Introduction to Bioinformatics for Computer Scientists

Lecture 11

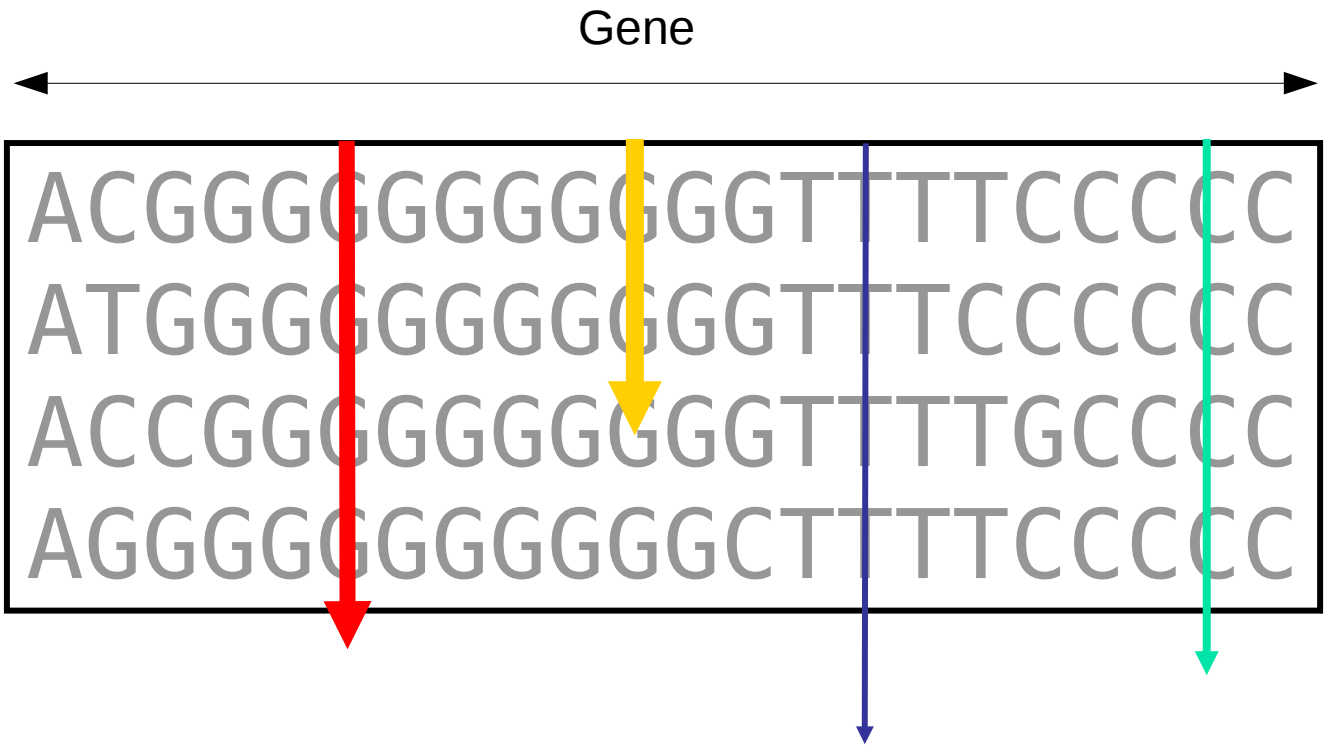
Course Beers

- Next Thursday, Jan 16 at Vogelbräu
- Remember, drinks are on me

Plan for next lectures

- Today (Alexis):
  - More on Models
  - Data Structures for unrooted Phylogenetic Trees
  - Implementing and Optimizing Likelihood Calculations
  - Parallel Likelihood Calculations
- Lecture 12 (Alexis): Bayesian Statistics & MCMC methods
- Lecture 13 (Alexis): Advanced MCMC
- Lecture 14 (Alexis): Population genetics
- Lecture 15 (Alexis): Course summary

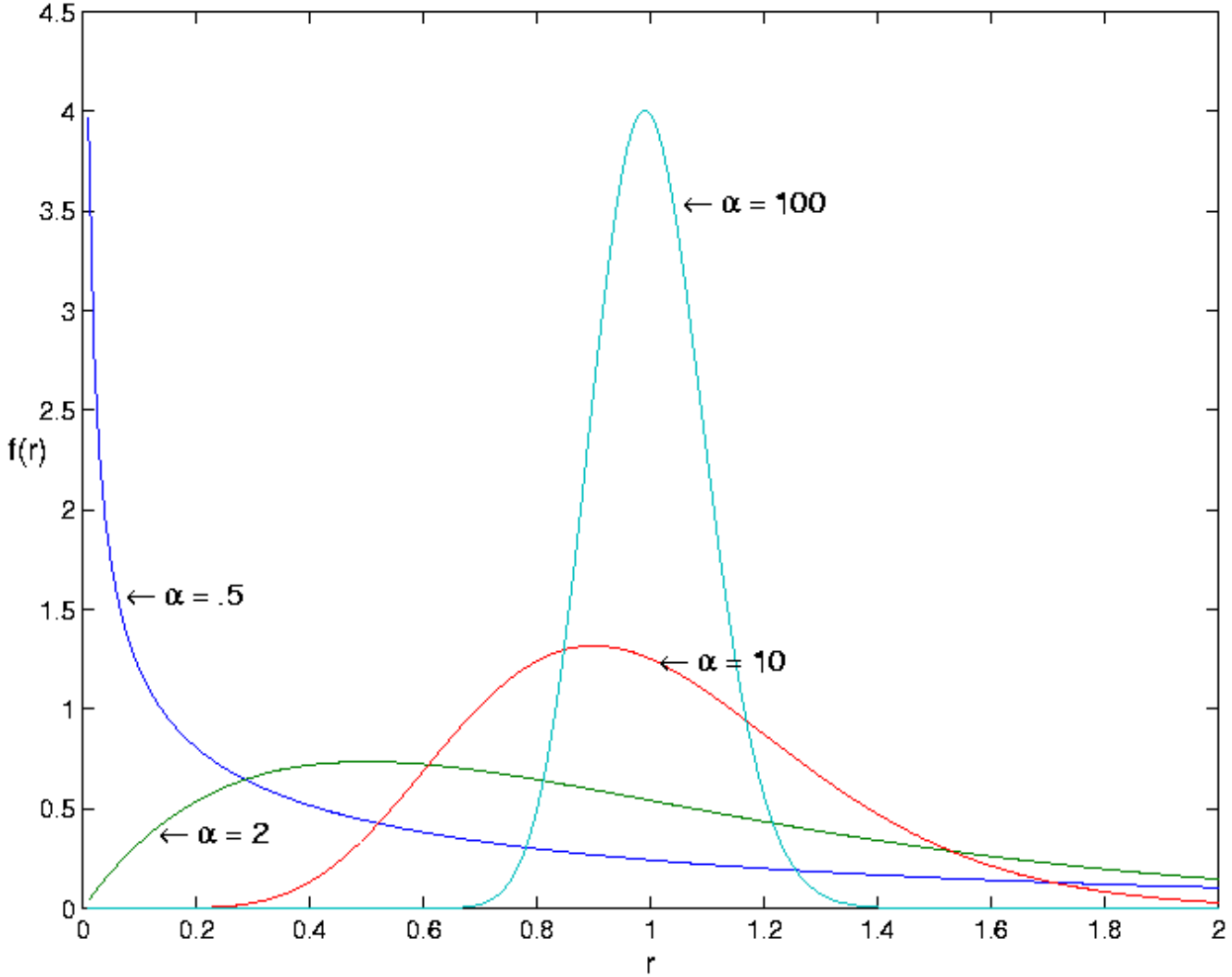
Rate Heterogeneity among Sites



- Among-site rate heterogeneity
  - Biological phenomenon

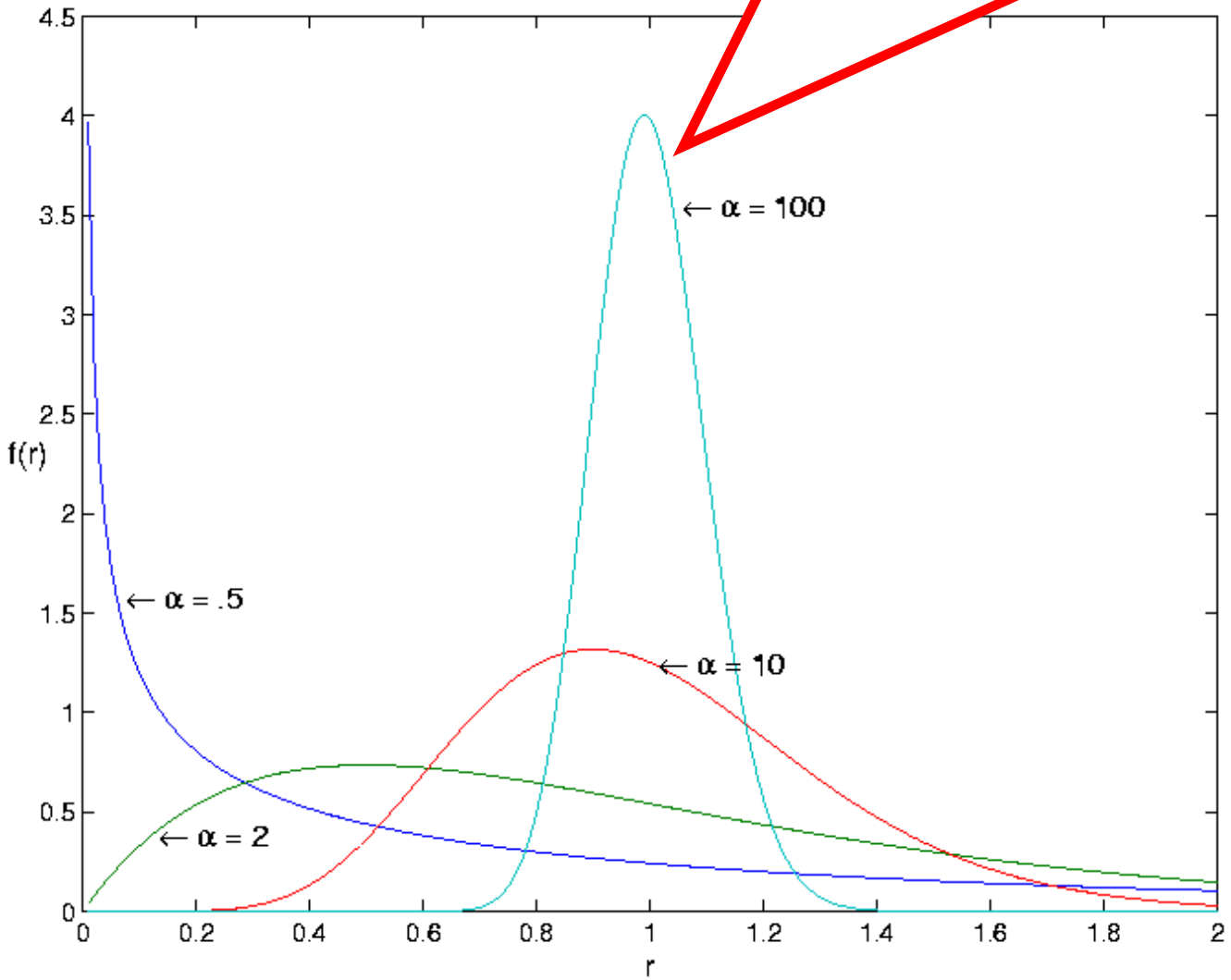
    → different sites/columns evolve at different speeds
  - Need to accommodate this in our models

Γ-Distribution

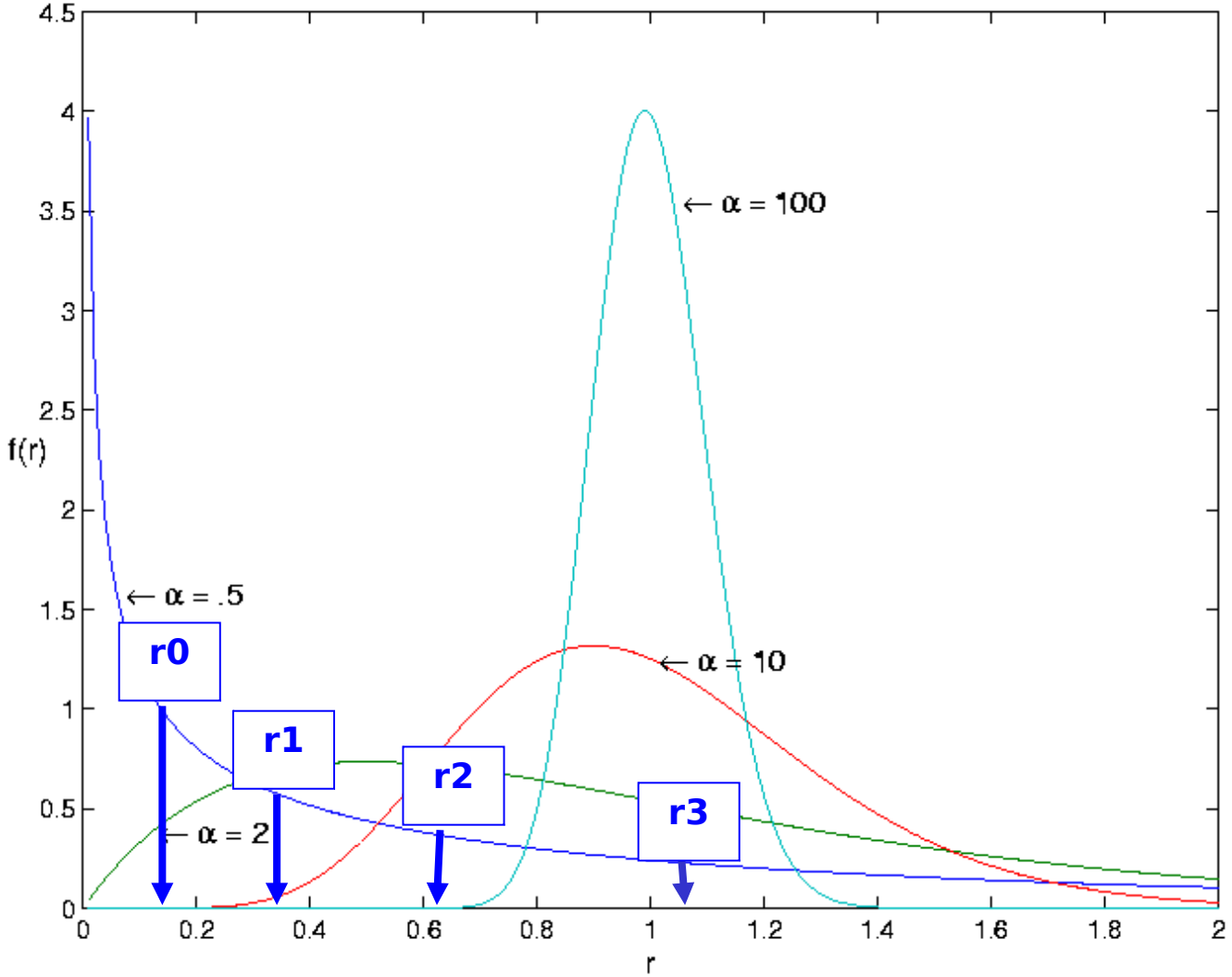


Γ-Distribution

Small α ➔high rate heterogeneity
Large α ➔low rate heterogeneity



Discrete Γ-Distribution



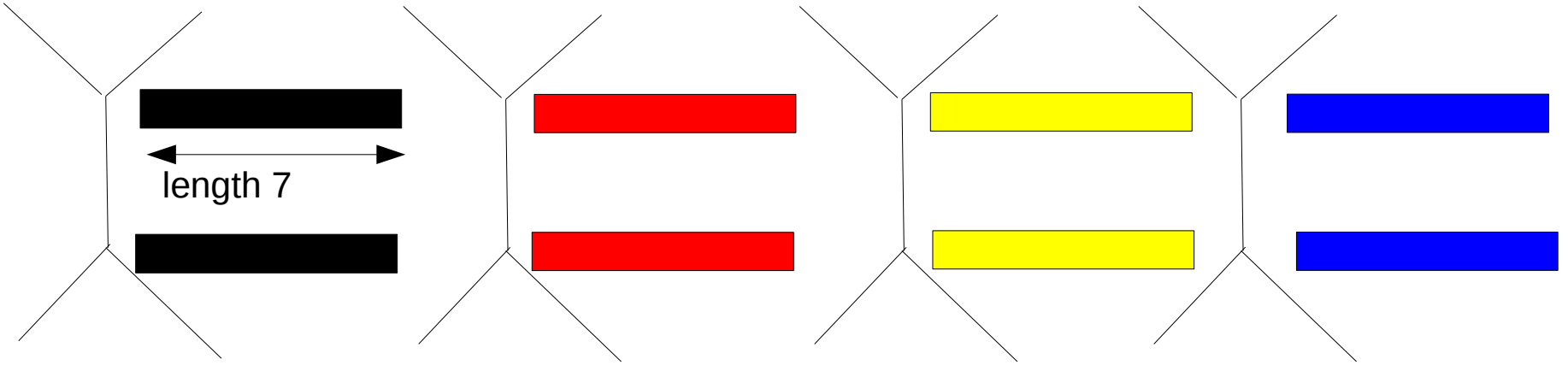
An Abstract View of Γ

rate 0
$P(t) = e^{Qr_0 t}$

rate 1
$P(t) = e^{Qr_1 t}$

rate 2
$P(t) = e^{Qr_2 t}$

rate 3
$P(t) = e^{Qr_3 t}$



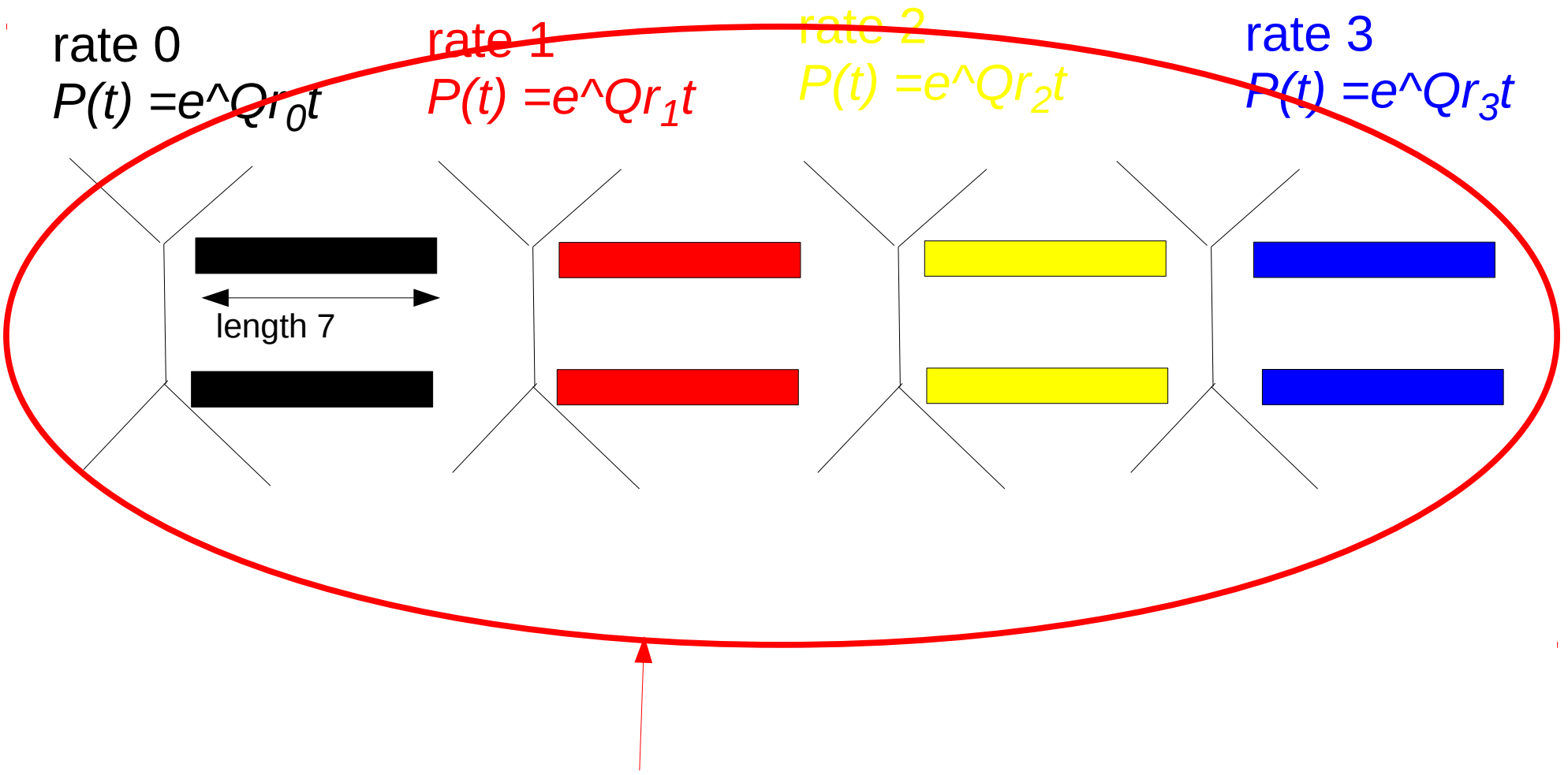
This is the integral of the likelihood we approximate via discretization

$$LnL(i) = \log(\tfrac{1}{4} * (L_0 + L_1 + L_2 + L_3))$$

Log likelihood at site i

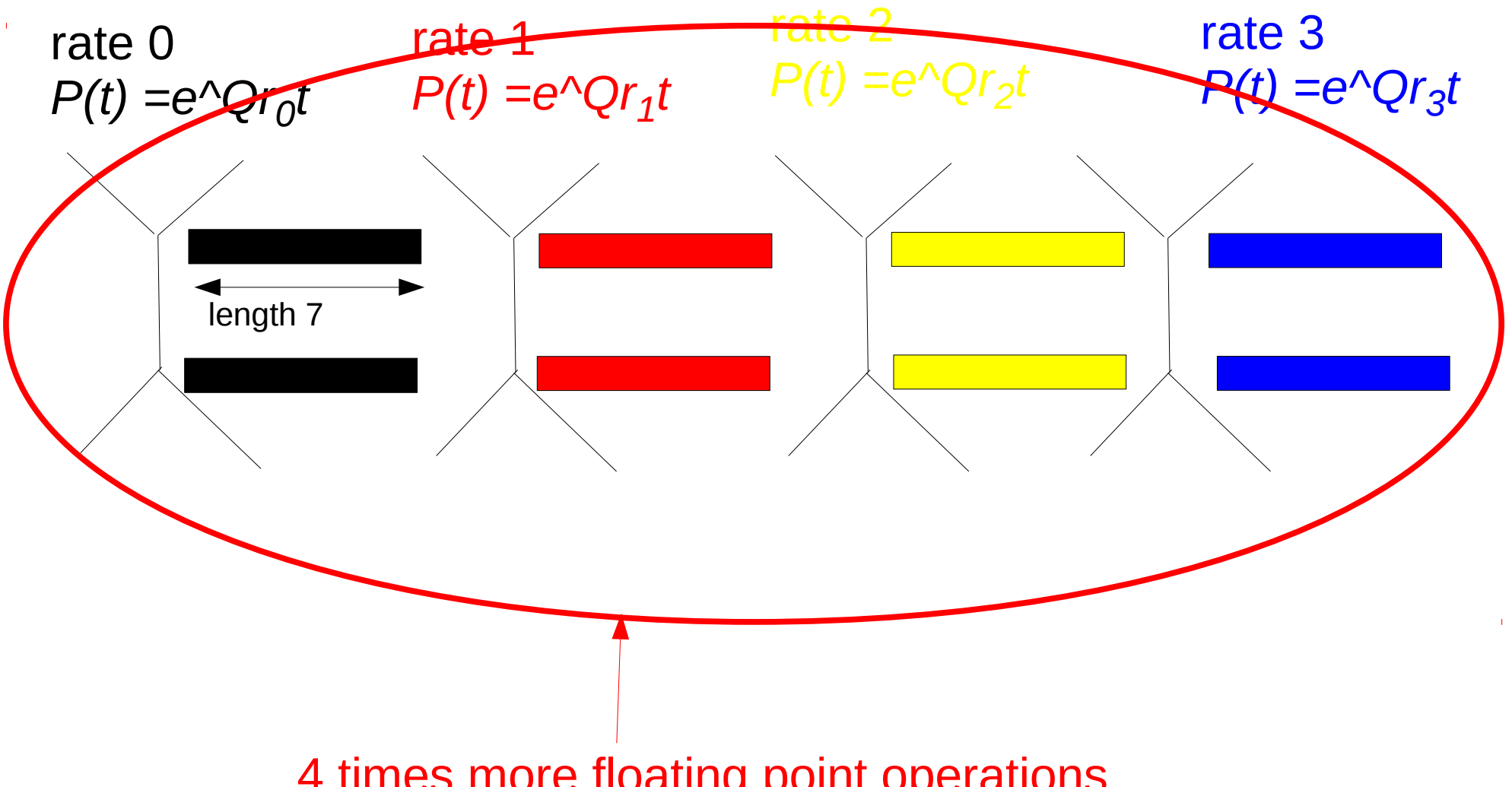
All Γ rates have equal probability

An Abstract View of Γ

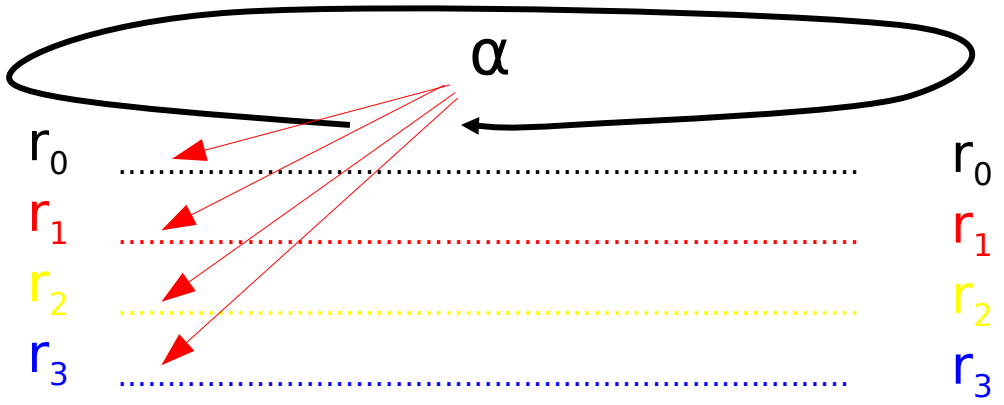


4 times higher memory consumption

An Abstract View of Γ



Γ Model of Rate Heterogeneity with 4 discrete rates




```
Species209    NNNNNNNNNNN NNNNNNNNNNN NNNNNNNNNNN NNNNNNNNNNN
Species159    UAUCUGGUUG AUCCUGCCAG UAGUAUNUGC UUGUCUCAAA
Species109    NNNNNNNNNNN NNNNNNNNNNN NNNNAUAUGC UUGUCUC--A
Species025    NNNNNNNNNNN NNNNNNNNNNN NNNNNNNNNNN NNNNNNNAAA
Species004    NNNNNNNNNNN NNNNNNNNNNN NNNNNNNNNNN NNNNNNNNNN
Species186    UACCUGGUUG AUCCUGCCAG UAGUAUAUGC UUGUCUCAAA
Species034    NNNNNNNNNNN NNNNNNNNNNN NNNNNNNNNNN NNNNNNNAAA
Species003    NNNNNNNNNNN NNNNNNNNNNN NNNNNNNNNNN NNNNNNNAAA
Species192    NNNNNNNNNNN NNNNNNNNNNN NNNNNNNNNNN NNNNNNCAAA
Species132    NNNNNNNNNNN NNNNNNNNNNN UAGUAUAUGC UUGUCUCAAA
Species172    NNNNNNNNNNN NNNGAAUU-G UAUUANANGC -UGUUUCAAA
```

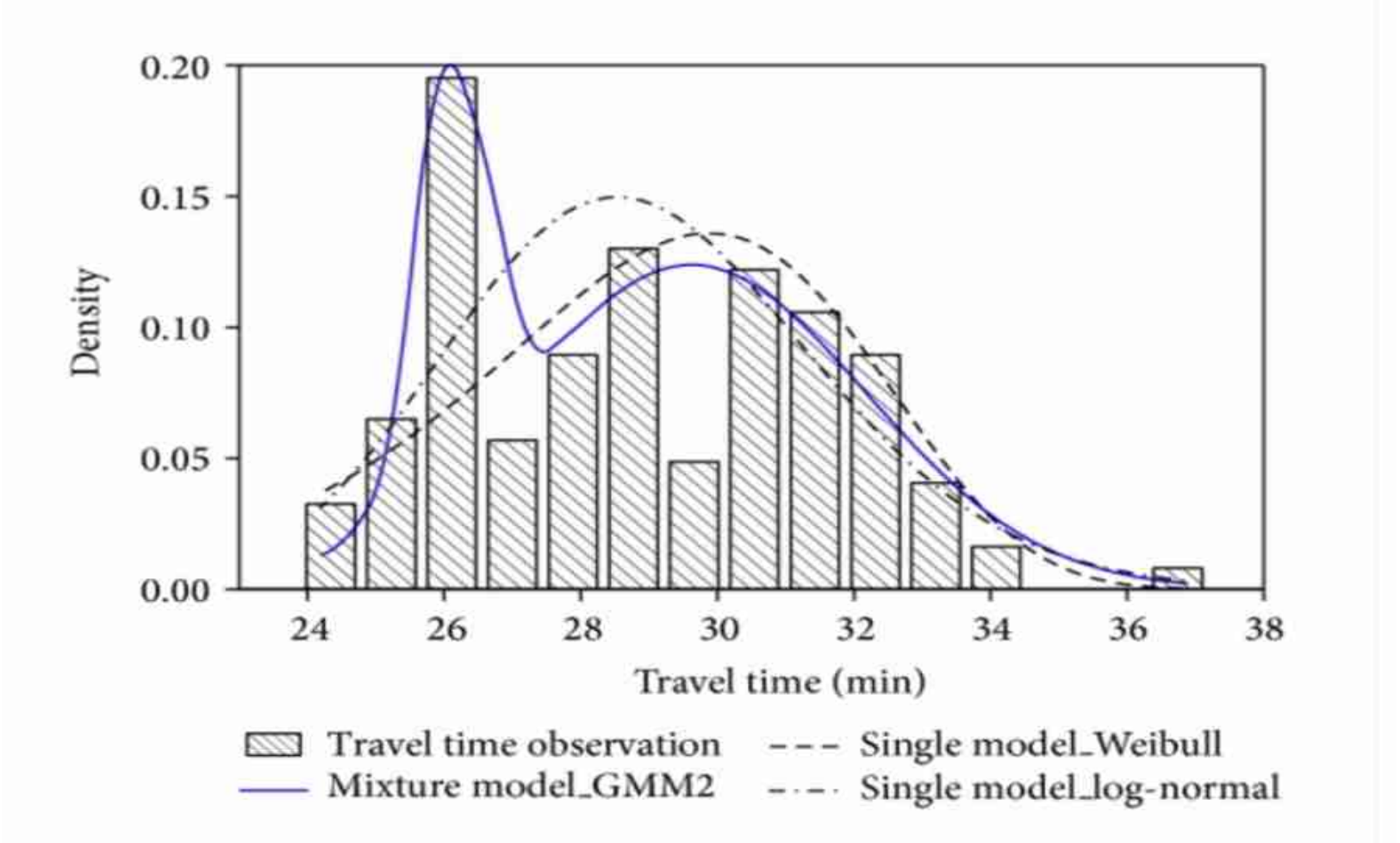
Mixture Models

- The of rate heterogeneity is a simple example of a so-called mixture model
- From Wikipedia: “In statistics, a mixture model is a probabilistic model for representing the presence of subpopulations within an overall population, without requiring that an observed data set should identify the sub-population to which an individual observation belongs. Formally a mixture model corresponds to the mixture distribution that represents the probability distribution of observations in the overall population.”
- The Γ model gives us 4 discrete evolutionary rates over which we integrate (add) the likelihood for each site, without assigning a specific rate to a specific site

Mixture Models

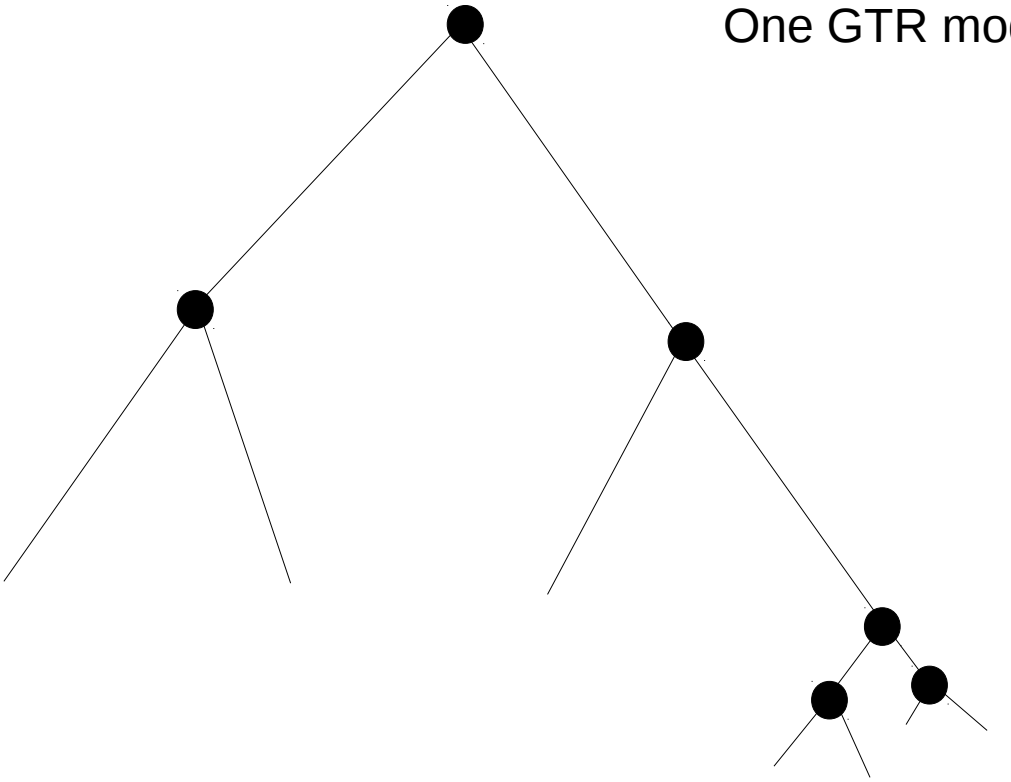
- We can also imagine to integrate the likelihood over a set of
  - distinct *Q* matrices
  - distinct base frequencies
  - or combinations thereof
- The LG protein substitution model is an example thereof:
- It uses 4 distinct empirical *Q* matrices and 4 distinct sets of base frequencies π over which we integrate just like for the *Γ* model

An example



Taken from: “Measuring Service Reliability Using Automatic Vehicle Location Data”
→ bus service reliability

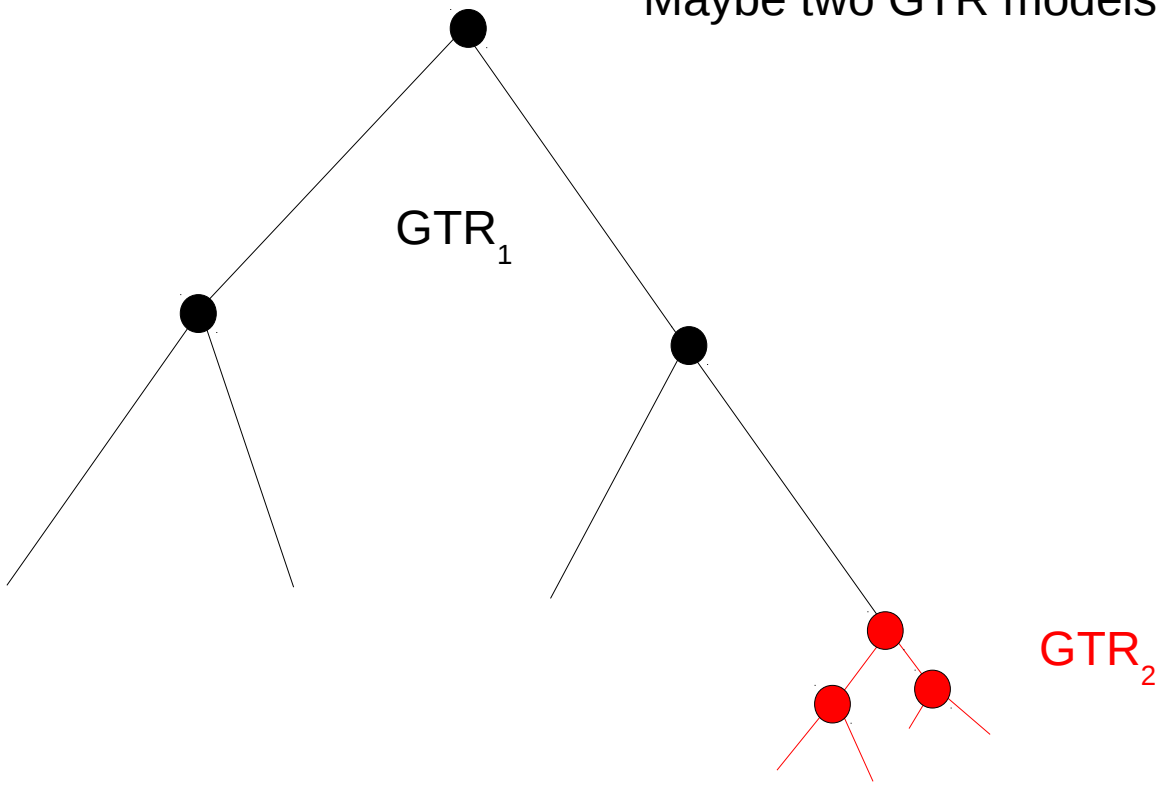
Heterotachous Models



One GTR model for the entire tree

Heterotachous Models

Maybe two GTR models describe this better?



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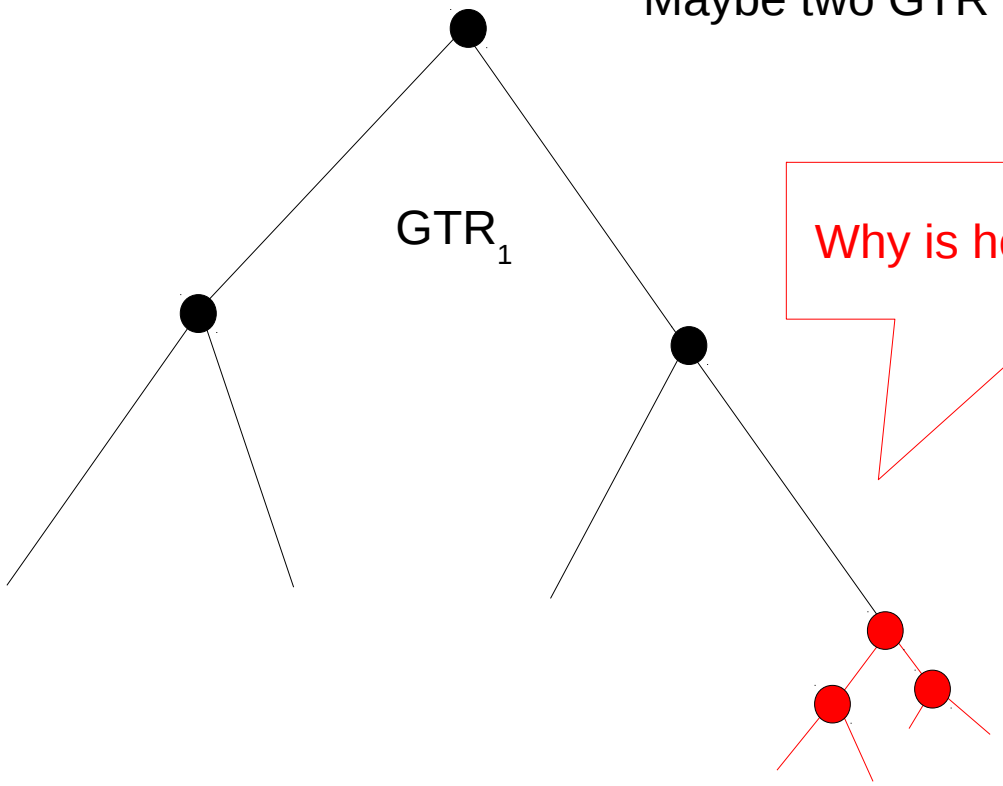
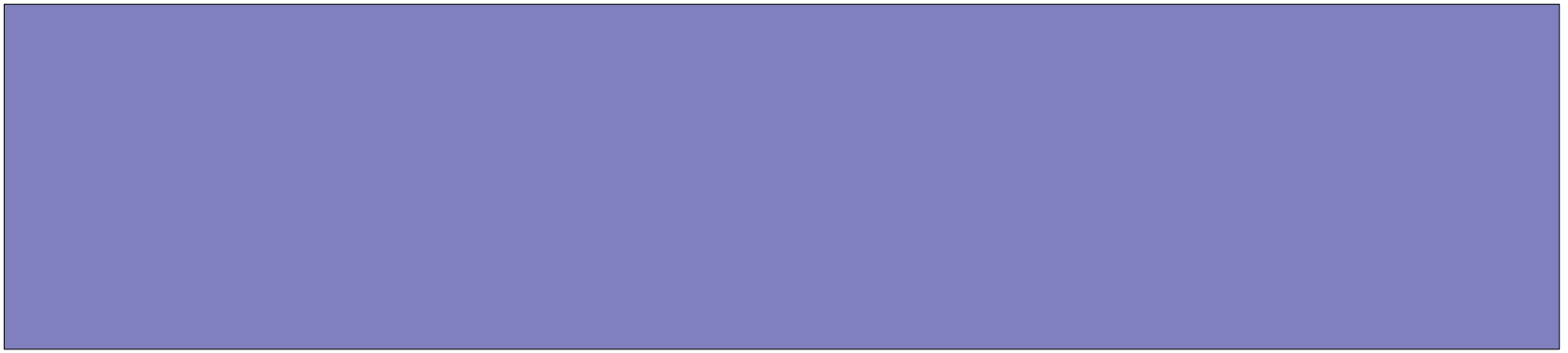


Why is heterotachy difficult?

What is a partitioned dataset?



Multi-gene or whole-genome alignment

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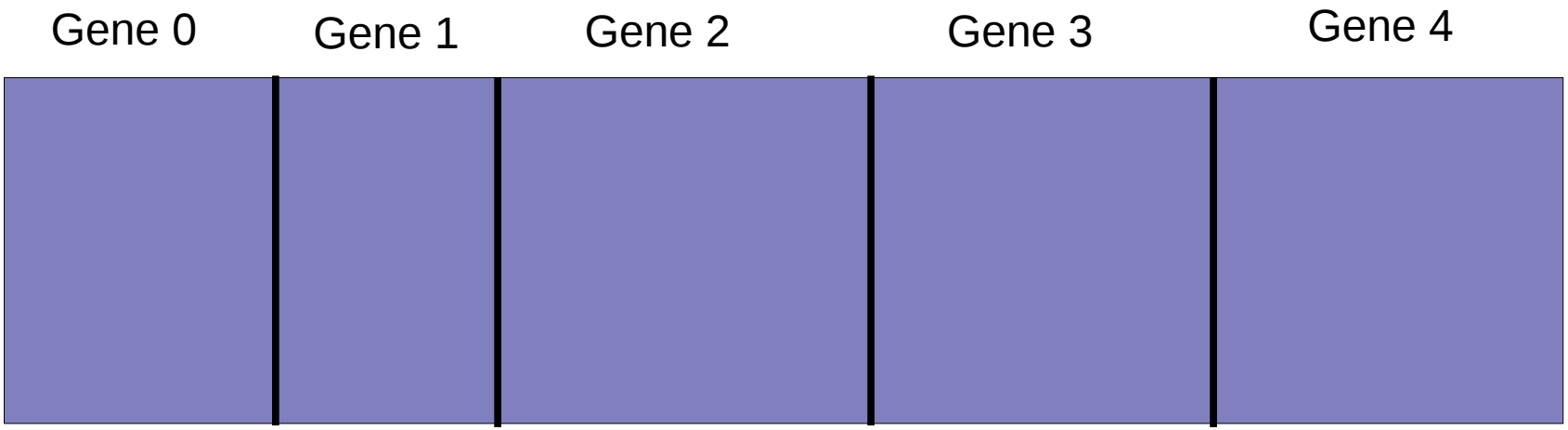

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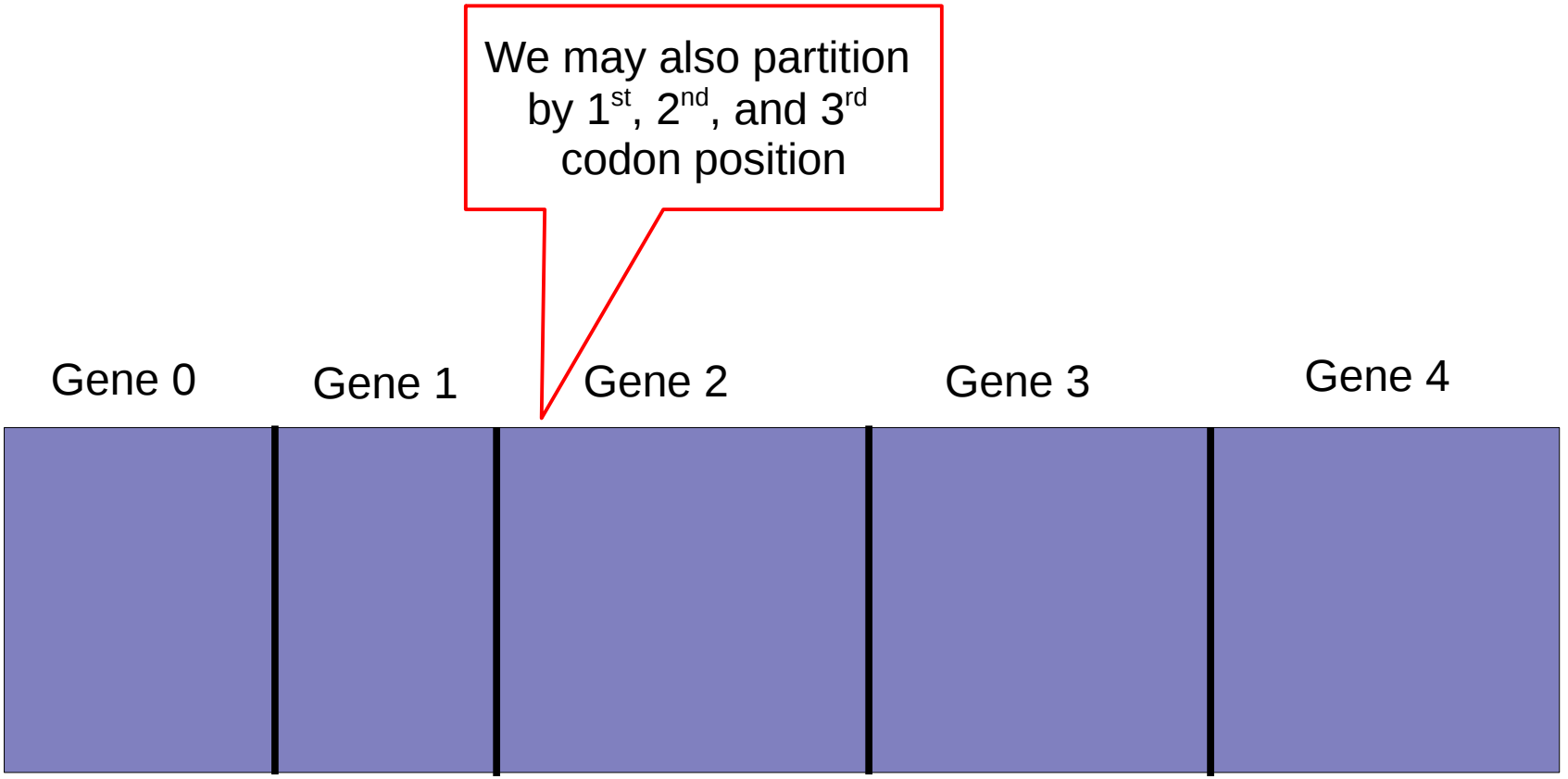

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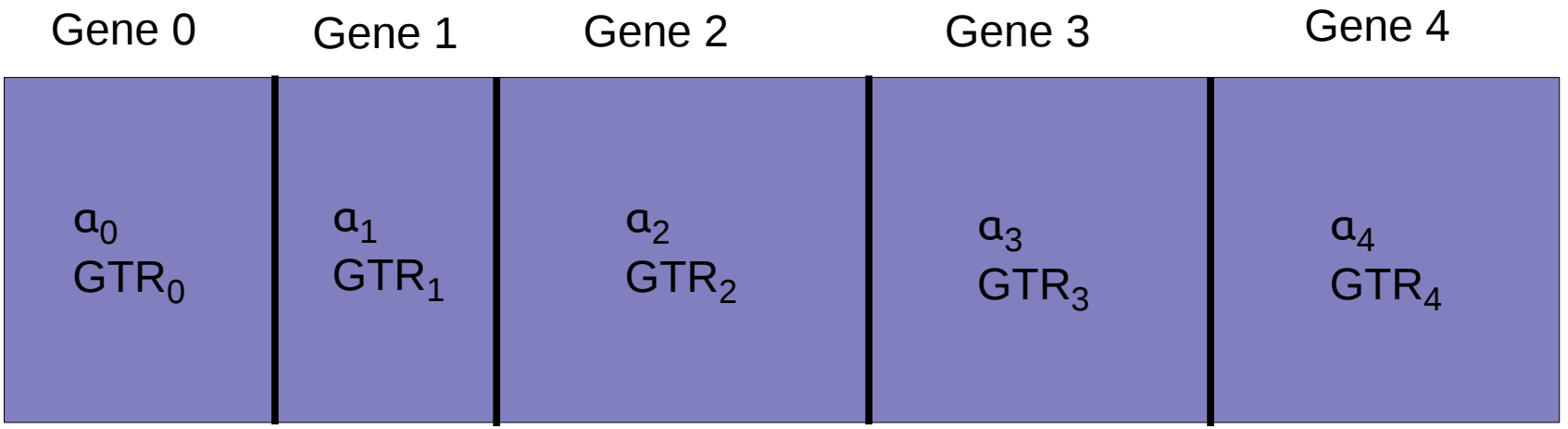

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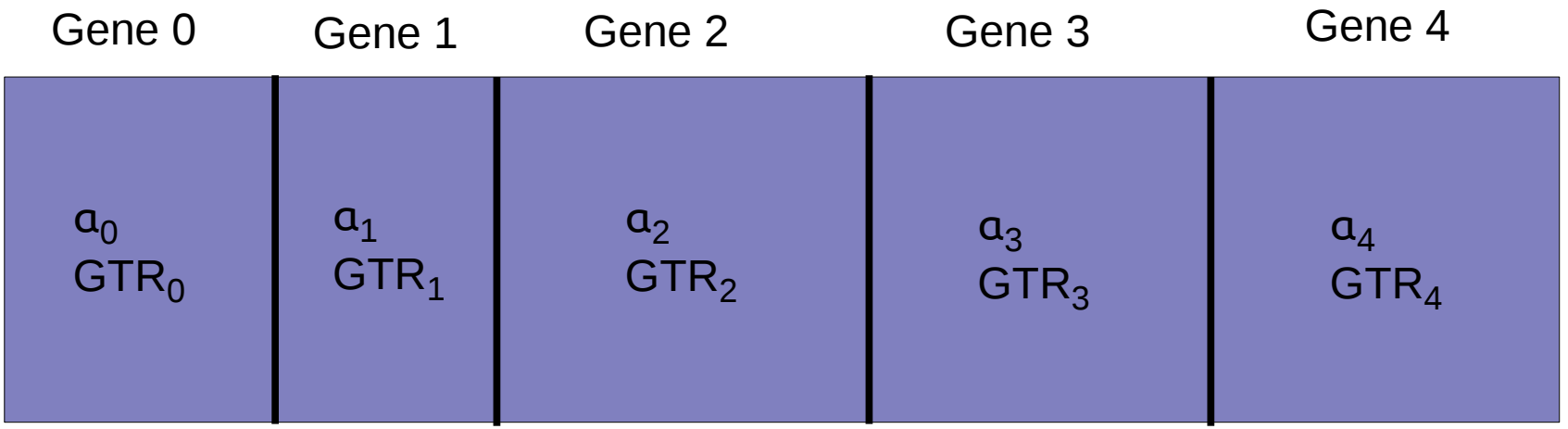
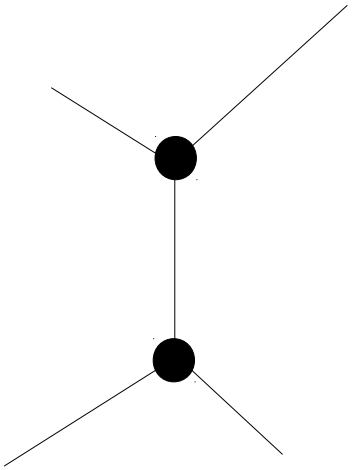
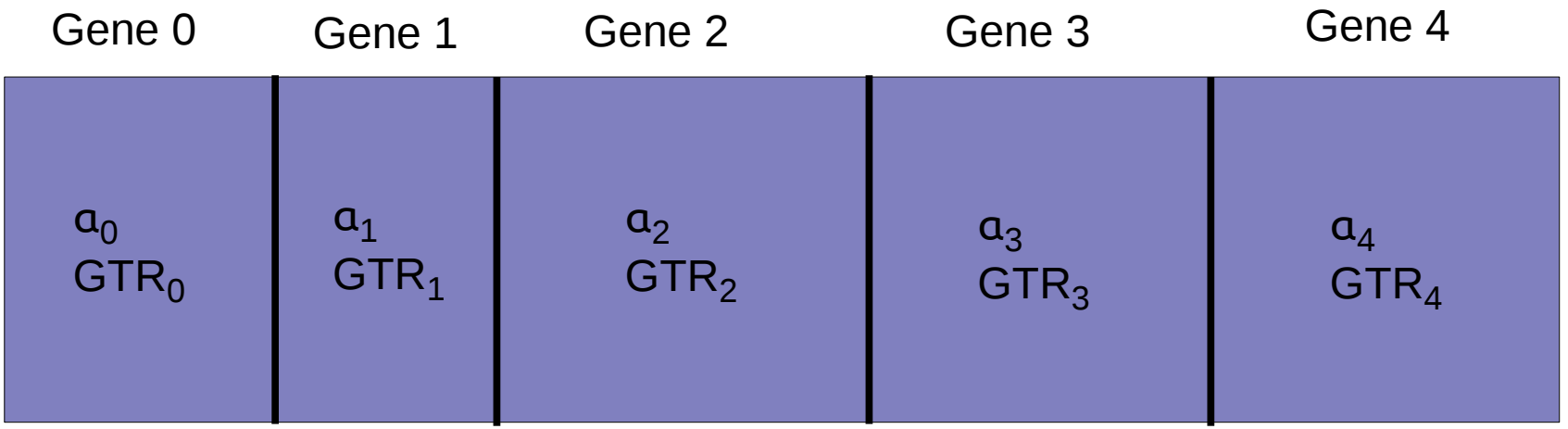
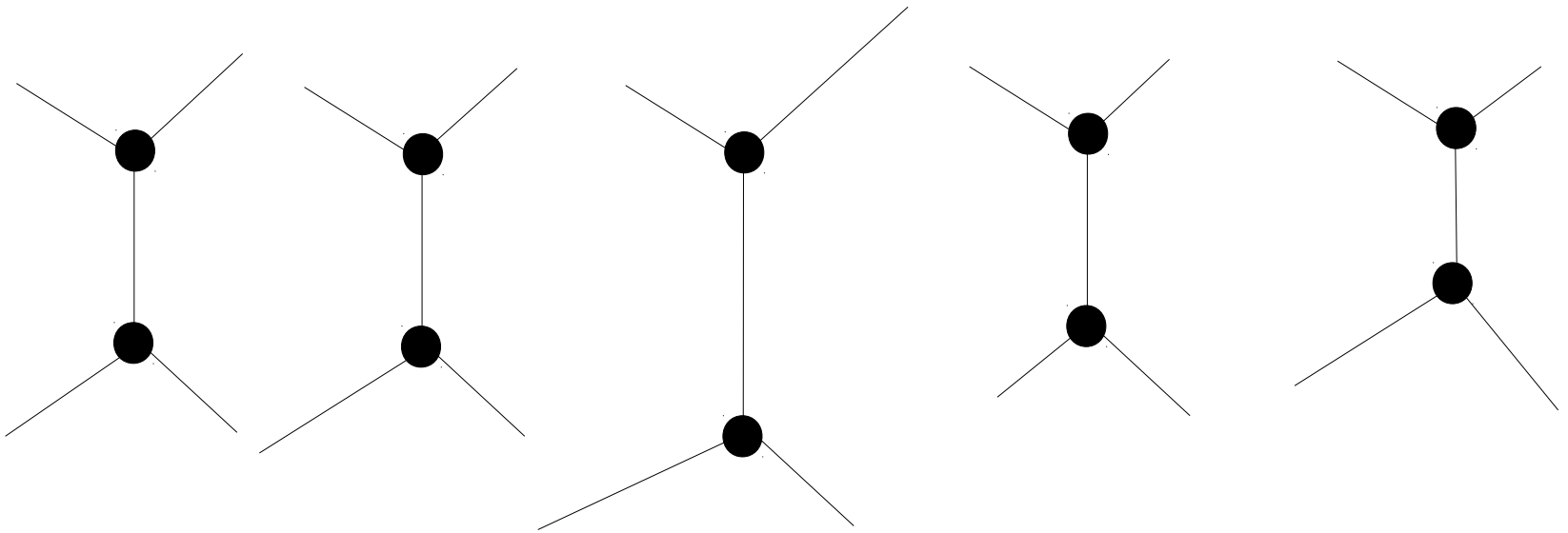




Joint branch length estimate

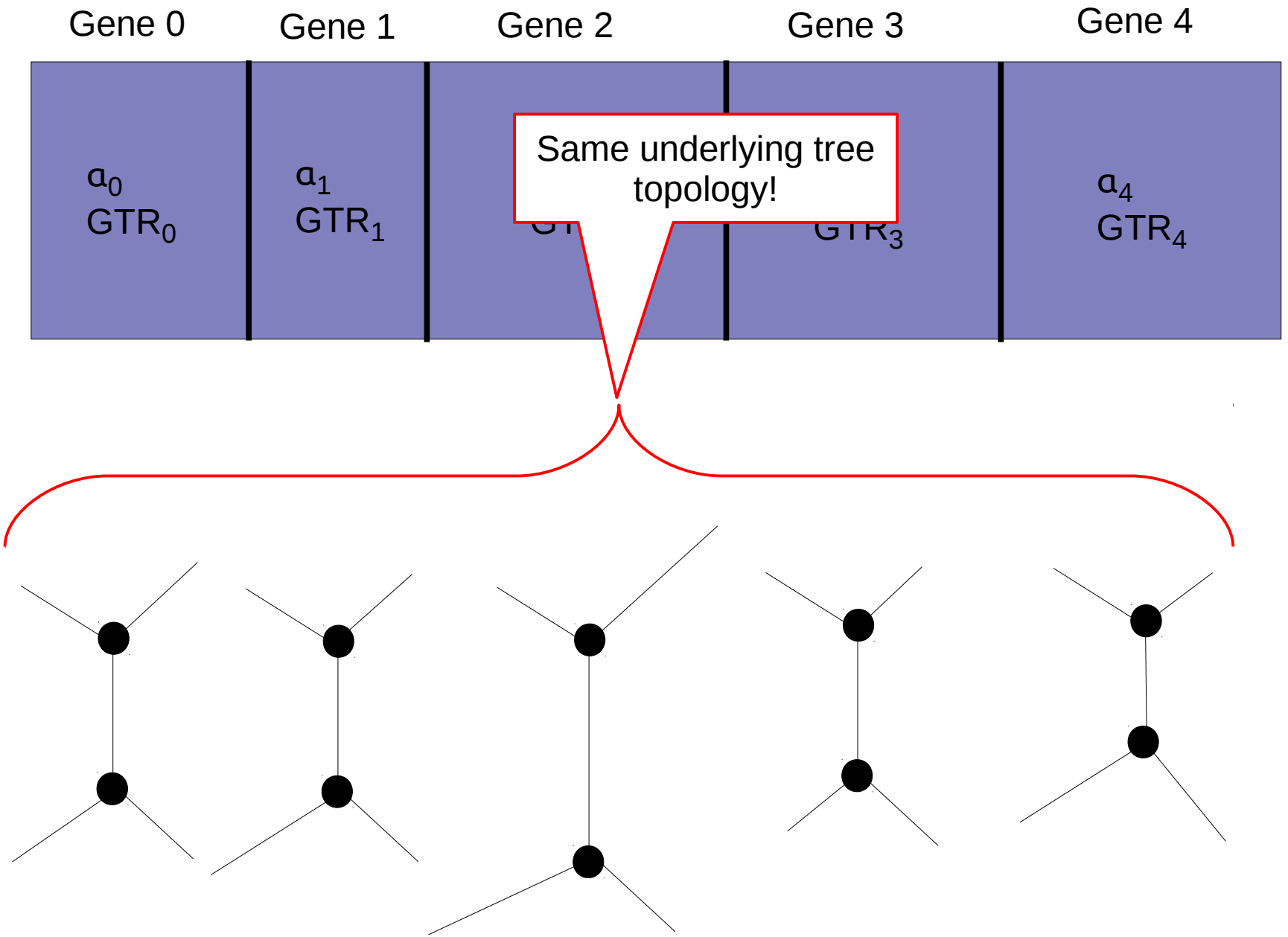
What is a partitioned dataset?





per-partition branch length estimate

What is a partitioned dataset?



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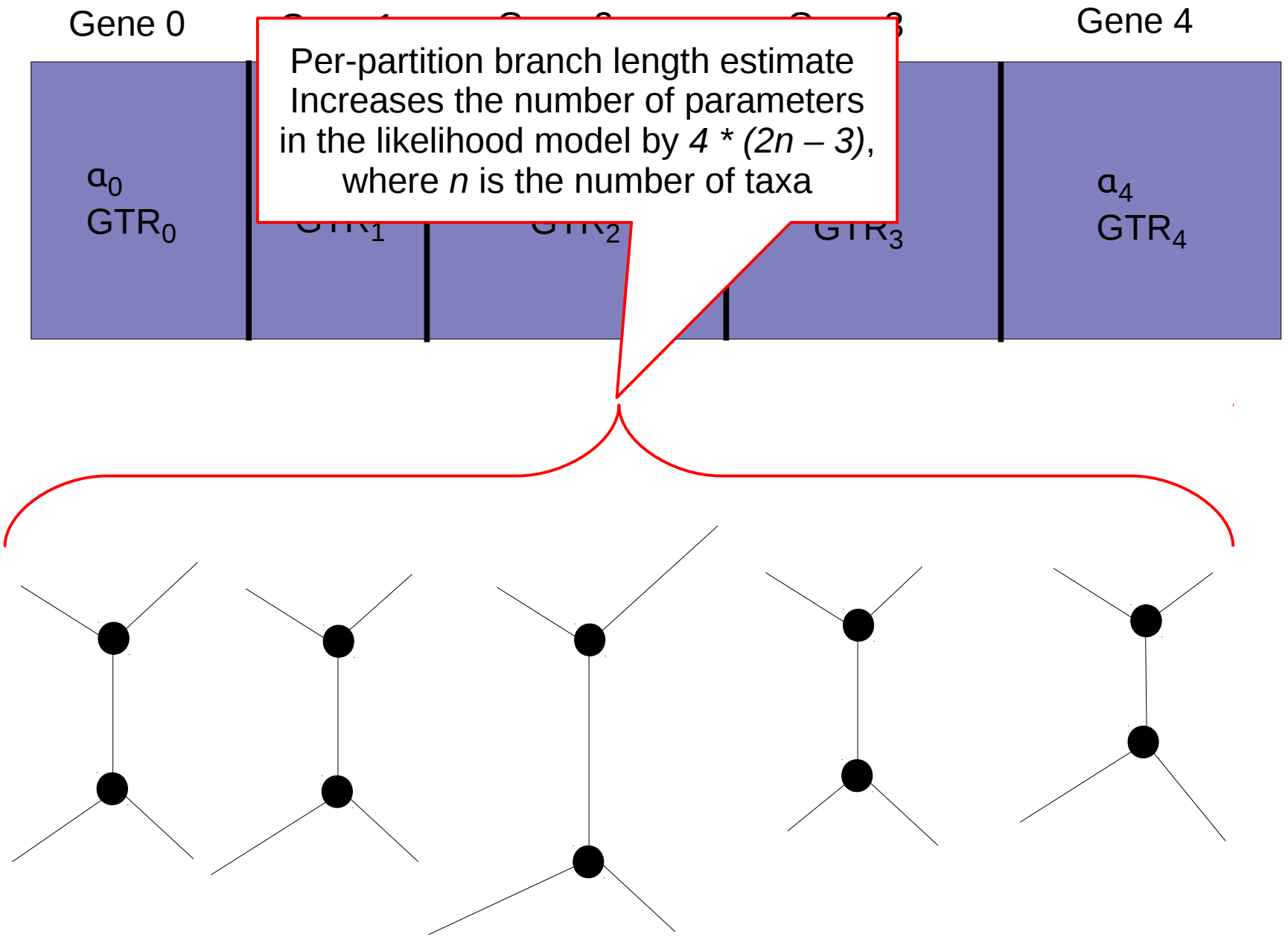

Models and Parameters

- If we add an additional parameter to a model, the likelihood will improve
- However, this does not mean anything, as
  - We might be over-parameterizing
  - The key question is if the more complex model yields a different tree topology
- So, how do we determine the best-fit model for a given dataset?

Model Testing

- If models are nested we can use a likelihood ratio test
- Model *A* is nested in model *B* if parameters in model *A* are a subset of the parameters in model *B*
- For instance: the *Jukes Cantor (JC)* model is nested in the *General Time Reversible (GTR)* model of nucleotide substitution
- $LR = P(\mathbf{D}|A) / P(\mathbf{D}|B) = L(A) / L(B)$
- $\Delta = ln(LR^2) = 2\,(ln(L(A)) - ln(L(B))$
- Compare Δ to x^2 distribution with $k_A - k_B$ degrees of freedom to determine if the Δ is significant or not
- The degrees of freedom difference is the difference in the number of free parameters in the models
- How many free parameters do the *JC* and *GTR* models have?

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- How many free parameters do the *JC* and *GTR* models have?

We are only allowed to compare likelihoods on the same data **D**!

What if Models are not nested?

- One can use other criteria such as
  - *Akaike Information Criterion (AIC)*
  - *Bayesian Information Criterion (BIC)*
- I will spare you the details, but the basic idea always is:
  - Compute likelihood of alternative models
  - Penalize the more parameter-rich models

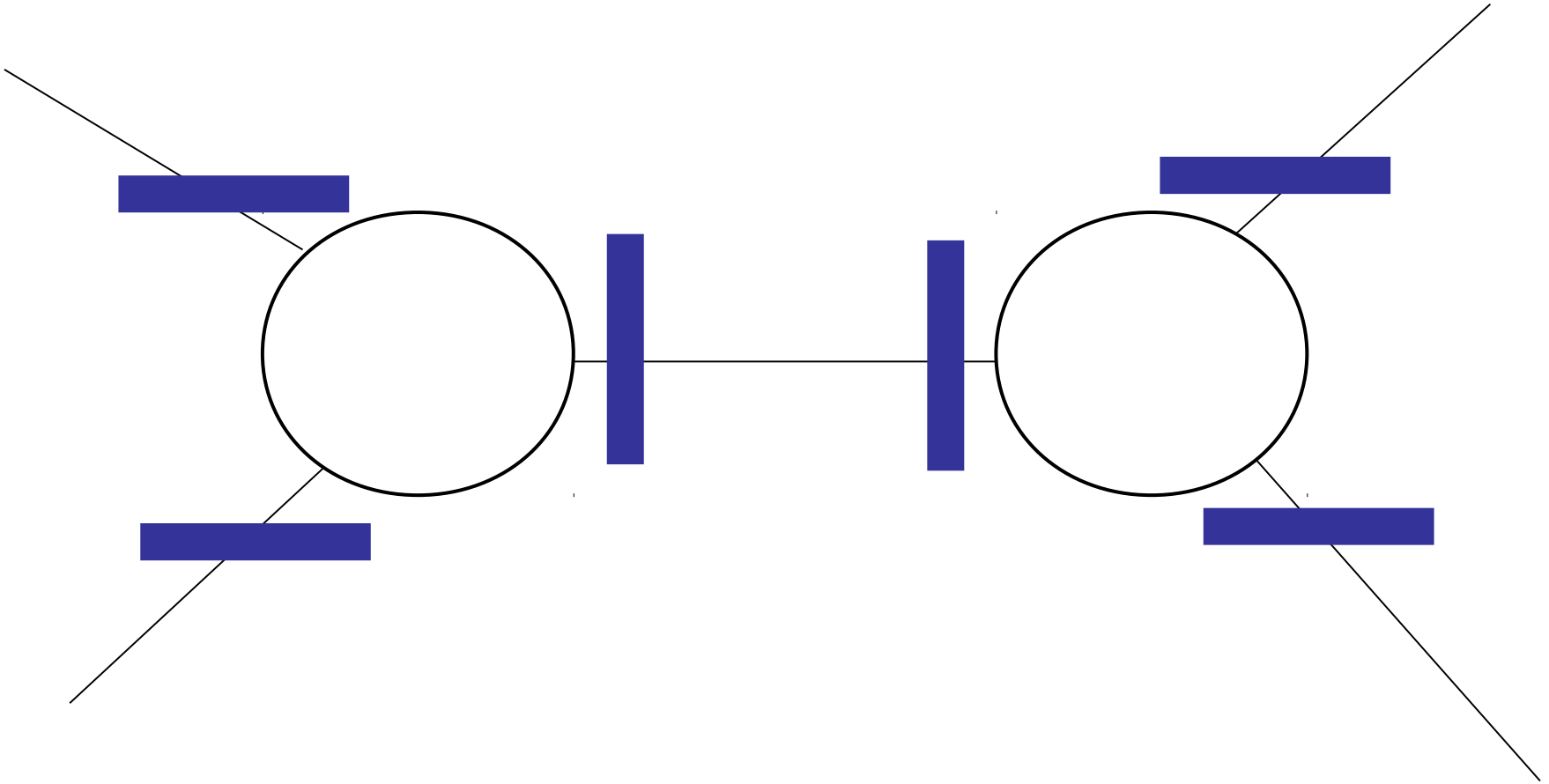
Outline

- More on Models
- Data Structures for unrooted Phylogenetic Trees
- Implementing and Optimizing Likelihood Calculations
- Parallel Likelihood Calculations

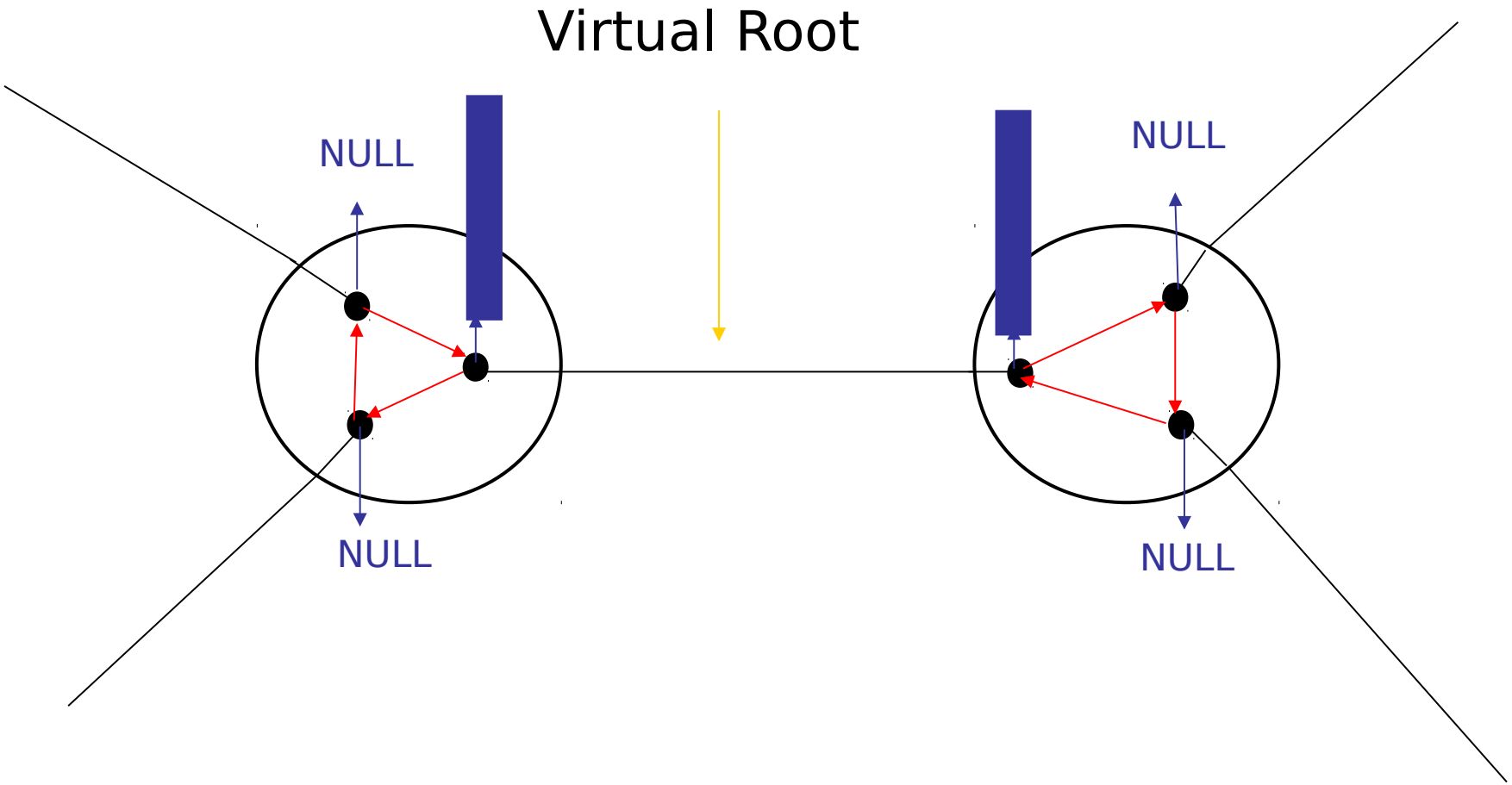
Data Structures for unrooted Trees

- Unrooted trees with dynamically changing virtual roots need a dedicated tree data structure
- Why can the virtual root positions change dynamically?
- If we apply a topological move (NNI, SPR, TBR) will we have to re-compute all conditional likelihood vectors?

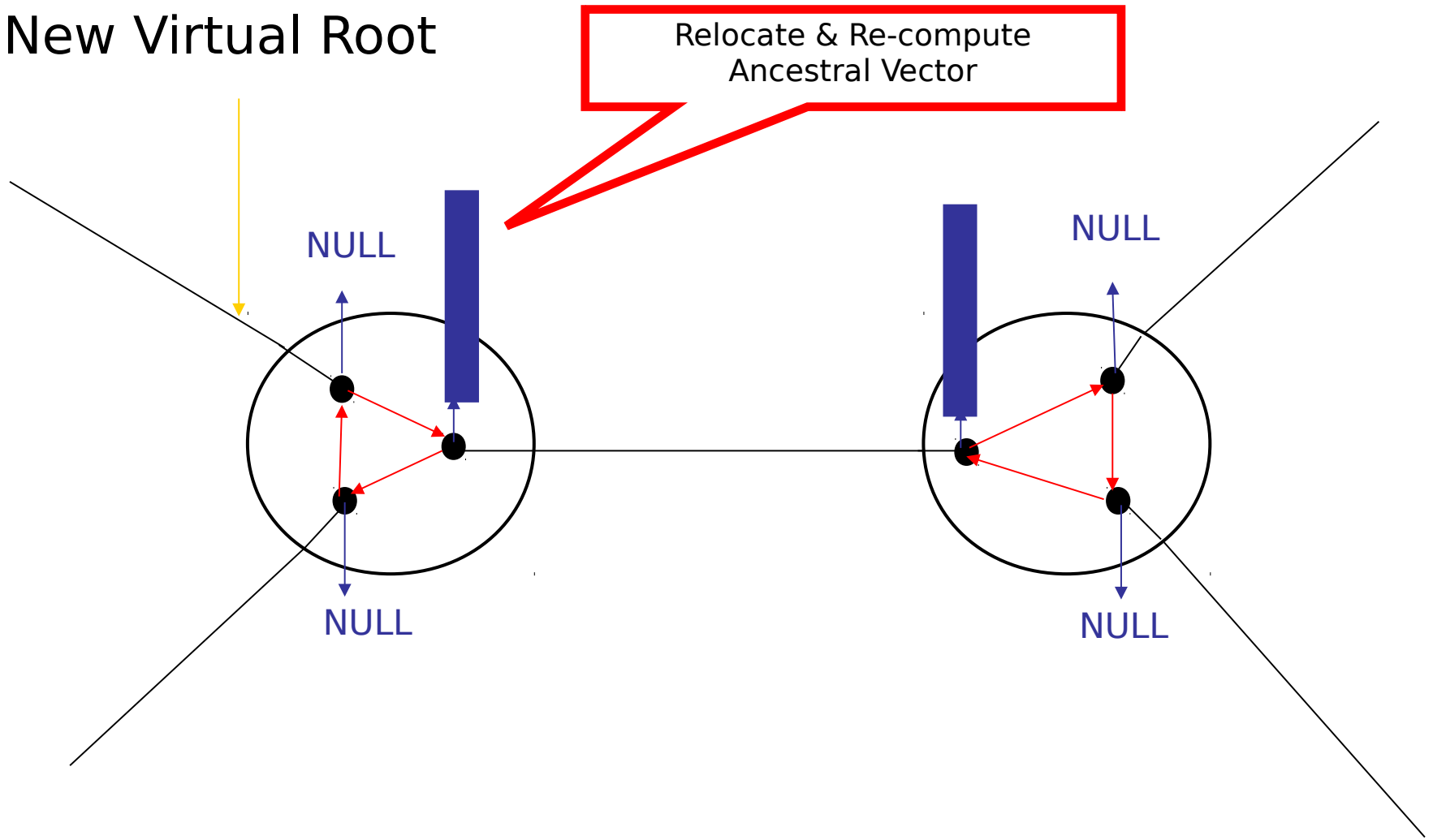
Memory Organization: Conditional Likelihood Vectors with an Unrooted View



Memory Organization: Conditional Likelihood Vectors with a Rooted View

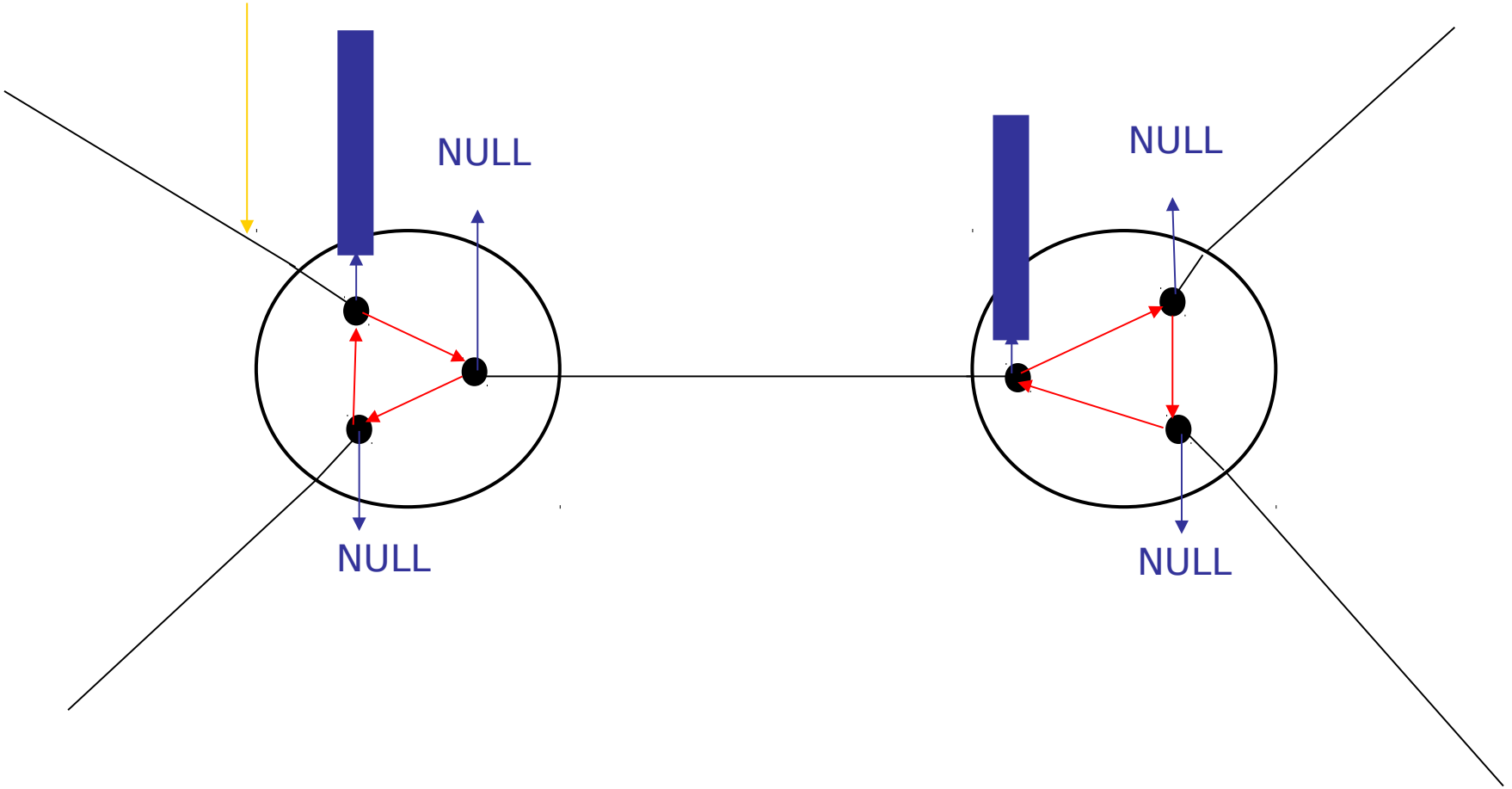


Memory Organization: CLVs with a Rooted View

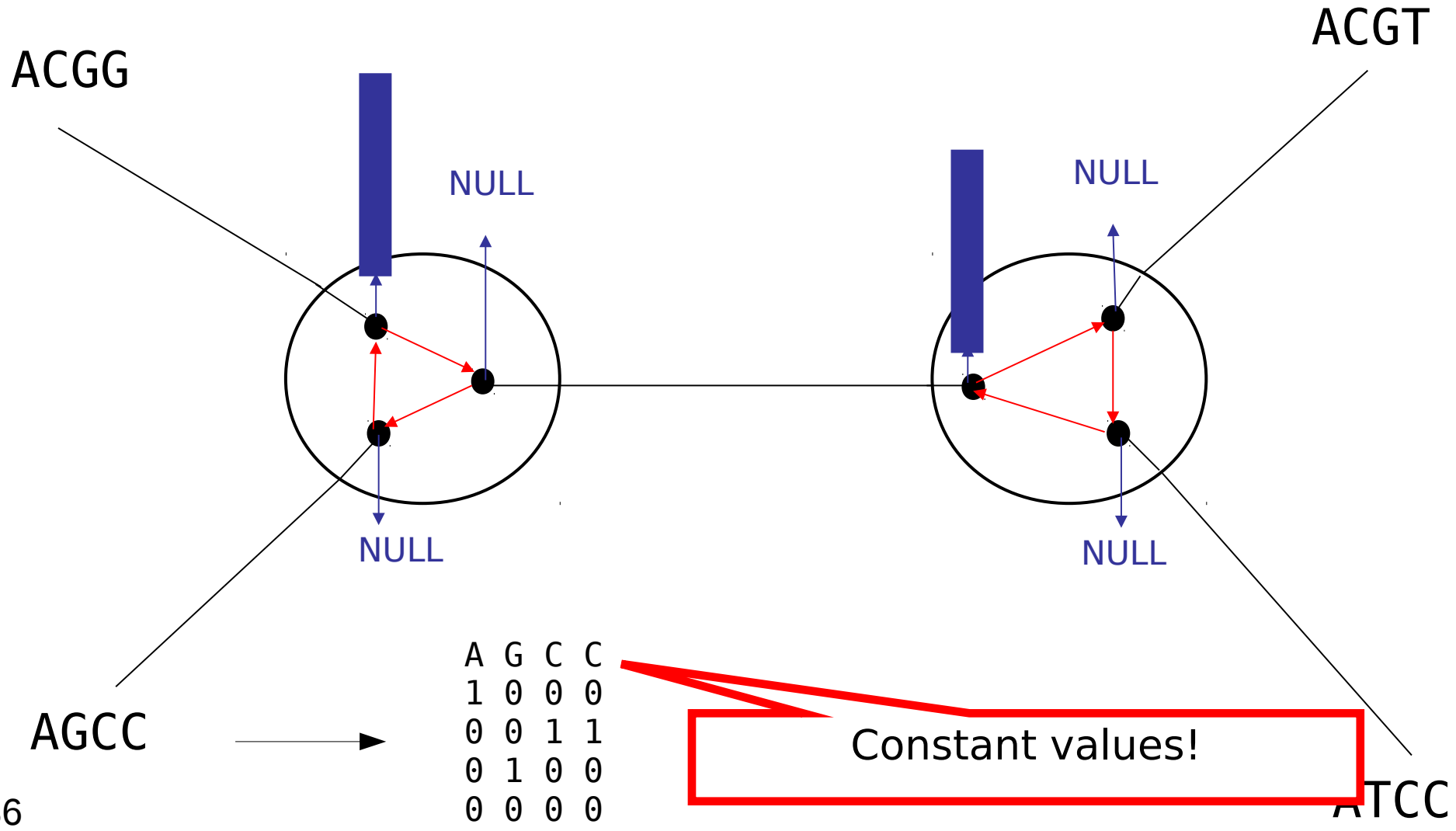


Memory Organization: Ancestral Vectors with a Rooted View

New Virtual Root



Memory Organization: Tip Vectors



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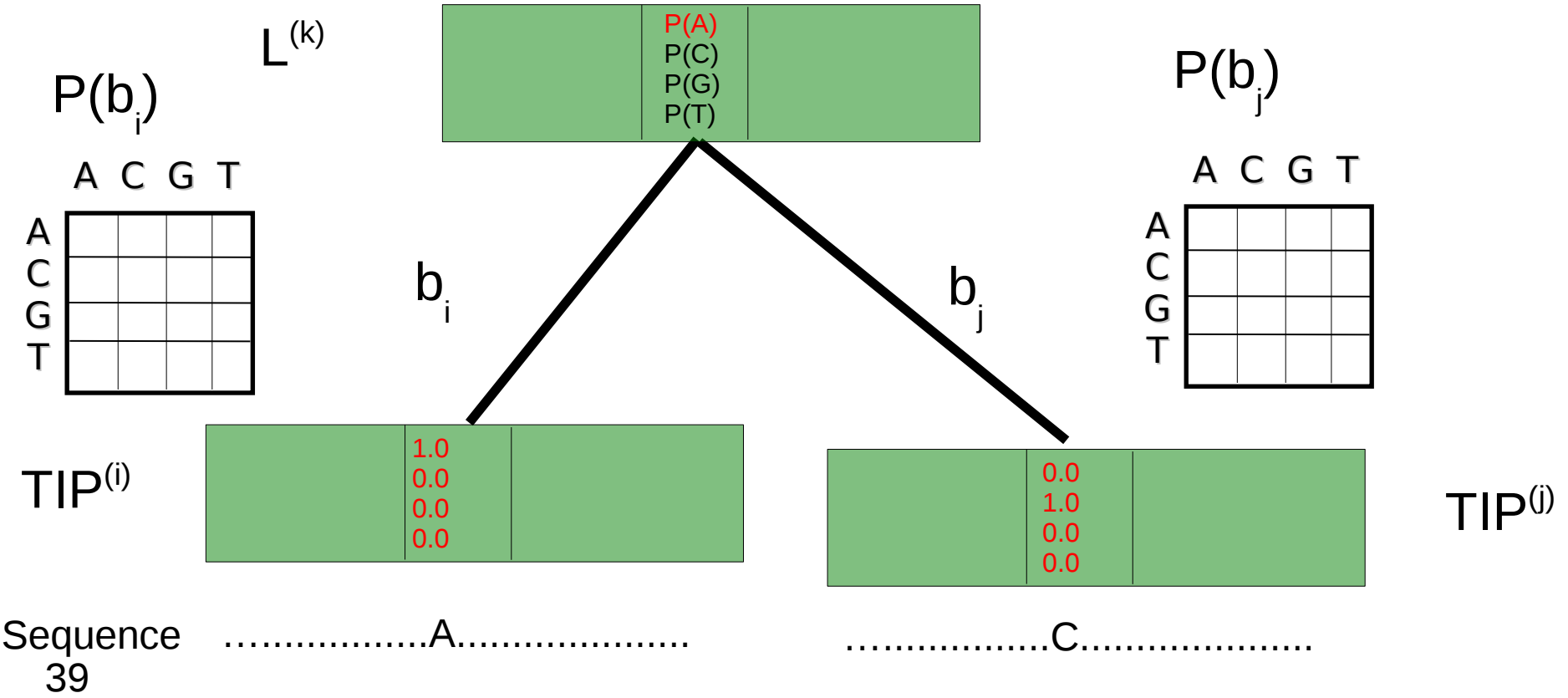
Optimization of Likelihood Calculations

- Use SSE3 & AVX vector intrinsics
- Also: GPUs, FPGAs, the Intel Xeon PHI
- Special implementations (why?) for computing CLVs:

What happens when we compute this inner vector?

$$\vec{L}_A^{(k)}(c) = \left(\sum_{S=A}^{T} P_{AS}(b_i)\vec{L}_S^{(i)}(c)\right)\left(\sum_{S=A}^{T} P_{AS}(b_j)\vec{L}_S^{(j)}(c)\right)$$



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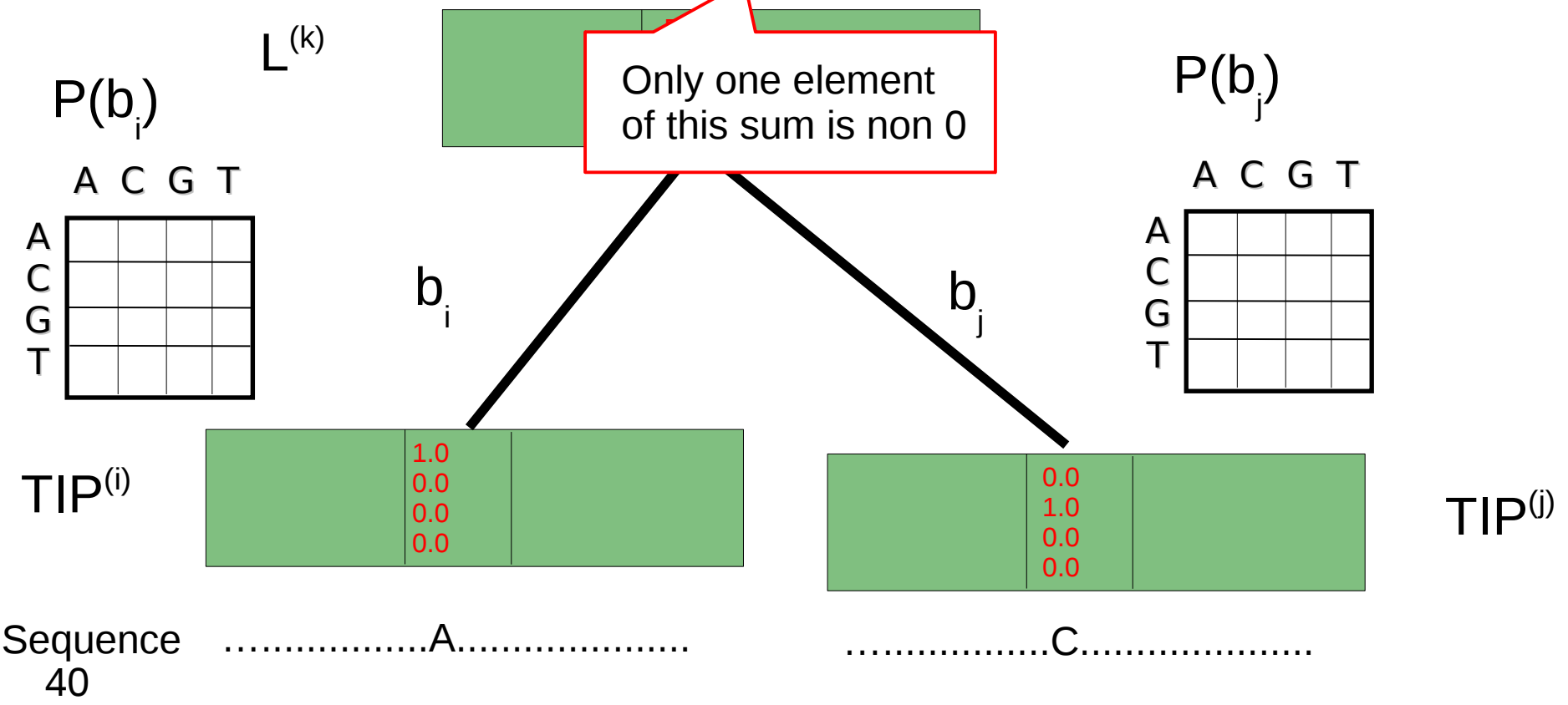

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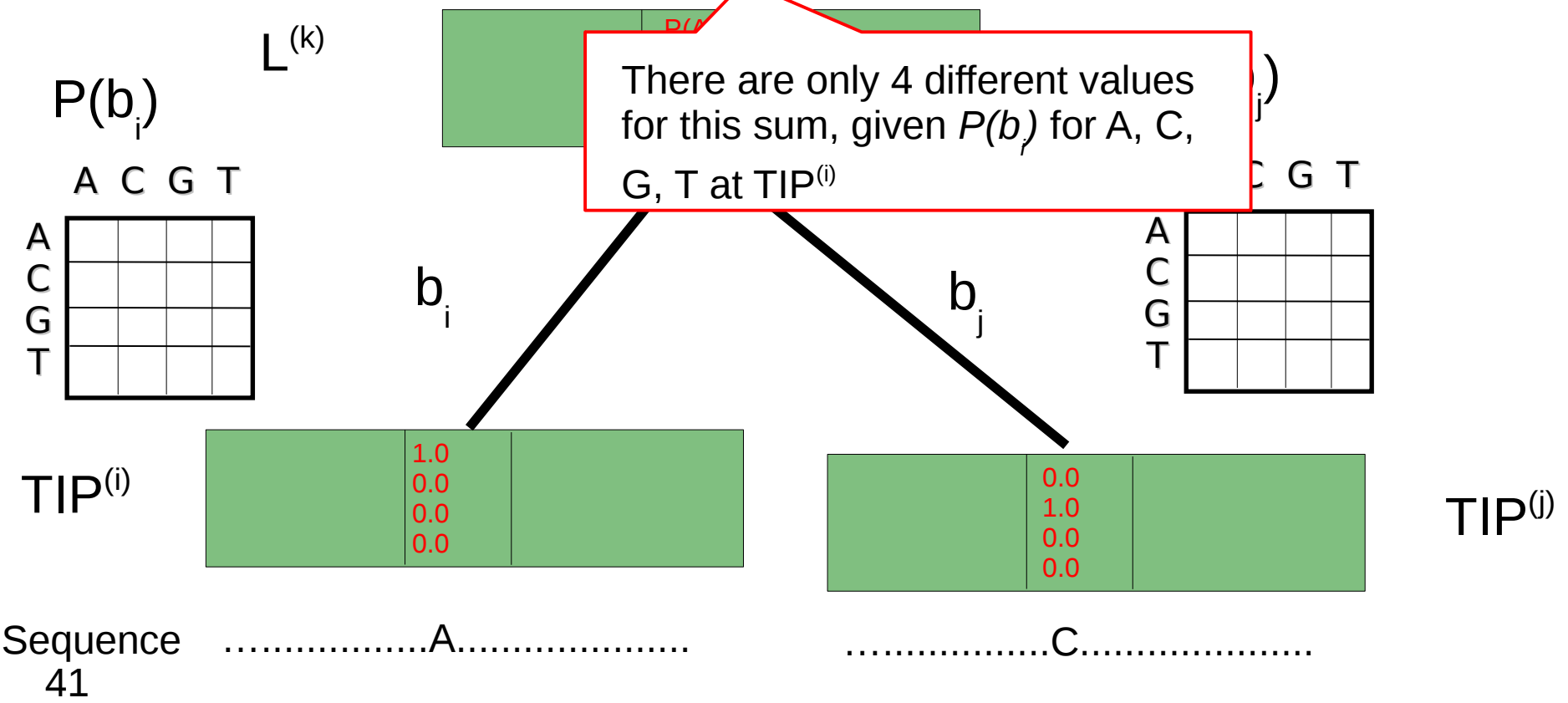
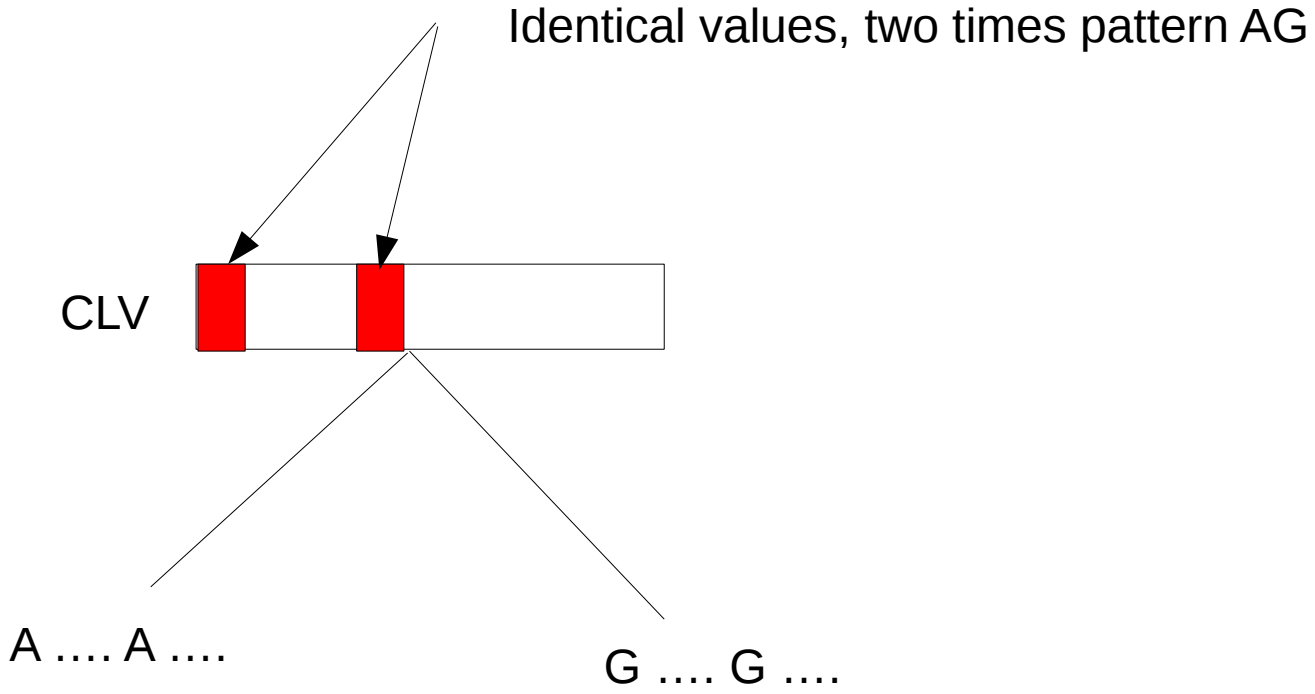


Repeating Patterns



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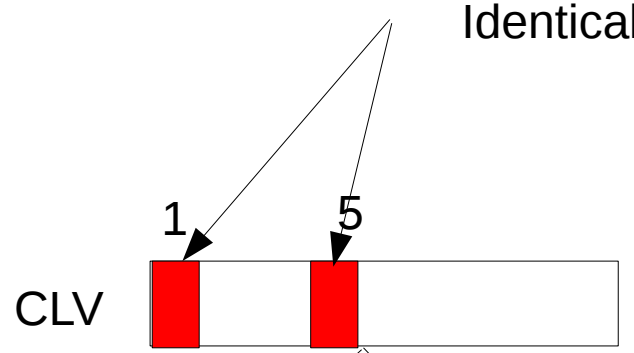

A .... A ....
1 5

G .... G ....
1 5

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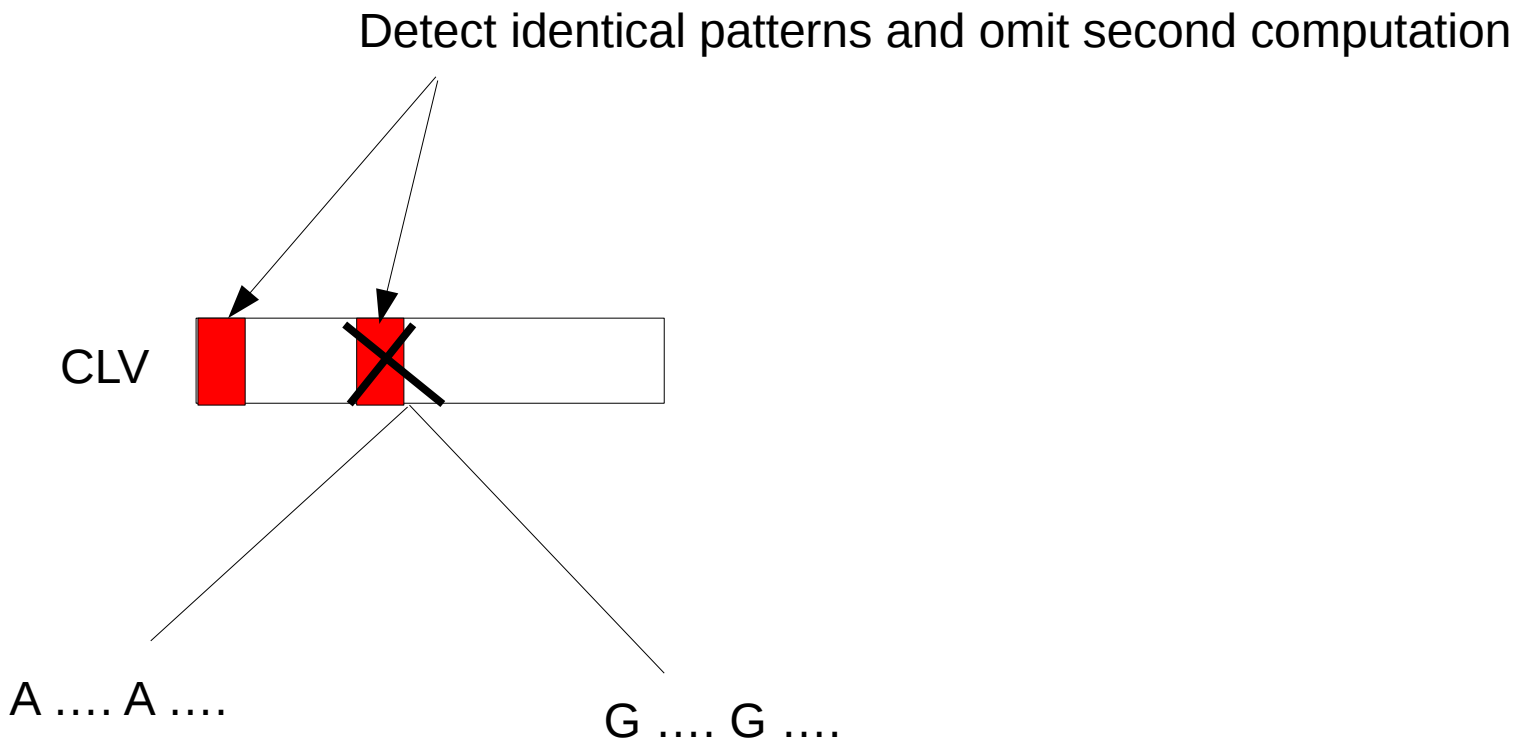
Result of this product is identical at alignment positions c = 1 and c = 5

Repeating Patterns



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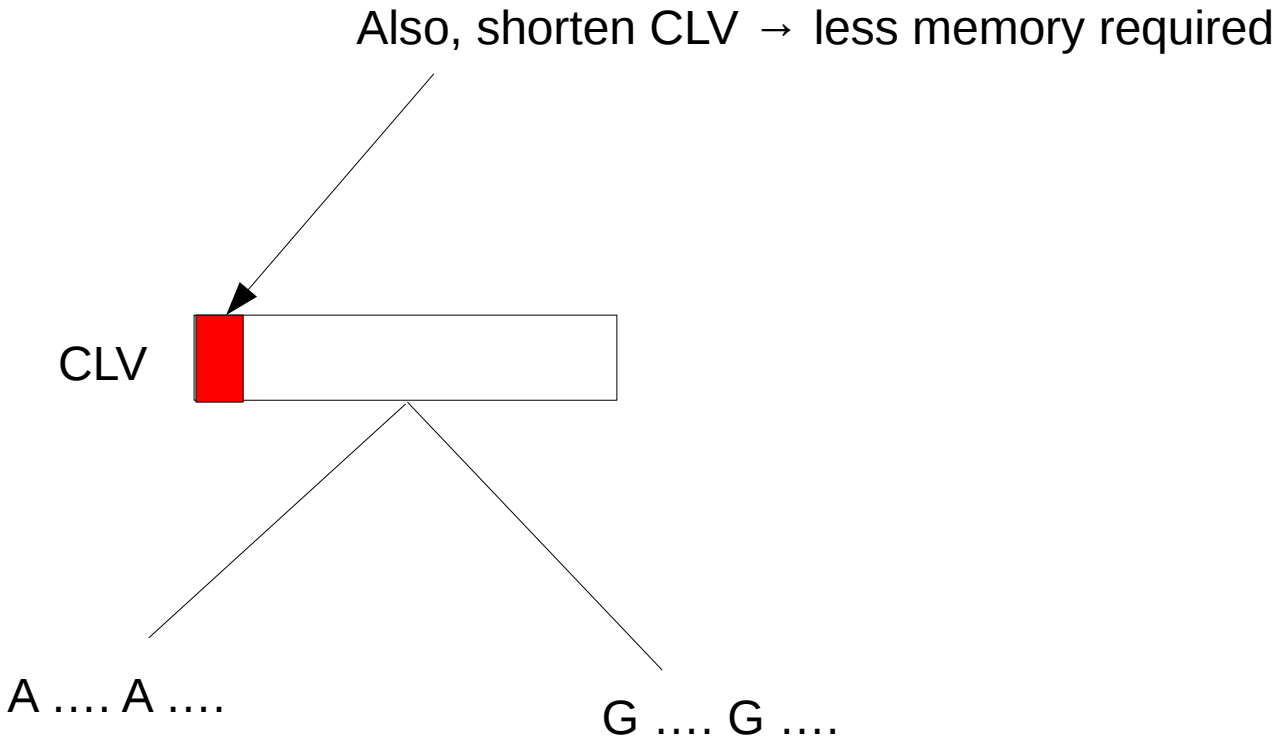

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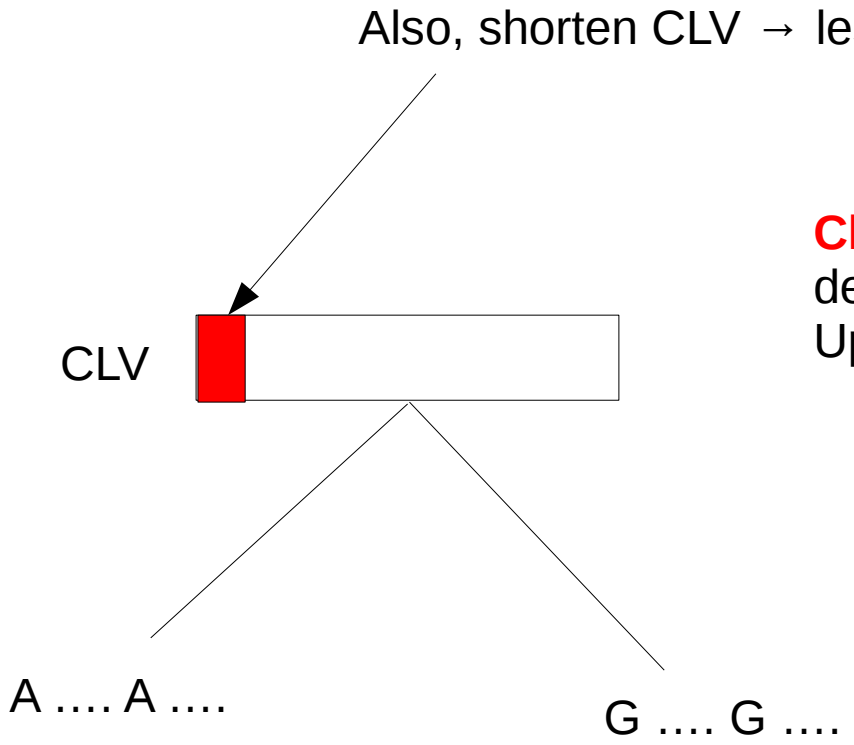
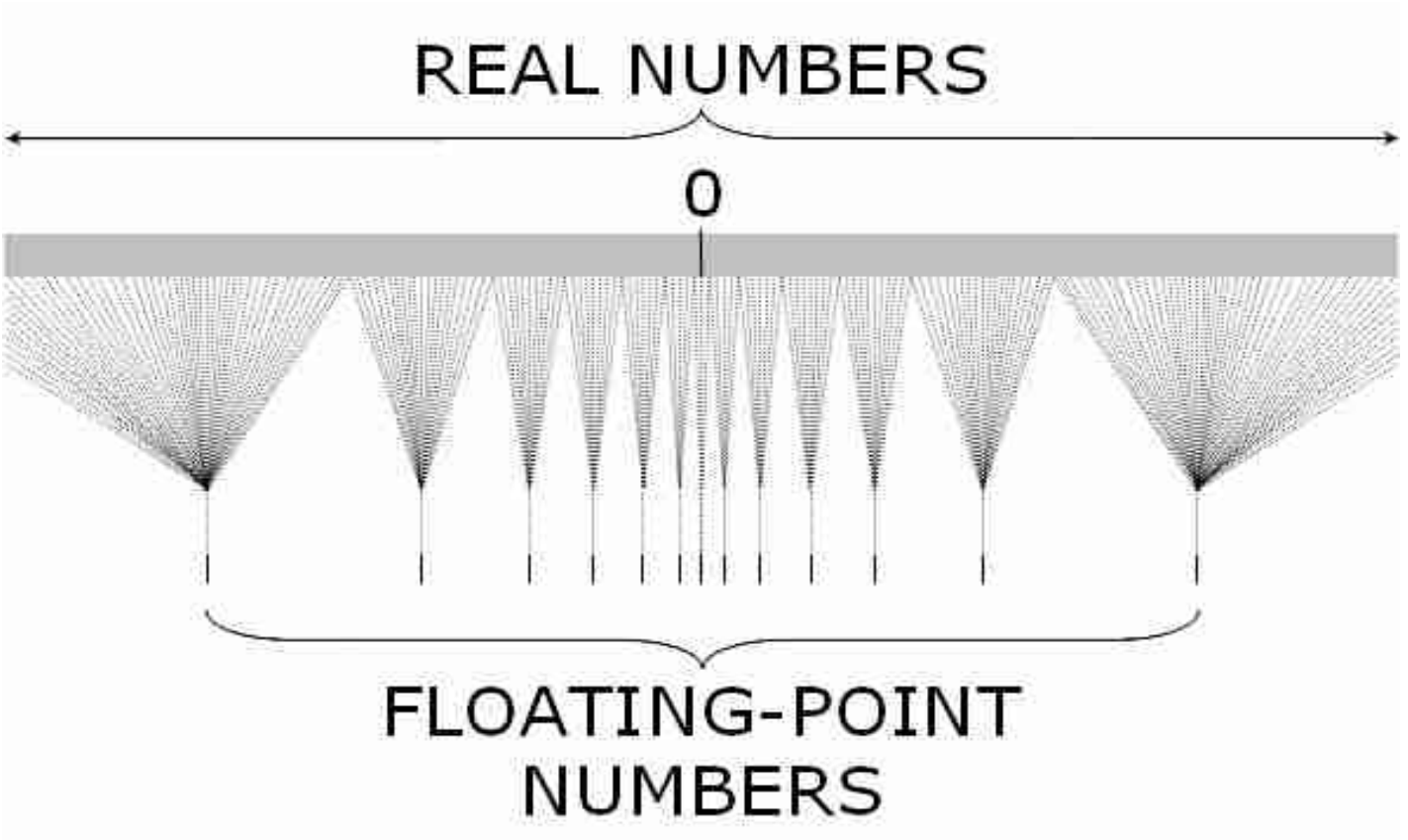


Challenge: Efficient data structure to detect & store repeats
Up to 10-fold run-time improvements

K Kobert, A Stamatakis, T Flouri
Efficient detection of repeating sites to accelerate phylogenetic likelihood calculations
Systematic Biology 66 (2), 205-217, 2017.

Floating Point Numbers

- Machine numbers are an imperfect mapping of the infinite real numbers to a finite number of machine values!



Floating Point Arithmetics: The Root of All Evil

- Computational science mostly relies on floating-point intensive codes
- How do we verify these codes?
- We stand on shaky grounds
- Scientists using those codes assume that there are no bugs
- Double precision arithmetics required for certain applications
- Who knows what de-normalized floating point numbers are?

→ Please have a look at:

J. Björndalen, O. Anshus: “Trusting floating point benchmarks-are your benchmarks really data-independent?” Applied Parallel Computing. State of the art in Scientific Computing 2010; pp 178-188, Springer.

and at my micro-benchmark at:
https://github.com/stamatak/denormalizedFloatingPointNumbers

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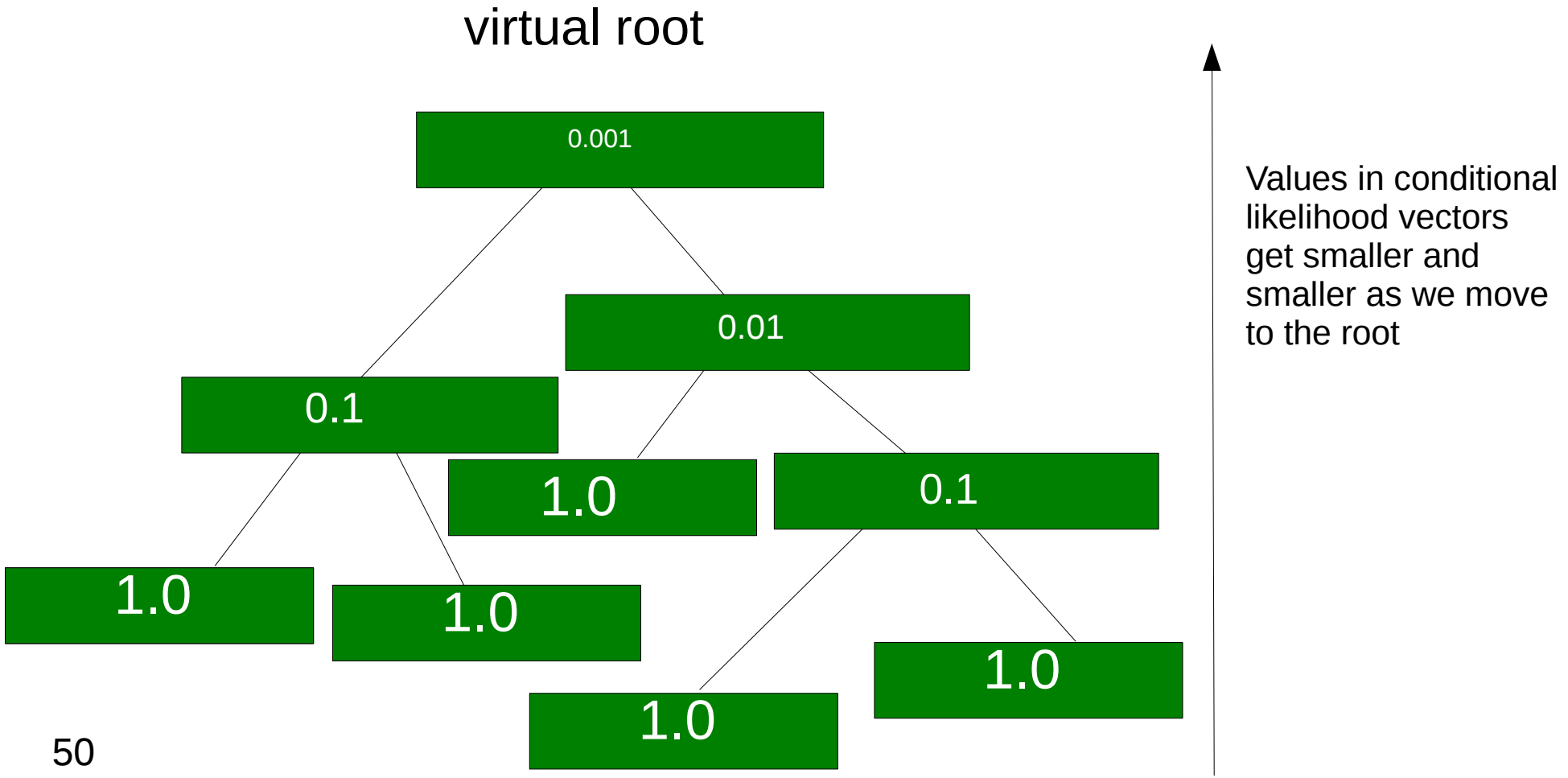
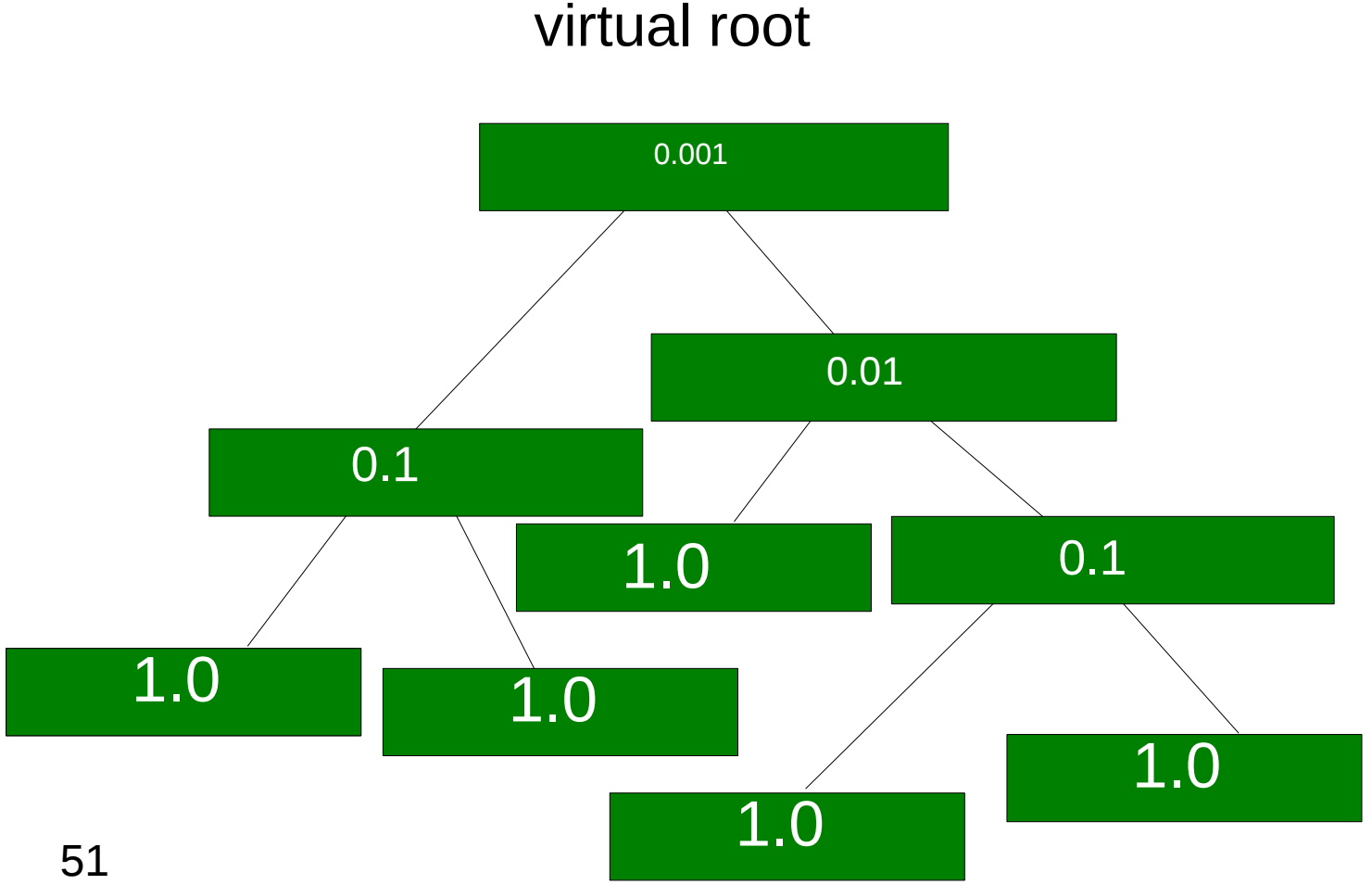
Why is this relevant when Talking about Maximum Likelihood?

Post-order Traversal



Post-order Traversal

We need to apply numerical scaling techniques to avoid underflow!



Values in conditional likelihood vectors get smaller and smaller as we move to the root → this needs to be handled!

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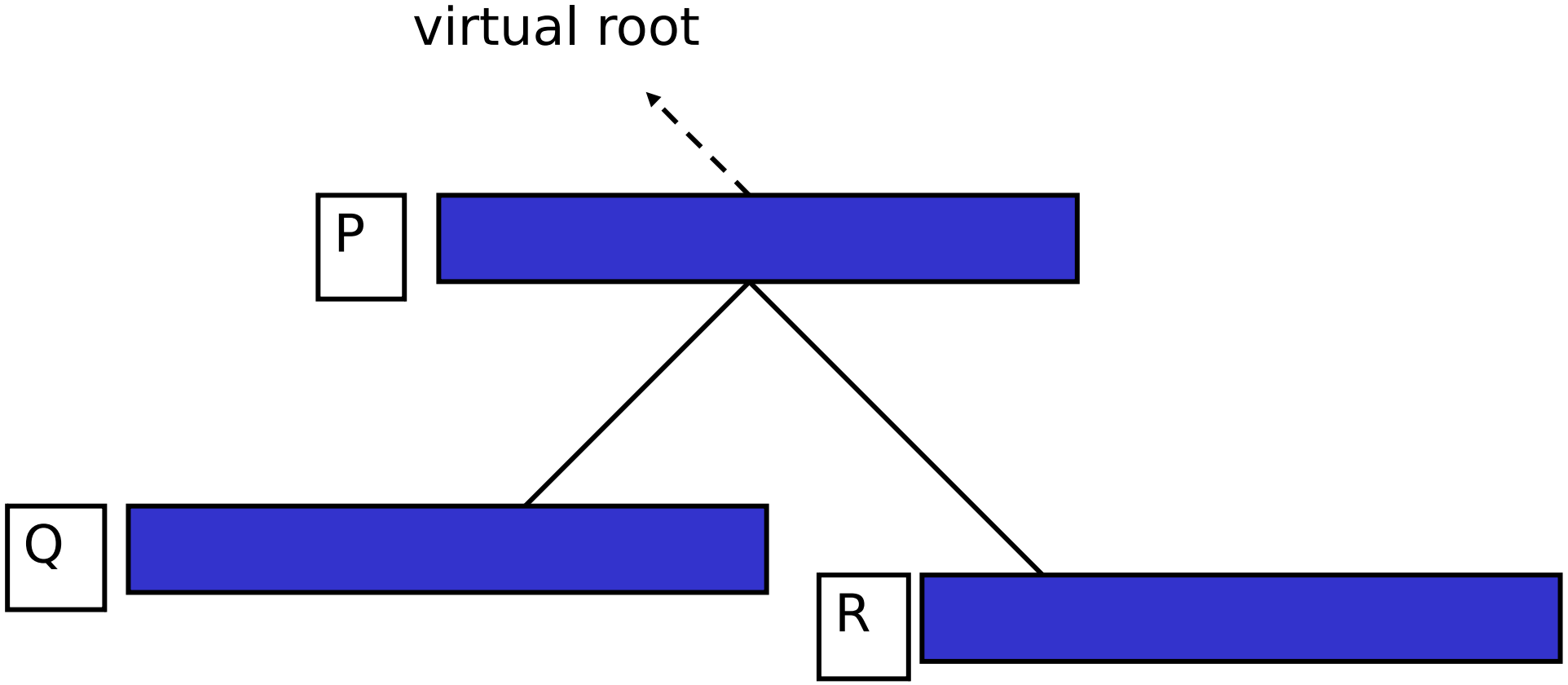
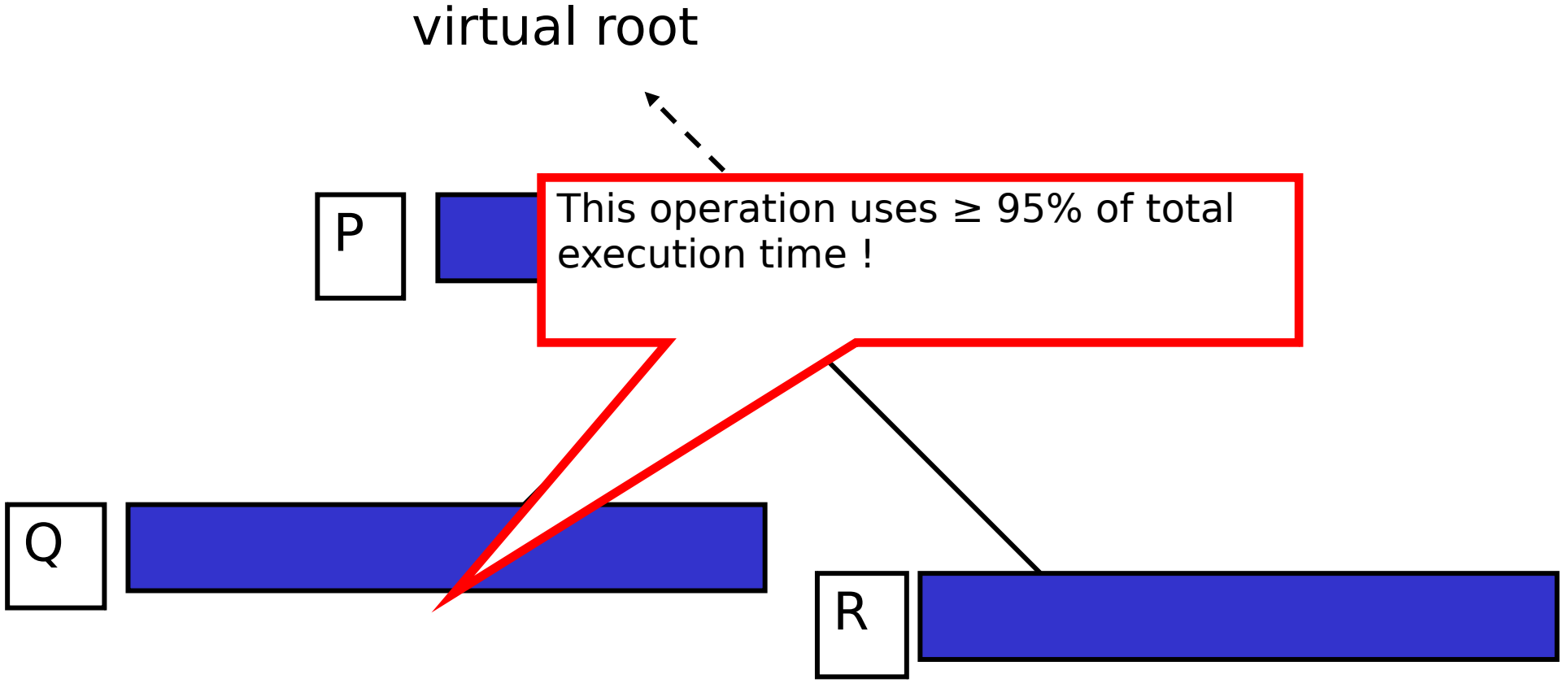
Loop Level Parallelism



P[i] = f(Q[i], R[i])

Loop Level Parallelism



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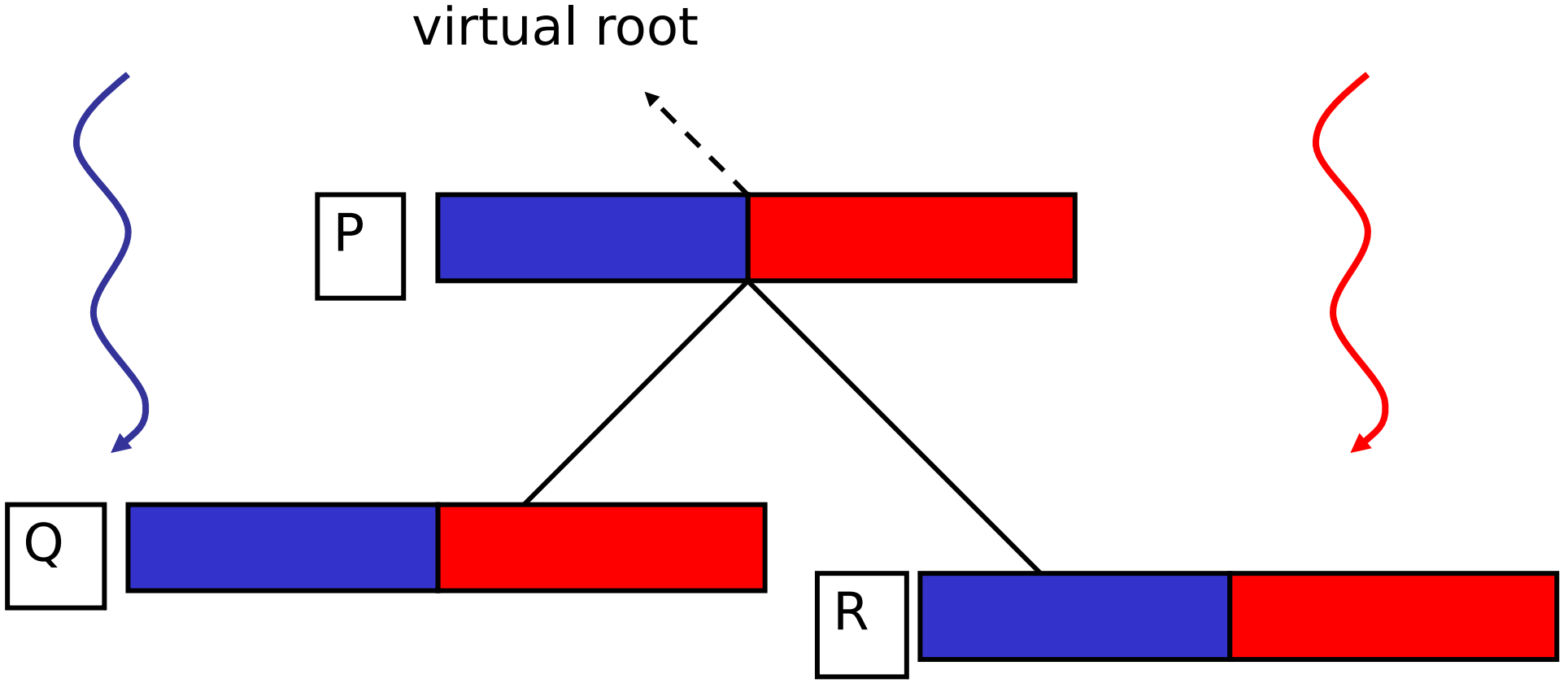
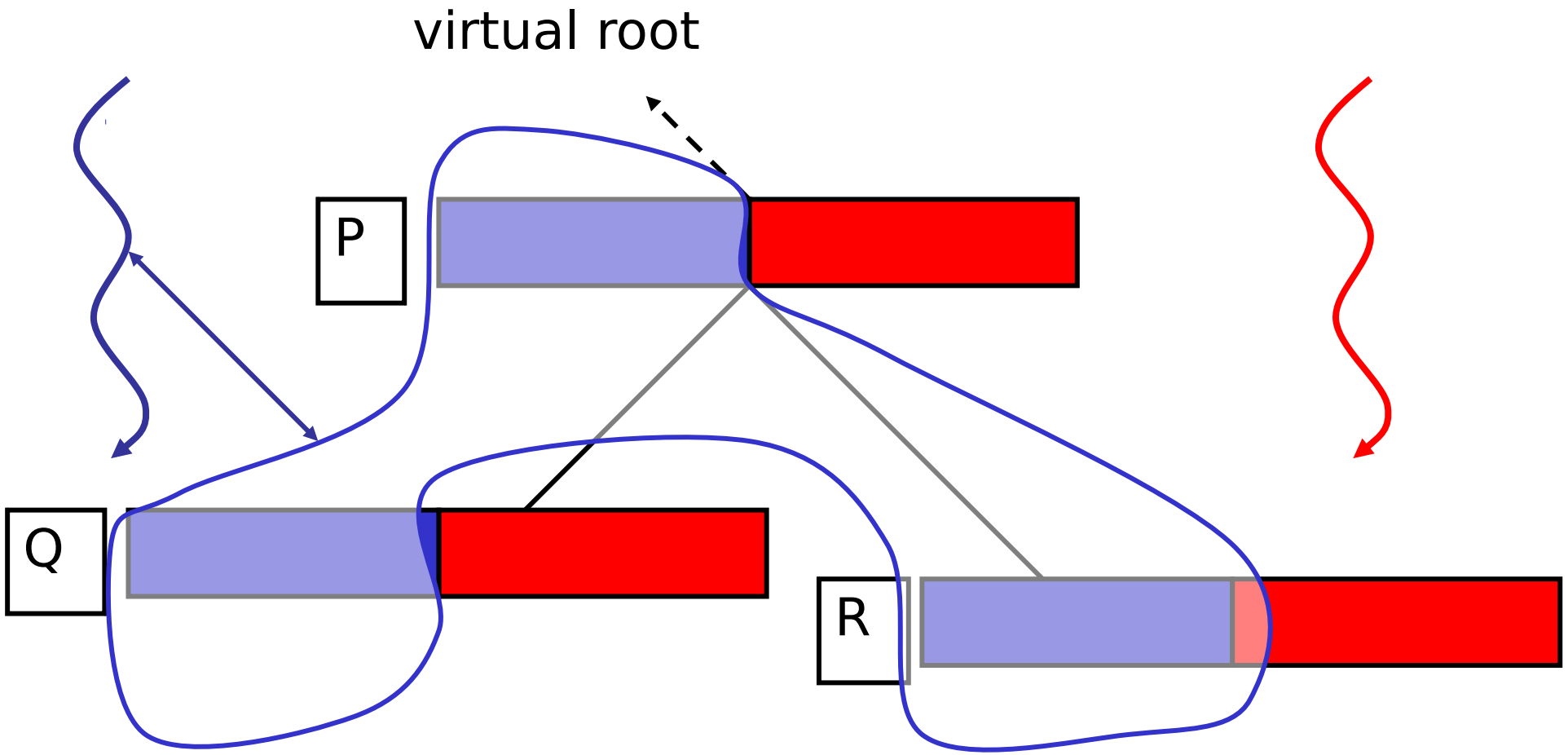
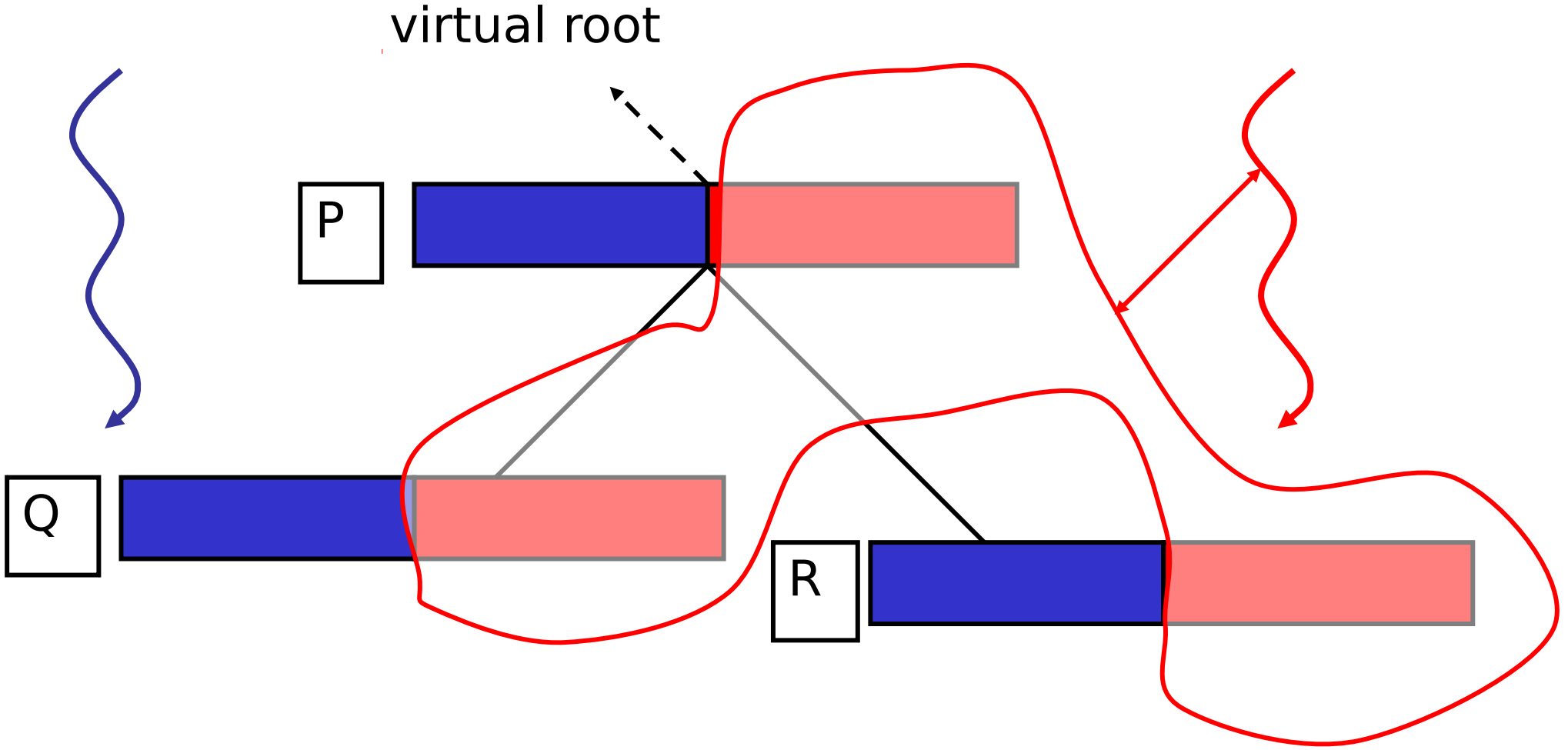
Loop Level Parallelism



Loop Level Parallelism



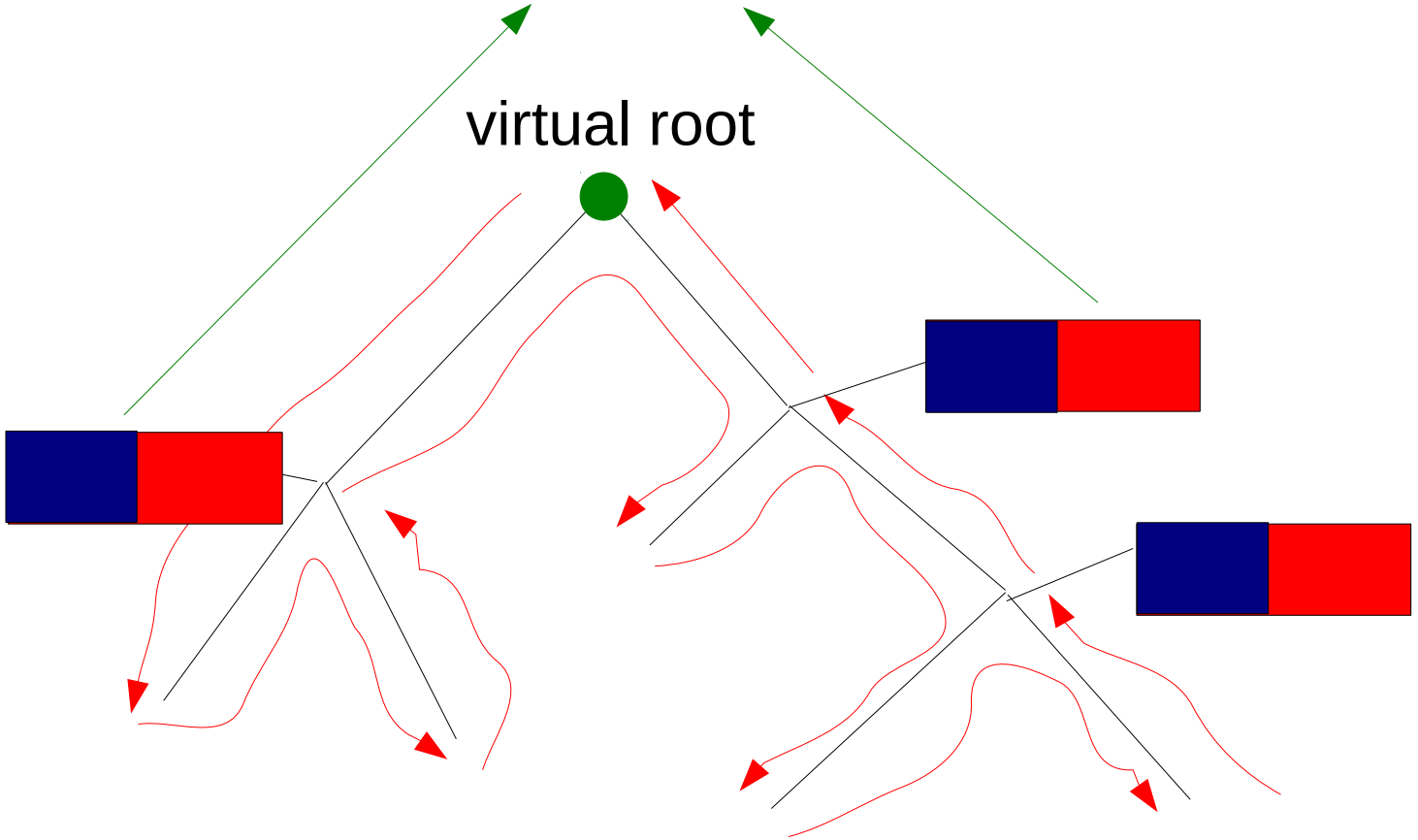
Loop Level Parallelism



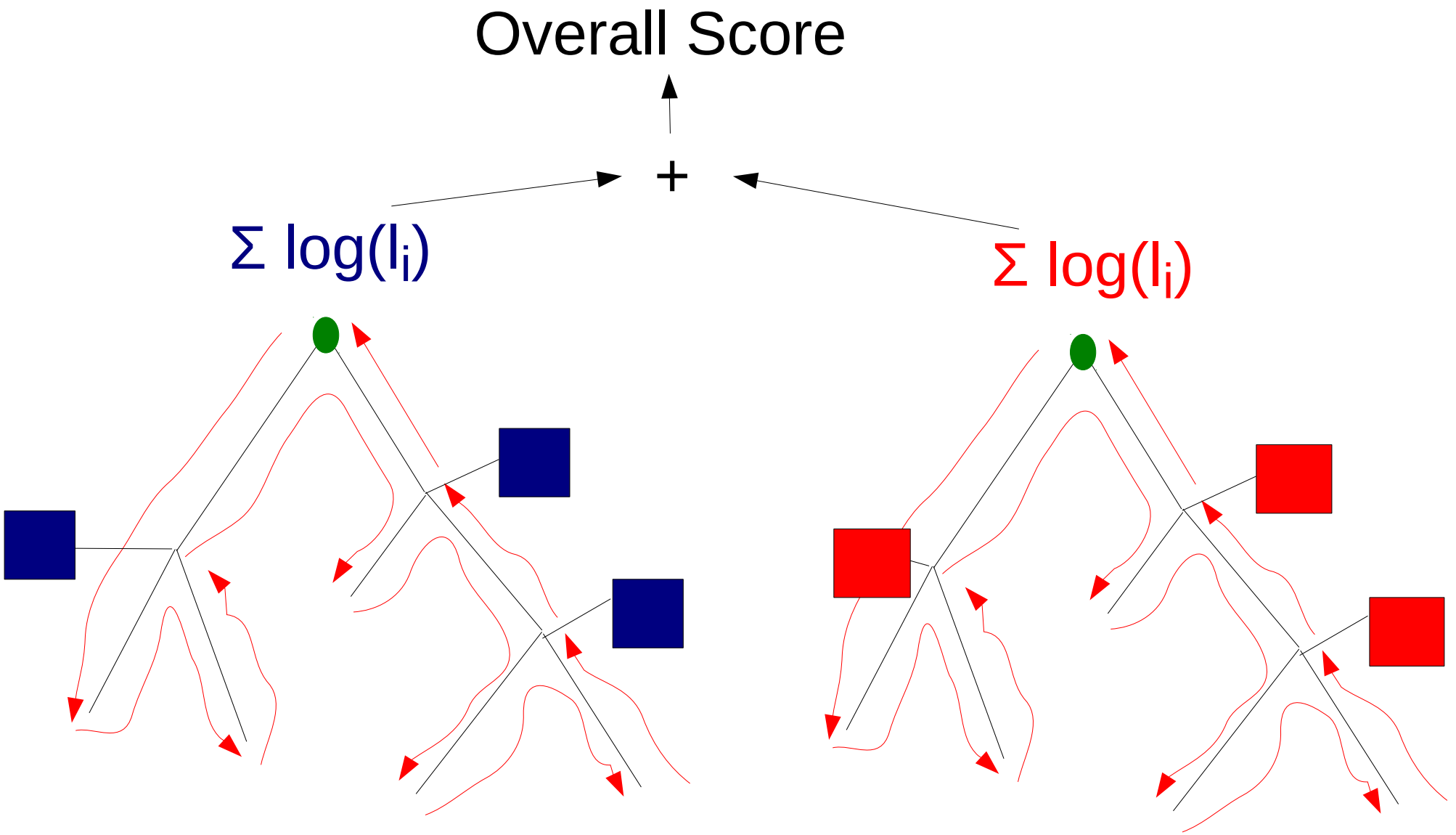
Parallel Post-order Traversal

Only need to synchronize at the root
→ MPI_Reduce() to calculate:

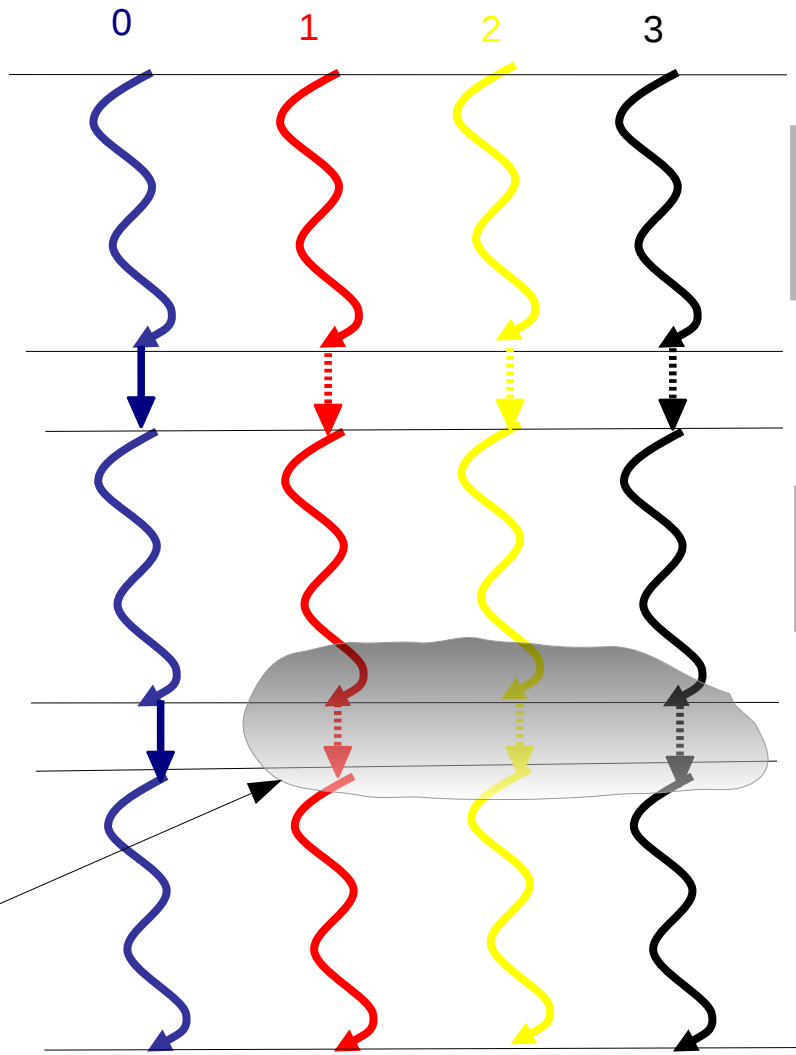
$\Sigma \log(l_i)$



Parallel Post-order Traversal



Classic Fork-Join with Busy-Wait



Broadcast Traversal — Trigger

Compute all vectors in Traversal descriptor

Reduce $\Sigma \log(l_i)$ — Barrier

Broadcast Traversal — Trigger

Compute all vectors in Traversal descriptor

Reduce $\Sigma \log(l_i)$ — Barrier

Broadcast new α params. — Trigger

Compute all vectors in Traversal descriptor

Reduce $\Sigma \log(l_i)$ — Barrier

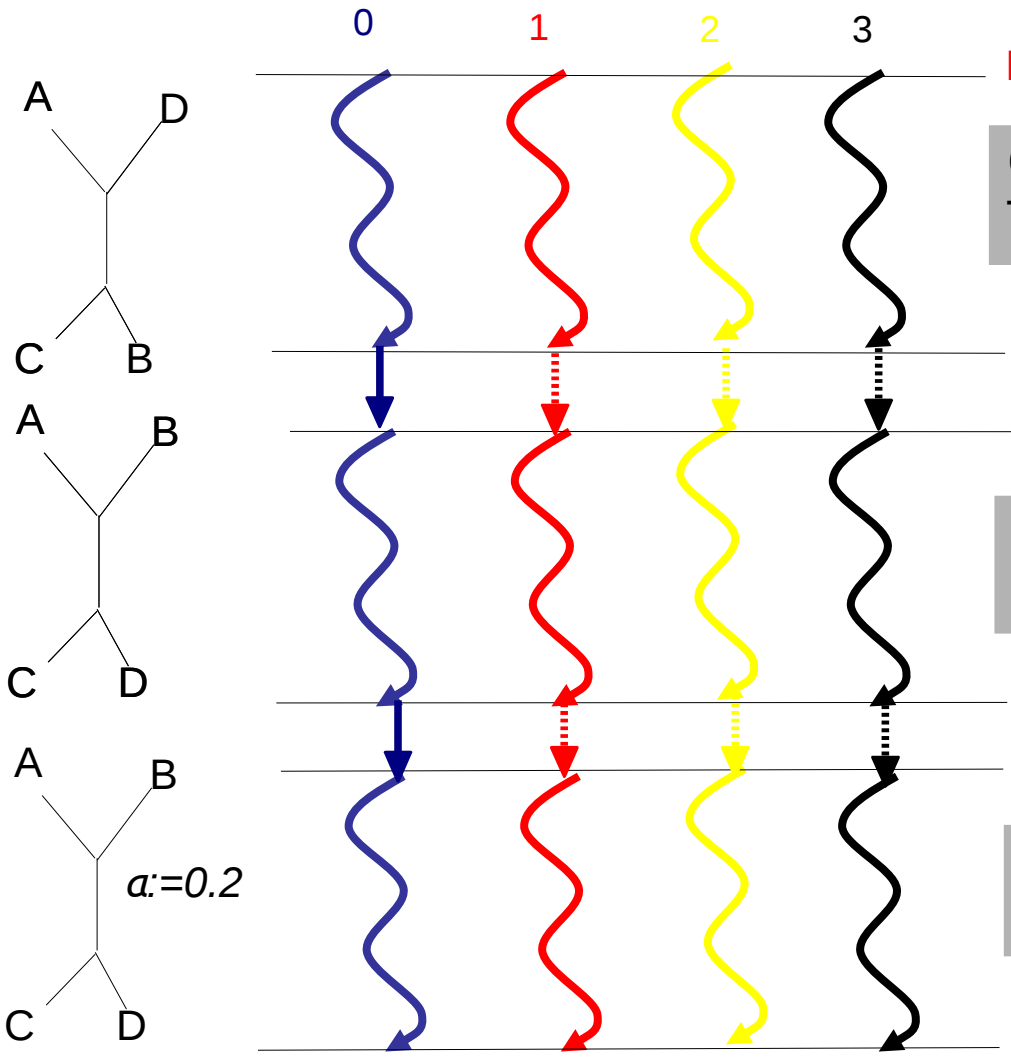
Busy wait

Synchronizations in RAxML with Pthreads

- RAxML Pthreads for a run time of about **10 seconds** on 16 cores/threads
- 404 taxa 7429 sites: **194,000** Barriers
- 1481 taxa 1241 sites: **739,000** Barriers
- A paper on performance of alternative PThreads barrier implementations:

  S.A. Berger, A. Stamatakis: "Assessment of Barrier Implementions for Fine-Grain Parallel Regions on Current Multi-core Architectures", *IEEE Cluster* 2010.

Classic Fork-Join with Busy-Wait



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Compute all vectors in Traversal descriptor

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Compute all vectors in Traversal descriptor

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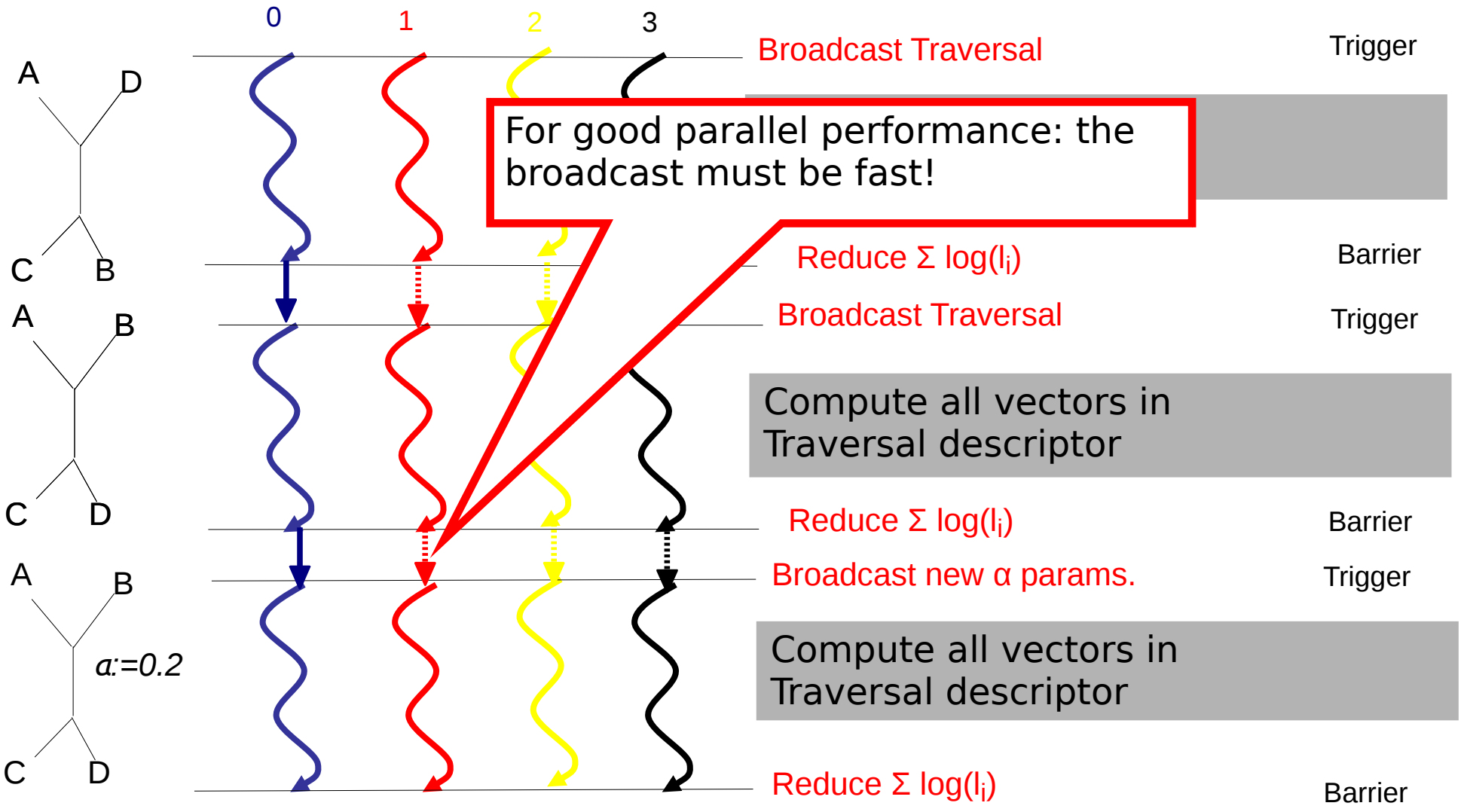
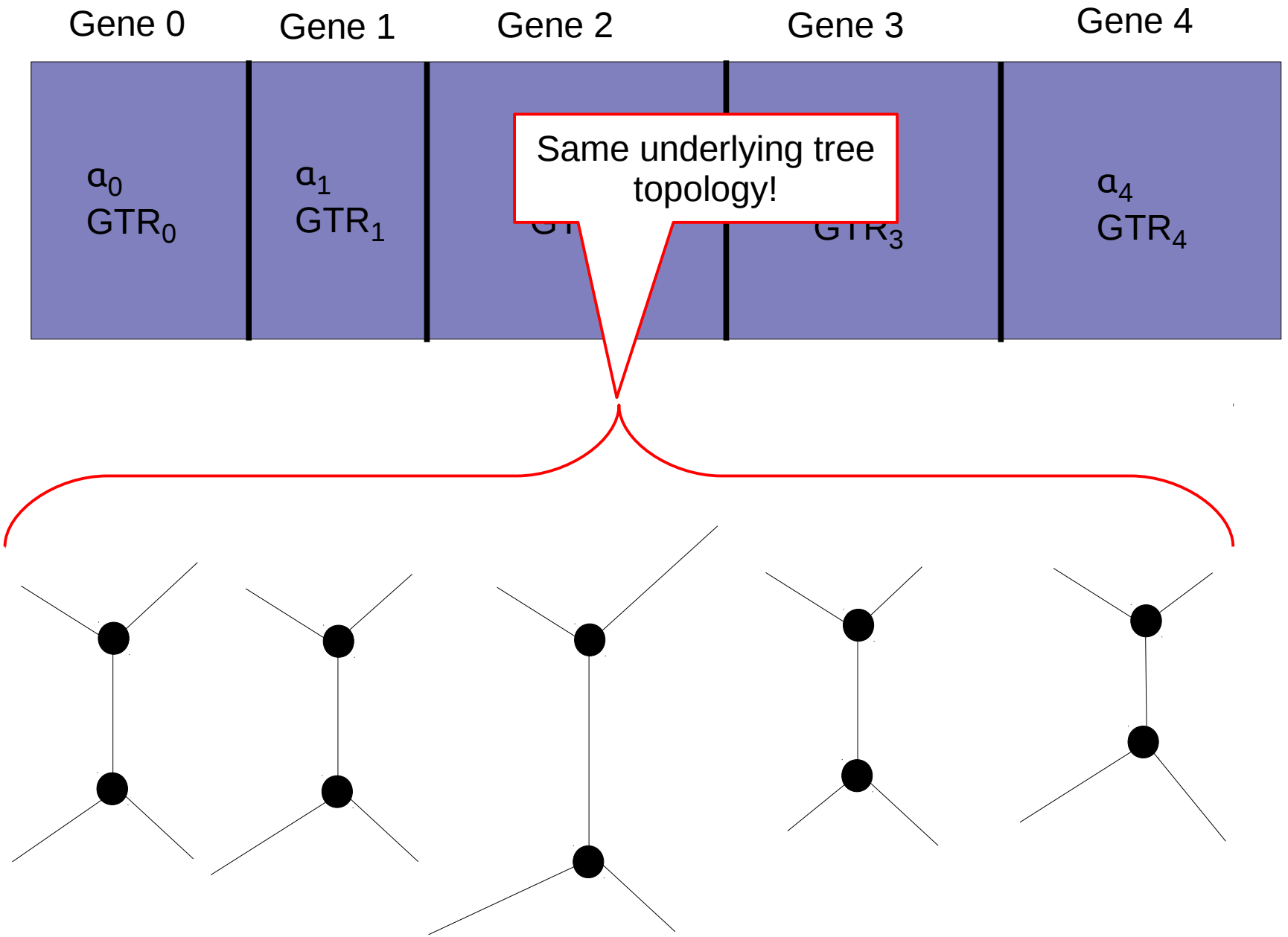
Compute all vectors in Traversal descriptor

Reduce $\Sigma \log(l_i)$ — Barrier

Classic Fork-Join with Busy-Wait



Problems start with partitioned datasets!

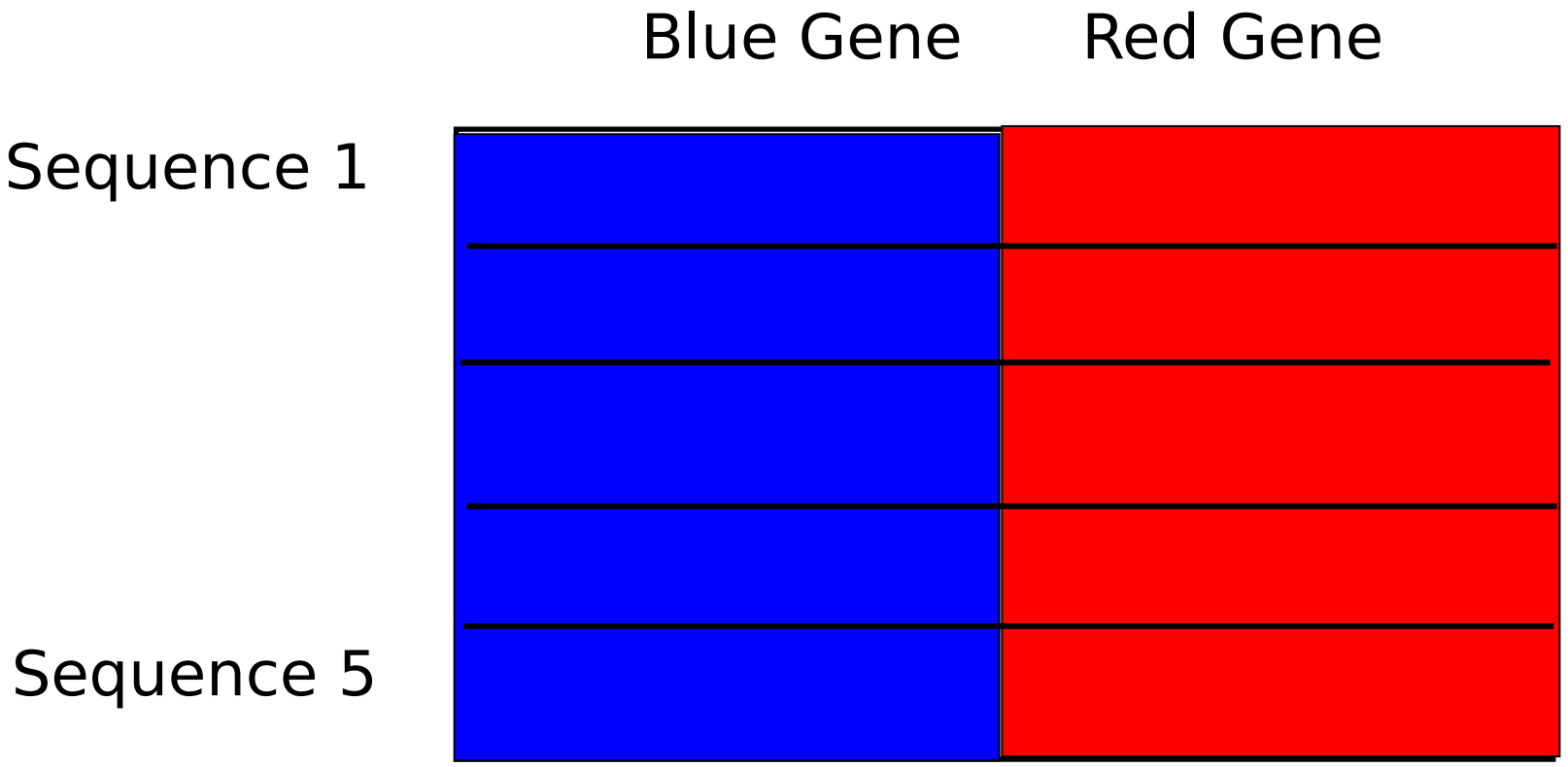


Parallel Performance Problems

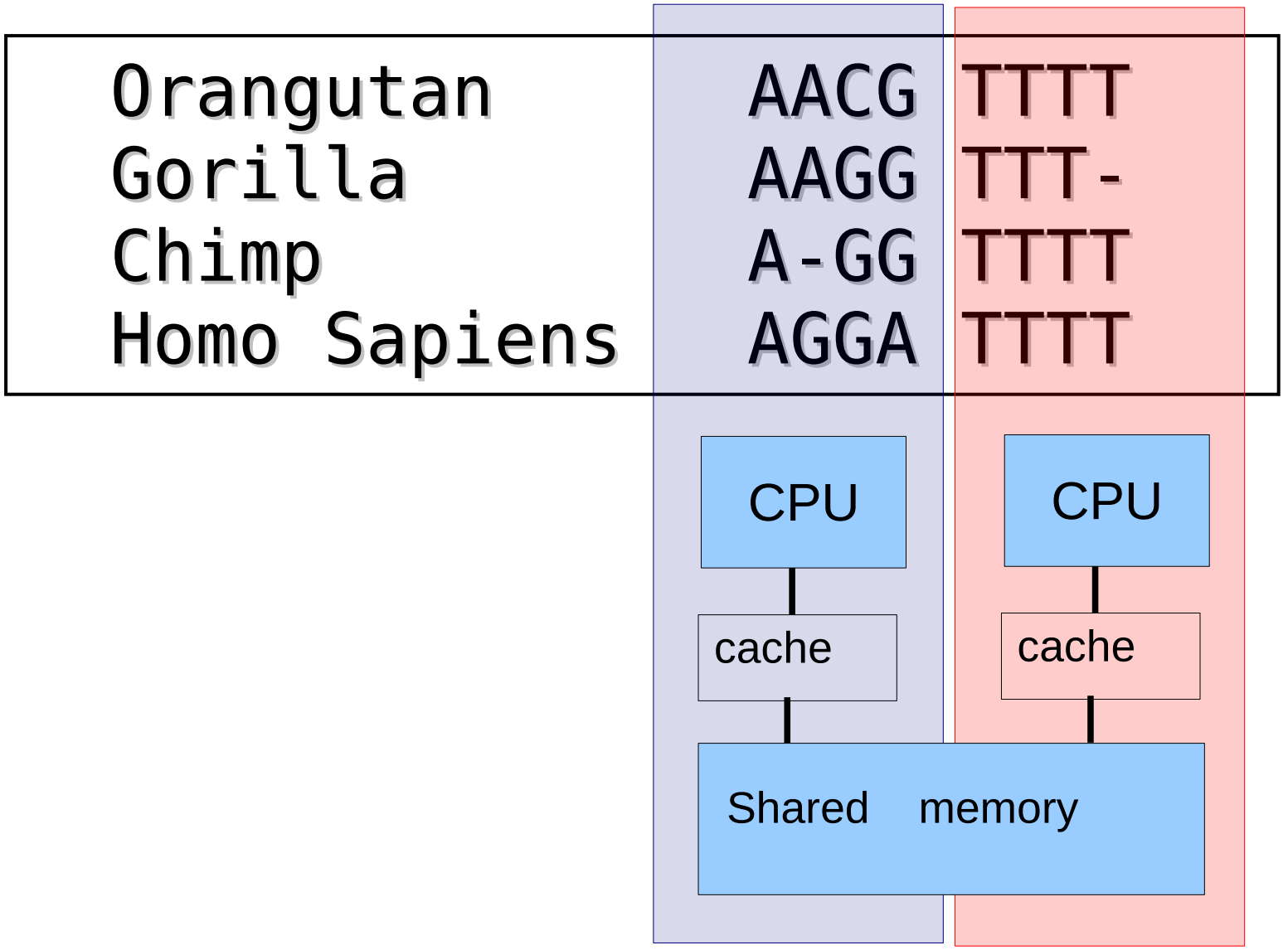
- They all start with partitioned datasets!
- How do we distribute partitions to processors?
- How do we calculate parameter changes?
- How much time does our broadcast take?
- Goal: Keep all processors busy all the time

  → minimize communication and synchronization!

Example

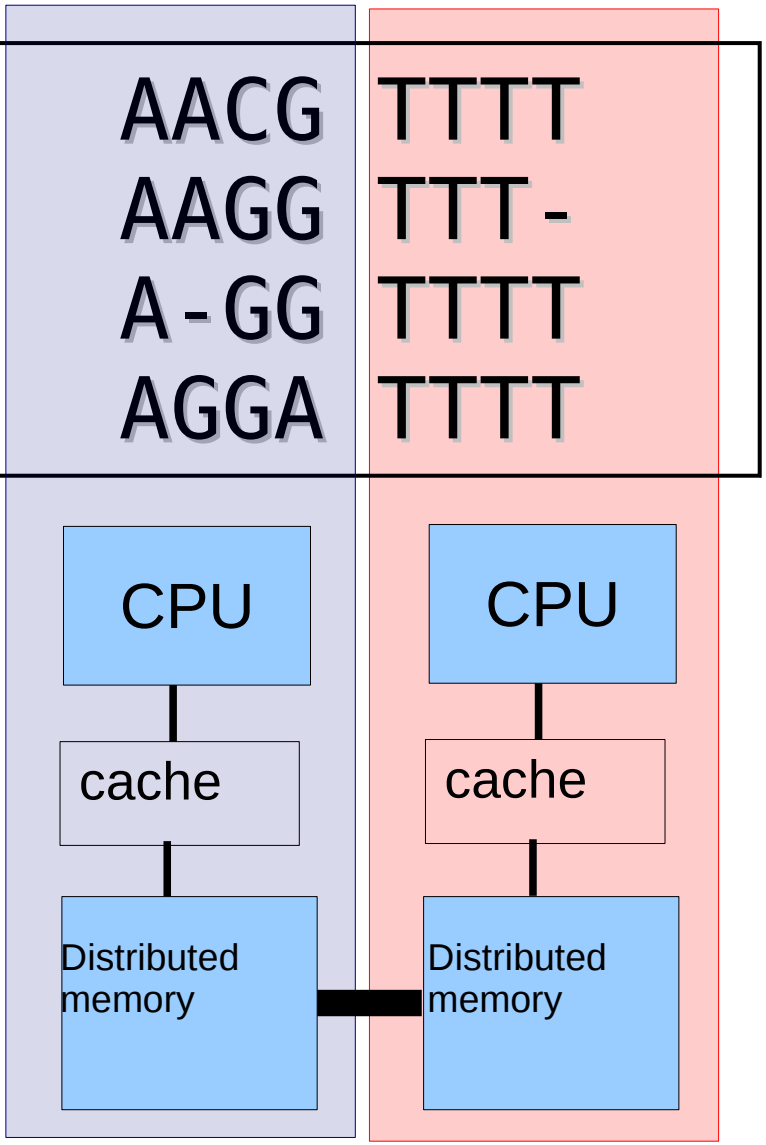


Data Distribution



Data Distribution

```
Orangutan      AACG TTTT
Gorilla        AAGG TTT-
Chimp          A-GG TTTT
Homo Sapiens   AGGA TTTT
```



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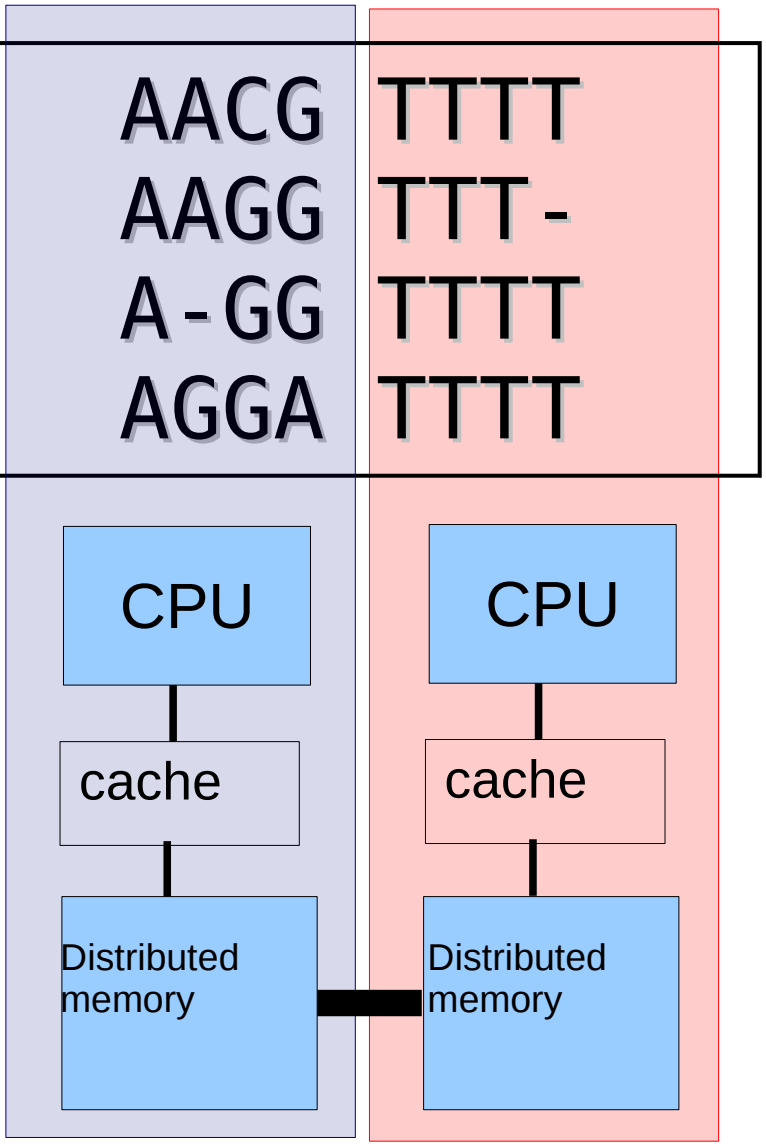

Partitioned data distribution is not that trivial!

Data Distribution I

```
Orangutan      AACG TTTT
Gorilla        AAGG TTT-
Chimp          A-GG TTTT
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```

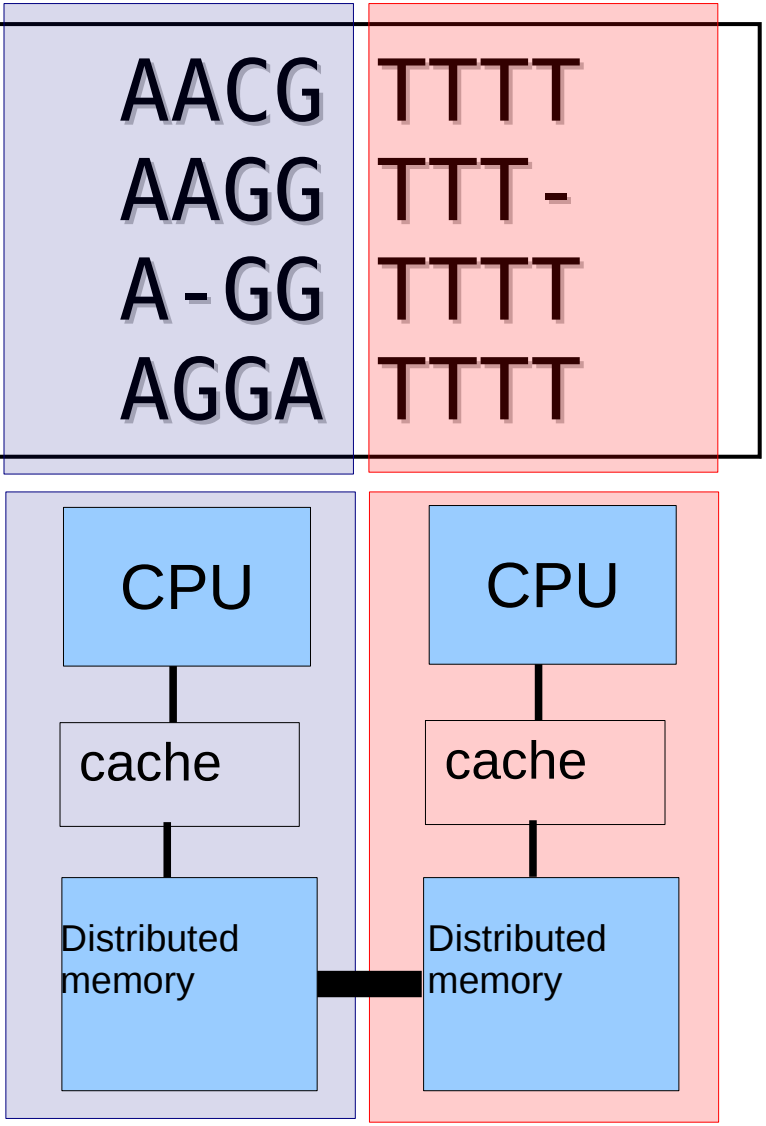

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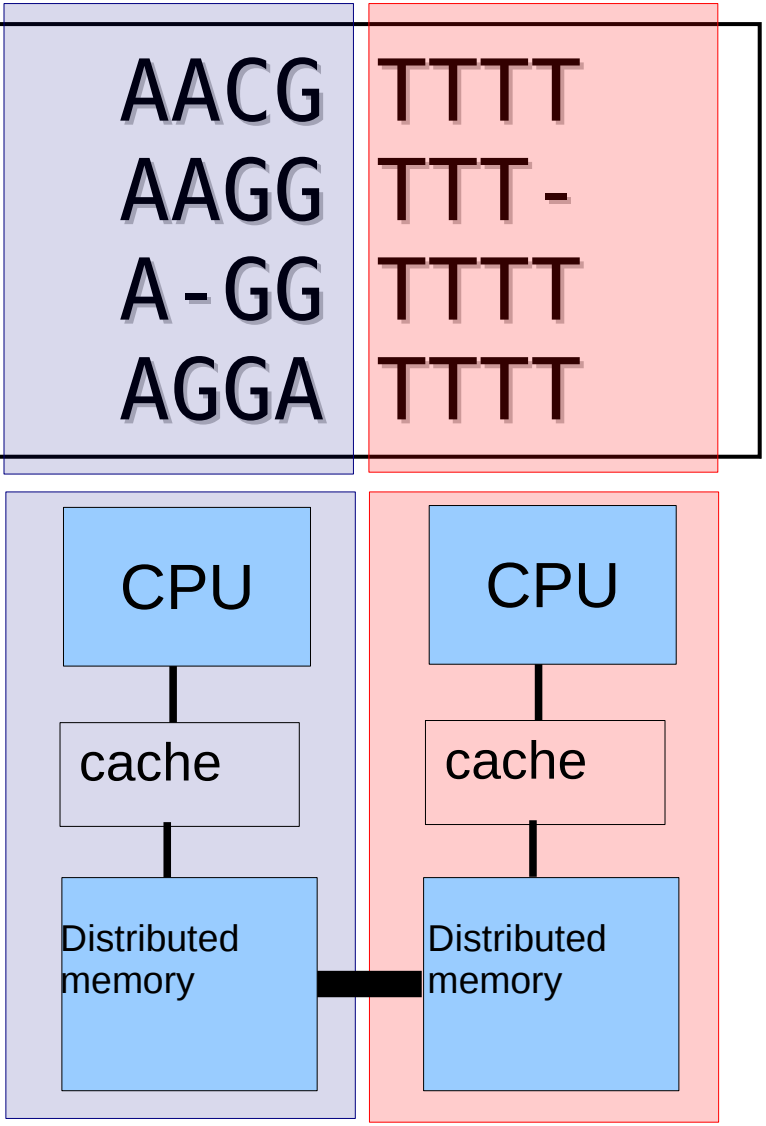
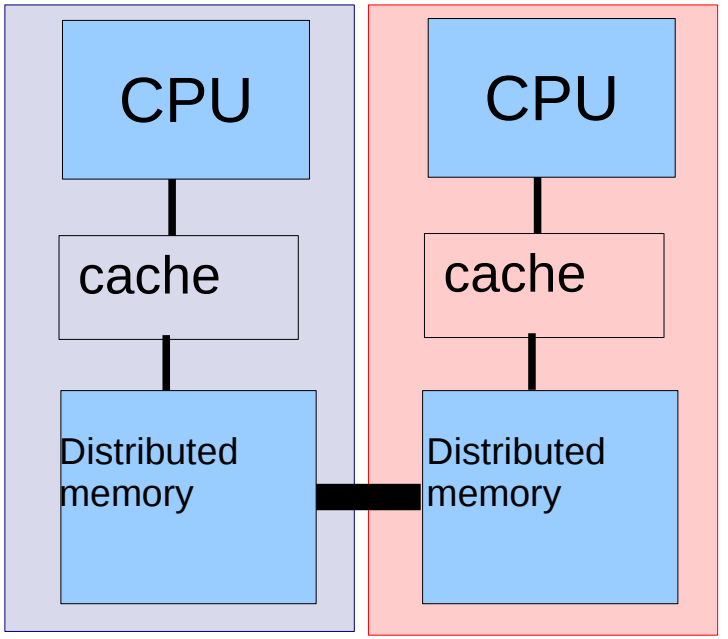


Works well when we have more partitions than processors:
May lead to load imbalance not all processors obtain equal number of sites!

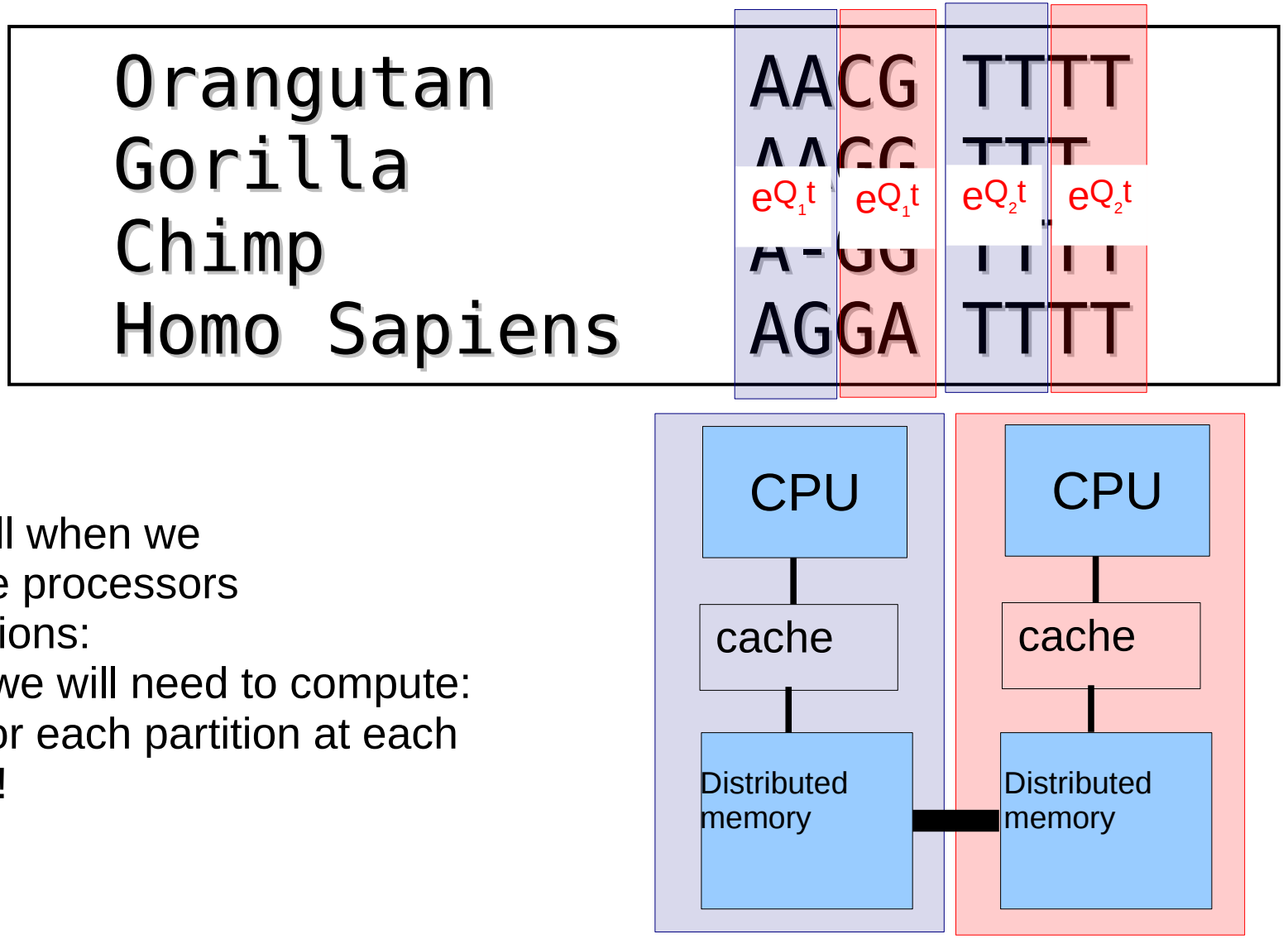
Data Distribution II

```
Orangutan      AACG TTTT
Gorilla        AAGG TTT-
Chimp          A-GG TTTT
Homo Sapiens   AGGA TTTT
```



Works well when we have more processors than partitions:
However we will need to compute: $P(t)=e^{Qt}$ for each partition at each processor!

Data Distribution II



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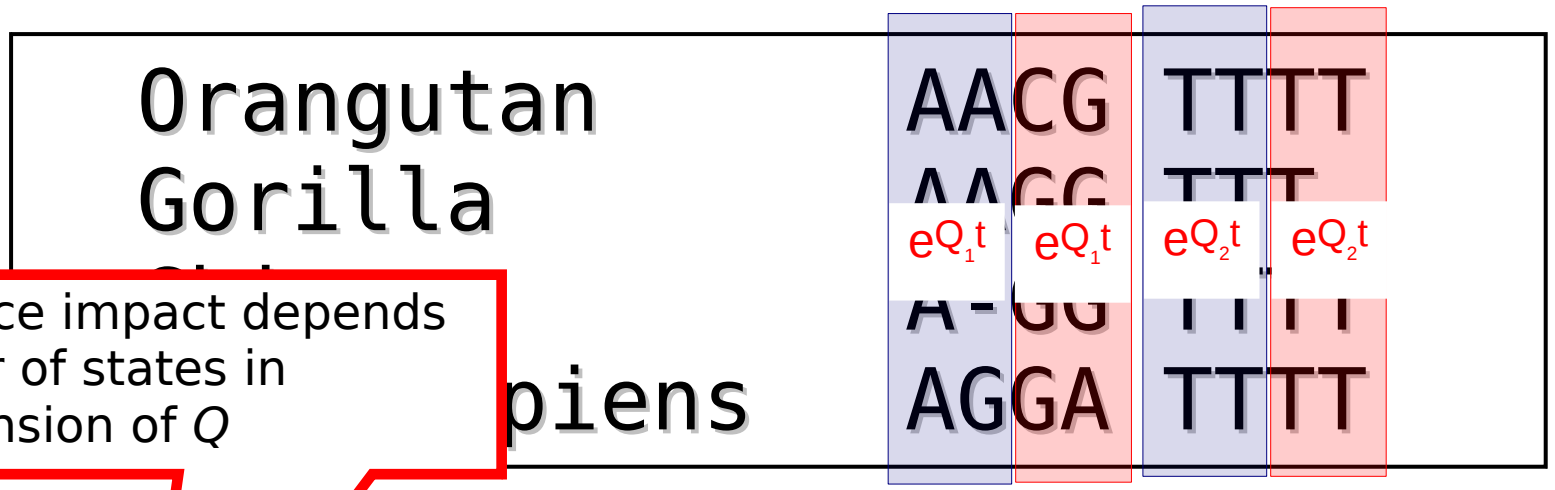
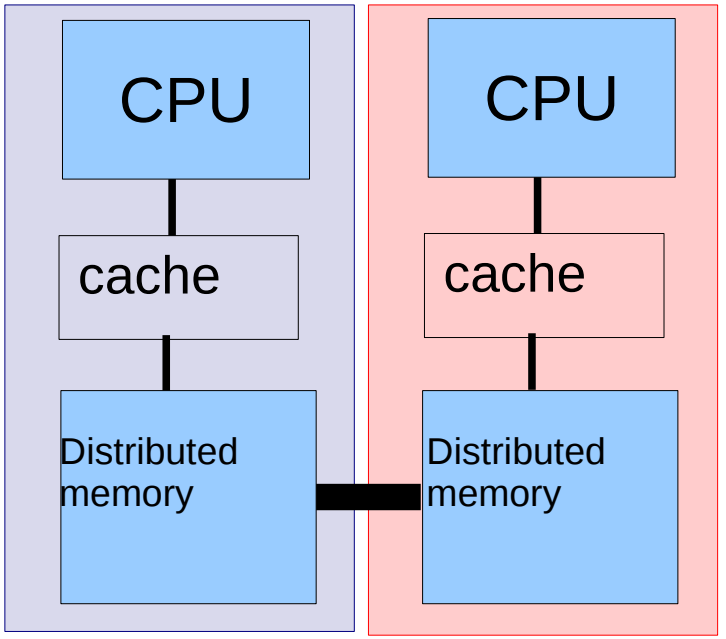
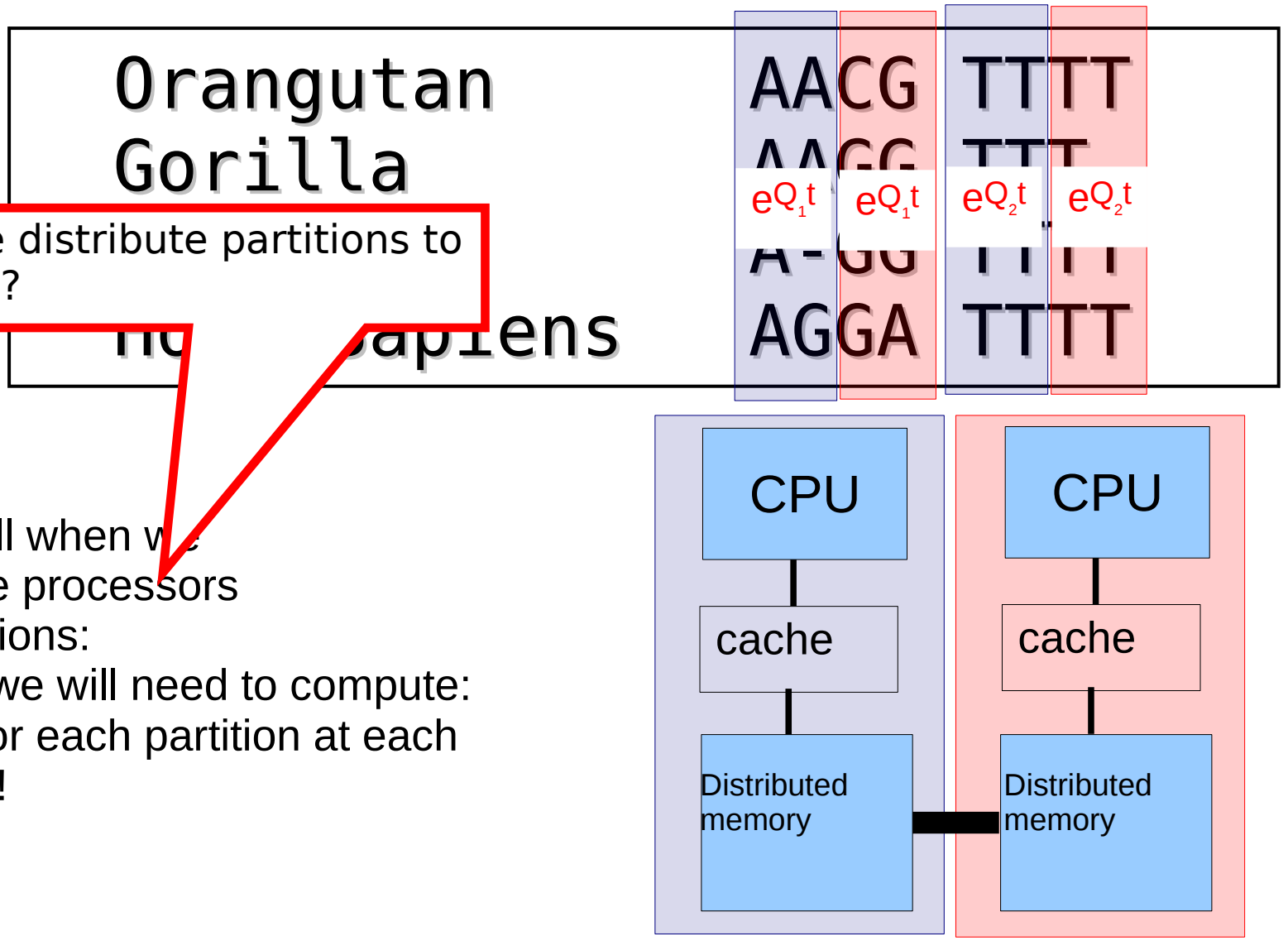


Performance impact depends on number of states in data/dimension of *Q*

Works well when have more processors than partitions:
However we will need to compute: $P(t)=e^{Qt}$ for each partition at each processor!

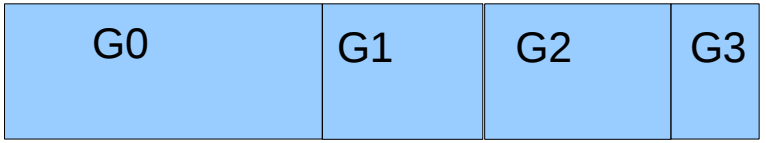


Data Distribution II



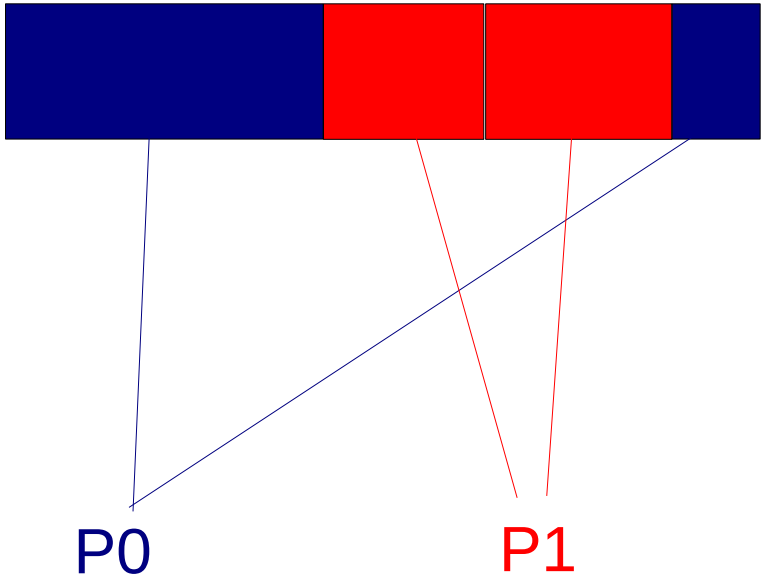
Works well when we have more processors than partitions:
However we will need to compute: $P(t)=e^{Qt}$ for each partition at each processor!

Load Balance I

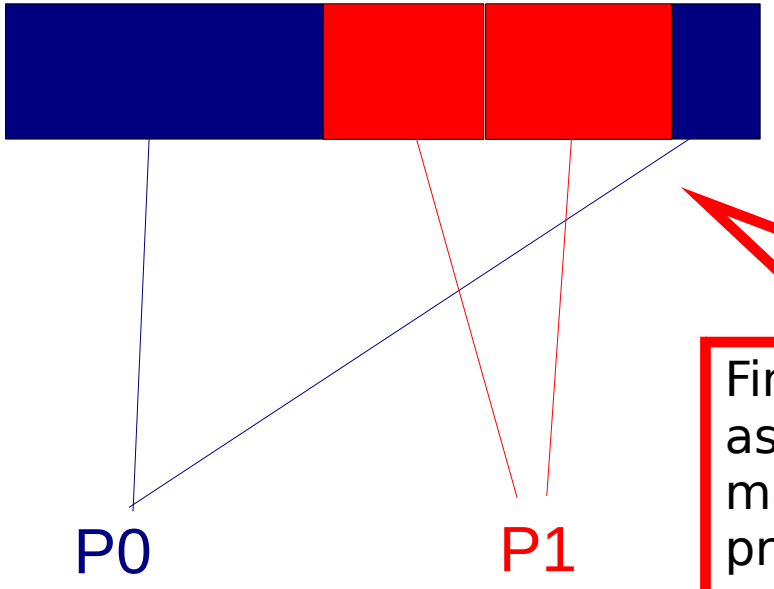


P0 P1

Load Balance I



Load Balance I



Find the partition-to-processor assignment such that the maximum number of sites per processor is minimized
→ this is NP-hard

Load Balance I

- The **multiprocessor job scheduling problem** in phylogenetics
  - Problem when #partitions >> #cores
  - Tested per-site (cyclic/modulo) data distribution versus per partition data distribution
  - We used the Longest Processing Time (LPT) heuristics for assigning partitions to processors
  - 25 taxa, 220,000 sites, 100 genes
    - GAMMA model

      naïve: **613** secs

      LPT: **550** secs
    - CAT model

      naïve: **298** secs

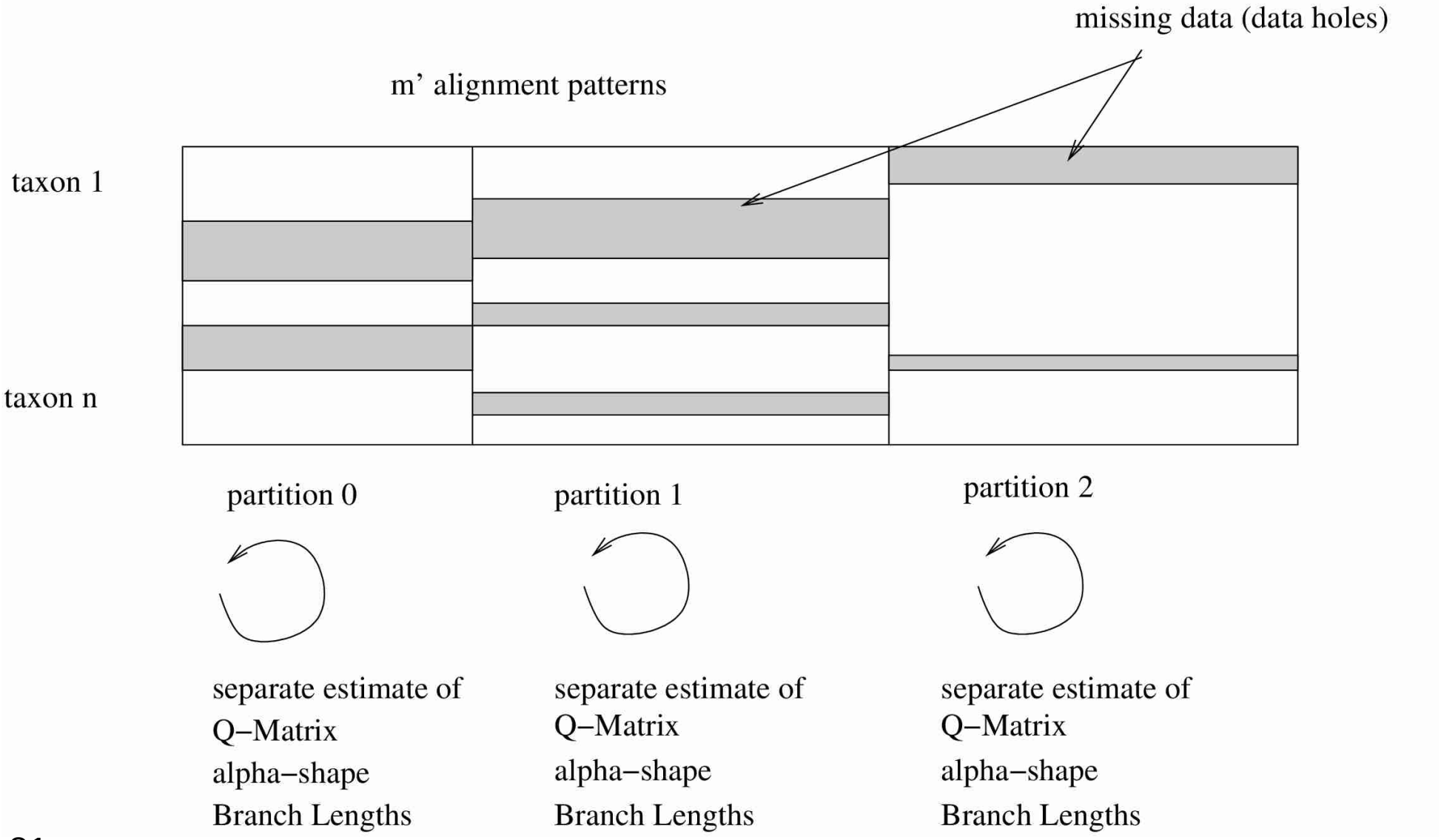
      LPT: **127** secs
  - Larger protein dataset under Γ model of rate heterogeneity: 10-fold performance improvement!

J. Zhang, A. Stamatakis: "The Multi-Processor Scheduling Problem in Phylogenetics", 11th IEEE HICOMB workshop (in conjunction with IPDPS 2012).

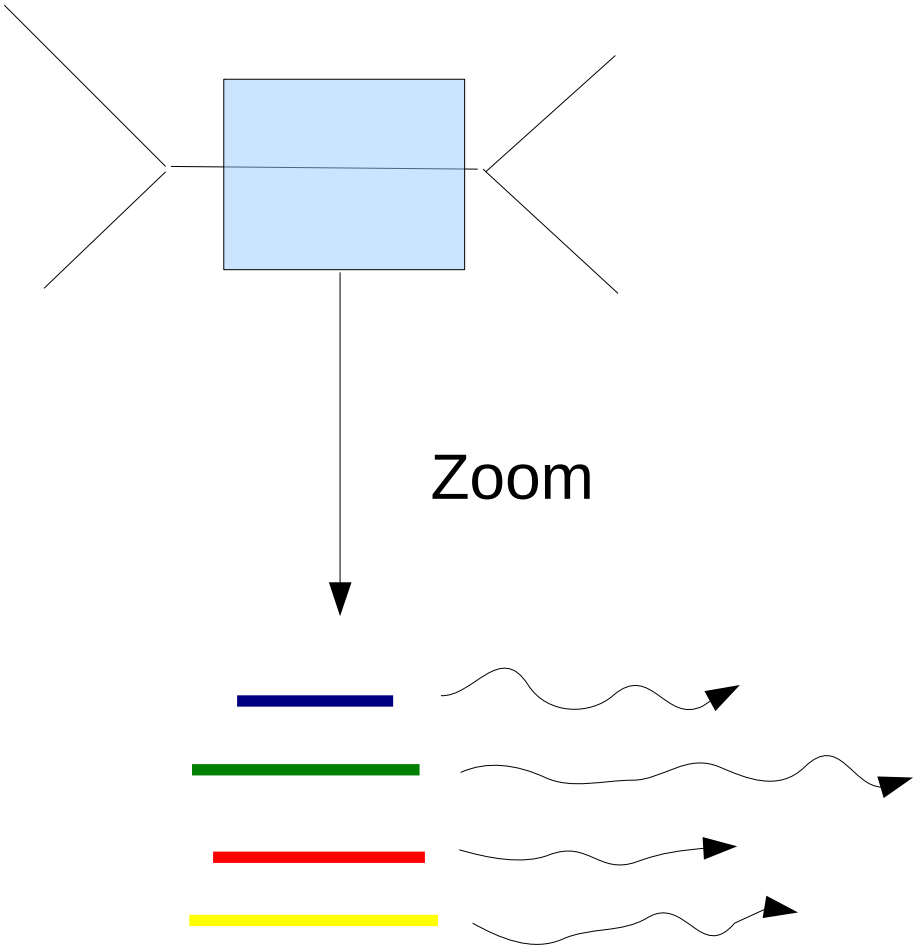
LPT heuristics for multi-processor scheduling

- Sort jobs (partitions) by processing length (partition length) in decreasing order
- Remove a job (partition) from the sorted list and assign it to the processor with the earliest end time (the smallest sum of partition lengths)
- Repeat until the sorted list is empty
- Upper bound: *4/3 – 1/(3p) * OPT,* where *p* is the number of processors
- Graham, R. L.: "Bounds on Multiprocessing Timing Anomalies". *SIAM Journal on Applied Mathematics* 17 (2): 416–429, 1969.
- Remark: LPT works surprisingly well (see our paper on the phylogenetic problem where we also tested other heuristics)

Partitioned Branch Lengths & other parameters



Load-Balance II



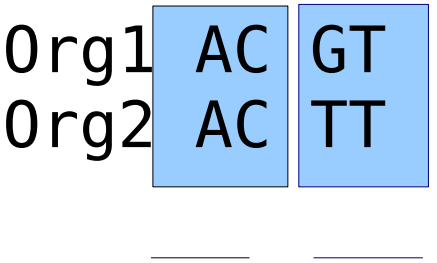
Synchronization Points

- Assume 10 branches
- Each branch requires 10 Newton-Raphson Iterations
- Each NR Iteration requires a synchronization via a reduction operation
- One branch/partition at a time: 100 sync. points, less work (only one partition) per sync. point
- All branches concurrently: 10 sync. points, more work per sync. point
- Branches will need distinct number of operations
- Add convergence state → bit vector

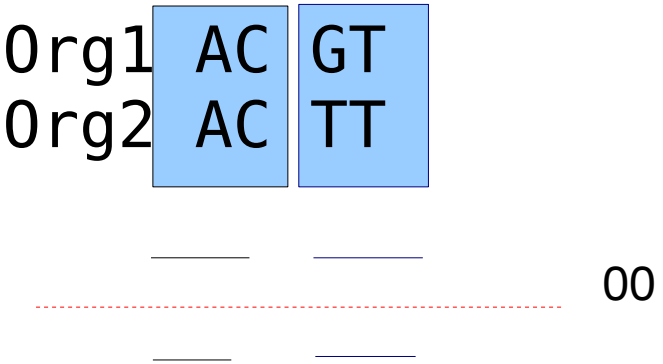
Synchronization Points

```
Org1 AC GT
Org2 AC TT
```

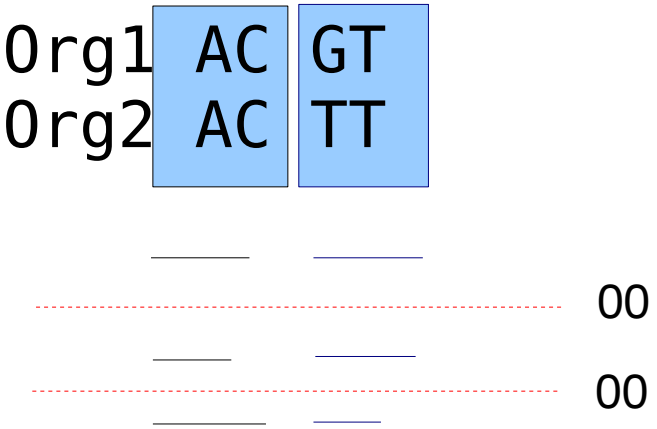
Synchronization Points



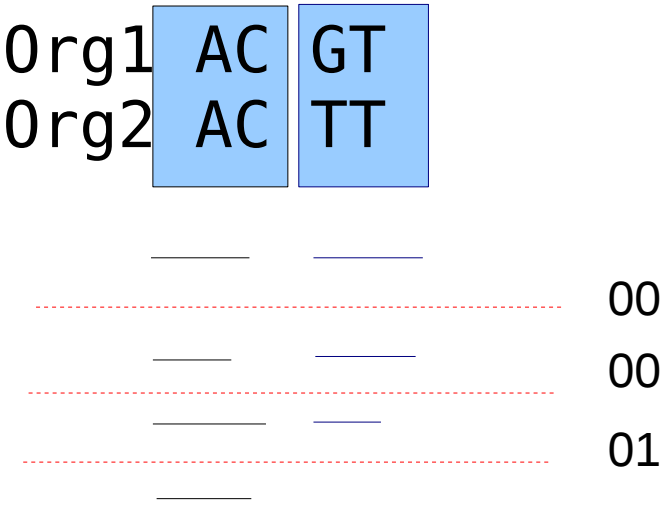
Synchronization Points



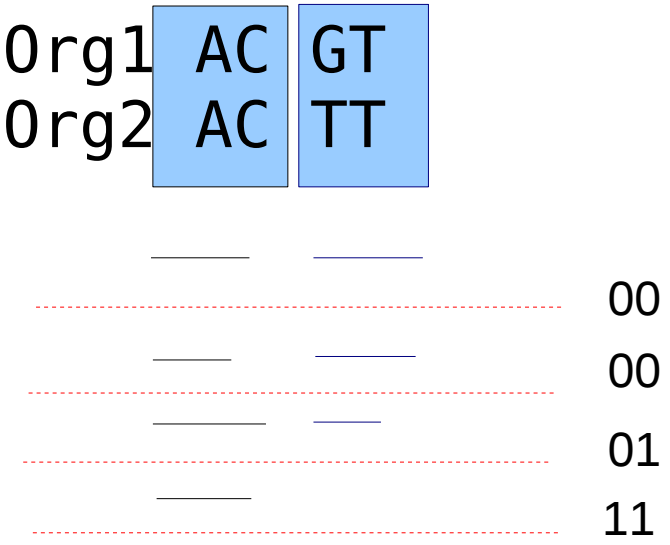
Synchronization Points



Synchronization Points

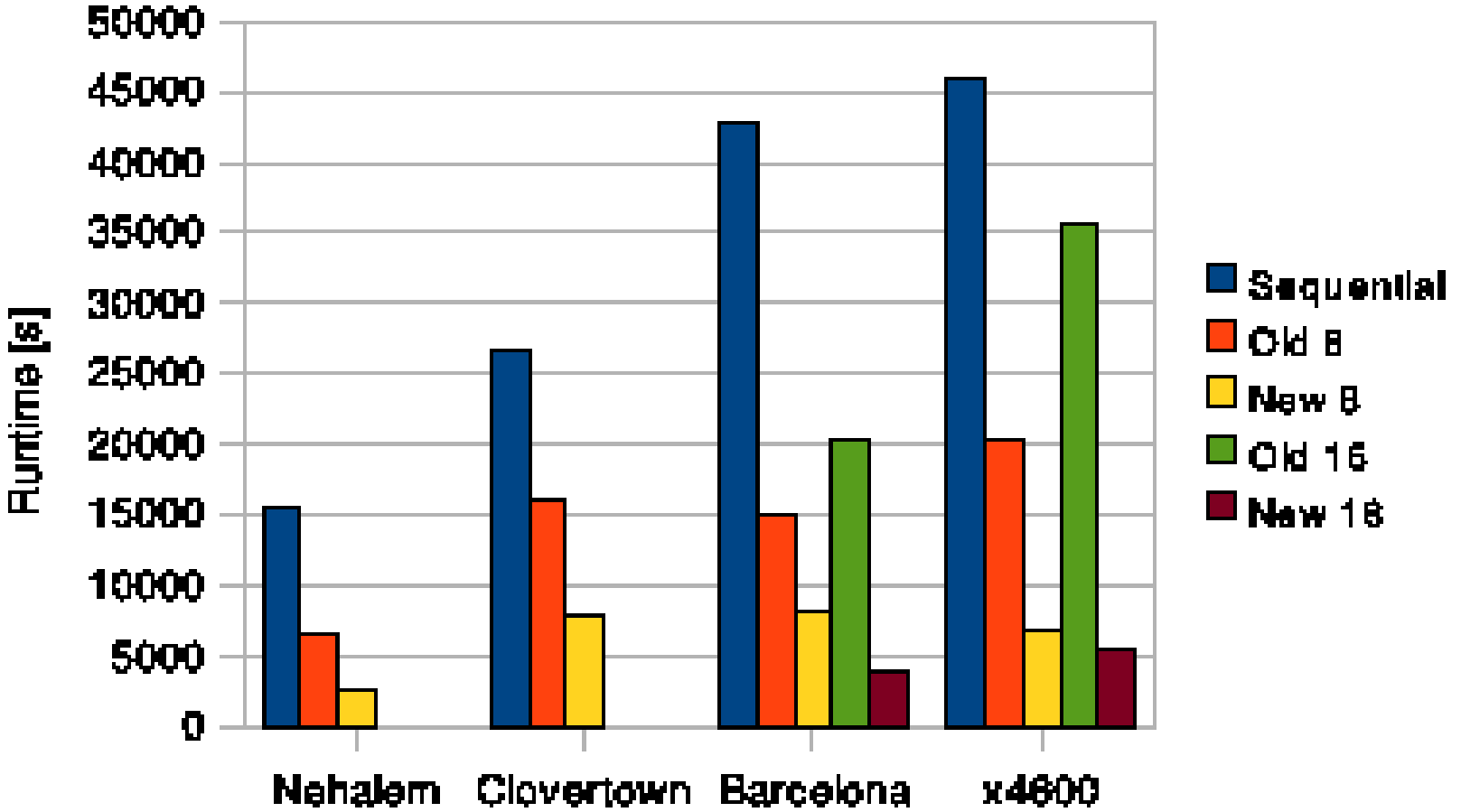


Synchronization Points



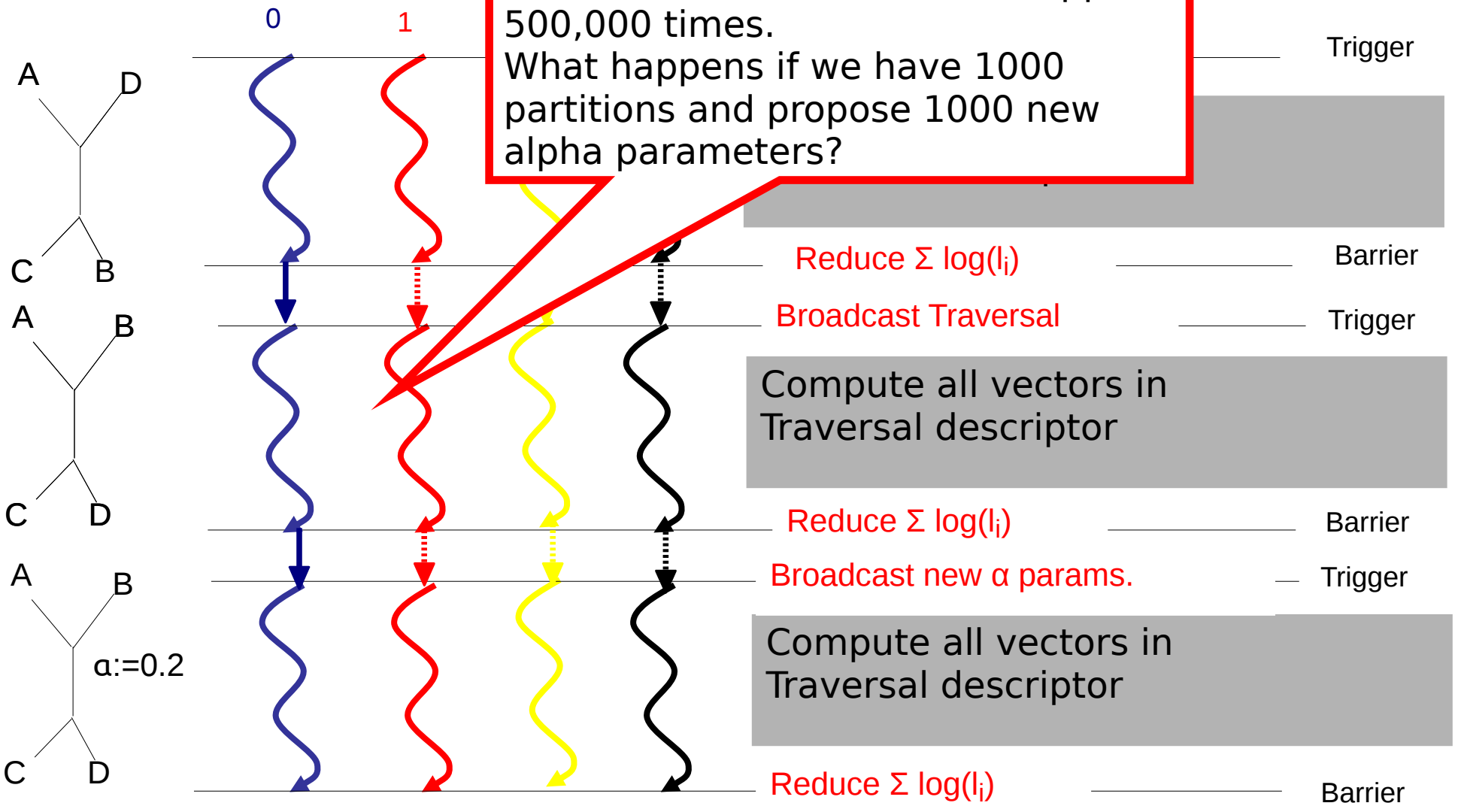
In this example: 4 instead of 7 sync points!

Load Balance II

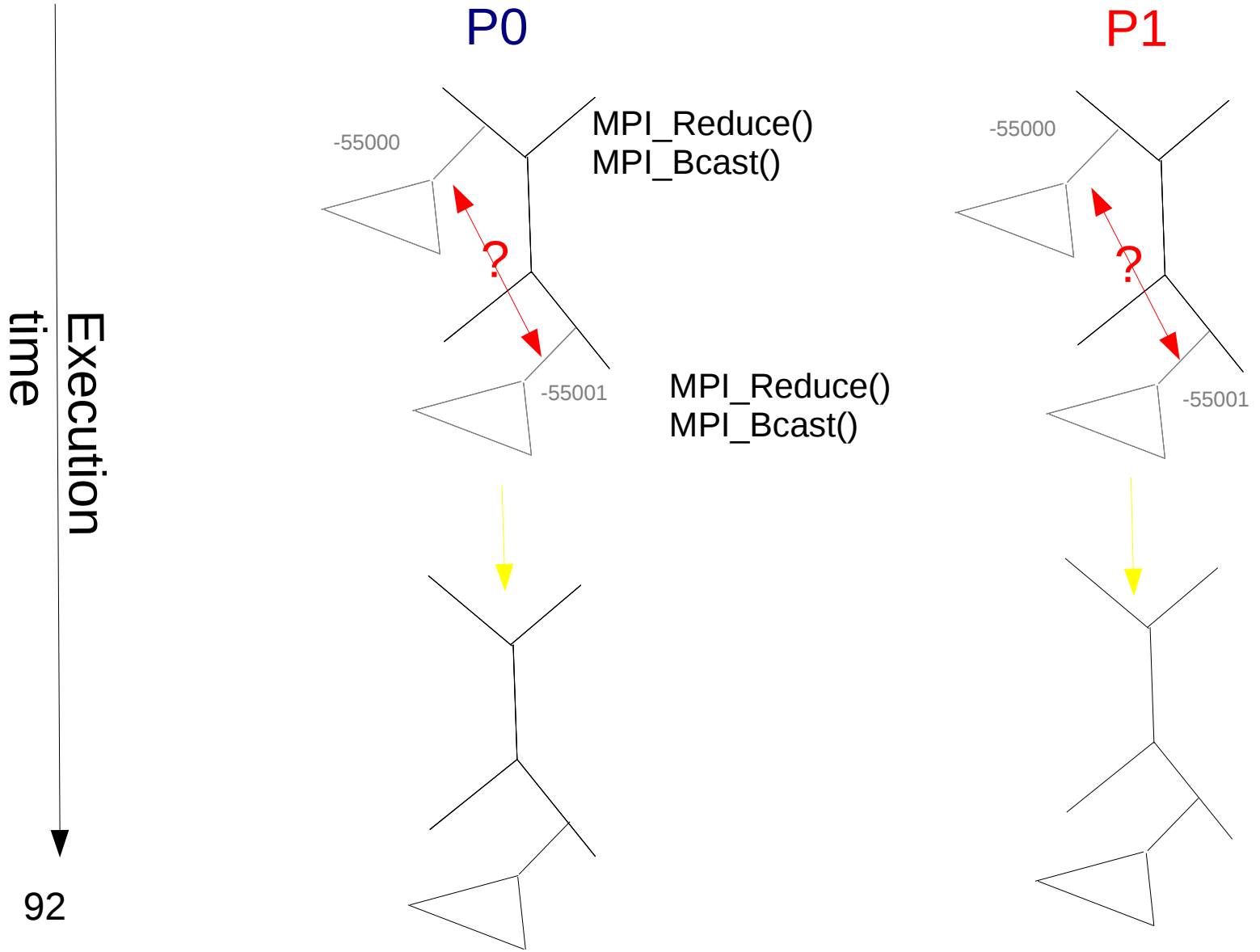


A. Stamatakis, M. Ott: "Load Balance in the Phylogenetic Likelihood Kernel". Proceedings of ICPP 2009, Vienna, Austria, September 2009.

Classic Fork-Join with



Alternative MPI parallelization



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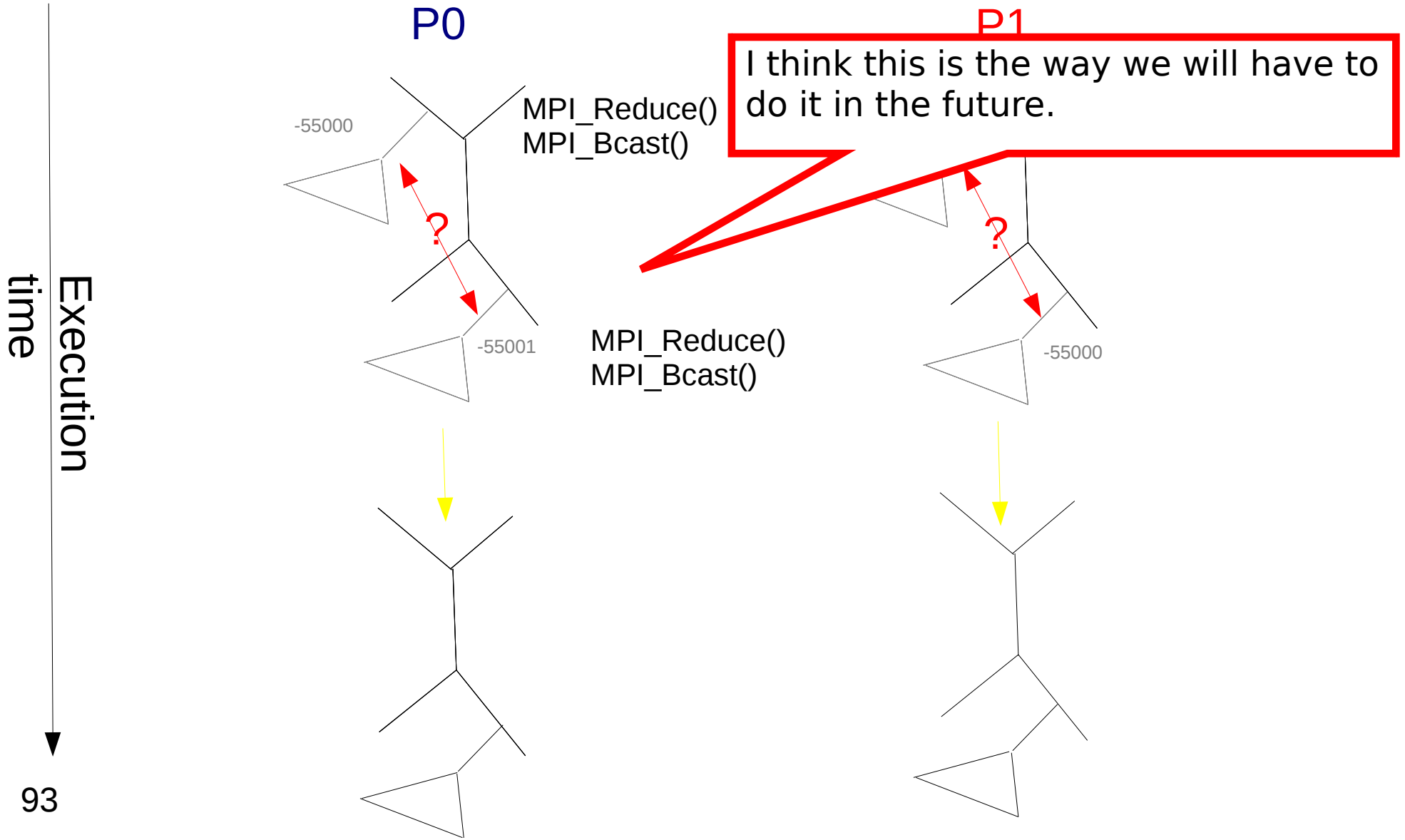

ExaML

- New code implementing this new parallelization scheme
- https://github.com/stamatak/ExaML
- A. Stamatakis, A. J. Aberer: "Novel Parallelization Schemes for Large-Scale Likelihood-based Phylogenetic Inference", accepted for publication at *IPDPS 2013*, Boston, USA, 2013.
- Up to 3 times faster than RAxML-Light (2012) on large, partitioned datasets
- Tested with up to 1536 cores on our cluster at HITS
- Future developments
  - 20,000,000 CPU hors on SuperMUC for
    - Improving scalability
    - Implementing fault tolerance
    - Execute 1KITE tree inferences
    - Further details → ask Andre Aberer