Interaction analysis in the metric of time

Andrea Bellavia

Unit of Nutritional Epidemiology, Unit of Biostatistics
Institute of Environmental Medicine
Karolinska Institutet, Stockholm
andrea.bellavia@ki.se

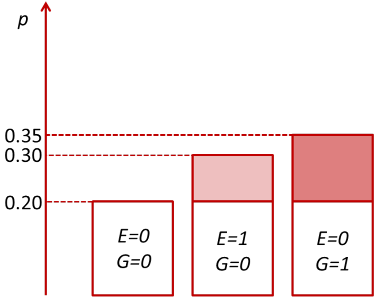
Aging Research Center
29 September 2015

Concept of Interaction

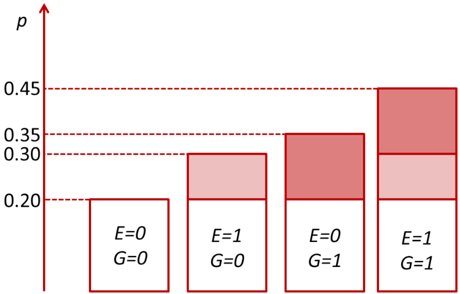
- The effect of a given exposure on the outcome of interest may depend on the presence or absence of another exposure
- When this happens we say that there is an interaction between the two exposures
- Interaction can be defined on the additive or multiplicative scale

Dichotomous exposures

- Suppose we have a dichotomous outcome Y and two dichotomous exposures G and E
- We are interested in $P(Y=1|G=g, E=e)$, the probability of Y given the two exposures



Additive Interaction

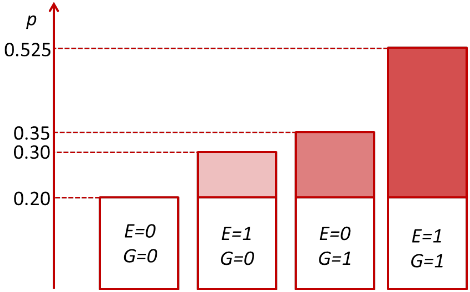


Definition of additive interaction

$$p_{11} = p_{10} + p_{01} - p_{00}$$

$$0.35 + 0.30 - 0.20 = 0.45$$

Multiplicative Interaction



Definition of multiplicative interaction

$$p_{11} = (p_{10} \times p_{01})/p_{00}$$

$$(0.35 \times 0.30)/0.20 = 0.525$$

Additive vs Multiplicative Interaction

- The sign of the interaction depends on the chosen scale. A common situation is to have negative interaction on the multiplicative scale, but positive interaction on the additive scale
- In general, if both exposures have an effect on the outcome there must be an interaction on some scale
- Additive interaction is the more relevant public health measure. For example it can be used to determine which group should be treated
- Evaluating and presenting interaction according to both scales has been widely recommended

Statistical interaction

- Statistical interaction is commonly assessed by including a product term in the regression model
- The concept of statistical and biological interaction must be distinguished
- Whether additive or multiplicative interaction is evaluated depends on the chosen statistical model
- A statistical model on the linear scale can be used to evaluate statistical interaction on the additive scale

$$P(Y = 1|G = g, E = e) = \alpha_0 + \alpha_1 g + \alpha_2 e + \alpha_3 ge$$

- A statistical model on the log-linear scale can be used to evaluate statistical interaction on the multiplicative scale

$$\log[P(Y = 1|G = g, E = e)] = \beta_0 + \beta_1 g + \beta_2 e + \beta_3 ge$$

Interaction in survival analysis

- Cox regression, the most common statistical approach for time-to-event data, is a log-linear model
- Inclusion of a product-term in a Cox regression model allows evaluating departures from multiplicative interaction
- This issue is rarely acknowledged and Cox regression is generally used to "assess interaction"
- One must be cautious when interpreting interaction coefficients. A non-significant product-term does not exclude the presence of additive interaction

Interaction in survival analysis

Cox regression

$$h(t; g, e) = h_0(t)e^{\beta_1 g+\beta_2 e+\beta_3 ge}$$

- e^{β_3} gives a measure of multiplicative interaction for hazard ratios
- A possible measure of additive interaction is the relative excess risk due to interaction on the hazard ratio scale (*RERI* - Li & Chambless, 2007)

$$RERI_{HR} = e^{\beta_1+\beta_2+\beta_3} - e^{\beta_1} - e^{\beta_2} + 1$$

RERI - properties and limitations

- *RERI* equal to 0 implies that interaction is additive. Positive or negative values indicate the presence of super-additivity or sub-additivity, respectively
- Major statistical software calculate *RERI* with confidence intervals
- However, *RERI* only suggests the direction of the interaction, without any indication on the magnitude of the combined effect
- Moreover, this measure is more reliable if the outcome is rare

Example

- Data "kidney_ca" from *http://portal.uni-freiburg.de/imbi/Royston-Sauerbrei-book/index.html#datasets*
- Effect of novel treatment in predicting survival after renal carcinoma
- Another important covariate is kidney removal (Yes/No)
- The treatment effect on survival may depend on the previous removal of a kidney

Example - Cox regression

- Model without interaction:

```
stcox trt rem
```

	HR	95% CI
trt	0.744	(0.587, 0.927)
rem	0.809	(0.648, 1.009)

- The model assumes multiplicativity of the effects. What is the HR comparing participants with (trt=0, rem=0) and (trt=1, rem=1)?
- 0.744*0.809=0.602

Example - Cox regression with interaction term

- By including an interaction term in a Cox model we assess if the combined effect is different from the expected one in the model without interaction:

```
gen interaction=trt*rem
stcox trt rem interaction
```

- $\exp(\beta_3) = 1.035$ - $95\% CI: 0.664, 1.611$
- We have no evidence of departure from multiplicativity of the effects
- The combined effect estimated from this new model is 0.601, similar to the one obtained from the model without interaction (this prediction can be easily obtained by: `stcox trt#rem`)

Example - RERI

- Multiplicativity of effects, with dichotomous exposures, implies the presence of super-additivity. From a Cox model this can be assessed by calculating the RERI:

```
nlcom exp(_b[trt]+_b[rem]+_b[interaction])
      -exp(_b[trt])-exp(_b[rem])+1
```

- $RERI = 0.07$ - $95\% CI : -0.27, 0.42$
- Super-additivity of the effects is confirmed, even if far from significance
- We have no information on the magnitude of the interaction effect

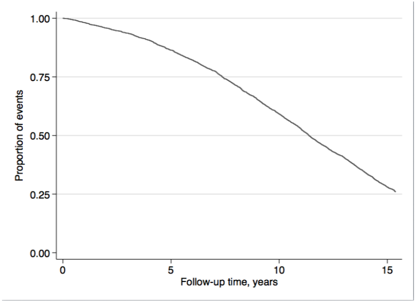
Interaction in the metric of time

- We introduced the concept of interaction in the metric of time and proposed to use a linear regression model for survival percentiles to evaluate additive interaction in survival analysis (Epidemiology - In press (2016))

Survival Percentiles

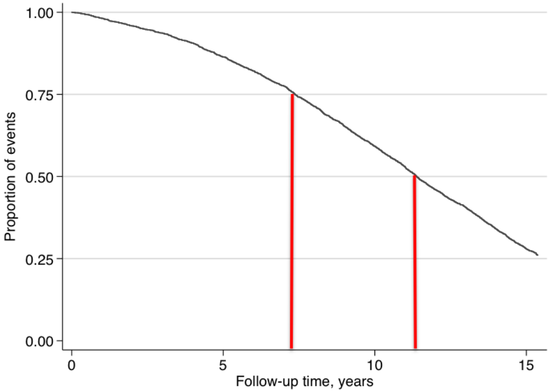
- In time-to-event analysis we define the pth survival percentile as the time t by which p% of the study population has experienced the event of interest, and (1-p)% have not
- Example - The minimal value of T is 0, when everyone is alive. The time by which 50% of the participants have died is called 50th survival percentile, or median survival
- In the same way we can define all survival percentiles
- Survival percentiles are depicted in the survival curve

Survival Percentiles (2)



- In the classical approach the time is fixed and the probability (risk) is evaluated. Here the probability is fixed and the time by which that proportion of cases is achieved is evaluated

Survival Curve

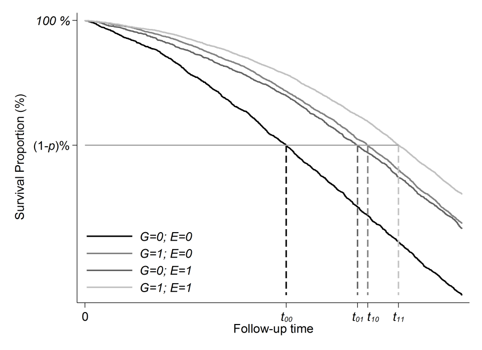


- The 25th survival percentile and the 50th survival percentile (median survival) are shown in the figure

Interaction in the context of survival percentiles

- We can define a measure of additive interaction at the pth percentile as:

$$I_p = (t_{11} - t_{00}) - [(t_{10} - t_{00}) + (t_{01} - t_{00})]$$



Additive interaction in the metric of time

- Survival percentiles can be modeled with quantile regression for censored outcomes
- Among these Laplace regression provides great advantages, being a linear model
- Inclusion of an interaction term in a Laplace regression model will serve as a statistical test for additive interaction

$$T(p|G=g,E=e) = \beta_{p0} + \beta_{p1} \cdot g + \beta_{p2} \cdot e + \beta_{p3} \cdot g \cdot e$$

- β_{p3} represents the excess in survival due to the presence of both predictors G and E

Multiplicative interaction in the metric of time

- Thanks to properties of the quantiles, a multiplicative model for survival percentiles can be estimated by operating a logarithmic transformation of the outcome

$$\log[T(p|G = g, E = e)] = \beta^*_{p0} + \beta^*_{p1} \cdot g + \beta^*_{p2} \cdot e + \beta^*_{p3} \cdot g \cdot e$$

- $\exp(\beta^*_{p3})$ will test for the presence of multiplicative interaction between G and E in predicting survival

Example - Laplace regression

- Additive model on median survival, without interaction:

```
laplace survtime trt rem, failure(_d) quantile(.5)
```

	50th PD	95% CI
rem	71 days	(-2, 144)
trt	95 days	(22, 168)

Example - Laplace regression with interaction

- By including an interaction term in an additive Laplace model we assess the excess in median survival due the presence of both predictors:

```
laplace survtime trt rem interaction, failure(_d)
quantile(.5)
```

- $\beta_3 = 46 days$ - $95\% CI : -105, 197$
- We have a strong (non-significant), additive interaction. The interaction term has a clear and useful interpretation: the beneficial treatment accrues 46 additional days of survival if no kidney was removed

Example - Multiplicative Laplace regression with interaction

- By including an interaction term in a multiplicative Laplace model we assess departures from multiplicativity of the effects:

```
laplace survtime trt rem interaction, failure(_d)
quantile(.5) link(log)
```

- $\exp(\beta_3) = 1.003$ - $95\% CI : 0.551, 1.828$
- As before, we have no evidence of interaction on the multiplicative scale

Summary

- Interaction can be evaluated on the additive or multiplicative scale. These two measures have different public health meaning and relevance
- Statistical modeling of interaction through multiplicative models (Cox regression, logistic regression..) will investigate the presence of multiplicative interaction
- In the presence of time-to-event outcomes, evaluating survival percentile can provide important advantages in interaction analysis
- Statistical evaluation can be easily conducted using linear model for conditional percentiles of censored outcomes
- In the example that was used multiplicative interaction was absent, but there was a strong additive interaction effect of 46 additional days of median survival