Latent Variable Indirect Response Modeling of Continuous and Categorical Clinical Endpoints

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Overview

- Indirect response (IDR) modeling as an effective paradigm for exposure-response modeling of clinical trial endpoints to guide clinical drug development
  - Ordered categorical endpoint modeling
    - Latent variable representation
  - IDR modeling of endpoints in placebo-controlled clinical trials
    - Model representation: link with change-from-baseline IDR model representation
    - An equivalence between Type I and Type III IDR models: interpretation

- Modeling extra correlation between continuous and ordered categorical endpoints

- Application to ustekinumab data
Ordered Categorical Endpoint Modeling: Latent Variable Representation

- Example: 20%, 50%, and 70% improvement in the American College of Rheumatology disease severity criteria (ACR20/50/70)
  - Combine into one variable ACR: ACR20/50/70 achieved \(\iff\) ACR \(\leq k, k = 1, 2, \text{ or } 3\)

- Latent variable representing underlying disease condition (similar to Hutmacher et al 2008):
  - \(\text{Dis}(t) = B_0 F_p(t) F_d(t) \exp(\sigma \varepsilon_t)\)
  - \(B_0\), baseline; \(0 < F_p(t) \leq 1\), placebo effect; \(0 < F_d(t) \leq 1\), drug effect

- Define \(R_fB(t) = \% \text{ reduction from baseline}\), and calculate:
  - \(R_fB(t) = \left[\text{Dis}(0) - \text{Dis}(t)\right]/\text{Dis}(0) = 1 - F_p(t) F_d(t) \exp(-\sigma \varepsilon_{i0}) \exp(\sigma \varepsilon_{it})\)
  - \(\log[1 - R_fB(t)] = \log[F_p(t)] + \log[F_d(t)] - \sigma \varepsilon_{i0} + \sigma \varepsilon_{it}\)
  - Define: \(z(t) = \log[1 - R_fB(t)], R(t) = \log[F_p(t)] + \log[F_d(t)] - \sigma \varepsilon_{i0}, \varepsilon = \varepsilon_{it}\)
    \(\iff\)
    - \(z(t) = R(t) + \sigma \varepsilon\)

- Assumption: ACR20/50/70 met, if \% reduction from baseline \(R_fB(t)\) crosses certain thresholds
- Equivalently when \(z(t) = \log[1 - R_fB(t)]\) crosses certain thresholds
Probit Regression

- Let $\beta_k$, $k = 1, 2, \text{ or } 3$, be the thresholds, i.e. $\text{ACR} \leq k \iff z(t) < \beta_k$

- Using the probit link, i.e., assuming $\varepsilon \sim N(0, 1)$:
  - $\text{prob}(\text{ACR} \leq k) = \text{prob}(z(t) < \beta_k) = \text{prob}[\varepsilon < (\beta_k - R(t))/\sigma] = \Phi[(\beta_k - R(t))/\sigma]$

- Write
  - $\gamma_k = \beta_k/\sigma$, $g(t) = -\log[F_p(t)]/\sigma$, $f_d(t) = -\log[F_d(t)]/\sigma$, $\eta = -\varepsilon_{i0}$

- Then
  - $\Phi^{-1}[\text{prob}(\text{ACR} \leq k)] = \gamma_k + g(t) + f_d(t) + \eta$
  - which is the standard form of probit regression
  - Constraint: $0 \leq g(t) < 1$, but can be reparameterized such that $-\infty \leq g(t) < 0$

- Using the logistic distribution for $\varepsilon$ leads to a similar logistic regression form, i.e., with $\Phi$ replaced by the logit function
Choosing Model Terms

- Probit regression:
  \[ \Phi^{-1} \left[ \text{prob}(ACR \leq k) \right] = \gamma_k + g(t) + f_d(t) + \eta \]

- Placebo model: Should have \( \text{prob}(ACR \leq k) \) at \( t=0 \), thus \( g(0) = -\infty \)
  - Choose \( g(t) = \log[1 - \exp(-rt)] \)
  - \( g(t) = 0 \Rightarrow \gamma_k \) represent steady-state probabilities

- Desired to use IDR model for \( f_d(t) \); to interpret as drug effect, needs \( f_d(t) = 0 \)
  - \( f_d(t) = DE[1 - R(t)] \)
  \[
  \frac{d R(t)}{dt} = k_{in} \left( 1 - \frac{C_p}{IC_{50} + C_p} \right) - k_{out} R(t)
  \]
  - \( R(0) = 1 \)

- \( f_d(t) \) turns out to be equivalent to a reduction-from-baseline IDR model
  - Proof: plug \( f_d(t) \) into the differential equation
Probit regression model takes form of
\[ \Phi^{-1}[\text{prob}(ACR \leq k)] = f_{k,p}(t) + f_d(t) \]
- \( f_d(t) \) represents increase in beneficial effect

Equally reasonable to model
\[ \Phi^{-1}[\text{prob}(ACR > k)] = g_{k,p}(t) + g_d(t) \]
- \( g_d(t) \) represents reduction in harm

Algebraically, for general symmetric link functions:
- \( g_{k,p}(t) = -f_{k,p}(t) \), \( g_d(t) = -f_d(t) \)

If \( f_d(t) \) takes form of reduction-from-baseline IDR model, then \( g_d(t) \) takes form of corresponding increase-from-baseline IDR model
- Proof: plug \( g_d(t) \) into the differential equation
General IDR Model Symmetry

• As (perhaps) expectedly:
  Type I/III reduction-from-baseline IDR model
  \[\Leftrightarrow\]
  Type III/I increase-from-baseline IDR model
  – Proof: differential equation algebra

• (Perhaps) unexpectedly:
  – No such symmetry holds for Type II/IV IDR models

• Holds regardless of categorical or continuous endpoint modeling
Applying IDR Model to Clinical Endpoints

- Clinical endpoint modeling
  - Disease scores lack physiological interpretation
  - Improvement can be caused by increasing benefit or reducing harm
  - May need to try all IDR models (Hutmacher et al 2008)

- Only 3 identifiable IDR models to try instead of 4

- Compared with simple correlation methods (e.g., using AUC), IDR models, using only 1 more parameter ($k_{out}$), allows the efficient use of all exposure and efficacy observations
Model Extra Correlation between Two Endpoints

- Bivariate normal Residual errors of (latent) endpoints $X, Z$:
  - $(\varepsilon_x, \varepsilon_z) \sim N(\mu_x, \sigma_x^2, \mu_z, \sigma_z^2, \rho)$
  - Conditional distribution:
    - $Z|X=x \sim N(\mu_z + \sigma_z / \sigma_x \rho(x - \mu_x), (1 - \rho^2) \sigma_z^2)$
    - May choose $\sigma_z = 1$

- Implementation sketch in NONMEM:
  - $\text{SIG} = \text{THETA}(.)$
  - $\rho = \text{THETA}(.)$
  - IF(continuous observation) THEN
    - $RES = (DVctu - PREDctu) / \text{SIG}$
    - $LKPASI = \exp(-RES^2/2) / (\sqrt{2\pi} \times \text{SIG})$
  - ELSE IF(categorical observation) THEN
    - $PREDcond = PREDdis + \rho \times RES$
    - $INT1 = (\alpha_1 - PREDcond) / \sqrt{1 - \rho^2}$
    - $INT2 = (\alpha_2 - PREDcond) / \sqrt{1 - \rho^2}$
    - ...
    - IF($DV.EQ. k$) THEN $\text{LKACR} =$
  - ENDIF
  - $Y = LKPASI \times \text{LKACR}$
Application: Study Design and Data

Study PSUMMIT I (used for initial model development)

- TNF naïve subjects with active psoriatic arthritis
- Week 0 – 12: PBO / 45mg / 90mg / Loading + Q12 weeks
- Week 12 – 24: PBO crossover
- ~600 subjects, 2,000 PK records, 3,500 ACR scores, 2,300 PASI scores

Study PSUMMIT II (reserved for model validation)

- Similarly designed, except that ~50% subjects were TNF experienced
- ~300 subjects, half data records

Clinical endpoints

- ACR20/50/70: collected at Weeks 4, 8, 12, 16, 20 and 24
- PASI scores: treated as continuous, collected at Weeks 0, 12, 16 and 24
Overall PK/PD Model Diagram for both Endpoints (Type I IDR Model)

Drug Dose → Distribution → Concentration-Time → Elimination

Concentration-Time → Disease

Disease → Amelioration of Disease ($k_{out}$)

Disease → Formation of Disease ($k_{in}$)

Concentration-Time → Inhibitory Effect

Inhibitory Effect → Efficacy Time Profile

Placebo Effect

$CL$
Model Development


• ACR model component development:
  – Reasonable, NONMEM standard errors for drug effect model parameters relatively large (30-100%)

• PASI model component development:
  – placebo effect was insignificant – model reduced to regular Type I IDR model without placebo effect
  – Between-subject random effect on baseline
  – Reasonable, NONMEM standard errors for IC50 near 50%

• Extra correlation term estimated as 0.173, was significant with NONMEM objective function drop = 13
External Model Validation Visual Predictive Check (VPC) - ACR

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<tr>
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TNF0 = Naïve, TNF1 = Experienced
External Model Validation VPC: PASI

TNF0 = Naïve, TNF1 = Experienced
Conclusions

IDR models provide a predictive, parsimonious approach for efficient exposure-response modeling of clinical endpoints

- Change-from-baseline representation has nice characteristics
- Allows separate placebo modeling
- Practically, there are in essence only 3 IDR models instead of 4

Modeling extra-correlation between two endpoints can be implemented in NONMEM
References


