Computing Alignment Plots Efficiently

. . . in theory and practice

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Motivation

This talk is about *loss-free* local alignment of (biological) sequences.

Our loss-free alignment algorithms find *all* local alignments of two input sequences.

This is computationally very demanding.

What is in this talk?

A computational technique for computing multiple local alignments at the same time.

Some discussion about its efficient implementation.

Speedup results from different types of parallelism.

String Terminology

A *string* is a sequence of characters from an alphabet Σ.

Example (Genome Data)

Strings are sequences of characters from { A, C, G, T }

`CAGAGGATGAGGATG`

String Terminology

Contiguous subsequences are called *substrings/windows/factors*.

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We also consider not necessarily contiguous *subsequences*.

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Approximate String Comparison

Hamming distance: count mismatches.

dist(`bbbabababba`, `abbbbabaaba`) = 3

Used e.g. in dot-plots for local comparison.

String Alignment

Align the maximum number of letters, preserving order:

abbabbbabbaba

bbabaabbba

String Alignment

Align the maximum number of letters, preserving order:

```
abbabbba bbaba
 ||| | | || ||
 bba b aabb ba
```

String Alignment

Align the maximum number of letters, preserving order:

```
abbabbba□bbaba
 ||| | | || ||
□bba□b□aabb□ba
```

□ : inserted gaps

String Alignment

Align the maximum number of letters, preserving order:

```
abbabbba bbaba
 ||| | | || ||
 bba b aabb ba
```

The aligned letters form the *longest common subsequence (LCS)*.

String Alignment vs. LCS

The length of the LCS of two strings is a measure for their similarity.

We define the *LCS distance* as:

$$\text{dist}(x, y) = m + n - 2 \cdot |\text{LCS}(x, y)|$$

String Alignment and Edit Distances

Edit distance

Minimize the number of *insertions*, *deletions*, and *exchange operations*.

Weighted alignment

Assign weights to aligning each pair of characters from Σ using a *pairwise score matrix*.

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$O(n^2)$ Solutions for String Alignment

Longest common subsequence
Wagner & Fischer, '74

Global (weighted) alignment
Needleman & Wunsch, '70

Local alignment
Smith & Waterman '81

Faster but less accurate approaches

BLAST/similar approaches

Heuristic search based on frequent DNA substrings to “seed” alignments.

This is very fast!

Less sensitive for aligning regions of low similarity.

$\Rightarrow$ Can miss alignments!

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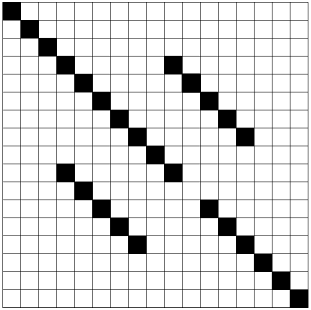
Dot-plots

Compare all substrings of a fixed length w using the Hamming distance.

Plot a point for every window pair scoring above threshold.

$\Rightarrow$ Does not account for gaps!



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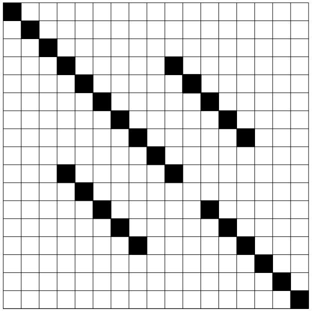


Alignment Plots

Input: Strings x and y, $|x| = m$, $|y| = n$, fixed window length w.

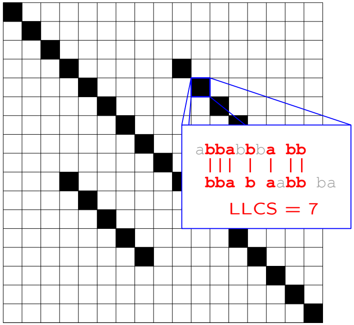
We compare all windows of length w in x to all windows of length w in y (pairwise).

We use a weighted alignment score for comparison.

Computing Alignment Plots

"Naive" algorithm:
Compute scores separately for each pair of windows in $O(mnw^2)$ time.

Heuristic improvements (Ott, 2008): $\times 25$ speedup, same asymptotic running time.



Computing Alignment Plots

Why?

Very sensitive *local* comparison. Finds things BLAST doesn't.

How big?

Input sequences can be very large: entire genomes should be possible (30MBases – 1TBase)

Window sizes?

Typical w-value: around 100.

New Algorithms for Alignment Plots

Algorithmic Improvements

We reduce dependency on window size: New practical $O(mnw)$ method.

Vector-Parallelism

We can (still) use vector-parallelism.

Parallel Computation

Multi-processor computation: running time $O(mnw/p)$ on p processors.

Algorithmic Tool: Semi-local String Comparison

Definition

Given two strings x and y, compute *highest-score matrix* A with

$$A(i,j) = |LCS(x, y_i \dots y_j)|.$$

We compare all substrings in y to entire string x.

Algorithm [Schmidt:98,Alves+:06]

We can compute A in $O(n^2)$ time.

Implicit Highest-Score Matrices

Theorem (Tiskin:05)

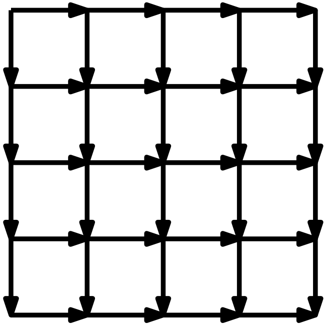
The highest-score matrix for comparing x and y can be represented by $O(m + n)$ ***critical points****.*

Seaweed Algorithm

We can compute critical points incrementally by dynamic programming in $O(mn)$.

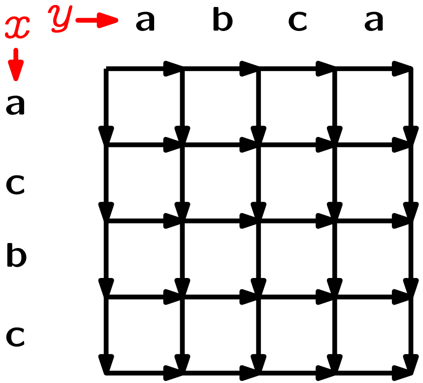
The Seaweed Algorithm

We draw the *alignment-dag*. . .



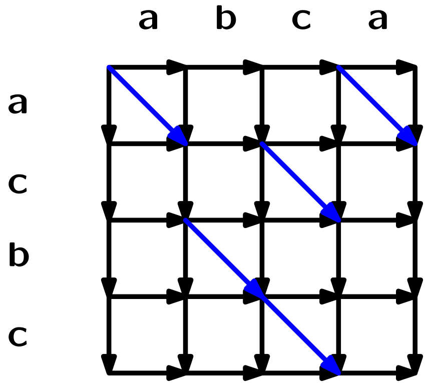
The Seaweed Algorithm

. . . that corresponds to the input strings.



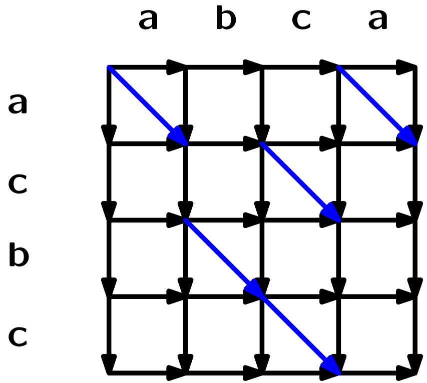
The Seaweed Algorithm

We insert blue edges for every match.



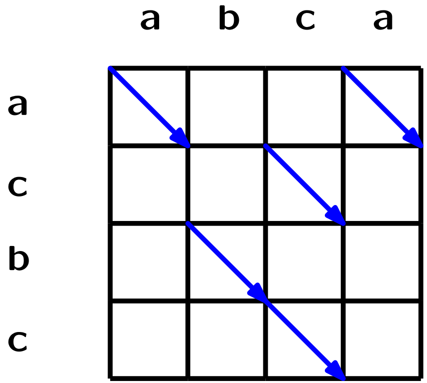
The Seaweed Algorithm

Blue edges have weight 1.



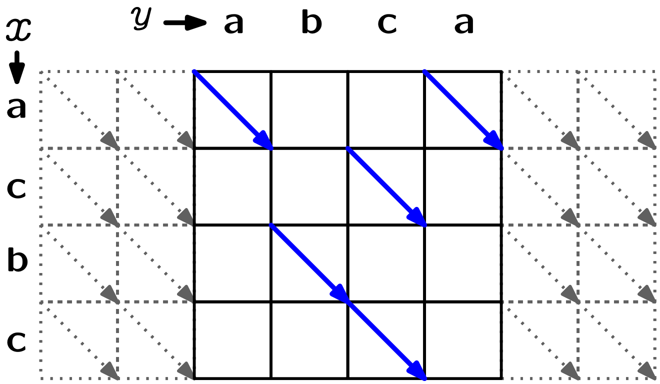
The Seaweed Algorithm

Black edges have weight 0.



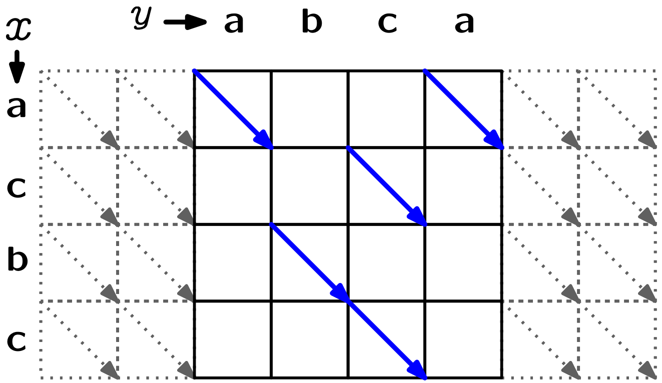
The Seaweed Algorithm

We can extend the dag with matches to the left and right.



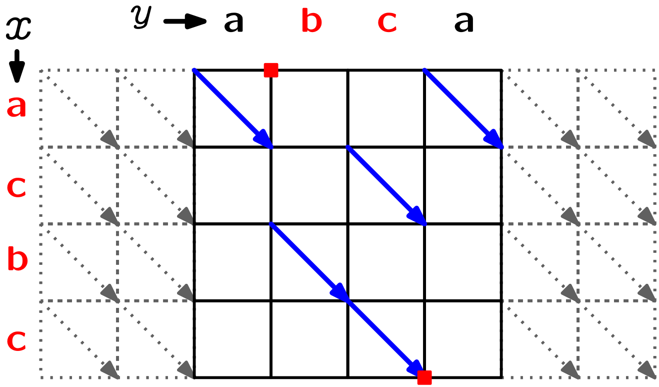
The Seaweed Algorithm

Drawing this dag partitions the plane into cells.



The Seaweed Algorithm

Alignment lengths in $A(i, j)$ correspond to longest paths.



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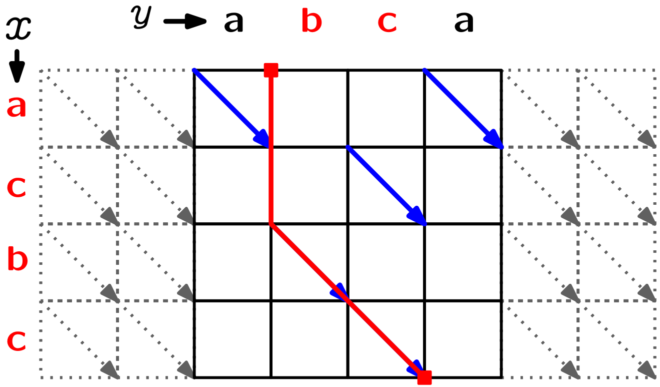
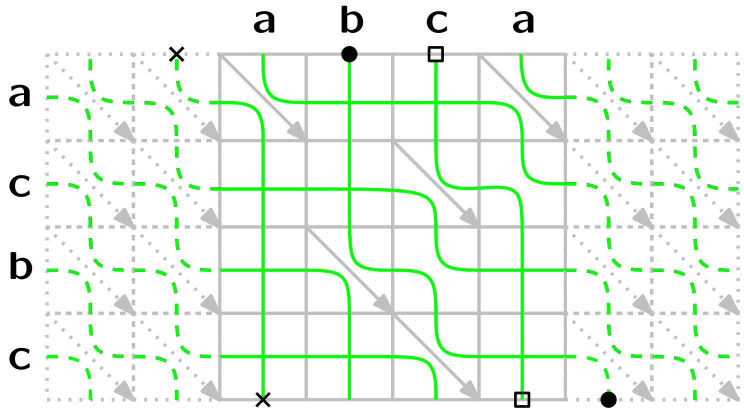


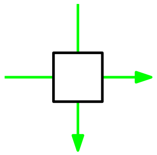
The Seaweed Algorithm

We compute the lengths of these paths implicitly by tracing *seaweeds*.



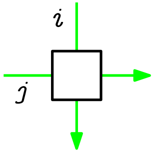
The Seaweed Algorithm

We trace seaweeds through cells.



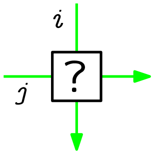
The Seaweed Algorithm

We trace seaweed start and end points.



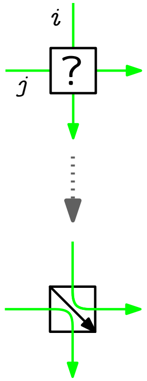
The Seaweed Algorithm

In a cell, seaweeds may or may not cross.



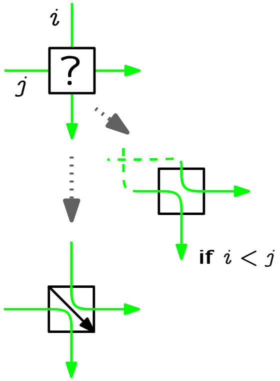
The Seaweed Algorithm

Seaweeds don't cross in match cells.



The Seaweed Algorithm

Two seaweeds are allowed to cross at most once.



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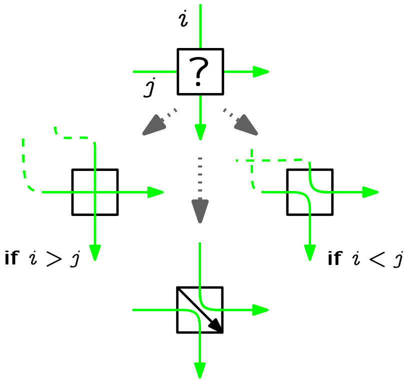
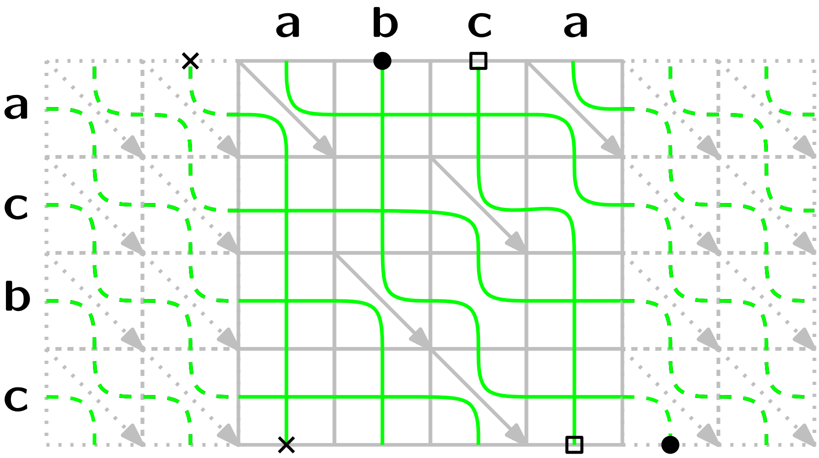


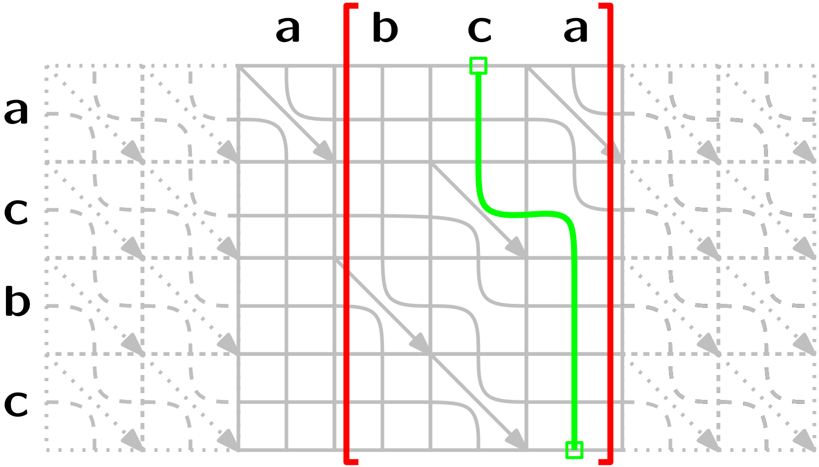
Querying the LCS Distance

Given all seaweeds. . .



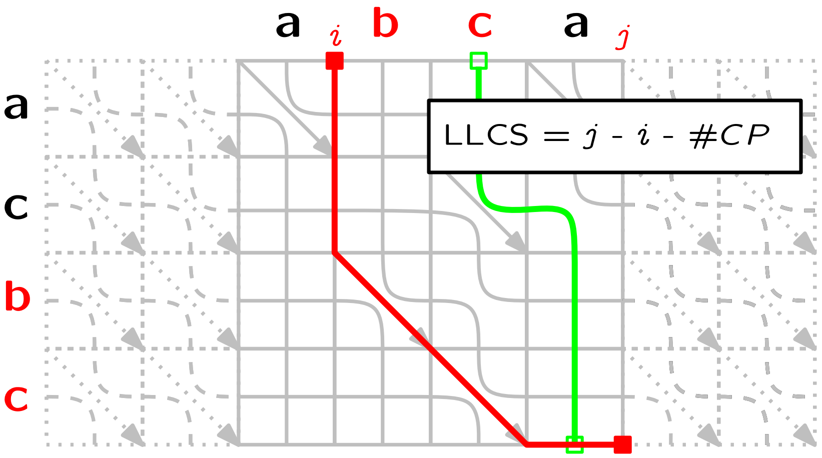
Querying the LCS Distance

. . . we can count critical points:



Querying the LCS Distance

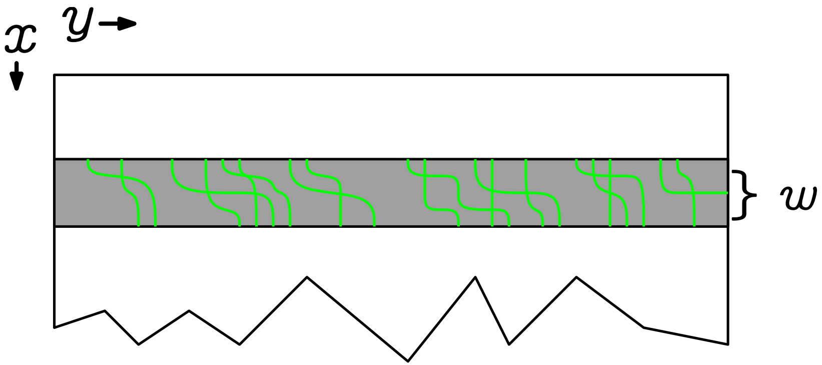
. . . and obtain the LLCS:



LLCS = j - i - $\#CP$

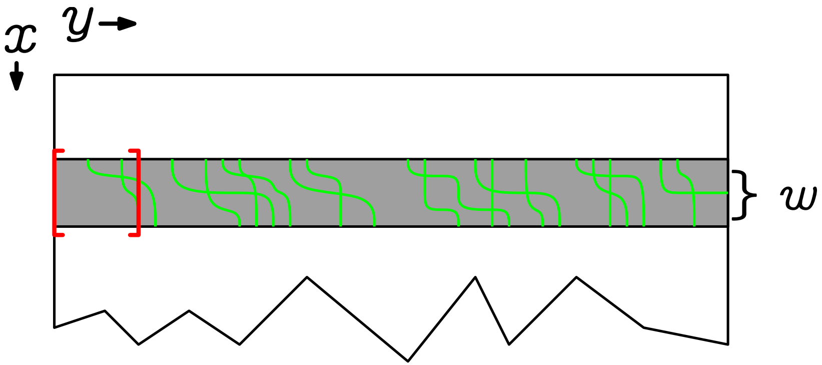
Computing Alignment Plots Using Seaweeds

We compute seaweeds for y against all substrings of x with length w.



Computing Alignment Plots Using Seaweeds

Inside each *strip*, we count seaweeds within a sliding w-window.



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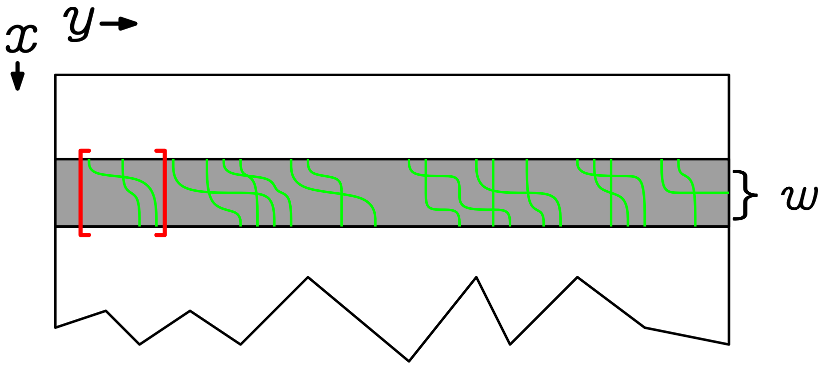

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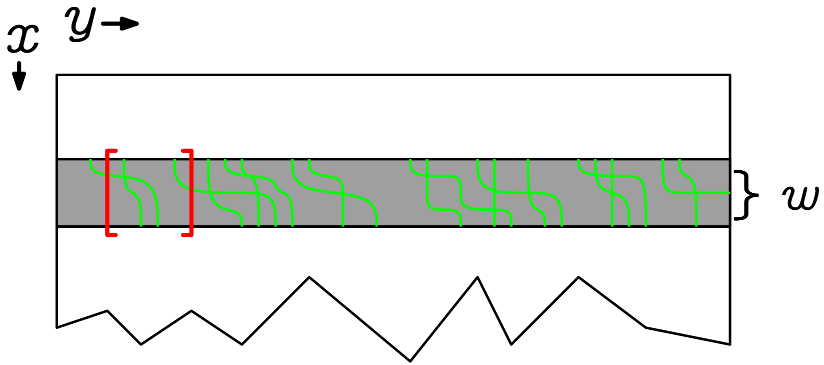

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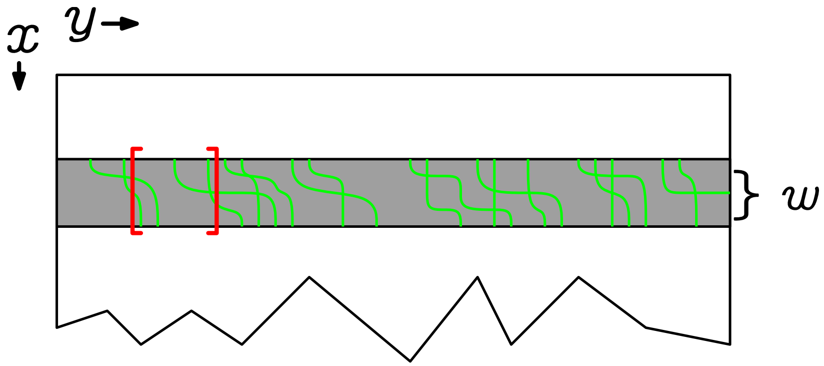

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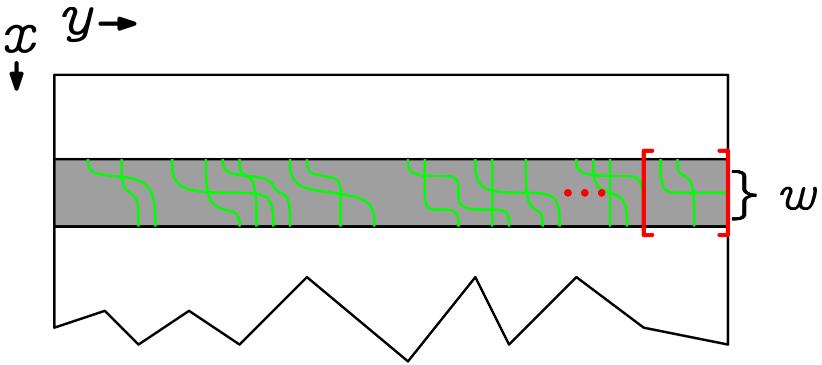


Computing Alignment Plots Using Seaweeds

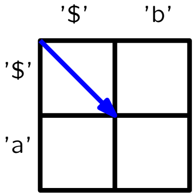
We have $m - w + 1$ strips, each strip takes time $O(nw)$ to process.

$\Rightarrow$ We get running time $O(mnw)$.

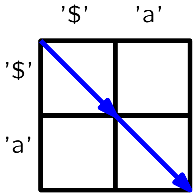
Further Notes on Seaweeds

We can deal with rational pairwise score matrices (constant factor slowdown).

$$w_{=} = 1$$
$$w_{\neq} = 0$$
$$w_{\sqcup} = -0.5$$



Mismatch

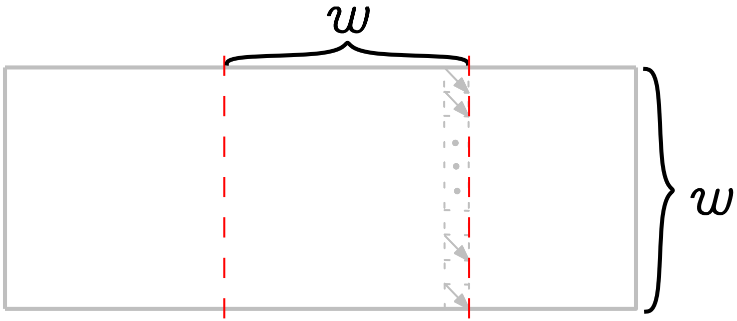


Match

$$S(x, y) = LLCS(x', y') - 0.5 \cdot (m + n)$$

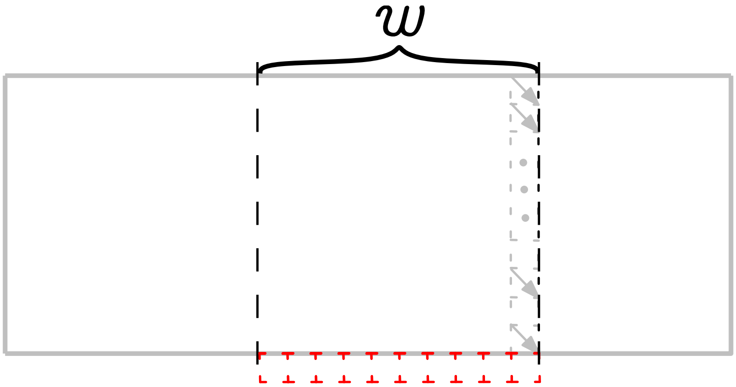
Vector-Parallel Seaweeds

Seaweed implementation using sliding w-window in a strip:



Vector-Parallel Seaweeds

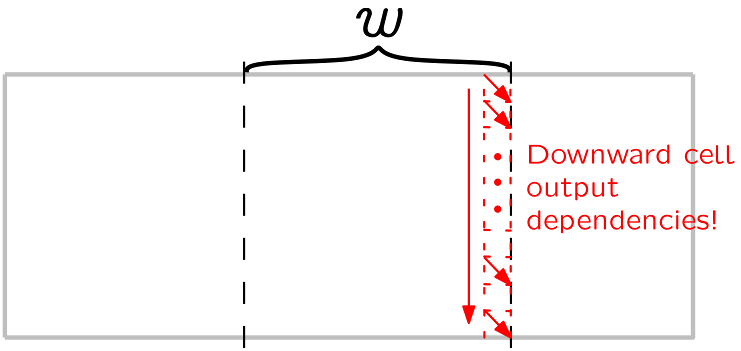
We only need to count the seaweeds which start and end within the w-window.



Store maximally w seaweeds which have reached the bottom.

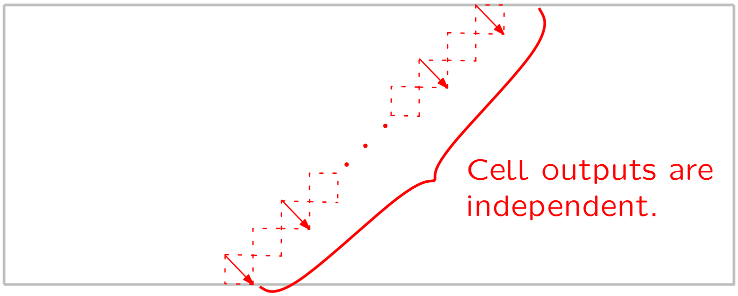
Vector-Parallel Seaweeds

Problem: data-dependency between cell outputs when computing seaweeds in columns.



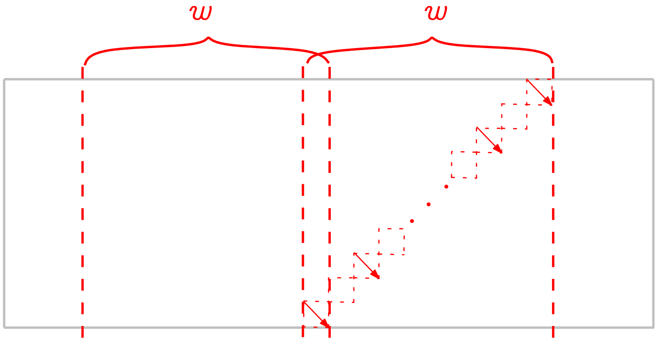
Vector-Parallel Seaweeds

Standard solution: Process cells in a *wavefront* in parallel.



Required Vector Element Size

We need to trace seaweeds over a maximum distance of $2w - 1$.



We need $O(\lceil \log_2 w \rceil + 1)$ bits for each vector element.

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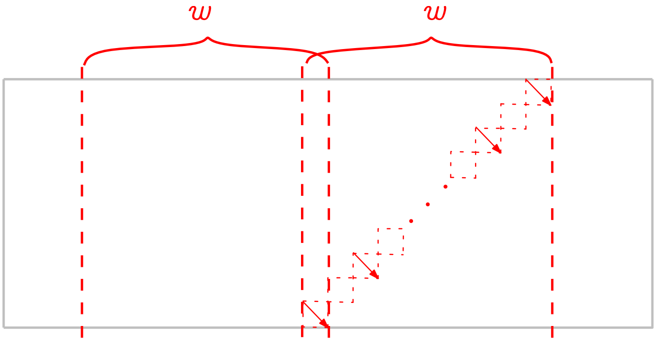

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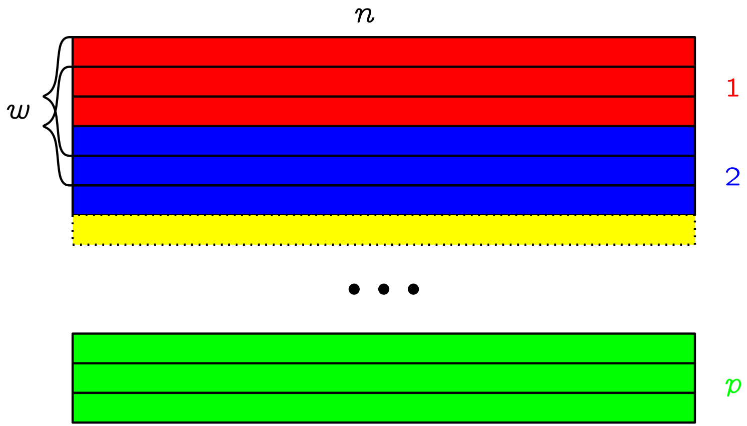
Using Coarse-Grained Parallelism

Computation for individual strips is independent:



Implementation Notes

Current implementation uses C++ and Intel Assembly (x86 and x86_64, MMX).

Explicit vectorisation of the inner loop using assembler code.

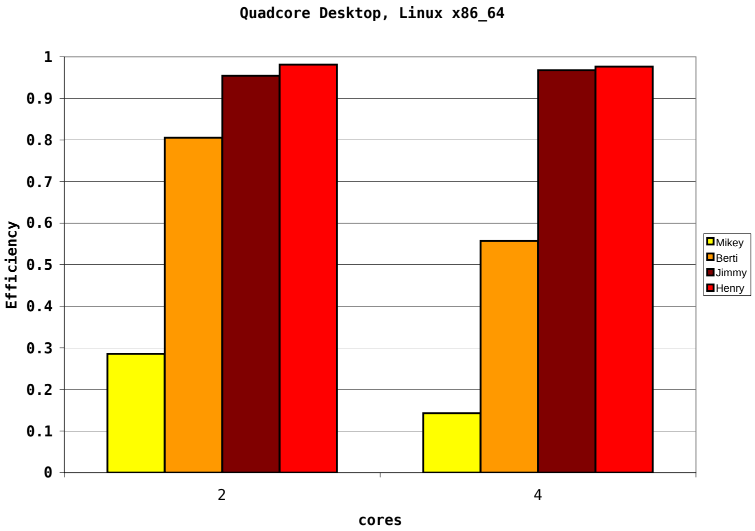
The core of the code consists of a small library for implementing operations on vectors of ω-bit integers.

Single CPU Execution Times

Data Set	Mikey	Berti	Jimmy	Henry
Input Size	2.7k × 0.6k	2.7k × 2.3k	15k × 97k	80k× 80k
Heur	5.1 (÷ 1.0)	41.1 (÷ 1.0)	2677 (÷ 1.0)	11708 (÷ 1.0)
BLCS	3.6 (÷ 1.4)	37.3 (÷ 1.1)	3680 (÷ 0.7)	16191 (÷ 0.7)
Sea-16	1.4 (÷ 3.6)	10.8 (÷ 3.8)	1026 (÷ 2.6)	4514 (÷ 2.6)
Sea-8	0.5 (÷ 10.2)	3.8 (÷ 10.8)	368 (÷ 7.3)	1614 (÷ 7.3)
Sea-8 SMP×2	0.3 (÷ 17.0)	3.4 (÷ 12.1)	210 (÷ 12.7)	821 (÷ 14.3)

(Execution times in seconds)

Parallel Efficiency using MPI



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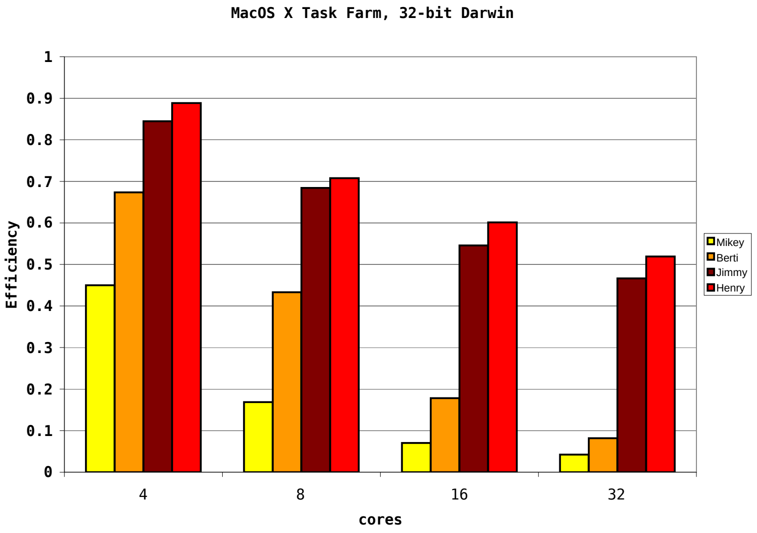
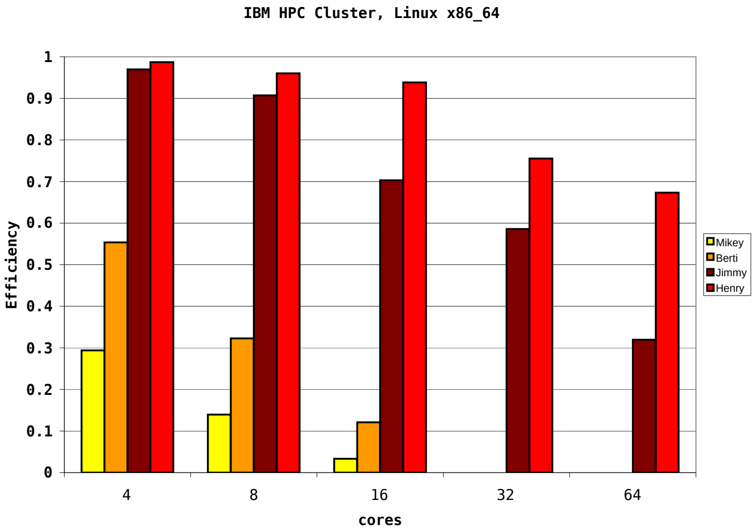


Parallel Efficiency using MPI



Summary

We have shown a new, fast algorithm for loss-free local sequence alignment.

Main contribution: reduced dependency of runtime on the length of the local alignments.

Method allows to use different types of parallelism.

Outlook

Better speedup for small problem sizes by smarter partitioning.

This is useful when using the code for small sequences as a web service, like BLAST.

Test suitability for GPU implementation.

Lots of inherent parallelism...

Exploit strip overlap: we can reduce complexity to $O(mn\sqrt{w})$.

The best known theoretical method has complexity $O(mn)$, but may not be practical.

Thanks for listening!

Questions?