A unified treatment of multiple testing with prior knowledge

Aaditya Ramdas

(+ Rina F. Barber, Martin J. Wainwright, Michael I. Jordan)

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Barber-Ramdas '16

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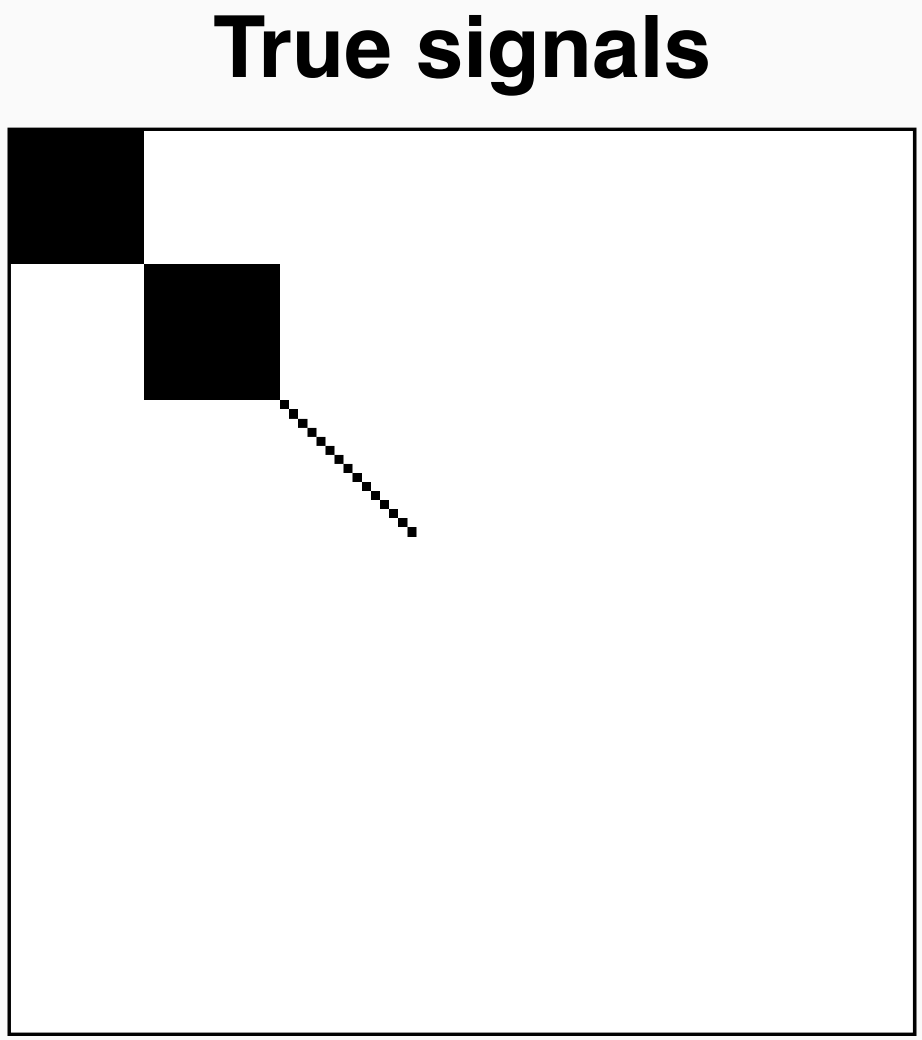
- **Special cases**: Benjamini-Hochberg procedure
  Simes test for the global null

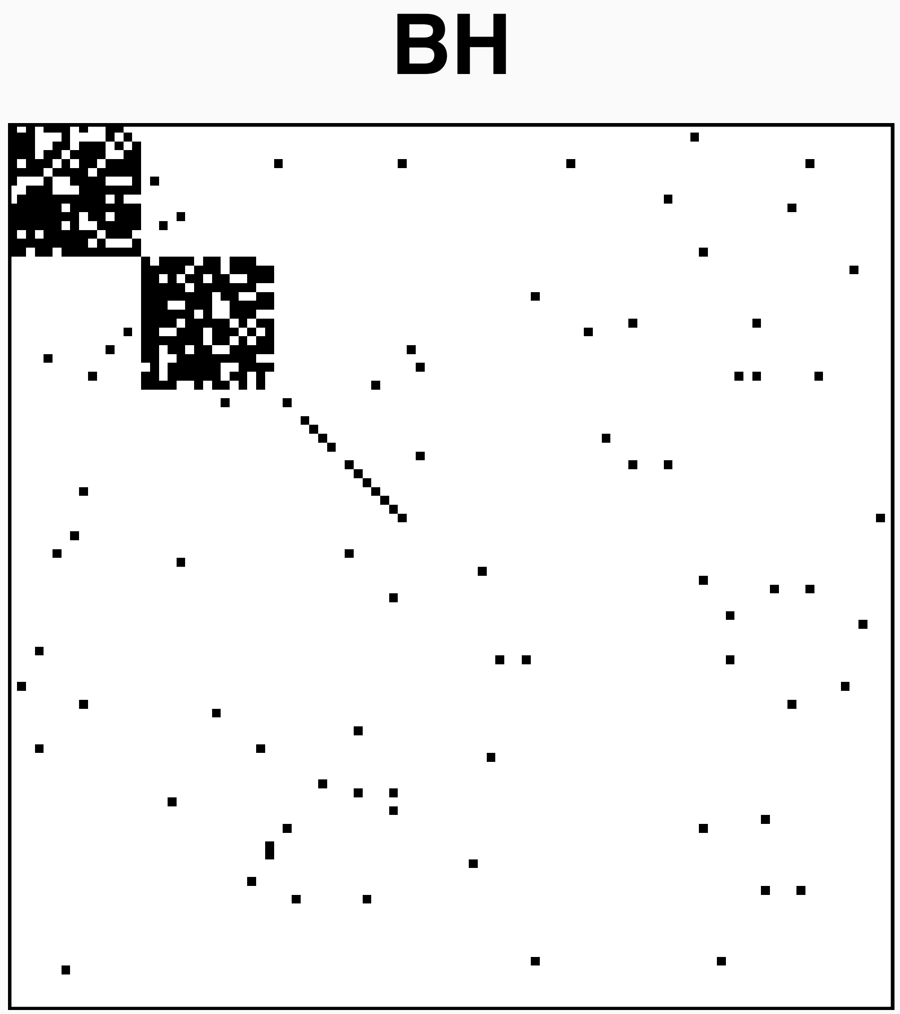
Barber-Ramdas '16



10,000 hypotheses in a100 x 100 grid.

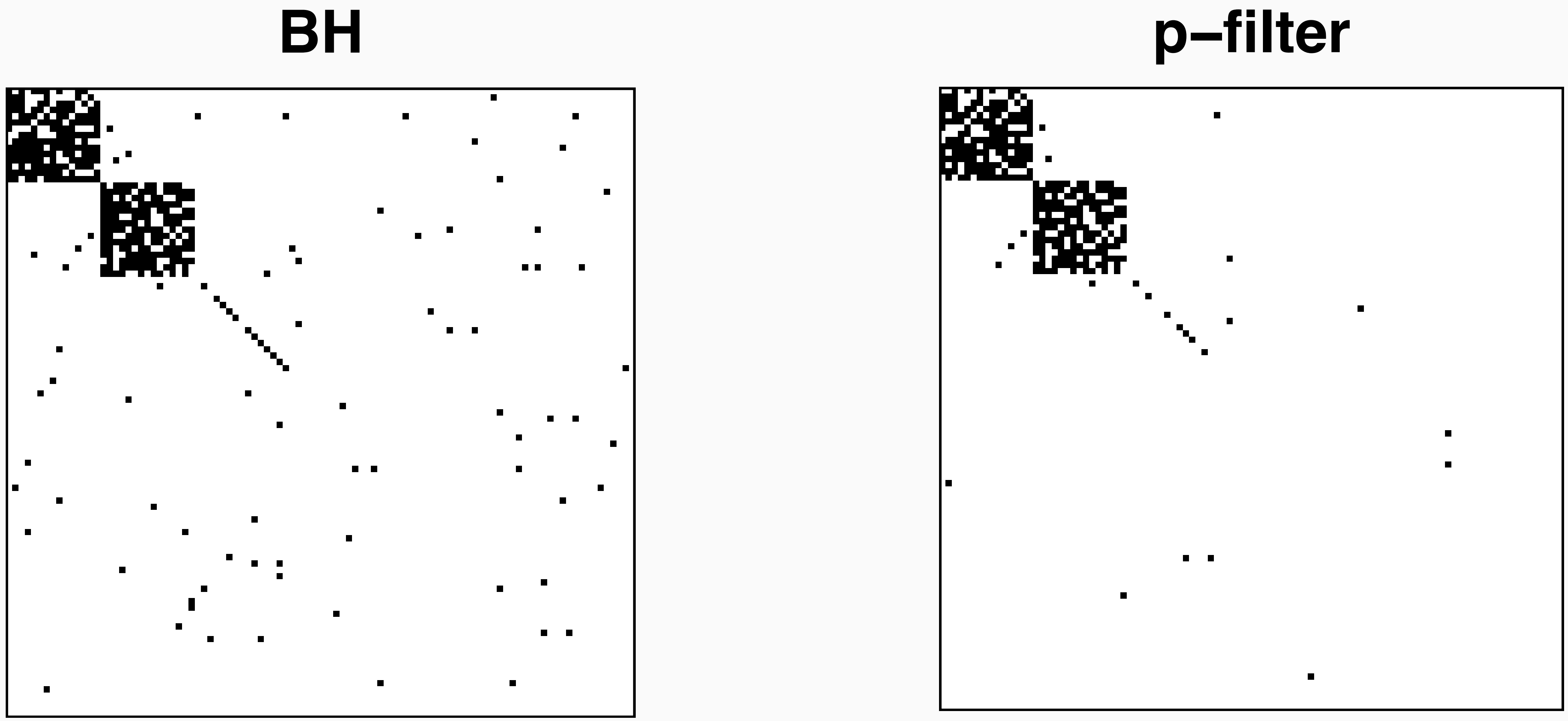
White (nulls) ~ N (0 , 1)
Black (non-nulls) ~ N(m , 1) for some m > 0

Barber-Ramdas '16



Target FDR = 0.2

Barber-Ramdas '16



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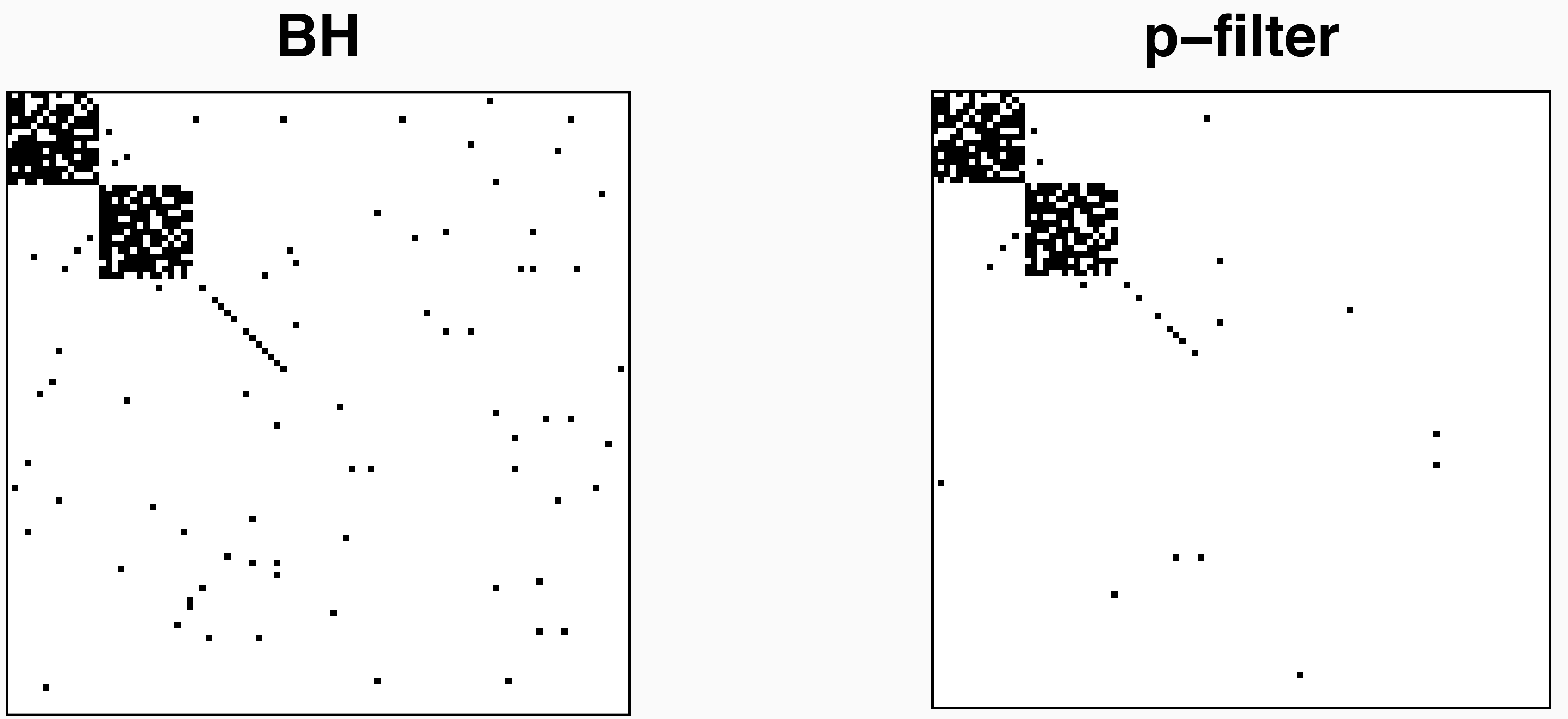

Target FDR = 0.2

3 partitions (rows, columns, entries)
Each target FDR = 0.2.

Barber-Ramdas '16

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We integrate all of the above in one framework.

(essentially "p-filter on steroids")

Benjamini-Hochberg controls FDR under independence and positive dependence.

$$\widehat{k} := \max\left\{k : P_{(k)} \leq \frac{\alpha \cdot k}{n}\right\}$$

$P_{(k)} = k\text{-th smallest value among the set of } P_i.$

$$\mathrm{FDR} := \mathbb{E}\left[\frac{\sum_{i \in \mathcal{H}_0} \mathbf{1}(i \in \mathcal{R})}{\sum_{i} \mathbf{1}(i \in \mathcal{R})}\right]$$

Benjamini-Hochberg '95

Prior-weighted BH controls FDR
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$$\widehat{k} := \max\left\{k : Q_{(k)} \leq \frac{\alpha \cdot k}{n}\right\}$$

$Q_{(k)}$ = k-th smallest value among the set of $Q_i := P_i / w_i$.

Genovese-Wasserman-Roeder '06

Penalty-weighted BH controls weighted-FDR under independence and positive dependence.

$$\widehat{k} := \max\left\{k : P_{(k)} \leq \frac{\alpha \cdot U_{(k)}}{n}\right\}$$

$U_{(k)}$ = sum of penalty weights of smallest k p-values.

$$\mathrm{FDR}_u := \mathbb{E}\left[\frac{\sum_{i \in \mathcal{H}_0} u_i \mathbf{1}(i \in \mathcal{R})}{\sum_i u_i \mathbf{1}(i \in \mathcal{R})}\right]$$

Benjamini-Yekutieli '97

Prior+penalty-weighted BH controls weighted-FDR under independence and positive dependence.

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$U_{(k)}$ = sum of penalty weights of smallest k p-values.

Blanchard-Roquain '08

Null-proportion adaptivity for BH controls FDR only under independence.

$$\widehat{k} := \max\left\{k : P_{(k)} \leq \frac{\alpha \cdot k}{\widehat{\pi}_0 \cdot n}\right\}$$

$$\widehat{\pi}_0 = \frac{1 + \sum_i \mathbf{1}\{P_i > \lambda\}}{n(1-\lambda)}$$

$$\mathbb{E}\left[\frac{1}{\widehat{\pi}_0}\right] \leq \frac{n}{|\mathcal{H}_0|}$$

Schweder-Spjotvoll '72, Storey et al. '03, Benj-Kriegier-Yeku '06

Null-proportion adaptivity for Prior+penalty-weighted BH controls weighted-FDR only under independence.

$$\widehat{k} := \max\left\{k : Q_{(k)} \le \frac{\alpha \cdot U_{(k)}}{\widehat{\pi}_0 \cdot n}\right\}$$

$$\widehat{\pi}_0 = \frac{\max_j u_j w_j + \sum_i u_i w_i \cdot \mathbf{1}\{P_i > \lambda\}}{n(1-\lambda)}$$

$$\mathbb{E}\left[\frac{1}{\widehat{\pi}_0}\right] \le \frac{n}{\sum_{i \in \mathcal{H}^0} u_i w_i}$$

New!

Reshaped BH controls FDR under arbitrary dependence.

$$\widehat{k} := \max\left\{k : P_{(k)} \leq \frac{\alpha \cdot \beta(k)}{n}\right\}$$

$$\beta(u) = \int_0^u x \; d\nu(x) \quad \text{where} \quad \nu([0,n]) = 1$$

Benjamini-Yekutieli '01, Blanchard-Roquain '08, Sarkar '08

Reshaped prior+penalty-weighted BH controls weighted-FDR under arbitrary dependence.

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New!

LEMMA 1 (Super-uniformity lemma). *Let* $f : [0,1]^n \mapsto [0,\infty)$ *be arbitrary, and let index* $i \in \mathcal{H}^0$ *refer to some null hypothesis.*

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(b) *If f is nonincreasing, then under positive dependence and super-uniformity, we have*

$$\mathbb{E}\left[\frac{\mathbf{1}\{P_i \le f(P)\}}{f(P)}\right] \le 1.$$

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(c) *For any constant $c > 0$ and any non-negative functions $f, \widetilde{f}$, under arbitrary dependence and super-uniformity, we have*

$$\mathbb{E}\left[\frac{\mathbf{1}\left\{P_i \leq c\beta_1(f(P))\beta_2(\widetilde{f}(P))\right\}}{cf(P)\widetilde{f}(P)}\right] \leq 1 \qquad \textit{for all pairs } \beta_1, \beta_2 \in \beta(\mathcal{V}).$$

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LEMMA 1 (Super-uniformity lemma). *Let $f : [0,1]^n \mapsto [0,\infty)$ be arbitrary, and let index $i \in \mathcal{H}^0$ refer to some null hypothesis.*

(a) If f is nonincreasing, has range $[0,1]$, and satisfies the LOOP condition (3.6), then under independence and uniformity, we have

$$\mathbb{E}\left[\frac{\mathbf{1}\{P_i \leq f(P)\}}{f(P)} \,\middle|\, P^{-i}\right] = 1, \quad \textit{and hence} \quad \mathbb{E}\left[\frac{\mathbf{1}\{P_i \leq f(P)\}}{f(P)}\right] = 1.$$

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The Simes test controls type-I error for the global null under positive dependence.

$$\text{Simes}(P) := \min_{1 \leq k \leq n} \frac{P_{(k)} \cdot n}{k}$$

We test if $\text{Simes}(P) \leq \alpha$, which happens iff $\widehat{k}_{BH} \geq 1$.

Simes '86

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It is uniformly distributed if P is entirely null.

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The reshaped prior-weighted Simes test controls type-I error for the global null under arbitrary dependence.

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Suppose we want to control the
penalty-weighted group-FDR for a single partition :

$$\underbrace{\overbrace{P_1}^{\text{weight } w_1^{(1)}}, \dots, \overbrace{P_{n_1}}^{\text{weight } w_{n_1}^{(1)}}}_{\text{Group } A_1, \text{ weights } u_1^{(2)}, w_1^{(2)}}, \dots, \underbrace{\overbrace{P_{n_1+\dots+n_{G-1}+1}}^{\text{weight } w_{n_1+\dots+n_{G-1}+1}^{(1)}}, \dots, \overbrace{P_n}^{\text{weight } w_n^{(1)}}}_{\text{Group } A_G, \text{ weights } u_G^{(2)}, w_G^{(2)}}$$

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$$\mathrm{gFDR}_{u^{(2)}} := \mathbb{E}\left[\frac{\sum_{g \in \mathcal{H}_0^G} u_g^{(2)} \mathbf{1}(g \in \mathcal{R}_G)}{\sum_g u_g^{(2)} \mathbf{1}(g \in \mathcal{R}_G)}\right]$$

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Solution : Calculate Simes p-value of each group, and then run BH on the Simes p-values.

New!

When we have **multiple partitions**, we would like to have "internally consistent" rejections, (also known as consonance+coherence) :

Barber-Ramdas '16

When we have **multiple partitions**, we would like to have "<u>internally consistent</u>" rejections, (also known as consonance+coherence) :

For every partition,

- Each rejected group should contain at least one rejected element.
- Each rejected element should be contained in some rejected group.

Barber-Ramdas '16

Eg: let's see what happens if we have **two partitions**, the finest one (each element is a group), and a coarser one, we want to control elementwise FDR and group FDR :

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$$\alpha_{\text{indiv}} = 0.1$$
$$\alpha_{\text{group}} = 0.2$$

						Simes p−value
Group 1	0.03	0.01	0.18	0.04	0.08	0.05
Group 2	0.05	0.11	0.06	0.01	0.89	0.05
Group 3	0.14	0.12	0.58	0.11	0.11	0.18
Group 4	0.88	0.24	0.09	0.66	0.45	0.45

Barber-Ramdas '16

Running BH+Simes on each partition separately might lead to "contradictory" findings.

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Naively intersecting the two sets of findings may control *neither* elementwise *nor* group *FDR.*

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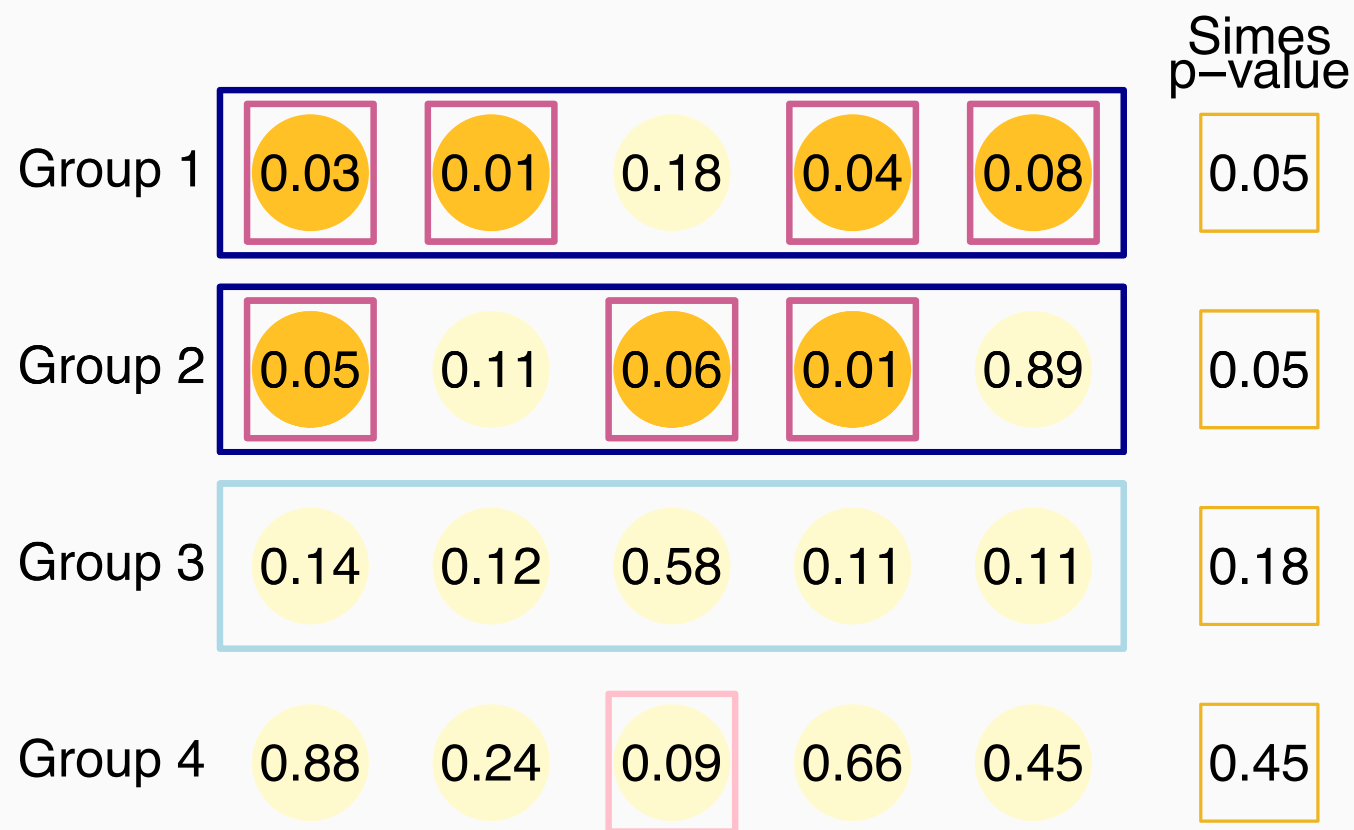

Barber-Ramdas '16

$$\underbrace{\overbrace{P_1}^{u_1^{(1)},w_1^{(1)}},\ldots,\overbrace{P_{n_1}}^{u_{n_1}^{(1)},w_{n_1}^{(1)}}}_{\text{Group 1, weights } u_1^{(2)},w_1^{(2)}},\ldots,\underbrace{\overbrace{P_{n_1+\cdots+n_{G-1}+1}}^{\text{weights ...}},\ldots,\overbrace{P_{n-\ell_2}}^{\text{weights ...}}}_{\text{Group } G\text{, weights } u_G^{(2)},w_G^{(2)}} \Bigg| \underbrace{\overbrace{P_{n-\ell_2+1}}^{\text{weights ...}},\ldots,\overbrace{P_n}^{u_n^{(1)},w_n^{(1)}}}_{\text{Leftover group } L^{(2)}}$$

New!

Our unifying framework can handle

$$\underbrace{\overbrace{P_1}^{u_1^{(1)},w_1^{(1)}} \;, \ldots, \; \overbrace{P_{n_1}}^{u_{n_1}^{(1)},w_{n_1}^{(1)}}}_{\text{Group 1, weights } u_1^{(2)},w_1^{(2)}} \;, \ldots, \underbrace{\overbrace{P_{n_1+\cdots+n_{G-1}+1}}^{\text{weights ...}}, \ldots, \; \overbrace{P_{n-\ell_2}}^{\text{weights ...}}}_{\text{Group } G\text{, weights } u_G^{(2)},w_G^{(2)}} \;\Big|\; \underbrace{\overbrace{P_{n-\ell_2+1}}^{\text{weights ...}}, \ldots, \; \overbrace{P_n}^{u_n^{(1)},w_n^{(1)}}}_{\text{Leftover group } L^{(2)}}$$

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- consisting of possibly-overlapping groups
- with group-level prior+penalty weights, along with

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Using the p-filter algorithm results in

- an internally consistent set of rejections,
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- under independence*, positive or arbitrary** dependence.

New!

Algorithm 1 The `p-filter` for multi-layer FDR control

Input: A vector of p-values $P \in [0,1]^n$;
M possibly incomplete partitions of possibly overlapping groups;
M target FDR levels $\alpha_1, \dots, \alpha_M$;
M sets of prior weights and/or penalty weights, one pair of weights for each group in each partition;
M thresholds for adaptive null proportion estimation $\lambda_1, \dots, \lambda_M$.

Initialize: Set $k_m = G_m$, and $\widehat{\pi}_m$ as in definition (7.2).

repeat

for $m = 1, \dots, M$ **do**

Update the mth vector: defining $\widehat{\mathcal{S}}_m(\vec{k})$ as in equation (7.4), let

$$k_m \leftarrow \max\left\{k'_m \in [0, G_m] : \sum_{g \in \widehat{\mathcal{S}}_m(k_1,\dots,k_{m-1},k'_m,k_{m+1},\dots,k_M)} u_g^{(m)} \geq k'_m\right\} \tag{7.8}$$

end for

until the vectors $k_1, \dots, k_M$ are all unchanged for one full cycle.

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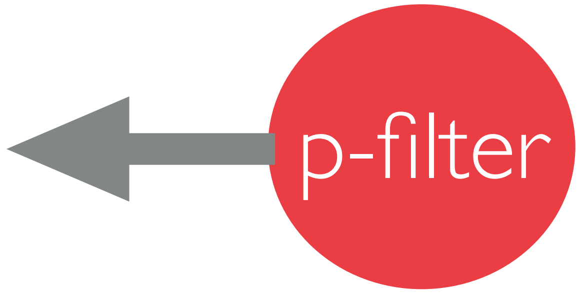
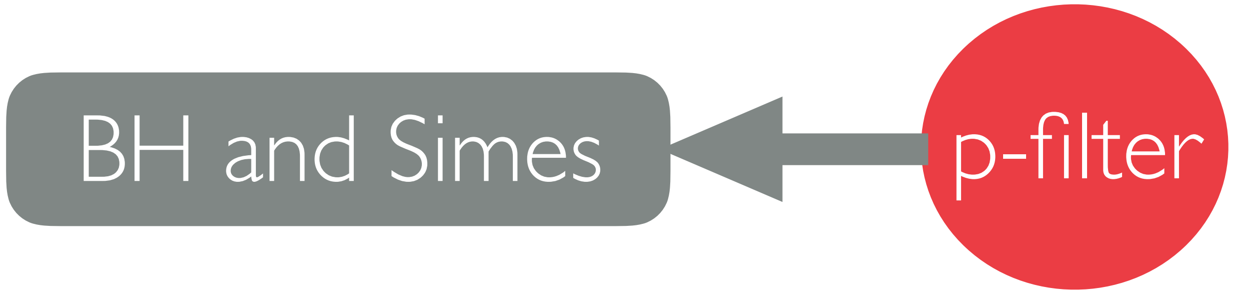
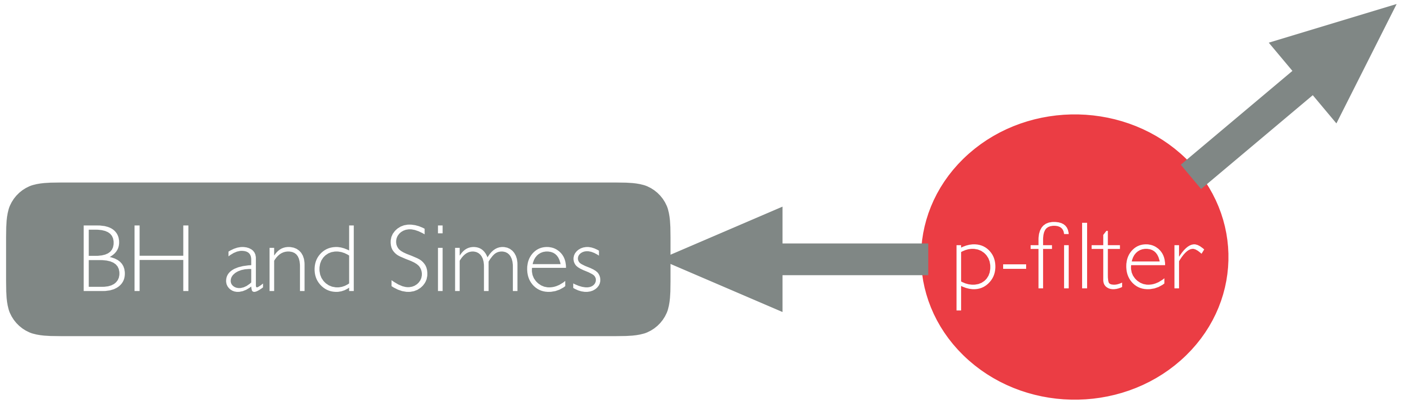
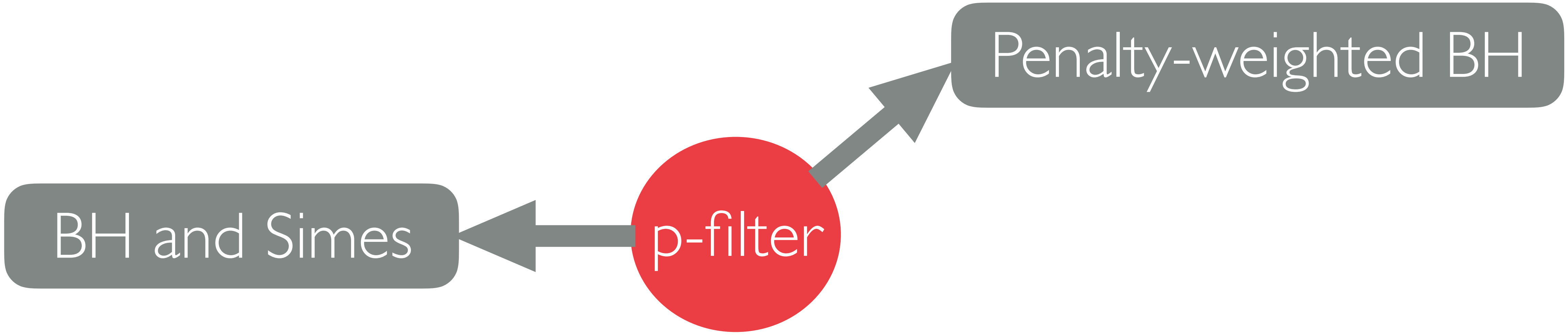
Theorem : The algorithm returns a set of rejected hypotheses and groups that are internally consistent, and weighted group FDR is simultaneously controlled for all partitions, under independence, positive dependence or arbitrary dependence.

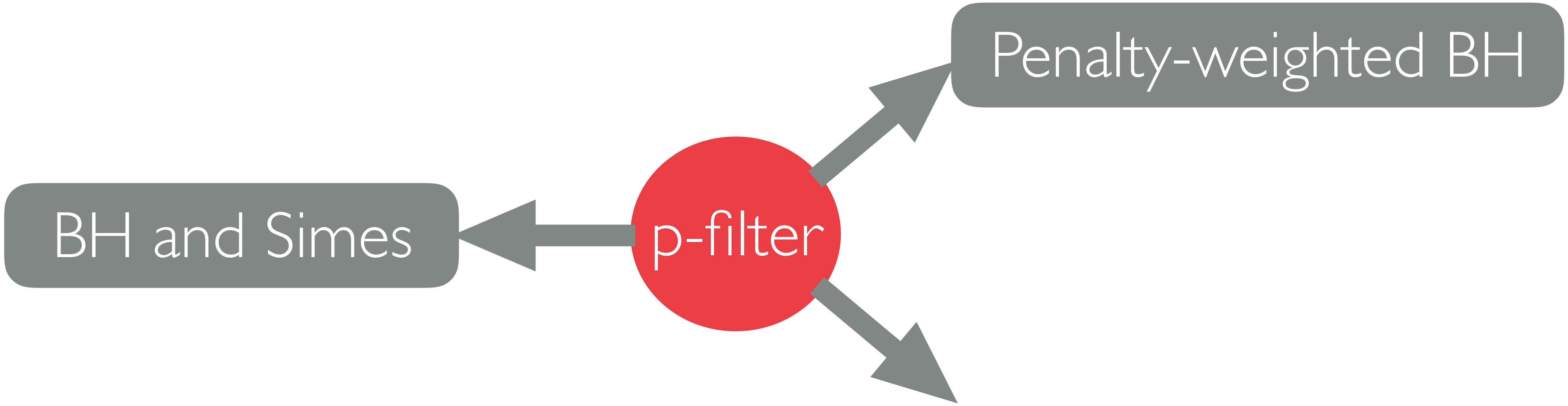

p-filter

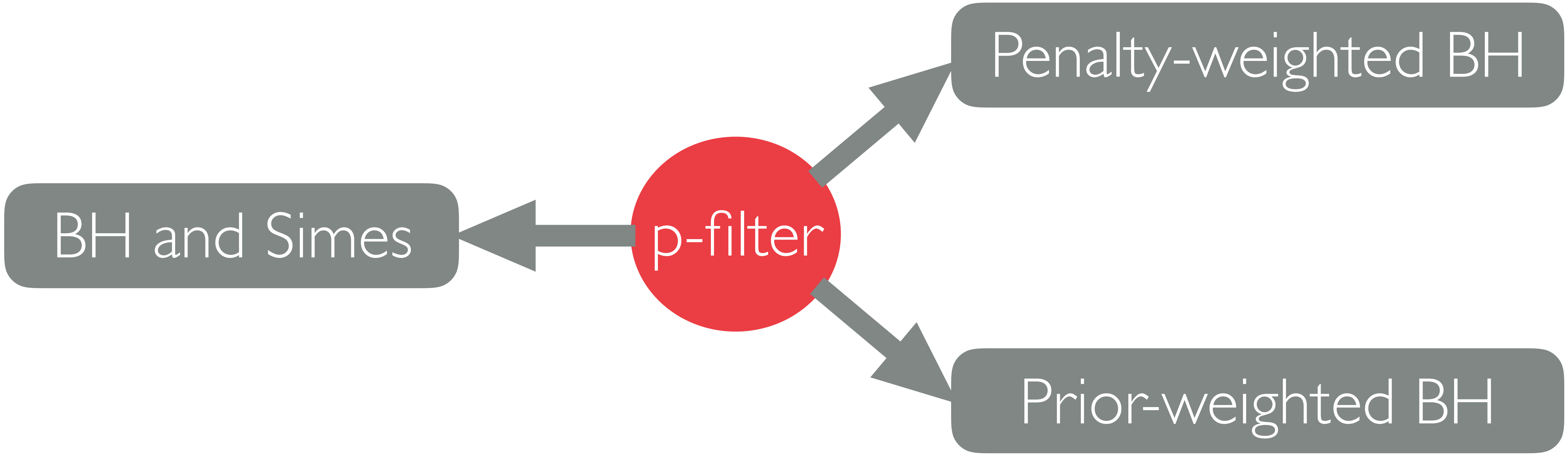

p-filter


BH and Simes
p-filter

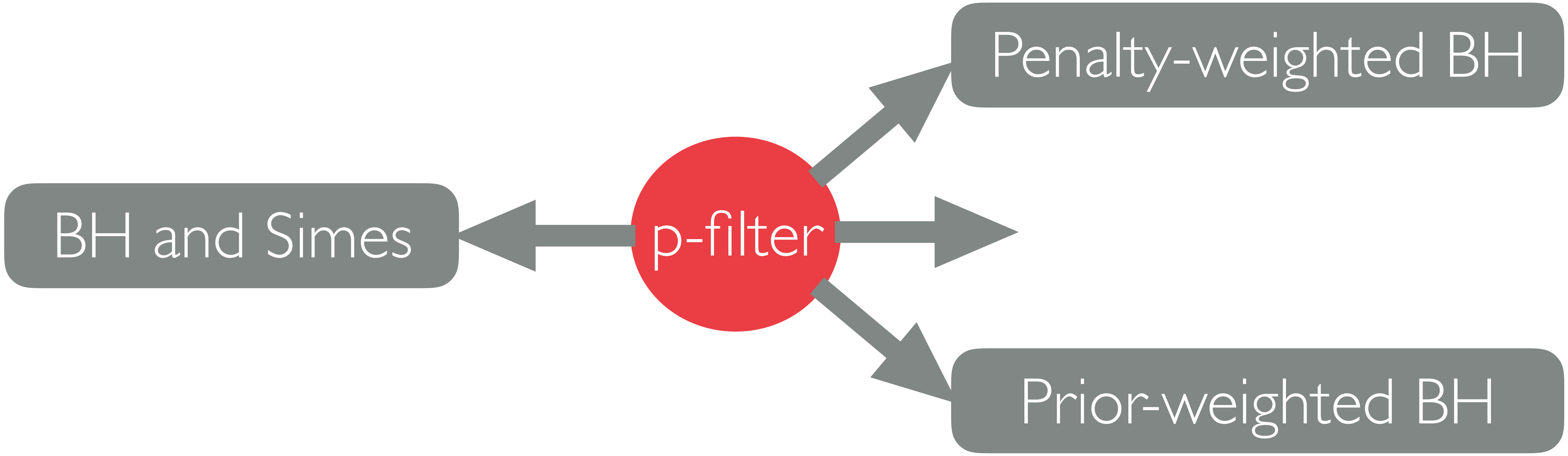

BH and Simes
p-filter

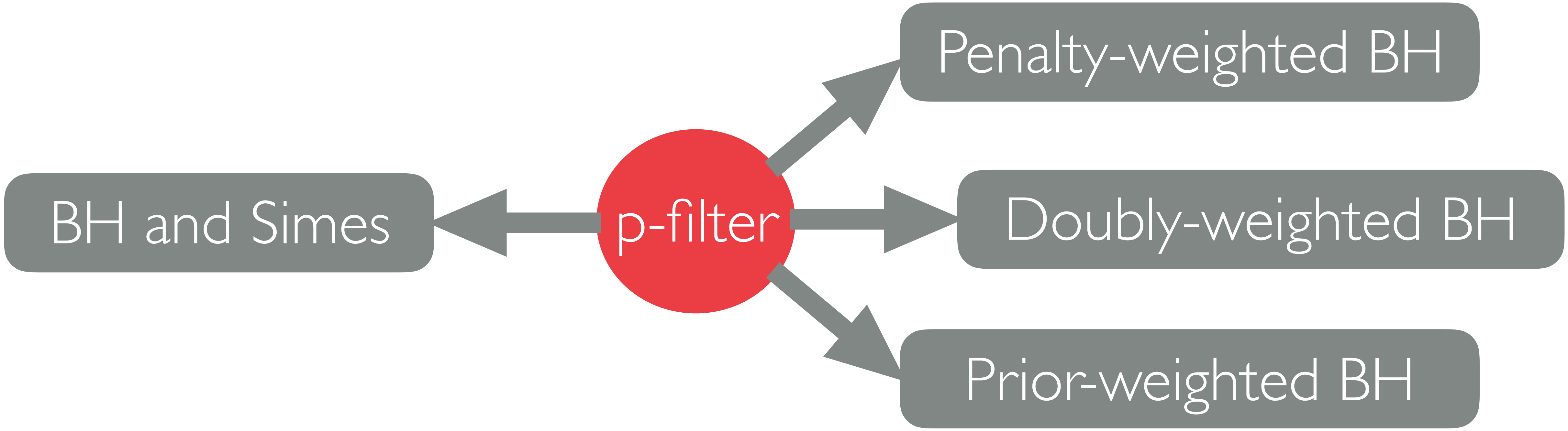

Penalty-weighted BH
BH and Simes
p-filter


Penalty-weighted BH
BH and Simes
p-filter

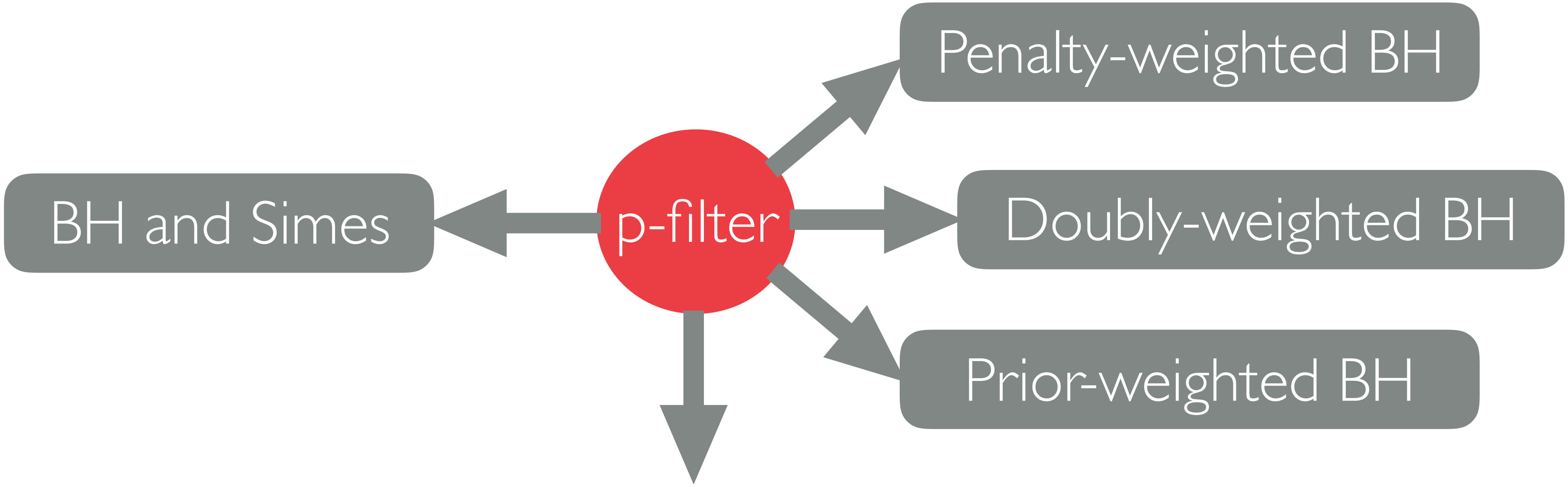


Penalty-weighted BH
BH and Simes
p-filter
Prior-weighted BH

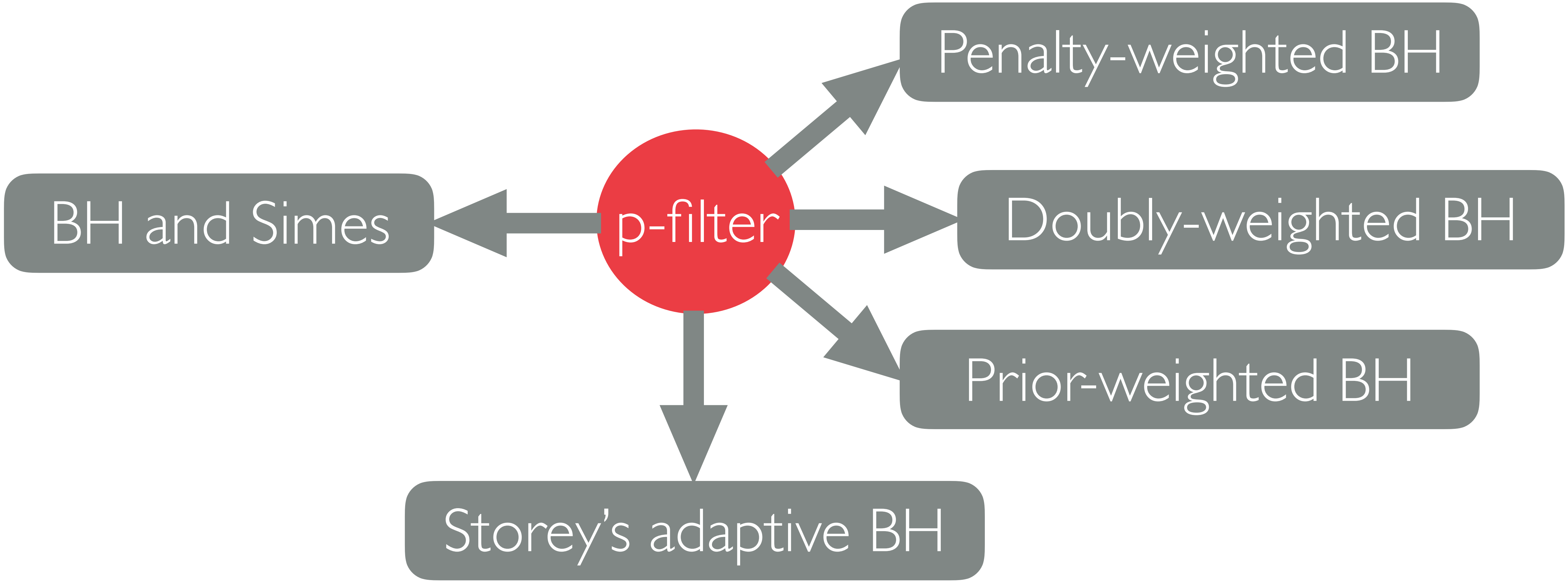

Penalty-weighted BH
BH and Simes
p-filter
Prior-weighted BH

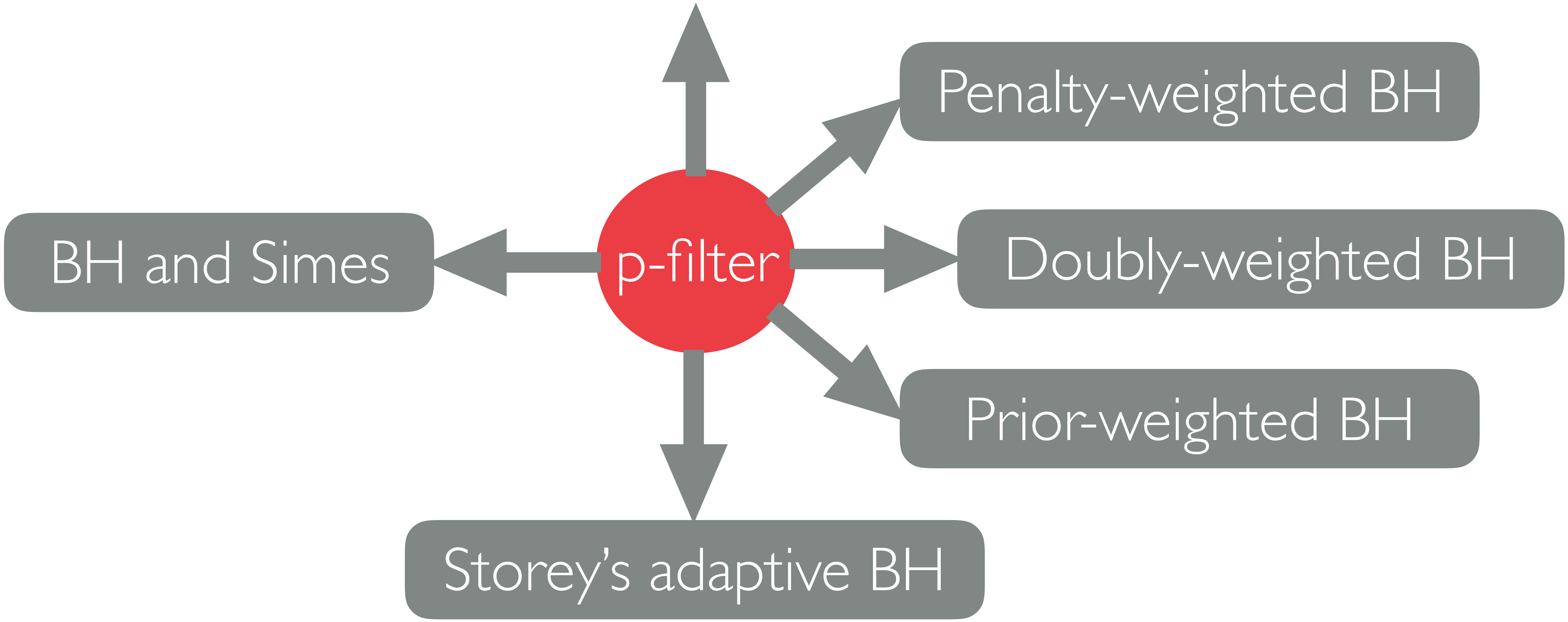


Penalty-weighted BH
BH and Simes
p-filter
Doubly-weighted BH
Prior-weighted BH



Penalty-weighted BH
BH and Simes
p-filter
Doubly-weighted BH
Prior-weighted BH


p-filter
BH and Simes
Penalty-weighted BH
Doubly-weighted BH
Prior-weighted BH
Storey's adaptive BH


Penalty-weighted BH
BH and Simes
p-filter
Doubly-weighted BH
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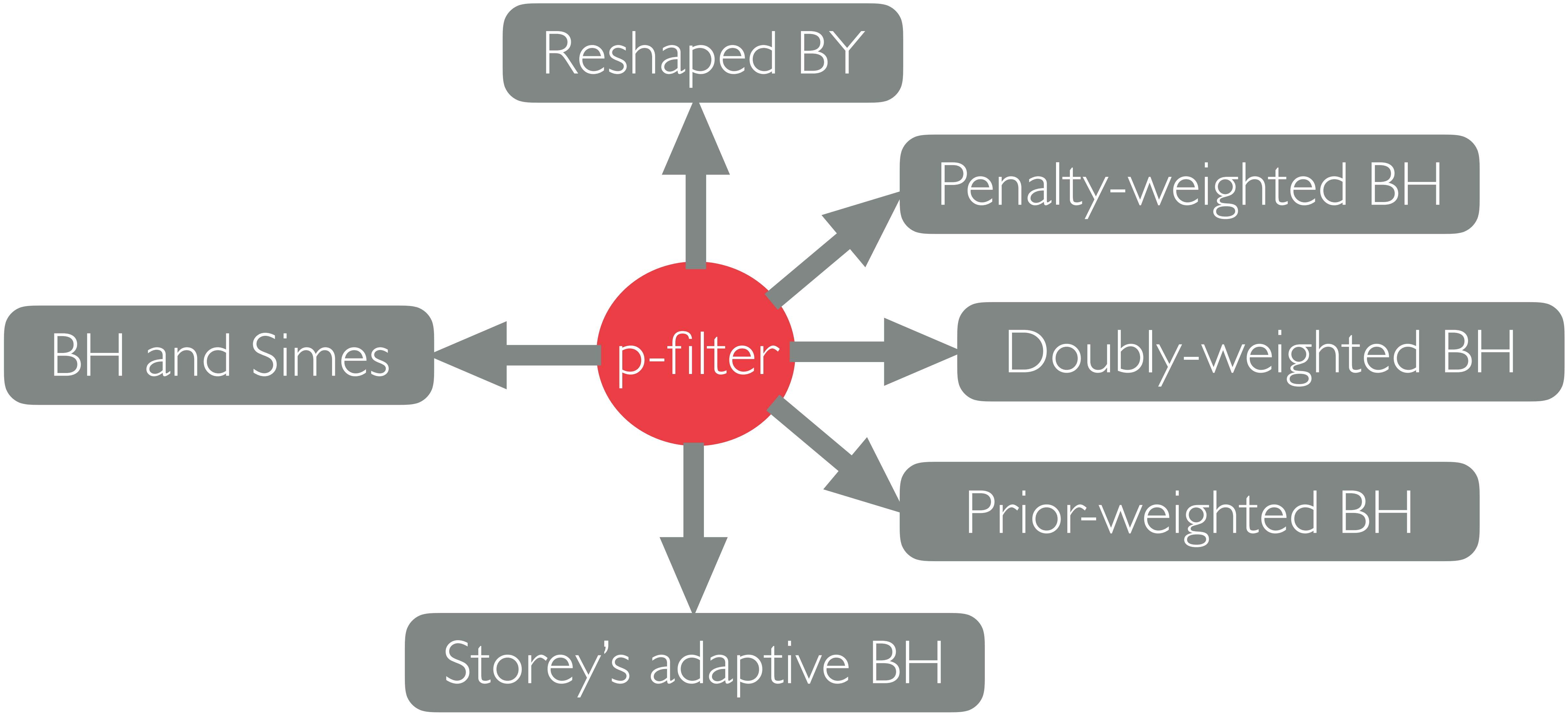
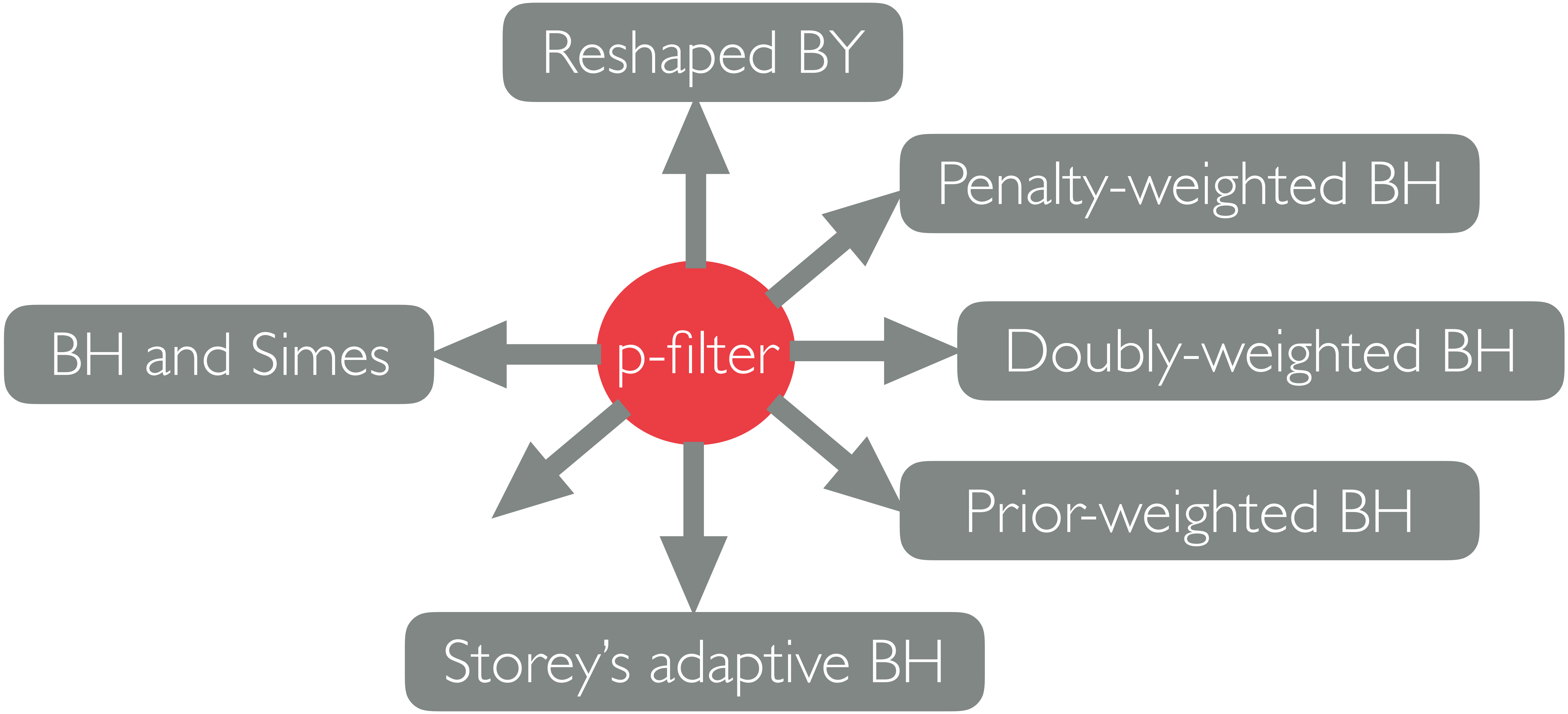


Reshaped BY
Penalty-weighted BH
BH and Simes
p-filter
Doubly-weighted BH
Prior-weighted BH
Storey's adaptive BH



Reshaped BY
Penalty-weighted BH
BH and Simes
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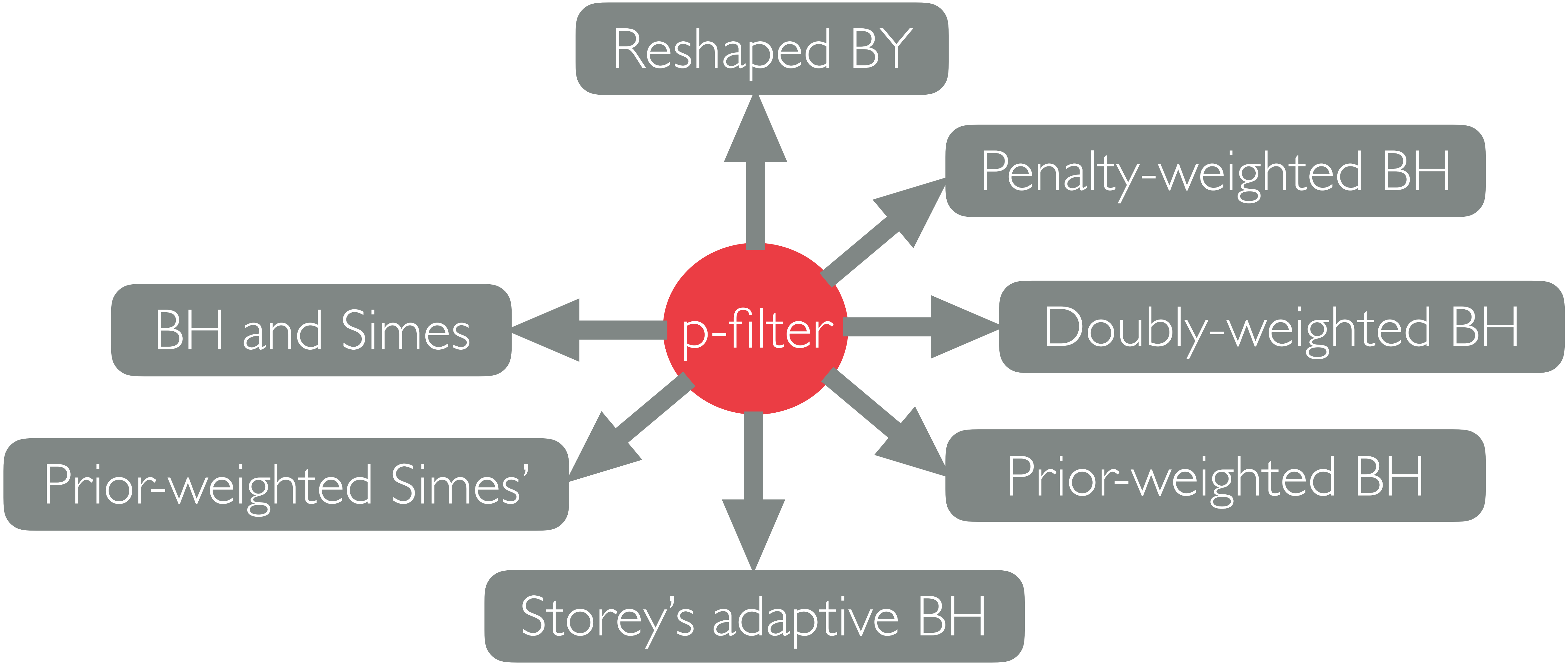
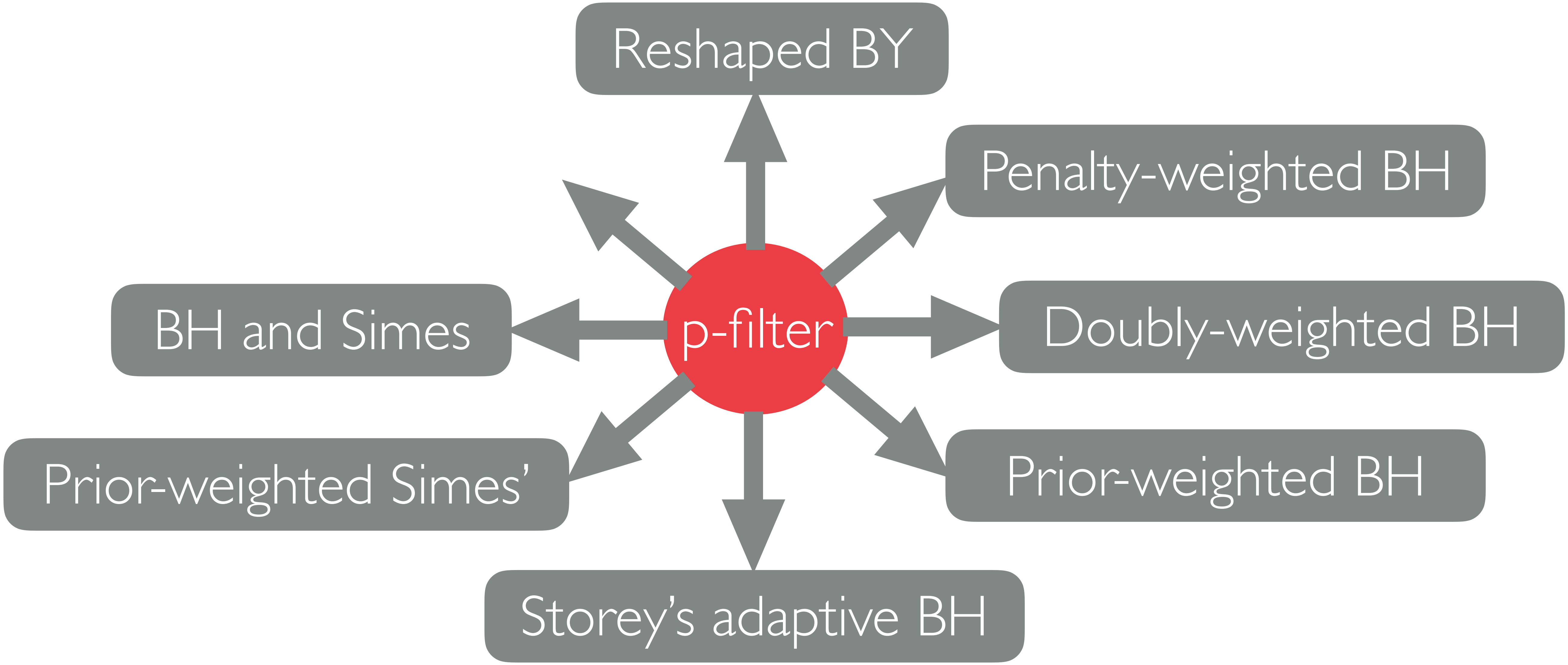

Reshaped BY
Penalty-weighted BH
BH and Simes
p-filter
Doubly-weighted BH
Prior-weighted Simes'
Prior-weighted BH
Storey's adaptive BH



Reshaped BY
Penalty-weighted BH
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p-filter
Doubly-weighted BH
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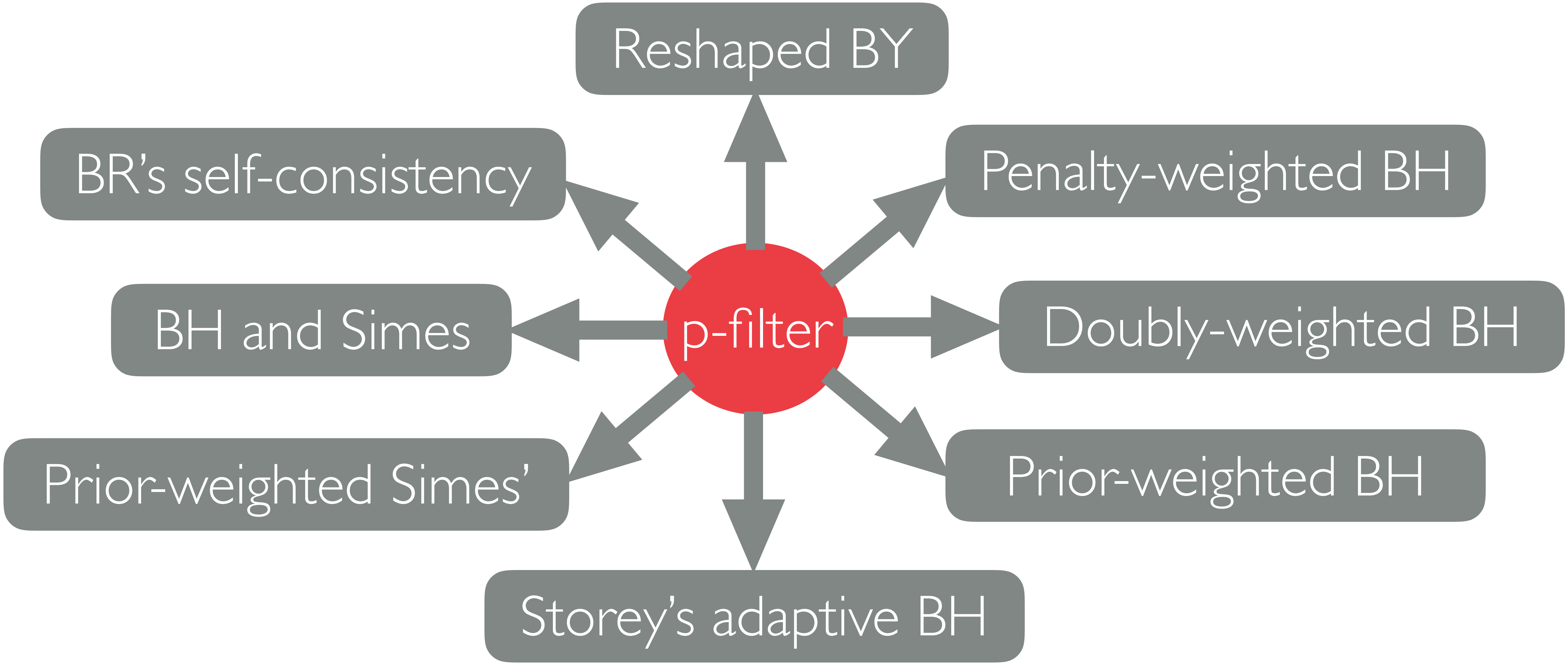
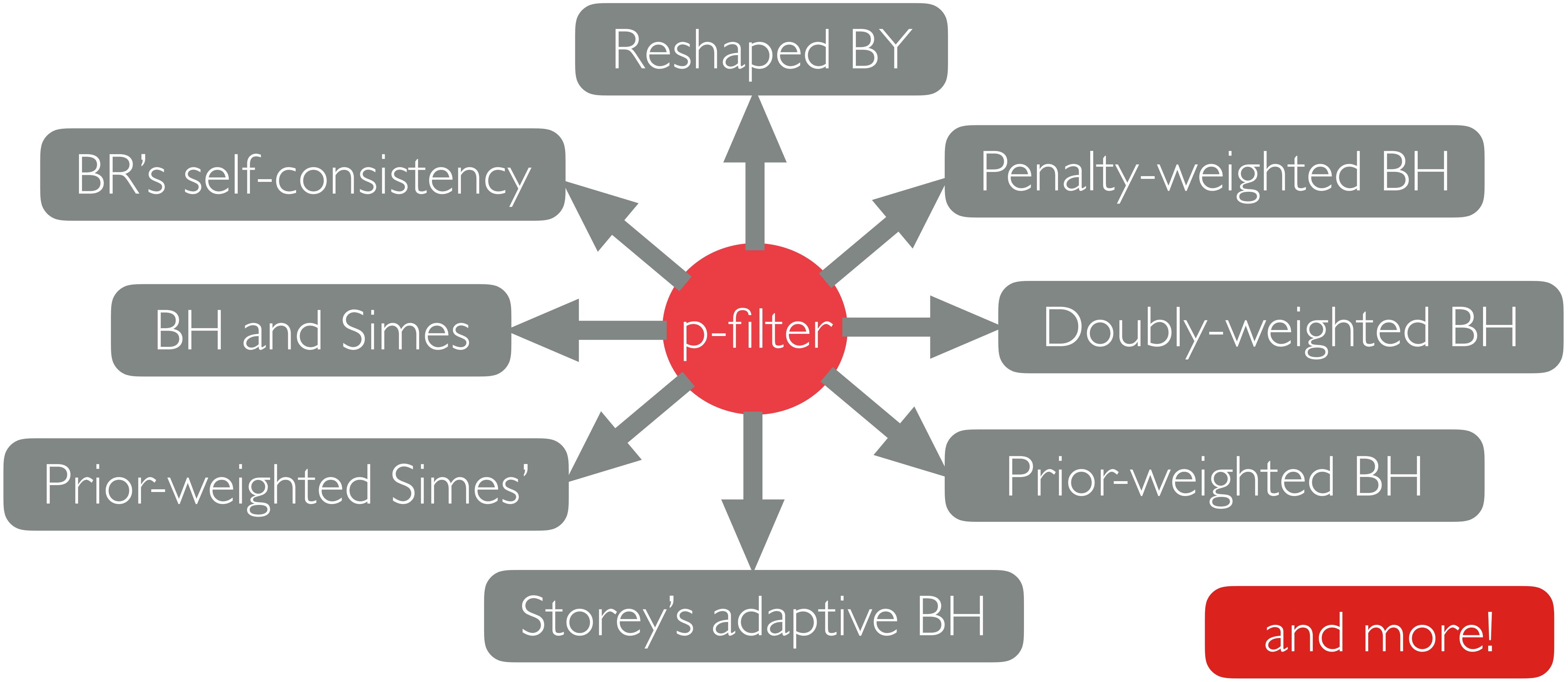
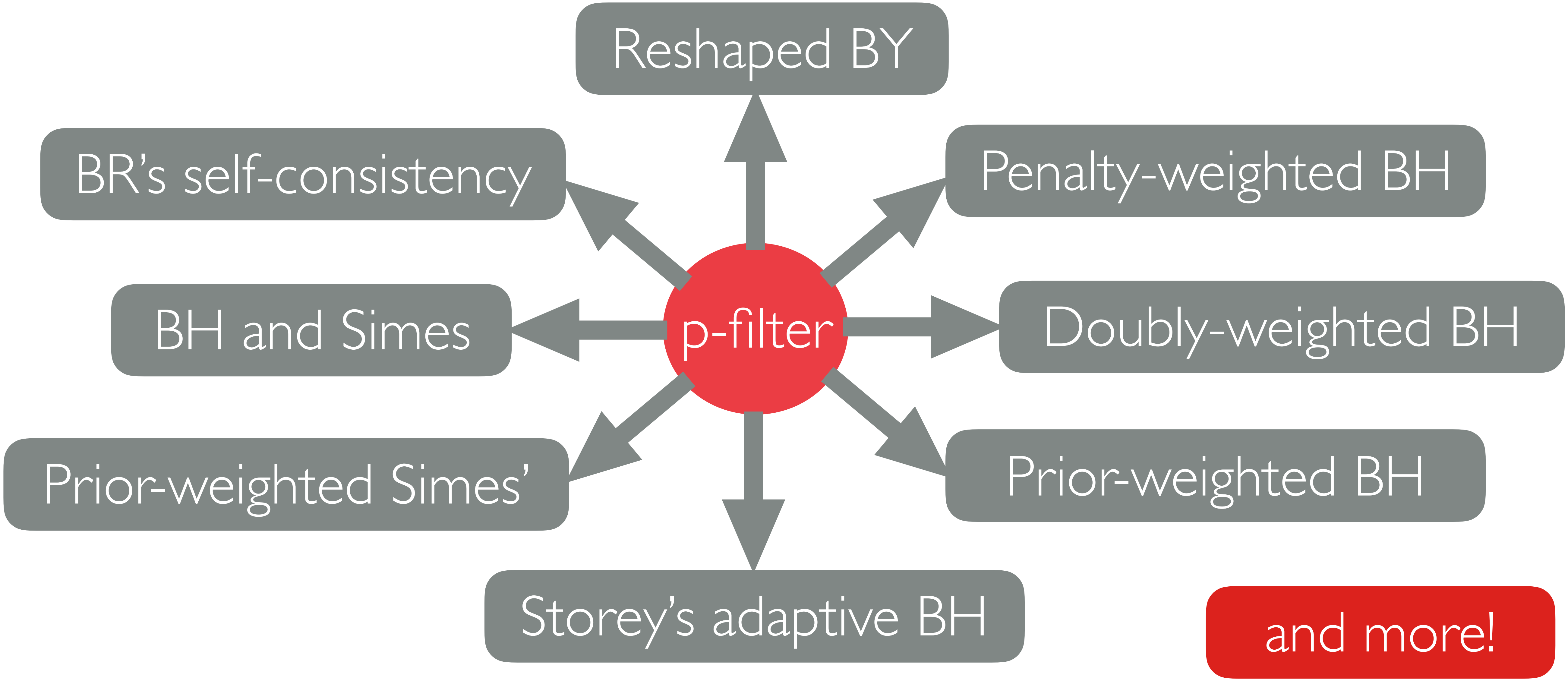
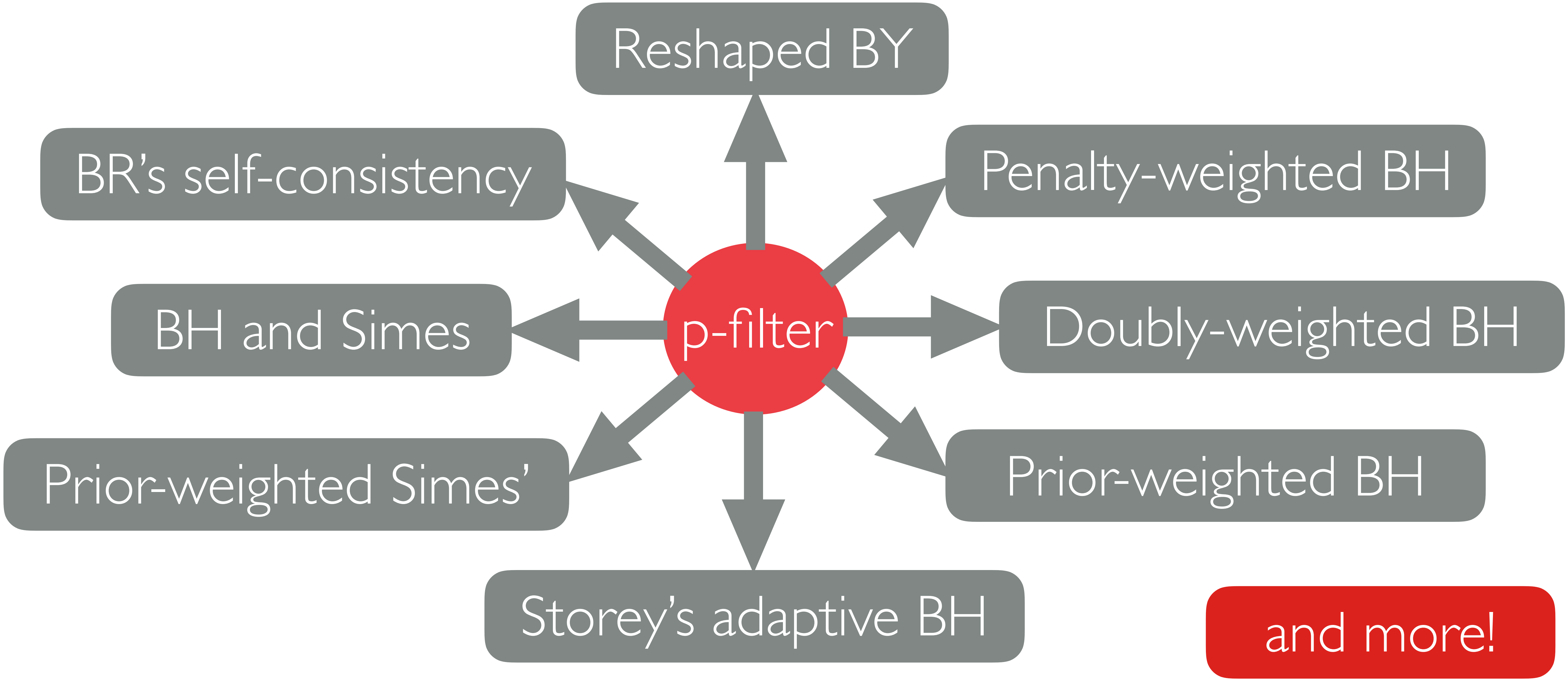

Reshaped BY
BR's self-consistency
Penalty-weighted BH
BH and Simes
p-filter
Doubly-weighted BH
Prior-weighted Simes'
Prior-weighted BH
Storey's adaptive BH


Reshaped BY
BR's self-consistency
Penalty-weighted BH
BH and Simes
p-filter
Doubly-weighted BH
Prior-weighted Simes'
Prior-weighted BH
Storey's adaptive BH
and more!



A unified treatment of multiple testing
with prior knowledge (on Arxiv)



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Aaditya Ramdas
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