**Supplementary Document**

1. **Results**
2. ***Variance and MSE***

The variance of the treatment parameter () decreased as the pair proportion decreased for all five survival models. At 90% pairing the nested MPL frailty model resulted in the highest variance of 0.007. The PWP model and the HKC model had the lowest variance of 0.004. At 50% pairing the nested MPL frailty model continued to have the highest variance of 0.009. Similar to the treatment variable, the nested MPL frailty model resulted in the highest variance, and the HKC model had the lowest variance for the ear () and interaction () variables. The interaction variable consistently had the highest variance of the three parameters, where the dynamic treatment effect and the static ear parameter had similar variances. All survival models had an increase in variance as pair proportion decreased from 90% to 10% (Figure 1-3). All results were comparable for the null simulations (Table 8 -11).

1. ***Type-1 Error***

All models for the treatment (), ear (), and interaction () parameters across the different pair proportions had type-1 error rates between 1.2% to 6.8% across all scenarios (Table 8 - 11). Though consistently near 5%, the type-1 error rates did fluctuate up and down at each change in pair proportion as seen in the type-1 error plot of Figure 5, which may be attributable to the variation across simulated trials, where more consistent estimates may be achieved with a larger number of simulated trials. For the parameter of ear () and the interaction () the logistic regression model resulted in the lowest type-1 error rate starting around 1% at 90% pairs and increasing to 4% by 10% pairs.

Table IV. Bias, Variance, MSE and Power results across all scenarios for the treatment parameter

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  |  | **= Treatment = 0.3** | | | |
| Pair % | Model | Bias (95% CI) | Variance | MSE | Power | |
| **90** | Logistic |  |  |  | 34.1% | |
|  | PWP | -0.082  (-0.210, 0.046) | 0.004 | 0.011 | 92.6% | |
|  | GF | -0.008  (-0.170, 0.154) | 0.005 | 0.005 | 94.8% | |
|  | NF MPLa | 0.003  (-0.161, 0.168) | 0.007 | 0.007 | 95.6% | |
|  | NF PPL | -0.018  (-0.171, 0.135) | 0.006 | 0.006 | 95.5% | |
|  | HKC | -0.082  (-0.210, 0.045) | 0.004 | 0.011 | 92.6% | |
| **80** | Logistic |  |  |  | 33.3% | |
|  | PWP | -0.074  (-0.204, 0.056) | 0.005 | 0.010 | 91.2% | |
|  | GF | -0.002  (-0.167, 0.163) | 0.005 | 0.005 | 94.7% | |
|  | NF MPLa | 0.010  (-0.155, 0.175) | 0.007 | 0.007 | 96.1% | |
|  | NF PPL | -0.011  (-0.167, 0.144) | 0.006 | 0.007 | 94.9% | |
|  | HKC | -0.075  (-0.204, 0.055) | 0.005 | 0.010 | 91.1% | |
| **70** | Logistic |  |  |  | 34.7% | |
|  | PWP | -0.073  (-0.203, 0.057) | 0.005 | 0.010 | 91.6% | |
|  | GF | 0.001  (-0.164, 0.164) | 0.006 | 0.006 | 94.1% | |
|  | NF MPLa | 0.012  (-0.155, 0.178) | 0.008 | 0.008 | 95.3% | |
|  | NF PPL | ﻿-0.010  (-0.165, 0.145) | 0.007 | 0.007 | 94.1% | |
|  | HKC | -0.074  (-0.204, 0.056) | 0.005 | 0.010 | 91.7% | |
| **60** | Logistic |  |  |  | 30.4% | |
|  | PWP | -0.076  (-0.215, 0.062) | 0.005 | 0.011 | 88.0% | |
|  | GF | -0.004  (-0.182, 0.174) | 0.006 | 0.006 | 91.4% | |
|  | NF MPLa | 0.007  (-0.176, 0.190 | 0.008 | 0.008 | 92.6% | |
|  | NF PPL | ﻿-0.014  (-0.181, 0.154) | 0.007 | 0.007 | 91.9% | |
|  | HKC | -0.077  (-0.216, 0.062) | 0.005 | 0.011 | 88.1% | |
| **50** | Logistic |  |  |  | 28.7% | |
|  | PWP | -0.075  (-0.224, 0.074) | 0.006 | 0.011 | 86.1% | |
|  | GF | -0.004  (-0.187, 0.180) | 0.007 | 0.007 | 90.0% | |
|  | NF MPLa | 0.009  (-0.176, 0.194) | 0.009 | 0.009 | 91.6% | |
|  | NF PPL | ﻿-0.013  (-0.188, 0.163) | 0.008 | 0.008 | 90.8% | |
|  | HKC | -0.076  (-0.225, 0.073) | 0.005 | 0.011 | 85.6% | |
| **10** | Logistic |  |  |  | 23.2% | |
|  | PWP | -0.078  (-0.246, 0.090) | 0.008 | 0.014 | 72.5% | |
|  | GF | -0.007  (-0.217, 0.203) | 0.009 | 0.009 | 78.3% | |
|  | NF MPLa | 0.007  (-0.208, 0.222) | 0.012 | 0.012 | 81.4% | |
|  | NF PPL | -0.016  (-0.218, 0.185) | 0.011 | 0.011 | 77.2% | |
|  | HKC | -0.078  (-0.246, 0.089) | 0.007 | 0.014 | 72.4% | |

aNF MPL convergence: 90%: 959 simulations, 80%: 959 simulations, 70%: 940 simulations, 60%: 941 simulations, 50%: 937 simulations, 10%: 907 simulations. GF = Gamma frailty, NF = nested frailty, MPL = maximum penalized likelihood estimation, PPL = penalized partial likelihood estimation, HKC = hierarchical Kendall copula

Table 5. Bias, Variance, MSE and Power results across all scenarios for the ear parameter

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  |  | **= Ear = 0.4** | | | |
| Pair % | Model | Bias (95% CI) | Variance | MSE | Power |
| **90** | Logistic |  |  |  | 53.4% |
|  | PWP | -0.110  (-0.226, 0.006) | 0.004 | 0.016 | 99.8% |
|  | GF | -0.010  (-0.164, 0.144) | 0.005 | 0.005 | 99.9% |
|  | NF MPLa | 0.003  (-0.153, 0.159) | 0.008 | 0.008 | 99.9% |
|  | NF PPL | -0.023  (-0.169, 0.124) | 0.006 | 0.006 | 100% |
|  | HKC | -0.110  (-0.225, 0.006) | 0.004 | 0.016 | 100 % |
| **80** | Logistic |  |  |  | 53.5% |
|  | PWP | -0.103  (-0.222, 0.017) | 0.005 | 0.015 | 99.7% |
|  | GF | -0.001  (-0.162, 0.160) | 0.005 | 0.005 | 100% |
|  | NF MPLa | 0.013  (-0.151, 0.177) | 0.008 | 0.008 | 100% |
|  | NF PPL | -0.014  (-0.165, 0.137) | 0.006 | 0.006 | 100% |
|  | HKC | -0.103  (-0.222, 0.016) | 0.004 | 0.014 | 100% |
| **70** | Logistic |  |  |  | 49.8% |
|  | PWP | -0.105  (-0.230, 0.019) | 0.005 | 0.016 | 99.1% |
|  | GF | -0.004  (-0.168, 0.159) | 0.006 | 0.006 | 99.7% |
|  | NF MPLa | 0.010  (-0.156 0.176) | 0.009 | 0.009 | 99.7% |
|  | NF PPL | ﻿-0.019  (-0.174, 0.137) | 0.006 | 0.007 | 99.7% |
|  | HKC | -0.105  (-0.229, 0.019) | 0.004 | 0.015 | 99.5% |
| **60** | Logistic |  |  |  | 47.9% |
|  | PWP | -0.105  (-0.237, 0.027) | 0.005 | 0.016 | 98.6% |
|  | GF | -0.004  (-0.182, 0.174) | 0.006 | 0.006 | 98.8% |
|  | NF MPLa | 0.009  (-0.173, 0.191) | 0.009 | 0.009 | 99.1% |
|  | NF PPL | ﻿-0.017  (-0.183, 0.149) | 0.007 | 0.007 | 99.4% |
|  | HKC | -0.105  (-0.236, 0.027) | 0.005 | 0.015 | 99.5% |
| **50** | Logistic |  |  |  | 45.1% |
|  | PWP | -0.102  (-0.244, 0.041) | 0.006 | 0.016 | 97.2% |
|  | GF | -0.001  (-0.189, 0.187) | 0.006 | 0.006 | 98.3% |
|  | NF MPLa | 0.013  (-0.177, 0.203) | 0.010 | 0.010 | 98.8% |
|  | NF PPL | ﻿-0.015  (-0.191, 0.162) | 0.007 | 0.008 | 99.0% |
|  | HKC | -0.102  (-0.244, 0.040) | 0.005 | 0.015 | 98.4% |
| **10** | Logistic |  |  |  | 34.4% |
|  | PWP | -0.101  (-0.272, 0.071) | 0.008 | 0.018 | 91.9% |
|  | GF | 0.002  (-0.221, 0.225) | 0.009 | 0.009 | 93.5% |
|  | NF MPLa | 0.018  (-0.207, 0.243) | 0.014 | 0.014 | 94.8% |
|  | NF PPL | -0.013  (-0.225, 0.198) | 0.012 | 0.012 | 94.9% |
|  | HKC | -0.100  (-0.272, 0.071) | 0.008 | 0.018 | 92.1% |

aNF MPL convergence: 90%: 959 simulations, 80%: 959 simulations, 70%: 940 simulations, 60%: 941 simulations, 50%: 937 simulations, 10%: 907 simulations. GF = Gamma frailty, NF = nested frailty, MPL = maximum penalized likelihood estimation, PPL = penalized partial likelihood estimation, HKC = hierarchical Kendall copula

Table 6. Bias, Variance, MSE and Power results across all scenarios for the interaction parameter

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  |  | **= Interaction = -0.25** | | | |
| Pair % | Model | Bias | Variance | MSE | Power |
| **90** | Logistic |  |  |  | 10.7% |
|  | PWP | 0.071  (-0.088, 0.229) | 0.009 | 0.014 | 46.8% |
|  | GF | 0.009  (-0.193, 0.212) | 0.010 | 0.010 | 55.1% |
|  | NF MPLa | 0.001  (-0.206, 0.204) | 0.013 | 0.013 | 59.1% |
|  | NF PPL | 0.018  (-0.177, 0.213) | 0.011 | 0.011 | 60.2% |
|  | HKC | 0.071  (-0.087, 0.229) | 0.007 | 0.012 | 56.2% |
| **80** | Logistic |  |  |  | 11.0% |
|  | PWP | 0.058  (-0.110, 0.226) | 0.009 | 0.012 | 52.0% |
|  | GF | -0.003  (-0.220, 0.213) | 0.011 | 0.011 | 59.0% |
|  | NF MPLa | -0.015  (-0.235, 0.205) | 0.014 | 0.014 | 61.9% |
|  | NF PPL | 0.005  (-0.202, 0.211) | 0.011 | 0.012 | 63.4% |
|  | HKC | 0.059  (-0.109, 0.226) | 0.008 | 0.011 | 59.5% |
| **70** | Logistic |  |  |  | 13.7% |
|  | PWP | 0.060  (-0.112, 0.233) | 0.010 | 0.013 | 49.6% |
|  | GF | 0.001  (-0.220, 0.221) | 0.011 | 0.011 | 55.4% |
|  | NF MPLa | -0.011  (-0.235, 0.214) | 0.015 | 0.015 | 58.3% |
|  | NF PPL | ﻿0.009  (-0.201, 0.219) | 0.012 | 0.012 | 60.1% |
|  | HKC | 0.061  (-0.111, 0.233) | 0.008 | 0.012 | 56.9% |
| **60** | Logistic |  |  |  | 11.5% |
|  | PWP | 0.065  (-0.113, 0.243) | 0.010 | 0.014 | 43.9% |
|  | GF | 0.003  (-0.23, 0.237) | 0.012 | 0.012 | 51.2% |
|  | NF MPLa | -0.007  (-0.245, 0.232) | 0.016 | 0.016 | 53.2% |
|  | NF PPL | ﻿0.012  (-0.207, 0.230) | 0.013 | 0.013 | 54.7% |
|  | HKC | 0.065  (-0.113, 0.0243) | 0.009 | 0.013 | 49.9% |
| **50** | Logistic |  |  |  | 11.5% |
|  | PWP | 0.063  (-0.133, 0.260) | 0.011 | 0.015 | 43.5% |
|  | GF | 0.004  (-0.241, 0.249) | 0.013 | 0.013 | 49.2% |
|  | NF MPLa | -0.008  (-0.255, 0.240) | 0.017 | 0.017 | 51.7% |
|  | NF PPL | ﻿0.012  (-0.223, 0.248) | 0.014 | 0.014 | 53.1% |
|  | HKC | 0.064  (-0.132, 0.260) | 0.010 | 0.014 | 49.3% |
| **10** | Logistic |  |  |  | 11.1% |
|  | PWP | 0.059  (-0.171, 0.290) | 0.015 | 0.018 | 35.1% |
|  | GF | -0.003  (-0.290, 0.283) | 0.017 | 0.017 | 38.8% |
|  | NF MPLa | -0.016  (-0.307, 0.275) | 0.023 | 0.023 | 41.6% |
|  | NF PPL | 0.006  (-0.268, 0.279) | 0.021 | 0.021 | 38.8% |
|  | HKC | 0.060  (-0.170, 0.290) | 0.014 | 0.018 | 36.5% |

aNF MPL convergence: 90%: 959 simulations, 80%: 959 simulations, 70%: 940 simulations, 60%: 941 simulations, 50%: 937 simulations, 10%: 907 simulations. GF = Gamma frailty, NF = nested frailty, MPL = maximum penalized likelihood estimation, PPL = penalized partial likelihood estimation, HKC = hierarchical Kendall copula

Table 7. Bias, Variance, MSE and Power results across all scenarios for the cluster parameters

|  |  |  |  |
| --- | --- | --- | --- |
|  |  | **= 0.30** | **= 0.15** |
| Pair % | Model | Bias (95% CI) | Bias (95% CI) |
| **90** | Logistic | - | - |
|  | PWP | - | - |
|  | GF | 0.101  (-0.048, 0.250) | - |
|  | NF MPL | -0.293  (-0.293, -0.293) | 0.280  (0.136, 0.424) |
|  | NF PPL | 0.019  (-0.087, 0.125) | -0.044  (-0.158, 0.070) |
|  | HKC | -0.005  (-0.108, 0.099) | 0.231  (0.111, 0.352) |
| **80** | Logistic |  |  |
|  | PWP |  |  |
|  | GF | 0.098  (-0.049, 0.245) | - |
|  | NF MPL | -0.293  (-0.293, -0.293) | 0.276  (0.135, 0.418) |
|  | NF PPL | 0.019  (-0.089, 0.127) | -0.047  (-0.158, 0.065) |
|  | HKC | -0.005  (-0.110, 0.101) | 0.229  (0.109, 0.349) |
| **70** | Logistic | - | - |
|  | PWP | - | - |
|  | GF | 0.101  (-0.043, 0.246) | - |
|  | NF MPL | -0.293  (-0.293, -0.293) | 0.281  (0.138, 0.424) |
|  | NF PPL | 0.023  (-0.091, 0.137) | -0.049  (-0.168, 0.069) |
|  | HKC | 0.001  (-0.117, 0.117) | 0.231  (0.110, 0.352) |
| **60** | Logistic | - | - |
|  | PWP | - | - |
|  | GF | 0.098  (-0.056, 0.252) | - |
|  | NF MPL | -0.293  (-0.293, -0.293) | 0.279  (0.127, 0.431) |
|  | NF PPL | 0.022  (-0.100, 0.144) | -0.051  (-0.175, 0.074) |
|  | HKC | 0.001  (-0.125, 0.128) | 0.23  (0.106, 0.354) |
| **50** | Logistic | - | - |
|  | PWP | - | - |
|  | GF | 0.097  (-0.060, 0.254) | - |
|  | NF MPL | -0.293  (-0.293, -0.293) | 0.276  (0.116, 0.436) |
|  | NF PPL | 0.016  (-0.117, 0.148) | -0.047  (-0.181, 0.087) |
|  | HKC | -0.006  (-0.140, 0.128) | 0.228  (0.097, 0.358) |
| **10** | Logistic | - | - |
|  | PWP | - | - |
|  | GF | 0.093  (-0.088, 0.274) | - |
|  | NF MPL | -0.293  (-0.293, -0.293) | 0.272  (0.079, 0.465) |
|  | NF PPL | 0.007  (-0.251, 0.264) | -0.040  (-0.283, 0.203) |
|  | HKC | 0.018  (-0.300, 0.335) | 0.228  (0.074, 0.381) |

GF = Gamma frailty, NF = nested frailty, MPL = maximum penalized likelihood estimation, PPL = penalized partial likelihood estimation, HKC = hierarchical Kendall copula

Table 8. Bias, Variance, MSE and Power results across all null scenarios for the treatment parameter

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  |  | **= Treatment = 0** | | | |
| **Pair %** | Model | Bias (95% CI) | Variance | MSE | Type I Error |
| **90** | Logistic |  |  |  | 5.6% |
|  | PWP | -0.008  (-0.140, 0.124) | 0.005 | 0.005 | 5.2% |
|  | GF | -0.007  (-0.017, 0.156) | 0.005 | 0.005 | 5.2% |
|  | NF MPLa | 0.001  (-0.164, 0.166) | 0.007 | 0.007 | 5.6% |
|  | NF PPL | -0.007  (-0.162, 0.148) | 0.006 | 0.006 | 4.9% |
|  | HKC | -0.008  (-0.140, 0.124) | 0.005 | 0.005 | 5.2% |
| **80** | Logistic |  |  |  | 5.2% |
|  | PWP | 0.001  (-0.134, 0.134) | 0.005 | 0.005 | 4.1% |
|  | GF | 0.001  (-0.165, 0.165) | 0.006 | 0.006 | 4.9% |
|  | NF MPLa | -0.007  (-0.160, 0.157) | 0.007 | 0.007 | 5.7% |
|  | NF PPL | 0.001  (-0.156, 0.157) | 0.007 | 0.007 | 4.3% |
|  | HKC | 0.001  (-0.134, 0.134) | 0.005 | 0.005 | 4.5% |
| **70** | Logistic |  |  |  | 4.1% |
|  | PWP | 0.001  (-0.132, 0.134) | 0.005 | 0.005 | 4.2% |
|  | GF | 0.002  (-0.163, 0.166) | 0.006 | 0.006 | 3.8% |
|  | NF MPLa | 0.009  (-0.158, 0.176) | 0.008 | 0.008 | 4.1% |
|  | NF PPL | 0.002  (-0.155, 0.159) | 0.007 | 0.007 | 3.9% |
|  | HKC | 0.001  (-0.132, 0.134) | 0.005 | 0.005 | 3.7% |
| **60** | Logistic |  |  |  | 4.3% |
|  | PWP | -0.002  (-0.145, 0.141) | 0.005 | 0.005 | 4.8% |
|  | GF | -0.002  (-0.180, 0.176) | 0.006 | 0.006 | 5.3% |
|  | NF MPLa | 0.007  (-0.176, 0.189) | 0.008 | 0.008 | 6.0% |
|  | NF PPL | -0.001  (-0.170, 0.167) | 0.007 | 0.007 | 4.6% |
|  | HKC | -0.002  (-0.144, 0.140) | 0.005 | 0.005 | 5.0% |
| **50** | Logistic |  |  |  | 5.5% |
|  | PWP | -0.002  (-0.152, 0.149) | 0.006 | 0.006 | 5.7% |
|  | GF | -0.001  (-0.184, 0.181) | 0.007 | 0.007 | 5.3% |
|  | NF MPLa | 0.007  (-0.177, 0.192) | 0.009 | 0.009 | 5.4% |
|  | NF PPL | -0.001  (-0.176, 0.174) | 0.008 | 0.08 | 5.1% |
|  | HKC | -0.002  (-0.151, 0.148) | 0.006 | 0.006 | 5.7% |
| **10** | Logistic |  |  |  | 4.4% |
|  | PWP | -0.004  (-0.172, 0.166) | 0.008 | 0.008 | 4.6% |
|  | GF | -0.005  (-0.214, 0.205) | 0.009 | 0.009 | 4.9% |
|  | NF MPLa | 0.006  (-0.207, 0.219) | 0.012 | 0.012 | 5.5% |
|  | NF PPL | -0.004  (-0.205, 0.197) | 0.011 | 0.011 | 4.6% |
|  | HKC | -0.004  (-0.172, 0.166) | 0.008 | 0.008 | 4.5% |

aNF MPL convergence: 90%: 989 simulations, 80%: 990 simulations, 70%: 990 simulations, 60%: 980 simulations, 50%: 974 simulations, 10%: 952 simulations. GF = Gamma frailty, NF = nested frailty, MPL = maximum penalized likelihood estimation, PPL = penalized partial likelihood estimation, HKC = hierarchical Kendall copula

Table 9. Bias, Variance, MSE and Power results across all null scenarios for the ear parameter

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  |  | **= Ear = 0** | | | |
| **Pair %** | Model | Bias (95% CI) | Variance | MSE | Type I Error |
| **90** | Logistic |  |  |  | 1.2% |
|  | PWP | -0.006  (-0.124, 0.112) | 0.005 | 0.005 | 2.1% |
|  | GF | -0.007  (-0.159, 0.146) | 0.005 | 0.005 | 2.6% |
|  | NF MPLa | 0.001  (-0.154 0.157) | 0.008 | 0.008 | 2.9% |
|  | NF PPL | -0.006  (-0.153, 0.140) | 0.006 | 0.006 | 4.8% |
|  | HKC | -0.006  (-0.124, 0.112) | 0.004 | 0.004 | 5.5% |
| **80** | Logistic |  |  |  | 1.3% |
|  | PWP | 0.002  (-0.121, 0.125) | 0.005 | 0.005 | 1.8% |
|  | GF | 0.003  (-0.158, 0.163) | 0.005 | 0.005 | 3.6% |
|  | NF MPLa | 0.010  (-0.152, 0.173) | 0.008 | 0.009 | 3.7% |
|  | NF PPL | 0.003  (-0.149, 0.155) | 0.006 | 0.006 | 4.6% |
|  | HKC | 0.002  (-0.121, 0.124) | 0.004 | 0.004 | 4.4% |
| **70** | Logistic |  |  |  | 1.4% |
|  | PWP | -0.002  (-0.129, 0.125) | 0.005 | 0.005 | 2.6% |
|  | GF | -0.003  (-0.166, 0.161) | 0.006 | 0.006 | 3.3% |
|  | NF MPLa | 0.006  (-0.160, 0.172) | 0.009 | 0.009 | 3.6% |
|  | NF PPL | -0.003  (-0.159, 0.153) | 0.006 | 0.006 | 5.4% |
|  | HKC | -0.002  (-0.129, 0.125) | 0.004 | 0.004 | 4.9% |
| **60** | Logistic |  |  |  | 1.8% |
|  | PWP | -0.001  (-0.137, 0.134) | 0.005 | 0.005 | 3.0% |
|  | GF | -0.001  (-0.178, 0.175) | 0.006 | 0.006 | 2.8% |
|  | NF MPLa | 0.008  (-0.171, 0.187) | 0.009 | 0.010 | 3.5% |
|  | NF PPL | -0.001  (-0.166, 0.164) | 0.007 | 0.007 | 5.2% |
|  | HKC | -0.001  (-0.136, 0.134) | 0.005 | 0.005 | 4.6% |
| **50** | Logistic |  |  |  | 2.5% |
|  | PWP | 0.002  (-0.143, 0.146) | 0.006 | 0.006 | 4.3% |
|  | GF | 0.002  (-0.185, 0.190) | 0.007 | 0.007 | 5.3% |
|  | NF MPLa | 0.011  (-0.181, 0.204) | 0.010 | 0.010 | 4.9% |
|  | NF PPL | 0.003  (-0.174, 0.179) | 0.008 | 0.008 | 6.4% |
|  | HKC | 0.002  (-0.143, 0.146) | 0.005 | 0.005 | 6.8% |
| **10** | Logistic |  |  |  | 4.0% |
|  | PWP | 0.004  (-0.172, 0.180) | 0.008 | 0.008 | 4.2% |
|  | GF | 0.007  (-0.217, 0.230) | 0.009 | 0.009 | 4.1% |
|  | NF MPLa | 0.019  (-0.207, 0.245) | 0.014 | 0.014 | 5.0% |
|  | NF PPL | 0.006  (-0.207, 0.219) | 0.012 | 0.012 | 4.6% |
|  | HKC | 0.004  (-0.172, 0.180) | 0.008 | 0.008 | 4.7% |

aNF MPL convergence: 90%: 989 simulations, 80%: 990 simulations, 70%: 990 simulations, 60%: 980 simulations, 50%: 974 simulations, 10%: 952 simulations.

Table 10. Bias, Variance, MSE and Power results across all null scenarios for the interaction parameter

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  |  | **= Interaction = 0** | | | |
| **Pair %** | Model | Bias (95% CI) | Variance | MSE | Type I Error |
| **90** | Logistic |  |  |  | 2.0% |
|  | PWP | 0.008  (-0.156, 0.172) | 0.009 | 0.009 | 2.7 % |
|  | GF | 0.007  (-0.200, 0.214) | 0.011 | 0.011 | 3.2% |
|  | NF MPLa | 0.001  (-0.210, 0.211) | 0.014 | 0.014 | 4.0% |
|  | NF PPL | 0.008  (-0.192, 0.207) | 0.011 | 0.011 | 4.8% |
|  | HKC | 0.008  (-0.156, 0.172**)** | 0.007 | 0.008 | 4.3% |
| **80** | Logistic |  |  |  | 2.2% |
|  | PWP | -0.004  (-0.177, 0.170) | 0.010 | 0.010 | 2.8% |
|  | GF | -0.004  (-0.224, 0.215) | 0.011 | 0.011 | 3.7% |
|  | NF MPLa | -0.011  (-0.233, 0.211) | 0.015 | 0.015 | 3.7% |
|  | NF PPL | -0.005  (-0.215, 0.205) | 0.012 | 0.012 | 5.6% |
|  | HKC | -0.003  (-0.176, 0.169) | 0.008 | 0.008 | 4.5% |
| **70** | Logistic |  |  |  | 2.8% |
|  | PWP | 0.001  (-0.177, 0.176) | 0.010 | 0.010 | 3.2% |
|  | GF | 0.001  (-0.223, 0.225) | 0.012 | 0.012 | 3.7 % |
|  | NF MPLa | -0.006  (0.233, 0.221) | 0.016 | 0.016 | 3.7% |
|  | NF PPL | 0.001  (-0.211, 0.213) | 0.013 | 0.013 | 4.6% |
|  | HKC | 0.001  (-0.176, 0.176) | 0.009 | 0.009 | 4.7% |
| **60** | Logistic |  |  |  | 2.2% |
|  | PWP | 0.003  (-0.182, 0.187) | 0.011 | 0.011 | 3.2% |
|  | GF | 0.002  (-0.234, 0.238) | 0.012 | 0.012 | 3.4% |
|  | NF MPLa | -0.006  (-0.247, 0.234) | 0.016 | 0.017 | 4.4% |
|  | NF PPL | 0.002  (-0.220, 0.223) | 0.013 | 0.013 | 4.4% |
|  | HKC | 0.002  (-0.180, 0.185) | 0.009 | 0.009 | 4.4% |
| **50** | Logistic |  |  |  | 3.3% |
|  | PWP | 0.002  (-0.198, 0.203) | 0.012 | 0.012 | 3.4% |
|  | GF | 0.003  (-0.245, 0.251) | 0.013 | 0.01 | 3.5% |
|  | NF MPLa | -0.005  (-0.259, 0.250) | 0.018 | 0.018 | 4.0% |
|  | NF PPL | 0.002  (-0.236, 0.241) | 0.015 | 0.015 | 4.7% |
|  | HKC | 0.003  (-0.197, 0.202) | 0.010 | 0.010 | 4.7% |
| **10** | Logistic |  |  |  | 4.3% |
|  | PWP | -0.004  (-0.238, 0.230) | 0.016 | 0.016 | 4.0% |
|  | GF | -0.007  (-0.297, 0.283) | 0.018 | 0.018 | 4.4% |
|  | NF MPLa | -0.016  (-0.313, 0.280) | 0.024 | 0.024 | 5.0% |
|  | NF PPL | -0.007  (-0.284, 0.271) | 0.022 | 0.022 | 3.7% |
|  | HKC | -0.004  (-0.238, 0.230) | 0.015 | 0.015 | 4.4% |

aNF MPL convergence: 90%: 989 simulations, 80%: 990 simulations, 70%: 990 simulations, 60%: 980 simulations, 50%: 974 simulations, 10%: 952 simulations.

Table 11. Bias, Variance, MSE and Power results across all null scenarios for the cluster parameters

|  |  |  |  |
| --- | --- | --- | --- |
|  |  | **= 0.3** | **= 0.15** |
| **Pair %** | Model | Bias (95% CI) | Bias (95% CI) |
| **90** | Logistic | - | - |
|  | PWP | - | - |
|  | GF | 0.105  (-0.054, 0.264) | - |
|  | NF MPLa | -0.292  (-0.302, -0.283) | 0.283  (0.122, 0.445) |
|  | NF PPL | 0.014  (-0.094, 0.121) | -0.050  (-0.168, 0.068) |
|  | HKC | -0.023  (-0.122, 0.076) | 0.230  (0.100, 0.359) |
| **80** | Logistic | - | - |
|  | PWP | - | - |
|  | GF | 0.102  (-0.058, 0.261) | - |
|  | NF MPLa | -0.293  (-0.293, -0.293) | 0.281  (0.125, 0.438) |
|  | NF PPL | 0.012  (-0.097, 0.122) | -0.052  (-0.167, 0.063) |
|  | HKC | -0.024  (-0.125, 0.077) | 0.228  (0.100, 0.355) |
| **70** | Logistic | - | - |
|  | PWP | - | - |
|  | GF | 0.105  (-0.051, 0.261) | - |
|  | NF MPLa | -0.292  (-0.305, -0.279) | 0.285  (0.125, 0.445) |
|  | NF PPL | 0.017  (-0.099, 0.133) | -0.054  (-0.175, 0.067) |
|  | HKC | -0.020  (-0.132, 0.092) | 0.230  (0.102, 0.358) |
| **60** | Logistic | - | - |
|  | PWP | - | - |
|  | GF | 0.103  (-0.061, 0.267) | - |
|  | NF MPLa | -0.293  (-0.293, -0.293) | 0.283  (0.119, 0.447) |
|  | NF PPL | 0.016  (-0.108, 0.139) | -0.056  (-0.182, 0.071) |
|  | HKC | -0.018  (-0.139, 0.102) | 0.228  (0.095, 0.362) |
| **50** | Logistic | **-** | **-** |
|  | PWP | **-** | **-** |
|  | GF | 0.101  (-0.068, 0.270) | - |
|  | NF MPLa | -0.292  (-0.315, -0.269) | 0.279  (0.104, 0.455) |
|  | NF PPL | 0.010  (-0.122, 0.142) | -0.052  (-0.186, 0.082) |
|  | HKC | -0.025  (-0.153, 0.104) | 0.226  (0.083, 0.370) |
| **10** | Logistic | - | - |
|  | PWP | - | - |
|  | GF | 0.094  (-0.104, 0.292) | - |
|  | NF MPLa | -0.292  (-0.312, -0.272) | 0.276  (0.063, 0.488) |
|  | NF PPL | 0.001  (-0.257, 0.257) | -0.045  (-0.282, 0.192) |
|  | HKC | 0.001  (-0.308, 0.308) | 0.225  (0.061, 0.390) |

aNF MPL convergence: 90%: 989 simulations, 80%: 990 simulations, 70%: 990 simulations, 60%: 980 simulations, 50%: 974 simulations, 10%: 952 simulations.

Table 12. Bias, Variance, MSE and Power results when no Sub-cluster variance for 90% pairs

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Parameter | Model | Bias | Variance | MSE | Power |
| Treatment = 0.3 |  |  |  |  |  |
|  | Logistic |  |  |  | 31.3% |
|  | PWP | -0.065 | 0.004 | 0.009 | 94.9% |
|  | GF | -0.007 | 0.005 | 0.005 | 96.6% |
|  | NF MPL | 0.004 | 0.006 | 0.006 | 97.4% |
|  | NF PPL | -0.008 | 0.006 | 0.006 | 97.1% |
|  | HKC | -0.064 | 0.004 | 0.008 | 96.1% |
| Ear = 0.4 |  |  |  |  |  |
|  | Logistic |  |  |  | 50.9% |
|  | PWP | -0.086 | 0.004 | 0.012 | 99.9% |
|  | GF | -0.004 | 0.005 | 0.005 | 100% |
|  | NF MPL | 0.011 | 0.007 | 0.007 | 100% |
|  | NF PPL | -0.006 | 0.005 | 0.005 | 100% |
|  | HKC | -0.087 | 0.003 | 0.011 | 100% |
| Interaction = -0.25 |  |  |  |  |  |
|  | Logistic |  |  |  | 10.1% |
|  | PWP | 0.053 | 0.008 | 0.011 | 58.9% |
|  | GF | 0.004 | 0.009 | 0.009 | 63.9% |
|  | NF MPL | -0.007 | 0.012 | 0.012 | 67.7% |
|  | NF PPL | 0.006 | 0.010 | 0.010 | 71.1% |
|  | HKC | 0.056 | 0.007 | 0.010 | 67.6% |
| Cluster = 0.15 |  |  |  |  |  |
|  | GF | -0.019 |  |  |  |
|  | NF MPL | -0.293 |  |  |  |
|  | NF PPL | 0.023 |  |  |  |
|  | HKC | 0.085 |  |  |  |
| Sub-Cluster = 0 |  |  |  |  |  |
|  | NF MPL | 0.309 |  |  |  |
|  | NF PPL | 0.008 |  |  |  |
|  | HKC | 0.280 |  |  |  |

Table 13. Bias, Variance, MSE and Power results when large Sub-cluster variance for 90% pairs

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Parameter | Model | Bias | Variance | MSE | Power |
| Treatment = 0.3 |  |  |  |  |  |
|  | Logistic |  |  |  | 35.2% |
|  | PWP | -0.118 | 0.005 | 0.019 | 74.0% |
|  | GF | 0.001 | 0.007 | 0.007 | 84.6% |
|  | NF MPL | 0.011 | 0.010 | 0.010 | 86.9% |
|  | NF PPL | -0.032 | 0.010 | 0.011 | 78.2 % |
|  | HKC | -0.119 | 0.005 | 0.019 | 74.1% |
| Ear = 0.4 |  |  |  |  |  |
|  | Logistic |  |  |  | 52.6% |
|  | PWP | -0.174 | 0.005 | 0.035 | 88.2% |
|  | GF | -0.002 | 0.007 | 0.007 | 94.3% |
|  | NF MPL | 0.007 | 0.013 | 0.013 | 95.5% |
|  | NF PPL | -0.058 | 0.011 | 0.015 | 89.3 % |
|  | HKC | -0.173 | 0.005 | 0.035 | 89.1% |
| Interaction = -0.25 |  |  |  |  |  |
|  | Logistic |  |  |  | 14.8% |
|  | PWP | 0.097 | 0.010 | 0.019 | 34.0% |
|  | GF | -0.004 | 0.015 | 0.015 | 44.3% |
|  | NF MPL | -0.013 | 0.019 | 0.019 | 46.8% |
|  | NF PPL | 0.029 | 0.018 | 0.019 | 35.8% |
|  | HKC | 0.100 | 0.009 | 0.019 | 36.4% |
| Cluster = 0.15 |  |  |  |  |  |
|  | GF | 0.807 |  |  |  |
|  | NF MPL | -0.293 |  |  |  |
|  | NF PPL | -0.017 |  |  |  |
|  | HKC | -0.185 |  |  |  |
| Sub-Cluster = 1.15 |  |  |  |  |  |
|  | NF MPL | -0.001 |  |  |  |
|  | NF PPL | -0.100 |  |  |  |
|  | HKC | -0.233 |  |  |  |

Table 14. Bias, Variance, MSE and Power results when no Sub-cluster or cluster variance for 90% pairs

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Parameter | Model | Bias | Variance | MSE | Power |
| Treatment = 0.3 |  |  |  |  |  |
|  | Logistic |  |  |  | 31.4% |
|  | PWP | 0.004 | 0.004 | 0.004 | 99.7% |
|  | GF | 0.004 | 0.004 | 0.004 | 99.7% |
|  | NF MPL | 0.005 | 0.002 | 0.002 | 100% |
|  | NF PPL | 0.008 | 0.004 | 0.004 | 100% |
|  | HKC | -0.002 | 0.004 | 0.004 | 99.2% |
| Ear = 0.4 |  |  |  |  |  |
|  | Logistic |  |  |  | 44.3% |
|  | PWP | -0.002 | 0.004 | 0.004 | 100% |
|  | GF | -0.002 | 0.004 | 0.004 | 100% |
|  | NF MPL | -0.006 | 0.002 | 0.002 | 100% |
|  | NF PPL | 0.006 | 0.004 | 0.004 | 100% |
|  | HKC | -0.015 | 0.004 | 0.004 | 100% |
| Interaction = -0.25 |  |  |  |  |  |
|  | Logistic |  |  |  | 13.3% |
|  | PWP | -0.001 | 0.008 | 0.008 | 79.1% |
|  | GF | -0.001 | 0.008 | 0.008 | 79.6% |
|  | NF MPL | -0.001 | 0.005 | 0.005 | 88.6% |
|  | NF PPL | -0.006 | 0.008 | 0.008 | 80.1% |
|  | HKC | 0.005 | 0.008 | 0.008 | 78.9% |
| Cluster = 0 |  |  |  |  |  |
|  | GF | 0.001 |  |  |  |
|  | NF MPL | 0.007 |  |  |  |
|  | NF PPL | 0.006 |  |  |  |
|  | HKC | 0.000 |  |  |  |
| Sub-Cluster = 0 |  |  |  |  |  |
|  | NF MPL | 0.013 |  |  |  |
|  | NF PPL | 0.011 |  |  |  |
|  | HKC | -0.004 |  |  |  |

Table 15. Average AIC of results for all scenarios

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | **Pair %** | | | | | |
| Model | **90%** | **80%** | **70%** | **60%** | **50%** | **10%** |
| Logistic | - | - | - | - | - | - |
| PWP | 22576.31 | 21202.32 | 19829.63 | 18468.57 | 17122.20 | 11888.87 |
| GF | 24937.37 | 23441.34 | 21941.95 | 20457.37 | 18986.52 | 13255.24 |
| NF MPL | - | - | - | - | - | - |
| NF PPL | 24893.55 | 23402.48 | 21908.34 | 20428.80 | 18965.31 | 13254.86 |
| HKC | 25153.65 | 23644.34 | 22135.47 | 20638.06 | 19155.18 | 13378.80 |

Figure 5. Line graphs for the bias, variance, MSE and power from all null simulations across pair percentages for the treatment effect.

Graphical user interface, chart

Description automatically generated

Figure 6. Line graphs for the bias, variance, MSE and power from all null simulations across pair percentages for the ear effect.

Graphical user interface, chart

Description automatically generated

Figure 7. Line graphs for the bias, variance, MSE and power from all null simulations across pair percentages for the interaction effect.

Graphical user interface, chart

Description automatically generated

Figure 8. Line graphs for the bias from all null simulations across pair percentages for the random effect.

Graphical user interface, chart

Description automatically generated