Disease Progress Models
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February 3, 2011
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

Equation model
Components of a Disease Progression Model

\[ S(t) = \text{Baseline} + \text{Natural History} + \text{Placebo} + \text{Active} \]

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!

Reproduction of an ad for Sucrosa placebo by AstraZeneca.

“It’s going to work.”

Photo of a man on a ladder with his arms outstretched enjoying the view out a window of the sky with clouds. Inside the window is a view of the sky or sea.

Sucrosa placebo
It’s a pill.”
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

Flow chart

Solid Organ Transplant (Cadaveric Donor? Matched or Unmatched? First Transplant?)
↓
Up-regulation of CD25+ T Cells (Measure CD25+ T Cells)
↓
Immune Inflammatory Response (Measure IL6, TNFalpha)
↓
Cell Death
↓
Administer Drug or Placebo

Rejection?
Linear Disease Progression Model
(adapted from Holford 1999)

Graph showing Status over time

\[ S(t) = S_0 + a \times t \]
Linear Disease Progression Model with Temporary ("Offset") Placebo or Active Drug Effect
(adapted from Holford 1997 & 1999)

\[ S(t) = S_0 + E(t) + a \times t \]

\[ E(t) = \beta \times C_p(t), \quad \beta \times C_e(t) \quad \text{or} \quad \frac{E_{\text{max}} \times C(t)}{E_{C_{50}} + C(t)} \]

\[ E(t) = \beta \times C_p(t), \quad \beta \times C_e(t) \quad \text{or} \quad \frac{E_{\text{max}} \times C(t)}{E_{C_{50}} + C(t)} \]

Graph showing status over time for temporary improvement and natural history
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
Effect Compartment

Visual of how the plasma concentration effects the site concentration
Evaluation of Effect of Eptastigmine on Trajectory of Alzheimer’s Disease

Graph of disease trajectory with and without eptastigmine.

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

AZT Treatment Effect on HIV

Graph showing CD4 count over time (weeks) comparing placebo with treatment

“...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.”

Tacrine Treatment of Alzheimer's Disease

Baseline Disease State: $S_0$

Natural History: $S_0 + \alpha \times t$

Placebo Response: $\beta_p \times C_{e,p}(t)$

Active Treatment Response: $\beta_a \times C_{e,A}(t)$

Tacrine Treatment of Alzheimer's Disease

Graph showing the response over time (days) for the disease, drug, placebo and total response.

Prednisone Treatment Effect on Muscular Dystrophy

Graph showing change in Average Muscle Strength Score over time (months) for placebo, prednisone, 0.3 mg/kg, prednisone, 0.75 mg/kg, and natural history of disease.

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

adapted from Holford 1999

\[ S(t) = S_0 + [E(t) + a] \times t \]

Graph showing status over time
Evaluation of Effect of Donepezil on Trajectory of Alzheimer's Disease

Graph showing cumulative weeks from baseline of the double-blind study

“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.”

Alternative Drug Effect Mechanisms Superimposed on a Linear Natural History Disease Progression Model
adapted from Holford 1999

Graph showing status over time for symptomatic (offset) improvement, modified disease progress slopes and natural history
Onset and Offset of Drug Effect Helps Distinguish Symptomatic from Disease Modifying Effects

Two graphs showing disease symptoms score over time (days) for untreated status, treated status, and drug concentrations over time.
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

Graph showing status over time for symptomatic, protective, both, and natural history of disease
Exponential “Zero Asymptotic” Disease Progression Functions

\[ S(t) = S_0 \times e^{k_{\text{prog}} \times t} \]

Zero Asymptote Disease Progression Function

\[ S(t) = S_0 \times e^{-k_{\text{prog}} \times t - \text{E}(t)} \]

Zero Asymptote Disease Progression Function Symptomatic (offset) drug effect

\[ S(t) = S_0 \times e^{-(k_{\text{prog}} + \text{E}(t)) \times t} \]

Zero Asymptote Disease Progression function
Disease modifying drug effect

Two graphs with one that shows the disease severity score over time (hr) for untreated status, treated status and drug concentrations. The other graph shows disease symptom score over time (hr) for untreated status, treated status and drug concentrations.
**Emax “Zero Asymptotic” Disease Progression Functions**

Two graphs showing the disease severity score over time (days) for untreated status, treated status and drug concentrations.

\[
S(t) = S_o + \frac{S_{\text{max}} \times t}{S_{50} + t}
\]

\[
S(t) = S_o + \frac{S_{\text{max}} \times t + E(t)}{S_{50} + t}
\]

\[
S(t) = S_o + \frac{S_{\text{max}} \times (1+E(t)) \times t}{S_{50} + t}
\]

\[
S(t) = S_o + \frac{S_{\text{max}} \times t}{S_{50} \times (1 + E(t)) + t}
\]
Non-Zero Asymptote Model

Graph indicating status over time for natural history, protective Sss, protective TP, and Symptomatic.
Non-Zero Asymptote Models

\[ S(t) = S_0 e^{-k_{\text{prog}} t} + S_{ss} (1 - e^{-k_{\text{prog}} t}) \]

Graph showing disease severity score over time (days) for untreated status, treated status symptomatic, treated status disease modifying Sss, treated status disease modifying Kprog, and concentrations
PSG DATATOP Cohort

A series of 7 graphs showing disease progression in individual subjects.
Inverse Bateman Function

Graph showing diseases severity score over time (days) for untreated status, treated status, and drug concentrations over time.

\[ HAMD(t) = S0 - \frac{Drec \times Krec \times \exp{(Kon \times t - Krec \times t)}}{Krec - Kon} \]
Physiological Models of Disease Progress

\[ K_{syn0} \quad \text{BASELINE} \quad K_{loss0} \]

\[ \downarrow \quad \downarrow \]

\[ K_{syn} \quad \text{STATUS} \quad K_{loss} \]

Either of these can change with time to produce disease progression
Physiological Models of Disease Progress

\[ dS = K_{syn} - k_{loss} \times PDI \times S \]

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

\[ K_{loss} = K_{loss0} \times \left[ 1 \times (Maxprog - 1) \times \left[ 1 - e^{\frac{\ln(2)}{t50_{loss}}} \right] \right] \]

\[ PDI = 1 - \frac{C_{e,A}}{C_{50} + C_{e,A}} \]

Drug action can be described using delay function such as an effect compartment
Disease Progression Due to Decreased Synthesis

Graph showing status over time for untreated, inhibit loss, and stimulate synthesis conditions.
Disease Progression Due to Increased Loss

Graph showing status over time for untreated, inhibit loss, and stimulate synthesis conditions.
Bone Mineral Density Change with Placebo and 3 doses of Raloxifene

Graph indicating BMD over Years for + Status, x 30 mg/d, ▼60 mg/d, and o 150 mg/d
Cell Transit Models

Utilizes a string of compartments to implement a delay to response

Graph indicating disease severity score over time (days)

Useful for modeling anemia and other chronic progressive diseases

Graph indicating disease severity score over time (days) for total response q 1 wk, total response q 3 wks, and total response q 6 wks
Models Describing Growth

\[ \frac{dR}{dt} = k_{\text{growth}} \times R - k_{\text{death}} \times R \times C_{e,A} \]

Graphic illustration

First order kinetics for input!
Effect of drug stimulates loss of response (R)
Growth Functions

Graph showing disease severity score over time (days) for untreated status, treated status, and drug concentrations over time.
Gompertz Growth Function Models

\[
\frac{dR_s}{dt} = K_{RS} x R_r + \beta x R_s x (\beta_{max} - R_s) \left[ K_{SR} \left[ 1 + \frac{E_{max} x C_{eA}}{EC50 + C_{eA}} \right] K_{SO} \right] x R_s
\]

\[
\frac{dR_r}{dt} = K_{SR} x R_s - K_{RS} x R_r
\]

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

Graph showing cell count over time (days) for responsive cell population – no drug, responsive cell population – low dose, and responsive cell population – 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

Then the Cumulative Hazard is

\[ H(t) = k \]

\[ H(t) = \int K \, dt = Kt \]

\[ Kt = \ln[S(t)] \]

Survival is \( S(t) = \exp[-Kt] \)
Hazard, Cumulative Hazard and Survival

Graph showing hazard over time (h) for hazard, cumulative hazard and survival.

In This Example Hazard Remains Constant

Cumulative Hazard (Risk) Increases With Time

Surviving Fraction Drops
Graph showing WBC over time (h) for WBC, survival, hazard, and cumulative hazard.
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