Modelling Genetic Variations with Fragmentation-Coagulation Processes

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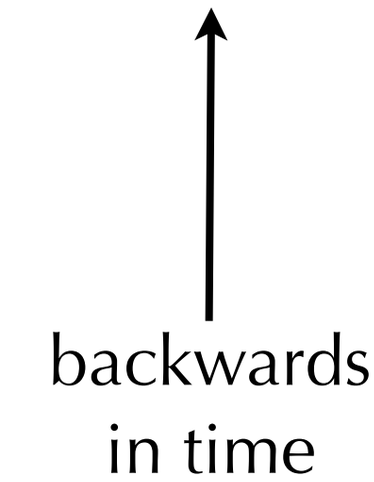
Genetic Variations in Populations

- Inferring histories of human populations.
- Understanding fundamental genetic processes.
- Associating genetic with phenotypic variations.
- Discovering genetic causes of diseases.

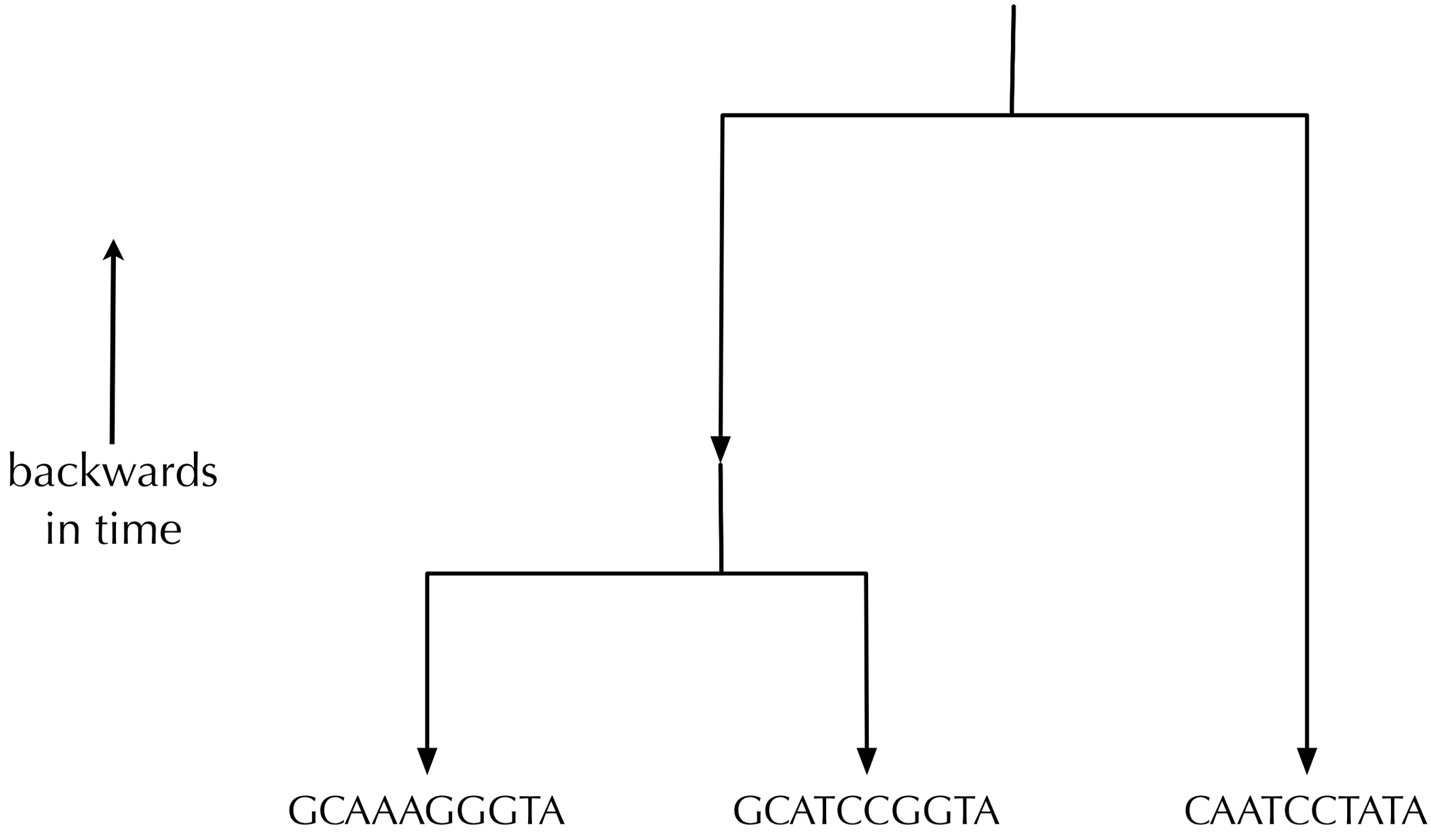
Ancestral Tree



GCAAAGGGTA GCATCCGGTA CAATCCTATA

[Kingman 1982]

Ancestral Tree



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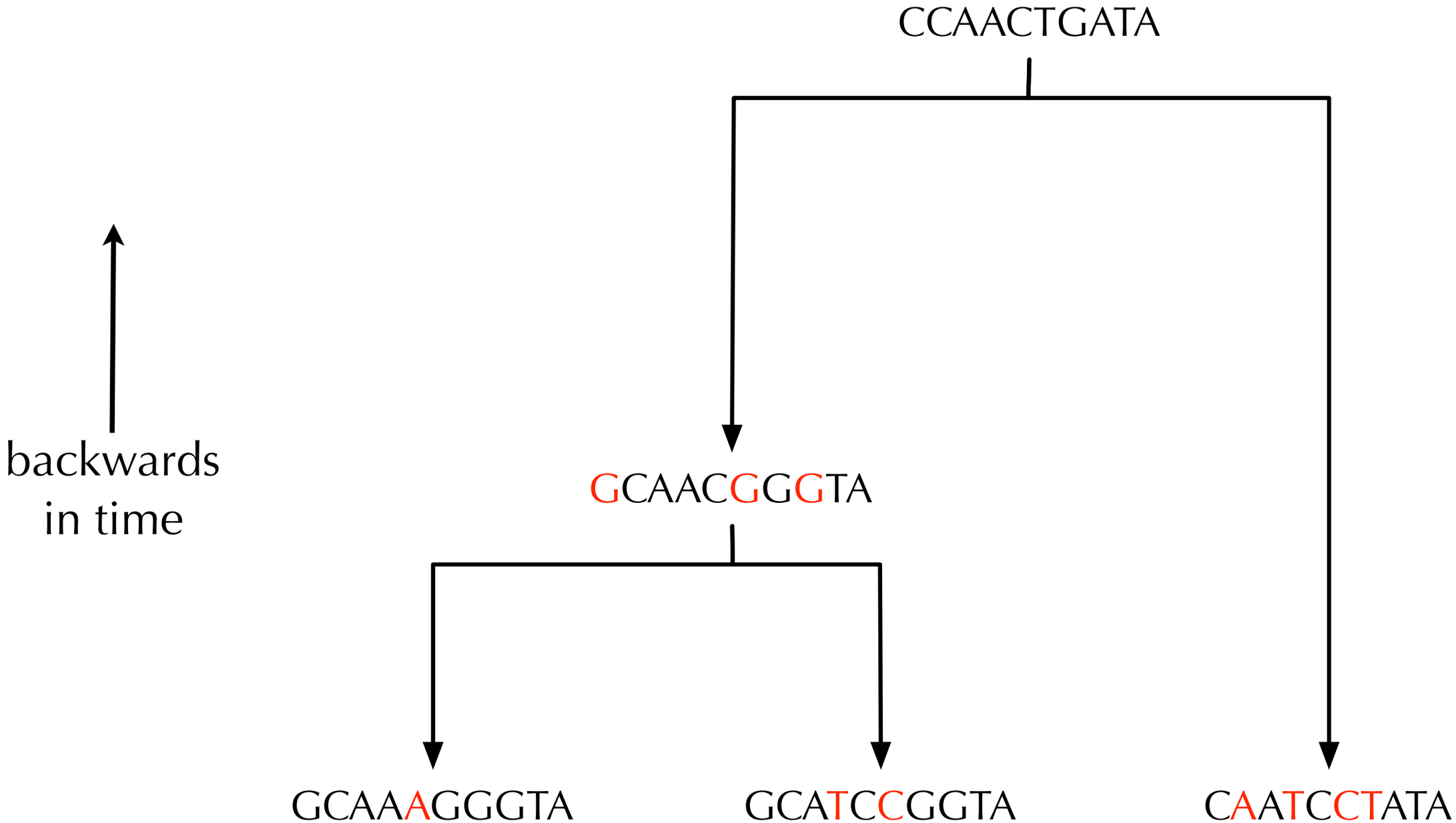
[Kingman 1982]

Ancestral Tree



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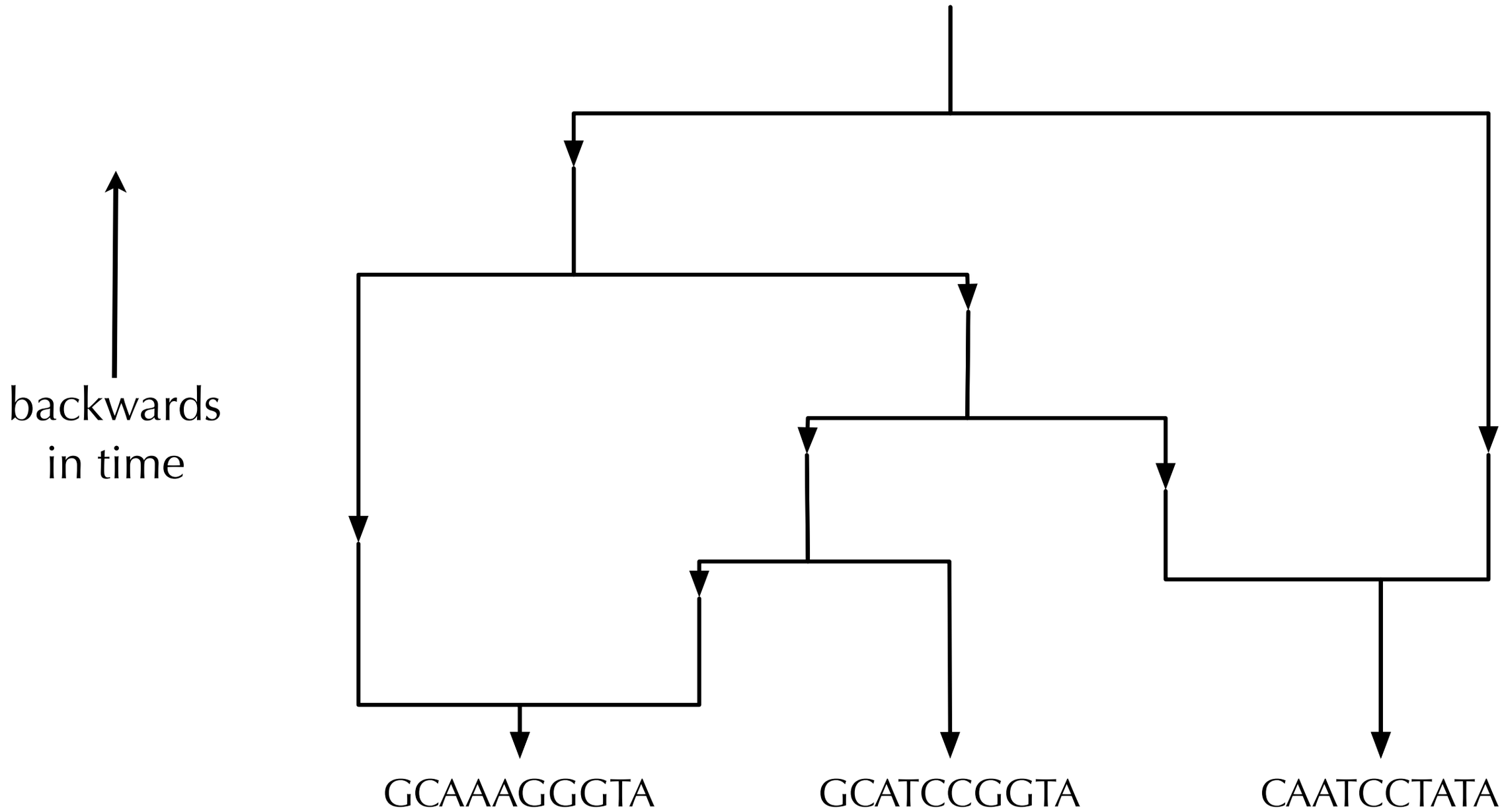
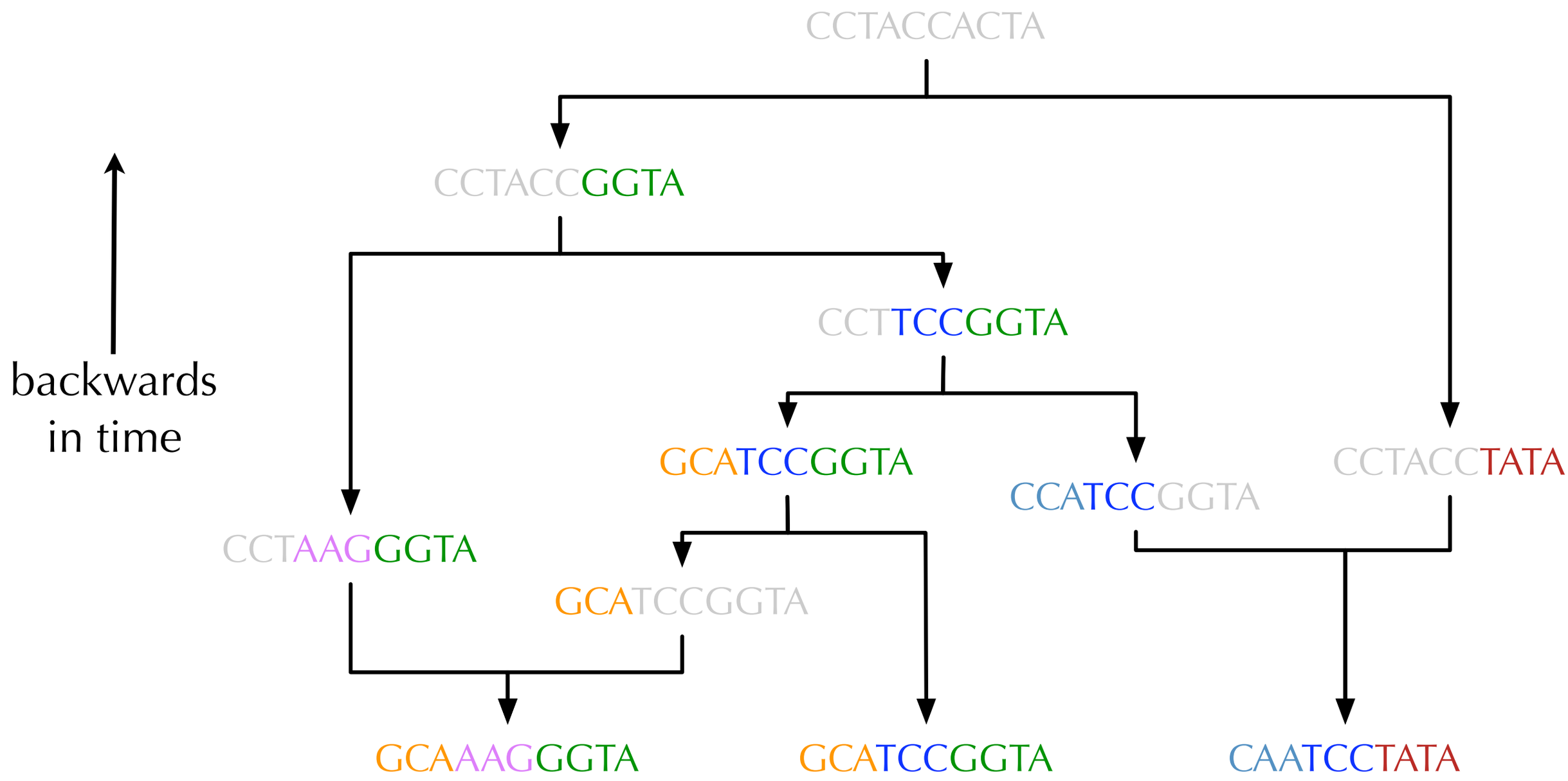
[Kingman 1982]

Ancestral Recombination Graph



[Hudson 1983]

Ancestral Recombination Graph



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[Hudson 1983]

Mosaic Structure

- Simplification:
  - Blocks of recurring segments;
  - Each DNA sequence composed of multiple blocks.

➡ Hidden Markov models.

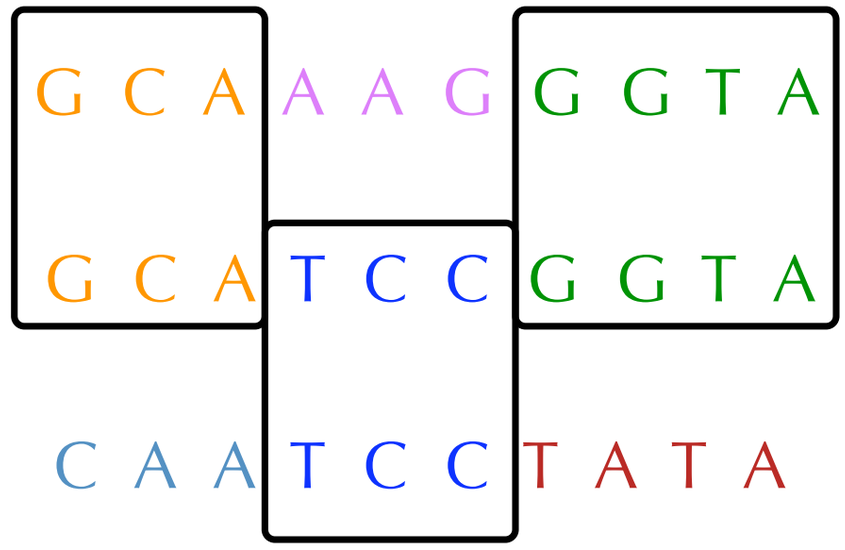


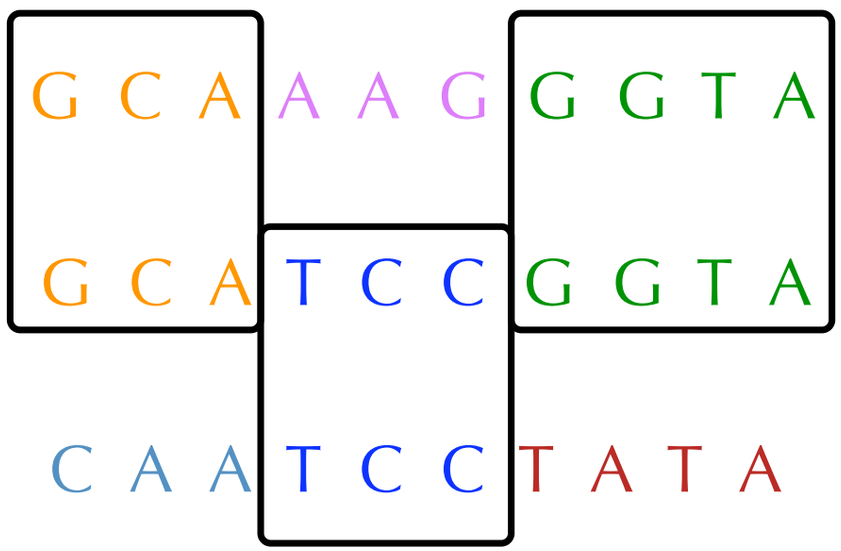
Figure from [Daly et al 2001]

Fragmentation-Coagulation Processes

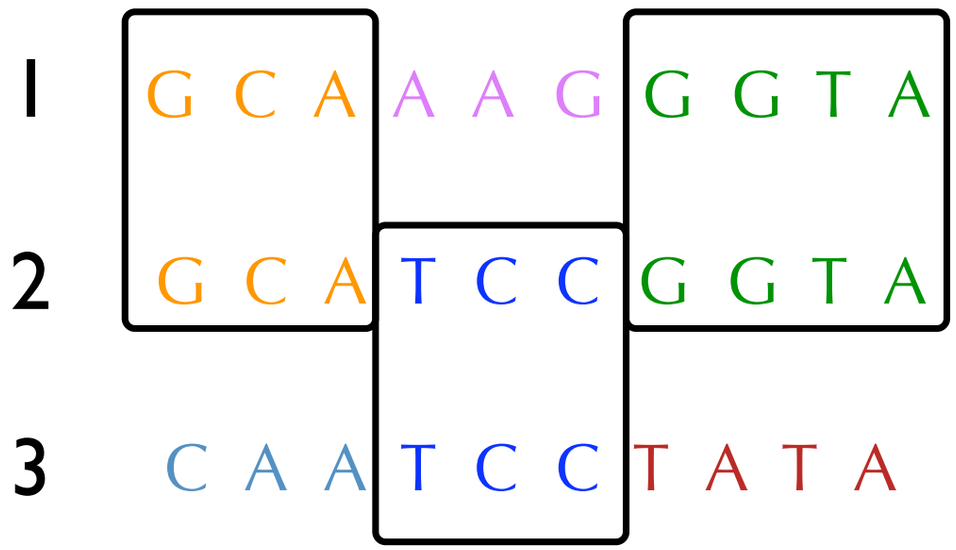
- No need for model selection---Bayesian nonparametric.
- No label switching problem---no labels.

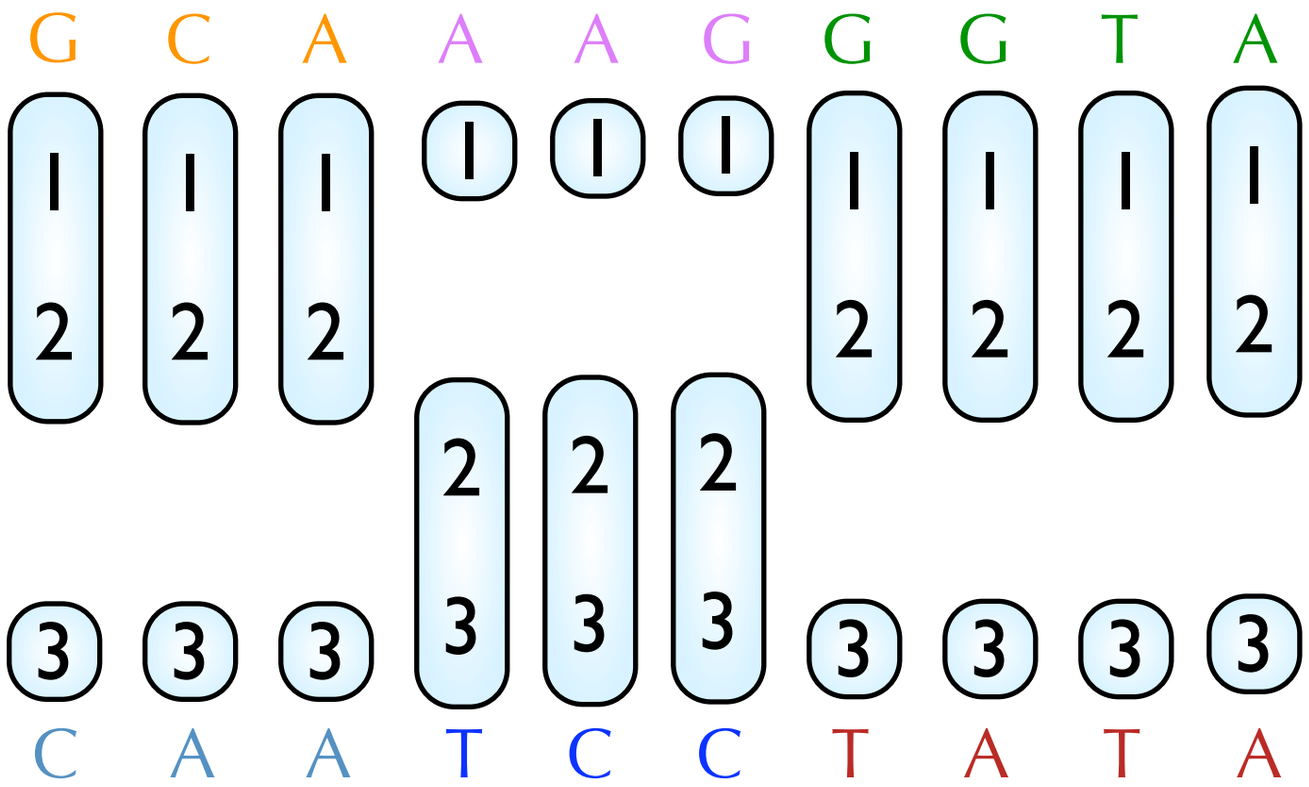
- Idea:
  - Use *unlabelled* partitions of sequences as basic representation.
  - Use a Markov process over partitions to model changing partition structure.

- Partition: set of clusters, e.g. {{1,2},{3}}
  - disjoint, non-empty, contains all sequences.
  - unlabelled



Markov Process over Partitions





$$\{\Pi_t : t = 1, 2, \ldots, T\}$$

$$\{\Pi_t : t \in [0, T]\}$$

Fragmentation-Coagulation Processes

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Fragmentation-Coagulation Processes

1

3

6

2

7

4

5

8

9

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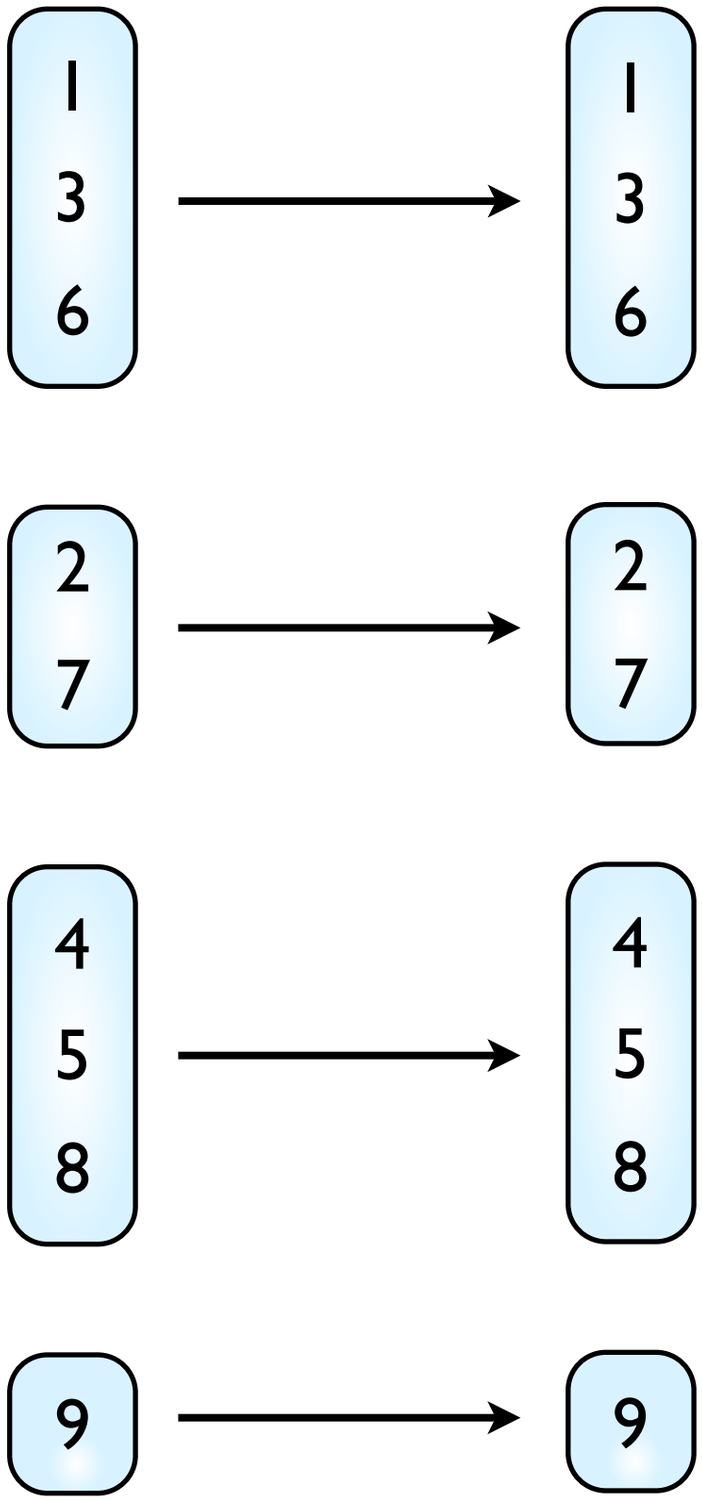
Fragmentation-Coagulation Processes



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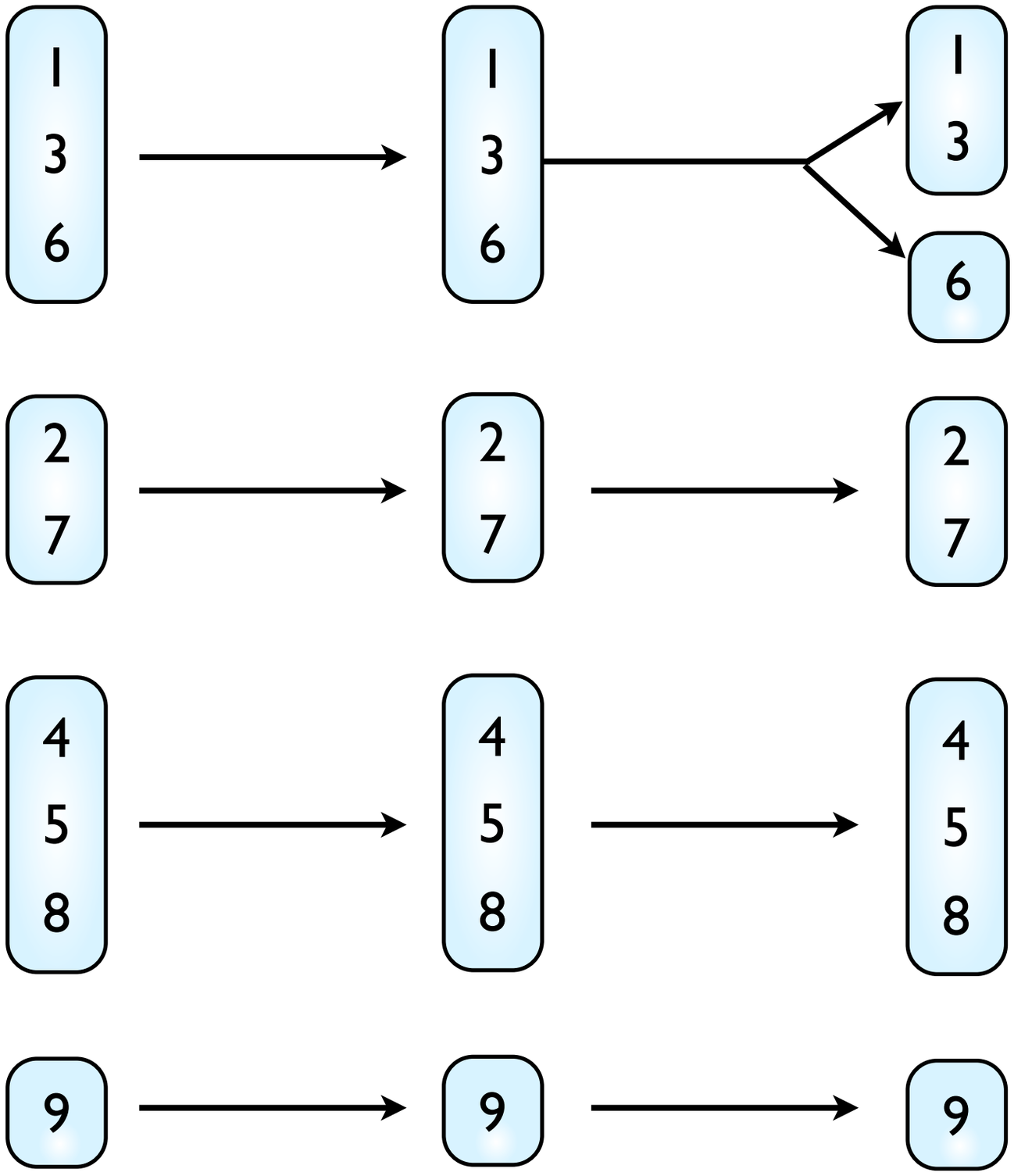

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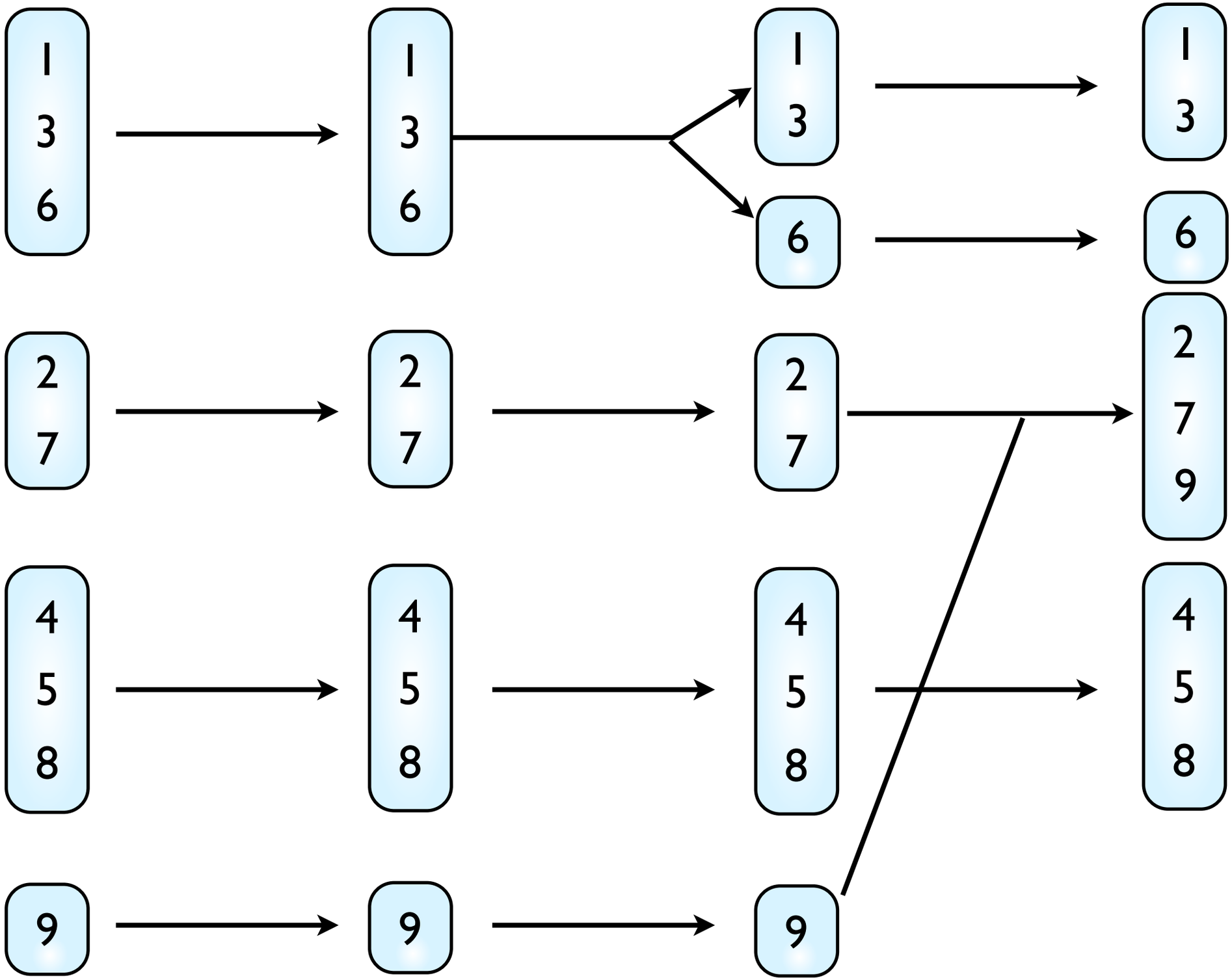

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Fragmentation-Coagulation Processes

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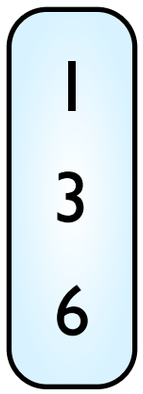
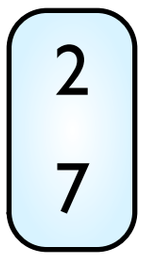
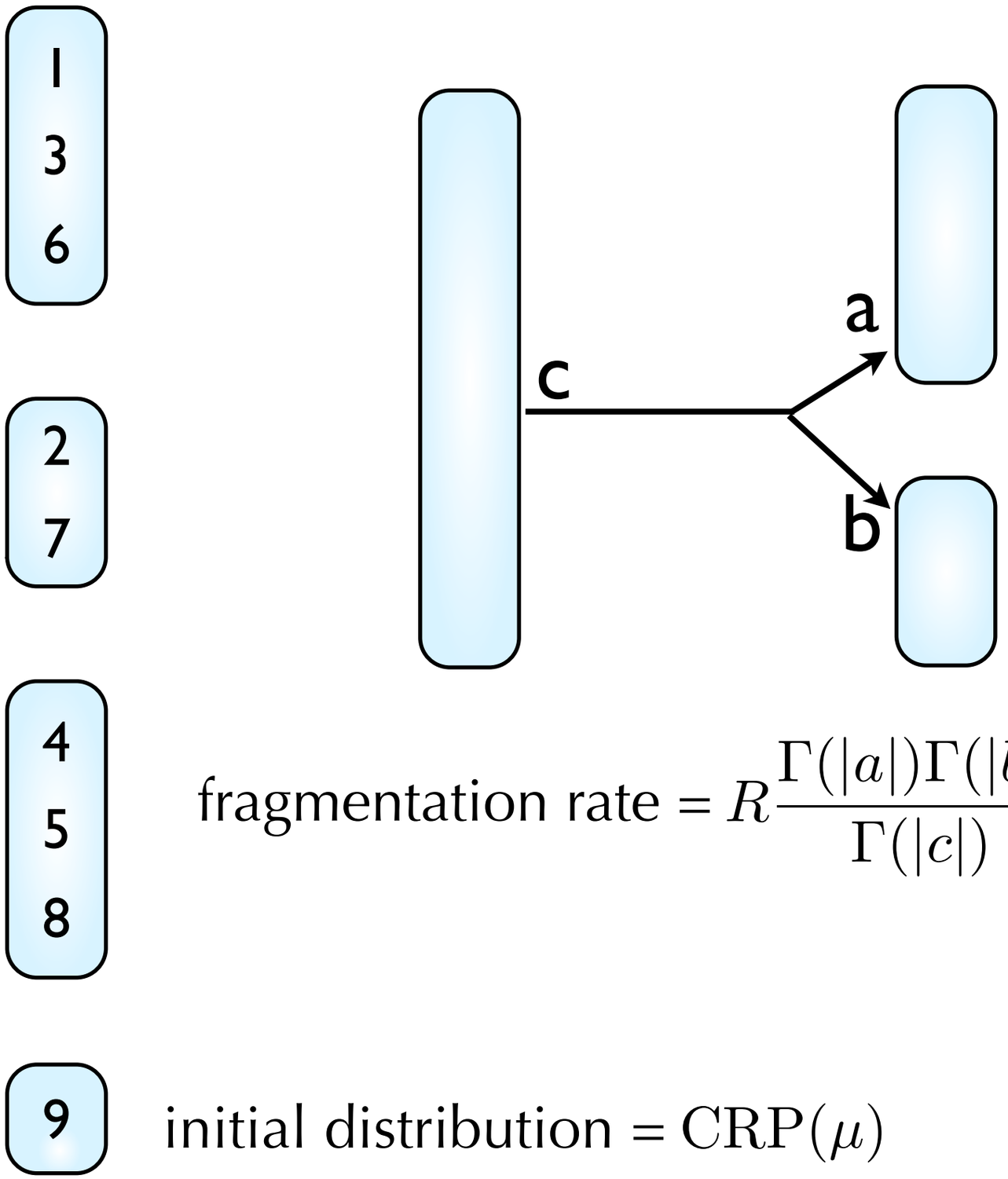




initial distribution = $\mathrm{CRP}(\mu)$

Fragmentation-Coagulation Processes



$$\text{fragmentation rate} = R\frac{\Gamma(|a|)\Gamma(|b|)}{\Gamma(|c|)}$$

$$\text{initial distribution} = \mathrm{CRP}(\mu)$$

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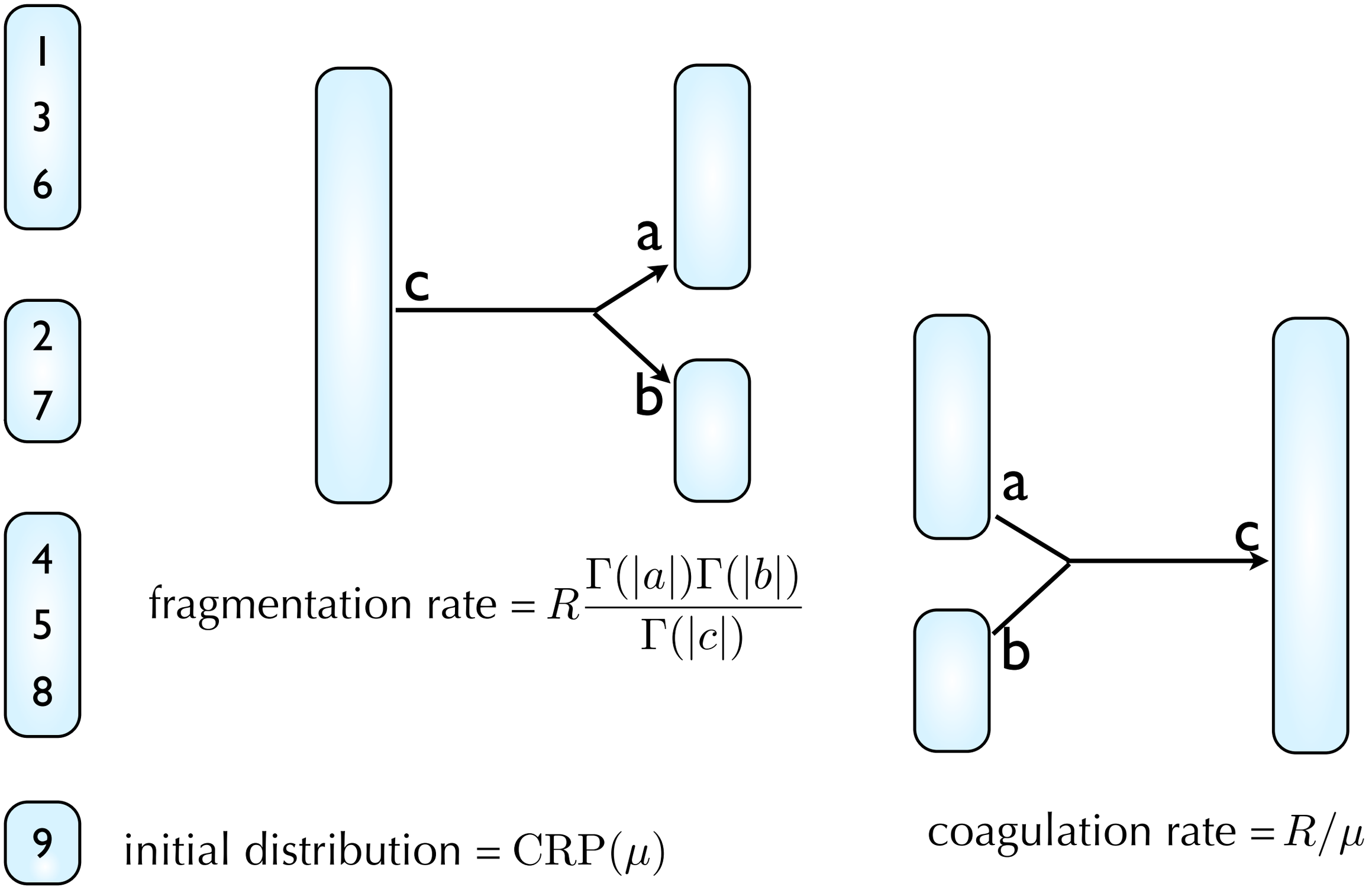
Fragmentation-Coagulation Processes



$$\text{fragmentation rate} = R\frac{\Gamma(|a|)\Gamma(|b|)}{\Gamma(|c|)}$$

$$\text{initial distribution} = \mathrm{CRP}(\mu)$$

$$\text{coagulation rate} = R/\mu$$

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Fragmentation-Coagulation Processes

- Markov.
- Stationary, with CRP(μ) as equilibrium distribution.
- Reversible.

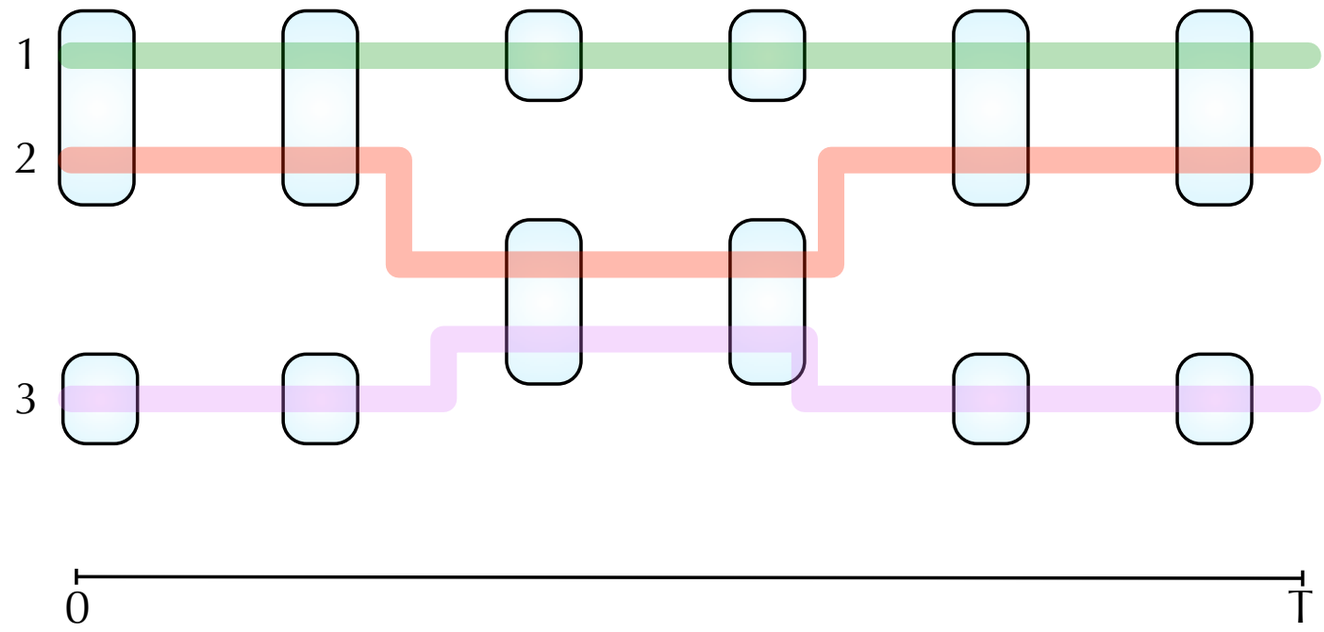
- Exchangeable.

- Dirichlet diffusion tree [Neal 2003] and Kingman's coalescent.

- Simplest example of exchangeable fragmentation-coalescence processes [Berestycki 2004].

Inference

- Gibbs sampling:
  - Resample trajectory of one sequence at each iteration.



- Dealing with continuous time dynamics:
  - Uniformisation based auxiliary variable Gibbs [Rao & Teh UAI 2011].
  - Forward filtering-backward sampling.

Inference

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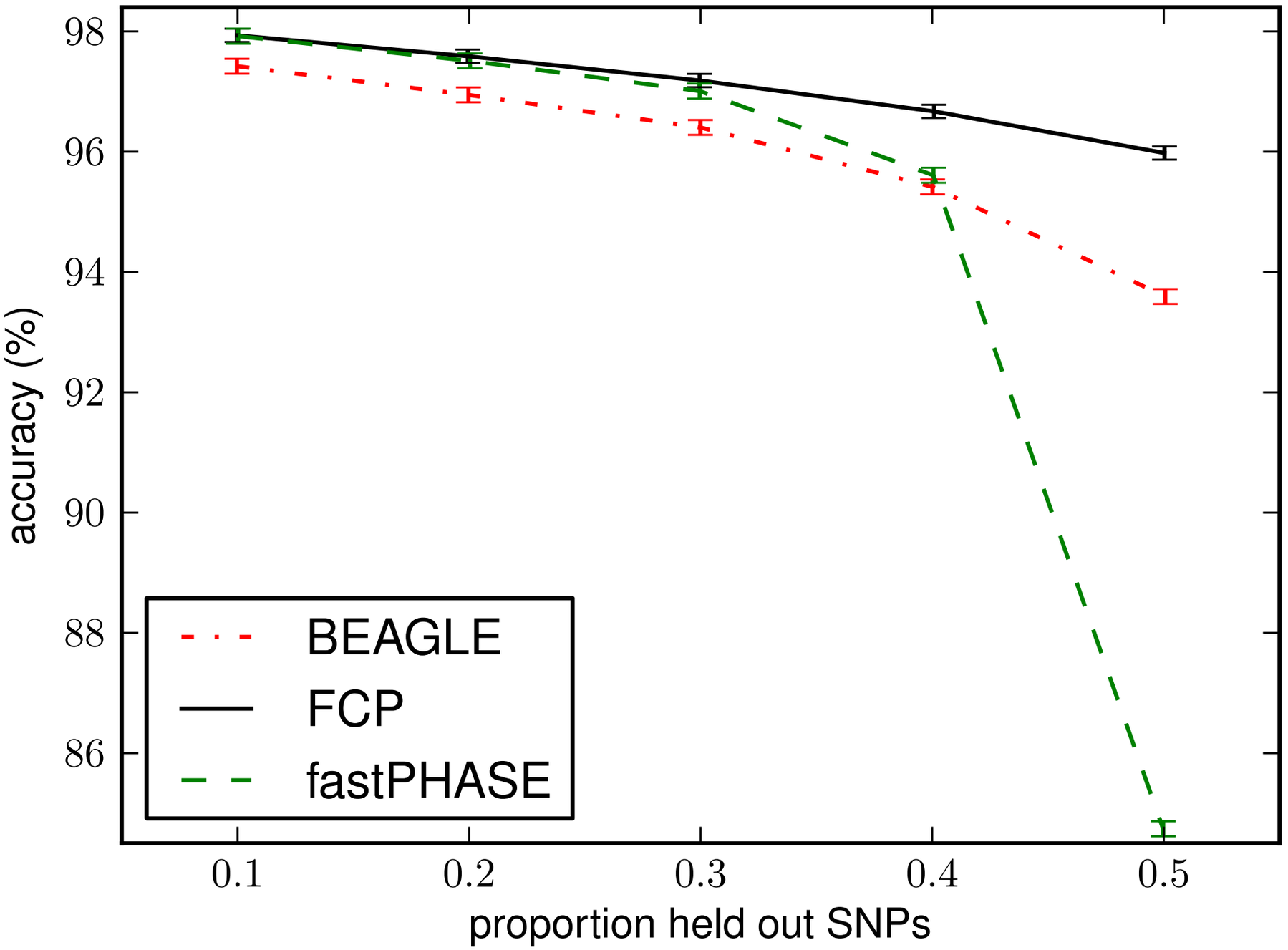
Imputation Results



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Summary

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- Modelling the mosaic structure of genetic variations.
- Fragmentation-coagulation processes.
- Bayesian nonparametrics.
- Label switching problem.
- State-of-the-art results.

- Future work: scaling up, and other statistical genetics applications.

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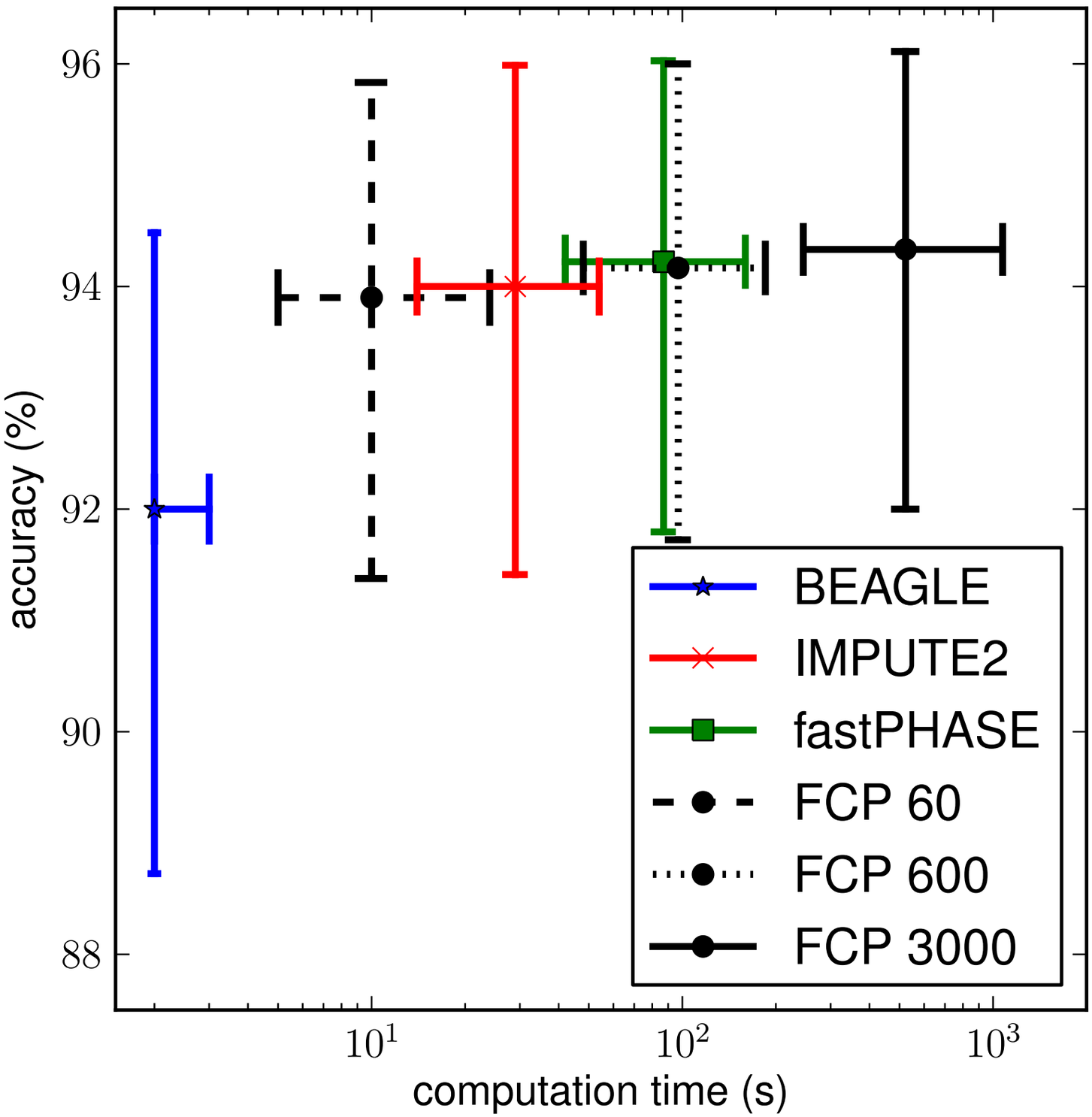
Thank You!

- Vinayak Rao and Andriy Mnih
- Chris Holmes, Gil McVean, Lancelot James
- NIPS organisers and audience

Appendix

Imputation Experiments: Unphased Data



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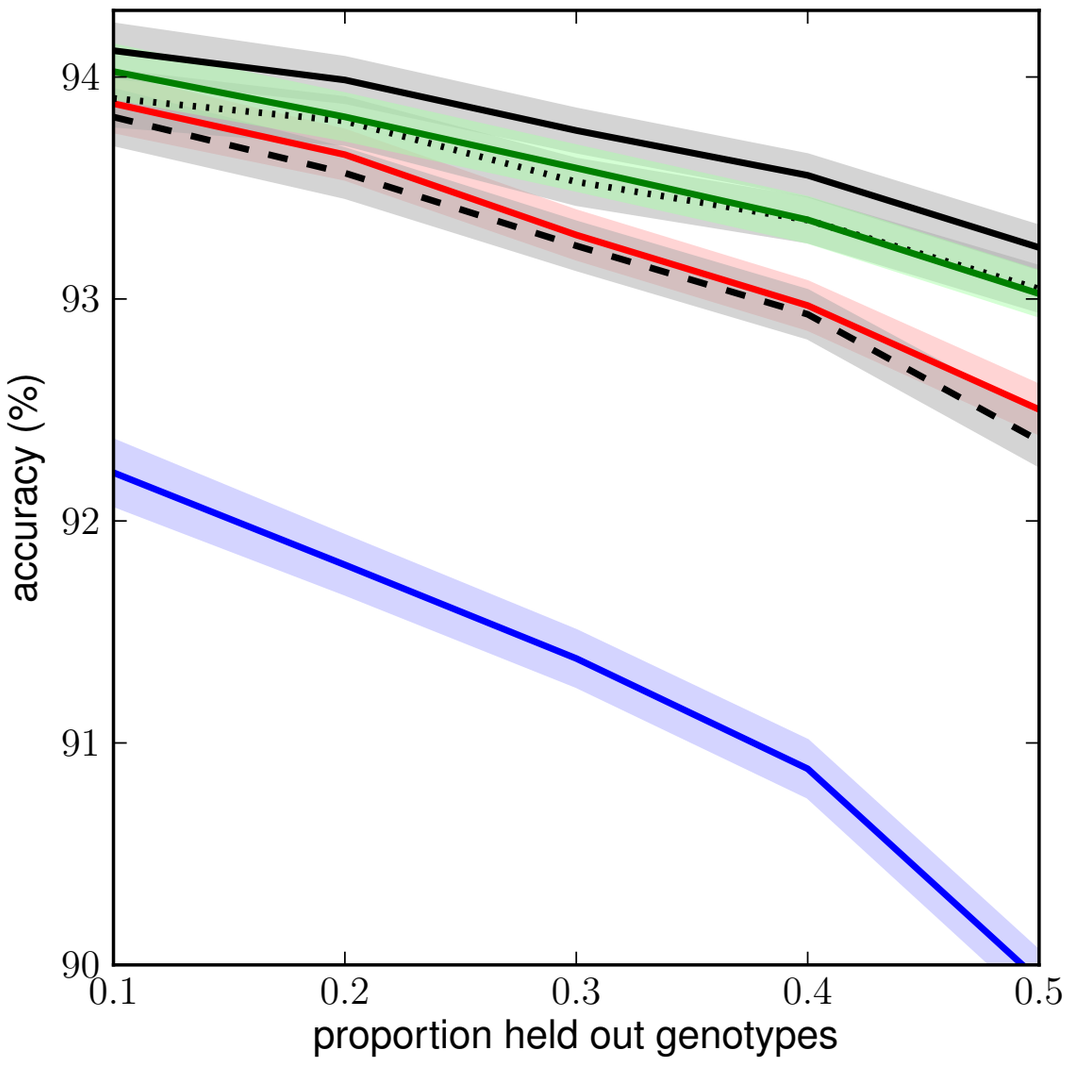
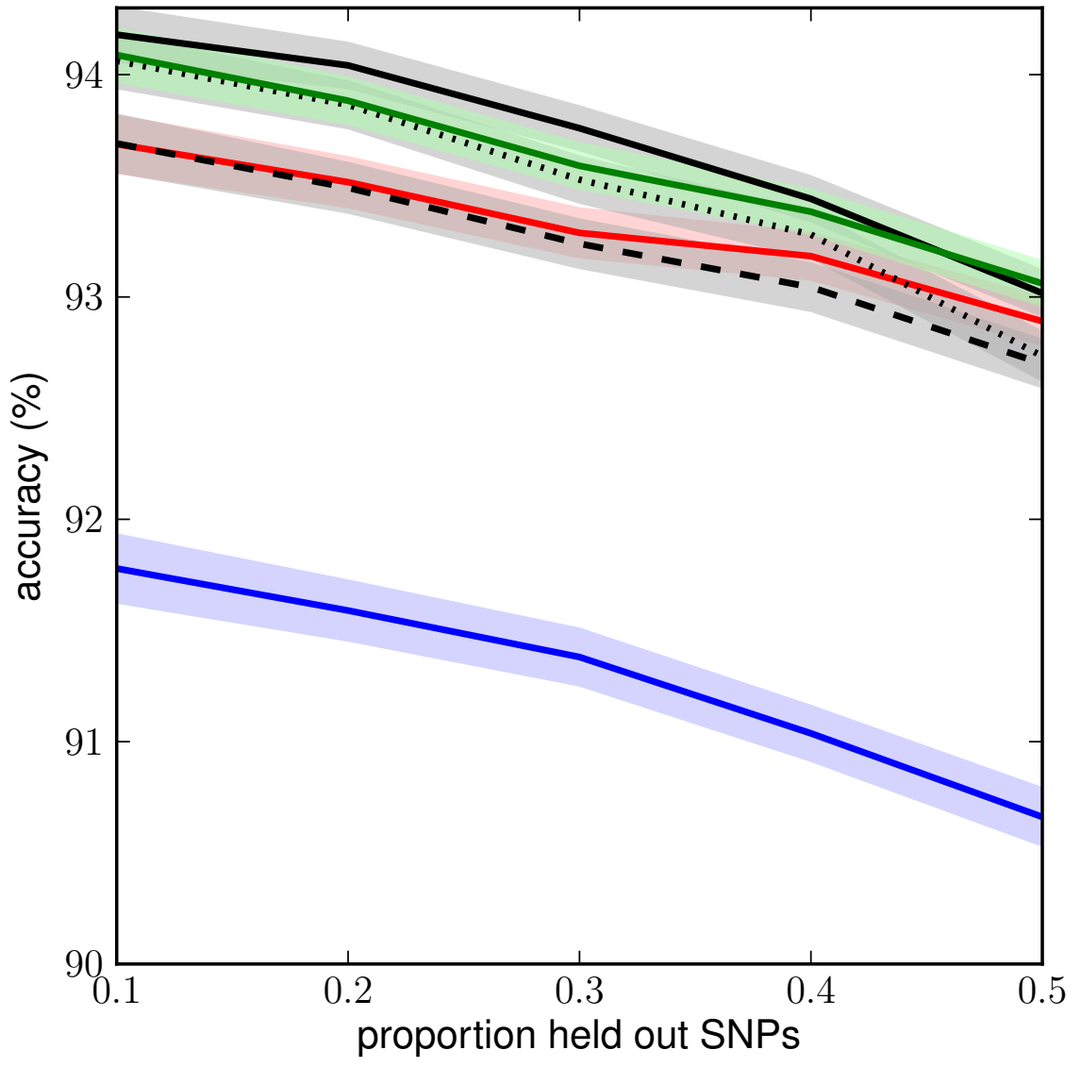
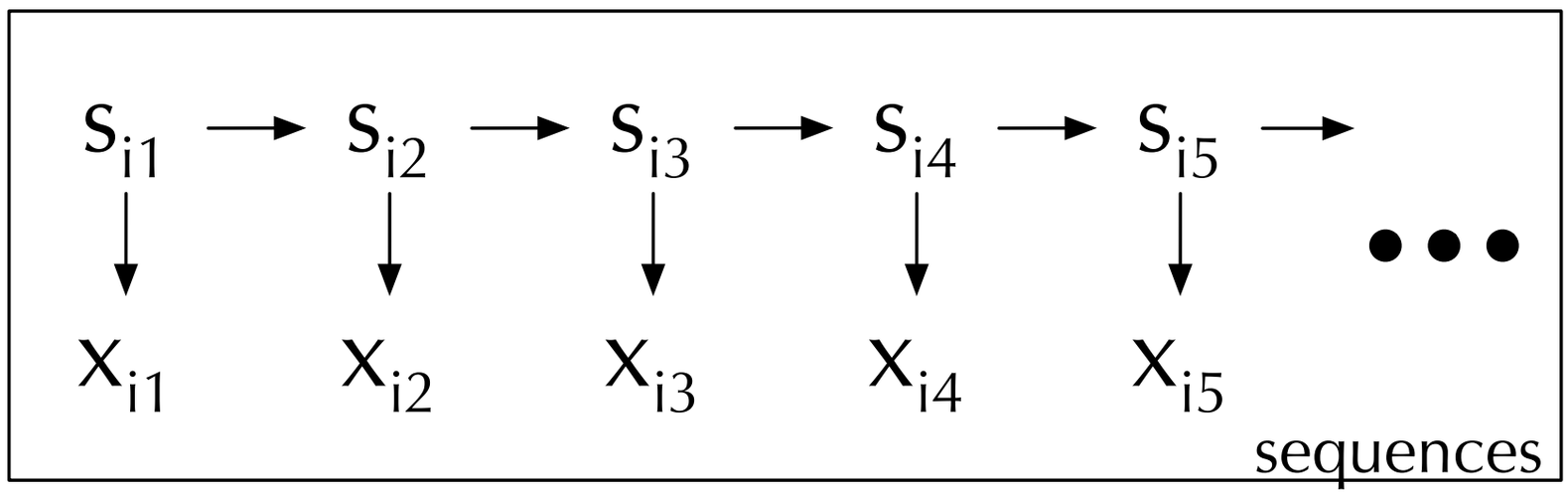
Imputation Experiments: Unphased Data



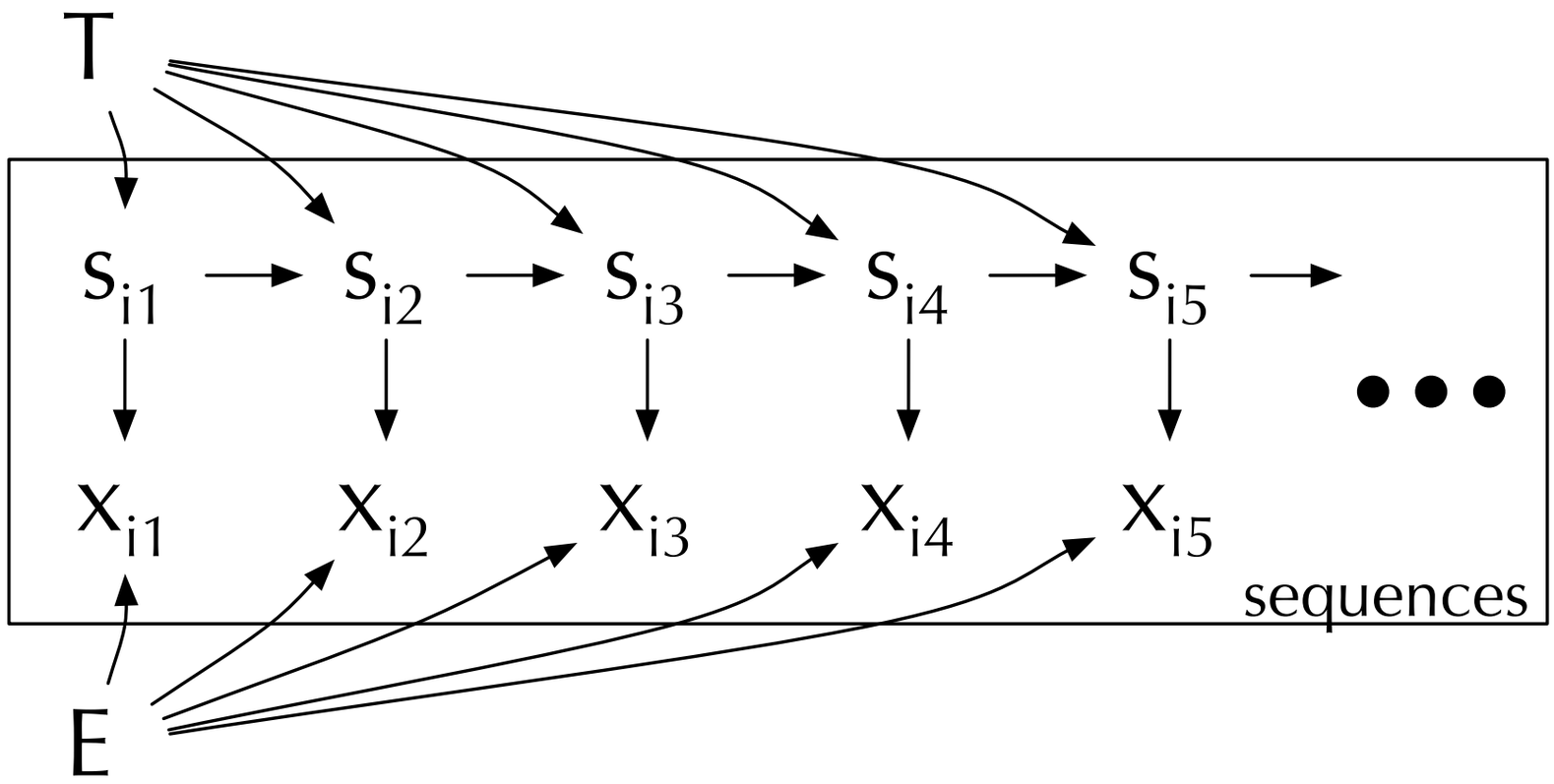


Hidden Markov Models



[Daly et al 2001], [Scheet & Stephens 2006]

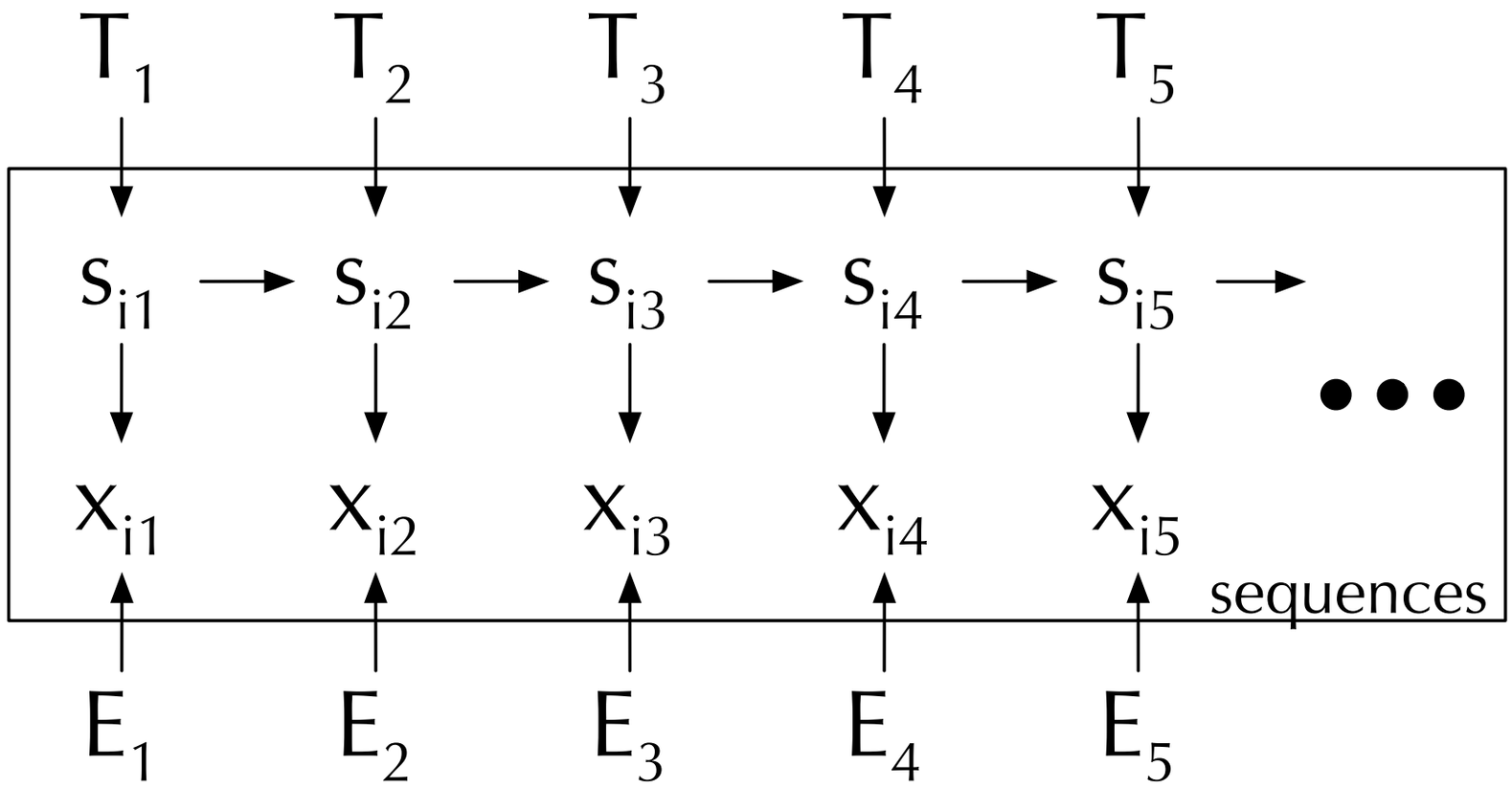
Hidden Markov Models



- Typical: stationary with shared transition and emission probabilities.

[Daly et al 2001], [Scheet & Stephens 2006]

Hidden Markov Models



- Typical: stationary with shared transition and emission probabilities.
- Here: non-stationary with location specific transition and emissions.

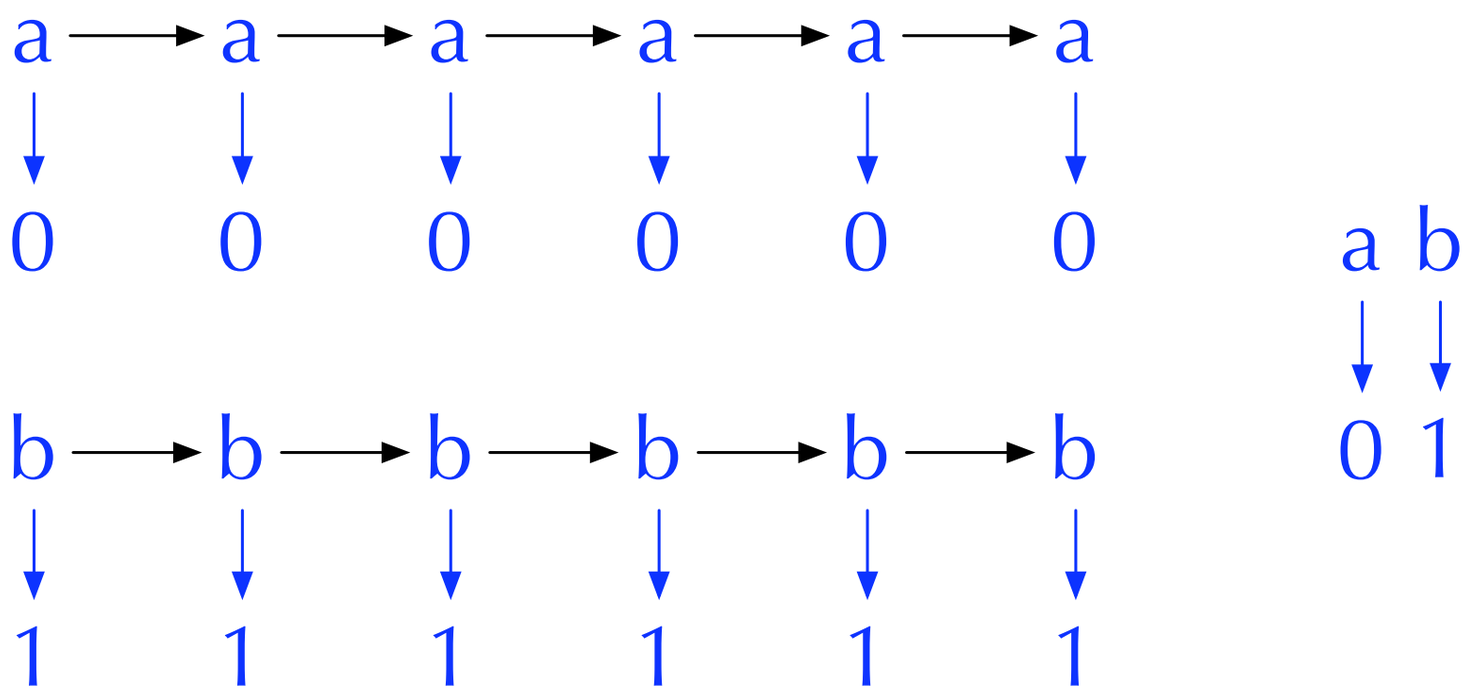
[Daly et al 2001], [Scheet & Stephens 2006]

HMM Label Switching Problem

0 0 0 0 0 0

1 1 1 1 1 1

HMM Label Switching Problem



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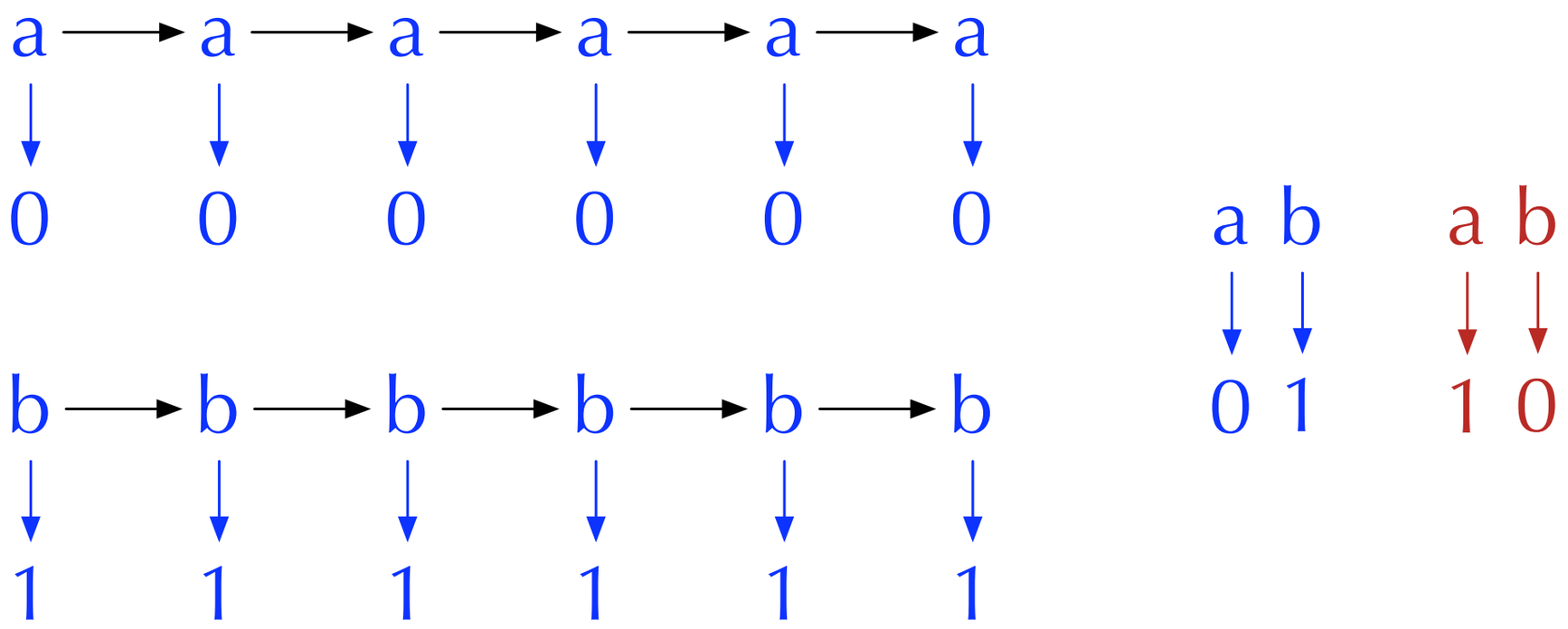

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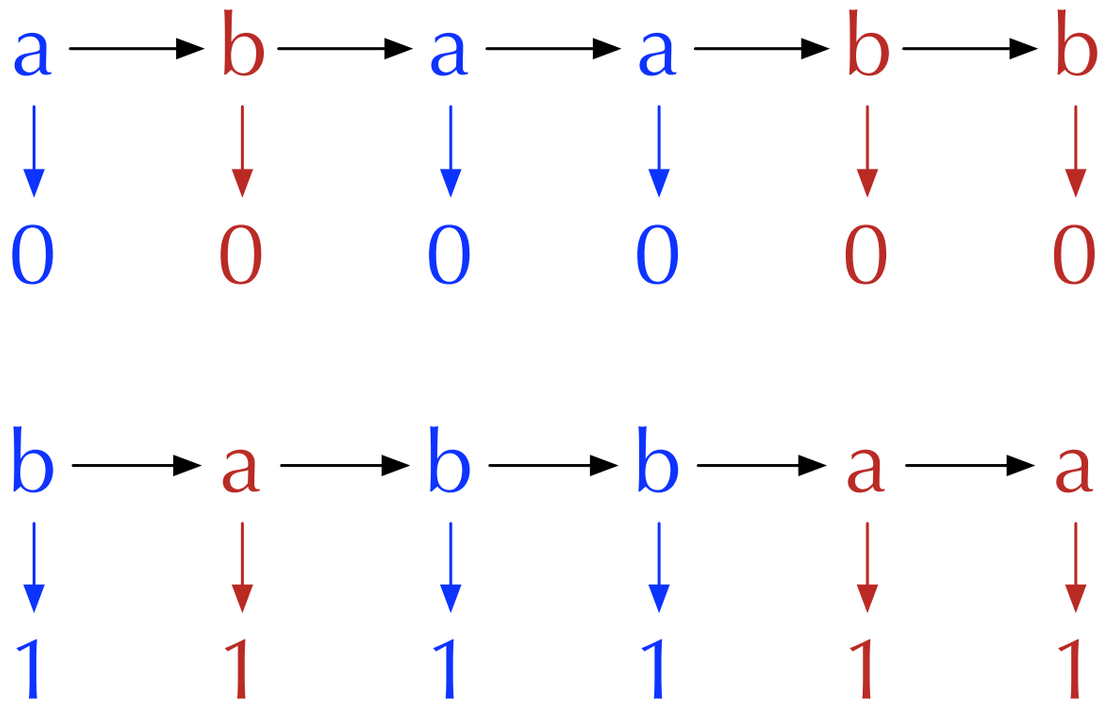

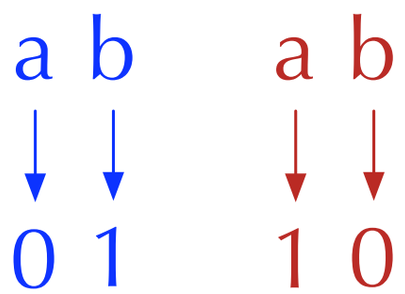

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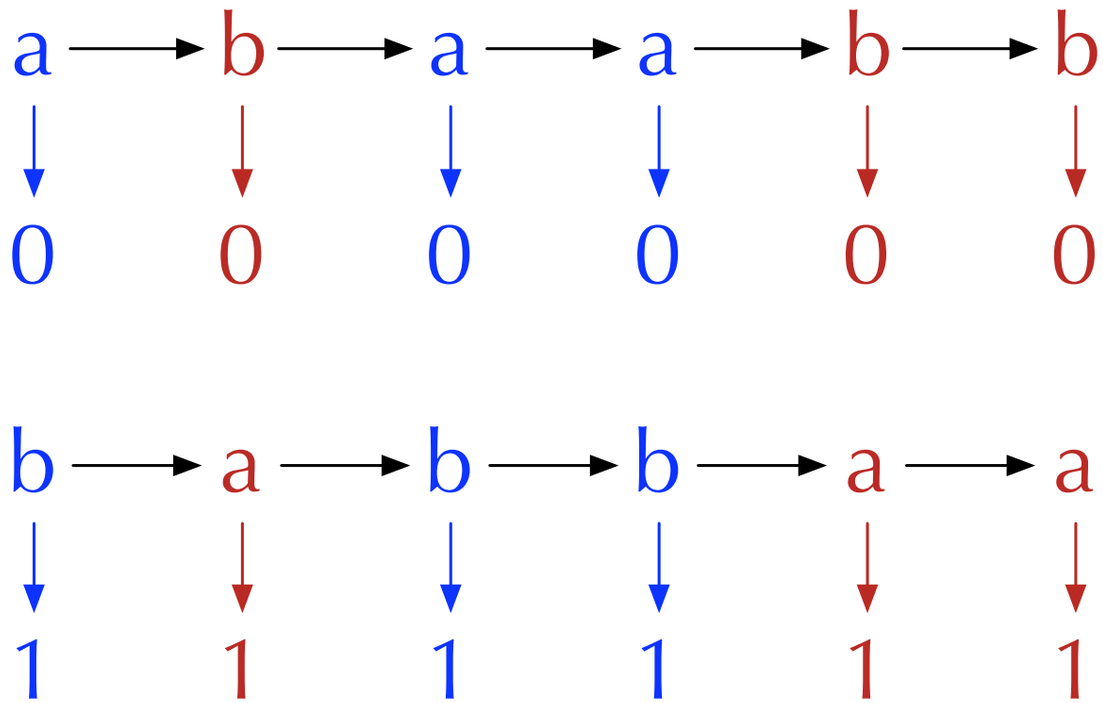

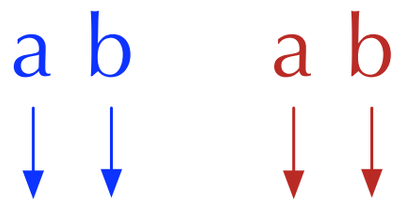

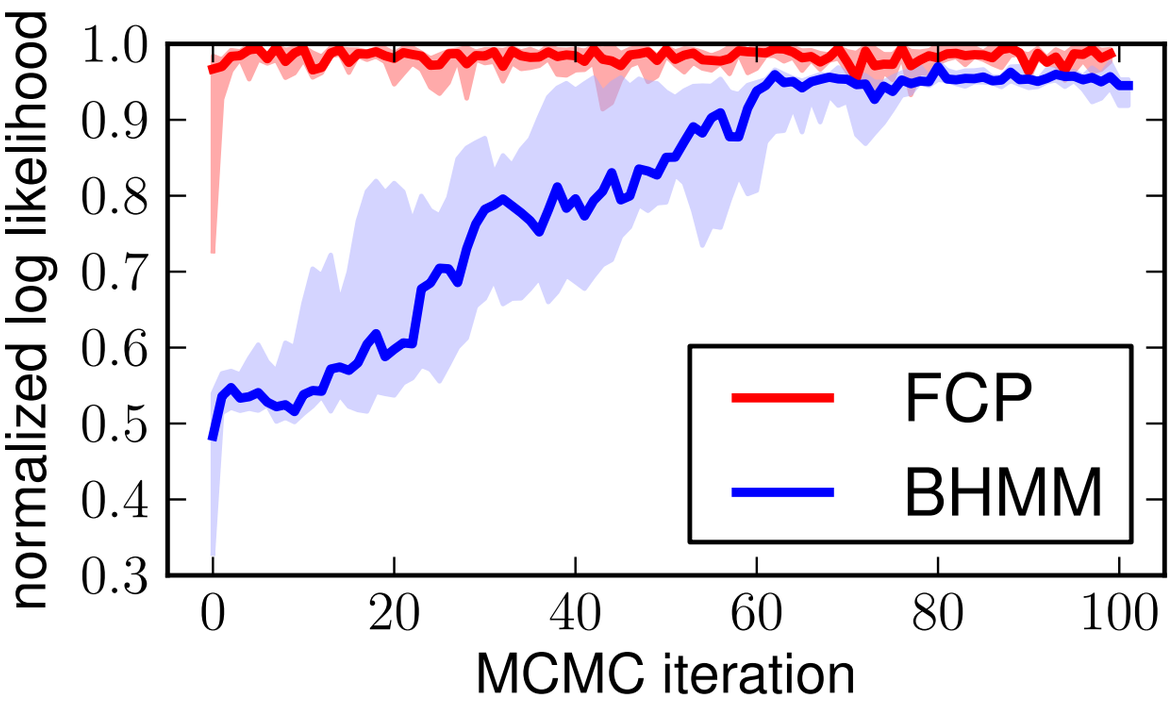

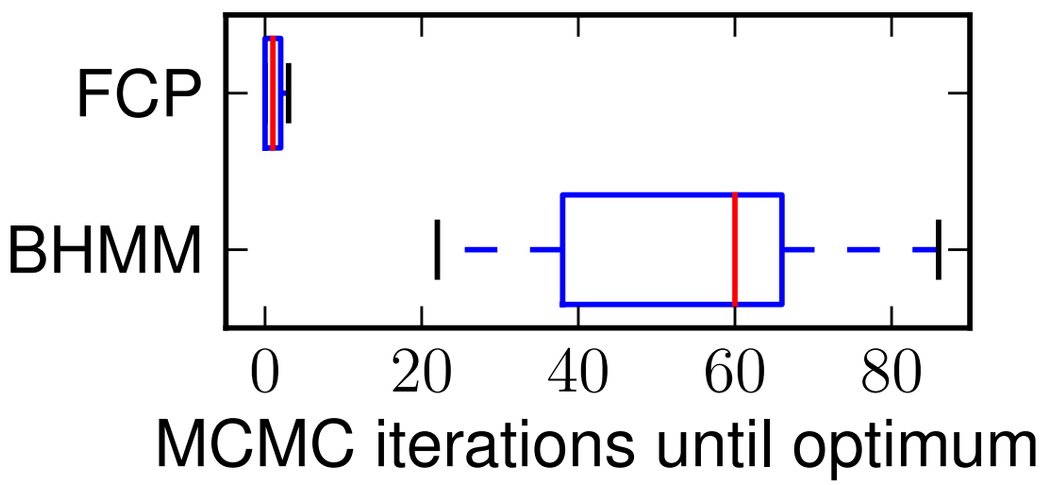

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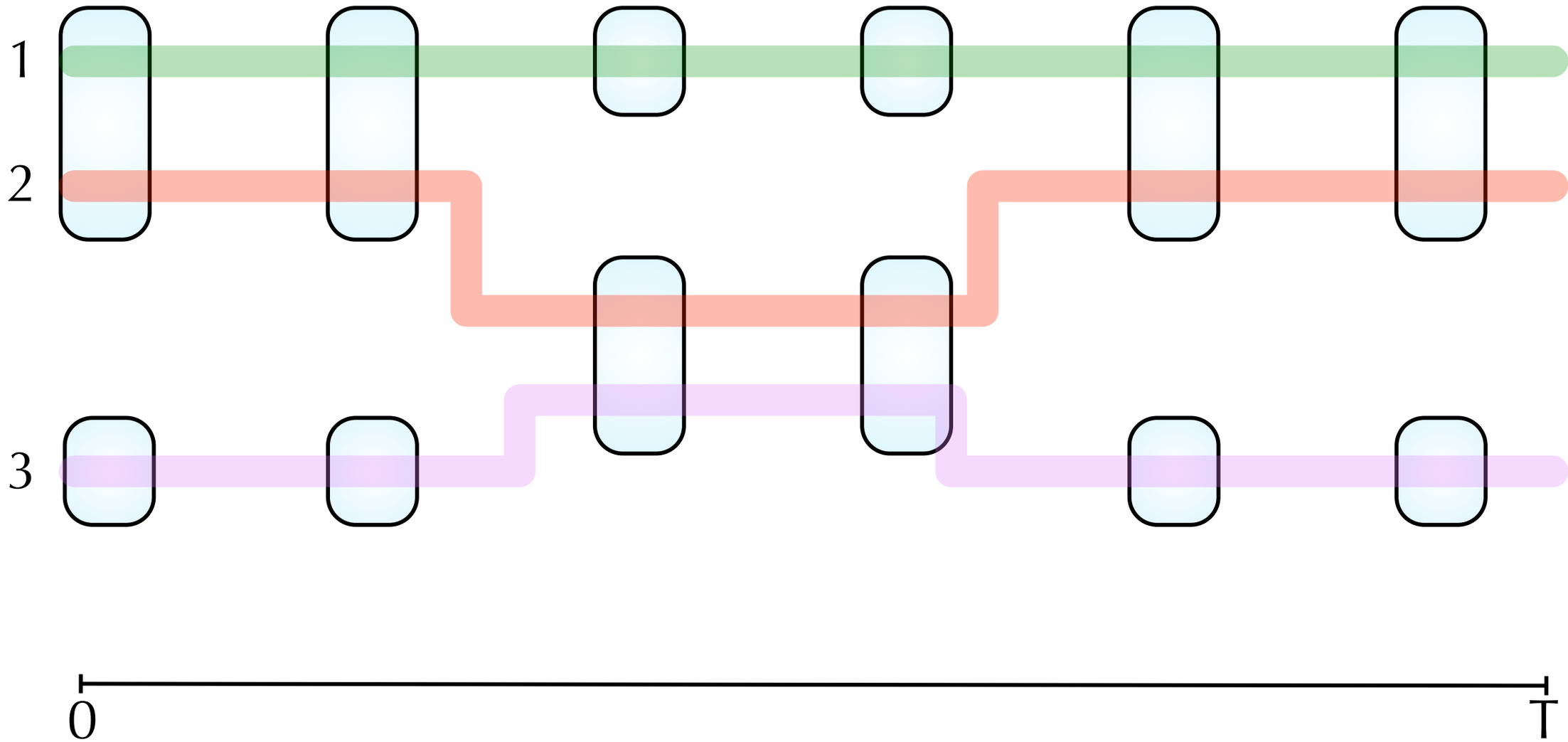
Chinese Restaurant Process Through Time



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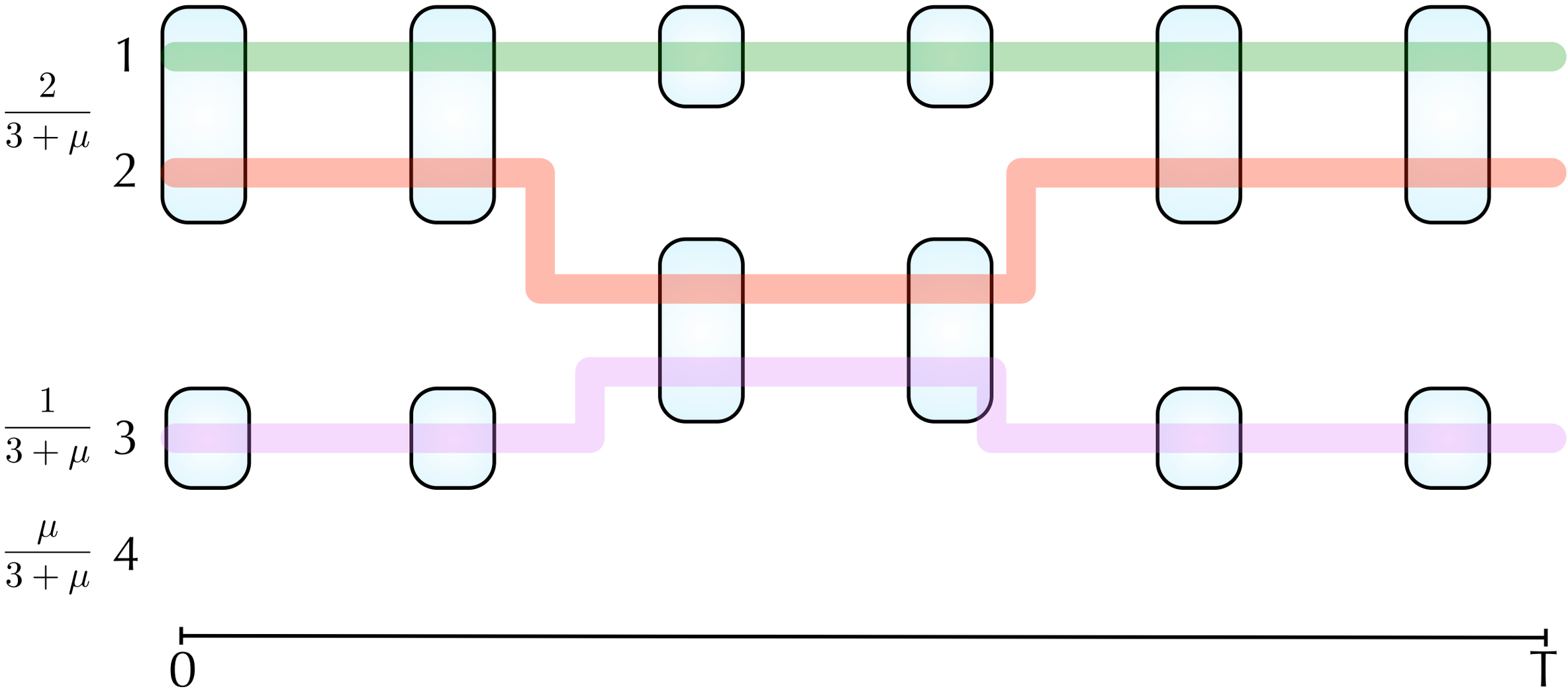

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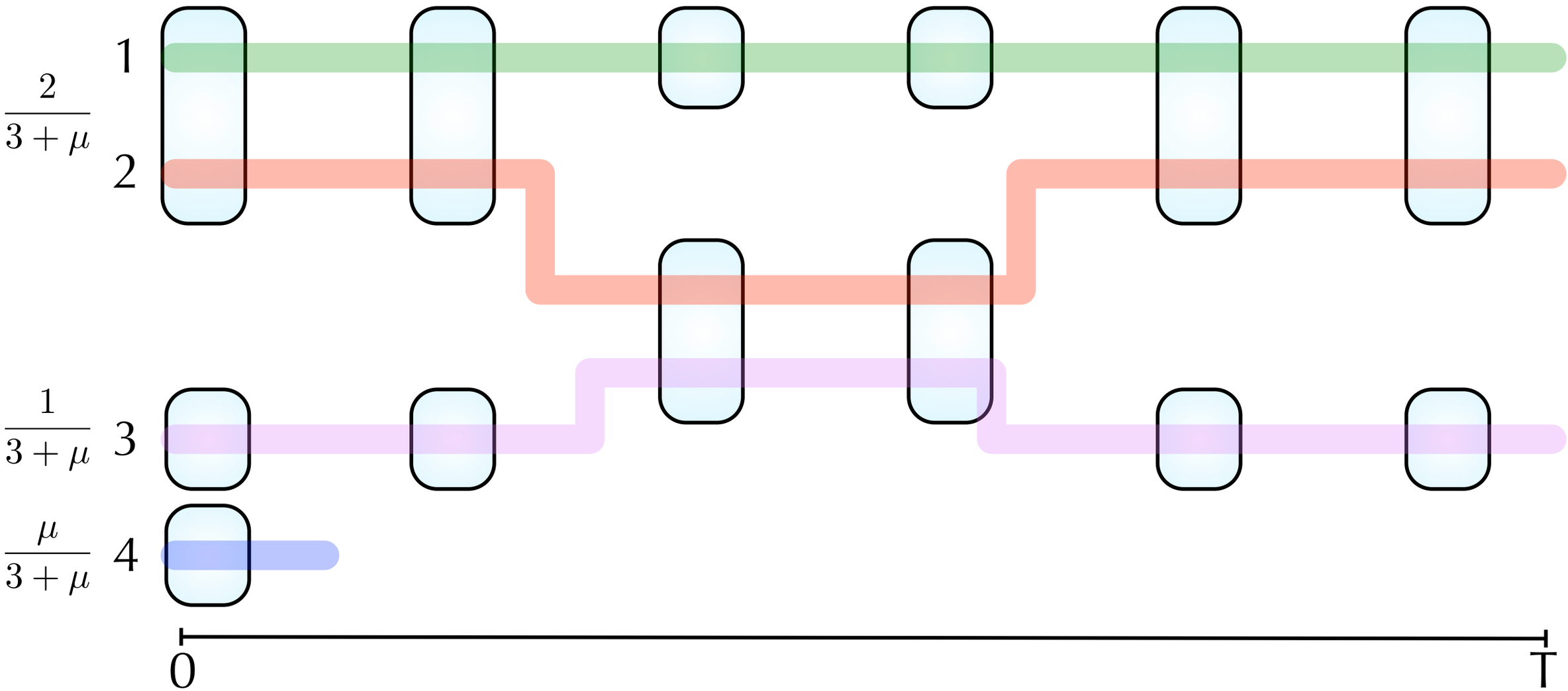

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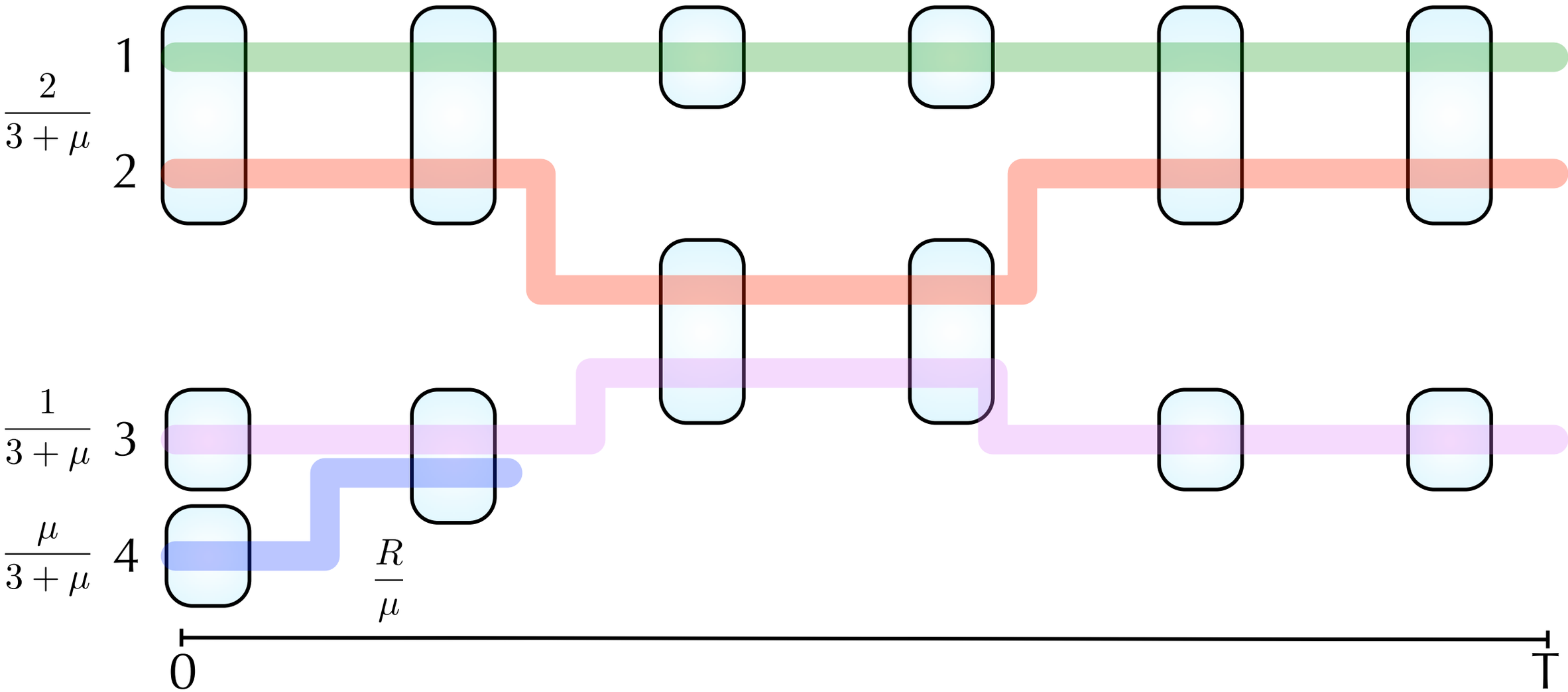

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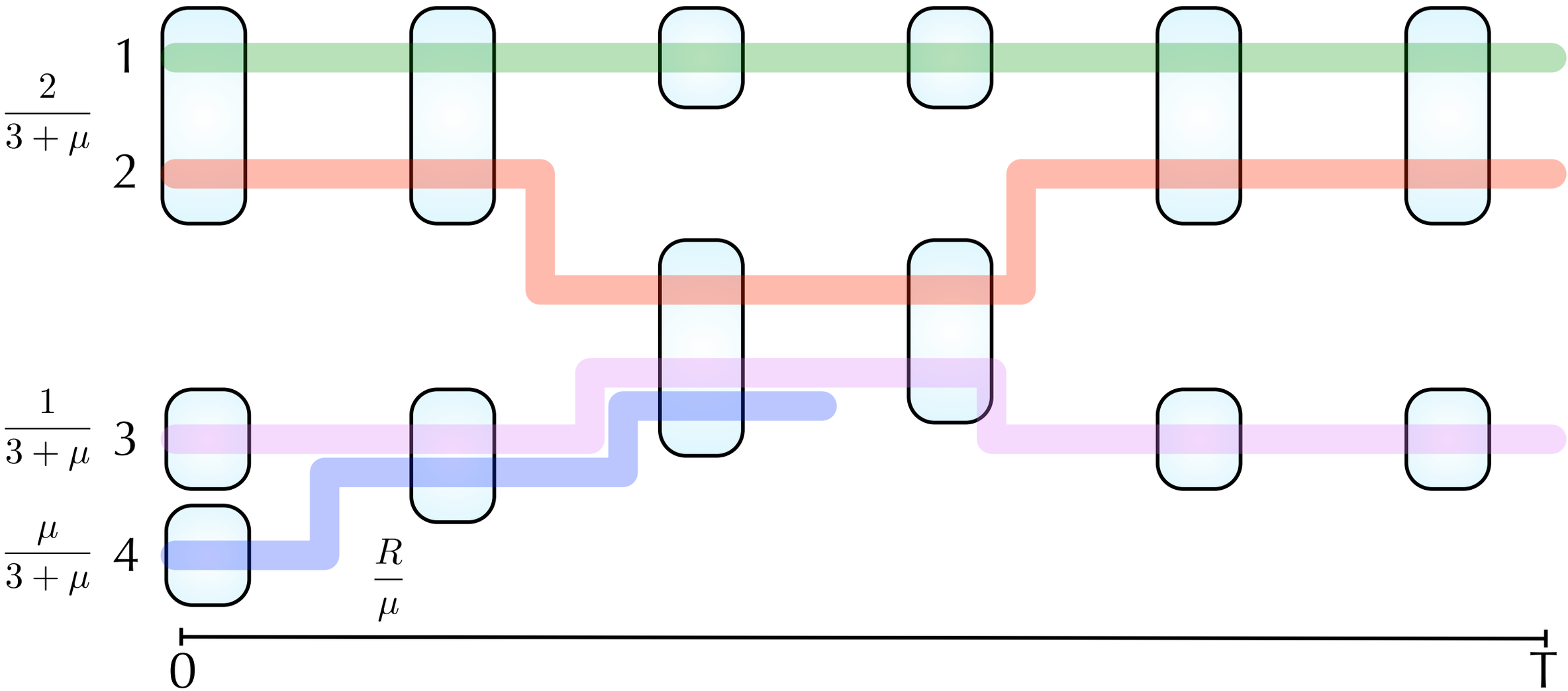

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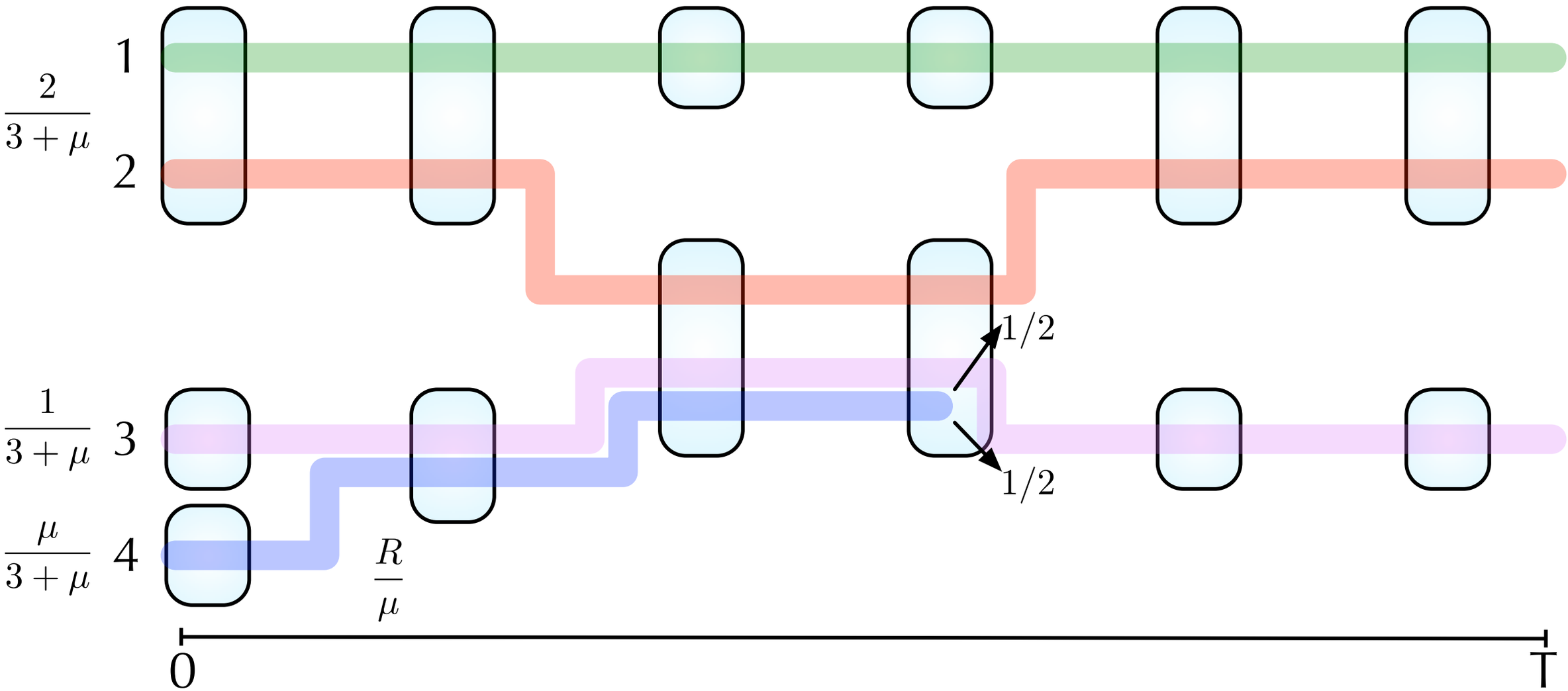

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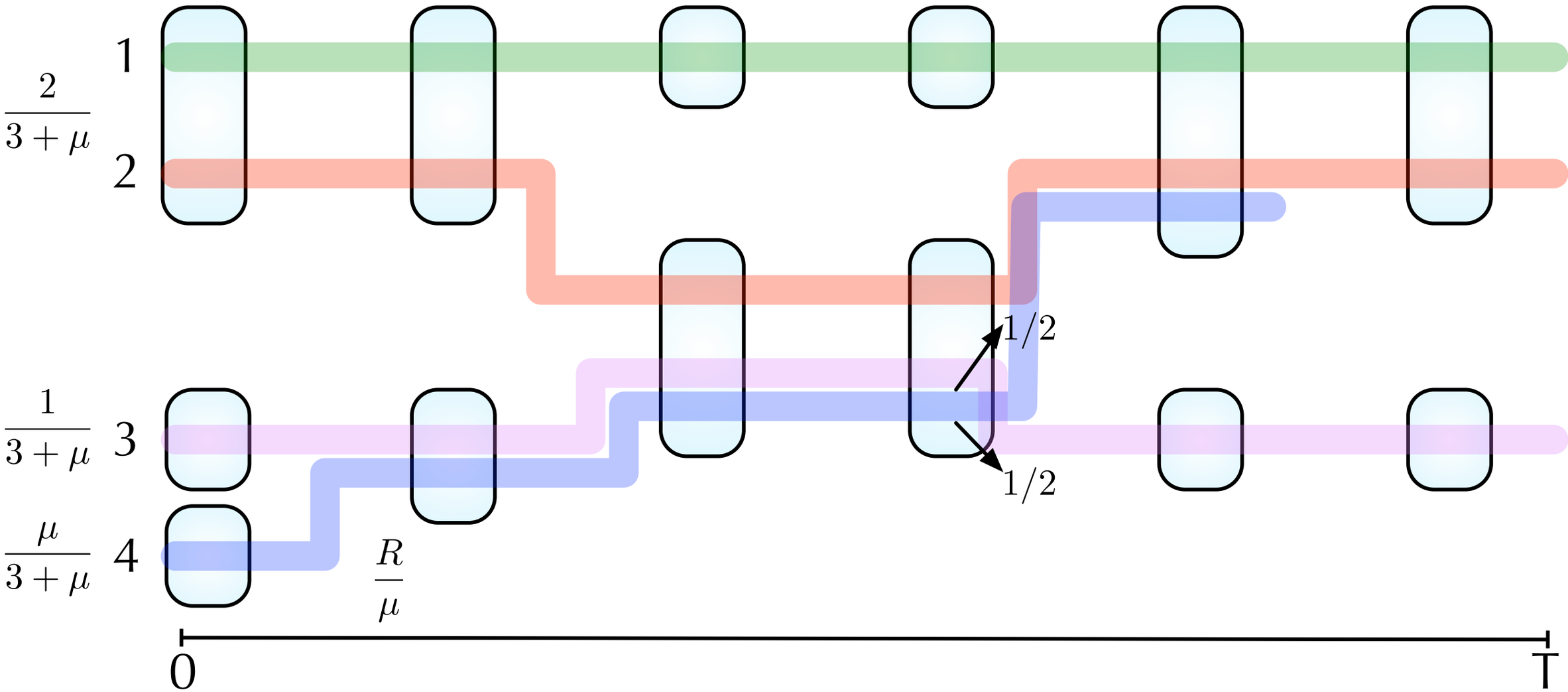

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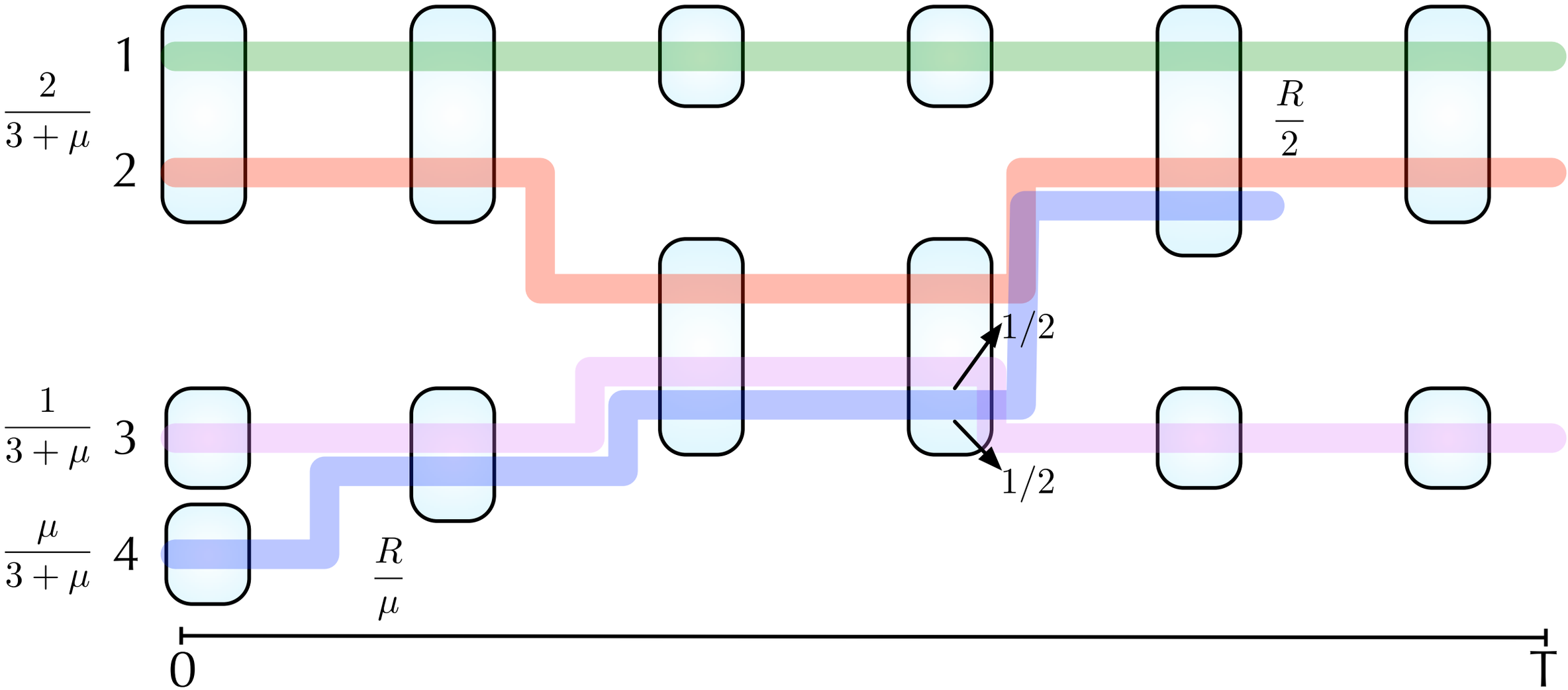

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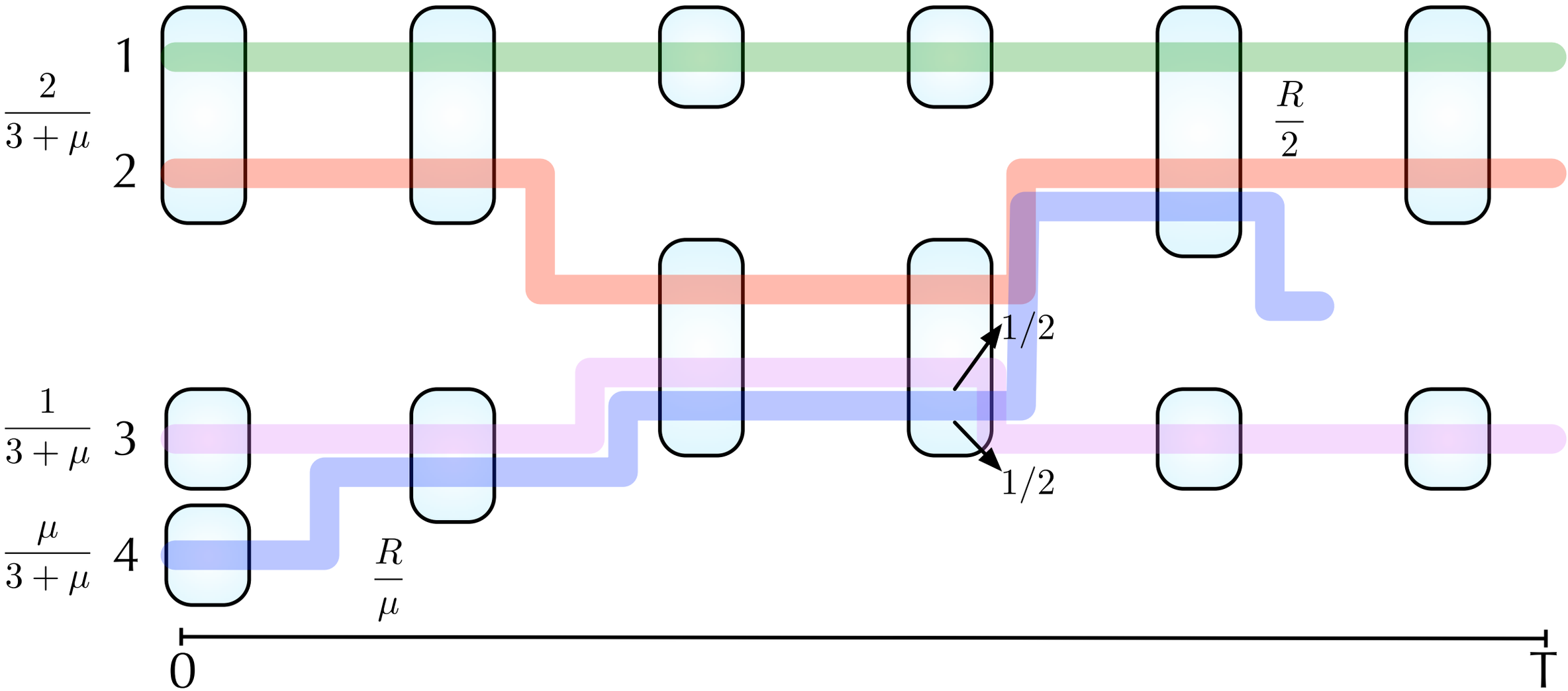

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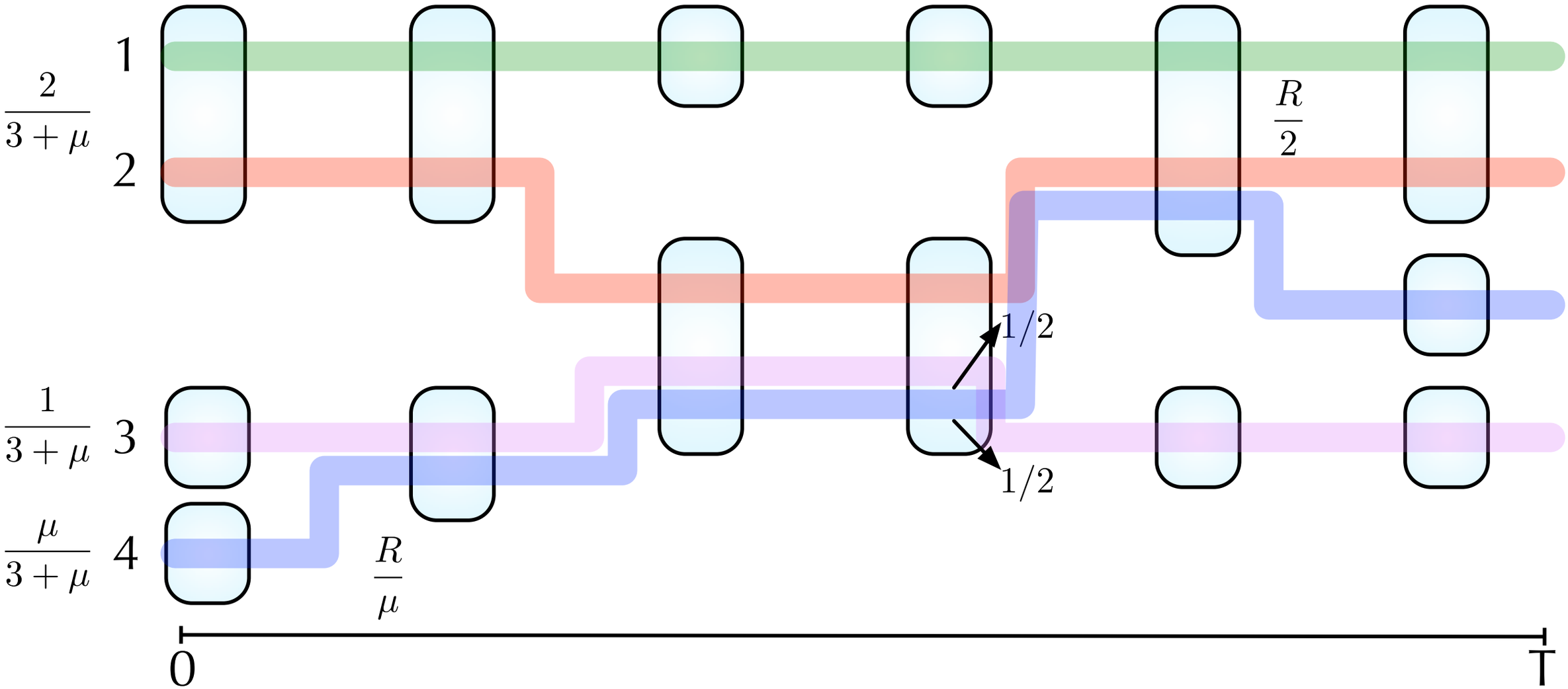

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Partitions

- Set [n] = {1,2,...,n} indexing n sequences.
- Partition of [n], e.g.:

$$\{\{1,3,6\},\{2,7\},\{4,5,8\},\{9\}\}$$

  - Non-empty;
  - Disjoint;
  - Union is [n]; and
  - Unlabelled.