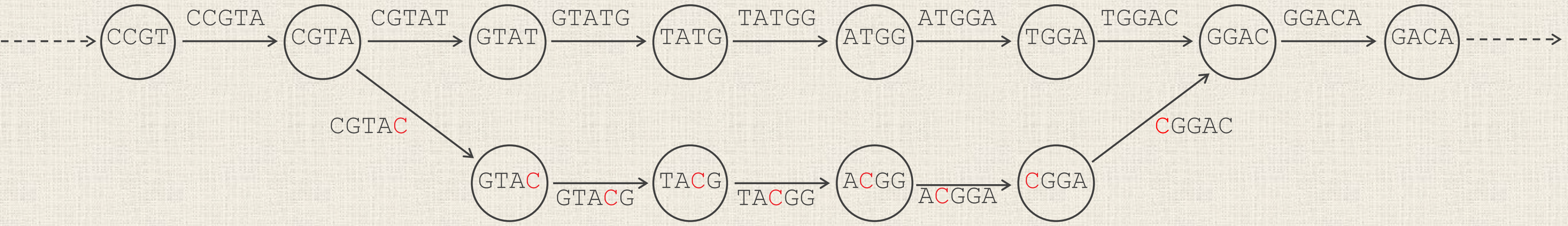
Bubble: Two disjoint short path (less than some threshold length) connecting the same pair of nodes in the de Bruijn graph.

STOP: How might we remove bubbles? What would cause your approach to go wrong?



Popping Bubbles

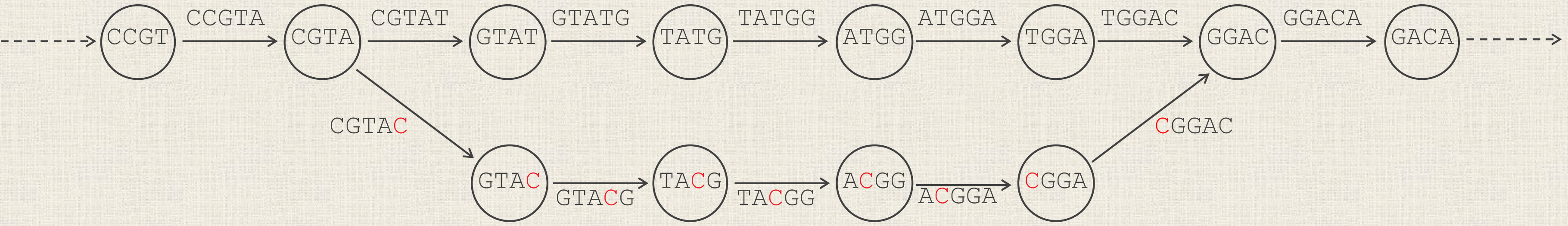
Inexact repeat: Repeated region in genome with minor variations; the variations look just like sequencing errors!



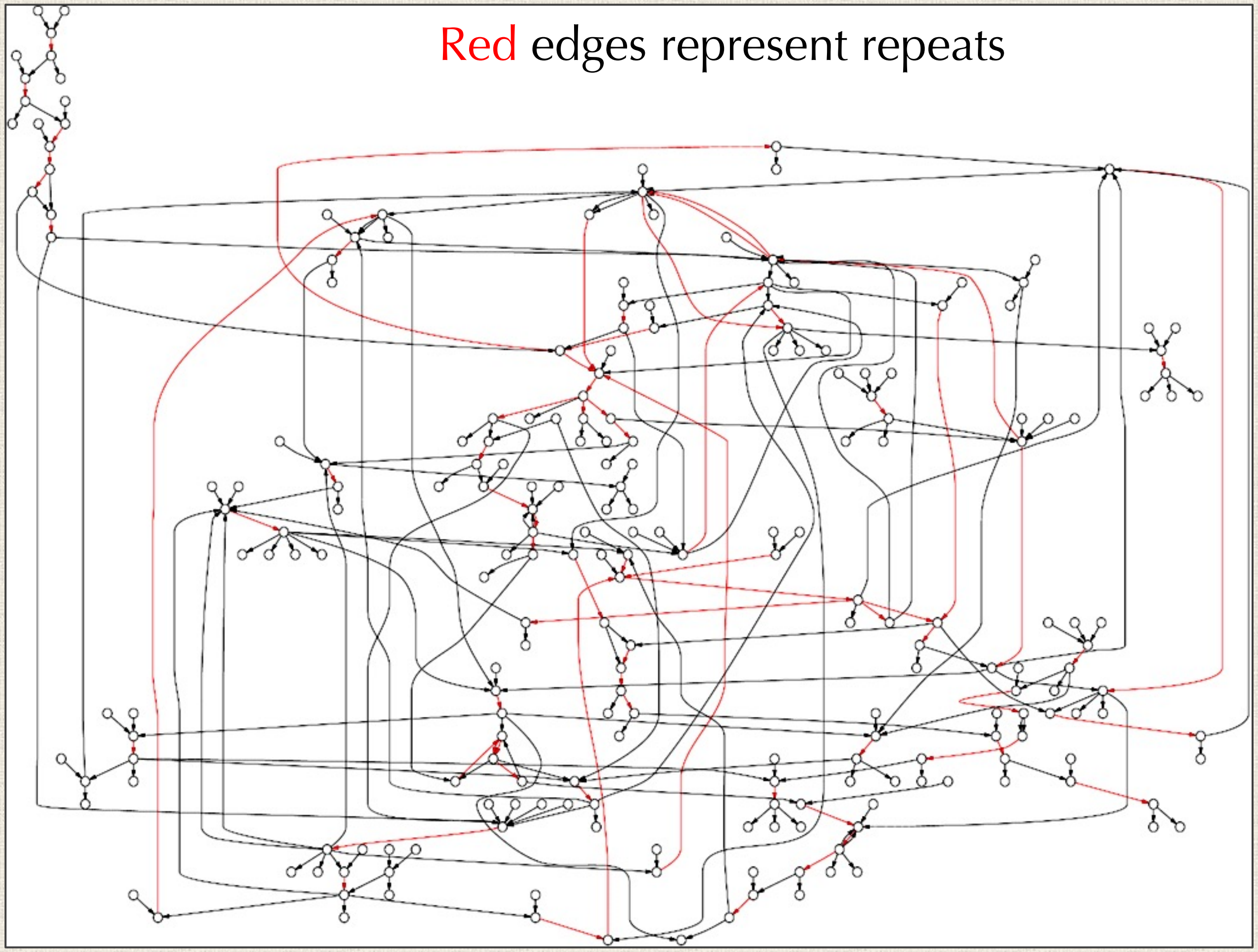
Popping Bubbles

Inexact repeat: Repeated region in genome with minor variations; the variations look just like sequencing errors!

Lower "multiplicity" paths are likely errors; this is one more benefit of higher coverage in assembly.

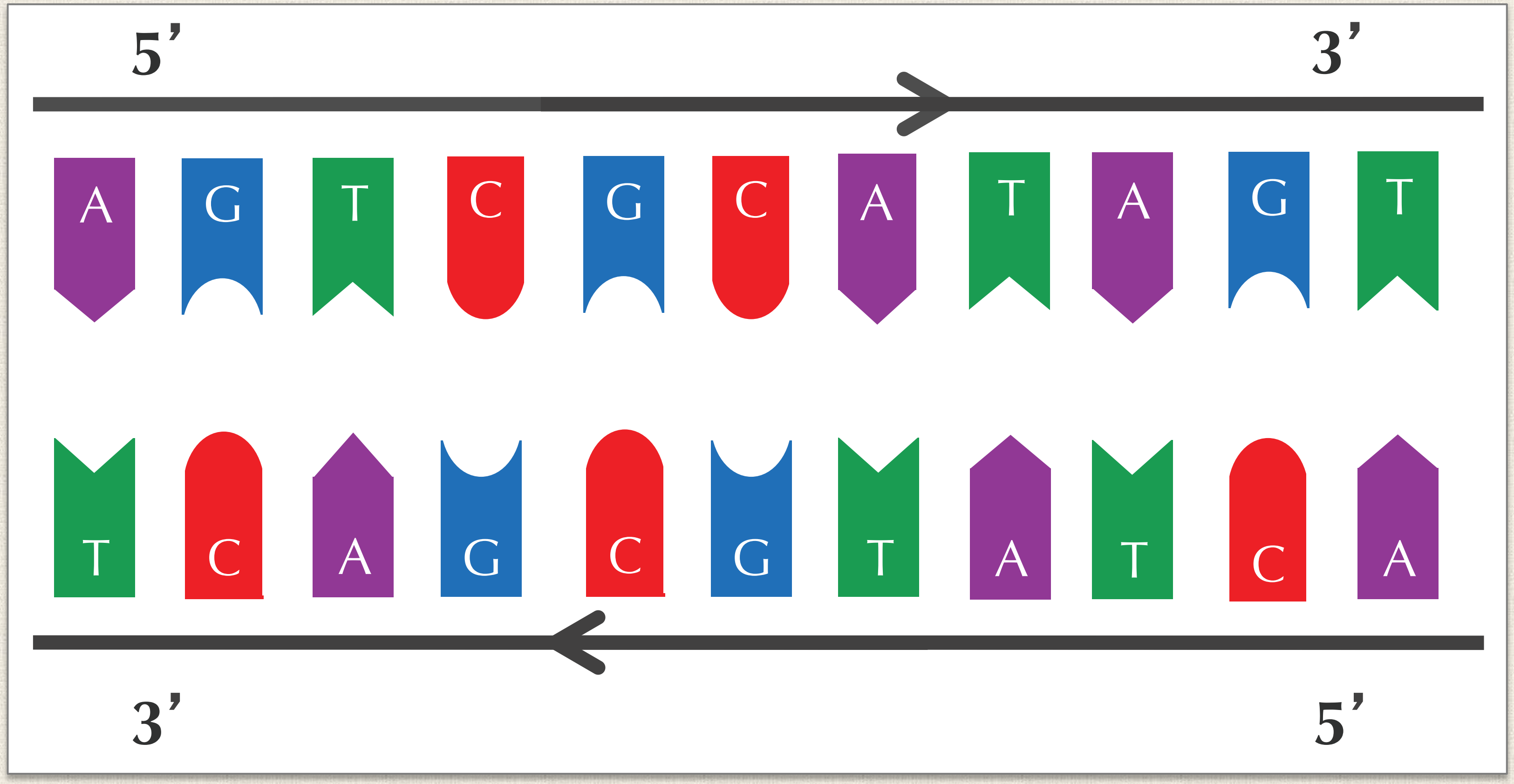


dB Graph of *N. meningitidis* (Bacterium) *After* Removing Bubbles



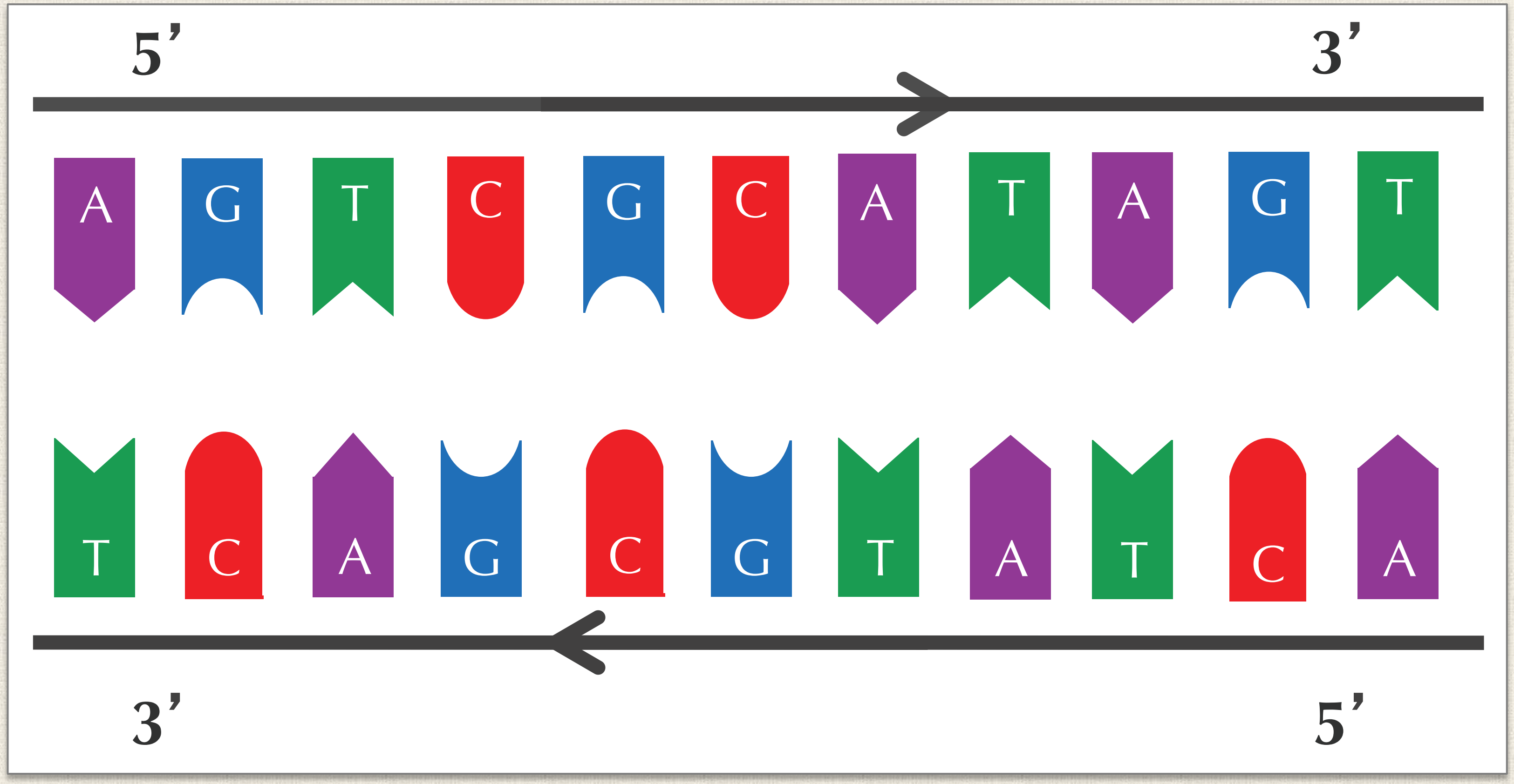
Pitfalls of Double-Stranded DNA

DNA is double-stranded, and the two strands are **reverse complements** of each other.



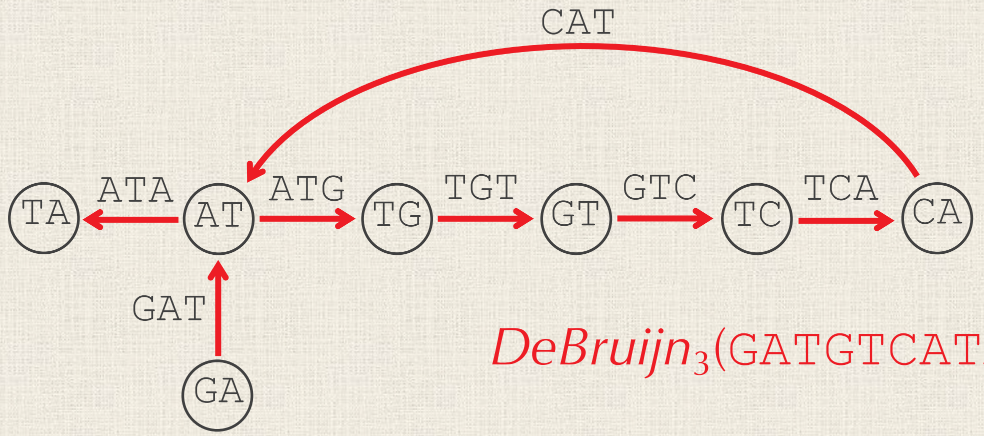
Pitfalls of Double-Stranded DNA

Reads may come from *either strand*, so we need to consider each read's reverse complement.

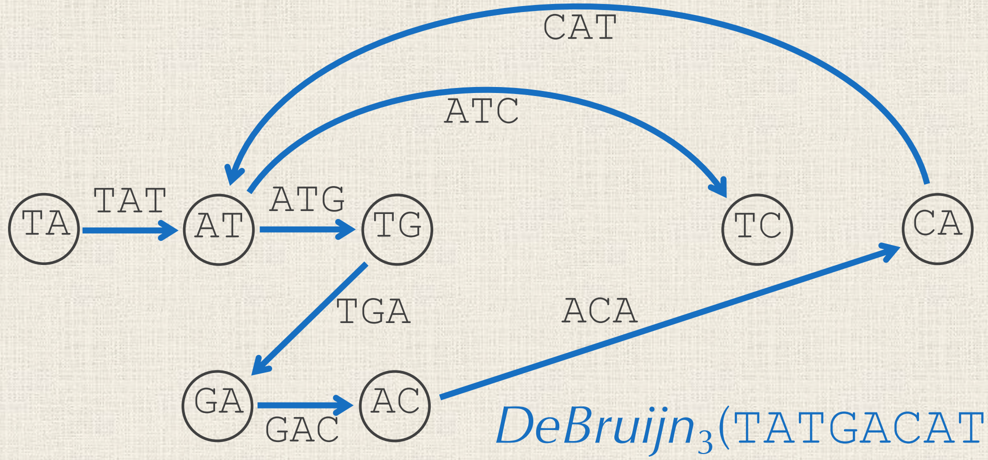


Pitfalls of Double-Stranded DNA

Note that this example is trivial if we had two de Bruijn graphs (one for the string, one for its reverse complement).



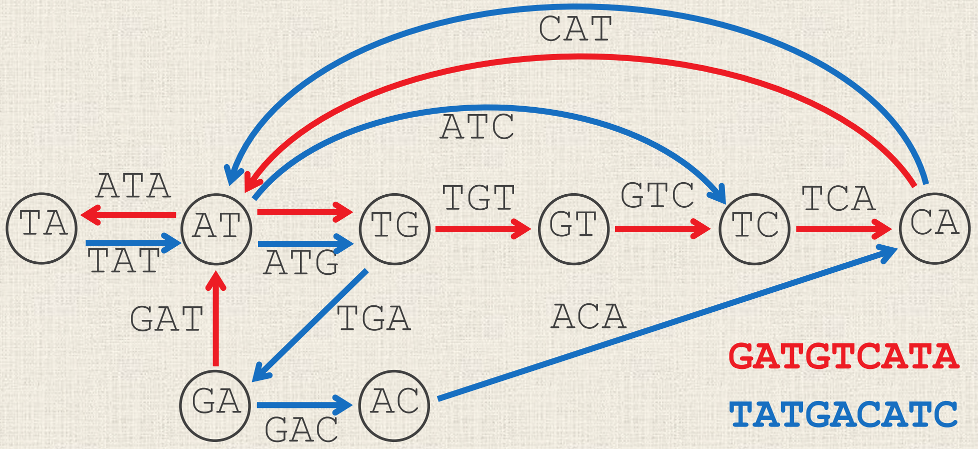
DeBruijn$_3$(GATGTCATA)



DeBruijn$_3$(TATGACATC)

Pitfalls of Double-Stranded DNA

The reality is that we see the amalgamation of both graphs.



Pitfalls of Double-Stranded DNA

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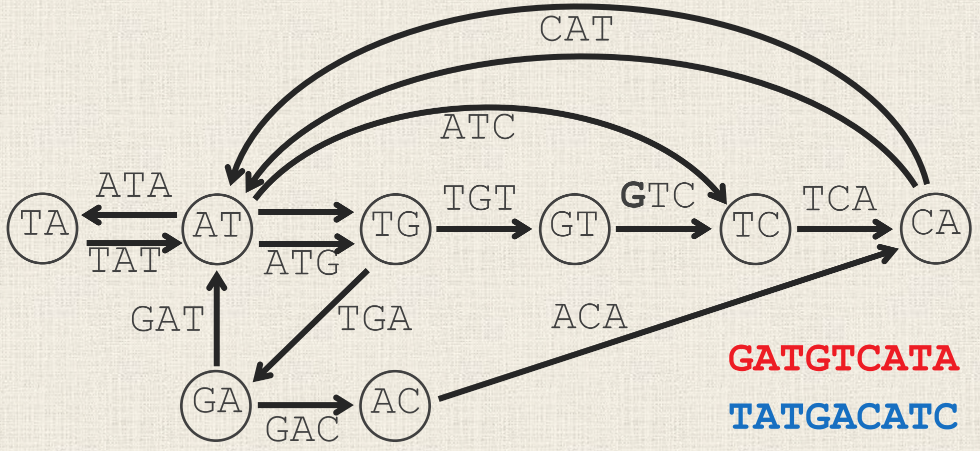
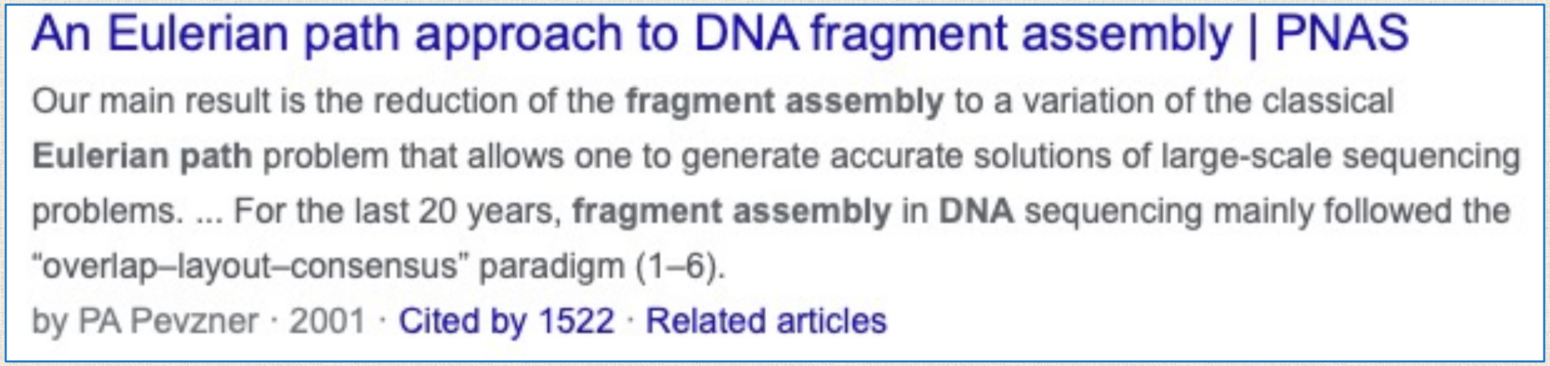


Even though neither string has a repeat, the graph becomes tangled because ATG and CAT are **inverted repeats:** the strings are reverse complements of each other.

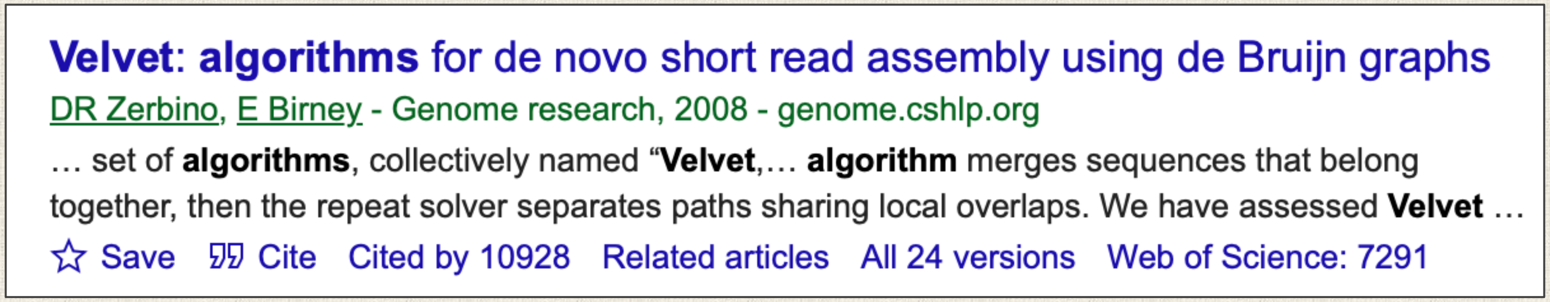
de Bruijn Assembly in Real Research



An Eulerian path approach to DNA fragment assembly | PNAS

Our main result is the reduction of the **fragment assembly** to a variation of the classical **Eulerian path** problem that allows one to generate accurate solutions of large-scale sequencing problems. ... For the last 20 years, **fragment assembly** in **DNA** sequencing mainly followed the "overlap–layout–consensus" paradigm (1–6).

by PA Pevzner · 2001 · Cited by 1522 · Related articles



Velvet: **algorithms** for de novo short read assembly using de Bruijn graphs

DR Zerbino, E Birney - Genome research, 2008 - genome.cshlp.org

… set of **algorithms**, collectively named "**Velvet**,… **algorithm** merges sequences that belong together, then the repeat solver separates paths sharing local overlaps. We have assessed **Velvet** …

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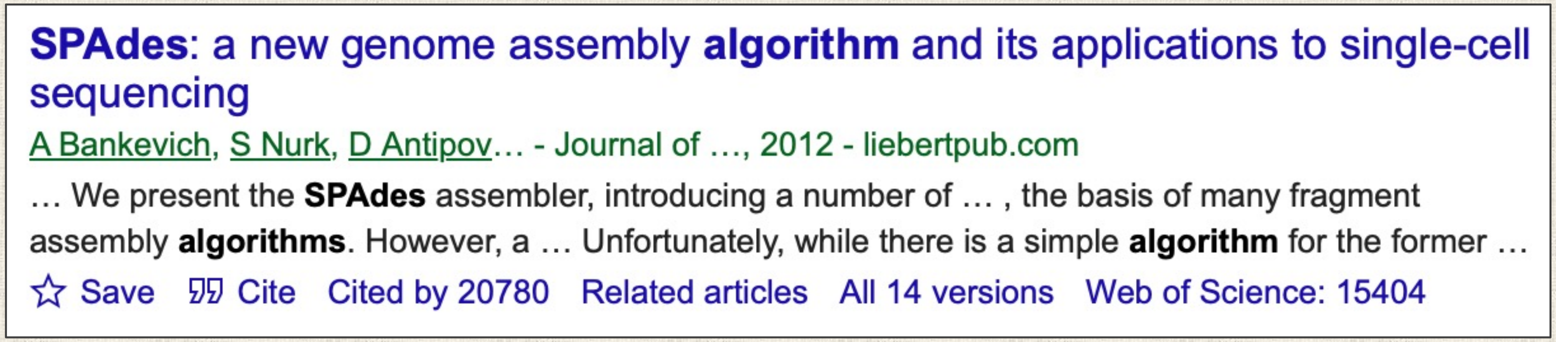

SPAdes: a new genome assembly **algorithm** and its applications to single-cell sequencing

A Bankevich, S Nurk, D Antipov… - Journal of …, 2012 - liebertpub.com

… We present the **SPAdes** assembler, introducing a number of … , the basis of many fragment assembly **algorithms**. However, a … Unfortunately, while there is a simple **algorithm** for the former …

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