Causal reasoning in survival analysis: Re-weighting and local independence graphs

Kjetil Røysland

UiO : University of Oslo

NORWEGIAN CANCER SOCIETY

From the media

DAGENS Medisin

Dagfinn Høybråtens utfordring bør gripes an med entusiasme

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Siste nytt | Helsepolitikk | Forskning | Kreft | Hjerte og kar | Legemidler | Folkehelse | Livsstil | Psykisk helse | Jobb og

Oppdatert 21.08.12 Nyheter

Har stoppet dialogen med HPV-aktør

Helsedirektoratet og Kreftregisteret har stoppet dialogen med firmaet bak en omstridt HPV-test. Nå går det mot rettssak.

0 Kommentarer » Skriv ut » Send »

Tagger: HPV-testing

Helsedirektoratet og Kreftregisteret har avslått anmodninger fra firmaet NorChip om henholdsvis et møte med helsedirektøren og utdyping av HPV-tall fra Kreftregisteret.

Relaterte artikler

21.05.12 Enda en HPV-test godkjent

Dagens Medisin 31.12.2011

Dagbladet 21.08.2012

GIR SKRAPE:: Harald Norvik har tidligere vært blant annet Statoil-sjef , SAS-styreformann og statssekretær for Arbeiderpartiet. Nå er han sterkt kritisk til Helsedepartementets behandling av firmaet NorChip, hvor han er styreleder. Foto: Bjørn Langsem/Dagbladet

Helseministeren får skrape fra tidligere Statoil-sjef

Harald Norvik slakter helseminister Anne-Grete Strøm-Erichsens saksbehandling.

HALLDOR HUSTADNES
hhu@dagbladet.no

lørdag 31. desember 2011, kl.10:48

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Norwegian secondary screening for cervical cancer

- Norwegian women between 25 and 69 years are advised to have a cytology test at least every third year,
- Women with an inconclusive test are subject to a secondary cytology and an HPV-test,
- The Cancer Registry concluded in 2012 that **PreTectProofer**, more often overlook cancer/pre-cancer than its competitors,
- This comparison could be unfair as PreTectProofer-tests were more frequently subject to subsequent cytology or HPV-tests.

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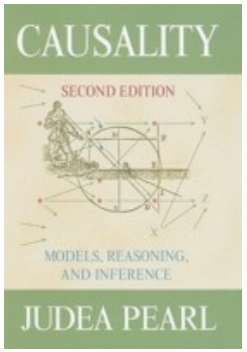
What if...

- What if PreTectProofer, *contrary to the fact*, had been subject to the same subsequent testing regime as the other tests?
- Would there still be a difference in later cancer detection after negative tests?
- How can we carry out such a comparison in a trustworthy way based the data we have?

Causal inference - seeing vs doing (Pearl)



- Naive statistics may give erroneous conclusions when not distinguishing statistical associations and causal effects,
- Randomized controlled trials are essential when assessing effects of new medical treatments, but are not always feasible,
- **Causal inference** combines statistics and mathematical modelling to squeeze out the available information on causal effects from observational data,

Basic idea: emulate randomized controlled trials.

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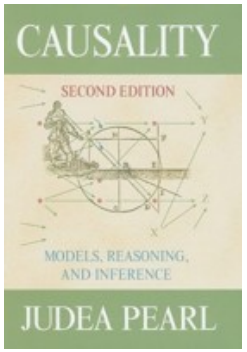

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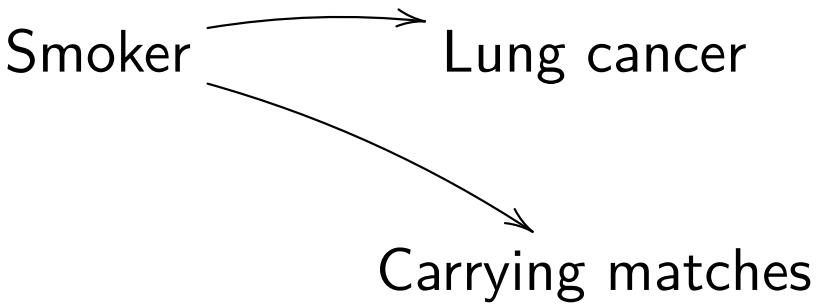
Causal diagrams: directed acyclic graphs



- Represents testable and untestable a priori understanding,
- Nodes represent variables, both measured and unmeasured,
- Each arrow can be interpreted as a direct causal effect,
- Includes common causes of any two variables in the graph.

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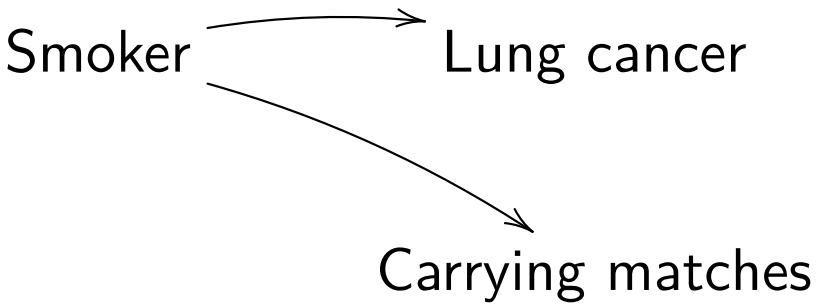

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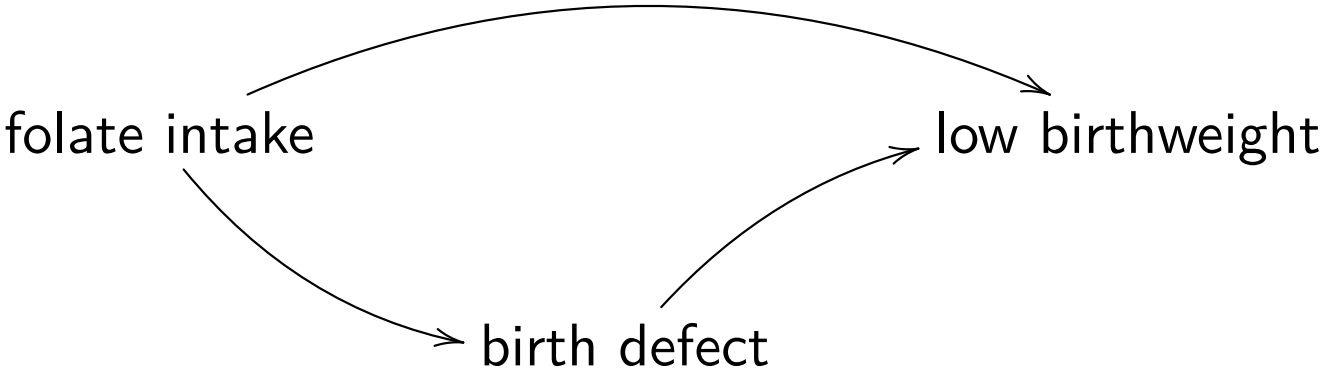
Example: adjustment for confounders (Hernan et al. 2002)



- Should one adjust for birth weight when estimating the effect of folate on birth defects?
- No, one should not adjust for a collider,
- Study on folic acid supplementation and neural tube defects:
  Adjusted OR 0.80 (0.62,1.21),
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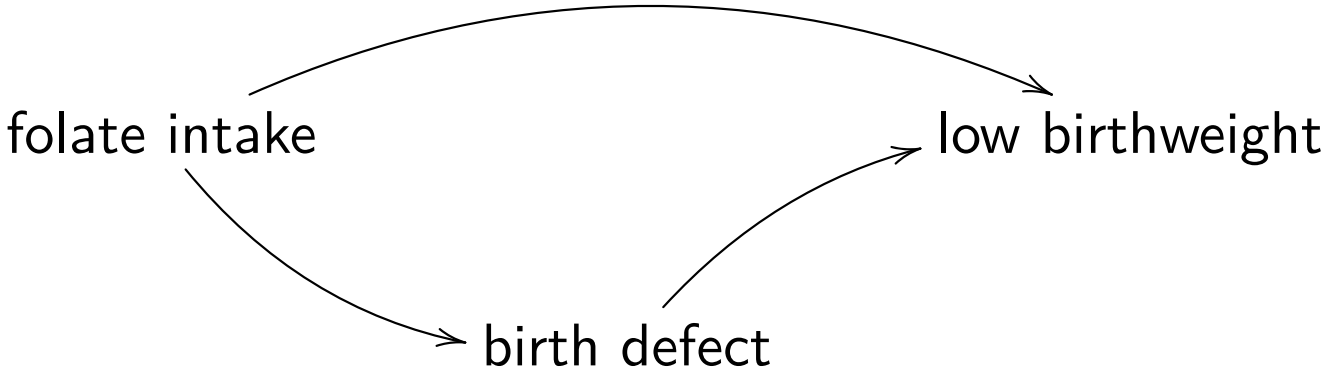

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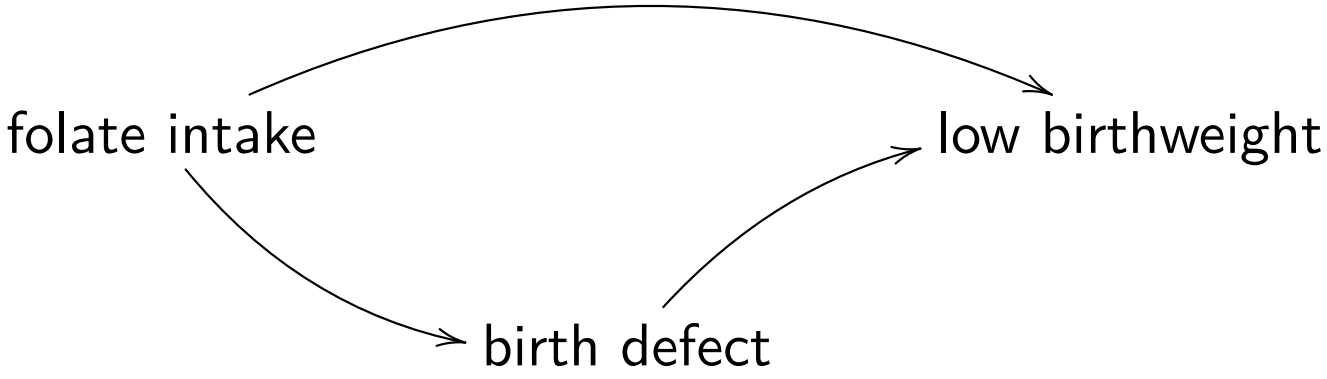

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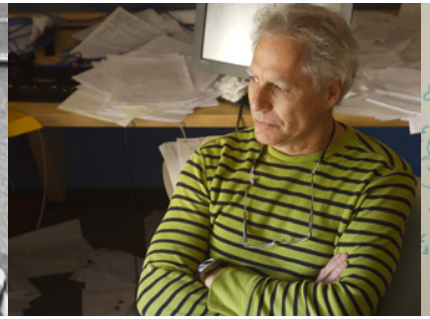
Causal diagrams

- Causal diagrams model spurious effects and causation in observational studies,
- Provides guidance for where to use various statistical methods to correct for selection effects and confounding,

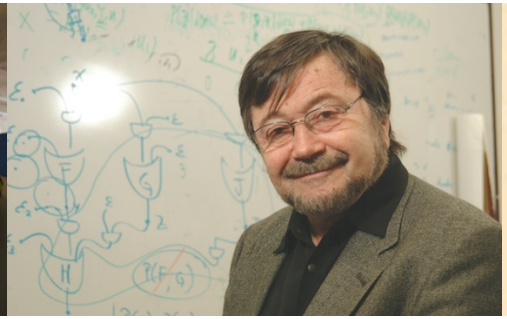
Indication of impact: Any recent issue of **Epidemiology** contains several articles that apply such techniques.

Key contributors:

Miguel Hernán
(Harvard)



James M. Robins
(Harvard)



Judea Pearl
(UCLA)

Trygve Haavelmo
(UIO)

However...

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- Mechanisms described in terms of **dynamical systems**,

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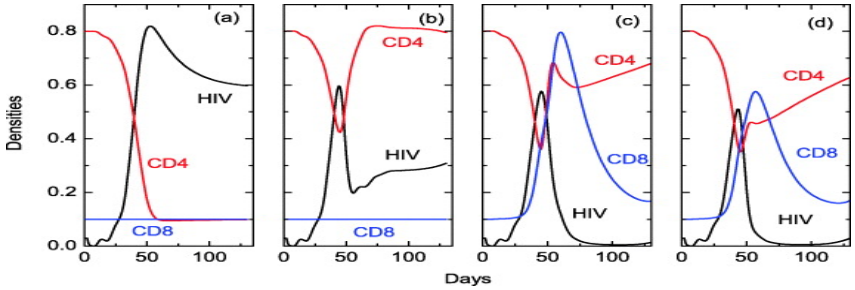

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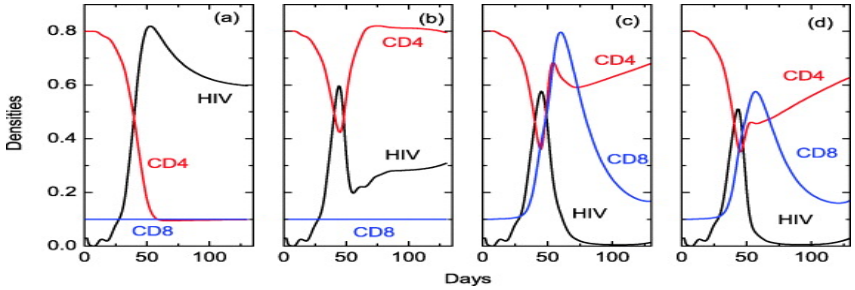

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Causal inference with processes

- Causal inference based on local independence and local characteristics,
- Diagrams where arrows represent direct effects at short term.

Promising results:

- Graphical reasoning that applies to survival data,
- Deeper understanding of time dependent confounding and marginal structural models,
- Deeper understanding of Kaplan-Meier estimates subject to censoring.

International collaboration: Vanessa Didelez at University of Bristol and Theis Lange at University of Copenhagen.

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Independent censoring

- Common assumption with the Kaplan-Meier estimator or Aalen's multiplicative intensity models in survival analysis,
- Seemingly identical individuals alive at t have the same risk of dying during $(t, t + \Delta]$, regardless of any previous censoring,
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Why do we want independent censoring?

- Weaker assumption than random censoring,
- Tempting to think that independent censoring would yield Kaplan-Meier curves as if censoring had been prevented,

However This is a claim about causation and can be treated using graphical techniques from causal inference.

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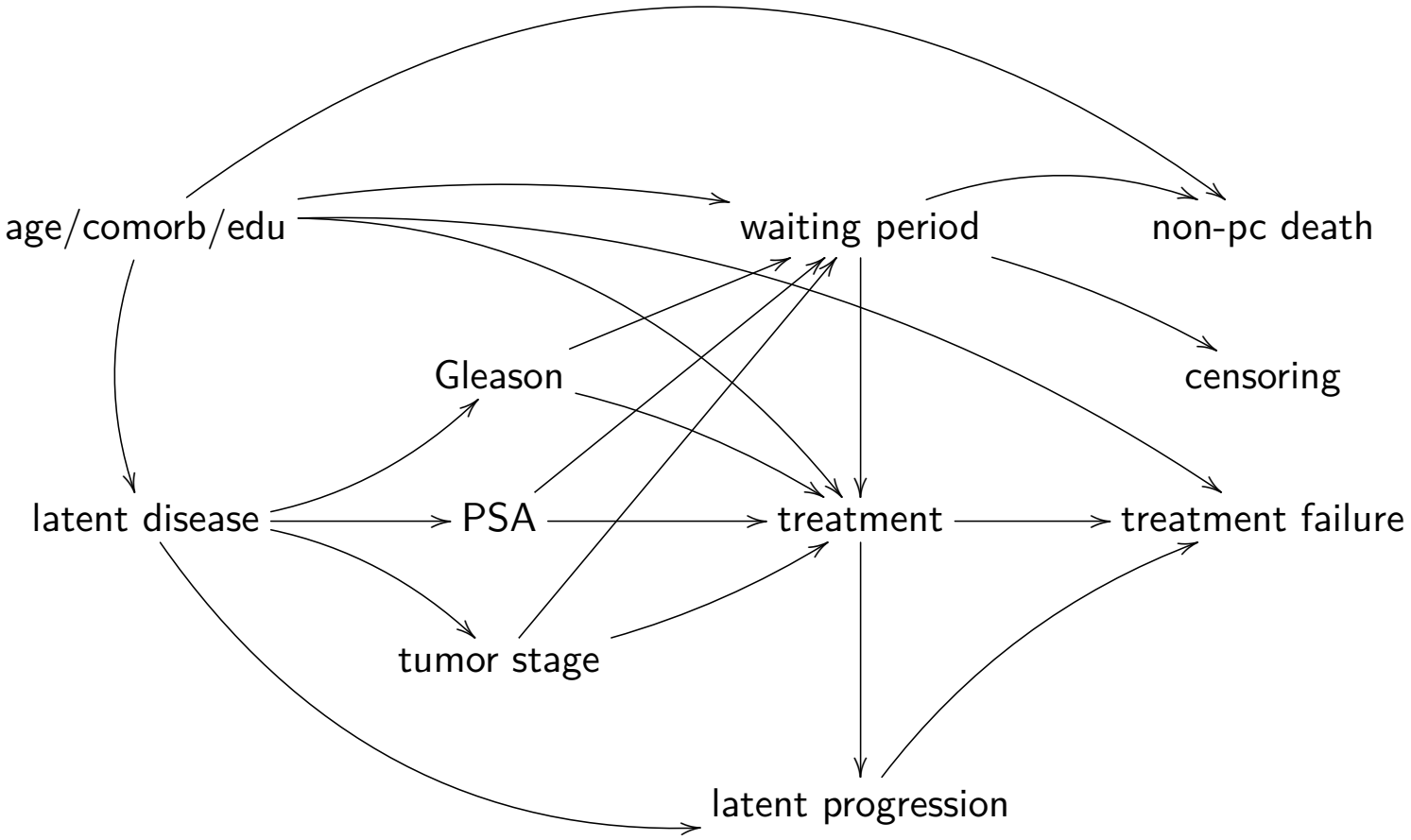
Characterizing joint densities: local independence graphs

Nodes represent baseline variables or counting processes such that:

- There is no arrow from a process to a baseline variable,
- The subgraph induced by the baseline variables defines a Bayesian network,
- Every counting process is locally independent of its non-parents, conditionally on the parent nodes.

Example: Prostate cancer - failure of curative treatment



Causal validity and censoring

- Hypothetical intervention that would change the hazard of censoring from α to 0,
- A model is *causally valid* for this intervention if the local characteristics for the remaining nodes remain unchanged,
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A counter-example to folklore perception

- U binary with $P(U = 1) = .8$
- C is time of censoring, with hazard,

$$U + 1$$

- T is time of event, with hazard,

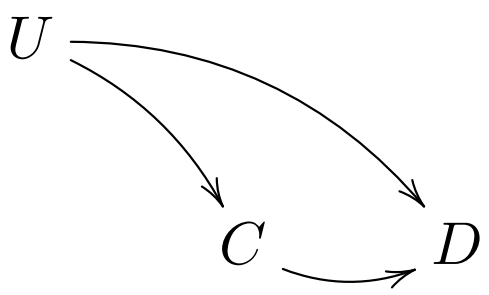
$$U + g(t, C) + 1,$$

where

$$g(t, c) := \frac{I(c \leq t)\left(4 - 8e^{-(c-t)}\right)}{(1 + 8e^{-(c+t)})(4 + e^{2t})}.$$

Example: local independence graphs

- Model is compatible with the local independence graph:



- Exact computation gives the (slightly surprising) local independence graph when U is omitted:

Note: Independent censoring when U is integrated out, but not independent censoring given U.

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- Suppose the larger model is causal with respect to C,
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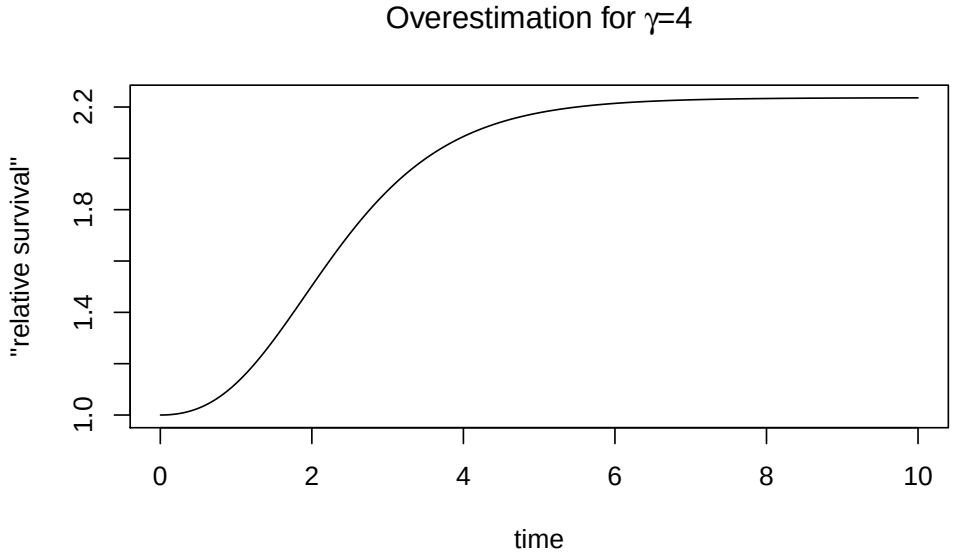

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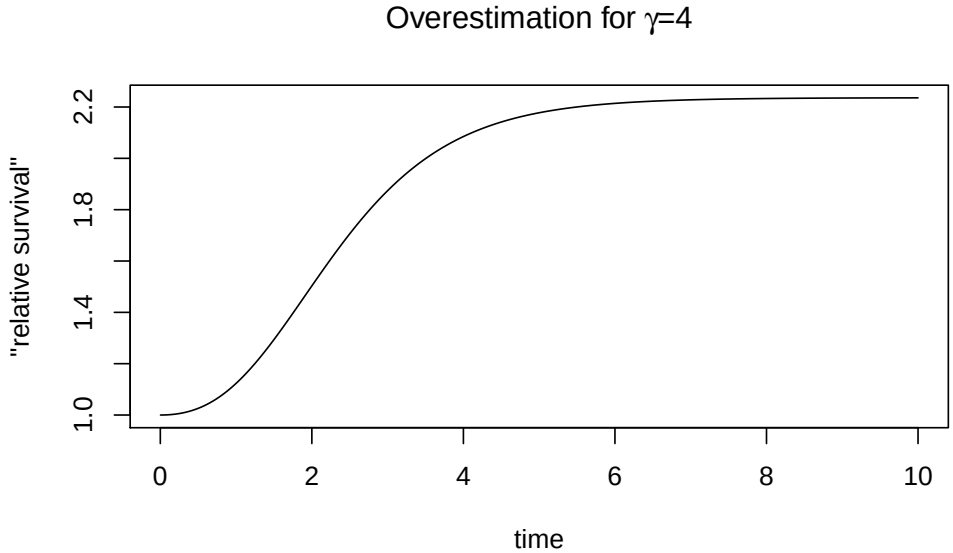

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- Andersen et al. (1993): *'Independent censoring is insufficient if the covariates fail to characterize the individual risks'*,
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Trails in directed graphs

- Enumeration of consecutive edges connecting V and V',
- A subset Z of vertices is said to block a trail $\mathcal{T}$ if either
  1. Z contains an arrow-emitting node in $\mathcal{T}$, or
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Trails from V to V'

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Causal validity

Local independence model with observable nodes $\mathcal{V}_0 \subset \mathcal{V}$ that are subject to censoring (represented by C).

Theorem (Røysland et al.)

If the full model is causal for prevention of censoring,

- C *has no descendants and*
- *Every back-door trail*

$$C \leftarrow \cdots \rightarrow V, \tag{3}$$

for $V \in \mathcal{V}_0$*, is blocked by* $\mathcal{V}_0$*,*

then the reduced model based on the observable components is both causal and subject to independent censoring.

Independent censoring: Summary

- Independent censoring is a special case of local independence,
- The claim *"independent censoring ensures that Kaplan-Meier gives survival as if censoring had been prevented" is not true,*
- *Causal validity is necessary for this to hold,*
- *Local independence models and δ-separation can be used to assess the validity in given scenarios.*

Causal reasoning with local characteristics

- Mechanism of each 'vertex' is captured by its **local characteristic**,
- The local characteristic of a counting process N is the intensity λ with respect to the filtration of all vertices,
- Consider an optional intervention (treatment regime) for this component that would replace λ with another process $\tilde{\lambda}$,
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Counterfactuals based on causal models

- Graphical model: collection of joint densities $\{P\}$,
- Change of intensity for N yields a counterfactual model $\{\tilde{P}\}$,
- If $\tilde{P} \ll P$ then we obtain $\tilde{P}$ by re-weighting P according to

$$W_t := \prod_{s \leq t} \left(\frac{\tilde{\lambda}_s}{\lambda_s} \right)^{\Delta N_s} \exp\left(\int_0^t \lambda_s - \tilde{\lambda}_s ds \right).$$

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- Not able to acquire all the information $\mathcal{F}$ about the scenario, only some abbreviated sub σ-algebra $\mathcal{G}$,
- Want to identify an effect

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  based on the observable frequencies $\{P|_{\mathcal{G}}\}$,
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Example: identifiable causal effects

Proposition

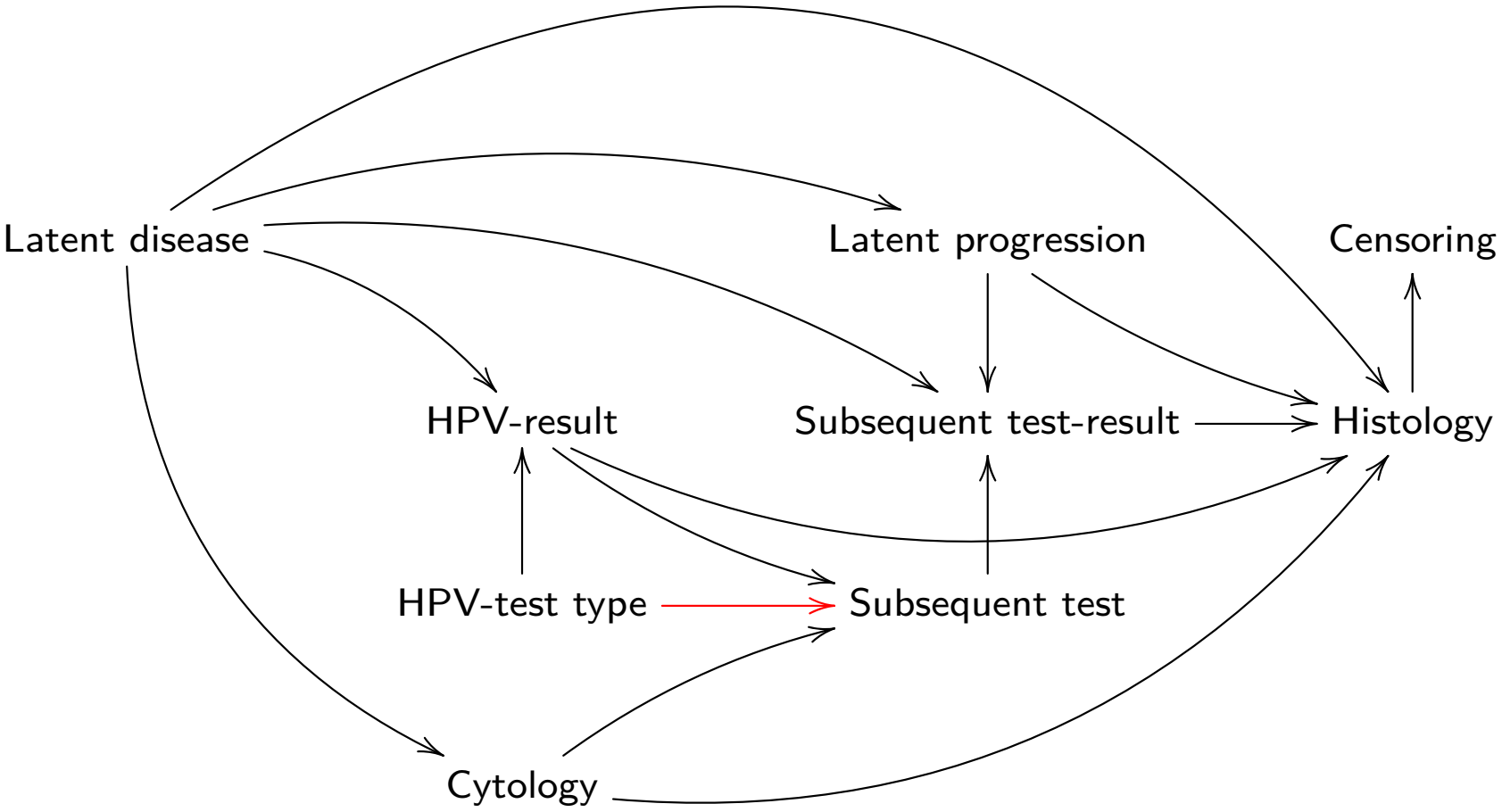
- *Causal model* $\{P\}$, *with vertices* $\mathcal{U} \cup \mathcal{V}_0$, *for an intervention on* $N^x \in \mathcal{V}_0$ *where* $\tilde{\lambda}$ *only depends on parents of* N^x,
- $\{\tilde{P}\}$ *is causal with respect an intervention that would prevent censoring* N^c, *and* N^c *has no descendants,*
- *Every trail from* $\mathcal{U}$ *that ends with an arrow into* N^c *or* N^x, *and every trail* $N^x \to \cdots \to N^c$, *are blocked by* $\mathcal{V}_0$,

then we can identify the intensity of every $N \in \mathcal{V}_0$, with respect to the history of $\mathcal{V}_0$, as if both censoring had been prevented and the hypothetical treatment regime had been carried out.

HPV-testing revisited

- Time to detection of cancer after negative HPV-test,
- Norchip's test is subject to more frequent subsequent testing,
- Want to compare the tests in a countefactual scenario where they had been subject to the same subsequent testing regimes.

Secondary HPV-screening: Short-term dependencies



Fair comparrisons

- Will compare the cumulative risk of CIN2+, conditionally on "Cytology" and "HPV-result", for the two test-types,
- "HPV-test type" $\rightarrow$ "Subsequent test" $\rightarrow$ "Subsequent test result" $\rightarrow$ "Histology" leads to unfair comparrisons,
- Fair comparrisons should only be concerned with trails from "HPV-test type" to "Histology" through "Latent disease".

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Estimating hypothetical effects: re-weighting

- Can impose the counterfactual regime by weighting the Proofer-women, at time t, according to W_t,
- W_t solves the stochastic differential equation:

$$W_t = 1 + \int_0^t W_{s-} dK_s,$$

where

$$K_t := \int_0^t (1 - \frac{\lambda_s^{\text{DNA}}}{\lambda_s^{\text{Proofer}}}) dM_s,$$

and λ^{Proofer} and λ^{DNA} are intensities of subsequent testing.

New quality registries: The need for causal inference

- Established quality registries to ensure high quality of treatments in Norwegian health care,
- Examine how well given treatments comply to guidelines, due to detailed information on specific patient groups,
- Evaluation of **treatment effects** requires causal reasoning,
- Opportunity to identify potential improvements in Norwegian health care based on available observational data.

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Ongoing projects: effect of cancer treatments

NORWEGIAN **CANCER** SOCIETY

- Radiation vs surgery after prostate cancer,
  - Norwegian men diagnosed with prostate cancer 2004 or 2005,
  - Collaborators: Sophie Fosså (OUS), Bjørn Møller (KRG) and Odd O. Aalen (IMB),
- Endocrine treatment after hormone sensitive breast cancer,
  - Collaborators: Eva Skovlund (FHI), Jan Nygård (KRG), Giske Ursin (KRG) and Odd O. Aalen (IMB),

Røysland
Counterfactual analyses with graphical models based on local independence
The Annals of Statistics, (2012)

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Røysland, Aalen, Nygaard, Lange, Didelez
Causal reasoning in survival analysis: Re-weighting and local independence graphs
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A structural approach to selection bias
Epidemiology, 2004

Hernán, Hernandez-Diaz, Werler, Mitchell
Causal knowledge as a prerequisite for confounding evaluation: an application to birth defects epidemiology
American journal of epidemiology, 2002