



Selection Bias in Pre-Specified Covariate Models

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Background

Covariate-parameter relations are often chosen *a priori*, as in the full model approach. The assumption of such analyses are often that estimates of pre-specified relations are unbiased. Similarly, in SCMs focused on some parameters only (partial SCM), it is often assumed that covariate relations for a parameter can be developed independently

Objective

- To investigate the influence of misspecification of pre-specified covariate-parameter relations on bias and Type 1 error
- Explore potential predictors which can be used to predict risk of bias and false positives

Methods

- Sparse and rich data were simulated from PK and PD models with a true covariate (binary 0/1) parameter relationship
- Estimation models where the true effect was ignored and the covariate was included on other parameters were fit to these data (alternate models)
- Bias and Type 1 error in parameter estimates of these alternate models were evaluated

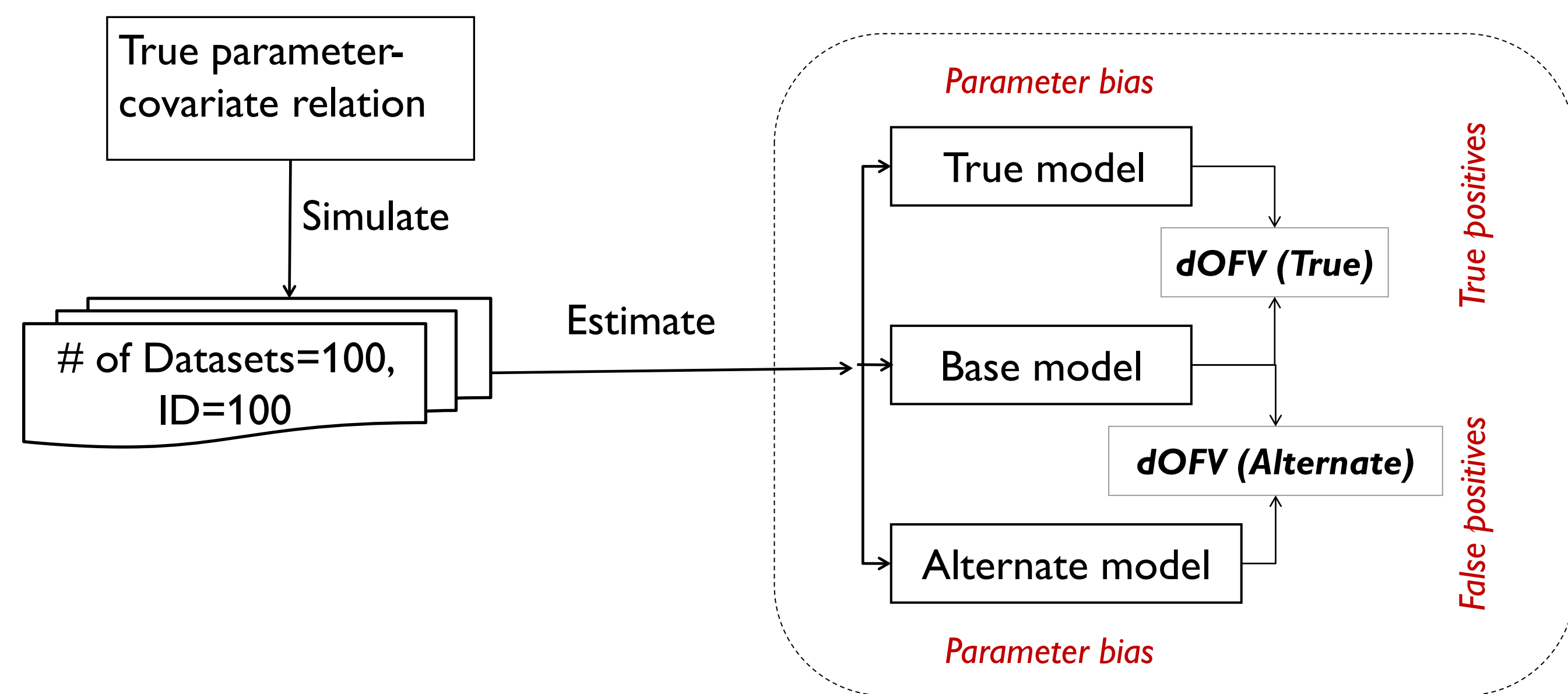


Figure 1: Schematic representation of stochastic simulations and re-estimations

- Predictors evaluated for Type 1 error inflation included: richness of the data, correlation between estimates, shrinkage, magnitude of covariate effects and sample size

Results

Table 1: Bias of covariate effect parameter (fractional effect) when the true relation is not included in the alternate model. Estimates in red indicate bias for covariate effect of true relations

| PK Rich Data – Bias on Cov Effect | | | | |
|-------------------------------------|-----------------|---------------|--------------|---------------|
| Simulation \ Alternate Model → | Cov on TVKA | Cov on TVCL | Cov on TVV | Cov on F |
| Cov on TVKA | -0.02 (0.05) | 0.03 (0.07) | 0.21 (0.10) | 0.11 (0.06) |
| Cov on TVCL | 0.03 (0.13) | -0.01 (0.03) | 0.05 (0.10) | -0.31 (0.04) |
| Cov on TVV | 0.40 (0.20) | 0.08 (0.09) | 0.001 (0.02) | -0.28 (0.04) |
| Cov on F | 0.56 (0.22) | -0.47 (0.05) | -0.46 (0.06) | 0.01 (0.02) |
| PK Sparse Data – Bias on Cov Effect | | | | |
| Simulation \ Alternate Model → | Cov on TVKA | Cov on TVCL | Cov on TVV | Cov on F |
| Cov on TVKA | -0.12 (0.22) | -0.12 (0.13) | 0.23 (0.06) | 0.08 (0.06) |
| Cov on TVCL | -0.35 (0.13) | -0.05 (0.21) | -0.08 (0.18) | -0.20 (0.05) |
| Cov on TVV | 0.98 (*) | -0.06 (0.21) | -0.02 (0.04) | -0.30 (0.04) |
| Cov on F | 0.94 (0.20) | -0.85 (0.12) | -0.52 (0.03) | -0.01 (0.02) |
| PD Rich Data – Bias on Cov Effect | | | | |
| Simulation \ Alternate Model → | Cov on Baseline | Cov on Ke0 | Cov on Emax | Cov on EC50 |
| Cov on Baseline | 0.01 (0.03) | 0.10 (0.15) | -0.55 (0.04) | 0.97 (0.07) |
| Cov on Ke0 | 0.04 (0.10) | 0.01 (0.07) | 0.05 (0.14) | -0.23 (0.22) |
| Cov on Emax | -0.30 (0.05) | 0.0 (0.1) | 0.02 (0.06) | 0.76 (0.39) |
| Cov on EC50 | 0.15 (0.09) | -0.10 (0.09) | 0.11 (0.15) | 0.04 (0.19) |
| PD Sparse Data – Bias on Cov Effect | | | | |
| Simulation \ Alternate Model → | Cov on Baseline | Cov on Ke0 | Cov on Emax | Cov on EC50 |
| Cov on Baseline | -0.001 (0.03) | 0.34 (0.27) | -0.56 (0.06) | 0.98 (*) |
| Cov on Ke0 | 0.03 (0.07) | -0.003 (0.12) | 0.02 (0.13) | -0.28 (-0.32) |
| Cov on Emax | -0.25 (0.05) | 0.04 (0.26) | 0.01 (0.06) | 0.97 (0.06) |
| Cov on EC50 | 0.15 (0.08) | -0.21 (0.13) | 0.17 (0.13) | 0.03 (0.12) |

Results

- Substantial bias was observed in the estimated alternate covariate relation when the true relation was not included (Table 1)
- Testing of alternate relations, as in a partial SCM, produced inflated Type 1 errors when the true relation was not included (Table 2)

Table 2: dOFV and Type 1 error for alternate models for PK based models. Estimates in red indicate the power of detecting the true covariate-parameter relation

| Sparse Data | | | | | | | | |
|--------------------------------|-------------|------------------|-------------|------------------|------------|------------------|----------|------------------|
| Simulation \ Alternate Model → | Cov on TVKA | | Cov on TVCL | | Cov on TVV | | Cov on F | |
| | dOFV | Type 1 Error (%) | dOFV | Type 1 Error (%) | dOFV | Type 1 Error (%) | dOFV | Type 1 Error (%) |
| Base | 1 | 5 | 1.3 | 11 | 0.9 | 5 | 0.9 | 3 |
| Cov on TVKA | 16.0 | 95 | 4.7 | 43 | 12.9 | 89 | 3.2 | 41 |
| Cov on TVCL | 12.1 | 82 | 39.5 | 100 | 8.4 | 67 | 15.3 | 92 |
| Cov on TVV | 27.0 | 100 | 1.6 | 25 | 74.6 | 100 | 37.0 | 100 |
| Cov on F | 9.4 | 92 | 45.8 | 99 | 107.3 | 100 | 114 | 100 |
| Rich Data | | | | | | | | |
| Simulation \ Alternate Model → | Cov on TVKA | | Cov on TVCL | | Cov on TVV | | Cov on F | |
| | dOFV | Type 1 Error (%) | dOFV | Type 1 Error (%) | dOFV | Type 1 Error (%) | dOFV | Type 1 Error (%) |
| Base | 1.2 | 7 | 1.2 | 6 | 1.2 | 4 | 1.1 | 8 |
| Cov on TVKA | 35.0 | 100 | 1.1 | 10 | 6.3 | 69 | 4.4 | 46 |
| Cov on TVCL | 1.2 | 5 | 84.2 | 100 | 1.4 | 15 | 32.5 | 100 |
| Cov on TVV | 6.6 | 73 | 1.5 | 13 | 78.3 | 100 | 26.6 | 100 |
| Cov on F | 9.1 | 84 | 42.8 | 100 | 36.6 | 100 | 117.3 | 100 |

- No reliable predictors of this increased risk of bias and false positives were identified, but sparseness of data and correlation between the estimates of typical value parameters of the true and the alternate relations correlated positively with risk of bias and false positives (Figure 2)

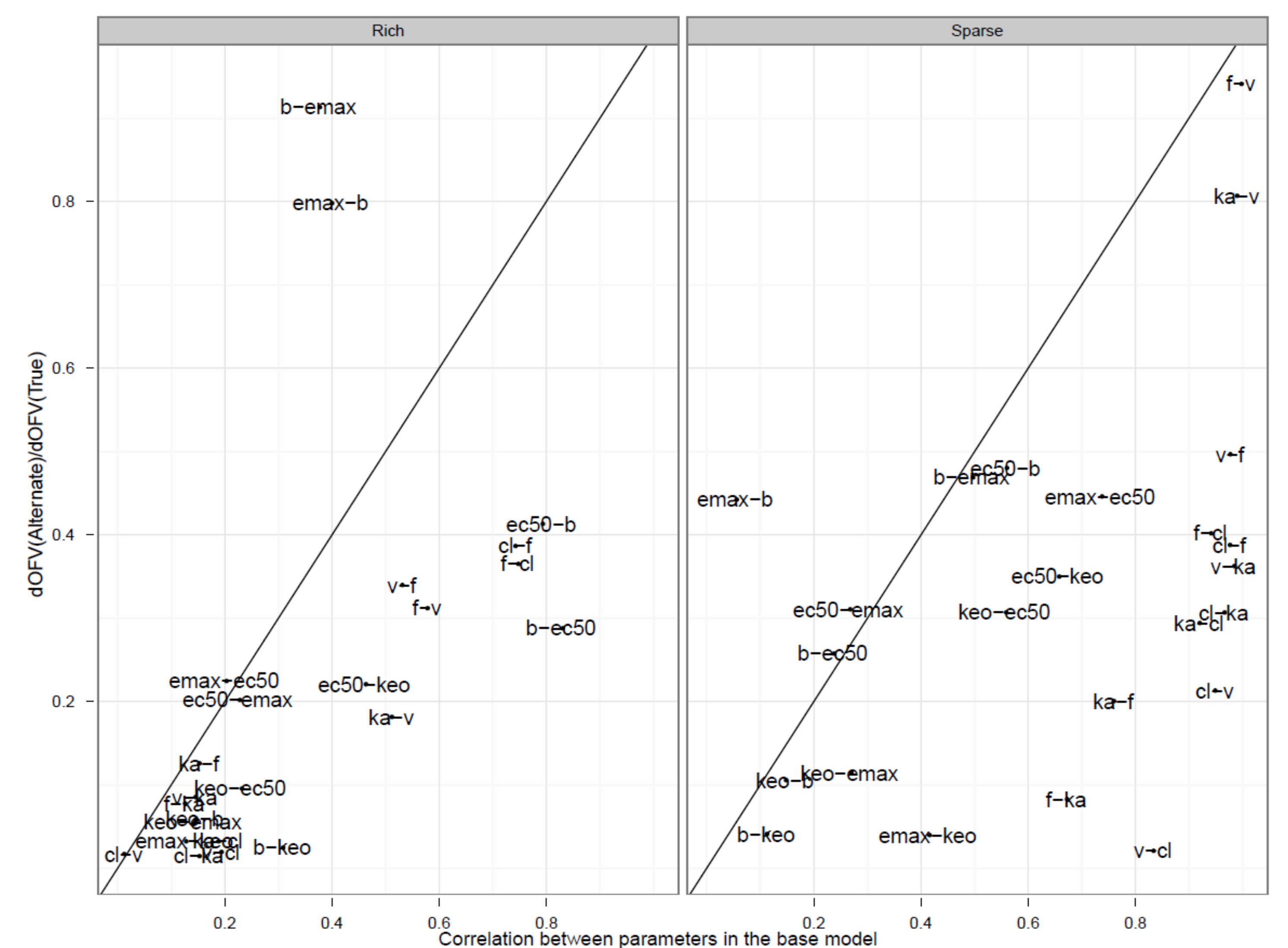


Figure 2: Correlation between parameters in the base model as potential predictors to evaluate risk of Type 1 error in alternate models where the true relation is ignored. Each plotting symbol represents; "true relation – alternate relation"

Conclusions

- If pre-specified covariate-parameter relations are misspecified, parameter estimates are biased
- With covariate relation misspecification there is an inflated Type 1 error when testing alternate models
- Predictors to identify these risks were not found



Table : Bias of parameter when the true relation is not included in the alternate model. for sparse and rich designs. Estimates in red indicate bias of the true relation parameter

| SPARSE DATA | | | | | |
|-----------------------------|-----------------------------|----------------------------|-----------------------------|----------------------------|-----------------------------|
| Bias on TVCL | | | | | |
| Simulation\Alternate Model→ | Base | Cov on TVKA | Cov on TVCL | Cov on TVV | Cov on F |
| Base | NA | 4.0 (2.7,5.4) | 4.6 (2.8, 6.4) | 4.0 (2.7, 5.3) | 4.5 (3.0, 5.9) |
| Cov on TVKA | -5.8 (-7.3, -4.2) | 3.3 (2.2, 4.5) | 4.0 (1.4, 6.5) | 3.2 (1.6, 4.9) | -9.9 (-11.6,-8.2) |
| Cov on TVCL | -47.7 (-49.0,-46.2) | -49.7 (-51.0,-48.5) | 2.9 (0.9,5.0) | -62.3 (-63.2,-61.3) | -38.7 (-40.1,-37.4) |
| Cov on TVV | 7.5 (7.0, 8.18) | 3.1 (2.5, 3.6) | 5.6 (5.0, 6.2) | 0.8 (0.2, 1.5) | 21.7 (21.0, 22.3) |
| Cov on F | -28.0 (-29.6, -26.5) | -24.7 (-25.5,-23.9) | 2.1 (1.3, 2.9) | -40.3 (-40.9, -39.7) | 2.4 (0.9, 3.9) |
| Bias on TVV | | | | | |
| Simulation\Alternate Model→ | Base | Cov on TVKA | Cov on TVCL | Cov on TVV | Cov on F |
| Base | NA | -44.0 (-51.1, -37.0) | -6.76 (-9.86,-3.6) | -4.9 (-7.7,-2.1) | -5.4 (-8.2, -2.7) |
| Cov on TVKA | 15.5 (12.7, 18.3) | -2.2 (-4.6, 0.17) | 0.2 (-4.1, 4.6) | 33.6 (32.2, 35.0) | 16.4(13.6, 19.2) |
| Cov on TVCL | 25.3 (24.0,26.6) | 22.0 (20.7,23.2) | -0.8 (-2.9,1.3) | 46.5 (44.6,48.4) | 28.7 (27.4, 30.0) |
| Cov on TVV | -37.0 (-38.0, -36.1) | -23.5 (-24.0,-23.0) | -37.9 (-39.0, -36.8) | 1.9 (0.09, 3.8) | -30.9 (-31.8, -29.9) |
| Cov on F | -12.0 (-13.5,-10.5) | -17.2 (-18.0,-16.4) | -15.8 (-16.4,-15.1) | 36.3 (35.1, 37.5) | 0.6 (-1.4, 2.6) |
| Bias on TVKA | | | | | |
| Simulation\Alternate Model→ | Base | Cov on TVKA | Cov on TVCL | Cov on TVV | Cov on F |
| Base | NA | -21.6 (-31.2, -12.1) | -24.50 (-9.8, -3.6) | -18.6 (-28.0, -9.2) | -20.4 (-29.9, -11) |
| Cov on TVKA | 27.9 (19.2, 36.5) | -8.4 (-14.8,-2.0) | -17.8 (-31.2, -4.3) | -30.5 (-41.2,-19.8) | 37.6 (28.6, 46.5) |
| Cov on TVCL | 73.3 (69.6,77.0) | 78.3 (74.4, 82.1) | -2 (-7.4, 3.4) | 82.5 (79.2,85.9) | 65.1 (61.9,68.3) |
| Cov on TVV | -80.4 (-84.8, -75.9) | -22.1 (-24.0,-20.2) | -82.5 (-87.6, -77.5) | 5.1 (0.3, 10.0) | -85.8 (-89.4, -82.3) |
| Cov on F | 28.1 (22.2, 33.9) | -7.9 (-10.9, -4.9) | 19.4 (17.1, 21.7) | 93.4 (90.2, 96.6) | 0.1 (-6.2, 6.5) |

| RICH DATA | | | | | |
|-----------------------------|---------------------------|--------------------------|---------------------------|--------------------------|---------------------------|
| Bias on TVCL | | | | | |
| Simulation\Alternate Model→ | Base | Cov on TVKA | Cov on TVCL | Cov on TVV | Cov on F |
| Base | NA | 0.07 (-0.5, 0.6) | 0.06 (-0.5, 0.7) | 0.06 (-0.5, 0.6) | -0.04 (-0.5, 0.67) |
| Cov on TVKA | 0.008 (-0.6, 0.6) | 0.3 (-0.2, 0.8) | -0.8 (-1.7, 0.1) | -0.1 (-0.7, 0.46) | -4.9 (-5.6,-4.1) |
| Cov on TVCL | -5.2 (-5.7,-4.6) | -5.2 (-5.8,-4.6) | 0.2 (-0.5, 1.0) | -5.2 (-5.8,-4.6) | -3.5 (-4.1,-2.9) |
| Cov on TVV | 0.3 (-0.3, 0.9) | 0.4 (-0.2,1.4) | -0.46 (-0.2, 1.1) | -0.2 (-0.8, 0.4) | 1.6 (0.9,2.3) |
| Cov on F | -5.7 (-6.3, -5.2) | -5.5 (-6.1, -5.0) | -0.8 (-1.4,-0.2) | -28.0 (-28.6,-27.3) | 0.1 (-0.6, 0.8) |
| Bias on TVV | | | | | |
| Simulation\Alternate Model→ | Base | Cov on TVKA | Cov on TVCL | Cov on TVV | Cov on F |
| Base | NA | 0.4 (-0.2,1.1) | 0.4 (-0.2, 1.1) | 0.67 (-0.03, 1.4) | 0.65 (-0.05, 1.3) |
| Cov on TVKA | 1.0 (0.2,1.7) | 0.06 (-0.7, 0.8) | 1.0 (0.2, 1.7) | -7.2 (-8.0,-6.4) | -3.9 (-4.7, -3.0) |
| Cov on TVCL | 0.04 (-0.6, 0.7) | 0.06 (-0.6,0.7) | -0.2 (-1.0, 0.5) | 0.11(-0.5,-0.7) | 1.6 (1.0, 2.3) |
| Cov on TVV | -5.8 (-6.4, -5.1) | -5.8 (-6.4, -5.2) | -5.8 (-6.4,-5.2) | -0.1 (-1.0, 0.8) | -4.5 (-5.1,-3.8) |
| Cov on F | -5.5 (-6.1, -4.9) | -5.4 (-6.0,-4.8) | -27.4 (-28.1,-26.7) | -0.15 (-0.6, 0.9) | 0.5 (-0.3, 1.3) |
| Bias on TVKA | | | | | |
| Simulation\Alternate Model→ | Base | Cov on TVKA | Cov on TVCL | Cov on TVV | Cov on F |
| Base | NA | -27.3 (-28.12,-26.5) | 1.9 (0.8,3.0) | 1.9 (0.9, 3.0) | 1.9 (0.9,3.0) |
| Cov on TVKA | -2.85 (-4.1, -1.5) | 0.4 (-0.9, 1.8) | -2.83 (-4.1, -1.5) | -2.5 (-3.8, -1.3) | -2.67 (-3.9, -1.3) |
| Cov on TVCL | -0.05 (-1.0, 0.9) | 0.25(-0.8, 1.3) | 0.9 (-0.03, 1.9) | -0.2 (-1.2, 0.8) | -0.05 (-1.1, 0.9) |
| Cov on TVV | 0.2 (-0.6, 1.2) | 1.3 (0.3, 2.2) | 0.1 (-0.7, 1.1) | -0.5 (-1.5, 0.5) | 0.3 (-0.5, 1.2) |
| Cov on F | 0.7 (-0.2, 1.6) | 3.3 (2.3, 4.3) | 2.3 (1.3,3.3) | 1.4 (0.5,2.3) | 1.4 (0.6, 2.3) |