DNA evolution, Automata and Clumps

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Biological Motivation

- **Promoters** are DNA sequences located upstream of the gene they regulate; regulation can be positive for enhancers or negative for repressors.
- The promoters contain binding sites for regulatory proteins such as **Transcription Factors** (**TFs**) that are **short stretches of DNA**.

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- The promoters contain binding sites for regulatory proteins such as **Transcription Factors** (**TFs**) that are **short stretches of DNA**.

- **Waiting time:** **how long** it takes for a **Transcription Factor** to **appear** in a **promoter** under a **probabilistic model of evolution** helps understanding the **overall evolution of promoters** within species and between species?

From infinitesimal to discrete evolution model

- $\mathbb{Q}(t)dt$ evolution matrix for **infinitesimal time**
- $\mathbb{P}(t)$ evolution matrix **from time** x and **time** $x+t$

$$\mathbb{P}(t) = e^{\mathbb{Q}(t)} \qquad \text{(Karlin-Taylor 1975)}$$

- $\mathbb{P}(1) = (\pi_{\alpha\to\beta})$ evolution matrix for **one generation** (**20 years**), $\quad \alpha, \beta \in \{\mathtt{A}, \mathtt{C}, \mathtt{G}, \mathtt{T}\}$

Initial $\nu(\alpha)$ and Substitution Probabilities $\pi_{\alpha\to\beta}$

α	$\nu(\alpha)$
A	0.23889
C	0.26242
G	0.25865
T	0.24004

$\rightsquigarrow$

substitution probability $\pi_{\alpha\to\beta}$ for one generation (20 years)

A	$\rightsquigarrow$	A	0.9999999763
A	$\rightsquigarrow$	C	$4.54999994943 \times 10^{-9}$
A	$\rightsquigarrow$	G	$1.57499995613 \times 10^{-8}$
A	$\rightsquigarrow$	T	$3.40000001733 \times 10^{-9}$
C	$\rightsquigarrow$	A	$6.14999993408 \times 10^{-9}$
C	$\rightsquigarrow$	C	0.99999996495
C	$\rightsquigarrow$	G	$7.14999984731 \times 10^{-9}$
C	$\rightsquigarrow$	T	$2.17499993935 \times 10^{-8}$
G	$\rightsquigarrow$	A	$2.17499993935 \times 10^{-8}$
G	$\rightsquigarrow$	C	$7.14999984731 \times 10^{-9}$
G	$\rightsquigarrow$	G	0.99999996495
G	$\rightsquigarrow$	T	$6.14999993408 \times 10^{-9}$
T	$\rightsquigarrow$	A	$3.40000001733 \times 10^{-9}$
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Probability of occurrence of a k-mer at time 1

- $S_n(0)$ **random DNA sequence** of **length** n at **time 0**
- $S_n(1)$ sequence obtained **from** $S_n(0)$ **by evolution** at **time 1**
- b a k-**mer** (word of **length** k over $\mathcal{A} = \{\mathsf{A},\mathsf{C},\mathsf{G},\mathsf{T}\}$)

- $\mathfrak{P}_n(b)$ probability that b
  - **occurs at time 1**
  - **while not occurring at time 0**

$$\mathfrak{P}_n(b) = \mathbb{P}(b \in S_n(1) \mid b \notin S_n(0))$$

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Expectation of the Waiting time $\mathfrak{E}_n(b)$

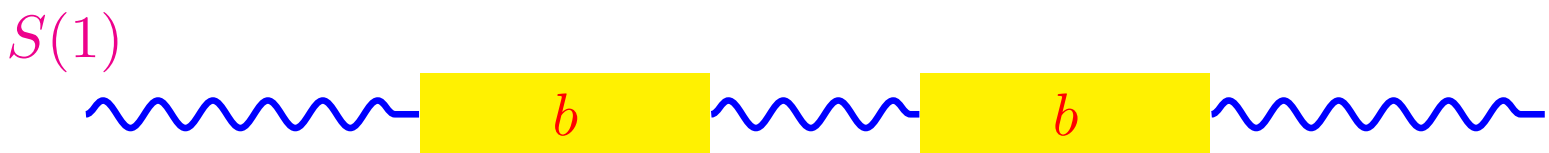
- $$\mathfrak{E}_n(b) \approx \frac{1}{\mathfrak{P}_n(b)} \quad (\textbf{geometric distribution} - \text{BehVin2010})$$

Plan of the talk

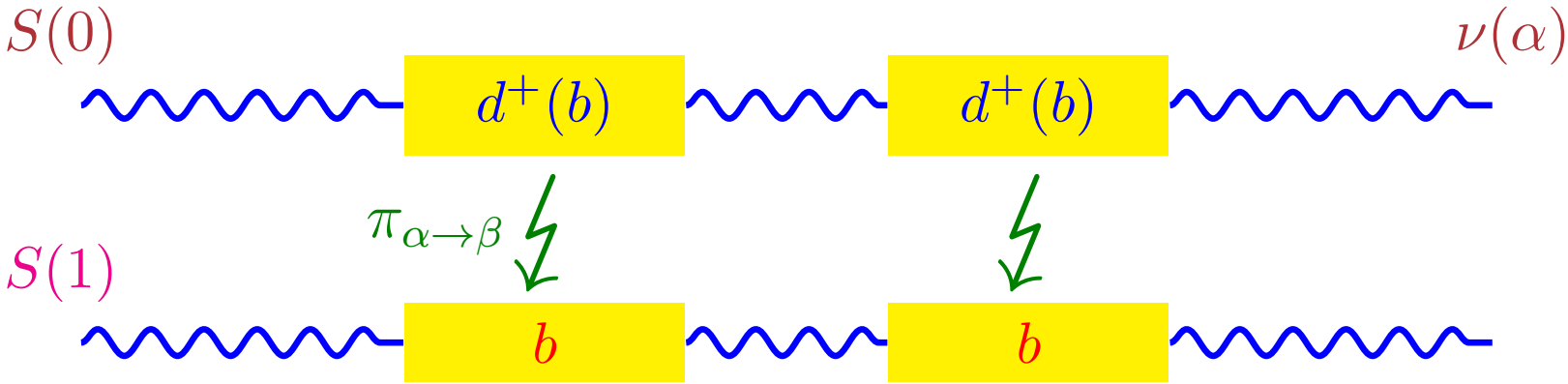
Different computations of $\mathfrak{P}_n$

1. Behrens-Vingron (2010)
   - Approach **neglecting words correlation**.
   - **Efficient computation** of $\mathfrak{P}_n$ with respect to this assumption.
2. Behrens-Nicaud-P.N. (2012)
   - **Rigorous and efficient approach by automata**.
   - Approach **hiding the quasi-linear behaviour** of $\mathfrak{P}_n$
3. P.N. (NCMA2012)
   - Approach by **clump analysis**, either by **combinatorics of words** or by **automata**.
   - **Proof** of the **quasi-linear behaviour** of $\mathfrak{P}_n$
4. P.N. (ALEA 2013)
   - **Explicit formula** for $\mathfrak{P}_n$

Behrens-Vingron 2010

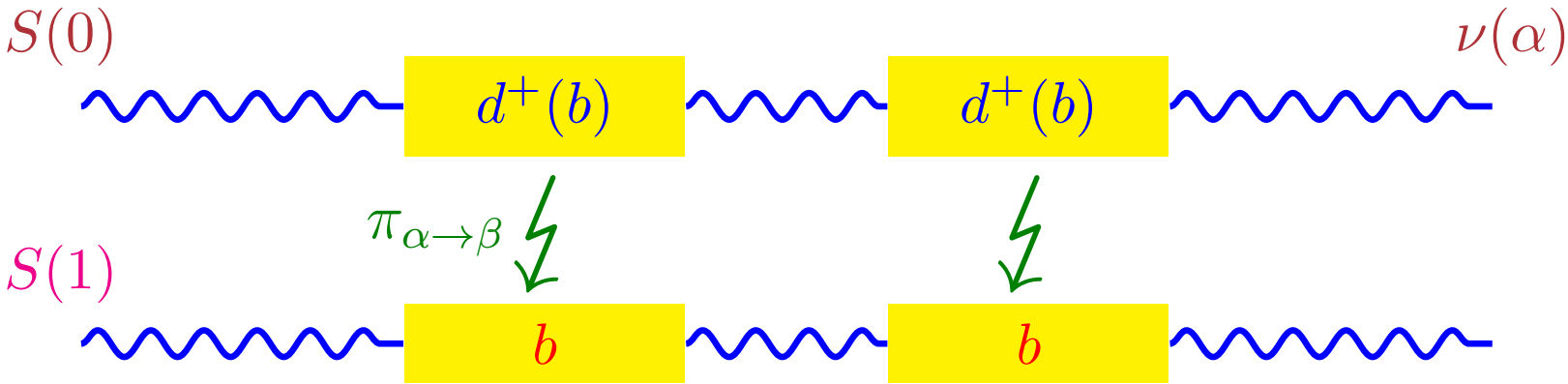


Behrens-Vingron 2010



- $d^+(b)$ neighbors of b by substitution

Behrens-Vingron 2010

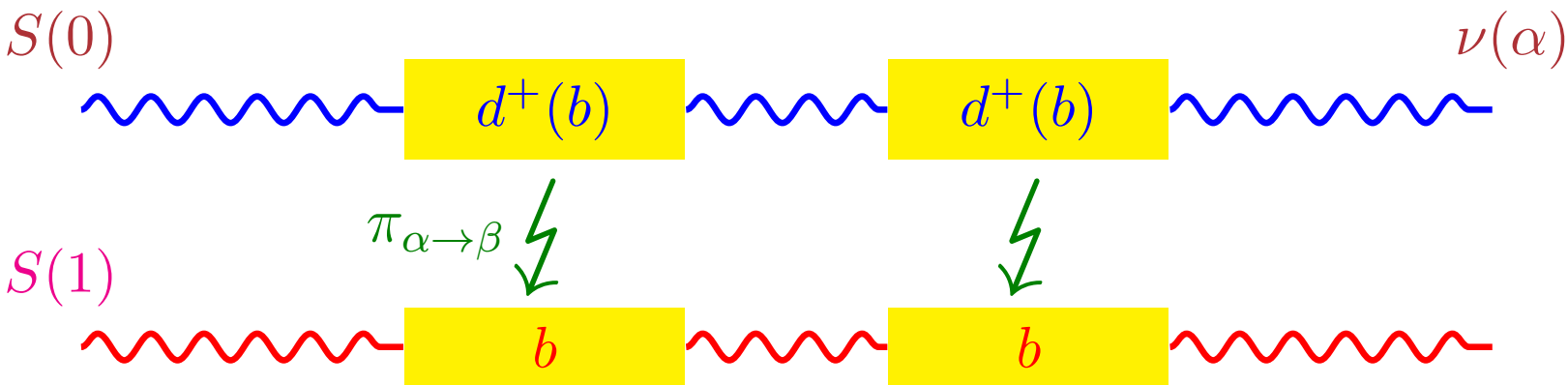


- $d^+(b)$ neighbors of b by substitution

$$\begin{cases} \mathfrak{P}_n \approx \displaystyle\sum_{i=1}^{\lfloor n/k \rfloor} (-1)^{i+1} \binom{n-i(k-1)}{i} \Phi^i \\ \Phi = \displaystyle\sum_{(a_1,\ldots,a_k)\in\mathcal{A}^k\setminus\{b_1,\ldots,b_k\}} \nu(a_1)\times\cdots\times\nu(a_k)\cdot\prod_{j=1}^{k}\pi_{a_i\to b_i}(1) \end{cases}$$

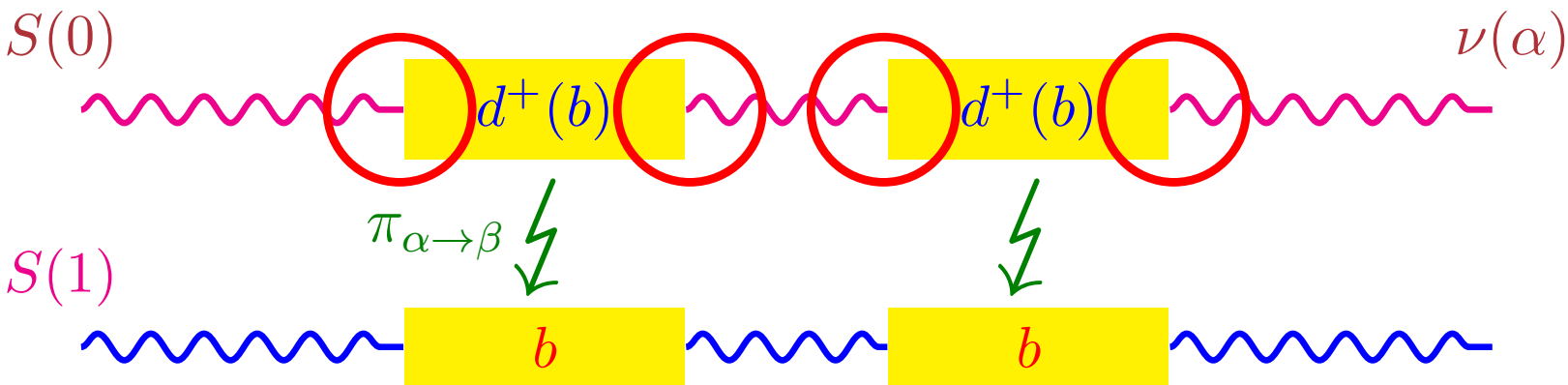
Approximations of Behrens-Vingron 2010

- occurrences of b in $S(1)$ **do not overlap**



Approximations of Behrens-Vingron 2010

- occurrences of b in $S(1)$ **do not overlap**
- possible **unwanted occurrences** of b at **junctions** in $S(0)$

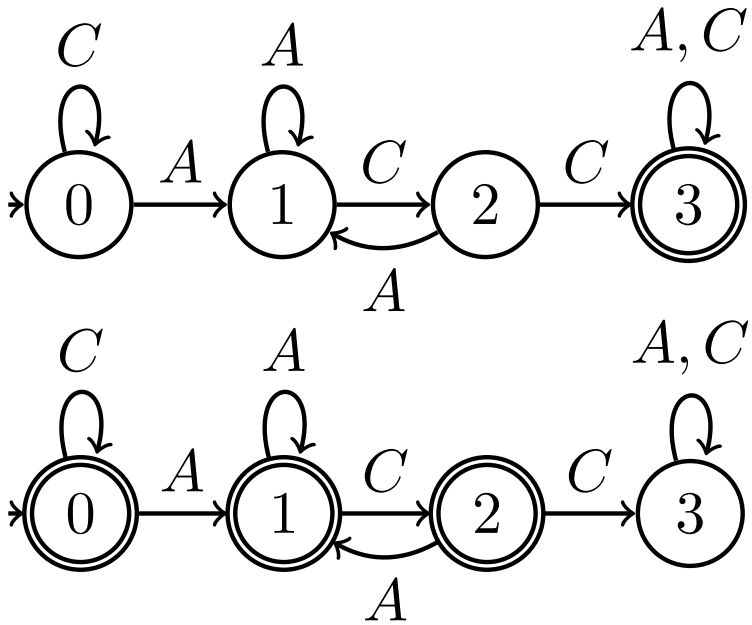


Behrens-Nicaud-P.N. 2012

Construct an **automaton**

- on the **alphabet** $\Sigma = \mathcal{A} \times \mathcal{A}$ with $\mathcal{A} = \{\mathtt{A}, \mathtt{C}, \mathtt{G}, \mathtt{T}\}$
- **recognizing sequences** $\mathsf{S}(b) = S(0) \otimes S(1)$
- **such that**
  1. $b \notin S(0)$
  2. $b \in S(1)$

Using the Knuth-Morris-Pratt automaton



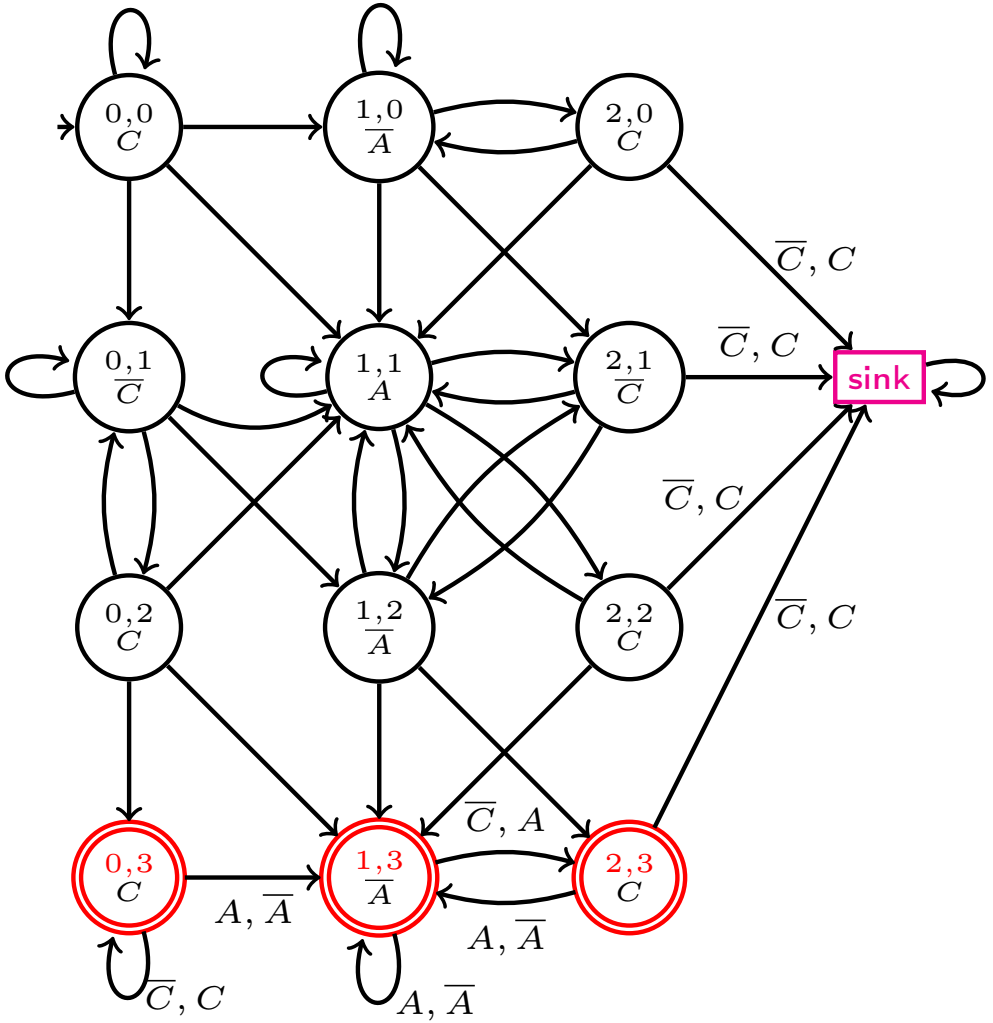
$$\mathcal{M}_{\mathsf{ACC}} = \{Q, \delta, s = 0, F\}$$

$$\overline{\mathcal{M}}_{\mathsf{ACC}} = \{Q, \delta, s = 0, Q \setminus F\}$$

$$\begin{cases} \mathcal{M}_b = (Q = \{0, \ldots, k\}, \delta_b, 0, \{k\}) \\ \overline{\mathcal{M}}_b = (Q = \{0, \ldots, k\}, \delta_b, 0, \{0, \ldots, k-1\}) \\ \mathcal{N}_b = \overline{\mathcal{M}}_b \otimes \mathcal{M}_b = (Q \times Q, \Delta, q'_0 = (0,0), F' = \{0,\ldots,k-1\} \times \{k\}) \end{cases}$$

$$\Delta((r,s),(\alpha,\beta)) = (\delta_b(r,\alpha), \delta_b(s,\beta))$$

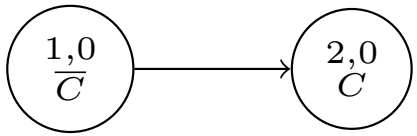
The automaton $\mathcal{N}_{\text{ACC}} = \overline{\mathcal{M}}_{\text{ACC}} \otimes \mathcal{M}_{\text{ACC}}$ with matrix $\mathbb{P}$



Notations for the transitions:

$$\begin{cases} A = \binom{A}{A}, & C = \binom{C}{C} \\ \overline{A} = \binom{A}{C}, & \overline{C} = \binom{C}{A} \end{cases}$$

a missing label of a transition is set to the letter at the bottom of its ending state



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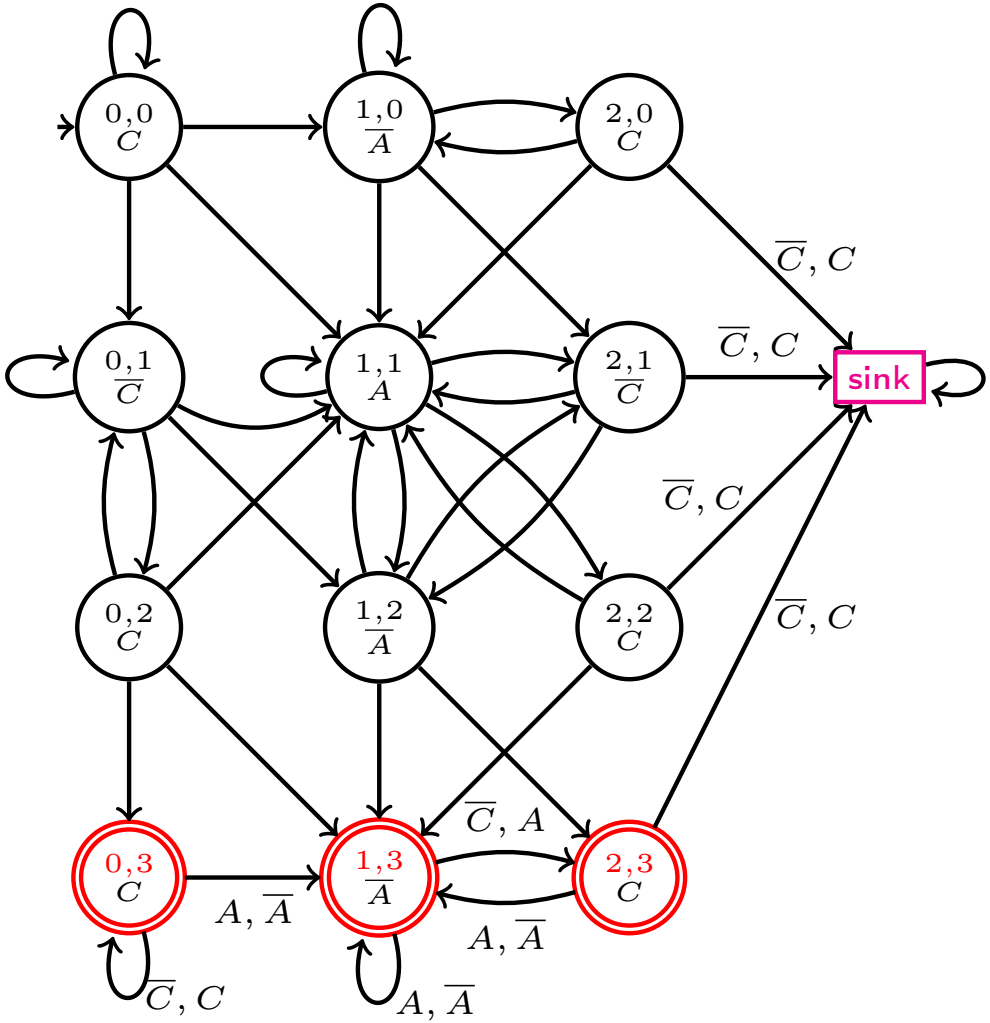

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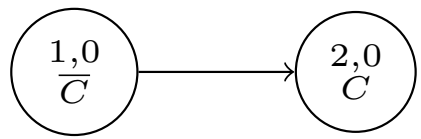

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$$\mathfrak{P}_n = \mathbf{P}(S_n(1) \in \mathcal{A}^\star b \mathcal{A}^\star | S_n(0) \notin \mathcal{A}^\star b \mathcal{A}^\star) = \frac{V_{q_0'} \mathbb{P}^n {V_{F'}}^t}{1 - V_{q_0'} \mathbb{P}^n V_{\mathsf{sink}}^t}$$

Results for 5-mers of DNA

	BNN		BV		
	$\mathbf{E}_{\mathrm{BNN}}(T_{1000})/10^6$	Rank	$\mathbf{E}_{\mathrm{BV}}(T_{1000})/10^6$	Rank	$\frac{\mathbf{E}_{\mathrm{BNN}}(T_{1000})}{\mathbf{E}_{\mathrm{BV}}(T_{1000})}$
CCCCC	9,105	1021	6,304	1	1.44
GGGGG	9,570	1022	6,666	142	1.44
TTTTT	10,401	1023	7,457	993	1.39
AAAAA	10,656	1024	7,654	1024	1.39
CGCGC	7,047	699	6,446	11	1.09
TCCCC	7,076	737	6,477	17	1.09
CCCCT	7,076	738	6,477	21	1.09
GCGCG	7,127	787	6,518	31	1.09
CTCTC	7,263	883	6,679	148	1.09
...	...	...	...	...	...

$$\left\{\begin{array}{l} 4\% \text{ of the } 5\text{-mers} \\ 0.2\% \text{ of the } 7\text{-mers} \\ 0.002\% \text{ of the } 10\text{-mers} \end{array}\right. \Bigg| \text{ verify } \frac{\mathbf{E}_{\mathrm{BNN}}(T_{1000})}{\mathbf{E}_{\mathrm{BV}}(T_{1000})} > 1.05\%$$

Numerical remarks

- **length** of promoters $n \in [500 - 2000]$
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We have

- p_r: **probability of Mutation** to b from a r-neighbour of b with $r \geq 2$
  $p_r \leq n \times \pi^r \leq 2000 \times 10^{-18} < 2.10^{-6} \times \pi$
- q_s: **probability** that s **1-neighbors simultaneously** mutate to b with $s \geq 2$
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Therefore assuming a single mutation in the promoter is numerically sound

Clump approach

Assuming a single mutation

Putative-hit positions.

- Given a **sequence $S(0)$ not containing a k-mer b**,
- a **putative-hit position** is any position of $S(0)$ that can **lead by a mutation to an occurrence of b in $S(1)$**,
- where we assume that a **single** mutation has occurred.

$$S(0) = \texttt{CCCAACAC}, \quad b = \texttt{ACC} \qquad \rightsquigarrow \qquad \underline{S}(0) = \underline{\texttt{C}}\texttt{CCA}\underline{\texttt{A}}\texttt{CAC},$$

putative-hit positions **underlined** in $\underline{S}(0)$.

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putative-hit positions **underlined** in $\underline{S}(0)$.

In a random sequence of length n with $\mathcal{A} = \{\texttt{A}, \texttt{C}\}$, let

- $H^{(n)}_{\texttt{A}\to\texttt{C}}$ number of putative-hit-positions $\texttt{A} \to \texttt{C}$,
- $H^{(n)}_{\texttt{C}\to\texttt{A}}$ number of putative-hit-positions $\texttt{C} \to \texttt{A}$,

Then

$$\mathfrak{P}_n \approx \mathbf{E}\big(H^{(n)}_{\texttt{A}\to\texttt{C}}\big) \times \pi_{\texttt{A}\to\texttt{C}} + \mathbf{E}\big(H^{(n)}_{\texttt{C}\to\texttt{A}}\big) \times \pi_{\texttt{C}\to\texttt{A}}$$

Computing via generating functions

Aim:

Compute

$$F_b(z, t_{\mathtt{A}\to\mathtt{C}}, t_{\mathtt{C}\to\mathtt{A}}) = \sum_{n\geq 0} \sum_{0\leq i\leq n-|b|} \sum_{0\leq j\leq n-|b|} f_{n,i,j}\, t^i_{\mathtt{A}\to\mathtt{C}}, t^j_{\mathtt{C}\to\mathtt{A}} z^n$$

where $f_{n,i,j}$ is the probability that a sequence $S_n(0)$ **with no** b, of length n, contains

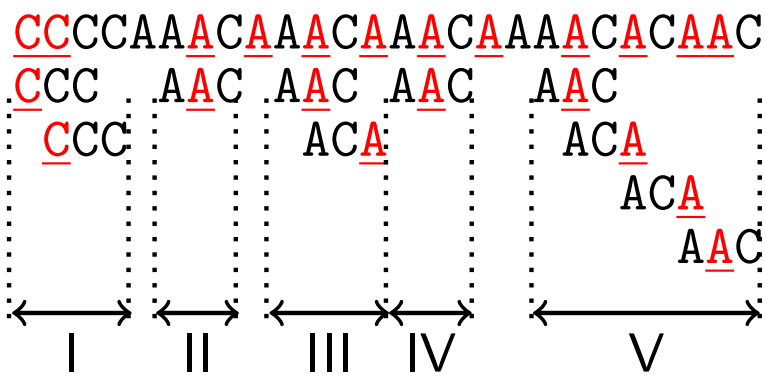
- i putative-hit positions $\mathtt{A}\to\mathtt{C}$
- and j putative-hit positions $\mathtt{C}\to\mathtt{A}$

We have

$$\mathfrak{P}_n = [z^n]\left(\pi_{\mathtt{A}\to\mathtt{C}} \left.\frac{\partial F(z, t_{\mathtt{A}\to\mathtt{C}}, 1)}{\partial t_{\mathtt{A}\to\mathtt{C}}}\right|_{t_{\mathtt{A}\to\mathtt{C}}=1} + \pi_{\mathtt{C}\to\mathtt{A}} \left.\frac{\partial F(z, 1, t_{\mathtt{C}\to\mathtt{A}})}{\partial t_{\mathtt{C}\to\mathtt{A}}}\right|_{t_{\mathtt{C}\to\mathtt{A}}=1}\right)$$

Putative-Hit-Positions and clump analysis

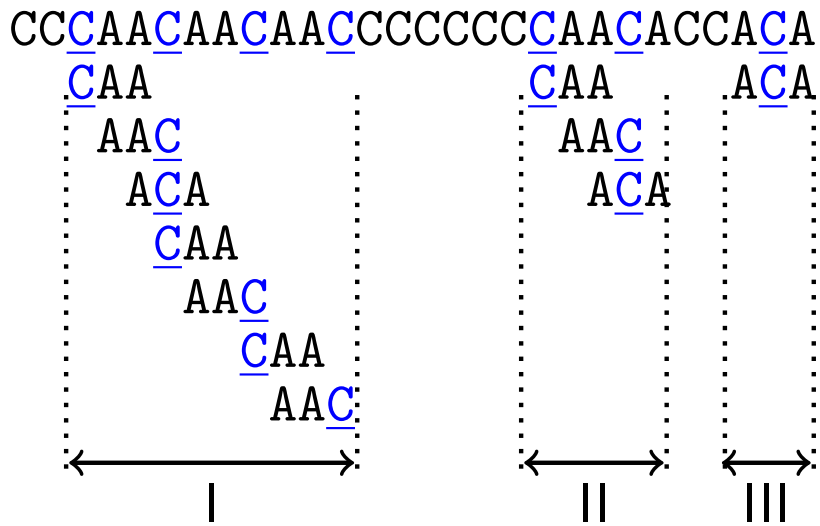
$\mathcal{A} = \{\mathtt{A}, \mathtt{C}\}$ $b = \mathtt{ACC} \longrightarrow d(\mathtt{ACC}, 1) = \{\mathtt{CCC}, \mathtt{AAC}, \mathtt{ACA}\}$



- (left) $b = \mathtt{ACC}$ - in clump I, when the right extension of a clump adds a new putative-hit position, this position is not necessarily in the extension, but possibly backwards left

Putative-Hit-Positions and clump analysis

$\mathcal{A} = \{\mathtt{A}, \mathtt{C}\} \quad b' = \mathtt{AAA} \longrightarrow d(\mathtt{AAA}, 1) = \{\underline{\mathtt{C}}\mathtt{AA}, \mathtt{A}\underline{\mathtt{C}}\mathtt{A}, \mathtt{AA}\underline{\mathtt{C}}\}$



- (right)$b' = \mathtt{AAA}$ - clump I contains 7 occurrences of $d(\mathtt{AAA})$, but only 4 putative-hit positions for $b' = \mathtt{AAA}$. The number of word occurrences is not the relevant statistics for counting putative-hit positions

Automata and Clumps

Clumps of the set of words $\mathcal{U} = \{aabaa, baab\}$

$\mathcal{E}_{w_1,w_2}$ correlation set from w_1 to w_2

$$\mathcal{E}_{aabaa,aabaa} = \{baa, abaa\} \qquad \mathcal{E}_{baab,baab} = \{aab\}$$
$$\mathcal{E}_{aabaa,baab} = \{b\} \qquad \mathcal{E}_{baab,aabaa} = \{aa\}$$

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Algorithm

1. Build the set of strings

$$X = \{aabaa.(\epsilon + \mathcal{E}_{aabaa,aabaa})\} \cup \{aabaa.\mathcal{E}_{aabaa,baab}\} \cup \{baab.(\epsilon + \mathcal{E}_{baab,baab})\} \cup \{baab.\mathcal{E}_{baab,aabaa}\}$$

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2. Build a trie $\mathcal{T}$ on X

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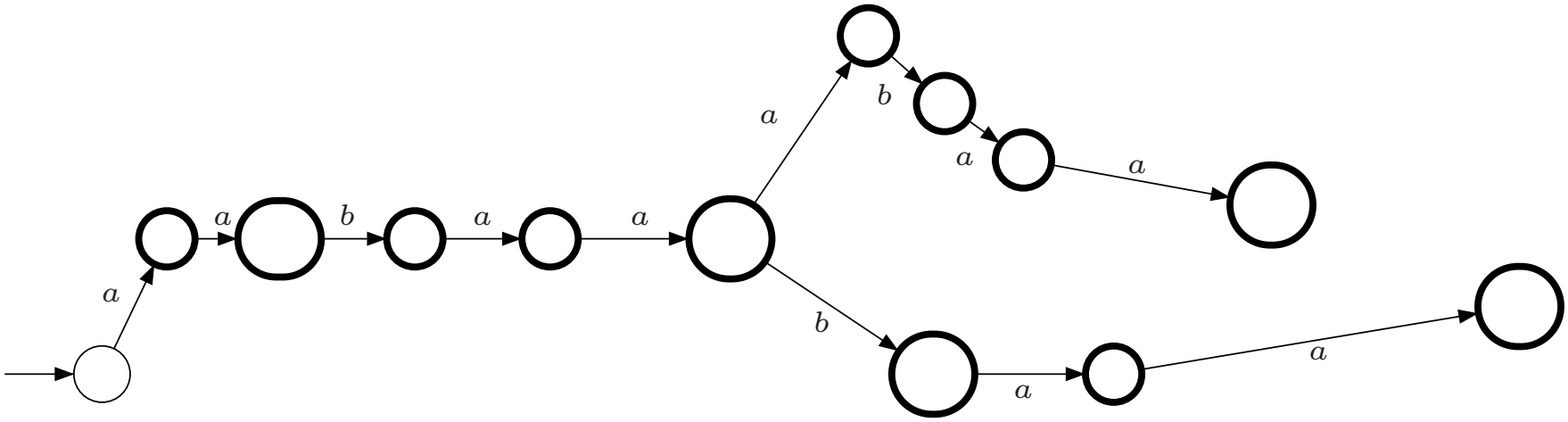
2. Build a trie $\mathcal{T}$ on X
3. Build a **Aho-Corasick like automaton** upon $\mathcal{T}$. For each node ν of $\mathcal{T}$ with "access word" v, use the transition function δ

   $\delta(\nu, \ell) =$ node accessed by the **longuest prefix** in X that is **suffix** of $v.\ell$

(Bassino-Clément-Fayolle-P.N. 2008)

$X = \{aabaa, aabaabaa, aabaaabaa, aabaab \quad \}$



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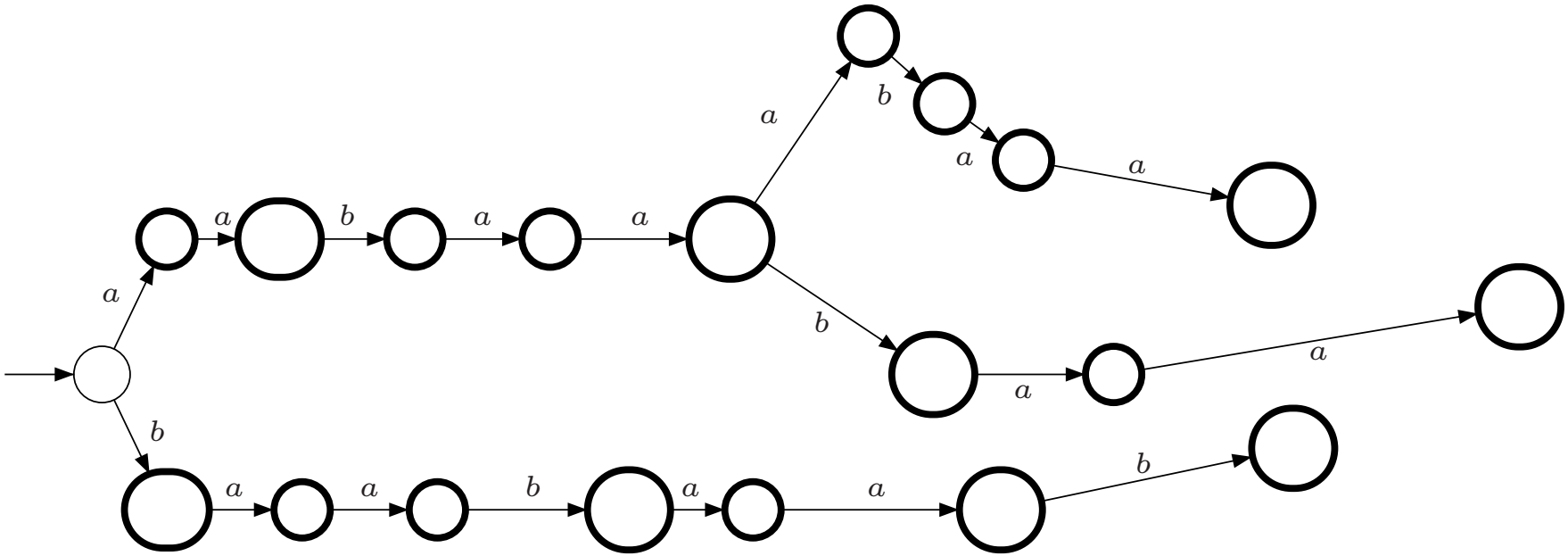
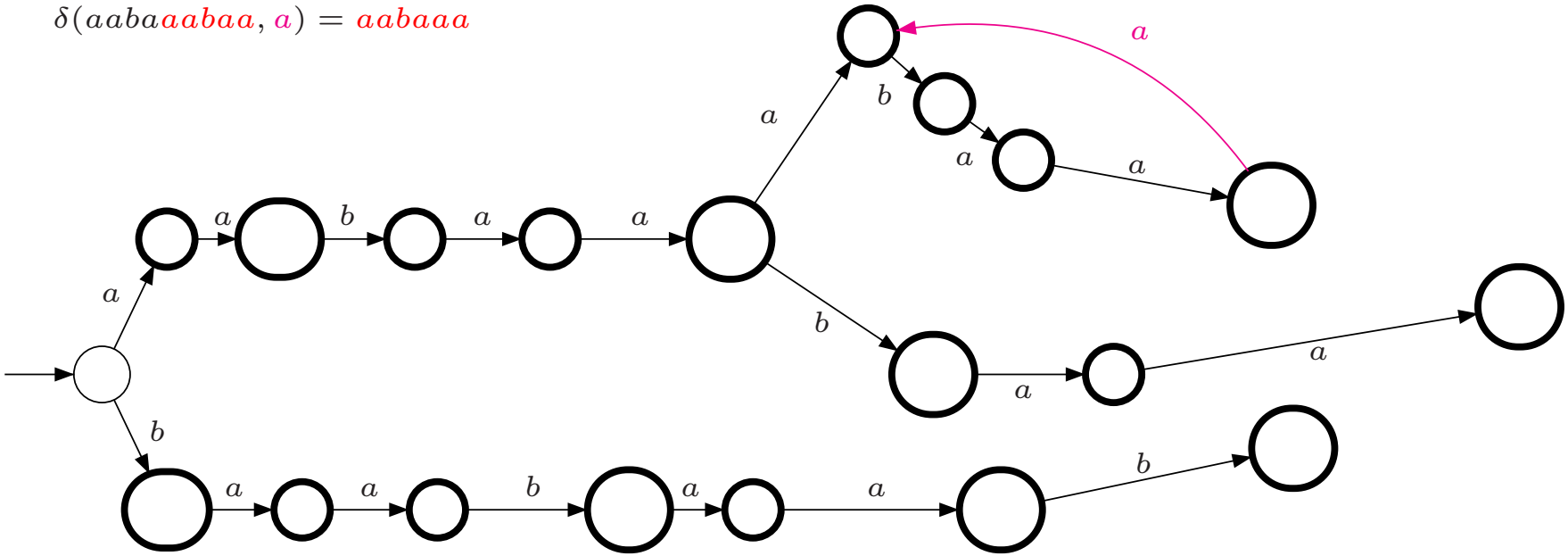
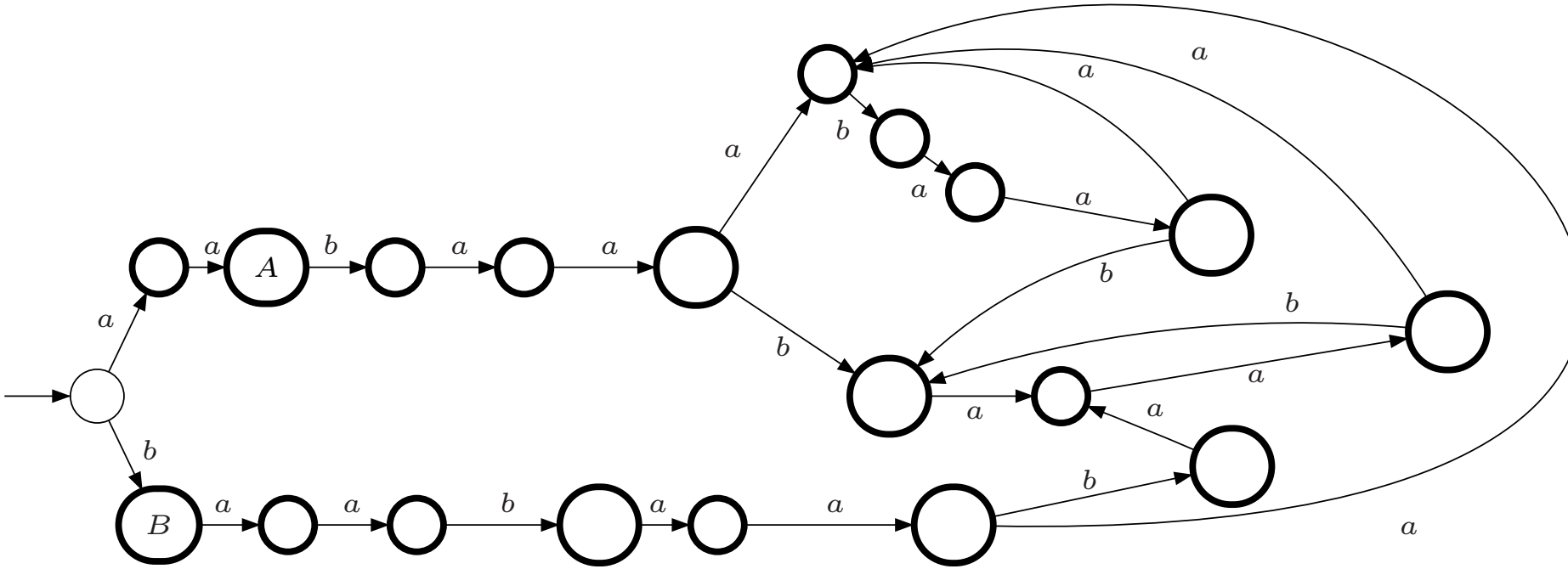


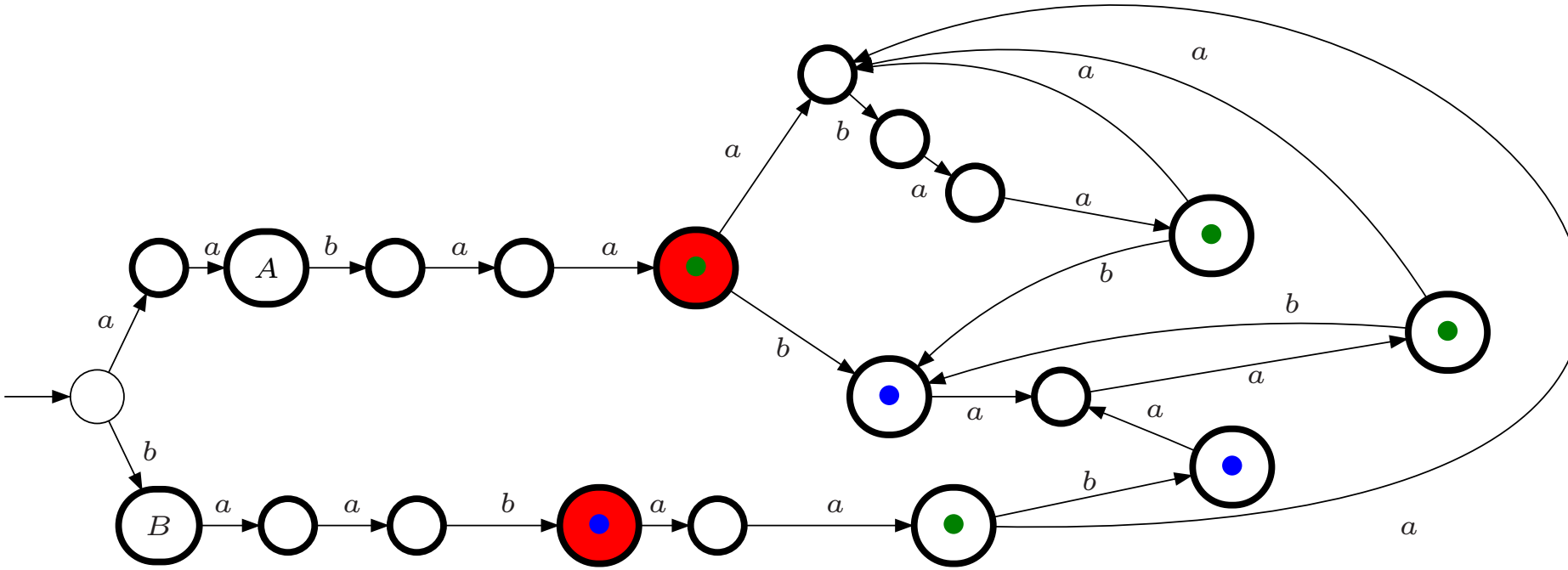
$X = \{aabaa, aabaabaa, aabaaabaa, aabaab, baab, baabaab\}$

$\delta(aabaaabaa, a) = aabaaa$





An automaton for $\mathcal{V} = \{v_1 = aabaa, v_2 = baab\}$. All transitions labeled by a and b ending respectively on state A and B are omitted.



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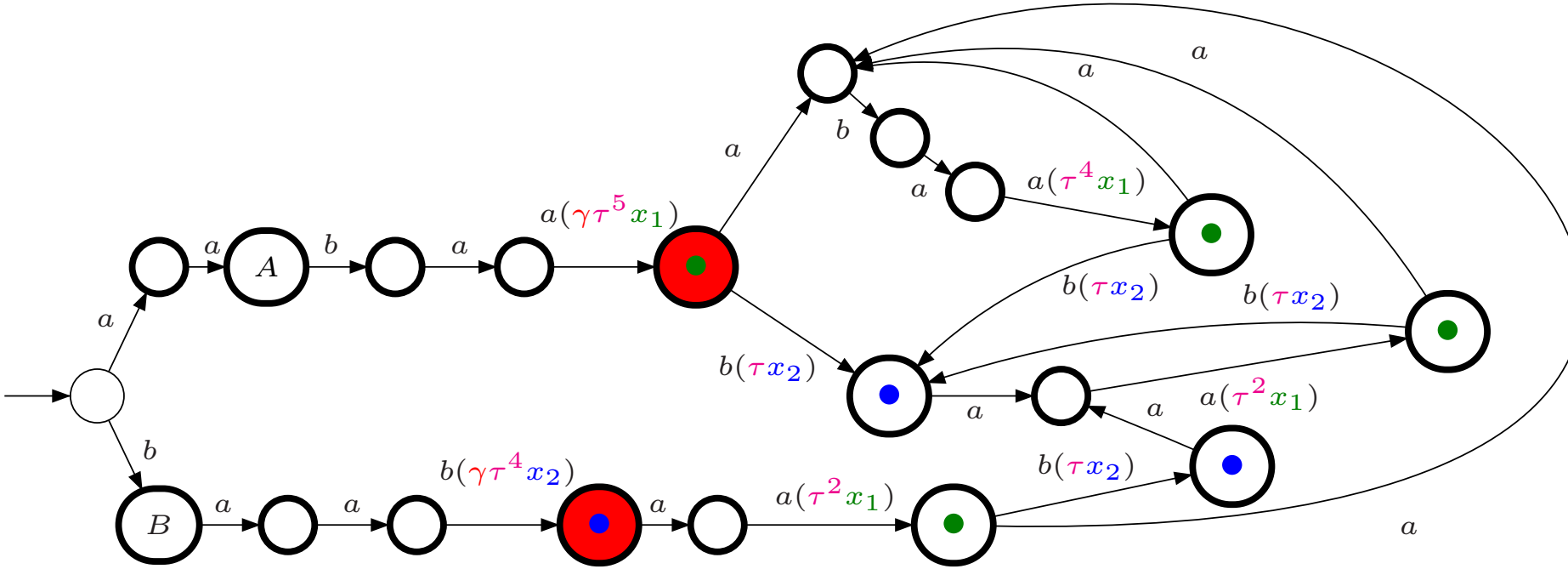
- ●, ● → the corresponding prefix (or state) ends with some occurrence of $aabaa, baab$.
- **red states** → states where we have entered a **new clump**



An automaton for $\mathcal{V} = \{v_1 = aabaa, v_2 = baab\}$. All transitions labeled by a and b ending respectively on state A and B are omitted.

- $\bullet$, $\bullet$ $\rightarrow$ the corresponding prefix (or state) ends with some occurrence of $aabaa, baab$.
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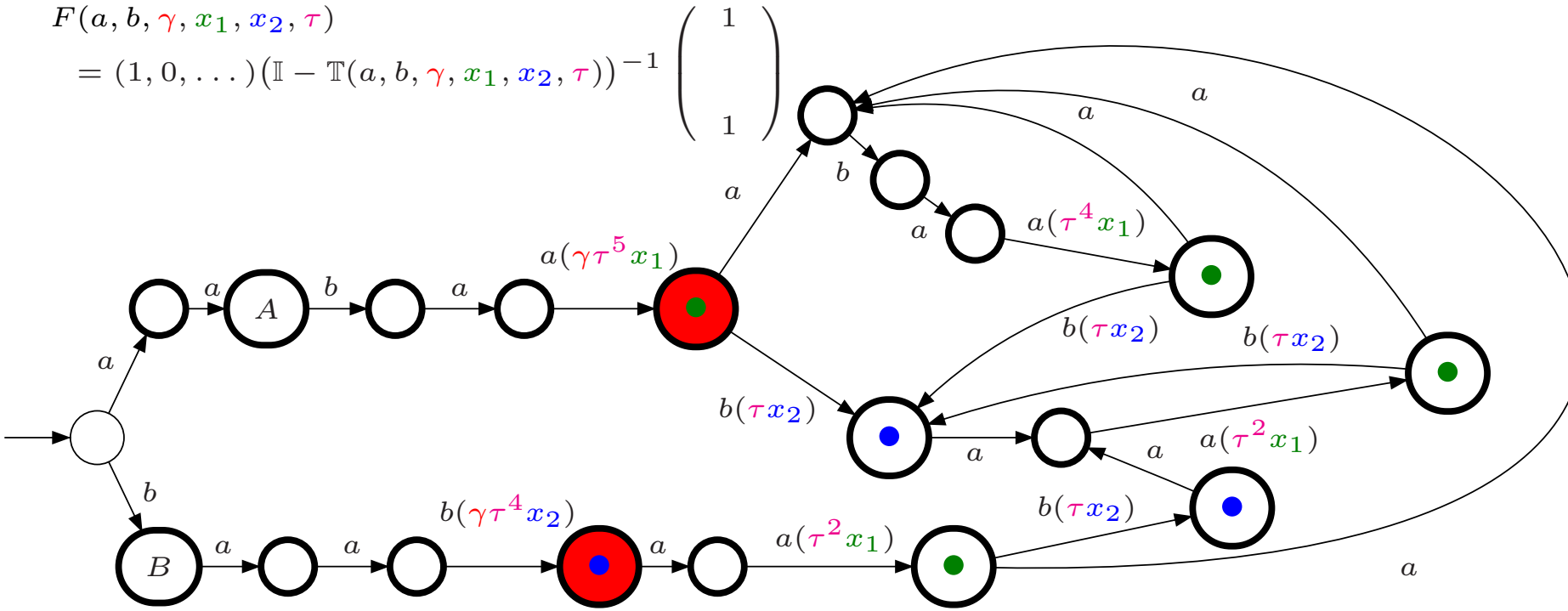
Formal weights on transitions

- $\gamma \rightarrow$ the number of clumps
- $\tau \rightarrow$ total length of clumps
- $x_1, x_2 \rightarrow$ occurrences of $aabaa, baab$

$$F(a,b,\gamma,x_1,x_2,\tau) = (1,0,\dots)\big(\mathbb{I}-\mathbb{T}(a,b,\gamma,x_1,x_2,\tau)\big)^{-1}\begin{pmatrix}1\\ \\ 1\end{pmatrix}$$



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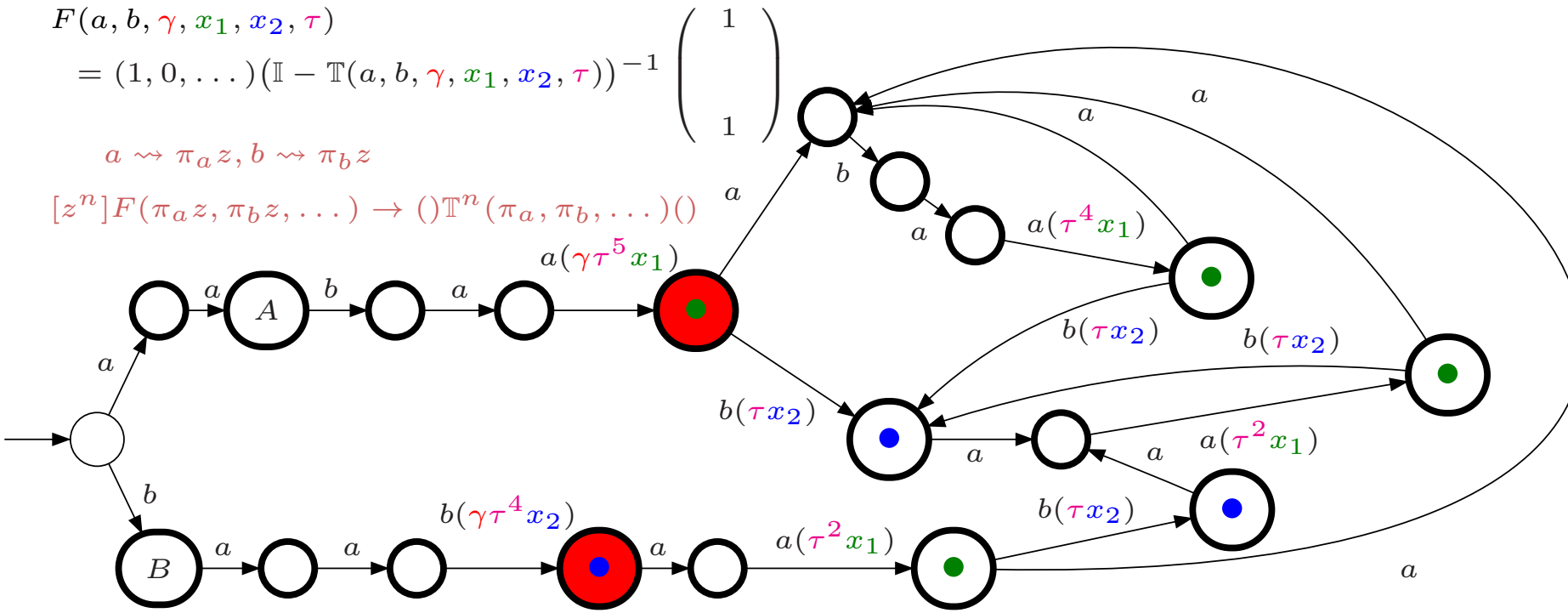

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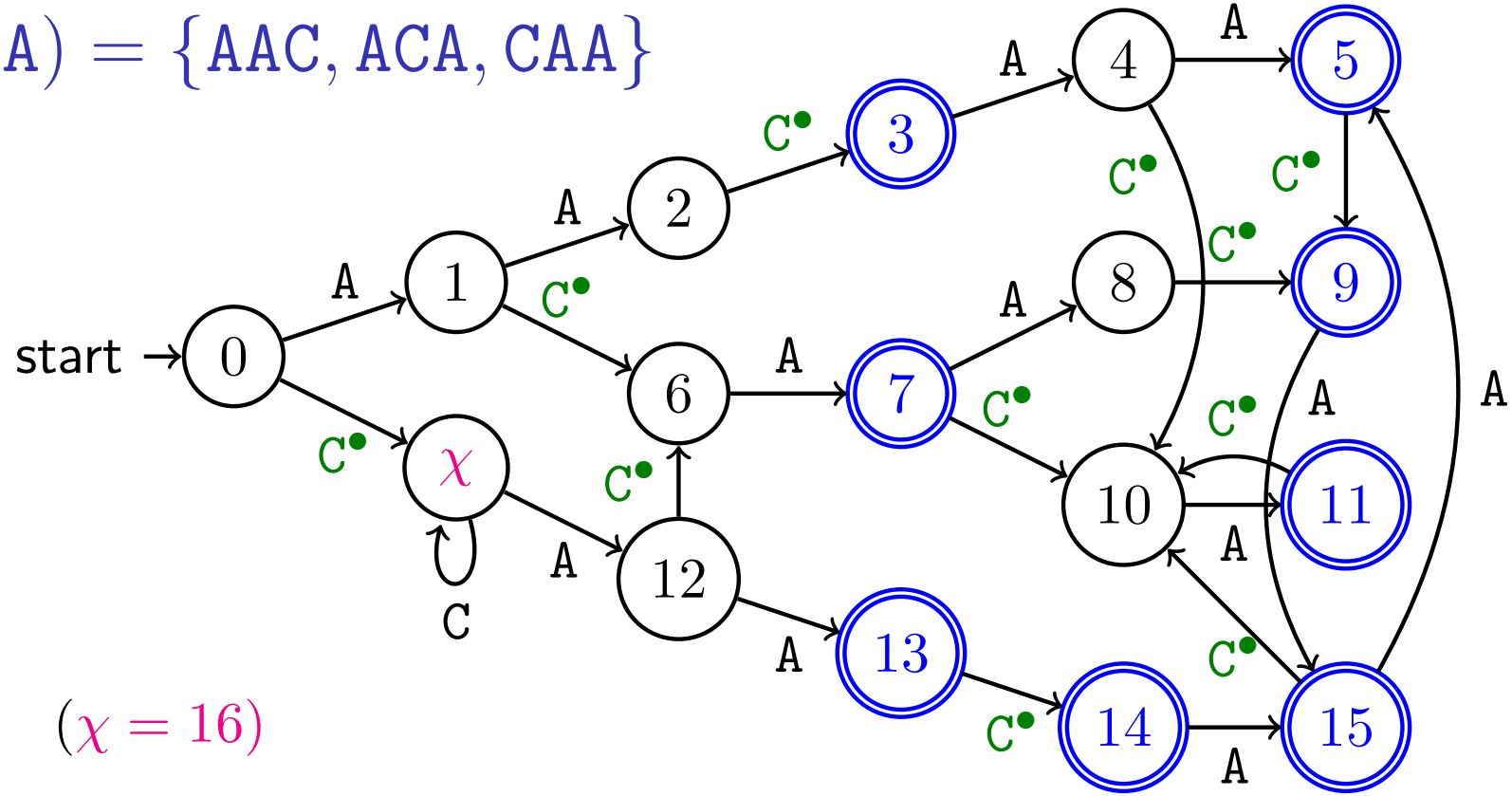
Automaton for constrained clumps of $d(\mathtt{AAA}) = \{\mathtt{AAC}, \mathtt{ACA}, \mathtt{CAA}\}$



$(\chi = 16)$

- **Double circles** signals an occurrence of a word of $d(aaa)$.
- **Avoiding** `AAA` leads to **missing transitions** `A`
- The **missing transitions** `C` **point to** the **state** χ.
- • **characters** mark **putative-hit-positions**

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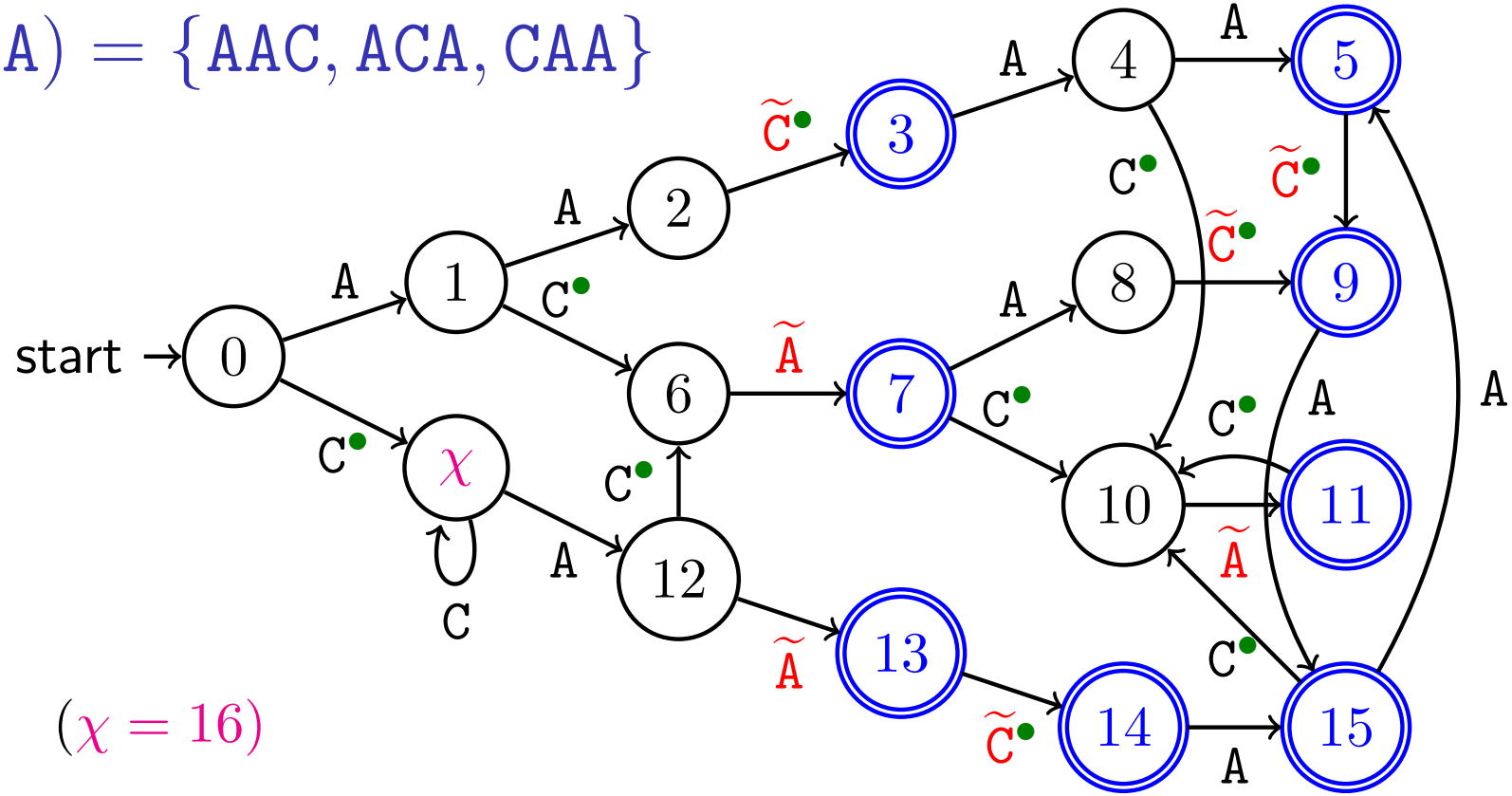

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- Transitions covered by tildes ($\widetilde{\mathtt{A}}, \widetilde{\mathtt{C}}$) emits a signal counting a putative-hit position.

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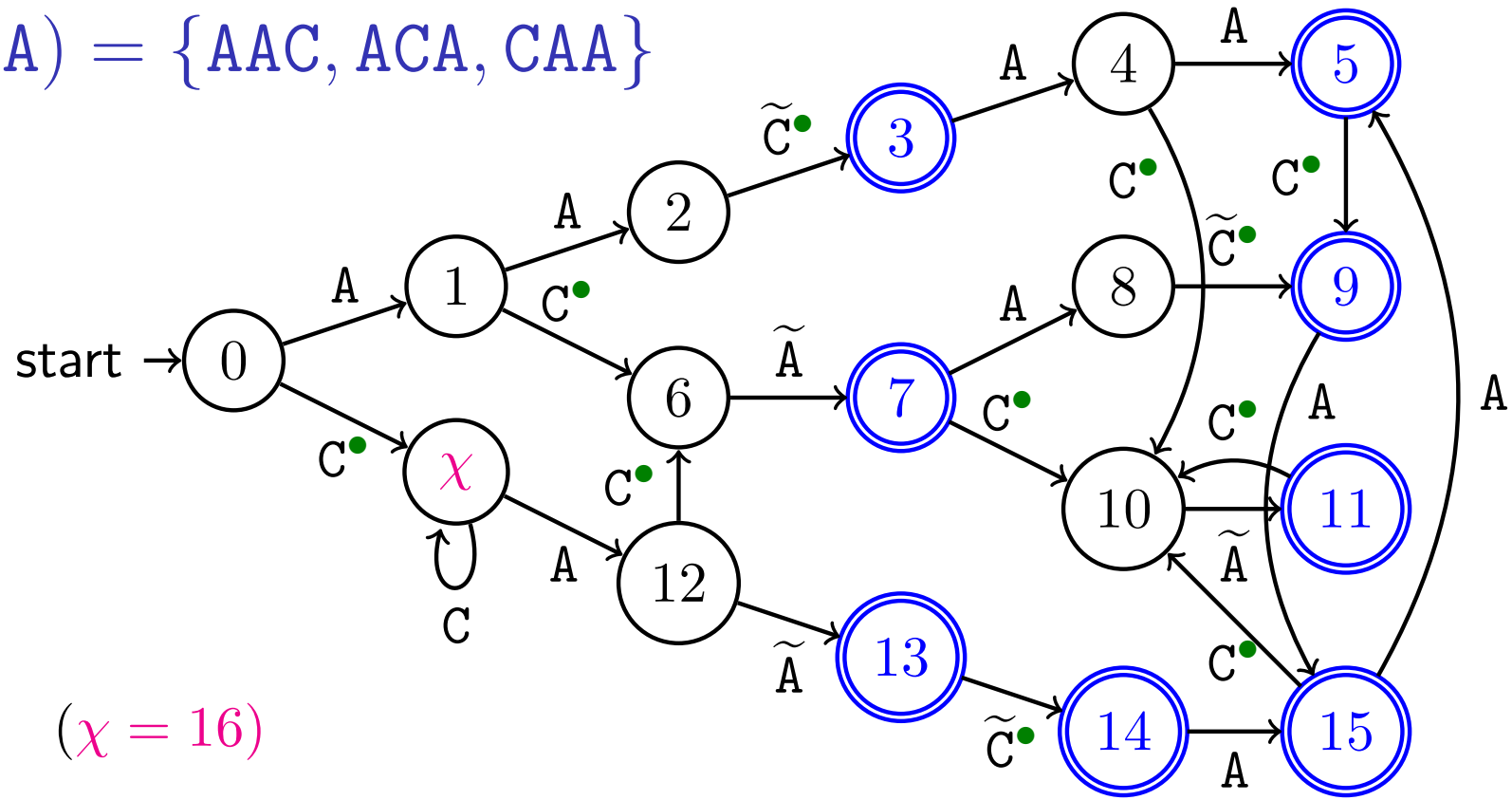

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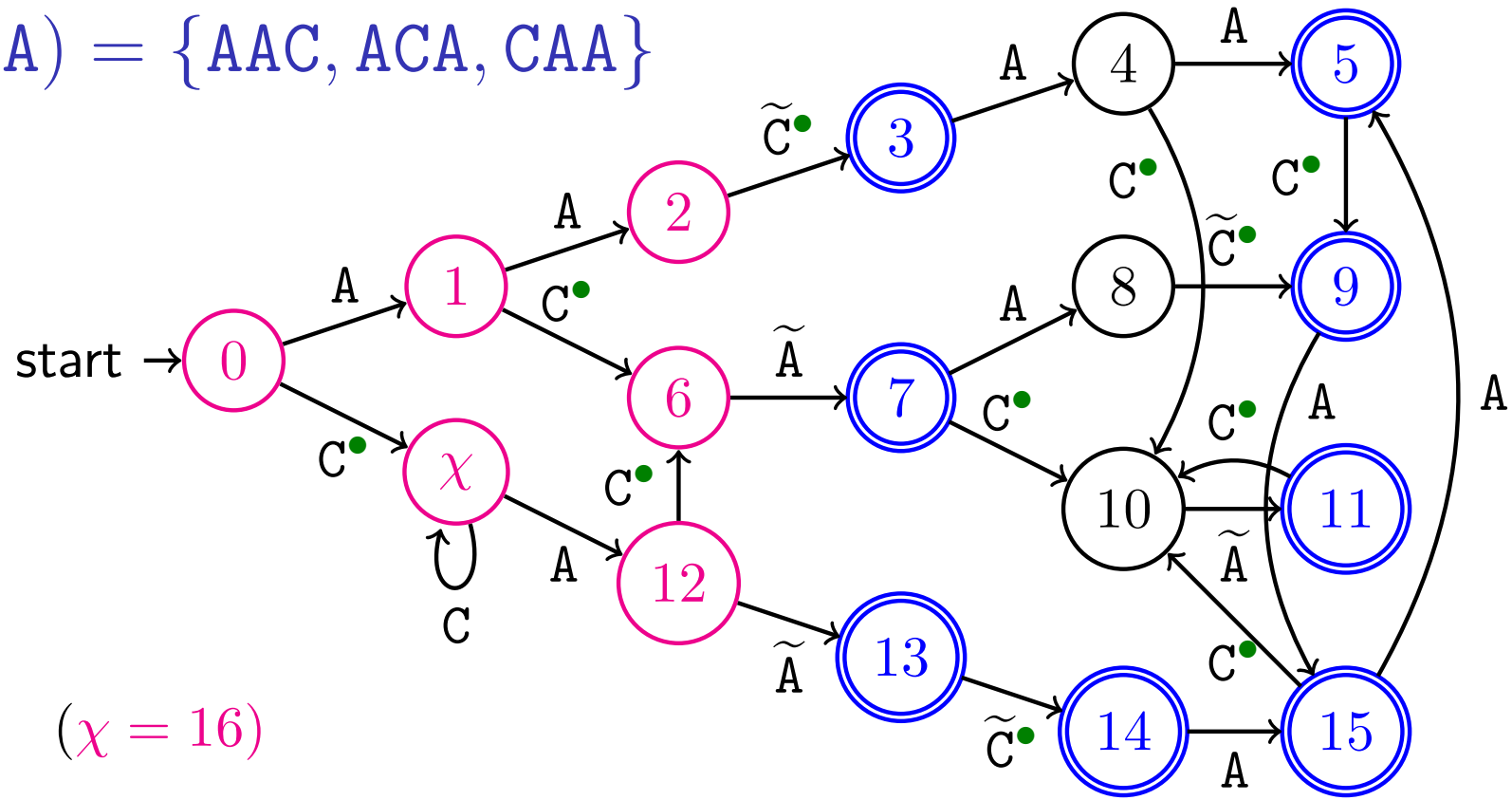

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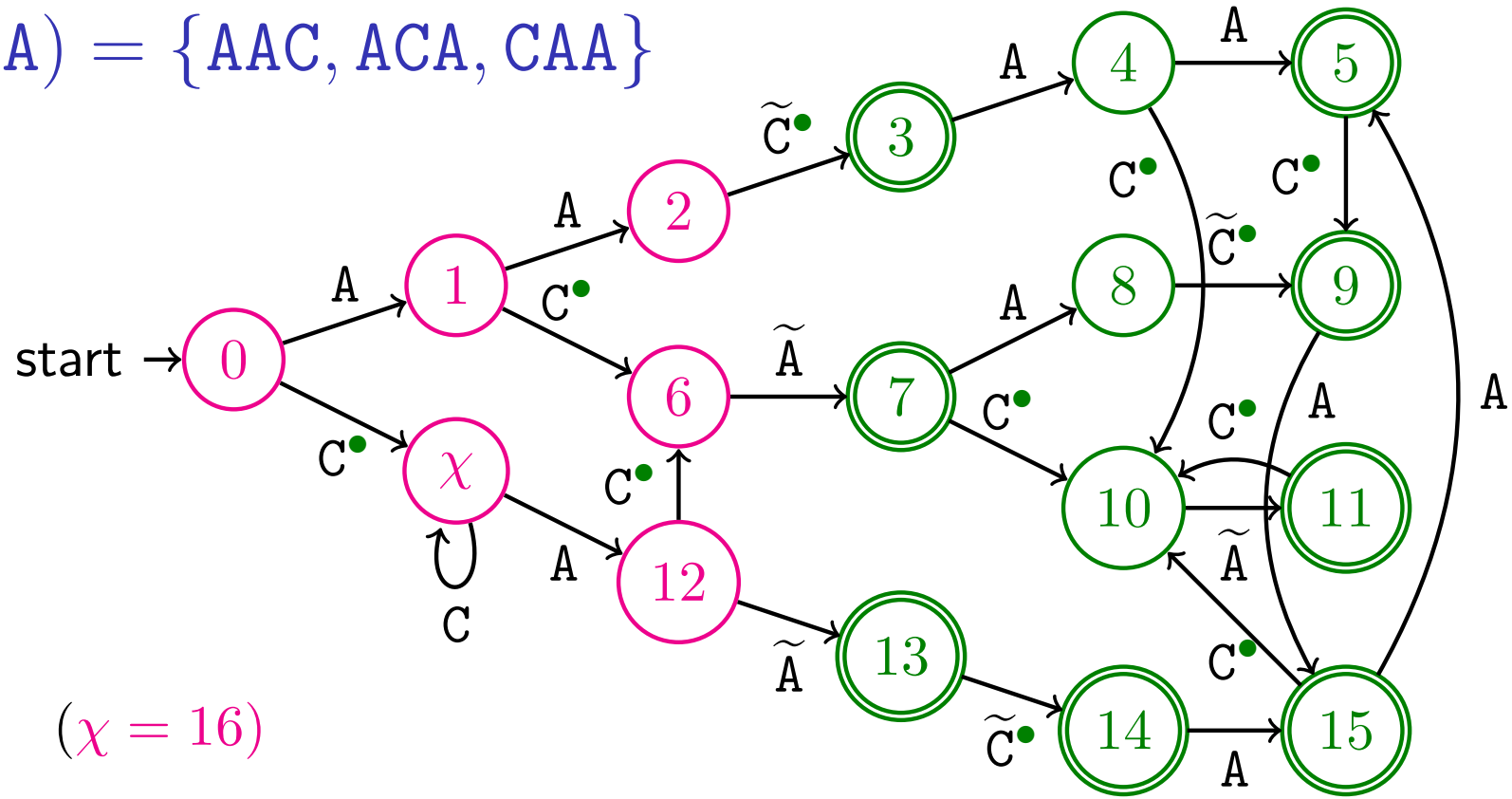

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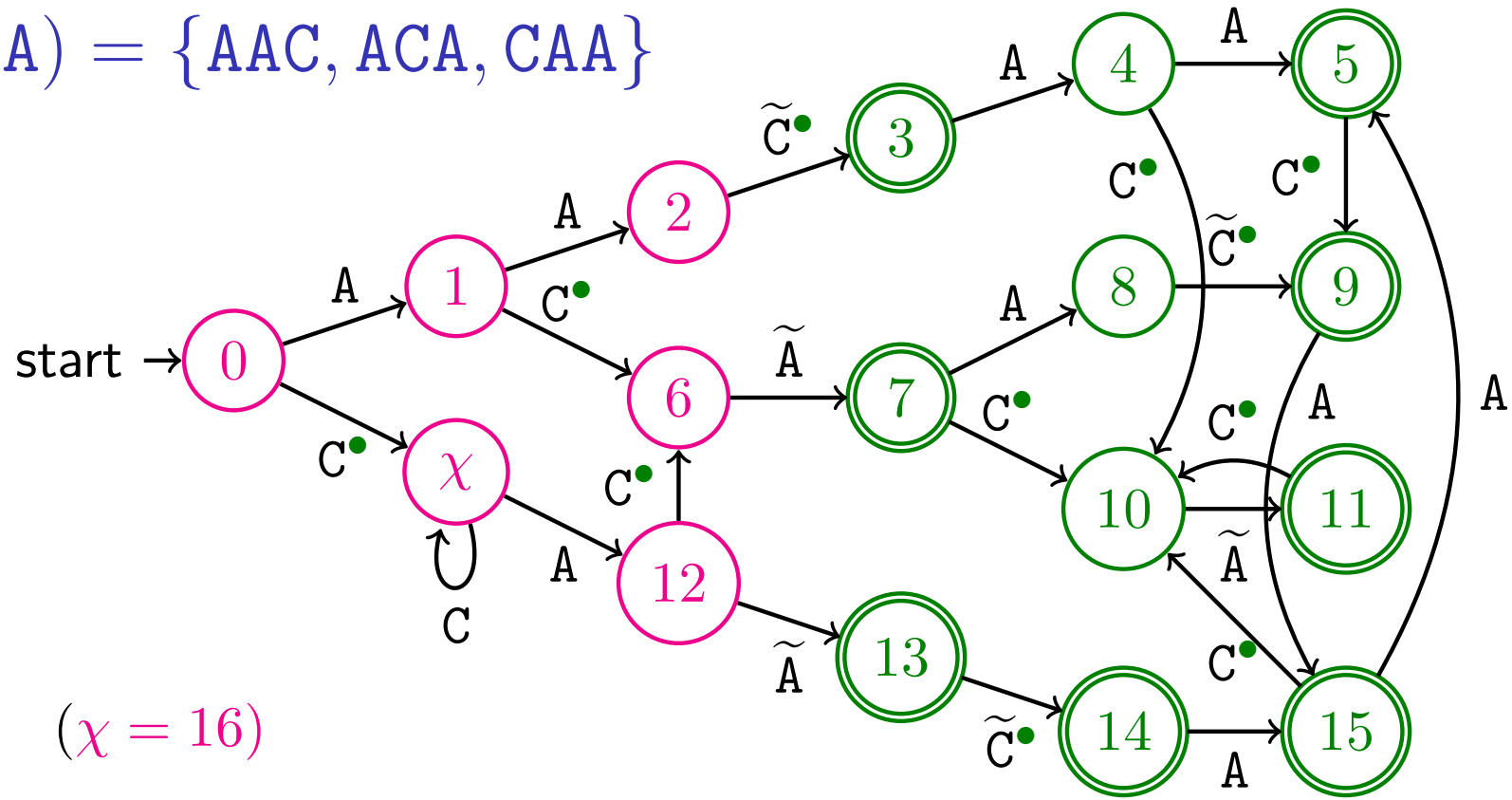

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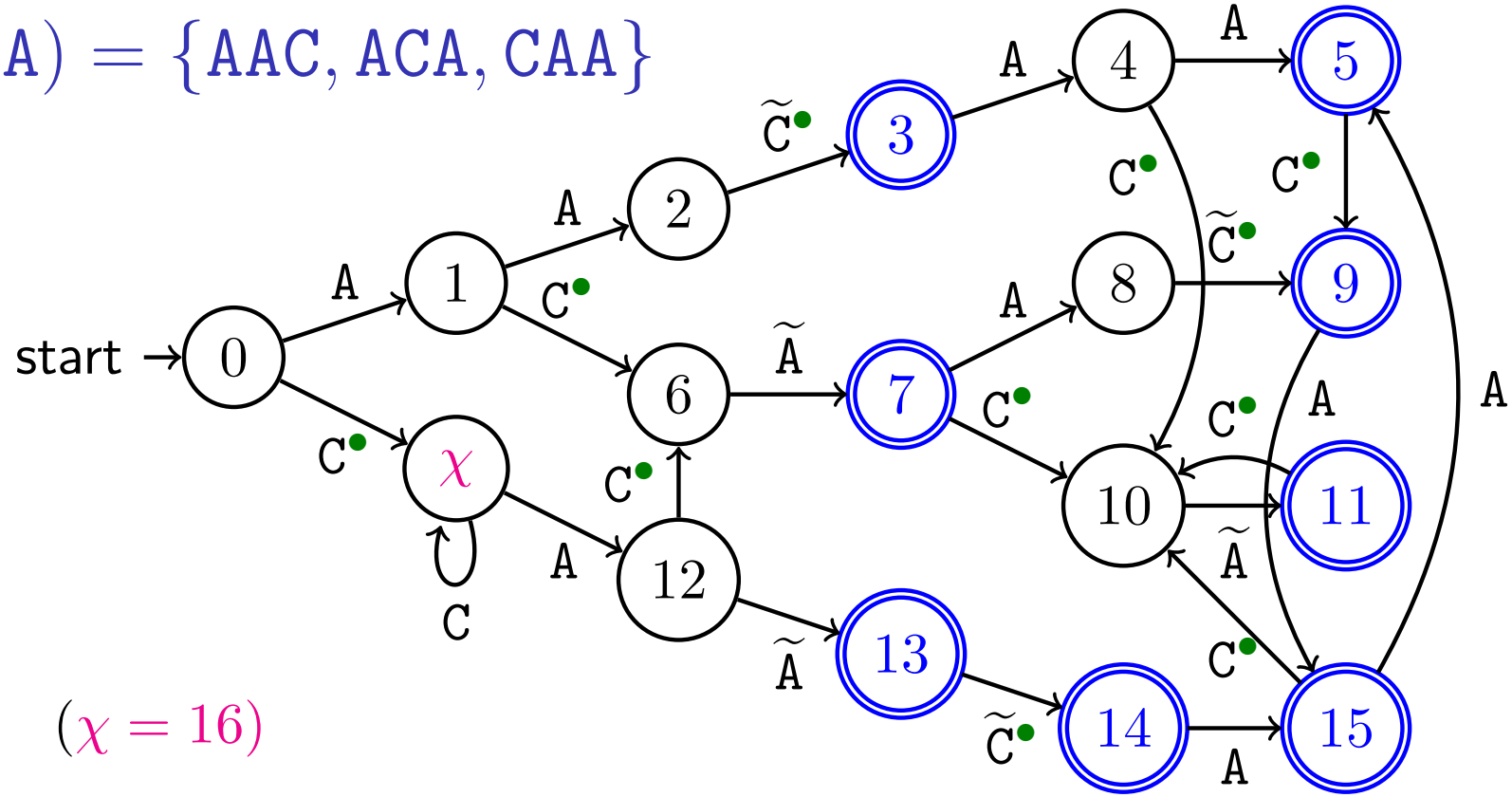
- **Clump-Core** of the automaton $E = Q \setminus \overline{E}$
- **Markov property:** $\forall q \in E, \qquad |\{w \in \mathcal{A}^{|b|}; \delta(x, w) = q\}| = 1$

Definition of an auxiliary function θ

$d(\mathtt{AAA}) = \{\mathtt{AAC}, \mathtt{ACA}, \mathtt{CAA}\}$



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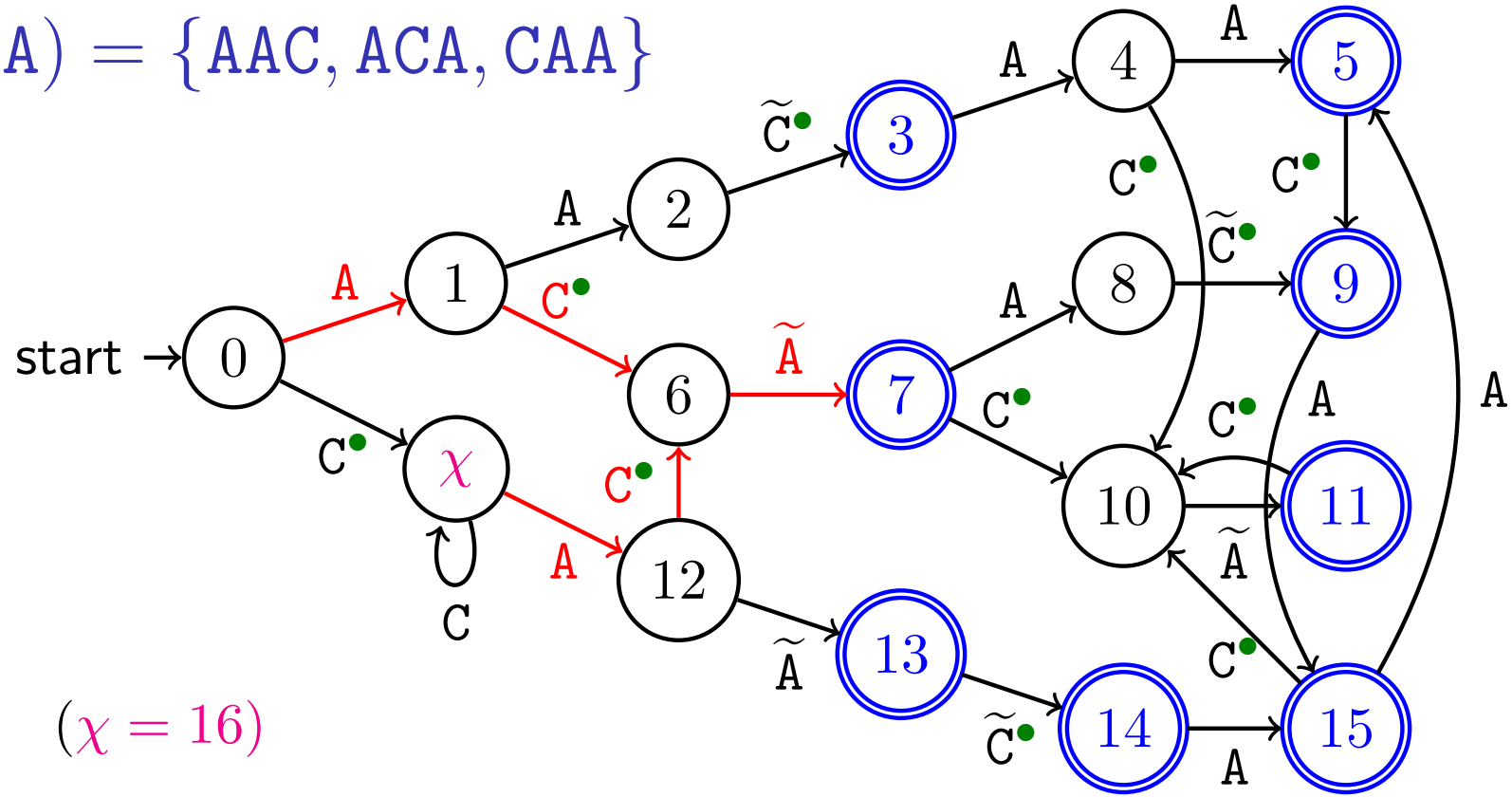

$(\chi = 16)$

$\theta(7) = \mathtt{ACA}$

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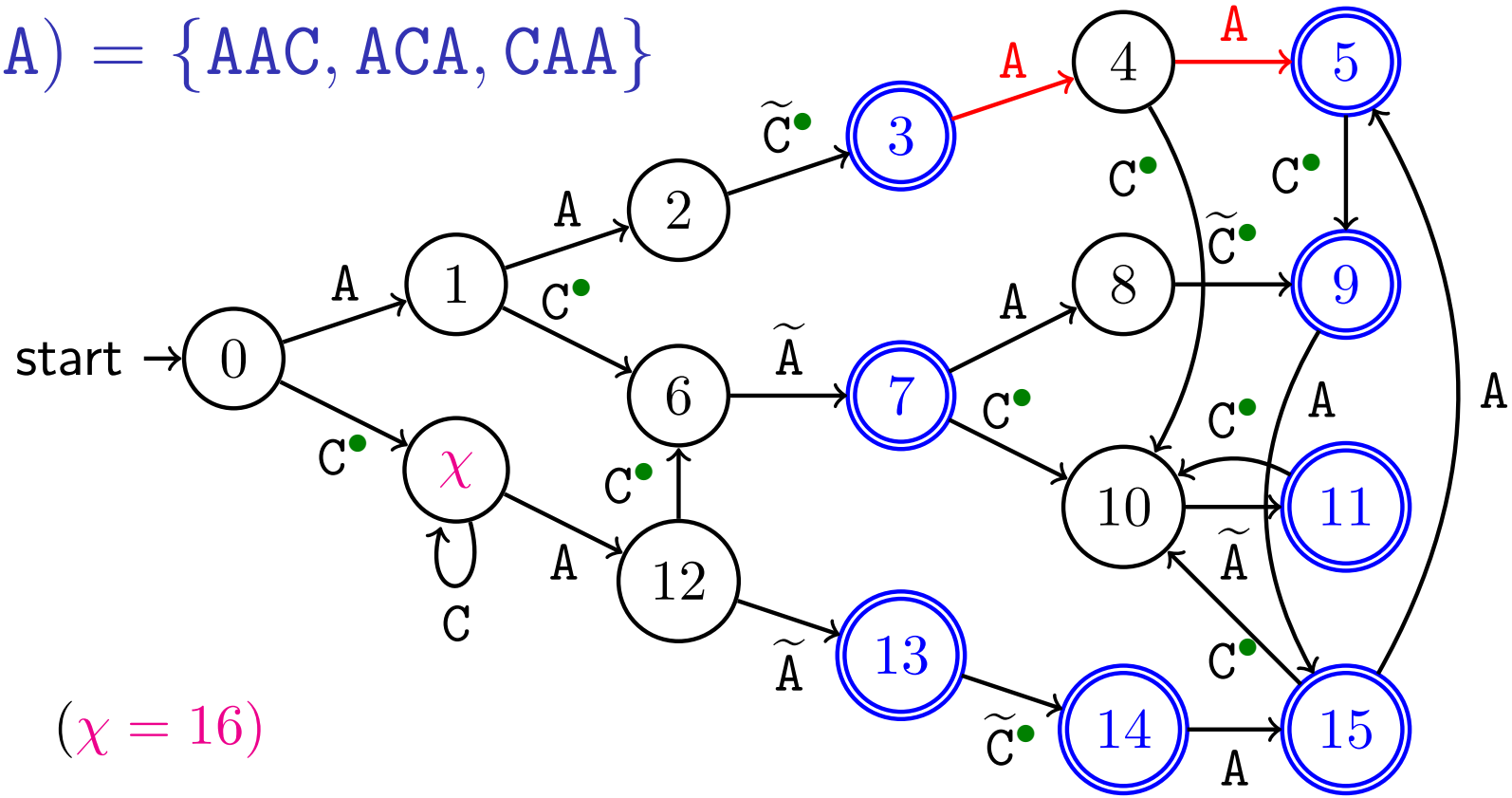

$(\chi = 16)$

$\theta(7) = \mathtt{ACA}\ , \quad \theta(5) = \mathtt{AA}$

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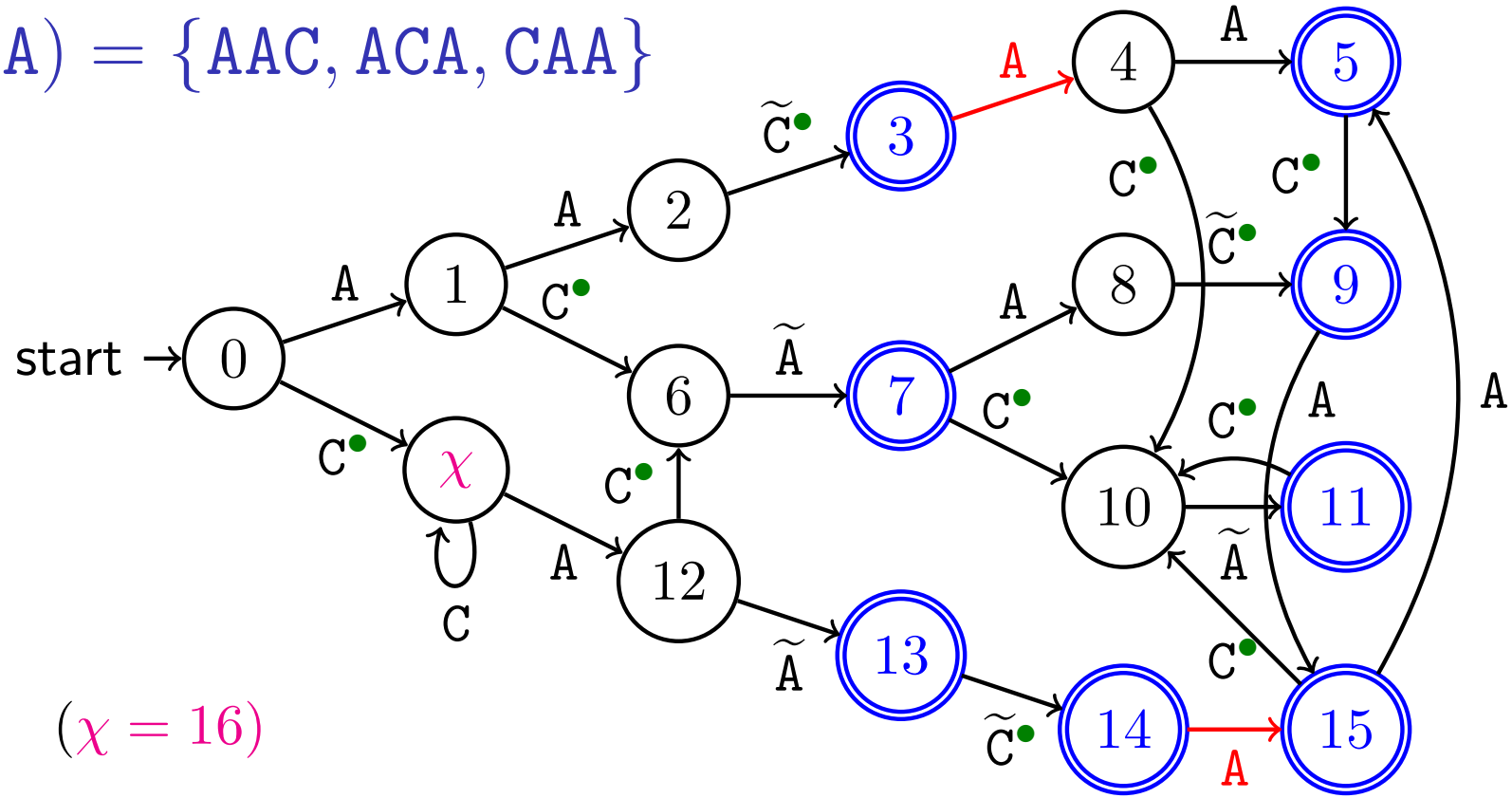

$(\chi = 16)$

$$\theta(7) = \mathtt{ACA}\ , \quad \theta(5) = \mathtt{AA}\ , \quad \theta(4) = \theta(15) = \mathtt{A}$$

Formal definition of θ

For each state $o \in O$ (recognizing an occurrence of $d(b)$),

$$\theta(o) = \left\{ w \text{ with } |w| \leq |b|, \text{ of } \textbf{maximal length}, \right. \left| \begin{array}{l} \text{verifying} \\ \end{array} \right| \begin{array}{l} (a) \text{ there exists } q \text{ such that } \delta(q, w) = o, \\ (b) \textbf{ there is no } u \in \widehat{\mathrm{Pref}}(w) \\ \qquad \text{such that } \delta(q, u) \in O \end{array}$$

By the **Markov** property, $\theta(o)$ defines a **unique word**

Adjacency matrix $\mathbb{H}(t) = (h_{ij}(t))$

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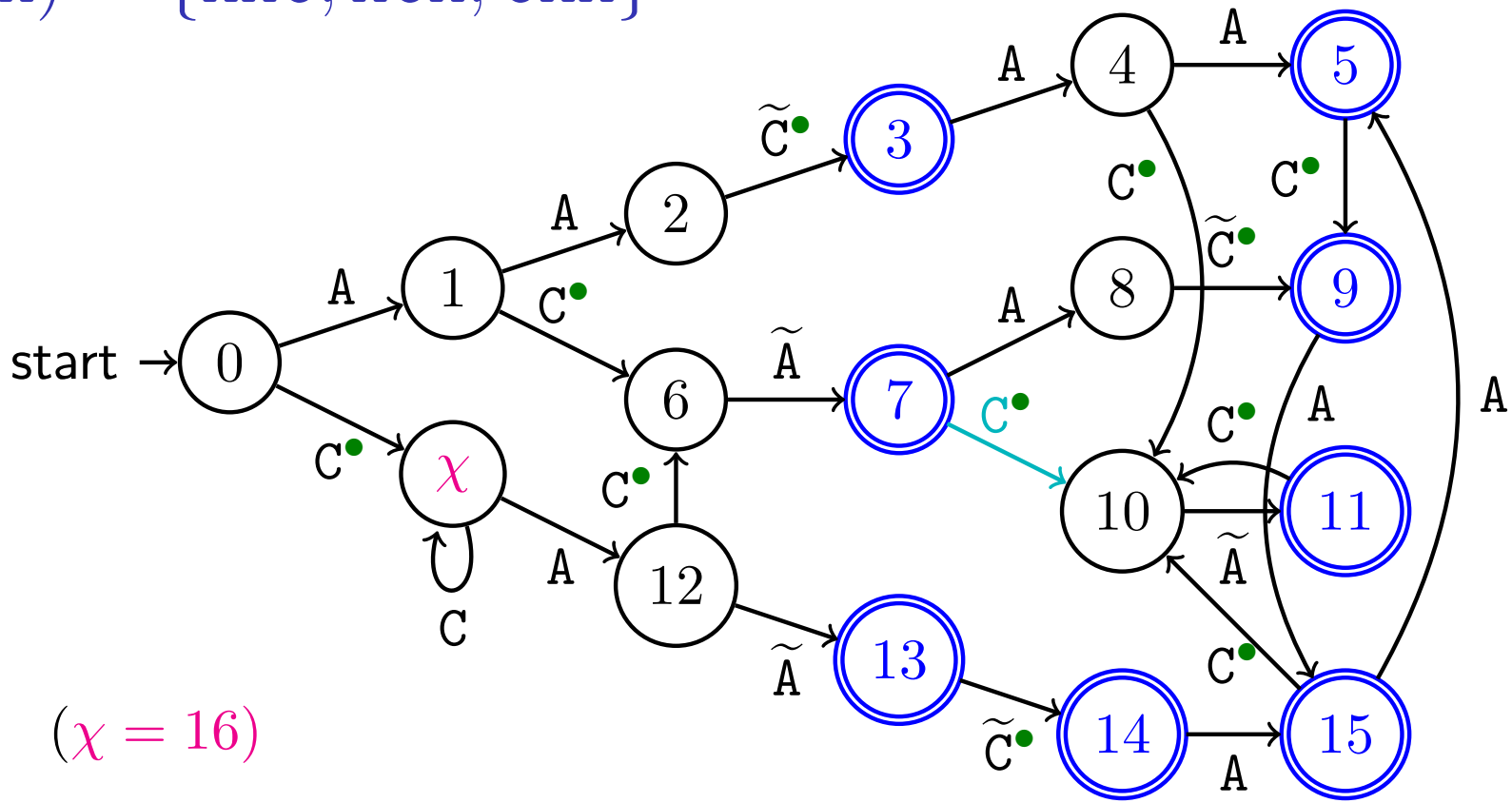

$(\chi = 16)$

- $h_{7,10}(t_{\mathtt{C}\to\mathtt{A}}) = \nu_{\mathtt{C}}$

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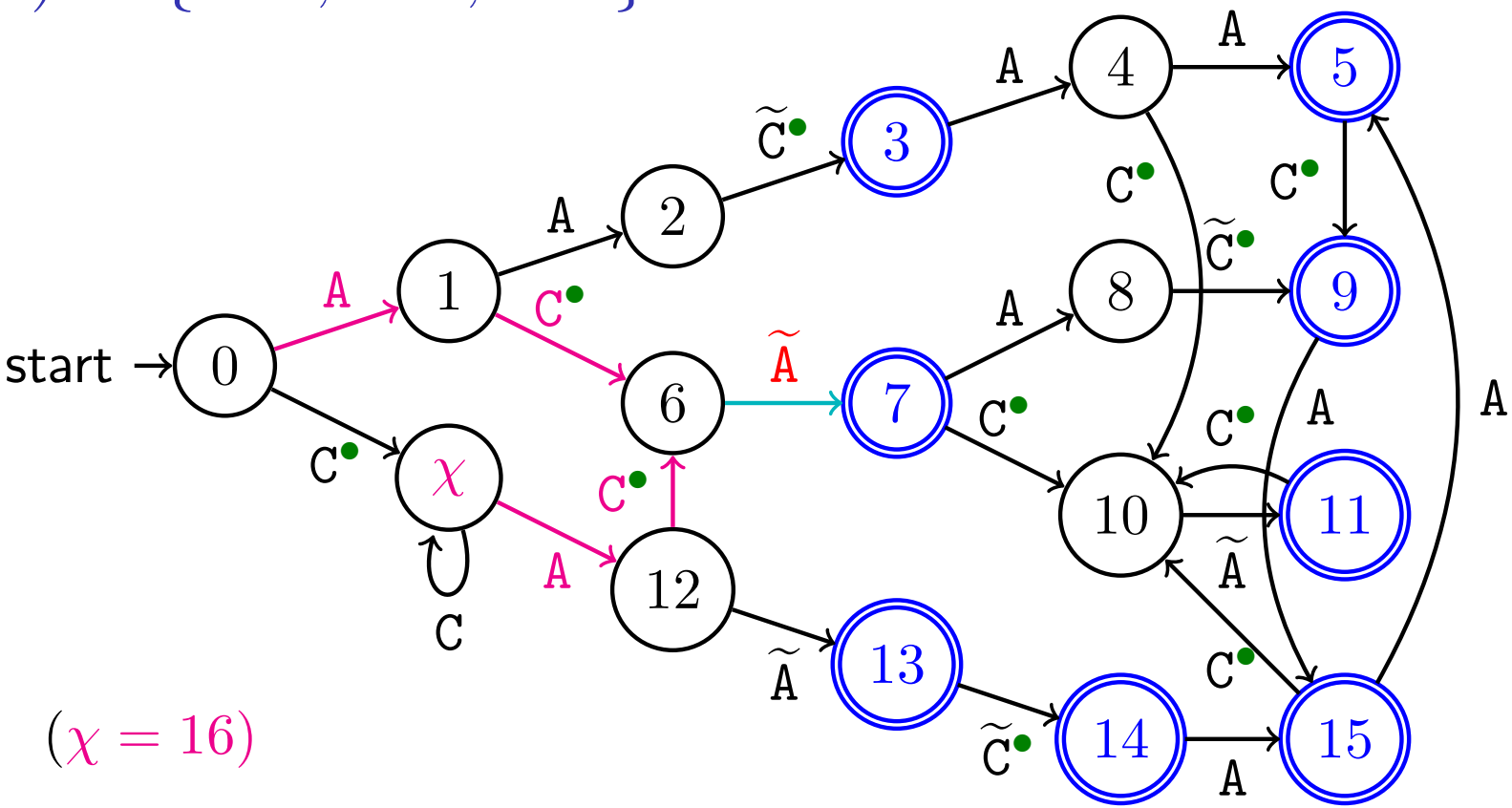

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- $h_{7,10}(t_{\mathtt{C}\to\mathtt{A}}) = \nu_{\mathtt{C}}$
- $h_{6,7}(t_{\mathtt{C}\to\mathtt{A}}) = \nu_{\mathtt{A}} t_{\mathtt{C}\to\mathtt{A}}$

$(\theta(7) = \mathtt{AC}^{\bullet}\mathtt{A})$

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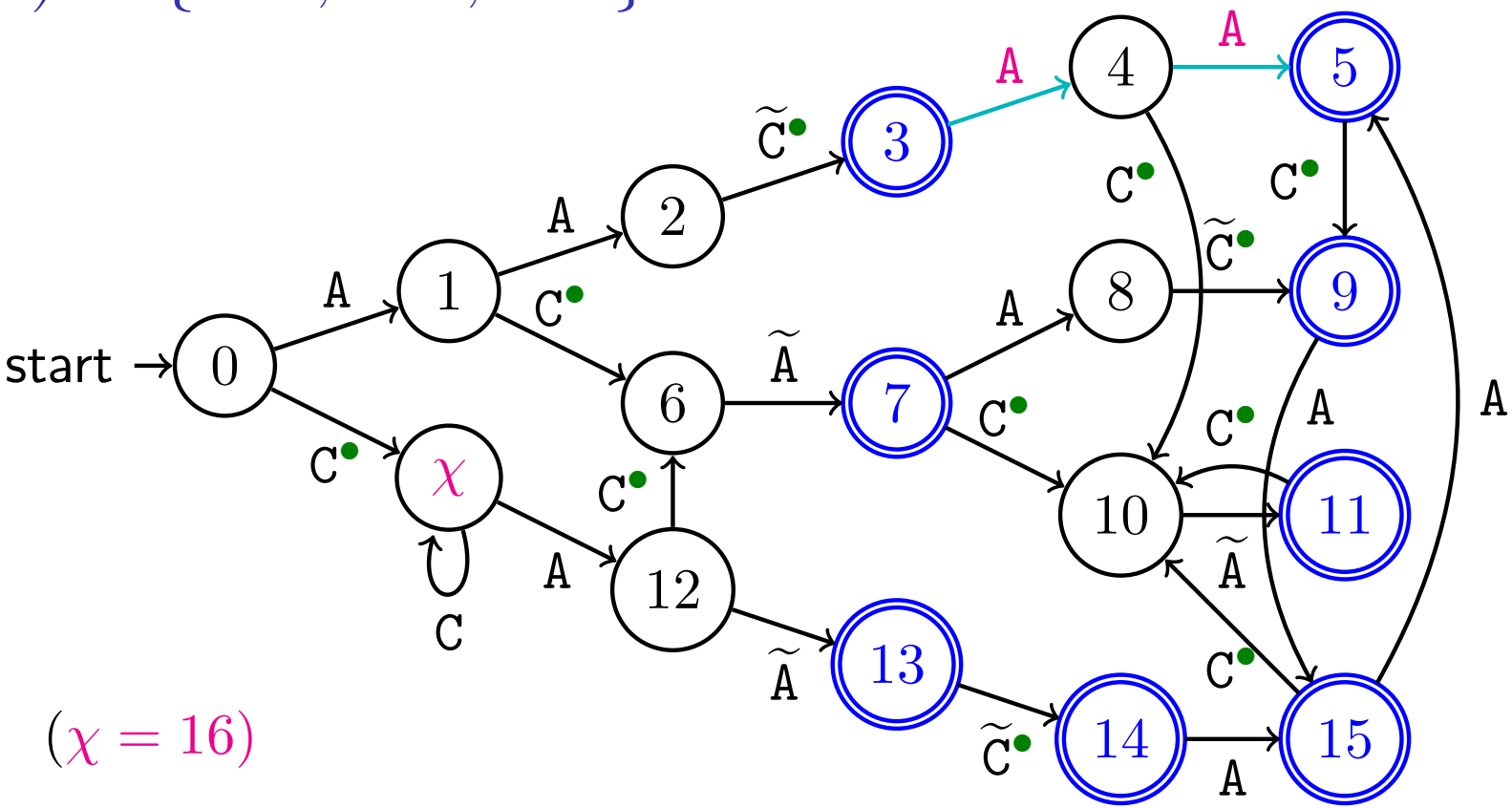

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- $h_{6,7}(t_{\mathtt{C}\to\mathtt{A}}) = \nu_{\mathtt{A}} t_{\mathtt{C}\to\mathtt{A}}$ $\quad (\theta(7) = \mathtt{AC^{\bullet}A})$
- $h_{3,4}(t_{\mathtt{C}\to\mathtt{A}}) = h_{4,5}(t_{\mathtt{C}\to\mathtt{A}}) = \nu_{\mathtt{A}}$ $\quad (\theta(5) = \mathtt{AA})$

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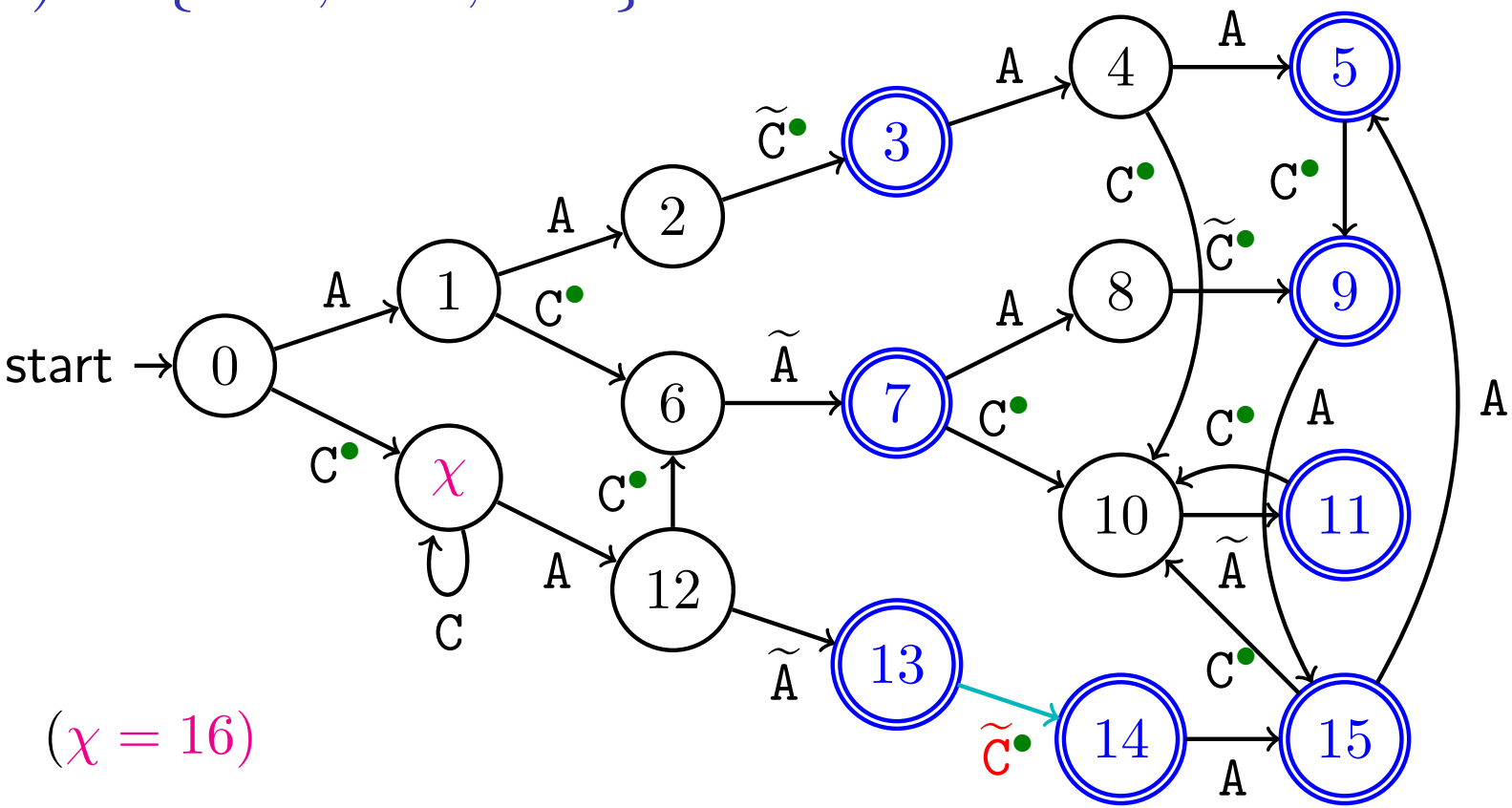

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- $h_{13,14}(t_{\mathtt{C}\to\mathtt{A}}) = \nu_{\mathtt{C}} t_{\mathtt{C}\to\mathtt{A}}$ $\quad (\theta(14) = \mathtt{C^{\bullet}})$

Formal definition of the adjacency matrix $\mathbb{H}(t)$

(a) $h_{ij}(t) = 0$ if there is no transition from i to j

(b) With $\delta(i, \alpha) = j$,

$$h_{i,j}(t) = \begin{cases} \nu(\alpha) \text{ if } \left| \begin{array}{l} j \notin O, \\ j \in O \text{ and } \theta(j) \text{ contains } \textbf{no putative-hit position} \end{array} \right. \\ \nu(\alpha) \times t \text{ elsewhere} \end{cases}$$

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From matrix to generating function

$$\begin{aligned} F_b(z,t) &= (1,0,\ldots,0) \times \left(\mathbb{I} + z\mathbb{H}(t) + \cdots + z^n\mathbb{H}^n(t) + \ldots\right) \times \mathbf{1}^t \\ &= (1,0,\ldots,0) \times (\mathbb{I} - z\mathbb{H}(t))^{-1} \times \mathbf{1}^t. \end{aligned}$$

Entries of $(\mathbb{I} - z\mathbb{H}(t))^{-1}$ **rational functions** in z and t

Rational functions and gfun

rational function $\frac{f(z)}{g(z)}$ $\rightarrow$ `gfun[diffeqtorec]` $\rightarrow$ **recurrence** equations

recurrence equations $\rightarrow$ `gfun[rectoproc]` $\rightarrow$ **procedure** Proc(n)=$[z^n]\frac{f(z)}{g(z)}$

Rational functions, Taylor coefficient of order n and `gfun`

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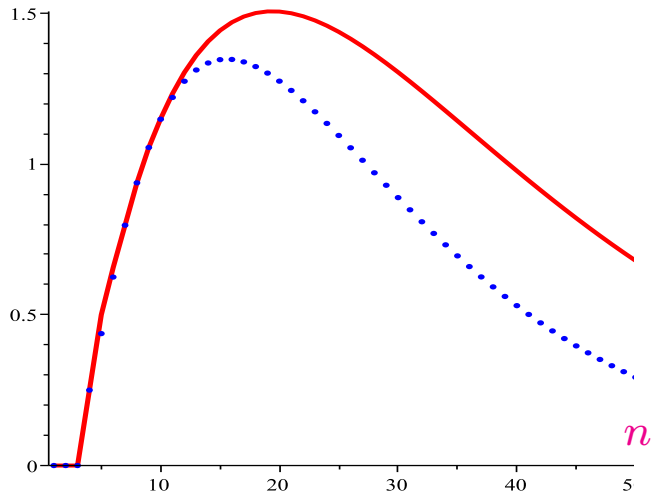
- η_n is the **unconditionned probability** of the expectation of the count of putative-hit positions
- **Conditionned expectation:** $\widetilde{\eta}_n=\eta_n/\widehat{f}_n^{(b)}$

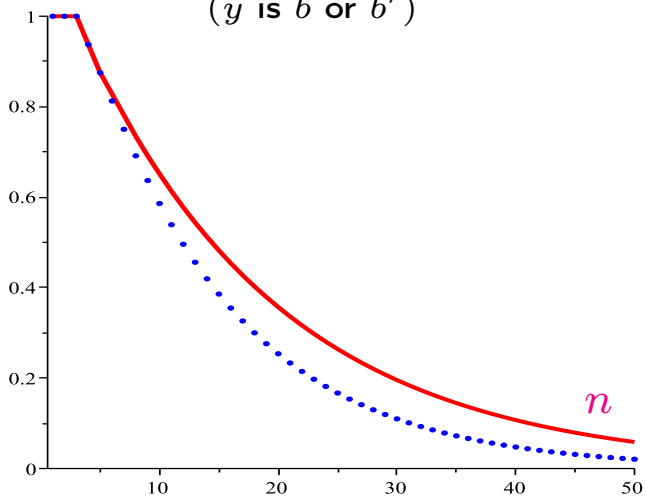
An unexpected behaviour

$\eta_n = \mathbf{E}(H_n^{(\mathtt{A}\to\mathtt{C})}) + \mathbf{E}(H_n^{(\mathtt{C}\to\mathtt{A})})$



$\widehat{f}_n^{(y)} = \mathbf{P}(|S_n(0)|_y = 0)$

(y is b or b')



$b = \mathtt{ACAC} \qquad b' = \mathtt{AACC}$

$\nu(\mathtt{A}) = \nu(\mathtt{C}) = \dfrac{1}{2}$

$\mathbf{E}(H_n^{(\mathtt{A}\to\mathtt{C})}) + \mathbf{E}(H_n^{(\mathtt{C}\to\mathtt{A})}) = \left.\dfrac{\partial F_b(z,t)}{\partial t}\right|_{t=1}$

$\pi_{\mathtt{A}\to\mathtt{C}} = \pi_{\mathtt{C}\to\mathtt{A}}$

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$t = t_{\mathtt{A}\to\mathtt{C}} = t_{\mathtt{C}\to\mathtt{A}}$

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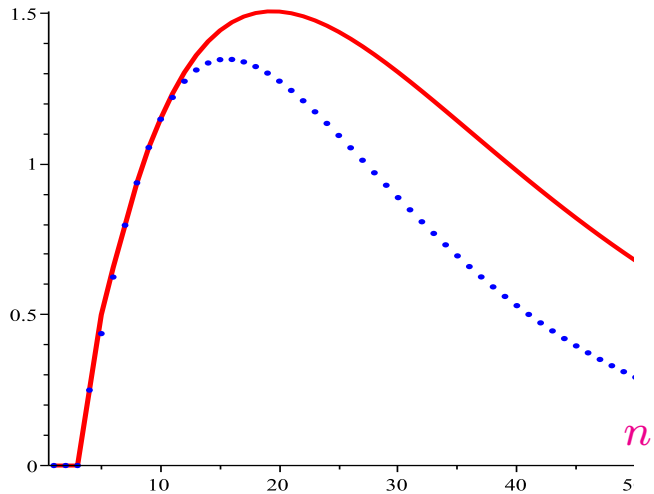

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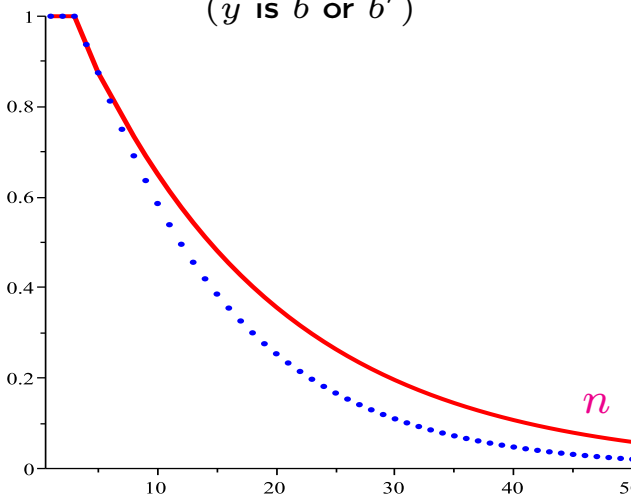
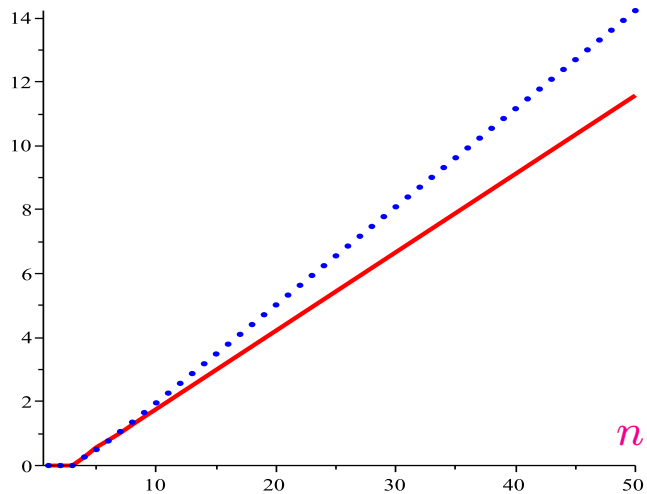


$\widetilde{\eta}_n = \eta_n \Big/ \widehat{f}_n^{(y)}$



$b = \mathtt{ACAC} \qquad b' = \mathtt{AACC}$

$\nu(\mathtt{A}) = \nu(\mathtt{C}) = \dfrac{1}{2}$

$\pi_{\mathtt{A}\to\mathtt{C}} = \pi_{\mathtt{C}\to\mathtt{A}}$

$\pi_{\mathtt{A}\to\mathtt{A}} = \pi_{\mathtt{C}\to\mathtt{C}}$

$$\mathbf{E}(H_n^{(\mathtt{A}\to\mathtt{C})}) + \mathbf{E}(H_n^{(\mathtt{C}\to\mathtt{A})}) = \left.\frac{\partial F_b(z,t)}{\partial t}\right|_{t=1}$$

$t = t_{\mathtt{A}\to\mathtt{C}} = t_{\mathtt{C}\to\mathtt{A}}$

A proof by singularity analysis

$$F_b(z,t) = \frac{P(z,t)}{Q(z,t)} \qquad P(z,t) \text{ and } Q(z,t) \text{ polynomials}$$

$$F_b(z,1) = \sum_{n\geq 0} \widehat{f}_n^{(b)} z^n = \frac{P(z,1)}{Q(z,1)}$$

$\widehat{f}_n^{(b)}$ probability that $S_n(0)$ has **no occurrence** of b.

$$E(z) = \sum_{n\geq 0} \mathbf{E}(H_n) z^n = \frac{P'_x(z,1)}{Q(z,1)} - \frac{P(z,1)Q'_x(z,1)}{Q^2(z,1)}$$

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The **dominant singularity** τ is the smallest positive solution of $Q(z,1) = 0$. Use suitable Cauchy integrals

$$\begin{cases} \widehat{f}_n^{(b)} = \psi \times \tau^{-(n-1)} \left(1 + \mathcal{O}\left(B^n\right)\right), \qquad (B<1) \\ \mathbf{E}(H_n) = [z^n]E(z) = \tau^{-n}(\phi_1 \times n + \phi_2) \times \left(1 + \mathcal{O}\left(B^n\right)\right) \end{cases}$$

$$\Longrightarrow \mathbf{E}(\widetilde{H}_n) = \frac{\mathbf{E}(H_n)}{\widehat{f}_n^{(b)}} = (c_1 \times n + c_2) \times \left(1 + \mathcal{O}\left(B^n\right)\right), \ (B<1).$$

General case

Compute $F_b(z, t_{\mathtt{A}\to\mathtt{C}}, t_{\mathtt{A}\to\mathtt{G}}, t_{\mathtt{A}\to\mathtt{T}}, t_{\mathtt{C}\to\mathtt{A}}, \ldots, t_{\mathtt{T}\to\mathtt{C}}, t_{\mathtt{T}\to\mathtt{G}})$

$$\widehat{f}_n^{(b)} = [z^n] F_b(z, 1, 1, \ldots, 1, 1)$$

$$\mathfrak{P}_n \approx [z^n] \sum_{\alpha\neq\beta\in\{\mathtt{A},\mathtt{C},\mathtt{G},\mathtt{T}\}} \left.\frac{\partial F_b(z, 1, \ldots, 1, \pi_{\alpha\to\beta} t_{\alpha\to\beta}, 1, \ldots)}{\partial t_{\alpha\to\beta}}\right|_{t_{\alpha\to\beta}=1} \Big/ \widehat{f}_n^{(b)}$$

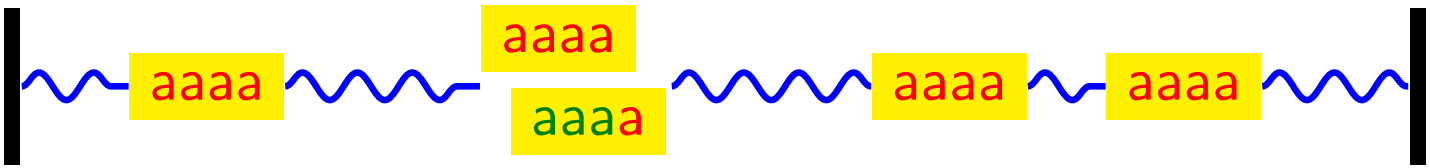
- The **dominant singularities** of **all the terms of the sum** are **equal** to the **dominant singularity** of $F_b(z, 1, 1, \ldots, 1, 1)$
- $\mathfrak{P}_n$ behaves **quasi-linearly**

Formal Languages Approach

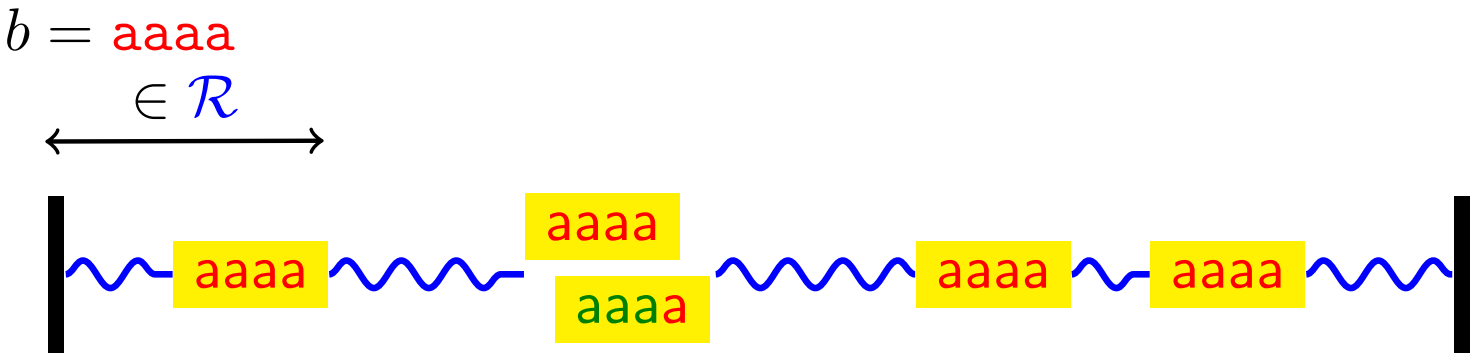
Assuming a single mutation

Guibas-Odlyzko decomposition - occurrences of a word u

$b =$ aaaa



Guibas-Odlyzko decomposition - occurrences of a word u



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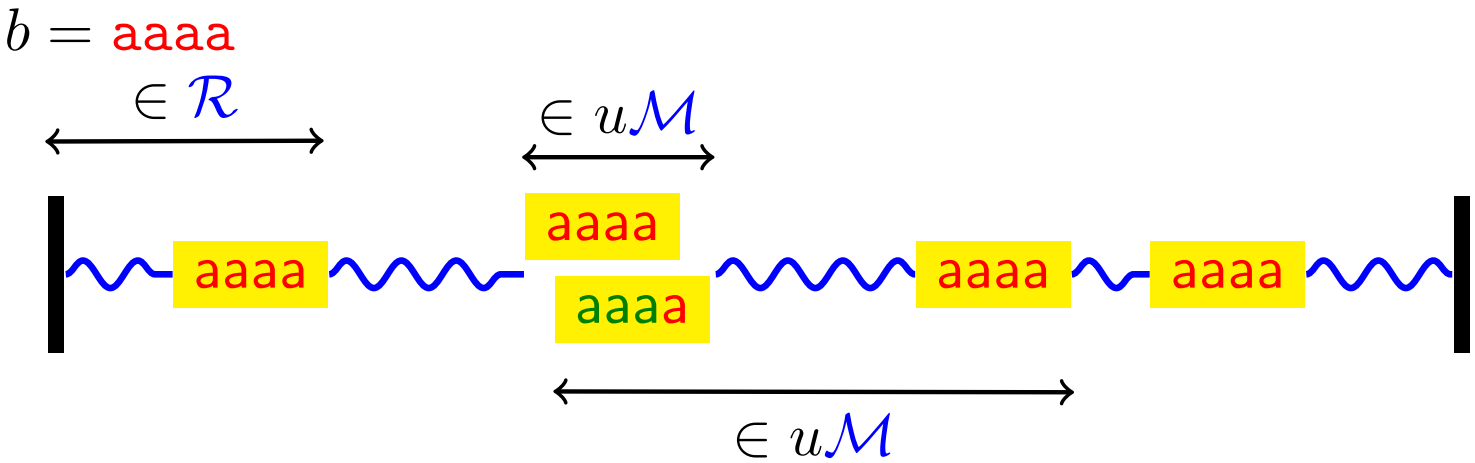
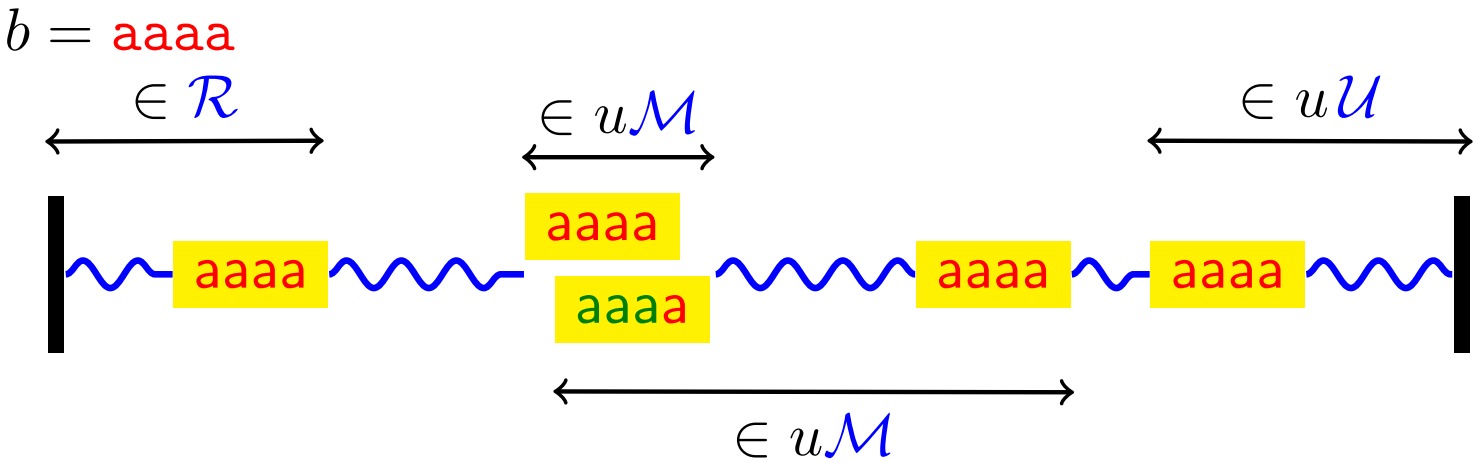
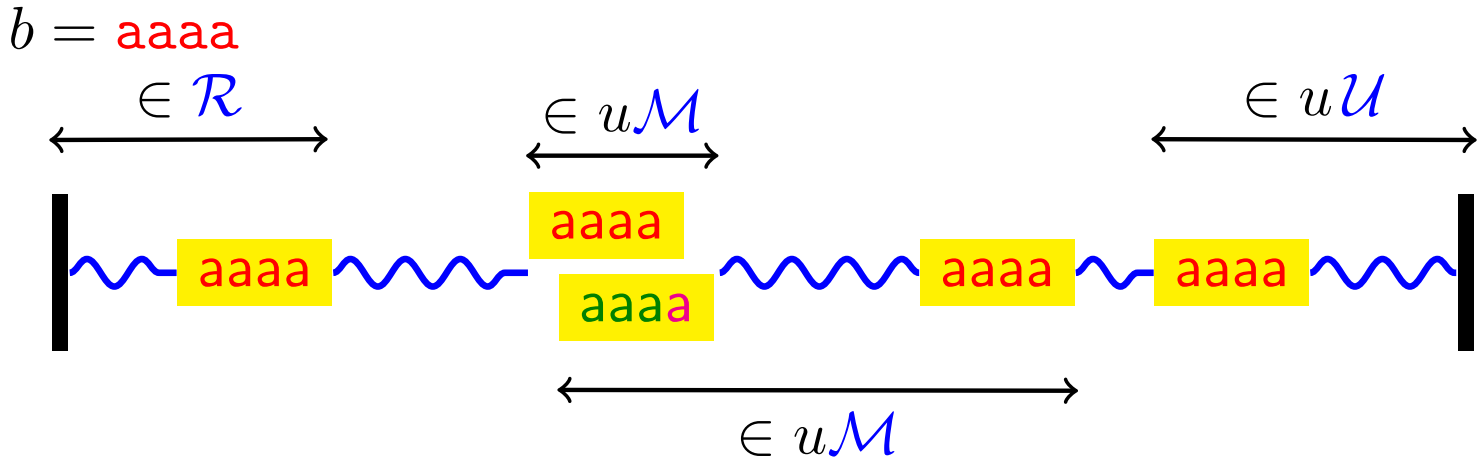


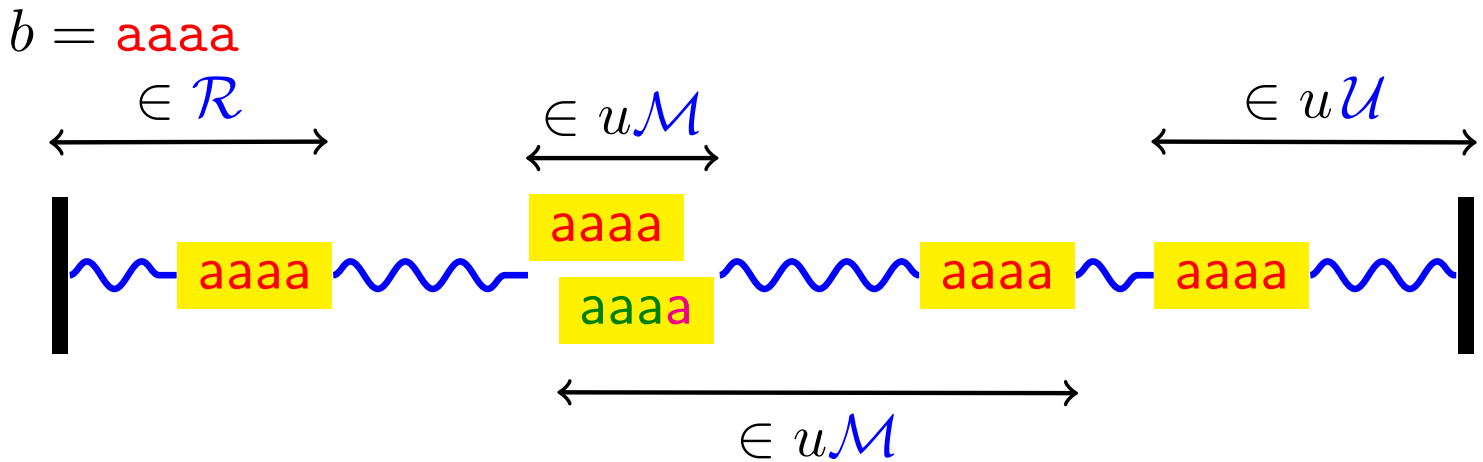
Guibas-Odlyzko decomposition - occurrences of a word u



Guibas-Odlyzko decomposition - occurrences of a word u

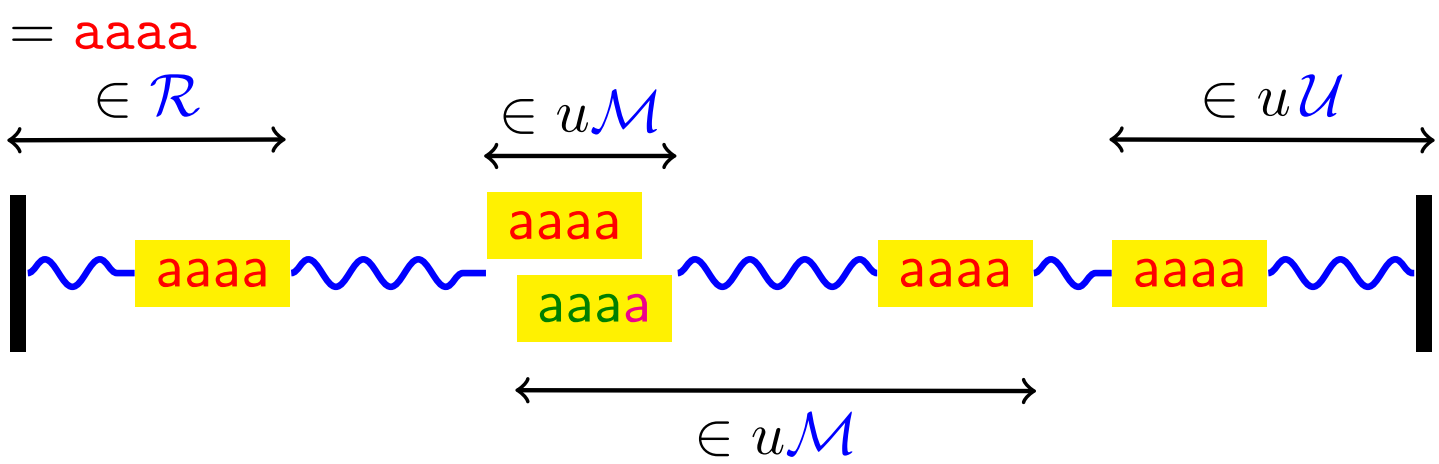


Guibas-Odlyzko decomposition - occurrences of a word u



- The "Right" language $\mathcal{R}$ associated to the word u is the set of words $\mathcal{R} = \{r \,|\, r = e \cdot u$ and there is no $v \in U$ such that $r = xvy$ with $|y| > 0\}$.
- The "Minimal" language $\mathcal{M}$ leading from a word u to a word u is the set of words $\mathcal{M} = \{m \,|\, u \cdot m = e \cdot u$ and there is no $v \in U$ such that $u \cdot m = xvy$ with $|x| > 0, |y| > 0\}$.
- The "Ultimate" language $\mathcal{U}$ of words following the last occurrence of the word u (such that this occurrence is the last occurrence of U in the text) is the set of words $\mathcal{U} = \{u \,|\,$ there is no $v \in U$ such that $u \cdot u = xvy$ with $|x| > 0\}$.
- The "Not" language $\mathcal{N}$ is the set of words with no occurrences of U, $\mathcal{N} = \{n \mid$ there is no $v \in U$ such that $n = xvy\}$.

Guibas-Odlyzko decomposition - occurrences of a word u



$$R(z) = \frac{\mathbf{P}(b)z^{|b|}}{D(z)}, \quad M(z) = 1 - \frac{1-z}{D(z)},$$
$$U(z) = \frac{1}{D(z)}, \quad Z(z) = \frac{C(z)}{D(z)},$$

with $D(z) = (1-z)C(z) + \mathbf{P}(b)z^{|b|}$,

$\mathcal{C}$ **autocorrelation set** of the word b

$\mathcal{C} = \{w; \quad b.w = u.b, \quad 0 \leq |w| < |b|\}$ $\quad C(z) = \sum_{w\in\mathcal{C}} \mathbf{P}(w)z^{|w|}$

One mutation $\rightsquigarrow$ One short clump in $S_n(1)$

- b **without autocorrelation**: **exactly one occurrence** of b in $S_n(1)$.
- b **with autocorrelation**: **exactly one short clump** $b.c$ with $c \in \mathcal{C}$ in $S_n(1)$.
- the **positions of mutation** within a **short clump** are **constrained**

$$\mathtt{X} \neq \mathtt{A} \quad b = \mathtt{AAAAA} \qquad \begin{matrix} 12345678 \\ \mathtt{XXXAAAAAAAAXXX} \end{matrix}$$

exactly one mutation occurred at **position** 4 or 5

The right generating function $F(z)$

- We need **avoiding** b outside of the short clump in $S_n(1)$
  $b.c$ **short clump** with $c \in \mathcal{C}$ $\quad \rightsquigarrow \quad$ **G.F.** $G_c(z)$

- $G_c(z) = R(z) \times \mathbf{P}(c) z^{|c|} \times U(z) = \dfrac{\mathbf{P}(b.c) z^{|b.c|}}{D^2(z)}$

- $N(z) = \dfrac{C(z)}{D(z)}$ $\qquad$ (**zero occurrence** of b in $S_n(0)$)

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- $D(z) = (1-z)C(z) + \mathbf{P}(b) z^{|b|}$

- $G_c(z)$ and $N(z)$ have the **same dominant singularity** ω

The right generating function $F(z)$

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- $G_c(z) = R(z) \times \mathbf{P}(c)z^{|c|} \times U(z) = \dfrac{\mathbf{P}(b.c)z^{|b.c|}}{D^2(z)}$
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- $D(z) = (1-z)C(z) + \mathbf{P}(b)z^{|b|}$
- $G_c(z)$ and $N(z)$ have the **same dominant singularity** ω
- $F(z) = \displaystyle\sum_{c \in \mathcal{C}} \frac{\mathbf{P}(b.c)z^{|b.c|}}{D^2(z)}$

Asymptotics

$\mathfrak{q}_n$ **approximation** of $\mathfrak{p}_n$ ω dominant singularity of $D(z)$

$$\mathfrak{q}_n = \frac{\mathbf{P}(b)}{C(\omega)D'(\omega)} \times \sum_{c \in \mathcal{C}} (|b| - |c|)\mathbf{P}(c)\omega^{|b.c|} \times \left((n - |b.c| + 1)\omega^{-1} + \frac{D''(\omega)}{D'(\omega)} \right) + o(\mathbf{P}(b)).$$

An even more approximated result

$$D(z) = (1-z)C(z) + \mathbf{P}(b)z^{|b|}$$

by bootstrapping $\omega \approx 1 + \dfrac{\mathbf{P}(b)}{C(1) + |b|\mathbf{P}(b)} \approx 1$

Using $\omega \approx 1$ gives

$$\mathfrak{q}_n^{(\text{approx})} = \frac{\mathbf{P}(b)}{C^2(1)} \times \sum_{c \in \mathcal{C}} (|b| - |c|)\mathbf{P}(c)(n - |b.c| + 1)$$

What about the approximations?

- The **distribution of letters** ν' on $S_n(1)$ is different of **the distribution** ν on $S_n(0)$
- There could have occurred **several mutations** **within occurrences** of b in $S_n(1)$
- It could have occurred **parasites mutations** outside of the occurrences of b in $S_n(1)$.

Distribution of letters in $S_n(1)$

$$\nu'(\alpha) = \nu(\alpha) \times p_{\alpha\to\alpha} + \sum_{\beta\neq\alpha} \nu(\beta) \times p_{\beta\to\alpha}$$

for small ϵ_α, we have $\nu'(\alpha) = \nu(\alpha) \times (1 + \epsilon_\alpha)$.

$$\eta = \max_{\alpha\in\mathcal{A}} \left| 1 - \frac{1}{1-\epsilon_\alpha} \right|$$

for any language $\mathcal{L} \in \mathcal{A}^n$,

$$(1-\eta)^n \sum_{w\in\mathcal{L}} \Pr_{(\nu)}(w) \leq \sum_{w\in\mathcal{L}} \Pr_{(\nu')}(w) \leq (1+\eta)^n \sum_{w\in\mathcal{L}} \Pr_{(\nu)}(w).$$

$$n \times \eta = o(1) \Longrightarrow \sum_{w\in\mathcal{L}} \Pr_{(\nu')}(w) = \sum_{w\in\mathcal{L}} \Pr_{(\nu)}(w) \times \big(1 + \mathcal{O}(n\eta)\big)$$

Several mutations within occurrences of b in $S_n(1)$

We can have **several short clumps**

1. Compute the generating function $I(z)$ of sequences with isolated occurrences of b
2. Starting from these isolated occurrences, extend the short clumps

(Bassino-Clément-Fayolle-P.N. 2008)

$b = aaaaa \qquad \mathcal{C} - \{\epsilon\} = \{a, aa, aaa, aaaa\}$

Prefix code $\mathcal{K} = \mathcal{C}_\circ - \mathcal{C}_\circ \mathcal{A}^+ \qquad \mathcal{C}_\circ = \mathcal{C} \setminus \epsilon \qquad \mathcal{K} = \{a\}$

$\mathcal{M} = \{a, b(b + ab + aab + aaab + aaaab)^\star aaaaa\}$

Properties

- $\mathcal{K} \subset \mathcal{M}$
- $\mathcal{M} - \mathcal{K} = \mathcal{L}b$

G.F. $I(z)$ of sequences with isolated occurrences of b

$$\mathcal{I} = \mathcal{R}.(\mathcal{M} - \mathcal{K})^{\star}.\mathcal{U}$$

$K(z) = \sum_{w \in \mathcal{K}} \mathbf{P}(w) z^{|w|}$ is a **polynomial**

$$\mathcal{M}(z) - K(z) = 1 - \frac{1-z}{D(z)} = \frac{p(z)\mathbf{P}(b)z^{|b|}}{D(z)}$$ with $p(z)$ polynomial.

$$I(z) = \frac{x\mathbf{P}(b)z^{|b|}}{D^2(z) \times \left(1 - \frac{xp(z)\mathbf{P}(b)z^{|b|}}{D(z)}\right)}$$

contribution γ_r of r clumps

$$\frac{\gamma_r}{\omega^n} = \frac{1}{\omega^n}[z^n] \frac{r!\left(\mathbf{P}(b)z^{|b|}\right)^r p^{r-1}(z)}{\left((1-z)C(z) + \mathbf{P}(b)z^{|b|}\right)^{r+1}} = \Theta(n^r)$$

Parasite mutations

$$\mathbf{P}(S_n(1) \textbf{after a parasite mutation })$$

$$\leq \mathbf{P}(S_n(1) \textbf{before the mutation }) \times \psi$$

where $\psi = \dfrac{\max_{\alpha,\beta\in\mathcal{A};\alpha\neq\beta} p_{\alpha\to\beta}}{\min_{\alpha\in\mathcal{A}} p_{\alpha\to\alpha}}$.

Theorem[P.N. 2013]. The conditioned probability $\mathfrak{p}_n$ that a random sequence of length n that does not contain a k-mer b at time 0 evolves at time 1 to a random sequence that contains this k-mer verifies

$$\mathfrak{p}_n = \mathfrak{q}_n \times (1 + \mathcal{O}(n\psi)) + \mathcal{O}(n^2\psi^2)$$

where

$$\begin{aligned}\mathfrak{q}_n = & \frac{\mathbf{P}(b)}{C(\omega)D'(\omega)} \\ & \times \sum_{c \in \mathcal{C}} (|b| - |c|)\mathbf{P}(c)\omega^{|b.c|} \\ & \times \left((n - |b.c| + 1)\omega^{-1} + \frac{D''(\omega)}{D'(\omega)} \right) + o(\mathbf{P}(b)).\end{aligned}$$

$$\psi = \frac{\max_{\alpha,\beta \in \mathcal{A}; \alpha \neq \beta} p_{\alpha \to \beta}}{\min_{\alpha \in \mathcal{A}} p_{\alpha \to \alpha}}$$

Numerical validation

$\mathcal{A} = \{\mathtt{A}, \mathtt{C}, \mathtt{G}, \mathtt{T}\}$ - uniform Bernoulli model for $S(0)$.

	$b = \mathtt{AAAAA}$ and for $\alpha \neq \beta$, $p_{\alpha\to\beta} = 10^{-8}$			
Length n	$\mathfrak{p}_n \times 10^6$	$\mathfrak{h}_n \times 10^6$	$\mathfrak{q}_n \times 10^6$	$\mathfrak{q}_n^{(\mathrm{approx})} \times 10^6$
10000	1.03335528	1.03335588	1.03335587	1.02703244
100000	10.3368481	10.3369021	10.3369021	10.2742439
10000000	1033.19278	1033.72699	1033.72698	1027.46750

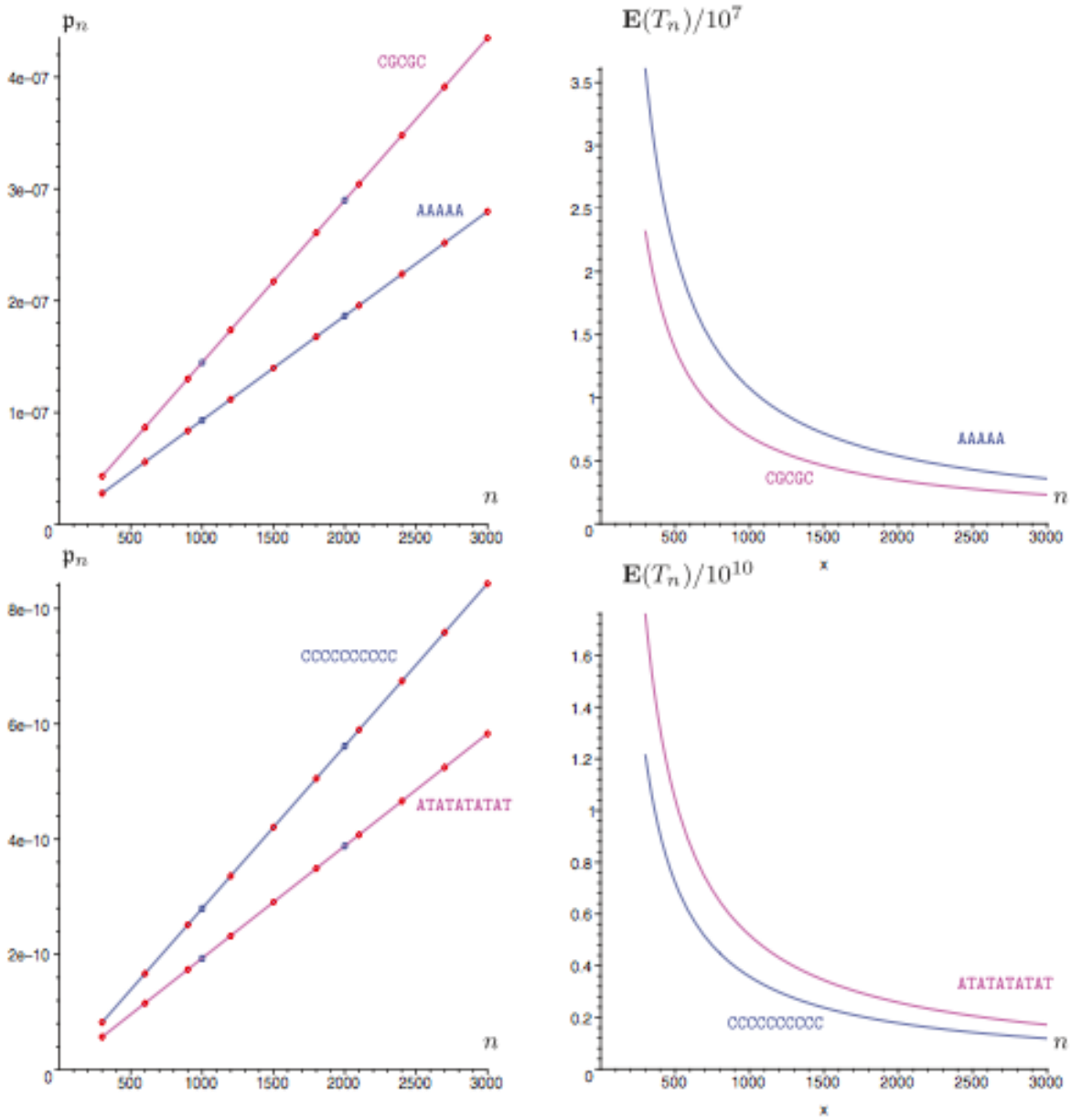

FIG. 5. Plots of the probability p_n **(left)** and of the expected waiting time $E(T_n)$ **(right)**. **(Top)** b = AAAAA (blue) and b' = CGCGC (magenta). **(Botton)** b = CCCCCC CCCC (blue) and b' = ATATATA TAT (magenta). In the linear plots of the probability, the anchors values for $n = 1000$ and $n = 2000$ (computed by automata) are represented by boxes; the straight lines are the straight lines going through the corresponding points and the circles are test values also computed by automata. The fit is perfect as expected from singularity analysis.

(from Behrens-Nicaud-P.N., JCB 19,5, 2012)