Exact Solution for the Approximate Suffix-Prefix Overlap Problem

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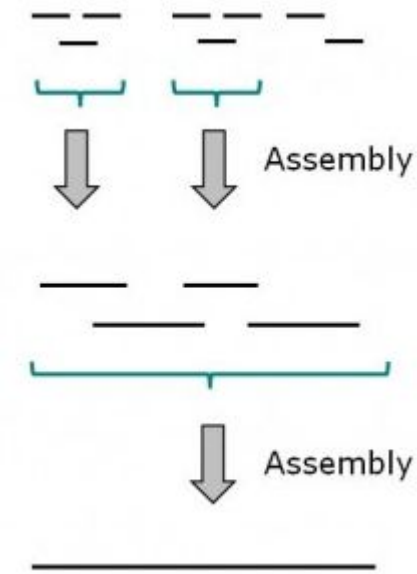
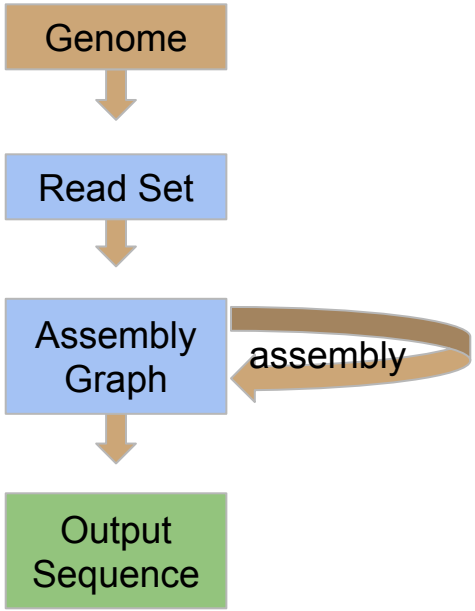
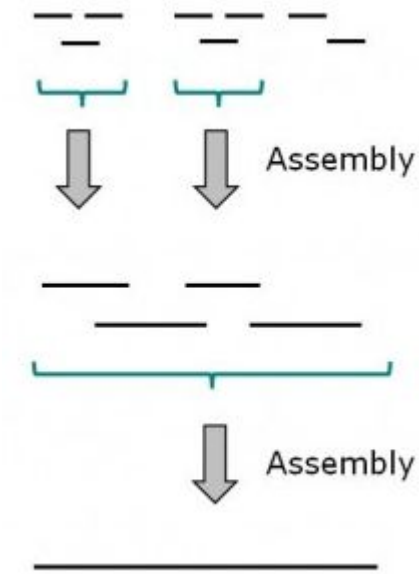
Context:
Sequence Assembly

- In-silico representation of a genome
- Can’t physically read the entire genome at once
- Need to assemble small reads into the entire genome



Context:
Sequence Assembly Pipeline





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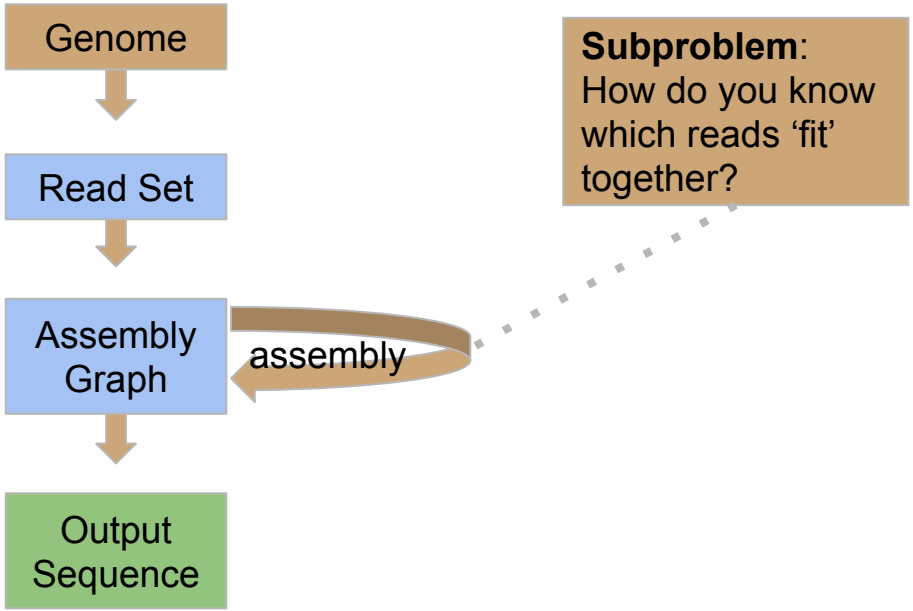
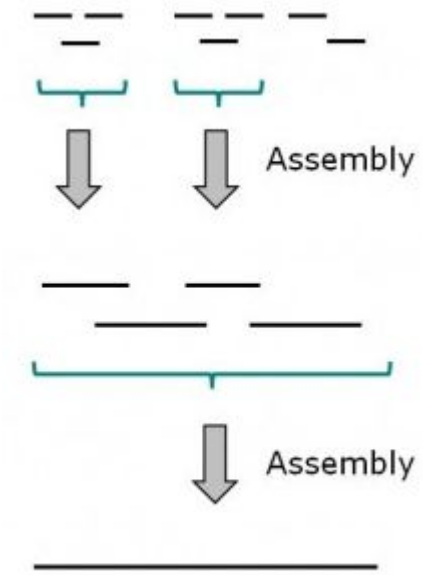
Sequence Assembly Pipeline



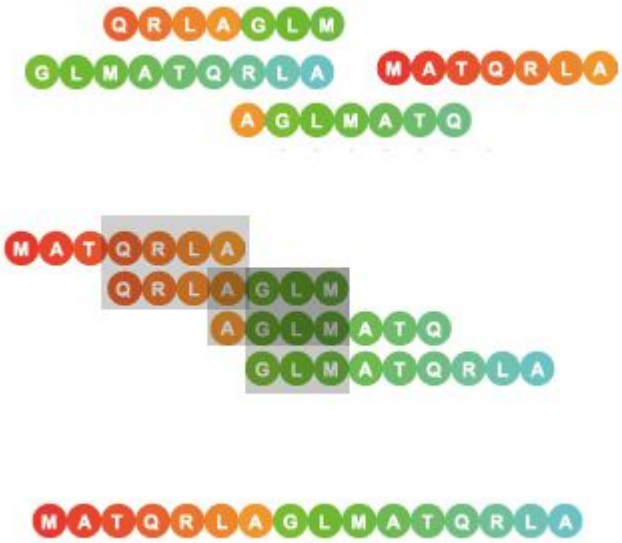


Context:
Approximate Suffix-Prefix Overlap Problem (ASPOP)

Subproblem of Sequence Assembly

- No knowledge of *where* a read is from
- Instead, guess which reads come from *common* locations (overlaps)

Given a set of **strings,**
return a set of **overlaps**

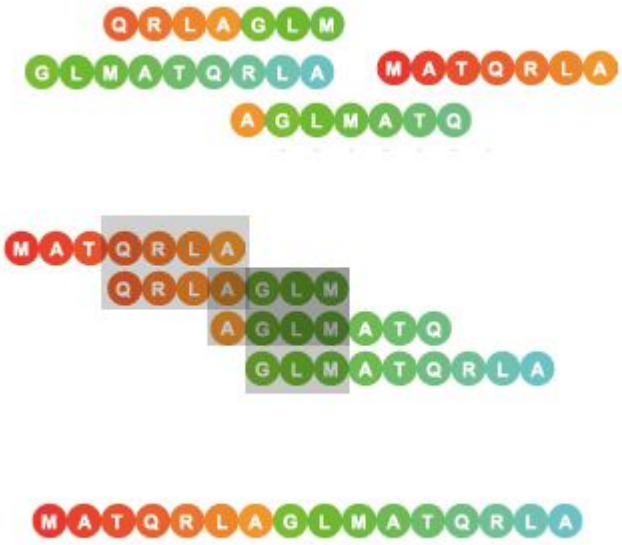


Context:
Approximate Suffix-Prefix Overlap Problem (ASPOP)

Read process is imperfect!

Overlaps must be allowed to be **approximate**
i.e. contain **errors**

TTGGGCAATGA
CCCCTTAGGC



Context:
Approximate Suffix-Prefix Overlap Problem (ASPOP)

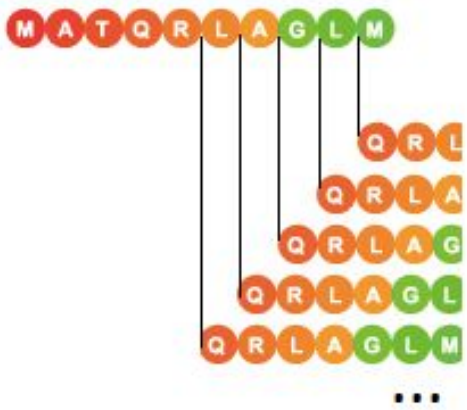
Heuristic solvers for the ASPOP exist

- Exact solution is prohibitively expensive

Can we solve it *exactly*?

Naive approach:

- For every pair of strings, check if any overlap of suffix-prefix is a *good solution*
  - *Moderate data set has 40 000 reads*
  - *This approach takes a long time!*

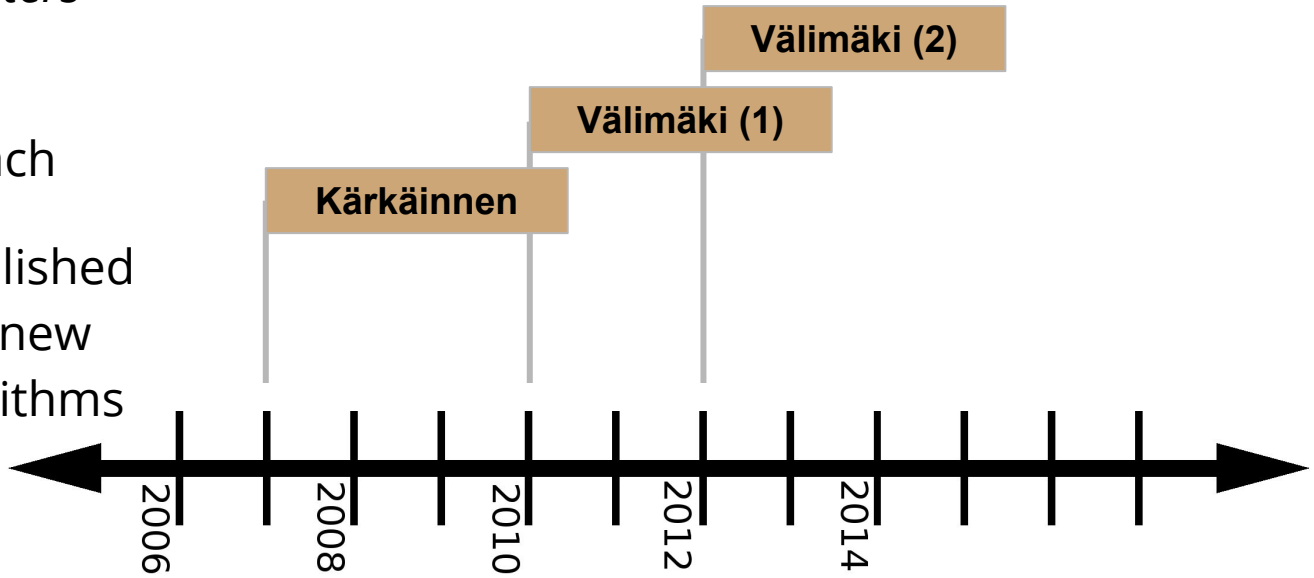


Existing Works

Many approaches are possible.
One approach: *suffix filters*

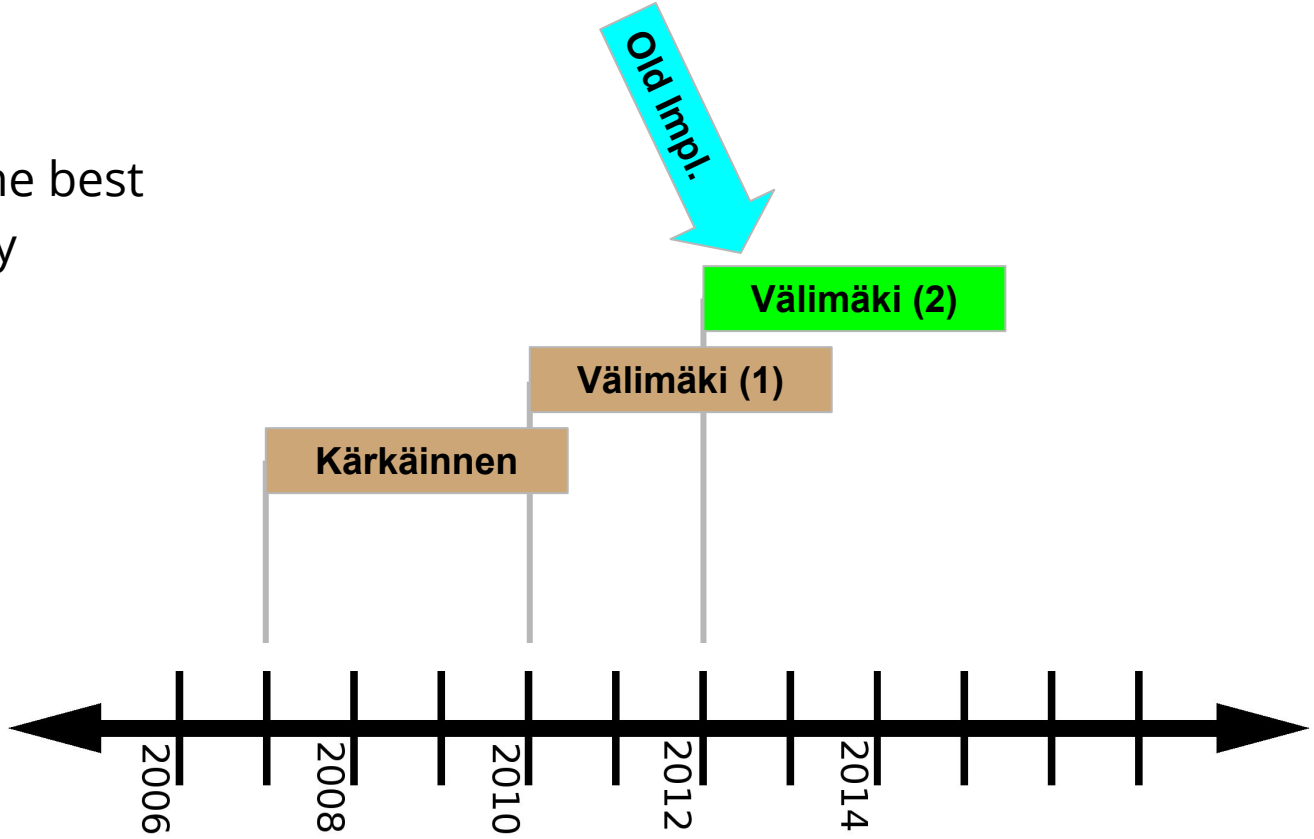
Kärkäinnen et al first introduced this approach

More papers were published since then, suggesting new faster suffix filter algorithms



Existing Works

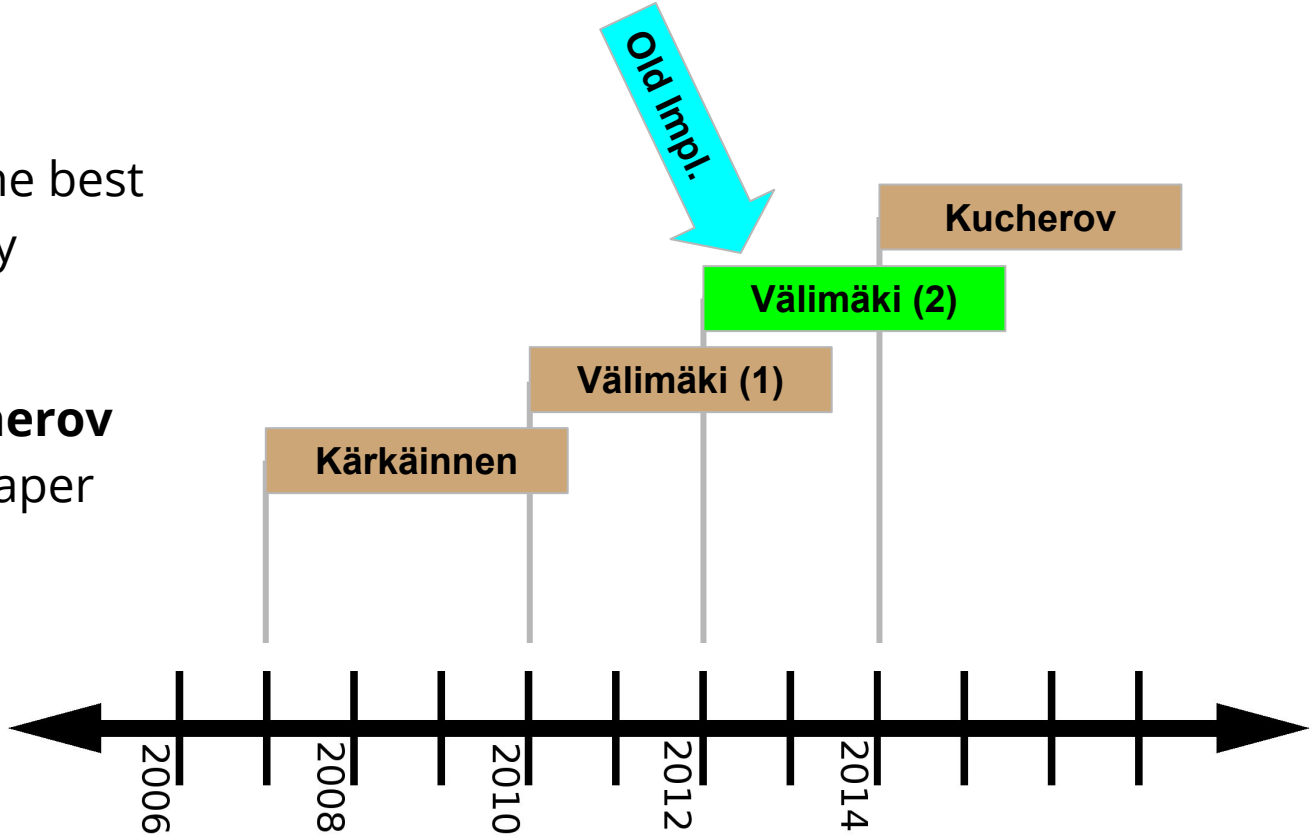
In-house solver uses the best algorithm as of 2012 by **Välimäki** et al.



Existing Works

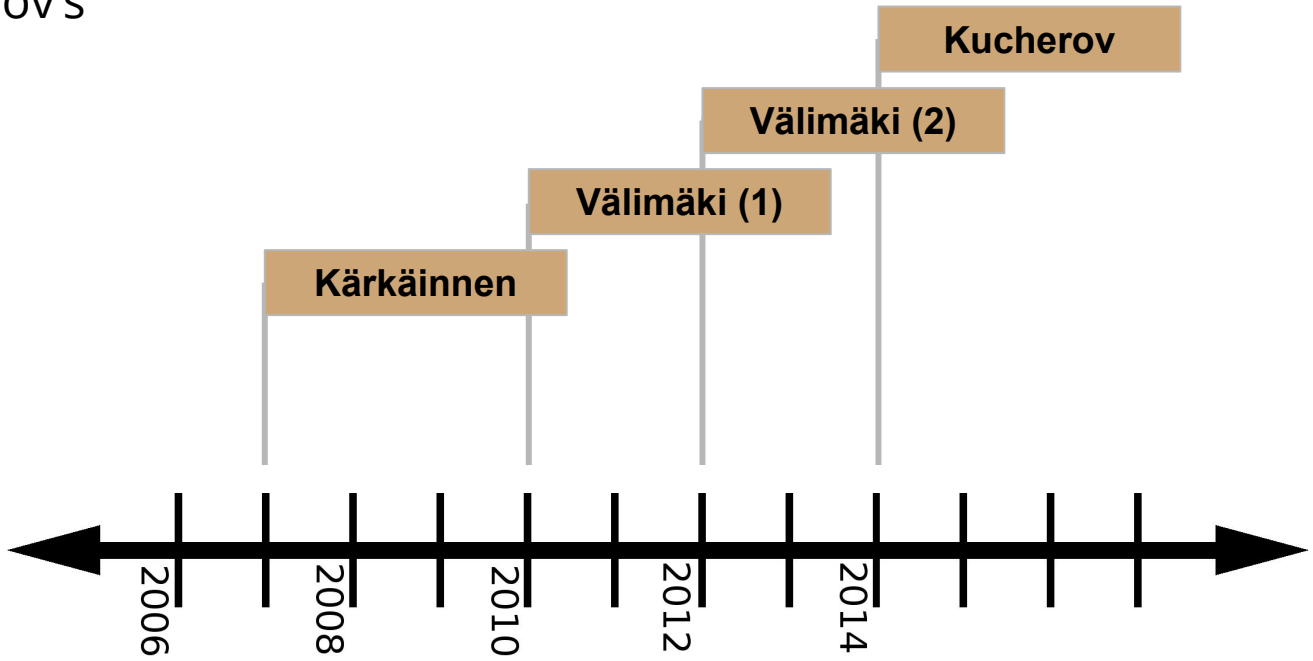
In-house solver uses the best algorithm as of 2012 by **Välimäki** et al.

In the meantime, **Kucherov** has published a new paper with a new algorithm.



My Task

1. Implement Kucherov's algorithm



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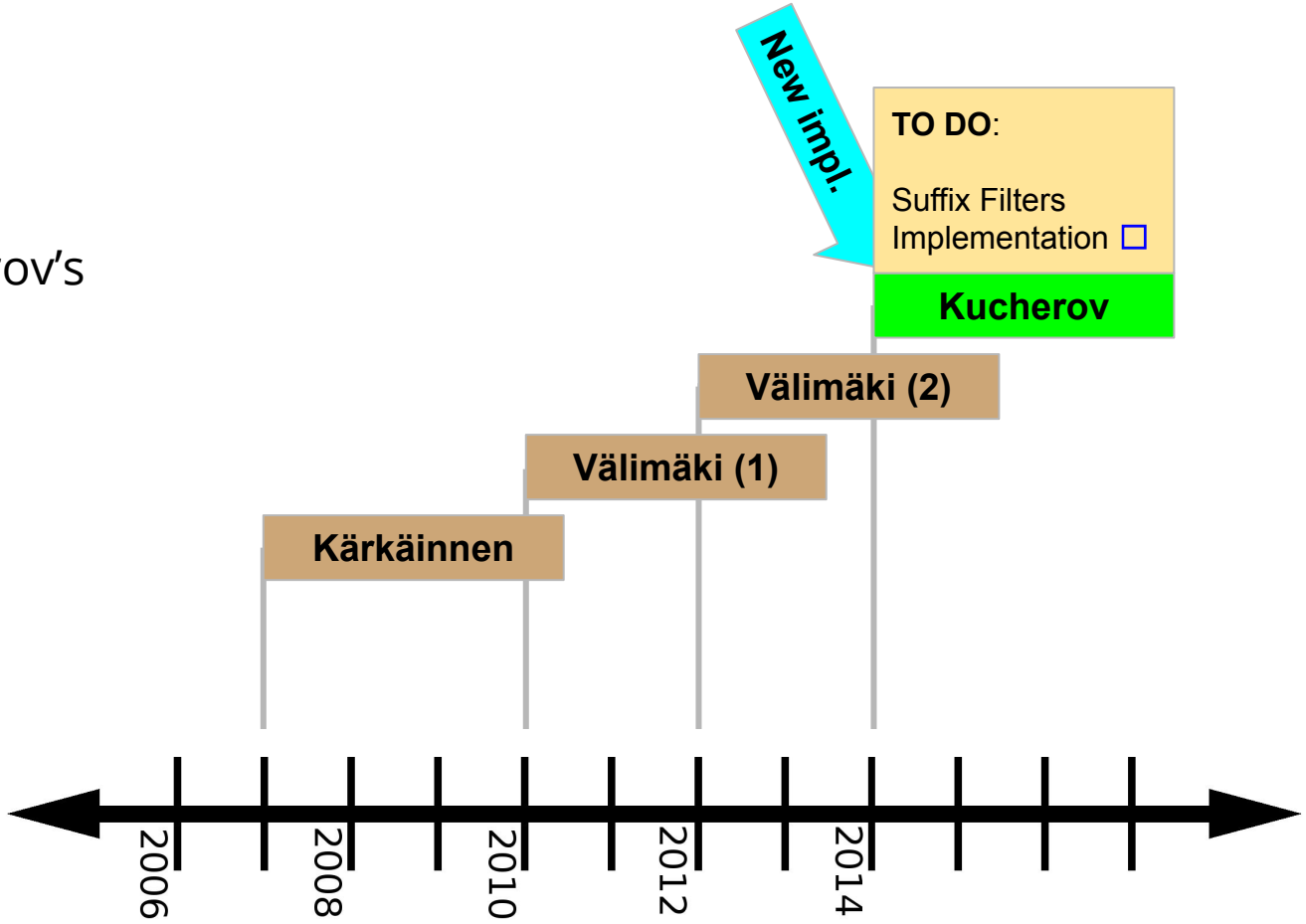
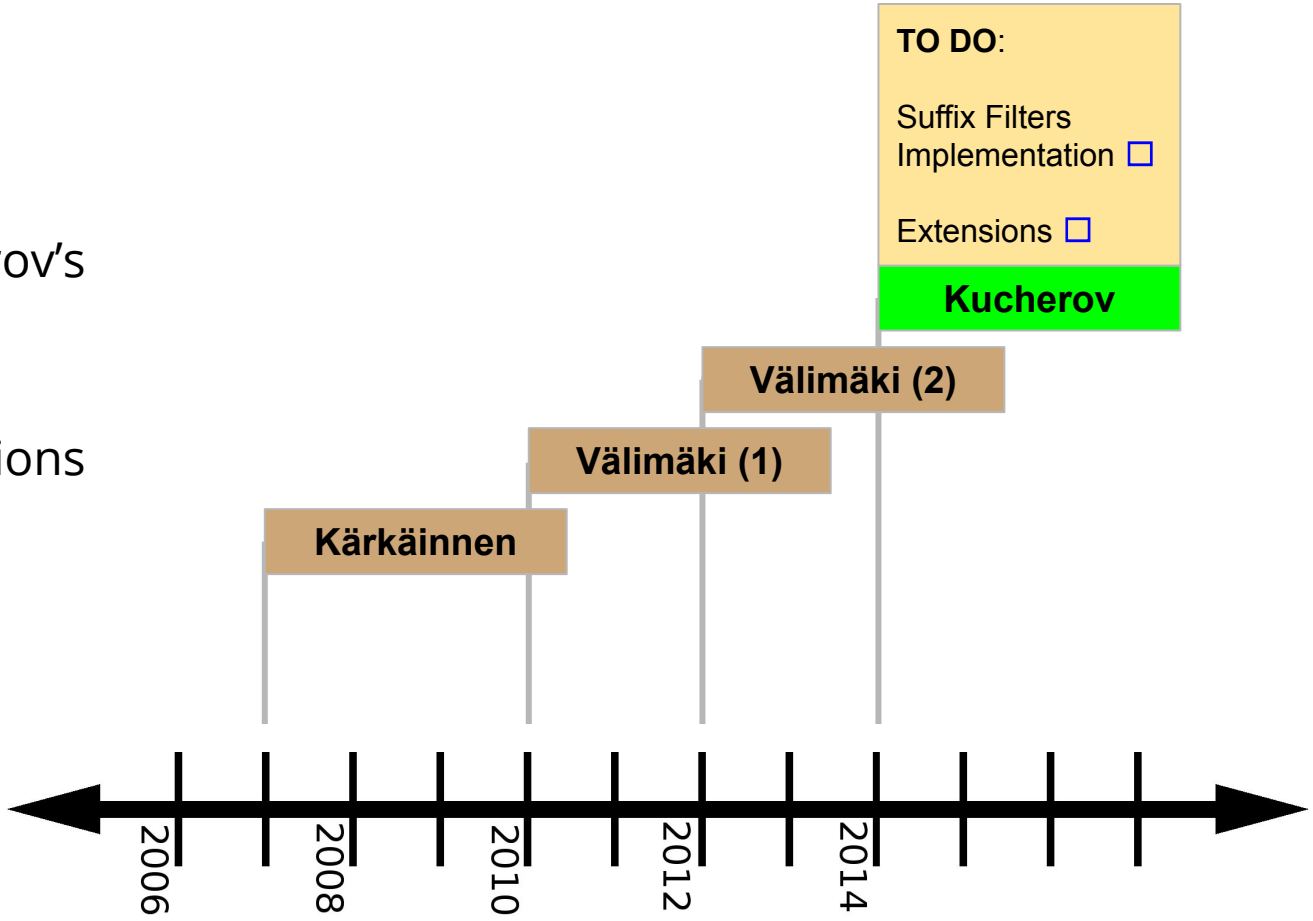


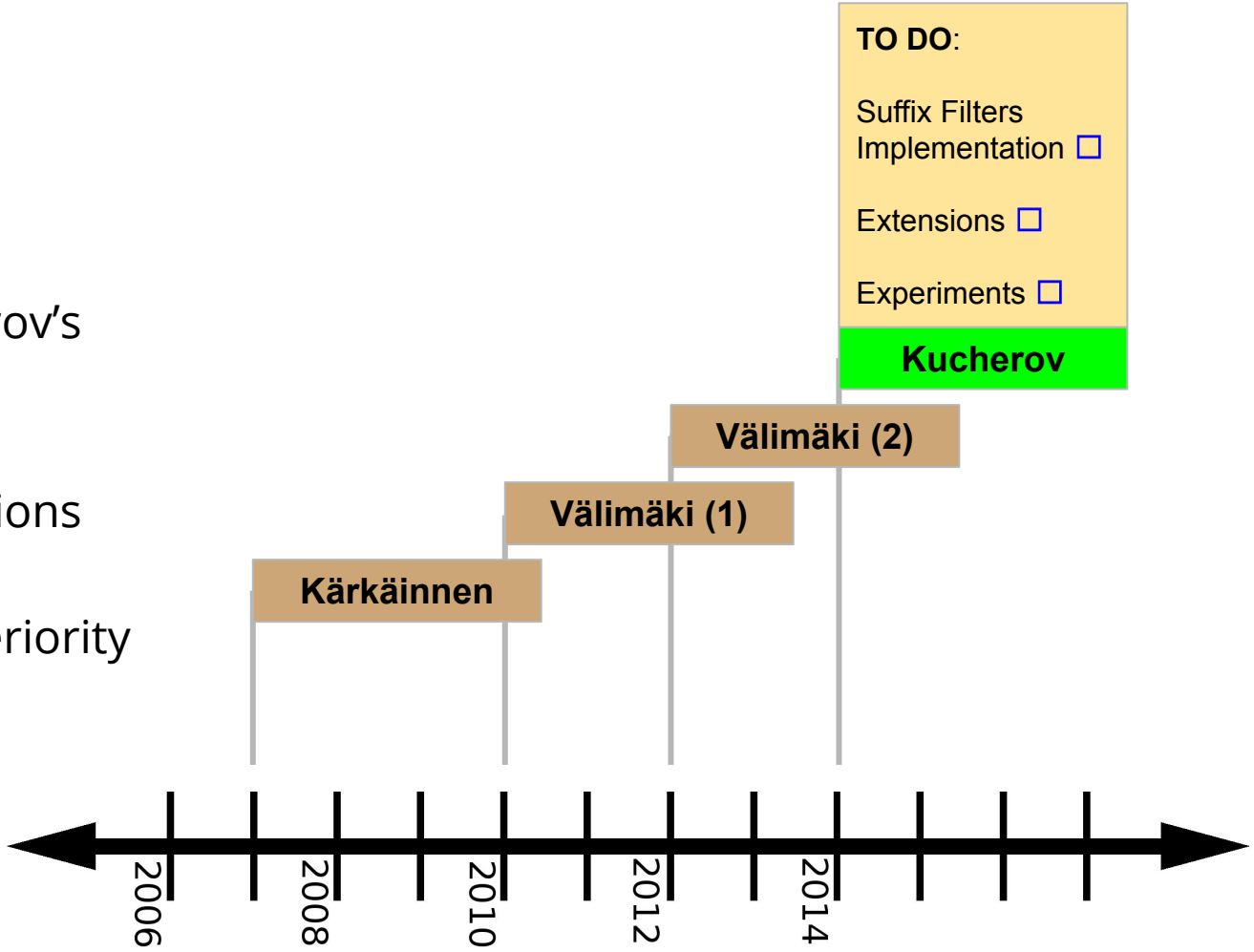
My Task

1. Implement Kucherov's algorithm
2. Implement extensions



My Task

1. Implement Kucherov's algorithm
2. Implement extensions
3. Demonstrate superiority experimentally



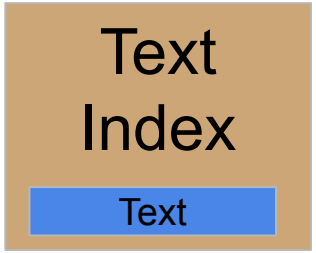
Solving ASPOP

- Naive solution is to check error of all overlaps pairwise
  - Too slow!

Solving ASPOP:
Using a text index

- Naive solution is to check error of all overlaps pairwise
  - Too slow!

- Take advantage of a **text index**. Find all matches of one string in <u>all others</u> at once.

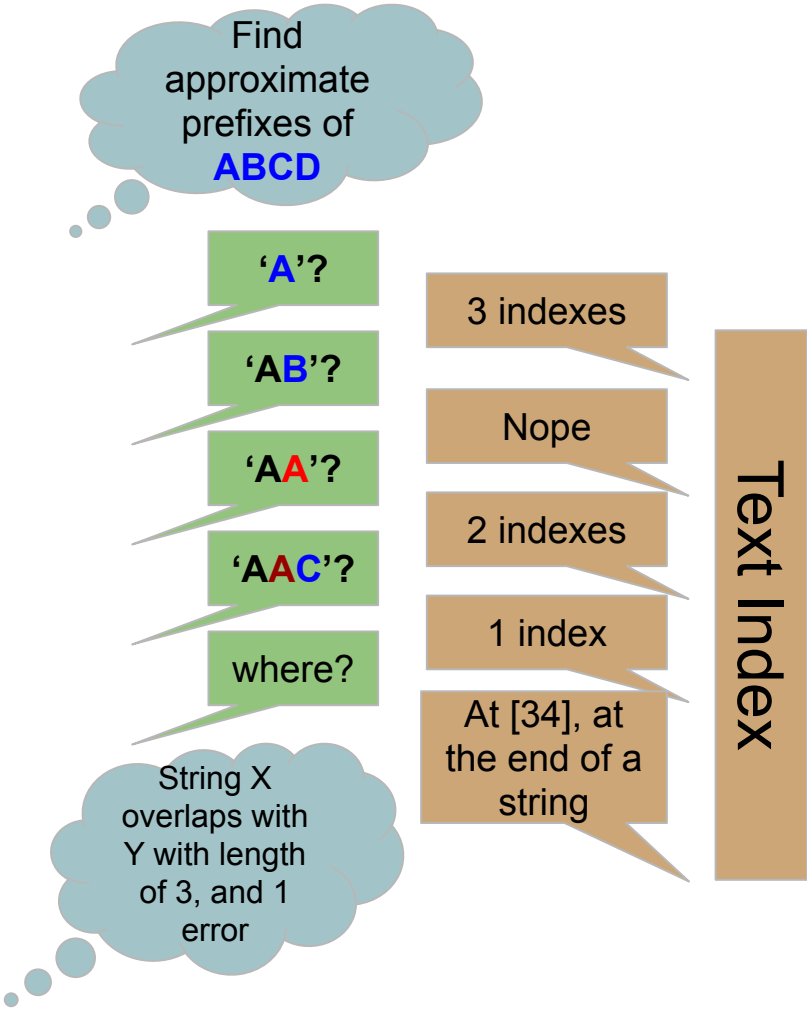


Question:
How to get **approximate** overlaps from **exact** queries?

Solving ASPOP: Using a text index

Approximate overlaps from **exact** queries:

- Index can only locate exact string/symbol occurrences.
- Get around this by strategically "asking" the index the right questions

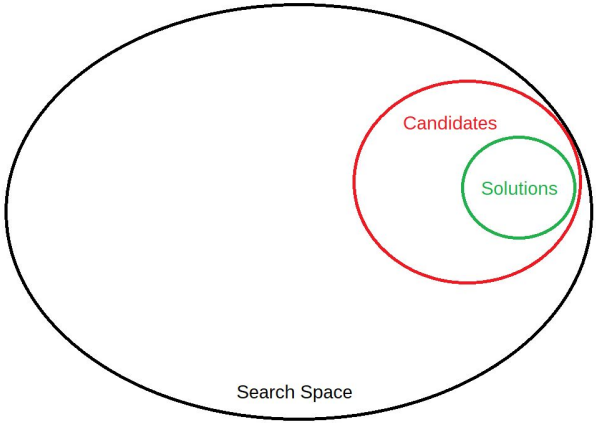


(Interlude):
Filter algorithm defined

Filter Algorithm:

- Break problem into 2 parts
  - Candidate generation step (aka search step)
  - Candidate verification step

- The sum of the two parts is faster than the naive approach



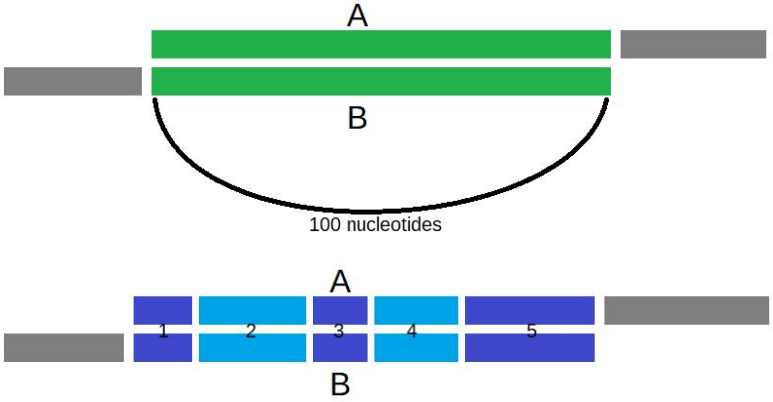
Solving ASPOP: Suffix filters

Observation:

Consider some overlap of length **100** between some A, B that we want to find.

- Say we have defined a maximum error rate of 4.0%

- Divide overlapping part into 5 blocks
  - Overlap ϵ solutions → at least 1 block has no errors.



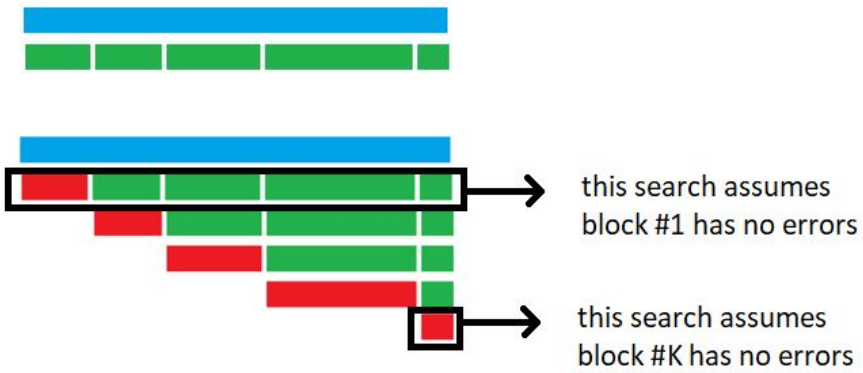
Solving ASPOP: Suffix filters

For each string **P** in the input read set:

1. Partition **P** into N blocks

2. Generate a set of assumptions
   - Block $\mathbf{P_1}$ has no errors
   - Block $\mathbf{P_2}$ has no errors

   …
3. Generate N searches of the index, each using 1 assumption.
   How the query is performed is dictated by a *filter* (~branch rules)



- If you partition **P** strategically, and your filters are lenient enough you are guaranteed that 1+ assumptions hold for every true solution → it will be found

- Total search cost is less than naive approach

Suffix Filter Algorithms: Välimäki

In their **1st** paper [V1]:

- Applied Kärkkäinen's suffix filters to the ASPOP

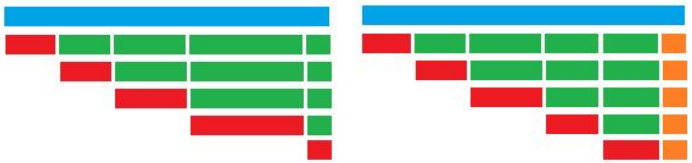
In their **2nd** paper [V2]:

- Identified a bottleneck in [V1] revolving around the **short last filters**
- Defined better filters which
  - Covered the same solutions
  - Avoided short last filter problem (faster)

Suffix Filter Algorithms: Kucherov

- Created a new *filtering scheme* that avoided the **short last filter** problem more efficiently than [V2]
  - by guaranteeing a redundant block so the short last filter could be avoided

- Defined a less wasteful *partitioning scheme*
  - which postpones search branching until the last possible moment



Progress:

TO DO:

Suffix Filters Implementation ☑

Extensions ☑

Experiments ☐

Progress:
Suffix Filters Implementation ✅

- New system is implemented in Rust
- Has **modes** for using available suffix filter algorithms
  - Including Kucherov's

Windows PowerShell

```
PS C:\Users\Christopher\Documents\GitHub\rust_overlaps> .\rust_overlaps.exe .
/data/5VM_real.p1.8000.fasta out.txt 0.02 20 -m=valimaki2
OK working.
OK wrote 349637 solutions.
OK completed in ~147 sec.
WORK NANOS:
        total    1174644525814
        search   723615174084     61.60%
        verif    451029351730     38.40%
PS C:\Users\Christopher\Documents\GitHub\rust_overlaps>
```

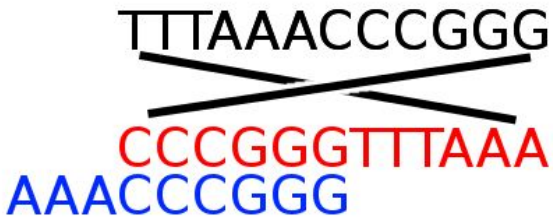
Windows PowerShell

```
PS C:\Users\Christopher\Documents\GitHub\rust_overlaps> .\rust_overlaps.exe .
/data/5VM_real.p1.8000.fasta out.txt 0.02 20 -m=kucherov_2
OK working.
OK wrote 349637 solutions.
OK completed in ~7 sec.
WORK NANOS:
        total    56851722587
        search   41494460592      72.99%
        verif    15357261995      27.01%
PS C:\Users\Christopher\Documents\GitHub\rust_overlaps>
```

Progress:
Algorithm extensions ✅

- Program supports all three extensions
- Each extension (when enabled) will find new types of solutions
  - **Reversals** : inverted overlaps
  - **Inclusions** : strings within each other
  - **Indels** : edit distance measure of error
- Each requires the algorithm to be adapted and elaborated

Reversals



Inclusions

Indels

Progress:
Experiments Phase 1 ✅

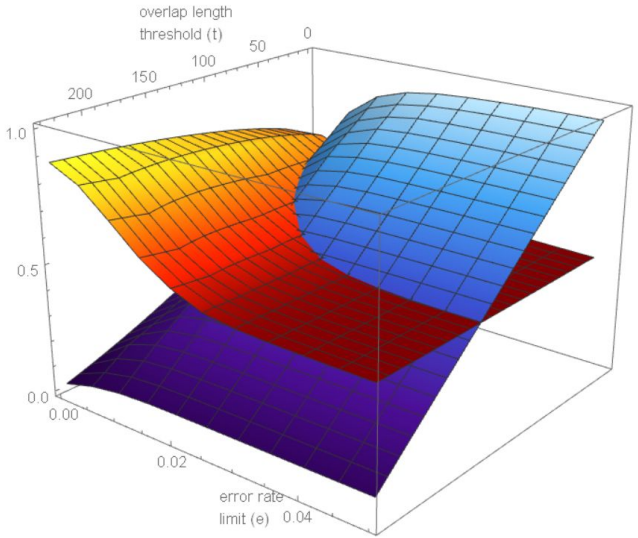
Seeks to identify relationship

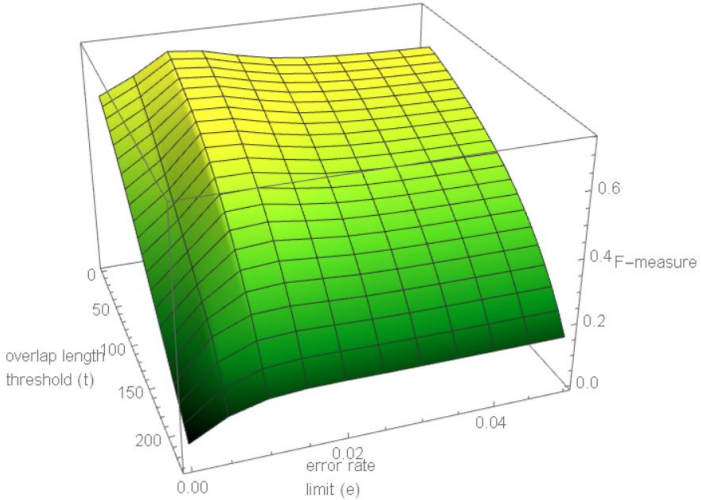
Input parameters

→ output quality (F-measure)

Observations:

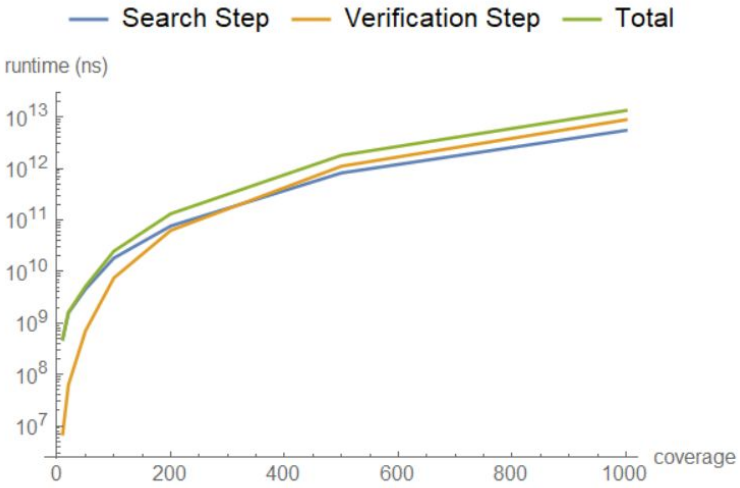
- Lower overlap-length threshold is consistently beneficial
- Decreasing precision plateaus towards higher error rate limits
- Settled on e=1.2% t=80



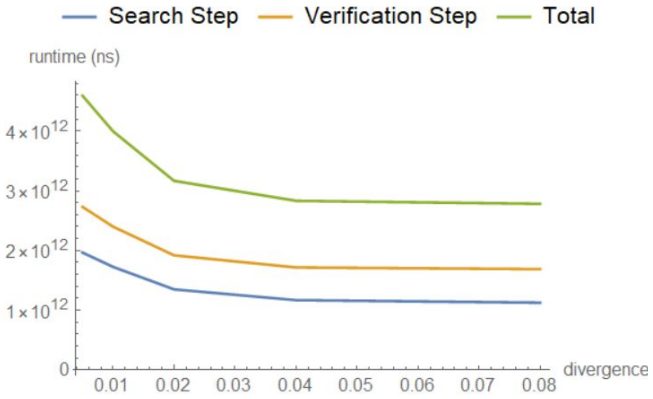


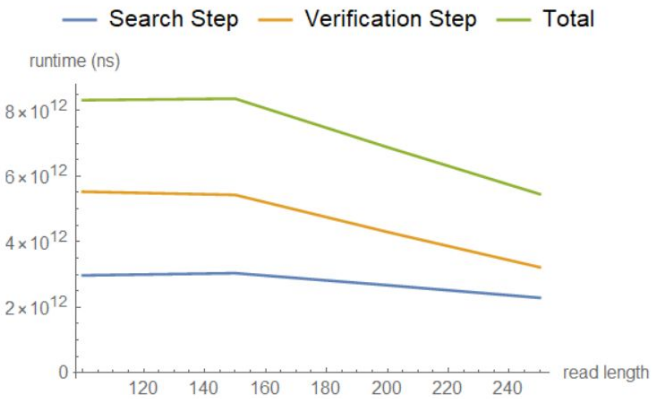
Progress:
Experiments Phase 2 □

Seeks to identify
Data set properties
→ runtime



Partitioned per **step**



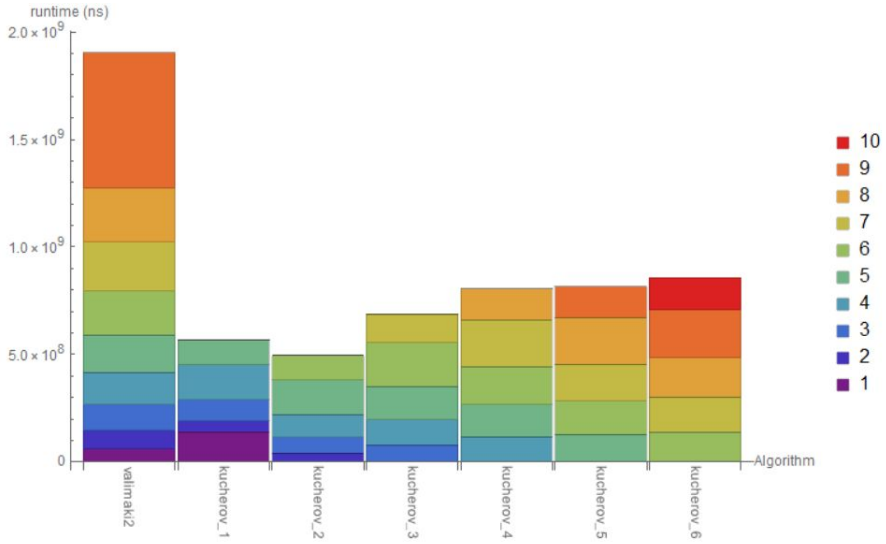


Progress:
Experiments Phase 2 □

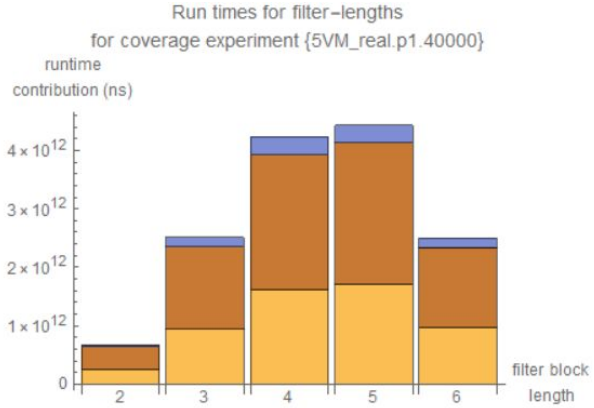
Seeks to identify

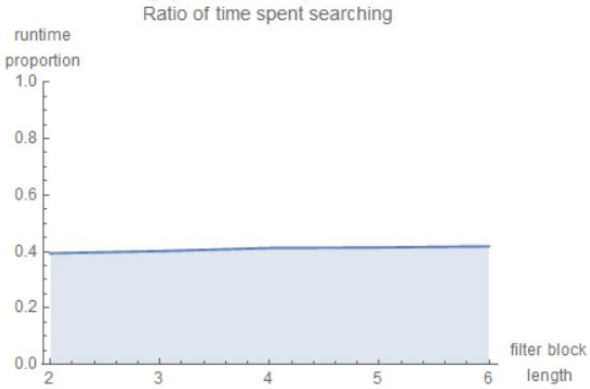
Data set properties

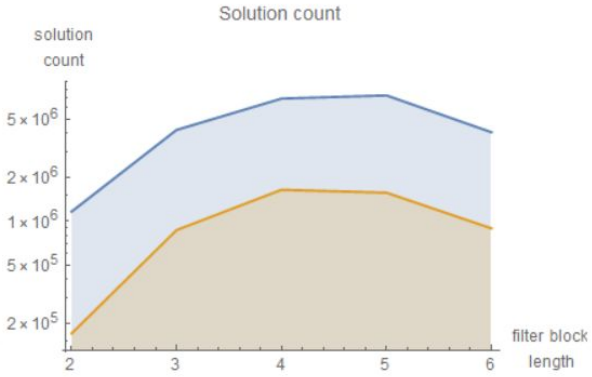
→ runtime



Partitioned per **filter**







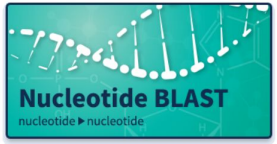
Progress:
Experiments Phase 3 □

Compare system performance in

- Output quality
- Runtime

As compared to existing solvers such as

- BLAST

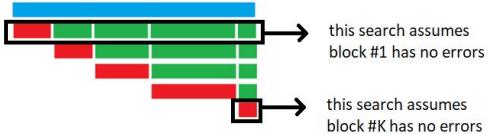


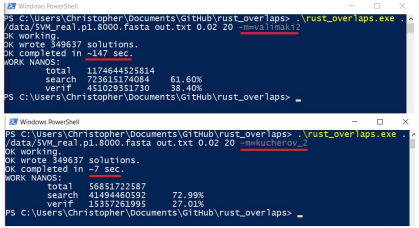
Future Work

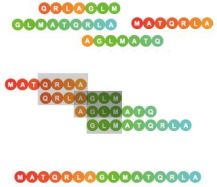
- Explore necessity of indels
  - Upside of using them: More solutions per coverage
  - Downside of using them: Slower runtime
- Optimize branching process for indels
  - Increase speed of indel-enabled solves

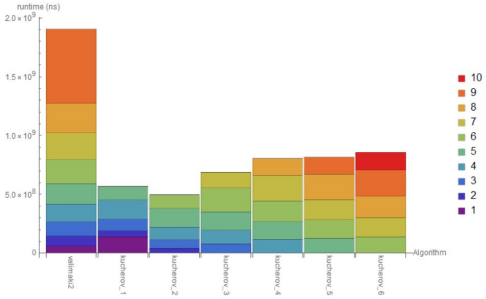
TTTAA • ACCCGGG
TGGGTTTAAAACCC

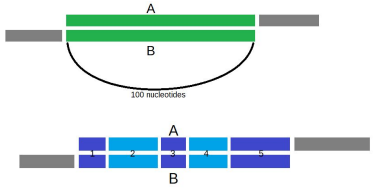
Question Time

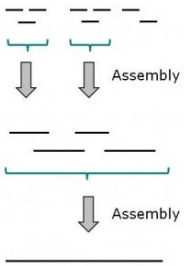


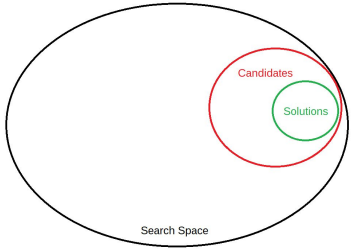


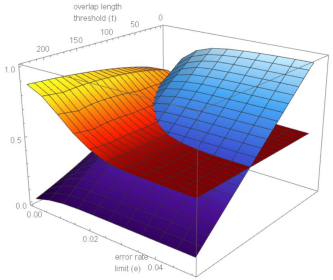


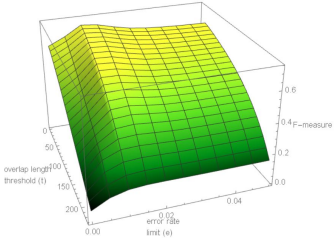


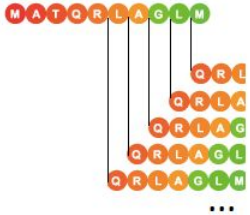


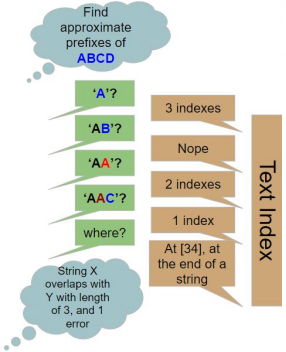


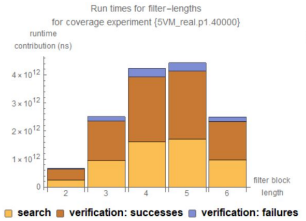




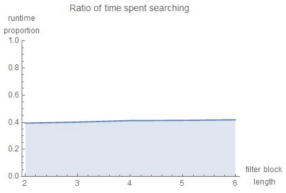




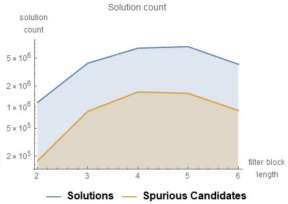




(a)



(b)



(c)

TTTAAACCCGGG
AATTTAAACCCGGGAA

TTTAA • ACCCGGG
TGGGTTTAAAACCC

TTTAAACCCGGG
CCCGGGTTTAAA
AAACCCGGG