Web-based Supplementary Materials for

"False Discovery Rate Estimation for Frequentist Pharmacovigilance Signal Detection Methods"

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Web Appendix A: Proof of the lemma

Lemma: If $P^* = 1 - 2|P - \frac{1}{2}|$ where P is a random variable defined on $[0, 1]$ whose pdf is

$$f(p) = \pi_0\{\pi_{0*} + (1 - \pi_{0*})f_{1*}(p)\} + (1 - \pi_0)f_1(p)$$

and where f_{1*} and f_1 are respectively non-decreasing and non-increasing differentiable convex functions, then P^* has a non increasing pdf.

Proof: Let F_{P*} and F denote the cdf of P^* and P.

$$\begin{aligned} F_{P*}(p^*) &= \Pr(P^* \leq p^*) \\ &= \Pr(P^* \leq p^* | P \leq \tfrac{1}{2}) \Pr(P \leq \tfrac{1}{2}) + \Pr(P^* \leq p^* | P > \tfrac{1}{2}) \Pr(P > \tfrac{1}{2}). \end{aligned}$$

For $P \in [0, \frac{1}{2}]$, $P^* = 2P$ and for $P \in [\frac{1}{2}, 1]$, $P^* = 2(1 - P)$.

Then,

$$\begin{aligned} F_{P*}(p^*) &= \Pr(2P \leq p^* \cap P \leq \tfrac{1}{2}) + \Pr\{2(1 - P) \leq p^* \cap P > \tfrac{1}{2}\} \\ &= \Pr(P \leq \tfrac{p^*}{2}) + \Pr(P \geq 1 - \tfrac{p^*}{2}) \\ &= F(\tfrac{p^*}{2}) + 1 - F(1 - \tfrac{p^*}{2}). \end{aligned}$$

It implies that

$$f_{P^*}(p^*) = \tfrac{1}{2}f(\tfrac{p^*}{2}) + \tfrac{1}{2}f(1 - \tfrac{p^*}{2})$$

and its derivative is

$$f'_{P^*}(p^*) = \tfrac{1}{4}f'(\tfrac{p^*}{2}) - \tfrac{1}{4}f'(1 - \tfrac{p^*}{2})$$

which is always non-positive since f is convex as a positive linear combination of convex functions. Thus f_{P*} is non-increasing.

In addition, the pdf of P can be expressed as:

$$f(p) = \pi_0\pi_{0*} + (1 - \pi_0\pi_{0*})f_{1P}(p)$$

which leads to:

$$\begin{aligned} f_{P^*}(p^*) &= \tfrac{1}{2}\{\pi_0\pi_{0*} + (1 - \pi_0\pi_{0*})f_{1P}(\tfrac{p^*}{2})\} + \tfrac{1}{2}\{\pi_0\pi_{0*} + (1 - \pi_0\pi_{0*})f_{1P}(1 - \tfrac{p^*}{2})\} \\ &= \pi_0\pi_{0*} + \tfrac{1}{2}(1 - \pi_0\pi_{0*})\{f_{1P}(\tfrac{p^*}{2}) + f_{1P}(1 - \tfrac{p^*}{2})\} \end{aligned}$$

Web Appendix B: Simulations

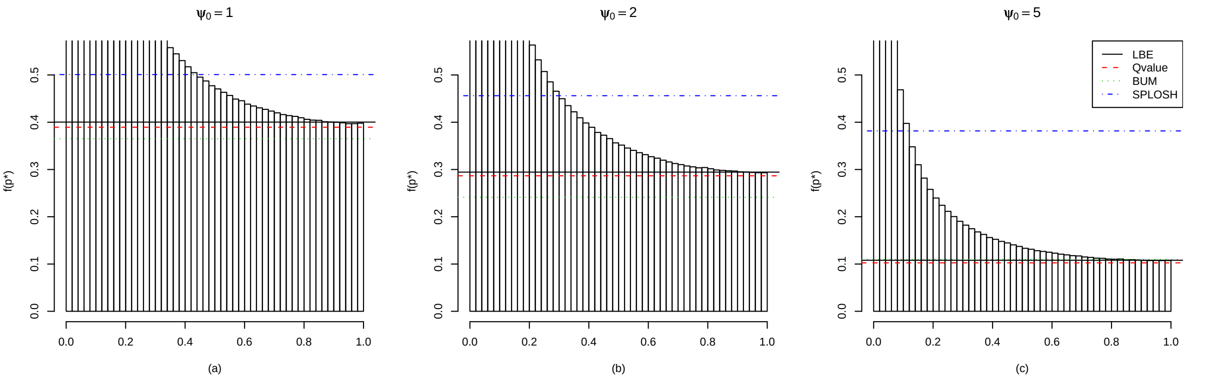

Figure 1: Marginal density histogram of the transformed P-values (P^*) obtained with RFET on the non-empty cells over the 500 generated datasets with the average estimates of $\pi_0\pi_0*$ obtained with LBE, Qvalue, BUM and SPLOSH.

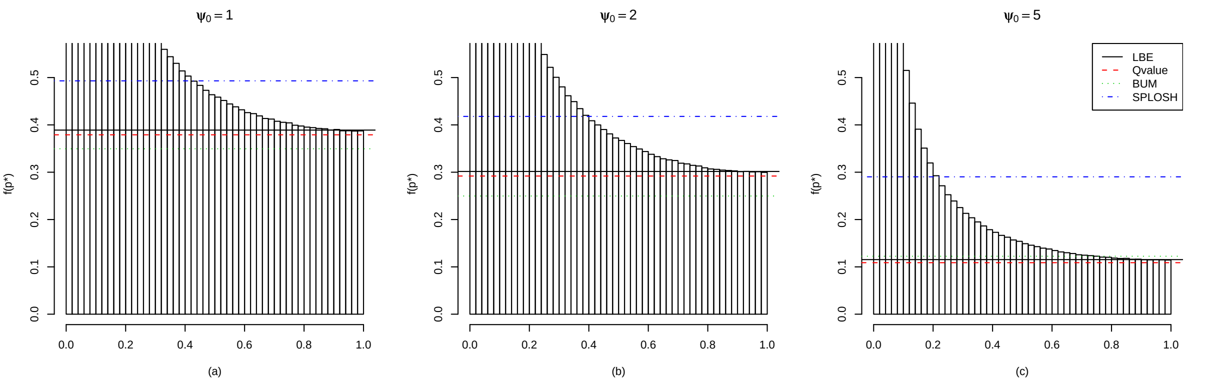

Figure 2: Marginal density histogram of the transformed P-values (P^*) obtained with ROR on the non-empty cells over the 500 generated datasets with the average estimates of $\pi_0\pi_0*$ obtained with LBE, Qvalue, BUM and SPLOSH.

Web Appendix C: Relative Bias

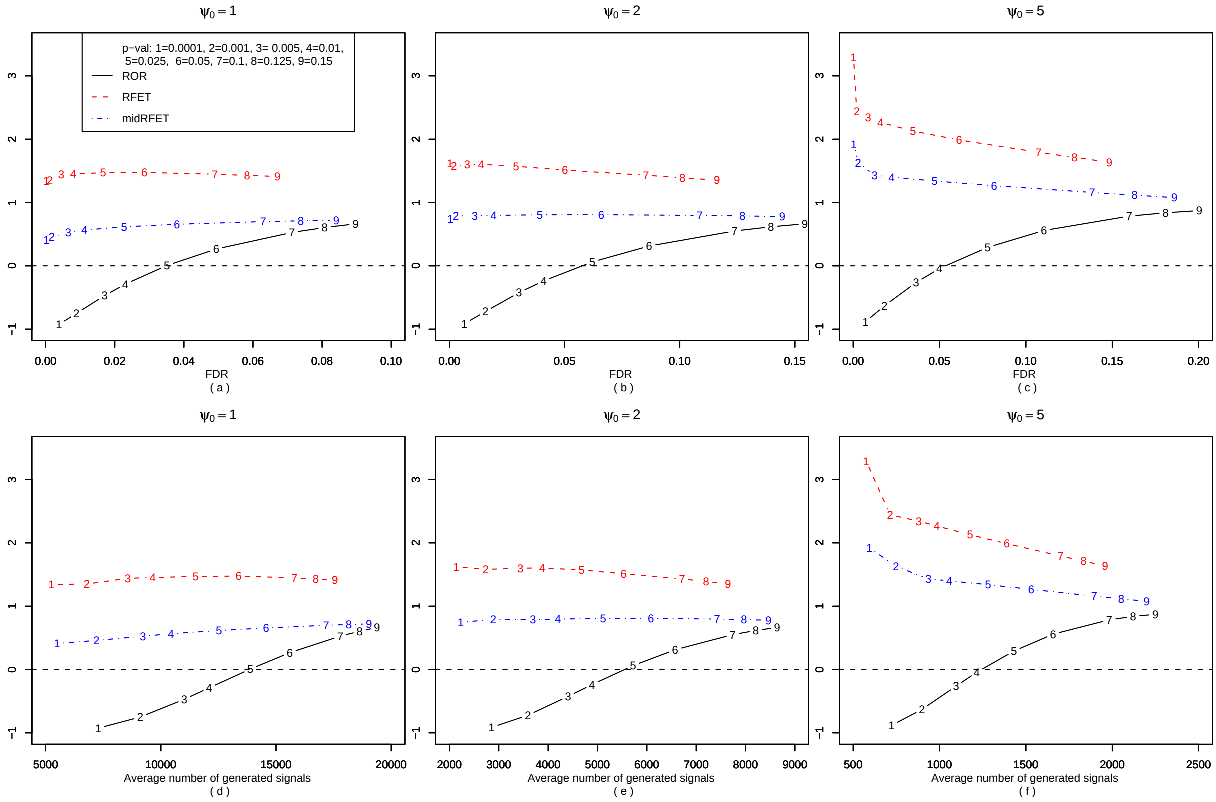

Figure 3: Relative bias for the FDR estimation in function of the FDR (a, b, c) or of the average number of generated signals (d, e, f). Results are presented for cells with $n_{ij} \geq 3$. The numbers on the curves indicate the results corresponding to the decision rules based on the P-values in the legend of Figure a.

Web Appendix D: Numerical results on the French Database

Table 1: The table above gives the number of generated signals (Sig.) and the FDR estimates ($\widehat{\text{FDR}}$) for several rejection regions of the form $[0,\gamma]$ resulting from the RFET, the midRFET and the ROR. Results are obtained with LBE and presented for the three null tested hypotheses ($\psi_0 = 1, 2$ and 5) and for cells with $n_{ij} \geq 1$ and $n_{ij} \geq 3$.

	RFET				midRFET				ROR	
	$n_{ij} \geq 1$		$n_{ij} \geq 3$		$n_{ij} \geq 1$		$n_{ij} \geq 3$		$n_{ij} \geq 3$	
γ	Sig.	$\widehat{\text{FDR}}$	Sig.	$\widehat{\text{FDR}}$	Sig.	$\widehat{\text{FDR}}$	Sig.	$\widehat{\text{FDR}}$	Sig.	$\widehat{\text{FDR}}$
$\boldsymbol{\psi_0 = 1}$										
0.0001	5630	0.001	5539	0.000	5942	0.001	5812	0.000	7680	0.000
0.0010	7594	0.008	7255	0.003	8201	0.007	7695	0.003	9395	0.002
0.0050	9922	0.029	9033	0.012	11058	0.026	9642	0.010	11137	0.008
0.0100	11519	0.051	10078	0.022	13142	0.043	10801	0.018	12194	0.015
0.0250	14692	0.099	11831	0.047	17453	0.081	12752	0.039	13946	0.033
0.0500	18542	0.157	13663	0.081	22638	0.125	14806	0.067	15585	0.058
0.1000	24358	0.239	16093	0.138	29846	0.190	17381	0.115	17797	0.102
$\boldsymbol{\psi_0 = 2}$										
0.0001	2399	0.002	2345	0.000	2522	0.002	2451	0.001	3221	0.000
0.0010	3174	0.012	3009	0.003	3439	0.012	3186	0.004	3910	0.003
0.0050	4231	0.047	3765	0.013	4751	0.045	4023	0.016	4712	0.014
0.0100	4915	0.080	4175	0.023	5673	0.075	4523	0.029	5156	0.026
0.0250	6407	0.154	4997	0.048	7820	0.136	5412	0.061	5891	0.058
0.0500	8287	0.238	5784	0.083	10422	0.204	6296	0.105	6652	0.102
0.1000	11266	0.350	6855	0.140	14534	0.293	7461	0.178	7663	0.177
$\boldsymbol{\psi_0 = 5}$										
0.0001	909	0.002	886	0.000	962	0.002	930	0.000	1214	0.000
0.0010	1208	0.018	1140	0.004	1304	0.018	1203	0.004	1453	0.003
0.0050	1590	0.067	1404	0.015	1773	0.066	1479	0.015	1695	0.013
0.0100	1832	0.117	1534	0.028	2118	0.112	1637	0.028	1865	0.024
0.0250	2370	0.227	1780	0.059	2899	0.204	1940	0.059	2123	0.052
0.0500	3068	0.350	2075	0.102	3935	0.301	2240	0.102	2362	0.093
0.1000	4227	0.508	2422	0.175	5681	0.417	2632	0.174	2714	0.162