ESTIMATION AND PREDICTION OF CHAOTIC PHARMACODYNAMIC SYSTEMS USING NONLINEAR MIXED-EFFECTS MODELS: THE BUTTERFLY EFFECT

Marc R. Gastonguay¹, Robert R. Bies²
Metrum Research Group LLC¹, Avon, CT 06001
University of Pittsburgh School of Pharmacy², Pittsburgh, PA 15261
Introduction

• Improvements in signal measurement and data collection have opened the possibility for quantitative modeling of oscillatory and chaotic physiologic systems in pharmacodynamics (PD).

• Chaotic physiologic endpoints include continuous measurements of EEG, ECG, respiratory and cardiovascular endpoints, for example.

• Typically, PD models of these types of data treat deterministic physiologic oscillations as random noise.

• Alternatively, physiologic oscillatory data could be modeled using chaotic dynamic models.
Objectives

• To explore mechanisms for incorporating chaotic dynamics in PK-PD models

• To simulate a hypothetical drug effect on a chaotic dynamic system

• To investigate the impact of adding random residual variability (VAR) to the chaotic pharmacodynamic model simulations

• To evaluate the estimation performance of nonlinear mixed effects models when applied to chaotic dynamic systems/models under varying magnitudes of VAR
The Chaotic Dynamic Model

• The quadratic map (Equation 1) was used as a general example of a nonlinear (chaotic) finite-difference equation.

\[ X_t = R \cdot X_{t-1} \cdot (1 - X_{t-1}) \]  \hspace{1cm} \text{Eq. 1}

where:

\( X_t \) is the PD observation for the current cycle in a series of observations (e.g. QT interval for current heart-beat)

\( X_{t-1} \) is the PD observation for the immediately preceding cycle (e.g. QT interval for previous heart-beat)

\( R \) is a model parameter, which may be a function of other covariates, such as drug concentration
Simulation Methods

• A hypothetical drug concentration-time relationship was simulated (without variability) using a one-compartment model with first-order absorption and elimination.

• The parameter R in the finite-difference equation was assumed to be directly proportional to plasma drug concentration.

• One individual’s PK-PD data were simulated for 1000 cycles (e.g. heart beats) without & with different levels of residual noise: $\varepsilon_t \sim \text{N}(0,\sigma^2)$.

• Data were simulated using a recursive prediction routine (ADVAN5) in the NONMEM software.
Estimation Methods

• For each simulation replicate/scenario, individual data were analyzed assuming that the PK-PD model was known (same as simulation model).

• Parameters for the one-compartment PK model were assumed to be known and were fixed to previously determined estimates.

• Parameters of the finite-difference PD model were estimated using NONMEM, and estimation bias was expressed as mean percent prediction error (%MPE).
Simulation Results

• A chaotic dynamic system was simulated, which resulted in the characteristic deterministic pattern on a return map plot (Figure 1, right panel). This is in contrast to a completely random system (Figure 1, left panel).

• Simulated PD data revealed a chaotic dynamic pattern, which was related to increasing drug concentration (Figure 2).
Figure 1: Return Map for Random vs. Chaotic Dynamic Systems

Random System

Chaotic System
Figure 2: Simulated Data Without Noise

chaotic state (e.g. arrhythmia)
Estimation Results: Model Fit

• Plots of observed (+), predicted (o) & the true system ( ) data vs. cycle number are presented as goodness of fit diagnostics (Figures 3 – 7).

• A drug effect model was necessary to describe the chaotic dynamic system.

• The predicted response was generally in good agreement with the underlying system data at low to moderate levels of residual variability ($\sigma^2 \leq 0.01$), but the PD system behavior was lost in both the observed and predicted response when measurement noise was large ($\sigma^2 = 0.1$).
Figure 3: No Drug Effect ($\sigma^2 = 0$)
Figure 4: PD Model Fit ($\sigma^2 = 0$)
Figure 5: PD Model Fit ($\sigma^2 = 0.001$)
Figure 6: PD Model Fit ($\sigma^2 = 0.01$)
Figure 7: PD Model Fit ($\sigma^2 = 0.1$)
Estimation Results

• Estimates of the fixed effect PD parameter were relatively accurate, with bias increasing as VAR increased.

• Because of the strong sensitivity to initial conditions, even moderate bias (~17%) in parameter estimation led to poor predictions of the chaotic system response over time, as indicated by diagnostic plots (Figure 7).
Table 1. Estimation Results

<table>
<thead>
<tr>
<th>DESCRIPTION</th>
<th>SIM THETA</th>
<th>EST THETA</th>
<th>BIAS (%MPE)</th>
<th>SIM SIGMA</th>
<th>EST SIGMA</th>
<th>BIAS (%MPE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ESTIMATE W DRUG; SIM SIGMA=0 (SD=0)</td>
<td>3.90</td>
<td>3.87</td>
<td>-0.9</td>
<td>0.000</td>
<td>0.003</td>
<td>N/A</td>
</tr>
<tr>
<td>ESTIMATE W/O DRUG; SIM SIGMA=0 (SD=0)</td>
<td>3.90</td>
<td>2.67</td>
<td>-31.6</td>
<td>0.000</td>
<td>0.026</td>
<td>N/A</td>
</tr>
<tr>
<td>ESTIMATE W DRUG; SIM SIGMA=0.001 (SD=0.032)</td>
<td>3.90</td>
<td>3.78</td>
<td>-3.0</td>
<td>0.001</td>
<td>0.007</td>
<td>639.6</td>
</tr>
<tr>
<td>ESTIMATE W DRUG; SIM SIGMA=0.01 (SD=0.1)</td>
<td>3.90</td>
<td>3.80</td>
<td>-2.6</td>
<td>0.010</td>
<td>0.018</td>
<td>82.2</td>
</tr>
<tr>
<td>ESTIMATE W DRUG; SIM SIGMA=0.05 (SD=0.251)</td>
<td>3.90</td>
<td>3.80</td>
<td>-2.6</td>
<td>0.063</td>
<td>0.069</td>
<td>9.2</td>
</tr>
<tr>
<td>ESTIMATE W DRUG; SIM SIGMA=0.076 (SD=0.276)</td>
<td>3.90</td>
<td>3.87</td>
<td>-0.7</td>
<td>0.076</td>
<td>0.090</td>
<td>17.9</td>
</tr>
<tr>
<td>ESTIMATE W DRUG; SIM SIGMA=0.09 (SD=0.3)</td>
<td>3.90</td>
<td>3.83</td>
<td>-1.8</td>
<td>0.090</td>
<td>0.100</td>
<td>11.6</td>
</tr>
<tr>
<td>ESTIMATE W DRUG; SIM SIGMA=0.1 (SD=0.316)</td>
<td>3.90</td>
<td>3.22</td>
<td>-17.5</td>
<td>0.100</td>
<td>0.127</td>
<td>26.7</td>
</tr>
</tbody>
</table>

where:

- SIM = simulation value, EST = estimation value
- THETA is the fixed effect parameter describing drug effect on R
- SIGMA is the variance of random residual noise ($\sigma^2$)
- Results are the average across 100 simulation & estimation replicates
Conclusions

• Simulation and parameter estimation for nonlinear finite-difference models can be accomplished using standard PK-PD modeling software.

• Accuracy of PD parameter estimation was dependent upon the level of measurement noise.

• Predictive performance for chaotic dynamic models is highly sensitive to estimation accuracy of PD model parameters (the so-called butterfly effect).
Discussion

• This example is purely an illustration; the finite-difference PD model for QT-interval prolongation or other chaotic dynamic endpoints is unknown.

• Even when the model structure is known, accurate estimation and prediction for chaotic dynamic systems in PK-PD models may be difficult at typically observed levels of process and measurement variability.
$PROBLEM 003, ESTIMATE
CHAOTIC PKPD IND DATA
$INPUT NOID TIME DV AMT CMT
$DATA INPUT4.TAB IGNORE=@
$SUB ADVAN5 TRANS1
   INFN=RUNLOG.FOR
$MODEL
   COMP=(DEPOT)
   COMP=(CENTRAL)
$PK
   IF(NEWIND.EQ.0) XLST=0.1
   K12=THETA(1)
   K20=THETA(2)
   SCL=THETA(3)
   S2=1
$ERROR
   CP=A(2)/S2
   RPAR=SCL*CP
   X=RPAR*XLST*(1-XLST)
   Y = X + ERR(1)
   PRVX=XLST
   XLST=X
   CNT=TIME
   ID=NOID
$THETA ;PK MODEL FIXED
   (0.05 FIX) ;K12
   (0.0005 FIX) ;K20
   (0, 2) ;SCL
$OMEGA 0.00001
$ESTIMATION MAX=9999
$TABLE CNT RPAR X PRVX CMTCP EVID ID TIME …
References


Cotton P. Chaos, other nonlinear dynamics research may have answers, applications for clinical medicine. JAMA 1991; 266(1):12-18.


References (continued)


For copies of this poster, please visit www.metrumrg.com