# Modelling multiple timescales using flexible parametric survival models

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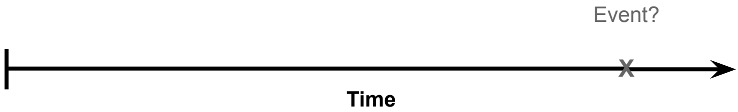
# About me

- I currently work at Karolinska Institutet (70%), and Red Door Analytics (30%)
- Background in maths and biostatistics
- Defended my thesis at Karolinska Institutet in March 2018
  - *Flexible parametric models for cancer patient survival: loss in expectation of life and further developments*

# Timescales

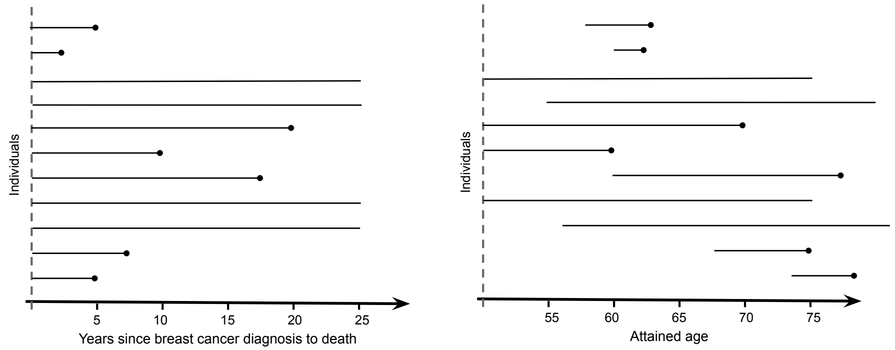
- Defining the timescale(s) of interest is essential in any time-to-event analysis
- Two main components of survival analysis are the event/outcome of interest and time(scale)
- The timescale is defined by the start and stop of follow-up time, and a time origin



# Timescales

- Different timescales could be important for different outcomes
  - Time since a cancer diagnosis to death
  - Attained age for the incidence disease
- Several timescales may also be simultaneously of interest
  - Incidence of breast cancer (attained age, time since childbirth)
  - Mortality rates in the population (calendar year, attained age)
  - Risk of infection after admittance to intensive care unit (time since admittance, calendar time)

# Timescales


Individuals
5
10
15
20
25
Years since breast cancer diagnosis to death
Individuals
55
60
65
70
75
Attained age

# How to model with multiple timescales?

- Common to model multiple timescales by splitting one one or more timescales[1, 2].
- For example, if we were to use a piece-wise constant exponential (Poisson) model:
  - Split your dataset up according to timescale 1
  - Split your dataset up according to timescale 2
  - Fit a Poisson model to this stacked dataset with
    - Categories for the timescales
    - Could use some smoothed function (e.g. spline)
- This can be computationally intensive.

# Example of split data

```
. list id hormon _t0 _t _d in 1/10
```

| | id | hormon | _t0 | _t | _d |
|---|---|---|---|---|---|
| 1. | 1 | 0 | 0 | 4.9665973 | 1 |
| 2. | 2 | 1 | 0 | 5.5251342 | 1 |
| 3. | 3 | 1 | 0 | 1.9494031 | 1 |
| 4. | 4 | 1 | 0 | 4.9474318 | 1 |
| 5. | 5 | 0 | 0 | 2.1136787 | 1 |
| 6. | 6 | 0 | 0 | 1.2265907 | 1 |
| 7. | 7 | 1 | 0 | 5.9467747 | 0 |
| 8. | 8 | 0 | 0 | 5.9166575 | 0 |
| 9. | 9 | 0 | 0 | 1.289563 | 1 |
| 10. | 10 | 0 | 0 | 5.5141825 | 0 |

```
. list id hormon fu _t0 _t _d in 1/10
```

| | id | hormon | fu | _t0 | _t | _d |
|---|---|---|---|---|---|---|
| 1. | 1 | 0 | 0 | 0 | 2 | 0 |
| 2. | 1 | 0 | 2 | 2 | 4.9665973 | 1 |
| 3. | 2 | 1 | 0 | 0 | 2 | 0 |
| 4. | 2 | 1 | 2 | 2 | 5 | 0 |
| 5. | 2 | 1 | 5 | 5 | 5.5251342 | 1 |
| 6. | 3 | 1 | 0 | 0 | 1.9494031 | 1 |
| 7. | 4 | 1 | 0 | 0 | 2 | 0 |
| 8. | 4 | 1 | 2 | 2 | 4.9474318 | 1 |
| 9. | 5 | 0 | 0 | 0 | 2 | 0 |
| 10. | 5 | 0 | 2 | 2 | 2.1136787 | 1 |

# Flexible parametric models on the hazard scale

- Flexible parametric survival model (FPM) use restricted cubic splines to model the baseline function
- Here the restricted cubic splines model the baseline log hazard function $\ln h(t)$
- With one timescale:

$$\ln(h(t|\mathbf{x})) = s(f(t)|\gamma_0) + \mathbf{x}'\beta$$

where $s(f(t);\gamma_0)$ represents the spline function, $\mathbf{x}$ are covariates, $t$ is time.

# Flexible parametric models on the hazard scale

- Note that it is more common to fit FPM on the log cumulative hazard scale
- To maximise the likelihood when modelling on the log hazard scale we have to numerically integrate
- FPMs are flexible, easy to include time-dependent effects, software allows for nice predictions [3].

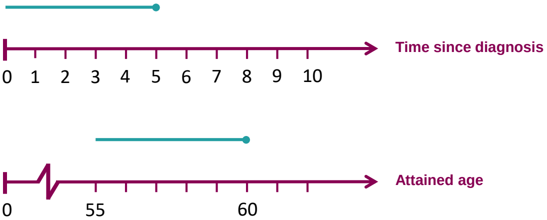
# Multiple timescales, again

To incorporate multiple timescales we utilise the fact that timescales increase with the same unit [4, 5, 6]

- One timescale is a function of the other
- Have to consider where the origin of each timescale is

# Multiple timescales, again

To illustrate, say an individual is diagnosed with a disease at age 55 and has follow-up for 5 years:



# Multiple timescales, again

Then we can extend this idea to the following:

- $t_{diag}$ = time since diagnosis of a disease
- $t_{age}$ = attained age
- $a$ = age at diagnosis (constant offset)

Then, we can write

$$t_{age} = t_{diag} + a$$

**Flexible parametric model with two timescales becomes:**

$$\ln(h(t_{diag}|a, \boldsymbol{x})) = \underbrace{s_1(f(t_{diag})|\gamma_1)}_{\text{Time since diagnosis}} + \underbrace{s_2(f(t_{diag} + a)|\gamma_2)}_{\text{Attained age}} + \boldsymbol{x}'\beta$$

# Why use multiple timescales?

- In most situations, using one primary timescale should be OK
  - Survival estimates from models with one timescale may be biased when the hazard rate of the event of interest is actually a function of two timescales [7]
- Part of the research question
- If it is of interest, there is now a user-friendly Stata command `stmt` [8]
  - Note that these models can also be fitted using `stmerlin`, a more generalised command (survival analysis using `merlin` [9])

# Modelling multiple timescales in Stata using `stmt`

- `stmt` is a Stata command which fits multiple timescales using FPMs on the log hazard scale [8]
- First timescale is specified using the `stset` command
- Second is specified in `stmt` options

---

**Title**

**stmt** — Modelling multiple timescales using flexible parametric survival models on the log hazard scale

**Syntax**

**stmt** [*varlist*] [*if*] [*in*] [, time1(*sub-options*) time2(*sub-options*) time3(*sub-options*) *options*]

# Modelling multiple timescales in Stata using `stmt`

- Covariates, and interactions with the timescale can be specified
- Numerical integration performed via Gauss-Legendre quadrature
- Requires `rcsgen` and `stpm2` to be installed
- Analytic derivatives for the score and Hessian are included to increase speed and accuracy when maximising the likelihood

# stmt syntax

**stmt syntax**

`stmt` *varlist* [*if*] [*in*], `time1(`*sub-options*`)`

[ `time2(`*sub-options*`)` `time3(`*sub-options*`)` `timeint(`*int_list*`)`

`timeintknots(`*int_list*`)` `timeintbknots(`*int_list*`)`

noconstant nodes(#) noorthog nohr verbose from(*matrix*) inith(*varname*)

*maximise_options*]

# `stmt` syntax

Time-scale specific sub-options include:

- The offset between the two timescales (`start()` option)
- Number and position of knots of restricted cubic splines
- Interactions with the timescale, i.e. HRs which change over the timescale
- Subgroup-specific timescale

# `stmt` postestimation command

It is also possible to predict from the fitted model using the `predict` command

- The linear predictor and hazard function
- Can specify which values of each timescale to predict over

**`predict` syntax**

`predict` *newvar* [*if*] [*in*], { `hazard` | `xb` } `time1var(`*varname*`)` `time2var(`*varname*`)` `time3var(`*varname*`)` [`at(`*varname* `#` [*varname* `#` `...`]`)` `ci` `nodes` `per` `zeros` `level(#)`]

# Example

- 2982 females diagnosed with breast cancer
- Our outcome of interest is death (due to any cause)
- We follow patients from primary surgery
- Grade of cancer is our exposure of interest (2 or 3)
- Timescales of interest
  1. Time since primary surgery
  2. Attained age

# stset

stset with time since surgery as timescale 1:

```
. stset survtime, f(dead==1) scale(12)
Survival-time data settings
         Failure event: dead==1
Observed time interval: (0, survtime]
     Exit on or before: failure
     Time for analysis: time/12
--------------------------------------------------------------------------
      2,982  total observations
          0  exclusions
--------------------------------------------------------------------------
      2,982  observations remaining, representing
      1,272  failures in single-record/single-failure data
 21,270.702  total analysis time at risk and under observation
                                                At risk from t =         0
                                     Earliest observed entry t =         0
                                          Last observed exit t =  19.28268
```

# stmt with one timescale

```
. stmt grade, time1(df(5)) nolog
Log likelihood = -3023.3924                          Number of obs = 2,982
```

| | Haz. ratio | Std. err. | z | P>\|z\| | [95% conf. | interval] |
|---|---|---|---|---|---|---|
| xb | | | | | | |
| grade | 1.659792 | .1152621 | 7.30 | 0.000 | 1.448582 | 1.901798 |
| rcs | | | | | | |
| __t1_s1 | .1130917 | .0309638 | 3.65 | 0.000 | .0524038 | .1737795 |
| __t1_s2 | .1179876 | .0291052 | 4.05 | 0.000 | .0609425 | .1750326 |
| __t1_s3 | -.1213544 | .0299503 | -4.05 | 0.000 | -.1800559 | -.062653 |
| __t1_s4 | -.0914425 | .0299644 | -3.05 | 0.002 | -.1501716 | -.0327134 |
| __t1_s5 | -.026898 | .0318642 | -0.84 | 0.399 | -.0893507 | .0355546 |
| _cons | -4.12488 | .1960625 | -21.04 | 0.000 | -4.509155 | -3.740604 |

```
Note: Estimates are transformed only in the first equation to hazard ratios.
 Quadrature method: Gauss-Legendre with 30 nodes
```

# stmt with two timescale

We use the time2() option with the start() sub-option to specify our second timescale, attained age

```
. stmt grade, time1(df(5)) time2(df(3) start(agesurgery)) nolog
Log likelihood = -2956.7515                              Number of obs = 2,982
------------------------------------------------------------------------------
             |  Haz. ratio   Std. err.      z    P>|z|     [95% conf. interval]
-------------+----------------------------------------------------------------
xb           |
       grade |   1.609036   .1118154     6.84   0.000     1.404151    1.843816
-------------+----------------------------------------------------------------
rcs          |
     __t1_s1 |    .078144   .0316819     2.47   0.014     .0160487    .1402394
     __t1_s2 |   .1307119   .0291879     4.48   0.000     .0735047     .187919
     __t1_s3 |  -.1186399   .0300058    -3.95   0.000    -.1774502   -.0598297
     __t1_s4 |  -.0946102   .0300088    -3.15   0.002    -.1534263   -.0357941
     __t1_s5 |   -.030988   .0318674    -0.97   0.331    -.0934469    .0314709
     __t2_s1 |   .2271669   .0260366     8.72   0.000     .1761361    .2781977
     __t2_s2 |  -.2377882   .0251054    -9.47   0.000    -.2869938   -.1885825
     __t2_s3 |  -.0887876   .0266178    -3.34   0.001    -.1409575   -.0366178
       _cons |  -4.048158   .1961963   -20.63   0.000    -4.432695    -3.66362
------------------------------------------------------------------------------
Note: Estimates are transformed only in the first equation to hazard ratios.
 Quadrature method: Gauss-Legendre with 30 nodes
```

# stmt with two timescales

We can add an interaction using the tvc() and dftvc() options:

```
. stmt grade, time1(df(5) tvc(grade) dftvc(2)) time2(df(3) start(agesurgery)) nolog
Log likelihood = -2953.3856                               Number of obs = 2,982
```

| | Haz. ratio | Std. err. | z | P>\|z\| | [95% conf. | interval] |
|---|---|---|---|---|---|---|
| xb | | | | | | |
| grade | 1.514219 | .1233225 | 5.09 | 0.000 | 1.290816 | 1.776287 |
| rcs | | | | | | |
| __t1_s1 | .5111851 | .2011859 | 2.54 | 0.011 | .116868 | .9055022 |
| __t1_s2 | .3295628 | .2191507 | 1.50 | 0.133 | -.0999648 | .7590903 |
| __t1_s3 | -.098055 | .0353463 | -2.77 | 0.006 | -.1673326 | -.0287775 |
| __t1_s4 | -.091684 | .0300071 | -3.06 | 0.002 | -.1504969 | -.0328711 |
| __t1_s5 | -.0309256 | .0319089 | -0.97 | 0.332 | -.093466 | .0316147 |
| __t2_s1 | .2274068 | .0260295 | 8.74 | 0.000 | .1763899 | .2784236 |
| __t2_s2 | -.2386316 | .0251059 | -9.51 | 0.000 | -.2878382 | -.189425 |
| __t2_s3 | -.0892667 | .0266396 | -3.35 | 0.001 | -.1414793 | -.0370541 |
| __t1_s_grade1 | -.1539901 | .0712874 | -2.16 | 0.031 | -.2937108 | -.0142695 |
| __t1_s_grade2 | -.068185 | .0770798 | -0.88 | 0.376 | -.2192586 | .0828886 |
| _cons | -3.884596 | .2262782 | -17.17 | 0.000 | -4.328093 | -3.441099 |

```
Note: Estimates are transformed only in the first equation to hazard ratios.
 Quadrature method: Gauss-Legendre with 30 nodes
```

# Predictions from `stmt`

We define our own timescale variables

- `time1` (time since surgery, 0-15 years)
- `time2` (attained age, 40 to 70 years)

and then predict the hazard using the `predict` command:

```
. predict h2, h time1var(time1) time2var(time2) at(grade 3) ci
```

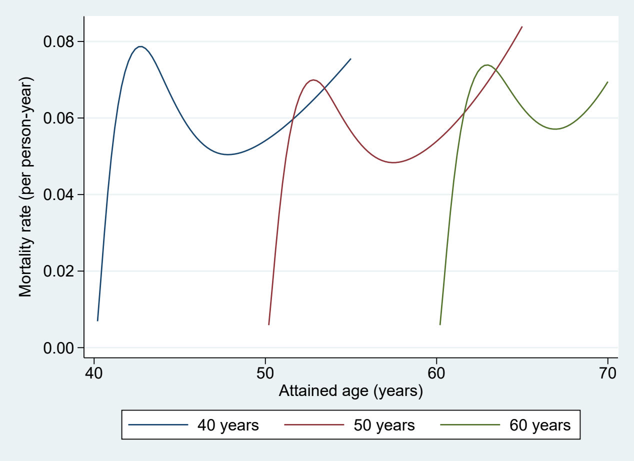
# Predictions from stmt

```
. list time1 time2 ageatsurgery h2 in 1/10
```

| | time1 | time2 | ageats~y | h2 |
|---|---|---|---|---|
| 1. | .2 | 40 | 39.8 | .00693705 |
| 2. | .2 | 40.1 | 39.9 | .00691959 |
| 3. | .2 | 40.2 | 40 | .00690231 |
| 4. | .2 | 40.3 | 40.1 | .0068852 |
| 5. | .2 | 40.4 | 40.2 | .00686827 |
| 6. | .2 | 40.5 | 40.3 | .0068515 |
| 7. | .2 | 40.6 | 40.4 | .00683491 |
| 8. | .2 | 40.7 | 40.5 | .00681849 |
| 9. | .2 | 40.8 | 40.6 | .00680223 |
| 10. | .2 | 40.9 | 40.7 | .00678614 |

# Different plots from these predictions

Fixing age at surgery, we can plot the mortality rate across attained age:

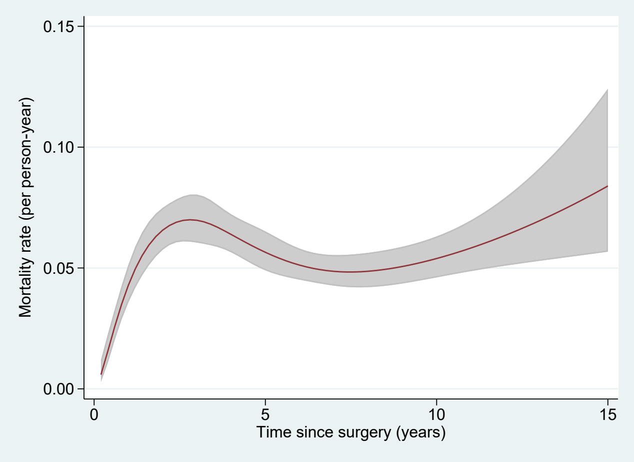


# Different plots from these predictions

Fixing age at surgery, we can plot the mortality rate across time since surgery:

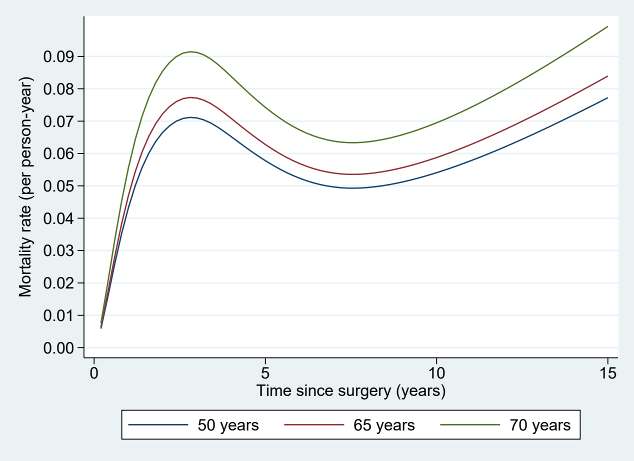
# Different plots from these predictions

Can also show confidence intervals (here for mortality rate for 50 year old at surgery):



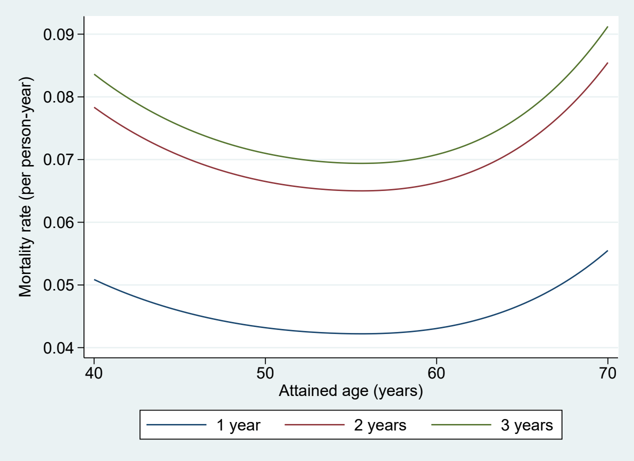
# Different plots from these predictions

Now we fix the attained age timescale:



# Different plots from these predictions

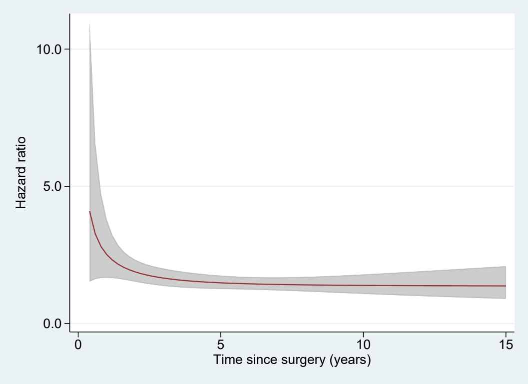
Or we can fix the time since surgery timescale:



# Hazard ratio using predictnl

```
 . predictnl lnhr= ///
> ln(predict(h time1var(time1) time2var(time2) at(grade 3))) ///
>- ln(predict(h time1var(time1) time2var(time2) at(grade 2))) ///
>, ci(lnhr_lci lnhr_uci)

. gen hr=exp(lnhr)
. gen hr_lci=exp(lnhr_lci)
. gen hr_uci=exp(lnhr_uci)
```



# Other information

- See our Stata Journal paper [8], and paper by Batyrbekova et al. [7]

The Stata Journal (2022)
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**Flexible parametric survival analysis with multiple timescales: Estimation and implementation using stmt**

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# Other information

- Red Door Analytics has plans for a course, see `https://reddooranalytics.se/services/training/` for updates
- Others have been working with extending this work:
  - `stmerlin` allows for other models with multiple timescales
  - Extensions to multi-state models to include multiple timescales [10]

# Other information

```
 //cox
stmerlin trt,      dist(cox)                                      ///
                time2(df(2) offset(agec) time noorthog)           ///
                time3(df(2) offset(yearc) time noorthog)

// royston parmer (FPM on log cumulative hazard)
stmerlin trt,      dist(rp) df(3)  noorthog                       ///
                time2(df(2) offset(agec) time noorthog)           ///
                time3(df(2) offset(yearc) time noorthog)
// stmerlin equivalent to stmt
stmerlin trt,      dist(rcs) df(3) noorthog                       ///
                time2(df(2) offset(agec) time  noorthog)          ///
               time3(df(2) offset(yearc) time noorthog)
//stmt
stmt trt,   time1(df(3)) noorthog                                 ///
        time2(df(2) start(agec) logtoff)                          ///
        time3(df(2) start(yearc) logtoff)                         ///
        nohr


 . timer list
   1:      99.07 /        1 =      99.0690
   2:       0.32 /        1 =       0.3150
   3:       7.07 /        1 =       7.0720
   4:       2.30 /        1 =       2.2970
```

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- Nurgul Batyrbekova, Karolinska Institutet
- Paul C Lambert, Karolinska Institutet, University of Leicester
- Therese Andersson, Karolinska Institutet

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