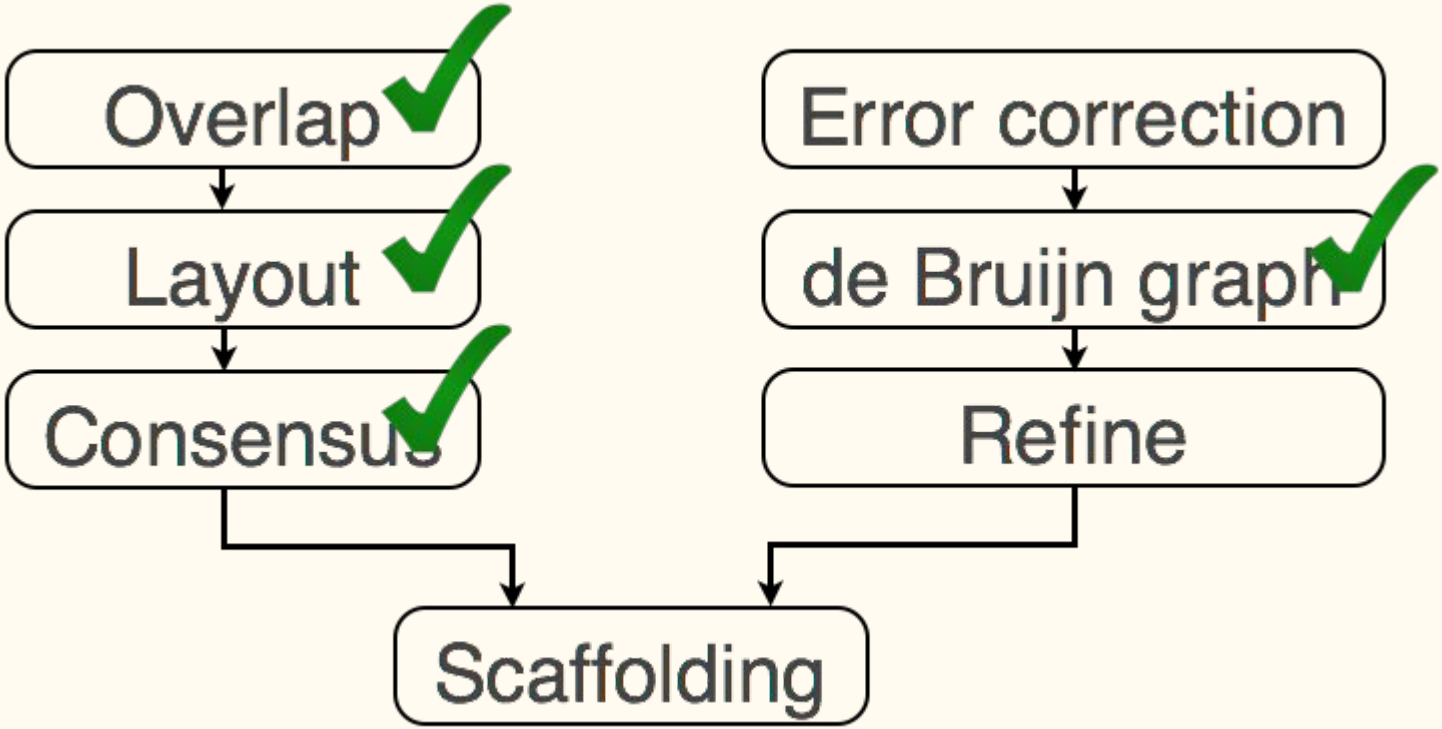
# Error correction

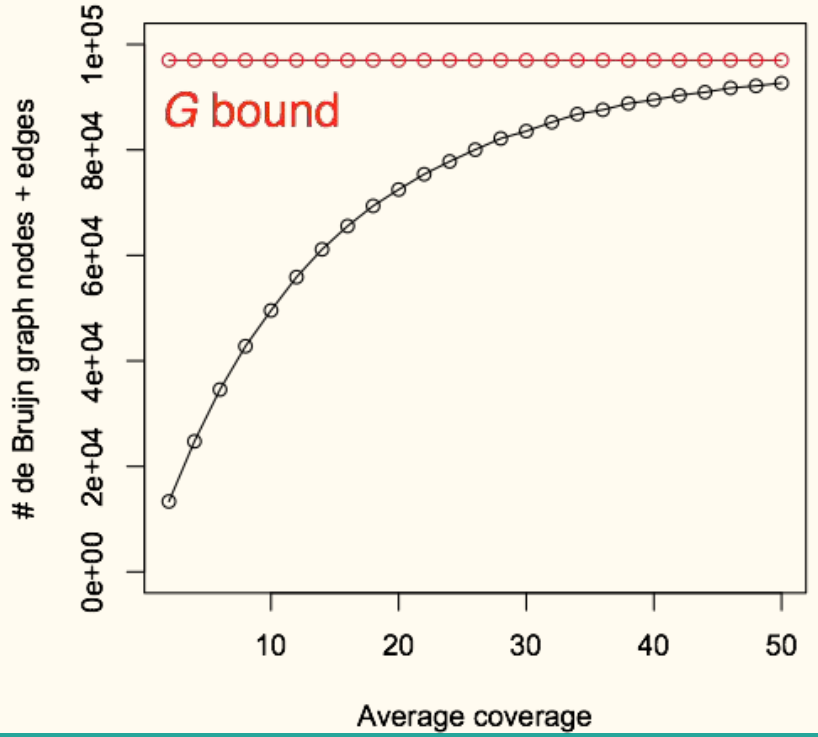
# Assembly paradigms

1: Overlap-Layout-Consensus (OLC) assembly  2: de Bruijn graph (DBG) assembly



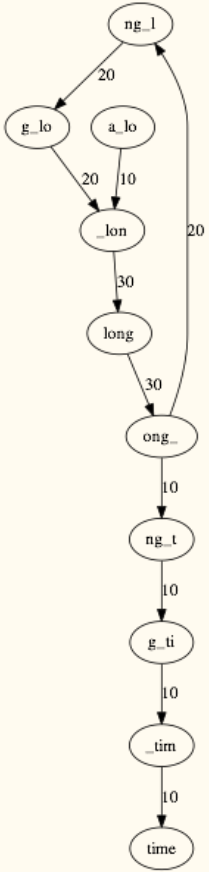
# Error correction

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



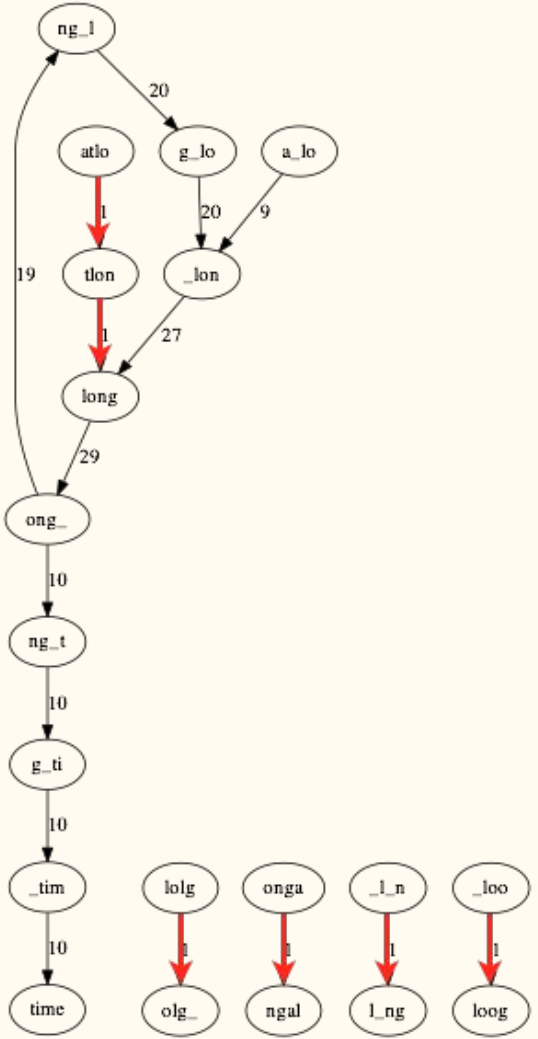

What about data with sequencing errors?

# Error correction



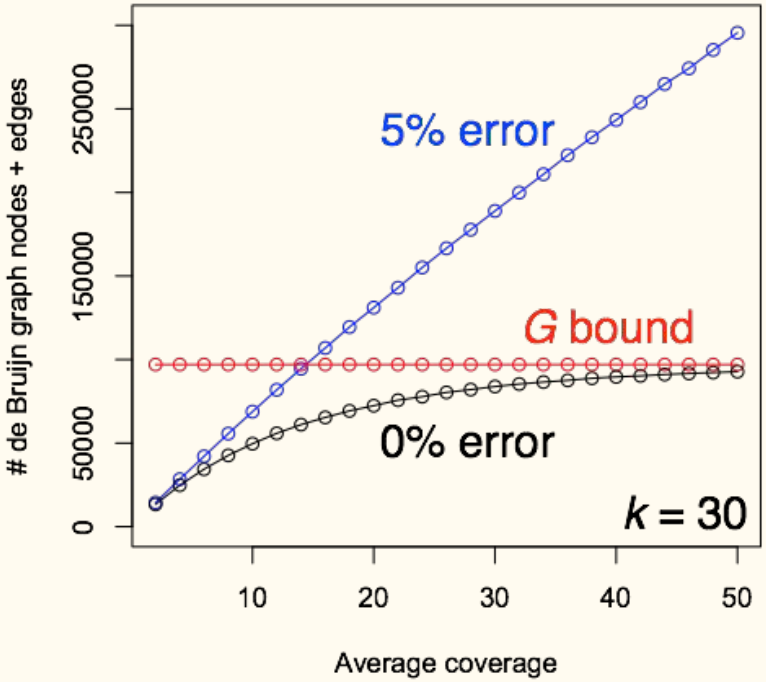

Take an example we saw (left) and mutate a $k$-mer character to a random other character with probability 1% (right)

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 $N$

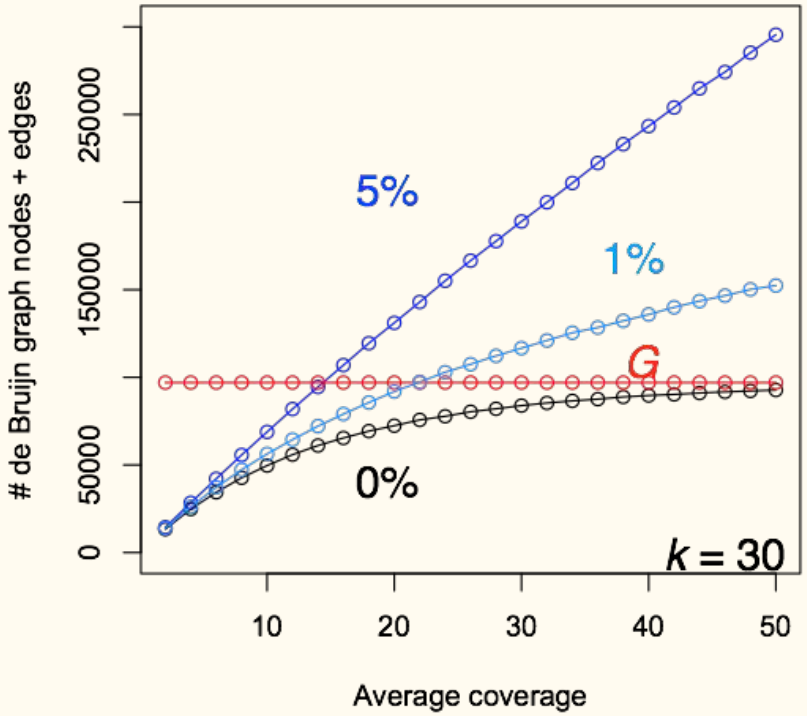



Same experiment as before but with 5% error added

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?

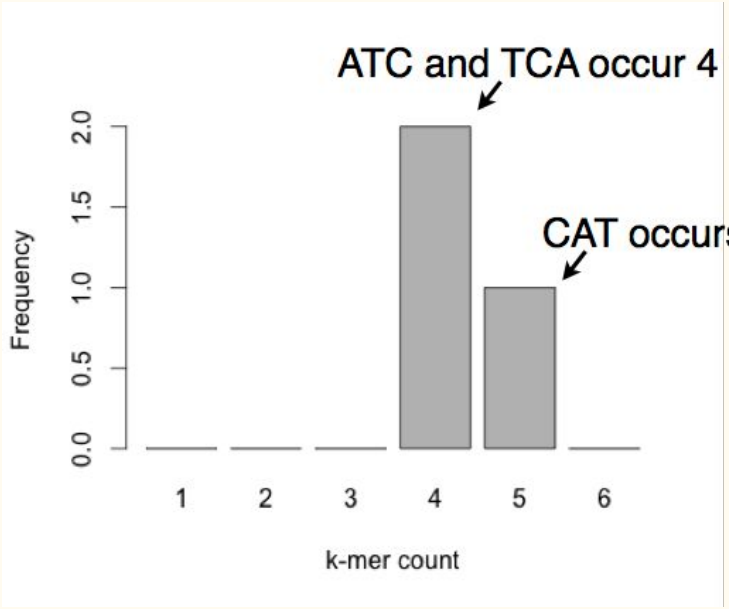
> Analogy: design a spell checker for a language you've never seen before. How do you come up with suggestions?

# 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:

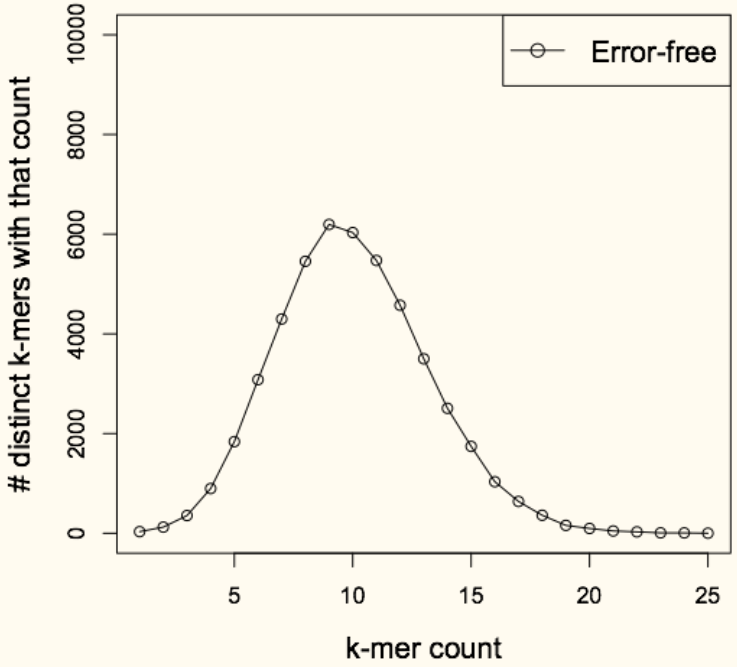


# Error correction

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

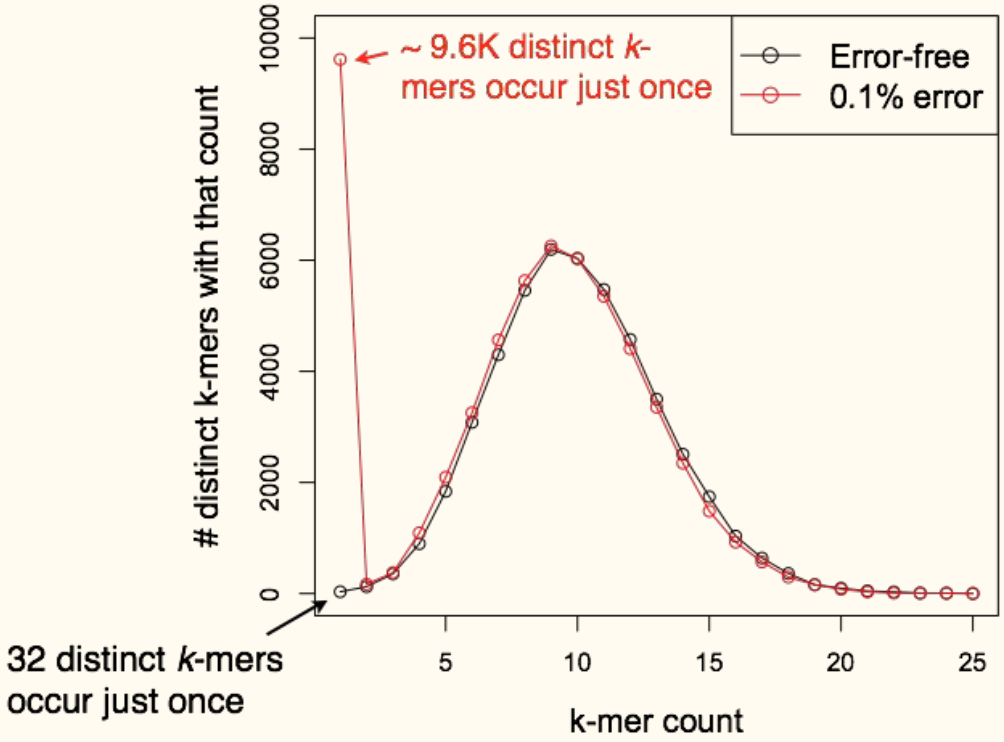
How would the picture change for data with 1% error rate?

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



# Error correction

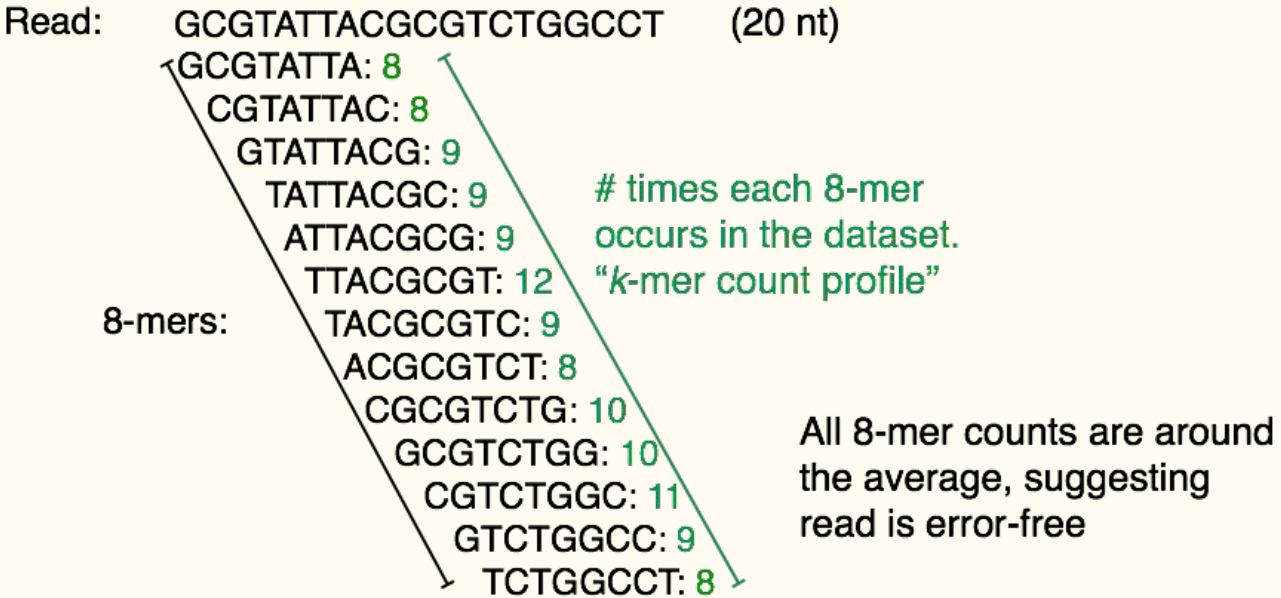
*k*-mers with errors usually occur fewer times than error-free *k*-mers



# Error correction

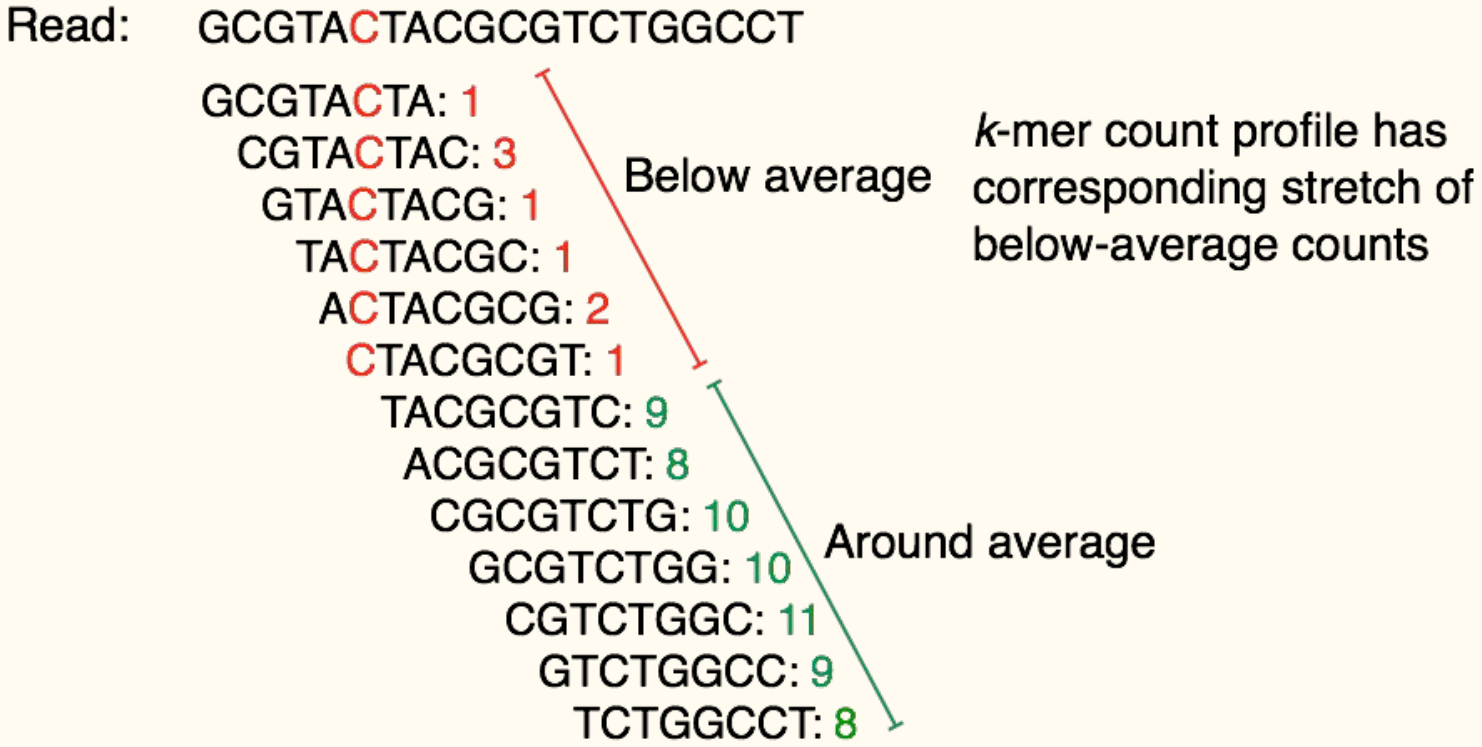
Idea: errors tend to turn frequent $k$-mers to infrequent $k$-mers, so corrections should do the reverse

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



# Error correction

Suppose there's an error

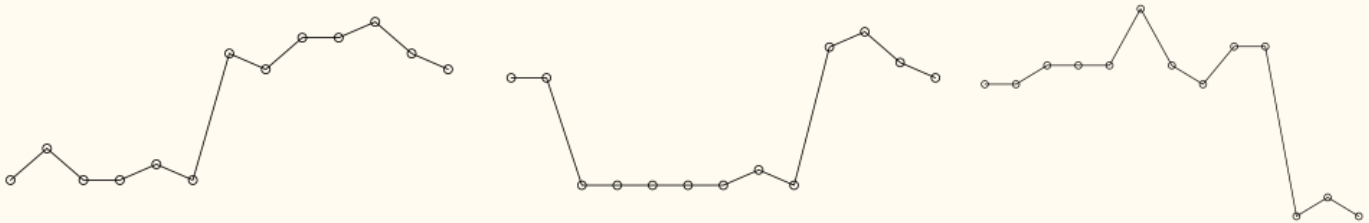


# Error correction

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

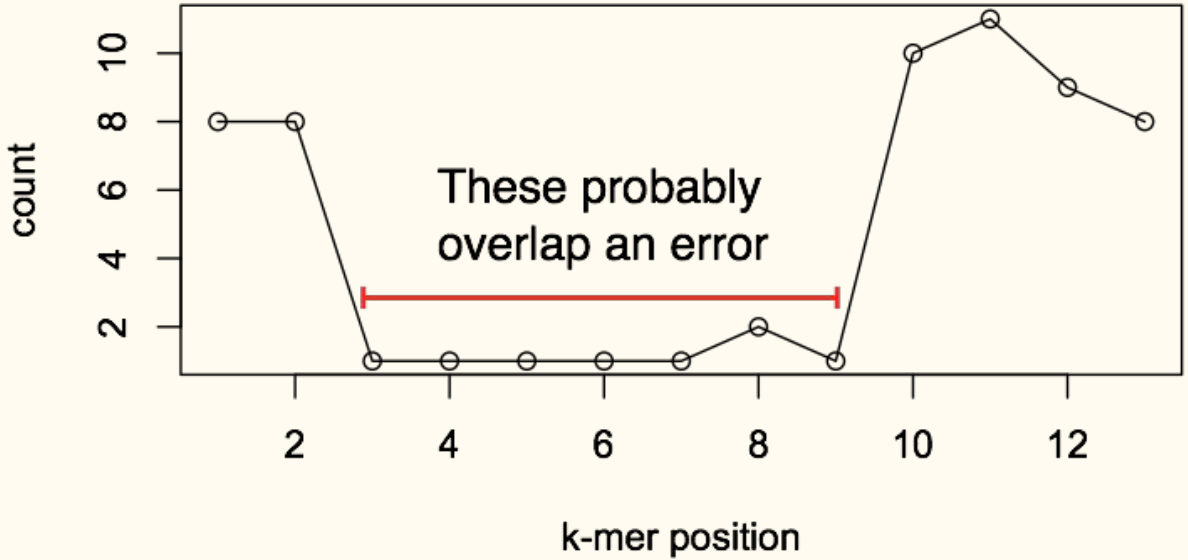
GCGTACTACGCGTCTGGCCTGCGTATTACACGTCTGGCCT GCGTATTACGCGTCTGGTCT

| | | |
|---|---|---|
| GCGTACTA: 1 | GCGTATTA: 8 | GCGTATTA: 8 |
| CGTACTAC: 3 | CGTATTAC: 8 | CGTATTAC: 8 |
| GTACTACG: 1 | GTATTACA: 1 | GTATTACG: 9 |
| TACTACGC: 1 | TATTACAC: 1 | TATTACGC: 9 |
| ACTACGCG: 2 | ATTACACG: 1 | ATTACGCG: 9 |
| CTACGCGT: 1 | TTACACGT: 1 | TTACGCGT: 12 |
| TACGCGTC: 9 | TACACGTC: 1 | TACGCGTC: 9 |
| ACGCGTCT: 8 | ACACGTCT: 2 | ACGCGTCT: 8 |
| CGCGTCTG: 10 | CACGTCTG: 1 | CGCGTCTG: 10 |
| GCGTCTGG: 10 | GCGTCTGG: 10 | GCGTCTGG: 10 |
| CGTCTGGC: 11 | CGTCTGGC: 11 | CGTCTGGT: 1 |
| GTCTGGCC: 9 | GTCTGGCC: 9 | GTCTGGTC: 2 |
| TCTGGCCT: 8 | TCTGGCCT: 8 | TCTGGTCT: 1 |



# Error correction

*k*-mer count profile indicates where errors are



# Error correction

Simple algorithm: given a count threshold $t$:

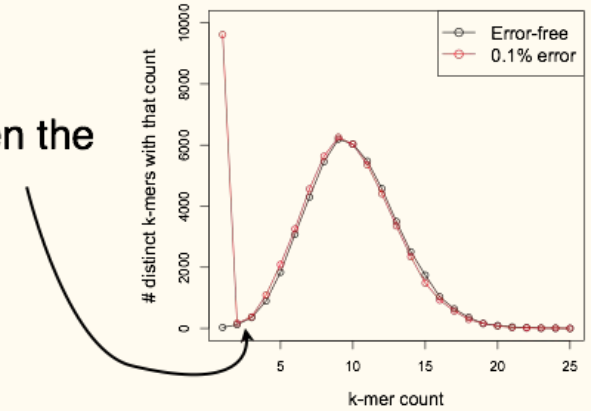
For each read:

For each k-mer:

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

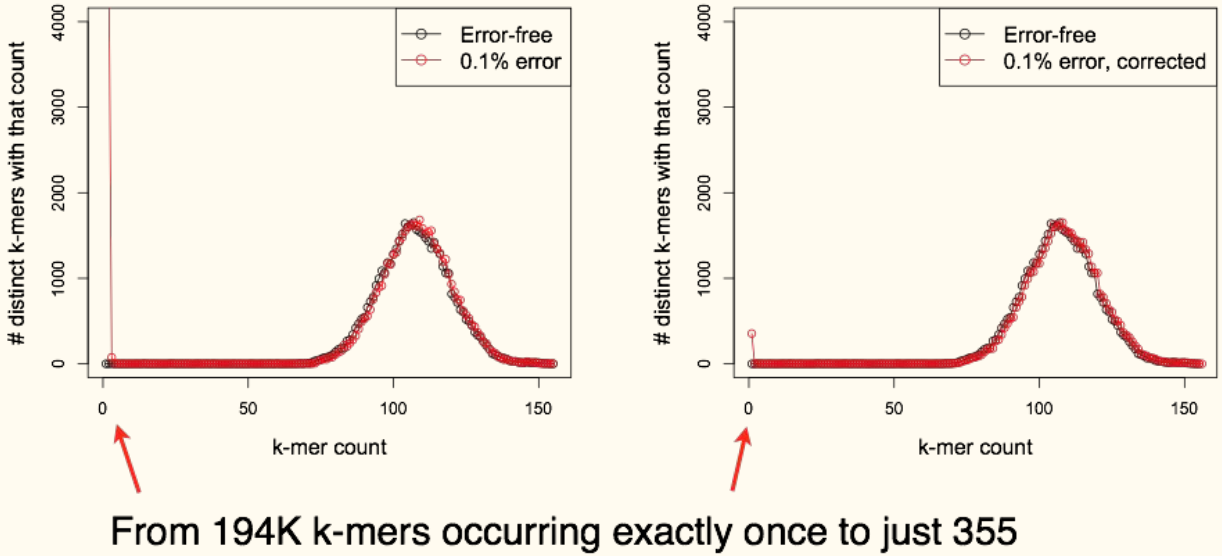
Examine $k$-mer's neighbors within certain Hamming/edit distance. If neighbor has count $\geq t$, replace old $k$-mer with neighbor.

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



# Error correction

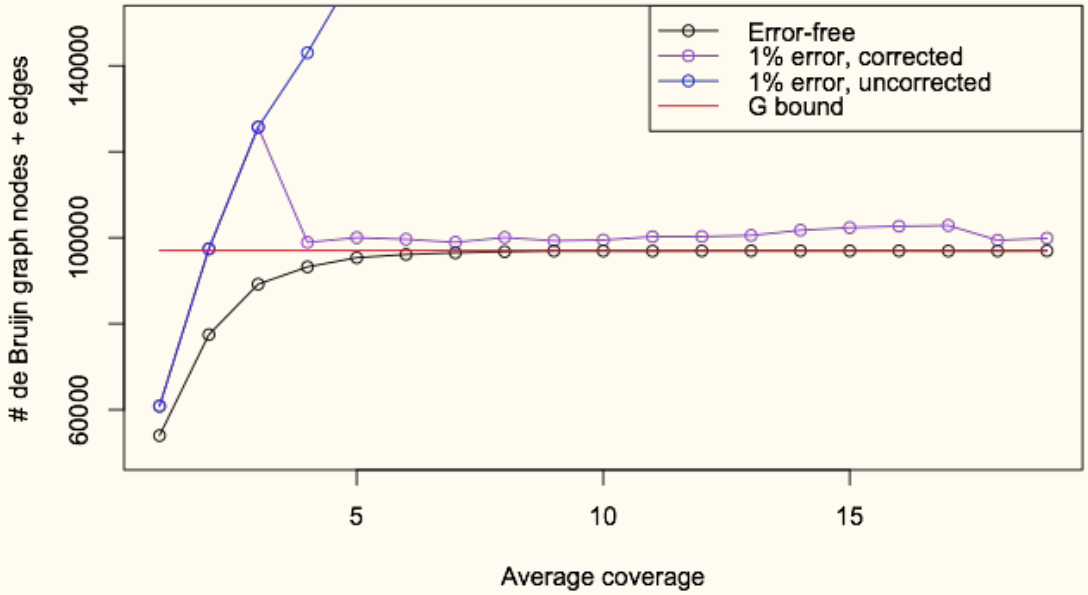
Corrects 99.2% of the errors in the example 0.1% error dataset



# 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.



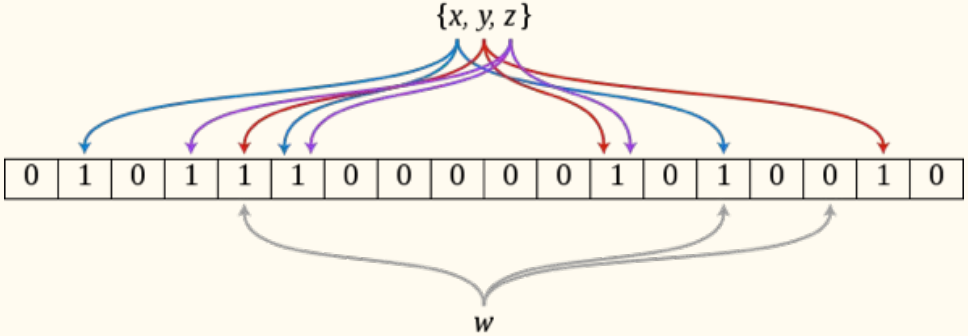
# Error correction

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

# Error correction: sketches

Sketch data structures are *extremely* compact, but *fail* sometimes
E.g. a Bloom Filter is like a hash set, but far smaller, and will sometimes say an object is in the set when it's not




CountMin sketches generalize Bloom Filters for histograms (sets where elements have associated counts); reported counts might be too high

These are candidates for compactly storing $k$-mer counts:

- http://en.wikipedia.org/wiki/Bloom_filter
- http://en.wikipedia.org/wiki/Count-Min_sketch