Modelling DNA sequence evolution with interacting particle systems

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Stochastic nucleotidic substitution models

Common assumptions of the usual models

- A DNA sequence is an element of $\{A, T, C, G\}^N$, $N \in \mathbb{N}^*$.
- **Independent** evolution of the sites according to a **Markovian kernel**.

Example: Jukes and Cantor model (1969)

- Rate matrix ($\lambda > 0$)

	A	T	C	G
A	·	λ	λ	λ
T	λ	·	λ	λ
C	λ	λ	·	λ
G	λ	λ	λ	·

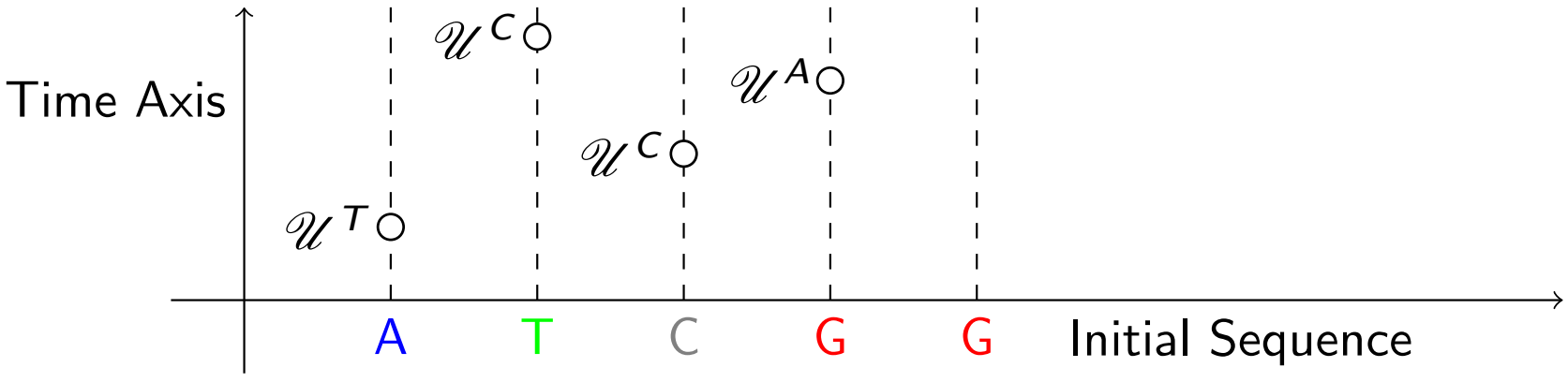
- **Diagonal** entry $-q_{aa}$ is the substitution rate of nucleotide a, here $q_{aa} = -3\lambda$.
- **Non-diagonal** entry q_{ab} is the substitution rate of nucleotide a by b, here $q_{ab} = \lambda$.

Modelisation

- At any site x, we run a **Poisson point process** with parameter 3λ.
- At any **point**, the nucleotide $\eta(x)$ is substituted by $a \in \{A, T, C, G\} \setminus \{\eta(x)\}$ with probability $1/3$.

Alternative, equivalent but faster modelisation

	A	T	C	G
A	$\cdot$	λ	λ	λ
T	λ	$\cdot$	λ	λ
C	λ	λ	$\cdot$	λ
G	λ	λ	λ	$\cdot$



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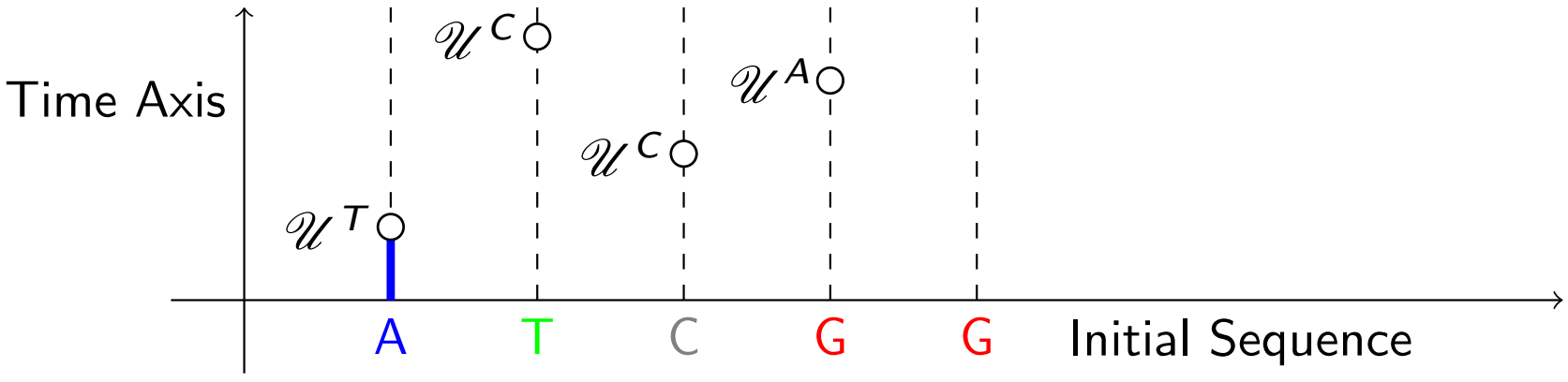

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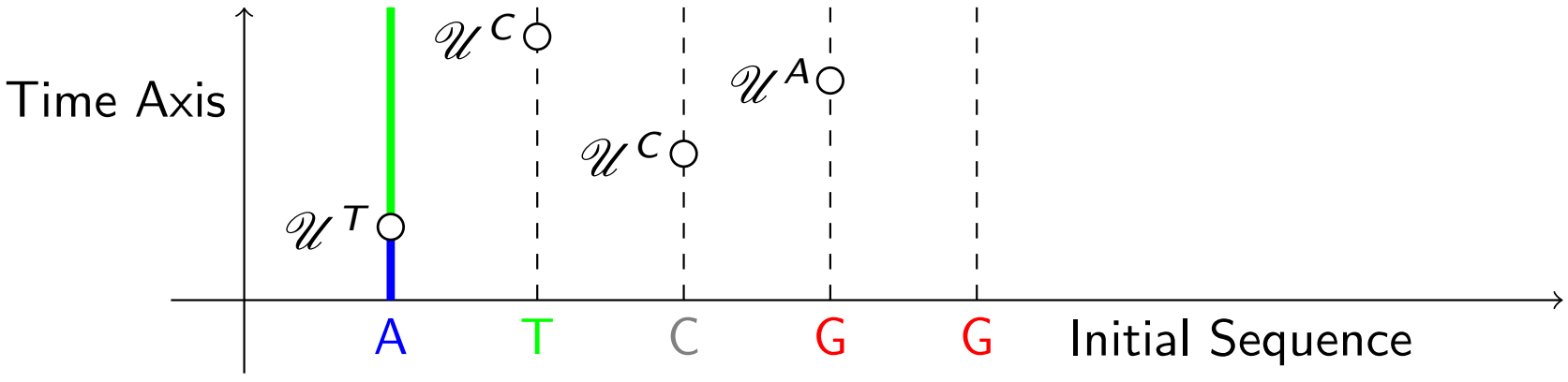

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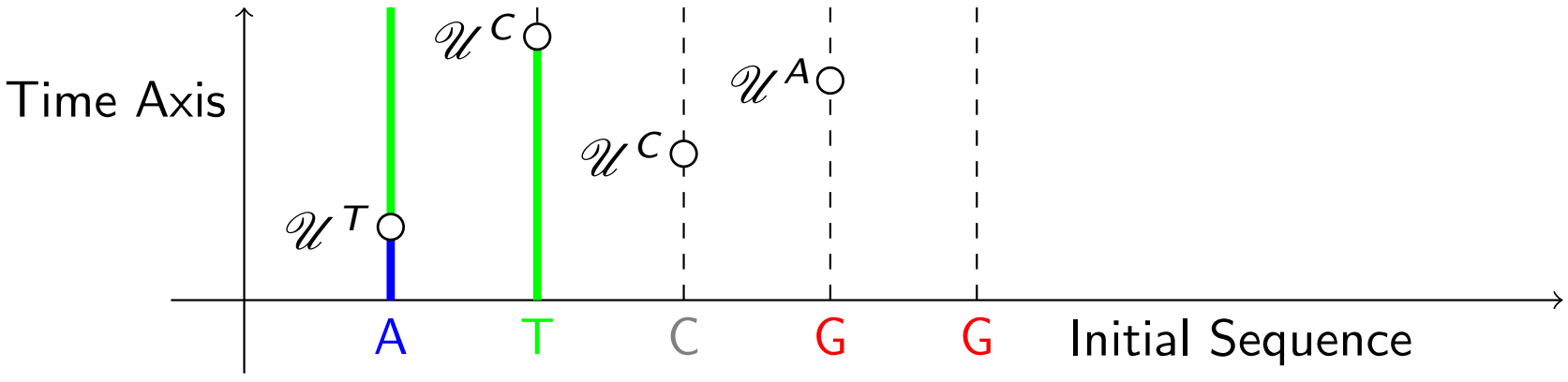

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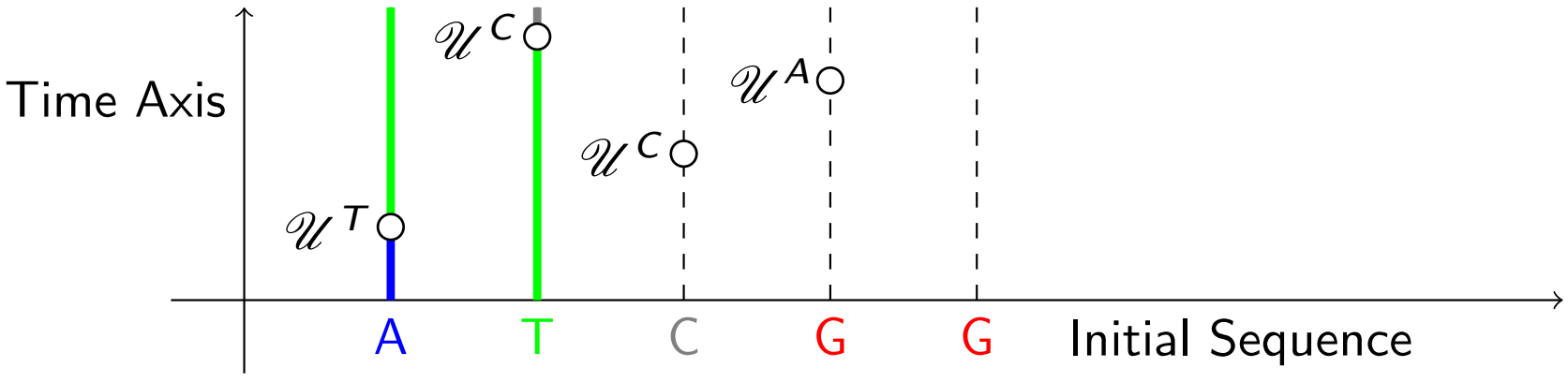

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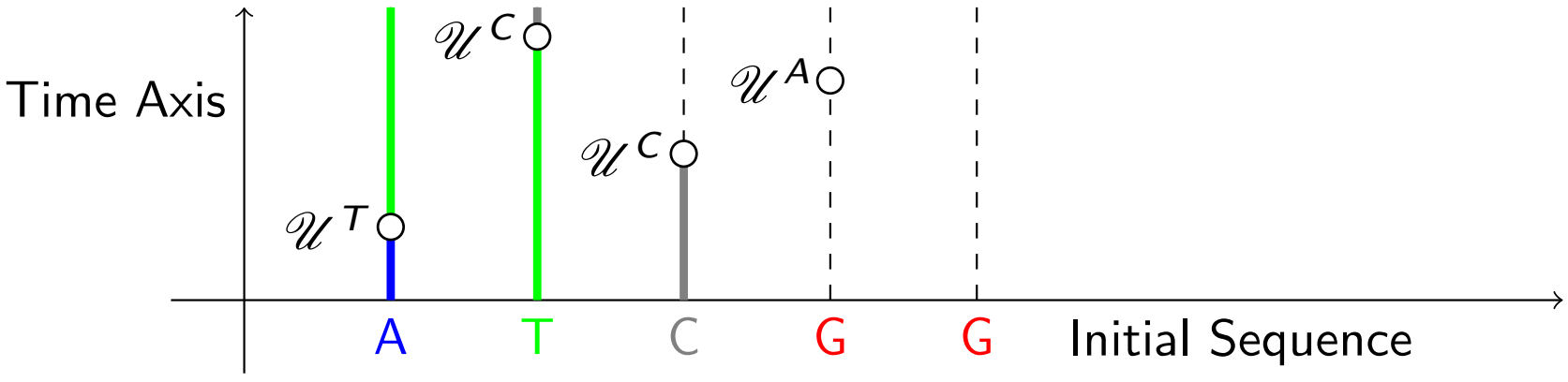

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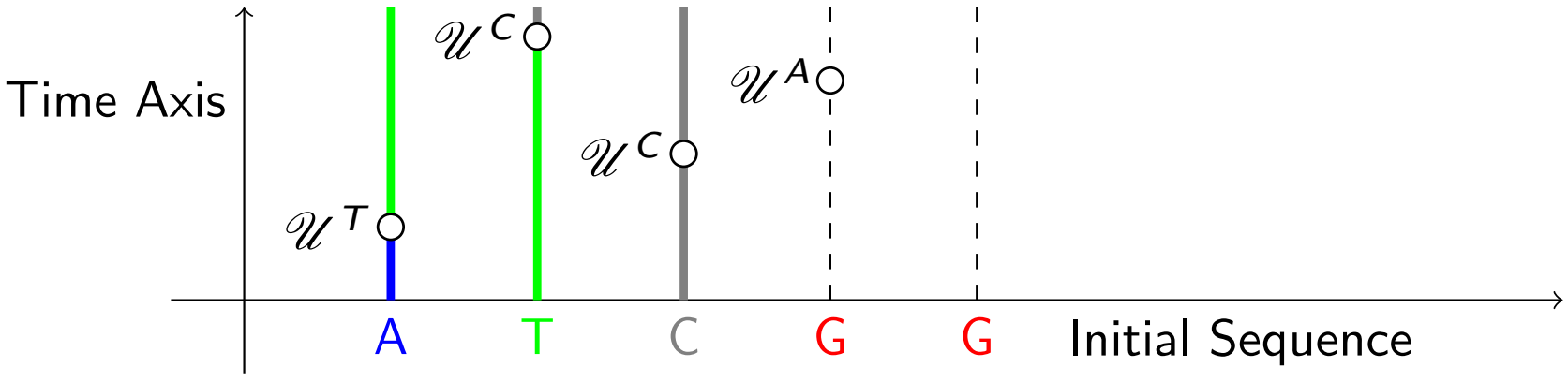

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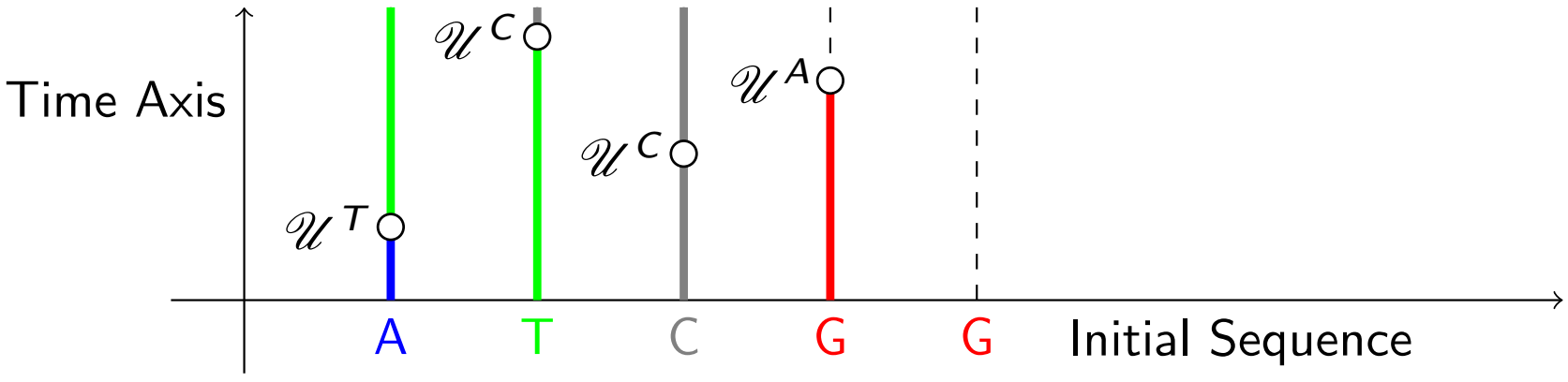

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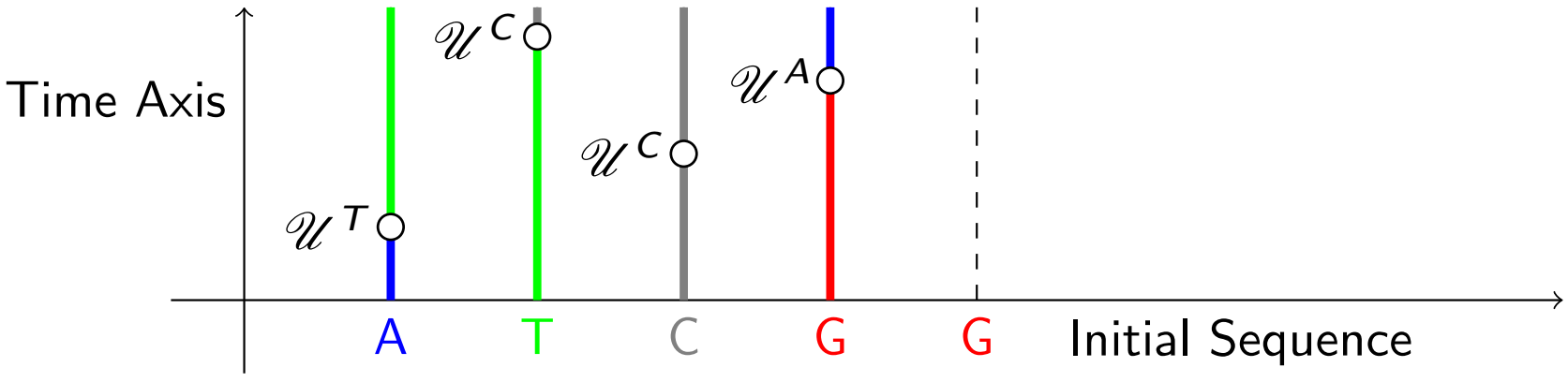

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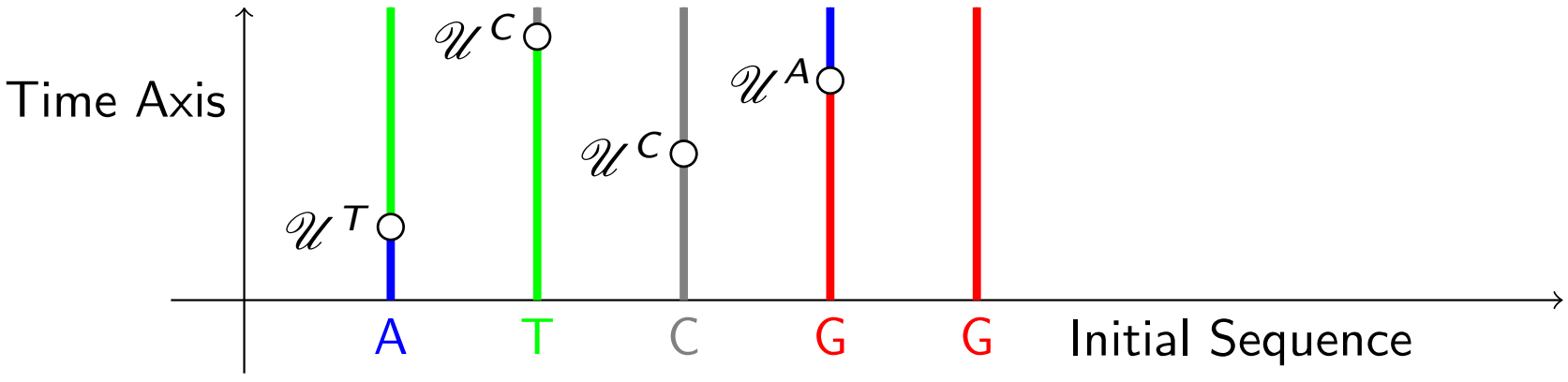

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Stochastic nucleotidic substitution models

Consequences

- Convergence in distribution at any site

- Convergenge in distribution of the whole sequence to the **product measure**.

Problems

- $(a_1 \dots a_\ell)_{\text{obs}} \neq (a_1)_{\text{obs}} \dots (a_\ell)_{\text{obs}}$.

- The substitution rate $\eta(x) \to a$ may **dépend** de $\eta(x-1)$, $\eta(x)$ and $\eta(x+1)$.

Famous example : CpG dinucleotides

- Rate C $\to$ T up to ten times larger when C is involved in a CpG (in fact C*pG).

JC+CpG model

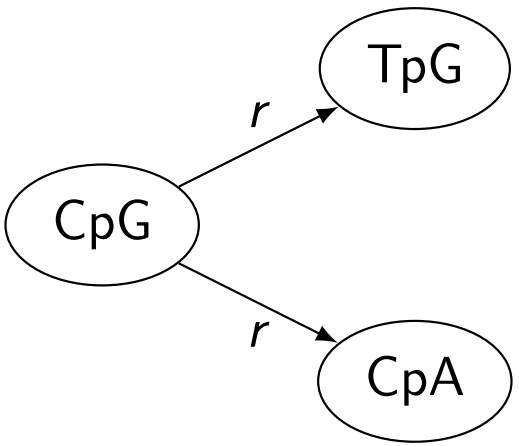
Bérard, Gouéré et Piau, *Mathematical Biosciences* (2008)

- A DNA sequence is now **doubly infinite**, that is, an element of $\{A, T, C, G\}^{\mathbb{Z}}$.

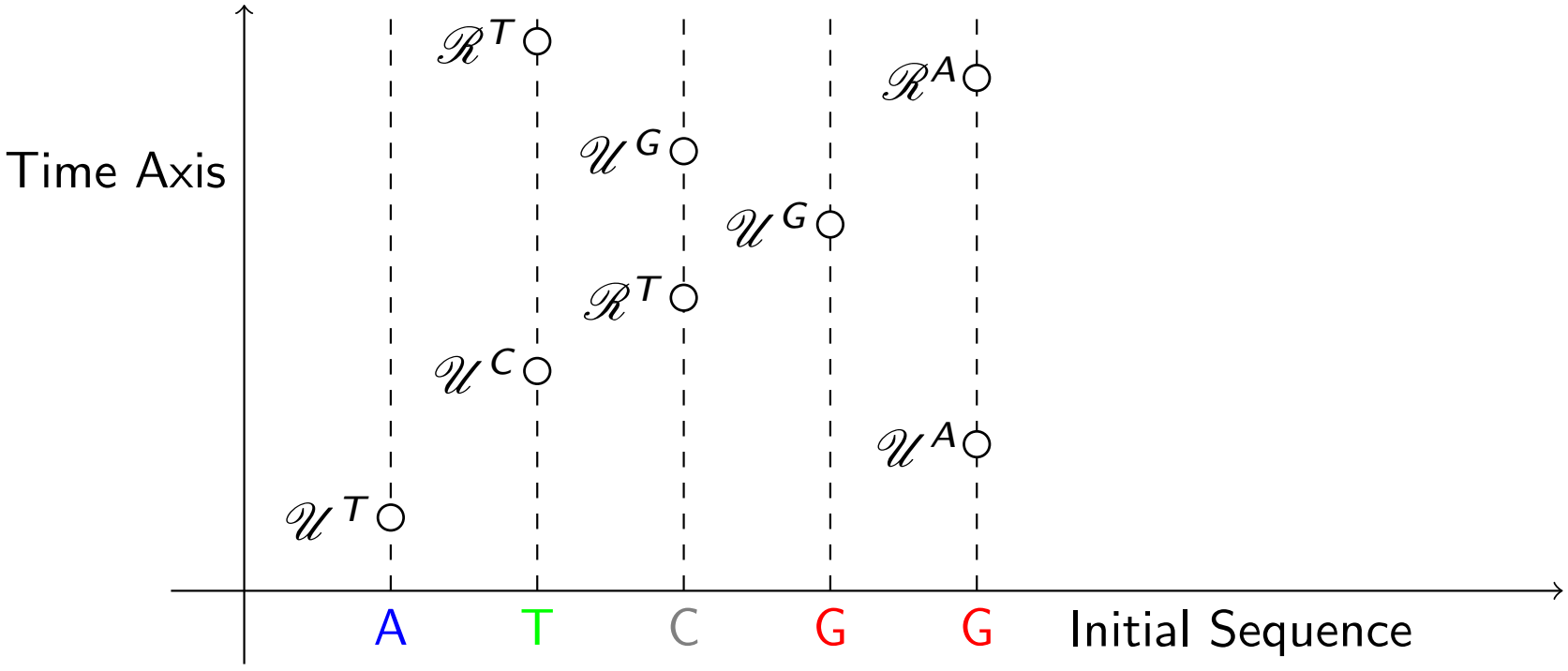
- **Keep** Jukes and Cantor model

	A	T	C	G
A	·	1	1	1
T	1	·	1	1
C	1	1	·	1
G	1	1	1	·

- **Superimpose** "double" substitution mechanism



Construction with marked Poisson point processes



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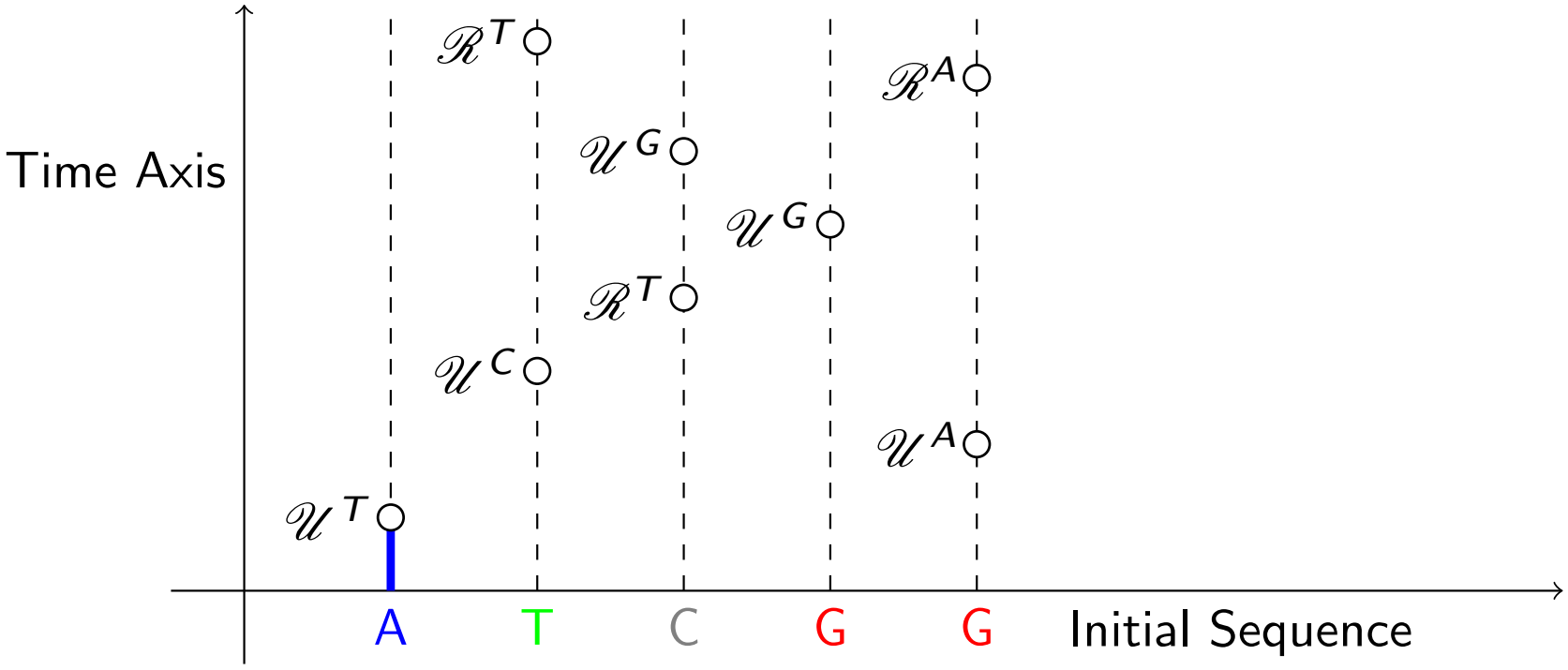

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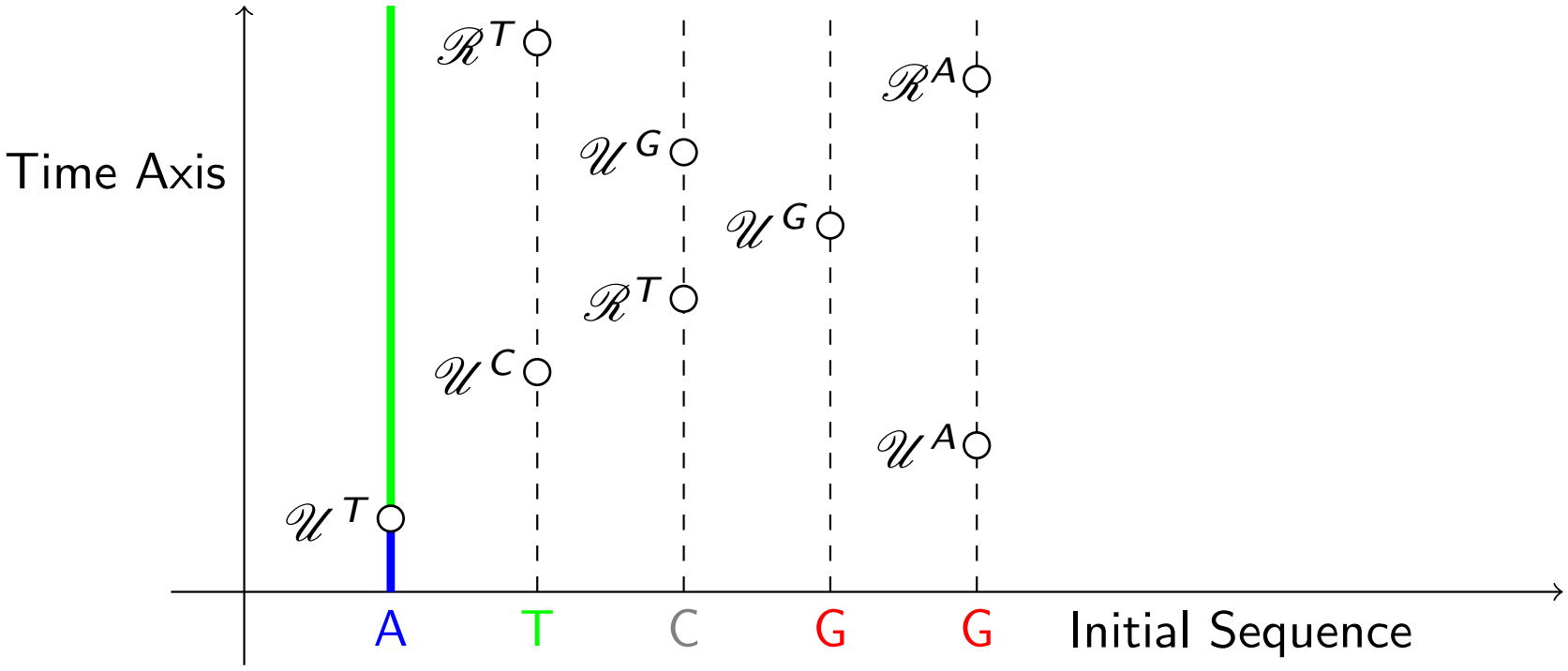

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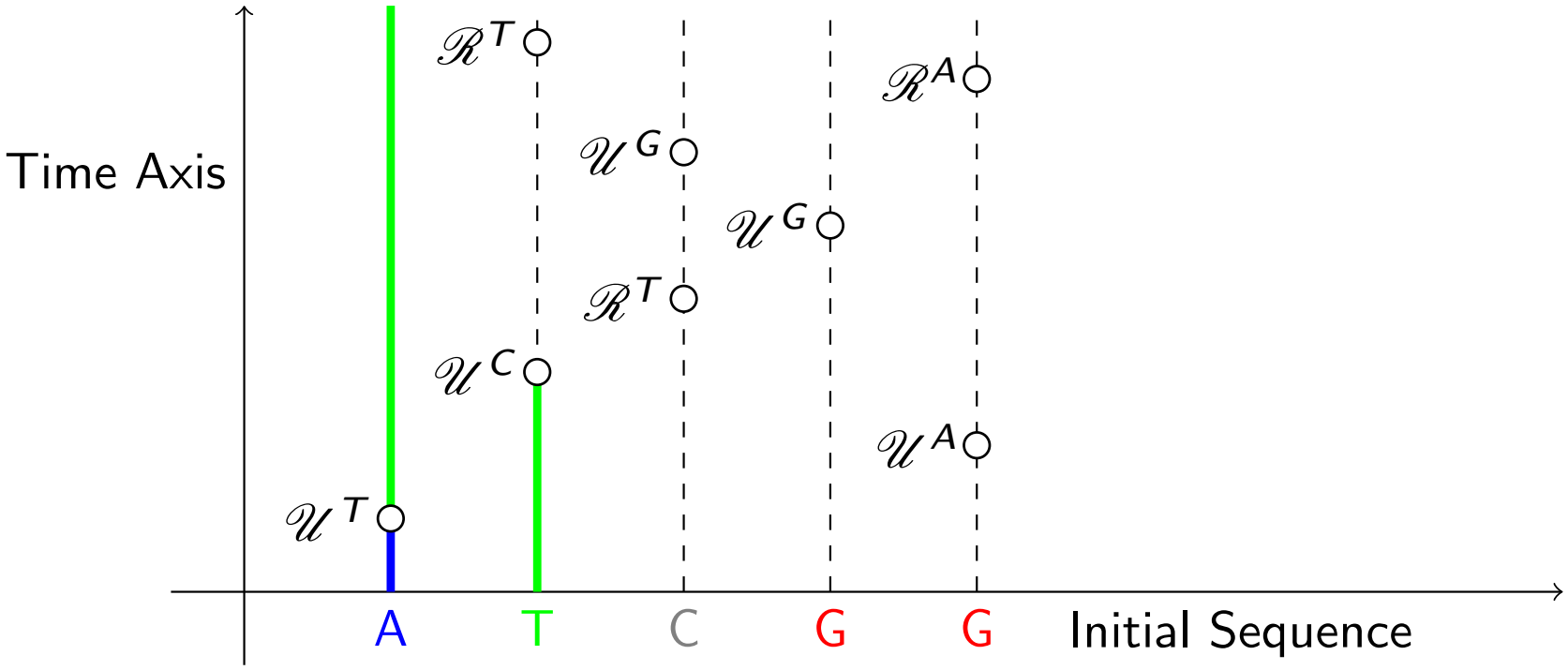

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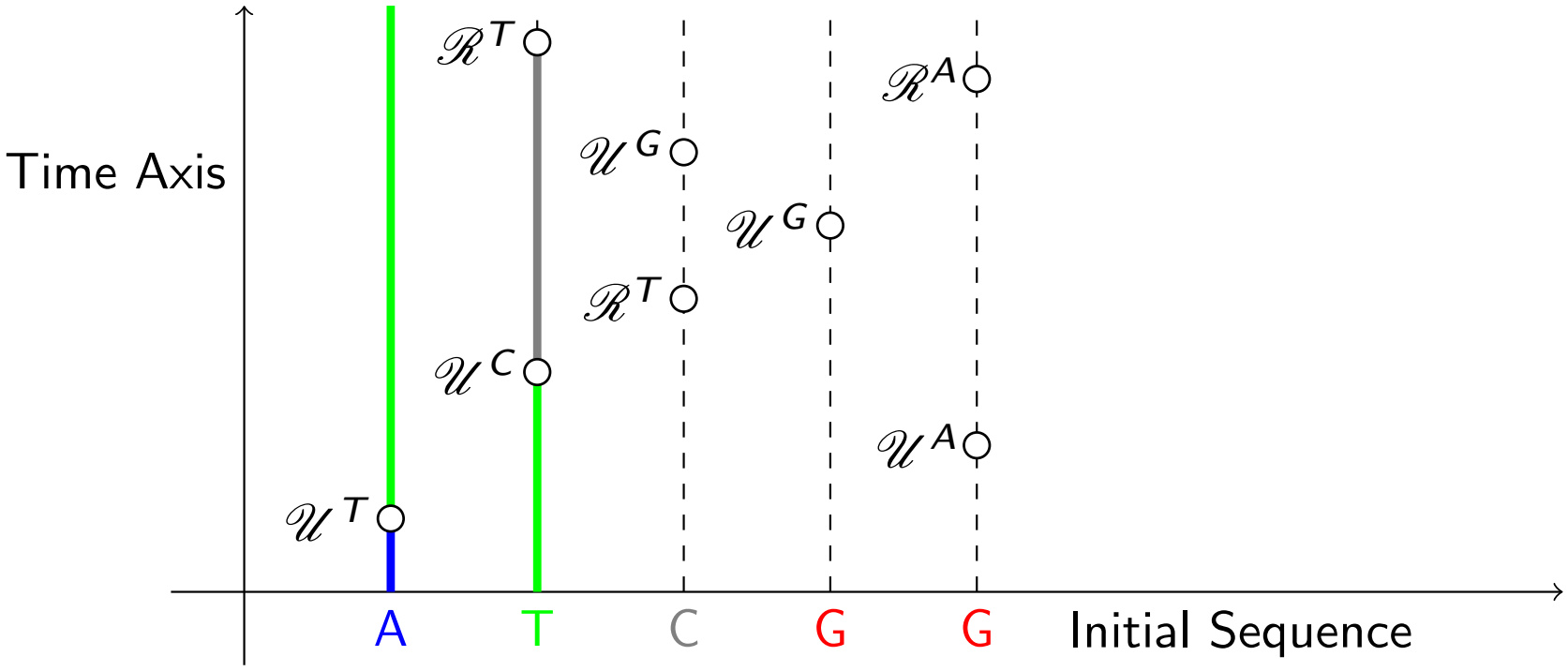

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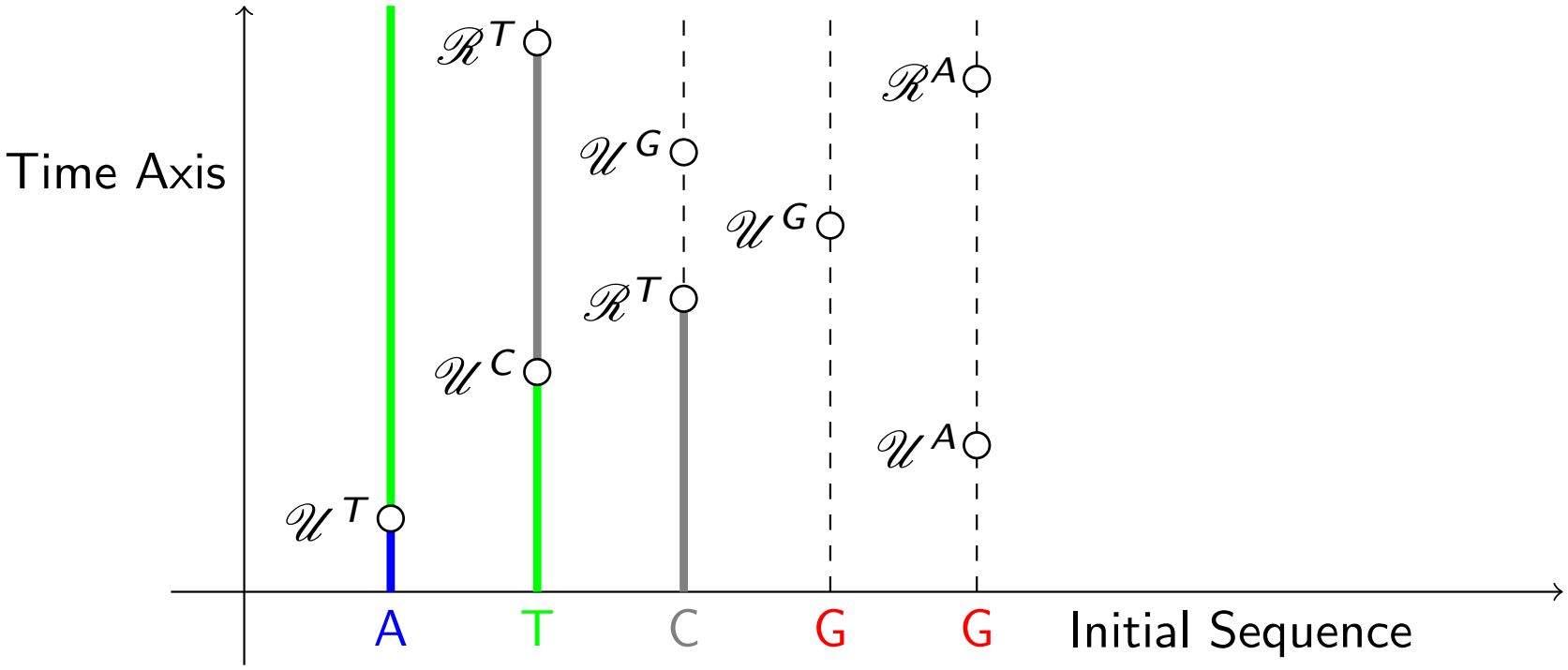

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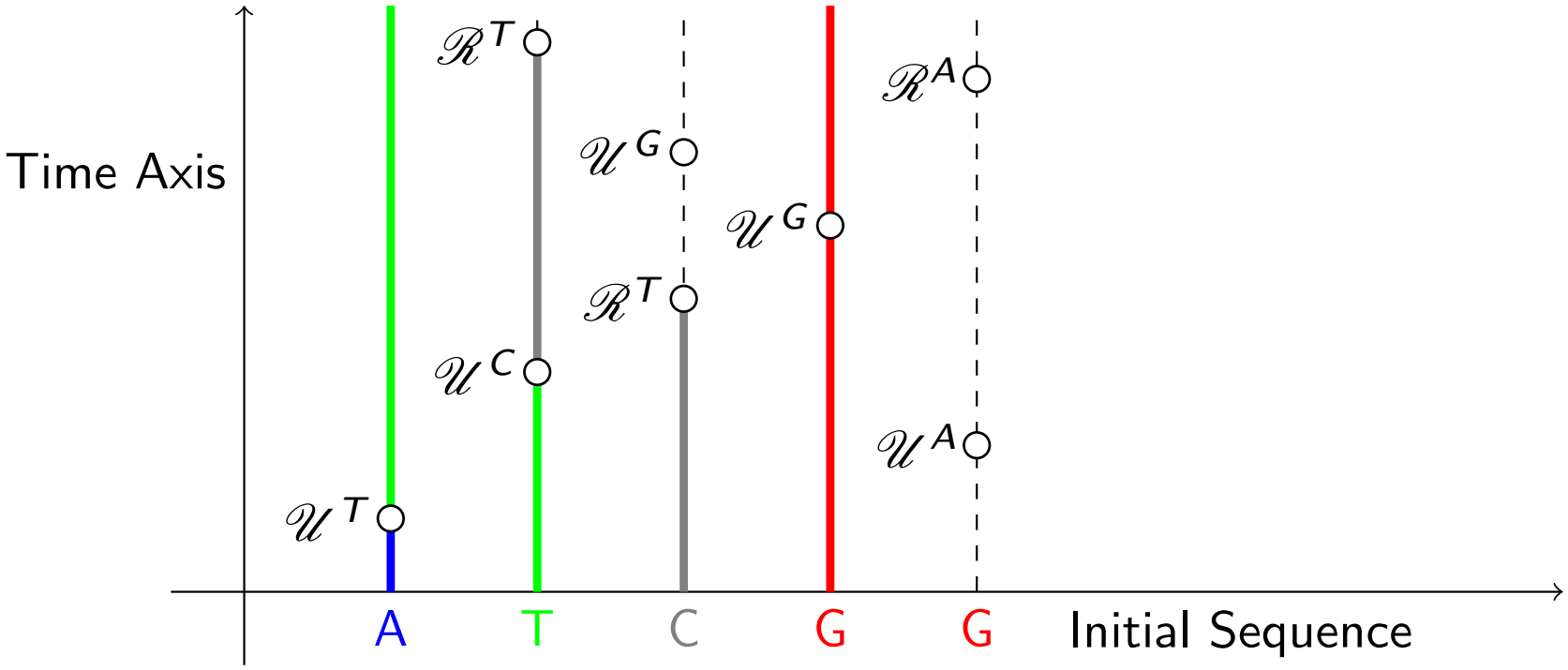

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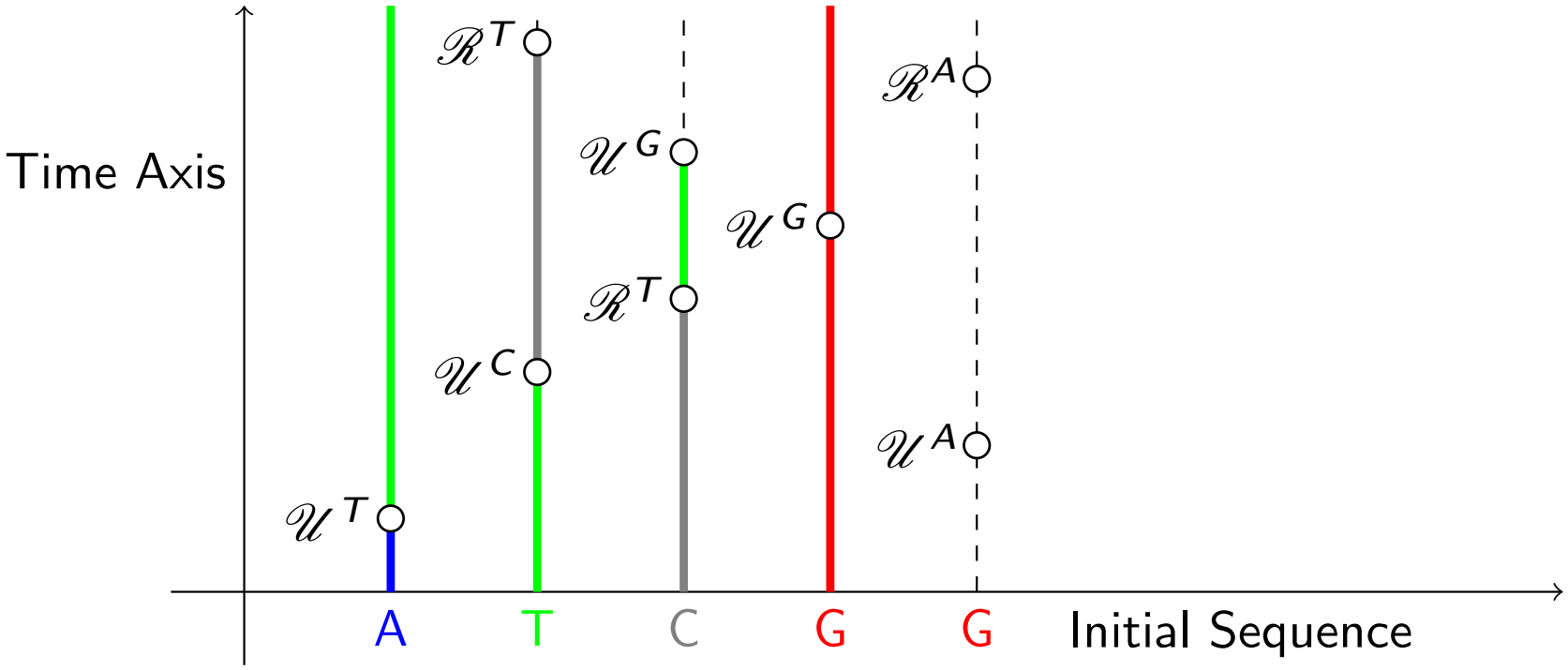

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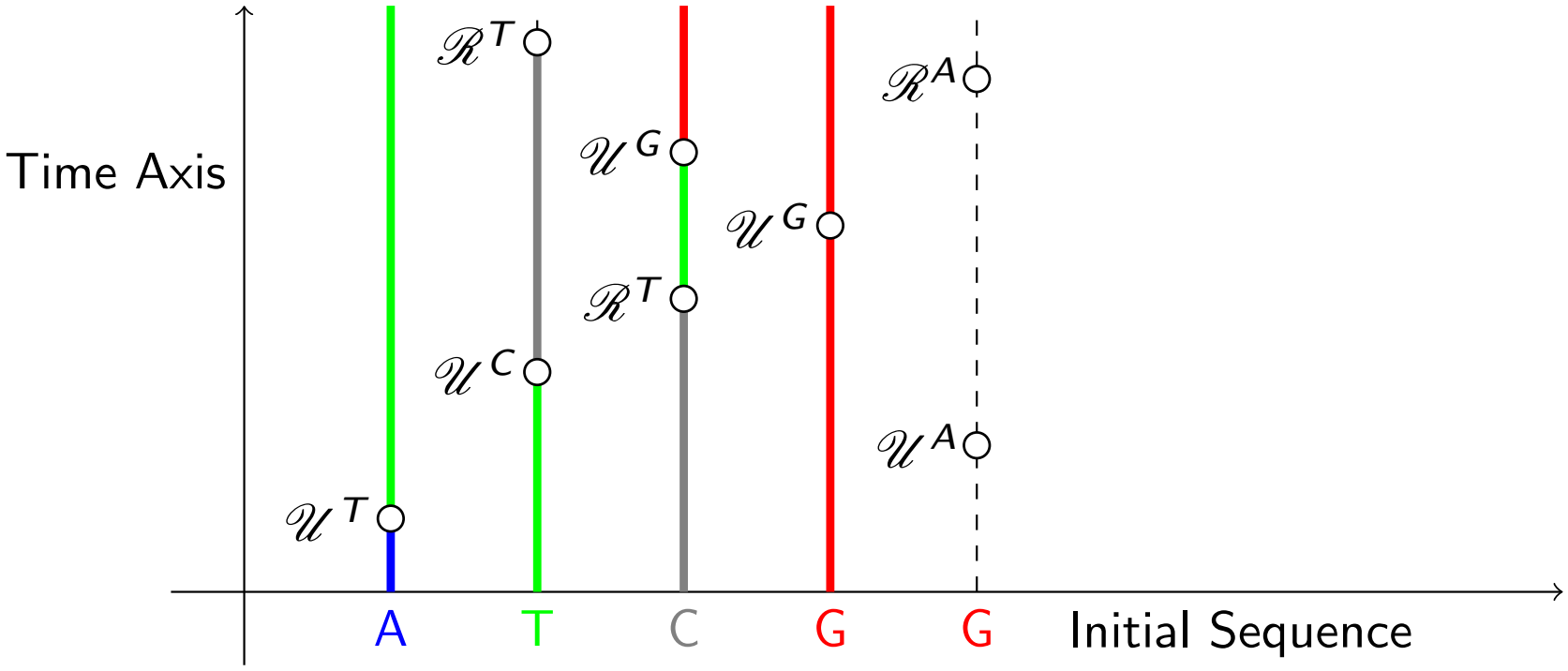

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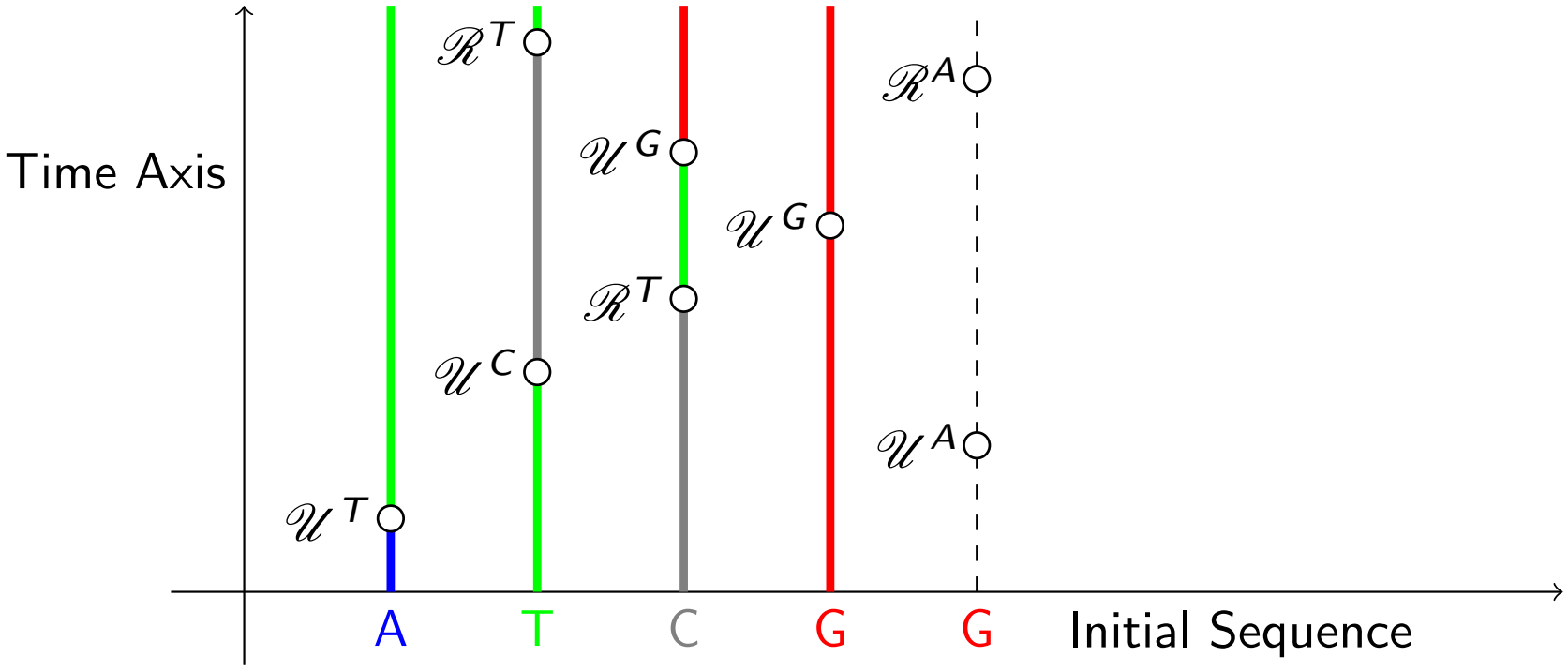

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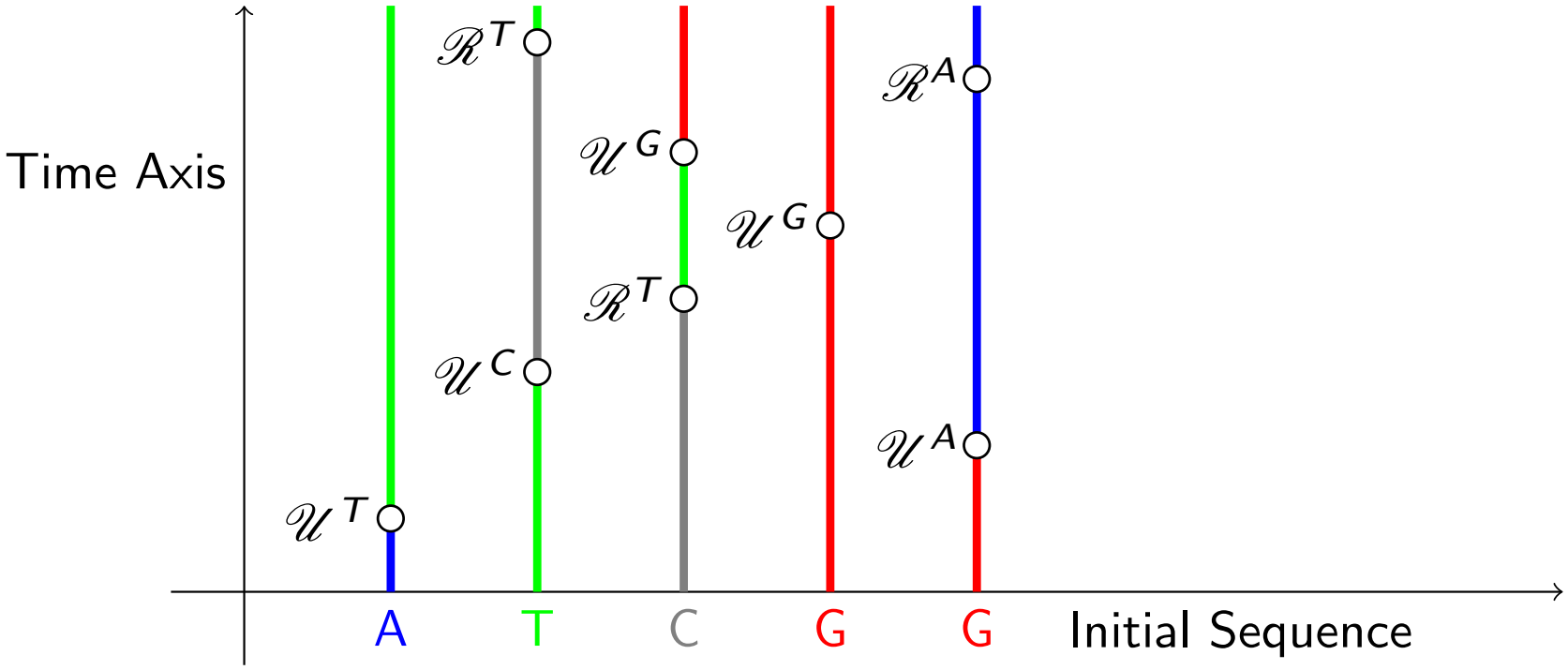

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To know more about interacting particle systems

Bible: **Liggett, *Interacting particle systems*, Springer (1985)**

Durrett, *Ten lectures on interacting particle systems*, Springer (1993)

Properties

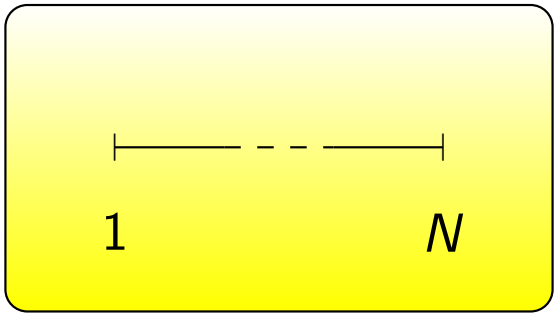
Bérard, Gouéré et Piau, *Mathematical Biosciences* (2008)

- **There exists a unique Markov process** on $\mathscr{A}^{\mathbb{Z}}$ with the transition rates defined before.

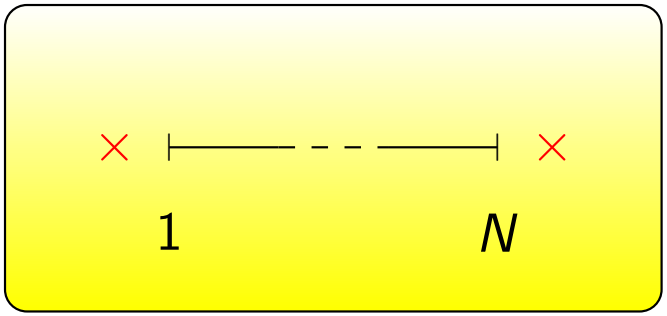
- The process is **ergodic**, its unique invariant probability measure π on $\mathscr{A}^{\mathbb{Z}}$ is **translation invariant** and **ergodic** with respect to the translations on $\mathbb{Z}$.

- Starting from equilibrium, any collections $(\eta_x)_{x\in I}$ and $(\eta_y)_{y\in J}$ are **indépendent** as soon as $\mathrm{dist}(I, J) \geqslant 3$.

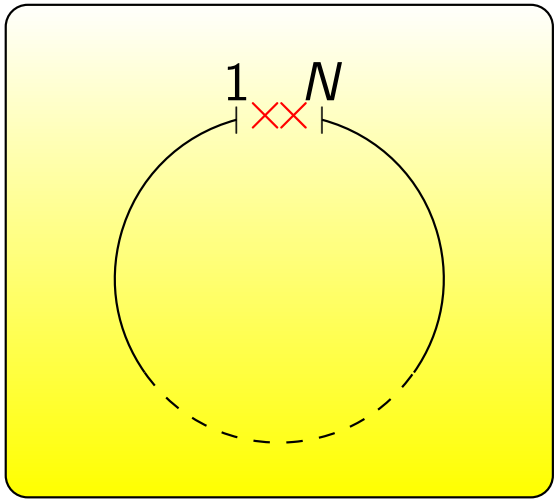
Simulate the evolution of a finite DNA sequence



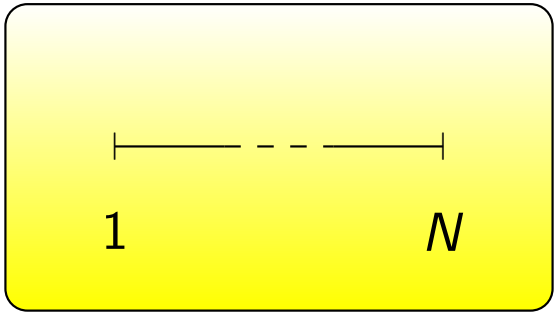
Add two artificial sites



Transform the linear sequence into a circular one



Run the evolution process with marked Ppp's and remove the two artificial sites



Example of translocation

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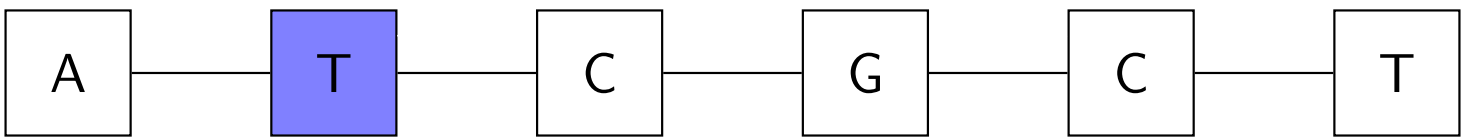

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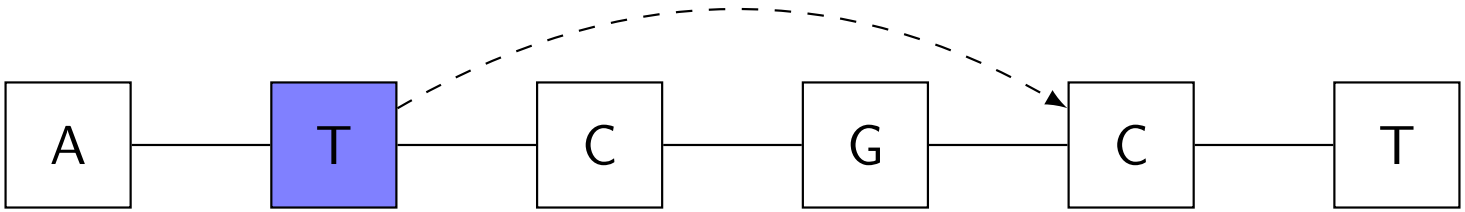

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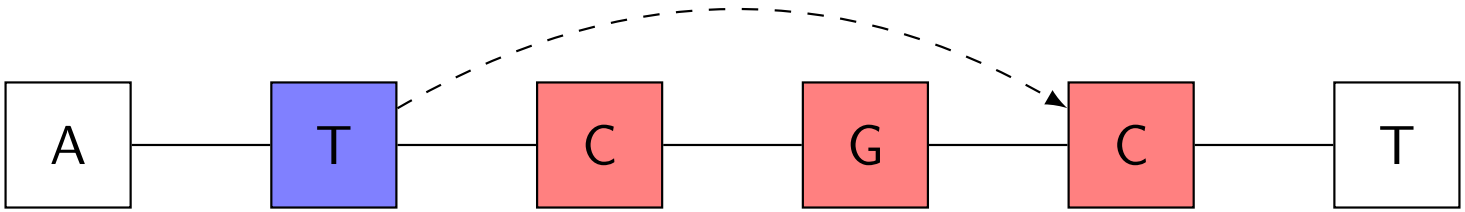

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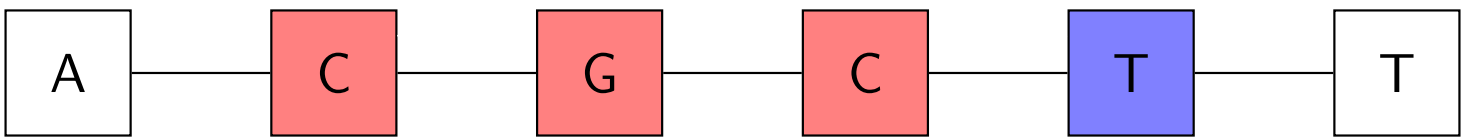


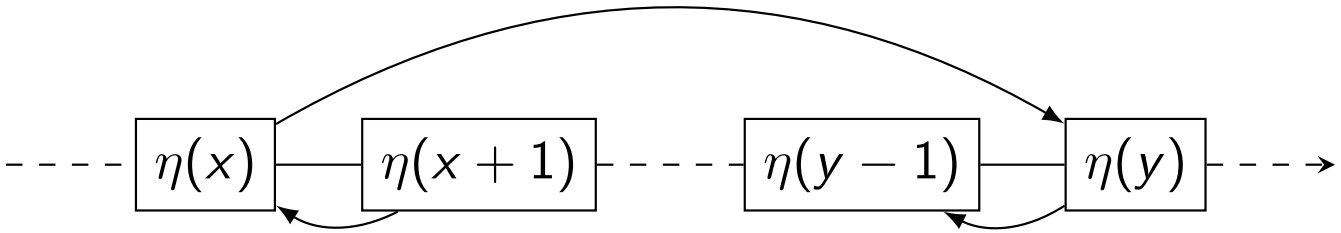
Definition with Markov generator

Translocation process

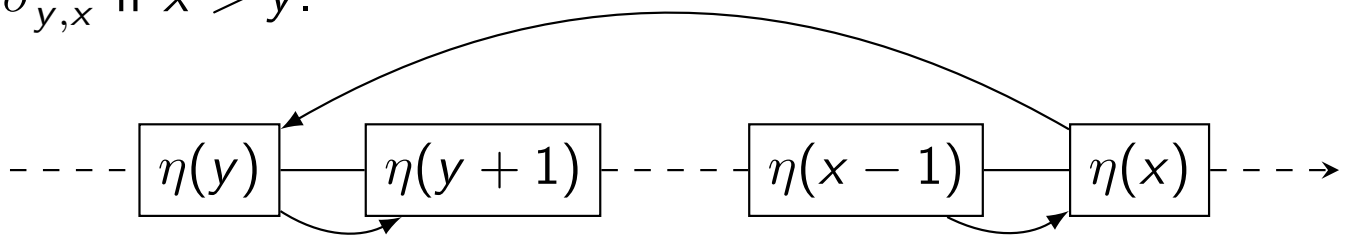
$$\mathscr{L}_2 f(\eta) = \sum_{x,y\in\mathbb{Z}} p(x,y)[f(\eta\circ\sigma_{x,y}) - f(\eta)], \tag{1}$$

with $\sigma_{x,y}$ defined for any $x < y$ by

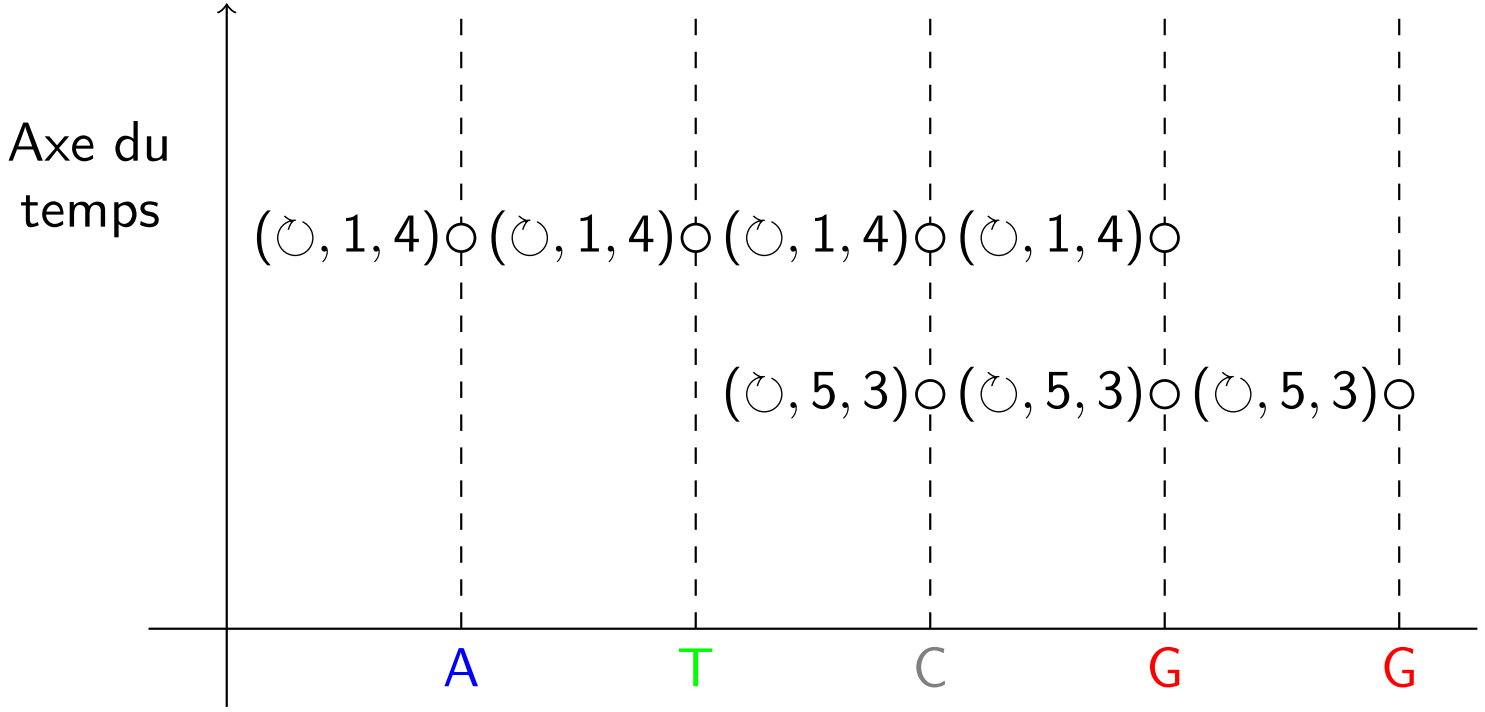
$$\sigma_{x,y}(z) = \begin{cases} z & \text{if} \quad z \notin \{x, x+1, \ldots, y\}, \\ y & \text{if} \quad z = x, \\ z-1 & \text{if} \quad x < z \leqslant y, \end{cases}$$



and by $\sigma_{y,x}^{-1}$ if $x > y$.



Construction with marked Poisson point processes



- Mark $(\circlearrowleft, x, y)$ distributed at rate $\rho p(x, y)$. If $x < y$, the contents of sites x, $x + 1$, ..., y are right circularly permuted. If $x < y$, the contents of sites y, $y + 1$, ..., x are left circularly permuted.

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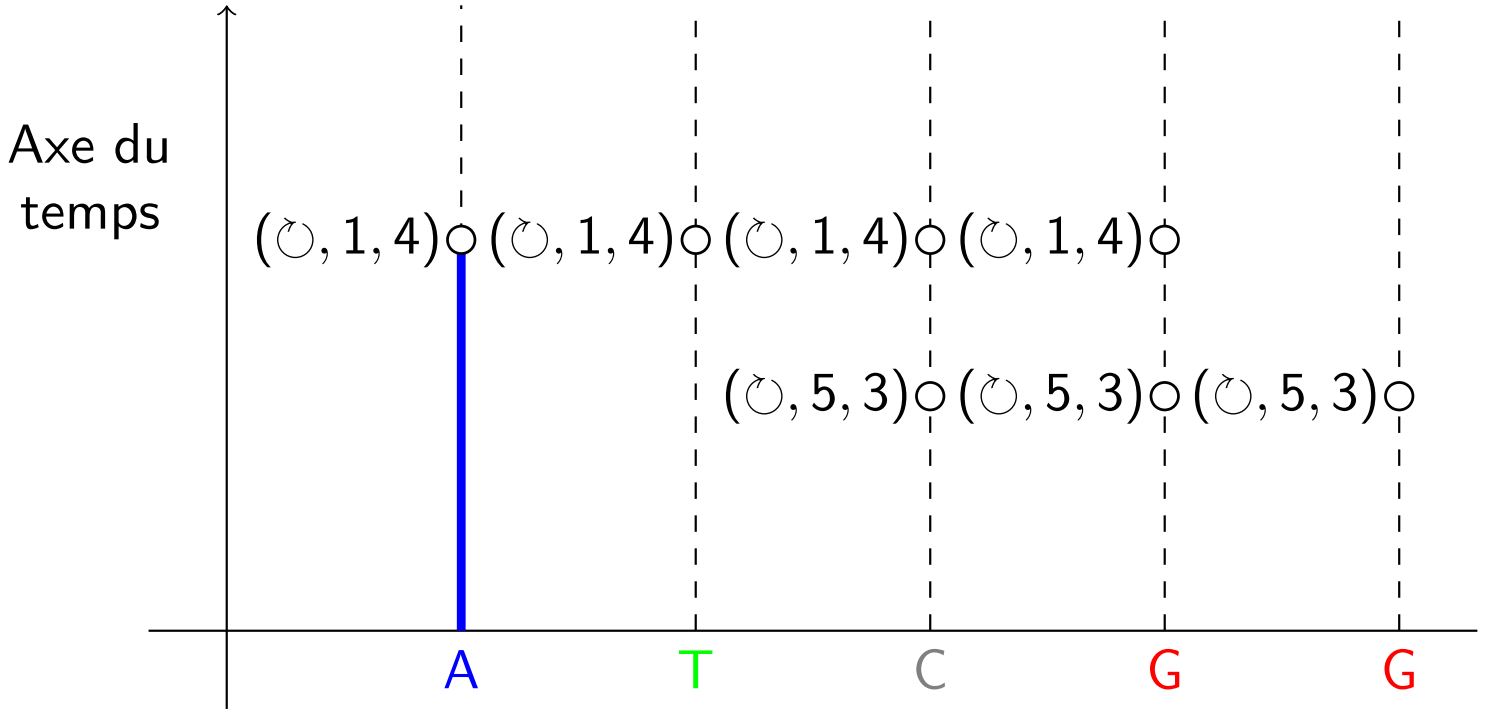

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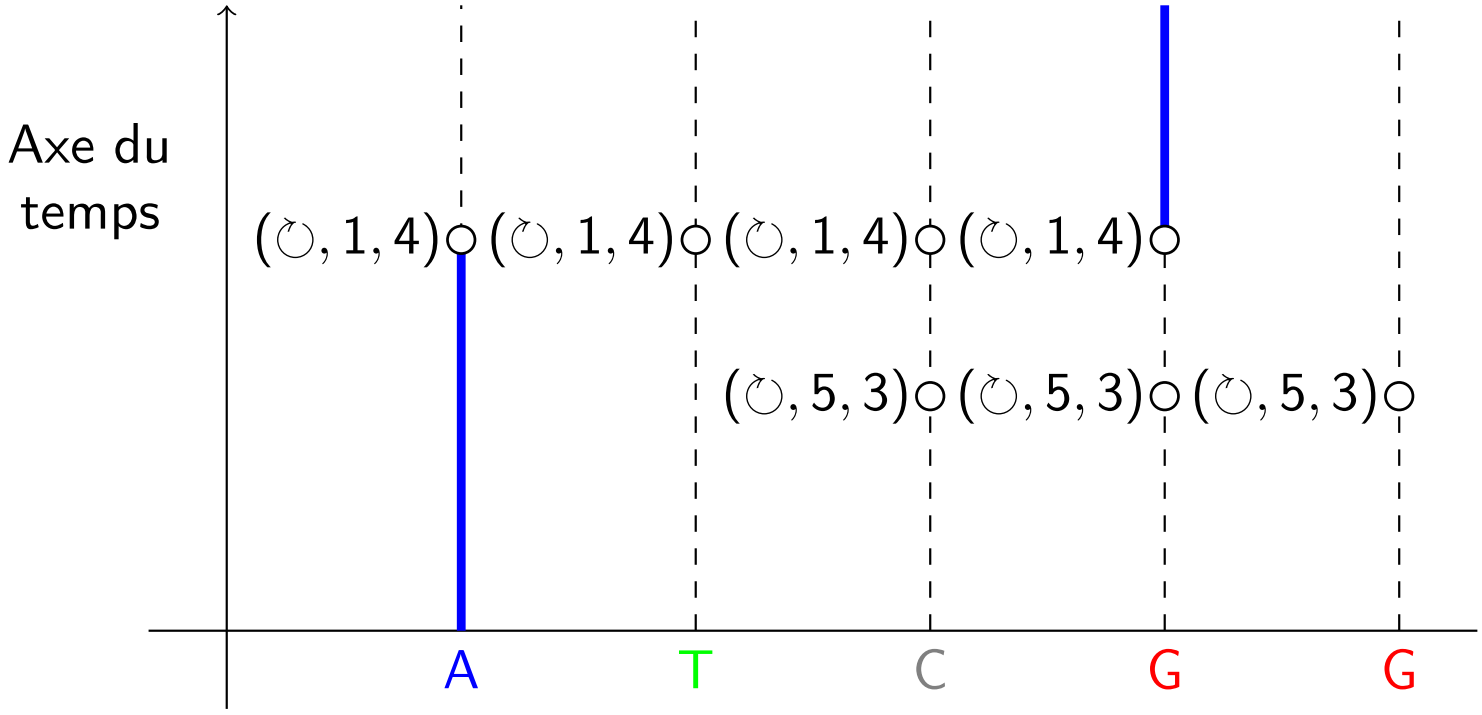

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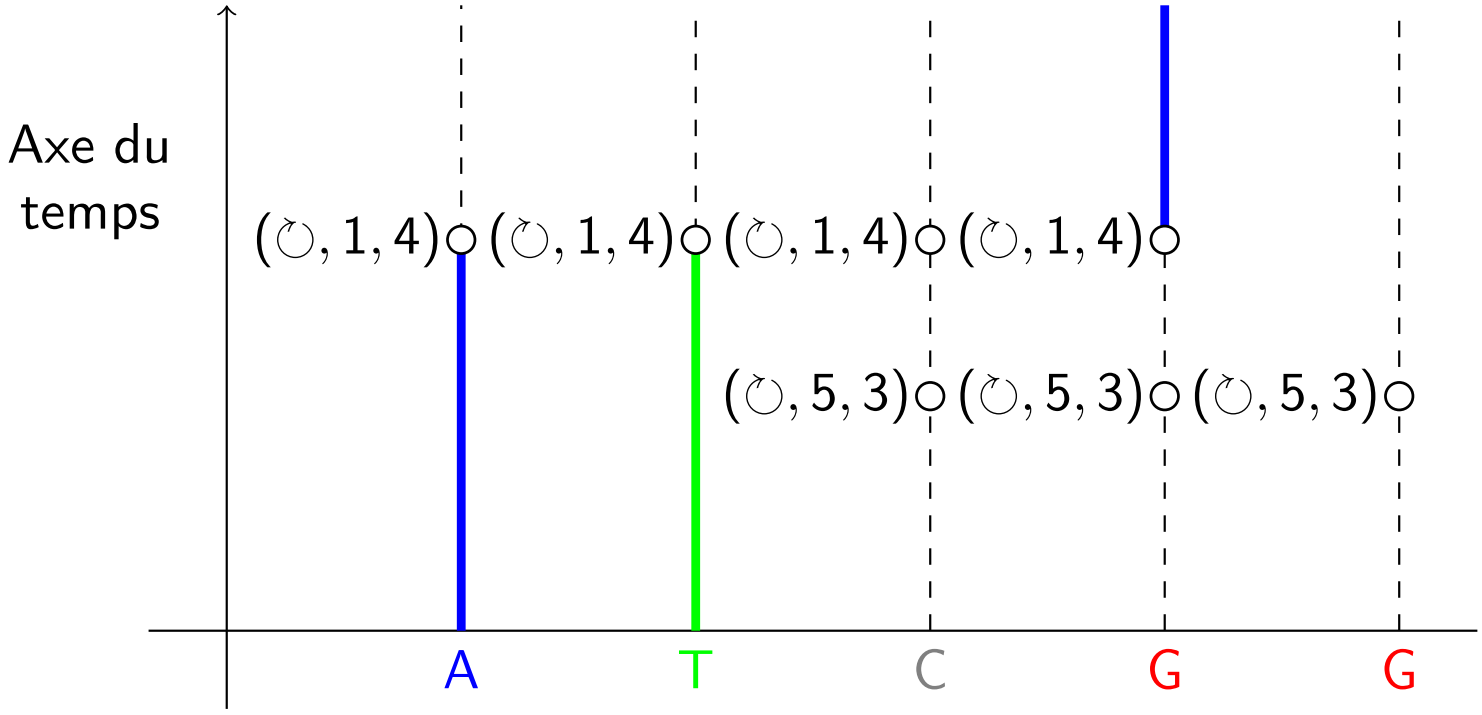

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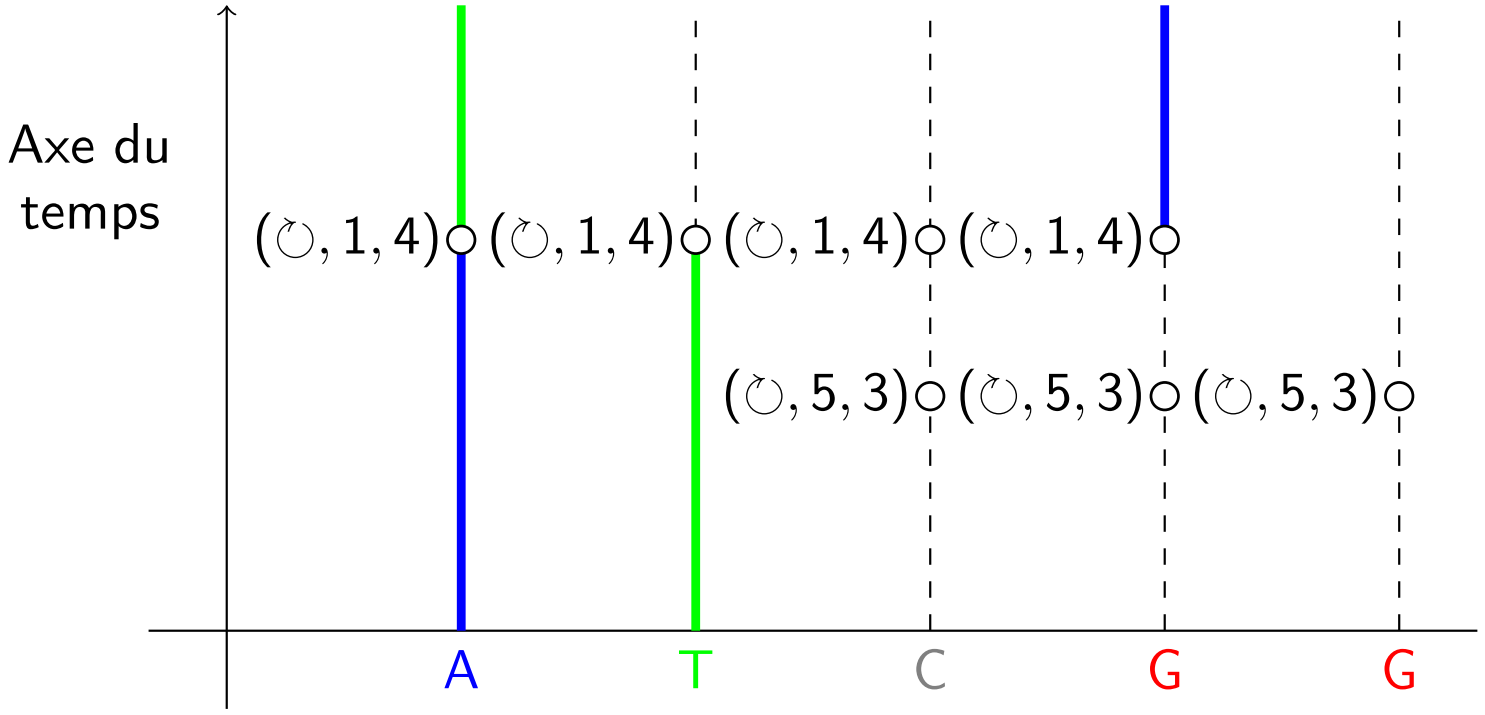

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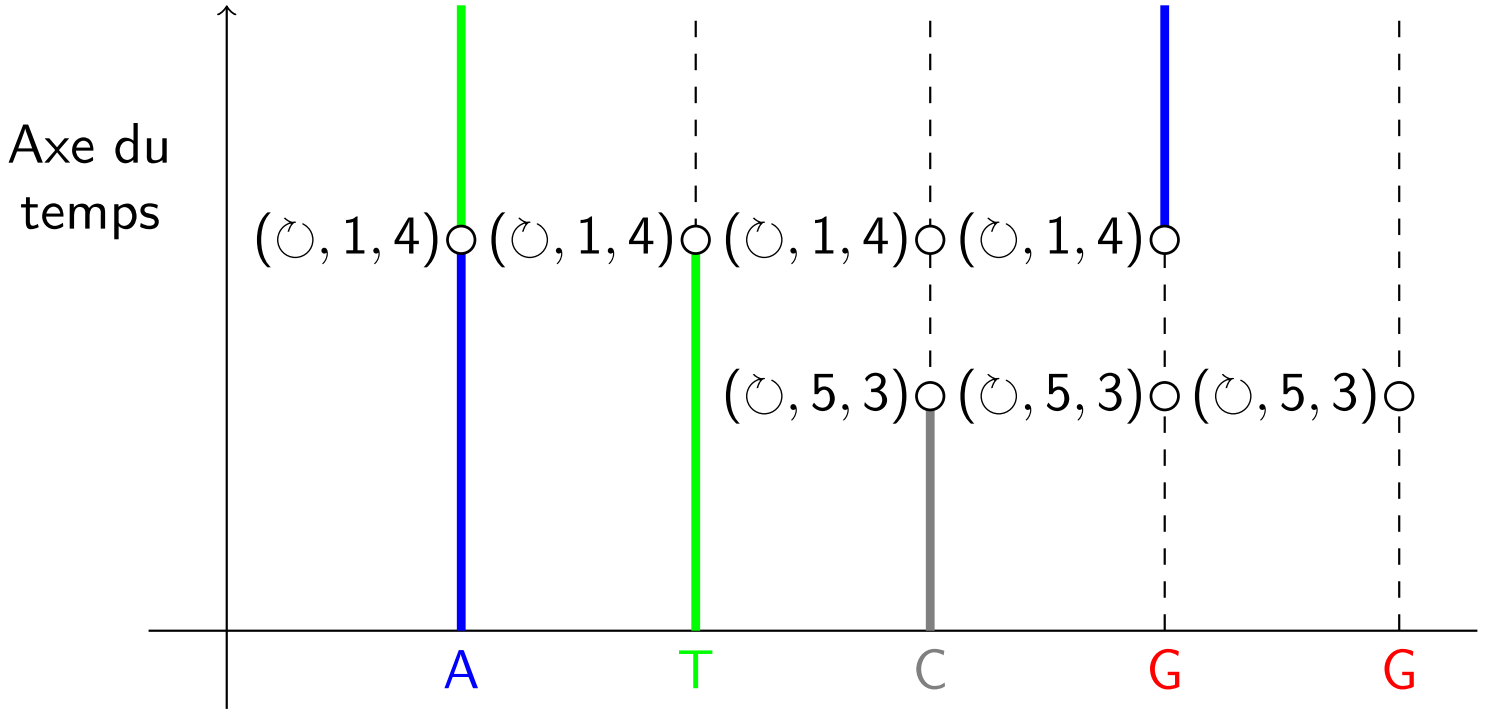

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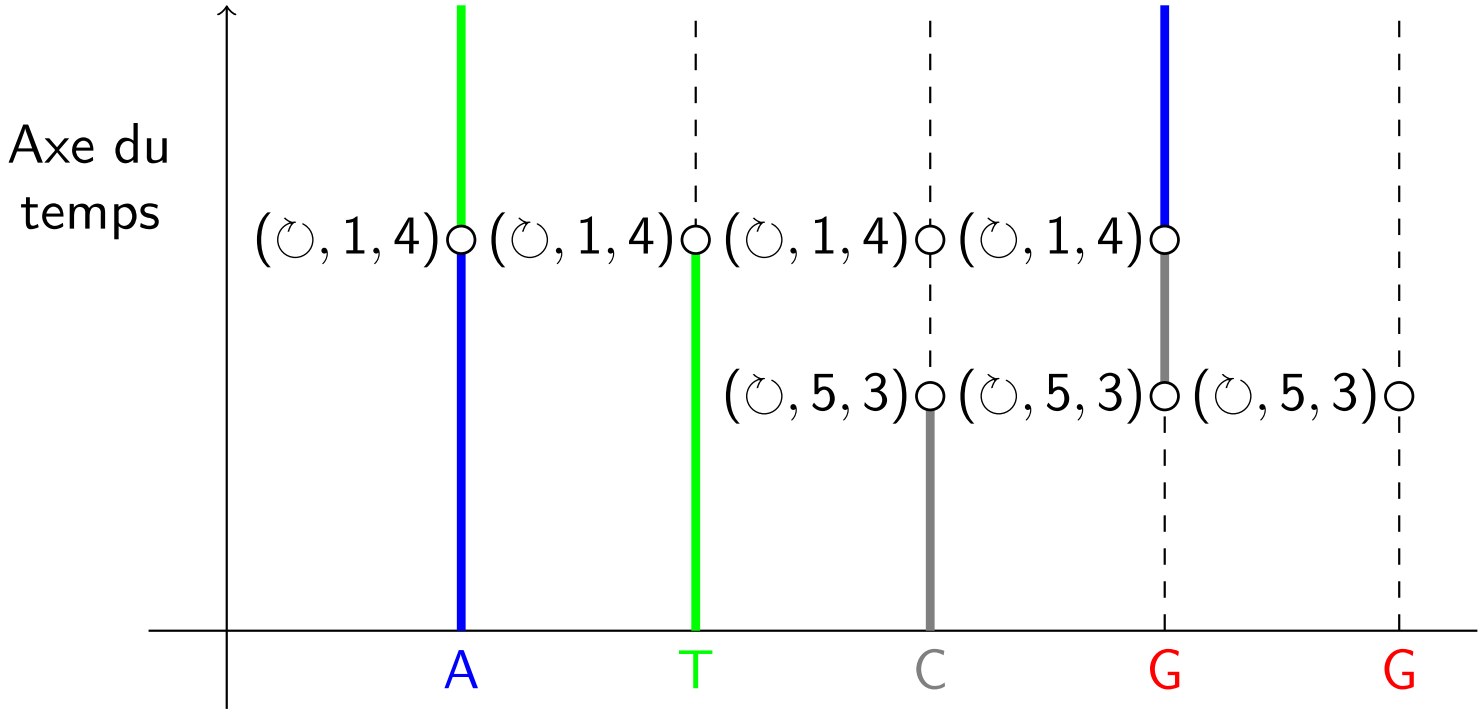

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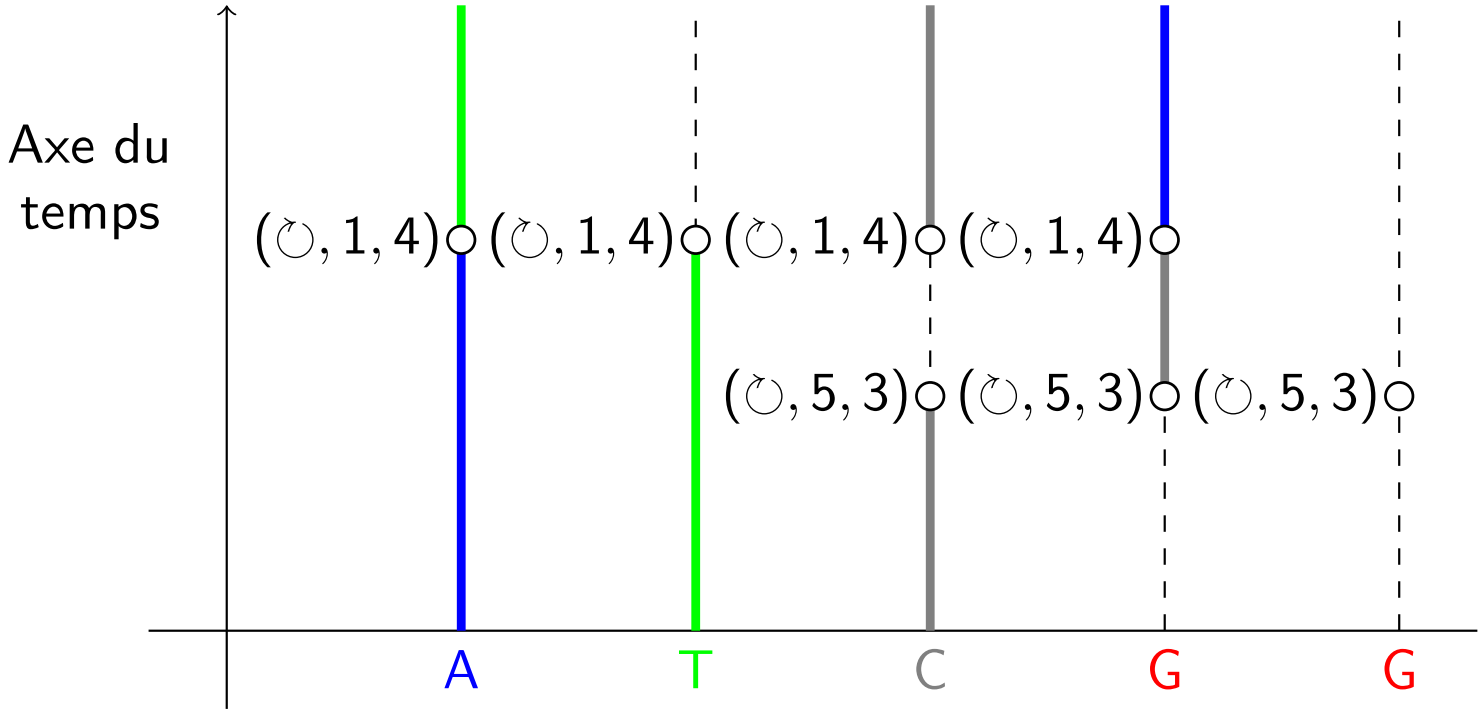

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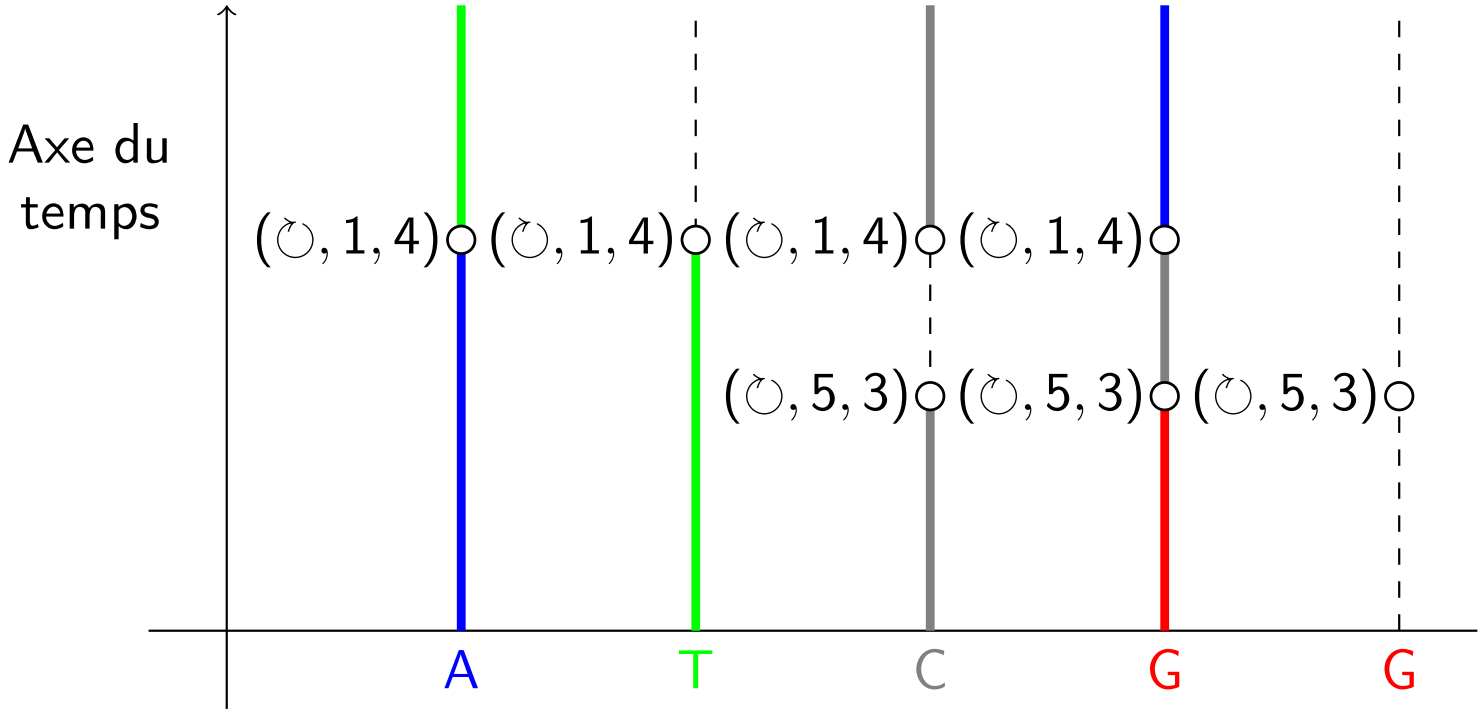

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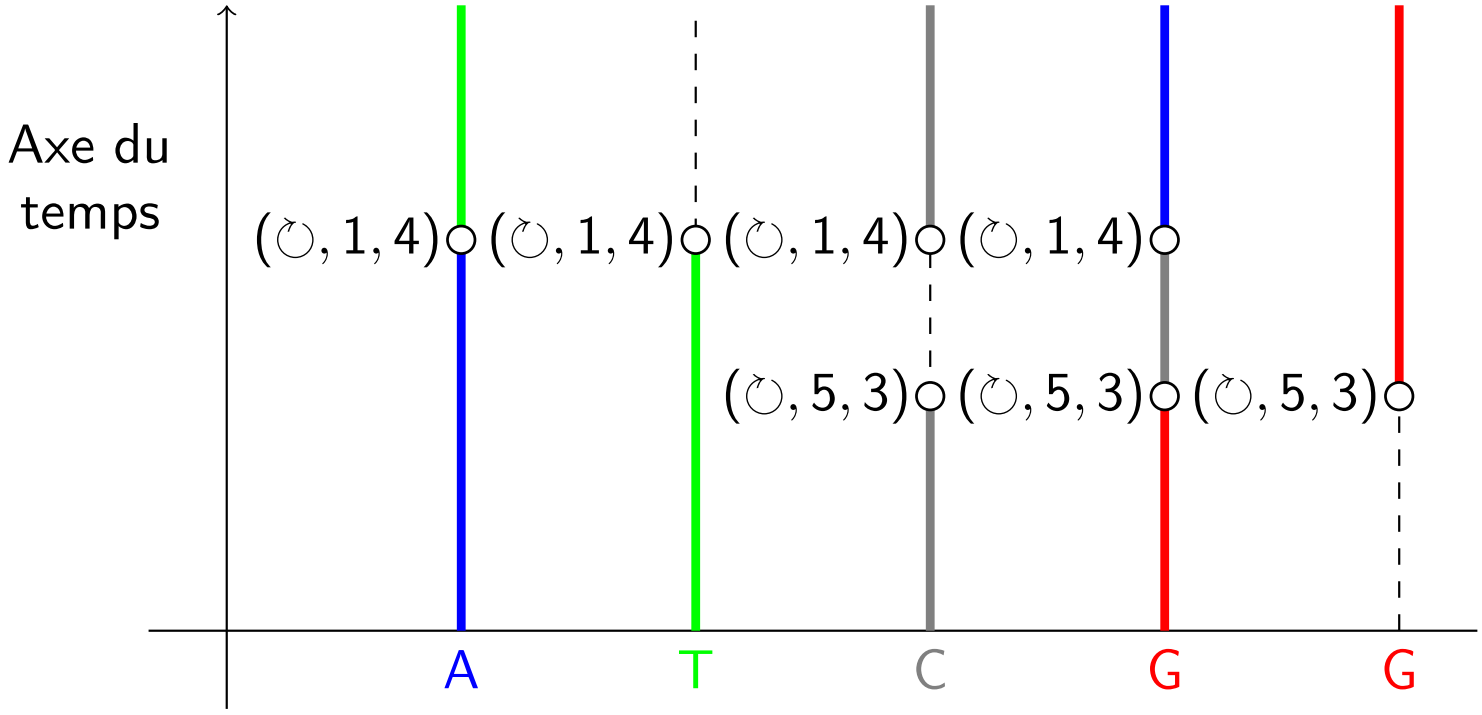

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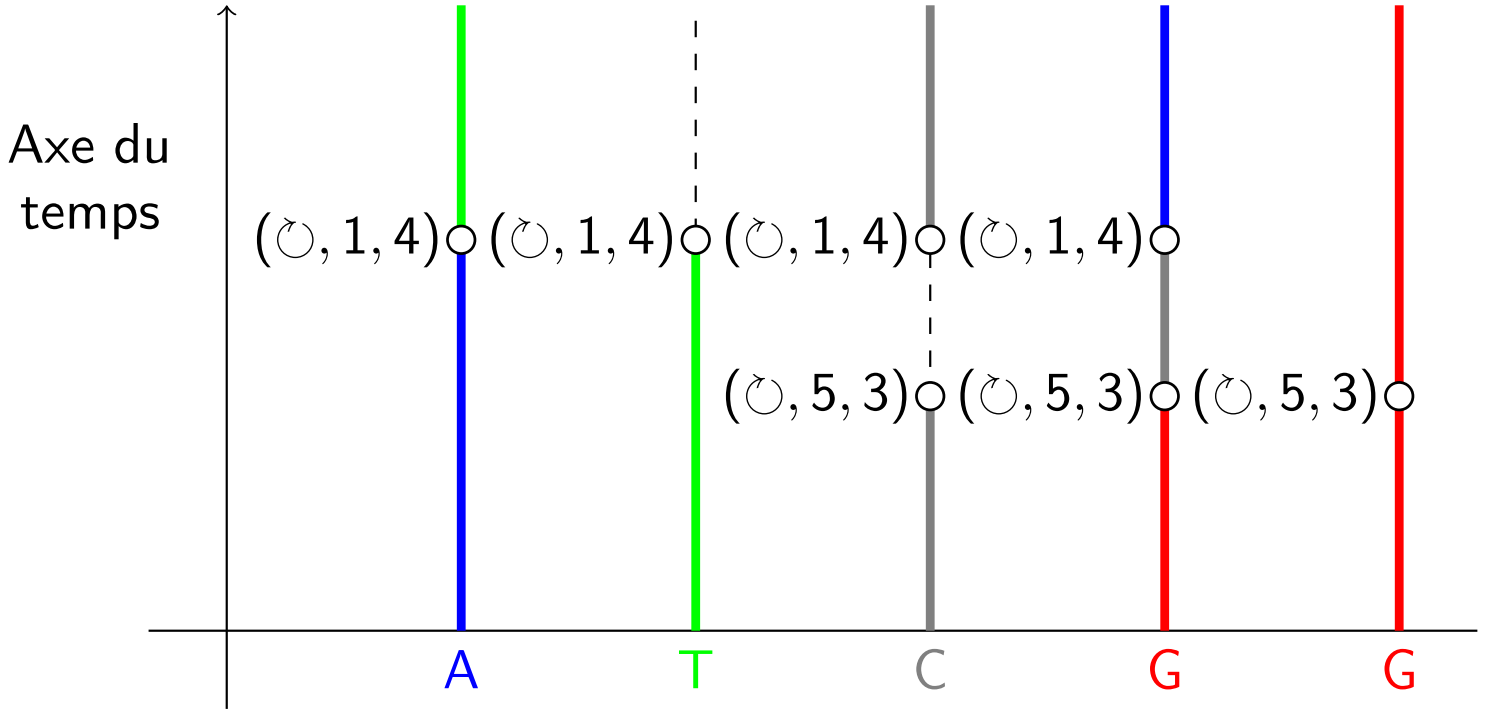

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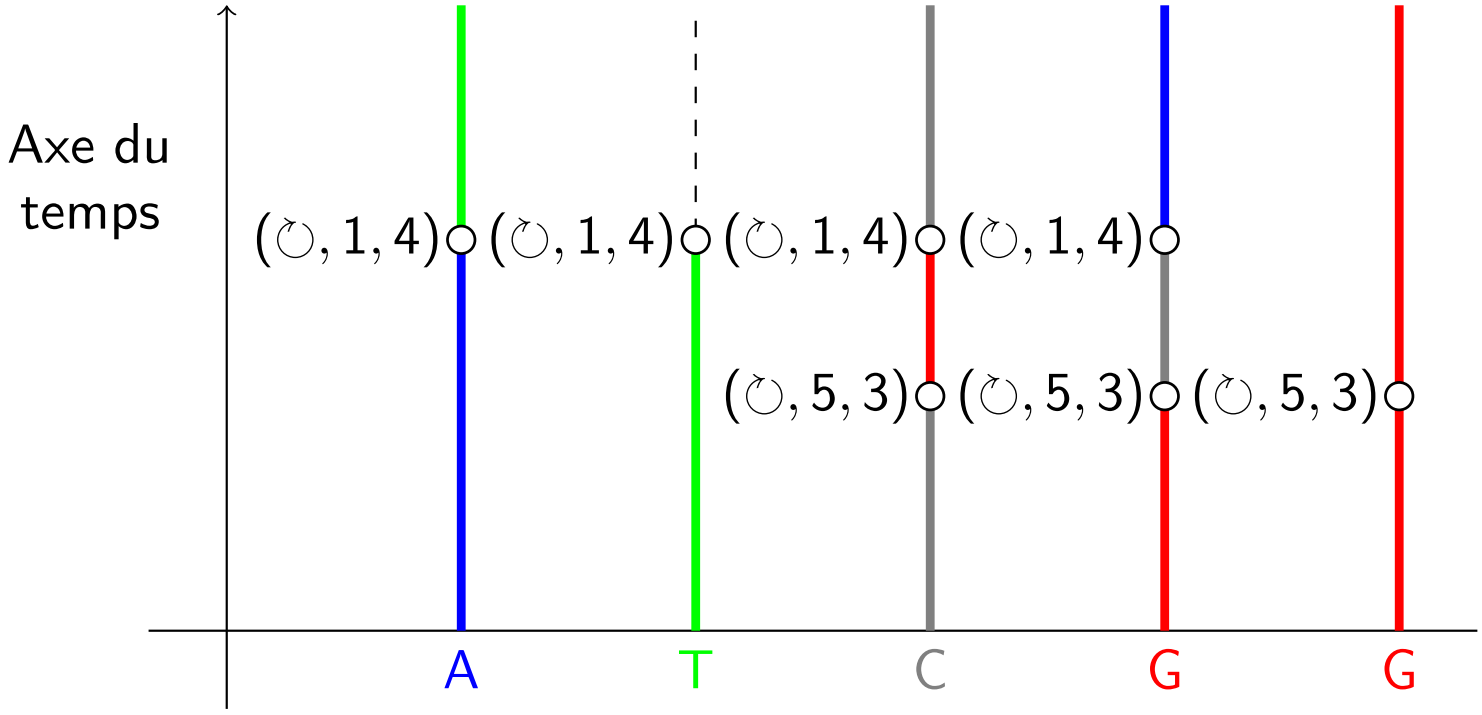

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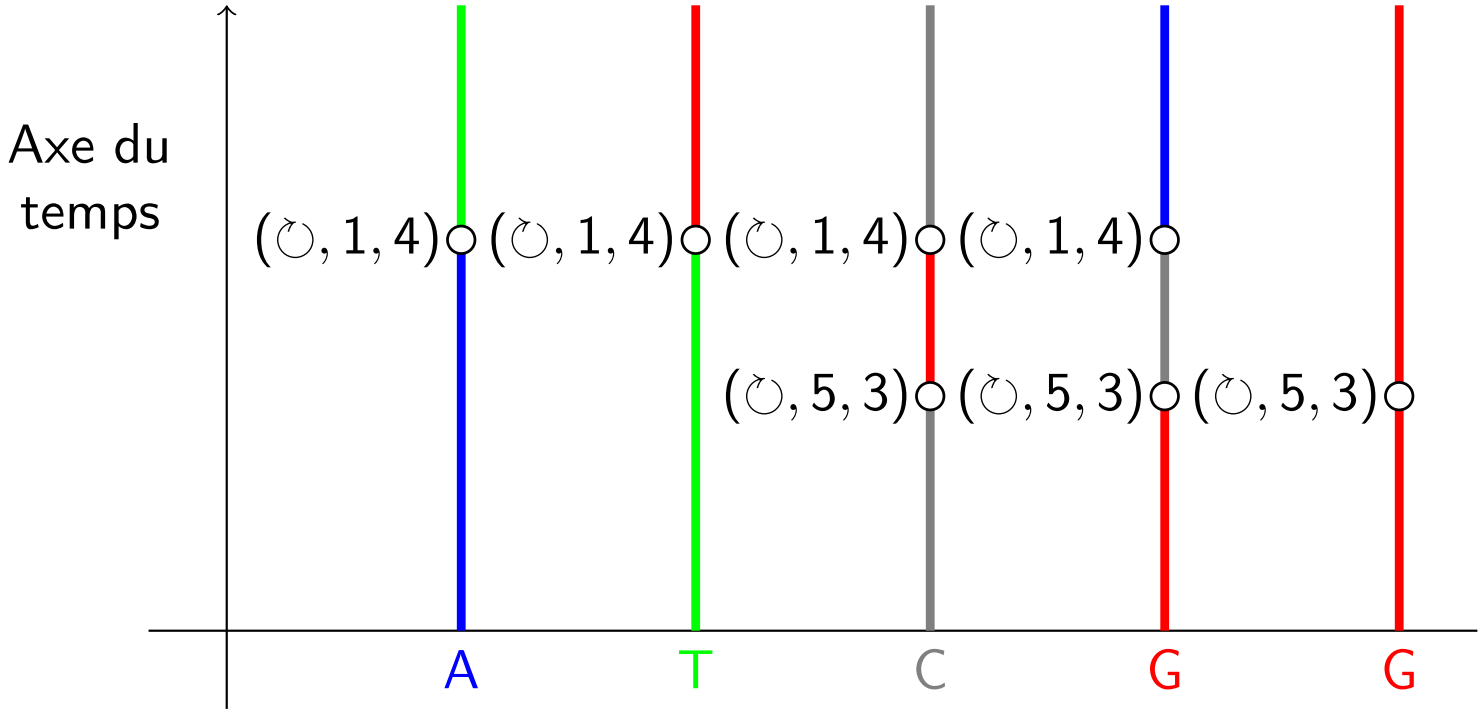

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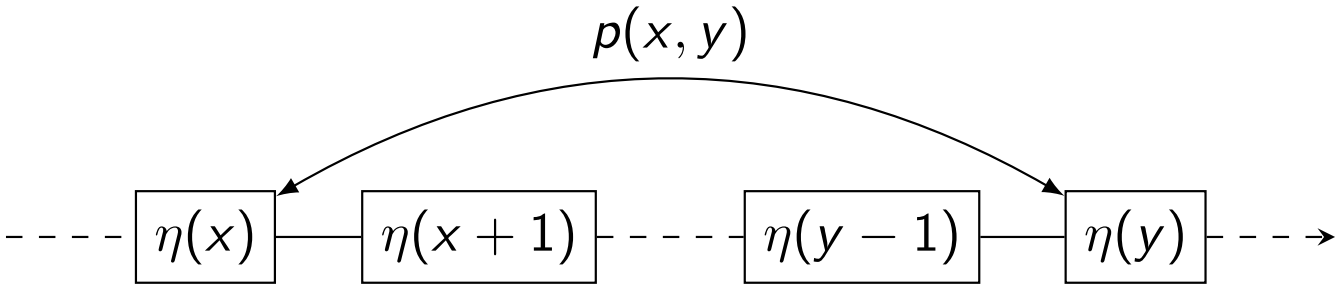
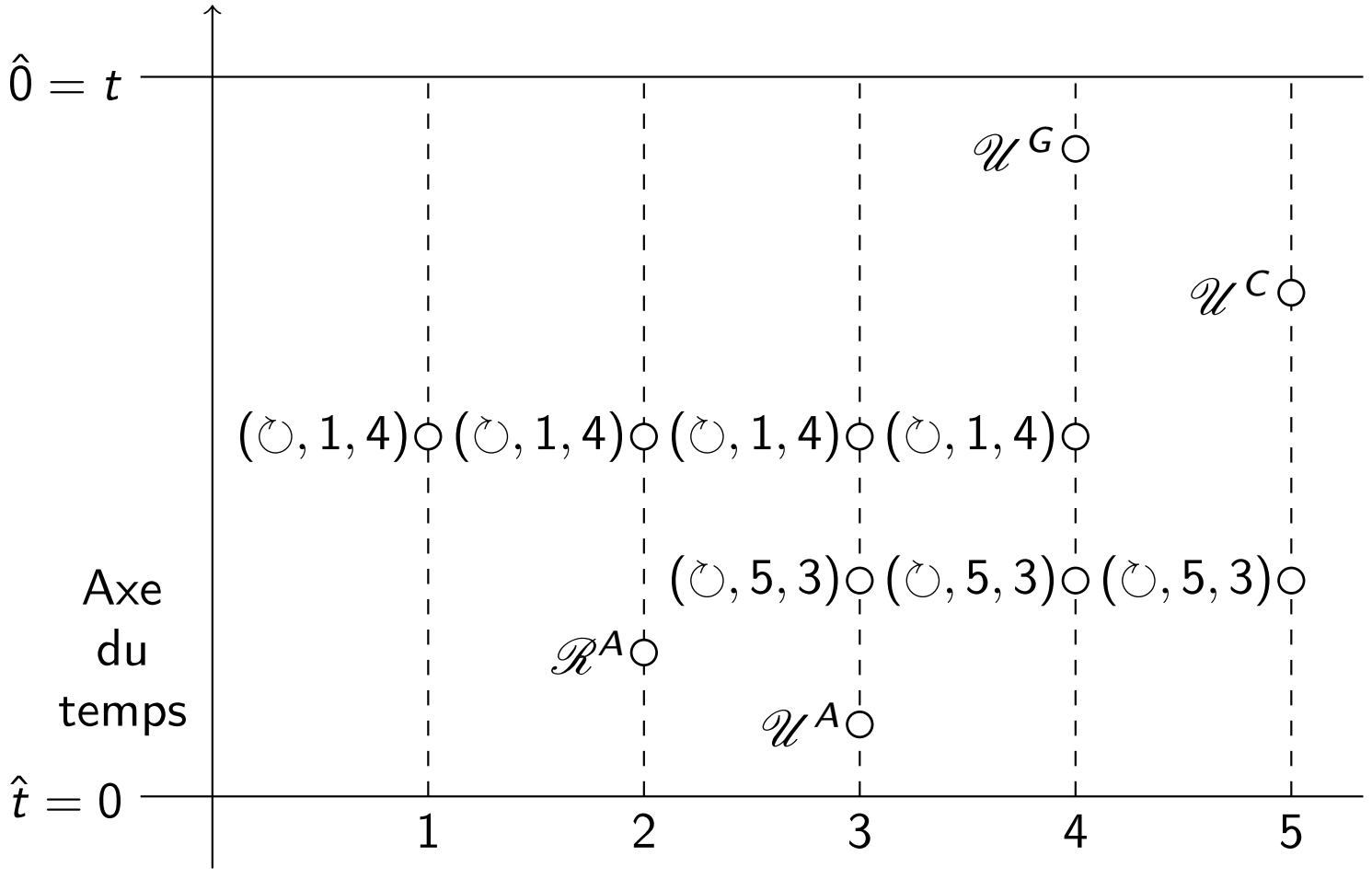
Spin + stirring

Ferrari, *Annals of Probability* (1990)



To prove ergodicity, Ferrari introduces the construction of a **dual process**

Introduction of a branching process



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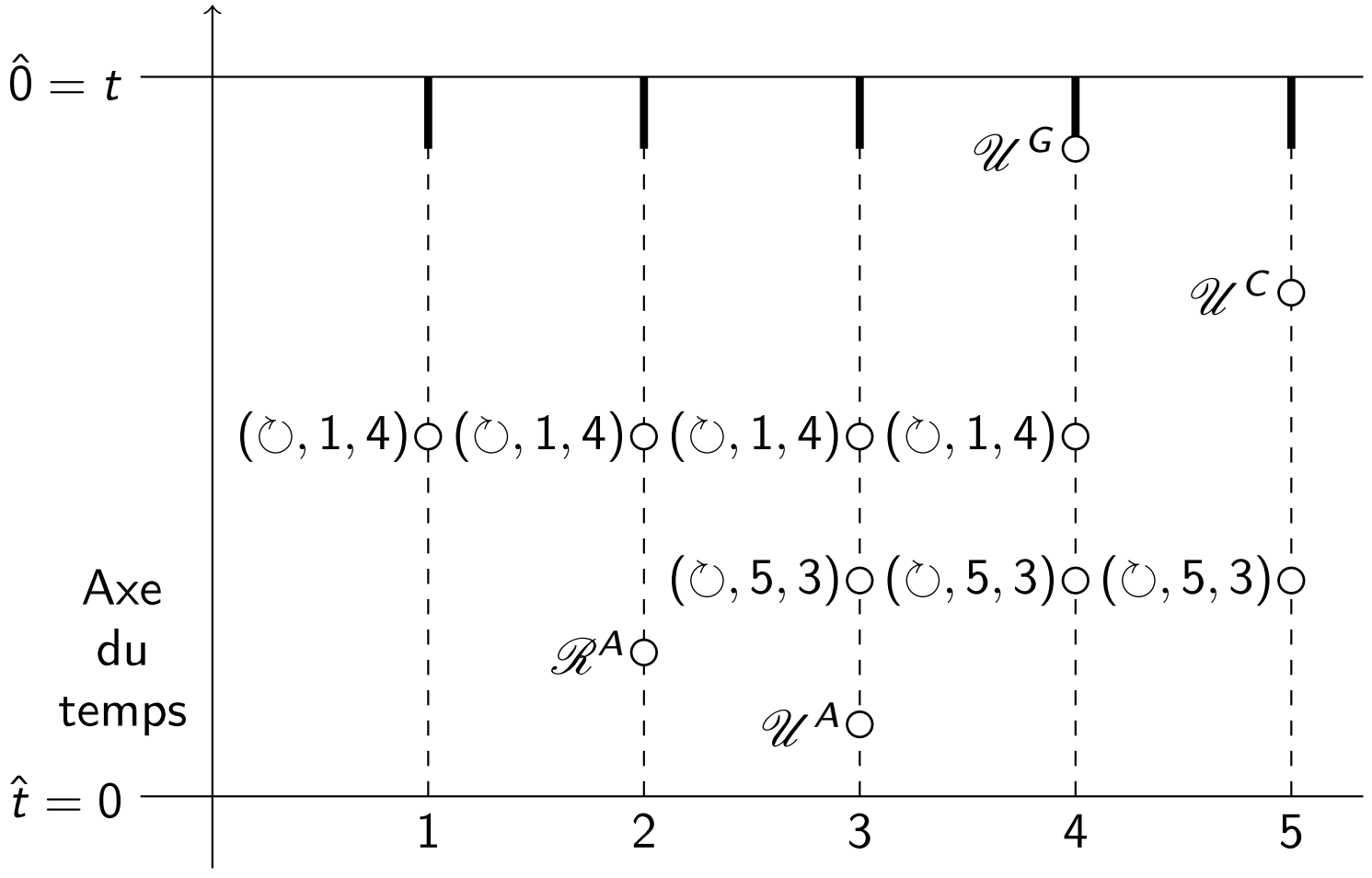

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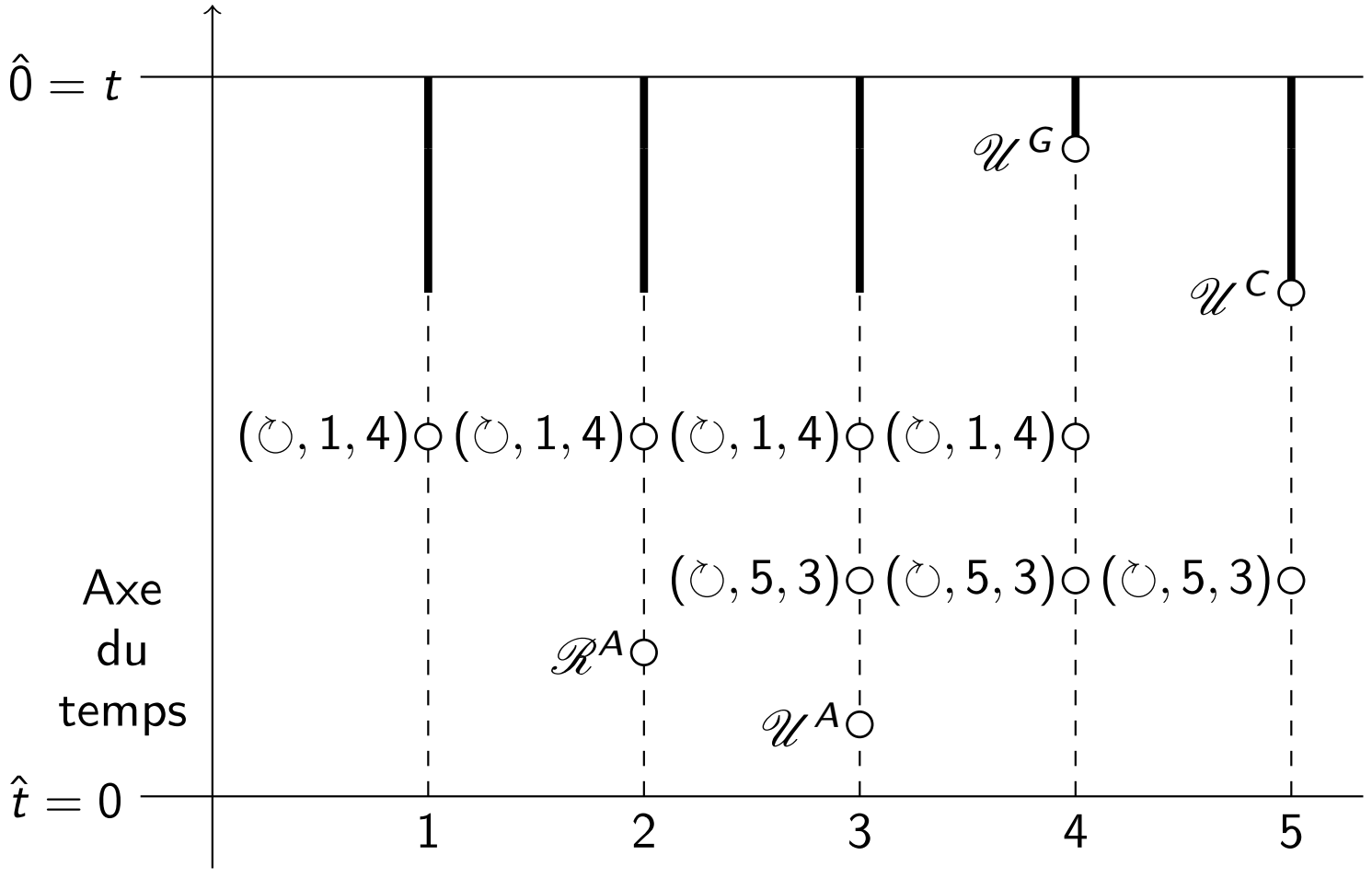

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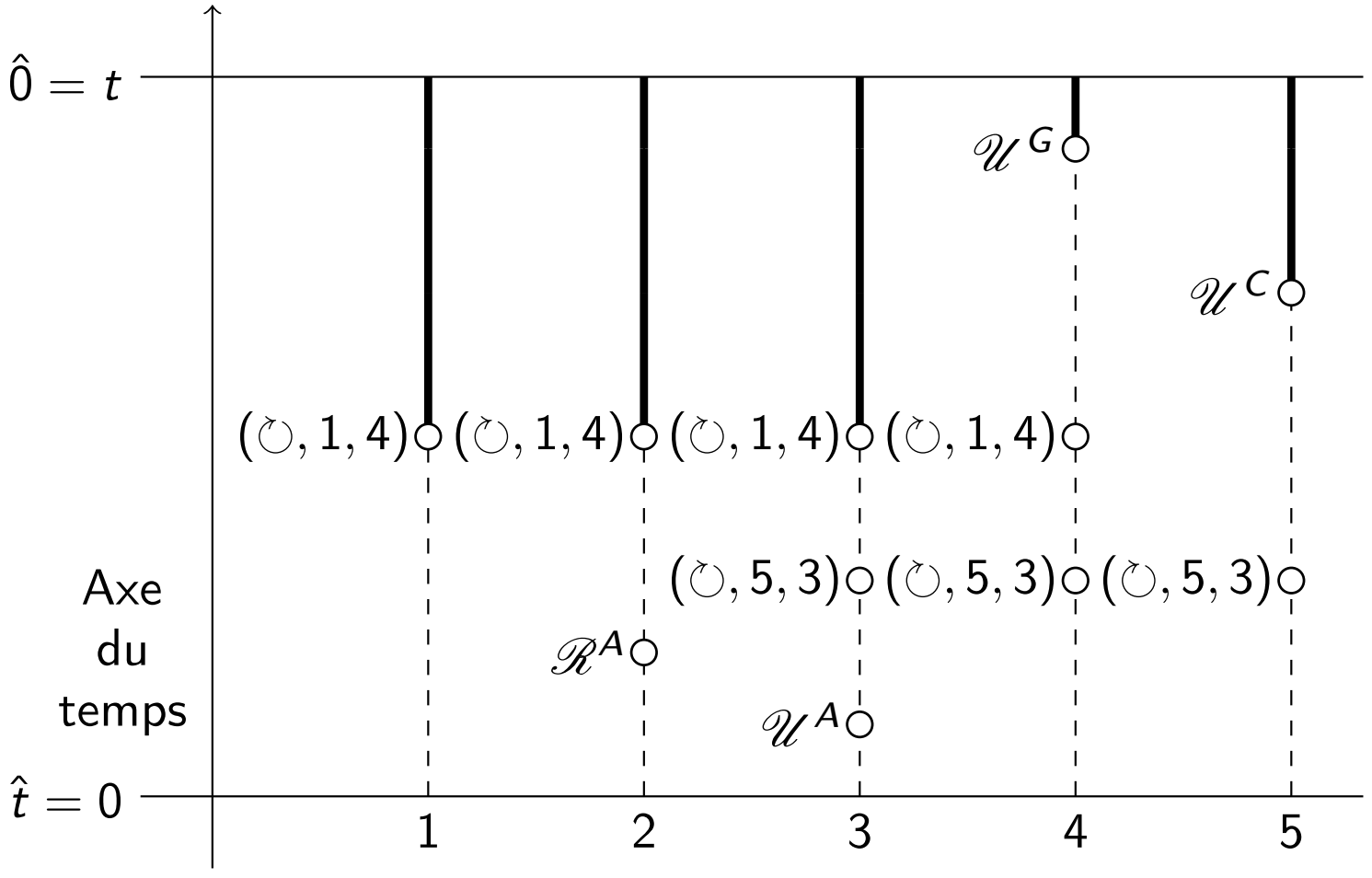

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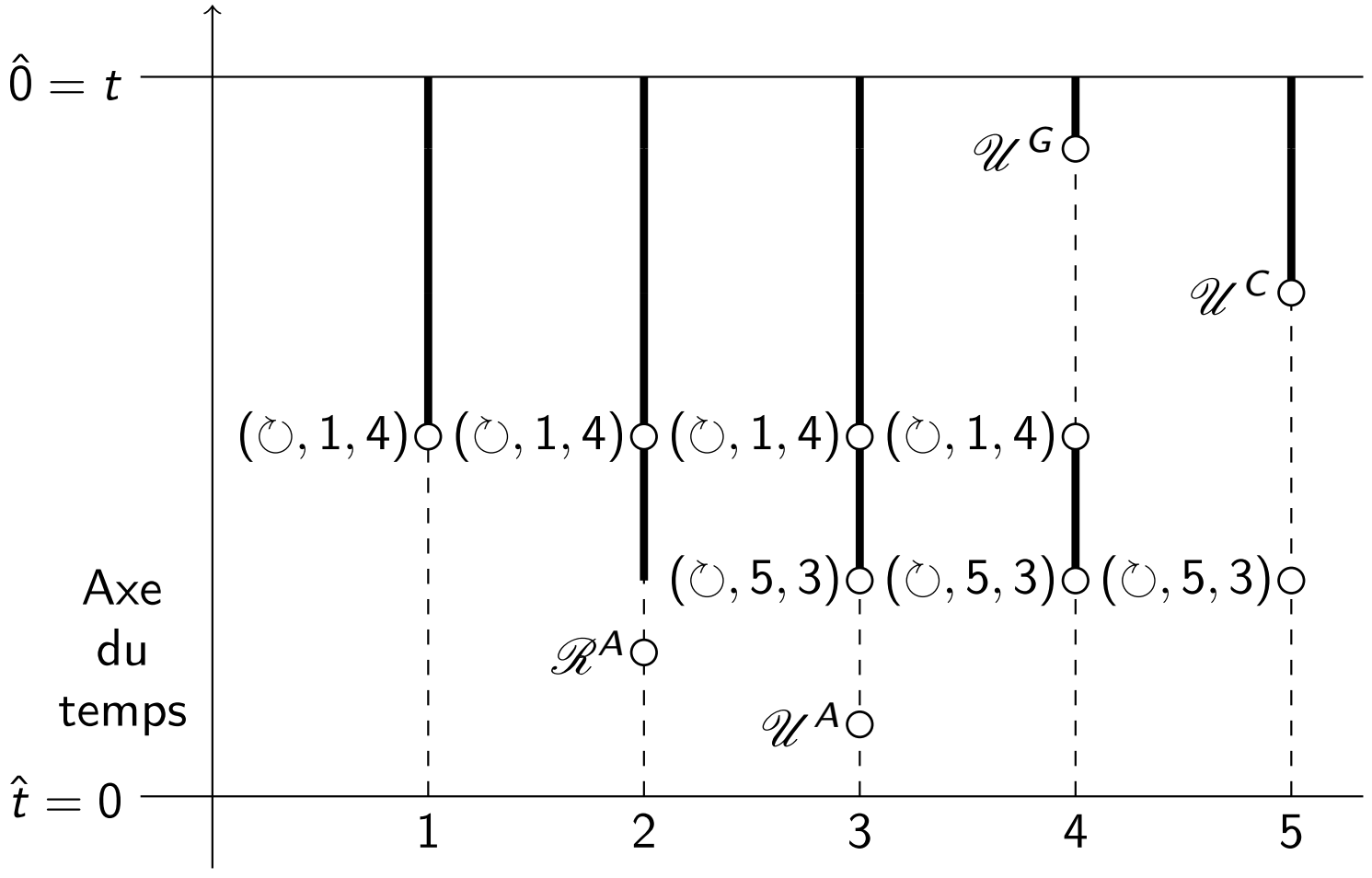

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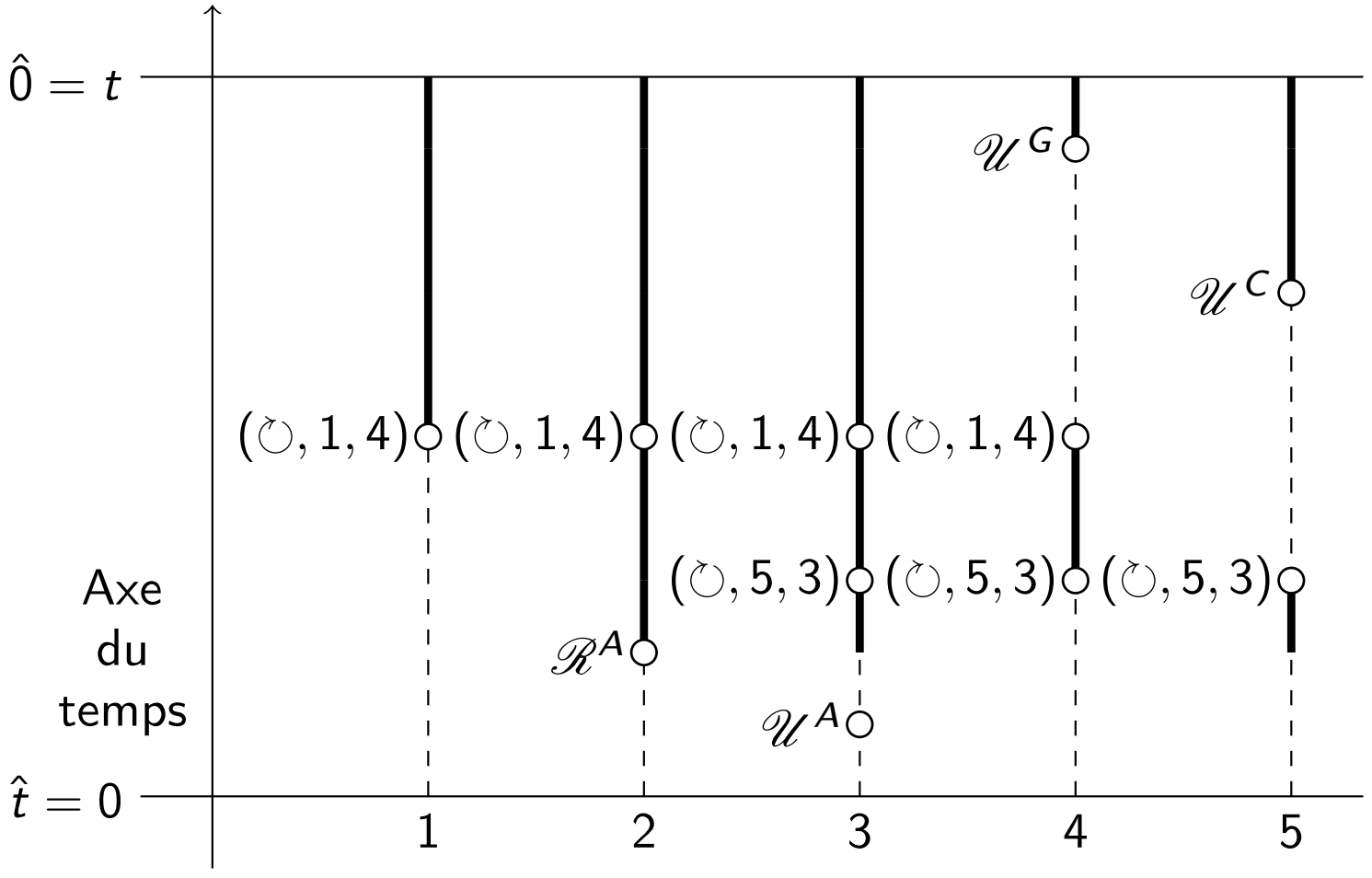

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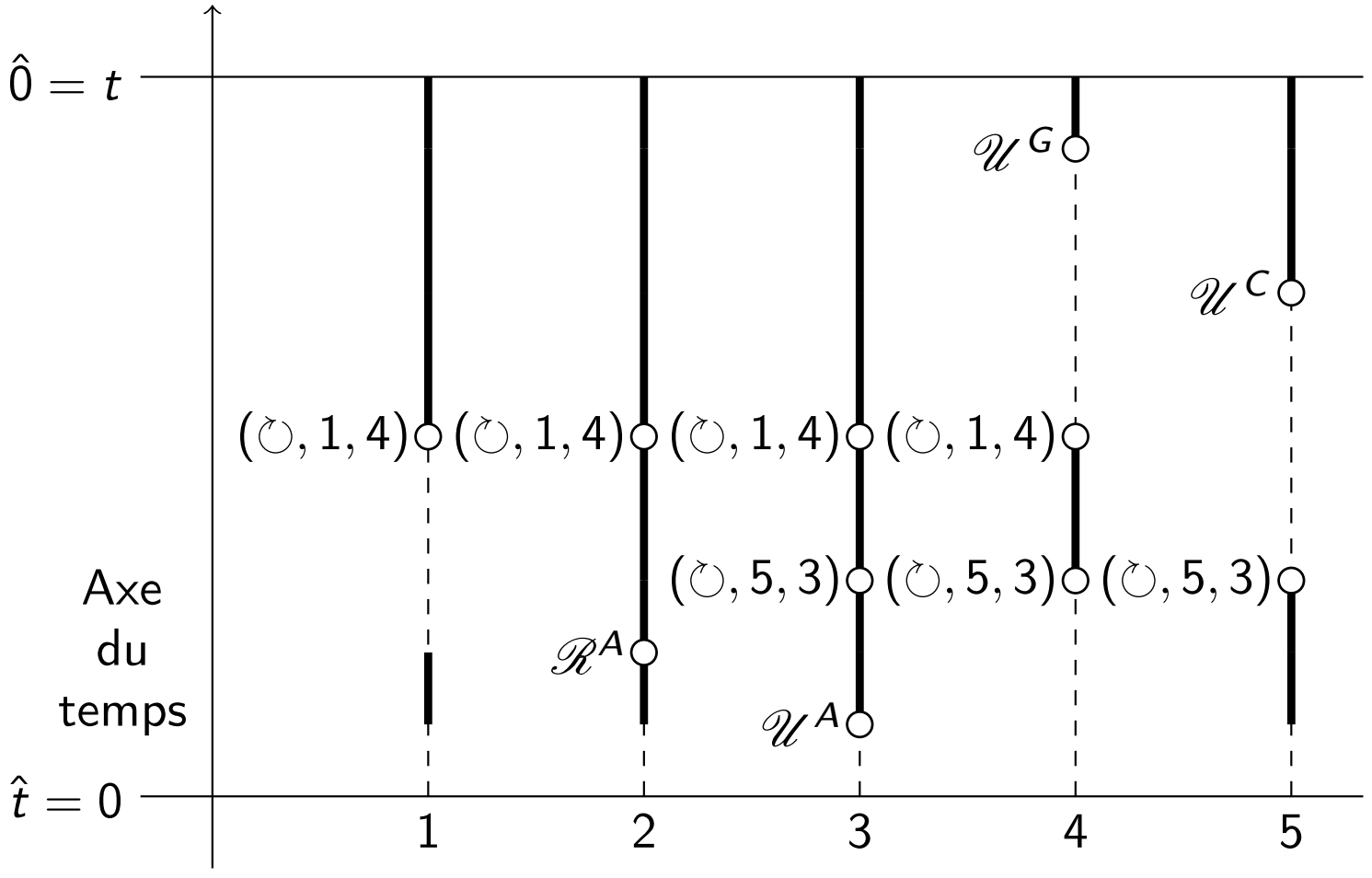

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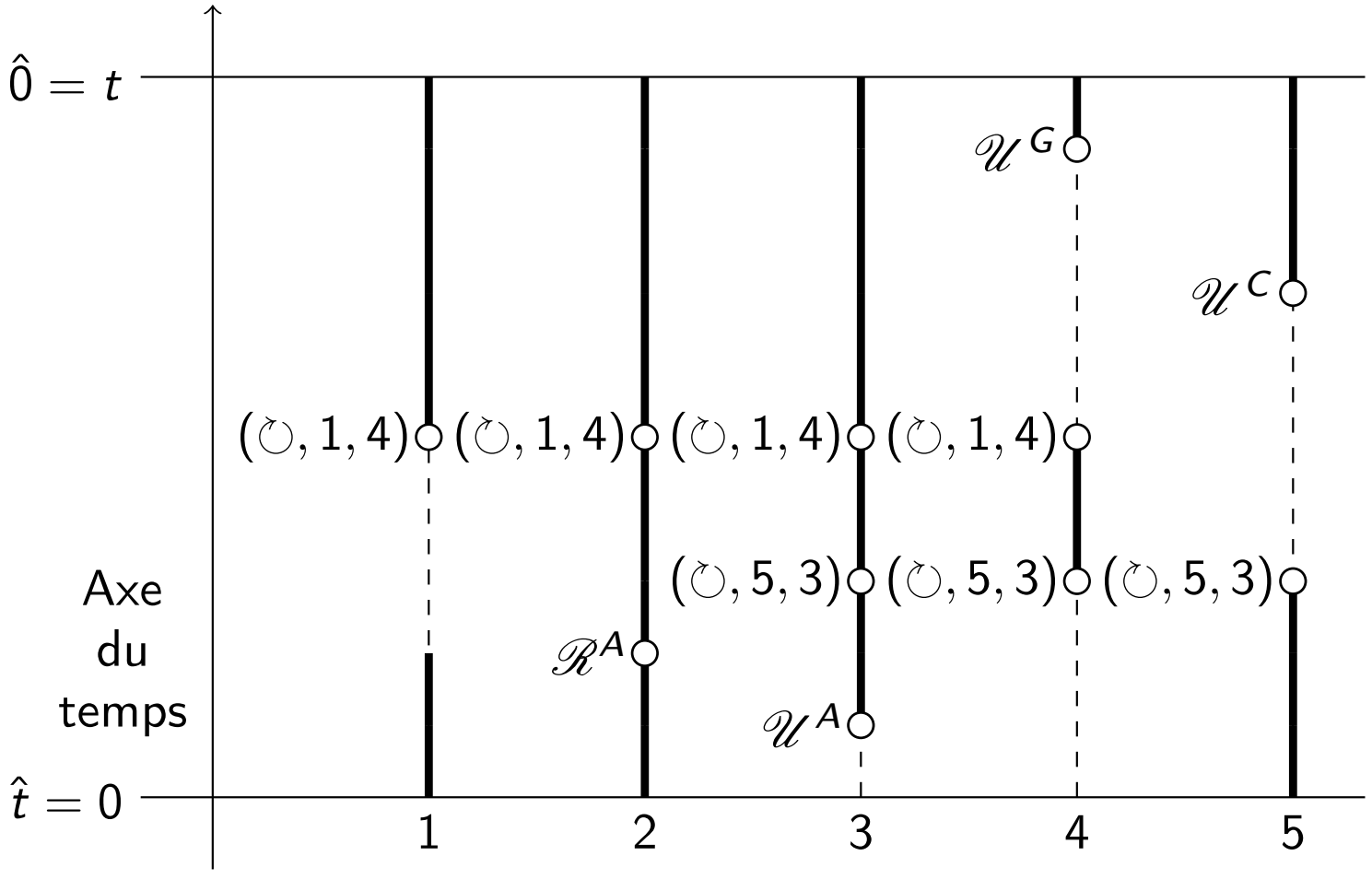

Results for independent evolution models

Falconnet, Gantert and Saada, (2012)

Assume that the substitution rates are **independent** and are Markovian. The the process is **ergodic** and the invariant measure is the product measure on $\mathbb{Z}$.

- Especially, for any usual substitution model (JC69, K80, T92, etc.) and any translocation mechanism invariant by translation, the dynamic of the process is ergodic.

Results for spin + stirring models

Neuhauser, *Annals of Probability* (1990)

Consider the Ising model. If the rate of stirring is small enough, then the process remains **ergodic**.

Ferrari, *Annals of Probability* (1990)

Define

$$\begin{aligned} m &= \inf\{c(x,\eta) \,:\, x \in \mathbb{Z}, \eta \in X\}, \\ K &= \sup\{c(x,\eta) \,:\, x \in \mathbb{Z}, \eta \in X\}, \\ h &= \max_{x\in\mathbb{Z}} |R_x|. \end{aligned} \tag{2}$$

Then if $m > 0$ and if

$$(h-1)(K-m) < 2m,$$

the process is **exponentially ergodic**.

Results for substitution process with translocation mechanism

Falconnet, Gantert et Saada, (2012)

Ferrari's result can be transposed. Define

$$\begin{aligned} m &= \inf\{c(x,a,\eta) \,:\, x \in \mathbb{Z}, a \in \mathscr{A}, \eta \in X\}, \\ K &= \sup\{c(x,a,\eta) \,:\, x \in \mathbb{Z}, a \in \mathscr{A}, \eta \in X\}, \\ h &= \max_{x\in\mathbb{Z}, a\in\mathscr{A}} |R_x^a|. \end{aligned} \tag{3}$$

Then if $m > 0$ and if

$$(h-1)(K-m) < |\mathscr{A}|m,$$

the process is **exponentially ergodic**.

Especially, JC+CpG+Translocation model is ergodic as soon as

$$r < 4\lambda.$$

Open questions

Contact process

The contact process is such that

$$c(x,\eta) = \begin{cases} \lambda[\eta(x-1)+\eta(x+1)] & \text{if} \quad \eta(x)=0, \\ 1 & \text{if} \quad \eta(x)=1, \end{cases}$$

where $\lambda \geqslant 0$. One can see that

$$m = \inf\{c(x,\eta) \,:\, x \in \mathbb{Z}, \eta \in X\} = 0,$$

hence the theorem cannot be used there.

One can show that there exists a critical value $\lambda_c(\rho)$ depending on ρ, but we do not know its behavior. At the moment, we only know that

$$\forall \rho \geqslant 0, \quad \lambda_c(\rho) \geqslant \frac{1}{2}, \quad \text{and}$$

$$\lambda_c(0) - \rho \leqslant \lambda_c(0) \leqslant (1+2\rho)\lambda_c(0).$$

Questions ouvertes

Modèle d'Ising

The one dimensional Ising model is defined as

$$c(x,\eta) = \begin{cases} \mathrm{e}^{-2\beta} & \text{if} \quad \eta(x-1) = \eta(x) = \eta(x+1), \\ \mathrm{e}^{2\beta} & \text{if} \quad \eta(x) \neq \eta(x-1) = \eta(x+1), \\ 1 & \text{else.} \end{cases}$$

This process is ergodic for any $\beta \geqslant 0$. We think that translocation mechanism should not change this fact.

Statistics

Would it be possible to use this model to improve DNA sequences alignment ?