個數資料於R(個序列)與C(個時間點)的交叉設計下之強韌概似推論法
Robust Likelihood inferences for RxC crossover designs for general count data

國立中央大學 統計研究所

報告人：劉 懿 萱

指導教授：鄒 宗 山 博士

Date：2023/06/26

Outline

01 緒論

- RxC交叉設計
- 簡單交叉試驗設計的個數型資料分析

02 實作模型

- AB|BA交叉設計下卜瓦松模型之強韌化
- 非強韌與強韌變異數估計量及檢定統計量

03 模擬研究

- 資料生成方式與模擬方式
- 參數估計量、參數估計量之樣本變異數、漸進變異數估計量與強韌變異數估計量平均值
- 型一誤差機率、95%信賴區間平均上下界、平均長度與覆蓋率

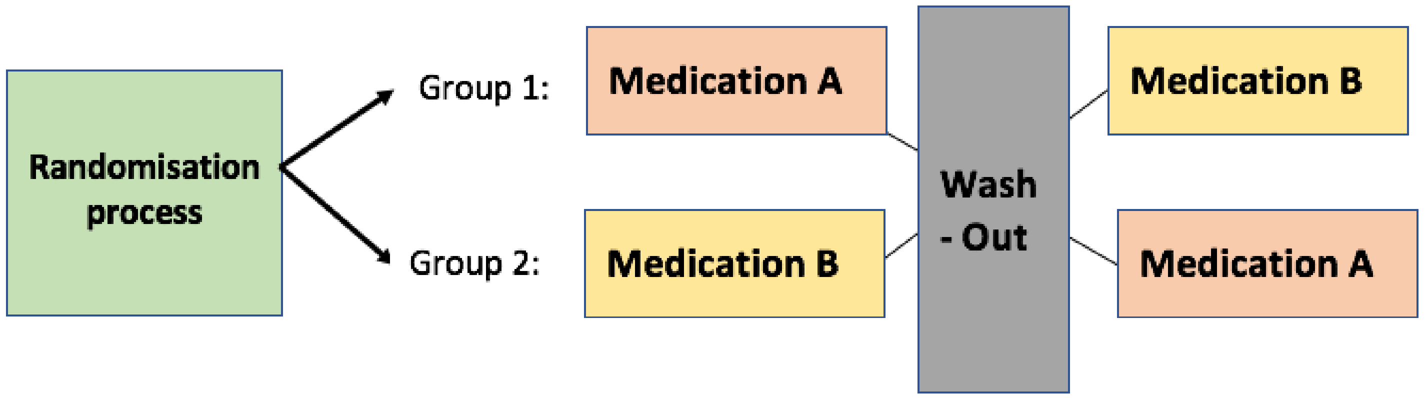
04 實例分析

- AB|BA藥物動力學研究資料

05 結論

- 簡單交叉設計方法比較
- 模擬結果與實例分析結果

RxC交叉設計



序列內均勻　每種藥在每個序列出現的次數相同

期間內均勻　每種藥在每個時間點出現的次數相同

Treatment	Period 1	Period 2
Sequence AB	A	B
Sequence BA	B	A

Treatment	Period 1	Period 2	Period 3
Sequence ABC	A	B	C
Sequence BCA	B	C	A
Sequence CAB	C	A	B

簡單交叉試驗設計的個數型資料分析(Lui, 2012)

Y_{ist}：第i位受試者於第t個時間點序列s的發作次數

受試者 $i=1,\dots,n_s$　　序列 $s=1,\ 2$　　時間點 $t=1,\ 2$

X_{ist}：受試者使用的藥物種類

$$x_{ist}=\begin{cases}1, & \text{藥物 B}\\ 0, & o.w.\end{cases}$$

Z_{it}：受試者用藥的時間點

$$z_{it}=\begin{cases}1, & \text{時間點 2}\\ 0, & o.w.\end{cases}$$

$$Y_{ist}\sim Poisson(E(Y_{ist}))\quad E(Y_{ist})=u_{is}\exp(x_{ist}\eta+z_{it}\gamma)$$

u_{is}：第i位受試者被分配至任意序列的隨機效應

η：B藥與A藥的藥效藥應差異

γ：時間點2與時間點1的差異

$$Y_{i12} \mid Y_{i1+} = y_{i1+} \sim Bin(y_{i1+}, \exp(\eta+\gamma)/(1+\exp(\eta+\gamma)))$$

$$P(Y_{+12} = y_{+12} \mid \underset{\sim}{y}_{1+}, \eta, \gamma) = \binom{y_{+1+}}{y_{+12}} p_1^{y_{+12}} (1-p_1)^{y_{+1+}-y_{+12}}$$

$$Y_{+12} (= \sum_{i=1}^{n_1} Y_{i12}) \qquad \underset{\sim}{y}_{1+}^{'} = (y_{11+}, y_{21+}, \ldots, y_{n_1 1+}) \qquad y_{+1+} = \sum_{i=1}^{n_1} y_{i1+} \qquad p_1 = \exp(\eta+\gamma)/(1+\exp(\eta+\gamma))$$

$$Y_{i22} \mid Y_{i2+} = y_{i2+} \sim Bin(y_{i2+}, \exp(\gamma)/(\exp(\eta)+\exp(\gamma)))$$

$$P(Y_{+22} = y_{+22} \mid \underset{\sim}{y}_{2+}, \eta, \gamma) = \binom{y_{+2+}}{y_{+22}} p_2^{y_{+22}} (1-p_2)^{y_{+2+}-y_{+22}}$$

$$Y_{+22} (= \sum_{i=1}^{n_2} Y_{i22}) \qquad \underset{\sim}{y}_{2+}^{'} = (y_{12+}, y_{22+}, \ldots, y_{n_2 2+}) \qquad y_{+2+} = \sum_{i=1}^{n_2} y_{i2+} \qquad p_2 = \exp(\gamma)/(\exp(\eta)+\exp(\gamma))$$

Conditional MLE of p_s is $\hat{p}_s = y_{+s2} / y_{+s+} \quad ,(s=1,2)$

$RM_T = \exp(\eta)$ 受試者於同一時間點服用A要與B藥的平均發病次數比值

Conditional MLE of p_s is $\hat{p}_s = y_{+s2} / y_{+s+}$,$(s=1,2)$

$$RM_T^2 = p_1(1-p_2)/p_2(1-p_1)$$

$$RM_T = \left(\frac{\hat{p}_1(1-\hat{p}_2)}{\hat{p}_2(1-\hat{p}_1)}\right)^{1/2} = \left(\frac{Y_{+12}Y_{+21}}{Y_{+11}Y_{+22}}\right)^{1/2}$$

$$Var(\log(RM_T)) = \frac{1}{4}\left(\frac{1}{y_{+1+}p_1(1-p_1)} + \frac{1}{y_{+2+}p_2(1-p_2)}\right)$$

$$Var(\log(RM_T)) = \frac{1}{4}\left(\frac{1}{Y_{+12}} + \frac{1}{Y_{+11}} + \frac{1}{Y_{+21}} + \frac{1}{Y_{+22}}\right)$$

$H_0 : \eta = 0 \ (RM_T = 1),\ H_1 : \eta \neq 0 \ (RM_T \neq 1)$

Reject $\boldsymbol{H_0}$ at the $\boldsymbol{\alpha}$-level if

$$\log(RM_T)/\sqrt{Var_{H_0}(\log(RM_T))} > Z_{\alpha/2} \text{ or } \log(RM_T)/\sqrt{Var_{H_0}(\log(RM_T))} < -Z_{\alpha/2}$$

where

$$Var_{H_0}(\log(RM_T)) = (1/y_{+1+} + 1/y_{+2+})/[4\hat{\bar{p}}(1-\hat{\bar{p}})],\ \hat{\bar{p}} = (Y_{+12}+Y_{+22})/(y_{+1+}+y_{+2+})$$

$$Y_{ist} \sim Poisson(E(Y_{ist})) \quad , \quad E(Y_{ist}) = \exp(\tau + x_{ist}\eta + z_{it}\gamma + g_s\delta)$$

受試者 $i = 1,\ldots,n_s$，序列 $s = 1,2$，時間點 $t = 1,2$

τ：A藥的藥效　　　η：A藥與B藥的藥效效應差異

γ：時間點2與時間點1的時間效應差異

δ：時間點2與時間點1的時間效應差異

對數概似函數

$$l\left(\tau,\eta,\gamma,\delta\right) = \sum_{i=1}^{n_1}[\tau y_{i11} - \exp(\tau) + (\tau+\eta+\gamma)y_{i12} - \exp(\tau+\eta+\gamma)]$$
$$+\sum_{i=1}^{n_2}[(\tau+\eta+\delta)y_{i21} - \exp(\tau+\eta+\delta) + (\tau+\gamma+\delta)y_{i22} - \exp(\tau+\gamma+\delta)]$$

一階偏微分、分數函數與最大概似估計量

$$S_\eta = \frac{\partial l}{\partial \eta} = \sum_{i=1}^{n_1}[y_{i12} - \exp(\tau+\eta+\gamma)] + \sum_{i=1}^{n_2}[y_{i21} - \exp(\tau+\eta+\delta)]$$

$$E(S_\eta) = E\left(\frac{\partial l}{\partial \eta}\right) = \sum_{i=1}^{n_1}[E(y_{i12}) - \exp(\tau+\eta+\gamma)] + \sum_{i=1}^{n_2}[E(y_{i21}) - \exp(\tau+\eta+\delta)] = 0$$

$$\hat{\eta} = \frac{1}{2}\log\left(\frac{Y_{+12}Y_{+21}}{Y_{+11}Y_{+22}}\right)$$

二階微分

$$\frac{\partial^2 l}{\partial \eta^2}=\frac{\partial^2 l}{\partial \tau \partial \eta}=\frac{\partial^2 l}{\partial \eta \partial \tau}=\sum_{i=1}^{n_1}[-\exp(\tau+\eta+\gamma)]+\sum_{i=1}^{n_2}[-\exp(\tau+\eta+\delta)]$$

費雪資訊矩陣與V矩陣

$$I=\begin{bmatrix} I_{\tau\tau} & I_{\tau\eta} & I_{\tau\gamma} & I_{\tau\delta} \\ I_{\eta\tau} & I_{\eta\eta} & I_{\eta\gamma} & I_{\eta\delta} \\ I_{\gamma\tau} & I_{\gamma\eta} & I_{\gamma\gamma} & I_{\gamma\delta} \\ I_{\delta\tau} & I_{\delta\eta} & I_{\delta\gamma} & I_{\delta\delta} \end{bmatrix} \qquad V=\begin{bmatrix} V_{\tau\tau} & V_{\tau\eta} & V_{\tau\gamma} & V_{\tau\delta} \\ V_{\eta\tau} & V_{\eta\eta} & V_{\eta\gamma} & V_{\eta\delta} \\ V_{\gamma\tau} & V_{\gamma\eta} & V_{\gamma\gamma} & V_{\gamma\delta} \\ V_{\delta\tau} & V_{\delta\eta} & V_{\delta\gamma} & V_{\delta\delta} \end{bmatrix}$$

A矩陣與B矩陣

當我們感興趣的參數為 $\theta=\eta$，干擾參數為 $\phi=(\tau,\gamma,\delta)$

$$A=I_{\theta\theta}-I_{\theta\phi}I_{\phi\phi}^{-1}I_{\phi\theta} \qquad B=V_{\theta\theta}-I_{\theta\phi}I_{\phi\phi}^{-1}V_{\phi\theta}-V_{\theta\phi}I_{\phi\phi}^{-1}I_{\phi\theta}+I_{\theta\phi}I_{\phi\phi}^{-1}V_{\phi\phi}I_{\phi\phi}^{-1}I_{\phi\theta}$$

非強韌與強韌變異數估計量及檢定統計量

非強韌變異數估計量與強韌變異數估計量

$$Var_{na}(\hat{\eta}) = \hat{A}^{-1} / N \qquad Var_{rb}(\hat{\eta}) = \boxed{\hat{A}^{-1}\hat{B}\hat{A}^{-1}} / N$$

非強韌與強韌華德檢定統計量

$$W_{na} = (\hat{\eta} - \eta_0)^2 / (\hat{A}^{-1} / N) \qquad W_{RB} = (\hat{\eta} - \eta_0)^2 / (\boxed{\hat{A}^{-1}\hat{B}\hat{A}^{-1}} / N)$$

非強韌與強韌概似比檢定統計量

$$LR_{na} = 2(l(\hat{\eta}, \hat{\tau}, \hat{\gamma}, \hat{\delta}) - l(\eta_0, \tilde{\tau}, \tilde{\gamma}, \tilde{\delta}))$$

$$LR_{rb} = 2\hat{A}\hat{B}^{-1}(l(\hat{\eta}_1, \hat{\eta}_2, \hat{\tau}, \hat{\gamma}_1, \hat{\gamma}_2, \hat{\delta}_1, \hat{\delta}_2) - l(\eta_0, \tilde{\tau}, \tilde{\gamma}_1, \tilde{\gamma}_2, \tilde{\delta}_1, \tilde{\delta}_2))2\boxed{(\hat{A} / \hat{B})}(l(\hat{\eta}, \hat{\tau}, \hat{\gamma}, \hat{\delta}) - l(\eta_0, \tilde{\tau}, \tilde{\gamma}, \tilde{\delta}))$$

非強韌與強韌分數檢定統計量

$$\tilde{S}_\eta = \sum_{i=1}^{n_1}[y_{i12} - \exp(\tilde{\tau} + \eta_0 + \tilde{\gamma})] + \sum_{i=1}^{n_2}[y_{i21} - \exp(\tilde{\tau} + \eta_0 + \tilde{\delta})]$$

$$S_{na} = \tilde{S}_\eta^2 / \boxed{(N\tilde{A})} \qquad S_{rb} = \tilde{S}_\eta^2 / \boxed{(N\tilde{B})}$$

資料生成方式(模擬次數10000次)

- 使用R套件simstudy內的genCorGen指令生成具有相關性卜瓦松個數資料
- 使用R套件內的gumbelcopula生成具有相關性的韋伯個數型資料
- 利用隨機效應生成Lui(2012)的相關性個數型資料

參數估計量與參數估計量之樣本變異數	$\hat{\eta}$ 、 $\hat{\eta}_{Lui}$ 、 $S^2(\hat{\eta})$
非強韌與強韌變異數估計量平均值	$Var_{na}(\hat{\eta})$ 、 $Var_{rb}(\hat{\eta})$ 、 $Var_{Lui}(\hat{\eta}_{Lui})$
非強韌與強韌華德檢定	W_{na} 、 W_{rb}
非強韌與強韌概似比檢定	LR_{na} 、 LR_{rb}
非強韌與強韌分數檢定	S_{na} 、 S_{rb}
95%信賴區間平均上下界、平均長度與覆蓋率	CI、AL與CP

表1：Lui(2012)相關性約0.6資料模擬結果

$\exp(\gamma)=2.0,\ E(u_{is})=3,\ \beta=1$

N	$\hat{\eta}/\hat{\eta}_{Lui}$	$S^2(\hat{\eta})$	$S^2(\hat{\eta}_{Lui})$	$Var_{na}(\hat{\eta})$	$Var_{rb}(\hat{\eta})$	$Var_{Lui}(\hat{\eta}_{Lui})$
30	-0.0003	0.0135	0.0135	0.0132	0.0129	0.0132
	/-0.0003	(0.1161)	(0.1161)	(0.1147)	(0.1136)	(0.1147)
60	0.0008	0.0066	0.0066	0.0064	0.0064	0.0064
	/0.0008	(0.0810)	(0.0810)	(0.0803)	(0.0798)	(0.0803)
100	-0.0006	0.0038	0.0038	0.0038	0.0038	0.0038
	/-0.0006	(0.0620)	(0.0620)	(0.0619)	(0.0616)	(0.0619)

表 2：Lui(2012)相關性約0.6資料模擬結果

N	Data	LR_{na}	LR_{rb}	S_{na}	S_{rb}	W_{na}	W_{rb}	Lui
30	Poisson	0.0497	0.0671	0.0530	0.0706	0.0477	0.0643	0.0516
	Weibull	0.0532	0.0593	0.0549	0.0604	0.0526	0.0585	0.0547
60	Poisson	0.0495	0.0529	0.0504	0.0532	0.0488	0.0525	0.0499
	Weibull	0.0497	0.0671	0.0530	0.0706	0.0477	0.0643	0.0516
100	Poisson	0.0532	0.0593	0.0549	0.0604	0.0526	0.0585	0.0547
	Weibull	0.0495	0.0529	0.0504	0.0532	0.0488	0.0525	0.0499

表 3：相關性約0.4卜瓦松個數資料與韋伯個數資料模擬結果

$$H_0 : \eta = 0,\ (\tau,\ \eta,\ \gamma,\ \delta) = (2.0,\ 0,\ -0.5\ ,\ -0.2)$$

N	Data	$\hat{\eta} / \hat{\eta}_{Lui}$	$S^2(\hat{\eta})$	$S^2(\hat{\eta}_{Lui})$	$Var_{na}(\hat{\eta})$	$Var_{rb}(\hat{\eta})$	$Var_{Lui}(\hat{\eta}_{Lui})$
50	Poisson	0.0011	0.0052	0.0052	0.0080	0.0050	0.0080
		/0.0011	(0.0719)	(0.0719)	(0.0896)	(0.0708)	(0.0895)
	Weibull	0.0010	0.0012	0.0012	0.0080	0.0012	0.0080
		/0.0010	(0.0347)	(0.0347)	(0.0894)	(0.0347)	(0.0893)
100	Poisson	0.0007	0.0025	0.0025	0.0040	0.0025	0.0040
		/0.0007	(0.0502)	(0.0502)	(0.0632)	(0.0499)	(0.0632)
	Weibull	0.0008	0.0006	0.0006	0.0040	0.0006	0.0040
		/0.0008	(0.0245)	(0.0245)	(0.0632)	(0.0246)	(0.0631)
300	Poisson	0.0003	0.0008	0.0008	0.0013	0.0008	0.0013
		/0.0003	(0.0288)	(0.0288)	(0.0365)	(0.0288)	(0.0364)
	Weibull	0.0008	0.0002	0.0002	0.0013	0.0002	0.0013
		/0.0008	(0.0141)	(0.0141)	(0.0364)	(0.0142)	(0.0364)

表 4：相關性約0.4卜瓦松個數資料與韋伯個數資料模擬結果

$$H_0 : \eta = 0,\ (\tau,\ \eta,\ \gamma,\ \delta) = (2.0,\ 0,\ -0.5\ ,\ -0.2)$$

N	Data	LR_{na}	LR_{rb}	S_{na}	S_{rb}	W_{na}	W_{rb}	*Lui*
50	Poisson	0.0145	0.0604	0.0148	0.0608	0.0142	0.0601	0.0148
	Weibull	0.0000	0.0528	0.0000	0.0529	0.0000	0.0527	0.0000
100	Poisson	0.0130	0.0557	0.0130	0.0563	0.0129	0.0555	0.0130
	Weibull	0.0000	0.0505	0.0000	0.0505	0.0000	0.0505	0.0000
300	Poisson	0.0128	0.0504	0.0128	0.0504	0.0128	0.0504	0.0128
	Weibull	0.0000	0.0491	0.0000	0.0492	0.0000	0.0490	0.0000

表 5-1：相關性約0.4卜瓦松個數資料與韋伯個數資料Wald Test模擬結果

$$H_0:\eta=0,\ (\tau,\ \eta,\ \gamma,\ \delta)=(2.0,\ 0,\ \text{-}0.5\ ,\ \text{-}0.2)$$

N	Data	W_{na}			W_{rb}		
		CI	AL	CP	CI	AL	CP
50	Poisson	(-0.1745, 0.1783)	0.3528	0.9852	(-0.1401, 0.1453)	0.2855	0.9435
	Weibull	(-0.1742, 0.1778)	0.3520	1.0000	(-0.0680, 0.0706)	0.1386	0.9512
100	Poisson	(-0.1231, 0.1253)	0.2484	0.9870	(-0.0978, 0.1006)	0.1984	0.9467
	Weibull	(-0.1229, 0.1252)	0.2481	1.0000	(-0.0476, 0.0495)	0.0972	0.9512
300	Poisson	(-0.0711, 0.0719)	0.1430	0.9872	(-0.0561, 0.0571)	0.1132	0.9502
	Weibull	(-0.0706, 0.0724)	0.1430	1.0000	(-0.0271, 0.0288)	0.0558	0.9518

表 5-2：相關性約0.4卜瓦松個數資料與韋伯個數資料Likelihood Ratio Test模擬結果

$$H_0 : \eta = 0,\ (\tau,\ \eta,\ \gamma,\ \delta) = (2.0,\ 0,\ \text{-}0.5\ ,\ \text{-}0.2)$$

N	Data	LR_{na}			LR_{rb}		
		CI	AL	CP	CI	AL	CP
50	Poisson	(-0.1743, 0.1770)	0.3513	0.9855	(-0.1367, 0.1392)	0.2760	0.9396
	Weibull	(-0.1741, 0.1765)	0.3506	1.0000	(-0.0667, 0.0687)	0.1354	0.9472
100	Poisson	(-0.1231, 0.1248)	0.2479	0.9870	(-0.0968, 0.0984)	0.1952	0.9443
	Weibull	(-0.1229, 0.1247)	0.2476	1.0000	(-0.0472, 0.0489)	0.0961	0.9495
300	Poisson	(-0.0711, 0.0718)	0.1429	0.9872	(-0.0560, 0.0566)	0.1127	0.9495
	Weibull	(-0.0706, 0.0723)	0.1429	1.0000	(-0.0270, 0.0286)	0.0556	0.9508

表 5-3：相關性約0.4卜瓦松個數資料與韋伯個數資料Score Test模擬結果

$$H_0:\eta=0,\ (\tau,\ \eta,\ \gamma,\ \delta)=(2.0,\ 0,\ \text{-}0.5\ ,\ \text{-}0.2)$$

N	Data	S_{na}			S_{rb}		
		CI	AL	CP	CI	AL	CP
50	Poisson	(-0.1742, 0.1763)	0.3505	0.9855	(-0.1400, 0.1440)	0.2841	0.9439
	Weibull	(-0.1739, 0.1758)	0.3497	1.0000	(-0.0681, 0.0704)	0.1384	0.9513
100	Poisson	(-0.1231, 0.1245)	0.2476	0.9870	(-0.0978, 0.1001)	0.1979	0.9470
	Weibull	(-0.1229, 0.1245)	0.2473	1.0000	(-0.0477, 0.0495)	0.0971	0.9513
300	Poisson	(-0.0711, 0.0717)	0.1429	0.9872	(-0.0562,0.0570)	0.1132	0.9506
	Weibull	(-0.0706, 0.0722)	0.1428	1.0000	(-0.0271, 0.0287)	0.0558	0.9518

Sushil Kale & V. H. Bajaj (2015)

- 比較新藥搭配食物服用的吸收度是否和舊藥相彷
- AB|BA交叉試驗設計，每個試驗序列隨機分配14位受試者(共28位)
- 以最高血中藥物濃度(C_{max})作為反應變數

單位：mg/ml

序列	編號	時間點1	時間點2	序列	編號	時間點1	時間點2
AB	02	605.45	326.19	**BA**	01	360.11	278.48
AB	03	608.67	578.66	**BA**	04	412.69	196.19
AB	07	392.45	1046.37	**BA**	05	423.98	681.34
AB	08	571.51	733.8	**BA**	06	1359.86	1191.91
AB	10	738.77	669.17	**BA**	09	2403.67	1449.63
AB	11	364.8	717.01	**BA**	12	409.05	468.31
AB	13	884.73	907.64	**BA**	15	2434.96	2509.14
AB	14	557.16	995.68	**BA**	16	476.31	265.09
AB	18	483.04	579.72	**BA**	17	565.66	1070.06
AB	19	123.9	297.07	**BA**	20	1344.96	1064.23
AB	21	2552.32	1702.07	**BA**	23	441.33	2057.38
AB	22	403.34	656.33	**BA**	24	1458.82	1899.42
AB	26	247.49	905.35	**BA**	25	500.45	945.48
AB	27	449.56	688.03	**BA**	28	139.61	213.63

表 6：AB|BA實例分析結果

$H_0:\eta=0$	強韌檢定統計量	P值	信賴區間	長度
W	0.0870	0.7680	(-0.1934, 0.3162)	0.5096
LR	0.0870	0.7680	(-0.1945, 0.2643)	0.4588
S	0.0871	0.7679	(-0.1922, 0.3083)	0.5004
Lui(2013)	13.5141	0.0000		

新藥與舊藥並沒有顯著差異

- Royall & Tsou(2003)的強韌概似函數應用於R個序列C個時間點的交叉設計下的個數型資料分析
- 經強韌化的卜瓦松概似函數應用於連續型資料的實例分析仍能得到正確的統計推論
- 參數之最大概似估計量具有一致性
- 強韌變異數估計量隨著樣本數增加會接近樣本變異數
- 強韌華德、概似比、分數檢定統計量的型一錯誤機率值與覆蓋率皆接近名目水準0.05與0.95

References

- Constantine, A. G., Robinson, N. I. (1997). The Weibull Renewal Function for Moderate To Large Arguments. *Computat. Statist. Data Anal*. **24**: 9–27.
- Ebbutt, A. F. (1984). Three-Period Crossover Designs for Two Treatments. *Biometrika*, **40**: 219-224.
- Ong, S. H., Atanu Biswas, Peitis S., and Low, Y. C. (2015). Count Distribution for Generalized Weibull Duration with Applications. *Communications in Statistics—Theory and Methods*, **44**: 4203–4216.
- Royall, R. M. & Tsou, T. S. (2003). Interpreting statistical evidence by using imperfect models: robust adjusted likelihood functions. *Journal of the Royal Statistical Society, Series B*, **65**: 391-404.
- Tsou, T. S. (2011). Robust likelihood inference for multivariate correlated count data. *Springer-Verlag Berlin Heidelberg*, **38**, 2901-2910.

Thanks!