## I. Dynamic Treatment Regimes in Public Health

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<td>9:00-9:05 am</td>
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| 9:05-9:35 am  | Estimation of Survival Distributions for Treatment Regimes in Two Stage Oncology Trials  
Marie Davidian, NC State University |
| 9:35-9:40 am  | Discussion                                                                         |
| 9:40-10:25 am | Estimating Mean Response as a Function of Treatment Duration in an Observational Study  
Anastasios A. (Butch) Tsiatis, NC State University |
| 10:25-10:30 am| Discussion                                                                         |
| 10:30-10:45 am| Break                                                                              |
| 10:45-11:45 am| SMART Designs for Developing Dynamic Treatment Regimes  
Susan A. Murphy, University of Michigan |
| 11:45-noon    | Discussion                                                                         |
I. Dynamic Treatment Regimes in Public Health

Objectives of this session:

- Introduce the notion of a *dynamic treatment regime* (or *adaptive treatment strategy*) through two case studies (*Marie*, *Butch*)

- Describe methods for making inference about particular dynamic treatment regimes from *randomized studies* and from *observational data* (*Marie*, *Butch*)

- Describe a general framework for thinking about and *designing* dynamic treatment regimes and in particular for identifying the “*best*” dynamic treatment regime (*Susan*)
Dynamic treatment regime:

- “Individually-tailored” sequence of treatment steps
- The next step of treatment is determined according to subject outcomes and information up to that point
- Consistent with clinical practice
I. Dynamic Treatment Regimes in Public Health

Dynamic treatment regime:

- “Individually-tailored” *sequence* of treatment steps
- The *next step* of treatment is determined according to *subject outcomes and information* up to that point
- Consistent with *clinical practice*

Issues:

- What are the *options* at each step?
- What *information* should be used to select an option at each step?
- What should be the *timing* of the steps?
- What is the “*best*” sequence of treatment steps?
- From what kinds of *studies* can we learn about all of this?
Estimation of Survival Distributions for Treatment Regimes in Two Stage Oncology Trials

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(Joint work with A.A. Tsiatis, J. Lunceford, A. Wahed)
1. Dynamic treatment regimes for cancer
2. Randomized oncology trials to compare dynamic regimes
3. Case study: CALGB 8923
4. Analysis
5. Wrinkles
6. Discussion
7. Demonstration using potential outcomes
8. References
1. Dynamic treatment regimes for cancer

Goals of cancer therapy:

- *Induce* remission of disease, usually using powerful chemotherapeutic agents

- *Maintain* remission as long as possible before relapse/recurrence, e.g., by administering additional agents that intensify or augment the effects of the initial induction therapy
1. Dynamic treatment regimes for cancer

A particular dynamic treatment regime: For a given patient

- **Step 1**: Treat with one or more courses of first-line *induction* chemotherapy $A$
- **Intermediate outcome**: Observe whether “*response*” occurs
- **Step 2**: If “*response*” occurs, give *maintenance* therapy $B$ ... 
  - ...else, if “*response*” does not occur (so $A$ *did not induce* a response), do something else, e.g., try a *second-line* therapy $B'$
- **Response** typically defined as complete or partial remission, tumor shrinkage, etc.

Primary outcome of interest: E.g., in cancer, *disease-free survival time*
**Schematically:** The specific regime “Give first-line induction therapy $A$ followed by maintenance $B$ if response else give second-line therapy $B’$”

- **Step 1**
  - (Primary Trt) $A$
  - (Intermediate Outcome) Response

- **Step 2**
  - (Secondary Trt) $B'$
1. Dynamic treatment regimes for cancer

**Options:** There may be *more than one* possible regime

- More than one possible *first-line induction* treatment (*Step 1*), e.g., two options $A_1$ and $A_2$

- More than one possible *maintenance* treatment if response occurs (*Step 2*), e.g., two options $B_1$ and $B_2$

- More than one possible *second-line induction* treatment if no response occurs (*Step 2*), e.g., two options $B'_1$ and $B'_2$
1. Dynamic treatment regimes for cancer

Eight possible regimes or strategies:

1. $A_1$ followed by $B_1$ if response, else $B'_1$
2. $A_1$ followed by $B_1$ if response, else $B'_2$
3. $A_1$ followed by $B_2$ if response, else $B'_1$
4. $A_1$ followed by $B_2$ if response, else $B'_2$
5. $A_2$ followed by $B_1$ if response, else $B'_1$
6. $A_2$ followed by $B_2$ if response, else $B'_2$
7. $A_2$ followed by $B_1$ if response, else $B'_1$
8. $A_2$ followed by $B_2$ if response, else $B'_2$

**Question:** How do these eight regimes compare on the basis of disease-free survival time?
2. Randomized trials for dynamic regimes

Possible ways to compare:

- An *eight-arm* randomized trial?
- Combine information from a *series* of trials?
- *Something else*?
2. Randomized trials for dynamic regimes

“SMART” Trial: Sequential Multiple Assignment Randomized Trial (Randomization at ●s)
2. Randomized trials for dynamic regimes

**In red:** Regime “$A_1$ followed by $B_1$ if response else $B'_1$”
2. Randomized trials for dynamic regimes

**SMART Trials**: Susan will lay out a rationale and framework for this kind of trial for *designing* and *comparing* dynamic treatment regimes!

- As long as the *number of options* at each “*decision node*” is the same with same probabilities, analysis is *straightforward*

- “*Balanced*”

**It turns out**: A certain kind of “*not quite as SMART*” trial is common in oncology . . .

- Analysis is a little more fancy . . .
3. Case study: CALGB 8923

Cancer and Leukemia Group B (CALGB) Protocol 8923: A trial with two randomizations, conducted in early 1990s

Background: Acute myelogenous leukemia (AML)

- At the time, standard induction chemotherapy (daunorubicin + cytarabine)

- Standard chemotherapy $\Rightarrow$ myelosuppression $\Rightarrow$ increased risk of death due to infection or bleeding

- Add to standard chemotherapy + granulocyte-macrophage colony-stimulating factor (GM-CSF) to reduce risk of these complications (but could possibly worsen leukemia...)

- Standard chemotherapy might be followed by “intensification treatment” if there is a response
3. Case study: CALGB 8923

As before:

- **Step 1** options: $A_1 =$ Standard chemotherapy, $A_2 =$ Standard chemotherapy + GM-CSF

- *If response*, **Step 2** options: $B_1, B_2 =$ “intensification” treatments I and II
3. Case study: CALGB 8923

Common oncology trial design: “Two stage randomization”

- After enrollment, randomize all subjects to induction therapies, e.g., $A_1$ or $A_2$ (“stage 1 randomization”)
- Observe intermediate outcome, e.g., “response”
- Randomize responding subjects to maintenance therapies, e.g., $B_1$ or $B_2$ (“stage 2 randomization”)
- Subjects not responding follow up with their physicians (no “stage 2” randomization; only option)
- Continue to monitor all subjects for the outcome of interest, survival time
- Sometimes: The nonresponders are randomized at stage 2, responders are not
3. Case study: CALGB 8923

Four possible regimes:

1. $A_1$ followed by $B_1$ if response else follow up = $A_1B_1$
2. $A_1$ followed by $B_2$ if response else follow up = $A_1B_2$
3. $A_2$ followed by $B_1$ if response else follow up = $A_2B_1$
4. $A_2$ followed by $B_2$ if response else follow up = $A_2B_2$

Question: How do these four regimes compare on the basis of disease-free survival time?

- E.g., mean disease-free survival time, proportion surviving without disease after 1 year, etc.
- Which regime to recommend?
3. Case study: CALGB 8923

CALGB 8923:

- Double-blind, placebo-controlled, two stage randomization trial
- \( A_1 = \) standard chemotherapy + placebo \( A_2 = \) standard chemotherapy + GM-CSF
- 338 elderly (> 60 years old) patients with AML
- “Response” = complete remission
- \( B_1, B_2 = \) intensification treatments I and II
- Goal: Compare the four regimes on the basis of disease-free survival
3. Case study: CALGB 8923

Schematic of CALGB 8923: Randomization at ●s
2. Randomized trials for dynamic regimes

Regime $A_1B_1$:
4. Analysis

Standard analysis:

- Compare *response rates* to $A_1$ and $A_2$
- Compare *survival* between $B_1$ and $B_2$ among *responders*
- Compare *survival* between $A_1$ and $A_2$, regardless of subsequent response/randomization

Issues:

- Does not address *directly* the question of interest
- An induction therapy ($A$) may yield *higher proportion of responders* but also have other effects that render subsequent intensification treatments ($B$) *less effective*
- “*Delayed effects*” (Susan)
4. Analysis

Question of interest: For each regime $A_j B_k$, $j = 1, 2$, $k = 1, 2$

- *Estimate* the mean disease-free survival time under regime $A_j B_k$
- I.e., estimate mean disease-free survival if the entire AML population were to follow regime $A_j B_k$
- “Following” $A_j B_k$ means give $A_j$ initially followed by $B_k$ if response else follow up

How to estimate this quantity from the data in the trial?
4. Analysis

**Basic idea:** To *estimate the mean* for $A_j B_k$, use data from all subjects whose *actual experience* is *consistent with* having followed $A_j B_k$

- **Assume** that whether response occurs depends only on $A$
- All subjects receiving $A_j$ who *respond* and then are randomized to $B_k$ are *consistent with* $A_j B_k$
- All subjects receiving $A_j$ who *do not respond* and hence are not randomized at stage 2 are *also consistent with* $A_j B_k$
- **Key:** Must *combine* survival times from these subjects in an *appropriate way* . . .

**An appropriate way:** This is an “*unbalanced*” SMART trial

- $\Rightarrow$ A *weighted average* of survival times
- Consider this *heuristically* . . .
4. Analysis

Consider $A_1$ only ($A_2$ analogous): Ideally, suppose everyone were randomized to $A_1B_1$

- Nonresponders to $A_1$ $\Rightarrow$ follow up
- Responders $\Rightarrow$ all get $B_1$
- Natural estimator: Sample average of all survival times (unweighted)

In the trial: Suppose responders are randomized to $B_1$ or $B_2$ with probability $1/2$

- Nonresponders to $A_1$ $\Rightarrow$ follow up (same as before)
- Half of responders get $B_1$, half get $B_2$
- The half who get $B_2$ have missing survival times as far as $A_1B_1$ is concerned
4. Analysis

Result: To estimate mean for $A_1B_1$ from the trial

- The \textit{nonresponders} represent themselves either way $\Rightarrow$ weight = 1
- Each \textit{responder} represents him/herself and another similar subject who got randomized to $B_2$ $\Rightarrow$ weight = 2
- Usual “\textit{inverse probability weighting}” for missing data
- To estimate mean for $A_1B_2$, switch the roles
4. Analysis

In symbols: Let

\[ T_i = \text{survival time for subject } i, \ i = 1, \ldots, n, \]
\[ R_i = 1 \text{ if } i \text{ responds to } A_1, \ R_i = 0 \text{ if not} \]
\[ Z_i = 1 \text{ for a responder randomized to } B_1, \ Z_i = 2 \text{ for } B_2 \]
\[ P(Z_i = 1 | R_i = 1) = \pi \ (= 1/2 \text{ in previous}) \]

Estimators: \[ n^{-1} \sum_{i=1}^{n} Q_i T_i \quad \text{or} \quad \left( \sum_{i=1}^{n} Q_i \right)^{-1} \sum_{i=1}^{n} Q_i T_i, \]

\[ Q_i = 1 - R_i + R_i I(Z_i = 1) \pi^{-1} \]

- \[ Q_i = 0 \text{ if } i \text{ is inconsistent with } A_1 B_1 \text{ (i.e., is consistent with } A_1 B_2) \]
- \[ Q_i = 1 \text{ if } R_i = 0 \]
- \[ Q_i = \pi^{-1} \text{ if } R_i = 1 \text{ and } Z_i = 1 \]
- To estimate \( S(t) = P(T_i > t) \), estimate \( F(t) = 1 - S(t) \) by replacing \( T_i \) by \( I(T_i \leq t) \)
5. Wrinkles

**Survival outcome:** Subjects may *die* before having a chance to respond

- *Nonresponders* at the time of death, $R_i = 0$

**Censoring:** Survival time may be right-censored at time $C_i$

- Assume $K_1(t) = P(C_i > t \mid A_1)$
- Consider *restricted survival time*, i.e., survival up to time $L$ such that $K_1(L) > 0$
- Observe $V_i = \min(T_i, C_i)$ and $\Delta_i = I(T_i < C_i)$
- If $T_i$ is *not censored* for subject $i$, $V_i = T_i$, $i$ represents $K_1^{-1}(V_i)$ individuals, including him/herself, who *could have* been uncensored
- *Estimator* becomes

$$n^{-1} \sum_{i=1}^{n} \frac{\Delta_i Q_i}{K_1(V_i)} V_i$$
5. Wrinkles

**Consent of responders:** In CALGB 8923, some subjects who *did respond refused to be randomized* at the second stage

- In CALGB 8923, \( \sim 90\% \) consent rate among responders
- *“Intention to treat”* perspective: Consider instead *offering* \( A_j \) followed by *offering* \( B_k \) if response else follow up
- *Redefine*, e.g., “\( A_1 \) followed by \( B_k \) if response *and consent* else follow up” (so make comparisons without regard to differential rates of consent)
- So *redefine* \( R_i = 1 \) if subject \( i \) *both* responds *and consents* to further participation
- … As opposed to attempt to ask the original *causal* question, with this *noncompliance* as a nuisance (\( \Rightarrow \) *observational study*)
6. Discussion

Remarks:

- Could equally well randomize subjects up front to regimes and use these same estimators
- Fancier (in terms of efficiency) estimators are possible
- Methods for testing also possible
- If SMART trial is balanced, no need to do weighting

Looking forward to Susan:

- Dynamic treatment regimes are what is done in clinical practice
- The regimes here are simple and preconceived: two stages only, decision rule at step 2 based on the single variable “response”
- Methods to design dynamic treatment regimes are needed
7. Demonstration using potential outcomes

One way to formalize the rationale for weighting: Again consider $A_1$ regimes only ($A_2$ analogous)

- Suppose there are $n$ subjects randomized to $A_1$ and that subject $i$ has potential outcomes $T_{11i}, T_{12i}$
- $T_{1ki} = \text{survival time } i \text{ would have if } i \text{ were to follow (or be offered)} A_1B_k$, $k = 1, 2$

Question of interest: Estimate mean disease-free survival if the entire AML population were to follow regime $A_1B_k$

- Distributions of the $T_{1k}$ represent survival in the population if all subjects followed $A_1B_k$, $k = 1, 2$
- $\Rightarrow$ Want to estimate $\mu_{1k} = E(T_{1ki})$
7. Demonstration using potential outcomes

Of course: Do not observe both of $T_{11i}, T_{12i}$ for each $i$

Do observe: $(R_i, R_iZ_i, T_i), i = 1, \ldots, n$

- $R_i = 1$ if $i$ responds, $R_i = 0$ if not
- $Z_i = k$ if $i$ is randomized at stage 2 to $B_k, k = 1, 2$
  (defined only if $R_i = 1$)
- $P(Z_i = 1 | R_i = 1) = \pi =$ probability of second stage randomization to $B_1$ (after first stage randomization to $A_1$) if response

Consider $k = 1$: Want to estimate $\mu_{11} = E(T_{11i}), k = 1, 2$, based on observed data $(R_i, R_iZ_i, T_i), i = 1, \ldots, n$

- The estimators discussed (based on observed data) may be shown to be consistent for $\mu_{11}$, e.g., $n^{-1} \sum_{i=1}^{n} Q_iT_i$
7. Demonstration using potential outcomes

Want to show: \[ E(Q_i T_i) = E(T_{11i}), \quad Q_i = 1 - R_i + R_i I(Z_i = 1) \pi^{-1} \]

Assume: For subjects randomized to \( A_1 \)

- If \( R_i = 0 \), \( T_{11i} \) and \( T_{12i} \) are the same; thus

\[ T_i = (1 - R_i)T_{11i} + R_i I(Z_i = 1)T_{11i} + R_i I(Z_i = 2)T_{12i} \]

Using: \( R_i(1 - R_i) = 0, \; I(Z_i = 1)I(Z_i = 2) = 0 \), etc.

\[ E(Q_i T_i) = E[T_{11i}\{(1 - R_i) + R_i I(Z_i = 1)\pi^{-1}\}] \]
\[ = E[T_{11i} E\{(1 - R_i) + R_i I(Z_i = 1)\pi^{-1}|R_i, T_{11i}\}] \]

so want to show

\[ E\{(1 - R_i) + R_i I(Z_i = 1)\pi^{-1}|R_i, T_{11i}\} = 1 \]
7. Demonstration using potential outcomes

\[
E\{(1 - R_i) + R_i I(Z_i = 1)\pi^{-1}|R_i, T_{11i}\}
\]
\[
= E\{(1 - R_i) + R_i I(Z_i = 1)\pi^{-1}|R_i = 0, T_{11i}\} P(R_i = 0|T_{11i})
\]
\[
+ E\{(1 - R_i) + R_i I(Z_i = 1)\pi^{-1}|R_i = 1, T_{11i}\} P(R_i = 1|T_{11i})
\]
\[
= P(R_i = 0|T_{11i}) + E\{ I(Z_i = 1)|R_1 = 1, T_{11i}\} \pi^{-1} P(R_i = 1|T_{11i})
\]
\[
= P(R_i = 0|T_{11i}) + P(R_i = 1|T_{11i}) = 1
\]

**Because:** By randomization,

\[
E\{ I(Z_i = 1)|R_1 = 1, T_{11i}\} = P(Z = 1|R = 1, T_{11i}) = P(Z = 1|R = 1) = \pi
\]

⇒ randomization ensures \(i\)’s assignment to \(B_1\) does not depend on \(i\)’s prognosis

**For \(k = 2\):** Same argument, now \(Q_i = 1 - R_i + R_i I(Z_i = 2)(1 - \pi)^{-1}\)
References


These slides available at:

http://www.stat.ncsu.edu/~davidian