Prediction and explanation in studies with rare events: problems and solutions

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Rare events: examples

Medicine:	
• Side effects of treatment	1/1000s to fairly common
• Hospital-acquired infections	9.8/1000 pd
• Epidemiologic studies of rare diseases	1/1000 to 1/200,000
Engineering:	
• Rare failures of systems	0.1-1/year
Economy:	
• E-commerce click rates	1-2/1000 impressions
Political science:	
• Wars, election surprises, vetos	1/dozens to 1/1000s

…

Problems with rare events

- ‚Big‘ studies needed to observe enough events
- Difficult to attribute events to risk factors

- Low absolute number of events
- Low event rate

Our interest

- Statistical models
  - for prediction of binary outcomes
  - should be interpretable,

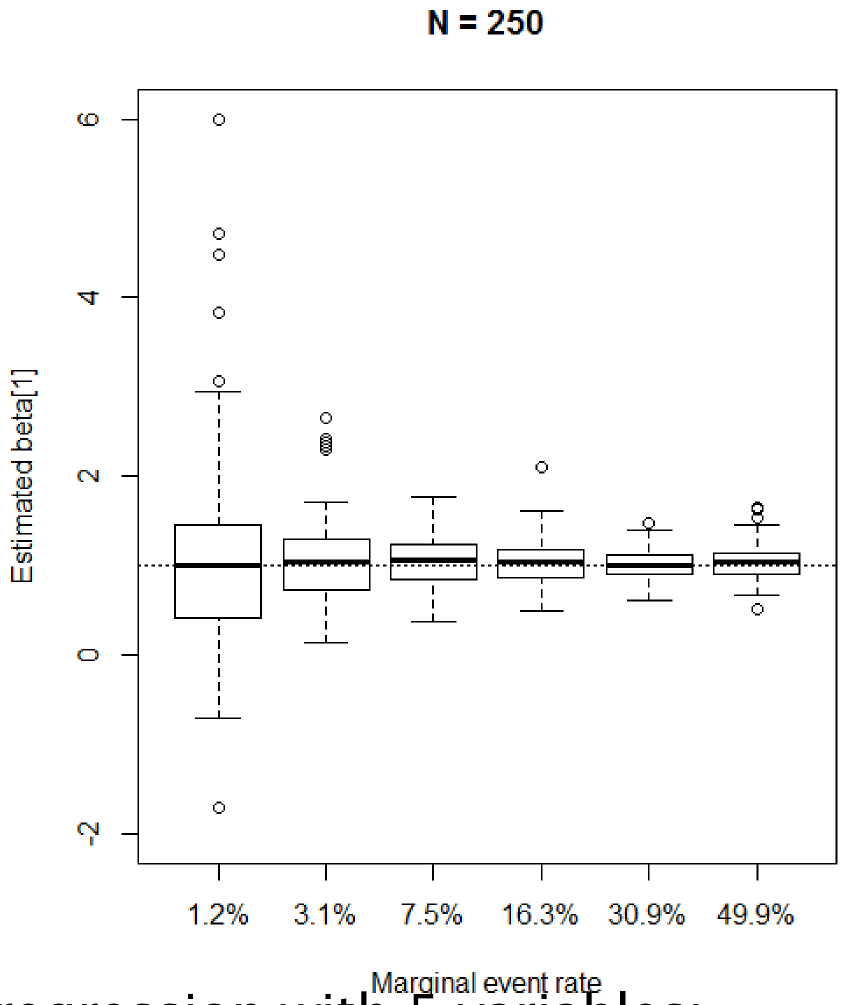
    i.e., ‚betas‘ should have a meaning

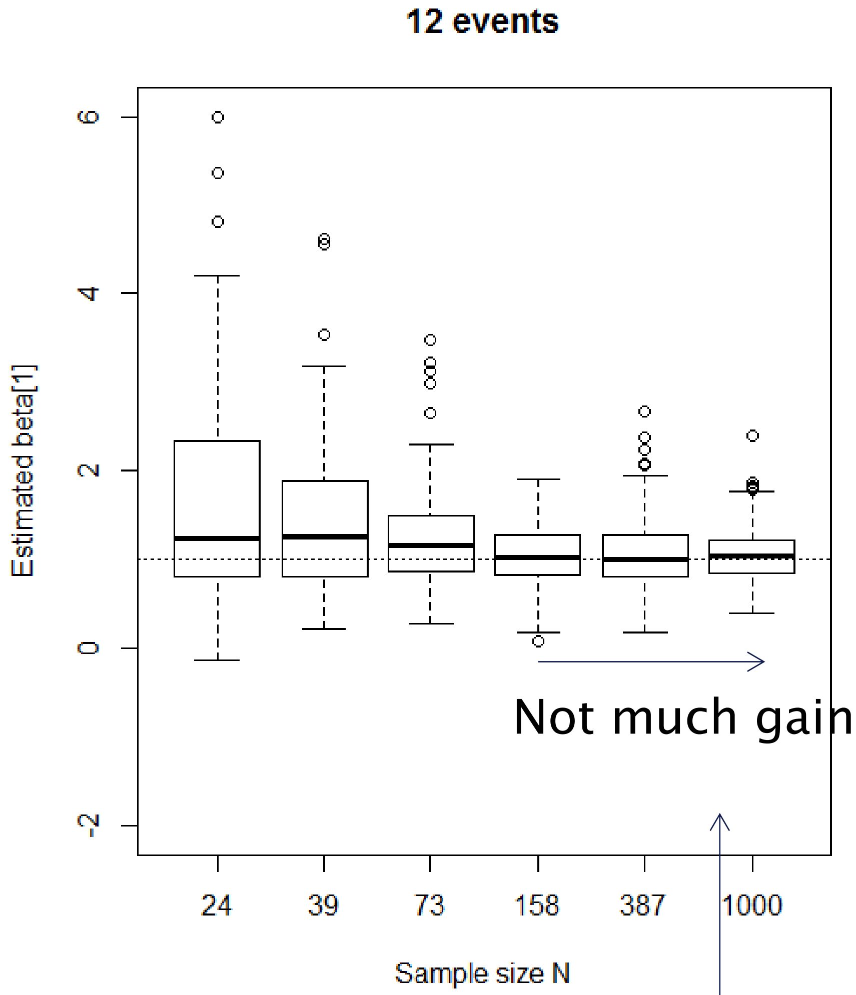
    → explanatory models based on logistic regression

$$\Pr(Y = 1) = \pi = [1 + \exp(-X\beta)]^{-1}$$

- How well can we estimate β if events ($y_i = 1$) are rare?

Rare event problems…





Not much gain!

Logistic regression with 5 variables:

- estimates are unstable (large MSE) because of few events
- removing some ‚non-events' does not affect precision

Penalized likelihood regression

$$\log L^*(\beta) = \log L(\beta) + A(\beta)$$

Imposes priors on model coefficients, e.g.

- $A(\beta) = -\lambda \sum \beta^2$ (ridge: normal prior)
- $A(\beta) = -\lambda \sum |\beta|$ (LASSO: double exponential)
- $A(\beta) = \frac{1}{2} \log \det(I(\beta))$ (Firth-type: Jeffreys prior)

in order to

- avoid extreme estimates and stabilize variance (ridge)
- perform variable selection (LASSO)
- correct small-sample bias in β (Firth-type)

Firth's penalization for logistic regression

In exponential family models with canonical parametrization the **Firth-type penalized likelihood** is given by

$$L^{*}(\beta) = L(\beta)\,\det(I(\beta))^{1/2},$$

where $I(\beta)$ is the Fisher information matrix and $L(\beta)$ is the likelihood.

Firth-type penalization

- **removes the first-order bias** of the ML-estimates of β,
- is **bias-preventive** rather than corrective,
- is available in **Software** packages such as SAS, R, Stata…

Firth‘s penalization for logistic regression

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Jeffreys invariant prior

where $I(\beta)$ is the Fisher information matrix and $L(\beta)$ is the likelihood.

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- **removes the first-order bias** of the ML-estimates of β,
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Firth‘s penalization for logistic regression

In logistic regression, the penalized likelihood is given by

$$L^*(\beta) = L(\beta)\det(X^t W X)^{1/2}, \text{ with}$$

$$W = \mathrm{diag}(\mathrm{expit}(\mathrm{X_i}\beta)(1 - \mathrm{expit}(\mathrm{X_i}\beta)))$$
$$= \mathrm{diag}(\pi_i(1 - \pi_i))\,.$$

- Firth-type estimates always exist.

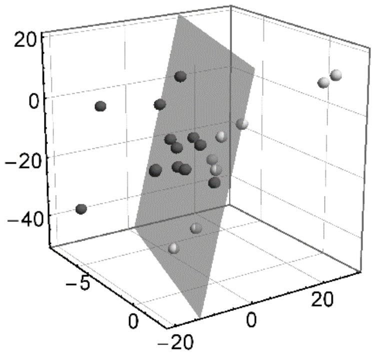
W is maximised at $\pi_i = \frac{1}{2}$, i.e. at $\beta = 0$, thus

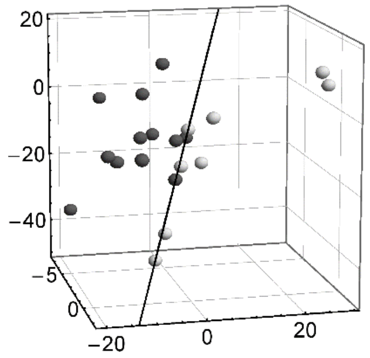
- predictions are usually pulled towards $\frac{1}{2}$,
- coefficients towards zero.

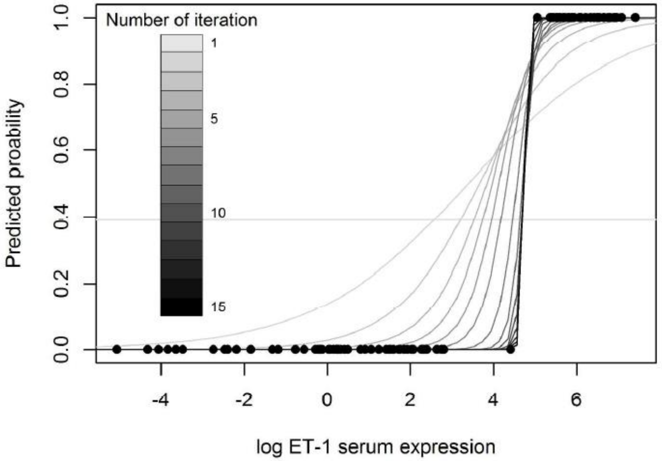
Shrinkage!

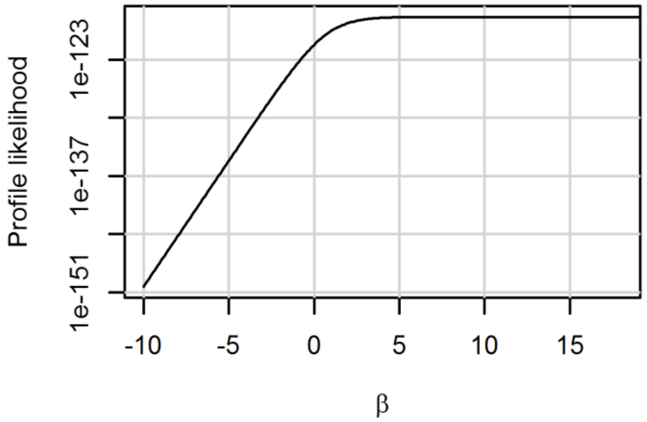
Firth‘s penalization for logistic regression

- Separation of outcome classes by covariate values (Figs. from Mansournia et al 2018)









- Firth‘s bias reduction method was proposed as solution to the problem of separation in logistic regression (Heinze and Schemper, 2002)
- Penalized likelihood has a unique mode
- It prevents infinite coefficients to occur

Firth‘s penalization for logistic regression

Bias reduction also leads to reduction in MSE:

- Rainey, 2017: Simulation study of LogReg for political science
  ‚Firth‘s methods dominates ML in bias and MSE‘

However, the predictions get biased…

- Elgmati et al, 2015

… and anti-shrinkage could occasionally arise:

- Greenland and Mansournia, 2015

Firth‘s Logistic regression

For logistic regression with one binary regressor*,
Firth’s bias correction amounts to adding 1/2 to each cell:

original

	A	B
Y=0	44	4
Y=1	1	1

Firth-type penalization $\longrightarrow$

augmented

	A	B
0	44.5	4.5
1	1.5	1.5

event rate $= \frac{2}{50} = 0.04$

$\text{OR}_{\text{BvsA}} = 11$

event rate $= \frac{3}{52} \sim 0.058$

$\text{OR}_{\text{BvsA}} = 9.89$

av. pred. prob. $= 0.054$

* Generally: for saturated models

Example of Greenland 2010

original

	A	B	
Y=0	315	5	*320*
Y=1	31	1	*32*
	346	*6*	*352*

augmented

	A	B	
Y=0	315.5	5.5	*321*
Y=1	31.5	1.5	*33*
	346.5	*6.5*	*354*

$$\text{event rate} = \frac{32}{352} = 0.091$$

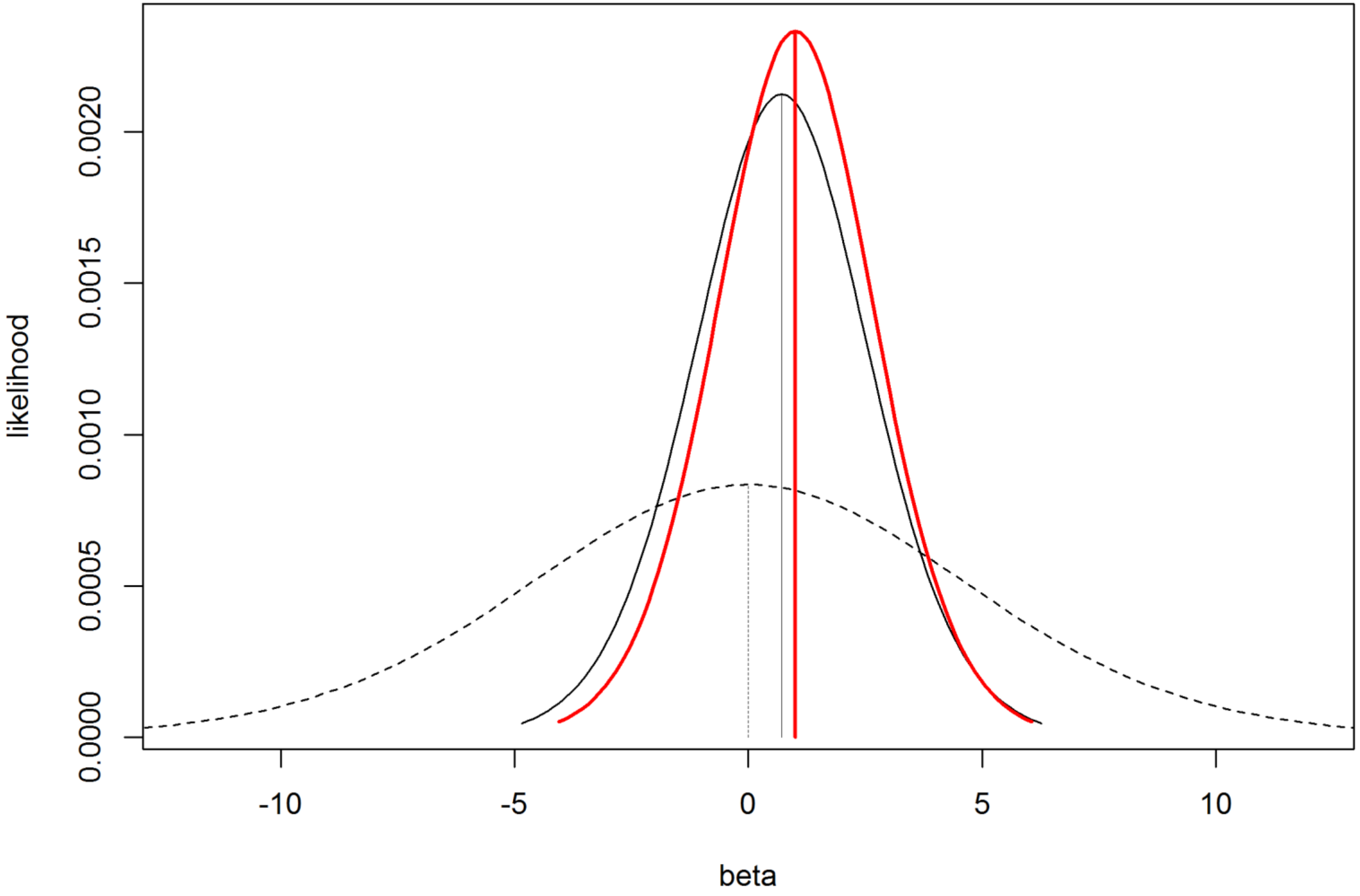
$$\text{event rate} = \frac{33}{354} = 0.093$$

$$OR_{BvsA} = 2.03$$

$$OR_{BvsA} = 2.73$$

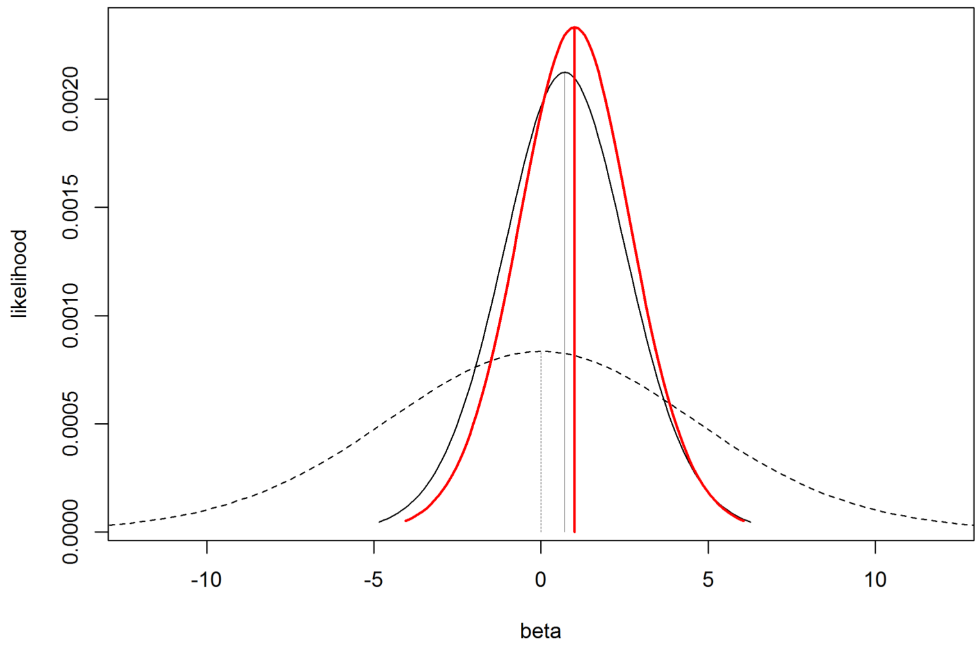
Greenland, AmStat 2010

Greenland example: likelihood, prior, posterior



Bayesian non-collapsibility: anti-shrinkage from penalization

- Prior and likelihood modes do not ‚collapse‘: posterior mode exceeds both
- The ‚shrunken‘ estimate is larger than ML estimate
- How can that happen???



An even more extreme example from Greenland 2010

- 2x2 table

	X=0	X=1	
Y=0	25	5	*30*
Y=1	5	1	*6*
	30	*6*	*36*

- Here we immediately see that the odds ratio = 1 ($\beta_1 = 0$)

- But the estimate from augmented data: odds ratio = 1.26 (try it out!)

Greenland, AmStat 2010

Simulating the example of Greenland

- We should distinguish BNC in a single data set from a systematic increase in bias of a method (in simulations)

	X=0	X=1	
Y=0	315	5	*320*
Y=1	31	1	*32*
	346	*6*	*352*

- Simulation of the example:
- Fixed groups x=0 and x=1, P(Y=1|X) as observed in example
- True log OR=0.709

Simulating the example of Greenland

- True value: log OR = 0.709

Parameter	ML	Jeffreys-Firth	
Bias β_1	*	+18%	
RMSE β_1	*	0.86	
Bayesian non-collapsibility $\boldsymbol{\beta_1}$		**63.7%**	

* Separation causes β_1 to be undefined ($-\infty$) in 31.7% of the cases

Simulating the example of Greenland

- To overcome Bayesian non-collapsibility,
  Greenland and Mansournia (2015)
  proposed not to impose a prior on the intercept

- They suggest a log-F(1,1) prior for all other regression coefficients

- The method can be used with conventional frequentist software
  because it uses a data-augmentation prior

Greenland and Mansournia, StatMed 2015

logF(1,1) prior (Greenland and Mansournia, 2015)

Penalizing by log-F(1,1) prior gives $L(\beta)^* = L(\beta) \cdot \prod \frac{e^{\frac{\beta_j}{2}}}{1+e^{\beta_j}}$.

This amounts to the following modification of the data set:

	x1	x2	y
1	*	*	*
1	*	*	*
1	*	*	*
1	*	*	*
1	*	*	*
1	*	*	*
1	*	*	*

$\rightarrow$

	x1	x2	y	
1	*	*	*	each assigned a weight of 1
1	*	*	*	
1	*	*	*	
1	*	*	*	
1	*	*	*	
1	*	*	*	
1	*	*	*	
0	1	0	0	each assigned a weight of ½
0	1	0	1	
0	0	1	0	
0	0	1	1	

- No shrinkage for the intercept, no rescaling of the variables

Simulating the example of Greenland

- Re-running the simulation with the log-F(1,1) method yields:

Parameter	ML	Jeffreys-Firth	logF(1,1)
Bias β_1	*	+18%	
RMSE β_1	*	0.86	
Bayesian non-collapsibility $\boldsymbol{\beta_1}$		**63.7%**	**0%**

* Separation causes β_1 be undefined ($-\infty$) in 31.7% of the cases

Simulating the example of Greenland

- Re-running the simulation with the log-F(1,1) method yields:

Parameter	ML	Jeffreys-Firth	logF(1,1)
Bias β_1	*	+18%	-52%
RMSE β_1	*	0.86	1.05
Bayesian non-collapsibility $\boldsymbol{\beta_1}$		**63.7%**	**0%**

* Separation causes β_1 be undefined ($-\infty$) in 31.7% of the cases

Other, more subtle occurrences of Bayesian non-collapsibility

- Ridge regression: normal prior around 0
- usually implies bias towards zero,
- But:
- With correlated predictors with different effect sizes, for some predictors the bias can be away from zero

Simulation of bivariable log reg models

- $X_1, X_2 \sim \text{Bin}(0.5)$ with correlation $r = 0.8, n = 50$
- $\beta_1 = 1.5$, $\beta_2 = 0.1$, ridge parameter λ optimized by cross-validation

Parameter	ML	Ridge (CV λ)	Log-F(1,1)	Jeffreys-Firth
Bias β_1	+40% (+9%*)	-26%	-2.5%	+1.2%
RMSE β_1	3.04 (1.02*)	1.01	0.73	0.79
Bias β_2	-451% (+16%*)	+48%	+77%	+16%
RMSE β_2	2.95 (0.81*)	0.73	0.68	0.76
Bayesian non-collapsibility $\boldsymbol{\beta_2}$		**25%**	**28%**	**23%**

*excluding 2.7% separated samples

Anti-shrinkage from penalization?

Bayesian non-collapsibility/anti-shrinkage

- can be avoided in univariable models,
  but no general rule to avoid it in multivariable models
- Likelihood penalization can often decrease RMSE
  (even *with* occasional anti-shrinkage)
- **Likelihood penalization ≠ guaranteed shrinkage**

Reason for anti-shrinkage

- We look at the association of X and Y

- We could treat the source of data as a ‚ghost factor' G
- G=0 for original table
- G=1 for pseudo data

- We ignore that the conditional association of X and Y is confounded by G

Example of Greenland 2010 revisited

original

	A	B	
Y=0	315	5	*320*
Y=1	31	1	*32*
	346	*6*	*352*

augmented

	A	B	
Y=0	315.5	5.5	*321*
Y=1	31.5	1.5	*33*
	347	*7*	*352*

To overcome both the overestimation and anti-shrinkage problems:

- We propose to adjust for the confounding by including the ‚ghost factor' G in a logistic regression model

FLAC: Firth‘s Logistic regression with Added Covariate

Split the augmented data into the original and pseudo data:

augmented

	A	B
0	315.5	5.5
1	31.5	1.5

original
G=0

	A	B
0	315	5
1	31	1

$OR_{BvsA} = 2.03$

\+

pseudo
G=1 ← Ghost factor

	A	B
0	0.5	0.5
1	0.5	0.5

Define **F**irth type **L**ogistic regression with **A**dditional **C**ovariate as an analysis including the ghost factor as added covariate:

$OR_{BvsA} = 1.84$

FLAC: **F**irth‘s **L**ogistic regression with **A**dded **C**ovariate

Beyond 2x2 tables:

Firth-type penalization can be obtained by solving modified score equations:

$$\sum_{i=1}^{N}(y_i - \pi_i)x_{ir} + h_i\left(\frac{1}{2} - \pi_i\right)x_{ir} = 0; \quad r = 0, \dots, p$$

where the h_i's are the diagonal elements of the hat matrix $H = W^{\frac{1}{2}}X(X'WX)^{-1}XW^{1/2}$

They are equivalent to:

$$\sum_{i=1}^{N}(y_i - \pi_i)x_{ir} + \sum_{i}^{N} h_i\left(\frac{1}{2} - \pi_i\right)x_{ir} =$$

$$= \sum_{i=1}^{N}(y_i - \pi_i)x_{ir} + \sum_{i=1}^{N}\frac{h_i}{2}(y_i - \pi_i) + \sum_{i=1}^{N}\frac{h_i}{2}(1 - y_i - \pi_i) = 0$$

FLAC: **F**irth‘s **L**ogistic regression with **A**dded **C**ovariate

- A closer inspection yields:

$$\sum_{i=1}^{N}\underbrace{(y_i-\pi_i)x_{ir}}_{\text{The original data}}+\underbrace{\sum_{i=1}^{N}\underbrace{\frac{h_i}{2}(y_i-\pi_i)x_{ir}}_{\text{Original data, weighted by } h_i/2}+\sum_{i=1}^{N}\underbrace{\frac{h_i}{2}(1-y_i-\pi_i)x_{ir}}_{\text{Data with reversed outcome, weighted by } h_i/2}}_{\text{Pseudo data}}=0$$

FLAC: **F**irth‘s **L**ogistic regression with **A**dded **C**ovariate

- A closer inspection yields:

$$\sum_{i=1}^{N} \underbrace{(y_i-\pi_i)x_{ir}}_{\text{The original data}} + \sum_{i=1}^{N}\frac{h_i}{2}\underbrace{\underbrace{(y_i-\pi_i)x_{ir}}_{\text{Original data, weighted by } h_i/2} + \sum_{i=1}^{N}\frac{h_i}{2}\underbrace{(1-y_i-\pi_i)x_{ir}}_{\text{Data with reversed outcome, weighted by } h_i/2}}_{\text{Pseudo data}} = 0$$

Ghost factor: G=0 G=1
(‚Added covariate‘)

FLAC: Firth‘s Logistic regression with Added Covariate

FLAC estimates can be obtained by the following steps:

1) Define an indicator variable G discriminating between original data ($G = 0$) and pseudo data ($G = 1$).
2) Apply ML on the augmented data including the indicator G in the model.

✓ unbiased pred. probabilities

FLIC

Firth's **L**ogistic regression with **I**ntercept **C**orrection:

1. Fit a Firth logistic regression model
2. Modify the estimated intercept $\hat{\beta}_0$ such that $\bar{\hat{\pi}} = \bar{y}$.

✓ unbiased pred. probabilities

effect estimates $\hat{\beta}_1, \ldots, \hat{\beta}_k$ are the same as with original Firth method

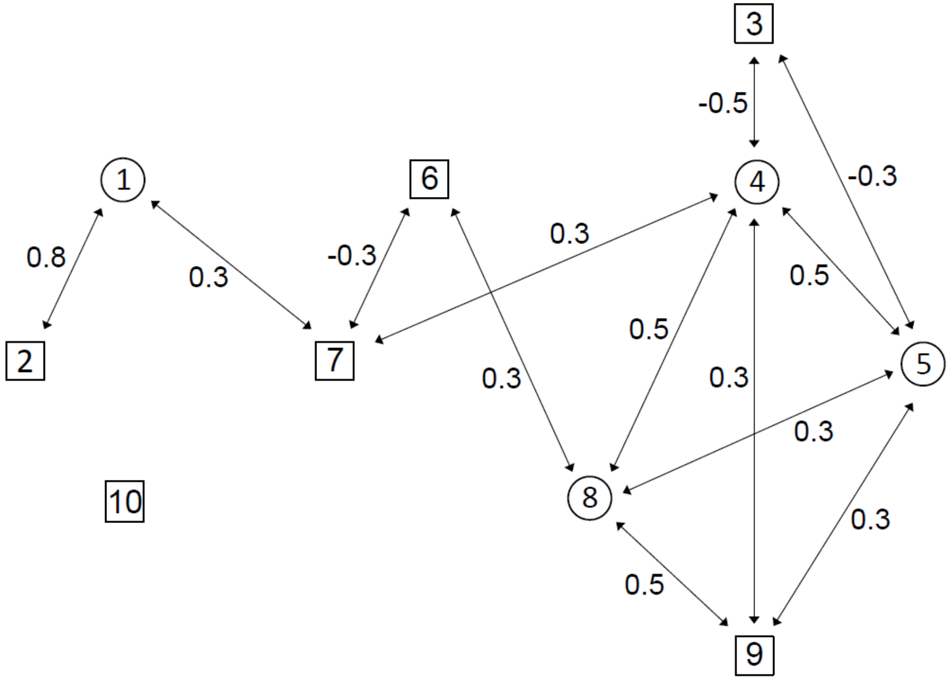
Simulation study: the set-up

We investigated the performance of FLIC and FLAC, simulating 1000 data sets for 45 scenarios with:

- 500, 1000 or 1400 observations,
- event rates of 1%, 2%, 5% or 10%
- 10 covariables (6 cat., 4 cont.),
  see Binder et al., 2011
- none, moderate and strong effects
  of positive and mixed signs

Main evaluation criteria:

bias and RMSE of predictions and effect estimates



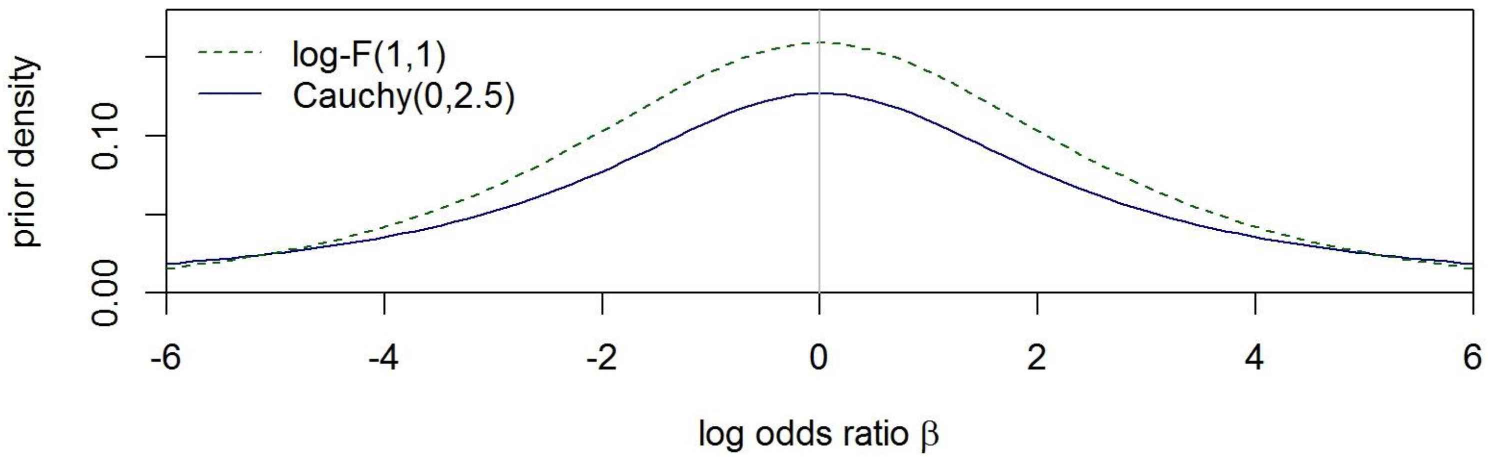
Other methods for accurate prediction

In our simulation study, we compared FLIC and FLAC to the following methods:

- weakened Firth-type penalization (Elgmati 2015),
  with $L(\beta)^* = L(\beta)\det(X^tWX)^\tau$, $\tau = 0.1$, WF
- ridge regression, RR
- penalization by log-F(1,1) priors, logF
- penalization by Cauchy priors with scale parameter=2.5. Cauchy

Cauchy priors

Cauchy priors (scale=2.5) have heavier tails than log-F(1,1)-priors:



We follow Gelman 2008:

- all variables are centered,
- binary variables are coded to have a range of 1,
- all other variables are scaled to have standard deviation 0.5,
- the intercept is penalized by Cauchy(0,10).

This is implemented in the function `bayesglm` in the R-package `arm`.

Simulation results

- Bias of $\hat{\beta}$: clear winner is Firth/FLIC method
  FLAC, logF, Cauchy: slight bias towards 0
- RMSE of $\hat{\beta}$:
  equal effect sizes: ridge the winner
  unequal effect sizes: very good performance of FLAC and Cauchy
  closely followed by logF(1,1)
- Calibration of $\hat{\pi}$:
  - often FLAC the winner
  - considerable instability of ridge

Comparison

FLAC

- No tuning parameter
- Transformation-invariant
- Often best MSE, calibration

Ridge

- Standardization is standard
- Tuning parameter
  – no confidence intervals
- Not transformation-invariant
- Performance decreases
  if effects are very different

Bayesian methods (Cauchy, logF)

- Cauchy: in-built standardization (bayesglm),
  no tuning parameter
- logF(m,m): choose m by '95% prior region' for parameter of interest
  m=1 for wide prior, m=2 less vague
- (in principle, m could be tuned as in ridge)
- logF: easily implemented
- Cauchy and logF are not transformation-invariant

Confidence intervals

It is important to note that:

- With penalized (=shrinkage) methods one cannot achieve nominal coverage over all possible parameter values
- But one can achieve nominal coverage averaging over the implicit prior

- Prior – penalty correspondence can be *a-priori* established if there is no tuning parameter
- Important to use profile penalized likelihood method
- Wald method ($\hat{\beta} \pm 1.96\, SE$) depends on unbiasedness of estimate

Gustafson&Greenland, StatScience 2009

Conclusion

We recommend FLAC for:

- Achieving unbiased predictions
- Good performance
- Invariance to transformations or coding
- Cannot be ‘outsmarted’ by creative coding

References

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Please cf. the reference lists therein for all other citations of this presentation.

Further references:

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- Rainey C. Estimating logit models with small samples. www.carlislerainey.com/papers/small.pdf (27 March 2017)