Gompertz regression parameterized as accelerated failure time model

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Introduction

- Why use parametric surival models?
  - → Can handle right-, left- or interval-censored data
  - → Cox regression can't handle left- or interval-censored data
  - → Produce better estimation if you have a theoretical expectation of the baseline hazard
  - → Can estimate expected life, not only hazard ratios (AFT-models)
  - → Can include random effects – frailty models (not discussed here)

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Introduction

- A model that is lacking an easy way to estimate in Stata
  → Gompertz regression parameterized as accelerated failure time model
  → Exist in R
    - eha-package, with command: aftreg

- Why use Stata?
  → Easy handling survival data
    - Data management
    - Setup
  → Good graphical possibility

Proportional hazard model

- Easy to compare with Cox regression
  - → Hazard ratios
  - → Plots
    - Cummulative hazard function
    - Survival function
  - → Commonly used

- Hazard function general form
  - → $h(t|x) = h_0(t)e^{xb}$

Accelerated failure time model

- Can be seen as a linear model (simplest form):
  → $\log(t) = a + bx + \varepsilon$
  → Useful in mediation

- Estimation on life scale
  → Estimation of expected baseline life
    - Area under the survival curve when all covariates are zero
  → Compare expected life between two groups
    - Logarithmic change in expected life compared to the baseline life expectancy
    - $\text{Expected life} = \text{Baseline life expectancy} * \exp(\text{effect})$

Accelerated failure time model

- Definiton of accelerated failure time model
  → For a group (X_1,X_2…X_p) , the model is written mathematically as $S(t|x) = S_0\left(\frac{t}{\eta(x)}\right)$, where $S_0(t)$ is the baseline survival function and $\eta(x)$ is an acceleration factor that is a ratio of survival times corresponding to any fixed value of S(t). The acceleration factor is given according to the formula $\eta(x) = e^{(a_1 x_1 + \cdots + a_p x_p)}$. (Qi, J (2009))

- Hazard function
  → $h(t|x) = \left[\frac{1}{\eta(x)}\right] h_0 \left[\frac{t}{\eta(x)}\right]$

- Log-linear from
  → $\log(t) = a + bx + \sigma\varepsilon$
  → Where t and ε following corresponing distributions

The Gompertz distribution

- When is it useful?
  → Adult and old age mortality for humans
    - Demographic models
    - Including models with treatment effects, such as cancer patiens
    - Can be problem with very old individuals

- Normal paramertization
  → $h(t) = \lambda e^{\gamma t}$
  → $\lambda > 0,\ \gamma \geq 0,\ t > 0$

The Gompertz distribution

- Suggested new parametrization by Broström, G & Edvinsson, S (2013)
  - → $\lambda \to \frac{\lambda}{\gamma},\ \gamma \to \frac{1}{\gamma}$
  - → $h(t) = \frac{\lambda}{\gamma} e^{t/\gamma}$
  - → $\lambda > 0,\ \gamma > 0,\ t > 0$

- Proof of new parametrization
  - → Hazard for AFT-model
  - → $h(t|x) = \left[\frac{1}{\eta(x)}\right] h_0 \left[\frac{t}{\eta(x)}\right]$
  - → Here, new gamma can be seen as an accelerated factor

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The Gompertz distribution

- Linear model: $\log(t) = a + bx + \varepsilon$
  - Here, ε is following a log-Gompertz or inverse Weibull distribution
  - Compare to the Weibull model, where ε follows a Gumbel distribution

- Likelihood function

→ Survival function: $S(t) = exp\{-\lambda(e^{t/\gamma} - 1)\}$

→ Density function: $F(t) = h(t)S(t)$

→ Hazard function: $h(t) = \frac{\lambda}{\gamma} e^{t/\gamma}$

→ $L(\alpha, \mu, \sigma) = \prod_{i=1}^{n} \{h_i(t_i)S_i(t_i)\}^{\delta_i} \{S_i(t_i)\}^{1-\delta_i}$

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Structural equation models and mediation

- Simple way to estimate linear models within a pathway framework
- Estimate all equations and combine for the direct and indirect effects
- Supported by most statistical programs
  → In Stata the gsem-command combined with simulation is preferable

Mediation in survival models

- What do we need to do?
  1. Estimate a parametric survival model
  2. Estimate the exposure on the mediator
     - First two steps directly from the gsem output
  3. Estimate the indirect, direct and total effect
  4. Estimate confidence intervals and significance
     - Step three and four can be done with either simulation or delta method
     - These models are simple for continous mediators, but can be tricky with binary or categorical mediators

Estimating confidence intervals

- Simulation
  - → Boostraping
    - Seems to be the more popular simulation method
    - Calculate point estimates for the indirect and direct effects
    - Simulate these point estimates
  - → Monte carlo simulation
    - More flexible to handle problematic correlations
    - Not as straight forward

- Delta method
    - Easiest method and probably most popular
    - Need a stronger assumption of normality

What I am working on

- A Stata command, **`staftgomp`**, to estimate the Gompertz regression parameterized as accelerated failure time model similar to what streg does

- A post-estimation command that would make it simple to estimate direct, indirect and total effect, with confidence intervals, for survival models

Example

- Scanian Economic Demographic Database (Bengtsson, T., Dribe, M. and Svensson, P. (2012))

- Longitudinal historical database
  - → Data from 17th century and onwards
  - → Here, data from individuals born between 1815-1860 are used
  - → Comes from five rural parishes in western Scania
  - → Consist of important life course events as birth and death, but also births of children, marriage or socioeconomic status are recorded

Data

- Variables used:
  → ”Treatment variable”:
    - Approximation of bad early life conditions
    - Infant mortality rate at the year of birth
    - High imr vs. low imr (binary)
    - Years of high diseaseload such as measles, smallpox and whooping cough (Quaranta, L. (2013))

  → Parental socioeconomic status
    - Socioceconomic status at birth (binary)
    - Confounder

  → Outcome
    - The individuals are followed until death or out-migration.

Pre-estimation

- Compare hazard estimations of Gompertz proportional hazard model and Cox regression
- Plot survival curve and compare with Kaplan-Maier
- If not acceptable test with different survival distribution until the parametric model is acceptable
  → Here, we choose Gompertz as it fits good and are supported theoretically for adult mortality

Gompertz proportional hazard

```
. streg imr_high ses, dist(gompertz)

Gompertz regression -- log relative-hazard form

No. of subjects =        3,756                  Number of obs    =      3,756
No. of failures =          880
Time at risk    =     19824107
                                                LR chi2(2)       =      26.53
Log likelihood  =   -1773.9194                  Prob > chi2      =     0.0000

------------------------------------------------------------------------------
          _t | Haz. Ratio   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
    imr_high |   1.259023   .0951873     3.05   0.002     1.085624    1.460119
         ses |   1.362878   .1010669     4.17   0.000     1.178513    1.576084
       _cons |   9.57e-06   8.25e-07  -134.05   0.000     8.08e-06    .0000113
-------------+----------------------------------------------------------------
      /gamma |   .0002332   8.35e-06    27.92   0.000     .0002168    .0002496
------------------------------------------------------------------------------
```

Cox regression

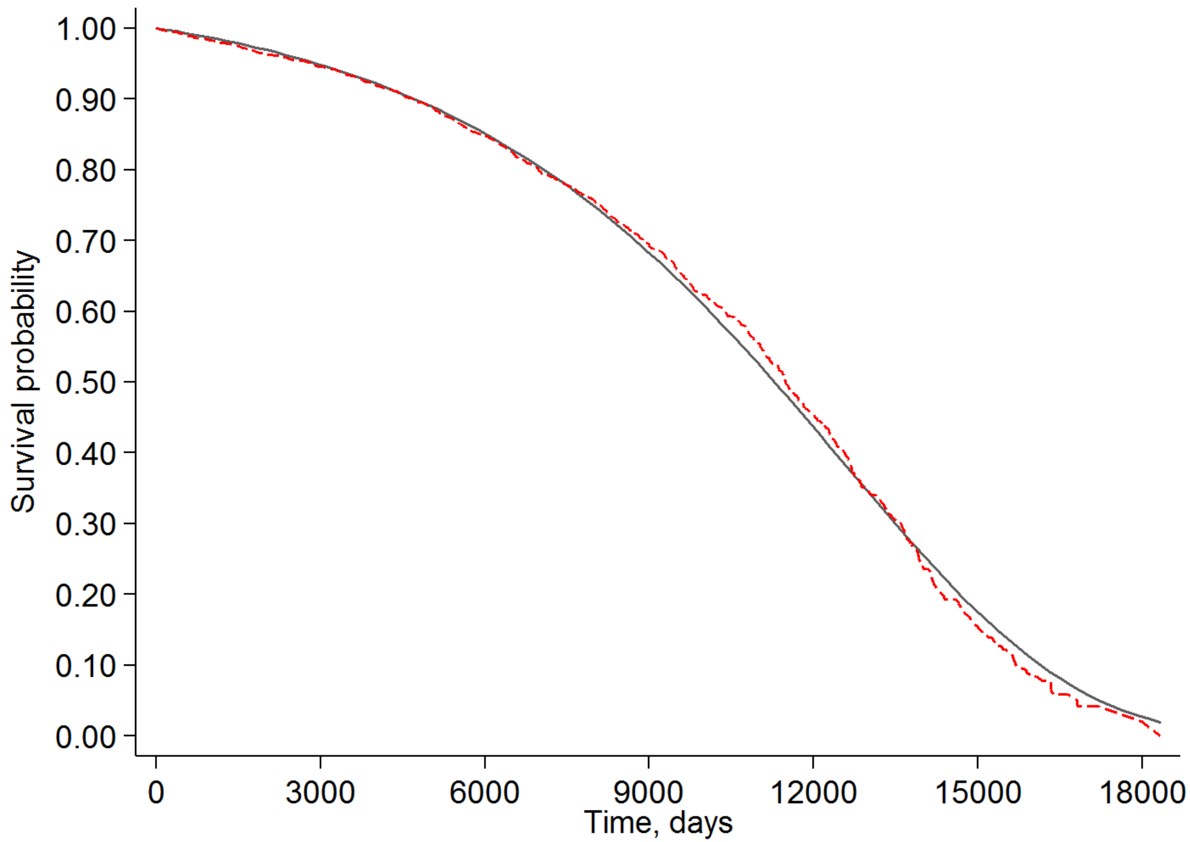
```
. stcox imr_high ses

Cox regression -- Breslow method for ties

No. of subjects =        3,756                  Number of obs    =      3,756
No. of failures =          880
Time at risk    =     19824107
                                                LR chi2(2)       =      28.17
Log likelihood  =   -5889.8259                  Prob > chi2      =     0.0000

------------------------------------------------------------------------------
          _t | Haz. Ratio   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
    imr_high |   1.261686   .0955679     3.07   0.002     1.087617    1.463614
         ses |   1.381581    .102833     4.34   0.000     1.194043    1.598573
------------------------------------------------------------------------------
```

Gompertz vs. Kaplan-Maier



Gompertz AFT model

```
. staftgomp imr_high ses

Gompertz AFT regression                               No. of obs =      3756
Log likelihood = -9325.8767                           LR chi2(2) =     14.34
Baseline life expectancy = 11669.94                  Prob > chi2 =    0.0008
------------------------------------------------------------------------------
          _t |      Coef.   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
xb           |
    imr_high |  -.0496389   .0261027    -1.90   0.057    -.1007992    .0015214
         ses |  -.0873728   .0273233    -3.20   0.001    -.1409255   -.0338202
-------------+----------------------------------------------------------------
bp           |
      lambda |   8.434053   .0451675   186.73   0.000     8.345526    8.522579
       gamma |  -2.931995    .102271   -28.67   0.000    -3.132442   -2.731547
------------------------------------------------------------------------------
```

Post-estimation

```
. lincom imr_high, eform

 ( 1)  [xb]imr_high = 0

------------------------------------------------------------------------------
          _t |     exp(b)   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
         (1) |    .951573   .0248386    -1.90   0.057     .9041146    1.001523
------------------------------------------------------------------------------


. nlcom exp([xb]imr_high)*11699

       _nl_1:  exp([xb]imr_high)*11699

------------------------------------------------------------------------------
          _t |      Coef.   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
       _nl_1 |   11132.45   290.5866    38.31   0.000     10562.91    11701.99
------------------------------------------------------------------------------
```

Post-estimation

- Baseline life expectancy

  → $\frac{11699}{365}\text{days} = 32{,}1\ \text{years}$

- Estimating for individuals after 16000 days

  → $\frac{11699+16000}{365}\text{days} = 75{,}9\ \text{years of age}$

- Effect of high imr during birth

  → $\frac{11132+16000}{365}\text{days} = 74{,}3\ \text{years of age}$

Conclusion

- Conclusion
  → Even if you survive over the age of 40 you still have a mean shorter life expectancy of 1,6 years if you were born in a year with high imr
  → Latent effect
  → Support for the fetal origins hypothesis
  → Is the estimate reasonable?

- If needed
  → Mediation analysis and calculation of direct, indirect and total effect of treatment
  → Here, total effect = direct effect