**SPAJoint: A Multivariate Saddlepoint Approximation for Time-to-Event and Tumor Response Joint Analysis**

**TABLE S1 Bias and standard error of estimates for joint model with bivariate random effects**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Parameter | True value | Fitted value | Average Bias | SE | SD |
| Simulation 1 |  |  |  |  |  |
|  | 0.8 | 0.742 | 0.058 | 0.480 | 0.522 |
|  | 1.2 | 1.184 | 0.016 | 0.602 | 0.623 |
|  | -0.2 | -0.197 | 0.003 | 0.000 | 0.317 |
|  | -0.8 | -0.800 | 0.000 | 0.297 | 0.283 |
|  | 0.5 | 0.436 | 0.064 | 0.352 | 0.228 |
|  | 0.5 | 0.430 | 0.070 | 0.709 | 0.233 |
|  | -0.8 | -0.682 | 0.118 | 1.332 | 0.455 |
| Simulation 2 |  |  |  |  |  |
|  | 0.8 | 0.782 | 0.018 | 0.481 | 0.505 |
|  | 1.2 | 1.202 | 0.002 | 0.604 | 0.634 |
|  | -0.2 | -0.190 | 0.010 | 0.000 | 0.322 |
|  | -0.8 | -0.795 | 0.005 | 0.296 | 0.315 |
|  | 0.5 | 0.445 | 0.055 | 0.353 | 0.240 |
|  | 0.5 | 0.402 | 0.098 | 0.704 | 0.219 |
|  | -0.6 | -0.613 | 0.013 | 1.380 | 0.520 |
| Simulation 3 |  |  |  |  |  |
|  | 0.8 | 0.717 | 0.083 | 0.476 | 0.469 |
|  | 1.2 | 1.153 | 0.047 | 0.600 | 0.621 |
|  | -0.2 | -0.179 | 0.021 | 0.000 | 0.324 |
|  | -0.8 | -0.776 | 0.024 | 0.294 | 0.295 |
|  | 0.5 | 0.457 | 0.043 | 0.354 | 0.255 |
|  | 0.5 | 0.401 | 0.099 | 0.700 | 0.192 |
|  | -0.4 | -0.391 | 0.009 | 1.184 | 0.500 |
| Simulation 4 |  |  |  |  |  |
|  | 0.8 | 0.733 | 0.067 | 0.473 | 0.469 |
|  | 1.2 | 1.189 | 0.011 | 0.602 | 0.610 |
|  | -0.2 | -0.185 | 0.015 | 0.000 | 0.304 |
|  | -0.8 | -0.807 | 0.007 | 0.297 | 0.303 |
|  | 0.5 | 0.438 | 0.062 | 0.352 | 0.240 |
|  | 0.5 | 0.356 | 0.144 | 0.687 | 0.165 |
|  | -0.2 | -0.183 | 0.017 | 1.249 | 0.567 |
| Simulation 5 |  |  |  |  |  |
|  | 0.8 | 0.730 | 0.070 | 0.476 | 0.464 |
|  | 1.2 | 1.219 | 0.019 | 0.606 | 0.643 |
|  | -0.2 | -0.188 | 0.012 | 0.000 | 0.292 |
|  | -0.8 | -0.799 | 0.001 | 0.296 | 0.306 |
|  | 0.5 | 0.448 | 0.052 | 0.354 | 0.264 |
|  | 0.5 | 0.384 | 0.116 | 0.695 | 0.146 |
|  | 0.2 | 0.166 | 0.034 | 1.173 | 0.522 |
| Simulation 6 |  |  |  |  |  |
|  | 0.8 | 0.797 | 0.003 | 0.483 | 0.525 |
|  | 1.2 | 1.208 | 0.008 | 0.610 | 0.585 |
|  | -0.2 | -0.196 | 0.004 | 0.000 | 0.301 |
|  | -0.8 | -0.725 | 0.075 | 0.299 | 0.312 |
|  | 0.5 | 0.522 | 0.022 | 0.375 | 0.284 |
|  | 0.5 | 0.426 | 0.074 | 0.711 | 0.214 |
|  | 0.4 | 0.356 | 0.044 | 1.199 | 0.617 |
| Simulation 7 |  |  |  |  |  |
|  | 0.8 | 0.752 | 0.048 | 0.479 | 0.477 |
|  | 1.2 | 1.209 | 0.009 | 0.604 | 0.611 |
|  | -0.2 | -0.179 | 0.021 | 0.000 | 0.309 |
|  | -0.8 | -0.811 | 0.011 | 0.295 | 0.283 |
|  | 0.5 | 0.449 | 0.051 | 0.354 | 0.247 |
|  | 0.5 | 0.405 | 0.095 | 0.702 | 0.235 |
|  | 0.6 | 0.560 | 0.040 | 1.371 | 0.577 |
| Simulation 8 |  |  |  |  |  |
|  | 0.8 | 0.750 | 0.050 | 0.483 | 0.487 |
|  | 1.2 | 1.217 | 0.017 | 0.606 | 0.627 |
|  | -0.2 | -0.188 | 0.012 | 0.000 | 0.312 |
|  | -0.8 | -0.780 | 0.020 | 0.297 | 0.301 |
|  | 0.5 | 0.480 | 0.020 | 0.360 | 0.255 |
|  | 0.5 | 0.474 | 0.026 | 0.721 | 0.257 |
|  | 0.8 | 0.723 | 0.077 | 1.250 | 0.418 |

**Table S2 Empirical Type I Error Rates of SPAJoint, SPALogit, SPACox, C&L, and C|L for genetic variants**

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| Event rate |  | MAF | Empirical Type I Error Rates | | | | |
| SPAJoint | SPALogit | SPACox | PR&PS | PR|PS |
| 0.5 | 0.8 | 0.01 | 0.007 | 0.052 | 0.047 | 0.000 | 0.053 |
| 0.1 | 0.003 | 0.063 | 0.069 | 0.002 | 0.059 |
| 0.3 | 0.005 | 0.045 | 0.045 | 0.001 | 0.042 |
| 0.6 | 0.01 | 0.006 | 0.048 | 0.028 | 0.001 | 0.047 |
| 0.1 | 0.003 | 0.088 | 0.053 | 0.004 | 0.070 |
| 0.3 | 0.008 | 0.061 | 0.064 | 0.001 | 0.056 |
| 0.4 | 0.01 | 0.006 | 0.050 | 0.048 | 0.000 | 0.049 |
| 0.1 | 0.003 | 0.044 | 0.048 | 0.000 | 0.048 |
| 0.3 | 0.003 | 0.244 | 0.054 | 0.005 | 0.198 |
| 0.2 | 0.01 | 0.002 | 0.047 | 0.051 | 0.000 | 0.044 |
| 0.1 | 0.006 | 0.070 | 0.070 | 0.001 | 0.067 |
| 0.3 | 0.003 | 0.106 | 0.042 | 0.001 | 0.067 |
| 0.1 | 0.01 | 0.007 | 0.047 | 0.048 | 0.000 | 0.047 |
| 0.1 | 0.009 | 0.070 | 0.048 | 0.000 | 0.054 |
| 0.3 | 0.000 | 0.314 | 0.047 | 0.004 | 0.239 |
| 0.2 | 0.8 | 0.01 | 0.005 | 0.045 | 0.056 | 0.000 | 0.055 |
| 0.1 | 0.000 | 0.075 | 0.056 | 0.001 | 0.069 |
| 0.3 | 0.000 | 0.092 | 0.048 | 0.001 | 0.079 |
| 0.6 | 0.01 | 0.005 | 0.059 | 0.051 | 0.001 | 0.061 |
| 0.1 | 0.000 | 0.055 | 0.052 | 0.000 | 0.054 |
| 0.3 | 0.000 | 0.116 | 0.062 | 0.003 | 0.099 |
| 0.4 | 0.01 | 0.003 | 0.057 | 0.041 | 0.002 | 0.048 |
| 0.1 | 0.000 | 0.074 | 0.053 | 0.001 | 0.066 |
| 0.3 | 0.000 | 0.060 | 0.061 | 0.000 | 0.066 |
| 0.2 | 0.01 | 0.009 | 0.047 | 0.045 | 0.000 | 0.041 |
| 0.1 | 0.000 | 0.058 | 0.050 | 0.002 | 0.059 |
| 0.3 | 0.000 | 0.046 | 0.052 | 0.000 | 0.050 |
| 0.1 | 0.01 | 0.006 | 0.049 | 0.052 | 0.000 | 0.043 |
| 0.1 | 0.000 | 0.056 | 0.054 | 0.000 | 0.052 |
| 0.3 | 0.000 | 0.043 | 0.046 | 0.000 | 0.047 |
| 0.1 | 0.8 | 0.01 | 0.008 | 0.049 | 0.052 | 0.002 | 0.049 |
| 0.1 | 0.002 | 0.064 | 0.045 | 0.000 | 0.048 |
| 0.3 | 0.000 | 0.072 | 0.055 | 0.002 | 0.062 |
| 0.6 | 0.01 | 0.001 | 0.050 | 0.045 | 0.001 | 0.039 |
| 0.1 | 0.000 | 0.044 | 0.052 | 0.001 | 0.046 |
| 0.3 | 0.000 | 0.054 | 0.061 | 0.002 | 0.055 |
| 0.4 | 0.01 | 0.003 | 0.056 | 0.049 | 0.000 | 0.050 |
| 0.1 | 0.000 | 0.062 | 0.045 | 0.000 | 0.061 |
| 0.3 | 0.001 | 0.095 | 0.038 | 0.002 | 0.063 |
| 0.2 | 0.01 | 0.002 | 0.051 | 0.048 | 0.002 | 0.049 |
| 0.1 | 0.001 | 0.053 | 0.045 | 0.001 | 0.046 |
| 0.3 | 0.000 | 0.156 | 0.041 | 0.002 | 0.119 |
| 0.1 | 0.01 | 0.004 | 0.058 | 0.058 | 0.001 | 0.051 |
| 0.1 | 0.000 | 0.047 | 0.039 | 0.001 | 0.039 |
| 0.3 | 0.000 | 0.175 | 0.050 | 0.002 | 0.147 |
| 0.01 | 0.8 | 0.01 | 0.002 | 0.049 | 0.035 | 0.001 | 0.049 |
| 0.1 | 0.000 | 0.111 | 0.046 | 0.001 | 0.085 |
| 0.3 | 0.000 | 0.059 | 0.038 | 0.000 | 0.046 |
| 0.6 | 0.01 | 0.011 | 0.049 | 0.038 | 0.001 | 0.051 |
| 0.1 | 0.006 | 0.050 | 0.060 | 0.000 | 0.042 |
| 0.3 | 0.001 | 0.094 | 0.055 | 0.001 | 0.076 |
| 0.4 | 0.01 | 0.010 | 0.046 | 0.037 | 0.000 | 0.052 |
| 0.1 | 0.005 | 0.051 | 0.036 | 0.002 | 0.047 |
| 0.3 | 0.000 | 0.090 | 0.045 | 0.000 | 0.069 |
| 0.2 | 0.01 | 0.005 | 0.064 | 0.037 | 0.002 | 0.043 |
| 0.1 | 0.001 | 0.085 | 0.034 | 0.001 | 0.058 |
| 0.3 | 0.000 | 0.113 | 0.053 | 0.002 | 0.097 |
| 0.1 | 0.01 | 0.008 | 0.046 | 0.035 | 0.000 | 0.030 |
| 0.1 | 0.001 | 0.156 | 0.046 | 0.003 | 0.123 |
| 0.3 | 0.000 | 0.070 | 0.053 | 0.001 | 0.068 |
| 0.002 | 0.8 | 0.01 | 0.034 | 0.051 | 0.025 | 0.001 | 0.046 |
| 0.1 | 0.001 | 0.055 | 0.033 | 0.000 | 0.055 |
| 0.3 | 0.001 | 0.074 | 0.016 | 0.000 | 0.041 |
| 0.6 | 0.01 | 0.041 | 0.049 | 0.041 | 0.000 | 0.063 |
| 0.1 | 0.000 | 0.079 | 0.045 | 0.002 | 0.060 |
| 0.3 | 0.000 | 0.053 | 0.031 | 0.000 | 0.043 |
| 0.4 | 0.01 | 0.050 | 0.050 | 0.094 | 0.010 | 0.067 |
| 0.1 | 0.009 | 0.051 | 0.017 | 0.000 | 0.031 |
| 0.3 | 0.000 | 0.063 | 0.048 | 0.000 | 0.058 |
| 0.2 | 0.01 | 0.037 | 0.052 | 0.042 | 0.001 | 0.110 |
| 0.1 | 0.000 | 0.058 | 0.055 | 0.000 | 0.069 |
| 0.3 | 0.000 | 0.240 | 0.030 | 0.004 | 0.163 |
| 0.1 | 0.01 | 0.004 | 0.051 | 0.098 | 0.001 | 0.052 |
| 0.1 | 0.000 | 0.081 | 0.049 | 0.002 | 0.065 |
| 0.3 | 0.000 | 0.087 | 0.046 | 0.000 | 0.050 |

**Table S3 Empirical Type I Error Rates of SPAJoint, SPALogit, SPACox, C&L, and C|L for CpG island loci**

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| Event rate |  | MAF | Empirical Type I Error Rates | | | | |
| SPAJoint | SPALogit | SPACox | PR&PS | PR|PS |
| 0.5 | 0.8 | 0.01 | 0.003 | 0.001 | 0.003 | 0.000 | 0.001 |
| 0.1 | 0.001 | 0.004 | 0.006 | 0.002 | 0.004 |
| 0.3 | 0.000 | 0.005 | 0.009 | 0.001 | 0.002 |
| 0.6 | 0.01 | 0.002 | 0.008 | 0.008 | 0.001 | 0.007 |
| 0.1 | 0.003 | 0.005 | 0.013 | 0.004 | 0.004 |
| 0.3 | 0.001 | 0.006 | 0.004 | 0.001 | 0.005 |
| 0.4 | 0.01 | 0.002 | 0.008 | 0.009 | 0.000 | 0.009 |
| 0.1 | 0.003 | 0.010 | 0.007 | 0.000 | 0.008 |
| 0.3 | 0.003 | 0.006 | 0.008 | 0.005 | 0.008 |
| 0.2 | 0.01 | 0.002 | 0.014 | 0.015 | 0.000 | 0.014 |
| 0.1 | 0.001 | 0.018 | 0.013 | 0.001 | 0.017 |
| 0.3 | 0.003 | 0.006 | 0.009 | 0.001 | 0.016 |
| 0.1 | 0.01 | 0.002 | 0.007 | 0.008 | 0.000 | 0.017 |
| 0.1 | 0.003 | 0.007 | 0.008 | 0.000 | 0.014 |
| 0.3 | 0.000 | 0.004 | 0.007 | 0.004 | 0.009 |
| 0.2 | 0.8 | 0.01 | 0.001 | 0.005 | 0.006 | 0.000 | 0.005 |
| 0.1 | 0.000 | 0.007 | 0.004 | 0.001 | 0.009 |
| 0.3 | 0.002 | 0.009 | 0.008 | 0.001 | 0.007 |
| 0.6 | 0.01 | 0.002 | 0.009 | 0.011 | 0.001 | 0.011 |
| 0.1 | 0.000 | 0.005 | 0.012 | 0.000 | 0.010 |
| 0.3 | 0.000 | 0.006 | 0.006 | 0.003 | 0.009 |
| 0.4 | 0.01 | 0.003 | 0.007 | 0.011 | 0.002 | 0.008 |
| 0.1 | 0.000 | 0.014 | 0.013 | 0.001 | 0.006 |
| 0.3 | 0.000 | 0.009 | 0.006 | 0.000 | 0.006 |
| 0.2 | 0.01 | 0.002 | 0.007 | 0.007 | 0.000 | 0.011 |
| 0.1 | 0.000 | 0.008 | 0.006 | 0.002 | 0.009 |
| 0.3 | 0.000 | 0.007 | 0.005 | 0.000 | 0.011 |
| 0.1 | 0.01 | 0.001 | 0.009 | 0.012 | 0.000 | 0.013 |
| 0.1 | 0.000 | 0.006 | 0.009 | 0.000 | 0.012 |
| 0.3 | 0.000 | 0.006 | 0.006 | 0.000 | 0.007 |
| 0.1 | 0.8 | 0.01 | 0.001 | 0.003 | 0.005 | 0.002 | 0.004 |
| 0.1 | 0.002 | 0.004 | 0.004 | 0.000 | 0.008 |
| 0.3 | 0.000 | 0.006 | 0.005 | 0.001 | 0.002 |
| 0.6 | 0.01 | 0.000 | 0.009 | 0.015 | 0.001 | 0.009 |
| 0.1 | 0.000 | 0.010 | 0.010 | 0.001 | 0.006 |
| 0.3 | 0.000 | 0.014 | 0.006 | 0.002 | 0.004 |
| 0.4 | 0.01 | 0.003 | 0.012 | 0.009 | 0.000 | 0.010 |
| 0.1 | 0.000 | 0.006 | 0.005 | 0.000 | 0.006 |
| 0.3 | 0.001 | 0.009 | 0.008 | 0.002 | 0.0099 |
| 0.2 | 0.01 | 0.002 | 0.011 | 0.015 | 0.002 | 0.019 |
| 0.1 | 0.001 | 0.012 | 0.012 | 0.001 | 0.014 |
| 0.3 | 0.000 | 0.009 | 0.011 | 0.002 | 0.009 |
| 0.1 | 0.01 | 0.004 | 0.008 | 0.008 | 0.001 | 0.011 |
| 0.1 | 0.000 | 0.007 | 0.009 | 0.001 | 0.009 |
| 0.3 | 0.000 | 0.005 | 0.010 | 0.002 | 0.017 |
| 0.01 | 0.8 | 0.01 | 0.002 | 0.007 | 0.015 | 0.000 | 0.004 |
| 0.1 | 0.002 | 0.004 | 0.004 | 0.000 | 0.008 |
| 0.3 | 0.000 | 0.009 | 0.008 | 0.002 | 0.003 |
| 0.6 | 0.01 | 0.001 | 0.009 | 0.013 | 0.001 | 0.011 |
| 0.1 | 0.003 | 0.010 | 0.016 | 0.000 | 0.008 |
| 0.3 | 0.001 | 0.014 | 0.010 | 0.001 | 0.006 |
| 0.4 | 0.01 | 0.001 | 0.014 | 0.017 | 0.000 | 0.012 |
| 0.1 | 0.005 | 0.011 | 0.016 | 0.002 | 0.014 |
| 0.3 | 0.000 | 0.012 | 0.014 | 0.000 | 0.009 |
| 0.2 | 0.01 | 0.005 | 0.008 | 0.014 | 0.002 | 0.013 |
| 0.1 | 0.001 | 0.011 | 0.012 | 0.001 | 0.008 |
| 0.3 | 0.000 | 0.010 | 0.011 | 0.002 | 0.009 |
| 0.1 | 0.01 | 0.003 | 0.006 | 0.005 | 0.000 | 0.010 |
| 0.1 | 0.001 | 0.006 | 0.006 | 0.003 | 0.013 |
| 0.3 | 0.000 | 0.007 | 0.003 | 0.001 | 0.008 |
| 0.002 | 0.8 | 0.01 | 0.001 | 0.014 | 0.018 | 0.000 | 0.006 |
| 0.1 | 0.000 | 0.015 | 0.009 | 0.002 | 0.005 |
| 0.3 | 0.001 | 0.010 | 0.013 | 0.001 | 0.007 |
| 0.6 | 0.01 | 0.001 | 0.015 | 0.011 | 0.000 | 0.013 |
| 0.1 | 0.000 | 0.010 | 0.009 | 0.002 | 0.009 |
| 0.3 | 0.000 | 0.011 | 0.016 | 0.000 | 0.015 |
| 0.4 | 0.01 | 0.002 | 0.013 | 0.014 | 0.010 | 0.019 |
| 0.1 | 0.001 | 0.011 | 0.017 | 0.000 | 0.011 |
| 0.3 | 0.000 | 0.010 | 0.008 | 0.000 | 0.013 |
| 0.2 | 0.01 | 0.003 | 0.012 | 0.012 | 0.001 | 0.011 |
| 0.1 | 0.000 | 0.010 | 0.010 | 0.000 | 0.009 |
| 0.3 | 0.000 | 0.011 | 0.013 | 0.004 | 0.010 |
| 0.1 | 0.01 | 0.003 | 0.011 | 0.011 | 0.001 | 0.012 |
| 0.1 | 0.000 | 0.008 | 0.009 | 0.002 | 0.015 |
| 0.3 | 0.003 | 0.007 | 0.008 | 0.000 | 0.010 |

Table S4 Partial parameter estimates (standard error) for bladder cancer.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Parameter | Joint with bivariate random effect | Independent random effect | Logistic model | Cox model |
|  | 0.152(0.492) | 0.011(0.295) | 0.014(0.298) |  |
|  | -0.124(0.955) | -0.104(0.525) | -0.100(0.528) |  |
|  | -2.060(2.265) | -2.055(1.064) | -2.058(1.065) |  |
|  | -0.585(0.400) | -0.360(0.198) |  | -0.361(0.198) |
|  | -0.906(0.800) | -0.204(0.393) |  | -0.205(0.393) |
|  | 3.283(1.829) | 0.790(0.705) |  | 0.788(0.706) |
|  | 2.248(0.557) |  |  |  |
|  | 2.089(0.969) |  |  |  |
|  | = -0.943(0.269) |  |  |  |

Table S5. Partial parameter estimates (standard error) for pancreatic cancer.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Parameter | Joint with bivariate random effect | Independent random effect | Logistic model | Cox model |
|  | -0.291(0.405) | -0.257(0.336) | -0.258(0.347) |  |
|  | -0.202(0.171) | 0.190(0.155) | -0.191(0.153) |  |
|  | 1.756(2.197) | 1.548(0.802) | 1.526(1.827) |  |
|  | -0.249(0.345) | -0.227(0.336) |  | -0.253(0.229) |
|  | 0.259(0.149) | 0.259(0.148) |  | 0.276(0.111) |
|  | -1.681(1.747) | -1.791(1.053) |  | -1.123(1.097) |
|  | 1.876(0.464) | 1.753(0.569) |  |  |
|  | 1.148(0.711) | 0.471(0.563) |  |  |
|  | = -0.874(0.317) |  |  |  |

Table S6. Partial parameter estimates (standard error) for colorectal cancer.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Parameter | Joint with bivariate random effect | Independent random effect | Logistic model | Cox model |
|  | -0.524(0.696) | -0.368(0.582) | -3.780(0.547) |  |
|  | 0.080(0.282) | 0.055(0.248) | 0.081(0.238) |  |
|  | -0.747(2.967) | -0.624(2.579) | -0.568(2.392) |  |
|  | 0.359(0.611) | 0.315(0.511) |  | 0.315(0.415) |
|  | 0.283(0.252) | 0.170(0.215) |  | 0.178(0.187) |
|  | 1.904(2.579) | 0.944(0.409) |  | 0.776(1.996) |
|  | 2.890(1.145) | 1.457(1.562) |  |  |
|  | 2.447(1.696) | 0.824(1.199) |  |  |
|  | = -0.945(0.436) |  |  |  |