

The resurrection of time as a continuous concept in biostatistics, demography and epidemiology

Bendix Carstensen Steno Diabetes Center,
Gentofte, Denmark
& Department of Biostatistics, University of Copenhagen
bxc@steno.dk
<http://BendixCarstensen.com>

Inference in Multistate models

P.K. Andersen & N. Keiding

Interpretability and Importance of Functionals in Competing Risks and Multistate Models, *Stat Med*, 2011 [?]:

Inference in Multistate models

P.K. Andersen & N. Keiding

Interpretability and Importance of Functionals in Competing Risks and Multistate Models, *Stat Med*, 2011 [?]:

1. Do not condition on the future

Inference in Multistate models

P.K. Andersen & N. Keiding

Interpretability and Importance of Functionals in Competing Risks and Multistate Models, *Stat Med*, 2011 [?]:

1. Do not condition on the future
2. Do not regard individuals at risk after they have died

Inference in Multistate models

P.K. Andersen & N. Keiding

Interpretability and Importance of Functionals in Competing Risks and Multistate Models, *Stat Med*, 2011 [?]:

1. Do not condition on the future
2. Do not regard individuals at risk after they have died
3. Stick to this world

Conditioning on the future

Conditioning on the future

- ▶ ... also known as “Immortal time bias”, see e.g. S. Suissa:
Immortal time bias in pharmaco-epidemiology, *Am. J. Epidemiol*, 2008 [?].

Conditioning on the future

- ▶ ... also known as “Immortal time bias”, see e.g. S. Suissa:
Immortal time bias in pharmaco-epidemiology, *Am. J. Epidemiol*, 2008 [?].
- ▶ Including persons' follow-up in the wrong state

Conditioning on the future

- ▶ ... also known as “Immortal time bias”, see e.g. S. Suissa:
Immortal time bias in pharmaco-epidemiology, *Am. J. Epidemiol*, 2008 [?].
- ▶ Including persons' follow-up in the wrong state
- ▶ ... namely one reached some time in the future

Conditioning on the future

- ▶ ... also known as “Immortal time bias”, see e.g. S. Suissa:
Immortal time bias in pharmaco-epidemiology, *Am. J. Epidemiol*, 2008 [?].
- ▶ Including persons' follow-up in the wrong state
- ▶ ... namely one reached some time in the future
- ▶ Normally caused by classification of **persons** instead of classification of **follow-up time**

Why these mistakes?

- ▶ Time is usually absent from survival analysis results

Why these mistakes?

- ▶ Time is usually absent from survival analysis **results**
- ▶ ... because time is taken to be a **response** variable observed for each **person**

Why these mistakes?

- ▶ Time is usually absent from survival analysis **results**
- ▶ ... because time is taken to be a **response** variable observed for each **person**
- ▶ Unit of analysis is often seen as the person

Why these mistakes?

- ▶ Time is usually absent from survival analysis **results**
- ▶ ... because time is taken to be a **response** variable observed for each **person**
- ▶ Unit of analysis is often seen as the person
- ▶ Non/Semi-parametric survival model interface invites this misconception

Why these mistakes?

- ▶ Time is usually absent from survival analysis **results**
- ▶ ... because time is taken to be a **response** variable observed for each **person**
- ▶ Unit of analysis is often seen as the person
- ▶ Non/Semi-parametric survival model interface invites this misconception
- ▶ **Persons** classified by exposure (the latest, often)

Why these mistakes?

- ▶ Time is usually absent from survival analysis **results**
- ▶ ... because time is taken to be a **response** variable observed for each **person**
- ▶ Unit of analysis is often seen as the person
- ▶ Non/Semi-parametric survival model interface invites this misconception
- ▶ **Persons** classified by exposure (the latest, often)
- ▶ The **real** unit of observation should be person-**time**

Why these mistakes?

- ▶ Time is usually absent from survival analysis **results**
- ▶ ... because time is taken to be a **response** variable observed for each **person**
- ▶ Unit of analysis is often seen as the person
- ▶ Non/Semi-parametric survival model interface invites this misconception
- ▶ **Persons** classified by exposure (the latest, often)
- ▶ The **real** unit of observation should be person-**time**
- ▶ ... intervals of time, each with different **value** of

Why these mistakes?

- ▶ Time is usually absent from survival analysis **results**
- ▶ ... because time is taken to be a **response** variable observed for each **person**
- ▶ Unit of analysis is often seen as the person
- ▶ Non/Semi-parametric survival model interface invites this misconception
- ▶ **Persons** classified by exposure (the latest, often)
- ▶ The **real** unit of observation should be person-**time**
- ▶ ... intervals of time, each with different **value** of
 - ▶ time

Why these mistakes?

- ▶ Time is usually absent from survival analysis **results**
- ▶ ... because time is taken to be a **response** variable observed for each **person**
- ▶ Unit of analysis is often seen as the person
- ▶ Non/Semi-parametric survival model interface invites this misconception
- ▶ **Persons** classified by exposure (the latest, often)
- ▶ The **real** unit of observation should be person-**time**
- ▶ ... intervals of time, each with different **value** of
 - ▶ time
 - ▶ other covariates

Time

- ▶ Time is a **covariate** — determinant of rates

Time

- ▶ Time is a **covariate** — determinant of rates
- ▶ **Response** variable in survival / follow-up is bivariate:

Time

- ▶ Time is a **covariate** — determinant of rates
- ▶ **Response** variable in survival / follow-up is bivariate:
 - ▶ **Differences** on the timescale (**risk** time, “exposure”)

Time

- ▶ Time is a **covariate** — determinant of rates
- ▶ **Response** variable in survival / follow-up is bivariate:
 - ▶ **Differences** on the timescale (**risk** time, “exposure”)
 - ▶ **Events**

Time

- ▶ Time is a **covariate** — determinant of rates
- ▶ **Response** variable in survival / follow-up is bivariate:
 - ▶ **Differences** on the timescale (**risk** time, “exposure”)
 - ▶ **Events**
- ▶ The relevant unit of observation is person-time:

Time

- ▶ Time is a **covariate** — determinant of rates
- ▶ **Response** variable in survival / follow-up is bivariate:
 - ▶ **Differences** on the timescale (**risk** time, “exposure”)
 - ▶ **Events**
- ▶ The relevant unit of observation is person-time:
 - ▶ small intervals of follow-up — “empirical rates”

Time

- ▶ Time is a **covariate** — determinant of rates
- ▶ **Response** variable in survival / follow-up is bivariate:
 - ▶ **Differences** on the timescale (**risk** time, “exposure”)
 - ▶ **Events**
- ▶ The relevant unit of observation is person-time:
 - ▶ small intervals of follow-up — “empirical rates”
 - ▶ (d_{it}, y_{it}) : (event, (sojourn) time) for individual i at time t .

Time

- ▶ Time is a **covariate** — determinant of rates
- ▶ **Response** variable in survival / follow-up is bivariate:
 - ▶ **Differences** on the timescale (**risk** time, “exposure”)
 - ▶ **Events**
- ▶ The relevant unit of observation is person-time:
 - ▶ small intervals of follow-up — “empirical rates”
 - ▶ (d_{it}, y_{it}) : (event, (sojourn) time) for individual i at time t .
 - ▶ y is the **response** time, t is the **covariate** time

Time

- ▶ Time is a **covariate** — determinant of rates
- ▶ **Response** variable in survival / follow-up is bivariate:
 - ▶ **Differences** on the timescale (**risk** time, “exposure”)
 - ▶ **Events**
- ▶ The relevant unit of observation is person-time:
 - ▶ small intervals of follow-up — “empirical rates”
 - ▶ (d_{it}, y_{it}) : (event, (sojourn) time) for individual i at time t .
 - ▶ y is the **response** time, t is the **covariate** time
- ▶ Covariates relate to each interval of follow-up

Time

- ▶ Time is a **covariate** — determinant of rates
- ▶ **Response** variable in survival / follow-up is bivariate:
 - ▶ **Differences** on the timescale (**risk** time, “exposure”)
 - ▶ **Events**
- ▶ The relevant unit of observation is person-time:
 - ▶ small intervals of follow-up — “empirical rates”
 - ▶ (d_{it}, y_{it}) : (event, (sojourn) time) for individual i at time t .
 - ▶ y is the **response** time, t is the **covariate** time
- ▶ Covariates relate to each interval of follow-up
- ▶ Allows **multiple** timescales, e.g. age, duration, calendar time

“Stick to this world”

In the paper by Andersen & Keiding this is primarily aimed at the use of “net survival”,

“Stick to this world”

In the paper by Andersen & Keiding this is primarily aimed at the use of “net survival”, that is the calculation of

$$\exp \left(- \int_0^t \lambda_c(s) ds \right)$$

for a single cause of death

— formally for a non-exhaustive exit rate from a state.

“Stick to this world”

In the paper by Andersen & Keiding this is primarily aimed at the use of “net survival”, that is the calculation of

$$\exp \left(- \int_0^t \lambda_c(s) ds \right)$$

for a single cause of death

— formally for a non-exhaustive exit rate from a state.

Survival probability in the situation where:

1. all other causes of death are absent

“Stick to this world”

In the paper by Andersen & Keiding this is primarily aimed at the use of “net survival”, that is the calculation of

$$\exp \left(- \int_0^t \lambda_c(s) ds \right)$$

for a single cause of death

— formally for a non-exhaustive exit rate from a state.

Survival probability in the situation where:

1. all other causes of death are absent
2. the mortality, λ_c from cause c is unchanged

“Stick to this world”

In the paper by Andersen & Keiding this is primarily aimed at the use of “net survival”, that is the calculation of

$$\exp \left(- \int_0^t \lambda_c(s) ds \right)$$

for a single cause of death

— formally for a non-exhaustive exit rate from a state.

Survival probability in the situation where:

1. all other causes of death are absent
2. the mortality, λ_c from cause c is unchanged

“Stick to this world”

In the paper by Andersen & Keiding this is primarily aimed at the use of “net survival”, that is the calculation of

$$\exp \left(- \int_0^t \lambda_c(s) ds \right)$$

for a single cause of death

— formally for a non-exhaustive exit rate from a state.

Survival probability in the situation where:

1. all other causes of death are absent
2. the mortality, λ_c from cause c is unchanged

... which is indeed **not** of this world.

Sticking to this world

- ▶ A further feature of “this world”:

Sticking to this world

- ▶ A further feature of “this world”:
- ▶ it is **continuous**

Sticking to this world

- ▶ A further feature of “this world”:
- ▶ it is **continuous**
- ▶ no thresholds in the effect of time

Sticking to this world

- ▶ A further feature of “this world”:
- ▶ it is **continuous**
- ▶ no thresholds in the effect of time
- ▶ specifically, death and disease rates vary **smoothly** by

Sticking to this world

- ▶ A further feature of “this world”:
- ▶ it is **continuous**
- ▶ no thresholds in the effect of time
- ▶ specifically, death and disease rates vary **smoothly** by
 - ▶ age

Sticking to this world

- ▶ A further feature of “this world”:
- ▶ it is **continuous**
- ▶ no thresholds in the effect of time
- ▶ specifically, death and disease rates vary **smoothly** by
 - ▶ age
 - ▶ calendar time

Sticking to this world

- ▶ A further feature of “this world”:
- ▶ it is **continuous**
- ▶ no thresholds in the effect of time
- ▶ specifically, death and disease rates vary **smoothly** by
 - ▶ age
 - ▶ calendar time
 - ▶ disease duration

Sticking to this world

- ▶ A further feature of “this world”:
- ▶ it is **continuous**
- ▶ no thresholds in the effect of time
- ▶ specifically, death and disease rates vary **smoothly** by
 - ▶ age
 - ▶ calendar time
 - ▶ disease duration
 - ▶ ...

DM mortality in Australia

- ▶ Rates will typically depend on several time scales

DM mortality in Australia

- ▶ Rates will typically depend on several time scales
- ▶ Mortality among Australian DM patients:

DM mortality in Australia

- ▶ Rates will typically depend on several time scales
- ▶ Mortality among Australian DM patients:
 - a : (current) age — time since birth

DM mortality in Australia

- ▶ Rates will typically depend on several time scales
- ▶ Mortality among Australian DM patients:
 - a : (current) age — time since birth
 - d : (current) duration of diabetes — time since diagnosis

DM mortality in Australia

- ▶ Rates will typically depend on several time scales
- ▶ Mortality among Australian DM patients:
 - a : (current) age — time since birth
 - d : (current) duration of diabetes — time since diagnosis
 - e : age at diagnosis of diabetes: $e = a - d$

DM mortality in Australia

- ▶ Rates will typically depend on several time scales
- ▶ Mortality among Australian DM patients:
 - a : (current) age — time since birth
 - d : (current) duration of diabetes — time since diagnosis
 - e : age at diagnosis of diabetes: $e = a - d$
- ▶ Only two time scales here: a and d

DM mortality in Australia

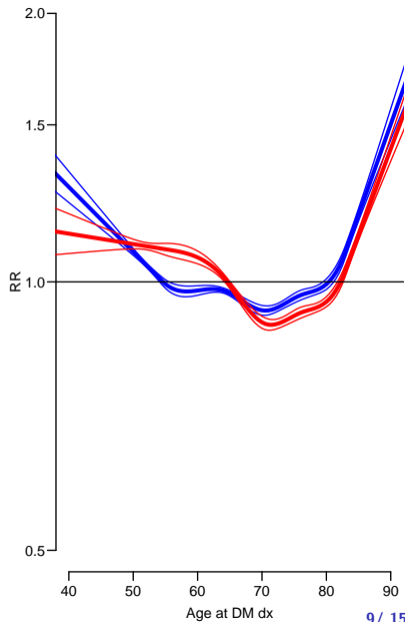
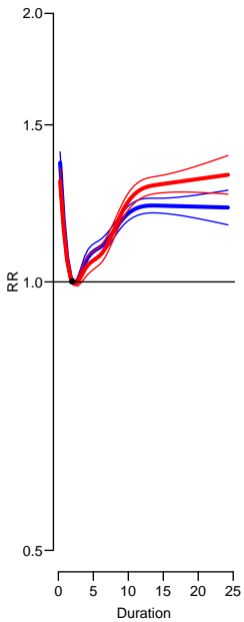
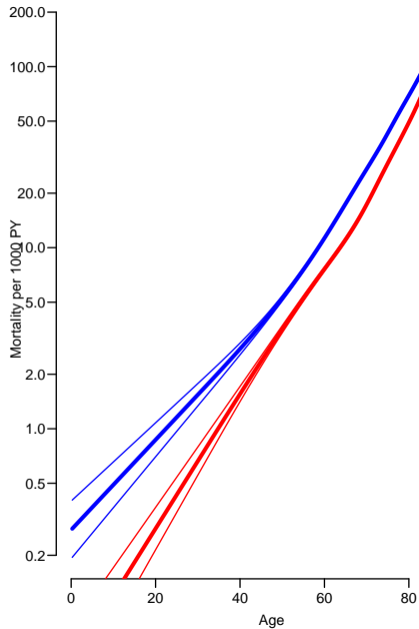
- ▶ Rates will typically depend on several time scales
- ▶ Mortality among Australian DM patients:
 - a : (current) age — time since birth
 - d : (current) duration of diabetes — time since diagnosis
 - e : age at diagnosis of diabetes: $e = a - d$
- ▶ Only two time scales here: a and d
- ▶ $\log(\lambda(a, d)) = f(a) + g(d) + h(e)$

DM mortality in Australia

- ▶ Rates will typically depend on several time scales
- ▶ Mortality among Australian DM patients:
 - a : (current) age — time since birth
 - d : (current) duration of diabetes — time since diagnosis
 - e : age at diagnosis of diabetes: $e = a - d$
- ▶ Only two time scales here: a and d
- ▶ $\log(\lambda(a, d)) = f(a) + g(d) + h(e)$
- ▶ Separate effects are not identifiable — only the 2nd order

DM mortality in Australia

- ▶ Rates will typically depend on several time scales
- ▶ Mortality among Australian DM patients:
 - a : (current) age — time since birth
 - d : (current) duration of diabetes — time since diagnosis
 - e : age at diagnosis of diabetes: $e = a - d$
- ▶ Only two time scales here: a and d
- ▶ $\log(\lambda(a, d)) = f(a) + g(d) + h(e)$
- ▶ Separate effects are not identifiable — only the 2nd order
- ▶ — this is the APC-modeling problem again



Australia DM mortality

- ▶ APC parametrization used (on the log-rate scale)

Australia DM mortality

- ▶ APC parametrization used (on the log-rate scale)
 - ▶ age at diagnosis, e , constrained to be 0 on average, with average slope 0

Australia DM mortality

- ▶ APC parametrization used (on the log-rate scale)
 - ▶ age at diagnosis, e , constrained to be 0 on average, with average slope 0
 - ▶ duration of diabetes, d , constrained to be 0 at $d = 2$ years

Australia DM mortality

- ▶ APC parametrization used (on the log-rate scale)
 - ▶ age at diagnosis, e , constrained to be 0 on average, with average slope 0
 - ▶ duration of diabetes, d , constrained to be 0 at $d = 2$ years
 - ▶ current age, a , models the age effect for duration 2 years

Australia DM mortality

- ▶ APC parametrization used (on the log-rate scale)
 - ▶ age at diagnosis, e , constrained to be 0 on average, with average slope 0
 - ▶ duration of diabetes, d , constrained to be 0 at $d = 2$ years
 - ▶ current age, a , models the **age effect for duration 2 years**
- ▶ Classical reporting of time scale effects as separate is not sensible:

Australia DM mortality

- ▶ APC parametrization used (on the log-rate scale)
 - ▶ age at diagnosis, e , constrained to be 0 on average, with average slope 0
 - ▶ duration of diabetes, d , constrained to be 0 at $d = 2$ years
 - ▶ current age, a , models the age effect for duration 2 years
- ▶ Classical reporting of time scale effects as separate is not sensible:
 - ▶ "... the effect of diabetes duration for a **fixed age**..."

Australia DM mortality

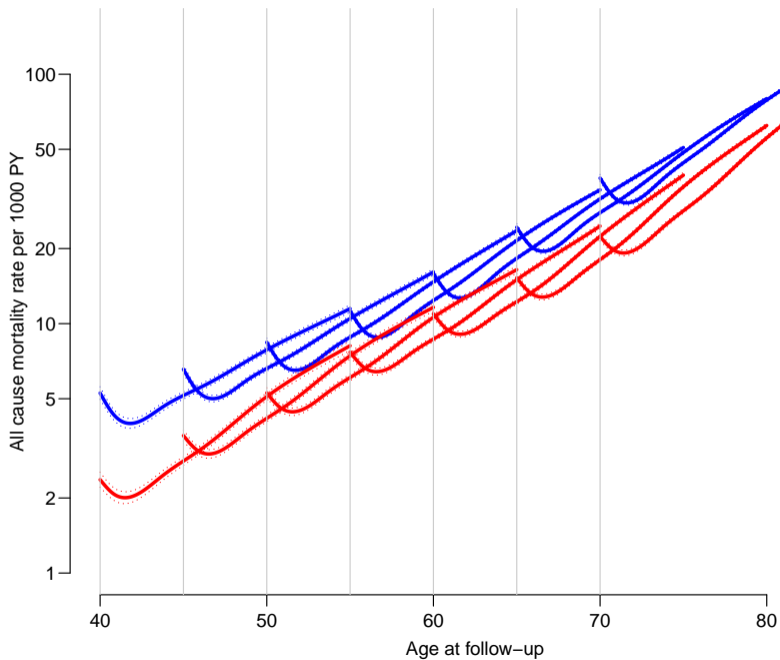
- ▶ APC parametrization used (on the log-rate scale)
 - ▶ age at diagnosis, e , constrained to be 0 on average, with average slope 0
 - ▶ duration of diabetes, d , constrained to be 0 at $d = 2$ years
 - ▶ current age, a , models the age effect for duration 2 years
- ▶ Classical reporting of time scale effects as separate is not sensible:
 - ▶ “... the effect of diabetes duration for a **fixed age**...”
 - ▶ — don't people get older as the duration of disease increase?

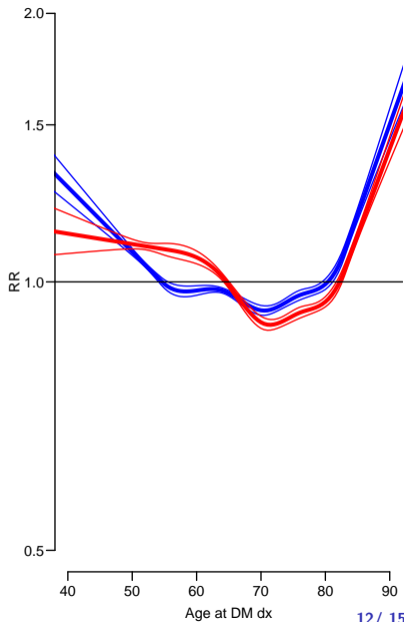
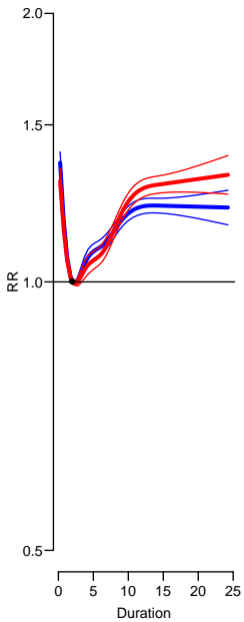
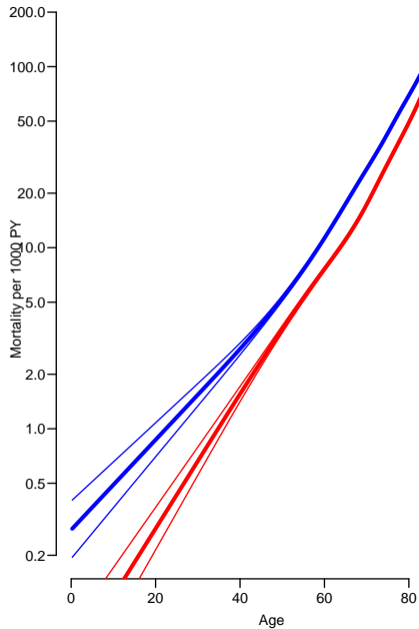
Australia DM mortality

- ▶ APC parametrization used (on the log-rate scale)
 - ▶ age at diagnosis, e , constrained to be 0 on average, with average slope 0
 - ▶ duration of diabetes, d , constrained to be 0 at $d = 2$ years
 - ▶ current age, a , models the age effect for duration 2 years
- ▶ Classical reporting of time scale effects as separate is not sensible:
 - ▶ “... the effect of diabetes duration for a **fixed age**...”
 - ▶ — don't people get older as the duration of disease increase?
- ▶ must be reported **jointly**

Australia DM mortality

- ▶ APC parametrization used (on the log-rate scale)
 - ▶ age at diagnosis, e , constrained to be 0 on average, with average slope 0
 - ▶ duration of diabetes, d , constrained to be 0 at $d = 2$ years
 - ▶ current age, a , models the age effect for duration 2 years
- ▶ Classical reporting of time scale effects as separate is not sensible:
 - ▶ “... the effect of diabetes duration for a **fixed age**...”
 - ▶ — don't people get older as the duration of disease increase?
- ▶ must be reported **jointly**
- ▶ show select fitted values to illustrate the actual effects (and their relative size)





Joint reporting of time effects

- ▶ Only possible in graphical form

Joint reporting of time effects

- ▶ Only possible in graphical form
- ▶ Reveals structures that can only be seen with difficulty from the separate effects

Joint reporting of time effects

- ▶ Only possible in graphical form
- ▶ Reveals structures that can only be seen with difficulty from the separate effects
- ▶ ... as well as structures that cannot

Joint reporting of time effects

- ▶ Only possible in graphical form
- ▶ Reveals structures that can only be seen with difficulty from the separate effects
- ▶ ... as well as structures that cannot
- ▶ Always has the form of predictions of rates:

Joint reporting of time effects

- ▶ Only possible in graphical form
- ▶ Reveals structures that can only be seen with difficulty from the separate effects
- ▶ . . . as well as structures that cannot
- ▶ Always has the form of predictions of rates:
- ▶ requires access to estimates of the **predicted rates**

Joint reporting of time effects

- ▶ Only possible in graphical form
- ▶ Reveals structures that can only be seen with difficulty from the separate effects
- ▶ ... as well as structures that cannot
- ▶ Always has the form of predictions of rates:
- ▶ requires access to estimates of the **predicted rates**
- ▶ ... which is a bit of a detour from Cox-type models.

Summary & Conclusions

- ▶ The world is continuous

Summary & Conclusions

- ▶ The world is continuous
- ▶ Effects of time likely to be continuously, smoothly varying

Summary & Conclusions

- ▶ The world is continuous
- ▶ Effects of time likely to be continuously, smoothly varying
- ▶ A single time scale is rarely sufficient

Summary & Conclusions

- ▶ The world is continuous
- ▶ Effects of time likely to be continuously, smoothly varying
- ▶ A single time scale is rarely sufficient
- ▶ Different timescales require joint reporting

Summary & Conclusions

- ▶ The world is continuous
- ▶ Effects of time likely to be continuously, smoothly varying
- ▶ A single time scale is rarely sufficient
- ▶ Different timescales require joint reporting
- ▶ Continuous time formulae easiest to handle and statistical models should reflect this:

Summary & Conclusions

- ▶ The world is continuous
- ▶ Effects of time likely to be continuously, smoothly varying
- ▶ A single time scale is rarely sufficient
- ▶ Different timescales require joint reporting
- ▶ Continuous time formulae easiest to handle and statistical models should reflect this:
 - ▶ Parametric form of time-effects allow direct implementation of probability theory

Summary & Conclusions

- ▶ The world is continuous
- ▶ Effects of time likely to be continuously, smoothly varying
- ▶ A single time scale is rarely sufficient
- ▶ Different timescales require joint reporting
- ▶ Continuous time formulae easiest to handle and statistical models should reflect this:
 - ▶ Parametric form of time-effects allow direct implementation of probability theory
 - ▶ Corrolary: Choice of time scales **s** is an **empirical** problem

Summary & Conclusions

- ▶ The world is continuous
- ▶ Effects of time likely to be continuously, smoothly varying
- ▶ A single time scale is rarely sufficient
- ▶ Different timescales require joint reporting
- ▶ Continuous time formulae easiest to handle and statistical models should reflect this:
 - ▶ Parametric form of time-effects allow direct implementation of probability theory
 - ▶ Corrolary: Choice of time scales **s** is an **empirical** problem
- ▶ Non/Semi-parametric survival model not well suited for this

Summary & Conclusions

- ▶ The world is continuous
- ▶ Effects of time likely to be continuously, smoothly varying
- ▶ A single time scale is rarely sufficient
- ▶ Different timescales require joint reporting
- ▶ Continuous time formulae easiest to handle and statistical models should reflect this:
 - ▶ Parametric form of time-effects allow direct implementation of probability theory
 - ▶ Corrolary: Choice of time scales **s** is an **empirical** problem
- ▶ Non/Semi-parametric survival model not well suited for this
- ▶ Stick to this world:

Summary & Conclusions

- ▶ The world is continuous
- ▶ Effects of time likely to be continuously, smoothly varying
- ▶ A single time scale is rarely sufficient
- ▶ Different timescales require joint reporting
- ▶ Continuous time formulae easiest to handle and statistical models should reflect this:
 - ▶ Parametric form of time-effects allow direct implementation of probability theory
 - ▶ Corrolary: Choice of time scales **s** is an **empirical** problem
- ▶ Non/Semi-parametric survival model not well suited for this
- ▶ Stick to this world:

Summary & Conclusions

- ▶ The world is continuous
- ▶ Effects of time likely to be continuously, smoothly varying
- ▶ A single time scale is rarely sufficient
- ▶ Different timescales require joint reporting
- ▶ Continuous time formulae easiest to handle and statistical models should reflect this:
 - ▶ Parametric form of time-effects allow direct implementation of probability theory
 - ▶ Corrolary: Choice of time scales **s** is an **empirical** problem
- ▶ Non/Semi-parametric survival model not well suited for this
- ▶ Stick to this world: Fewer tables — more graphs!

Summary & Conclusions

- ▶ The world is continuous
- ▶ Effects of time likely to be continuously, smoothly varying
- ▶ A single time scale is rarely sufficient
- ▶ Different timescales require joint reporting
- ▶ Continuous time formulae easiest to handle and statistical models should reflect this:
 - ▶ Parametric form of time-effects allow direct implementation of probability theory
 - ▶ Corrolary: Choice of time scales **s** is an **empirical** problem
- ▶ Non/Semi-parametric survival model not well suited for this
- ▶ Stick to this world: Fewer tables — more graphs!

Thanks for your attention

References