- Example: the following data are from a study on liver function outcomes for high risk overdose patients in which antidote and historical control groups are compared

Time to Hospital	Antidote		Control	
	Severe	Not Severe	Severe	Not Severe
Early	6	12	6	2
Delayed	3	4	3	0
Late	5	1	6	0

- These data do not present a complete or quasicomplete separation problem. However, due to the small cell counts, exact logistic regression is the appropriate method.

```
data liver;
   input time $ group $ status $ count @@;
datalines;
early   antidote severe 6 early   antidote not 12
early   control  severe 6 early   control  not  2
delayed antidote severe 3 delayed antidote not 4
delayed control  severe 3 delayed control  not 0
late    antidote severe 5 late    antidote not 1
late    control  severe 6 late    control  not 0
;
run;
```

```
proc logistic descending;
   freq count;
   class time (ref=‘early’) group(ref=‘control’) / param=ref;
   model status = time group / clparm=wald;
run;
```

Global Fit Statistics

Testing Global Null Hypothesis: BETA=0

Test	Chi-Square	DF	Pr > ChiSq
Likelihood Ratio	16.3913	3	0.0009
Score	13.4256	3	0.0038
Wald	10.2488	3	0.0166

MLE Estimates

Analysis of Maximum Likelihood Estimates

Parameter	DF	Estimate	Standard Error	Wald Chi-Square	Pr > ChiSq
Intercept	1	1.4132	0.7970	3.1439	0.0762
time delayed	1	0.7024	0.8344	0.7087	0.3999
time late	1	2.5533	1.1667	4.7893	0.0286
group antidote	1	-2.2170	0.8799	6.3480	0.0118

Odds Ratio Estimates

```
                      Odds Ratio Estimates

                                      Point          95% Wald
 Effect                            Estimate      Confidence Limits

 time    delayed vs early             2.019       0.393      10.359
 time    late vs early               12.849       1.305     126.471
 group   antidote vs control          0.109       0.019       0.611
```

- However, we would not report the maximum likelihood estimates and corresponding odds ratios due to sample size concerns.

- The following statements request an exact analysis:

```
proc logistic descending;
   freq count;
   class time (ref='early') group(ref='control') / param=ref;
   model status = time group / scale=none aggregate clparm=wald;
   exact 'Model 1' intercept time group / estimate=both;
   exact 'Joint Test' time group / joint;
run;
```

Exact Results

Exact Conditional Analysis

Exact Conditional Tests for Model 1

Effect	Test	Statistic	--- p-Value --- Exact	Mid
Intercept	Score	3.4724	0.1150	0.0922
	Probability	0.0457	0.1150	0.0922
time	Score	6.0734	0.0442	0.0418
	Probability	0.00471	0.0442	0.0418
group	Score	7.1656	0.0085	0.0050
	Probability	0.00698	0.0085	0.0050

Exact Conditional Tests for Joint Test

Effect	Test	Statistic	--- p-Value --- Exact	Mid
Joint	Score	13.1459	0.0027	0.0027
	Probability	0.000015	0.0015	0.0015
time	Score	6.0734	0.0442	0.0418
	Probability	0.00471	0.0442	0.0418
group	Score	7.1656	0.0085	0.0050
	Probability	0.00698	0.0085	0.0050

Exact Parameter Estimates for Model 1

Parameter		Estimate	Standard Error	95% Confidence Limits		Two-Sided p-value
Intercept		1.3695	0.7903	-0.2361	3.6386	0.1140
time	delayed	0.6675	0.8141	-1.2071	2.6444	0.6667
time	late	2.4388	1.1425	0.1364	6.4078	0.0331
group	antidote	-2.0992	0.8590	-4.5225	-0.3121	0.0154

Exact Odds Ratios for Model 1

Parameter		Estimate	95% Confidence Limits		p-Value
Intercept		3.934	0.790	38.037	0.1140
time	delayed	1.949	0.299	14.075	0.6667
time	late	11.460	1.146	606.546	0.0331
group	antidote	0.123	0.011	0.732	0.0154

Firth Bias Reduction Method

- An alternative strategy to exact methods is Firth's penalized likelihood method. This is a bias reduction method that adds a term to the usual log-likelihood function. When the resulting penalized likelihood method is maximized, it shrinks the estimates towards zero.

- Firth's method is especially useful when you are dealing with continuous explanatory variables and exact methods may not be applicable. It always produces parameter estimates when the issue is complete or quasi-complete separation.

- Request Firth's method using the FIRTH option in the MODEL statement of PROC LOGISTIC

    - Should always use CLPARM=PL option with Firth's method since the profile likelihood based confidence limits will be based on the penalized likelihood

```
proc logistic data=liver;
   freq count;
   class time (ref='early') group(ref='control') / param=ref;
   model status = time group / firth clparm=pl;
run;
```

```
 Parameter Estimates and Profile-Likelihood Confidence Intervals

      Parameter            Estimate     95% Confidence Limits

      Intercept              1.2077       -0.0769      2.8718
      time       delayed     0.6374       -0.9007      2.2523
      time       late        2.1543        0.4031      4.5421
      group      antidote   -1.9526       -3.7557     -0.5053
```

In general, exact tests are recommended for small sample situations, but the Firth penalized likelihood approach is a useful alternative, especially when exact methods are computationally infeasible

Firth’s method applied to previous example of completely separated data:

Gender	Region	Yes	No
Female	I	0	5
Female	II	1	0
Male	I	0	175
Male	II	53	0

```
proc logistic data=complete descending;
   freq count;
   model response = gender region / firth clparm=pl
   exact gender region;
run;
```

The exact results were non-conclusive because the computations ran into a degenerate distribution. The Firth method, however, does produce estimates.

Penalized Parameter Estimates

Analysis of Penalized Maximum Likelihood Estimates

Parameter	DF	Estimate	Standard Error	Wald Chi-Square	Pr > ChiSq
Intercept	1	-2.4001	1.6189	2.1978	0.1382
gender	1	-3.4599	2.1523	2.5843	0.1079
Region	1	10.5320	2.0164	27.2817	<.0001

Parameter Estimates and Profile-Likelihood Confidence Intervals

Parameter	Estimate	95% Confidence Limits	
Intercept	-2.4001	.	-0.2218
gender	-3.4599	-8.7265	.
region	10.5320	7.5460	16.2653

These estimates should be used cautiously. However, the confidence interval for region conveys the impression that region is an important effect.

One way to evaluate the parameter estimates is to collapse the two tables into one 2×2 table and add 0.5 to each of the counts. Collapsing over gender is justified since gender appears to have no effect:

Region	Yes	No
I	0.5	180.5
II	54.5	0.5

If you compute the odds ratio for this table, you obtain (0.5)(0.5)/(54.5)(180.5) = 0.00003, which is about the same as the exponentiated parameter for region. Thus, these estimates appear to be reasonable.