# Sequence Alignment & Computational Thinking

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Sept 3, 2013
QB Bootcamp Lecture 2

# Outline

Part 1: Overview & Fundamentals

Part 2: Sequence Analysis Theory

- Intro to alignment and algorithms
- Understanding Bowtie

Part 3: Genomics Resources

Part 4: Unix Primer

Part 5: Example Analysis

# Milestones in Molecular Biology

There is tremendous interest to sequence:

- What is your genome sequence?
- How does your genome compare to my genome?

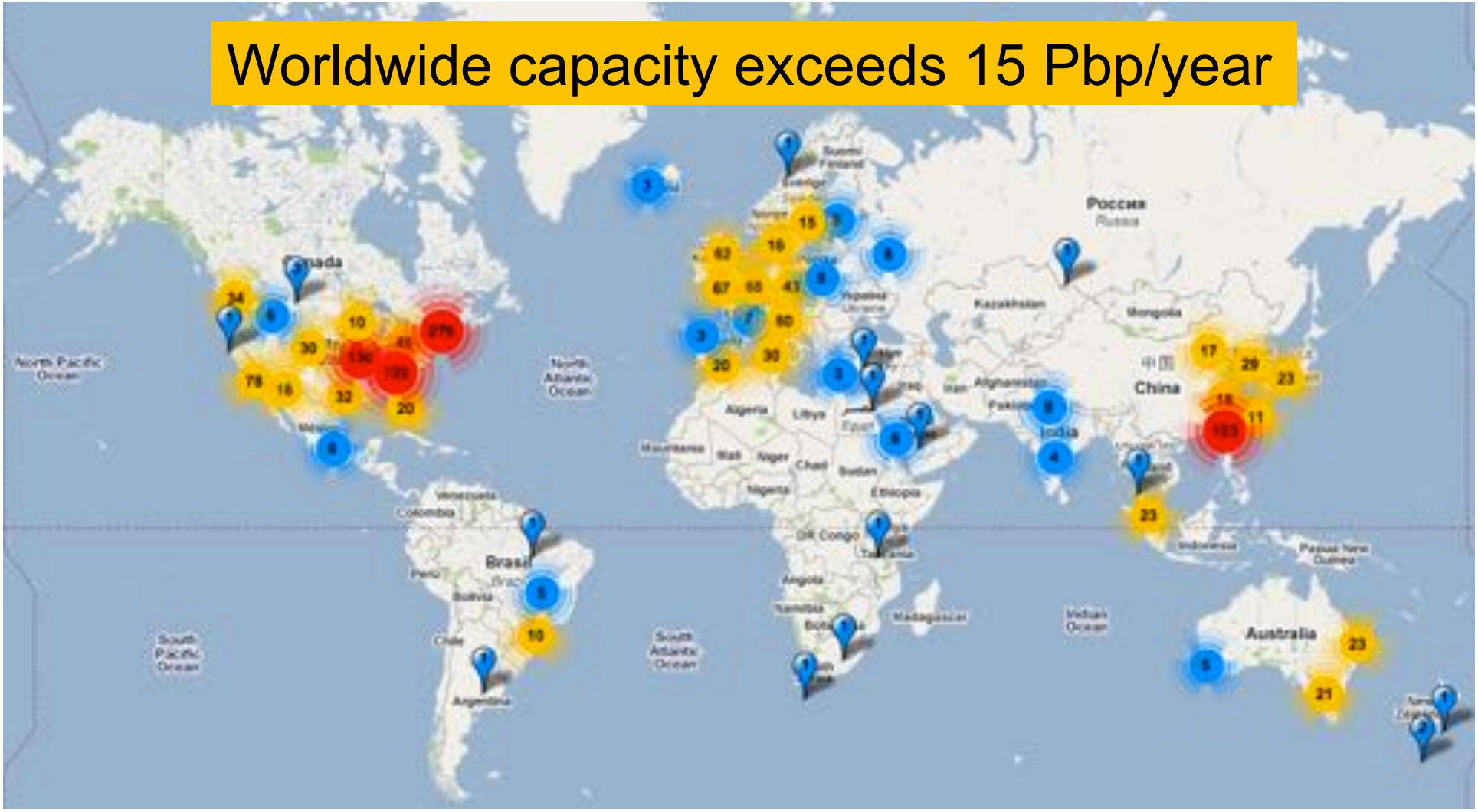
- Where are the genes and how active are they?
- How does gene activity change during development?
- How does splicing change during development?

- How does methylation change during development?
- How does chromatin change during development?
- How does is your genome folded in the cell?
- Where do proteins bind and regulate genes?

- What virus and microbes are living inside you?
- How has the disease mutated your genome?
- What drugs should we give you?

- …

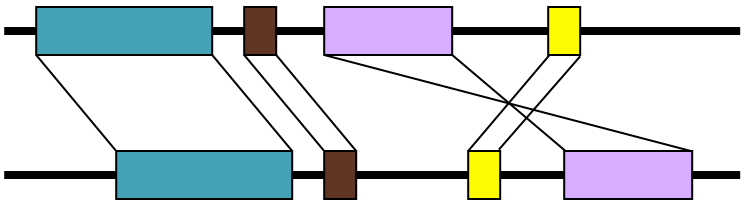
# Sequencing Centers




***Next Generation Genomics: World Map of High-throughput Sequencers***
http://pathogenomics.bham.ac.uk/hts/

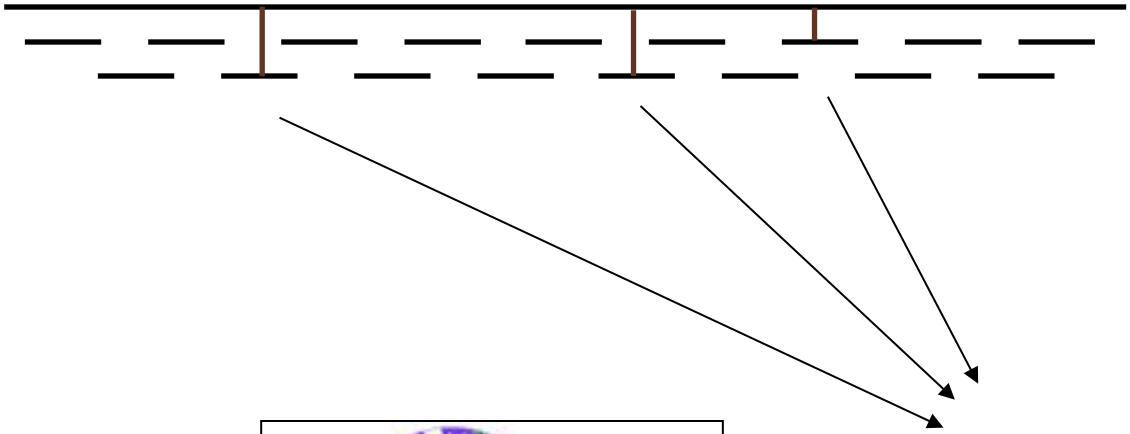
# Sequence Alignment

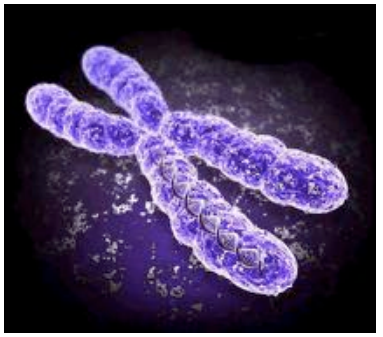
- A very common problem in computational biology is to find occurrences of one sequence in another sequence
  - Genome Assembly
  - Gene Finding
  - Comparative Genomics
  - Functional analysis of proteins
  - Motif discovery
  - SNP analysis
  - Phylogenetic analysis
  - Primer Design
  - Personal Genomics
  - …

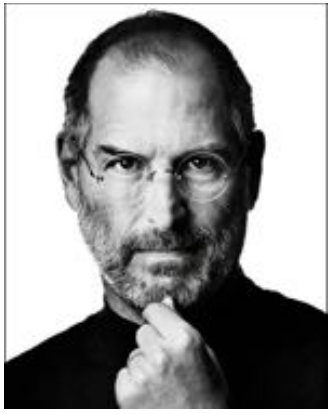


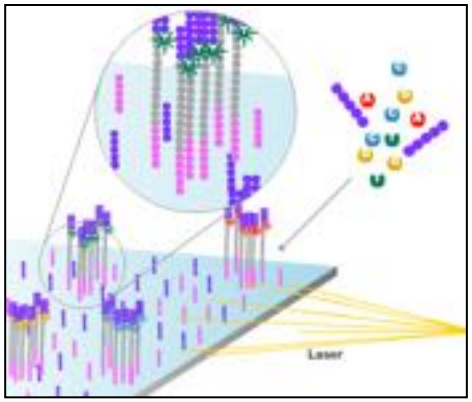
# Personal Genomics

How does your genome compare to the reference?










Heart Disease

Cancer

Creates magical technology

# Searching for GATTACA

- Where is GATTACA in the human genome?
- Strategy 1: Brute Force

| 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 | … |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| T | G | A | T | T | A | C | A | G | A | T | T | A | C | C | … |
| G | A | T | T | A | C | A | | | | | | | | | |

No match at offset 1

# Searching for GATTACA

- Where is GATTACA in the human genome?
- Strategy 1: Brute Force

| 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 | … |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| T | G | A | T | T | A | C | A | G | A | T | T | A | C | C | … |
| | G | A | T | T | A | C | A | | | | | | | | |

Match at offset 2

# Searching for GATTACA

- Where is GATTACA in the human genome?
- Strategy 1: Brute Force

| 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 | … |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| T | G | A | T | T | A | C | A | G | A | T | T | A | C | C | … |
| | | G | A | T | T | A | C | A | … | | | | | | |

No match at offset 3…

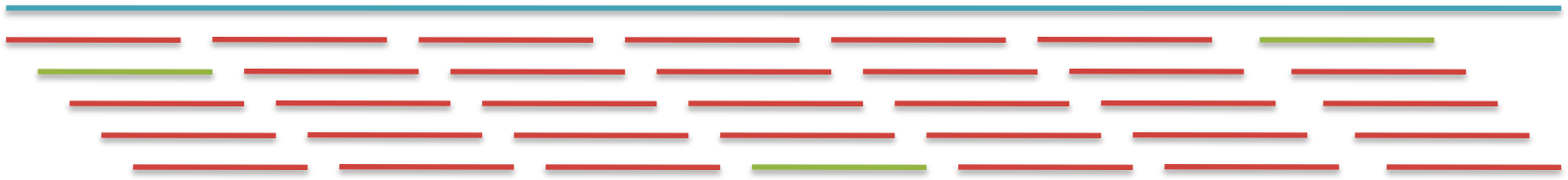
# Searching for GATTACA

- Where is GATTACA in the human genome?
- Strategy 1: Brute Force

| 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 | … |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| T | G | A | T | T | A | C | A | G | A | T | T | A | C | C | … |
| | | | | | | | | G | A | T | T | A | C | A | |

No match at offset 9 <- Checking each possible position takes time

# Brute Force Analysis



- Brute Force:
  - At every possible offset in the genome:
    - Do all of the characters of the query match?

- Analysis
  - Simple, easy to understand
  - Genome length = n [3B]
  - Query length = m [7]
  - Comparisons: (n-m+1) * m [21B]

- Overall runtime: O(nm)

[How long would it take if we double the genome size, read length?]

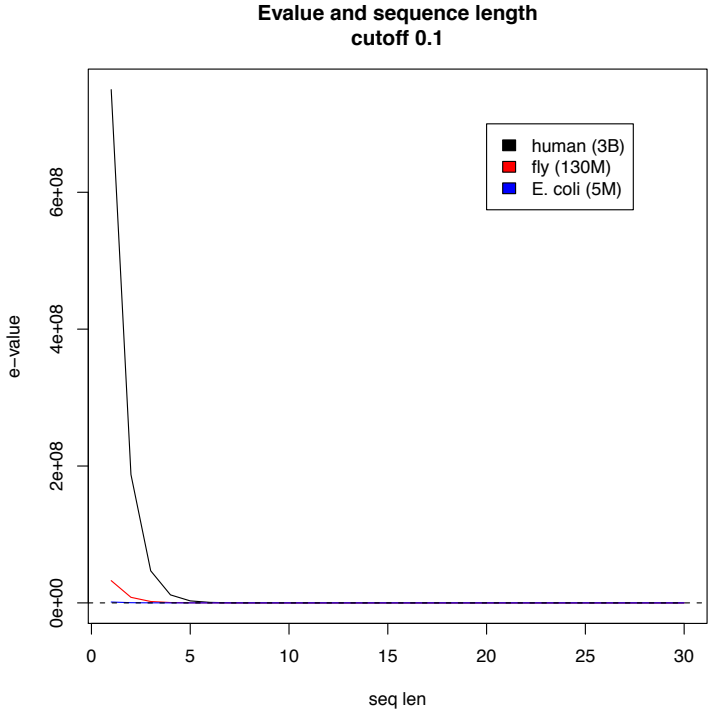
[How long would it take if we double both?]

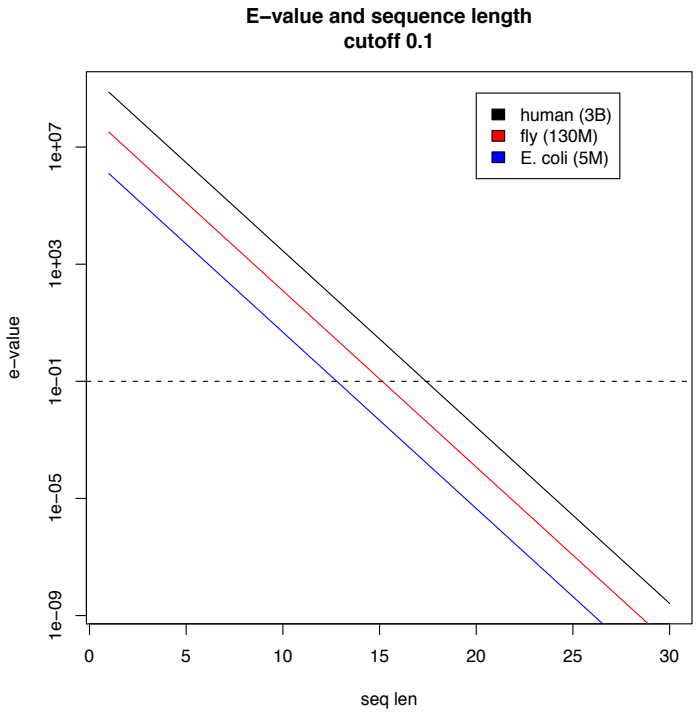
# Expected Occurrences

The expected number of occurrences (e-value) of a given sequence in a genome depends on the length of the genome and inversely on the length of the sequence

- 1 in 4 bases are G, 1 in 16 positions are GA, 1 in 64 positions are GAT, …
- 1 in 16,384 should be GATTACA
- $E=n/(4^m)$ [183,105 expected occurrences]

[How long do the reads need to be for a significant match?]



# Brute Force Reflections

Why check every position?

– GATTACA can't possibly start at position 15 [WHY?]

| 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 | … |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| T | G | A | T | T | A | C | A | G | A | T | T | A | C | C | … |
| | | | | | | | | G | A | T | T | A | C | A | |

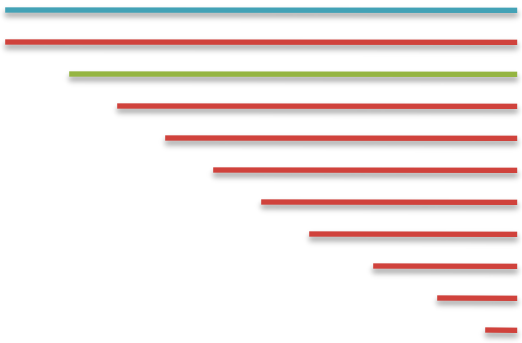
– Improve runtime to O(n + m) [3B + 7]
  - If we double both, it just takes twice as long
  - Knuth-Morris-Pratt, 1977
  - Boyer-Moyer, 1977, 1991

– For one-off scans, this is the best we can do (optimal performance)
  - We have to read every character of the genome, and every character of the query
  - For short queries, runtime is dominated by the length of the genome

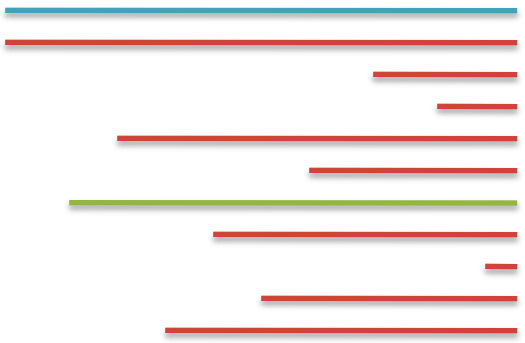
# Suffix Arrays: Searching the Phone Book

- What if we need to check many queries?
  - We don't need to check every page of the phone book to find 'Schatz'
  - Sorting alphabetically lets us immediately skip 96% (25/26) of the book *without any loss in accuracy*

- Sorting the genome: Suffix Array (Manber & Myers, 1991)
  - Sort every suffix of the genome



Split into n suffixes



Sort suffixes alphabetically

[Challenge Question: How else could we split the genome?]

# Searching the Index

- Strategy 2: Binary search
  - Compare to the middle, refine as higher or lower

- Searching for GATTACA
  - Lo = 1; Hi = 15;

Lo →

| # | Sequence | Pos |
|---|---|---|
| 1 | ACAGATTACC… | 6 |
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| 5 | ATTACC… | 10 |
| 6 | C… | 15 |
| 7 | CAGATTACC… | 7 |
| 8 | CC… | 14 |
| 9 | GATTACAGATTACC… | 2 |
| 10 | GATTACC… | 9 |
| 11 | TACAGATTACC… | 5 |
| 12 | TACC… | 12 |
| 13 | TGATTACAGATTACC… | 1 |
| 14 | TTACAGATTACC… | 4 |
| 15 | TTACC… | 11 |

Hi →

# Searching the Index

- Strategy 2: Binary search
  - Compare to the middle, refine as higher or lower

- Searching for GATTACA
  - Lo = 1; Hi = 15; Mid = (1+15)/2 = 8
  - Middle = Suffix[8] = CC

Lo →

| # | Sequence | Pos |
|---|---|---|
| 1 | ACAGATTACC… | 6 |
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    => Higher: Lo = Mid + 1

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- Searching for GATTACA
  - Lo = 1; Hi = 15; Mid = (1+15)/2 = 8
  - Middle = Suffix[8] = CC

    => Higher: Lo = Mid + 1

  - Lo = 9; Hi = 15;

| # | Sequence | Pos |
|---|---|---|
| 1 | ACAGATTACC… | 6 |
| 2 | ACC… | 13 |
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- Searching for GATTACA
  - Lo = 1; Hi = 15; Mid = (1+15)/2 = 8
  - Middle = Suffix[8] = CC

    => Higher: Lo = Mid + 1

  - Lo = 9; Hi = 15; Mid = (9+15)/2 = 12
  - Middle = Suffix[12] = TACC

| # | Sequence | Pos |
|---|---|---|
| 1 | ACAGATTACC… | 6 |
| 2 | ACC… | 13 |
| 3 | AGATTACC… | 8 |
| 4 | ATTACAGATTACC… | 3 |
| 5 | ATTACC… | 10 |
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Lo →

Hi →

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  - Compare to the middle, refine as higher or lower

- Searching for GATTACA
  - Lo = 1; Hi = 15; Mid = (1+15)/2 = 8
  - Middle = Suffix[8] = CC
    => Higher: Lo = Mid + 1

  - Lo = 9; Hi = 15; Mid = (9+15)/2 = 12
  - Middle = Suffix[12] = TACC
    => Lower: Hi = Mid - 1

  - Lo = 9; Hi = 11;

| | # | Sequence | Pos |
|---|---|---|---|
| | 1 | ACAGATTACC… | 6 |
| | 2 | ACC… | 13 |
| | 3 | AGATTACC… | 8 |
| | 4 | ATTACAGATTACC… | 3 |
| | 5 | ATTACC… | 10 |
| | 6 | C… | 15 |
| | 7 | CAGATTACC… | 7 |
| Lo → | 8 | CC… | 14 |
| | 9 | GATTACAGATTACC… | 2 |
| | 10 | GATTACC… | 9 |
| Hi → | 11 | TACAGATTACC… | 5 |
| | 12 | TACC… | 12 |
| | 13 | TGATTACAGATTACC… | 1 |
| | 14 | TTACAGATTACC… | 4 |
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    => Higher: Lo = Mid + 1

  - Lo = 9; Hi = 15; Mid = (9+15)/2 = 12
  - Middle = Suffix[12] = TACC
    => Lower: Hi = Mid - 1

  - Lo = 9; Hi = 11; Mid = (9+11)/2 = 10
  - Middle = Suffix[10] = GATTACC

| # | Sequence | Pos |
|---|---|---|
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Hi →

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  - Lo = 9; Hi = 11; Mid = (9+11)/2 = 10
  - Middle = Suffix[10] = GATTACC
    => Lower: Hi = Mid - 1

  - Lo = 9; Hi = 9;

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| 4 | ATTACAGATTACC… | 3 |
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| 15 | TTACC… | 11 |

Lo
Hi

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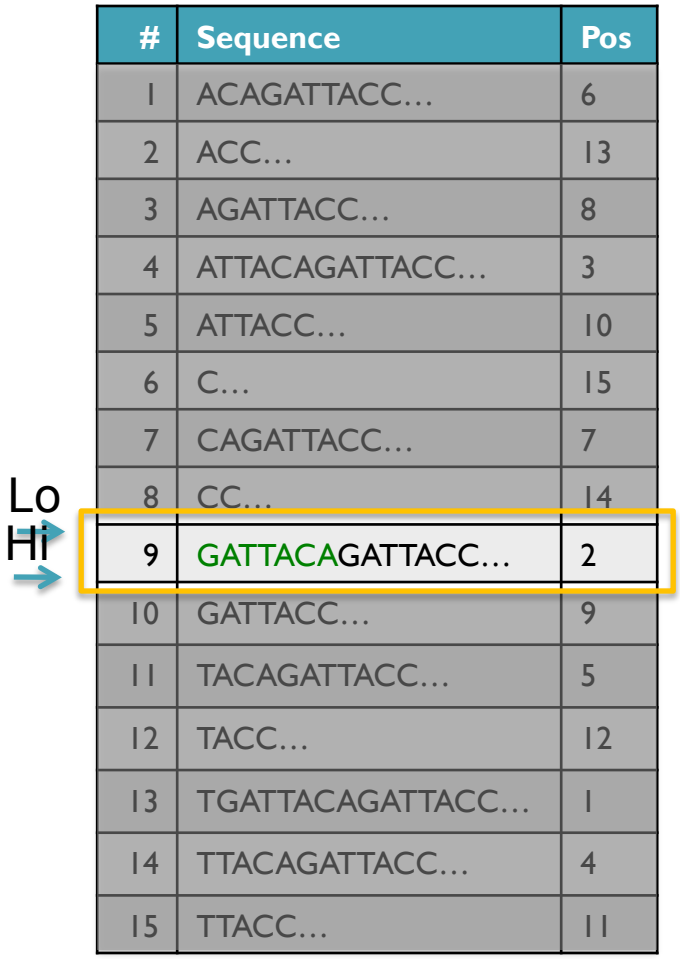
  - Middle = Suffix[8] = CC
    => Higher: Lo = Mid + 1

  - Lo = 9; Hi = 15; Mid = (9+15)/2 = 12
  - Middle = Suffix[12] = TACC
    => Lower: Hi = Mid - 1

  - Lo = 9; Hi = 11; Mid = (9+11)/2 = 10
  - Middle = Suffix[10] = GATTACC
    => Lower: Hi = Mid - 1

  - Lo = 9; Hi = 9; Mid = (9+9)/2 = 9
  - Middle = Suffix[9] = GATTACA…
    => Match at position 2!

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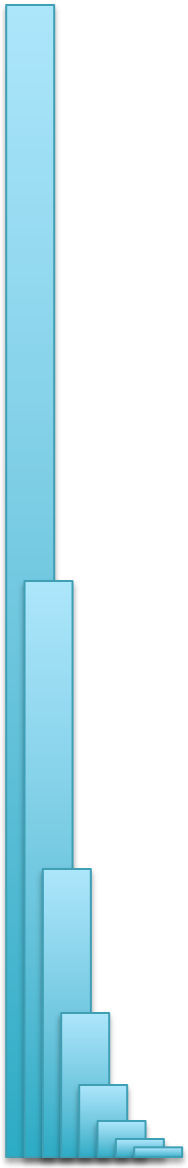
# Binary Search Analysis



- Binary Search
  - Initialize search range to entire list
    - mid = (hi+lo)/2; middle = suffix[mid]
    - if query matches middle: done
    - else if query < middle: pick low range
    - else if query > middle: pick hi range
  - Repeat until done or empty range [WHEN?]

- Analysis
  - More complicated method
  - How many times do we repeat?
    - How many times can it cut the range in half?
    - Find smallest x such that: $n/(2^x) \leq 1$; $x = \lg_2(n)$ [32]

- Total Runtime: O(m lg n)
  - More complicated, but much faster!
  - Looking up a query loops 32 times instead of 3B

[How long does it take to search 6B or 24B nucleotides?]

# Fast gapped-read alignment with Bowtie 2

Ben Langmead and Steven Salzberg (2012) Nature Methods. 9, 357–359

# In-exact alignment

- Where is GATTACA *approximately* in the human genome?
  - And how do we efficiently find them?

- It depends…
  - Define 'approximately'
    - Hamming Distance, Edit distance, or Sequence Similarity
    - Ungapped vs Gapped vs Affine Gaps
    - Global vs Local
    - All positions or the single 'best'?
  - Efficiency depends on the data characteristics & goals
    - Smith-Waterman: Exhaustive search for optimal alignments
    - BLAST: Hash-table based homology searches
    - Bowtie: BWT alignment for short read mapping

# Searching for GATTACA

- Where is GATTACA *approximately* in the human genome?

| 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 | … |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| T | G | A | T | T | A | C | A | G | A | T | T | A | C | C | … |
| G | A | T | T | A | C | A | | | | | | | | | |

Match Score: 1/7

# Searching for GATTACA

- Where is GATTACA *approximately* in the human genome?

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|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| T | G | A | T | T | A | C | A | G | A | T | T | A | C | C | … |
| | G | A | T | T | A | C | A | | | | | | | | |

Match Score: 7/7

# Searching for GATTACA

- Where is GATTACA *approximately* in the human genome?

| 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 | … |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| T | G | A | T | T | A | C | A | G | A | T | T | A | C | C | … |
| | | G | A | T | T | A | C | A | … | | | | | | |

Match Score: 1/7

# Searching for GATTACA

- Where is GATTACA *approximately* in the human genome?

| 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 | … |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| T | G | A | T | T | A | C | A | G | A | T | T | A | C | C | … |
| | | | | | | | | G | A | T | T | A | C | A | |

Match Score: 6/7 <- We may be very interested in these imperfect matches
Especially if there are no perfect end-to-end matches

# Similarity metrics

- Hamming distance
  - Count the number of substitutions to transform one string into another

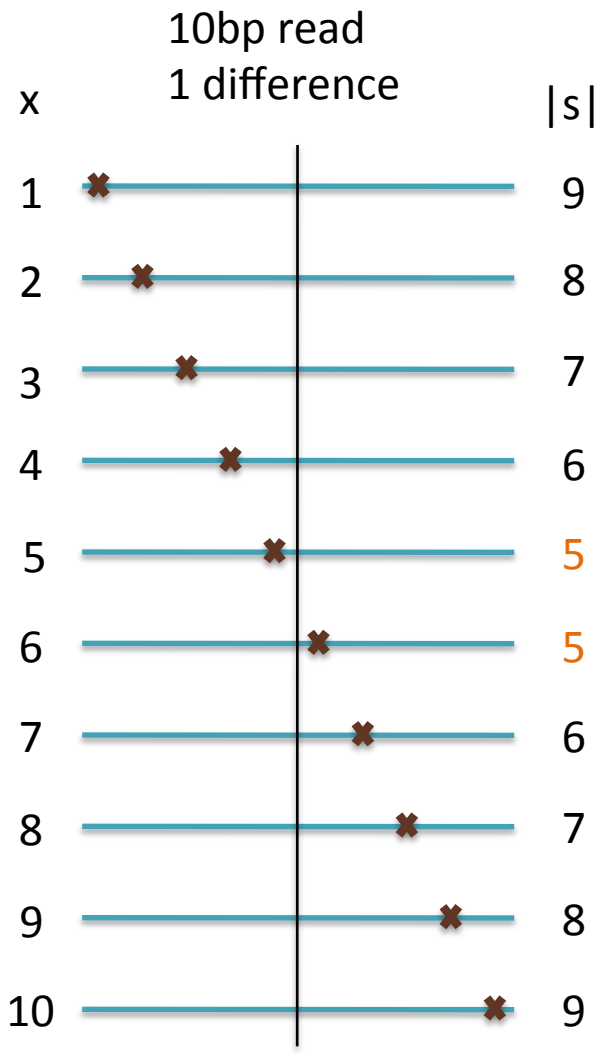
```
GATTACA          GATTTTTACA
|||x|||          ||||xxxxxx
GATCACA          GATTACA
   1                6
```

- Edit distance
  - The minimum number of substitutions, insertions, or deletions to transform one string into another

```
GATTACA          GATTTTTACA
|||x|||          ||||xxx|||
GATCACA          GATT---ACA
   1                3
```

# Seed-and-Extend Alignment

Theorem: An alignment of a sequence of length *m* with at most *k* differences ***must*** contain an exact match at least $s=m/(k+1)$ bp long
(*Baeza-Yates* and Perleberg, 1996)

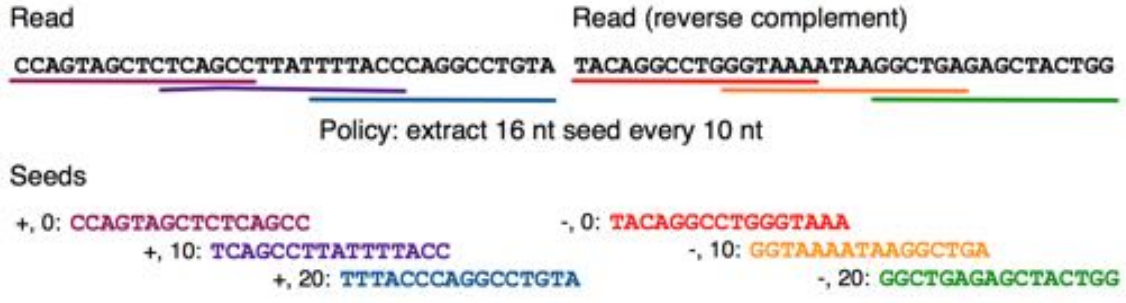



- Proof: Pigeonhole principle
  - 1 pigeon can't fill 2 holes

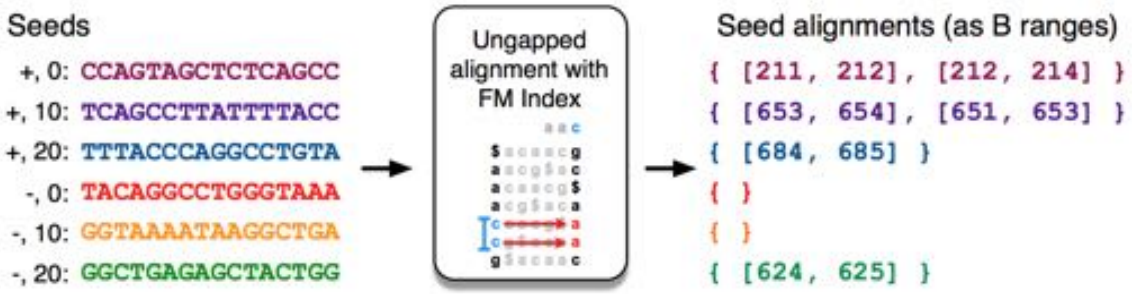
- Seed-and-extend search
  - Use an index to rapidly find short exact alignments to seed longer in-exact alignments
    - BLAST, MUMmer, Bowtie, BWA, SOAP, …
  - Specificity of the depends on seed length
    - Guaranteed sensitivity for k differences
    - Also finds some (but not all) lower quality alignments <- heuristic

# Algorithm Overview

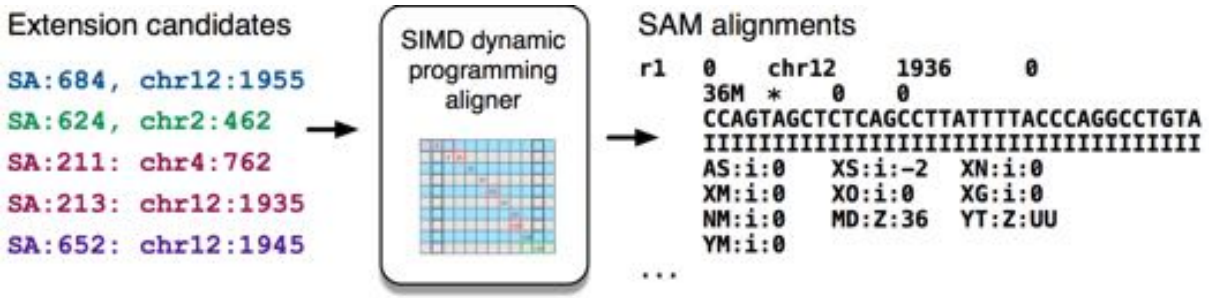
1. Split read into segments




2. Lookup each segment and prioritize




3. Evaluate end-to-end match



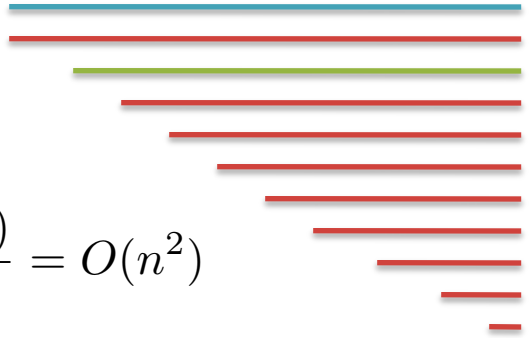
# Questions?

http://schatzlab.cshl.edu

# Suffix Array Construction

- How can we store the suffix array?

  [How many characters are in all suffixes combined?]



$$S = 1 + 2 + 3 + \cdots + n = \sum_{i=1}^{n} i = \frac{n(n+1)}{2} = O(n^2)$$

  - Hopeless to explicitly store 4.5 billion billion characters
  - Instead use implicit representation
    - Keep 1 copy of the genome, and a list of sorted offsets
    - Storing 3 billion offsets fits on a server (12GB)

- Searching the array is very fast, but it takes time to construct
  - This time will be amortized over many, many searches
  - Run it once "overnight" and save it away for all future queries

| Pos |
|---|
| 6 |
| 13 |
| 8 |
| 3 |
| 10 |
| 15 |
| 7 |
| 14 |
| 2 |
| 9 |
| 5 |
| 12 |
| 1 |
| 4 |
| 11 |

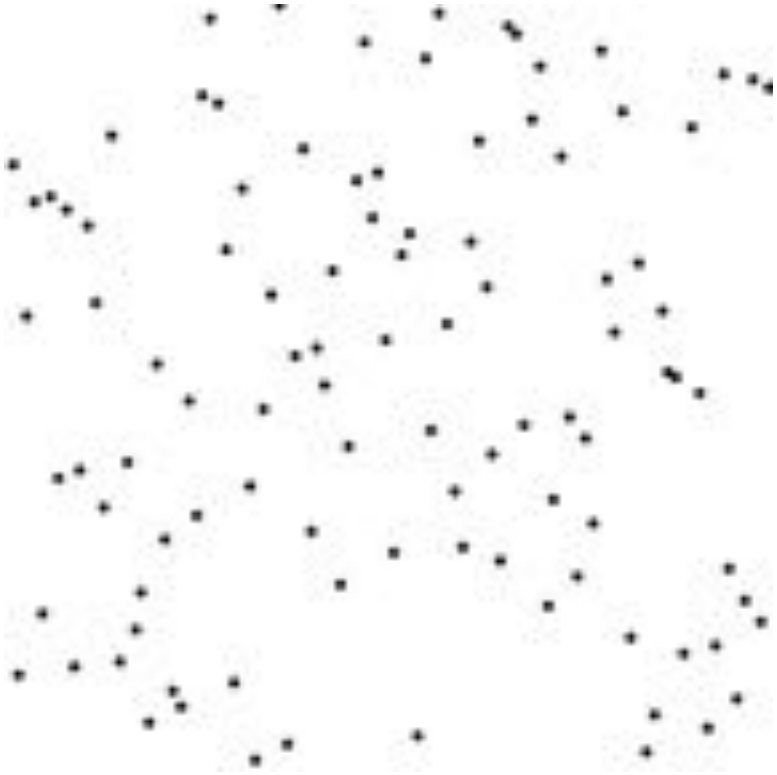
TGATTACAGATTACC

# Sorting

Quickly sort these numbers into ascending order:
14, 29, 6, 31, 39, 64, 78, 50, 13, 63, 61, 19

[How do you do it?]

6, 14, 29, 31, 39, 64, 78, 50, 13, 63, 61, 19
6, 13, 14, 29, 31, 39, 64, 78, 50, 63, 61, 19
6, 13, 14, 19, 29, 31, 39, 64, 78, 50, 63, 61
6, 13, 14, 19, 29, 31, 39, 64, 78, 50, 63, 61
6, 13, 14, 19, 29, 31, 39, 64, 78, 50, 63, 61
6, 13, 14, 19, 29, 31, 39, 50, 64, 78, 63, 61
6, 13, 14, 19, 29, 31, 39, 50, 61, 64, 78, 63
6, 13, 14, 19, 29, 31, 39, 50, 61, 63, 64, 78
6, 13, 14, 19, 29, 31, 39, 50, 61, 63, 64, 78
6, 13, 14, 19, 29, 31, 39, 50, 61, 63, 64, 78
6, 13, 14, 19, 29, 31, 39, 50, 61, 63, 64, 78



http://en.wikipedia.org/wiki/Selection_sort

# Selection Sort Analysis

- Selection Sort (Input: list of n numbers)

```
for pos = 1 to n
    // find the smallest element in [pos, n]
    smallest = pos
    for check = pos+1 to n
        if (list[check] < list[smallest]): smallest = check

    // move the smallest element to the front
    tmp = list[smallest]
    list[pos] = list[smallest]
    list[smallest] = tmp
```

- Analysis

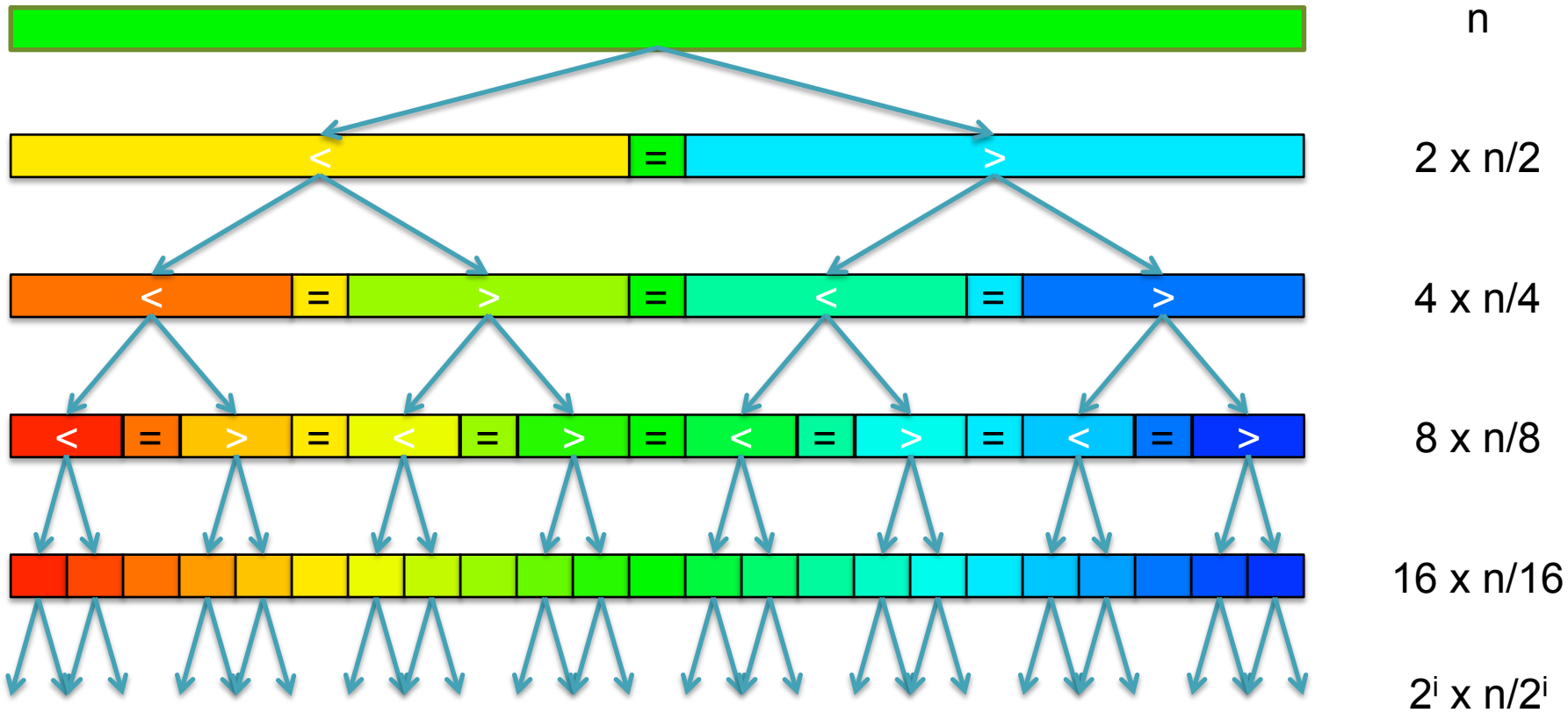
$$T = n + (n-1) + (n-2) + \cdots + 3 + 2 + 1 = \sum_{i=1}^{n} i = \frac{n(n+1)}{2} = O(n^2)$$

  - Outer loop: pos = 1 to n
  - Inner loop: check = pos to n
  - Running time: Outer * Inner = $O(n^2)$ [4.5 Billion Billion]

[Challenge Questions: Why is this slow? / Can we sort any faster?]

# Divide and Conquer

- Selection sort is slow because it rescans the entire list for each element
  - How can we split up the unsorted list into independent ranges?
  - Hint 1: Binary search splits up the problem into 2 independent ranges (hi/lo)
  - Hint 2: Assume we know the median value of a list




[How many times can we split a list in half?]

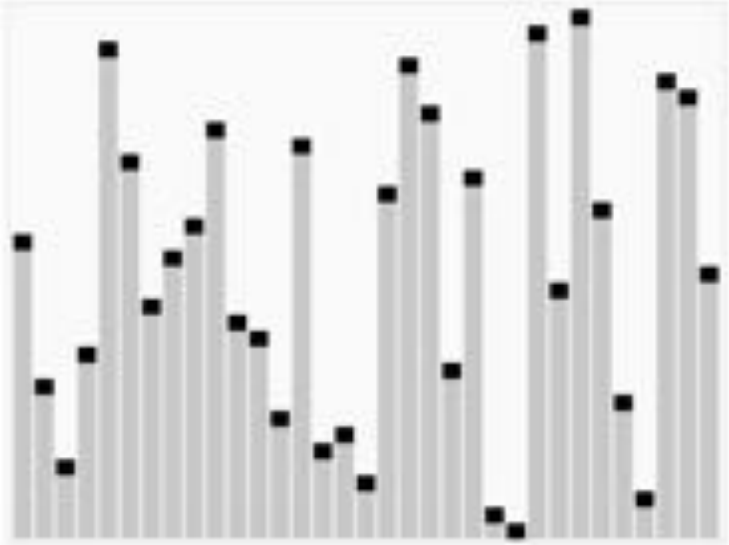
# QuickSort Analysis

- QuickSort(Input: list of n numbers)

```
// see if we can quit
if (length(list)) <= 1): return list

// split list into lo & hi
pivot = median(list)
lo = {}; hi = {};
for (i = 1 to length(list))
        if (list[i] < pivot): append(lo, list[i])
        else:                 append(hi, list[i])

// recurse on sublists
return (append(QuickSort(lo), QuickSort(hi))
```



http://en.wikipedia.org/wiki/Quicksort

- Analysis (Assume we can find the median in O(n))

$$T(n) = \begin{cases} O(1) & \text{if } n \leq 1 \\ O(n) + 2T(n/2) & \text{else} \end{cases}$$

$$T(n) = n + 2(\frac{n}{2}) + 4(\frac{n}{4}) + \cdots + n(\frac{n}{n}) = \sum_{i=0}^{lg(n)} \frac{2^i n}{2^i} = \sum_{i=0}^{lg(n)} n = O(n \lg n)$$

[~94B]

# QuickSort Analysis

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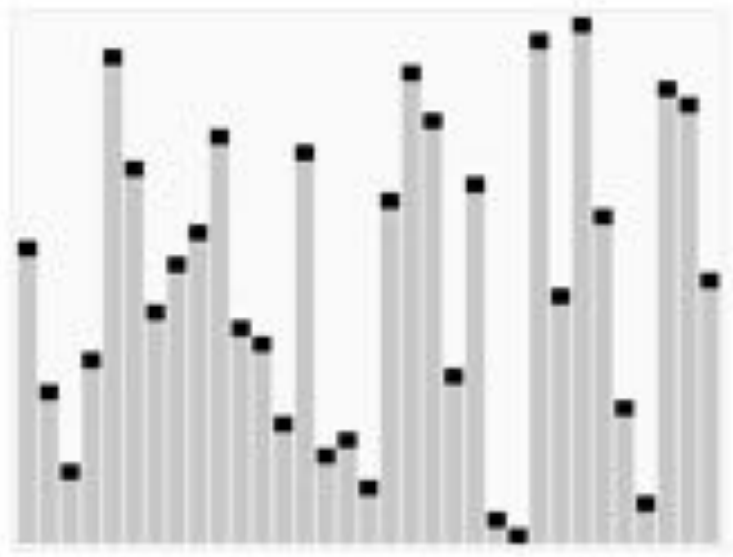

http://en.wikipedia.org/wiki/Quicksort

- Analysis (Assume we can find the median in O(n))

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[~94B]