Diffusion piecewise exponential models for survival extrapolation

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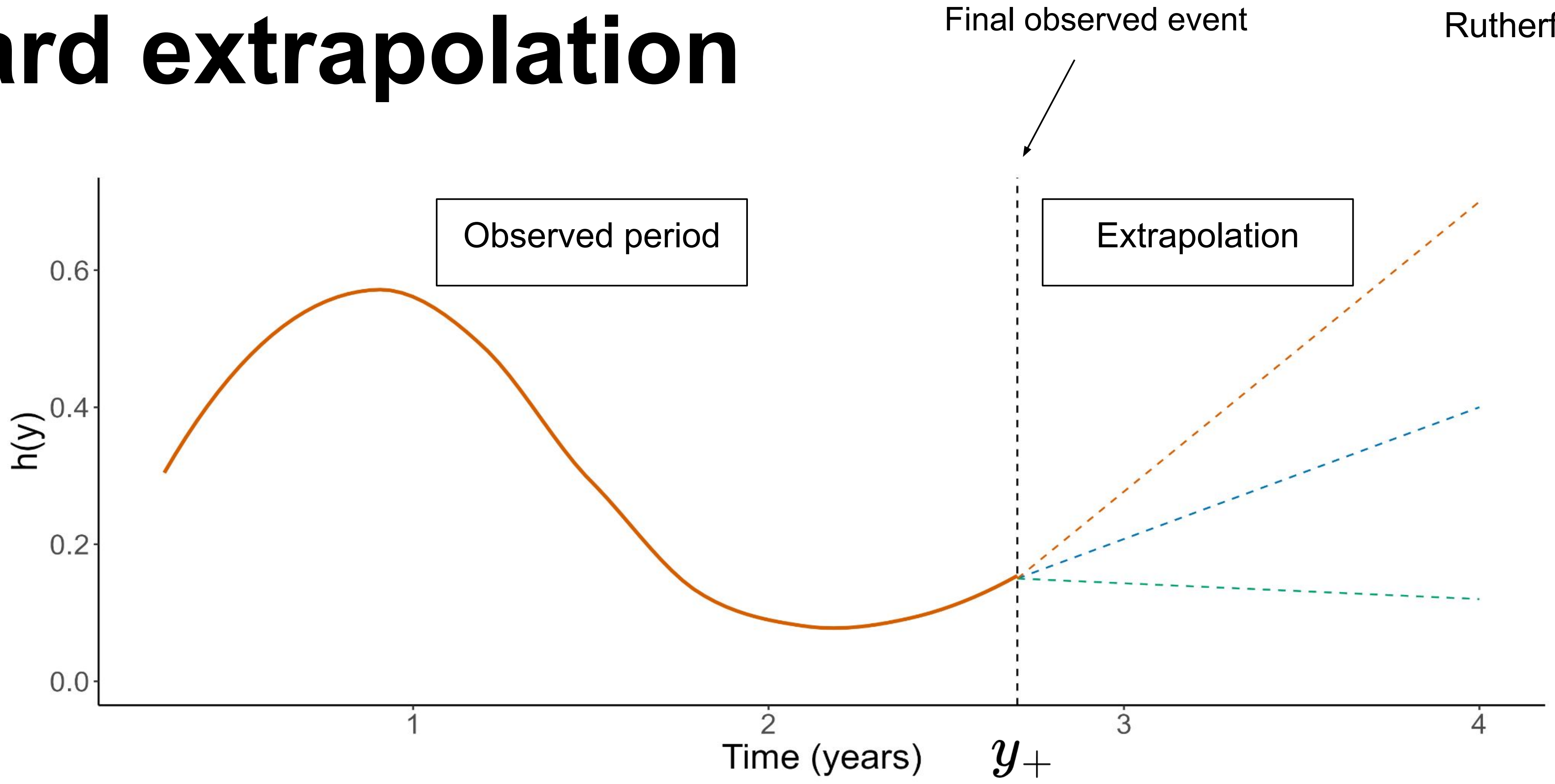
Extrapolating hazards

Hazard extrapolation

Jackson et al. (2017)
Rutherford et al. (2020)



Hazard extrapolation

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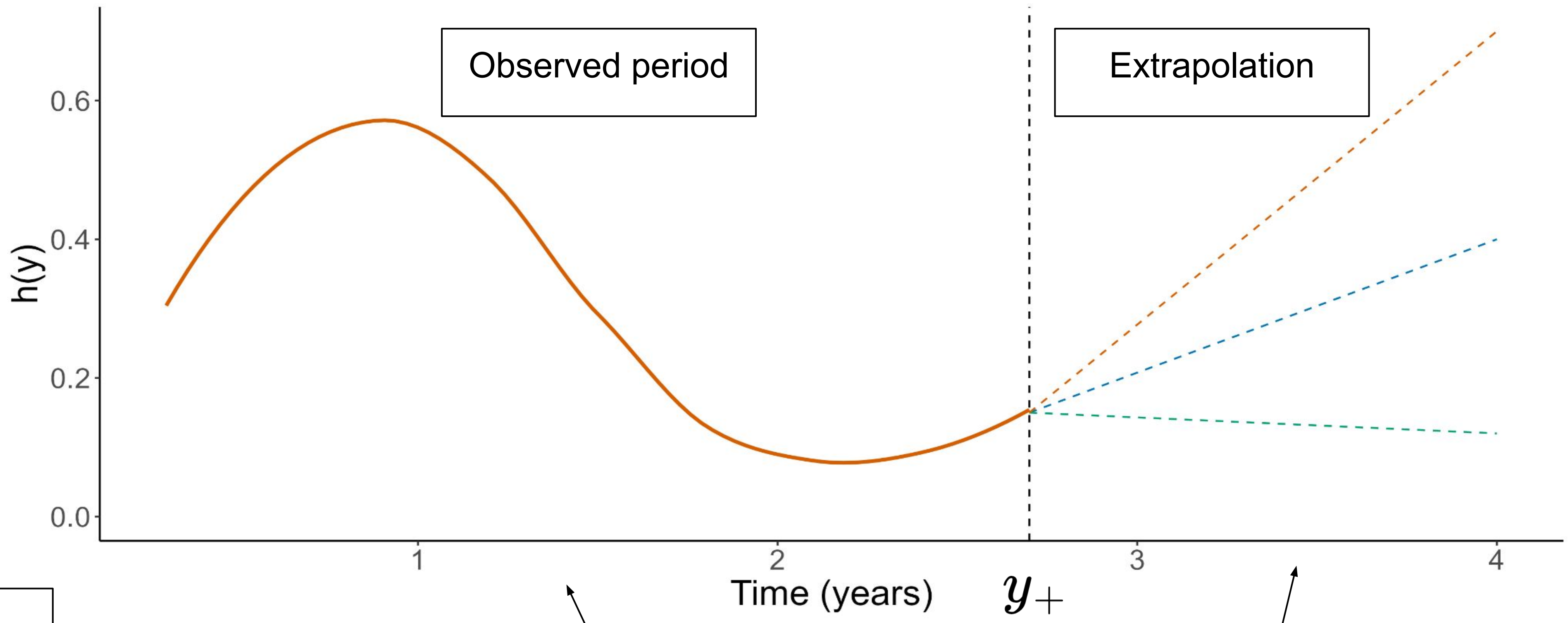
Final observed event



Expected survival - Benefit in economic model

$$\mathbb{E}\left[Y\right] = \int_0^{y_+} \exp\left(-\int_0^y h\left(u\right)du\right)dy + \int_{y_+}^{\infty} \exp\left(-\int_0^y h\left(u\right)du\right)dy$$

Rutherford et al. (2020)

Criteria for principled extrapolation

(See also *Jackson, 2023*)

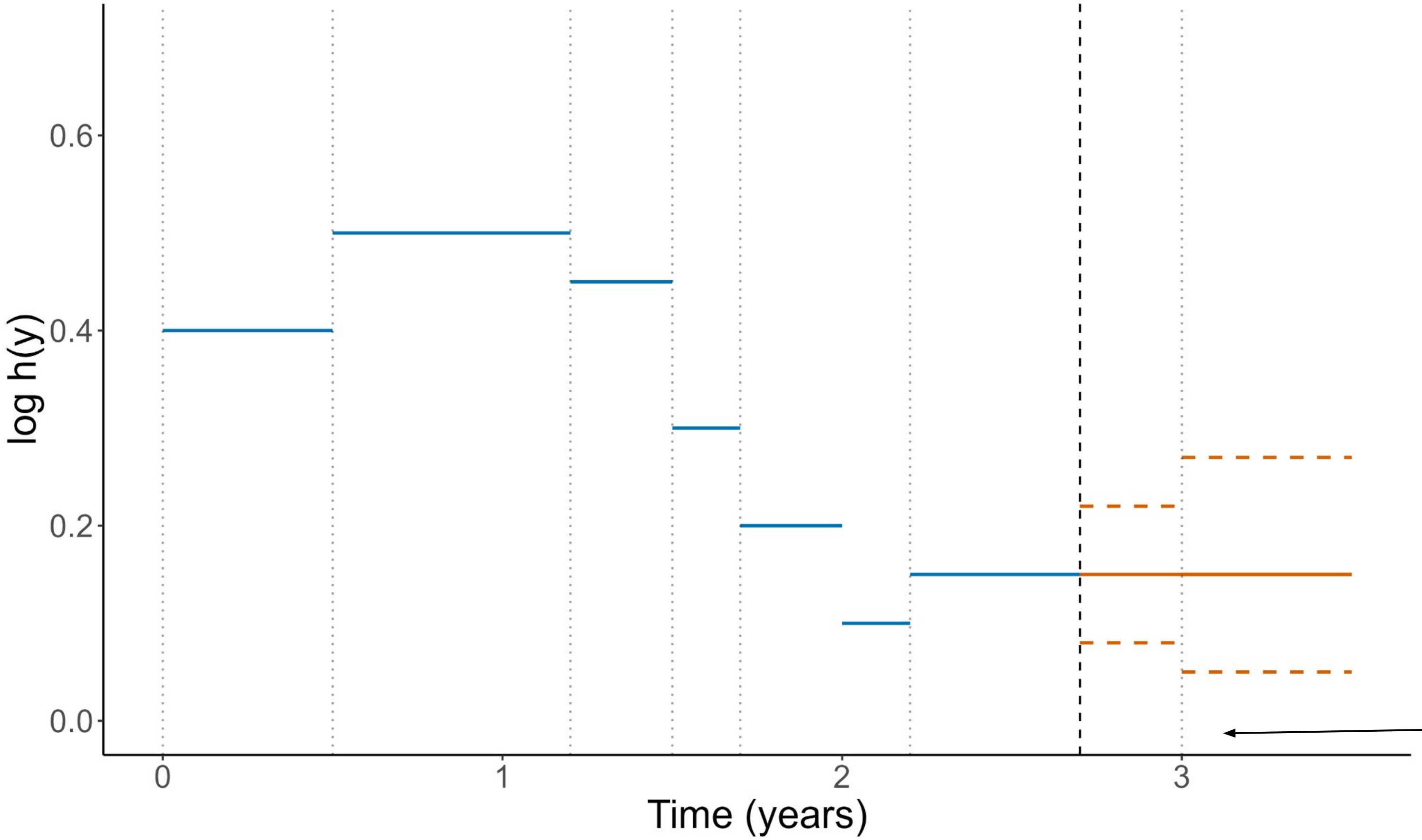
Observation period

- Flexible models - inferences driven by the data
  Recent examples: Dynamics survival models (Kearns et al., (2019)); M-splines (Jackson, 2023); Piecewise Exponential models (Cooney et al., 2023); Polyhazard models (Demiris et al., 2015, Hardcastle et al., 2024).
- Weakly informative prior information

Extrapolation period

- Inherently driven by prior assumptions
- **Note:** This is unavoidable!
- Assumptions should be explicit
- Minimal constraints on the form these assumptions can take

Piecewise exponential models



Local log-hazard

Knots

$$\log h(y) = \sum_{j=1}^{J} \alpha_j \mathbb{1}\left(y \in [s_{j-1}, s_j)\right)$$

Prior dependency for extrapolation, e.g

$$\alpha_j \sim \mathrm{Normal}\left(\alpha_{j-1}, \sigma^2\right)$$

Extrapolations very sensitive to choice of knot location

Diffusion piecewise exponential models

Diffusion piecewise exponential models

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Assume *a priori* that the knots arise from a Poisson Point process:

$$\{s_j\}_{j=1}^{J} \sim PP\left(\gamma, (0, y_+)\right)$$

Idea: Learn volatility of hazard function in extrapolation period from the observation period

Diffusion piecewise exponential models

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Idea: Learn volatility of hazard function in extrapolation period from the observation period

Assume *a priori* that local log-hazards $\left\{\alpha_j\right\}_{j=1}^{J}$ are discretisations of a diffusion:

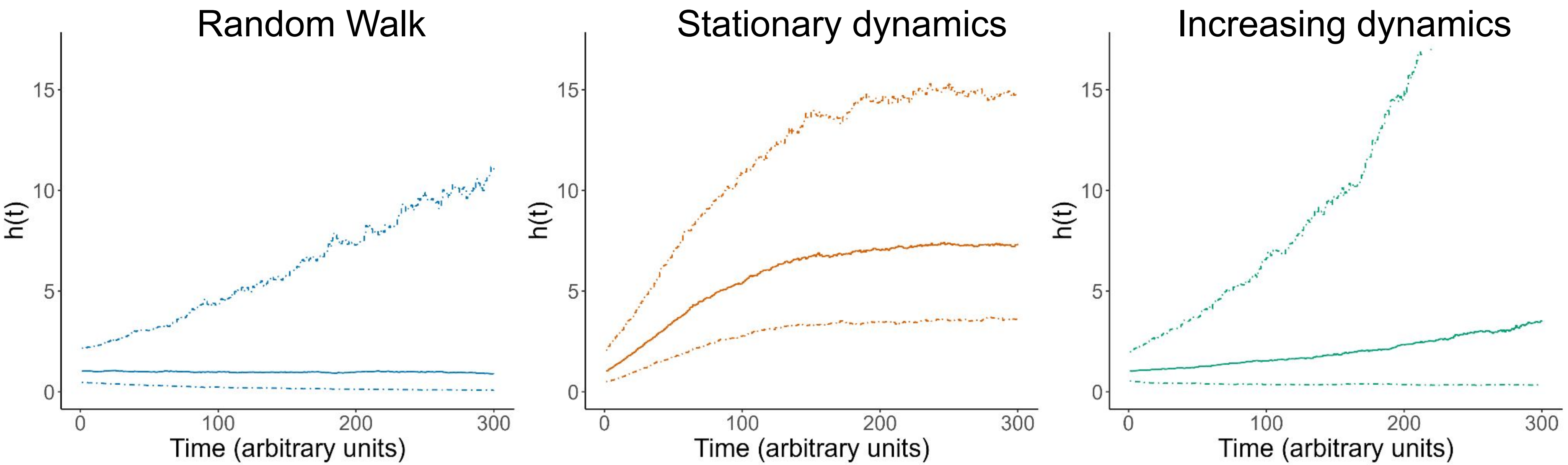
$$d\alpha_{\hat{y}} = \mu\left(\alpha_{\hat{y}}\right) d\hat{y} + \sigma\left(\alpha_{\hat{y}}\right) dW_{\hat{y}}$$

Drift coefficient

Roberts & Sangalli (2010)

Diffusion-based priors

Prior simulations



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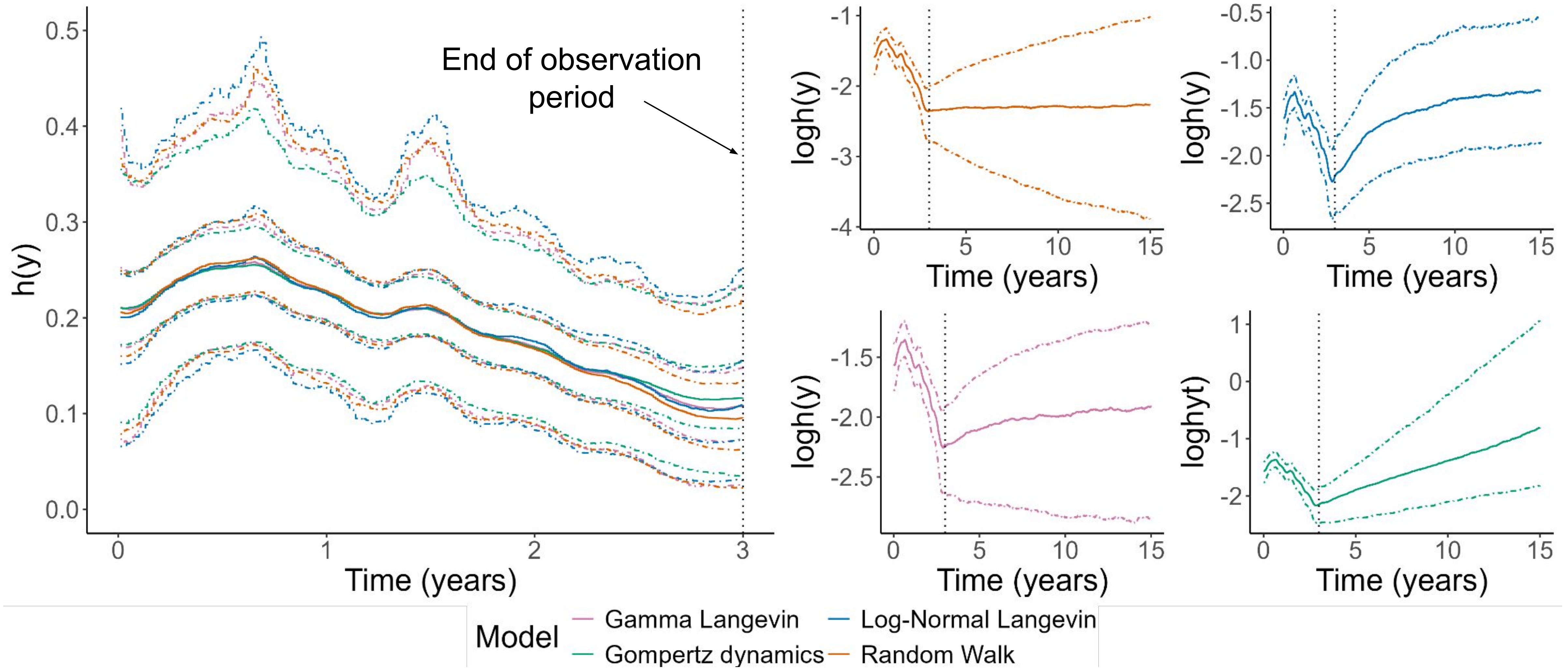
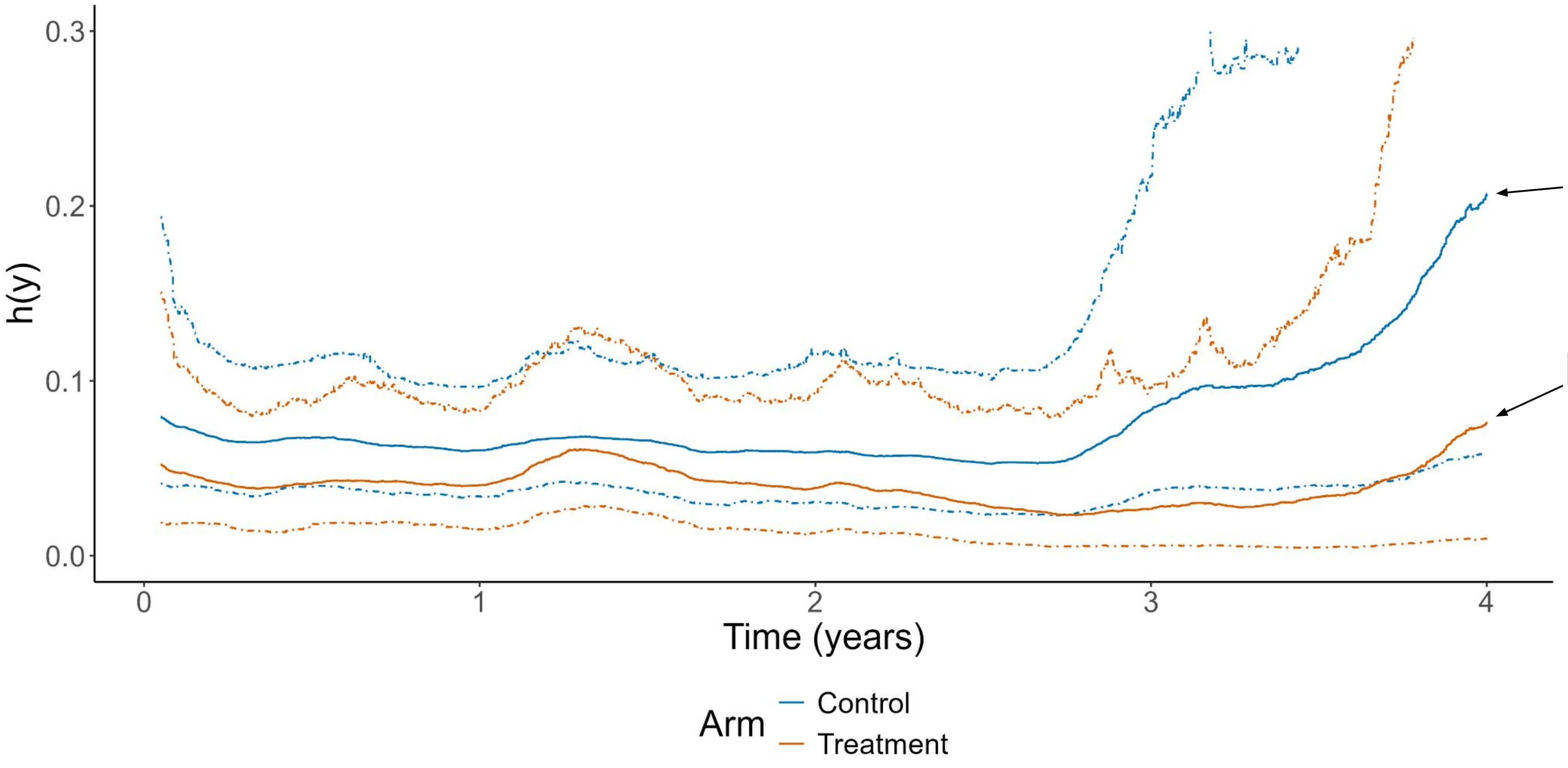
$$d\alpha_{\hat{y}} = \mu\left(\alpha_{\hat{y}}\right)d\hat{y} + \sigma\left(\alpha_{\hat{y}}\right)dW_{\hat{y}}$$

Drift coefficient - contains prior information about long-term hazard

Colon cancer data



Covariates - non-proportional hazards



Flexible baseline hazard

Non-proportional treatment effect

$$d\beta_y = \mu(\beta_y)dy + dW_y$$

Implementation

Fearnhead et al. (2018)

Implementation

- Current state-of-the-art for posterior inference in R is RStan.
- However, Stan cannot handle the prior on the number and location of knots:

$$\{s_j\}_{j=1}^{J} \sim PP\left(\gamma, (0, y_+)\right)$$

- Instead use MCMC scheme based on Piecewise Deterministic Markov Processes
- Computationally efficient with minimal user tuning
- Very new methodology - requires bespoke implementation

Fearnhead et al., (2018)
Bezanson et al., (2017)

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Julia implementation available via
DiffusionPiecewiseExponential.jl
package

R

- Mature statistical modelling ecosystem - especially for biostatistics
- Fantastic HTA packages

- Slow - very hard/impossible to write high-performance code natively in R
- Speed relies on C++

julia

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Analyse in R

Compute in Julia

Julia implementation

```
# Simulate data
Random.seed!(2352)
n = 100
y = rand(Exponential(1.0), n)
breaks = vcat(0.01,collect(0.26:0.25:1.01))
p = 1
cens = (y .< 1.0)
y[findall(y .> 1.0)] .= 1.0
covar = fill(1.0, 1, n)
dat = init_data(y, cens, covar, breaks)
```

Simulate and format data

```
# Initialise sampler
x0, v0, s0 = init_params(p, dat)
v0 = v0./norm(v0)
t0 = 0.0
state0 = ECMC2(x0, v0, s0, collect(.!s0), breaks, t0, length(breaks), true, findall(s0))
nits = 10_000
nsmp = 10
settings = Splitting(nits, nsmp, 1_000_000, 1.0, 5.0, 0.1, false, true, 0.01, 50.0)
```

MCMC settings

```
# Hazard times for diagnostics and burn in iterations
test_times = collect(0.2:0.2:1.0)
burn_in = 1_000
# Specify the prior
priors = BasicPrior(1.0, PC(1.0, 2, 0.5, Inf),
FixedW([0.5]), 1.0,
CtsPois(7.0, 1.0, 100.0, 1.1), # A Poisson process prior for the knots with intensity 7.0, and maximum knots = 100 on the interval (0.0,1.1)
[GaussLangevin(t -> log(0.29), t-> 0.4)], # A Gaussian stationary distribution for the log-hazard function with mean = log(0.29) and standard deviation = 0.4
[0.1], 2)
```

Specify priors

```
# Run the sampler for two chains
out1 = pem_fit(state0, dat, priors, settings, test_times, burn_in)
```

Run x2 MCMC chains

Julia implementation

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[0.1], 2)
```

Specify priors

CtsPois(7.0, …., 1.1)

- Poisson process prior with intensity 7 on the interval (0,1.1)

GaussLangevin(t -> log(0.29), t-> 0.4)

- A $\mathrm{Normal}(\log(0.29), 0.4)$ stationary distribution for the log-hazard

```julia
# Run the sampler for two chains
out1 = pem_fit(state0, dat, priors, settings, test_times, burn_in)
```

Run x2 MCMC chains

R implementation

```r
library(JuliaCall) # Package for calling Julia from R
julia_setup() # Package initialisation
julia_library("DiffusionPiecewiseExponential")
julia_library("Distributions")
julia_library("Random")
julia_library("LinearAlgebra")

set.seed(123)
n = 100
y = rexp(n, 1)
cens = as.numeric(y < 1)
for(i in 1:n){
  y[i] = ifelse(cens[i] == 1, y[i], 1)
}
julia_assign("n", as.integer(n))
julia_assign("y", y)
julia_assign("cens", cens)
julia_command("breaks = vcat(0.01,collect(0.26:0.25:1.01))")
julia_command("p = 1")
julia_command("covar = fill(1.0, 1, n)")

julia_source("Setup.jl")

julia_command("priors = BasicPrior(1.0, PC(1.0, 2, 0.5, Inf), FixedW([0.5]), 1.0,
CtsPois(7.0, 1.0, 30.0, 1.1),
[GaussLangevin(t -> log(0.29), t-> 0.4)],
[0.1], 2)")
julia_command("julia_output = pem_fit(state0, dat, priors, settings, test_times, burn_in)")
R_output = julia_eval("julia_output")
```

R implementation uses JuliaCall package to call Julia from R

Load julia packages

- Generate/format data in R
- Assign data in julia using “julia_assign”

- “julia_command” runs julia commands from R
- Return model output to R using julia_eval

References

Bezanson, J., Edelman, A., Karpinski, S., & Shah, V. B. (2017). Julia: A fresh approach to numerical computing. *SIAM review*, 59(1), 65-98.

Demiris, N., Lunn, D., and Sharples, L. D. (2015). Survival extrapolation using the poly-Weibull model. *Statistical Methods in Medical Research*, 24(2): 287–301.

Fearnhead, P., Bierkens, J., Pollock, M., & Roberts, G. O. (2018). Piecewise Deterministic Markov Processes for Continuous-Time Monte Carlo. *Statistical Science*, *33*(3), 386-412.

Hardcastle, L., Livingstone, S., Baio, G. Averaging polyhazard models using Piecewise deterministic Monte Carlo with applications to data with long-term survivors. 2024, arxiv:2406.14182

Jackson, C. H. (2023). survextrap: a package for flexible and transparent survival extrapolation. *BMC Medical Research Methodology*, 23(1): 282.

Jackson, C., Stevens, J., Ren, S., Latimer, N., Bojke, L., Manca, A., & Sharples, L. (2017). Extrapolating survival from randomized trials using external data: a review of methods. *Medical decision making*, *37*(4), 377-390.

Roberts, G. O., & Sangalli, L. M. (2010). Latent diffusion models for survival analysis. *Bernoulli*, *16*(2), 435-458.

Rutherford, M. J., Lambert, P. C., Sweeting, M. J., Pennington, R., Crowther, M. J., & Abrams, K. R. (2020). NICE DSU technical support document 21: flexible methods for survival analysis. *Decision Support Unit, ScHARR, University of Sheffield*.

Discussion

Summary

- Introduced the **Diffusion Piecewise Exponential model** for survival extrapolation
- Extrapolations are driven through an underlying diffusion and a prior on knot locations
- Provides flexible, data-driven inferences for the observation period
- Extrapolations driven by explicit prior assumptions
- Implementation in julia can be called via R: DiffusionPiecewiseExponential.jl

Additional Points

- Several possibilities for long-term drifts
- Currently improving elicitation procedures
- R package in the works - julia code completely hidden
- Preprint available now:

Diffusion piecewise exponential models for survival extrapolation using Piecewise Deterministic Monte Carlo.
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