Asymptotic properties of the K in a row design

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MaSeMo : Markov, Semi-Markov Models and Associated Fields

(from Theory to Application and back) 1-4 Jul 2025 Paris (France)

Contents

Framework: percentile finding

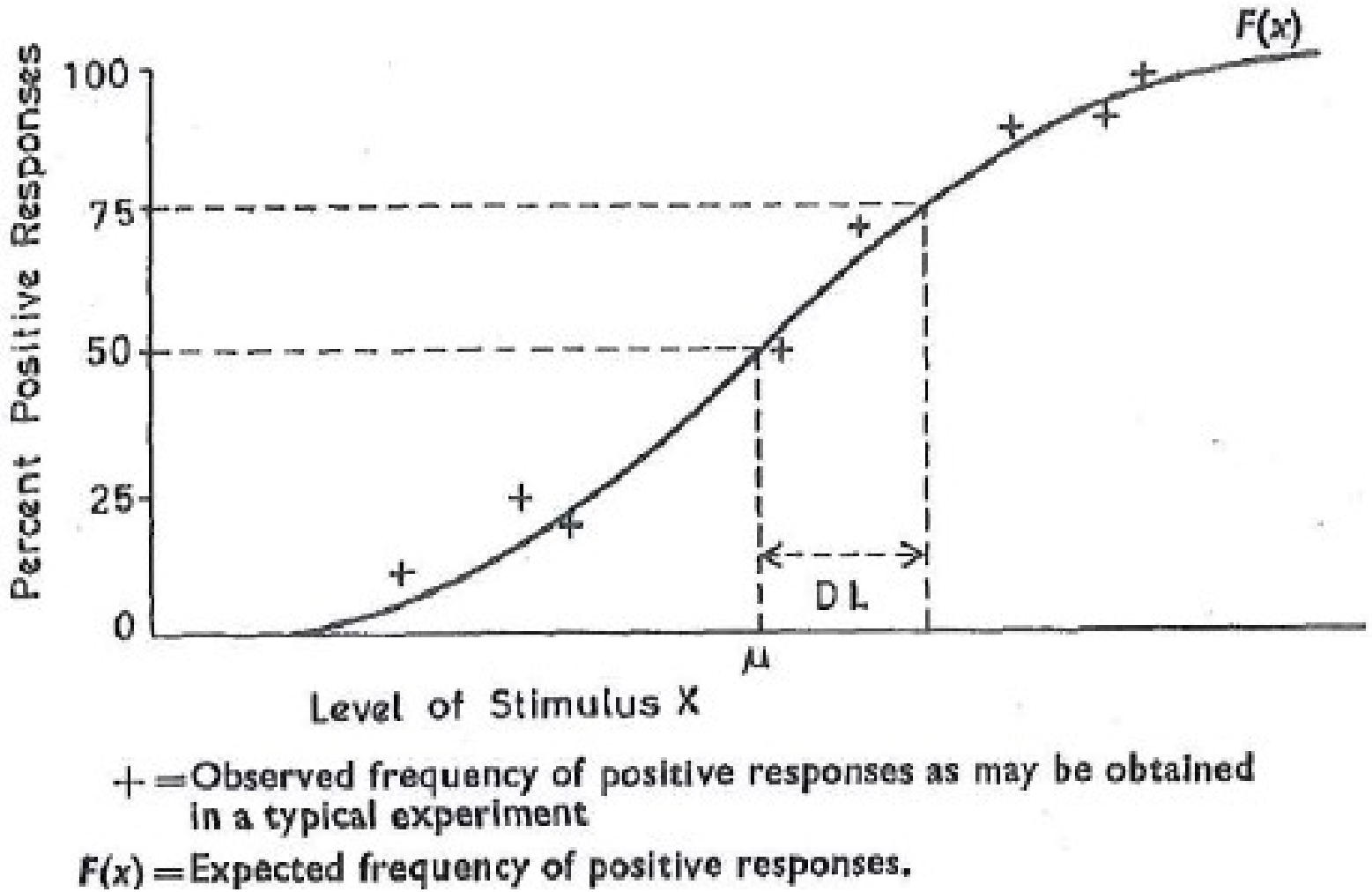


Figure: Wheteril and Levitt (1965). Stimulus and response.

Framework: toxicity of a new drug

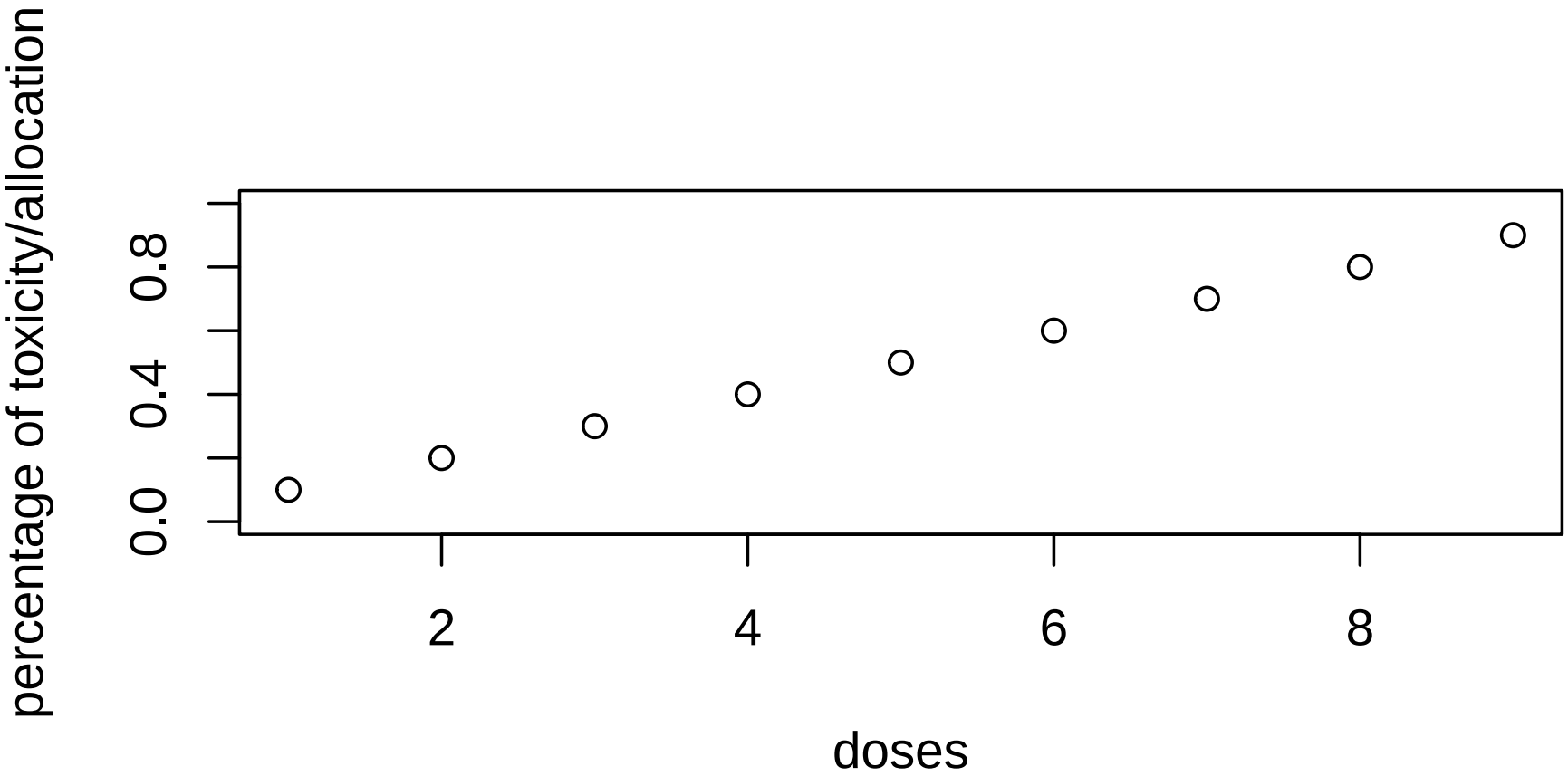


Figure: Response toxicity for 10 different doses.

Framework: toxicity of a new drug

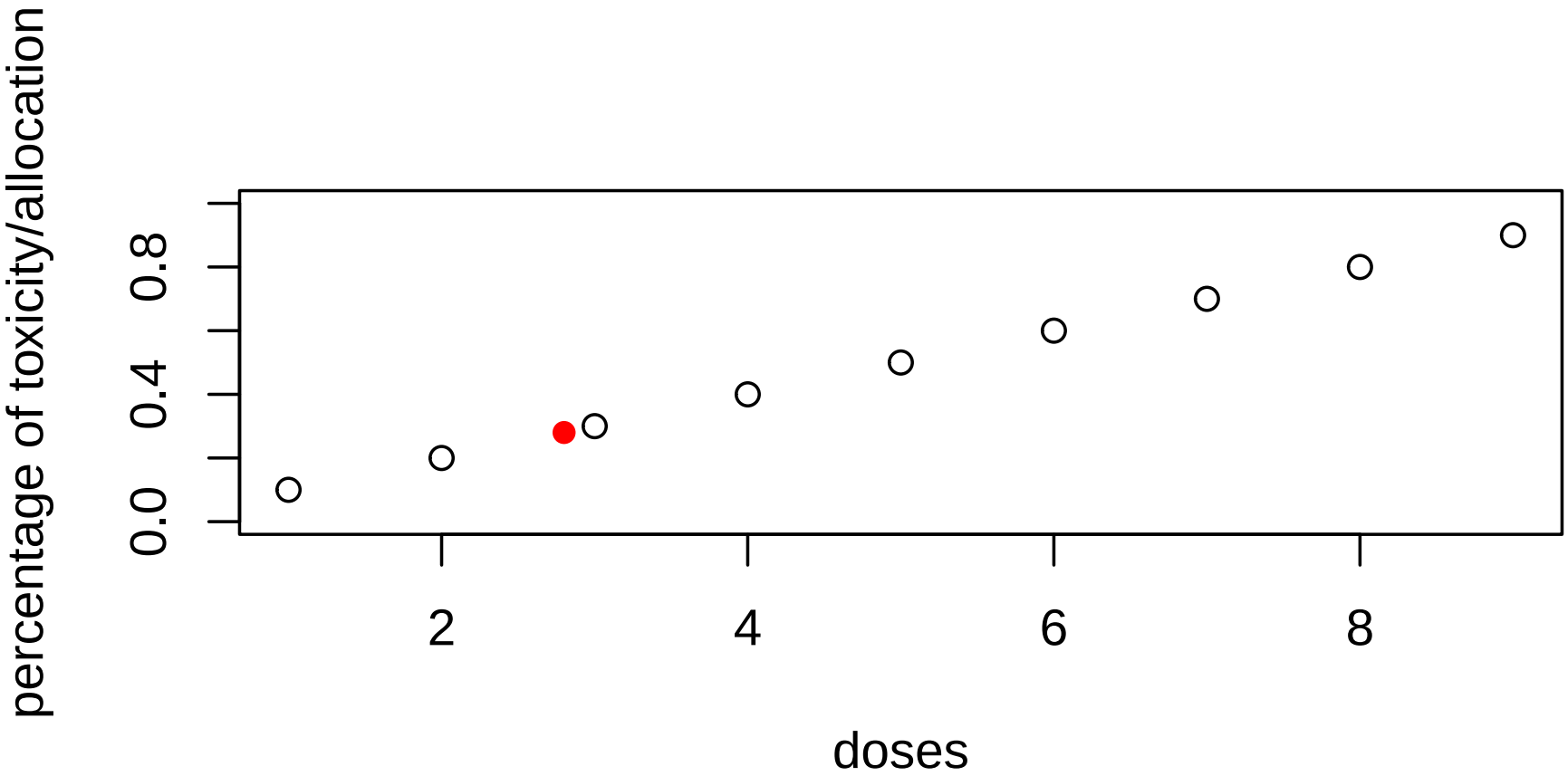


Figure: We look for the percentile 0.28

Framework: toxicity of a new drug

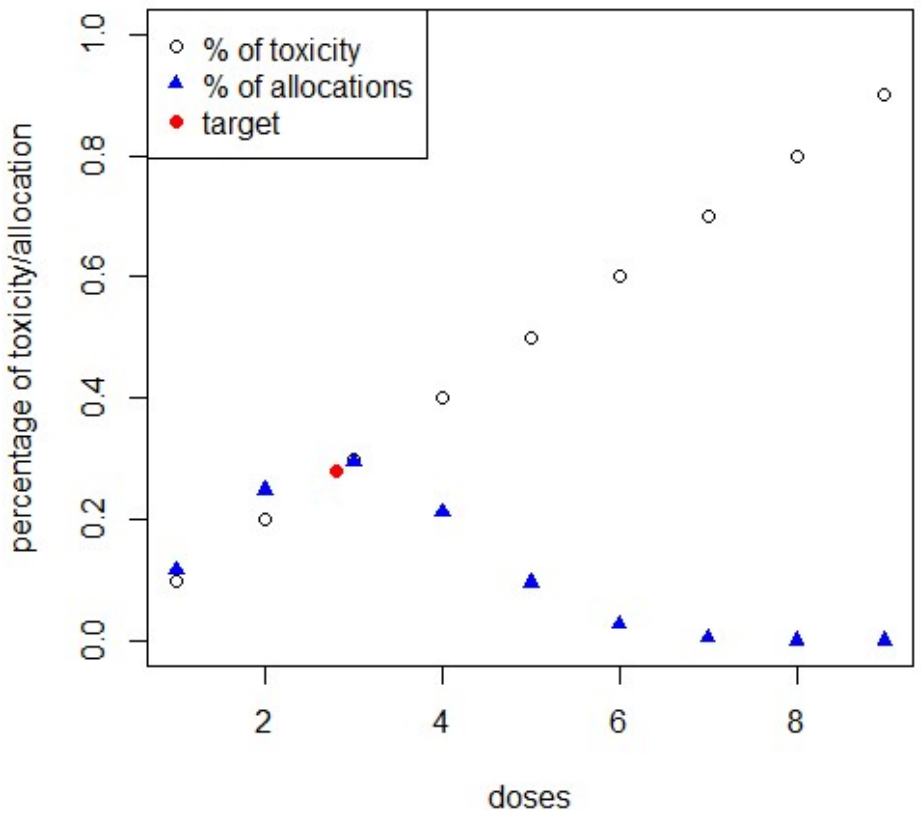


Figure: We consider a design that concentrates allocations around the target

Framework: percentile finding

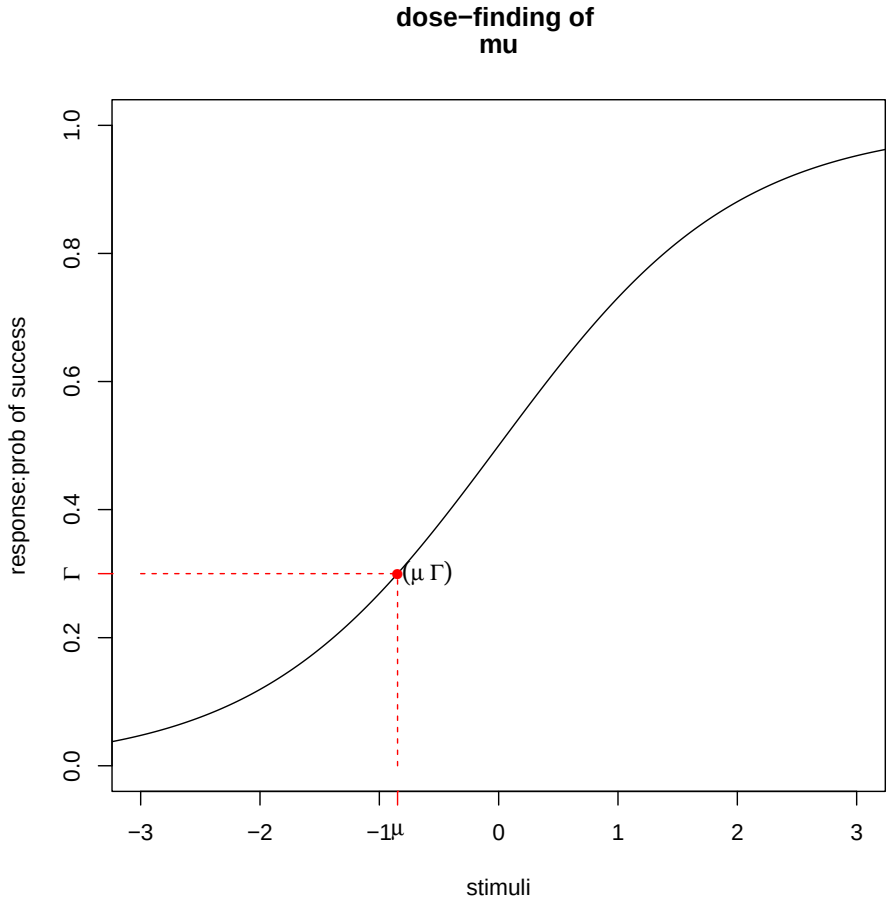


Figure: Our goal is to find the stimulous which is perceived by the Γ percent of the population.

Notation

- The dose space (design space): $\mathcal{X}$
- Permissible doses: $\mathcal{X}_0 = \{d_1 < d_2 < \cdots < d_M\} \subset \mathcal{X}$
- Design: $\{X_n\}_{n\in\mathbb{N}}$ sequence of doses assigned to patients.
- The nth patient response is:

$$Y_n = \begin{cases} 1 & \text{if toxicity (or efficacy) ;} \\ 0 & \text{otherwise} \end{cases}$$

- Response function

$$P(Y_n = 1 \mid X_n = x) = F(x), \quad P(Y_n = 0 \mid X_n = x) = \overline{F}(x), \quad x \in \mathcal{X}$$

Assumption: the toxicity increases with the dose.

Dose finding designs

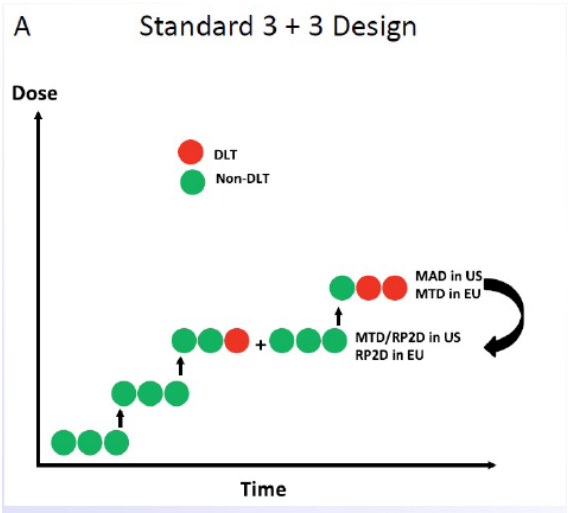


Figure: I

- Remains a favored design for phase I trials.(Rogatko et al. Clin. Canc. Resch,2005)
- The dose chosen has a toxicity rate in [0.16, 0.27] (Ivanova (2006), Stat. Med.), it can be out of the therapeutical area.

Dose finding designs: Bayesian methods (CRM)

- Assume as response function

$$F(x) = P(Y_n = 1 | X_n = x;\ a) = (tanh(x) + 1)^a$$

- Prior distribution for a [exponential, normal, etc]
- A posteriori response distribution $\widetilde{F}$
- Next patient assigned to dose d^*, the closest dose to the desired dose:

$$d^* = min_{x \in \mathcal{X}_0} |\widetilde{F}(x) = P(Toxicity | Dose = x) - \Gamma|$$

First order Up and down designs

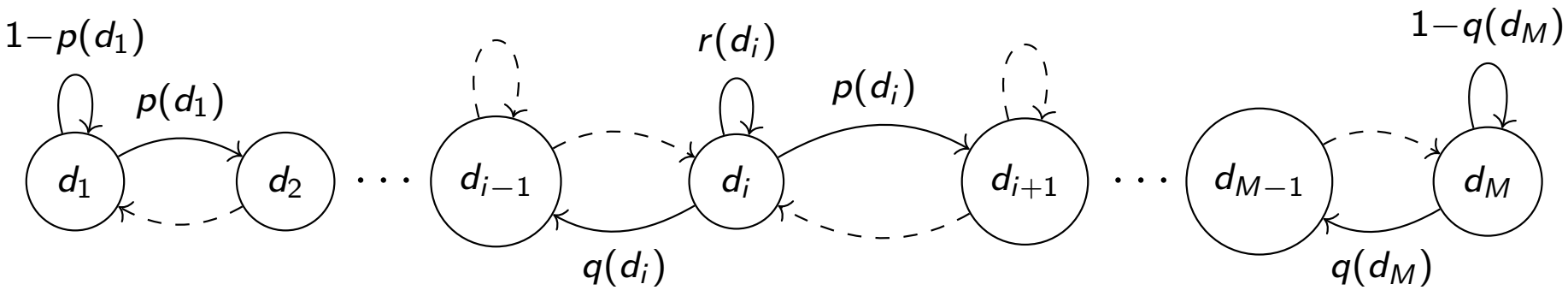


Figure: Basic structure that represents the dynamics for first order Up and down designs.

- $p(x)$ is a strictly decreasing function in $\mathcal{X}$.
- In practice: piling up doses in the borders means a bad selection of permissible doses (a bad design).

K-in-a-row design. Definition

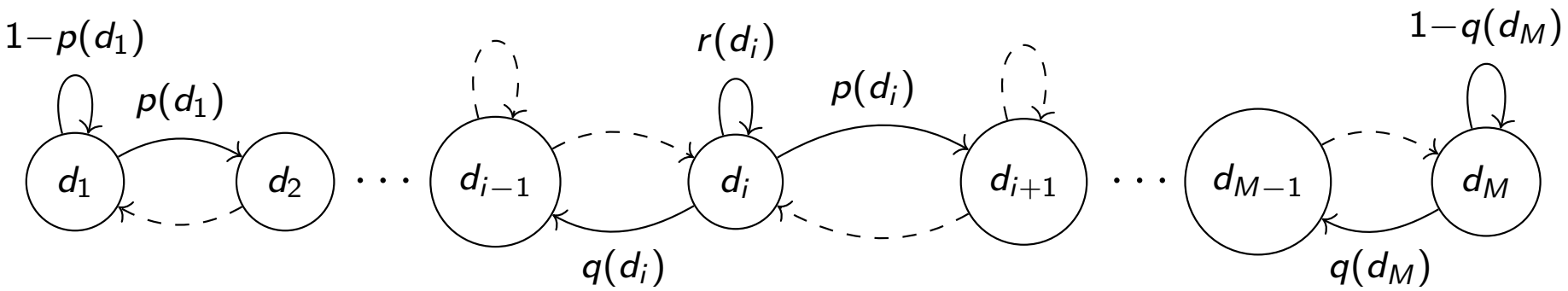
- When $\Gamma < 0.5$, $X_n = d_i$, $d_0 = d_1$ and $d_{M+1} = d_M$

$$X_{n+1} = \begin{cases} d_{i-1} & \text{if } Y_n = 1; \\ d_i & \text{if } Y_n = 0 \text{ and } X_{n-w} \neq d_i \text{ for some } 1 \leq w < K-1, \\ d_{i+1} & \text{if } Y_n = 0 \text{ and } X_{n-K+1} = X_{n-K+2} = \cdots = X_n = d_i. \end{cases}$$

In words

$$X_{n+1} = \begin{cases} \text{One down} & \text{if toxicity ;} \\ \text{One up} & \text{if } K \text{ consecutive non-toxicities;} \\ \text{Stay} & \text{non-toxicity but less than } K \text{ consecutive.} \end{cases}$$

First order UD: Stationary distribution



• As UD design is a regular and finite Markov Chain: there exists a stationary distribution $\boldsymbol{\pi} = \{\pi_i\}_{i=1}^{M}$

$$\pi_{i+1} = \pi_1 \prod_{j=1}^{i} \lambda_j,\ i = 1, \ldots, M-1; \qquad \pi_1 = \left(1 + \sum_{i=2}^{M} \prod_{j=1}^{i-1} \lambda_j\right)^{-1}. \quad (1)$$

with

$$\lambda_i = \frac{p(d_i)}{q(d_{i+1})}.$$

Unimodality

- As $p(x)$ is decreasing

$$\lambda_i = \frac{p(d_i)}{q(d_{i+1})} \begin{matrix} \downarrow \\ \uparrow \end{matrix} = \downarrow \qquad i = 1, \ldots, M-1$$

- As the sequence $\{\lambda_i\}_{i=1}^{M-1}$ is decreasing, $\boldsymbol{\pi}$ is unimodal.

- **Proposition:** Let i^* the smallest integer such that $\lambda_{i^*} \leq 1$, then the mode is at d_{i^*}, and spans to d_{i^*+1} when $\lambda_{i^*} = 1$.

The balance point

Definition

The *balance point* is the dose $x^* \in \mathcal{X}$ such that $p(x^*) = q(x^*)$.

Theorem

Consider an UD design with balance point $d_1 < x^* < d_M$. *Let*

$$d_{i'} = min_i\{d_i \in \mathcal{X}_0 : \ d_i > x^*\}$$

denote the distance between them by $\Delta = d_{i'} - d_{i'-1}$; *and let* $x' = \arg_x\{p(x) = q(x + \Delta)\}$.

The mode of π *is* $d^* = \begin{cases} d_{i'} & if\ d_{i'-1} < x'; \\ d_{i'-1} & if\ d_{i'-1} \in (x', x^*). \end{cases}$

Example

- Consider $\Gamma \leq 0.50$ and $b = \Gamma/(1-\Gamma)$

$$p(x) = b[1 - F(x)]; \quad r(x) = (1-b)[1 - F(x)]; \quad q(x) = F(x)$$

Then $x^* = F^{-1}(\Gamma)$ AND the mode of $\boldsymbol{\pi}$ will stay close to $F^{-1}(\Gamma)$

- This feature makes this family of UD designs (Durham and Flournoy(1994), Stat. Dec. Theory Rel. topics., conference book) appropriate for estimating any percentile of F.

Definition

- When $\Gamma < 0.5$, $X_n = d_i$, $d_0 = d_1$ and $d_{M+1} = d_M$

$$X_{n+1} = \begin{cases} d_{i-1} & \text{if } Y_n = 1; \\ d_i & \text{if } Y_n = 0 \text{ and } X_{n-w} \neq d_i \text{ for some } 1 \leq w < K-1, \\ d_{i+1} & \text{if } Y_n = 0 \text{ and } X_{n-K+1} = X_{n-K+2} = \cdots = X_n = d_i. \end{cases}$$

In words, if a toxic response is observed, the next allocation is the immediately lower permissible dose; otherwise, the same dose is administered until K consecutive non-toxic responses are observed, after which the next individual receives the immediately higher permissible dose.

It is not a Markov chain

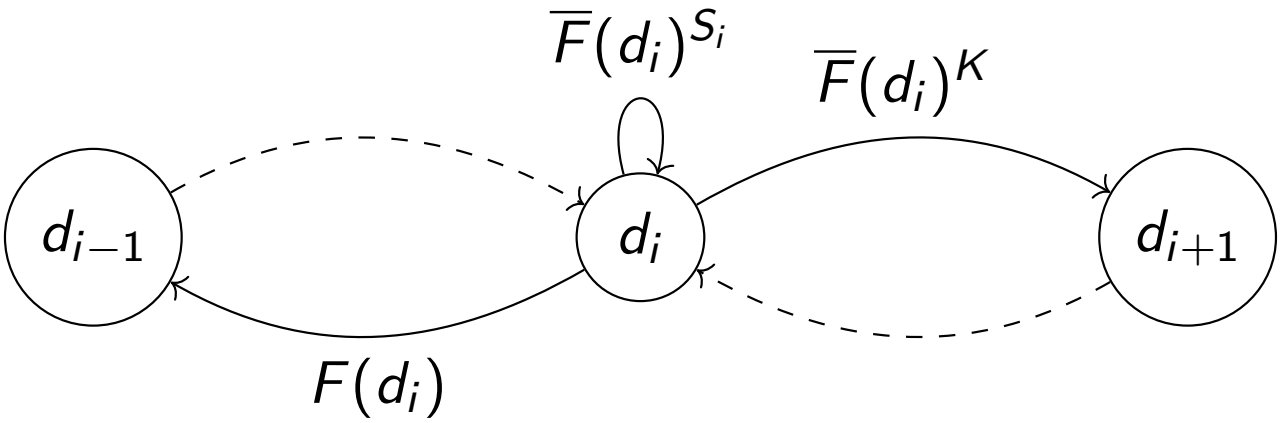


Figure: Proxy to explain the K-in-a-row design.

$0 \leq S_i < K$ is a random variable

A representation of the K-in-a-row

- IF the last $s-1$ patients are assigned to d_i without toxicity responses

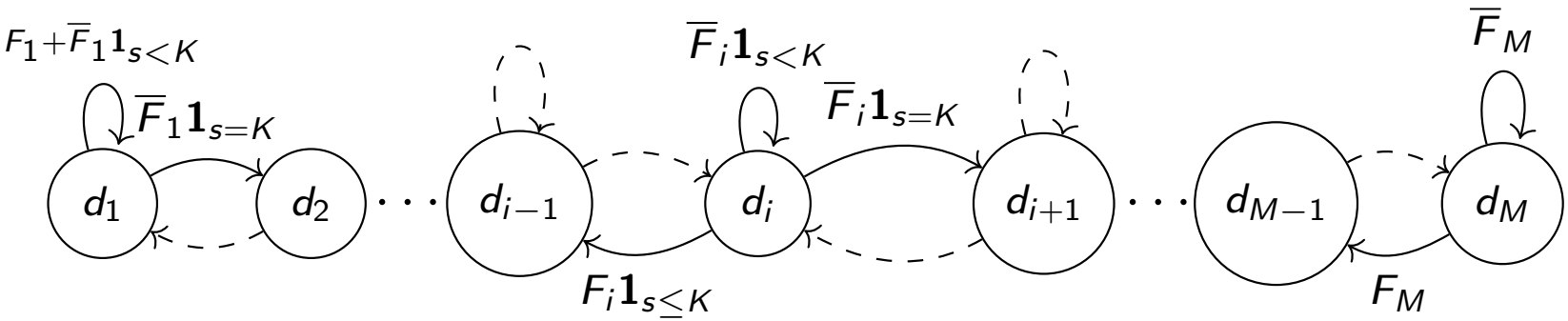


Figure: $\mathbf{1}_A$ is the indicator function of the event A.

The K-in-a-row as a semi-Markov process

Subrogated to the process $\{X_n\}_{n\in\mathbb{N}}$, we define two processes

- Jumping times: $T_r = min\{n > T_{r-1} : X_n \neq X_{n-1}\}, \quad r \geq 1., \ T_0 = 1.$
- Embedded chain: $Z_r = X_{T_r}$, $r \geq 1$ points to the dose where X_n arrives immediately after a jump.
- For any $n \geq 1$,

$$X_n = Z_r, \ T_r \leq n < T_{r+1}. \tag{2}$$

From Chapter 10 in Cinlar, $\{Z_r, T_r\}_{r\geq 0}$ is a homogeneous Markov renewal process in the state space $\mathcal{X}_0$ and, from (2), $\{X_n\}_{n\in\mathbb{N}}$ is a Semi-Markov process. From Barbu-Limnios, $\{X_n\}_{n\in\mathbb{N}}$ is a Semi-Markov process in discrete time in the state space $\mathcal{X}_0$.

The "sojourn time" in a dose

- S_i number of patients consecutively allocated in the dose d_i.

$$\mathrm{P}(T_{r+1} - T_r = s | X_{T_r} = d_i) = \mathrm{P}(S_i = s), \quad i = 1, \ldots, M, \tag{3}$$

- The expectations are

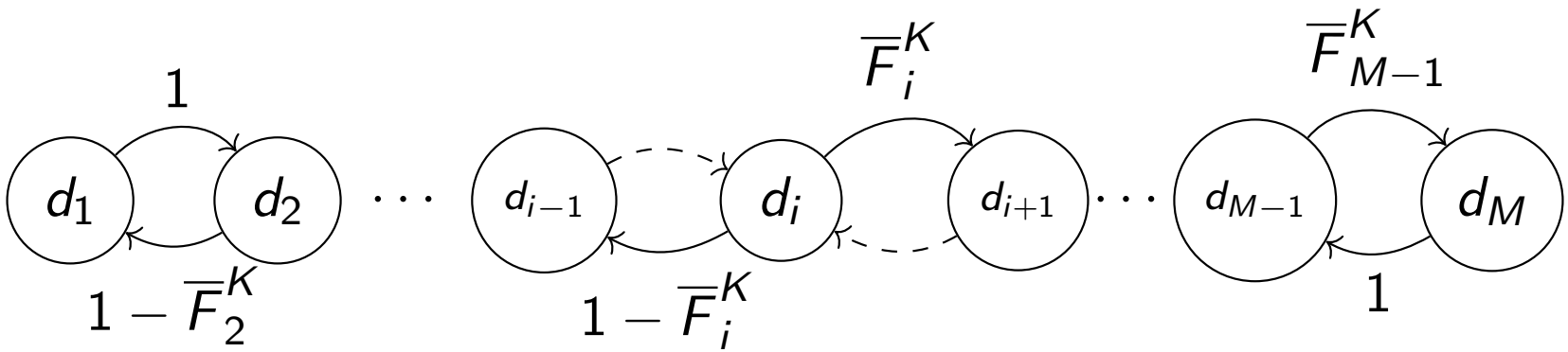
$$\mathrm{E}[S_i] = \frac{1 - \overline{F}_i^K}{F_i}; \quad S_i \in \{1, \ldots, K\} \ \ 2 \leq i \leq M - 1 \tag{4}$$

$$\mathrm{E}[S_1] = \frac{1 - \overline{F}_1^K}{F_1 \overline{F}_1^K} \quad \text{and} \quad \mathrm{E}[S_M] = \frac{1}{F_M} \quad S_1 \text{ and } S_M \text{ unbounded} \tag{5}$$

(Philippou A et al. (1983) Stat. Prob. Lett.)

The embedded chain

- It is a random walk with reflecting barriers:



Proposition

The process $\{Z_r\}_{r\in\mathbb{N}}$ is an UDD with balance point x^*. The stationary distribution $\{\pi_i^Z\}_{i=1}^M$ is unimodal.

From now on, x^* is $F(x^*) = 1 - 0.5^{1/K}$.

Scope of the K-in-a-row

- The balance point is a proxy of the mode's location

K	1	2	3	4	5	6	7	8
$1-0.5^{1/K}, \Gamma \leq .5$	.500	.293	.206	.159	.129	.109	.094	.083
$0.5^{1/K}, \Gamma \geq .5$	.500	.707	.794	.841	.871	.891	.906	.917

Table: Quantiles of KR balance points for $K = 1, \ldots, 9$. $1 - .5^{1/K}$ for $\Gamma \leq 0.5$ and $.5^{1/K}$ for $\Gamma \geq 0.5$.

The mean time in a dose

• The mean time that, in the stationary setting, the process stays in the same state

$$\mathrm{E}[S] = \sum_{i=1}^{M} \mathrm{E}[S_i]\pi_i^Z.$$

• This value appears in the expression of the stationary distribution of the KR process.

• Observe that for each $r \in \mathbb{N}$

$$\mathrm{E}[T_{r+1} - T_r] = \sum_{i=1}^{M} \mathrm{E}[T_{r+1} - T_r \mid Z_r = d_i]\mathrm{P}(Z_r = d_i)$$
$$\to \mathrm{E}[S],\ r \to \infty.$$

Stationary distribution

- Considering

$$\pi_i = \lim_{n\to\infty} \mathrm{P}(X_n = d_i | X_0 = d_j), \quad i, j = 1, \ldots, M.$$

Theorem

The process $\{X_n\}_{n\in\mathbb{N}}$ *has stationary distribution* $\{\pi_i\}_{i=1}^{M}$, *where*

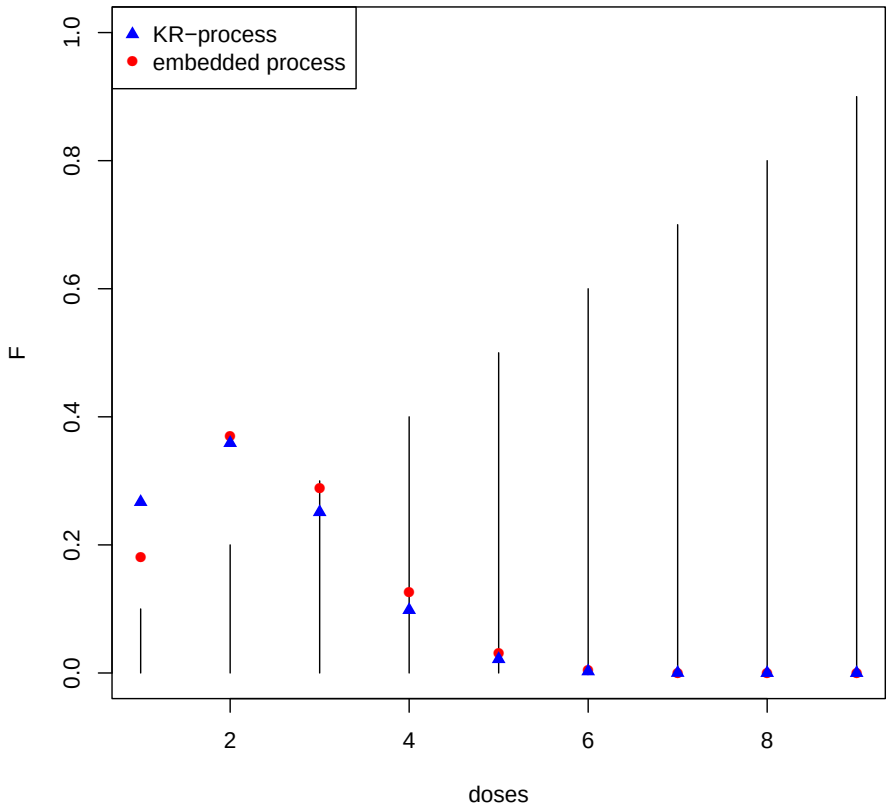
$$\pi_i = \pi_i^Z \frac{\mathrm{E}[S_i]}{\mathrm{E}[S]}, \quad i = 1, \ldots, M, \tag{6}$$

Example

Down-Shifting $P[S_i = s]$									
i	1	2	3	4	5	6	7	8	9
F_i	0.1	0.2	0.3	0.4	0.5	0.6	0.7	0.8	0.9
$\mathrm{E}[S_i]$	3.72	2.44	2.19	1.96	1.75	1.56	1.39	1.24	1.11
π_i^Z	0.18	0.37	0.29	0.13	0.03	0.004	0.0002	7E-6	6E-8
π	0.271	0.36	0.25	0.1	0.02	0.003	0.0001	3E-6	2E-8

Table: Mean sojourn times in each dose and stationary distributions for the 3R design and its embedded process. Observe that $\mathrm{E}[S] = 2.51$.

Example



Unimodality

Proposition

For each dose d_i, $i = 1, \ldots, M-1$, the asymptotic adjacent dose-allocation ratio is

$$\lambda_i = \frac{\pi_{i+1}}{\pi_i} = \frac{F_i}{F_{i+1}} \left(\frac{\overline{F}_i^K}{1 - \overline{F}_i^K} \right).$$

Besides, for each i,

$$\pi_i = \pi_1 \prod_{j=1}^{i-1} \lambda_j, \; i = 2, \ldots, M; \quad \pi_1 = \left(1 + \sum_{i=2}^{M} \frac{F_1}{F_i} \prod_{j=1}^{i-1} \frac{\overline{F}_j^K}{1 - \overline{F}_j^K} \right)^{-1}. \quad (7)$$

Dynamics of the K-in-a-row

$$\lambda_i = \frac{a_i}{r_i}, \quad i = 1, \cdots, M-1$$

1. The ratio a_i is the *odds* that the embedded chain will increase from dose d_i for each $i = 1, \ldots, M$.

$$a_i = \frac{\overline{F}_i^K}{1 - \overline{F}_i^K} \text{ is } \begin{cases} > 1 & \text{if } d_i < x^*; \\ = 1; & \text{if } d_i = x^*; \\ < 1 & \text{if } d_i > x^*. \end{cases} \tag{8}$$

2. The toxicity *increase factor* from d_i to d_{i+1} is $r_i = F_{i+1}/F_i$ for each $i = 1, \ldots, M-1$. Note that $1/F_i > r_i > 1$.

Sketch of the proofs

Let r and a be two real values such that $r > 0$ and $a \in (0, 1)$; $K \geq 2$.

$$g_1(r) = \frac{r(1-ra)^K}{1-(1-ra)^K}$$
decreasing in $r \in (1, a^{-1})$.

$$g_2(a) = r\frac{a}{1-a}(1-a^{1/K})$$
increasing in $a \in (0, 1)$.

$\downarrow$ $\downarrow$

$\{\lambda_i\}_{i=1}^{M-1}$ is strictly decreasing.

$d_i \in \chi_0$, $d_i < x^*$ and $\lambda_i \leq 1$ THEN $d_{i+1} \geq x^*$.

Assume $\lambda_i < \lambda_{i+1}$, contradiction with

$$a_{i+1}r_i = \frac{r_i(1-r_iF_i)^K}{[1-(1-r_iF_i)^K]} \qquad F_{i+1} = r_iF_i = r\left(\frac{a}{1-a}\right)(1-a^{1/K})$$

Dynamics of the K-in-a-row

$$\lambda_i = \frac{a_i}{r_i} = \begin{cases} > 1 & \text{KR tends higher;} \\ = 1; & \text{equilibrium;} \\ < 1 & \text{KR tends lower.} \end{cases} \tag{9}$$

Unimodality

Theorem

Consider the KR Process $\{X_n\}_{n\in\mathbb{N}}$ *with space of permissible doses* $\chi_0 = \{d_1 < \ldots, < d_M\}$ *and*

$$F(d_1) < \cdots < F(d_M)$$

Then

- *The sequence* $\{\lambda_i\}_{i=1}^{M-1}$ *is strictly decreasing.*
- *The stationary distribution* $\{\pi_i\}_{i=1}^{M}$ *of* $\{X_n\}_{n\in\mathbb{N}}$ *is strongly unimodal.*

Location

Theorem

In the same conditions as the previous results, denote

$$i' = \begin{cases} M & \text{if } d_M < x^* \\ \min\{i : d_i > x^*\} & \text{else.} \end{cases}$$

The mode of $\{\pi_i\}_{i=1}^M$ *is*

1. d_1 if $d_1 \geq x^*$;
2. d_M if $d_M \leq x^*$;
3. $d_{i'-1}$ if $d_1 < x^* \leq d_M$ and $\lambda_{i'-1} < 1$;
4. $d_{i'}$ if $d_1 < x^* \leq d_M$ and $\lambda_{i'-1} > 1$;
5. $\pi_{i'-1} = \pi_{i'}$ if $d_1 < x^* < d_M$ and $\lambda_{i'-1} = 1$.

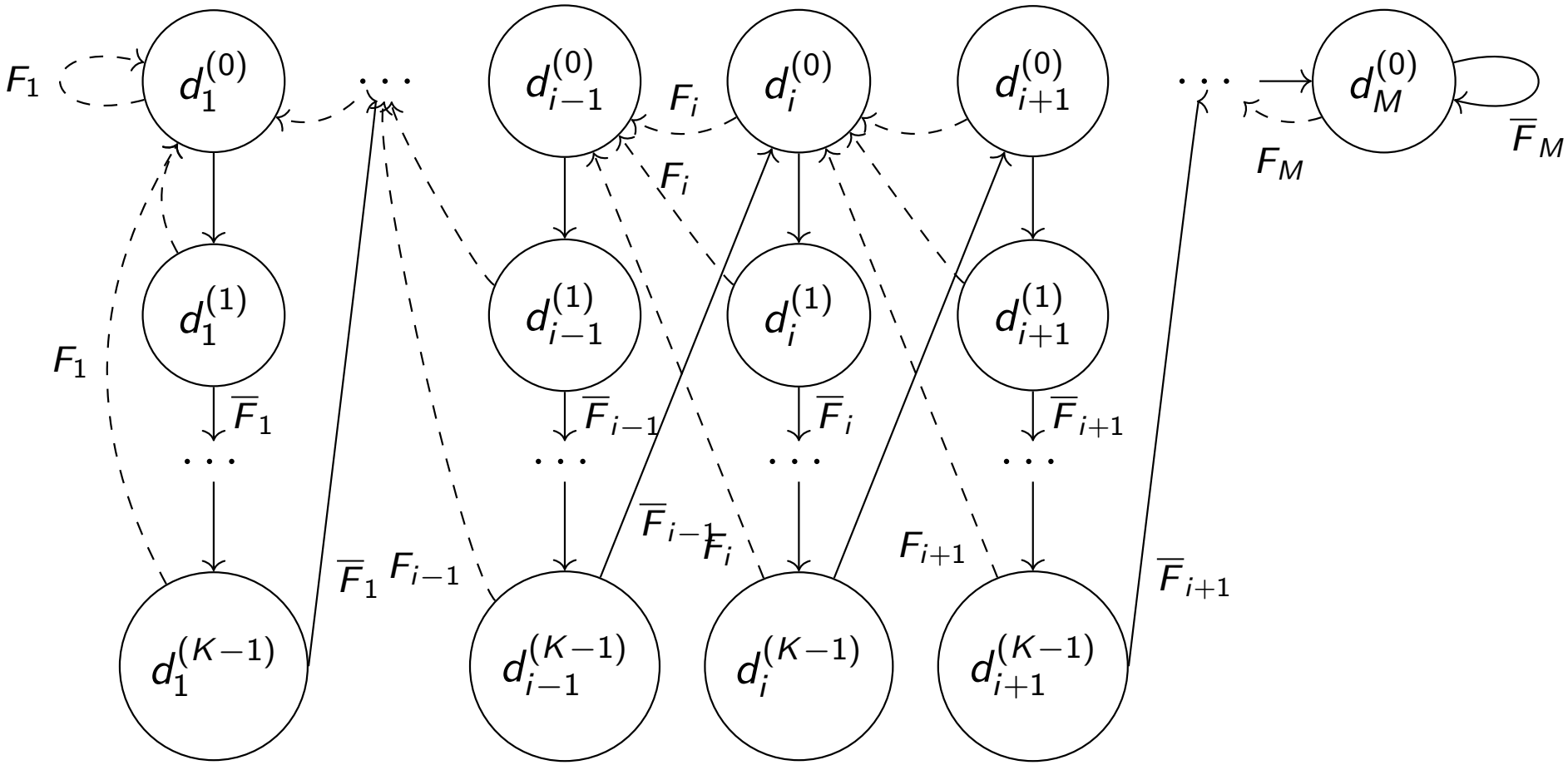
$\{\pi_i\}$ and $\{\pi_i^Z\}$

Theorem

Let iZ^* and i^* be the dose indices of the modes of $\{\pi_i^Z\}$ and $\{\pi_i\}$, respectively. Then

$$i^* = \begin{cases} iZ^* - 1 = 1 & \text{if } d_1 > x^* \quad \Rightarrow \quad d_{i^*} < d_{iZ^*} \\ iZ^* & \text{if } d_1 < d_{iZ^*} < x^* < d_{M-1} \quad \Rightarrow \quad d_{i^*} = d_{iZ^*} \\ iZ^* - 1 & \text{if } d_1 < x^* < d_{iZ^*} < d_{M-1} \quad \Rightarrow \quad d_{i^*} < d_{iZ^*} \\ iZ^* = M - 1 & \text{if } d_{M-1} < x^* \text{ and } \lambda_{M-1} \leq 1 \quad \Rightarrow \quad d_{i^*} = d_{iZ^*} \\ iZ^* + 1 = M & \text{if } d_{M-1} < x^* \text{ and } \lambda_{M-1} > 1 \quad \Rightarrow \quad d_{i^*} > d_{iZ^*} \end{cases}$$

KR process as a Markov chain: extended state space



Example $K = 2$

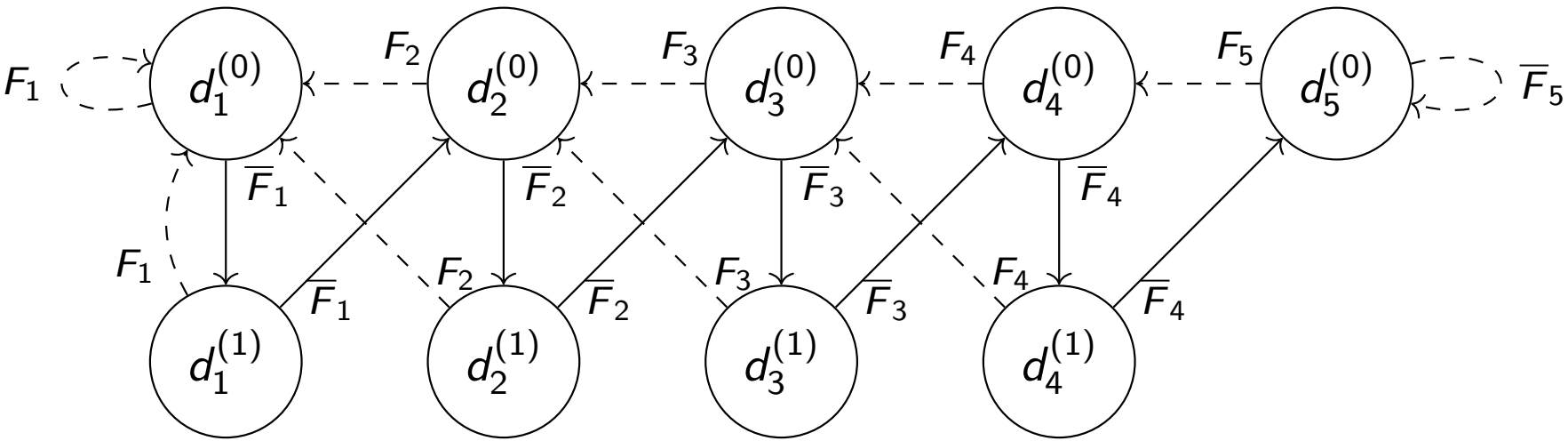


Figure: Transition paths in the expanded KR process for $K = 2$ and $M = 5$ doses.

Example $K = 2$

$$\mathbf{P}_E = \left(\begin{array}{cc|ccccccccc} & & \text{i=1} & & \text{i=2} & & \text{i=3} & & \text{i=4} & & \text{i=5} \\ i & w & 0 & 1 & 0 & 1 & 0 & 1 & 0 & 1 & 0 \\ \hline 1 & 0 & F_1 & \overline{F}_1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ & 1 & F_1 & 0 & \overline{F}_1 & 0 & 0 & 0 & 0 & 0 & 0 \\ 2 & 0 & F_2 & 0 & 0 & \overline{F}_2 & 0 & 0 & 0 & 0 & 0 \\ & 1 & F_2 & 0 & 0 & 0 & \overline{F}_2 & 0 & 0 & 0 & 0 \\ 3 & 0 & 0 & 0 & F_3 & 0 & 0 & \overline{F}_3 & 0 & 0 & 0 \\ & 1 & 0 & 0 & F_3 & 0 & 0 & 0 & \overline{F}_3 & 0 & 0 \\ 4 & 0 & 0 & 0 & 0 & 0 & F_4 & 0 & 0 & \overline{F}_4 & 0 \\ & 1 & 0 & 0 & 0 & 0 & F_4 & 0 & 0 & 0 & \overline{F}_4 \\ 5 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & F_5 & 0 & \overline{F}_5 \end{array}\right) \tag{10}$$

Stationary distribution

$$\pi_i^{(0)} = \pi_1^{(0)} \prod_{j=1}^{i-1} \lambda_j^{(0)},\ i = 2, \ldots, M, \text{ where } \lambda_i^{(0)} = \begin{cases} \dfrac{\overline{F}_i^K}{1 - \overline{F}_{i+1}^K} & 1 \leq i \leq M - \\ \dfrac{\overline{F}_{M-1}^K}{F_M} & i = M - 1; \end{cases} \tag{11}$$

Then

$$\widetilde{\pi}_i = \begin{cases} \pi_1^{(0)} \mathrm{E}[S_1] \overline{F}_1^K & i = 1; \\ \pi_i^{(0)} \mathrm{E}[S_i] & 2 \leq i \leq M - 1; \\ \pi_M^{(0)} & i = M; \end{cases}$$

Finally, $1 = \sum_{i=1}^{M} \widetilde{\pi}_i = \pi_i^{(0)} \left(\mathrm{E}[S_1] \overline{F}_1^K + \sum_{i=1}^{M-1} \mathrm{E}[S_i] \prod_{j=1}^{i-1} \lambda_j^{(0)} + \prod_{j=1}^{M-1} \lambda_j^{(0)} \right).$

Benefits of the SMK

- Provides a more succinct, and more descriptive expression for the stationary distribution than the Markov chain.
- The unimodality proof only uses [AS1] and, so, does not require embedding the allocation chain in the continuous dose space $\mathcal{X}$ and explicitly using a continuous response function F. Our proof is closely related with the evolution of the embedded chain of the semi-Markov process and the increase ratio of toxicity in [AS1].
- The mode of the stationary distribution of $\{X_n\}_{n\geq 1}$ is explicitly identified. The conditions of the process to determine exactly the mode are given. This is better than bounding it as was the most precision obtained up to now in the literature.

MERCI/THANKS

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