Modeling time-varying behavioral variables in HIV prevention trials

James Y. Dai

Fred Hutchinson Cancer Research Center

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Features of HIV prevention trials

Healthy, sexually active participants

- typically placebo controlled and double blind, but some open label
- time-to-HIV acquisition endpoint, quarterly or monthly visits
- extensive sexual risk taking data and product use data, collected longitudinally
- the prevention effect depends on sexual risk taking and adherence

Secondary analysis involves adjusting for sexual risk taking and adherence

Challenges when modeling behavioral data in prevention trials

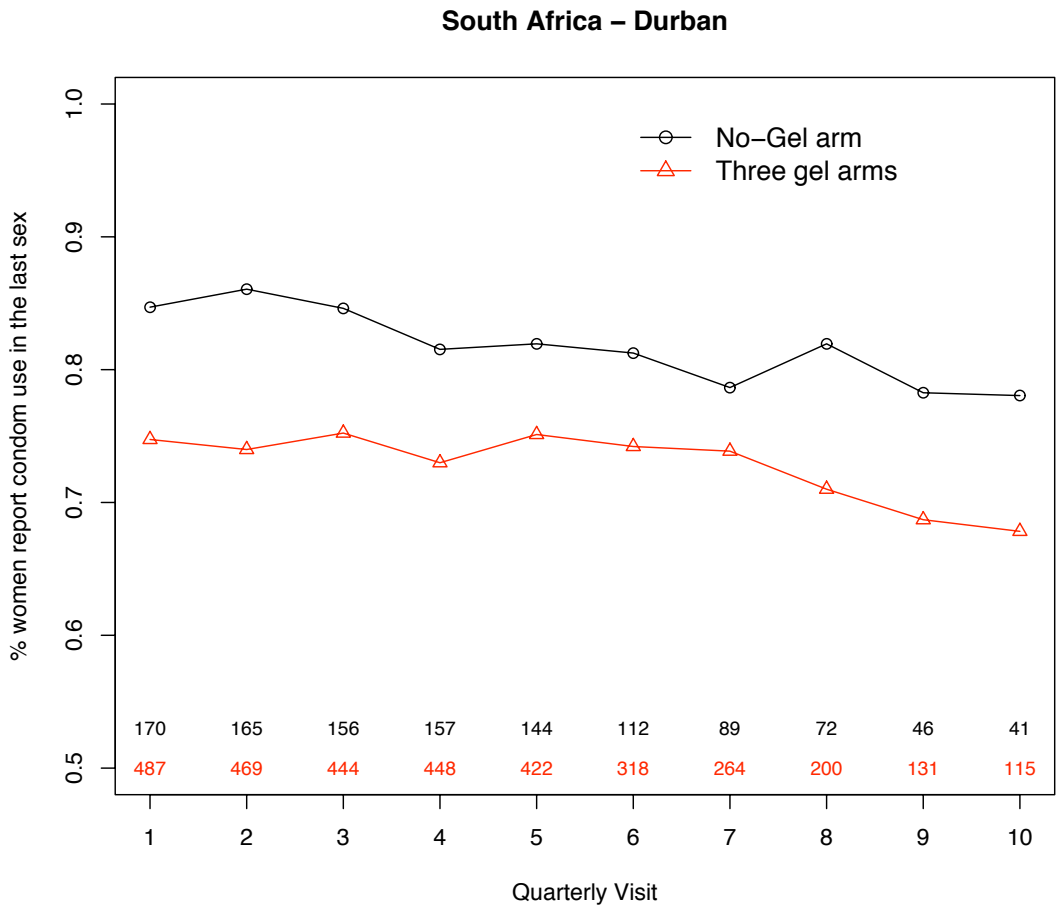
- post-randomization selection bias:
  - risk compensation/behavioral disinhibition(open label)
  - differential adherence because of adverse effect (blind trials),
- measurement error, over-report of adherence, biomarker
- longitudinal covariates with time-to-event endpoint for causal inference

HPTN 035 trial

- HPTN 035 was a multi-site phase 2B trial that tested the safety and effectiveness of two vaginal microbicide gel:
  - BufferGel: maintain normal PH
  - 0.5% PRO 2000 Gel: inhibit viral attachment and entry
  - Placebo Gel
  - No-Gel
- The motivation is to let women have self-initiated prevention method,
- topical use of gel; before sex act
- Rationale of adding the No-Gel arm; but it is unblinded

Differential condom use

- All four arms receive standard treatment: condom counseling and provision
- Differential condom-use post treatment assignment



Explanation: Risk compensation/behavioral disinhibition

- Because male partners know whether women are getting a gel or not, they could change sexual risk taking - self-reported condom use in last sex act

perceived reduction in risk $\rightarrow$ altered behavior

- Consistent use of condoms offers over 90% protection
- Treatment (gel) effect may be offset by decreased condom-use!

ITT analyses

	Hazard Ratio vs Placebo Gel (95% CI), p value	Hazard Ratio vs No Gel (95% CI), p value
PRO 2000 Gel	0.70 (0.46, 1.08), p=0.10	0.67 (0.44, 1.02), p=0.06
BufferGel	1.10 (0.75-1.62), p=0.63	1.05 (0.72-1.55), p=0.78

BufferGel	PRO 2000	Placebo	No Gel
71.8%	71.9%	71.3%	80.7%

How to adjust for differential condom-use?

Related works in modeling longitudinal post-randomization variables

- For the MIRA trial, Rosenblum et al (JRSSA 2009) estimated the direct effects of assignment to the diaphragm arm.
    - "controlled" direct effect if participants in both arms are constrained to use condoms consistently, or not use at all.
    - assume sequential ignorability that conditional on covariates, condom use can be viewed as if "randomized".
    - Inverse probability weighted estimators

Our thinking of this problem

- The ability to manipulate behavioral intermediates, such as condom use, is limited.
- The behavior of condom-use is not well understood, nor it is well predicted.
- there are subgroups in the population who does not use condom. this is precisely the reason to develop microbicide for women,

Principal Stratification at a single time point

principal stratum	U	No-Gel $X(0)$	Gel $X(1)$
Low Condom	1	0	0
Risk Gambling	2	1	0
High Condom	3	1	1

- assume a monotonicity assumption
- Risk gambling stratum drives the phenomena of risk disinhibition
- estimate the principal effect within low condom user, and the effect in high condom user.

How to model longitudinal condom use by principal stratification?

principal stratification with time-varying variables

Our approach

- The number of possible strata is 3^k, k is the number of visits.
- average condom use seems stable over time, but women could switch condom use status
- we put constrait on time-varying strata by a partially Hidden Markov Model (pHMM)

principal stratification with time-varying variables

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Related work: Lin, Ten Have and Elliott (JASA 2008)

- longitudinal adherence and longitudinal outcomes
- the large number of principal strata were collapsed into superclasses in which principal effects were defined.
- Bayesian MCMC to fit the model

Notations

for subject i in $1:n$

$$
\begin{aligned}
Z_i &\quad \text{treatment assignment 0, 1} \\
a_j &\quad \text{discrete time for visits, } j = 1, \ldots J \\
T_i &\quad \text{time to HIV infection} \\
C_i &\quad \text{time to censor} \\
Y_i &= \min(T_i, C_i) \text{observed infection-free time} \\
\Delta_i &= 1_{[T_i < C_i]} \text{Indicator of censoring} \\
X_{ij} &\quad \text{condom use in last sex act in the } j^{th} \text{ visit} \\
\overline{X}_{ij} &= \{X_{i1}, .., X_{ij}, a_j = Y_i\} \text{the observed condom-use history} \\
W_i &\quad \text{Baseline Covariates}
\end{aligned}
$$

Observed data:

$$(Z_i, Y_i, \Delta_i, \bar{X}_{ij}, W_i).$$

Principal stratification on longitudinal condom-use

latent pattern of potential condom use

$$\bar{U}_{iJ} = \begin{pmatrix} X_{i1}(0) & X_{i2}(0) & \cdots & X_{iJ}(0) \\ X_{i1}(1) & X_{i2}(1) & \cdots & X_{iJ}(1) \end{pmatrix}.$$

- Consider $\{U_{ij}, j = 1, ...J\}$ a sequence of sexual risk taking behavior under either treatment assignment

Table: At j^{th} visit

		Condom-only	Gel + Condom
principal state	U_{ij}	$X_{ij}(0)$	$X_{ij}(1)$
Low - Condom	1	0	0
Risk Gambling	2	1	0
High-Condom	3	1	1

Estimand: cumulative relative risk

Cumulative relative risk (CRR)

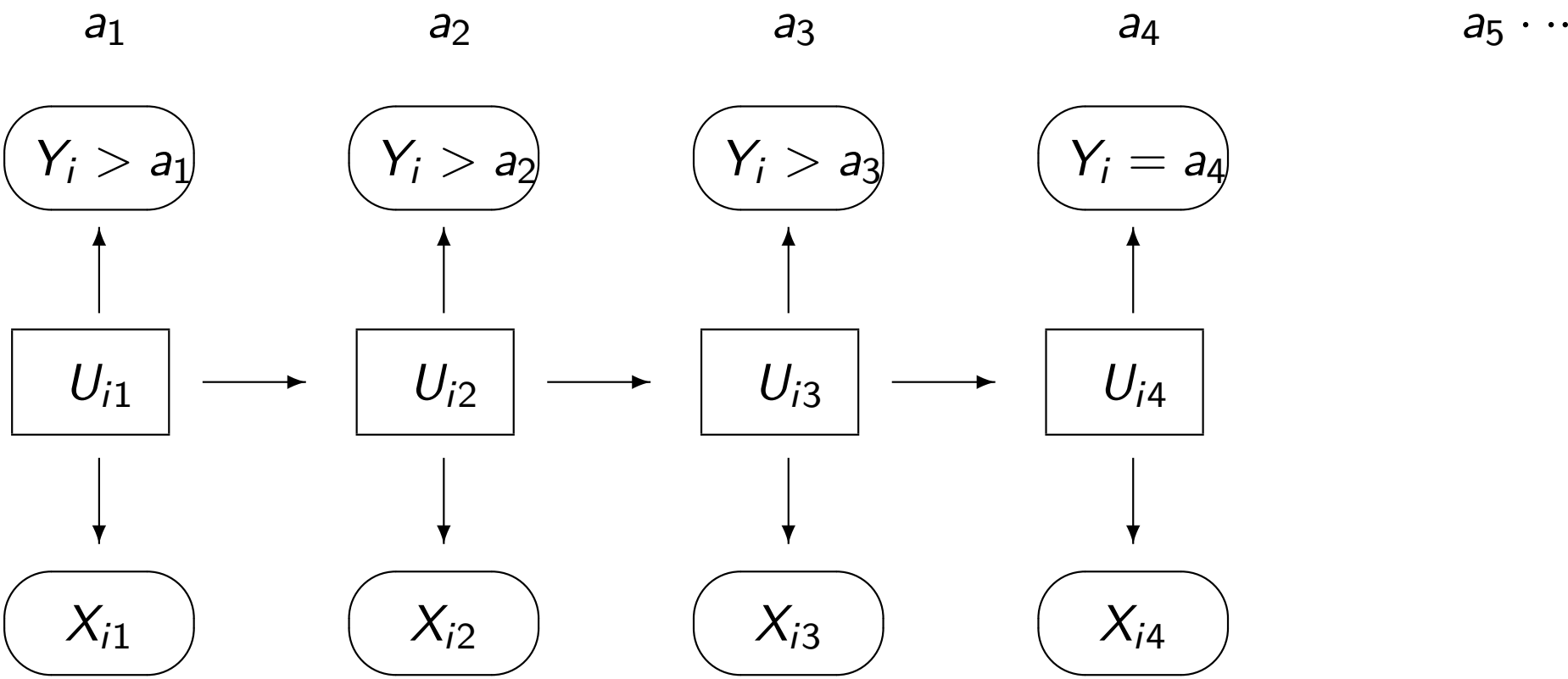
$$\text{CRR}(j)^1 = \frac{1 - \Pr(T_i(1) > a_j | \bar{U}_{ij} = 1)}{1 - \Pr(T_i(0) > a_j | \bar{U}_{ij} = 1)}$$

$$\text{CRR}(j)^3 = \frac{1 - \Pr(T_i(1) > a_j | \bar{U}_{ij} = 3)}{1 - \Pr(T_i(0) > a_j | \bar{U}_{ij} = 3)}$$

For women whose partner uses condom all the time regardless treatment assignment, how much protection she will get if she was assigned to PRO2000 arm as compared to No-Gel arm?

For women whose male partner never use condom regardless treatment assignment, how much protection she will get if she was assigned to PRO2000 arm as compared to No-Gel arm?

Hidden Markov Models



- U_{ij} is a partially observed, latent process that determines X_{ij} and at-risk probability
- The markov chain stops when HIV $+$, or censoring.

HMM assumptions

- Markov property on the partially hidden states U_{ij}

$$\begin{aligned} & \Pr(U_{ij} = s | U_{ij-1} = r, ..., U_{i1}) \\ = \; & \Pr(U_{ij} = s | U_{ij-1} = r) \\ = \; & q_{sr}, \end{aligned}$$

- Conditional independence

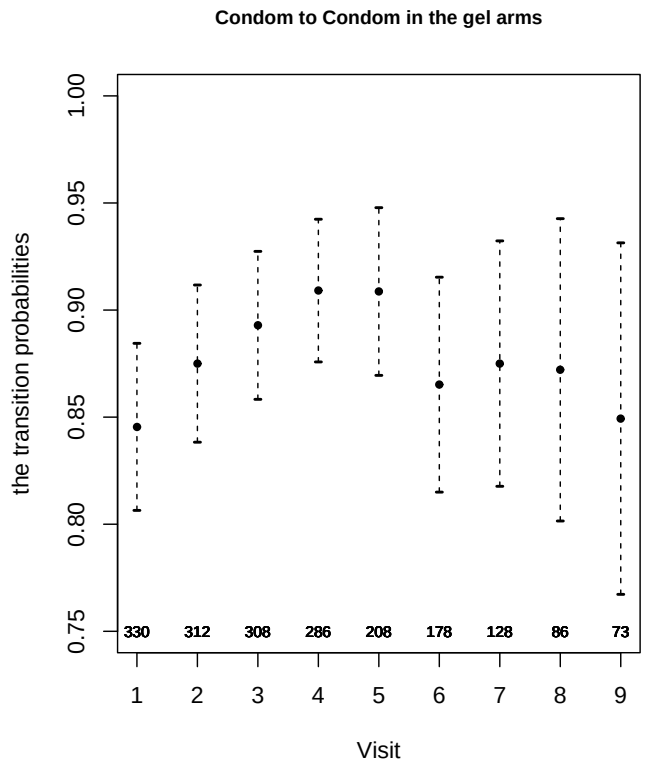
$$\begin{aligned} & \Pr(T_i(z) = a_j | T_i(z) \geq a_j, U_{ij}, U_{ij-1}, ..., U_{i1}) \\ = \; & \Pr(T_i(z) = a_j | T_i(z) \geq a_j, U_{ij}), \end{aligned}$$

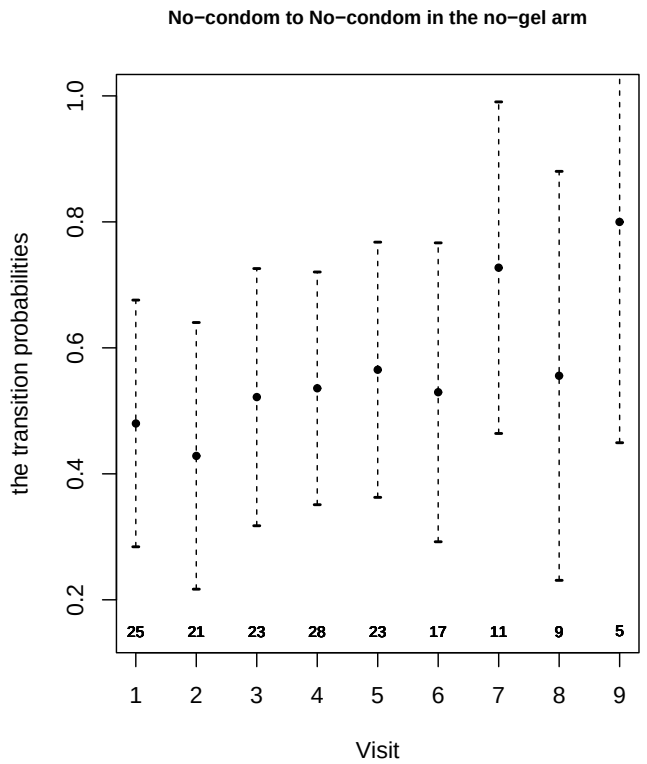
so that

$$\Pr(T_i(z) > a_j | \bar{U}_{ij}) = \prod_j [1 - \Pr(T_i(z) = a_j | T_i(z) \geq a_j, U_{ij})]$$

Checking Markov assumption

partially HMM, some states are observable!





additional standard assumptions

- randomization

$$\mathbf{Z} \perp (\bar{U}_i, T_i(0), T_i(1), C_i(0), C_i(1), Y_i(0), Y_i(1), \Delta_i(0), \Delta_i(1)) | W_i$$

- SUTVA (Stable Unit Treatment Value Assumption)

- Independent censoring

Identifiability of parameters

- denote $\mathbf{\Theta}$ the set of parameters in HMM
  p_s the initial probability for state s
  q_{st} the transition matrix
  π_{sj} the probability of HIV acquisition for s state at a_j
  β_s the treatment effect for s state

- denote the $\mathbf{\Omega}$ the set of parameters that describe the observed process X_{ij} and $Y_i|X_{ij}$

- $\mathbf{\Omega}$ is reparameterization of $\mathbf{\Theta}$, and $\mathbf{\Omega}$ is identifiable

Likelihood

$$\prod_{i=1}^{n}[f\Pr(Y_i,\Delta_i,\bar{X}_i 1_{[a_j<Y_i]}|Z_i,W_i)]^{Z_i}[(1-f)\Pr(Y_i,\Delta_i,\bar{X}_i 1_{[a_j<Y_i]}|Z_i,W_i)]^{1-Z_i}$$

$$= \prod_{i=1}^{n}[f\sum_{\bar{U}_i\in\bar{X}_i}\Pr(Y_i,\Delta_i|\bar{U}_i,Z_i,W_i)\Pr(\bar{U}_i|Z_i,W_i)]^{Z_i}$$

$$[(1-f)\sum_{\bar{U}_i\in\bar{X}_i}\Pr(Y_i,\Delta_i|\bar{U}_i,Z_i,W_i)\Pr(\bar{U}_i|Z_i,W_i)]^{1-Z_i}$$

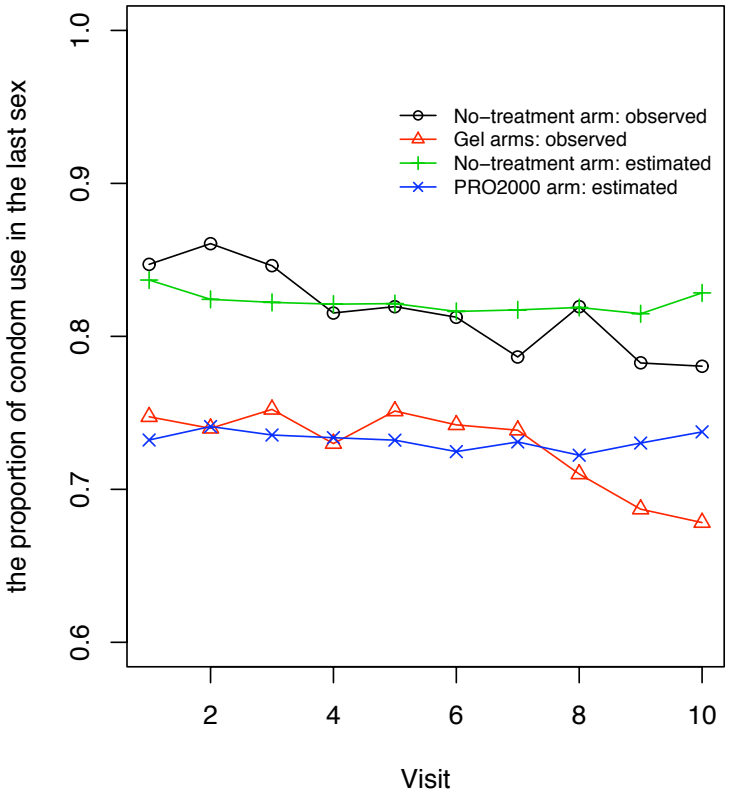
$$\propto \prod_{i=1}^{n}\left\{f\sum_{\bar{U}_i\in\bar{X}_i}[\prod_{j=1}^{J_i-1}(1-\lambda_{ij}(1))\lambda_{iJ_i}(1)]^{\Delta_i}[\prod_{j=1}^{J_i}(1-\lambda_{ij}(1))]^{1-\Delta_i}p_{U_{i1}}\prod_{j=2}^{J_i}q_{U_{ij}U_{ij-1}}\right\}^{Z_i}$$

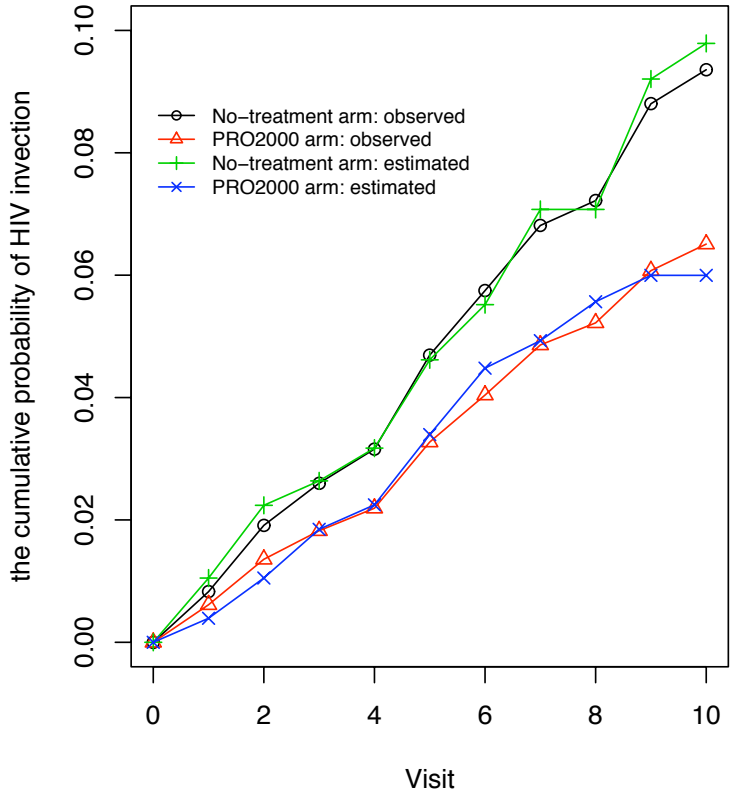
$$\times\left\{(1-f)\sum_{\bar{U}_i\in\bar{X}_i}[\prod_{j=1}^{J_i-1}(1-\lambda_{ij}(0))\lambda_{iJ_i}(0)]^{\Delta_i}[\prod_{j=1}^{J_i}(1-\lambda_{ij}(0))]^{1-\Delta_i}p_{U_{i1}}\prod_{j=2}^{J_i}q_{U_{ij}U_{ij-1}}\right\}^{1-Z_i}$$

estimation procedure

- modified Baum-Welch (backward-forward) algorithm
- baseline predictors are incorporated in both markov-state and disease risk models
- bootstrap to get the variance estimate

Model diagnostics





estimates of causal effects

The ITT effect of PRO/2000 gel assignment compared to the No-gel assignment

	Cumulative Relative Risk	
principal stratum	estimate	95% C.I.
Low - Condom	0.56	[0.16,2.04]
Risk Gambling	1.02	[0.22,4.70]
High - Condom	0.70	[0.45,1.09]

Parameters in markov chain

Baseline distribution of condom-use states

Low-Condom	Risk Gambling	High-Condom
0.15	0.16	0.70

Transition matrix of markov states

	Low-Condom	Risk Gambling	High-Condom
Low-Condom	0.532	0.270	0.198
Risk Gambling	0.282	0.003	0.715
High-Condom	0.084	0.090	0.826

Summary

- We proposed a principal stratification approach to adjust for time-varying post-treatment behavior.
- Using HMM models, we exploits the pattern of behavioral risk taking, and the transient nature of prevention effect.
- limitation: condom-use is self reported.
- could be extended to deal with longitudinal compliance

Aknowledgement

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