An Overview and Recent Developments in the Analysis of Multistate Processes

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Joint Work with

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Introduction

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- Participants' follow-up may end with different endpoint (e.g., various causes of death), and include developing some intermediate outcomes (e.g. cancer metastasis or a non-fatal stroke).
- Multistate modeling offers a versatile methodology for analyzing longitudinal processes involving transitions between different health states and alternative endpoints.

Example - COVID19 Patients Disease Course

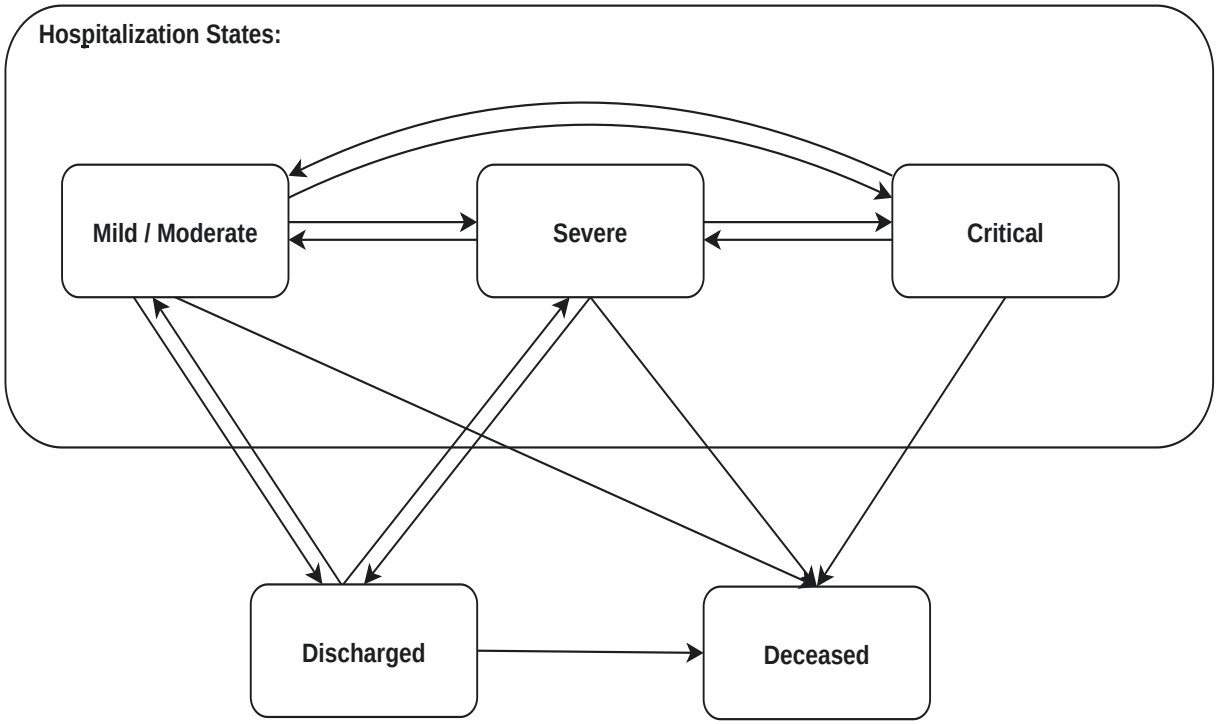

Fig. 3 Multistate model. Patients disease course transitions between 5 possible clinical states: mild or moderate, severe, critical, discharged, and deceased. Each transition was modeled using a set of Cox regression models, adjusting for right censoring, recurrent events, competing events, left truncation, and time-dependent covariates.

Rossman et al. (2021), Nature Communications.

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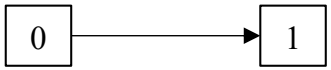
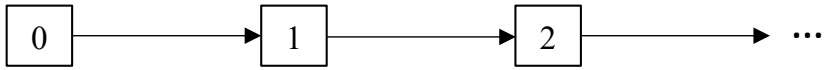
  - We provided a prediction for the total occupancy on a calendar scale, for any real or hypothetical arrival scenario.

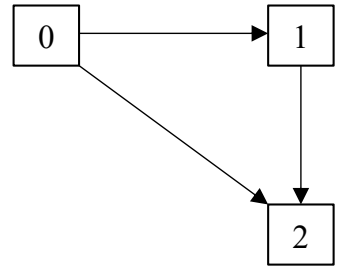
Additional Examples



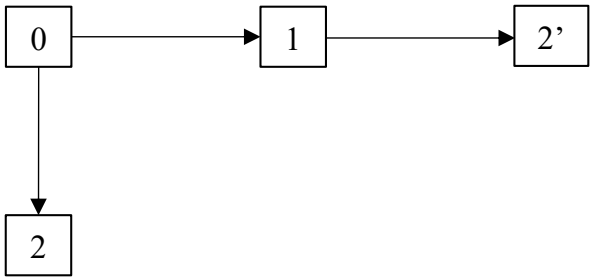
a) A 2-state failure process



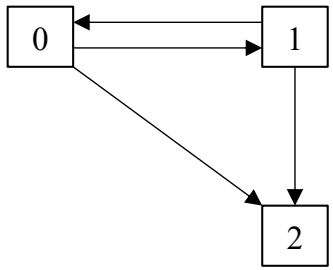
b) A recurrent event process



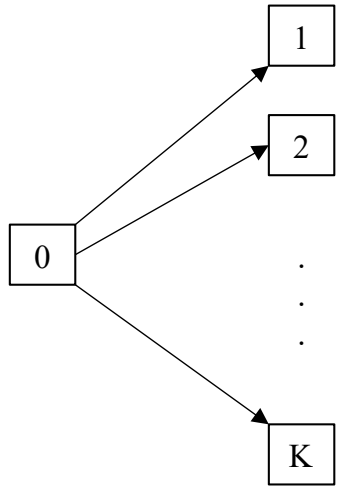
c) A 3-state illness-death process



d) A 4-state illness-death process



e) A reversible illness-death process



f) A competing-risks process

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- Software availability.

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- Within-subject dependence: the sample comprises of independent individuals and random effects accounting for subject-specific unobserved covariates.
- Between-subjects dependence: the dataset consists of clustered data, such as families or centers, where failure times of individuals within each cluster are presumed to be correlated.

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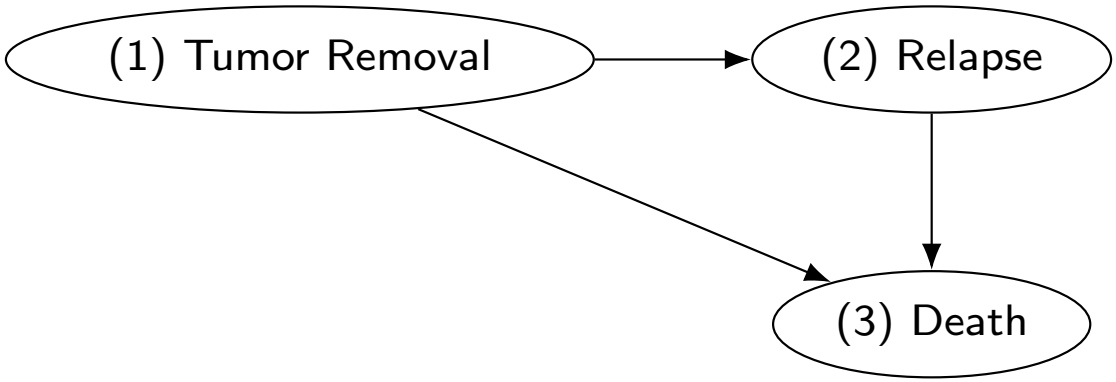

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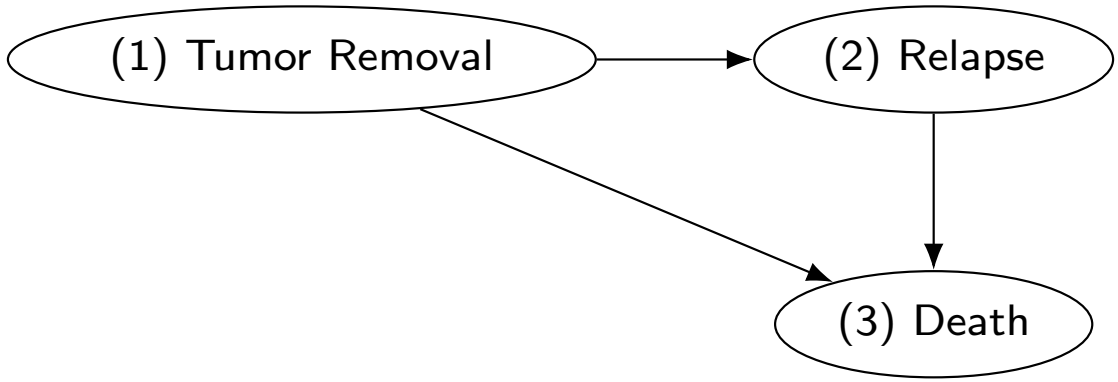

Of the 1546 patients, 924 showed a relapse of the disease (63%), 106 died without evidence of relapse (7%), and 771 patients died after a relapse (79% of the patients who showed a relapse of the cancer).

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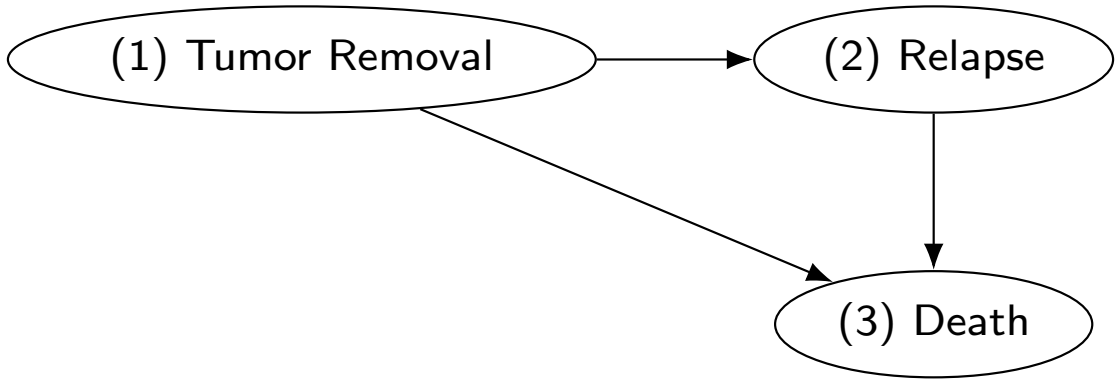

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Baseline Covariates: age at tumor removal, menopausal status, tumor size, tumor grade, number of positive lymph nodes, levels of estrogen and progesterone receptors in the initial biopsy, hormonal therapy, chemotherapy.

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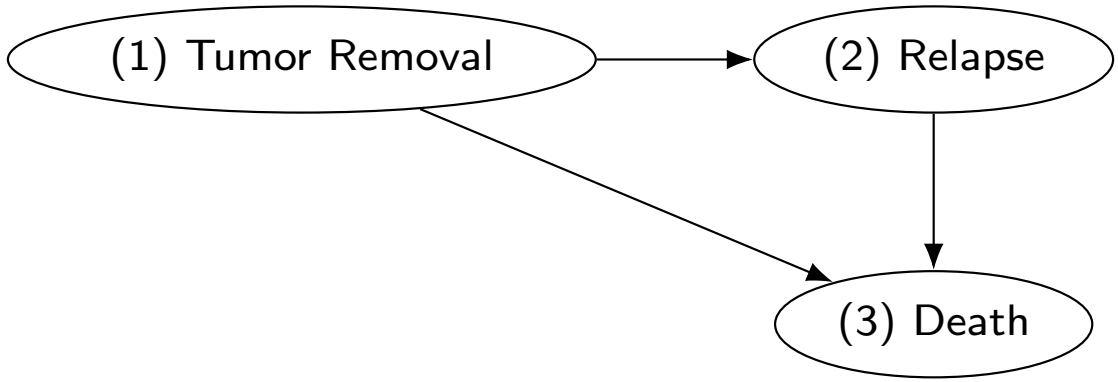

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Our goal: modeling and estimating the transitions

$$1 \to 2 \quad 1 \to 3 \quad 2 \to 3$$

Illness-Death Cox and AFT models - methods and software

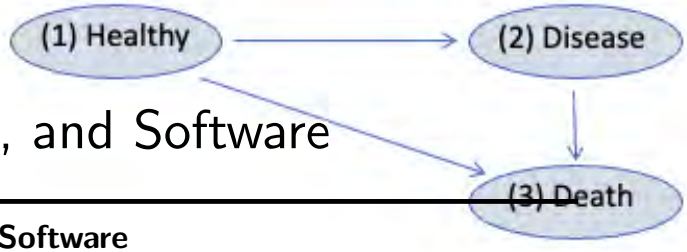
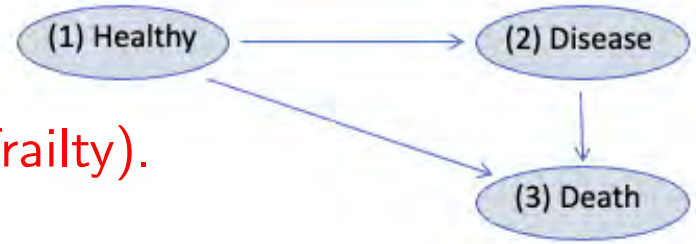


Table: Models, Estimation Procedures, and Software

Authors	Model	Estimation Procedure	Software
Xu et al. (Biometrics, 2010)	Cox, gamma frailty, semiparametric	Semi-parametric MLE	None
Lee et al. (JRSS-C, 2015)	Cox, gamma frailty, semiparametric	Bayesian	R package `SemicompRisks`
Jiang and Haneuse (SJS, 2017)	Transformation model, known transformation function, non-parametric frailty at the price of known error distribution	Semiparametric efficient score	None
Lee et al. (2017)	AFT, additive normal frailty, parametric and semiparametric	Bayesian	R package `SemicompRisks`
Gorfine et al. (JASA, 2021)	Cox, marginalized gamma frailty, semiparametric	Pseudo-likelihood approach	GitHub - frailty-LTRC
Katz and Gorfine (Biometrics, 2023)	AFT, multiplicative gamma frailty, semiparametric	Semi-parametric MLE	GitHub - semicompAFT

Illness-Death with Frailty and Cox-type Models

Frailty-based Cox-type approach of Xu et al. (2010):



w in an unobserved subject-specific random effect (frailty).

T_1 - age at diagnosis, T_2 - age at death

$$h_{12}^c(t|\mathbf{Z}, w) = \lim_{\Delta \to 0} \Delta^{-1} \Pr(T_1 \in [t, t+\Delta)] | T_1 \geq t, T_2 \geq t, \mathbf{Z}, w)$$

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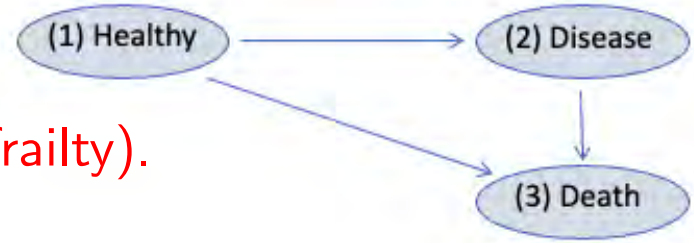

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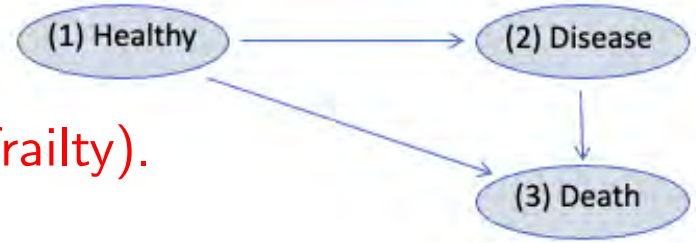

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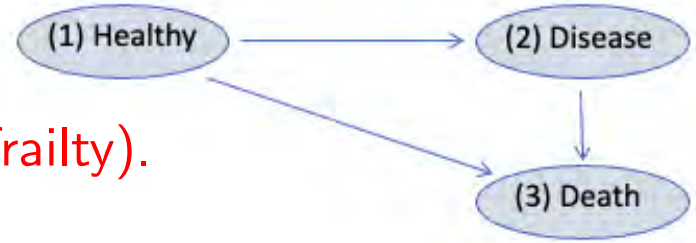

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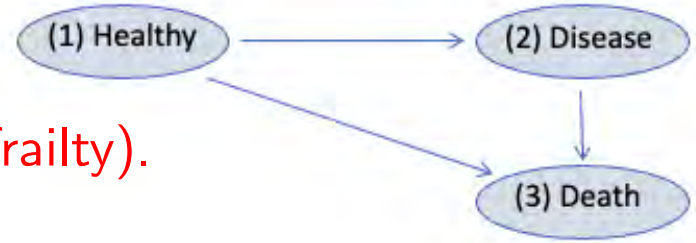

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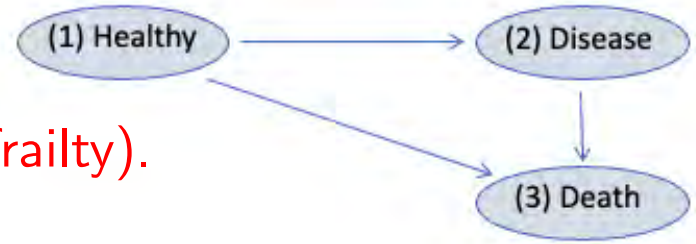

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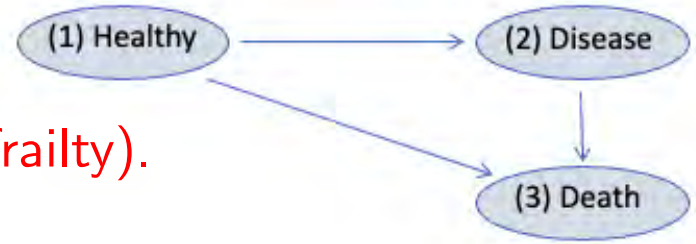

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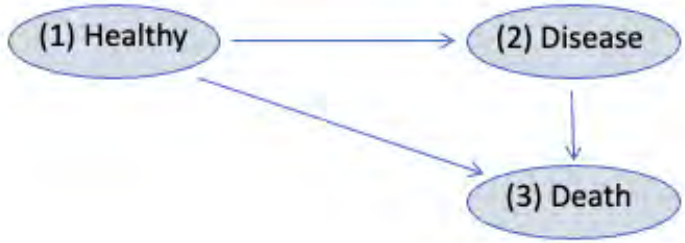
Limitations: the marginal distribution wrt w does not take a simple form and includes the parameter of the frailty distribution.

Other relevant works: Lee et al. (2015); Jiang and Haneuse (2017).



Instead of the approach (Xu et al., 2010):

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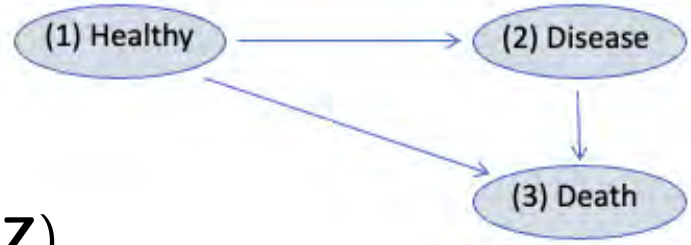

Gorfine et al. (2021) assume conditional hazards

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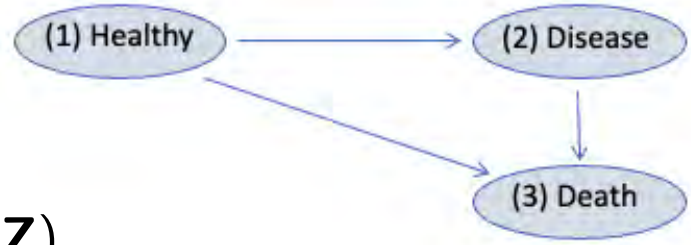

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w in an unobserved subject-specific random effect, and marginal hazards (with respect to w) of the form

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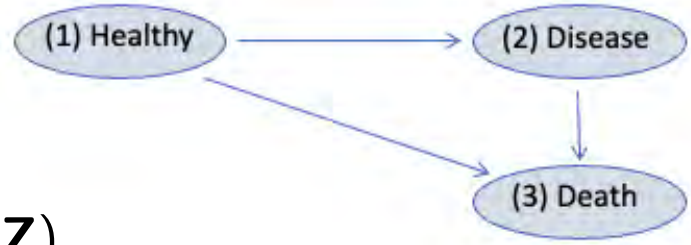

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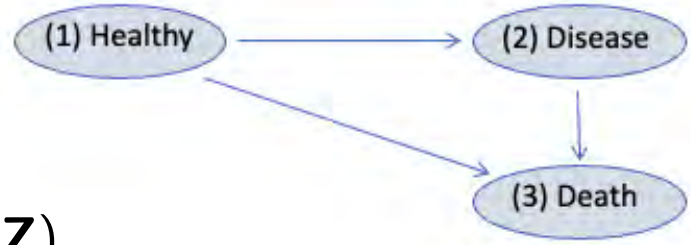
$$\begin{aligned} h^c_{12}(t|\mathbf{Z}, w) &= w\alpha_{12}(t|\mathbf{Z}) \\ h^c_{13}(t|\mathbf{Z}, w) &= w\alpha_{13}(t|\mathbf{Z}) \\ h^c_{23}(t|t_1, \mathbf{Z}, w) &= w\alpha_{23}(t|t_1, \mathbf{Z}) \end{aligned}$$

w in an unobserved subject-specific random effect, and marginal hazards (with respect to w) of the form

$$\begin{aligned} h_{12}(t|\mathbf{Z}) &= h_{012}(t)\exp(\beta_{12}^T\mathbf{Z}) \\ h_{13}(t|\mathbf{Z}) &= h_{013}(t)\exp(\beta_{13}^T\mathbf{Z}) \\ h_{23}(t|t_1, \mathbf{Z}) &= h_{023}(t)\exp(\beta_{23}^T\mathbf{Z}) \end{aligned}$$

The functions α_{jk}, $jk \in \{12, 13, 23\}$, are determined by the distribution of w and the marginalized hazards.



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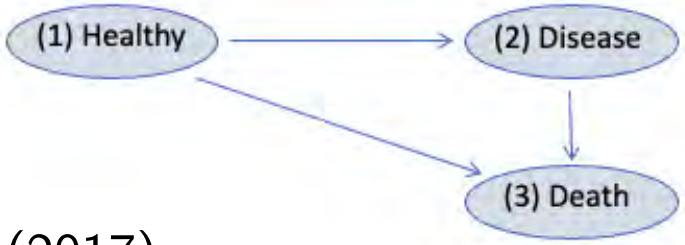
The functions α_{jk}, $jk \in \{12,13,23\}$, are determined by the distribution of w and the marginalized hazards.

The goal: estimating β_{jk} and $h_{012}(\cdot)$, $jk \in \{12,13,23\}$.

Illness-Death with Frailty and AFT Models



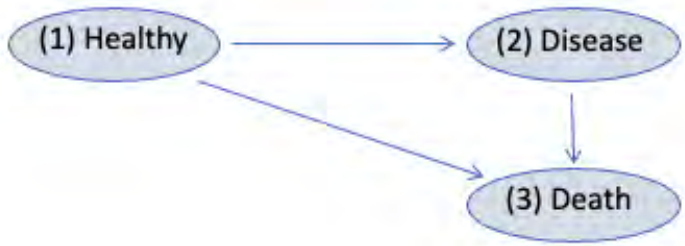
An additive frailty-based AFT approach of Lee et al. (2017):

$$
\begin{aligned}
\log T_1 &= \beta_{12}^T \mathbf{Z} + w + \epsilon_{12} \;\; , T_1 > 0 \\
\log T_2 &= \beta_{13}^T \mathbf{Z} + w + \epsilon_{13} \;\; , T_2 > 0 \text{ given being free of disease} \\
\log T_2 &= \beta_{23}^T \mathbf{Z} + w + \epsilon_{23} \;\; , T_2 > t_1 > 0 \text{ given diagnosed at } t_1
\end{aligned}
$$

Limitations: the conditional hazard does not admit a simple interpretation in terms of the unobserved frailty w, and could be be a non-monotone function of w.

Illness-Death with Frailty and AFT Models - an Alternative Approach

A marginalized frailty-based AFT approach of Kats and Gorfine (2023):



$$
\begin{aligned}
\log T_1 &= \beta_{12}^T \mathbf{Z} + U_{12} \ , T_1 > 0 \\
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U_{12}, U_{13}, U_{23} are random errors with unspecified distributions.

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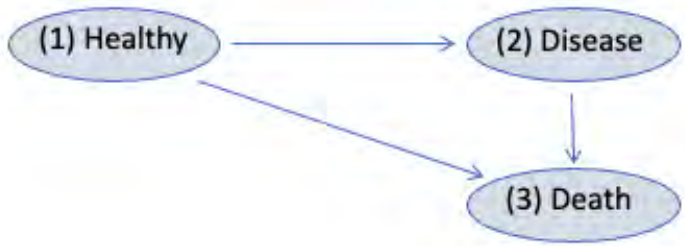

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U_{12}, U_{13}, U_{23} are random errors with unspecified distributions. The dependence between T_1 and T_2 is incorporated via the following conditional baseline hazard functions of $exp(U_{jk})$, $jk \in 12, 13, 23$:

$$
\begin{aligned}
\lambda_{12}(t|w) &= w\lambda_{12}(t) \ , t > 0 \\
\lambda_{13}(t|w) &= w\lambda_{13}(t) \ , t > 0 \text{ given being free of disease} \\
\lambda_{23}(s|t_1, w) &= w\lambda_{23}(s) \ , s > t_1 > 0 \text{ given diagnosed at } t_1
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$$

$\lambda_{jk}(\cdot)$ are unspecified, and w in an unobserved subject-specific random effect.

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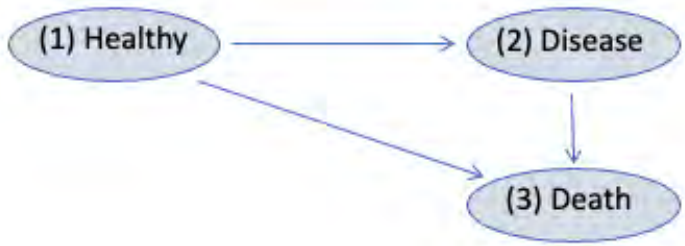

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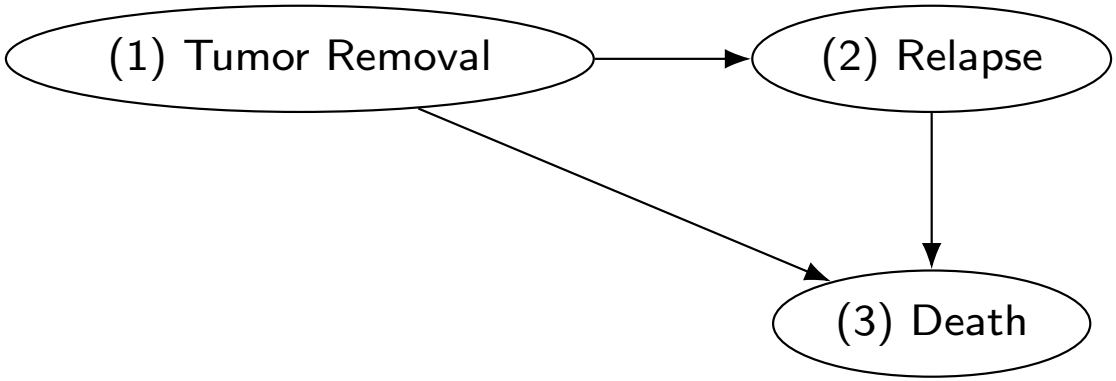
$$

$\lambda_{jk}(\cdot)$ are unspecified, and w in an unobserved subject-specific random effect.

The hazards of this multiplicative model demonstrate monotonic increase as a function of w across all error distributions. Consequently, this model offers a simpler interpretation regarding the influence of unobserved frailty effects.

Rotterdam Tumor bamk Data

1546 breast cancer patients who had node-positive disease and underwent a tumor removal surgery.



Of the 1546 patients, 924 showed a relapse of the disease (63%), 106 died without evidence of relapse (7%), and 771 patients died after a relapse (79% of the patients who showed a relapse of the cancer).

Baseline Covariates: age at tumor removal, menopausal status, tumor size, tumor grade, number of positive lymph nodes, levels of estrogen and progesterone receptors in the initial biopsy, hormonal therapy, chemotherapy.

Our goal: modeling and estimating the transitions

$$1 \to 2 \quad 1 \to 3 \quad 2 \to 3$$

	AFT-multiplicative				Cox-marginalized				Cox-conditional		
	Est (SE)	**exp**	***p*-value**	**Holm**	**Est (SE)**	**exp**	***p*-value**	**Holm**	**PM (SE)**	**exp**	**Credible interval**
σ	2.18 (0.73)	-	0.003	0.058	2.52 (0.54)	-	0.000	**0.000**	1.47 (0.23)	-	(1.046,1.956)
Transition: surgery → relapse											
Age at surgery (divided by 10)	0.14 (0.06)	1.15	0.012	0.185	−0.15 (0.06)	0.86	0.014	0.262	−0.22 (0.08)	0.80	(0.685,0.918)
log of lymph nodes	−0.40 (0.05)	0.67	0.000	**0.000**	0.42 (0.04)	1.53	0.000	**0.000**	0.71 (0.07)	2.03	(1.795,2.326)
log of estrogen+1	0.07 (0.03)	1.07	0.030	0.390	−0.03 (0.02)	0.97	0.186	1.000	−0.10 (0.04)	0.90	(0.839,0.964)
log of progesterone+1	0.09 (0.02)	1.09	0.000	**0.005**	−0.04 (0.02)	0.96	0.065	1.000	−0.11 (0.03)	0.90	(0.845,0.958)
Postmenopausal (vs. premenopausal)	−0.34 (0.15)	0.71	0.023	0.328	0.13 (0.13)	1.14	0.296	1.000	0.34 (0.19)	1.40	(0.980,2.081)
Tumor size (ref < 20 mm)											
20–50 mm	−0.32 (0.09)	0.73	0.001	**0.015**	0.20 (0.07)	1.22	0.006	0.116	0.40 (0.12)	1.49	(1.180,1.882)
> 50 mm	−0.49 (0.11)	0.61	0.000	**0.000**	0.38 (0.11)	1.46	0.001	**0.020**	0.79 (0.16)	2.19	(1.625,3.007)
Hormone therapy	0.60 (0.13)	1.83	0.000	**0.000**	−0.38 (0.08)	0.68	0.000	**0.000**	−0.88 (0.15)	0.41	(0.310,0.541)
Chemotherapy	0.49 (0.11)	1.64	0.000	**0.000**	−0.37 (0.11)	0.69	0.001	**0.023**	−0.79 (0.16)	0.46	(0.329,0.615)
Tumor grade 3 (vs. 2)	−0.25 (0.09)	0.78	0.004	0.081	0.21 (0.08)	1.23	0.008	0.155	0.44 (0.13)	1.56	(1.216,1.986)
Transition: surgery → death											
Age at surgery (divided by 10)	−0.43 (0.14)	0.65	0.002	0.051	1.32 (0.37)	3.74	0.000	**0.009**	1.43 (0.18)	4.20	(2.987,5.923)
log of lymph nodes	−0.14 (0.08)	0.87	0.091	1.000	0.13 (0.12)	1.14	0.298	1.000	0.44 (0.15)	1.54	(1.163,2.092)
log of estrogen+1	0.04 (0.04)	1.04	0.287	1.000	−0.01 (0.06)	0.99	0.816	1.000	−0.11 (0.08)	0.89	(0.765,1.040)
log of progesterone+1	0.01 (0.04)	1.01	0.827	1.000	0.08 (0.06)	1.08	0.205	1.000	0.01 (0.07)	1.01	(0.884,1.163)
Postmenopausal (vs. premenopausal)	−0.15 (0.34)	0.86	0.647	1.000	−0.30 (0.50)	0.74	0.554	1.000	−0.35 (0.70)	0.70	(0.179,2.997)
Tumor size (ref. < 20 mm)											
20–50 mm	−0.13 (0.15)	0.88	0.376	1.000	−0.16 (0.25)	0.85	0.526	1.000	−0.04 (0.28)	0.96	(0.554,1.653)
> 50 mm	−0.19 (0.18)	0.82	0.275	1.000	0.15 (0.31)	1.16	0.634	1.000	0.58 (0.35)	1.79	(0.933,3.488)
Hormone therapy	0.41 (0.18)	1.51	0.019	0.290	−0.21 (0.25)	0.81	0.389	1.000	−0.69 (0.29)	0.50	(0.275,0.851)
Chemotherapy	1.13 (0.30)	3.09	0.000	**0.005**	−0.22 (0.81)	0.81	0.789	1.000	−0.78 (0.63)	0.46	(0.130,1.531)
Tumor grade 3 (vs. 2)	−0.06 (0.13)	0.94	0.641	1.000	−0.01 (0.28)	0.99	0.961	1.000	0.21 (0.27)	1.23	(0.750,2.148)
Transition: relapse → death											
Age at surgery (divided by 10)	0.00 (0.07)	1.00	0.956	1.000	0.03 (0.08)	1.03	0.700	1.000	0.08 (0.07)	1.08	(0.931,1.232)
log of lymph nodes	−0.25 (0.07)	0.78	0.000	**0.010**	0.25 (0.05)	1.28	0.000	**0.000**	0.38 (0.07)	1.47	(1.271,1.687)
log of estrogen+1	0.04 (0.05)	1.04	0.341	1.000	−0.03 (0.02)	0.97	0.193	1.000	−0.10 (0.04)	0.90	(0.838,0.973)
log of progesterone+1	0.13 (0.04)	1.14	0.001	**0.021**	−0.08 (0.02)	0.92	0.000	**0.003**	−0.19 (0.04)	0.83	(0.771,0.884)
Postmenopausal (vs. premenopausal)	−0.21 (0.17)	0.81	0.203	1.000	−0.05 (0.13)	0.95	0.731	1.000	0.04 (0.20)	1.04	(0.705,1.527)
Tumor size (ref. < 20 mm)											
20–50 mm	−0.37 (0.14)	0.69	0.008	0.131	0.23 (0.07)	1.26	0.001	**0.024**	0.46 (0.14)	1.58	(1.234,2.112)
> 50 mm	−0.52 (0.17)	0.60	0.002	**0.044**	0.40 (0.10)	1.49	0.000	**0.002**	0.67 (0.18)	1.96	(1.405,2.764)
Hormone therapy	0.39 (0.14)	1.48	0.005	0.090	−0.18 (0.09)	0.84	0.037	0.633	−0.48 (0.16)	0.62	(0.452,0.835)
Chemotherapy	0.23 (0.18)	1.25	0.205	1.000	−0.16 (0.13)	0.85	0.227	1.000	−0.18 (0.17)	0.84	(0.604,1.179)
Tumor grade 3 (vs. 2)	−0.26 (0.13)	0.77	0.047	0.569	0.21 (0.09)	1.23	0.024	0.440	0.43 (0.14)	1.54	(1.177,2.034)

AFT – additive: Lee et al. (2017) resulted in convergence failure (due to the use of sojourn time which is negatively correlated with time from surgery to relapse).

AFT- multiplicative: Katz & Gorfine (2023)

Cox – marginalized: Gorfine et al. (2021)

Cox-conditional: Lee et al. (2015)

Results:
- Strong dependence between within-subject failure times.
- The directions of the covariates' effect under these models are similar, but inference results are somewhat different.
- GOF assessment: models lacking frailty exhibit poorer fit to the data compared to the models that incorporate frailty (Katz & Gorfine, 2023).

Multistate Models with Frailty Approach

- Existing frailty-based methods can be extended to other types of multi-state models, but in some cases it could be challenging.

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- A relatively simple setting - multiple non-terminal events and a vector of random effects (frailties) capturing multiple levels of dependence among the event.
- More "complex" multistate settings with frailties - could be changing.
- Additional work is required to extend existing estimation methods to the case of time dependent covariates with frailties.

Thanks!

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