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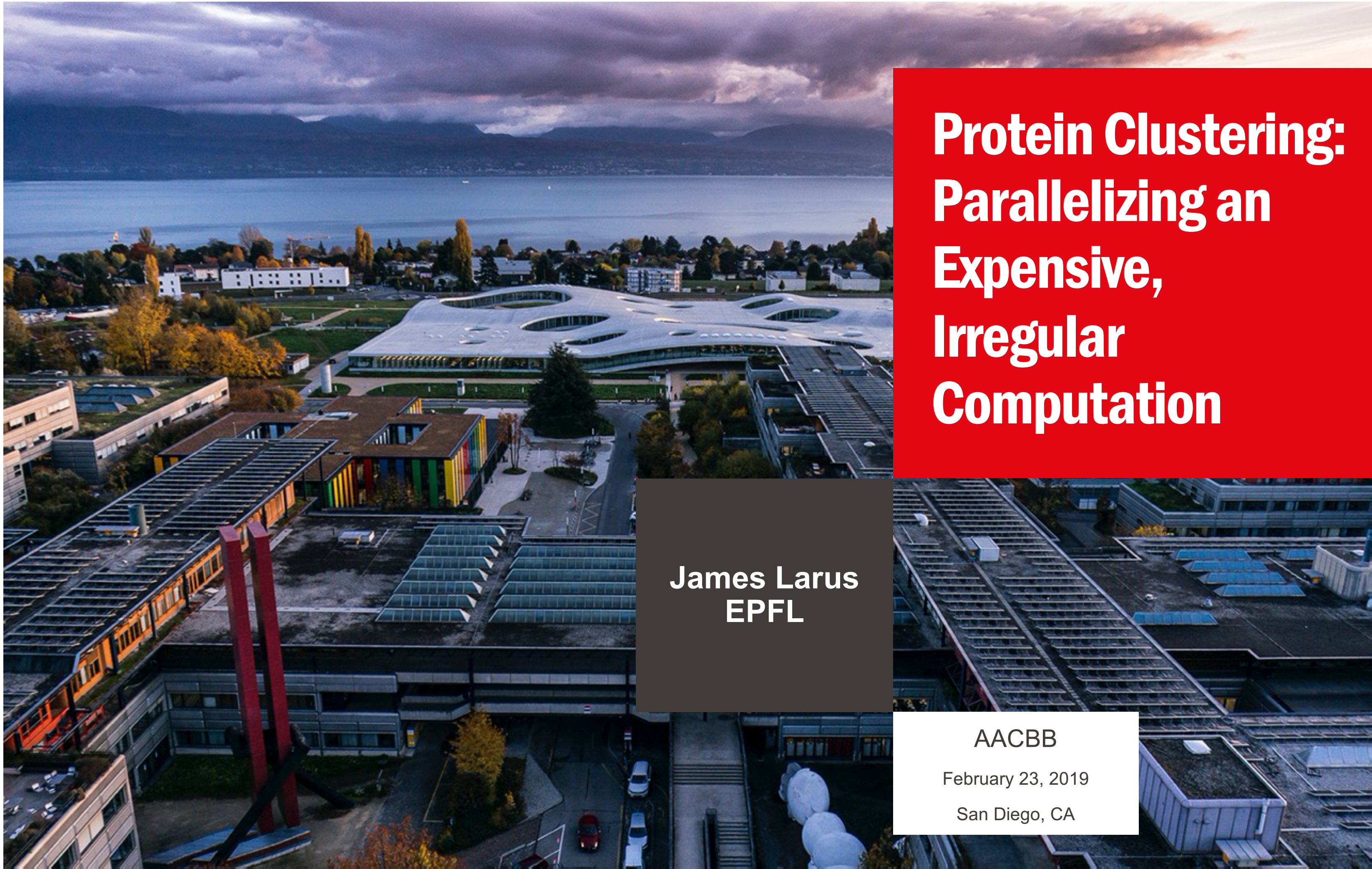

Protein Clustering: Parallelizing an Expensive, Irregular Computation

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February 23, 2019

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PhD research

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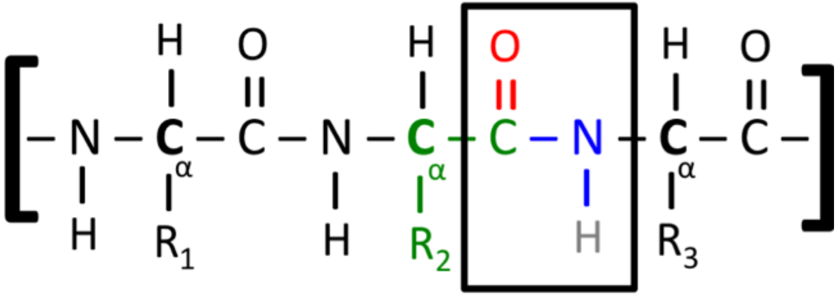
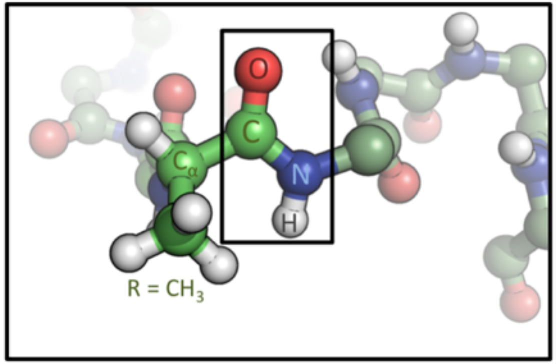
PhD “Parallel and Scalable Bioinformatics”, April 2020

What’s a protein?



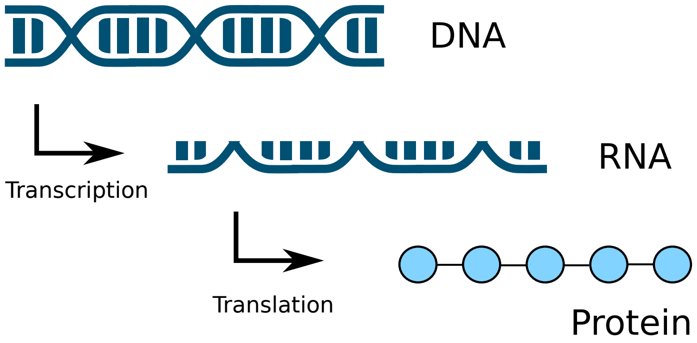
- Linear polymer of amino acids
  - Fold into complex 3D structures

- Perform many biological functions



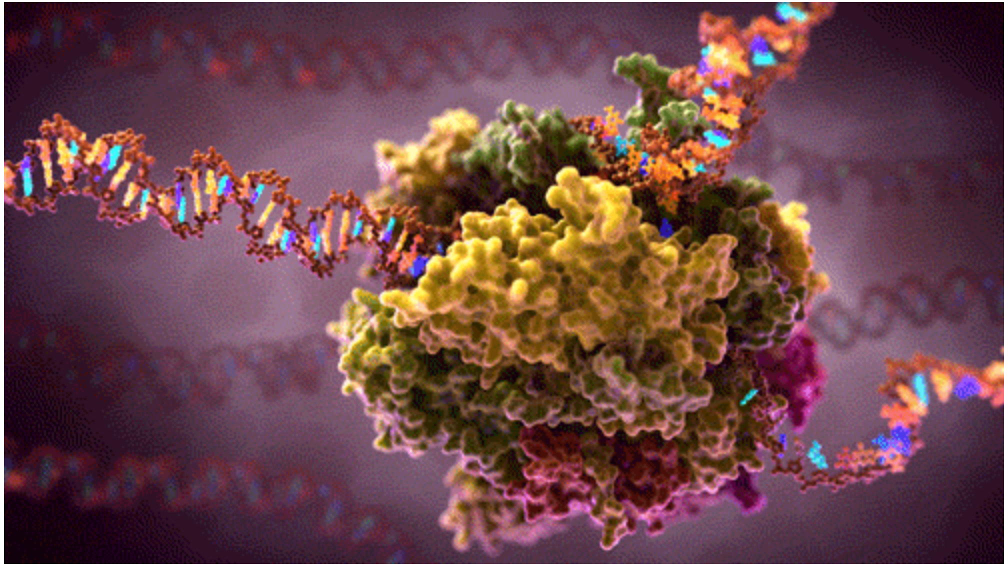
Central dogma of molecular biology

- Gene Expression
  - DNA → Protein
- Encoded by genes in genome
- 19,000 – 20,000 proteins in humans
  - 1.5% of human genome
- Composed of 20 amino acids



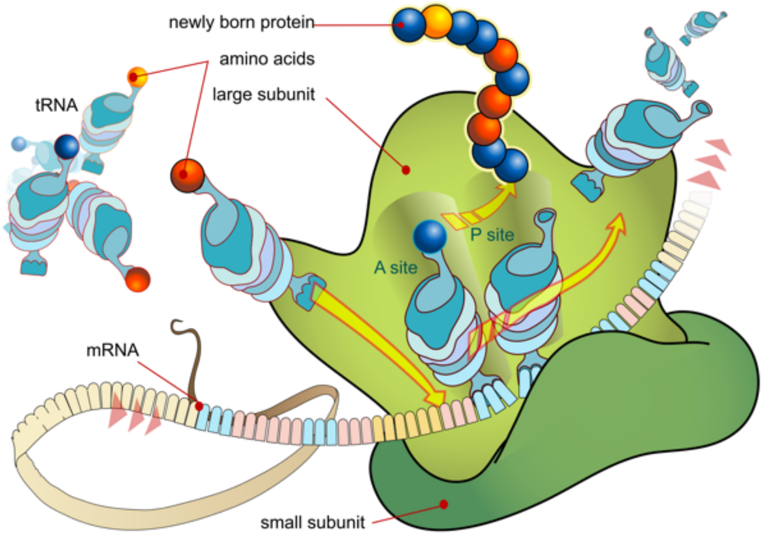
Transcription

- Transcribe DNA to *RNA* inside the nucleus



Translation

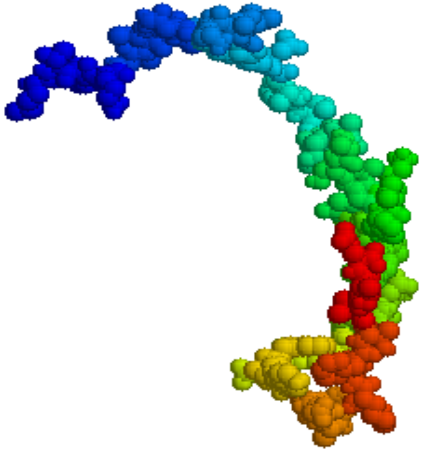
- Once in cytoplasm, mRNA is translated to polypeptide



https://en.wikipedia.org/wiki/Translation_(biology)#/media/File:Ribosome_mRNA_translation_en.svg

Folding

- Polypeptides fold spontaneously, or are assisted by chaperone proteins



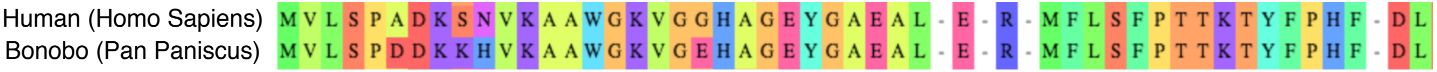
Proteins & evolution

- **Homologous** – similar due to shared ancestry
- **Ortholog** – similar proteins diverged through speciation

- Similarities between proteins are proxies for similarities between genes
  - Infer function of new protein because of its similarity to known protein
    - Extrapolation from small number of model organisms
  - Infer evolutionary relationships between species
    - X evolved from Y
    - X, Y have common ancestor

- Several of 100 most-cited scientific papers are sequence homology

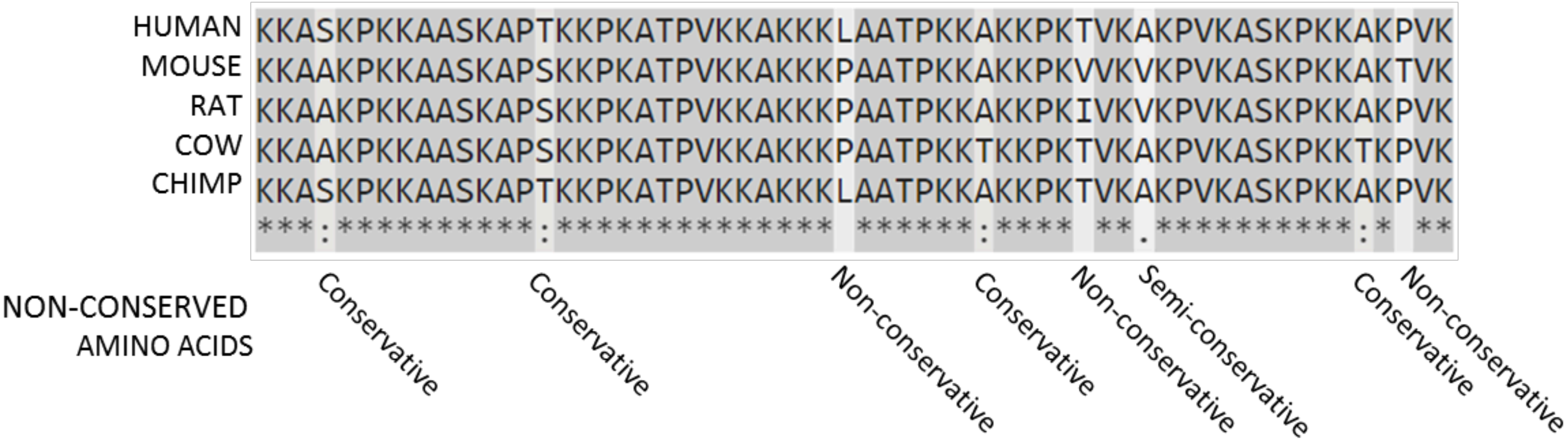
Sequence homology



```
Human (Homo Sapiens)  MVLSPADKSNVKAAWGKVGGHAGEYGAEAL-E-R-MFLSFPTTKTYFPHF-DL
Bonobo (Pan Paniscus) MVLSPDDKKHVKAAWGKVGEHAGEYGAEAL-E-R-MFLSFPTTKTYFPHF-DL
```

Alignment showing protein similarity between hemoglobin α-subunits from human and bonobo proteins

Histone H1 (residues 120-180)



```
HUMAN KKASKPKKAASKAPTKKPKATPVKKAKKKLAATPKKAKKPKTVKAKPVKASKPKKAKPVK
MOUSE KKAAKPKKAASKAPSKKPKATPVKKAKKKPAATPKKAKKPKVVKVKPVKASKPKKAKTVK
  RAT KKAAKPKKAASKAPSKKPKATPVKKAKKKPAATPKKAKKPKIVKVKPVKASKPKKAKPVK
  COW KKAAKPKKAASKAPSKKPKATPVKKAKKKPAATPKKTKKPKTVKAKPVKASKPKKTKPVK
CHIMP KKASKPKKAASKAPTKKPKATPVKKAKKKLAATPKKAKKPKTVKAKPVKASKPKKAKPVK
      ***:**********:************** ******:**** **.**********:* **
```

Identifying similar proteins

- Input → sequenced proteins
- Output → sets of homologous proteins

- All-against-all comparison
  - O(n^2) in number of sequences
  - Sequence comparison also O(n^2) in length of sequences (Smith-Waterman)

- OMA protein database contains proteins from 2000 genomes
  - Required more than 10 million CPU hours

Improvement needed!

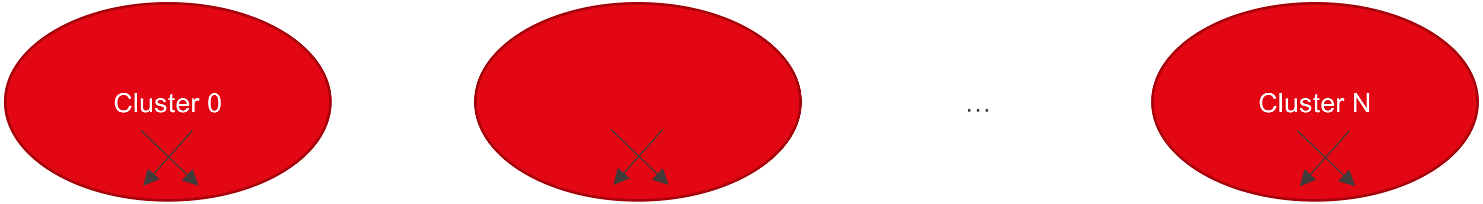
"Computing orthologs between all complete proteomes has recently gone from typically a matter of CPU weeks to hundreds of CPU years, and new, faster algorithms and methods are called for."

– Quest for Orthologs consortium, 2014

Incremental greedy protein clustering

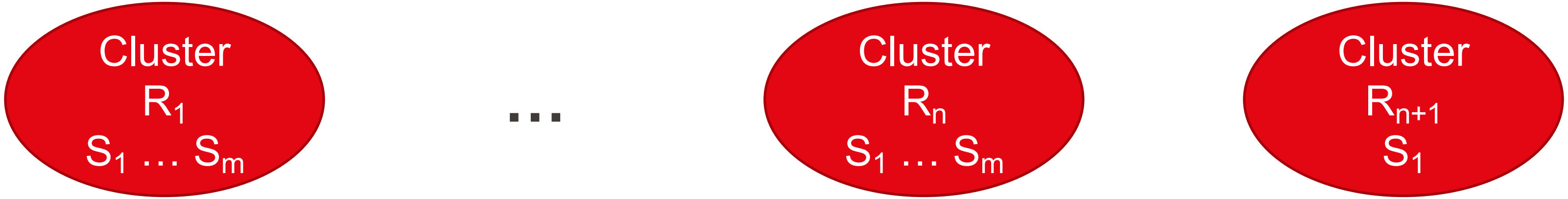
- **Speeding up all-against-all protein comparisons while maintaining sensitivity by considering subsequence-level homology**, *PeerJ*, 2014, Wittwer, Pilizota, Altenhoff, Dessimoz.

- Cluster similar proteins, then perform all-against-all comparison within each cluster
- Reduces computation time by ~75%
- Identify >99.6% of pairs found by all-vs-all



Cluster representative

- Input sequences compared against a cluster **representative**
  - Homologies are transitive
    - A, B homologous; B, C homologous ➔ A, C homologous
- No matches? Create a new cluster!



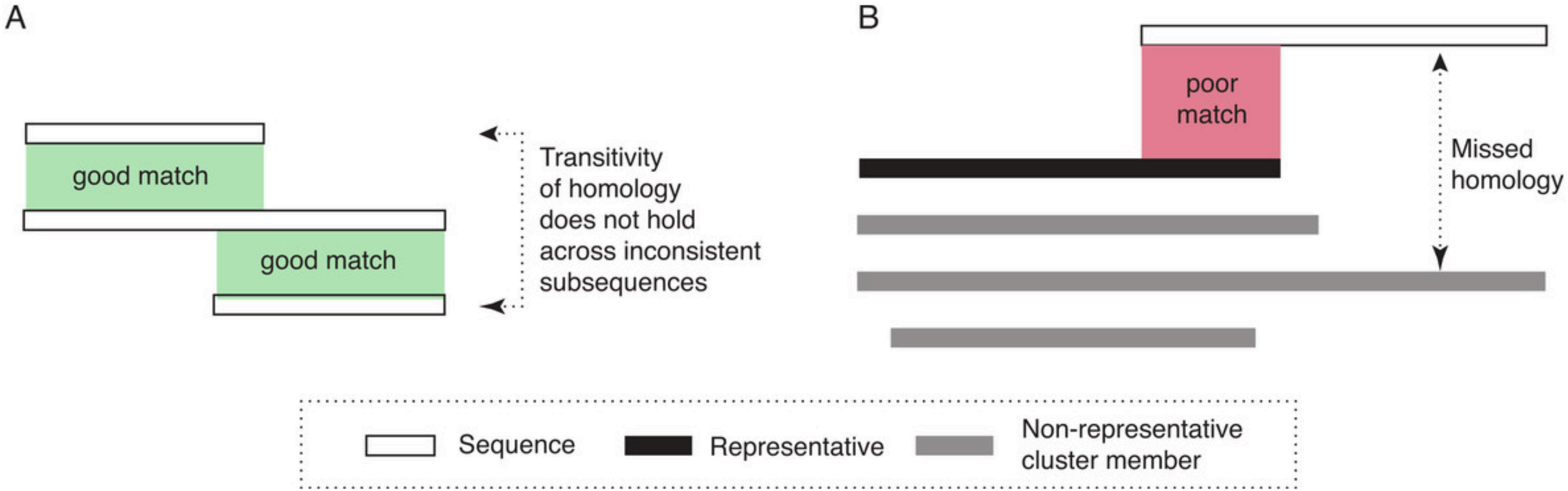
Cluster R_1 $S_1 \ldots S_m$

…

Cluster R_n $S_1 \ldots S_m$

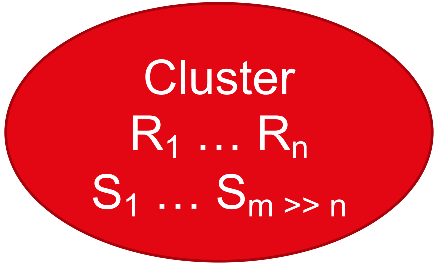
Cluster R_{n+1} S_1

Proteins not transitive



Clustering, v2

- Multiple representatives
- Ensure all sequences in a cluster are covered (± *T* residues)



Cluster

$R_1 \ldots R_n$

$S_1 \ldots S_{m >> n}$

Incremental greedy protein clustering

- Reduction in computation time of ~75%
  - Clusters are small, on average

- Accuracy is excellent
  - Maintain >99.6% of all pairs identified by all-against-all (naive)

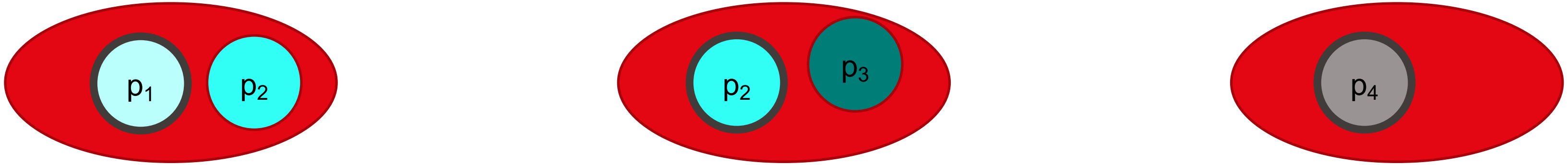
But,

- Algorithm is not easily parallelized

- Order in which clusters and representatives are chosen affects result
- Data (clusters) is shared – difficult to distribute

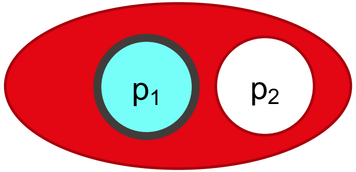
Our approach: precise clustering

- **Precise clustering (PC)**
  - All significant pairs are members of at least one cluster
  - Compare within cluster and find similarity
- A pair of proteins is **significant** if their similarity is above a threshold
  - $f(p_1,\ \ p_2) > T$
- PC is not a partition – a protein can be in more than one cluster
  - Relation f is not transitive, i.e. similarity is not equivalence



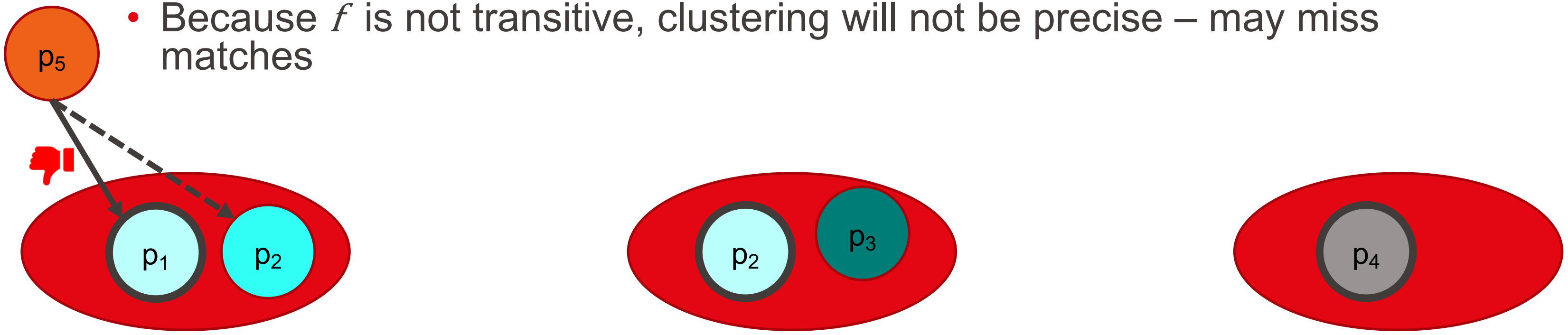
Cluster representative

- Each cluster has a unique **representative *R_C***
  - $\forall e \in C, \quad f(e, R_C) > T$
- Two elements in cluster may not be similar: $e_1, e_2 \in C \;\not\vdash\; f(e_1, e_2) > T$



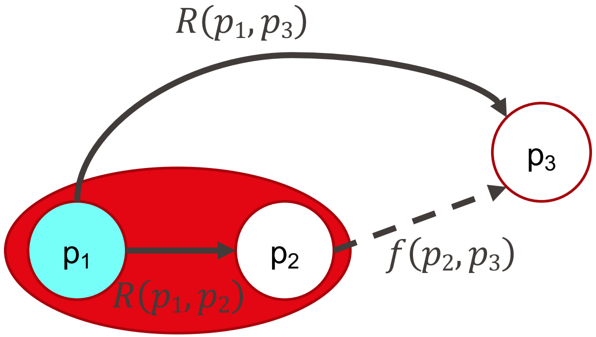
Approach 1

- New element e is compared against cluster representatives
  - If similar, e is added to cluster
- This does not work!
  - e, other than representative, will not be compared against subsequent elements
  - Because f is not transitive, clustering will not be precise – may miss matches



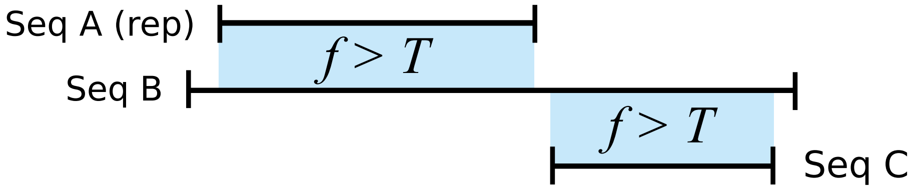
Transitive similarity

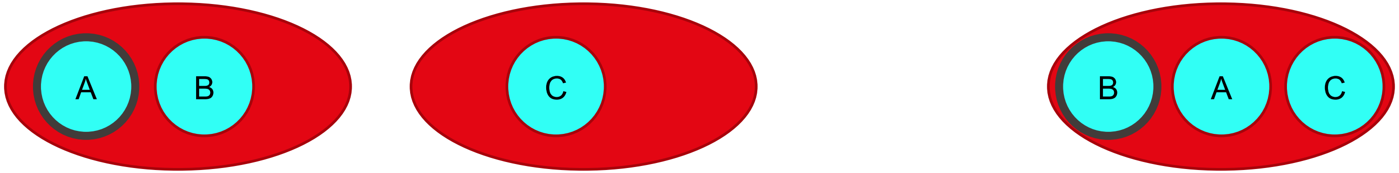
- Transitivity $\mathbf{R(e_1, e_2)}$ implies e_2 will be similar to e_3 if e_1 is similar to e_3
  - $\forall(i,j,k) \in S,\ R(i,j)\ \Rightarrow f(i,k) > T\ \wedge\ f(j,k) > T$



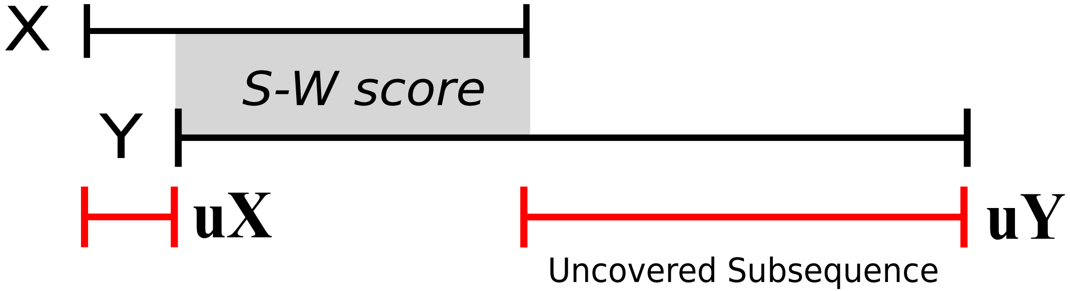
Protein similarity

- Similarity function f
  - Smith Waterman alignment >T (threshold parameter)
- Not transitive
- Comparison order matters





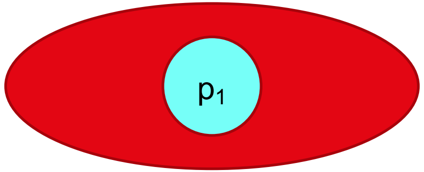
Protein transitivity



$$R(X, Y) \implies score > minT,\ uY < maxU$$
$$R(Y, X) \implies score > minT,\ uX < maxU$$

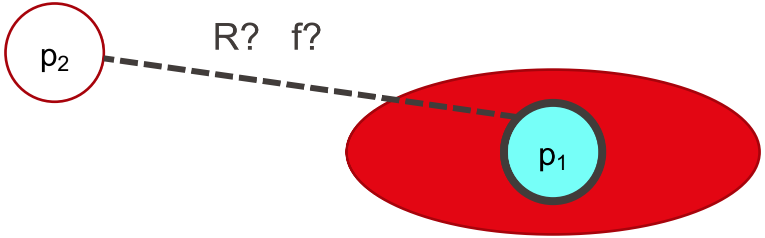
Incremental greedy precise clustering

- Construct clusters one element at a time
- First element becomes cluster representative



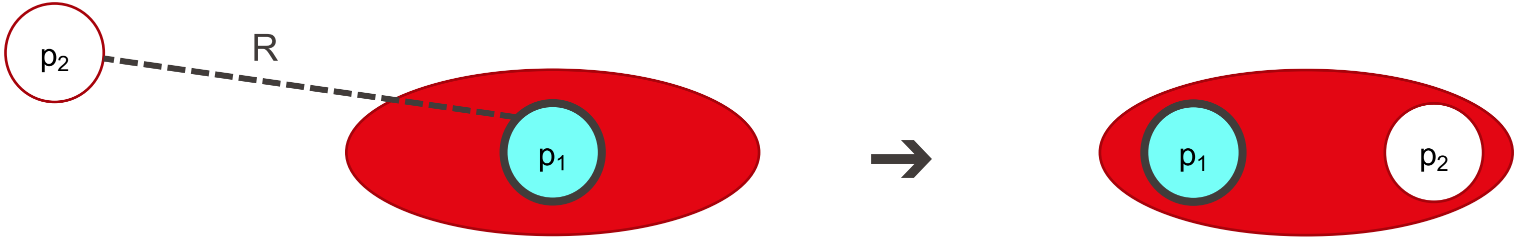
Incremental greedy precise clustering

- Compare subsequent elements against cluster representative



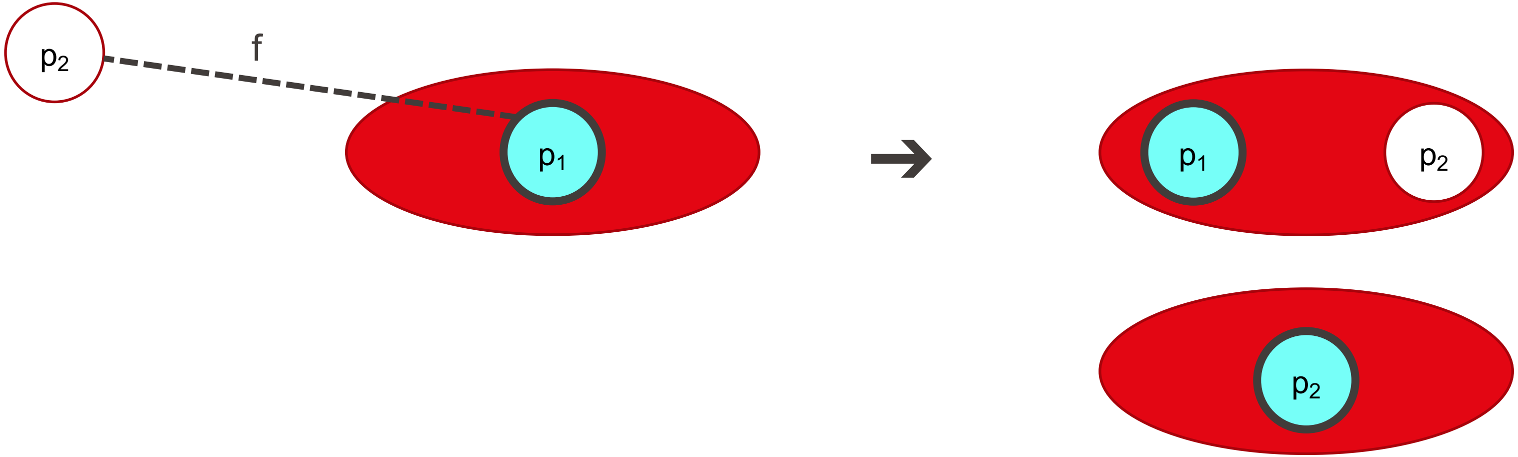
Incremental greedy precise clustering

- If **transitively similar**, add to cluster



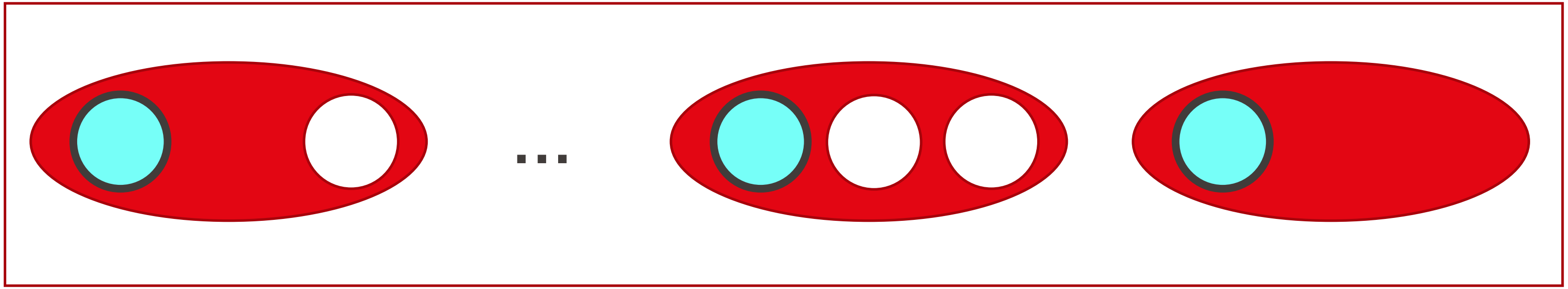
Incremental greedy precise clustering

- If **only similar**, add to cluster and create a new cluster



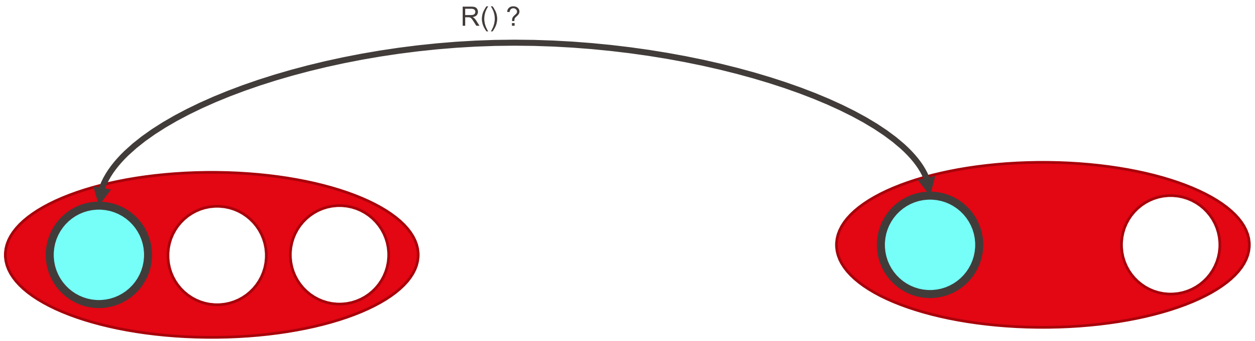
Incremental greedy precise clustering

- Continue until all elements clustered

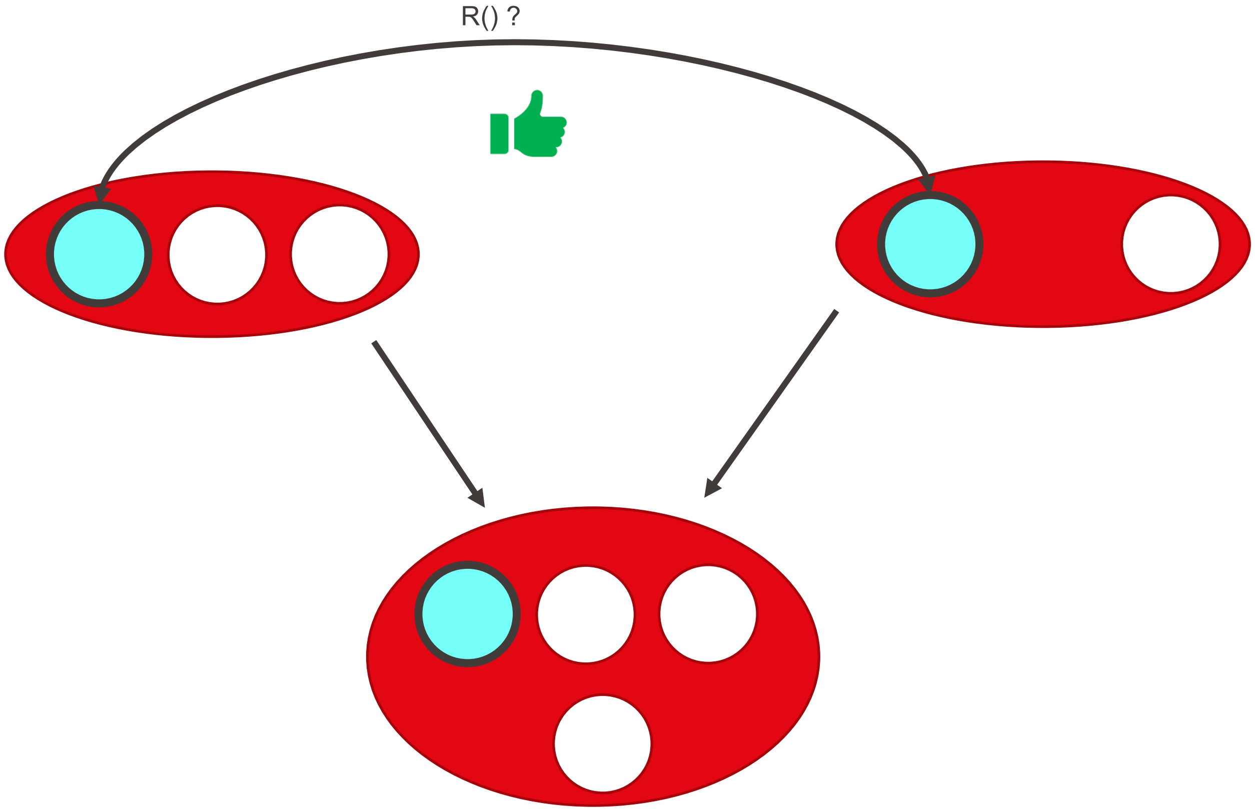


Parallelism

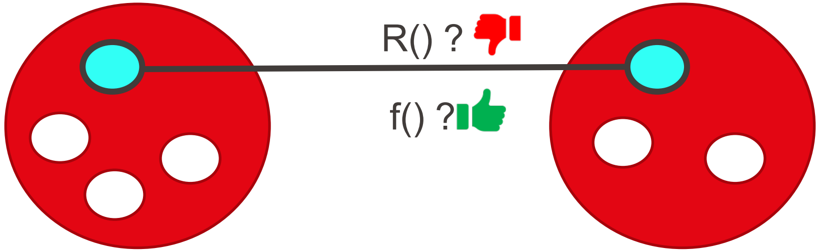
- Unlike original Wittwer algorithm, order does not matter for precise clustering
- Clusters can be constructed independently and **merged**

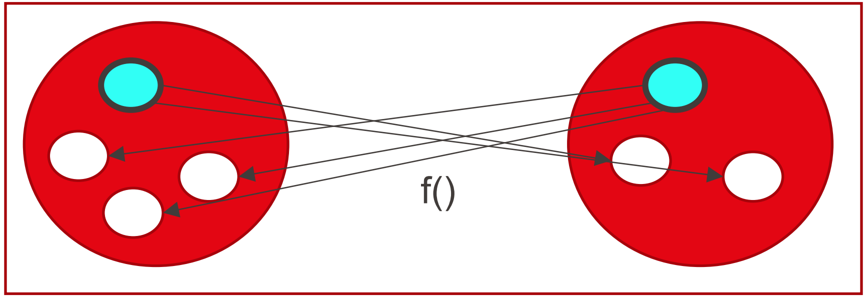


Merging clusters

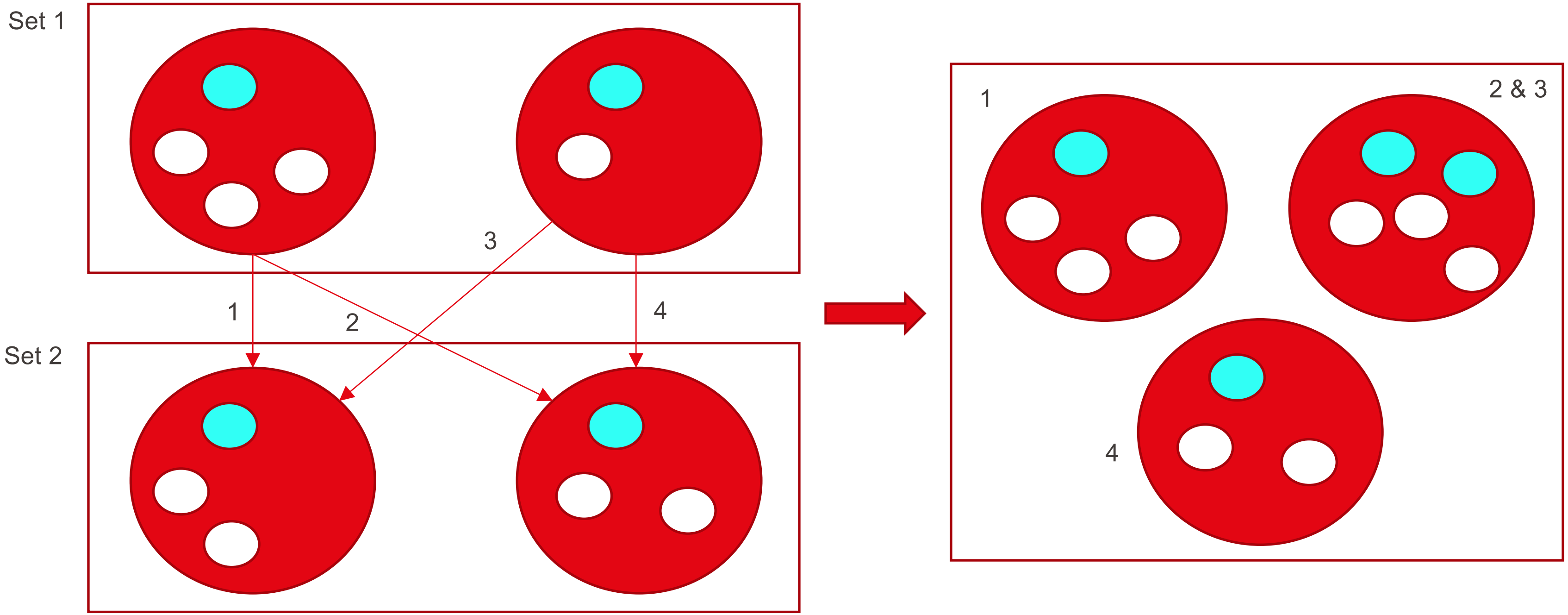


Merging clusters

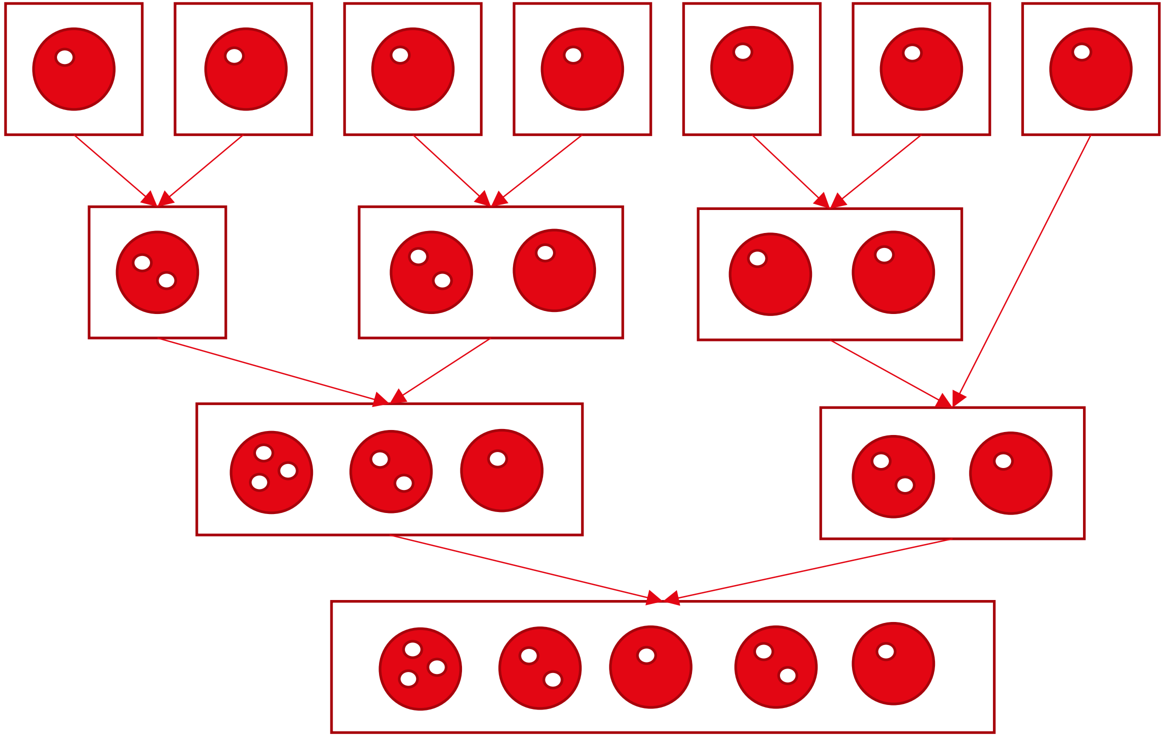




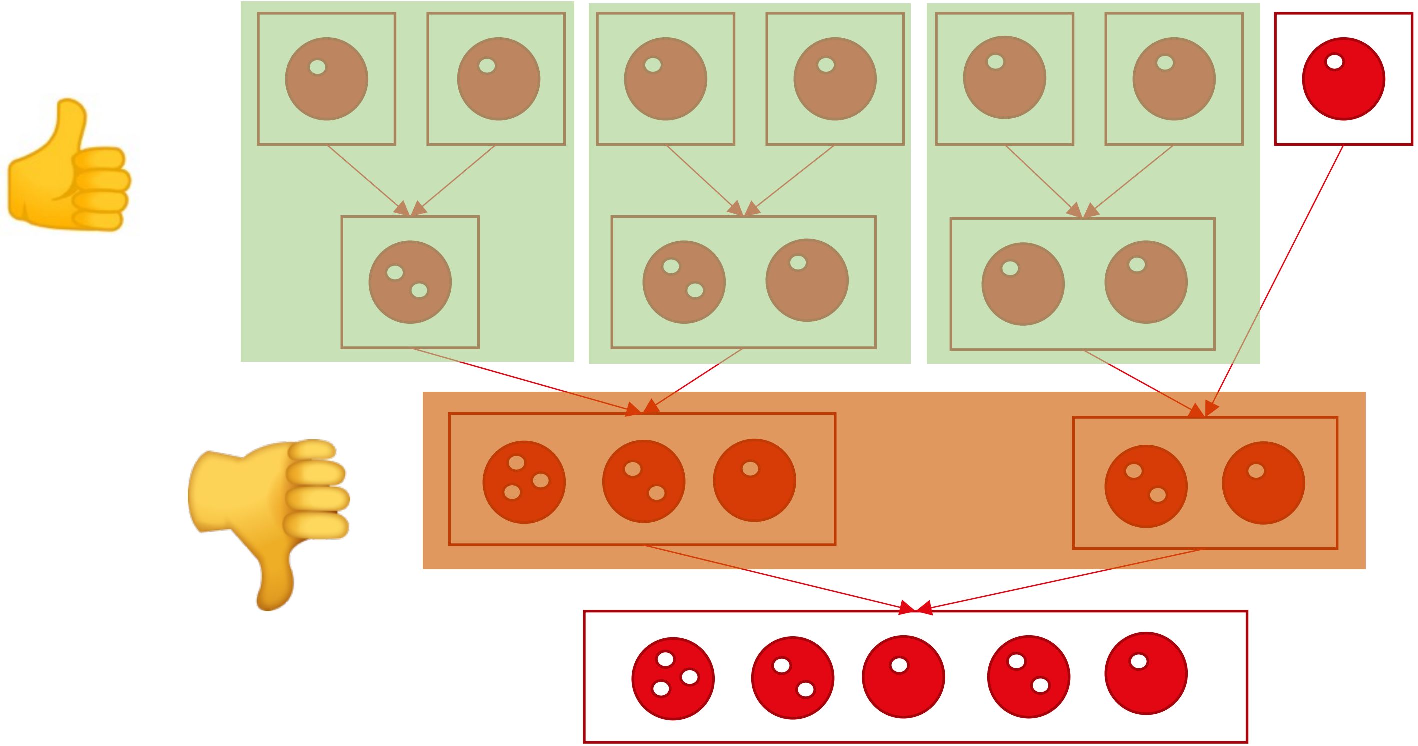
Merging sets of clusters



Cluster merge

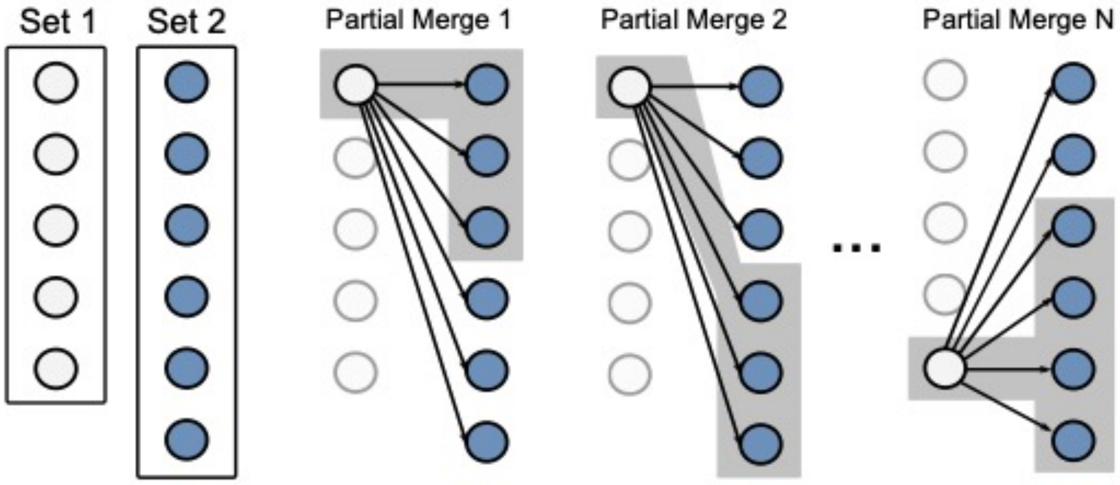


Parallelization 1

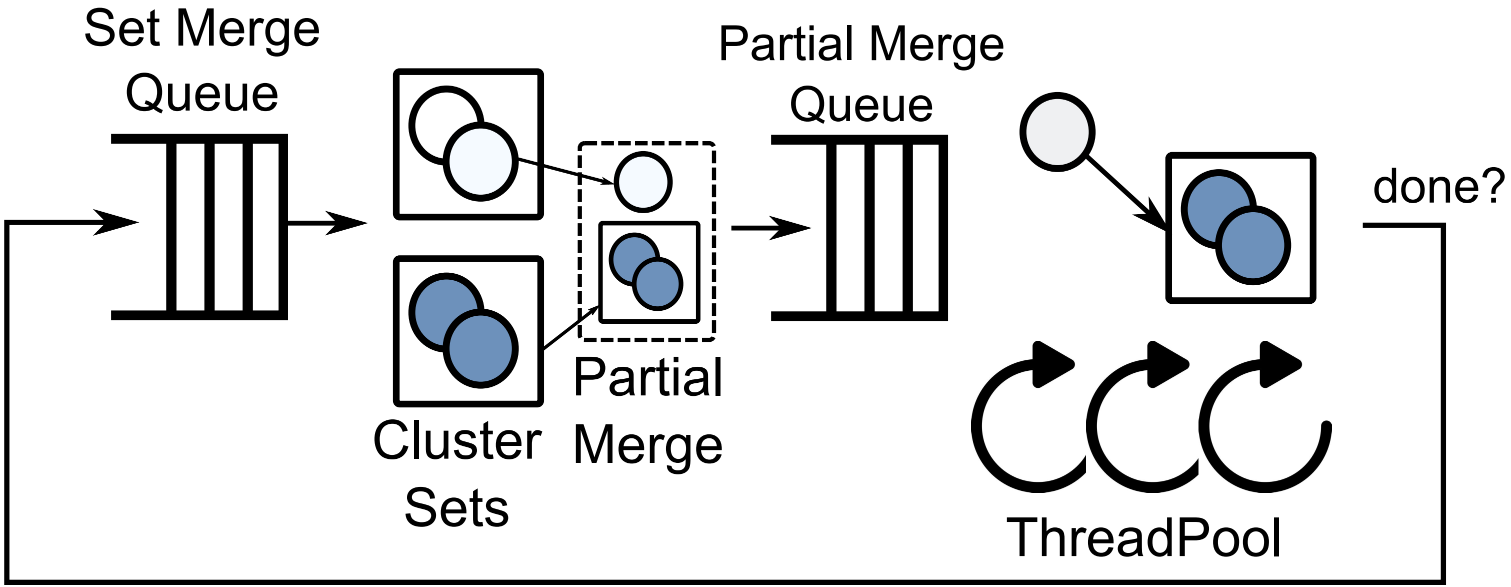


Parallelization 2

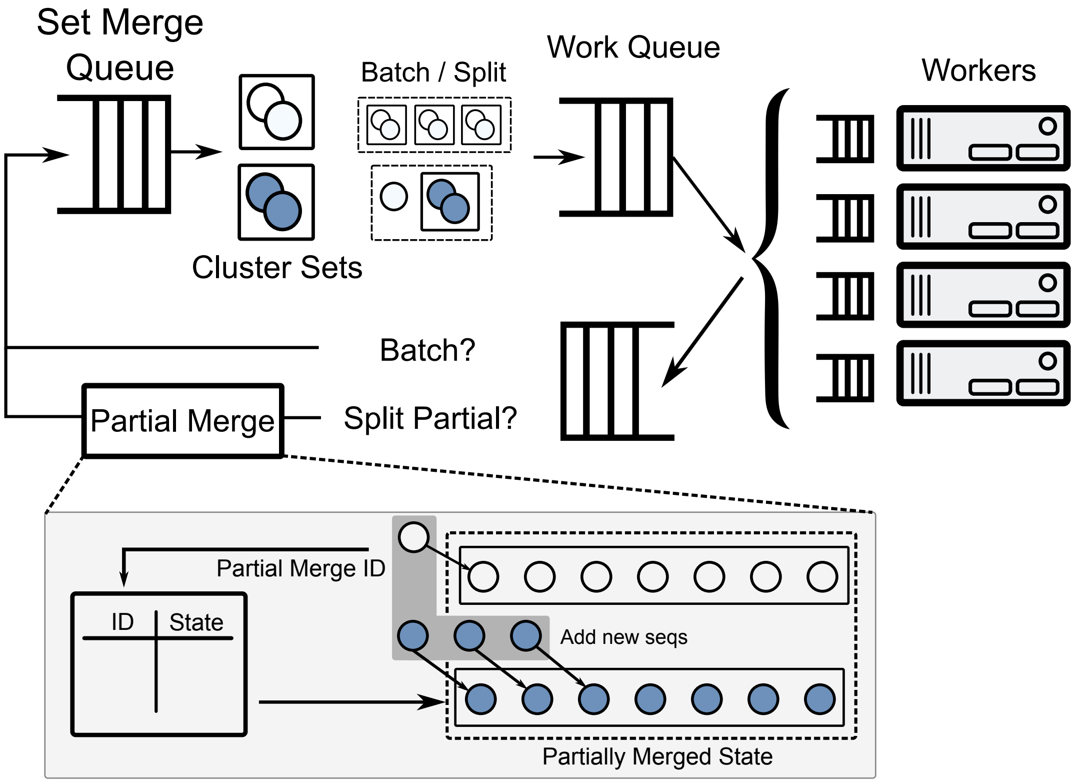
- Parallelize merge of two large sets
- Each computation is a *partial merge*



Shared-memory (Shared-CM)

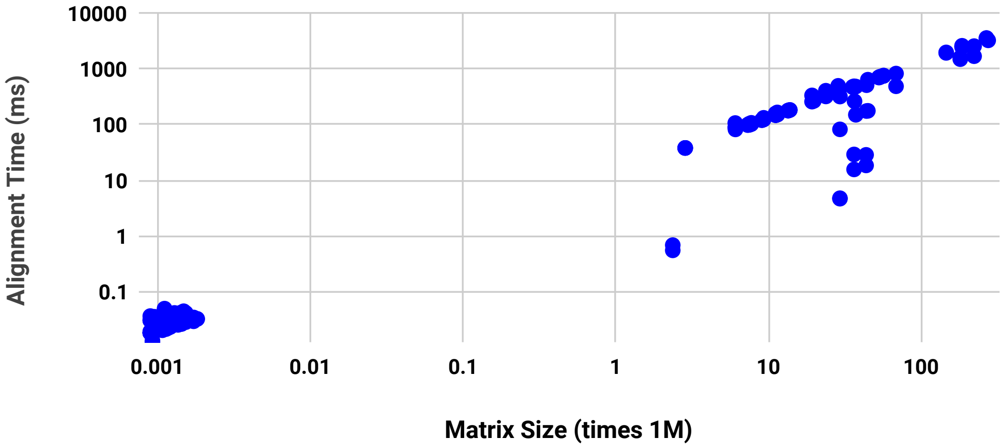


Distributed (Dist-CM)



Dist-CM optimization

- Every remote worker has copy of all sequences
  - Sequences named by index (4-byte)
- Workers cache copies of sets and only transfer diffs
- Careful queue management
- Aggressive load balancing



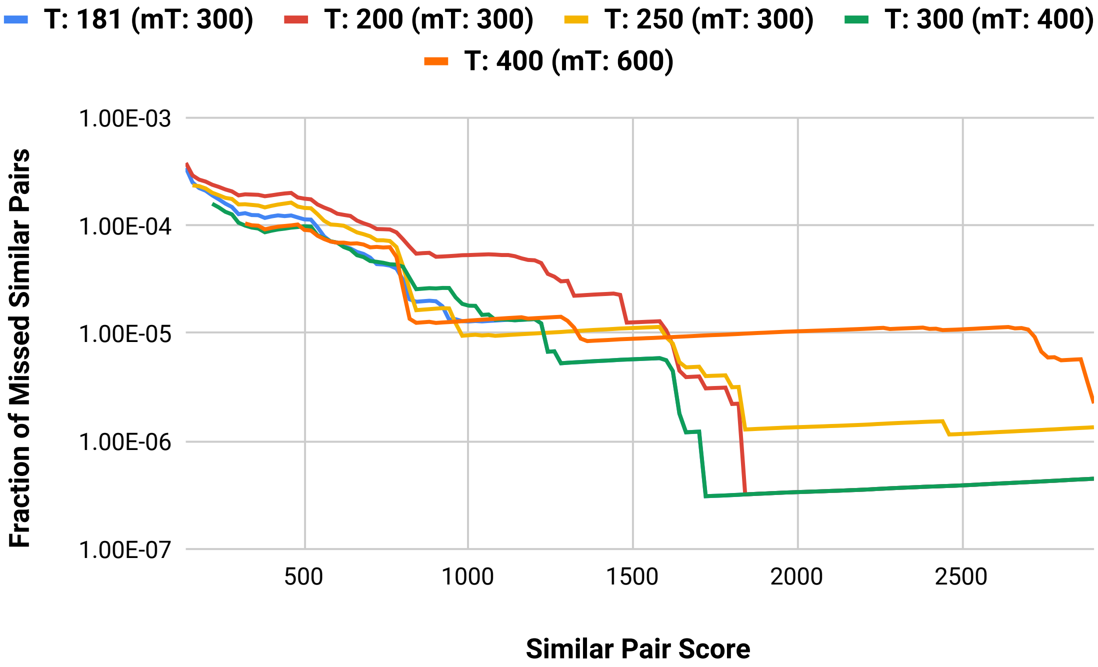
Evaluation

- Recall
  - Number of significant pairs, relative to all-against-all
- Scalability / performance

Recall

- Dataset
  - 13 bacterial genomes, ~59,000 sequences
- Similarity
  - S-W threshold of 181 with PAM250 substitution matrix (Wittwer)
- Transitivity
  - mT = 250, mU = 15
- Increment greedy clustering (1 / 3 representatives)
  - 99.6% / 99.9% recall (compared all-vs-all)
- Precise cluster merge (Shared-CM/Dist-CM)
  - 99.8 ± 0.01% recall
  - Missed 10^{-6} significant pairs, mainly low scoring ones (avg. 191, median 235)

Sensitivity analysis

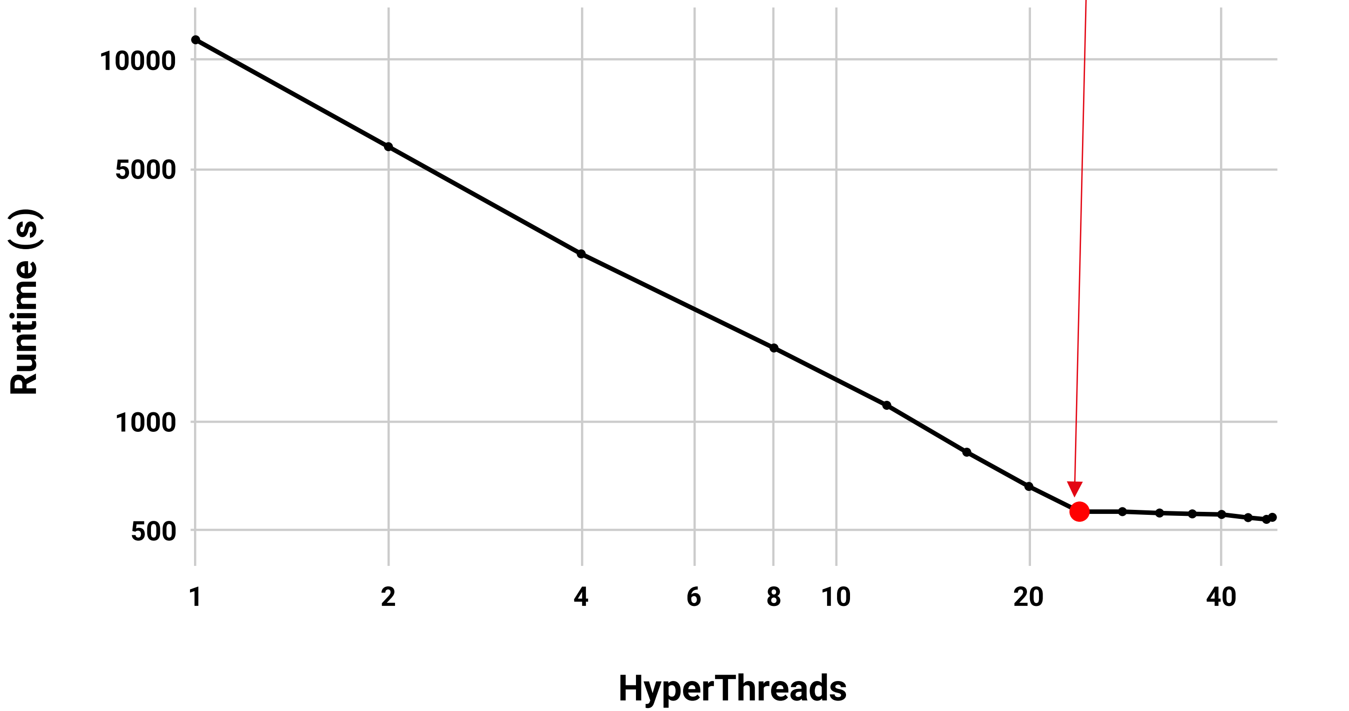


Shared-memory speedup

- Smaller data set (28,600 sequences)
- Incremental greedy clustering [Wittwer] (1 / 3 representatives)
  - 4x / 2x faster than all-vs-all
- Original clustering (1 representative)
  - 89,486 seconds = 24.9 hours
- Shared-CM (48 thread)
  - 1,486 seconds = 0.41 hours

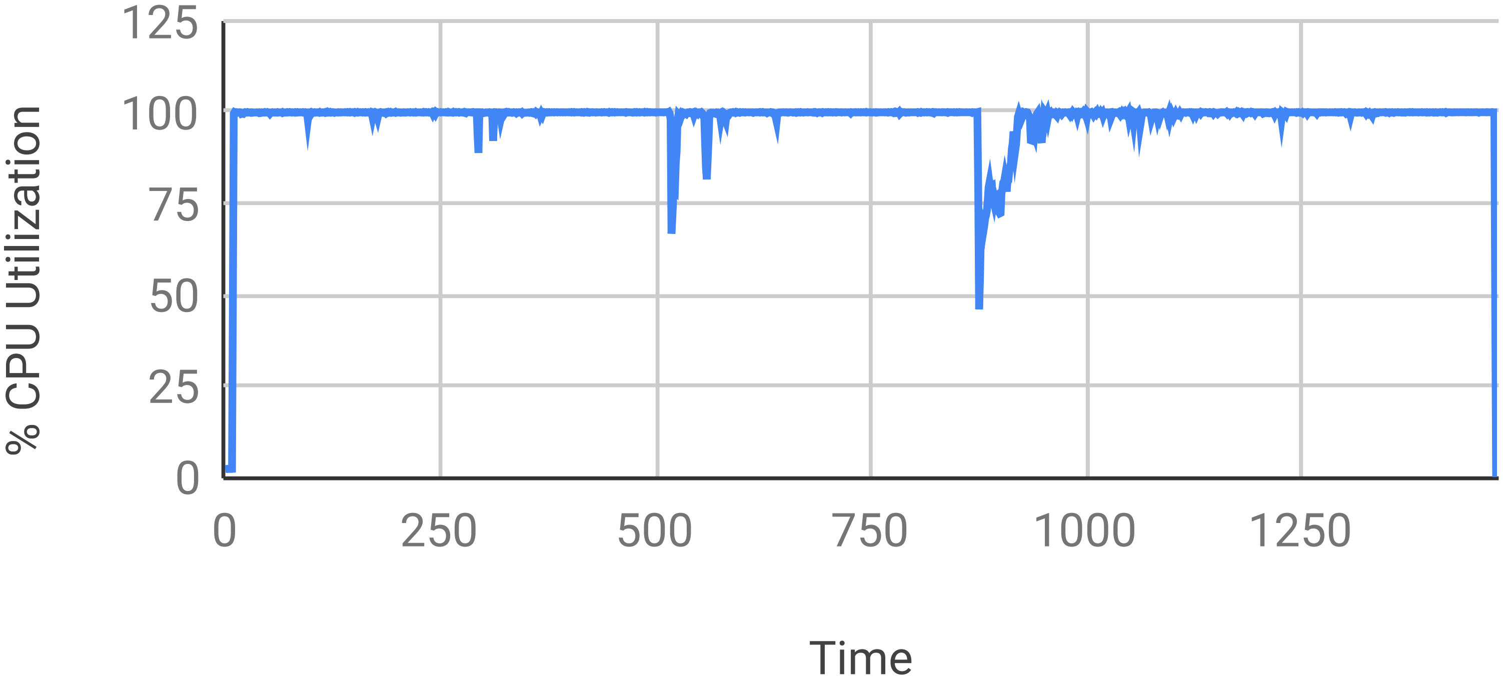
60.2x speedup

Shared-memory scalability



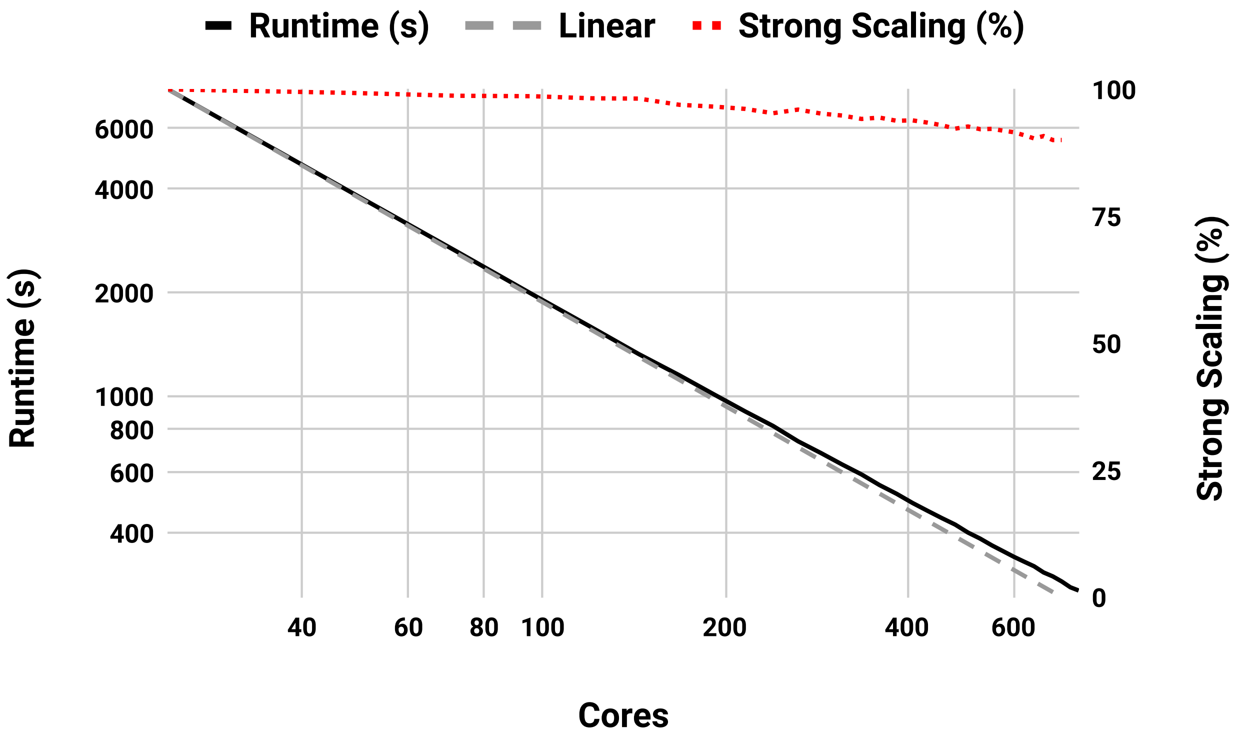
24 core Xeon
48 threads
Hyperthreading of no benefit

Shared-memory scalability



Distributed – strong scaling

Dataset fixed
Vary number of nodes

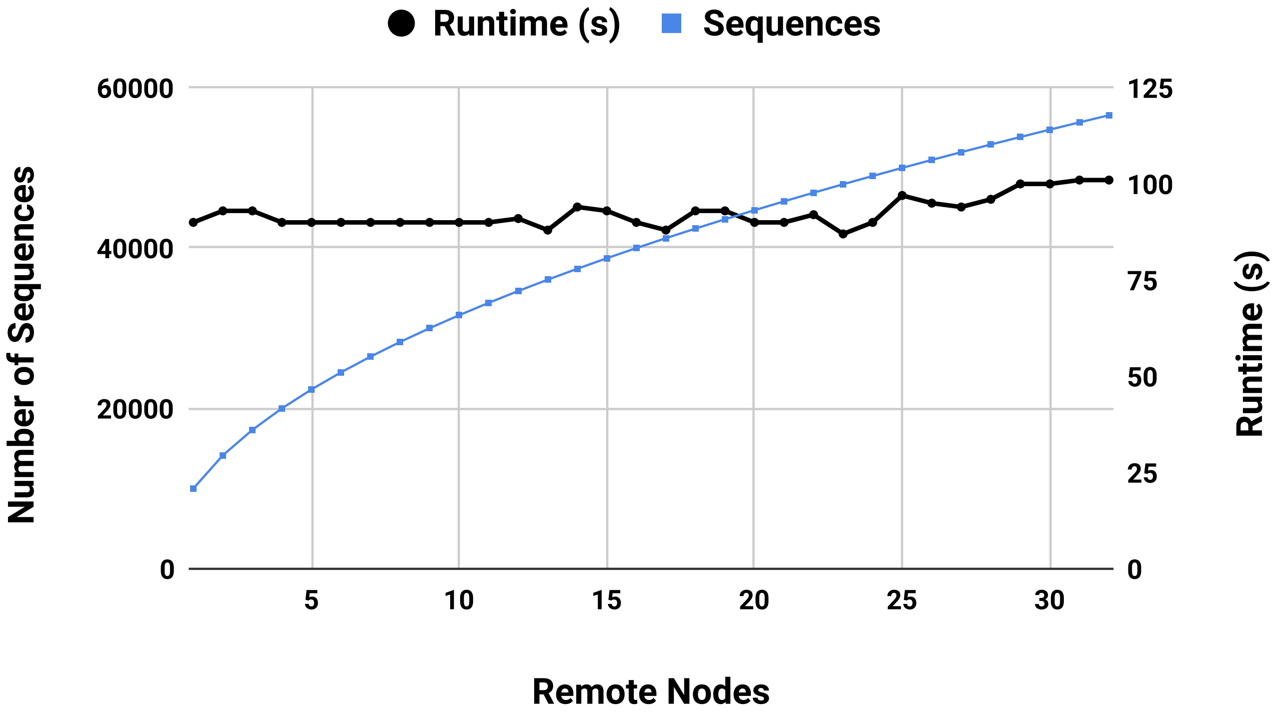


Dist-CM
604x on 32 nodes (768 cores)
79% efficiency

1,400x over Wittwer

Distributed – weak scaling

Dataset grows $\sim\sqrt{n}$



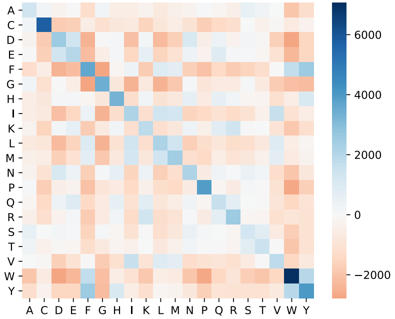
Dataset composition

- Dataset of 13 bacterial genomes
  - 59,013 sequences
- Dataset of 33 closely related Streptococcus bacteria genomes
  - 69,648 sequences
- Closely related ⇒ fewer clusters
  - Closer to $O(n \lg n)$ performance
- Shared-CM (48 threads)
  - Streptococcus 283 sec. and 10,500 clusters
  - (vs 1,486 sec. and 33,562 clusters)

Improvements / Future work

- Larger, more diverse datasets (w/ friends from UNIL)
- Seeding clusters with known significant pairs

- Hardware acceleration of Smith-Waterman comparison
  - Proteins are long (300 - 30,000 amino acids)
  - Alphabet is richer (20 amino acids)
  - More complex scoring function.



Conclusion

- Think beyond DNA!
  - Proteins are richer and more challenging than DNA
- Hardware acceleration is premature if your application does not have near-linear speedup on a cluster
  - Bioinformatics need parallel algorithms and implementations
- Keeping cores busy is key to efficient parallelism
  - Communications efficiency
  - Work distribution and load balancing

EPFL

Merci

James Larus

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