Rare events-driven stability of stochastic chemical reaction systems

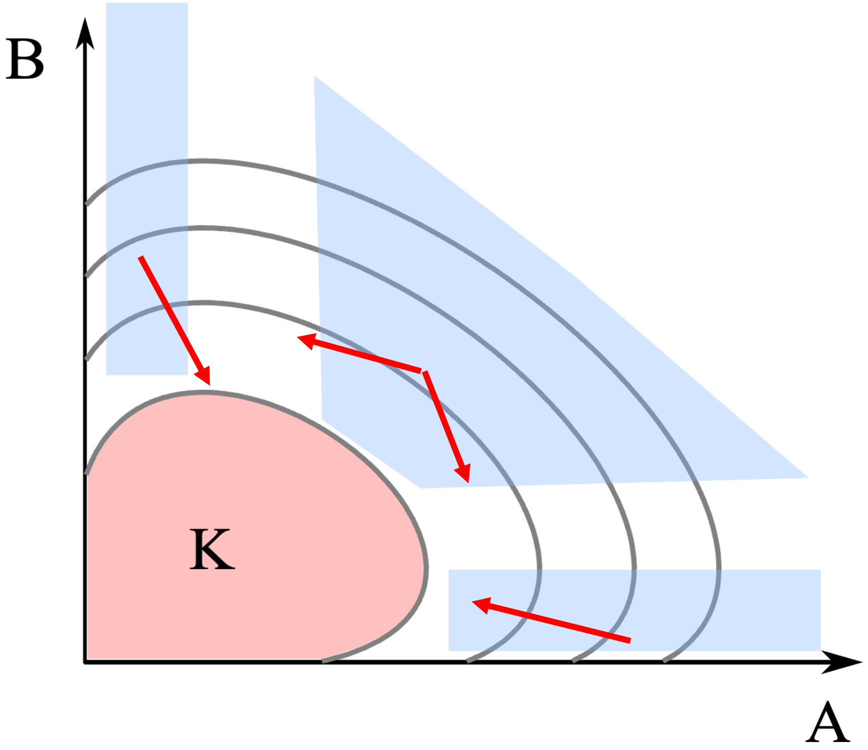
Jinsu Kim

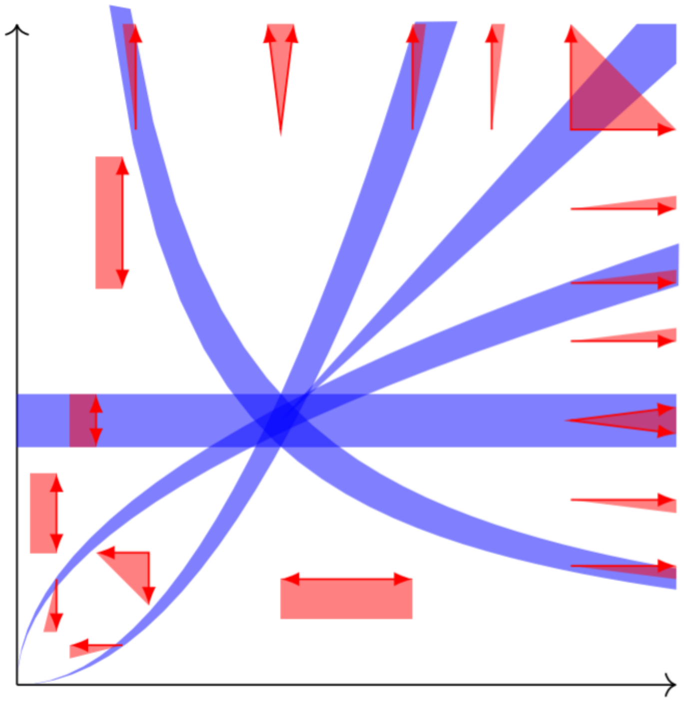
Department of Mathematics, POSTECH, Korea

December 17th, 2021

BK21 Four POSTECH Math Workshop

Local behavior vs non-local behavior for stability





- Anderson (2011)
- Anderson-K (2018)
- Anderson-Cappelletti-Nguyen-K (2020)
- And all other studies that used Lyapunov functions

- Brunner and Craciun (2018)

Slow stabilization of protein folding processes

ANNUAL REVIEW OF BIOPHYSICS [Volume 37, 2008, Volume 37,]

Review Article

The Protein Folding Problem

Ken A. Dill[1,2], S. Banu Ozkan[3], M. Scott Shell[4], and Thomas R. Weikl[5]

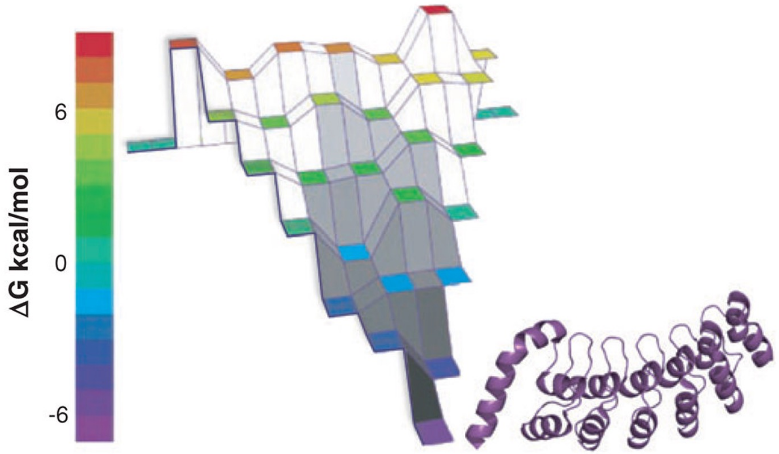


Figure 6.
The experimentally determined energy landscape of the seven ankyrin repeats of the Notch receptor (16,157,209). The energy landscape is constructed by measuring the stabilities of folded fragments for a series of overlapping modular repeats. Each horizontal tier presents the partially folded fragments with the same number of repeats. Reprinted from Reference 157 with permission.

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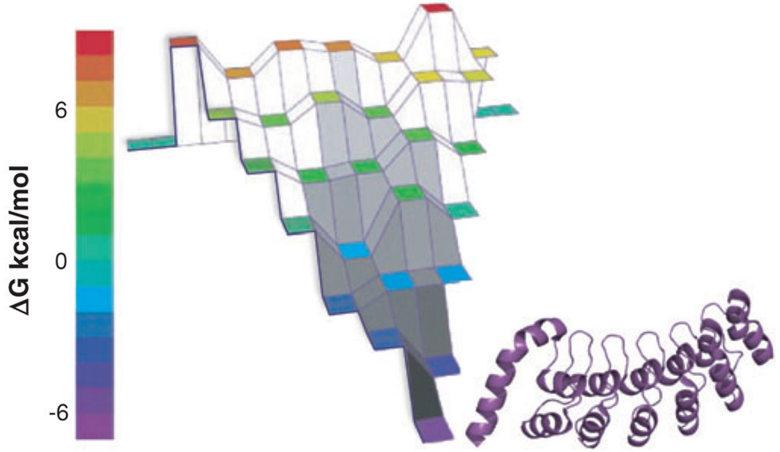

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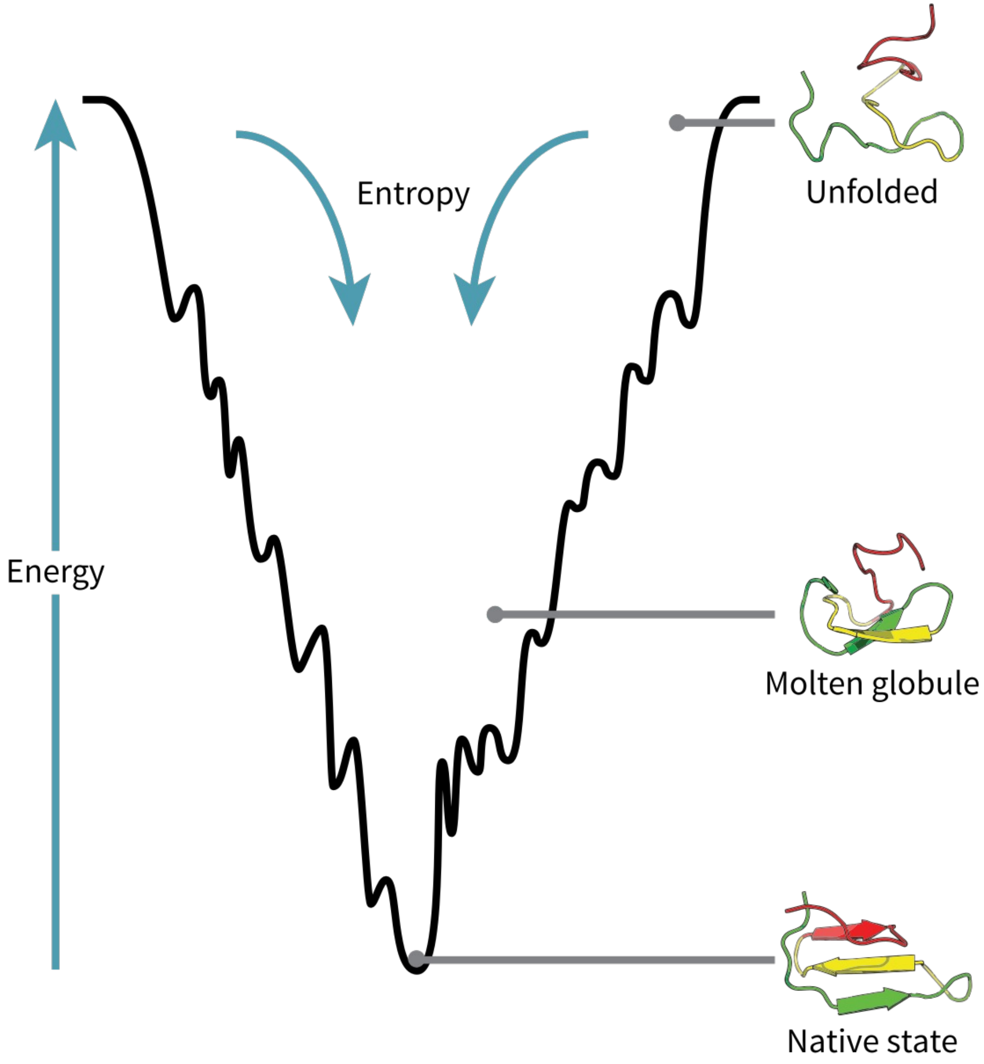
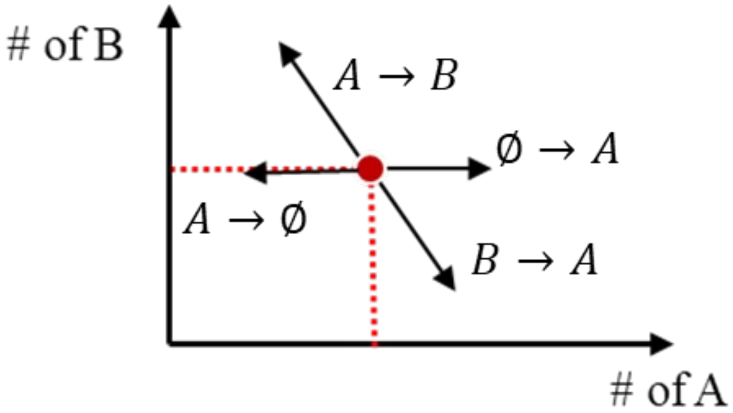
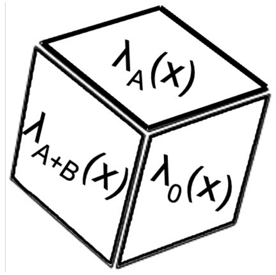


https://en.wikipedia.org/wiki/Folding_funnel

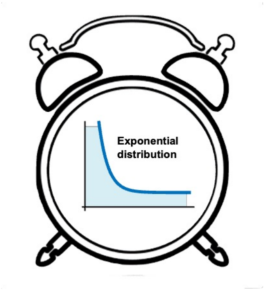
Stochastic modeling for reaction networks

$$B \underset{\kappa_2}{\overset{\kappa_1}{\rightleftharpoons}} A, \qquad A \underset{\kappa_4}{\overset{\kappa_3}{\rightleftharpoons}} \emptyset$$





Where to go



When to go

Stability, (Non) exponential ergodicity and slow mixing

$$B \rightleftharpoons 2B, \quad A + B \rightleftharpoons \emptyset$$

Stability, (Non) exponential ergodicity and slow mixing

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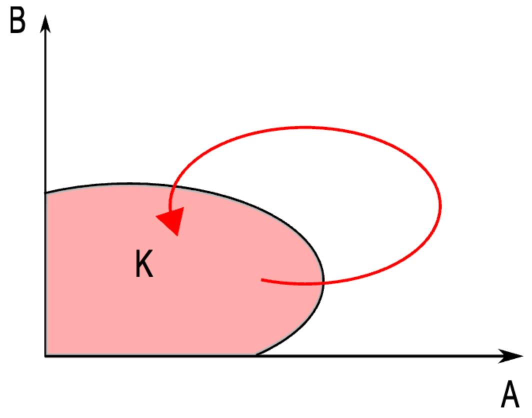
1. Positive recurrence (Ergodic, Stability): by zero deficiency

$$\lim_{t\to\infty} P(X(t) = x) = \pi(x) \quad \text{for any } x.$$

(Anderson-Craciun-Kurtz 2010, Anderson-Cappelletti-Koyama-Kurtz 2018)



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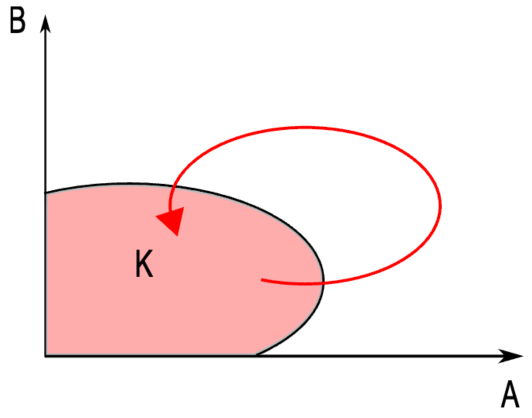

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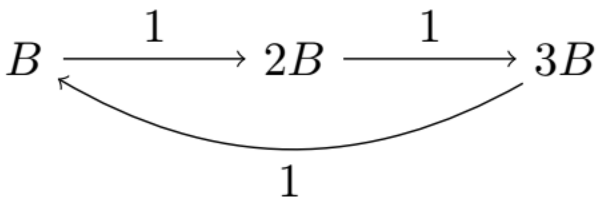
2. Non-exponential ergodicity. (Minjoon Kim-K, 2024+)

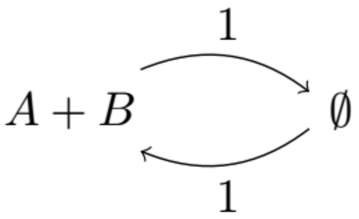
Slow mixing

3. $\tau_\epsilon^{(n,0)} = \inf\{t \geq 0 : \|P_{(n,0)}(X(t) = \cdot) - \pi(\cdot)\|_{TV} \leq \epsilon\} = O(n^2).$

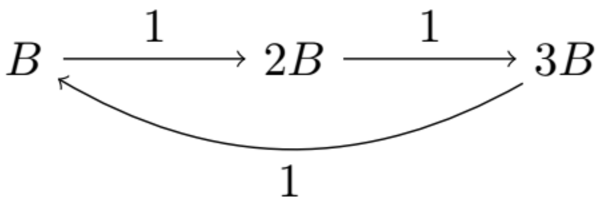
(Louis Fan-K-Chaojie Yuan, 2024+)

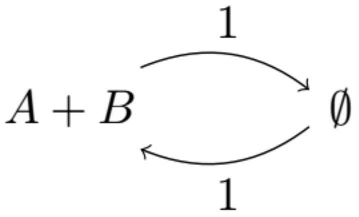
Stability, (Non) exponential ergodicity, and slow mixing





Stability, (Non) exponential ergodicity, and slow mixing





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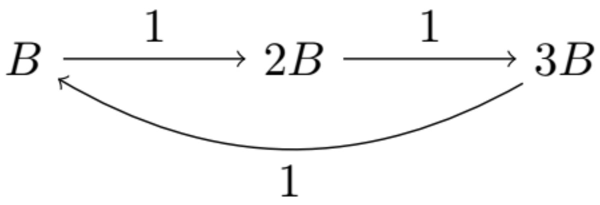

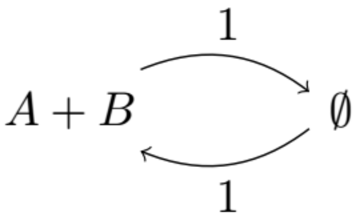

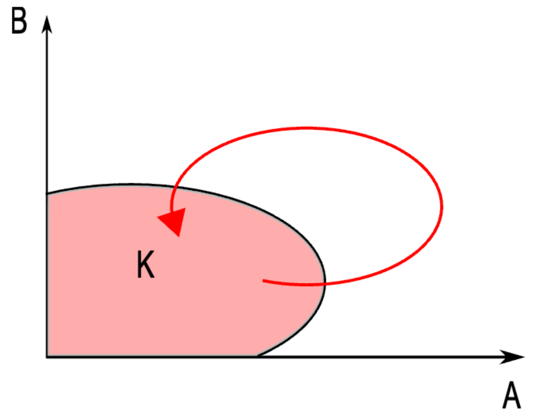

1. Positive recurrence (Ergodic, Stability)??

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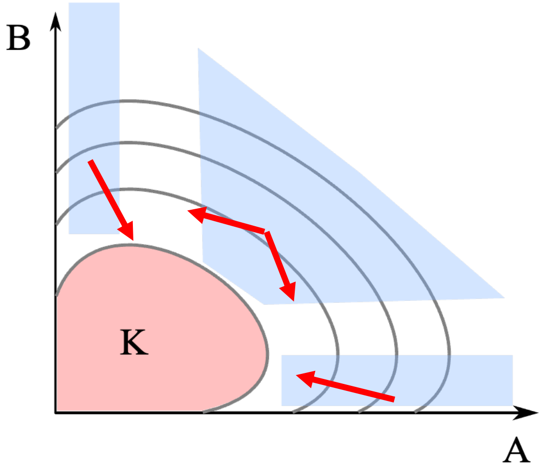
Lyapunov function?

$$B \xrightarrow{1} 2B \xrightarrow{1} 3B, \qquad 3B \xrightarrow{1} B \qquad\qquad A + B \underset{1}{\overset{1}{\rightleftarrows}} \emptyset$$

$$\mathcal{A}V(x) := \lim_{h\to 0} \frac{E_x(V(X(h)) - V(x)}{h} = \sum_{y\to y'} \lambda_{y\to y'}(x)(V(x+y'-y) - V(x)) < -\epsilon,$$

for every x but finitely many.



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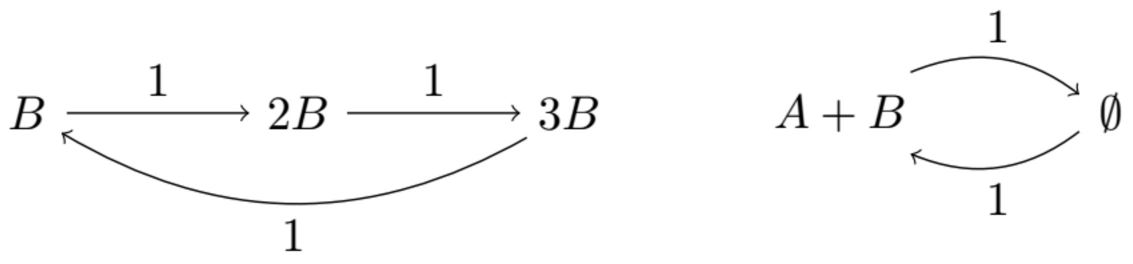

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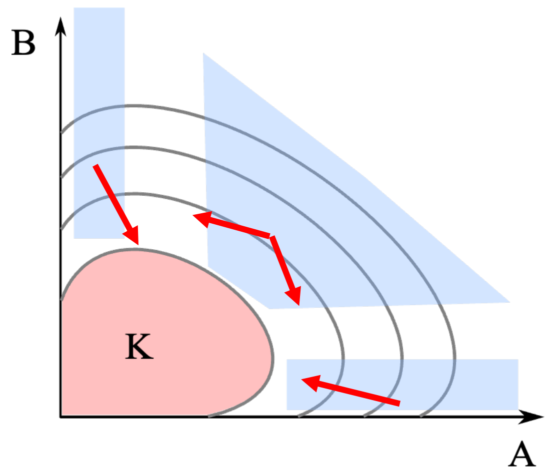
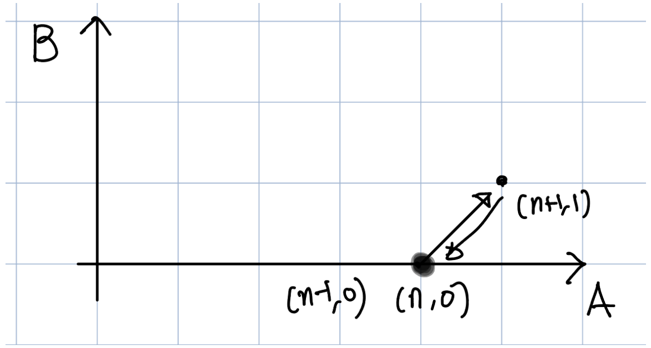


Using the dominant flows at $x = (n, 0)$ and $x + (1,1)$, we need to construct $V(x)$ such that



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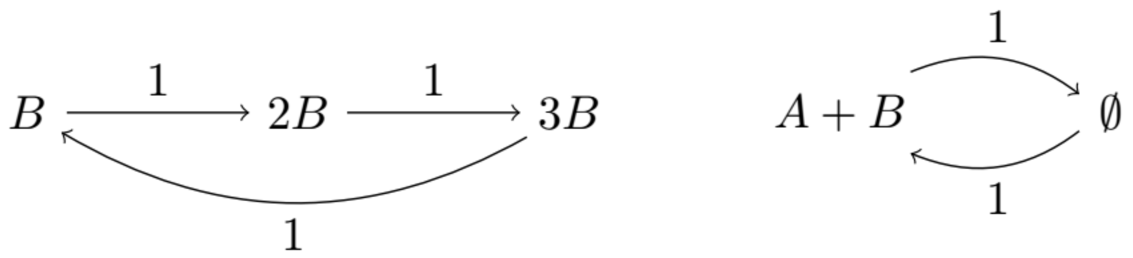

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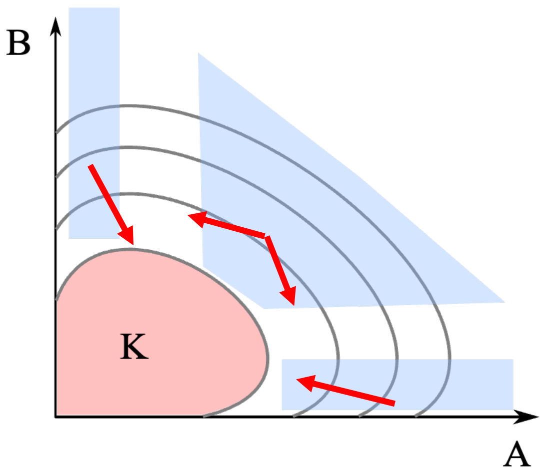

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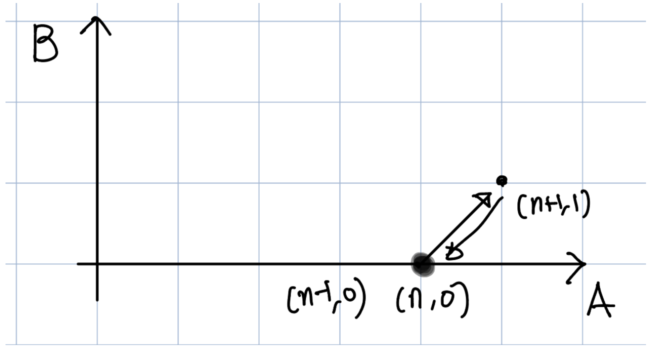
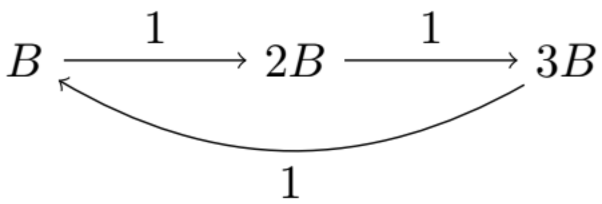
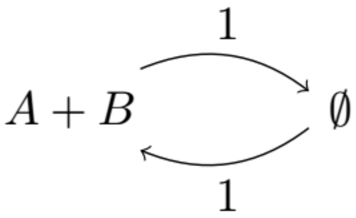
$$V(x + (1,1)) - V(x) < 0 \quad \text{and} \quad V(x) - V(x + (1,1)) < 0.$$



Consider more steps of *X*





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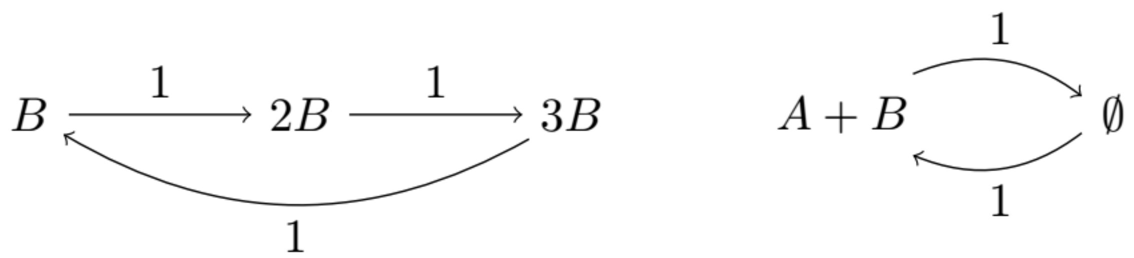

So we think of the 4-steps skeleton process. $\widetilde{X}_4(k) = X(T_{4k})$, where T_k is the k th jump time of X.

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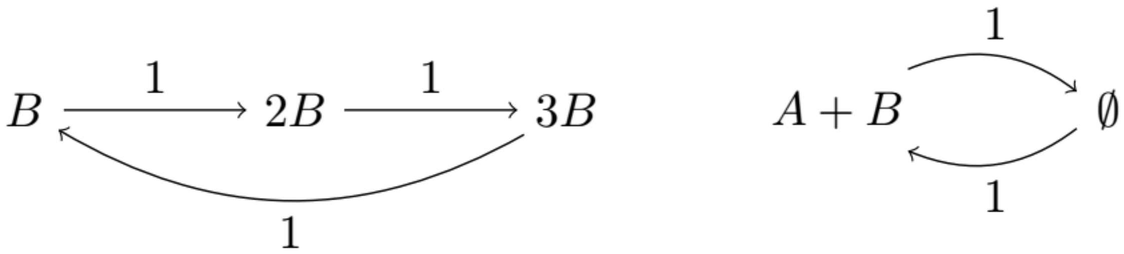

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If $\widetilde{X}_4(k)$ is positive recurrent, then X is positive recurrent. (Norris 97, Anderson-Cappelletti-K 2020)

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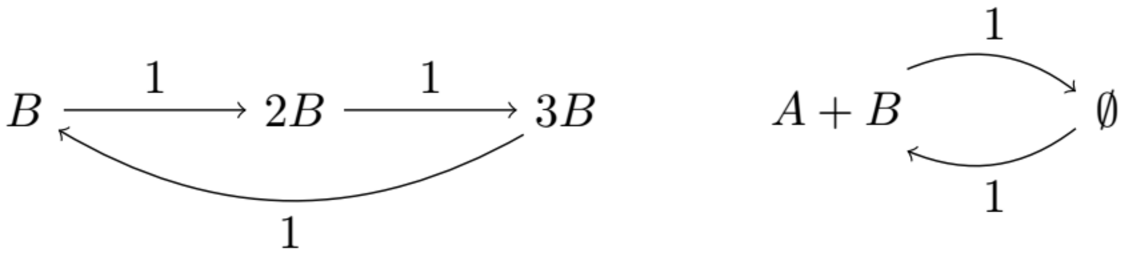

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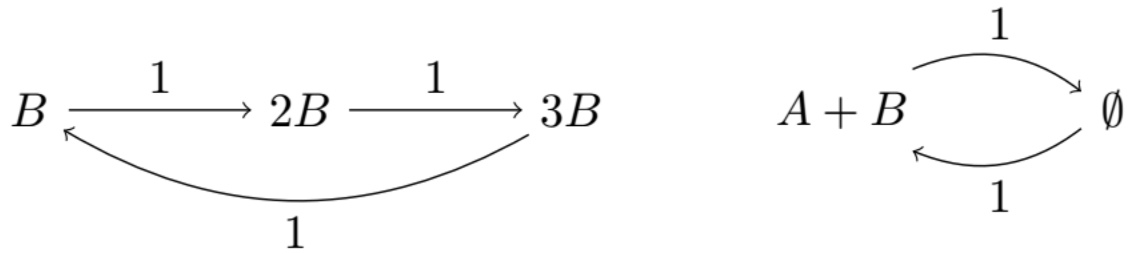

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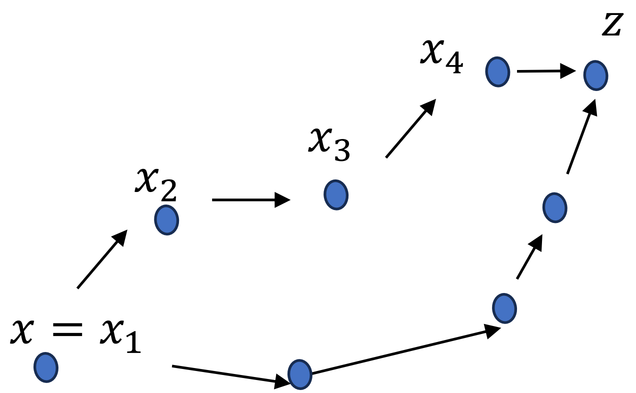

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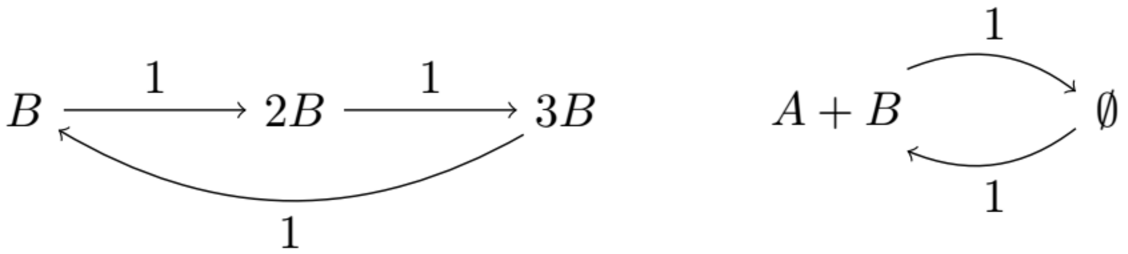

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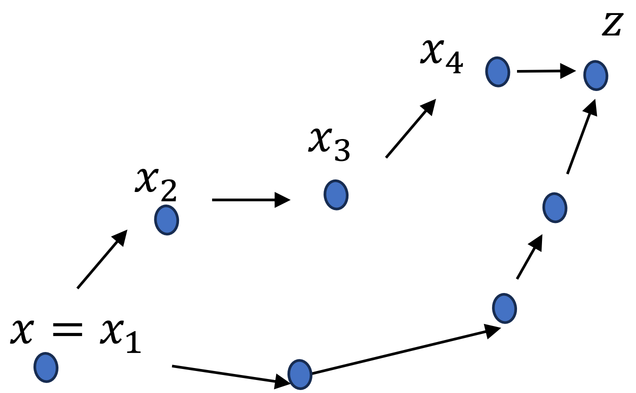
$$\sum_{x \rightsquigarrow z} \frac{\lambda_1(x_1)}{\sum_{y \to y'} \lambda_{y \to y'}(x_1)} \frac{\lambda_2(x_2)}{\sum_{y \to y'} \lambda_{y \to y'}(x_2)} \frac{\lambda_3(x_3)}{\sum_{y \to y'} \lambda_{y \to y'}(x_3)} \frac{\lambda_4(x_4)}{\sum_{y \to y'} \lambda_{y \to y'}(x_4)}.$$



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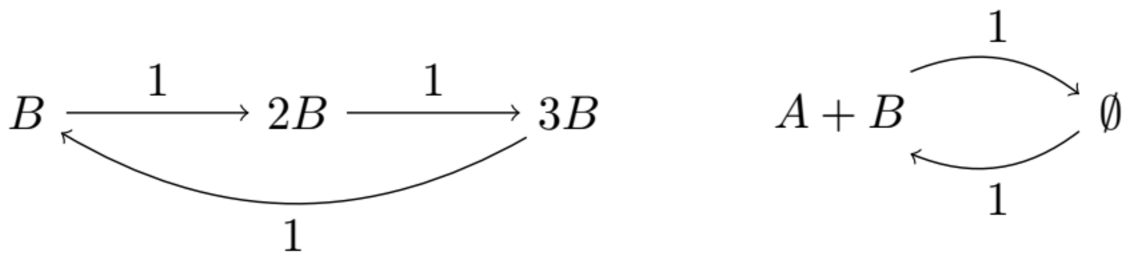

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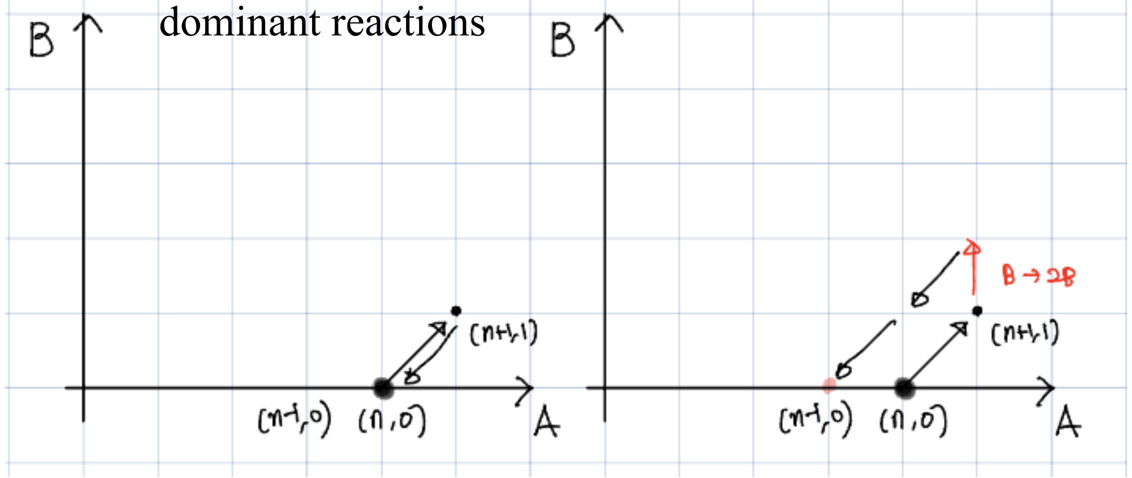
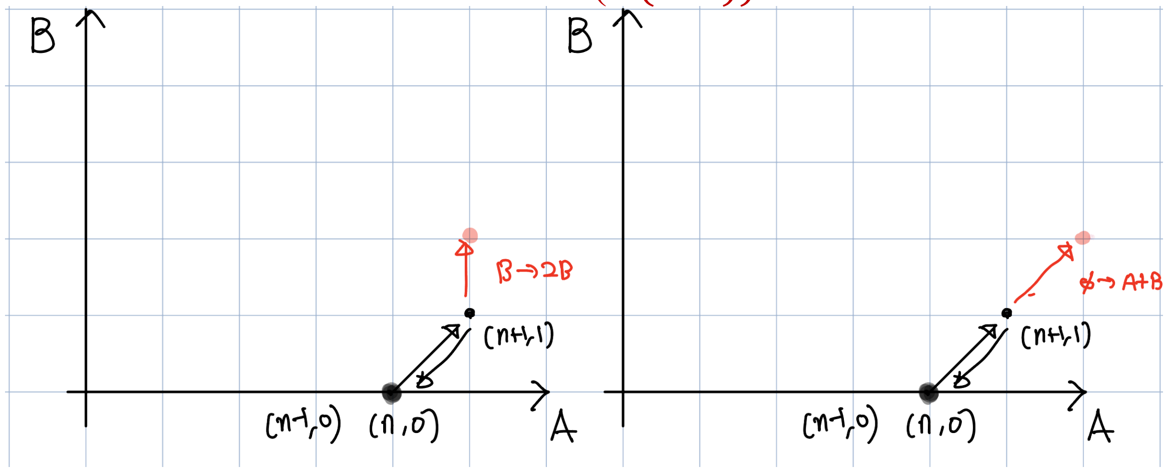
A path with only dominant reactions



A path with dominant reactions but one rare event ($O(n^{-1})$).



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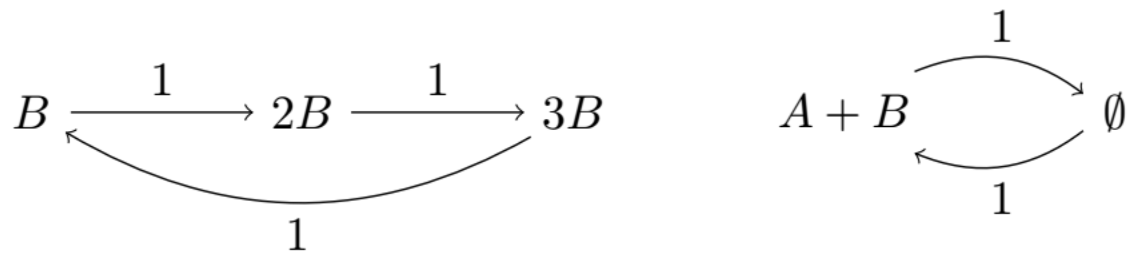

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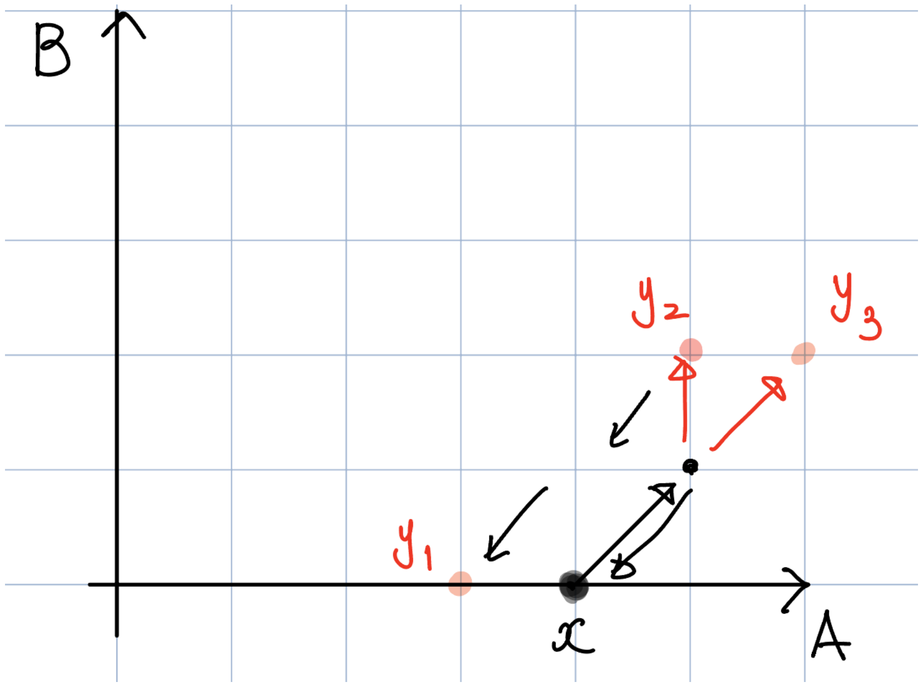
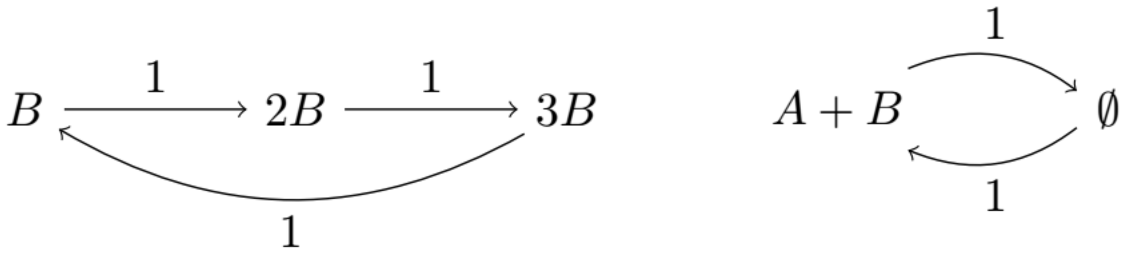


How about even more steps of *X* ?



So we think of 10-steps skeleton process. $\widetilde{X}_{10}(k) = X(T_{10k}),$ where T_k is the k th jump time of X.

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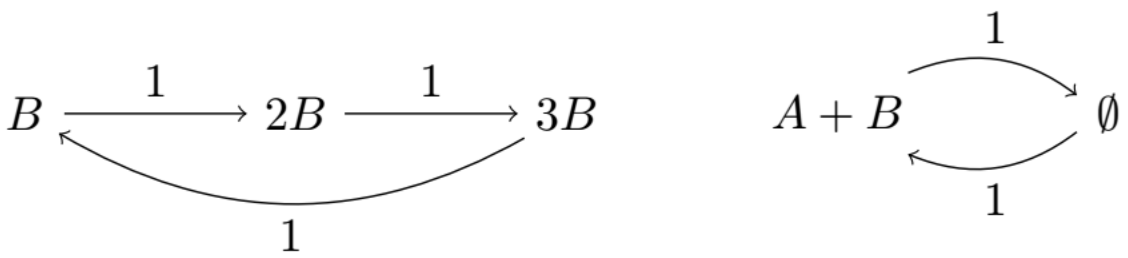

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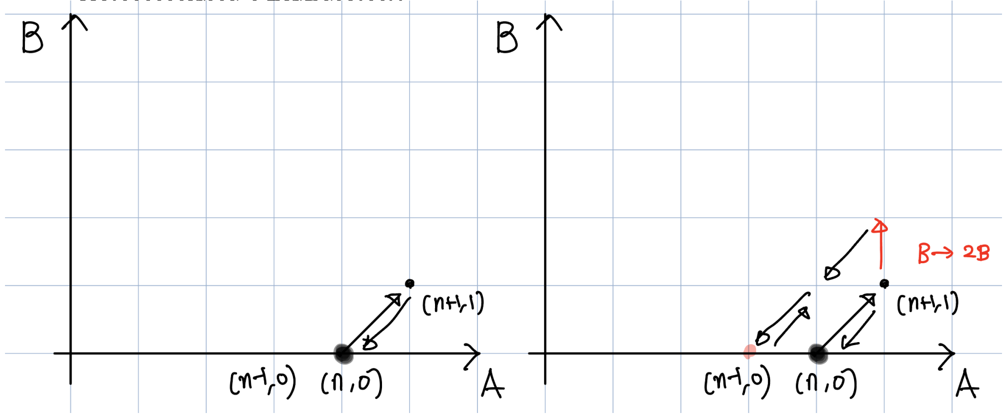

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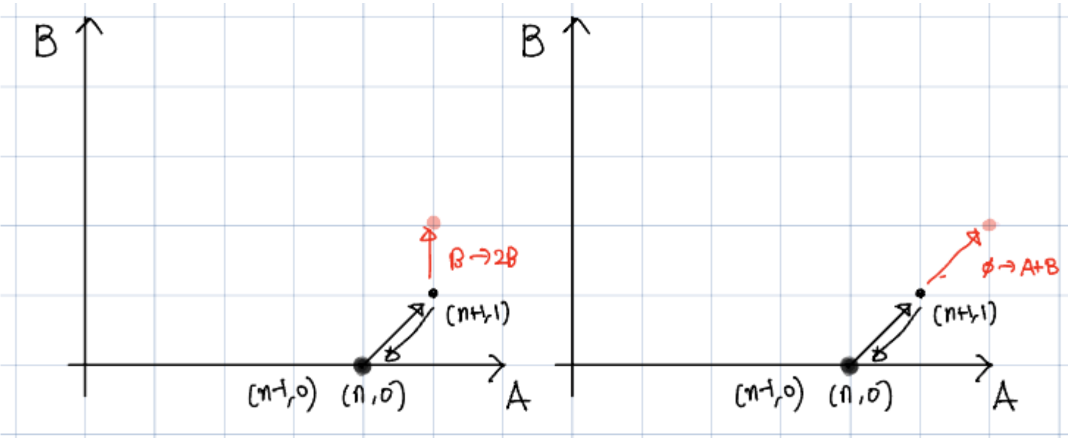

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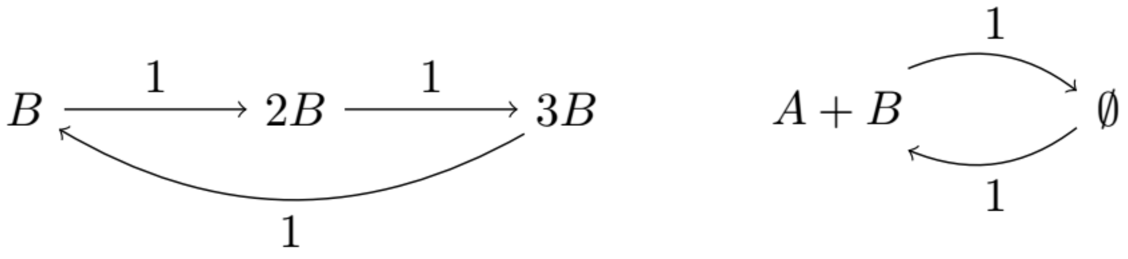

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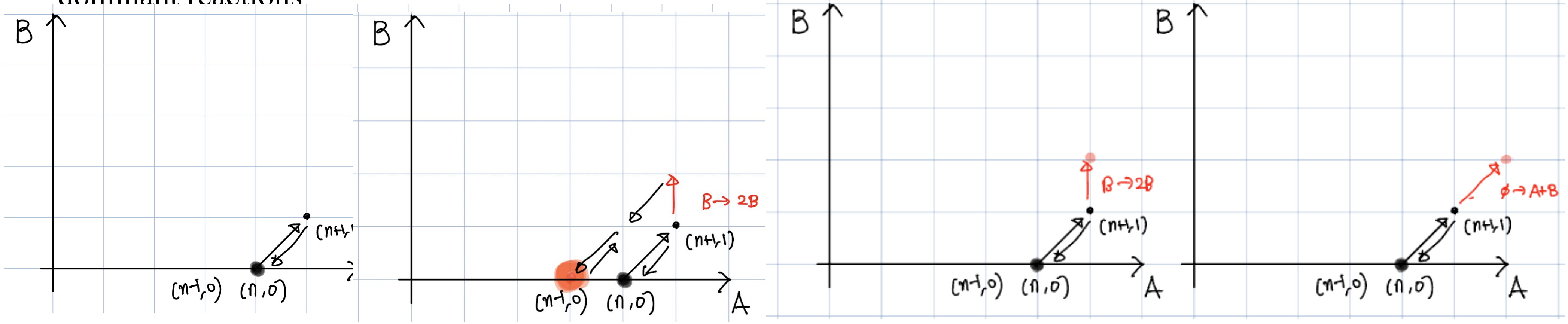

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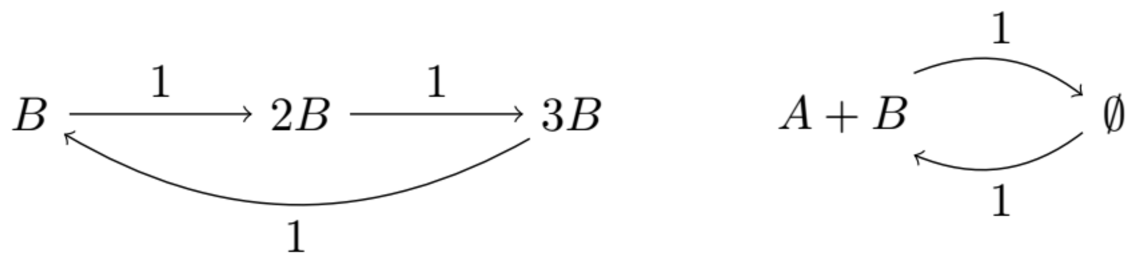

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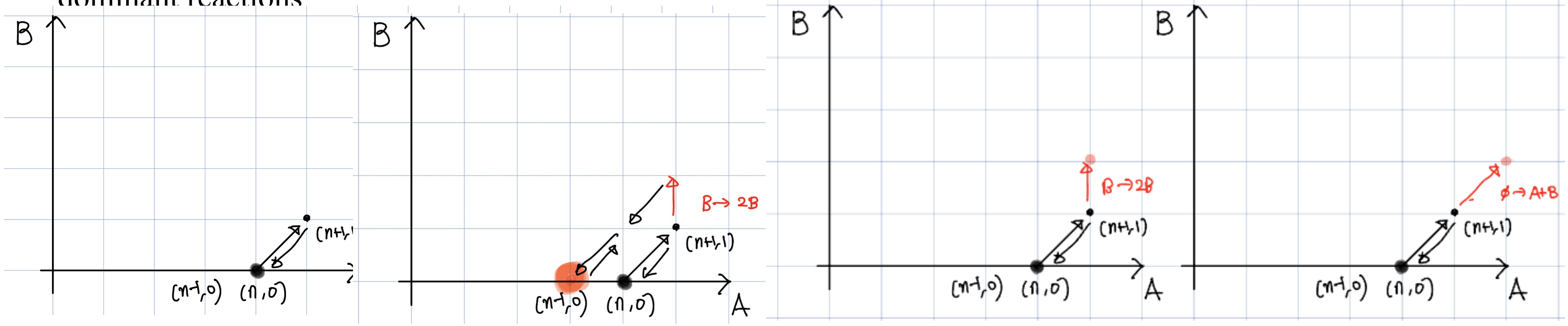

Excepts these five paths of 10 steps, all other paths involve rarer events ($O(n^{-2})$), hence they are ignorable in the Lyapunov analysis

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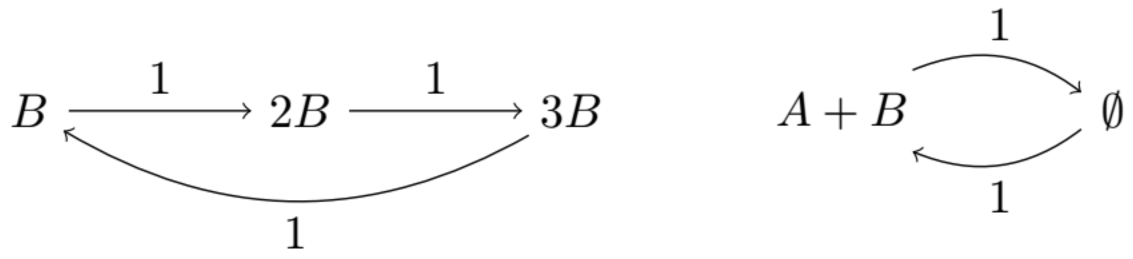

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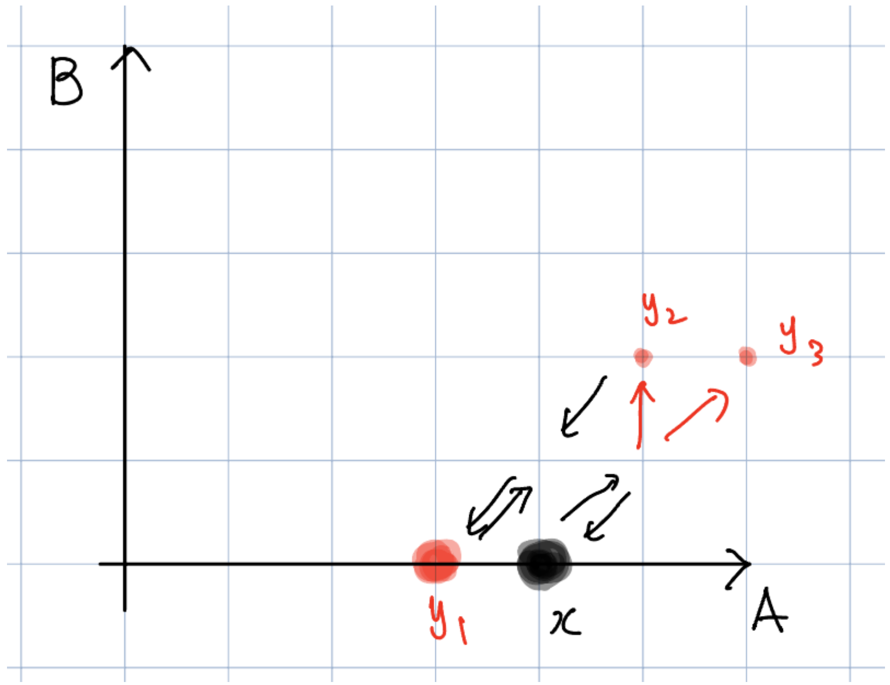
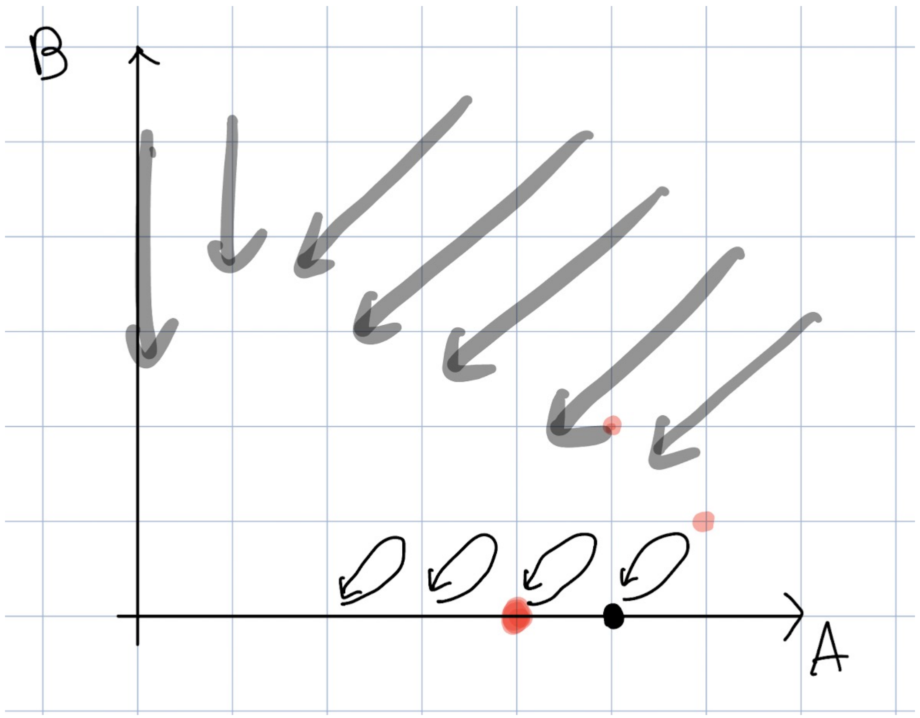
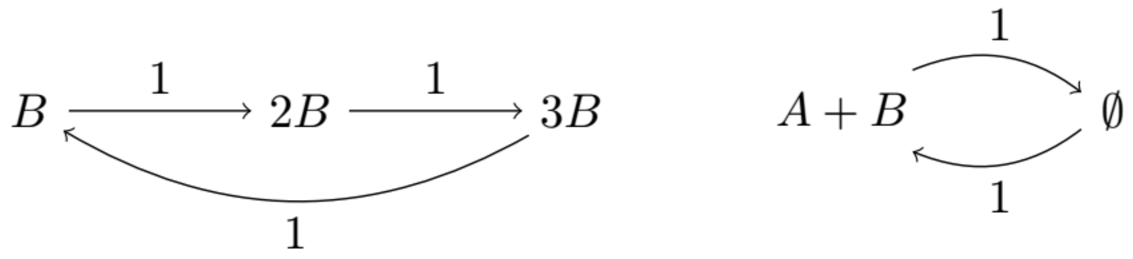
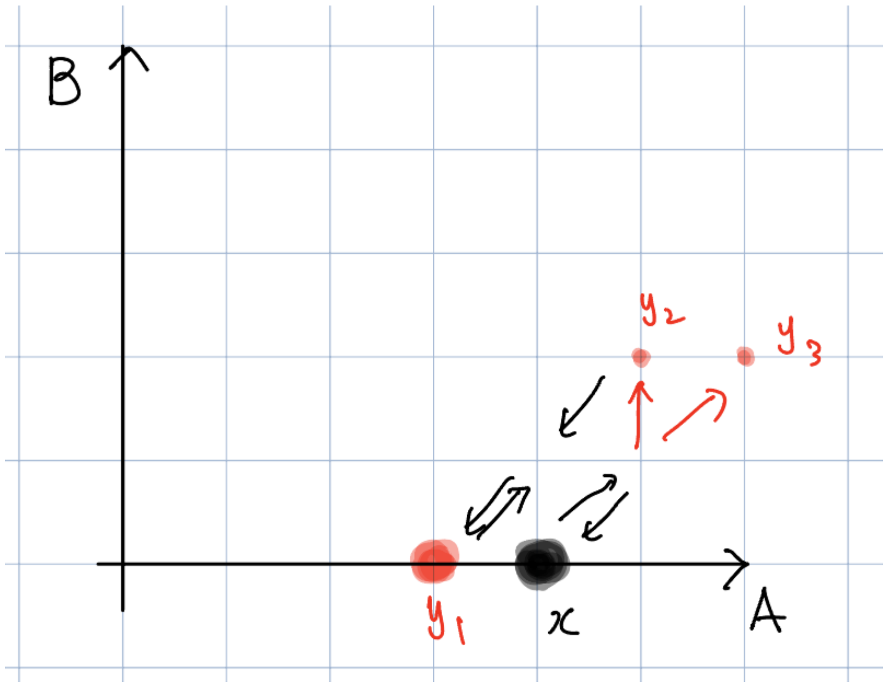


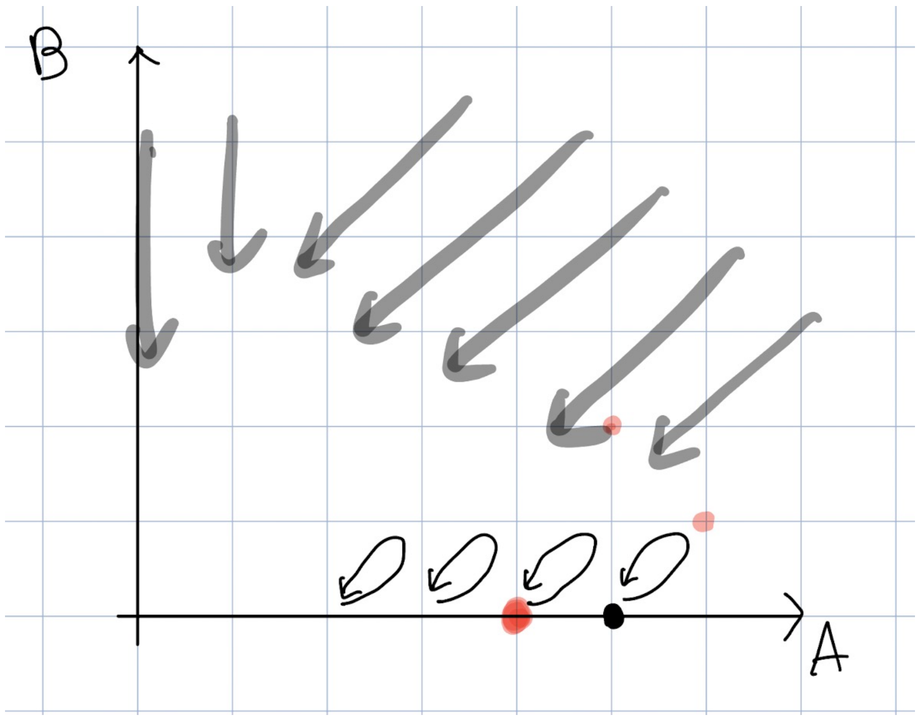


How about even more steps of X ?



So we think of 10-steps skeleton process. $\widetilde{X}_{10}(k) = X(T_{10k}),$ where T_k is the k th jump time of X.





Use an embedded Markov chain to show positive recurrence of the original Markov chain.

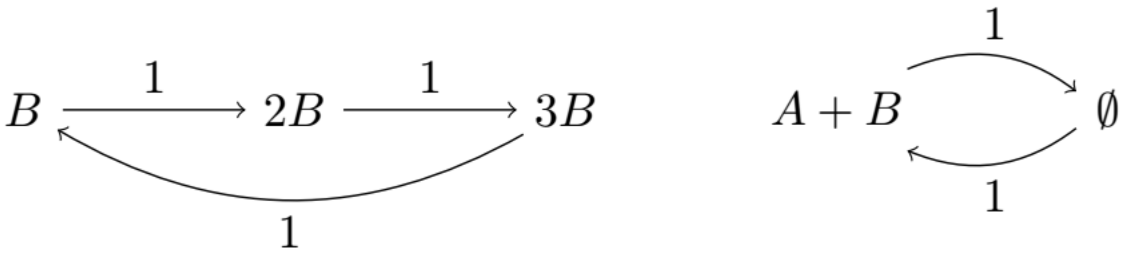
Theorem. *If the transition intensities of $X(t)$ are polynomials, then positive recurrence of $\tilde{X}_m$ implies positive recurrence of $X(t)$ for any m.*

Theorem. *If there exists a positive function $V(x)$ such that* (Meyn-Tweedie 92)

1. $V(x) \to \infty$ *as* $|x| \to \infty$, *and*
2. $\widetilde{A}_m V(x) := E(V(\widetilde{X}_m(1)) - V(x) = \sum_z P\left(\widetilde{X}_m(1) = y | \widetilde{X}_m(0) = x\right)(V(z) - V(x)) < -1$ *for all x but finitely many,*

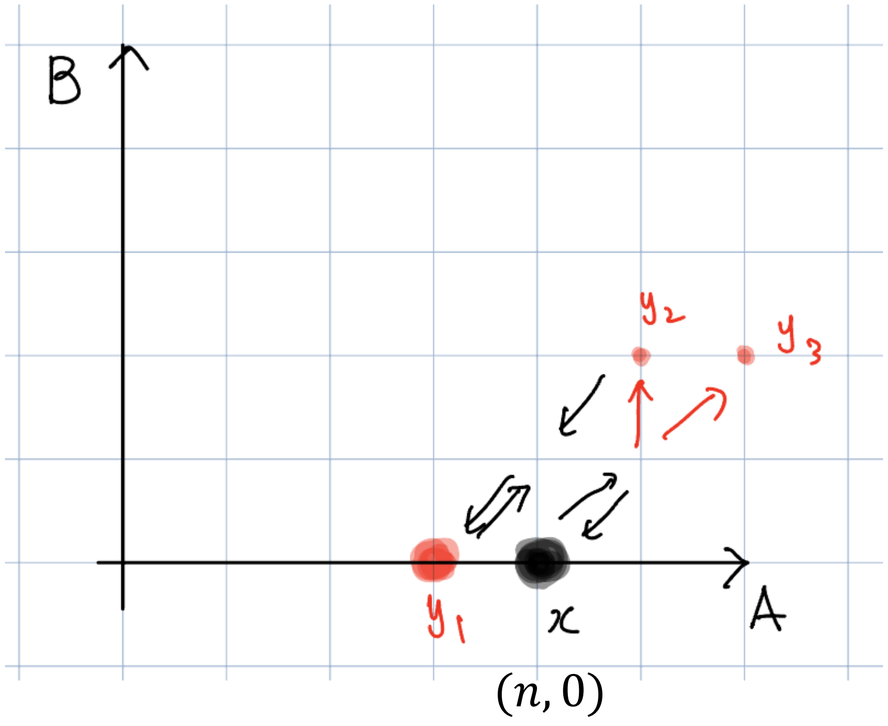
then $\widetilde{X}_m$ is positive recurrent.

Use an embedded Markov chain to show positive recurrence of the original Markov chain.



$$V(a,b) = a^2 + b^2$$

$$
\begin{aligned}
\tilde{A}_{10} V(x) = \; & P(\tilde{X}_{10}(1) = x \mid \tilde{X}_{10}(0) = x)\,(V(x) - V(x)) \\
& + P(\tilde{X}_{10}(1) = y_1 \mid \tilde{X}_{10}(0) = x)\,(V(y_1) - V(x)) \\
& + P(\tilde{X}_{10}(1) = y_2 \mid \tilde{X}_{10}(0) = x)\,(V(y_2) - V(x)) \\
& + P(\tilde{X}_{10}(1) = y_3 \mid \tilde{X}_{10}(0) = x)\,(V(y_3) - V(x)) \\
& + O(n^{-2})
\end{aligned}
$$



Use an embedded Markov chain to show positive recurrence of the original Markov chain.

$$B \xrightarrow{1} 2B \xrightarrow{1} 3B, \quad 3B \xrightarrow{1} B$$

$$A + B \underset{1}{\overset{1}{\rightleftarrows}} \emptyset$$

$$V(a, b) = a^2 + b^2$$

$$\tilde{A}_{10} V(x) = P(\tilde{X}_{10}(1) = x \mid \tilde{X}_{10}(0) = x)\,(V(x) - V(x))$$

$$+ \; P(\tilde{X}_{10}(1) = y_1 \mid \tilde{X}_{10}(0) = x)\,(V(y_1) - V(x))$$

$4O(n^{-1})$ $\qquad -2n$

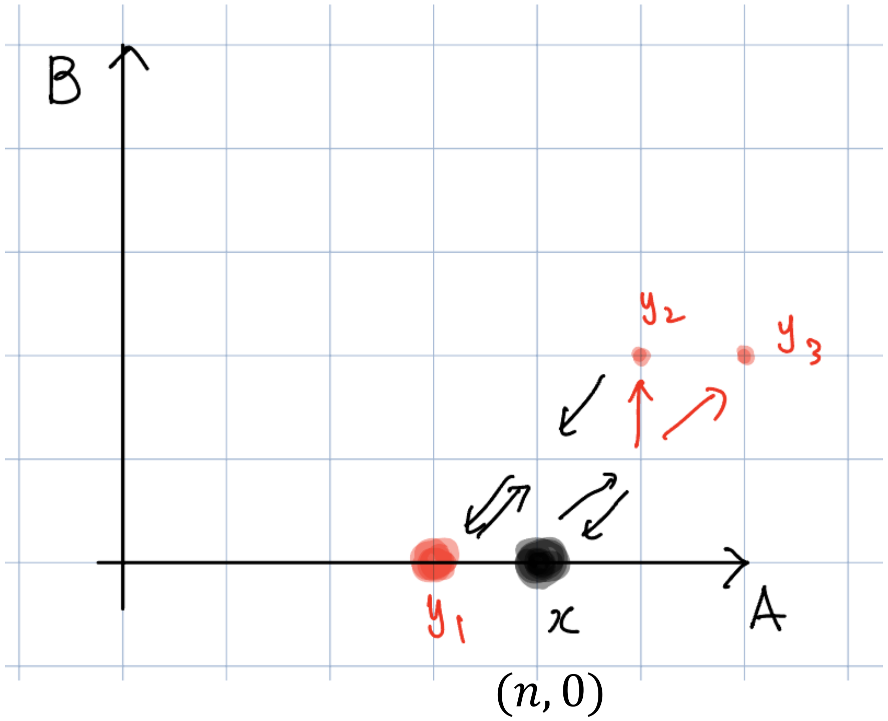
$$+ \; P(\tilde{X}_{10}(1) = y_2 \mid \tilde{X}_{10}(0) = x)\,(V(y_2) - V(x))$$

$O(n^{-1})$ $\qquad 2n$

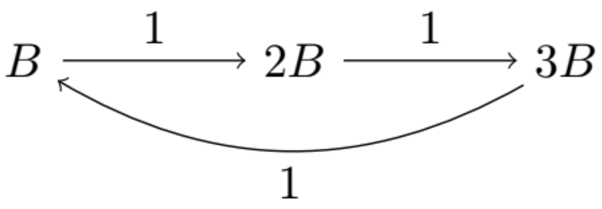
$$+ \; P(\tilde{X}_{10}(1) = y_3 \mid \tilde{X}_{10}(0) = x)\,(V(y_3) - V(x))$$

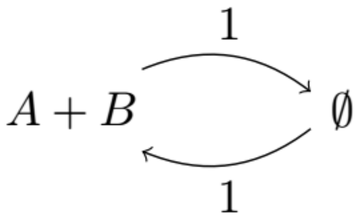
$O(n^{-1})$ $\qquad 4n$

$$+ \; O(n^{-2})$$



Use an embedded Markov chain to show positive recurrence of the original Markov chain.





$$V(a,b) = a^2 + b^2$$

$$\tilde{A}_{10}V(x) = P(\tilde{X}_{10}(1)=x \mid \tilde{X}_{10}(0)=x)\,(V(x)-V(x))$$

$$+\ P(\tilde{X}_{10}(1)=y_1 \mid \tilde{X}_{10}(0)=x)\,(V(y_1)-V(x))$$

$4O(n^{-1})$ $\quad -2n$

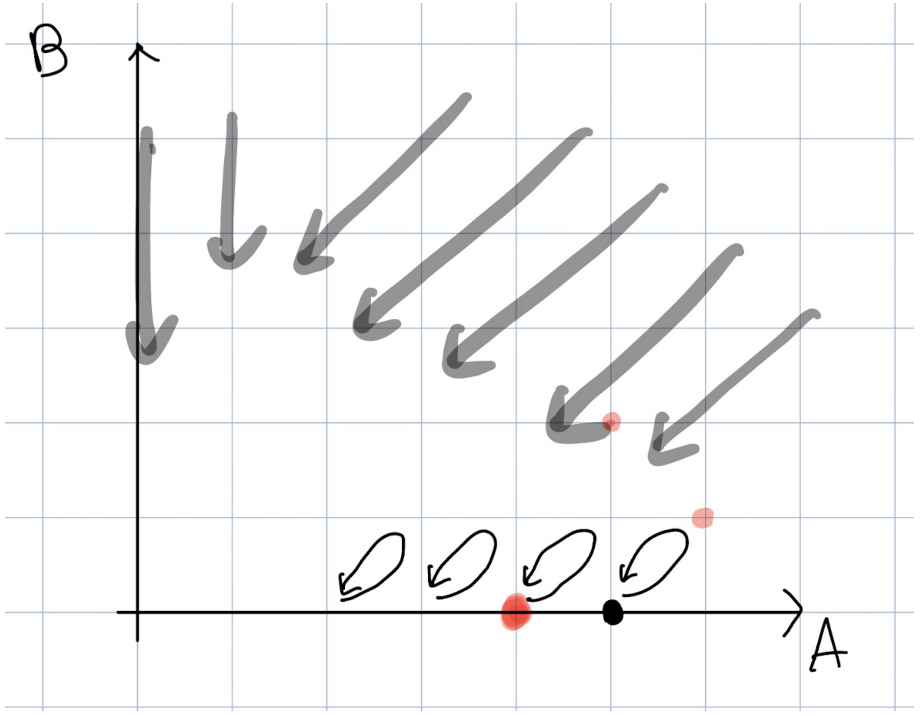
$$+\ P(\tilde{X}_{10}(1)=y_2 \mid \tilde{X}_{10}(0)=x)\,(V(y_2)-V(x))$$

$O(n^{-1})$ $\quad 2n$

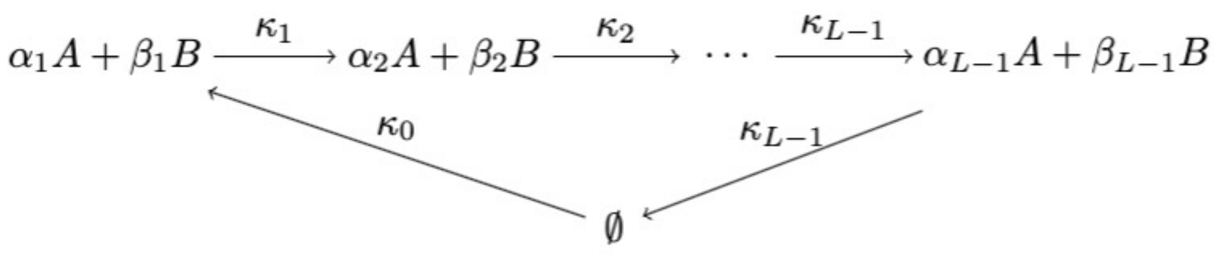
$$+\ P(\tilde{X}_{10}(1)=y_3 \mid \tilde{X}_{10}(0)=x)\,(V(y_3)-V(x))$$

$O(n^{-1})$ $\quad 4n$

$$+\ O(n^{-2})$$



General structural conditions?



(α_i and β_i are increasing)

$+$ reactions that are not too strong

General structural conditions?

$$\begin{array}{ccccccc} \alpha_1 A + \beta_1 B & \xrightarrow{\kappa_1} & \alpha_2 A + \beta_2 B & \xrightarrow{\kappa_2} & \cdots & \xrightarrow{\kappa_{L-1}} & \alpha_{L-1} A + \beta_{L-1} B \\ & \nwarrow^{\kappa_0} & & \emptyset & & \swarrow_{\kappa_{L-1}} & \end{array}$$

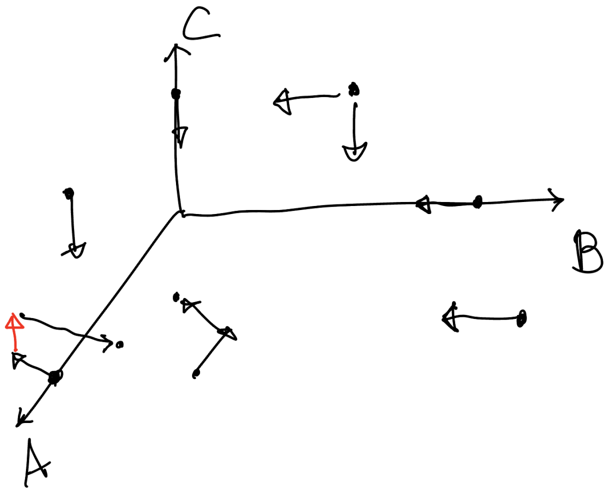
(α_i and β_i are increasing)

+ reactions that are not too strong

More than two species??

$$\begin{array}{ccc} \emptyset & \longrightarrow & A + 2B + C \\ \nwarrow & & \swarrow \\ & 2A + B + 2C & \end{array}$$

$$B \rightleftharpoons 2B, \quad C \rightleftharpoons 2C$$



General structural conditions?

$$\alpha_1 A + \beta_1 B \xrightarrow{\kappa_1} \alpha_2 A + \beta_2 B \xrightarrow{\kappa_2} \cdots \xrightarrow{\kappa_{L-1}} \alpha_{L-1} A + \beta_{L-1} B$$

$$\emptyset \xrightarrow{\kappa_0} \alpha_1 A + \beta_1 B, \qquad \alpha_{L-1} A + \beta_{L-1} B \xrightarrow{\kappa_{L-1}} \emptyset$$

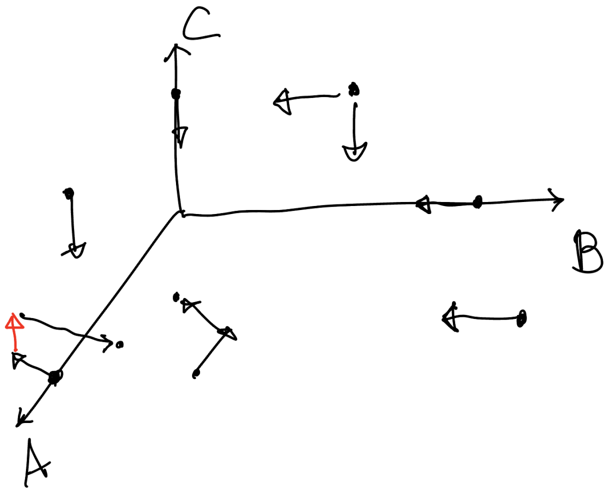
(α_i and β_i are increasing)

+ reactions that are not too strong

More than two species??

$$\emptyset \longrightarrow A + 2B + C, \qquad A + 2B + C \longrightarrow 2A + B + 2C, \qquad 2A + B + 2C \longrightarrow \emptyset$$

$$B \rightleftharpoons 2B, \quad C \rightleftharpoons 2C$$



These trapping at boundaries often induce slow mixing. (Minjoon's poster)

Thanks