Computer are dumb

(And why you care.)

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Outline

- Algorithms and scaling
- Heuristics in computation
- Some thoughts on hardware
- Are you right? (Or at least not wrong?)
- Whose fault is it that you're probably wrong? (RCR training!)

Consider: finding SNPs.

Given: reference genome, sequence reads, mapping.

The mapping contains a list of reads, mapped locations within reference, and the location of differences.

How can we find all single-nucleotide variation?

Approach one: by genome

```
for location in genome:
  reference = genome[location]
  bases = get_overlapping(location)
  for base in bases:
      if base != reference:
          # count SNP
```

Approach two: by read

```
for read in mapped_reads:
  for differences in read:
    # count SNP
```

Approach one: by genome

```
for location in genome:
  reference = genome[location]
  bases = get_overlapping(location)
  for base in bases:
     if base != reference:
          # count SNP
```

How does this algorithm scale?

Imagine:

 increasing size of genome

 increasing number of reads

Approach two: by read

```
for read in mapped_reads:
  for differences in read:
     # count SNP
```

How does *this* algorithm scale?

Scaling and Big-O notation

- The first approach scales with both the size of the genome and the number of reads:

  $t \sim O(N * M)$

- The second approach scales with just the number of reads:

  $t \sim O(M)$

Scaling and Big-O notation

- The first approach scales with both the size of the genome and the number of reads:

$$\boxed{t \sim O(N * M)}$$

- why would you want this??

- The second approach scales with just the number of reads:

$$t \sim O(M)$$

What about a different problem?

- I am interested in locations X, Y, and Z.

- Give me all SNPs at or near those locations.

```
for location in list_of_locations:
  reference = genome[location]
  bases = get_overlapping(location)
  for base in bases:
      if base != reference:
          # count SNP
```

Important note

- *Algorithm* scaling is independent of the actual time it takes to run.

- Scaling tells you how time-to-run scales as the problem size changes, nothing more.

Easy-to-check vs easy-to-find

Given a number, factor it into only prime numbers.

This is hard.

Given a set of prime numbers, verify that they multiple to yield a particular number.

This is easy.

Easy-to-check vs easy-to-find, #2

Suppose:

50 dorm rooms, two students per room
100 students can be admitted, of 400 total
Dean has list of students that cannot be paired.

It is *easy to check* any particular list of student/room combinations for validity.

In general, it is *extremely hard* to quickly find a guaranteed solution.

Heuristics

- "Heuristics" are short cuts that usually work (but occasionally go horribly wrong).

- Not all problems are amenable.
  - Prime numbers? No good, *fast* short cut.
  - Housing? Sure – start with a random solution, eliminate one of each pair that conflicts, until you find a non-conflict..

- Heuristics rely on assumptions about the specific type of problem you're going to tackle, and don't always work.
  - If the Dean is evil, he can construct a list of incompatible roommates that breaks your process.
  - Or he can just gives you a really long list of incompatible roommates.

Example: BLAST

BLASTN filters sequences for exact matches between “words” of length 11:

```
GAGGGTATGACGATATGGCGATGGAC
||x|||||x|||||||||||x|x||x
GAcGGTATcACGATATGGCGgT-Gag
```

This results in a O(n log n) algorithm.

Example: BLAST

…but what about pathological situations?

```
GAGGGTATGACGATATGGCGATGGAC
||x|||||x|||||x|||||x|x||x
GAcGGTATcACGATGTGGCGgT-Gag
```

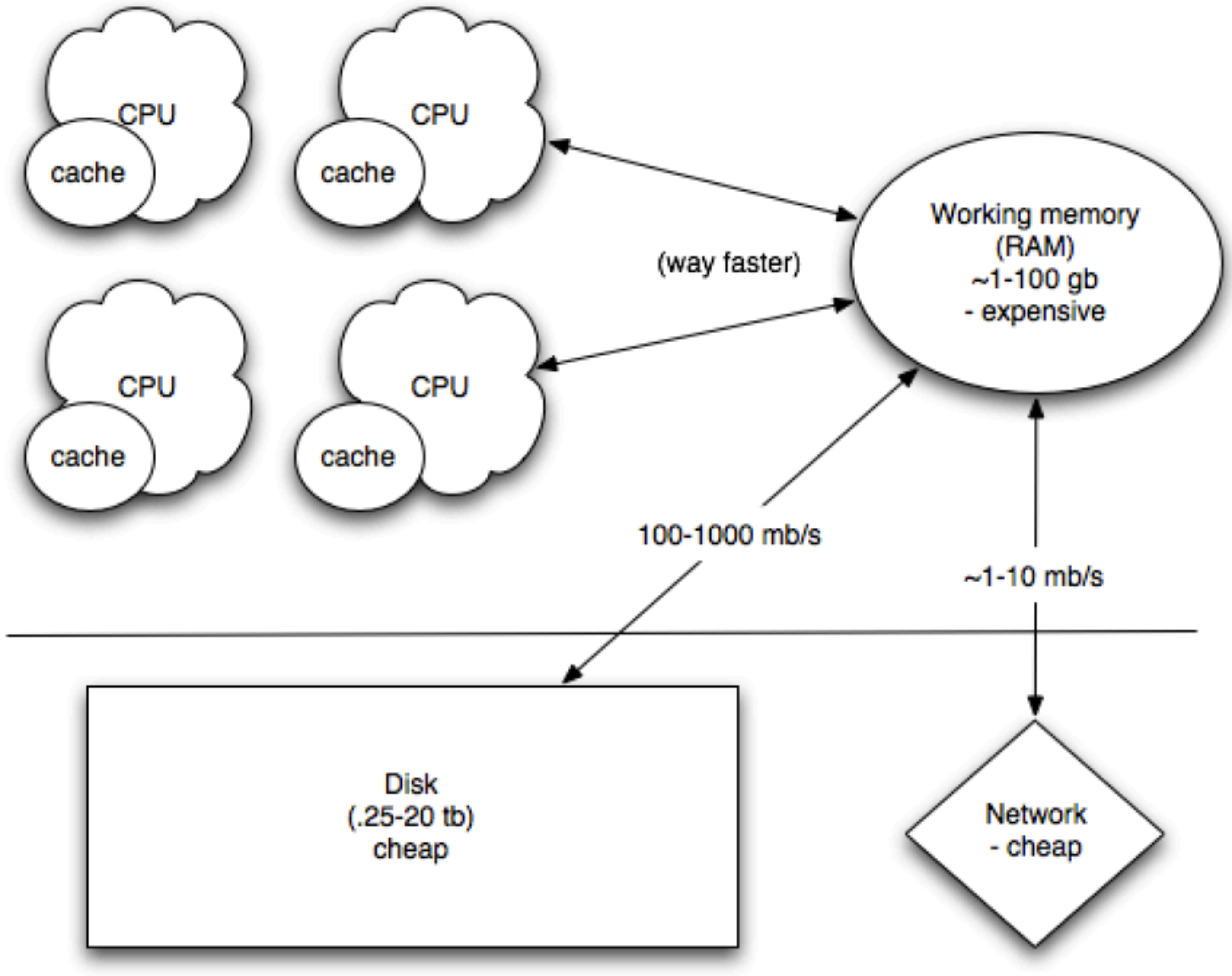
This will not be scored as a match, because BLAST *only* scores matches with a core "seed" match of 11 bases.

Heuristics

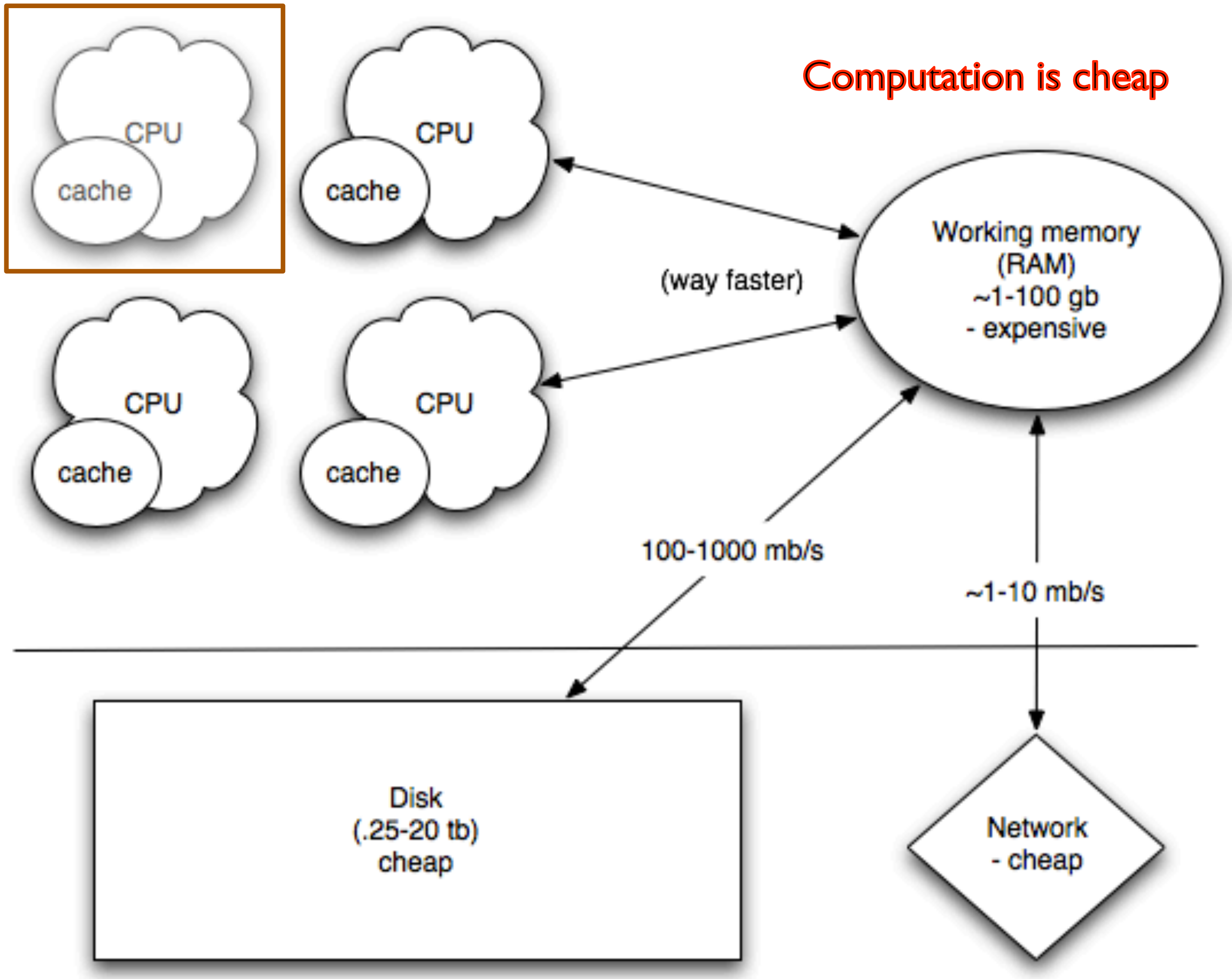
- Often take advantage of "fast" operations on computers.

- What operations are fast are governed by
  - Algorithmic considerations / fundamental CS
  - Hardware and software implementations

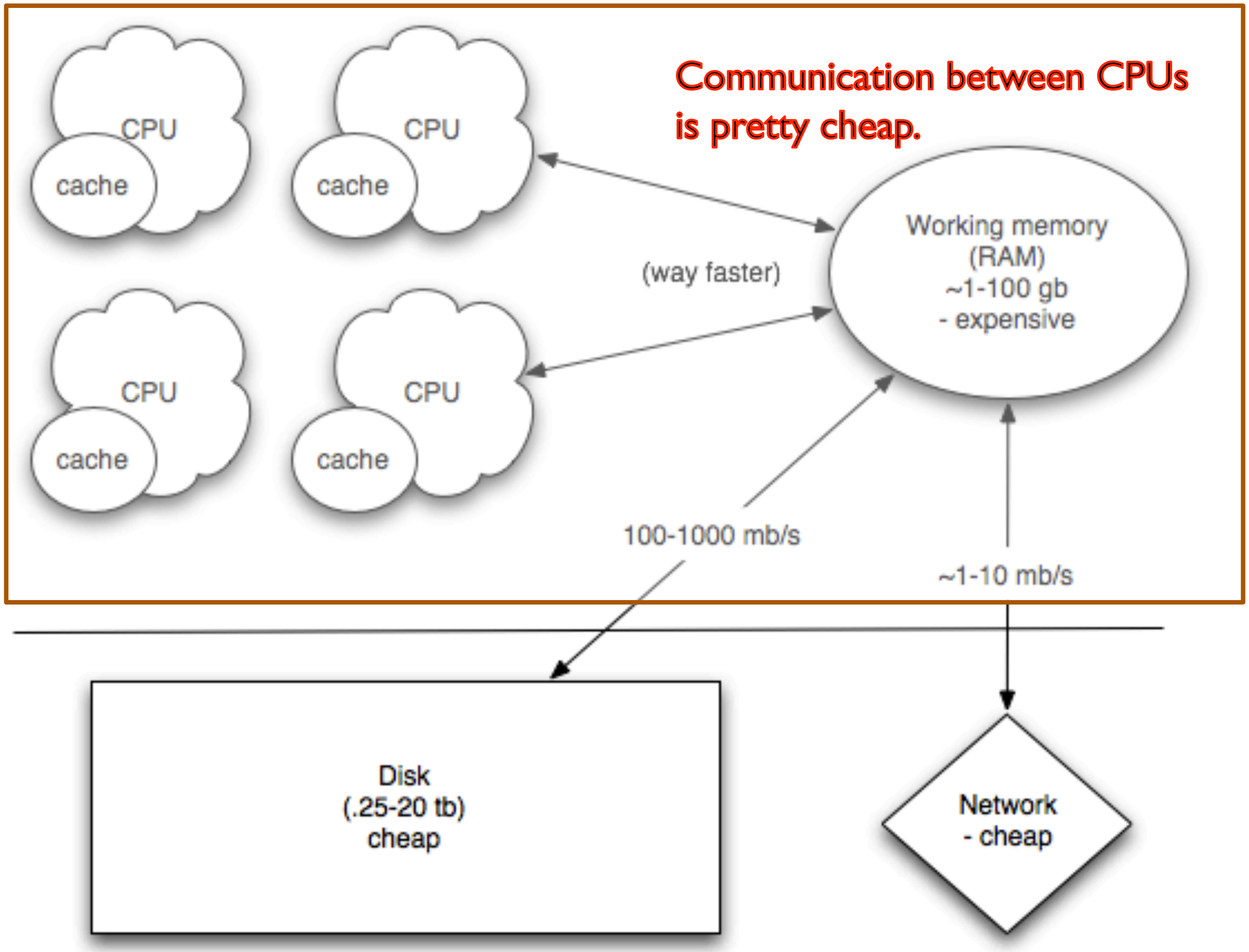
Computer architecture



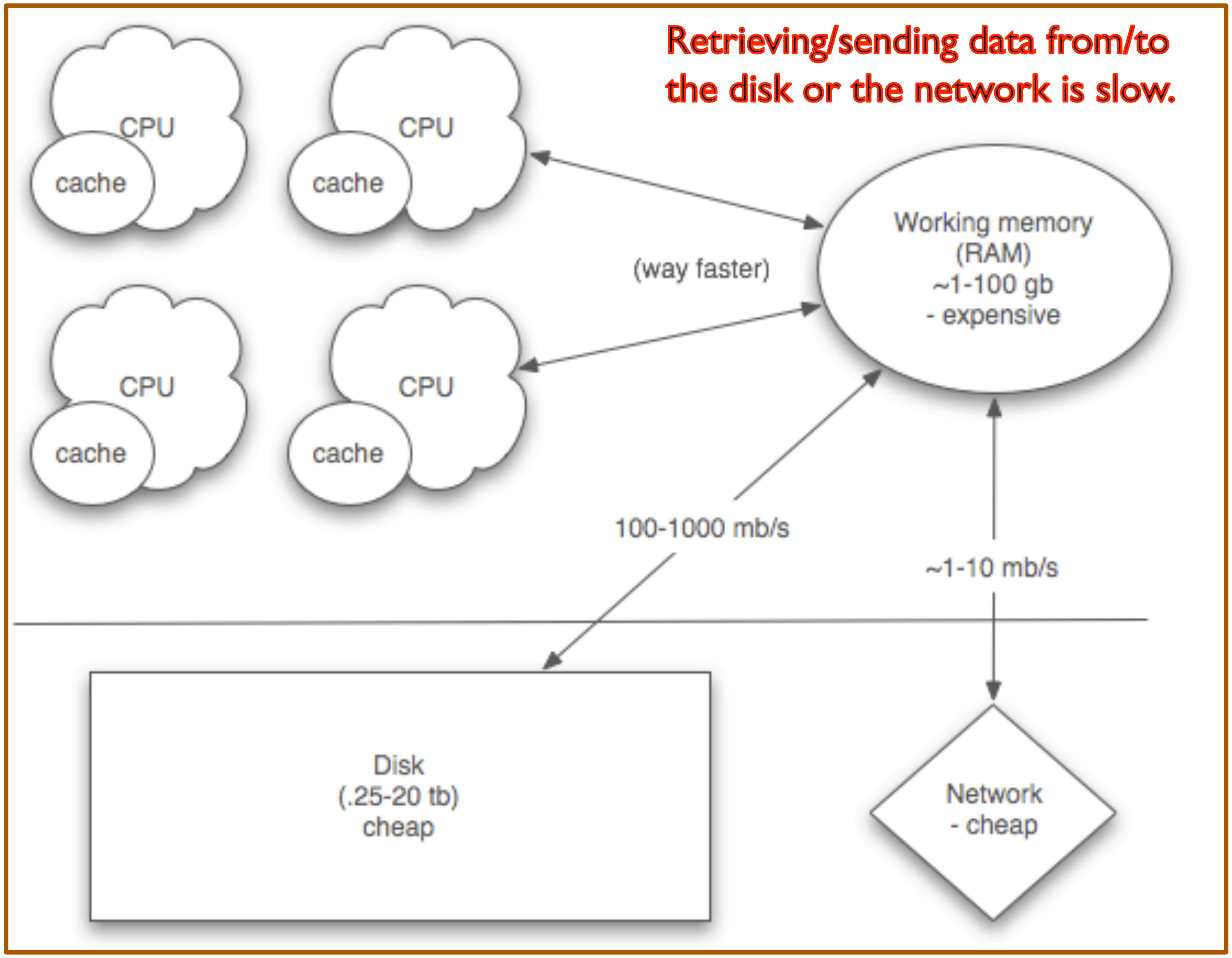
Computer architecture



Computer architecture

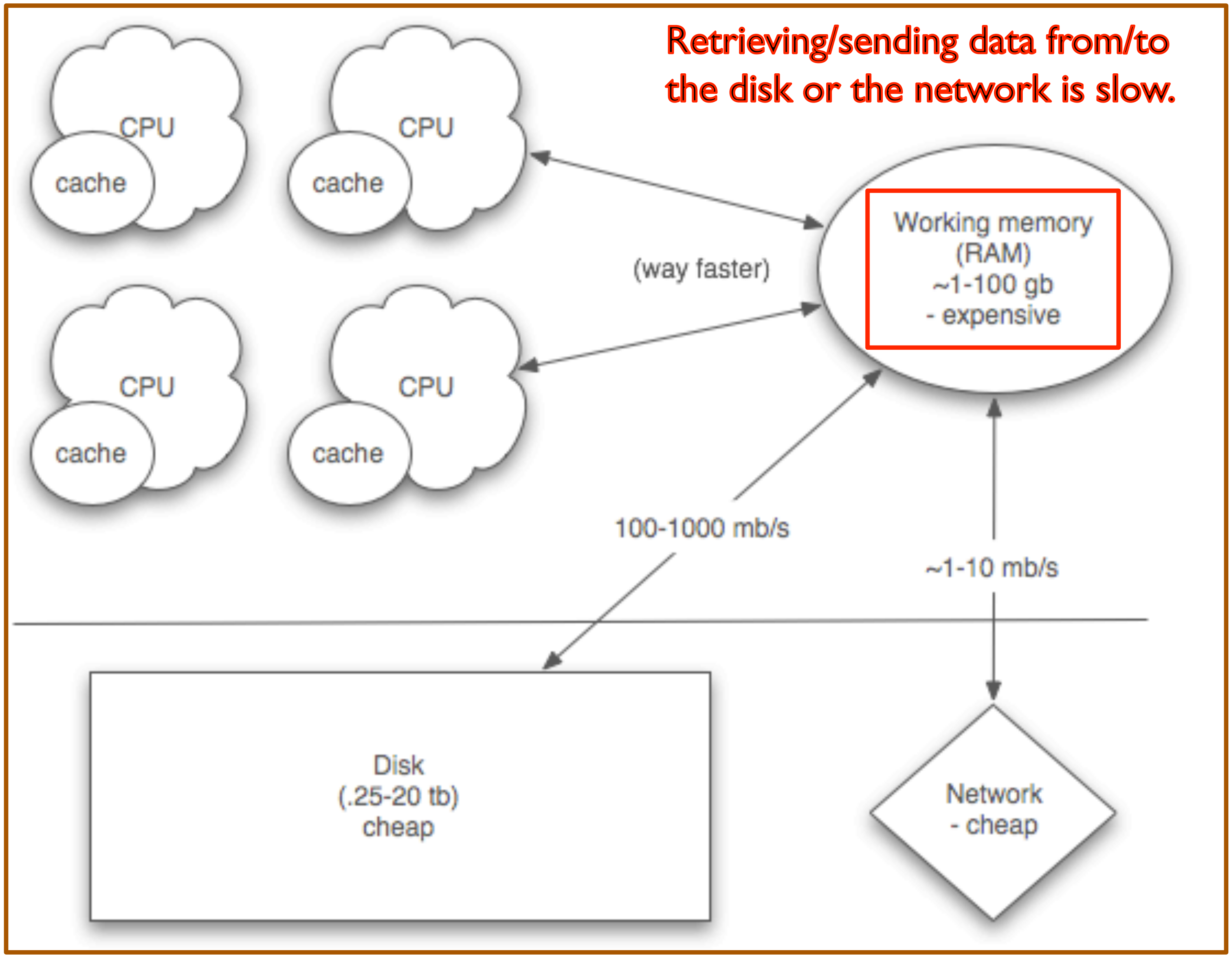


Computer architecture



Retrieving/sending data from/to the disk or the network is slow.

Computer architecture


Retrieving/sending data from/to the disk or the network is slow.
CPU
cache
CPU
cache
CPU
cache
CPU
cache
(way faster)
Working memory (RAM) ~1-100 gb - expensive
100-1000 mb/s
~1-10 mb/s
Disk (.25-20 tb) cheap
Network - cheap

Questions to ask

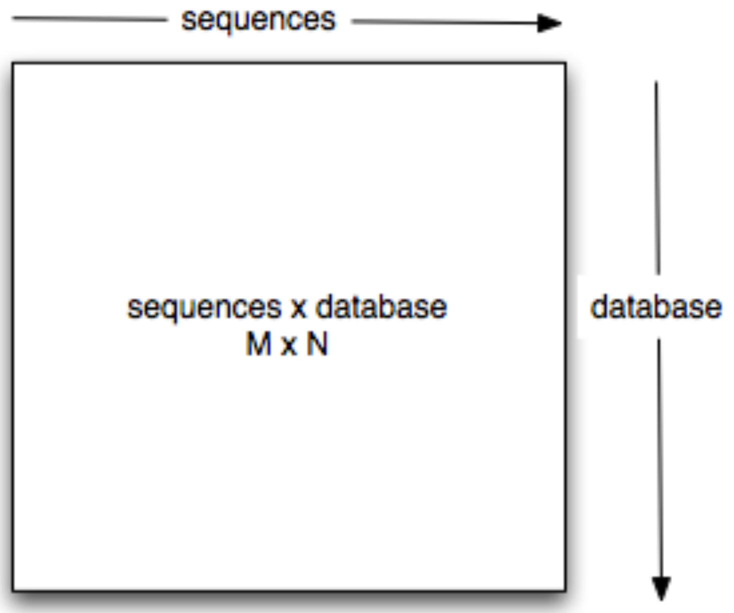
- Can I split my problem up into small chunks?

  (because, if so, I can use more than one computer effectively.)

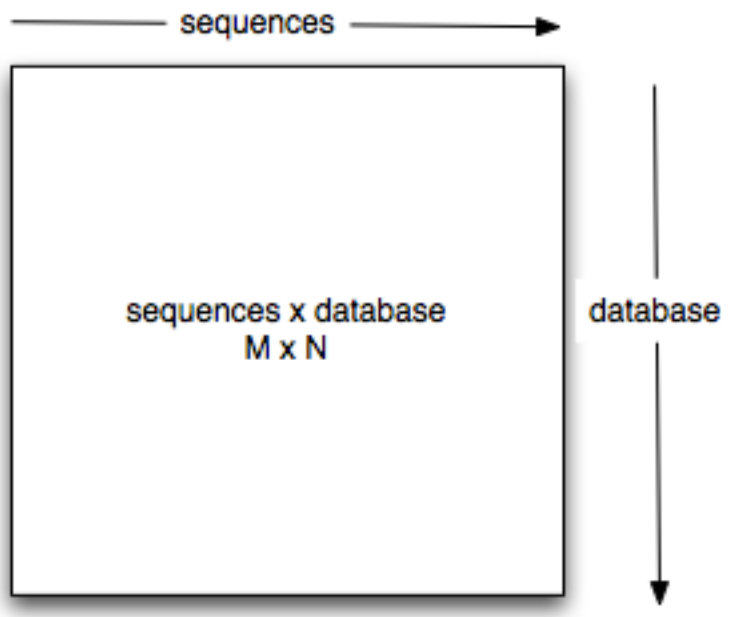
- How does my computation scale?

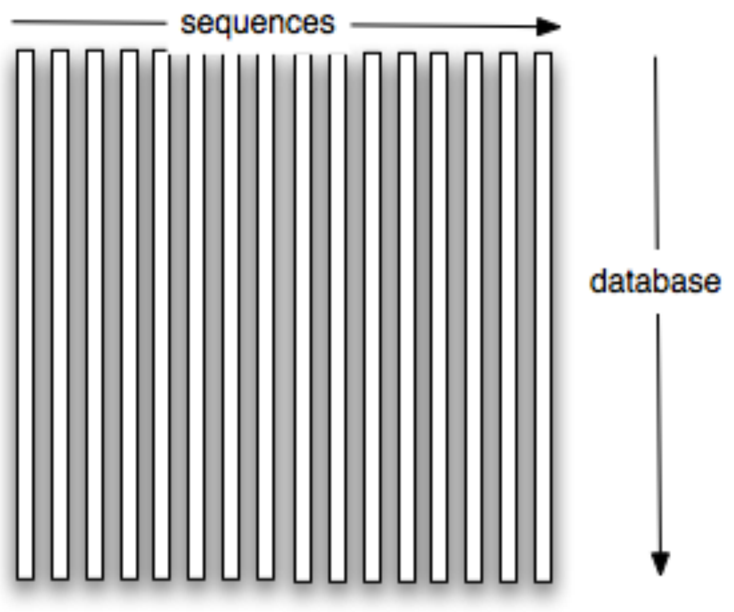
- How does my memory use scale?

Sequence comparison: n^2



…but "embarrassingly parallel"





M problems, each 1 x N in size

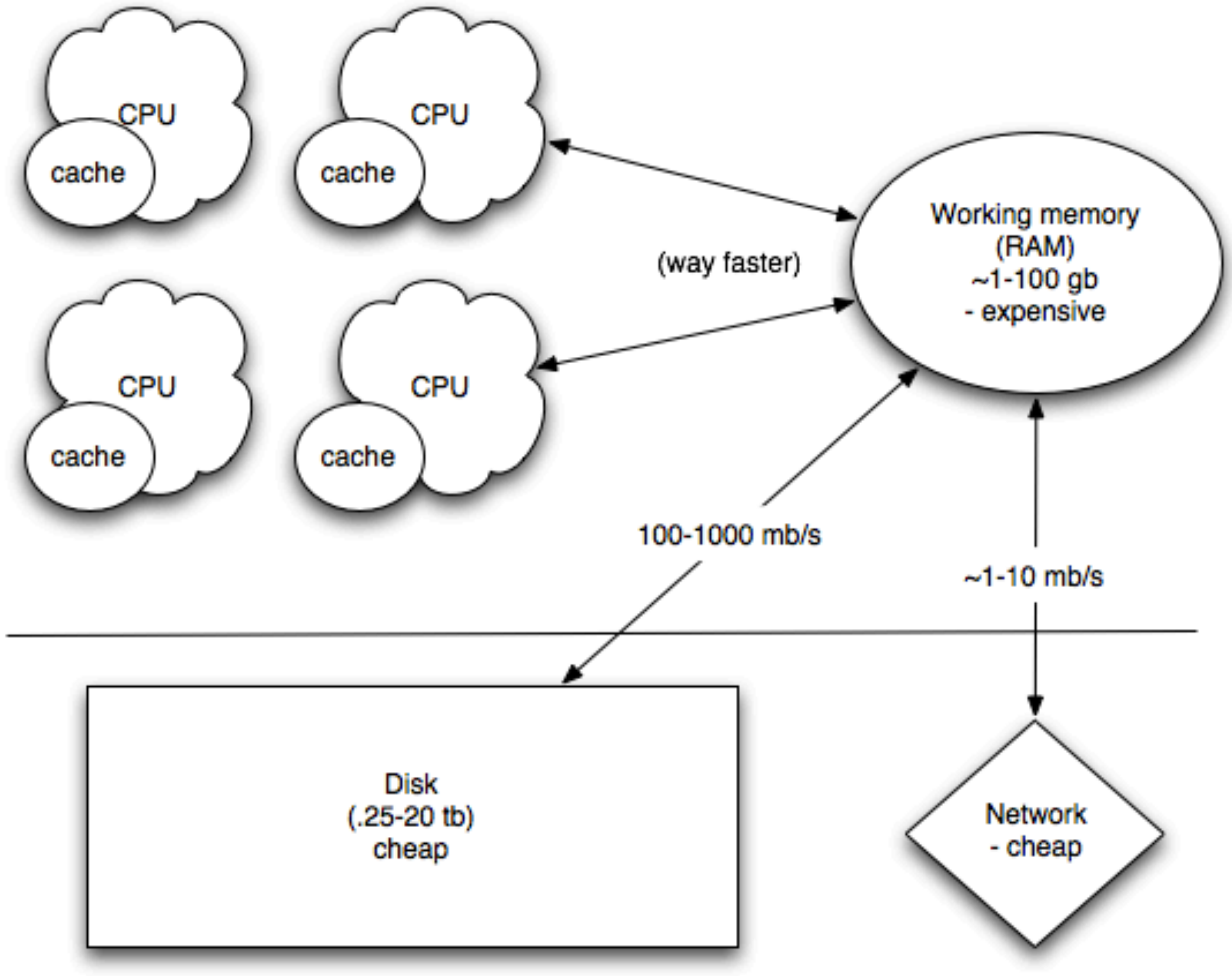
Mapping is embarrassingly parallel.

You need to calculate individual overlaps.

Assembly is not.

You need to calculate *all overlaps*.

Communication between CPUs is slow; this is main factor in splitting up tasks.



None of this is the #1 problem you will face with bioinformatics.

Here is the #1 problem:

How would you know if your answer was right or wrong?

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Here is the #1 problem:

How would you know if your answer was right or wrong?

If you can't answer this question, then what's the point?

Controls

- Just as with experiments, you can put negative and positive controls in your bioinformatics.

- e.g. with BLAST,
    - Do you see expected matches with the parameters and database you’re using?

- Positive controls are often easier than negative, in “discovery-driven” science…

Internal controls

- Molecules and sequences for which you have expectations.

- “I know this gene comes up, based on qPCR. I expect to see it in my mRNAseq.”

External controls

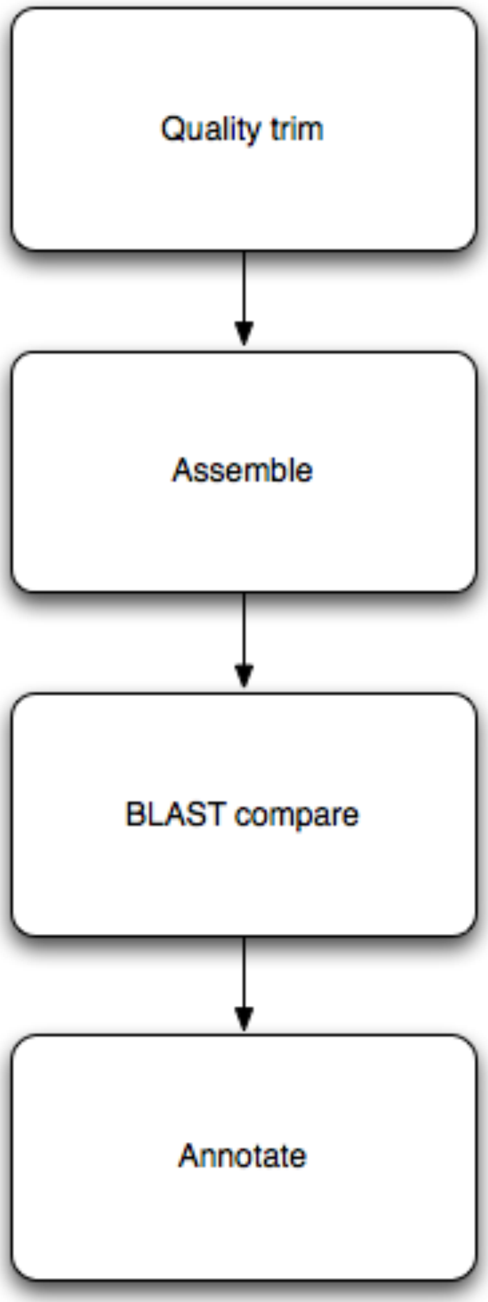
- Does the whole process work?
- "I can reproduce what this other person/ lab did, with their data, when I use my own software."
- This is much more rarely done…

Black box nature of algorithms

- When you listen to a computational biologist explain their clever algorithm…
- …it's a mistake to think that they necessarily know what's going on.
- Software is full of bugs and unintended consequences.

Pipelines

- Each step can be understood, and tested/ controlled individually.
- Each step is re-usable! Just need to figure out input/output formats.
- Automate, automate, automate.



Tracking the process

- How do you know that your software *today* is doing the same thing it was doing last month? Or last year? Or in the hands of that other graduate student?

- There are tools and processes for dealing with this
  - Version control (think "change tracking" in Word)
  - Automated testing (think "automated positive/ negative controls")

Replication vs Reproducibility

- Replication: identical results.
  - Same parameters => same results

- Reproducibility: similar results.
  - Similar parameters => similar results
  - (What's "similar"?)

- Corroboration:
  - Similar results seen in a different system

What should our standards be?

- For *scientists*, reproducibility is extremely important.
- Replication … less so. It's very challenging to *exactly* replicate a given experimental situation.
- But, there is a pragmatic reason to think about replication, too.

Replication in computational science

- We have spent mucho time making sure that computers do the same thing *every time*, at the micro level.

- If you observe *unplanned* variation in a computational system, then:
  - You either are using one of the approximate subsystems, like floating point;
  - *Or* **you have a bug.**

Replication in computational science

- So, *proximate to an analysis*, you should be able to exactly replicate a particular result from a computational analysis.

- Then, changing
  - Data sets
  - Hardware
  - Underlying software

- …may result in observed differences.

Concluding thoughts

- Every step of the process needs to be critically thought about and controlled.
- Choice of algorithms can be important, but depends on your problem: the convenient tool in your toolbox may not be well suited to your problem.