and

$$\mathrm{Var}(\mathrm{SI}) = E\left(\mathrm{SI}^2\right) - (\mu_{\mathrm{SI}})^2,$$

where $E\left(\mathrm{SI}^2\right) = \int p^2 (F(p))^3 f(p)\, dp$ denoted as the second raw moment of SI.

With a given distribution function $F(p)$, the expected value and the variance of order statistics could be derived (see David and Nagaraja, 2003). However, the population distribution may be unknown or difficult to determine. Several results of nonparametric bounds for the moments of order statistics have been provided. David (1981) summarized the distribution-free bounds on the expected values of the order statistics when the observations $p_{T_1}, p_{T_2}, \ldots, p_{T_4}$ are i.i.d. from a population with expectation μ and variance σ^2. The earliest result provided in Gumbel (1954) and Hartley and David (1954) concerns the minimum,

$$\mu_{\mathrm{SI}} \le \mu + \sigma(n-1)(2n-1)^{-1/2} = \mu + 1.1339\sigma, \tag{11.14}$$

where the sample size is $n = 4$.

However, the observations may be dependent and/or are from a different distribution. It could be obtained in Arnold and Groeneveld (1979) that the bound in Equation 11.14 becomes

$$\mu_{\mathrm{SI}} \le \mu + \sigma(n-1)^{1/2} = \mu + 1.73205\sigma \tag{11.15}$$

when independence cannot be assumed. On the other hand, for the variance of order statistics, the upper bounds for the variance of order statistics derived by Papadatos (1995) can be used. That is,

$$\mathrm{Var}(\mathrm{SI}) < n\sigma^2 = 4\sigma^2. \tag{11.16}$$

In order to obtain the estimates of expectation and variance of SI, the sample mean and sample variance of the observations $p_{T_1}, p_{T_2}, \ldots, p_{T_4}$ could be used to replace μ and σ^2, respectively, in the bound 11.14 or 11.15 of μ_{SI} and the bound 11.16 of Var(SI).

As a result, the 95% confidence low bound of SI can be obtained. We then claim switching if the 95% confidence low bound for SI is larger than p_{S_0}.

11.4.3 Alternating Index (AI)

A similar idea can be applied to develop an alternating index under an appropriate study design. Under the modified Balaam's crossover design of (TT, RR, TRT, RTR), biosimilarity for "R to T to R" and "T to R to T" needs to be assessed for the evaluation of alternating. For example, the assessment of differences between "R to T" and "T to R" for alternating of "R to T to R" needs to be evaluated in order to determine whether the drug effect has returned to the baseline after the second switch.