Isotonic subgroup selection

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Novartis Stats Methods Seminar

Collaborators

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University of Bristol

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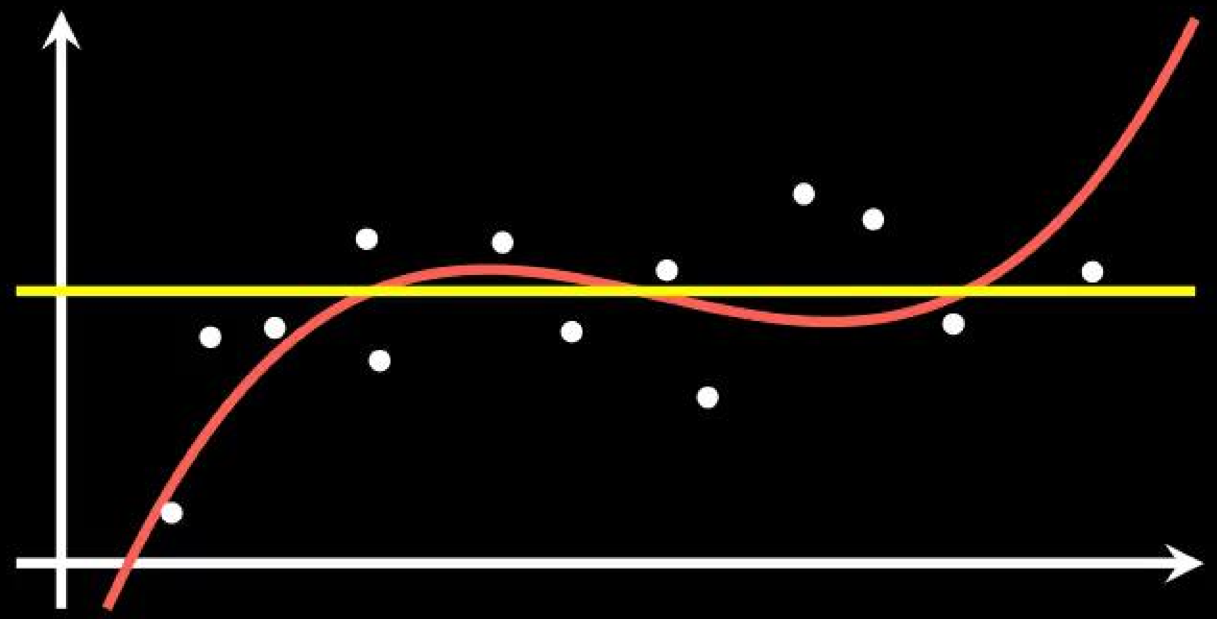

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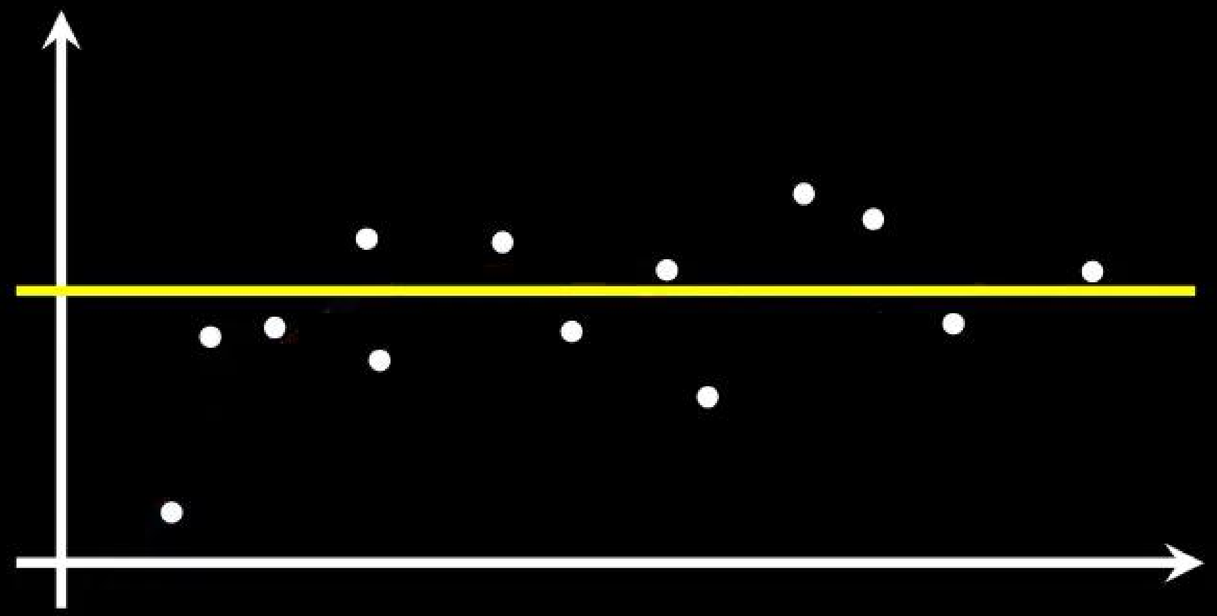

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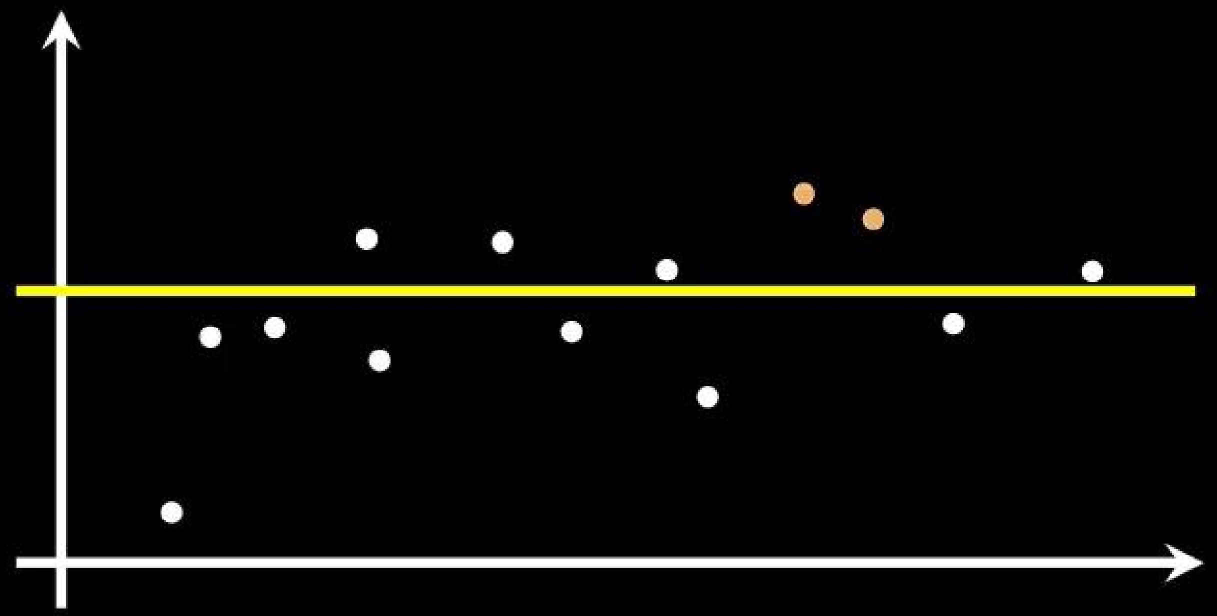

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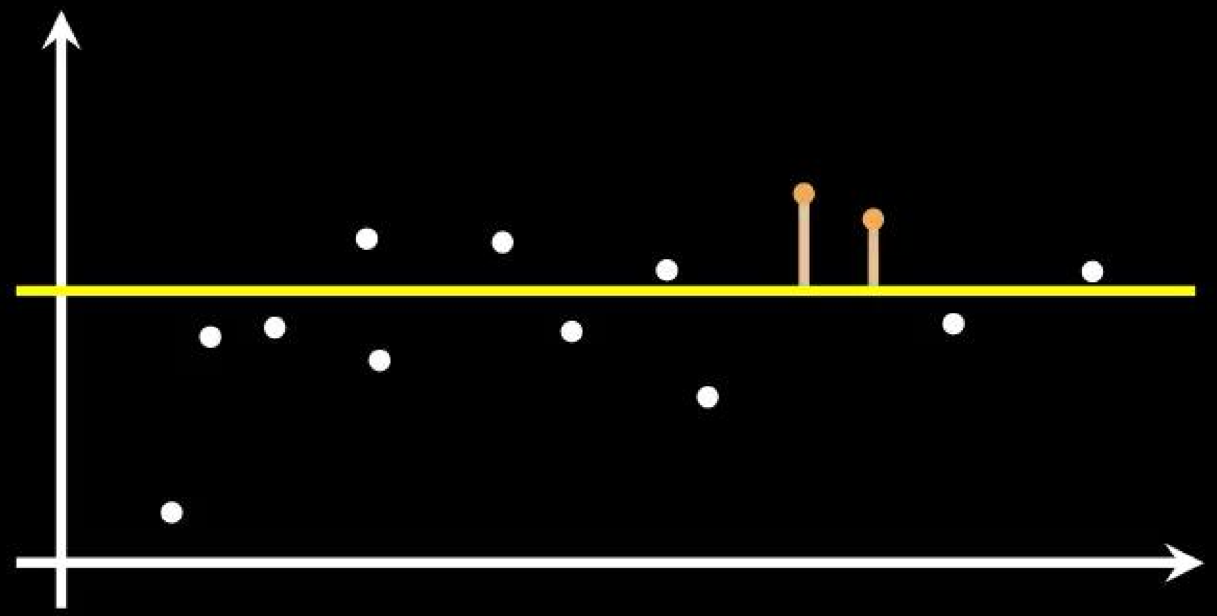

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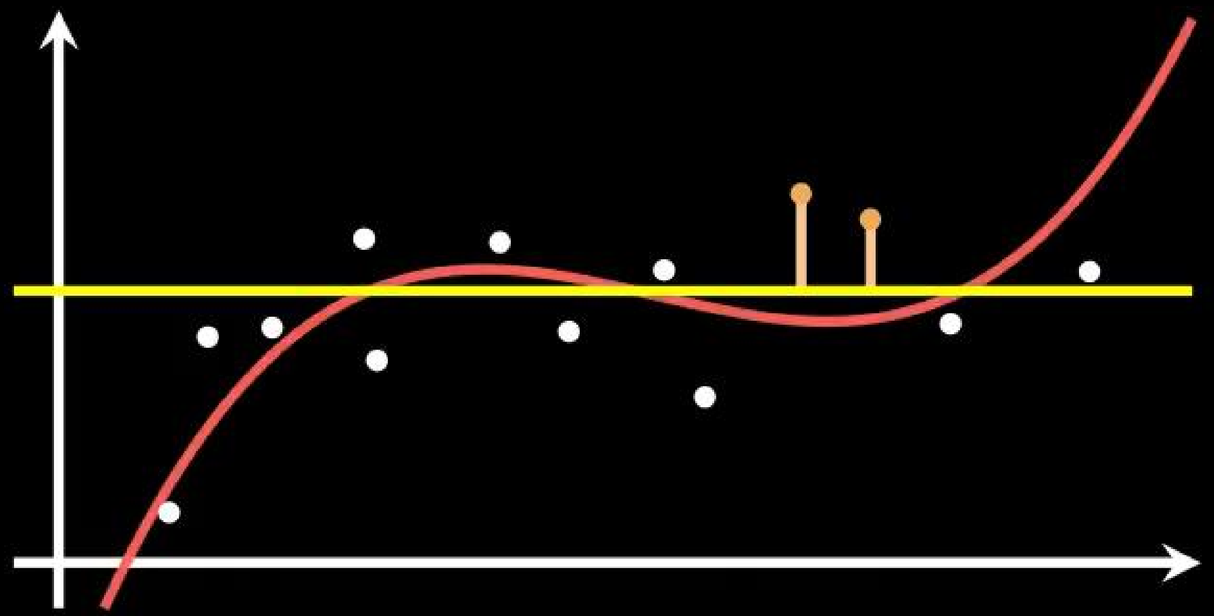

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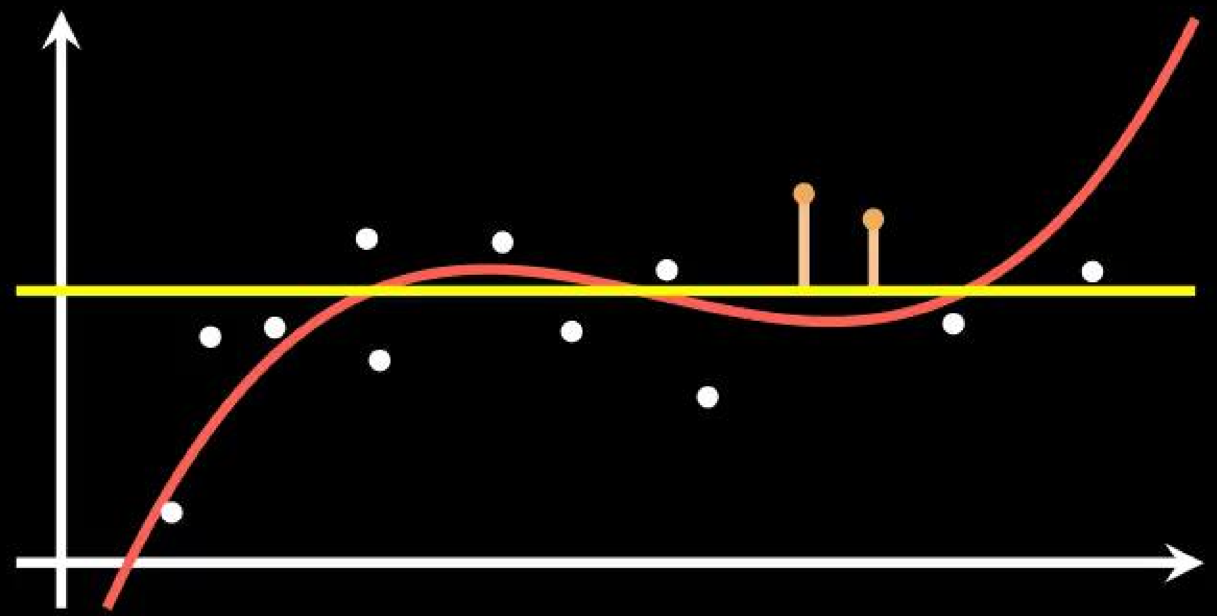

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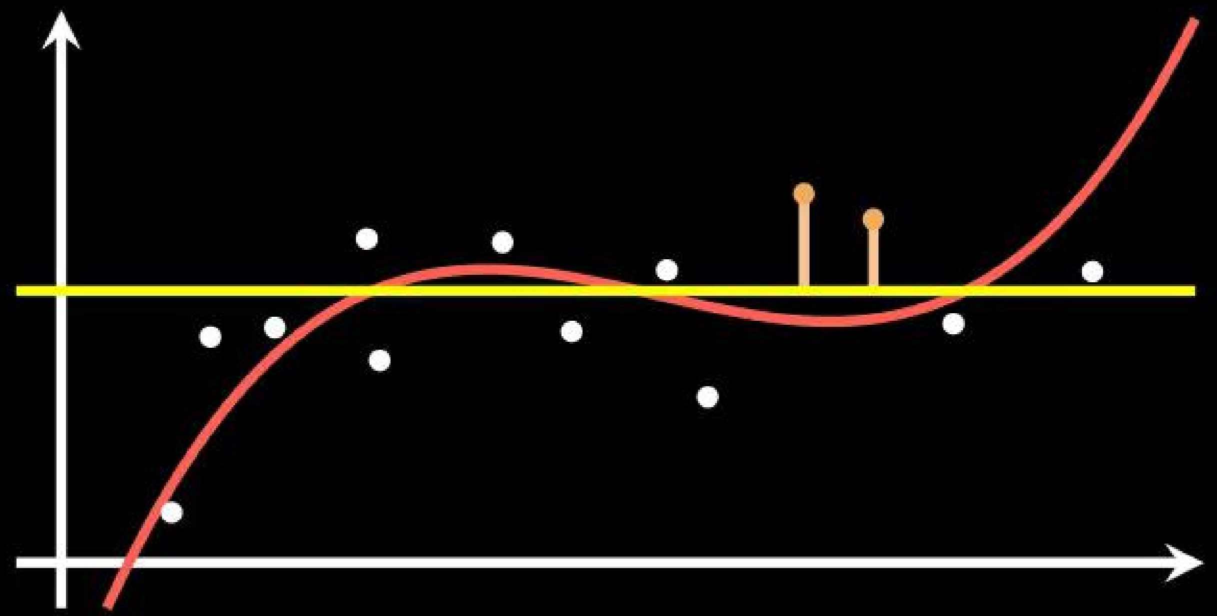

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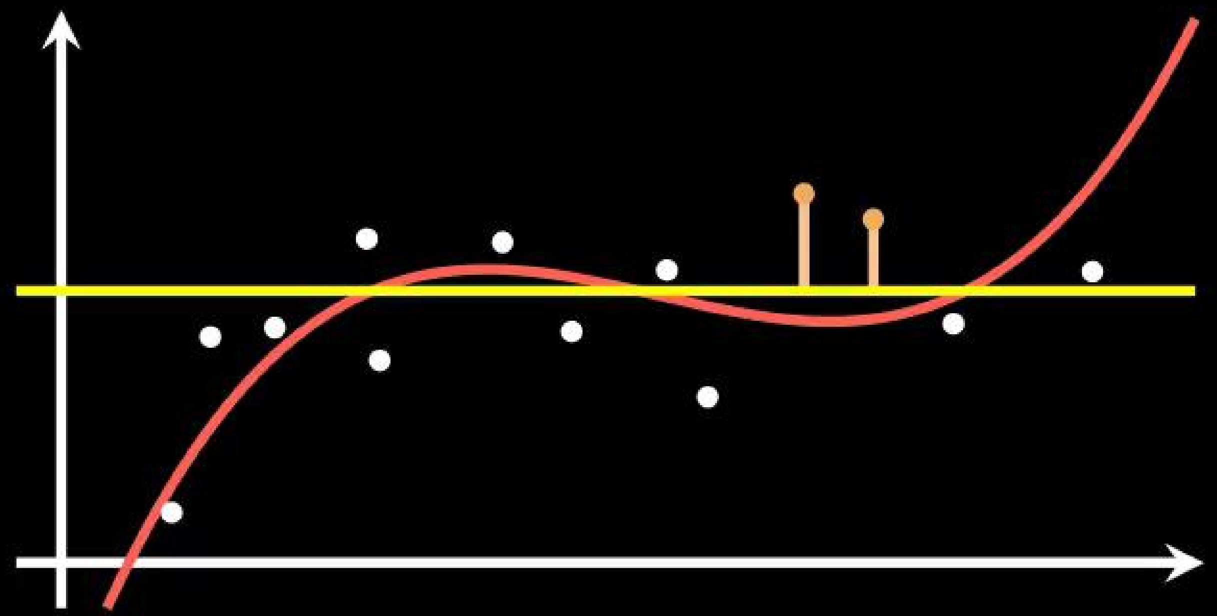

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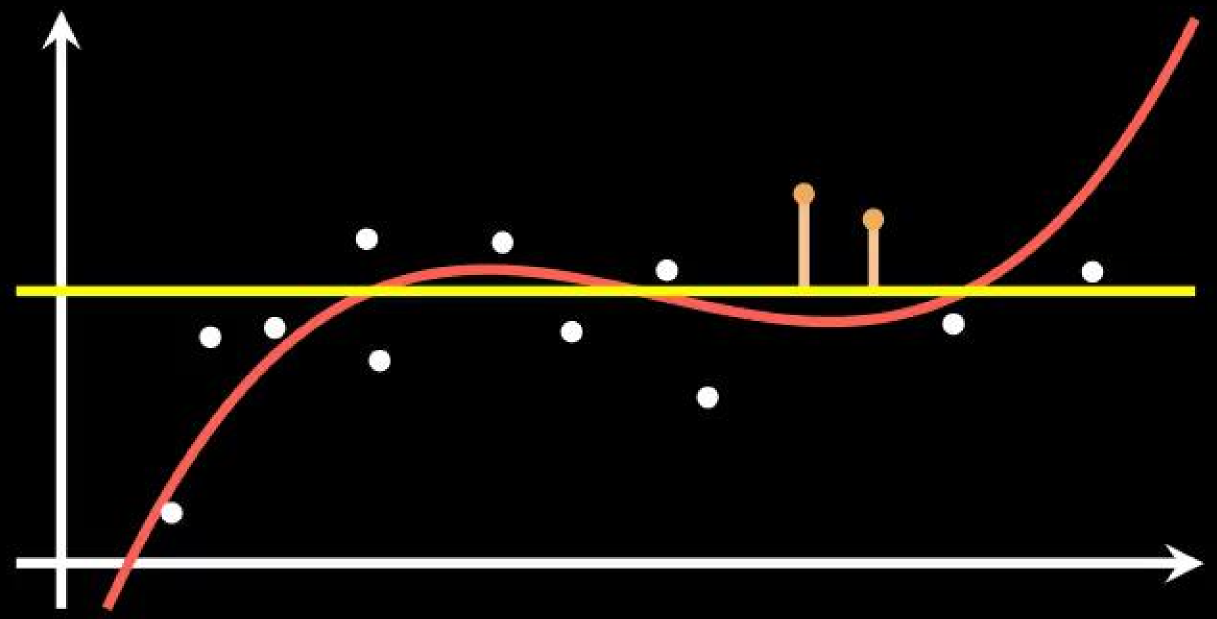

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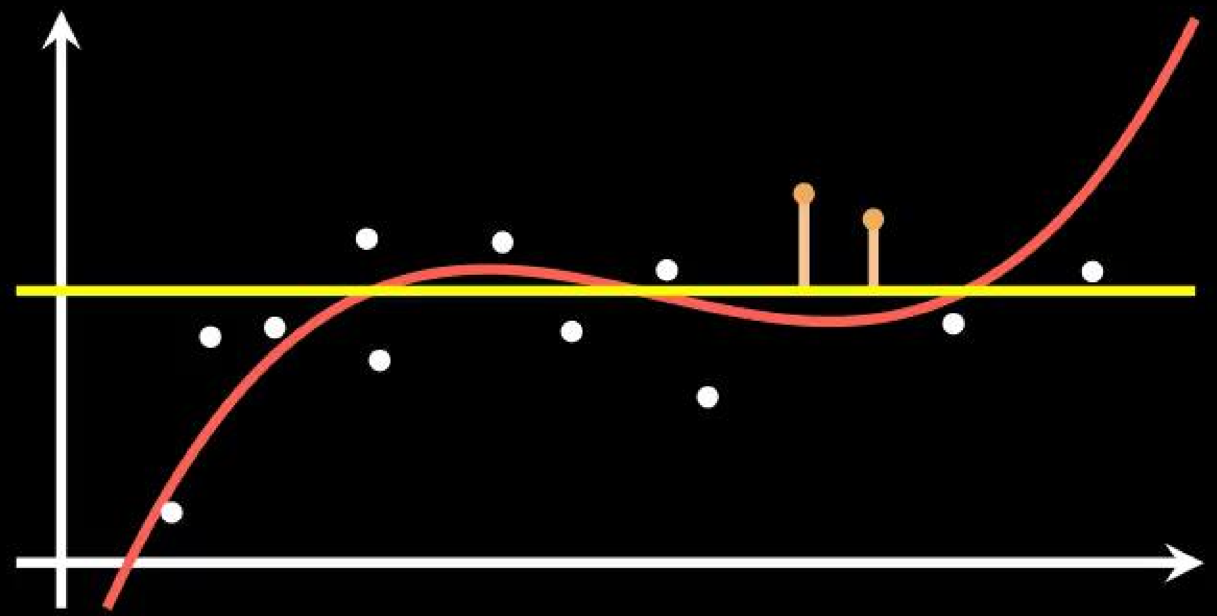

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$\longrightarrow$ Asymmetry of errors

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Setting:

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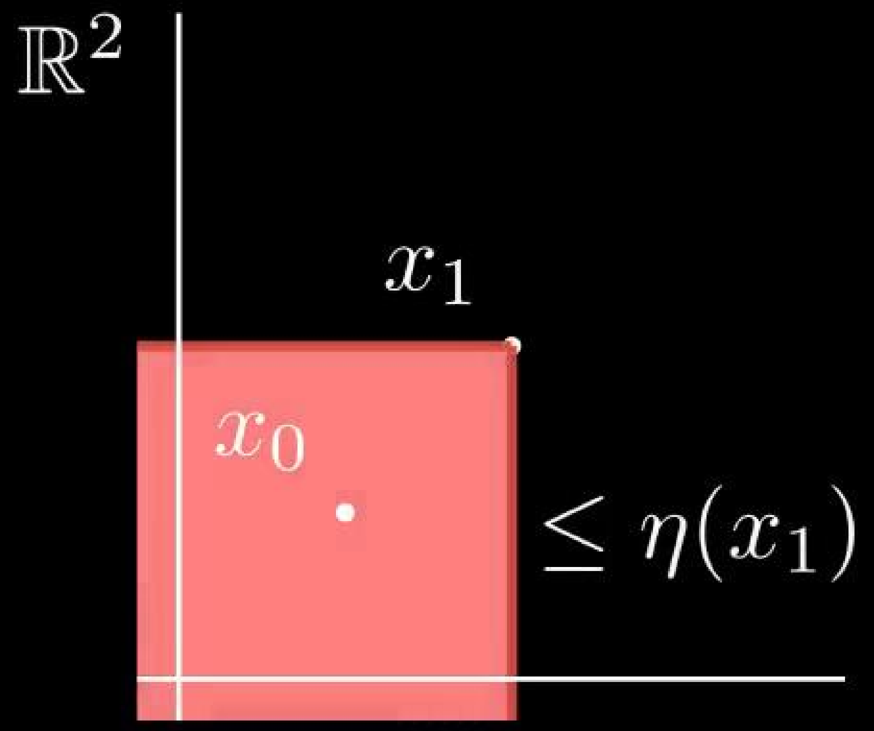

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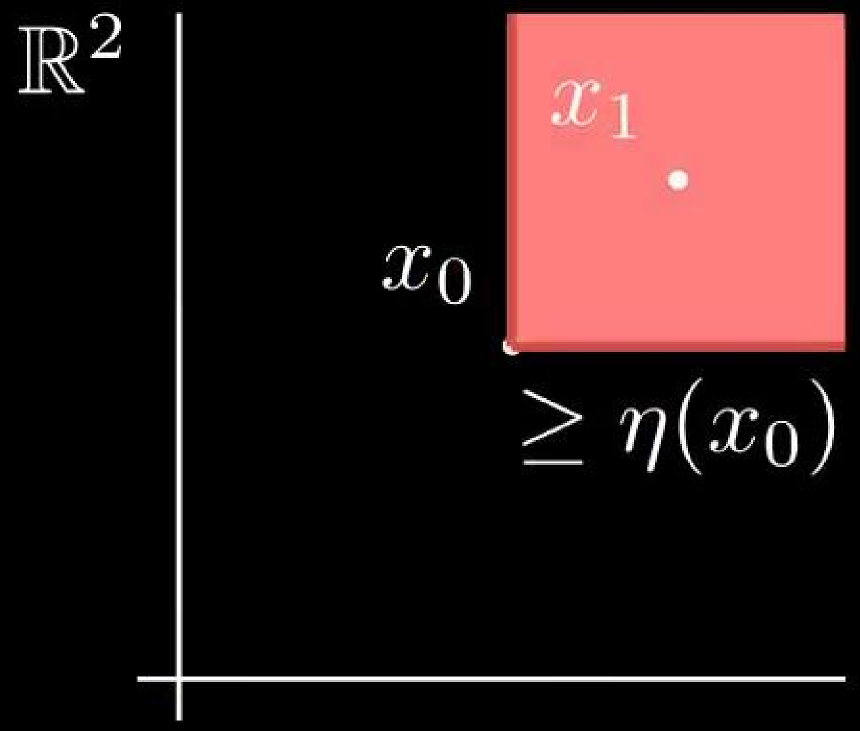

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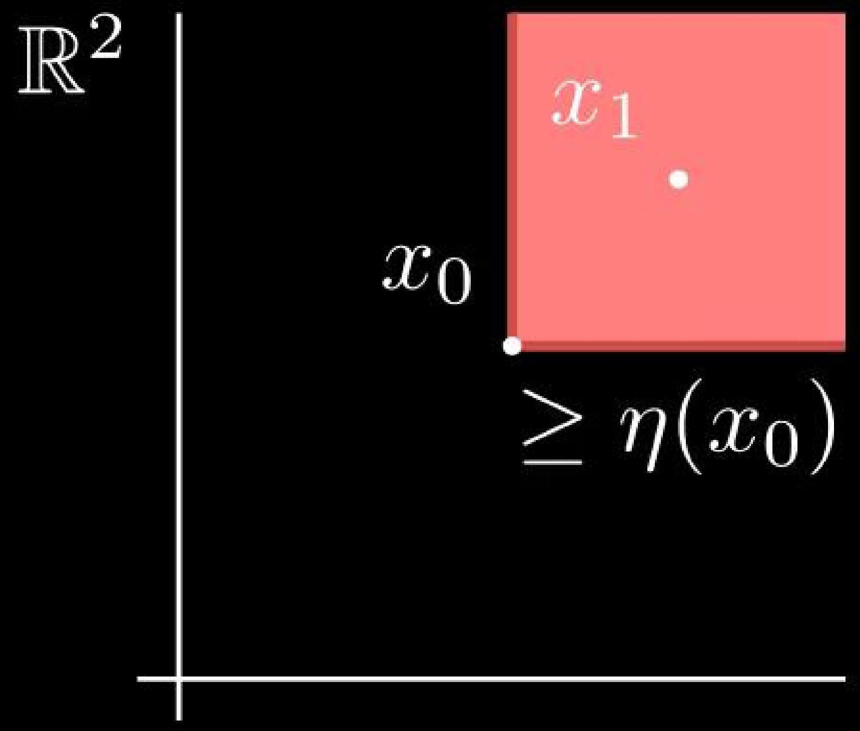

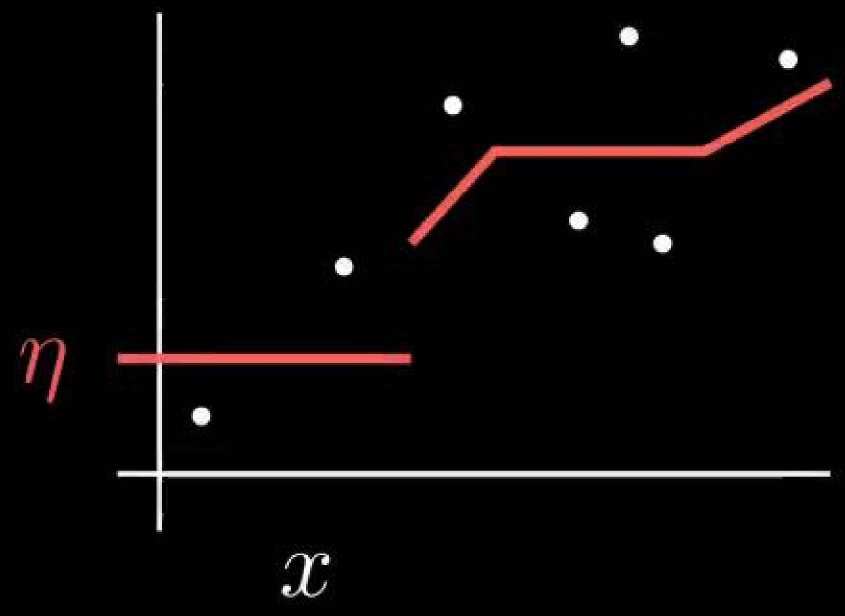

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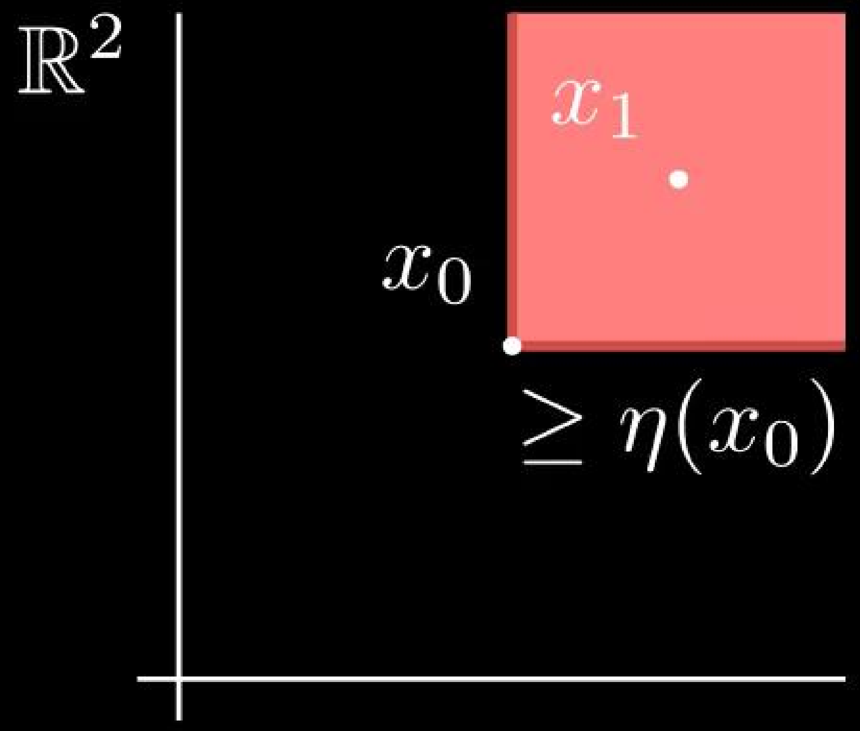
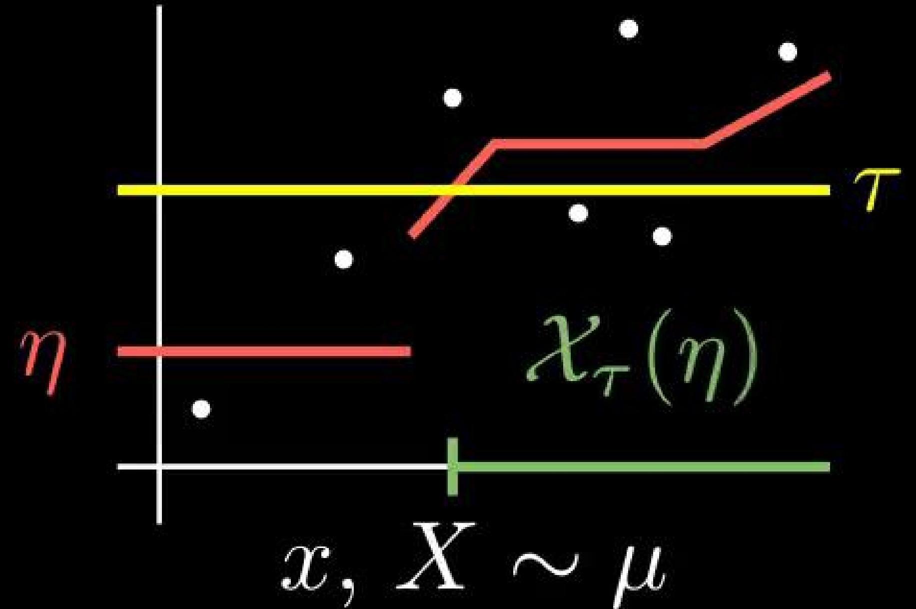


Notation:

- Fix $\tau \in \mathbb{R}$. Define τ-superlevel set by

$$\mathcal{X}_\tau(\eta) := \{x \in \mathbb{R}^d : \eta(x) \geq \tau\}$$

- Denote the marginal distribution of X by μ.



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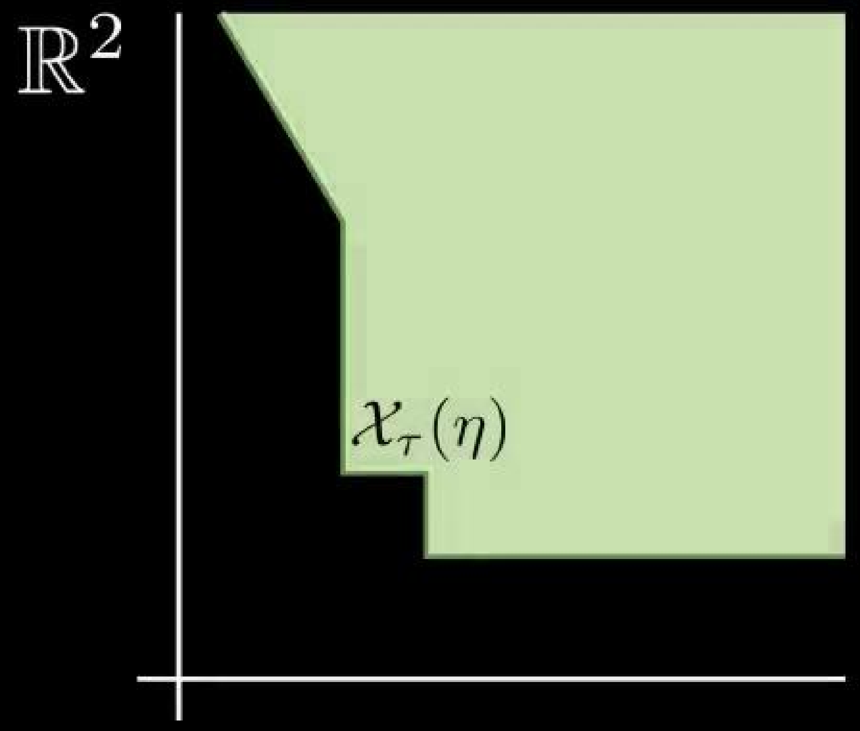

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Type I error control: Fix $\alpha \in (0,1)$. Require $\forall P \in \mathcal{P}_{\mathrm{Mon},d}(\sigma)$:

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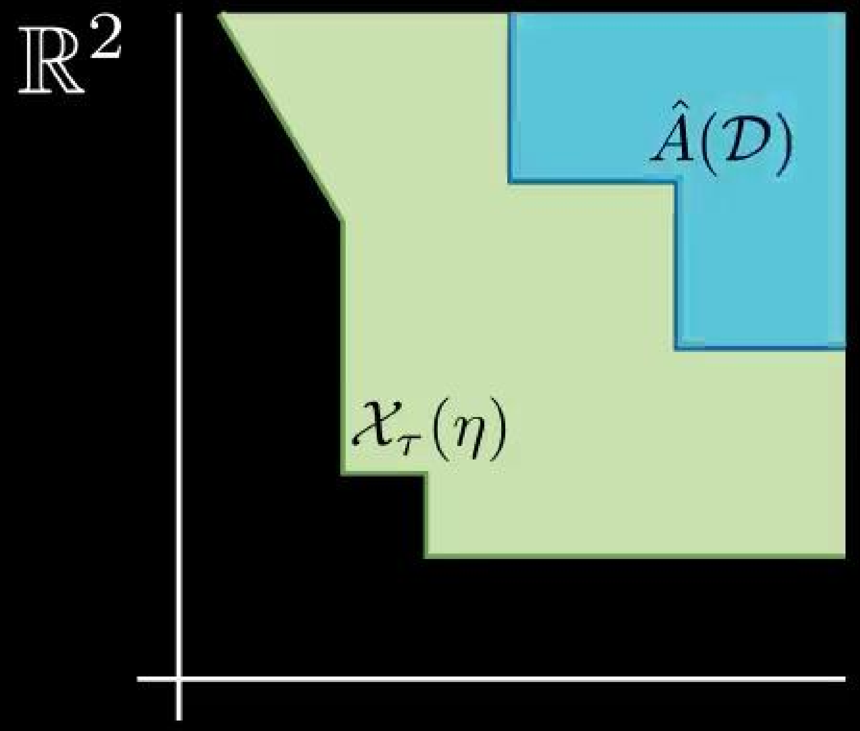

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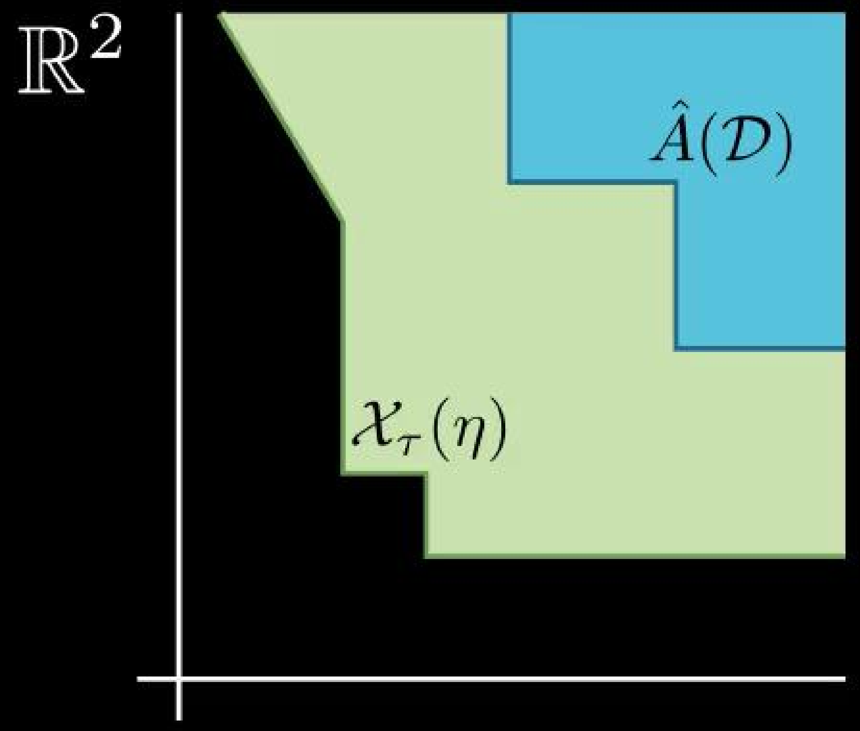

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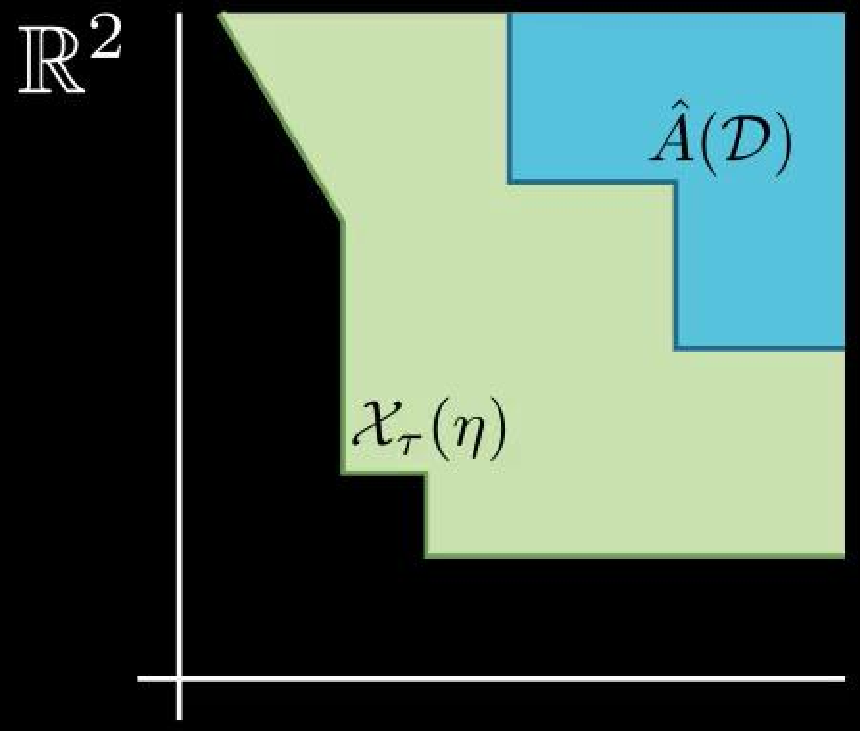

Example:

Type I error: $\hat{A}$ should contain only those HIV-patients for whom the conditional probability of not facing a negative event within the next 5 years is at least 98%.

High-level strategy

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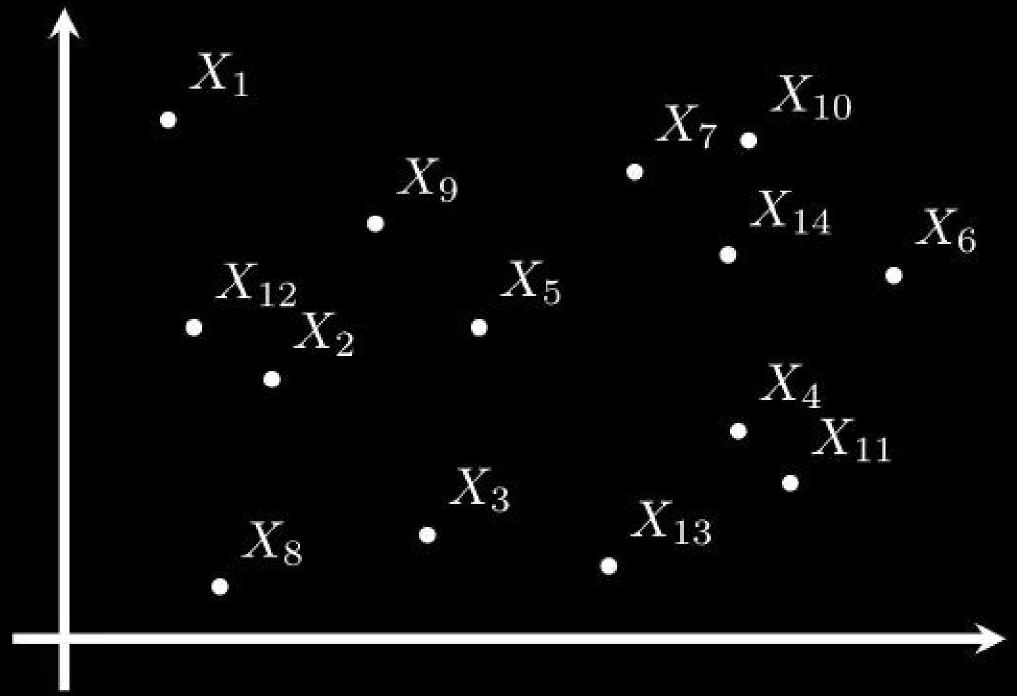

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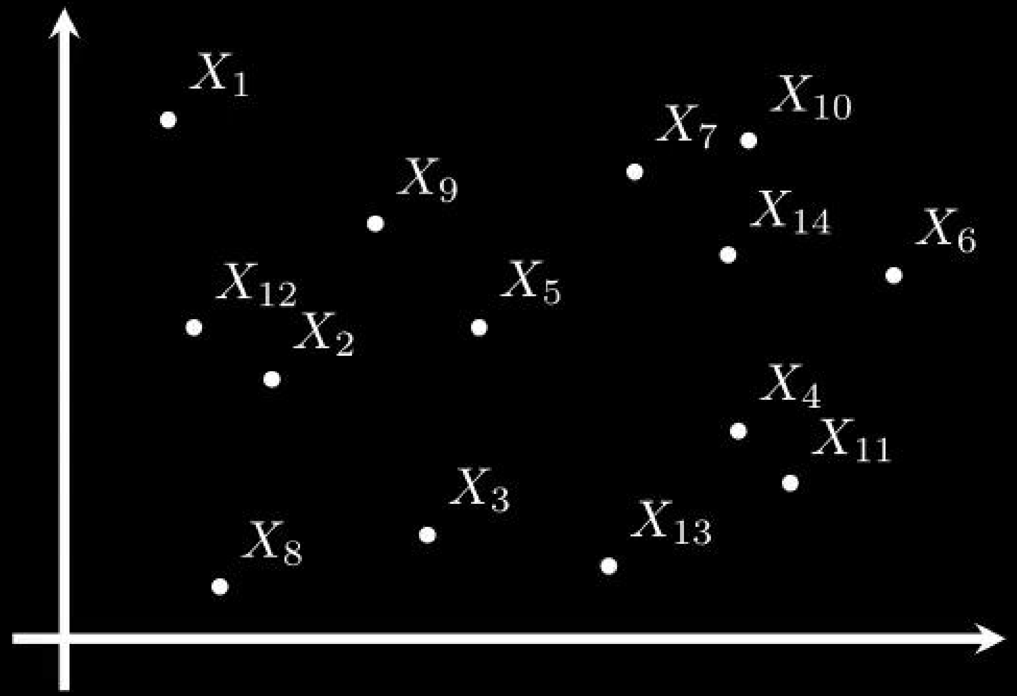

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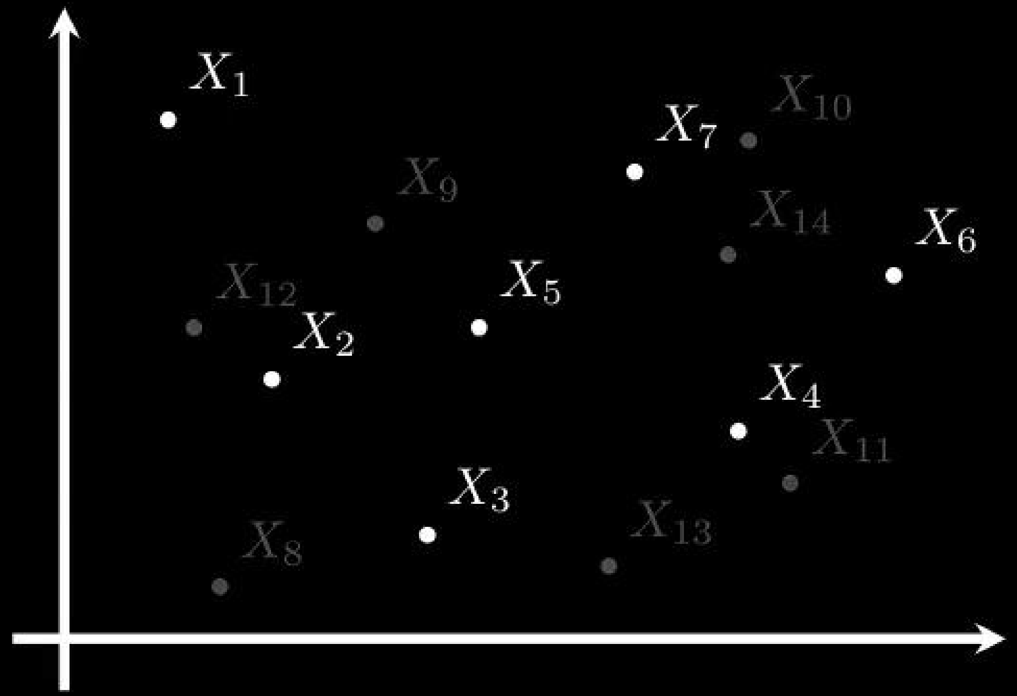

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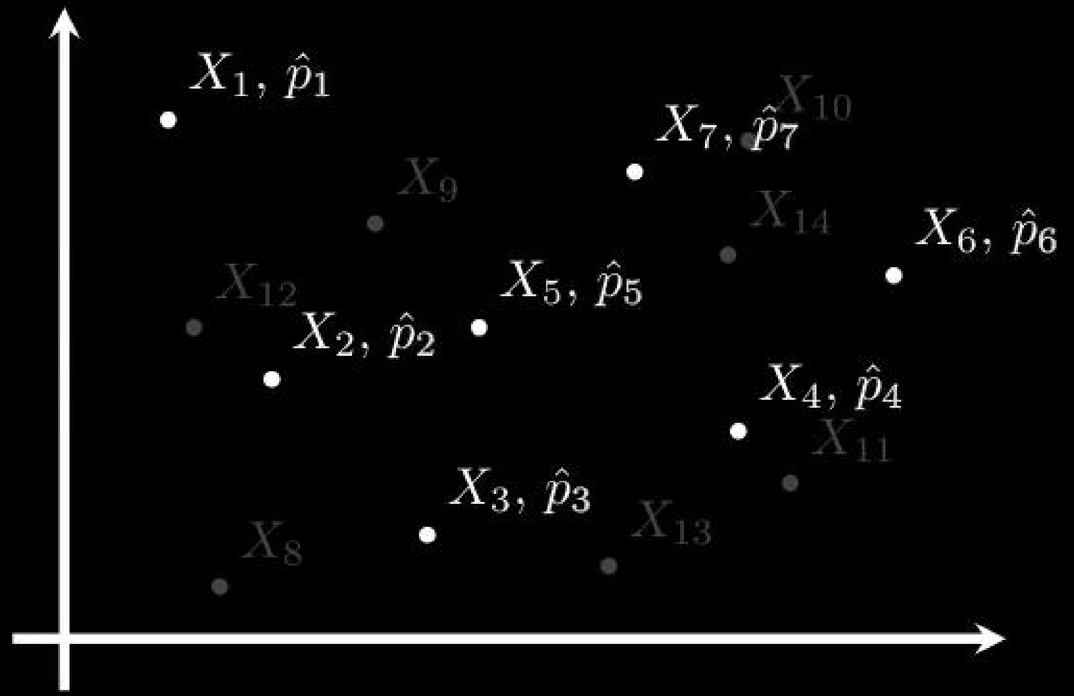

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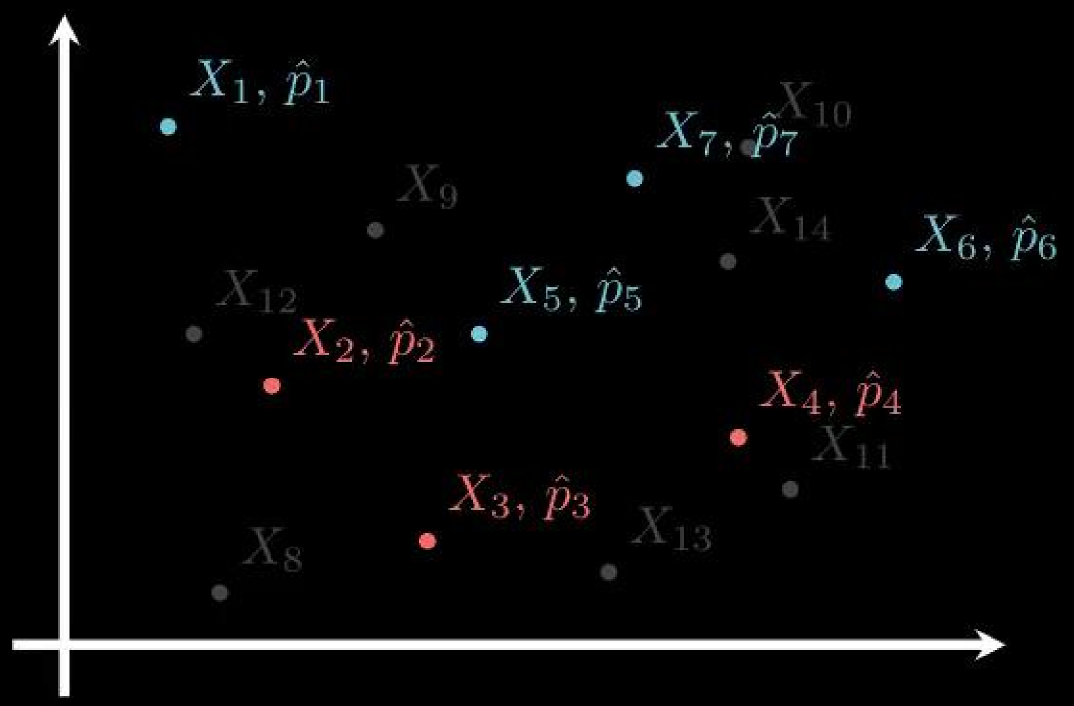

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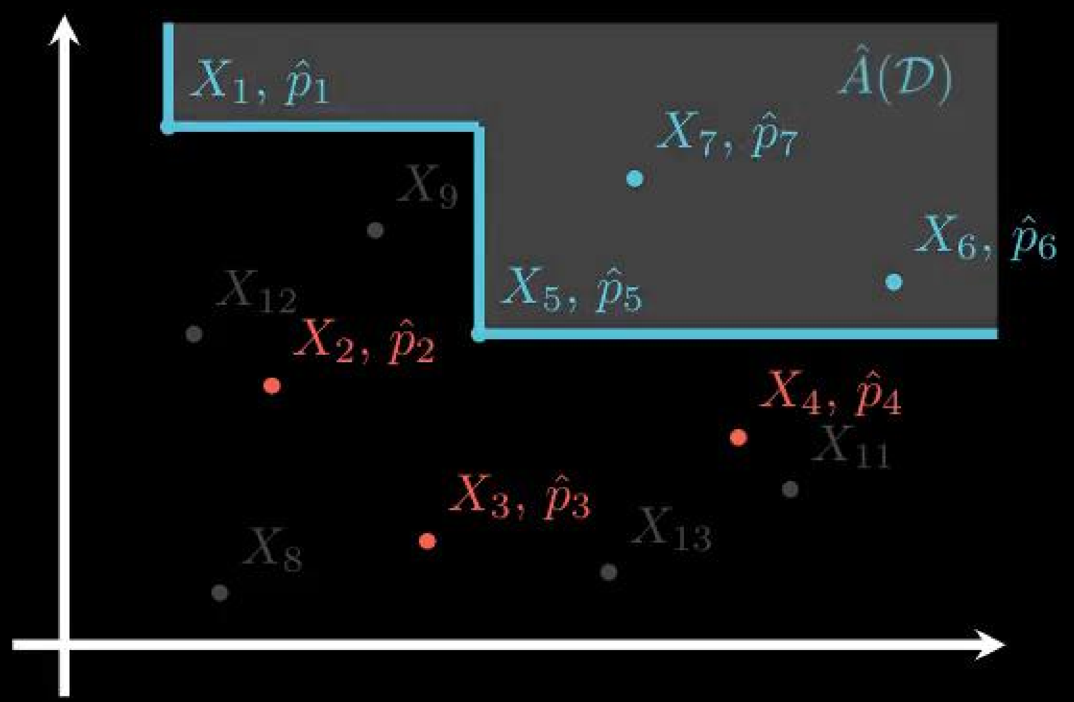

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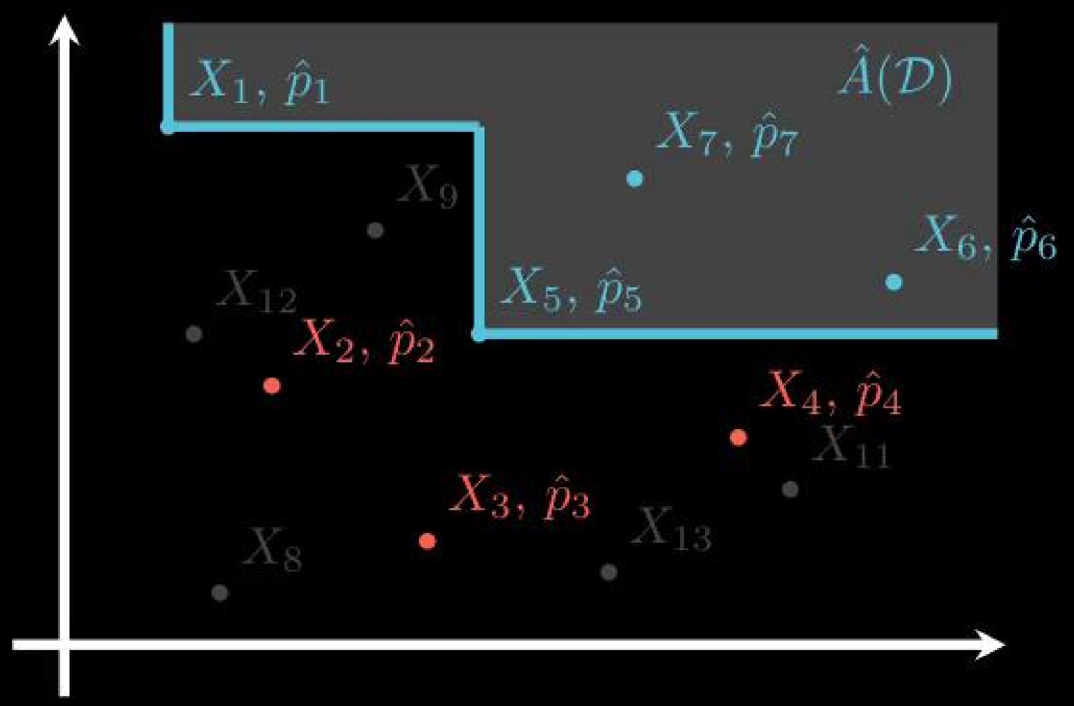

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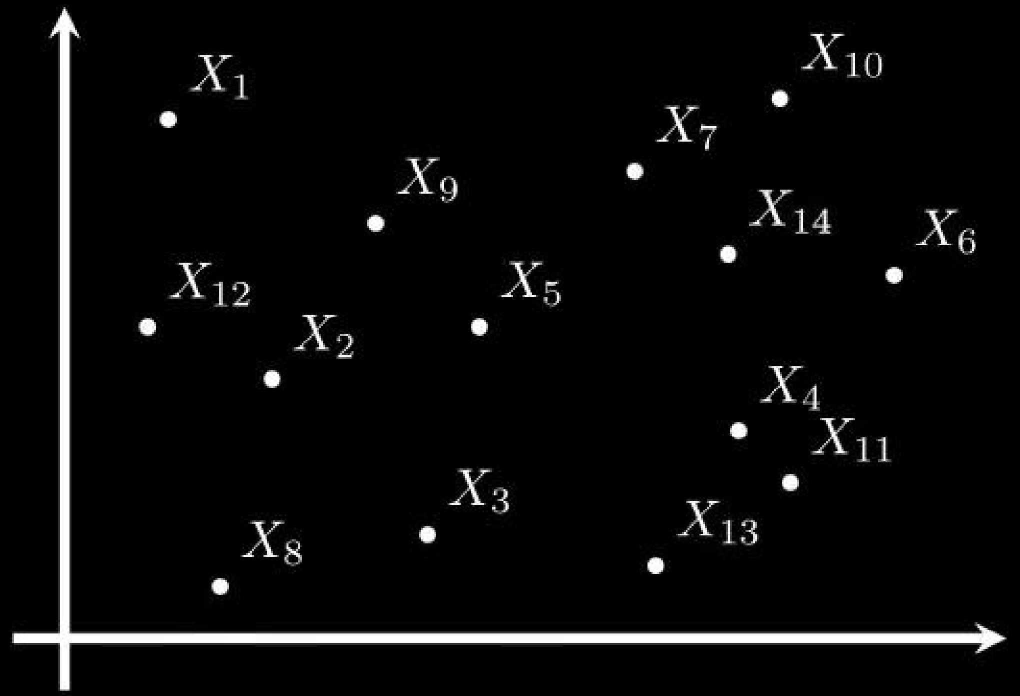

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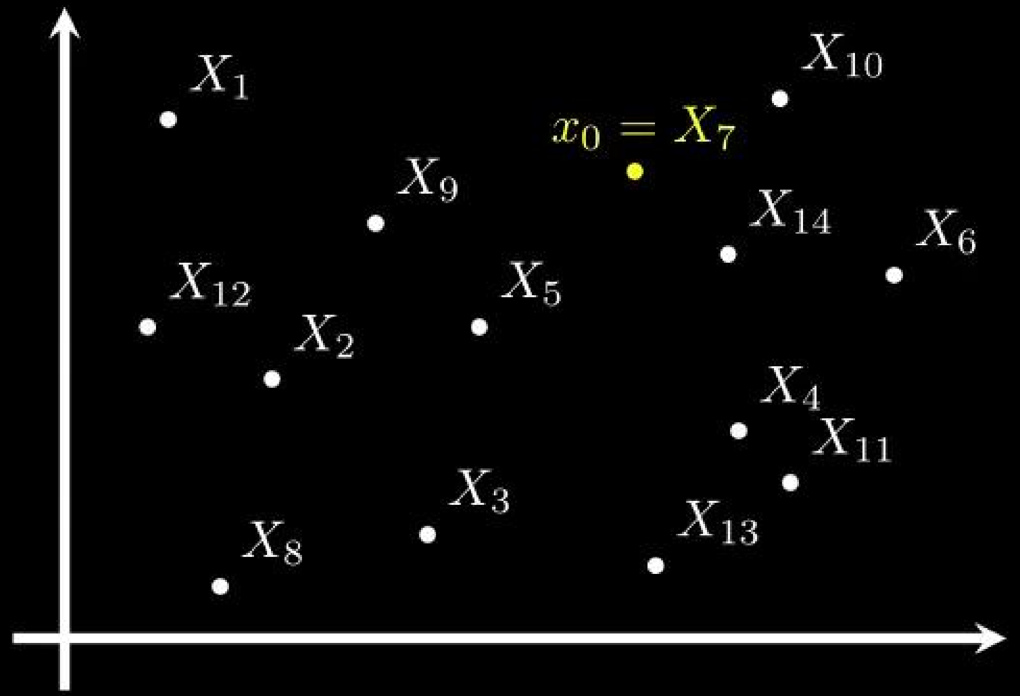

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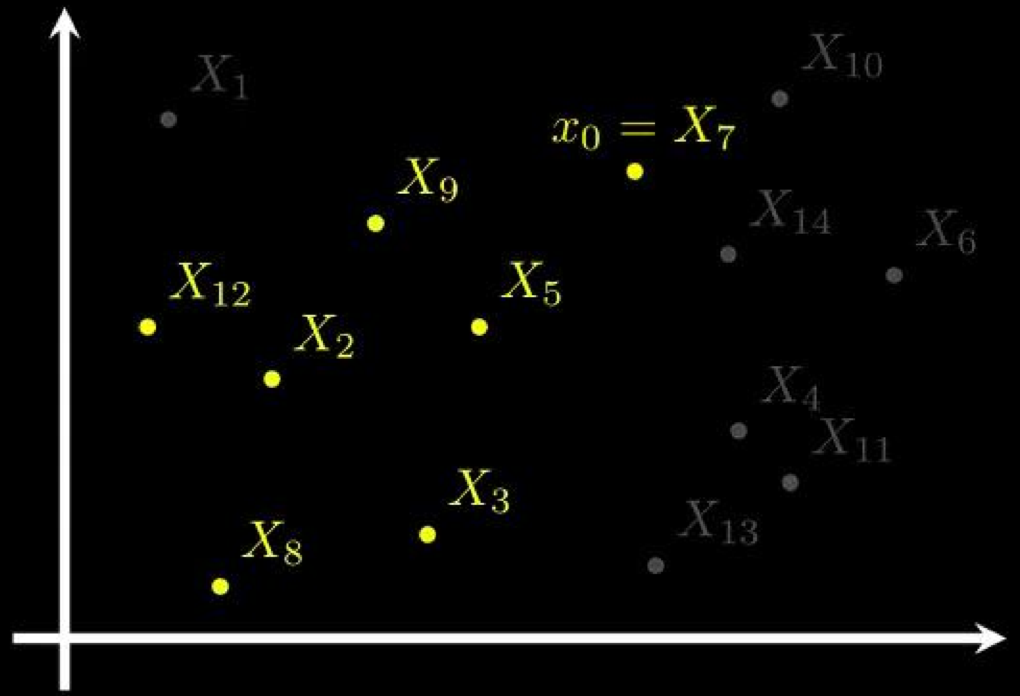

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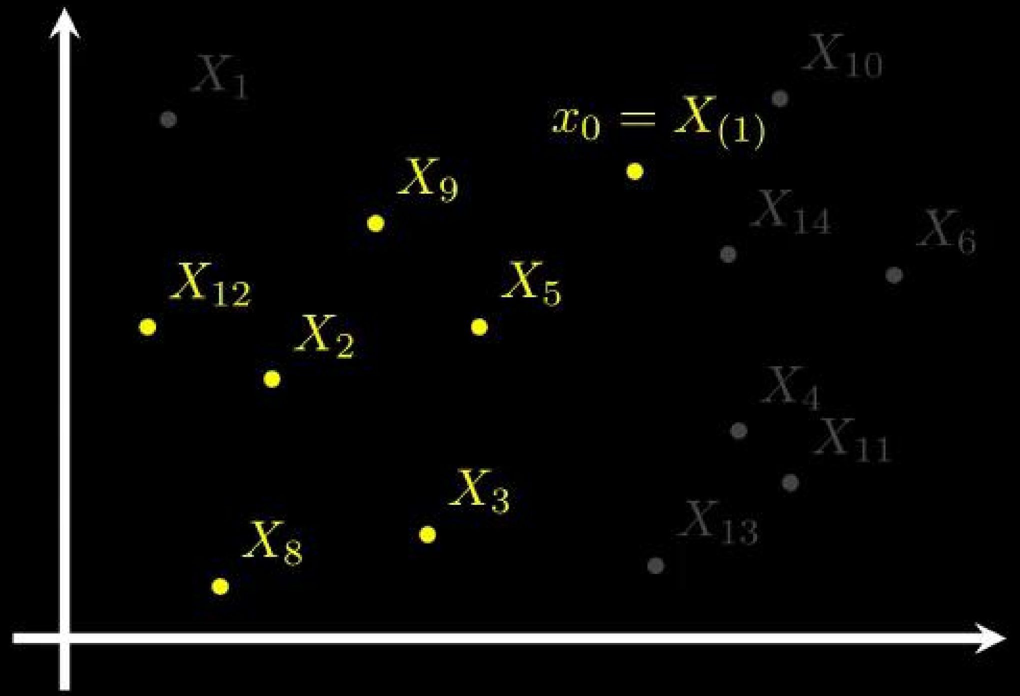

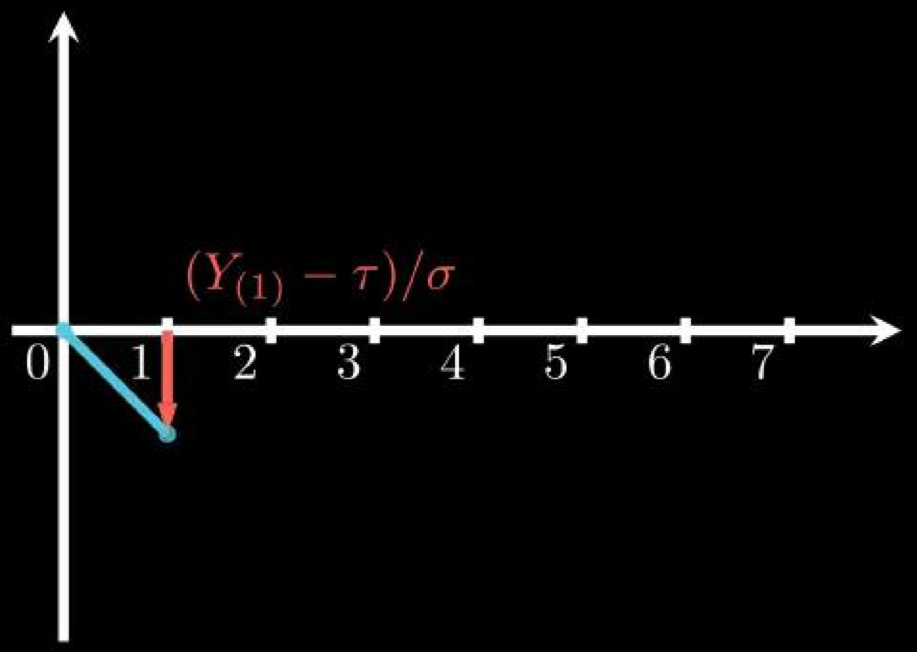

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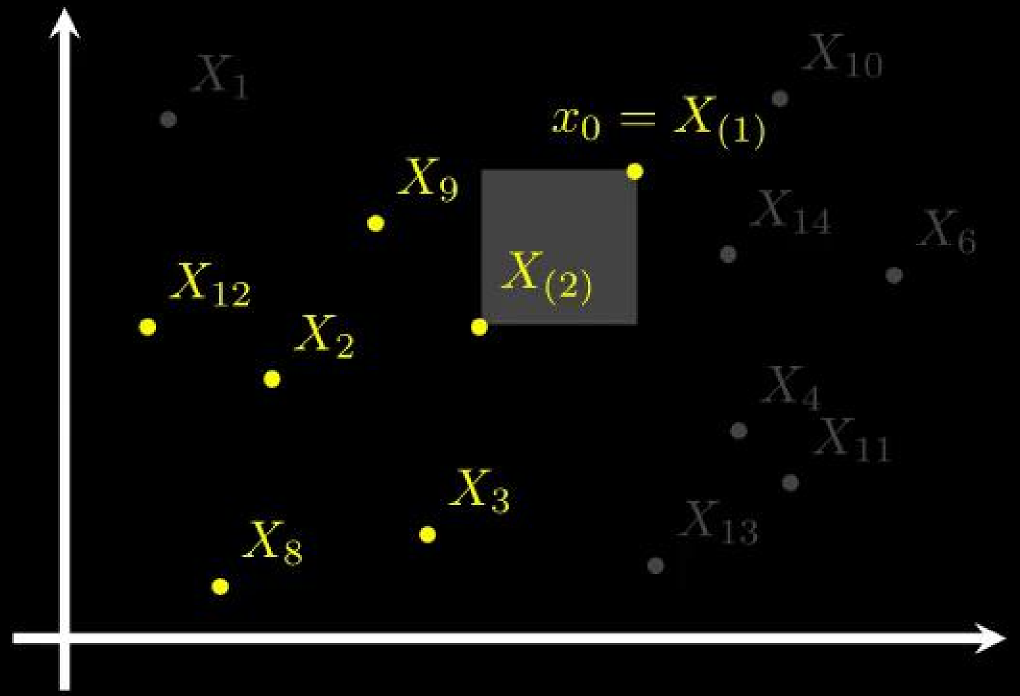

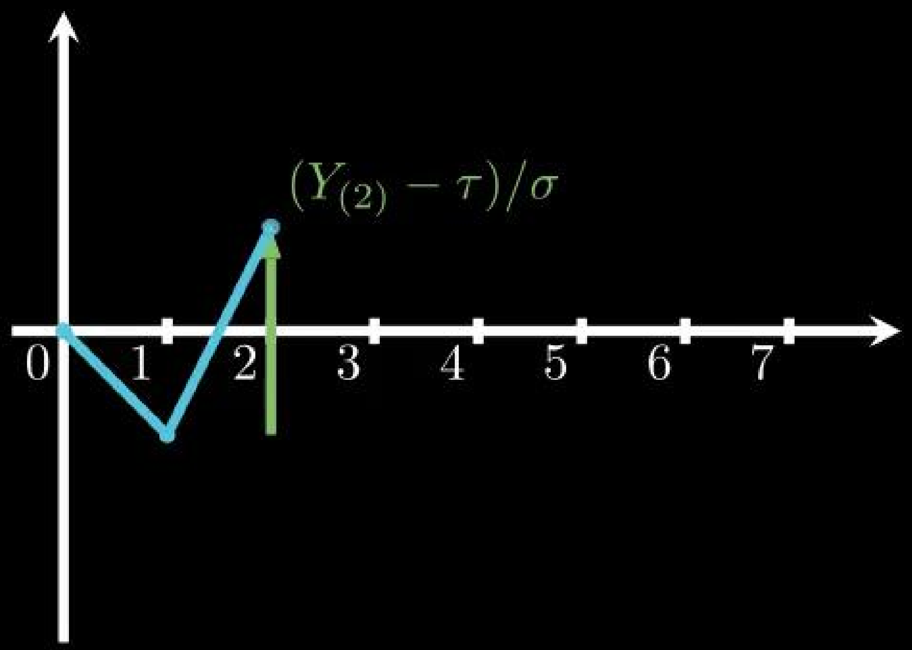

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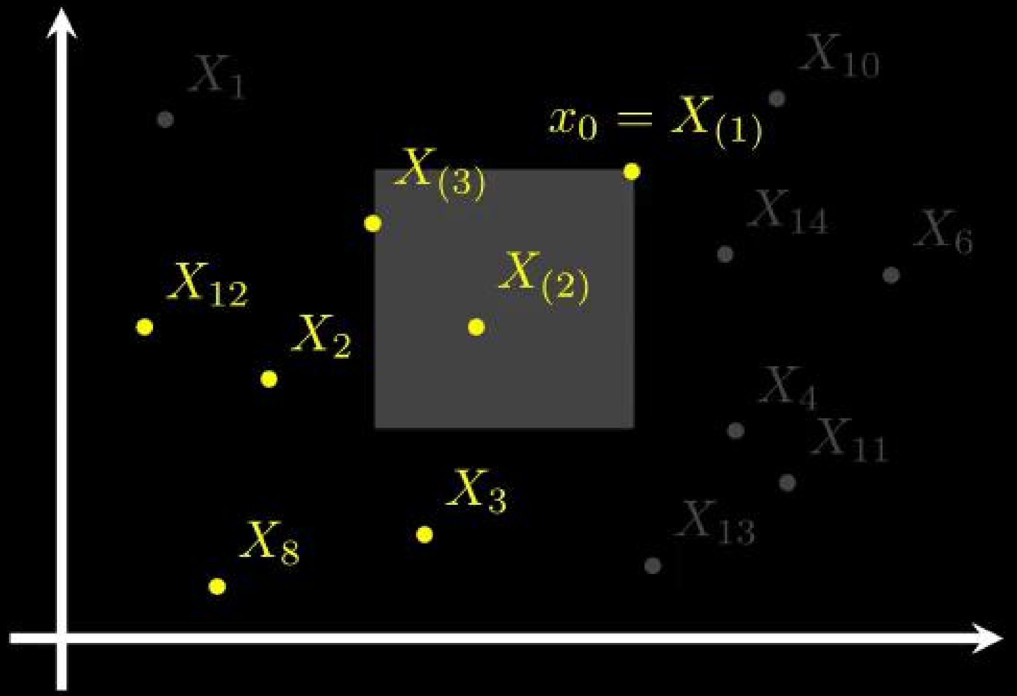

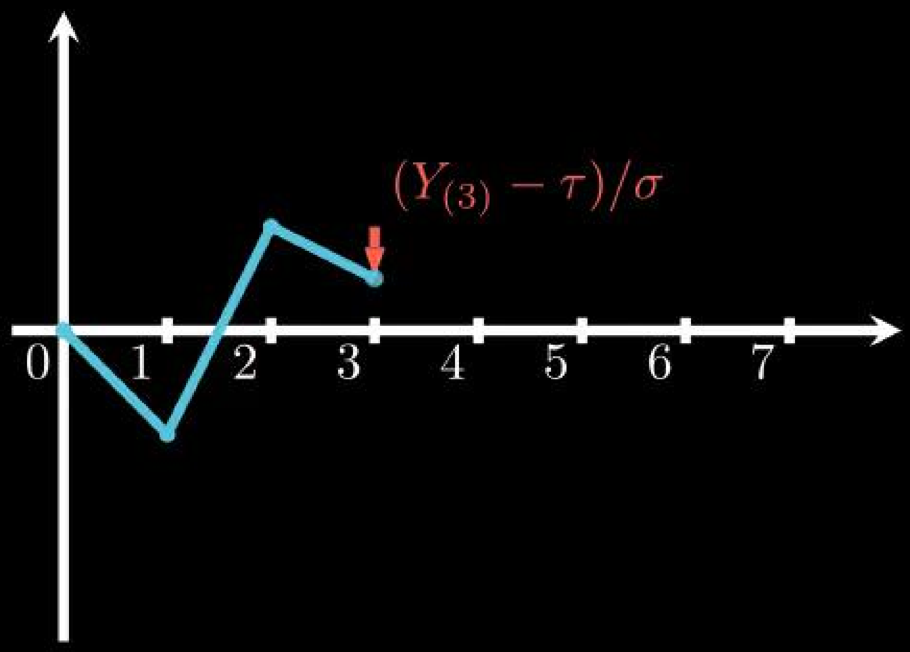

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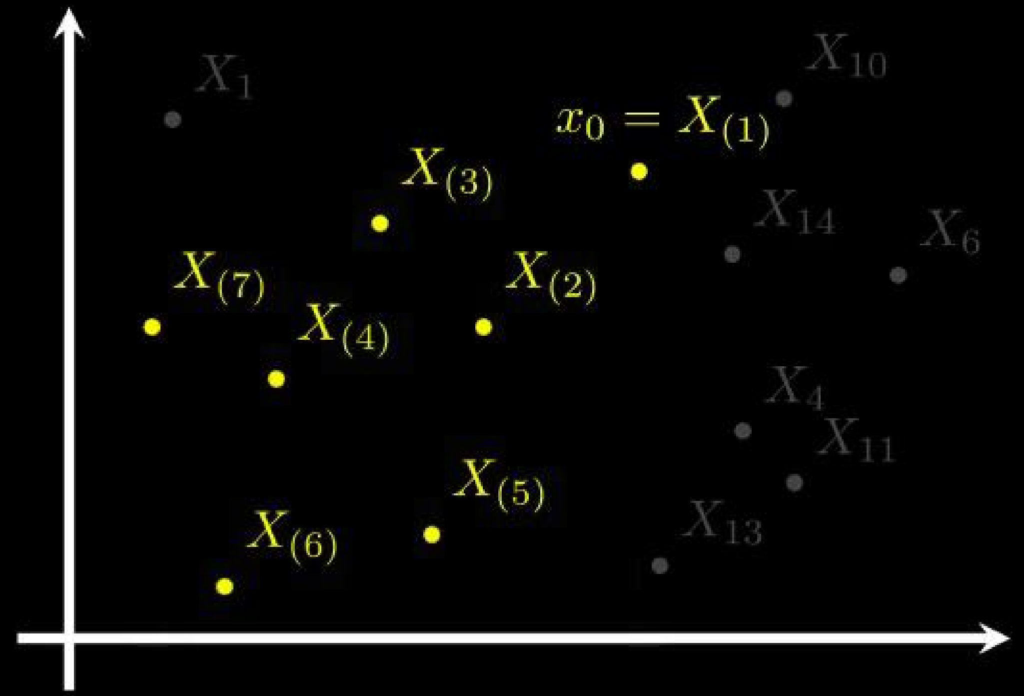

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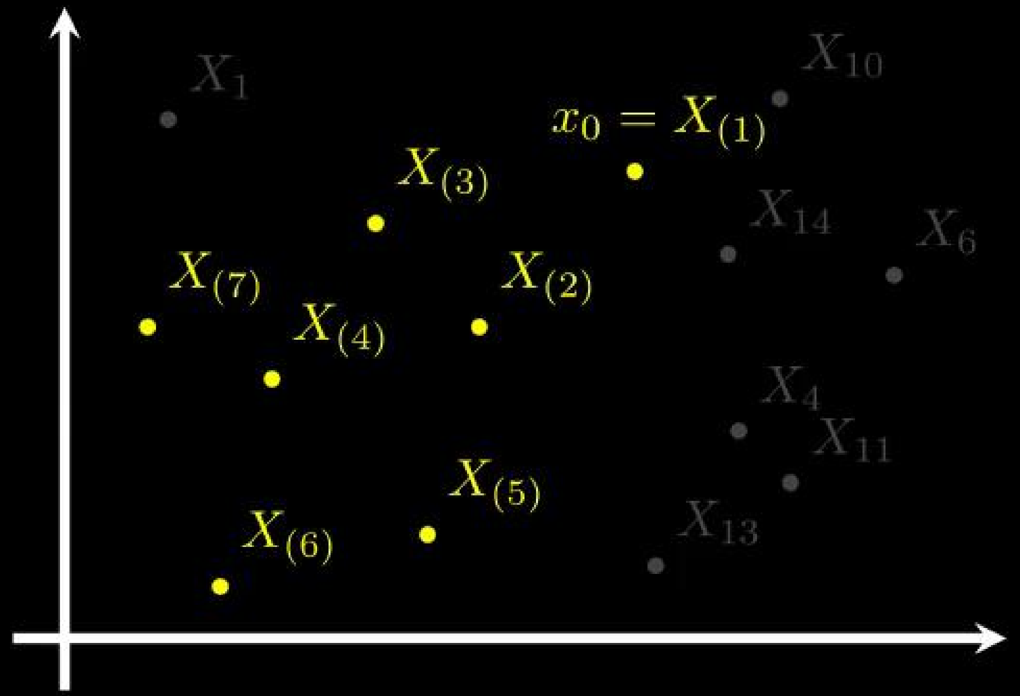

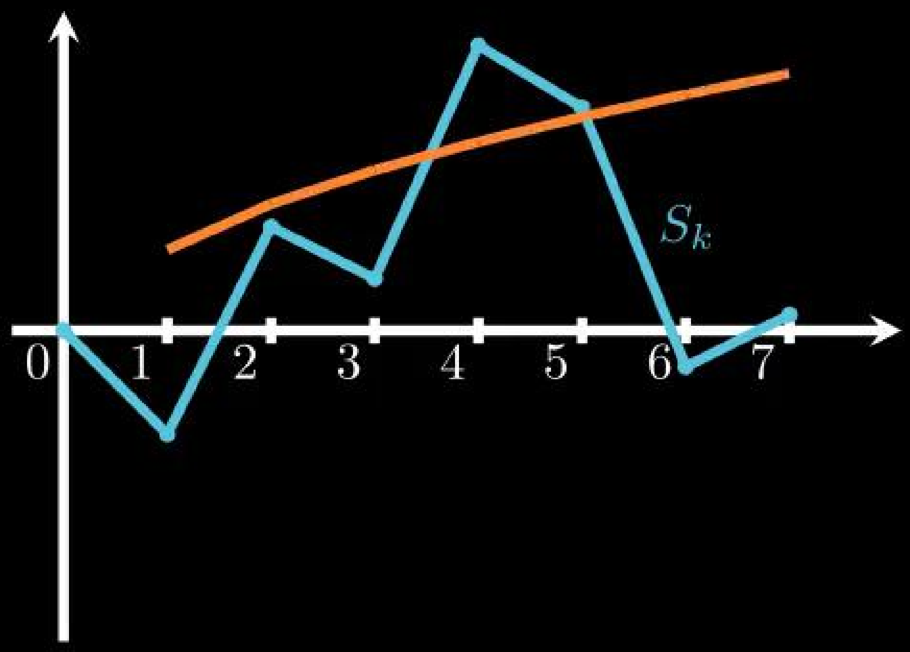

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Then S_k is a supermartingale under $P \in H_0(x_0)$. Combination with time-uniform bounds by Howard et al. (2021) gives p-values from this martingale test (Duan et al., 2020).

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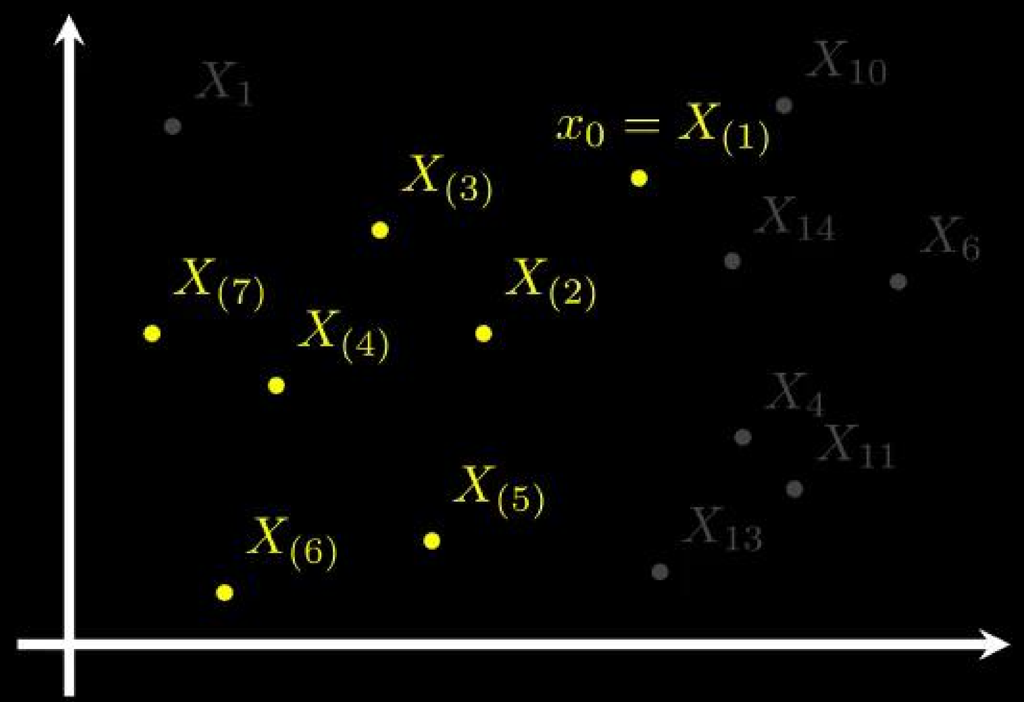

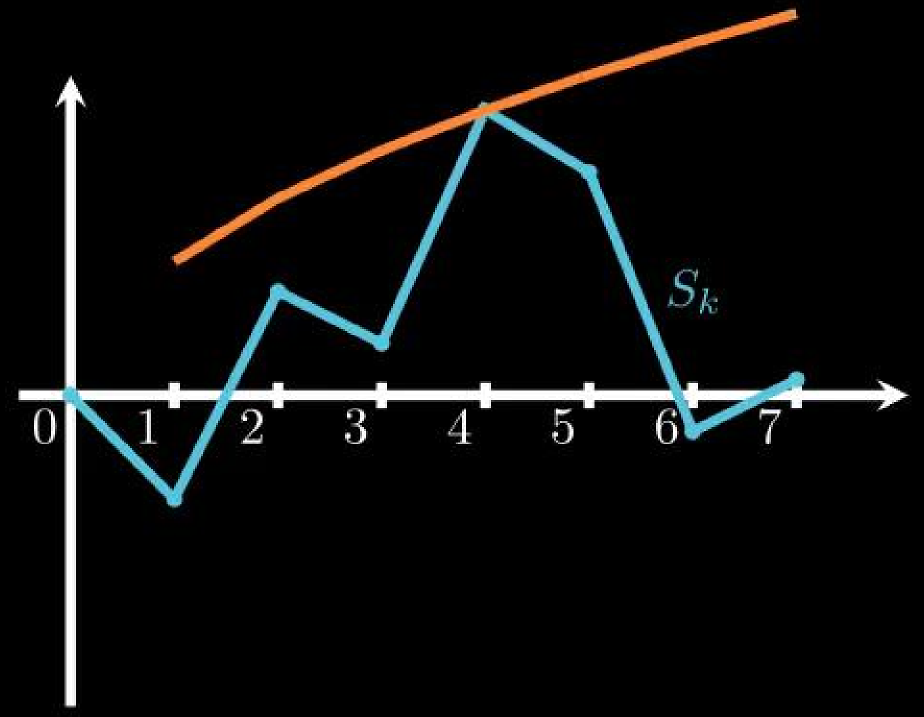

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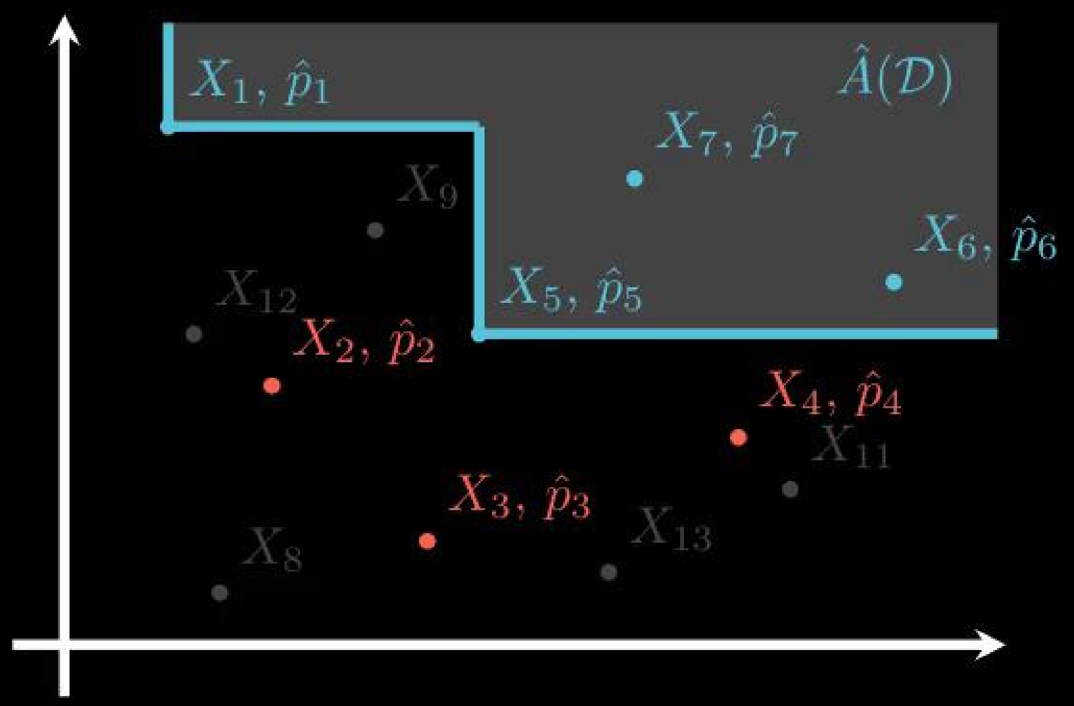

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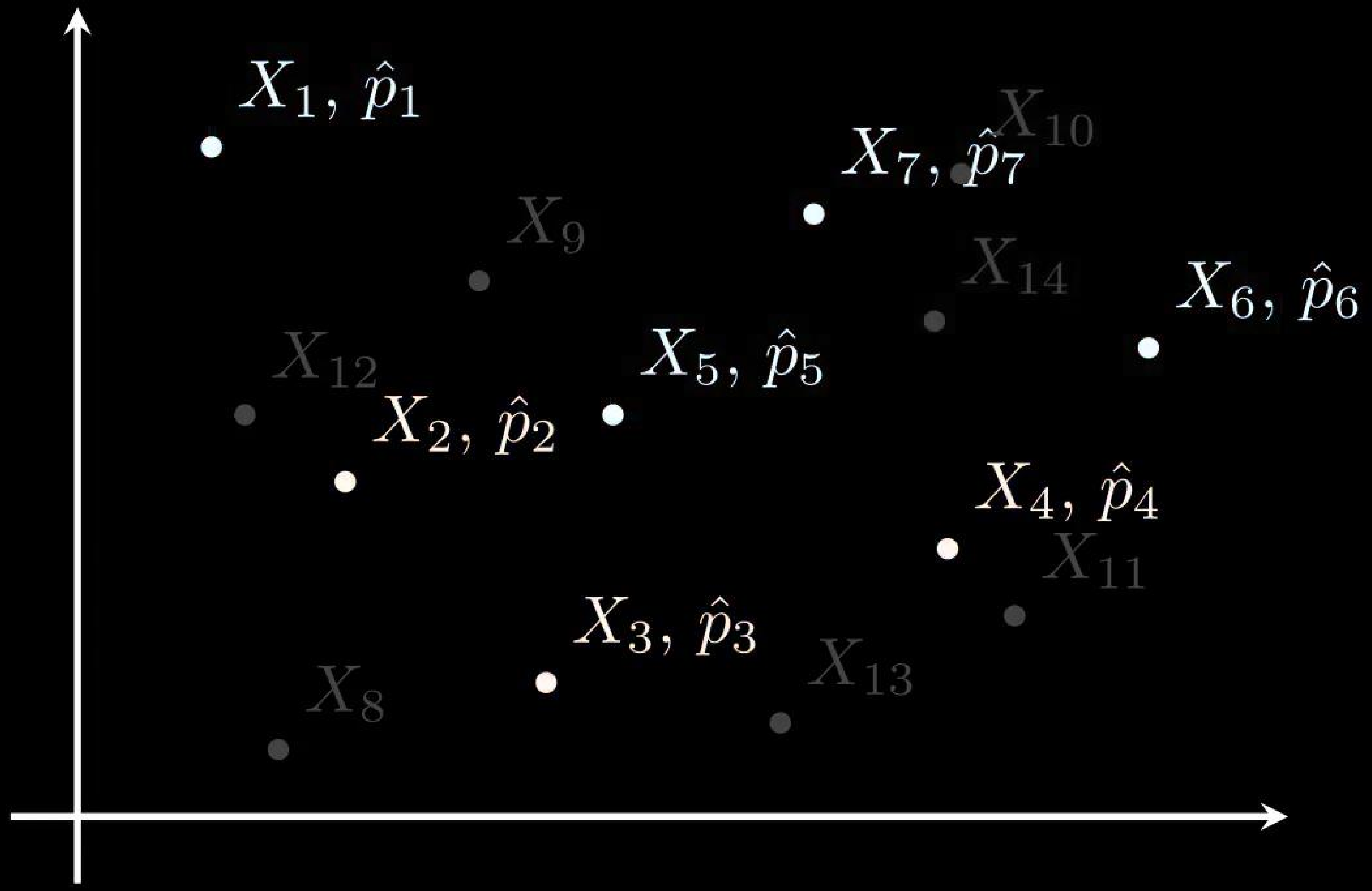

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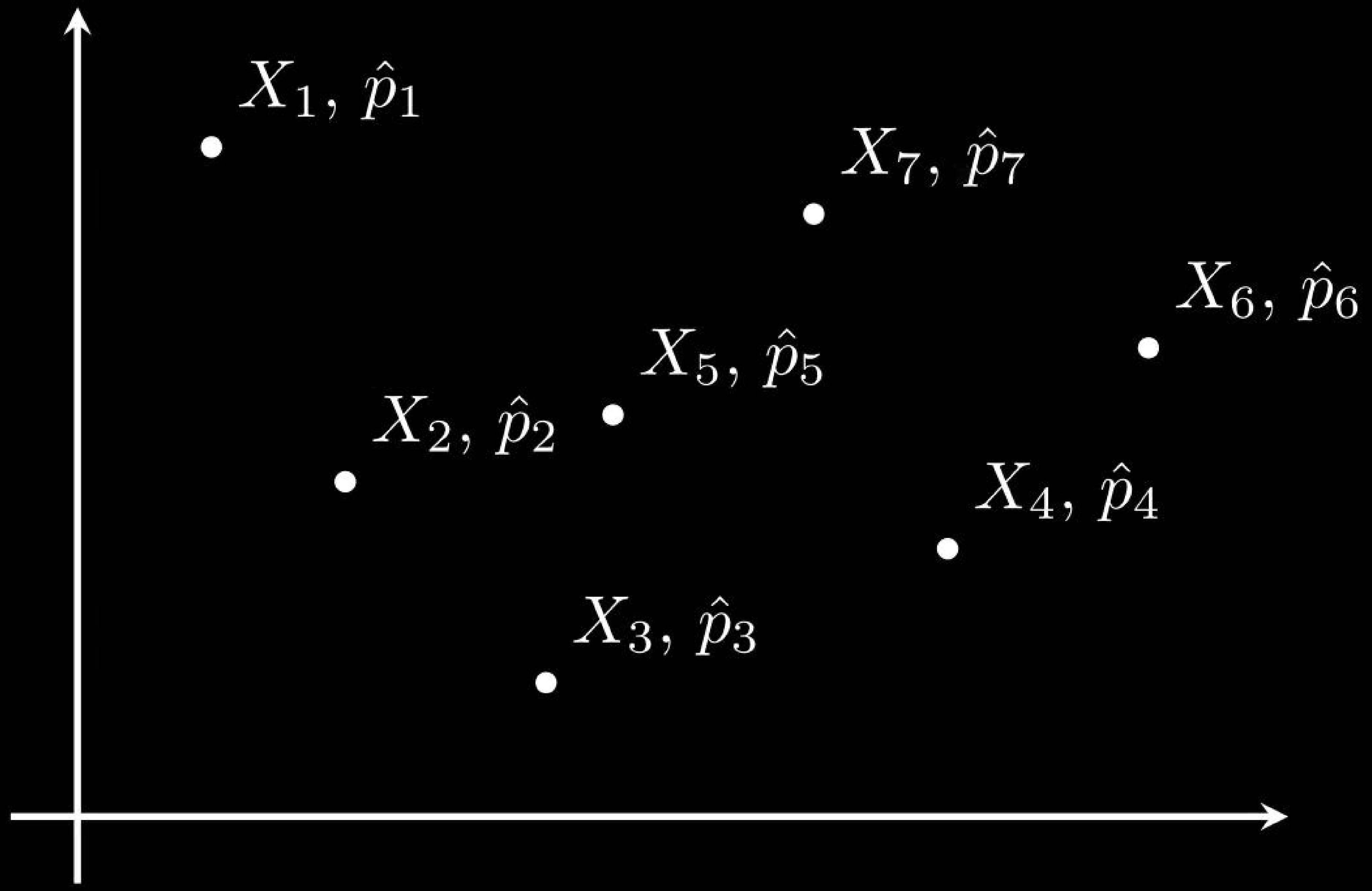

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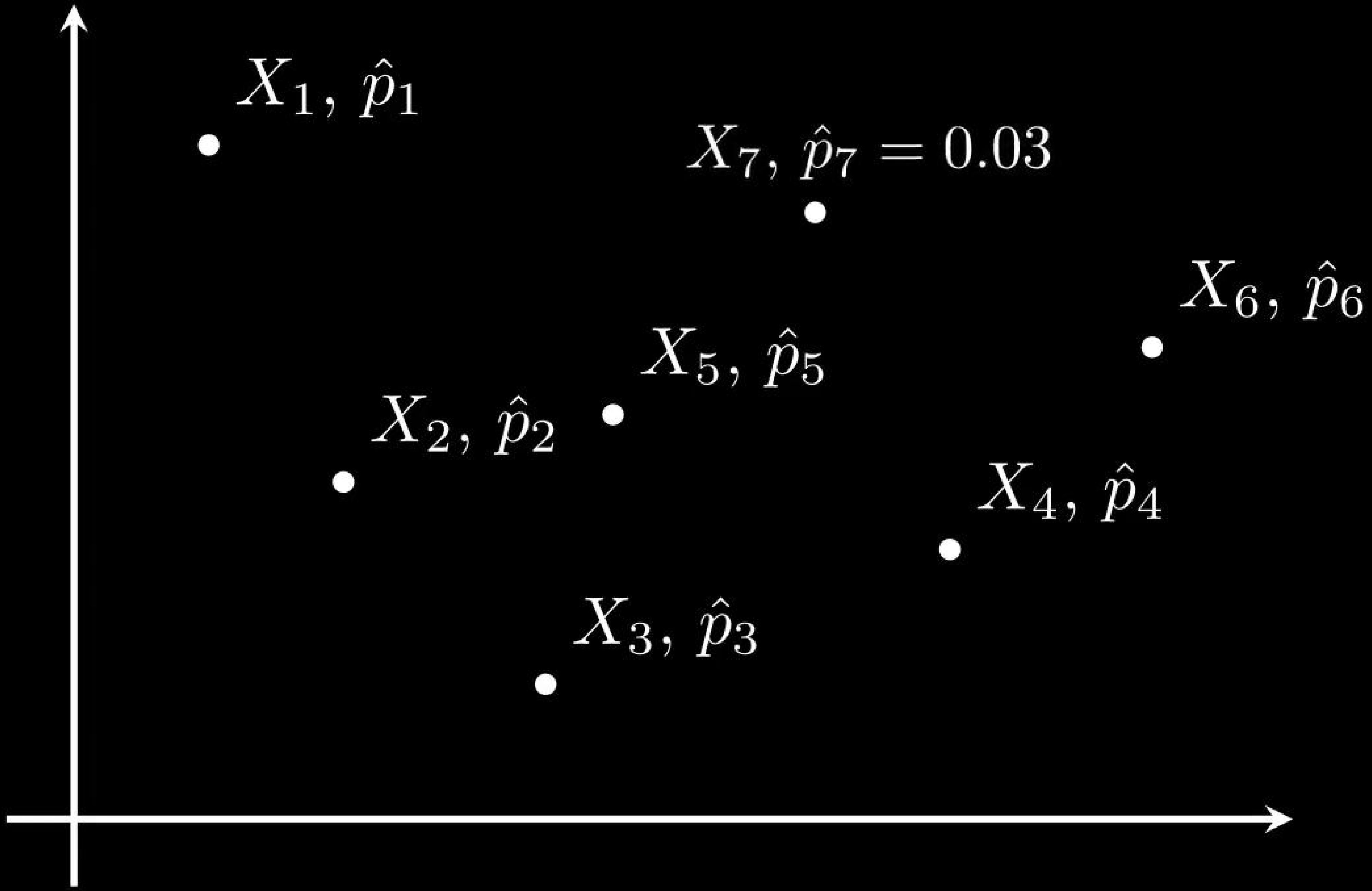

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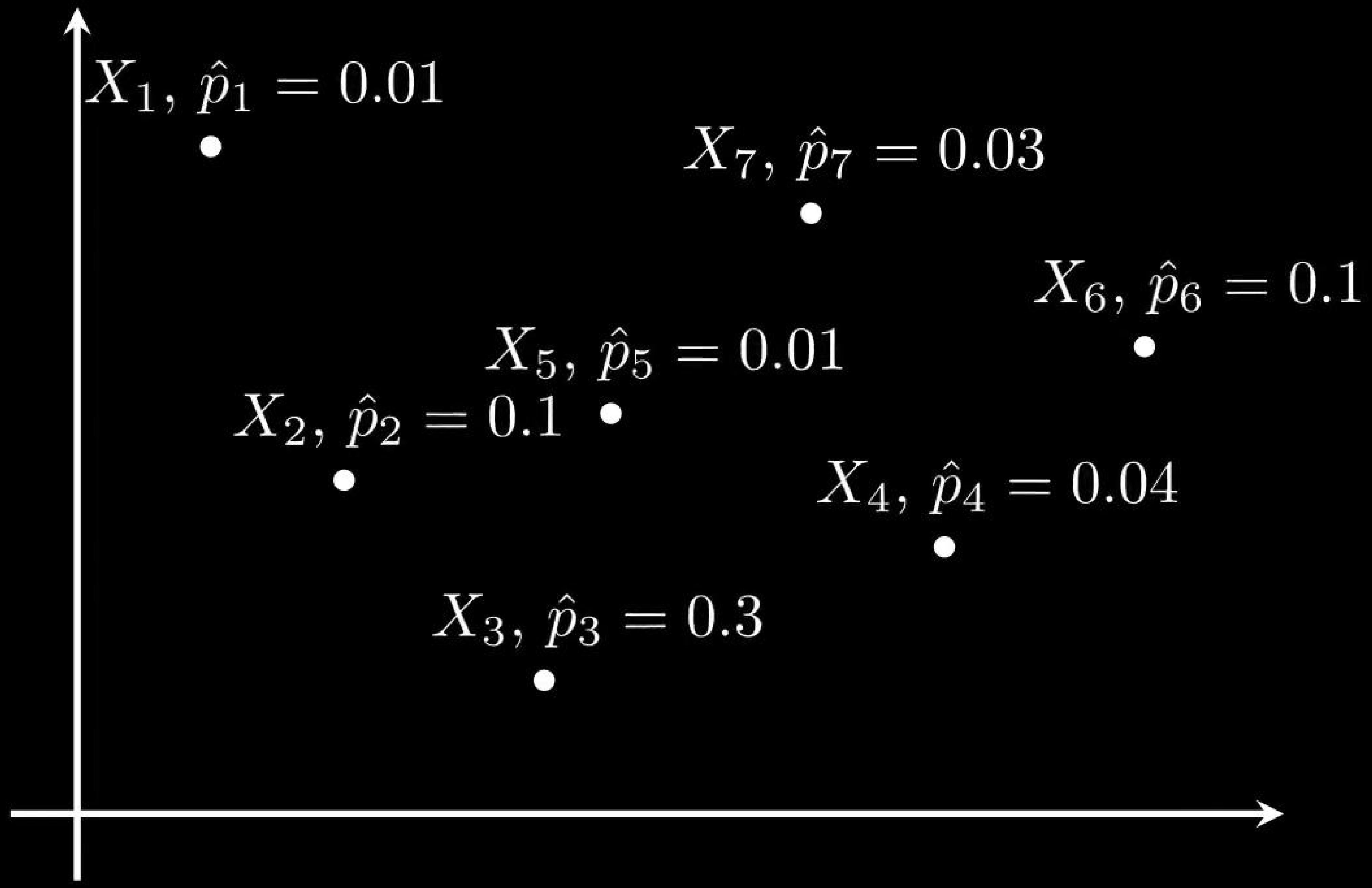

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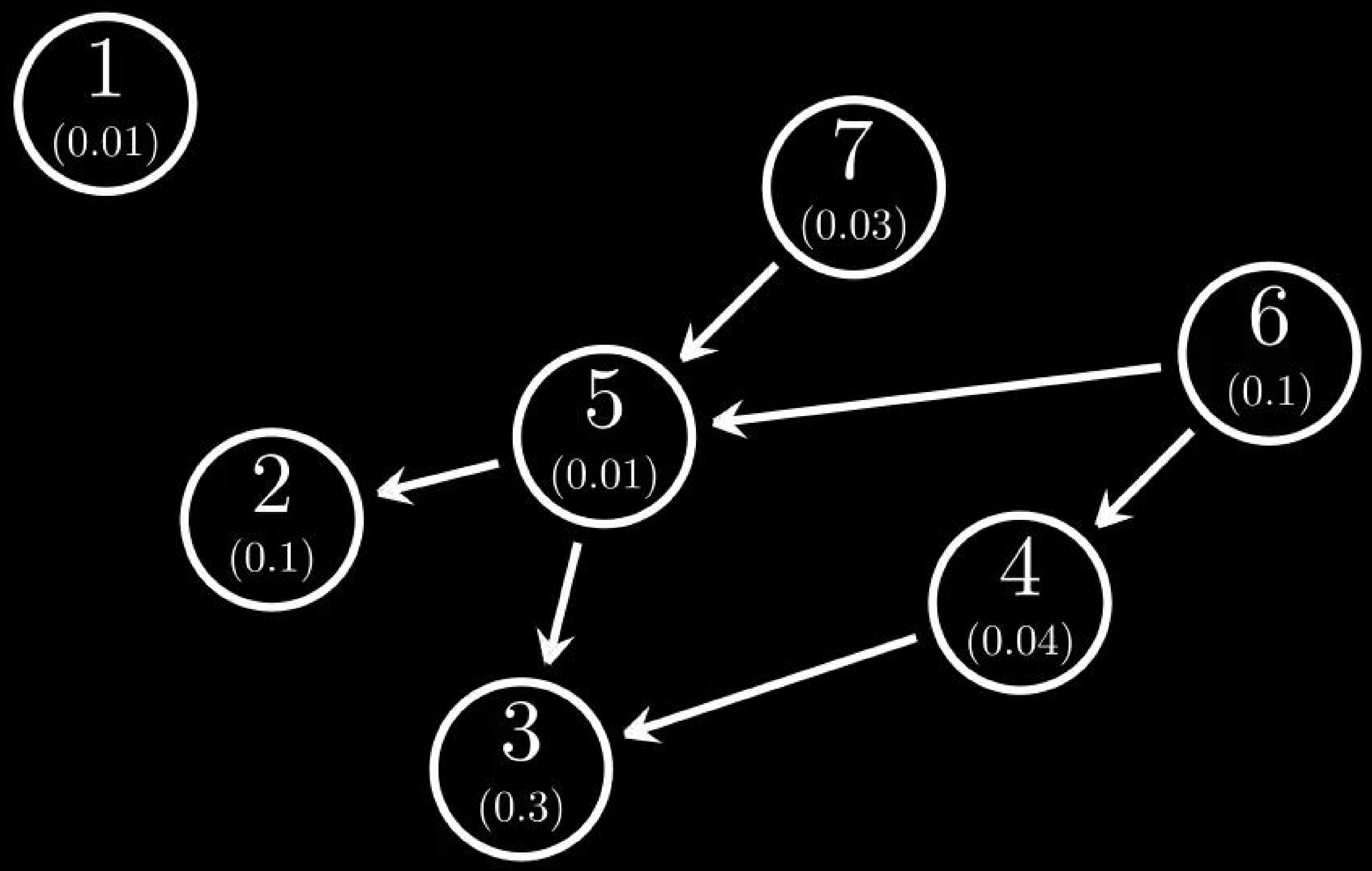

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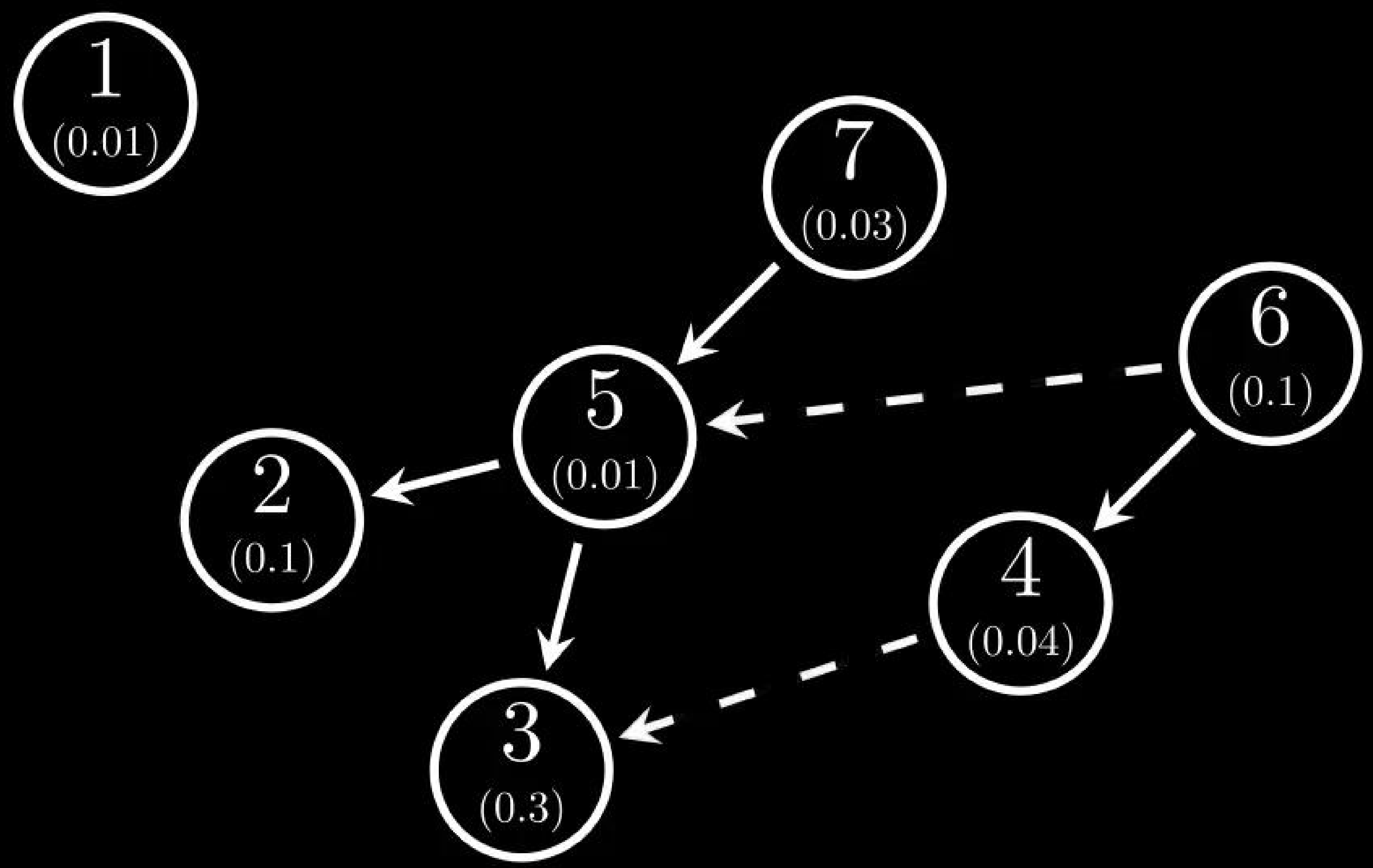

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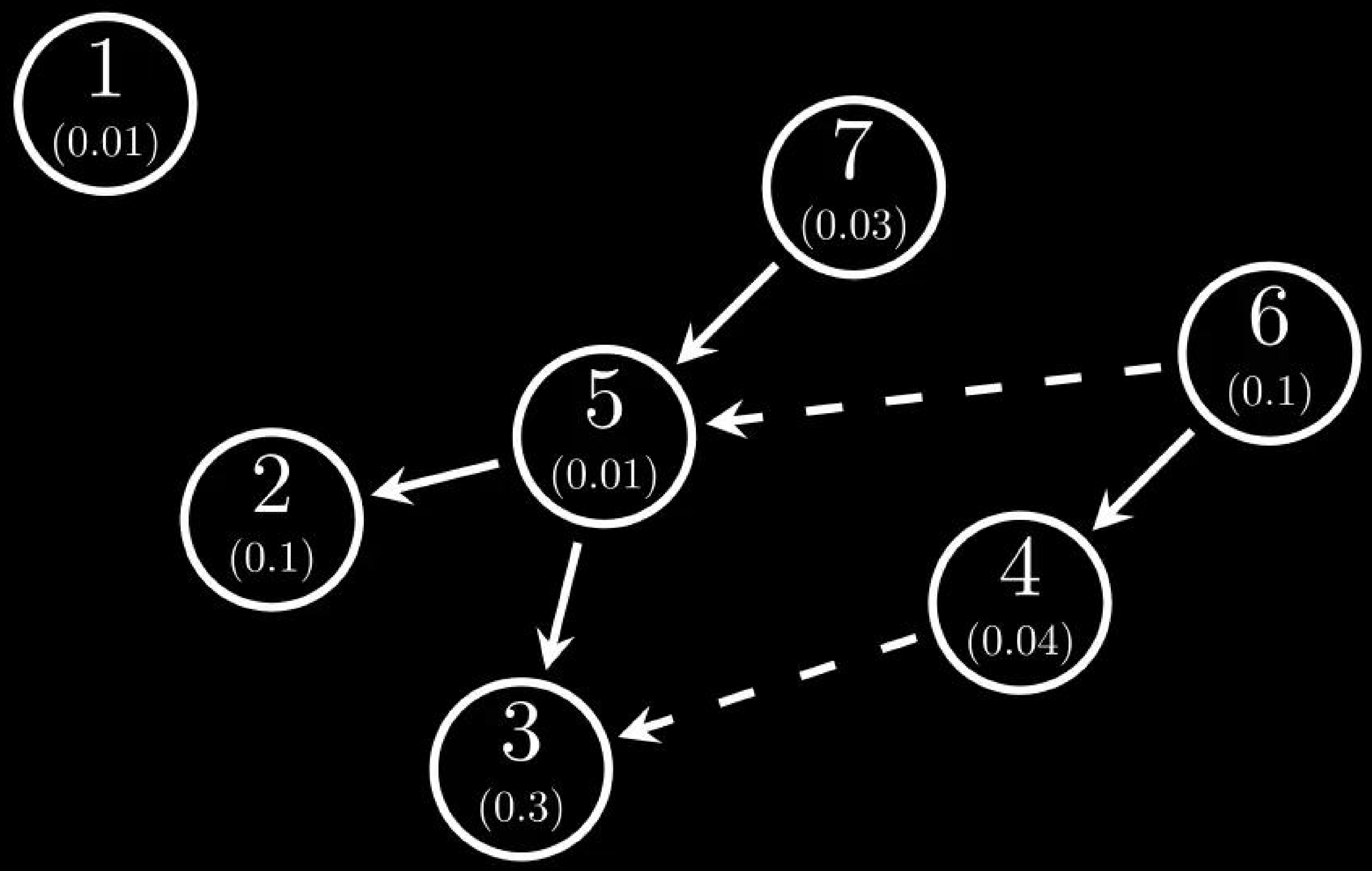

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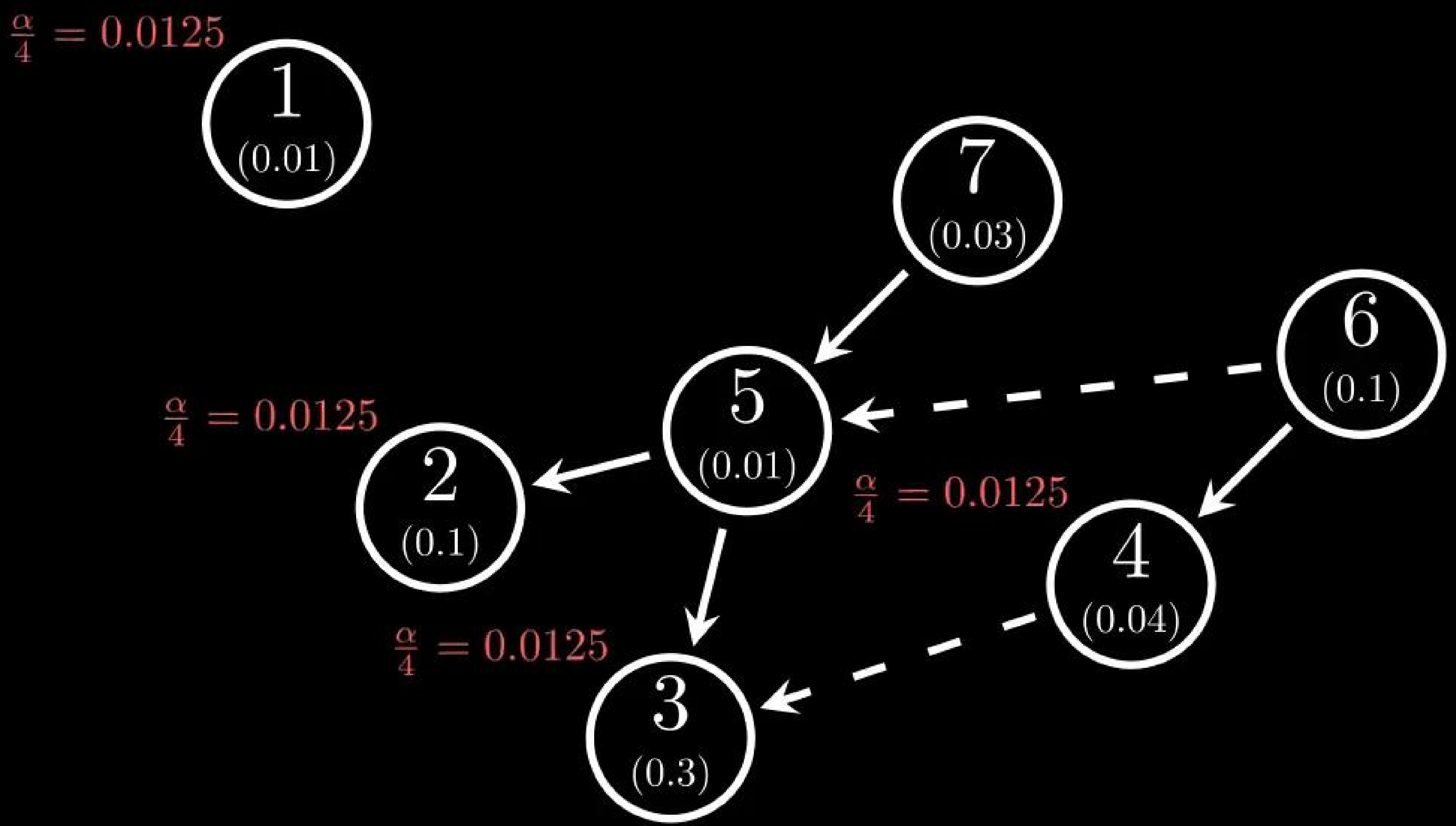

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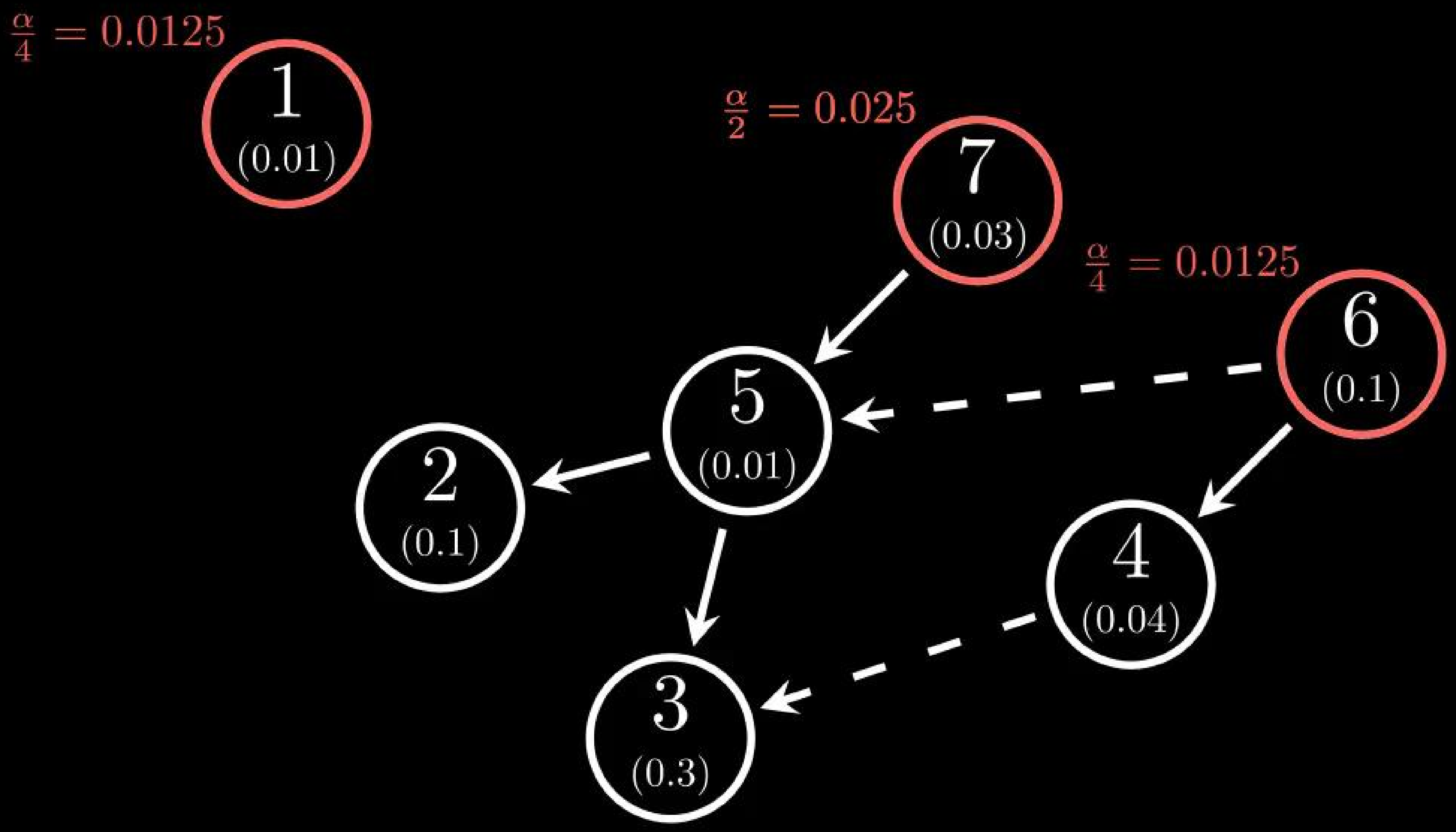

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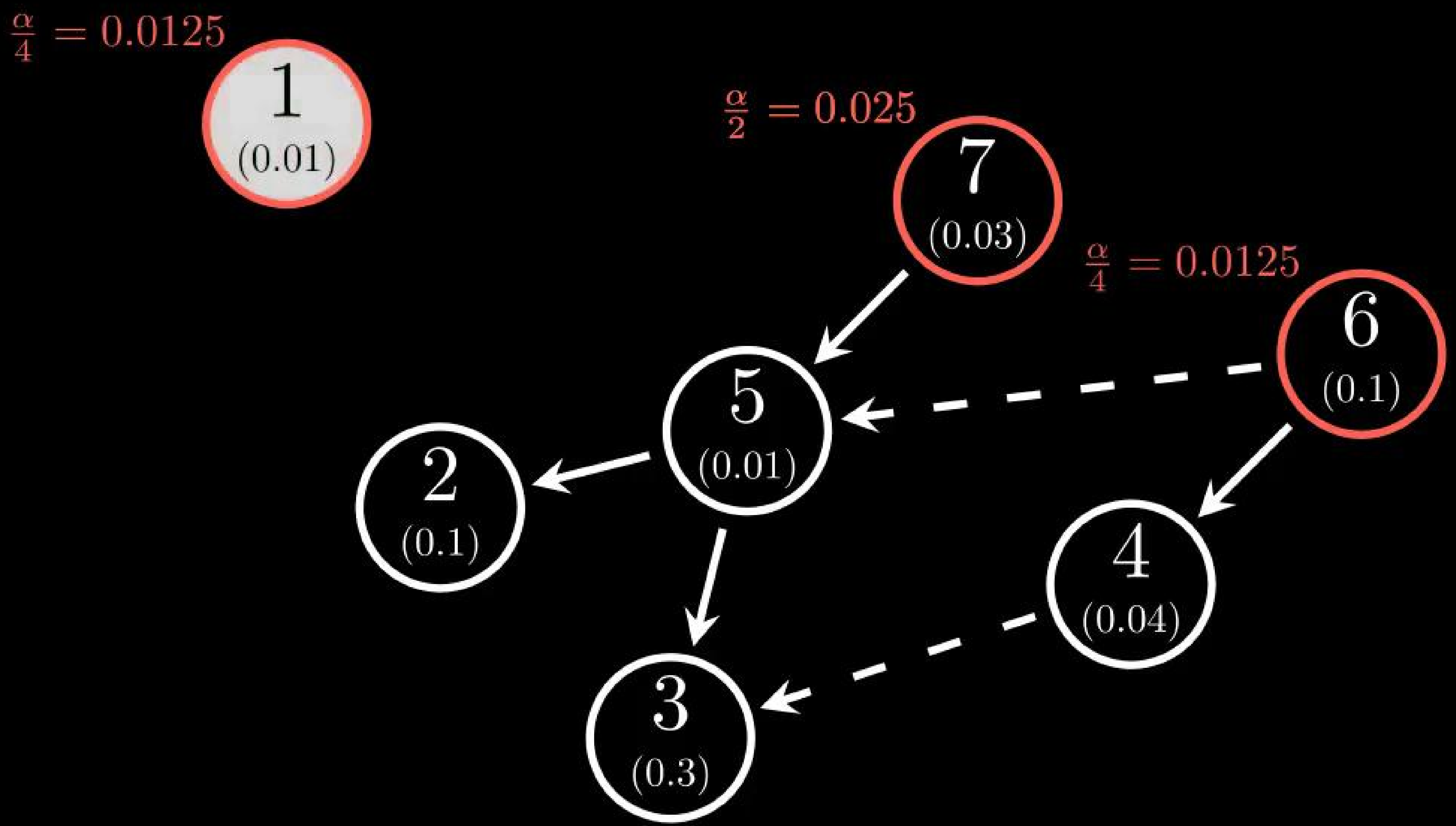

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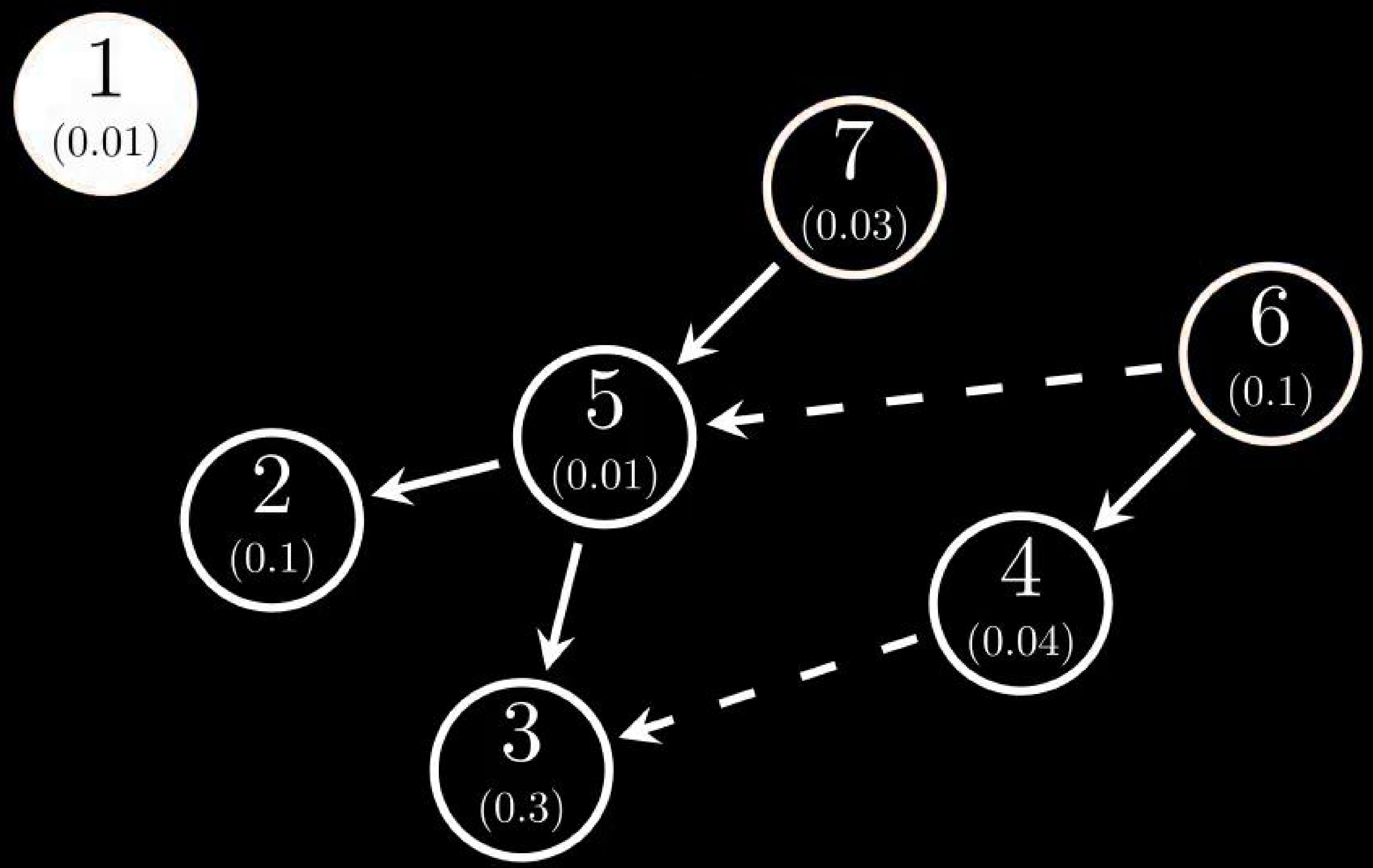

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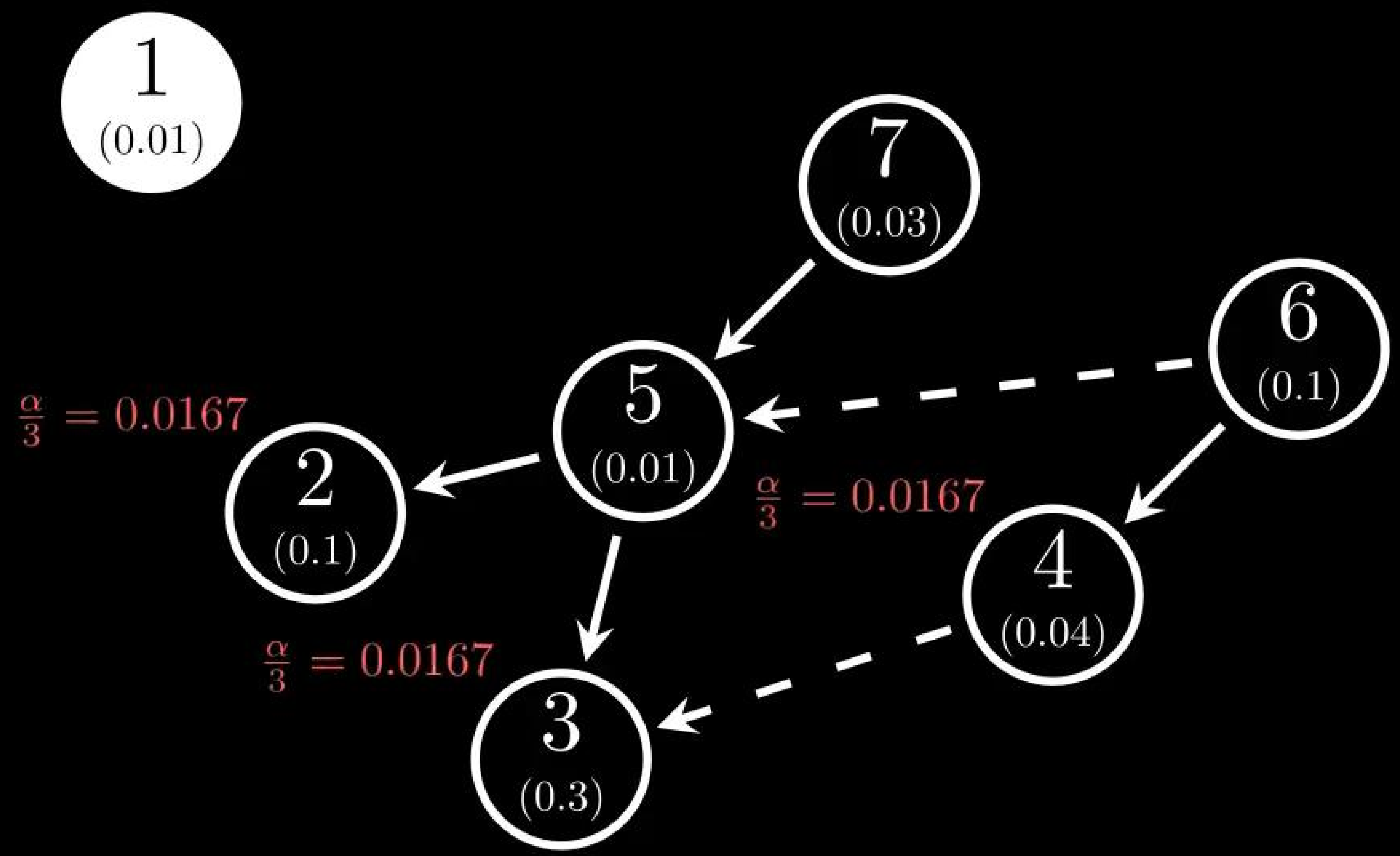

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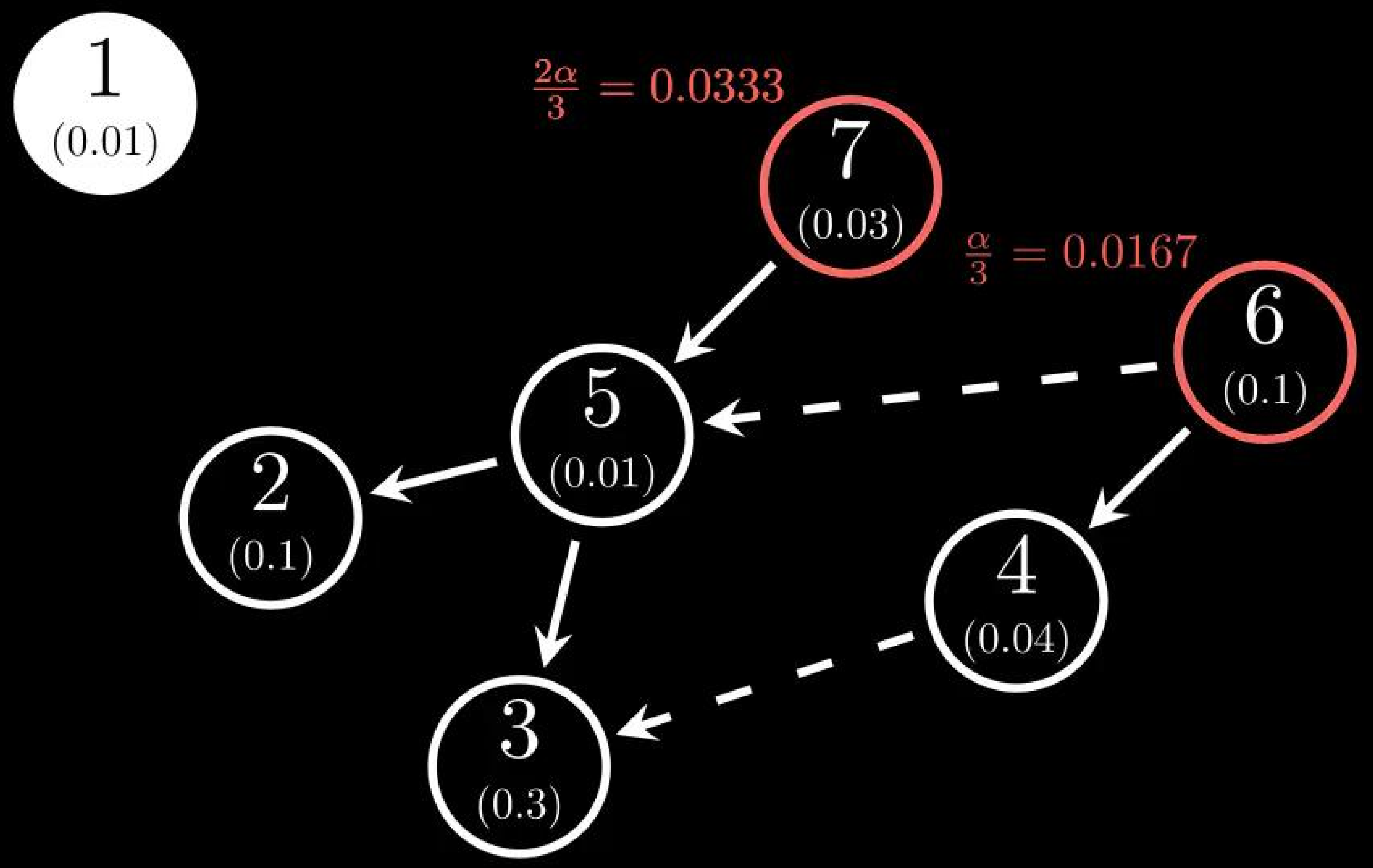

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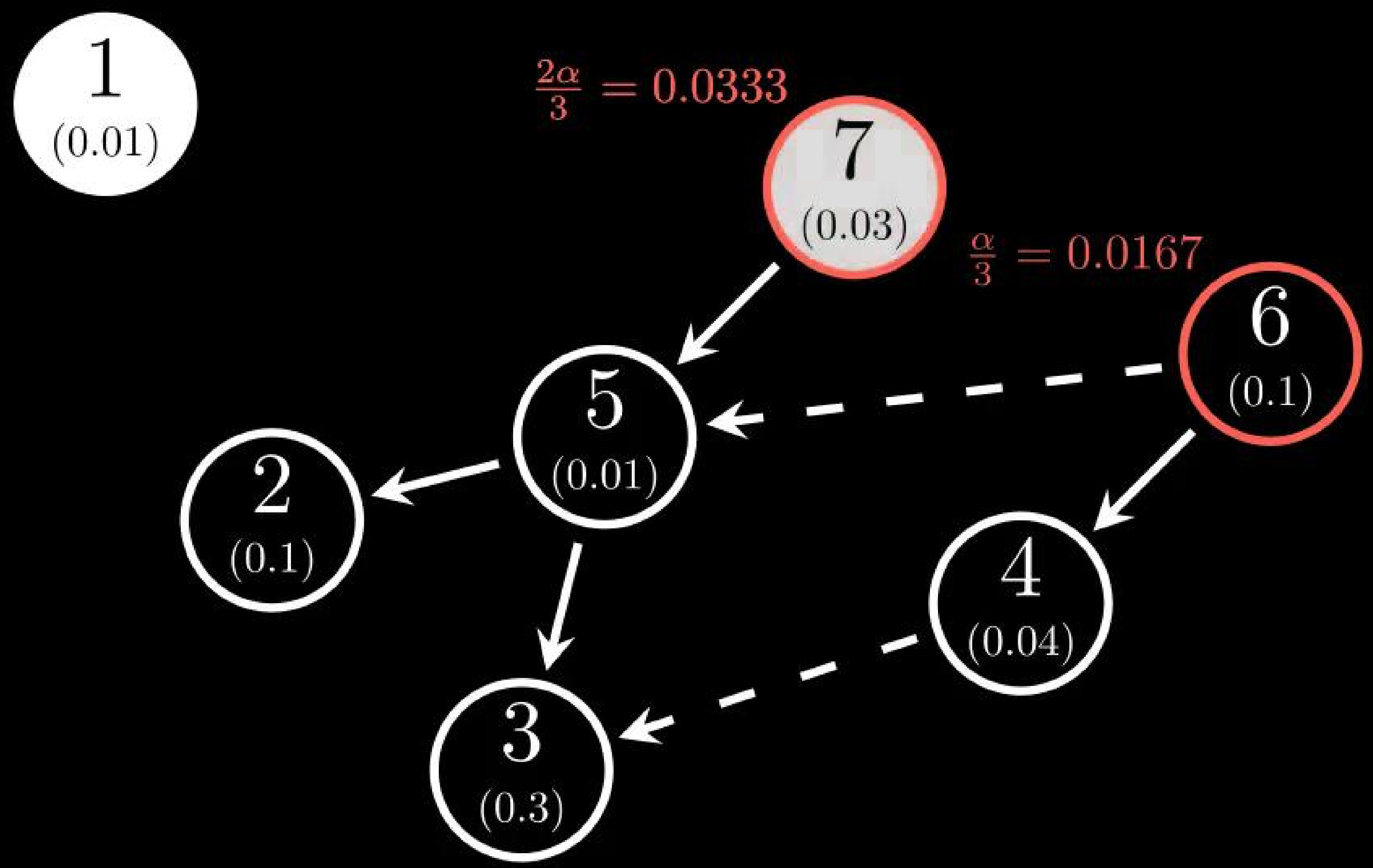

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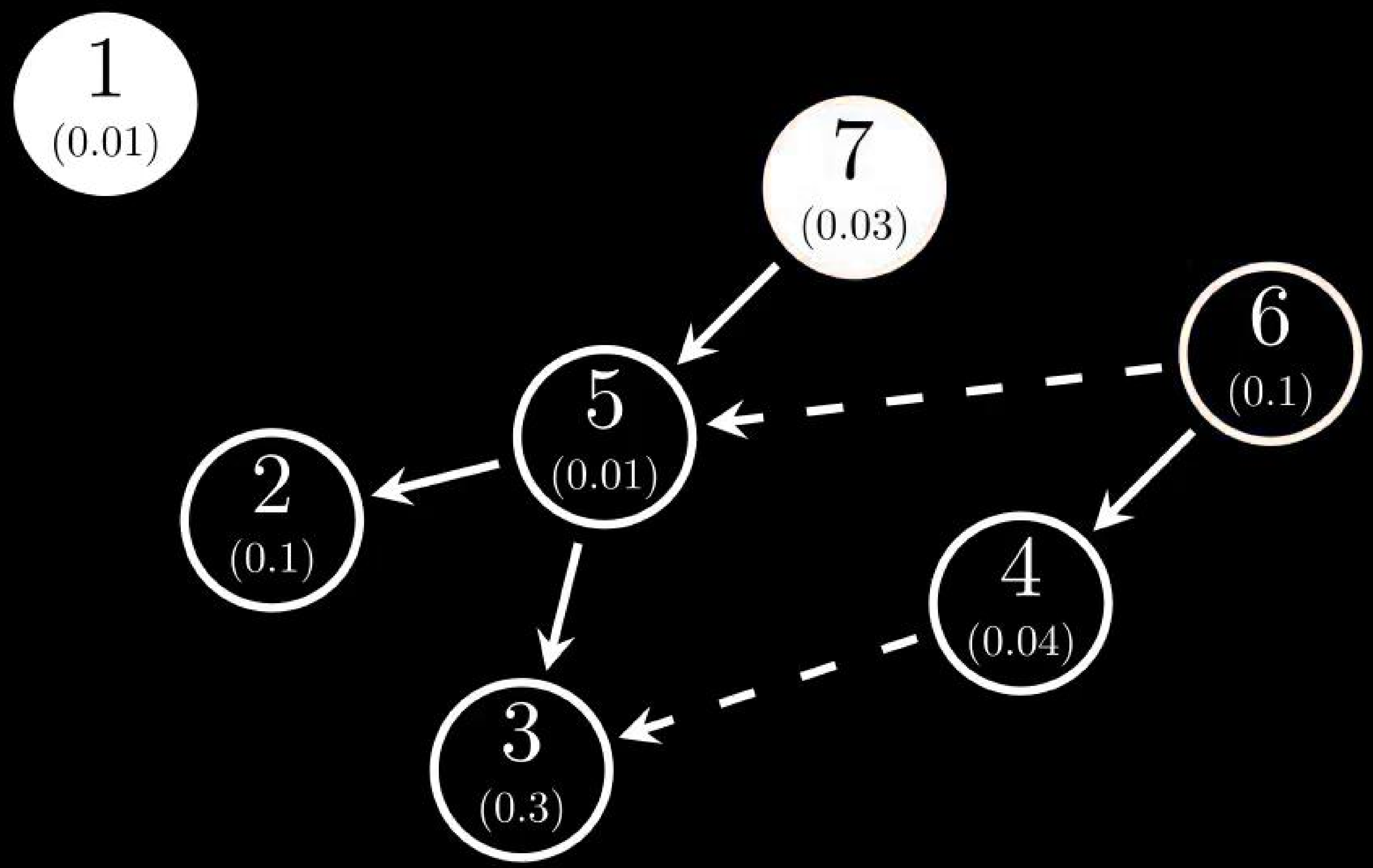

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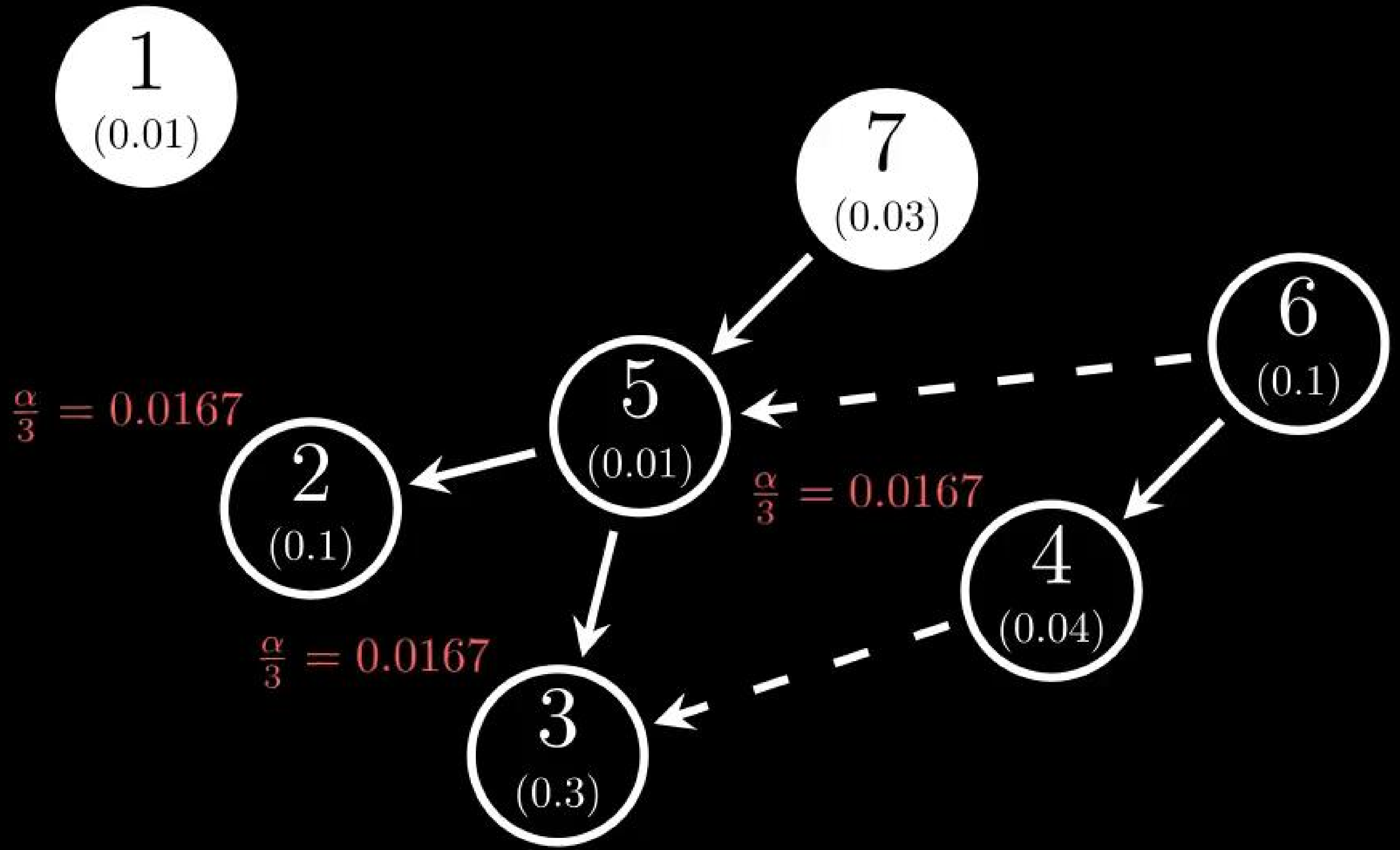

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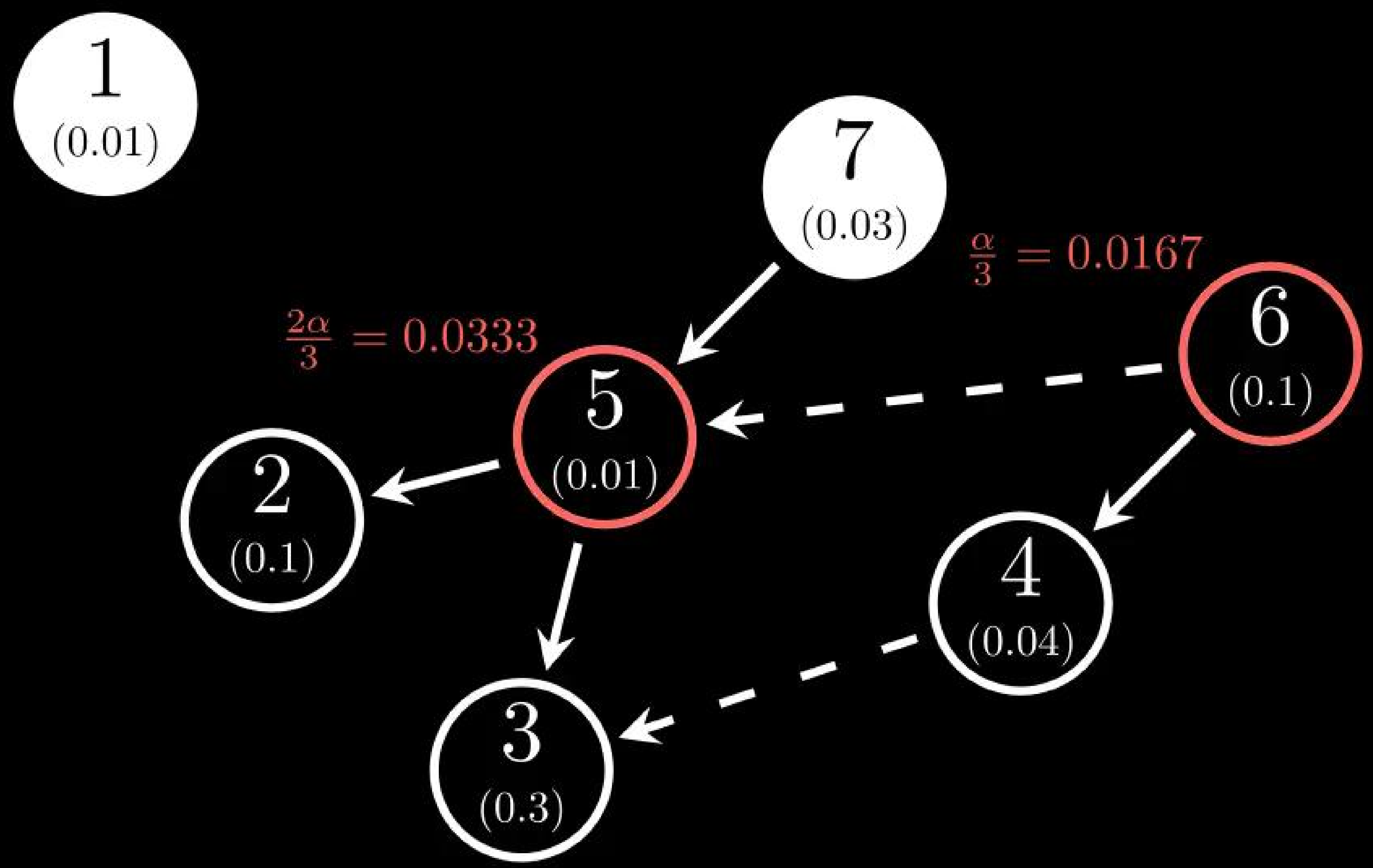

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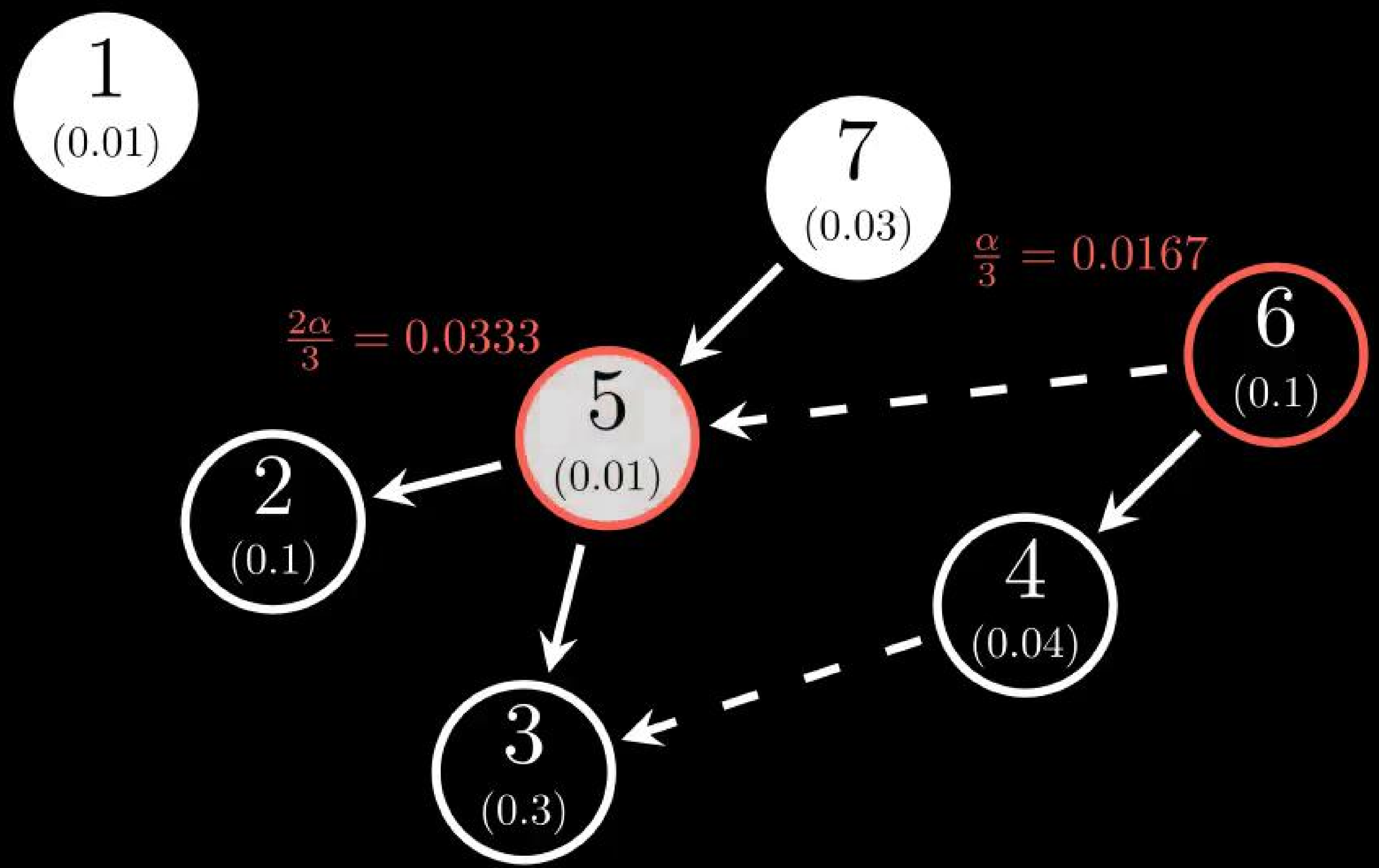

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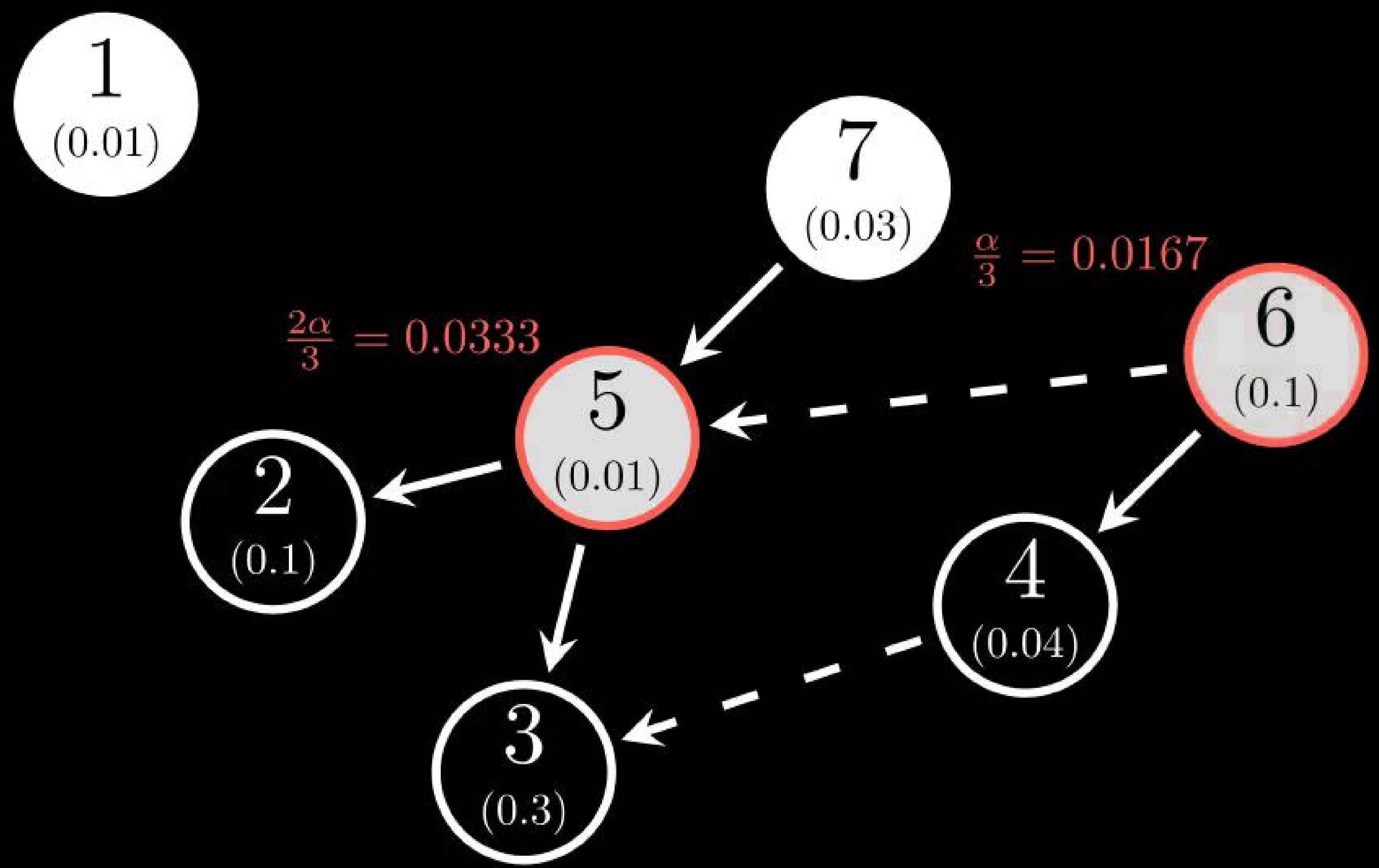

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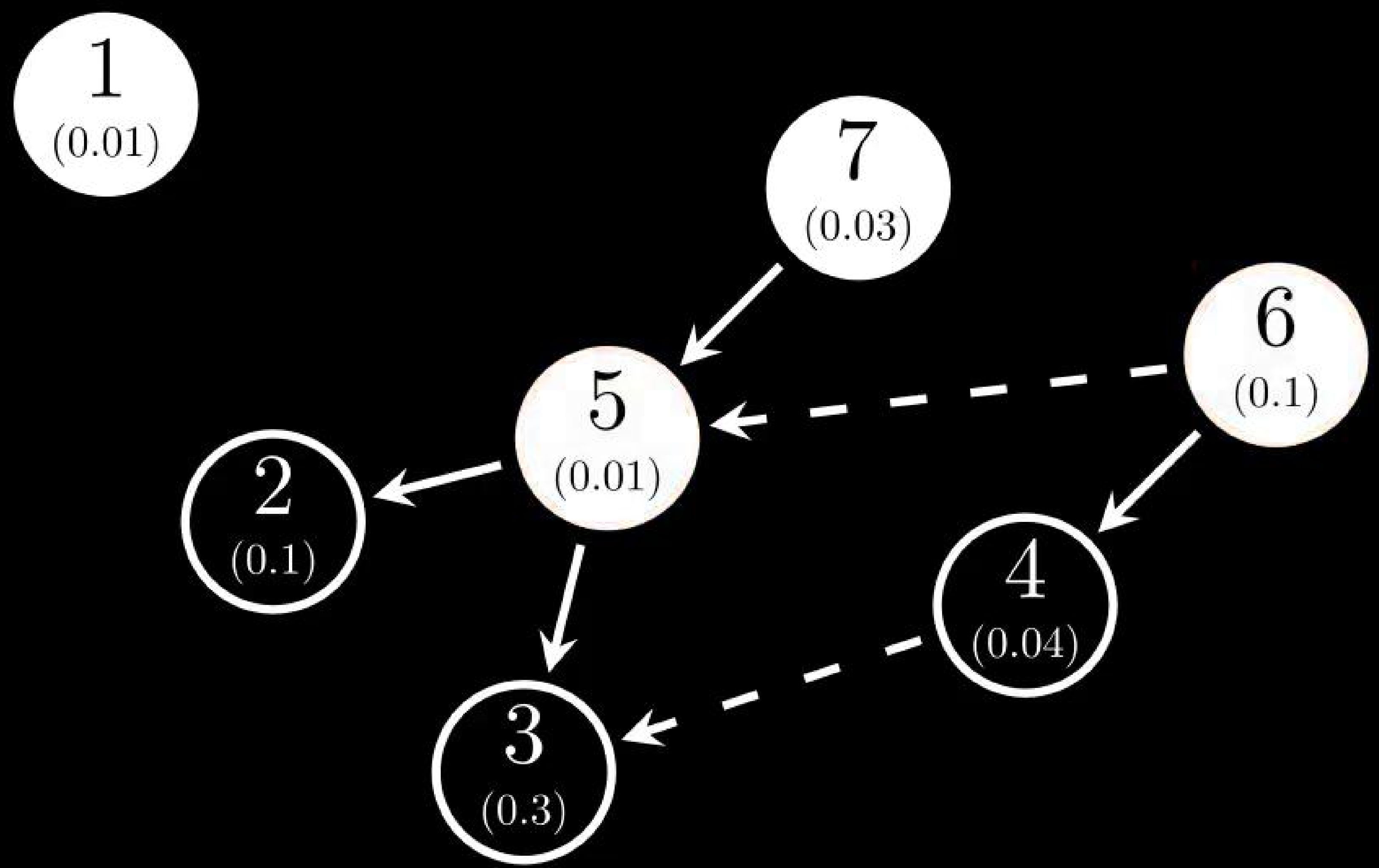

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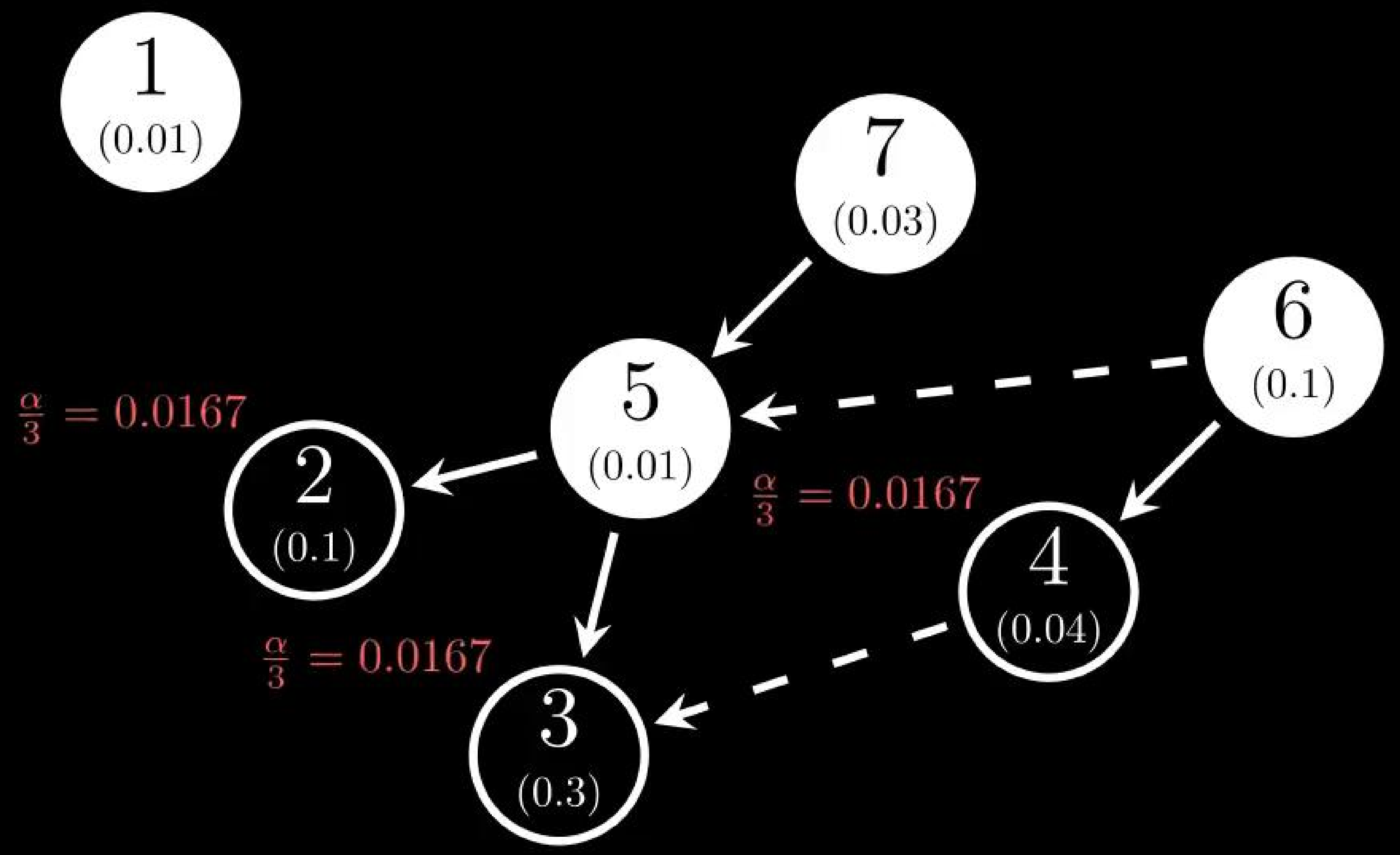

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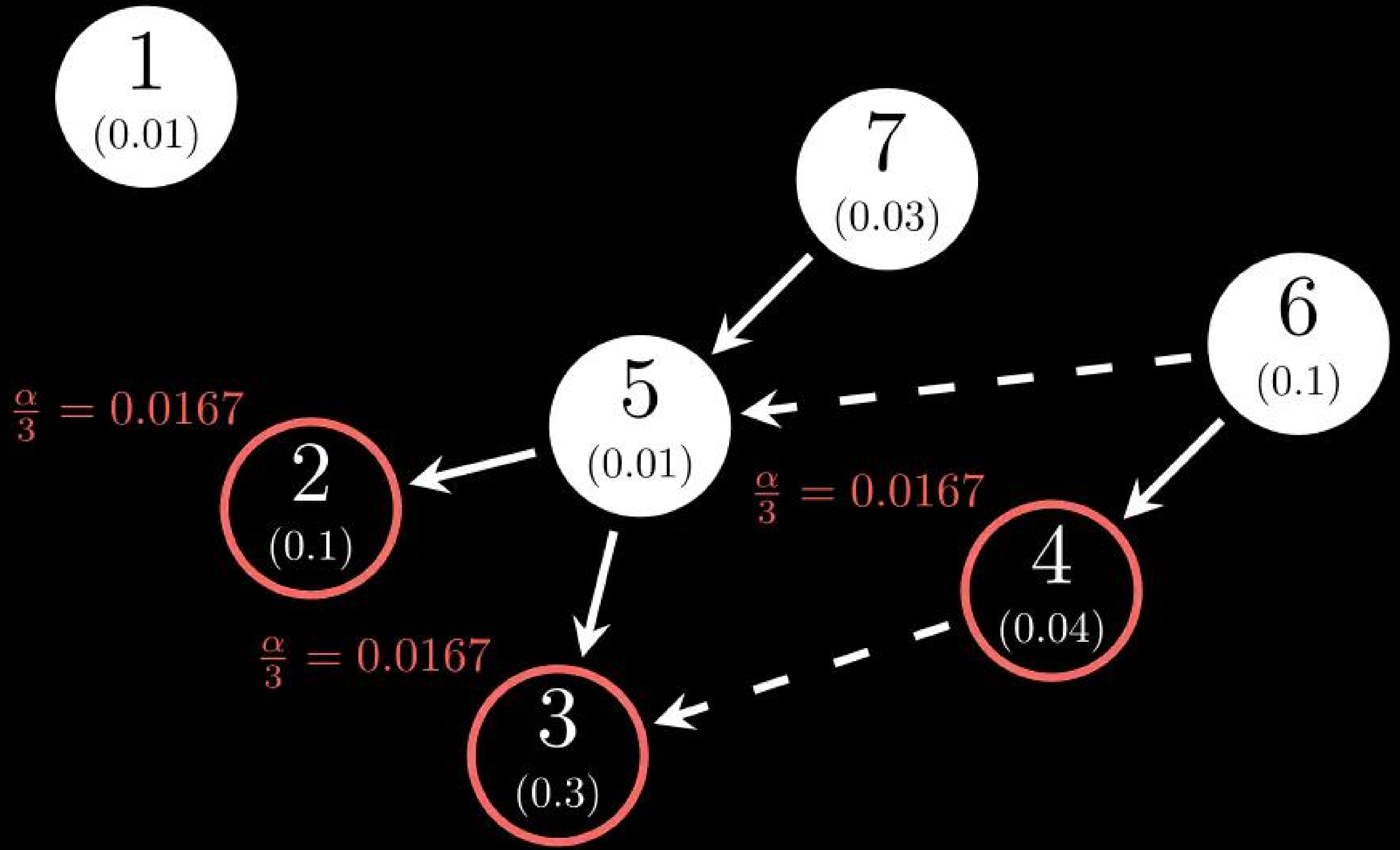

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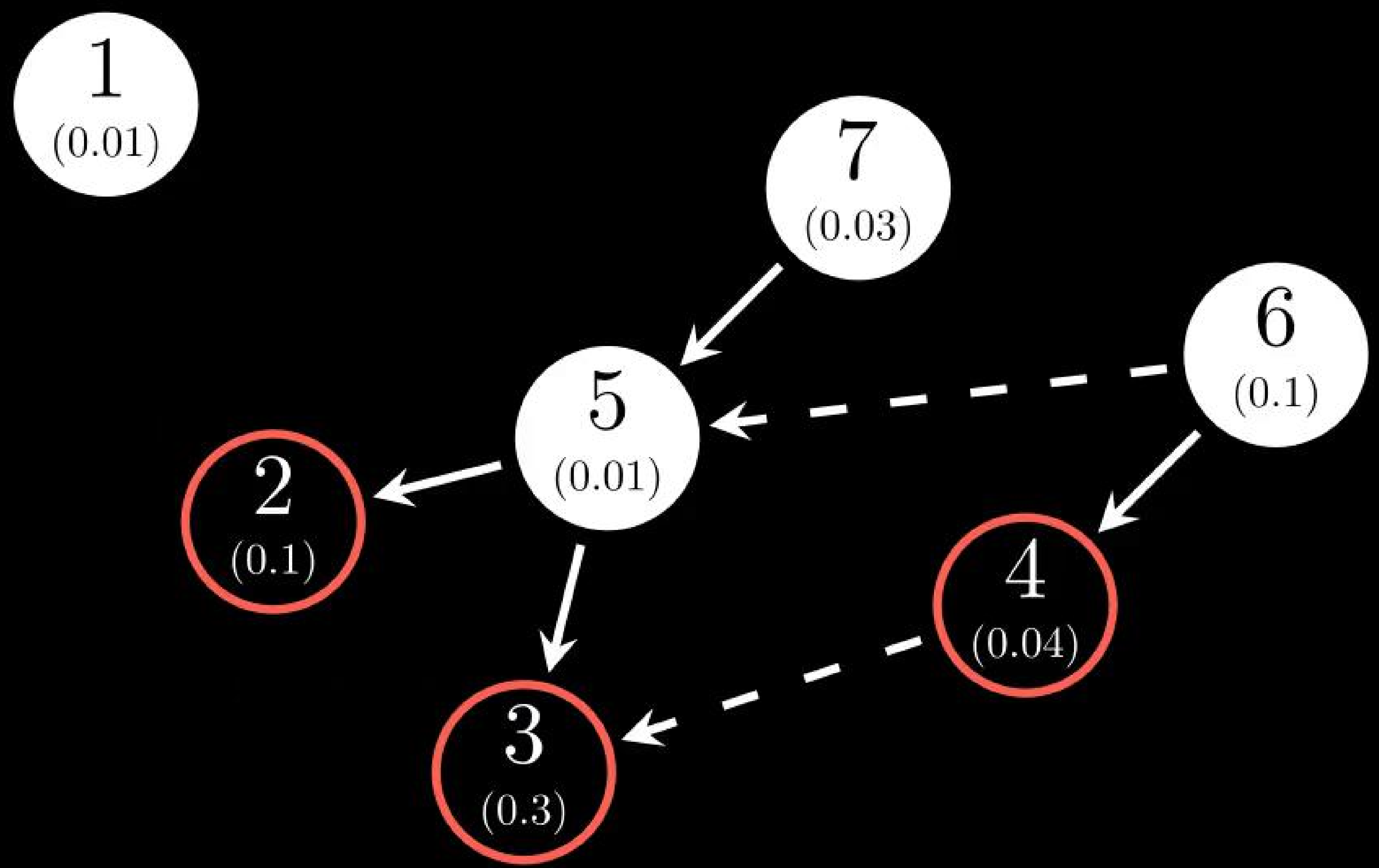

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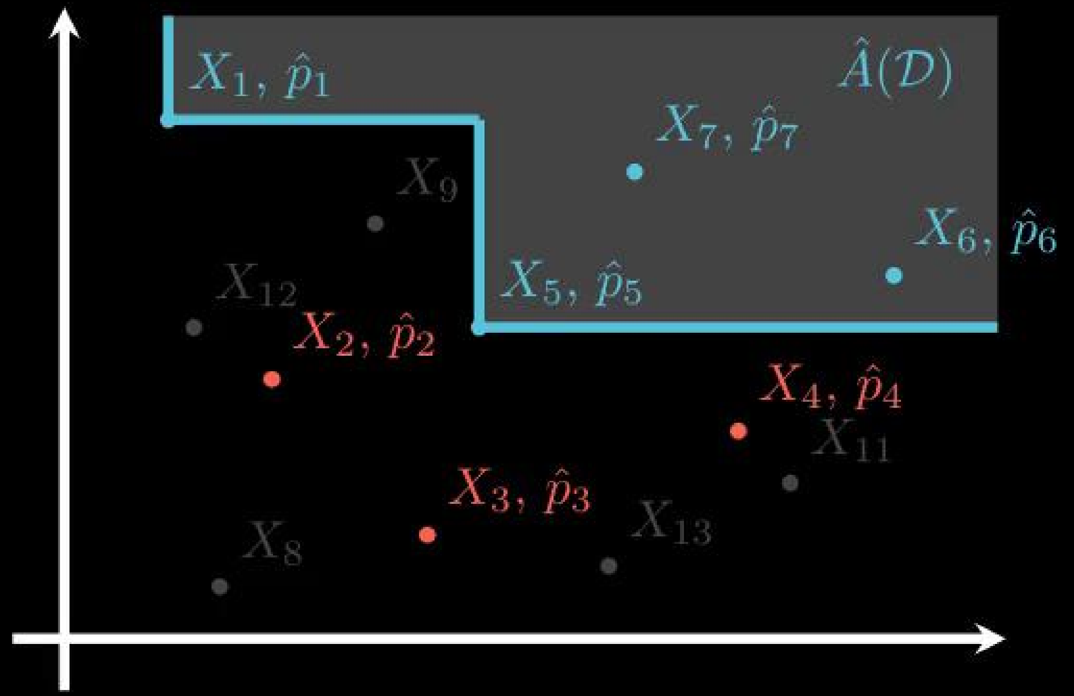

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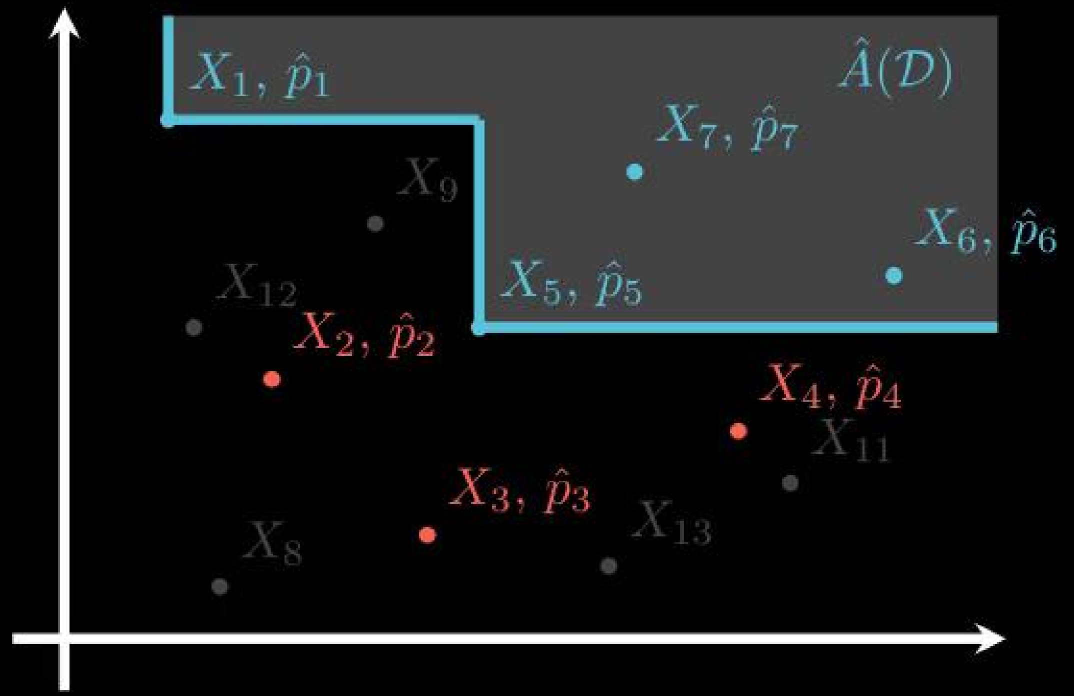

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Theoretical guarantees

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Study/data: AIDS Clinical Trials Group Study 175 (Hammer et al., 1996) — focus on those 532 patients treated with zidovudine. Median follow-up duration of 143 weeks.

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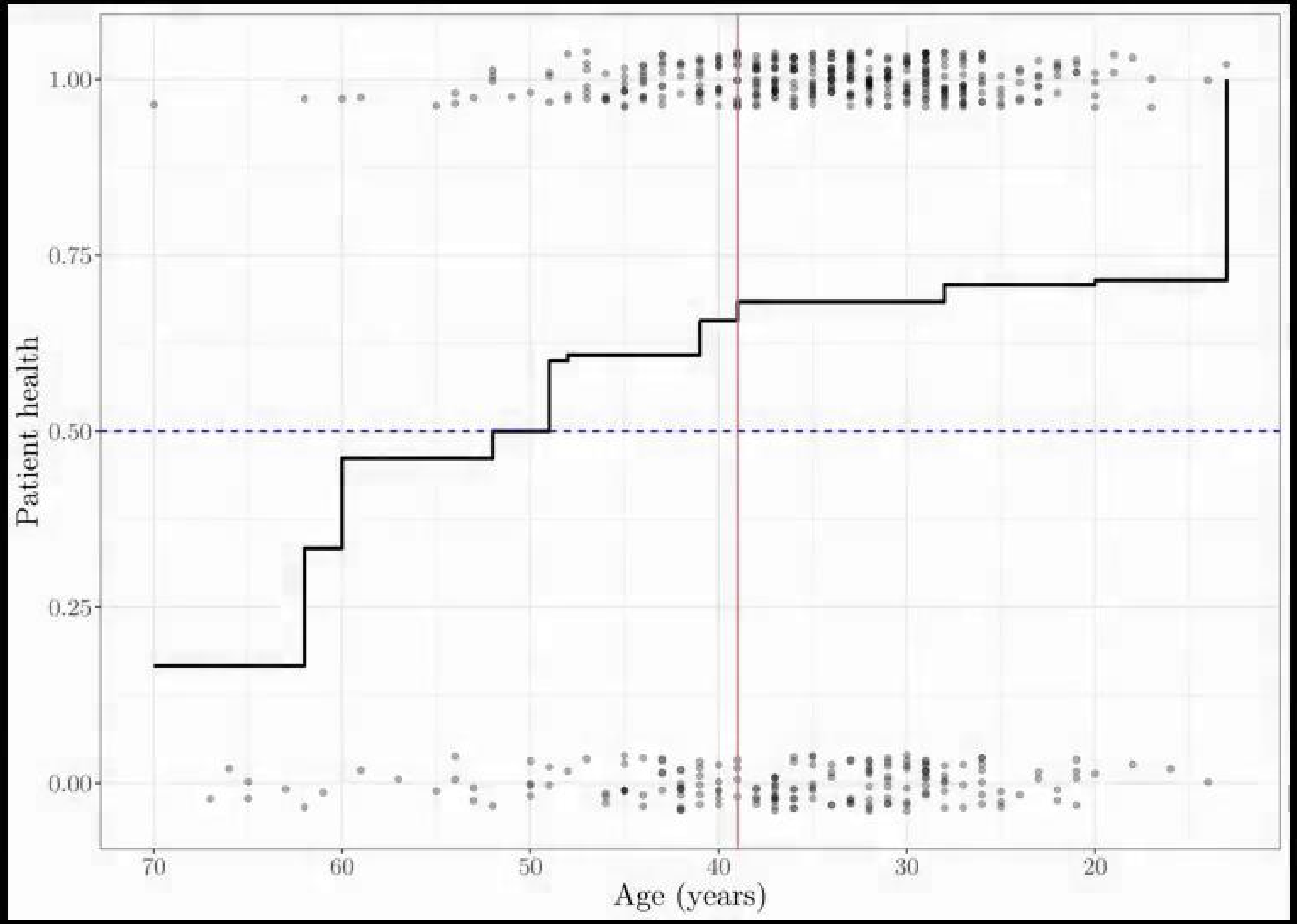

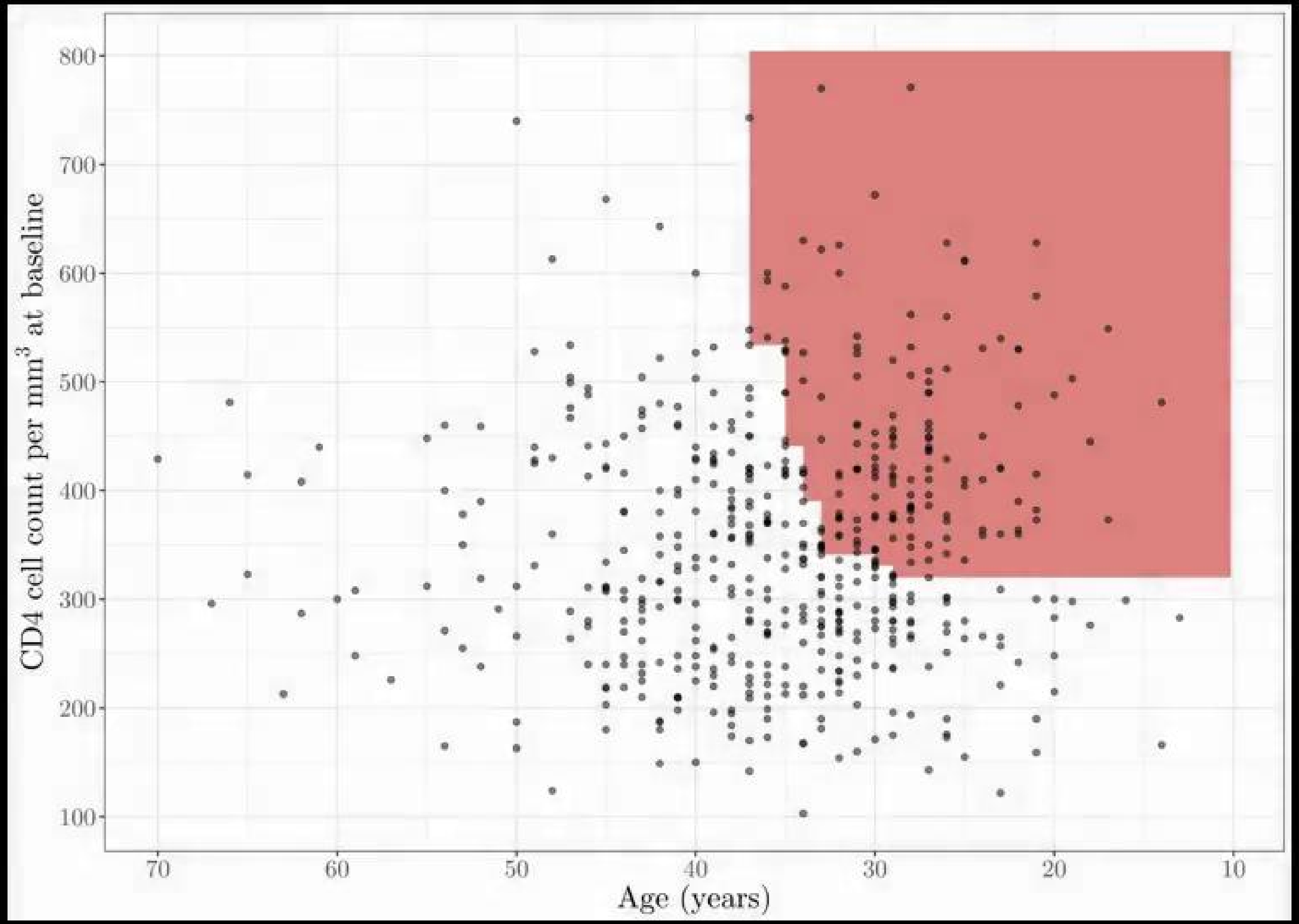

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For $\ell \in \{0, 1\}$, let $\tilde{\eta}^{\ell}(x) := \mathbb{E}(\tilde{Y} | X = x, T = \ell)$, and define the *heterogeneous treatment effect* $\eta(x) := \tilde{\eta}^1(x) - \tilde{\eta}^0(x)$.

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Write $\pi(x) := \mathbb{P}(T = 1|X = x)$ for the *propensity score*, and consider the *inverse propensity weighted response*

$$Y := \frac{T - \pi(X)}{\pi(X)\bigl(1 - \pi(X)\bigr)} \cdot \tilde{Y},$$

so that $\mathbb{E}(Y|X = x) = \eta(x)$ for all $x \in \mathbb{R}^d$.

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Hence, for P such that $\mathcal{D} = \bigl((X_1, Y_1), \ldots, (X_n, Y_n)\bigr) \sim P^n$, we have $\tilde{\eta}^1(x) \geq \tilde{\eta}^0(x) + \tau$ for all $x \in \hat{A}^{\mathrm{ISS}}$ with probability at least $1 - \alpha$ whenever $P \in \mathcal{P}_{\mathrm{Mon},d}(\sigma)$.

Heterogeneous treatment effects: application

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Study/data: AIDS Clinical Trials Group Study 175 (Hammer et al., 1996). Treatments: zidovudine only ($T = 0$, $n = 532$) versus zidovudine together with zalcitabine ($T = 1$, $n = 524$).

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Application of our method: Let $\tilde{Y}$ be the difference in CD4 cell count between week 20 and week 0.
Calculate inverse propensity weighted responses Y_i with $\pi(x) \equiv 1/2$.
Apply our method with $\tau = 1/2$ (and $\alpha = 0.05$) to transformed responses $\mathbb{1}\{Y_i \geq 0\}$.
Reasoning: $\mathbb{P}(Y_i \geq 0 \mid X_i = x) \geq 1/2 \iff \eta(x) \geq 0$ (under symmetry).

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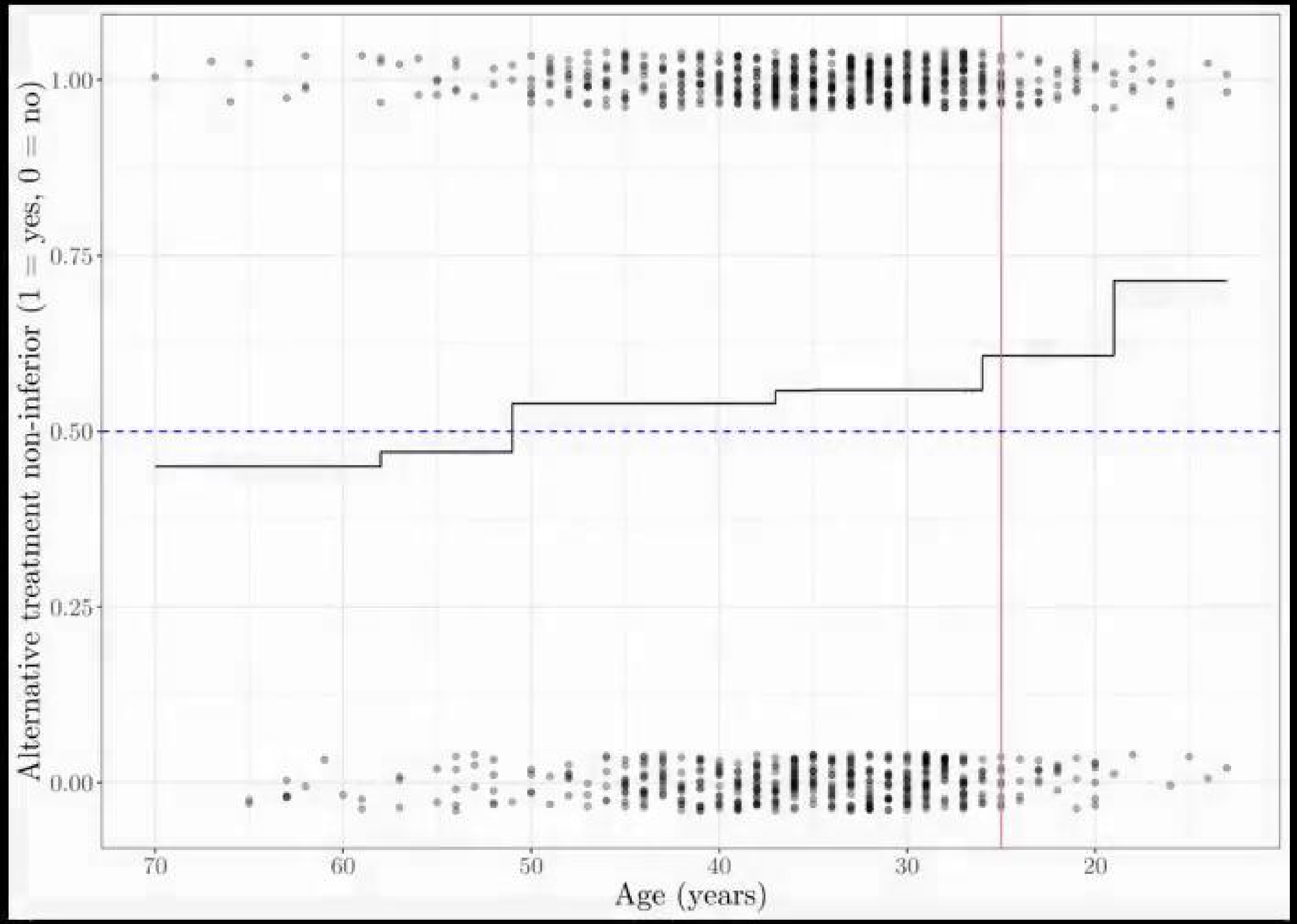

Extensions in the paper

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Take-home messages

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In common situations, no smoothing-parameters have to be specified.

References and acknowledgement

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Thank you!

Main reference:

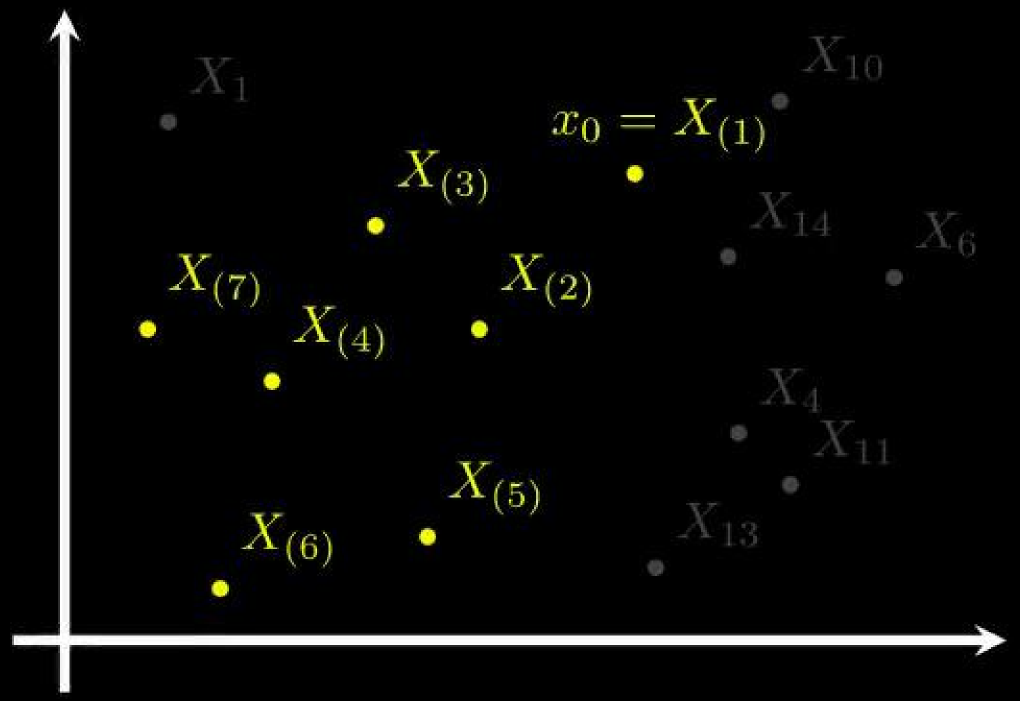
Müller, M. M., Reeve, H. W. J., Cannings, T. I. and Samworth, R. J. (2024) Isotonic subgroup selection. *J. Roy. Statist. Soc., Ser. B (to appear). arXiv:2305.04852*.

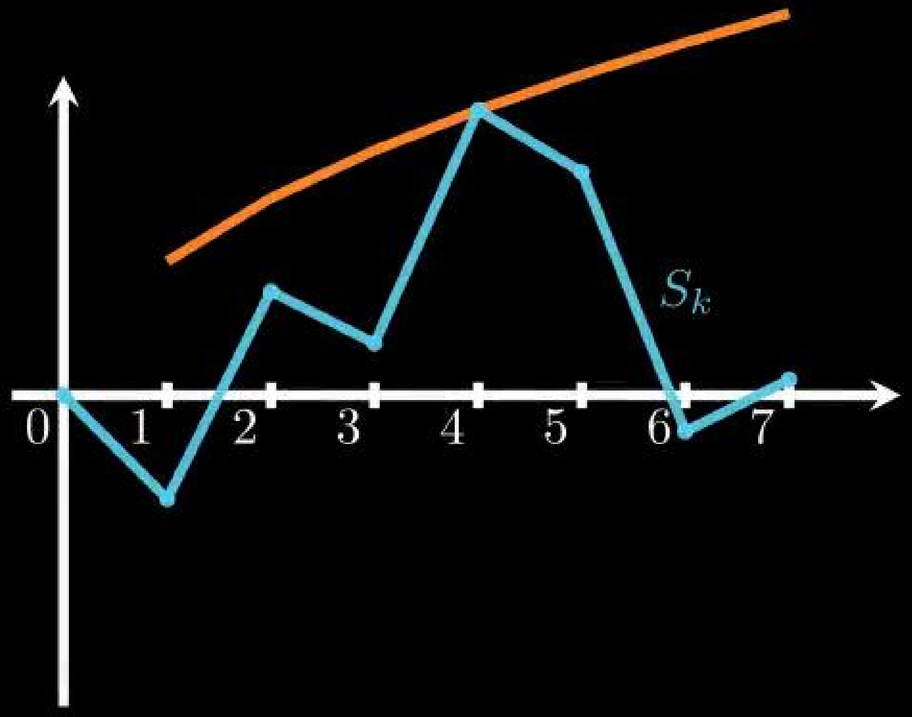
See manuelmmueller.github.io for data and R-code.

Appendix

Construct p-values $\hat{p}_i$ for $H_0(X_i)$, $i \in [m]$

Given $x_0 \in \mathbb{R}^d$, we seek a p-value for $H_0(x_0) := \{P \in \mathcal{P}_{\mathrm{Mon},d}(\sigma) : \eta(x_0) < \tau\}$.





Denote $\mathcal{I}(x_0) := \{i \in [n] : X_i \preccurlyeq x_0\}$, $n(x_0) := |\mathcal{I}(x_0)|$.

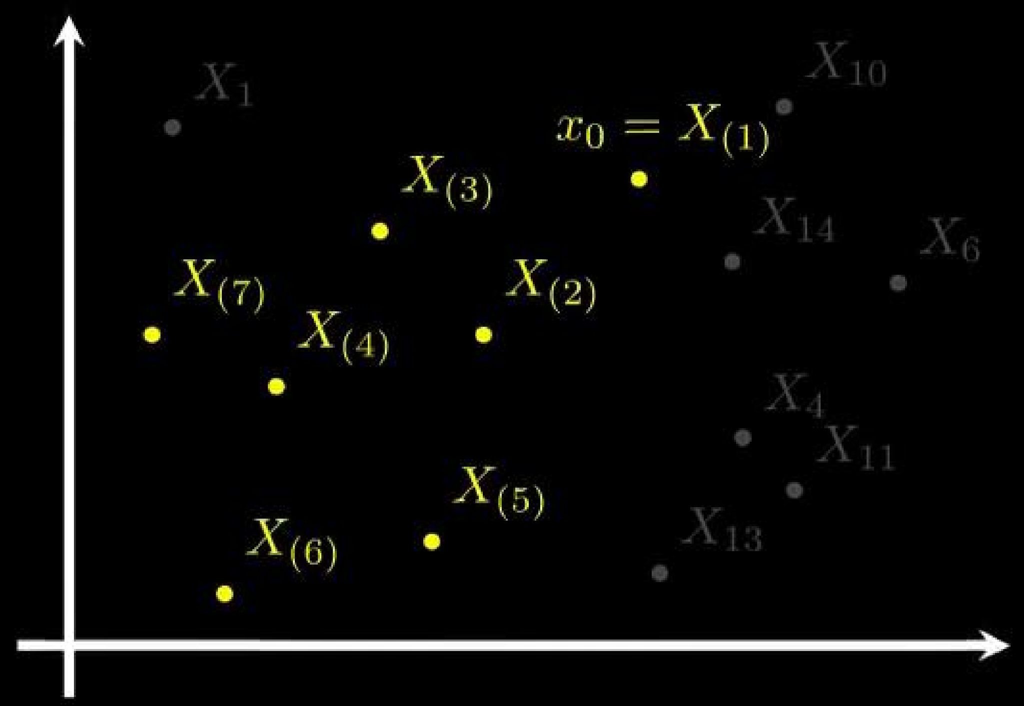
Let $X_{(j)}$ be the jth nearest neighbour of x_0 among X_i, $i \in \mathcal{I}(x_0)$, in sup-norm and let $Y_{(j)}$ be the corresponding response.

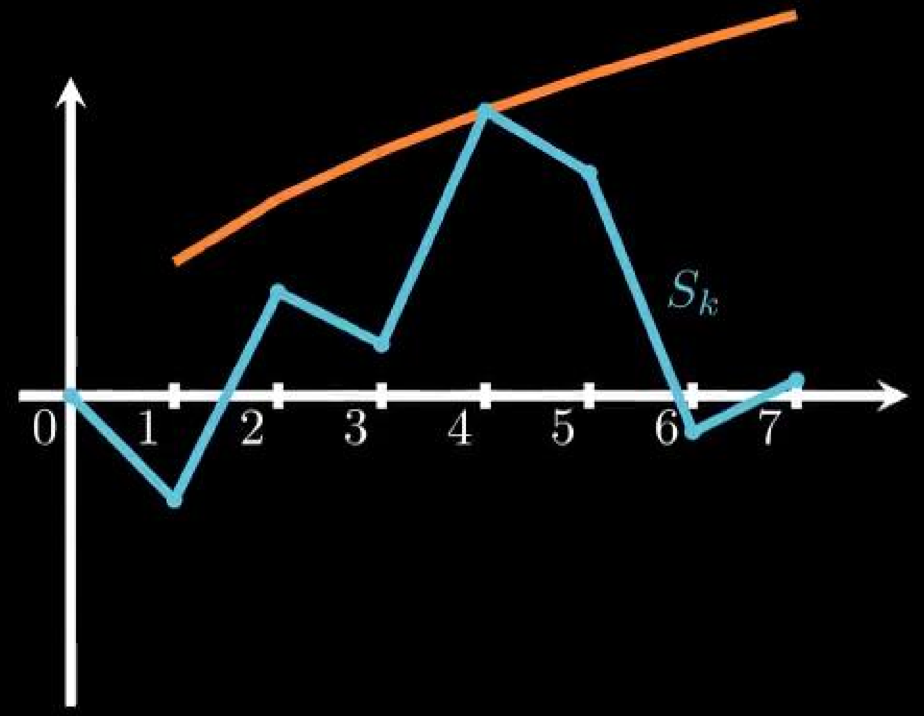
Let

$$S_k := \sum_{j=1}^{k} \frac{Y_{(j)} - \tau}{\sigma}.$$

Then S_k is a supermartingale under $P \in H_0(x_0)$. Combination with time-uniform bounds by Howard et al. (2021) gives p-values from this martingale test (Duan et al., 2020).

Construct p-values $\hat{p}_i$ for $H_0(X_i)$, $i \in [m]$





Definition. For $\sigma > 0$, $x \in \mathbb{R}^d$, let

$$\hat{p}_{\sigma,\tau}(x) := 1 \wedge \min_{k \in [n(x)]} 5.2 \exp\left\{-\frac{(S_k \vee 0)^2}{2.0808k} + \frac{\log\log(2k)}{0.72}\right\},$$

whenever $n(x) > 0$, and $\hat{p}_{\sigma,\tau}(x) := 1$ otherwise.

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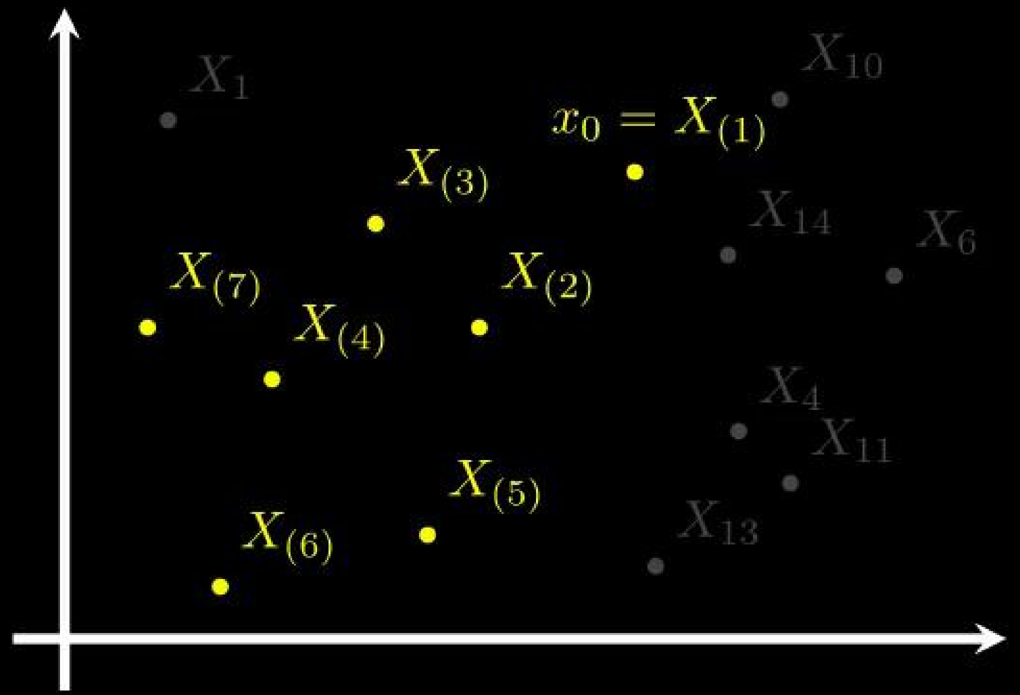

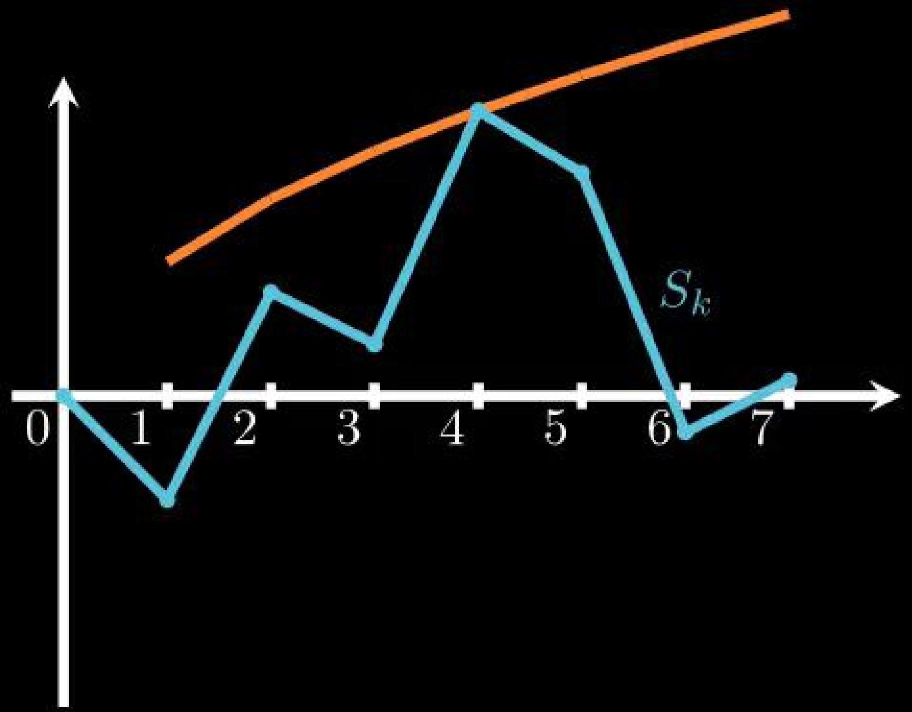

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Lemma. When $\eta(x) < \tau$, we have $\mathbb{P}\{\hat{p}_{\sigma,\tau}(x) \le t \mid (X_i)_{i \in [n]}\} \le t$ for all $t \in (0,1)$.

Further conditions are needed for power

Let $\hat{\mathcal{A}}_n(\tau, \alpha, \mathcal{P})$ denote the set of *data-dependent selection sets* controlling Type I error over $\mathcal{P}$.
Recall $R_\tau(\hat{A}) := \mathbb{E}\big\{\mu\big(\mathcal{X}_\tau(\eta) \setminus \hat{A}\big)\big\}$.

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Proposition. For any $n \in \mathbb{N}$, $\alpha \in (0,1)$, $\sigma > 0$,

$$\sup_{P \in \mathcal{P}_{\mathrm{Mon},d}(\sigma)} \inf_{\hat{A} \in \hat{\mathcal{A}}_n(\tau, \alpha, \mathcal{P}_{\mathrm{Mon},d}(\sigma))} R_\tau(\hat{A}) \geq 1 - \alpha.$$

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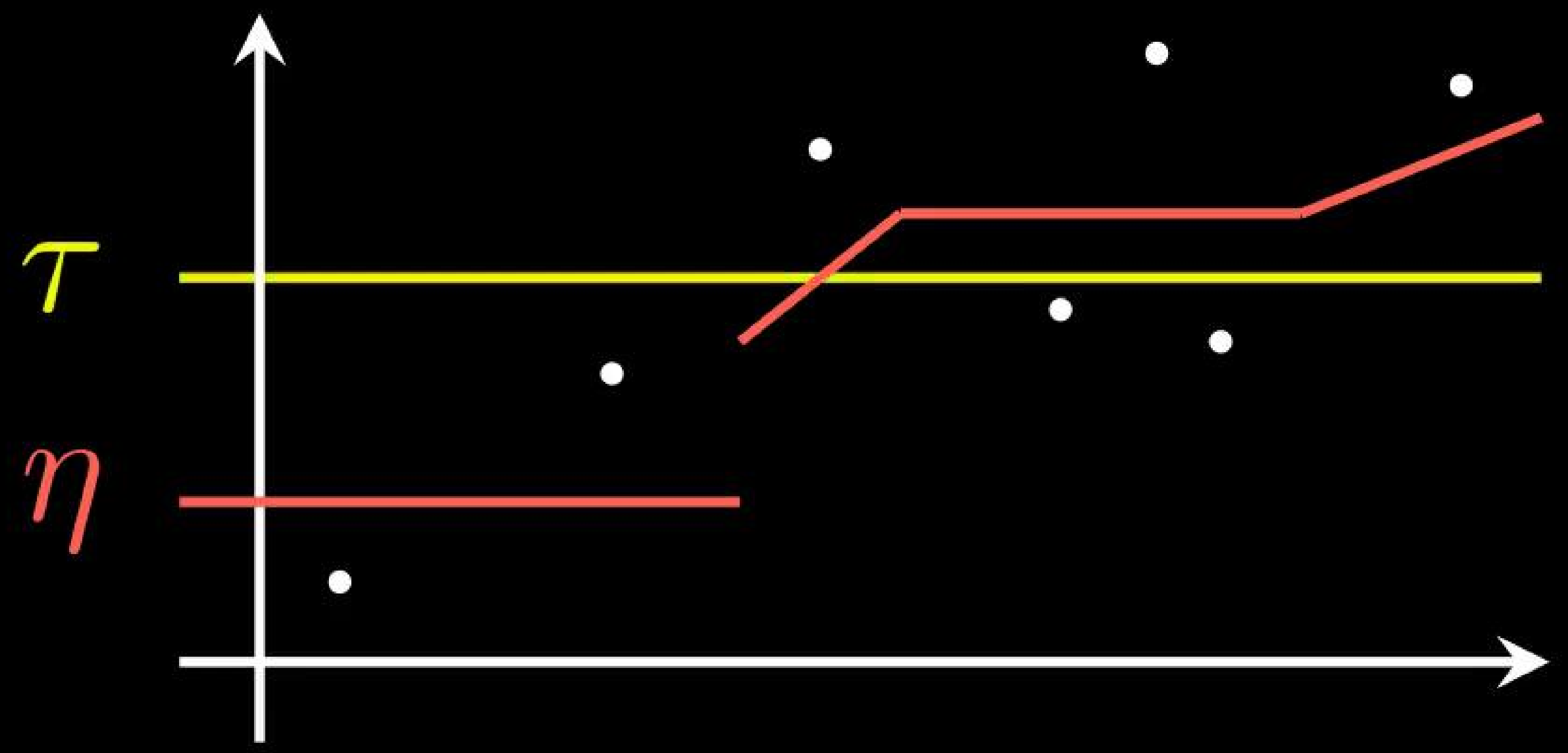

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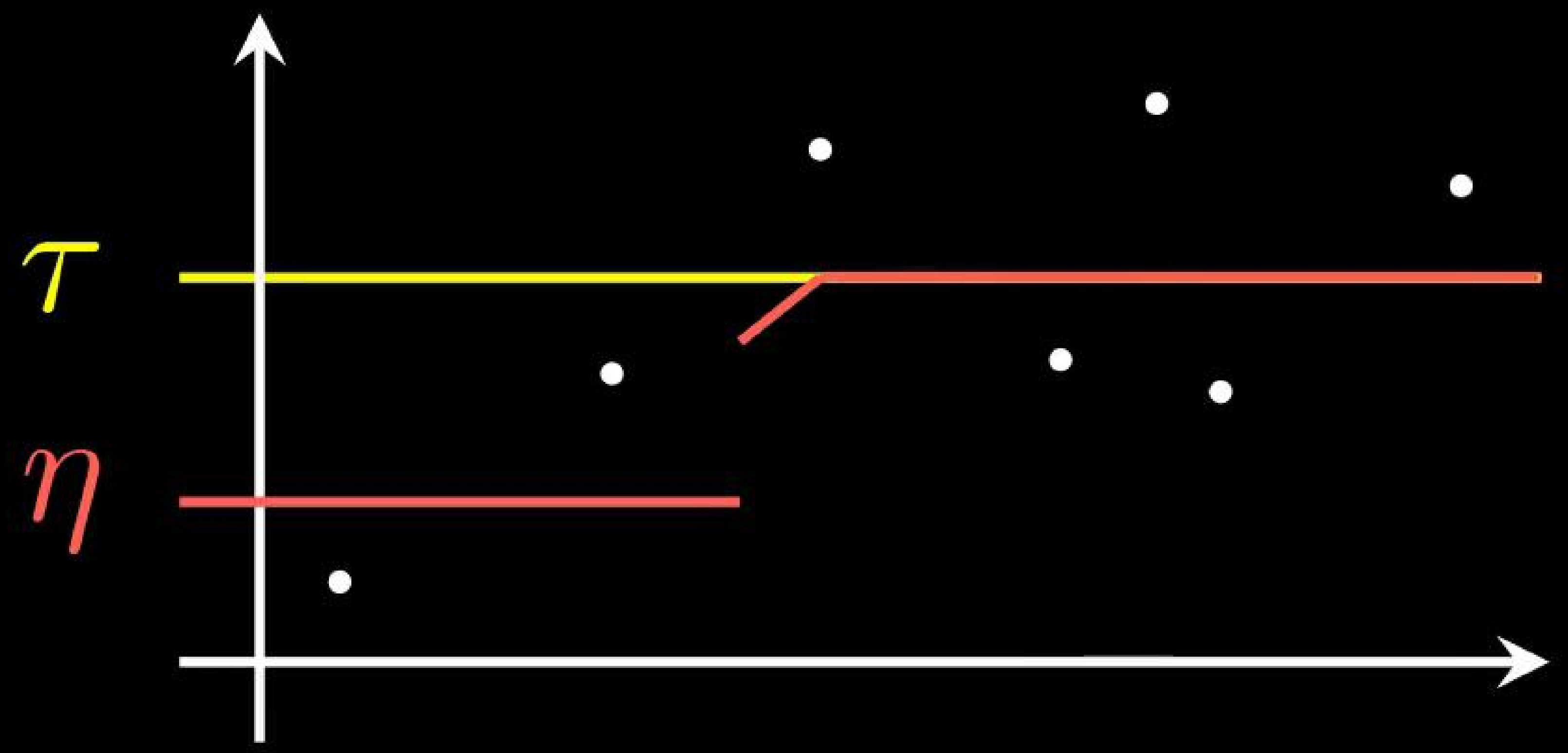

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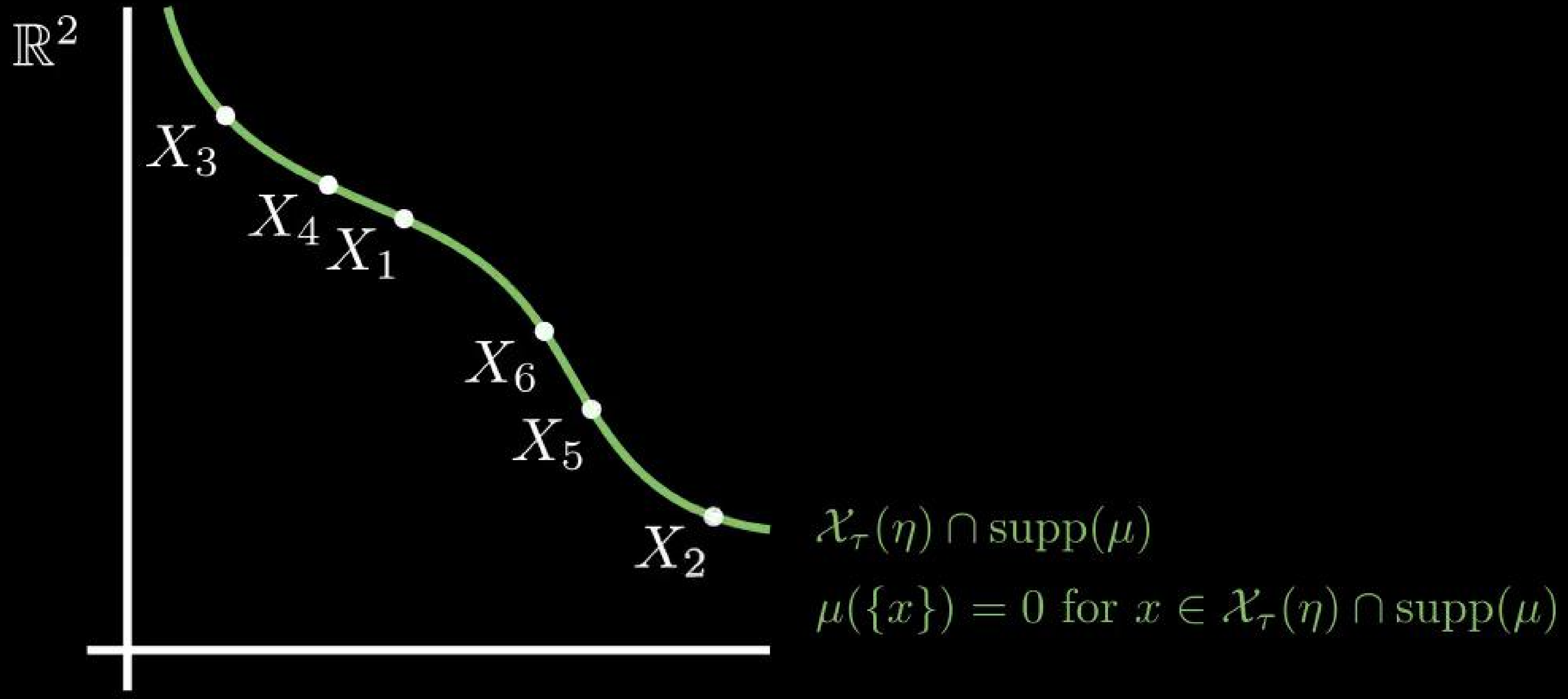

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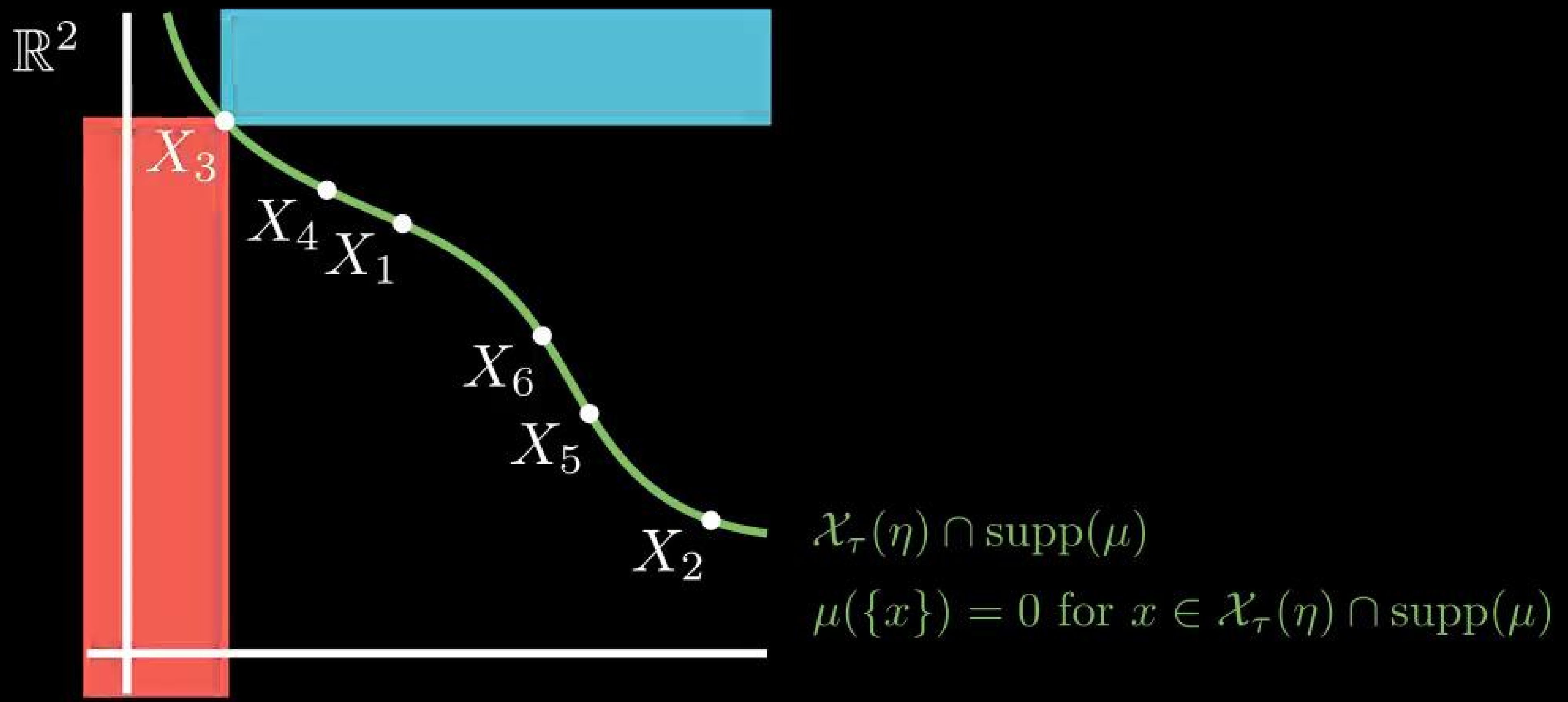

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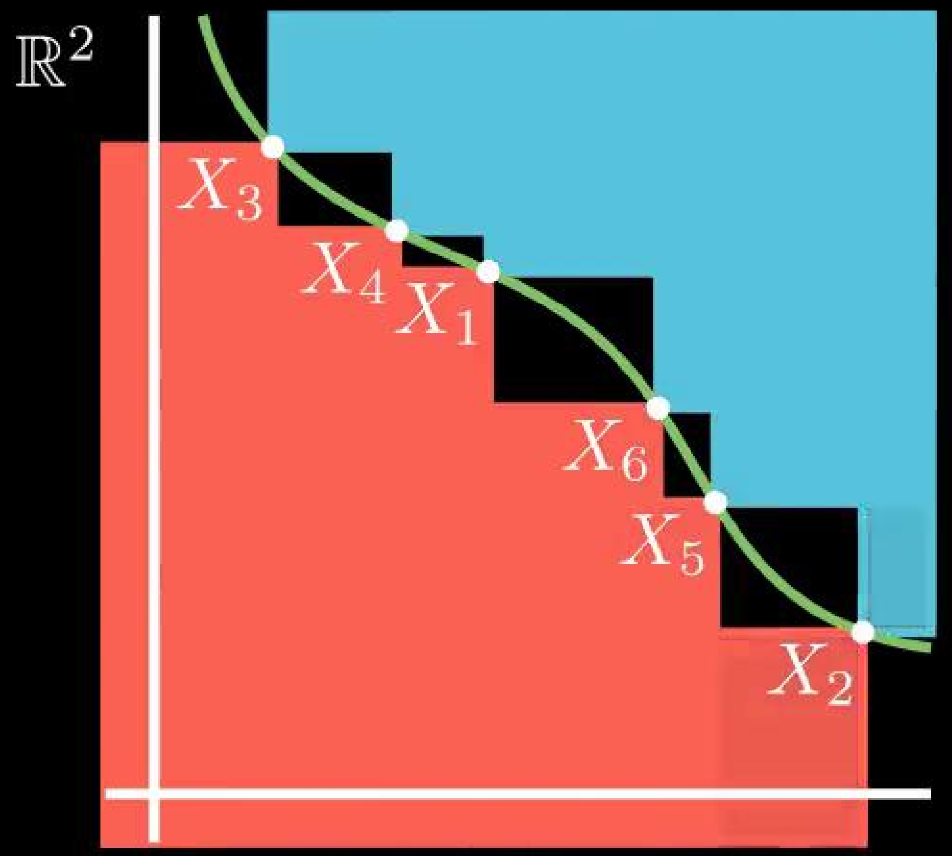

$\mathcal{X}_\tau(\eta) \cap \mathrm{supp}(\mu)$

$\mu(\{x\}) = 0$ for $x \in \mathcal{X}_\tau(\eta) \cap \mathrm{supp}(\mu)$

Power

Definition. Let $\sigma, \gamma, \lambda > 0$ and $\theta > 1$. $\mathcal{P}_{\mathrm{MonReg}} \equiv \mathcal{P}_{\mathrm{MonReg},d}(\sigma, \tau, \gamma, \lambda, \theta)$ denotes the set of distributions $P \in \mathcal{P}_{\mathrm{Mon},d}(\sigma)$ for which additionally

1. $\eta\big(x + r(1, \ldots, 1)^\top\big) \geq \tau + \lambda \cdot r^\gamma$ for all $x \in \mathcal{X}_\tau(\eta) \cap \mathrm{supp}(\mu)$ and $r \in (0, 1]$;
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Theorem. $\exists C(d, \theta) \geq 1$, such that for any $n \geq 1$, $m \in [n]$ and $\alpha \in (0, 1)$,

$$\sup_{P \in \mathcal{P}_{\mathrm{MonReg}}} R_\tau(\hat{A}^{\mathrm{ISS}}) \leq 1 \wedge C(d, \theta) \left\{ \left(\frac{\sigma^2}{n\lambda^2} \log_+\left(\frac{m \log_+ n}{\alpha} \right) \right)^{1/(2\gamma+d)} + \left(\frac{\log_+ m}{m} \right)^{1/d} \right\},$$

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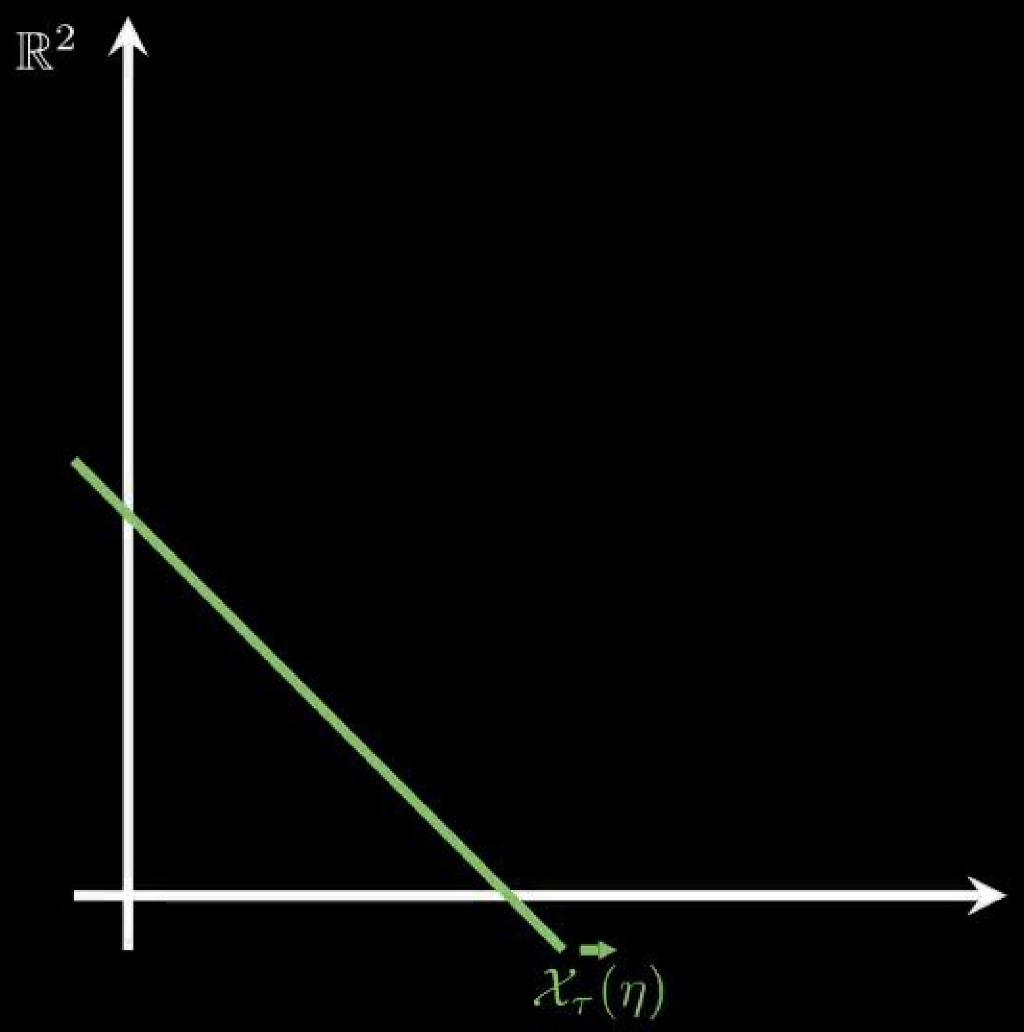

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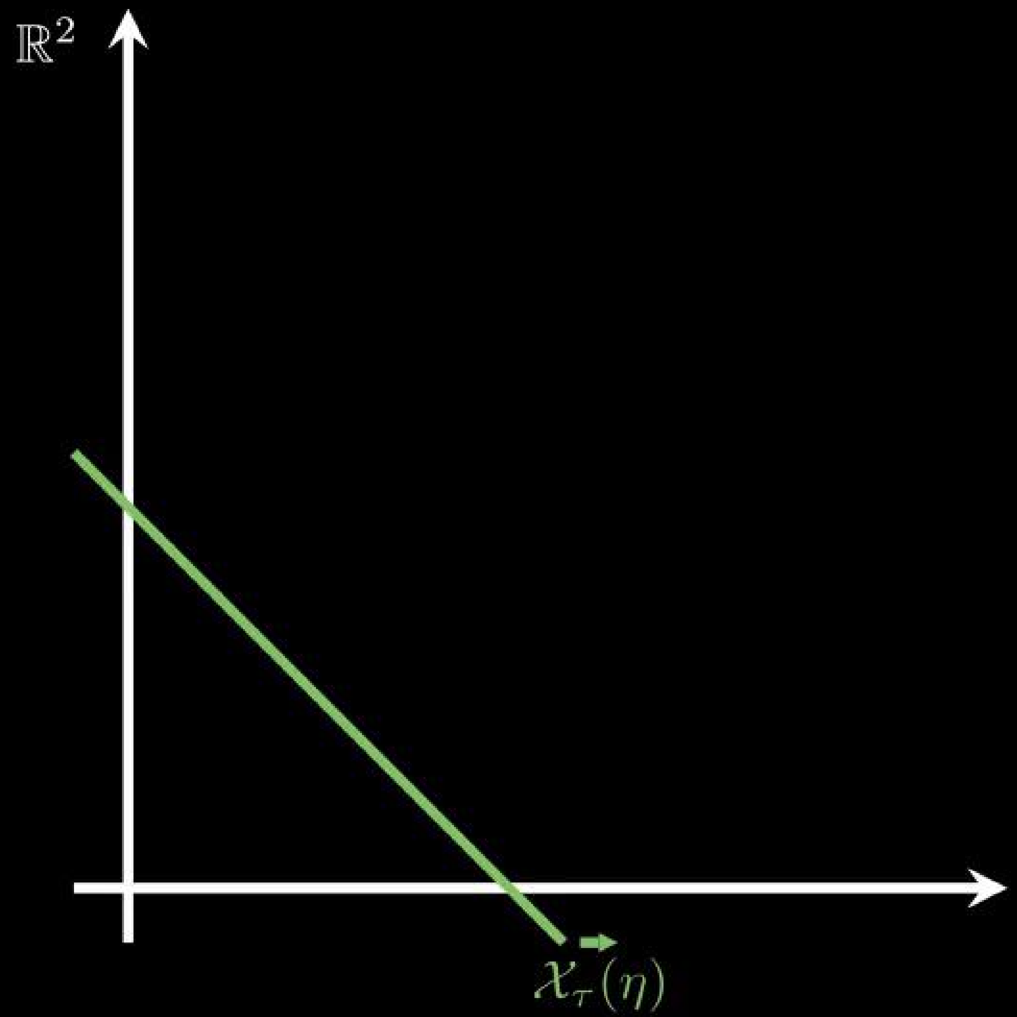

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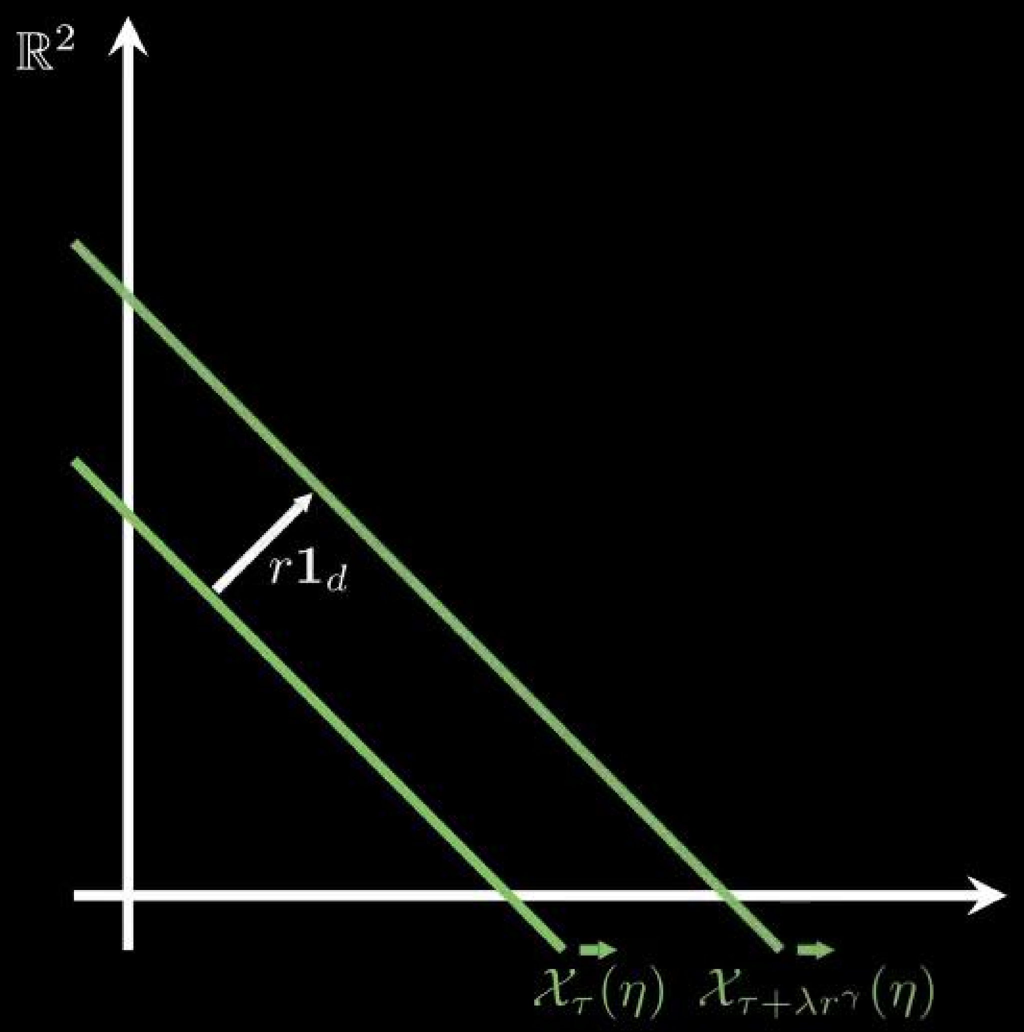

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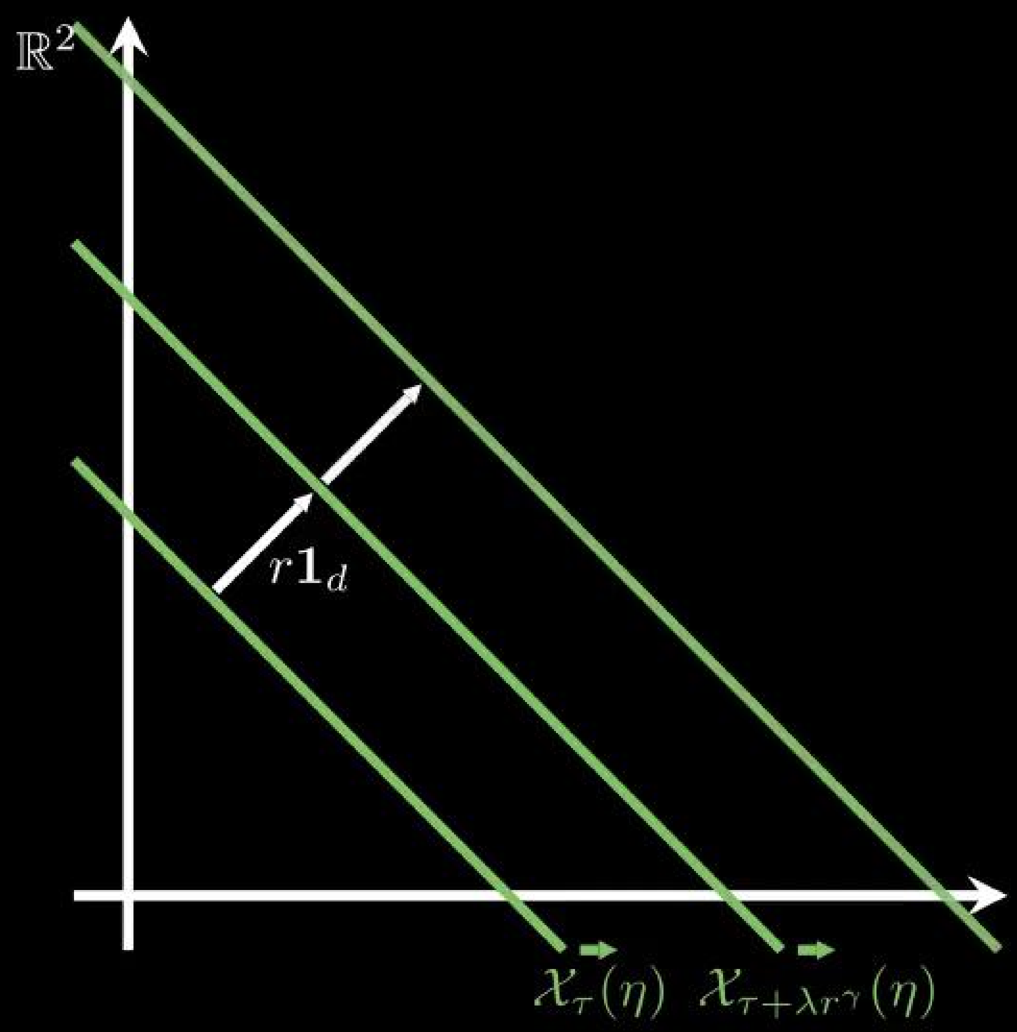

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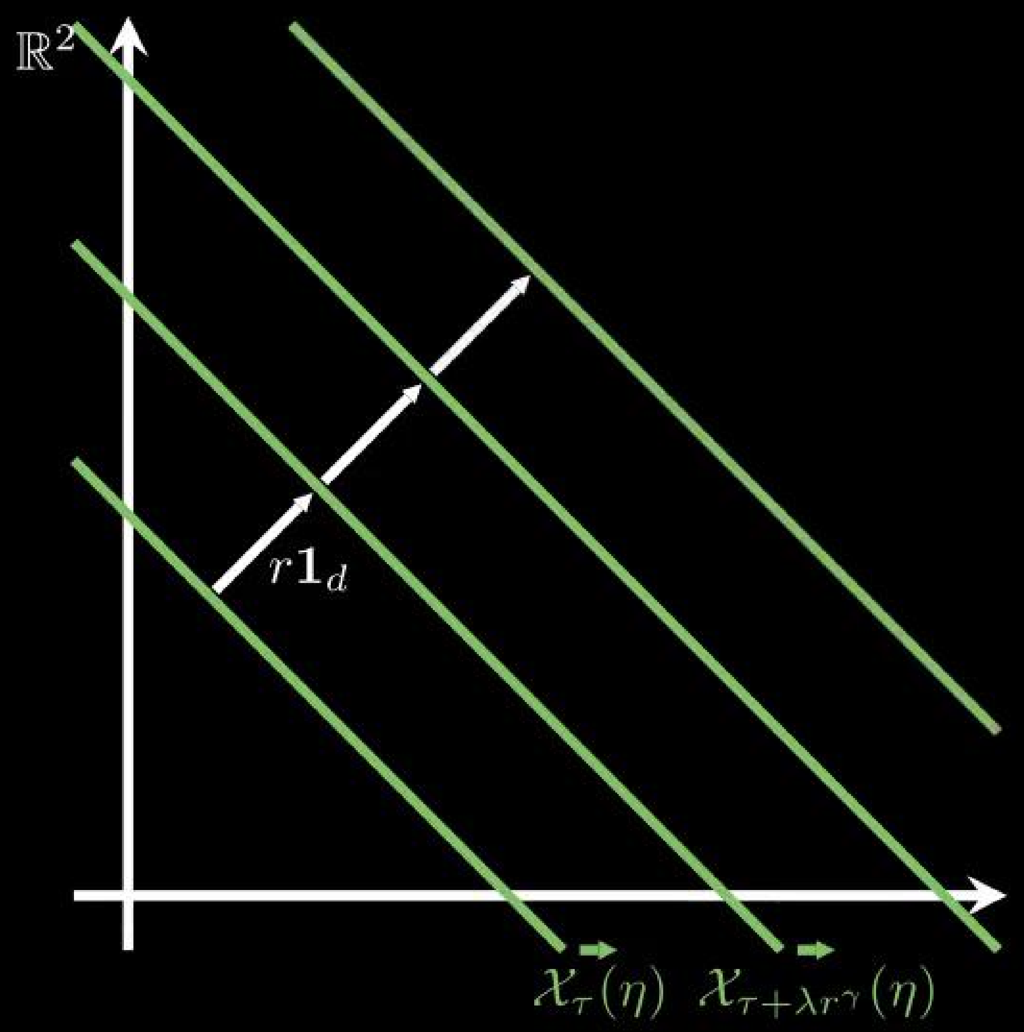

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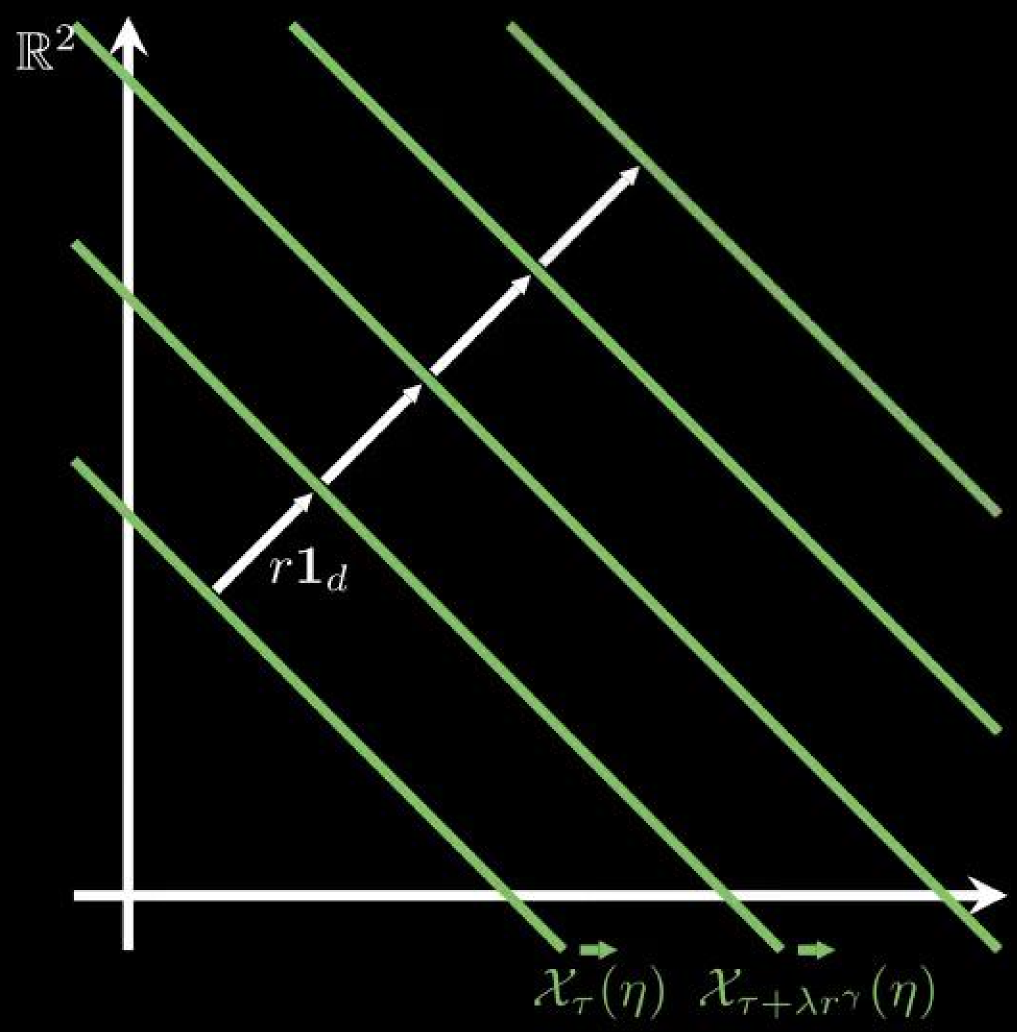

Let $r > 0$ be small.

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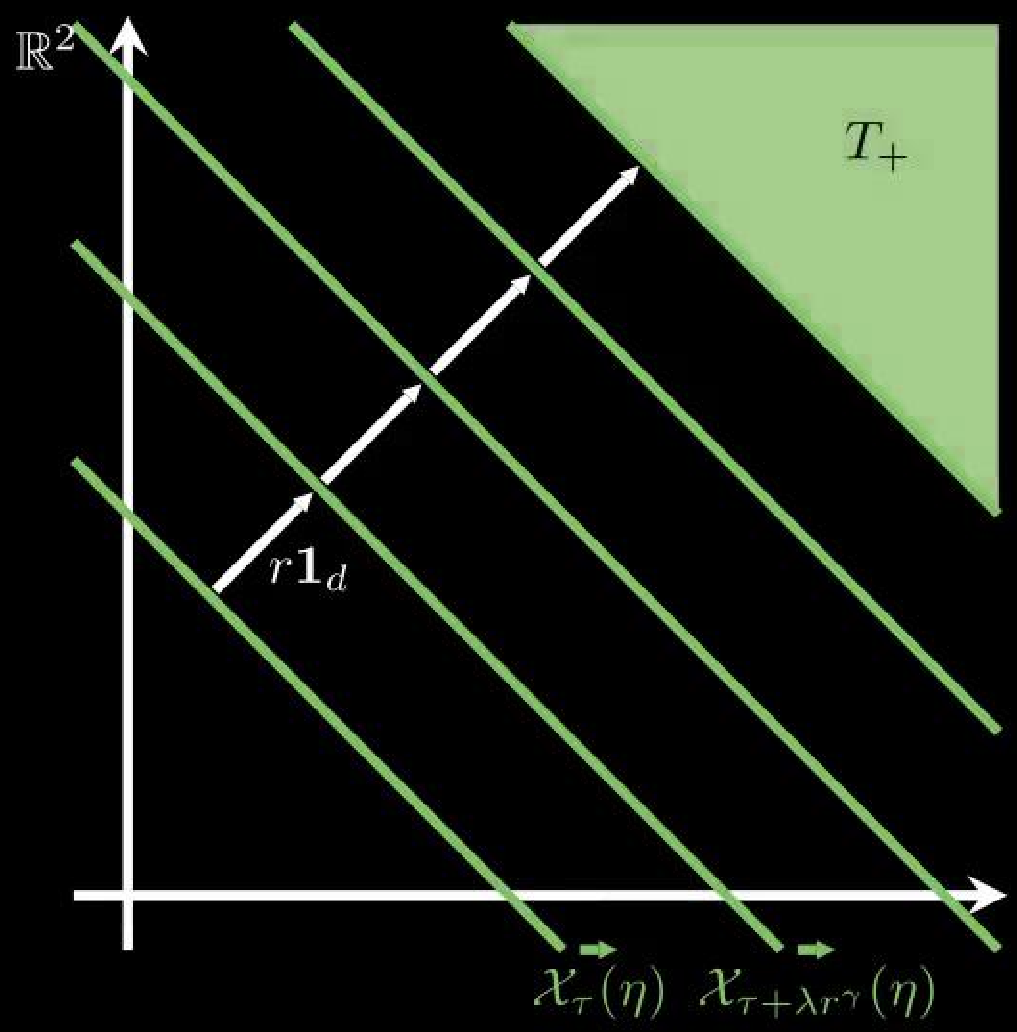

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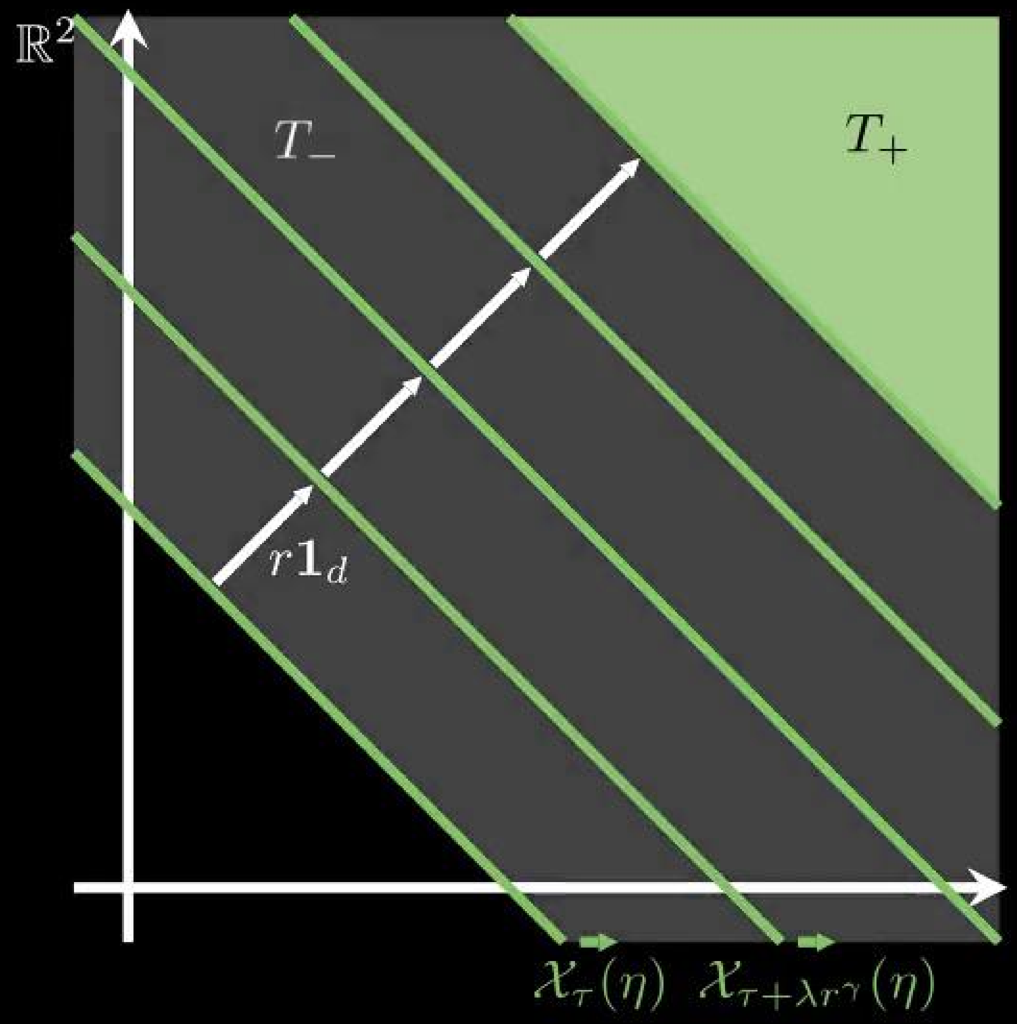

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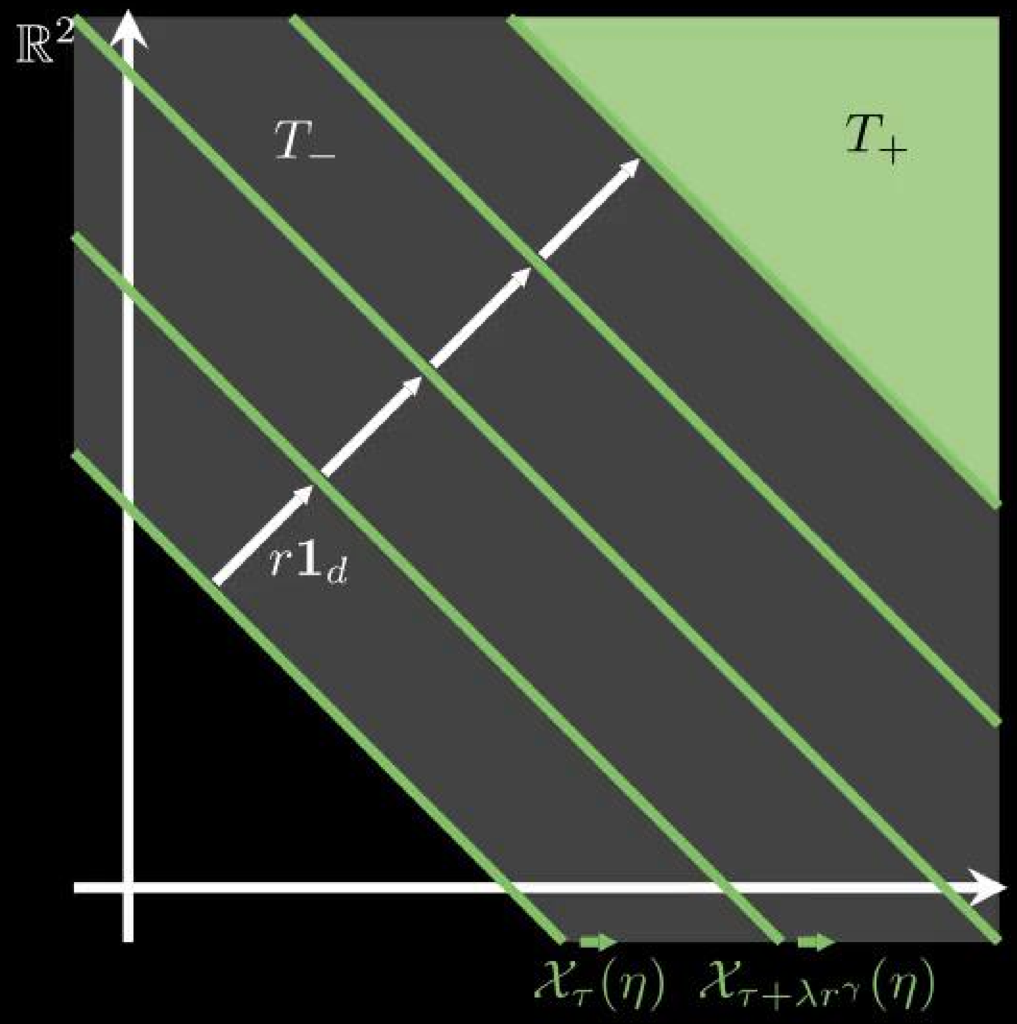

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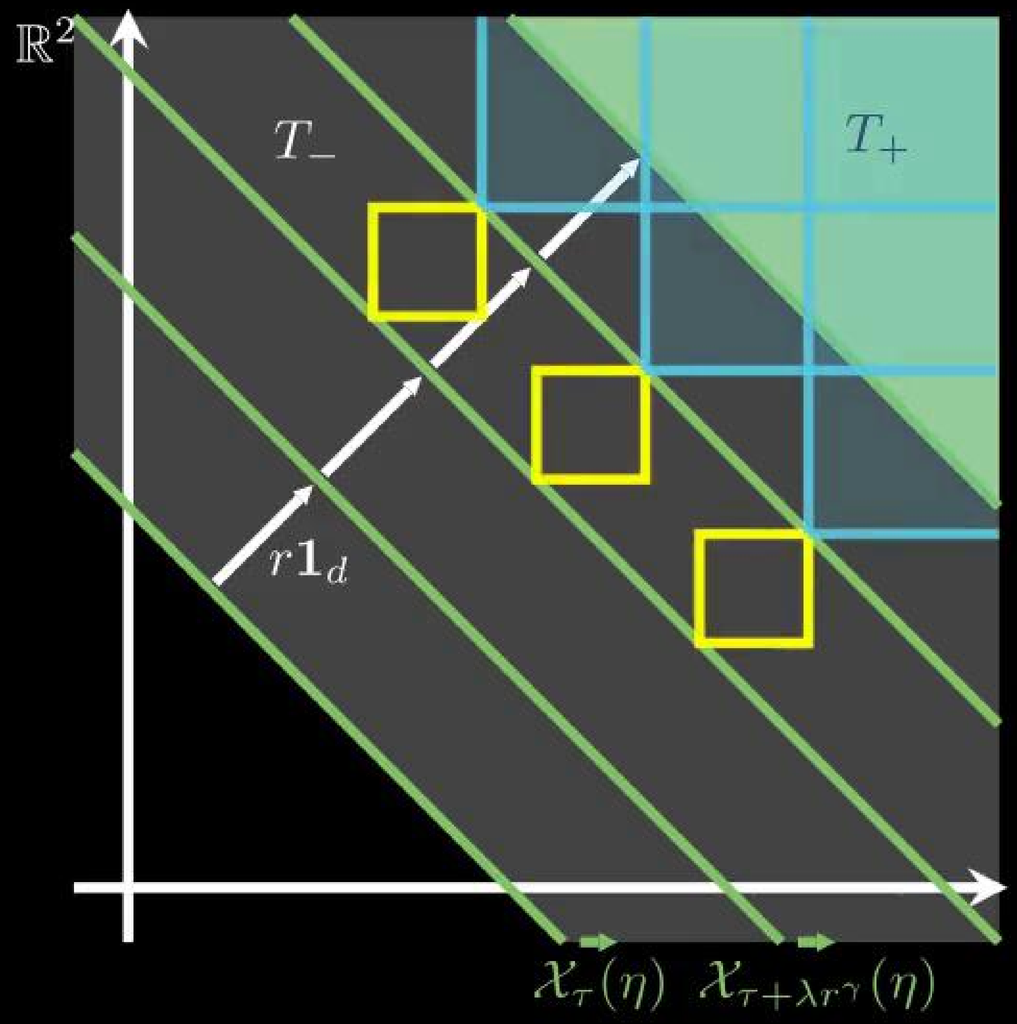

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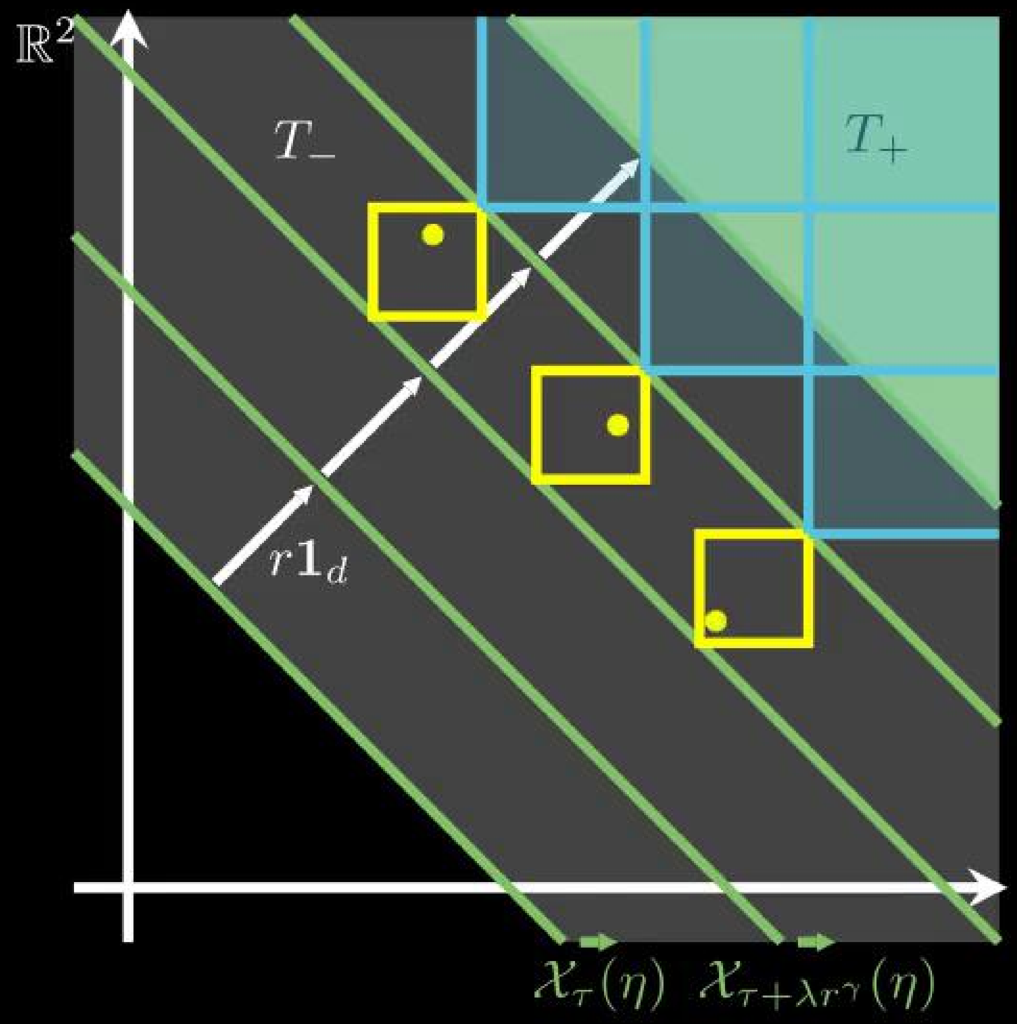

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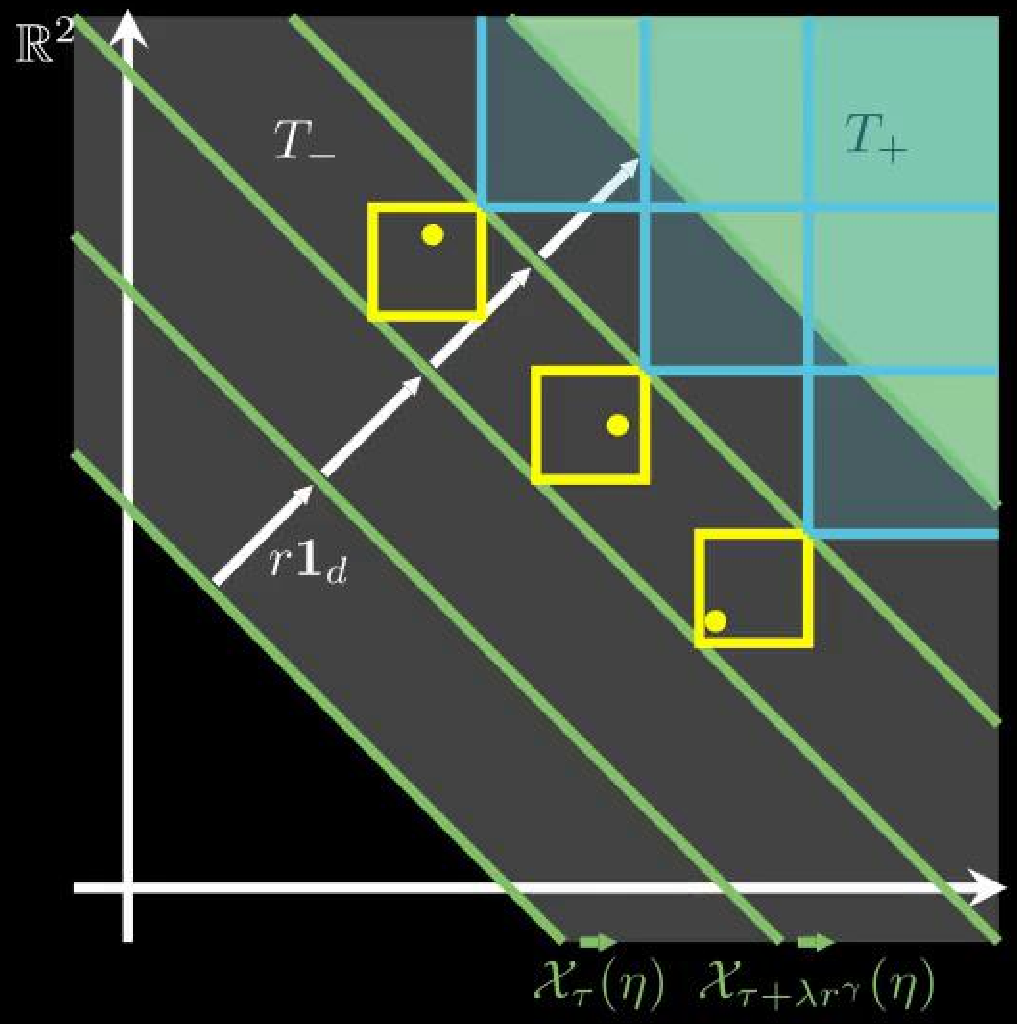

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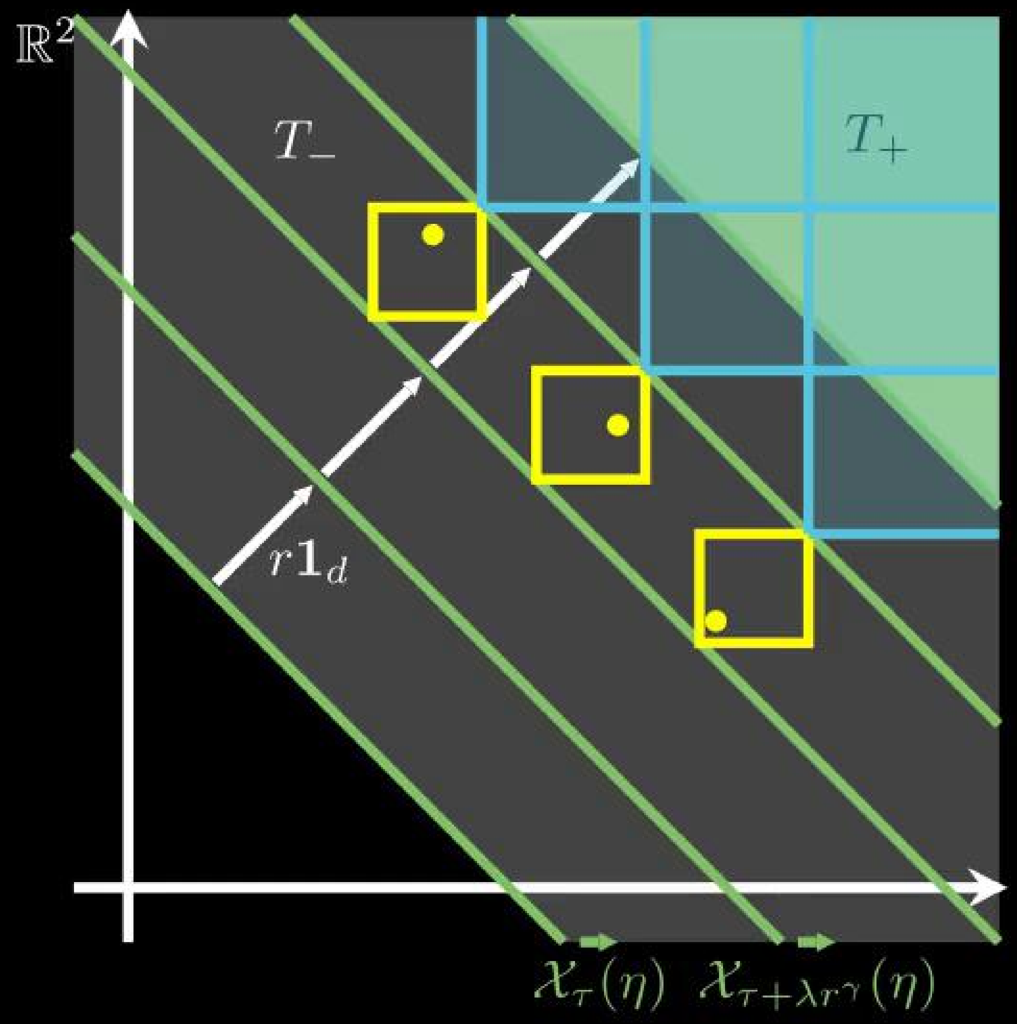

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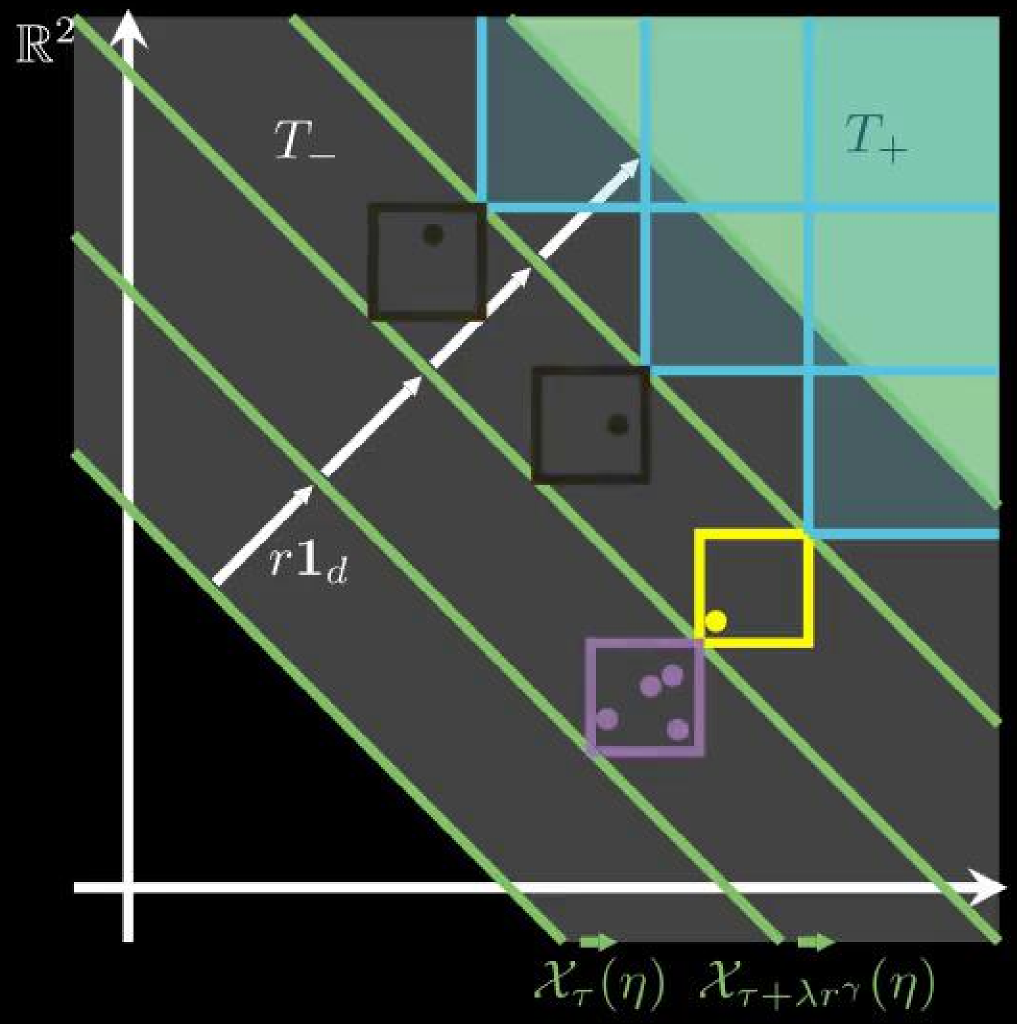

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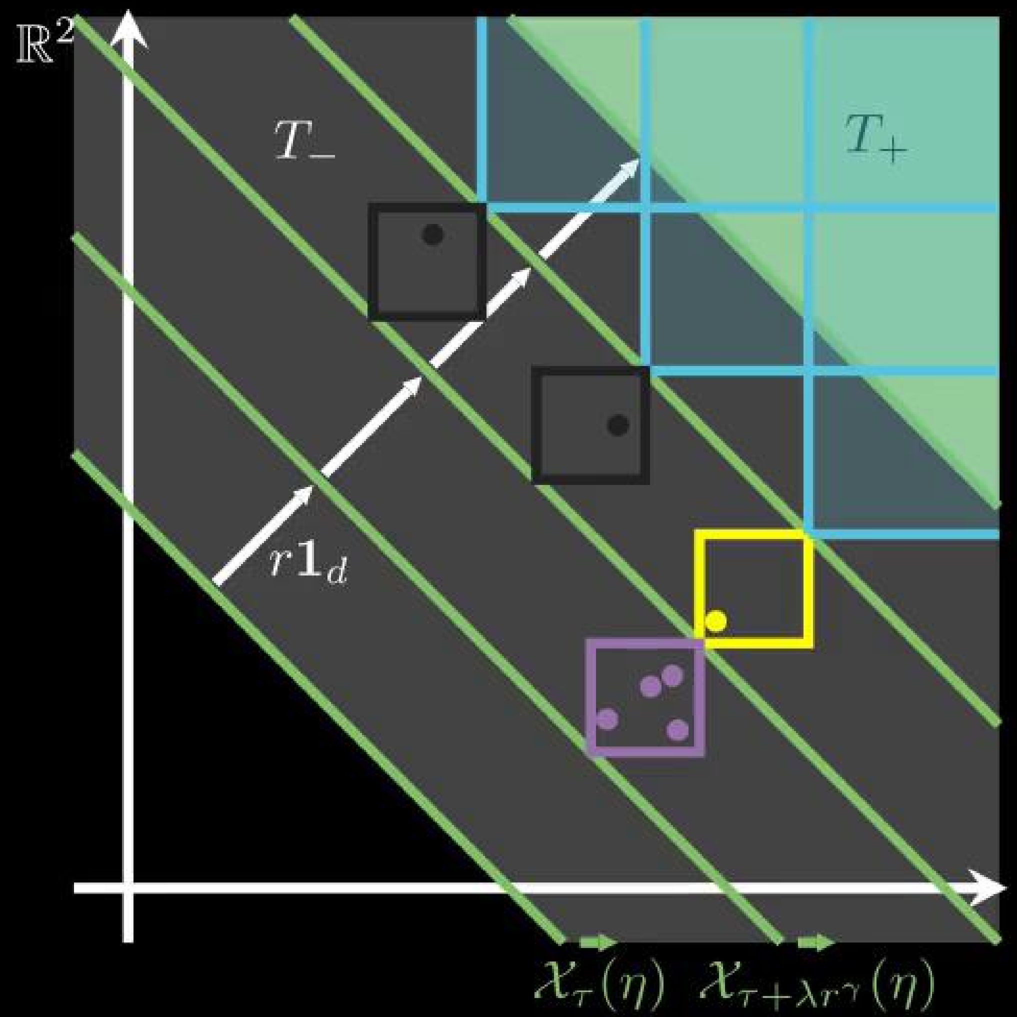

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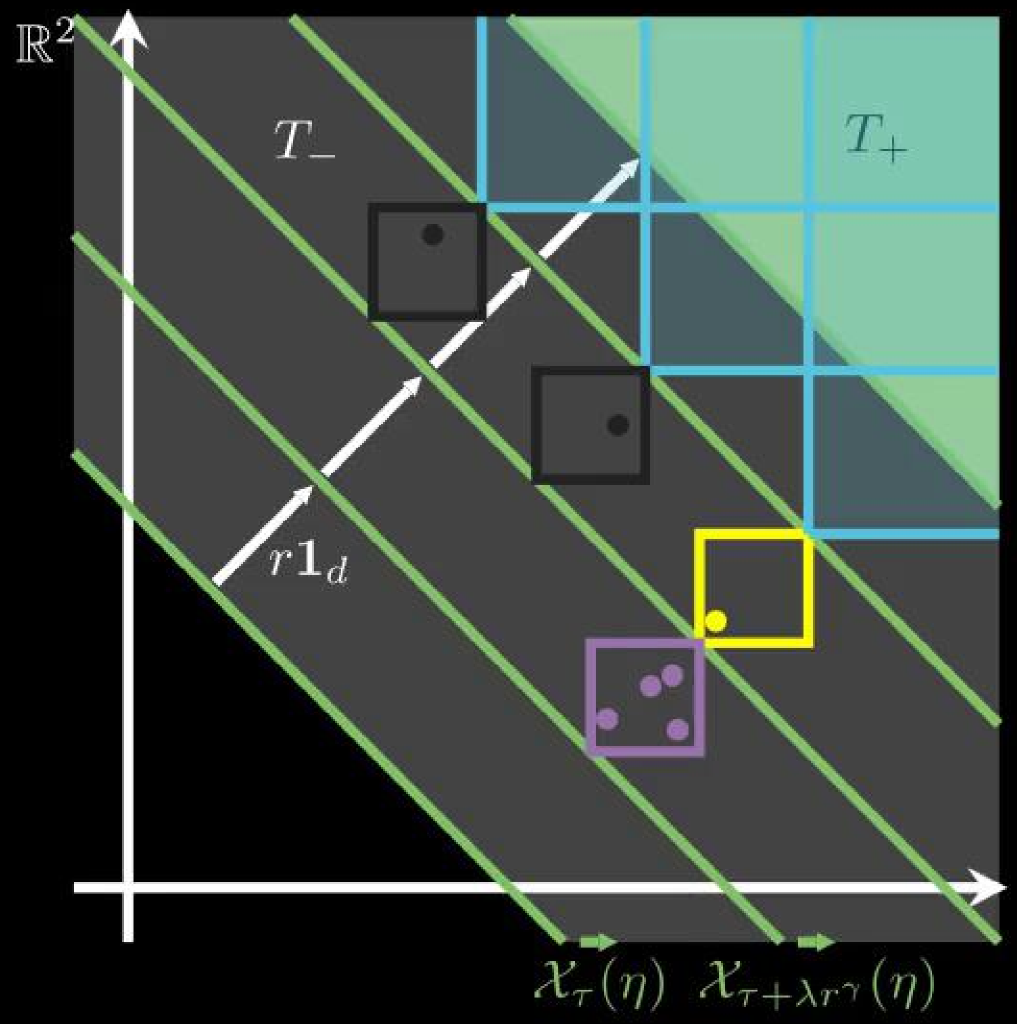

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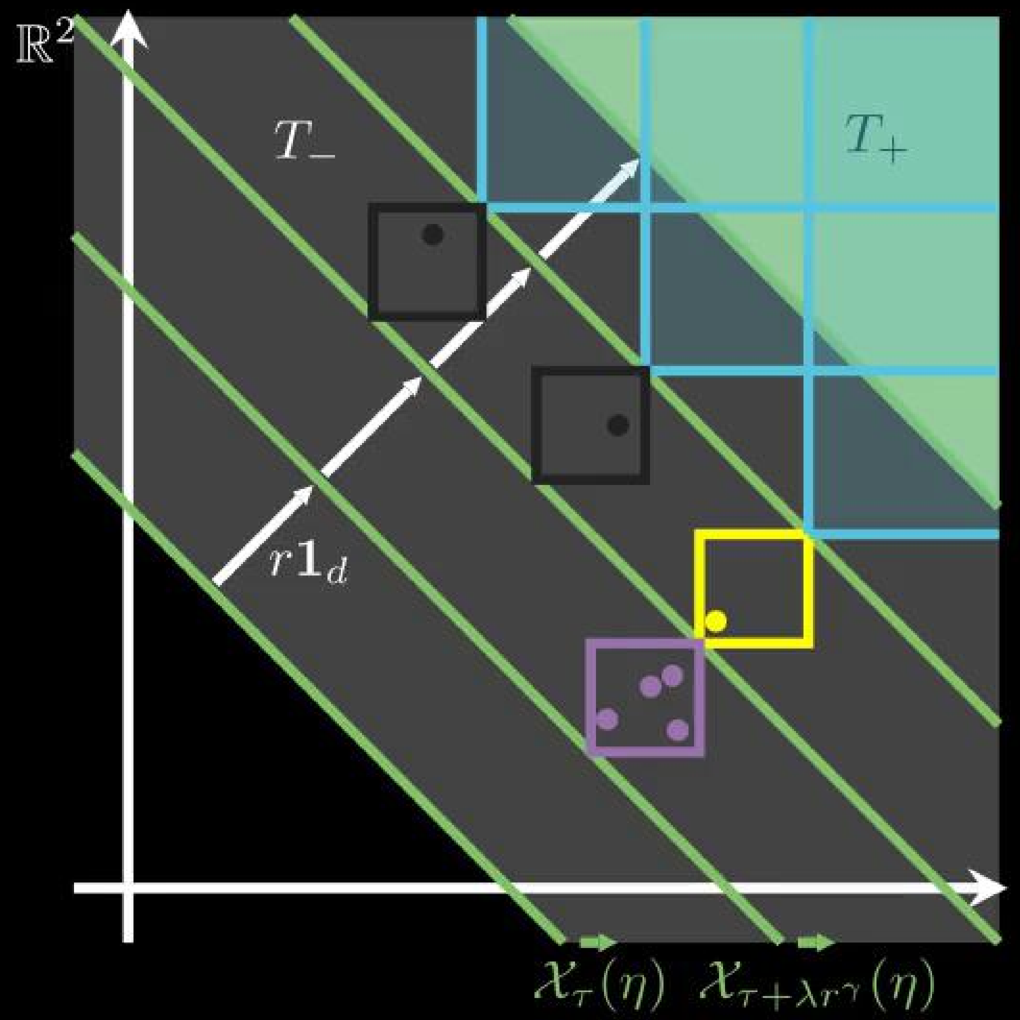

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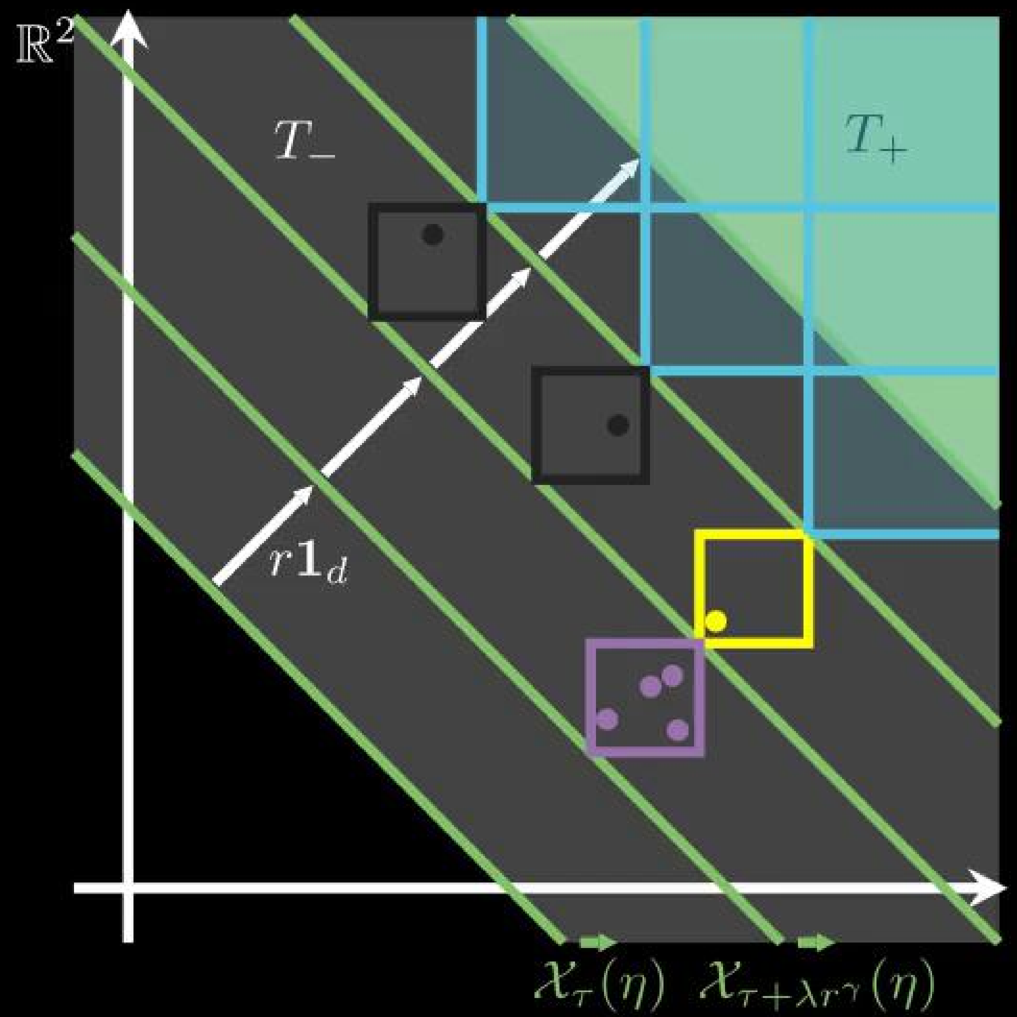

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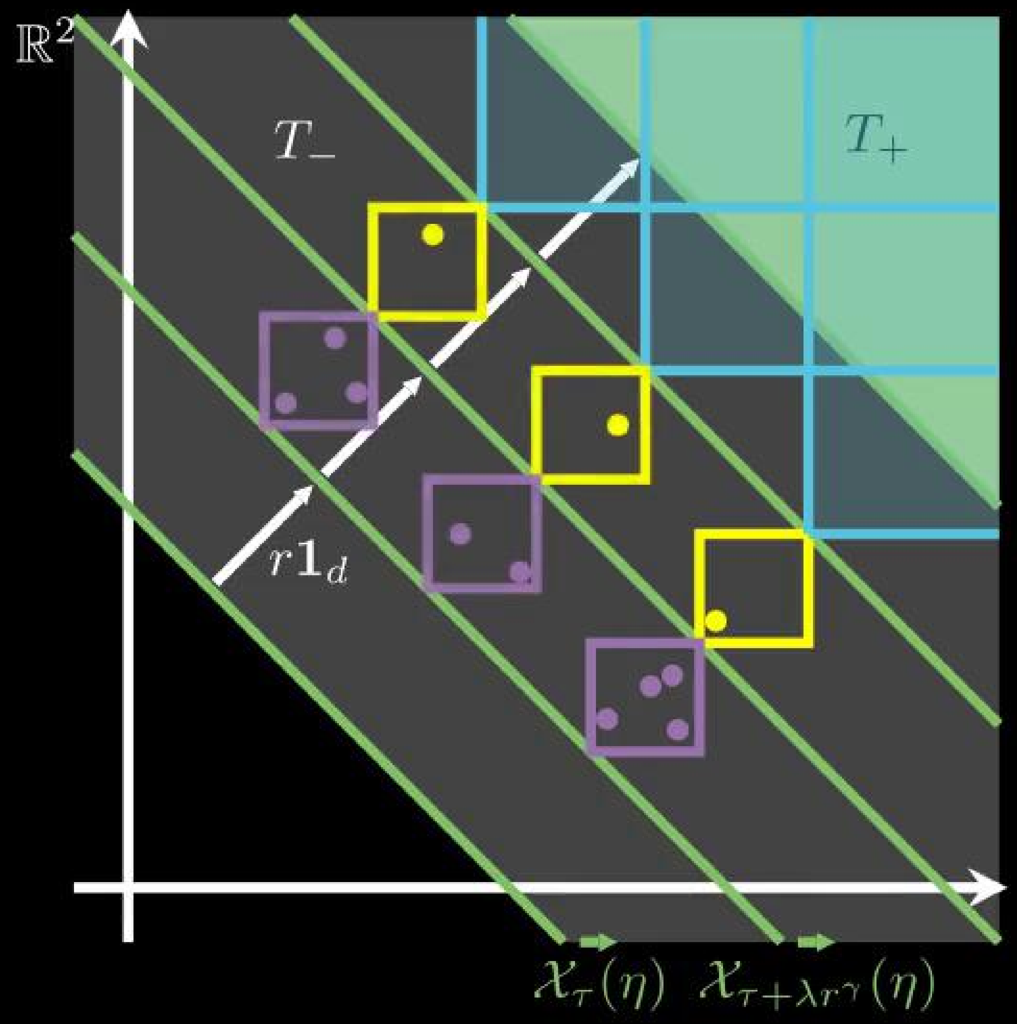

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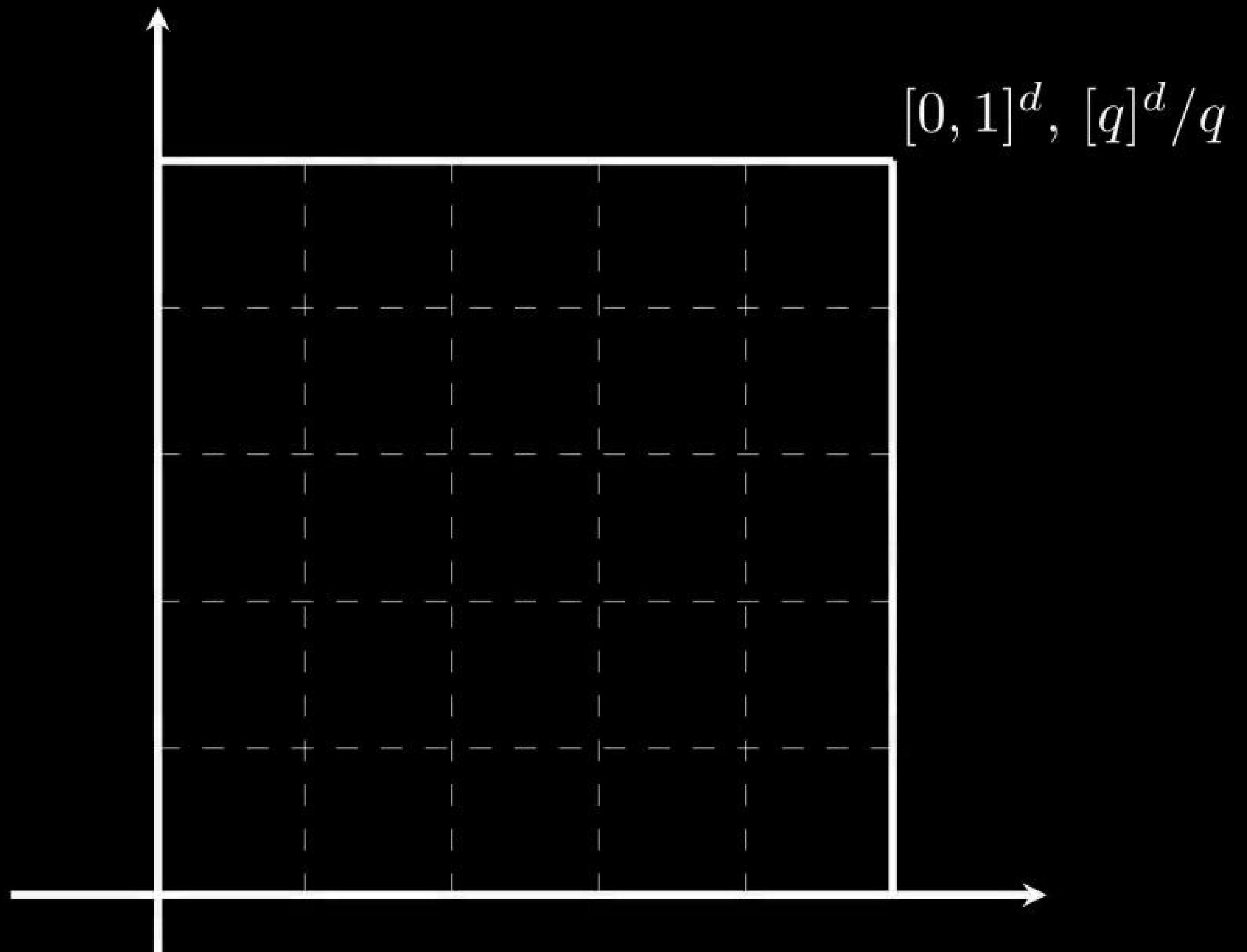

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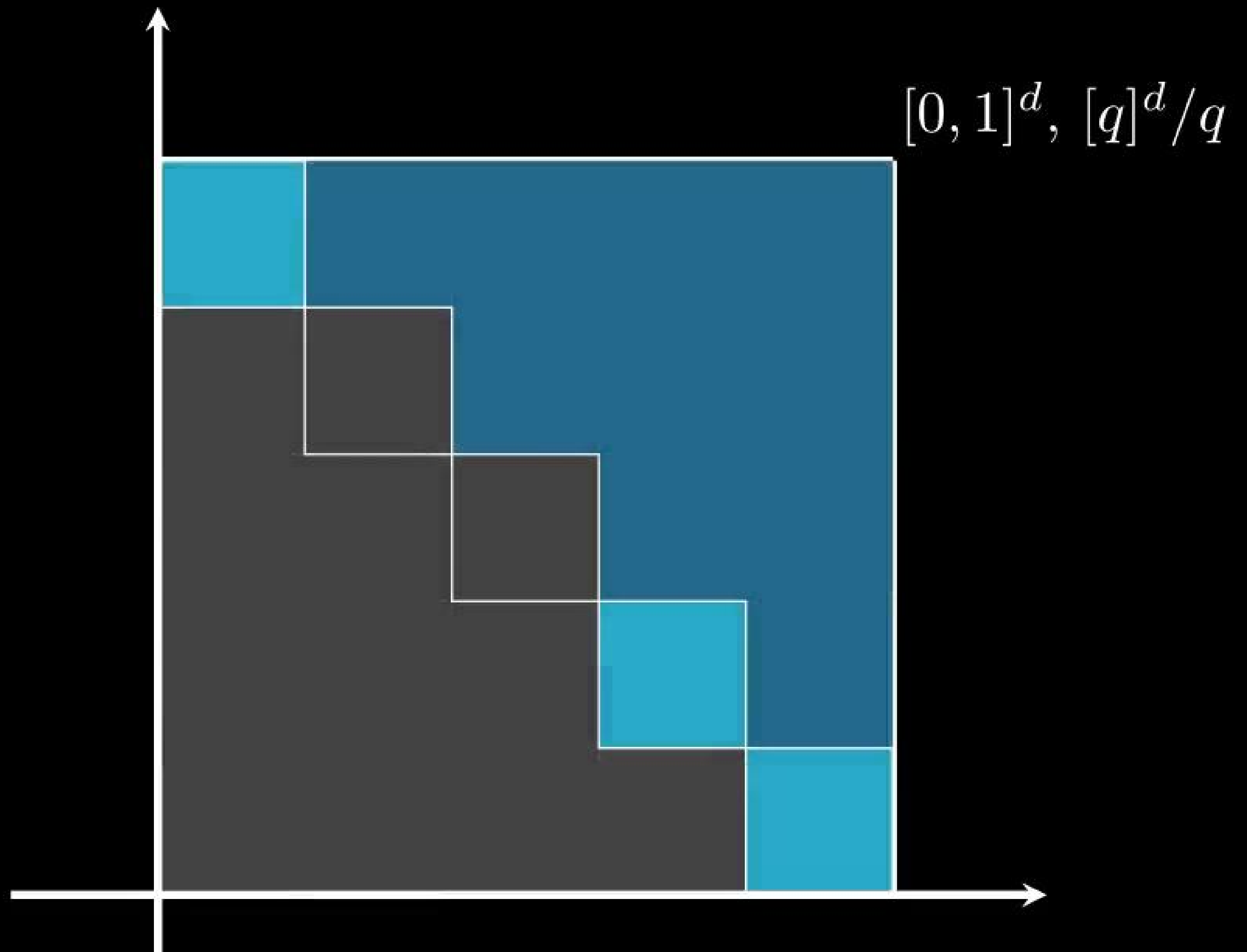

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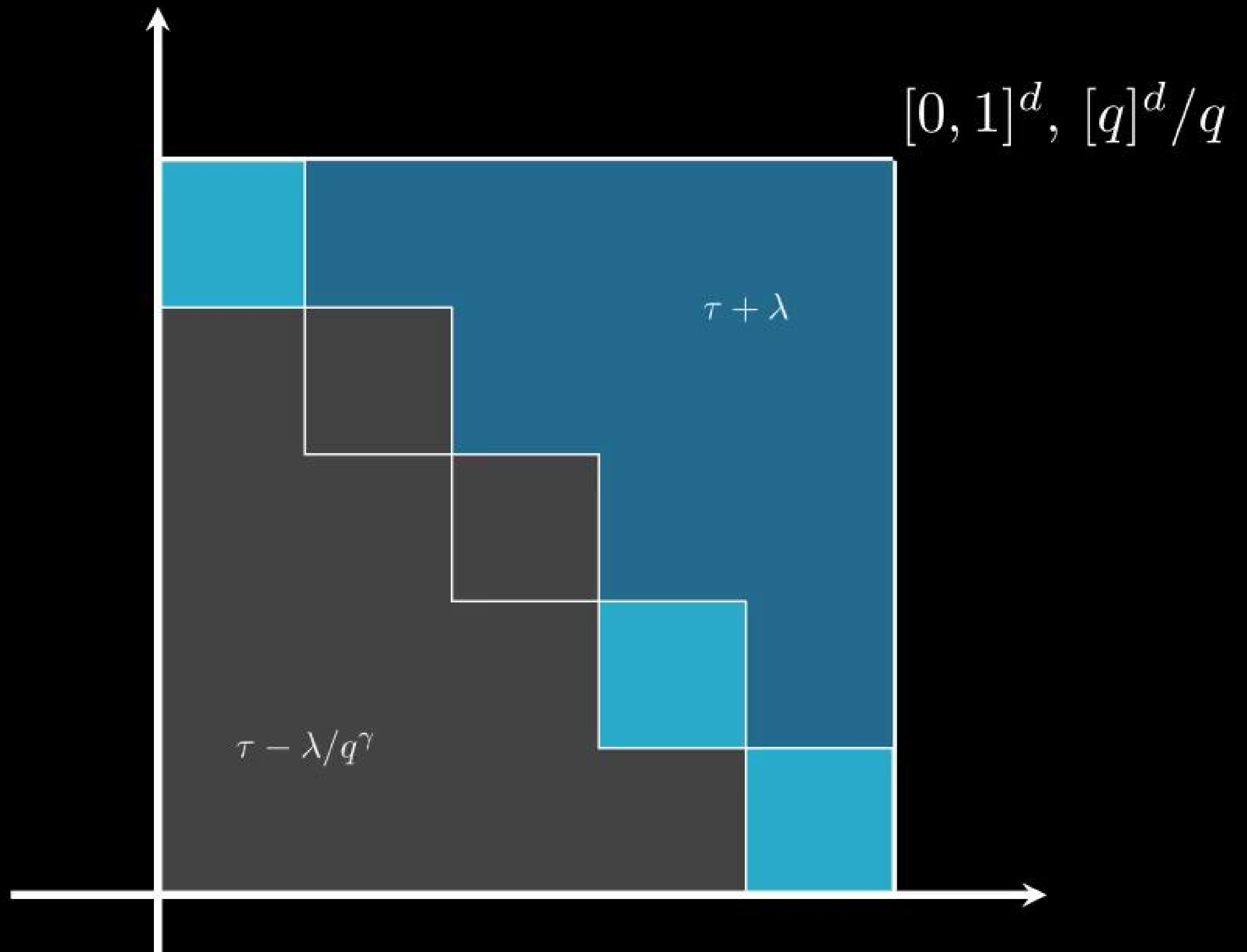

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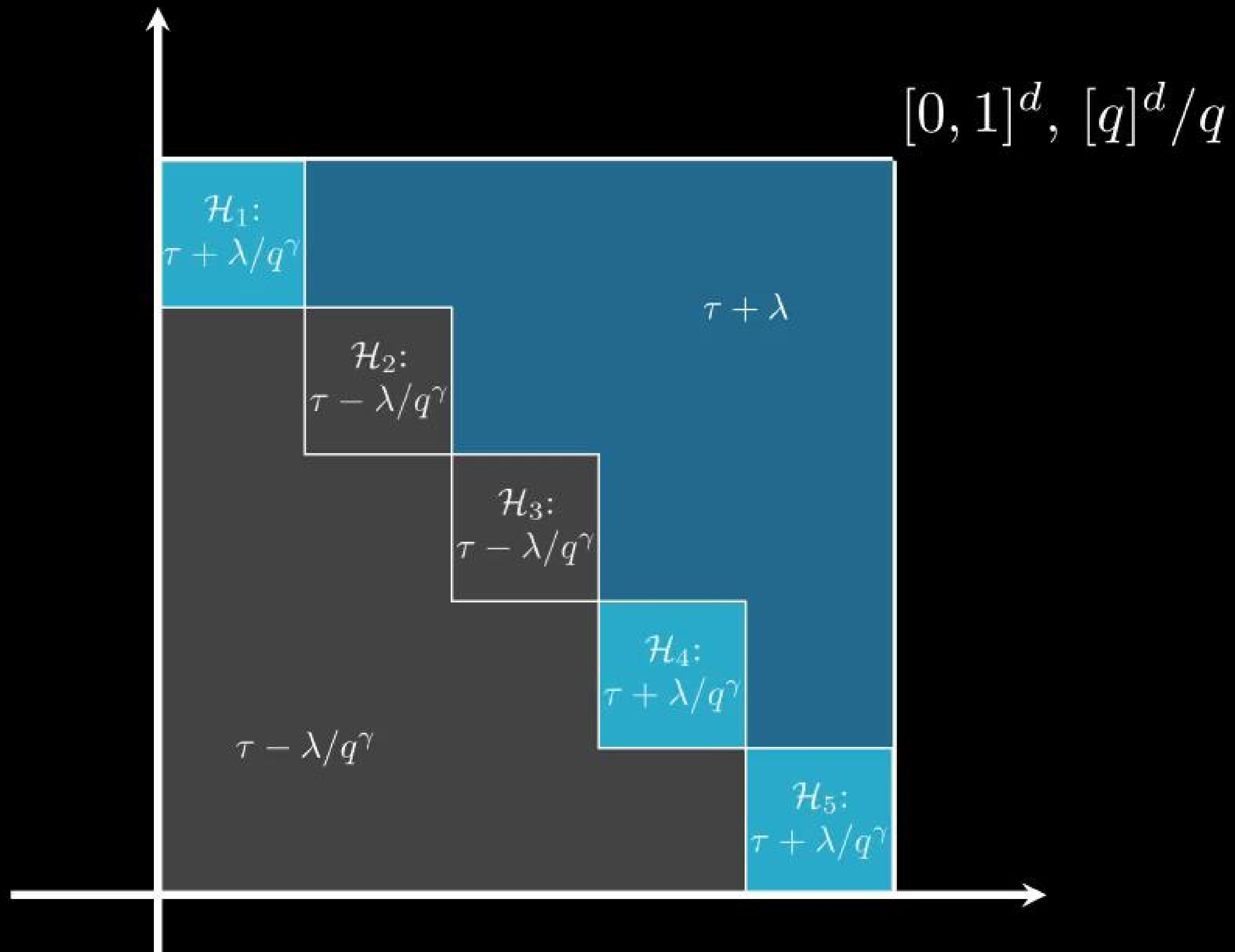

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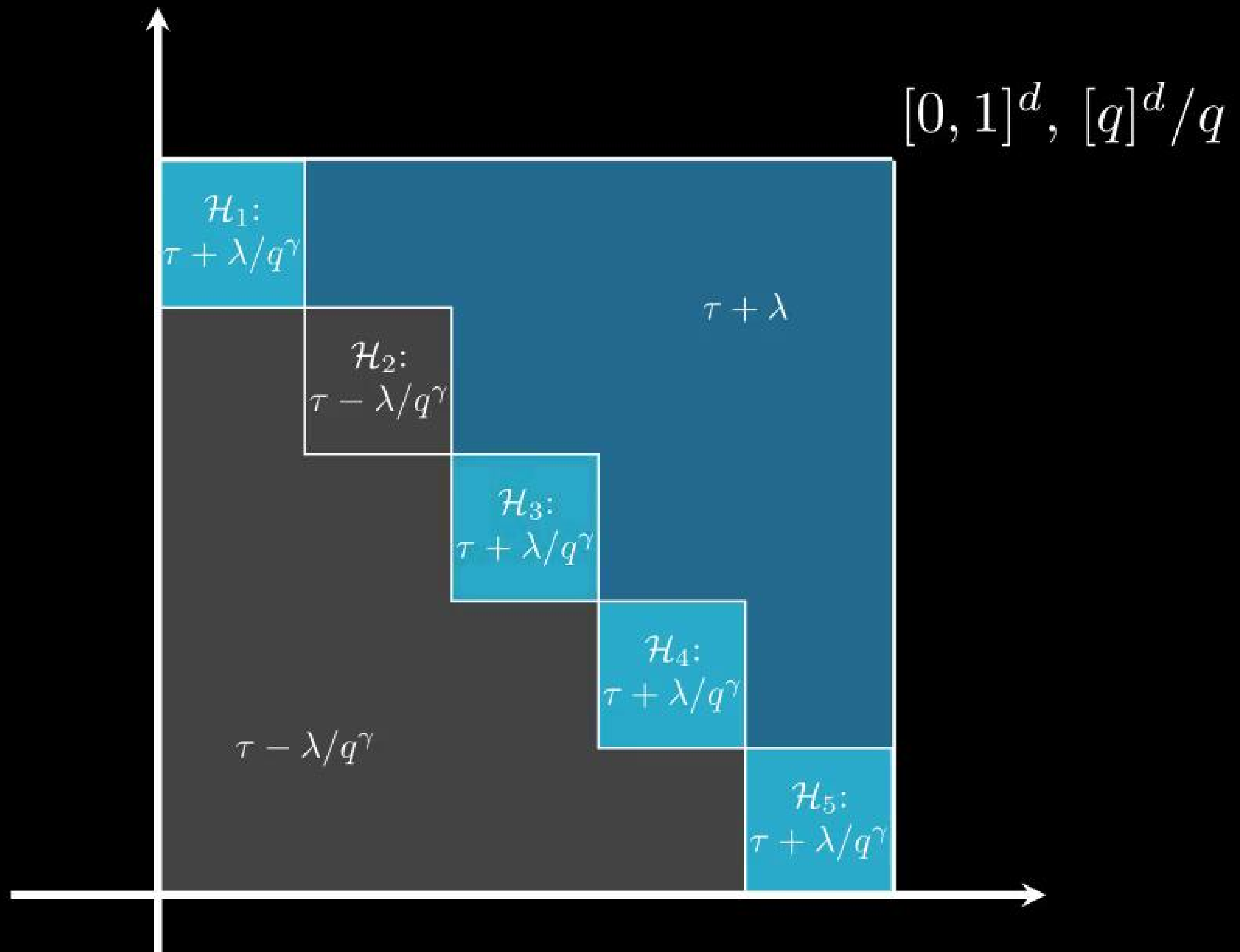

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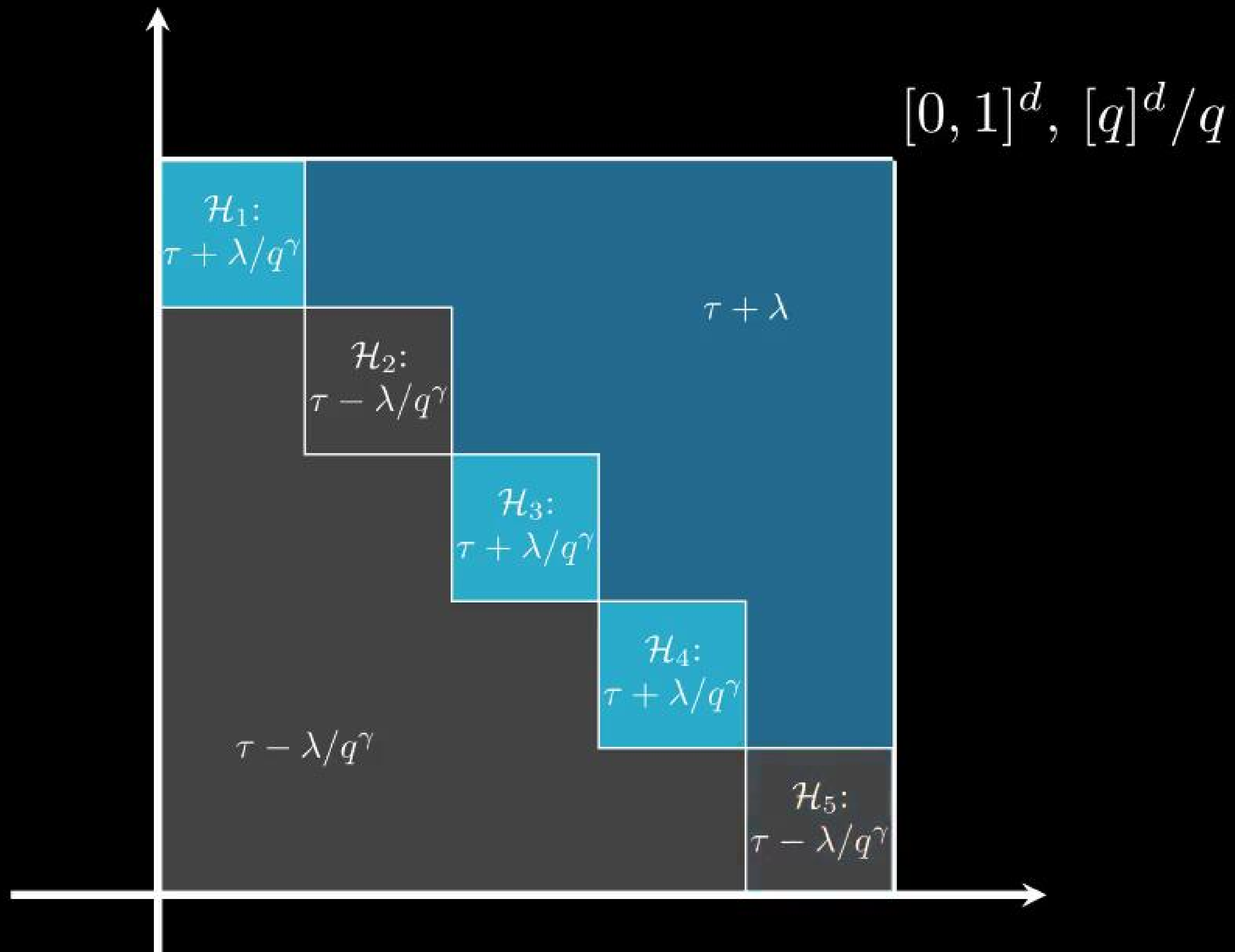

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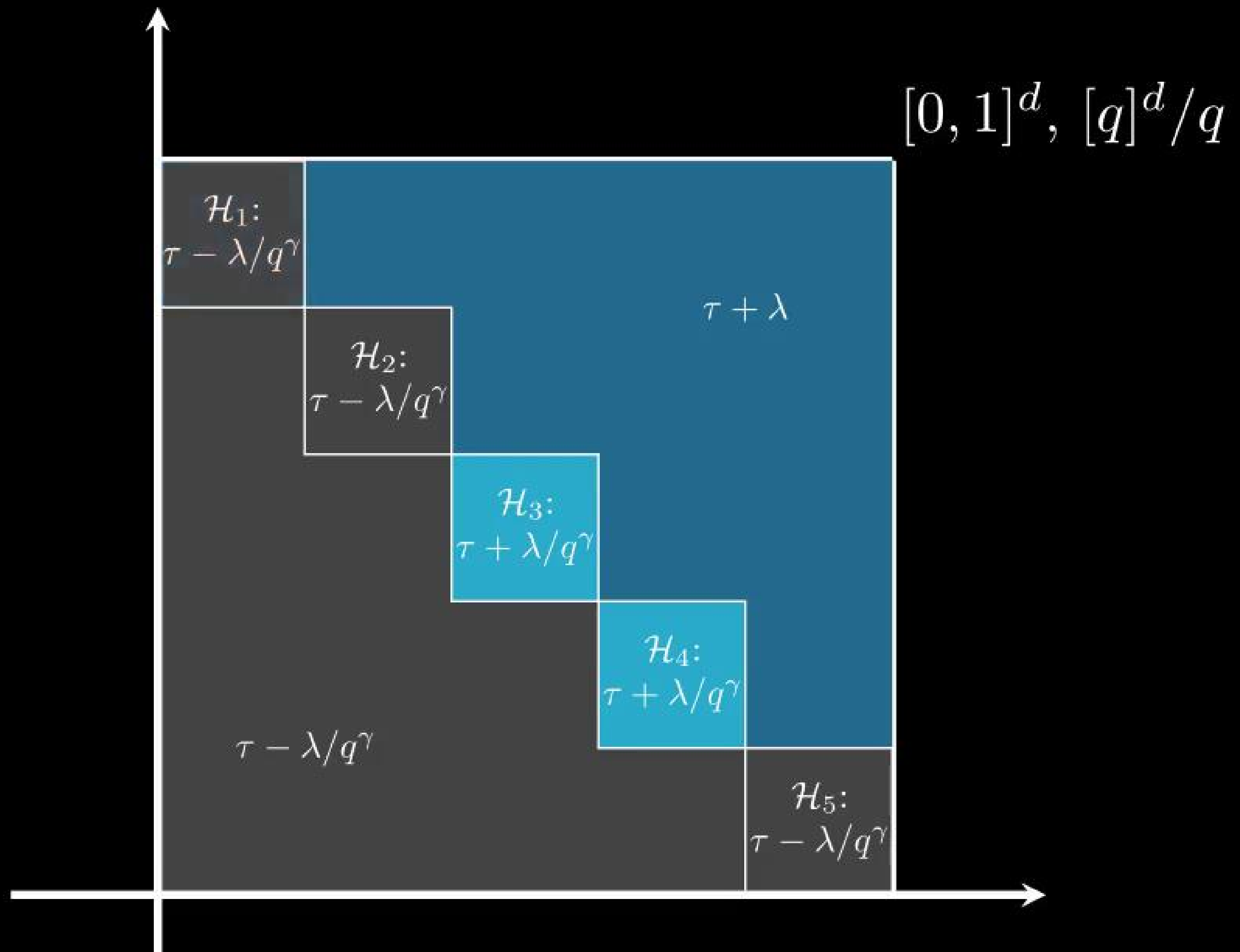

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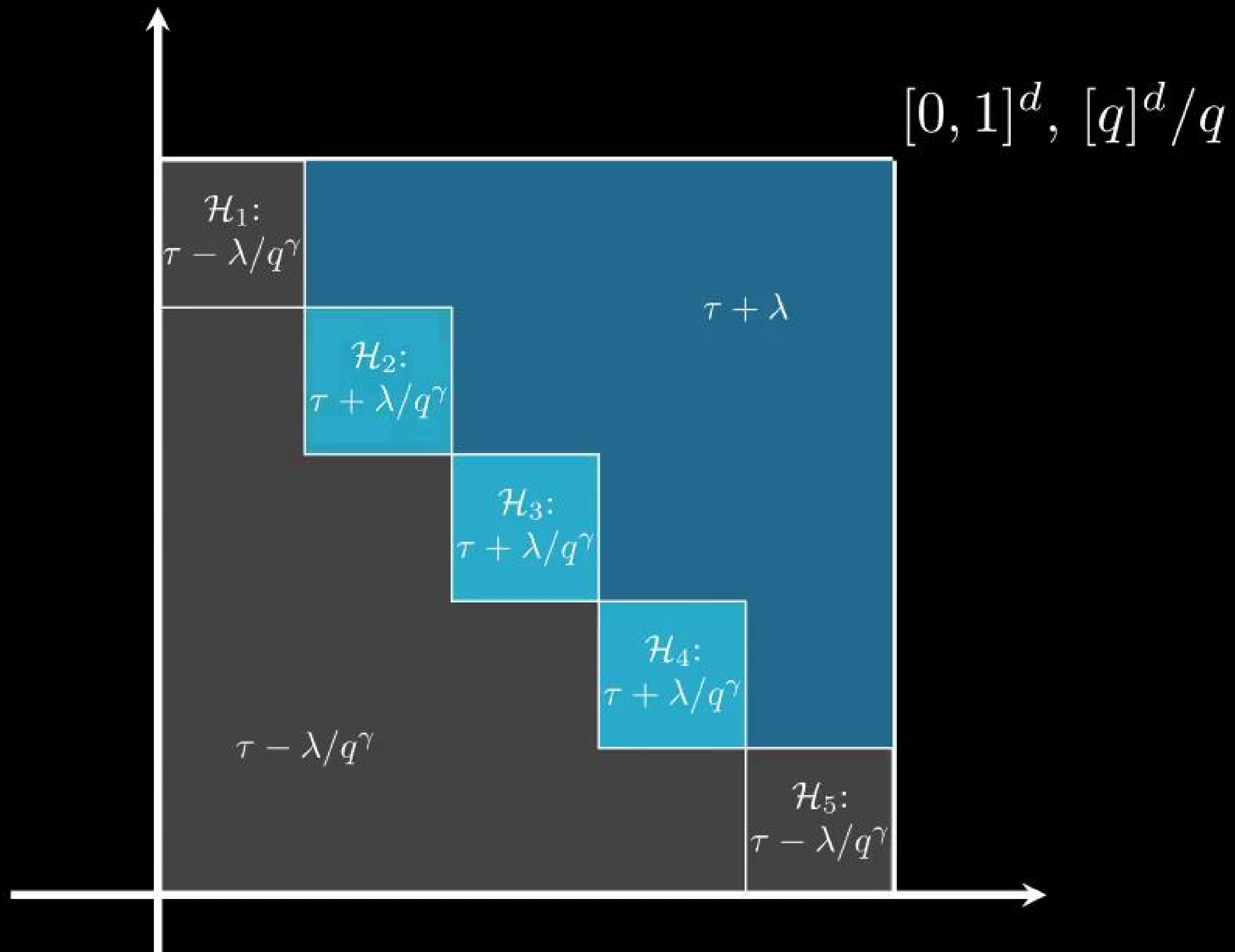

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Definition. Let $\hat{\sigma}^2_{0,k} := \frac{1}{k}\sum_{j=1}^{k}\big(Y_{(j)} - \tau\big)_+^2$ and $\bar{Y}_{1,k} := \frac{1}{k}\sum_{j=1}^{k} Y_{(j)}$ for $k \in [n(x)]$ and $\hat{\sigma}^2_{1,k} := \frac{1}{k}\sum_{j=1}^{k}\big(Y_{(j)} - \bar{Y}_{1,k}\big)^2$ for $k \in \{2, \ldots, n(x)\}$. Denote $\bar{Y}_{1,0} := 0$, and $\hat{\sigma}^2_{1,k} := 1$ for $k \in \{0, 1\}$. For $k \in [n(x)]$, define

$$\bar{p}^k_\tau(x) := \frac{1}{\hat{\sigma}^k_{0,k} e^{k/2}} \cdot \prod_{j=1}^{k} \hat{\sigma}_{1,j-1} \exp\left\{ \frac{\big(Y_{(j)} - \bar{Y}_{1,j-1}\big)^2}{2\hat{\sigma}^2_{1,j-1}} \right\},$$

where $\bar{p}^k_\tau(x) := 1$ if $\hat{\sigma}_{0,k} = 0$, and $\bar{p}_\tau(x) := 1 \wedge \min_{k \in [n(x)]} \bar{p}^k_\tau(x)$.

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Lemma. When $\eta(x) < \tau$, we have $\mathbb{P}\{\bar{p}_\tau(x) \leq t | \mathcal{D}_X\} \leq t$ for all $t \in (0, 1)$.

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Simulations

We conduct a simulation study to compare with other choices of multiple testing procedure. We take $\mu = \mathrm{Unif}\big([0,1]^d\big)$, $Y - \eta(X)|X \sim \mathcal{N}(0, \sigma^2)$ and our regression functions η are obtained by rescaling f to $[0,1]$ on $[0,1]^d$:

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(d)	$\mathbb{1}_{(0.5,1]}\big(x^{(1)}\big)$	$1/2$	0
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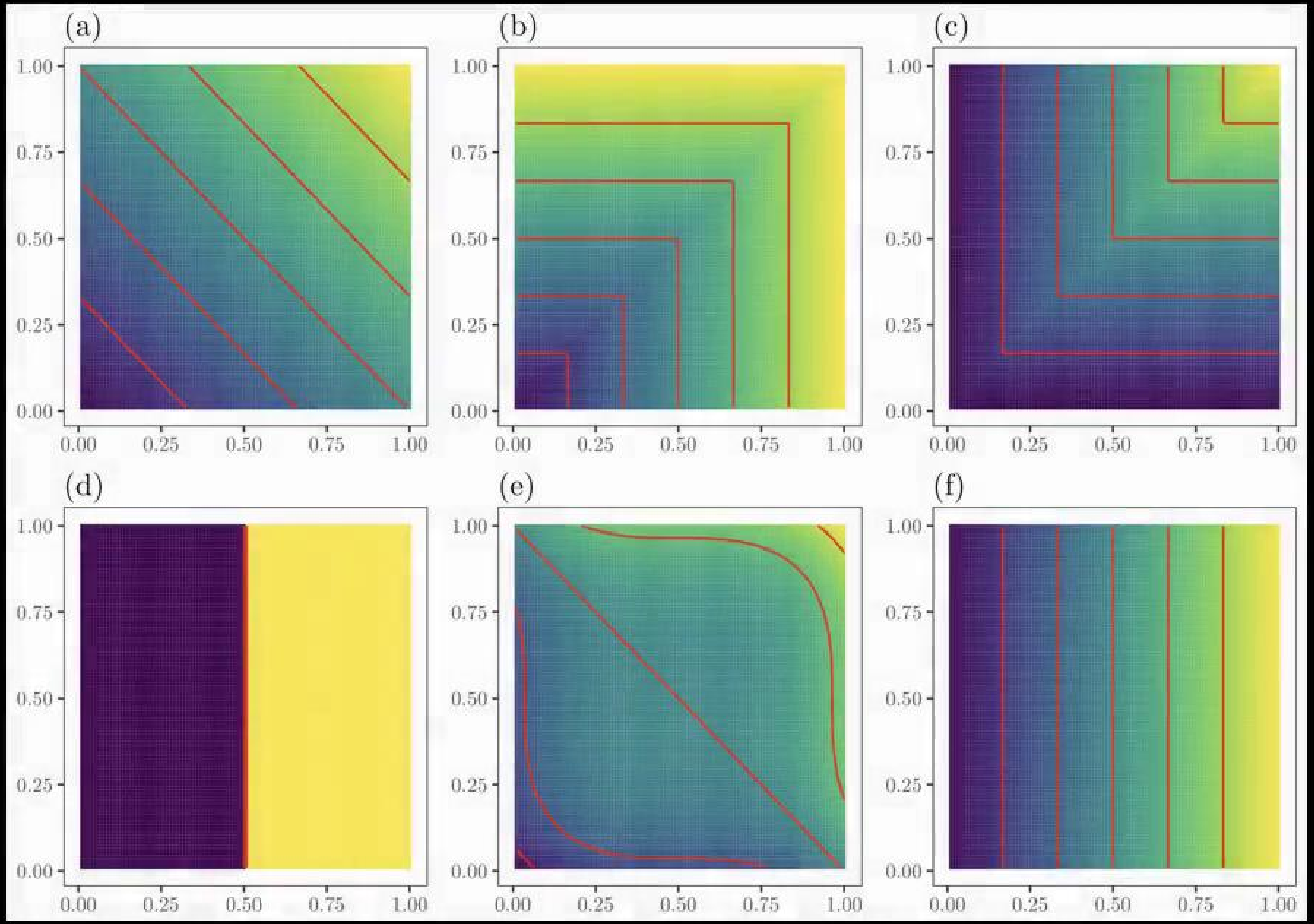

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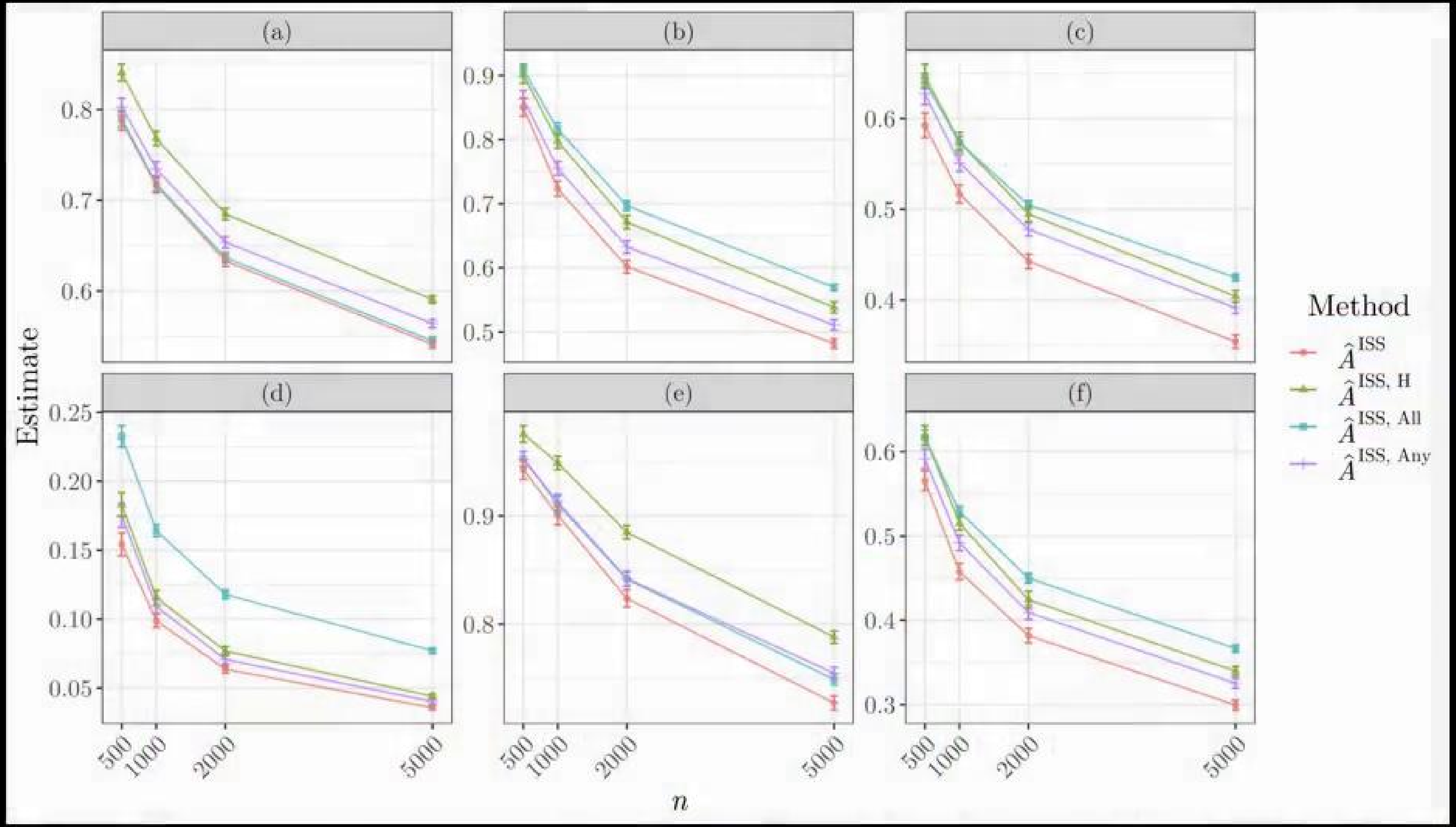

Here, $d = 2$, $\sigma = 1/4$.
See also Meijer and Goeman (2015).