Genes, life-course and heart failure – intro to PhD project

Anders Munch

September 30, 2020

Introduction to PhD project

- The problem
- The data
- Some thoughts/ideas so far

People involved

- Thomas Gerds and Claus Ekstrøm from here
- Christian Torp-Pedersen, Professor of Cardiology and Senior Consultant, Gentofte Hospital and University of Copenhagen
- Charlotte Andersson, MD PhD, Herlev Hospital and Boston Medical Center

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- Heterogeneous disease / syndrome.
- Better HF sub-diagnoses or disease pattern $\rightarrow$ identify genetic effects.
- Use machine learning for this ...

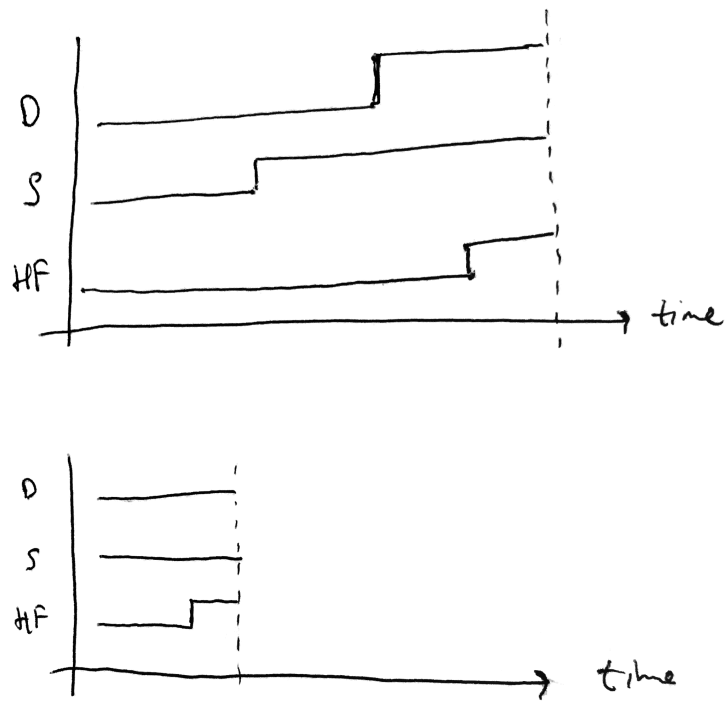
Data

Coronary arteries examiniation: $\sim 6,000$ individuals + DST data. Weird selection criteria, non-representative population.

Blood donors: $\sim 300,000$ individuals in "computer room". Very healthy individuals.

Framingham: Participants from a small city. Detailed medical information measured repeatedly over many years and generations. Genetic data for later generations.

Initial thoughts



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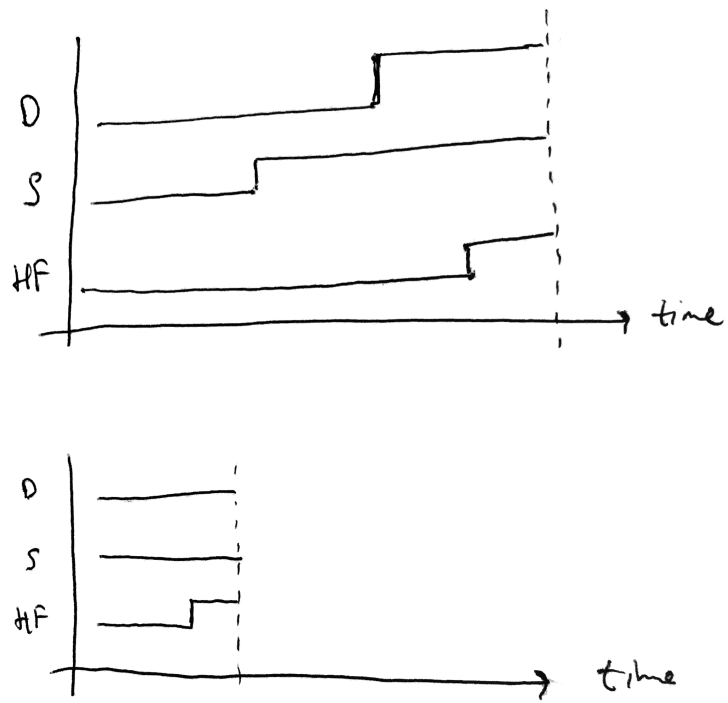
Cluster disease patterns



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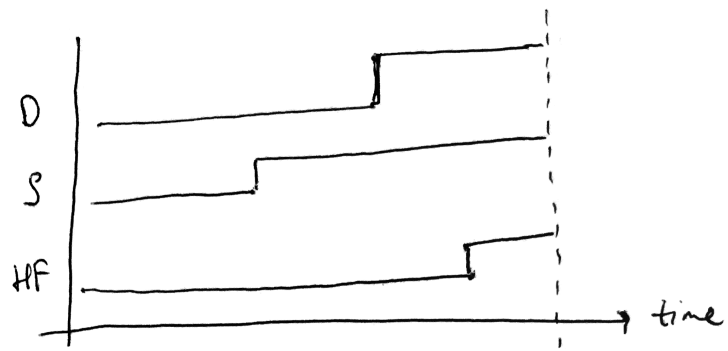

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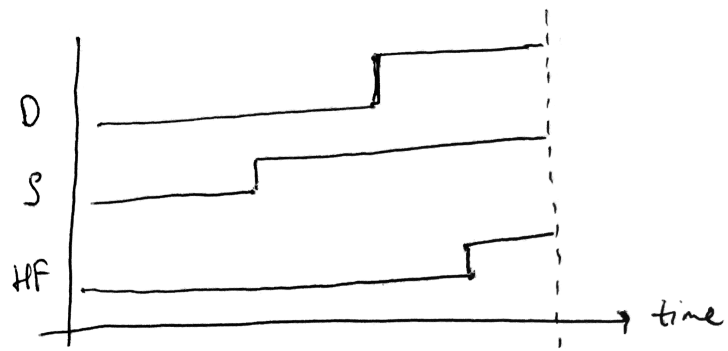
Local independence?



Formalization of the problem

One rough initial formalization

We observe a multivariate process $X = (G, D, Y)$,

$$Y(t), \quad D(t), \quad G(t) = G, \quad t \in [0, T],$$

where $Y \in \{0, 1\}$ denotes if heart failure has occurred, D denotes status of some disease (for instance diabetes or not at time t), G is constant and contains genetic information, and T is time of death.

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Later

- much more complicated D
- very high-dimensional G

For now, focus on the time dynamic issues so we assume both are one-dimensional.

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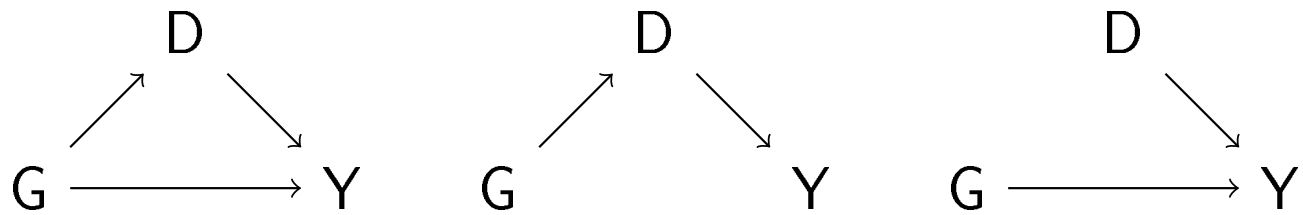
Doubtful illustrations



What does the above mean when D and Y are processes?

Local independence

Local independence

Definition (Informal)

For a multivariate stochastic X

$$X(t) = (X^1(t), X^2(t), \ldots, X^k(t)), \quad t \in [0, T],$$

with $V := \{1, \ldots, k\}$, we say that for $A, B, C \subset V$, X^B is *locally independent* of X^A given X^C if

$$X^B(t) \perp\!\!\!\perp X^A([0, t)) \mid X^C([0, t)), \quad \forall t \in [0, T].$$

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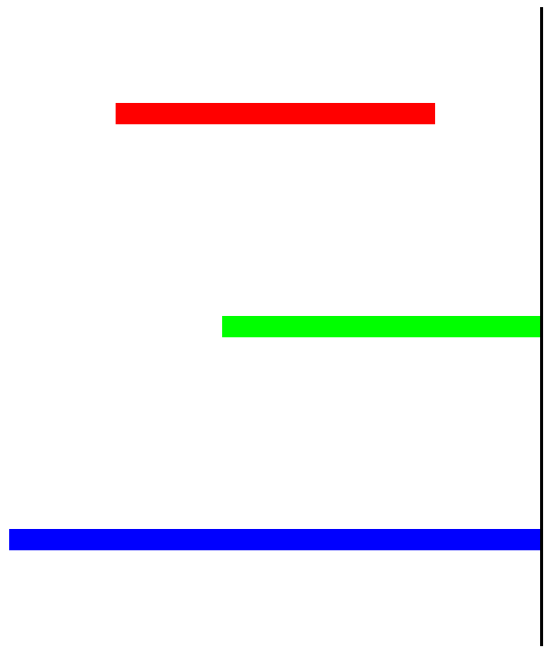
"In words, the process X^B is locally independent of X^A given X^C if, for each time point, the past up until time t of X^C gives us the same *predictable* information about $\mathbb{E}[X^\beta(t) \mid \mathcal{F}_t^{A \cup C}]$ as the past of $X^{A \cup C}$ until time t." [Mogensen et al., 2020]

Local independence – visualization



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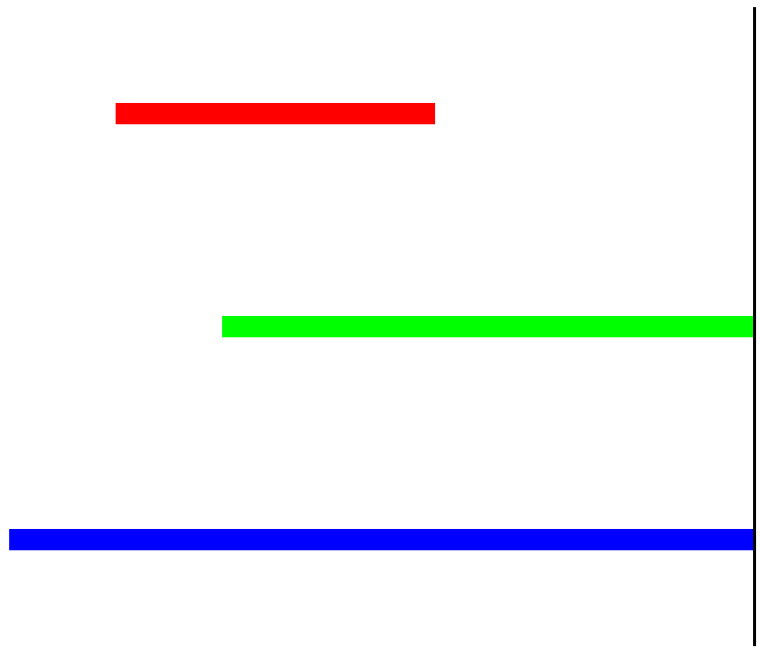

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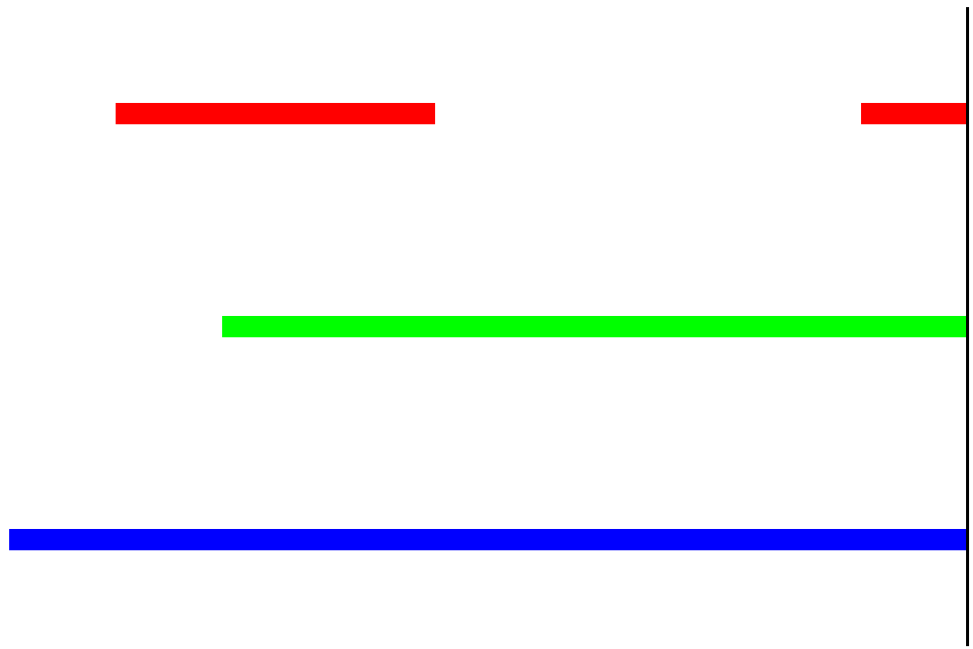

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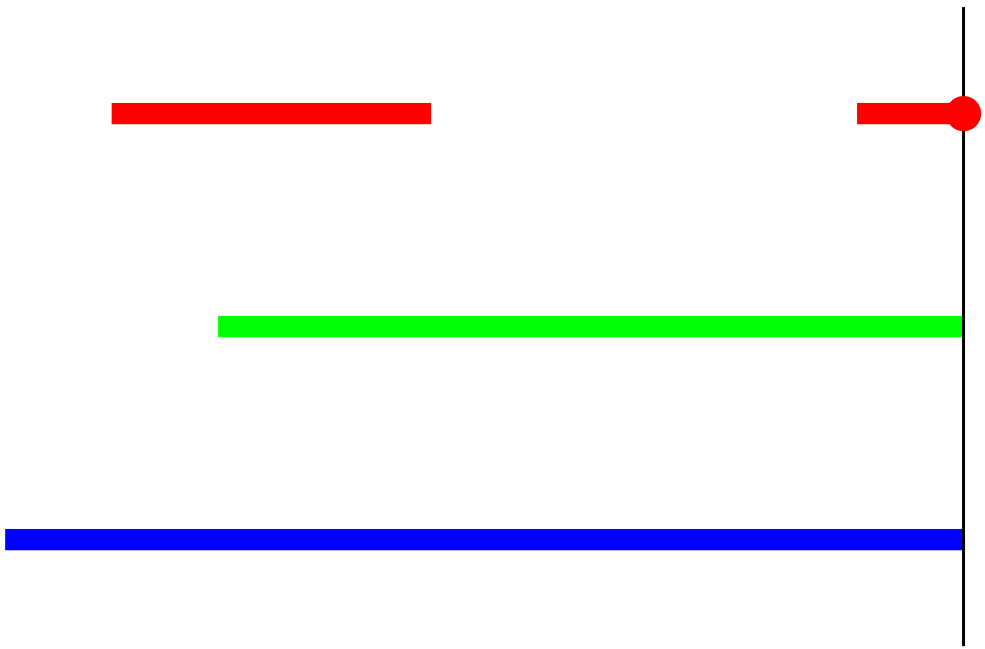

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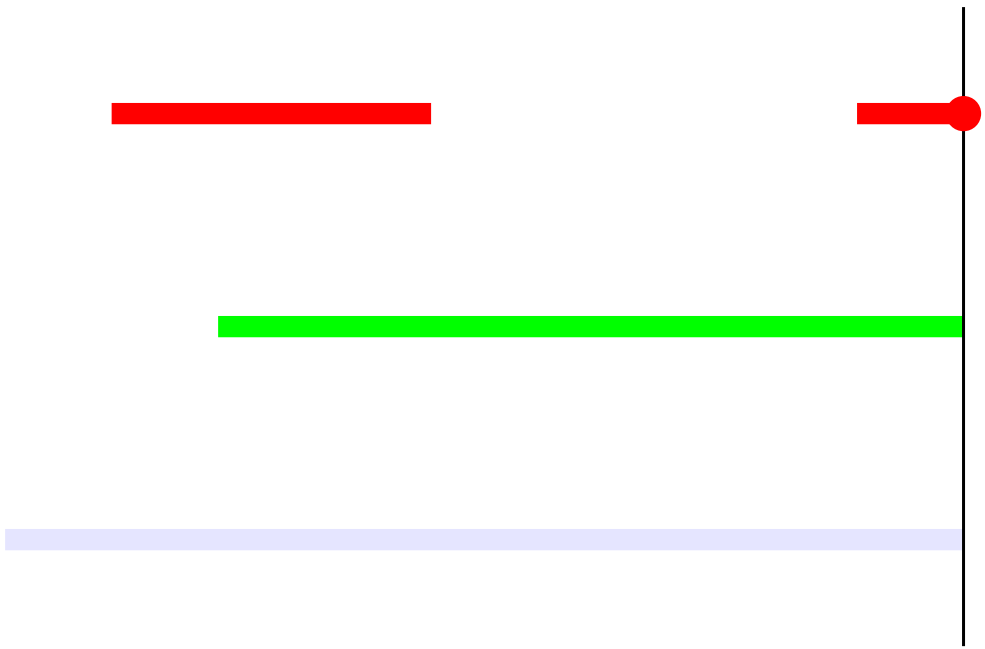

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> *"We suggest that when people attempt to draw causal diagrams it is often most natural to think of the nodes as processes and use local independence" [Aalen et al., 2016, p.2300].*

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3. “Dynamic” point of view

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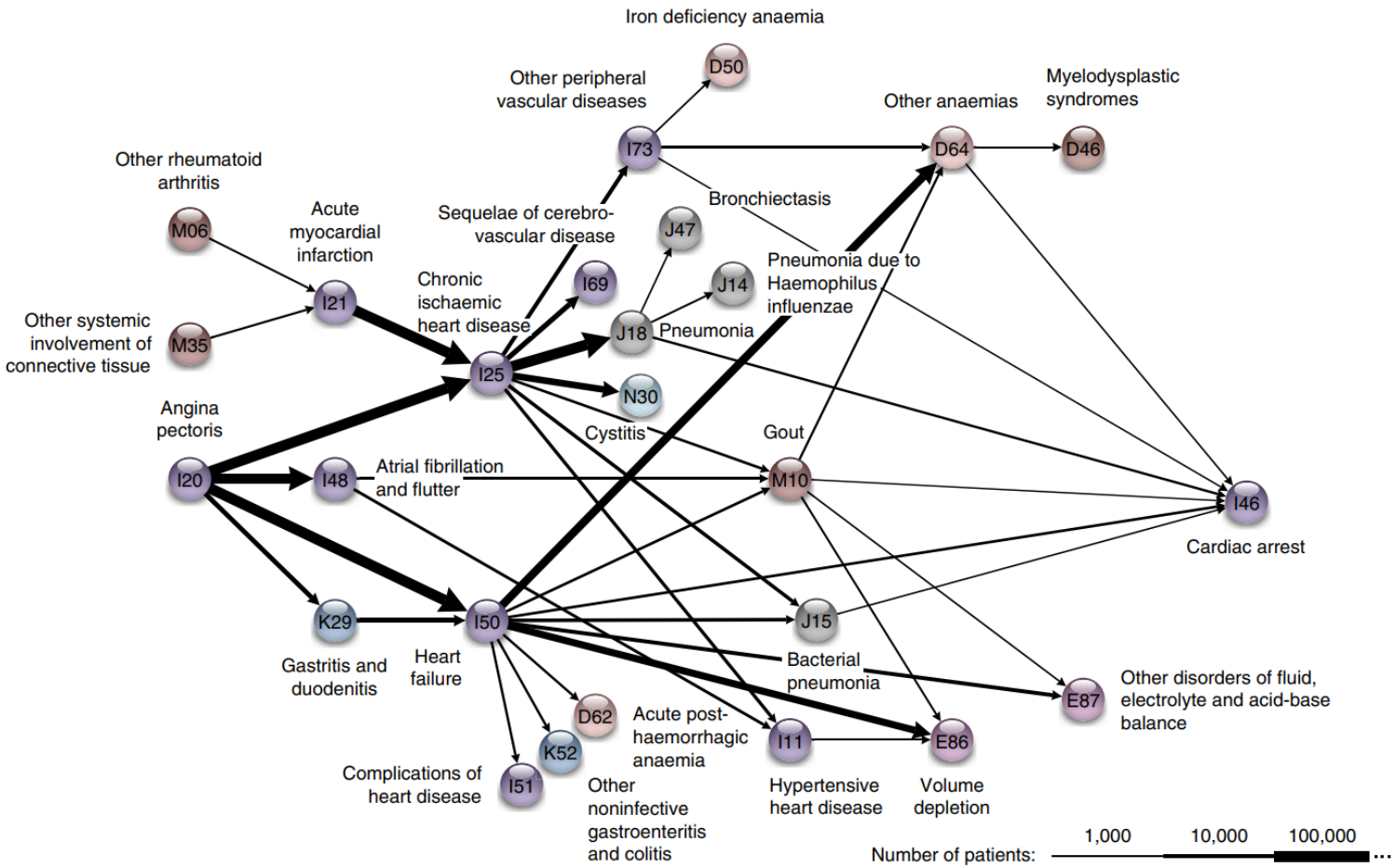

1. Clustering disease patterns – use local dependence?

Brunak Group's approach to clustering

- Matching every exposed patient to a non-exposed group with similar age and sex.
- Test for association between diagnoses occurring within 4 years, and then test for "temporal direction".
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Try to use local dependence?

- Better way to model "temporal association"? Nicer interpretation?
- Easier to handle stopped processes – take death and censoring into account.
- Perhaps fewer arbitrary choices.

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Example:

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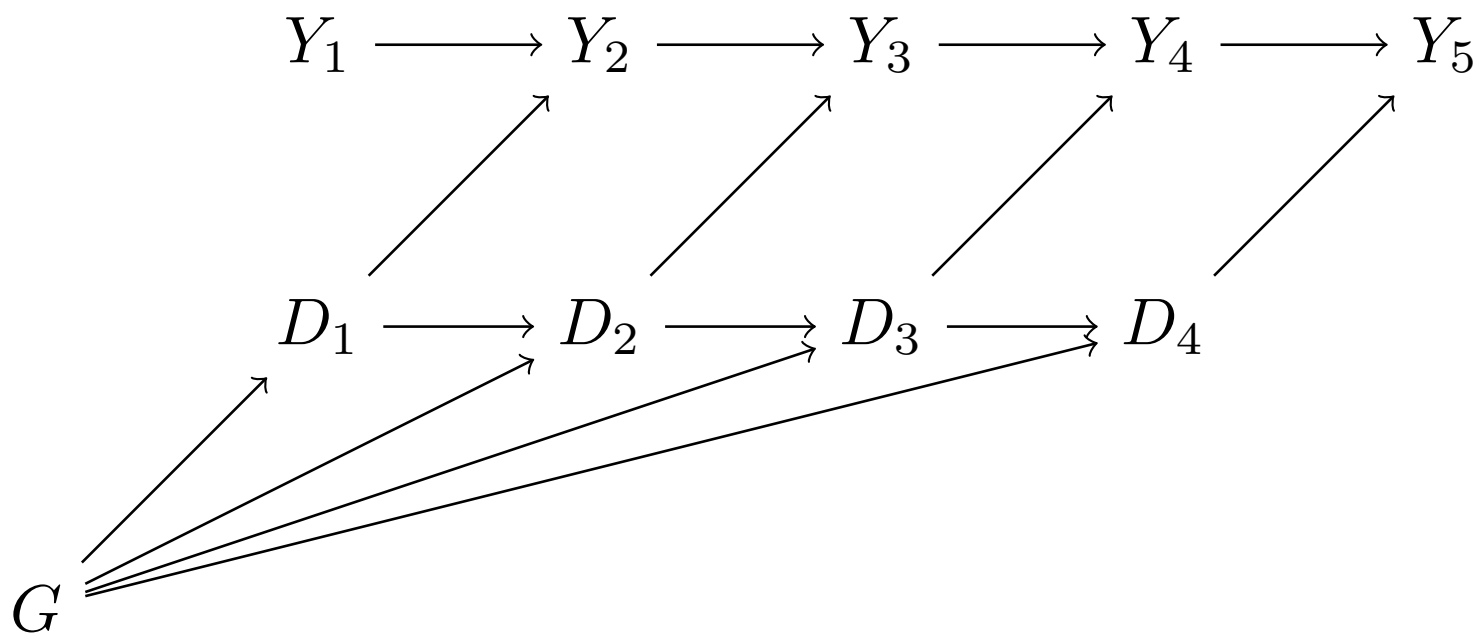
In addition, causal mechanisms can be "smeared out" or "distorted" by discretization [Aalen et al., 2016].

2. Mediation in time – visualization



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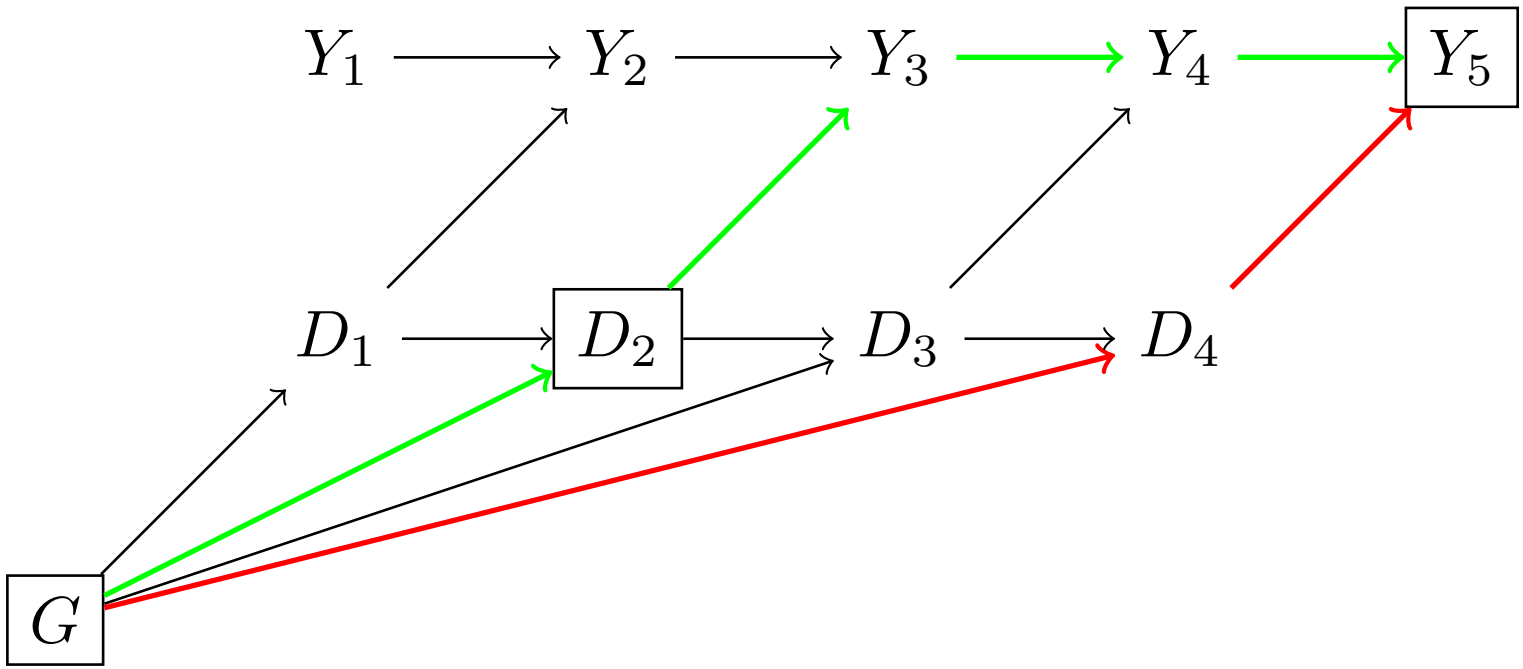

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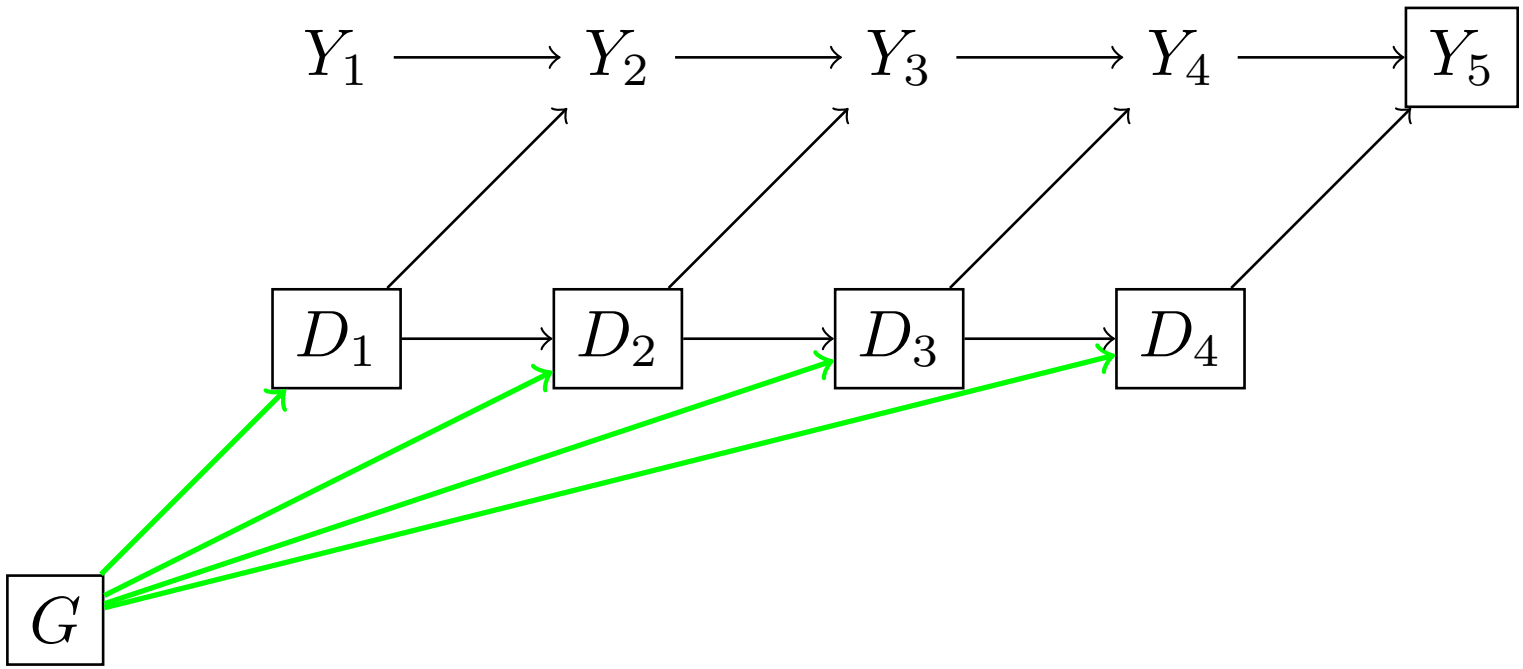

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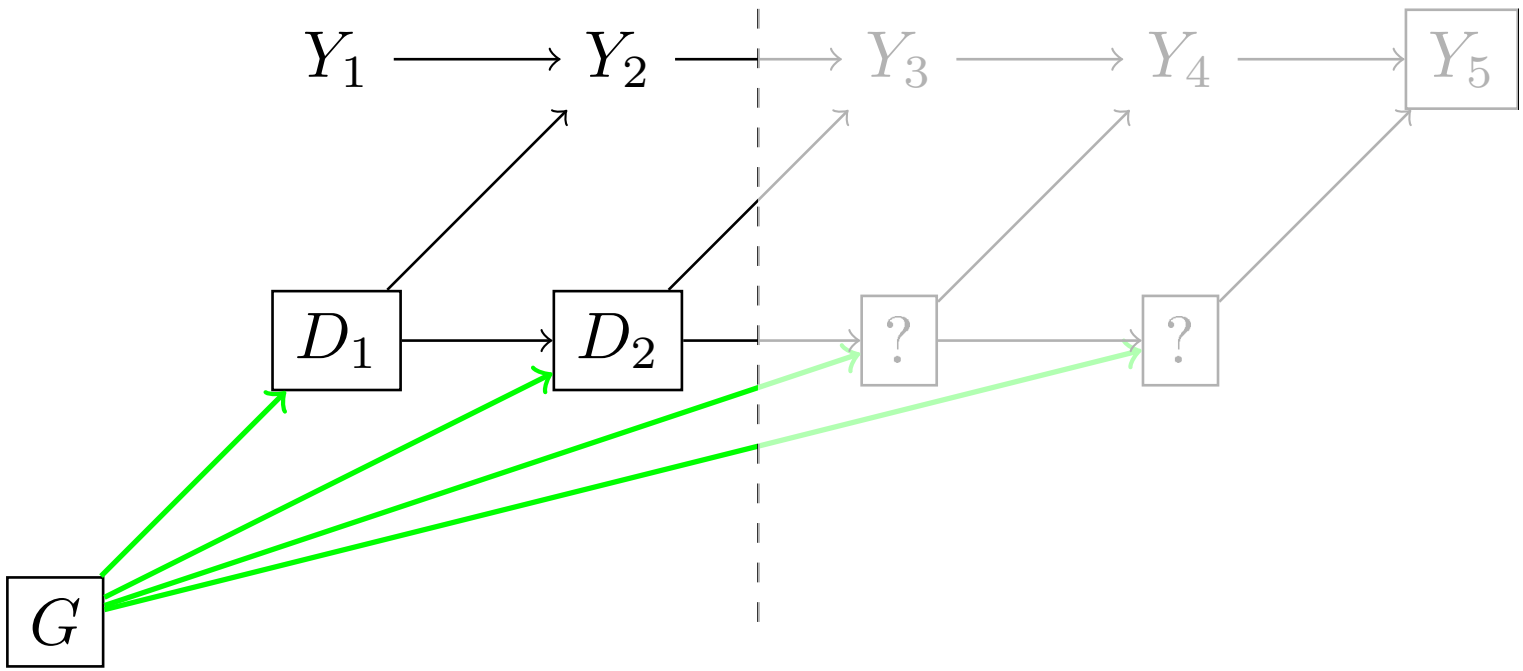

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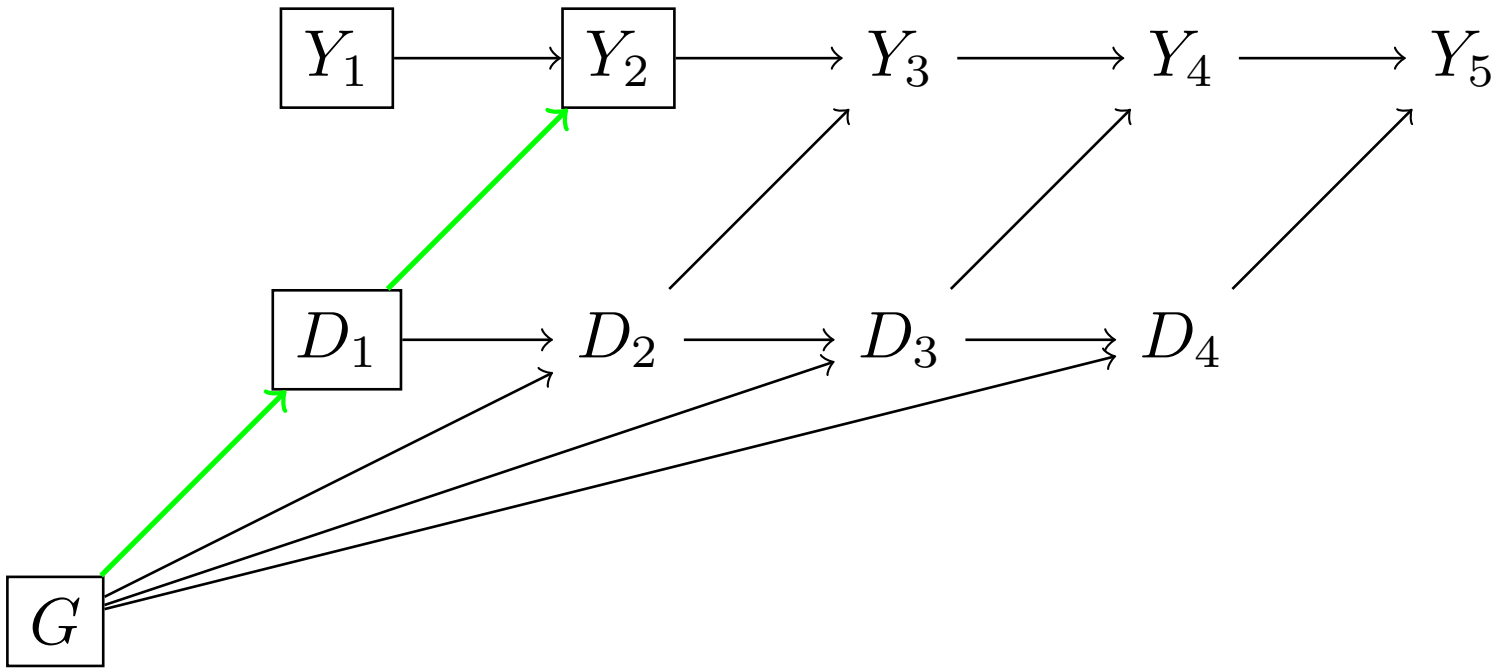

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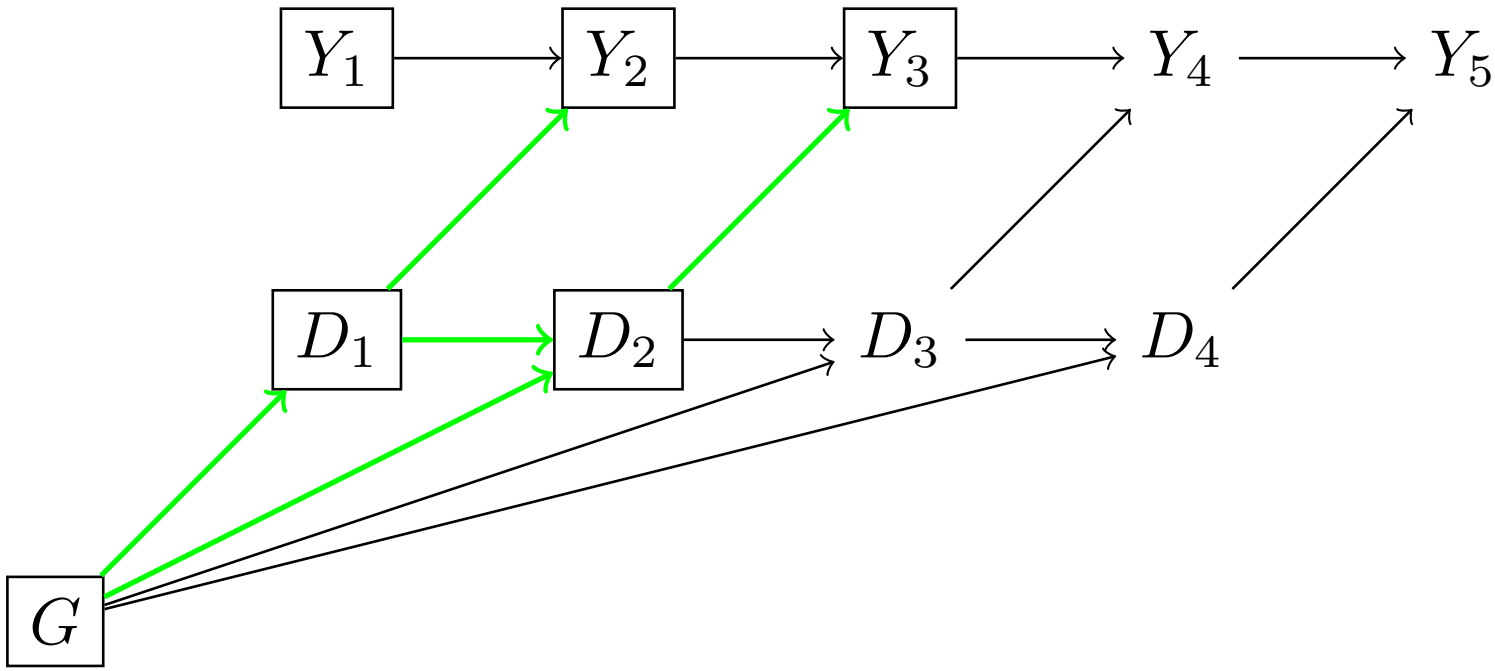

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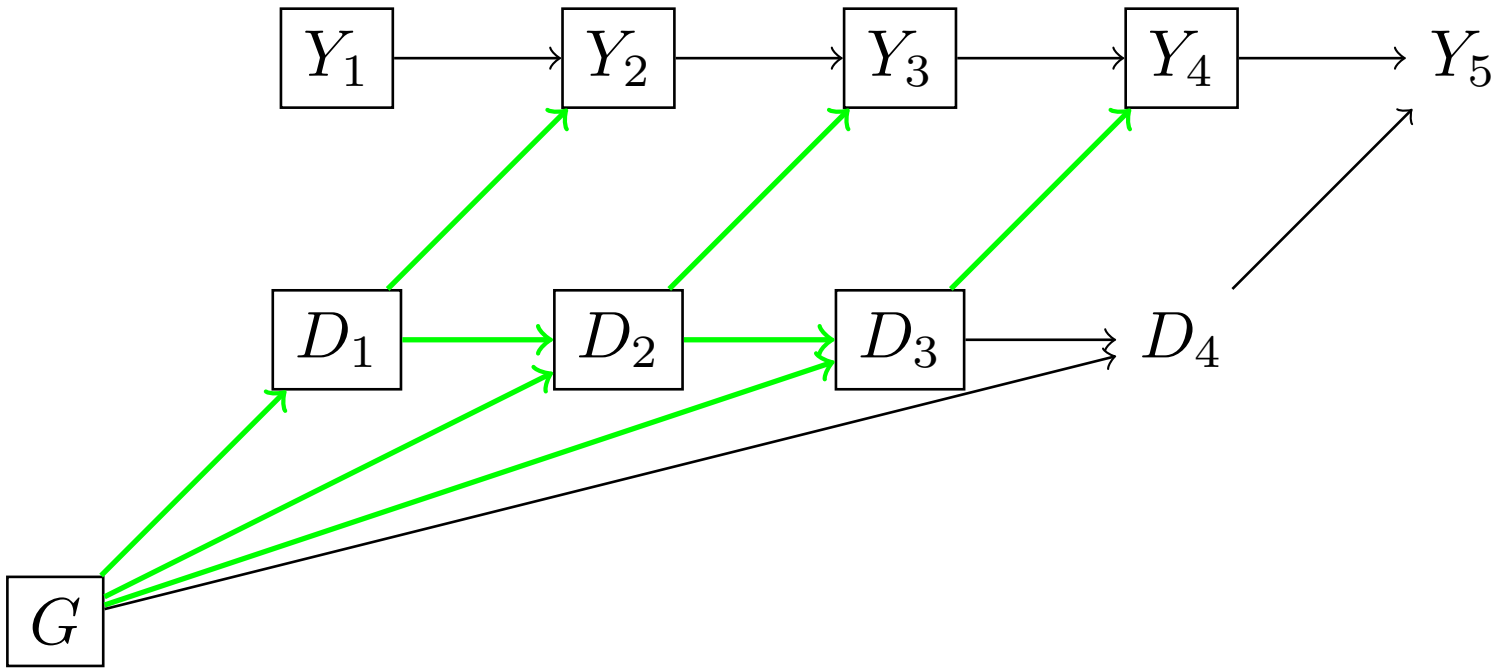

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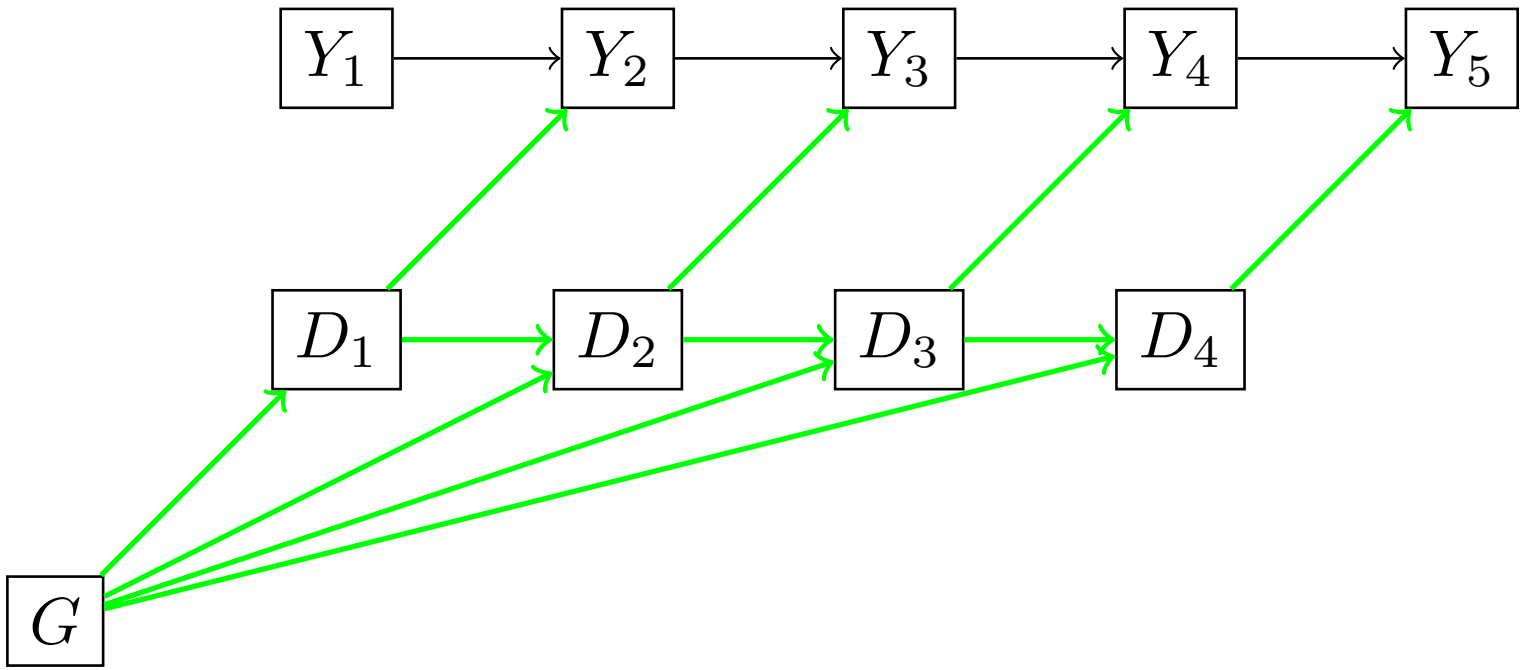

2. Mediation analysis in time – use local independence?

"If a direct effect cannot reasonably be defined as a controlled or natural direct effect in the counterfactual sense because the required hypothetical manipulation of the mediator is inconceivable, then we can alternatively view these effects as being represented by flow in a dynamic system, so that the direct effect corresponds to the flow not passing through the mediator." [Aalen et al., 2012]

3. Fixed time points (landmark analysis)

Overcome the time problem by fixing time points

Fix t_0 and $l > 0$ and consider

$$\mathrm{P}\left(Y(t_0 + l) = 1 \mid D(t_0), T > t_0\right).$$

- Reasonable if t_0 and $t_0 + l$ denote some meaningful time of intervention and follow-up time, respectively.
- Lose information about what happens between t_0 and $t_0 + l$.

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Local independence

- No need to fix time points.
- Better to capture "mechanistic workings"?

Relevance of local independence (summary)

1. Model of temporal dependence $\rightarrow$ Better way to compare (stopped) processes. Use obtained clusters as sub-diagnoses of HF.
2. An approach to mediation in a dynamical system $\rightarrow$ Answer questions about causal pathways for HF.
3. "Dynamic" point of view $\rightarrow$ Allows a more "exploratory" approach.

Major challenge

Most likely it will *not* hold that $G \not\to Y \mid D$. Then what?

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Effect estimation

Could we construct a good measure for the "strength" of the dependence? Should this measure be time-dependent? How should it be interpreted?

Time periods of dependence and independence?

Would it be more informative to try and identify age spans during which dependence is present?

Other (major) challenges

Missing data

Missing observations, censoring, selection bias, discretization.

Interpretation

Does the concept of local independence lead to models with a clear interpretation? Does it bring us closer to causal interpretations – and if so, in what sense?

High-dimensional data

Genes...

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Questions / discussion

Local independence – mathematical definition

$X(t)$ is a multivariate stochastic càdlàg process

$$X(t) = (X^1(t), X^2(t), \ldots, X^k(t)), \quad t \in [0, T],$$

on $[0, T]$. For any $C \subset V := \{1, \ldots, k\}$ let $\mathcal{F}_t^C$ denote the completed and right continuous version of $\sigma\{X_s^c : s \leq t, c \in C\}$.
For $\beta \in V, C \subset V$, let $\Lambda^{C,\beta}$ denote the compensator of $\mathbb{E}[X^\beta(t) \mid \mathcal{F}_t^C]$, i.e., $\Lambda^{C,\beta}$ is a $\mathcal{F}_t^C$-predictable process and

$$\mathbb{E}[X^\beta(t) \mid \mathcal{F}_t^C] - \Lambda^{C,\beta}$$

is a martingale.
Then for $A, B, C \subset V$, X^B is said to be *locally independent* of X^A given X^C if there exists an $\mathcal{F}_t^C$-predictable version of $\Lambda^{C \cup A,\beta}$ for all $\beta \in B$. This is written as

$$A \not\to B \mid C.$$