CSE 549: Genome Assembly
De Bruijn Graph

Stony Brook University

All slides in this lecture **not** marked with "*" courtesy of Ben Langmead.

Real-world assembly methods

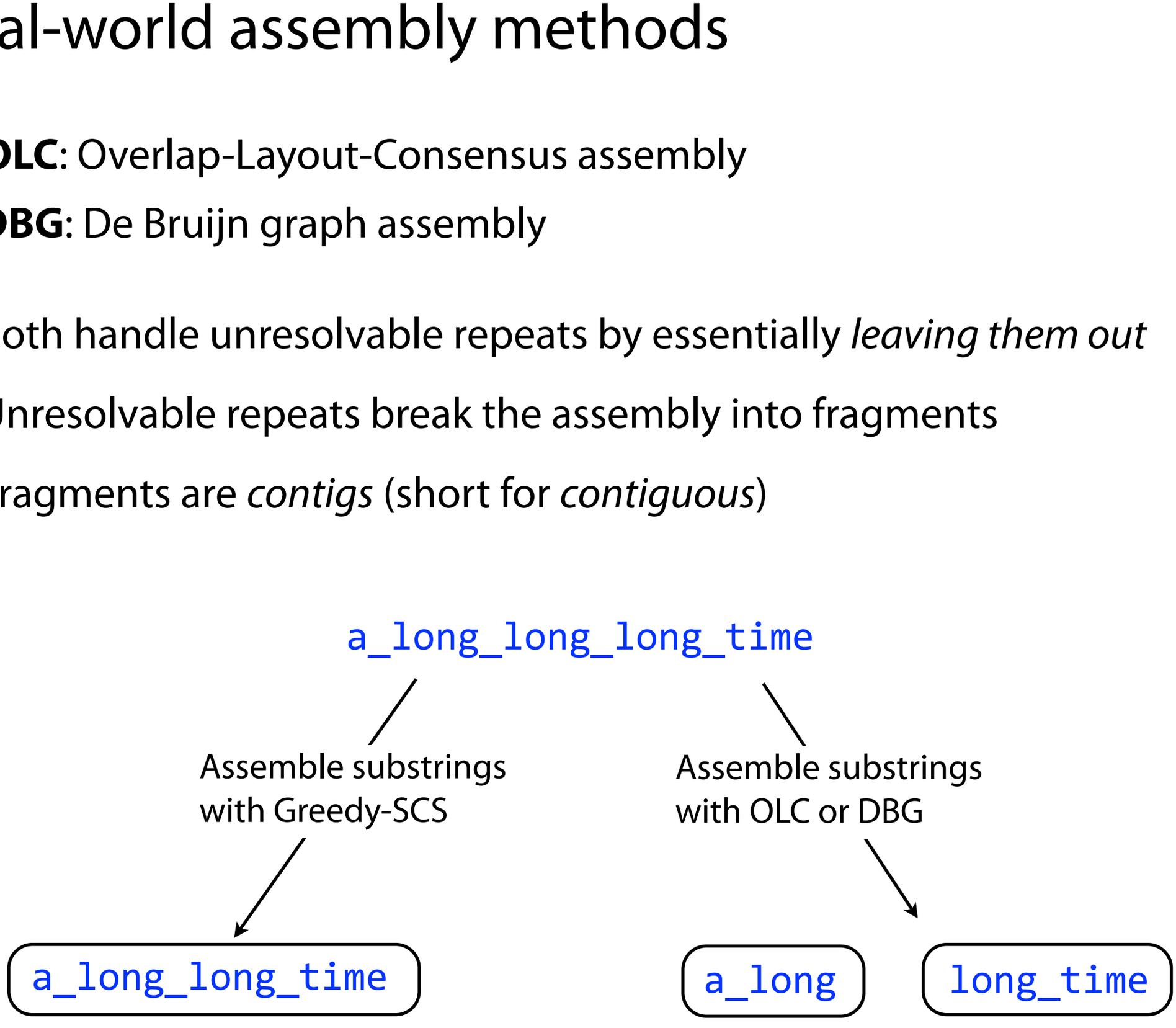
OLC: Overlap-Layout-Consensus assembly

DBG: De Bruijn graph assembly

Both handle unresolvable repeats by essentially *leaving them out*

Unresolvable repeats break the assembly into fragments

Fragments are *contigs* (short for *contiguous*)



De Bruijn graph assembly

A formulation conceptually similar to overlapping/SCS, but has some potentially helpful properties not shared by SCS.

k-mer

"*k*-mer" is a substring of length *k*

S: GGCGATTCATCG

A 4-mer of *S*: ATTC

All 3-mers of *S*:

GGC
GCG
CGA
GAT
ATT
TTC
TCA
CAT
ATC
TCG

mer: from Greek meaning "part"

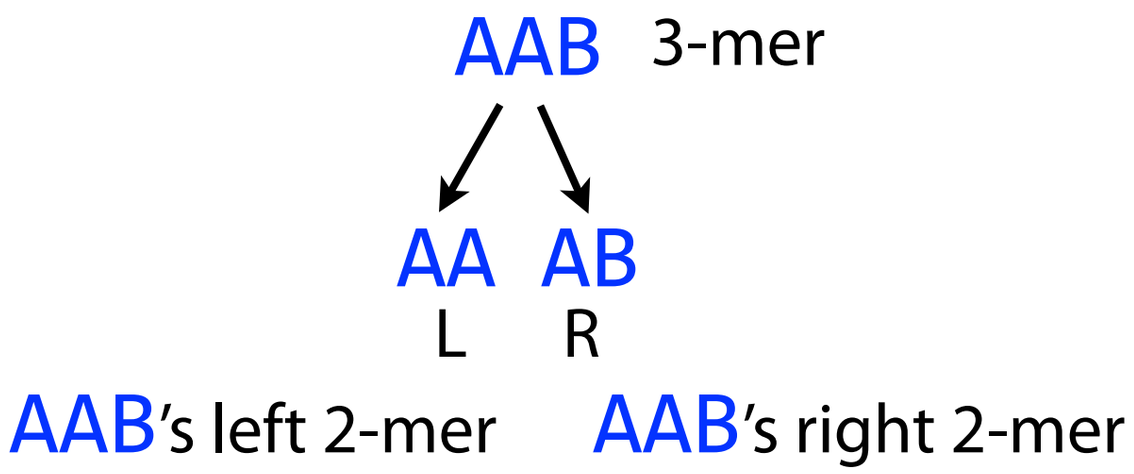
I'll use "*k*-1-mer" to refer to a substring of length *k* - 1

De Bruijn graph

As usual, we start with a collection of reads, which are substrings of the reference genome.

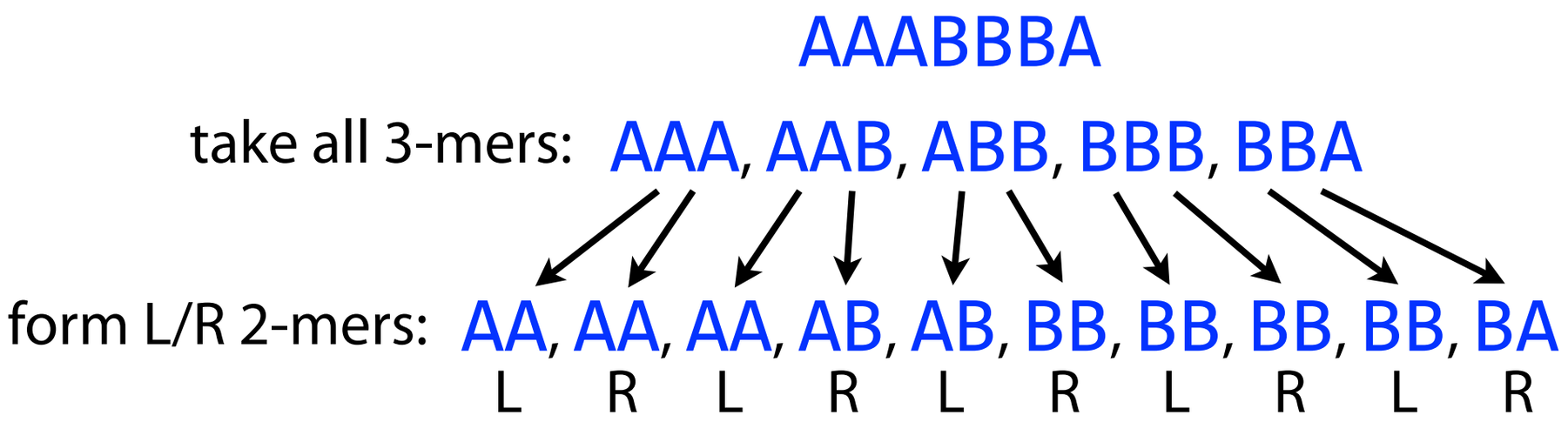
AAA, AAB, ABB, BBB, BBA

AAB is a *k*-mer (*k* = 3). AA is its *left* *k*-1-mer, and AB is its right *k*-1-mer.

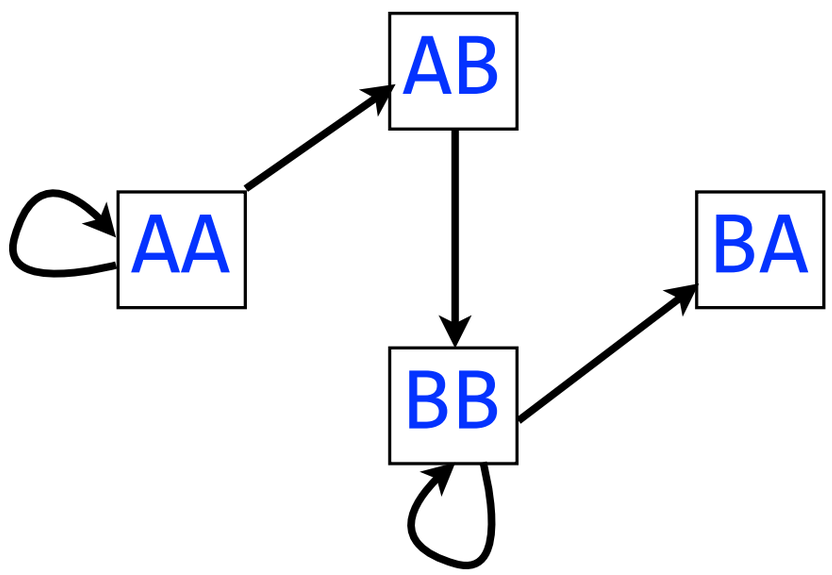


De Bruijn graph

Take each length-3 input string and split it into two overlapping substrings of length 2. Call these the *left* and *right 2-mers*.

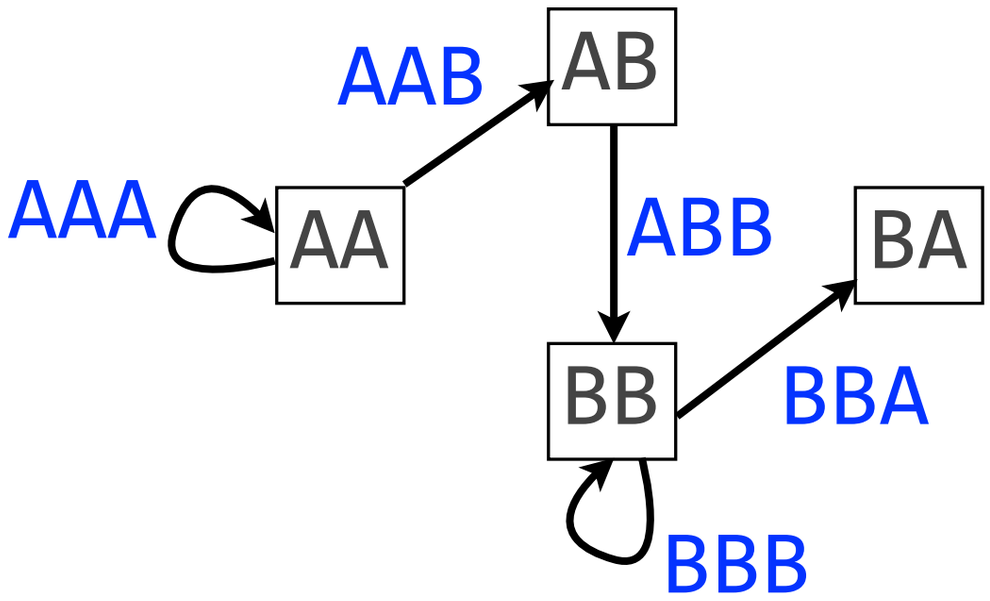


Let 2-mers be nodes in a new graph. Draw a directed edge from each left 2-mer to corresponding right 2-mer:



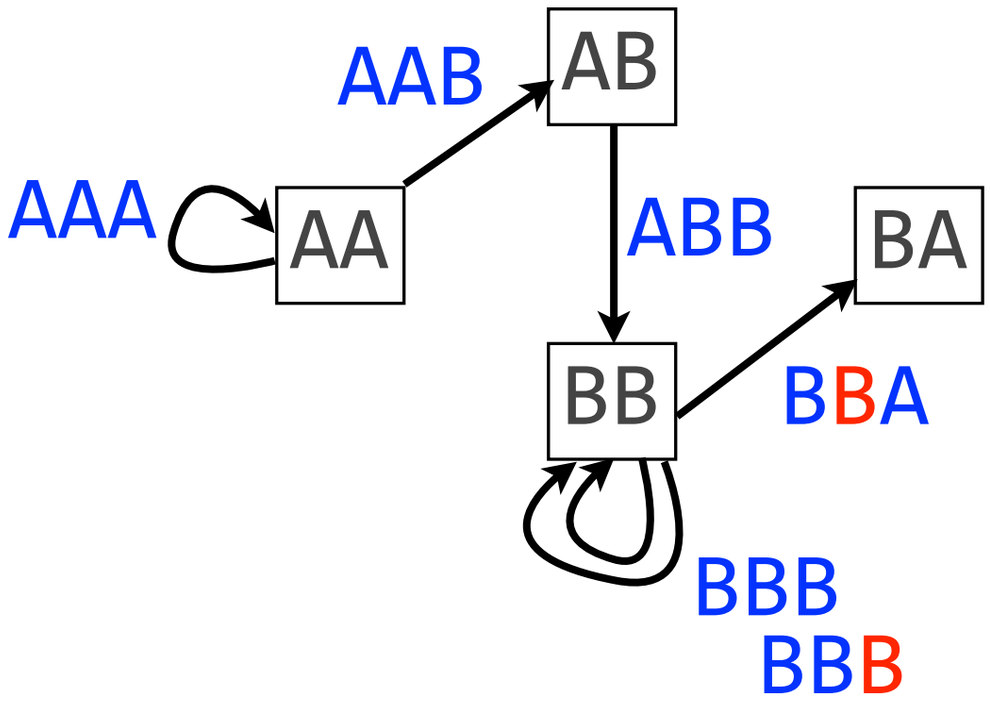
Each *edge* in this graph corresponds to a length-3 input string

De Bruijn graph



An edge corresponds to an overlap (of length *k*-2) between two *k*-1 mers.
More precisely, it corresponds to a *k*-mer from the input.

De Bruijn graph



If we add one more B to our input string: AAABBBBA, and rebuild the De Bruijn graph accordingly, we get a *multiedge*.

Directed multigraph

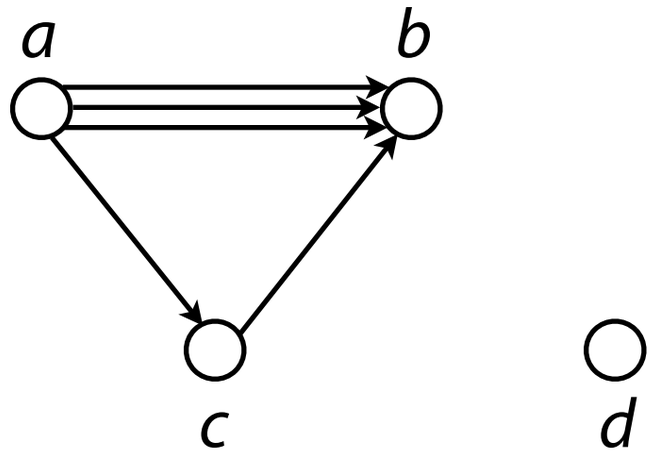
Directed **multigraph** $G(V, E)$ consists of set of *vertices, V* and **multiset** of *directed edges, E*

Otherwise, like a directed graph

Node's *indegree* = # incoming edges

Node's *outdegree* = # outgoing edges

De Bruijn graph is a directed multigraph



$V = \{ a, b, c, d \}$

$E = \{ (a, b), (a, b), (a, b), (a, c), (c, b) \}$

Repeated

Eulerian walk definitions and statements

Node is *balanced* if indegree equals outdegree

Node is *semi-balanced* if indegree differs from outdegree by 1

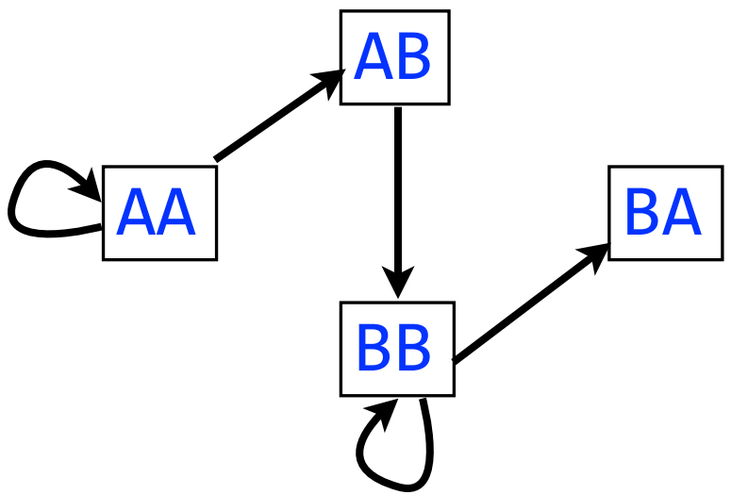
Graph is *connected* if each node can be reached by some other node

Eulerian walk visits each edge exactly once

Not all graphs have Eulerian walks. Graphs that do are *Eulerian*.
(For simplicity, we won't distinguish Eulerian from semi-Eulerian.)

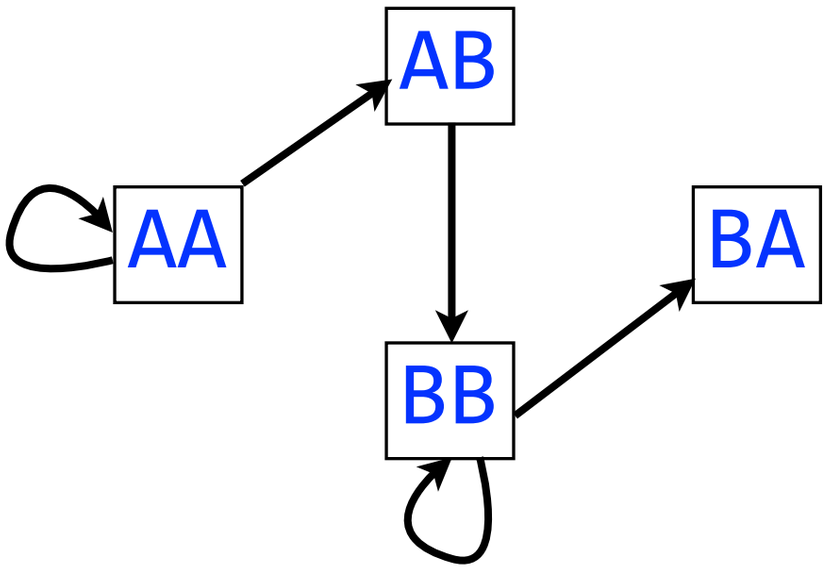
A directed, connected graph is Eulerian if and only if it has at most 2 semi-balanced nodes and all other nodes are balanced

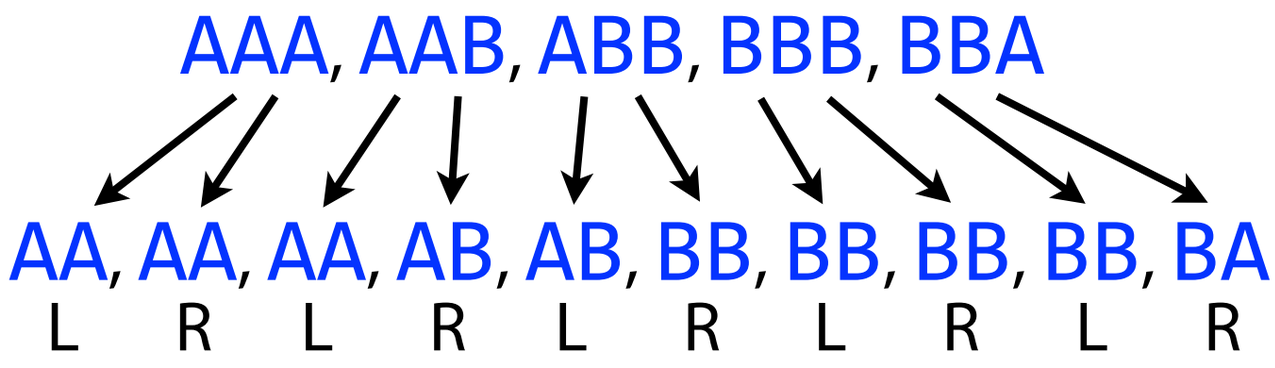
Jones and Pevzner section 8.8



De Bruijn graph

Back to our De Bruijn graph





Is it Eulerian? Yes

Argument 1: AA → AA → AB → BB → BB → BA

Argument 2: AA and BA are semi-balanced, AB and BB are balanced

De Bruijn graph

A procedure for making a De Bruijn graph for a genome

Assume *perfect sequencing* where each length-*k* substring is sequenced exactly once with no errors

Pick a substring length *k*: 5

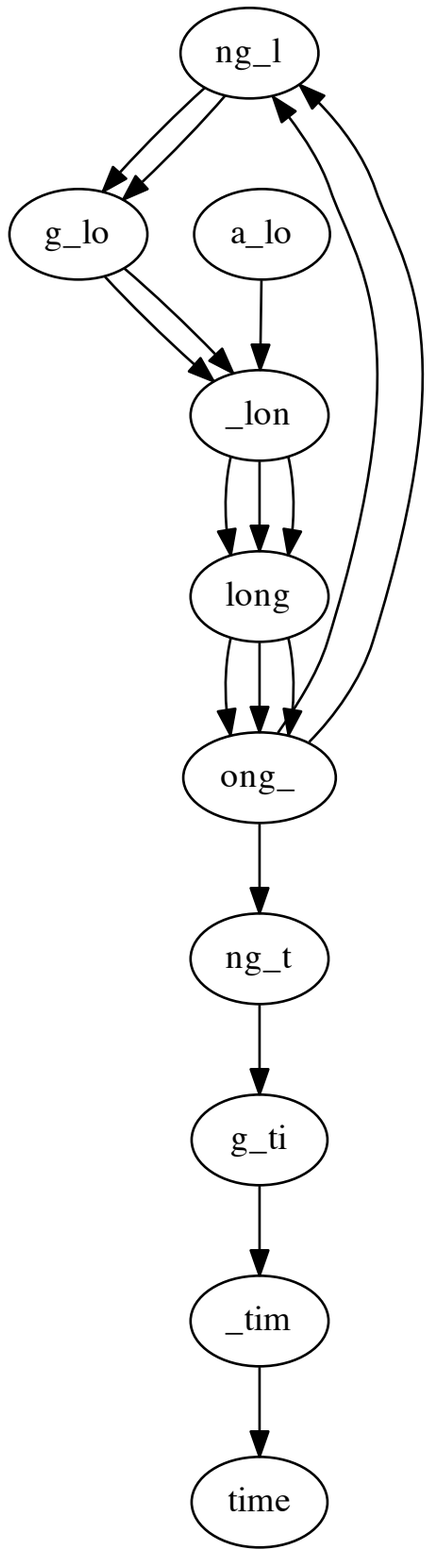
Start with an input string: `a_long_long_long_time`

Take each *k* mer and split into left and right *k*-1 mers

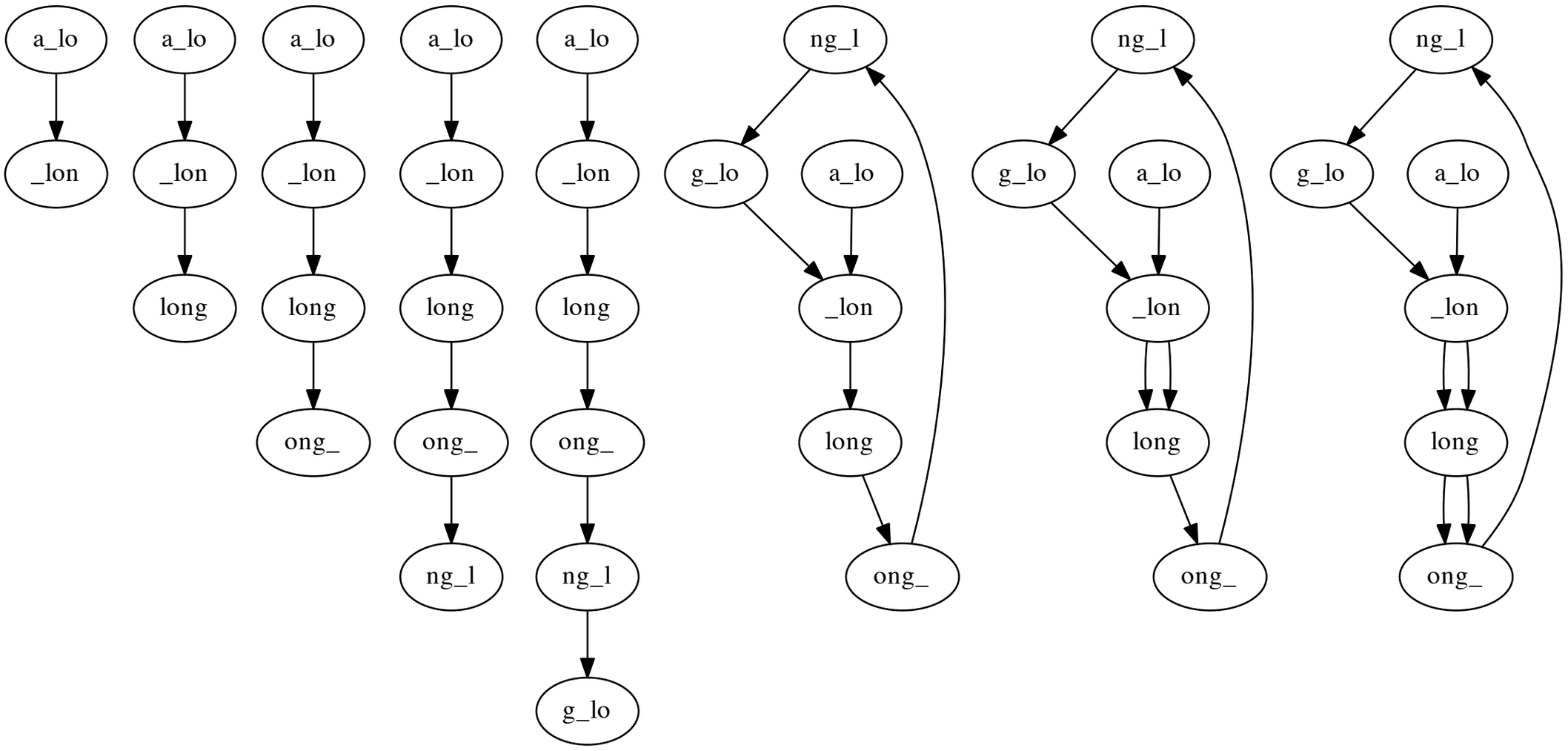
`long_`

`long ong_`

Add k-1 mers as nodes to De Bruijn graph (if not already there), add edge from left *k*-1 mer to right *k*-1 mer



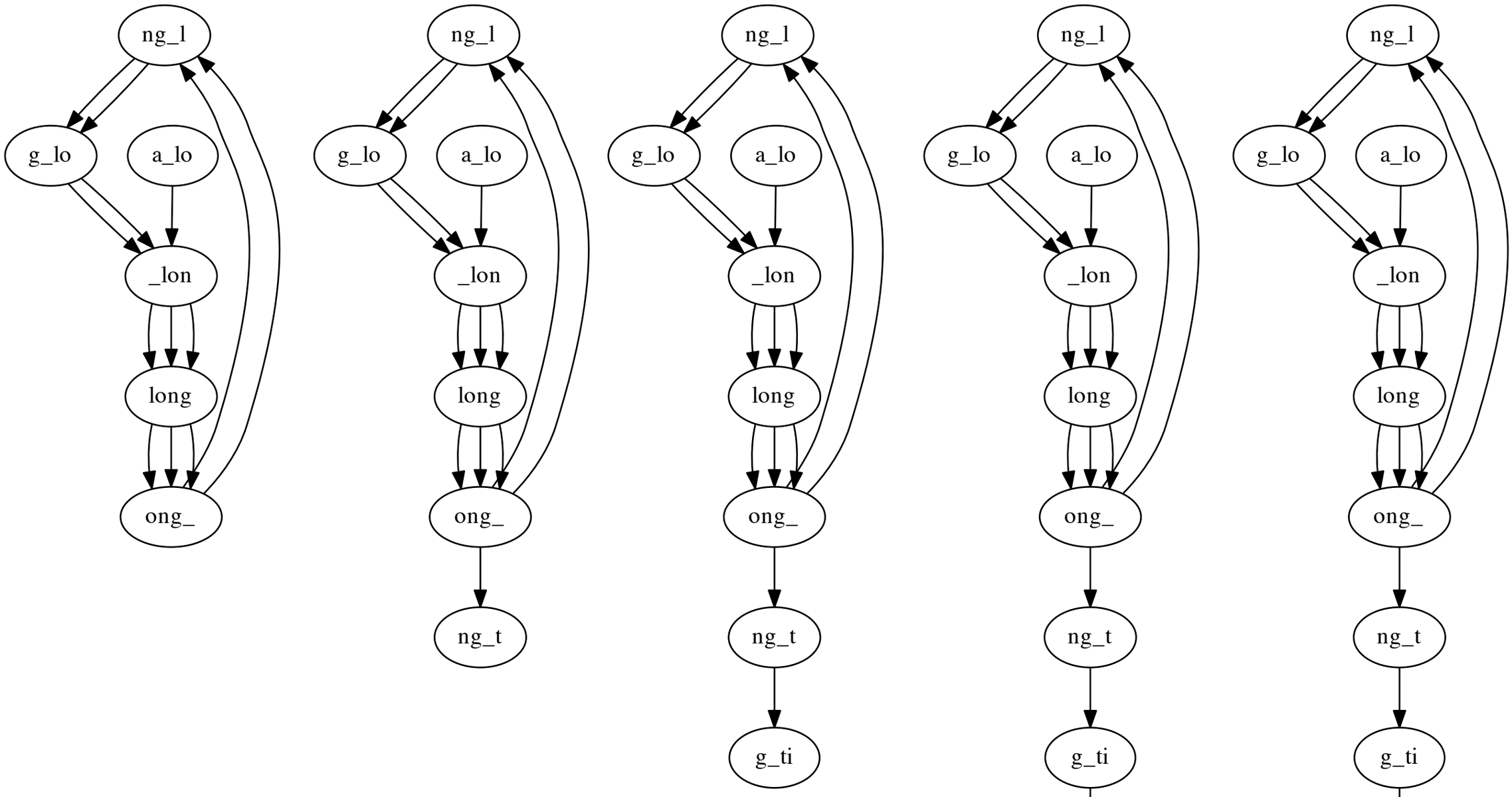
De Bruijn graph



First 8 *k*-mer additions, $k = 5$

`a_long_long_long_time`

De Bruijn graph



Last 5 *k*-mer additions, *k* = 5

`a_long_long_long_time`

Finished graph

De Bruijn graph

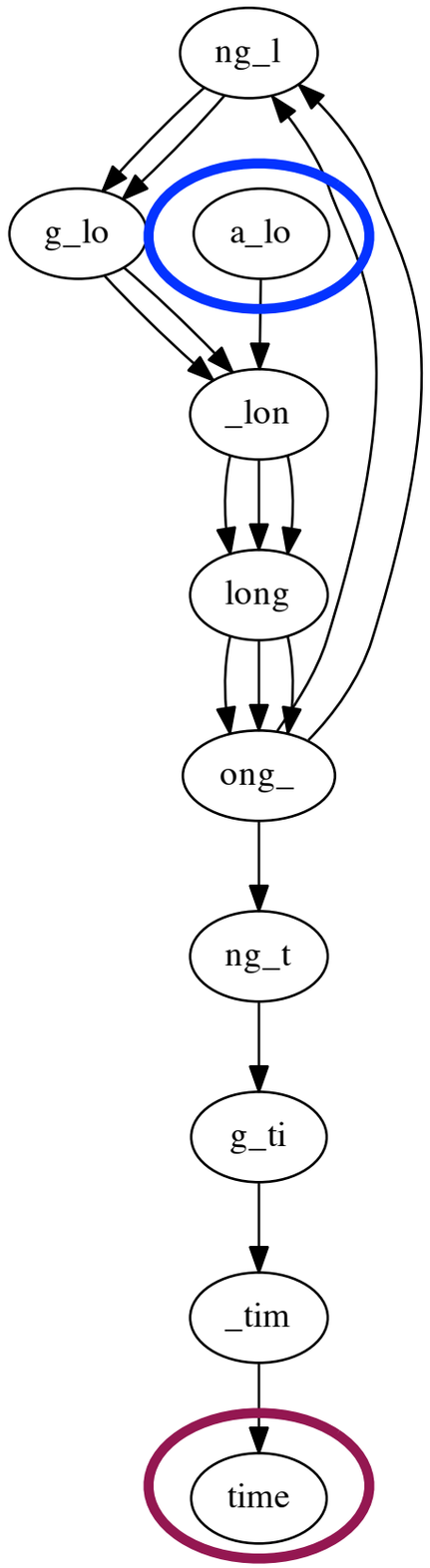
With perfect sequencing, this procedure always yields an Eulerian graph. Why?

Node for *k*-1-mer from left end is semi-balanced with one more outgoing edge than incoming *

Node for *k*-1-mer at right end is semi-balanced with one more incoming than outgoing *

Other nodes are balanced since # times *k*-1-mer occurs as a left *k*-1-mer = # times it occurs as a right *k*-1-mer

* Unless genome is circular



De Bruijn graph implementation

```
class DeBruijnGraph:
    """ A De Bruijn multigraph built from a collection of strings.
        User supplies strings and k-mer length k.  Nodes of the De
        Bruijn graph are k-1-mers and edges join a left k-1-mer to a
        right k-1-mer. """

    @staticmethod
    def chop(st, k):
        """ Chop a string up into k mers of given length """
        for i in xrange(0, len(st)-(k-1)): yield st[i:i+k]

    class Node:
        """ Node in a De Bruijn graph, representing a k-1 mer """
        def __init__(self, km1mer):
            self.km1mer = km1mer

        def __hash__(self):
            return hash(self.km1mer)

    def __init__(self, strIter, k):
        """ Build De Bruijn multigraph given strings and k-mer length k """
        self.G = {}     # multimap from nodes to neighbors
        self.nodes = {} # maps k-1-mers to Node objects
        self.k = k
        for st in strIter:
            for kmer in self.chop(st, k):
                km1L, km1R = kmer[:-1], kmer[1:]
                nodeL, nodeR = None, None
                if km1L in self.nodes:
                    nodeL = self.nodes[km1L]
                else:
                    nodeL = self.nodes[km1L] = self.Node(km1L)
                if km1R in self.nodes:
                    nodeR = self.nodes[km1R]
                else:
                    nodeR = self.nodes[km1R] = self.Node(km1R)
                self.G.setdefault(nodeL, []).append(nodeR)
```

Chop string into *k*-mers

For each *k*-mer, find left and right *k*-1-mers

Create corresponding nodes (if necessary) and add edge

De Bruijn graph

For Eulerian graph, Eulerian walk can be found in O(| *E* |) time. | *E* | is # edges.

Convert graph into one with Eulerian *cycle* (add an edge to make all nodes balanced), then use this recursive procedure

Insight: If C is a cycle in an Eulerian graph, then after removing edges of C, remaining connected components are also Eulerian

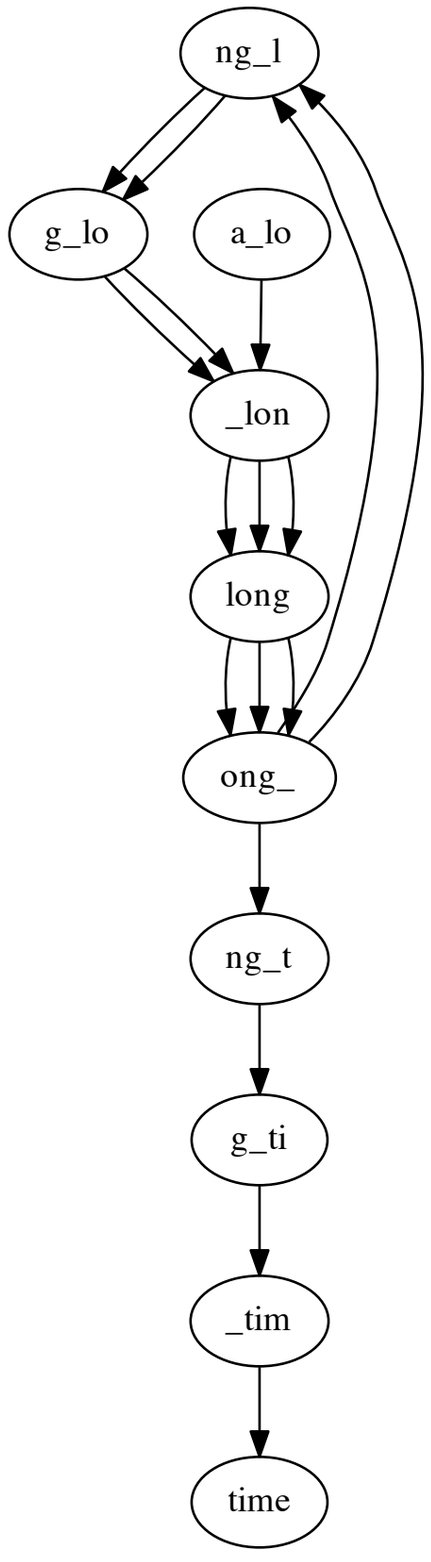
```
# Make all nodes balanced, if not already

tour = []
# Pick arbitrary node
src = g.iterkeys().next()

def __visit(n):
    while len(g[n]) > 0:
        dst = g[n].pop()
        __visit(dst)
    tour.append(n)

__visit(src)
# Reverse order, omit repeated node
tour = tour[::-1][:-1]

# Turn tour into walk, if necessary
```

http://www.algorithmist.com/index.php/Eulerian_tour

De Bruijn graph

Full illustrative De Bruijn graph and Eulerian walk:

http://nbviewer.ipython.org/7237207



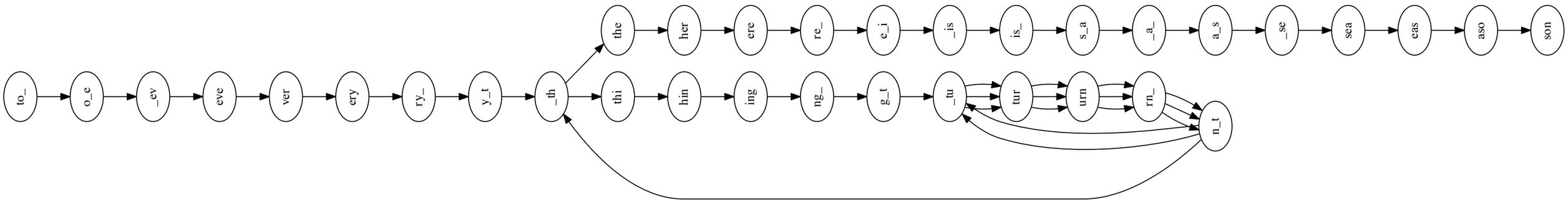
Example where Eulerian walk gives correct answer for small *k* whereas Greedy-SCS could spuriously collapse repeat:

```
>>> G = DeBruijnGraph(["a_long_long_long_time"], 5)
>>> print G.eulerianWalkOrCycle()
['a_lo', '_lon', 'long', 'ong_', 'ng_l', 'g_lo',
'_lon', 'long', 'ong_', 'ng_l', 'g_lo', '_lon',
'long', 'ong_', 'ng_t', 'g_ti', '_tim', 'time']
```

De Bruijn graph

Another example Eulerian walk:

```
>>> st = "to_every_thing_turn_turn_turn_there_is_a_season"
>>> G = DeBruijnGraph([st], 4)
>>> path = G.eulerianWalkOrCycle()
>>> superstring = path[0] + ''.join(map(lambda x: x[-1], path[1:]))
>>> print superstring
to_every_thing_turn_turn_turn_there_is_a_season
```

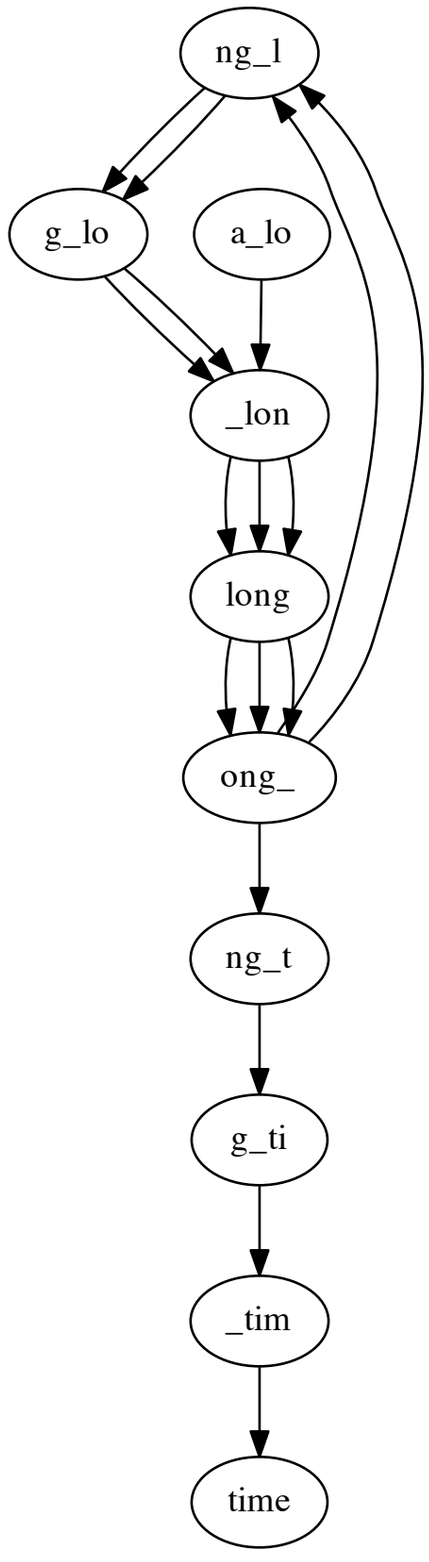


Recall: This is not generally possible or tractable in the overlap/SCS formulation

De Bruijn graph

Assuming perfect sequencing, procedure yields graph with Eulerian walk that can be found efficiently.

We saw cases where Eulerian walk corresponds to the original superstring. Is this always the case?



De Bruijn graph

No: graph can have multiple Eulerian walks, only one of which corresponds to original superstring

Right: graph for ZABCDABEFABY, $k = 3$

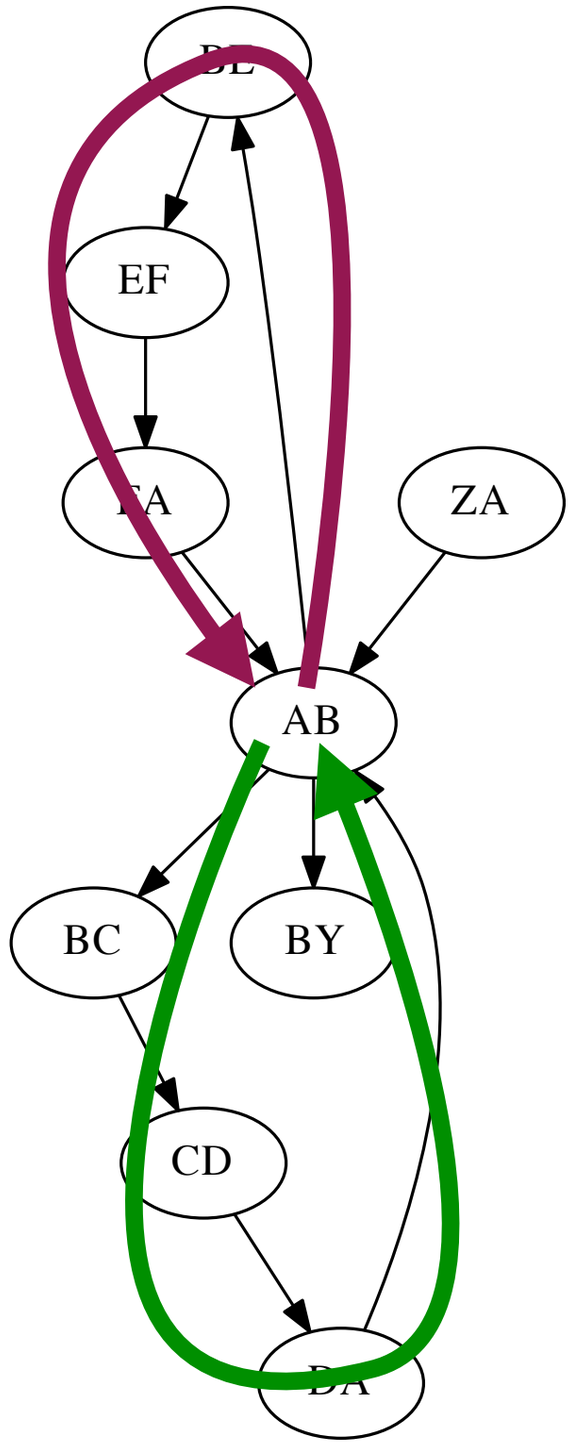
Alternative Eulerian walks:

ZA → AB → BE → EF → FA → AB → BC → CD → DA → AB → BY

ZA → AB → BC → CD → DA → AB → BE → EF → FA → AB → BY

These correspond to two edge-disjoint directed cycles joined by node AB

AB is a repeat: ZABCDABEFABY



De Bruijn graph

Case where $k = 4$ works:

```
>>> st = "to_every_thing_turn_turn_turn_there_is_a_season"
>>> G = DeBruijnGraph([st], 4)
>>> path = G.eulerianWalkOrCycle()
>>> superstring = path[0] + ''.join(map(lambda x: x[-1], path[1:]))
>>> print superstring
to_every_thing_turn_turn_turn_there_is_a_season
```

But $k = 3$ does not:

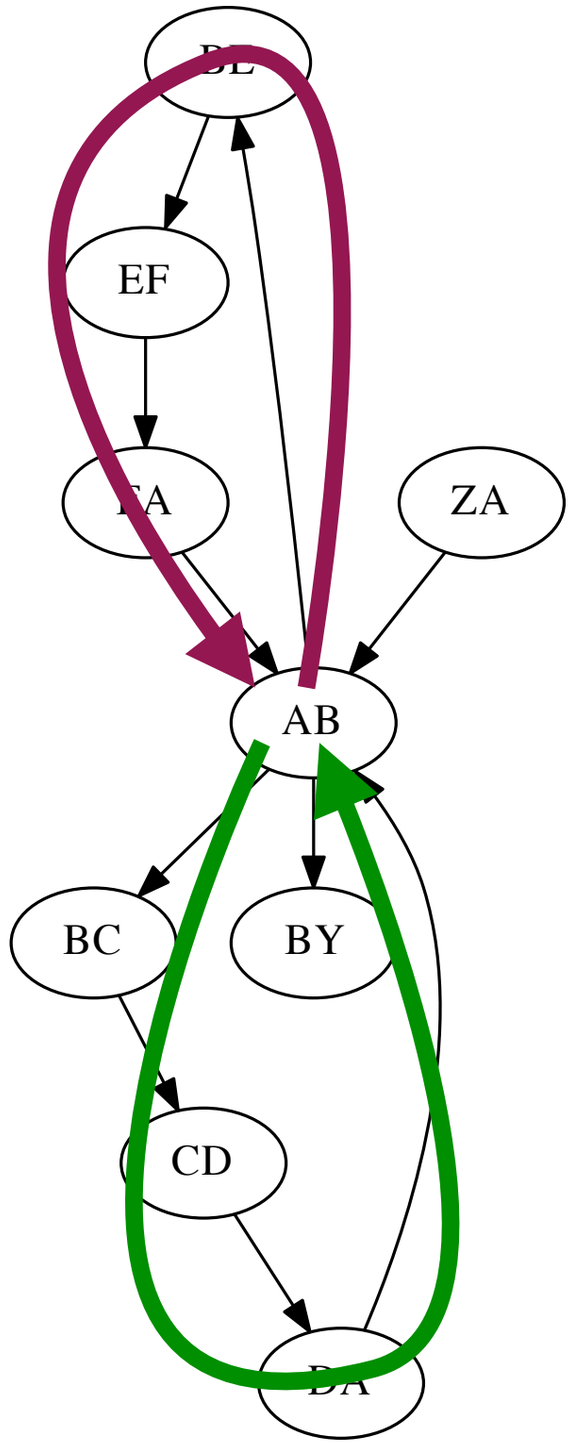
```
>>> st = "to_every_thing_turn_turn_turn_there_is_a_season"
>>> G = DeBruijnGraph([st], 3)
>>> path = G.eulerianWalkOrCycle()
>>> superstring = path[0] + ''.join(map(lambda x: x[-1], path[1:]))
>>> print superstring
to_every_turn_turn_thing_turn_there_is_a_season
```

Due to repeats that are unresolvable at $k = 3$

De Bruijn graph

This is the first sign that Eulerian walks can't solve all our problems

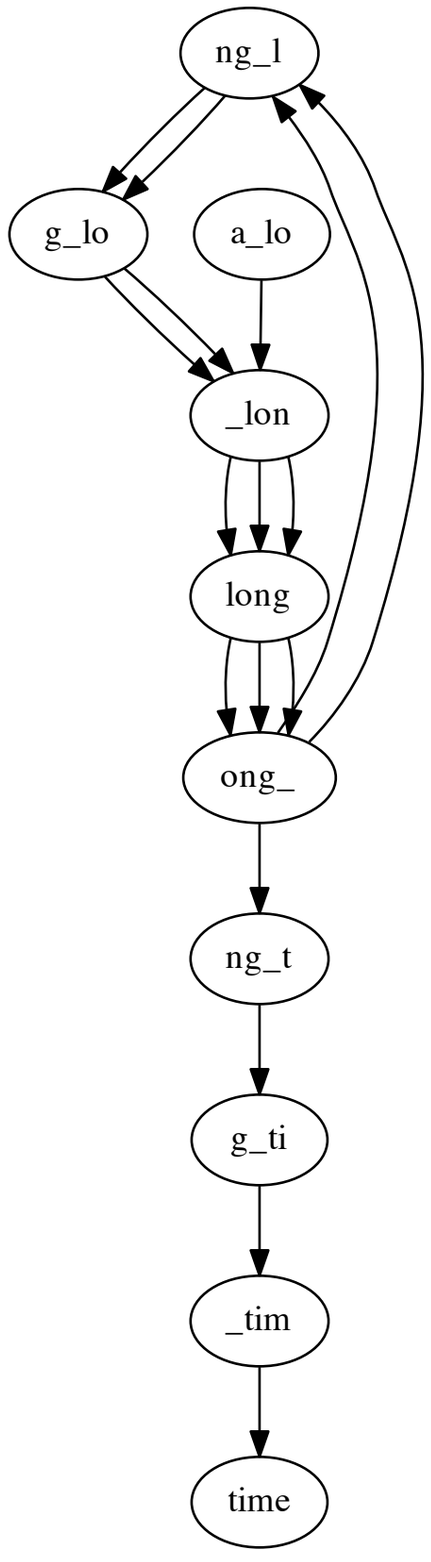
Other signs emerge when we think about how actual sequencing differs from our idealized construction



De Bruijn graph

Gaps in coverage can lead to *disconnected* graph

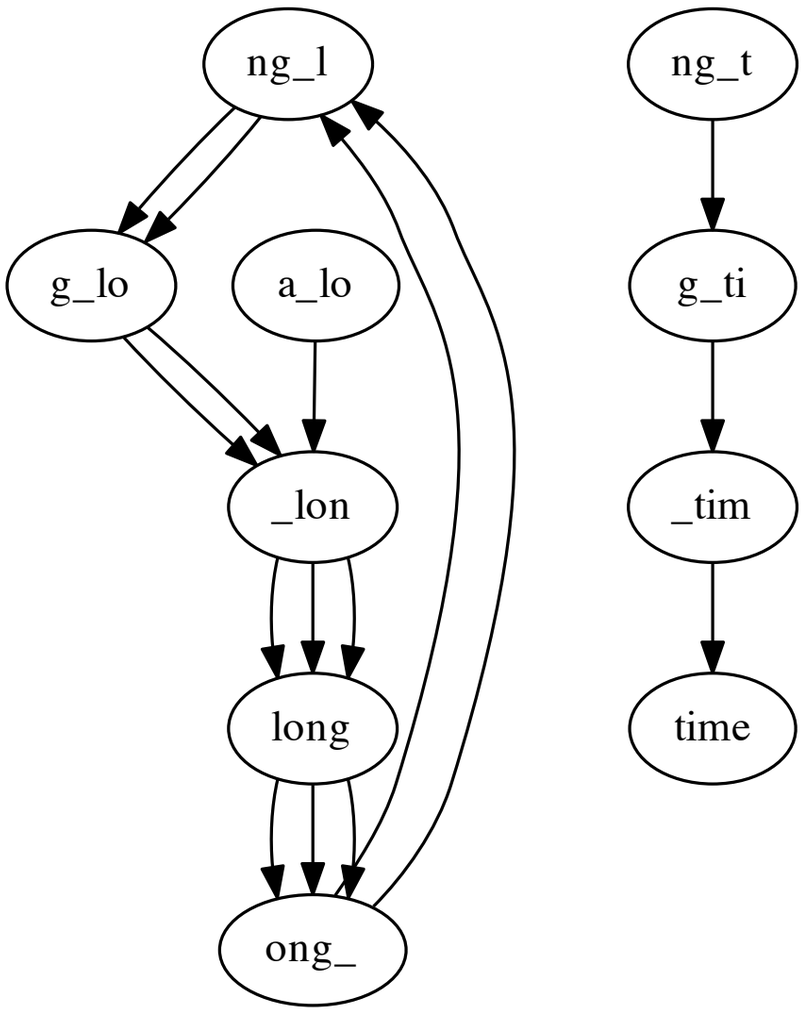
Graph for `a_long_long_long_time`, $k = 5$:



De Bruijn graph

Gaps in coverage can lead to *disconnected* graph

Graph for `a_long_long_long_time`, $k = 5$ but *omitting* `ong_t` :



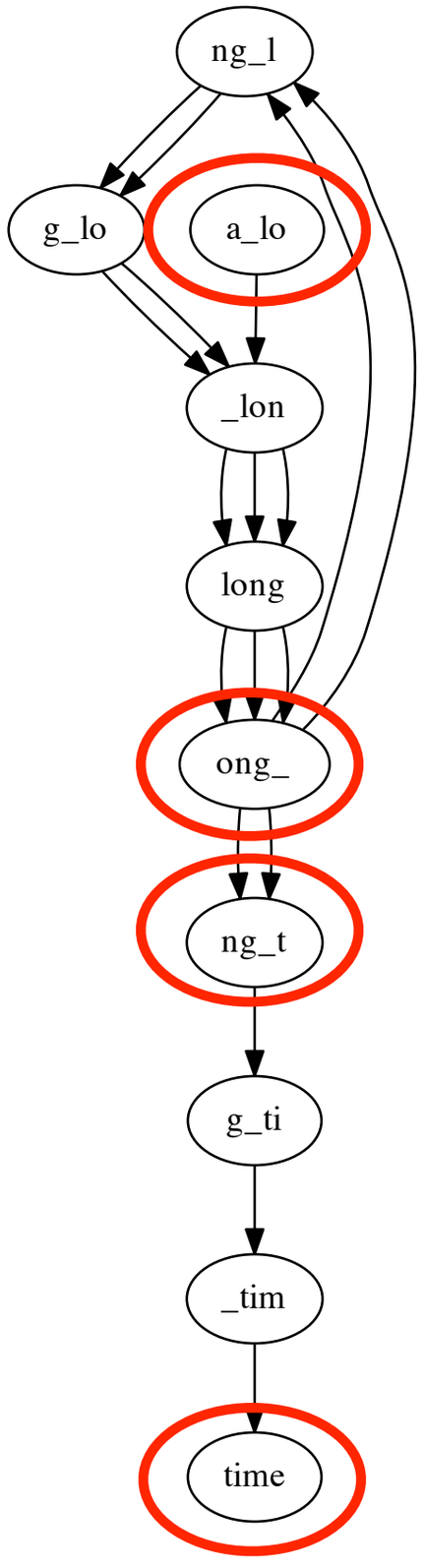
Connected components are individually Eulerian, overall graph is not

De Bruijn graph

Differences in coverage also lead to non-Eulerian graph

Graph for `a_long_long_long_time`,
$k = 5$ but with *extra copy* of `ong_t` :

Graph has 4 semi-balanced nodes,
isn't Eulerian

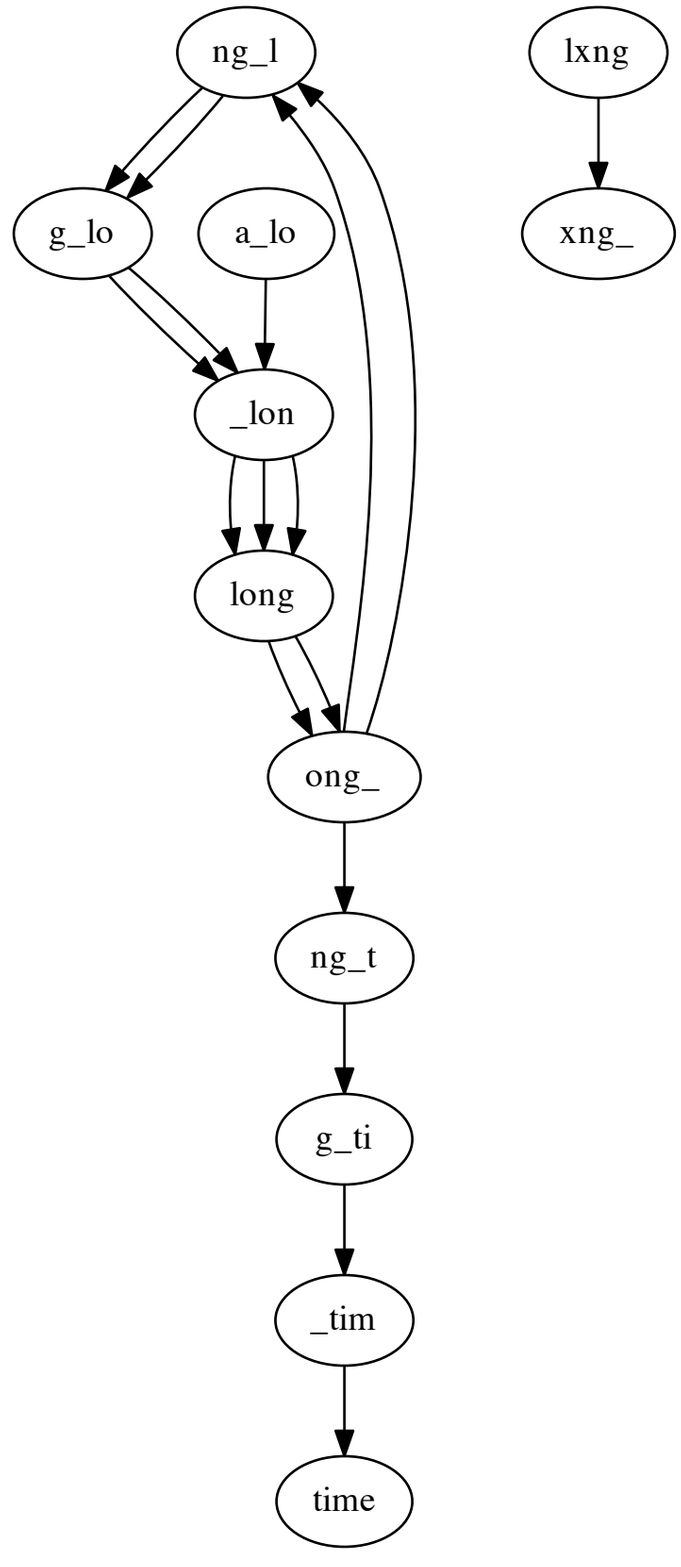


De Bruijn graph

Errors and differences between chromosomes also lead to non-Eulerian graphs

Graph for `a_long_long_long_time`, $k = 5$ but with error that turns a copy of `long_` into `lxng_`

Graph is not connected; largest component is not Eulerian



De Bruijn graph

Casting assembly as Eulerian walk is appealing, but not practical

Uneven coverage, sequencing errors, etc make graph non-Eulerian

Even if graph were Eulerian, repeats yield many possible walks

Kingsford, Carl, Michael C. Schatz, and Mihai Pop. "Assembly complexity of prokaryotic genomes using short reads." *BMC bioinformatics* 11.1 (2010): 21.

De Bruijn Superwalk Problem (DBSP) is an improved formulation where we seek a walk over the De Bruijn graph, where walk contains each read as a *subwalk*

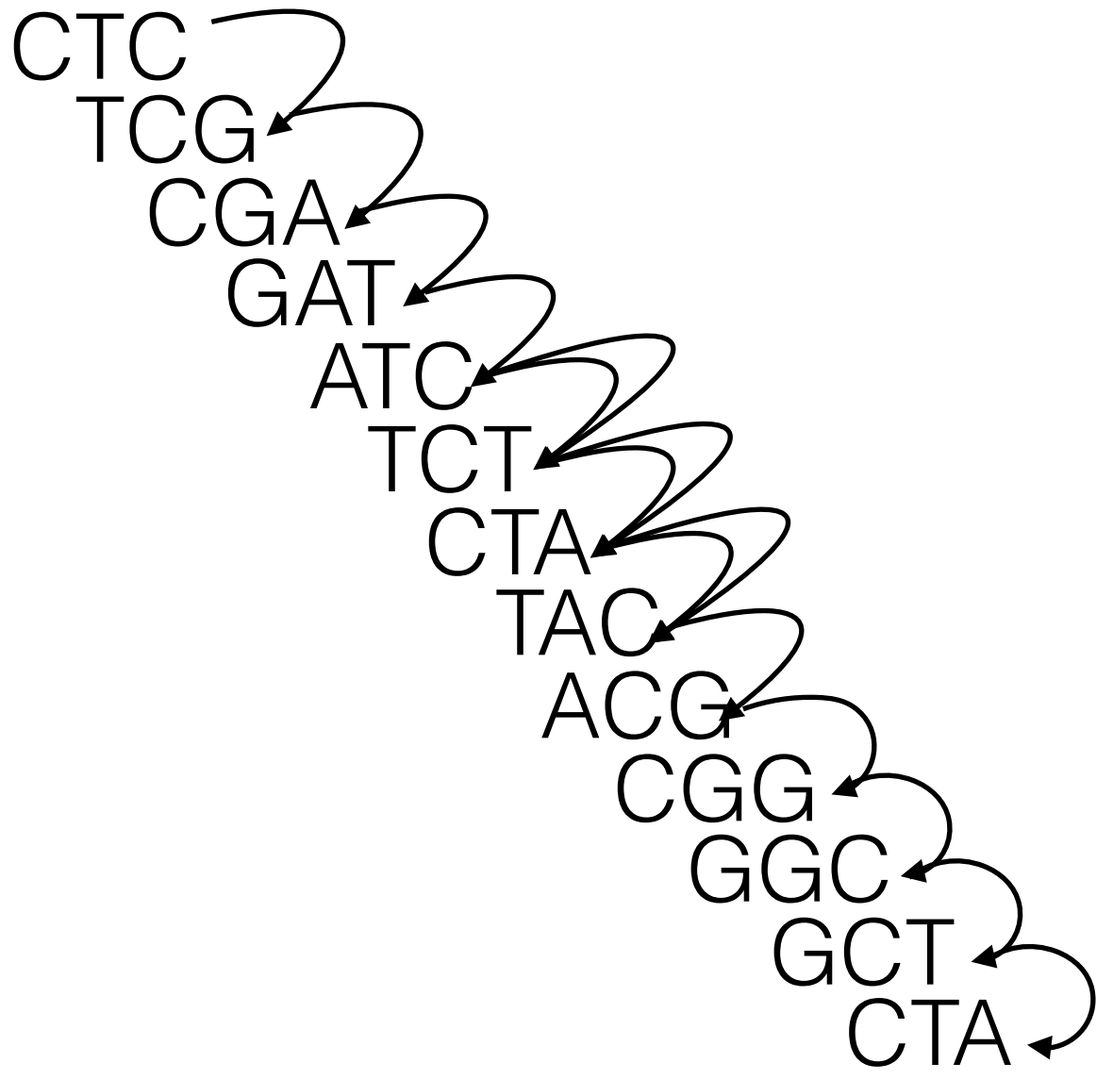
Proven NP-hard!

Medvedev, Paul, et al. "Computability of models for sequence assembly." *Algorithms in Bioinformatics*. Springer Berlin Heidelberg, 2007. 289-301.

Uneven coverage foils Eulerian Paths

r1: CTCGATCTAC
r2: ATCTACGGCTA

k=4



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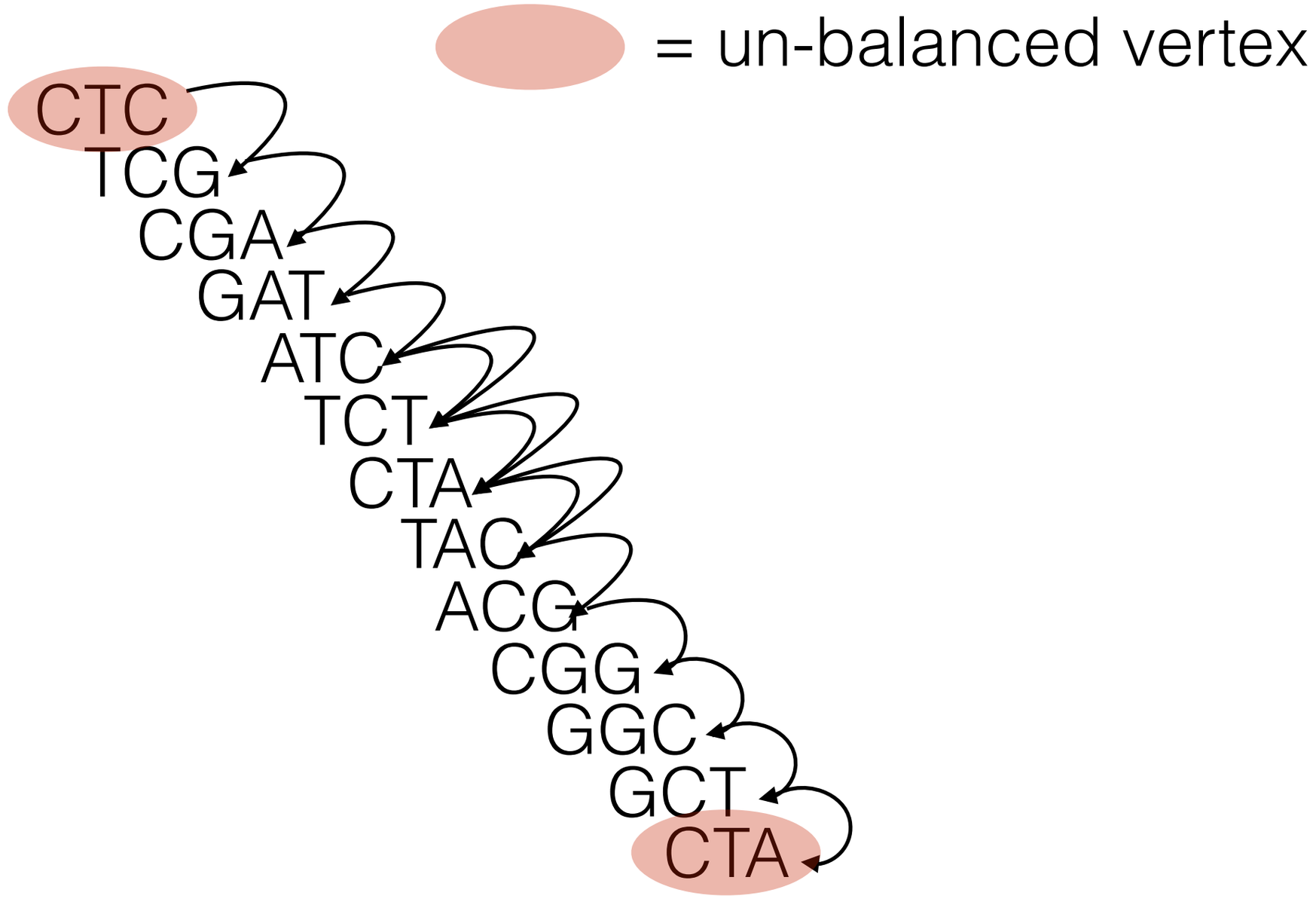

Uneven coverage foils Eulerian Paths

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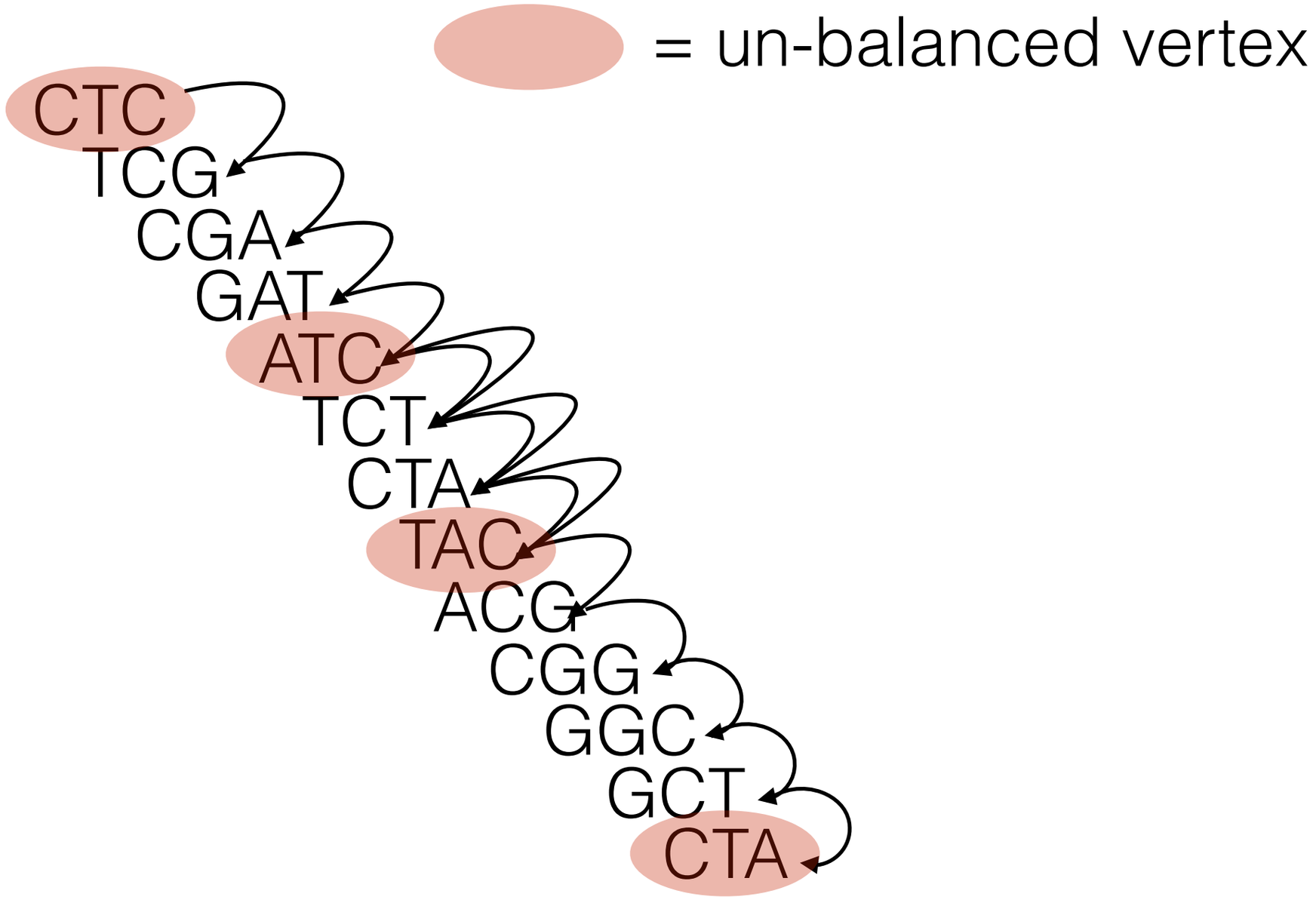


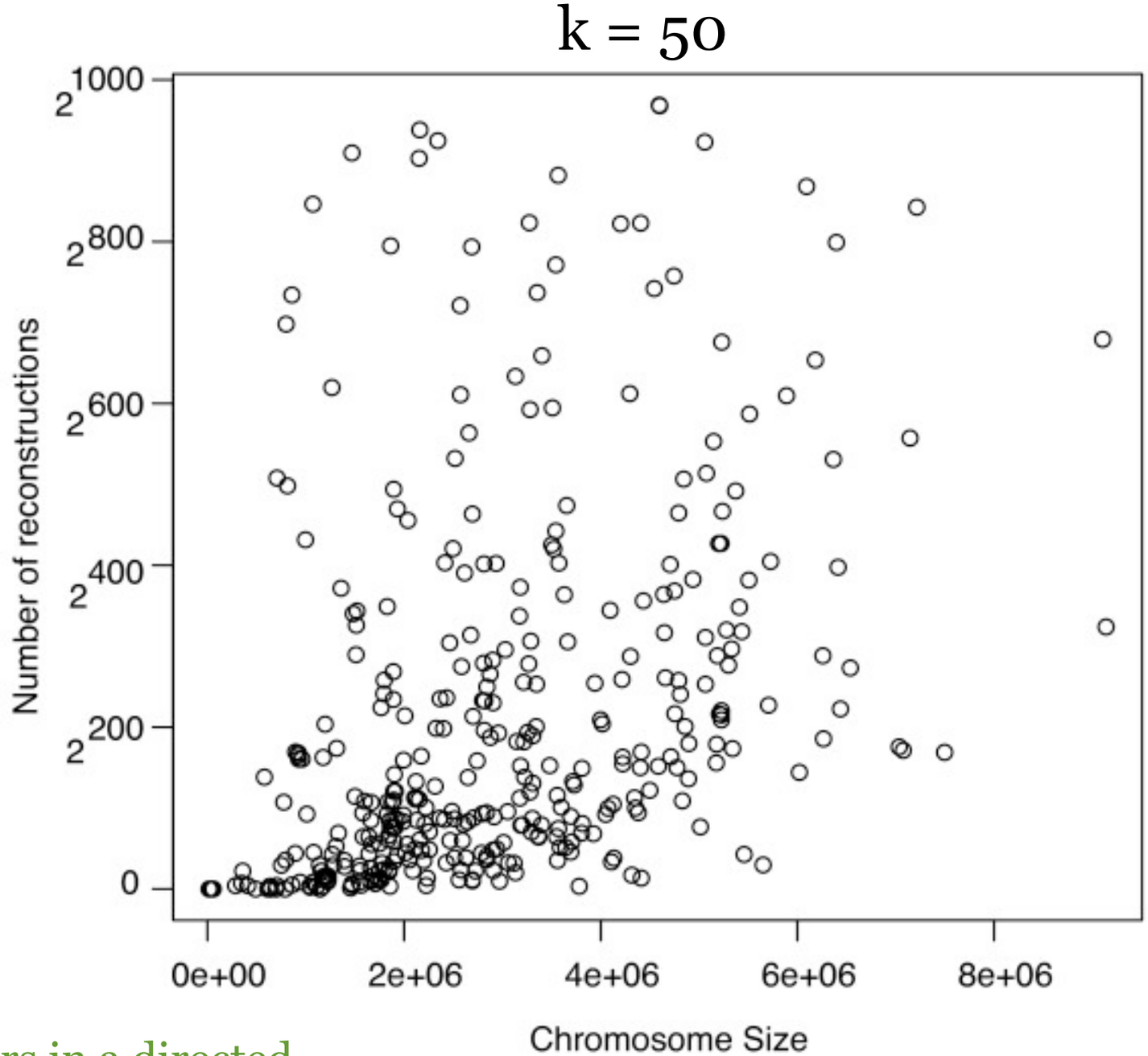
The Problem with Eulerian Paths

There are typically an astronomical number of possible Eulerian tours with perfect data.

Adding back constraints to limit # of tours leads to a NP-hard problem.

With imperfect data, there are usually NO Eulerian tours

Estimating # of parallel edges is usually tricky.

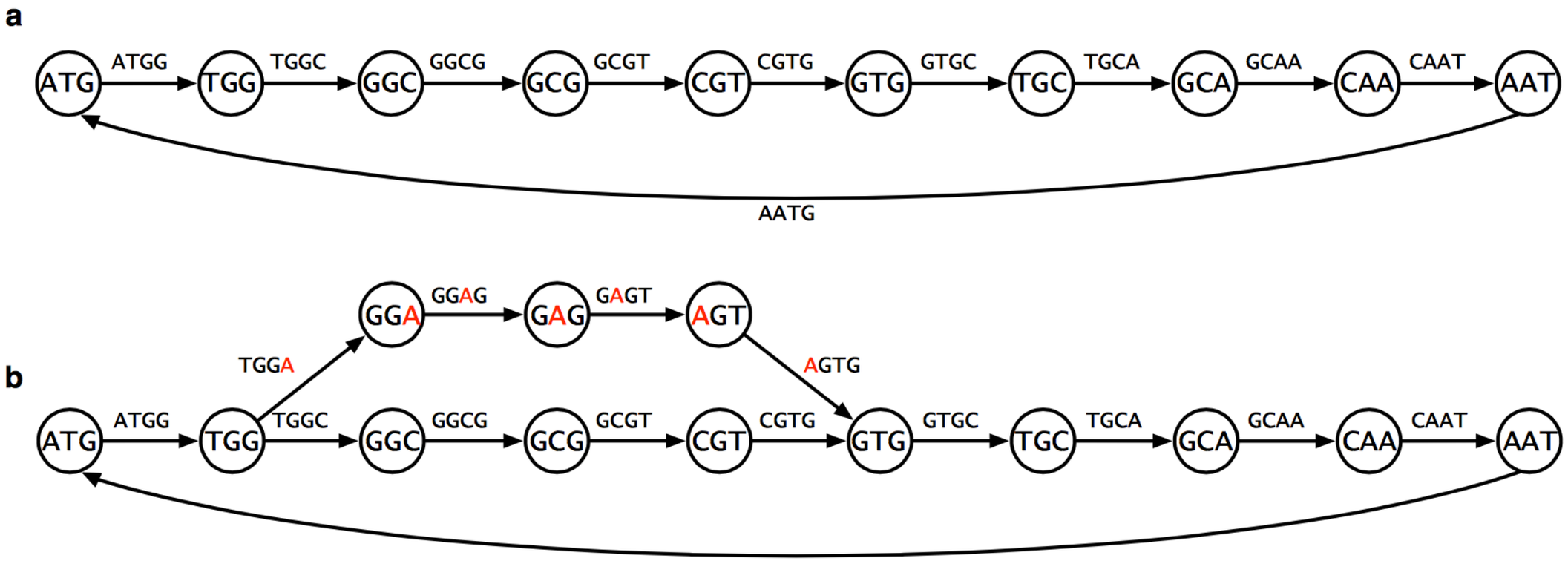


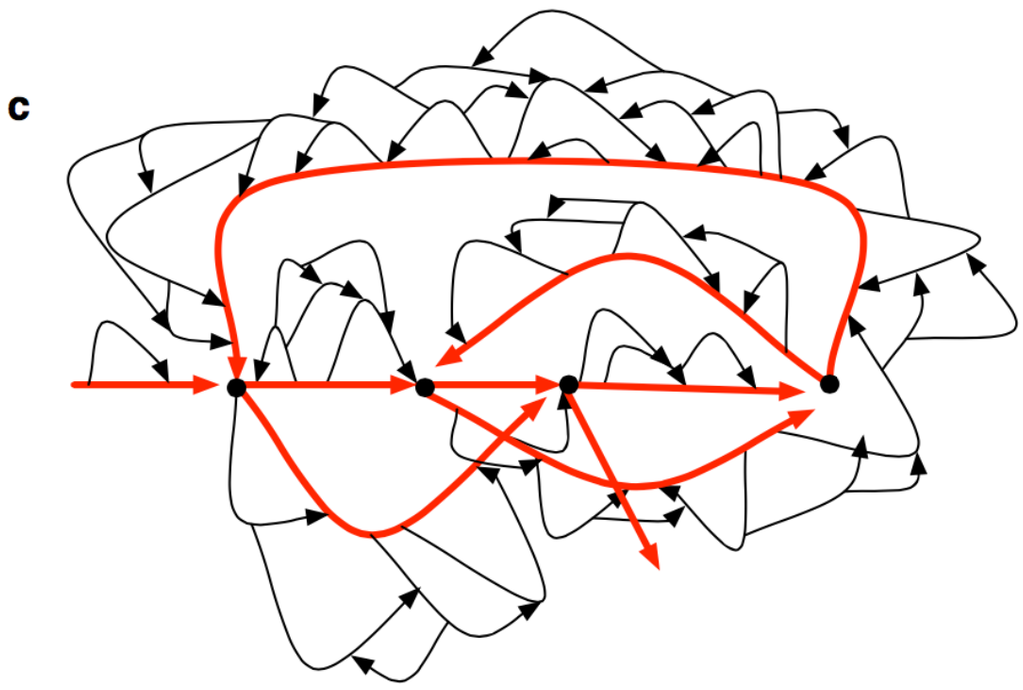
(Kingsford, Schatz, Pop, 2010)

Aside: counting # of Eulerian tours in a directed graph is easy, but in an undirected graph is #P-complete (hard).

* slide courtesy of Carl Kingsford

Bursting bubbles





Compeau, Phillip EC, Pavel A. Pevzner, and Glenn Tesler. "How to apply de Bruijn graphs to genome assembly." *Nature biotechnology* 29.11 (2011): 987-991.

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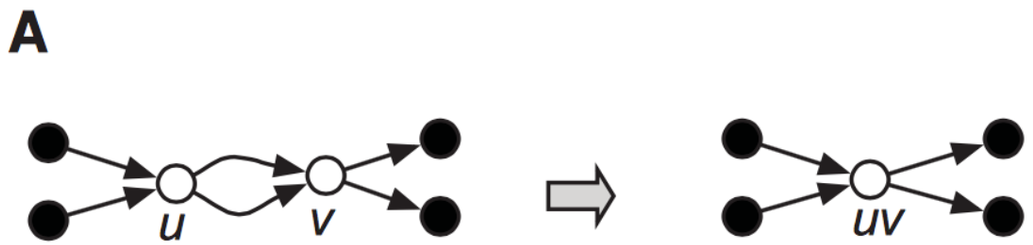
Other useful transformations

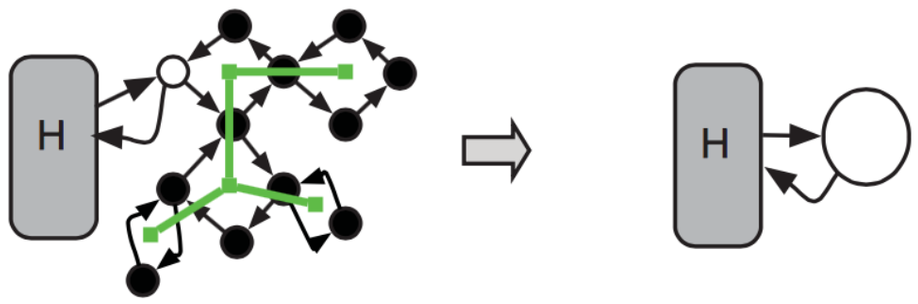


Path compression

collapse nodes u,v if v must follow u and u must precede v

(Kingsford, Schatz, Pop, 2010)

Other useful transformations



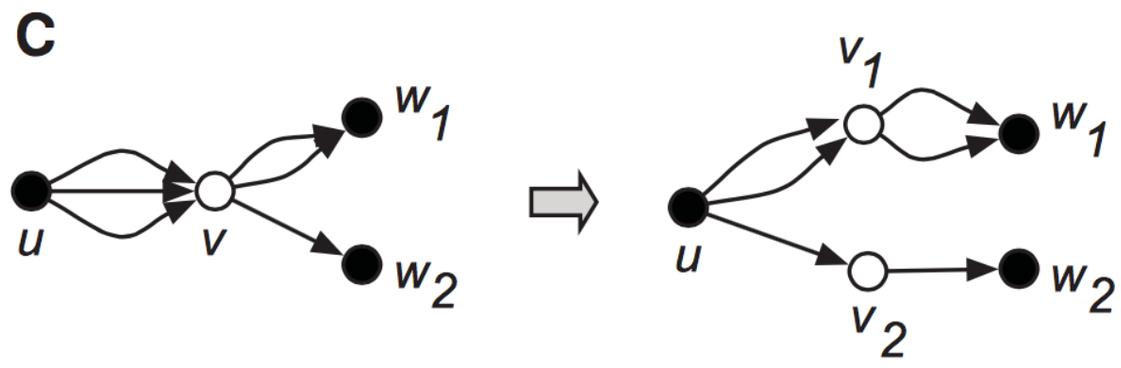
Compressing subtrees of the cycle graph

Trees in the cycle graph represent subgraphs with unique solutions, and can therefore be collapsed

Can obtain from G a cycle graph, **cycle**(G) (green above), where each vertex is a simple cycle and an edge connects two cycles if they share a node in the Eulerian graph G

(Kingsford, Schatz, Pop, 2010)

Other useful transformations

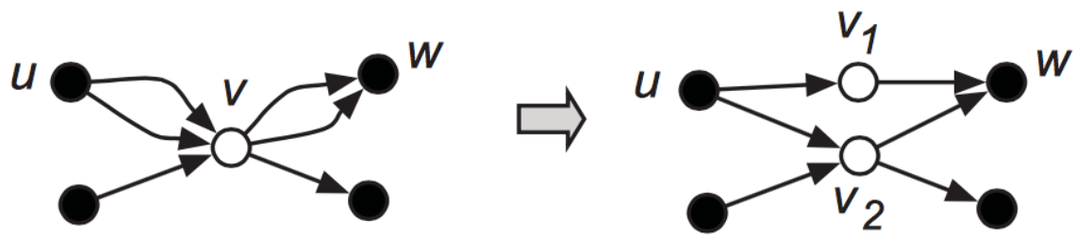


Splitting half decision nodes

"Half-decision" nodes (those with a single predecessor or successor) can be split into multiple nodes that can often be further compressed with path-compression

(Kingsford, Schatz, Pop, 2010)

Other useful transformations

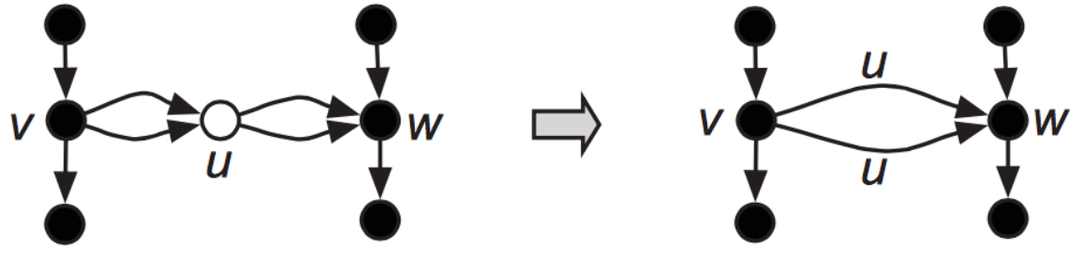


Exploiting edge multiplicities

Let u→v→w be 3 nodes in a path s.t. u→v has the highest multiplicity of edges entering v and v→w has the highest multiplicity of edges laving v. Let $c_{u\to v}$ and $c_{v\to w}$ be multiplicities of u→v and v→w. If u ≠ w, we can infer that u→v→w must be part of any Eulerian tour if $c_{u\to v} > d^+(v) - c_{v\to w}$ where $d^+(v)$ is the out-degree of v.

(Kingsford, Schatz, Pop, 2010)

Other useful transformations



Converting non-decision nodes to edges

Replacing non-decision nodes with edges, along with the other transformations considered here, results in a graph containing either just a single node, or only decision nodes that have both more than one predecessor and more than on successor.

(Kingsford, Schatz, Pop, 2010)

De Bruijn graph

In practice, De Bruijn graph-based tools give up on unresolvable repeats and yield fragmented assemblies, just like OLC tools.

But first we note that using the De Bruijn graph representation has **other advantages**...

De Bruijn graph

Say a sequencer produces **d** reads of length **n** from a genome of length **m**

d = 6 x 10^9 reads
n = 100 nt
} ≈ 1 sequencing run

m = 3 x 10^9 nt ≈ human

To build a De Bruijn graph in practice:

Pick *k*. Assume *k* ≤ shortest read length (*k* = 30 to 50 is common).

For each read:

For each *k*-mer:

Add *k*-mer's left and right *k*-1-mers to graph if not there already. Draw an edge from left to right *k*-1-mer.

De Bruijn graph

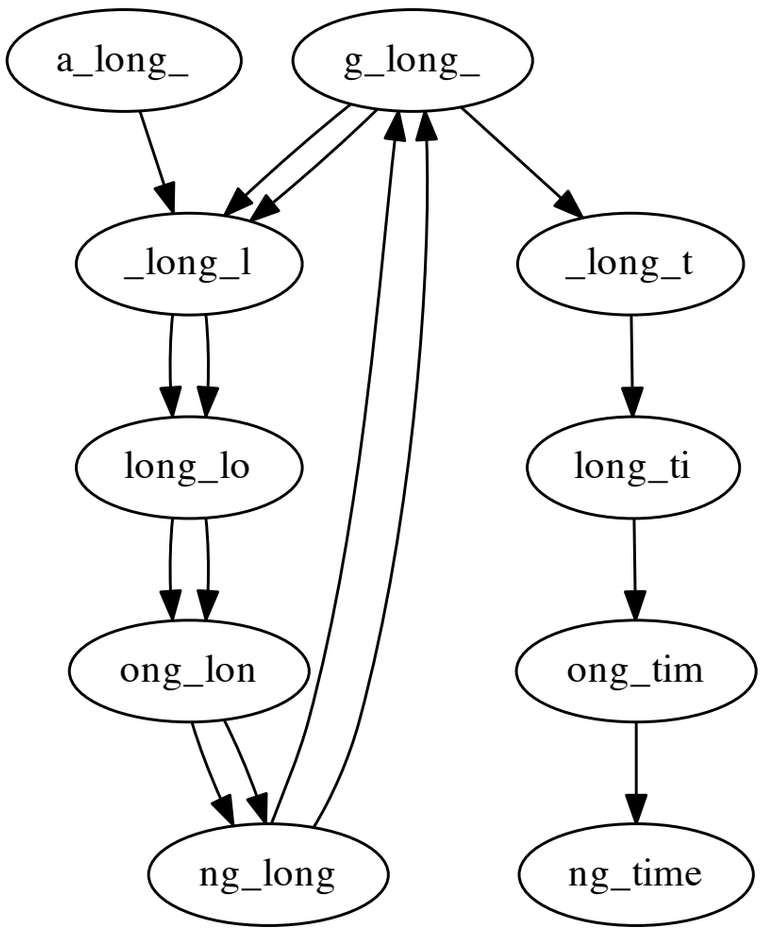
Pick $k = 8$

Genome: a_long_long_long_time

Reads: a_long_long_long, ng_long_l, g_long_time

k-mers:

```
a_long_l          ng_long_   g_long_t
 _long_lo          g_long_l   _long_ti
  long_lon                     long_tim
   ong_long                     ong_time
    ng_long_
     g_long_l
      _long_lo
       long_lon
        ong_long
```



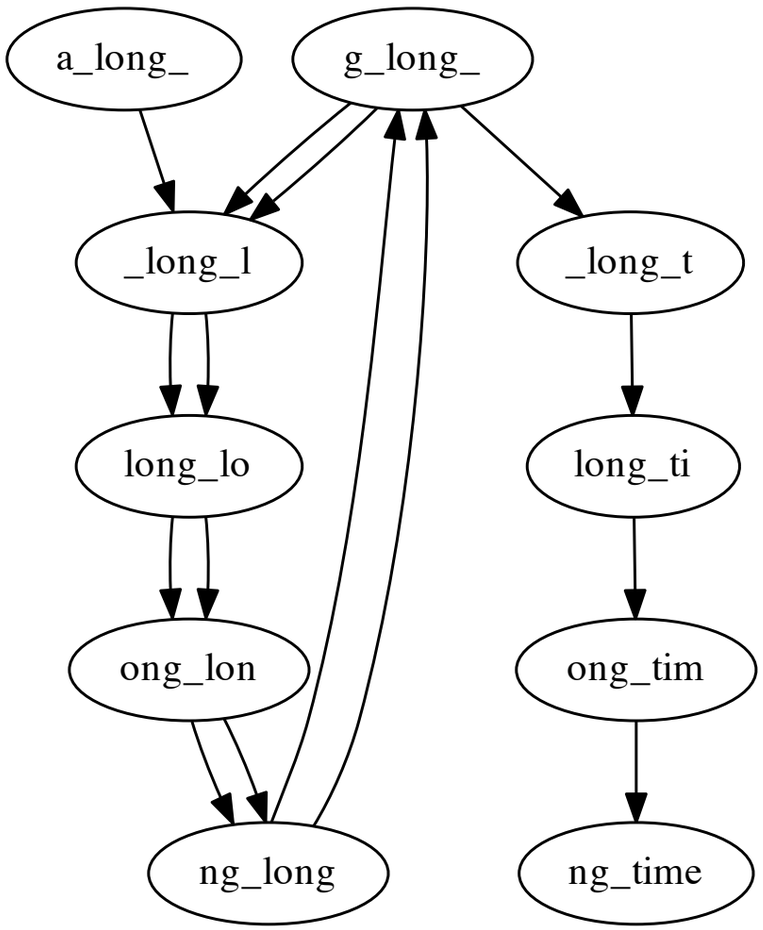
Given n (# reads), N (total length of all reads) and k, and assuming $k <$ length of shortest read:

Exact number of k-mers: $N - n(k-1)$ $O(N)$

This is also the number of edges, $|E|$

Number of nodes $|V|$ is at most $2 \cdot |E|$, but typically much smaller due to repeated k-1-mers

De Bruijn graph



How much work to build graph?

For each *k*-mer, add 1 edge and up to 2 nodes

Reasonable to say this is O(1) expected work

Assume hash map encodes nodes & edges

Assume *k*-1-mers fit in O(1) machine words, and hashing O(1) machine words is O(1) work

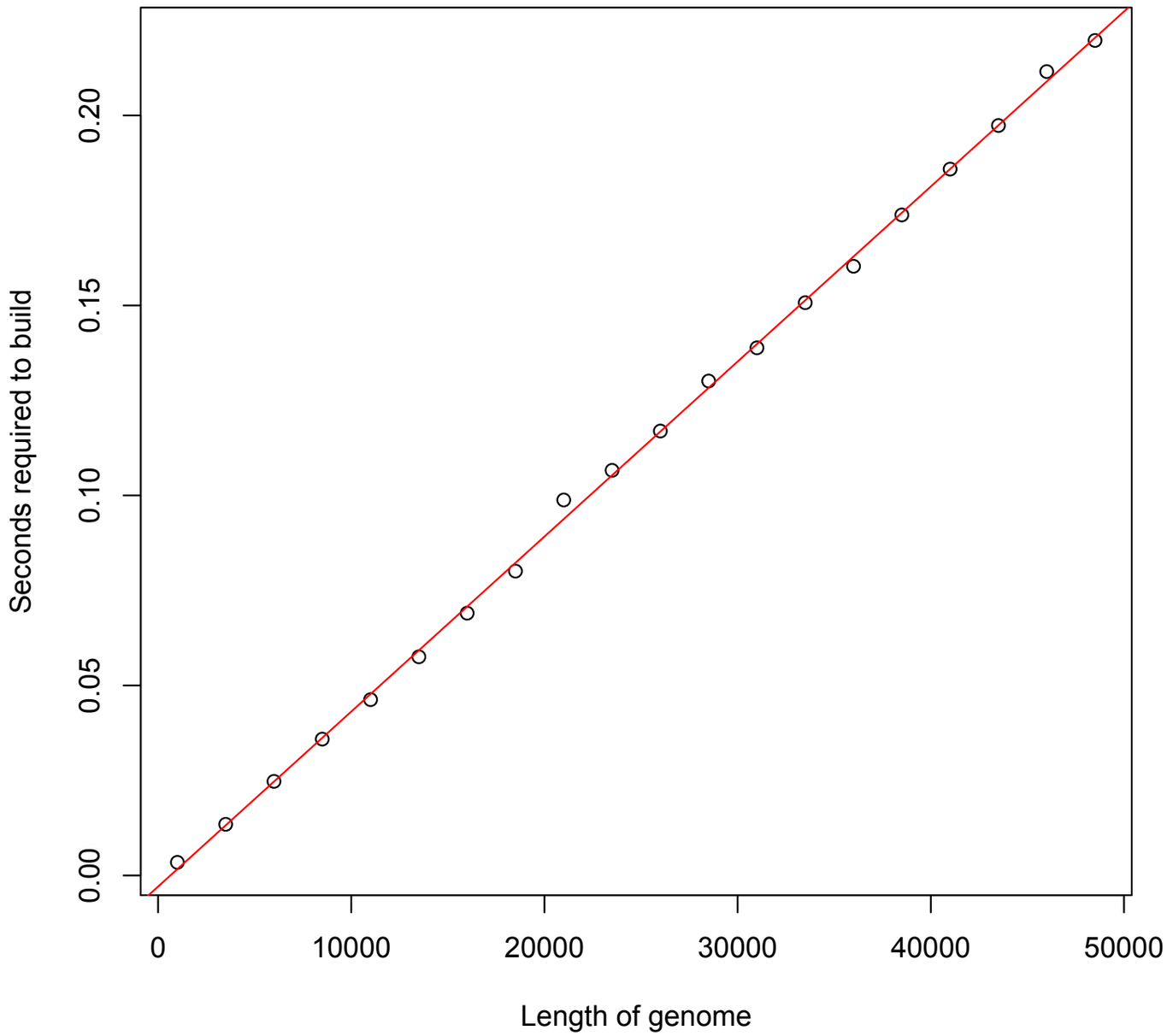
Querying / adding a key is O(1) expected work

O(1) expected work for 1 *k*-mer, O(*N*) overall

De Bruijn graph

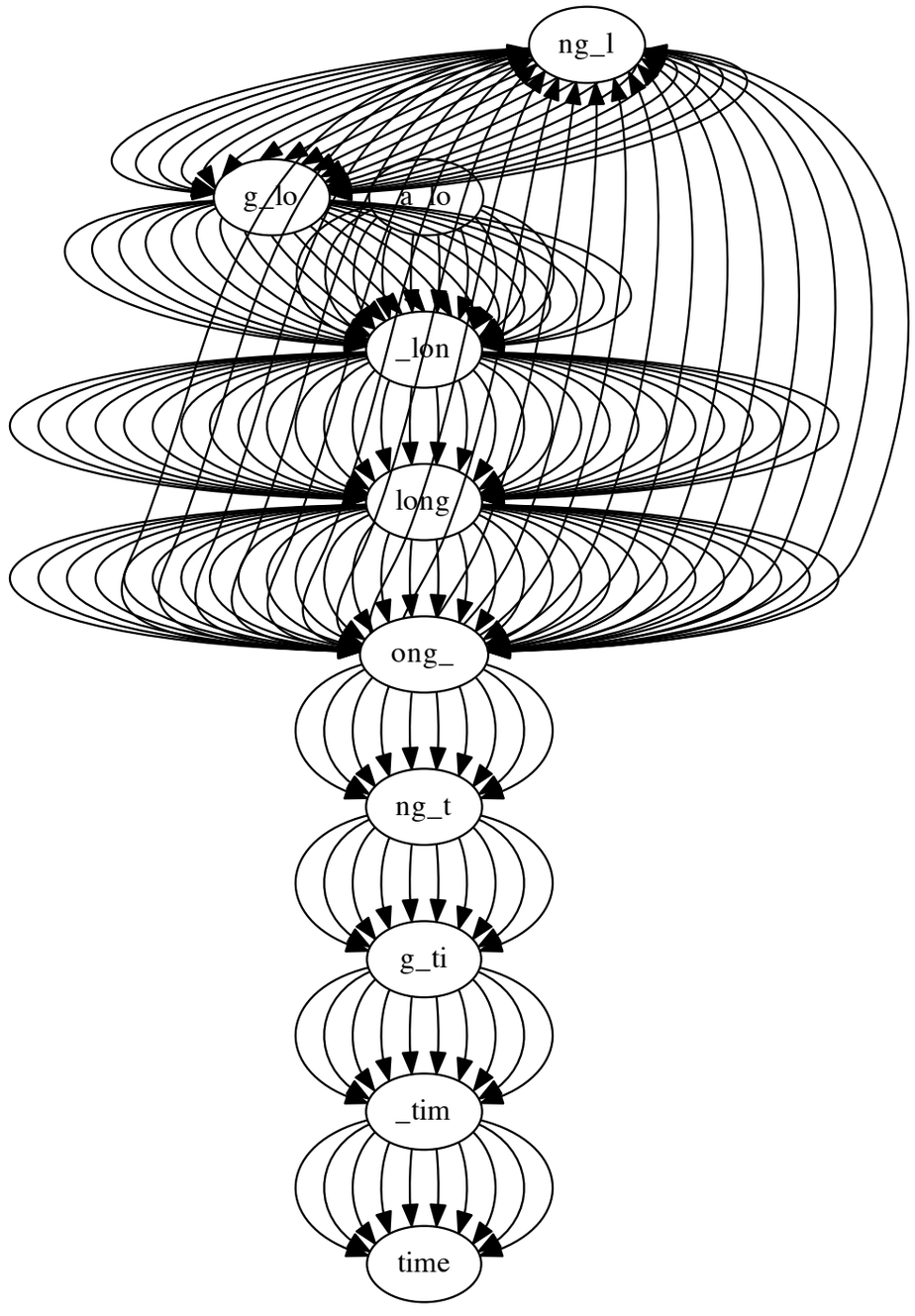
Timed De Bruijn graph construction applied to progressively longer prefixes of lambda phage genome, $k = 14$

O(N) expectation appears to work in practice, at least for this small example



De Bruijn graph

In typical assembly projects,
average coverage is ~ 30 - 50



De Bruijn graph

Recall *average coverage*: average # reads covering a genome position

```
                                CTAGGCCCTCAATTTTT
                               CTCTAGGCCCTCAATTTTT
                              GGCTCTAGGCCCTCATTTTTT
                          CTCGGCTCTAGCCCCTCATTTT
                               TATCTCGACTCTAGGCCCTCA
                               TATCTCGACTCTAGGCC
                           TCTATATCTCGGCTCTAGG
                      GGCGTCTATATCTCG
                      GGCGTCGATATCT
                      GGCGTCTATATCT
                      GGCGTCTATATCTCGGCTCTAGGCCCTCATTTTTT
```

177 nucleotides

35 nucleotides

Average coverage = 177 / 35 ≈ 7x

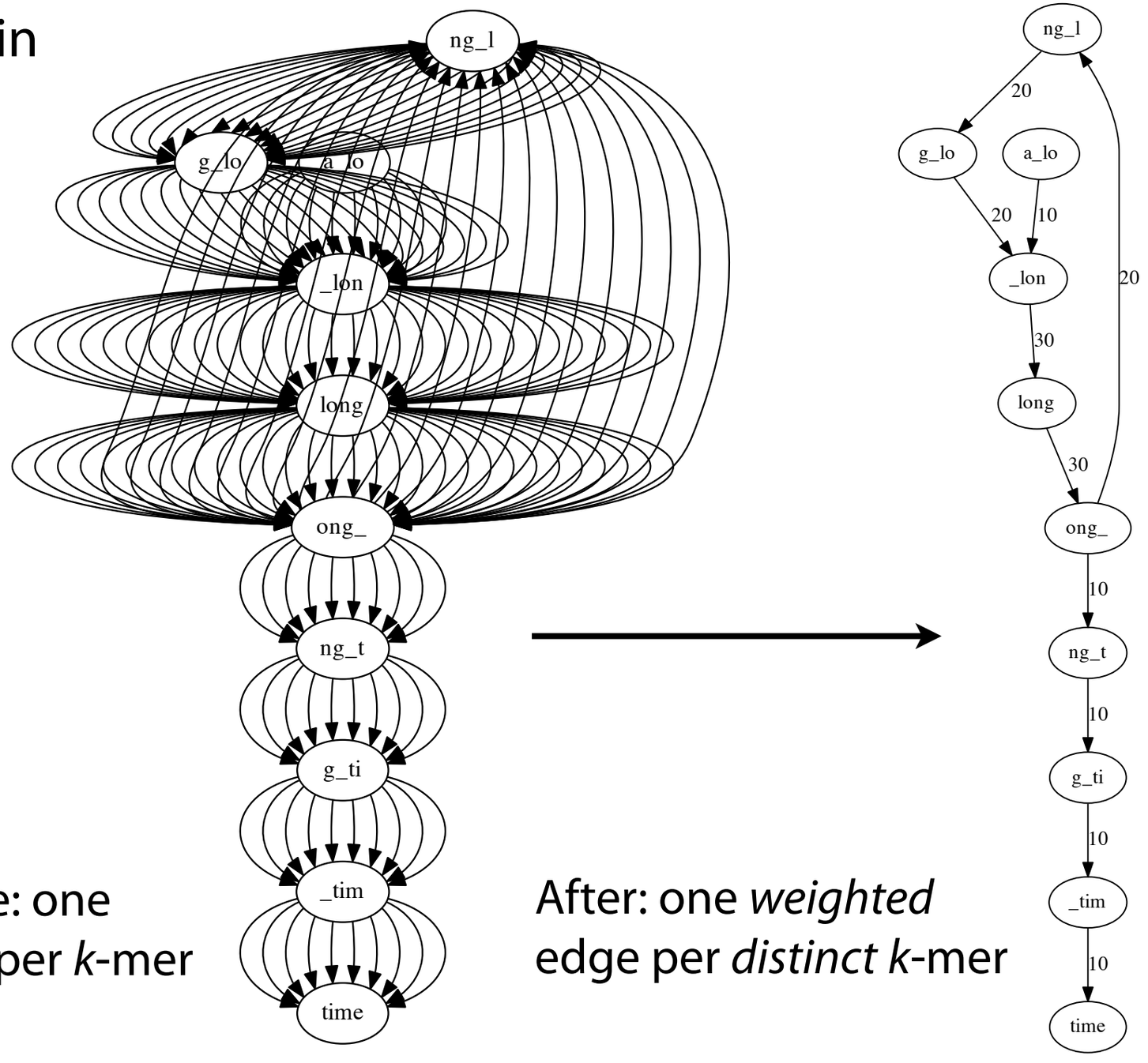
De Bruijn graph

In typical assembly projects, average coverage is ~ 30 - 50

Same edge might appear in dozens of copies; let's use edge *weights* instead

Weight = # times *k*-mer occurs

Using weights, there's one *weighted* edge for each *distinct k*-mer



Before: one edge per *k*-mer

After: one *weighted* edge per *distinct k*-mer

De Bruijn graph

of nodes and edges both O(*N*); *N* is total length of all reads

Say (a) reads are error-free, (b) we have one *weighted* edge for each *distinct k*-mer, and (c) length of genome is *G*

> There's one node for each distinct *k*-1-mer, one edge for each distinct *k*-mer
>
> Can't be more distinct *k*-mers than there are *k*-mers in the genome; likewise for *k*-1-mers

So # of nodes and edges are also both O(*G*)

Combine with the O(*N*) bound and the # of nodes and edges are both O(min(*N*, *G*))

De Bruijn graph

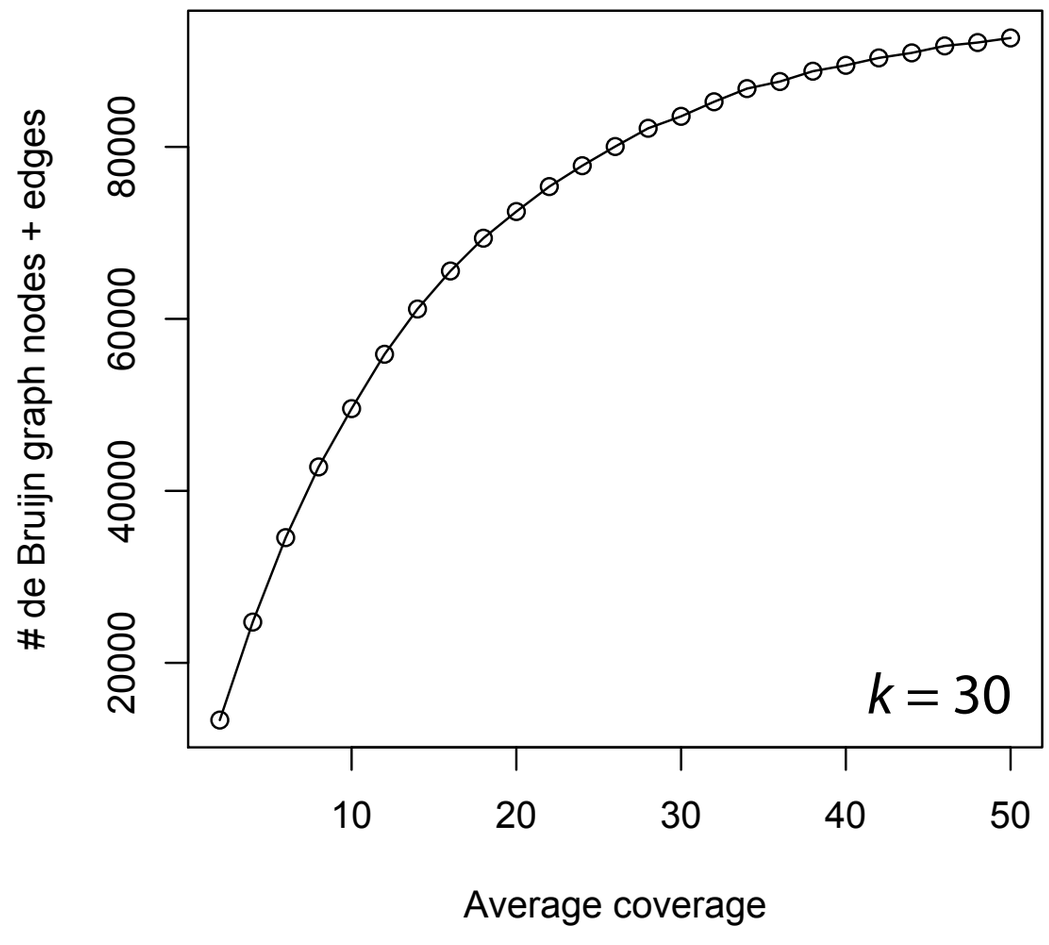
With high average coverage, O(*G*) size bound is advantageous

Genome = lambda phage (~ 48.5 K nt)

Draw random *k*-mers until target average coverage is reached (x axis)

Build De Bruijn graph and total the # of nodes and edges (y axis)

Size of De Bruijn graph grows sublinearly when average coverage is high



De Bruijn graph

What De Bruijn graph advantages have we discovered?

Can be built in O(N) expected time, N = total length of reads

With perfect data, graph is O(min(N, G)) space; G = genome length

Note: when average coverage is high, $G \ll N$

Compares favorably with overlap graph

Space is O($N + a$).

Fast overlap graph construction (suffix tree) is O($N + a$) time

a is O(n^2)

De Bruijn graph

What did we give up?

Reads are immediately split into shorter *k*-mers; can't resolve repeats as well as overlap graph

Only a very specific type of "overlap" is considered, which makes dealing with errors more complicated, as we'll see

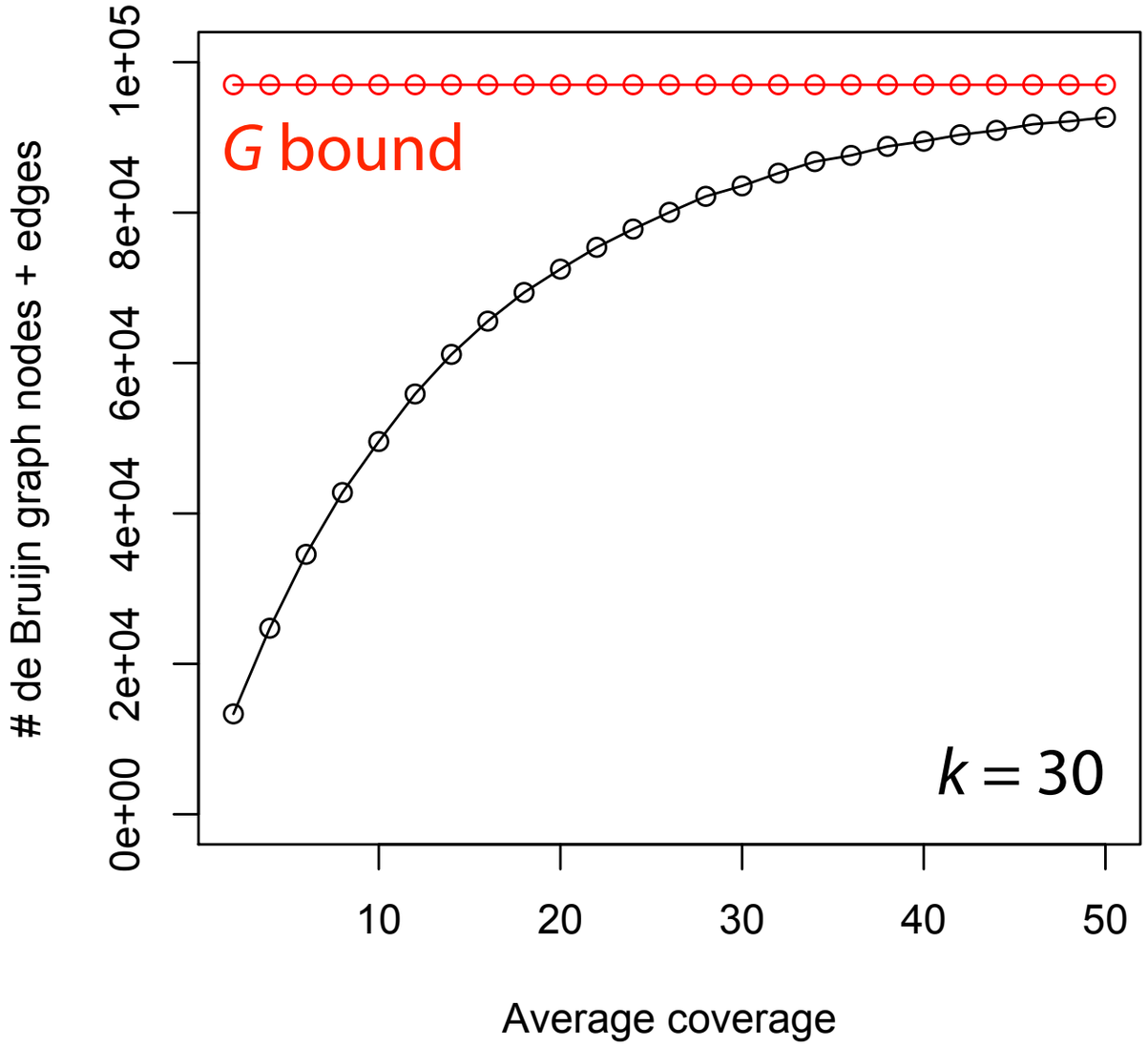
Read coherence is lost. Some paths through De Bruijn graph are inconsistent with respect to input reads.

This is the OLC ⟷ DBG tradeoff

Single most important benefit of De Bruijn graph is the O(min(*G*, *N*)) space bound, though we'll see this comes with large caveats

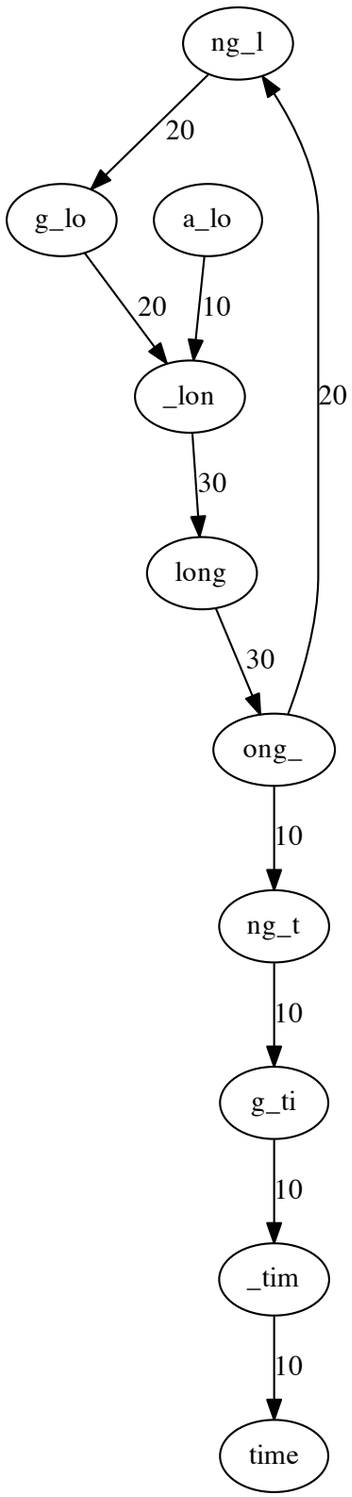
Error correction

When data is error-free, # nodes, edges in de Bruijn graph is O(min(*G*, *N*))



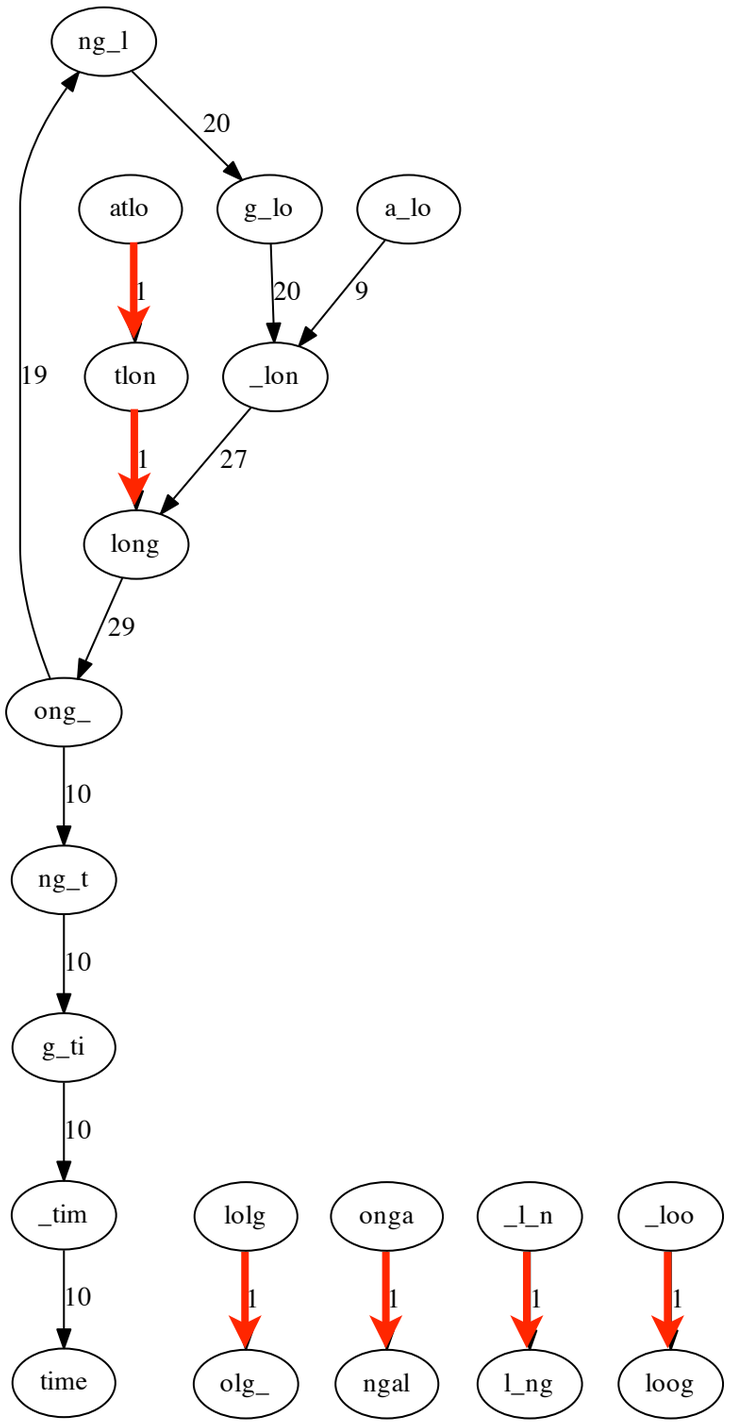
What about data with sequencing errors?

Error correction



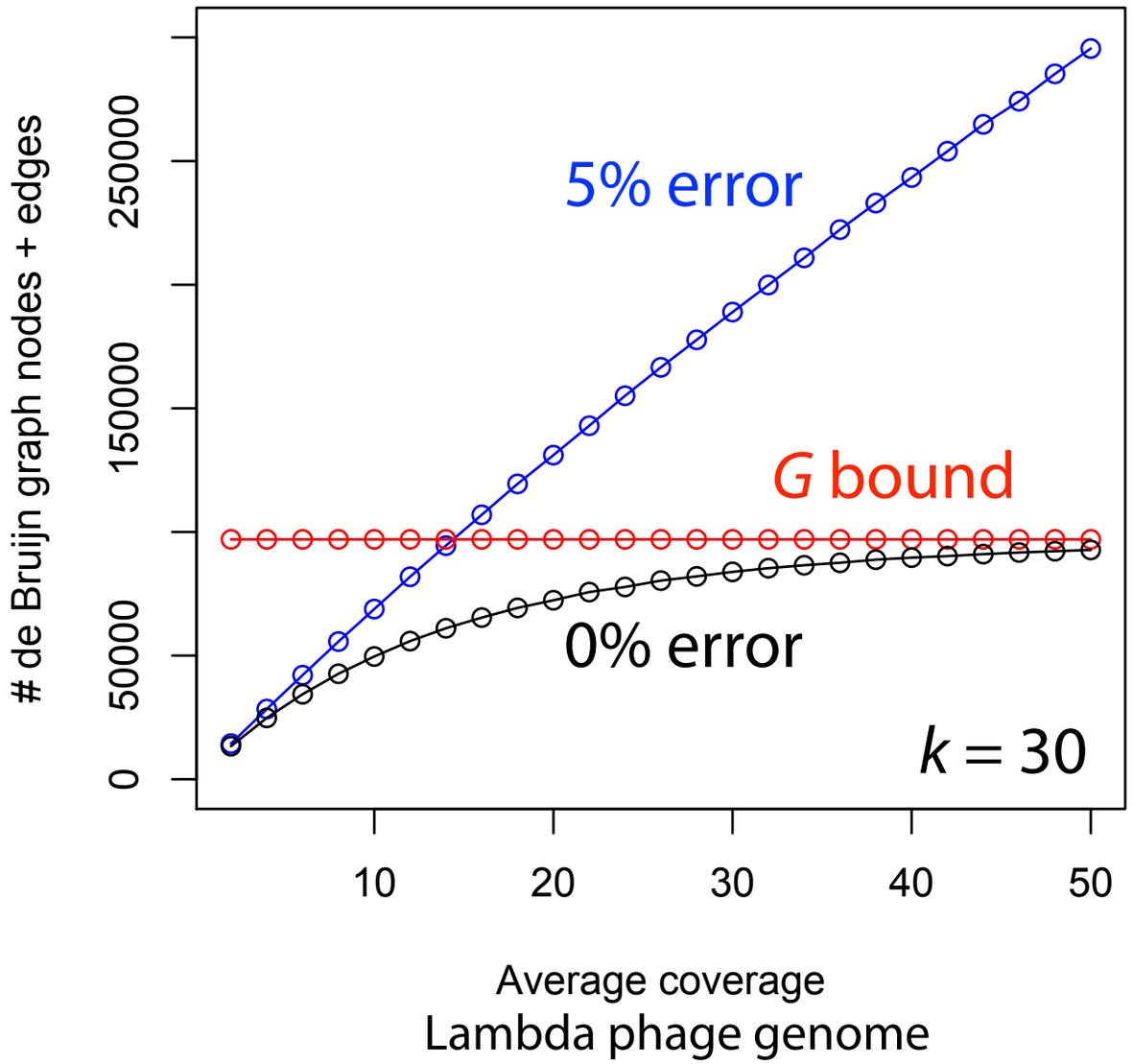
Take an example we saw (left) and mutate a *k*-mer character to a random other character with probability 1% (right)

6 errors result in 10 new nodes and 6 new weighted edges, all with weight 1



Error correction

As more *k*-mers overlap errors, # nodes, edges approach *N*

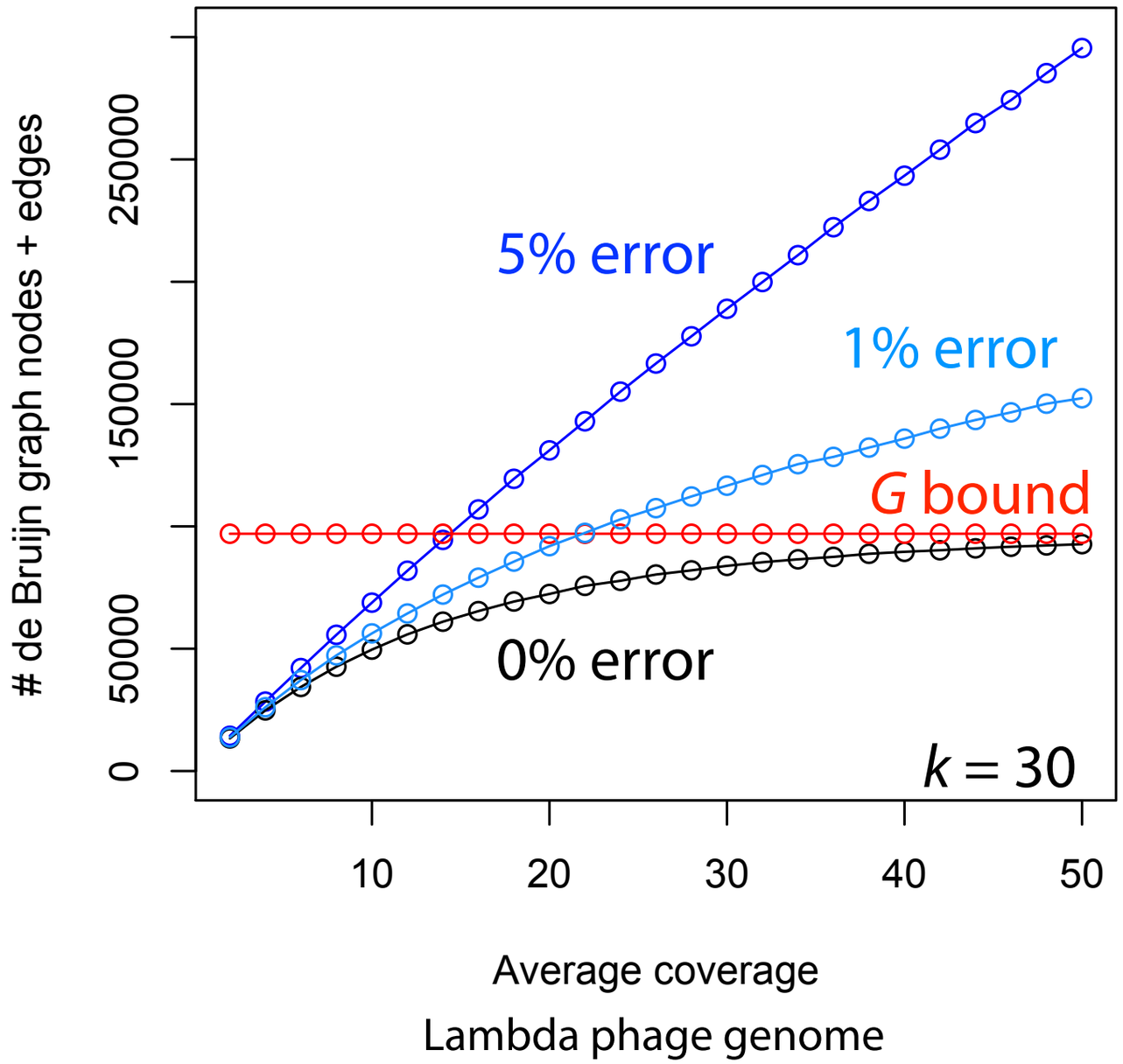


Same experiment as before but with 5% error added

Errors wipe out much of the benefit of the *G* bound

Instead of $O(\min(G, N))$, we have something more like $O(N)$

Error correction



Error correction

If we can correct sequencing errors up-front, we can prevent De Bruijn graph from growing much beyond the *G* bound

How do we correct errors?

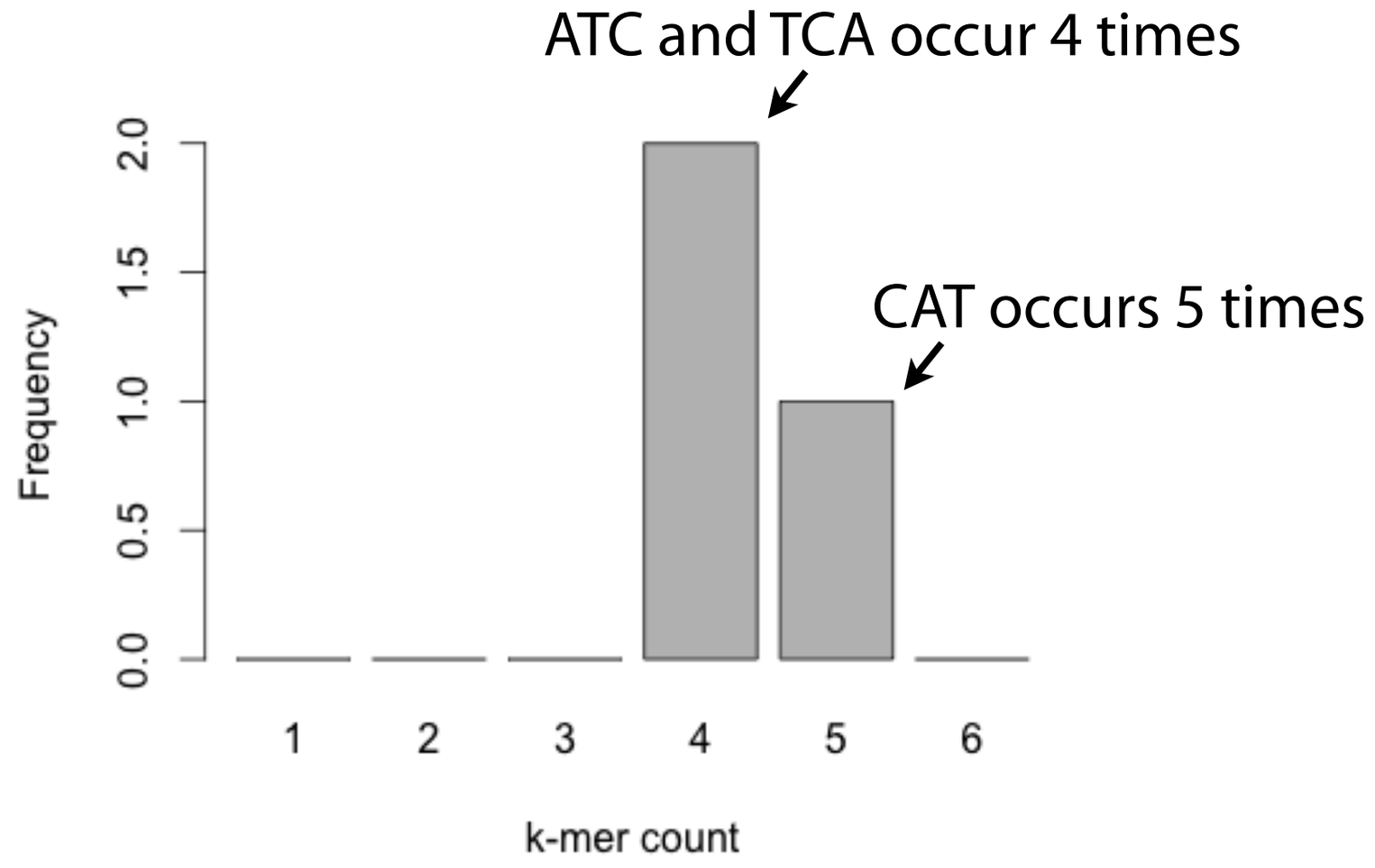
Analogy: design a spell checker for a language you've never seen before. How do you come up with suggestions?

Error correction

k-mer count histogram:

x axis is an integer *k*-mer count, y axis is # distinct *k*-mers with that count

Right: such a histogram for 3-mers of CATCATCATCATCAT:

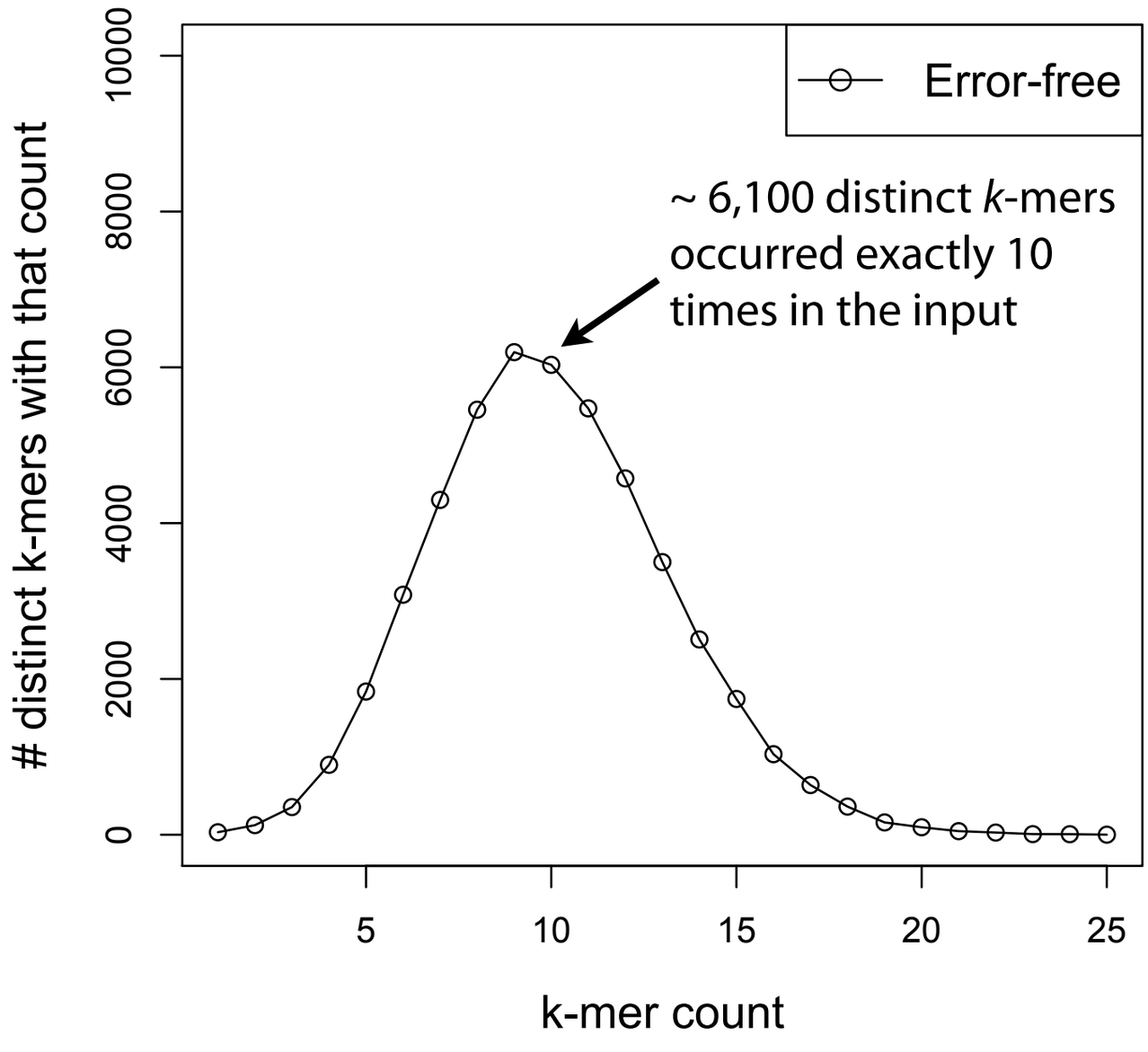


Error correction

Say we have error-free sequencing reads drawn from a genome.
The amount of sequencing is such that average coverage = 200.
Let $k = 20$

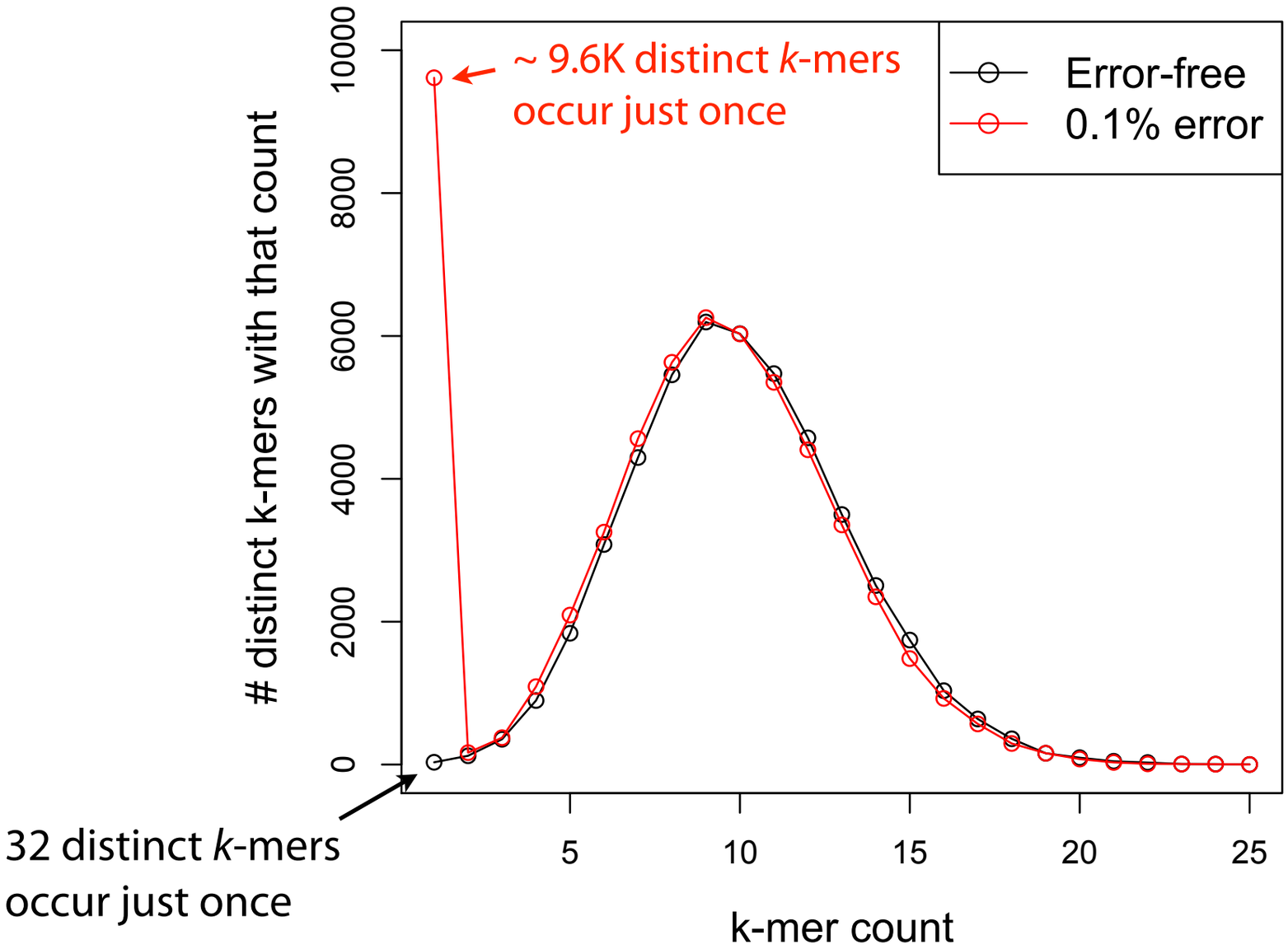
How would the picture change for data with 1% error rate?

Hint: errors usually change high-count *k*-mer into low-count *k*-mer



Error correction

k-mers with errors usually occur fewer times than error-free *k*-mers



Error correction

Idea: errors tend to turn frequent *k*-mers to infrequent *k*-mers, so corrections should do the reverse

Say we have a collection of reads where each distinct 8-mer occurs an average of ~10 times, and we have the following read:

Read: `GCGTATTACGCGTCTGGCCT` (20 nt)

8-mers:

```
GCGTATTA: 8
 CGTATTAC: 8
  GTATTACG: 9
   TATTACGC: 9
    ATTACGCG: 9
     TTACGCGT: 12
      TACGCGTC: 9
       ACGCGTCT: 8
        CGCGTCTG: 10
         GCGTCTGG: 10
          CGTCTGGC: 11
           GTCTGGCC: 9
            TCTGGCCT: 8
```

times each 8-mer occurs in the dataset.
"*k*-mer count profile"

All 8-mer counts are around the average, suggesting read is error-free

Error correction

Suppose there's an error

Read: GCGTACTACGCGTCTGGCCT

```
GCGTACTA: 1
 CGTACTAC: 3
  GTACTACG: 1
   TACTACGC: 1
   ACTACGCG: 2
    CTACGCGT: 1
     TACGCGTC: 9
      ACGCGTCT: 8
       CGCGTCTG: 10
        GCGTCTGG: 10
         CGTCTGGC: 11
          GTCTGGCC: 9
           TCTGGCCT: 8
```

Below average

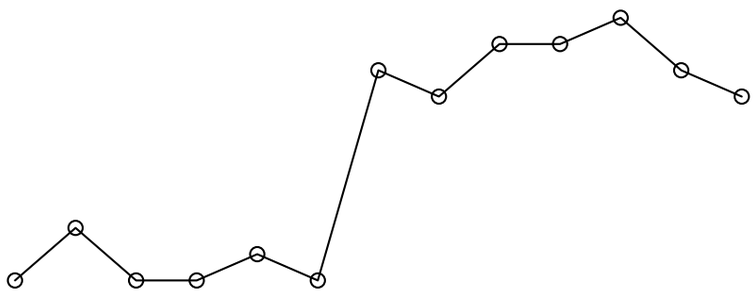
k-mer count profile has corresponding stretch of below-average counts

Around average

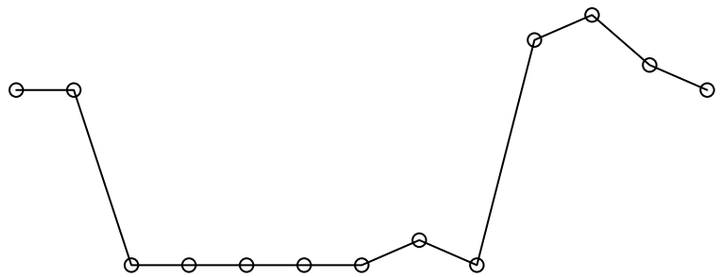
Error correction

k-mer count profiles when errors are in different parts of the read:

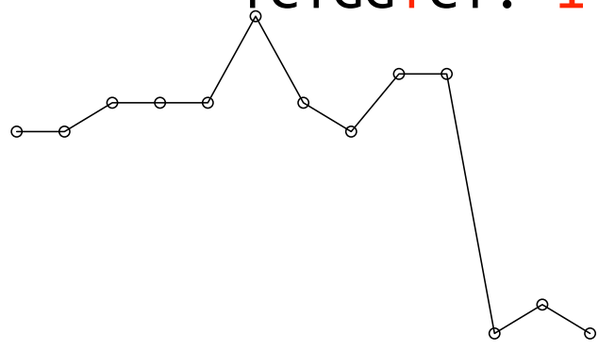
```
GCGTACTACGCGTCTGGCCT
GCGTACTA: 1
 CGTACTAC: 3
  GTACTACG: 1
   TACTACGC: 1
    ACTACGCG: 2
     CTACGCGT: 1
      TACGCGTC: 9
       ACGCGTCT: 8
        CGCGTCTG: 10
         GCGTCTGG: 10
          CGTCTGGC: 11
           GTCTGGCC: 9
            TCTGGCCT: 8
```



```
GCGTATTACACGTCTGGCCT
GCGTATTA: 8
 CGTATTAC: 8
  GTATTACA: 1
   TATTACAC: 1
    ATTACACG: 1
     TTACACGT: 1
      TACACGTC: 1
       ACACGTCT: 2
        CACGTCTG: 1
         GCGTCTGG: 10
          CGTCTGGC: 11
           GTCTGGCC: 9
            TCTGGCCT: 8
```

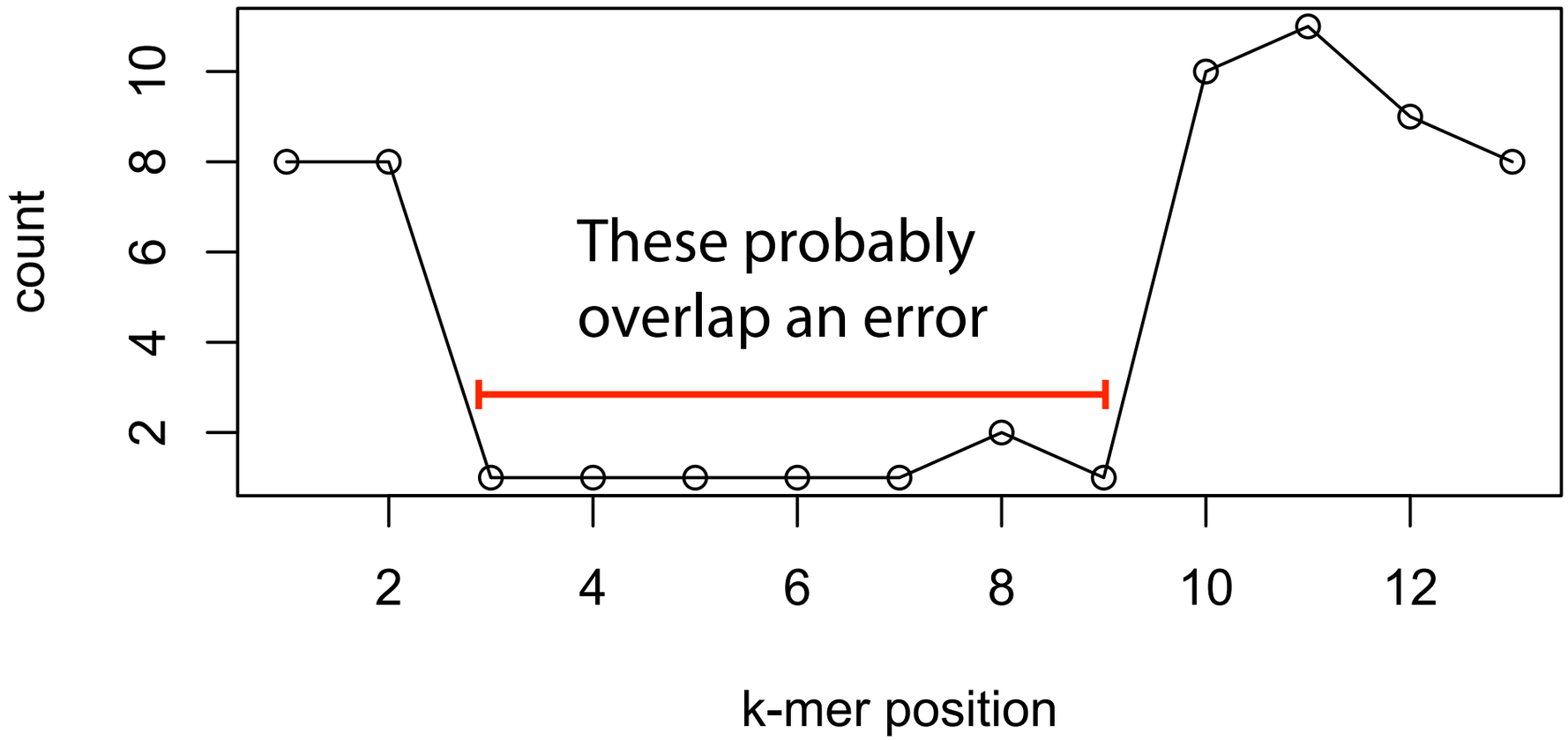


```
GCGTATTACGCGTCTGGTCT
GCGTATTA: 8
 CGTATTAC: 8
  GTATTACG: 9
   TATTACGC: 9
    ATTACGCG: 9
     TTACGCGT: 12
      TACGCGTC: 9
       ACGCGTCT: 8
        CGCGTCTG: 10
         GCGTCTGG: 10
          CGTCTGGT: 1
           GTCTGGTC: 2
            TCTGGTCT: 1
```



Error correction

k-mer count profile indicates where errors are



Error correction

Simple algorithm: given a count threshold *t*:

For each read:

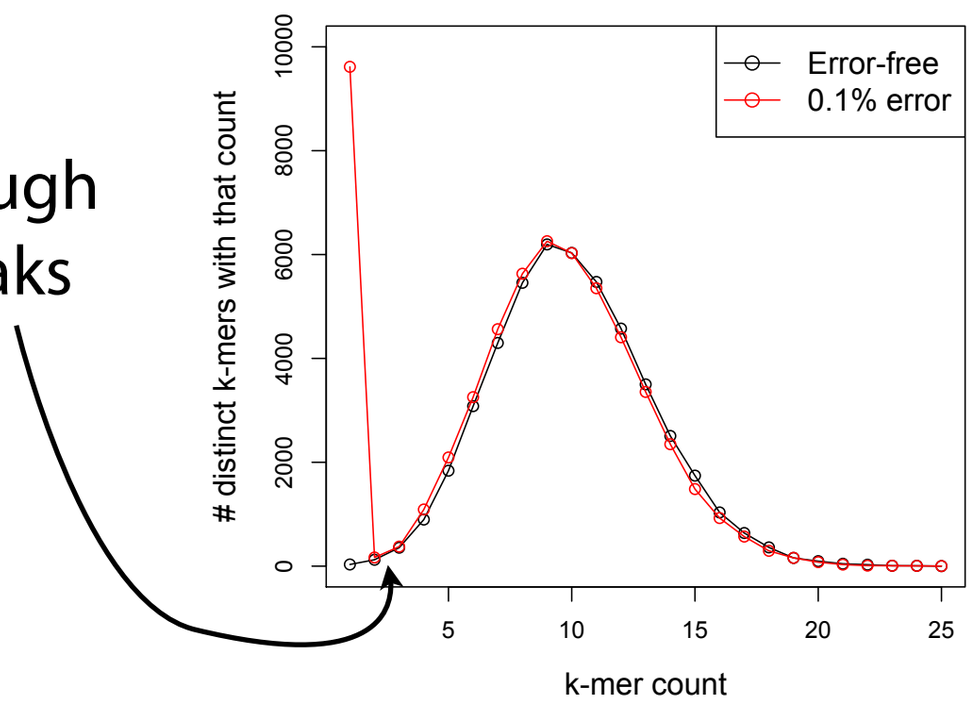
For each k-mer:

If *k*-mer count < *t*:

Examine *k*-mer's neighbors within certain Hamming/edit distance.

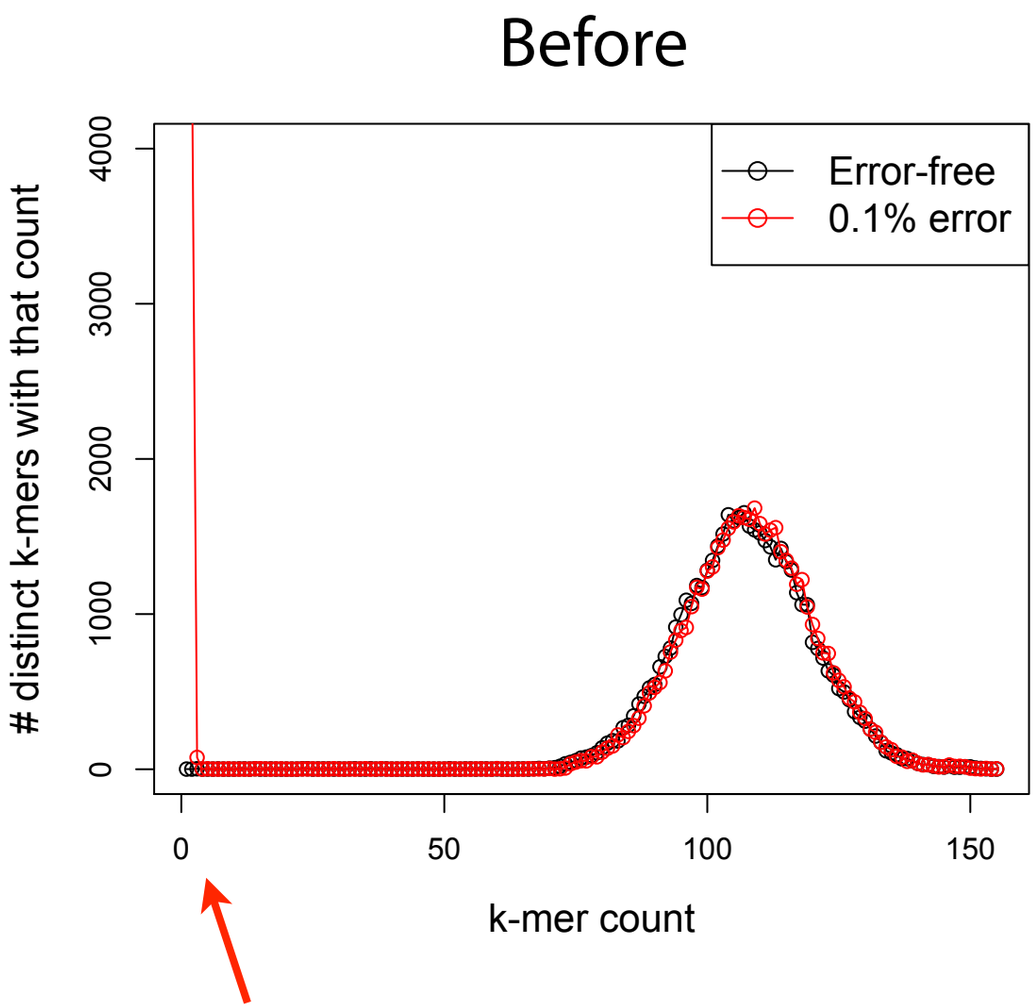
If neighbor has count ≥ *t*, replace old *k*-mer with neighbor.

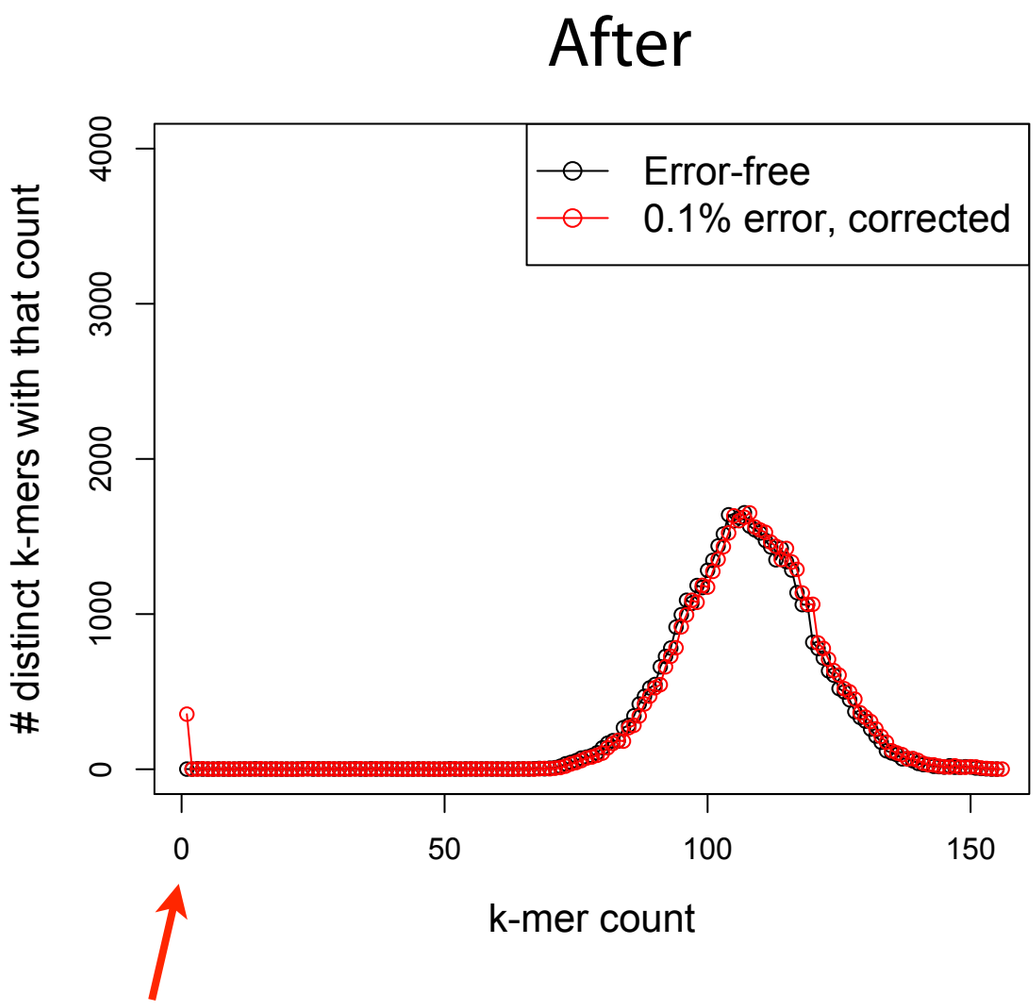
Pick a *t* that lies in the trough (the dip) between the peaks



Error correction: results

Corrects 99.2% of the errors in the example 0.1% error dataset



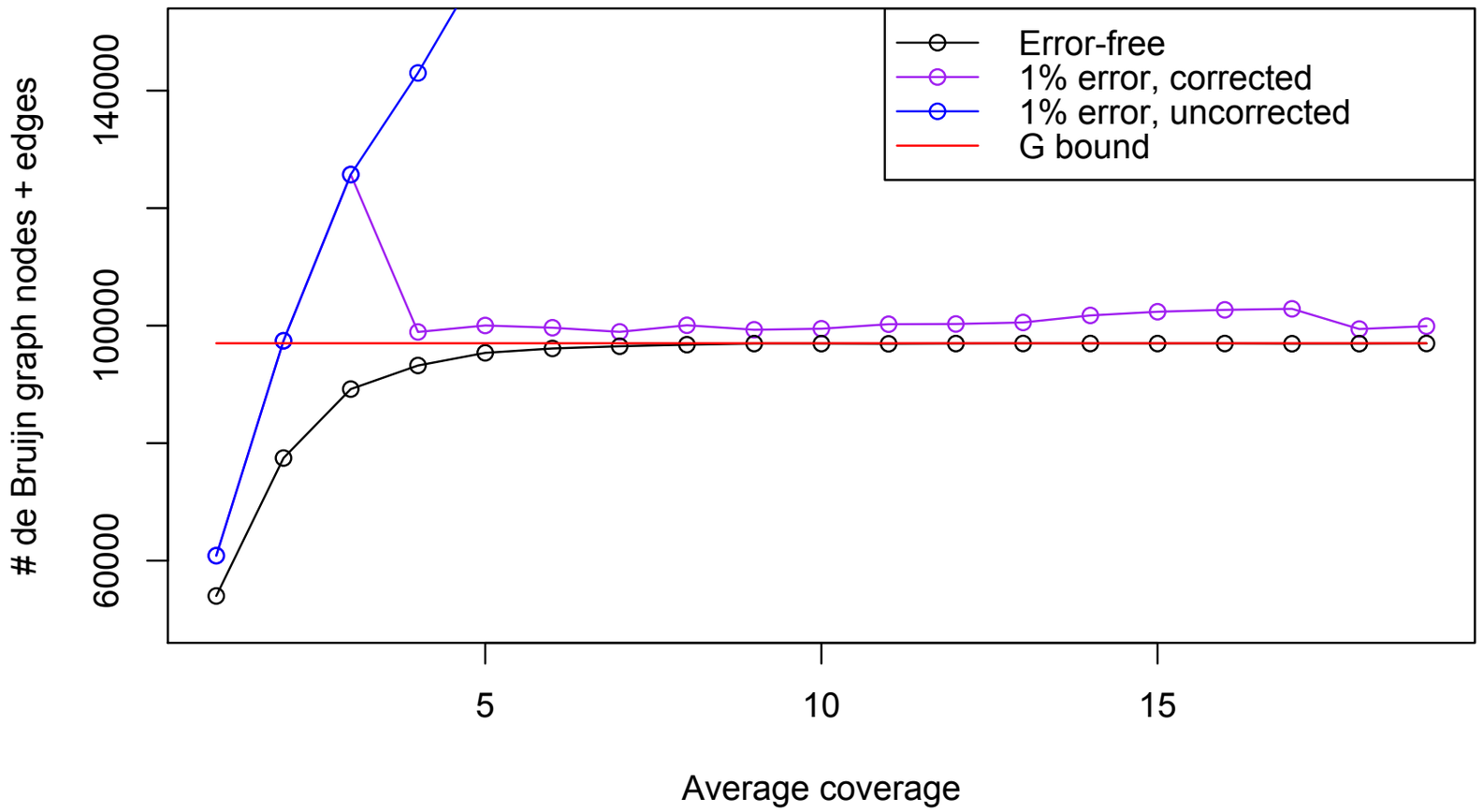


From 194K k-mers occurring exactly once to just 355

Error correction: results

For uncorrected reads, De Bruijn graph size is off the chart

For corrected reads, De Bruijn graph size is near G bound



Error correction

For error correction to work well:

- Average coverage should be high enough and *k* should be set so we can distinguish infrequent from frequent *k*-mers
- *k*-mer neighborhood we explore must be broad enough to find frequent neighbors. Depends on error rate and *k*.

Data structure for storing *k*-mer counts should be substantially smaller than the De Bruijn graph

- Otherwise there's no point doing error correction separately
- Counts don't have to be 100% accurate; just have to distinguish frequent and infrequent