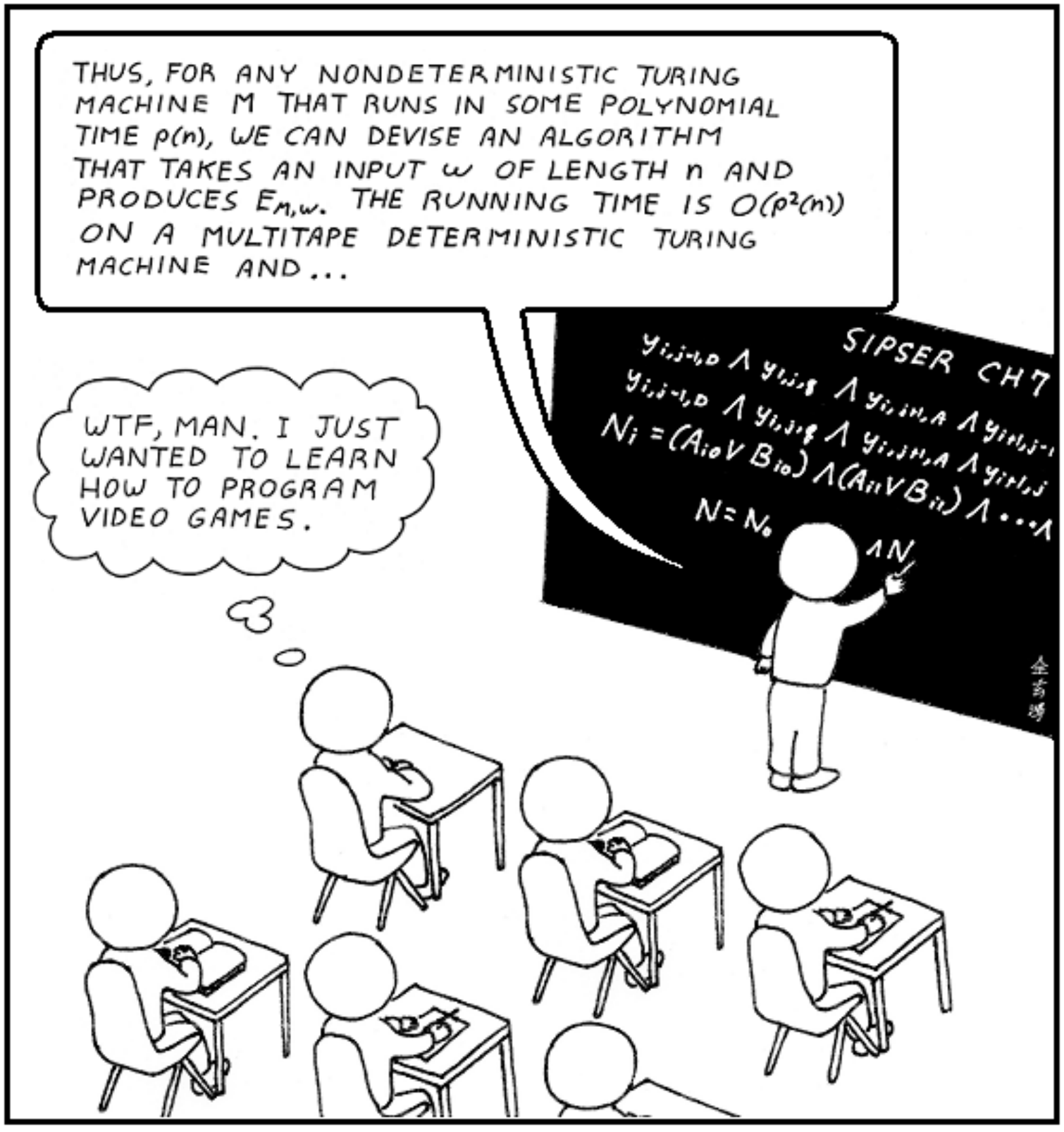
CSE 549:
Computational Biology

Computer Science for Biology

What is Computer Science?



http://people.cs.pitt.edu/~kirk/cs2110/computer_science_major.PNG

What is Computer Science?

Not actually simple to define constructively

Still debate whether certain areas constitute CS

Computer science is the scientific and practical approach to computation and its applications. It is the systematic study of the feasibility, structure, expression, and mechanization of the methodical procedures (or algorithms) that underlie the acquisition, representation, processing, storage, communication of, and access to information* …

What isn't Computer Science?

Don't install operating systems (may develop them)

Don't set up the office network (may study / design network protocols)

Not about Hacking together a program or learning a web-framework — programming ≠ CS (may study formal languages and develop new programming languages, and programming is a skill many computer scientists learn / master.)

*http://www.cs.bu.edu/AboutCS/WhatIsCS.pdf

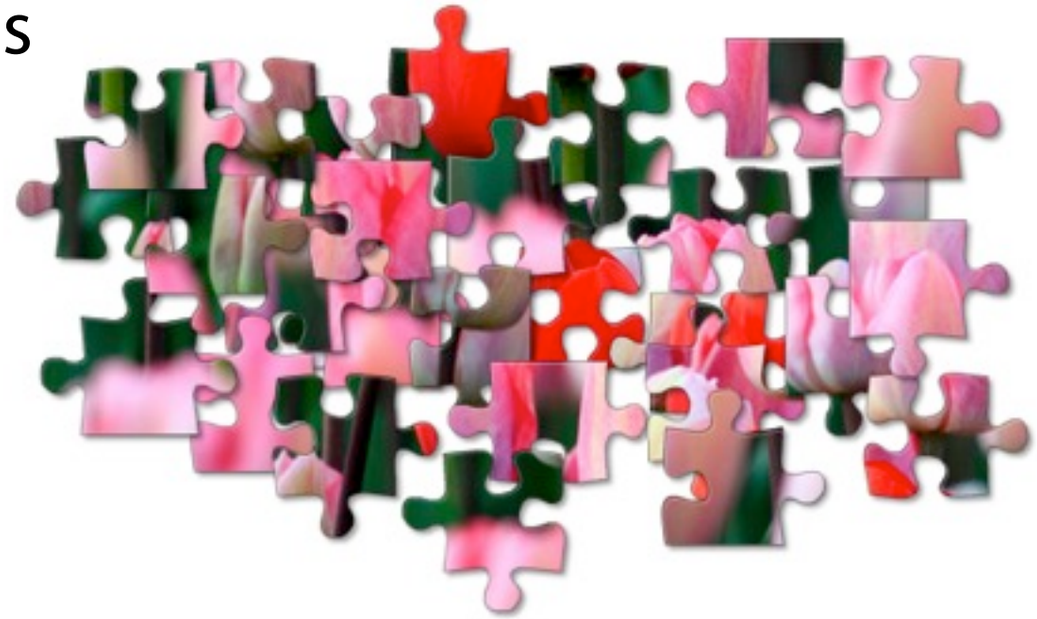
What is Computer Science?

Concerned with the development of provably **correct** and **efficient** computational procedures (algorithms & data structures) to answer **well-specified** problems.

To answer a computational question, we first need a well-formulated problem.

Assembly

Reads



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Reference genome

How to assemble puzzle without the benefit of knowing what the finished product looks like?

Input DNA

Next 5 slides courtesy of Ben Langmead

Assembly

Whole-genome "shotgun" sequencing starts by copying and fragmenting the DNA

("Shotgun" refers to the random fragmentation of the whole genome; like it was fired from a shotgun)

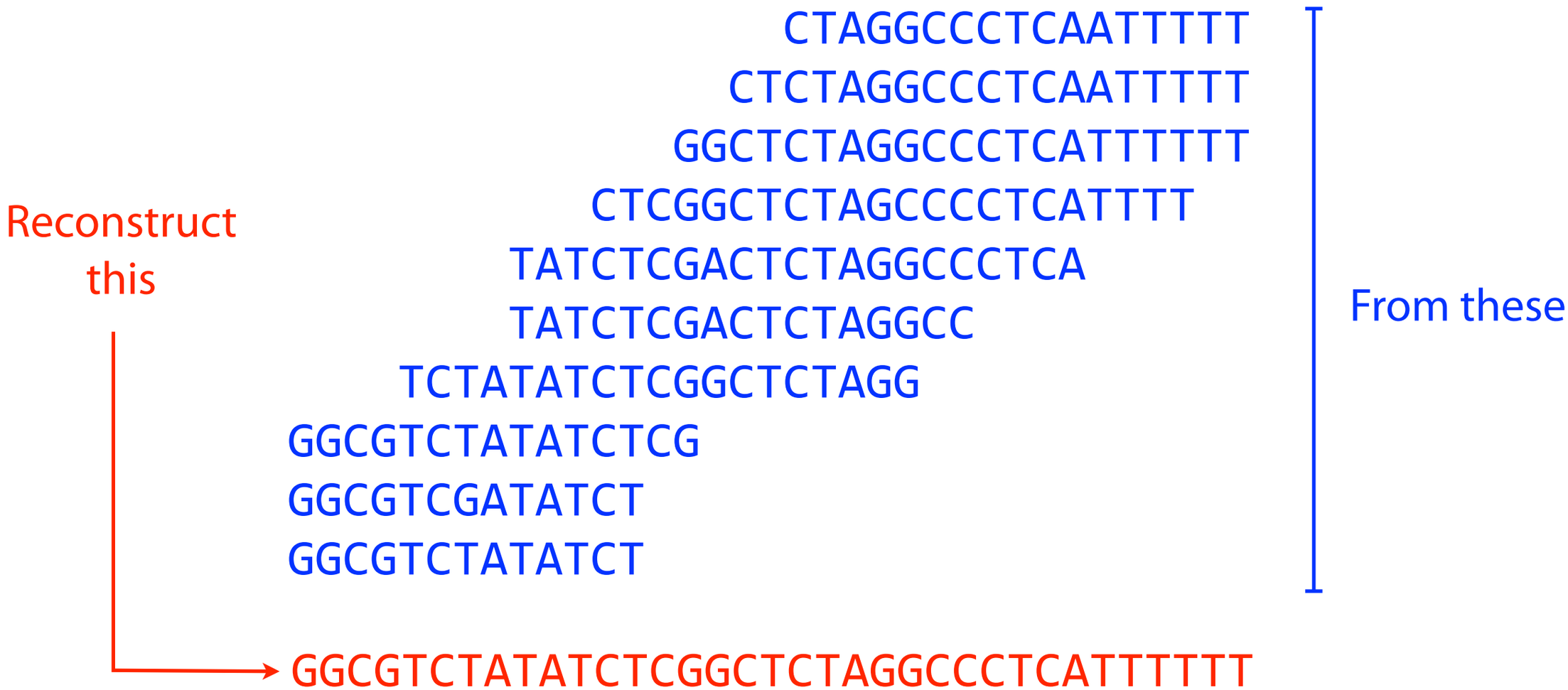
Input: GGCGTCTATATCTCGGCTCTAGGCCCTCATTTTTT

Copy: GGCGTCTATATCTCGGCTCTAGGCCCTCATTTTTT
GGCGTCTATATCTCGGCTCTAGGCCCTCATTTTTT
GGCGTCTATATCTCGGCTCTAGGCCCTCATTTTTT
GGCGTCTATATCTCGGCTCTAGGCCCTCATTTTTT

Fragment: GGCGTCTA TATCTCGG CTCTAGGCCCTC ATTTTTT
GGC GTCTATAT CTCGGCTCTAGGCCCTCA TTTTTT
GGCGTC TATATCT CGGCTCTAGGCCCT CATTTTTT
GGCGTCTAT ATCTCGGCTCTAG GCCCTCA TTTTTT

Assembly

Assume sequencing produces such a large # fragments that almost all genome positions are *covered* by many fragments...



Assembly

...but we don't know what came from where

CTAGGCCCTCAATTTTT
GGCGTCTATATCT
CTCTAGGCCCTCAATTTTT
TCTATATCTCGGCTCTAGG
GGCTCTAGGCCCTCATTTTTT
CTCGGCTCTAGCCCCTCATTTT
TATCTCGACTCTAGGCCCTCA
GGCGTCGATATCT
TATCTCGACTCTAGGCC
GGCGTCTATATCTCG

From these

Reconstruct this

GGCGTCTATATCTCGGCTCTAGGCCCTCATTTTTT

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To answer a computational question, we first need a well-formulated problem.

Given: a collection, R, of sequencing reads (strings)

Find: The genome (string), G, that generated them

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Not well-specified.
What makes one genome more likely than another?
What constraints do we place on the space of solutions?

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To answer a computational question, we first need a well-formulated problem.

Given: a collection, R, of sequencing reads (strings) ✔

Find: The shortest genome (string), G, that contains all of them

Shortest Common Superstring

Given: a collection, $S = \{s_1, s_2, \ldots, s_k\}$, of sequencing reads (strings)

Find*: The shortest possible genome (string), G, such that $s_1, s_2, \ldots, s_k$ are all substrings of G

How, might we go about solving this problem?

*for reasons we'll explore later, this isn't actually a great formulation for genome assembly.

Shortest common superstring

Given a collection of strings *S*, find *SCS*(*S*): the shortest string that contains all strings in *S* as substrings

Without requirement of "shortest," it's easy: just concatenate them

Example: *S*: BAA AAB BBA ABA ABB BBB AAA BAB

Concatenation: BAAAABBBAABAABBBBBBAAABAB

24

SCS(S): AAABBBABAA

10

AAA
AAB
ABB
BBB
BBA
BAB
ABA
BAA

Slide courtesy of Ben Langmead

Shortest common superstring

Can we solve it?

Imagine a modified overlap graph where each edge has cost = - (length of overlap)

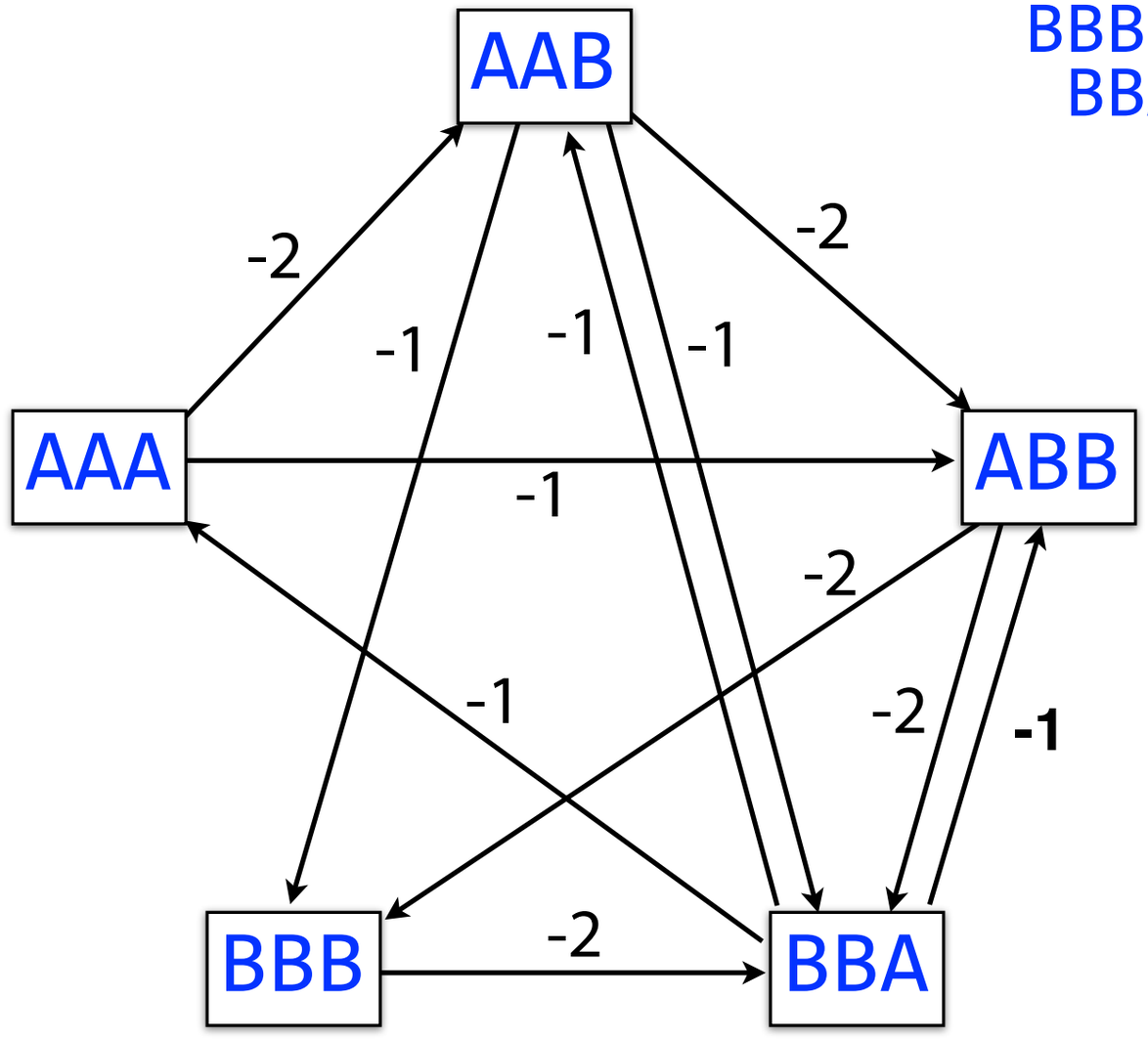
SCS corresponds to a path that visits every node once, minimizing total cost along path

That's the *Traveling Salesman Problem* (*TSP*), which is NP-hard!

S: AAA AAB ABB BBB BBA

SCS(S): AAABBBA

AAA
AAB
ABB
BBB
BBA



Slide courtesy of Ben Langmead

Shortest common superstring

Say we disregard edge weights and just look for a path that visits all the nodes exactly once

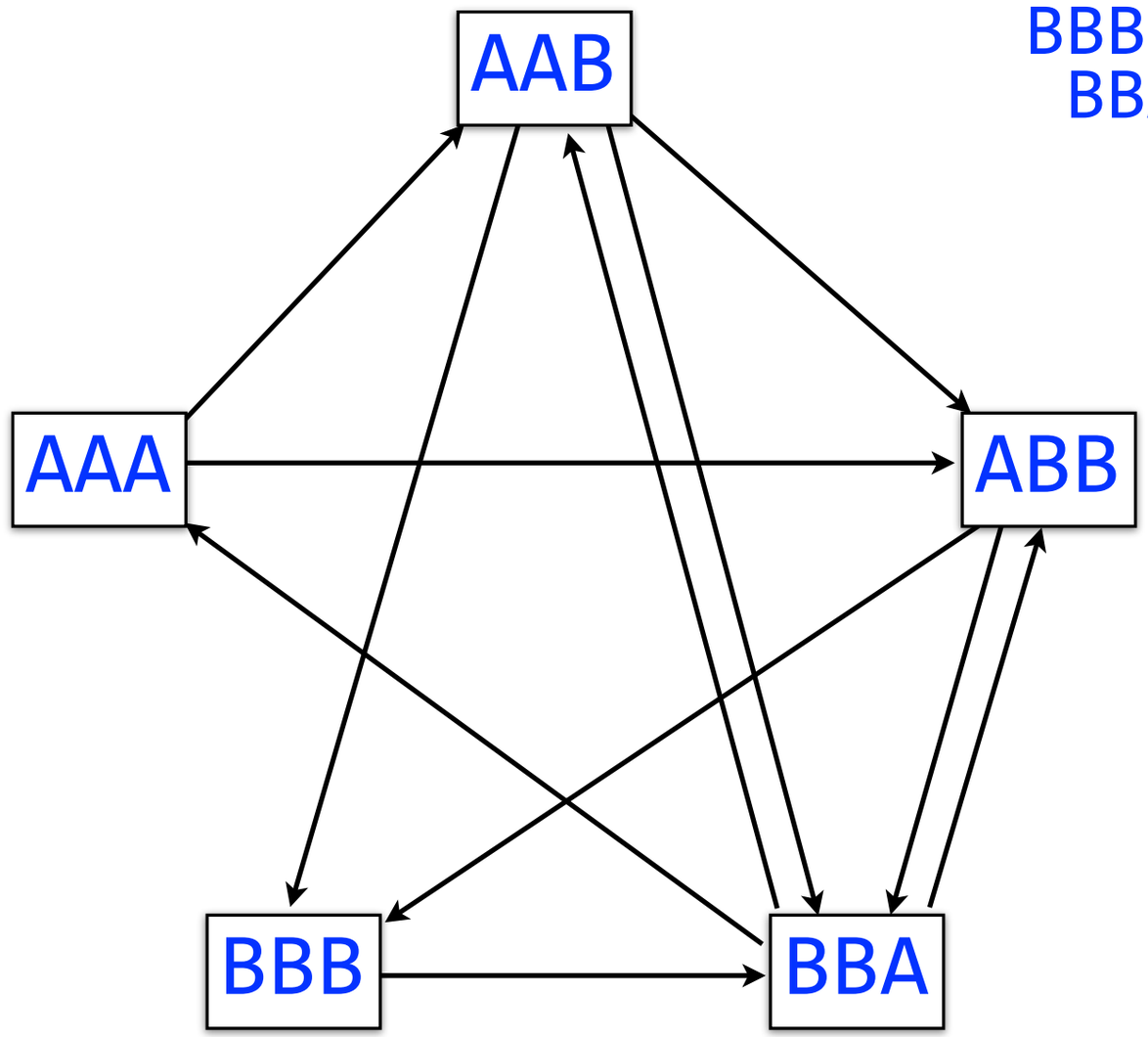
That's the *Hamiltonian Path* problem: NP-complete

Indeed, it's well established that SCS is NP-hard

S: AAA AAB ABB BBB BBA

SCS(S): AAABBBA

AAA
AAB
ABB
BBB
BBA



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Shortest common superstring & friends

Traveling Salesman, Hamiltonian Path, and Shortest Common Superstring are all NP-hard

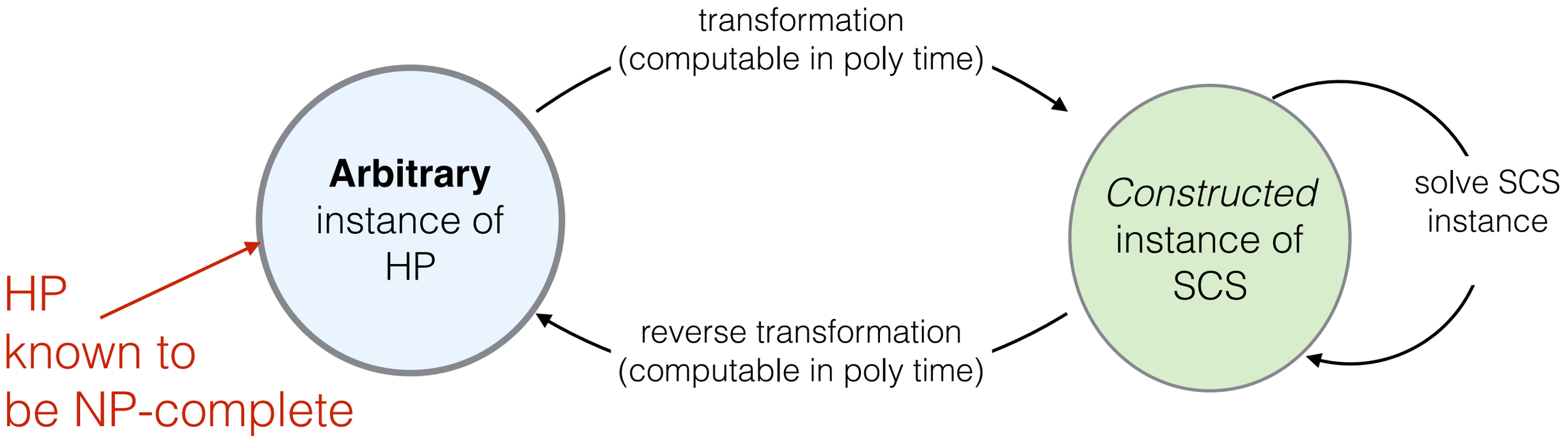
For refreshers on Traveling Salesman, Hamiltonian Path, NP-hardness and NP-completeness, see Chapters 34 and 35 of "Introduction to Algorithms" by Cormen, Leiserson, Rivest and Stein, or Chapters 8 and 9 of "Algorithms" by Dasgupta, Papadimitriou and Vazirani (free online: http://www.cs.berkeley.edu/~vazirani/algorithms)

Slide courtesy of Ben Langmead

Important note: The fact that we modeled SCS as NP-hard problems (TSP and HP) **does not** prove that (the decision version of) SCS is NP-complete. To do that, we must **reduce** a known NP-complete problem to **SCS**.

Given an instance I of a known hard problem, generate an instance I' of SCS such that if we can solve I' in polynomial time, then we can solve I in polynomial time. This *implies* that SCS is *at least* as hard as the hard problem.

This can be done e.g. with HAMILTONIAN PATH



Shortest Common Superstring

The fact that SCS is **NP-complete** means that it is unlikely that there exists *any* algorithm that can solve a general instance of this problem in time polynomial in n — the number of strings.

If we give up on finding the *shortest* possible superstring G, how does the situation change?

Shortest Common Superstring

There's a "greedy" *heuristic* that turns out to be an *approximation algorithm* (provides a solution within a constant factor of the the optimum)

At each step, chose the pair of strings with the maximum overlap, merge them, and return the merged string to the collection.

Greedy conjecture factor of 2-OPT *is* the worst case

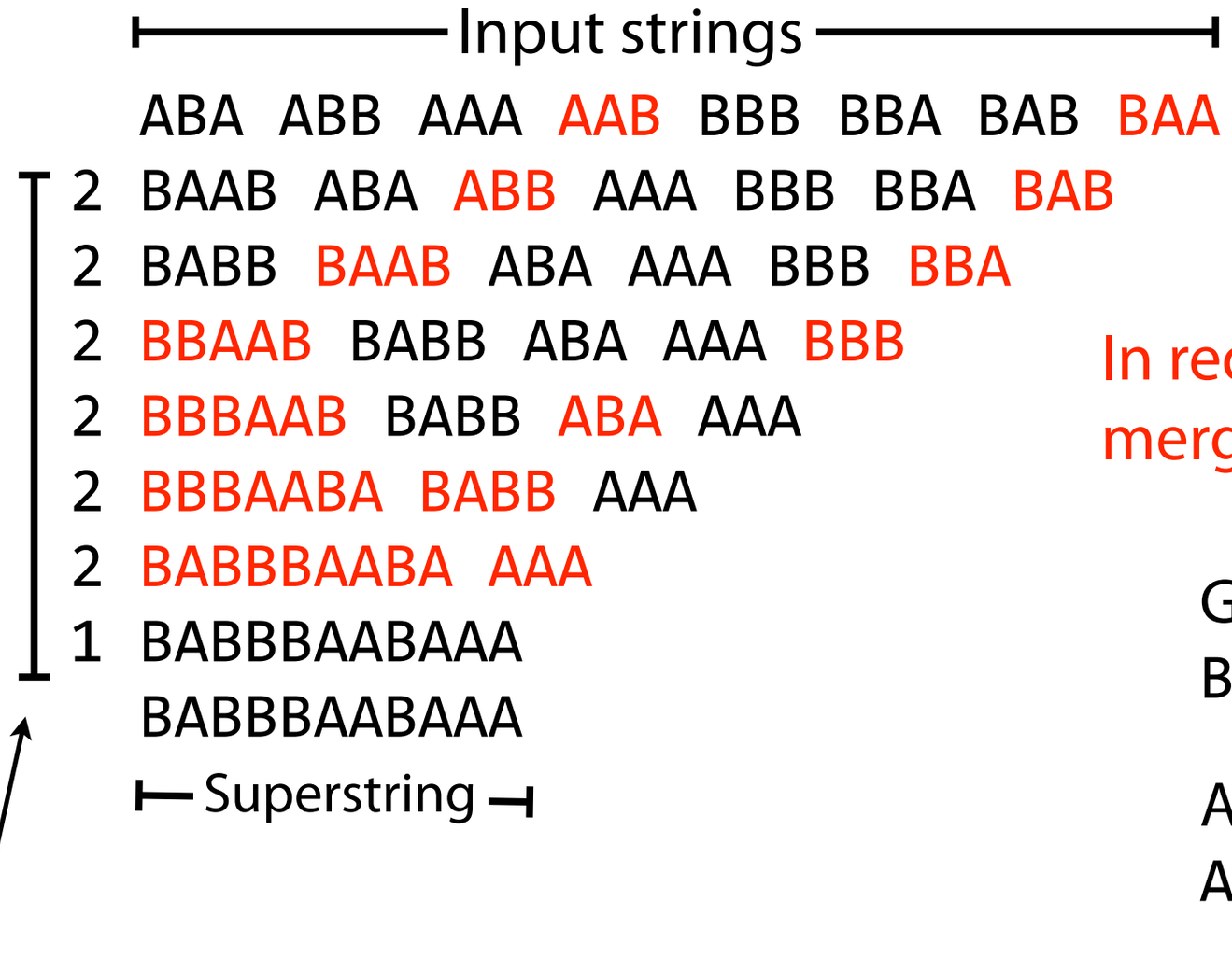
Different approx. (**not all greedy**)

ratio	authors	year
	approximating SCS	
3	Blum, Jiang, Li, Tromp and Yannakakis [4]	1991
$2\frac{8}{9}$	Teng, Yao [23]	1993
$2\frac{5}{6}$	Czumaj, Gasieniec, Piotrow, Rytter [8]	1994
$2\frac{50}{63}$	Kosaraju, Park, Stein [15]	1994
$2\frac{3}{4}$	Armen, Stein [1]	1994
$2\frac{50}{69}$	Armen, Stein [2]	1995
$2\frac{2}{3}$	Armen, Stein [3]	1996
$2\frac{25}{42}$	Breslauer, Jiang, Jiang [5]	1997
$2\frac{1}{2}$	Sweedyk [21]	1999
$2\frac{1}{2}$	Kaplan, Lewenstein, Shafrir, Sviridenko [12]	2005
$2\frac{1}{2}$	Paluch, Elbassioni, van Zuylen [18]	2012
$2\frac{11}{23}$	Mucha [16]	2013

Golovnev, Kulikov, & Mihajlin. "Approximating Shortest Superstring Problem Using de Bruijn Graphs." Combinatorial Pattern Matching. Springer Berlin Heidelberg, 2013.

Shortest common superstring: greedy

Greedy-SCS algorithm in action ($l = 1$):



In red are strings that get merged before the next round

Greedy answer:
BABBBAABAAA

Actual SCS:
AAABBBABAA

Rounds of merging, one merge per line.
Number in first column = length of overlap merged before that round.

Slide courtesy of Ben Langmead

Shortest common superstring: greedy

Greedy-SCS algorithm in action ($l = 1$):

Note: approx. guarantee
is on length of the superstring
Actual result may be very different.

Input strings

```
   ABA ABB AAA AAB BBB BBA BAB BAA
2  BAAB ABA ABB AAA BBB BBA BAB
2  BABB BAAB ABA AAA BBB BBA
2  BBAAB BABB ABA AAA BBB
2  BBBAAB BABB ABA AAA
2  BBBAABA BABB AAA
2  BABBBAABA AAA
1  BABBBAABAAA
   BABBBAABAAA
```

Superstring

In red are strings that get
merged before the next round

Greedy answer:
BABBBAABAAA

Actual SCS:
AAABBBABAA

Rounds of merging, one merge per line.
Number in first column = length of overlap merged before that round.

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