1. What is a dynamic treatment regime?

**Clinical practice:** Treatment of ongoing illness is itself ongoing
- Providers do not make a "once-and-for-all" decision, e.g., "take drug A no matter what happens to you, just keep taking it"
- Rather, providers routinely "adjust," change, add, or discontinue treatment based on progress, side effects, patient burden, compliance, etc.
- I.e., treatment in practice involves decisions made sequentially over time based on observation of the patient

**Dynamic treatment regime:**
- Also known as an adaptive treatment strategy
- A set of rules that dictate how to make sequential decisions on the treatments to give next based on observation of the patient up to that point
- Is termed dynamic or adaptive because treatment decisions are based on observation of the patient...
- ...in contrast to a nondynamic regime, where the sequence of treatments is decided in advance (i.e., does not adapt to the condition of the patient)

**How are these decisions typically made?**
- "Clinical judgment" based on experience
- "Practice guidelines" based on pieced-together clinical evidence and expert opinion, e.g., NIH guidelines for treatment of HIV-infection at http://www.aidsinfo.nih.gov/
- "Educated guesses"  
- The "art of medicine"

**Ideal:** Practice guidelines on how to make decisions sequentially that
- maintain flexibility to "individualize" treatment while providing "rules" that are focused on "optimizing" care
- have been developed based on principled evidence

**Dynamic treatment regime:** Ingredients
- A sequence of decision points at which decisions on treatment are made
- At each point, the next step of treatment is determined according to subject outcomes and information up to that point... 
- ...based on a decision rule that takes these variables as input and outputs the next treatment step
- Allows treatment to be "individualized" through a principled set of rules that operationalize clinical practice
1. What is a dynamic treatment regime?

**Key message of this talk:** Statisticians should be very interested in developing methods to construct and study dynamic treatment regimes!

**Very important:** Do not confuse the dynamic treatment regimes themselves with the type of study from which inference on their effects may be drawn!

- Jamie Robins has pioneered a framework on making causal inference on dynamic treatment regimes from observational data
- This does not mean they are a ‘causal inference thing’ or an ‘observational study thing’
- This does not mean one cannot conduct (randomized) studies to make (causal) statements about dynamic treatment regimes!

A concrete setting in which to think about all of this...

2. 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

**Primary outcome of interest:** E.g., in cancer, disease-free survival time

**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), try second-line therapy $B_0$
- “Response” typically defined as complete or partial remission, tumor shrinkage, etc.

**Decision rule:** The decision rule to determine the step 2 treatment takes the variable “response or not?” as input

**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 $B_0'$ and $B_0''$

**Eight possible regimes or strategies:**

1. $A_1$ followed by $B_1$ if response, else $B_0''$
2. $A_1$ followed by $B_1$ if response, else $B_0'$
3. $A_1$ followed by $B_1$ if response, else $B_0''$
4. $A_1$ followed by $B_1$ if response, else $B_0'$
5. $A_2$ followed by $B_1$ if response, else $B_0''$
6. $A_2$ followed by $B_1$ if response, else $B_0'$
7. $A_2$ followed by $B_1$ if response, else $B_0''$
8. $A_2$ followed by $B_1$ if response, else $B_0''$

**Natural question:** Which is the best regime to recommend to the population?

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

Possible ways to compare:
- An eight-arm randomized trial?
- Combine information from a series of trials?

Why not deduce this from results a series of trials?
- In one trial, \( A_1 \) is compared against \( A_2 \) in terms of response rate
- In another trial, \( B_1 \) and \( B_2 \) are compared on the basis of survival in subjects who responded to their first-line chemotherapy
- In yet another, \( B'_1 \) and \( B'_2 \) are compared (survival) in subjects for whom first-line therapy did not induce response
- Can’t we just “piece together” the results from these separate trials to figure out the best regime?
- E.g., figure out the best “\( A \)” treatment for inducing response and then the best “\( B \)” and “\( B_0 \)” treatments for prolonging survival and base the regime on those?

One problem with this: Delayed effects
- E.g., \( A_1 \) may yield higher proportion of responders than \( A_2 \) but may also have other effects that render subsequent intensification treatments (\( B \)) less effective in regard to survival
- \( \Rightarrow \) Must evaluate entire regimes

A way to do this...

“SMART”: Sequential Multiple Assignment Randomized Trial, e.g., Lavori and Dawson (2003) (Randomization at \( \ast \))

Advantage of SMART design: Results can be used to construct better dynamic treatment regimes (later...)

It turns out: A certain kind of “not quite as SMART” is common in oncology...
- ...but way these trials are analyzed does not focus on comparing the embedded dynamic treatment regimes!

An example...
3. Randomized trials for dynamic regimes

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 → myelosuppression → 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

**CALGB 8923:** Double-blind, placebo-controlled trial
- 338 elderly (> 60 years old) patients with AML
- "Response" — complete remission
- Carried out according to a common oncology trial design...

**Two stage randomization design**
- After enrollment, randomize all subjects to induction therapies, A_1 or A_2 ("stage 1 randomization")
- Observe intermediate outcome, "response"
- Randomize responding subjects to maintenance therapies, 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, disease-free survival time
- Sometimes: The nonresponders are randomized at stage 2, responders are not

**Four possible regimes:**
1. A_1 followed by B_1 if response else follow up = A_1 B_1
2. A_1 followed by B_2 if response else follow up = A_1 B_2
3. A_2 followed by B_1 if response else follow up = A_2 B_1
4. A_2 followed by B_2 if response else follow up = A_2 B_2

**Schematic of CALGB 8923: Randomization at **
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

**Problem:**
Does not address directly the question of which overall dynamic treatment regime to recommend!

- Can’t “piece this together”
- It turns out that estimating relevant quantities associated with dynamics regimes from such a trial is straightforward!

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**4. Analysis**

**Demonstration:**
For each regime $A_jB_k, j = 1, 2, k = 1, 2$
- Estimate the mean disease-free survival time under regime $A_jB_k$
- I.e., estimate mean disease-free survival if the entire AML population were to follow regime $A_jB_k$
- “Following” $A_jB_k$ means give $A_j$ initially followed by $B_k$ if response else by follow-up if no response

**How to estimate this quantity from the data in the trial?**

**Reasonable assumption:**
Whether a response occurs depends on the first step “A” treatment received but not on possible subsequent treatment

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**4. Analysis**

**Basic idea:** To estimate the mean for $A_jB_k$, use data from all subjects whose actual experience is consistent with having followed $A_jB_k$
- All subjects receiving $A_j$ who respond and then are randomized to $B_k$ are consistent with $A_jB_k$
- All subjects receiving $A_j$ who do not respond and hence are not randomized at stage 2 are also consistent with $A_jB_k$

**Key:** Must combine survival times from these subjects in an appropriate way...

**An appropriate way:** This is an unbalanced SMART design
- A weighted average of survival times
- Consider this heuristically...

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**4. Analysis**

**Consider $A_1$ only ($A_2$ analogous):** Ideally, suppose everyone in the trial followed $A_1B_1$
- Nonresponders to $A_1$ follow up
- Responders 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 $A_1$ 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

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**4. Analysis**

**Result:** To estimate mean survival for $A_1B_k$ from the trial
- The nonresponders represent themselves either way $\to$ weight $= 1$
- Each responder represents him/herself and another similar subject who got randomized to $B_k$ $\to$ weight $= 2$
- Usual “inverse probability weighting” for missing data
- To estimate mean for $A_1B_1$, switch the roles
- Note: Survival times from nonresponders would be used to estimate the means for both $A_1B_1$ and $A_1B_2$

**In symbols:** Suppose n subjects end up randomized to $A_1$

<table>
<thead>
<tr>
<th>$T_i$</th>
<th>survival time for subject $i, i = 1, \ldots, n$</th>
</tr>
</thead>
<tbody>
<tr>
<td>$R_i = 1$</td>
<td>if $i$ responds to $A_1, R_i = 0$ if not</td>
</tr>
<tr>
<td>$Z_i = 1$ for a responder randomized to $B_1$, $Z_i = 2$ for $B_2$</td>
<td></td>
</tr>
<tr>
<td>$P(Z_i = 1</td>
<td>R_i = 1) = \pi$ (= 1/2 in previous)</td>
</tr>
</tbody>
</table>

**Estimators:**

$$Q_i = \sum_{i=1}^{n} Q_i T_i$$

$$Q_i = 1 - R_i + R_i P(Z_i = 1) \pi^{-1}$$

**Note:**
- $Q_i = 0$ if $i$ is inconsistent with $A_1B_k$ (i.e., is consistent with $A_1B_2$)
- $Q_k = 1$ if $R_i = 0$
- $Q_k = \pi^{-1}$ if $R_i = 1$ and $Z_i = 1$
- To estimate $S(t) = P(T_i > t)$, estimate $F(t) = 1 - S(t)$ by replacing $T_i$ by $1(T_i \leq t)$
4. Analysis

One way to formalize: Represent in terms of potential outcomes (aka counterfactuals)

- Suppose i has potential outcomes $T_{1i1}$, $T_{1i2}$
- $T_{1i1}$ = survival time i would have if i were to follow $A_i$, $B_i$, $k = 1, 2$

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

- Distributions of the $T_{1i}$ represent survival in the population if all subjects followed $A_i B_i$, $k = 1, 2$
  - Want to estimate $\mu_{1i} = E(T_{1i1})$
  - Similarly, if interested in the survival distribution if all subjects followed $A_i B_i$, want to estimate $S(T_{1i1} > t) = E[I(T_{1i1} > t)]$

4. Analysis

Connection: For subjects randomized to $A_i$

- Assume that when $R_i = 0$, $T_{1i1}$ and $T_{1i2}$ are the same
- Then $T_i = (1 - R_i)T_{1i1} + R_i(T_i = 1)T_{1i1} + R_i I(Z_i = 2)T_{1i2}$

Want to show: $E(Q, T_i) = E(T_{1i1}, Q_i = 1 - R_i + R_i I(Z_i = 1)\epsilon^{-1}$

- Using $R_i(1 - R_i) = 0, I(Z_i - 1) = 0$, etc.
  - $E(Q, T_i) = E(T_{1i1}, (1 - R_i) + R_i I(Z_i = 1)\epsilon^{-1})$
  - $= E(T_{1i1}, (1 - R_i) + R_i I(Z_i = 1)\epsilon^{-1}|R_i, T_{1i1})$

So equivalently want to show

$$E(1 - R_i) + R_i I(Z_i = 1)\epsilon^{-1}|(R_i, T_{1i1}) = 1$$

4. Analysis

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 $K_i(t) = P(C_i > t | A_i)$
- Consider restricted survival time, i.e., survival up to time L such that $K_i(L) > 0$
- 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 $K_i^{-1}(V_i)$ individuals, including him/herself, who could have been uncensored
  - Estimator becomes $n^{-1} \sum_{i=1}^{n} \Delta_i Q_i / R_i(V_i)$

Similar consistency arguments possible

4. Analysis

Of course: Do not observe both of $T_{1i1}$, $T_{1i2}$ for each i

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

$T_i$ = survival time for subject i

- $R_i = 1$ if i responds to $A_i$, $R_i = 0$ if not
- $Z_i = k$ for a responder randomized to $B_i$, $k = 1, 2$, where
  - $P(Z_i = 1 | R_i = 1) = \pi, P(Z_i = 2 | R_i = 1) = 1 - \pi$

Consider $k = 1$: Want to estimate $\mu_{1i} = E(T_{1i1}), k = 1, 2$, based on observed data $(R_i, R_i Z_i, T_i), i = 1, \ldots, n$

- Need to make a connection between the observed data and the potential outcomes...
  - ...to show that $n^{-1} \sum_{i=1}^{n} Q_i T_i$ is a consistent estimator for $\mu_{1i}$

4. Analysis

Consent of responders: In CALGB 8923, some subjects who did not respond refused to be randomized at the second stage

- In CALGB 8923, ~90% consent rate among responders
- “Intention to treat” perspective: Consider instead offering $A_j$ followed by offering $B_j$ if response else follow up
- Redefine, e.g., “$A_j$ followed by $B_j$ if response and consent else follow up” (so compare without regard to differential consent rates)
- So redefine $R_i = 1$ if subject i both responds and consents to further participation, $R_i = 0$ if either no response or no consent

...As opposed to attempting to ask the original causal question, with this noncompliance as a nuisance (→ observational study)
4. Analysis

Remarks:
- Could equally well randomize subjects up front to regimes and use these same estimators
- Lunceford et al. (2002): Asymptotic theory, standard errors, Wald tests comparing means, survival distributions
- Extension to ≥ 2 stages, general SMART designs: Murphy (2005)
- If SMART is balanced, no need to do weighting

5. Constructing dynamic treatment regimes

A bigger question:
- The foregoing applies to studying and comparing simple regimes that are preconceived
- E.g., the decision rule at step 2 is based only on the single variable “response”
- More refined decision rules that take into account additional information in order to better “individualize” treatment?
- How to construct dynamic treatment regimes???

5. Constructing dynamic treatment regimes

Issues:
- What are the options at each step?
- What should be the timing of the steps?
- What information (variables) should be used to select an option at and/or timing for each step?
- How many such variables be summarized to create decision rules that make sense to clinicians and patients?
- What is the “best” sequence of treatment steps?
- From what kinds of studies can we learn about all of this?

5. Constructing dynamic treatment regimes

SMART designs:
- Can form the basis for comparing specific simple regimes…
- …but also have potential in constructing regimes
- Key: Randomization at each step provides a basis for identifying important “tailoring variables” at each step, i.e., variables that affect outcome differentially by treatment at that step…
- …and hence should be incorporated in the decision rule at that step
- Challenge: Methods for identifying tailoring variables must incorporate effect of future treatment decisions when evaluating present treatment decision (Murphy, Robins, Parimigiani, computer scientists, …) – need to be evaluated in real medical contexts
- Variable selection to determine tailoring variables – needs to focus on decision-making, not prediction!

5. Constructing dynamic treatment regimes

Another approach: Exploit mechanistic models

Structured Treatment Interruption (STI) for acute HIV-1 infection:
- Potent antiretroviral therapy cannot be taken continually
- Side effects, burden, cost, development of drug resistance, …
- Cycles of therapy followed by interruption
- When to interrupt? When to re-initiate? On what basis?

HIV dynamic models: Formalize hypotheses about interplay between HIV and immune system happening within a subject
5. Constructing dynamic treatment regimes

Nonlinear dynamical system: Ordinary differential equations, \( U = \frac{di}{dt} \)

\[
T_1 = \lambda_1 - d_1 T_1 - (1 - c_1 w(t)) k_1 V T_1 \\
T_2 = \lambda_2 - d_2 T_2 - (1 - f_1 w(t)) k_2 V T_2 \\
T_1' = (1 - c_1 w(t)) k_1 V T_1 - \delta T_1' - m_1 T_1' \\
T_2' = (1 - f_1 w(t)) k_2 V T_2 - \delta T_2' - m_2 T_2' \\
V_1 = (1 - c_1 w(t)) 10^5 N T_1' V_1 - \delta V_1 - (1 - c_1 w(t)) p_1 10^5 k_1 T_1 V_1 \\
V_2 = (1 - f_1 w(t)) 10^5 N T_2' V_2 - \delta V_2
\]

\[V_{ST1} = e_2 w(t) 10^5 N T_2' + T_2' - c V_{ST1}\]

\[E = \lambda E + \frac{e_1(T_2 + T_2')}{T_2 + T_2'} + K_E - \frac{d_2(T_2 + T_2')}{T_2 + T_2'} E - \delta_E E
\]

Initial conditions \( \{T_1(0), T_2(0), T_2(0), T_2(0), V_1(0), V_{ST1}(0)\} \)

Treatment input: \( u(t) = 1 \) if therapy given at time \( t \), \( 0 \) if not

\( \Rightarrow \) CD4 count = \( T_1 + T_2 \), viral load = \( V_1 + V_{ST1} \)

5. Constructing dynamic treatment regimes

Statistical model:
- Each subject has his/her own dynamic parameters \( \lambda_1, k_1, \lambda_2, k_2, c, \delta, m_1, m_2 \) etc.
- These vary in the population
- Observations on some of the model states subject to variation
- Nonlinear mixed effects model

Challenge: Can this mathematical/statistical model be used to develop dynamic regimes to recommend to a population?

- I.e., determine the input function \( w(t) \)
- Control theory: Mathematical theory for modifying the behavior of dynamical systems through control of system inputs
- Use feedback control methods to design dynamic STI regimes

5. Constructing dynamic treatment regimes

Main measures: CD4 t-cell count and viral load

6. Discussion

Closing thoughts: Dynamic treatment regimes operationalize how clinicians practice medicine

- Statisticians should be open to thinking about treatment as sequential multi-stage decision-making
- We should be encouraging studies to evaluate regimes rather than single steps of treatment
- Methods for doing this exist!
- We should be interested in developing and evaluating methods for constructing better dynamic regimes

6. Discussion

Interested in learning more? You’re in luck!

SAMS 2007 Summer Program on Challenges in Dynamic Treatment Regimes and Multistage Decision-Making

- Program committee: Susan Murphy, Butch Tsiatis, Dan Scharfstein, Marie Davidian, Joelle Pineau
- Two-week intensive study of all of this!
- Statisticians, applied mathematicians, computer scientists, clinicians, behavioral scientists, 
- Tutorials, workshops, working groups
- Details will be forthcoming
Some references


These slides available at:
http://www.stat.ncsu.edu/~davidian

Greenberg Lecture III: Dynamic Regimes