

Text S1

For $k = 1, \dots, 22$ gut microbiota spp. groups with $j = 1, \dots, 16$ patterns, let the p-values of the patterns $j_{k,4}$, $j_{k,4}$ without day 120 ($j_{k,3}$), $j_{k,4}$ without days 30 and 120 ($j_{k,2}$), and $j_{k,4}$ without days 10, 30, and 120 ($j_{k,1}$), be denoted as $P_{j_{k,4}}$, $P_{j_{k,3}}$, $P_{j_{k,2}}$, and $P_{j_{k,1}}$, respectively (obtained using Tuke's method). These patterns are considered to be part of the pattern family j_k . We aim to test the following:

$$H_0 : \min (|\mu_{j_{k,4}}|, |\mu_{j_{k,3}}|, |\mu_{j_{k,2}}|, |\mu_{j_{k,1}}|) \geq 0.67$$

$$H_1 : \min (|\mu_{j_{k,4}}|, |\mu_{j_{k,3}}|, |\mu_{j_{k,2}}|, |\mu_{j_{k,1}}|) < 0.67$$

which corresponds to

$$H_0 : \{|\mu_{j_{k,4}}| \geq 0.67\} \cap \{|\mu_{j_{k,3}}| \geq 0.67\} \cap \{|\mu_{j_{k,2}}| \geq 0.67\} \cap \{|\mu_{j_{k,1}}| \geq 0.67\}$$

$$H_1 : \{|\mu_{j_{k,4}}| < 0.67\} \cup \{|\mu_{j_{k,3}}| < 0.67\} \cup \{|\mu_{j_{k,2}}| < 0.67\} \cup \{|\mu_{j_{k,1}}| < 0.67\}$$

Given an arbitrary significance level α^* , the following procedures are performed after finding a four time point pattern $j_{k,4}$ whose mean is significantly close to zero:

1. If $P_{j_{k,4}} < \alpha^*/2$, then $j_{k,3}$ is tested at significance level $\alpha^*/2$
2. If $P_{j_{k,3}} < \alpha^*/3$, then $j_{k,2}$ is tested at significance level $\alpha^*/3$
3. If $P_{j_{k,2}} < \alpha^*/4$, then $j_{k,1}$ is tested at significance level $\alpha^*/4$

The Bonferroni adjusted p-value for gut microbiota spp. group k is denoted as

$$P_k = (\text{num patterns tested in gut microbiota spp. group } k) \times \min_{j \in k} (P_{j_{k,4}})$$

Without loss of generality, we will prove that the FDR is controlled when step 1 is implemented - proofs for the other steps are similarly formed. This proof relies on the proof provided in Guo et al. (2010). We let V be the number of false positives, $I_1 = \{1 \leq k \leq 22 | H_1\}$ be the set of indices of false null hypotheses, $\alpha^* = \alpha \times R / (22 \times 16)$ (obtained from Guo et al., 2010), and $I(\cdot)$ be an indicator function. We then

express V as:

$$\begin{aligned} V &= \sum_{k \in I_1} I(\cup_{j=1}^{16} (\text{Reject } H_0 \text{ for } j_k | H_0)) \\ &= \sum_{k \in I_1} I(\cup_{j=1}^{16} ((\alpha^*/2 \leq P_{j_{k,4}} \leq \alpha^* | H_0) + (P_{j_{k,4}} \leq \alpha^*/2, P_{j_{k,3}} \leq \alpha^*/2 | H_0))) \end{aligned}$$

Then

$$\begin{aligned} FDR &= E \left\{ \frac{V}{R \vee 1} \right\} \\ &= E \left\{ \frac{E(V | R = r)}{R \vee 1} \right\} \\ &= E \left[\frac{\sum_{j \in I_1} \Pr \{ \cup_{j=1}^{16} ((\alpha^*/2 \leq P_{j_{k,4}} \leq \alpha^* | H_0) + (P_{j_{k,4}} \leq \alpha^*/2, P_{j_{k,3}} \leq \alpha^*/2 | H_0)) | R = r \}}{R \vee 1} \right] \\ &= \sum_{r=1}^{22} \sum_{k \in I_1} \frac{1}{r} \Pr \{ \cup_{j=1}^{16} ((\alpha^*/2 \leq P_{j_{k,4}} \leq \alpha^*, R = r | H_0) + (P_{j_{k,4}} \leq \alpha^*/2, P_{j_{k,3}} \leq \alpha^*/2, R = r | H_0)) \} \\ &\leq \sum_{r=1}^{22} \sum_{k \in I_1} \sum_{j=1}^{16} \frac{1}{r} \{ \Pr(\alpha^*/2 \leq P_{j_{k,4}} \leq \alpha^*, R = r | H_0) + \Pr(P_{j_{k,4}} \leq \alpha^*/2, P_{j_{k,3}} \leq \alpha^*/2, R = r | H_0) \} \end{aligned}$$

The above inequality follows from the Bonferroni inequality

$$\begin{aligned} &\leq \sum_{r=1}^{22} \sum_{k \in I_1} \sum_{j=1}^{16} \frac{1}{r} \{ \Pr(\alpha^*/2 \leq P_{j_{k,4}} \leq \alpha^*, R = r | H_0) + \\ &\quad \max(\Pr(P_{j_{k,4}} \leq \alpha^*/2, R = r | H_0), \Pr(P_{j_{k,3}} \leq \alpha^*/2, R = r | H_0)) \} \\ &= \sum_{r=1}^{22} \sum_{k \in I_1} \sum_{j=1}^{16} \frac{1}{r} \{ \Pr(\alpha^*/2 \leq P_{j_{k,4}} \leq \alpha^* | H_0) \times \Pr(R^{(-k)} = r - 1) + \\ &\quad \max(\Pr(P_{j_{k,4}} \leq \alpha^*/2 | H_0), \Pr(P_{j_{k,3}} \leq \alpha^*/2 | H_0)) \times \Pr(R^{(-k)} = r - 1) \} \end{aligned}$$

The above simplification results from the assumption that each gut microbiota spp. group

is independent of each other, where $R^{(-k)}$ denotes the number of rejections in the step up procedure with critical constants $a_l = \frac{l+1}{22}, l = 1, \dots, 22-1$ based on $\{P_1, \dots, P_{22}\} \setminus \{P_k\}$

$$\leq \sum_{r=1}^{22} \sum_{k \in I_1} \sum_{j=1}^{16} \frac{1}{r} \left\{ \alpha^*/2 \times \Pr(R^{(-k)} = r - 1) + \max(\alpha^*/2, \alpha^*/2) \times \Pr(R^{(-k)} = r - 1) \right\}$$

The above inequality follows from $\Pr(\text{pvalue} \leq p) \leq p$, for any $p \in (0, 1)$ under H_0

$$\begin{aligned}
&= \sum_{r=1}^{22} \sum_{k \in I_1} \sum_{j=1}^{16} \frac{1}{r} \left\{ \alpha^* \times \Pr \left(R^{(-k)} = r - 1 \right) \right\} \\
&= \sum_{r=1}^{22} \sum_{k \in I_1} \sum_{j=1}^{16} \frac{1}{r} \left\{ \alpha \times R / (22 \times 16) \times \Pr \left(R^{(-k)} = r - 1 \right) \right\} \\
&= \frac{m_1}{22} \alpha \\
&\leq \alpha
\end{aligned}$$