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 $\Leftrightarrow$ ACR $\leq$ k, k= 1, 2, or 3
- Latent variable representing underlying disease condition (similar to Hutmacher et al 2008):
  - $Dis(t) = B_0 F_p(t) F_d(t) \exp(\sigma \varepsilon_t)$
  - B_0, baseline; $0<F_p(t)\leq 1$, placebo effect; $0<F_d(t)\leq 1$, drug effect
- Define RfB(t) = % reduction from baseline, and calculate:
  - $RfB(t) = [Dis(0) - Dis(t)]/Dis(0) = 1 - F_p(t) F_d(t) \exp(-\sigma\varepsilon_{i0}) \exp(\sigma\varepsilon_{it})$
  - $\log[1 - RfB(t)] = \log[F_p(t)] + \log[F_d(t)] - \sigma\varepsilon_{i0} + \sigma\varepsilon_{it}$
  - Define: $z(t) = \log[1 - RfB(t)]$, $R(t) = \log[F_p(t)] + \log[F_d(t)] - \sigma\varepsilon_{i0}$, $\varepsilon=\varepsilon_{it}$

    $\Leftrightarrow$
  - $z(t) = R(t) + \sigma\varepsilon$
- Assumption: ACR20/50/70 met, if % reduction from baseline RfB(t) crosses certain thresholds
- Equivalently when z(t) = log[1 - RfB(t)] crosses certain thresholds

Probit Regression

- Let β_k, k = 1,2, or 3, be the thresholds, i.e. ACR ≤ k ⇔ z(t) < β_k
- Using the probit link, i.e., assuming $\varepsilon \sim N(0,1)$:
  - prob(ACR ≤ k) = prob(z(t) < β_k) = prob[ε < (β_k - R(t))/σ] = Φ[(β_k - R(t))/σ]
- 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
  - Φ^{-1} [prob(ACR ≤ k)] = $\gamma_k + g(t) + f_d(t) + \eta$
  - which is the standard form of probit regression
  - Constraint: 0 ≤ g(t) < 1, but can be reparameterized such that -∞ ≤ g(t) < 0
- Using the logistic distribution for ε leads to a similar logistic regression form, i.e., with Φ replaced by the logit function

Choosing Model Terms

- Probit regression:
  - Φ^{-1} [prob(ACR ≤ k)] = γ_k + g(t) + $f_d(t)$ + η
- Placebo model: Should have prob(ACR ≤ k)] at t=0, thus g(0)=-∞
  - Choose g(t) = log[1 – exp(-rt)]
  - g(t) = 0 ⇒ γ_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

Link Model Symmetry

- 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:
  - SIG = THETA(.)
  - ρ = THETA(.)
  - IF(continuous observation) THEN
    - RES = (DVctu - PREDctu)/SIG
    - LKPASI = EXP(-RES**2/2) / (sqrt(2*3.14)*SIG)
  - ELSE IF(categorical observation) THEN
    - PREDcond = PREDdis+ ρ*RES
    - INT1 = (ALPHA1 – PREDcond) / sqrt(1 - ρ^2)
    - INT2 = (ALPHA2 – PREDcond) / sqrt(1 - ρ^2)
    - …
    - IF(DV.EQ. k) THEN LKACR =
  - ENDIF
  - Y = LKPASI * 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

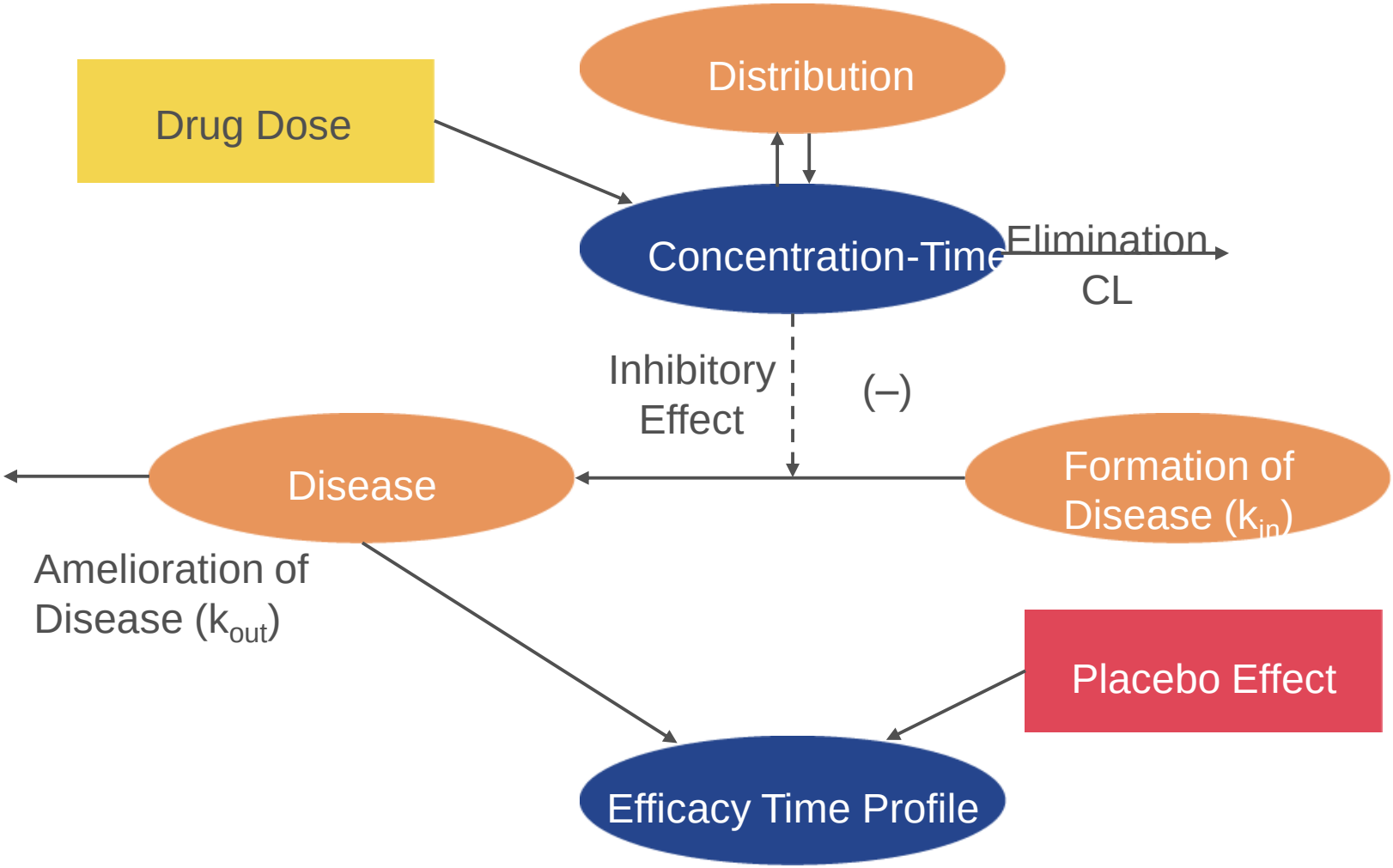
Study PSUMMIT II (reserved for model validation)

- 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)

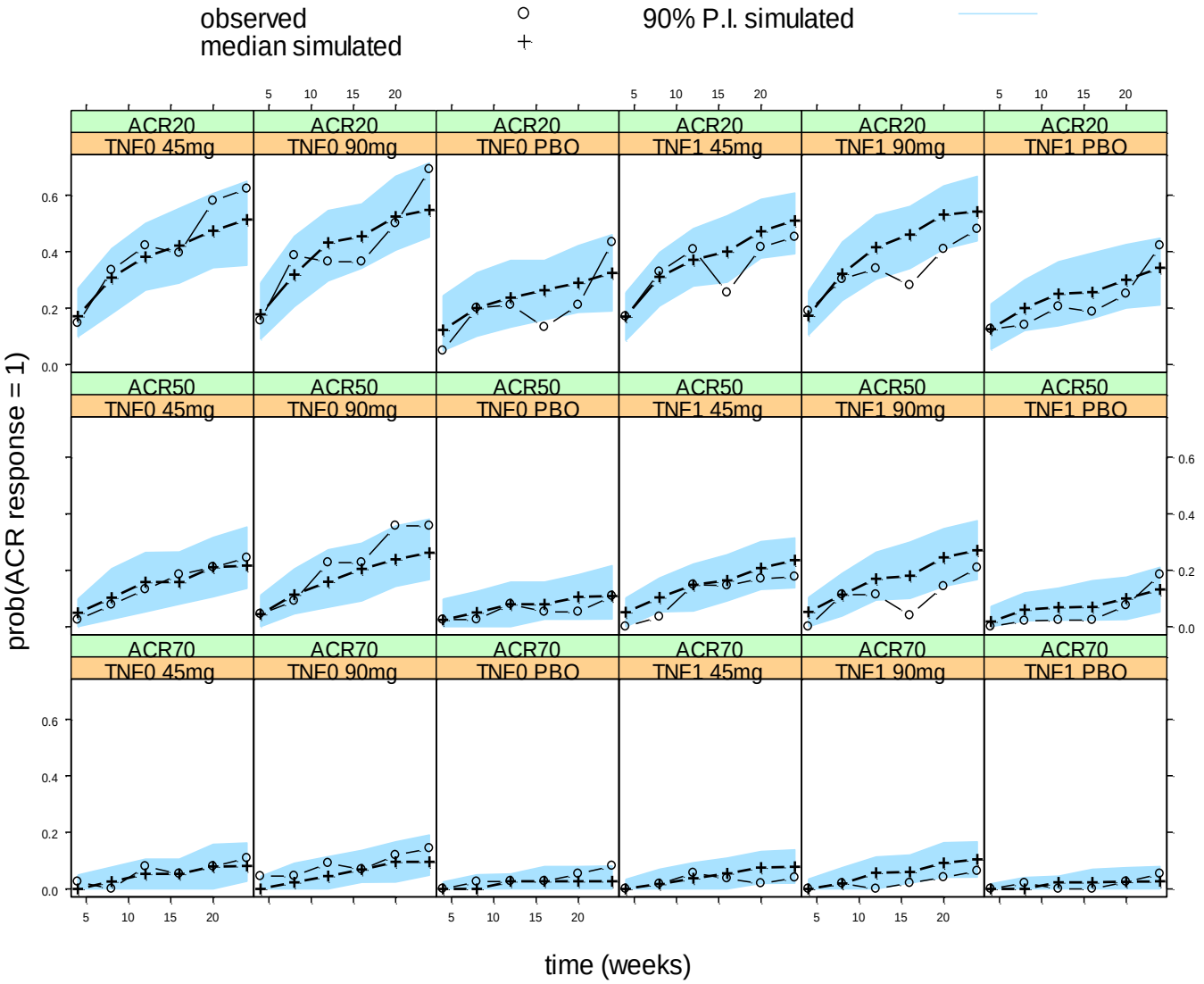


Model Development

- PK modeling: Confirmatory (Hu & Zhou 2008, Hu et al 2011)
- 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

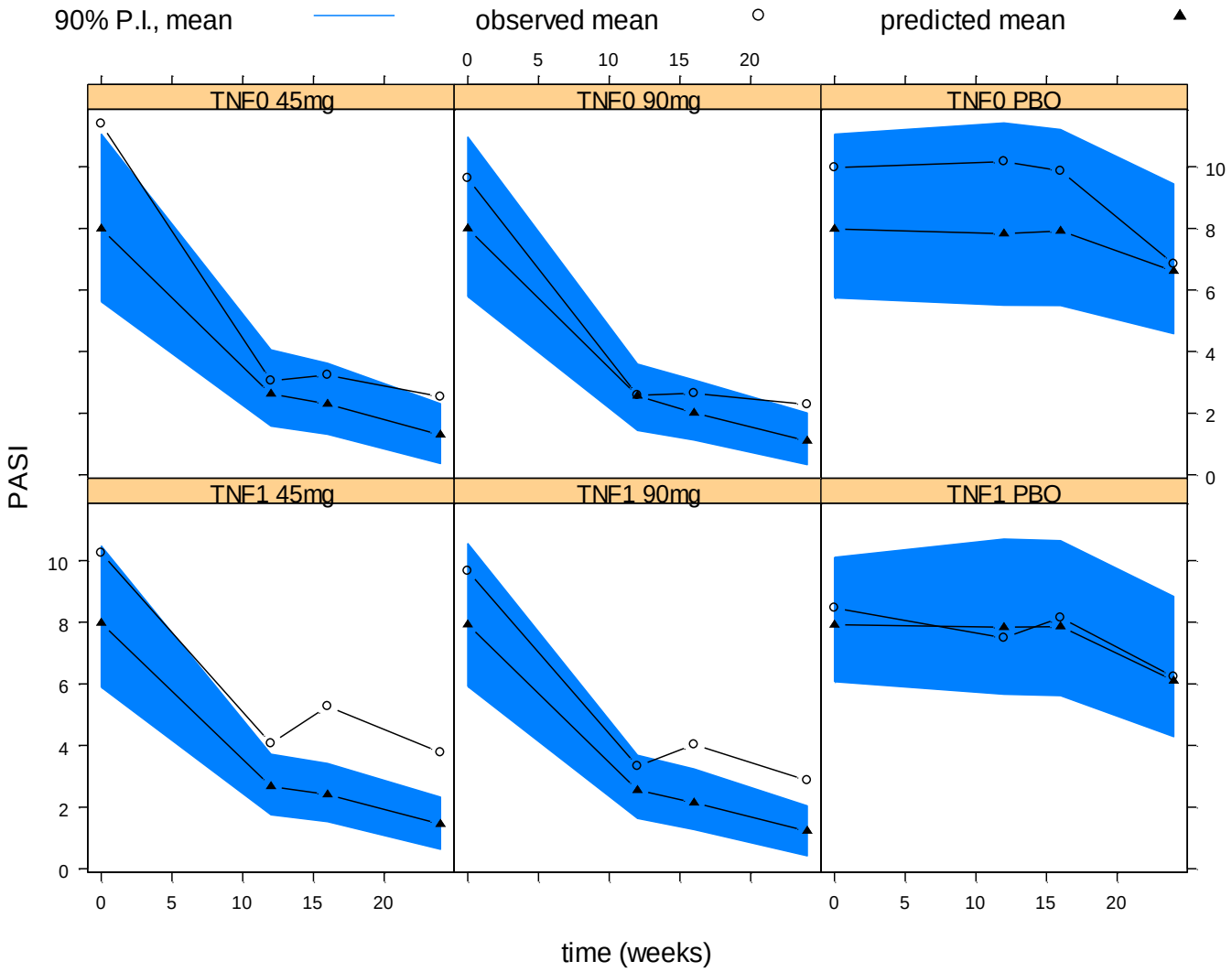
External Model Validation Visual Predictive Check (VPC) - ACR

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

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