Timing infectious disease control to minimize the risk of pathogen emergence

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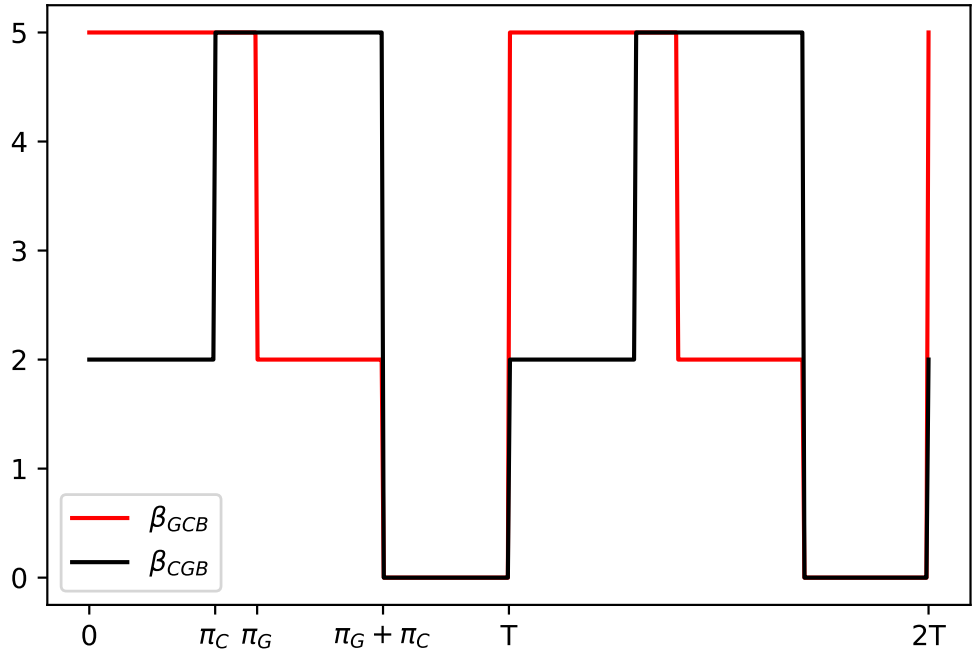
Motivation

- Infectious diseases have been a significant challenge throughout human history, causing widespread outbreaks and devastating consequences.
- However, advancements in modeling techniques have allowed us to better understand and predict disease trends, leading to more effective strategies for minimizing their impact

Outline

Introduction



The question:
What is the best time to take action to reduce the risk of pathogens ?
The answer:
The best time to control the pathogen is at the end of a favorable period.

Introduction

We consider the deterministic SI model

$$\frac{dS}{dt} = \lambda - \beta(t)\frac{SI}{S+I} - \mu S \tag{1.1}$$

$$\frac{dI}{dt} = \beta(t)\frac{SI}{S+I} - \mu I \tag{1.2}$$

where

- $S(t), I(t)$ are *susceptible* and *infected* individual in population ,
- $\beta(t)$ is transition rate,
- λ the recruitment rate,
- μ death rate.

The stochastic model

The stochastic dynamics is described by the transitions:

$$X^{(K)} \to X^{(K)} + 1 \text{ with rate } \quad \beta(t)X^{(K)}(t)\left(1 - \frac{X^{(K)}(t)}{K}\right) \tag{1.3}$$

$$X^{(K)} \to X^{(K)} - 1 \text{ with rate } \quad \mu X^{(K)}(t) \tag{1.4}$$

where:

- K the capacity: the maximal host population
- $X^{(K)}(t)$ the number of infected host at time t
- $S^{(K)}(t) = K - X^{(K)}(t)$ the number of susceptible host.

Theorem (Law of large numbers (Kurtz [4]))

Fixed $T > 0$, if $x(t) = (s(t), i(t))$ solution of the dynamic system:

$$\begin{cases} \dot{s} = \lambda - \mu s - \beta \dfrac{si}{s+i} \\ \dot{i} = \beta \dfrac{si}{s+i} - \mu i. \end{cases} \tag{1.5}$$

with initial condition if $x_0 \in \mathbb{R}$ and in probability

$$\lim_{K \to \infty} \frac{X^{(K)}(0)}{K} = x_0,$$

then for every $\epsilon > 0$,

$$\lim_{K \to +\infty} \mathbb{P}\left(\sup_{t \leq T} \left| \frac{X^K(t)}{K} - x(t) \right| > \epsilon \right) = 0 \tag{1.6}$$

The constant case

The constant case:

- The reproductive number $R_0 = \dfrac{\beta}{\mu}$
- The extinction time $\tau_0^{(K)} = \inf\left\{t > 0 : X^{(K)}(t) = 0\right\}$

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- The extinction time $\tau_0^{(K)} = \inf\left\{t > 0 : X^{(K)}(t) = 0\right\}$
- If $R_0 < 1$
  - $\tau_0^{(K)}$ is stochastically dominated by an exponential random variable of parameter $\mu - \beta$.
    $\Rightarrow$ The expected time to extinction is at most equal to $\frac{1}{\mu-\beta}$.

The constant case

- If $R_0 > 1$
  - The take off probability: for large capacity K, the pathogen reaches a fixed proportion $x_0 K$ with $0 < x_0 < 1$ is

$$\mathbb{P}\left(X^{(K)} \text{ takes off }\right) \sim 1 - \frac{\mu}{\beta}\,. \tag{2.1}$$

  - We assume that $\frac{X^{(K)}(0)}{K} \to x_0 \in (0,1)$. Andersson and Djehiche [1] proved that the mean extinction time of this process is exponential in the capacity K:

$$\mathbb{E}\left[\tau_0^{(K)}\right] \sim \sqrt{\frac{2\pi}{K}}\frac{R_0}{(R_0-1)^2}e^{KV_0}\,, \quad \text{with} \quad V_0 = \ln R_0 - 1 + \frac{1}{R_0} > 0\,. \tag{2.2}$$

Quasi stationary distribution in the constant case

- There exists a quasi stationary distribution α on $\{1, \ldots, K\}$ (Darroch and Seneta [2, 3]) :
  For every starting point $x = 1, \ldots, K$,

$$\lim_{t \to +\infty} \mathbb{P}_x \left(X^{(K)}(t) \in A \mid \tau_0 > t \right) = \alpha(A) \,. \tag{2.3}$$

- There exists another probability π on $\{1, \ldots, K\}$, and a number $\theta > 0$, such that for any $x, y \in \{1, \ldots, K\}$:

$$\lim_{t \to +\infty} e^{-\theta t} \mathbb{P}_x \left(X^{(K)}(t) = y \right) = \pi_x \alpha_y \,,$$

$$\lim_{t \to +\infty} e^{-\theta t} \mathbb{P}_x \left(\tau_0^{(K)} > t \right) = \pi_x \,.$$

- If t is large enough, then the deterministic approximation $x(t)$ is close to its equilibrium value x_{eq}.
- If $t << 1/\theta$, then the quasi stationary distribution α will be concentrated on the equilibrium value x_{eq}.

The periodic case

- The reproduction number is given by

$$R_0 = \frac{\langle \beta \rangle}{\mu}, \qquad \text{with} \quad \langle \beta \rangle = \frac{1}{T} \int_0^T \beta(s/T)\, ds = \int_0^1 \beta(u)\, du\,. \tag{3.1}$$

- If $R_0 < 1$
  - $\tau_0^{(K)}$ is stochastically dominated by the absorption time $\tau_0(Z^{(T,+)})$ of a linear birth-death process with birth rate $t \to \beta(t/T)$ and death rate μ.
- If $R_0 > 1$ the behavior depends strongly on the length of period T

Short period approximation

Theorem

When $T \to 0$, the process $X^{(K,T)}$ converges in distribution to the process $\bar{X}^{(K)}$, for Skorokhod topology on the space $D([0,\infty[)$ of cadlag processes defined on $[0,\infty[$.

Corollary

When $T \to 0$ the time of extinction of $X^{(K,T)}$ converges to the time of extinction of $\bar{X}^K$. In consequence, when $R_0 = \langle\beta\rangle/\mu > 1$, this time is exponential in the carrying capacity K.

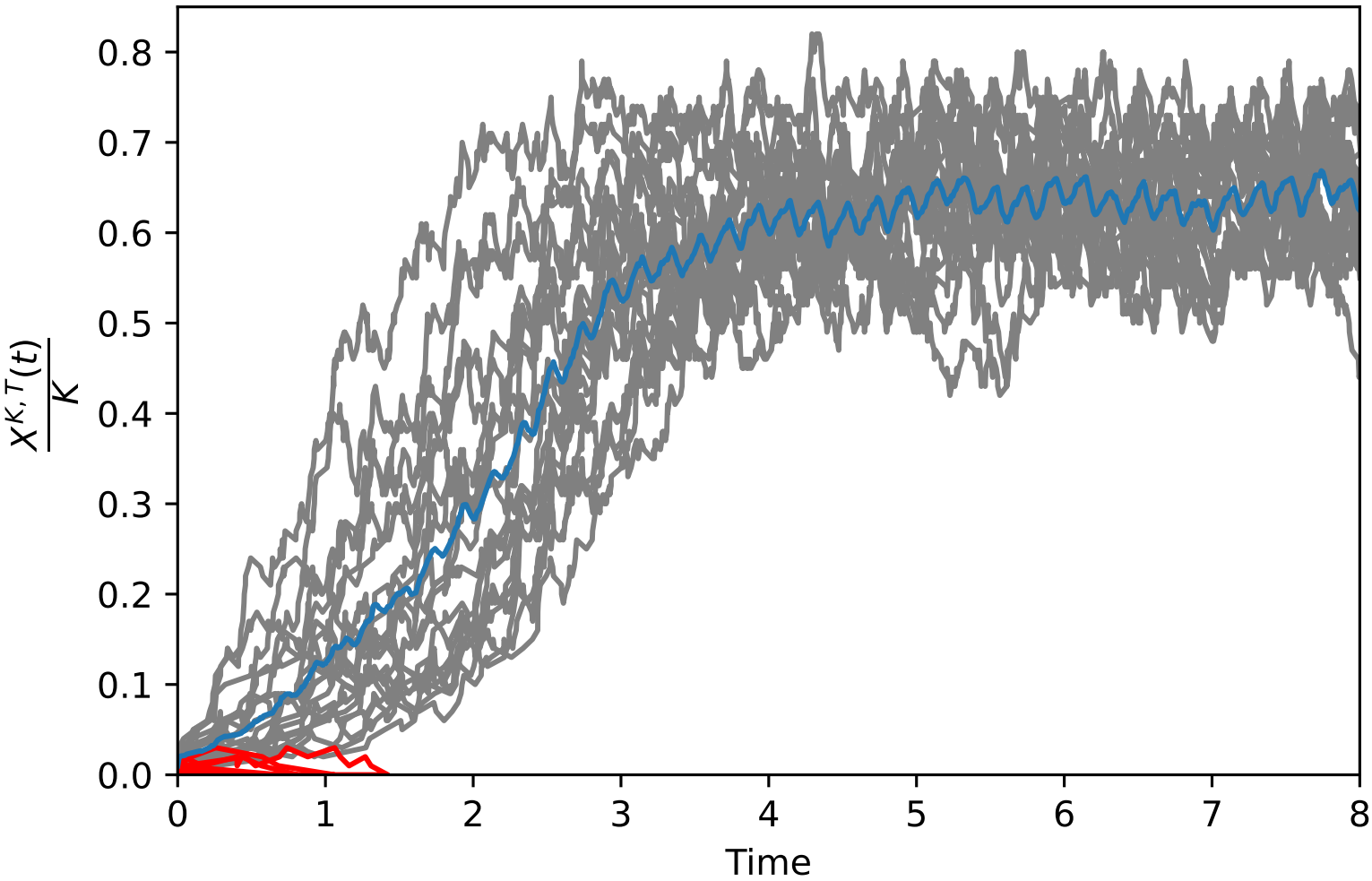

Figure: **Periodic quasistationnary distribution and Homogenization.** Parameters set: There is 1 infected individual introduced for all processes, carrying capacity $K = 100$, $T = 0.2$, $\beta(t/T) = \beta_0 \mathbb{1}_{(0 \leq t/T \leq 1-\gamma)}$, $\beta_0 = 4.0$, $\gamma = 0.3$, $\mu = 1$.

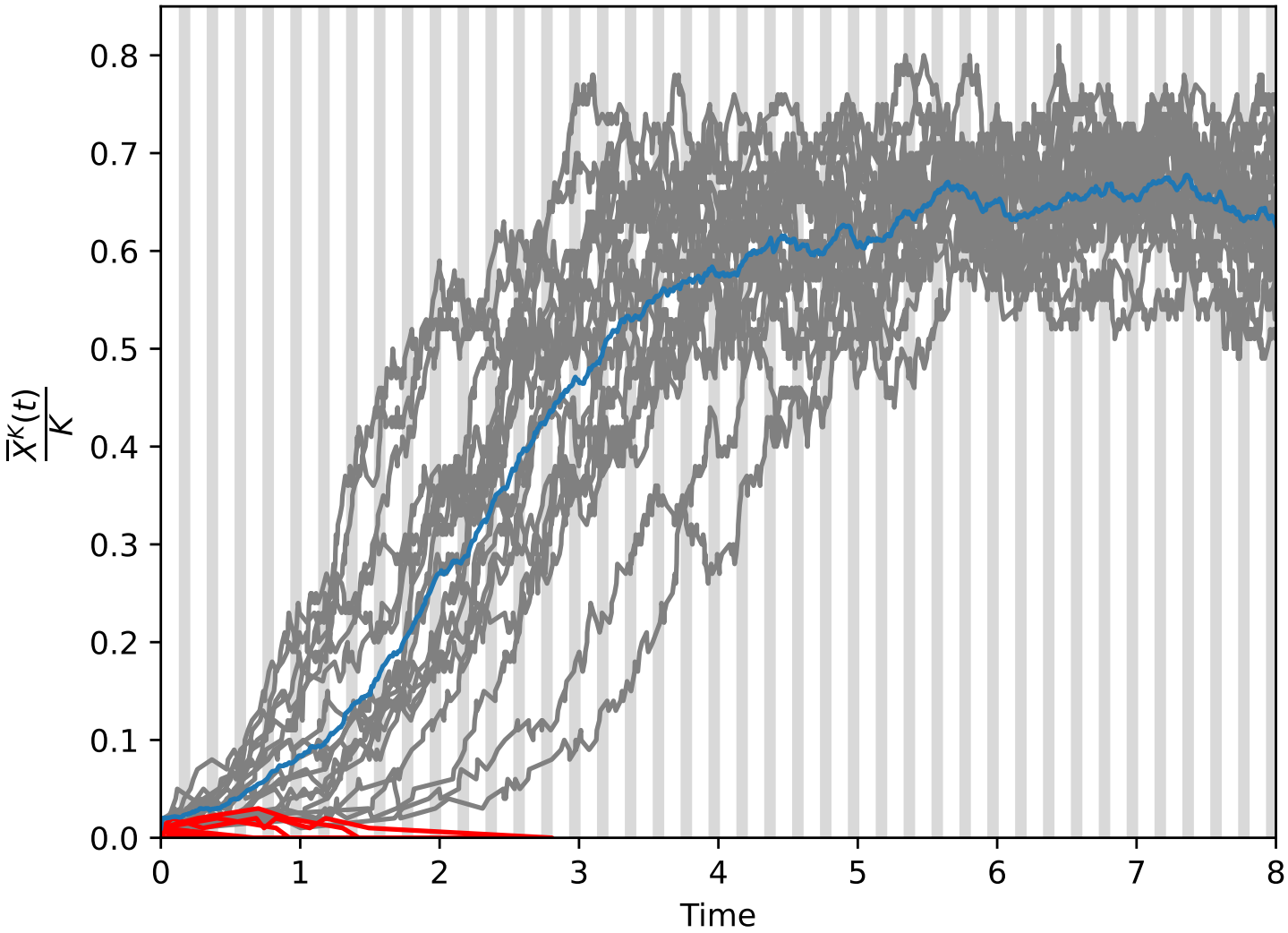

Figure: **Periodic quasistationary distribution and Homogenization.** Parameters set: $K = 100, T = 0.2$. $\beta(t) = \beta_0\,(1-\gamma)$, $\beta_0 = 4.0$, $\gamma = 0.3$, $\mu = 1$.

Long period approximation

We restrict ourselves to step transmission functions

$$t \to \beta(t/T) = \beta_0 \, \mathbb{1}_{(0 \leq \frac{t}{T} \leq 1-\gamma)} \qquad (t \in [0, T]), \tag{3.2}$$

with $\gamma \in (0, 1)$ and $\beta_0 > \mu$.

- The take-off probability: if $t_0 \in (t_c^K, 1-\gamma)$

$$\mathbb{P}\left(\text{take off} \mid X(t_0 T) = 1\right) \simeq \begin{cases} 1 - \frac{\mu}{\beta_0} & \text{if} \quad 0 < t_0 < t_c^K \, . \\ 0 & \text{if } t_0 > t_c^K \, . \end{cases} \tag{3.3}$$

where

$$t_c^K = 1 - \gamma - \frac{\log K}{T(\beta_0 - \mu)} \tag{3.4}$$

Long period approximation

- The probability of surviving the **first period**, conditionally on *take-off* is:

$$p_{per} \simeq 1 - (1 - e^{-\gamma\mu T})^{K x_{eq}} . \tag{3.5}$$

where x_{eq} the equilibrium value.
Indeed:

  - The probability that one infected individual alive at time $(1-\gamma)\,T$ survives the winter period is $e^{-\gamma\mu T}$
  - Conditionally on $X((1-\gamma)T) = M$ the probability that one individual survives the first period is $1 - \left(1 - e^{-\gamma\mu T}\right)^M$
  - We make the approximation $X((1-\gamma)T) \simeq K x_{eq}\,((1-\gamma)T)$

Long period approximation

We can define a critical capacity as

$$K_C = \frac{e^{\gamma\mu T}}{x_{eq}}\,. \tag{3.6}$$

- If $K \ll K_C$, then $p_{per} \simeq 0$ and thus, even if there is a take off, with high probability the pathogen will not survive the first period.
- If $K \gg K_C$, the pathogen survives is a geometric random variable of parameter $1 - p_{per}$,

$$\mathbb{E}\left[\tau_0^{(K,T)} \mid \text{take off}\right] \simeq T\frac{1}{1-p_{per}} \simeq T(1-e^{-\gamma\mu T})^{-Kx_{eq}}\,. \tag{3.7}$$

$\Rightarrow$ The mean extinction time is thus exponential in the carrying capacity.

Long period approximation

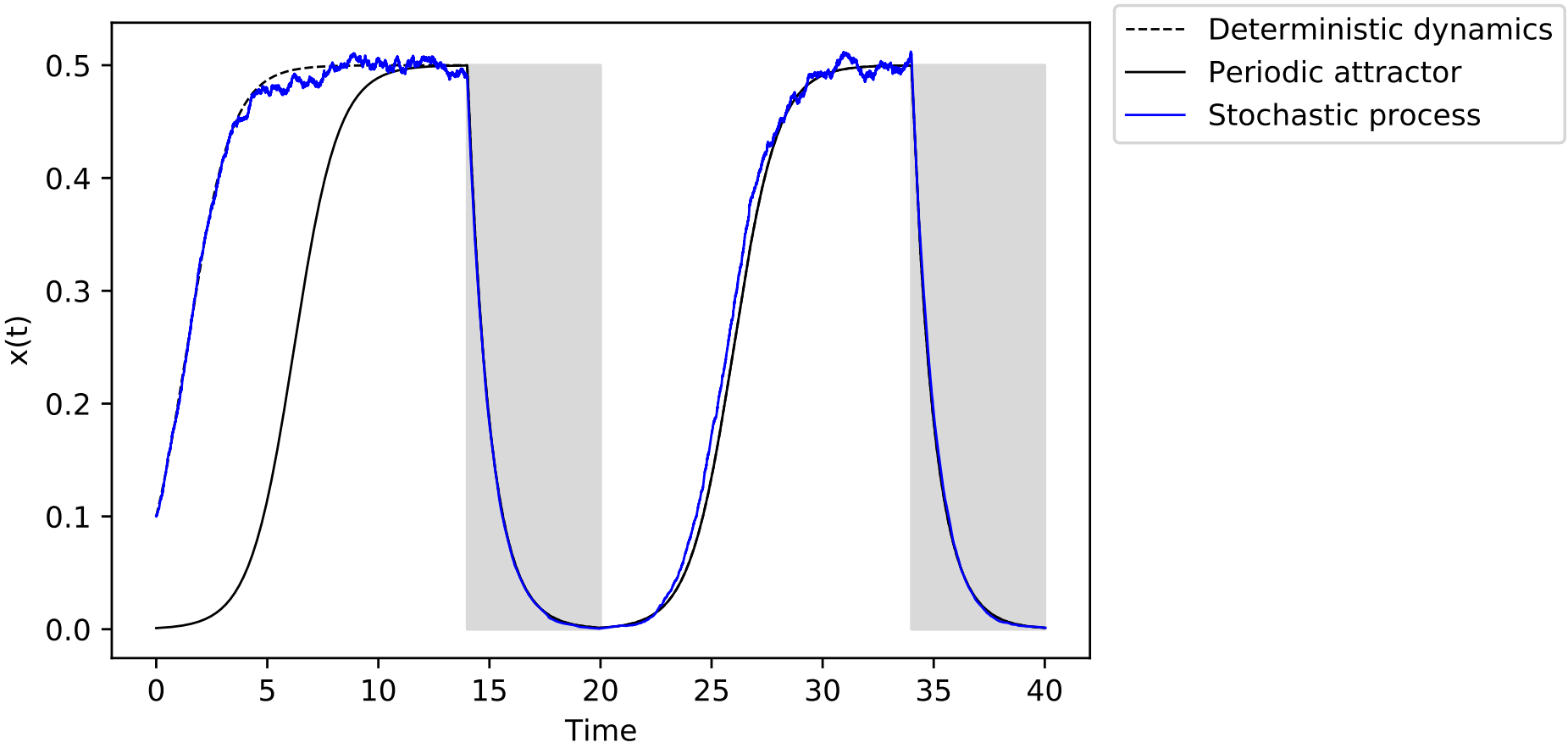

Figure: **The periodic attractor in deterministic and stochastic model**. Parameter values : $\mu = 1, \gamma = 0.3, \beta_0 = 2, T = 20, \beta(t) = \beta_0 \mathbb{1}_{(0 \leq \lfloor t/T \rfloor < 1-\gamma)}$, $X^{(K,T)}(0) = 10$, $x_0 = 0.1$, $K = 10^4$, $T = 20$.

The optimal timing of disease control strategies

- Let $\pi_G T, \pi_C T$ and $\pi_B T$: the **Good**, **Controlled** and **Bad** periods

$$\beta_{GCB} = \begin{cases} \beta_G & 0 \leq t/T < \pi_G \\ \beta_C & \pi_G \leq t/T < \pi_G + \pi_C \\ 0 & \pi_G + \pi_C \leq t/T < 1 \end{cases}, \beta_{CGB} = \begin{cases} \beta_C & 0 \leq t/T < \pi_C \\ \beta_G & \pi_C \leq t/T < \pi_G + \pi_C \\ 0 & \pi_G + \pi_C \leq t/T < 1 \end{cases} \tag{4.1}$$

- **The risk** is defined as the probability that a pathogen introduced randomly in the **first period** $[0, T]$ manages to **survive** the **first period** :

$$r = \frac{1}{T} \int_0^T p_1(t_0)\, dt_0 = \int_0^1 p_1(t_0 T) dt_0\,, \tag{4.2}$$

with $p_1(t_0 T) = \mathbb{P}\left(X^{(K,T)}(T) > 0 \mid X^{(K,T)}(t_0 T) = 1\right)$.

Heuristics for large periods

First case : weak control : $\beta_C > \mu$.

- $$r_{GCB} \simeq (\pi_G(1-\mu/\beta_G)+\pi_C(1-\mu/\beta_C))\Big(1-(1-e^{-\pi_B\mu T})^{K(1-\mu/\beta_C)}\Big) \tag{4.3}$$

- $$r_{CGB} \simeq (\pi_G(1-\mu/\beta_G)+\pi_C(1-\mu/\beta_C))\Big(1-(1-e^{-\pi_B\mu T})^{K(1-\mu/\beta_G)}\Big) \tag{4.4}$$

Therefore, since $\beta_C < \beta_G$, we have for the approximations $r_{CGB} > r_{GCB}$.
$\Rightarrow$ The strategy GCB is better than the strategy CGB. This is confirmed by the simulations, see Figure 4.

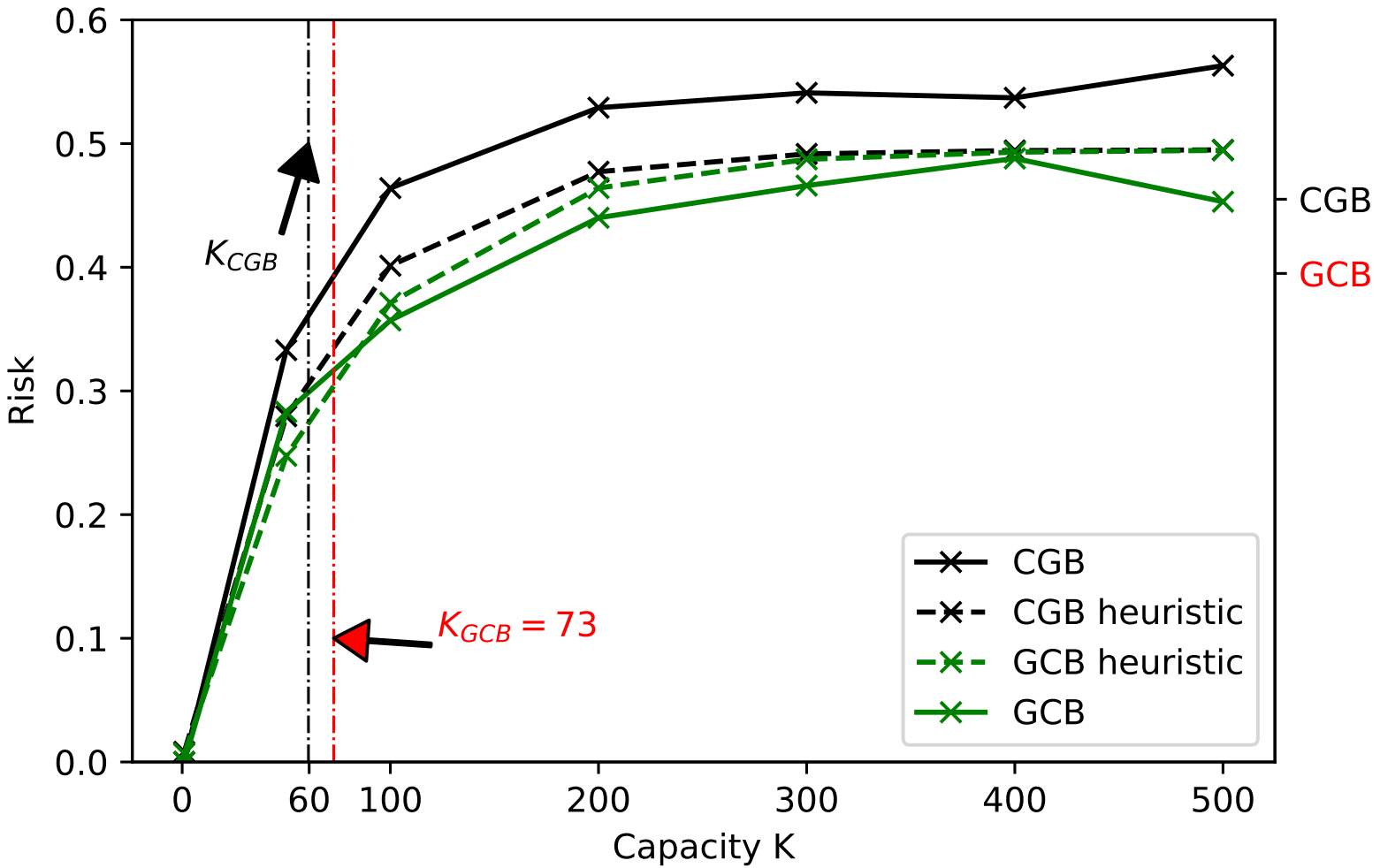

Figure: **Weak Control : The risk as a function of the capacity K of the environment**
Parameters : $\beta_G = 5$, $\beta_C = 2$, $\mu = 0.5$, $T = 20$, $\pi_G = \pi_C = 0.3$, $\pi_B = 0.4$.

Heuristics for large periods

Second case : strong control: $\beta_C < \mu$.

- $$r_{GCB} \simeq \pi_G(1-\mu/\beta_G)\left(1-(1-p_{GCB})^{K(1-\mu/\beta_G)}\right) \tag{4.5}$$
$$r_{CGB} \simeq \pi_G(1-\mu/\beta_G)\left(1-(1-p_{CGB})^{K(1-\mu/\beta_G)}\right) \tag{4.6}$$

- The probability of survival time t for a birth death process with birth rate $\lambda(s)$ and death rate $\mu(s)$ is given by

$$\mathbb{P}\left(X(t)>0|X(0)=1\right) = \left(1+\int_0^t \mu(s)e^{-\varphi(s)\,ds}\right)^{-1} \tag{4.7}$$

with $\varphi(t) = \int_0^t(\lambda(s)-\mu(s))\,ds$.
$\Rightarrow r_{GCB} < r_{GBC}$

Therefore GCB is better than CGB (see Figure 5).

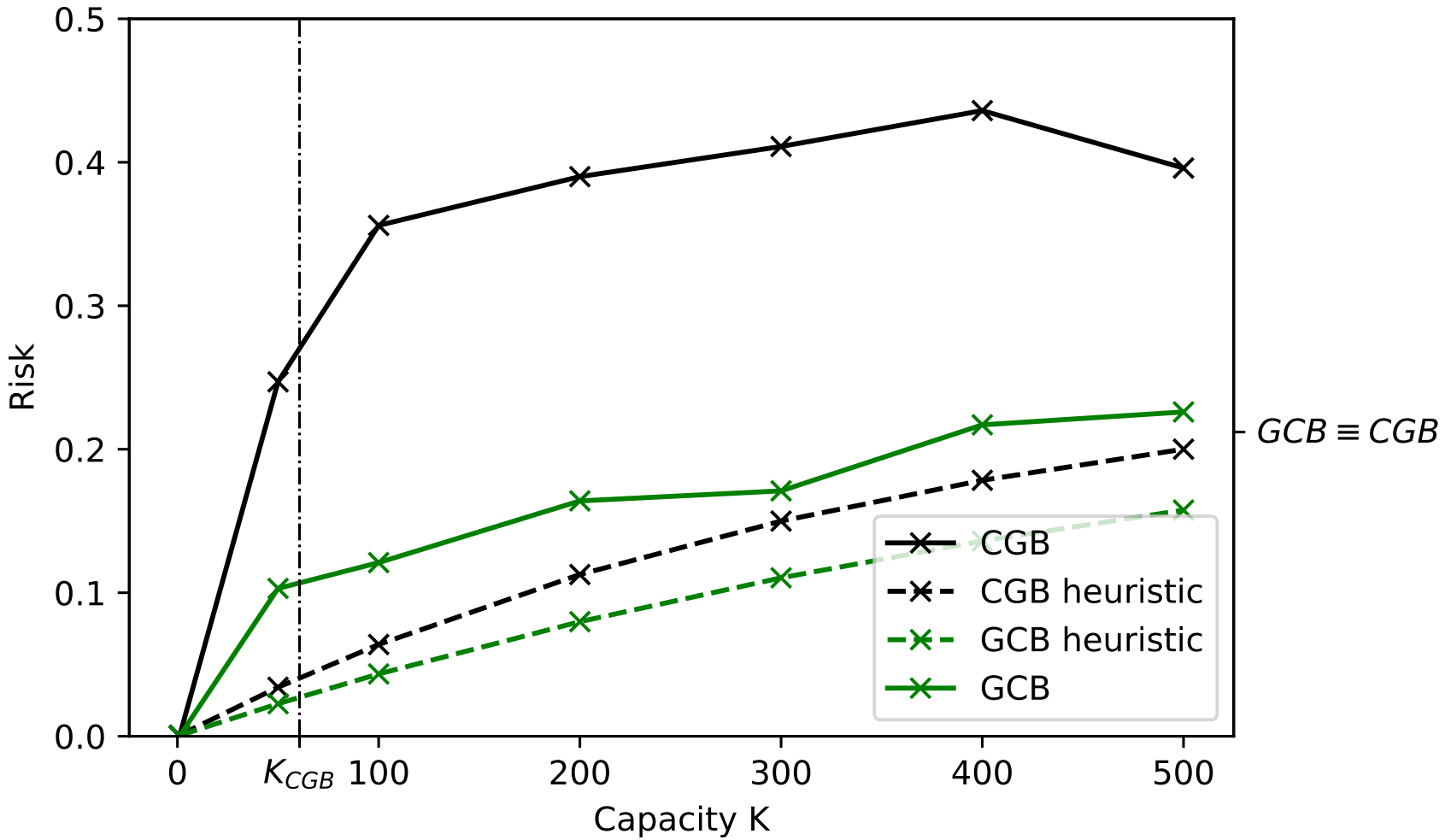

Figure: **Strong control : The risk as a function of the capacity K of the environment**
Parameters : $\beta_G = 4$, $\beta_C = 0.2$, $\mu = 0.5$, $T = 20$,$\pi_G = \pi_C = 0.3$, $\pi_B = 0.4$.

Comparison with the branching process (no density dependence)

- Risk of pathogen emergence is well approximated by

$$\tilde{r} = \int_0^1 (1 - \frac{\mu}{\beta(t)}) \mathbb{1}_{(t \notin WIC)} dt, \quad \text{with } WIC = \{t : \exists s > t, \varphi(s) > \varphi(t)\} \tag{4.8}$$

- $\beta_G > \beta_C > \mu$,

$$\tilde{r}_{GCB} < \tilde{r}_{CGB} \tag{4.9}$$

  Therefore, as in the density dependent case, it is better to act just before the winter (Figure 4).

- $\beta_G > \mu > \beta_G$,

$$\tilde{r}_{GCB} = \tilde{r}_{CGB} = \frac{\varphi(1)}{\beta_G} \tag{4.10}$$

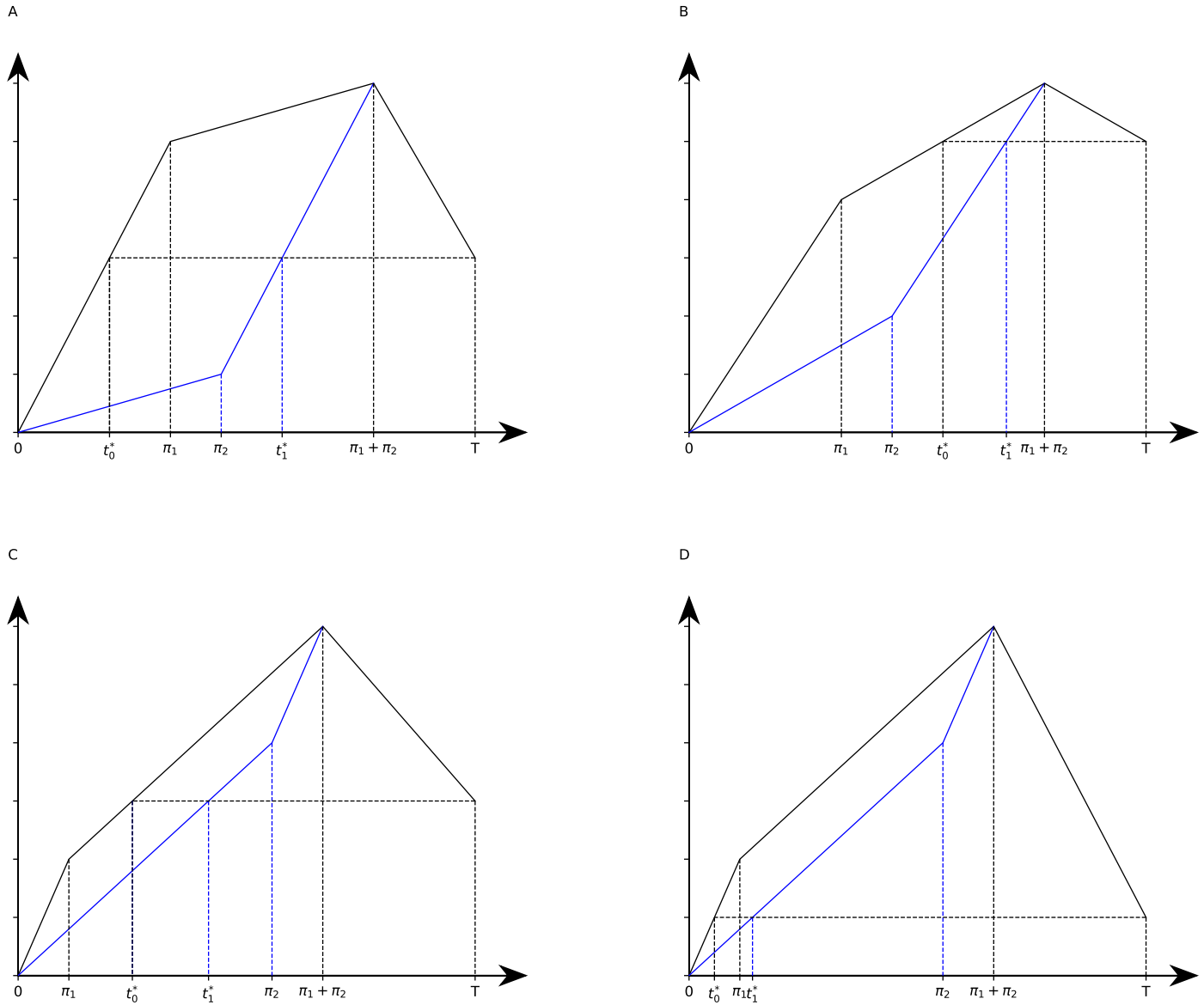

Figure: **Risk for branching process with weak control : GCB vs CGB.** The integrated rate is drawn in black for strategy GCB and in blue for strategy CGB

Reference

[1] Hå kan Andersson and Boualem Djehiche. A threshold limit theorem for the stochastic logistic epidemic. *J. Appl. Probab.*, 35(3):662–670, 1998. ISSN 0021-9002. doi: 10.1239/jap/1032265214. URL https://doi.org/10.1239/jap/1032265214.

[2] J. N. Darroch and E. Seneta. On quasi-stationary distributions in absorbing discrete-time finite Markov chains. *J. Appl. Probability*, 2:88–100, 1965. ISSN 0021-9002. doi: 10.2307/3211876. URL https://doi.org/10.2307/3211876.

[3] J. N. Darroch and E. Seneta. On quasi-stationary distributions in absorbing continuous-time finite Markov chains. *J. Appl. Probability*, 4:192–196, 1967. ISSN 0021-9002. doi: 10.2307/3212311. URL https://doi.org/10.2307/3212311.

[4] Thomas G. Kurtz. Strong approximation theorems for density dependent Markov chains. *Stochastic Processes Appl.*, 6(3):223–240, 1977/78. ISSN 0304-4149. doi: 10.1016/0304-4149(78)90020-0. URL https://doi.org/10.1016/0304-4149(78)90020-0.

Thanks for listening!