CONSEQUENCES OF FASTER ALIGNMENT OF SEQUENCES

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FASTER ALGORITHMS?

Some classic problems on sequences have $\tilde{O}(n)$ algorithms:

- ✓ Exact Pattern Matching
- ✓ Pattern Matching with don't cares
- ✓ Longest Common Substring

While other classic problems don't have $O(n^{2-\varepsilon})$ algorithms:

- ➢ Local Alignment
- ➢ Edit Distance
- ➢ Longest Common Subsequence (LCS)

Isn't quadratic time efficient enough?

LOCAL ALIGNMENT

$O(n^2)$ is not that efficient…

Input: Two (DNA) sequences of length n.

AGCCCGTCTACGTGCAACCGGGGAAAGTATA
AAACGTGACGAGAGAGAGAACCCATTACGAA

Output: The optimal alignment of two substrings.

	A	C	G	T	–
A	+1	-1.4	-1.8	-0.7	-1
C	-1.4	+1	-0.5	-1	-1
G	-1.8	-0.5	+1	-1.9	-1
T	-0.7	-1	-1.9	+1	-1
-	-1	-1	-1	-1	-∞

C C G – T C T A C G
C C C A T – T A C G

+1 +1 -0.5 -1 +1 -1 +1 +1 +1 +1 = +4.5

Solved daily on huge sequences: $n = 3 \cdot 10^9$ for the human genome.

Algorithms:

Smith-Waterman dynamic programming $O(n^2)$.

Compression tricks $O\left(\frac{n^2}{\log n}\right)$.

LOCAL ALIGNMENT

When $\mathrm{n} = 3 \cdot 10^9$, $O(n^2/\log n)$ is too slow!

In practice? Heuristics.

<u>Most cited paper in the 90s:</u>

BLAST: Basic Local Alignment Search Tool

A *heuristic* algorithm for Local Alignment.

Can we find an $O(n \log n)$ algorithm??

(that would probably be efficient…)

How about $O(n^{1.5})$ or even $O(n^{1.8})$?

<u>Today</u>: Theoretical evidence that the answer is “no”!

HARDNESS FOR EASY PROBLEMS

How can we prove that a problem requires $\sim n^2$ time?

Prove NP-Hardness?	***$O(n^4)$ vs $O(n \log n)$?***
Unconditional Lower bounds ?	***No superlinear bounds***
Lower bounds for classes of algorithms ?	***Not a complete answer.***

IDEA: REDUCTIONS

Theorem: Problem X is NP-hard

X is in P

Every NP-complete problem is in P

<u>Conclusion</u>: **X is probably not in P…**

OUR APPROACH

A surprising algorithm for problem Y

Unexpected breakthroughs in different areas

<u>Conclusion</u>: **Such algorithm is unlikely…**

A refined version of NP-hardness…

MAIN RESULT

“Theorem”:

If Local Alignment can be solved in $n^{1.99}$ time, then:

- 3-SUM can be solved in $n^{1.99}$ time!

  Refuting the 3-SUM conjecture

- CNF-SAT can be solved in 1.99^n time!

- Max-4-Clique can be solved in $n^{3.99}$ time!

3SUM

Most famous example of this approach

Input: A list of n numbers

-15	-6	33	8	1	-21	4	-30	7	…	107

Output: Are there 3 numbers that sum to 0?

Trivial: $O(n^3)$, Simple: $O(n^2)$, Best: $O(n^2/\log^2 n)$

[STOC 10': Patrascu] The 3SUM Conjecture:
3SUM cannot be solved in $O(n^{2-\varepsilon})$ time for any $\varepsilon > 0$.

[Gajentaan – Overmars 95'] and many others:

- A long list of *3SUM-hard* problems.

3SUM-HARD PROBLEMS

The 3SUM Conjecture:
3SUM cannot be solved in $O(n^{2-\varepsilon})$ time for any $\varepsilon > 0$.

The 3SUM conjecture implies the following lower bounds:

[C.G. 95': Gajentaan -- Oevrmars]
- 3-Points-On-A-Line requires $n^{2-o(1)}$ time.

Computational Geometry

[SODA 01': Barequet – Har Peled]
- Polygon Containment requires $n^{2-o(1)}$ time.

[STOC 10': Patrascu] and [STOC 09': Vassilevska – Williams]
- Zero-Triangle requires $n^{3-o(1)}$ time.

Graph Algorithms

[ICALP 13': A. -- Lewi]
- Zero-4-Path requires $n^{3-o(1)}$ time.

[ICALP 14': Amir – Chan -- Lewenstein – Lewenstein]
- A lower bound for Jumbled Pattern Matching.

Stringology

MAIN RESULT

“Theorem”:

If Local Alignment can be solved in $n^{1.99}$ time, then:

- 3-SUM can be solved in $n^{1.99}$ time!

  Refuting the 3-SUM conjecture

- CNF-SAT can be solved in 1.99^n time!

  Refuting the Strong Exponential Time Hypothesis (SETH)

- Max-4-Clique can be solved in $n^{3.99}$ time!

THE STRONG EXPONENTIAL TIME HYPOTHESIS

Very useful for proving lower bounds…

<u>CNF-SAT</u>: Given a CNF formula on n variables and m clauses, is it satisfiable?

[01': Impagliazzo – Paturi -- Zane]
<u>The Strong Exponential Time Hypothesis (SETH):</u>
"CNF-SAT cannot be solved in $(2-\varepsilon)^n\ poly(m)$ time."

There are faster algorithms for k-SAT but they become $\sim 2^n$ as k grows.

SETH HARDNESS

The Strong Exponential Time Hypothesis (SETH):

"CNF-SAT cannot be solved in $2^{(1-\varepsilon)n}\, poly(m)$ time."

Theorem(s): *The SETH implies the following lower bounds:*

[SODA 10': Patrascu -- Williams]

- k-Dominating-Set requires $n^{k-o(1)}$ time.

[STOC 13': Roditty – Vassilevska Williams]

- A $\left(\frac{3}{2} - \varepsilon\right)$-approximation for the diameter requires $(mn)^{1-o(1)}$ time.

[FOCS 14': A. – Vassilevska Williams]

- Dynamic Reachability requires $m^{1-o(1)}$ amortized update time.

[FOCS 14': Bringmann]

- Computing the Frechet distance requires $n^{2-o(1)}$ time.

MAIN RESULT

"Theorem":

If Local Alignment can be solved in $n^{1.99}$ time, then:

- 3-SUM can be solved in $n^{1.99}$ time!
  Refuting the 3-SUM conjecture
- CNF-SAT can be solved in 1.99^n time!
  Refuting the Strong Exponential Time Hypothesis (SETH)
- Max-4-Clique can be solved in $n^{3.99}$ time!
  A longstanding open problem

Computational Geometry

Satisfiability Algorithms

Graph Algorithms

Bottom line: Local Alignment probably requires $\sim n^2$ to solve optimally, and we should settle for heuristics in practice…

PLAN

- Motivation
- Main Results
- Other Results
- Proof examples:
  - CNF-SAT to LCS*
  - Sketch: 3-SUM to Local Alignment
- Open problems

MORE RESULTS

The conjectures imply tight lower bounds for:

- Edit Distance with gap penalties
- Normalized LCS
- Multiple Local Alignment
- Partial Match

- LCS*

The simplest problem that requires $n^{2-o(1)}$ *time?*

LCS*

The Longest Common Substring with don't cares problem (LCS*)

<u>Input</u>: Two string of length n, containing don't care characters *.

S = RESEARCH_P*P*RS_ARE_*OOL

T = GO*GLE_SE*R*H_IS_U*EFUL

<u>Output</u>: The longest common substring.

<u>Theorem:</u> The SETH implies that LCS* on ***binary*** strings requires $n^{2-o(1)}$ time!

CNF-SAT TO LCS*

Theorem: The SETH implies that LCS* on ***binary*** strings requires $n^{2-o(1)}$ time!

Proof: $O(n^{2-\varepsilon})$ alg for LCS* => $2^{\left(1-\frac{\varepsilon}{2}\right)n}$ alg for CNF-SAT

Given a CNF formula with m clauses

$$\varphi(x_1, \dots, x_n) = \underbrace{(\neg x_1 \vee x_{17} \vee \cdots \vee x_{10})}_{\boldsymbol{C_1}} \wedge \cdots \wedge \underbrace{(x_2 \vee x_5 \vee x_{21})}_{\boldsymbol{C_m}}$$

Split the variables and enumerate over partial assignments

$U_1 = \{x_1, \dots, x_{n/2}\}$ $\quad$ $U_2 = \{x_{n/2+1}, \dots, x_n\}$

$$\alpha = \begin{pmatrix} x_1 = T \\ x_2 = F \\ \vdots \\ x_{n/2} = T \end{pmatrix} \qquad \beta = \begin{pmatrix} x_{n/2+1} = F \\ x_{n/2+2} = F \\ \vdots \\ x_n = T \end{pmatrix}$$

There are $N = 2^{n/2}$ such α's and β's

Goal of alg: find a pair such that $(\alpha \cdot \beta)$ sat φ.

CNF-SAT TO LCS*

<u>Theorem:</u> The SETH implies that LCS* on ***binary*** strings requires $n^{2-o(1)}$ time!

<u>Proof</u>: $O(n^{2-\varepsilon})$ alg for LCS* => $2^{\left(1-\frac{\varepsilon}{2}\right)n}$ alg for CNF-SAT

$$\varphi \text{ is satisfiable} \Leftrightarrow \exists \alpha, \beta : \forall C_i : (\alpha \cdot \beta) \text{ sat } C_i$$

<u>Idea</u>: construct strings S, T of length $\sim(2^{n/2}m)$ such that

$$\text{LCS*}(S,T) = m \Leftrightarrow \exists \alpha, \beta : \forall C_i : (\alpha \cdot \beta) \text{ sat } C_i$$

<u>Done</u>: we get a $\left(2^{n/2}m\right)^{2-\varepsilon} = 2^{\left(1-\frac{\varepsilon}{2}\right)n} poly(m)$ alg for CNF-SAT

CNF-SAT TO LCS*

Theorem: The SETH implies that LCS* on ***binary*** strings requires $n^{2-o(1)}$ time!

Proof: Construct strings S, T of length $O(2^{n/2}m)$ such that

$$\text{LCS*}(S,T) = m \Leftrightarrow \exists \alpha, \beta : \forall C_i : \ (\alpha \cdot \beta) \text{ sat } C_i$$

Define strings of length m:

$$T_\alpha = [0 \ \ * \ \ * \ \ 0 \ \ * \ \ \cdots \ \ 0]$$

$$T_\alpha[i] = \begin{cases} * & \alpha \text{ sat } C_i \\ 0 & \text{otherwise} \end{cases}$$

$$S_\beta = [0 \ \ 0 \ \ 1 \ \ 0 \ \ 1 \ \ \cdots \ \ 0]$$

$$S_\beta[i] = \begin{cases} 0 & \beta \text{ sat } C_i \\ 1 & \text{otherwise} \end{cases}$$

Then: $\mathrm{T}_\alpha \equiv S_\beta \Leftrightarrow \forall C_i : \ (\alpha \cdot \beta) \text{ sat } C_i$

Construct S,T in $O(2^{n/2}\, m)$ time:

$$T = [\cdots \ T_{\alpha 1} \cdots] \ \$ \ \boxed{[\cdots T_{\alpha 2} \cdots]} \ \$ \ \cdots \ \$ \ [\cdots T_{\alpha N} \cdots]$$

$$S = [\cdots \ S_{\beta 1} \cdots] \ \# \ [\cdots S_{\beta 2} \cdots] \ \# \ \cdots \ \# \ \boxed{[\cdots S_{\beta N} \cdots]}$$

■

3-SUM TO LOCAL ALIGNMENT

3-SUM on n numbers

-15	-6	33	$\boldsymbol{x \in [\pm n^3]}$	-30	7	…	107

$|\Sigma| \sim n^3$?

[ESA 14': A. – Lewi – Williams]

$n^{o(1)}$ instances of 3-Vector-SUM on n vectors

		$\boldsymbol{v_x = (x_1, \dots, x_d)}$	…	

$|\Sigma| \sim \log n$

$x_i \in [\pm \log n]$ and $d = O\left(\frac{\log n}{\log \log n}\right)$

$\exists v_a, v_b, v_c : v_a + v_b + v_c = (0, \dots, 0)$?

$|\Sigma| \sim n^{\varepsilon} \log n$

Hashing…

Define substrings of length d:
$S_x = [\dots, \ '(h(x), x_i)', \dots]$

Σ contains pairs
$(h(x), x_i)$

3-SUM TO LOCAL ALIGNMENT

Define substrings of length d:
$S_x = [\ldots,\ '(h(x), x_i)',\ \ldots]$

Σ contains pairs
$(h(x), x_i)$

Our scoring matrix enforces that:

$(h(x), x_i)$ and $(h(y), y_i)$ will “match” iff:

$x_i + y_i + z_i = 0$ where z is determined by $h(x), h(y)$

CONCLUSION

The reductions explain the lack of progress
and prove that new ideas are required for faster algorithms

*"An **opportunity** to solve many famous open problems while working on your favorite problem!"*

- Subquadratic Edit Distance?
- Subquadratic LCS?
- Subcubic Protein Folding?
- Subcubic Tree Edit Distance?

Thank You!
Questions?