多结局事件发生时间型数据的分析

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单一结局生存分析

- 记T是结局时间，累计发生率为$F(t)=P(T<t)$
- 当存在随机删失，删失时间为C，观察到的数据为

$$\tilde{T}=\min\{T,C\},\quad \Delta=I\{T\le C\}$$

- 可以通过研究风险函数(hazard)识别累计发生率函数：

$$F(t)=1-\exp\left\{-\int_0^t d\Lambda(u)\right\}$$

- 其中

$$\begin{aligned} d\Lambda(t) &= P(t\le T<t+dt \mid T\ge t) \\ &= P(t\le \tilde{T}<t+dt,\Delta=1 \mid \tilde{T}\ge t) \end{aligned}$$

单一结局生存分析

- 参数估计
  - Weibull分布
- 非参数估计.
  - Kaplan−Meier
  - Nelson−Aalen
- 半参数估计
  - 比例风险模型，即Cox回归
  - 加速失效模型(AFT)
- 检验：对数秩(log rank)检验

R代码：单一结局

- library(survival)
- #非参数估计
- fit.km = survfit(Surv(ftime, fstatus) ~ group, data)
- surv_test = survdiff(Surv(ftime, fstatus) ~ group, data)
- p = 1 - pchisq(surv_test$chisq, length(surv_diff$n)-1)
- #Cox回归估计
- fit.ph = coxph(Surv(ftime, fstatus) ~ X, data)

竞争风险(Competing risks)

- 研究对象存在多个互斥的结局，如心血管疾病相关死亡(CVD)和非心脏病相关死亡(NCVD)
- 不妨设只有两个结局事件，记T是事件发生时间，J是事件类型：
  - $J=1$ 主要结局
  - $J=2$ 竞争事件
- 事件j的累计发生率 $P(T<t, J=j)$

两种竞争风险模型

- 特定原因风险(cause−specific hazard)

$$d\Lambda_j(t) = P(t \le T < t + dt, J = j \mid T \ge t)$$

- 总事件发生率

$$F(t) = P(T < t) = 1 - \exp\{-\Lambda_1(t) - \Lambda_2(t)\}$$

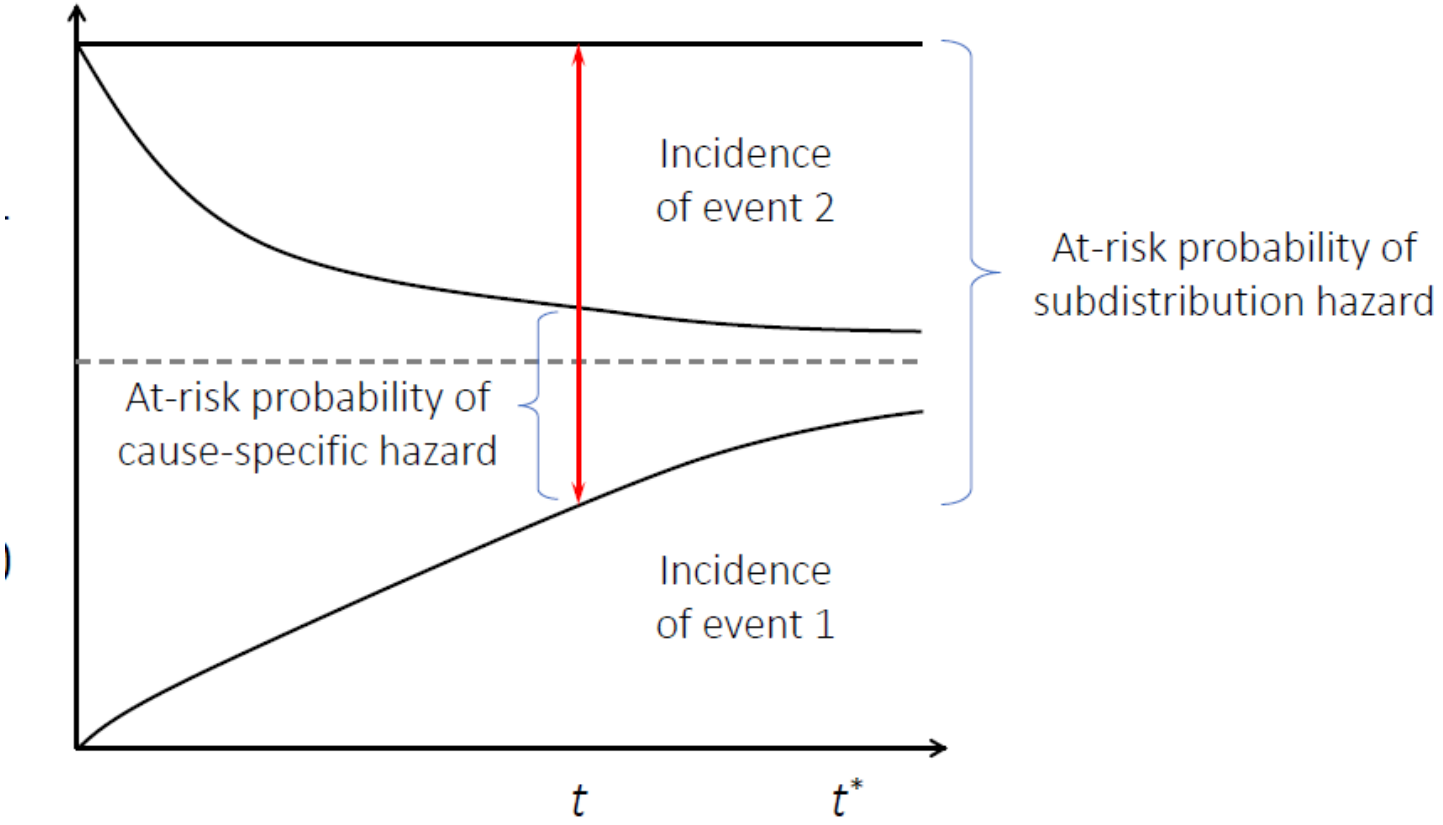
- 子分布风险(subdistribution hazard)，Fine−Gray模型

$$d\Lambda_j^{\text{sub}}(t) = P(t \le T < t + dt, J = j \mid \{T \ge t\} \bigcup \{T < t, J \ne j\})$$

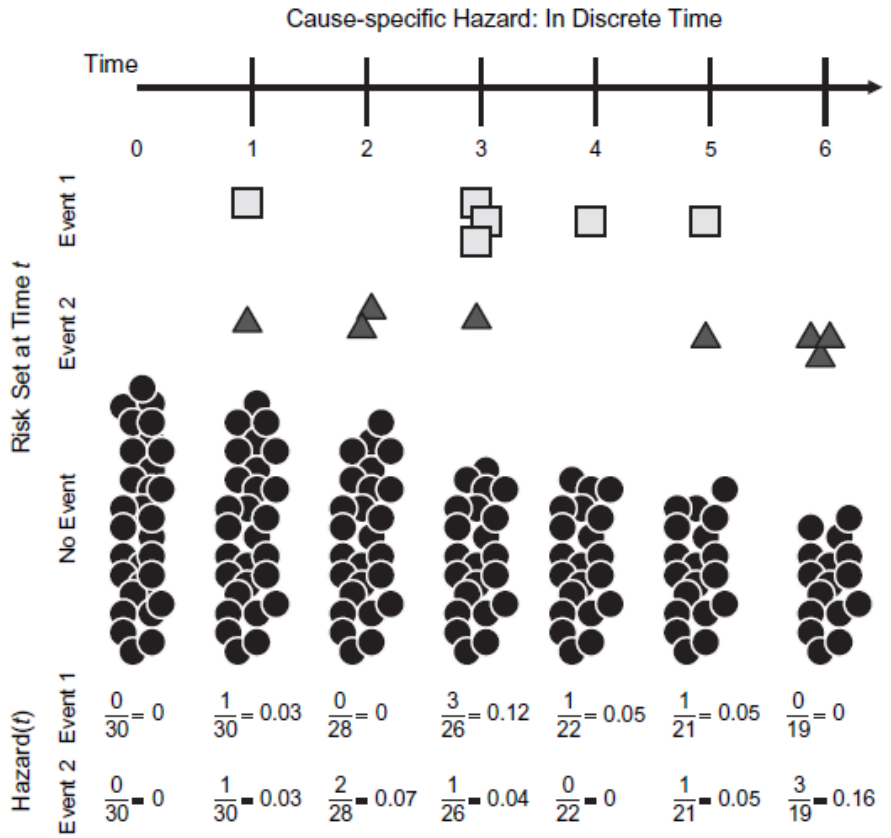
- 事件j的发生率

$$F_j(t) = P(T < t, J = j) = 1 - \exp\{-\Lambda_j^{\text{sub}}(t)\}$$

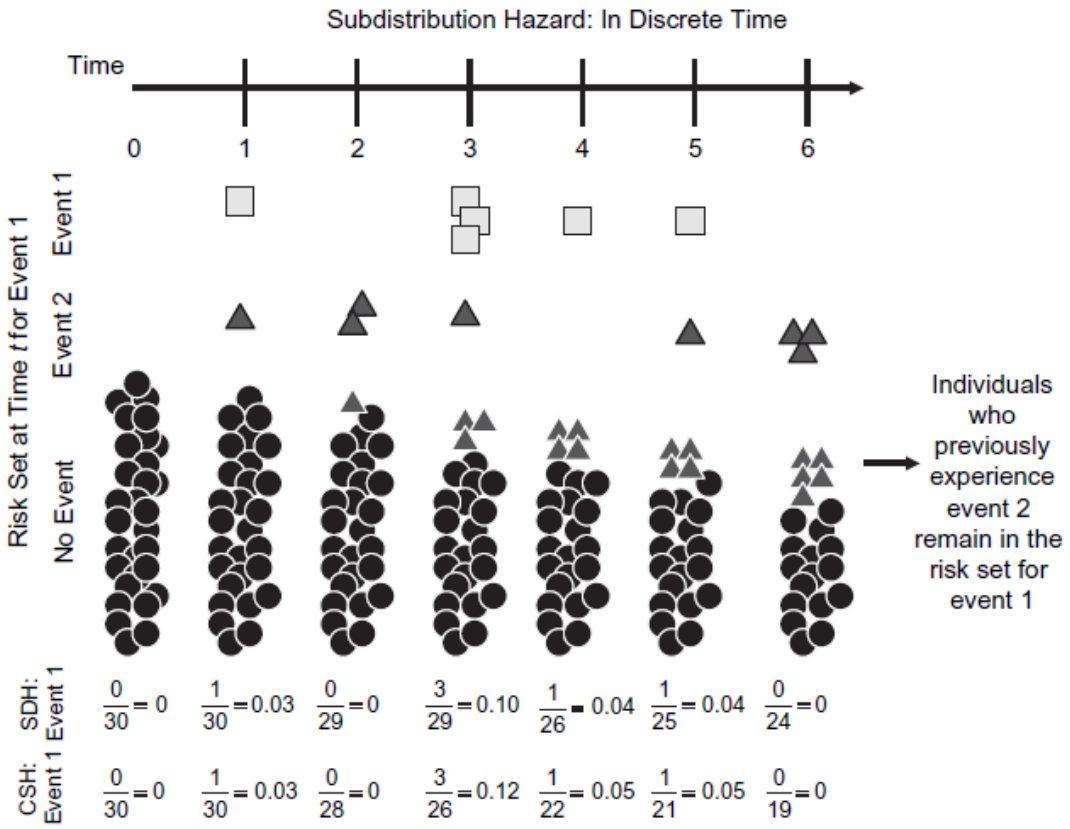
两种竞争风险模型


Incidence
of event 2
At-risk probability of
subdistribution hazard
At-risk probability of
cause-specific hazard
Incidence
of event 1
t
t*

特定原因风险


Cause-specific Hazard: In Discrete Time
Time
0
1
2
3
4
5
6
Risk Set at Time t
Event 1
Event 2
No Event
Hazard(t)
Event 1
Event 2
0/30 = 0
1/30 = 0.03
0/28 = 0
3/26 = 0.12
1/22 = 0.05
1/21 = 0.05
0/19 = 0
0/30 = 0
1/30 = 0.03
2/28 = 0.07
1/26 = 0.04
0/22 = 0
1/21 = 0.05
3/19 = 0.16

子分布风险


Subdistribution Hazard: In Discrete Time
Time
0
1
2
3
4
5
6
Risk Set at Time t for Event 1
Event 1
Event 2
No Event
Individuals who previously experience event 2 remain in the risk set for event 1
SDH: Event 1
0/30 = 0
1/30 = 0.03
0/29 = 0
3/29 = 0.10
1/26 = 0.04
1/25 = 0.04
0/24 = 0
CSH: Event 1
0/30 = 0
1/30 = 0.03
0/28 = 0
3/26 = 0.12
1/22 = 0.05
1/21 = 0.05
0/19 = 0

R代码：竞争风险

- 估计子分布风险
- library(cmprsk)
- 估计特定原因风险，把竞争事件当做删失
- library(survival) 或 library(riskRegression)

- 实例：干细胞移植
- 主要结局事件：死亡
- 竞争事件：复发

R代码：数据格式

- 多结局格式
- T.relapse　　D.relapse
- T.death　　D.death
- 竞争风险格式
- ftime = (T.death + T.relapse - abs(T.death - T.relapse))/2
- fstatus = D.death + 2*D.relapse
- fstatus[fstatus>2] = 2

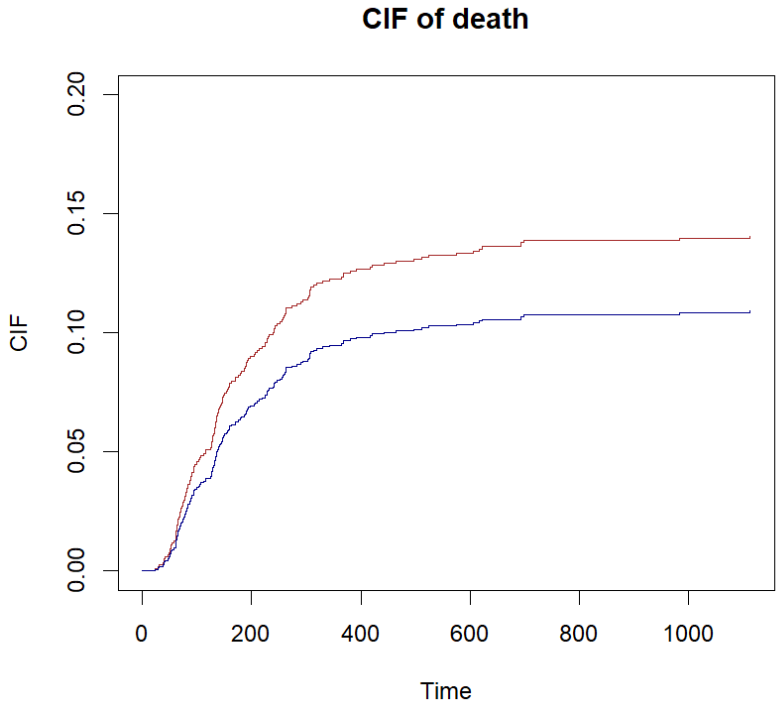
R代码：F–G模型拟合

- fit = crr(ftime, fstatus, cov1=X, failcode=1, cencode=0)
- summary(fit)

```
> summary(fit)
Competing Risks Regression

Call:
crr(ftime = ftime, fstatus = fstatus, cov1 = X, failcode = 1,
    cencode = 0)

       coef exp(coef) se(coef)      z p-value
SEX -0.0969     0.908    0.162 -0.597   0.550
CR  -0.3658     0.694    0.218 -1.675   0.094
MRD -0.3682     0.692    0.196 -1.874   0.061
ALL -0.0333     0.967    0.196 -0.169   0.870

    exp(coef) exp(-coef)  2.5% 97.5%
SEX     0.908       1.10 0.660  1.25
CR      0.694       1.44 0.452  1.06
MRD     0.692       1.45 0.471  1.02
ALL     0.967       1.03 0.658  1.42

Num. cases = 1161
Pseudo Log-likelihood = -1149
Pseudo likelihood ratio test = 6.06  on 4 df,
```

R代码：F-G模型预测

- prd = predict(fit,X[1:2,])
- plot(prd, col=c('brown','darkblue'), lty=c(1,1), ylim=c(0,0.2), ylab='CIF', xlab='Time', main='CIF of death')



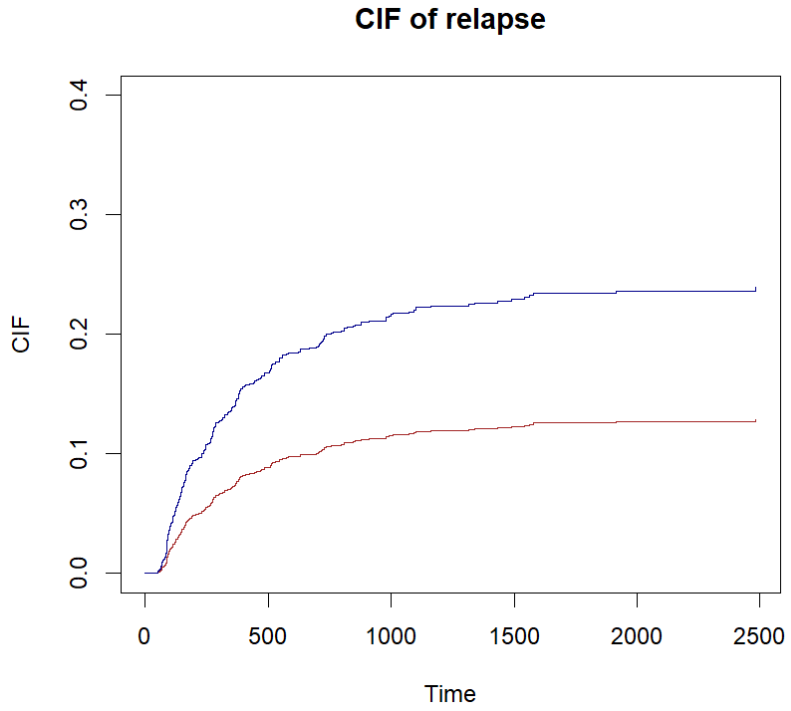
R代码：F–G模型拟合

- fit = crr(ftime, fstatus, cov1=X, failcode=2, cencode=0)
- summary(fit)

```
> summary(fit)
Competing Risks Regression

Call:
crr(ftime = ftime, fstatus = fstatus, cov1 = X, failcode = 2,
    cencode = 0)

      coef exp(coef) se(coef)     z p-value
SEX  0.223     1.250    0.141  1.59 1.1e-01
CR  -0.745     0.475    0.169 -4.41 1.0e-05
MRD  0.910     2.483    0.138  6.59 4.4e-11
ALL -0.653     0.521    0.150 -4.36 1.3e-05

    exp(coef) exp(-coef)  2.5% 97.5%
SEX     1.250      0.800 0.949 1.647
CR      0.475      2.107 0.341 0.661
MRD     2.483      0.403 1.895 3.255
ALL     0.521      1.921 0.388 0.698

Num. cases = 1161
Pseudo Log-likelihood = -1539
Pseudo likelihood ratio test = 82.2  on 4 df,
```

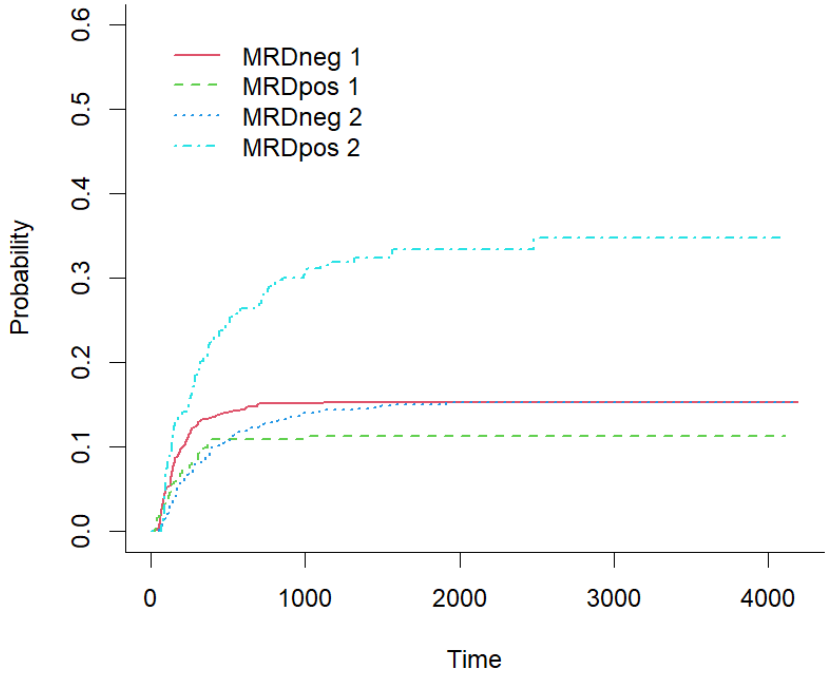
R代码：F-G模型预测

- prd = predict(fit, X[1:2,])
- plot(prd, col=c('brown','darkblue'), lty=c(1,1), ylim=c(0,0.2), ylab='CIF', xlab='Time', main='CIF of relapse')



R代码：G模型拟合

- MRD = factor(dat$MRD, 0:1, c('MRDneg', 'MRDpos'))
- fit = cuminc(ftime, fstatus, group=MRD)
- plot(fit, ylim=c(0,0.6), col=2:5, lwd=rep(1.5,4), xlab='Time')



R代码：G模型检验

- fit = cuminc(ftime, fstatus, group=MRD)

```
> fit
Tests:
       stat           pv df
1  2.948029 8.598237e-02  1
2 48.250581 3.750888e-12  1
Estimates and Variances:
$est
              1000      2000      3000      4000
MRDneg 1 0.1515152 0.1528152 0.1528152 0.1528152
MRDpos 1 0.1124912 0.1124912 0.1124912 0.1124912
MRDneg 2 0.1399757 0.1525951 0.1525951 0.1525951
MRDpos 2 0.3076018 0.3341931 0.3480260 0.3480260

$var
                 1000         2000         3000         4000
MRDneg 1 0.0001500254 0.0001512566 0.0001512566 0.0001512566
MRDpos 1 0.0003318142 0.0003318142 0.0003318142 0.0003318142
MRDneg 2 0.0001406322 0.0001569549 0.0001569549 0.0001569549
MRDpos 2 0.0007084065 0.0007716605 0.0009311776 0.0009311776

> fit$Tests
       stat           pv df
1  2.948029 8.598237e-02  1
2 48.250581 3.750888e-12  1
```

R代码：特定原因风险拟合

- fit1 = survfit(Surv(ftime, fstatus==1) ~ 1, subset = (dat$MRD==1))
- fit2 = survfit(Surv(ftime, fstatus==2) ~ 1, subset = (dat$MRD==1))
- cumhaz1 = fit1$cumhaz
- cumhaz2 = fit2$cumhaz
- time = fit1$time
- cif1 = cumsum(exp(-cumhaz1-cumhaz2) * diff(c(0, cumhaz1)))
- plot(time, cif1, type='s', ylim=c(0,0.4), xlab='Time', ylab='CIF', main='CIF of death')

R代码：特定原因风险拟合

- library(riskRegression)
- m.event = CSC(Hist(ftime, fstatus) ~ A + cov1, data)
- m.censor = coxph(Surv(ftime, fstatus==0) ~ A + cov1, x = TRUE, y = TRUE, data)
- m.treatment = glm(A ~ cov1, data, family = binomial(link="logit"))
- m.ate <- ate(event = m.event,
  treatment = m.treatment,
  censor = m.censor,
  estimator = c(“GFORMULA”,“IPTW”,“AIPTW”),
  data, times = seq(100,2000,100),
  cause = 1, se = TRUE, band = TRUE)

R代码：因果作用

- summary(m.ate)
- 比较不同的估计方法：g−formula、逆概率加权、增广逆概率加权(双稳健)
- 累计发生率
- print(setkeyv(as.data.table(ateRobust, type = "meanRisk"), "time"))
- 因果作用定义为累计发生率的差异
- print(setkeyv(as.data.table(ateRobust, type = "diffRisk"), "time"))

R代码：因果作用

```
> summary(ateRobust)
     Average treatment effect for cause 1

 - Treatment            : A (2 levels: "0" "1")
 - Event                : fstatus (cause: 1, competing risk(s): 2, censoring: 0)
 - Time  [min;max]      : ftime [24;4190]
 - Eval. time             :   100   200   300   400   500   600   700   800   900  1000
              <char> <char> <int> <int> <int> <int> <int> <int> <int> <int> <int> <int>
      number at risk    0     231   213   200   186   180   177   174   172   169   163
      number at risk    1     839   748   701   672   661   645   637   626   621   577
  1100  1200  1300  1400  1500  1600  1700  1800  1900  2000
 <int> <int> <int> <int> <int> <int> <int> <int> <int> <int>
   157   145   139   133   123   114   106   100    92    87
   537   500   465   434   408   377   336   310   291   269

 Estimation procedure
 - Estimators : G-formula Inverse probability of treatment weighting Augmented estimator
 - Uncertainty: Gaussian approximation
                where the variance is estimated via the influence function

 Testing procedure
 - Null hypothesis     : given two treatments (A,B) and a specific timepoint, equal risks
 - Confidence level    : 0.95

 Results:
 - Difference in standardized risk (B-A) between time zero and 'time'
                reported on the scale [-1;1] (difference between two probabilities)
 (difference in average risks when treating all subjects with the experimental treatment (B),
                              vs. treating all subjects with the reference treatment (A))
```

R代码：因果作用

```
> ateRobust
     Average treatment effect for cause 1

 - Treatment            : A (2 levels: "0" "1")
 - Event                : fstatus (cause: 1, competing risk(s): 2, censoring: 0)
 - Time  [min;max]      : ftime [24;4190]
 - Eval. time             :   100   200   300   400   500   600   700   800
              <char> <char> <int> <int> <int> <int> <int> <int> <int> <int>
     number at risk    0     231   213   200   186   180   177   174   172
     number at risk    1     839   748   701   672   661   645   637   626
  900  1000  1100  1200  1300  1400  1500  1600  1700  1800  1900  2000
<int> <int> <int> <int> <int> <int> <int> <int> <int> <int> <int> <int>
  169   163   157   145   139   133   123   114   106   100    92    87
  621   577   537   500   465   434   408   377   336   310   291   269

 Estimation procedure
 - Estimators : G-formula Inverse probability of treatment weighting Augmented estimator
 - Uncertainty: Gaussian approximation
                where the variance is estimated via the influence function

 Results
 - Standardized risks   :    [min;max]
    A=A    A=B      risk.A      risk.B difference (B-A) ratio (B/A)
<char> <char>      <char>      <char>           <char>      <char>
     0      1 [0.02;0.11] [0.05;0.15]      [0.01;0.05] [1.38;3.60]

 - Computation time     : 1.430272 secs (point estimate)
                          21.64798 secs (iid)
```

R代码：因果作用

- 比较不同的估计方法：g-formula、逆概率加权、增广逆概率加权(双稳健)

```
> print(setkeyv(as.data.table(ateRobust, type = "diffRisk"),"time"))
Key: <time>
        type estimator  time  level   estimate          se         lower      upper      p.value
      <char>    <char> <num> <char>      <num>       <num>         <num>      <num>        <num>
 1: diffRisk  GFORMULA   100    0.1 0.01357444 0.008148867 -0.0023970451 0.02954593 0.0957518380
 2: diffRisk      IPTW   100    0.1 0.03948960 0.010631483  0.0186522753 0.06032692 0.0002036850
 3: diffRisk     AIPTW   100    0.1 0.03941843 0.010638164  0.0185680154 0.06026885 0.0002110746
 4: diffRisk  GFORMULA   200    0.1 0.02703292 0.015250630 -0.0028577693 0.05692360 0.0762988226
 5: diffRisk      IPTW   200    0.1 0.05284810 0.017239501  0.0190592948 0.08663690 0.0021728929
 6: diffRisk     AIPTW   200    0.1 0.05279826 0.017229995  0.0190280877 0.08656843 0.0021816374
 7: diffRisk  GFORMULA   300    0.1 0.03439389 0.018829917 -0.0025120699 0.07129985 0.0677666231
 8: diffRisk      IPTW   300    0.1 0.04868465 0.020166527  0.0091589805 0.08821031 0.0157727708
 9: diffRisk     AIPTW   300    0.1 0.04867039 0.020128596  0.0092190669 0.08812172 0.0156072600
10: diffRisk  GFORMULA   400    0.1 0.03839505 0.020637264 -0.0020532496 0.07884334 0.0628188256
11: diffRisk      IPTW   400    0.1 0.03962159 0.021915259 -0.0033315268 0.08257471 0.0706149995
12: diffRisk     AIPTW   400    0.1 0.03963305 0.021863709 -0.0032190335 0.08248513 0.0698731400
13: diffRisk  GFORMULA   500    0.1 0.03975472 0.021258943 -0.0019120401 0.08142149 0.0614805576
14: diffRisk      IPTW   500    0.1 0.03994268 0.022254958 -0.0036762408 0.08356159 0.0726893187
15: diffRisk     AIPTW   500    0.1 0.03996389 0.022200369 -0.0035480370 0.08347581 0.0718377213
```

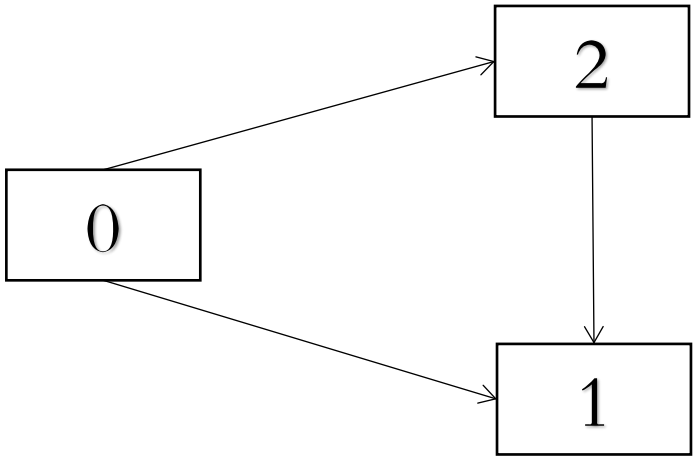
半竞争风险

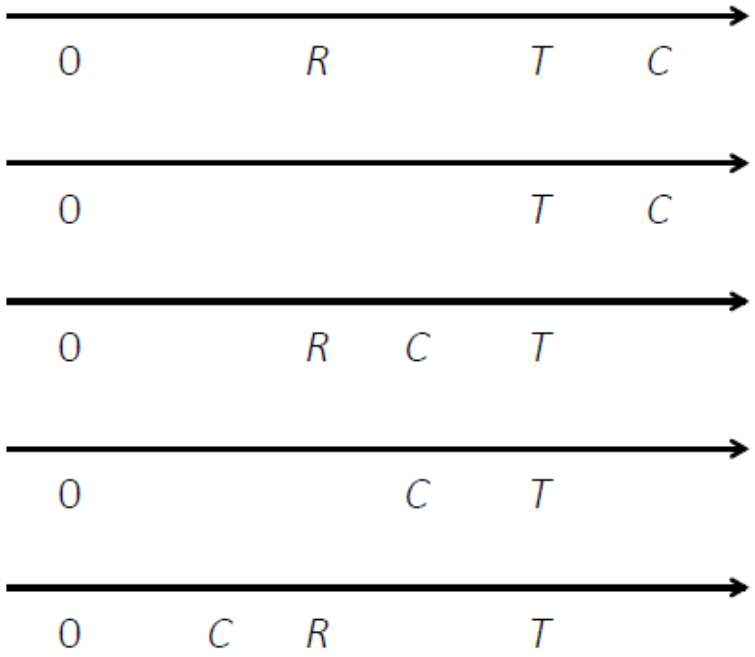
- 中间事件可以被最终事件截断，但最终事件不会被中间事件截断
- 记最终事件发生时间为T，中间事件发生时间为R
- 如果研究对象发生中间事件，则$R < T$
- 如果研究对象不发生中间事件，可记$R = \infty$
- 设随机删失时间为C，观察到的数据为

$$\min\{T, C\},\ I\{T \le C\},\ \min\{R, T, C\},\ I\{R \le T, R \le C\}$$

半竞争风险

- 疾病-死亡(Illness-death)模型
- 最终事件：死亡
- 中间事件：心脏相关疾病





特定原因风险

- 不经历中间事件，直接发生最终事件的风险

$$d\Lambda_{01}(t) = P(t \le T < t + dt, R > t \mid T \ge t, R \ge t)$$

- 发生中间事件的风险

$$d\Lambda_{02}(t) = P(t \le R < t + dt \mid T \ge t, R \ge t)$$

- 经历中间事件，发生最终事件的风险

$$d\Lambda_{21}(t;r) = P(t \le T < t + dt \mid T \ge t, R = r)$$

马氏性和半马氏性

- 为了化简

$$d\Lambda_{21}(t;r) = P(t \le T < t + dt \mid T \ge t, R = r)$$

- 马氏性(Markov)：

$$d\Lambda_{21}(t) =: d\Lambda_{21}(t;r) = P(t \le T < t + dt \mid T \ge t, R < t)$$

- 半马氏性(Semi−Markov)：

$$d\Lambda_{21}(u) =: d\Lambda_{21}(t;r) = P(u \le T - R < u + du \mid T - R \ge u)$$

共享碎片(frailty)模型

- 不经历中间事件，直接发生最终事件的风险

$$d\Lambda_{01}(t) = \lambda_{01}(t; x, \gamma)dt$$

- 发生中间事件的风险

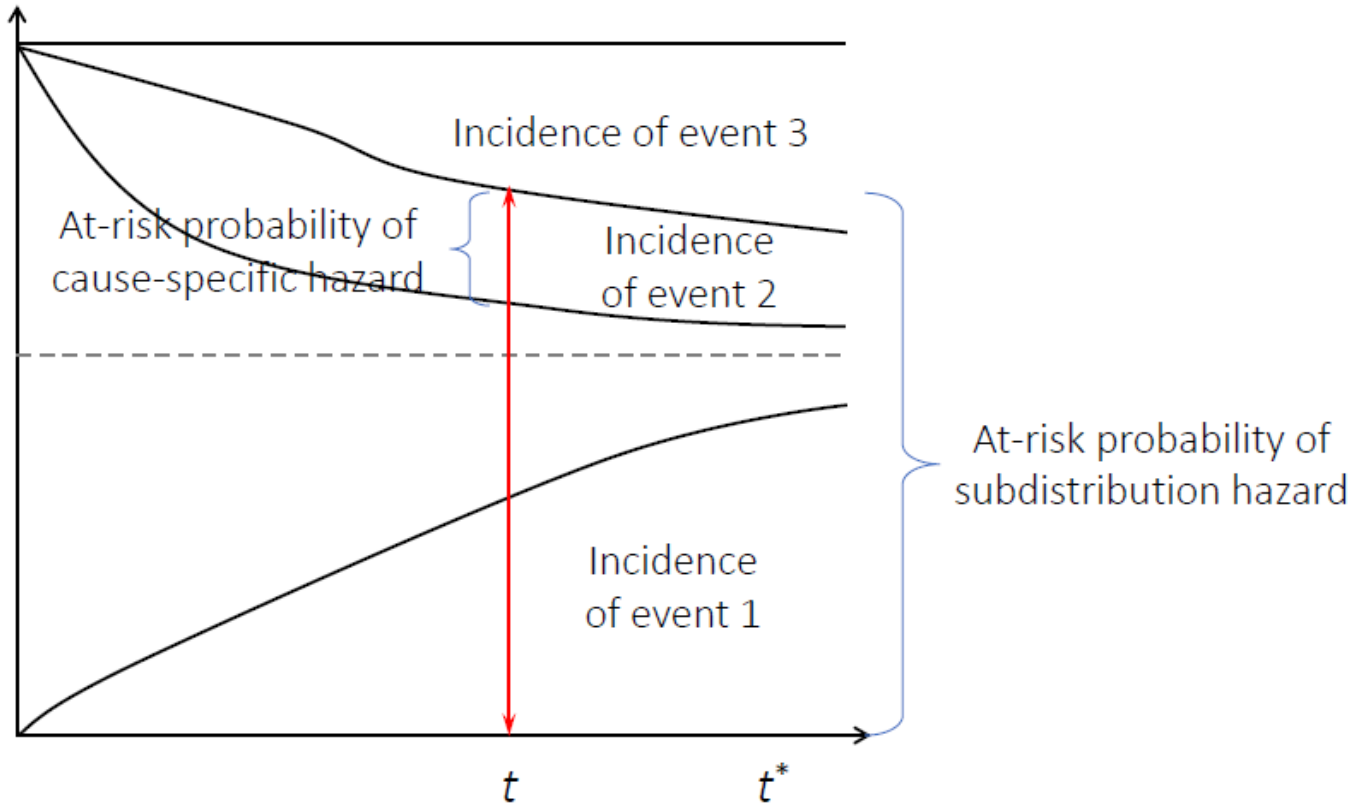
$$d\Lambda_{02}(t) = \lambda_{02}(t; x, \gamma)dt$$

- 经历中间事件，发生最终事件的风险

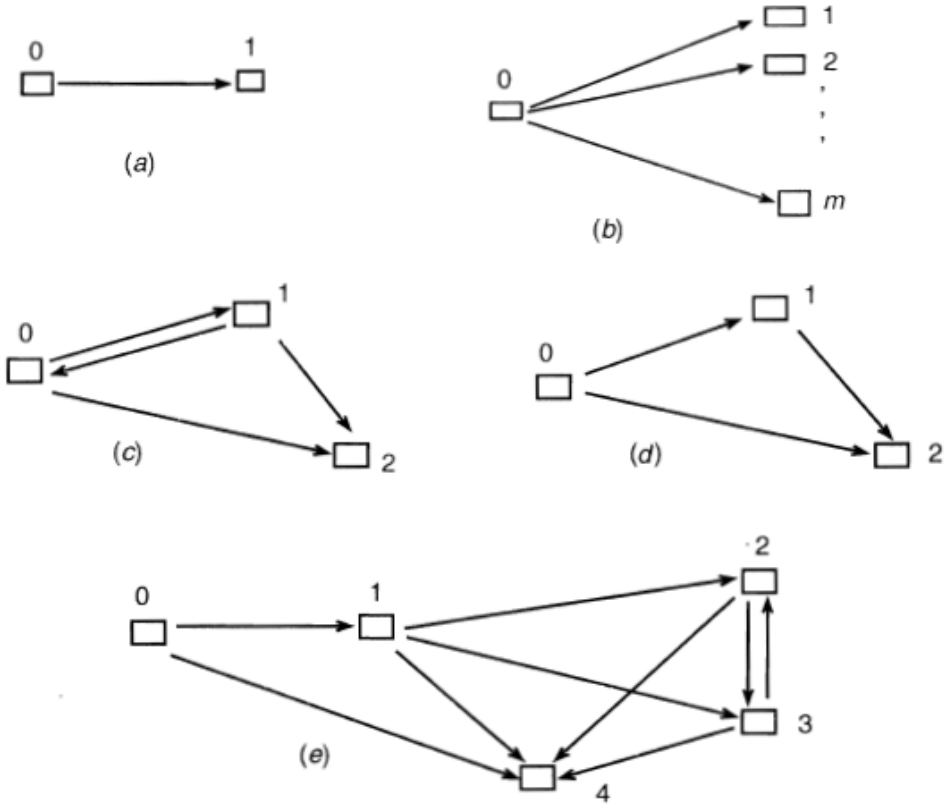
$$d\Lambda_{21}(t; r) = \lambda_{21}(t; r, x, \gamma)dt$$

- 其中x是观测到的协变量，γ是未观测到的随机变量
- 参数可通过极大似然方法估计

半竞争风险


Incidence of event 3
At-risk probability of
cause-specific hazard
Incidence
of event 2
At-risk probability of
subdistribution hazard
Incidence
of event 1
t
t*

多状态模型



多状态模型的风险函数

- 假设马氏性
- 从状态i到状态j的风险函数(转移速率)

$$d\Lambda_{ij}(t) = P(S(t) = j \mid S(u), 0 < u < t^{-}; S(t^{-}) = i)$$

$$= P(S(t) = j \mid S(t^{-}) = i)$$

- 事件集和风险集

$$dN_{ij}(t) = \#\{S(t^{-}) = i, S(t) = j\}, \quad Y_{ij}(t) = \#\{S(t^{-}) = i\}$$

- Aalen–Johansen估计量

$$d\hat{\Lambda}_{ij}(t) = \frac{dN_{ij}(t)}{Y_{ij}(t)}$$

多状态模型的因果推断

- 潜在结果框架
- 在完全随机化试验中，

$$d\Lambda^a(t) = P(t \le T < t + dt \mid A = a, T \ge t)$$

- 如果存在基线混杂，最简单的办法是用倾向得分的倒数加权
- ps = predict(glm(A ~ X, family='binomial'), type='response')
- wts = A/ps + (1-A)/(1-ps)
- fit = survfit(Surv(time, status) ~ A, weights=wts)
- 方差不再正确

多状态模型的因果推断

- 假设处理变量A是二值的
- 问题：哪条转移路径存在因果作用？

$$H_0: \quad d\Lambda_{ij}^{a=1}(t) \equiv d\Lambda_{ij}^{a=0}(t)$$

- 假设：随机化试验，任意两个状态之间不存在未观测的混杂
- 方法：对数秩检验(R的survdiff函数)
- 如果存在基线混杂，需要构造新的统计量

如何选择待估量(估计目标)

- 国际人用药品注册技术协调会ICH E9 (R1)《临床试验中的估计目标与敏感性分析》提出了五种策略
- 疗法策略 treatment policy strategy
- 组合策略 composite variable strategy
- 在治策略 while on treatment strategy
- 假想策略 hypothetical strategy
- 主层策略 principal stratum strategy

疗法策略

- 把中间事件作为治疗的一部分，与意向性治疗(intention−to−treat)密切相关

$$P(T^{a=1} < t) - P(T^{a=0} < t)$$

- 忽略中间事件，只收集最终事件数据
- 衡量了处理的总作用

组合策略

- 只要中间事件发生或最终事件发生，就认为结局发生
- 例子：无进展生存(progression−free survival)

$$P(T^{a=1} \wedge R^{a=1} < t) - P(T^{a=0} \wedge R^{a=0} < t)$$

- 更一般的，可把中间事件和最终时间的某种函数作为结局
- 例子：质量调整生存时间(quality−adjusted survival time)

在治策略

- 如果发生了中间事件，则认为最终事件不发生

$$P(T^{a=1} < t, R^{a=1} \geq T^{a=1}) - P(T^{a=0} < t, R^{a=0} \geq T^{a=0})$$

- 与竞争风险模型相对应
- 由于处理组和对照组不发生中间事件的人群可能存在系统性差异，在治策略实际上代表了直接治疗作用与经由中间事件的竞争作用之和

假想策略

- 假想一种场景，中间事件被控制，然后比较假想场景中处理组和对照组的最终事件
- 有多种假想方式，对应着不同的假设

1. 控制中间事件的流行率(prevalence)
2. 控制中间事件的瞬时风险(hazard)
3. 中间事件不发生

- 与中介分析相对应

主层策略

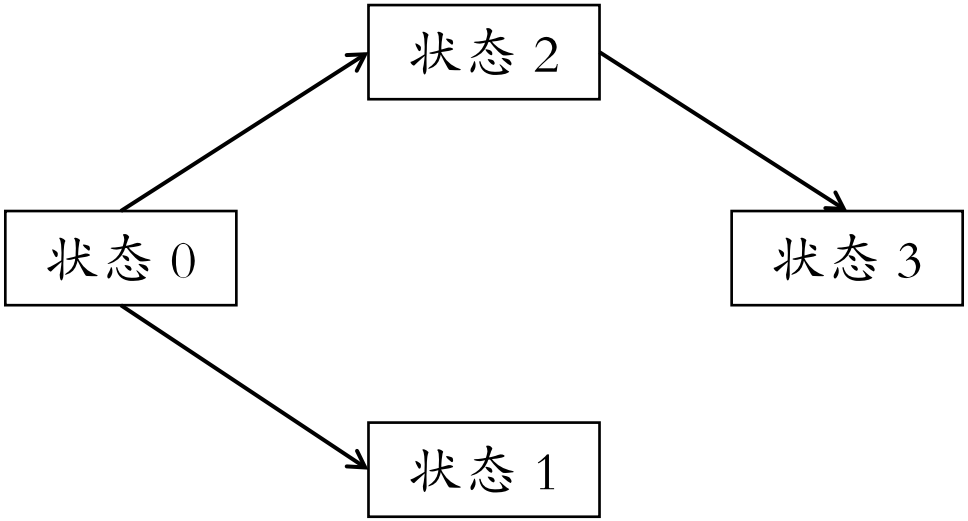
- 限制目标总体

$$P(T^{a=1} < t \mid R^{a=1} \geq T^{a=1}, R^{a=0} \geq T^{a=0})$$
$$-P(T^{a=0} < t \mid R^{a=1} \geq T^{a=1}, R^{a=0} \geq T^{a=0})$$

- 衡量了处理在子人群上的直接作用
- 目标人群不可识别
- 需要假来设识别这一估计目标，一般是主层可忽略性
- 主层策略指导临床实践有难度

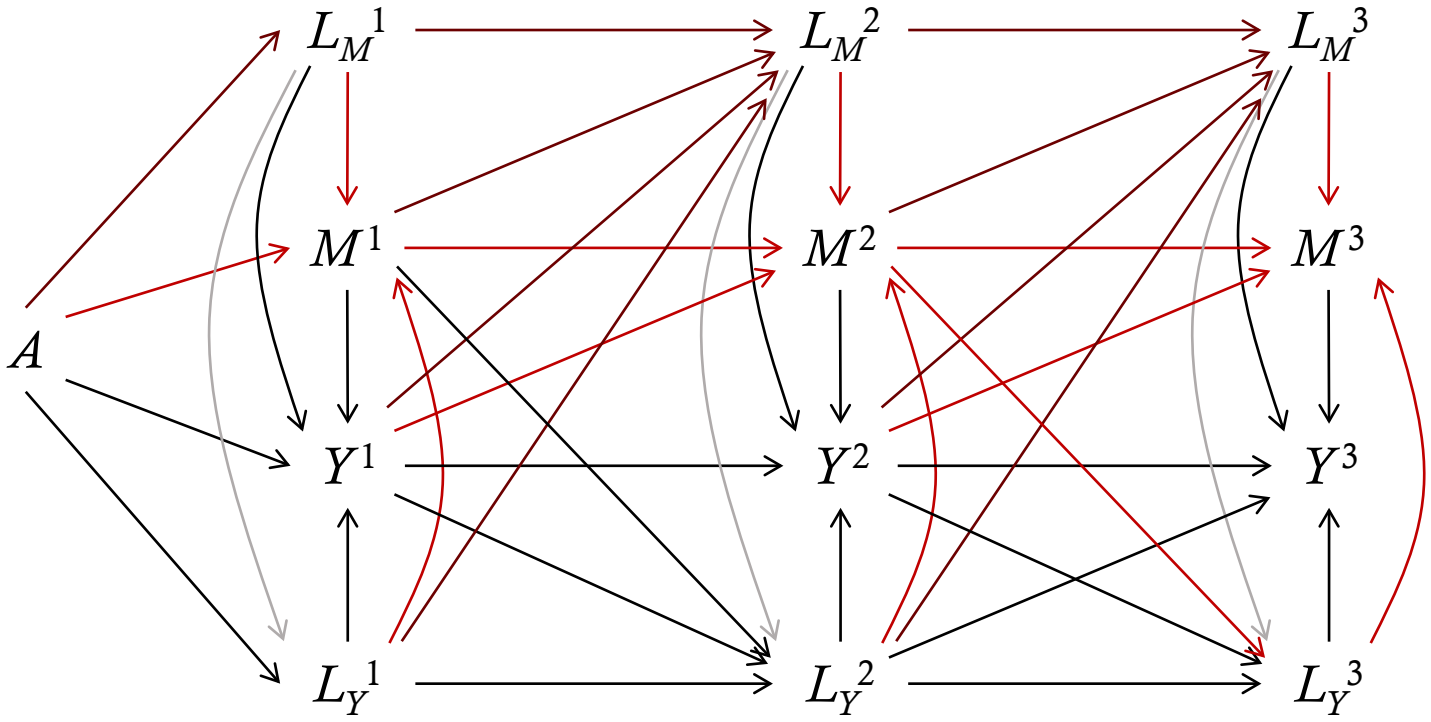
统计学角度：直接作用

- 方法1：中介分析，目标是估计出直接作用和间接作用，一般需要序贯可忽略性假设
- 方法2：主分层，考察无论是否接受处理都不会发生中间事件的人群，一般需要主层可忽略性假设



中介分析的两种框架

- 经典中介分析：序贯可忽略性(sequential ignorability)
- 是否发生j事件与是否潜在发生k事件独立



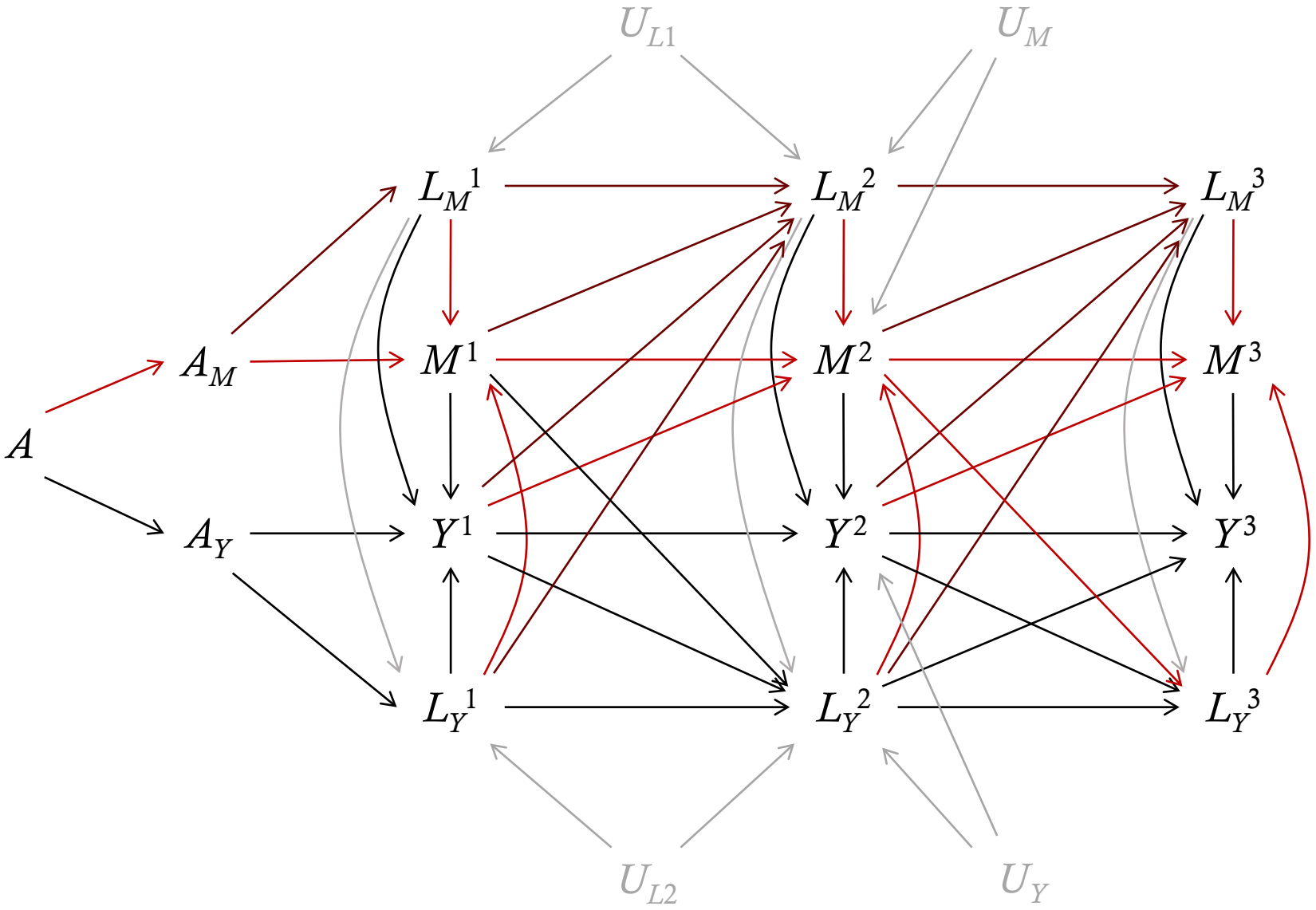
中介分析的两种框架

- 序贯可忽略性难以解释
- 可分作用(separable effects)：可分处理成分(dismissible treatment components)
- 每一个处理部分只影响一个事件的风险

$$d\Lambda_1{}^{a=(a_1,a_2)}(t) = d\Lambda_1{}^{a_1}(t)$$
$$d\Lambda_2{}^{a=(a_1,a_2)}(t) = d\Lambda_2{}^{a_2}(t)$$

- 估计目标：

$$F_j{}^{a=(a_1,a_2)}(t)$$


U_{L1}
U_M
$L_M{}^1$
$L_M{}^2$
$L_M{}^3$
A_M
M^1
M^2
M^3
A
A_Y
Y^1
Y^2
Y^3
$L_Y{}^1$
$L_Y{}^2$
$L_Y{}^3$
U_{L2}
U_Y

欢迎交流讨论！