Simulation study on different approaches to model ordered categorical data

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Summary

Aim
To conduct a methodological study of different approaches to model 11-points ordered categorical data in order to assess accuracy in drug effect detection.

Method
100 simulations were produced based on the estimation of an initial dataset including 231 patients suffering from painful distal diabetic neuropathy. Patients were only placebo treated and had scored their pain intensity twice a day. Visual analogue scale (VAS) pain ratings were recorded and graded as 11 categories ordinal data. For data analysis, three population pharmacodynamic models were developed using non-linear mixed effects modeling (NONMEM) using 3 different models: ordinal categorical model, truncated Poisson model (count model), continuous model. Parameter estimates issued from the estimation step were used to re-simulate 100 samples stochastic simulations. Subsequently, a drug effect based on the dose was added and appended on the baseline model to simulate datasets using an ordinal categorical model. New drug effect datasets were estimated and re-simulated with the same design as above.

Results
All models were successfully implemented in NONMEM. The ordinal model was composed of 11 parameters for the baseline profile, whereas all the other models had 2 or 3 parameters. Simulated categorical pain values were collected and compared together with simulated dependent value (DV). Stochastic Simulations and Estimations (SSE) method presented mean parameter values of estimation from 100 stochastic simulated samples. Results indicated that the ordinal model gave a 12000 points lower objective function value (OFV) than Poisson model in placebo analysis. The continuous model required a discretization of the simulated values and presented difficulties estimating the drug effect (bias of -85 %, no interindividual variability). The truncated Poisson model simulated values concentrated around two tail sides in placebo model and instability with drug model (high bias with dose 100).
Conclusion
For 11 categorical VAS rating, the ordered categorical model describes accurately both placebo and drug data. Continuous model describes placebo model well, but not drug effect due to lack of interindividual variability. The Poisson model has the highest average OFV compared to the other models as well as the poorest simulated distribution of scores. However, for both truncated Poisson model and continuous model there are still other potential methods that may improve results.
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Introduction

Simulation in pharmaceutical industry

Simulation technology in pharmaceutical industry is a 20-year old strategy mimicking the real environment situation on computers. It’s used to describe, explain, investigate, and predict the behavior on later time \cite{1}. By developing pharmacokinetic (PK)/pharmacodynamics (PD) models, that are mathematical tools that can transform all the momentous factors like trial design, drug behaviors, disease progress etc, information of clinical trials can be used more adequately.

Further simulation of clinical trials can be important component in drug development to reflect and explain complicated unpredictable problems as well as to predict clinical data synchronously.

A report from FDA \cite{2} represented a 20-year decrease in introductions of new molecular/chemical entities (NMEs) worldwide. The average investment needed for a new successful drug has risen to $800M and continues to grow. It indicates that many of new drug studies were probably not efficient and that there was high clinical failure rate of phase 3 trials. Nowadays there are rising demands of methods that approach faster and cheaper optimized drug developing studies.

To summarize, simulation can provide information 1) before starting experiment on human as reference for what is missing and uncertain and how the uncertainty impacts on trials. 2) to identify why problem happen and give suggestion to achieve the greatest power. 3) on partial risks and events with little cost and in a more effective way.

Population modeling

Usually individual modeling predict a model fit with individual subject reflecting dose-expose- response relationships. But the challenge resides in the fact that each individual presents specific characteristics and different subjects reflects different drug effect due to age, gender, race or even for the same person different times. In
this challenging situation population models are developed in order to represent a

group of subjects with similar characteristics and some variability between them. There are two types of variability that can be quantified in population models: 

interindividual variability (IIV) and residual variability (RV, residual error). IIV describes the variability between individuals and impacts on typical values. RV represents the variability between individual observations such as measurement errors or errors of record when samples were taken different times. Sometimes, variability can differ from one occasion to another to separate this kind of variability from the others, an inter-occasion variability IOV should be added into the model.[3].

Random effects IIV and IOV, in some cases, are dependent on some known constant factors (e.g. sex) or known changing factors (e.g. age). Then a covariate model should be added to describe these relationships.

The IIV can be introduced as an additive model, a proportional model or an exponential model to describe in which magnitude changes affect the predicted value. RV models can be divided into homoscedastic RV models and heteroscedastic RV models depending on constant RV or varying RV. Covariate models could be selected using two methods: a stepwise covariate model building (SCM) method [4] or a stepwise generalized additive model (GAM) method [5] [6]. No matter which model is used, the aim is to provide more accurate prediction and to reflect true relations within clinical data.

**Non-linear Mixed Effects Modeling (NONMEM)**

Starting in the 1970s, Lewis B. Sheiner, from University of California, San Francisco (UCSF), developed a new statistical methodology in quantitative clinical pharmacology. The solution consisted in the use of non-linear mixed effect (NLME) models to optimize, in a first time, warfarin and digoxin therapeutic dosage regimens [9]. As computer technology was expanding, NLME modeling methodology was implemented as a prototype software, written in FORTRAN, which was specifically designed for digoxin research firstly in 1977 [10]. In 2004, the 6th version of
NONMEM released as a mature tool was commercialized by Globomax and designed to fit general non-linear regression models to population data \[^7\].

In population PK/PD modeling, the basic implementation allow users to estimate THETA parameters which referred to typical population values as well as ETA parameters describing random effects \[^8\]. This hierarchical measurement can be defined with the following equation:

\[
\phi_i = \theta \times \exp(\eta_i) \quad \eta_i \sim N(0, \omega^2) \quad (1)
\]

\(\theta\) is the typical individual value of parameter. \(\eta_i\) describes the interindividual variability.

\[
Y_{ij} = \theta_i + \epsilon_{ij} \quad \epsilon_{ij} \sim N(0, \sigma^2) \quad (2)
\]

\(Y_{ij}\) is the \(j\)th observation of in \(i\)th subject. \(\epsilon_{ij}\) is a normally distributed residual variability with variance of the \(\sigma^2\), describing the residual error (additive in this equation). \(\phi_i\) represents the vector of individual parameters of \(i\)th subject.

Consequently, with this strategy, parameter theta can be estimated even only sparse data available. And this model with variability can simulates new dataset which could mimic as real data.

**Measurements (VAS) for pain value**

In the available initial dataset, observations were collected from patients who suffered from painful distal diabetic neuropathy. Values that were recorded during 18 weeks were pain intensity rates. Analysis of pain has been studied for more than hundred years. Pain is defined as an adaptive sensation which is an intense sign to protect the body from tissue injury. When the aching sensor appears and acts on a specialized
high-threshold sensory apparatus, the noxious stimuli are transduced into an electrical activity and then transferred to spinal cord and are receipted in the brain cortex as nociceptive pain. Painful reaction can also be produced when there is inflammation like when a tissue is injured or a tumour cell is releasing inflammatory mediators, changing the responsiveness of neurons in the central nervous system (CNS). The neuropathic pain is, on contrary, usually caused by damage or dysfunction of the peripheral or central nervous system. If the regeneration of axon and neuron is intercepted by damaged tissues and they are not regenerated appropriately it may be harmful for neuron functions. In the condition, patients will suffer from exaggerated pain without discernable noxious stimuli. Carpal tunnel syndrome, spinal cord after trauma injuries, brain after stroke\textsuperscript{[11]} or even degenerative neural cells in diabetics, can cause neuropathic pain\textsuperscript{[11][12]}.

Furthermore, pain is subjective: there is no physiological measurement, it is hard to built an animal experimental model. The response of pain can be based on culture, personality, responsibility and other factors personal to the subjects. It also changes with disease progression. For that reason, there was a need for some kind of measurement tools such like the visual analogue scale (VAS) or the Likert scale to assess pain intensity.

The Visual analogue scale (VAS) is a continuous scale that needs respondents to record their level of pain by indicating a position along a continuous line between two end-points described with words item like in the picture showed below.

The score is measured as the distance from the mark to the minimal point. VAS was
developed to measure a characteristic or an attitude like pain\textsuperscript{[14]}, hunger\textsuperscript{[15]} or mood\textsuperscript{[16]} and assessed validity by being correlated to an established scale\textsuperscript{[13]}. VAS can be continuous or discrete between 0 and 10. In fact, VAS is required to transform a subjective experience into an intensity assessment. The result of VAS is suitable for statistic analysis and easily understood by respondents.

Likert scale is termed by the name of the scientist \textit{Likert Rensis} who published his paper: A Technique for the Measurement of Attitudes in 1932 that describe his method to assess pain level using Likert questionnaire item. Now the method is used in survey research commonly. A risk is that sometimes respondents avoid using extreme item and prefer to try to balance their answers in the mild statement. Likert scale result is scored as ordered-categorical and discrete scales data due to obvious symmetrical questionnaire design.

VAS and Likert scales have been compared a lot in different research areas\textsuperscript{[17][18][19]}, it indicated that there is no major difference between the two methods.

\textbf{Comparison of ordinal, count and continuous scales}

Clinical data are traditionally defined as discrete or continuous; discrete data can be ordinal, count data and continuous data are variables with an infinite number of values. In clinical trial, the nature of the data vary through different measurements, for example, sleep stage (ordinal data), blood pressure (continuous data), and number of specific cells like platelets (count data).

Count data contains non-negative integer values. Usually a count is understood as the number of times an event occurs. In NONMEM, modeling count data is quite a novel practice. B.Frame et al. described the use of a Poisson distribution model to evaluate the anti-epileptic response to pregabalin as a mixture model, which assume that there are subpopulations in the dataset\textsuperscript{[20]}. Study have been performed, E.Plan et al. successfully evaluated and compared six count models with different estimation methods\textsuperscript{[21]}. J.Latz et al. described one application of count models in research on
absolute neutrophils count (ANC) \(^{[22]}\).

Continuous data can be any numeric value. In clinical trials, continuous data can be recorded at many different points (length, size, width, time, temperature, cost, etc.). For pain value on VAS, Sheiner gives example of treating pain relief scores as continuous data \(^{[23]}\). P.A.Lockwood et al. also treated chronic neuropathic pain as continuous data to identify possible dose \(^{[24]}\). R.Richter et al. used a continuous model to describe painful diabetic neuropathy to prove the validity of pregabalin \(^{[25]}\).

Categorical data ranges a finite number of values; naturally ordered or unordered variables, even binary variables. Concerned data can be divided into several categories. In clinical researches, ordinal scales have been used as an instrument to measure different phenomena. Several methodological studies have been performed about the bias of estimated parameters \(^{[26]}\), different odds model \(^{[27]}\) and Markov model implementation on sleep data \(^{[28]}\). Eleven categories ordinal model has not been used to our knowledge due to a low stability related to too many parameters (N-1 parameters for N categories model). Commonly 5 or 6 categories are used\(^{[28]}\), but it is still possible for high categories model to assess pain value or VAS data.

**Estimation methods**

In NONMEM, there are three different algorithms for estimating parameters: First-order (FO), the first order conditional estimation (FOCE) and Laplacian methods. The principle of all methods is to maximize the likelihood (\(L\)) of parameter values \(^{[7]}\). The FO method uses a first order Taylor-series expansion linearizing the model with \(\eta\) equal to 0. FOCE does the same with a linearization around the individual values of \(\eta\). However, the interaction between \(\eta\) and \(\varepsilon\) (residual error) is calculated by using FOCE interaction (FOCE-I) method. The Laplacian method performs a second order derivation.

A maximum likelihood estimate is the most probable estimation of a parameter. In NONMEM a proportional value of the maximum likelihood is calculated as the
objective function value (OFV) \[^{29}\]. Under the assumption that random effects are normally distributed the OFV is approximated to -2 log-likelihood (-2LL); and to maximize likelihood is transferred as minimize -2LL. When comparing two models with the same algorithm, the difference of OFV is accounted. The difference of OFV between two nested models is approximately $\chi^2$ distributed, so a significantly better fit of the full model (the model with more parameters) is a decrease in OFV that the value follows $\chi^2$ distribution (one extra parameter gives $-3.84$ with a $p<0.05$ significance level) \[^{7}\].

**Stochastic Simulations and Estimations (SSE)**

Stochastic Simulations and Estimations (SSE) is a Monte Carlo method to investigate relations between simulation model and estimation models (at least one) based on Perl-speaks-NONMEM (PsN, the latest version is 2.3.1\[^{31}\]). SSE is a two stage method: 1) simulations of new datasets from the original model 2) estimations of the datasets. The new dataset will be estimated by estimation models automatically and present statistical results after estimation. The two-stage process can be circulated as users’ control. Each simulation is based on a different random seed number \[^{30}\]. The advantage of SSE is that it offers a convenient method to compare more than one estimated model under the same conditions and presents statistic comparison of parameters including: Mean value, Median value, Standard Error, Skewness, Kurtosis, Bias, Mean Square Error and statistics of OFV changes.
Results

Parameters used in simulation
All estimation models were implemented successfully in NONMEM VI. Parameters used in simulations are presented in Table 1 for placebo data and Table 2 for drug data.

The first simulation of ordinal model

![Figure 1: Probabilities of ordered categorical scores in simulated data and observed dependent variable (DV). Probabilities of 11 categories from real data are plotted with green histogram. The first simulated dataset (by ordinal model) was used to obtain ranged simulated probabilities of each category. The average value, the 5th percentile and 95th percentile are represented in blue, red and brown smooth lines respectively.](image)

A comparison between the first simulation with the ordinal categorical model with
dependent values (DV) of the initial data presented adequate representation of the simulation for each categorical value in figure 1. 100 simulated datasets offer a wide range of data by using different random seed numbers. All the observed data were in the range of simulated data as showed above, the range more concentrated around tails compared with relative ‘big’ range around peak. To sum up, all the simulated categories fitted perfectly DVs except P3, P4 and P6 that appeared reasonably within the range.

**Predictive Performance of placebo model**

![Probabilities Comparison of Placebo Model](image)

Figure 2: The probabilities comparison of placebo model with range based on 100 simulations. Upper bound and lower bound of each error bar represent 95th percentile and 5th percentile, respectively, derived from 100 simulated datasets. 3 different models were tested and compared with DV.

Placebo analysis results were presented in figure 2. 5th percentile and 95th percentile gave range according to 100 simulated dataset with all the three models mentioned before. To all appearances, ordinal categorical model fitted best with DV with a larger range observed by comparing each categorical values. For continuous model, simulated continuous data were rounded to integer values for a convenient comparison with other models. After rounding, the blue histograms could be used to describe continuous model’s simulation. Compared with DV, continuous model put
up a good performance especially on P2 and P8 in this placebo data research. Although ordinal model fitted better, continuous model still exhibits the reasonable trend. But a visible dissimilitude was presented at P9 with the continuous model; even the 5\textsuperscript{th} percentile error bound was higher than the 95\textsuperscript{th} percentile of DV which means it could hardly mimic P9 probability at that value. However, the continuous model was still simulating better than the count model. With purple histograms, it is hard to distinguish really a peak on continuous curve compared with other models. Only at P2 and P8, count model had accurate result with small error range.

![Figure 3: Probabilities of 100 simulated DVs from 3 placebo models versus probability of DV. Diagonal line is available as reference for the best performance (identity line). X axis presents the probability of DV, the aim value. Y axis presents alternatives value from simulations (with prediction intervals).](image)

Figure 3 offered a different version to describe results from the 3 models. For the results of alternative plot above, the closer to the diagonal line the more precise simulated results were. Obviously, all the ordinal model points were on the identity line (blue colour). Continuous model surrounded diagonal line closely, compared to the count model which circled around the line dispersedly.
Stochastic Simulations Estimations result for placebo model

In Table 1 and 2, θ (THETA) is abbreviated as TH and numbered.
<table>
<thead>
<tr>
<th>Ordinal Model OFV</th>
<th>TH_1_Baseline(ETA)</th>
<th>TH_2</th>
<th>TH_3</th>
<th>TH_4</th>
<th>TH_5</th>
<th>TH_6</th>
<th>TH_7</th>
<th>TH_8</th>
<th>TH_9</th>
<th>TH_10</th>
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</thead>
<tbody>
<tr>
<td>True value</td>
<td>7.86 (11.1)</td>
<td>-1.73</td>
<td>-1.95</td>
<td>-1.55</td>
<td>-1.54</td>
<td>-1.51</td>
<td>-1.49</td>
<td>-1.80</td>
<td>-2.22</td>
<td>-2.09</td>
</tr>
<tr>
<td>Mean value</td>
<td>70.92 (11.02)</td>
<td>-1.73</td>
<td>-1.95</td>
<td>-1.55</td>
<td>-1.54</td>
<td>-1.51</td>
<td>-1.49</td>
<td>-1.80</td>
<td>-2.22</td>
<td>-2.09</td>
</tr>
<tr>
<td>RMSE</td>
<td>2.93 (10.002)</td>
<td>3.49</td>
<td>2.29</td>
<td>1.81</td>
<td>1.61</td>
<td>1.72</td>
<td>1.75</td>
<td>1.95</td>
<td>3.23</td>
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<tr>
<td>Bias</td>
<td>0.048 (0.052)</td>
<td>-0.11</td>
<td>0.10</td>
<td>-0.03</td>
<td>0.03</td>
<td>0.04</td>
<td>0.08</td>
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<td>6.08 (2.33)</td>
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<tr>
<td>RMSE</td>
<td>22.86 (79.11)</td>
<td>-22.6 (-79.03)</td>
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<td>Mean value</td>
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<td>5.22 (0.86)</td>
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<tr>
<td>RMSE</td>
<td>33.69 (92.30)</td>
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<tr>
<td>Bias</td>
<td>-33.69 (-92.3)</td>
<td>0.54</td>
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Residue Error = THETA(2)*EPS(1), EPS Fix to 1
TH_2 Sigma Transfer

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TH_2 Sigma Transfer

Table 1: SSE result of 100 samples from 3 different models based on Placebo data.
In Table 1, 100 simulations were performed to calculate mean values of OFV and each parameter, as well as statistics for bias and root mean square error (RMSE). Interindividual variability was also listed in the brackets after thetas. For the ordinal model, the OFV was 1000 points lower than for the count model, although there were 10 thetas in the ordinal categorical model. Actually, the continuous model is not nested with the other two models, therefore it is not correct to compare the OFV between them. And both count and continuous models involved large bias (80%, 92% respectively) compared to the true value.

Drug effect model

![Drug effect VS Dose](image)

Figure 4: Plot of drug effect versus dose. Only 3 doses were tested: 0, 100, 200 and 300. The slope of drug effect line was 0.045.

For the drug data, a linear drug effect was added and presented in *figure 4*. At dose 0, there was no drug effect on baseline, whereas the drug effect was observed with doses up until 300.
### Table 2: SSE result of 100 simulations from 3 different models based on drug model

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<th>Count Model OFV</th>
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*True values: 7.86 (11.1) 0.045 (0.09) -1.73 -1.95 -1.55 -1.54 -1.51 -1.49 -1.80 -2.22 -2.09*

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<tr>
<td><strong>TH_3_Sigma_Transfer</strong></td>
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<table>
<thead>
<tr>
<th></th>
<th>Ordinal Model OFV</th>
<th>Continuous Model OFV</th>
<th>Count Model OFV</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>TH_1</strong></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td><strong>TH_2_Slop</strong></td>
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</tbody>
</table>

#### Residue Error $= \text{THETA}(\eta) \text{EPS}(1) \text{EPS}(1) \text{EPS}(1)$

**Bias:**

- Residue Error = 83.88
- TH_1_Baseline = 61.73

**RMSE:**

- Residue Error = 0.006 (0.06) TH_1_Fix
- TH_1_Sigma_Transfer = 1.37

**Mean:**

- Residue Error = 0.006 TH_1_Fix
- TH_1_Sigma_Transfer = 1.37

**Count Model OFV**

- TH_1_Lamda(ETA) = 100
- TH_2_Slop = 0.02

**Continuous Model OFV**

- TH_1 = 499
- TH_2_Slop = 2.02

**Ordinal Model OFV**

- TH_1_Baseline = 49.9
- TH_2_Slop = 0.02

**RMSE:**

- TH_1_Lamda(ETA) = 49.9
- TH_2_Slop = 0.02

**Bias:**

- TH_1_Lamda(ETA) = 87.2
- TH_2_Slop = 87.2

**Mean:**

- TH_1_Lamda(ETA) = 100
- TH_2_Slop = 0.02
TH1 was the baseline of each model with interindividual variable (ETA) been given in following bracket. Population PD model for drug data was initialized by attaching drug component onto baselines as described in Equation 3. Parameters of drug effect models were listed in Table 2 with TH2 defined as slope parameter of drug effect.

The residual error of continuous model was termed as sigma. In SSE procedure, an extra theta multiplying sigma parameter fixed to 1 was used. The value of parameter theta was approximated to the square root of parameter sigma due to different matrices.

Results of categorical probability with drug model

The following figures present the results of 100 simulations based on estimations of drug data. Figures were stratified by doses.

**Dose 0**

![Probability Comparison based on 0 dose](image)

Figure 5: Comparison between simulated results from 3 drug models versus dependent value. Plotted based on dose equal to 0.
In figure 5, probabilities of simulated categorical data were compared between models without dose effect (dose=0). The profile of each individual model was similar to placebo result showed in figure 2 except for the continuous model. Ordinal categorical model still performed the best in drug model analysis with a range that contained scale of each observed categorical value. However simulation results for continuous model changed a lot even with no dose input. Compared with placebo result, continuous model over-simulated probabilities on P0, P1 and P2, whereas it under-mimicked probabilities on P4, P5, P6 and P7. P3, P8 and P10 were acceptable but P9 was observed an inaccuracy that the 5th percentile data approximated to average value of true data. However, P9 was still better presented than with the count model. Count model manifested a normally distributed profile with inconspicuous peak around P5 and simulated badly P9 and P10. Figure 6 presented the same situation with the continuous model simulating as badly as the count model.
Figure 7: Comparison between simulated results from 3 drug models versus dependent value. Plotted based on dose equal to 100.

Figure 8: Plots of comparison between simulated probability versus true data when dose equal to 100
When a low dose (dose=100) was added into models, there were more possibilities to mimic low probabilities values for all categories, for example, 10 times higher probability recalled on P0 for true data (2% in figure 5 and about 20% in figure 7). Homologically, distinct decreases happened on high categories for all the models. Obviously, a larger probability of P0 was observed with the count model which is almost double than the observed DV as well as a large scale of error range attached from 25% to 47%. A continuous under-simulation of P2 to P6 is also visualized in figure 6. Out of that, P2 represented the second peak on DV probabilities curve which appeared in DV and Ordinal model. But for count and continuous model, out of P0, no second peak at all was seen. For all, the ordinal model recalled the best and the count model performed the worst in dose 100.

**Dose 200**

![Probability Comparison based on 200 dose](image)

Figure 9: Comparison between simulated results from 3 drug models versus dependent value. Plotted based on dose equal to 200.
With the dose increased to 200, fewer observations were simulated at high categories and more samples were concentrated around low categories. In figure 9, the ordinal model performed well and the count model predicted as well as the ordinal model, which is only a 7% (68% compared with true value 61%) error at P0 category. Continuous model simulated quite an imprecise probability at both P0 and P1 indicating that simulated error continued to enlarge from dose 100, and none of simulated results touched range of true value, at the same time continuous error scale more centralized than others.

Figure 10: Plots of comparison between simulated probability versus true data when dose equal to 200
Dose 300

Figure 11: Comparison between simulated results from 3 drug models versus dependent value. Plotted based on dose equal to 300.

Figure 12: Plots of comparison between simulated probability versus true data when dose equal to 300.
With dose at 300, drug effect was increasing to 14 as figure 4 plotted which pointing out a powerful drug effect that will increase possibility to simulate low categorical value. All of this can be proved in figure 11 and 12. For all, still the continuous model had the under-prediction at P0 and P1. All the other simulated data decreased and concentrated at 0.

**Discussion**

The first aim of this thesis was to study models to estimate 11 categorical original VAS data. The study was successfully conducted. Accuracy of ordinal categorical model can be partly reflected from bias of SSE result. The baseline bias of ordinal model were 0.048% and 2.06% for placebo data and drug data, respectively; they were considered low and steady. During estimations, ordinal model resulted in 100% successful minimizations, whereas about 10% to 50% terminated with the two other models. This condition also supported ordinal model as the best stable model in this 3 different strategies. When comparing the accuracy of the same model in both placebo data and drug data, drug data parameters were highly biased. The possible reasons could be: 1) different sample size. The study strategy for drug model was simulating 4 different gradient doses and combine subgroups with the same dose. As doses were created randomly by NONMEM, different sample size may affect result; 2) drug effect. When drug effect was added into the model, there were more lower values simulated. With the dose increasing, more and more zeroes were simulated. With large proportion of zero, bias was amplified which reflected a lower capability of assessing observed data. The reason 2 is the major problem.

Two algorithms were used with the 3 models: Laplacian method for ordinal model and Poisson distribution model, FOCE for continuous model. The reason for using FOCE method with the continuous model is based on usual practice and previous research which indicating higher proportion of successful minimizations and lower run times with FOCE than with LAPLACE. In fact, more research will investigate the different methods later.
In the thesis, a linear drug effect was selected. Some researches give non-linear drug effect examples\cite{33}\cite{35}. An Emax model can be described as

\[
\text{Drug effect} = E_{\text{max}} \frac{D^\gamma}{D^\gamma + ED_{50}^\gamma}
\]

The effect curve with Emax model was plotted below which recall the drug effect curve proportionally.

![Drug effect VS Dose](image)

Figure 7: Effect versus dose in Emax drug model. \( E_{\text{max}} \) is the maximum effect of drug, \( \gamma \) is Hill coefficient. \( D \) and \( ED_{50} \) present dose and 50% effect dose respectively. The plot presented the situation when \( E_{\text{max}} = 2, ED_{50} = 150, \gamma = 1 \).

On one hand, \( E_{\text{max}} \) and \( ED_{50} \) are different between subjects; with Emax model, simulations will describe better interindividual variability within observations. On the other hand, it makes more physiological sense to describe a model for human body to receive a drug effect with upper bound (around 1.5 in Figure 7). However, Emax model requires two extra parameters during estimation compared to one in Slope drug model (Equation 3). In early investigations, with Emax model, high probability of minimization failure rate was observed. That is the reason to choose simple slope model as linear effect.

From the probability simulations on placebo data, Poisson model described results unsuccessfully, which proved that the Poisson model cannot fit the dataset well.
Initial Poisson model ranges the distribution from 0 to infinity., in order to fit 11 categorical data, an upper boundary was created by the implementation of a truncation at 10 (equation 8). There are other Poisson models that can be used to characterize count data. For example Poisson with Markovian features (PMAK), Poisson with a mixture distribution for individual observations (PMIX), Zero Inflated Poisson (ZIP) and Generalized Poisson (GP) \[^{21}\] \[^{36}\]. GP model has been proved to recall better simulated effect with VAS data (unpublished result). There is still opportunity to develop better count model.

The continuous model was performing worse with drug data than placebo data. The fundamental reason was that no individual variability could be implemented into the model (ETA fix to 0). One possible improvement could be to introduce an auto-correlation factor. Correlation factor describes the possible relationship between residual errors from two dependent variables. One correlation function can be added to handle the lack of independence otherwise assumed in the model.

**Materials and Methods**

**Data Collection**
The original dataset analyzed in my research was measured from 231 patients who suffered from painful distal diabetic neuropathy. Totally 100 samples were collected from the entire patients and measured twice a day during 18 weeks. Patients were only placebo treated and had scored their pain intensity twice a day. Measure time was not regular from patients and statement of subjects were measured by using 11 point (0-10, 0=No pain, 1=minimum, 10=maximum pain) Visual Analogue scale (VAS) to describe how strongly their feelings of pain. Other information like Sex, Race, Height and Bodyweight were not input into models. There was no missing data in original dataset.

**Computer Software**
All datasets and results were stored as Microsoft Excel 2007 Format. Data analyze
included estimation and simulation with PKPD models were completed on NONMEM VI \cite{7}. Pearl speaks NONMEM (PsN) v.2.3.0 \cite{31} was used to run NONMEM. R program version 2.7.2 \cite{32} is also used during data processing. SigmaPlot (SPSS, Version 8.0, 2002) is used for adjusting data and results plotting.

**Analytical strategy**

**Placebo data analysis**
In my design, for comparing different approaches, an ordered categorical dataset was simulated based on original dataset. Approximately 23100 observations listed with 231 subjects which followed by ordinal categorical dependent value scaled from 0 to 10. New ordinal categorical dataset was estimated by three different approaches: ordinal categorical model, Count (truncated Poisson) model and continuous model to assess parameters (typical value, random effect and residual error included). After assessment, the second simulation was used to create more datasets for results analyzing. All of estimations and simulations were repeated 100 times. Finally, a lot of simulated datasets were prepared for analyzing and comparison within three models.

**Drug effect data analysis**
Compared with placebo data, no real clinical data was prepared for drug analysis. So the drug dataset was presented by giving an extra drug effect based on ordinal structural placebo model. 3 dose levels were given respectively: Dose=0, 100, 200, 300, as well as the drug component were added by a linear slope function (equation 3) on the baseline. Equation 3 described as below:

\[
\text{DRG} = \text{SLP} \times \text{DOSE} \tag{3}
\]

The DRG was the drug effect, SLP presented the slope to describe relationship between drug effect and corresponding doses. A drug effect model was used which firstly described by Sheiner et al \cite{37}. Because of no initial clinical drug data, for acceleration, the slope was given as 0.045 with corresponding interindividual variability setting to 0.09. Following the same design, parameters would be
estimated from drug effect dataset and re-simulation finished to describe effects based on different models.

**Ordinal categorical model**

An 11 categorical proportional odds model was used here for handling simulated dataset. The proportional odds model was presented in 1994 by L. Sheiner et al.\(^{[23]}\) for mixed effect analysis on categorical pain relief data.

For the \(n\)th observation in the \(i\)th individual, the ordinal categorical variable with \(I\) categories is \(Y_{in}\). The possibility that observation \(Y_{in}\) is larger or equal to a known constant score \(j\) had been given by equation 4

\[
\text{logit}[P(Y_{in} \geq j \mid \eta_i)] = f_j + \eta_i, \quad j = 2, \ldots, I
\]  

(4)

\(\eta_i\) is the interindividual variability that follows normal distribution with mean equal to zero and variance within \(\omega^2\). Function \(f_j\) is the baseline conditions.

So the individual probability is calculated by equation 5

\[
P(Y_{in} \geq j \mid \eta_i) = \frac{e^{f_j + \eta_i}}{1 + e^{f_j + \eta_i}}
\]  

(5)

Each individual scores were derived from upper level of cumulative probability as described in equation 6. As I have 11 categories which \(I\) could be define as 11.

\[
P(Y_{in} = 1 \mid \eta_i) = 1 - P(Y_{in} \geq 2 \mid \eta_i)
\]

\[
P(Y_{in} = 2 \mid \eta_i) = P(Y_{in} \geq 2 \mid \eta_i) - P(Y_{in} \geq 3 \mid \eta_i)
\]

\[\cdots\]

\[
P(Y_{in} = I \mid \eta_i) = P(Y_{in} \geq I \mid \eta_i)
\]  

(6)

11-category in ordinal model required 10 THETA, as equation 6 described, the last categorical probability was calculated by using 100% minus the sum of other
categorical probabilities.

Drug effect and placebo effect can be attached on the baseline condition \( f_j \) that operated following equation 7.

\[
\begin{align*}
  f_2 &= \alpha_2 + g(X_i) \\
  f_3 &= \alpha_2 + \alpha_3 + g(X_i) \\
  &\vdots \\
  f_m &= \alpha_2 + \sum_{k=3}^{m} \alpha_k + g(X_i)
\end{align*}
\]

(7)

In equation 7, \( \alpha \) is the baseline parameter which specify with different categories. For example \( \alpha_2 \) was the baseline parameter of probability that predicted value larger or equal to score 2.

\( g(X_i) \) was the function to describe drug effect as covariate which is equal to DRG (equation 3) as linear effect. The boundary of function \( g(X_i) \) was \((-\infty, 0]\) that to make sure no minus effect added.

**Count model**

For the count data, Poisson distribution model (PS) was developed to calculate probability of an observation appears \(^3\). The density function \( f \) for the Poisson random variable \( Y \) with mean number of counts \( \lambda \) was described in equation 8.

\[
P_{PS}(Y_i = n) = \frac{e^{-\lambda} \times \lambda^n}{n!}
\]

(8)

For the Poisson model successfully implement In NONMEM IV, factorial of 11 categorical count data was transformed in obedience of improved Stirling’s Formula \(^4\) which described as equation 9 \(^{33}\).
Poisson distribution can simulate nonnegative integer observations from 0 to infinite, so for my 11 categorical dataset a truncated model was used to constrict subjects’ observations between 0 to 10. (Equation 10)

\[
P_{TR}(Y_i = n \mid n \in [0,10]) = \frac{P_{PS}(n)}{\sum_{n=0}^{10} P_{PS}(n)}
\]

Drug effect of Poisson model was added on \( \lambda \) function proportionally. The Laplacian method was used to minimize -2 log likelihood of Poisson distribution density function during the estimations. All the initial value of parameters listed in Table 2.

**Continuous model**

The continuous model was developed from a logistic model which predicts probabilities between 0 and 1. The logistic model can transfer any normally distributed random number from minus infinite to positive infinite back to a limited range between 0 to 1 (equation 11).

\[
\logit(p) = \ln \frac{p}{1-p} = f(P, X)
\]

\[
\Leftrightarrow p = \frac{e^{f(P,X)}}{1+e^{f(P,X)}}
\]

\(f(P,X)\) was the function described how the probability (P) varies with baseline conditions and covariate X. The continuous data was prepared by 10 times of \( p \) to confirm all the observations in the bounds of [0, 10]. Drug effect was attached on baseline with same design of above.

**Estimation of parameters**

Each ordinal simulated dataset was estimated by 3 different models and re-simulated by the same. The Laplacian method was used to minimize -2 log Likelihood of Poisson model and also performed on ordinal model. Bayesian estimated
(POSTHOC) method (FOCE) was used for estimation as continuous data. All scripts presented in appendix.

**Simulation results comparison**
For comparing accuracy of simulation between 3 models, 100-fold re-simulations were finished. With placebo data simulation, final re-simulation created a new dataset with more than 2310000 observations. Probability of each specific categorical scale was calculated and stored. Since 100 simulated probabilities of each category were measured completely, plots of each categorical comparison among models were built as well as other plots were also built for comparing dependent value versus simulated dependent value.

**Statistical analysis**
The Stochastic Simulations and Estimations method calculated not only the average value of each parameters and OFV but also providing a convenient method for stability and accuracy analysis \[^5\]. Bias and RMSE were calculated as equation 12 \[^30\] and listed in *Table 1* for placebo model and *Table 2* for Drug model.

\[
\text{Bias} = 100\% \times \text{mean } (\text{Est-True})/\text{True} \\
RMSE = 100\% \\
\times
\]

(12)

The 5th and 95th percentile of categorical probabilities were calculated and added as the error range on the histograms (*Fig. 1 and 2*).
Acknowledgements

I would like to thank my supervisor and my first teacher in pharmacometrics, Elodie Plan. You are always so kind and explain me with patience.

Prof. Mats Karlsson, my supervisor. Thank you for giving me helps and supports and offering me opportunity to get into this new world.

Paul, Martin, Stefanie, Guangli, Åsa…… thank you for bearing with my silly questions.
References


measurement of clinical phenomena. Research in Nursing and Health 13, 227±236.


Appendix

1. NONMEM code for Ordinal categorical model with Drug effect

$PROB PAIN with Ordered Categorical Data MODEL
$INPUT DROP ID DROP MDV DV BASE TIME TFLA CL V SEX RACE AGE
$DATA nm01_all.csv IGNORE=@ IGNORE=(TFLA.EQ.1)
$THETA
  7.86 ; B1
  (0, 0.045) ; SLOPE
  (-INF,-1.73,0) ; B2
  (-INF,-1.95,0) ; B3
  (-INF,-1.55,0) ; B4
  (-INF,-1.54,0) ; B5
  (-INF,-1.51,0) ; B6
  (-INF,-1.49,0) ; B7
  (-INF,-1.80,0) ; B8
  (-INF,-2.22,0) ; B9
  (-INF,-2.09,0) ; B10
$OMEGA  11.1 ; ETA1
  0.09 ; SLOPE
$SPRED
;Baseline values
  B1  =THETA(1)
  B2  =THETA(3)
  B3  =THETA(4)
  B4  =THETA(5)
  B5  =THETA(6)
  B6  =THETA(7)
  B7  =THETA(8)
  B8  =THETA(9)
  B9  =THETA(10)
  B10 =THETA(11)
IF(ICALL.EQ.4) THEN ; Simulation start
  IF(NEWIND.NE.2) THEN
    CALL RANDOM (3,R)
    IF(R.LE..25) DOS=0
    IF(R.GT..25.AND.R.LE..50) DOS=100
    IF(R.GT..50.AND.R.LE..75) DOS=200
    IF(R.GT..75) DOS=300
  ENDIF
  DOSE=DOS
ENDIF

SLP = THETA(11)*EXP(ETA(2)) ; SLOPE
DRG = DOSE * SLP ; Drug-Effect

LGE1 =B1+ETA(1)-DRG
LGE2 =B2+LGE1
LGE3 =B3+LGE2
LGE4 =B4+LGE3
LGE5 =B5+LGE4
LGE6 =B6+LGE5
LGE7 =B7+LGE6
LGE8 =B8+LGE7
LGE9 =B9+LGE8
LGE10 =B10+LGE9

; Probabilities for Y>=2, Y>=3...
PGE1 = EXP(LGE1)/(1+EXP(LGE1))
PGE2 = EXP(LGE2)/(1+EXP(LGE2))
PGE3 = EXP(LGE3)/(1+EXP(LGE3))
PGE4 = EXP(LGE4)/(1+EXP(LGE4))
PGE5 = EXP(LGE5)/(1+EXP(LGE5))
PGE6 = EXP(LGE6)/(1+EXP(LGE6))
PGE7 = EXP(LGE7)/(1+EXP(LGE7))
PGE8 = EXP(LGE8)/(1+EXP(LGE8))
PGE9 = EXP(LGE9)/(1+EXP(LGE9))
PGE10 = EXP(LGE10)/(1+EXP(LGE10))

; Probabilities for Y=1, Y=2, Y=3, Y=4, Y=5, Y=6, Y=7, Y=8, Y=9, Y=10
P0 = (1-PGE1)
P1 = (PGE1-PGE2)
P2 = (PGE2-PGE3)
P3 = (PGE3-PGE4)
P4 = (PGE4-PGE5)
P5 = (PGE5-PGE6)
P6 = (PGE6-PGE7)
P7 = (PGE7-PGE8)
P8 = (PGE8-PGE9)
P9 = (PGE9-PGE10)
P10 = PGE10

;Select appropriate P(Y=m)
IF (DV .EQ. 0) Y = P0
IF (DV .EQ. 1) Y = P1
IF (DV .EQ. 2) Y = P2
IF (DV .EQ. 3) Y = P3
IF (DV .EQ. 4) Y = P4
IF (DV .EQ. 5) Y = P5
IF (DV .EQ. 6) Y = P6
IF (DV .EQ. 7) Y = P7
IF (DV .EQ. 8) Y = P8
IF (DV .EQ. 9) Y = P9
IF (DV .EQ. 10) Y = P10

sp = P0 + P1 + P2 + P3 + P4 + P5 + P6 + P7 + P8 + P9 + P10 ;make sure sp = 1

IF (ICALL .EQ. 4) THEN
    CALL RANDOM (2,R)
    IF (R .LE. PGE10) DV = 10
    IF (R .LE. PGE9 AND R .GT. PGE10) DV = 9
    IF (R .LE. PGE8 AND R .GT. PGE9) DV = 8
    IF (R .LE. PGE7 AND R .GT. PGE8) DV = 7
    IF (R .LE. PGE6 AND R .GT. PGE7) DV = 6
    IF (R .LE. PGE5 AND R .GT. PGE6) DV = 5
    IF (R .LE. PGE4 AND R .GT. PGE5) DV = 4
    IF (R .LE. PGE3 AND R .GT. PGE4) DV = 3
    IF (R .LE. PGE2 AND R .GT. PGE3) DV = 2
    IF (R .LE. PGE1 AND R .GT. PGE2) DV = 1
    IF (R .GT. PGE1) DV = 0
ENDIF

$SIMULATION (606510) (57264 UNIFORM) (910335 UNIFORM)
$ESTIMATION MAXEVAL=9999 METHOD=COND LAPLACE LIKE PRINT=1
2. NONMEM code of Truncated Poisson model

$PROB Poisson model

$SINPUT ID TIME DV DOSE

$DATA /users/users6/yang/pain-value/model_from_Mats/Data/sim_Drug.csv

IGNORE=@

$OMEGA  1.58       ;S0
0.315      ; SLOPE

$PRED

IF(ICALL.EQ.4) THEN ;simulation start

CALL RANDOM (3,R)
IF(R.LE..25) DOS=0
IF(R.GT..25.AND.R.LE..50) DOS=100
IF(R.GT..50.AND.R.LE..75) DOS=200
IF(R.GT..75) DOS=300
ENDIF
DOSE=DOS
ENDIF

SLP = THETA(2)*EXP(ETA(2)) ;SLOPE
DRG = DOSE * SLP ;Drug-Effect

TVS1= THETA(1)/10
PHI1 = LOG(TVS1/(1-TVS1))+ETA(1)
S0 = EXP(PHI1)/(1+EXP(PHI1))

IPR=LOG(S0/(1- S0))
IPRED = EXP(IPR-DRG)/(1+EXP (IPR-DRG))
LAM = 10*IPRED

;Truncated Poisson distribution;
IF (ICALL.EQ.4) THEN
   IF(MDV.EQ.0) THEN
   PRN=0
   N=0
   CALL RANDOM (2,R)
   DO WHILE (R.GT.PRN)
      FAC=1
      IF (N.GT.0) FAC=SQRT(2*3.1415)*(N**(N+0.5))*EXP(-N)*(1+1/(12*N))
      POI=EXP(-LAM)*(LAM**DV)/FAC
      POI= EXP(-LAM+N*LOG(LAM)-LOG(FAC))
      SUM1= 1+ LAM+ (LAM**2)/2+ (LAM**3)/6+ (LAM**4)/24+ (LAM**5)/120+
             (LAM**6)/720
      SUM2= (LAM**7)/5040+ (LAM**8)/40320+ (LAM**9)/362880+ (LAM**10)/3628800
      SUM= EXP(-LAM)*(SUM1+SUM2)
      YY = POI/SUM
      Y= -2*LOG(YY) ; -2LL method
      PRN=YY+PRN
      IF (PRN.LT.R) N=N+1
   END DO
   DV=N
   ENDIF
$THETA (0,6.48,10) ; THETA1
(0,0.0215) ; SLOPE
$ESTIMATION MAXEVAL=9999 METHOD=COND LAPLACE -2LL PRINT=0
$SIMU (987987) (987987 UNIFORM) (876555 UNIFORM)
3. **NONMEM code of continuous model**

$PROB$ Continuous data model

$INPUT$ ID TIME DV DOSE

$DATA /users/users6/yang/pain-value/model_from_Mats/Data/sim_Drug.csv IGNORE=@

$THETA (0, 5.83, 10) ; baseline
(0, 0.00892) ; SLOPE

$OMEGA 0 FIX ; baseline
0 FIX ; SLOPE

$PRED

IF(ICALL.EQ.4) THEN
  IF(NEWIND.NE.2) THEN
  CALL RANDOM (2, R)
  IF(R.LE..25) DOS=0
  IF(R.GT..25.AND.R.LE..50) DOS=100
  IF(R.GT..50.AND.R.LE..75) DOS=200
  IF(R.GT..75) DOS=300
  ENDIF
  DOSE=DOS
  ENDIF

SLP = THETA(2)*EXP(ETA(2)) ; SLOPE
DRG = DOSE * SLP ; Drug-Effect

TVS0 = THETA(1)/10
PHI = LOG(TVS0/(1-TVS0))+ETA(1)
S0 = EXP(PHI)/(1+EXP(PHI))

IPR = LOG(S0/(1- S0))
IPRED = EXP (IPR + EPS(1)-DRG)/(1+EXP (IPR + EPS(1)-DRG))
Y = 10*IPRED

$SIGMA .206 ; variance prop residue error, initial estimate
$ESTIMATION\ METHOD=1\ INTER\ MAXEVAL=9999\ POSTHOC$

$SIMULATION\ (987987)\ (876555\ UNIFORM)$