A Multistate Model Incorporating a Relative Survival Framework and Mixed Time Scales

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Present at Symposium for statisticians @ Cancer Registry of Norway, 11 September 2024

About me

- Born and raised in Taipei, Taiwan
- Came to Sweden for my exchange studies at Lund University in 2018
- 2018-2020: MSc in Epidemiology at KI
- 2021-current: PhD student in Biostatistics at KI
- PhD project title: Extrapolating Survival with Applications to Health Technology Assessment
- Supervisors: Paul Dickman, Mark Clements, Magnus Björkholm, Shuang Hao, Torsten Dahlén

This presentation is based on the paper co-authored with Paul Dickman and Mark Clements, published in *PharmacoEconomics*.

PharmacoEconomics
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ORIGINAL RESEARCH ARTICLE

A Multistate Model Incorporating Relative Survival Extrapolation and Mixed Time Scales for Health Technology Assessment

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Research question

Title:
A Multistate Model Incorporating a Relative Survival Framework and Mixed Time Scales

Key question to answer

How can we incorporate relative survival extrapolation[1] into multistate models to improve long-term predictions?

- We introduce a multistate model that integrates long-term projections of general population mortality rates.
- To implement this, we need to address survival predictions from mix timescales in a competing risks setting.

Andersson et al, Stat in Med, 2013.

Multistate models

- Mutually exclusive disease/health states
- A set of transition-specific survival models[2]
- Each state is associated with costs and length of stay

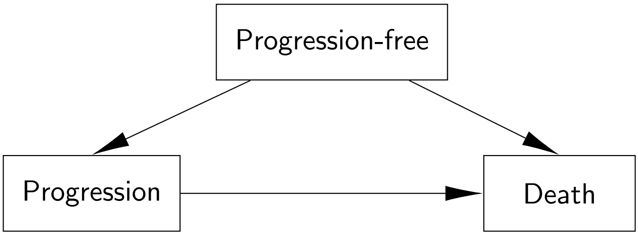


Figure: An illness-death model.

Crowther and Lambert, Stat in Med, 2017. Briggs and Sculpher, PharmEcon, 1998.

Relative survival framework

- Relative survival ratio

$$R(t) = \frac{S(t)}{S^*(t)},$$

where $S(t)$ is all-cause survival, and $S^*(t)$ is expected survival.

Relative survival framework

- Relative survival ratio

$$R(t) = \frac{S(t)}{S^*(t)},$$

where $S(t)$ is all-cause survival, and $S^*(t)$ is expected survival.

- The analogue on a hazard scale is

$$\lambda(t) = h(t) - h^*(t),$$

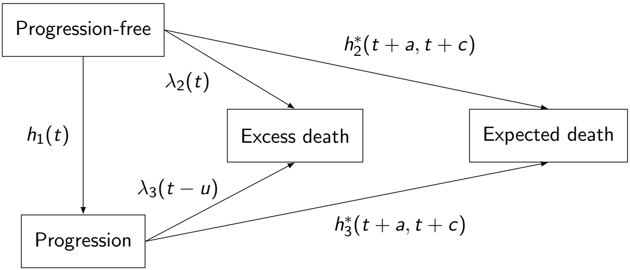
$\lambda(t)$: excess hazard; $h(t)$: all-cause hazard from the patient survival data; $h^*(t)$: expected hazard from the general population mortality rates.

$$h(t) = h^*(t) + \lambda(t)$$

$$S(t) = S^*(t)^* R(t),$$

where $S(t)$: all-cause survival; $S^*(t)$: expected survival; $R(t)$: relative survival.

Multistate model incorporating relative survival framework



Time scales:

t: Time since study entry

a: Age at study entry

c: Calendar year at study entry

u: Time at progression

Figure: An illness-death model incorporating a relative survival framework and mixed time scales.

Motivating example: CLL-8 trial

- A clinical trial of chronic lymphocytic leukemia treatments (CLL-8 trial[3]) compared the new treatment (RFC) vs. the traditional treatment (FC). The median age at study entry was 61 years.

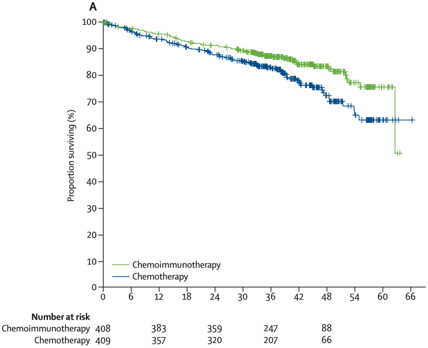
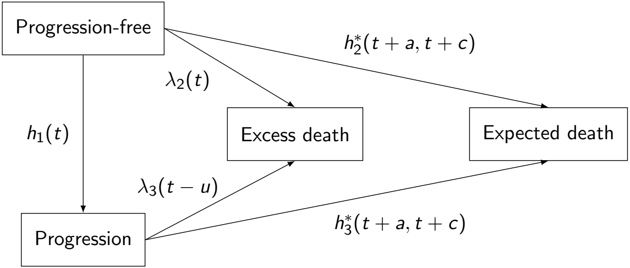


Figure: Figure retrieved from the CLL-8 trial by Hallek et al.[3]
Chemoimmunotherapy: RFC; chemotherapy: FC.

Motivating example: CLL-8 trial

1. Prepare a population mortality file
2. Fit flexible parametric (relative survival[4]) models[5] for the transitions $h(t)$ or $\lambda(t)$, with treatment as a covariate and df=2, dftvc=2.
3. Simulate 1 million individuals from the fitted survival models (`microsimulation` package)



Time scales:

t: Time since study entry

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Figure: An illness-death model incorporating a relative survival framework and mixed time scales.

Motivating example: CLL-8 trial: Hazard functions

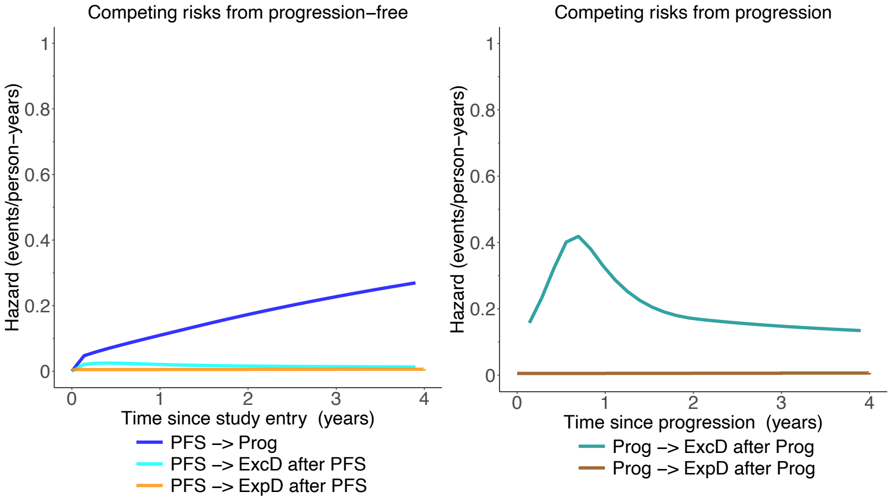
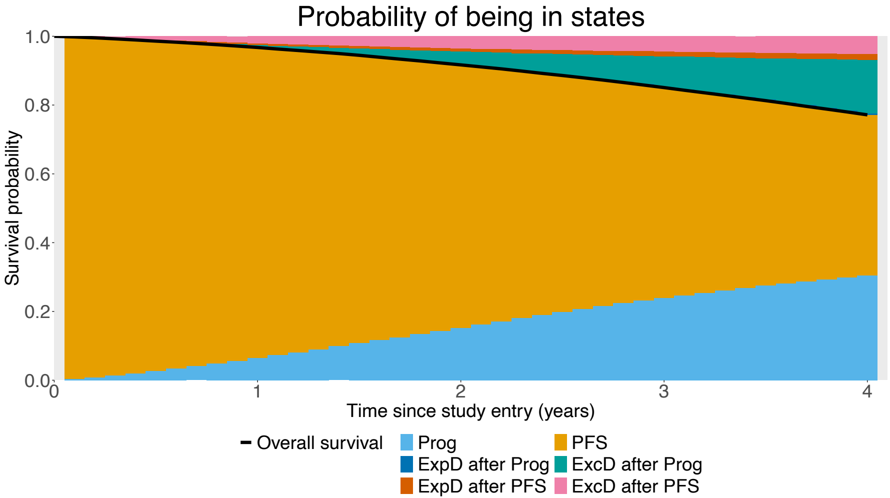


Figure: Prog: progression; PFS: progression-free survival; ExpD: expected death; ExcD: excess death. *We only show the RFC arm here.

Motivating example: CLL-8 trial: Probabilities of being at states



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Survival extrapolation

Drummond et al., *BMC Health Services Research*, 2023[6]

..the length of the available clinical studies may be short at the time that the health technology assessment is conducted, and hence **extrapolation** to long term endpoints will be required...

Survival extrapolation within an all-cause survival framework

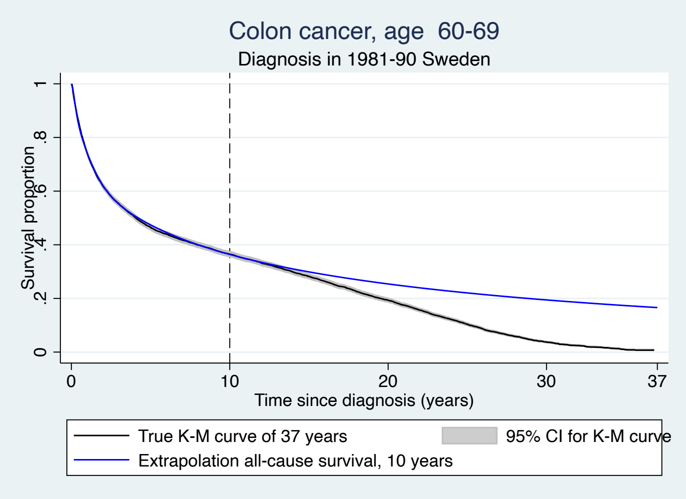


Figure: Example of poor survival extrapolation.

Survival extrapolation within a relative survival framework

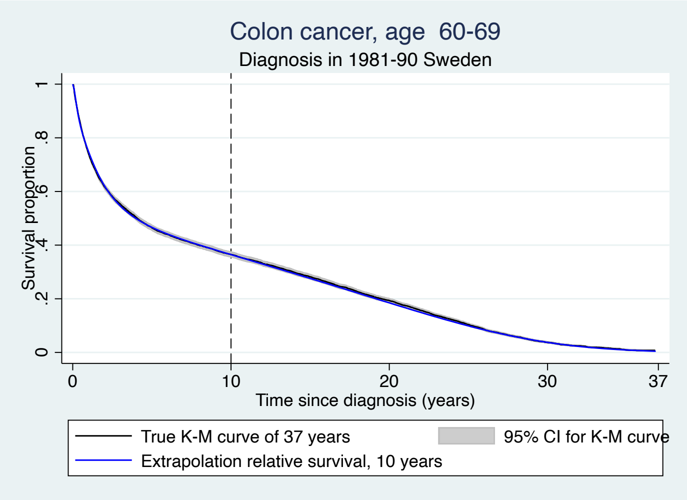


Figure: Ideal survival extrapolation can be achieved by relative survival extrapolation[1](Andersson, Stat in Med, 2013).

Survival extrapolation within a relative survival framework

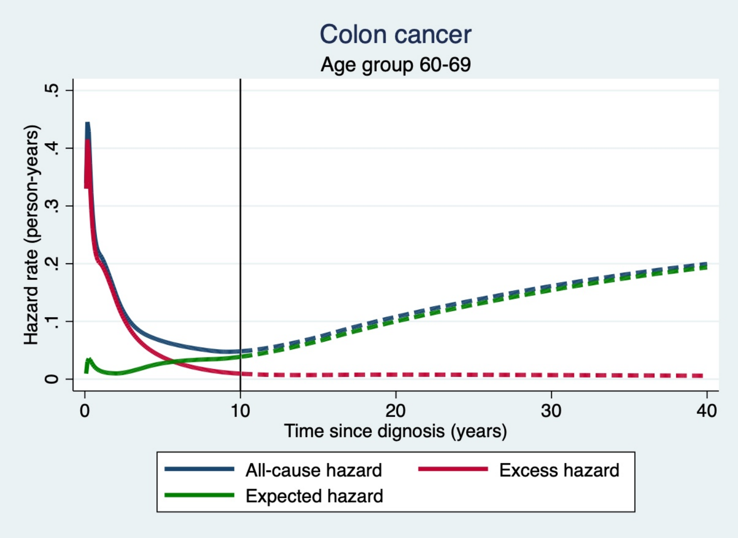


Figure: Illustrating hazard functions for survival extrapolation using a relative survival framework.

Survival extrapolation for CLL-8 trial

- Williams et al.[7] applied a (semi-Markov) multistate model to extrapolate survival of 4 years to 15 years for the CLL-8 trial[3].
- The transitions were modelled with the standard parametric models within an all cause survival framework ($h_1(t)$ and $h_3(t)$ with Gompertz, and $h_2(t)$ with generalized-gamma distributions).

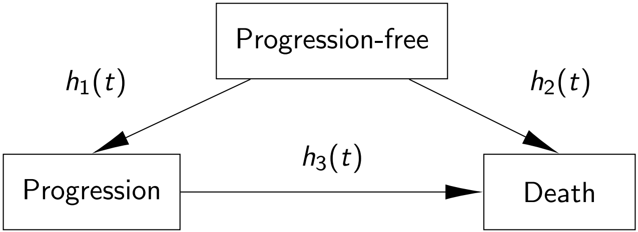


Figure: An illness-death model.

Williams, Med Dis Mak, 2017.

Survival extrapolation for CLL-8 trial

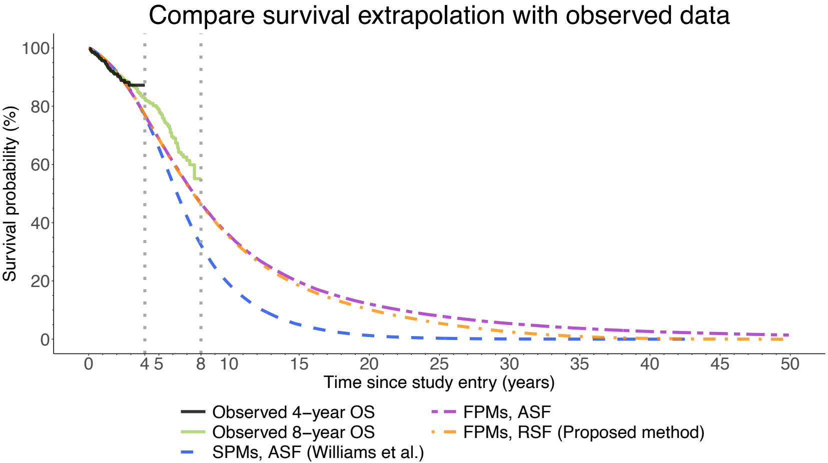
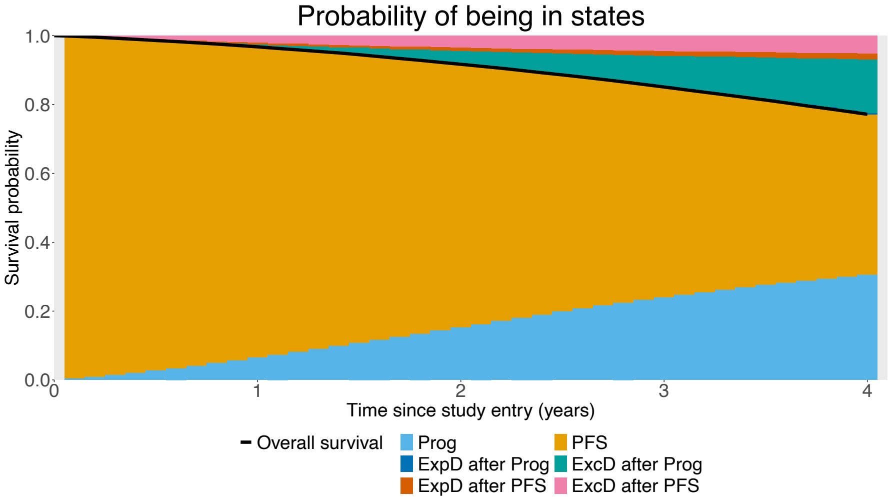


Figure: Compare survival extrapolation for the RFC arm with the observed OS. SPMs, standard parametric models; FPMs, flexible parametric models; ASF, all-cause survival framework; RSF, relative survival framework. *We only show the RFC arm here.

Survival extrapolation for CLL-8 trial



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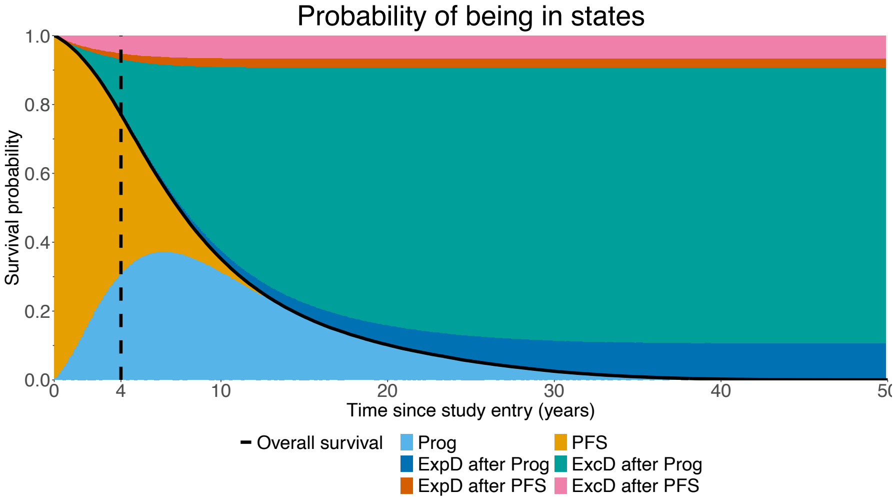


Figure: Prog: progression; PFS: progression-free survival; ExpD: expected death; ExcD: excess death.*We only show the RFC arm here.

Discussion: Summary

1. We introduce a multistate model incorporating a relative survival framework and mixed time scales. (Implemented in the `microsimulation` and `rstpm2` packages on CRAN.)
2. This model serves as a parametric approach to integrate relative survival in multistate models[8].
3. It allows relative survival extrapolation to be carried out in a multistate setting.

Manevski, Stat Methods in Med Res, 2022.

Discussion: Is the extrapolation reasonable?

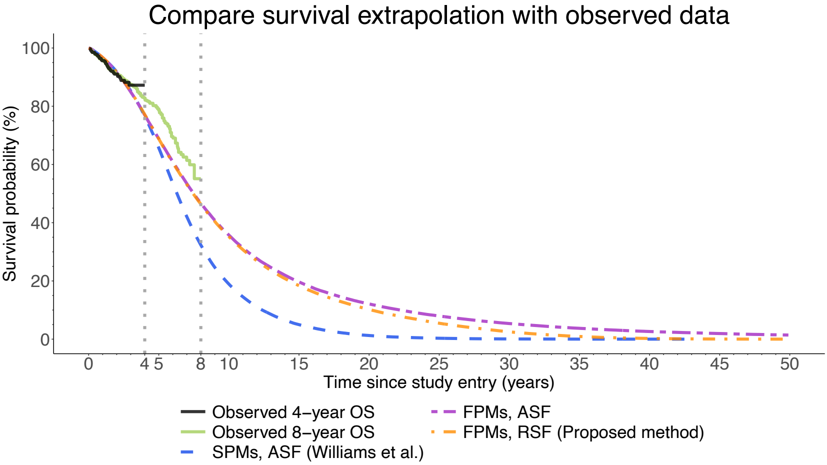
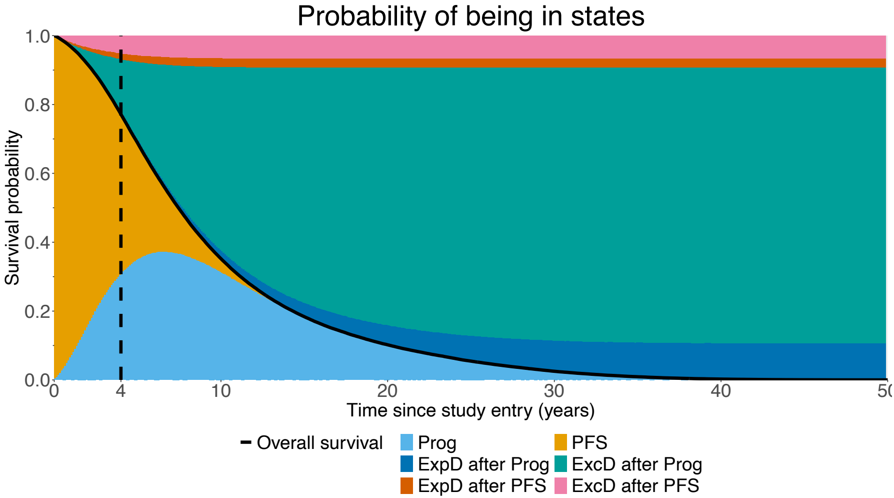


Figure: Compare survival extrapolation for the RFC arm with the observed OS. SPMs, standard parametric models; FPMs, flexible parametric models; ASF, all-cause survival framework; RSF, relative survival framework. *We only show the RFC arm here.

Discussion: Extrapolate transition to progression



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Discussion: Extrapolate transition to progression

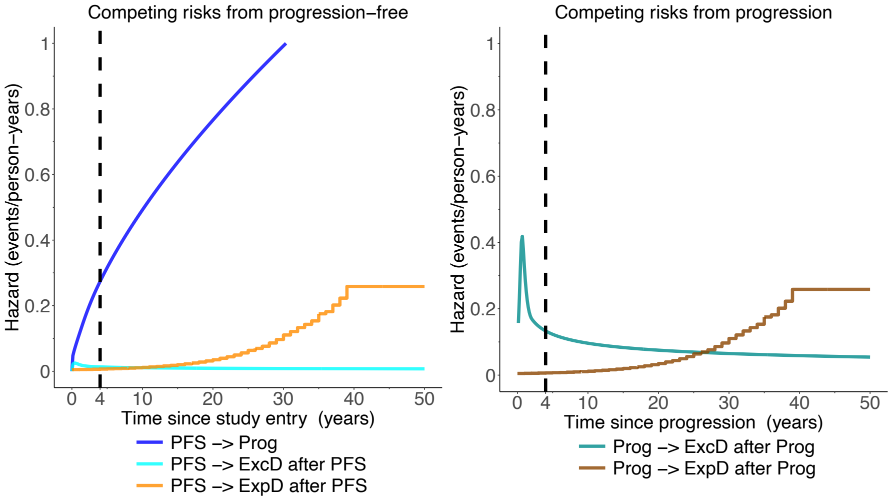

Figure: Prog: progression; PFS: progression-free survival; ExpD: expected death; ExcD: excess death. *We only show the RFC arm here.

Discussion: Extrapolate transition to progression

Question

Any suitable approach to extrapolate progression rate in an illness-death model?

1. In an oncological RCT, the intermediate state is typically defined as disease progression to a more advanced stage, such as metastasis, relapse, etc.
2. Impose constraint on parameters during model fitting, e.g., change knot position in a spline model. Domain experts' opinions matter.
3. Select other parametric distributions which are clinically plausible.
4. Use long-term data, for example, cancer register data, to aid survival extrapolation for short-term data like RCTs.

Conclusions

PharmacoEconomics
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The slides can be found @
`https://enochytchen.com/talks/2024-microsim/2024-microsim.pdf`
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9. Verdecchia A, Capocaccia R, Egidi V, Golini A. A method for the estimation of chronic disease morbidity and trends from mortality data. *Statistics in Medicine* 1989;**8**:201–216.

Extrapolate transition to progression

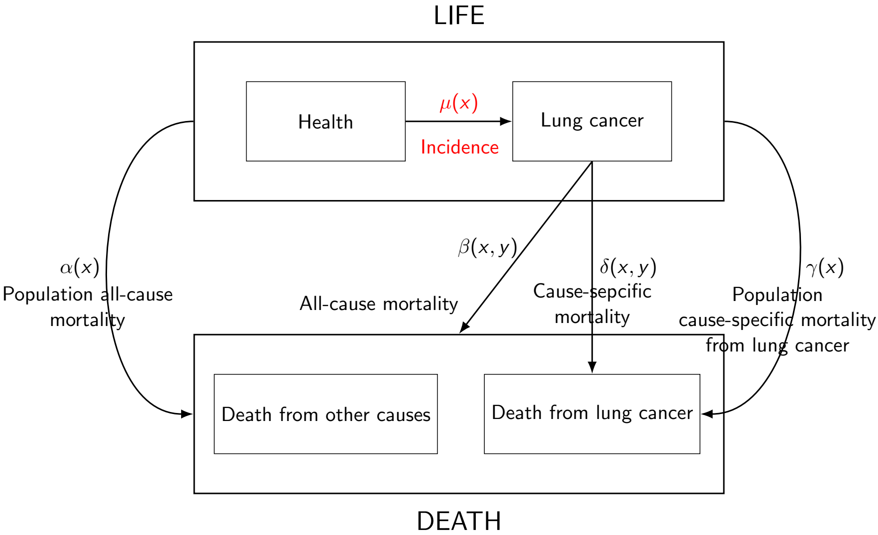

Figure: Adapted from Verdecchia, Stat in Med, 1989[9]. Estimating incidence of lung cancer with other known parameters: $\alpha(x)$, $\beta(x, y)$, $\delta(x, y)$, $\gamma(x)$.

Extrapolate transition to progression

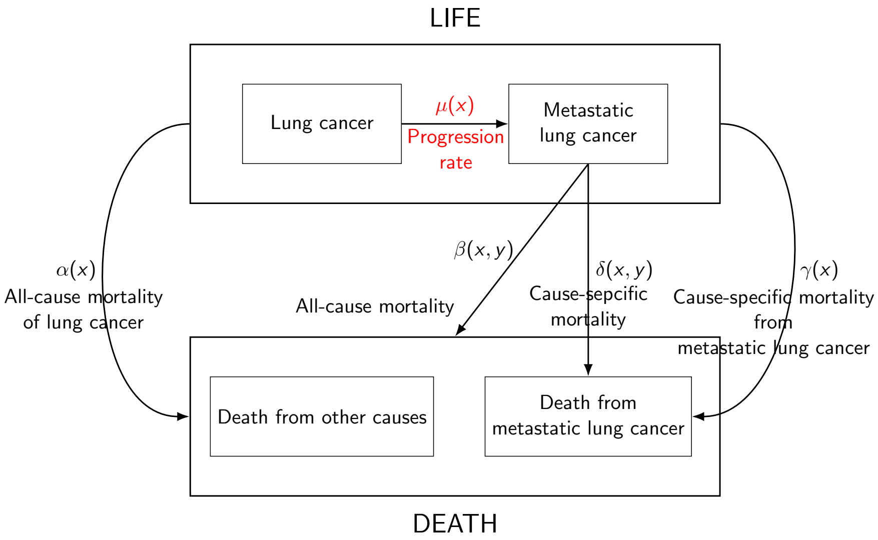

Figure: Estimating progression rate of lung cancer with other known parameters: $\alpha(x)$, $\beta(x, y)$, $\delta(x, y)$, $\gamma(x)$.