The theoretical analysis of sequencing bioinformatic algorithms

. . . or, what I did during my sabbatical. . .

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These slides and associated survey paper draft are available via this link.

Theoretical analysis of algorithm (TAA) performance

Performance: runtime, memory use, or accuracy

Examples

- Insertion sort runs in worst-case $\Theta(n^2)$ time
- Expected lookup time in a hash table is $\mathcal{O}(1)$

Goals [Rou19]

- *Predict* the empirical performance of an alg
- *Design* algorithms that perform well in practice (i.e. be a yardstick)

Techniques for the theoretical analysis of algorithms (TAA) [Rou19]

- Traditional worst-case analysis
  - Constants: dropped
  - Inputs: worst-case
  - Parameter: input size
- Parametrized worst-case analysis
- AofA [SF13]
- Average-case analysis
- Semi-random models

The central dogma of computer science

and its relationship to sequencing bioinformatics

Theoretical analysis of algorithms (TAA) achieves its two goals

- Leads to design of new algorithms that perform well in practice
- Predicts the empirical performance of algorithms

Is it true for algorithms for sequencing data?

- TAA led to the development of ILPs, HMMs, machine learning, etc...
- These are applied in but not developed specifically for bioinformatics
- Has TAA achieved its goals when applied to problems whose main application is sequencing bioinformatics?

Plan for talk

Motivating questions for sequencing bioinformatics

- What TAA techniques have been applied?
- To what extent has TAA achieved its goals?
- What can be done to improve the applicability of TAA?

A first attempt to systematically and critically study the application of TAA to sequencing bioinformatics.

Outline

- Comprehensive look at one problem
  - Edit distance
- Highlights
  - Compact data structures
  - Accuracy of genome assembly algorithms
  - Accuracy of structural variation detection algorithms

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Edit distance

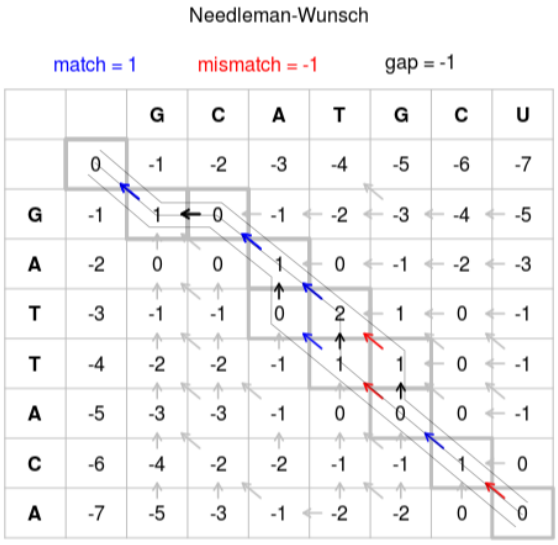
Given two strings A and B of equal length n over a constant sized alphabet, what is the minimum number of substitutions, insertions and deletions needed to transform A into B.

- a.k.a Levenshtein distance or unit-cost edit distance
- Extensions not considered here

In practice

Algorithms

- Needleman-Wunsch
- Banded alignment
- Myers bitparallel technique: optimization to use bitvector operations



Software

- Edlib and SeqAn: banded alignment + Myers
- Parasail: Needleman Wunsch + parallelism
- BGSA: Needleman Wunsch + Myers + parallelism
- Specialized hardware approaches: GPUs, FPGAs, custom processors

Edlib, 100,000nt sequences, single-core

- 1s for divergence of 1%
- 30s for divergence of 40%

Traditional worst-case analysis

Design of alg that works well in practice? Yes

- Needleman-Wunsch alg, by Wagner and Fischer [WF74]
  - Runtime: worst-case $\Theta(n^2)$
  - Can probably credit traditional worst-case analysis with design
  - Basis of other algorithms that work well in practice.

Predict empirical performance of alg? Yes

- Needleman-Wunsch: runtime analysis is actually every-case.

Traditional worst-case analysis led us astray.

- Four-Russians algorithm
  - Runtime: worst-case $\Theta(\frac{n^2}{\log^2 n})$
  - Factor of 5 speedup for $n = 2^{18}$ [Rej]
  - would not exceed 10 even for billion chars
  - not used in practice

Barrier results

- Under strong exponential time hypothesis, there cannot be a strongly sub-quadratic algorithm [BI18]
- We are unlikely to design substantially better algorithms using traditional worst-case analysis as a guide....but we can if you use a different analysis technique

Worst-case analysis parametrized by edit distance (k)

Banded alignment [Ukk85]

- Run time is $\Theta(nk)$ in every case
- No significant implementation constants or data structures

Design of alg that works well in practice? Yes

- Used in edlib, seqan

Predict empirical performance of alg? Yes

- Separates banded alignment from Needleman Wunsch when $k = o(n)$
- Even when $k = dn$, for some constant d, the analysis captures the constant speedup over Needleman Wunsch

For $k = \Theta(n)$, barrier results apply

- Unfortunately this an important case in practice

Worst-case analysis parametrized by entropy and compressibility

Parameter: Entropy of the input h ($0 \leq h \leq 1$)

- Run time: $\mathcal{O}(\frac{hn^2}{\log n})$ for most inputs [CLZU03]

Parameter: Size of compressed input ℓ

- Run time: $\mathcal{O}(\ell n)$ for run-length encoded strings [Mäk03, CLZU03, ALM02]
- Run time: $\mathcal{O}(\ell n \sqrt{\log(n/\ell)})$ for slp-compressed strings [Gaw12]

Achieves design goal? No

- h and ℓ are high in practice

Average-case analysis

a.k.a distributional analysis or random model

Input: Follow a distribution

Performance measured as a function of distribution

- e.g. expected value
- e.g. value "with high probability"

What can we hope to achieve?

- Performance goal? No
- Design goal? Yes, e.g. strongly sub quadratic alg in the model

Uniformly random model

- DNA is not uniformly random
- A and B are related

Indel channel model [GS20]

- A uniformly random
- B mutated from A with subs, dels, and ins at constant probability
- $\mathcal{O}(n \log n)$ algorithm w.h.p.
- Needs to be implemented
- Is the algorithm's runtime and accuracy robust on real data?

Semi-random models

Description

Input: Combination of

- Adversary
- Randomness following a distribution

Performance measure

- Worst-case over choices of adversary
- Average-case over random distribution

Need middle ground between adversary and randomness

- A needs to make sense biologically
- A and B must be dependent on each other

E.g. smoothed analysis [AK12]

- Adversary chooses A and B and a longest common subsequence of them
- Each nucleotide not involved in LCS is perturbed independently
- Each nucleotide involved in LCS is perturbed identically in A and B

Semi-random models

[BSS20]

Model

- Adversary chooses a seed string s
- s is randomly permuted to get A
- Adversary (knowing A and s) constructs B

Algorithm

- Approximation ratio: $1 + o(1)$
- Expected runtime: $\Theta(n^{1.898})$
- $<$ 9x speedup over $\Theta(n^2)$ for $n = 10^9$

Average-case and semi-random model summary

- Promising active direction
- The design goal not achieved so far

Analyzing with advice

[GH17]

Idea: Perhaps the formulation of the computational problem is not general enough.

Suppose that for an input A and B, the alg has access to $\log n$ "correlated" instances.

Alg can find edit distance in $\mathcal{O}(n \log n)$ time with high probability.

What are "correlated instances?"

- Same positional edit sequence
- Not clear where such data might be available

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Memory use of compact data structures

A success story

Compact/succinct data structures

- Allow efficient queries using as little space as possible (e.g. BWT)
- Higher-order constants retained during analysis

Successfully developed for sequencing bioinformatics

- BOSS data structure for de Bruijn graph [BOSS12]
  - $4m + o(m)$ bits, where m is the number of edges
  - used in MEGAHIT [LLL+16] assembler and basis for VG toolkit [Sir17, GSN+18]
- Pufferfish k-mer index [ASSP18], used in Salmon [PDL+17]
- Counting quotient filter, used by for k-mer counting [PBJP17]
- Minia, a de Bruijn graph representation in an assembler [CR12]
- Rainbowfish, a representation of colored de Bruijn graph [APP17]
- BBhash, minimum perfect hash function for k-mers [LRCP17]

Summary

- Design of alg that works well in practice? Yes
- Predict empirical performance of alg? Yes

Accuracy of genome assembly algorithms

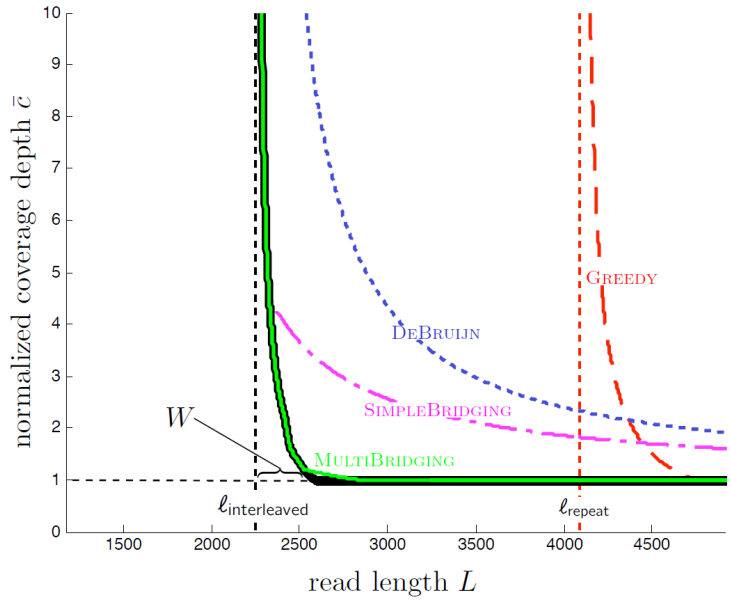
Theoretical analysis attempts

Measure what percentage of all "inferable" contigs are reported [TM17]

- Technically challenging

Measure the conditions under which an algorithm can fully reconstruct the genome [BBT13]

- Shannon assembler [KHM+16]



Accuracy of genome assembly algorithms

Reality

In practice

- Most alg design is driven by accuracy on empirical data (e.g. N50)
- Most algs use complex heuristics that are difficult to analyze
- Plenty use of theory (e.g. combinatorial algorithms)...but not to analyze accuracy

Summary

- Design? Mostly no..
- Performance? No

Assemblathon2 [BFA+13] conclusions for short read assemblers

- Rank of assemblers using experimental evaluation depended on dataset and evaluation metrics/parameters.
- Reviewer: "on any reasonably challenging genome, and with a reasonable amount of sequencing, assemblers neither perform all that well nor do they perform consistently" [TB]

Accuracy of structural variation detection algorithms

Current tools

- Many based on combinatorial algorithms
- Only a few have any theoretical measurement of accuracy
  - e.g. CLEVER [MCC+12] calculates the false discovery rate

What would it take to measure accuracy?

- A model for the distribution of variant type, location, and frequency.
- Our understanding of the biological generative model is incomplete.

Accuracy in practice [KML+19, CDSP19]

- Accuracy on simulated much higher than on real data
- Tools suffer from low recall
- Ranking of tools according to accuracy varied across variant subtypes

Summary

- Design? Mostly no..
- Performance? No
- Open challenge: Come up with generative model for structural variants such that algs designed to maximize expected accuracy on this model outperform existing tools in practice, with an observed accuracy matching the predicted one

Conclusions

What have we learned?

Has TAA been successful in sequencing bioinformatics? Anecdotally:

- Most papers do not perform TAA
- Or perform it but say alg performs much better in practice
- Its impact has been limited in best

Challenges of TAA in sequencing bioinformatics

- Traditional worst-case analysis too pessimistic
- Technology evolves fast and there is a lot of time pressure to {develop, analyze, apply} algorithm
- Researcher background

Is TAA even necessary?

- Empirical evaluation is powerful and essential — but not enough
- Known problems:
  - Benchmarks and critical assessments are not always available
  - Incentives favor overfitting the data
  - Absolute/relative performance does not always generalize

Conclusions

What can be done?

Recognize the Theoretical Analysis of Sequencing Bioinformatics Algorithms (TASBA) as its own research area.

- . . . as opposed to a side note in an algorithm paper

General goals of TASBA research program:

- Develop TAA techniques that are simple yet predictive of empirical performance
- Establish best practices for the application of TAA techniques
- Establish the most effective way to combine empirical and theoretical analysis techniques.

Immediate goals

- Find old success stories
- Look at bioinformatics algorithms more generally
- Develop new success stories. Retrospective is OK.

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