Disease Progress Models

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Motivations for Disease Progression Models

* Visualization of the time course of disease in treated and untreated conditions
* Simulation of
  - Future course of disease
  - Various disease interventions to evaluate treatment options
  - Clinical trial designs
* Framework for regulatory submissions

New Objectives for Clinical Trials

* In a confirmatory trial, the purpose of that trial is to test the null hypothesis.
  - Clinical trials usually focused on testing null hypothesis because there is an alternative model that can be accepted in place of the null model.
* Testing the null hypothesis is an easy question to answer robustly
  - Traditionally statistics has been focused on questions that are easy to answer but not necessarily on answering the right questions.
* "Far better an approximate answer to the right question, which is often vague, than an exact answer to the wrong question, which can always be made precise." - Tukey

New Objectives for Clinical Trials

* Developing an exposure response surface is not an easy question to answer but maybe it's the right question to ask
  - Usually requires assumptions which weakens the robustness of the answers.
    * Assumptions reduce inferential certainty because if the assumptions are wrong, then the model based conclusions are wrong.
    * It is the quality of the attendant assumptions, not their existence, that is the issue.
  - A summary of the surface function, such as an average over the response surface can provide robust answers to simpler questions.
    * The margins of a high dimensional surface are usually well estimated, even with modeling.
    * If a model is used to address the right question, the answer will have uncertainty associated with that answer, but summarizing or integrating over that model in order to answer simpler questions can still provide robust answers.

Evaluating a Response Surface

* During drug development patients can have different responses
  - Differing sensitivity contributes to the variability (e.g. noise) in the outcome of the study.
    * Impossible to study all combinations of doses or treatments by patient type
  - Need to develop the dose response surface without data from every type of patient given every dose level and duration of therapy
* The time course of disease in the untreated patient is also variable
  - Characterizing the time course of placebo response allows better evaluation of drug effect
* Clinical markers of outcome are inherently variable as well
  - Residual error for HAMD is notable
  - Repeated measures assessments are generally more able to evaluate the central trend of a response
* Model based evaluations provides a basis for developing exposure response surface by making scientifically valid assumptions

Evaluating a Response Surface

* Models increase the amount of information recovered from a clinical trial.
  - Information obtained from any scientific study can be detected based on the ratio of signal to noise.
  - In any given study, the information is the total variation in the data, the signal is the variation due to identifiable causes such as differences in dose, and the noise is the residual or unexplained variation.
  - Models increase information by turning noise into signal by providing a basis for explaining the variation

Clinical Pharmacology

=

Disease Progress + Drug Action*

*It also follows that

"Drug Action" = Drug Effect + Placebo Effect

- The effect of a drug involves understanding the progression of the disease and the effect of placebo as well as the effect of administering a test drug

PKPD Models

* **Pharmacokinetic (dose, concentration, time)**
  - drug disposition in individuals & populations
  - disease state effects (renal & hepatic dysfunction)
  - intervention effects (hemodialysis)
  - concurrent medication effects
  - pharmacogenetic influences
* **Pharmacodynamic (dose or concentration, effect, time)**
  - physiologic & biomarkers
  - surrogate endpoints
  - clinical effects and endpoints

Disease Progression Model

* **Quantitative model that accounts for the time course of disease status, *S(t)*:**
  - "**Symptoms**" - measures of how a patient feels or functions ***("clinical endpoints")***
  - "**Signs**" - physiological or biological measurements of disease activity ***("biomarkers")***
    * ***"Surrogate Endpoints"*** (validated markers predictive of, or associated with Clinical Outcome)
    * ***"Outcomes"*** (measures of global disease status, such as pre-defined progression or death)

An Old Model with a New Meaning

$$E(t) = E0 + \frac{\text{Emax} \bullet Cp(t)}{EC_{50} + Cp(t)}$$

Disease Status

Disease Progression

Drug Action

Components of a Disease Progression Model

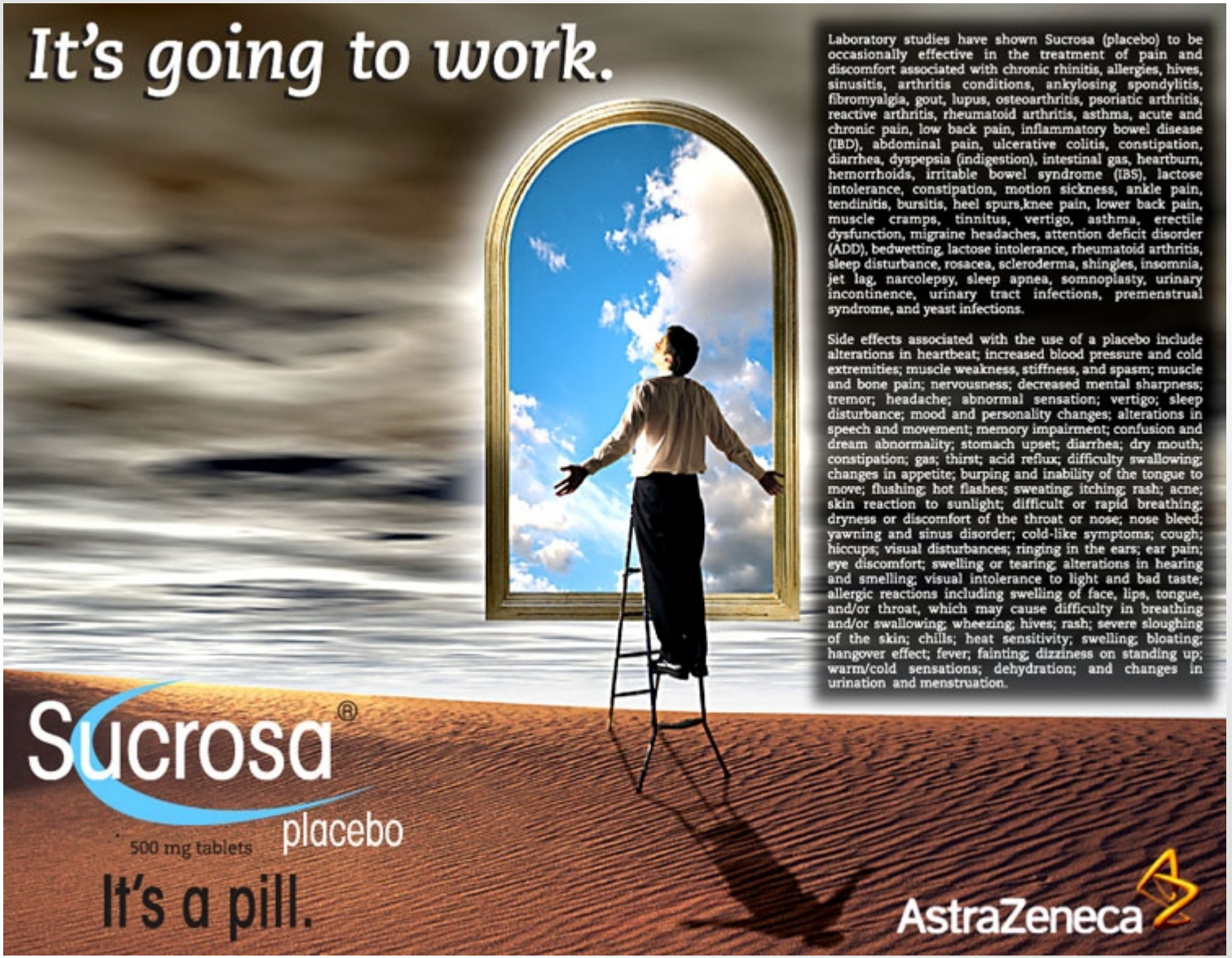
$$S(t) = Baseline + Natural\ History + Placebo + Active$$

* Baseline Disease State, S_0
* Natural History
* Placebo Response
* Active Treatment Response

Placebo Response

* Placebo response is the change in disease progression in untreated patients who are randomized to receive placebo as treatment for their disease in a clinical trial
  - Usually transient improvement in clinical status followed by relapse to pre-study status
  - In depression trials, the placebo response may be at least partly due to the interaction and attention that the enrolled patients receive regardless of treatment
    * The placebo response time course in depression trials appears to be somewhat dependent on study design – more intensive clinical visits usually result in greater placebo response that is more persistent
* Placebo response tends to be variable both in magnitude and duration and is often more notable when the clinical status is evaluated subjectively

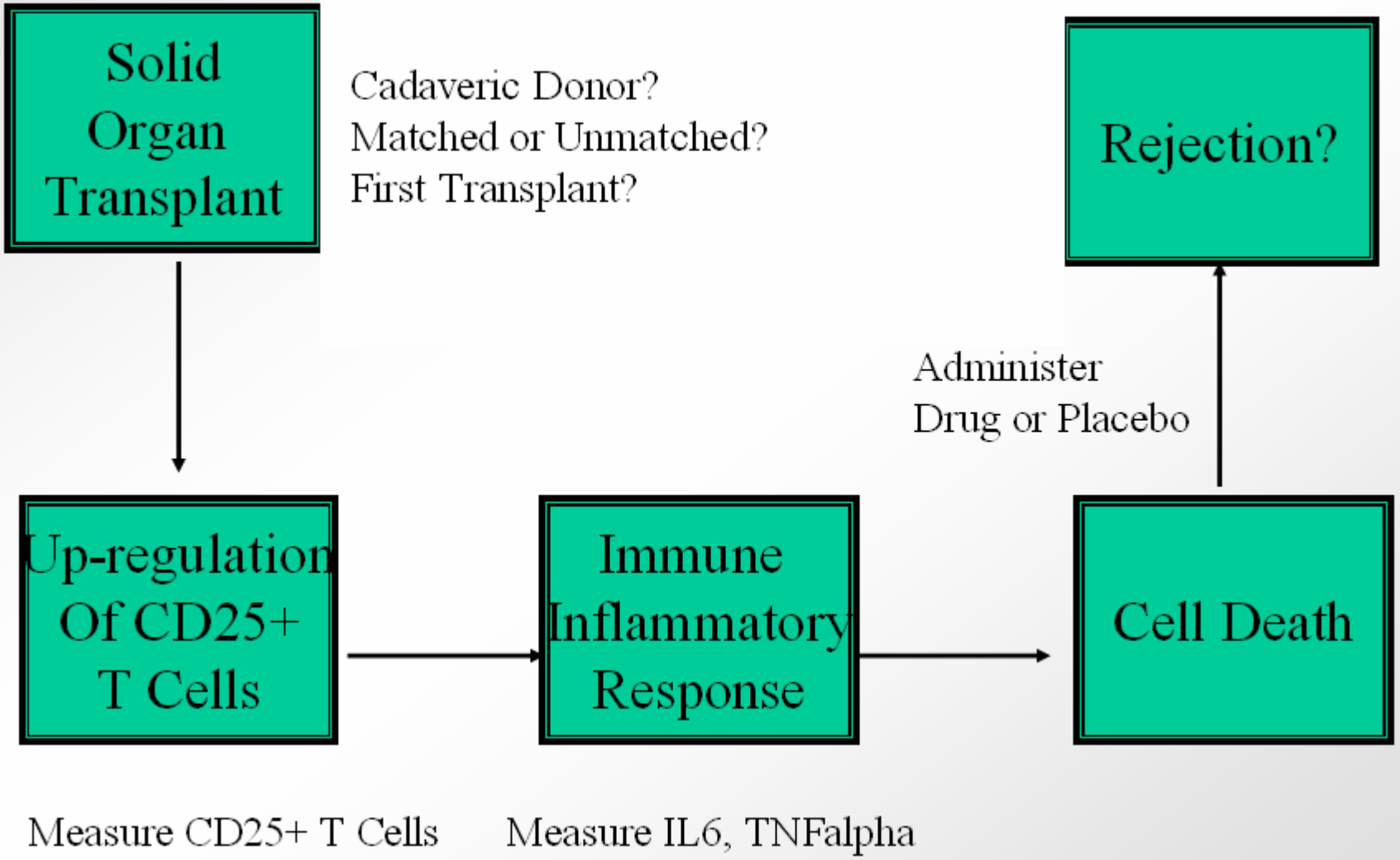
Placebo Response is an Issue!



Model Building Process

* Talk to a Disease Specialist
* Draw pictures of time course of disease
* Translate into disease progress model
* Explain the models/parameters to the Specialist
* Ask Disease Specialist for advice on factors influencing parameters
* Translate into models with appropriate parameters and covariates

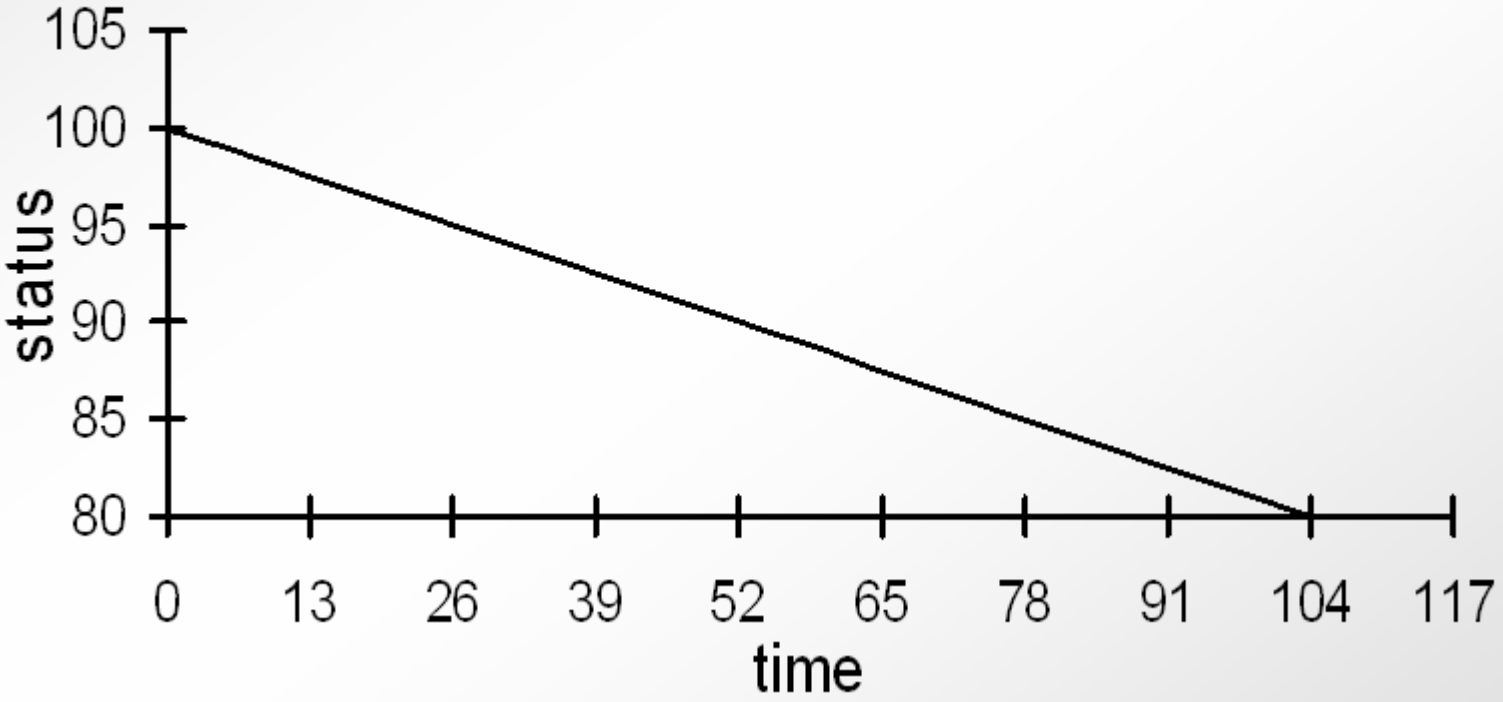
Example Construction of a Disease Model



Linear Disease Progression Model

(adapted from Holford 1999)

$$S(t) = S_0 + \alpha \cdot t$$

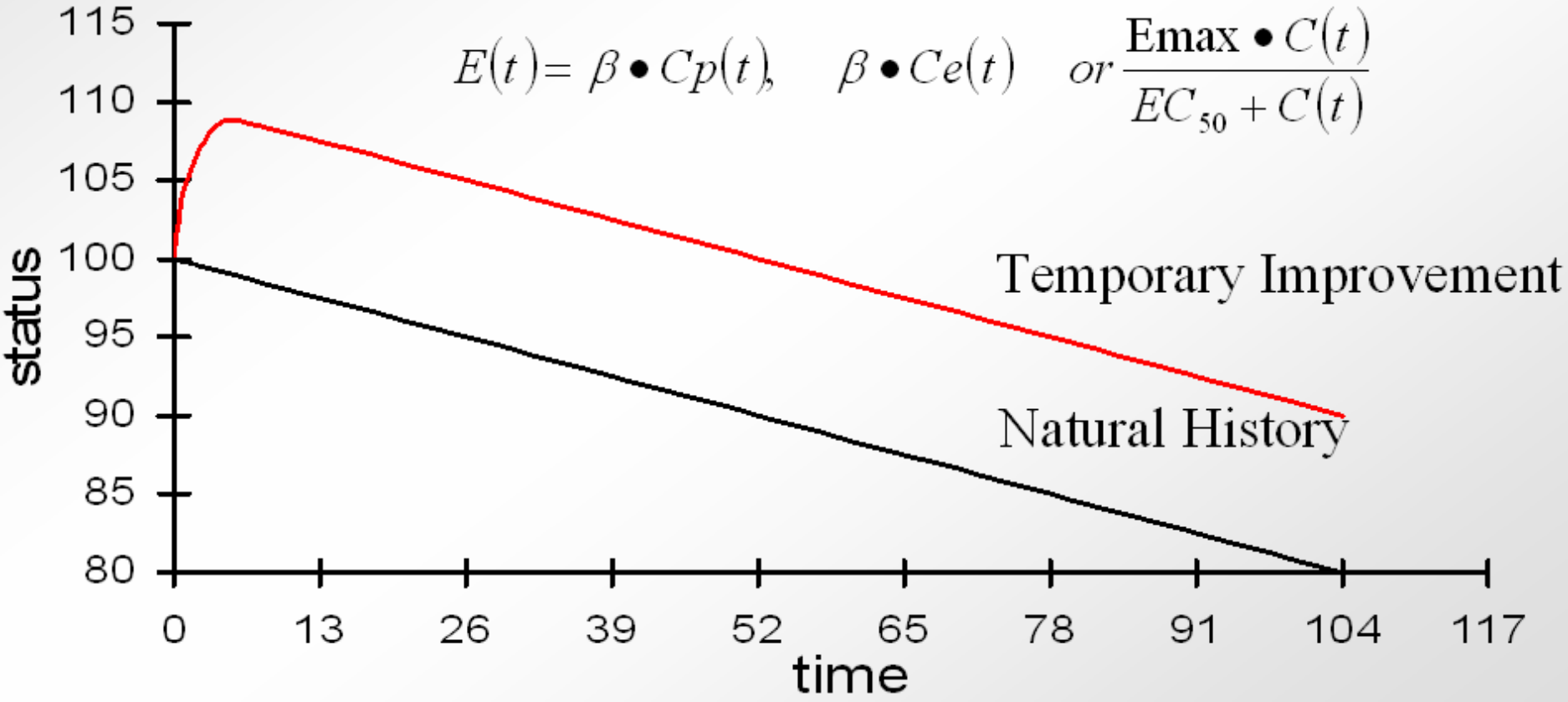


Linear Disease Progression Model with Temporary ("Offset") Placebo or Active Drug Effect

(adapted from Holford 1997 & 1999)

$$S(t) = S_0 + E(t) + \alpha \bullet t$$

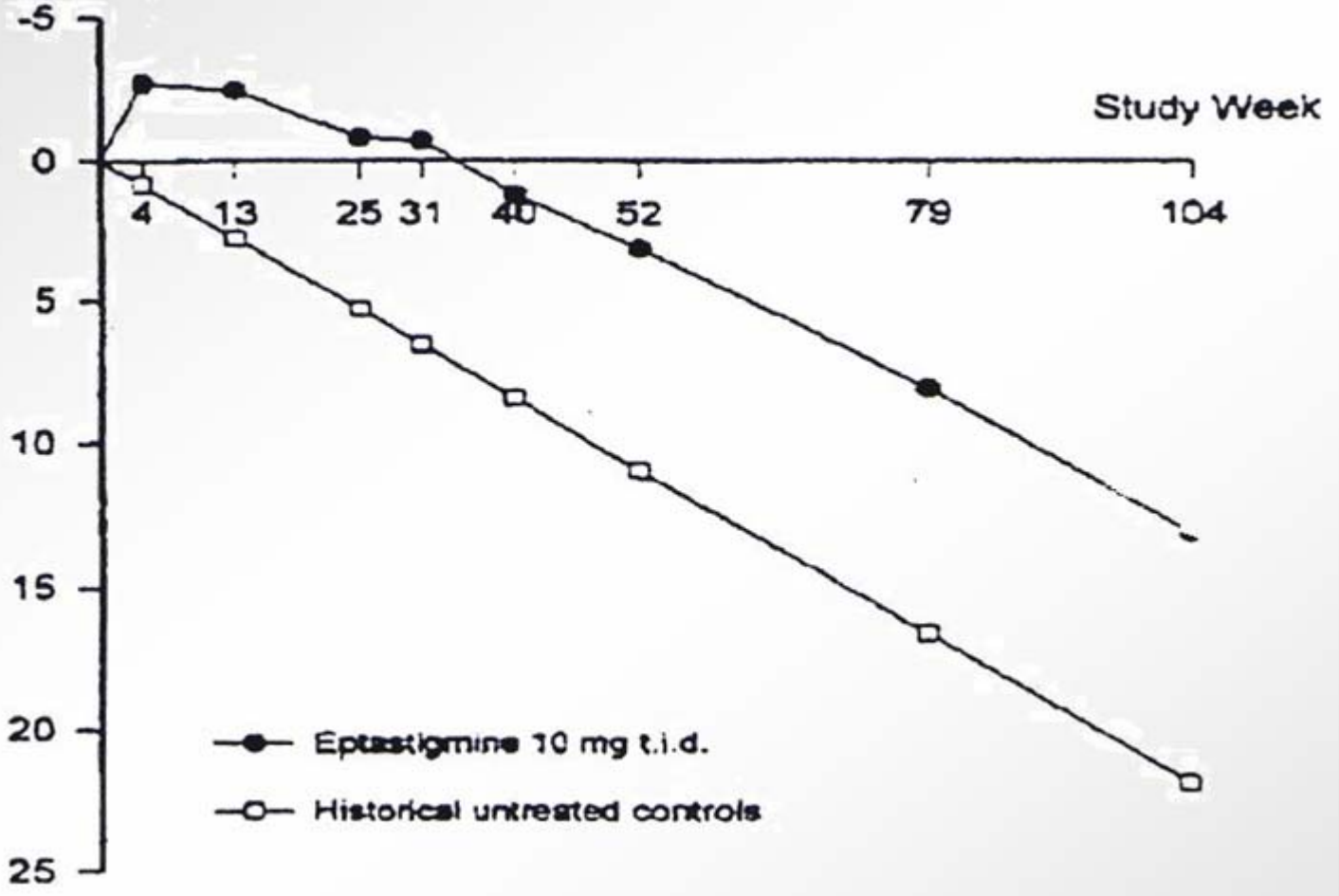
$$E(t) = \beta \bullet Cp(t), \quad \beta \bullet Ce(t) \quad or \frac{\text{Emax} \bullet C(t)}{EC_{50} + C(t)}$$



Handling Pharmacokinetic Data for Disease Progress Models

* Use actual measured concentrations
  - This is easy to do
* Use a "Link" model to create a lag between observed concentrations and observed effect
  - This is more "real" as the time course for change in disease status is usually not the same as the time course of the drug

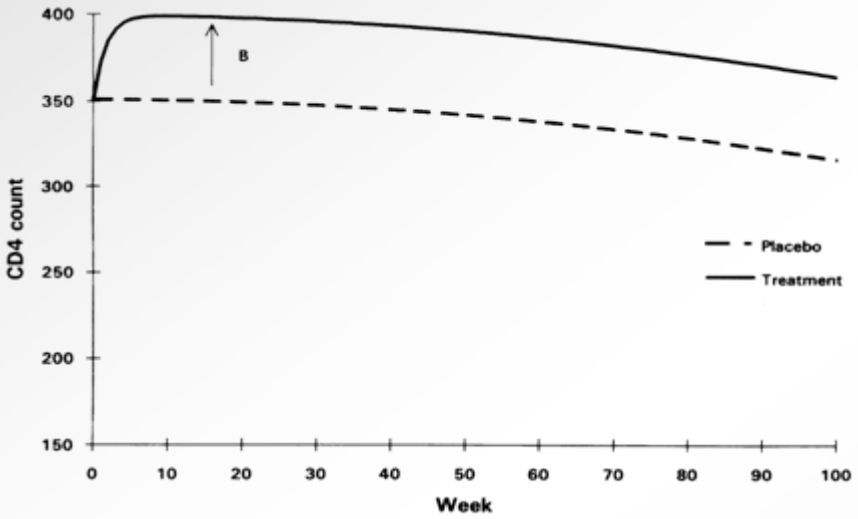
Evaluation of Effect of Eptastigmine on Trajectory of Alzheimer's Disease



Reported an "annual worsening" of approximately 10.9 points on ADAS-Cog

Imbimbo BP, Verdelli G, Martelli P, Marchesini D. "Two year treatment of Alzheimer's disease with eptastigmine". The Eptastigmine Study Group. Dementia and Geriatric Cognitive Disorders 1999 10(2):139-147

AZT Treatment Effect on HIV



"A parametric model of disease progression can be estimated with use of data collected in a conventionally designed study. These parametric models may provide insight into the optimal use of drugs. This model suggests that zidovudine does not change the underlying course of HIV infection but simply delays the time course. The model also suggests that the magnitude of this delay is larger when treatment is begun earlier in the course of the disease."

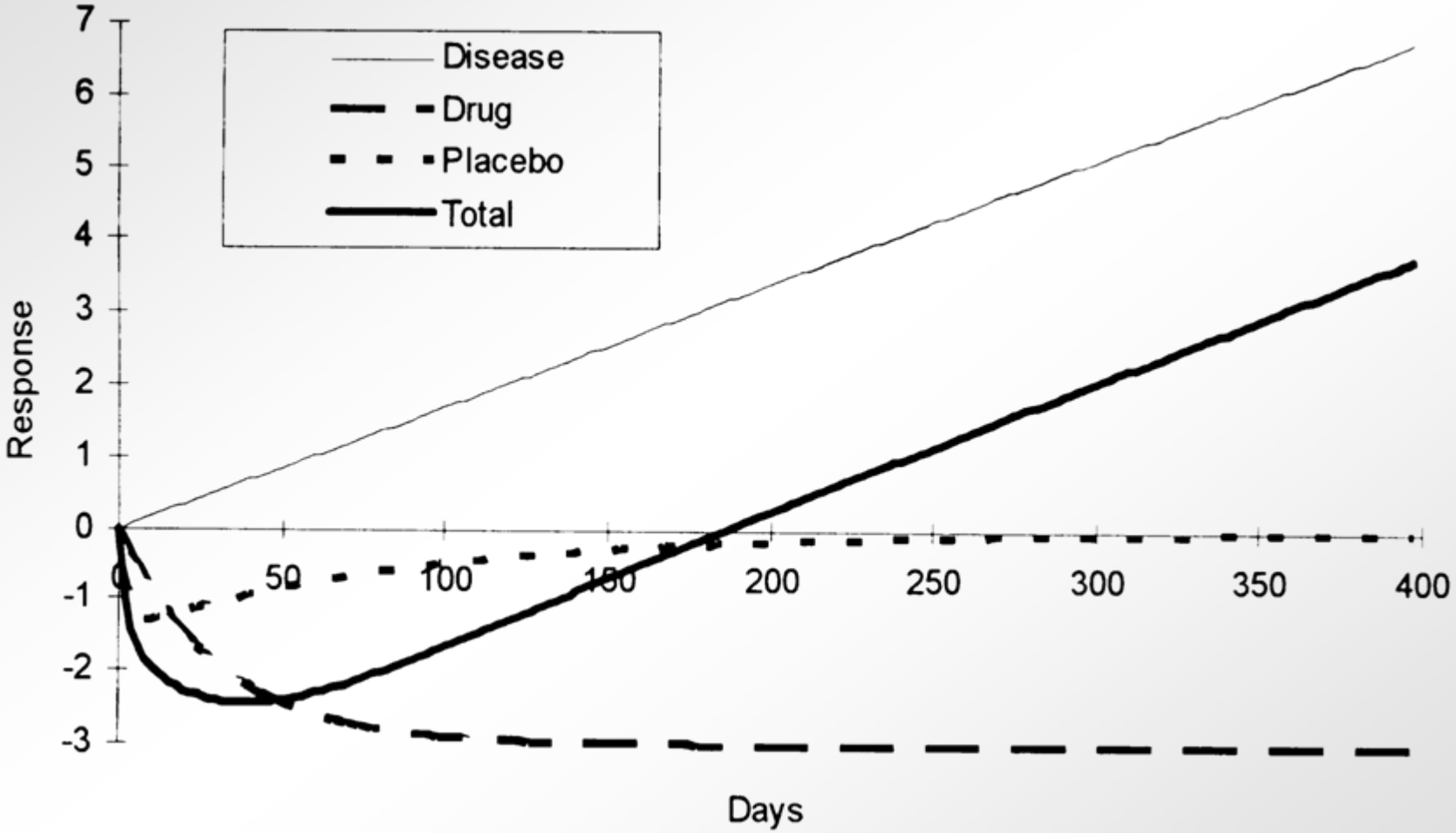
Sale M, Sheiner LB, Volberding P, Blaschke TF. "Zidovudine response relationships in early human immunodeficiency virus infection. Clin Pharmacol Ther. 1993 Nov;54(5):556-66.

Tacrine Treatment of Alzheimer's Disease

* Baseline Disease State: S_0
* Natural History: $S_0 + \alpha \cdot t$
* Placebo Response: $\beta_p \cdot C_{e,p}(t)$
* Active Treatment Response: $\beta_a \cdot C_{e,A}(t)$

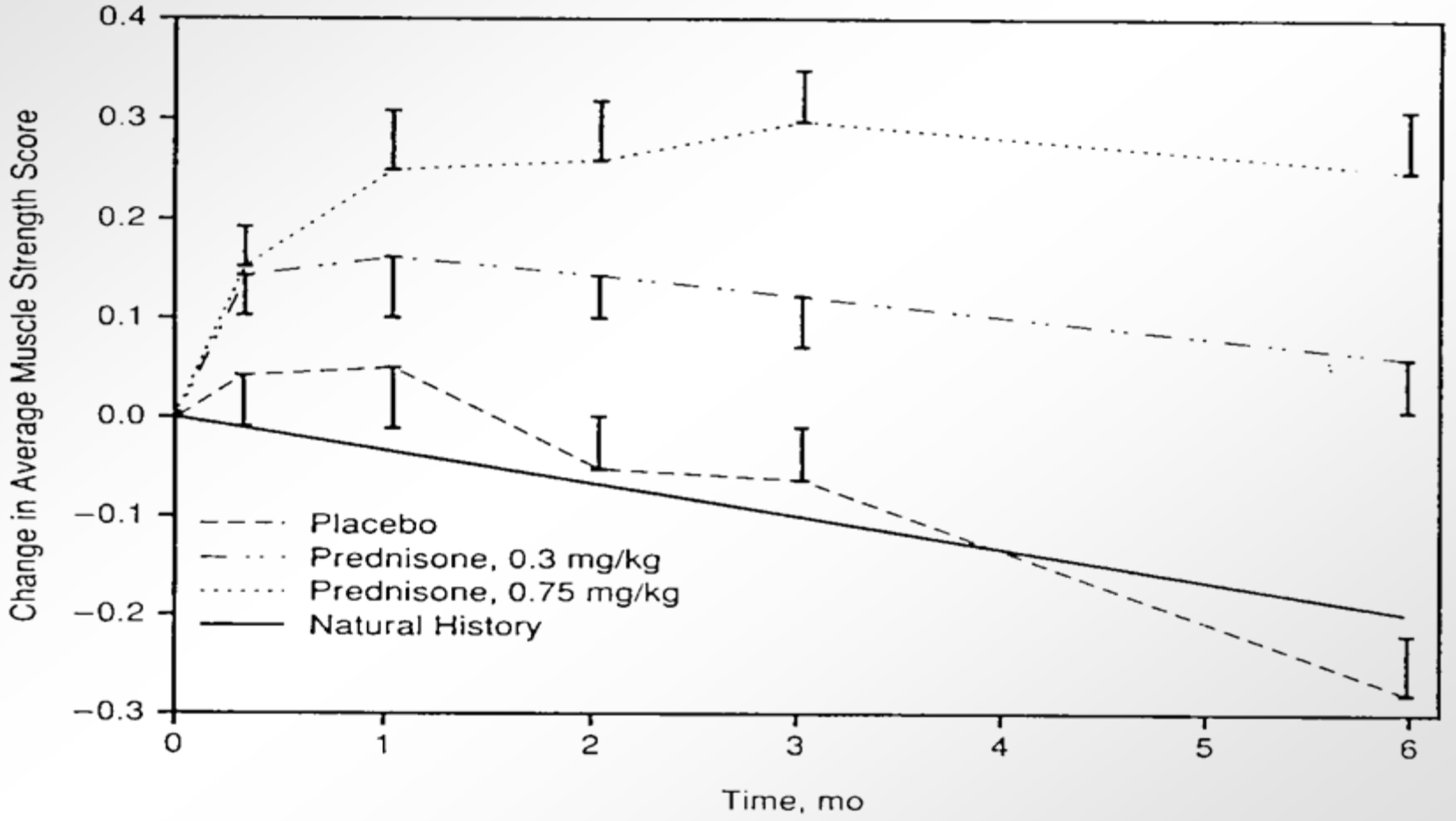
Holford & Peace, Proc Natl Acad Sci 89 (1992):11466-11470

Tacrine Treatment of Alzheimer's Disease



Holford & Peace, Proc Natl Acad Sci 89 (1992):11466-11470

Prednisone Treatment Effect on Muscular Dystrophy

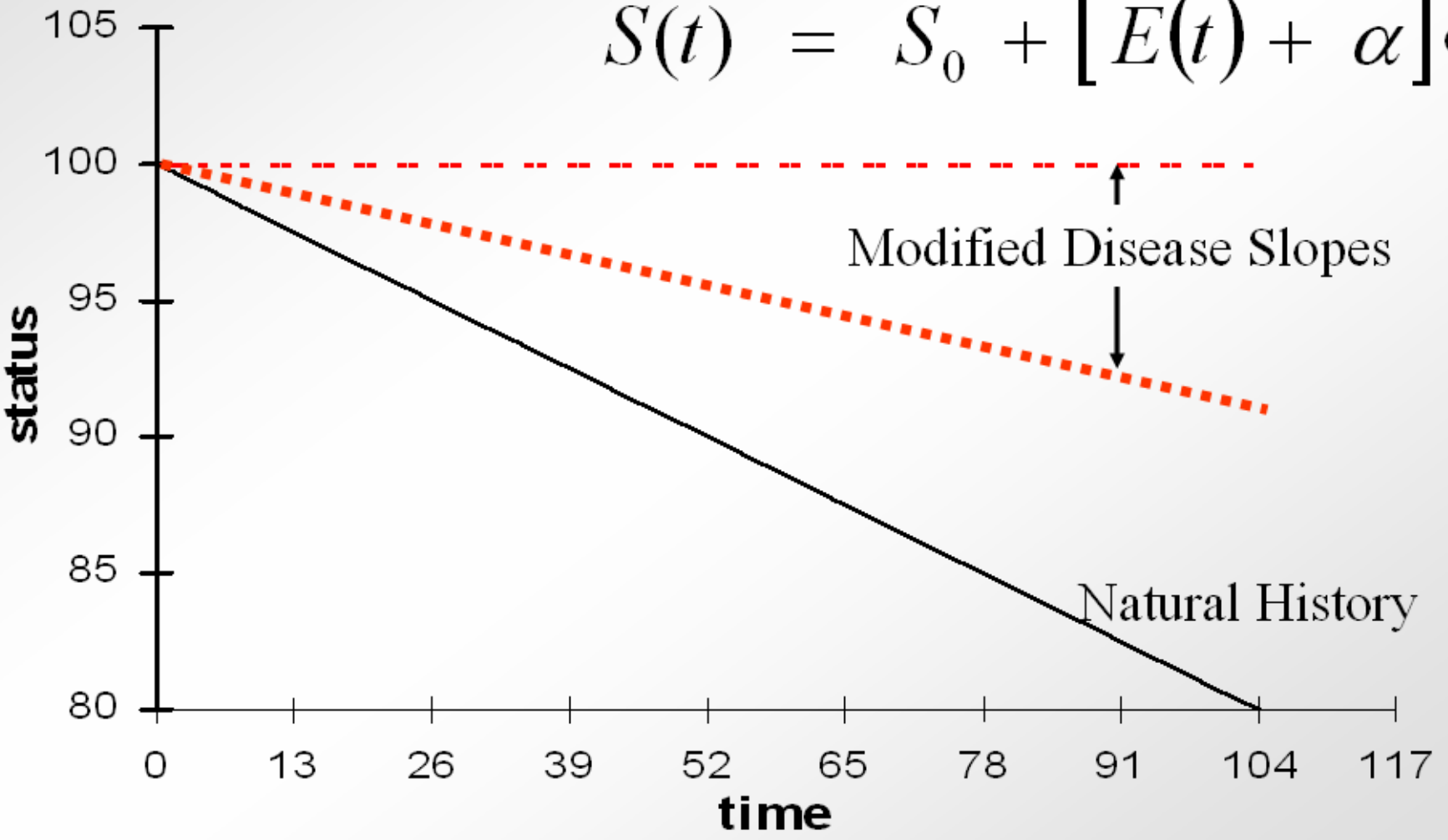


Griggs et al. Arch Neurol (1991); 48: 383-388

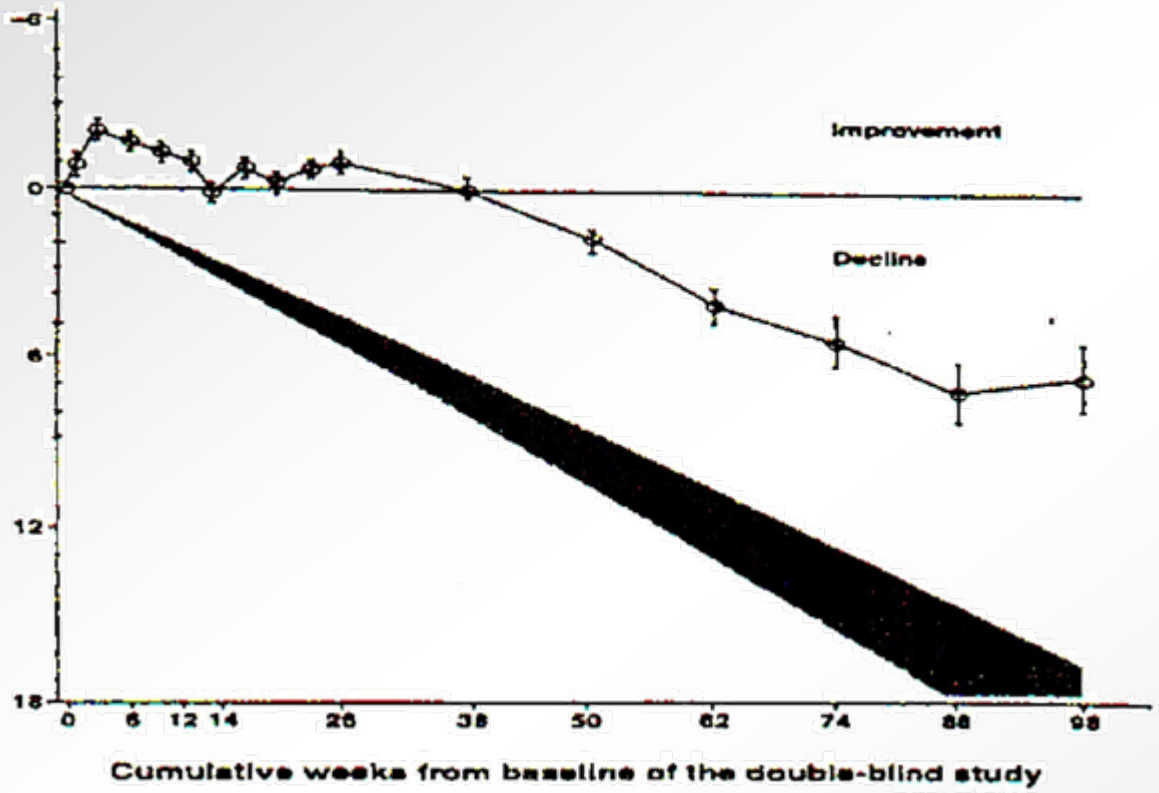
Linear Disease Progression Model with Disease Modifying ("Slope") Active Drug Effect

adapted from Holford 1999

$$S(t) = S_0 + [E(t) + \alpha] \bullet t$$



Evaluation of Effect of Donepezil on Trajectory of Alzheimer's Disease

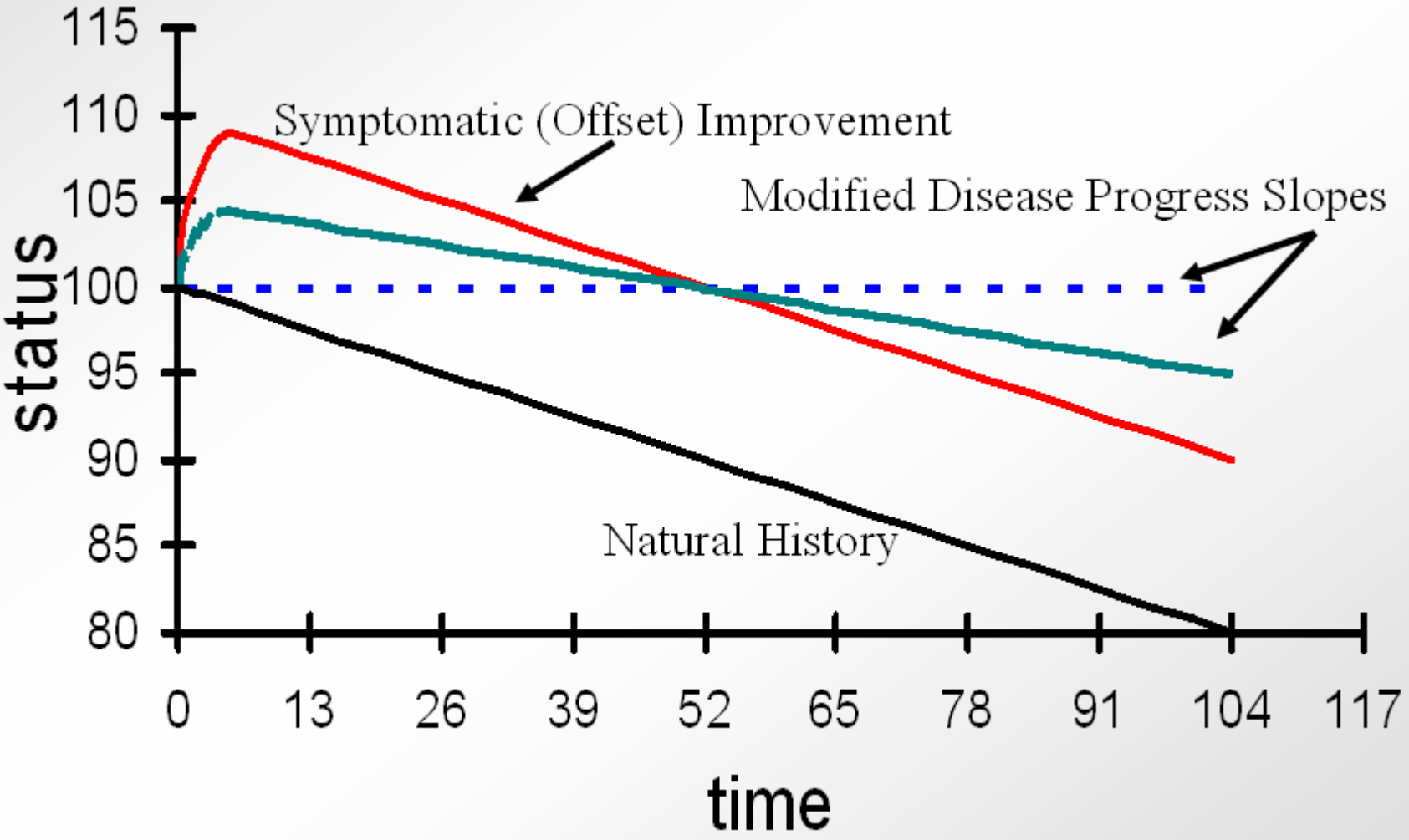


"During the first 6-9 months of the study, mean ADAS-cog scores showed evidence of clinical improvement from baseline. After this time scores gradually deteriorated. Overall the decline was less than that estimated if this cohort of patients had not been treated."

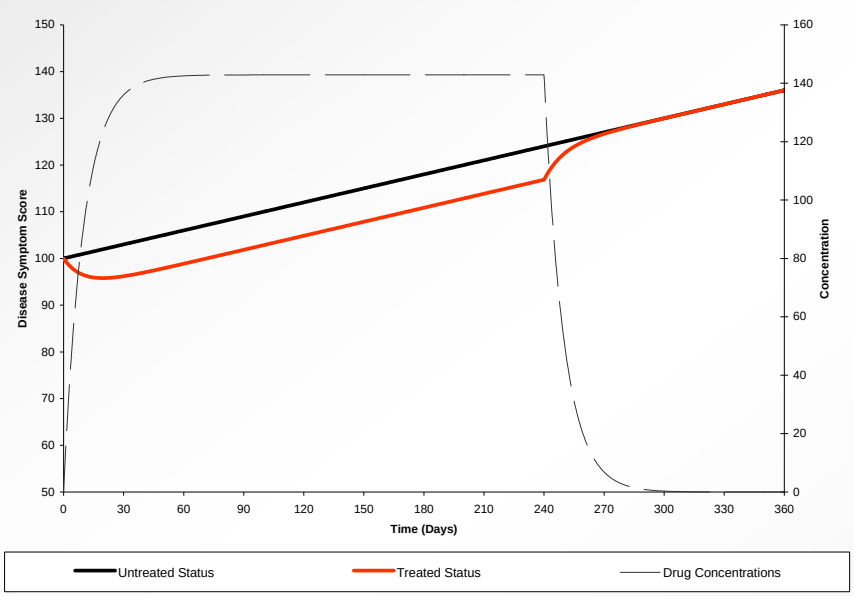
Rogers SL, Doody RS, Pratt RD, Ieni JR. "Long term efficacy and safety of donepezil in the treatment of Alzheimer's disease: final analysis of the results of a US multicentre open label extension study". European Neuropsychopharmacology 2000 May;10(3):195-203

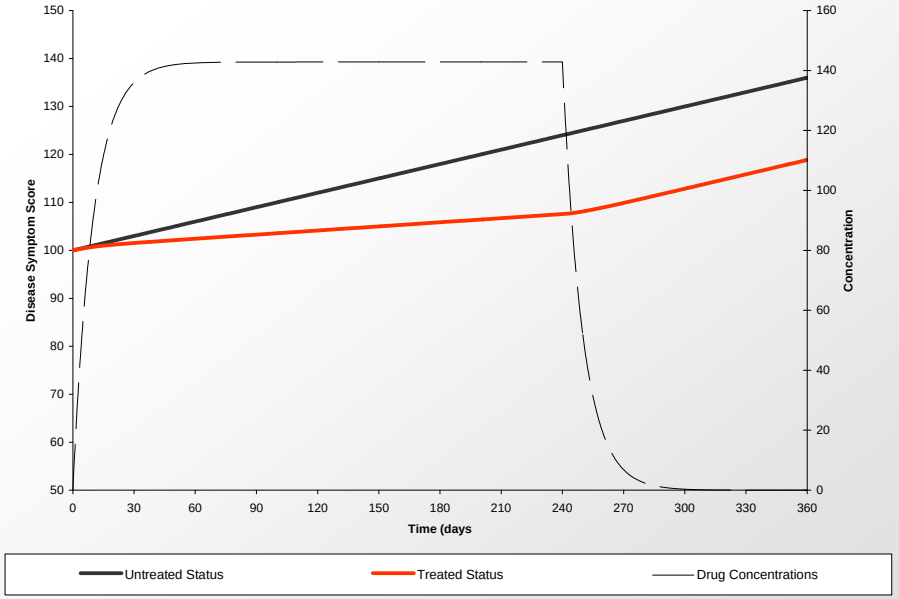
Alternative Drug Effect Mechanisms Superimposed on a Linear Natural History Disease Progression Model

adapted from Holford 1999



Onset and Offset of Drug Effect Helps Distinguish Symptomatic from Disease Modifying Effects





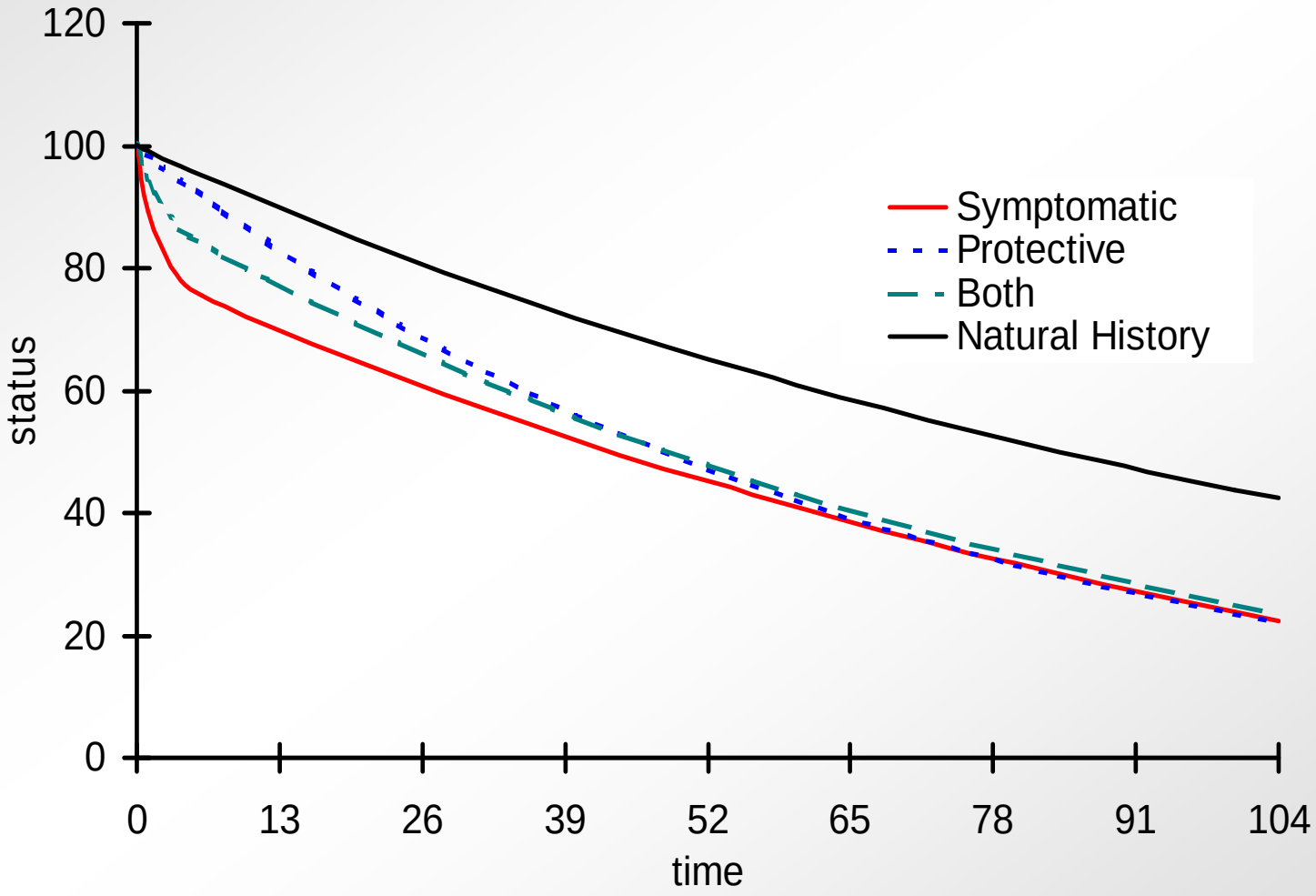
Asymptotic Progression Models

* Useful if the marker of disease progression has a natural limit (0 or some other value)
* Zero Asymptote (S_0, k_{prog})
  - Spontaneous recovery or return to a 0 value of disease progression marker
  - Several functions used to describe
    * Exponential
    * Emax functions
* Non-Zero Asymptote (S_0, S_{ss}, k_{prog})
  - Progression to maximal or "burned out" state (S_{ss})
  - Several functions used to describe
    * Emax functions
    * Growth functions

Dealing with Asymptotic Functions

* Both zero and nonzero asymptotic models can be altered to include
  - Offset Pattern
  - Slope Pattern
  - Both Offset and Slope Patterns
* Selection of the function depends on nature of the marker of disease progression being evaluated

Zero Asymptote Model



Exponential "Zero Asymptotic" Disease Progression Functions

$$S(t) = S_0 \bullet e^{-k_{prog} \bullet t}$$

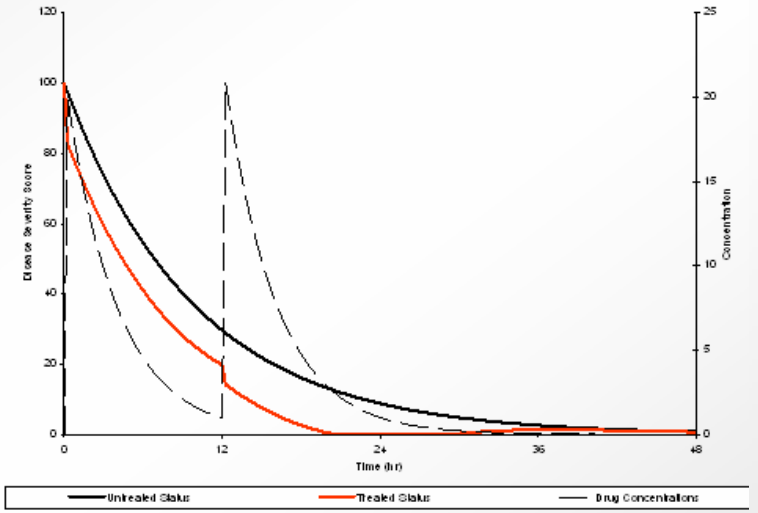
Zero Asymptote Disease Progression Function

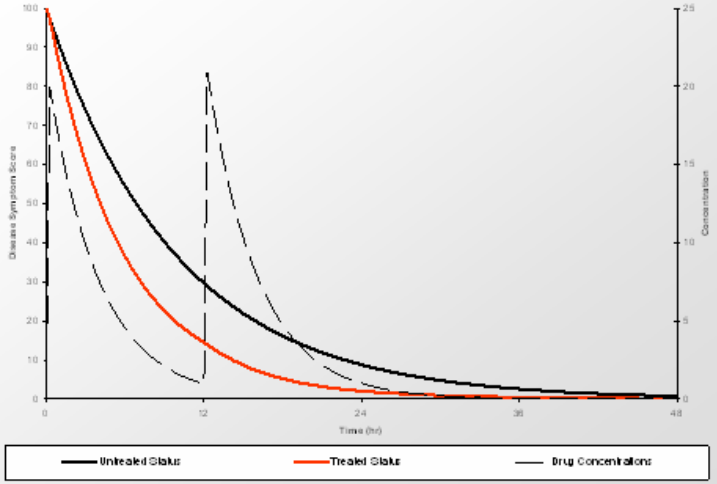
$$S(t) = S_0 \bullet e^{-k_{prog} \bullet t} - E(t)$$

Zero Asymptote Disease Progression Function
Symptomatic (Offset) Drug Effect

$$S(t) = S_0 \bullet e^{-(k_{prog} + E(t)) \bullet t}$$

Zero Asymptote Disease Progression Function
Disease Modifying Drug Effect





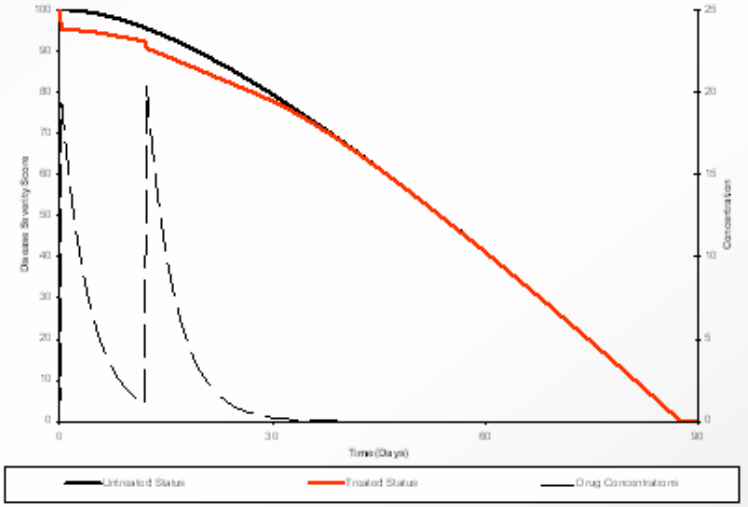
Emax "Zero Asymptotic" Disease Progression Functions

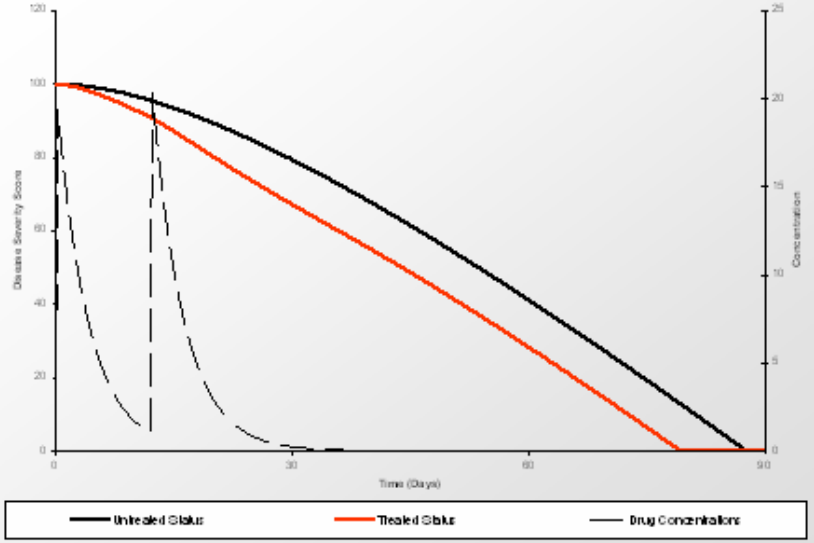
$$S(t) = S_0 + \frac{S_{\max} \bullet t}{S_{50} + t}$$

$$S(t) = S_0 + \frac{S_{\max} \bullet t}{S_{50} + t} + E(t)$$

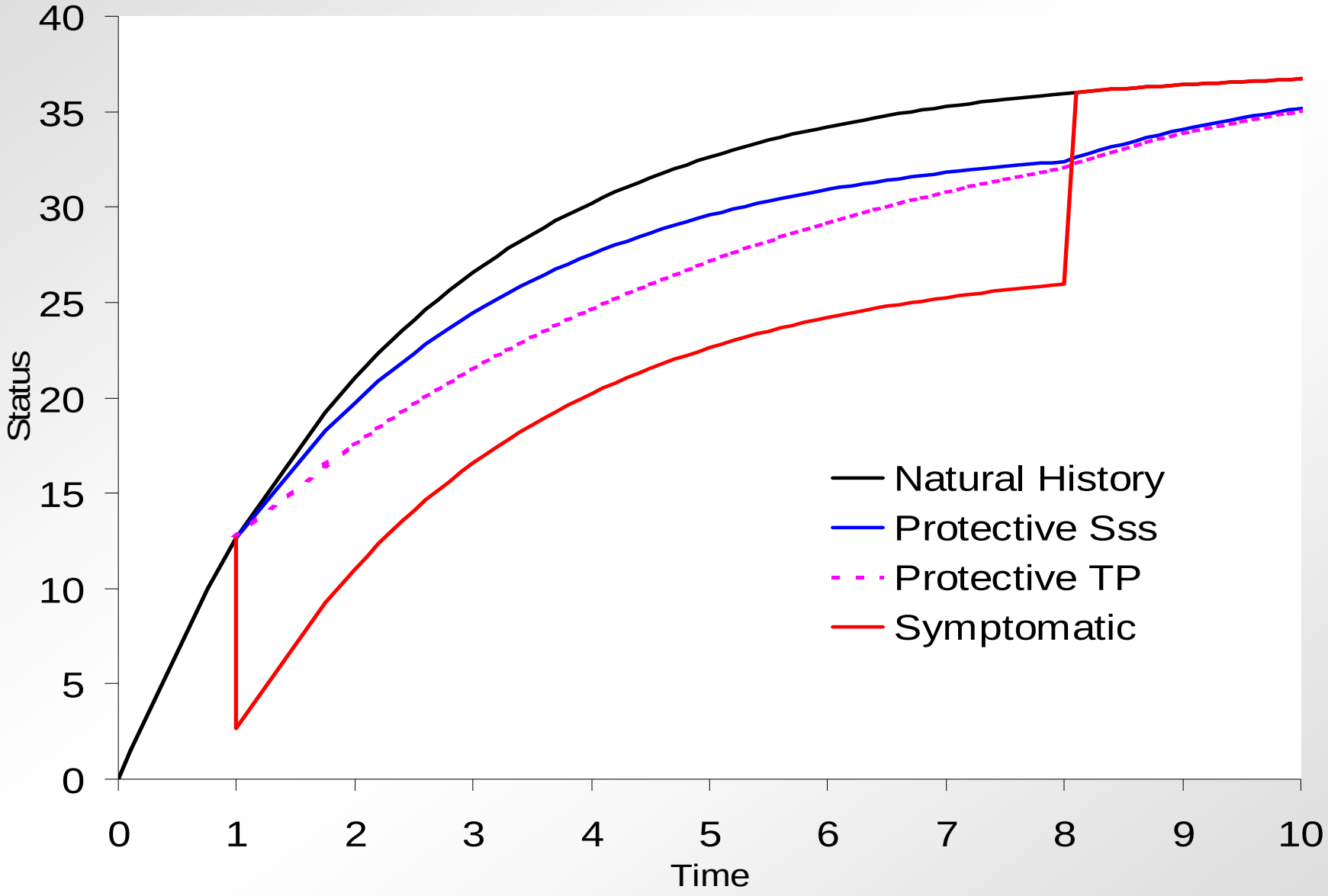
$$S(t) = S_0 + \frac{S_{\max} \bullet (1 + E(t)) \bullet t}{S_{50} + t}$$

$$S(t) = S_0 + \frac{S_{\max} \bullet t}{S_{50} \bullet (1 + E(t)) + t}$$





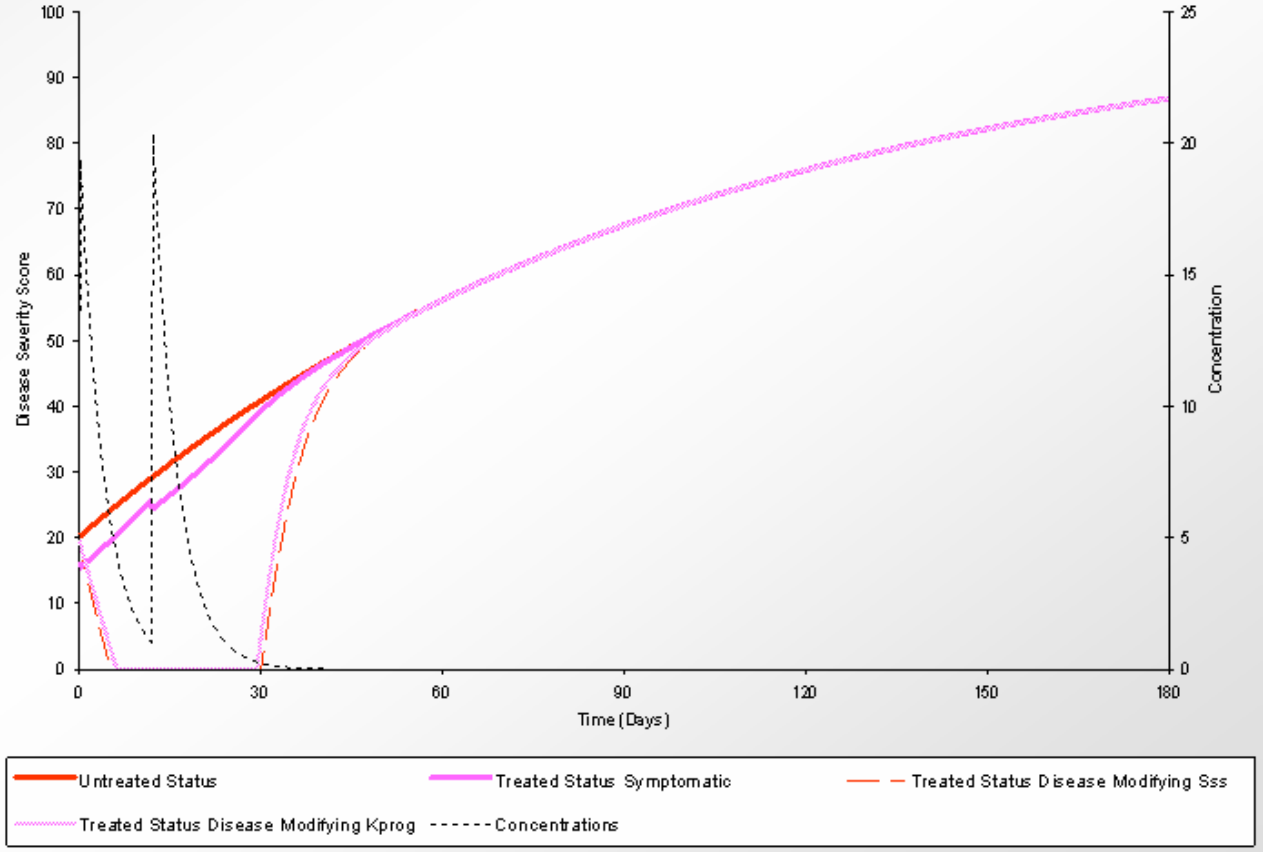
Non-Zero Asymptote Model



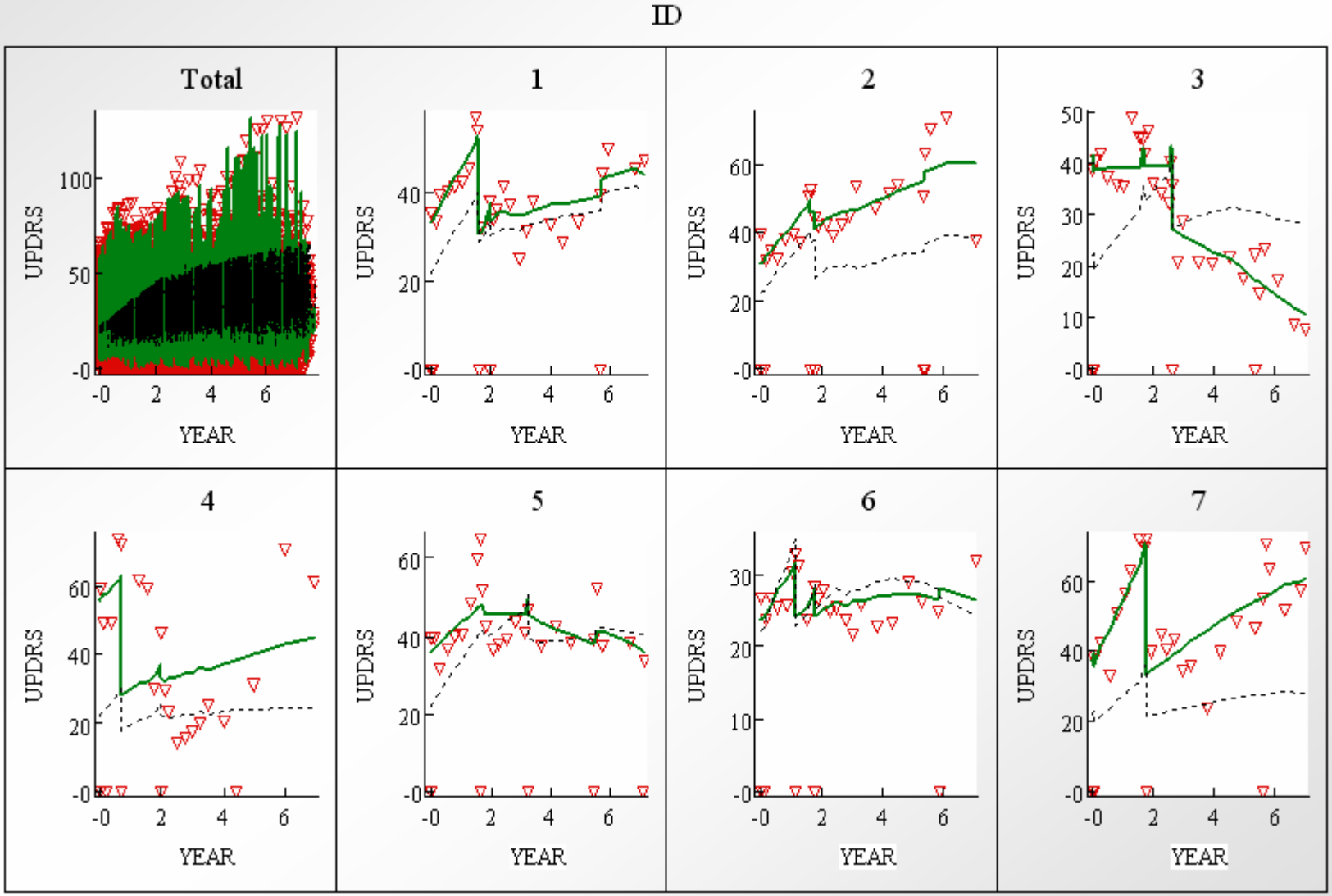
Non-Zero Asymptote Models

$$S(t) = S_0 \cdot e^{-k_{prog} \bullet t} + S_{SS} \cdot \left(1 - e^{-k_{prog} \bullet t}\right)$$

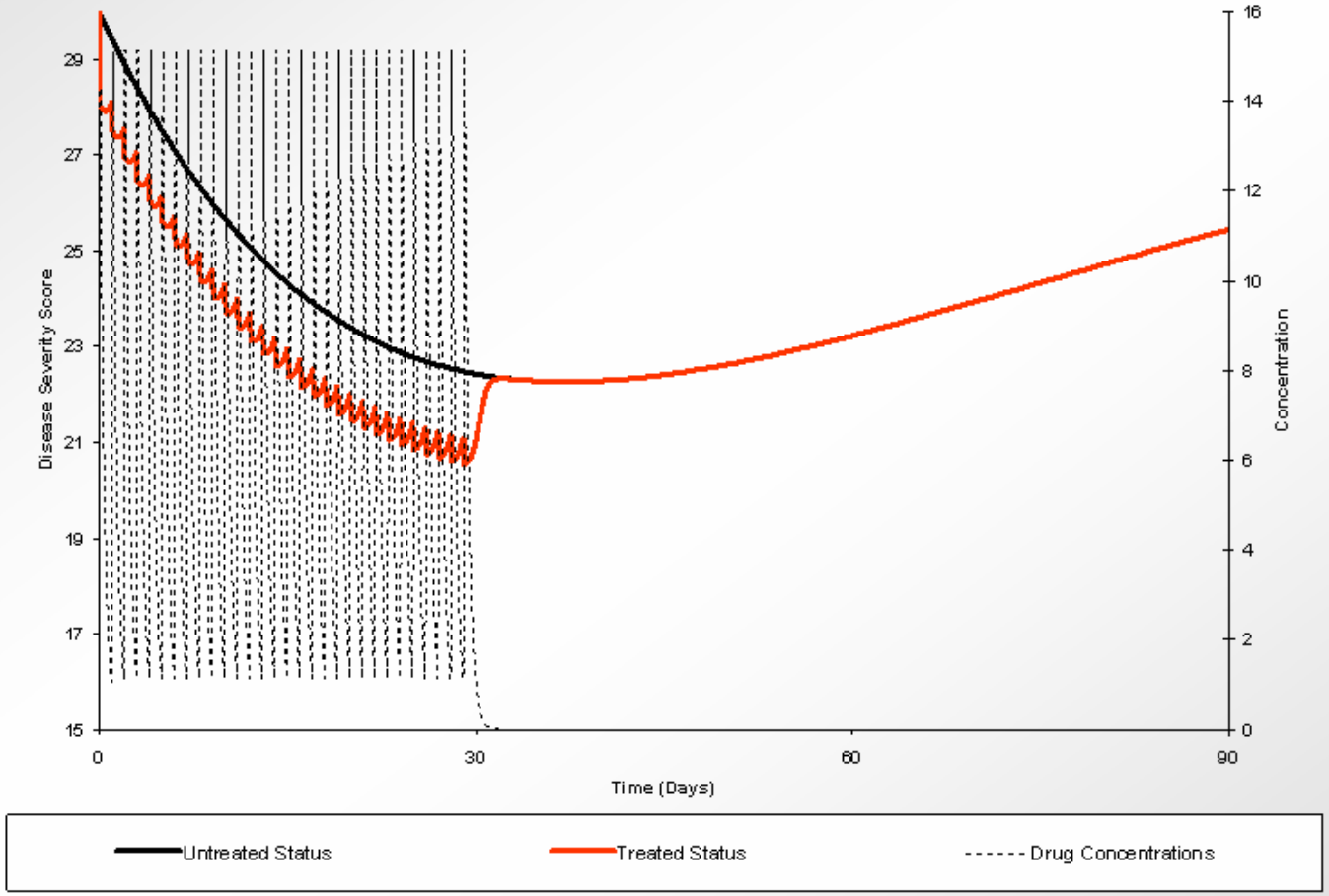
Effect of drug can be added as "offset" for symptomatic improvement
If the drug has disease modifying activity, the effect can reduce Sss
or it can slow kprog



PSG DATATOP Cohort

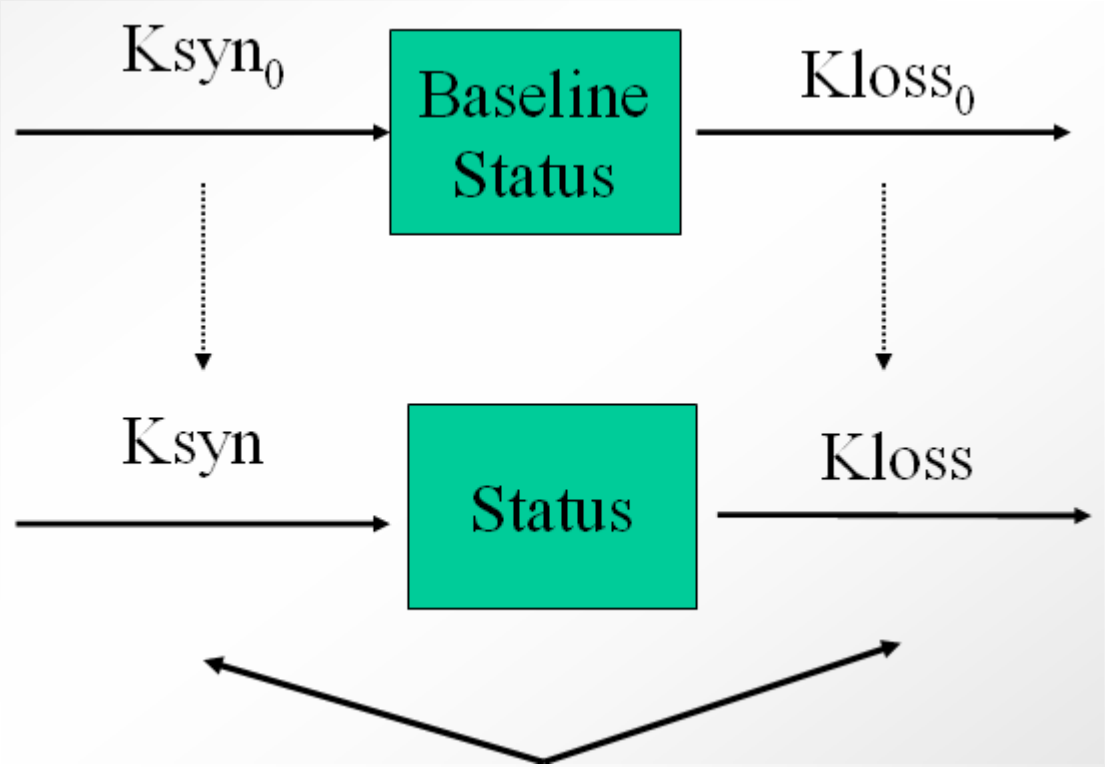


Inverse Bateman Function



$$HAMD(t) = S0 - \frac{Drec \bullet Krec}{Krec - Kon} \bullet \exp\left(Kon \bullet t - Krec \bullet t\right)$$

Physiological Models of Disease Progress



Either of these can change with time to produce disease progression

Physiological Models of Disease Progress

$$\frac{dS}{dt} = K_{syn} - k_{loss} \cdot PDI \cdot S$$

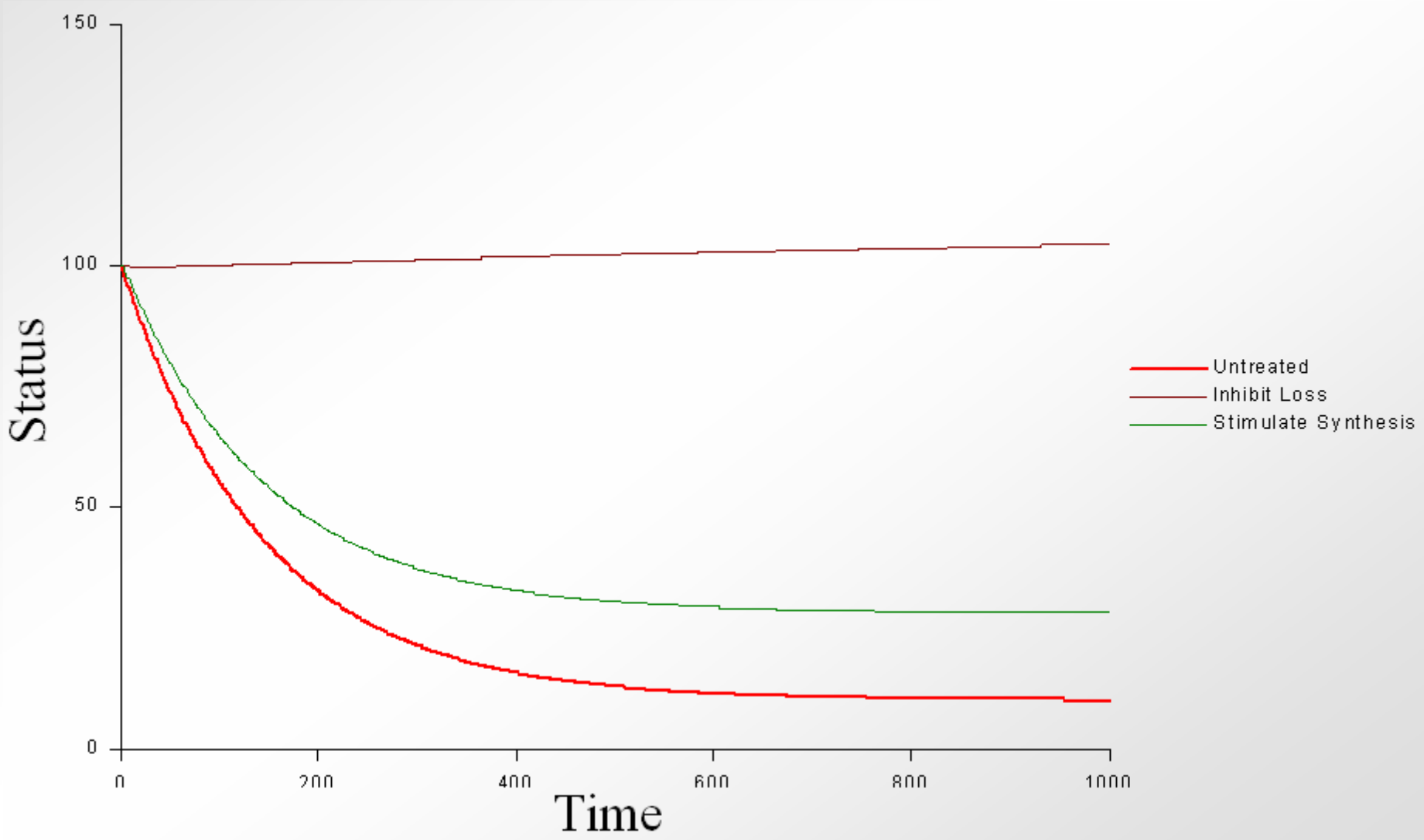
Disease is caused by build up or loss of a particular endogenous substance

$$Kloss = K_{loss0} \cdot \left(1 + (Maxprog - 1) \cdot \left(1 - e^{\ln(2)/t50loss \cdot t}\right)\right)$$

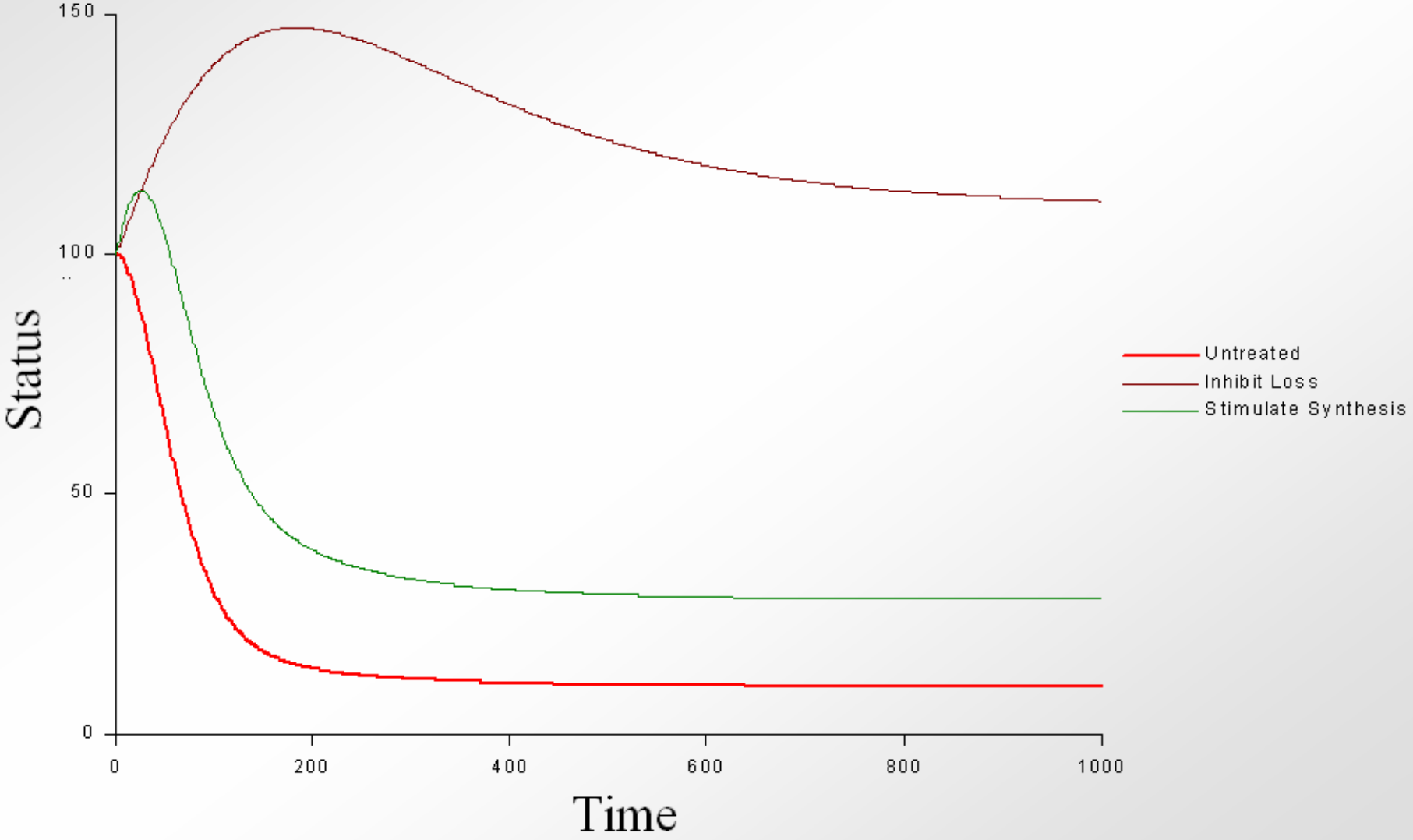
$$PDI = 1 - \frac{C_{e,A}}{C50 + C_{e,A}}$$

Drug action can be described using delay function such as an effect compartment

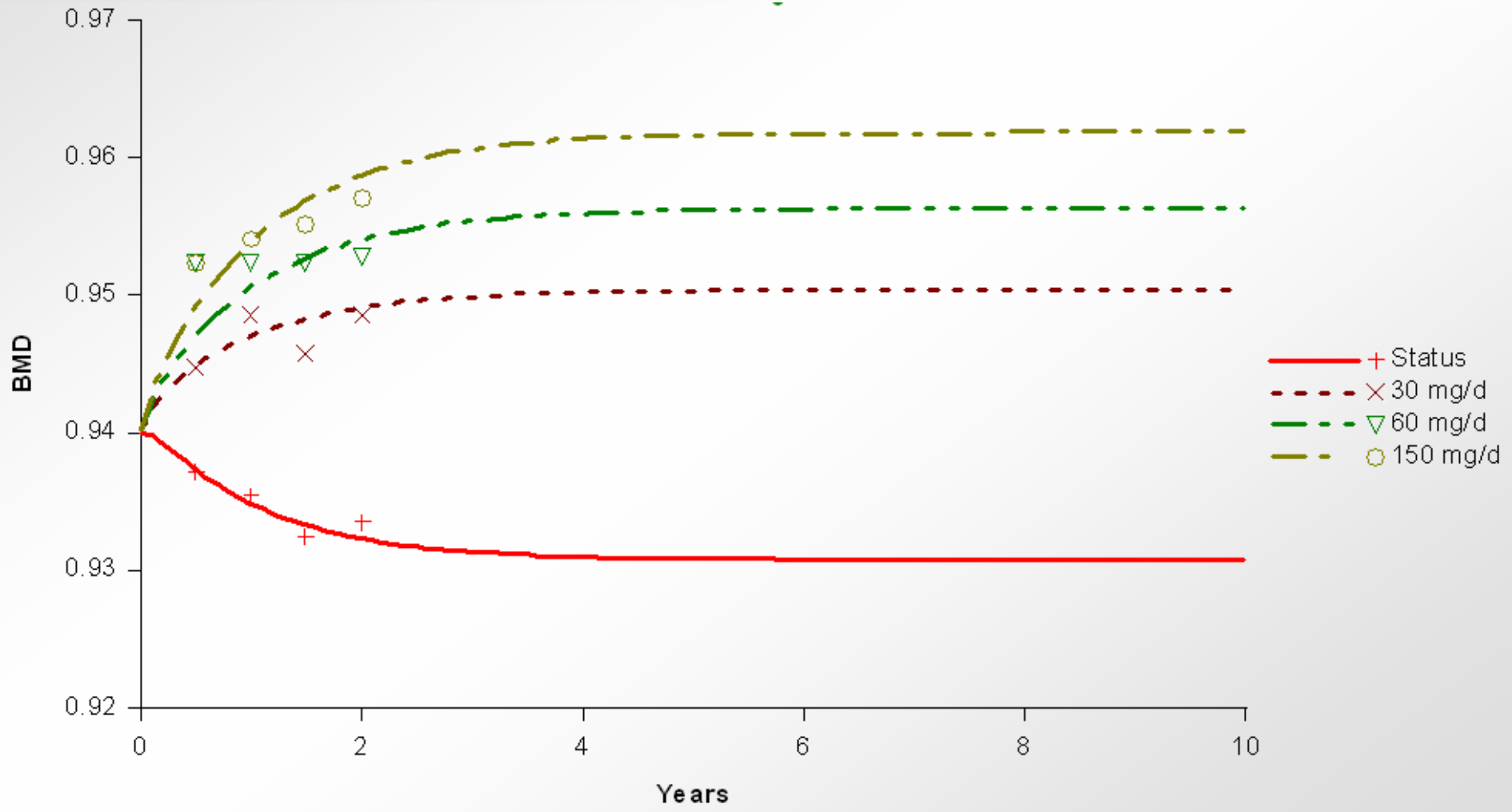
Disease Progression Due to Decreased Synthesis



Disease Progression Due to Increased Loss

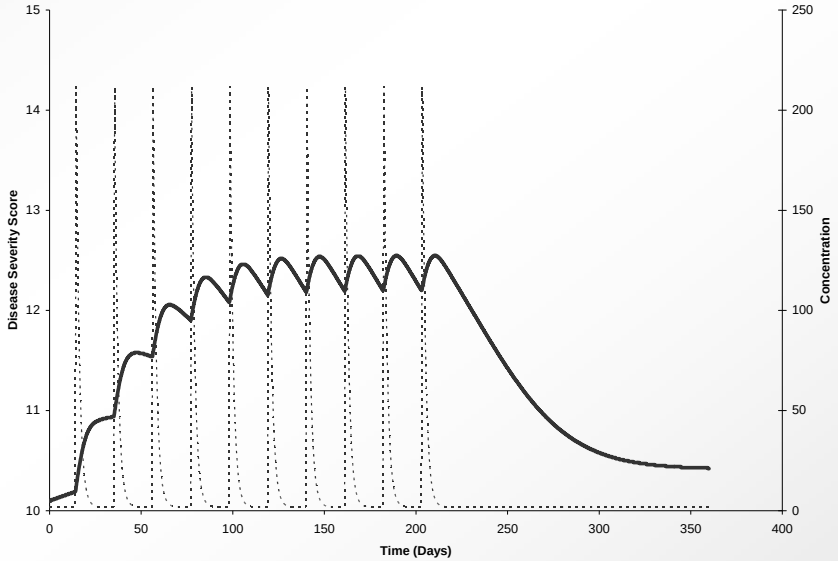


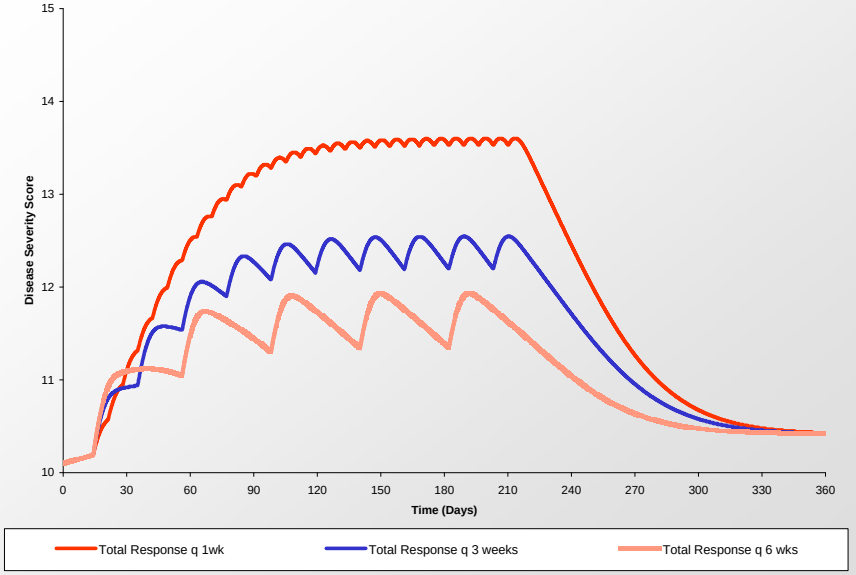
Bone Mineral Density Change with Placebo and 3 doses of Raloxifene



Cell Transit Models

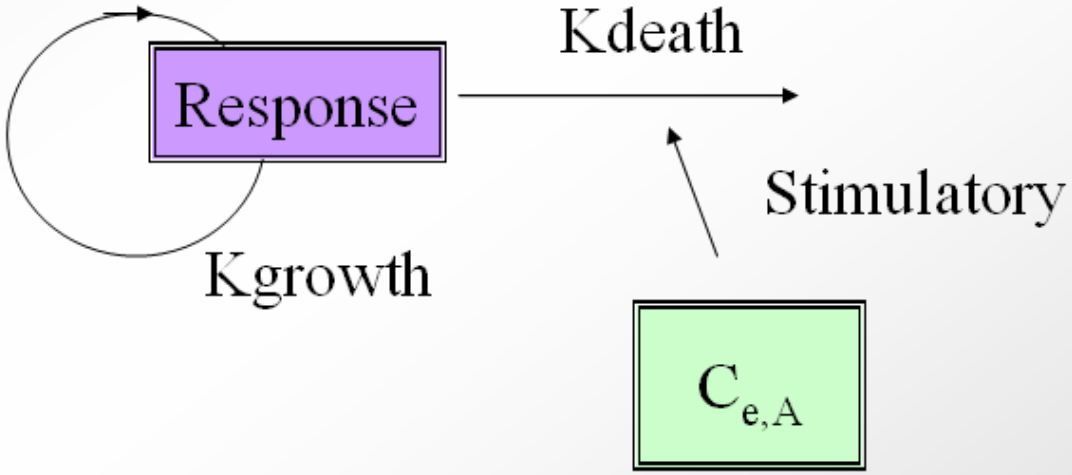
* Utilizes a string of compartments to implement a delay to response
* Useful for modeling anemia and other chronic progressive diseases





Models Describing Growth

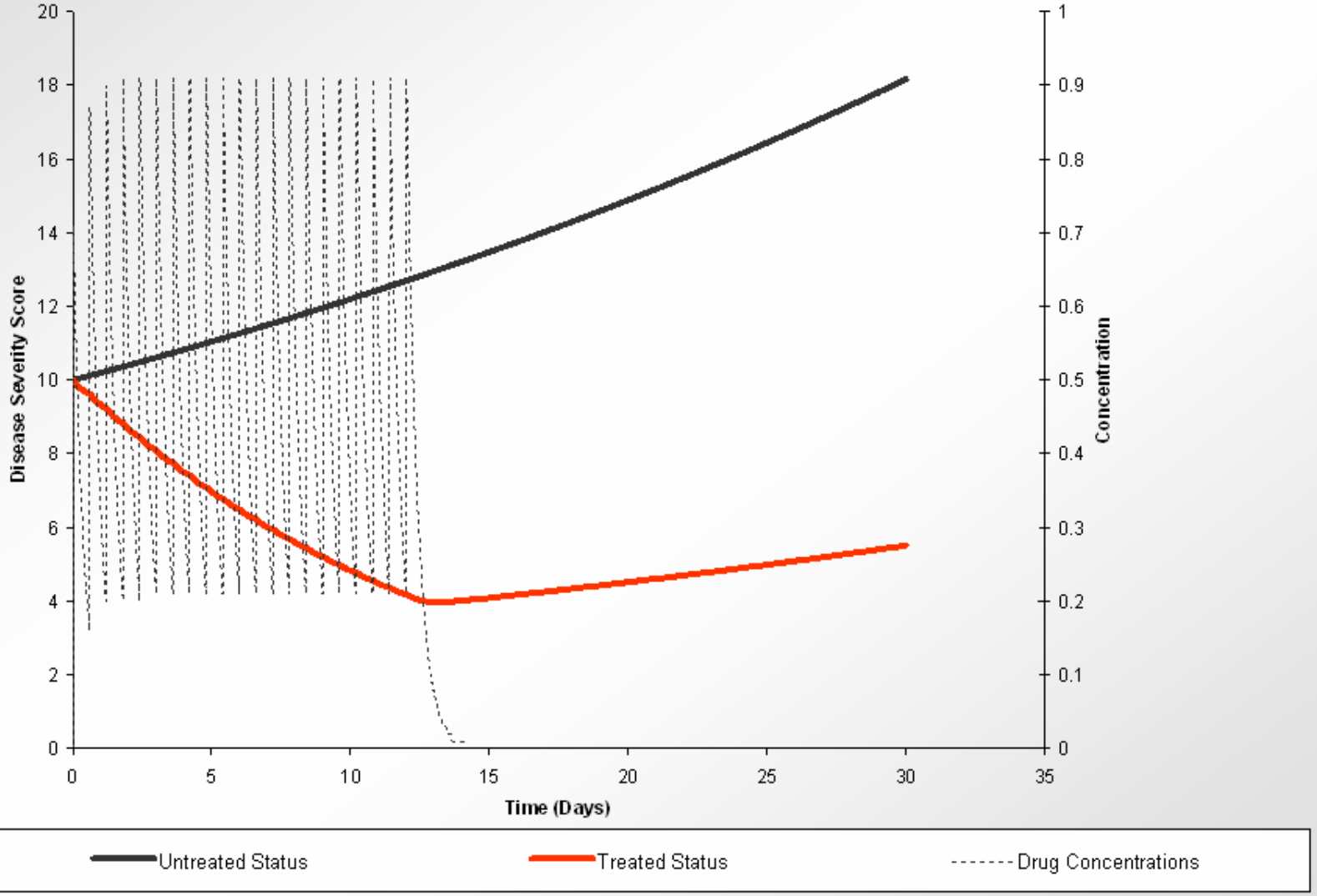
$$\frac{dR}{dt} = k_{growth} \bullet R - k_{death} \bullet R \bullet C_{e,A}$$



First order kinetics for input!

Effect of drug stimulates loss of response (R)

Growth Functions



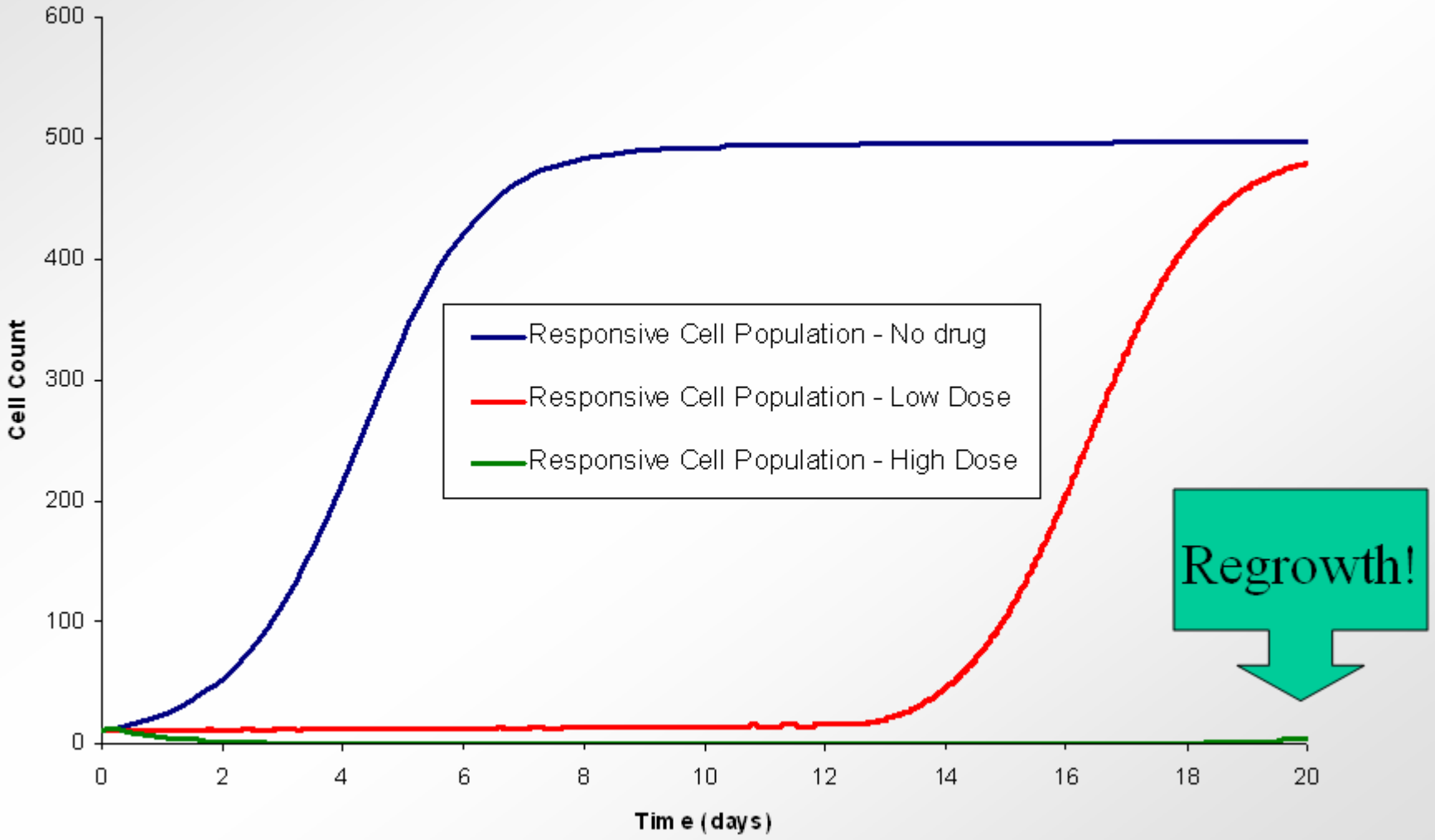
Gompertz Growth Function Models

$$\frac{dRs}{dt} = K_{RS} \bullet Rr + \beta \bullet Rs \bullet (\beta_{\max} - Rs) - \left[K_{SR} + \left(1 + \frac{E\max \bullet C_{e,A}}{EC50 + C_{e,A}} \right) \bullet K_{SO} \right] \bullet Rs$$

$$\frac{dRr}{dt} = K_{SR} \bullet Rs - K_{RS} \bullet Rr$$

Describes the Formation of Two Responses: Sensitive (Rs) and Resistant (Rr)
Defines a Maximal Response
Drug Effect is Delayed via Link Model and Limited via Emax Model

Growth Curves for 3 Treatments - Untreated, Low and High Dose



Using Survival Functions to Describe Disease Progress

* Empirical means of evaluating the relationship between the drug effect and the time course of disease progress
* Links the pharmacodynamics to measurement of outcome

Survival Function

* S(t) = P(T > t)
* Monotone, Decreasing Function
* Survival is 1 at Time=0 and 0 as Time Approaches Infinity.
* The Rate of Decline Varies According to Risk of Experiencing an Event
* Survival is Defined as

$$S(t) = \exp(-H(t))$$

Hazard Functions

* Hazard Functions Define the Rate of Occurrence of An Event
  - Instantaneous Progression
  - PKPD Model Acts on Hazard Function
* Cumulative Hazard is the Integral of the Hazard Over a Pre-Defined Period of Time
  - Describes the Risk
  - Translates Pharmacodynamic Response into a Useful Measure of Outcome
    * Assessment of Likely Benefit or Adverse Event
    * Comparison With Existing Therapy

Hazard Functions

* Define "T" as Time To Specified Event (Fever, Infection, Sepsis following chemotherapy)
  - T is Continuous (i.e. time)
  - T is Characterized by:
    * Hazard: Rate of Occurrence of Event
    * Cumulative Hazard or Risk
    * Survival: Probability of Event NOT Occurring Before Time = t

Hazard Functions

* Hazard is Assumed to be a Continuous Function
  - Can be Function of Biomarkers (e.g. Neutrophil Count)
* Hazard Functions can be Adapted for Any Clinical Endpoints Evaluated at Fixed Time Points (e.g. During Chemotherapy Cycle)
* The Hazard Function is Integrated Over Time to Yield Cumulative Probability of Experiencing an Event by a Specified Time (Risk).

Using Hazard Functions in PK/PD Models

* If Hazard Function is Defined as a Constant Rate “K” Such that

$$h(t) = k$$

* Then the Cumulative Hazard is

$$H(t) = \int_0^t K dt = Kt$$

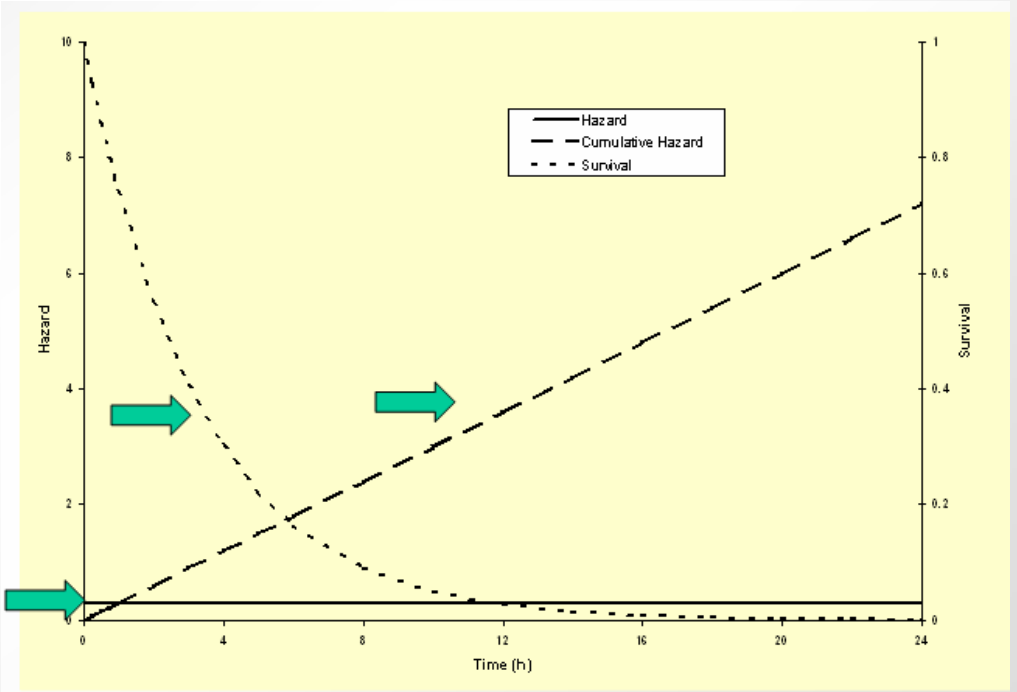
$$Kt = -\ln\left[S(t)\right]$$

* Survival is

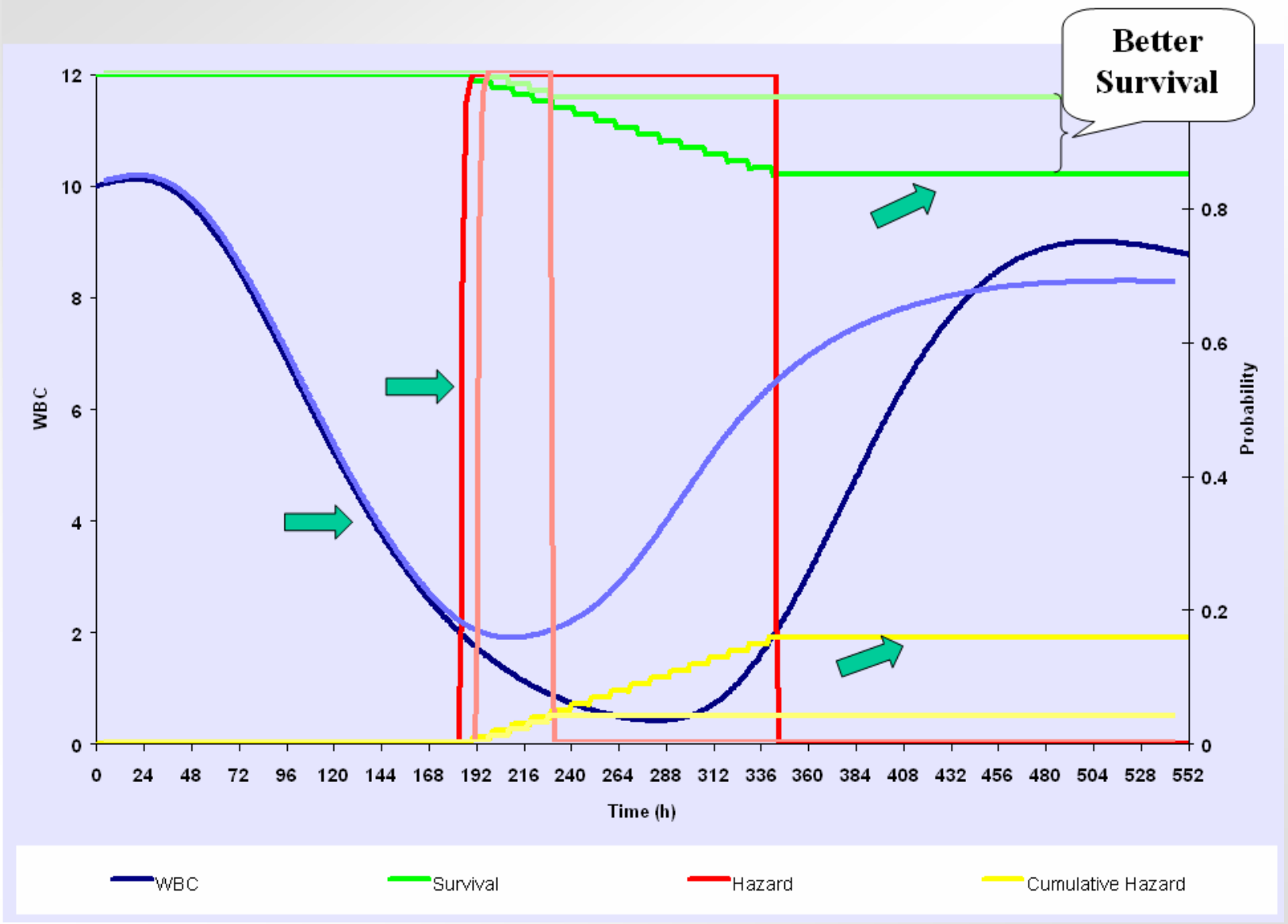
$$S(t) = \exp\left[-Kt\right]$$

Hazard, Cumulative Hazard and Survival

* In This Example Hazard Remains Constant
* Cumulative Hazard (Risk) Increases With Time
* Surviving Fraction Drops



Comparing Hematopoietic Factors Using Hazard Functions



Disease Progress Models

* Alzheimer's Disease
  - Linear: Drug effects symptomatic
* Diabetic Neuropathy
  - Linear: Drug effect both?
* Parkinson's Disease
  - Asymptotic: Drug effect both?
* Osteoporosis
  - Inhibition of Bone Loss (estrogen)
* In most cases, the functions used to describe the trajectory of the disease marker are empirical. Whenever possible, mechanistic models should be used – but for most diseases mechanisms are not always clearly understood

Summary

* Accounting for Disease Progress is Important For the Analysis of Drug Effects
  - Better Able to Discern True Effect
  - Improves Reliability of Simulation Work
  - Developing New Drug Candidates
  - Visualize the Drug Use Better
  - Convert Data into Understanding!
* Issues Associated With Building Disease Progress Models
  - Lack of Available Data for Untreated Patients
  - Time Required to Collect Data
  - Variability Inherent in Data May Require Large Numbers of Subjects to Determine Parameters Accurately