

# Inference for Dynamic Treatment Regimes in Two-Stage Clinical Trials (and More Generally)

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# Outline

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1. What is a dynamic treatment regime?
2. Dynamic treatment regimes for cancer
3. Randomized oncology trials to compare dynamic regimes
4. Analysis
5. Dynamic treatment regimes  
more generally
6. Discussion

# 1. What is a dynamic treatment regime?

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**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 “*manage*” a patient’s illness
- 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*

# 1. What is a dynamic treatment regime?

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## 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*

# 1. What is a dynamic treatment regime?

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**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)

# 1. What is a dynamic treatment regime?

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## 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?

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

**Important:** Do not *confuse* 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
- Also, don't confuse the *regimes themselves* with *response-adaptive designs* for studying traditional treatments

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

## 2. Dynamic treatment regimes for cancer

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### 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*

## 2. Dynamic treatment regimes for cancer

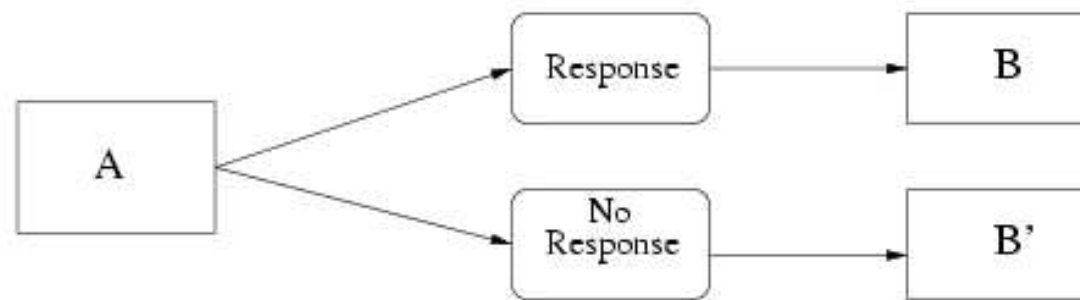
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**A particular dynamic treatment regime:** For a given patient

- *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  $B'$
- “*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*

**Schematically:** The specific regime “Give first-line induction therapy  $A$  followed by maintenance  $B$  if response else if no response give second-line therapy  $B'$ ”



*Step 1*

*Step 2*

(Induction Trt)

(Intermediate Outcome)

(Maintenance Trt)

## 2. Dynamic treatment regimes for cancer

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**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  $B'_2$

## 2. Dynamic treatment regimes for cancer

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### 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  $B'_2$

**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

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## Possible ways to compare:

- An *eight-arm* randomized trial?
- Combine information from a *series* of trials?

### 3. Randomized trials for dynamic regimes

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#### 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'*" treatments for prolonging survival and *base the regime on those*?

### 3. Randomized trials for dynamic regimes

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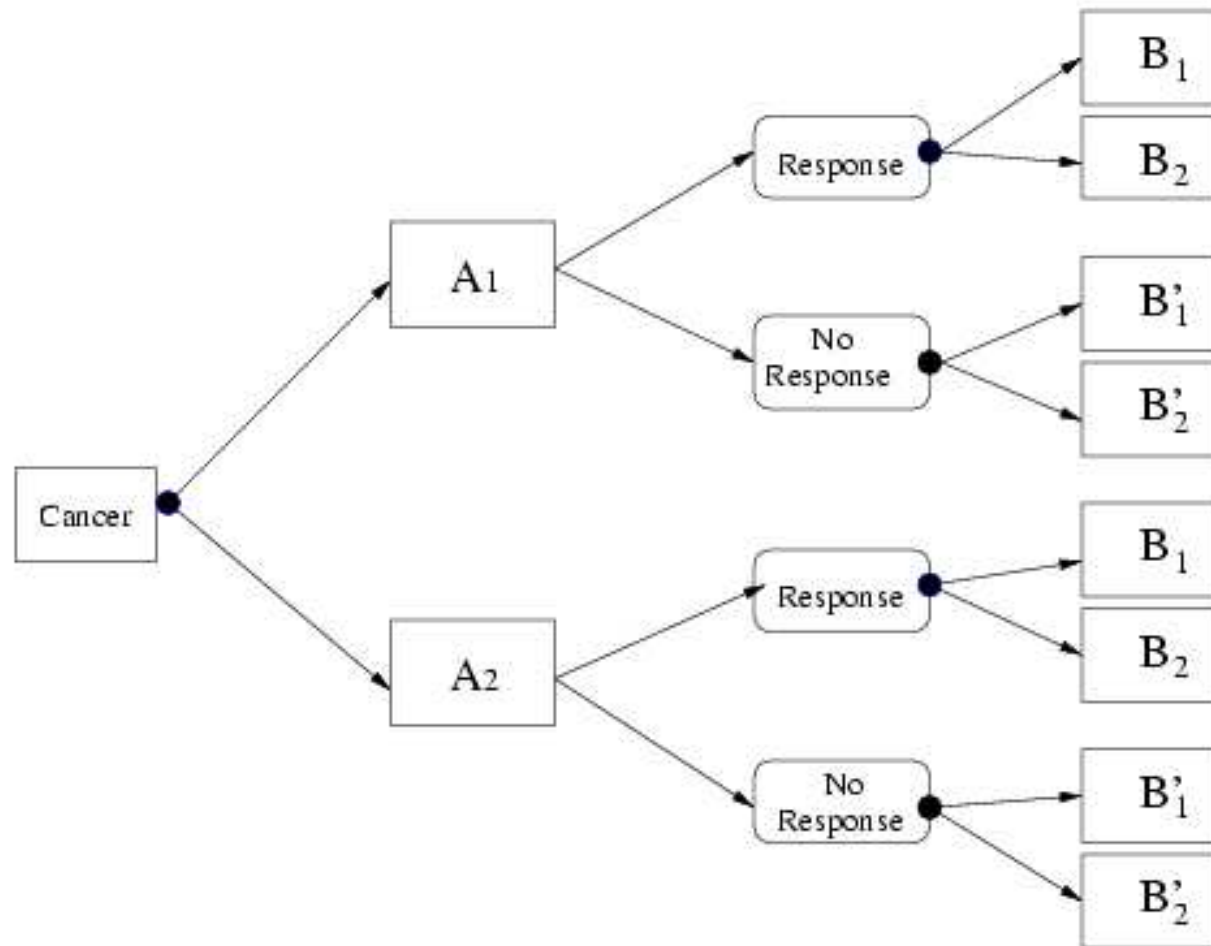
**One problem with this:** *Delayed effects*

- 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*
- $\implies$  Must evaluate *entire regimes*

**A way to do this...**

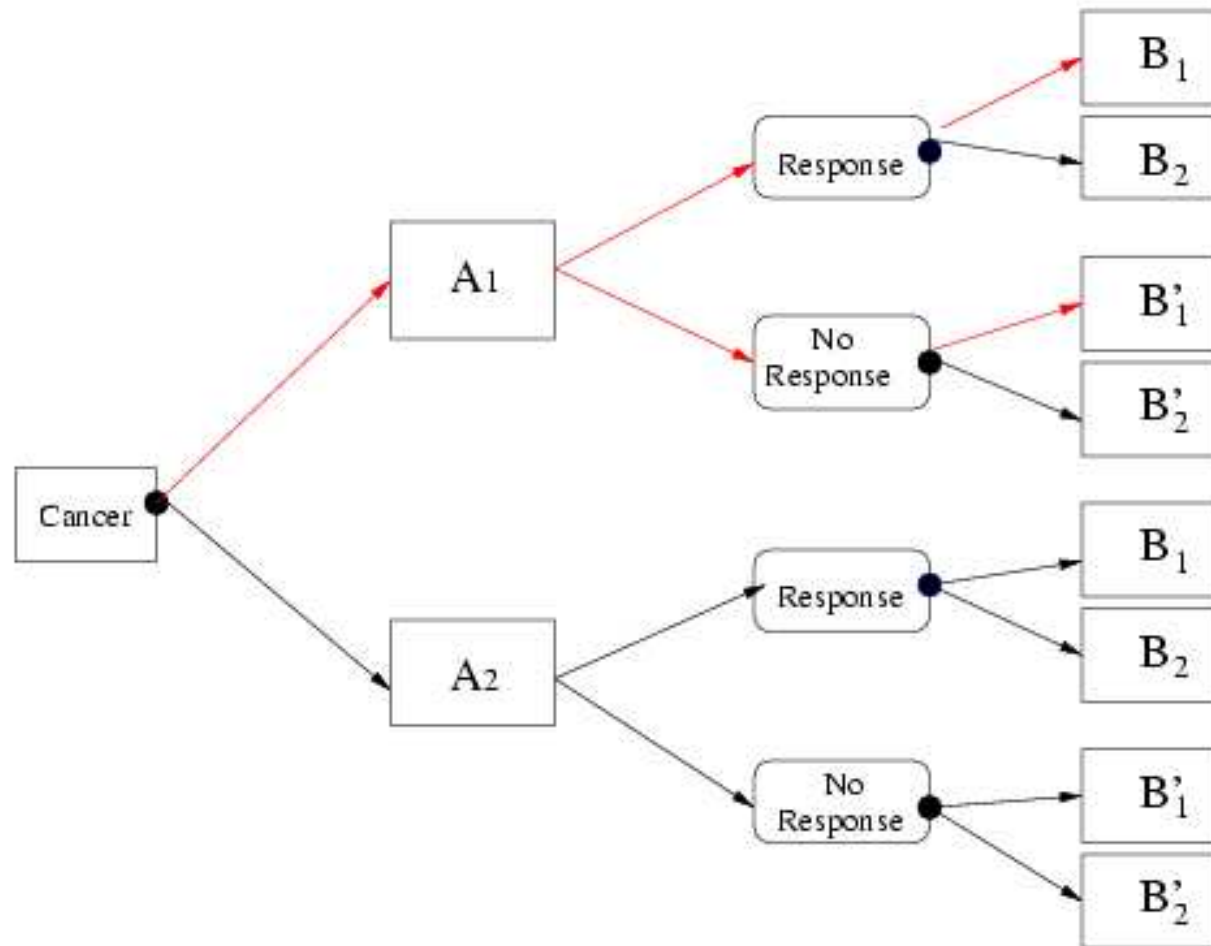
### 3. Randomized trials for dynamic regimes

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



### 3. Randomized trials for dynamic regimes

**In red:** Regime “ $A_1$  followed by  $B_1$  if response else  $B'_1$ ”



# 3. Randomized trials for dynamic regimes

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**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

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**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. Randomized trials for dynamic regimes

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## 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

## 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*...

### 3. Randomized trials for dynamic regimes

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#### “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*

### 3. Randomized trials for dynamic regimes

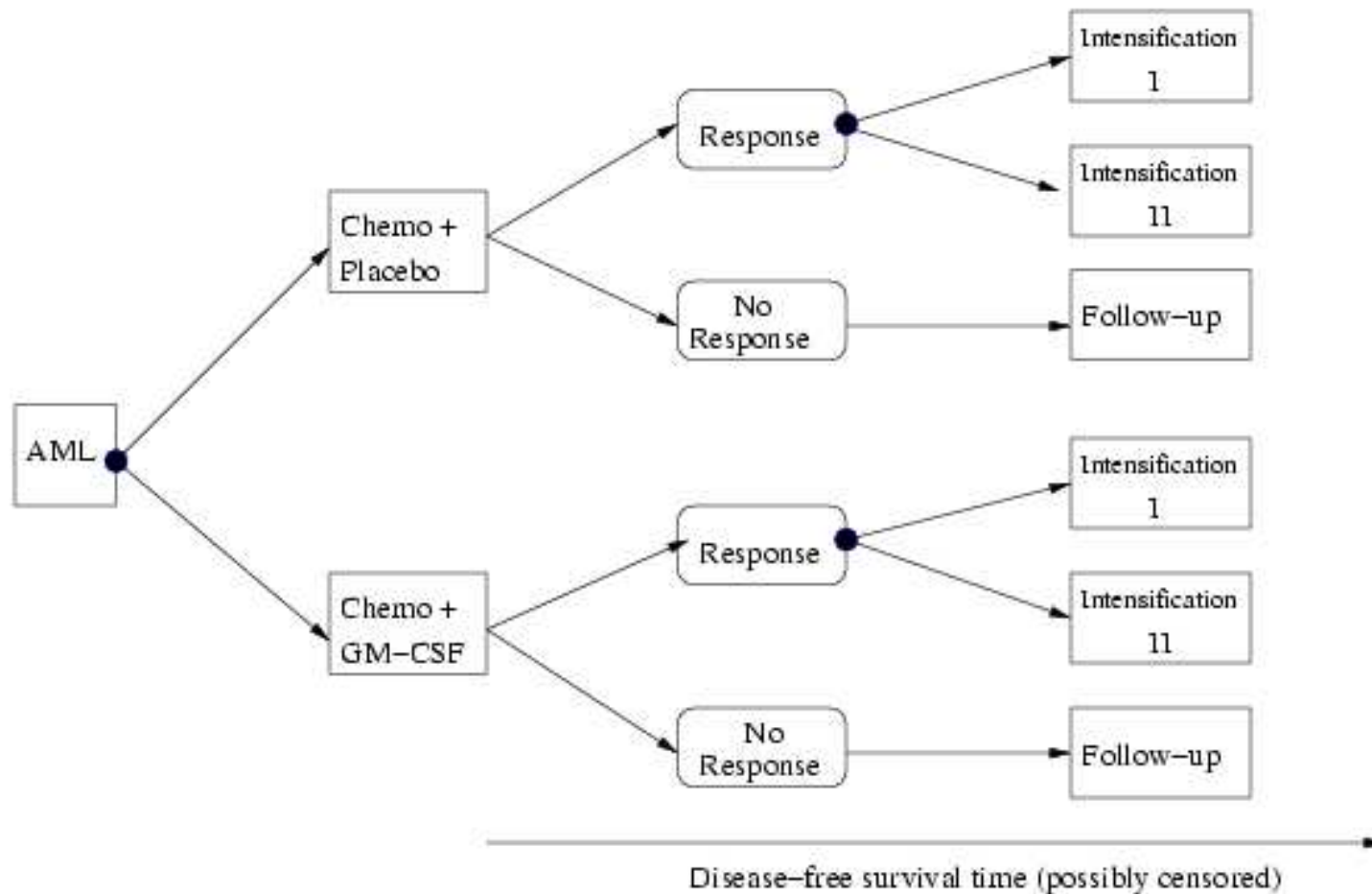
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#### Four possible regimes:

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 =  $A_2B_2$

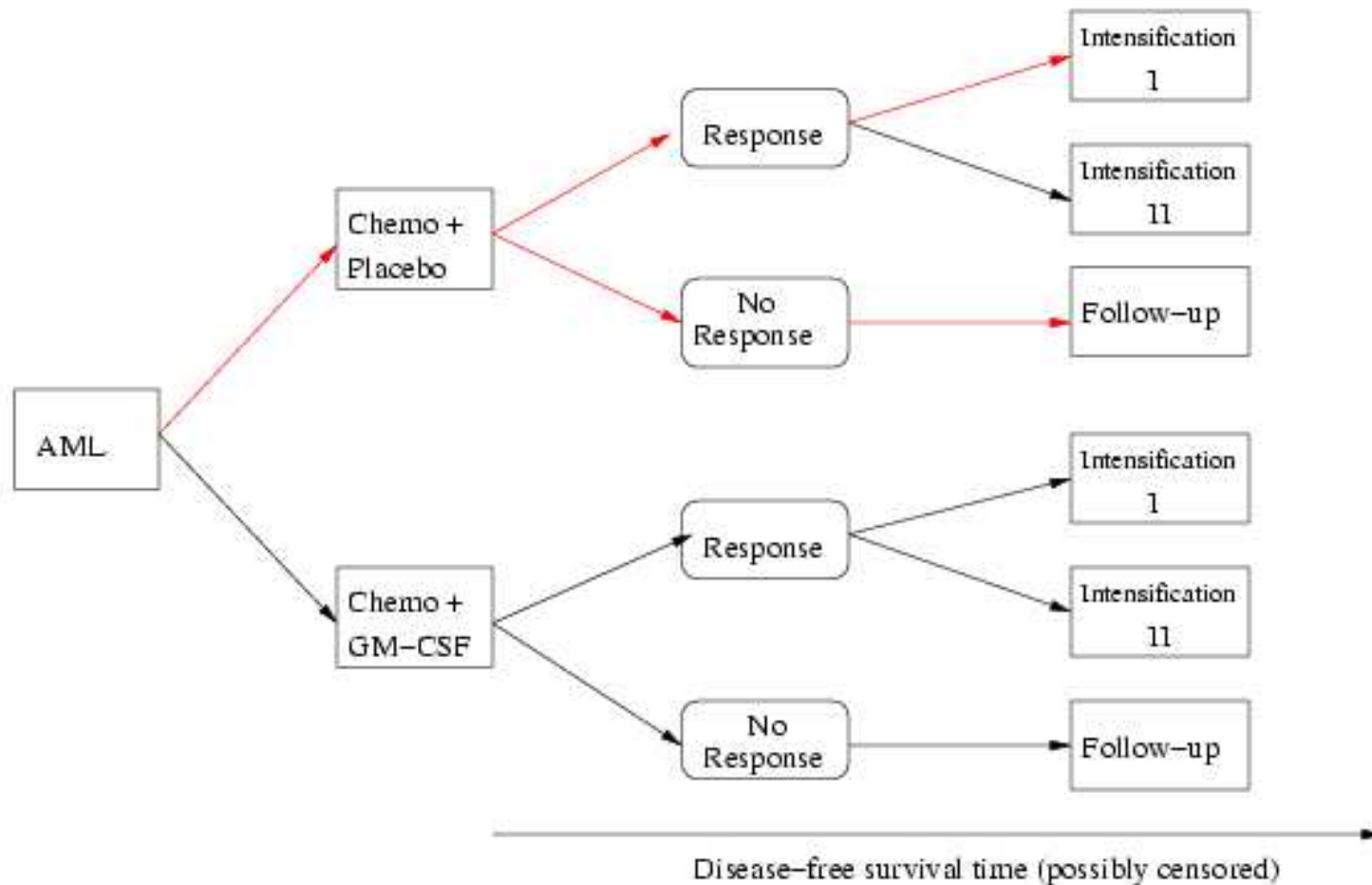
### 3. Randomized trials for dynamic regimes

**Schematic of CALGB 8923:** Randomization at ●s



### 3. Randomized trials for dynamic regimes

Regime  $A_1B_1$ :



# 4. Analysis

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## 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*

## 4. Analysis

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**Demonstration:** 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 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

## 4. Analysis

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

- 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 design

- $\Rightarrow$  A *weighted average* of survival times
- *Heuristically*...

## 4. Analysis

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**Consider  $A_1$  only** ( $A_2$  analogous) : *Ideally*, suppose *everyone* in the trial *followed*  $A_1B_1$

- *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 end up randomized to  $B_2$  have *missing* survival times as far as  $A_1B_1$  is concerned

## 4. Analysis

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

- The *nonresponders* represent themselves either way  $\Rightarrow$  weight = 1
- Each *responder* represents him/herself and another similar subject who got randomized to  $B_2 \Rightarrow$  weight = 2
- Usual “*inverse probability weighting*” for missing data
- To estimate mean for  $A_1B_2$ , switch the roles
- *Note*: Survival times from *nonresponders* would be used to estimate the means for *both*  $A_1B_1$  *and*  $A_1B_2$

## 4. Analysis

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

$T_i$  = survival time for subject  $i$ ,  $i = 1, \dots, n$ ,

$R_i = 1$  if  $i$  responds to  $A_1$ ,  $R_i = 0$  if not

$Z_i = 1$  for a responder randomized to  $B_1$ ,  $Z_i = 2$  for  $B_2$

$P(Z_i = 1 | R_i = 1) = \pi$  (= 1/2 in previous)

**Estimators:**  $n^{-1} \sum_{i=1}^n Q_i T_i$  or  $\left( \sum_{i=1}^n Q_i \right)^{-1} \sum_{i=1}^n Q_i T_i$ ,

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

- $Q_i = 0$  if  $i$  is inconsistent with  $A_1 B_1$  (i.e, is consistent with  $A_1 B_2$ )
- $Q_i = 1$  if  $R_i = 0$
- $Q_i = \pi^{-1}$  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  $I(T_i \leq t)$

## 4. Analysis

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**One way to formalize:** What are we *estimating*?

- Suppose  $i$  has *potential outcomes* (aka *counterfactuals*)  $T_{11i}, T_{12i}$
- $T_{1ki}$  = survival time  $i$  *would have* if  $i$  *were to follow*  $A_1B_k, k = 1, 2$

**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  $\mu_{1k} = E(T_{1ki})$
- *Similarly*, if interested in the *survival distribution* if all subjects followed  $A_1B_k,$   
 $\Rightarrow$  Want to estimate  $S(t) = P(T_{1ki} > t) = E\{I(T_{1ki} > t)\}$

## 4. Analysis

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

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

$T_i$  = survival time for subject  $i$

$R_i = 1$  if  $i$  responds to  $A_1$ ,  $R_i = 0$  if not

$Z_i = k$  for a responder randomized to  $B_k$ ,  $k = 1, 2$ , where

$$P(Z_i = 1 | R_i = 1) = \pi, P(Z_i = 2 | R_i = 1) = 1 - \pi$$

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

- 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  $\mu_{11}$

## 4. Analysis

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**Connection:** For subjects *randomized* to  $A_1$

- *Assume* that when  $R_i = 0$ ,  $T_{11i}$  and  $T_{12i}$  are *the same*
- Then  $T_i = (1 - R_i)T_{11i} + R_i I(Z_i = 1)T_{11i} + R_i I(Z_i = 2)T_{12i}$

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

- *Using*  $R_i(1 - R_i) = 0$ ,  $I(Z_i = 1)I(Z_i = 2) = 0$ , etc.

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

- So *equivalently* want to show

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

## 4. Analysis

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$$\begin{aligned} & E\{(1 - R_i) + R_i I(Z_i = 1)\pi^{-1} | R_i, T_{11i}\} \\ &= E\{(1 - R_i) + R_i I(Z_i = 1)\pi^{-1} | R_i = 0, T_{11i}\} P(R_i = 0 | T_{11i}) \\ &+ E\{(1 - R_i) + R_i I(Z_i = 1)\pi^{-1} | R_i = 1, T_{11i}\} P(R_i = 1 | T_{11i}) \\ &= P(R_i = 0 | T_{11i}) + E\{I(Z_i = 1) | R_i = 1, T_{11i}\} \pi^{-1} P(R_i = 1 | T_{11i}) \\ &= P(R_i = 0 | T_{11i}) + P(R_i = 1 | T_{11i}) = 1 \end{aligned}$$

**Because:** By *randomization*,

$$E\{I(Z_i = 1) | R_i = 1, T_{11i}\} = P(Z = 1 | R = 1, T_{11i}) = P(Z = 1 | R = 1) = \pi$$

$\Rightarrow$  *randomization* ensures  $i$ 's assignment to  $B_1$  *does not depend on*  $i$ 's prognosis

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

## 4. Analysis

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**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*  $K_1(t) = P(C_i > t | A_1)$
- 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  $n^{-1} \sum_{i=1}^n \frac{\Delta_i Q_i}{K_1(V_i)} V_i$
- Similar *consistency* arguments possible

## 4. Analysis

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**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 compare without regard to differential consent rates)
- So *redefine*  $\Rightarrow R_i = 1$  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 ( $\Rightarrow$  *observational study*)

# 4. Analysis

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## 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
- *Semiparametric efficient estimators, theory*: Wahed and Tsiatis (2004, 2006)
- Extension to  $\geq 2$  *stages*, general *SMART* designs: Murphy (2005), Tsiatis and Davidian (200x)
- If SMART is *balanced*, *no need* to do *weighting*

## 4. Analysis

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**Of course:** This isn't the *only way* to think about this problem

- E.g., Thall, Milliken, and Sung (2000)
- The key is thinking of *entire regimes* rather than individual *steps* of treatment

**Issues in designing and analyzing SMARTs:**

- *Sample size calculation*
- *Efficiency* as number of steps *increases*
- One possibility: Exploit *experimental design* principles, e.g., *fractional factorial*?

# 5. Constructing dynamic treatment regimes

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## 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?
- E.g., *demographic*, *physiological* characteristics; evolving *longitudinal biomarkers*; previous *treatment history*; *side effects* experienced; etc. . .
- ⇒ How to *construct* dynamic treatment regimes???

# 5. Constructing dynamic treatment regimes

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## 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 should 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

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## 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

# 5. Constructing dynamic treatment regimes

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## Open problems:

- Methods for identifying *tailoring variables* must incorporate *effect of future treatment decisions* when evaluating *present treatment decision* and have been developed (Murphy, Robins, Müller, Parimigiani, computer scientists, ORers, . . .)
- But need to be adapted to and evaluated in *real medical contexts* where the usual *issues* associated with human study arise
- *Variable selection* to determine *tailoring variables* – needs to focus on *decision-making*, *not prediction*

# 5. Constructing dynamic treatment regimes

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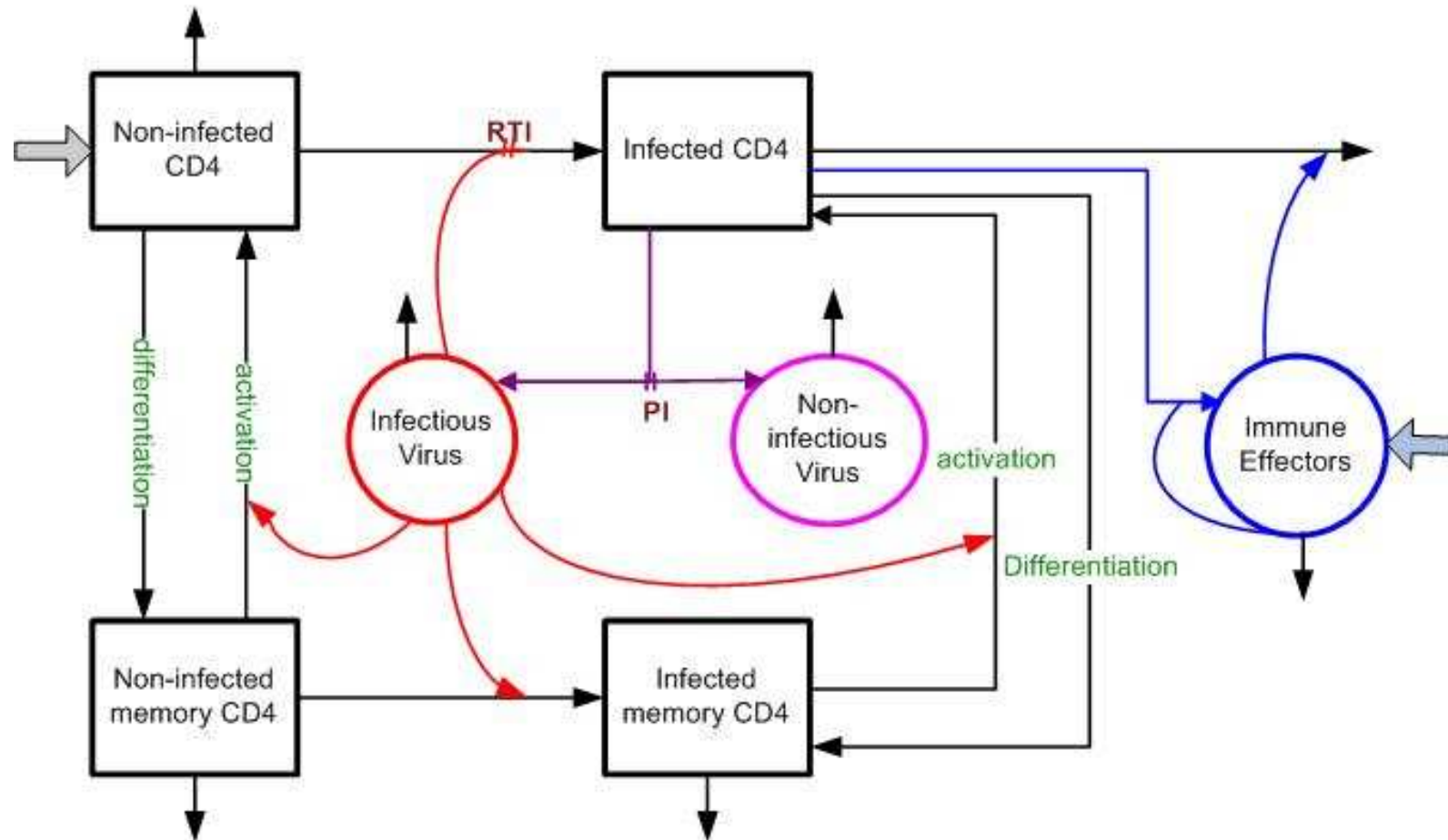
**Another approach:** Exploit *mechanistic models*

**Structured Treatment Interruption (STI) for acute HIV-1 infection:**

- Potent antiretroviral therapy *cannot be taken continually*
- Side effects, burden, cost, development of drug resistance, ...
- $\Rightarrow$  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



## 5. Constructing dynamic treatment regimes

**Nonlinear dynamical system:** Ordinary differential equations,  $\dot{U} = \frac{dU}{dt}$

$$\dot{T}_1 = \lambda_1 - d_1 T_1 - \{1 - \epsilon_1 u(t)\} k_1 V_I T_1$$

$$\dot{T}_2 = \lambda_2 - d_2 T_2 - \{1 - f \epsilon_1 u(t)\} k_2 V_I T_2$$

$$\dot{T}_1^* = \{1 - \epsilon_1 u(t)\} k_1 V_I T_1 - \delta T_1^* - m_2 E T_1^*$$

$$\dot{T}_2^* = \{1 - f \epsilon_1 u(t)\} k_2 V_I T_2 - \delta T_2^* - m_2 E T_2^*$$

$$\begin{aligned} \dot{V}_I = & \{1 - \epsilon_2 u(t)\} 10^3 N_T \delta (T_1^* + T_2^*) - c V_I - \{1 - \epsilon_1 u(t)\} \rho_1 10^3 k_1 T_1 V_I \\ & - \{1 - f \epsilon_1 u(t)\} \rho_2 10^3 k_2 T_2 V_I \end{aligned}$$

$$\dot{V}_{NI} = \epsilon_2 u(t) 10^3 N_T \delta (T_1^* + T_2^*) - c V_{NI}$$

$$\dot{E} = \lambda_E + \frac{b_E (T_1^* + T_2^*)}{(T_1^* + T_2^*) + K_b} E - \frac{d_E (T_1^* + T_2^*)}{(T_1^* + T_2^*) + K_d} E - \delta_E E$$

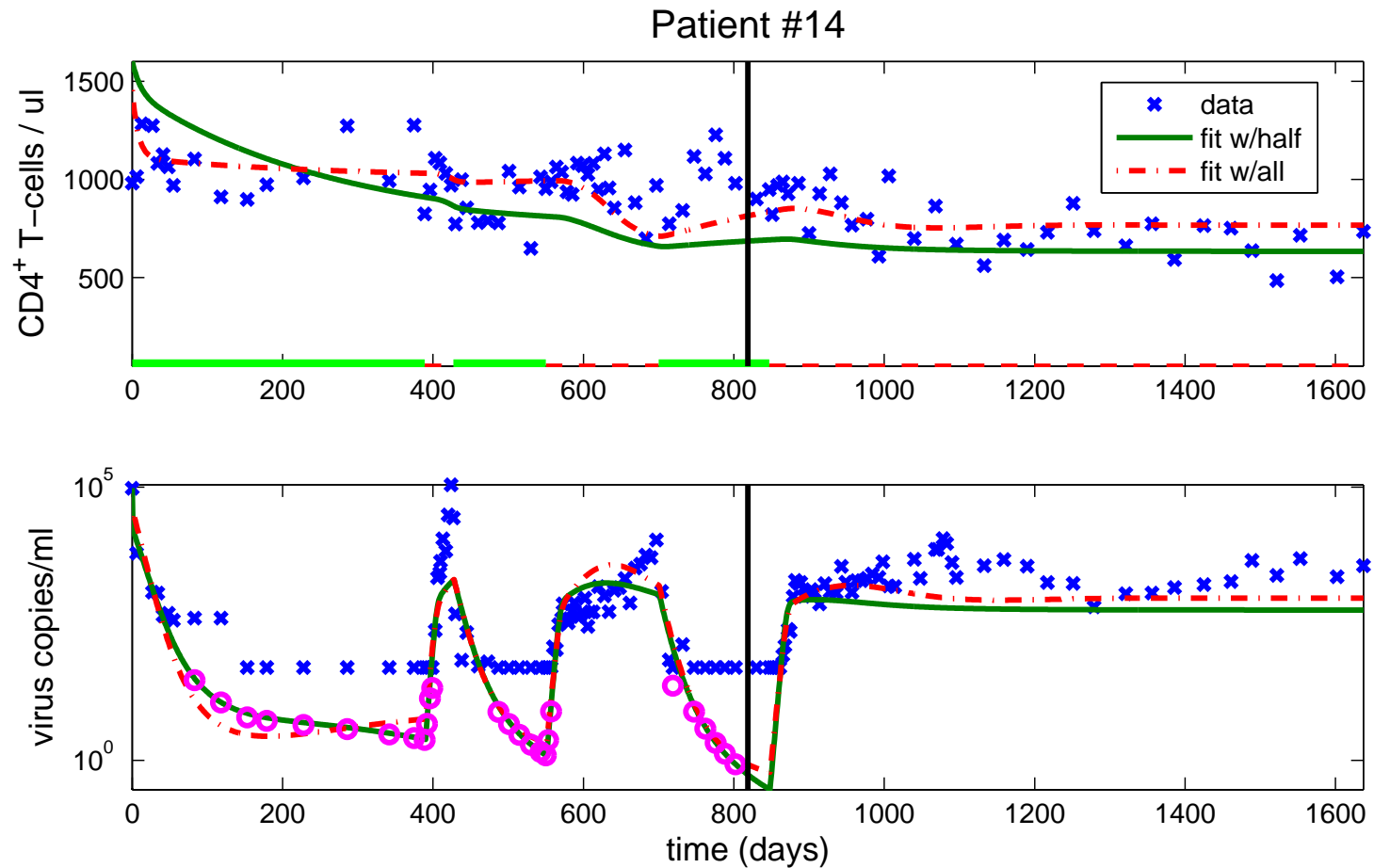
+ *initial conditions*  $\{T_1(0), T_2(0), T_1^*(0), T_2^*(0), V_I(0), V_{NI}(0)\}$

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

$$\Rightarrow \text{CD4 count} = T_1 + T_2, \quad \text{viral load} = V_I + V_{NI}$$

# 5. Constructing dynamic treatment regimes

**Main measures:** *CD4 T-cell count* and *viral load*



# 5. Constructing dynamic treatment regimes

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## Statistical model:

- Each subject has his/her own *dynamic parameters*  $\lambda_1, k_1, \epsilon_1, \lambda_2, k_2, \epsilon_2, c, \delta, m_1, m_2$  etc.
- These *vary* in the population according to some distributions
- *Observations* on only some of the model states, subject to *variation*
- *Hierarchical nonlinear model*

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

- I.e., determine the *input function*  $u(t)$
- *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

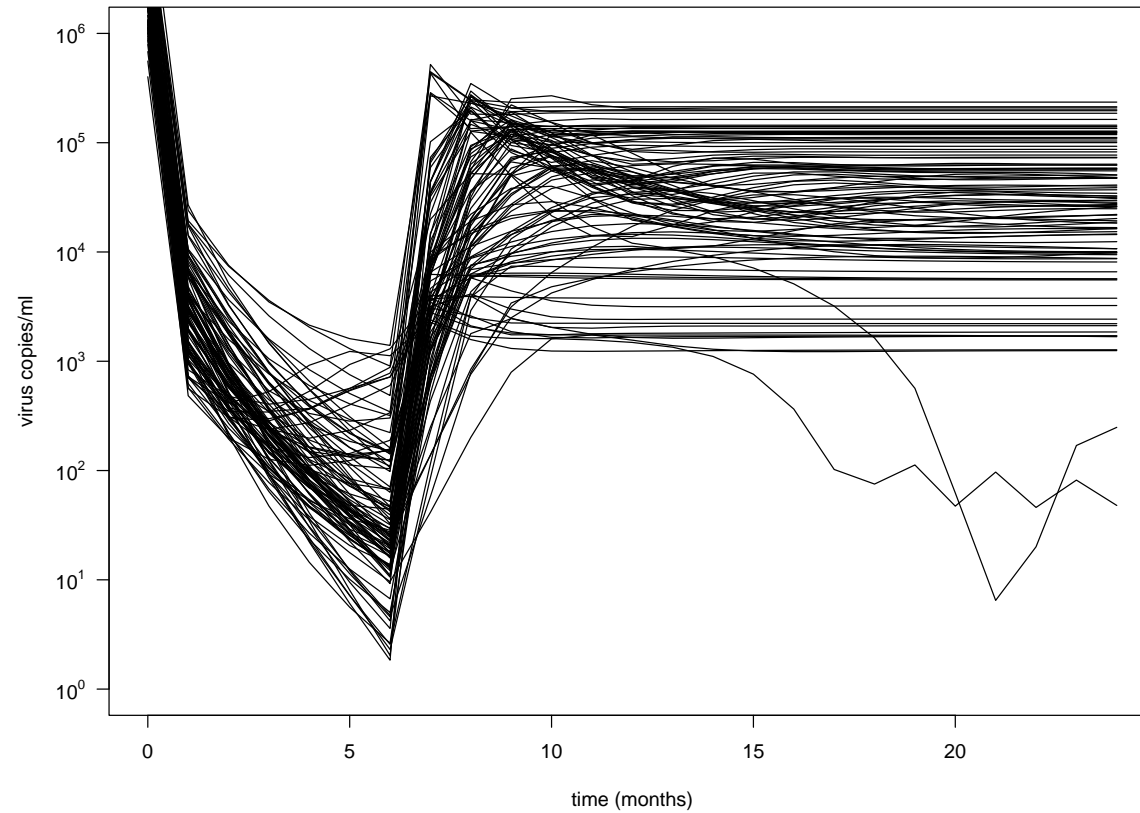
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**We'll see:** Collaboration with *H.T. Banks* (applied mathematician at NCSU) and *Eric Rosenberg* (immunologist/infectious disease physician at Mass General Hospital) to develop methods to do this

- More *realistic HIV dynamic models* informed by intensive *longitudinal data* from Eric's *acute infection cohort*
- Devising *control theoretic methods* that yield *practically feasible* inputs
- *Statistical-model-based simulation* to determine effect on population
- Run a *clinical trial* to evaluate treatment strategies suggested by the models

# 5. Constructing dynamic treatment regimes

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## 6. Discussion

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**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*
- Lots of relevant research in *diverse fields* that needs to be *exploited* and *synthesized*

## 6. Discussion

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**Interested in learning more?** You're *in luck!*

*SAMSI 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, June 18–29, 2007
- Statisticians, applied mathematicians, computer scientists, ORers, clinicians, behavioral scientists, engineers, ...
- Tutorials, workshops, working groups

<http://www.samsi.info/programs/2007adaptivetreatmentprogram.shtml>



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# Slides available at

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