GSERM - **St. Gallen 2019** Cox and Discrete-Time Models

June 20, 2019 (afternoon session)

Cox (1972)

Basic idea:

$$h_i(t) = h_0(t) \exp(\mathbf{X}_i \beta)$$

Note:

- $h_0(t) \equiv h(t|X=0)$
- Changes in **X** shift h(t) proportionally

Cox (1972) (continued)

HR =
$$\frac{h_0(t)\exp(X_1\hat{\beta})}{h_0(t)\exp(X_0\hat{\beta})}$$
$$= \exp[(1-0)\hat{\beta}]$$
$$= \exp(\hat{\beta})$$

Cox (1972) (continued)

Also, because

$$S(t) = \exp[-H(t)]$$

then

$$S(t) = \exp\left[-\int_0^t h(t) dt\right]$$

$$= \exp\left[-\exp(\mathbf{X}_i\beta) \int_0^t h_0(t) dt\right]$$

$$= \left[\exp\left(-\int_0^t h_0(t) dt\right)\right]^{\exp(\mathbf{X}_i\beta)}$$

$$= \left[S_0(t)\right]^{\exp(\mathbf{X}_i\beta)}$$

Partial Likelihood

Assume N_C distinct event times t_i , with no "ties."

Then:

$$\begin{aligned} & \Pr(\text{Individual } k & & \text{expressed observation experiences the event of interest the eyent at } t_j) \\ & = & \frac{h_k(t_j)}{\sum_{\ell \in R_j} h_\ell(t_j)} \end{aligned}$$

Partial Likelihood (continued)

$$L_{i} = \frac{h_{0}(t_{j}) \exp(\mathbf{X}_{i}\beta)}{\sum_{\ell \in R_{j}} h_{0}(t_{j}) \exp(\mathbf{X}_{\ell}\beta)}$$

$$= \frac{h_{0}(t_{j}) \exp(\mathbf{X}_{i}\beta)}{h_{0}(t_{j}) \sum_{\ell \in R_{j}} \exp(\mathbf{X}_{\ell}\beta)}$$

$$= \frac{\exp(\mathbf{X}_{i}\beta)}{\sum_{\ell \in R_{j}} \exp(\mathbf{X}_{\ell}\beta)}$$

$$L = \prod_{i=1}^{N} \left[\frac{\exp(\mathbf{X}_{i}\beta)}{\sum_{\ell \in R_{j}} \exp(\mathbf{X}_{\ell}\beta)} \right]^{C_{i}}$$

$$\ln L = \sum_{i=1}^{N} C_{i} \left\{ \mathbf{X}_{i}\beta - \ln \left[\sum_{\ell \in R_{j}} \exp(\mathbf{X}_{\ell}\beta) \right] \right\}$$

Notes on Partial Likelihood

- PL is
 - Consistent
 - Asymptotically normal
 - Slightly inefficient (but asymptotically efficient)
- Considers order of events, but not actual duration
- Censored events: Modify R_j
- No <u>ties</u>

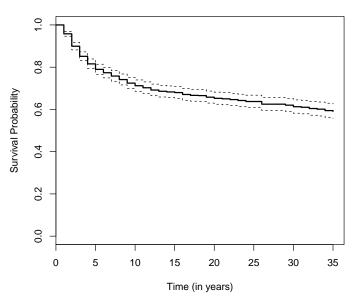
Example: Interstate War, 1950-1985

- Dyad-years for "politically-relevant" dyads
- N = 827. NT = 20448.
- Covariates:
 - Whether (=1) or not the two countries are *allies*,
 - Whether (=1) or not the two countries are *contiguous*,
 - The capability ratio of the two countries,
 - The lower of the two countries' (GDP) growth (rescaled),
 - The lower of the two countries' democracy (POLITY IV) scores (rescaled to [-1,1]), and
 - The amount of trade between the two countries, as a fraction of joint GDP.

The Data

```
> summarv(OR)
     dyadid
                                                                    futime
                       year
                                     start
                                                      stop
        : 2020
                         :1951
                                        : 0.00
                                                        : 1.00
                                                                        : 5.00
 Min.
                  Min.
                                Min.
                                                Min.
                                                                Min.
 1st Qu.:100365
                  1st Qu.:1965
                                1st Qu.: 5.00
                                                1st Qu.: 6.00
                                                                1st Qu.:23.00
 Median: 220235
                  Median:1972
                                Median :11.00
                                                Median :12.00
                                                                Median :31.00
 Mean
        :253305
                  Mean
                         :1971
                                Mean
                                        :12.32
                                                Mean
                                                        :13.32
                                                                Mean
                                                                        :28.97
 3rd Qu.:365600
                  3rd Qu.:1979
                                3rd Qu.:19.00
                                                3rd Qu.:20.00
                                                                3rd Qu.:35.00
 Max.
        :900920
                  Max.
                         :1985
                                Max.
                                        :34.00
                                                Max.
                                                        :35.00
                                                                Max.
                                                                        :35.00
   dispute
                       allies
                                        contig
                                                        trade
 Min.
        :0.00000
                  Min.
                         :0.0000
                                   Min.
                                           :0.0000
                                                    Min.
                                                            :0.00000
 1st Qu.:0.00000
                   1st Qu.:0.0000
                                   1st Qu.:0.0000
                                                    1st Qu.:0.00000
 Median : 0.00000
                   Median : 0.0000
                                   Median :0.0000
                                                    Median :0.00020
 Mean
        :0.01981
                   Mean
                          :0.3563 Mean
                                           :0.3099
                                                    Mean
                                                            :0.00231
 3rd Qu.:0.00000
                   3rd Qu.:1.0000
                                   3rd Qu.:1.0000
                                                    3rd Qu.:0.00120
        :1.00000
                   Max.
                          :1.0000
                                 Max.
                                           :1.0000
                                                    Max.
                                                            :0.17680
 Max.
    growth
                      democracy
                                          capratio
        :-0.264900
                    Min.
                            :-1.0000
                                      Min. : 0.0100
 Min.
 1st Qu.:-0.004800
                     1st Qu.:-0.8000
                                       1st Qu.: 0.0462
 Median: 0.014700
                    Median :-0.7000
                                      Median: 0.2220
        : 0.007823
                           :-0.3438
                                      Mean : 1.6677
 Mean
                    Mean
 3rd Qu.: 0.027800
                     3rd Qu.: 0.2000
                                       3rd Qu.: 1.1560
 Max.
        : 0.164700
                     Max.
                            : 1.0000
                                       Max.
                                              :78.9296
```

The Data (Kaplan-Meier plot)



Software

R:

- coxph in survival (preferred)
- cph in design
- Plots: plot(survfit(PHobject))

Stata:

- Basic command = stcox
- stset first
- Options: robust, various methods for ties, postestimation commands

Model Fitting

```
> ORCox.br<-coxph(OR.S~allies+contig+capratio+growth+democracy+trade,
                 data=OR,na.action=na.exclude,method="breslow")
> summary(ORCox.br)
 n= 20448, number of events= 405
             coef exp(coef) se(coef) z Pr(>|z|)
allies
       -0.34849
                   0.70576 0.11096 -3.141 0.001686 **
contig 0.94861
                   2.58213 0.12173 7.793 6.55e-15 ***
capratio -0.22303
                   0.80009 0.05164 -4.319 1.57e-05 ***
growth -3.69487 0.02485 1.19950 -3.080 0.002068 **
democracy -0.38194   0.68254   0.09915 -3.852   0.000117 ***
trade -3.22857
                   0.03961 9.45588 -0.341 0.732776
Signif. codes: 0 *** 0.001 ** 0.01 * 0.05 . 0.1
```

Model Fitting (continued)

```
exp(coef) exp(-coef) lower .95 upper .95
allies
           0.70576
                      1.4169 5.678e-01 8.772e-01
contig
          2.58213 0.3873 2.034e+00 3.278e+00
capratio
          0.80009
                   1.2499 7.231e-01 8.853e-01
growth
           0.02485 40.2402 2.368e-03 2.608e-01
democracy
           0.68254
                   1.4651 5.620e-01 8.289e-01
trade
           0.03961
                     25.2436 3.540e-10 4.433e+06
Concordance= 0.714 (se = 0.015)
Rsquare= 0.01 (max possible= 0.234)
Likelihood ratio test= 210.3 on 6 df,
                                      p=0
Wald test
                   = 159.8 on 6 df,
                                      0=q
Score (logrank) test = 185.8 on 6 df,
                                      0=q
```

Interpretation: Hazard Ratios

$$HR = \exp[(\mathbf{X}_j - \mathbf{X}_k)\hat{\beta}]$$

Means:

- $HR = 1 \leftrightarrow \hat{\beta} = 0$
- $HR > 1 \leftrightarrow \hat{\beta} > 0$
- $HR < 1 \leftrightarrow \hat{\beta} < 0$

Percentage difference = $100 \times \{\exp[(\mathbf{X}_j - \mathbf{X}_k)\hat{\beta}] - 1\}$.

Example: Hazard Ratios

From above:

```
exp(coef) exp(-coef) lower .95 upper .95 allies 0.70576 1.4169 5.678e-01 8.772e-01 contig 2.58213 0.3873 2.034e+00 3.278e+00 capratio 0.80009 1.2499 7.231e-01 8.853e-01 growth 0.02485 40.2402 2.368e-03 2.608e-01 democracy 0.68254 1.4651 5.620e-01 8.289e-01 trade 0.03961 25.2436 3.540e-10 4.433e+06
```

Interpretation:

- · Countries which are allies have an expected $(0.706-1) \times 100) = 29.4$ percent lower hazard of conflict than those that are not.
- · Contiguous countries have $(2.582-1) \times 100 = 158$ percent higher hazards of conflict than non-contiguous ones.
- · A one-unit increase in democracy corresponds to a $(0.683-1) \times 100=31.7$ percent decrease in the expected hazard of conflict.

Hazard Ratios: Scaling Covariates

```
It is good for one-unit changes to be meaningful / realistic...
> OR$growthPct<-OR$growth*100
> summary(coxph(OR.S~allies+contig+capratio+growthPct+democracy+trade,
               data=OR,na.action=na.exclude, method="breslow"))
         exp(coef) exp(-coef) lower .95 upper .95
allies
           0.70576
                      1.4169 5.678e-01 8.772e-01
contig
          2.58213 0.3873 2.034e+00 3.278e+00
capratio
          0.80009 1.2499 7.231e-01 8.853e-01
growthPct 0.96373 1.0376 9.413e-01 9.867e-01
democracy
          0.68254 1.4651 5.620e-01 8.289e-01
trade
           0.03961
                      25.2436 3.540e-10 4.433e+06
```

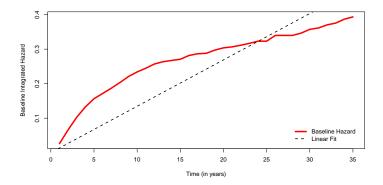
Note:

- · Previous HR for growth = 0.02485
 ightarrow 97.5 percent decrease in $\hat{h}(t)$
- · HR for growthPct is now 0.964; 1 unit increase \rightarrow 4% decrease in $\hat{h}(t)$
- Same result, proportionally: $0.96373^{100} = 0.02485$

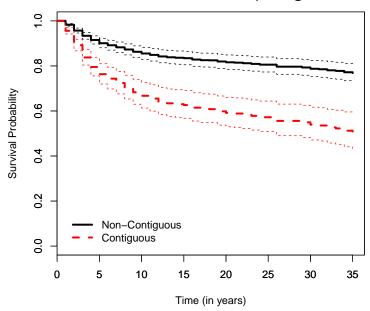
Baseline Hazards

Because the Cox model is semiparametric, it uses a conventional / univariate (Nelson-Aalen) estimate of the "baseline" hazard:

OR.BH<-basehaz(ORCox.br,centered=FALSE)



Comparing Survival Curves



Ties...

∃ ties...

Their presence biases $Cox \hat{\beta}s$ toward zero.

- Call $d_i > 0$ the number of events occurring at t_i , and
- D_j the set of d_j observations that have the event at t_j .

Ties (continued)

Means of handling ties:

· Breslow:

$$L_{\mathsf{Breslow}}(\beta) = \prod_{i=1}^{N} \frac{\exp\left[\left(\sum_{q \in D_{j}} \mathbf{X}_{q}\right) \beta\right]}{\left[\sum_{\ell \in R_{j}} \exp(\mathbf{X}_{\ell} \beta)\right]^{d_{j}}}$$

· Efron

$$\ln L_{\mathsf{Efron}}(\beta) = \sum_{j=1}^{J} \sum_{i \in D_j} \left\{ \mathbf{X}_i \beta - \frac{1}{d_j} \sum_{k=1}^{d_j - 1} \ln \left[\sum_{\ell \in R_j} \exp(\mathbf{X}_{\ell} \beta) - k \left(\frac{1}{d_j} \sum_{\ell \in D_j} \exp(\mathbf{X}_{\ell} \beta) \right) \right] \right\}$$

Ties (continued)

· "Exact" (partial likelihood)

$$\ln L_{\mathsf{Exact}}(\boldsymbol{\beta}) = \sum_{j=1}^{J} \left\{ \sum_{i \in R_j} \delta_{ij}(\mathbf{X}_i \boldsymbol{\beta}) - \ln[f(r_j, d_j)] \right\}$$

where

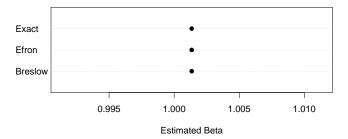
$$f(r,d) = g(r-1,d) + g(r-1,d-1) \exp(\mathbf{X}_k \boldsymbol{\beta}),$$

$$k = r \text{th observation in } R_j,$$

$$r_j = \text{cardinality of } R_j, \text{ and}$$

$$g(r,d) = \begin{cases} 0 \text{ if } r < d, \\ 1 \text{ if } d = 0 \end{cases}$$

Ties: Example



Ties: Example (continued)

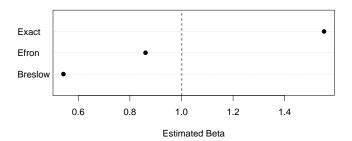
```
Data$Tied<-round(Data$T,0)

DataT.S<-Surv(Data$Tied,Data$C)

DT.br<-coxph(DataT.S^X,data=Data,method="breslow")

DT.ef<-coxph(DataT.S^X,data=Data,method="efron")

DT.ex<-coxph(DataT.S^X,data=Data,method="exact")
```



Ties: Practical Advice

- All approx. are identical if ∄ ties
- Few ties = similar results
- When ties are present, Breslow < Efron < "Exact" methods
- If you want to learn more about ties in the Cox model, read my paper....

Cox vs. Parametric Models

Conceptual considerations:

- Theory
- Nature of h(t)
- Relative importance: Bias vs. efficiency
- Need / willingness for out-of-sample predictions / forecasting

Cox, On His Model

Reid: "What do you think of the cottage industry that's grown up around [the Cox model]?"

Cox: "In the light of further results one knows since, I think I would normally want to tackle the problem parametrically... I'm not keen on non-parametric formulations normally."

Reid: "So if you had a set of censored survival data today, you might rather fit a parametric model, even though there was a feeling among the medical statisticians that that wasn't quite right."

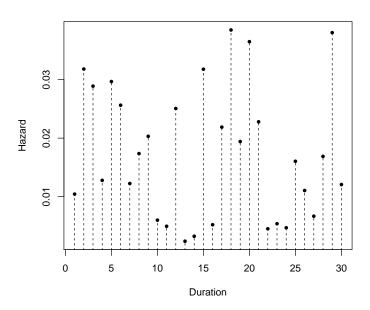
Cox: "That's right, but since then various people have shown that the answers are very insensitive to the parametric formulation of the underlying distribution. And if you want to do things like predict the outcome for a particular patient, it's much more convenient to do that parametrically."

- From Reid (1994).

Extensions

- Cox Models for repeated events
- Models with "frailties"
- Competing risks / "cured" subpopulations
- etc.

The Discrete-Time Idea



Process:

$$t \in \{1, 2, ... t_{\mathsf{max}}\}$$

Density:

$$f(t) = \Pr(T = t)$$

CDF:

$$F(t) = Pr(T \le t)$$

= $\sum_{j=1}^{t} f(t_j)$

Survival function:

$$S(t) \equiv \Pr(T \ge t)$$

$$= 1 - F(t)$$

$$= \sum_{j=t}^{t_{max}} f(t_j)$$

Hazard function:

$$h(t) \equiv \Pr(T = t | T \ge t)$$

= $\frac{f(t)}{S(t)}$

Conditional Pr(Survival):

$$\Pr(T > t | T \ge t) = 1 - h(t)$$

Implies:

$$\begin{split} S(t) &= & \Pr(T > t | T \ge t) \times \Pr(T > t - 1 | T \ge t - 1) \times \Pr(T > t - 2 | T \ge t - 2) \times \dots \\ &\times \Pr(T > 2 | T \ge 2) \times \Pr(T > 1 | T \ge 1) \\ &= & [1 - h(t)] \times [1 - h(t - 1)] \times [1 - h(t - 2)] \times \dots \times [1 - h(2)] \times [1 - h(1)] \\ &= & \prod_{j=0}^{t} [1 - h(t - j)] \end{split}$$

which means:

$$f(t) = h(t)S(t)$$

$$= h(t) \times [1 - h(t-1)] \times [1 - h(t-2)] \times ...$$

$$\times [1 - h(2)] \times [1 - h(1)]$$

$$= h(t) \prod_{i=1}^{t-1} [1 - h(t-j)]$$

General Discrete-Time Model: Likelihood

$$L = \prod_{i=1}^{N} \left\{ h(t) \prod_{i=1}^{t-1} [1 - h(t-j)] \right\}^{Y_{it}} \left\{ \prod_{i=0}^{t} [1 - h(t-j)] \right\}^{1 - Y_{it}}$$

Ordered-Categorical Models

For K small:

$$\Pr(T_i \leq k) = \frac{\exp(\tau_k - \mathbf{X}_i \beta)}{1 + \exp(\tau_k - \mathbf{X}_i \beta)}$$

$$\ln \left[\frac{\Pr(T_i \leq \kappa)}{\Pr(T_i > \kappa)} \right] = \tau_{\kappa} - \mathbf{X}_i \beta$$

Grouped-Data ("BTSCS") Approaches

$$Pr(Y_{it} = 1) = f(\mathbf{X}_{it}\beta)$$

- logit
- probit
- c-log-log
- etc.

BTSCS: Advantages

- Easily estimated, interpreted and understood
- Natural interpretations:
 - $\hat{\beta}_0 \approx$ "baseline hazard"
 - · Covariates shift this up or down.
- Can incorporate data in time-varying covariates
- Lots of software

(Potential) Disadvantages

• Requires time-varying data

Must deal with time dependence explicitly

Temporal Issues in Grouped-Data Models

(Implicit) "Baseline" hazard:

$$h_0(t) = \frac{\exp(\beta_0)}{1 + \exp(\beta_0)}$$

 \longrightarrow No temporal dependence / "flat" hazard

Temporal Issues in Grouped-Data Models

Time trend:

$$\Pr(Y_{it} = 1) = f(\mathbf{X}_{it}\beta + \gamma T_{it})$$

- $\hat{\gamma} > 0 \, o \, {
 m rising \; hazard}$
- $\hat{\gamma} < 0 \rightarrow$ declining hazard
- $\hat{\gamma} = 0 \,
 ightarrow \,$ "flat" (exponential) hazard

Variants/extensions: Polynomials... $Pr(Y_{it} = 1) = f(\mathbf{X}_{it}\beta + \gamma_1 T_{it} + \gamma_2 T_{it}^2 + \gamma_3 T_{it}^3 + ...)$

Temporal Issues in Grouped-Data Models

"Time dummies":

$$Pr(Y_{it} = 1) = f[\mathbf{X}_{it}\beta + \alpha_1 I(T_{i1}) + \alpha_2 I(T_{i2}) + \dots + \alpha_{t_{max}} I(T_{it_{max}})]$$

→ BKT's cubic splines; might also use:

- Fractional polynomials
- Smoothed duration
- Loess/lowess fits
- Other splines (B-splines, P-splines, natural splines, etc.)

Discrete-Time Model Selection

- Theory
- Formal tests

Fitted values

Equivalency One: $Cox \equiv Conditional \ Logit$

$$ext{Pr}(Y_i = j) = rac{\exp(\mathbf{X}_{ij}eta + \mathbf{Z}_j\gamma)}{\sum_{\ell=1}^J \exp(\mathbf{X}_{i\ell}eta + \mathbf{Z}_\ell\gamma)}$$
 $ext{Pr}(Y_i = j) = rac{\exp(\mathbf{X}_{ij}eta)}{\sum_{\ell=1}^J \exp(\mathbf{X}_{i\ell}eta)}$
 $ext{$L_k = rac{\exp(\mathbf{X}_keta)}{\sum_{\ell\in R_i} \exp(\mathbf{X}_\elleta)}.$}$

The point: $Cox \equiv Conditional logit$

Cox-Poisson Equivalence

Grouped-data duration models and the continuous-time Cox model are equivalent.

Cox-Poisson Equivalence

Cox:

$$S_i(t) = \exp\left[-\exp(\mathbf{X}_i\beta)\int_0^t h_0(t) dt\right]$$

Poisson:

$$\Pr(Y = y) = \frac{\exp(-\lambda)\lambda^y}{y!}$$

$$Pr(Y_{it} = 0) = exp(-\lambda)$$
$$= exp[-exp(\mathbf{X}_i\beta)]$$

Example: Oneal & Russett (1950-1985)

```
No time variable / "flat" hazard:
> OR.logit<-glm(dispute~allies+contig+capratio+growth+democracy+trade,
              data=OR.na.action=na.exclude.familv="binomial")
> summary(OR.logit)
Coefficients:
            Estimate Std. Error z value Pr(>|z|)
(Intercept) -4.32668 0.11451 -37.785 < 2e-16 ***
allies
            -0.47969 0.11275 -4.255 2.09e-05 ***
          1.35358 0.12091 11.195 < 2e-16 ***
contig
capratio -0.19620 0.05011 -3.916 9.01e-05 ***
growth
          -3.42753 1.25181 -2.738 0.00618 **
democracy -0.40120 0.10063 -3.987 6.70e-05 ***
trade
         -21.07611
                      11.30396 -1.864 0.06225 .
Signif. codes: 0 *** 0.001 ** 0.01 * 0.05 . 0.1
```

Example, Continued

Linear trend:

```
> OR$duration<-OR$stop
> OR.trend<-glm(dispute~allies+contig+capratio+growth+democracy+trade
            +duration,data=OR,na.action=na.exclude,family="binomial")
> summary(OR.trend)
Coefficients:
           Estimate Std. Error z value Pr(>|z|)
allies
       -0.362966 0.114140 -3.180 0.001473 **
contig 0.996908 0.123978 8.041 8.91e-16 ***
capratio -0.235655 0.052763 -4.466 7.96e-06 ***
growth -3.957428 1.225716 -3.229 0.001244 **
democracy -0.361150
                    0.099515 -3.629 0.000284 ***
trade
       -2.870981
                    9.861298 -0.291 0.770947
duration -0.091189
                    0.008098 -11.260 < 2e-16 ***
```

Signif. codes: 0 *** 0.001 ** 0.01 * 0.05 . 0.1

Example, Continued

```
Fourth-Order polynomial trend:
OR$d2<-OR$duration^2*0.1
OR$d3<-OR$duration^3*0.01
OR$d4<-OR$duration^4*0.001
OR.P4<-glm(dispute~allies+contig+capratio+growth+democracy+trade
           +duration+d2+d3+d4.data=OR.na.action=na.exclude.
           family="binomial")
> summary(OR.P4)
Coefficients:
          Estimate Std. Error z value Pr(>|z|)
allies
         0.995584 0.124074 8.024 1.02e-15 ***
contig
capratio -0.228355 0.052257 -4.370 1.24e-05 ***
growth
         -3.864329 1.245617 -3.102 0.00192 **
democracy
         -0.392457 0.100693 -3.898 9.72e-05 ***
         -4.032292 9.631171 -0.419 0.67546
trade
duration
         0.058036 0.091465 0.635 0.52574
d2
          -0.274958 0.128454 -2.141 0.03231 *
d3
          0.136086 0.063230 2.152 0.03138 *
d4
          -0.018863
                   0.009914 -1.903 0.05709 .
```

Signif. codes: 0 *** 0.001 ** 0.01 * 0.05 . 0.1 1

Polynomial Improvement?

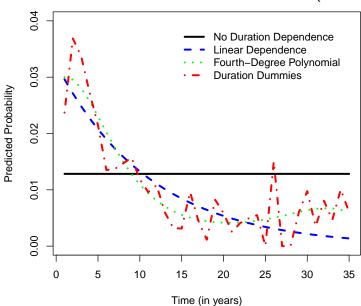
Example: "Time Dummies"

```
"Time dummies":
> OR.dummy<-glm(dispute~allies+contig+capratio+growth+democracy+trade
          +as.factor(duration),data=OR,na.action=na.exclude,
          family="binomial")
> summary(OR.dummy)
Coefficients:
                      Estimate Std. Error z value Pr(>|z|)
(Intercept)
                      -3.61115
                                 0.18219 -19.820 < 2e-16 ***
allies
                      -0.36922
                                0.11441 -3.227 0.001251 **
contig
                       0.99389
                                0.12417 8.005 1.20e-15 ***
capratio
                      -0.22778
                                 0.05219 -4.364 1.27e-05 ***
growth
                      -3.97619
                                1.24940 -3.182 0.001460 **
democracy
                      -0.39559
                                 0.10077 -3.926 8.65e-05 ***
trade
                      -3.46727
                                9.62606 -0.360 0.718700
as.factor(duration)2
                     0.45489
                                 0.19606 2.320 0.020331 *
as.factor(duration)3
                     0.36020
                                 0.20632 1.746 0.080843 .
as.factor(duration)4
                                 0.22175 0.640 0.522289
                      0.14188
   <output omitted>
as.factor(duration)33 -1.64467
                                 1.01715 -1.617 0.105891
as.factor(duration)34 -0.86966
                                 0.73158 -1.189 0.234541
as.factor(duration)35 -1.38777
                                1.01857 -1.362 0.173049
```

Signif. codes: 0 *** 0.001 ** 0.01 * 0.05 . 0.1 1

"Time Dummies," continued

Predicted "Hazards" (Probabilities)



Cox / Poisson Equivalence

Cox model:

OR.Cox<-coxph(Surv(OR\$start,OR\$stop,OR\$dispute)~allies+contig+capratio+growth+democracy+trade,data=OR,method="breslow")

Poisson:

