Isotonic subgroup selection

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Task. *Subgroup selection* in regression: Identify a subset of the covariate domain on which the regression function satisfies a particular property (e.g. exceeds a threshold) with the same data.

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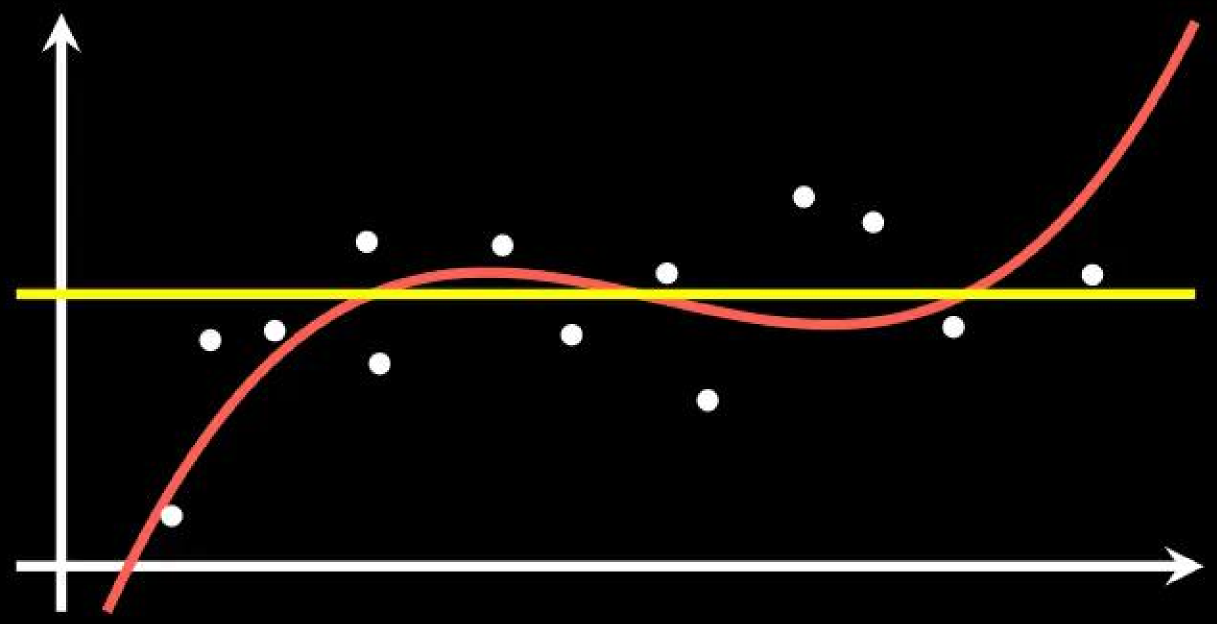

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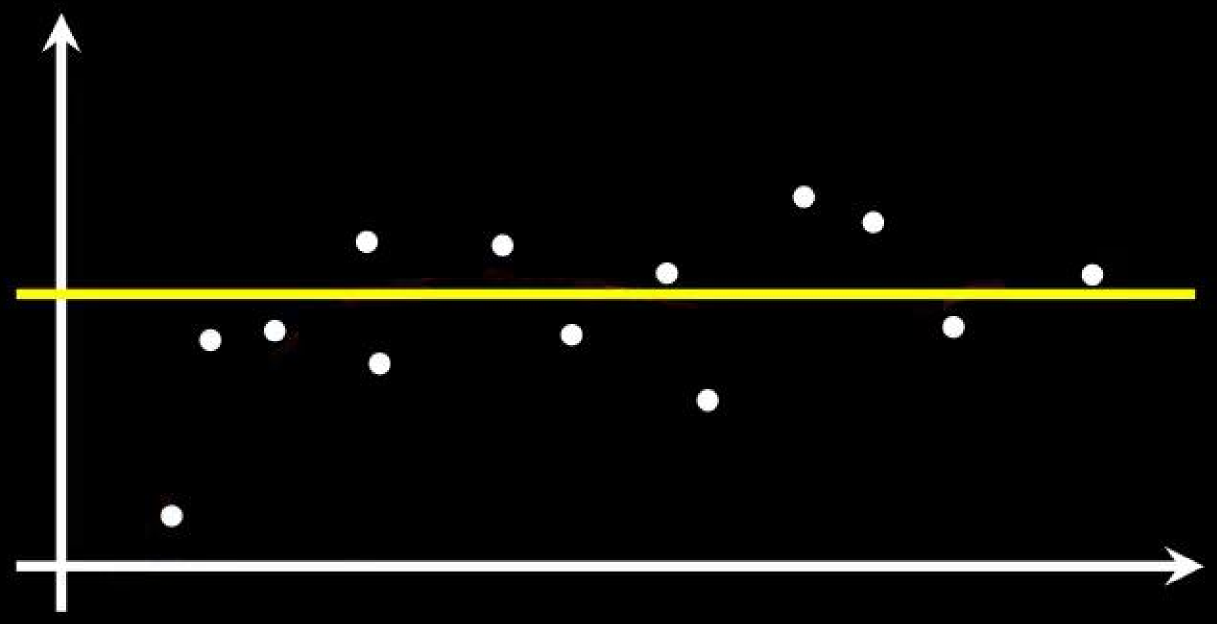

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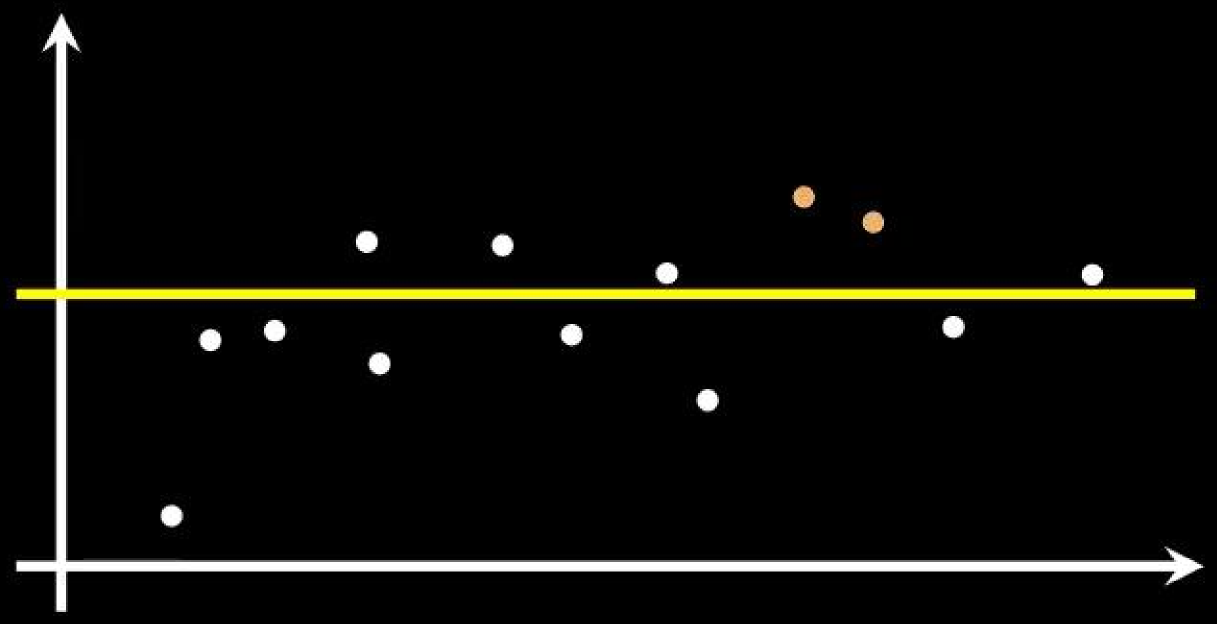

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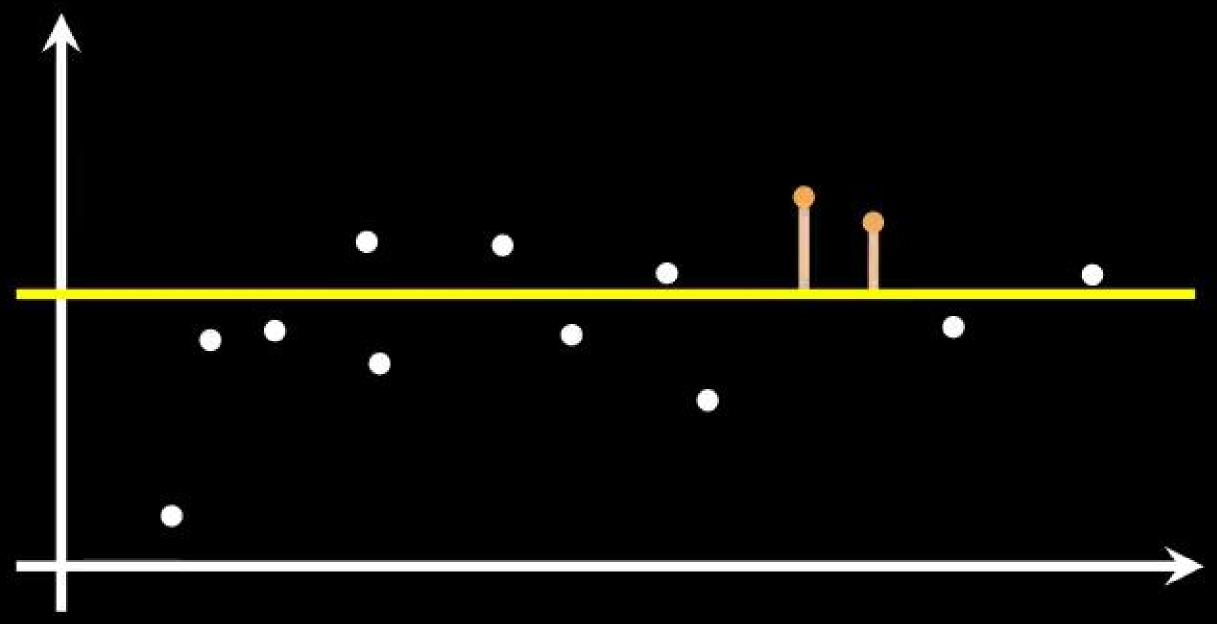

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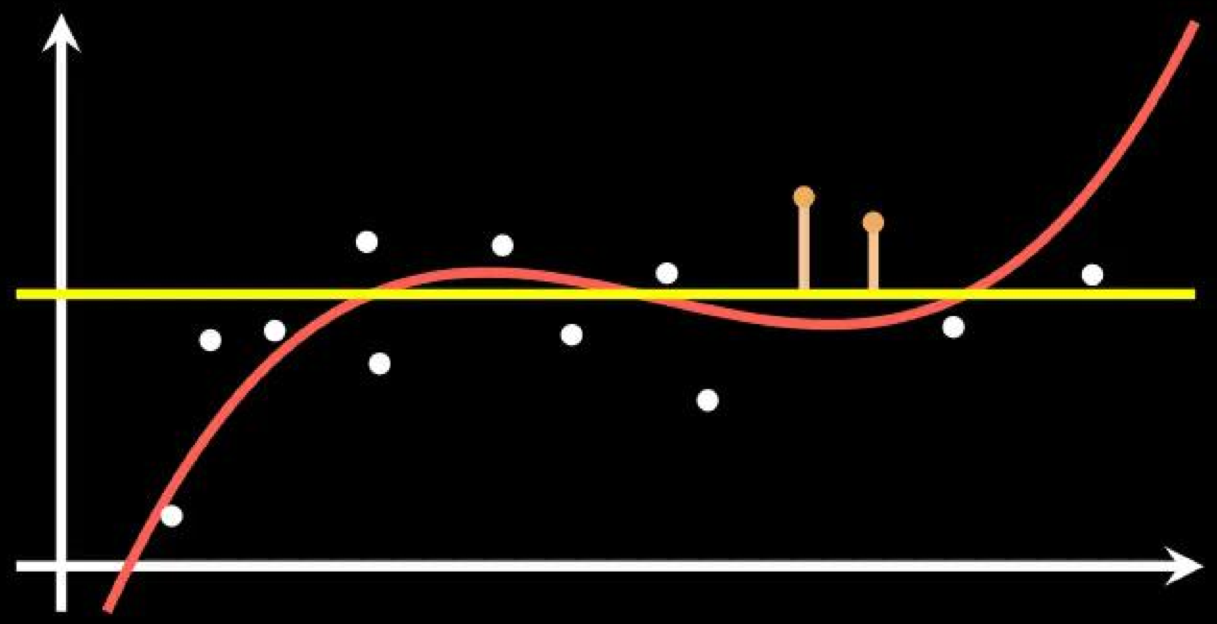

Example. Efficacy of a new vaccine.

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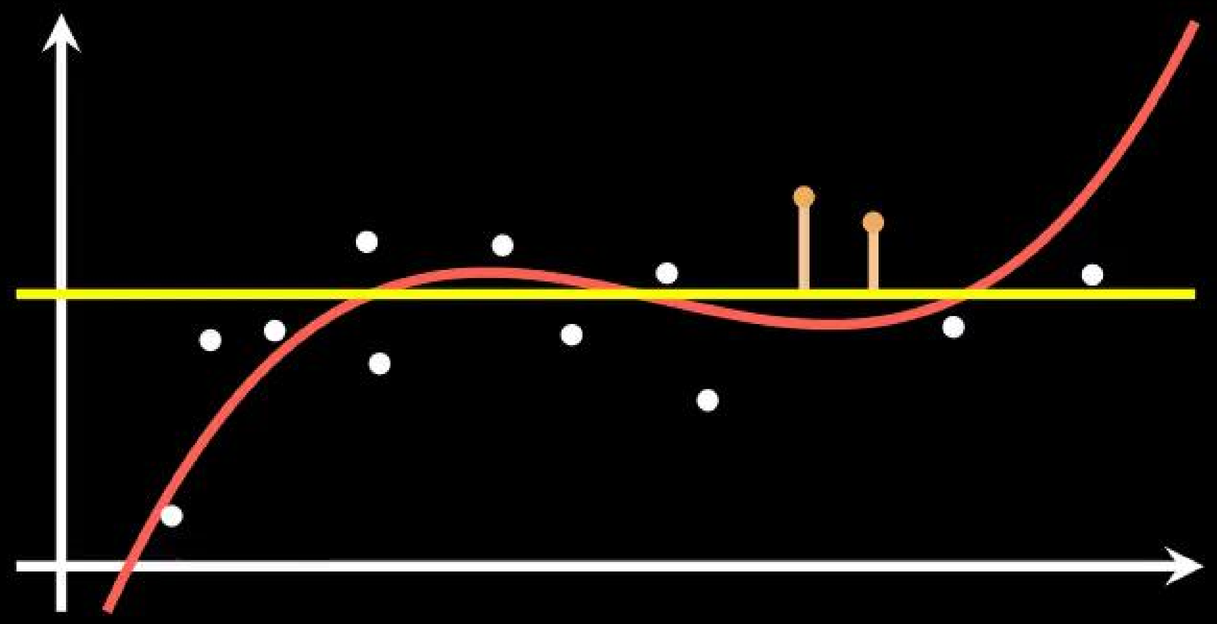

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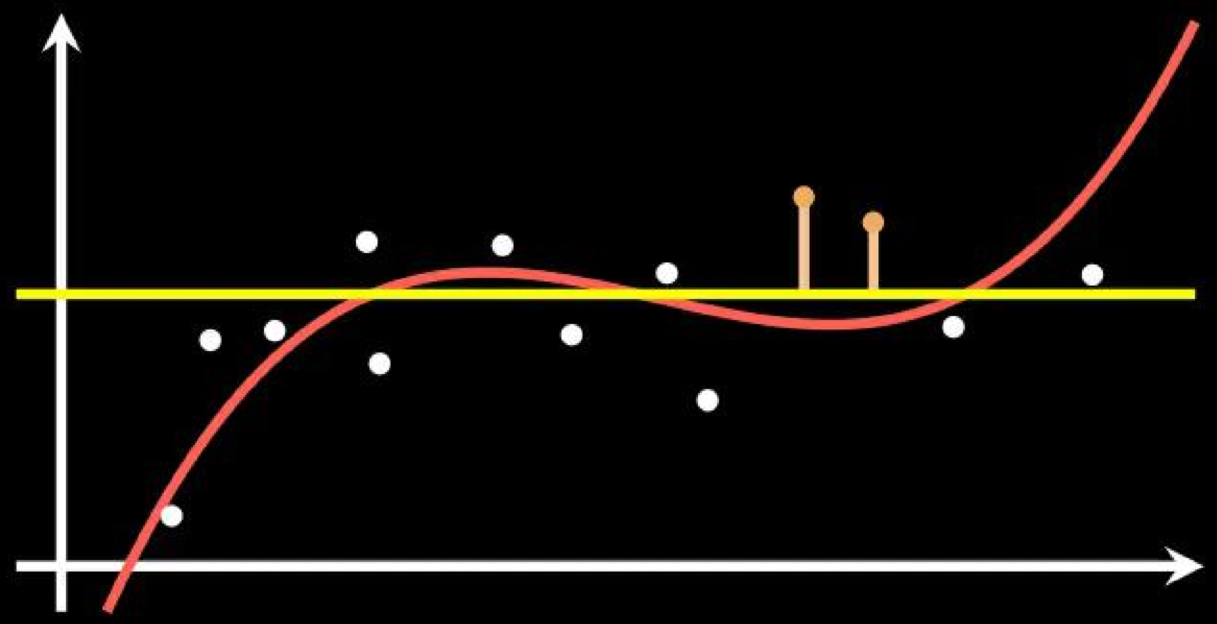

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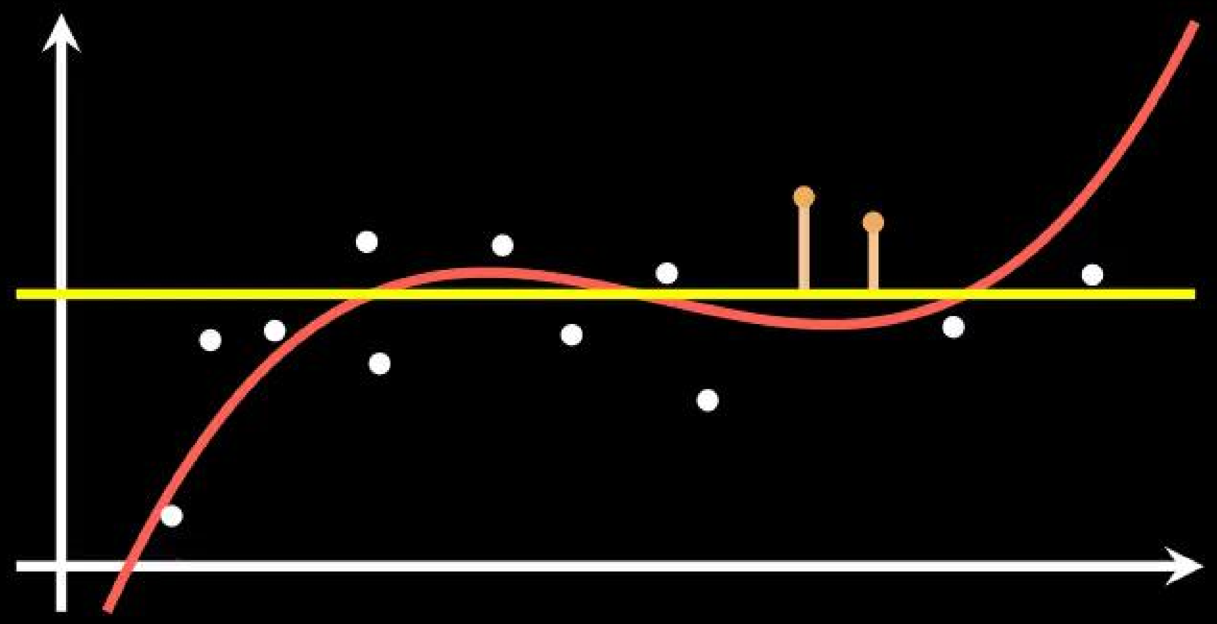

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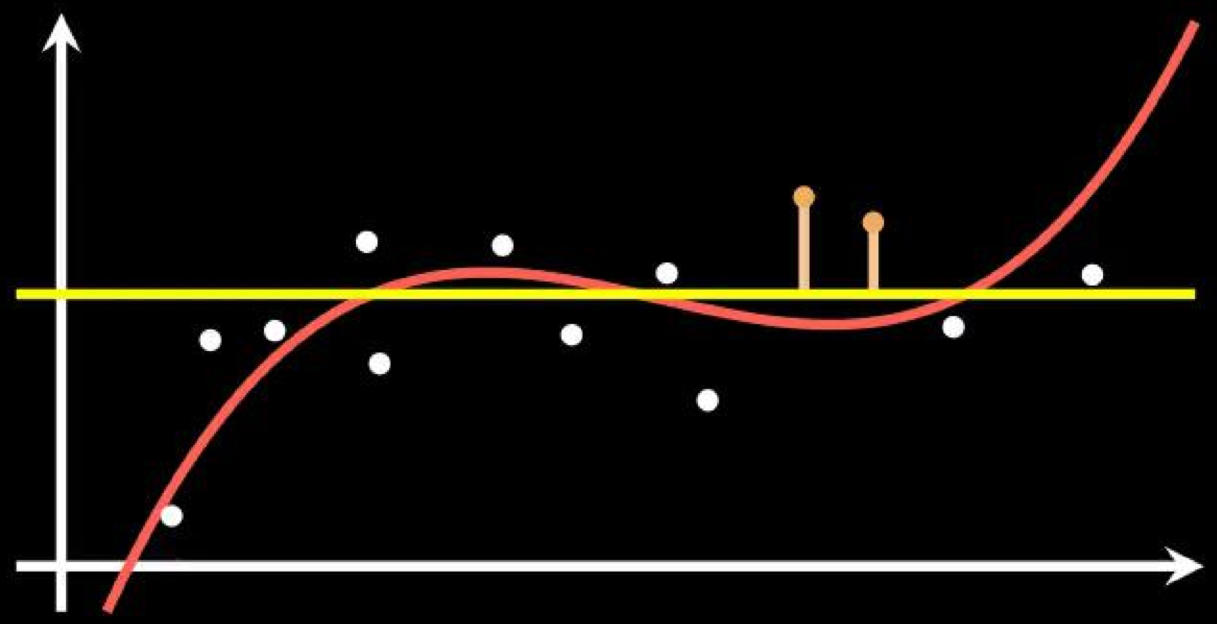

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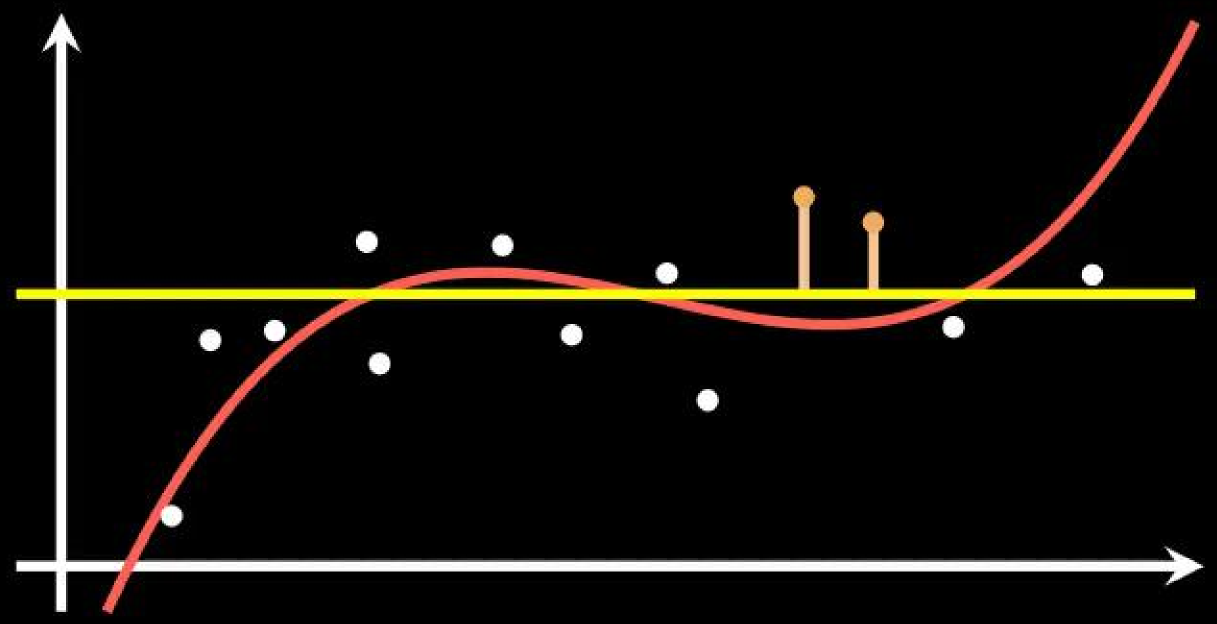

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$\longrightarrow$ Asymmetry of errors

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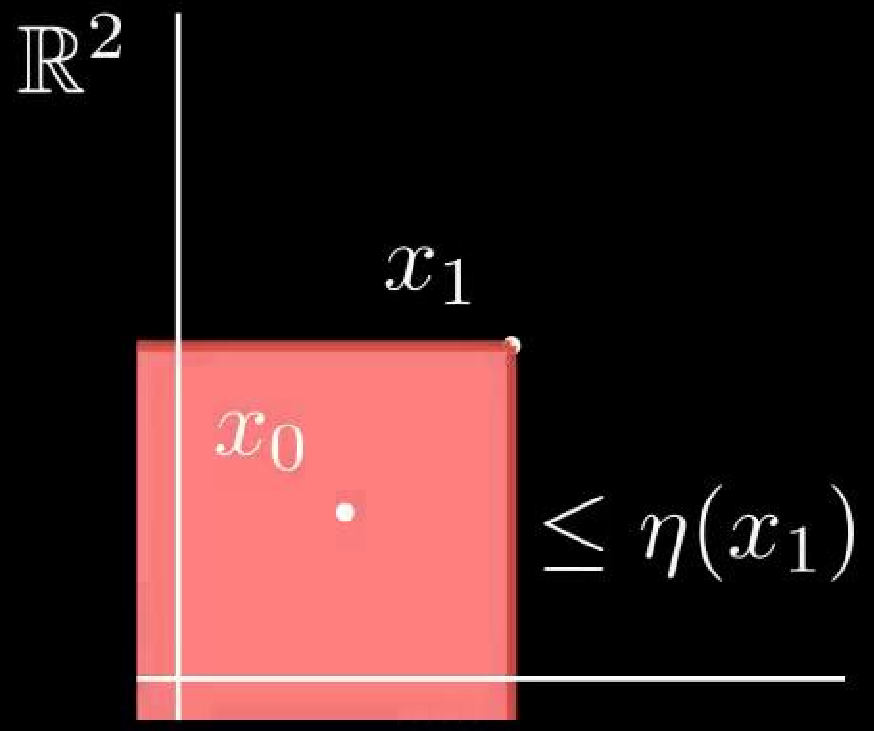

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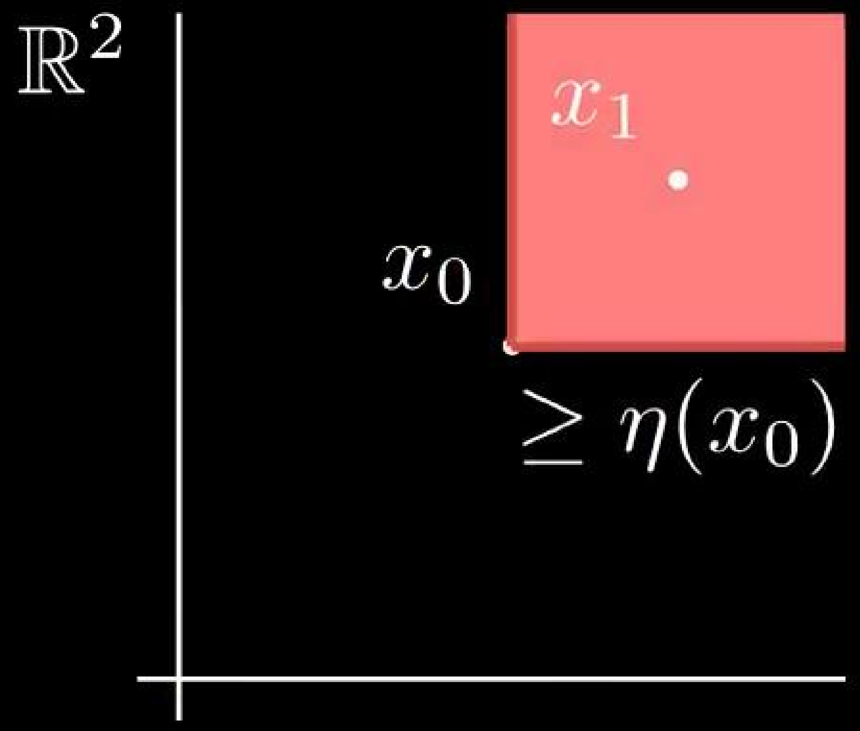

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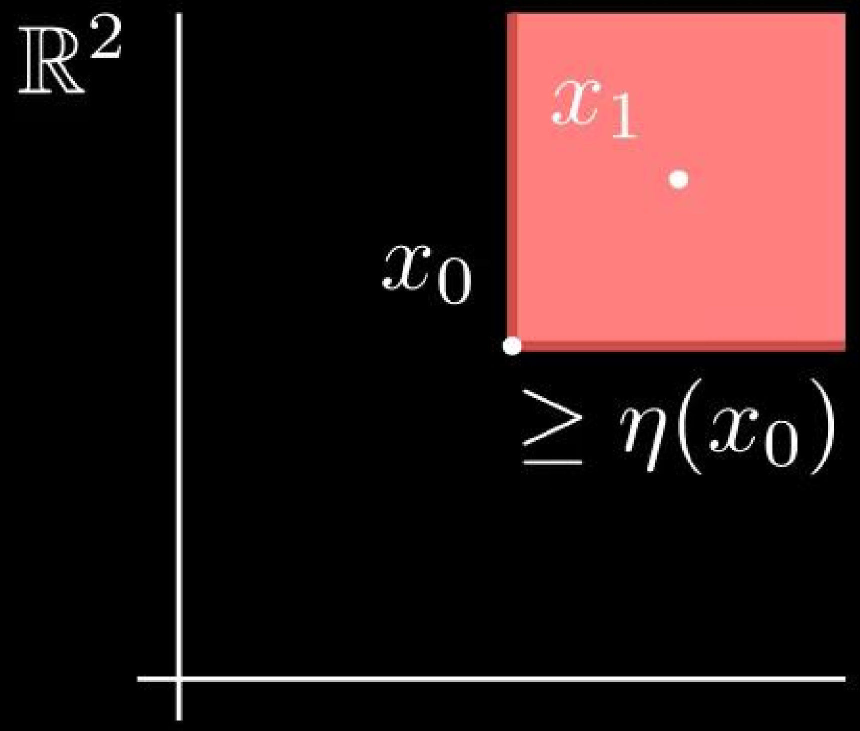

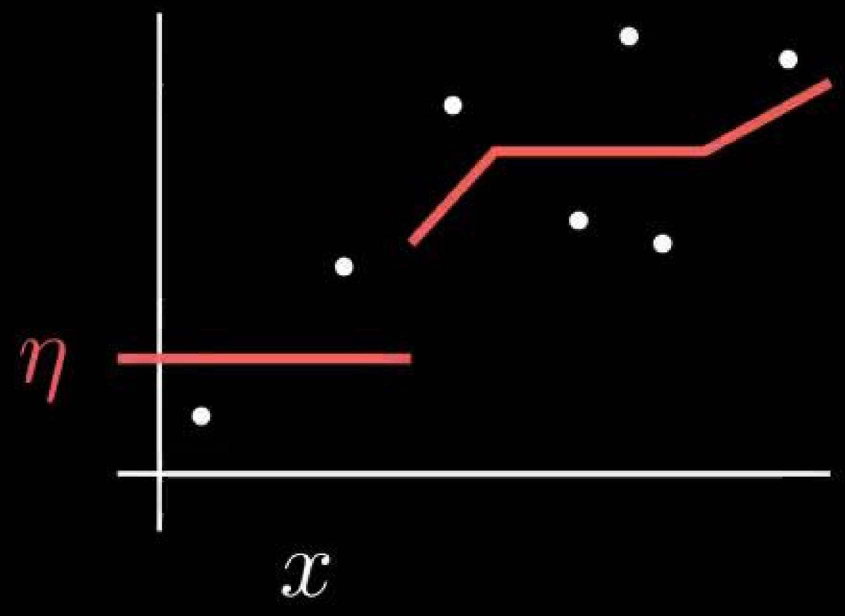

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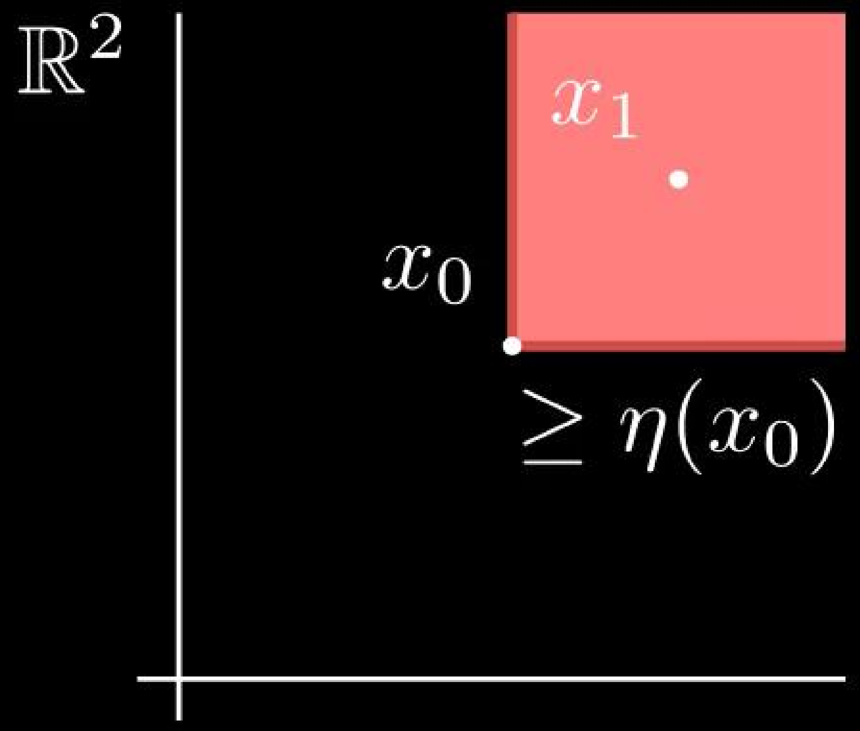
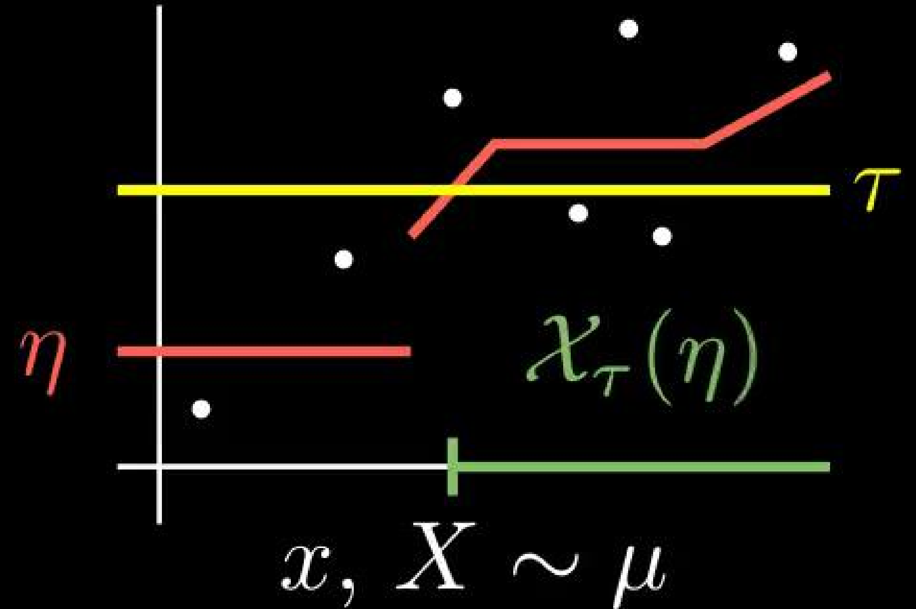


Notation:

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

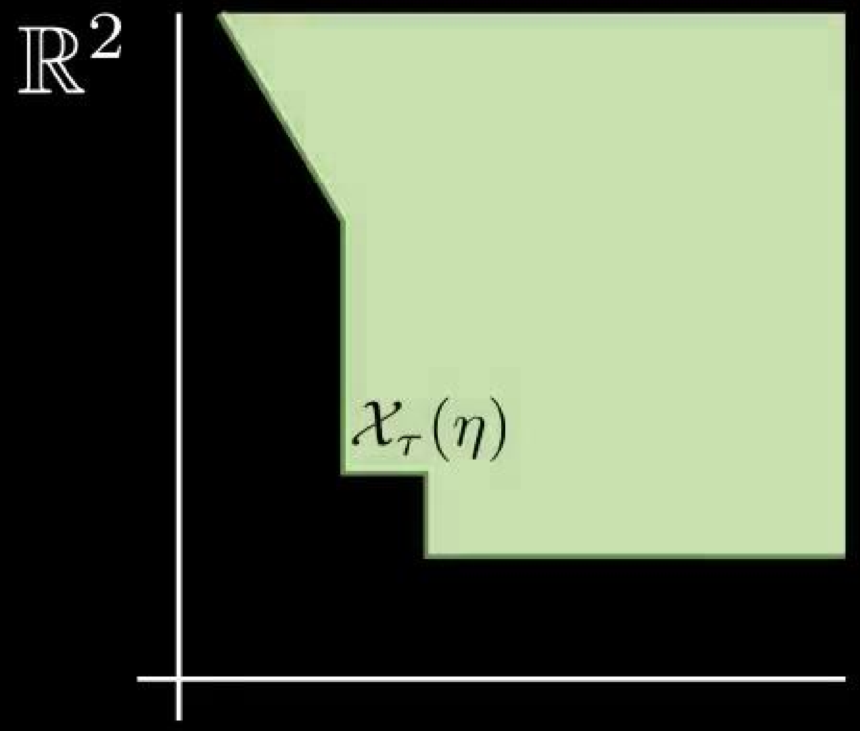
$$\mathcal{X}_\tau(\eta) := \{x \in \mathbb{R}^d : \eta(x) \geq \tau\}$$

- Denote the marginal distribution of X by μ.



Goal

Writing $\mathcal{D} := \big((X_1, Y_1), \ldots, (X_n, Y_n)\big) \sim P^n$, we want $\hat{A} : \mathcal{D} \mapsto \hat{A}(\mathcal{D}) \subseteq \mathbb{R}^d$ such that:



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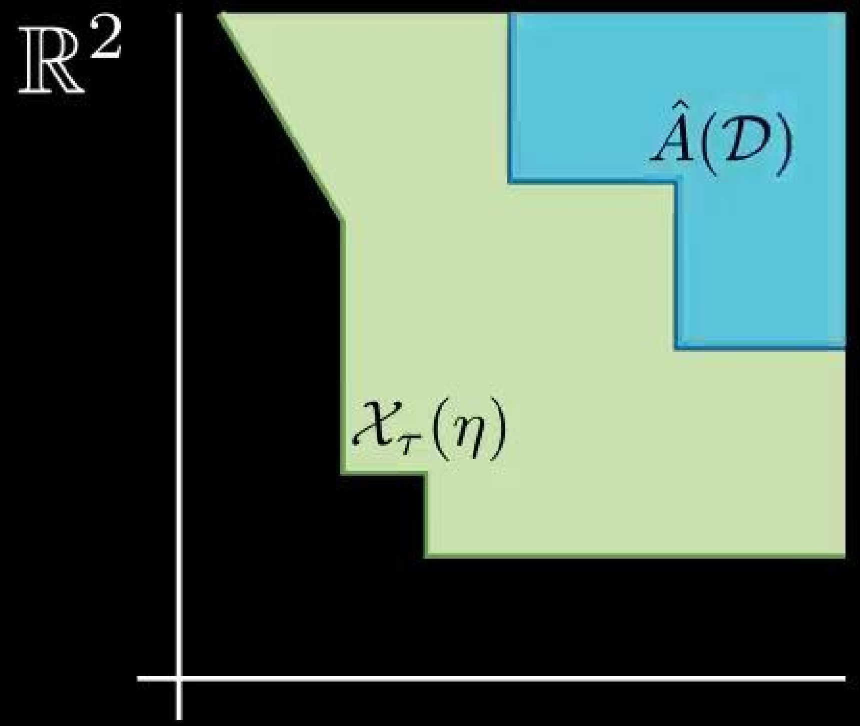
Type I error control: Fix $\alpha \in (0, 1)$. Require

$$\inf_{P \in \mathcal{P}_{\mathrm{Mon},d}(\sigma)} \mathbb{P}\big\{\hat{A}(\mathcal{D}) \subseteq \mathcal{X}_\tau(\eta)\big\} \geq 1 - \alpha.$$



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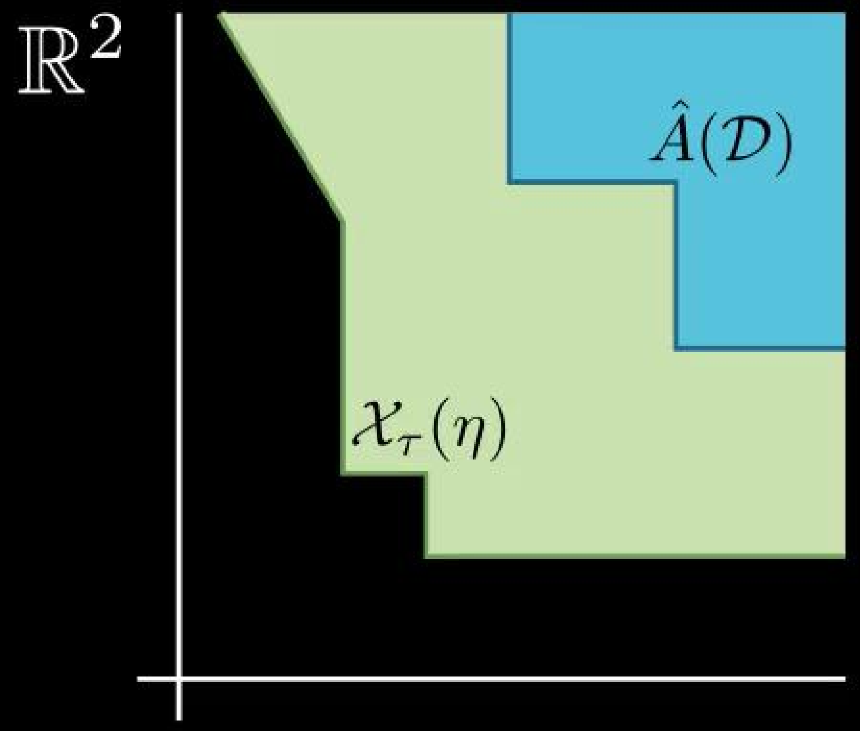

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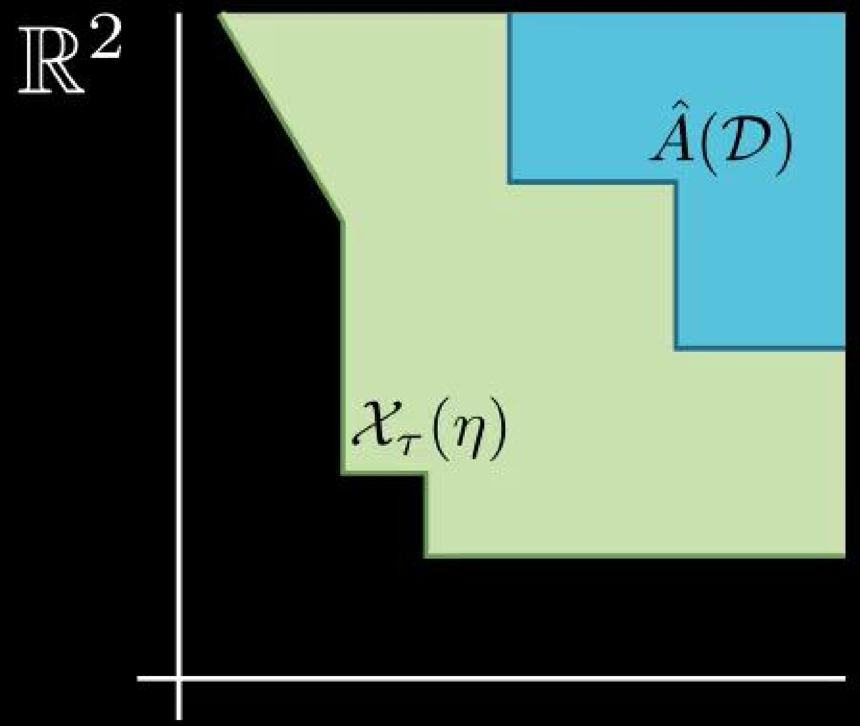

Example:

Type I error: $\hat{A}$ should contain only those for whom the conditional probability of <u>not</u> having sudden cardiac death within the next 5 years is at least 98%.

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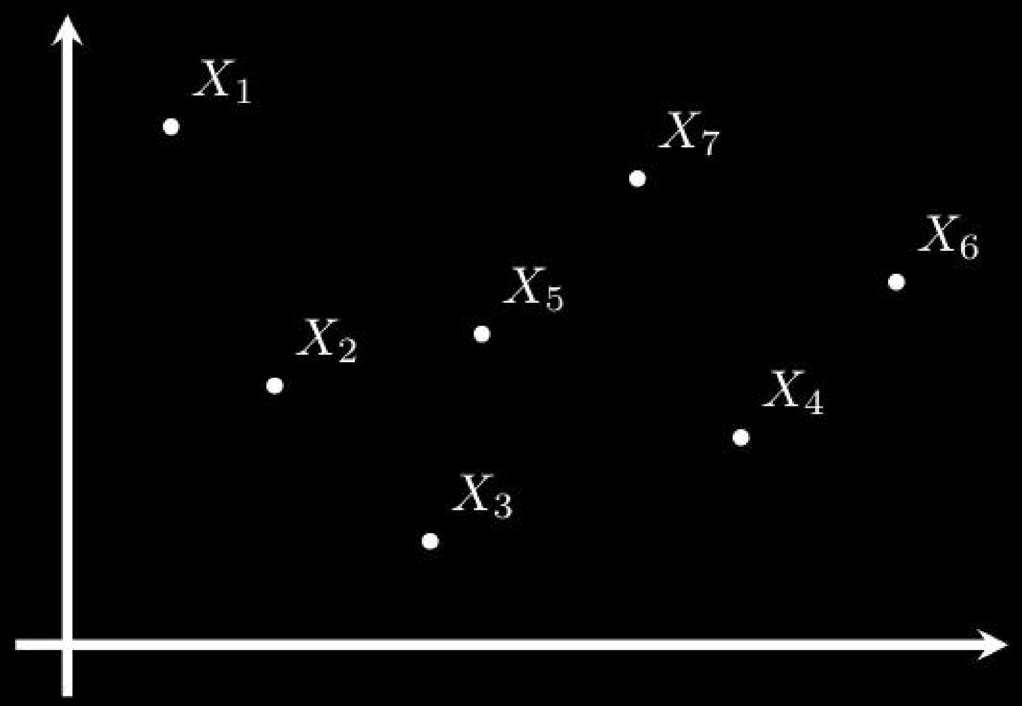

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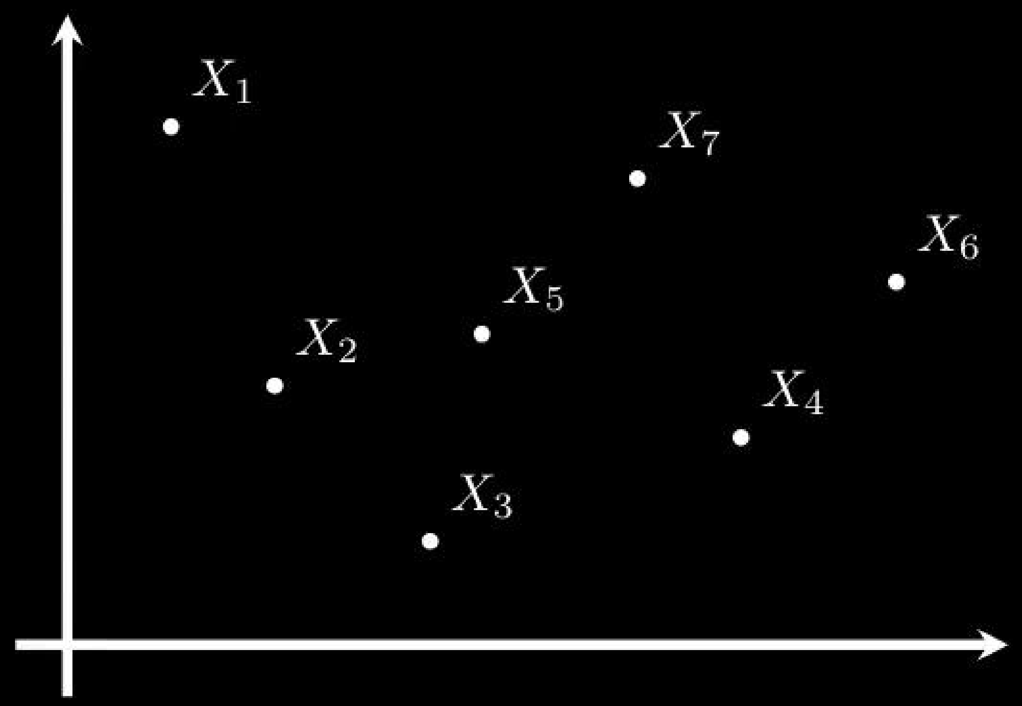

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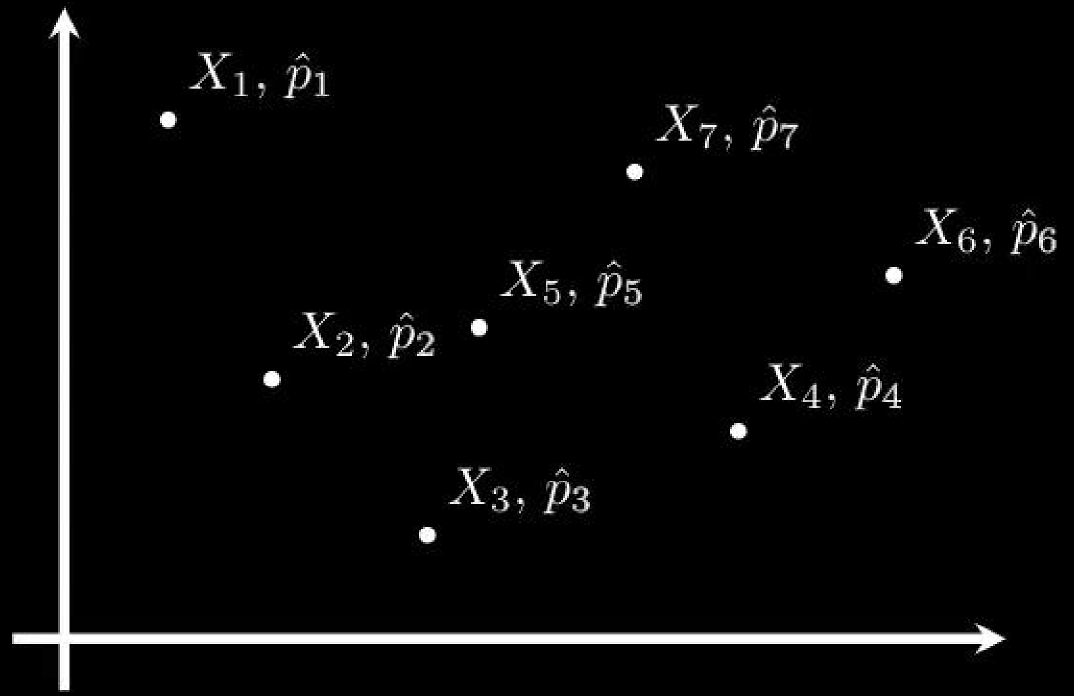

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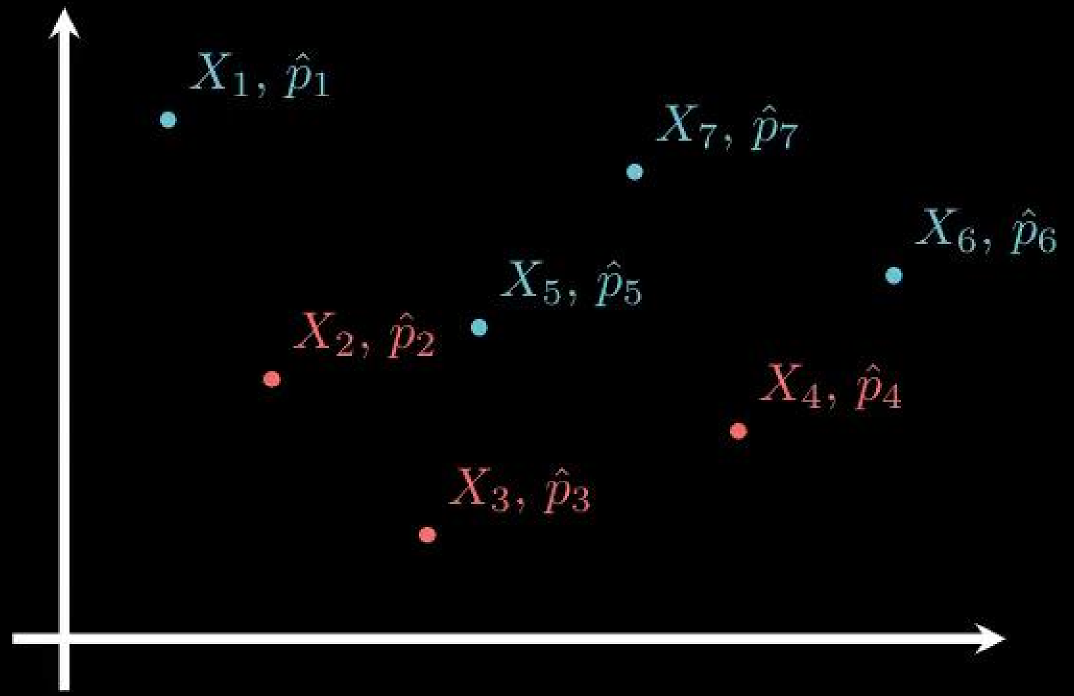

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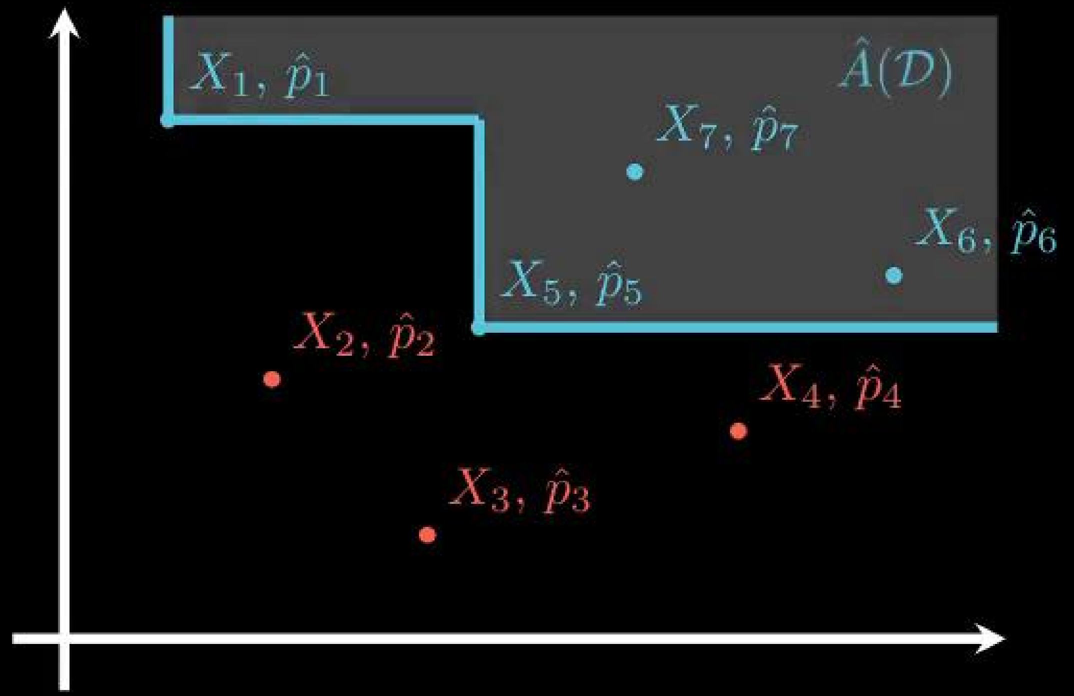

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3. Output $\hat{A} := \{x \in \mathbb{R}^d : X_\ell \preccurlyeq x \text{ for some } \ell \in \mathcal{R}_\alpha\}$.

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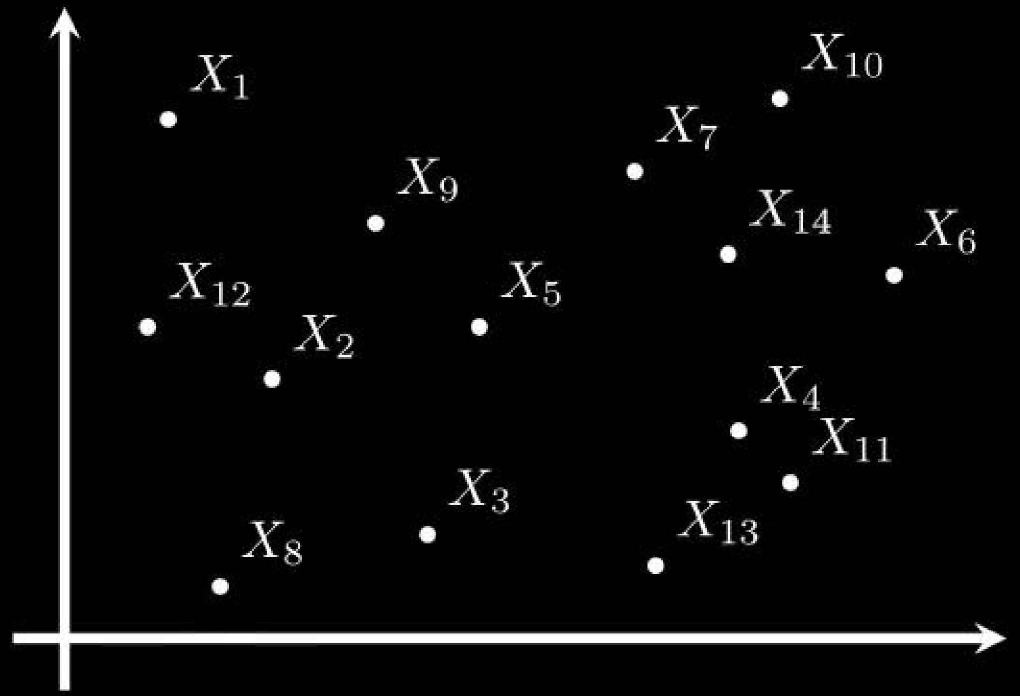

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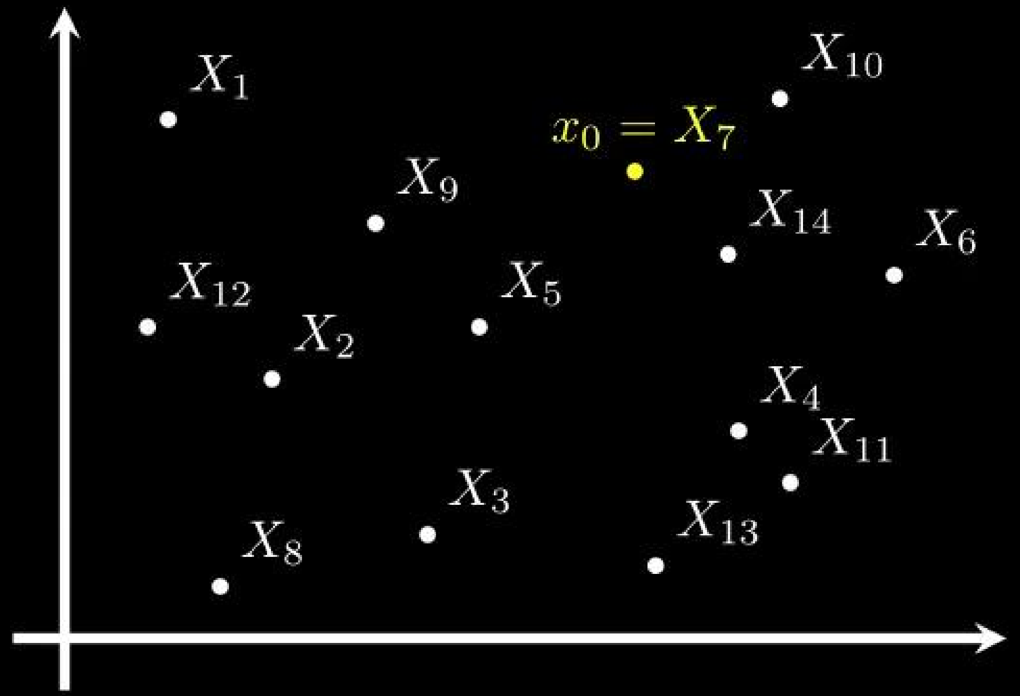

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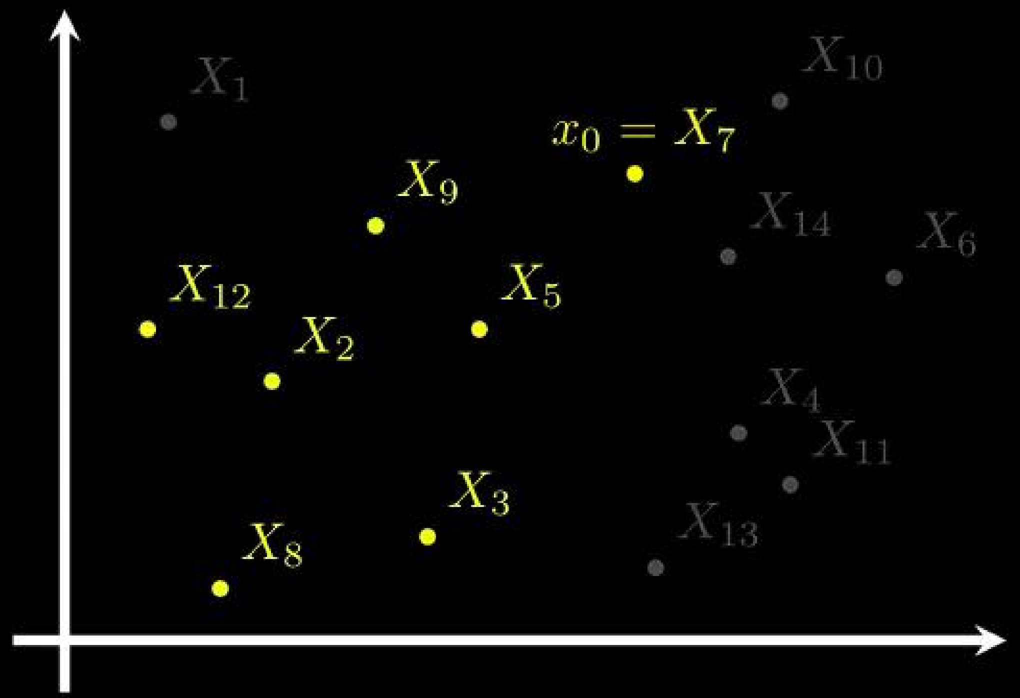

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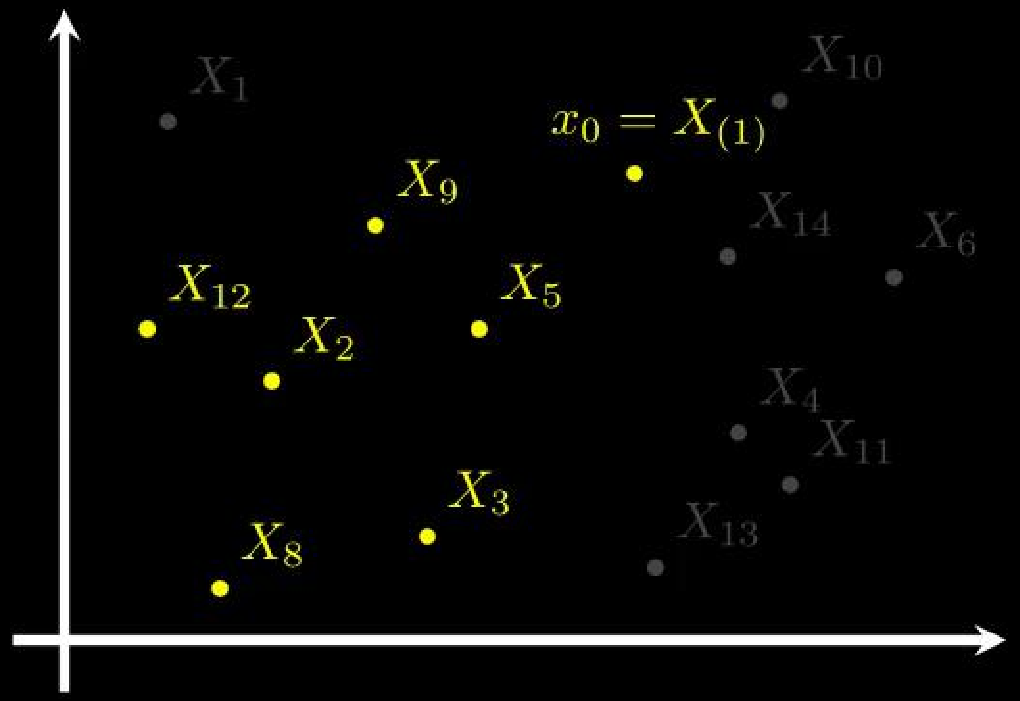

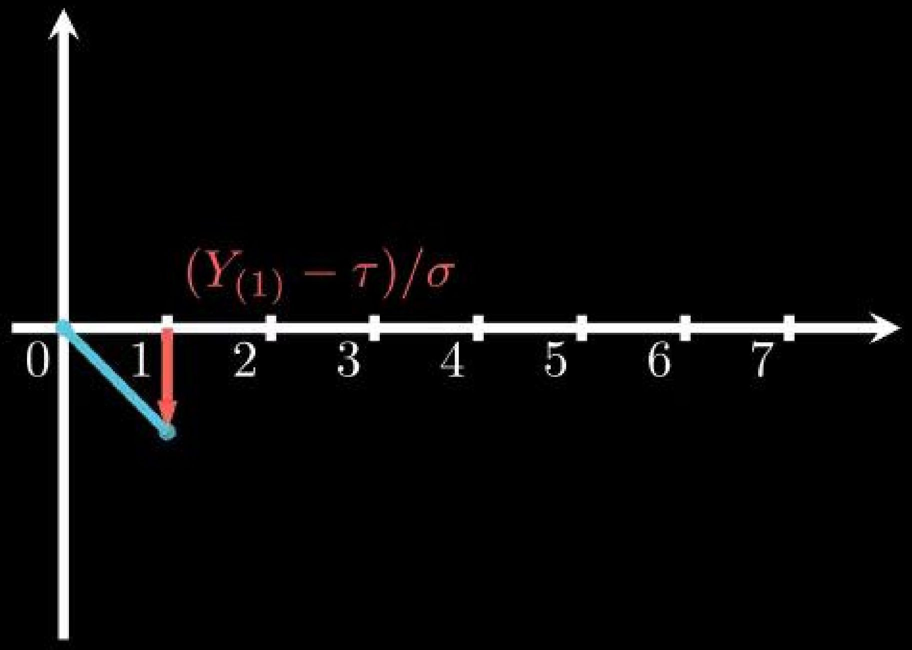

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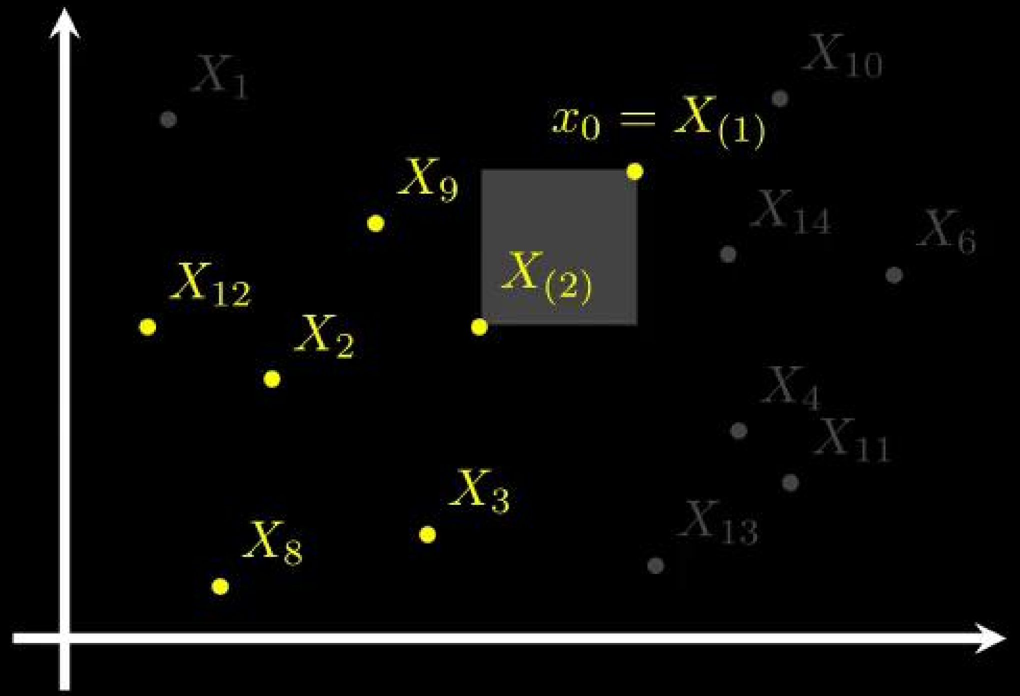

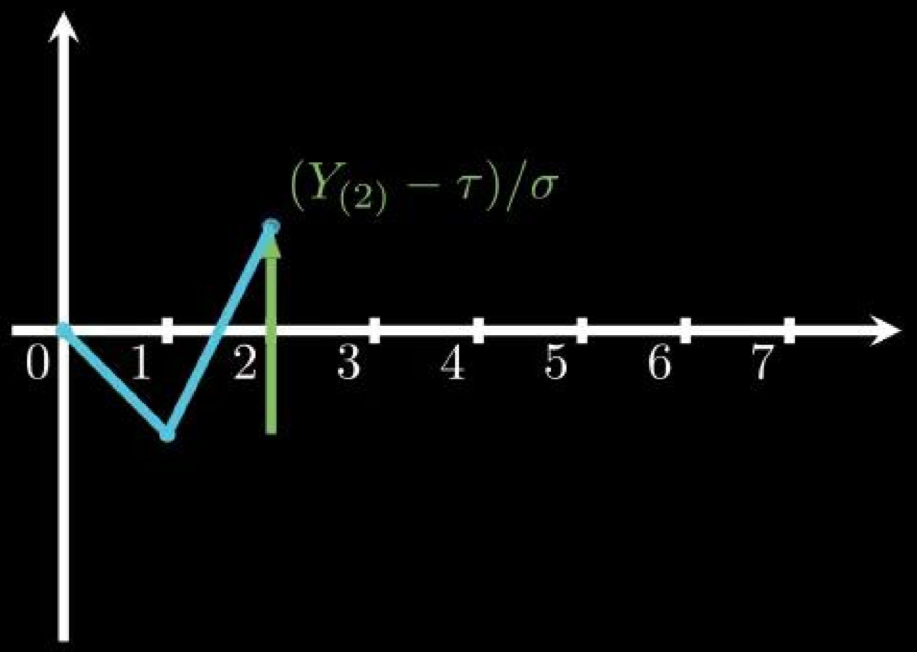

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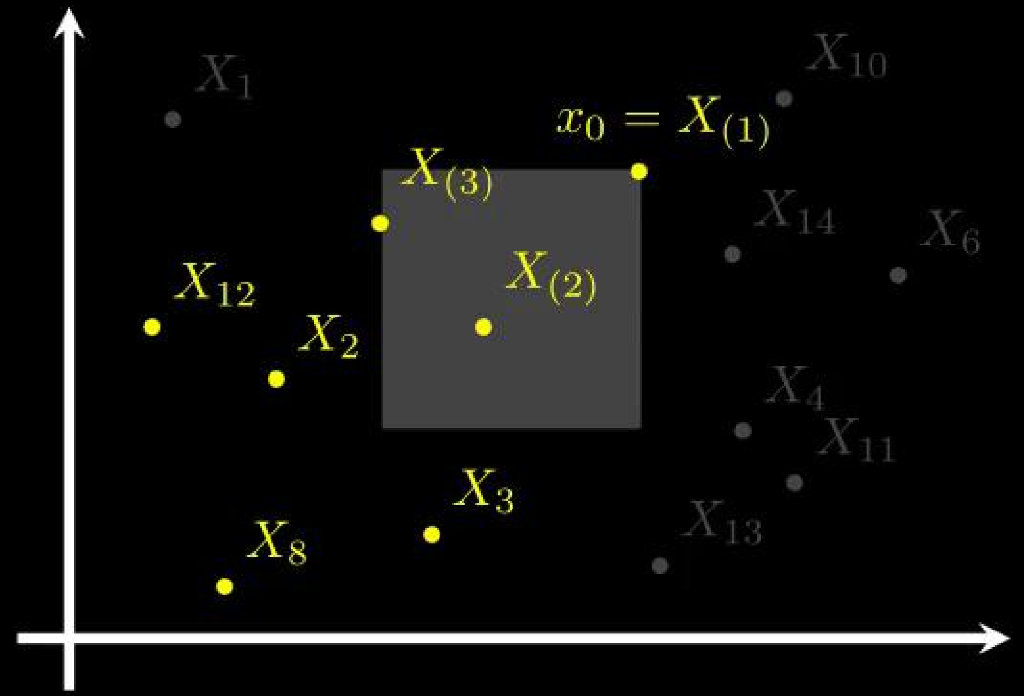

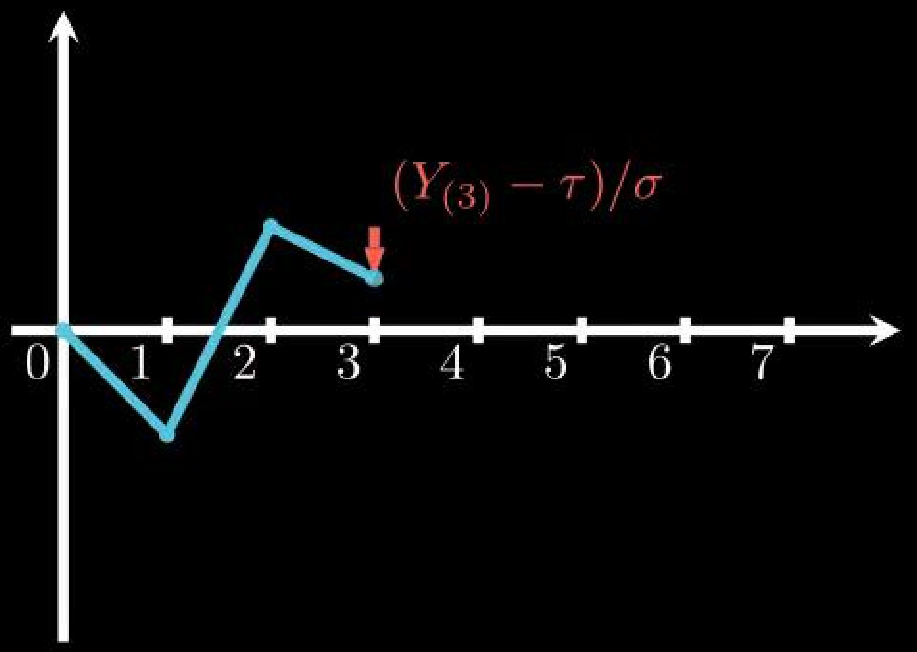

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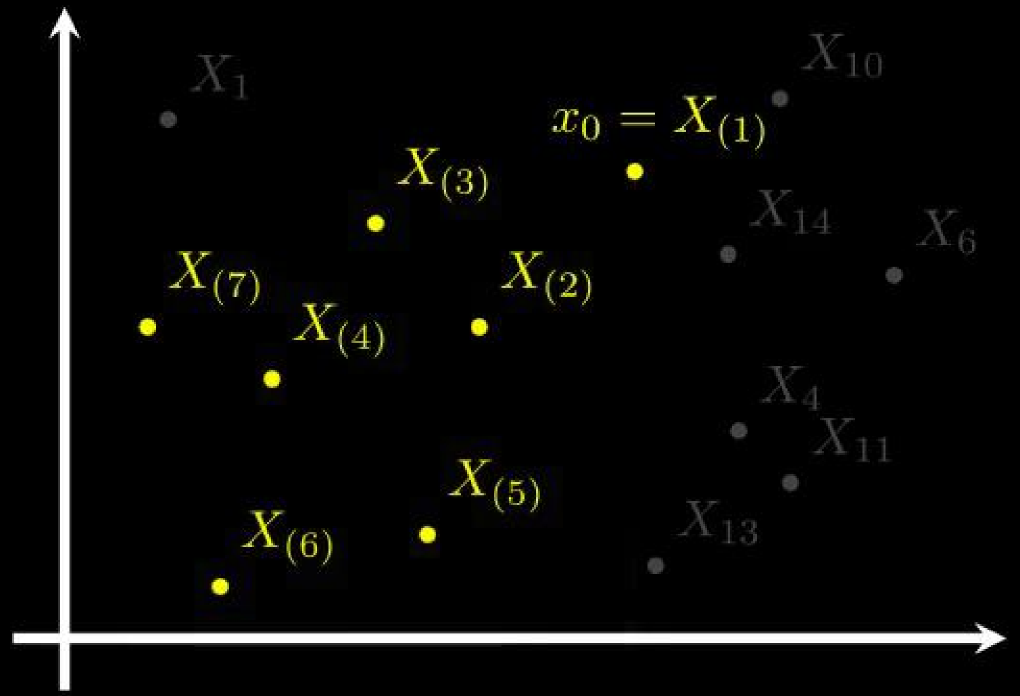

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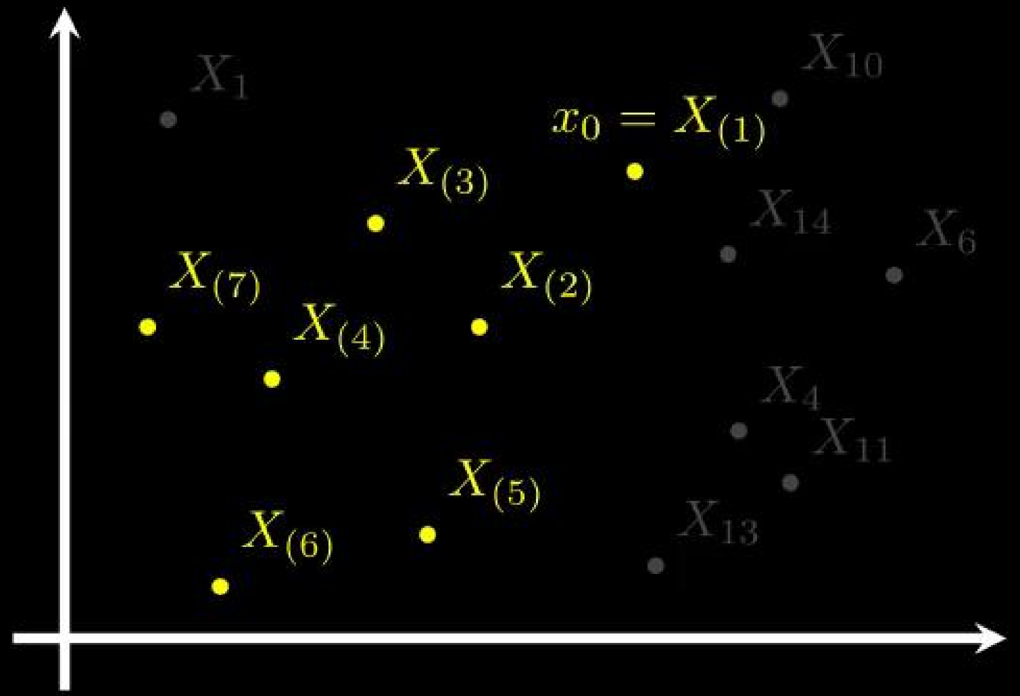

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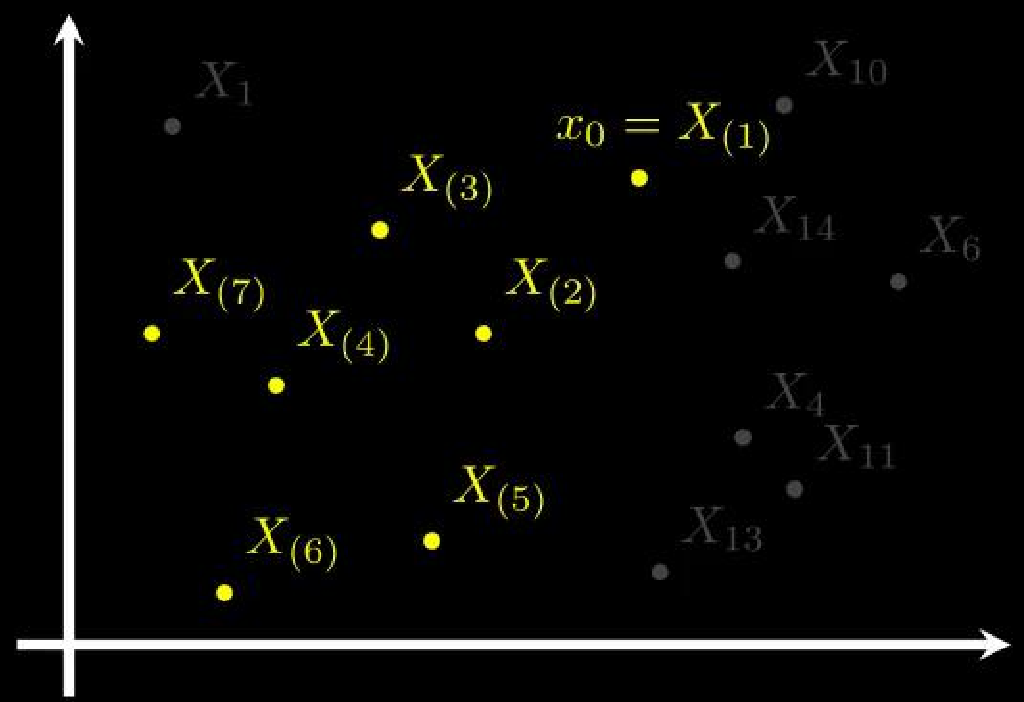
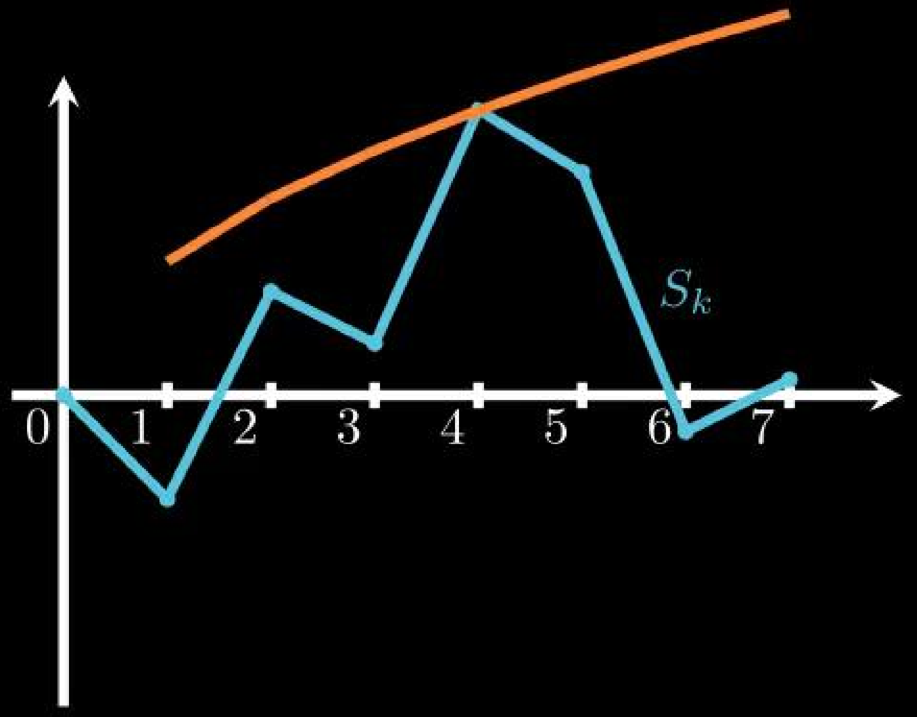
Then S_k is a supermartingale under $P \in H_0(x_0)$. Combination with time-uniform bounds by Howard et al. (2021) gives p-values from this martingale test (Duan et al., 2020).

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

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





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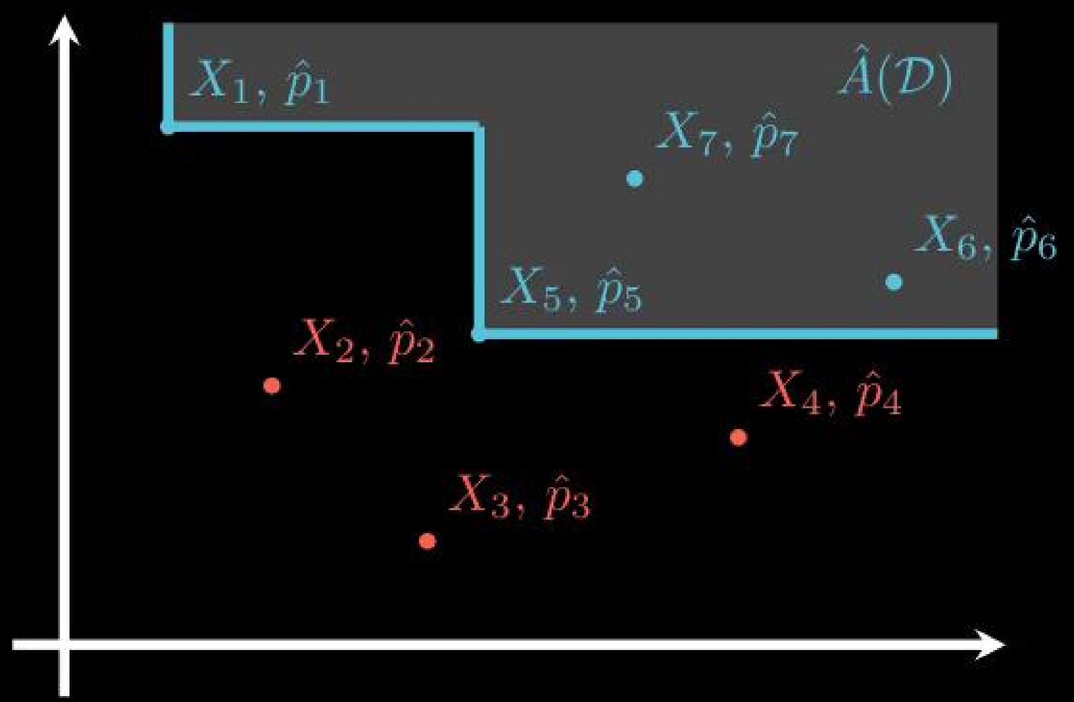
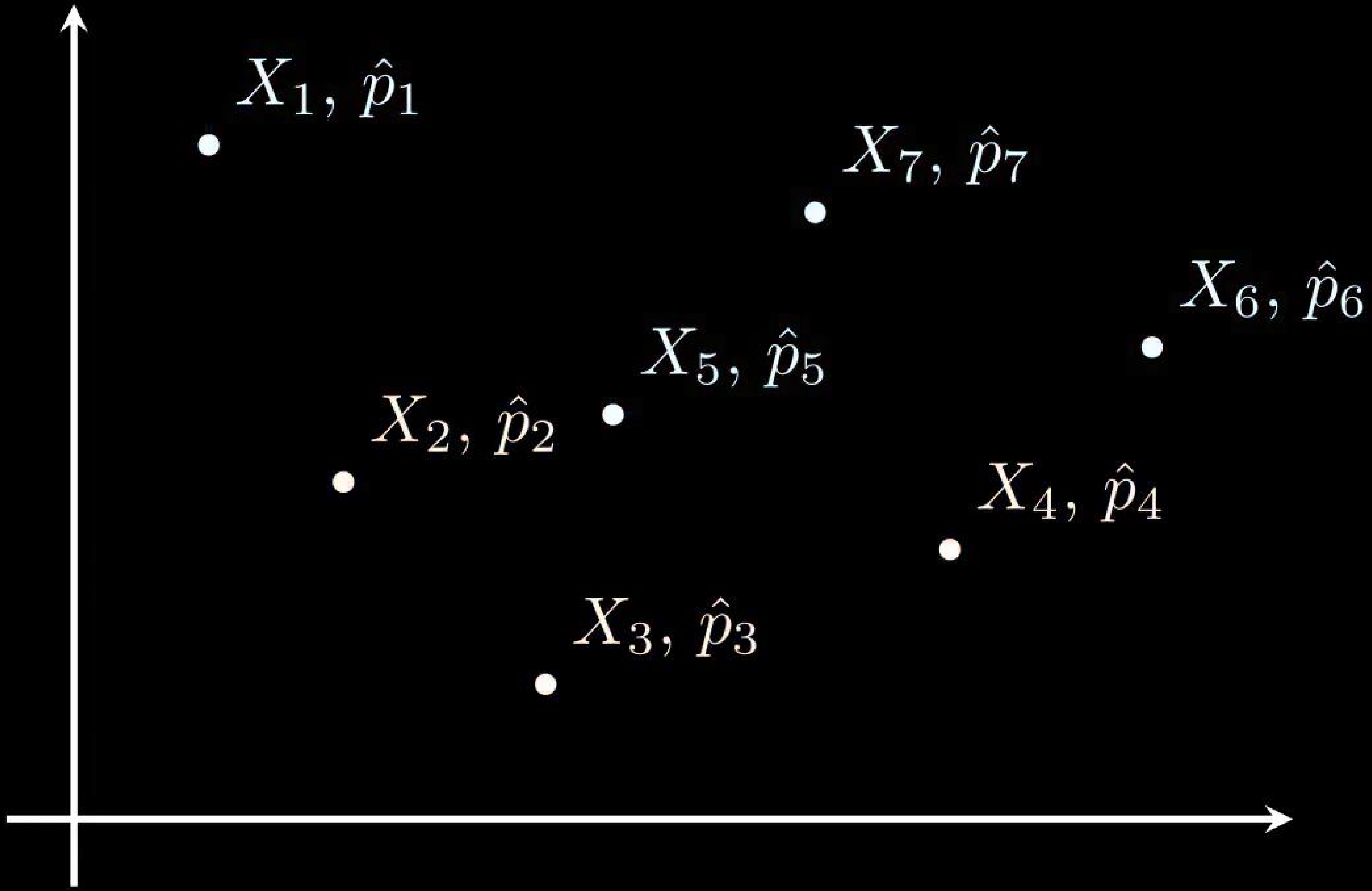


High-level strategy:

1. Calculate *p-values* $\hat{p}_i$ for $H_0(X_i)$;
2. Apply a *multiple testing procedure* with FWER-control at level α to reject $\mathcal{R}_\alpha \subseteq [n]$;
3. Output $\hat{A} := \{x \in \mathbb{R}^d : X_\ell \preccurlyeq x \text{ for some } \ell \in \mathcal{R}_\alpha\}$.

Multiple testing procedure

Key idea: logical relationships of hypotheses $H_0(X_i)$, $i \in [n]$, induce DAG with vertex set $[n]$. We combine the sequential rejection principle (Goeman and Solari, 2010) with careful α-budget allocation to construct a *DAG testing procedure.*



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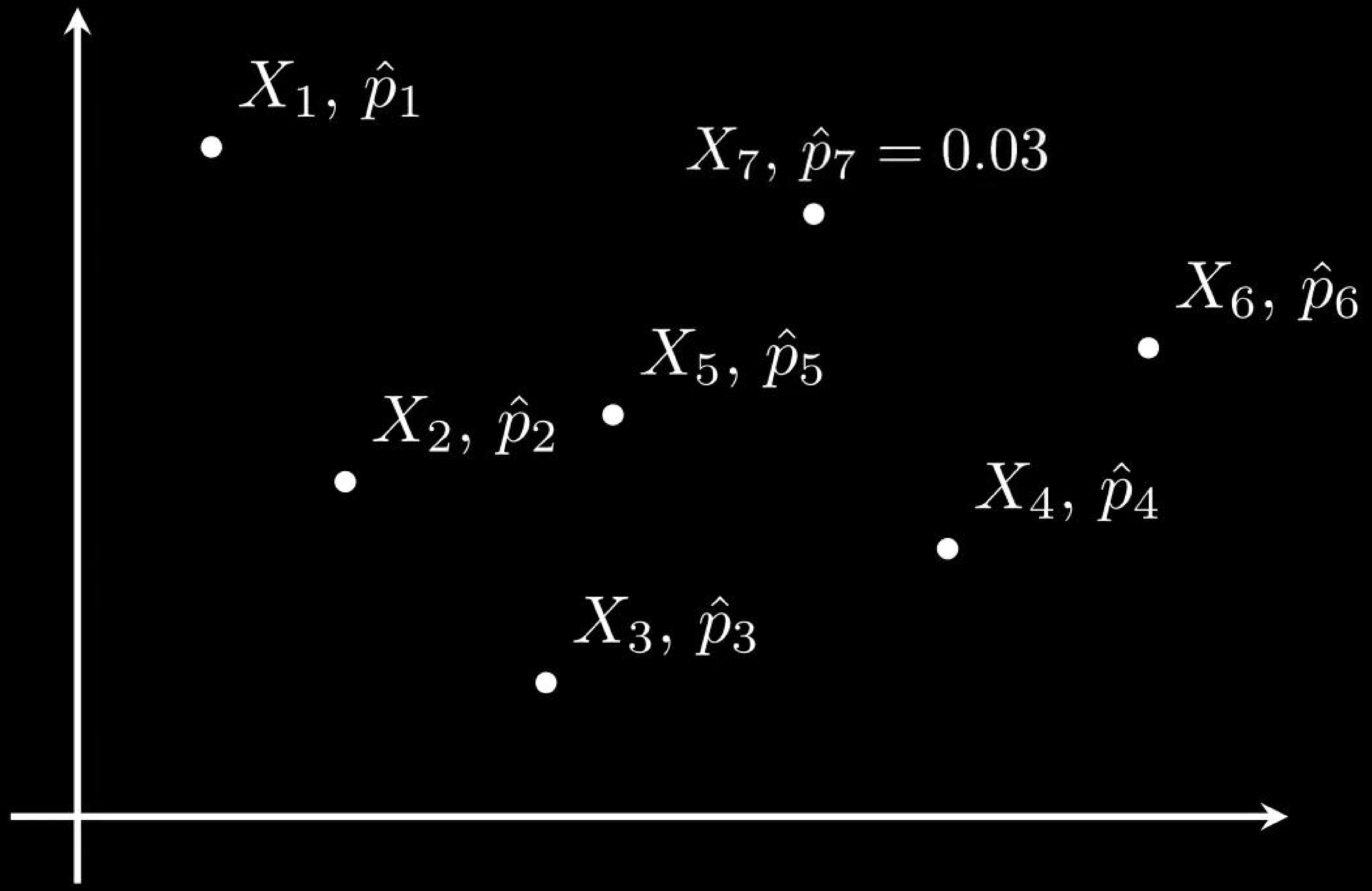

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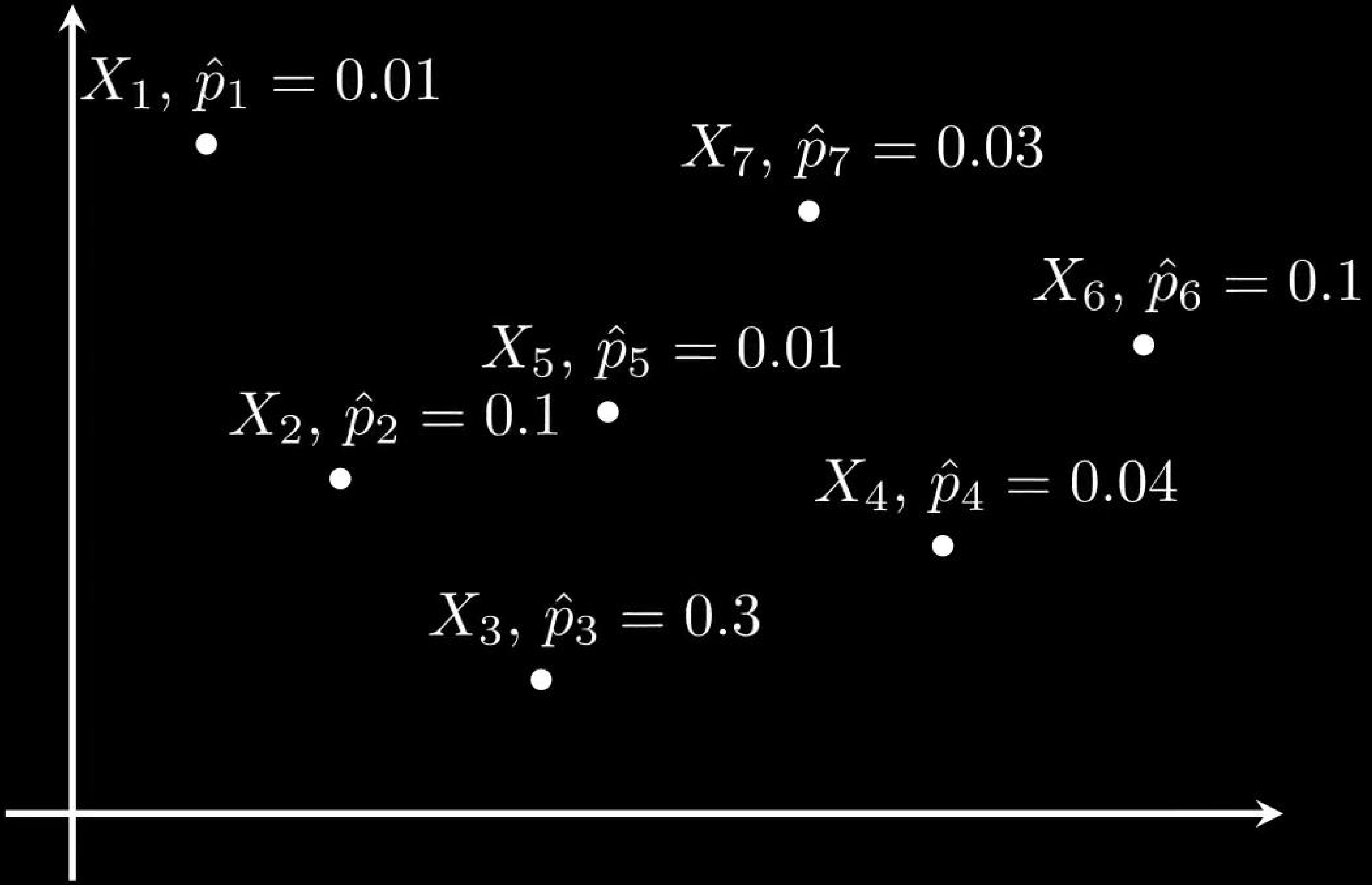

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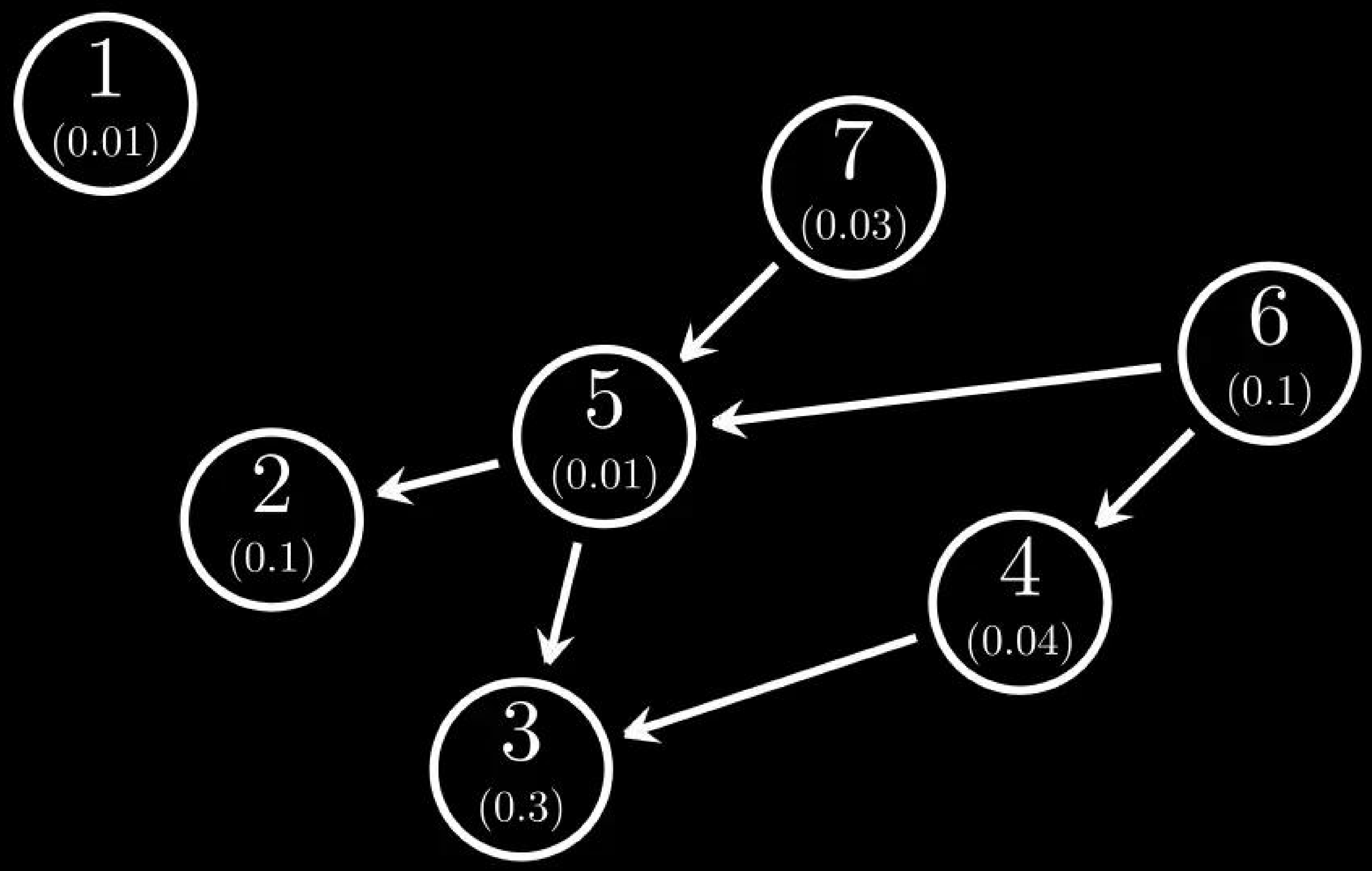

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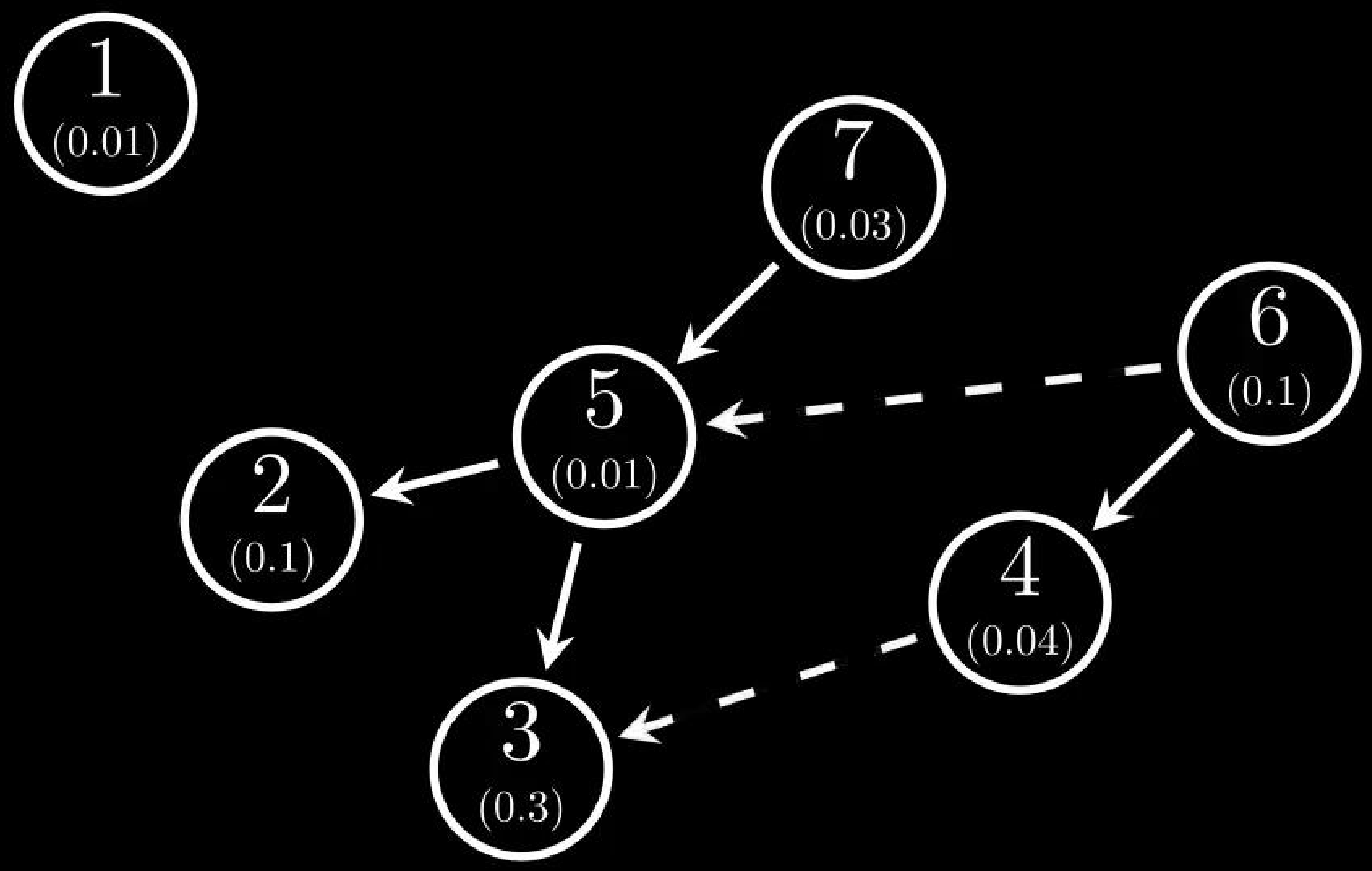

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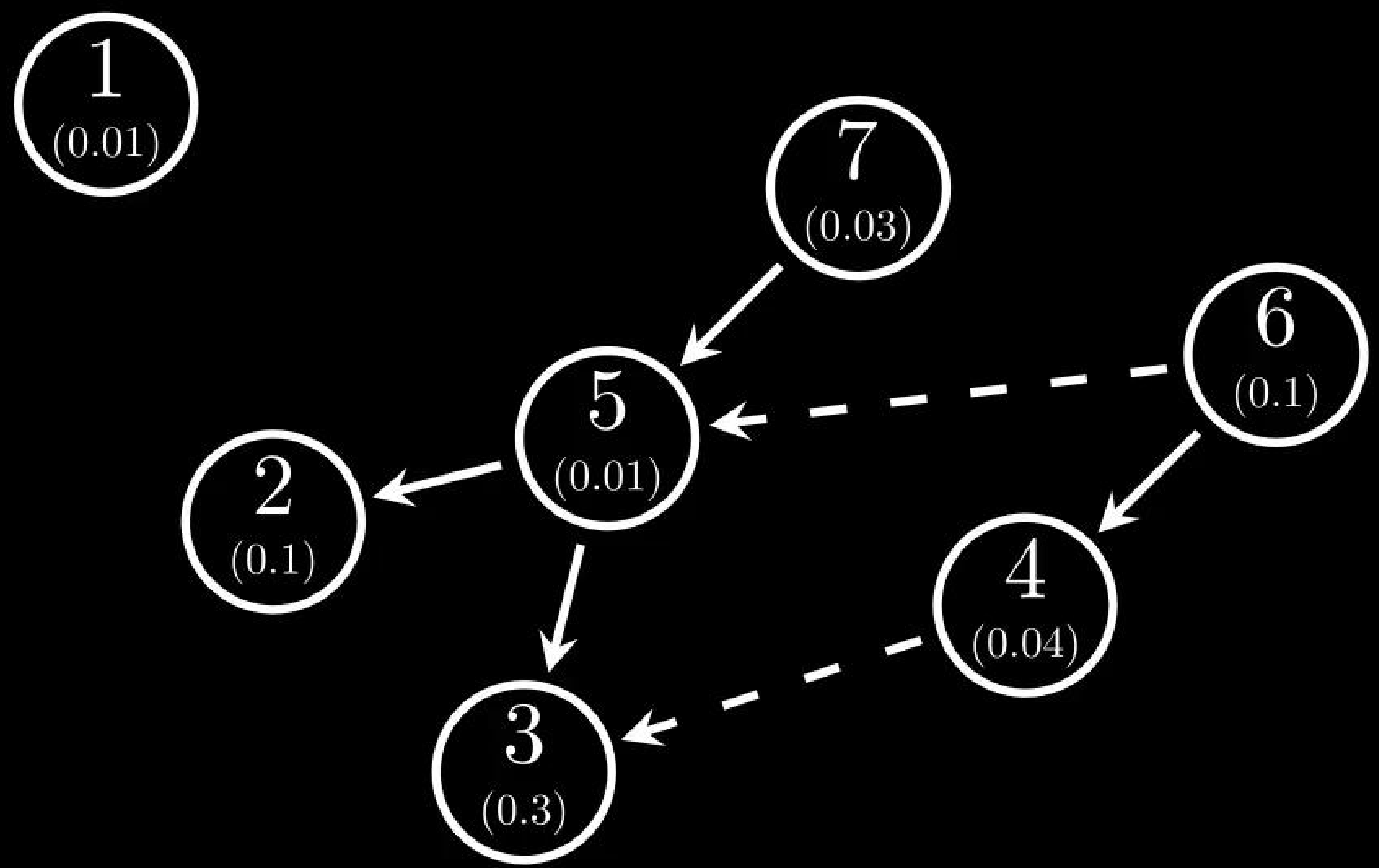

Here: $\alpha = 0.05$.

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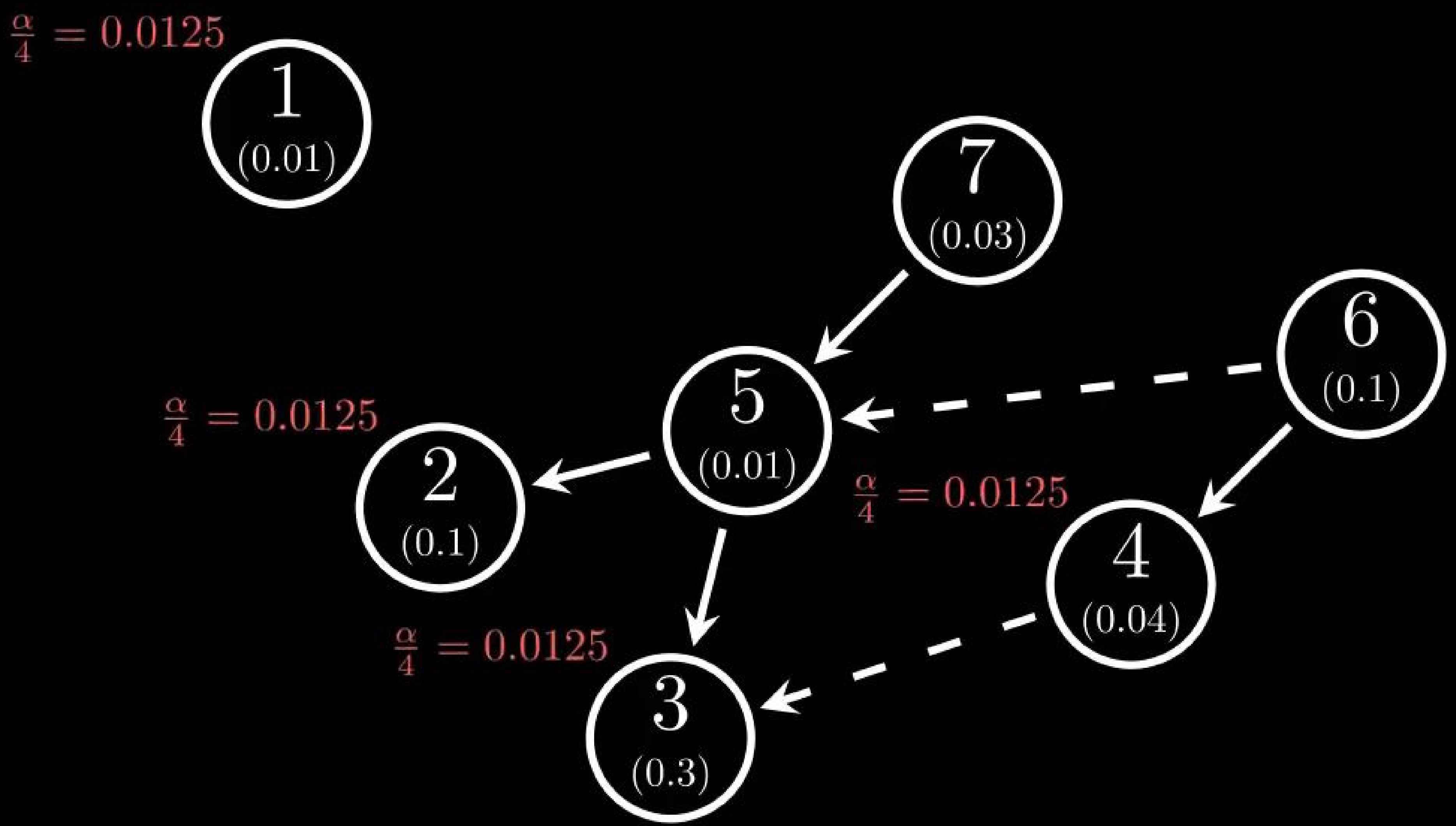

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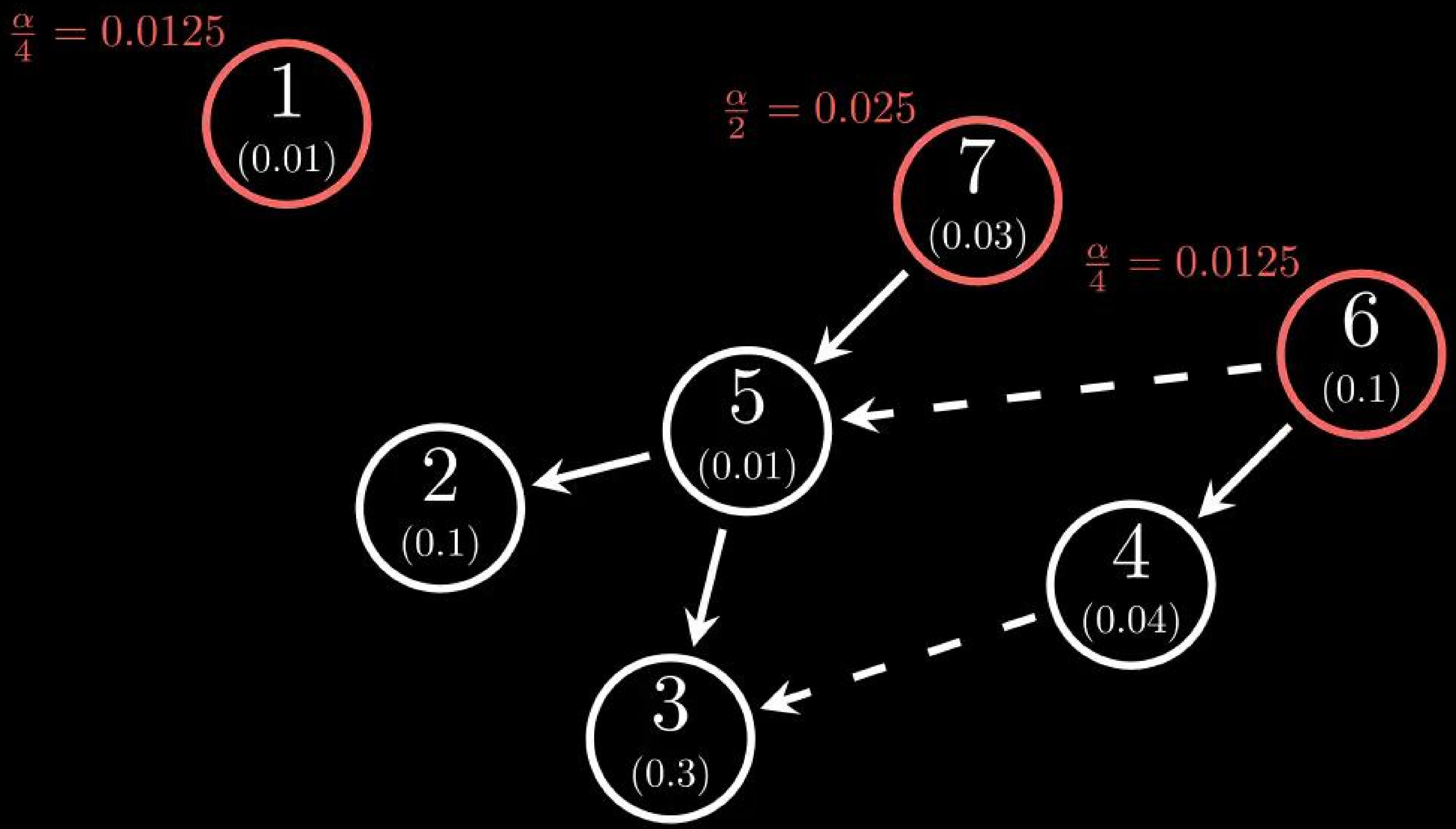

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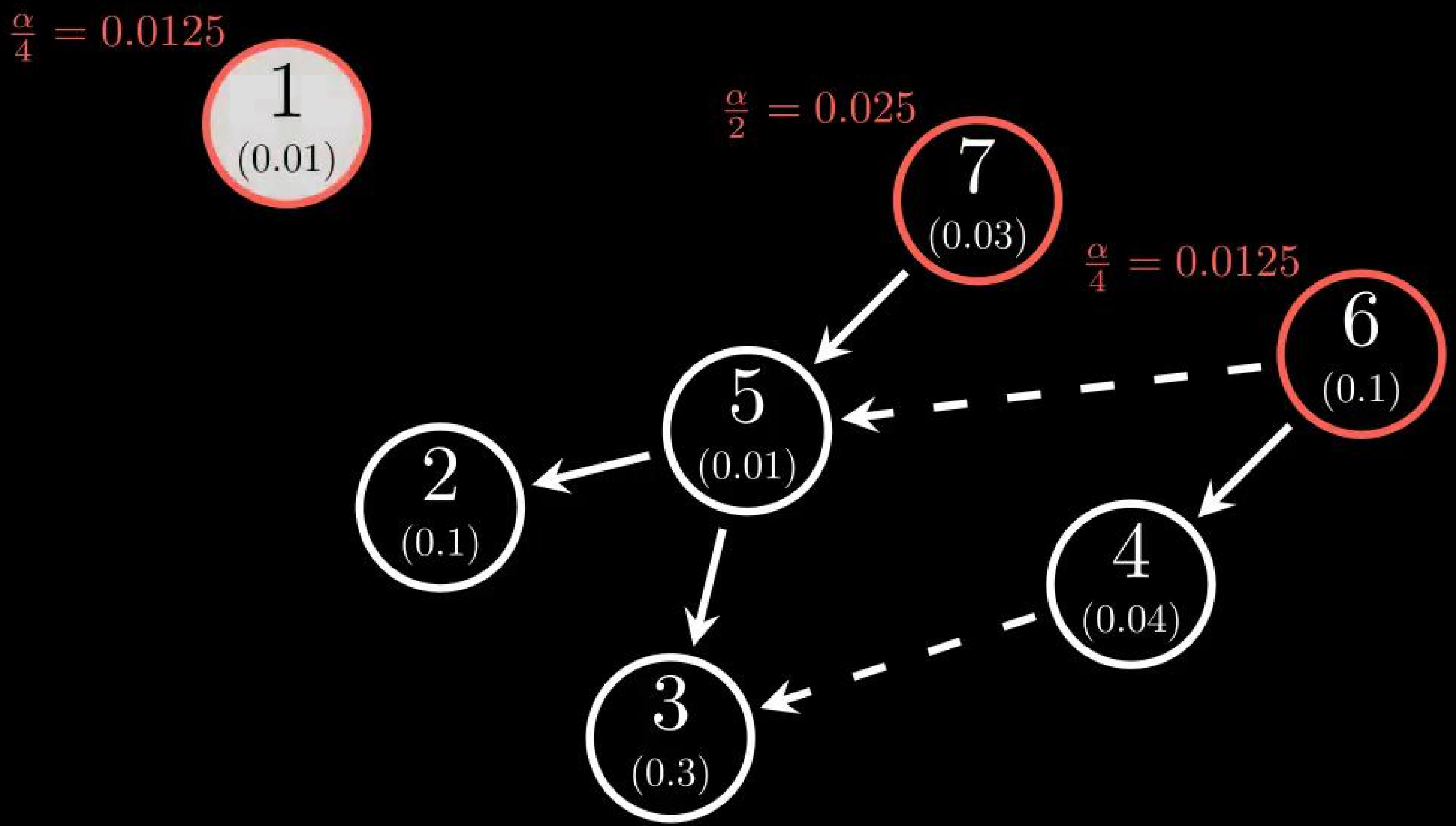

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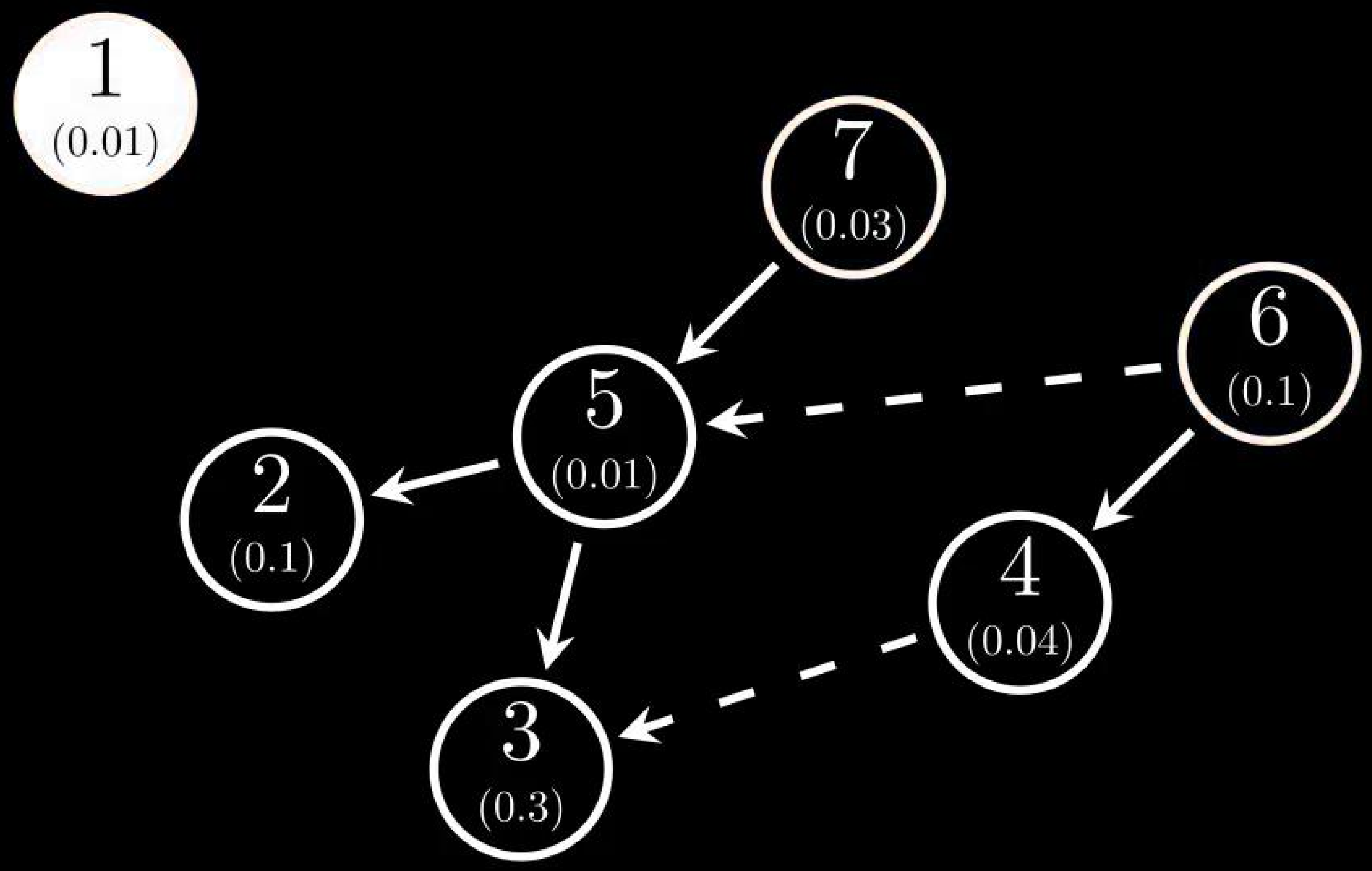

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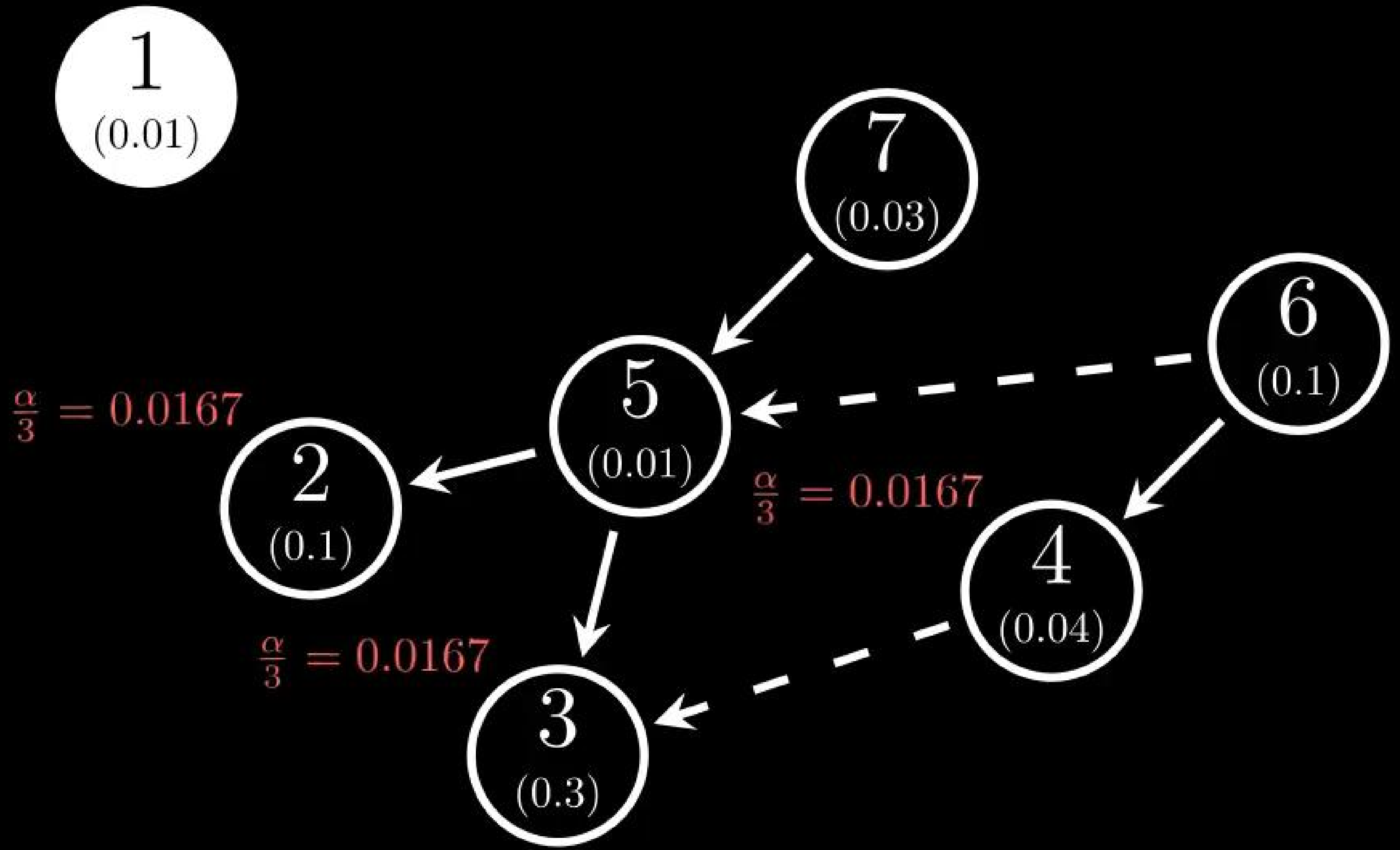

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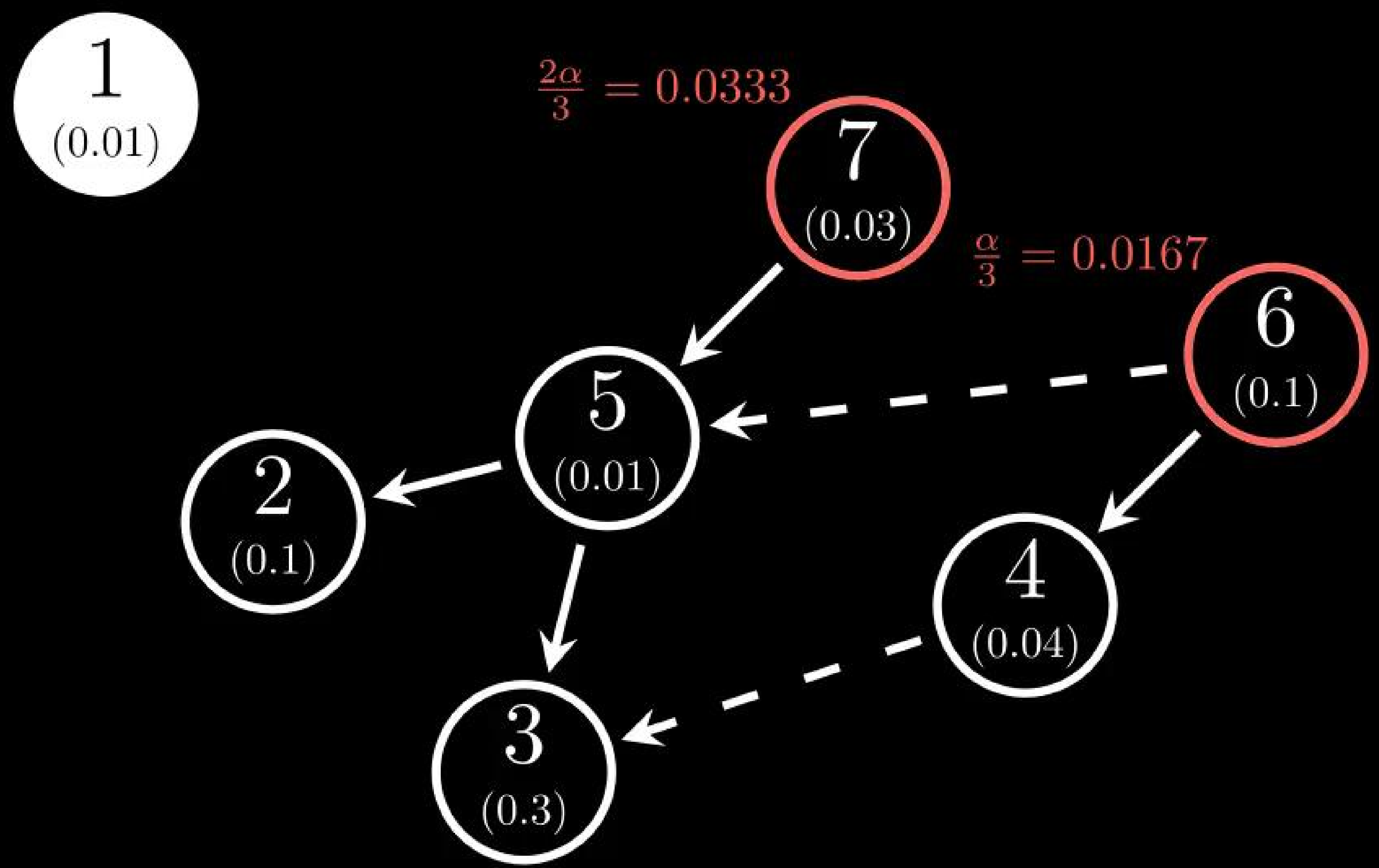

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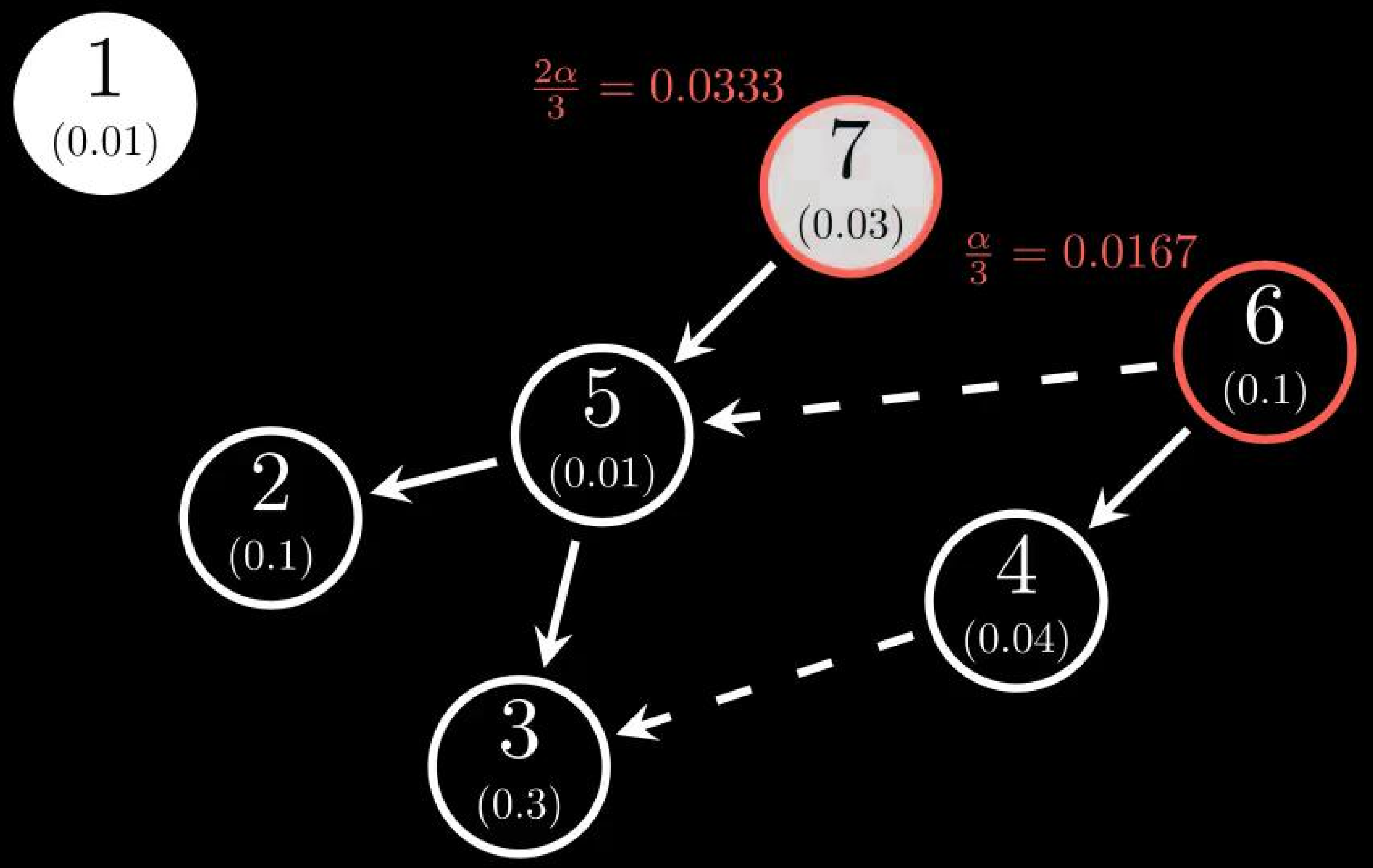

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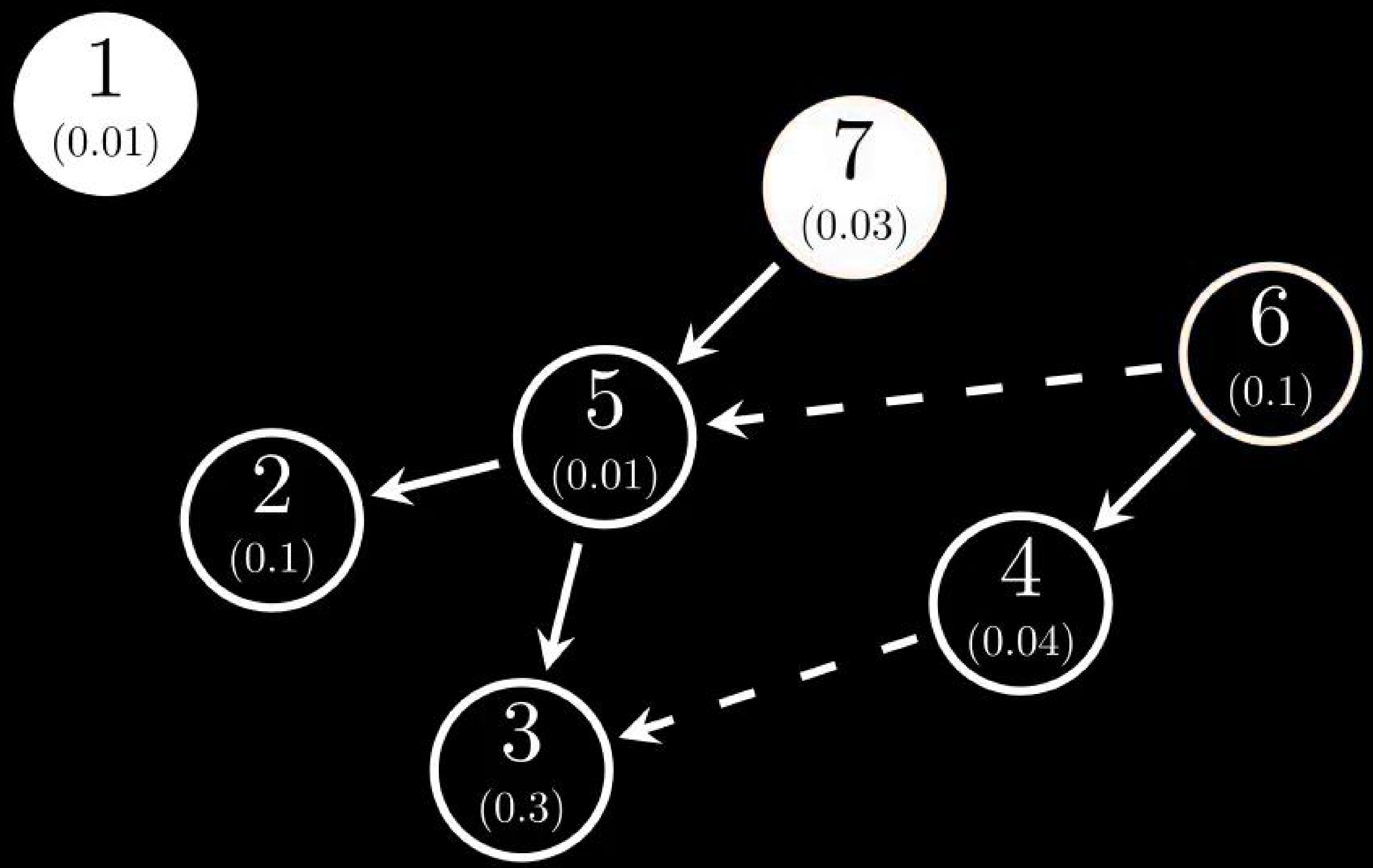

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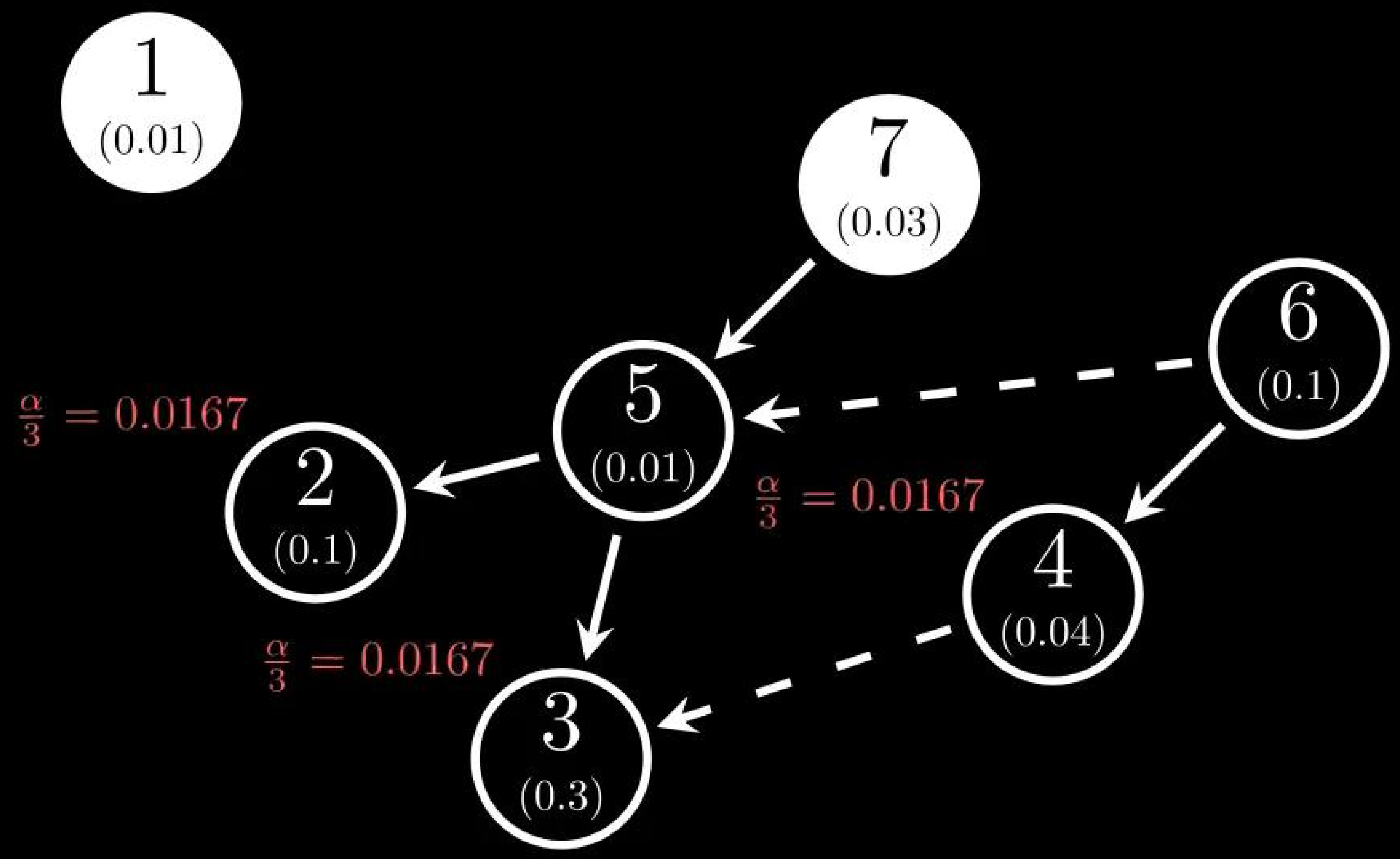

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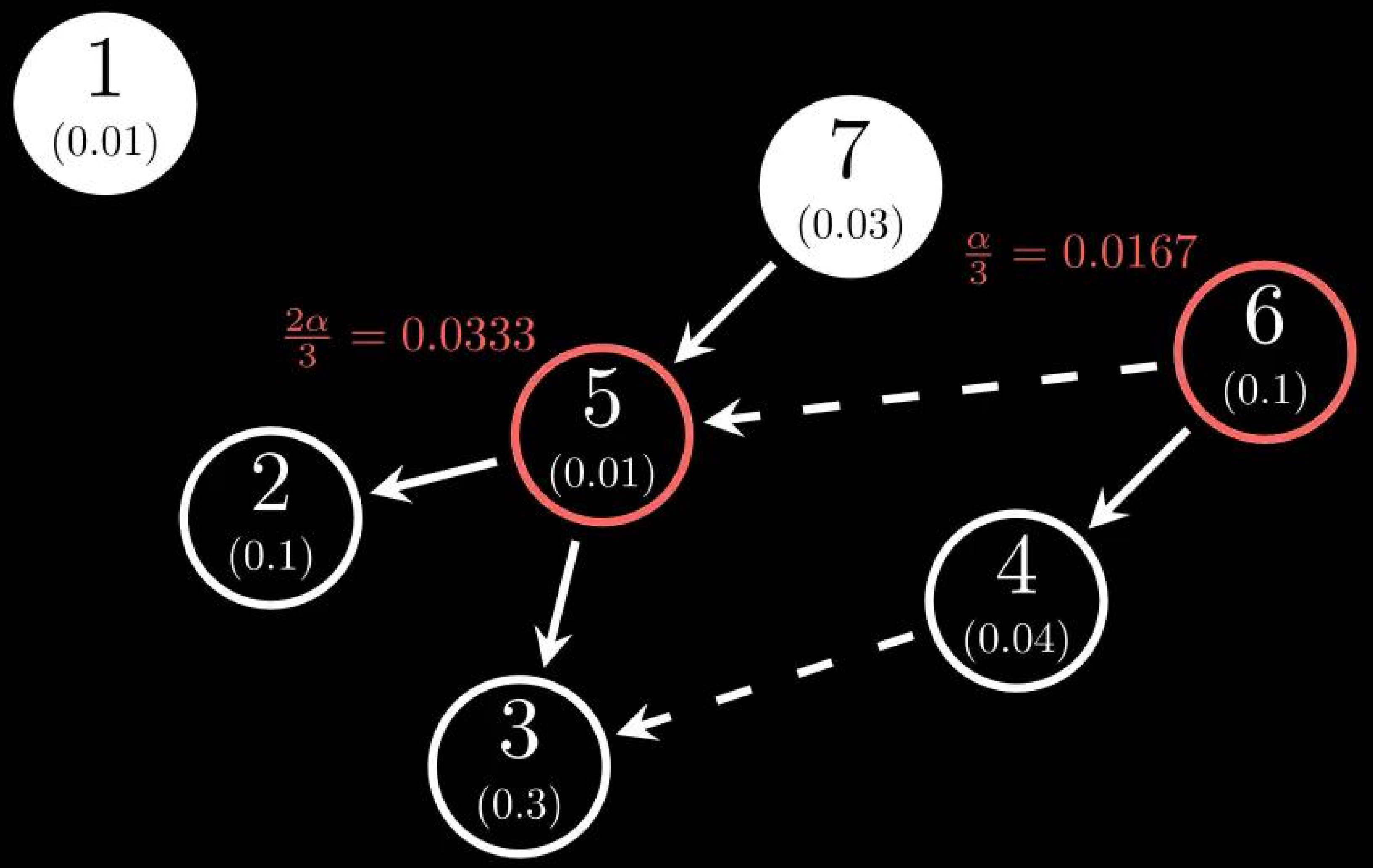

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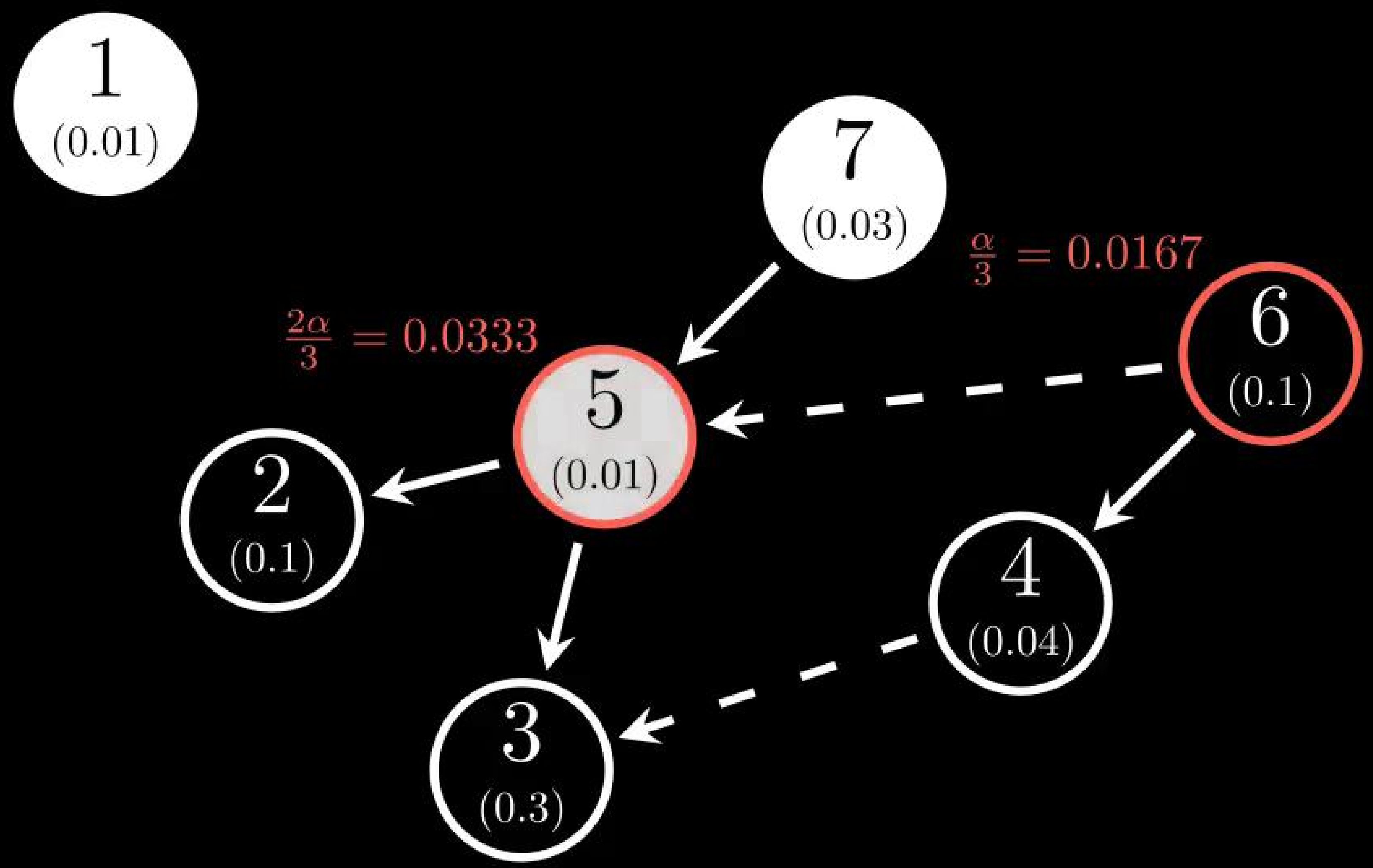

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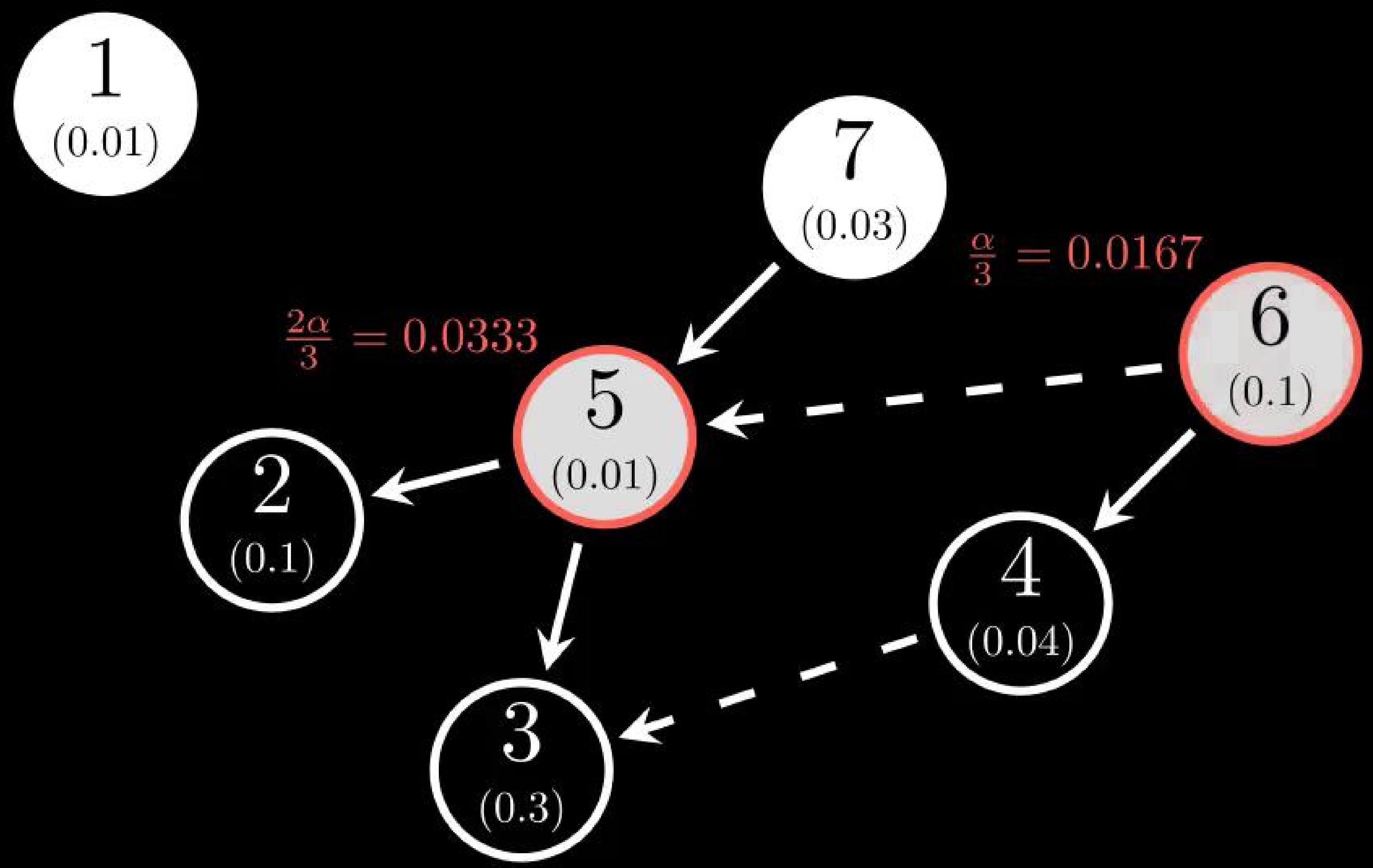

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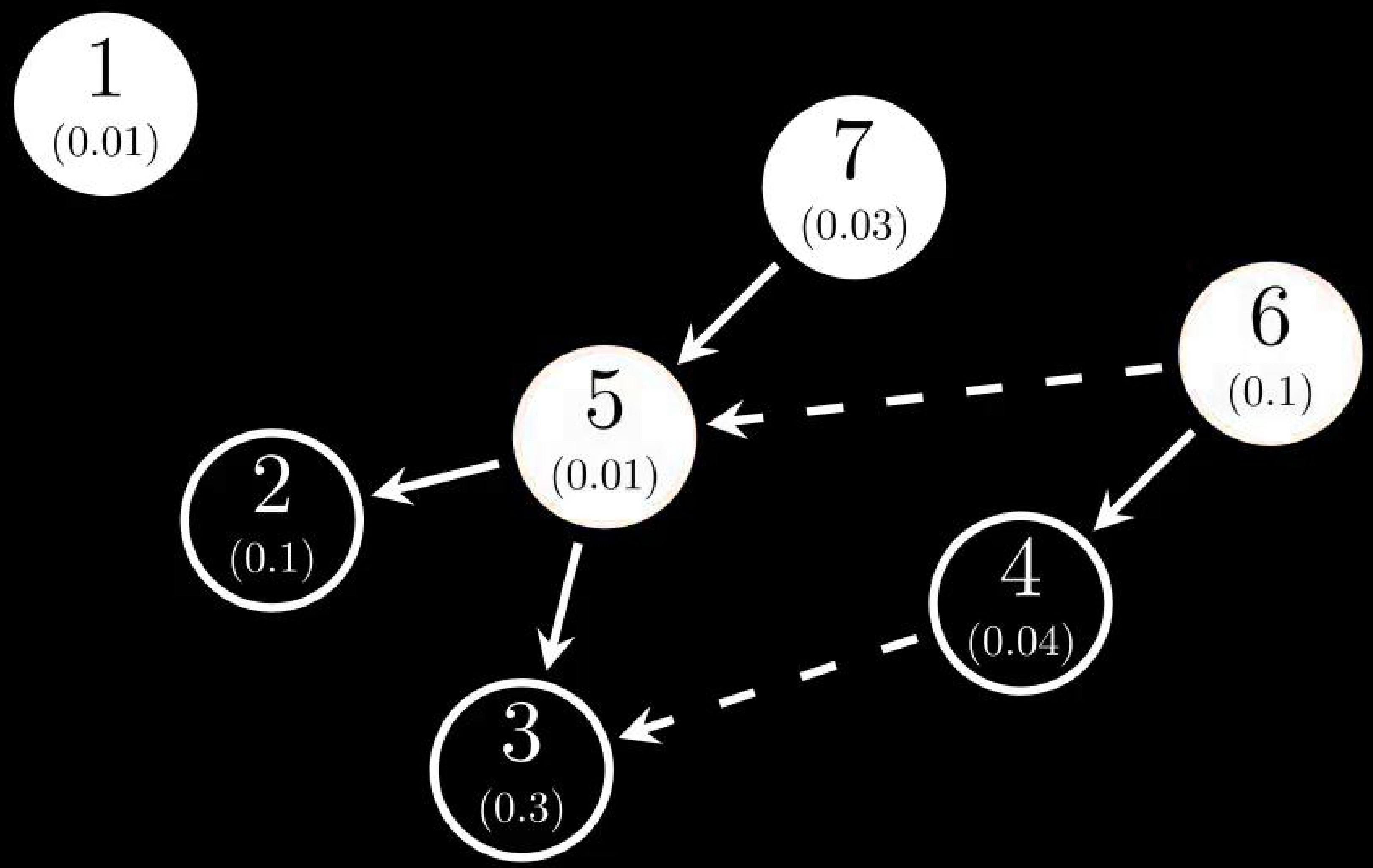

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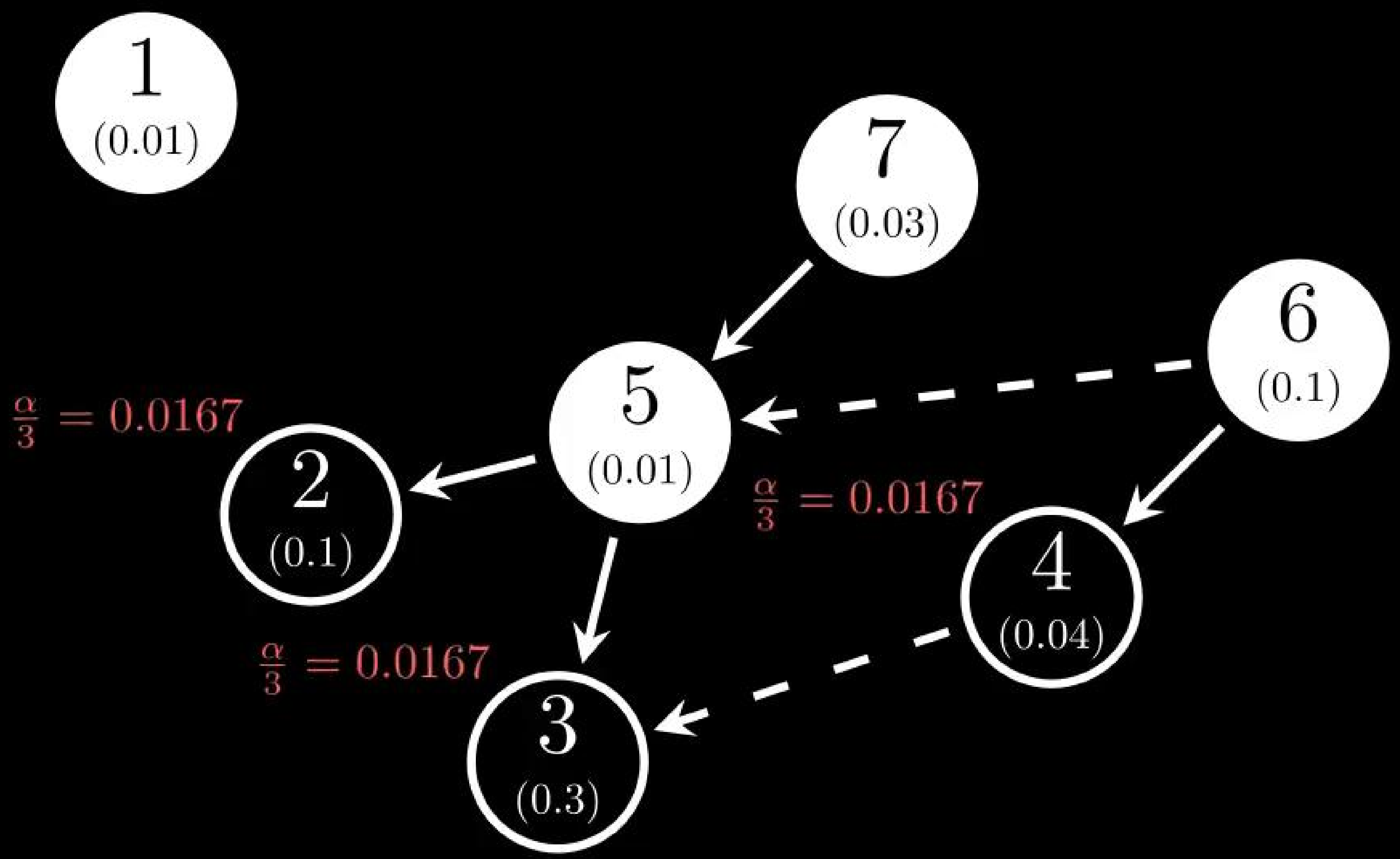

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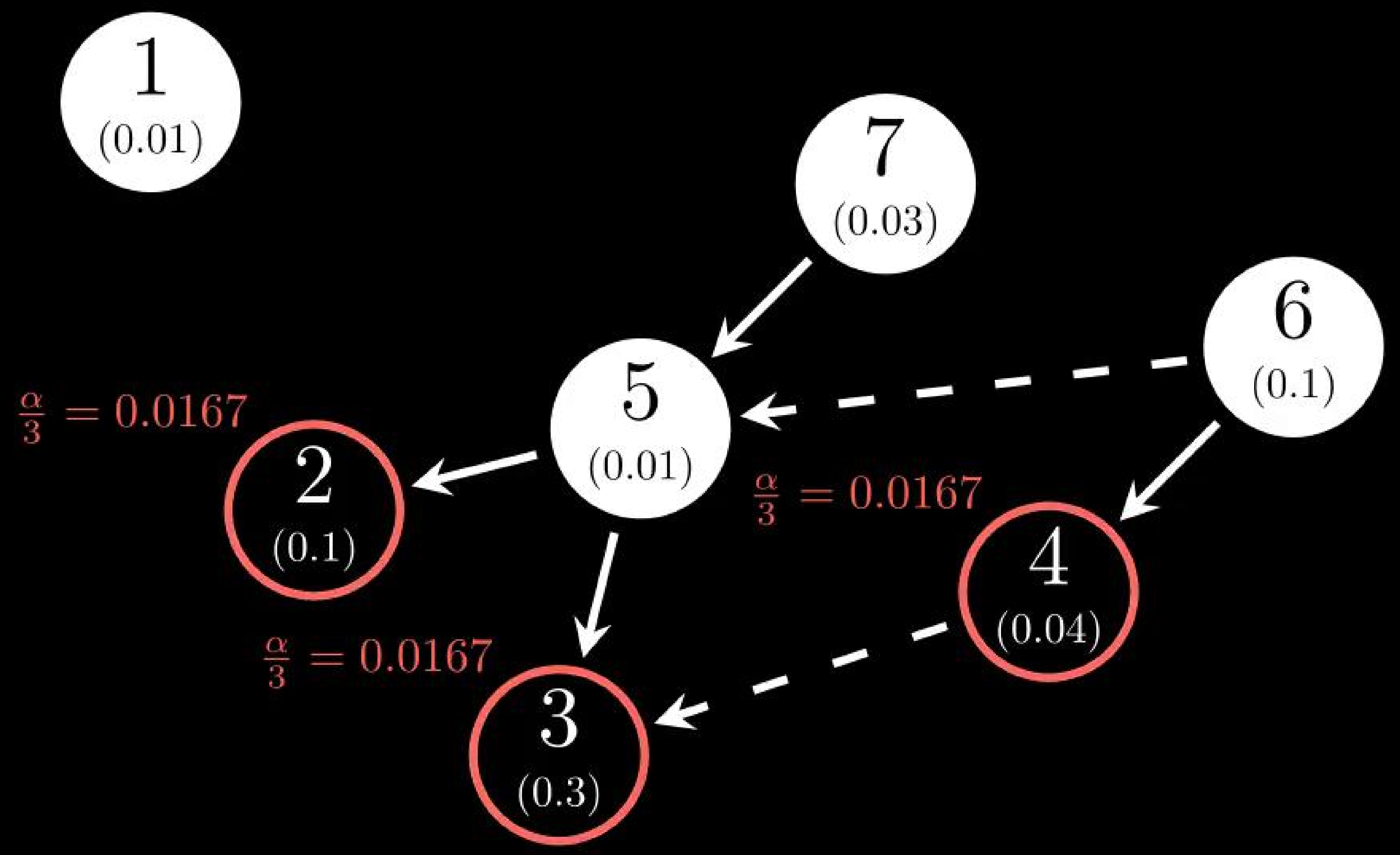

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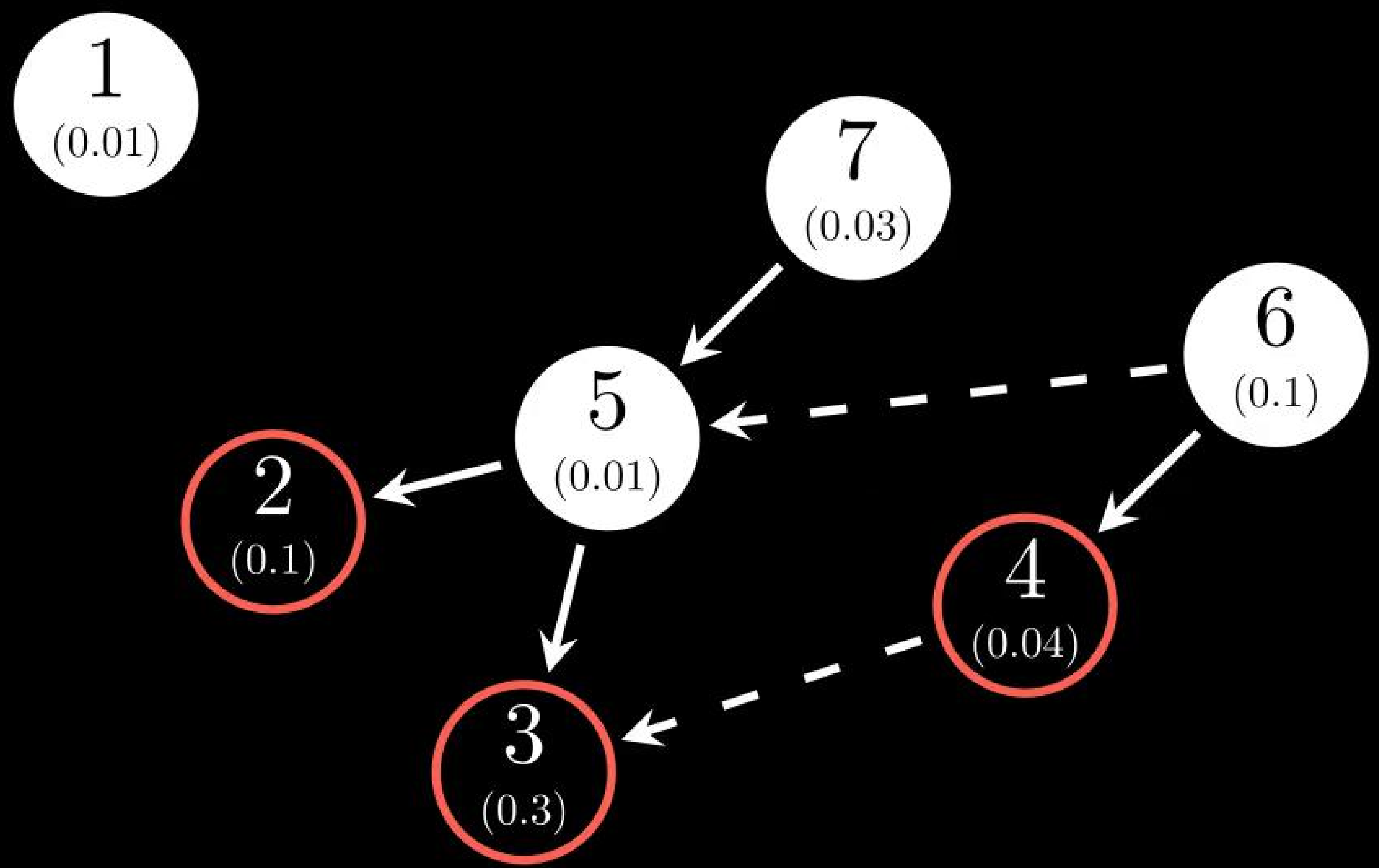
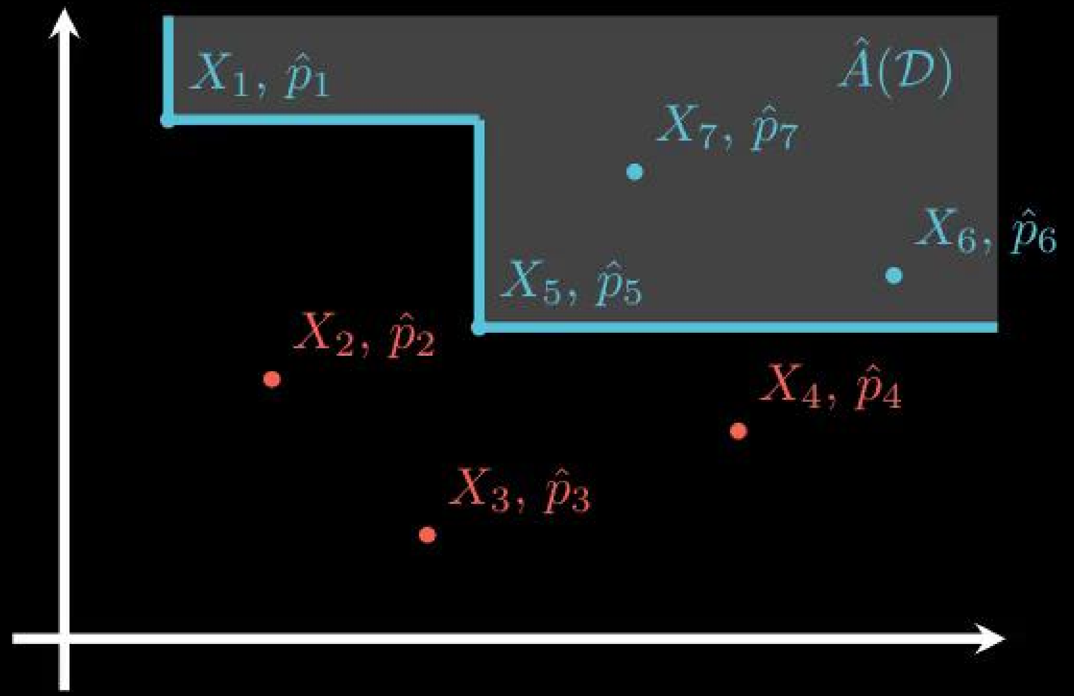


Here: $\alpha = 0.05$. The procedure terminates with $\mathcal{R}_\alpha = \{1, 5, 6, 7\}$.

High-level strategy

For $x_0 \in \mathbb{R}^d$, define null hypothesis $H_0(x_0) := \{P \in \mathcal{P}_{\mathrm{Mon},d}(\sigma) : \eta(x_0) < \tau\}$.



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1. Calculate *p-values* $\hat{p}_i$ for $H_0(X_i)$;
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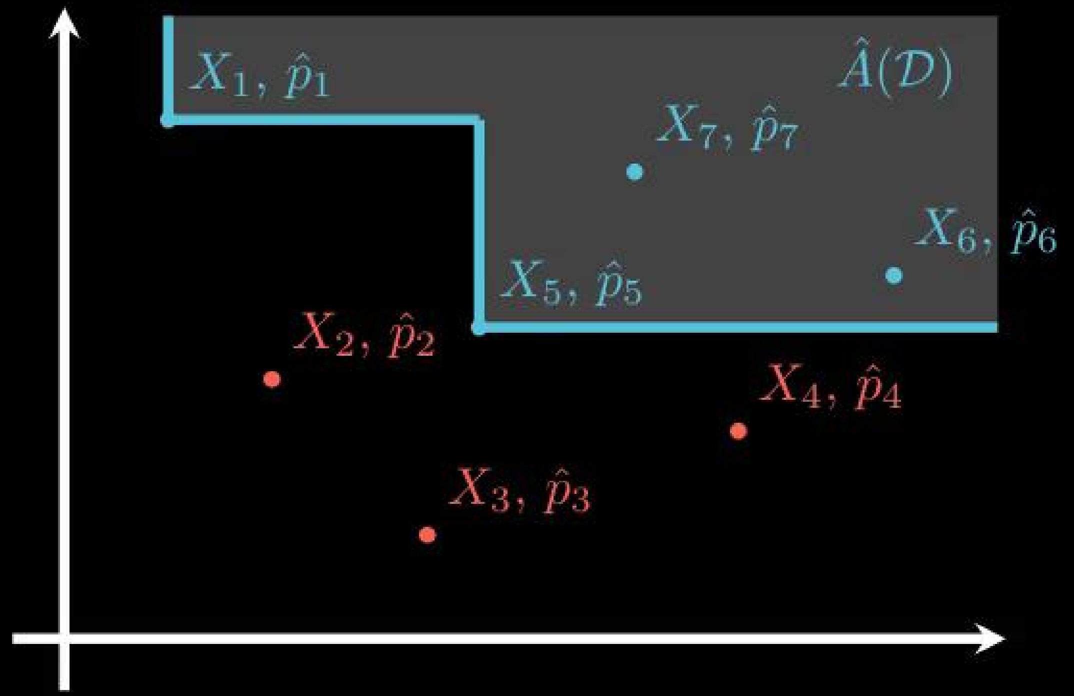

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Type I error control

Combining the presented p-value construction with the just illustrated multiple testing procedure defines the proposed procedure $\hat{A}^{\mathrm{ISS}} \equiv \hat{A}^{\mathrm{ISS}}_{\sigma,\tau,\alpha}$. Recall that we write $\mathcal{D} = \big((X_1, Y_1), \ldots, (X_n, Y_n)\big) \sim P^n$.

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Theorem. For any $n \geq 1$, $\alpha \in (0,1)$, $\sigma > 0$, we have

$$\inf_{P \in \mathcal{P}_{\mathrm{Mon},d}(\sigma)} \mathbb{P}\big(\hat{A}^{\mathrm{ISS}}_{\sigma,\tau,\alpha}(\mathcal{D}) \subseteq \mathcal{X}_\tau(\eta) \bigm| \mathcal{D}_X\big) \geq 1 - \alpha.$$

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 $R_\tau(\hat{A}) := \mathbb{E}\{\mu(\mathcal{X}_\tau(\eta) \setminus \hat{A})\}$.

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

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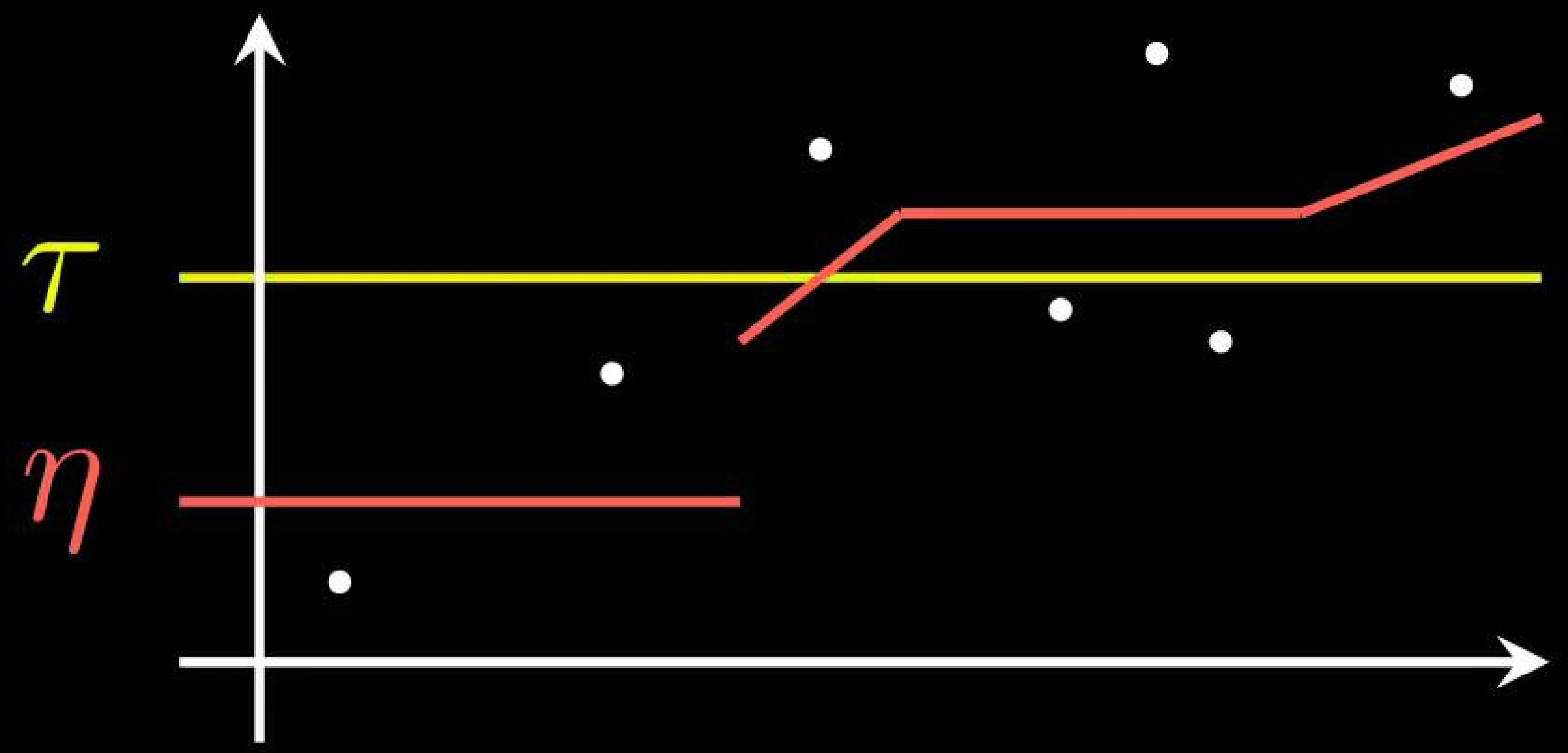

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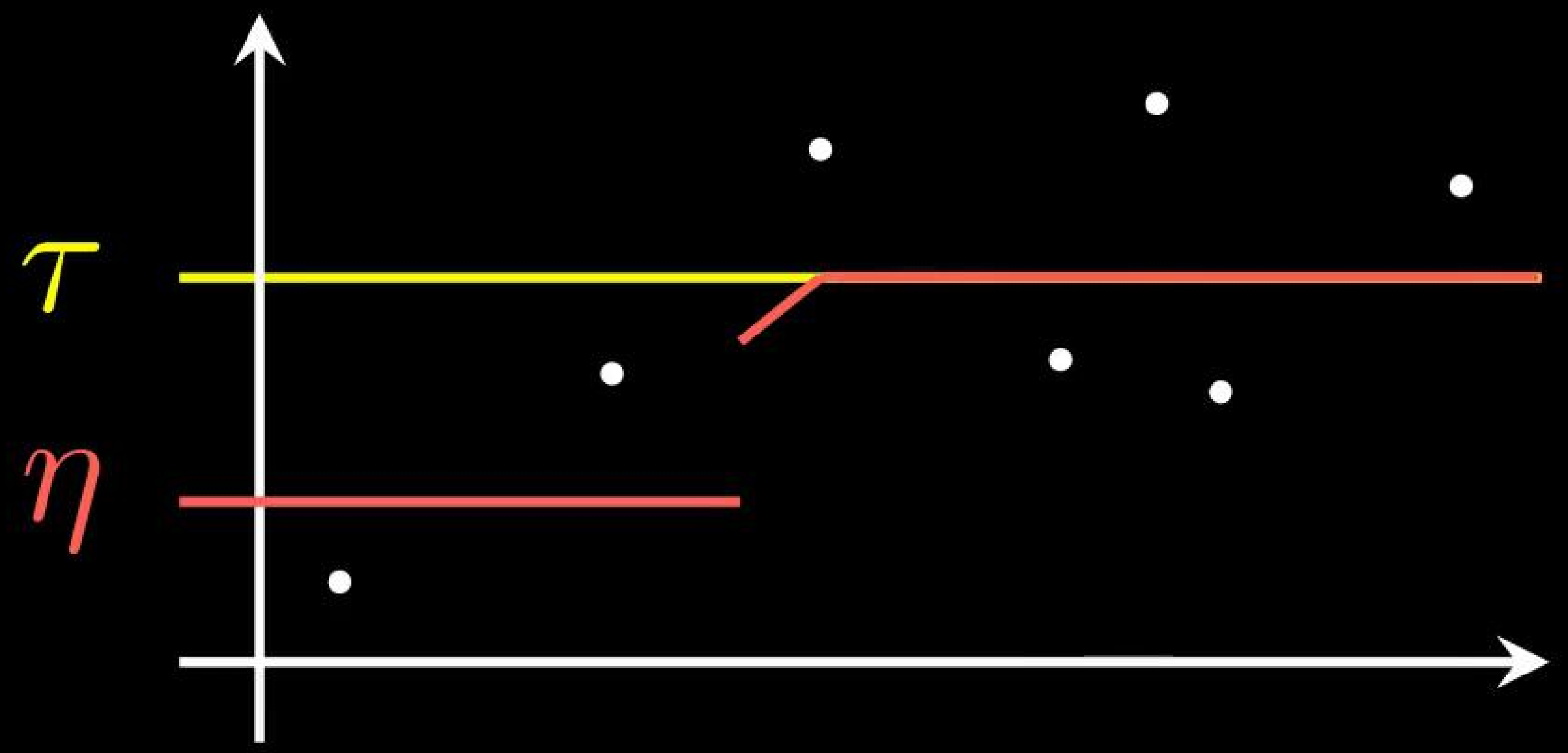

Power

Definition. For $\sigma, \gamma, \lambda > 0$ and $\theta > 1$, let $\mathcal{P}_{\mathrm{MonReg},d}(\sigma, \tau, \gamma, \lambda, \theta) \subseteq \mathcal{P}_{\mathrm{Mon},d}(\sigma)$ denote the class 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. Let $\sigma, \gamma, \lambda > 0$ and $\theta > 1$. There exists $C \geq 1$, depending only on (d, θ), such that for any $n \geq 1$ and $\alpha \in (0, 1)$,

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where $\log_+ x := \log(x \vee e)$ for $x \in \mathbb{R}$.

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$$\inf_{\hat{A} \in \hat{\mathcal{A}}_n(\tau,\alpha,\mathcal{P}_{\mathrm{MonReg}})} \sup_{P \in \mathcal{P}_{\mathrm{MonReg}}} R_\tau(\hat{A}) \geq c\left[1 \wedge \left\{\left(\frac{\sigma^2}{n\lambda^2}\log_+\left(\frac{1}{5\alpha}\right)\right)^{1/(2\gamma+d)} + \frac{1}{n^{1/d}}\right\}\right],$$

where for brevity $\mathcal{P}_{\mathrm{MonReg}} \equiv \mathcal{P}_{\mathrm{MonReg},d}(\sigma,\tau,\gamma,\lambda,\theta)$.

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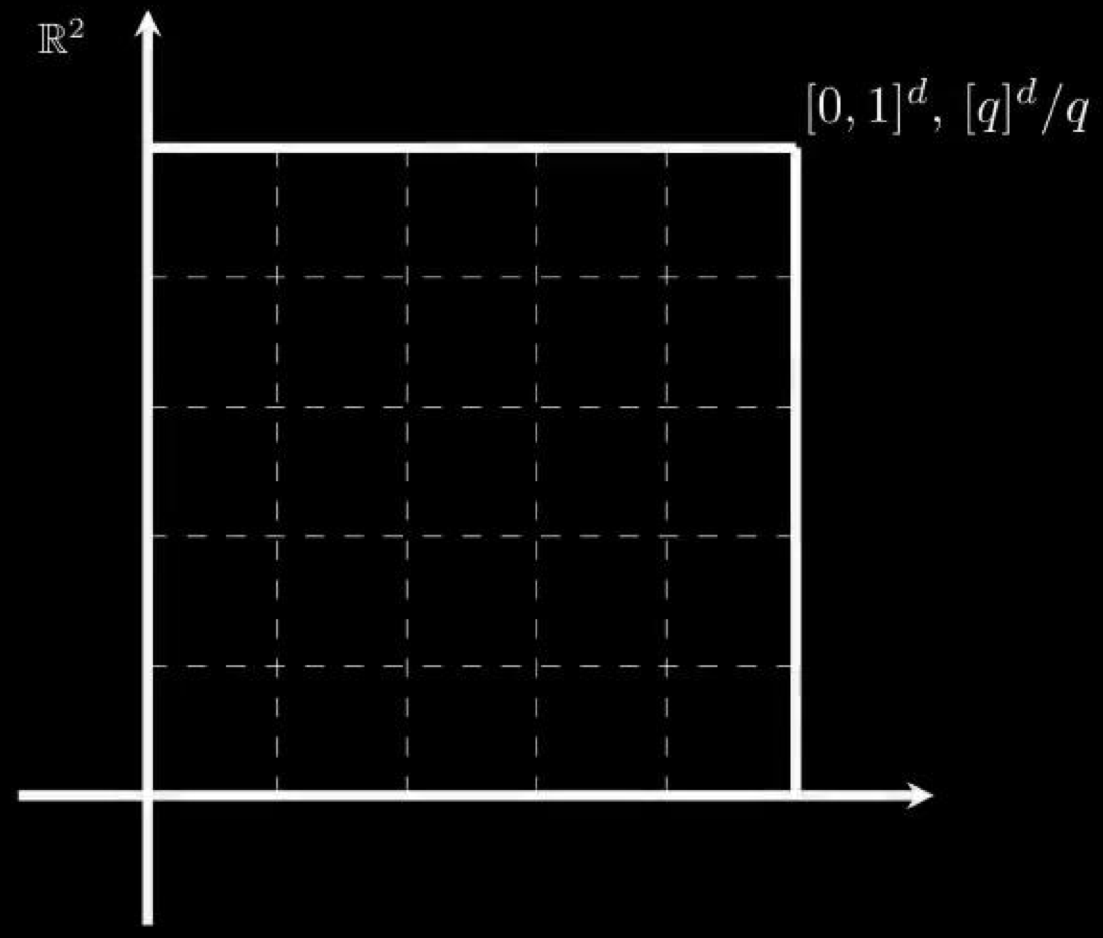

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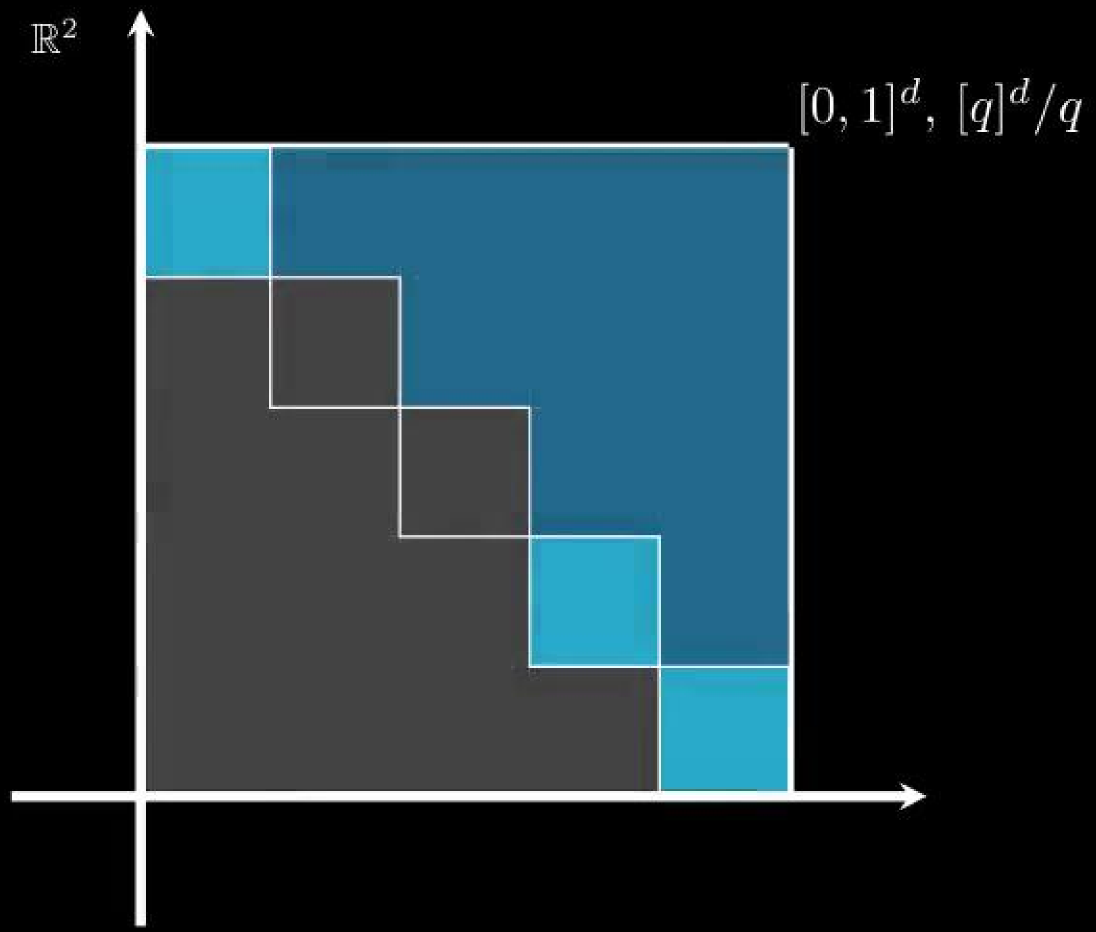

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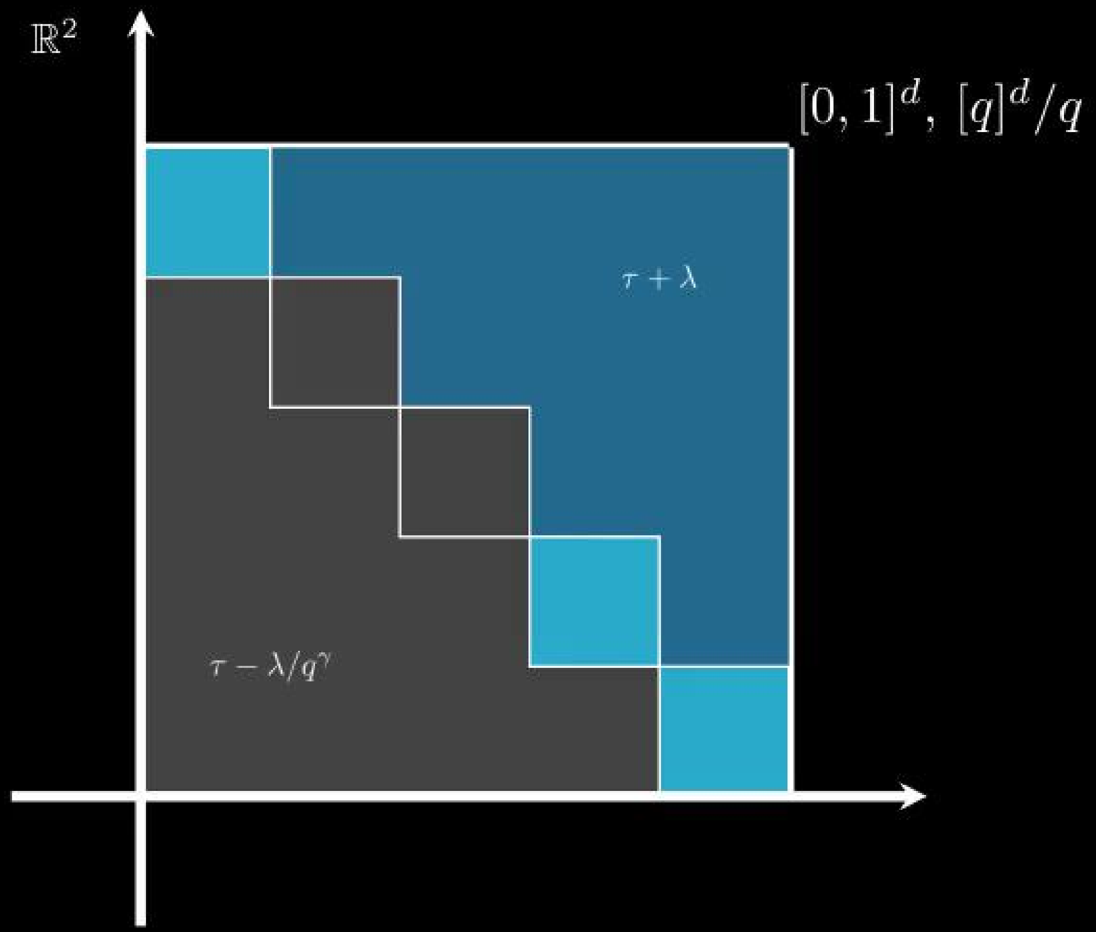

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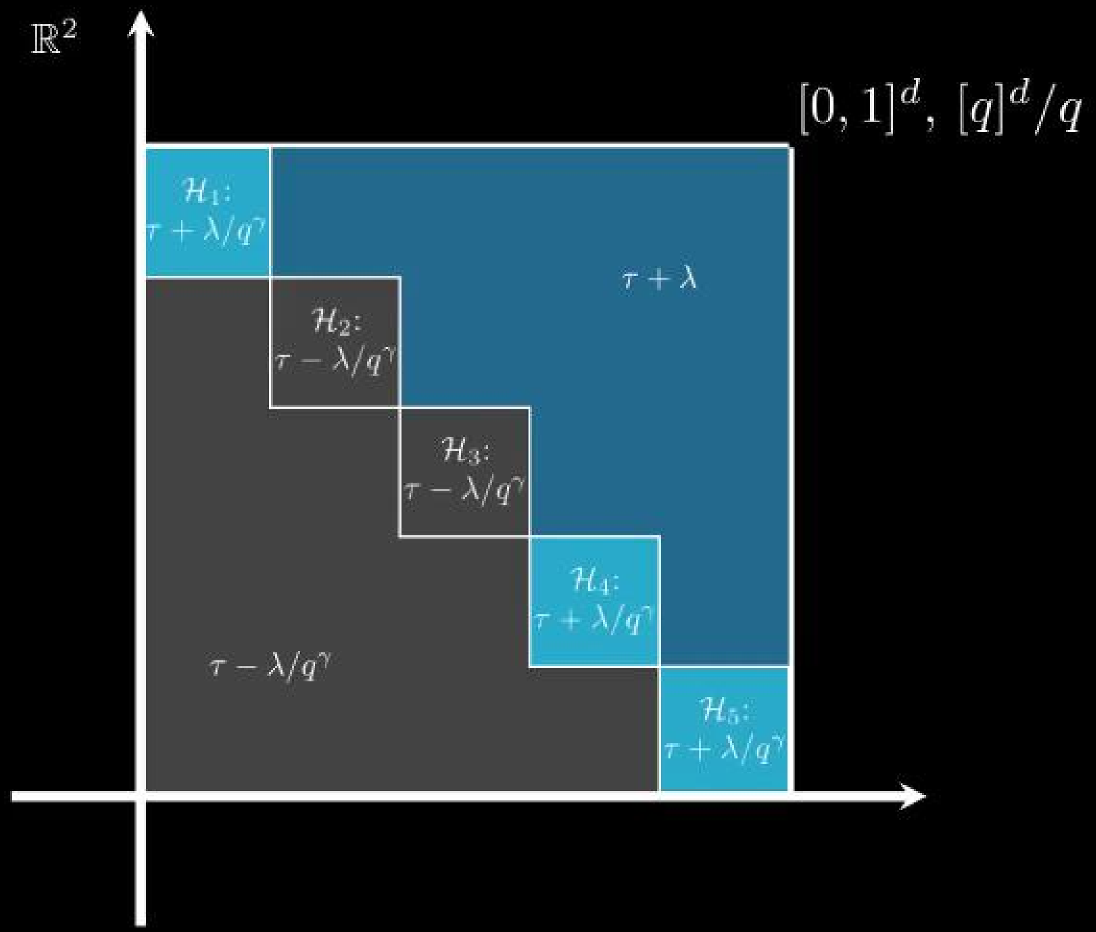

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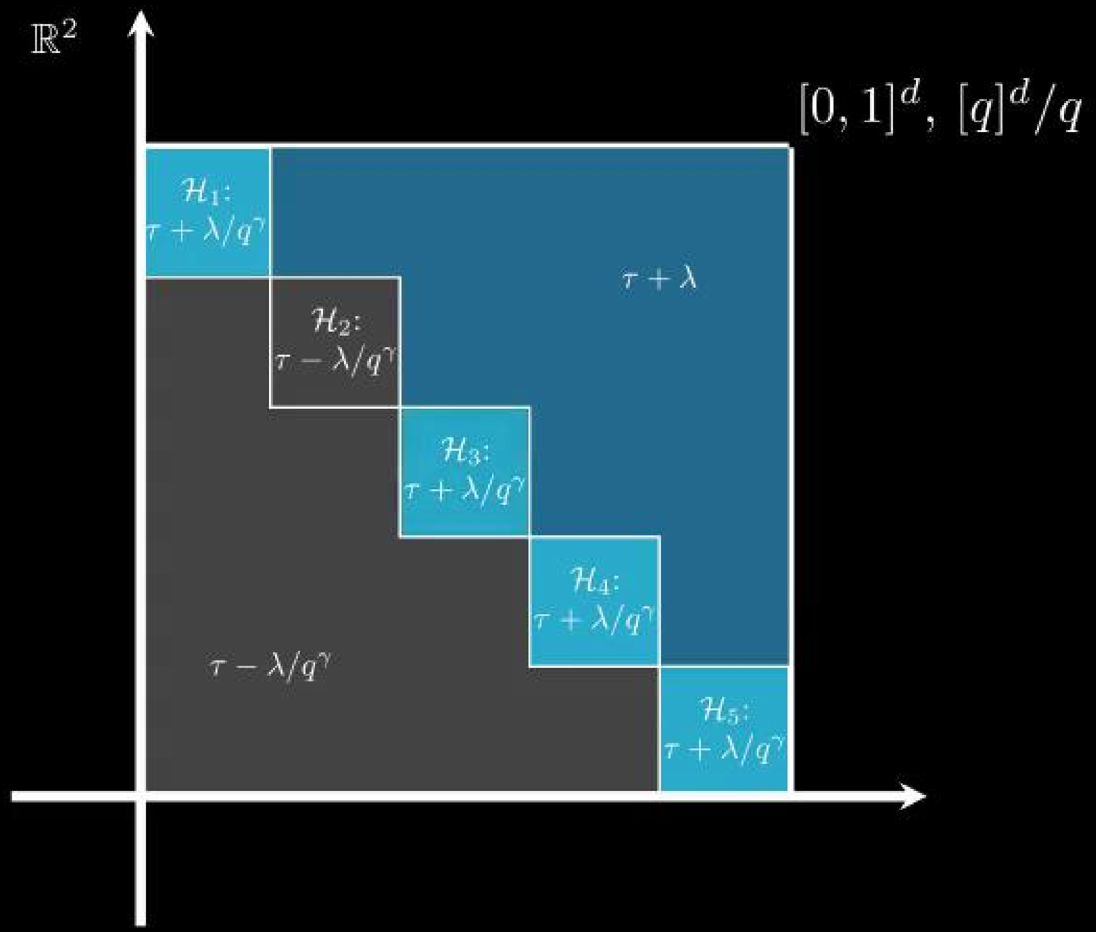

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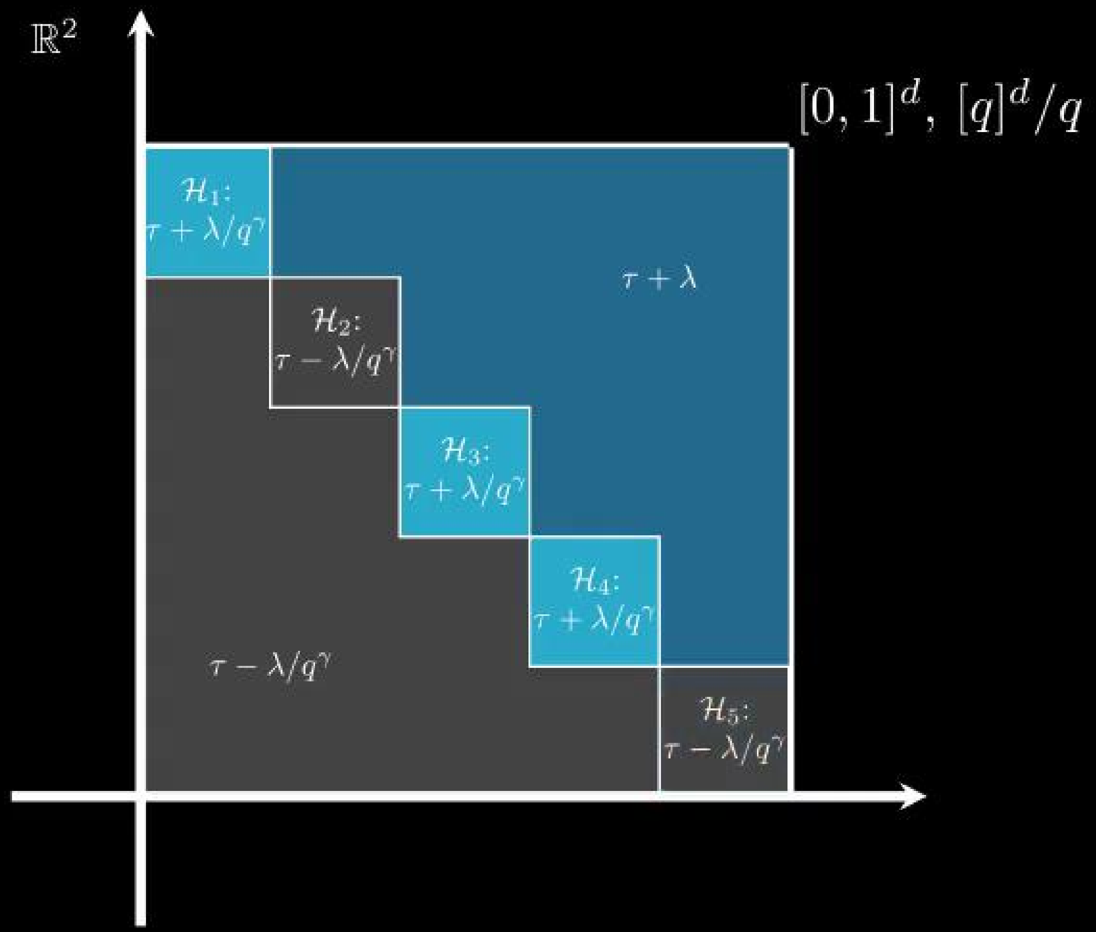

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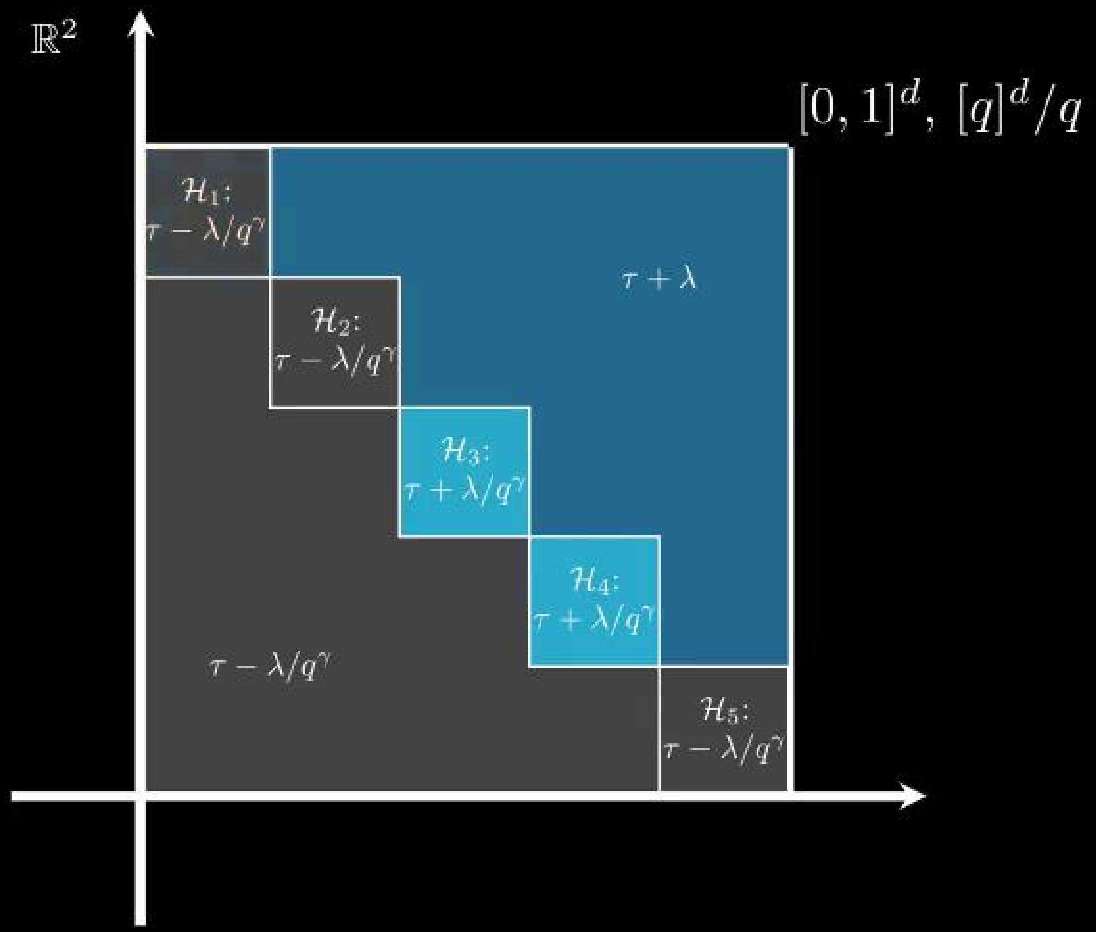

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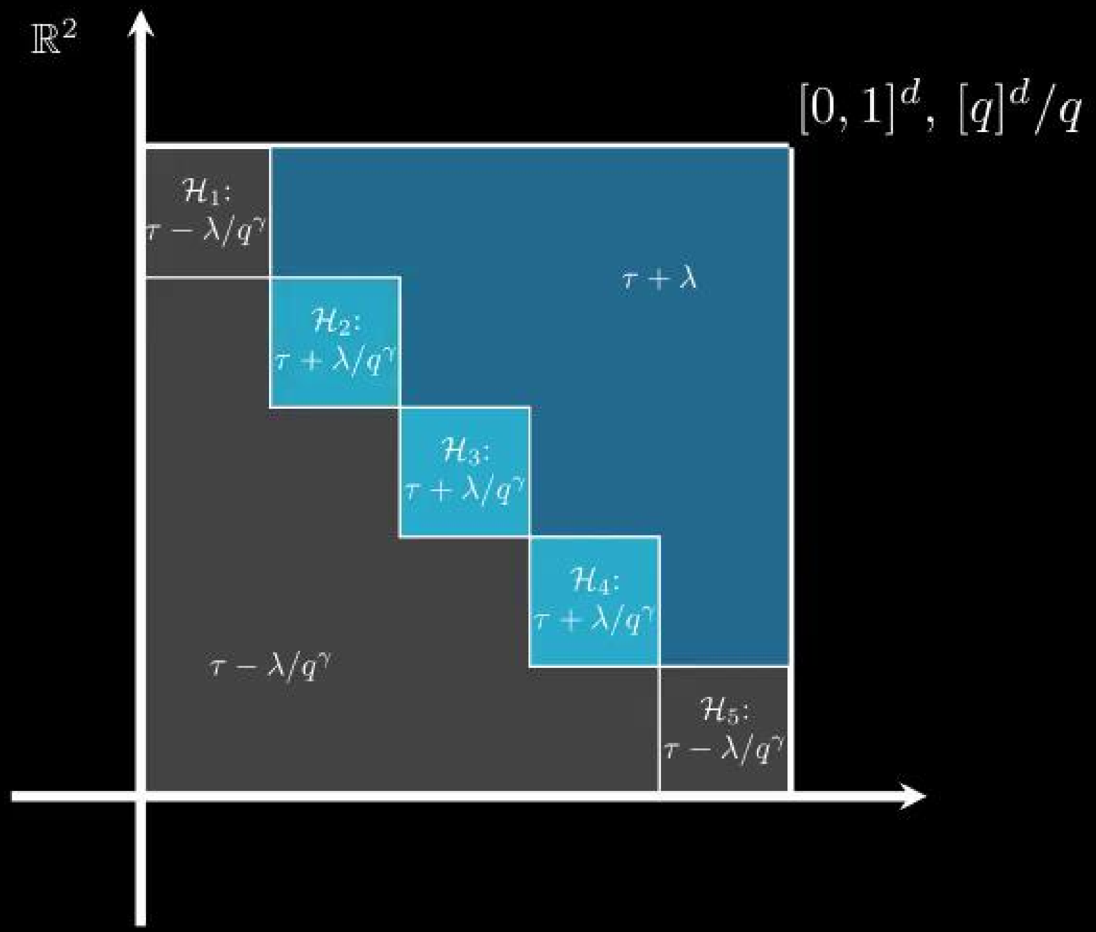

Heterogeneous treatment effects

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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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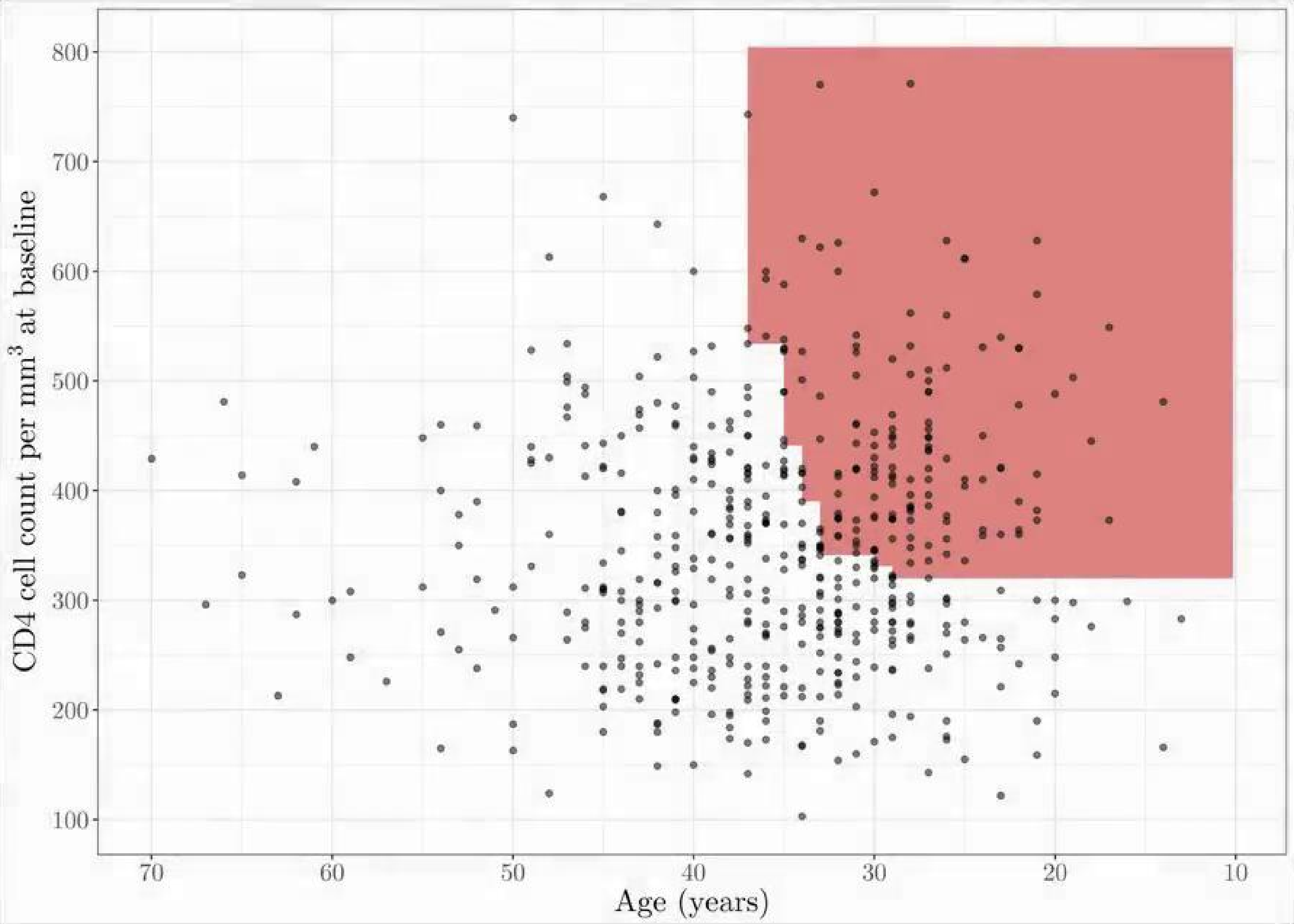
Hence, if we compute $\mathcal{D} = \big((X_1, Y_1), \ldots, (X_n, Y_n)\big) \sim P^n$, then $\mathbb{P}\big(\hat{A}^{\mathrm{ISS}}(\mathcal{D}) \subseteq \mathcal{X}_\tau(\eta)\big) \geq 1 - \alpha$ whenever $P \in \mathcal{P}_{\mathrm{Mon},d}(\sigma)$.

Application

Primary endpoint: reduction of the CD4 cell count by 50%, development of AIDS, or death, with median follow-up duration 143 weeks (Hammer et al., 1996). Let $\alpha = 0.05$ and $\tau = 1/2$.



Extensions in the paper

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Take-home messages

Subgroup selection with strong Type I error guarantees is possible in the isotonic regression setting.

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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:

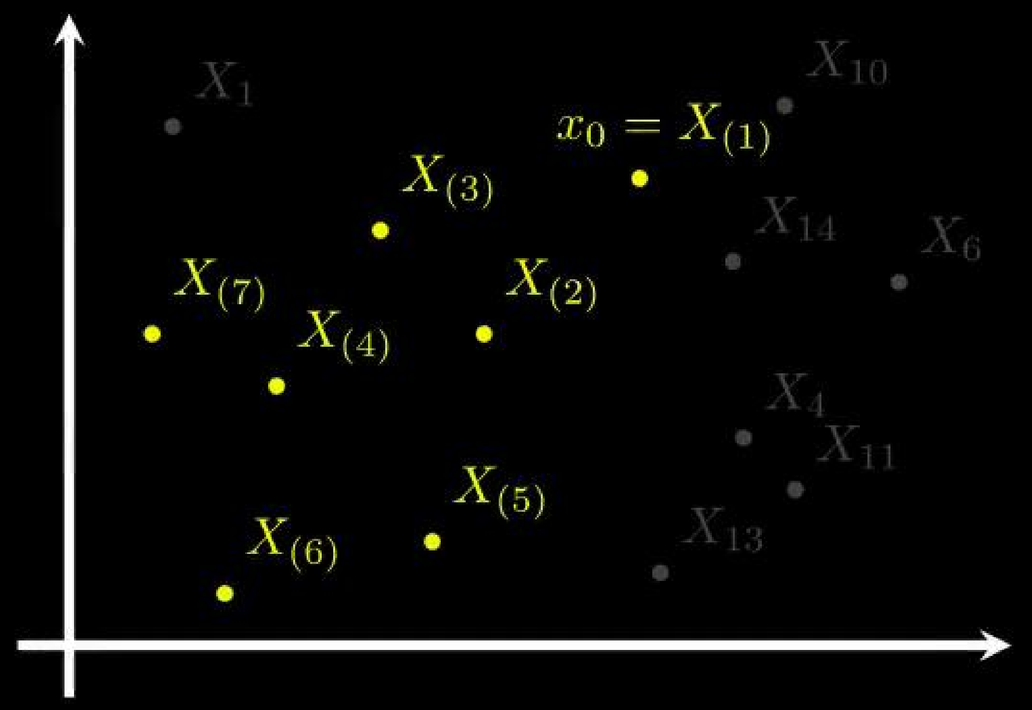
Müller, M. M., Reeve, H. W. J., Cannings, T. I. and Samworth, R. J. (2023) Isotonic subgroup selection. *arXiv preprint arXiv:2305.04852*.

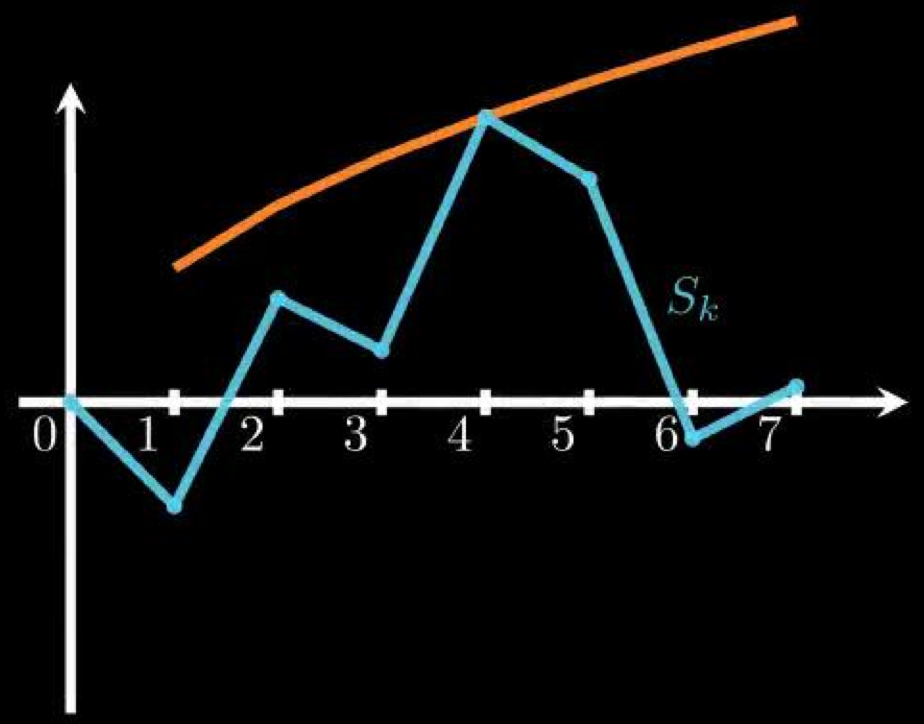
See manuelmmueller.github.io for data and `R`-code.

Appendix

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

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

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).

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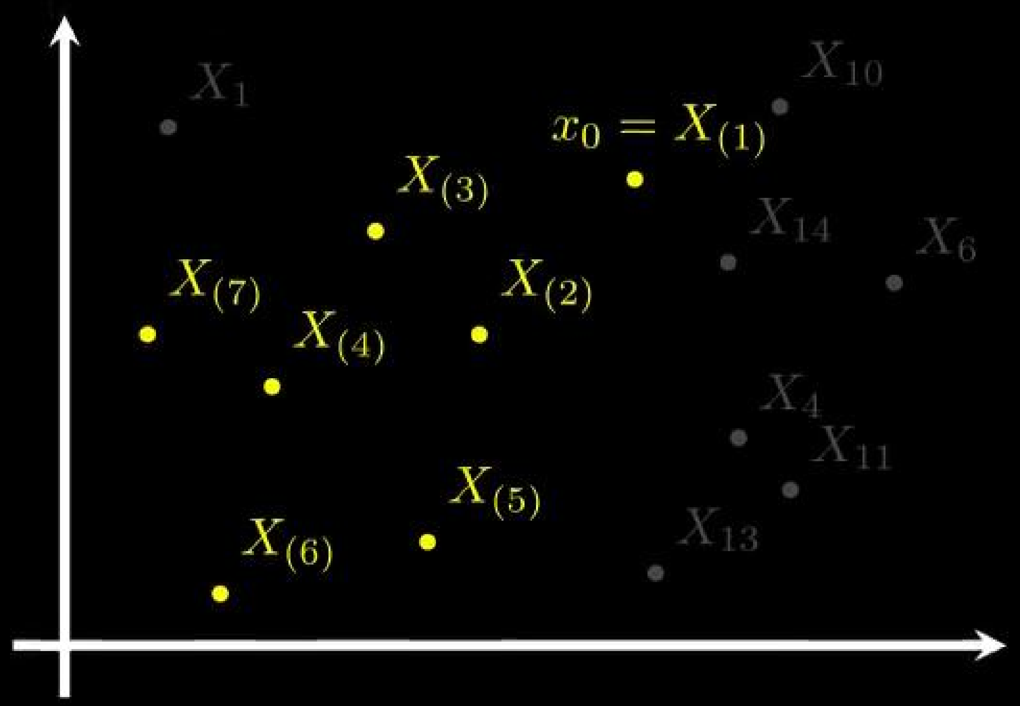

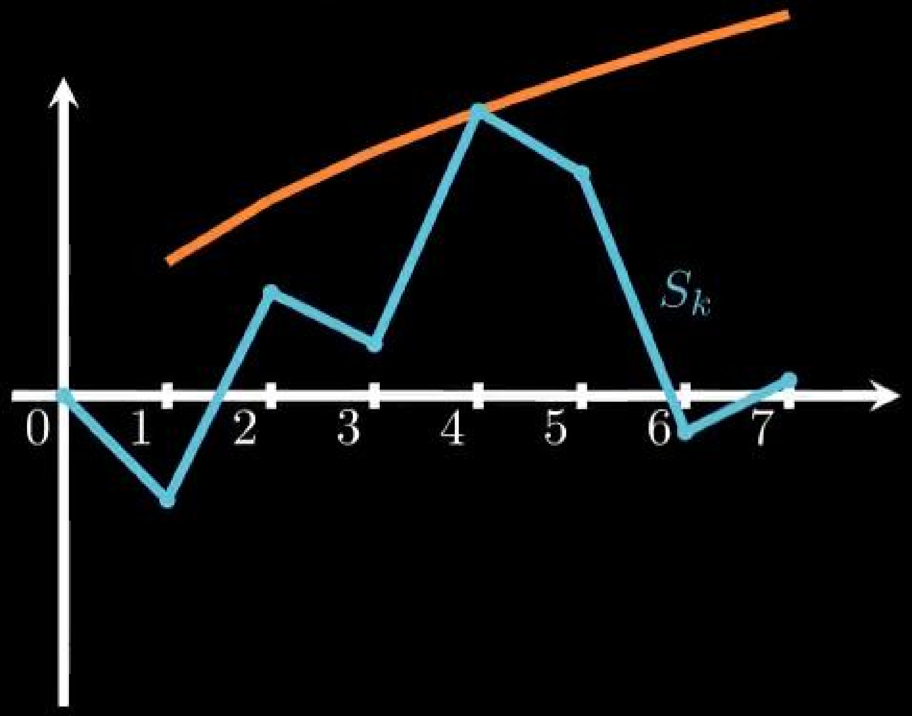

Definition. For $\sigma > 0$, $x \in \mathbb{R}^d$, let

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

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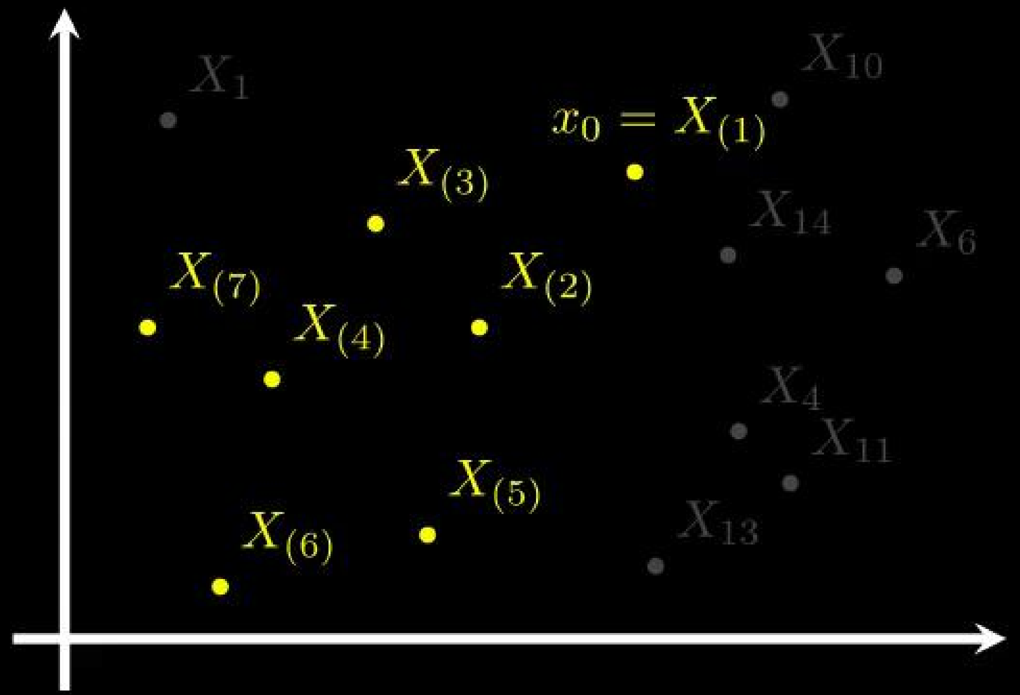

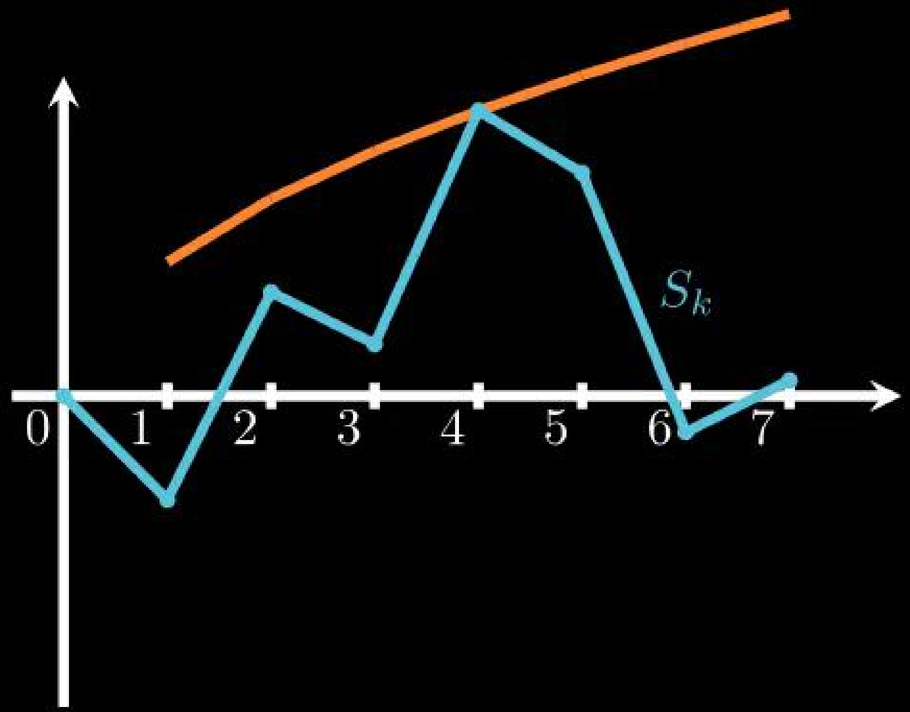

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Lemma. When $\eta(x) < \tau$, we have $\mathbb{P}\{\hat{p}_{\sigma,\tau}(x) \le t \mid (X_i)_{i\in[n]}\} \le t$ for all $t \in (0,1)$.

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Label	Function f	τ	$\gamma(P)$
(a)	$\sum_{j=1}^{d} x^{(j)}$	$1/2$	1
(b)	$\max_{1 \le j \le d} x^{(j)}$	$1/2^{1/d}$	1
(c)	$\min_{1 \le j \le d} x^{(j)}$	$1 - 1/2^{1/d}$	1
(d)	$\mathbb{1}_{(0.5,1]}\big(x^{(1)}\big)$	$1/2$	0
(e)	$\sum_{j=1}^{d} \big(x^{(j)} - 0.5\big)^3$	$1/2$	3
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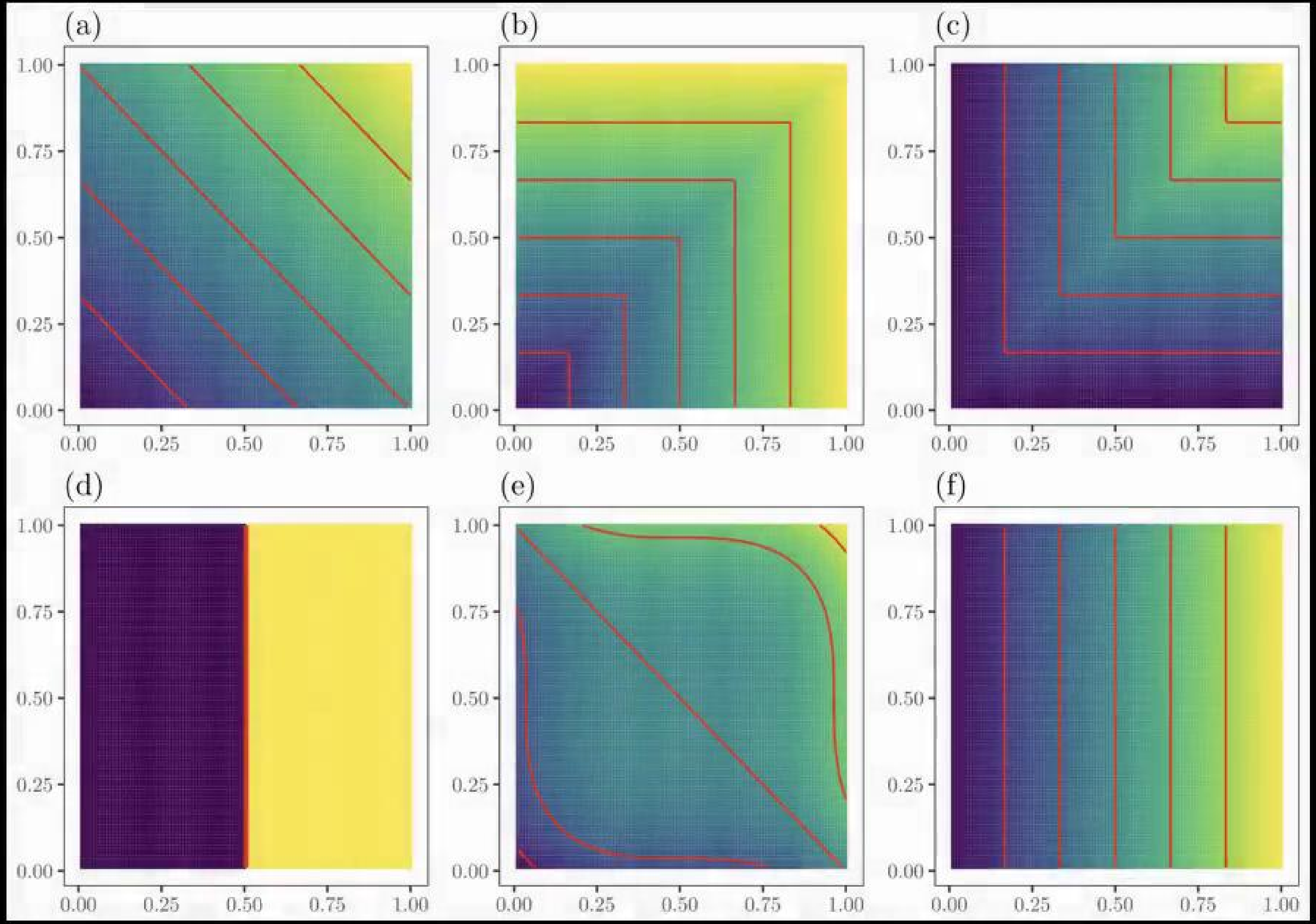

Simulations

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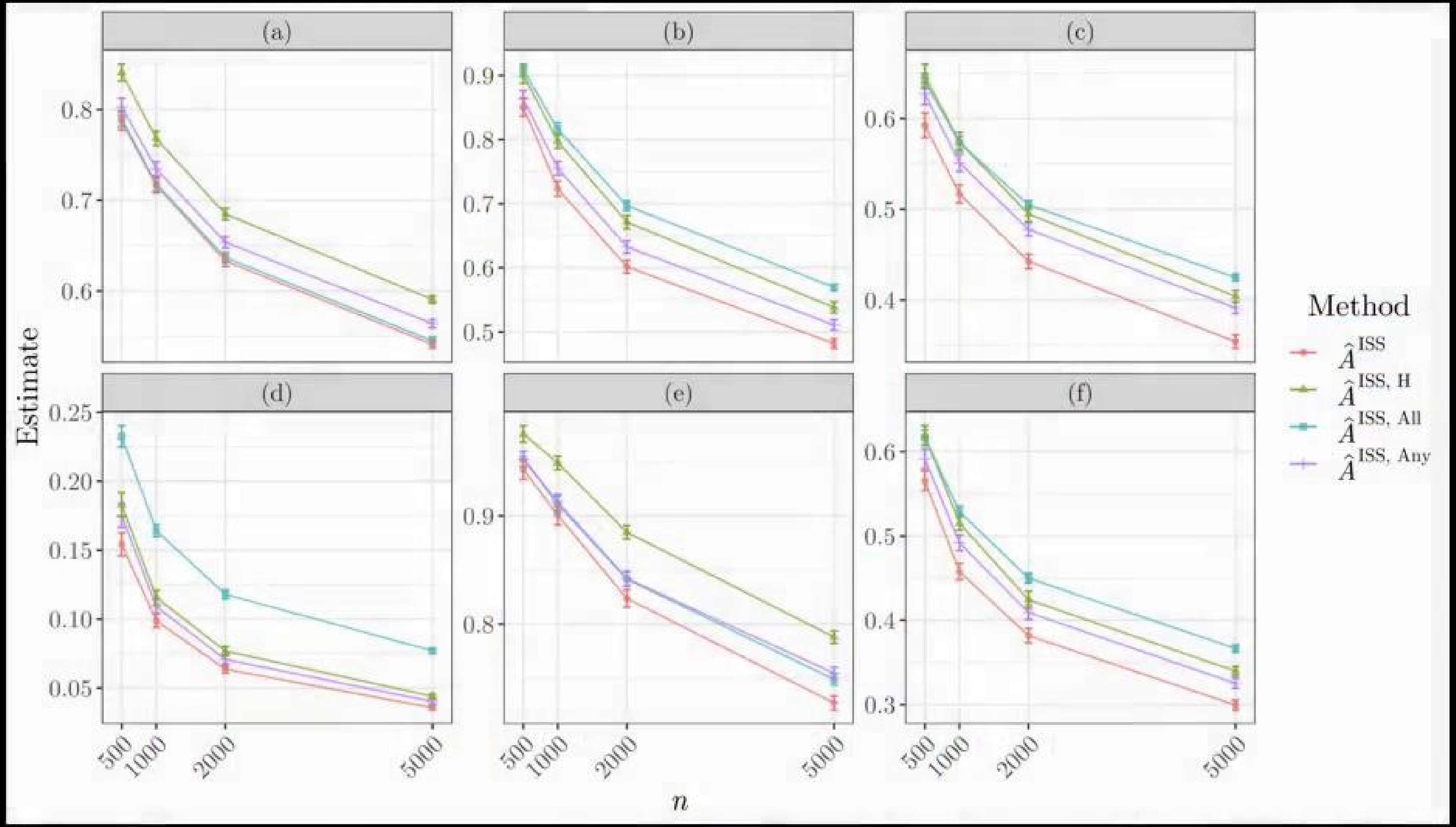
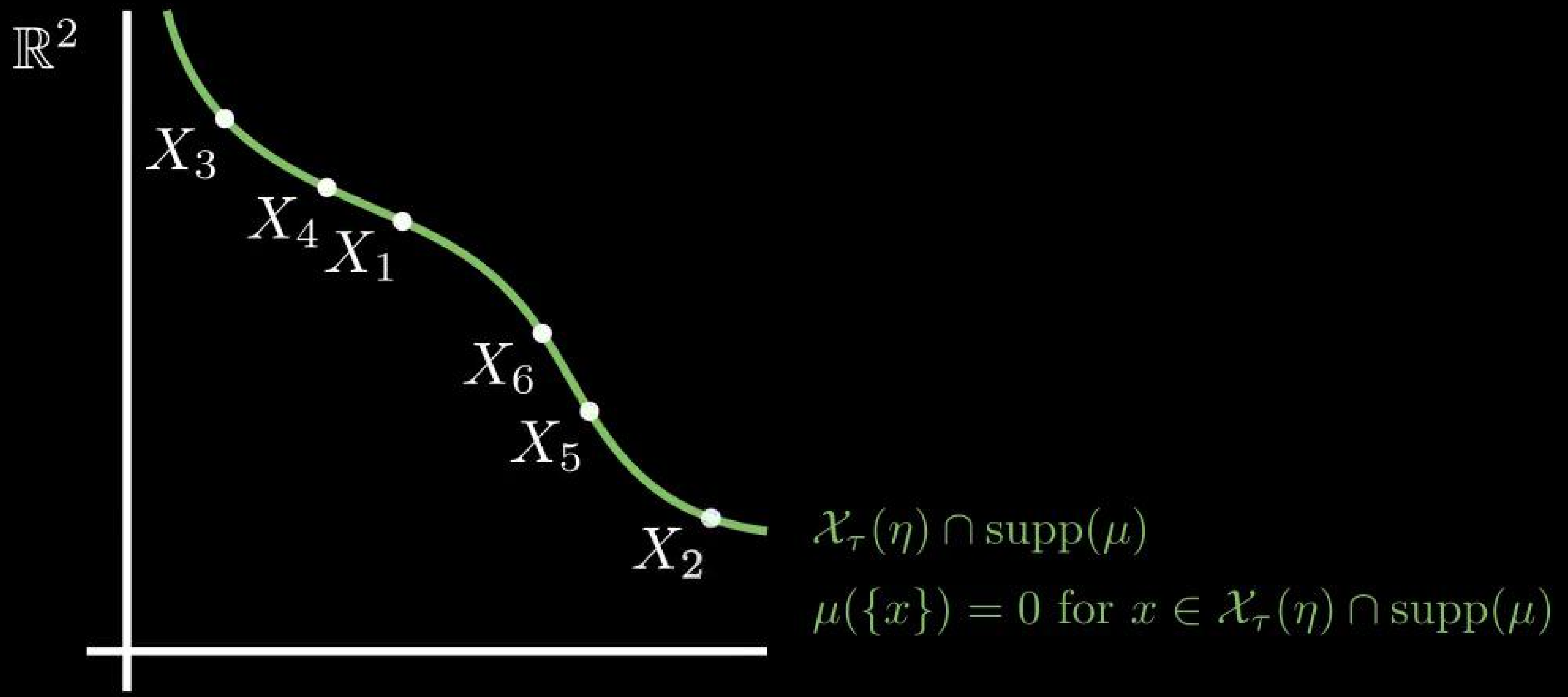


Here, $d = 2$, $\sigma = 1/4$.

See also Meijer and Goeman (2015).

Density condition



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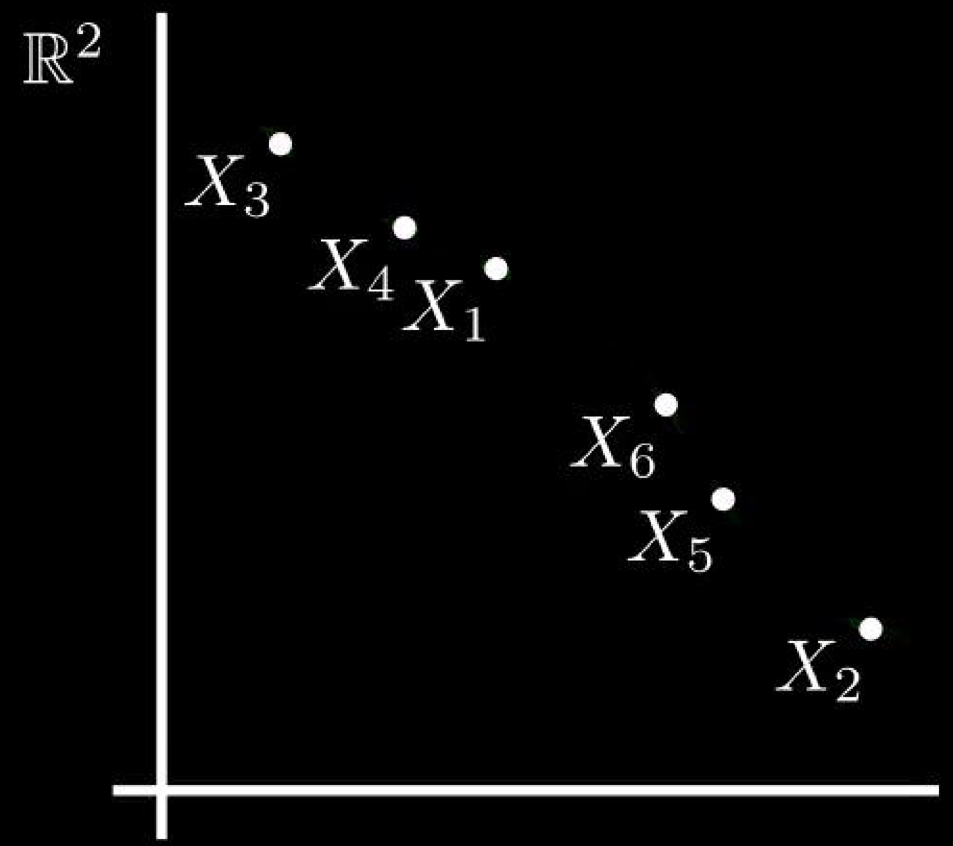

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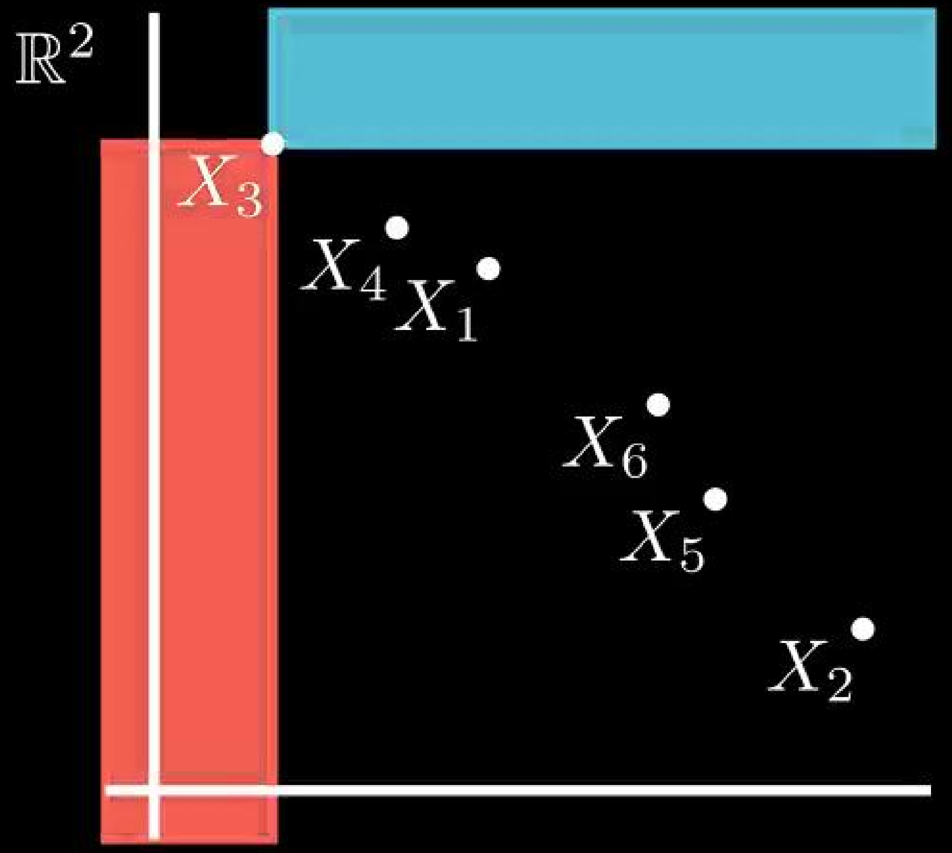

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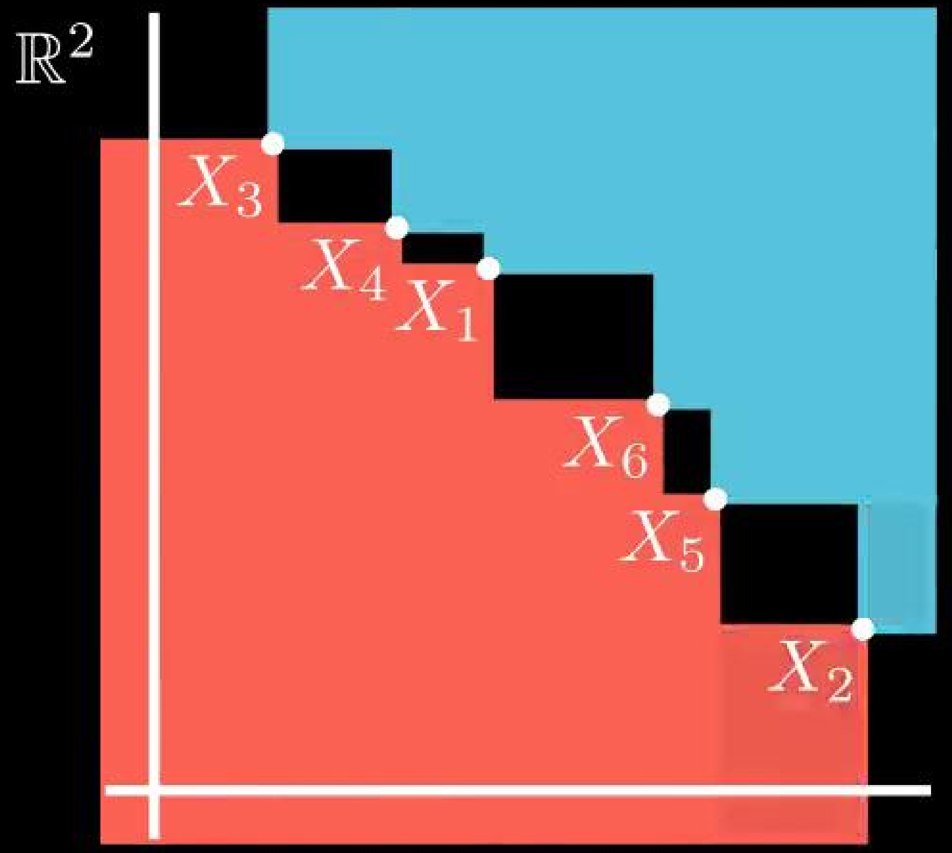

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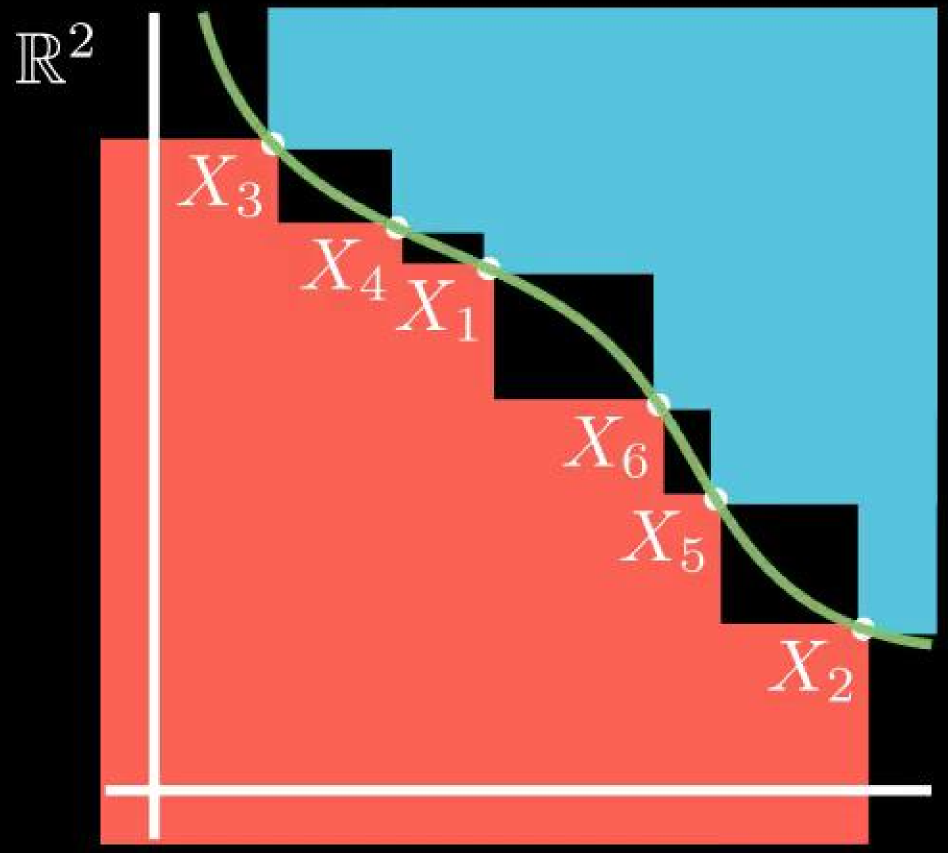

$\mathcal{X}_\tau(\eta) \cap \mathrm{supp}(\mu)$

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

Proof of the upper bound (for $m \in [n]$)

Theorem. There exists $C \geq 1$, depending only on (d, θ), such that for any $P \in \mathcal{P}_{\mathrm{MonReg},d}(\sigma, \tau, \gamma, \lambda, \theta)$, $\alpha \in (0,1)$ and $m \in [n]$,

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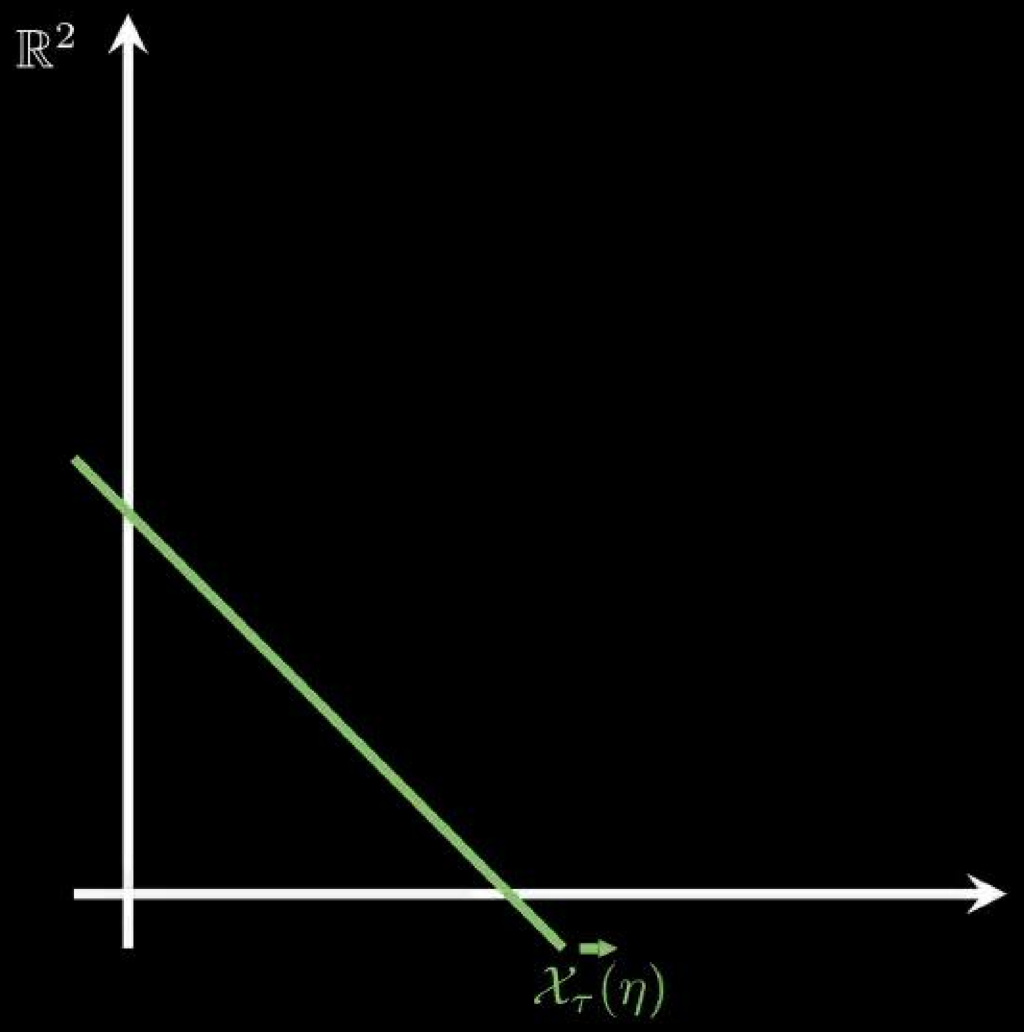

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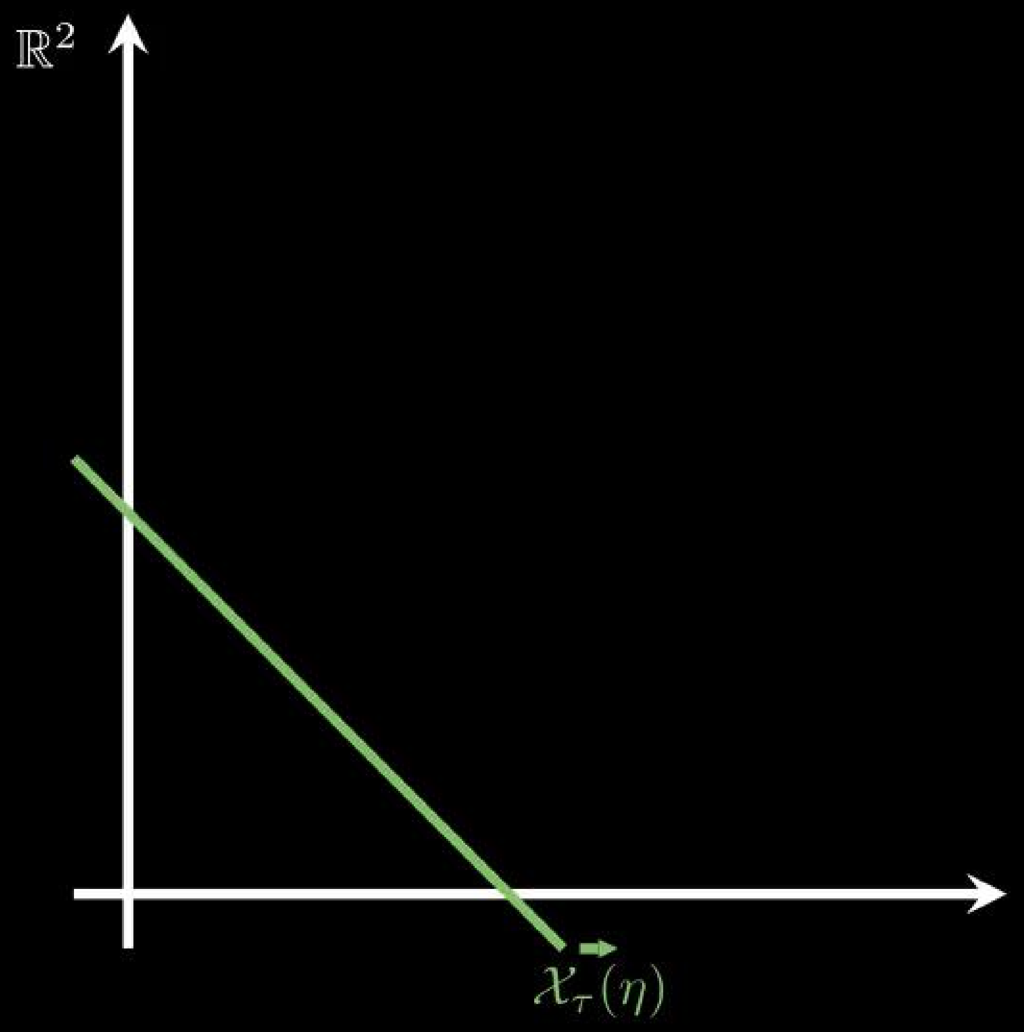

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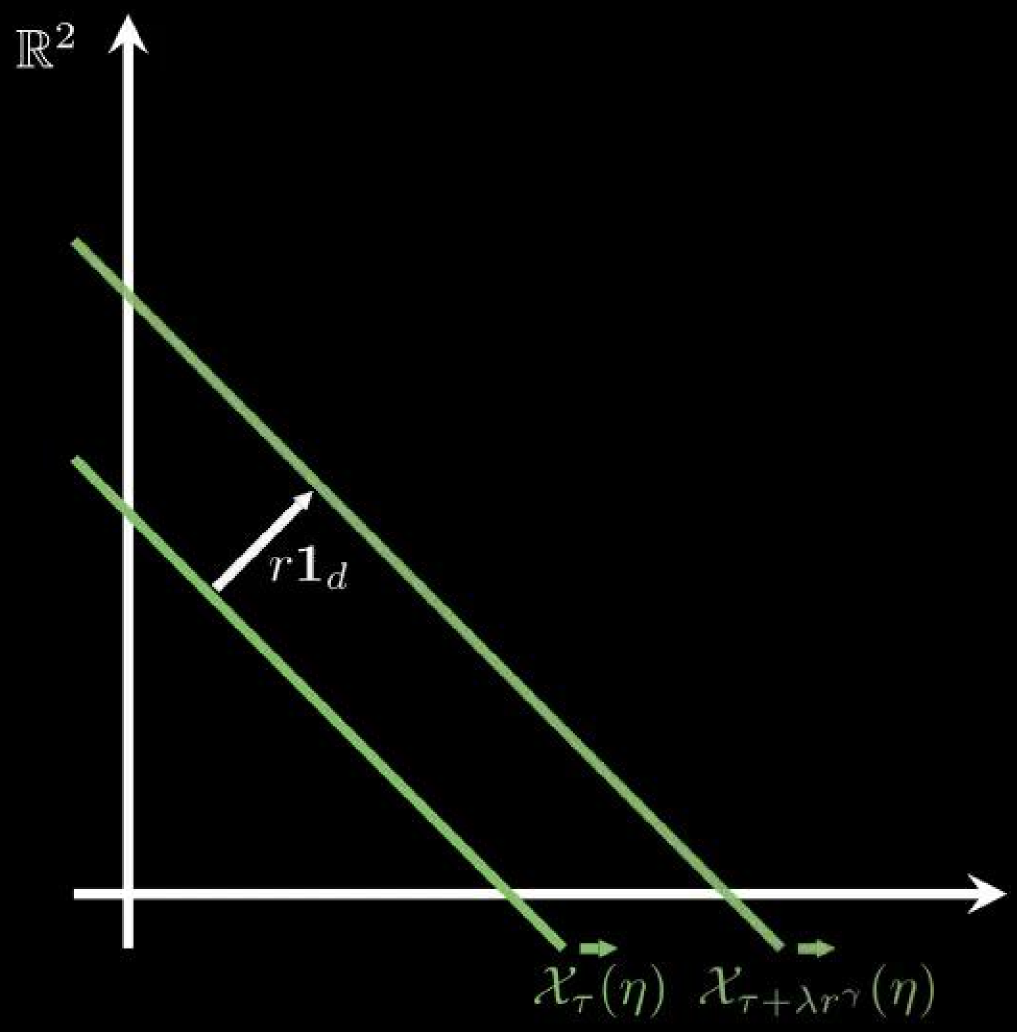

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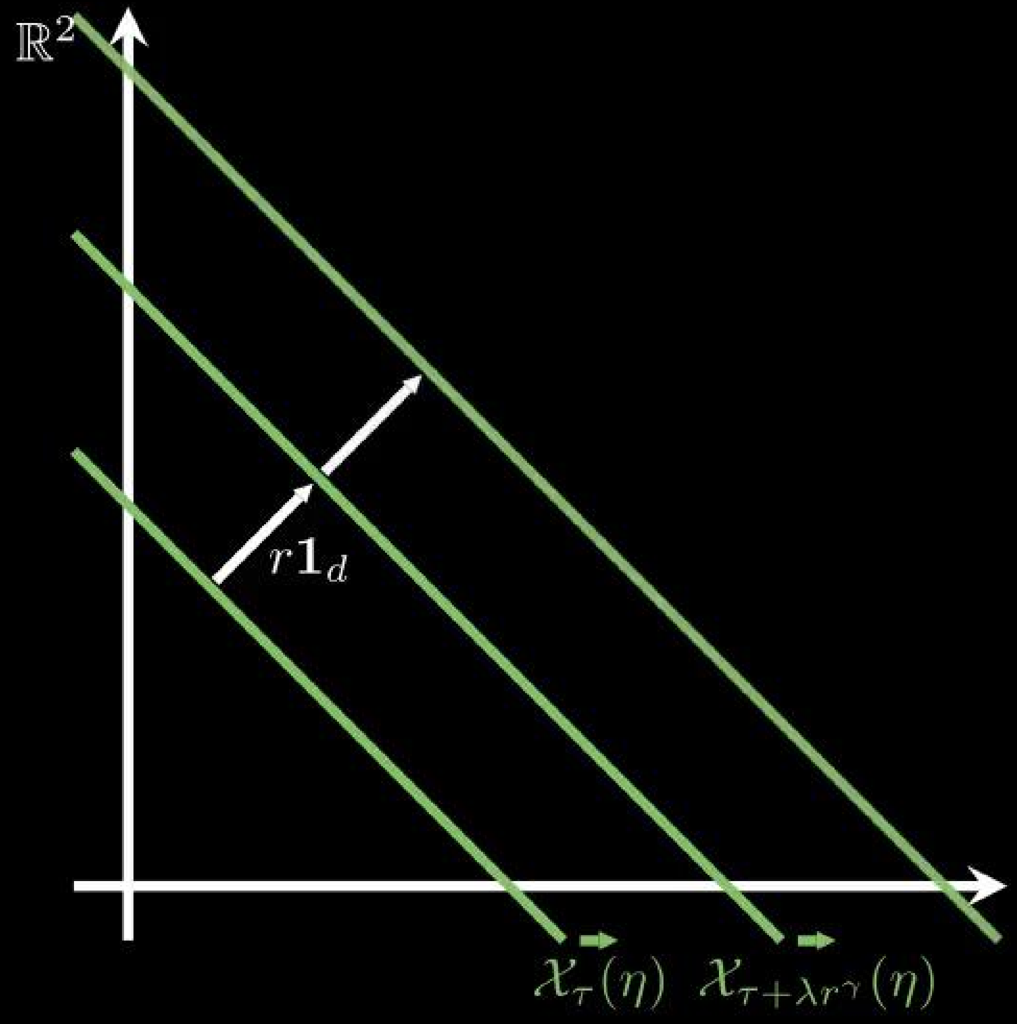

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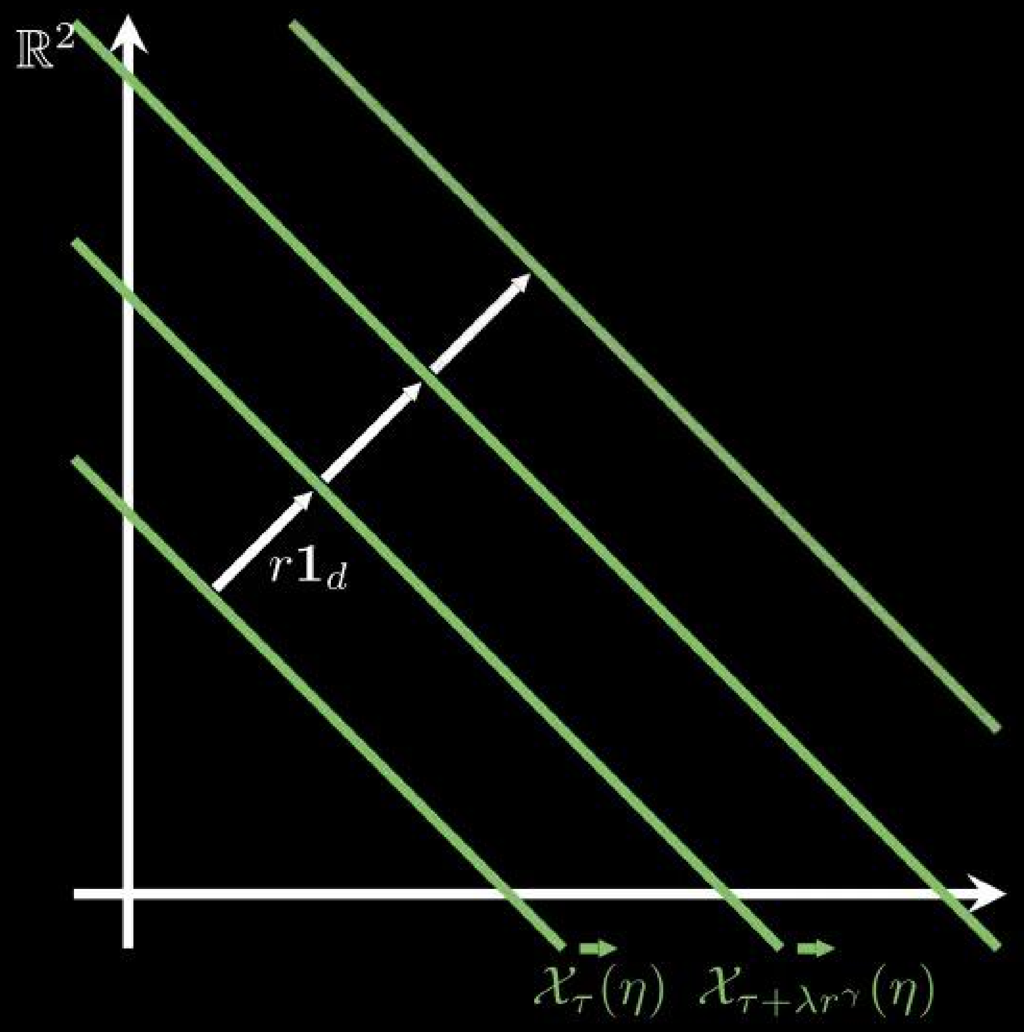

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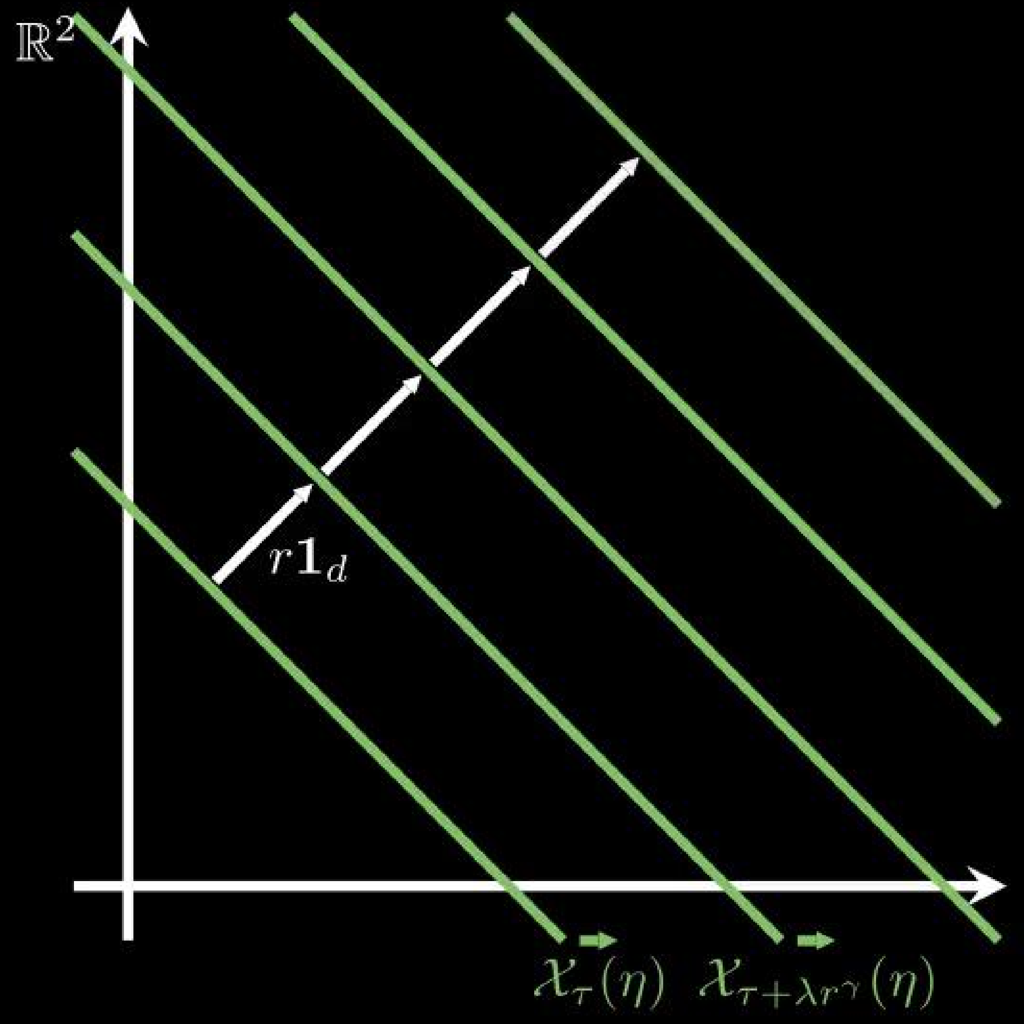

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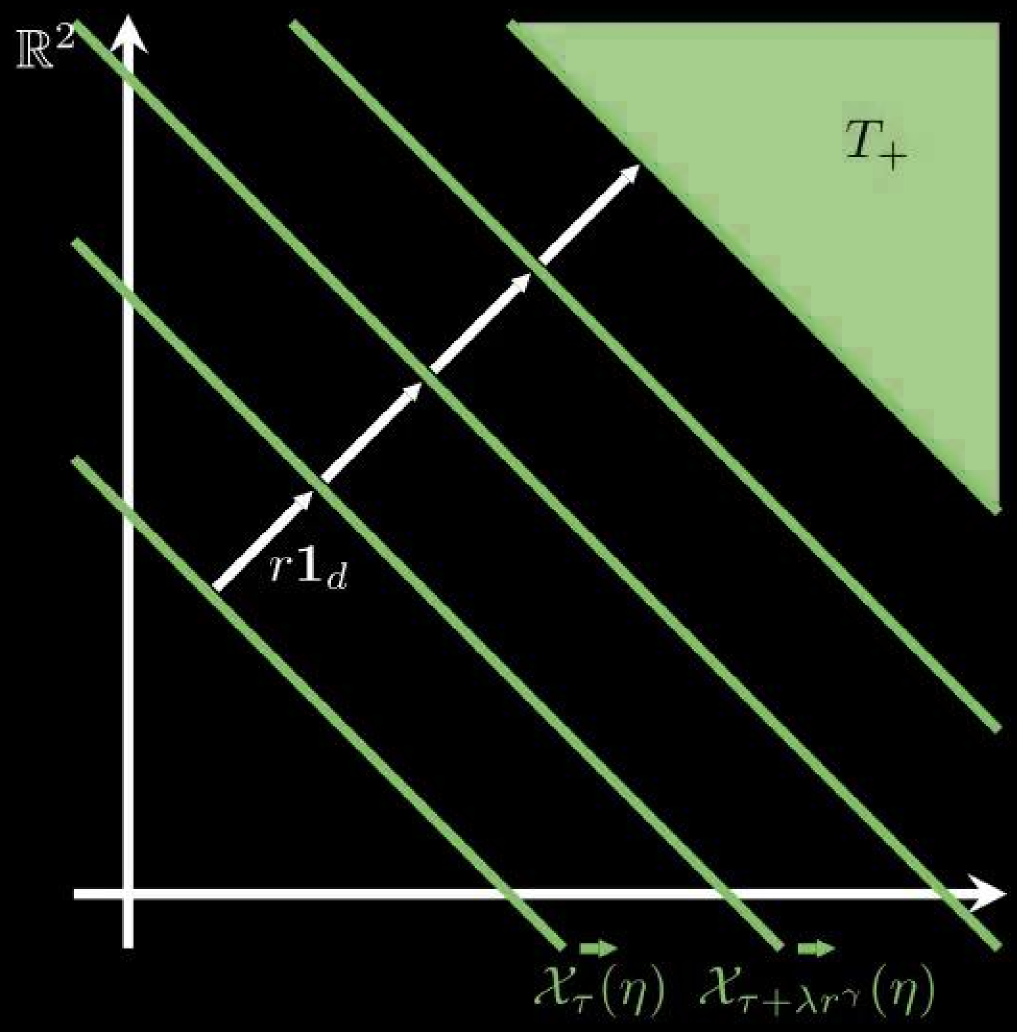

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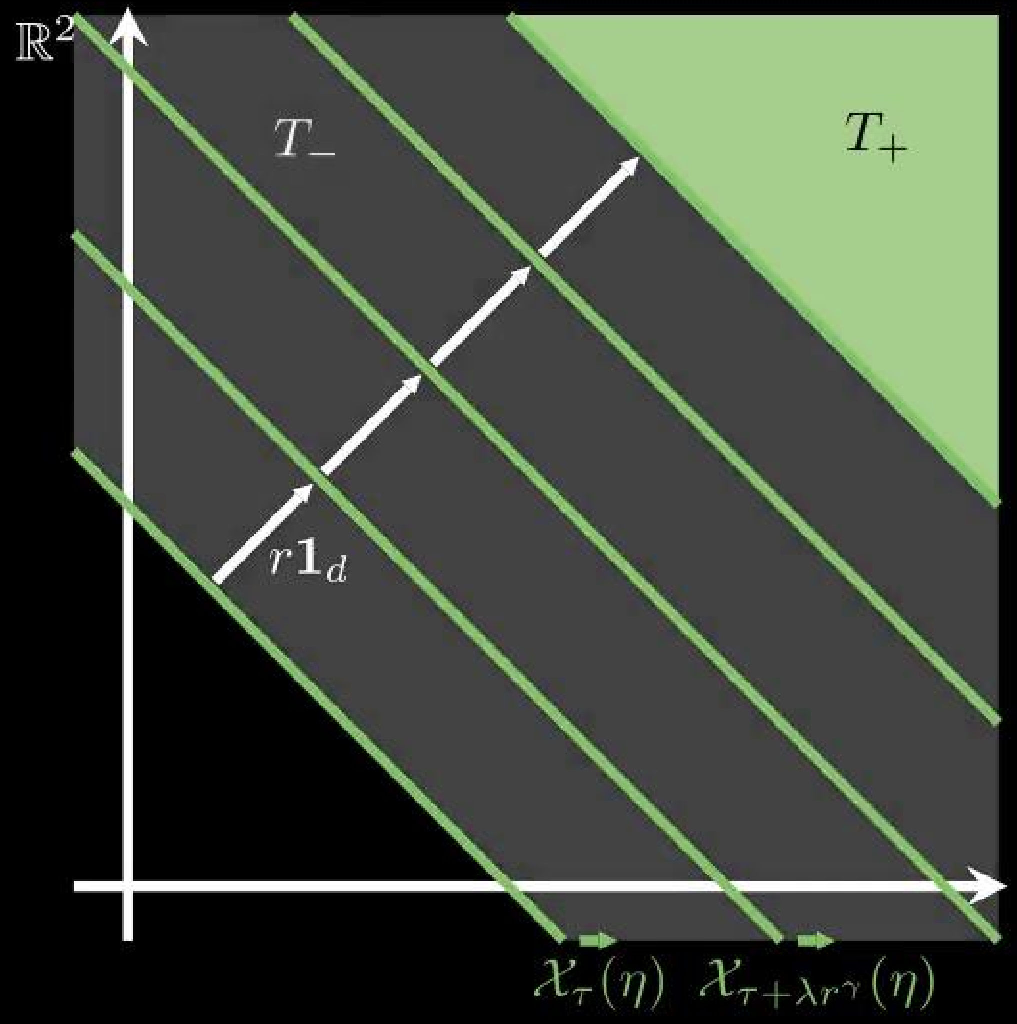

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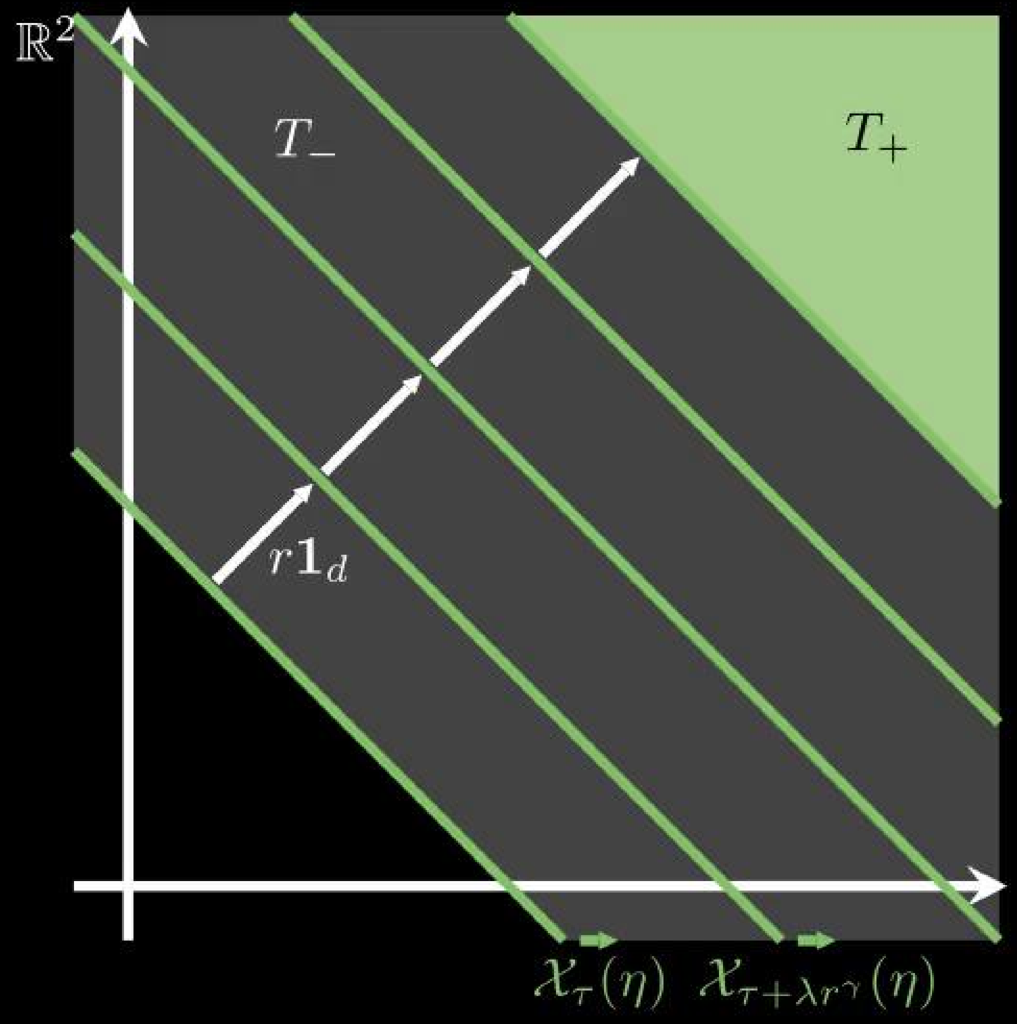

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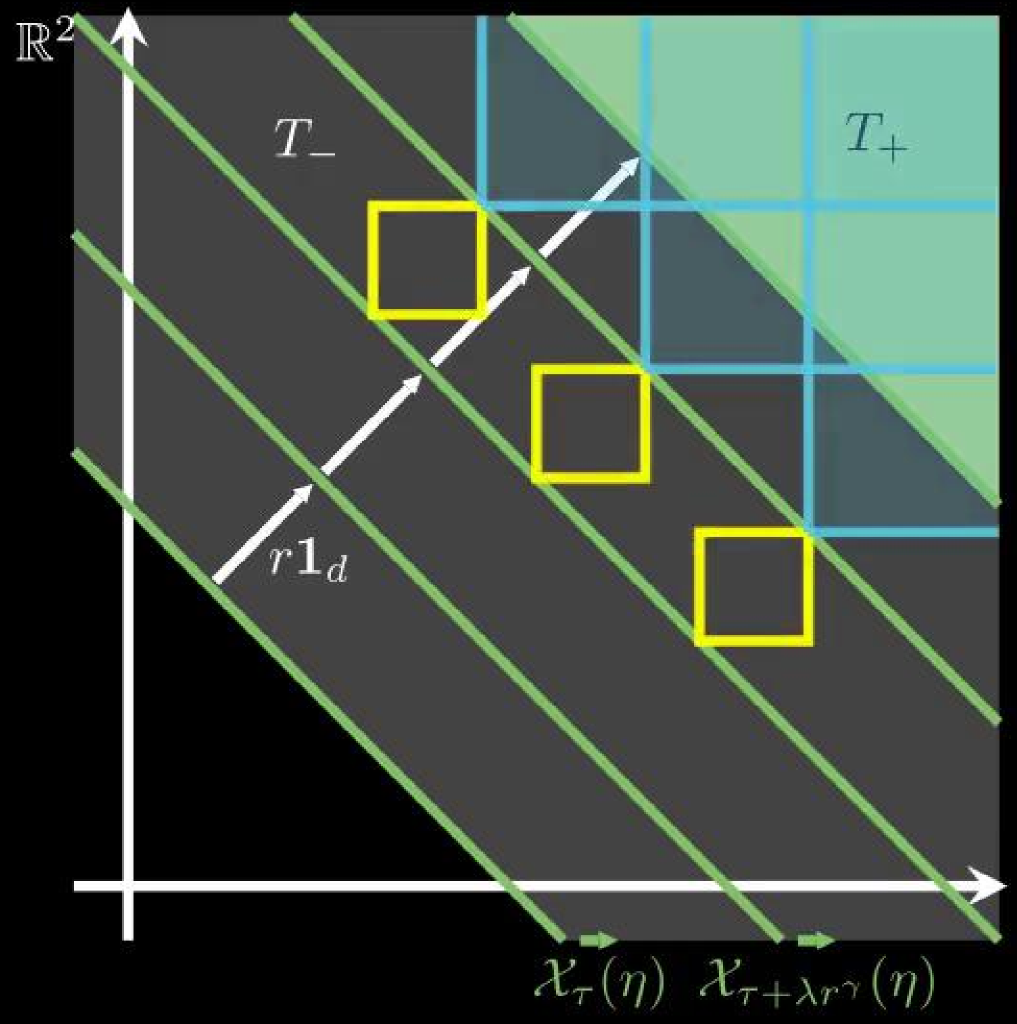

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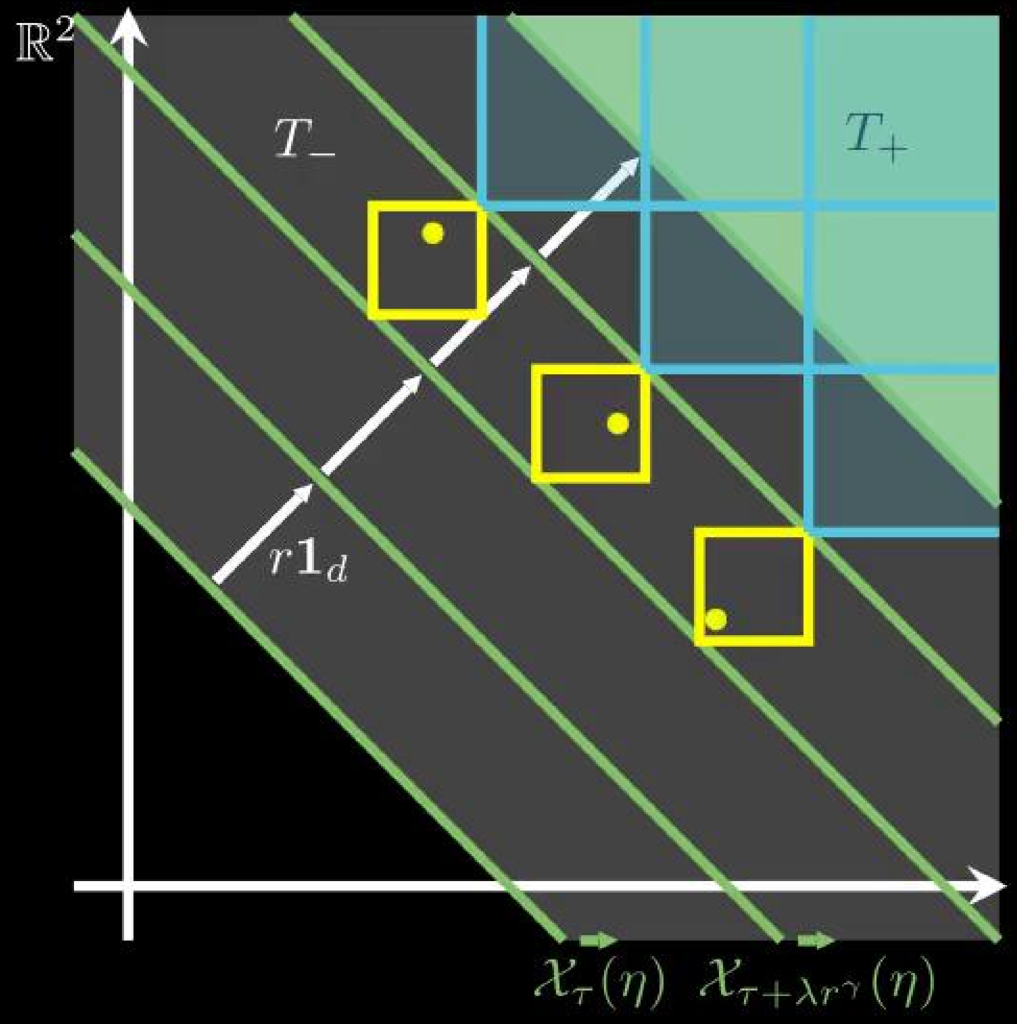

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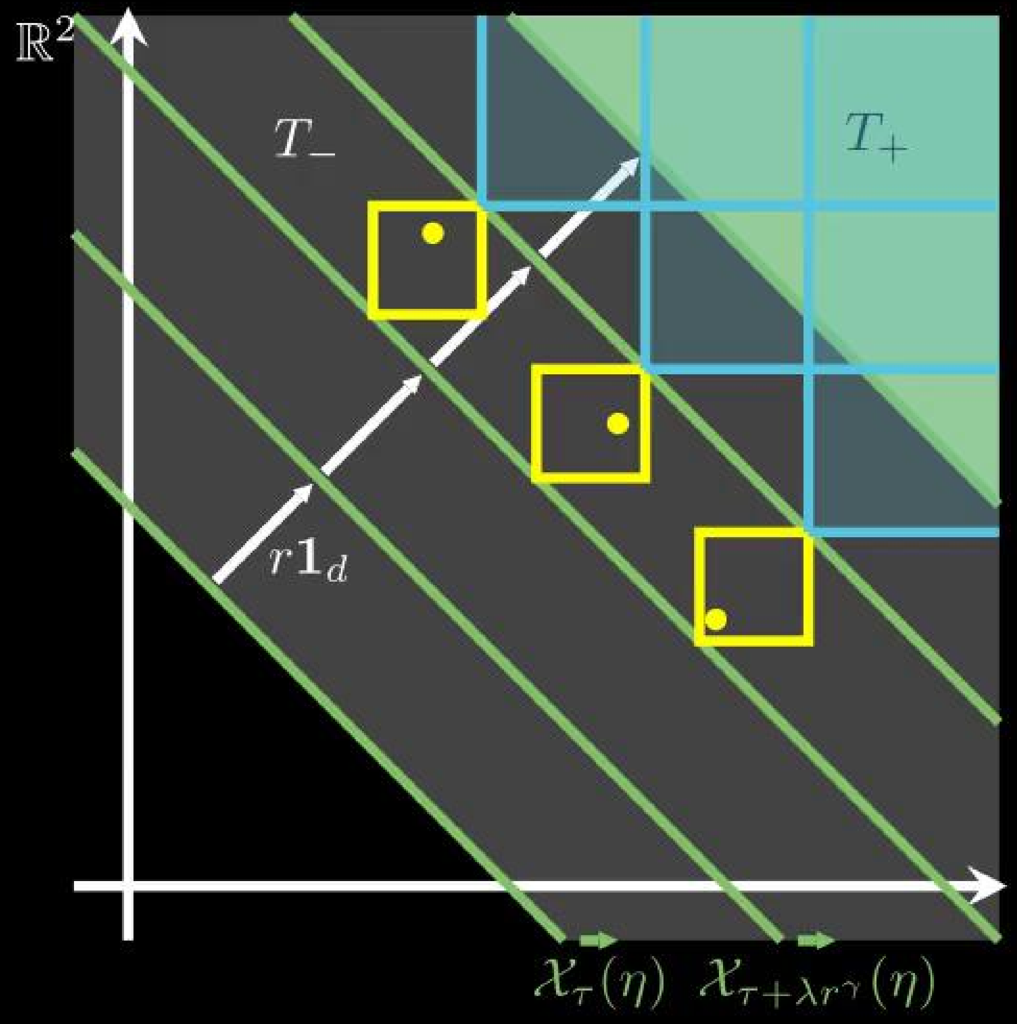

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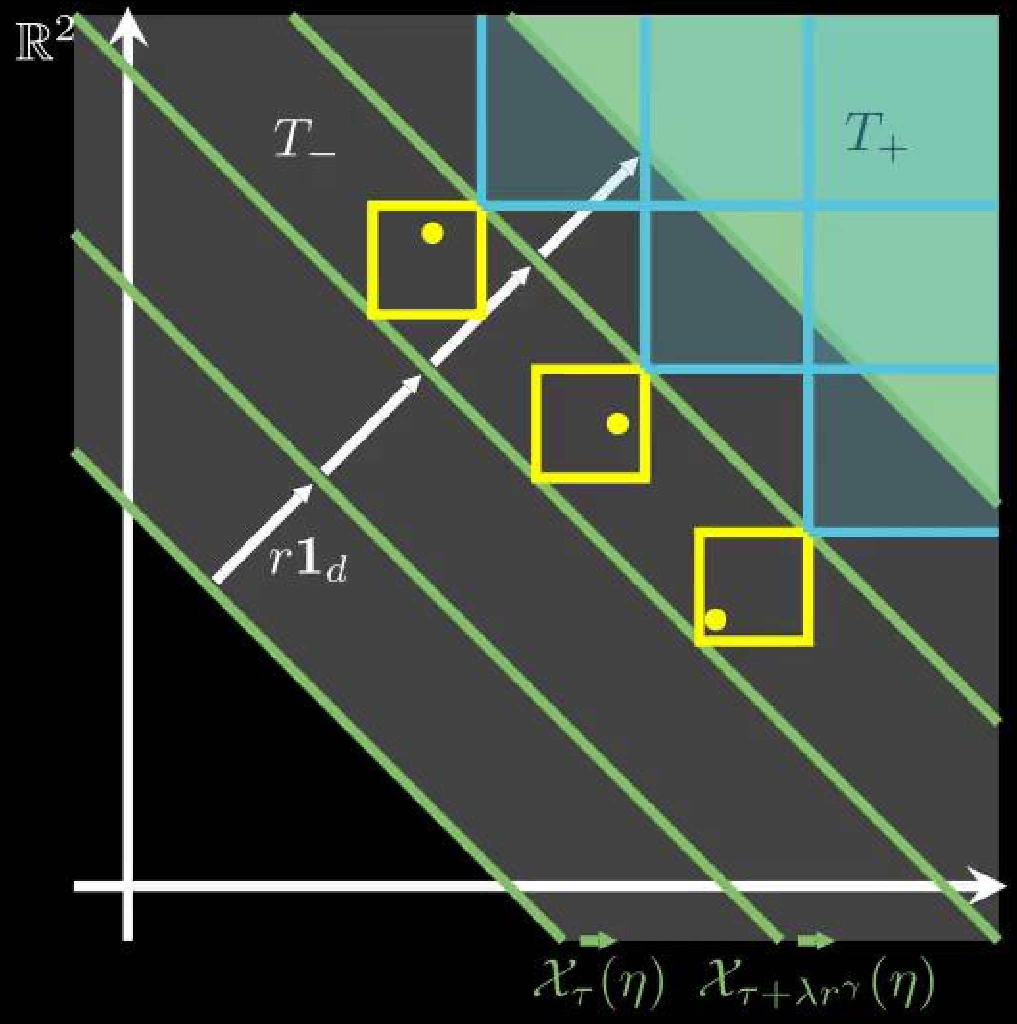

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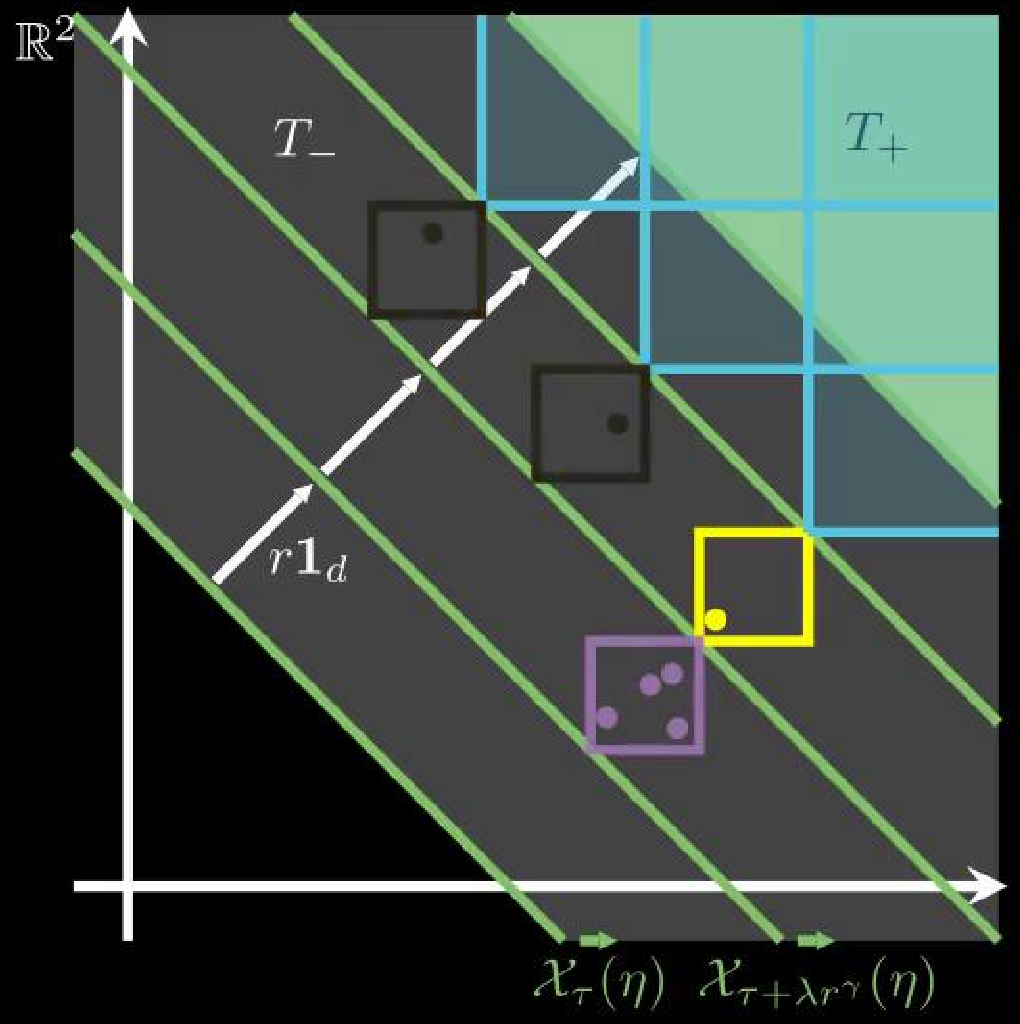

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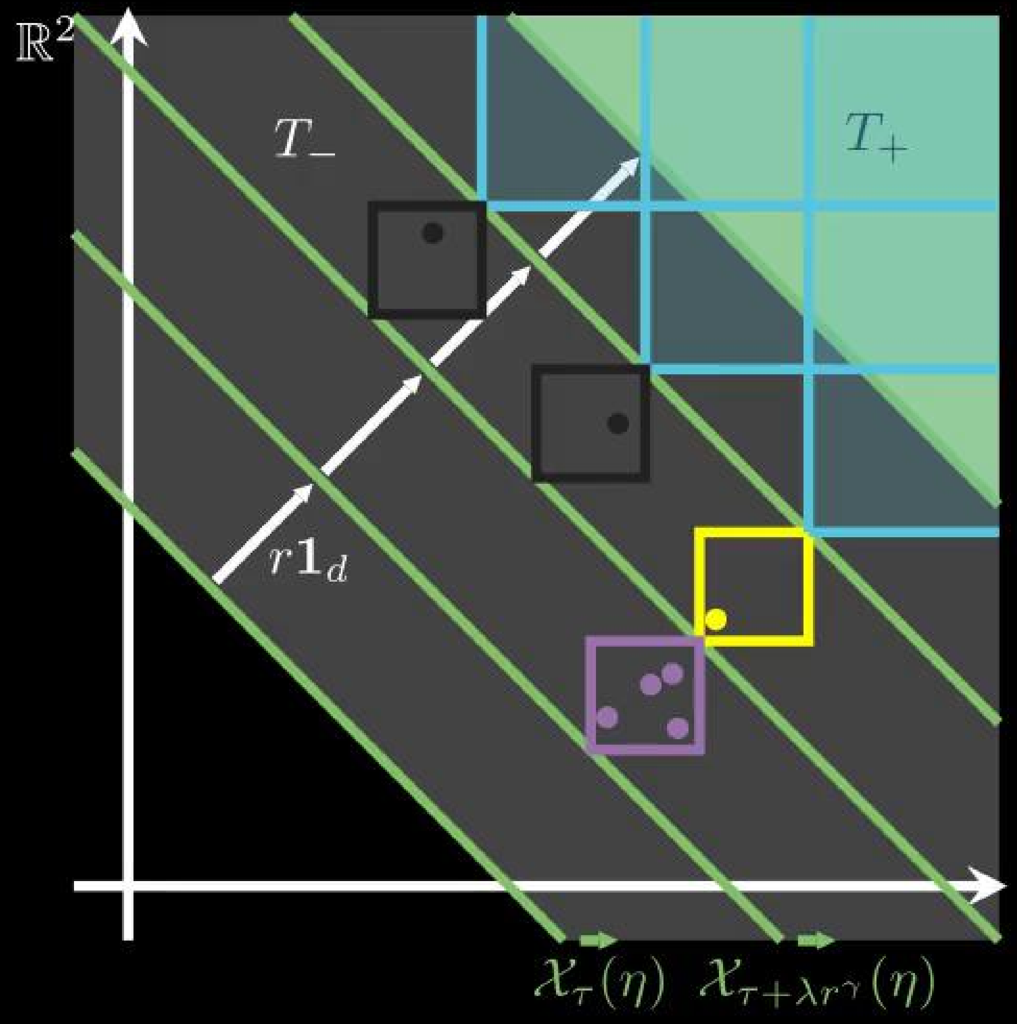

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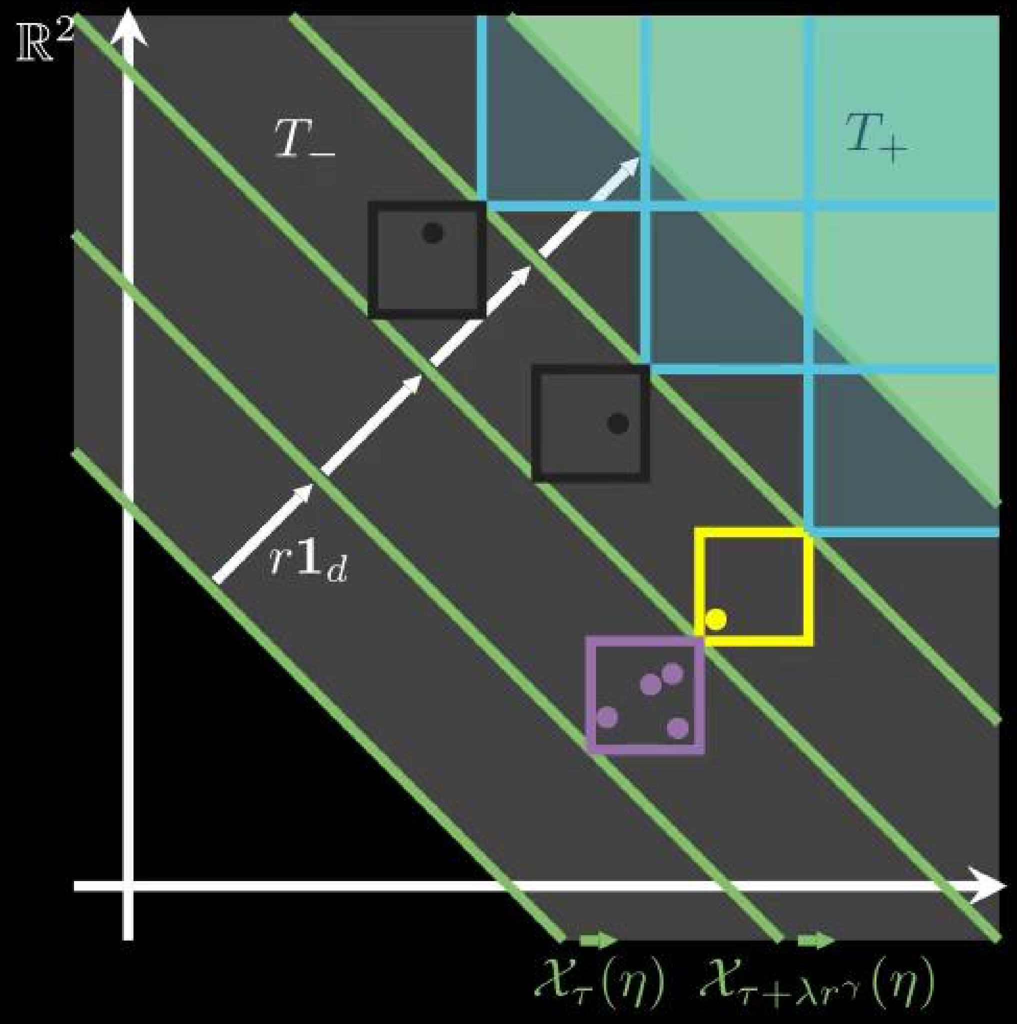

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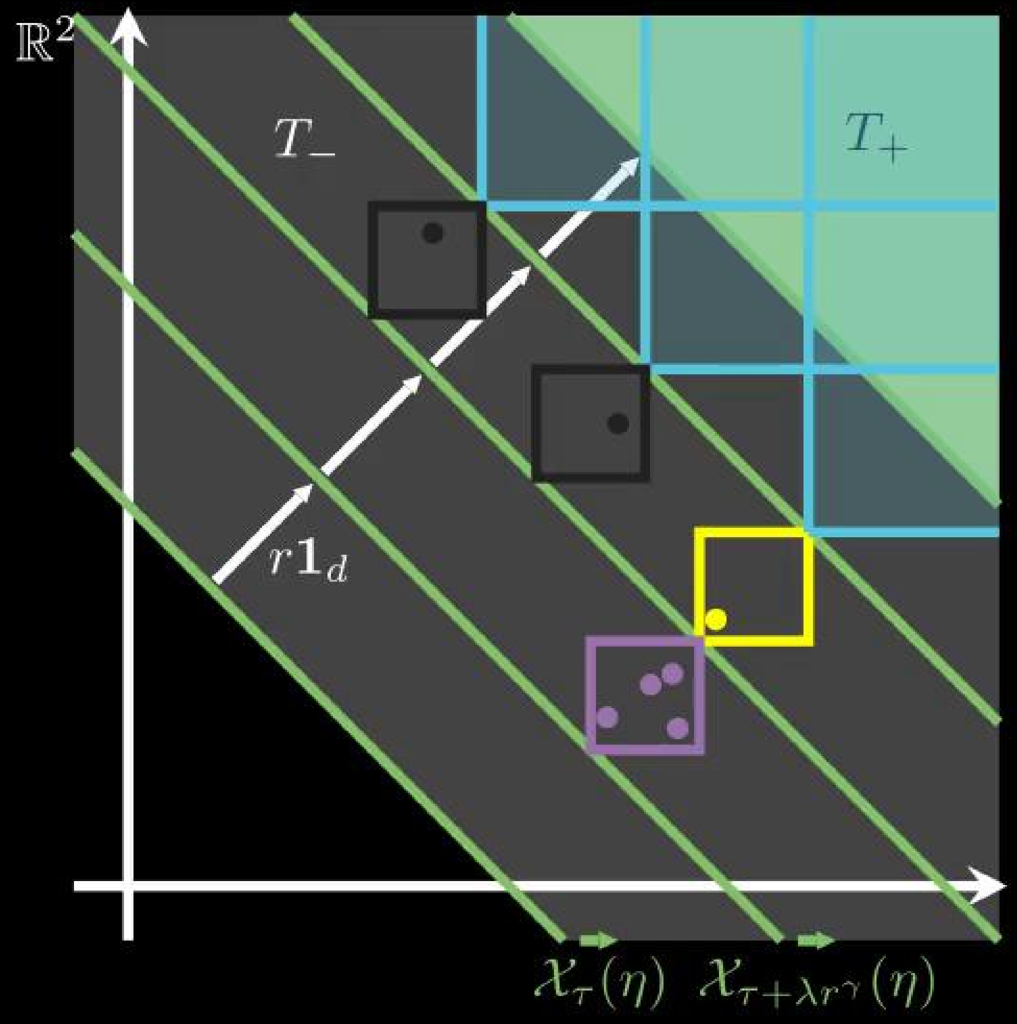

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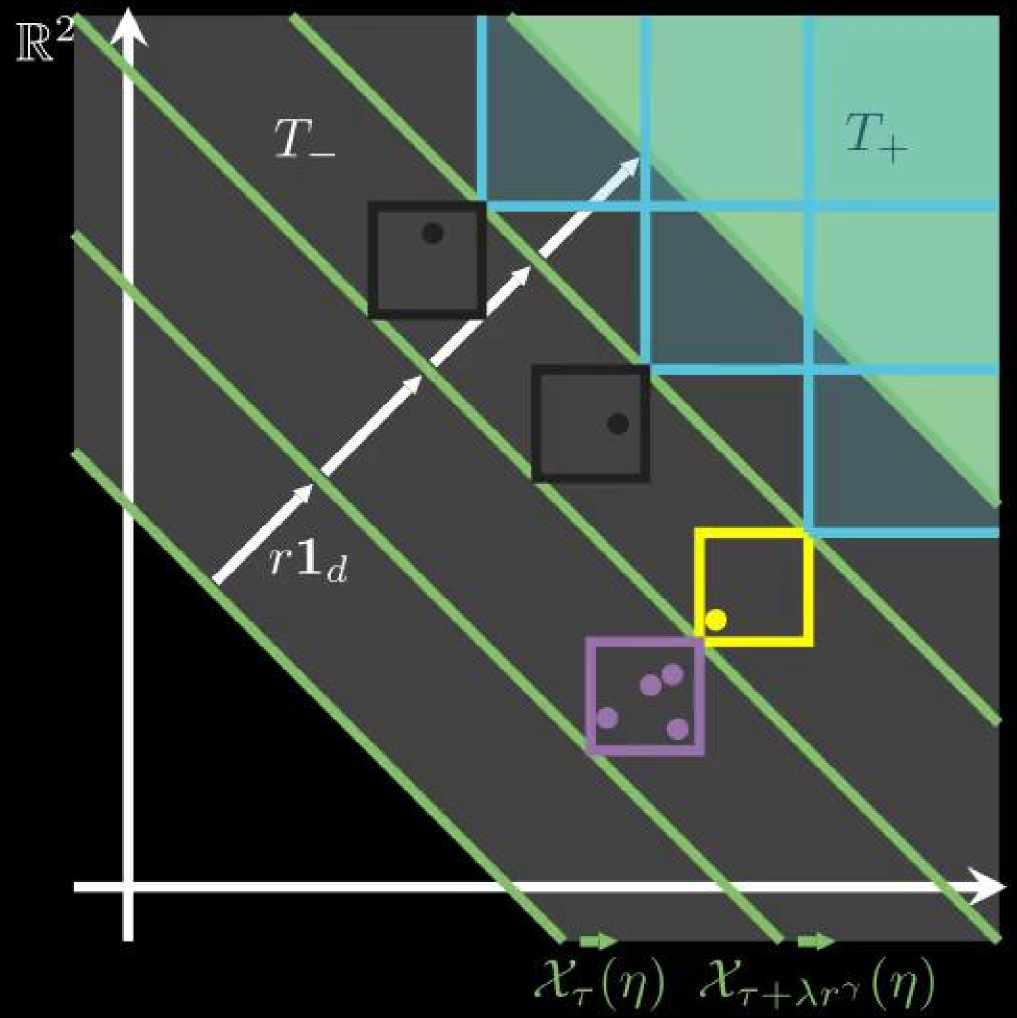

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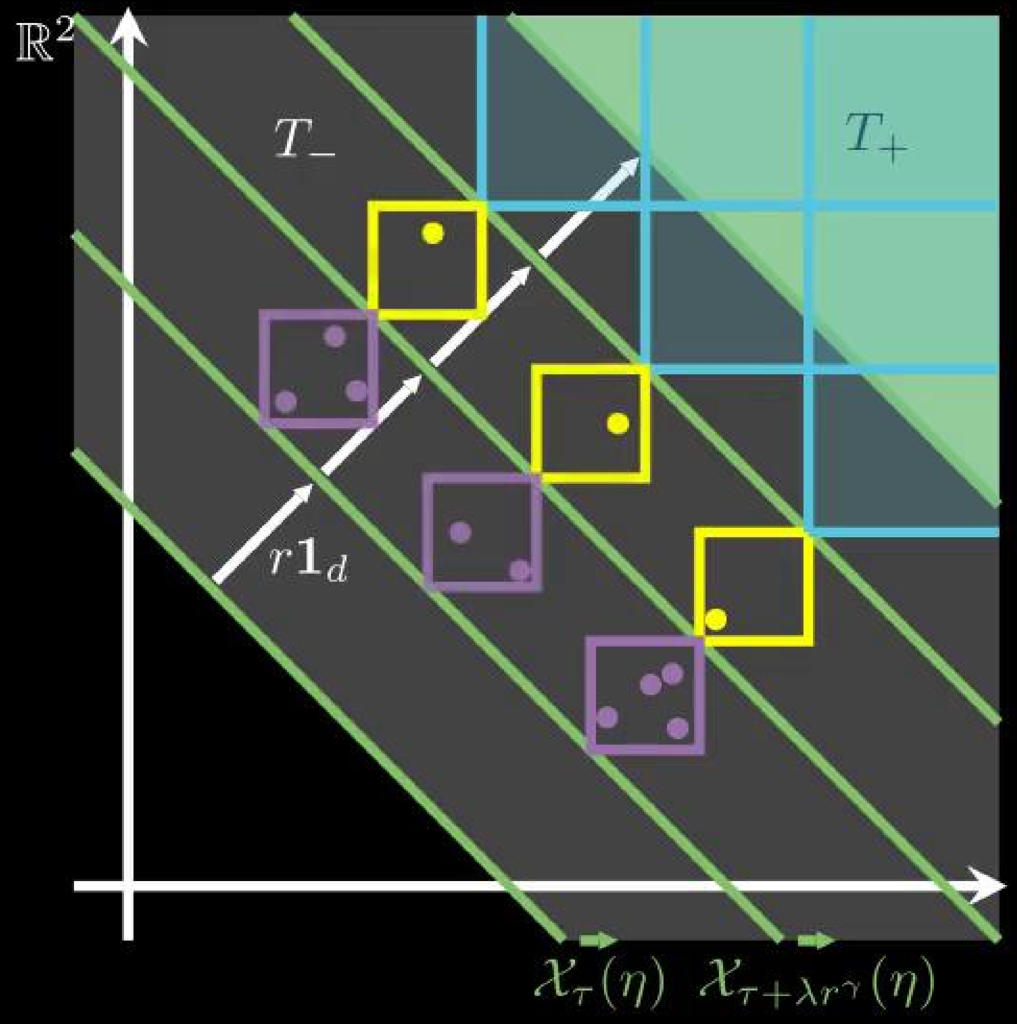
Sufficient: $\boxed{r \overset{!}{\gtrsim} \left\{\frac{\sigma^2}{n\lambda^2}\log\left(\frac{\log n}{\alpha}\right)\right\}^{1/(2\gamma+d)}}$.

Proof of the upper bound (for $m \in [n]$)

Theorem. There exists $C \geq 1$, depending only on (d,θ), such that for any $P \in \mathcal{P}_{\mathrm{MonReg},d}(\sigma,\tau,\gamma,\lambda,\theta)$, $\alpha \in (0,1)$ and $m \in [n]$,

$$R_\tau(\hat{A}^{\mathrm{ISS}}) \leq 1 \wedge C\left\{\left(\frac{\sigma^2}{n\lambda^2}\log_+\left(\frac{m\log_+ n}{\alpha}\right)\right)^{1/(2\gamma+d)} + \left(\frac{\log_+ m}{m}\right)^{1/d}\right\}.$$



Let $r > 0$ be small.

$\mu\{\mathcal{X}_\tau(\eta) \setminus T_+\} = \mu(T_-) \approx 4r \approx r$.

Need $q :\approx 1/r^{d-1}$ boxes to cover T_+.

Out of $(X_i)_{i\in[m]}$ roughly mr^d in each box.

At least one per box if $mr^d \gtrsim \log q \Longleftarrow \boxed{r \overset{!}{\gtrsim} \left(\frac{\log m}{m}\right)^{1/d}}$.

Have $\hat{p} \leq \alpha$ if $S_k \gtrsim \sqrt{k\{\log((\log n)/\alpha)\}}$ (Howard et al, 2021).

Box contains roughly nr^d points with expected response $\geq \tau + \lambda r^\gamma$.

For $k \approx nr^d$, have $S_k \approx nr^d \cdot \frac{\lambda r^\gamma}{\sigma} \gtrsim \sqrt{nr^d\{\log((\log n)/\alpha)\}}$.

Sufficient: $\boxed{r \overset{!}{\gtrsim} \left\{\frac{\sigma^2}{n\lambda^2}\log\left(\frac{m\log n}{\alpha}\right)\right\}^{1/(2\gamma+d)}}$.