Circulation theory of enzyme kinetics

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We consider the following m-step($n \geq 2$) enzyme kinetics model:

$$E + S \rightleftharpoons ES \rightleftharpoons EP_1 \rightleftharpoons EP_2 \rightleftharpoons \cdots EP_{m-2} \rightleftharpoons E + P \tag{1}$$

where E is an enzyme turning the substrate S into the product P. From the perspective of a single enzyme molecule, this enzyme kinetics can be modeled as n-step Markov chain $(\xi_l)_{l \geq 0}$, with finite state space S defined on some space $(\Omega, \mathcal{F}, P)$. When $n = 2$, this Markov chain only have two state E and ES, we say that the state space $S = \{1, 2\}$.

Definition 0.1. Let $\mathbb{Z}$ be the set of integers, and a periodic function f which maps $\mathbb{Z}$ to S is called circuit function. If s is the smallest positive integer which satisfied $f(n + s) = f(n)$ for $\forall n \in \mathbb{Z}$, then we called it the period of f.

Definition 0.2. Two circuit functions f and g in S are called equivalent if there exists some $m \in \mathbb{Z}$ such that $g(n) = f(n + m)$ for $\forall n \in \mathbb{Z}$.

Definition 0.3. For a circuit function f in S with period s that satisfies $f(1) = i_1$, $f(2) = i_2$, $f(3) = i_3$. The equivalence class that f belongs is a cycle $c = (i_1, i_2, \ldots i_s)$

According to above definitions, $c_1 = (1, 2, 3), c_2 = (3, 1, 2)$ and $c_3 = (2, 3, 1)$ represent the same cycle. So a cycle is also a equivalence class on the space of all circuit functions under the equivalence relation.

For presentation purposes, if the order sequence $i_1, i_2, \ldots, i_s$ occurs in the cycle c continuously, we denote that $[i_1, i_2, \ldots, i_s] \in c$. Specially, if $[i_1] \in c$, the point i_1 occurrs in c, and $[i_1, i_2] \in c$ denotes the edge $i_1 i_2$ exists in the cycle c. For the cycle $c_1 = (1, 2)$, we use k_{12} to denote the number of cycle c_1.

Definition 0.4. Let $\mathcal{C}_n(\omega)$ be the class of cycles occurring along the sample path $(\xi_l)_{l \geq 0}$ until time n. Then we use $\mathcal{C}_\infty$ to represent the limit of $\mathcal{C}_n$ as $n \to \infty$. This convergence has been proofed in [].

Definition 0.5. Let $k_{c,n}$ denote the number of time that cycle c is formed by a Markov chain up to time n. Then the sample circulation J_n^c along cycle c by time t is defined as

$$J_n^c = \frac{1}{n} k_{c,n} \quad \forall c \in \mathcal{C}_\infty$$

and the circulation w^c along cycle c is a nonnegative real number defined as the following almost sure limit:

$$w_c = \lim_{n \to \infty} J_n^c \quad \forall c \in \mathcal{C}_\infty, \quad a.s.$$

which represents the number of times that cycle c ic formed per unit time. Let $J_n = (J_n^c)_{c \in C_\infty}$ and $w = (w_c)_{c \in C_\infty}$.

For the enzyme kinetics model, if the state space $S = \{1, 2, \ldots, m\}$, then C_∞ has $2m + 2$ cycles, including n 1-state cycles, n two-state cycles and two n-state cycles

Let $|c|$ denotes the length of cycle c, and $E = \{\mu = (\mu_c)_{c \in C_\infty} \in [0,1]^r : \sum_{c \in C_\infty} |c|\mu_c = 1\}$, then the circulation distribution $w = (w_c)_{c \in C_\infty} \in E$.
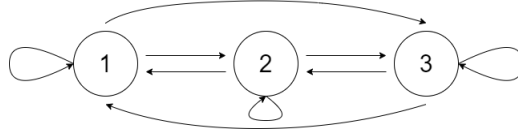
Definition 0.6. We say that J_n^c satisfies a large deviation principle with rate n and good rate function $I :$ $E \to [0, \infty]$ if:

$$\lim_{n \to \infty} \frac{1}{n} \log \mathbb{P}(J_n^c = \nu_c, c \in C_\infty) = -I(\nu), \quad \forall \nu \tag{2}$$

where $\sum_{c \in C_\infty} |c|\nu_c = 1$, and $\nu = (\nu_c)_{c \in C_\infty} \in E$.

1 Large deviation of circulation for finite Markov chains

1.1 Large deviation of circulation for three state Markov chains

Figure 1: 3-state transition diagram

Theorem 1.1. *For the three-state Markov chains, let $S = \{1, 2, 3\}$, J_n satisfies a large deviation principle, and its rate function is*

$$I_3^c(\nu) = \sum_{c \in C_\infty} \nu_c \log \frac{\nu_c}{w_c} + \sum_{i \in S} (\nu^i - \nu_i) \log \frac{\nu^i - \nu_i}{w^i - w_i} \tag{3}$$

$$- (\tilde{\nu} - \sum_{i \in S} \nu_i) \log(\frac{\tilde{\nu} - \sum_{i \in S} \nu_i}{\tilde{w} - \sum_{i \in I} w_i}) \tag{4}$$

$$- \sum_{i \in S} \nu^i \log(\frac{\nu^i}{w^i}) \tag{5}$$

where $S = \{1, 2, 3\}$ is the state space for Markov chains

$$C_\infty^3 = \{(1), (2), (3), (1,2), (2,3), (1,3), (1,2,3), (1,3,2)\}$$

is the class of all cycles occurring. ν_c is the frequence of cycle c occurring, w_c is the cycle skipping rate on c.

Let $\nu^i = \sum_{c \supseteq (i)} \nu_c$, such as $\nu^1 = \nu_1 + \nu_{12} + \nu_{13} + \nu_{123} + \nu_{132}$. Let $\tilde{\nu} = \nu_1 + \nu_2 + \nu_3 + \nu_{12} + \nu_{13} + \nu_{23} + \nu_{123} + \nu_{132}$ represent the sum of all the elements of ν. And w^i, w_i is similarly defined for w.

Proof. For the n-step path, after counting all the cycles, it maybe remain some points which haven't form cycles, we call this chain the derived chains. Refer to the Appendix, $\mathcal{E}(G^3(k))$ represents the amount of path with k cycle occuring, and $\Pi_{i,j \in S} p_{ij}^{\sum_{c \ni [i,j]} k_c}$ is the probability of the part formed all cycles. Obviously, the length of the derived chains is no more than 2 (the amount of states is three), then $\min_{\{i,j\}} p_{ij}^2$, $\max_{\{i,j\}} p_{ij}^2$ are the lower and upper bound respectively. So

$$\mathbb{P}(J_n^c = \frac{k_c}{n}, c \in \mathcal{C}_\infty) \geq \mathcal{E}(G^3(k)) \Pi_{i,j \in S} p_{ij}^{\sum_{c \ni [i,j]} k_c} \min_{\{i,j\}} p_{ij}^2$$

The length of the derived chains is no more than 2. And the steps in the derived chains is included in the n steps, so

$$\mathbb{P}(J_n^c = \frac{k_c}{n}, c \in \mathcal{C}_\infty) \leq \binom{n}{2} \mathcal{E}(G^3(k)) \Pi_{i,j \in S} p_{ij}^{\sum_{c \ni [i,j]} k_c} \max_{\{i,j\}} p_{ij}^2$$

We know

$$\frac{1}{n} \log \binom{n}{2} \leq \frac{1}{n} \log \frac{n^2}{(2)^2} = O(\frac{\log n}{n})$$

so

$$\mathbb{P}(J_n^c = \frac{k_c}{n}, c \in \mathcal{C}_\infty) = \exp(O(\log n)) \mathcal{E}(G(k)) \Pi_{i,j \in S} p_{ij}^{\sum_{c \ni [i,j]} k_c}$$

We could neglect the influence of the derived chains.

Let

$$K_n = \left\{ k = (k_c)_{c \in \mathcal{C}_\infty} : \sum_{c \in \mathcal{C}_\infty} k_c |c| \leq n \right\},$$

and this set includes all possible situations of each cycles occuring amount. It can easily observe that the size of this set $|K_n| \leq n^3$, $\frac{1}{n} K_n \in E$.

For $\forall k \in K_n$, let $\mu_n(k) = \frac{1}{n} k \in E$. Let us put

$$Q_n(a) = \max_{k \in K_n : \mu_n(k) \in B_a(\nu)} \mathcal{E}(G(k)) \Pi_{i,j \in S} p_{ij}^{\sum_{c \ni [i,j]} k_c}$$

where $B_a(\nu)$ is the open neighborhood of ν with the total vaiation distance $d(\alpha, \beta) = \frac{1}{2} \sum_{s=1}^r |\alpha_s - \beta_s|$ and radius a. For enough large n, clearly

$$Q_n(a) \leq \mathbb{P}(J_n \in B_a(\nu), c \in \mathcal{C}_\infty) \leq |K_n| Q_n(a).$$

Stirling's formula gives $\frac{1}{n} \log \binom{k}{k'} = h(\frac{k}{n}) - h(\frac{k'}{n}) - h(\frac{k-k'}{n}) + O(\frac{\log n}{n})$ where $h(x) = x \log(x)$. We find that

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$$\frac{1}{n}\log\mathcal{E}(G^3(k))\Pi_{i,j\in S}p_{ij}^{\sum_{c\ni[i,j]}k_c}$$

$$= h(\nu_{12}+\nu_{13}+\nu_{23}+\nu_{123}+\nu_{132}) + h(\nu_1+\nu_{12}+\nu_{13}+\nu_{123}+\nu_{132})$$

$$+ h(\nu_2+\nu_{12}+\nu_{123}+\nu_{132}+\nu_{23}) + h(\nu_3+\nu_{13}+\nu_{123}+\nu_{132}+\nu_{23})$$

$$- [h(\nu_1)+h(\nu_2)+h(\nu_3)+h(\nu_{12})+h(\nu_{13})+h(\nu_{23})+h(\nu_{123})+h(\nu_{132})]$$

$$- \Big(h(\nu_{12}+\nu_{13}+\nu_{123}+\nu_{132}) + h(\nu_{12}+\nu_{123}+\nu_{132}+\nu_{23})$$

$$+ h(\nu_{13}+\nu_{123}+\nu_{132}+\nu_{23})\Big) + \sum_{i,j\in S,p_{ij}\neq 0}\Big(\sum_{c\ni[i,j]}\nu_c\Big)\log p_{ij} + O(\frac{\log n}{n})$$

Merging all the same items, then

$$\frac{1}{n}\log\mathcal{E}(G^3(k))\Pi_{i,j\in S}p_{ij}^{\sum_{c\ni[i,j]}k_c}$$

$$= -\Big(\nu_1\log(\frac{1}{p_1}\frac{\nu_1}{\nu^1}) + \nu_2\log(\frac{1}{p_2}\frac{\nu_2}{\nu^2}) + \nu_3\log(\frac{1}{p_3}\frac{\nu_3}{\nu^3})$$

$$+ \nu_{12}\log(\frac{1}{p_{12}p_{21}}\frac{\nu_{12}}{\nu_{12}+\nu_{23}+\nu_{13}+\nu_{123}+\nu_{132}}\frac{\nu^1-\nu_1}{\nu^1}\frac{\nu^2-\nu_2}{\nu^2})$$

$$+ \nu_{13}\log(\frac{1}{p_{13}p_{31}}\frac{\nu_{13}}{\nu_{12}+\nu_{23}+\nu_{13}+\nu_{123}+\nu_{132}}\frac{\nu^1-\nu_1}{\nu^1}\frac{\nu^3-\nu_3}{\nu^3})$$

$$+ \nu_{23}\log(\frac{1}{p_{23}p_{32}}\frac{\nu_{23}}{\nu_{12}+\nu_{23}+\nu_{13}+\nu_{123}+\nu_{132}}\frac{\nu^3-\nu_3}{\nu^3}\frac{\nu^2-\nu_2}{\nu^2})$$

$$+ \nu_{123}\log(\frac{1}{p_{12}p_{23}p_{31}}\frac{\nu_{123}}{\nu_{12}+\nu_{23}+\nu_{13}+\nu_{123}+\nu_{132}}\frac{\nu^1-\nu_1}{\nu^1}\frac{\nu^2-\nu_2}{\nu^2}\frac{\nu^3-\nu_3}{\nu^3})$$

$$+ \nu_{132}\log(\frac{1}{p_{13}p_{32}p_{21}}\frac{\nu_{132}}{\nu_{12}+\nu_{23}+\nu_{13}+\nu_{123}+\nu_{132}}\frac{\nu^1-\nu_1}{\nu^1}\frac{\nu^2-\nu_2}{\nu^2}\frac{\nu^3-\nu_3}{\nu^3})\Big)$$

Refer to [Jiang], the calculation formula for circulation is:

$$w_c = p_{i_1i_2}p_{i_2i_3}\cdots p_{i_{m-1}i_1}\frac{D(\{i_1,i_2,\cdots i_s\}^c)}{\sum_{j\in S}D(\{j\}^c)}$$

With this formula, we know

$$w_{12}+w_{13}+w_{23}+w_{123}+w_{132} = \frac{(1-p_{11})(1-p_{22})(1-p_{33})}{\sum_{i\in I}D(\{i\}^c)}$$

$$= \frac{\Pi_{i,j}D(\{i,j\}^c)}{\sum_{i\in I}D(\{i\}^c)}$$

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Since the property of circulation, $p_{ij} = \frac{\sum_{c \ni [i,j]} w_c}{\sum_{c \ni (i)} w_c}$, So

$$\frac{1}{n} \log \mathcal{E}(G^3(k)) \Pi_{i,j} p_{ij}^{\sum_{c \ni [i,j]} k_c}$$

$$= \sum_{c \in \mathcal{C}_\infty} \nu_c \log \frac{\nu_c}{w_c} + \sum_{i \in S} (\nu^i - \nu_i) \log \frac{\nu^i - \nu_i}{w^i - w_i}$$

$$- (\tilde{\nu} - \sum_{i \in S} \nu_i) \log(\frac{\tilde{\nu} - \sum_{i \in S} \nu_i}{\tilde{w} - \sum_{i \in S} w_i})$$

$$- \sum_{i \in S} \nu^i \log(\frac{\nu^i}{w^i})$$

Now we find that

$$\frac{1}{n} \mathbb{P}(J_n \in B_a(\nu)) = O(\frac{\log n}{n}) + \frac{1}{n} \log Q_n(a)$$

$$= O(\frac{\log n}{n}) - \min_{k \in K_n : \mu_n(k) \in B_a(\nu)} I_3^c(\mu_n(k))$$

And we know: (i) $\bigcup_{n \in \mathbb{N}} \{\mu_n(k) : k \in K_n\} \bigcap E$ is dense in E. (ii) $\mu \to I_3^c(\mu)$ is continuous on E. It is analogous to the proof of Sanov's Theorem, then

$$\lim_{n \to \infty} \frac{1}{n} \mathbb{P}(J_n \in B_a(\nu)) = - \inf_{k \in K_n : \mu_n(k) \in B_a(\nu)} I_3^c(\nu)$$

If the size of neighborhood $B_a(\nu)$ is enough small,

$$\lim_{n \to \infty} \frac{1}{n} \mathbb{P}(J_n = \nu) = -I_3^c(\nu)$$

$\square$

Corollary. *For the two-state Markov chains, we have:*

$$I_2^c(\nu) = \nu_1 \log(\frac{\nu_1}{\nu_1 + \nu_{12}} / \frac{w_1}{w_1 + w_{12}}) + \nu_2 \log(\frac{w_2}{w_1 + w_{12}}) + 2\nu_{12} \log(\frac{\nu_{12}}{\nu_1 + \nu_{12}} / \frac{w_{12}}{w_1 + w_{12}})$$

Corollary. *I_3^c is finite, continuous, positive and strictly convex*

Proof. Since $h(x) = x \log x$ is finite on the interval $[0,1]$, obviously, $I_3^c(\nu)$ is finite on E. Splitting item $\sum_{c \in \mathcal{C}_\infty} \nu_c \log \frac{\nu_c}{w_c}$, and employ Log sum inequality.

$$I_3^c(\nu) = \left(\sum_{i \in S} \nu_i \log \frac{\nu_i}{w_i} + \sum_{i \in S} (\nu^i - \nu_i) \log \frac{\nu^i - \nu_i}{w^i - w_i} - \sum_{i \in S} \nu^i \log \frac{\nu^i}{w^i} \right)$$

$$+ \left(\sum_{c \in \mathcal{C}_\infty, c \neq \nu_i} \nu_c \log \frac{\nu_c}{w_c} - (\tilde{\nu} - \sum_{i \in S} \nu_i) \log(\frac{\tilde{\nu} - \sum_{i \in S} \nu_i}{\tilde{w} - \sum_{i \in S} w_i}) \right)$$

$$= \left(\sum_{i \in S} \nu_i \log \frac{\nu_i}{\nu^i} / \frac{w_i}{w^i} + \sum_{i \in S} (\nu^i - \nu_i) \log(\frac{\nu^i - \nu_i}{\nu^i} / \frac{w^i - w_i}{w^i}) \right)$$

$$+ \left(\sum_{c \in \mathcal{C}_\infty, c \neq \nu_i} (\tilde{\nu} - \sum_{i \in S} \nu_i) \log(\frac{\nu_c}{\tilde{\nu} - \sum_{i \in S} \nu_i} / \frac{w_c}{\tilde{w} - \sum_{i \in S} w_i}) \right)$$

$$\geq 0$$

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The convex can be proofed with the same way by Log sum inequality. □

## 1.2 Large deviation of circulation for finite state Markov chains

Theorem 1.2. *For the m-state Markov chains, if the rate function exists, it is*

$$I_m^c(\nu) = [h(\nu_{12} + \nu_{1m} + \nu^+ + \nu^-) - h(\nu_{12}) - h(\nu_{1m}) + h(\nu^+) + h(\nu^-)] + \sum_{i \in S}[h(\nu^i) - h(\nu^i - \nu_i)]$$

$$+ \max_{\nu_{ij}^+ + \nu_{ij}^- = \nu_{ij}, i \neq 1, j \neq m} \left\{ [h(\nu_{12} + \nu_{23}^+ + \nu^+) - h(\nu_{23}^+) - h(\nu_{12} + \nu^+)] \right.$$

$$+ [h(\nu_{34}^+ + \nu_{23}^+ + \nu^+) - h(\mu_{34}^+) - h(\nu_{23}^+ + \nu^{)}] + \cdots +$$

$$+ [h(\nu_{m-1,m}^+ + \nu_{m-2,m-1}^+ + \nu^+) - h((\nu_{m-1,m}^+) - h(\nu_{m-2,m-1}^+ + \nu^+)]$$

$$+ [h(\nu_{1m} + \nu_{m-1,m}^- + \nu^-) - h(\nu_{m-1,m}^-) - h(\nu_{1m} + \nu^-)]$$

$$+ [h(\nu_{m-1,m}^- + \nu_{m-2,m-1}^- + \nu^-) - h(\nu_{m-2,m-1}^-) - h(\nu_{m-1,m}^- + \nu^-)]$$

$$+ \cdots + + h(\nu_{23}^- + \nu_{34}^- + \nu^-) - h(\nu_{23}^- - h(\nu_{34}^- + \nu^-)) \left. \right\} + \sum_{i,j} (\sum_{c \ni [i,j]} \nu_c) \log p_{ij}$$

Proof. If the rate function exists, we know:

$$I_m^c(\nu) = \frac{1}{n} \log \mathcal{E}(G^m(k)) \Pi_{i,j \in S} p_{ij}^{\sum_{c \ni [i,j]} k_c}.$$

The accumulation part in $\mathcal{E}(G^m(k))$ has no more than n^{m-1} items, and $\frac{1}{n} \log n^{m-1} = O(\frac{\log n}{n})$. The other technology for simplification has been mentioned in Theorem 1.1 many times. □
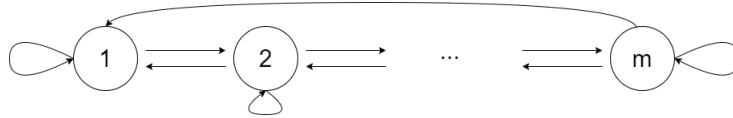
Figure 2: n-state transition diagram

Theorem 1.3. *For the m-state Markov chains, and the non-zero terms only have $\{p_{i,i+1}, i = 1, \ldots m - 1\} \bigcup \{p_{i,i-1}, i = 2, \ldots m-1\} \bigcup \{p_{m,1}\}$, $(w_c)_{c \in \mathcal{C}_\infty}$ satisfies a large deviation principle, and its rate function is*

$$I_{m'}^c(\nu) = \sum_{i \in S} \sum_{c \ni [i]} \nu_c \log \left(\frac{\nu_c}{\nu^i} / \frac{w_c}{w^i} \right)$$

Proof. The proof is similar in spirit to that of Theorem 1.1, the main difference lies in the simplification of rate function. Let

$$K_n = \left\{ k = (k_c)_{c \in \mathcal{C}_\infty} : \sum_{c \in \mathcal{C}_\infty} k_c |c| \leq n \right\},$$

and

$$Q_n(a) = \max_{k \in K_n : \mu_n(k) \in B_a(\nu)} \mathcal{E}(G^{m'}(k)) \Pi_{i,j \in S} p_{ij}^{\sum_{c \ni [i,j]} k_c}.$$

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We only need to simply the following formula.

$$\frac{1}{n}\log \mathcal{E}(G^{m'}(k))\Pi_{i,j\in S}p_{ij}^{\sum_{c\ni[i,j]}k_c}$$

$$= -\left(\sum_{i\in S}\nu_i\log(\frac{1}{p_i}\frac{\nu_i}{\nu^i}) + \nu_{12}\log\frac{1}{p_{12}p_{21}}\frac{\nu_{12}}{\nu_{12}+\nu_{23}+\nu_{12\ldots m}}\frac{\nu^1-\nu_1}{\nu^1}\frac{\nu^2-\nu_2}{\nu^2}\right.$$

$$+\nu_{m-1,m}\log\frac{1}{p_{m-1,m}p_{n,m-1}}\frac{\nu_{m-1,m}}{\nu_{m-1,m}+\nu_{m-2,m-1}+\nu_{12\ldots m}}\frac{\nu^{m-1}-\nu_{m-1}}{\nu^{m-1}}\frac{\nu^m-\nu_m}{\nu^m}$$

$$+\sum_{i=2}^{m-2}\nu_{i,i+1}\log(\frac{1}{p_{i,i+1}p_{i+1,i}}\frac{\nu_{i,i+1}(\nu_{i,i+1}+\nu_{1,2,\ldots m})}{(\nu_{i,i+1}+\nu_{i+1,i+2}+\nu_{1,2,\ldots m})(\nu_{i-1,i}+\nu_{i,i+1}+\nu_{1,2,\ldots m})}\frac{\nu^i-\nu_i}{\nu^i}\frac{\nu^{i+1}-\nu_{i+1}}{\nu^{i+1}})$$

$$\left.+\nu_{1,2,\ldots m}\log(\frac{1}{p_{12}p_{23}\cdots p_{m-1,s}p_{s,1}}\nu_{1,2,\ldots m}\frac{\Pi_{i=2}^{m-2}(\nu_{i,i+1}+\nu_{1,2,\ldots m})}{\Pi_{i=2}^{m-1}(\nu^i-\nu_i)}\Pi_{i=1}^{m}\frac{\nu^i-\nu_i}{\nu^i})\right)$$

$$= -\left(\sum_{i\in S}\nu_i\log(\frac{1}{p_i}\frac{\nu_i}{\nu^i}) + \nu_{1,2}\log(\frac{1}{p_{12}p_{21}}\frac{\nu_{12}(\nu^1-\nu_1)}{\nu^1\nu^2}) + \nu_{m-1,m}\log\frac{1}{p_{m-1,m}p_{n,m-1}}\frac{\nu_{m-1,m}(\nu^{m-1}-\nu_{m-1})}{\nu^{m-1}\nu^m}\right.$$

$$+\sum_{i=2}^{m-2}\nu_{i,i+1}\log(\frac{1}{p_{i,i+1}p_{i+1,i}}\frac{\nu_{i,i+1}(\nu_{i,i+1}+\nu_{1,2,\ldots m})}{\nu^i\nu^{i+1}})$$

$$\left.+\nu_{1,2,\ldots m}\log(\frac{1}{p_{12}p_{23}\cdots p_{m-1,m}p_{m,1}}\nu_{1,2,\ldots m}\frac{\Pi_{i=1}^{m-1}(\nu_{i,i+1}+\nu_{1,2,\ldots m})}{\Pi_{i=1}^{m}\nu^i})\right)$$

Because $p_{ij}=\frac{\sum_{c\ni[i,j]}w_c}{\sum_{c\ni(i)}w_c}$, and w substitute for p_{ij} in th formula above, the rate function $I_n^{c'}(\nu)$ would be obtained. The rest proof is same as Theorem 1.1. □

Corollary. $I_{n'}^{c}(\nu)$ *is finite, continuous, positive and strictly convex*

Proof. The finiteness and continuity is obvious, and we also can employ Log-sum inequality to proof its positivity convexity. □

2 Appendix

Consider the first n-step of the above Markov chains (ξ_l), we assume that $\xi_n = \xi_1$, and the number of cycle c occurring is k_c. If marking each occurence of state pair (s,t) in $\xi_1,\ldots,\xi_n$ by drawing an arrow from s to t, we can obtain an oriented graph $G^m(k)$. And we employ $\mathcal{E}(G^m(k))$ to denote the number of Euler circuits on $G^m(k)$, by the way, $\mathcal{E}_i(G^m(k))$ denotes the number of Euler circuits which start from states i, i.e. $\xi_1 = i$.

Theorem 2.1. *For the graph $G^m(k)$ induced by the Markov chains $(\xi_l)_{l\geq 0}$, if the size of state space is s,*

then we have the following formula:

$$\mathcal{E}_1(G^m(k)) = \binom{k_{12} + k_{1m} + k^+ + k^-}{k_{12}, k_{1m}, k^+, k^-}\binom{k_1 + k_{12} + k_{1m} + k^+ + k^-}{k_{12} + k_{1m} + k^+ + k^-}\left[\Pi_{i \in S, i \neq 1}\binom{\sum_{c \ni [i]} k_c - 1}{\sum_{c \ni [i]} k_c - k_i - 1}\right]$$

$$\left[\sum_{k_{23}^+ + k_{23}^- = k_{23}} \sum_{k_{34}^+ + k_{34}^- = k_{34}} \cdots \sum_{k_{m-1,m}^+ + k_{m-1,m}^- = k_{m-1,m}} \binom{k_{23}^+ + k_{12} + k^+ - 1}{k_{23}^+}\binom{k_{34}^+ + k_{23}^+ + k^+ - 1}{k_{34}^+}\right.$$

$$\cdots \binom{k_{m-1,m}^+ + k_{m-2,m-1}^+ + k^+ - 1}{k_{m-1,m}^+}\binom{k_{1,m} + k_{m-1,m}^- + k^- - 1}{k_{m-1,m}^-}\binom{k_{m-1,m}^- + k_{m-2,m-1}^- + k^- - 1}{k_{m-2,m-1}^-}$$

$$\left.\cdots \binom{k_{23}^- + k_{34}^- + k^- - 1}{k_{23}^-}\right]$$

where k^+ and k^- are the number of cycle $\{1, 2, \ldots, s\}$, $\{s, m-1, \ldots, 1\}$ respectively. And $k_{s,t}^+$ represents the number of cycles of which the state s occurring fistly among cycles $\{s, t\}$, so $k_{s,t}^-$ is number of remains.

Proof. We use following three steps to count all the Euler circuits. 1. This Markov chains starts from state 1, hence we pick the cycles which includes state 1, i.e. $\{1\}, \{1, 2\}, \{1, m\}, \{1, 2, \ldots, m\}, \{1, \ldots, m-1, m, 2\}$. And line them up, the number of permutations is:

$$\binom{k_1 + k_{12} + k_{1m} + k^+ + k^-}{k_1, k_{12}, k_{1m}, k^+, k^-}$$

2. Next we need to insert the other 2-state cycles into it based on above permutation. For the cycle $\{s-1, s\}$, $s \in \{3, 4, \ldots, m\}$, it firstly be inserted into the cycle $\{1, 2, \ldots, m\}$) and $\{s-2, s-1\}$ which start from state $\{s-2\}$ if $s \neq 3$. The cycle $\{s-1, s\}$ that has been inserted all states from state $s-1$, next we insert the remains that starts from state s, the optional cycles have $(1, s, m-1, \ldots, 2)$ and $(s, s+1)$ which start from state $\{s+1\}$ if $s \neq m$.

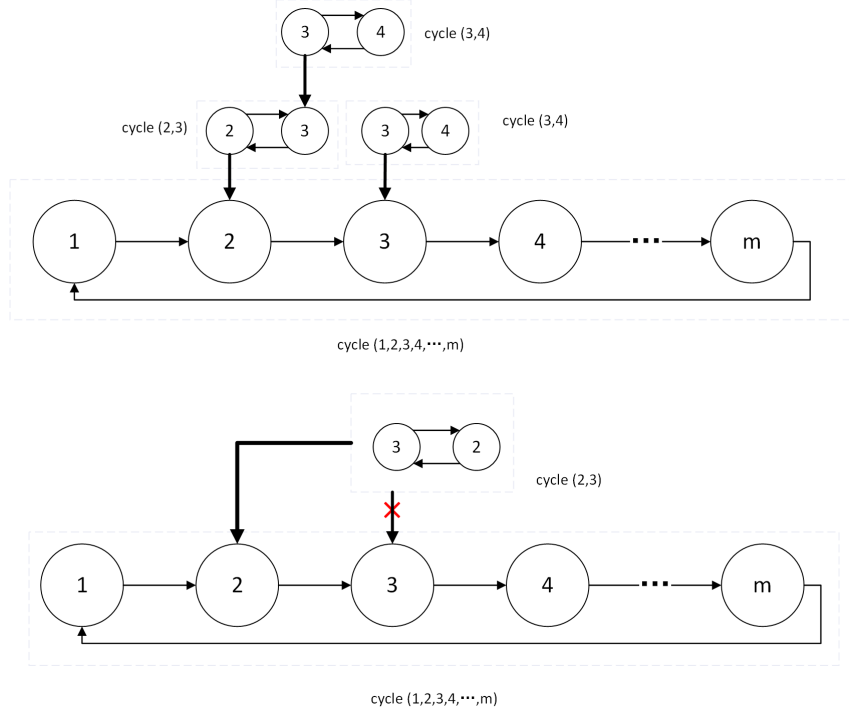If we change the order of inserting, the cycle would not occurr at the inserting point.

$$\sum_{k_{23}^+ + k_{23}^- = k_{23}} \sum_{k_{34}^+ + k_{34}^- = k_{34}} \cdots \sum_{k_{m-1,m}^+ + k_{m-1,m}^- = k_{m-1,m}} \binom{k_{23}^+ + k_{12} + k^+ - 1}{k_{23}^+}\binom{k_{34}^+ + k_{23}^+ + k^+ - 1}{k_{34}^+}$$

$$\cdots \binom{k_{m-1,m}^+ + k_{m-2,m-1}^+ + k^+ - 1}{k_{m-1,m}^+}\binom{k_{1,m} + k_{m-1,m}^- + k^- - 1}{k_{m-1,m}^-}\binom{k_{m-1,m}^- + k_{m-2,m-1}^- + k^- - 1}{k_{m-2,m-1}^-}$$

$$\cdots \binom{k_{23}^- + k_{34}^- + k^- - 1}{k_{23}^-}$$

3. Consider the one of the above permutation, we insert the other 1-state cycles into it, i.e. $(2), (3), \ldots, (s)$. The number of permutations is:

$$\Pi_{i \in S, i \neq 1}\binom{\sum_{c \ni [i]} k_c - 1}{\sum_{c \ni [i]} k_c - k_i - 1}$$

$\square$

Corollary. *If $p_{1m} = 0$, the number of Euler circuits is*

$$\mathcal{E}(G^{m'}(k)) = \exp(O\log n)\binom{k_{12} + k_{1,2...,m}}{k_{12}}\Pi_{i=2}^{m-1}\binom{k_{1,2...,m} + k_{i-1,i} + k_{i,i+1}}{k_{i,i+1}}\Pi_{i\in S}\binom{\sum_{i\ni c}k_c}{\sum_{i\ni c}k_c - k_i}$$

(6)

Proof. Because $p_{1m} = 0$, $k^- = 0$, we do not need to consider insert 2-state cycle into $(1, m)$ and $(1, m, m-1, \dots, 2)$. Compairing to Theorem 2.1, only the second step is different, it is:

$$\Pi_{i=2}^{m-1}\binom{k_{1,2...,m} + k_{i-1,i} + k_{i,i+1}}{k_{i,i+1}}$$

In addition, the path starting from other states which is not state 1 should be considered, so

$$\mathcal{E}(G^{m'}(k)) \leq n\binom{k_{12} + k_{1,2...,m}}{k_{12}}\Pi_{i=2}^{m-1}\binom{k_{1,2...,m} + k_{i-1,i} + k_{i,i+1}}{k_{i,i+1}}\Pi_{i\in S}\binom{\sum_{i\ni c}k_c}{\sum_{i\ni c}k_c - k_i}$$

We can get 6. ∎

Corollary. *Consider the graph $G(k)$ induced by the Markov chains $(\xi_l)_{l\geq 0}$. If $s = 2$, we have:*

$$\mathcal{E}(G^2(k)) = \exp(O\log n)\binom{k_1 + k_{12}}{k_1}\binom{k_2 + k_{12}}{k_2}$$

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If $s = 3$, we have:

$$\mathcal{E}(G^3(k)) = \exp(O(\log(n))) \binom{k_{12} + k_{13} + k_{123} + k_{132}}{k_{12}, \ k_{13}, \ k_{123}, \ k_{132}}$$

$$\binom{k_1 + k_{12} + k_{13} + k_{123} + k_{132}}{k_1} \binom{k_{12} + k_{13} + k_{123} + k_{132} + k_{23}}{k_{23}}$$

$$\binom{k_{12} + k_{123} + k_{132} + k_{23} + k_2}{k_2} \binom{k_{13} + k_{123} + k_{132} + k_{23} + k_3}{k_3}$$