Modélisation d'une probabilité d'infection en présence d'immunité

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Outline of the talk

1. Logistic regression: introduction and the problem of immunes
2. Estimation in logistic regression with immunes
3. Simulation results
4. Discussion

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Logistic regression for binary responses

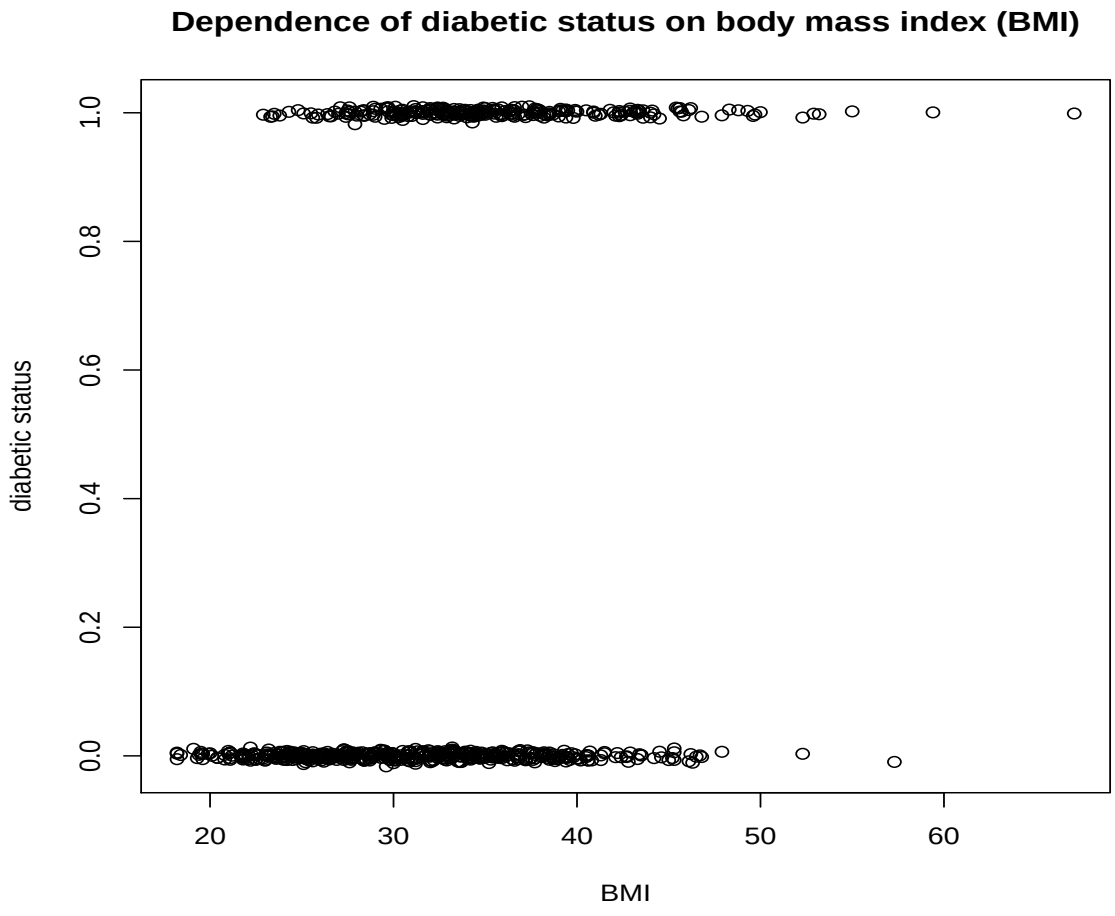
Logistic regression deals with the statistical analysis of binary 0 or 1 data.

Example: Study on diabetes among 768 females Pima Indians in Phoenix, USA.

$\hookrightarrow$ investigates the effect of risk factors (or covariates) on the fact of being diabetic (1) or not (0):

1. age of the woman
2. body mass index (BMI = weight[kg]/height[m]^2)
3. ...

Binary response data: an example



It seems that the number of 1's tends to increase relative to the number of 0's with increasing BMI. Thus BMI seems to be a positiver risk factor for getting diabete.

Logistic regression: the mathematical formulation

The logistic regression model is appropriate for analyzing such data:

$$\mathbb{P}(Y_i = 1|X_{i1}, X_{i2}) = \frac{\exp(\beta_0 + \beta_1 X_{i1} + \beta_2 X_{i2})}{1 + \exp(\beta_0 + \beta_1 X_{i1} + \beta_2 X_{i2})}$$

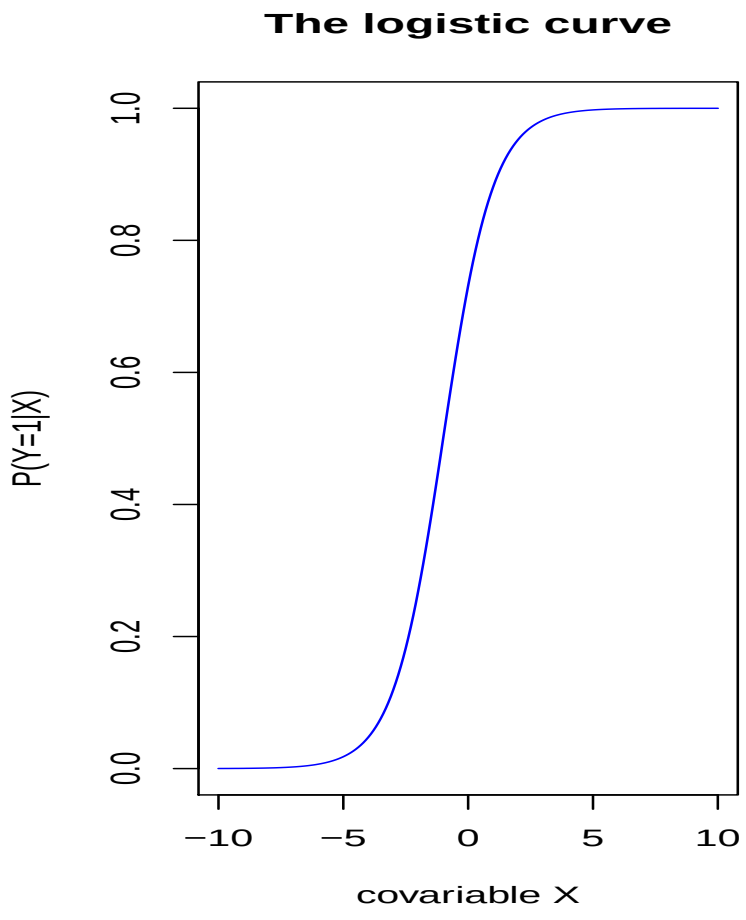
with $X_{i1} =$ age, $X_{i2} =$ BMI, for the i-th woman.

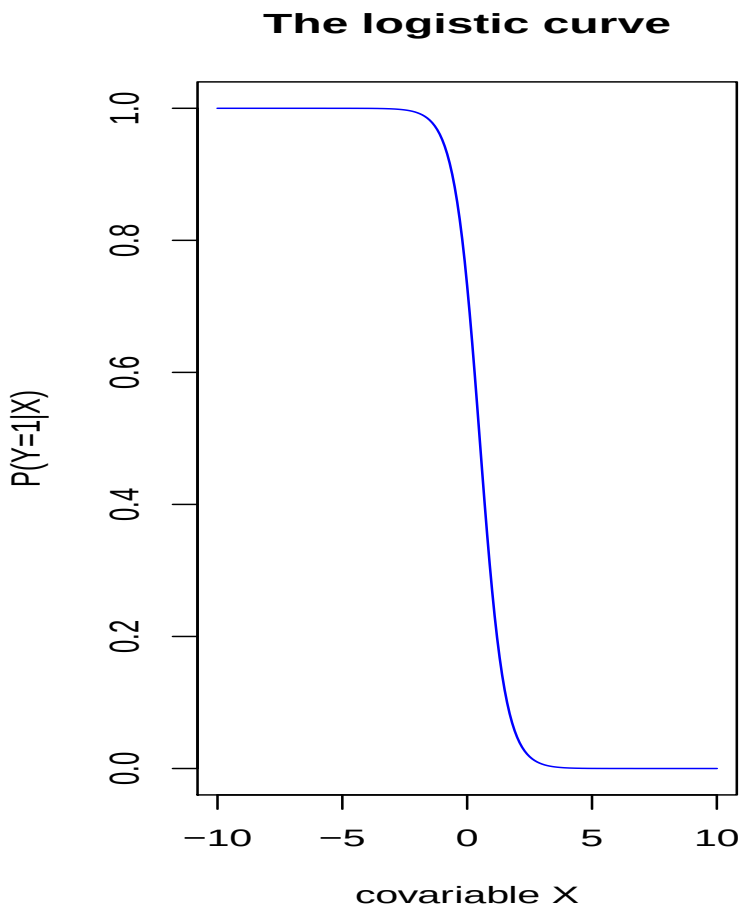
The combination $\beta_0 + \beta_1 X_{i1} + \beta_2 X_{i2}$ is called the linear predictor.

An alternative way of writing this model is as:

$$\underbrace{\log\left(\frac{\mathbb{P}(Y_i = 1|X_{i1}, X_{i2})}{1 - \mathbb{P}(Y_i = 1|X_{i1}, X_{i2})}\right)}_{\text{logit}(\mathbb{P}(Y_i=1|X_{i1},X_{i2}))} = \beta_0 + \beta_1 X_{i1} + \beta_2 X_{i2}$$

The logistic curve: examples





Statistical analysis of binary data

Objectives: From a sample of n individuals $(Y_i, X_{i1}, \ldots, X_{i2})$:

1. estimate the parameters β_j,
2. test hypothesis about the β_j, such as $H_0 : \beta_j = 0$ vs $H_1 : \beta_j \neq 0$,
3. predict a particular probability $\pi_i = \mathbb{P}(Y_i = 1 | X_{i1}, X_{i2})$ as:

$$\widehat{\pi}_i = \frac{\exp(\widehat{\beta}_0 + \widehat{\beta}_1 X_{i1} + \widehat{\beta}_2 X_{i2})}{1 + \exp(\widehat{\beta}_0 + \widehat{\beta}_1 X_{i1} + \widehat{\beta}_2 X_{i2})}$$

Maximum likelihood estimation

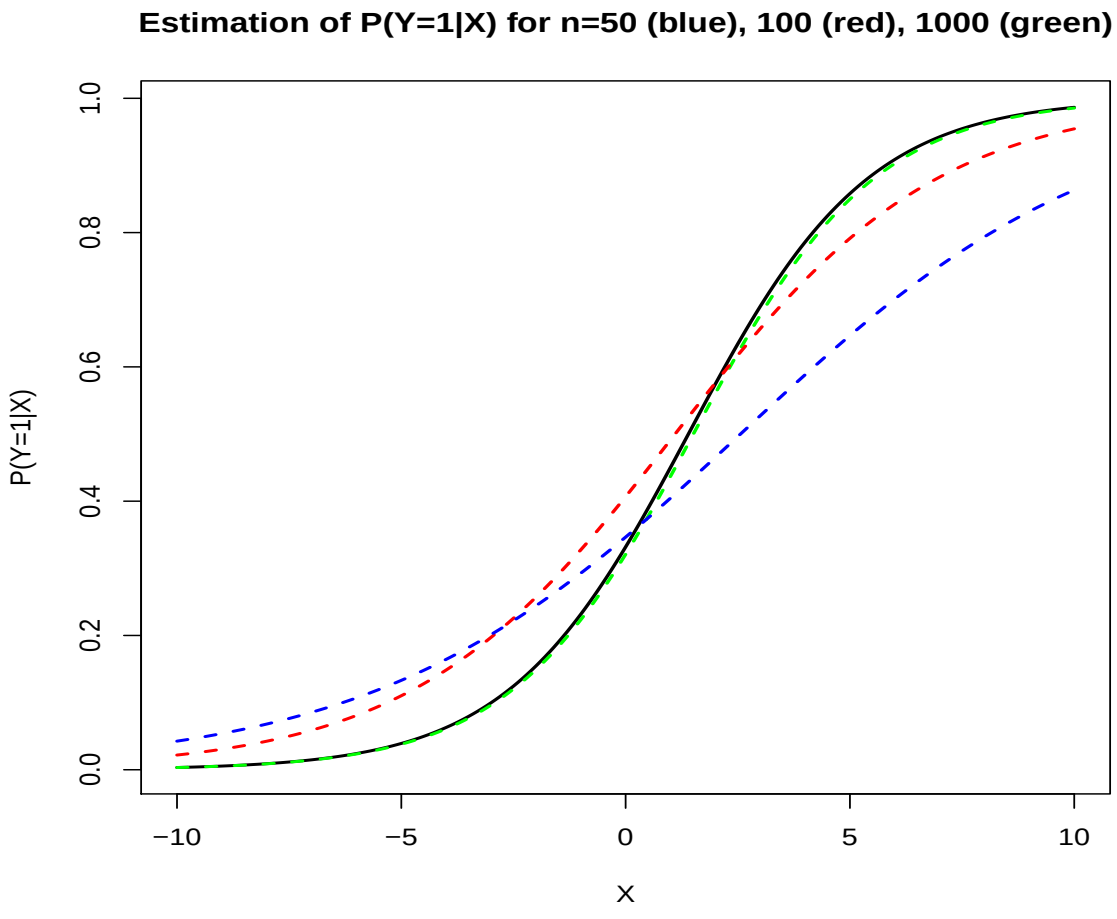
β is estimated by the value $\widehat{\beta}_n$ which maximizes the likelihood

$$L_n(\beta) = \prod_{i=1}^{n} \left[\mathbb{P}(Y_i = 1|X_{i1}, X_{i2})\right]^{Y_i} \left[\mathbb{P}(Y_i = 0|X_{i1}, X_{i2})\right]^{1-Y_i}$$

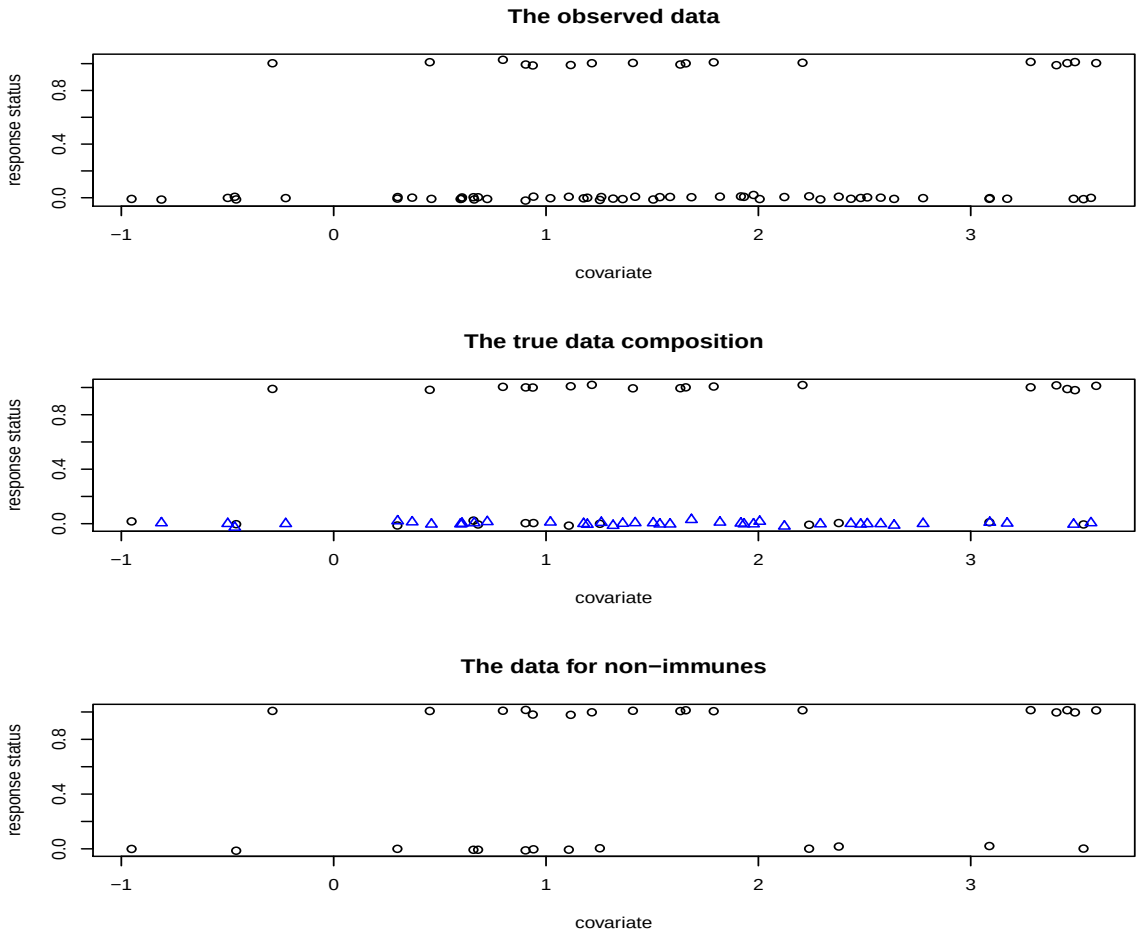
This estimator has some nice properties:

1. $\widehat{\beta}_n$ "is closer and closer" to the unknown β,
2. $\widehat{\beta}_n$ is distributed approximately as a normal law $\Rightarrow$ confidence intervals, p-values.

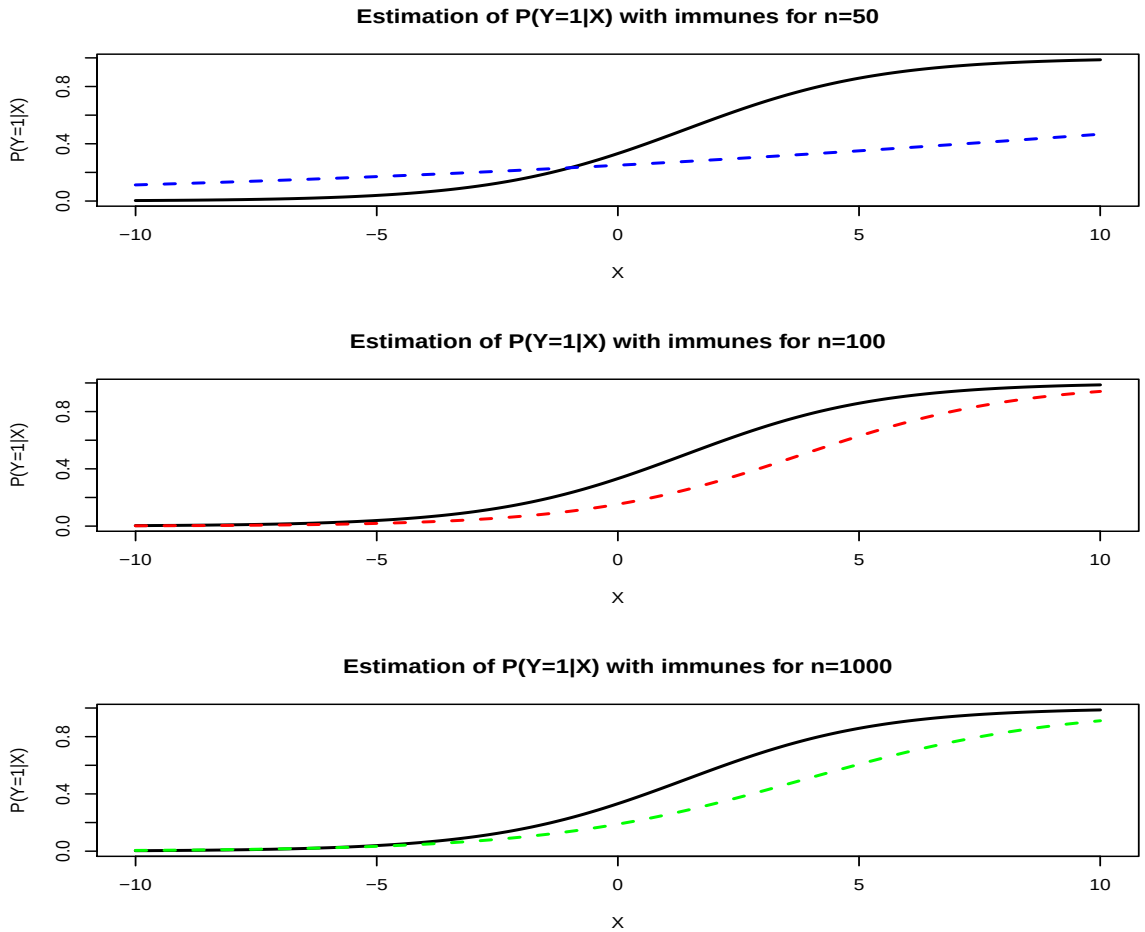
Estimation of the logistic curve



The problem of immunes



Estimation of the logistic curve with immunes



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The proposed estimation procedure

With immunity, we are in fact led to estimate the β_j in the model:

$$\begin{cases} \mathbb{P}(Y_i = 1 | X_{i1}, X_{i2}, \mathbf{S_i = 1}) = \frac{\exp(\beta_0 + \beta_1 X_{i1} + \beta_2 X_{i2})}{1 + \exp(\beta_0 + \beta_1 X_{i1} + \beta_2 X_{i2})} \\ \\ \mathbb{P}(Y_i = 1 | X_{i1}, X_{i2}, \mathbf{S_i = 0}) = 0 \end{cases}$$

where $S_i = 0$ if the patient is immune and $S_i = 1$ otherwise (susceptible).

This problem falls within the general context of zero-inflated regression:

- zero-inflated Poisson: Lambert (1992), Dietz and Bohning (2000), Lam (2006), Xiang *et al.* (2007),...
- zero-inflated binomial: Hall (2000),...
- zero-inflated proportional odds: Kelley and Anderson (2008)

The proposed estimation procedure

Estimation is still possible if we can model the probability of being cured, for example, by a logistic regression model:

$$\mathbb{P}(S_i = 1|Z_{i1}, Z_{i2}) = \frac{\exp(\theta_0 + \theta_1 Z_{i1} + \theta_2 Z_{i2})}{1 + \exp(\theta_0 + \theta_1 Z_{i1} + \theta_2 Z_{i2})}$$

since then:

$$\mathbb{P}(Y = 1|\mathbf{X}_i, \mathbf{Z}_i) = \frac{e^{\beta'\mathbf{X}_i + \theta'\mathbf{Z}_i}}{(1 + e^{\beta'\mathbf{X}_i})(1 + e^{\theta'\mathbf{Z}_i})}$$

and β and θ are estimated by maximizing the likelihood

$$L_n(\beta, \theta) = \prod_{i=1}^{n} \left[\frac{e^{\beta'\mathbf{X}_i + \theta'\mathbf{Z}_i}}{(1 + e^{\beta'\mathbf{X}_i})(1 + e^{\theta'\mathbf{Z}_i})}\right]^{Y_i} \left[1 - \frac{e^{\beta'\mathbf{X}_i + \theta'\mathbf{Z}_i}}{(1 + e^{\beta'\mathbf{X}_i})(1 + e^{\theta'\mathbf{Z}_i})}\right]^{1-Y_i}$$

The identifiability issue

Some important regularity conditions:

- The covariates are bounded. The $X_{i1}, X_{i2}, \ldots$ are linearly independent. The $Z_{i1}, Z_{i2}, \ldots$ are linearly independent

  $\hookrightarrow$ "classical conditions" for standard logistic regression.

- There exists one continous covariate V which is in $\mathbf{X}_i$ but not in $\mathbf{Z}_i$. Moreover, at the model-building stage, it is known that V is in $\mathbf{X}_i$.

Parameter exchangeability

Recall that

$$L_n(\beta,\theta)=\prod_{i=1}^{n}\left[\frac{e^{\beta'\mathbf{X}_i+\theta'\mathbf{Z}_i}}{(1+e^{\beta'\mathbf{X}_i})(1+e^{\theta'\mathbf{Z}_i})}\right]^{Y_i}\left[1-\frac{e^{\beta'\mathbf{X}_i+\theta'\mathbf{Z}_i}}{(1+e^{\beta'\mathbf{X}_i})(1+e^{\theta'\mathbf{Z}_i})}\right]^{1-Y_i}$$

If $\mathbf{X}_i=\mathbf{Z}_i$ (contain the same covariates) then: $L_n(\beta,\theta)=L_n(\theta,\beta)=$

$$\prod_{i=1}^{n}\left[\frac{e^{(\theta+\beta)'\mathbf{X}_i}}{(1+e^{\theta'\mathbf{X}_i})(1+e^{\beta'\mathbf{X}_i})}\right]^{Y_i}\left[1-\frac{e^{(\theta+\beta)'\mathbf{X}_i}}{(1+e^{\theta'\mathbf{X}_i})(1+e^{\beta'\mathbf{X}_i})}\right]^{1-Y_i}$$

For example, $\beta=(1,3)$ and $\theta=(2,3.5)$. β and θ are exchangeable and cannot be identified from the data.

$\Rightarrow$ the model is non-identifiable. No convergent estimation procedure can exist.

Assuming there is one covariate in $\mathbf{X}_i$ which is not in $\mathbf{Z}_i$ $\Rightarrow$ $\mathbf{X}_i\neq\mathbf{Z}_i$.

Linear predictors (l.p.) exchangeability

The same likelihood value

$$L_n(\beta,\theta)=\prod_{i=1}^{n}\left[\frac{e^{\beta'\mathbf{X}_i+\theta'\mathbf{Z}_i}}{(1+e^{\beta'\mathbf{X}_i})(1+e^{\theta'\mathbf{Z}_i})}\right]^{Y_i}\left[1-\frac{e^{\beta'\mathbf{X}_i+\theta'\mathbf{Z}_i}}{(1+e^{\beta'\mathbf{X}_i})(1+e^{\theta'\mathbf{Z}_i})}\right]^{1-Y_i}$$

can arise from the following two models:

$$\begin{cases}\mathbb{P}(Y_i=1|\mathbf{X}_i,S_i=1)=\frac{e^{\beta'\mathbf{X}_i}}{1+e^{\beta'\mathbf{X}_i}}\\ \mathbb{P}(S_i=1|\mathbf{Z}_i)=\frac{e^{\theta'\mathbf{Z}_i}}{1+e^{\theta'\mathbf{Z}_i}}\end{cases}\qquad\begin{cases}\mathbb{P}(Y_i=1|\mathbf{X}_i,S_i=1)=\frac{e^{\theta'\mathbf{Z}_i}}{1+e^{\theta'\mathbf{Z}_i}}\\ \mathbb{P}(S_i=1|\mathbf{Z}_i)=\frac{e^{\beta'\mathbf{X}_i}}{1+e^{\beta'\mathbf{X}_i}}\end{cases}$$

The l.p. $\beta'\mathbf{X}_i$ and $\theta'\mathbf{Z}_i$ are exchangeable and the sub-models for Y_i and S_i cannot be identified from the data $\Rightarrow$ the model is non-identifiable.

Knowing, prior to model fitting, which l.p. the covariate V is attached to will force each l.p. to be attached to the correct sub-model.

Identifiability of finite mixture of logistic regressions

The condition that V is continuous should be understood with respect to the problem of:

Mixture of c logistic regressions (Follmann and Lambert, 1991) with constant mixing probabilities.

The model is identifiable if the number of distinct covariate combinations values is "sufficiently large". Specifically, FL show that c has to be constrained by

$$c \leq \sqrt{N+2} - 1$$

with N the number of distinct observed values of the covariate vector.

$\hookrightarrow$ a single $0/1$ covariate will identify only one component,

$\hookrightarrow$ a mixture of two Bernoulli distributions is identifiable if the number of unique combinations of the covariate vector is at least 7.

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A numerical investigation of identifiability

We simulate data from the model defined by

$$\begin{cases} \log\left(\frac{\mathbb{P}(Y=1|\mathbf{X}_i,S_i)}{1-\mathbb{P}(Y=1|\mathbf{X}_i,S_i)}\right) = \beta_1 + \beta_2 X_{i2} + \beta_3 Z_{i2} + \beta_4 Z_{i3} + \beta_5 Z_{i4} & \text{if } S_i = 1 \\ \mathbb{P}(Y=1|\mathbf{X}_i,S_i) = 0 & \text{if } S_i = 0 \end{cases}$$

and

$$\log\left(\frac{\mathbb{P}(S=1|\mathbf{Z}_i)}{1-\mathbb{P}(S=1|\mathbf{Z}_i)}\right) = \theta_1 + \theta_2 Z_{i2} + \theta_3 Z_{i3} + \theta_4 Z_{i4},$$

where $X_{i2} \sim \mathcal{N}(0,1)$, $Z_{i2} \sim \mathcal{N}(1,1)$, and Z_{i3} and Z_{i4} are indicator variables built from a categorical variable with 3 categories.

A numerical investigation of identifiability (ctd)

Results for $\beta = (-1.7, -2, -3.4, 5, .3)$ and $\theta = (.71, 1, 2, -3)$ (25% of immunes).

	$\widehat{\beta}_n$					$\widehat{\theta}_n$			
n	$\widehat{\beta}_{1,n}$	$\widehat{\beta}_{2,n}$	$\widehat{\beta}_{3,n}$	$\widehat{\beta}_{4,n}$	$\widehat{\beta}_{5,n}$	$\widehat{\theta}_{1,n}$	$\widehat{\theta}_{2,n}$	$\widehat{\theta}_{3,n}$	$\widehat{\theta}_{4,n}$
100	-1.709	-2.513	-3.843	5.540	0.301	0.824	0.976	2.558	-3.576
	(1.819)	(1.015)	(1.667)	(2.503)	(3.132)	(2.319)	(3.073)	(2.691)	(2.941)
	[1.348]	[0.715]	[1.204]	[1.845]	[2.296]	[1.838]	[2.118]	[2.084]	[2.376]
500	-1.695	-2.093	-3.286	4.954	0.301	0.761	0.988	2.316	-2.745
	(0.999)	(0.543)	(1.063)	(1.265)	(1.848)	(1.203)	(1.566)	(1.485)	(2.489)
	[0.741]	[0.395]	[0.760]	[0.953]	[1.481]	[0.986]	[1.060]	[1.135]	[1.830]

Note: $(\cdot)$: root mean square error. $[\cdot]$: mean absolute error. The percentage of infected among the susceptibles is 30%. All results are based on 1000 replicates.

A numerical investigation of identifiability (ctd)

Results for $\beta = (-1.7, -2, -3.4, 5, .3)$ and $\theta = (-.3, -1, 2.1, 1)$ (50% of immunes).

	$\widehat{\beta}_n$					$\widehat{\theta}_n$			
n	$\widehat{\beta}_{1,n}$	$\widehat{\beta}_{2,n}$	$\widehat{\beta}_{3,n}$	$\widehat{\beta}_{4,n}$	$\widehat{\beta}_{5,n}$	$\widehat{\theta}_{1,n}$	$\widehat{\theta}_{2,n}$	$\widehat{\theta}_{3,n}$	$\widehat{\theta}_{4,n}$
100	-1.716	-2.641	-3.816	5.866	0.302	-0.279	-1.537	2.616	1.352
	(2.455)	(1.491)	(1.866)	(3.121)	(3.133)	(1.942)	(1.909)	(2.749)	(3.155)
	[1.830]	[1.127]	[1.467]	[2.531]	[2.296]	[1.484]	[1.334]	[2.143]	[2.469]
500	-1.714	-2.281	-3.764	5.295	0.301	-0.313	-1.317	2.364	1.211
	(1.341)	(0.794)	(1.257)	(1.929)	(1.907)	(1.071)	(1.222)	(1.689)	(1.881)
	[1.053]	[0.597]	[0.951]	[1.554]	[1.431]	[0.858]	[0.760]	[1.263]	[1.474]

A numerical investigation of identifiability (ctd)

Results for $\beta = (-1.7, -2, -3.4, 5, .3)$ and $\theta = (.4, -1, -.6, -2)$ (75% of immunes).

	$\widehat{\beta}_n$					$\widehat{\theta}_n$			
n	$\widehat{\beta}_{1,n}$	$\widehat{\beta}_{2,n}$	$\widehat{\beta}_{3,n}$	$\widehat{\beta}_{4,n}$	$\widehat{\beta}_{5,n}$	$\widehat{\theta}_{1,n}$	$\widehat{\theta}_{2,n}$	$\widehat{\theta}_{3,n}$	$\widehat{\theta}_{4,n}$
100	-1.581 (2.951) [2.157]	-2.792 (2.412) [1.897]	-3.847 (3.687) [2.912]	5.502 (5.192) [4.434]	0.248 (3.214) [2.488]	0.469 (2.256) [1.803]	-1.571 (2.042) [1.287]	-0.501 (2.356) [1.896]	-1.846 (3.517) [2.834]
500	-1.530 (1.446) [1.022]	-2.435 (1.466) [1.142]	-3.714 (1.934) [1.563]	5.331 (3.221) [2.659]	0.292 (2.110) [1.700]	0.464 (1.335) [1.076]	-1.323 (0.976) [0.611]	-0.562 (1.678) [1.307]	-1.901 (1.978) [1.509]

Simulation study: the normal approximation

We simulate data from the model defined by

$$\begin{cases} \log\left(\frac{\mathbb{P}(Y=1|\mathbf{X}_i,S_i)}{1-\mathbb{P}(Y=1|\mathbf{X}_i,S_i)}\right) = \beta_1 + \beta_2 X_{i2} & \text{if } S_i = 1 \\ \mathbb{P}(Y=1|\mathbf{X}_i, S_i) = 0 & \text{if } S_i = 0 \end{cases}$$

and

$$\log\left(\frac{\mathbb{P}(S=1|\mathbf{Z}_i)}{1-\mathbb{P}(S=1|\mathbf{Z}_i)}\right) = \theta_1 + \theta_2 Z_{i2},$$

where $X_{i2} \sim \mathcal{N}(0,1)$ and $Z_{i2} \sim \mathcal{N}(1,1)$.

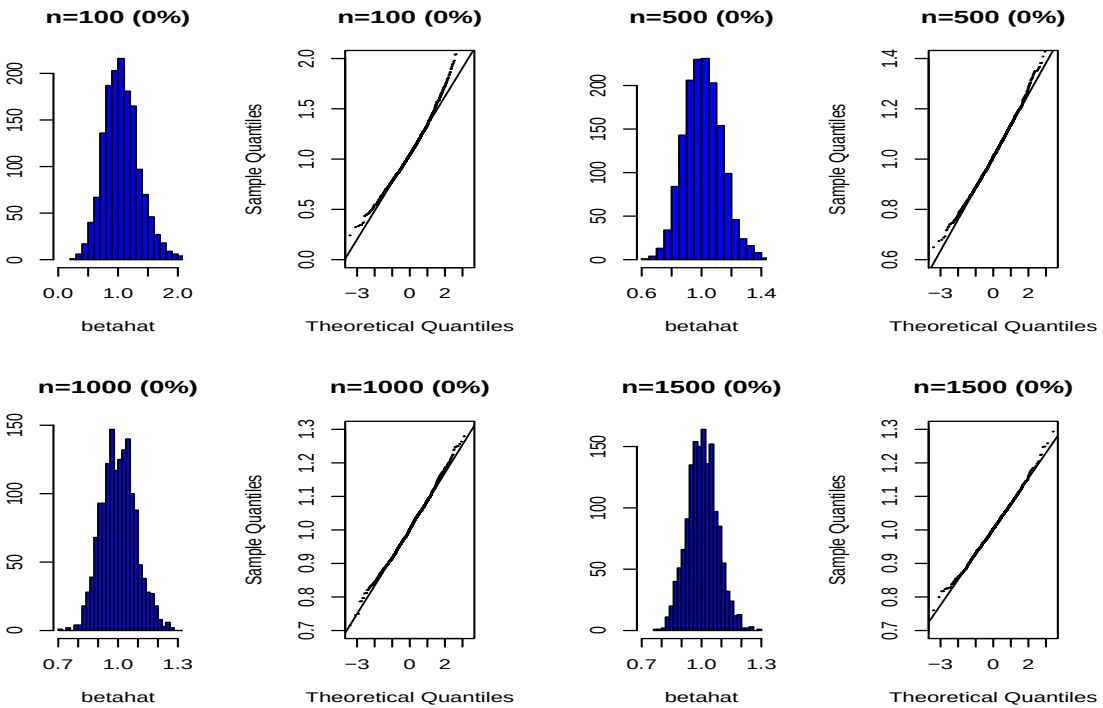
The sample size is taken: $n = 100, 500, 1000, 1500$ and the percentage of immunes in the sample: 25%, 50%, and 75%.

Simulation results for $\beta = (-.8, 1)$

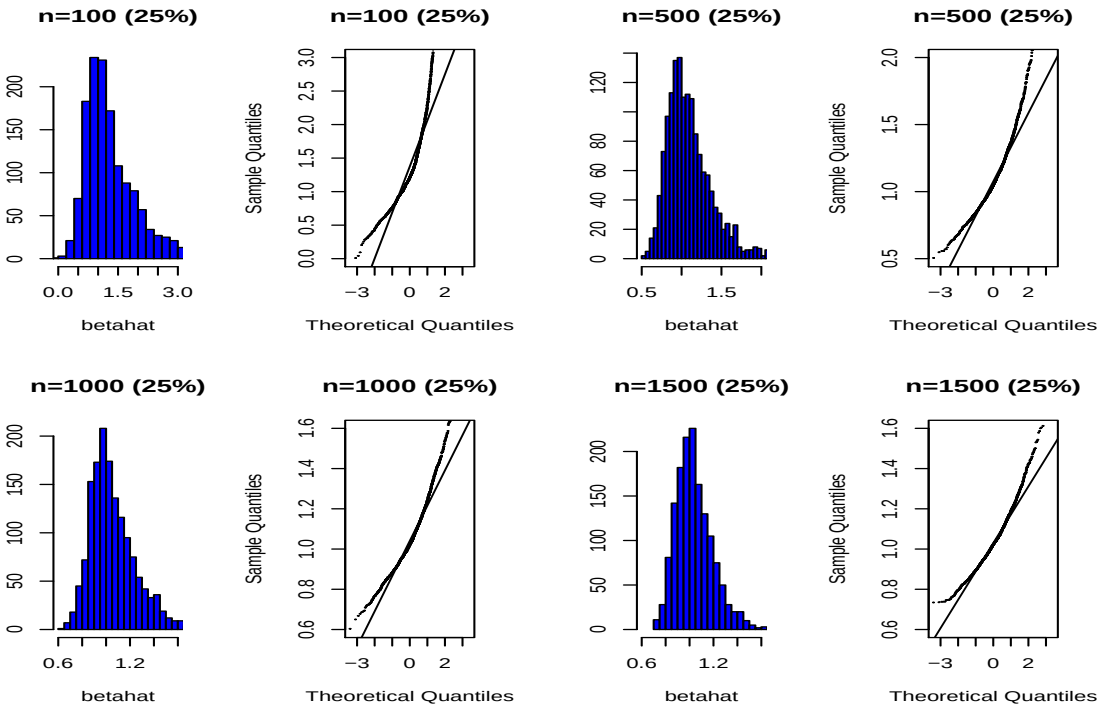
	percentage of immunes in the sample							
	0%		25%		50%		75%	
n	$\widehat{\beta}_{1,n}$	$\widehat{\beta}_{2,n}$	$\widehat{\beta}_{1,n}$	$\widehat{\beta}_{2,n}$	$\widehat{\beta}_{1,n}$	$\widehat{\beta}_{2,n}$	$\widehat{\beta}_{1,n}$	$\widehat{\beta}_{2,n}$
100	-0.834	1.064	-0.773	1.114	-0.787	1.137	-0.750	0.917
	(0.258)	(0.301)	(0.583)	(0.412)	(0.825)	(0.603)	(0.921)	(0.858)
	[0.202]	[0.232]	[0.465]	[0.324]	[0.657]	[0.440]	[0.784]	[0.568]
		0.965		0.109		0.096		0.121
500	-0.807	1.012	-0.783	1.111	-0.788	1.129	-0.791	1.120
	(0.107)	(0.125)	(0.320)	(0.354)	(0.428)	(0.389)	(0.707)	(0.538)
	[0.085]	[0.099]	[0.264]	[0.227]	[0.352]	[0.270]	[0.603]	[0.407]
		1		0.985		0.85		0.267
1000	-0.801	1.004	-0.794	1.058	-0.798	1.060	-0.797	1.108
	(0.077)	(0.085)	(0.241)	(0.202)	(0.310)	(0.247)	(0.683)	(0.482)
	[0.062]	[0.068]	[0.201]	[0.147]	[0.253]	[0.178]	[0.569]	[0.354]
		1		1		1		0.567
1500	-0.805	1.003	-0.801	1.040	-0.799	1.040	-0.802	1.057
	(0.061)	(0.074)	(0.210)	(0.159)	(0.277)	(0.191)	(0.600)	(0.361)
	[0.048]	[0.059]	[0.176]	[0.119]	[0.228]	[0.141]	[0.493]	[0.276]
		1		1		1		0.861

Note: $(\cdot)$: root mean square error. $[\cdot]$: mean absolute error. For each % of immunes, the % of infected among the susceptibles is 30%.

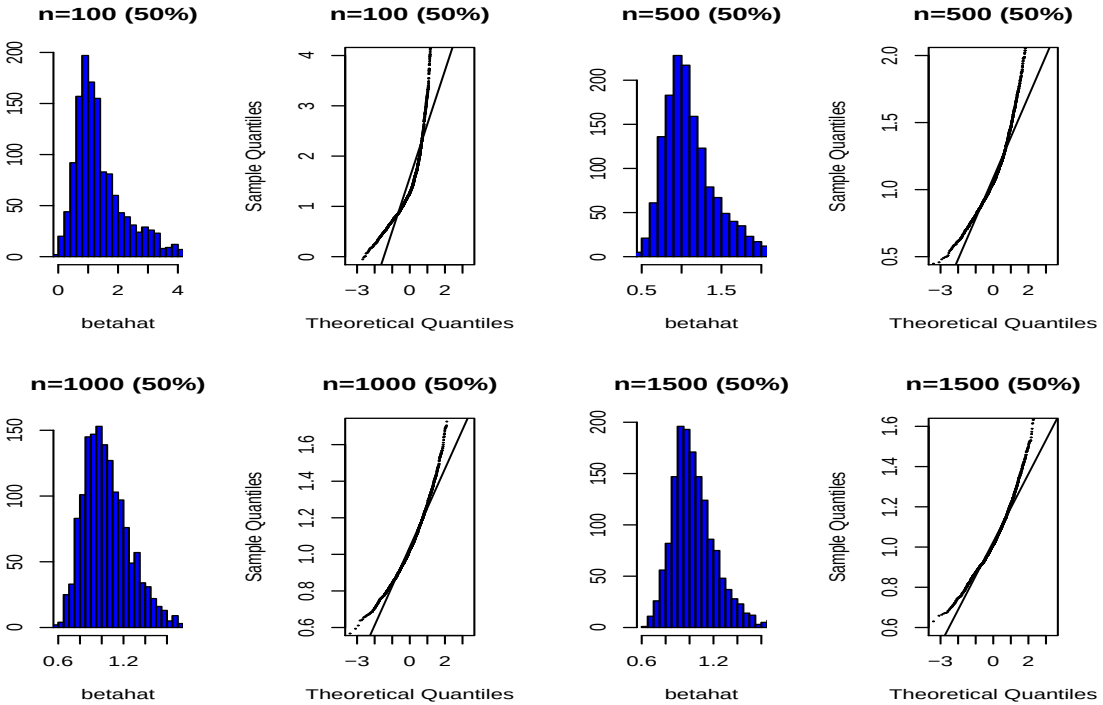
Histograms and Q-Q plots for $\widehat{\beta}_{2,n}$ (no immunes)



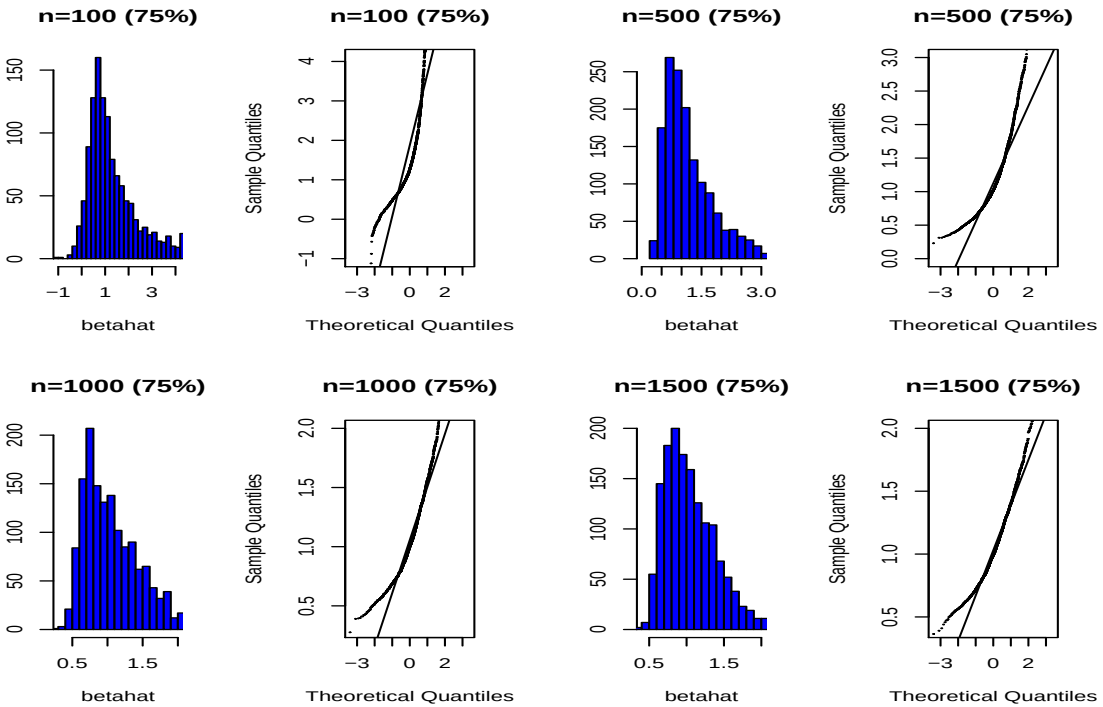
Histograms and Q-Q plots for $\widehat{\beta}_{2,n}$ (25% of immunes)



Histograms and Q-Q plots for $\widehat{\beta}_{2,n}$ (50% of immunes)



Histograms and Q-Q plots for $\widehat{\beta}_{2,n}$ (75% of immunes)



Simulation results for $\beta = (-.8, 0)$

	percentage of immunes in the sample							
	0%		25%		50%		75%	
n	$\widehat{\beta}_{1,n}$	$\widehat{\beta}_{2,n}$	$\widehat{\beta}_{1,n}$	$\widehat{\beta}_{2,n}$	$\widehat{\beta}_{1,n}$	$\widehat{\beta}_{2,n}$	$\widehat{\beta}_{1,n}$	$\widehat{\beta}_{2,n}$
100	-0.815	-0.001	-0.721	-0.007	-0.734	0.000	-0.746	-0.004
	(0.224)	(0.229)	(0.465)	(1.341)	(0.800)	(2.109)	(1.966)	(3.258)
	[0.177]	[0.179]	[0.377]	[0.762]	[0.636]	[1.111]	[1.516]	[1.715]
		0.052		0.077		0.069		0.087
500	-0.801	-0.001	-0.748	0.007	-0.750	0.001	-0.775	-0.006
	(0.097)	(0.099)	(0.280)	(0.415)	(0.520)	(0.469)	(1.209)	(0.711)
	[0.078]	[0.080]	[0.241]	[0.231]	[0.422]	[0.241]	[1.007]	[0.363]
		0.041		0.058		0.052		0.057
1000	-0.803	-0.001	-0.759	0.008	-0.763	0.005	-0.793	0.005
	(0.067)	(0.066)	(0.221)	(0.237)	(0.367)	(0.266)	(1.154)	(0.312)
	[0.053]	[0.053]	[0.182]	[0.137]	[0.299]	[0.140]	[0.911]	[0.175]
		0.042		0.045		0.037		0.048
1500	-0.801	0.000	-0.782	0.009	-0.784	0.003	-0.783	0.009
	(0.053)	(0.054)	(0.208)	(0.168)	(0.328)	(0.212)	(1.149)	(0.258)
	[0.042]	[0.043]	[0.178]	[0.099]	[0.267]	[0.102]	[0.901]	[0.144]
		0.051		0.048		0.027		0.039

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Discussion and perspectives

- Logistic regression with a cure fraction can be viewed as a zero-inflated Bernoulli regression problem. The proposed model extends the ones previously investigated in the domain.
- Confidence bands for the probability of infection are under investigation.
- Robustness to misspecification of the model for the cure fraction.
- Further generalization: random-effects logistic regression for clustered data (family, treatment).